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Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries

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Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries

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About this Report

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

About Spectrum Research, Inc.

For over a decade, Spectrum Research, Inc. (SRI) has developed a solid reputation for providing high-quality evidence-based products and clinical research consulting. SRI is a partner in the AHRQ-funded Pacific Northwest Evidence-Based Practice Center together with the Oregon Health and Sciences University and the University of Washington. Spectrum's evidence-based practice (EBP) reports have been used by a variety of agencies and private organizations. Our reports provide an independent assessment of current evidence/research and have been used for policy formulation, creation of clinical recommendations and consideration of future research needs. Reports include full health technology assessments (HTAs) and comparative effectiveness reviews as well as smaller evidence briefs and rapid reviews for the purpose of understanding evidence and improving health-care delivery.

TABLE OF CONTENTS

TABLES

FIGURES

EXECUTIVE SUMMARY

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in both men and women in the United States.[52] One or more types of CVD effect an estimated 82,600,000 adults (> 1 in 3), half of which are 60 years of age or older. By 2030, the prevalence of CVD in the US population is projected to rise to 40.5%.[26] When considered separately from other CVDs, stroke is the fourth leading cause of death (behind heart disease, cancer, and chronic lower respiratory disease).[52] The American Heart Association estimates that about 800,000 Americans experience a new or recurrent stroke each year; 87% of these are ischemic in nature, mostly due to thromboembolic events.[42] The carotid arteries provide the main blood supply to the brain and narrowing of these arteries (stenosis) due to atherosclerosis accounts for nearly 20% to 25% of these strokes.[21,49] The most common site of plaque formation and stenosis in the carotid artery is near the bifurcation of the common carotid artery into the internal and external carotid arteries.[2,13] Medical risk factors for carotid artery atherosclerosis are similar to those for other cardiovascular diseases.

Intracranial arteries may be affected by atherosclerotic disease as well and intracranial stenosis is an important cause of ischemic stroke worldwide. While all traditional risks factors are associated with ICAD, it appears that the presence of diabetes and metabolic syndrome are particularly associated with the development of atherosclerotic disease of the intracranial vasculature.

Therapeutic options for atherosclerotic carotid stenosis include medical therapy alone, carotid endarterectomy (CEA) and medical therapy, or carotid angioplasty and stenting (CAS) and medical therapy. Management of risk factors (e.g. smoking) is also an important part of any therapeutic approach. Medical therapy has changed significantly in the past decade. Randomized comparisons of CEA with current best medical therapy are lacking. Given the changes in approach to medical therapy in the past decade, landmark trials completed in the early 1980s and 1990s comparing CEA with medical therapy alone may not be applicable to contemporary practice.[38,50] Evaluation of current best medical therapy is beyond the scope of this report.

For many years, CEA has been considered the gold-standard to restore vascular patency in the surgical management of carotid artery stenosis. However, recently, CAS, a less invasive surgical procedure, has become an alternative to CEA, particularly in persons who may be at high risk for surgically-related morbidity and mortality. Much of the evidence available for guiding decision making in the management of patients with carotid artery disease comes from randomized controlled trials conducted in symptomatic patients. A patient with carotid stenosis is considered symptomatic if they have neurological evidence of an ipsilateral stroke, transient ischemic attack (TIA) or transient monocular blindness. However, less is known about the efficacy of medical

treatment, CEA and CAS in patients without these symptoms and thus the management of patients with asymptomatic carotid disease is still evolving.

The target populations for carotid artery stenting are symptomatic patients with moderate (50%-69%) or severe (70%-99%) carotid artery stenosis at risk for stroke and asymptomatic patients with stenosis of 60% or greater who are not able to tolerate general anesthesia for CEA. Current U.S. Food and Drug Administration (FDA) labeling requires that stents only be used in asymptomatic patients with ≥70% stenosis. All patients must have a reference vessel diameter within the range of 4.0mm and 9.0 mm at the target lesion. FDA indications also include history of contralateral vocal cord damage, previous ipsilateral neck surgery and restenosis after CEA. Drug eluting stents have not been approved for use in the carotid or intracranial vessels.

The primary therapeutic approach for intracranial atherosclerotic disease (ICAD) is medical therapy. More recently, angioplasty with or without stenting has been reported. Surgical options are limited. Approval of intracranial stents by the U.S. Food and Drug Administration (FDA) has been through the humanitarian device exemption (HDE) process for use in persons with 70%–99% stenosis of an intracranial vessel experiencing recurrent intracranial stroke secondary to atherosclerotic disease that is refractory to medical therapy.

The public health, societal and economic burden of stroke is high. It is therefore important that decisions related to treatment options include consideration of the best evidence available on efficacy, effectiveness and safety. This technical review systematically assesses the evidence on this topic based on the context and final key questions provided by the Washington State Health Technology Assessment Program. The Washington State Healthcare Authority's Health Technology Assessment program selected this topic for review based on high levels of concern around efficacy and cost and on medium levels of concern around safety.

Key Questions

This review seeks to answer the following key questions:

1. In symptomatic or asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness of:

    a. Extracranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?

    b. Extracranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?

2. In asymptomatic or symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is the evidence of short- and long-term comparative efficacy and

effectiveness of intracranial artery stenting and medical therapy compared with medical therapy alone?

3. What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?

4. Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other comorbidities, ethnicity, or disability)?

5. What is the evidence of cost-effectiveness of CAS compared with other treatment options (medical therapy, CEA) in the short-term and the long term?

The focus of this HTA is on treatment of atherosclerotic disease in the extracranial carotid arteries and intracranial arteries in adult patients comparing the use of stents with other treatment options. Treatment of atherosclerotic disease or other conditions of the extracranial portions of the vertebral and basilar arteries was not included in this report. Given that the benefits and risks of treatment may be different for asymptomatic and symptomatic disease, the population subsets were evaluated separately. Input from clinical experts was incorporated to formulate final inclusion and exclusion criteria and confirm focus on primary outcomes. Research reports were selected for summarization based on the following general inclusion criteria. For a detailed description of the inclusion and exclusion criteria, please refer to the PICO table in section 3.1.1 of this report.

- *Population.* 1) Adults with extracranial carotid artery stenosis undergoing primary treatment for symptomatic or asymptomatic atherosclerotic carotid artery stenosis who have not had previous revascularization. 2) Adults with atherosclerotic stenosis of intracranial arteries
- *Intervention.* Stenting of carotid arteries (with or without use of embolic protection devices or strategies) or stenting of intracranial arteries, using FDA approved devices
- *Comparator.* Medical therapy or surgical alternatives including carotid endarterectomy (CEA)
- *Outcomes.* The primary critical outcomes for long term efficacy included any stroke, ipsilateral stroke, death, the composite of stroke or death. Primary critical outcomes for safety were periprocedural (30 day) any stroke, death, the composite of stroke or death, myocardial infarction, major bleeding complications and persistent cranial nerve palsy. Additional outcomes are listed in the inclusion/exclusion table below.

- *Study design.* The focus for all key questions was on evidence judged to have the least potential for bias. Therefore, we concentrated on results from randomized controlled trials and comparative nonrandomized controlled trials (i.e. cohorts, registries). Only peer-reviewed articles published in English were considered.

Methods for evaluating comparative effectiveness

The scope of this report and final key questions were refined based on input from clinical experts from a variety of disciplines and public comments received on draft key questions. Clinical expert input was sought to confirm primary outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature across a number of databases including PubMed and EMBASE to identify relevant peer reviewed literature as well as of other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature.

Pertinent studies were critically appraised independently by two reviewers based on Spectrum's Class of Evidence (CoE) system which evaluates the methodological quality and potential for bias based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results: Summary of the highest quality evidence on primary outcomes

The following summaries of evidence for primary findings have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report.
A summary of the primary results for each key question are provided below with a focus on the primary outcomes described above. Details of these and other outcomes are available in the full report. RCTs and comparative nonrandomized controlled trials are the focus for for this

summary. The overall strength (quality) of evidence across studies is summarized in tables below. This is followed by a section called "Synoposis and remaining questions".

Key Question 1. In symptomatic or asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness of

a. Extracranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?

b. Extracranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?

Efficacy and Effectiveness in Asymptomatic Patients

Summary regarding efficacy (RCT data)

CAS versus medical therapy alone: No RCT evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis were found.

CAS compared with CEA: Two RCTs evaluated the efficacy of CAS and medical therapy versus CEA and medical therapy in patients of average surgical risk: One (Kentucky 2004)[12] was conducted in asymptomatic patients only, and one trial (CREST)[14] enrolled both symptomatic and asymptomatic patients. A third trial was conducted in high-risk patients (SAPPHIRE)[25] and is described in with Key Question 4 on special populations.

Across the two RCTs included in this section with regard to efficacy:

- Neither RCT evaluated the short-term efficacy of CAS and medical therapy compared with CEA and medical therapy for death or MI.
- Data on outcomes up to 4 years were reported for the CREST and Kentucky trials.
    - **Stroke:** Kentucky reported no stroke events at 4 years for either CAS or CEA treatment groups.
    - **Ipsilateral stroke:** No statistical difference was reported in in the CREST study. No ipsilateral stroke events were seen in either treatment arm of the Kentucky trial.
    - **Any periprocedural stroke or death or post-procedural ipsilateral stroke:** In the CREST trial, there was no statistical difference in risk of this composite outcome at 4 years.

- **Other outcomes:** The Kentucky 2004 study reported no difference in vessel patency at 4 years between CEA and CAS treatment groups. No patients in either group experienced symptoms of cerebral ischemia. Hospital length of stay, postprocedural pain and time to return to full activity were similar between treatment groups.

Summary regarding effectiveness (nonrandomized comparative studies)

CAS versus medical therapy alone: One retrospective, single-center cohort, Sherif et al. 2005,[53] followed patients for a median 2.1 years and reported Kaplan-Meier estimates for a projected 5 years of follow-up using a propensity score-adjusted analysis. Compared to patients in the medical therapy group, patients in the CAS group had significantly decreased rates of all outcomes (any stroke, death, and any stroke or death). This study was considered to be at moderately high risk of bias.

CAS compared with CEA: Primary outcomes following CAS and medical therapy compared with CEA and medical therapy up to 4 years were reported in three nonrandomized comparative studies (2 clinical cohorts,[18,62] and one registry[6]) all of which were described in the AHRQ report. .

- **Any stroke:** There were no statistical differences between treatments at 1.5 years in one prospective registry study or in one prospective cohort study at 4 years.
- **Death:** No statistical difference at 1.5 or 4 years was reported in one prospective registry and one prospective cohort study, respectively.
- **Any stroke or death:** No statistical difference at 1.5 or 4 years as reported in two studies (1 prospective registry and 1 prospective cohort).
- **Myocardial infarction (MI):** Across two prospective studies (1 registry and 1 cohort) at 1.5 and 4 years, no statistical difference was seen between treatments, although somewhat higher rates of MI were seen following CEA.
- **Any periprocedural stroke, death or post-procedural ipsilateral stroke:** At 2.8 years no statistical difference was seen between groups in one prospective cohort study.
- **Cognitive function, ADLs, Depression:** Three small prospective cohort studies (all considered to be at moderately high risk of bias) reported on various secondary outcomes.[16,22,37] Overall, no statistical differences between treatment groups were seen for most measures, which may partly be a function of sample size. One small study reported improvement in working memory after CAS (compared with CEA) and in processing speed following CEA (compared with CAS). [37]

Efficacy and Effectiveness in Symptomatic Patients

Summary regarding efficacy (RCT data)

CAS versus medical therapy alone: No RCT evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS compared with CEA: Ten reports from seven RCTs evaluated the efficacy of CAS and medical therapy versus CEA and medical therapy among symptomatic patients.[3-5,11,14,19,20,28,44,55] For the purposes of this HTA, short term outcomes were considered all outcomes occurring after 30 days and before 12 months, and longer-term outcomes were considered all outcomes occurring at or after 12 months. All seven RCTs evaluated long-term outcomes, and two RCTs evaluated short term outcomes[20,43]. One additional trial was conducted in high-risk patients (SAPPHIRE)[25] and is described in Key Question 4 on special populations.

CAS compared with CEA, Short term efficacy:

- **Any stroke (excluding periprocedural)**: There was no significant difference between treatments in risk of any stroke at 4 months in one large RCT.
- **Ipsilateral stroke (excluding periprocedural)**: There was no significant difference between treatments in risk of ipsilateral stroke at 4 months in one large RCT.
- **Death**: One RCT reported a significant increase in risk of death at 4 months for CAS compared with CEA (RD = 1.4, 95% CI: 0.3, 2.6).
- **Any stroke or death (including periprocedural)**: Across two RCTs, there was a significant increase in risk at 4 months in one large RCT (RD: 3.32, 95% CI 1.13, 5.52); however, no statistically significant difference between treatment arms at 6 months.
- **Death or any periprocedural stroke or postprocedural ipsilateral stroke**: In one large RCT there was a significant increase in risks for CAS compared with CEA (RD = 5.36%, 95% CI: 1.28, 9.42).
- **Cognitive function, blood pressure:** Two RCTs reported on cognitive function and blood pressure at 4 months. Overall, there were no statistical differences between treatment groups for change in measures of cognitive function or blood pressure.

CAS compared with CEA, Long term efficacy:

- **Any stroke (excluding periprocedural)**: No statistical differences between treatment groups were seen at two years (2 RCTs) or four years (2 RCTs). Risks ranged from 0% - 3.8% in both treatment groups.

- **Ipsilateral stroke (excluding periprocedureal**): No statistical differences were seen at two years (2 RCTs), or four years (2 RCTs) or 5.4 years (1 RCT). In the largest trials (CREST, SPACE, EVA-3s),[14,19,44] rates ranged from 1.5%-2.2% following CAS and 1.5% - 2.4%.

- **Death**: No statistical differences were seen at two years (2 RCTs), four years (2 RCTs) or 5.4 years (1 RCT). The pooled estimate across five studies failed to reach statistical significance.

- **Any stroke or death (including periprocedural)**: Lack of estimate stability across two small studies precludes the ability to draw meaningful conclusions.

- **Death or any periprocedural stroke or postprocedural ipsilateral stroke**: The pooled estimate across five studies reporting data for 2, 4 or 5.4 years failed to reach significance. Risks for this composite ranged from 0%-9.2% following CAS and 0%-10% for CEA.

- **Restenosis**: The pooled estimate for risk of restenosis (≥70%) across three RCTs reporting data for 2, 4 or 5.4 years failed to reach significance. Risks for restenosis ranged from 0%–18.8% following CAS and 0%–4.6% for CEA.

Summary regarding effectiveness (nonrandomized comparative studies)

CAS versus medical therapy alone: No nonrandomized comparative studies evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS compared with CEA: Outcomes following CAS and medical therapy compared with CEA and medical therapy up to 4 years were reported by two nonrandomized prospective cohort studies included in this report.[18,62] any stroke or death at 4 years showed a statistically significant difference between groups as reported by one study, with lower rates following CAS compared with CEA.[62] All other outcomes (any stroke, all-cause death, MI, and any periprocedural stroke or death or post-procedural ipsilateral stroke), reported by one study each, did not differ statistically between treatment groups, although consistently lower rates were reported following CAS. Both studies were considered to be at moderately high risk of bias.

Key Question 2. In asymptomatic or symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is the evidence of short- and long-term comparative efficacy and effectiveness of intracranial artery stenting and medical therapy compared with medical therapy alone?

Asymptomatic Intracranial Disease

No studies in asymptomatic patients meeting our inclusion criteria were found.

Symptomatic Intracranial Disease

Summary of RCT data: The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was the only RCT identified.[17]

- **Efficacy:** Based on Kaplan–Meier analysis, 1 year probabilities are summarized below:
    - **Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days:** This was the studies primary endpoint. Stenting was associated with a significantly higher probability of this composite outcome (20.0%) than medical therapy (12.2%), P = .009.
    - **Any stroke**: Probabilities were significantly higher in patients assigned to receive stents (22.3%) than in those assigned to intensive medical care (14.9%)
    - **Death:** The probabilities were not statistically different between groups
    - **Any stroke or death:** Probabilities at 1 year were 23.4% and 17.5% respectively for the stenting and medical therapy arms, a marginally insignificant result.
    - **Myocardial infarction:** The probabilities were not statistically different between treatment groups.
    - **Any major hemorrhage:** The probability of major hemorrhage was significantly greater in the stent group (9.0%) than in the medical treatment group (1.8%), p <0.001.
- **Safety:** This RCT was terminated early based on significantly higher risk of periprocedural (30 day) stroke or death in the stenting group (14.7%) compared with the medical management group (5.8%) and a futility analysis which demonstrated that no benefit in the stenting group would be shown had the trial been run to completion. The probability of any stroke was 14.7% for stenting and 5.3 % for medical therapy, (p = 0.03) RD of 9.4% (NNH 11), while there was no statistical differences in death between the groups.

Summary of nonrandomized studies: No nonrandomized comparative studies were found so no conclusions regarding comparative effectiveness or safety can be made. Five prospective case series met the inclusion criteria.[1,9,23,32,61] The longest follow-up was an average of 22 months.

- **Longer term effectiveness:** The risks of stroke and for any stroke or death by longest follow-up were lower than those reported in the RCT. Risk of in-stent restenosis ranged from 7.5%-32.3% with the majority reported as being asymptomatic.
- **Safety:**
  - For 30 day periprocedural safety outcomes, risks for stroke and any stroke or death were lower than those reported in the RCT and risk of death was similar.
  - Reported complications included access site complications (11.4%) stent thrombosis (0%–3.1%) and transient vasospasm (1.6%–11.4%). Vessel dissection/perforation occurred in 0%–6.4% across four studies.

Key Question 3. What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?

Safety in Asymptomatic Patients

Summary of RCT data

CAS versus medical therapy alone: No RCTs evaluated adverse events and complications for CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis

CAS compared with CEA: Two RCTs (CREST, Kentucky) provided data comparing CAS with medical therapy to CEA with medical therapy during the peri-procedural timeframe.[12,54]

- **Any periprocedural stroke:** Across two RCTs, risk of periprocedural stroke was slightly higher, though not statistically significant, for CAS compared to CEA; however, in one RCT no stroke events were reported in either treatment group.
- **Periprocedural death:** In 2 RCTs no deaths were reported during the periprocedural period.
- **Periprocedural stroke or death:** The risk of stroke or death was 2.5% for CAS and 1.4% for CEA based on the CREST study. The difference was not statistically significant.
- **Periprocedural myocardial infarction (MI):** In asymptomatic patients, in one RCT (CREST) there was a statistically non-significant lower risk of periprocedural MI for CAS compared to CEA.
- **Periprocedural cranial nerve palsy:** Risk of periprocedural cranial nerve palsy was significantly lower for CAS compared to CEA in one RCT; another reported no events in either treatment arm. RD = -3.9% across studies.

- **Periprocedural bleeding Complications:** In one RCT (CREST) there were no significant difference in risks of periprocedural bleeding complications (bleeding event requiring transfusion, hematoma requiring treatment, retroperitoneal hemorrhage, moderate or minor bleeding) between CAS and CEA; however, there was a statistically significant decrease in risks of surgical wound complications (hematoma requiring treatment and other complications) among CAS compared to CEA .

Summary of nonrandomized comparative studies

CAS versus medical therapy alone: One small, retrospective, single-center cohort study, Bosiers et al. 2005,[10] reported 30-day stroke or death rates. No statistically significant difference was reported between those who received CAS versus medical therapy alone. This study was considered to be at a moderately high risk of bias.

CAS compared with CEA: Periprocedural outcomes following CAS and medical therapy compared with CEA and medical therapy were reported in seven cohorts studies[10,15,18,30,35,41,62] and three registries.[33,39,48] All cohort studies were considered to be at moderately high risk of bias. For the registries, one was considered to be at a moderately low risk of bias and reported in-hospital outcomes,[48] one a moderately high risk of bias,[33] and the third at a high risk of bias.[39]

- **Any periprocedural stroke:** Across five small cohort studies (1 prospective and 4 retrospective), there were no statistical differences between treatment groups in the risk of periprocedural stroke. Confidence intervals were large and overlapped across studies. Across two large prospective registry studies, only one reported a statistically significant difference favoring CEA at 30 days.
- **Periprocedural death:** No statistical differences in risk of death were seen across four small cohort studies. One of the two included prospective registry studies reported a statistically significant greater risk of death at 30 days following CAS compared with CEA while the second study, which reported in-hospital events, failed to reach statistical significance.
- **Periprocedural stroke or death:** Across six cohort studies, no statistical difference between groups was reported for this composite outcome. One of two included registries reported a statistically significant increased risk of periprocedural stroke or death at 30 days in persons receiving CAS compared with CEA (confidence intervals were large), while the other larger registry reported much lower in-hospital risks for both groups and failed to find a statistical difference. The risk of periprocedural stroke or death following CAS was less than 3% in six of the eight studies.
- **Periprocedural myocardial infarction (MI):** No statistical differences in MI risk were seen across five studies.
- **Periprocedural ipsilateral stroke:** No statistical difference between groups in the risk of in-hospital ipsilateral stroke was found as reported by one large prospective registry.

- **Periprocedural transient ischemic attack (TIA):** One small retrospective cohort study and one large prospective registry that reported in-hospital events found no significant differences in the risk of periprocedural TIA between CAS and CEA.
- **Periprocedural cranial nerve palsy:** Across two retrospective cohort studies and one large prospective registry (in-hospital data), no significant differences in the risk of cranial nerve palsy were reported following CAS compared with CEA.
- **Periprocedural bleeding complications:** The risk of hematoma was reported by two retrospective cohort studies with no significant differences between treatment groups; however, in the smaller of the two cohorts, the risk following CAS was twice that seen following CEA (RD = 4.1%).
- **Intracranial hemorrhage (ICH):** Administrative data provided the only evidence for this outcome. As reported by two administrative database studies, the incidence of ICH was rare in both groups; however, the risk was six times greater following CAS compared with CEA.
- **Other complications:** Administrative data provided the only evidence for these outcomes. Unspecified cardiac complications were reported by three administrative database studies, two of which reported a marginally significant increased risk following CAS while the third administrative study found no difference between the treatment groups. The risk of venous thromboembolism was reported by one administrative study with no statistically significant difference between groups.

Safety in Symptomatic Patients

Summary of RCT data

CAS versus medical therapy alone: No RCTs comparing CAS and medical therapy with medical therapy alone in symptomatic patients were identified.

CAS compared with CEA: For the comparison of CAS and medical therapy with CEA and medical therapy, a total of ten studies from eight RCTs reported on various outcomes during the periprocedural period.[3,11,19,20,28,43,44,47,54,55]

- **Any periprocedural stroke:** Across six RCTs, risk of periprocedural stroke was significantly greater for CAS compared to CEA (Pooled RD: 3.39%, 95% CI .15%, 6.6%). This difference in risk suggests that for every 30 persons treated, there will be one additional stroke for CAS compared with CEA. In analysis excluding older studies (which enrolled patients prior to 2000), studies with 10 or fewer patients per arm and studies that did not use embolic protection devices, pool risk difference remained significant favoring CEA (RD: 2.88%, 95% CI: 1.3, 4.44, NNH 35, 95% CI 23, 75) across for studies. This estimate is reflected in the evidence tables below.

- **Periprocedural death:** Across four RCTs, the rates of periprocedural death ranged from 0% to 1.3% for CAS and 0.5% to 2.0% for CEA. There was no difference in risk of periprocedural death between CAS and CEA in any individual RCT, nor when studies were combined in a pooled analysis.
- **Periprocedural stroke or death:** The risk of stroke or death was 7.1% for CAS and 4.1% for CEA based on pooled data across seven RCTs reporting this composite, neither of which fell below 6%. Three of the four largest RCTs reported significant increases in risk of stroke or death for CAS compared to CEA. In meta-analysis of seven RCTs, the RD of 2.75%, 95% CI -0.39%, 5.88% was not statistically significant; however, there was considerable heterogeneity in this analysis. Analyiss excluding older, small studies and those which did not use EPDs resulted a pooled RD of 3.1%, 95% CI 1.4%, 4.7%); Number needed to harm was 33 (94% CI 21, 70) as reflected in the evidence table below.
- **Periprocedural myocardial infarction (MI):** Across four RCTs, periprocedural MI in individual studies ranged from 0.4% to 1.0% for CAS and 0.6% to 2.3% for CEA. There were no differences in risk between CAS and CEA in any individual study in symptomatic patients, nor when studies were combined in a pooled analysis.
- **Periprocedural ipsilateral stroke:** In pooled estimates across three studies, there was a suggestion of an increased risk of ipsilateral stroke for CAS compared to CEA (RD = 4.47% (`1.98%, 10.91%); however, it was not statistically significant and confidence intervals were wide. Sensivity analysis removing an older study which did not use embolic protection yielded a risk difference of 2.37% (95% CI 0.42%, 4.3%) corresponds to a NNH of 42.
- **Periprocedural fatal, major or disabling stroke:** Across five RCTs contributing data for this composite endpoint, the pooled risk difference between treatment groups and not statistically significant (RD: 0.88%, 95% CI -0.39%, 2.15%).
- **Periprocedural cranial nerve palsy:** In five RCTs, risk of cranial nerve injury or palsy was lower for CAS (0% to 1.1%) compared to CEA (2.3% to 7.8%). Three of the largest RCTs reported a significant reduction in risk for CAS compared with CEA. In pooled estimates risk of cranial nerve palsy was significantly lower among patients who received CAS compared with those having CEA (RD: -5.19%, 95% CI -4.14, -6.24).
- **Periprocedural hematoma:** In four RCTs, periprocedural rates of "severe hematoma requiring treatment" ranged from 0.4% to 5.7% for CAS, and from 0.8% to 2.0% for CEA treatment groups. There was no difference in risk between CAS and CEA treatment groups.

Summary of nonrandomized comparative studies

CAS versus medical therapy alone: No nonrandomized comparative studies evaluating periprocedural outcomes following CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS compared with CEA: Periprocedural outcomes following CAS and medical therapy compared with CEA and medical therapy were reported in a total of seven cohort studies[10,15,18,30,34,35,62] and three registries.[33,39,48] All cohort studies were considered to be at moderately high risk of bias. For the registries, one was considered to be at a moderately low risk of bias and reported in-hospital outcomes only,[48] one a moderately high risk of bias,[33] and the third at a high risk of bias.[39]

- **Any periprocedural stroke:** No significant differences in the risk of any stroke between groups were reported across five cohort studies whereas data from two large prospective registry studies (one reporting in-hospital events) consistently showed a statistical increased risk following CAS.
- **Periprocedural death:** No statistical differences in risk of death were seen across three small cohort studies. Both of the included prospective registry studies reported a higher risk of death following CAS compared with CEA at 30 days and during the in-hospital period (wide confidence interval in the latter study suggests instability of the estimate).
- **Periprocedural stroke or death:** Across five cohort studies, no statistical difference between groups was reported for this composite outcome. Wide confidence intervals suggest instability of estimates. One of two included prospective registries reported an increased in-hospital risk of periprocedural stroke or death in persons receiving CAS compared with CEA, while the other larger registry reported similar risks for both groups at 30 days. The risk of periprocedural stroke or death following CAS was less than 6% in six of the seven studies.
- **Periprocedural myocardial infarction (MI):** No statistical differences in MI risk were seen across two cohort studies and two prospective registries.
- **Periprocedural ipsilateral stroke:** CAS was associated with a three-fold greater risk of ispilateral stroke compared with CEA during the in-hospital period as reported in one large prospective registry.
- **Transient ischemic attack (TIA):** No significant differences in the risk of TIA following CAS versus CEA were reported by one small retrospective cohort study and one large registry study reporting in-hospital data only.
- **Periprocedural cranial nerve palsy:** Across one retrospective cohort study and one large prospective registry (in-hospital data), no significant differences in the risk of cranial nerve palsy were reported following CAS compared with CEA.
- **Periprocedural bleeding complications:** The risk of hematoma was reported by one retrospective cohort study with no significant differences found in patients who undergone CAS compared with CEA.
- **Intracranial hemorrhage (ICH):** Administrative data provided the only evidence for this outcome. The risk of any ICH was five and half times greater following CAS compared with CEA. Risks following CAS were also greater for the subcategories of acute ICH and subarachnoid hemorrhage, but were not significantly different between

groups when considering nontraumatic extradural hemorrhage and unspecified hemorrhage.

- **Other complications:** Administrative data provided the only evidence for this outcome. Risk of unspecified cardiac complications and venous thromboembolism did not differ between CAS and CEA as reported by one administrative database study.

Key Question 4. Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other comorbidities, ethnicity, or disability)?

Differential Efficacy and Safety in Asymptomatic patients

CAS versus medical therapy alone: No RCT data were available. One retrospective cohort study evaluated the differential effectiveness of CAS versus medial therapy alone for severity of baseline stenosis.[53]

- ***Severity of ipsilateral stenosis*:**
  - **Effectiveness:**
    - *Stroke (median 25 months):* Data from one non-randomized retrospective study suggested that stroke risk increased with the degree of stenosis in the medical therapy group but remained stable in those treated with CAS.

CAS versus CEA: One RCT (CREST) evaluated whether patient sex conferred differential safety outcomes[29]. In addition, one prospective cohort study,[30] one registry study[33] and five administrative database studies[7,24,36,46,60] are included in this report. Data from one trial of asymptomatic high risk patients were also included, however, no direct comparison with average risk patients could be made.[25,58]

- ***Age***. No RCT data were available. Data from one registry study were available:
  - **Safety:** Age (< 65 versus ≥ 65) did not modify the treatment effect of CEA versus CAS in asymptomatic patients for the following outcomes:
    - *Periprocedural death*
    - *Periprocedural stroke*
    - *Periprocedural MI*
    - *Periprocedural death, stroke, or MI (composite)*

- ***Sex*:** Data from one RCT (CREST) were available:

- **Safety:** Sex did not modify the treatment effect of CEA versus CAS in asymptomatic patients for the following outcomes:
  - *Periprocedural stroke*
  - *Periprocedural stroke or death (composite)*
  - *Periprocedural MI*
  - *Periprocedural death, stroke, or MI (composite)*

- **Efficacy:** Sex did not modify the treatment effect of CEA versus CAS in asymptomatic patients for the following outcomes:
  - *Ipsilateral stroke (4 years)*
  - *Ipsilateral stroke or death (composite) (4 years).*

- ***High surgical risk****:* Data for asymptomatic patients were available from the SAPPHIRE trial of high risk patients, however, no direct comparison with average risk patients could be made and therefore evaluation of differential efficacy is not possible:
  - **Efficacy:**
    - *Ipsilateral stroke or death (composite) (1 year):* lower rates following CAS versus CEA.
    - *Ipsilateral stroke or death (3 years):* similar stroke risk regardless of treatment group.
    - *Stroke (3 years):* similar stroke risk regardless of treatment group.

Differential Efficacy and Safety in Symptomatic patients

CAS versus CEA:

Differential efficacy, effectiveness and safety were evaluated. Patient-level data were available for age and sex for six trials (Leicester, EVA-3S, SPACE, BACASS, ICSS, and CREST) as reported in the Bonati systematic review.[8] Data from four individual trials were also included (EVA-3S, SPACE, ICSS, and CREST).[19,20,27,29,44,56] In addition, one prospective cohort study,[30] one registry study[33] and four administrative database studies[7,24,46,51] were included in this report. Data from one trial of symptomatic high risk patients were also included, however, no direct comparison with average risk patients could be mad, thus no evaluation of differential effectiveness is possible.[25,58]

- ***Age:***
  - **Safety:** A meta-analysis of patient-level safety data from five RCTs suggested:
    - *Periprocedural stroke or death (composite):* Age (< 70 versus ≥ 70 years) may modify this outcome such that in patients 70 years of age and older CEA is favored while those under 70 years of age had similar results

regardless of treatment group. Sensitivity analysis across three studies (excluding older, small studies and those which did not use embolic protection) more strongly indicates that age modifies the effect of treatment.

