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Screening For Asymptomatic Carotid Artery Stenosis

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Structured Abstract

Background: Cerebrovascular disease is the third leading cause of death in the U.S. The proportion of all strokes attributable to previously asymptomatic carotid stenosis is low. In 1996, the United States Preventive Services Task Force concluded that there was insufficient evidence to recommend for or against screening of asymptomatic persons for CAS using physical exam or carotid ultrasound.

Purpose: To examine the evidence of benefits and harms of screening asymptomatic patients with duplex ultrasound and treatment with carotid endarterectomy (CEA) for carotid artery stenosis (CAS).

Data Sources: MEDLINE and Cochrane Library searches (January 1994-April 2007), recent systematic reviews, reference lists of retrieved articles, and expert suggestions.

Study Selection: English language studies were selected to answer the following: Is there direct evidence that screening with ultrasound for asymptomatic CAS reduces strokes? What is the accuracy of ultrasound to detect CAS? Does intervention with CEA reduce morbidity or mortality? Does screening or CEA result in harm? The following study types were selected: randomized controlled trials (RCT) of screening for CAS; RCTs of CEA versus medical treatment; systematic reviews of screening tests; observational studies of harms from CEA.

Data Extraction: Studies were reviewed, abstracted, and rated for quality using predefined USPSTF criteria.

Data Synthesis: There have been no RCTs of screening for CAS. According to systematic reviews, the sensitivity of ultrasound is approximately 94% and the specificity is approximately 92%. Treatment of CAS in selected patients with selected surgeons could lead to an approximately 5% absolute reduction in strokes over 5 years. Thirty-day stroke and death rates from CEA vary from 2.7% to 4.7% in RCTs; higher rates have been reported in observational studies (up to 6.7%).

Limitations: There is inadequate evidence to stratify people into categories of risk for clinically important CAS. The RCTs of CEA versus medical treatment were conducted in selected populations with selected surgeons.

Conclusions: The actual stroke reduction from screening asymptomatic patients and treatment with CEA is unknown; the benefit is limited by a low overall prevalence of treatable disease in the general asymptomatic population and harms from treatment.

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INTRODUCTION

Cerebrovascular disease is the third leading cause of death in the U.S.[1] Approximately 500,000 Americans each year suffer a first stroke.[1] The mortality rate for cerebrovascular disease has declined by nearly 70% since 1950.[2] Much of the decrease is likely due to reduced cigarette smoking and improved control of hypertension.

In addition to controlling such risk factors as tobacco use and hypertension, carotid endarterectomy (CEA) has been proposed as a strategy for reducing the burden of suffering due to stroke. Randomized controlled trials (RCTs) have shown that CEA effectively reduces stroke among people who have severe carotid artery stenosis (CAS) and have had a transient ischemic attack (TIA) or "minor stroke." It is not clear, however, whether screening asymptomatic people (i.e., those who have never had a TIA) to detect CAS and treatment with CEA is effective in reducing stroke.

In 1996, the USPSTF concluded that there was insufficient evidence to recommend for or against screening of asymptomatic persons for CAS using physical exam or carotid ultrasound.[3] This recommendation was based on new evidence at the time, including the Asymptomatic Carotid Artery Study (ACAS), a RCT involving 1662 subjects with asymptomatic stenosis greater than 60%. Results of ACAS suggested that the overall benefit of treatment with CEA depends greatly on the perioperative complications. At that time, there was limited information about CEA complications in the general population. After a trend of declining usage of CEA, the publication of ACAS led to a reversal and the number of carotid endarterectomies performed in the U.S. increased significantly.[4-6] Data then began to emerge about complication rates from CEA performed in community and academic settings.[7] Since the previous Task Force review, the largest RCT of CEA versus medical treatment of asymptomatic CAS, the Asymptomatic Carotid Surgery Trial (ACST), has been published.

This review updates the 1996 Task Force review of screening for CAS, focusing on duplex ultrasound as the screening test (with various confirmation tests) and CEA as the treatment for clinically important CAS. It draws upon the 1996 recommendation, updates the evidence on the natural history of CAS, the accuracy of screening tests, and the benefits of treatment for CAS with CEA, and includes a systematic review of the evidence since 1994 on the harms of carotid endarterectomy. Medical interventions were not reviewed in this report. The USPSTF has reviewed screening for several identified CAS and stroke factors, including hyperlipidemia, hypertension, aspirin prophylaxis, and smoking. The evidence reports and recommendations are available at the AHRQ website at www.preventiveservices.ahrq.gov**.**

BACKGROUND

What is Carotid Artery Stenosis?

Carotid artery stenosis refers to pathologic atherosclerotic narrowing of the extracranial carotid arteries. While one might expect that the amount of narrowing of the carotid artery that constitutes a diagnosis of carotid artery stenosis is correlated to the stroke risk, this relationship has not been clearly demonstrated. The risk is difficult to determine, and consequently CAS is variably defined. More recent RCTs evaluating the benefit of CEA defined CAS as 60-99% (i.e., ACAS, ACST) while earlier RCTs used 50-99%.

Prevalence and Clinical Importance of Carotid Artery Stenosis in the General Population

The prevalence of carotid artery stenosis has been studied in several population-based cohort and cross-sectional studies. These prevalence estimates are based on a positive test result on a screening carotid ultrasound, a test with limited reliability and accuracy. Estimates of the prevalence of CAS from population-based studies range from 0.5% to 8%.[8-12] Based on the population-based studies and the accuracy of ultrasound, we estimate the actual prevalence of clinically important CAS (60%-99%) in the general primary care population to be approximately 1% or less; in those aged 65 years and older we estimate prevalence to be about 1%. See below in the Results section for a more detailed discussion of prevalence.

A "clinically important degree of CAS" is defined as the percentage of stenosis that corresponds to a substantially increased risk of stroke. Stroke risk depends on more than the degree of carotid artery narrowing; it is therefore difficult to define categories of CAS that are associated with various risk levels of stroke in asymptomatic people. Another difficulty is that all prospective studies of stroke risk have measured CAS by carotid ultrasound, an imperfect "gold standard." In the population-based Cardiovascular Health Study of people ages 65 years and older, the risk of stroke rose as severity of stenosis increased above 50%, declining at the very highest degrees of CAS (probably due to collateral circulation). The estimated 5-year risk of ipsilateral stroke for asymptomatic people with CAS $\geq$ 50% was approximately 4% and for CAS $\geq$ 70% approximately 8%.[10] Other studies have also shown an increased risk with greater degrees of stenosis and with multiple risk factors.[13, 14] Most studies of treatment for CAS consider stenosis $\geq$ 50% or $\geq$ 60% as clinically important.

CAS-Related Stroke Burden

The contribution of CAS to overall stroke burden is difficult to approximate. Approximately 88% of strokes are ischemic; 20% or less of these are due to "large artery stenosis".[10, 15-20] A subgroup of this "large artery stenosis" category is due to stenosis of the carotid bifurcation or proximal carotid artery that is approachable by CEA and a proportion of patients in this subgroup are asymptomatic. A recent follow-up study of people in a large RCT of carotid endarterectomy found that approximately 45% of strokes among asymptomatic people with severe carotid artery stenosis were unrelated to the carotid artery stenosis and could not have been prevented by CEA.[21] Thus, screening asymptomatic people for CAS to perform CEA would potentially have an effect on 10% or fewer of all strokes. Because of the large number of strokes each year, this constitutes a considerable health burden.

Risk Factors for Carotid Artery Stenosis

There is much literature on the risk factors for developing CAS; however, there are few studies that associate risk factors with a clinically important degree of stenosis, such as ≥ 60 %. This literature relies on ultrasound measurement of CAS, which again includes some misclassification.

Important risk factors or combinations thereof for clinically significant CAS are age > 65 years, male sex, smoking, heart disease, and hypertension.[9, 22-27] The presence of the strongest reported risk factors, smoking or heart disease, approximately doubles the risk of CAS. [25, 26] However, no single risk factor and no clinically-useful risk model incorporating multiple factors, clearly discriminates people who have clinically important CAS from people who do not.

METHODS

This review updates the 1996 USPSTF review of screening for CAS, focusing on duplex ultrasound as the screening test (with various confirmatory tests) and CEA as the treatment for clinically important CAS. Medical interventions and screening with carotid auscultation were not reviewed in this report. The USPSTF has reviewed screening for several known risk factors of carotid artery stenosis and stroke, including hyperlipidemia, hypertension, aspirin prophylaxis, and smoking. The evidence reports and recommendations are available at the Agency for Healthcare Research and Quality (AHRQ) website at www.preventiveservices.ahrq.gov**.**

An analytic framework was developed for this review following USPSTF methods and is shown in Figure 1.[28] The USPSTF developed 4 key questions (KQ) from the analytic framework to guide its consideration of the benefits and harms of screening with ultrasound for CAS. The key questions were:

KQ1. Is there direct evidence that screening adults with duplex ultrasound for asymptomatic CAS reduces fatal and/or nonfatal stroke?

KQ2. What is the accuracy and reliability of duplex ultrasound to detect clinically important CAS?

KQ3. For people with asymptomatic CAS 60%-99%, does intervention with CEA reduce CAS-related morbidity or mortality?

KQ4. Does screening or CEA for asymptomatic CAS 60%-99% result in harm?

The USPSTF designated three key questions (1-3) as subsidiary questions for which they requested non-systematic reviews to assist them in updating their recommendations. KQ4 was the only key question for which the USPSTF requested a systematic evidence review.

