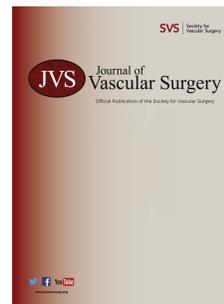


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SOCIETY FOR VASCULAR SURGERY CLINICAL PRACTICE GUIDELINES FOR MANAGEMENT OF EXTRACRANIAL CEREBROVASCULAR DISEASE

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2 **MANAGEMENT OF EXTRACRANIAL CEREBROVASCULAR DISEASE**

3

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8

9 **ABSTRACT**

10 Management of carotid bifurcation stenosis in stroke prevention has been the subject of
11 extensive investigations, including multiple randomized controlled trials. The proper treatment of
12 patients with carotid bifurcation disease is of major interest to vascular surgeons and other
13 vascular specialists. In 2011, the Society for Vascular Surgery published guidelines for treatment
14 of carotid artery disease. At the time, several randomized trials, comparing carotid
15 endarterectomy (CEA) and carotid artery stenting (CAS), were published. Since that publication,
16 several studies and a few systematic reviews comparing CEA and CAS have been published, and
17 the role of medical management has been re-emphasized. The current publication updates and
18 expands the 2011 guidelines with specific emphasis on five areas: is carotid endarterectomy
19 recommended over maximal medical therapy in low risk patients; is carotid endarterectomy
20 recommended over trans-femoral carotid artery stenting in low surgical risk patients with
21 symptomatic carotid artery stenosis of >50%; timing of carotid Intervention in patients
22 presenting with acute stroke; screening for carotid artery stenosis in asymptomatic patients; and
23 optimal sequence for intervention in patients with combined carotid and coronary artery disease.

1 A separate implementation document will address other important clinical issues in
2 extracranial cerebrovascular disease. Recommendations are made using the GRADE (Grades of
3 Recommendation Assessment, Development and Evaluation) approach, as has been done with
4 other Society for Vascular Surgery guidelines. The committee recommends CEA as the first-line
5 treatment for symptomatic low risk surgical patients with stenosis of 50% to 99% and
6 asymptomatic patients with stenosis of 70% to 99%. The perioperative risk of stroke and death in
7 asymptomatic patients must be <3% to ensure benefit for the patient. In patients with recent
8 stable stroke (modified Rankin 0-2), carotid revascularization is considered appropriate in
9 symptomatic patients with greater than 50% stenosis and is recommended and performed as soon
10 as the patient is neurologically stable after 48 hours but definitely before 14 days of onset of
11 symptoms. In the general population, screening for clinically asymptomatic carotid artery
12 stenosis in patients without cerebrovascular symptoms or significant risk factors for carotid
13 artery disease is not recommended. In selected asymptomatic patients who are at increased risk
14 for carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis as
15 long as the patients would potentially be fit for and willing to consider carotid intervention if
16 significant stenosis is discovered. In patients with symptomatic carotid stenosis 50-99%, who
17 require both CEA and CABG, we suggest CEA before or concomitant with CABG to potentially
18 reduce the risk of stroke and stroke/death. The sequencing of the intervention depends on clinical
19 presentation and institutional experience

20

21 **SUMMARY OF RECOMMENDATIONS**

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

1 1.1. In low surgical risk patients with asymptomatic carotid bifurcation atherosclerosis and a
2 stenosis of >70% (**documented by validated duplex ultrasound or CTA/angiography**), we
3 recommend carotid endarterectomy with best medical therapy over maximal medical therapy
4 alone, for the long-term prevention of stroke and death. **Level of recommendation: Grade 1**
5 **(Strong), Quality of Evidence: B (Moderate).**

6

7 **2. Is carotid endarterectomy recommended over trans-femoral carotid artery stenting in**
8 **low surgical risk patients with symptomatic carotid artery stenosis of >50%?**

9 **2.1** We recommend carotid endarterectomy over trans-femoral carotid artery stenting in
10 low/standard risk patients with a >50% symptomatic carotid artery stenosis. **Grade 1 (Strong),**
11 **Quality of Evidence: A (High).**

12

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

15 **3.1.** In patients with recent stable stroke (modified Rankin 0-2), we recommend carotid
16 revascularization for symptomatic patients with greater than 50% stenosis to be performed as
17 soon as the patient is neurologically stable after 48 hours but definitely before 14 days of onset
18 of symptoms. **Level of recommendation: Grade 1 (Strong), Quality of Evidence: B**
19 **(Moderate).**

20 **3.2.** In patients undergoing revascularization within the first 14 days after onset of symptoms, we
21 recommend carotid endarterectomy rather than carotid stenting. Level of recommendation:
22 **Grade 1 (Strong), Quality of Evidence: B (Moderate).**

23

1 **3.3.** We recommend against revascularization regardless of the extent of stenosis in patients who
2 suffered a disabling stroke, have a modified Rankin score ≥ 3 whose area of infarction exceeds
3 30% of the ipsilateral middle cerebral artery territory or who have altered consciousness to
4 minimize the risk of postoperative parenchymal hemorrhage. **These patients can be re-**
5 **evaluated for revascularization later if neurologic recovery is satisfactory. Level of**
6 **Recommendation: Grade 1 (Strong), Quality of Evidence: C (Low)**

7

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

9 **4 A. Is screening for asymptomatic carotid stenosis recommended in the general**
10 **population?**

11 **4.1** We recommend against the routine screening for clinically asymptomatic carotid artery
12 stenosis in individuals without cerebrovascular symptoms or significant risk factors for carotid
13 artery disease. **Level of recommendation: Grade 1 (Strong), Quality of Evidence: B**
14 **(Moderate).**

15

16 **4 B. Is screening for carotid stenosis recommended for high-risk asymptomatic patients?**

17 **4.2.** In selected asymptomatic patients who are at increased risk for carotid stenosis, we suggest
18 screening for clinically asymptomatic carotid artery stenosis particularly if patients are willing to
19 consider carotid intervention if significant stenosis is discovered. **Level of recommendation:**
20 **Grade 2 (Weak), Quality of Evidence: B (Moderate).**

21

22 **4 C. What imaging test is best for screening for carotid stenosis in asymptomatic patients?**

1 **4.3** In asymptomatic patients who are undergoing screening for carotid artery stenosis, we
2 recommend Duplex ultrasound performed in an accredited vascular laboratory as the imaging
3 modality of choice over CTA, MRA, or other imaging modalities. **Level of recommendation:**
4 **Grade 1 (Strong), Quality of Evidence: B (Moderate).**

5 **5. What is the optimal sequence for intervention in patients with combined carotid and**
6 **coronary artery disease?**

7
8 **5.1** In patients with symptomatic carotid stenosis 50-99%, who require both CEA and CABG, we
9 suggest CEA before or concomitant with CABG to potentially reduce the risk of stroke and
10 stroke/death. The sequencing of the intervention depends on clinical presentation and
11 institutional experience **Level of recommendation: Grade 2 (Weak), Quality of Evidence: C**
12 **(Low).**

13
14 **5.2** In patients with severe (70-99%) bilateral asymptomatic carotid stenosis or severe
15 asymptomatic stenosis and contralateral occlusion, we suggest CEA before or concomitant with
16 CABG. **Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).**

17
18 **5.3** In patients requiring carotid intervention staged or synchronous with coronary intervention,
19 we suggest that the decision between carotid endarterectomy and carotid stent be based on timing
20 of procedure, need for anticoagulation or antiplatelet therapy, patient anatomy and patient
21 characteristics. **Level of recommendation: Grade 2 (Weak), Quality of Evidence: B**
22 **(Moderate).**

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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 trials²⁻⁶ 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

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

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

17 In 2011, the Society for Vascular Surgery published clinical practice guidelines for the
18 management of extracranial carotid artery disease in the *Journal of Vascular Surgery*.¹⁵ A
19 multispecialty document also was published on the “Management of Patients with Extracranial
20 Carotid and Vertebral Artery Disease.”¹⁶ More recently, the European Society for Vascular
21 Surgery published their guidelines “Management of Atherosclerotic Carotid and Vertebral Artery
22 Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery
23 (ESVS).”¹⁷ Because of these publications, the Society for Vascular Surgery elected to update the

1 2011 Guidelines, since vascular surgeons play a major role, if not predominant role, in the
2 management of patients with carotid bifurcation disease.