- **Efficacy:** Efficacy data from three trials were available and suggested:
  - *Death, stroke, or MI (composite) (120 days):* Age (< 70 versus ≥ 70 years) did not modify treatment outcome (ICSS trial).
  - *Ipsilateral stroke or death (composite) (2 years):* Age (< 68 versus ≥ 68 years) significantly modified treatment outcome such that patients 68 years of age and older had significantly better outcomes following CEA, while those under 68 years of age had similar outcomes regardless of treatment received (SPACE trial).
  - *Ipsilateral stroke (4 years):* Age (< 70 versus ≥ 70 years) did not modify treatment outcome (EVA-3S trial).

- ***Sex:***
  - **Safety:** Data from a meta-analysis of patient-level data from six RCTs were available. Additional data from one RCT was available.
    - *Periprocedural stroke or death (composite):* Sex did not significantly modify treatment outcome according to a meta-analysis of patient-level safety data from six RCTs and sensivity analyses across 4 studies.
    - *Periprocedural stroke:* Sex did not significantly modify treatment outcome (CREST trial).
    - *Periprocedural MI:* Sex did not significantly modify treatment outcome (CREST trial).
    - *Periprocedural death, stroke, or MI (composite:)* Sex significantly modified treatment effect such that females had significantly lower rates of this outcome when treated with CEA versus CAS, while in males there was no difference between treatment groups (CREST trial).
  - **Efficacy:** Data from three trials were available. Sex did not modify any of the following treatment outcomes:
    - *Death, stroke, or MI (composite) (120 days):* (ICSS trial)
    - *Ipsilateral stroke or death (composite) (2 years):* (SPACE trial)
    - *Ipsilateral stroke (4 years):*(combined data from EVA-3S, CREST)
    - *Stroke or death (4 years):* (CREST trial)

- ***Diabetes:***
    - **Efficacy**: Data from two trials suggested that diabetes status did not modify treatment outcome in terms of:
        - *Death, stroke, or MI (composite) (120 days):* (ICSS trial).
        - *Ipsilateral stroke (4 years):* (EVA-3S trial).

- ***Type of symptomatic qualifying event****:*
    - **Safety:** Data from one trial suggested that type of symptomatic qualifying event (ie., stroke, transient ischemic attack, ocular, or multiple events) did not modify treatment outcome in terms of:
        - *Periprocedural ipsilateral stroke or death (composite):* (CREST trial).
        - *Periprocedural stroke*: (CREST trial).

    - **Efficacy:** Data from two trials suggested that type of symptomatic qualifying event (ie., stroke, transient ischemic attack, ocular, or multiple events) did not modify treatment outcome in terms of:
        - *Ipsilateral stroke or death (composite) (2 years):* (SPACE trial).
        - *Ipsilateral stroke (4 years):* (EVA-3S trial).

- ***Severity of ipsilateral stenosis****:*
    - **Efficacy:** Data from three trials suggested that severity of stenosis in the ipsilateral artery did not modify treatment outcome in terms of:
        - *Death, stroke, or MI (composite) (120 days):* (ipsilateral stenosis of 50-69% versus 70-99%) (ICSS trial).
        - *Ipsilateral stroke or death (composite) (2 years):* (ipsilateral stenosis of < 70% versus ≥ 70%) (SPACE trial).
        - *Ipsilateral stroke (4 years):* (ipsilateral stenosis of < 90% versus ≥ 90%) (EVA-3S).

- ***Severity of contralateral stenosis****:*
    - **Safety:** Data from one trial suggested that severity of contralateral stenosis did not modify treatment outcome in terms of:
        - *Periprocedural ipsilateral stroke or death (composite):* (contralateral stenosis of < 70% versus 70–99%) (SPACE trial).

    - **Efficacy:** Data from three trials suggested that severity of stenosis in the contralateral artery did not modify treatment outcome in terms of:
        - *Stroke, death, or MI (composite) (120 days):* (contralateral stenosis of 0-49% versus 50–69% versus 70–99% versus 100%) (ICSS trial).

        - *Ipsilateral stroke or death (composite) (2 years):* (contralateral stenosis of < 70% versus 70–99% versus 100%) (SPACE trial).
        - *Ipsilateral stroke (4 years):* (contralateral stenosis of < 70% versus 70–100%) (EVA-3S trial).

- ***Time to treatment****:*
    - **Efficacy:** Data from two trials suggested that time to treatment (< 14 days versus ≥ 14 days) did not modify treatment outcome in terms of:
        - *Stroke, death, or MI (composite) (120 days):* (ICSS trial).
        - *Ipsilateral stroke (4 years):* (EVA-3S trial).

- ***Hypertension****:*
    - **Efficacy:** Data from two trials were available:
        - *Stroke, death, or MI (composite) (120 days):* Baseline hypertensive status modified the treatment effect such that patients without treated hypertension favor CEA while those without treated hypertension have similar outcomes regardless of treatment group (ICSS trial).
        - *Ipsilateral stroke (4 years):* Baseline hypertensive status did not modify treatment outcome (EVA-3S trial).

- ***Smoking status****:*
    - **Efficacy:** Data from one trial suggested that baseline smoking status did not modify treatment outcome in terms of:
        - *Ipsilateral stroke (4 years):* (EVA-3S).

- ***High surgical risk****:* Data from the SAPPHIRE trial in high risk surgical patients were available; no comparison to patients with average surgical risk was made. Data were also available from one prospective nonrandomized comparative study.
    - **Safety:** Regardless of treatment received, patients had similar risk of:
        - *Periprocedural stroke, death, or MI (composite):* (SAPPHIRE trial).
        - *Periprocedural non-disabling stroke:* Data from one nonrandomized prospective cohort study suggested that CEA risk grades did not modify outcome in terms of periprocedural non-disabling stroke.

    - **Efficacy:** Regardless of treatment received, patients had similar risk of:
        - *Ipsilateral stroke or death (composite) (1 year):* (SAPPHIRE trial).
        - *Ipsilateral stroke or death (composite) (3 years):* (SAPPHIRE trial).
        - *Stroke (3 years):* (SAPPHIRE trial).

Key Question 5. What is the evidence of cost-effectiveness of CAS compared with other treatment options (medical therapy, CEA) in the short-term and the long term?
No full economic studies comparing the cost effectiveness of CAS with medical therapy versus medical therapy alone or comparing intracranial vessel stenting and alternative treatments were found.

CAS versus CEA: Five cost-utility studies comparing carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA) met the inclusion criteria[31,40,45,57,59]: One study was of asymptomatic patients, two studies focused on symptomatic patients and two studies provided a subgroup analysis for both symptomatic statuses.

Asymptomatic patients (overall strength of evidence, low):

- Across two cost utility studies, the evidence suggested CAS to be a plausible, but not verifiably superior treatment for high surgical risk patients. Over 1-year time horizon studies reported ICERs of $49,514 and $67,891. Primary limitations of these studies should, however, be considered and relate to methods for parameter estimation and concerns regarding the reliability extrapolating beyond the last follow-up of the SAPPHIRE trial should be noted. Variation in methodology for determining patient utility estimates across studies contributed to potential discrepancy in the results between the studies and concerns regarding the validity of the utilities used.
- When focusing on patients with standard surgical risk, CEA was found to be slightly less expensive and provided slightly more quality-adjusted life years (QALYs) in one study. In that sense, it CEA was the preferred treatment given commonly assumed cost-effectiveness thresholds.

Symptomatic patients (overall strength of evidence, low):

- Evidence across four cost-utility studies indicated that CEA tended to be more cost-effective than CAS in symptomatic patients. Two out of the four studies examining symptomatic patients found there to be insufficient evidence to strongly favor one treatment method over the other.
- In two studies focused on symptomatic patients, one concluded that CAS was at best non-inferior in terms of clinical outcomes, however, its long-run cost savings failed to compensate for the greater upfront procedural costs. The second study found CEA to be both more effective and less costly for symptomatic patients (CEA dominated CAS). The first study authors chose not to report a specific ICER due to variability in models when different data sources were used.
- In the two studies that presented sub-group results for symptomatic patients, CAS was not found to be an economically attractive alternative. CEA dominated CAS in one and was preferred in the other.

Summary and overall strength of evidence

The tables below summarize the overall quality (strength) of evidence (SoE) for key findings for the primary outcomes based on the highest quality data available. Additional information on lower quality studies is available in the full report.

Key Question 1: What is the evidence for efficacy and effectiveness?

Asymptomatic

Randomized controlled trials (RCTs)

Quality of evidence summary for Key Question 1: In asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Asymptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)† RR (95% CI)**	**Favors**
Any stroke	4 years 1 RCT N = 85	Low	0.0% (0/43)	0/0% (0/42)	Not estimable	NA
Ipsilateral stroke	4 years 2 RCTs N = 1181 N = 85	Low	1.5% (9/584) 0.0% (0/43)	0.9% (5/582) 0.0% (0/43)	RD = 0.7 (-0.57, 1.9) RR = 1.78 (0.60, 5.28) Not estimable	NS NA
Any periprocedural stroke or death or post-procedural ipsilateral stroke	4 years 1 RCT N = 1181	Low	4.5% (24/594)	2.7% (13/587)	RD = 1.9 (-0.5, 4.3) HR = 1.9 (0.95, 3.7)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; NS: not statistically significant; RD: risk difference; RR: risk ratio.
*A total of 2 RCTs are represented in the table.
†A negative risk difference favors CAS and positive risk difference favors CEA

Nonrandomized comparative studies

Quality of evidence summary for Key Question 1: In asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative effectiveness of extracranial CAS and medical therapy compared with medical therapy alone.

KQ1: Asymptomatic CAS vs. medical therapy only			Treatment Groups		Effect Size	
Outcome	**Studies* N Follow-up (median)**	**Overall quality of evidence**	**CAS (%)†**	**Medical (%)†**	**Adjusted HR (95% CI)†**	**Favors**
Any stroke	1 retrospective registry N = 946 2.1 years	Low	9	11	0.5 (0.2, 0.9)	CAS
Death	1 retrospective registry N = 946 2.1 years	Low	20	32	0.7 (0.5, 0.9)	CAS
Any stroke or death	1 retrospective registry N = 946 2.1 years	Low	29	38	0.7 (0.5, 0.9)	CAS

CAS: carotid artery stenting; CI: confidence interval; HR: hazard ratio.

*A total of 1 nonrandomized study is represented in the table.

†Kaplan-Meier estimates for projected 5 years of follow-up. Authors conducted a propensity-score adjusted analysis with the following baseline clinical characteristics were entered into a multivariate probit model to define a propensity score: age, gender, body mass index, degree of carotid stenosis, diabetes, hypertension, hyperlipidemia, smoking, congestive heart failure, coronary artery disease, history of myocardial infarction, peripheral artery disease, concomitant malignancy, American Society of Anesthesiologists classification (I to IV), Asymptomatic Carotid Atherosclerosis Study eligibility, and the date of CAS to account for temporal trends during the study period.

Quality of evidence summary for Key Question 1: In asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative effectiveness of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Asymptomatic CAS vs. CEA			Treatment Groups		Effect Size	
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)† RR/HR (95% CI)**	**Favors**
Any stroke	1 prospective cohort N = 269 4 years	Insufficient	9.2	5.7	RD = -3.5 (-12.5, 3.2) RR = 1.6 (0.6, 4.2)	NS
	1 prospective registry‡ N = 1672 1.5 years	Low	3.8§	2.6§	Adjusted HR = 1.4 (0.8, 2.5)	NS
Death	1 prospective cohort N = 269 4 years	Insufficient	22.2	19.7	RD = -2.4 (-14.0, 8.5) RR = 1.1 (0.7, 1.9)	NS
	1 prospective registry‡ N = 1672 1.5 years	Low	7.4§	7.4§	Adjusted HR = 0.7 (0.5, 1.1)	NS
Any stroke or death	1 prospective cohort N = 269 4 years	Insufficient	25.8	23.2	RD = -2.6 (-14.7, 8.8) RR = 1.1 (0.7, 1.8)	NS
	1 prospective registry‡ N = 1672 1.5 years	Low	9.9§	8.9§	Adjusted HR = 0.9 (0.6, 1.3)	NS
MI	1 prospective cohort N = 269 4 years	Insufficient	7.9	10.1	RD = 2.2 (-7.1, 10.1) RR = 0.8 (0.3, 2.0)	NS
	1 prospective registry‡ N = 1672 1.5 years	Low	3.2§	4.8§	Adjusted HR = 0.6 (0.4, 1.1)	NS

KQ1: Asymptomatic CAS vs. CEA			Treatment Groups		Effect Size	
Outcome	Studies* N range Follow-up	Overall quality of evidence	CAS (%)	CEA (%)	RD % (95% CI)† RR/HR (95% CI)	Favors
Any periprocedural stroke or death or post-procedural ipsilateral stroke	1 prospective cohort N = 1518 2.8 years	Low	3.3**	2.5**	RR = 0.8 (0.5, 1.4)††	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NS: not statistically significant; RD: risk difference; RR: risk ratio.

*A total of 3 nonrandomized studies are represented in the table.

†A positive risk difference favors CAS and negative risk difference favors CEA.

‡Propensity score-matched analysis. The model included the following baseline characteristics: age, sex, race, documented transient ischemic attack, prior coronary artery bypass grafting, documented ischemic stroke, myocardial infarction, nitrates, beta blockers, calcium channel blockers, statins, angiotensin-converting enzyme (ACE)-inhibitors, diuretics, insulin, smoking, unstable/stable angina, diabetes, congestive heart failure, ACE/angiotensin receptor blocker, hypercholesterolemia, history of atrial fibrillation, and history of treated hypertension.

§Kaplan Meier rate estimates as reported by the authors.

**5 year Kaplan Meier rate estimates as reported by the authors.

††Calculated from raw data by the Agency for Healthcare Quality and Research (AHRQ).

Symptomatic

Randomized controlled trials (RCTs)

Quality of evidence summary for Key Question 1: In symptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Symptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	Studies* N range Follow-up	Overall quality of evidence	CAS (%)	CEA (%)	RD % (95% CI)† RR (95% CI)	Favors
Any stroke (excluding periprocedural)	4 months 1 RCT N = 1710	Moderate	0.8% (7/853)	0.9% (8/857)	RD = -0.11 (-0.99, 0.77) RR = 0.88 (0.32, 2.42)	NS
	2-4 years 2 RCTs N = 1712	Moderate	3.5% (30/866)	3.5% (30/846)	RD‡ = -0.08 (-1.82, 1.66) RR‡ = 0.98 (0.59, 1.61)	NS

KQ1: Symptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)† RR (95% CI)**	**Favors**
Ipsilateral stroke (excluding periprocedural)	4 months 1 RCT N = 1710	Moderate	0.7% (6/853)	0.5% (5/857)	RD = 0.12 (-0.63, 0.87) RR = 1.20 (0.37, 3.93)	NS
	2-5.4 years 4 RCTs N = 3120	Moderate	2.0% (31/1577)	1.9% (30/1543)	RD‡ = -0.01 (-1.36, 1.34) RR‡ = 0.97 (0.55, 1.73)	NS
Death	4 months 1 RCT N = 1710	Moderate	2.3% (19/853)	0.8% (7/857)	RD = 1.37 (0.23, 2.51) RR = 2.69 (1.14, 6.36)	CEA
	2-5.4 years 5 RCTs (including periprocedural) N = 1934	Moderate	7.9% (77/975)	8.2% (79/959)	RD‡ = -0.10 (-2.17, 1.96) RR‡ = 0.97 (0.72, 1.30)	NS
	2-5.4 years 2 RCTs (excluding periprocedural) N = 1308	Moderate	4.1% (27/664)	3.7% (24/644)	RR‡ = 0.38 (-1.87, 2.64) RR‡ = 1.09 (0.64, 1.87)	NS
Any stroke or death (including periprocedural)	4-6 months 2 RCTs N = 527 N =1710	Moderate	11.8% (31/262) 8.5% (72/853)	9.8% (26/265) 4.7% (40/857)	RD = 1.65 (-3.17, 6.46) RR = 1.18 (0.72, 1.94) RD = 3.32 (1.13, 5.52) RR = 1.75 (1.20, 2.54)	NS CEA
	2-4 years 2 RCTs N = 124	Low	1.6% (1/63)	4.9% (3/61)	RD‡= -2.18 (-7.33, 2.96) RR‡ = 0.43 (0.07, 2.69)	NS
Any periprocedural stroke or death or post-procedural ipsilateral stroke	6 months 1 RCT N = 527	Moderate	10.2% (27//262)	4.2% (11/265)	RD = 5.36 (1.28, 9.43) RR = 2.34 (1.19, 4.63)	CEA
	2-5.4 years 5 RCTs N = 2728	Low	8.1% (112/13 81)	6.6% (89/1347)	RD‡ = 1.28 (-1.64, 4.19) RR‡ = 1.20 (0.89, 1.62)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NR: not reported; NS: not statistically significant; RD: risk difference; RR: risk ratio.

NOTE: CAS and CEA patients received different anti-platelet interventions in two trials (EVA, SPACE)

*A total of 7 RCTs are represented in the table.

†A negative risk difference favors CAS and positive risk difference favors CEA

‡Effect size estimates from pooled meta-analysis with weighting based on sample size; data for n/N are numbers of total events/total number of patients

Nonrandomized comparative studies

Quality of evidence summary for Key Question 1: In symptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative effectiveness of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Symptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)† RR (95% CI)**	**Favors**
Any stroke	1 prospective cohort N = 128 4 years	Insufficient	7.2	17.8	RD = 10.7 (-3.2, 22.0) RR = 0.4 (0.1, 1.3)	NS
Death	1 prospective cohort N = 128 4 years	Insufficient	10.4	24.9	RD = 14.5 (-2.0, 28.3) RR = 0.4 (0.2, 1.2)	NS
Any stroke or death	1 prospective cohort N = 128 4 years	Insufficient	12.4	33.5	RD = 20.8 (4.0, 34.5) RR = 0.4 (0.2, 0.9)	CAS
MI	1 prospective cohort N = 128 4 years	Insufficient	7.1	12.6	RD = 5.4 (-11.4, 17.6) RR = 0.6 (0.1, 2.6)	NS
Any periprocedural stroke or death or post-procedural ipsilateral stroke	1 prospective cohort N = 684 2.8 years	Low	4.9‡	8.7‡	NR	NS§

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NR: not reported; NS: not statistically significant; RD: risk difference; RR: risk ratio.

*A total of 2 nonrandomized studies are represented in the table.

†A positive risk difference favors CAS and negative risk difference favors CEA.

‡5 year Kaplan Meier rate estimates as reported by the authors.

§As reported by the authors, "rates were similar between groups" (P = .07).

Key Question 2: What is the evidence of short- and long-term comparative efficacy and of safety (peri-procedural, 30-day outcomes) in persons with atherosclerotic intracranial artery stenosis?

Asymptomatic

None

Symptomatic

Efficacy

Quality of evidence summary for Key Question 2: In persons with atherosclerotic intracranial artery stenosis what is the evidence of short- and long-term comparative efficacy of CAS and aggressive medical therapy compared with medical therapy alone.

KQ2: Efficacy of intracranial artery stenting versus medical therapy			Treatment Groups Probability (%) 1 year (95% CI) Patient Events (n/N)		Effect size*	
Outcome	**Studies† N range Follow-up**	**Overall quality of evidence**	**CAS**	**Medical**	***P*-value‡**	**Favors**
Any stroke	1 RCT N = 451 1 year	Low	22.3 (17.2–28.7) (50/224)	14.9 (10.6–20.7) (32/227)	.03	Medical RD 7.4% NNH 13
Death	1 RCT N = 451 1 year	Low	3.4 (1.6–7.2) (7/224)	4.1 (2.0–8.5) (7/227)	.95	NS
Any stroke or death	1 RCT N = 451 1 year	Low	23.4 (18.1–29.8) (52/224)	17.5 (12.8–23.6) (37/227)	.06	NS
Study's Primary Outcome: Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days	1 RCT N = 451 1 year	Low	20.0 (15.2–26.0) (46/224)	12.2 (8.4–17.6) (26/227)	.009	Medical RD 7.8% NNH 13
Myocardial infarction	1 RCT N = 451 1 year	Low	2.2 (0.8–5.8) (5/224)	4.0 (1.9–8.4) (7/227)	.60	NS

KQ2: Efficacy of intracranial artery stenting versus medical therapy			Treatment Groups Probability (%) 1 year (95% CI) Patient Events (n/N)		Effect size*	
Outcome	**Studies† N range Follow-up**	**Overall quality of evidence**	**CAS**	**Medical**	***P*-value‡**	**Favors**
Any major hemorrhage	1 RCT N = 451 1 year	Low	9.0 (5.9–13.5) (22/224)	1.8 (0.7–4.8) (5/227)	< .001	Medical RD 7.2% NNH 14

CAS: carotid artery stenting; CI: confidence interval; NS: not statistically significant.

*Authors do not report effect size; probabilities and p-values are provided.

†Only 1 RCT (SAMMPRIS trial) is represented in the table.

‡The p-value is for the comparison, with the use of the log-rank test, of the time-to-event curves for the two treatment groups for each of the specified adverse events.

Safety (Periprocedural, 30-day outcomes)

Quality of evidence summary for Key Question 2: In persons with atherosclerotic intracranial artery stenosis what is the evidence of the safety (peri-procedural, 30 day outcomes) of CAS and aggressive medical therapy compared with medical therapy alone.

KQ2: Safety of intracranial artery stenting versus medical therapy			Treatment Groups Probability (%) 1 year (95% CI) Patient Events (n/N)		Effect size*	
Outcome	**Studies† N range**	**Overall quality of evidence**	**CAS**	**Medical**	***P*-value‡**	**Favors**
Any stroke	1 RCT N = 451	Low	14.7 (10.7–20.1) (33/224)	5.3 (3.1–9.2) (12/227)	.03	Medical RD 9.4% NNH 11
Death	1 RCT N = 451	Low	2.2 (0.9–5.3) (5/224)	0.4 (0.1–3.1) (1/227)	.95	NS
Any stroke or death	1 RCT N = 451	Low	14.7 (10.7–20.1) (33/224)	5.8 (3.4–9.7) (13/227)	.009	Medical RD 8.9% NNH 11
Myocardial infarction	1 RCT N = 451	Low	0.5 (0.1–3.2) (NR)	1.3 (0.4–4.1) (NR)	.60	NS
Any major hemorrhage	1 RCT N = 451	Low	8.0 (5.1–12.5) (NR)	0.9 (0.2–3.5) (NR)	< .001	Medical RD 7.9% NNH 13

CAS: carotid artery stenting; CI: confidence interval; NS: not statistically significant.

*Authors do not report effect size; probabilities and p-values are provided.

†Only 1 RCT (SAMMPRIS trial) is represented in the table.

‡The p-value is for the comparison, with the use of the log-rank test, of the time-to-event curves for the two treatment groups for each of the specified adverse events.

Key Question 3: What is the evidence for safety (peri-procedural, 30-day outcomes)?

Asymptomatic

Randomized controlled trials (RCTs)

Quality of evidence summary for Key Question 3: In asymptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Asymptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)† RR range (95% CI)**	**Favors**
Any stroke	2 RCTs N = 1191 N = 85	Moderate	2.5% (15/594) 0.0% (0/43)	1.4% (8/597) 0.0% (0.42)	RD = 1.2 (-0.4,2.7) RR = 1.9 (0.8, 4.4) Not estimable	NS
Death	1 RCT N = 85	Low	0.0% (0/43)	0.0% (0/42)	Not estimable	NA
Any stroke or death	2 RCTs N = 1191 N = 85	Moderate	2.5% (15/594) 0.0% (0/43)	1.4% (8/597) 0.0% (0/42)	RD = 1.2 (-0.4,2.7) RR = 1.9 (0.8, 4.4) Not estimable	NS NA
MI	1 RCT N = 1191	Moderate	1.2% (7/594)	2.2% (13/597)	RD = -1.0 (-2.5, 0.4) RR = 0.6 (0.2, 1.4)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; RD: risk difference; RR: risk ratio.

*A total of 2 RCTs are represented in the table.

†A negative risk difference favors CAS and positive risk difference favors CEA.

Nonrandomized comparative studies

Quality of evidence summary for Key Question 3: In asymptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS compared with medical therapy alone.

KQ3: Asymptomatic CAS vs. medical therapy only			Treatment groups		Effect size	
Outcome	**Studies N**	**Overall quality of evidence**	**CAS (%)**	**Medical (%)**	**RD % (95% CI)* RR (95% CI)**	**Favors**
Any stroke or death	1 retrospective cohort N = 75	Insufficient	1.7	0	RD = 1.7 (-9.0, 17.7) RR = not estimable	NS

CAS: carotid artery stenting; CI: confidence interval; NS: not statistically significant; RD: risk difference; RR: risk ratio.

*A positive risk difference favors CAS and negative risk difference favors CEA.

Quality of evidence summary for Key Question 3: In asymptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Asymptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)† RR range (95% CI)**	**Favors**
Any stroke	5 cohorts (2 pro, 3 retro) N, 87–269	Insufficient	0–8.5	1.8–2.1	RD = -6.3 to 2.0 CI low range (-16.4, -3.9) CI high range (3.8, 10.5) <u>4 studies</u> RR = 0.5–4.0 CI low range (0.1, 0.5) CI high range (4.9, 32.9) <u>1 study</u> RR = not estimable	NS
	2 prospective registries N = 5268, 30 Day)	Low	3.2 (59/1850)	1.7 (58/3418)	RD = -1.5 (-2.5 to -0.6) RR = 1.88 (1.31-2.69	1 CEA
	N = 5316 (in hospital)	Low	0.7 (2/273)	0.7 (35/5043)	RD = 0 (-1.9 to 0.6) RR = 1.06 (0.26-4.37)	1 NS (in hospital)
Death	4 cohorts (1 pro, 3 retro) N, 87–269	Insufficient	0–1.1	0–2.0	RD = -0.4 to 2.0 CI low range (-9.4, -2.9) CI high range (2.2, 10.5) <u>1 study</u>	NS

KQ3: Asymptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)† RR range (95% CI)**	**Favors**
					RR = 1.6 (0.1, 24.6) 3 studies RR = not estimable	
	2 prospective registries N = 5268 (30 day) N = 5316 (in hospital)	Low Low	1.6 (29/1850) 0.4 (1/273)	0.7 (25/3418) 0.2 (10/5043)	RD = -0.8 (-1.6 to -0.2) RR = 2.14 (1.26-3.65) RD = -0.2 (-1.8 to 0.2) RR = 1.85 (0.24-14.38)	1 CEA 1 NS (in hospital
Any stroke or death	6 cohorts (3 pro, 3 retro) N, 87–1518	Insufficient	0–3.8	0–4.0	RD = -1.7 to 2.0 CI low range (-9.0, -2.2) CI high range (0.7, 14.5) 5 studies RR = 0.6–1.5 CI low range (0.04, 0.71) CI high range (3.1, 23.9) 1 study RR = not estimable	NS
	2 prospective registries N = 1416 (30 days) N = 5316 (in hospital	Insufficient Low	10.9 (11/101) 0.7 (2/273)	4.0 (53/1315) 0.9 (45/5043)	RD = -6.9 (-14.5 to -2.0) RR = 2.70 (1.46-5.01) RD = 0.2 (-1.8 to 0.8) RR = 0.82 (0.20-3.37)	1 CEA 1 NS (in hospital)
Ipsilateral stroke	1 prospective registry N = 5316 (in hospital)	Low	0.4	0.6	RD = 0.2 (-1.5 to 0.6) RR = 0.6 (0.1-4.5)	NS
MI	3 cohorts (1 pro, 2 retro) N, 87–269	Insufficient	0–1.1	0–1.4	RD = 0 to 1.2 CI low range (-9.4, -2.7) CI high range (3.9, 7.1) 2 studies RR = 0.3–1.2 CI low range (0.01, 0.07) CI high range (8.5, 9.4) 1 study RR = not estimable	NS
	2 prospective registries N = 5268 (30 day) N = 5316 (in hospital)	Low Low	1.1 (20/1850) 0.7 (2/273)	1.0 (35/3418) 1.0 (50/5043)	RD = -0.1 (-0.7 to 0.5) RR = 1.06 (0.61-1.82) RD = 0.3 (-1.7 to 0.9) RR = 0.74 (0.18-3.02)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR: risk ratio.

*A total of 9 nonrandomized studies are represented in the table.

†A positive risk difference favors CAS and negative risk difference favors CEA.

Symptomatic

Randomized controlled trials (RCTs)

Quality of evidence summary for Key Question 3: In symptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Symptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies* N range**	**Overall quality of evidence**	**CAS† (% range)**	**CEA† (% range)**	**RD range, % (95% CI)‡ RR range (95% CI)**	**Favors**
Any stroke	4 RCTs§ N = 4754	Moderate	6.8% (163/2393)	4.0% (94/2361)	RD = 2.9 (1.3, 4.4) NNH = 35 (22, 75) RR = 1.7 (1.2, 2.5)	CEA
Death	4 RCTs N = 3530	Low	1.1% (19/1774)	0.7% (13/1756)	RD = 0.4 (-0.3, 1.0) RR = 1.4 (0.7, 2.9)	NS
Any stroke or death	4 RCTs§ N = 4754	Moderate	7.1% (171/2393)	4.1% (98/2361)	RD = 3.1 (1.4, 4.7) NNH = 33 (2, 70) RR = 1.8 (1.2, 2.6)	CEA
Ipsilateral stroke	3 RCTs N = 2923	Moderate	6.5% (96/1467)	3.8% (56/1456)	RD = 4.5 (-1.9, 10.9) RR = 1.8 (0.9, 3.4)	NS
Fatal, major or disabling stroke	5 RCTs N = 4764	Moderate	3.0% (73/2396)	2.1% (49/2368)	RD = 0.9 (-0.4, 2.2) RR = 1.5 (1.0, 2.1)	NS
MI	4 RCTs N = 3600	Moderate	0.6% (11/1813)	1.3% (23/1787)	RD = -0.4 (-1.0, 0.1) RR = 0.5 (0.2, 1.0)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; RD: risk difference; RR: risk ratio.

NOTE: CAS and CEA patients received different anti-platelet interventions in two trials (EVA, SPACE)

*A total of 6 RCTs are represented in the table.

† Effect size estimates from pooled meta-analysis with weighting based on sample size; data for n/N are numbers of total events/total number of patients

‡A negative risk difference favors CAS and positive risk difference favors CEA. Significance based on evaluation of risk difference

§Based on sensitivity analysis which excluded older, small studies and those which did not use embolic protection.

Nonrandomized comparative studies

Quality of evidence summary for Key Question 3: In symptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Symptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies N range**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
Any stroke	5 cohorts (2 pro, 3 retro) N, 75–155	Insufficient	2.9–10.0	2.4–7.2	RD = -7.1 to 2.6 CI low range (-22.9, -8.7) CI high range (2.5, 10.9) RR = 0.6–3.5 CI low range (0.1, 0.6) CI high range (3.0, 19.6)	NS
	2 prospective registries N = 3645 (30 day)	Low	6.1 (95/1547)	4.1 (85/2098)	RD = -2.1 (-3.6 to -0.7) RR = 1.52 (1.14-2.02)	CEA
	N = 2761 (in hospital)	Low	5.1 (8/156)	1.4 (37/2605)	RD = -3.7 (-8.4 to -1.1) RR = 3.61 (1.71-7.62)	
Death	3 cohorts (1 pro, 2 retro) N, 75–155	Insufficient	0–1.6	0–1.3	RD = -1.6 to 0 CI low range (-10.2, -6.9) CI high range (6.4, 8.6) RR = not estimable for all studies	NS
	2 prospective registries N = 3645 (30 day)	Low	2.0 (31/1547)	1.1 (23/2098)	RD = -0.9 (-1.8 to -0.1) RR = 1.83 (1.07-3.12)	CEA
	N = 2761 (in hospital)	Low	1.3 (2/156)	0.2 (5/2605)	RD = -1.1 (-4.4 to -0.1) RR = 6.68 (1.31-34.15)	CEA (in-hospital)
Any stroke or death	5 cohorts (2 pro, 3 retro) N, 75–684	Insufficient	2.6–7.9	2.4–7.2	RD = -1.6 to 2.6 CI low range (-12.6, -3.9) CI high range (1.2, 10.9) RR = 0.6–1.6 CI low range (0.1, 0.7) CI high range (3.0, 18.6)	NS
	2 prospective registries N = 5149 (30 day)	Insufficient	4.9 (7/142)	4.4 (220/5007)	RD = -0.5 (-5.5 to 2.1) RR = 1.12 (0.54-2.34)	NS
	N = 2761 (in hospital)	Low	5.1 (8/156)	1.6 (42/2605)	RD = -3.5 (-8.2 to-0.9) RR = 3.18 (1.52-6.66)	CEA (in-hospital)

KQ3: Symptomatic CAS vs. CEA			Treatment groups		Effect size	
Outcome	**Studies N range**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
Ipsilateral stroke	1 prospective registry N = 2761	Low	3.9	1.2	RD = -2.7 (-7.0 to -0.5) RR = 3.2 (1.4, 7.6)	CEA
MI	2 cohorts (1 pro, 1 retro) N = 128, 155	Insufficient	0	0	RD = 0 CI low range (-8.0, -5.7) CI high range (4.0, 4.4) RR = not estimable	NS
	2 prospective registries N = 3645 (30 day)	Low	1.4 (21/1547)	1.3 (27/2098)	RD = -0.1 (-0.9 to 0.7) RR = 1.05 (0.60-1.86)	NS
	N = 2761 (in hospital)	Low	1.3 (2/156)	1.3 (34/2605)	RD = 0 (-3.3 to 1.1) RR = 0.98 (0.24-4.05)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR: risk ratio.