Data Sources and Searches

We searched for English language literature published January 1, 1994 to April 2, 2007 in MEDLINE that addressed key questions 1, 2, and 3. In addition we identified additional studies through the reference lists of major review articles and through consultations with experts. For key question 3, we performed a MEDLINE search for RCTs, systematic reviews and meta-analyses that compared CEA with medical therapy for asymptomatic people with CAS. We

identified one in-process RCT by its inclusion in a systematic review, and included it when it was published.

For key question 4, we performed a systematic search for English language articles published between January 1, 1994, and April 2, 2007, through a MEDLINE search using the focused MeSH terms "endarterectomy, carotid" and "outcome and process assessment." In addition we selected a key study from this search and identified related articles through MEDLINE. Additional studies were identified through a search of the Cochrane database, through discussions with experts, and by hand-searching of reference lists from major review articles and studies.

Study Selection

Titles and abstracts of articles retrieved for KQ1-3 were non-systematically selected and reviewed by two reviewers. The process was considered non-systematic because articles were selected for review and abstracted by one reviewer. Articles for KQ1 were selected for inclusion if they were RCTs, compared screened versus non-screened groups, used ultrasound, MRA or computed tomography as screening modalities, reported outcomes of strokes or death in asymptomatic subjects, and were performed in a population generalizable to U.S. For KQ2, the authors included systematic reviews that compared screening tests (Ultrasound, MRA, or computed tomography screening) to angiography in asymptomatic subjects and were performed in a population generalizable to U.S. Articles for KQ3 were selected for inclusion if they were RCTs of CEA comparing surgical treatment to medical treatment, reported 30-day complication rates (stroke and death) of CEA, included only asymptomatic patients, and were performed in a population generalizable to the U.S.

For KQ4, three reviewers independently reviewed the abstracts and selected articles from titles and abstracts based on inclusion and exclusion criteria. In general, studies were selected if they were large, multi-institution, prospective studies that reported 30 day mortality/stroke outcomes for asymptomatic patients undergoing CEA. Studies were excluded if they did not report outcomes by symptomatic status, included patients receiving CEA combined with other major surgeries, were not performed in the U.S., included patients with restenosis, or were studies of patient populations at extremely high risk. Detailed search terms and inclusion/exclusion criteria are described in Appendix 1. Abstracts that were selected by fewer than three reviewers were discussed and selected based on consensus.

Data Extraction and Quality Assessment

For all citations that met the eligibility criteria, the full articles were reviewed and quality-rated independently by two reviewers. Consensus about article inclusion, content, and quality was achieved through discussion by the two reviewers; disagreements were resolved by the involvement of a third reviewer. Data on the following items were extracted from the included studies for KQ4: source population, sample size, average age, proportion white, proportion male, average degree of stenosis, and the proportion of subjects with important comorbidities, including contralateral stenosis, smoking, diabetes, hypertension, and coronary artery disease. Quality evaluations of articles for all KQs were performed using standard USPSTF methodology

on internal and external validity.[28] We evaluated the quality of RCTs and cohort studies on the following items: initial assembly of comparable groups, maintenance of comparable groups, important differential loss to follow-up or overall high loss to follow-up, measurements (equality, reliability, and validity of outcome measurements), clear definition of the interventions and appropriateness of outcomes. We evaluated systematic reviews and meta-analyses on the following items: comprehensiveness of sources considered, search strategy, standard appraisal of included studies, validity of conclusions, recency and relevance. More complete criteria and definitions for USPSTF quality ratings are listed in the Appendix 2.

Data Synthesis and Analysis

Data from the included studies for KQ1-3 were synthesized qualitatively in tabular and narrative format because of the non-systematic nature of the review. Data from the systematically reviewed KQ4 was also synthesized qualitatively and not quantitatively because of the different patient characteristics and varied outcome assessments. Synthesized evidence was organized by key question.

Role of the Funding Source

The general work of the USPSTF is supported by the Agency for Healthcare Research and Quality. This specific review did not receive separate funding.

RESULTS

Summary of Results

We found no direct evidence of the benefit of screening with ultrasound for CAS in asymptomatic adults (KQ1). Two systematic reviews were found on the accuracy of ultrasound screening (KQ2); the sensitivity is approximately 94% and the specificity is approximately 92% for CAS of 60%-99%. Three fair or good quality RCTs were found and reported that in selected patients with selected surgeons treatment with CEA for asymptomatic CAS could lead to an approximately 5% absolute reduction in strokes over 5 years (KQ3).

For the systematic review for KQ4, the initial literature search returned 397 titles. The titles, abstracts and full articles were reviewed by three reviewers. 232 studies were excluded after review of returned titles by three reviewers. Most of the studies were excluded at the title stage for the following reasons: not on CEA, not multi-site, or only included outcomes for symptomatic subjects. 134 studies were excluded at the abstract stage (Figure 2). The majority of studies were excluded for including only symptomatic subjects, not multi-site, no relevant outcomes, or small sample size. Three full articles were identified through expert consultation or from reviewing the reference lists of major review articles. 20 full articles were excluded because of incorrect study type, not multi-site, only included symptomatic subjects, or did not report relevant outcomes. Fourteen articles were ultimately included for key question 4 on the harms of CEA. In addition, three good or fair quality RCTs identified for KQ3 also provided evidence on harms under trial conditions.

The harms of CEA for asymptomatic CAS, reported in most studies as thirty-day stroke and death rates, vary from 2.7% to 4.7% in the RCTs; higher rates have been reported in observational studies (up to 6.7%). Details of the results of the literature search and synthesis are below under the corresponding key question subheading.

Key Question 1. Is there direct evidence that screening adults with ultrasound for asymptomatic CAS reduces fatal and/or nonfatal stroke?

We found no studies that addressed this question.

Key Question 2. What is the accuracy and reliability of ultrasound to detect clinically important CAS?

We found two meta-analyses on the accuracy of ultrasound to detect clinically important stenosis. A recent meta-analysis included studies published from 1993 through 2001, and estimated the accuracy of carotid duplex ultrasound using digital subtraction angiography as the reference standard.[29] Carotid duplex ultrasound had an estimated sensitivity of 86% (95% CI, 84% to 89%) and a specificity of 87% (95% CI, 84% to 90%) for detecting CAS of 70%-99%.[29] A second meta-analysis of carotid duplex ultrasound found similar sensitivity and specificity for carotid duplex ultrasound to detect 70% or greater stenosis, 90% (95% CI, 84-94%) and 94% (95% CI, 88-97%) respectively.[30] To detect CAS ≥ 50%, the authors suggested a cut-point that had a sensitivity of 98% and a specificity of 88%. Reading from a graph in this paper and using the same cut point as was suggested for detecting ≥ 70% CAS, we estimate that the sensitivity of carotid duplex ultrasound to detect CAS ≥ 60% is about 94%, with a specificity of about 92%.

The reliability of carotid duplex ultrasound is questionable. One meta-analysis noted that the measurement properties used among various ultrasound laboratories varied greatly, to a clinically important degree.[30]

We found one meta-analysis on accuracy of MRA and one meta-analysis on the accuracy of CT in detecting clinically important carotid stenosis. The meta-analysis on the accuracy of MRA reported that MRA has about the same accuracy as ultrasound.[29] CTA has gained wide acceptance in some centers as a follow up test to ultrasound in confirming CAS. In certain cases, it has been used in place of vascular arteriogram. A recent systematic review found that its accuracy is not greatly different from that of ultrasound and MRA.[31] Although CTA is safer than angiography as a confirmatory test, it is unlikely to be a useful screening test due to its cost, radiation exposure and injection of intravenous contrast dye. MRA does not use contrast dye or have significant radiation exposure. It is, however, time-consuming and costly and is also not suitable as a screening test at this time. Currently, the most available and acceptable screening test for CAS remains carotid duplex ultrasound.

The prevalence of CAS has been studied in several population-based cohort studies. These prevalence estimates are based on a positive test result on a screening carotid ultrasound, which, as noted above, has less than perfect accuracy. The Cardiovascular Health Study (CHS) of 5441 community-dwelling people ages 65 years and older showed a 3.4% observed prevalence for 50-99% CAS and a 0.5% observed prevalence of 70-99% CAS.[10] In the Framingham Study, the

observed prevalence of CAS ≥ 60% was 3.3% among participants 65 years and older.[9] Meissner and colleagues found an 8% prevalence of 50-99% CAS in a randomly selected cohort of 1475 older adults in Minnesota. Several other smaller population-based cohort studies reported similar results.[8, 11, 12]

These studies used carotid duplex ultrasound, which likely resulted in an overestimate of the prevalence due to the test's high number of false positives in low prevalence groups. For example, a screening test with a sensitivity of 94% and a specificity of 92% used in a population with a true 1% prevalence of CAS 60%-99% would estimate the prevalence to be 8.9%. At a true prevalence of 5%, this test would estimate the prevalence to be 12.3%. This illustrates the number of false positive tests generated when using a screening test in a low-prevalence population.

We estimate that the actual prevalence of CAS 60%-99% in the general primary care population is less than 1%; and about 1% in individuals 65 and older. People with more cardiovascular risk factors or existing atherosclerotic disease may have a higher prevalence. As noted earlier, however, a risk stratification tool to identify people at higher risk for CAS is not available.

Two lines of evidence allow us to estimate the prevalence of CAS 60%-99% to be about 1% in the general population of asymptomatic people over age 65. First, the population-based Cardiovascular Health Study findings for people 65 and older used stroke risk to define the clinical importance of various degrees of CAS.[10] This study found that 0.5% of the population had a 5-year stroke risk of 5%, corresponding to CAS of 70% or greater. The second line of evidence comes from studies of the prevalence of CAS 60%-99% as measured by duplex ultrasound. Data from the Cardiovascular Health Study, the Framingham Study, and the Minnesota cohort show prevalence of CAS 60%-99% measured by duplex ultrasound was from 3% to 8%.[8-12] Given a sensitivity of ultrasound of 94% and a specificity of 92% for this degree of CAS, the true prevalence of CAS 60%-99% corresponding to these measured values would all be less than 1%. From these 2 lines of evidence, we estimate that the true prevalence of CAS 60%-99% in the general population of asymptomatic people 65 and older to be about 1%.