3

4 **METHODOLOGY**

5 *Guideline framework*

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

- 11 **I. Is carotid endarterectomy recommended over maximal medical therapy for**
12 **asymptomatic carotid stenosis in low surgical risk patients?**
- 13 **II. Is carotid endarterectomy recommended over trans-femoral carotid artery**
14 **stenting in low surgical risk patients with symptomatic carotid artery stenosis of**
15 **>50%?**
- 16 **III. What is the optimal timing of carotid intervention in patients presenting with**
17 **acute stroke?**
- 18 **IV. Screening for carotid artery stenosis in asymptomatic patients**
- 19 **V. What is the optimal sequence for intervention in patients with combined carotid**
20 **and coronary artery disease?**

21

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

1 transcarotid artery reconstruction (TCAR) etc., these topics were addressed in separate
2 Comprehensive Implementation Document, which will be used as a reference for further details
3 to the readers in regard to Management of Patients with Extracranial Cerebrovascular Disease.

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

10 The committee used the GRADE approach to rate the certainty of evidence (confidence
11 in the estimates) and to grade the strength of recommendations.¹⁸ This system, adopted by more
12 than 100 other organizations, is adapted by SVS to express the level of certainty as A, B and C;
13 consistent with high, moderate and low certainty; respectively. GRADE categorizes
14 recommendations as strong (GRADE 1) or weak (also called conditional, GRADE 2) on the
15 basis of the certainty of evidence, the balance between desirable and undesirable effects, the
16 patient's values and preferences, and other decisional factors. GRADE 1 recommendations
17 are meant to identify practices for which benefit clearly outweighs risk that can be adopted as a
18 standard of care. GRADE 2 recommendations are made when the benefits and risks are more
19 closely matched or less certain; a situation in which shared decision making is critical. Detailed
20 explanation of the GRADE approach has been presented to the vascular surgery community.^{19, 20}
21 The Committee reached consensus about all the recommendations and the level of supporting
22 evidence.

23 *Evidence synthesis*

1 The Committee commissioned several systematic reviews that are published separately in
2 a document titled as the technical review supporting guidelines.¹⁴ The protocols and inclusion
3 criteria for the reviews were determined a priori through collaboration between the committee
4 and Mayo Clinic evidence-based Practice Center. The questions selected for the guideline were
5 specified using the PICO framework (population, intervention, comparison, outcomes) and
6 chosen based on daily clinical dilemmas faced by patients and surgeons in practice. Patient-
7 important outcomes²¹ were chosen for decision making. Meta-analyses were conducted when
8 appropriate.

9 To make the guideline more practical and helpful to clinicians, the committee drafted a
10 second document²² in which implementation details were provided to facilitate adoption and
11 operationalization of the recommendations. The implementation document is not an SVS
12 guideline and should be considered as best practices identified by the committee based on their
13 knowledge of the literature and clinical expertise.

14
15 *Evidence to decision framework:*

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

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

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- 1 **Q1. Is carotid endarterectomy recommended over maximal medical therapy in low**
 2 **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

3

4 ***Evidence and rationale***

5 There have been several controlled randomized trials that have compared CEA with best
 6 medical therapy. The results of ACAS² and ACST⁵ favored CEA in the management of low
 7 surgical risk patients with severe asymptomatic carotid artery stenosis. ACAS which randomized
 8 1662 patients to immediate CEA versus medical therapy demonstrated the superiority of CEA
 9 over antiplatelet therapy alone for asymptomatic patients with carotid stenosis of >60% (5.1%
 10 for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53%
 11 [95% confidence interval, 22% to 72%]).² This trial recommended CEA for patients (aged <80
 12 years) as long as the expected combined stroke and mortality rate for the individual surgeon was
 13 not >3%. This trial's conclusions were supported by a subsequent larger randomized controlled
 14 trial that randomized 3120 patients to immediate CEA versus medical therapy.⁵ This trial also

1 showed an advantage in limiting stroke and death at 5 years for CEA compared to maximal
2 medical therapy (4.1% vs 10.0%, 95% CI; 4.0-7.8). The long-term effectiveness of CEA in
3 asymptomatic patients was confirmed by the long-term results of ACST, as reported by Halliday
4 et al. This randomized trial compared CEA to medical arm, where patients primarily received
5 antithrombotic and antihypertensive therapy, showed that in the CEA arm (aged <75 years)
6 experienced significantly lower perioperative and 10-year stroke rates (13.3% vs 17.9%).²³ The
7 strength of these conclusions have been questioned, based on the relatively modest absolute
8 benefits of CEA and the contention that the medical therapy arm did not reflect contemporary
9 medical management.^{24, 25} The question of whether modern medical therapy (including statins)
10 is equivalent or superior to CEA or CAS has not yet been addressed by well-designed,
11 appropriately funded, prospective, multicenter, and randomized trials. However when the stroke
12 rate of patients receiving lipid lowering medication in the ACST trial were analyzed, patients
13 undergoing CEA on lipid lowering medication had a lower stroke incidence compared to medical
14 therapy but the effect of CEA was not as great (0.7 vs 1.3% per year [p<0.0001] for those on
15 lipid-lowering therapy, and 1.8 vs 3.3% per year [p<0.0001] for those not on lipid lowering
16 therapy.²³

17 More recently, Howard et al conducted a prospective population based cohort study
18 (Oxford Vascular Study) and systematic review and meta-analysis to analyze the correlation
19 between ipsilateral stroke and the degree of asymptomatic carotid stenosis in patients treated
20 with contemporary best medical therapy. They also conducted a. 2,354 consecutive patients
21 (2,178 patients had carotid imaging) were enrolled that included 207 with 50%-99%
22 asymptomatic carotid stenosis. The ipsilateral stroke rate at 5 years in patients with 70%-99%
23 carotid stenosis was 14.6% (6/53) in contrast to none in 154 patients with 50%-<70% stenosis

1 ($P<.0001$). For patients with 80%-99% carotid stenosis, the ipsilateral stroke rate was
2 significantly greater than those with 50%-<80% stenosis: 5/34 (18.3%) in contrast to one out of
3 173 (1%) ($P<.0001$). During their systematic review of 56 reports consisting of 13,717 patients,
4 23 studies provided data on ipsilateral stroke and the degree of asymptomatic carotid stenosis in
5 8,419 patients. Ipsilateral stroke was also linearly associated with the degree of ipsilateral carotid
6 stenosis ($P<.0001$). Patients with 70%-99% carotid stenosis (386/3,778 patients) had higher risk
7 of ipsilateral stroke than those with 50%-<70% stenosis (181/3,806 patients) (OR 2.1, $P<.0001$).
8 They concluded that the benefit of carotid endarterectomy might be underestimated in patients
9 with severe stenosis (>70%). Meanwhile, the 5 year stroke risk was relatively low in patients
10 with <70% stenosis on contemporary best medical therapy.²⁶

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

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

3 There are now several upcoming multicenter randomized trials designed to answer the
4 role of modern pharmacologic therapy in the management of asymptomatic carotid stenosis.
5 These trials include the Stent- Protected Angioplasty in Asymptomatic Carotid Artery Stenosis
6 (SPACE-II) study²⁵ and CREST-2.³²

7 **1.1 Recommendation: In low surgical risk patients with asymptomatic carotid**
8 **bifurcation atherosclerosis and a stenosis of >70% (documented by validated**
9 **duplex ultrasound or CTA/angiography), we recommend carotid**
10 **endarterectomy with best medical therapy over maximal medical therapy alone**
11 **for the long-term prevention of stroke and death. GRADE I, B.**

- 1 **Q2. Is carotid endarterectomy recommended over trans-femoral carotid artery stenting in**
 2 **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

3

4 ***Evidence and rationale***

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

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

3 The threat of stroke in symptomatic patients with <50% stenosis is generally considered
4 to be small and typically does not warrant intervention. ECST and NASCET demonstrated that
5 CEA was unable to reduce the subsequent neurologic event rates in patients with symptoms of
6 cerebral ischemia and bifurcation stenosis of <50% diameter reduction and was actually
7 associated with increased morbidity compared with medical management.³³⁻³⁵

8 NASCET and ECST both demonstrated the benefit of CEA compared to maximal
9 medical treatment in neurologically symptomatic patients with carotid stenosis that reduced
10 diameter >50%.^{6, 33-35} NASCET demonstrated a relative risk reduction of 65% and an absolute
11 risk reduction in stroke of 17% at 2 years (26% in medical arm vs 9% in surgical arm) for
12 patients with >70% carotid stenosis. ECST demonstrated a similar reduction in stroke risk after
13 3 years. The medical arm had a 26.5% stroke risk compared to the surgical group of 14.9%, an
14 absolute reduction of 11.6%. In both studies, the risk of stroke in the medical arm, and therefore
15 the benefit of CEA, increased with the degree of stenosis. The results of these trials established
16 CEA as the treatment of choice for patients with severe carotid stenosis and have been widely
17 accepted throughout the medical community. The benefit of CEA in stenosis of 50% to 69% was
18 more moderate— 15.7% stroke after CEA vs 22.2% stroke with medical therapy at 5 years—but
19 still statistically significant.⁴