*A total of 9 nonrandomized studies are represented in the table.

†A positive risk difference favors CAS and negative risk difference favors CEA.

Key Question 4: What is the evidence on of differential efficacy or safety for special populations?

Asymptomatic

Quality of evidence summary for Key Question 4: Is there evidence of differential efficacy or safety for special populations?

KQ4: Asymptomatic CAS vs. Medical Therapy						
Outcome	**Studies N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**CAS* HR (95% CI)**	**Medical Therapy* HR (95% CI)**	**Interaction p-values**
Subgroup: Ipsilateral stenosis (IS)						
Stroke	1 retrospective cohort study N = 946 25 mos. (median)	Insufficient	IS: 70-79% (n = 307)	aHR: 1.32 (0.43, 4.11)	aHR: 1.0	NR
			IS: 80-89% (n = 366)	aHR: 0.91 (0.33, 2.49)	aHR: 2.36 (1.02, 5.44)	
			IS: 90-99% (n = 273)	aHR: 0.98 (0.27, 3.61)	aHR: 3.17 (1.15, 4.11)	

aHR: adjusted hazard ratios; n/a: not applicable; NR: not reported; NS: not statistically significant

NOTE. A positive risk difference favors CAS and negative risk difference favors medial therapy; a HR > 1 indicates a greater risk of stroke.

*n/N for each outcome not reported

Quality of evidence summary for Key Question 4: Is there evidence of differential efficacy or safety for special populations?

KQ4: Asymptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
Subgroup: Age						
Death	1 registry N = 5268 Periprocedural	Insufficient	Age: < 65 yrs	RR: 1.78 (0.58, 5.49)	NS	P = 0.71
			Age: ≥65 yrs	RR: 2.26 (1.24, 4.14)	CEA	
Stroke	1 registry N = 5268 Periprocedural	Insufficient	Age: < 65 yrs	RR: 1.78 (0.75, 4.24)	NS	P = 0.89
			Age: ≥65 yrs	RR: 1.91 (1.29, 2.82)	CEA	
MI	1 registry N = 5268 Periprocedural	Insufficient	Age: < 65 yrs	RR: 2.97 (0.71, 12.36)	NS	P = 0.12
			Age: ≥65 yrs	RR: 0.88 (0.48, 1.61)	NS	
Subgroup: Sex						
Ipsi-lateral stroke	1 RCT N = 1181 4 yrs.	Low	Female	HR: 1.59 (0.53, 4.75)	NS	P = 0.71
			Male	HR: 2.16 (0.91, 5.10)	NS	
Stroke or Death	1 RCT N = 1181 4 yrs.	Moderate	Female	HR: 1.59 (0.53, 4.75)	NS	P = 0.71
			Male	HR: 2.16 (0.91, 5.10)	NS	
Stroke	1 RCT N = 1181 Periprocedural	Moderate	Female	HR: 2.11 (0.55, 8.15)	NS	P = 0.82
			Male	HR: 1.75 (0.57, 5.37)	NS	
Stroke or Death	1 RCT N = 1181 Periprocedural	Moderate	Female	HR: 2.11 (0.55, 8.15)	NS	P = 0.82
			Male	HR: 1.75 (0.57, 5.37)	NS	

KQ4: Asymptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
MI	1 RCT N = 1181 Periprocedural	Moderate	Female	HR: 0.67 (0.15, 3.01)	NS	P = 0.74
			Male	HR: 0.48 (0.15, 1.56)	NS	
Subgroup: Surgical risk						
Stroke (non-dis-abling)	1 prospective cohort study N = 106 Periprocedural	Insufficient	CEA Risk Grade I†	RR: 3.68 (0.16, 85.98)	NS	*P* < 0.72
			CEA Risk Grade II†	RR: 1.88 (0.09, 37.63)	NS	
			CEA Risk Grade III†	RR: 1.65 (0.19, 14.62)	NS	

n/a: not applicable; HR: hazard ratio; NR: not reported; NS: not statistically significant; RR: risk ratio

NOTE. A positive risk difference favors CAS and negative risk difference favors CEA; a HR > 1 favors CEA and a HR < 1 favors CAS.

*A total of 3 studies are represented in the table.

†CEA Risk Grades: I, neurologically stable patients with no major medical or angiographically defined risks but with unilateral or bilateral ulcerative/stenotic CA disease; II, neurologically stable patients with no major medical risks but with significant angiographically defined risks; III, neurologically stable patients with no major medical risks and with or without significant angiographically defined risks.

Symptomatic

Quality of evidence summary for Key Question 4: Is there evidence of differential efficacy or safety for special populations?

KQ4: Symptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
Subgroup: Age						
Stroke or Death	Meta-analysis 5 RCTs N = 3470 Periprocedural	Moderate	Age: < 70 yrs	0.56% (-1.55%, 2.6%) 1.14 (0.70, 1.84)	NS	*P* = 0.07 (RD) *P* = 0.04 (RR)
			Age: ≥ 70 yrs	8.28% (0.14%, 16.4%) 2.14 (1.47, 3.10)	CEA	
	Meta-analysis-Sensitvity analysis: 3 of the 5 RCTs N = 3433	Moderate	Age: < 70 yrs	0.47% (-1.89%, 2.83%) 1.08 (0.68, 1.72)	NS	P = 0.003 (RD) P = 0.03 (RR)
			Age: ≥ 70 yrs	5.68% (3.18%, 8.18%) 2.14 (1.45, 3.17)	CEA	
Ipsi-lateral Stroke or Death	1 RCT N = 1214 2 yrs.	Moderate	Age: < 68 yrs	-4% (-8%, 0%) 0.54 (0.29, 1.02)	NS	*P* = 0.005 (RD) *P* = 0.006 (RR)
			Age: ≥ 68 yrs	5% (0%, 1%) 1.63 (1.02, 2.61)	CEA	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Low	Age: < 68 yrs	HR: ~1.10 (0.45, 2.70)	NS	*P* = 0.08
			Age: ≥ 68 yrs	HR: ~3.40 (1.40, 8.10)	CEA	
Subgroup: Sex						
Stroke or Death	Meta-analysis 6 RCTs N = 4774 Periprocedural	Moderate	Female	2.6% (-2.1%, 7.2%) 1.5 (1.0, 2.3)	NS	*P* = 0.66 (RD) *P* = 0.51 (RR)
			Male	4.0% (-0.1%, 8.1%) 1.9 (1.1, 3.1)	CEA	
Stroke	1 RCT N = 1321 Periprocedural	Moderate	Female	HR: 2.80 (1.11, 7.07)	CEA	*P* = 0.17
			Male	HR: 1.28 (0.65, 2.52)	NS	

KQ4: Symptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
MI	1 RCT N = 1321 Periprocedural	Moderate	Female	HR: 1.26 (0.28, 5.63)	NS	*P* = 0.11
			Male	HR: 0.25 (0.07, 0.88)	CAS	
Ipsi-lateral Stroke or Death	1 RCT N = 1214 2 yrs.	Moderate	Female	2% (-4%, 7%) 1.24 (0.58, 2.66)	NS	*P* = 0.73 (RD) *P* = 0.69 (RR)
			Male	0% (-4%, 4%) 1.04 (0.69, 1.58)	NS	
Ipsi-lateral stroke	2 RCTs N = 1848 4 yrs.	Low	Female	HR: ~0.65-1.58 (0.25, 3.08)	NS	*P* ≥ 0.05
			Male	HR: ~1.10-3.30 (0.62, 7.40)	NS	
Stroke or Death	1 RCT N = 1321 4 yrs.	Moderate	Female	HR: 1.58 (0.81, 3.08)	NS	*P* = 0.56
			Male	HR: 1.23 (0.71, 2.14)	NS	
Subgroup: Diabetes						
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Low	Diabetes: Yes	HR: ~1.20 (0.30, 3.75)	NS	*P* = 0.27
			Diabetes: No	HR: ~2.60 (1.20, 5.60)	CEA	
Subgroup: Type of symptomatic qualifying event						
Stroke	1 RCT N = 1208 Periprocedural	Insufficient	Qualifying event: Stroke	4% (1%, 8%) 3.26 (1.21, 8.77)	CEA	*P* = 0.46 (RD) *P* = 0.53 (RR)
			Qualifying event: TIA	3% (0%, 7%) 2.13 (0.88, 5.12)	NS	
			Qualifying event: Ocular	0% (-5%, 6%) 1.15 (0.24, 5.55)	NS	
Ipsi-lateral stroke or Death	1 RCT N = 1196 Periprocedural	Low	Qualifying event: Stroke	-1% (-6%, 3%) 0.84 (0.47, 1.53)	NS	*P* = 0.48 (RD) *P* = 0.55 (RR)

KQ4: Symptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
			Qualifying event: TIA	2% (-4%, 7%) 1.27 (0.61, 2.64)	NS	
			Qualifying event: Ocular	-1% (-7%, 4%) 0.71 (0.16, 3.09)	NS	
			Qualifying event: Multiple events	7% (-2%, 15%) 4.77 (0.55, 41.19)	NS	
			Qualifying event: Other	7% (-14%, 27%) 1.69 (0.08, 37.26)	NS	
Ipsi-lateral stroke or Death	1 RCT N = 1196 2 yr.	Low	Qualifying event: Stroke	4% (-2%, 9%) 1.56 (0.84, 2.93)	NS	*P* = 0.13 (RD) *P* = 0.25 (RR)
			Qualifying event: TIA	1% (-5%, 7%) 1.14 (0.61, 2.11)	NS	
			Qualifying event: Ocular OR Other	0% (-6%, 6%) 1.07 (0.34, 3.39)	NS	
			Qualifying event: Multiple events	15% (4%, 27%) 9.53 (1.24, 73.48)	CEA	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Insufficient	Qualifying event: Stroke	HR: ~3.00 (1.60, 6.80)	CEA	*P* ≥ 0.16
			Qualifying event: TIA	HR: ~1.50 (0.45, 5.15)	NS	
			Qualifying event: Ocular	HR: ~2.00 (0.10, 4.30)	NS	
Subgroup: Severity of Ipsilateral Stenosis						
Ipsi-lateral stroke or Death	1 RCT N = 1196 2 yrs.	Moderate	Ipsilateral stenosis < 70%	2% (-3%, 7%) 1.31 (0.67, 2.58)	NS	*P* = 0.54 (RD) *P* = 0.49 (RR)
			Ipsilateral stenosis ≥ 70%	0% (-4%, 4%) 0.99 (0.64, 1.52)	NS	

KQ4: Symptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Low	Ipsilateral stenosis < 90%	HR: ~2.30 (1.00, 5.40)	NS	*P* = 0.61
			Ipsilateral stenosis ≥ 90%	HR: ~1.65 (0.60, 4.30)	NS	
Subgroup: Severity of Contralateral Stenosis						
Ipsi-lateral stroke or Death	1 RCT N = 1196 Periprocedural	Low	Contra-lateral stenosis < 70%	1% (-2%, 4%) 1.20 (0.76, 1.88)	NS	*P* = 0.14 (RD) *P* = 0.16 (RR)
			Contra-lateral stenosis 70-99%	-8% (-20%, 4%) 0.38 (0.08, 1.79)	NS	
Ipsi-lateral stroke or Death	1 RCT N = 1196 2 yr.	Low	Contra-lateral stenosis < 70%	-7% (-12%, -2%) 0.57 (0.39, 0.83)	CAS	*P* = 0.82 (RD) *P* = 0.89 (RR)
			Contra-lateral stenosis 70-99%	-13% (-33%, 7%) 0.41 (0.09, 1.83)	NS	
			Contra-lateral stenosis 100%	-5% (-27%, 17%) 0.70 (0.13, 3.73)	NS	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.		Contra-lateral stenosis < 70%	HR: ~2.20 (1.10, 4.30)	CEA	*P* = 0.65
			Contra-lateral stenosis 70-100%	HR: ~1.45 (0.30, 6.50)	NS	
Subgroup: Time to Treatment						
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Insufficient	Time to treatment: < 14 days	HR: ~6.75 (0.80, ≥8)	NS	*P* = 0.40
			Time to treatment: ≥ 14 days	HR: ~1.70 (0.80, 3.45)	NS	

KQ4: Symptomatic CAS vs. CEA						
Outcome	**Studies* N range Follow-up**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
Subgroup: Hypertension						
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Insufficient	Hyper-tension: Yes	HR: ~1.80 (0.85, 3.65)	NS	*P* = 0.62
			Hyper-tension: No	HR: ~2.90 (0.75, ≥8)	NS	
Subgroup: Smoking Status						
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Low	Smoking: Yes	HR: ~1.75 (0.5, 6.1)*	NS	*P* = 0.81
			Smoking: No	HR: ~2.10 (1.00, 4.40)*	NS	
Subgroup: Surgical Risk						
Stroke (non-dis-abling)	1 prosp. cohort study N = 106 Periprocedural	Insufficient	CEA Risk Grade I ††	RR: Not Estimable	n/a	Not Estimable
			CEA Risk Grade II †	RR: Not Estimable	NS	
			CEA Risk Grade III †	RR: 3.43 (0.28, 41.32)	NS	

n/a: not applicable; HR: hazard ratio; NR: not reported; NS: not statistically significant; RD: risk difference; RR: risk ratio

NOTE. A positive risk difference favors CAS and negative risk difference favors CEA; a HR > 1 favors CEA and a HR < 1 favors CAS.

*A total of 7 studies are represented in the table.

†CEA Risk Grades: I, neurologically stable patients with no major medical or angiographically defined risks but with unilateral or bilateral ulcerative/stenotic CA disease; II, neurologically stable patients with no major medical risks but with significant angiographically defined risks; III, neurologically stable patients with no major medical risks and with or without significant angiographically defined risks.

Key Question 5: What is the evidence of cost-effectiveness?

Note: GRADE has not been developed to evaluate the quality of cost-effectiveness evidence.

KQ5: Stenting compared with other treatment options (medical therapy, CEA)					
Population	**Studies***	**Countries**	**QHES Range†**	**Overall quality of evidence**	**Conclusions**
Asymptomatic Atherosclerotic Stenosis	3 cost-utility analyses	USA	84-99	Low	• Two studies based on data from the SAPPHIRE trial in high surgical risk patients reported ICERs of $49,514 and $67,891 for a 1-year time horizon, suggesting that CAS may be plausible but but not verifiably superior treatment. One study reported that over a life-time horizon CAS may be more cost-effective, however, methodological concerns regarding extrapolation of data for life-time time horizon and determination of utilities were noted • In one evaluation in patients with standard surgical risk, CEA was the preferred treatment given commonly assumed cost-effectiveness thresholds
Symptomatic Atherosclerotic Stenosis	4 cost-utility analyses	USA Sweden	94-100	Low	• Evidence across four cost-utility studies indicated that CEA tended to be more cost-effective than CAS in symptomatic patients. Two out of the four studies examining symptomatic patients found there to be insufficient evidence to strongly favor one treatment method over the other. • Subanalysis of patients from the SAPPHIRE trial of high surgical risk patients found CAS to be the more expensive treatment option with negligible QALY improvement leading to extremely high ICERs.
Intracranial Atherosclerotic Stenosis	No studies identified			No Evidence	N/A

CAS: carotid artery stenting; CEA: carotid endarterectomy; ICER: incremental const-effectiveness ratio; N/A: not applicable; QALY: quality-adjusted life years; SAPPHIRE: Stenting and Angioplasty With Protection in Patients At High-Risk for Endarterectomy.

*A total of 5 studies are represented in the table.

†Quality of Health Economic Studies (QHES) scores ranged from 84-100, which primarily reflects the quality of reporting on specific factors that are important in economic analyses. It does not provide for evaluation of quality with respect to modeling assumptions or extensive consideration of data quality and included outcomes measures relevant to a specific topic

Synopsis and remaining questions

Synopsis of highest evidence for primary outcomes: Asymptomatic patients with extracranial carotid atherosclerotic stenosis

- **CAS versus current best medical therapy**: Efficacy cannot be assessed as no RCTs were found. Evidence from one retrospective registry study suggests that CAS was favored over medical therapy and was graded as insufficient.
- **Short- and long-term efficacy CAS versus. CEA**: The overall strength (quality) of evidence was considered low regarding short and long-term efficacy data from two RCTs (CREST and Kentucky 2004) comparing CAS with CEA for outcomes past the periprocedural period. Event rates were similar and no statistical differences between treatments were seen for stroke, ipsilateral stroke and vessel patency up to 4 years. The rate of the composite of any periprocedural stroke or death or post-procedural ipsilateral stroke was 4.5% for CAS and 2.7% for CEA at 4 years. The difference was not statistically significant. Small sample sizes likely contributed to lack of statistical significance for some outcomes.
- **Safety CAS versus CEA**: The overall strength (quality) of evidence was moderate that there were no statistical differences between treatment groups for safety outcomes (30-day periprocedural period) including stroke, the composite of death or stroke and myocardial infarction, primarily based on analysis of asymptomatic patients in the CREST trial. The risk of stroke and for the composite of death or stroke was 2.5% for CAS and 1.4% for CEA, but the difference (1.2%) failed to reach statistical difference.
- **No differential treatment or safety effects** in special populations were identified, however, the data were limited and the overall strength of evidence grades were as follows:
    - Insufficient with respect to percent of ipsilateral stenosis for the comparison of CAS with medical therapy (cohort data only);
    - Insufficient with respect to age and surgical risk for the comparison of CAS with CEA (registry data)
    - Moderate with respect to sex (1 RCT).
- **Full economic evaluations**: One study suggests that CAS may be plausible but not verifiably superior for a one year time horizon in high risk patients; another reported CAS may be more cost effective given a life-time horizon and a third CEA as preferred. The overall strength of evidence was low.

Synopsis of highest evidence for primary outcomes: Symptomatic patients with extracranial carotid atherosclerotic stenosis

- **CAS with best medical therapy**: No comparative studies were found.

- **Short- and long-term efficacy CAS versus CEA**: The overall strength (quality) of evidence was considered moderate to low regarding short and long-term efficacy.
    - Short term: There is moderate evidence for the following:
        - When periprocedural strokes were excluded, risk of any stroke and risk of ipsilateral stroke were similar between treatment groups at 4 months (1RCT);
        - Risk of any stroke or death was significantly higher in patients receiving CAS at 4-6 months across two RCTs when periprocedural events were included. Risk of any periprocedural stroke or death or postprocedural ipsilateral stroke was significantly higher up to 6 months (1RCT)
        - Risk of death at 4 months was signigicantly higher following CAS (1RCT).
    - Longer term: Length of follow-up ranged from 2-5.4 years across 5 RCTs, 3 of which used embolic protection. Longest follow-up in these 3 RCTs was 4 years.
        - There is moderate evidence that risk of death was similar between treatment groups regardless of whether periprocedural death was included across 5 RCTs at up to 5.4 years follow-up.
        - There is low evidence that there were no signicant differences between treatments for he composite of death or any stroke (including periprocedural) or the composite of any periprocedural stroke or death or postprocedural ipsilateral stroke at follow-up to 5.4 years across 5 RCTs
- **Safety of CAS versus CEA:**
    - Based on meta-analyses of the four more recent RCTs which employed embolic protection, there is moderate evidence that the risk of stroke and the composite of any stroke or death are significantly higher in symptomatic persons who received CAS compared with CEA. The risk of any stroke or death was 7.1% for CAS and 4.1% for CEA, RD 3.1% (1.4%, 4.7%), NNH = 35. These risks are primarily influenced by stroke risk.
    - There is moderate evidence that no significant risk differences between treatments for the following outcomes: death, ipsilateral stroke, fatal, major or disabling stroke or MI.
- **Differential treatment efficacy or safety effects for special populations**
    - Age: There is moderate evidence from meta-analysis of more RCTs (using embolic protection) that age modifies the effect of treatment. In symptomatic persons with regard to risk of periprocedural death or stroke, CEA is favored in those age $\geq$ 70 years old while those under 70 years of age had similar results regardless of treatment group.
    - Sex: there is moderate evidence from meta-analysis of RCTs that sex does not modify treatment effect or safety.

  - Surgical risk: There is insufficient evidence from RCTs. Efficacy data from the SAPPHIRE trial of 96 symptomatic high surgical patients undergoing CAS versus CEA suggested these patients had similar risks for efficacy and safety outcomes.
  - There is moderate evidence from 1 RCT and low evidence from another RCT that severity of ipsilateral stenosis does not modify treatment or safety effects. This trial did not include and compare treatment outcomes from standard/average risk patients thus direct comparisons and conclusions cannot be made.
  - There is insufficient to low evidence from individual RCTs that treatment or safety effects are not modified by diabetes, type of symptomatic qualifying event, severity of contralateral stenosis, time to treatment, hypertension or smoking.
- **Full economic evaluations**: Low evidence across four cost-utility studies indicated that CEA tended to be cost effective than CAS. Subanalysis of the SAPPIRE trial found CAS to be more expensive with negligible improvement in QALY.

Synopsis of highest evidence primary outcomes: Intracranial stenting for atherosclerotic disease

- No studies in asymptomatic persons were found.
- The overall strength of evidence is low for efficacy and safety based on one study in symptomatic persons. The one available RCT was terminated because of safety concerns. Stenting was associated with a significantly higher probability (20.0%) of stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days compared with medical therapy (12.2%).
- No studies evaluating differential effectiveness in special populations were found.
- No economic studies were found.

Limitations of the literature and remaining questions

This report synthesizes studies comparing stenting with other treatment options for the treatment of atherosclerotic disease in the carotid arteries and intracranial arteries, with a focus on the highest quality, least biased evidence available in the peer reviewed literature. There are a number of questions that remain.

- In order to weigh whether or not to recommend an invasive procedure with serious risks in a healthy asymptomatic person, there should be clear evidence that benefits outweigh the risks. Benefits of CAS compared with current medical therapy have not been shown. There are no high quality data comparing stenting with current best medical practices in asymptomatic patients and limited data from randomized controlled trials in asymptomatic, low-risk patients comparing CAS with CEA. Although statistical significance was not reached, risk of stroke or death was lower following CEA in asymptomatic patients, but trials lacked a medical treatment comparator.
- Do any long-term benefits (>5 years) of CAS outweigh risks associated with periprocedural events (e.g. stroke)? The longest follow-up reported in more contemporary studies using embolic protection devices was 4 years. The number of individuals with available data at longer follow-up times was not uniformly reported

across studies and in some studies although statistical projection of longer term outcomes was reported, actual data are needed. Long-term data for implanted devices is essential.

- It is important to study the impact of improvements in stent technology and techniques (e.g. different embolic protection mechanisms), operator experience, surgical technique and medical therapy (including more active lifestyle counseling) on the bigger context of comparative effectiveness of CAS, medical therapy and CEA for the treatment of atherosclerotic carotid stenosis in not known. Although there is potential for improvements in devices to decrease risk of stroke and death with CAS, no published studies have included treatment arms for CAS, medical therapy and CEA in the same underlying population to allow for direct comparisons of current best treatments. For asymptomatic patients in particular, this is an important question. In addition, data on the risks and benefits of CAS and CEA from methodologically rigorous studies outside of high volume centers participating in RCTs is essential to understand what the risks and benefits would be in actual use.
- Based on available evidence, intracranial artery stenting in the treatment of intracranial atherosclerotic disease has substantial risk of harm. The only comparative study available was terminated early based on due to increased risk of stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery. The extent to which intracranial stenting is an effective treatment for primary treatment or in patients failed medical therapy, thrombectomy or PTA is not clear.
- Is CAS efficacious and safe in "high risk" patients? There does not appear to be a standard definition of "high risk" and many factors are considered when determining a patient's surgical risk. Although one RCT (SAPPHIRE) explicitly sought to evaluate the efficacy of CAS in "high risk" patients compared with CEA, because there was no direct comparison with a group of "standard" risk patients, firm conclusions cannot be drawn.
- The extent to which there is differential efficacy and safety in some special populations is not clear. Overall, studies were underpowered to detect modification of treatment.
- The cost-effectiveness of CAS is not established based on published studies. Although full economic analyses were available and based on data from RCTs, methodological concerns and potential for bias limit the usefulness of these analyses firm conclusions.

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1. Appraisal

1.1. Rationale

The public health burden of stroke and its associated morbidity and mortality combined with its impact on patient quality of life is substantial. The direct and indirect costs of stroke care to patients, the health care system and society are also substantial. Together all of these factors provide impetus to consider and evaluate the efficacy, effectiveness and safety of treatment options. There are uncertainties regarding the evidence on the use of stents for the treatment of atherosclerotic carotid stenosis and intracranial atherosclerotic disease compared with other treatment options. The Washington State Healthcare Authority's Health Technology Assessment program selected this topic for review based on high levels of concern around efficacy and cost and on medium levels of concern around safety.

Objective of this HTA: To systematically review, critically appraise, analyze and synthesize research evidence comparing the efficacy, effectiveness, and safety of carotid artery stenting procedures for subjects with symptomatic or asymptomatic atherosclerotic carotid stenosis or atherosclerotic stenosis of intracranial arteries. The differential effectiveness and safety as well as the cost-effectiveness of CAS were also evaluated. Review was limited to FDA-approved devices.

1.2. Key Questions

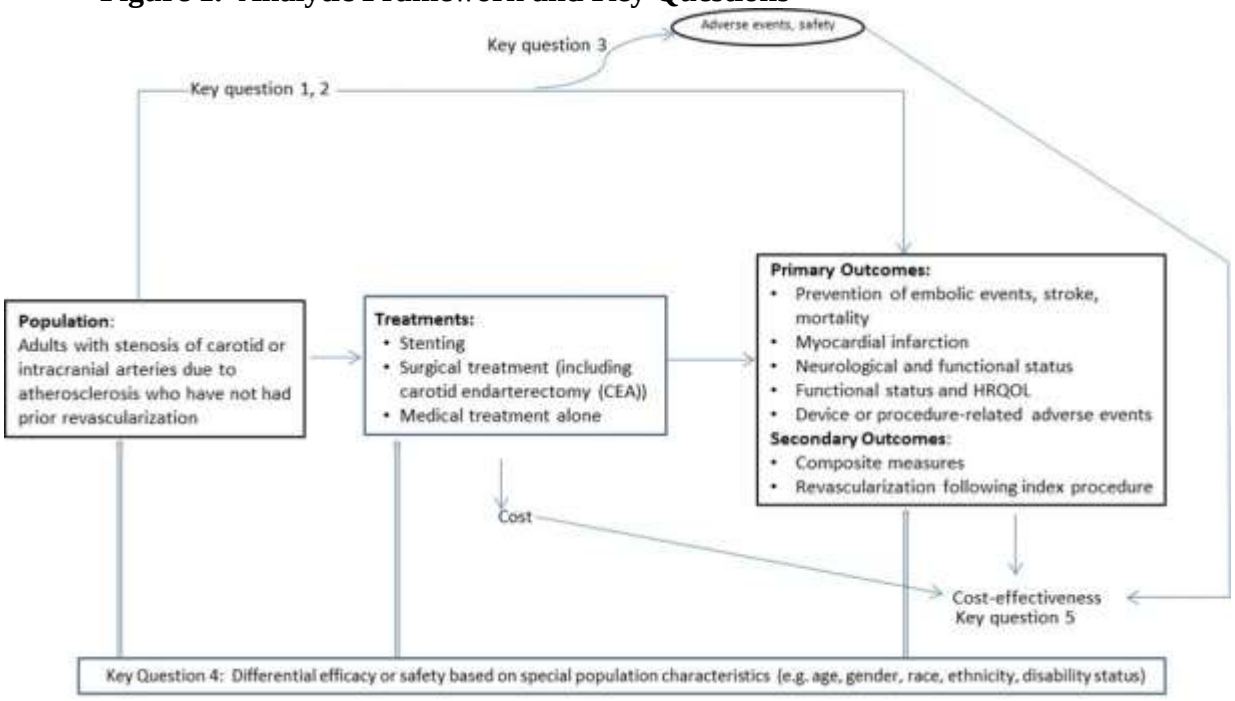
Input from clinical experts and from comments generated by public review of key questions was incorporated into the formulation of the final key questions and scope of this report.

1. In symptomatic or asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness of:
    a. Extracranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?
    b. Extracranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?
2. In asymptomatic or symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is the evidence of short- and long-term comparative efficacy and effectiveness of intracranial artery stenting and medical therapy compared with medical therapy alone?

3. What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?
4. Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other comorbidities, ethnicity, or disability)?
5. What is the evidence of cost-effectiveness of CAS compared with other treatment options (medical therapy, CEA) in the short-term and the long term?

Figure 1 provides the analytic framework for this HTA. Key question 1 evaluates efficacy and effectiveness of stenting in carotid compared with other treatment options and key question 2 evaluates efficacy and effectiveness of stenting intracranial artery atherosclerosis. Key question 3 compares the safety of stenting with other treatment options and key question 4 evaluates whether the efficacy, effectiveness or safety of treatment is differentially influenced by patient or other factors. Key question five assesses the cost-effectiveness of stenting compared with other treatment options.

Figure 1. Analytic Framework and Key Questions



1.3. Key considerations highlighted by clinical experts:

1. Interventions:

Individual patients may present with circumstances that need to be considered in determining the best treatment options. Patient co-morbidities and other factors that may contribute to the overall picture of patient suitability for surgical intervention need to be considered and the risks and benefits of the available treatment options need to be carefully weighed in consultation with the patient. Variations due to tortuosity, calcification, intracranial arterial stenosis, collateral circulation, aneurysms, and arteriovenous malformation have important implications that must be considered in applying treatment recommendations to individual patients.[47]

Carotid stenting is seen as an alternative to CEA in patients who are at high risk of surgically related morbidity and mortality. Device approval and use clinically has focused on treating such high risk patients. Clinical experts suggested that there is no standardized definition of "high surgical risk" or for who might be at "average" or "standard" risk. As discussed elsewhere in this report, a number of factors that may put patients at high risk for CEA surgery have been suggested. The recent AHRQ HTA (2012)[150] systematically identified a list of such factors from a number sources: factors listed in the CMS decision memo,[1] factors reported to be significant in multivariate analyses of published literature for predictive models, inclusion criteria for the SAPPHIRE trial designed to evaluate high risk patients,[183] factors listed in the reference surgical risk classification tool[172] and definitions factors described in a recent systematic review.[158] Factors such as cardiac co-morbidities, obesity, type of neurological event and presence of pulmonary disease may place patients at high risk of surgery.

With regard to intracranial stenting, comments from experts on the draft of this report suggest that primary stenting of intracranial arteries does not appear to have a clinical advantage over PTA in patients with medically refractory stenosis but may be beneficial as a bailout for failed PTA or failed thrombectomy.