Key Question 3. For people with asymptomatic CAS 60%-99%, does intervention with CEA reduce CAS-related morbidity or mortality?

We identified 5 RCTs comparing CEA and medical management for asymptomatic CAS: the Walter Reed Army Medical Center Study (WRAMC) study [32], the Mayo Asymptomatic Carotid Endarterectomy Study (MACE) [33], the Veterans Affairs Cooperative Study (VACS), [34] the Asymptomatic Carotid Atherosclerosis Study (ACAS) [35], and the Asymptomatic Carotid Surgery Trial (ACST). [36] In addition, we reviewed two systematic reviews (Benavente [37] and Cochrane [38]) of CEA for asymptomatic CAS and one post hoc analysis of ACAS results.[39] Both the Benavente and Cochrane systematic reviews were published before the ACST trial reported its results, and thus did not include this study. Otherwise, these reviews found the same studies as are reviewed here, with the exception of an unpublished RCT from France included in the Benavente report that we did not include because we could not examine its validity.

The table in Appendix 3 summarizes study characteristics and outcomes. We reviewed two good quality studies (ACAS, ACST) and one fair quality study (VACS). We excluded the WRAMC study because it did not use ultrasound assessment of CAS, had a small number of participants, and used unclear definitions of outcomes. We excluded the MACE study because of its small number of participants, small number of strokes, and the lack of aspirin treatment in the surgical group.

The three fair or good quality studies, VACS, ACAS, and ACST, compared CEA plus medical management to medical management alone in subjects without symptoms attributable to the studied artery (Table 1). Medical management included the standard risk factor management at the time of the trials, including aspirin and some degree of blood pressure and lipid control. In the VACS, 444 men with 50%-99% stenosis confirmed by angiography were randomized and followed for a mean of 47.9 months.[40] All subjects were male, 88% were white, and the median age was 64.5 years. The participants had a generally high cardiovascular risk; approximately 50% were current cigarette smokers, about 30% had diabetes, and 63% had hypertension. After 4 years of follow-up, the stroke rate was lower in the CEA group than in the medical treatment group, 8.6% versus 12.4%. However, there was also a 4.7% incidence of perioperative stroke or death in the CEA group. When all strokes or perioperative events were considered, there was no difference between CEA and medical management.

ACAS screened about 42,000 people and selected 1,662 with angiographically confirmed CAS ≥ 60% for randomization to CEA or medical therapy.[35] Subjects were 95% white, 66% male, and had a mean age of 67 years. Again, the participants had a high cardiovascular risk; about 20% had had a previous contralateral CEA, over 20% had had a previous contralateral TIA or stroke, 64% had hypertension, 26% smoked cigarettes, and 23% had diabetes. Surgeons with low CEA complication rates were selected for participation in the study.

After 2.7 years follow-up, ACAS authors estimated 5-year outcomes based on Kaplan-Meier curves. The authors estimated that the 5-year rate of ipsilateral stroke and any perioperative stroke or death was lower in the CEA group than in the medical group, 5.1% versus 11.0%. (Relative risk reduction [RRR] 0.53; 95% CI 0.22-0.72) If strokes associated with angiography were included, the difference between groups was 5.6% versus 11.0%, or an absolute difference of 5.4% over 5 years. These rates include a perioperative rate of stroke or death of 2.7% overall (1.7% for men and 3.6% for women). The estimated RRR for men was greater than for women: 0.66 and 0.17, respectively. There was no statistically significant difference between treatment groups in all-cause mortality.

The ACST is the most recent and largest RCT of CEA versus medical treatment for asymptomatic CAS. This international, multicenter trial randomized 3,120 subjects with ≥ 60% CAS and followed them for a mean of 3.4 years.[36] Both groups received medical management by their primary care providers. Although it is difficult to determine the intensity of medical management, the mean systolic blood pressure at baseline for all subjects was 153 mmHg and mean total cholesterol was 224 mg/dL. Aspirin was widely used. More than 50% of the patients were on antihypertensive medications but the achieved systolic blood pressure was not reported. Lipid lowering agents were used with less frequency at the beginning of the study, and were used by more than 50% of participants during the last 3 years of the study.

In ACST, the degree of CAS was determined by ultrasound. Angiography was not required but was often used for confirmation of CAS during the first few years of the study, and less frequently used in the final years. As in the ACAS study, patients were carefully selected and were generally at high cardiovascular risk. Mean age was 68 years, 66% were male, 65% had hypertension, 20% had diabetes, and 24% had had a previous contralateral CEA. As in ACAS, the ACST surgeons were carefully selected for low complication rates. The perioperative rate of stroke or death was 3.1% overall, but higher for women (3.7%) than for men (2.4%).

After 3.4 years follow-up, the ACST authors estimated 5-year outcomes. They estimated that the CEA group would have a lower 5-year rate of any stroke or perioperative death than the medical group, 6.4% versus 11.8% (difference 5.35%; 95% CI 2.96%-7.75%). About half of the strokes prevented by CEA were disabling. There was no statistically significant difference between groups in all-cause mortality.

Before the ACST was published, 2 reviews of CEA for asymptomatic CAS were reported.[37, 38] Benavente performed a meta-analysis using data from WRAMC, MACE, VACS, ACAS, and Association Universitaire de Recherche en Chirurgie (AURC, an unpublished trial in France).[37] Little information is available about the methodology of AURC. Benavente and his colleagues found a rate of all strokes plus perioperative stroke or death of 7.4% and 9.2% for the surgical group and medical group, respectively and an OR of 0.68 (95% CI, 0.51-0.90). These rates included a pooled estimate for perioperative complications of 2.4%.

The Cochrane review published in 2002 combined data from the ACAS and VACS; the combined RR for CEA versus medical management was 0.68 (95% CI, 0.48-0.97) for ipsilateral stroke or perioperative death at five years.[38] Subjects in the surgical group had statistically significantly lower rates of any stroke or perioperative death at five years, compared to medical management (RR 0.76, 95% CI 0.58-0.99).

There are important limitations of the RCTs on CEA for asymptomatic CAS. The participants in the RCTs were a highly select group of subjects and surgeons, a situation that reduces the findings' generalizability to the primary care setting. In addition, the 30-day perioperative results of the RCTs were reported as a combined outcome that did not include an important complication, acute non-fatal myocardial infarction. Another important limitation of the RCTs on treatment with CEA is that the medical treatment arm in the RCTs was ill-defined, was not kept constant over the course of the study, and was likely not comparable to current standards of optimal medical management.

In summary, the 2 largest and best-conducted RCTs (and meta-analyses including one of those RCTs) have shown a reduction in the important outcome of stroke and perioperative death from CEA as compared with medical treatment for CAS of 60%-99% in selected patients with selected surgeons.

Is there a population subgroup for which the magnitude of benefits from CEA may be greater than in other subgroups?

Studies reviewed for KQ3 and KQ 4 were examined for demographic and co-morbidity subanalyses. Please see the section after KQ4 results for a detailed discussion.

Key Question 4. Does treatment for asymptomatic CAS 60%-99% with CEA result in harm?

The potential harms of a program of screening for CAS for the purpose of performing CEA include (1) the harms associated with false positive screening tests (e.g., anxiety, labeling, the harms of any confirmatory work-up, such as angiography, or the harms of unnecessary CEA in people who do not undergo angiography); and (2) the harms of CEA itself (e.g., bleeding, infection, stroke, and death). We found no studies exploring anxiety or labeling among people with falsely positive ultrasound screening tests. We did find evidence concerning the harms of angiography and CEA.

Harms Associated with Cerebral Angiography

Although cerebral angiography is the "gold standard" for confirming CAS, a small percentage of patients will be harmed by the angiogram procedure itself. In the ACAS study, for example, 1.2% of patients who had an angiogram had a non-fatal stroke. In the VACS study, this was 0.4%.(30, 35) Other prospective studies of cerebral angiogram have found rates of persistent neurological complications of 0.1%-0.5%.[41-43] However, several of these prospective studies found higher rates in subjects with CAS or cardiovascular disease. This may explain the higher rate of angiogram complications in the ACAS study.

Because of the increased risk of stroke, there is disagreement on whether cerebral angiography should be used to confirm a positive ultrasound screening test. There is considerable variation in current practice. Some surgeons do other confirmatory tests, such as MRA or CTA, while others request angiography prior to CEA. Kresowik reported in 2004 a ten-state aggregate preoperative angiogram utilization rate of 64% (for symptomatic and asymptomatic patients combined).[44] Although MRA and CTA are not as accurate as angiography – and thus may lead to unnecessary CEA in patients with false positive screening tests – they are not associated with complicating strokes.

Harms Associated with CEA for Asymptomatic CAS

Study characteristics

We identified fourteen good or fair quality studies that met our inclusion criteria and evaluated CEA complications in patients with asymptomatic CAS. Detailed study characteristics, quality ratings, and results of the observational studies are displayed in a table in Appendix 4. Thirteen observational studies were secondary analyses of administrative databases: two studies were performed using data on patients attending a Veterans Affairs medical center; [45, 46] seven studies used data from patients receiving Medicare benefits;[44, 47-52] and four studies used a similar dataset of patients admitted to six New York hospitals.[7, 53-55] The final study was a systematic review of studies published between 1994 and 2000 on harms of CEA.[56] The primary perioperative complication measure in the studies was either death/stroke or

death/stroke/myocardial infarction within 30 days of surgery. All of the observational studies included patients referred to a hospital or medical center for CEA as a result of CAS. There was little data about the severity of stenosis. The studies included both patients who did and did not have neurological symptoms, but we only reviewed studies that reported complication rates separately for asymptomatic patients. Mean age of patients ranged from 67 to 74 years. Six of the studies collected information on race. In those studies that reported race, the participants were largely white (range 87-95%). Although the subjects in the two Veterans Affairs studies were almost entirely all male subjects, the other studies did include 36-47% female subjects.