20 **Carotid endarterectomy versus trans-femoral CAS in symptomatic stenosis.**

21 A number of trials have examined the role of TF-CAS in the management of
22 neurologically symptomatic patients with >50% diameter stenosis. Several early trials such as
23 SAPHIRE, in high surgical risk patients, demonstrated overall equivalence of CAS and CEA in

1 the management of carotid stenosis, although the number of symptomatic patients was too small
2 for subgroup analysis.³⁶ Two large prospective randomized European trials, EVA-3S¹¹ and
3 SPACE1,¹² examined the role of CAS vs CEA in neurologically symptomatic patients. EVA-3S
4 showed statistically inferior 30-day outcomes for CAS compared with CEA. The 30-day
5 incidence of any stroke or death was 3.9% after CEA (95% confidence interval [CI], 2.0 to 7.2)
6 and 9.6% after TF-CAS (95% CI, 6.4 to 14.0); the relative risk of any stroke or death after
7 stenting as compared with endarterectomy was 2.5 (95% CI, 1.2 to 5.1). The 30-day incidence of
8 disabling stroke or death was 1.5% after endarterectomy (95% CI, 0.5 to 4.2) and 3.4% after
9 stenting (95% CI, 1.7 to 6.7); the relative risk was 2.2 (95% CI, 0.7 to 7.2). This study was
10 criticized because of the relatively low level of experience (minimum of 12 CAS cases or 35
11 supra-aortic trunk cases of which 5 were CAS procedures) required in the CAS arm. The Stent-
12 Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial
13 was designed to test “equivalence” between CEA and CAS in patients with neurologic
14 symptoms. This trial stopped after recruitment of 1200 patients due to the futility of proving
15 equivalence between the two treatments. The rate of death or ipsilateral stroke at 30 days was
16 6.84% for CAS and 6.34% for CEA in 1183 randomized patients. However, the study was not
17 powered appropriately and failed to show non-inferiority of CAS compared with CEA ($P < .09$).
18 More recently two large randomized trials comparing CEA to TF-CAS in symptomatic patients
19 have been completed. The International Carotid Stenting Study Trial (ICST),¹⁰ enrolled 1713
20 patients and demonstrated an increased peri-procedural stroke risk for CAS (7.7%) compared
21 with CEA (4.1%) in neurologically symptomatic patients. This observed difference was
22 significant ($P < .002$). The rate of any stroke or death within 30 days of treatment in the stenting
23 group was more than twice the rate recorded in the endarterectomy group (7.4% vs 3.4%, $P <$

1 .0004). In addition, the composite end-point of stroke, death, and MI significantly favored CEA
2 (5.2%) vs CAS (8.5%; $P<.006$). These findings are similar to those of the symptomatic patients
3 enrolled in the CREST Trial.⁹ In CREST the peri-procedural rate of stroke and death was
4 significantly higher in trans-femoral CAS versus CEA for symptomatic patients ($6.0\%\pm 0.9\%$
5 versus $3.2\%\pm 0.7\%$; HR, 1.89; 95% CI, 1.11 to 3.21; $P<0.02$). The rate of MI was lower after
6 CAS versus CEA for symptomatic patients ($1.0\%\pm 0.4\%$ versus $2.3\%\pm 0.6\%$; HR, 0.45; 95% CI,
7 0.18 to 1.11; $P<0.08$) however, the differences were not significant. The Carotid Stenosis
8 Trialists' Collaboration (CSTC) performed a meta-analysis of 4754 patients from the four
9 randomized trials comparing CEA to TF-CAS. These investigators demonstrated a CEA-versus
10 TF-CAS periprocedural HR of 1.61 (95% CI 0.90–2.88) favoring CEA for patients aged 65–69
11 years and an HR of 2.09 (1.32–3.32) for patients aged 70–74 years.³⁷ If octogenarians (>80
12 years) are removed from the data to allow CREST to be compared to other trials in which these
13 patients were not enrolled, the results demonstrated that the 30-day stroke and death rate was
14 significantly lower for the patients undergoing CEA ($2.6\%\pm 0.7\%$ for CEA and $5.6\%\pm 1.0\%$ for
15 CAS; $p=.006$).³⁷ As shown in Figure 1 pooled analysis of 30-day outcomes of stroke and death
16 are lower in symptomatic patients treated with CEA versus TF-CAS.¹⁴

17 The long-term outcomes of CAS versus CEA in symptomatic patients has been examined
18 using a preplanned pooled analysis of individual patient data from the above described EVA-3S,
19 SPACE, ICSS, and CREST Trials.³⁸ These four trials randomized a total of 4754 symptomatic
20 patients with >50% ICA stenosis. Median length of follow-up was 2-6.9 years. The risk of stroke
21 or death within 120 days of the index procedure was 5.5% for CEA and 8.7% for CAS (risk
22 difference 3.2% [95%CI 1.7-4.7]). Beyond the peri-procedural period of 120 days there was no
23 difference in annual rate of late ipsilateral stroke (annual event rate 0.60% CEA versus 0.64%

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

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

22 Timing of CEA

1 There is increasing evidence that CEA provides maximum benefit if performed in <14 days for
2 patients presenting with TIA or amaurosis fugax.¹⁷ Natural history studies reported that the
3 incidence of recurrent symptoms after the index TIA ranges from 5%-8% at 48 hours, 4%-17%
4 at 72 hours, 8%-22% at 7 days and 11%-25% at 14 days.¹⁷

5 **Transcarotid artery revascularization (TCAR)**

6 Early data suggests that TCAR may have a role in the treatment of patients with
7 symptomatic carotid occlusive disease. Studies have shown that TCAR has a similar rate of
8 diffusion-weighted infarcts (DWI) on post-procedure MRI compared to CEA while trans-femoral
9 CAS is associated with a 2-3 fold higher rate of DWI.⁴² Up to 50% of the DWI and strokes that
10 occur following trans-femoral CAS are contralateral suggesting arch pathology as the etiology.⁴³
11 Two recent trials ROADSTER-1 and ROADSTER-2 have been completed.⁴⁴⁻⁴⁶ The incidence of
12 30-day stroke in the symptomatic per protocol patients in both of these trials was 0.6% in each
13 trial. There were no deaths in the per protocol symptomatic patients in Roadster 2 for a combined
14 30-day stroke and death rate of 0.6%.^{44, 45} A more recent study that examined 3286 propensity
15 matched patients from the Vascular Quality Initiative demonstrated a significantly lower
16 incidence of in-hospital stroke and death in patients treated with TCAR versus TF-CAS 1.6% vs
17 3.1% (RR 0.51, 95% CI 0.37-.72).⁴⁷ There was no difference in myocardial infarction between
18 the groups. Lastly, Malas and coworkers examined a more recent cohort of patient from the VQI
19 Trans-carotid Revascularization Project.⁴⁸ These investigators propensity score matched 6,384
20 pairs of patients who had undergone either TCAR or CEA. In this cohort there were 3,333
21 symptomatic patients that were compared. There was no difference in in-hospital stroke and
22 death between symptomatic patients undergoing TCAR versus CEA (2.2% vs 2.6%, p=.46) and
23 TCAR was associated with a lower incidence of cranial nerve injury and shorter hospital stay.