Comments on the draft report from one expert also indicate that historically, the 3% and 6% benchmarks for the composite of stroke or death following CEA were arbitrarily established based on work and consensus of an ad hoc committee[37] set in 1989 and were carried forward to clinical guidelines for CAS.[137]

Several experts commented that there have been improvements in technology, operator experience, surgical technique and medical therapy that may not be reflected in the available comparative literature, particularly older studies, and indicate that rates for stroke/death composites have decreased with time.

2. Professional considerations:

Utilization trends and regional variation

Using discharge data from the National Inpatient Sample from 1998 to 2008, a recently published article investigated utilization trends over time for carotid endarterectomy (CEA) and carotid artery stenting (CAS).[168] Evaluation of 253,651 carotid revascularization procedures revealed a downward trend in the overall rate of interventions performed which was driven by a significant decrease in the rate of CEAs – the much more commonly performed procedure – over the course of the study period (lowest rates in 2007). Conversely, a significant increase in the rate of CAS performed was seen during this time (highest rates in 2006).

Provider experience

With the growing popularity and use of carotid stenting to treat atherosclerotic carotid artery stenosis the impact of the treating physician's experience level on outcomes has been scrutinized. The literature provides conflicting results regarding this topic. A recent observational study conducted using administrative data on Medicare beneficiaries (age 65 years or older) that underwent carotid stenting from 2005 to 2007 reported on 24,701 procedures performed by 2339 operators and found that lower annual operator volume and early provider experience were associated with increased 30-day mortality.[139] Similarly, a subanalysis of the CAPTURE 2 study investigated physician- and site-related variables associated with differential outcomes for CAS in asymptomatic nonoctogenarians and found that both site and operator volume were the most important determinant of perioperative CAS outcome; a threshold of 72 cases was found to be necessary for consistently achieving a stroke and death rate below 3%. There was no evidence that hospital type (community, private, teaching) or hospital geographic location (midwest, northeast, south, west) had significant influence on outcomes and no difference between various physician specialties (interventional cardiology, vascular surgery) was seen.[83] A previously published pooled analysis of individual patient data from EVA-3S, SPACE, and ICSS randomized controlled trial showed that the excess stroke or death risk associated with stenting was higher among centers enrolling fewer than 50 patients into the trial than in the larger centers. However, the differences were not significant and the risk of stenting was still higher than endarterectomy in the larger centers.[40] A recent Cochrane systematic review conducted a subanalysis of eight of the included RCTs that specified the amount of pre-trial experience their physicians performing CAS and found that there was no significant difference in the primary safety outcome between those trials that required 10 or fewer procedures and those that required greater than 10.[41] Furthermore, when CAS outcomes from the SVS Vascular Registry were analyzed by center by the number of procedures performed (< 25, 25-50, > 50), no statistically significant difference was seen.[166]

Provider specialty

In the United States, CAS is performed by physicians from a wide range of specialties; however, cardiologists currently play the most prominent role in CAS. According to a recent study analyzing Medicare beneficiaries, cardiologists accounted for one-third of all operators and performed over half of the 28,700 CAS procedures reported between 2005 and 2007.[140] In contrast, 27.3% of procedures were performed by surgeons (vascular, general, neurosurgery, cardiothoracic), 17.8% by radiologists, and the remaining 3.2% by other specialties (primarily neurology and internal medicine).

Facility/provider standards

Two private organizations, Intersocietal Commission for the Accreditation of Carotid Stenting Facilities (ICACSF) and Accreditation for Cardiovascular Excellence (ACE), currently provide accreditation for facilities that perform stenting of the extracranial carotid artery. In order to be accredited by these organizations a facility must meet the specified standards of quality of care in carotid stenting. Each organization has a set of standards encompassing such things as facility and equipment requirements, personnel standards, physician training and education, case volume, and quality assurance and safety programs. The Centers for Medicare and Medicaid (CMS) has created a list of minimum standards modeled in part on professional society statements on competency. CMS requires that facilities meet CSM's personnel, equipment, programming, emergency management, and data collection standards in order to receive coverage of CAS for high risk patients. For more detailed information about these private organization and CMS standards as well as a list of CMS approved hospitals in Washington State see Appendix I.

1.4. Washington State utilization and cost data

Data in this section were provided by the Washington State Health Technology Assessment Program.

Figure 1 – Carotid Artery Stenting Procedures - Paid Amounts by Agency and Year, 2009-2012

Agency/Year	2009	2010	2011	2012	4 Yr Overall Total[1]	Avg % Change	
PEBB**							
PEBB Average Annual Members	**210,501**	**213,487**	**212,596**	**212,684**		**0.3%**	
Carotid Artery Stenting							
Carotid Artery Stent Patients	18	12	10	12	51	-10.2%	*
Carotid Artery Stent Procedures [2]	19	12	10	12	53	-11.4%	*
Total Paid	**$501,687**	**$188,391**	**$211,519**	**$66,304**	**$967,901**	**-39.6%**	*
Average Paid per Procedure [3]	$17,121	$15,699	$9,857	$5,525	$14,892	-29.8%	
Average Paid, PEBB Primary	**$33,066**	**$26,011**	**$26,598**	**$29,261**	**$33,672**	**-3.0%**	
PEBB Primary % of procedures	52.6%	58.3%	40.0%	16.7%	43.4%	-26.3%	
Comparator Procedure - Endarterectomy							*
Endarterectomy Patients	57	60	56	54	214	**-2.0%**	*
Endarterectomy Procedures[2]	57	65	59	61	242	**2.3%**	
Total Paid, Endarterectomy	**$249,225**	**$276,084**	**$258,463**	**$288,503**	**$1,072,275**	**4.9%**	
Average Paid, PEBB Primary Endarterectomy	$16,781	$15,281	$19,313	$15,864	$17,284	-0.4%	
Medicaid							
Medicaid FFS Population	**463,966**	**474,676**	**473,356**	**477,727**		**1.0%**	
Carotid Artery Stenting							
Carotid Artery Stent Patients	21	24	26	11	78	-12.6%	*
Carotid Artery Stent Procedures [2]	21	25	26	11	82	-12.0%	*
Total Paid	**$170,064**	**$228,546**	**$183,868**	**$132,089**	**$714,567**	**-5.0%**	*
Average Paid per Procedure [3]	$8,098	$9,142	$7,072	$12,008	$8,714	20.0%	
Average Paid, Non-medicare	**$9,149**	**$11,358**	**$10,948**	**$7,468**	**$10,229**	**-3.7%**	
Non-medicare % of procedures	85.7%	80.0%	61.5%	81.8%	75.6%	1.1%	
Comparator Procedure - Endarterectomy							
Endarterectomy Patients	65	52	63	51	226	**-6.7%**	*
Endarterectomy Procedures[2]	68	54	64	52	235	**-7.7%**	*
Total Paid, Endarterectomy	**$411,449**	**$288,334**	**$509,735**	**$547,618**	**$1,757,135**	**17.4%**	*
Average Paid, Non-medicare	$7,958	$7,434	$12,437	$14,200	$10,554	25.0%	

*Average % Change was adjusted for population. **Public Employee Benefits

[1] Patients who receive treatment in multiple years are counted only once in the "4 Yr Overall" total.

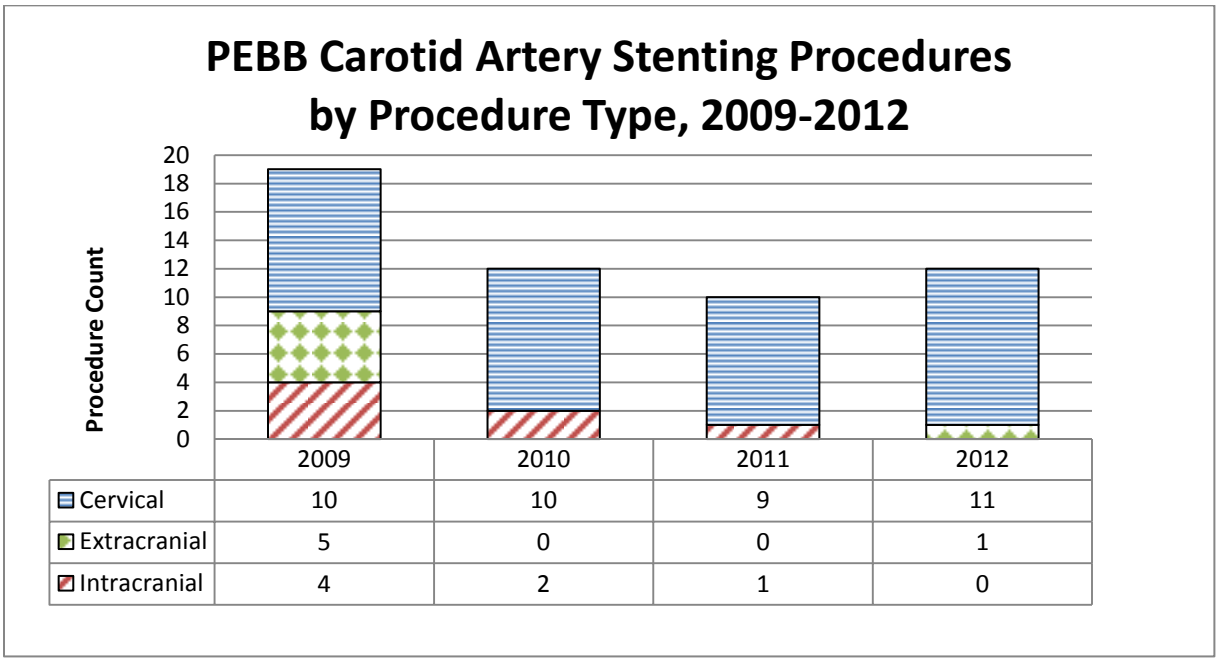
[2] Repeated procedures

Agency Repeated Procedures	Carotid Artery Stent	Endarterectomy	Both
PEBB Patient Count	2	38	0
Medicaid Patient Count	4	9	3

[3] Procedure amounts include directly related charges for up to 3 days before and after the stent placement. One outlier (above 2 standard deviation from the mean) was excluded from each of the PEBB averages for 2009 and 2011.

L&I had no claims during 2009-2012 for Carotid Artery Stenting procedures, and 1 claim for endarterectomy.

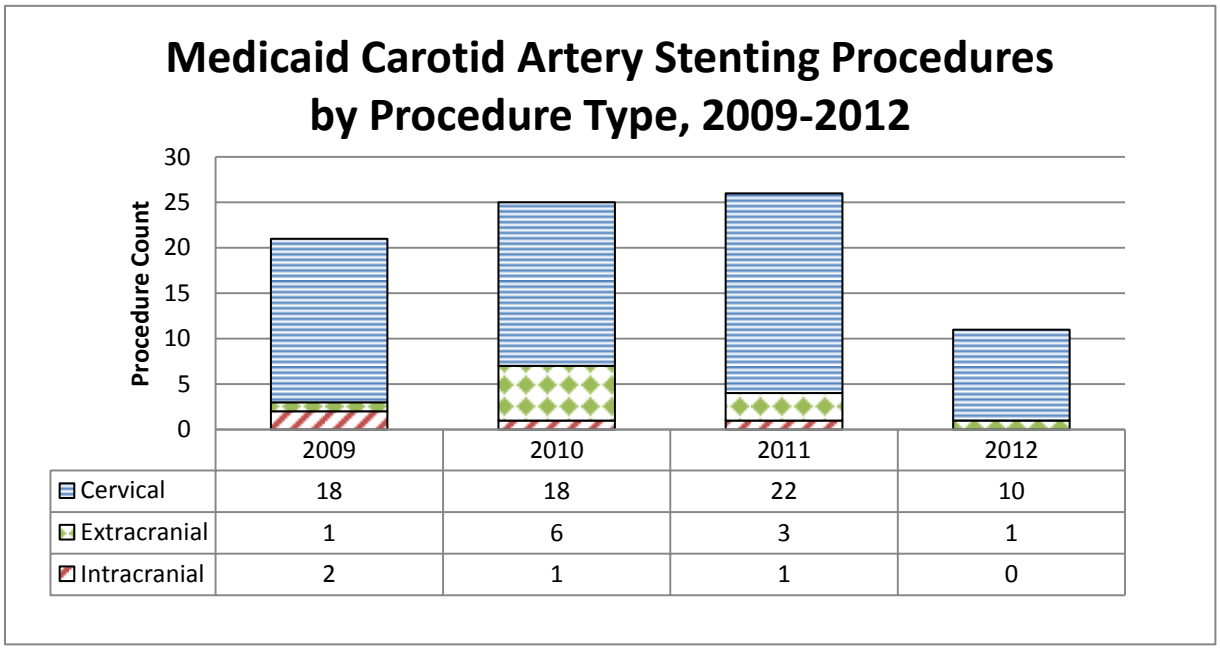
Figure 2a. PEBB Carotid Artery Stenting Patients by Payer and Procedure Type, 2009-2012



	2009	2010	2011	2012
Cervical	10	10	9	11
Extracranial	5	0	0	1
Intracranial	4	2	1	0

NOTE: Cervical procedures make up about 90% of PEBB CAS procedures. Cervical procedures allowed amount averaged around $25K per procedure, while extra- and intra-cranial procedures averaged $23K and $36K respectively.

Figure 2b. Medicaid Carotid Artery Stenting Patients by Payer and Procedure Type, 2009-2012



	2009	2010	2011	2012
Cervical	18	18	22	10
Extracranial	1	6	3	1
Intracranial	2	1	1	0

NOTE: Cervical procedures make up about 80% of Medicaid CAS procedures. Cervical procedures allowed amount averaged around $7K per procedure, while extra- and intra-cranial procedures averaged $6K and $5K respectively.

Figure 3a. PEBB Carotid Artery Stenting Patients by Age and Gender, 2009-2012

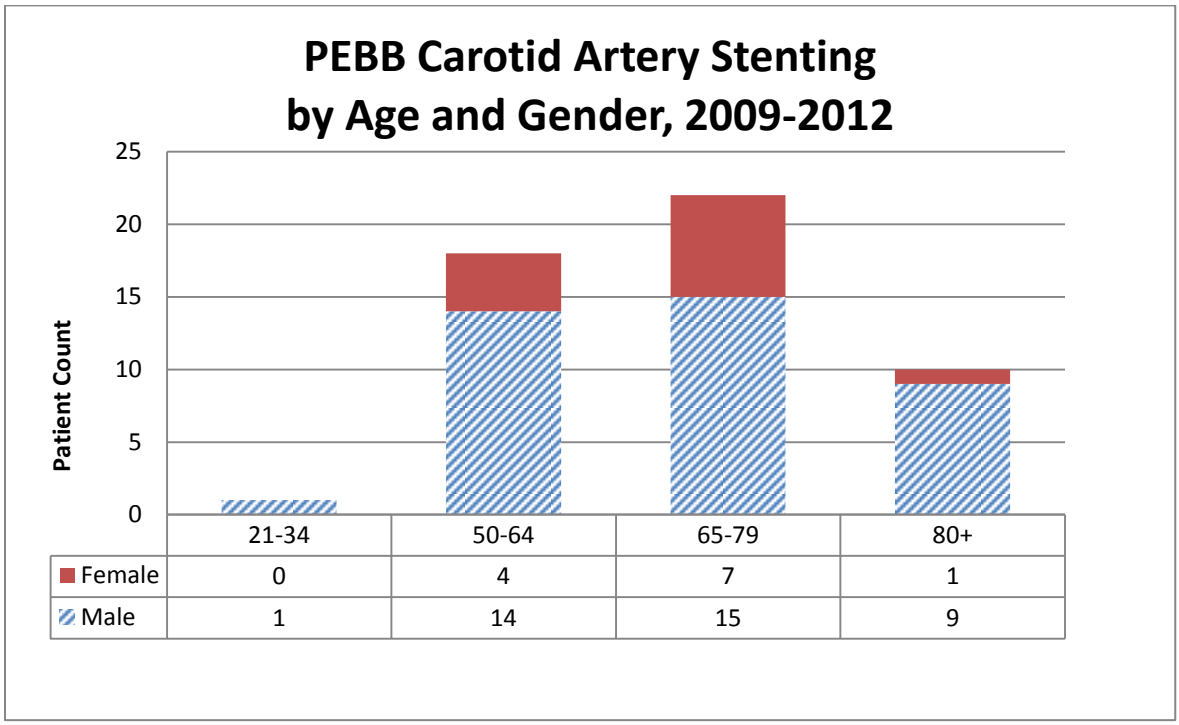


Figure 3b. Medicaid Carotid Artery Stenting Patients by Age and Gender, 2009-2012

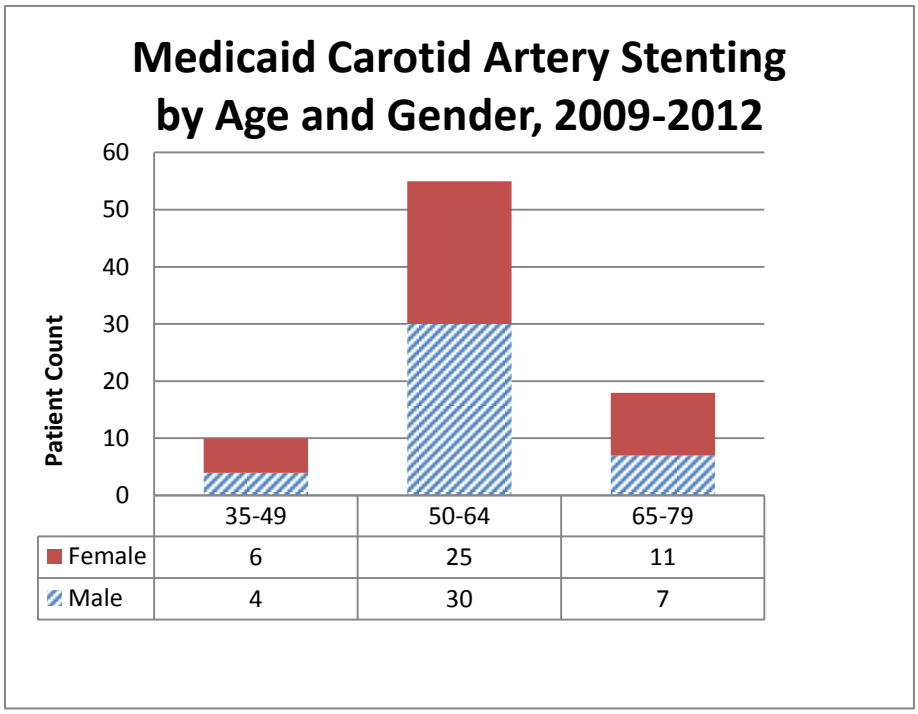


Figure 4a. Carotid Artery Stenting Average Allowed Amounts, 2009-2012

Per Procedure Avg Allowed Charges by Agency and Payer	PEBB Primary (n=23)	PEBB Medicare (n=30)	Medicaid Non-Medicare (n=62)	Medicaid Medicare (n=20)
Breakdown 1				
Professional Services	$3,500	$1,815	$1,391	$1,516
Facility/Other	$38,110	$30,657	$11,360	$7,662
Breakdown 2				
Stent Placement	$6,378	$1,685	$1,071	$1,431
Study	$126	$65	$12	$3
Facility/DRG	$32,588	$29,059	$10,825	$5,683
Anesthesia	$481	$149	$213	$199
Imaging	$1,516	$589	$387	$399
Patient Care	$521	$924	$243	$1,463
Avg Allowed/Procedure (95% upper limit)	**$41,610 ($128,502)**	**$32,472 ($116,983)**	**$12,750 ($43,174)**	**$9,178 ($33,328)**

Figure 4b. Inpatient vs Outpatient Average Allowed Amounts, 2009-2012

Per Procedure Avg Allowed Charges by Agency, Payer and Setting	PEBB Primary (n=23)	PEBB Medicare (n=30)	Medicaid Non-Medicare (n=62)	Medicaid Medicare (n=20)
Inpatient	**83%**	**63%**	**71%**	**30%**
Professional Services	$3,587	$1,365	$1,502	$1,937
Facility	$39,456	$45,569	$15,811	$25,296
Avg Allowed/Procedure	**$43,043**	**$46,934**	**$17,313**	**$27,233**
Outpatient	**17%**	**37%**	**29%**	**70%**
Professional Services	$3,088	$2,593	$478	$105
Facility	$31,718	$4,900	$1,118	$1,336
Avg Allowed/Procedure	**$34,806**	**$7,492**	**$1,596**	**$1,441**

Figure 5a – PEBB Carotid Artery Stenting Top Diagnoses, 2009-2012

Diagnosis Description CAS	Patient Count N = 53
OCL CRTD ART WO INFRCT	31
OCL CRTD ART W INFRCT	7
OCL MLT BI ART WO INFRCT	3
OCL VRTB ART W INFRCT	3
CRBL ART OCL NOS W INFRC	2
NONRUPT CEREBRAL ANEURYM	2
CRBL ART OC NOS WO INFRC	1
CRNRY ATHRSCL NATVE VSSL	1
CVA	1
DISSECT CAROTID ARTERY	1
OCL BSLR ART WO INFRCT	1
OCL VRTB ART WO INFRCT	1
PERIPH VASCULAR DIS NOS	1
STRICTURE OF ARTERY	1

Figure 5b – Medicaid Carotid Artery Stenting Top Diagnoses, 2009-2012

Medicaid Diagnosis Description CAS	Patient Count n = 82
OCL CRTD ART WO INFRCT	47
OCL CRTD ART W INFRCT	17
CRBL ART OCL NOS W INFRC	3
OCL BSLR ART W INFRCT	2
OCL MLT BI ART WO INFRCT	2
OCL VRTB ART W INFRCT	2
OCL VRTB ART WO INFRCT	2
COR ATH UNSP VSL NTV/GFT	1
CVA	1
DISSECT CAROTID ARTERY	1
NONRUPT CEREBRAL ANEURYM	1
OCL BSLR ART WO INFRCT	1
OCL MLT BI ART W INFRCT	1

Figure 6a. PEBB Emergency Room Visits and Readmissions within 30 days, 2009-2012

PEBB ER Visits	
Carotid Artery Stenting Patients	
Overall	11 of 53 (21%) CAS patients had 12 ER visits within 30 days, averaging around day 13 post-procedure. Three ER visits resulted in readmission.
By Procedure Type	8 Cervical patients had post-procedure ER visits (28%) compared to 1 Intracranial patient (14%) and 2 extracranial patients (33%).
Endarterectomy Patients	
Overall	31 of 214 (14%) endarterectomy patients had 48 ER visits within 30 days post procedure, averaging day 11.
PEBB Readmissions	
Carotid Artery Stenting Patients	
Overall	5 of 53 (10%) patients were readmitted within 30 days.
By Procedure Type	One each intracrantial, extracranial and three cervical patients were readmitted (14%, 17% and 8% respectively).
Endarterectomy Patients	
Overall	16 of 214 (7.5%) patients were readmitted within 30 days.

Figure 6b. Medicaid Emergency Room Visits and Readmissions within 30 days, 2009-2012

Medicaid ER Visits	
Carotid Artery Stenting Patients	
Overall	17 of 82 (21%) of CAS patients had 26 ER visits within 30 days, averaging around day 10 post-procedure. Seven ER visits resulted in readmission.
By Procedure Type	15 Cervical patients had post-procedure ER visits (22%) compared to 2 extracranial patients (18%).
Endarterectomy Patients	
Overall	48 of 226 (21%) endarterectomy patients had 81 ER visits within 30 days post procedure, averaging day 11.
Medicaid Readmissions	
Carotid Artery Stenting Patients	
Overall	Fifteen of 82 (18%) patients were readmitted within 30 days.
By Procedure Type	68 cervical, 3 extracranial and 2 intracranial patients were readmitted within 30 days (16%, 27% and 50% respectively).
Endarterectomy Patients	
Overall	14 of 226 (6.2%) patients were readmitted within 30 days.

Related Medical Codes

Type	Code	Description	Category
DRG	M034	Carotid artery stent procedure w MCC	Main procedure, inpatient
DRG	M035	Carotid artery stent procedure w CC	Main procedure, inpatient
DRG	M036	Carotid artery stent procedure w/o CC/MCC	Main procedure, inpatient
APDRG	892	Carotid Artery Stent procedure	Main procedure, inpatient
Type	**Code**	**Description**	**Category**
CPT	0075T	Transcatheter placement of extracranial vertebral or intrathoracic carotid artery stent(s), including radiologic supervision and interpretation, percutaneous; initial vessel	Main Procedure - extracranial
CPT	0076T	Transcatheter placement of extracranial vertebral or intrathoracic carotid artery stent(s), including radiologic supervision and interpretation, percutaneous; each additional vessel	Main Procedure - extracranial
CPT	35301	Thromboendarterectomy, including patch graft, if performed; carotid, vertebral, subclavian, by neck incision	Endartarectomy comparator
CPT	37215	Transcatheter placement of Intravascular Stent(s), Cervical carotid artery, percutaneous; without distal embolic protection	Main Procedure - Cervical
CPT	37216	Transcatheter placement of Intravascular Stent(s), Cervical carotid artery, percutaneous; with distal embolic protection	Main Procedure - Cervical
CPT	61635	Transcatheter placement of intravascular stent(s), intracranial (e.g., atherosclerotic stenosis), including balloon angioplasty, if performed	Main procedure - intracranial

2. Background

2.1. Epidemiology and burden of disease

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in both men and women in the United States.[157] One or more types of CVD effect an estimated 82,600,000 adults (> 1 in 3), half of which are 60 years of age or older.[157] By 2030, the prevalence of CVD in the US population is projected to rise to 40.5%.[89]

When considered separately from other CVDs, stroke is the fourth leading cause of death (behind heart disease, cancer, and chronic lower respiratory disease).[157] The American Heart Association estimates that about 800,000 Americans experience a new or recurrent stroke each year; 87% of these are ischemic in nature, mostly due to thromboembolic events.[126] The carotid arteries provide the main blood supply to the brain and narrowing of these arteries (stenosis) due to atherosclerosis accounts for nearly 20% to 25% of these strokes.[68,146] The most common site of plaque formation and stenosis in the carotid artery is near the bifurcation of the common carotid artery into the internal and external carotid arteries.[23,47] The extracranial portions of the artery are primarily affected. The risk of stroke depends upon the severity of the carotid stenosis. According to the North American Symptomatic Carotid Endarterectomy Trial (NASCET), 75% to 94% stenosis is associated with a stroke risk of up to 27% in symptomatic patients and 18.5% in asymptomatic patients.[97] However, this relationship in asymptomatic patients was less clear in other studies.[88,185] Carotid artery stenosis is also associated with an increased risk of cardiovascular events, such as myocardial infarction.[55,68,146] Medical risk factors for carotid artery atherosclerosis are similar to those for other cardiovascular diseases and include age, hypertension, insulin-dependent diabetes, cigarette smoking, metabolic syndrome, end-stage renal disease and chronic kidney disease and hypercholesterolemia/obesity.[122]

Intracranial arteries may be affected by atherosclerotic disease as well and intracranial stenosis is an important cause of ischemic stroke worldwide, accounting for 8 to 10% of strokes in North America and 30% to 50% in Asian countries.[81,85,112,160] The prevalence of intracranial atherosclerotic disease (ICAD) is higher in Asian, black, and Hispanic individuals than in Caucasians, while the reverse is true for extracranial carotid disease.[110,160] The major intracranial arteries that may be involved include the intracranial internal carotid artery, middle cerebral artery, vertebral artery and basilar artery.[110] The frequency and natural history of intracranial atherosclerotic disease (ICAD) is different from extracranial carotid atherosclerosis. The natural history has frequently been characterized on a vessel by vessel basis as there are apparent difference in morbidity and mortality based on the location of stenosis. While all traditional risks

factors are associated with ICAD, it appears that the presence of diabetes and metabolic syndrome are particularly associated with the development of atherosclerotic disease of the intracranial vasculature.[32,152] A study by Sacco et al found that the prevalence of intracranial stenosis was greater in African Americans and Hispanics than in Caucasians; however, this was due to the greater prevalence of insulin-dependent diabetes and hypercholesterolemia in these racial populations.[160]

Persons with carotid artery and/or intracranial artery atherosclerosis will generally have concomitant medical problems such as diabetes, high cholesterol or hypertension and various risk factors such as smoking and obesity. The standard of care is to address these problems and risk factors independent of the atherosclerotic artery disease.

Symptomatic versus asymptomatic carotid stenosis

Much of the evidence available for guiding decision making in the management of patients with carotid artery disease comes from randomized controlled trials conducted in symptomatic patients. A patient with carotid stenosis is considered symptomatic if they have neurological evidence of an ipsilateral stroke, transient ischemic attack (TIA) or transient monocular blindness. However, less is known about the efficacy of medical treatment, CEA and CAS in patients without these symptoms and thus the management of patients with asymptomatic carotid disease is still evolving. Recently, an assessment conducted by the AHRQ that focused on evaluation of management of carotid stenosis in asymptomatic patients was released.[150]

Asymptomatic disease may be discovered via several general mechanisms. A patient who presents with symptoms related to one carotid artery may have concomitant obstruction in the other carotid artery which is discovered via the evaluation of the symptomatic side. During routine history and physical exam, a clinician may hear a bruit on auscultation and/or an individual may have multiple risk factors for cardiovascular disease (e.g. diabetes, smoking) prompting further evaluation. Although there is controversy regarding screening for carotid disease, persons may participate in screening programs, sometimes paying out of pocket for such services. Findings from such screening exams may then prompt additional evaluation and initiation of treatment. In 2007, the U.S. Preventive Services Task Force published a recommendation statement regarding screening for asymptomatic carotid artery stenosis in which they conclude that screening should be discouraged in the adult general population.[13] After review of the evidence, they determined that there is moderate certainty that the service has no net benefit or that the harms outweigh the benefits (Grade D recommendation). This recommendation is currently in the process of being updated.

Anatomy of the carotid arteries and intracranial arteries

Carotid Arteries

There are two common carotid arteries, one on the right and one on the left, each of which branches into an external and internal portion, creating a total of four carotid arteries. The external carotid artery supplies blood to the face, scalp, tongue, and neck. In the neck, it usually runs medially and anteriorly to the internal carotid artery. The internal carotid artery supplies blood to the front part of the brain, the eye and its appendages, and sends branches to the forehead and nose. The distal common carotid artery typically bifurcates into the internal and external carotid arteries at the level of the thyroid cartilage; this bifurcation is the most common site of atherosclerosis plaque build-up. Considerable variation exists in the normal anatomy of the carotid and other arteries that supply blood to the face and brain. Most commonly, all three major arteries that arise from the aortic arch – the innominate (or brachiocephalic), left common carotid and left subclavian – have separate origins as they branch off the aortic arch. In some instances, the innominate and the left common carotid share a branch origin off the aortic arch, while in other cases, the left common carotid originates separately off the innominate artery. The internal carotid artery can also vary in length and tortuosity (e.g. coiling, kinking).

Intracranial Arteries

Blood is carried into the brain primarily by two paired arteries, namely the internal carotid arteries and the vertebral arteries. The internal carotid arteries supply the front areas of the brain and the vertebral arteries supply the back areas. After passing through the skull, the right and left vertebral arteries join together to form a single basilar artery; the basilar artery and the internal carotid arteries "communicate" with each other in a ring at the base of the brain called the Circle of Willis. The configuration of the circle of Willis is quite variable which has implications for treatment for individual patients. Intracranial atherosclerotic disease likely causes stroke by two primary mechanisms, which are not mutually exclusive: thrombus formation at the site of stenosis with subsequent embolization to distal portions of the involved vessel or complete or near-complete occlusion causing a reduction of blood flow to areas without sufficient collateral flow resulting ultimately in ischemia.[95] Intracranial arteries evaluated in this report include internal carotid artery, middle cerebral artery, vertebral artery and basilar artery.