The Bratzler study from 1998 used a claims database and medical records from Medicare recipients who received a CEA in 1993 or 1994.[47] We quality rated this study as good: data for outcomes were collected from two sources – claims data and medical records, correlation between data abstractors was high, and there were standard definitions of outcomes. The fair quality study by Cebul and colleagues used Ohio Medicare claims data on patients who received a CEA between July 1993 and June 1994; this was a predominantly white population and the study used only a subset of all patients receiving CEA during the timeframe.[48]

Two good quality studies on the same database of patients undergoing CEA at Veterans Affairs medical centers had well-defined inclusion criteria and abstraction processes and used methods that likely limited differential outcome measurement, including contacting all patients and families 30 days after surgery.[45, 46] Two good quality studies by Kresowik and colleagues used Medicare claims databases from ten states – the first for June 1995 to May 1996 and the second for June 1998 to May 1999.[44, 51] These studies were very large and included medical record data in addition to data in the claims database. Another good quality study by Kresowik and colleagues used similar methods as above but used the Iowa Medicare database.[52] A fair quality study by Karp and colleagues used Medicare claims data from the state of Georgia; there was limited agreement between the reviewer and the physicians in this study on indications for surgery.[50]

Four studies used the same database of Medicare recipients from 6 New York hospitals who underwent CEA in 1997 or 1998.[7, 53-55] The individual studies used similar methods but had different research questions and consequently excluded cases with missing data using different criteria. While these four studies had some limitations, the overall quality of the studies was rated as good quality for the following reasons: both outpatient and inpatient data were used for outcome measurement, studies used trained independent abstractors, two investigators independently reviewed records of subjects with an outcome, and there was limited exclusions of cases due to missing data.

The 2007 study by Halm and colleagues was performed on a administrative database of Medicare recipients in New York State who received a CEA between January 1998 and June 1999.[49] Several limitations lead to a fair quality rating including the exclusion of a large number of cases due to missing data. The systematic review by Bond and colleagues included studies that reported 30 day stroke and death rates by indication and excluded studies on combined CEA and coronary artery bypass grafting[56]. This study had several limitations resulting in a fair quality rating including a lack of discussion on the standard assessment of study quality.

Summary of Study Results

The 30-day perioperative stroke or death rates in asymptomatic subjects in the Medicare and New York City studies ranged from 2.3% to 3.7%. One Veterans Affairs study showed a perioperative stroke or death rate of 1.6%.[45] The systematic review of 103 studies found an overall stroke and death rate at 30 days of 3.0% in studies published since 1995.[56]

The observational studies reporting perioperative non-fatal MIs showed a rate of approximately 0.7% to 1.1%. [7, 45, 50] Patients with more co-morbidities had a rate of non-fatal myocardial infarction up to 3.3%.[7] The rate of non-fatal perioperative myocardial infarction reported for the surgical group in the RCTs varied: 1.9% in VACS and 0.6% in ACST.[34, 36] The subjects did not receive routine post-operative electrocardiograms or serum markers of myocardial involvement.

Two Medicare-based studies found variation in perioperative stroke and death among 10 states.[44, 51] In the first study, the state-wide rates ranged from 2.3% in Indiana to 6.7% in Arkansas.[51] A follow-up study for the same ten states found similar results as in 2001, with rates ranging from 1.4% in Georgia to 6.0% in Oklahoma.[44]

There is little information in these studies about rates of other complications, including the impact on quality of life. None of the observational studies we evaluated gave specific rates of other complications for asymptomatic patients. However, among the RCTs, the VACS reported surgical complications rates of 3.8% for cranial nerve injuries (none of these injuries were permanent), 5.2% for hypotension, and 25% for hypertension.[40]

Is there a population subgroup for which the magnitude of benefits from CEA may be greater than in other subgroups?

Studies reviewed for KQ3 and KQ4 were examined for demographic and co-morbidity subanalyses; the methods of these studies are discussed in more detail below.

Age

In ACAS, subjects younger than 68 years old had a RRR from CEA of 0.60 over five years for ipsilateral stroke or perioperative stroke or death (95% CI, 0.11-0.82).[35] For subjects over 68 years old, there was no significant benefit to CEA at five years (RRR 0.43, -0.07-0.70). Sub-analysis showed that the RRRs were not statistically significantly different by gender. In ACST, subgroup analysis was performed using the outcome: non-perioperative carotid territory strokes.[36] In the subgroup analysis, patients under age 65 and between 65 and 74 years old showed similar 5-year estimated absolute risk reduction (ARR) for non-perioperative strokes, 7.8% (95% CI: 4.3-11.3) and 7.5% (95% CI: 4.7-10.3), respectively. However, for patients over 74 years old, the number of non-perioperative strokes at five years was not statistically significantly different between the CEA and medical management groups (ARR 3.3, 95% CI: -1.9 – 8.4).

Sex

Subgroup analysis in ACAS reported that for ipsilateral stroke or perioperative events, men had a relative risk reduction (RRR) of 0.66 over five years (95% CI, 0.36-0.82) and women had a RRR of 0.17 (-0.96-0.65). In ACST, the subgroup analysis reported a significant benefit to CEA in reducing non-perioperative carotid territory ischemic strokes in men (ARR 8.2%, 95% CI: 5.6-10.8).[36] In women, there was less but still significant benefit for those randomized to the CEA group (ARR 4.1%, 95% CI: 0.7-7.4). A later subgroup analysis by gender was published in a letter to the editor and used the outcome of stroke or perioperative death at six years. Using their 6-year projections, the absolute difference between CEA and medical groups for stroke or perioperative death was 4.0% (standard error (SE) = 2.2, p = 0.07) for women and 6.6% (SE =1.6, p = 0.0001) for men.[57] The 30-day rates of perioperative stroke or death in ACAS and ACST were higher in women than men and may explain the sex differences in risk reduction. None of the observational studies directly compared rates of perioperative complications in women with those in men.

Race/Ethnicity

The RCTs of CEA versus medical treatment included few people from minority groups. Only one observational study evaluated racial and ethnic variations in CEA perioperative outcomes. Horner, et al compared outcome rates for blacks, Hispanics, and whites.[45] Perioperative stroke or death rates were 2.1% for blacks, 2.2 for Hispanics, and 1.6% for whites and were not statistically significantly different. For outcomes other than stroke or death, there were some statistically significant differences by race/ethnicity: blacks had a significantly lower rate of any other complications; and blacks and Hispanic patients had a higher rate than whites of return to the operating room due to CEA complications (4.6% for black patients, 7.8% for Hispanics, and 3.6% for white patients).

Contralateral Occlusion

Baker, et al used the data from ACAS to evaluate outcomes of CEA by the presence of contralateral occlusion.[39] He identified 1,648 subjects from ACAS who had a baseline carotid ultrasound, and calculated rates of adverse outcomes for those with and without contralateral occlusion on the baseline ultrasound. Men, whites, and those with a history of TIA or stroke were more likely to have contralateral occlusion. Cumulative 5 year rates of perioperative stroke or death or subsequent ipsilateral stroke for those without contralateral occlusion were 11.7% for the medical group and 5.0% for the surgical group. This translates into a statistically significant absolute risk reduction (ARR) of 6.7% and a RRR of 57%. For the same outcome, subjects with contralateral occlusion had 5 year estimated rates of 3.5% in the medical group and 5.5% in the surgical group for a non-significant increase in risk of 2.0%. Subjects with and without contralateral occlusion had similar rates of perioperative outcomes. Authors, therefore, concluded that subjects with contralateral occlusion did not benefit and may even be harmed from CEA.

Comorbidities

In ACST, subgroup analysis was performed using the outcome: non-perioperative carotid territory strokes.[36] In the subgroup analysis, there was greater risk reduction in non-perioperative strokes in those with higher pre-randomization cholesterol levels: subjects with a cholesterol level less than 250 mg/dL had an ARR of 4.6% at five years, while those with a cholesterol level greater than 250 mg/dL had an ARR of 11.7% at five years. Further subanalyses indicated that the ARR for non-perioperative strokes at five years was not significantly different by pre-randomization blood pressure, degree of carotid stenosis, status of the contralateral carotid artery, diabetes, or CHD.

Only one observational study, Halm, et al, examined CEA outcomes categorized by co-morbidities.[7] Comorbidities categories were defined using the Revised Cardiac Risk Index. The Revised Cardiac Risk Index uses six risk factors to predict major cardiac complications of surgery: high-risk type of surgery, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes, and serum creatinine >2.0 mg/dL.[58] Asymptomatic subjects with no risk factors, one risk factor, and two risk factors had 30-day stroke/death rates of 1.28%, 2.21%, and 2.77%, respectively. Subjects with three or more risk factors or an end-stage disease had a perioperative stroke/death rate of 5.56%.

In summary, subgroup analyses have raised interesting questions for future research about the benefits of CEA for women and for individuals older than 75, without hypercholesterolemia, and with higher levels of co-morbidities. Individuals with contralateral carotid occlusion likely do not benefit from CEA. There are, of course, limitations to the use of subgroup analyses to determine the benefits of CEA, in that the studies under review were not designed to study the subgroups and may not be powered to detect differences between the subgroups. From current evidence, there is no subgroup that we can definitely conclude would benefit from CEA to a much greater degree than others.