1 The impact of developing a TCAR program on overall carotid revascularization outcomes was
2 examined by Columbo and coworkers. These investigators compared the risk of MACE defined
3 as stroke, death and MI in centers who performed only CEA vs those centers that performed both
4 CEA and TCAR. At one year the incidence of MACE was 10% lower at centers that performed
5 both TCAR and CEA vs CEA alone (OR 0.9, .81-.99, p=.04).⁴⁹ While these studies appear
6 promising and have been supported by a clinical competency statement from the SVS⁵⁰ it is
7 important to remember that to date the vast majority of TCAR procedures have been performed
8 in patients at high anatomic or medical risk for CEA and there is currently inadequate data to
9 make a recommendation on the role of TCAR in low surgical risk patients with symptomatic
10 carotid stenosis. In summary, TCAR is superior/preferable over TF-CAS or CEA in high surgical
11 risk patients (anatomically and physiologically). (See Implementation Document)

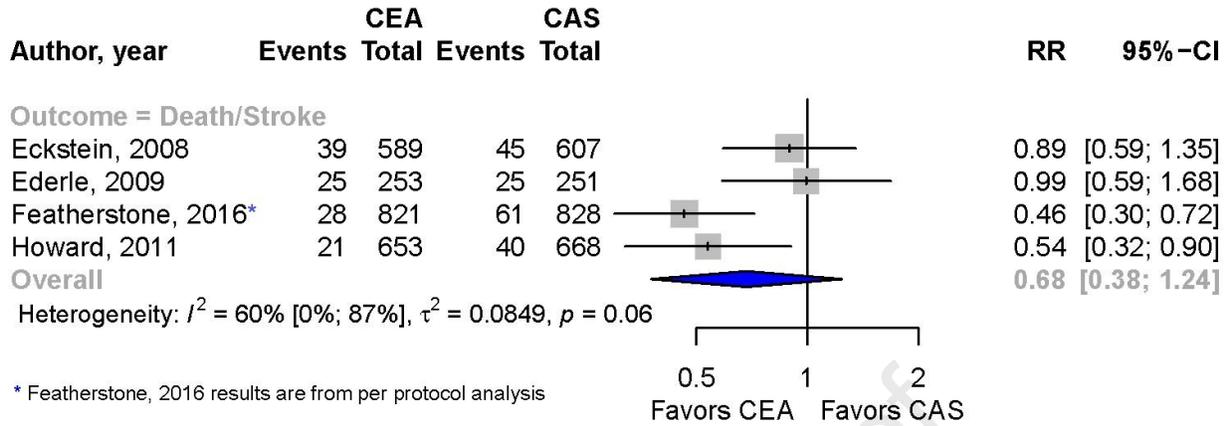
12
13 **Recommendation: 2.1 We recommend carotid endarterectomy over trans-femoral carotid**
14 **artery stenting in low/standard risk patients with a >50% symptomatic carotid artery**
15 **stenosis.**

16 **GRADE I, A.**

17

18

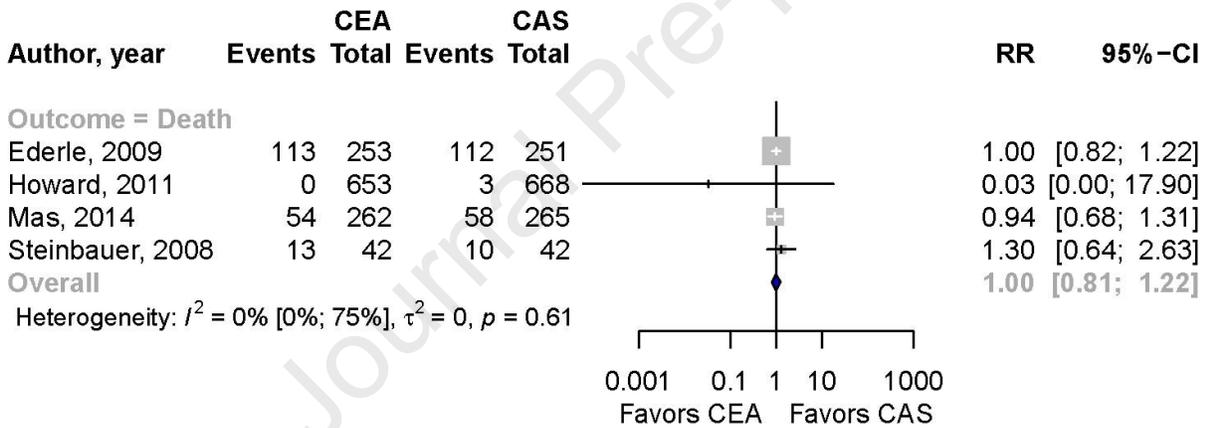
1 **Figure 1. 30 day death and stroke**



2

3

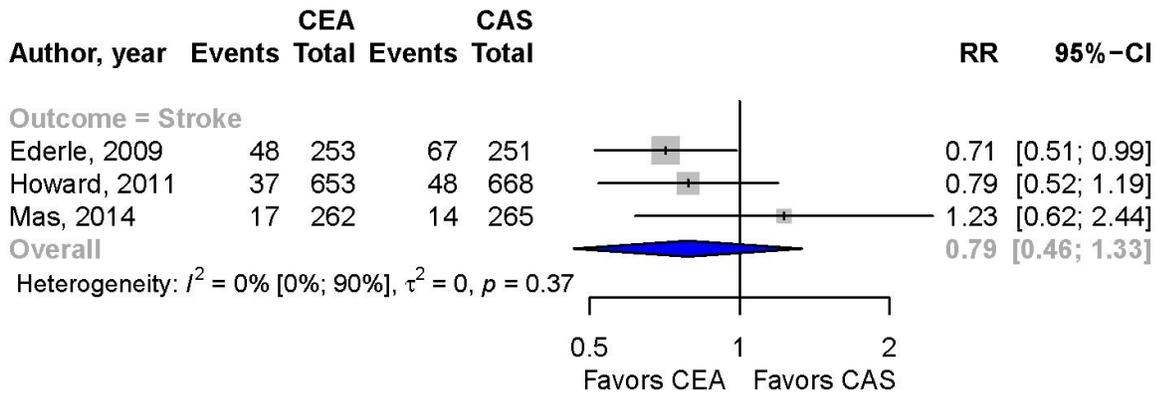
4 **Figure 2. Five year risk of death**



5

6

7 **Figure 3. Five year risk of any stroke**



8

1

2 **Q3. What is the optimal timing of carotid Intervention in patients presenting with acute**
 3 **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

4

5 ***Evidence and rationale***

6 ***Patients***

7

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

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

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

6 However, in acute stroke patients who present obtunded or severely neurologically
7 debilitated, it is often necessary to delay the CEA as they may face a higher risk of hemorrhagic
8 transformation of an infarct or intracerebral hemorrhage (ICH). Patients with a significant
9 neurologic deficit (modified Rankin >2), with an area of infarction exceeding 30% of the middle
10 cerebral artery (MCA) territory, and those with altered consciousness should not undergo CEA
11 until significant neurologic improvement has occurred. Factors that have been found to
12 influence outcomes include the extent of hemispheric involvement, time to the initiation of
13 therapy, time to perfusion, age, blood glucose, and female sex. The most important of these
14 appears to be the degree of hemispheric involvement (< 30% of middle cerebral artery by
15 volume), time to re-perfusion, and age.⁵¹⁻⁵³

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

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

1 In an analysis of the Vascular Quality Initiative (VQI) of 8,408 patients, results were comparable
2 among patients who underwent surgery after 48 hours but less than 14 days post-stroke to those
3 performed later than 14 days after index event. When cohorts were analyzed to 3-8 days and 8-
4 14 days, multivariate analysis demonstrated that performing CEA between 3-7 days post-stroke
5 was protective for postoperative stroke/death ($p=0.003$) and any postoperative complication
6 ($p=0.028$). The authors concluded that surgery should be delayed for at least 48 hours after an
7 acute stroke and should be performed within 14 days post-stroke.⁵⁹ Avgerinos et al corroborated
8 this data suggesting CEA's performed 2-5 days after index neurological event have similar
9 outcomes to CEA's performed later.⁶⁰

10 These findings confirmed the results of an analysis of the Swedish Vascular Registry,
11 including 2,596 patients who underwent CEA for symptomatic carotid stenosis, including stroke.
12 The combined stroke/death rate was 11.5% among those undergoing surgery within the first 2
13 days of the neurologic event, as opposed to 3.6%, 4.0%, and 5.4% among those undergoing CEA
14 between 3-7, 8-14, and 15-180 days following the acute neurologic event, respectively. A
15 multivariate analysis demonstrated that patients who underwent CEA within the first 2 days
16 following an acute neurologic event experienced a relative OR of 4.24 (CI, 2.07-8.70, $p < 0.001$)
17 for perioperative complications compared to those undergoing surgery within 3-7 days.⁵⁸ These
18 data were corroborated by Hasan et al¹⁴ in their meta-analysis concerning timing of intervention
19 after index stroke. Avgerinos et al demonstrated an increased risk of complications if the CEA
20 was performed within 48 hours of index event (RR = 2.3053) for stroke but no difference
21 between 2- 14 days.⁶⁰ This short delay may allow more complete patient evaluation and let the
22 symptoms stabilize and plateau.