2.2. Treatment options

Therapeutic options for atherosclerotic carotid stenosis include medical therapy alone, carotid endarterectomy (CEA) and medical therapy, or carotid angioplasty and stenting (CAS) and medical therapy. Management of risk factors (e.g. smoking) is also an important part of any therapeutic approach. For many years, CEA has been considered the gold-standard to restore vascular patency in the surgical management of carotid artery stenosis. However, recently, CAS, a less invasive surgical procedure, has become an alternative to CEA.

Based on landmark trials of CEA, upper limits for periprocedural (within 30 days) death or stroke rates that must be achieved for CEA to provide a net clinical benefit have been established in the literature and among experts: Rates must be < 3% for asymptomatic patients and < 6% for symptomatic patients.[21] These same criteria are applied to outcomes following CAS.

The primary therapeutic approach for intracranial atherosclerotic disease (ICAD) is medical therapy. More recently, angioplasty with or without stenting has been reported. Surgical options are limited. External to internal carotid bypass in patients with poor hemodynamic reserve has been proposed, but is not widely recommended.[110]

2.3. Technology

Carotid angioplasty and stenting (CAS)

A newer procedure, percutaneous CAS, has become an accepted alternative to open surgery in the treatment of carotid artery disease. It does not require general anesthetic or open access to the atherosclerotic lesion. Because it is minimally invasive, patients are often discharged from the hospital the next day following the procedure, depending on individual progress. During CAS, the clinician threads a catheter up from the groin, around the aortic arch, and up the carotid artery. The catheter has an attached balloon which expands the artery and inserts a stent to hold the artery open. Multiple stents may be placed depending on lesion length. Because there is a risk of disrupting the plaque along the artery walls during this type of procedure, CAS is usually performed along with an embolic protection device (EPD) which is used to capture any debris that becomes dislodged, reducing the risk of embolization. Currently, The Centers for Medicare and Medicare have limited there coverage to procedures using FDA-approved CAS systems in conjunction with FDA-approved or -cleared EPDs only.[5] CAS may be recommended or considered in patients with symptomatic severe stenosis (>70%) and abnormal anatomy precluding surgical access, medical comorbidities that put them at high-risk for surgery, or radiation-induced stenosis or restenosis after CEA. The

American Heart Association further recommends that CAS be performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%.[159] In asymptomatic patients, the effectiveness of CAS compared with medical therapy alone is not well understood; however, CAS might still be considered in highly selected patients with carotid stenosis of at least 60% by angiography or 70% by validated Doppler ultrasound.[47]

The first stents for use in the carotid artery were approved in 2004. CAS was approved originally only for use in high risk surgical patients. In 2011, the FDA cleared the use of stents to treat standard risk surgical patients, expanding the indications for their use for the RX Acculink stent. All approved devices for carotid use appear to be described as bare metal stents only. Approval is for symptomatic patients with ≥50% stenosis and for asymptomatic patients with ≥80% stenosis. Some stent labels specify vessel diameter (most describe 4.0–9.0mm with some ranging up to 9.5 mm) at the target lesion. FDA labeling does not specify use in extracranial versus intracranial vessels, but trials have focused on extracranial disease as this is the most common area requiring treatment for atherosclerosis. For detailed information on FDA approved stents see Appendix I.

Embolic protection devices (EPDs)

There is evidence indicating that there is a significantly higher incidence of microemboli following CAS compared with CEA.[103,169,192] The catheters, wires, balloons and stents used to navigate and manipulate the plaque-lined vessels may inadvertently break-off and release embolic particles into the blood stream during the procedure and concerns regarding the risk of procedure-related thromboembolic complications have prompted the widespread use of embolic protection devices (EPDs) during carotid artery stenting.

There are three primary types of EPDs: distal filter devices, distal occlusion balloons, and proximal occlusion balloons. Distal filter devices are metal, mesh-like devices placed distal to the atherosclerotic target lesion before balloon expansion and stent insertion and collapsed and withdrawn once the procedure is complete, trapping plaque or other emboli-causing debris. Occlusion balloons work by blocking the vessel either beyond (distal) or before (proximal) the target lesion and trapping any embolic debris that may dislodge in the stagnant column of blood, which is aspirated completely before the balloon is deflated and antegrade blood flow is restored. Since blood flow is disrupted, use of these types of EPDs relies on a good supply of collateral blood through the Circle of Willis to avoid ischemia during the procedure. In general, potential problems with EPD use include difficulty manipulating the device through the target lesion (especially in tortuous vessels), trouble with deployment, vessel injury or dissection caused by the guide wire, and difficulties with device retrieval.[56,145]

Indirect comparisons from many series and registries have shown a benefit of embolic protection devices. Two systematic reviews comparing case-series of CAS with and without the use of EPDs found that EPD use significantly reduced the risk of thromboembolic complications (range, 1.8%–2.6% vs. 4.2%–5.5%).[75,106] Similarly, when data from Global Carotid Artery Stent Registry, consisting of 12,392 procedures in 53 centers, was evaluated by use of EPDs, the incidence of any stroke or death was 2.2% in those who underwent CAS with protection versus 5.3% in those who underwent unprotected CAS.[179] Furthermore, a subanalysis of the EVA-3S RCT comparing patients from the CAS arm who received EPD versus those who did not suggested that the use of cerebral protection devices reduces periprocedural stroke. In fact, The Safety Committee recommended stopping unprotected CAS because the 30-day rate of stroke was four-times higher.[127]

A recent meta-analysis published in 2012 by Bersin et al. investigated the use of proximal occlusion devices in 2,397 patients who underwent carotid artery stenting and reported a very low rate of adverse events at 30 days.[38] This was a single-arm study and did not compare stenting with proximal occlusion devices to stenting without EPD or with filter EPDs. The incidence of stroke was 1.7% and the incidence of death was 0.4%.

In the United States, the use of embolic protection devices is recommended by expert consensus and professional society guidelines.[151] Although there is some controversy regarding the use of EPDs, it has been generally accepted by the medical community, and use of an embolic protection device has been required by Centers for Medicare and Medicaid Services to qualify for reimbursement.[5]

Evaluation of the evidence on the use of EPDs is in not part of the scope of this report and the previous information was provided for background purposes only.

Intracranial artery atherosclerotic disease and stenting

Intracranial atherosclerotic stenosis accounts for a large majority of ischemic strokes worldwide[81,110] and the rate of recurrent stroke with medical therapy alone is unacceptably high. Some of the best evidence comes from The Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) study trial, a randomized clinical trial that compared warfarin and aspirin for preventing stroke and vascular death in 569 patients with symptomatic stenosis of a major intracranial artery.[52] Ischemic stroke accounted for the majority of events in WASID and occurred in a total of 106 patients (19.0%). Seventy-seven (73%) of these strokes were in the territory of the stenotic artery, 60 (78%) of which occurred within the first year underscoring the need for rapid

assessment and management.[105] Furthermore, the degree of stenosis was found to be associated with outcomes with those with severe (70%-99%) intracranial stenosis having a higher stroke rate at 1 and 2 years, 18% and 19%, respectively, compared with 6% at 1 year and 10% at 2 years for those with stenosis < 70%.[105]

The primary strategies for treating intracranial atherosclerotic disease are intensive medical therapy including use of antiplatelet therapy and risk factor management, and angioplasty with stenting. Currently, only two devices have some level of FDA approval for intracranial vessel stenting: NEUROLINK® System (Guidant) and the Wingspan™ Stent System with Gateway™ PTA Balloon Catheter (Stryker Neurovascular). However, the NEUROLINK System is no longer being manufactured making the Wingspan the only FDA device currently available on the market. Approval of intracranial stents by the U.S. Food and Drug Administration (FDA) has been through the humanitarian device exemption (HDE) process. This form of FDA approval is available for devices used in the treatment or diagnosis of conditions that affect fewer than 4,000 individuals in the United States per year; the FDA only requires data showing "probable safety and effectiveness." A humanitarian use device (HUD) may only be used after an internal review board (IRB) approval has been obtained for the use of the device for the FDA approved indication. In March 2012, the FDA issued a safety communication related to the Wingspan System, limiting its use to a narrow, select group of patients who meet very specific criteria (see Indications and Contraindications section below). Generally, a patient may be treated with Wingspan only if its use has been approved in advance by the treating physician's Institutional Review Board (IRB). The Wingspan Stent System should not be used for the treatment of stroke with an onset of symptoms within seven days or less of treatment; or for the treatment of transient ischemic attacks (TIAs).

Treatment of extracranial portions of the basilar artery and the vertebral artery was not included in the scope of this report.

2.4. Comparators

Medical therapy

Medical therapy has changed in the past decade. Findings from the recent AHRQ report indicated that there had been a significant reduction in ipsilateral stroke incidence over time with medical therapy alone. They report a reduction of nearly 1% per year of follow-up between 2000 and 2010 for use of current best medical therapy in asymptomatic patients.[150]

Conservative medical therapy for carotid artery stenosis currently consists of the treatment of vascular risk factors through pharmacotherapy and lifestyle modification. Antiplatelet medications such as aspirin and clopidogrel (Plavix) are given to reduce the risk of stroke caused by blood clots. Current guideline statements recommend the use of aspirin 75 to 325 mg daily in patients with symptomatic obstructive or nonobstructive atherosclerosis of the extracranial carotid artery for prevention of MI and other ischemic cardiovascular events; the benefit has not been established for prevention of stroke in asymptomatic patients, however.[47] Blood thinners, such a Coumadin, may also be prescribed. Hypertension significantly increases the risk of stroke, and the relationship between blood pressure and stroke is "continuous, consistent, and independent of other risk factors" [53] so it is crucial that blood pressure be controlled, usually with antihypertensive medication, to a level consistently below 140/90 mmHg and ideally below 120/80 mmHg.[54] A strong relationship also exists between total cholesterol, low-density lipoprotein cholesterol, and the extent of carotid artery atherosclerosis and wall thickness,[54] thus statins are often prescribed for patients with carotid artery disease. Recommended lifestyle changes include quitting smoking (smoking nearly doubles the risk of stroke),[165,182] controlling diabetes, eating a healthy diet, maintaining a healthy weight, exercising regularly, and regular medical check-ups to control hypertension and cholesterol.

Carotid endarterectomy (CEA) for extracranial carotid artery stenosis

CEA is the most commonly performed surgical treatment for carotid artery stenosis (≥50%)[159] and its aim is to prevent adverse events secondary to atherosclerotic disease, i.e. ischemic stroke. General or local/regional anesthesia may be used for CEA with similar risks.[116] Typically, patients are able to go home 1 to 3 days following the procedure. During CEA, the vascular surgeon opens the carotid artery and removes the plaque-laden inner lining, widening the artery and restoring blood flow. CEA may be recommended for patients who have had a transient ischemic attack (TIA) or a mild stroke due to ipsilateral severe (70%–99%) carotid artery disease. In these symptomatic patients, CEA has been shown to be effective in preventing future ipsilateral ischemic events, provided that the perioperative (30-day) combined risk of stroke and death is not higher than 6%.[159] Asymptomatic patients may also be candidates for the procedure if they have > 70% stenosis of the internal carotid artery and the surgery can be performed with a low risk of perioperative stroke, MI, or death.[47]

Randomized comparisons of CEA with current best medical therapy are lacking. Given the changes in approach to medical therapy in the past decade, landmark trials completed in the early 1980s and 1990s comparing CEA with medical therapy alone may not be applicable to contemporary practice.[115,150] The recent AHRQ report for

included trials of CEA versus medical therapy alone, asymptomatic carotid stenosis patient not receive what is currently considered best medical treatment, include statin use or specific targets for management of diabetes and hypertension. In addition, since the early 1990s when most trials were performed, enhanced understanding of the role that lifestyle factors play in the risk of stroke has led to more aggressive counseling around making lifestyle changes. These early trials established the benefits of CEA, providing additional evidence for defining the balance of acceptable procedure-related risk of death and stroke with benefits related to reduction of future stroke.[21] These landmark trials further delineated benefits and harms following CEA in terms of degree of stenosis, presence or absence of neurologic symptoms and clinician expertise required to enhance outcomes.[6-10,35,88,92,131]

2.5. Indications and Contraindications

The target populations are symptomatic patients with moderate (50%-69%) or severe (70%-99%) carotid artery stenosis at risk for stroke and asymptomatic patients with stenosis of 60% or greater. Current U.S. Food and Drug Administration (FDA) labeling, however, requires that stents only be used in asymptomatic patients with greater than ≥70% stenosis. All patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

CAS with EPD is a procedure and thus does not require FDA approval. However, the devices used for CAS and for EPD do require FDA approval. A number of devices have been approved for use specifically in the carotid arteries. FDA labeling stipulates use of embolic protection devices. Detailed product information by stent type is provided in Appendix I.

FDA indications for devices approved for use in the **carotid arteries** are:

- Inability to tolerate general anesthesia for CEA.
- History of damage to the contralateral vocal cord (previous CEA or neck surgery).
- Previous neck surgery on the ipsilateral side.
- Neck irritation.
- Restenosis after CEA.

Contraindications for FDA-approved **carotid stents** include:

- Unfavorable anatomy, making it difficult to place the stent and embolic protection device.

- Unstable carotid plaque or aortic arch plaque.
- Allergy to nickel-titanium.
- Anticoagulant or antiplatelet medication is contraindicated.
- Uncorrected bleeding disorder.
- Lesions at the opening of the common carotid artery.

Approval of **intracranial stents** by the U.S. Food and Drug Administration (FDA) has been through the humanitarian device exemption (HDE) process. ALL of the following criteria/indications must be met in order for a patient to be approved:

- Age between 22 and 80 years
- Two or more stroke despite aggressive medical management
- Most recent stroke occurred more than 7 days prior to planned treatment with Wingspan
- 70%-99% stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes
- Good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment.

Contraindications for FDA-approved **intracranial stents** include:

- Treatment of acute strokes (i.e. onset of symptoms within 7 days or less of treatment)
- Treatment of transient ischemic attacks (TIAs)
- Highly calcified lesions that could prevent access or appropriate expansion of stent.
- Antiplatelet or anticoagulation therapy is contraindicated.

Drug eluting stents have not been approved for use in the carotid or intracranial vessels. Use of coronary drug eluting stents has been reported in case series and is an off-label use of these devices. As they are not FDA approved for carotid or intracranial stenting they are not included in the scope of this report.

2.6. Potential complications/harms.

For revascularization of the carotid arteries, the primary focus on potential complications in trials has been on periprocedural outcomes such as stroke and death. Additional potential harms and complications for the primary interventions compared (CAS and CEA) are outlined below.

Reported complications following carotid artery CAS include myocardial infarction, ipsilateral stroke, transient ischemic attack, cranial nerve palsy, bleeding complications, intracranial hemorrhage, and venous thromboembolism. Complications arising from intracranial CAS include access site complications, vessel dissection/perforation, vasospasm, hematoma, hypertension, stent thrombosis, and extracranial parent vessel dissection related to guide catheter manipulation.

Problems with EPD use include intolerance of the device, failure of the device, slow flow or no flow, particularly in the case of large plaques, and increased risk for stroke. Other problems include difficulty manipulating the device through the target lesion, trouble with deployment, vessel injury or dissection caused by the guide wire, and difficulties with device retrieval.[56,145]

Complications related to CEA include those inherent in any major surgery such as infection, deep vein thrombosis, nerve damage, pulmonary complications, pain, and effects from anesthesia. In addition, complications specific to CEA may also include cerebral nerve palsy (which may be transient), intracerebral hemorrhage, thromboembolism from the operated vessel, and hematoma.

2.7. Clinical Guidelines

Sources, including the National Guideline Clearinghouse (NGC), major bibliographic databases, professional societies, and Medline were searched for guidelines related to carotid artery stenting for the treatment of carotid artery stenosis. Key word searches were performed: "carotid AND stent* AND stenosis." Sixteen documents were recovered that contained specific recommendations regarding this topic.

- National Guideline Clearinghouse (NCG): Thirteen potential current guidelines were retrieved, six of which provided relevant guidance.
- National Institute for Health and Clinical Excellence (NICE): Four potential current guidelines were retrieved, three of which provided relevant guidance.
- Other sources: Twenty-five potential current guidelines were retrieved, seven of which provided relevant guidance.

A brief synopsis of each guideline is included below. Details of each included recommendation for extracranial and intracranial CAS can be found in Tables 1 and 2 that follow.

Extracranial CAS

National Guideline Clearinghouse

- ***Canadian Stroke Strategy, 2010: Canadian Best Practice Recommendations for Stroke Care***.[118] Recommends against CAS in older patients and recommends CAS as an option for patients not able to undergo CEA especially if asymptomatic or remotely symptomatic.
- ***National Stroke Foundation, 2010: Clinical Guidelines for Stroke Management.***[18] Recommends against CAS in most cases.
- ***Singapore Ministry of Health, 2009: Stroke and Transient Ischaemic Attacks Assessment, Investigation, Immediate Management and Secondary Prevention.***[17] CAS may be considered in patients who are not suitable for CEA.
- ***Scottish Intercollegiate Guidelines Network, 2008: Management of Patients with Stroke or TIA: Assessment, Investigation, Immediate Management and Secondary Prevention.***[16] Generally recommends against CAS except in cases such as failed medical therapy.
- ***Catalan Agency for Health Information, Assessment and Quality, 2008: Clinical Practice Guideline for Primary and Secondary Prevention of Stroke.***[14] Recommends CAS as an option for asymptomatic or symptomatic patients deemed unsuitable for CEA.

National Institute for Health and Clinical Excellence (NICE)

- ***National Institute for Health and Clinical Excellence, 2008: Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA).***[15] Finds no basis for use of carotid stenting.
- ***National Institute for Health and Clinical Excellence, 2011: Carotid artery stent placement for symptomatic extracranial carotid stenosis.***[20] Recommends CAS as secondary treatment to CEA.
- ***National Institute for Health and Clinical Excellence, 2011: Carotid artery stent placement for asymptomatic extracranial carotid stenosis.***[19] Generally recommends against any use of CAS for asymptomatic carotid artery stenosis.

Professional Societies/Other

- ***American Heart Association/American Stroke Association, 2011: Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack.*** [73] CAS is recommended for patients with moderate (50%–69%) to severe (70%–99%) stenosis at high risk for CEA or with recent TIA or ischemic stroke.
- ***American Heart Association/American Stroke Association, 2011: Guidelines for the Primary Prevention of Stroke.***[79] Prophylactic CAS could be considered for asymptomatic patients but is not a well-established alternative to CEA.

- ***American Heart Association/American Stroke Association, 2013: Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals.***[100] Considers the usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients to be unestablished. Additional randomized trial data are needed.
- ***American Stroke Association/American College of Cardiology Foundation/American Heart Association/American Association of Neuroscience Nurses/American Association of Neurological Surgeons/American College of Radiology/American College of Radiology/American Society of Neuroradiology/Congress of Neurological Surgeons/Society of Atherosclerosis Imaging and Prevention/Society for Cardiovascular Angiography and Interventions/Society for Interventional Radiology/Society for NeuroInterventional Surgery/Society for Vascular Medicine/Society for Vascular Surgery, 2011: Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease.***[47] Generally recommends CAS when conditions are not suitable for CEA, recommends against CAS in high-risk patients/conditions.
- ***Society for Vascular Surgery, 2011: Updated Society for Vascular Surgery Guidelines for Management of Extracranial Carotid Disease.*** [151] Generally recommends CAS as secondary treatment to CEA or for high levels of stenosis.
- ***Croatian Society of Neurovascular Disorders/Croatian Society of Neurology/Croatian Society of Ultrasound in Medicine and Biology/Croatian Society for Radiology/Croatian Society of Vascular Surgery/Croatian Society of Neurosurgery, 2010: Recommendations for the Management of Patients with Carotid Stenosis.***[60] Considers CAS investigational and recommends against CAS except in cases such as contraindications for CEA or inaccessible surgical site.
- ***European Society for Vascular Surgery, 2008: Invasive Treatments for Carotid Stenosis: Indications, Techniques.***[117] Generally recommends CAS only if CEA has higher peri-procedural risk.
- ***American Society of Interventional and Therapeutic Neuroradiology/American Society of Neuroradiology/Society of Interventional Radiology, 2003: Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent Placement.***[36] Generally recommends CAS for severe, symptomatic stenosis especially when associated with other conditions that could complicate surgery, and recommends against CAS when associated with intracranial conditions or asymptomatic.

Intracranial CAS

National Guideline Clearinghouse

- ***American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology/American Society of Neuroradiology, 2005: Intracranial Angioplasty & Stenting for Cerebral Atherosclerosis.***[90] Recommends CAS if medical therapy has failed.
- ***Singapore Ministry of Health, 2009: Stroke and Transient Ischaemic Attacks Assessment, Investigation, Immediate Management and Secondary Prevention.***[17] Recommends intracranial angioplasty with or without stenting as a treatment option for symptomatic patients who have >50% stenosis and who have failed medical therapy.

Professional Societies/Other

- ***American Heart Association/American Stroke Association, 2011: Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack.*** [73] Considers the usefulness of angioplasty and/or stent placement for symptomatic stenosis (50%–99%) of a major intracranial artery unknown and investigational.
- ***American Heart Association/American Stroke Association, 2013: Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals.***[100] Considers the usefulness of emergent intracranial angioplasty and/or stenting to be unestablished. These procedures should be used in the setting of clinical trials only.

Table 1. Clinical Practice Guidelines for Extracranial Carotid Artery Stenosis

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
National Guideline Clearinghouse						
Canadian Stroke Strategy Canadian Best Practice Recommendations for Stroke Care (2010)	Through 6/30/10	CAS for symptomatic and asymptomatic carotid artery stenosis	4 RCTs (CREST, EVA-3S, SPACE, ICSS)	CAS may be considered for patients who are not operative candidates for technical, anatomic or medical reasons. Interventionalists should have expertise in carotid procedures and an expected risk of peri-procedural morbidity and mortality rate of less than 5%.	NR	A
				CEA is more appropriate than CAS for patients >70 who are otherwise fit for surgery because stenting carries a higher short-term risk of stroke and death.	NR	A

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
				CAS may be considered in asymptomatic or remotely symptomatic patients (60-99% carotid stenosis, >3 months) who are not operative candidates for technical, anatomic or medical reasons provided there is a <3 percent risk of peri-procedural morbidity and mortality.	NR	A
National Stroke Foundation Clinical Guidelines for Stroke Management (2010)	Through 2/19/10	CAS for carotid artery stenosis	1 Cochrane review; 1 RCT (SPACE)	CAS should NOT routinely be undertaken for patients with carotid stenosis.	A	NR
				While stenting is not routinely recommended it may be considered as an alternative in certain circumstances, that is in patients who meet criteria for CEA but are deemed unsuitable due to conditions that make them technically unsuitable for open surgery (e.g. high carotid bifurcation, symptomatic carotid restenosis, previous neck radiotherapy, possible medical co-morbidities, or age >80y).	NR	NR
Singapore Ministry of Health Stroke and Transient Ischaemic Attacks. Assessment, Investigation, Immediate Management and Secondary Prevention (2009)	NR	CAS for symptomatic and asymptomatic extracranial carotid artery stenosis	1 RCT (SAPPHIRE);	Carotid artery stenting may be considered in patients who are not suitable for carotid endarterectomy.	A	1++
Scottish Intercollegiate Guidelines Network Management of Patients with Stroke or TIA: Assessment, Investigation, Immediate Management and Secondary	2000 to 2007	Carotid angioplasty and CAS and endovascular stenting for carotid artery stenosis and extracranial cervical arterial dissection	1 Cochrane review; 2 case series	Carotid angioplasty and stenting is not recommended without ongoing randomized controlled trials. Angioplasty and stenting may be considered for patients with high risk of stroke recurrence and a "hostile surgical neck" (for example, previous radical neck dissection or radiotherapy)	A	NR

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
Prevention. A National Clinical Guideline (2008)				Endovascular stenting is not routinely recommended for extracranial cervical arterial dissection or cervical artery pseudo-aneurysms. Stenting may be considered if recurrent ischaemic events occur despite medical therapy or where traumatic dissection has occurred with a high risk of stroke.	D	NR
Catalan Agency for Health Information, Assessment and Quality Clinical Practice Guideline for Primary and Secondary Prevention of Stroke (2008)	Through 9/07	CAS for symptomatic or asymptomatic carotid artery stenosis	1 systematic review of RCTs	Asymptomatic and symptomatic patients: The use of endovascular techniques with stent implantation should be individualized in patients with high surgical risk, in cases where there are technical difficulties for the performance of a CEA or within the context of a clinical trial.	B	1+
National Institute for Healthcare and Excellence (NICE)						
National Institute for Health and Clinical Excellence Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA) (2008)	NR	CAS for symptomatic carotid artery stenosis	NR	No basis was found for CAS.	NR	NR
National Institute for Health and Clinical Excellence Carotid artery stent placement for symptomatic extracranial carotid stenosis (2011)	8/28/10 to 1/06/11	CAS for symptomatic carotid artery stenosis	NR	Current evidence on the safety and efficacy of carotid artery stent placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit or research.	NR	NR

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
National Institute for Health and Clinical Excellence Carotid artery stent placement for asymptomatic extracranial carotid stenosis (2011)	8/28/10 to 1/06/11	CAS for asymptomatic carotid artery stenosis	NR	Current evidence on the safety of carotid artery stent placement for asymptomatic extracranial carotid stenosis shows well documented risks, in particular the risk of stroke. The evidence on efficacy is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.	NR	NR
Other sources						
American Heart Association/ American Stroke Association Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack (2011)	Through 7/09	CAS for symptomatic carotid artery stenosis	5 RCTs (CAVATAS, SAPPHIRE, EVA-3S, SPACE, CREST)	CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography.	I	B
				CAS in the below setting (see Class IIb Recommendations) is reasonable when performed by operators with established peri-procedural morbidity and mortality rates of 4% to 6%, similar to those observed in trials of CEA and CAS.	IIa	B
				Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation induced stenosis or restenosis after CEA, CAS may be considered.	IIb	B
				When the degree of stenosis is <50%, there is no indication for carotid revascularization by either CEA or CAS.	III	A

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
American Heart Association/ American Stroke Association Guidelines for the Primary Prevention of Stroke (2011)	12/06 to 4/09	CAS for asymptomatic carotid stenosis	2 RCTs (SAPPHIRE, CREST) 1 non-randomized trial (CaRESS), Registries (NR)	Prophylactic carotid artery stenting might be considered in highly selected patients with an asymptomatic carotid stenosis (>60% on angiography, >70% on validated Doppler ultrasonography, or >80% on computed tomographic angiography or MRA if the stenosis on ultrasonography was 50% to 69%). The advantage of revascularization over current medical therapy alone is not well established.	IIb	B
				The usefulness of CAS as an alternative to CEA in asymptomatic patients at high risk for the surgical procedure is uncertain	IIb	C
American Heart Association/ American Stroke Association Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association (2013)	NR	Emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries	8 retrospective case-series	The usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients is not well established	IIb	C
				Use of these techniques may be considered in certain circumstances, such as in the treatment of acute ischemic stroke resulting from cervical atherosclerosis or dissection. Additional randomized trial data are needed.	IIb	C
American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American	Through 05/10	Carotid artery balloon angioplasty and CAS for symptomatic extracranial carotid disease	5 RCTs (CREST, SAPPHIRE, EVA-3S, SPACE, ICSS)	CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when diameter of lumen of internal carotid artery is reduced by >70% as documented by noninvasive imaging or >50% as documented by catheter angiography and anticipated rate of peri-procedural stroke or mortality is <6%.	I	B

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery (2011)				It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention.	IIa	B
				It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.	IIa	B
				Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.	IIb	B
				In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, effectiveness of revascularization versus medical therapy alone is not well established.	IIb	B
				Except in extraordinary circumstances, carotid revascularization by either CEA or CAS is not recommended when atherosclerosis narrows lumen by <50%.	III	A
				Carotid revascularization is not recommended for patients with chronic total occlusion of targeted carotid artery.	III	C
				Carotid revascularization is not recommended for patients with severe disability caused by cerebral infarction that precludes preservation of useful function.	III	C

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
Society for Vascular Surgery Updated Society for Vascular Surgery Guidelines for Management of Extracranial Carotid Disease (2011)	NR	Carotid artery balloon angioplasty and CAS for symptomatic extracranial carotid disease	4 RCTs (CREST, SAPPHIRE, EVA-3S, SPACE1); 2 non-randomized trials (CaRESS, ICSS)	For neurologically symptomatic patients with stenosis <50% or asymptomatic patients with stenosis <60% diameter reduction, optimal medical therapy is indicated. There are no data to support CAS or CEA in this patient group.	I	B
				In most patients with carotid stenosis who are candidates for intervention, CEA is preferred to CAS for reduction of all-cause stroke and peri-procedural death. Data from CREST suggest that patients aged <70 years may be better treated by CAS, but these data need further confirmation.	I	B
				CEA is preferred over CAS in patients aged >70 years of age, with long (>15-mm) lesions, preocclusive stenosis, or lipid-rich plaques that can be completely removed safely by a cervical incision in patients who have a virgin, nonradiated neck.	I	A
				Neurologically asymptomatic patients deemed “high risk” for CEA should be considered for primary medical management. CEA can be considered in these patients only with evidence that perioperative morbidity and mortality is <3%. CAS should not be performed in these patients except as part of an ongoing clinical trial.	I	B
				CAS is preferred over CEA in symptomatic patients with ≥50% stenosis and tracheal stoma, situations where local tissues are scarred and fibrotic from prior ipsilateral surgery or external beam radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body. CEA may be preferable in situations where ipsilateral tissue planes remain relatively intact.	II	B

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
				CAS is preferred over CEA in symptomatic patients with ≥50% stenosis and severe uncorrectable CAD, congestive heart failure, or chronic obstructive pulmonary disease.	II	C
				There are insufficient data to recommend CAS as primary therapy for neurologically asymptomatic patients with 70% to 99% diameter stenosis. Data from CREST suggest that in properly selected asymptomatic patients, CAS is equivalent to CEA in the hands of experienced interventionalists. Operators and institutions performing CAS must exhibit expertise sufficient to meet the previously established AHA guidelines for treatment of patients with asymptomatic carotid stenosis. Specifically, combined stroke and death rate must be <3% to ensure benefit for the patient.	II	B
Croatian Society of Neurovascular Disorders/ Croatian Society of Neurology/ Croatian Society of Ultrasound in Medicine and Biology/Croatian Society for Radiology/ Croatian Society of Vascular Surgery/Croatian Society of Neurosurgery Recommendations for the Management of Patients with Carotid Stenosis	NR	CAS for carotid artery stenosis and intracranial artery stenosis	6 RCTs (CREST, SAPPHIRE, CAVATAS, SPACE, ICSS, EVA-3S); 3 registry studies (ARCHeR, EXACT, CAPTURE)	Carotid percutaneous transluminal angioplasty and stenting (CAS) is recommended in selected patients.	I	A
				For patients with hemodynamically significant intracranial stenosis that have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors), the usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain and is considered investigational.	II	C

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
(2010)				CAS should be restricted to the following subgroups of patients with severe symptomatic carotid artery stenosis: those with contraindications for CEA, stenosis at a surgically inaccessible site, restenosis after earlier CEA, and post-radiation stenosis.	IV	GCP
				Carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis.	IV	GCP
European Society for Vascular Surgery Invasive Treatments for Carotid Stenosis: Indications, Techniques (2009)	NR	CAS for symptomatic and asymptomatic carotid artery stenosis	11 RCTs (CAVATAS, Kentucky, Leicester, Wallstent, SAPPHIRE, EVA-3S, SPACE, BACASS, ARCHeR, NASCET, ACAS)	CAS should be offered to symptomatic patients, if they are at high risk for CEA, in high-volume centers with documented low peri-procedural stroke and death rates or inside an RCT.	C	NR
				It is advisable to offer CAS in asymptomatic patients only in high-volume centers with documented low peri-procedural stroke and death rates or within well-conducted clinical trials.	C	NR
				CAS should not be offered to asymptomatic 'high-risk' patients if the peri-interventional complication rate is >3%.	C	NR
				CAS is indicated in case of contralateral laryngeal nerve palsy, previous radical neck dissection, cervical irradiation, with prior CEA (restenosis), with high bifurcation or intracranial extension of a carotid lesion, provided that the peri-interventional stroke or death rate is higher than that accepted for CEA.	C	NR
				CAS is not advisable in patients with extensive aortic and supra-aortic vessel plaques, calcification and tortuosity, unless performed in high-volume centers with documented low peri-procedural stroke and death rate.	C	NR