DISCUSSION

CAS is one of several etiological factors for stroke, an important health problem with a high burden of disease in the U.S. It is important to consider the possibility that screening asymptomatic people with ultrasound to detect clinically important CAS for the purpose of performing CEA could reduce the large burden of suffering due to stroke. Although the percentage of all strokes that could potentially be reduced by screening for CAS is relatively small, this is a large number of strokes when considered across the entire country.

The magnitude of contribution of CAS to the morbidity and mortality associated with stroke is not well characterized nor is the natural progression of CAS. We estimate the prevalence of CAS 60-99% in the general population over 65 years old to be about 1%. CAS is more prevalent in older adults, smokers, those with hypertension, and those with heart disease. Unfortunately, research has found no single risk factor or clinically useful risk stratification tool that can reliably and accurately distinguish people who have clinically important CAS from people who do not.

Duplex ultrasound is a non-invasive screening test. Its reported accuracy is approximately 94% sensitive and 92% specific for CAS of 60%-99%. In a low-prevalence population, the number of

false positive tests is high. In the case of screening for CAS, false positive tests are important. If all positive tests are followed by cerebral angiography, about 1% of people will suffer a non-fatal stroke as a result of the angiogram. If positive tests are not followed by confirmatory angiography but rather by MRA or CTA – tests with <100% accuracy – then some people will have unnecessary CEA. CEA is associated with important complications, including a perioperative stroke or death rate of 2.4% to 3.7% and, therefore, some people will be harmed unnecessarily.

Under carefully controlled conditions, treatment with CEA for asymptomatic CAS can result in a net absolute reduction in stroke rates – approximately 5% over 5-6 years (about 2.5% absolute risk reduction for disabling strokes). This benefit has been shown in selected patients with selected surgeons, and must be weighed against a small increase in non-fatal MIs. The net benefit for CEA largely depends on people surviving the perioperative period without complications. The two RCTs that found a benefit to surgery over medical management had 30-day perioperative rates of stroke and death of 2.7 – 2.8%. In large observational studies using administrative databases, the average complication rates ranged from 1.6 to 3.7%; statewide rates varied greatly by state, with a range of 2.3 – 6.7%.

Other issues prevent the determination of a good estimate of benefit from CAS screening in the general primary care setting. First, the patients and surgeons in the RCTs of CEA treatment were highly selected; the patients had high stroke risk. Secondly, the absolute benefit of screening and CEA treatment depends on a low perioperative rate of stroke or death. A small increase in perioperative strokes or death could counteract the benefits. There is no validated strategy for reliably identifying patients that are at high enough risk for stroke to benefit from CEA but with low enough risk for perioperative complications. Thirdly, the beneficial outcome of decreased strokes in the RCTs does not account for additional harms of CEA, including non-fatal myocardial infarction. Additionally, the absolute risk reduction in the CEA trials is relatively small (on the order of 4% to 6% over 6 years in ACST).

Another important limitation of the evidence on the benefit of treatment with CEA is that the medical treatment arm in the RCTs was ill-defined, and likely did not include intensive blood pressure and lipid control, as is standard practice today. It is difficult to determine what effect current standard medical therapy would have on overall benefit from CEA. The use of current medical therapy could have reduced the stroke rate in the medical treatment arm of these trials, thus likely reducing the overall benefit to treatment with CEA.

Another issue regarding the evidence on CEA is the timing of strokes and perioperative death. The timing is different in the arms of the RCTs; the events in the CEA arm occur earlier than those in the medical arm. The Kaplan-Meier curves in ACST cross from net harm to net benefit only at about 1.5 years after CEA for men, and at nearly 3 years after CEA for women.[57, 59-62] The estimated survival from these curves beyond the actual follow-up time may not be applicable. It is possible that the benefit from CEA will be limited to a specific time period and does not continue unabated into the future, as projected in the trials. Thus, the actual (not projected) risk reduction for CEA over 5-10 years is still uncertain. The evidence would suggest that the absolute benefit of screening and CEA in people with asymptomatic CAS in the general population is small.

Table 2 shows hypothetical outcomes of a screening program for asymptomatic carotid artery stenosis. These calculations are based on a number of assumptions that may limit the widespread applicability to certain populations. These assumptions include: the use of ultrasound as the initial screening test with a sensitivity of 0.94 and specificity of 0.92; the prevalence in general primary care population older than 65 years is 1%; all patients with a positive test go to surgery; and the event rate with CEA (perioperative stroke or death) is 3.1%. Further detail on assumptions is available in Table 2. According to these calculations the best trade-off between benefits and harms comes from a strategy of carotid duplex ultrasound screening followed by MRA confirmation. Given this strategy, about 23 strokes would be prevented over 5 years by screening 100,000 people with a true prevalence of clinically important CAS of 1%. Thus, about 4,348 people would need to undergo screening to prevent one stroke (number needed to screen, NNS) after 5 years. Double this number (8,696) would need to be screened to prevent one disabling stroke. If it were possible to define a higher risk population with an actual prevalence of 5%, and using the screening and confirmation strategy defined above, about 217 strokes would be prevented over 5 years by screening 100,000 people. This translates into a NNS of about 461 to prevent one stroke over 5 years, or a NNS of 922 to prevent one disabling stroke over 5 years. An additional 34 people would have a non-fatal myocardial infarction as a result of screening. However, risk assessment tools that accurately identify persons at high risk of a stroke from CAS are not available and, therefore, it is not possible to identify people from a high-risk group with a prevalence of 5% who might benefit from screening and treatment with CEA.

Asymptomatic CAS likely contributes a relatively small portion of the overall stroke burden. Although this report did not review the evidence on medical treatment, there are accepted medical strategies to prevent stroke. Until we address the gaps in the evidence that screening and treatment with CEA provides overall benefits to the general population, clinicians' efforts might be more practically focused on optimizing medical management.

EMERGING ISSUE – STENTING FOR CAROTIC ARTERY STENOSIS

The use of carotid artery angioplasty with stenting for CAS has increased in recent years. This technology has emerged as a potential alternative to CEA for patients who are not candidates for CEA because of high-risk comorbidities.

A Cochrane Systematic Review of 5 RCTs of stenting versus CEA for symptomatic and asymptomatic patients at high risk for complications from CEA found no difference in 30-day or 1-year outcomes between treatment groups.[63] No study has randomized asymptomatic patients similar to those in the ACAS or ACST trials to stenting versus CEA, and no trial has reported results beyond one year. The largest study that reported the most positive results showed a non-statistically significant trend toward a reduction in perioperative stroke, death, and non-fatal MI.[64] This study, however, was terminated early because of slow recruitment. Thus, we cannot determine whether there are any differences in the benefits of stenting compared with CEA.

RESEARCH GAPS

High quality studies of the true prevalence (rather than ultrasound-based prevalence) of clinically important CAS in usual primary care populations are needed. Other research gaps include: 1) evidence for a validated, reliable risk stratification tool that would allow us to distinguish those people who might benefit from screening from those who would more likely be harmed; 2) evidence on improved screening strategies that do not generate large numbers of false positive tests and unnecessary harms; and 3) further studies on confirmatory strategies that do not lead to additional harms.

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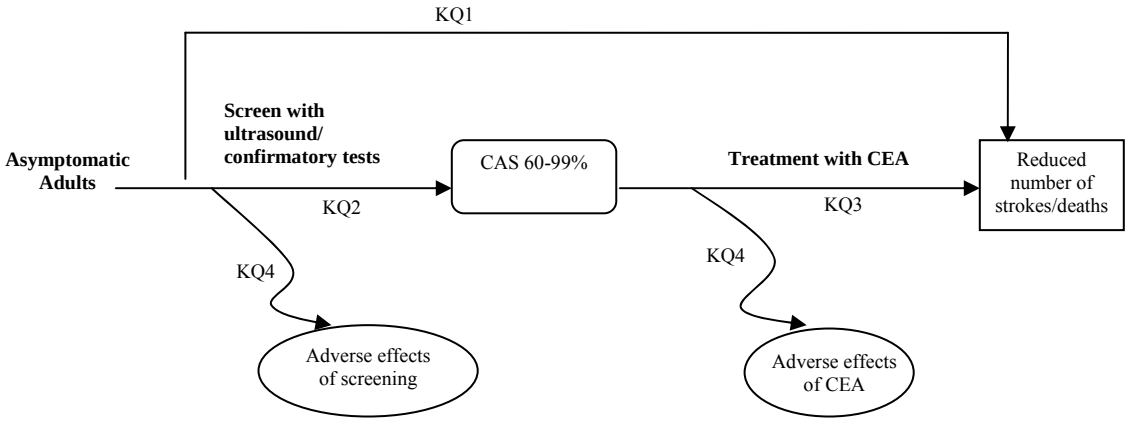
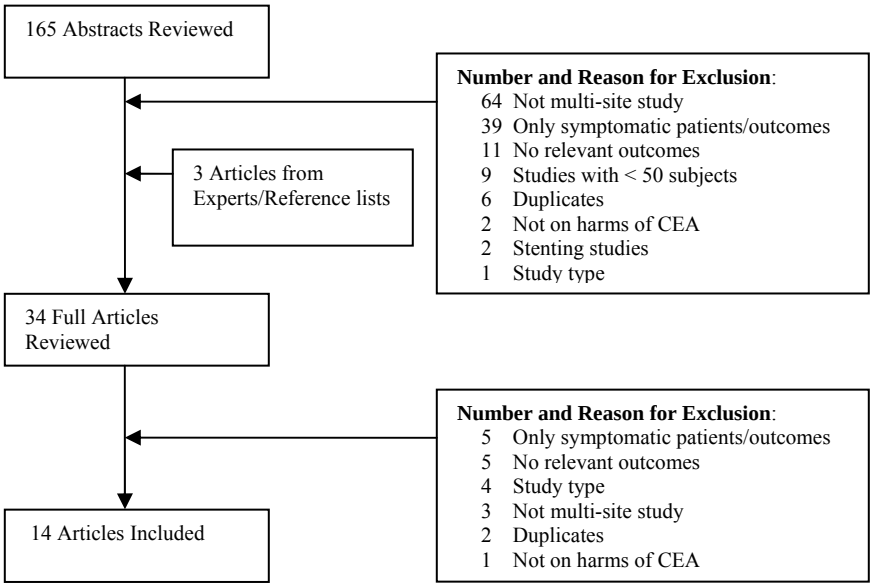
Figure 1. Analytic Framework for Screening for Carotid Artery Stenosis



KQ = key question; CAS = carotid artery stenosis; CEA = carotid endarterectomy

Figure 2. Literature search results for key question 4 on the harms of carotid endarterectomy.