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

8 **Recommendations for management of acute neurologic syndrome:**

9 **3.1 In patients with recent stable stroke (modified Rankin 0-2), we recommend carotid**
10 **revascularization for symptomatic patients with greater than 50% stenosis to be performed**
11 **as soon as the patient is neurologically stable after 48 hours but definitely before 14 days of**
12 **onset of symptoms. (Grade I, B)**

13 **3.2 In patients undergoing revascularization within the first 14 days after onset of**
14 **symptoms, we recommend carotid endarterectomy rather than carotid stenting. (Grade I,**
15 **Level B)**

16 **3.3 We recommend against revascularization regardless of the extent of stenosis in**
17 **patients who suffered a disabling stroke, have a modified Rankin score ≥ 3 whose area of**
18 **infarction exceeds 30% of the ipsilateral middle cerebral artery territory or who have**
19 **altered consciousness to minimize the risk of postoperative parenchymal hemorrhage.**
20 **These patients can be re-evaluated for revascularization later if neurologic recovery is**
21 **satisfactory. (Grade I, C)**

22

23

1 **Q4.**

2 **A. Is screening for asymptomatic carotid stenosis recommended in the general**
 3 **population?**

4

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 $\geq 50\%$ carotid stenosis, incidence of stroke or death related to carotid disease	Any

5

6 ***Evidence and rationale***

7 There is no consensus on which patient populations should undergo carotid screening for
 8 the detection of asymptomatic carotid disease, and there is unfortunately no direct evidence on
 9 the benefits of screening with regard to the actual outcomes of future stroke. The rationale
 10 behind screening for asymptomatic disease is based upon the assumptions that unheralded stroke
 11 is often the first symptom of significant carotid atherosclerosis, and that the medical, surgical or
 12 endovascular treatment of identified severe carotid artery stenosis can prevent future cerebral

1 infarction. The efficacy of screening is directly related to the prevalence of disease in the
2 designated population. Screening has been found to reduce the risk of stroke in a cost-effective
3 manner when the prevalence of significant stenosis is $\geq 20\%$.⁶⁸ With a prevalence of $<5\%$ in the
4 general population^{68, 69}, screening does not appear to reduce stroke risk, and may in fact be
5 harmful if it leads to inappropriately performed invasive procedures. The rate of false positive
6 carotid Duplex ultrasound tests may additionally be increased in a population with such a low
7 prevalence of disease.⁷⁰ Because of the relatively low prevalence of disease, widespread
8 screening of the general population, therefore, is clearly not indicated. This position is supported
9 by multiple professional organizations including the National Stroke Association, Canadian
10 Stroke Consortium,^{71, 72} and the United States Preventive Services Task Force (USPSTF).⁷⁰

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

14

15

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

3

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 $\geq 50\%$ 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

4
 5 ***Evidence and rationale***

6 *Atherosclerotic risk factors / medical comorbidities predisposing towards an increased*
 7 *prevalence of carotid artery stenosis*

8 Screening has been found to reduce the risk of stroke in a cost-effective manner when the
 9 prevalence of significant stenosis is $\geq 20\%$.⁶⁸ Therefore, specific high-risk asymptomatic

1 populations have been proposed as appropriate for carotid screening. The American Stroke
2 Association / American Heart Association Stroke Council concluded that screening of highly
3 selected populations might be of benefit.⁷³ Multiple societies including the American College of
4 Cardiology Foundation and others have recommended screening for asymptomatic patients who
5 have a carotid bruit on physical examination, and for those in whom coronary artery bypass
6 grafting is planned.⁷⁴ The Society for Vascular Surgery has advocated for consideration of
7 carotid artery screening in high-risk patients 55 years or older with cardiovascular risk factors.⁷⁵

8 Several groups have attempted to further refine and identify population subsets where the
9 prevalence of carotid stenosis is $\geq 20\%$, possibly justifying screening in asymptomatic cases. In
10 a report of a single-institution screening program, a model identifying patients at high-risk for \geq
11 50% asymptomatic stenosis was proposed. Patients screened were older than 60 years of age and
12 had one or more of the following risk factors: hypertension, coronary artery disease, current
13 cigarette smoking, and / or a first-degree family member with a history of stroke. The prevalence
14 of significant stenosis was only 2% if none of these risk factors were present, but increased
15 dramatically with the coexisting presence of additional risk factors; the prevalence of carotid
16 stenosis was 14% with two risk factors, 16% with three risk factors, and 67% with four risk
17 factors.⁷⁶ In another analysis from the same institution, patients with both hypertension and
18 known cardiac disease of any type had a prevalence of carotid stenosis $\geq 50\%$ of 22.1%.⁷⁷

19 Similarly, a report from the Western New York stroke screening program identified the
20 following variables to be associated with $\geq 60\%$ carotid stenosis: age ≥ 65 (Odds Ratio, 4.1),
21 current smoking (Odds Ratio, 2), coronary artery disease (Odds Ratio, 2.4), and
22 hypercholesterolemia (OR 1.9).⁷⁸ Patients undergoing coronary artery bypass surgery were noted
23 to have a prevalence of significant carotid stenosis of 8%. The American College of Cardiology

1 / American Heart Association guidelines note that screening before coronary artery bypass
2 grafting is probably indicated in the following subset of patients: age ≥ 65 , presence of left main
3 coronary artery stenosis, history of smoking, history of transient ischemic attack, stroke or
4 carotid bruit, and known peripheral arterial disease.⁷⁸ Based upon these and other reports, the
5 Society for Vascular Surgery does advocate carotid artery screening in high-risk patients 55
6 years or older with appropriate cardiovascular risk factors.^{75, 79}

7 Other investigators have noted that the prevalence of occult carotid stenosis is increased
8 in diabetics as compared to non-diabetics (8.7 vs 2.8%, $p < 0.01$),⁸⁰ and in hemodialysis patients
9 undergoing tunneled catheter placement (9.8%).⁸¹ In a study of 1500 subjects specifically
10 recruited for carotid screening, the overall prevalence of significant stenosis was 5.2%.
11 Independent predictors of an increased prevalence of carotid stenosis included: hypertension,
12 diabetes mellitus, cigarette smoking, hypercholesterolemia, and a family history of stroke.⁸² One
13 investigator has recommended screening of asymptomatic patients is appropriate if they are ≥ 60
14 years of age and have three or more traditional atherosclerotic risk factors.⁸³

15 Unfortunately, few direct comparative studies evaluate the efficacy of screening with
16 respect to the actual clinical outcomes of stroke or death. Most studies in the literature use the
17 prevalence of significant carotid stenosis in the studied populations as the actual outcome
18 measure. In a report by Berens, et al, more than 1000 patients 65 years or older who were
19 undergoing cardiac surgery were screened with carotid duplex scans prior to surgery. The
20 prevalence of disease was 17% for $\geq 50\%$ stenosis, and 5.9% for $\geq 80\%$ stenosis. Using
21 multivariate analysis, five variables were found to be significant independent predictors of \geq
22 80% stenosis: female sex, peripheral vascular disease, history of transient ischemic attack or
23 stroke, smoking history and left main coronary disease. If all patients with at least one of those

1 risk factors were screened, the mathematical model predicted that 95% of patients with $\geq 80\%$
2 stenosis would be identified prior to their cardiac operation.⁸⁴

3 In Lin, et al, the outcome of 3233 patients who underwent cardiac surgery was studied,
4 and comparisons performed between those who underwent a preoperative carotid duplex scan
5 (N=515) and those who did not (N=2718). There was no difference between risk factors or a
6 history of prior transient ischemic attack between the two cohorts. Among patients who had
7 screening with ultrasonography prior to isolated coronary artery bypass grafting (n=306), the
8 incidence of significant disease was relatively low: 25 (8.2%) had unilateral moderate (50-69%)
9 stenosis, 10 (3.3%) had bilateral moderate stenosis, 9 (2.9%) had unilateral severe (70-99%)
10 stenosis, 2 (0.7%) had bilateral severe stenosis, 5 (1.6%) had unilateral total occlusion, and 1
11 (0.3%) had bilateral total occlusion. The outcomes with regard to perioperative mortality and
12 stroke did not differ between those who had a Duplex and those who did not. Operative
13 intervention of severe carotid stenosis prior to CABG occurred in two of 17 (11.8%) of patients
14 identified.⁸⁵

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

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

- 1 • Patients with hypertension, hypercholesterolemia and coronary artery disease

2 ***Subgroups***

3 *Patients with peripheral arterial disease*

4 Patients with lower extremity peripheral arterial disease have an increased prevalence of
5 carotid artery stenosis and may benefit from screening.^{86, 87} The prevalence of $\geq 60\%$ carotid
6 artery stenosis in patients with symptomatic lower extremity peripheral arterial disease is likely \geq
7 20%, and was nearly 25% in one epidemiological study.⁸⁷

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

18 *Patients undergoing coronary artery bypass surgery*

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

1 undergoing coronary angioplasty as well.¹⁰⁸ Among patients undergoing coronary artery bypass,
2 a carotid bruit and diabetes mellitus increased the predictive value.¹⁰⁴ Additionally, carotid
3 stenosis in coronary bypass patients is noted to be a risk factor for perioperative stroke.¹⁰⁴
4 Considering the prevalence of occult carotid disease, carotid screening in patients who are
5 undergoing coronary artery bypass is felt to be appropriate. The evidence in favor of screening
6 in patients who have documented coronary artery disease without plans for coronary artery
7 bypass procedures is less robust.