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
American Society of Interventional and Therapeutic Neuroradiology/ American Society of Neuroradiology/ Society of Interventional Radiology Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent Placement (2003)	NR	Cervical carotid angioplasty and CAS for carotid artery stenosis	3 RCTs (CAVATAS, WALLSTENT, SAPPHIRE); 1 other randomized trial	Indications for CAS: • Symptomatic, severe stenosis surgically difficult to access (e.g., high bifurcation requiring mandibular dislocation). • Symptomatic, severe stenosis in a patient with significant medical disease that would make the patient high risk for surgery. • Symptomatic severe stenosis and one of the following conditions: a. Significant tandem lesion that may require endovascular therapy b. Radiation-induced stenosis c. Restenosis after CEA d. Refusal to undergo CEA after proper informed consent e. Stenosis secondary to arterial dissection f. Stenosis secondary to fibromuscular dysplasia g. Stenosis secondary to Takayasu arteritis • Severe stenosis associated with contralateral carotid artery occlusion requiring treatment before undergoing cardiac surgery. • Severe underlying carotid artery stenosis revealed after recanalization of carotid occlusion after thrombolysis for acute stroke (presumed to be the etiology of the treated occlusion) or to enable thrombolysis for acute stroke. • Pseudoaneurysm. • Asymptomatic preocclusive lesion in a patient otherwise meeting first three criteria.	NR	NR
				Relative Contraindications: • Asymptomatic stenosis of any degree, except in particular circumstances, as described above. • Symptomatic stenosis associated with an intracranial vascular malformation. • Symptomatic stenosis in a patient with a subacute cerebral infarction. • Symptomatic stenosis in a patient with a significant contraindication to	NR	NR

Organization(s) Title (Year)	Search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
				angiography.		
				Absolute Contraindications: • Carotid stenosis with angiographically visible intraluminal thrombus. • A stenosis that cannot be safely reached or crossed by an endovascular approach.	NR	NR

Abbreviations: ARCHeR: ACCULINK for Revascularization of Carotids in High Risk Patients; ACAS: Asymptomatic Carotid Atherosclerosis Study; BACASS: Basel Carotid Artery Stenting Study; CAPTURE: Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events; CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems

CAS: carotid artery stenting; CAVATAS: Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA: carotid endarterectomy; CREST: Carotid Revascularization Endarterectomy versus Stenting Trial; EVA-3S: Endarterectomy versus Angioplasty in patients with Severe carotid Stenosis Study; EXACT: Emboshield and Xact Post Approval Carotid Stent Trial; ICSS: International Carotid Stenting Study; NASCET: North American Symptomatic Carotid Endarterectomy Trial; NR: not reported; RCT: randomized controlled trial; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE: Stent-Protected Angioplasty versus Carotid Endarterectomy; SSYLVIA: Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries

Table 2. Clinical Practice Guidelines for Intracranial Carotid Artery Stenosis

Organization(s)	Literature search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
National Guideline Clearinghouse						
American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology/ American Society of Neuroradiology Intracranial Angioplasty & Stenting for Cerebral Atherosclerosis (2005)	NR	Intracranial CAS and angioplasty for asymptomatic and symptomatic intracranial artery stenosis	1 non-randomized, multicenter trial (SSYLVIA); 1 prospective, multicenter single-arm trial (WINGSPAN)	For symptomatic patients with a >50% intracranial stenosis who have failed medical therapy, balloon angioplasty with or without stenting should be considered.	NR	NR
				Patients who have an asymptomatic intracranial arterial stenosis should first be counseled regarding optimizing medical therapy. There is insufficient evidence to make definitive recommendations regarding endovascular therapy in asymptomatic patients with severe intracranial atherosclerosis. They should be counseled regarding the nature and extent of their disease, monitored for new neurological symptoms, and have periodic non-invasive imaging at regular intervals of 6–12 months (magnetic resonance angiography or computed tomographic angiography) initially, and then by cerebral angiography if warranted. At a minimum, optimal prophylactic medical therapy should be instituted, which might include antiplatelet and/or statin therapy.	NR	NR
				Continued evaluation and improvements in both pharmacological and catheter-based therapies are needed to reduce the stroke burden from intracranial atherosclerosis.	NR	NR
Singapore Ministry of Health Stroke and Transient Ischaemic Attacks. Assessment, Investigation,	NR	Intracranial angioplasty with or without stenting	1 non-randomized multicenter trial (SSYLVIA); 1 prospective multicenter	Intracranial angioplasty with or without stenting may be considered as a treatment option for symptomatic patients who have >50% stenosis and who have failed medical therapy.	C	2+

Organization(s)	Literature search dates	Procedure(s) evaluated	Evidence base available	Recommendations	Class/ Grade of Recommendation	Level of Evidence
Immediate Management and Secondary Prevention (2009)			single-arm trial (WINGSPAN)			
Other Sources						
American Heart Association/ American Stroke Association Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack (2011)	Through 7/2009	Intracranial angioplasty with or without stenting	NIH Wingspan Registry; 10 case series	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, the usefulness of angioplasty and/or stent placement is unknown and is considered investigational.	IIb	C
American Heart Association/ American Stroke Association Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association (2013)	NR	Emergent intracranial angioplasty with or without stenting	3 case-series (including 1 non-randomized single-center trial, the SARIS study)	The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials	IIb	C

Abbreviations: ARCHeR: ACCULINK for Revascularization of Carotids in High Risk Patients; ACAS: Asymptomatic Carotid Atherosclerosis Study; BACASS: Basel Carotid Artery Stenting Study; CAPTURE: Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events; CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems

CAS: carotid artery stenting; CAVATAS: Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA: carotid endarterectomy; CREST: Carotid Revascularization Endarterectomy versus Stenting Trial; EVA-3S: Endarterectomy versus Angioplasty in patients with Severe carotid Stenosis Study; EXACT: Emboshield and Xact Post Approval Carotid Stent Trial; ICSS: International Carotid Stenting Study; NASCET: North American Symptomatic Carotid Endarterectomy Trial; NR: not reported; RCT: randomized controlled trial; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE: Stent-Protected Angioplasty versus Carotid Endarterectomy; SSYLVIA: Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries

2.8. Previous Systematic Reviews/Technology Assessments

Previous health technology assessments

Eight prior Health Technology Assessments (HTAs) have evaluated the safety and/or efficacy of CAS compared with CEA for treatment of carotid artery disease (Table 3). Overall, for periprocedural (≤30 days) outcomes, the results from prior HTAs suggest that individuals undergoing CAS tend to have a higher risk of stroke and death, a lower risk of periprocedural (≤ 30 days) MI and cranial nerve palsy, and a similar risk of bleeding complications compared to CEA patients. For long-term (>30 day) outcomes, differences in risks of stroke, death and MI between individuals undergoing CAS and CEA were attenuated. These findings were largely consistent among HTAs evaluating the safety and efficacy for asymptomatic and symptomatic patients separately; although data among asymptomatic patients is lacking. Table 3 provides an overview of previous health technology assessments.

Previous systematic reviews

Four systematic reviews (SRs)[41,74,121,138] and eight meta-analyses[30,34,38,64,86,154,156,184] have evaluated the safety and/or efficacy of CAS compared with CEA for treatment of carotid artery disease. These prior reviews primarily evaluate on the same set of RCTs comparing CAS with CEA. Overall, for periprocedural (≤30 days) outcomes, the results of prior SRs and meta-analyses suggest that individuals undergoing CAS tend to have a higher risk of stroke, death, stroke or death, or disabling stroke or death, but a lower risk of MI and cranial nerve injury, and similar risk of death, hematoma compared to individuals undergoing CEA. Only 3 prior SRs/meta-analyses evaluated long-term (>30 day) outcomes,[41,64,156] which indicate that the differences in risks of stroke and death between individuals undergoing CAS and CEA were attenuated. Two prior SRs/met-analyses evaluated the safety and efficacy for asymptomatic and symptomatic patients separately and the results were largely consistent[30,41]; although data among asymptomatic patients is lacking. Several SR's/meta-analyses also suggest that the increased risk of stroke for CAS may be limited to older patients,[41,64,74] and that CAS may also increase risk of restenosis.[30,41] Table 4 provides an overview of previous systematic reviews.

Table 3. Overview of previous health technology assessments of treatments for carotid artery stenosis

Assessment (year)	Lit search dates	Focus/ procedure(s) evaluated	Key Questions	Evidence base	Conclusion
Agency for Healthcare Research and Quality (AHRQ) (2012)	from inception through May 2012.	Adults with **asymptomatic** carotid artery stenosis. Lesions: atherosclerotic narrowing of the lumen of the carotid bifurcation or the extracranial part of the internal carotid artery between 50 to 99 percent. Medical therapy alone, CEA and medical therapy compared with medical therapy alone, CAS and medical therapy compared with medical therapy alone, and CAS and medical therapy compared with CEA and medical therapy	1. **In asymptomatic** patients with carotid artery stenosis, what is the evidence on long-term clinical outcomes (at least 12 months of follow-up) including stroke, death, MI, and other cardiovascular events the following interventions? a. Medical therapy alone b. CEA and medical therapy versus medical therapy alone c. CAS and medical therapy versus medical therapy alone d. CAS and medical therapy versus CEA and medical therapy 2. Among comparative studies (CEA and medical therapy versus medical therapy alone, CAS and medical therapy versus medical therapy alone, CAS and medical therapy versus CEA and medical therapy), what is the impact of the following patient, intervention, and study characteristics on treatment effect? • Demographic and other baseline features including the assessment the applicability of studies to patients ≥ 65 years with asymptomatic carotid artery stenosis, subgroup of patients ≥ 80 years, and sex • Clinical and anatomic features of carotid artery stenosis • Average or high risk for CEA due to comorbid diseases • Types of stents used and use of embolic protection devices • Concurrent and postoperative treatments • Length of follow-up • Methodological quality of studies 3. Among comparative studies (CEA and medical therapy versus medical therapy alone; CAS and medical therapy versus medical therapy alone; CAS and medical therapy versus CEA and medical therapy), what is the evidence on adverse events and complications during the periprocedural period?	• 60 eligible studies/68 articles • **Medical therapy alone**: 41 studies met inclusion criteria (nine quality-A, 14 quality-B, and 18 quality-C studies) • **CEA + medical therapy vs. medical therapy alone** : three RCTs (quality-A) and seven nonrandomized comparative studies (2 quality B, 5 quality C) • **CAS and medical therapy vs. medical therapy alone**: two nonrandomized controlled trials (one quality B, one quality C) • **CAS + medical therapy vs. CEA + medical therapy**: three RCTs (CREST, SAPPHIRE and Kentucky (Brooks) 2004) (one quality-A and two quality-B), eight nonrandomized comparative studies (one quality B, seven quality C), and two registries (quality C)	• **The summary incidence rate** of quality-A and -B studies of medical therapy alone was 1.59 percent per year of follow-up It significantly decreased in recent studies (recruitment closure year between 2000 and 2010) compared with older studies, recruitment closure year before 2000 (1.1 versus 2.3 percent per year of follow-up). • **Medical therapy**: Moderate strength of evidence among 20 quality-A and -B studies that medical therapy alone can reduce the incidence rate of ipsilateral stroke over time in patients with asymptomatic carotid stenosis. Incidence rates of ipsilateral stroke, ipsilateral stroke or TIA, any territory stroke, and death significantly decreased between 2000 and 2010 as compared with older studies (those with recruitment closure year before 2000). In contrast, inclusion of all studies regardless of their methodological quality resulted in reduction of incidence rates of ipsilateral stroke and ipsilateral stroke or TIA, but not for any territory stroke or death. • **CEA + medical therapy vs. medical therapy alone**: Moderate strength of evidence from 3 quality A RCTs, that CEA and medical therapy can reduce the risk of ipsilateral stroke as compared with medical therapy alone, but their results may not be applicable to contemporary clinical practice. There were no differences between the two treatment groups for the risk of any death, fatal stroke, or CVD death based on meta-analysis. *Adverse Events* - Moderate evidence (results may not translate to contemporary clinical practice) of an increased risk of adverse events including any stroke, death, or MI with CEA and medical therapy as compared with medical therapy alone • **CAS and medical therapy vs. medical therapy alone:** The strength of evidence was graded as insufficient because of a lack of RCTs for both efficacy and adverse events.

Assessment (year)	Lit search dates	Focus/ procedure(s) evaluated	Key Questions	Evidence base	Conclusion
					• **CAS and medical therapy versus CEA and medical therapy:** The strength of evidence was graded as insufficient because in these trials, the included populations had extreme clinical heterogeneity. No statistically significant differences in the risk of ipsilateral stroke or the risk of the composite endpoint of ipsilateral stroke were found between CAS and CEA in two RCTs. *Adverse Events*- Strength of evidence insufficient due to heterogeneity and point estimates in opposite directions. No statistical differences in risk of periprocedural events between interventions • **Subgroup analysis:** The strength of evidence is graded as insufficient for all comparisons.
Blue Cross Blue Shield (BCBS) Technology Evaluation Center (2012)	1994-May 2010	CAS with EPD alone and compared to CEA and best medical therapy in patients with carotid artery stenosis Does CAS with EPD meet the BCBS Association TEC criteria to reduce stroke risk from symptomatic or asymptomatic carotid stenosis? Combines studies of symptomatic and asymptomatic	1. Is the periprocedural death/stroke rate with CAS < 3% for asymptomatic and < 6% for symptomatic patients? 2. For those subgroups defined by a) medical comorbidities or b) unfavorable anatomy, are periprocedural death/stroke rate with CAS < 3% for asymptomatic and < 6% for symptomatic patients? 3. How do the benefits and harms of CAS, CEA, and best medical therapy compare?	• 5 RCTs (N = 2431 CAS; N = 2399 CEA): SAPPHIRE, SPACE, EVA-3S, ICSS, CREST • 18 multicenter, prospective registries (including 1 abstract, 1 FDA document, and 1 presentation)	• In patients selected because of medical comorbidities and/or unfavorable anatomy, there is generalizable and applicable evidence that CAS is performed with periprocedural death/stroke rates exceeding 3% for asymptomatic and 6% for symptomatic patients and, therefore, not accompanied by net clinical benefit • In symptomatic patients not selected on the basis of medical comorbidities and/or unfavorable anatomy, results from 4 randomized, controlled trials provide strong evidence that CAS should not be performed • In the single trial (CREST) enrolling asymptomatic patients, 30-day death/stroke rates following CAS were higher than following CEA; moreover, lacking comparison of intervention with current best medical therapies makes conclusions regarding any intervention in asymptomatic carotid artery disease questionable
California Technology Assessment Forum (CTAF) (2010)	Prior search updated to include Jan 2009-Sept 2010	Update to 2009 CTAF review on the efficacy of CAS compared with CEA (RCTs only)	TA Criterion: 1. Technology must have the appropriate regulatory approval 2. Scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes 3. Technology must improve the net health outcomes 4. Technology must be as beneficial as any established alternatives	• 5 RCTs (9 publications): 2 new RCTs (ICSS, CREST), updates on 3 (CAVATAS, SPACE, SAPPHIRE)	• Based on currently available publications, it is impossible to conclude that CAS improves the net health outcomes as much as or more than the established alternative of CEA for atherosclerotic carotid stenosis; in most of the RCT data, CEA outperformed CAS

Assessment (year)	Lit search dates	Focus/ procedure(s) evaluated	Key Questions	Evidence base	Conclusion
			5. The improvement must be attainable outside the investigational setting		
California Technology Assessment Forum (CTAF) (2009)	Prior search updated to include Jan 2005-May 2009	Update to 2005 CTAF review on the efficacy of CAS compared with CEA (RCTs only)	Same as above	• 11 RCTs (29 publications): 6 RCTs described in detail in 2005 report (see below), 1 RCT long-term follow-up (SAPPHIRE), 5 new RCTs (SPACE, EVA-3S, BACASS, TESCAS-C, Steinbauer 2008)	• Based on currently available publications, it is impossible to conclude that CAS improves the net health outcomes as much as or more than the established alternative of CEA for atherosclerotic carotid stenosis
California Technology Assessment Forum (CTAF) (2005)	1966-August 2005	Review the scientific evidence for the use of CAS for patients with carotid artery stenosis.	Same as above	• 6 RCTs (Leicester, CAVATAS, WALLSTENT, Kentucky 2001/2004, SAPPHIRE) • 6 non-randomized comparative trials (Jordan 1997, Jordan 1998, Gray 2002, CaRESS 2003/2005, Hobson 1999, AbuRahma 2001) • 25 case-series	• Based on currently available publications, it is impossible to conclude that CAS improves the net health outcomes as much as or more than the established alternative of CEA for atherosclerotic carotid stenosis
National Institute for Health and Clinical Excellence (NICE) (2010)	-August 28, 2010 and updated to January 6, 2011	Treatment of asymptomatic extracranial carotid artery stenosis using CAS	None stated. Look at: • Efficacy (mortality, stroke, composite endpoints of stroke or death, arterial patency) • Safety (mortality, stroke, MI, composite endpoints of stroke or death, other)	• 2 meta-analyses (Meier 2010, Ederle 2007) • 2 RCTs (CREST, Kentucky 2004) • 2 nonrandomized controlled trials (Giles 2010, Giacovelli 2010) • 3 case-series • 3 case reports	• Current evidence on the safety of CAS placement for asymptomatic extracranial carotid stenosis shows well-documented risks, in particular the risk of stroke. The evidence on efficacy is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
National Institute for Health and Clinical Excellence (NICE) (2010)	-August 28, 2010 and updated to January 6, 2011	Treatment of symptomatic extracranial carotid artery stenosis using CAS	None stated. Look at: • Efficacy, > 30 days f/u (mortality, stroke, composite endpoints of stroke or death, arterial patency) • Safety (mortality, stroke and/or TIA, MI, composite endpoints of stroke or death, other)	• 2 meta-analyses (Meier 2010, Bonati 2010) • 4 RCTs (SPACE, EVA-3S, ICSS, CREST) • 2 nonrandomized controlled studies (Giles 2010, Giacovelli 2010) • 5 case-series • 4 case reports	• Current evidence on the safety and efficacy of CAS placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit or research
KCE (2005)	January 1998-December 2004	Summarize the evidence of effectiveness and cost-effectiveness of CAS relative to CEA in patients suitable for surgery	1. Is CAS superior to all other available strategies in certain well specified indications? 2. Is there clinical equivalence between CAS and other available strategies in certain well specified indications, to warrant further experimentation? 3. What are the conditions that are needed for a safe use of CAS?	• 2 RCTs (EVA-3S, SAPPHIRE) • 4 nonrandomized (Becquemin 2003, Hobson 2004, McKinlay 2003, Kastrup 2004) • Registry (Wholey 2003)	• There is no convincing evidence that CAS is superior, inferior or non-inferior to CEA in well-defined patient populations (absence of evidence) • CEA is the standard of treatment of carotid artery stenosis in well-defined populations at high risk for stroke. This holds particularly for older patients. • CAS in asymptomatic patients should be discouraged • Studies from the United States found that initial hospital costs or charges for CAS (without cerebral protection) are higher

Assessment (year)	Lit search dates	Focus/ procedure(s) evaluated	Key Questions	Evidence base	Conclusion
					than for CEA • At equal effectiveness, the additional costs of devices make CAS less cost-effective compared to CEA. Stroke rate is the major determinant for the relative cost-effectiveness of CAS

BACASS: Basel Carotid Artery Stenting Study; CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CAVATAS: Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA: carotid endarterectomy; CREST: Carotid Revascularization Endarterectomy versus Stenting Trial; CVD: cerebrovascular disease; EPD: embolic protection device; EVA-3S: Endarterectomy versus Angioplasty in patients with Severe carotid Stenosis Study; ICSS: International Carotid Stenting Study; KCE: Federaal Kenniscentrum voor de Gezondheidszorg (Belgium); MI: myocardial infarction; RCT: randomized controlled trial; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE: Stent-Protected Angioplasty versus Carotid Endarterectomy; TESCAS-C: Trial of Endarterectomy versus Stenting for the Treatment of Carotid Atherosclerotic Stenosis in China; TIA: transient ischemic attack.

Table 4. Overview of previous systematic reviews of treatments for carotid artery stenosis

Review (year)	Lit search dates	Focus/procedure(s) evaluated	Key Questions	Evidence base	Conclusion
Liu (2012)	1990-2010	Systematic review and meta-analysis comparing CAS versus CEA in the treatment of carotid stenosis	• Primary outcomes: death, stroke, and MI	• 13 RCTs (N = 3761 CAS; N = 3740 CEA): Leicester, WALLSTENT, Kentucky 2001, Kentucky 2004, CAVATAS, SAPPHIRE, EVA-3S, SPACE, TESCAS-C, Steinbauer 2008, BACASS, ICSS, CREST	• CAS is inferior to CEA with regard to the incidence of stroke or death for periprocedural outcomes, especially in symptomatic patients; however, CAS was associated with a lower incidence of MI
Economopoulus (2011)	January 1, 1990-May 21, 2010	Meta-analysis of short-term and long-term comparison between CEA and CAS synthesizing all available data coming from published RCTs	• Short-term outcomes were the following: death, stroke, MI, death or stroke, death or ipsilateral stroke, death or disabling stroke, death or stroke or MI, and cranial nerve injury. • Long-term outcomes were the following: death, stroke, MI, death or stroke, death or ipsilateral stroke, death or disabling stroke, death or stroke or MI.	• 13 RCTs (20 publications/abstracts, N = 3754 CAS; N = 3723 CEA): Leicester, Kentucky 2001, Kentucky 2004, WALLSTENT, TESCAS-C, BACASS, EVA-3S, SAPPHIRE, SPACE, Steinbauer 2008, CAVATAS, ICSS, CREST	• Significantly less frequent stroke events after CAE at long-term f/u • The outcomes of CAE seem superior to CAS, but there may be subgroups, particularly younger patients, in whom the results seem equivalent
Guay (2011)	July 2000-July 2010	Meta-analysis comparing CAS with CEA for the treatment of symptomatic or asymptomatic carotid artery stenosis in terms of stroke, MI, and death at 30 days	• 30 day stroke, MI, and death • symptomatic or nonsymptomatic	• 10 RCTs (N = 6950; CAVATAS, Leicester, Steinbauer 2008, SAPPHIRE, EVA-3S, CREST, ICSS, SPACE, Kentucky 2001, Kentucky 2004)	• Compared with CAS, CEA decreases the risk of stroke at 30 days, increases the risk of MI, and does not affect the risk of death.
Murad (2011)	2008-July 2010; previous review in 2008 included 10 RCTs	Systematic review and meta-analysis comparing efficacy and safety of CEA vs. CAS in patients with carotid artery disease	• Death, nonfatal stroke, and nonfatal MI • symptomatic or nonsymptomatic	• 13 RCTs (N = 7484; Leicester, WALLSTENT, Kentucky 2001, Kentucky 2004, CAVATAS, SAPPHIRE, EVA-3S, SPACE, TESCAS-C, BACASS, Steinbauer 2008, CREST, ICSS)	• Compared with CEA, CAS significantly increases the risk of any stroke and decreases the risk of MI • Outcome data in asymptomatic patients were sparse and imprecise; hence, these conclusions apply primarily to symptomatic patients
Yavin (2011)	1948-July 2010	Meta-analysis comparing safety and efficacy of CEA versus CAS in the	• Primary outcomes: 30-day periprocedural rate of stroke, death, and MI • Secondary outcomes: 30-day	• 12 RCTs (N = 6973; Leicester, Kentucky 2001, Kentucky 2004, WALLSTENT,	• In comparison with CEA, CAS is associated with a greater odds of stroke and a lower odds of MI • While the results support the

Review (year)	Lit search dates	Focus/procedure(s) evaluated	Key Questions	Evidence base	Conclusion
		treatment of carotid artery stenosis	periprocedural rate of disabling stroke, stroke or death, or stroke, MI or death; incidences of restenosis, cranial neuropathy, and access-related hematoma	SAPPHIRE, SPACE, TECAS-C, BACASS, EVA-3S, Steinbauer 2008, ICSS, CREST)	continued use of CEA as the standard of care in the treatment of carotid artery stenosis, CAS is a viable alternative in patients at elevated risk of cardiac complications
Arya (2011)	Not given	Meta-analysis comparing the 30-day and long-term morbidity and mortality results of CEA compared to CAS	• 30-day risk of stroke and stroke/death • Long-term risk of stroke and restenosis • Subgroup analysis of symptomatic vs. asymptomatic patients	• 11 RCTs (N = 3631 CAS ; N = 3596 CEA) used for primary analyses (Leicester, SPACE, ICSS, CREST, SAPPHIRE, CAVATAS, WALLSTENT, Leicester, Kentucky 2001, Kentucky 2004, Link 2000) • 5 prospective nonrandomized studies (N = 548 CAS; N = 991 CEA) used only in secondary analyses (CaRESS 2005, Becquemin 2003, Endo 2004, Roh 2005, Iihara 2006)	• The 30-day RR of stroke, stroke/death and long-term risk of stroke and restenosis are consistently higher for CAS • Data is lacking on risks in asymptomatic patients (with 1 exception - Kentucky 2004 - no controlled trials have specifically addressed the asymptomatic population)
Bangalore (2011)	through June 2010	Meta-analysis of the periprocedural and intermediate to long-term benefits and harms of CAS compared with CEA	• Periprocedural (≤ 30-day) outcomes: death, MI, or stroke; death or any stroke; any stroke; and MI • Intermediate to long-term outcomes: composite of periprocedural death, MI, or stroke plus ipsilateral stroke or death thereafter; periprocedural death or stroke plus ipsilateral stroke thereafter; death or any stroke; and any stroke • Other: cranial nerve injury; carotid restenosis	• 13 RCTs (N = 3754 CAS; N = 3723 CEA): WALLSTENT, BACASS, Kentucky 2001, Kentucky 2004, CAVATAS, CREST, EVA-3S, ICSS, Leicester, SAPPHIRE, SPACE, Steinbauer 2008, TESCAS-C	• CAS was associated with an increased risk of both periprocedural and intermediate to long-term outcomes, but with a reduction in periprocedural MI and cranial nerve injury
Bonati (2012)	Through January 2011	Systematic review and meta-analysis of the benefits and risks of CAS versus CEA or medical therapy in patients with symptomatic or asymptomatic carotid stenosis	• Periprocedural (≤ 30-day) outcomes: death; stroke; ipsilateral stroke; death or stroke; fatal, major or disabling stroke; MI; cranial nerve palsy, access site hematoma • Intermediate to long-term outcomes: stroke; ipsilateral stroke; death or stroke; severe restenosis	• 16 Trials (N=7572) (EVA-3S 2004, 2006, CREST 2010, CAVATAS-CEA 2001, CAVATAS-MED 2009, WALLSTENT 2001, TESCAS-C 2006, BACASS 2008,ICSS 2010, Leicester 1998, Kentucky 2001, Kentucky 2004, Regensburg (Steinbauer) 2008, Beijing (Liu) 2009, SAPPHIRE 2004, ICSS 2010, Beijing 2003, SPACE 2006)	• CAS is associated with an increased risk of peri-procedural stroke or death compared with CEA. • This excess risk appears to be limited to older patients. • The longer term efficacy of CAS and the risk of restenosis are unclear and require further follow-up of existing trials. • Further trials are needed to determine the optimal treatment for asymptomatic carotid stenosis.
Bersin (2012)	Does not state (submitted January 2012)	Meta-analysis of the effect of proximal occlusion devices in carotid stenting on 30-day adverse events ***Does not compare use of EPD versus no EPD***	• Periprocedural (≤ 30-day) outcomes: composite of major adverse cardiovascular and cerebral events, death, MI, stroke, or intolerance (device use interruption or alternate device use)	• Single-arm trials: EMPiRE, ARMOUR, Nikas 2012 • Registry Studies: Stabile 2010, Reimers 2005, Stabile 2012.	• In CAS procedures performed with proximal occlusion devices, incidence of stroke was 1.71%, of myocardial infarction was 0.02% and death was 0.40%. • Age and diabetic status were found to be the only significant independent risk predictors of adverse events

Review (year)	Lit search dates	Focus/procedure(s) evaluated	Key Questions	Evidence base	Conclusion
Gahremanpour (2012)	Through August 2011	Systematic review of the benefits and safety of CAS and CEA Summary of the effect of EPD in CAS on 30-day adverse events	• Periprocedural (≤ 30-day) outcomes: death, MI, or stroke; death or any stroke; death or disabling stroke	• 41 studies included in the review • RCTs (Leicester 1998, WALLSTENT 2001, Kentucky 2001, Kentucky 2004, EVA-3S 2006, TESCAS-C 2006, SAPPHIRE 2008, SPACE 2008, Steinbauer 2008, BACASS 2008, CAVATAS 2009, CREST 2010, ICSS 2010) • 1 prospective nonrandomized study (CaRESS 2005) • Registry studies of CAS and CEA (SECURITY 2011, SAPPHIRE 2009, CREATE 2007, PASCAL 2007, ARCHer 20006, BEACH 2006, CREATE SpiderOTW 2006, MAVErIC 1+2 2006, MAVErIC Int'l 2006, CABERNET 2005, Mo.Ma 2005, PRIAMUS 2005)	• Within the 30-day periprocedural period, carotid stenting was associated with higher risks of stroke, especially for patients aged >70 years, whereas carotid endarterectomy was associated with a higher risk of myocardial infarction. • Carotid artery stenting is an equivalent alternative to carotid endarterectomy when patient age and anatomy, surgical risk, and operator experience are considered in the choice of treatment approach.
Roffi (2009)	Through July 2009	Meta-analysis of the efficacy of CAS versus CEA (RCT's only)	• Periprocedural (≤ 30-day) outcomes: death, MI, or stroke; death or any stroke; death or disabling stroke	• RCTs of CAS vs. CEA (Leicester 1998, WALLSTENT 2001, Kentucky-Sympt 2001, Kentucky-Asympt 2004, EVA-3S 2006, SAPPHIRE 2004, SPACE 2006, BACASS 2008, CAVATAS 2001, ICSS 1009) • Registry studies of CAS (CAPTURE1007, CASES PMS 2007, PRO-CAS 2008, SAPPHIRE-W 2009, SVS 2009, EXACT 2009, CAPTURE 2009	• Randomized Controlled Trials: CAS was associated with a significantly increased risk of death or stroke rate at 30 days compared with CEA (OR 1.60(1.26–2.02)). • Beyond 30 days, long-term follow-up of the trials previously reported suggest that both revascularization techniques are equivalent in terms of stroke prevention. • CAS registries have, for the most part, reported rates of death/stroke in the range of current recommendation for CEA (<6%) in over 20 000 patients, despite the fact that the majority of patients were at high risk for surgery.
Ringleb 2008	Search was limited to publications between October 2004 and March 2007	Meta-analysis of the efficacy of CAS vs. CEA (RCT's only)	• Periprocedural (≤ 30-day) outcomes: death, or stroke; 30-day death or disabling stroke	• N=2,985 (8 trials) (EVA-3S, SPACE, Leicester, WALLSTENT, CAVATAS, Kentucky-A, Kentucky-B, SAPPHIRE)	• Risk of any stroke or death within 30 days after treatment was greater for EAS versus CEA**:** OR 1.38 (1.04-1.83) • There was an increase of the odds of suffering from disabling stroke or death for CAS versus CEA, though not significant (OR, 1.37; 95% CI, 0.92-2.04; *P*=.12) • In the analysis of the large trials with symptomatic patients, the risk of any stroke or death was not significantly different between CAS and CEA (OR=1.29 (95% CI 0.94-1.76; *P* = .11); For the endpoint disabling stroke or death, the OR was 1.33 (95% CI 0.89-1.93; *P* =.17)

ARCHeR: ACCULINK for Revascularization of Carotids in High Risk Patients; ACAS: Asymptomatic Carotid Atherosclerosis Study; ARMOUR: Proximal Protection with the Mo.Ma Device During Carotid Artery Stenting; BACASS: Basel Carotid Artery Stenting Study; BEACH: Boston Scientific EPI: A Carotid Stenting Trial for High-

Risk Surgical Patients; CABERNET: Carotid Artery revascularization using the Boston Scientific FilterWire EX1/EZ and the EndoTex NexStent; CAPTURE: Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events; CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CASES-PMS: Carotid Artery Stenting With Emboli Protection Surveillance–Post-Marketing Study; CAVATAS: Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA: carotid endarterectomy; CREATE: Carotid Revascularization with ev3 Arterial Technology Evolution; CREST: Carotid Revascularization Endarterectomy versus Stenting Trial; EMPiRE: Embolic Protection with Reverse Flow Study of the GORE Neuro Protection System in Carotid Stenting of Subjects at High Risk for Carotid Endarterectomy; EPD: embolic protection device; EVA-3S: Endarterectomy versus Angioplasty in patients with Severe carotid Stenosis Study; EXACT: Emboshield and Xact Post Approval Carotid Stent Trial; ICSS: International Carotid Stenting Study; MAVErIC: Medtronic AVE Self-expanding CaRotid Stent System with distal protection In Carotid Stenosis; Mo.Ma: Mo.Ma proximal flow blockage cerebral protection device; MI: myocardial infarction; NASCET: North American Symptomatic Carotid Endarterectomy Trial; NR: not reported; OR: odds ratio; PASCAL: Performance And Safety of the Medtronic AVE Self-Expandable Stent in Treatment of Carotid Artery Lesions; PRIAMUS: PRoximal flow blockage cerebral protection during cArtoid stenting; PRO-CAS: Prospective registry of CAS (installed by the German Society of Angiology/Vascular Medicine and the German Society of Radiology); RCT: randomized controlled trial; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SECURITY: Registry Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy; SPACE: Stent-Protected Angioplasty versus Carotid Endarterectomy; TESCAS-C: Trial of Endarterectomy versus Stenting for the Treatment of Carotid Atherosclerotic Stenosis in China.