CEA = carotid endarterectomy

Table 1. Evidence Table for Randomized Controlled Trials for Effectiveness of Surgery versus Medical Management for Asymptomatic Carotid Artery Stenosis

Study	Sample Size & Basic Demographics	Mean Follow-up Time	30-day Perioperative Complic. Rate :	Five Year Outcomes :*	Quality Rating
VACS[31]	Total = 444 MM = 233 CEA = 211 Mean age: 65 years Male 100% White: 86-88%	48 months	Stroke or death: 4.7% MI: 1.9%	Five-year incidence of any stroke & perioperative death: MM: 44.2% CEA: 41.2% RR 0.92 (95% CI, 0.69-1.22)	Fair
ACAS[32]	Total = 1659 MM = 834 CEA = 825 Mean age: 67 years Male: 66% White: 94-95%	2.7 years	Stroke or death: 2.7% MI: NR% Sex: Women: 3.6% Men: 1.7%	Rate of perioperative stroke or death & subsequent ipsilateral stroke: MM = 11% CEA = 5.1% RRR = 53% (95% CI, 22-72%) ARR = 5.9% Sex: W: RRR 17% (95% CI, -%96-65%) M: RRR 66% (95% CI, 36-82%) Age: < 68: RRR 0.60 (95% CI, 0.11-0.82) ≥ 68: RRR 0.43 (95% CI, -0.07-0.70)	Good
ACST[33]	Total = 3,120 MM = 1,560 CEA = 1,560 Mean age = 68 years Male 66% White: NR	3.4 years	Stroke or death: 2.8% MI: 0.6 % Sex: ∞ Women: 3.1% Men: 2.2% Age: < 65: 2.4% 65-74: 2.3% ≥ 75: 3.3%	Five-year incidence of any stroke & perioperative death: MM = 11.8% (SE 1.00) CEA = 6.4% (SE 0.70) ARR = 5.4% (95% CI 2.96-7.75) Sex: § W: ARR= 4.1% (95% CI 0.74-7.41) M: ARR= 8.2% (95% CI 5.64-10.78) Age: § < 65: ARR 7.8% (95% CI 4.28-11.31) 65-74: ARR 7.5% (95% CI4.67-10.30) ≥ 75: ARR 3.3%	Good

* Standard errors and 95% confidence intervals are listed here if reported in the studies.

§ Five-year non-perioperative stroke;

VACS = Veterans Affairs Cooperative Study, ACAS = Asymptomatic Carotid Atherosclerosis Study, ACST = Asymptomatic Carotid Surgery Trial, NR=Not reported, MM = medical management group, CEA = carotid endarterectomy group, NR = not reported, MI = myocardial infarction, CI = confidence interval, RR = relative risk, ARR = absolute risk reduction, RRR = relative risk reduction, SE = standard error, W = women, M = men

Table 2: Projected Outcomes of Screening 100,000 Asymptomatic Adults for Carotid Artery Stenosis

	True Prevalence of CAS = 1%	True Prevalence of CAS = 5%
Number screened	100,000	100,000
Number of patients with CAS in population	1,000	5,000
Number of positive screening tests	8,860	12,300
True positives (TPs)	940	4,700
False positives (FPs)	7,920	7,600
Total number sent to surgery (FPs/TPs)		
a) no confirmatory test	a) 8,860 (7,920/940)	a) 12,300 (7,600/4,700)
b) confirmation by angiogram	b) 940 (0/940)	b) 4,700 (0/4,700)
c) confirmation by MRA	c) 1,685 (792/893)	c) 5,225 (760/4,465)
Strokes caused by angiogram confirmation	106	148
Perioperative strokes or death caused by operating on patients with false positive results		
a) no confirmatory test	(a) 246	(a) 236
b) confirmation by angiogram	(b) 0	(b) 0
c) confirmation by MRA	(c) 25	(c) 24
Non-fatal myocardial infarction among patients undergoing CEA: Total (FPs/TPs)		
a) no confirmatory test	(a) 54 (48/6)	(a) 79 (49/30)
b) confirmation by angiogram	(b) 6 (0/6)	(b) 30 (0/30)
c) confirmation by MRA	(c) 10 (5/5)	(c) 34 (5/29)
Outcome events in TPs (no or angiography/MRA confirmation)		
Medical Treatment	111/105	555/527
CEA Treatment	60/57	301/286
Difference – events prevented by CEA	51/48	254/241
Perioperative events in FPs (no/angiography/MRA confirmation)		
Medical Treatment	0/0/0	0/0/0
CEA Treatment	246/106/25	236/148/24
Difference - events caused by CEA	246/106/25	236/148/24
Total stroke and perioperative death events caused or prevented by CEA (TPs + FPs)		
a) No confirmatory test	195 events caused	18 events prevented
b) Angiography confirmation	55 events caused	106 events prevented
c) MRA confirmation	23 events prevented	217 events prevented
NNS to prevent one stroke over 5 years		
a) No confirmatory test	a) Events caused > prevented	a) 5,556
b) Angiography confirmation	b) Events caused > prevented	b) 944
c) MRA confirmation	c) 4,348	c) 461
NNS to prevent one disabling stroke over 5 years		
a) No confirmatory test	a) Events caused > prevented	a) 11,112
b) Angiography confirmation	b) Events caused > prevented	b) 1,888
c) MRA confirmation	c) 8,696	c) 922

Abbreviations: CAS = carotid artery stenosis; FPs = false positives; TPs = true positives; MRA = magnetic resonance angiography; CEA = carotid endarterectomy; NNS = number needed to screen

Screening and Confirmatory Testing Assumptions:

1) Screening test is carotid duplex ultrasound, with sensitivity for CAS 60%-99% of 0.94; specificity of 0.92;
2) Confirmatory test is either (a) none, (b) cerebral angiogram (sensitivity and specificity = 100%), or (c) MRA (sensitivity = 0.95 and specificity = 0.90);

3) True prevalence in general > 65 year old primary care population = 1%; high risk group = 5%;
4) Stroke complication rate with angiography = 1.2%;
5) All patients with positive test go to surgery;
6) Perioperative stroke or death rate with CEA (whether patient is TP or FP) = 3.1% (as in ACST);
7) Perioperative non-fatal MI rate with CEA (whether patient is TP or FP) = 0.6% (as in ACST);
8) "Events" are all strokes and perioperative deaths 5 years after CEA;
9) Probability of event is 11.8% for medical (11.8%) and 6.4% for treatment with CEA treatment (ACST);
10) One-half of strokes prevented are non-disabling;
11) No benefit is received from medical or CEA treatment
for patients with false positive screening test results.

Appendix 1. Literature Search and Inclusion/exclusion Criteria for Key Questions

Key Question 4. CEA complication rates

Literature Search

1. endarterectomy, carotid [mesh] **AND** outcome and process assessment (health care) [mesh]. Yield = 690. Limited to "usa [ad]", which picks up the country designation USA in the author affiliation/address field. This yielded 209 items.

2. Related article search through PubMed
Related articles to: Feasby, Hospital and surgeon determinants of carotid endarterectomy outcomes. Arch Neurol. 2002 Dec; 59(12):1877-81. Yield = 27 studies.

Inclusion/Exclusion Criteria for Complication Rates of CEA

Inclusion

Studies that include complication rates related to CEA by 30 day mortality or stroke for asymptomatic patients
Studies that evaluate differences in outcomes by technique, including:
- Different types of patches
- Shunting
- Eversion techniques

Studies that evaluate differences in outcomes by surgical specialty, including:
- Neurosurgeon
- Vascular surgeon
- General surgeon

Studies that evaluate differences in outcomes by non-surgical factors:
- Anesthesia type
- Intraoperative ultrasound or other imaging
- Intraoperative angiography

Studies that evaluate differences in outcomes by patient factors:
- Age
- Gender
- Race

Studies that include more than one surgeon and more than one hospital
Studies evaluating complication differences by surgical specialty, training, or experience
Studies evaluating complication differences by surgeon or hospital volume and by setting
Studies that have complication rates for asymptomatic patients
Case series, RCTs, meta-analysis

Exclusion

Studies evaluating only patients with combined CEA and coronary artery bypass graft
Studies that include only patients receiving stenting, angioplasty, endovascular treatment
Studies that include only symptomatic patients or don't separate rates by symptom status
Non-United States studies
Review articles without outcome data
Studies that include only patients with prior stroke
Studies evaluating re-stenosis outcomes only
Recurrent stenosis studies
Quality improvement studies without complication rates listed
Utilization studies without complication rates