8 *Asymptomatic patients with an audible carotid bruit*

9 The finding of an audible bruit in the neck is felt to be a sign of turbulent blood flow at
10 the bifurcation, and of carotid artery atherosclerosis. However, this physical finding is not
11 particularly specific or sensitive for clinically significant carotid artery stenosis. In a reported
12 meta-analysis of studies describing the relationship between carotid bruits and carotid stenosis,
13 28 prospective cohort articles involving more than 17,000 patients were analyzed.¹⁰⁹ Stroke
14 rates were 1.6 per 100 patient-years for those with bruits compared with 1.3 per 100 patient-
15 years for those without carotid bruits. Clearly, the presence of a carotid bruit likely increases the
16 risk of cerebrovascular disease, and therefore may justify screening in otherwise asymptomatic
17 patients.

18 In the Northern Manhattan study, the presence of $\geq 60\%$ carotid stenosis was 2.2%, and
19 the presence of a carotid bruit was 4.1% among 686 asymptomatic subjects.¹¹⁰ The positive
20 predictive value of an ipsilateral carotid bruit was 25%, and the negative predictive value was
21 99%. Sensitivity was 56%, specificity was 98%, and overall accuracy was 97.5%. However, in
22 another observational study of more than 1500 patients who underwent carotid ultrasonography
23 specifically because of the presence of an audible bruit, 31% of subjects had a significant (\geq

1 50%) stenosis.¹¹¹ However, in patients with 50-99% carotid stenosis, carotid bruits had an
2 accuracy of 75%, a sensitivity of 71%, a specificity of 81%, and a positive likelihood ratio of
3 3.65. Therefore, although carotid bruits are not necessarily accurate enough to confirm or to
4 exclude significant carotid stenoses, these signs are felt to be an appropriate indication for further
5 directed screening with carotid duplex ultrasonography, particularly if the carotid bruit is noted
6 in a patient with other atherosclerotic risk factors.

7 *Asymptomatic patients with prior neck irradiation*

8 With an increased use and success of radiotherapy to treat head and neck malignancies,
9 survival of these diseases has gained remarkable progress.¹¹² Vascular injury and carotid
10 stenosis has received increased attention. Patients who have had neck irradiation more than five
11 years prior have an eight times higher risk of developing carotid stenosis compared to those with
12 a post-radiotherapy time interval of less than 60 months. Severe post-radiotherapy carotid
13 stenosis is additionally associated with age, smoking and heart disease. Patient who have
14 undergone prior radiotherapy of the head and neck may have a prevalence of significant carotid
15 stenosis that may justify screening in asymptomatic cases.¹¹³ The highest incidence of carotid
16 stenosis is noted approximately 15 years following radiation exposure, with ipsilateral rates of
17 stenosis as high as 21.3%.^{15, 113, 114} Unlike typical atherosclerotic disease which often involves
18 only the carotid bifurcation, the distribution of radiation induced carotid disease may involve the
19 proximal common carotid arteries as well; extensive proximal disease would have obvious
20 implications for surgical or endovascular treatment of such lesions, if indicated.

21 It has been proposed by some that patients with prior radiotherapy undergo screening
22 Duplex evaluation even in the absence of clinical cerebrovascular symptoms.¹¹⁴ However, the
23 optimal timing and frequency of screening are undefined, and this concept is not universally

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

3 *Patients with abdominal aortic aneurysm (AAA)*

4 While patients with peripheral arterial disease and severe coronary artery disease are
5 clearly at greatly increased risk for having occult carotid artery stenosis, the correlation in
6 patients with abdominal aortic aneurysm is not as robust. The prevalence of carotid stenosis of
7 $\geq 70\%$ was noted to be 8.8% in a population of AAA patients as compared with 12.5% in a
8 cohort of PAD patients.¹¹⁵ In a prospective study of patients with AAA, the prevalence of
9 asymptomatic carotid stenosis $\geq 70\%$ was found to be 10.8%.¹¹⁶ No correlation was noted
10 between the size of the AAA and the degree or presence of carotid stenosis. In an additional
11 report of 332 patients with AAA who underwent carotid duplex scans, a higher prevalence of
12 carotid stenosis was noted; 30.4% were found to have $\geq 50\%$ stenosis in at least one or both
13 carotid arteries.¹¹⁷ However, several additional studies have revealed a prevalence of carotid
14 stenosis in patients with abdominal aortic aneurysms as less than 20%.¹¹⁸ Clearly, the correlation
15 of carotid atherosclerosis with isolated abdominal aneurysmal disease is not felt to be as
16 significant as the relationship with coronary and lower extremity atherosclerotic occlusive
17 disease, and therefore the routine screening for carotid stenosis in asymptomatic patients with
18 AAA but without other defined high-risk factors is not recommended.¹¹⁹

19 *Patients with clinically occult cerebral infarction or high risk factors on brain imaging*

20 Finally, asymptomatic patients in whom brain imaging has identified cerebral infarction
21 despite the absence of any corresponding history of neurological symptoms represent a
22 population that may benefit from imaging of the carotid artery. An increased subsequent stroke
23 rate of 4.4% in patients with 60-79% initially asymptomatic stenosis has been reported if a silent

1 infarct was identified on brain imaging studies.¹²⁰ Therefore, screening is generally
2 recommended in patients with asymptomatic cerebral infarctions.¹²⁰ The detection of cerebral
3 emboli using Transcranial Doppler (TCD) studies also has a high positive predictive value to
4 identify asymptomatic patients at high risk of stroke; patients with ≥ 2 microemboli / hour on
5 TCD had a markedly increased risk of 1-year ipsilateral ischemic stroke compared with patients
6 with asymptomatic carotid stenosis without TCD-detected microemboli (15.6% vs 1.0%,
7 respectively; $P < 0.0001$).¹²¹ However, at the current time it is unclear how this technology might
8 be practically applied to all asymptomatic patients with known carotid stenosis.

9
10 **Recommendation: 4.2 In selected asymptomatic patients who are at increased risk for**
11 **carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis**
12 **particularly if patients are willing to consider carotid intervention if significant stenosis is**
13 **discovered. (GRADE 2, B)**

14 **These high-risk groups include:**

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

21 **Other remarks:**

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

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

4 **C. What imaging test is best for screening for carotid stenosis in asymptomatic**
 5 **patients?**
 6

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 $\geq 50\%$ and $\geq 70\%$ carotid stenosis	Any

7
 8 ***Evidence and rationale***

9 The most important features of imaging of carotid bifurcation disease are the degree of
 10 stenosis and the character of the plaque.^{2, 6, 15, 33, 122} A higher degree of stenosis is generally
 11 thought to represent a progressively increased risk of future stroke.^{6, 33} However, plaque
 12 morphology clearly plays a significant role as well.¹²² Morphological features of the plaque

1 likely related to the risk of future stroke include heterogeneity, measurement of plaque area and
2 juxtaluminal black area, Gray-Scale Median, and echogenicity.

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

12 Determination of the degree of carotid stenosis is based upon analysis of hemodynamic
13 parameters obtained from Doppler analysis, including the peak systolic and end diastolic
14 velocities. Ultrasound criteria for the degree of carotid stenosis should be defined based on
15 angiographic / imaging correlation in each vascular laboratory. The most commonly recognized
16 consensus criteria include a cutoff peak systolic velocity of the internal carotid artery of ≥ 125
17 cm / sec to denote an angiographic stenosis of $\geq 50\%$. A combination of peak systolic velocity
18 of 230 cm / sec and an end diastolic velocity of ≥ 100 cm / sec, or peak systolic velocity ratio
19 between the internal and common carotid artery of ≥ 4 can be used to predict a stenosis of \geq
20 70%.¹²⁶ Using these criteria, the reported sensitivity, specificity and accuracy of Duplex in
21 predicting 50-69% or $\geq 70\%$ stenosis are 93, 68, and 85% and 99, 86 and 95% respectively.¹²⁵
22 The major limitations of Duplex ultrasound include its dependence on a skilled operator, and its
23 inability to completely image the proximal and intracranial vasculature. Certain anatomic

1 features can also reduce the accuracy of Duplex imaging, including severe vascular calcification
2 and arterial tortuosity.¹⁵

3 Current contrast enhanced magnetic resonance angiography can provide three
4 dimensional images which may rival those of formal arteriography.⁷⁵ Its main advantages
5 include the absence of radiation, and avoidance of iodinated based contrast materials.
6 Additionally, MRA can be combined with MR brain imaging, delineating clinically silent
7 cerebral infarction. It can also evaluate plaque morphology, particularly the presence of
8 intraplaque hemorrhage.¹²⁷ Contraindications include the presence of metallic implants,
9 including some pacemakers and defibrillators. MRA has no role, however, in screening for
10 carotid artery disease, due to its considerable expense.