2.9.Medicare and Representative Private Insurer Coverage Policies

Information on the CMS national coverage decision and a sample of bell-weather payer policies are provided below. As required by the Health Technology Assessment program, only two payer policies are required. The table below provides an overview of policy decisions.

- **Medicare (National Coverage Determination)**
  The Centers for Medicare and Medicaid Services (CMS) will cover PTA both with and without the placement of a stent (CAS) when used in accordance with FDA-approved protocols for carotid artery dilation for patients who are at high risk for the likely alternative treatment carotid endarterectomy (CEA) or in FDA-approved Category B Investigational Device Exemption (IDE) clinical trials and Post-Approval studies. Coverage for all other devices is at the discretion of local CMS contractors.

- **Aetna**
  Aetna considers extracranial PTA of the carotid and vertebral arteries with or without stent implantation and embolic protection in symptomatic patients with >50% stenosis medically necessary. Aetna considers intracranial artery stenting to be investigational.

- **BlueCross BlueShield of North Carolina (Corporate Policy)**
  BCBSNC will provide coverage for carotid angioplasty with associated stenting and embolic protection for patients with 50-99% stenosis (NASCET measurement), symptoms of focal cerebral ischemia (TIA or monocular blindness) in previous 120 days

with symptom duration less than 24 hours or nondisabling stroke, and anatomic contraindications for carotid endarterectomy. Carotid angioplasty with or without stenting and embolic protection is considered investigational for all other indications.

- **Health Net**
  Health Net considers endovascular carotid balloon angioplasty with or without stent implantation medically necessary for patients in a FDA approved protocol governing Category B IDE trial, or have a carotid artery narrowed by fibromuscular dysplasia or a vasculitic condition, or symptomatic recurrent carotid artery stenosis after carotid endarterectomy, or patients at high risk for adverse perioperative outcomes such that carotid endarterectomy would be prohibitive, or a surgically hostile neck. This technique is considered investigational for patients with significant atherosclerotic stenosis at the bifurcation of the carotid arteries.

- **Priority Health**
  Priority Health covers extracranial carotid artery stenting with devices approved for indications of use, patients with a reference vessel diameter within the range of 4.0–9.0 mm at the target lesion, and >70% stenosis of the common or internal carotid artery by ultrasound with or without neurological symptoms, >60% stenosis by angiogram without symptoms, or >50% stenosis by angiogram with symptoms. Intracranial angioplasty is considered investigational and not covered.

- **Cigna**
  Cigna covers carotid artery stenting with a FDA approved system for patients at high risk for adverse events from carotid endarterectomy and requires revascularization and has >50% stenosis of the common or internal carotid artery by ultrasound, magnetic resonance imaging, or arteriogram with neurological symptoms or >80% stenosis without neurological symptoms.

Table 5. Overview of payer policies for carotid artery stenting

Payer (year)	Stent(s) evaluated	Evidence base available	Policy	Rationale
Centers for Medicare & Medicaid Services (CMS): **Pub 100-03 National Coverage Determinations: 20.7 – PTA, Version 10** **(2013)**	NR	Unable to determine	• CAS (with PTA) is covered when used in accordance w/ FDA-approved protocols governing Category B IDE clinical trials or post-approval studies if used with an FDA-approved or -cleared embolic protection device • CAS (with PTA and embolic protection) is covered for: o Patients at high risk for CEA with symptomatic carotid artery stenosis >70 % with FDA-approved carotid artery stenting systems and embolic protection devices o Patients at high risk for CEA with symptomatic carotid artery stenosis between 50 % and 70% in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the NCD on carotid artery stenting (CAS) post-approval studies o Patients at high risk for CEA with asymptomatic carotid artery stenosis >80 %, in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the NCD on CAS post- approval studies • Facilities must meet CSM's personnel, equipment, programming, emergency management, and data collection standards in order to receive coverage of CAS for high risk patients • Coverage of PTA with stenting not specifically addressed or discussed in this NCD is at local Medicare contractor discretion.	• NR
Aetna: **Pub 0276 Clinical Policy Bulletin: Angioplasty and Stenting of Extra-Cranial and Intra-Cranial Arteries** **(2013)**	NR	1 NICE rapid review, CMS national coverage report, additional studies	Extracranial • Aetna considers PTA of the extra-cranial carotid and vertebral arteries, with or without stent implantation and embolic protection, medically necessary in symptomatic individuals with ≥50% stenosis of the carotid artery or the vertebral artery Intracranial • Aetna considers PTA, with or without stenting, of the intra-cranial arteries experimental and investigational for the prophylaxis or treatment of both atherosclerotic stenosis of intra-cranial arteries	• Preliminary retrospective evidence that balloon angioplasty, with or without stenting, may be effective in treating symptomatic patients with intra-cranial stenoses
BlueCross BlueShield of North Carolina: **Corporate Medical Policy: Carotid Artery Angioplasty/ Stenting (CAS)** **(2012)**	NR	unspecified RCTs, unspecified database studies, unspecified non-randomized studies	• BCBSNC will provide coverage for carotid angioplasty with associated stenting and embolic protection when it is considered to be medically necessary if the medical criteria and guidelines listed below are met o Carotid angioplasty with associated stenting and embolic protection may be considered medically necessary in patients with 50-99% stenosis (NASCET measurement) o Symptoms of focal cerebral ischemia (transient ischemic attack or monocular blindness) in previous 120 days with symptom duration less than 24 hours, or nondisabling stroke o Anatomic contraindications for carotid endarterectomy such as prior radiation treatment or neck surgery, lesions surgically inaccessible, spinal immobility, or tracheostomy • The ACT-1 clinical trial is considered a covered clinical trial for	• The evidence does not support use of CAS in carotid artery disease for the average risk patient, since early adverse events are higher with CAS and long-term outcomes are not better. Data from RCTs and large database studies establish that the risk of CAS exceeds the threshold set to indicate overall benefit from the

Payer (year)	Stent(s) evaluated	Evidence base available	Policy	Rationale
			patients who meet trial eligibility • Carotid angioplasty with or without associated stenting and embolic protection is considered investigational (not covered) for all other indications, including but not limited to, patients with carotid stenosis who are suitable candidates for CEA and patients with carotid artery dissection	procedure
Health Net: **Policy NMP142 National Medical Policy: Carotid Angioplasty and Stenting** **(2012)**	NR	4 RCTs, 1 HTA, 6 non-randomized studies, 1 meta-analysis, additional studies	• Health Net, Inc. considers this technique medically necessary if: o Patient is enrolled in a Food and Drug Administration (FDA) approved protocol governing category B Investigational Device Exemption (IDE) trials o Carotid artery is narrowed by fibromuscular dysplasia or a vasculitic condition o Symptomatic recurrent carotid artery stenosis after carotid endarterectomy o Patients at high risk for adverse perioperative outcomes (e.g., atherosclerotic obstructive lesions, severe cardiac dysfunction, requirement for combined coronary and carotid vascularization, severe pulmonary dysfunction, contralateral internal carotid artery occlusion and previous ipsilateral carotid endarterectomy) such that carotid endarterectomy would be prohibitive o A surgically hostile neck (e.g., high carotid bifurcation, prior non-vascular surgery, prior radiation to the neck) • Endovascular carotid balloon angioplasty, with or without stent implantation, is under investigation in patients with significant atherosclerotic stenosis at the bifurcation of the carotid arteries • ICD-9 Codes: 433.10, 433.11 • CPT Codes: 35475, 36100, 36215, 36216, 36217, 37205, 37206, 37215, 37216, 75650, 75660, 75662, 75665, 75671, 75676, 75680, 75960, 0005T, 0006T, 0075T, 0076T; (2011 revisions: 37205, 37206, 75960) • HCPCS Codes: C1725, C1874, C1875, C1876, C1877, S2211	• Significantly higher risk of 30-day death or any stroke after CAS • Limited evidence and a clinical rationale to suggest CAS may be beneficial in the group of patients at increased anatomic risk
Priority Health: **Policy 91495-R4 Medical Policy: Carotid and Intracranial Stenting** **(2012)**	NR	2 RCTs	Extracranial • Priority Health will cover carotid artery stenting when *all* of the following are present: o Device is FDA approved for indications of use o Patient must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion • *Either* of the following: o Patient *with* neurological symptoms and a > 70% stenosis of the common or internal carotid artery by ultrasound or > 50% stenosis of the common or internal carotid artery by angiogram o Patient *without* neurological symptoms and a > 70% stenosis of the common internal carotid artery by ultrasound or > 60% stenosis of the common internal carotid artery by angiogram Intracranial • Intracranial angioplasty, with or without stenting for the treatment of atherosclerotic lesions, intracranial vasospasm, or any other indication, is considered investigational and not a covered benefit	• Increased dislocation of microemboli during CAS is thought to be the underlying cause for the increased risk of neurologic complications, risk may be reduced with the use of embolic protection devices • Outcome did not statistically differ between treatment groups in intention-to-treat analysis, and occurrence favored stenting in analysis of those actually treated, target vessel revascularization rates, as well as incidence of major

Payer (year)	Stent(s) evaluated	Evidence base available	Policy	Rationale
			• ICD-9 Codes: 433.10, 433.11, 433.30, 433.31 • CPT/HCPCS Codes: 37215, 37216, 0075T, 0076T • Codes not covered: 61630, 61635, 61640, 61641, 61642	ipsilateral stroke within 1 year of treatment, were significantly lower in the stent versus endarterectomy group
Cigna: **Policy 0101: Carotid Artery Stenting for Carotid Artery Stenosis** **(2011)**	NR	19 RCTs (n = 7484), 5 meta-analyses, 2 HTAs, 1 NIH sponsored study, 1 NICE rapid review, unspecified non-randomized trials, additional studies	• Cigna covers carotid artery stenting using a FDA-approved carotid stent system for carotid artery stenosis as medically necessary when the following criteria are met: ○ The individual is at high risk for adverse events from carotid endarterectomy and requires revascularization, the individual has ONE of the following, as demonstrated on ultrasound, magnetic resonance angiography, or arteriogram: neurological symptoms and > 50% stenosis of the common or internal carotid artery ○ No neurological symptoms and > 80% stenosis of the common or internal carotid artery • CPT Codes: 37215, 37216, 0075T, 0076T • ICD-9 Codes: 433.10, 433.11, 433.30, 433.31	• Evidence that CAS is safe and effective in treating severe (50–70%) carotid artery stenosis in high-risk symptomatic patients, limited evidence that CAS can reduce severe (>80%) stenosis in patients who have not yet begun to experience neurological symptoms. Clinical equipoise of CAS and CEA; needs to be confirmed in additional prospective, randomized clinical trials
CMS: **Decision Summary** **(2006)**	NR	14 case series reports	• The treatment of cerebral artery stenosis >50% in patients with intracranial atherosclerotic disease with intracranial PTA and stenting is reasonable and necessary when furnished in accordance with the FDA-approved protocols governing Category B-IDE clinical trials	• NR

ACT-1: Asymptomatic Carotid Trial; BCBSNC: Blue Cross and Blue Shield of North Carolina; CAS: Carotid Artery Stenting; Category B-IDE: Investigational Device Exemption; CEA: Carotid Endarterectomy; CMS: Center for Medicaid & Medicare Services; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; FDA: Food and Drug Administration ; ICD-9: International Classification of Diseases ; NASCET: North American Symptomatic Carotid Endarterectomy Trial; NCD: National Coverage Determination; NICE: National Institute for Health and Care Excellence; NR: not reported; PTA: Percutaneous Transluminal Angioplasty.

2.10. Other Significant Evidence

As of June 2013, five comparative clinical trials were found evaluating carotid artery stenting versus either medical therapy or carotid endarterectomy that have yet to publish their data. Four of the five are in asymptomatic patients. Three are currently recruiting participants, one completed enrollment in 2011, and one (ACT-I) was terminated as a business decision by the sponsor. A brief overview of these trials can be found below.

Trial	Sponsor	Status	Start Date	Purpose
Stenting Versus Best Medical Treatment of Asymptomatic High Grade Carotid Artery Stenosis	Vienna General Hospital	Completed 2011 (last updated 2013)	March 2004	To analyze neurological and cardiovascular outcome of asymptomatic patients treated with elective CAS plus best medical treatment compared to best medical treatment only
Carotid Endarterectomy Versus Carotid Artery Stenting in Asymptomatic Patients (ACST-2)	University of Oxford	Currently recruiting participants	January 2008	To look at the immediate (within one month) risks (MI, stroke and death) and long term benefits of CEA versus CAS in asymptomatic patients
Comparing Carotid Stenting With Endarterectomy in Severe Asymptomatic Carotid Stenosis	Carmel Medical Center	Currently recruiting participants	January 2009	Comparison of cardiovascular mortality and morbidity which includes cardiac and neurological morbidity (TIA and CVA) in the two invasive treatments of asymptomatic carotid artery stenosis (i.e. CAS and CEA)
Carotid Endarterectomy Versus Carotid Artery Stenting? A Prospective Comparison of Neuropsychological Outcome in Patients With Carotid Stenosis	University Ghent	Currently recruiting participants	April 2011	To observe the absence or presence of preoperative impairments, postoperative changes in cognitive performance and possible differences between CEA and CAS regarding postoperative neuropsychological functions
Carotid Stenting versus Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I)	Abbot Vascular	Terminated– business decision by the sponsor and not a result of any patient or product safety issues	April 2005	To demonstrate the non-inferiority of CAS using the Emboshield® Embolic Protection System with the Xact® Carotid Stent System to CEA for the treatment of asymptomatic extracranial carotid atherosclerotic disease

Abbreviations: CAS: carotid artery stenting; CEA: carotid endarterectomy; CVA: cerebrovascular accident; MI: myocardial infarction; TIA: transient ischemic attack.

3. The Evidence

3.1.Methods of the Systematic Literature Review

3.1.1. Inclusion/exclusion

The focus of this HTA is on treatment of atherosclerotic disease in the carotid arteries and intracranial arteries in adult patients comparing the use of stents with other treatment options. Given that the benefits and risks of treatment may be different for asymptomatic and symptomatic disease, the population subsets were evaluated separately. Input from clinical experts was incorporated to formulate final inclusion and exclusion criteria.

- *Population.* 1) Adults with extracranial carotid artery stenosis undergoing primary treatment for symptomatic or asymptomatic atherosclerotic carotid artery stenosis who have not had previous revascularization. 2) Adults with atherosclerotic stenosis of intracranial arteries
- *Intervention.* Stenting of carotid arteries (with or without use of embolic protection devices or strategies) or stenting of intracranial arteries, using FDA approved devices
- *Comparator.* Medical therapy or surgical alternatives including carotid endarterectomy (CEA)
- *Outcomes.* The primary critical outcomes for long term efficacy included any stroke, ipsilateral stroke, death, the composite of stroke or death. Primary critical outcomes for safety were periprocedural (30 day) any stroke, death, the composite of stroke or death, myocardial infarction, major bleeding complications and persistent cranial nerve palsy. Additional outcomes are listed in the inclusion/exclusion table below.
- *Study design.* The focus for all key questions was on evidence judged to have the least potential for bias.

Inclusion and exclusion criteria are summarized in Table 6

Table 6. Summary of inclusion and exclusion criteria

	Include	Exclude
Population	1) Adults with extracranial carotid artery stenosis undergoing primary treatment for *de novo* symptomatic or asymptomatic atherosclerotic carotid artery disease • Eligible stenosis: atherosclerotic narrowing of the lumen of the carotid artery between 50 to 99 percent, as defined by any invasive imaging modality (digital subtraction angiography) or noninvasive imaging modality (carotid duplex ultrasound (DUS), computed tomography angiography (CTA) or magnetic resonance angiography (MRA)). • Unilateral and bilateral stenosis 2) Adults with symptomatic or asymptomatic atherosclerotic disease of the intracranial carotid artery distribution undergoing primary treatment for *de novo* atherosclerotic disease.	• Patients < 18 years of age • Patients having re-treatment for re-stenosis (For Key Question 4, to evaluate the extent to which there is differential effectiveness in high versus. standard surgical risk patients, we included comparative studies that in which up to 30% of patient population may have had prior CEA, angioplasty or have presented for treatment for restenosis.) • Patients requiring treatment for conditions other than atherosclerotic disease including aneurysm, pseudoaneurysm, trauma, post-radiation stenosis, AVM, etc. • Patients with total ipsilateral carotid occlusion (100% obstructed) as they are not generally candidates for revascularization • Patients with extracranial vertebral artery disease, subclavian or innominate artery disease
Intervention	• External carotid artery stenting (with or without protection devices or strategies) using FDA approved device • Stenting of intracranial arteries	• Stenting of the extracranial vertebral artery, subclavian or innominate arteries • Comparisons of different stent types or techniques for stenting • Comparison of angioplasty versus angioplasty with stenting • Angiography without stenting (stenting must be used in ≥ 80% of persons in that treatment arm) • Comparisons of different protective filters or deployment • Non-FDA approved devices or devices not in final stages for FDA approval
Comparators	• Medical therapy • Surgical alternatives including carotid endarterectomy (CEA)	• Comparisons of different surgical techniques or CEA methods • Comparison of different medical therapies • Comparisons between CEA and medical therapy alone
Outcomes	<u>Primary outcomes :</u> • Prevention of embolic events and stroke (fatal and nonfatal) • Death (cardiovascular-related) • Myocardial infarction (fatal and nonfatal) • Neurological status (e.g. ischemic visual symptoms) • Functional status (including cognitive function) • HRQOL and patient reported outcomes <u>Secondary outcomes</u> • Composite outcomes measures • Re-vascularization after index procedures <u>Safety: (devices, periprocedural or procedure related)</u> • Mortality • Embolic complications (including stroke or ischemic attack) • Evaluation against acceptable peri-procedural death/stroke rate of <3% for asymptomatic persons with at least 5 year life expectancy and <6% for symptomatic persons with at least 2 year	• Computational fluid dynamics, flow simulation or evaluation of flow

	Include	Exclude
	projected life expectancy. • Stent thrombosis • Intracranial hemorrhage • Other reported complications or events (e.g. myocardial infarction, facial or cranial neuropathy)	
Study design	• Randomized controlled trials (RCTs) for Key Questions 1, 2 and 4. Non-randomized comparative studies with low potential for bias will be considered. Studies with ≥ 30 patients per intervention group will be considered. Studies based on administrative data will be considered if no high quality (e.g. RCT, high quality cohort) studies with low risk of bias are available. Case series will be excluded if comparative studies are available. Prospective case series will be included if comparative studies are not available. • Recent, high quality systematic reviews, comparative effectiveness reviews or HTAs may be included as part of the evidence synthesis to address specific questions. • For Key Question 3 (safety), in addition to data from RCTs, non-randomized studies, including prospective case series designed specifically to evaluate adverse events may be considered. • Formal, full economic studies will be sought for Key Question 5.	• Studies that do not encapsulate current best medical therapy • Animal, laboratory or in vitro studies • Non-clinical studies, • Studies for which data for asymptomatic and symptomatic patients could not be separated. • Studies of technique, imaging options, flow dynamics, etc. • Studies of genetic markers or non-treatment related risk factors for re-stenosis • Series with N < 100 for studies of carotid disease; series with N < 50 for studies of intracranial arteries; (prospective series only, considered if comparative studies are not available).. • Studies based on administrative data if studies with lower potential for bias are available. (May be included for background/context only but will not be included in grading of evidence base)
Publication	• Studies published in English in peer-reviewed journals, published HTAs or publically available FDA reports • Full formal economic analyses (e.g. cost-utility studies) published in English in HTAs or in a peer-reviewed journal published after those represented in previous HTAs	• Studies reporting only on the technical aspects of stenting (e.g., imaging, type of catheter, etc.) • Abstracts, editorials, letters • Unpublished studies • Duplicate publications of the same study which do not report on unique outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

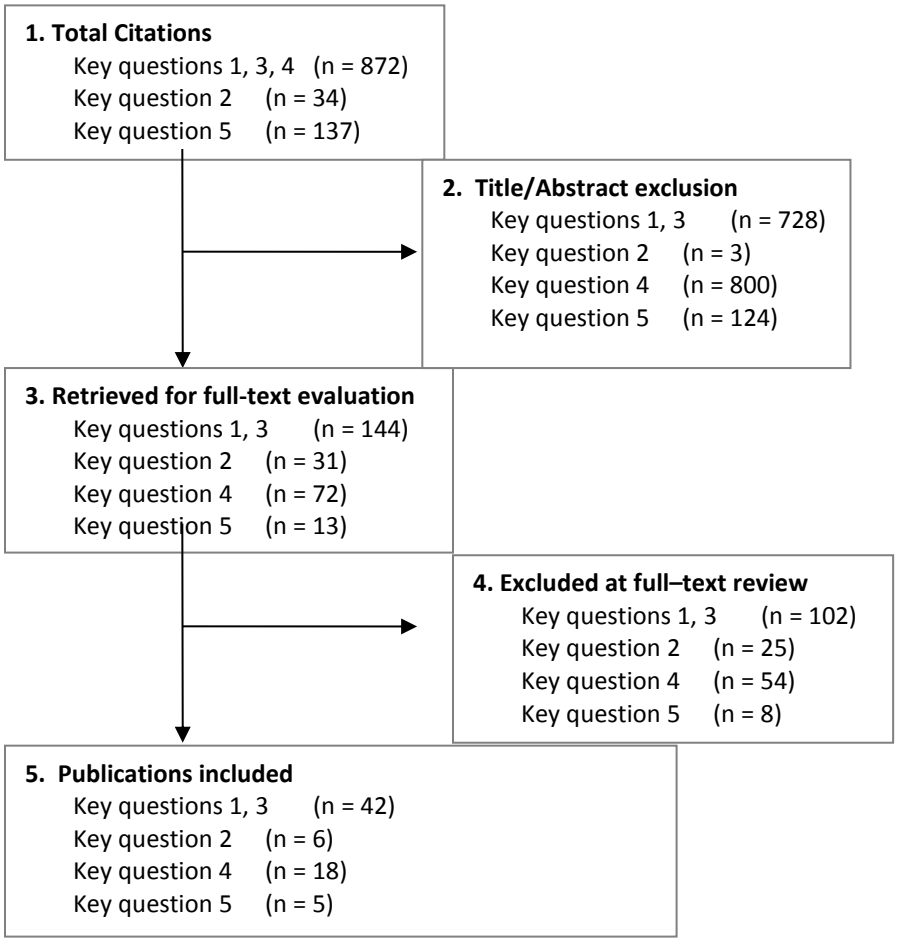
3.1.2. Data sources and search strategy

Electronic databases searched included PubMed, EMBASE, ClinicalTrials.gov, *The Cochrane Library*, AHRQ, and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and relevant FDA reports. Reference lists of all eligible studies were also searched. For studies related to atherosclerotic carotid stenosis, searches were conducted through February 2013. For the treatment of intracranial artery atherosclerotic disease, searches were conducted through January 2013. For studies related to economics and cost-effective, searches were conducted through March 2013. The search strategies and relevant dates are shown in Appendix B.

Figure 1 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed in Appendix C.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search and selection took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. All possible relevant articles were then using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using the set of *a priori* inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Figure 2. Flow chart showing results of literature search



3.1.3. Data extraction

Reviewers extracted the following data from the included comparative clinical studies: study population characteristics, study type, patient demographics, study interventions, follow-up time, study outcomes, complications/adverse events. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Detailed abstraction for case series was not done. For economic studies, study funding and location, population characteristics, treatments evaluated, methods used (including perspective, model used, and time horizon), evidence base and assumptions, cost estimates, economic parameters and perspectives, and results for base-case and any sensitivity analyses were abstracted. Detailed abstraction tables may be found in Appendix F (key questions 1, 2, 3, and 5) and G (key question 4).

3.2. Methods of Data Analysis and Evidence Synthesis

3.2.1. Data analysis and synthesis of evidence

Studies of asymptomatic and symptomatic patients were evaluated separately. Study, treatment, population, and outcome characteristics were summarized in text and/or summary tables. Results are summarized in tables and/or figures. Risk differences, and associated confidence intervals were used to describe effect size for hard outcomes (e.g. death, stroke) when in may be reasonable to consider causality. Risk ratios were also provided. When possible, data from RCTs were pooled. Requirements for pooling include similar methodology, similar clinical characteristics (including study population, interventions, and how the outcome was determined),[72] and similar follow-up. Data were not pooled from nonrandomized trials. Meta-analysis was performed to compare the effect of carotid artery stenting (CAS) with carotid endarterectomy (CEA) using Review Manager (RevMan) 5.2 software used for preparing Cochrane Reviews. A random effects was model used. The Mantel-Haenszel method was implemented to generate pooled estimates. The effect size was measured by the risk difference and risk ratio between treatments together with 95% confidence intervals. Studies with zero events in each study arm were excluded from the meta-analysis of the outcome for which there were no events.[72] The inclusion of completed trials with those which were terminated prior to complete enrollment may be a source of heterogeneity for pooled analyses. The BACASS and Leicester studies had 20 or fewer total patients. These two studies in addition to the Regensburg, studies enrolled patients prior to the year 2000. Four studies did not include stenting with the use of embolic protection.[45,46,141,170] These additional factors may also be sources of heterogeneity for pooled analyses. Heterogeneity was explored by performing analyses which excluded older studies, small studies and those which did not use embolic protection as these were considered possible sources of clinical heterogeneity based on visual inspection of forest plots. In addition a

limited comparison of our meta-analysis results to those from the recent Cochrane review by Bonati as a sensitivity analysis was done.[41] Patient-level data were available for some analyses in this Cochrane review. Tests for statistical interaction were performed if patient event data were available to evaluate potential differential effects and safety for population subgroups using RevMan. Risk difference and risk ratios were presented for primary outcomes. Number needed harm or number needed to treat was reported only for outcomes that were well measured, when the following conditions were met: the risk difference between treatments was statistically significant and there was reason to believe that the association was causal. Statistical significance based on evaluation of risk difference was used.

Outcomes

The primary critical outcomes for short- and long-term efficacy and effectiveness included any stroke, ipsilateral stroke, death, the composite of stroke or death. These are the primary outcomes for which the overall strength (quality) of evidence was evaluated. Additional outcomes of interest included changes in functional status, quality of life and cognitive ability. Restenosis and need for revascularization procedures following the index procedure were considered secondary outcomes as were other composite measures. Composite endpoints (with the exception of the composite of stroke or death) were not considered primary outcomes for this HTA report. Such endpoints are challenging to interpret when components are equally weighted and when the direction of the events for some component(s) move in the opposite direction of other components. This may result in lack of statistical significance between treatments in the composite endpoint, difficulty in evaluating the types of events which drive any effects seen and different observed behavior across study arms.

Primary critical outcomes for safety were periprocedural stroke, death, the composite of stroke or death, myocardial infarction, major bleeding complications and persistent cranial nerve palsy. These are the primary outcomes for which the overall strength of evidence was evaluated. Given the recommendations made in clinical guidelines for the treatment of atherosclerotic carotid stenosis, evaluation of reported outcomes against acceptable peri-procedural death or stroke rate of <3% for asymptomatic persons with at least 5 year life expectancy and <6% for symptomatic persons with at least 2 year projected life expectancy was sought. Unfortunately, studies did not provide data on the potential life expectancy of patients in their studies.

There was variability in how "periprocedural" was defined across RCTs. The precise period was not described in the following studies: Regensberg,[170] Kentucky 2001[45] or Kentucky 2004.[46] Definitions for the other studies were as follows:

- CREST (all studies)[48,167]: 30-days from intervention (for those who did not undergo procedure w/in 30 days of randomization - 36 days from randomization)
- EVA (2006)[128]: 30 days after treatment - excludes events occurring between randomization and treatment
- SPACE (2006)[153]: 30 days after treatment (for those who did not undergo treatment - 30 days from randomization)
- ICSS (2010)[65]: evaluated 30 days after treatment; Two analyses were conducted: Intention to treat (ITT) included all events occurring up to 120 days after randomization and per protocol analysis within 30 days of treatment.
- Leicester[141]: 30 days after treatment
- BACASS[93]: 1 month after procedure

Definitions or criteria for determining some outcomes were not always provided in studies and changes in protocol were generally not described in published studies. Outcomes criteria/definitions related to myocardial infarction changed during the CREST trial, which may influence the rates of MI.[2] For evaluation of myocardial infarction, reliance on periprocedural elevations in cardiac enzymes alone may lead to misclassification. Outcomes from formal economic analyses may include various incremental cost effectiveness ratios and related parameters, e.g. cost per quality of life year gained.

Various assessment and outcomes measures for stroke severity, functional status, health-related quality of life or cognitive status were reported in included studies. Measures used in RCTs are summarized in Table 7 below. Additional detail on information on measures used in nonrandomized studies is contained in Appendix H.