Pseudoaneurysm studies
Bilateral CEA studies
Emergent CEA studies
Studies including outcomes for only one surgeon or only one clinical site
Studies with < 50 subjects
Not on harms of CEA
No relevant or 30 day outcomes
High risk or special populations
Incorrect study type

Inclusion/Exclusion Criteria for Key Questions 1-3

Key Question 1. Benefits of screening

Randomized Controlled Trial (RCT)
Compared screened versus non-screened groups
Outcomes of strokes or death
Outcomes specific for asymptomatic subjects
Population generalizable to U.S.
Published in English

Key Question 2. Accuracy and reliability of screening

Ultrasound, MRA, or computed tomography screening
Asymptomatic subjects
Systematic reviews of studies that compared screening test to gold standard of angiography
Population-based prevalence studies
Population generalizable to U.S.
Published in English

Key Question 3. Benefits of CEA

RCTs of CEA comparing surgical treatment to medical treatment
Reported 30-day complication rates of CEA
Outcomes of stroke and/or death
Outcomes specific for asymptomatic subjects
Population generalizable to U.S.
Published in English

Appendix 2. USPSTF Hierarchy of Research Design and Quality Rating Criteria[1,2]

HIERARCHY OF RESEARCH DESIGN

I Properly conducted randomized controlled trial (RCT)
II-1: Well-designed controlled trial without randomization
II-2: Well-designed cohort or case-control analytic study
II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

DESIGN-SPECIFIC CRITERIA AND QUALITY CATEGORY DEFINITIONS

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equally to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.
Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rates less than 80 percent or attention to some but not all important confounding variables.
Poor: Major section or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups
    - -for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups

- -for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of the interventions
- All important outcomes considered

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening tests; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100 broad-spectrum of patients.

Fair: Evaluates relevant available screening tests; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has fatal flaw such as: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate result in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner;
includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50-100 subjects) and a "medium" spectrum of patients.

Poor: Has fatal flaw such as: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum patients.

1. Harris R, Atkins D, Berg AO, Best D, Eden KB, Feightner JW et al. *US Preventive Services Task Force Procedure Manual*. Rockville, MD: Agency for Healthcare Research and Quality, 2001.

2. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001; 20(3 Suppl):21-35.

Appendix 3. Evidence Table for Randomized Controlled Trials for Effectiveness of Surgery versus Medical Management for Asymptomatic Carotid Artery Stenosis. Part I of Evidence Table.

Study	Sample Size & Intervention Groups	Demographics/ Comorbidities	Source of Patients	Prerandomization Evaluation & Required Stenosis	Required Preoperative A-gram? A-gram Complic. Rate
WRAMC[29]	Total = 29 ASA = 14 CEA = 15	Mean age = 63 years Male 72% HTN 69% DM 14% ↑Chol 10% Smoke 72%	Not reported	OPG	Yes
MACE[30]	Total = 71 ASA = 35 CEA = 36	70% > 65 years Male 56-60% White HTN 63% DM 14-19% ↑Chol 44-66% Smoke 67-74%	Not reported	OPG, U/S, or angiogram	Yes
VACS[31]	Total = 444 MM = 233 CEA = 211	Mean age 65 years Male 100% White 86-88% HTN 63-64% DM 27-30% ↑Chol NR Smoke 49-52% Contralateral TIA/stroke = 32%	Not reported	A-gram ≥ 50%	Yes 0.4%
ACAS[32]	Total = 1659 MM = 834 CEA = 825	Mean age = 67 years Male 66% White 94-95% HTN 64% DM 23% CAD 69% ↑Chol % NR Smoke 26% Contralateral CEA= 20%	Vascular ultrasonography laboratories, physicians who found bruits during evaluation for PVD or contralateral CEA	U/S or angiogram ≥ 60%	Yes 1.2%
ACST[33]	Total = 3,120 MM = 1,560 CEA = 1,560	Mean age = 68 years Male 66% HTN 65% DM 20% ↑Chol 73% Smoke NR Non-DM CAD 27% Contralateral CEA 24%	Medical and surgical clinics	U/S ≥ 60%	No

§ Five-year non-perioperative stroke; † Not statistically significantly different; ◊ Statistically significantly different; ‡No significant benefit to CEA in this group; ∞ Statistical significance between groups not reported

WRAMC = Walter Reed Army Medical Center Study; MACE = Mayo Asymptomatic Carotid Endarterectomy Study; VACS = Veterans Affairs Cooperative Study; ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; NR=Not reported, MM = Medical Management; ASA = aspirin; CEA = carotid endarterectomy group; HTN = hypertension; DM = diabetes mellitus; ↑Chol = hyperlipidemia; CAD = coronary artery disease; TIA = transient ischemic attack; OPG = ocular pneumoplethysmography; U/S = ultrasound; PVD = peripheral vascular disease; MI = myocardial infarction; CI = confidence interval; RR = relative risk; ARR = absolute risk reduction; RRR = relative risk reduction; SE = standard error; W = women; M = men

Appendix 3. Evidence Table for Randomized Controlled Trials for Effectiveness of Surgery versus Medical Management for Asymptomatic Carotid Artery Stenosis. Part II of Evidence Table.

Study	Mean Follow-up Time	30-day Complic. Rate of CEA : Stroke/Death, MI	Results: any CVA & Perioper. Stroke/death (95% CI)	Rate of Perioperative CVA/Death & Subseq. Ipsilat. Stroke (95% CI)	Quality Rating
WRAMC[29]	3 years	Not reported	ASA = 0/15 CEA = 3/15	Not reported	Poor
MACE[30]	23.6 months	Stroke/death: 4% MI: 8%	ASA = 0% CEA = 8.3%	Not reported	Poor
VACS[31]	48 months	Stroke/death: 4.7% MI: 1.9%	Five-year incidence of death or stroke: MM: 44.2%† CEA: 41.2% RR 0.92 (0.69-1.22)	Not reported	Fair
ACAS[32]	2.7 years	Stroke/death: 2.7% MI: NR% Sex:† Women: 3.6% Men: 1.7%	RRR = 20% (-2-37%)	Five Year:◊ MM = 11% CEA = 5.1% RRR = 53% ARR = 5.9% Sex:† W: RRR 0.17‡ (-0.96-0.65) M: RRR 0.66 (0.36-0.82) Age: † < 68: RRR 0.60 (0.11-0.82) ≥ 68: RRR 0.43 ‡ (-0.07-0.70)	Good
ACST[33]	3.4 years	stroke/death: 2.8% MI: 0.6 % Sex: ∞ W: 3.1% M: 2.2% Age: ∞ < 65: 2.4% 65-74: 2.3% > 75: 3.3%	Five year: ◊ MM = 11.8% CEA = 6.4% ARR = 5.4% RRR = 46% Sex: § ∞ W: ARR = 4.1% M: ARR= 8.2% Age: § ∞ < 65: ARR 7.8% 65-74: ARR 7.5% ≥ 75: ARR 3.3%‡	Not reported	Good

§ Five-year non-perioperative stroke; † Not statistically significantly different; ◊ Statistically significantly different; ‡No significant benefit to CEA in this group; ∞ Statistical significance between groups not reported

WRAMC = Walter Reed Army Medical Center Study; MACE = Mayo Asymptomatic Carotid Endarterectomy Study; VACS = Veterans Affairs Cooperative Study; ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; NR=Not reported, MM = Medical Management; ASA = aspirin; CEA = carotid endarterectomy group; HTN = hypertension; DM = diabetes mellitus; ↑Chol = hyperlipidemia; CAD = coronary artery disease; TIA = transient ischemic attack; OPG = ocular pneumoplethysmography; U/S = ultrasound; PVD = peripheral vascular disease; MI = myocardial infarction; CI = confidence interval; RR = relative risk; ARR = absolute risk reduction; RRR = relative risk reduction; SE = standard error; W = women; M = men

Appendix 4. Evidence Table on Complications Rates for Carotid Endarterectomy. Part I of Evidence Table.

			Total Population	
Study Reference	**Design Setting Source population**	**Population Selection**	**N**	**Characteristics**
Bratzler 1996[47]	Retrospective, observational study using Medicare claims database and medical records 8 hospitals in Oklahoma (OK) OK Medicare beneficiaries	1993-1994 All CEA cases from the OK Medicare claims data; hospital selection not specified; all surgeons performing CEA in the 8 study hospitals	813 CEAs (774 patients)	Median-73 yrs % White NR % Female NR 26% DM 20% COPD 10% CHF 67% CHD 71% HTN 26% Smoke 98% had stenosis > 60%
Cebul 1998[48]	Retrospective, cohort study using Medicare provider analysis and review files 115 hospitals/478 surgeons in Ohio (OH)	7/93 – 6/94 Random sample of 700 of 4,120 non-HMO Medicare beneficiaries in OH (18 patients had no medical record; 4 had stroke; 3 had bilateral carotid procedures during same hospitalization); hospitals performing CEA in OH	678 patients	Mean-73.1 yrs 94% White 46% Female 26% DM 16% COPD 9% CHF % CHD NR 71% HTN 31%[1] Smoke % stenosis NR
Halm 2003[7] **Rockman 2005[55]** **Halm 2005[53]** **Press 2006[54]**	Cross-sectional study based on medical record review of in- and outpatient records 4 university hospitals, 2 community hospitals served by 67 surgeons	1/97 – 12/98 Reviewed 2,365 of 2,390 CEAs based on hospitals' databases. Cases excluded if re-operation, surgery combined with other major procedure, no CEA performed or missing data. Each hospital contributed 130-583 cases.	2124	Mean-72 yrs 87% White 43% Female 29% DM 9% COPD 8% CHF % CHD NR 73% HTN % Smoke NR 96% had > 50% stenosis
Halm 2007[49]	Retrospective, observational study using New York State Medicare claims database and medical records	1/98 – 6/99 Reviewed 10, 817 eligible cases (94.8%). Excluded reoperations, CEA combined with CABG, or no CEA performed. 551 cases excluded because of missing data.	9588	Mean – 74.6 yrs 93% White 56% Male 30% DM 19% COPD 10% CHF 62% CHD
VA - NSQIP **Samsa 2002[46]**	Secondary analysis of VA NSQIP data 132 VA medical centers Patients undergoing surgery at a VA medical center	1994-1995 1996-1997 94% of those available for assessment included in database, most excluded because of multiple index operations; 5 of the 123 VAs assessed < 80% of eligible cases. All VA hospitals performing major surgery; all surgeons performing surgery at VA hospitals.	7,842	Mean-68 yrs 91% White 2% Female 17% DM 17% COPD 2% CHF % CHD NR % HTN NR % Smoke NR % Stenosis NR

Appendix 4. Evidence Table on Complications Rates for Carotid Endarterectomy. Part I of Evidence Table.