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

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

21

22 **Recommendation: 4.3 In asymptomatic patients who are undergoing screening for carotid**
23 **artery stenosis, we recommend duplex ultrasound performed in an accredited vascular**

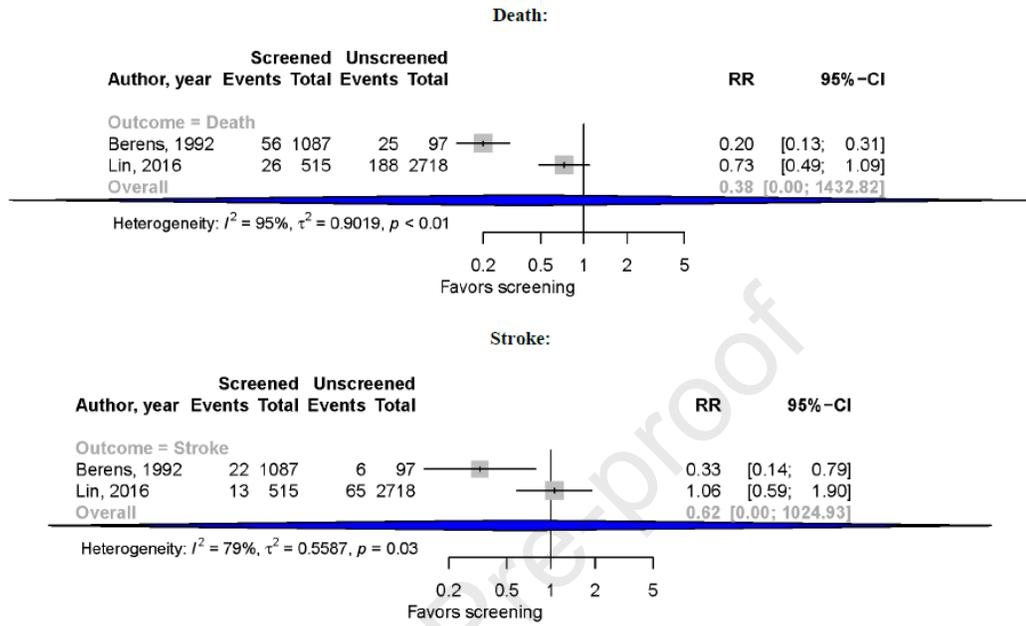
1 **laboratory as the imaging modality of choice over CTA, MRA, or other imaging modalities.**

2 **(GRADE 1, B)**

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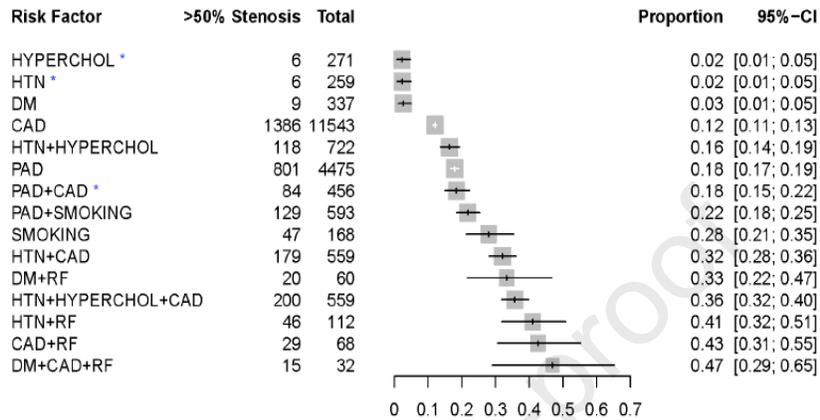
1 **Figure 4.****Comparative studies**

2

3

1 **Figure 5.****Q4: Screening high risk patients****Non-comparative studies (Yield of screening for carotid stenosis cases based on risk factor)**

> 50% stenosis:



* >70% stenosis

2

3 Hyperchol – Hypercholesterolemia

4 HTN – Hypertension

5 DM – Diabetes mellitus

6 CAD – Coronary artery disease

7 PAD – Peripheral artery disease

8 RF – Renal failure

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

3

4 Carotid endarterectomy (CEA)

5

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

6

7 **Evidence and rationale**

1 The recommendation for staged or synchronous carotid interventions in patients with 50-
2 99% stenosis and a history of stroke or TIA in the preceding 6 months who require CABG is
3 supported by the literature.¹²⁸⁻¹³³ However, the optimal timing for these interventions is unclear.
4 In patients with severe (>70%) stenosis and symptomatic disease, there is minimal literature to
5 address the timing of intervention.¹³⁴ In an analysis of multiple observational studies, patients
6 undergoing combined CABG and CEA compared to CABG first had a similar risk of death (RR
7 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
8 comparing CABG first to CEA first, the groups had a similar risk of death (RR 0.94 [0.44;2.01]),
9 stroke (RR 1.4 [0.64; 3.06]), and MI (RR 0.51 [0.22; 1.18]). Finally, if the group of CABG first
10 is compared to the group with CEA first, the risks of death, stroke, and MI are also similar. As
11 expected, there is a small trend toward higher risk of MI if the CEA is performed first, and an
12 increased trend toward risk of stroke if the CABG is done first, but these differences are not
13 significant.

14 One of the most controversial issues is the role of prophylactic CEA/CAS in CABG
15 patients with unilateral 70-99% asymptomatic stenosis, where the stroke risk may be less than
16 2%..^{135, 136} There are two randomized controlled trials^{137, 138} comparing combined CEA/CABG
17 with a strategy of CABG first and delayed CEA in patients with unilateral asymptomatic carotid
18 stenosis, and several observational series. In the Illuminati et al series,¹³⁷ the risk of stroke with
19 CABG first was higher than the combined series, yet in the Weimar series¹³⁸ the contrary was
20 true. Due to small numbers in both series these differences were not significant and therefore one
21 must assess larger series to obtain a meaningful interpretation.

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

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

5 **Patient's values and preferences**

6 Patients undergoing CABG are already at increased risk of stroke, and therefore many
7 would prefer combined treatment to potentially decrease their risk with one procedure. However,
8 if patients are severely symptomatic for either coronary disease or carotid disease, they may be
9 more likely to wish for symptomatic relief rather than overall risk reduction. If anatomically
10 suitable, CAS seems favorable for symptomatic patients. In addition, patients with coronary
11 disease amenable to percutaneous coronary intervention should be treated in that manner,
12 followed by treatment of the carotid stenosis. In addition, patients should be considered for CEA
13 with regional anesthesia prior to CABG if possible.¹³⁹⁻¹⁴¹

14 **Recommendations:**

15 **5.1 In patients with symptomatic carotid stenosis 50-99%, who require both CEA and**

16 **CABG, we suggest CEA before or concomitant with CABG to potentially reduce the**
17 **risk of stroke and stroke/death. The sequencing of the intervention depends on clinical**
18 **presentation and institutional experience (GRADE 2, C)**

19 **5.2 In patients with severe (70-99%) bilateral asymptomatic carotid stenosis or severe**

20 **asymptomatic stenosis and contralateral occlusion, we suggest CEA before or**
21 **concomitant with CABG (Grade 2, C)**

22 **5.3 In patients requiring carotid intervention staged or synchronous with coronary**

23 **intervention, we suggest that the decision between carotid endarterectomy and carotid**