			Total Population	
Study Reference	**Design Setting Source population**	**Population Selection**	**N**	**Characteristics**
Horner 2002[45]	Secondary analysis of data in VA NSQIP examining differences in CEA outcomes by ethnic group 132 VA Medical Centers Patients having CEA	10/94 – 9/97 Limited to men having CEA	6551	20% ≥ 75 yrs 91% White 0% Female 29% DM 12% COPD 2% CHF % CHD NR % HTN NR % Smoke NR % Stenosis NR
Karp 1998[50]	Retrospective, cross-sectional study Medicare beneficiaries who underwent CEA in Georgia	1993 Excluded 35 cases due to missing data.	1945	Mean-72.3 yrs 91% White 47% Female 22% DM 24% COPD 8% CHF % CHD NR % HTN NR % Smoke NR 69% > 75%
Kresowik 2000[52]	Retrospective, observational study using Medicare database and medical records 30 hospitals in Iowa Iowa Medicare beneficiaries	1994 & 6/95 to 5/96 All CEA cases from the Iowa Medicare claims database (Part A & B); all hospitals in Iowa performing CEA on Medicare patients; all surgeons in Iowa performing CEA on Medicare patients	2063	Median-74 yrs % White NR 40% Female % DM NR % COPD NR % CHF NR % CHD NR % HTN NR % Smoke NR % Stenosis NR
Kresowik 2001[51]	Retrospective, observational study using Medicare database and medical records 10 states Medicare beneficiaries	6/95 – 5/96 Random sample of 10,561 from 28,083 procedures identified from the MEDPAR Part A claims.	10,030 patients	Mean-73.6 yrs % White NR 43% Female % DM NR % COPD NR % CHF NR % CHD NR % HTN NR % Smoke NR % Stenosis NR
Kresowik 2004[44]	Retrospective, observational study using Medicare database and medical records 10 states Medicare beneficiaries	6/98 – 5/99 Random sample of procedures identified from the MEDPAR Part A claims.	9,945 patients	Mean-NR % White NR 43% Female % DM NR % COPD NR % CHF NR % CHD NR % HTN NR % Smoke NR % Stenosis NR

Percentages have been rounded.

[1]Past or present smoker; NR = Not Reported, CEA = carotid endarterectomy DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease, CHF = congestive heart failure, CHD = coronary heart disease, HTN = hypertension, CVA = stroke, MI = myocardial infarction, HMO = health maintenance organization, VA = Veterans affairs, NSQIP = National VA Surgical Quality Improvement Program, CVA = cerebral vascular accident, CABG = coronary artery bypass graft, ESRD = end stage renal disease, OR = odds ratio, MI = myocardial infarction, MEDPAR = Medicare Provider Analysis and Review

Appendix 4. Evidence Table on Complications Rates for Carotid Endarterectomy. Part II of Evidence Table.

	Total Asymptomatic Population				
Study Reference	**N (% Total)**	**Characteristics**	**Outcomes 30-day Stroke/Death Other Complications (Asymptomatic)**	**Threats to Internal Validity External Validity**	**Quality Rating**
Bratzler 1996[47]	347 (43%)	Not reported	Overall = 3.7% High volume hospital (>100 cases/year) = 3.5% Low volume hospital = 5.2% 3% HTN 2% wound hematoma 2% pneumonia	Data collected from medical record and claims database Reviewer blinding not discussed No comprehensive evaluation, outcomes determined by coding or documentation in chart Generalizability low, select population	Good
Cebul 1998[48]	167 (25%)	Not reported	2.4% Hospital-specific stroke/death rates inversely related to the number of procedures, ranging from 7.7% lowest quartile to 2.5% highest quartile Asymptomatic patients at higher-volume hospitals (greater than median) had no strokes or death at 30 days compared to 4.9% and 4.6% in lower volume hospitals. Outcomes did not differ significantly by surgeon volume. Undergoing surgery in a higher volume hospital was associated with a 71% reduction in risk of stroke or death at 30 days, after adjusting for patient characteristics (OR=0.29 (o.12-0.69)).	No assessment of patients, outcomes determined from readmission data; study did not include outpatient visits Predominantly white population	Fair
Halm 2003[7] **Rockman 2005[55]** **Halm 2005[53]** **Press 2006[54]**	1413 (65%)	Not reported	Asymptomatic with no co-morbidities = 1.28% Low comorbidity (1 cardiac risk factor) = 2.21% Moderate (2) = 2.77% High (ESRD, severe disability or over 2 risk factors) = 5.56% Mean complication rate across groups = 2.6%	Complication rates (especially CVA) are underestimated by administrative database. No assessment of patients by neurologist All hospitals in 1 region, may not be generalizable.	Good

Appendix 4. Evidence Table on Complications Rates for Carotid Endarterectomy. Part II of Evidence Table.

	Total Asymptomatic Population				
Study Reference	**N (% Total)**	**Characteristics**	**Outcomes 30-day Stroke/Death Other Complications (Asymptomatic)**	**Threats to Internal Validity External Validity**	**Quality Rating**
Halm 2007[49]	72%	Not reported	Asymptomatic without high comorbidity = 2.69% Asymptomatic with high comorbidity = 7.13%	Large number of cases excluded due to missing data. Complication rates (especially CVA) are underestimated by administrative database. No assessment of patients by neurologist All hospitals in 1 region, may not be generalizable.	Fair
VA - NSQIP **Samsa 2002[46]**	3,231	not reported	30-day death, CVA, MI Overall = 2.4% 1994-95 = 2.7% 1996-97 = 2.2%	Reviewer not blinded to treatment, hospital course Loss to follow-up not discussed, although likely very little No comprehensive exam by neurologist for outcome assessment No discussion of hospital selection Other complications not listed Generalizability low select population (white males)	Good
Horner 2002[45]	2852 (44%)	20% $\geq$ 75 yrs 92% White 0% Female 28% DM 10% COPD 2% CHF % CHD NR % HTN NR % Smoke NR % Stenosis NR	Stroke or death: 1.6% white 2.1% black 2.2% Hispanic Stroke, MI or death 2.3% white 2.1% black 3.2% Hispanic	Little selection within VA (VA patients are a selected subgroups of US population)	Good
Karp 1998[50]	972 (51%)	Not reported	Mortality=0.8% Mod/Severe Stroke =1.0% MI = 0.8% Combined (above) = 2.6% All Stroke = 2.4% Symptomatic patients: Mortality = 1.7% Mod/Severe Stroke = 2.7% MI = 1.4% Combined (above) = 5.8% All stroke = 4.7% Found statistically significant increase in morbidity, mortality and less severe complications at hospitals performing $\leq$10 CEAs.	No comprehensive exam by neurologist for outcome assessment No discussion of hospital selection Generalizability low (all males, mostly white)	Fair

Appendix 4. Evidence Table on Complications Rates for Carotid Endarterectomy. Part II of Evidence Table.

	Total Asymptomatic Population				
Study Reference	**N (% Total)**	**Characteristics**	**Outcomes 30-day Stroke/Death Other Complications (Asymptomatic)**	**Threats to Internal Validity External Validity**	**Quality Rating**
Kresowik 2000[52]	671 (20% '94; 40% '95-96)	Not reported	Overall = 3.4% 1994 = 3.8% 1995-96 = 3.3%	Unclear when reports of outcomes were given to hospitals & surgeons. No comprehensive evaluation, depended on medical records for outcomes. Relied on claims database for readmissions for stoke, death occurring after discharge. Generalizability	Good
Kresowik 2001[51]	3120 (39%)	Not reported	Combined events 3.7% Mortality 1.1% The combined event rate by state for asymptomatic patients ranged from 2.3% to 6.7%. Mortality ranged from 0.5% to 2.5%. Only 2 states significantly different from the mean.	Missed nonfatal neurologic events occurring after discharge that did not result in another hospitalization.	Good
Kresowik 2004[44]	4093	Not reported	Combined events 3.8% The combined event rate by state for asymptomatic patients ranged from 1.4% to 6.0%. Only 3 states significantly different from the mean.	Missed nonfatal neurologic events occurring after discharge that did not result in another hospitalization.	Good

Percentages have been rounded.
[1]Past or present smoker;
NR = Not Reported, CEA = carotid endarterectomy DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease, CHF = congestive heart failure, CHD = coronary heart disease, HTN = hypertension, CVA = stroke, MI = myocardial infarction, HMO = health maintenance organization, VA = Veterans affairs, NSQIP = National VA Surgical Quality Improvement Program, CVA = cerebral vascular accident, CABG = coronary artery bypass graft, ESRD = end stage renal disease, OR = odds ratio, MI = myocardial infarction, MEDPAR = Medicare Provider Analysis and Review