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

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8

Journal Pre-proof

Figure 1. 30 day death and stroke

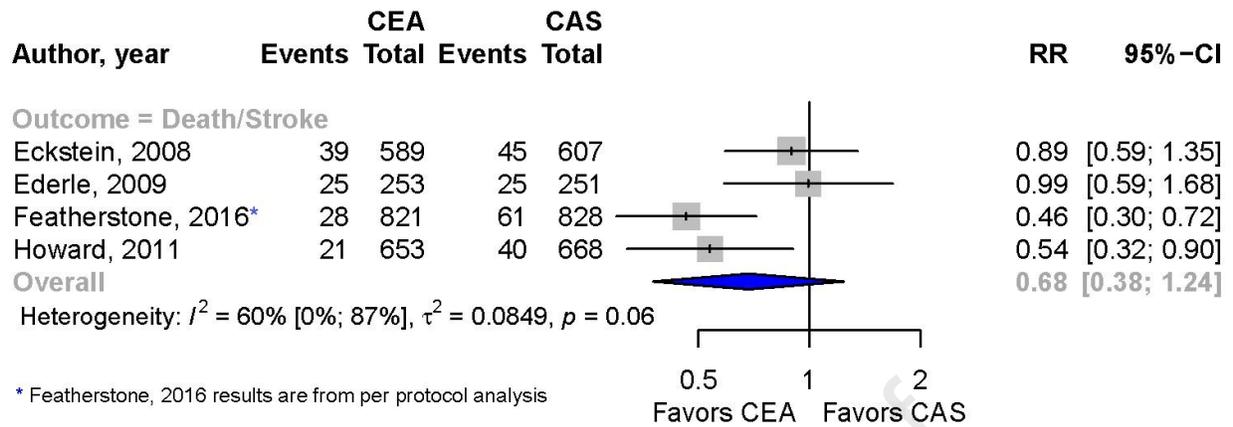


Figure 2. Five year risk of death

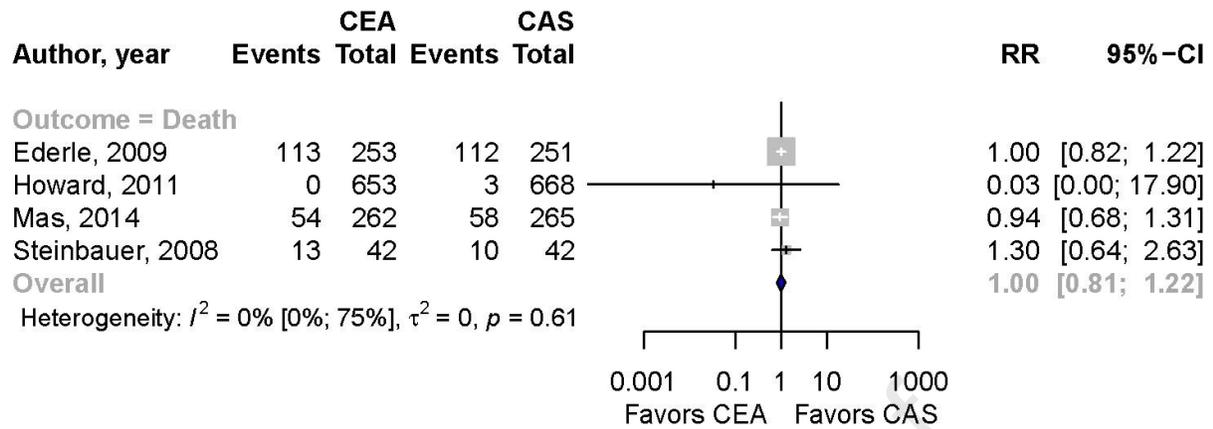


Figure 3. Five year risk of any stroke

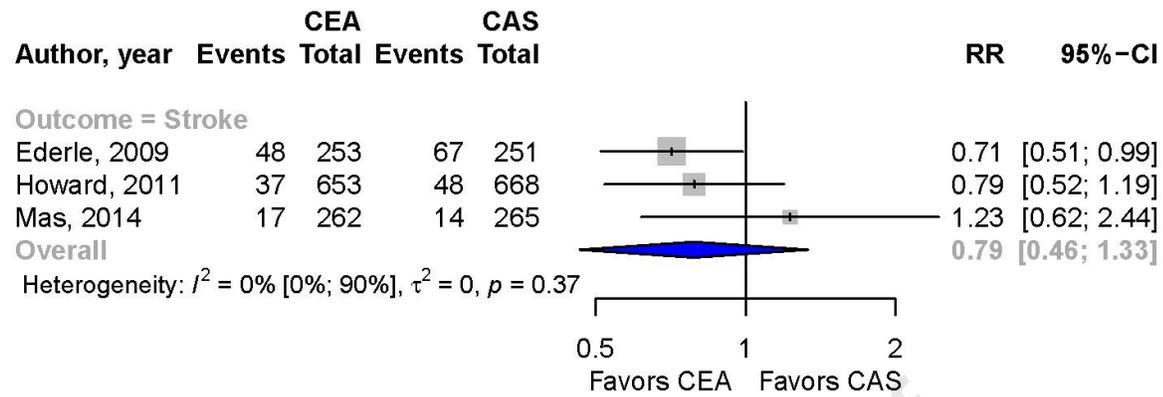


Figure 4.

Comparative studies

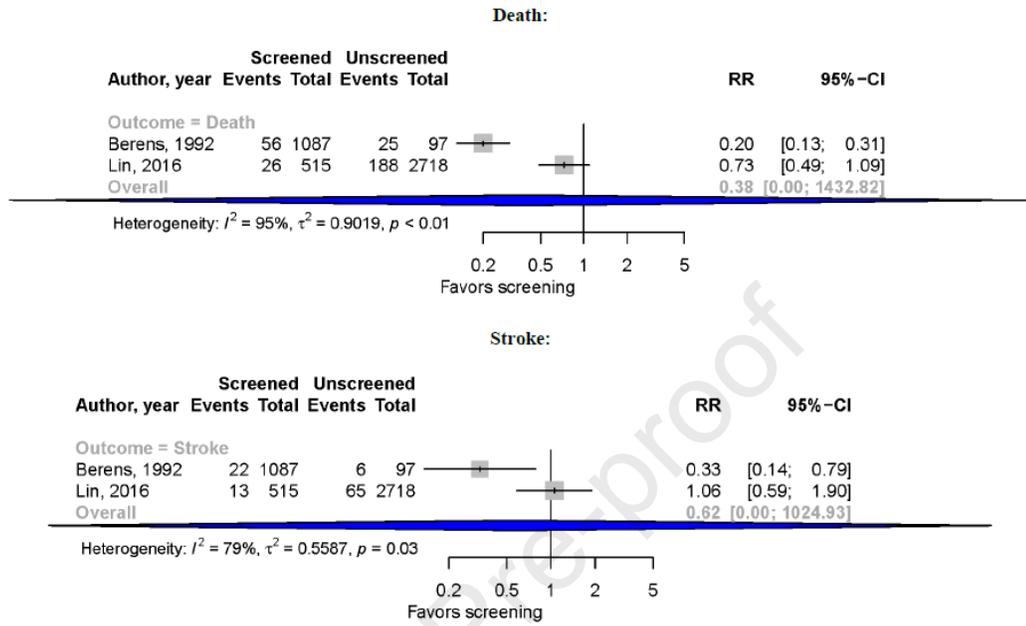
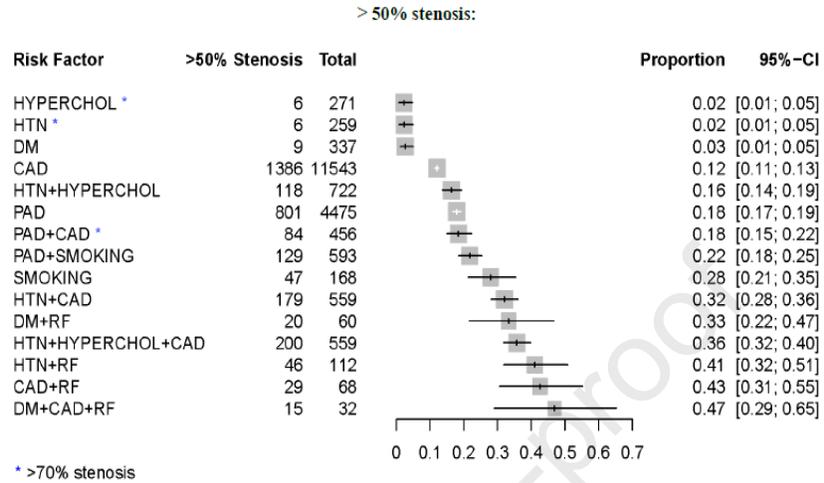


Figure 5.

Q4: Screening high risk patients

Non-comparative studies (Yield of screening for carotid stenosis cases based on risk factor)



Hyperchol – Hypercholesterolemia

HTN – Hypertension

DM – Diabetes mellitus

CAD – Coronary artery disease

PAD – Peripheral artery disease

RF – Renal failure