Table 7. Description of instruments used in included RCTs

Measure Clinician or patient reported Instrument type	Reported in these RCTs	Components Score Range	Interpretation	Validity and reliability	MCID
National Institutes of Health Stroke Scale (NIHSS) CBO Disease Specific	Brooks (2001) Brott (2010) Eckstein (2008) Ringleb (2006)	11 subscales (13 items): • Level of consciousness • Horizontal eye movement • Visual field test • Facial palsy • Motor arm • Motor leg • Limb ataxia • Sensory • Language • Dysarthria • Extinction and inattention Score range 0-42	0 = No stroke symptoms 1-4 = Minor stroke 5-15 = Moderate stroke 16-20 = Moderate to severe stroke 21-42 = Severe stroke	5 studies[78,80,104,136,177,182] Intraclass correlation coefficient 0.93 and 0.95 [80]	NR
Barthel Index CBO Disease Specific	Brooks (2001) Brooks (2004)	5 subscales (10 items): • Self-care • Walking • Transfers • Controlling bowels and bladder • Feeding Score range: 0-100	Lower score = greater disability	9 studies[58,62,82,84,98,123,149,161,162] Reliability coefficient .4±.2 [84] Validity rho 0.89 (week 1) 0.95 (week 3) and 0.98 (week 6)[98] Spearman correlation coefficient median 0.96 [123] Overall reliability kappa = 0.46 [149] Internal consistency reliability coefficient 0.9 [162]	1.85 in stroke patients
Pain Scale PRO General	Brooks (2001) Brooks (2004)	1 subscale (1 item): • Pain Score range: 0-10	Higher score = greater pain	NR	NR
Modified Rankin Scale (mRS) PRO Disease specific	Brooks (2001) Brott (2010) CAVATAS (2001) Eckstein (2008) Ederle (2010) Mas (2006)	1 subscale (1 item): • Degree of disability or dependence in daily activities Score range: 0-6	0 = No symptoms 1 = No significant disability 2 = Slight disability 3 = Moderate disability 4 = Moderately severe disability 5 = Severe disability 6 = Dead	4 studies[164,180,181,190] Intraclass correlation coefficient 0 .947 (neurologists) and 0.963 (nurses/physiotherapists) [164] Unweighted kappa 0.44, weighted kappa	NR

Measure Clinician or patient reported Instrument type	Reported in these RCTs	Components Score Range	Interpretation	Validity and reliability	MCID
	Mas (2008) Ringleb (2006)			0.78 [180] Unweighted kappa 0.25, weighted kappa 0.71 [181] Intraclass correlation coefficient 0.675 [190]	
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) PRO General Health	Brott (2010)	8 subscales (36 items): • Physical functioning • Bodily pain • Physical role limitations • General health • Vitality • Social functioning • Emotional role limitations • Mental health Score range: 0-100	Lower score = greater disability	2 studies[28,57] Cronbach's alpha >0.7 [28] Intraclass correlation coefficient 0.28 [57]	NR
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Physical component PRO Physical health	Brott (2010)	• None Score range: 0-100	Lower score = greater disability	1 study[57]	NR
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Mental component PRO Mental health	Brott (2010)	• None Score range: 0-100	Lower score = greater disability	NR	NR
Transient Ischemic Attack (TIA) Stroke Questionnaire PRO Disease specific	Brott (2010)	3 subscales (8 items): • History of TIA • History of stroke • Sudden onset of any various focal neurologic symptoms consistent with TIA or stroke Score range: NA	NA	NR	NR
Oxfordshire Handicap Scale (OHS) CBO Disease specific	Naylor (1998)	1 subscale • Post-operative stroke Score range: 0-6	Lower score = less disability	NR	NR

ADL: Activities of daily living; CBO: clinician-based outcome;: IADL: Instrumental activities of daily living; MCID: Minimal clinically important difference; mRS: Modified Rankin Scale; NA: not applicable; NR: not reported; NIHSS: National Institutes of Health Stroke Scale; OHS: Oxfordshire Handicap Scale; PRO: patient-reported outcome; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; TIA: Transient Ischemic Attack;

3.2.2. Study quality assessment: Class of evidence (CoE) and risk of bias evaluation
The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual clinical studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine,[147] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,[31] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[22,178] No standard, universally accepted method of critical appraisal of economic analyses is currently in use. Completeness of reporting for economic studies was assessed using the Quality of Quality of Health Economic Studies (QHES)[144] and combined with other factors are important in critical appraisal of studies from health economist and epidemiologic perspectives. Although the precise guidelines that characterize high quality administrative database studies are still under development,[114] a number of criteria that should be met in a high quality administrative database study have been suggested.[114,174] A 12- item checklist based on these criteria was used as a basis for general critical appraisal of administrative studies. Based on the focus of using the studies with the least potential for bias as the primary evidence base and given concerns that administrative studies are at high risk of bias, the were not considered as part of the primary evidence base and not included in the determination of overall strength of evidence.

Details of the Class of Evidence/risk of bias evaluation and overall strength of evidence (SoE) methodology are found in Appendix D. Comparative studies chosen for inclusion were appraised and study limitations assessed based on the quality criteria listed in Appendix D. Standardized guidelines were used to determine the class of evidence for each comparative study included in this assessment. Determination of overall strength of evidence based on GRADE was done for the primary critical outcomes and focused on the highest quality evidence available to address the questions.

3.3. Quality of Literature Available

Quality of retained studies
The systematic search of bibliographic data bases produced 1043 citations using the search strategies in Appendix B. A total of 71 articles are contained in this report; 42 for key questions 1 and 3 (15 publications from 9 RCTs, 27 nonrandomized comparative studies), six for key question 2 (1 RCT, 5 case-series), 18 for key question 4 (1 meta-analysis, 8 publication from 5 RCTs, 9 nonrandomized comparative studies), and five formal economic evaluations for key question 5.

A 2012 AHRQ[150] review included 3 RCTS (CREST, SAPPHIRE, KENTUCKY 2004),[46,48,183] one of which was conducted in high-risk patients (SAPPHIRE).[183] Because the

SAPPHIRE trial addresses the efficacy and effectiveness of a special population (high-risk patients), we have limited our discussion of this study to key Question 4. Therefore, for the purposes of this HTA, data for the comparison of efficacy and effectiveness of CAS versus CEA (Key Question 1b) was contributed by two RCTs (CREST and KENTUCKY 2004).[46,48]

Over 20 systematic reviews were identified via our search, including a recent Cochrane Review [41]. Summarized patient-level data from this review's meta-analyses were used for some analyses for comparison to our meta-analyses and to provide information to answer key question 4. All others were excluded for one or more of the following reasons: failure to separate data by symptom status, inclusion of studies which did not meet our inclusion criteria, lack of clarity regarding timing of outcomes, failure to include the most recent randomized controlled trials, uncertainty regarding the quality of systematic search methods, lack of critical appraisal of individual studies failure to address the key questions and scope.

For the evaluation of the primary outcomes for efficacy and periprocedural safety of carotid artery stenting, the primary evidence base comes from randomized controlled trials. The primary evidence base on effectiveness comes from comparative nonrandomized studies (cohort and registry studies). Administrative data studies were considered to be at high risk of bias and were not considered to be part of the primary body of evidence. Of the 11 administrative database studies described for additional context, eight studies met half or fewer of the 12 criteria considered important for a quality database study.

Six of the included trials were terminated early:

- The EVA,[128] SPACE[153] and Leicester (Naylor)[141] trials were stopped secondary to concerns over the safety of stenting and/or based on interim futility analysis.
- SAPPHIRE[183] was terminated early due to slowed recruitment
- BACASS[93] and Regensburg (Steinbauer)[170] were stopped early for the stated reasons that the ICSS[65] and SPACE trials respectively were being initiated.

Two RCTs (BACASS, Regensburg) enrolled ≤10 participants in each treatment arm; one study enrolled patient prior to the year 2000 (Leichester).

Data from many retained studies were used to provide information across multiple key questions. Exceptions to this were studies specific to stent use in treatment of intracranial atherosclerotic disease and those specific to economic evaluation. The key questions related to these topics had a discrete body of literature.

Detailed critical appraisal information on included studies is found in Appendix E. Most RCTs were considered to be at moderately low risk of bias. The primary ICSS report was rated as having low risk of bias.[65] Aside from sample size concerns noted by the authors of

these studies, primary reports on the CREST trial.[48,167] were also considered highest quality for RCTs. The lowest quality RCTs were the BACASS, Regengsberg and both Kentucky trials, based on failure to report randomization sequence generation, concealment of allocation and small sample size.

Use of embolic protection: Six of the ten included RCTs reported using embolic protection methods (CREST, SAPPHIRE, EVA-3S, ICSS, SPACE, BACASS)[48,63,65,87,93,129] and three stated that they did not (Regensberg, Kentucky 2001 and 2004)[45,46,170] and use was not clear in one study (Leicester).[141] For nonrandomized studies, 12 of the 17 included studies reported using embolic protection in at least 80% of patients.[33,49,50,59,69,96,107,113,125,142,166,189] In five other studies use was not reported or no clearly stated.[43,102,108,119,163]

Key Question 1

Asymptomatic patients:

- For the comparison of CAS versus medical therapy alone, no randomized studies were found for asymptomatic patients. One retrospective, single-center cohort study provides the evidence based for effectiveness and was considered to be at moderately high risk of bias.[163]
- For the comparison of CAS with medical therapy to CEA with medical therapy, two RCTS on asymptomatic patients provided the evidence base for evaluation of efficacy.[46,48] Both were considered to be at moderately low risk of bias.
- With respect to effectiveness in asymptomatic patients, four nonrandomized comparative studies (two clinical cohorts,[59,189] 1 registry provide the evidence base.[33] In addition one administrative study[176] is included in this report. All cohort and registry studies were considered to be at moderately high risk of bias; the administrative study was considered at high risk of bias.

Symptomatic Patients:

- For the comparison of CAS versus medical therapy alone, no randomized studies were found for symptomatic patients. One retrospective, single-center cohort study provides the evidence based for effectiveness and was considered to be at moderately high risk of bias.[163]
- Ten reports from seven RCTS on symptomatic patients provided the evidence base for evaluation of efficacy of CAS versus CEA.[26,27,29,45,48,63,65,93,129,170] All studies were considered to be at moderately low risk of bias.
- Data on effectiveness following CAS and medical therapy compared with CEA and medical therapy up to 4 years were reported by two nonrandomized prospective cohort studies included in this report.[59,189] Both studies were considered to be at moderately high risk of bias.

Key Question 2

For coherence, information on efficacy and safety are presented for this question which focuses on stent use for treatment of atherosclerotic disease in intracranial arteries. One RCT in symptomatic patients provides the primary evidence base for both efficacy and safety.[51] This RCT was considered to be at moderately low risk of bias. No comparative nonrandomized studies were identified. Five prospective case series (4 multicenter and 1 single-center)[12,42,71,101,188] that reported outcomes following angioplasty and stenting for symptomatic intracranial atherosclerosis using FDA approved devices for this indication. These were all considered at high risk of bias; individual class of evidence evaluation was not done for these studies.

Key Questions 3

Data from RCTs and non-randomized studies were included for the evaluation of safety.

Asymptomatic patients:

- For the comparison of CAS and medical therapy versus medical therapy alone, no randomized studies were found for symptomatic patients. One retrospective, single-center registry study provides the evidence based for effectiveness and was considered to be at moderately high risk of bias.[163]

- Two RCTs provided data comparing CAS with medical therapy to CEA with medical therapy during the peri-procedural timeframe.[46,167] Both were considered to be at moderately low risk of bias.
- In addition to data from RCTs, periprocedural outcomes following CAS and medical therapy compared with CEA and medical therapy were reported in a total of 21 nonrandomized comparative studies (7 cohorts,[43,49,59,96,108,125,189] 3 registries,[102,119,142] and 11 administrative[39,76,77,111,132,134,135,155,173,176,187]). All cohort and registry studies were considered to be at moderately high risk of bias; administrative studies were considered to be at high risk of bias.

Symptomatic Patients:

- No studies comparing CAS and medical therapy with medical therapy alone in symptomatic patients were identified.
- For the comparison of CAS and medical therapy with CEA and medical therapy, a total of ten studies from eight RCTs reported on various outcomes during the periprocedural period.[26,45,63,65,93,128,129,141,167,170]
- In addition to data from RCTs, periprocedural and others safety outcomes following CAS and medical therapy compared with CEA and medical therapy were reported in a total of 18 nonrandomized comparative studies (7 cohorts,[43,49,59,96,107,108,189] 3 registries,[102,119,142] and 8 administrative[39,76,77,132,134,135,155,173]). All clinical and registry studies were

considered to be at moderately high risk of bias; administrative studies were considered to be at high risk of bias.

Key Question 4

For evaluation of differential effectiveness and safety in special populations data from RCTs and observational studies were included.

Asymptomatic patients:

- For CAS versus medical therapy alone, no RCT data were available and one retrospective cohort study was found.[163] This study was considered to be at moderately high risk of bias.
- One RCT (CREST) was available to evaluate differential safety outcomes.[94] Data from one additional trial (SAPPHIRE)[87,183] of asymptomatic high risk patients were also included, however, no direct comparison with average risk patients could be made. These studies were considered to be at moderately low risk of bias.
- In addition, one prospective cohort study,[96] one registry study,[102] which were considered at moderately high risk of bias were included. Five administrative database studies are also summarized and were considered to be at high risk of bias.[39,77,111,132,187]

Symptomatic Patients:

- For the comparison of CAS with CEA, patient-level data were available for age and sex for six trials (Leicester, EVA-3S, SPACE, BACASS, ICSS, and CREST) as reported in the Bonati systematic review.[41] Otherwise, four trials were included (EVA-3S, SPACE, ICSS, and CREST).[63,65,91,94,129,171] The ICSS[65] was rated as having low risk of bias and all others were considered to be at moderately low risk of bias. Data from one trial for symptomatic high risk patients (SAPPHIRE) were also included, however, no direct comparison with average risk patients could be made.[87,183]
- In addition, one prospective cohort study,[96] one registry study[102] and four administrative database studies[39,77,132,155] were included. The cohort studies were considered to have moderately high risk of bias and the administrative studies were considered to be at high risk of bias.

Key Question 5

Five cost-utility studies meeting the inclusion criteria were identified.[99,124,130,175,186] Quality of Health Economic Studies (QHES)[144] scores ranged from 84-100, which primarily reflects the quality of reporting on specific factors that are important in economic analyses. It does not provide for evaluation of quality with respect to modeling assumptions or extensive consideration of data quality and included outcomes measures relevant to a specific topic. In general, the quality of the individual studies was considered moderate to high. One study considered only asymptomatic patients,[130] two studies concentrated on symptomatic

patients[99,186] and two studies provided a subgroup analysis for both symptomatic statuses.[124,175]

3.4. Patient Population(s)

Population characteristics from included studies for this HTA are briefly summarized in this section for reference. Detailed information on demographics in individual studies can be found in the Appendices. In particular, a number of studies have been described in the literature as primarily relating to patients at standard/average risk or at high risk for complications of surgery.

Surgical Risk

Carotid stenting is seen as an alternative to CEA in patients who are at high risk of surgically related morbidity and mortality.

A number of factors that may put patients at high risk for CEA surgery have been suggested. The recent AHRQ HTA (2012)[150] systematically identified a list of such factors from a number sources: factors listed in the CMS decision memo,[1] factors reported to be significant in multivariate analyses of published literature for predictive models, inclusion criteria for the SAPPHIRE trial designed to evaluate high risk patients,[183] factors listed in the reference surgical risk classification tool,[172] and definitions factors described in a recent systematic review.[158] The AHRQ HTA thus proposed the conditions listed below as those which may be associated with increased risk for periprocedural adverse events following CEA.[150] Note that these factors are not necessarily limited to patients enrolled in the SAPPHIRE trial of high-risk patients. For example, stroke was the qualifying event for treatment in 32%–65% of standard/average risk symptomatic patients as reported by the CREST and Kentucky trials.[45,167]

Detailed information on demographics in individual RCTs can be found in the Appendices.

Factors which may increase risk for periprocedural adverse events following CEA.

	SAPPHIRE Trial of high-risk patients	Asymptomatic Patient Trials (Kentucky, CREST)[46,167]	Symptomatic Patient Trials (BACASS, CREST, EVA-3S, ICSS, Kentucky, Leicester, Regensburg, SPACE)[45,63,65,129,141,167,170]
Number of patients	N = 334	N = 1266 (range, 85 – 1181 per trial)	N = 4982 (range, 17 – 1710 per trial)
Symptomatic (% patients)	28.8%	0%	100%
High surgical risk factors			
Age > 80 years	19.9% (mean age: 73)	NR (mean age: 68 – 69)	NR (mean age: 68 – 70)
Contralateral occlusion (i.e., contralateral stenosis of 100%)	24.5%	2.5 – 8.2%	2.9%- 13.5%§
Contralateral stenosis > 50%	NR	NR	34.1 – 83.7%**
Previous CEA with recurrent stenosis	22.4%	NR	2.9%††
Cardiac factors			
Congestive heart failure	18.4%	NR	2.7 – 4%‡‡
Atrial fibrillation	NR	NR	0 – 7%§§
Left ventricular ejection fraction < 30%	NR	NR	NR
Unstable angina	19.4%*	NR	NR
History of MI	32.5%	NR	12 – 18%‡‡
History of open-heart surgery	37.1%†	25%†	13.5 – 16.9%†
Severe pulmonary disease	15.4%‡	NR	NR
Neurologic factors			
Preoperative ipsilateral stroke	NR	NR	NR
Stroke as an indication for CEA	NR (25.5% with history of stroke)	0%	32.2 – 65%***
Crescendo transient ischemic attack /stroke	NR	NR	NR
Cerebral events (versus ocular events)	NR	NR	NR
History of transient ischemic attack/ stroke in the prior six months (contralaterally)	NR (32.6% with history of TIA)	NR	NR (10 – 43% with TIA as qualifying event***)
Stenosis of ipsilateral internal carotid siphon	NR	NR	NR
Bifurcation of carotid artery at the level of C2 in conjunction with short neck	NR	NR	NR
Severe obesity	NR	NR	NR
Emergency CEA	NR	NR	NR
Prior radiation treatment to the neck	NR	NR	NR

*class 3 or 4 angina (according to Canadian Cardiovascular Society guidelines)

†CABG; for asymptomatic patients, data reported for CREST trial only (N = 1181); for symptomatic patients, data reported for CREST (N = 1321) and ICSS (N = 1710) only

‡chronic obstructive pulmonary disease

§ data NR for Kentucky (N = 104), Leicester (N = 17), or Regensburg (N = 87)

**Data reported for ICSS (N = 1710) and SPACE (N = 1183) trials only

†† data reported for EVA-3S (N = 527)

‡‡ data reported for EVA-3S (N = 527) and ICSS (N = 1710) trials only

§§Atrial fibrillation or atrial flutter, data reported for ICSS (N = 1710) and CREST (N = 1321) only

*** data NR for CREST (N = 1321) or Kentucky trials (N = 104)

Patient Characteristics in Trial of Intracranial Stenting

The pathophysiology and treatment options for intracranial atherosclerotic disease are somewhat different than those for extracranial carotid atherosclerotic disease. Patient characteristics from the only RCT on intracranial artery stenting are summarized below.

Baseline characteristics of patients from included RCTs comparing CAS with CEA for symptomatic carotid artery disease.

SAMMPRIS trial[51]		
Baseline demographics and characteristics	**Treatment groups % (n)**	
	CAS + medical therapy (N =224)	**Medical therapy only (N = 227)**
Demographics		
Male	56.7	63.9
Mean age ± SD (years)	61.0 ± 10.7	59.5 ± 11.8
Current Smoker	24.2	30.4
Mean % stenosis (± SD)	80 ± 7	81 ± 7
Comorbidities		
Hypertension	89.7	89.4
Diabetes	47.3	45.4
Lipid disorder	86.6	89.4
History of coronary artery disease	21.0	26.0
History of stroke other than qualifying event	26.8	25.6
Already receiving antithrombotic therapy at time of qualifying event	64.7	62.1
Qualifying event		
Stroke	63.4	67.0
TIA	36.6	33.0

AFib = atrial fibrillation; AFlutter = atrial flutter; CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; ND = not defined; NR = not reported; PVD = peripheral vascular disease; TIA = transient ischemic attack.

4. Results

4.1. Key Question 1: Extracranial Carotid Artery Stenosis Stenting Efficacy and Effectiveness

In symptomatic or asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness of:

a. Extracranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?

b. Extracranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?

Key Question 1 focuses on outcomes beyond the 30 day (1 month) periprocedural period. For the purposes of this HTA, short term outcomes were considered all outcomes occurring after 30 days and before 12 months, and longer-term outcomes were considered all outcomes occurring at or after 12 months. A positive risk difference (RD) favors CAS and negative RD favors CEA, however if the value of "0" is included in the confidence interval, the result was not statistically significant.

4.1.1. Asymptomatic

Summary regarding efficacy (RCT data)

CAS versus medical therapy alone: No RCT evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis were found.

CAS compared with CEA: Two RCTs evaluated the efficacy of CAS and medical therapy versus CEA and medical therapy in patients of average surgical risk: One (Kentucky 2004)[46] was conducted in asymptomatic patients only, and one trial (CREST)[48] enrolled both symptomatic and asymptomatic patients. A third trial was conducted in high-risk patients (SAPPHIRE)[87] and is described in with Key Question 4 on special populations.

Across the two RCTs included in this section with regard to efficacy:

- Neither RCT evaluated the short-term efficacy of CAS and medical therapy compared with CEA and medical therapy for death or MI.
- Data on outcomes up to 4 years were reported for the CREST and Kentucky trials.
    - **Stroke:** Kentucky reported no stroke events at 4 years for either CAS or CEA treatment groups.

- **Ipsilateral stroke:** No statistical difference was reported in in the CREST study; no ipsilateral stroke events were seen in either treatment arm of the Kentucky trial.
- **Any periprocedural stroke or death or post-procedural ipsilateral stroke:** In the CREST trial, there was no statistical difference in risk of this composite outcome at 4 years.
- **Other outcomes:** The Kentucky 2004 study reported no difference in vessel patency at 4 years between CEA and CAS treatment groups. No patients in either group experienced symptoms of cerebral ischemia. Hospital length of stay, postprocedural pain and time to return to full activity were similar between treatment groups.

Summary regarding effectiveness (nonrandomized comparative studies)

CAS versus medical therapy alone: One retrospective, single-center cohort, Sherif et al. 2005,[163] followed patients for a median 2.1 years and reported Kaplan-Meier estimates for a projected 5 years of follow-up using a propensity score-adjusted analysis. Compared to patients in the medical therapy group, patients in the CAS group had significantly decreased rates of all outcomes (any stroke, death, and any stroke or death). This study was considered to be at moderately high risk of bias.

CAS compared with CEA: Primary outcomes following CAS and medical therapy compared with CEA and medical therapy up to 4 years were reported in four nonrandomized comparative studies (2 clinical cohorts,[59,189] 1 registry[33] and 1 administrative[176]) included in this report, including those described in the AHRQ report. All cohort studies were considered to be at moderately high risk of bias while the registry was considered to have a moderately low risk of bias. Risk of bias in the administrative study was considered to be high.

- **Any stroke:** There were no statistical differences between treatments at 1–1.5 years in one prospective registry study and one administrative study or in one prospective cohort study at 4 years.
- **Death:** A marginally significant statistical increase in death was seen at 1 year in a large administrative study but no statistical difference at 1.5 or 4 years as reported in one prospective registry and one prospective cohort study, respectively.
- **Any stroke or death:** No statistical difference at 1.5 or 4 years as reported in two studies (1 prospective registry and 1 prospective cohort).
- **Myocardial infarction (MI):** Across two prospective studies (1 registry and 1 cohort) at 1.5 and 4 years, no statistical difference was seen between treatments, although somewhat higher rates of MI were seen following CEA. By contrast, one

large administrative study reported a slight increase in MI risk at one year following CAS.

- **Any periprocedural stroke, death or post-procedural ipsilateral stroke:** At 2.8 years no statistical difference was seen between groups in one prospective cohort study.
- **Cognitive function, ADLs, Depression:** Three small prospective cohort studies (all considered to be at moderately high risk of bias) reported on various secondary outcomes.[33,50,69,113] Overall, no statistical differences between treatment groups were seen for most measures, which may partly be a function of sample size. One study reported improvement in working memory after CAS (compared with CEA) and in processing speed following CEA (compared with CAS).

Detailed results:

Efficacy in asymptomatic patients (RCTs)

CAS and medical therapy compared with medical therapy alone: No RCTs evaluated the efficacy of CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis.

CAS with medical therapy versus CEA with medical therapy: Two RCTs evaluated the efficacy of CAS and medical therapy versus CEA and medical therapy: one (Kentucky 2004)[46] was conducted in asymptomatic patients only (N = 85), and one trial (CREST)[48] enrolled both symptomatic and asymptomatic patients (total N = 1321 and N = 1181, respectively), with randomization blocked by symptom status. A third trial was conducted in high-risk patients (SAPPHIRE)[87] and is described in with Key Question 4 on special populations. Therefore, treatment assignment was randomly assigned among asymptomatic patients. However, this stratified study was not powered to detect significant associations in subgroup analyses; therefore, it is possible that real differences exist between the interventions but were not detected because of inadequate sample size. Data for the asymptomatic patients is reported in this section.

Neither the Kentucky nor the CREST study reported on death or MI as separate outcomes at times beyond 30 days.

Any stroke

One RCT (Kentucky) examined the risk of any stroke at 4 years; however, zero events were reported for both treatment groups; thus, no estimate of efficacy of CAS versus CEA could be deducted from this study.[46]

Ipsilateral stroke

Both RCTs (CREST, Kentucky) reported data on ipsilateral stroke. CREST reported ipsilateral stroke as a composite of 'any periprocedural (within 30 days) stroke or postprocedural (> 30 days) ipsilateral stroke' at 4-year follow-up.[48] Although CREST does not explicitly report data limited to the post-procedural period, data are available to allow removal of periprocedural events; therefore we calculated the risk of postprocedural ipsilateral stroke. At 4-year follow-up risk of ipsilateral stroke was similar for CAS and CEA (CAS vs. CEA RD = 0.67%, 95%CI = -0.57, 1.90). Although Kentucky did not explicitly report data on ipsilateral strokes, they reported no stroke events for either CAS or CEA arms at 4 years. No estimate of efficacy of CAS versus CEA with respect to ipsilateral stroke could be deducted from this study.

Any periprocedural stroke or death or post-procedural ipsilateral stroke

One RCT (CREST) reported data on stroke or death up to 4 years.[48] Authors reported stroke or death as a composite of 'any periprocedural stroke or death or post-procedural ipsilateral stroke'. At 4-year follow-up, CAS patients had a nonsignificant 2% higher risk of stroke or death as compared with CEA (RD = 1.9%, 95% CI = -0.5, 4.3, HR 1.86, 95% CI 0.95, 3.66). Data were not available to separate periprocedural events. The SAPPHIRE trial of high surgical risk patients reported no differences in 3-year ipsilateral stroke or death (RD, -8% (-19%, 3%) between CAS and CEA treatment groups.[87] See Key Question 4 for additional details.

Patency

One RCT (Kentucky) reported on patency of the reconstructed artery up to 4 years.[46] Similar patency for both treatment arms was seen, and no individual in either treatment group experienced symptoms of cerebral ischemia.

Other Outcomes

One RCT reported similar lengths of hospital stay (CAS: 1.5 ± 0.8 days versus CEA: 1.7 ± 2.5 days), perception of pain (Average 24-hour postprocedure pain scale (0-10) for CAS: 1.1 versus CEA: 2.0), and return to full activity (Average days for CAS: 8.6 ± 5.9 versus CEA: 9.8 ± 6.1) for CAS and CEA.[46]

Effectiveness in asymptomatic patients (Nonrandomized comparative studies)

CAS and medical therapy compared with medical therapy alone: Only one retrospective, single-center cohort, Sherif et al. 2005,[163] was found that reported on long-term clinical outcomes following CAS and medical therapy (n = 421) compared with medical therapy alone (n = 525) and was included in the AHRQ report.[150] Patients undergoing CAS were similar those having CEA with respect to age (72 and 73 years) and male gender (68% and 62%). The median follow-up period was 2.1 years (absolute range, 6–72). Outcomes of

stroke and/or death were reported using Kaplan-Meier estimates for a projected 5 years of follow-up using a propensity-score adjusted analysis (age, gender, body mass index, baseline degree of carotid stenosis, diabetes, hypertension, hyperlipidemia, smoking, congestive heart failure, coronary artery disease, history of MI, peripheral artery disease, concomitant malignancy, American Society of Anesthesiologists classification, Asymptomatic Carotid Atherosclerosis Study eligibility, and the date of CAS to account for temporal trends). This study was considered to be at moderately high risk of bias. Compared to patients in the medical therapy group, patients in the CAS group had a significantly decreased risk for all outcomes:

- **Any stroke**: 9% versus 11% (adjusted hazard ratio (HR) = 0.47; 95% CI, 0.24–0.91)
- **Death:** 20% versus 32% (adjusted HR = 0.67; 95% CI, 0.46–0.97)
- **Any stroke or death:** 29% versus 62% (adjusted HR = 0.66; 95% CI, 0.47–0.91)

CAS and medical therapy compared with CEA and medical therapy: For the comparison of CAS and medical therapy with CEA and medical therapy in asymptomatic patients, data abstracted from the 2012 AHRQ report[150] were combined with data from studies that were published after the AHRQ search or which appeared to have met the inclusion criteria but didn't appear to have been summarized in that report. Overall this section includes data from four nonrandomized, comparative studies describing the primary outcomes (e.g. stroke, death). Two prospective cohort studies[59,189] and one prospective registry study (which conducted a propensity score matched analysis),[33] all included in the AHRQ report, constitute the primary body of evidence. Across these three studies, sample sizes ranged from 269 to 1672 with mean follow-up periods of 1.5 to 4 years. Patient ages were similar (range, mean 70-72 years) and the proportion of males ranged from 62%-71%; in two of these studies demographics for the asymptomatic population were not reported separately so they reflect the entire study population.[59,189] The fourth study was an administrative study not included in the AHRQ report that looked at the Center for Medicare and Medicaid Services (CMS) provider analysis data (N = 10,958, mean age 76 years, 57.5% male) and reported adjusted estimates for primary outcomes at 1 year of follow-up.[176] In addition three small studies (N = 60, N = 46, N = 46) provided data on secondary outcomes (e.g. cognitive function).[50,69,113] Data are summarized in Tables 8 and 9, respectively.

All cohort studies were considered at moderately high risk of bias while the risk of bias in the registry study was considered to be moderately low. The administrative study was considered to be at high risk of bias. Concerns regarding such studies include questions of coding accuracy and variability of algorithms used to identify patients as previously described in the methods section of this report.

Any stroke

No statistically significant differences in the risk of any stroke following CAS compared with CEA were reported by one cohort study and one registry study. Risks were 9.2% and 5.7%, respectively, at 4 years in the clinical study[189] and 3.8% and 2.6% (Kaplan Meier rate estimates), respectively, at 1.5 years in the registry study.[33] Similarly, in one large administrative study with 1 year of follow-up, no significant difference in the risk of any stroke was reported between groups (CAS 5.3%; CEA 4.1%).[176]

Death

Data from two studies (1 cohort, 1 registry) showed no statistically significant differences between treatment groups. The risk of all-cause death at 4 years in the cohort study[189] was 22.2% following CAS compared with 19.7% after CEA and at 1.5 years in the registry study Kaplan Meier rate estimates were identical (7.4% for both groups).[33] In a third study, a large administrative database analysis, a marginally significant statistical increase in death following CAS was seen at 1 year: 9.9% and 6.1%; adjusted HR = 1.30 (95% CI, 1.01–1.69).[176]

Any stroke or death

No statistically significant differences in the risk of any stroke or death between CAS and CEA were reported by two studies. In the cohort study, the risk at 4 years was 25.8% versus 23.2%, respectively,[189] and in the registry, Kaplan Meier rate estimates of any stroke (nonfatal) or death were 9.9% and 8.9%, respectively, at 1.5 years of follow-up.[33]

Myocardial infarction (MI)

Across one cohort and one registry study, the risk of MI did not differ significantly between groups. At 4 years of follow-up, risks were 7.9% with CAS versus 10.1% with CEA in the cohort study[189] and Kaplan Meier rate estimates were 3.2% and 4.8%, respectively, at 1.5 years in the registry.[33] By contrast, CAS resulted in a marginally significant increased rate of MI compared with CEA at 1 year as reported by one large administrative database study: 4.8% and 2.5%; adjusted HR = 1.56 (95% CI, 1.07–2.27).[176]

Any stroke or transient ischemic attack (TIA)

Only one registry with 1.5 years of follow-up provided data for this outcome and reported similar Kaplan Meier rate estimates of any stroke (fatal or nonfatal) or TIA after CAS and CEA, respectively: 5.5% and 5.0%.[33]

Any periprocedural stroke or death or post-procedural ipsilateral stroke

Only one cohort with a mean follow-up of 2.8 years analyzed this outcome. De Rango, et al. 2011 reported 5-year Kaplan Meier estimates of any stroke or death up to 30 days or

ipsilateral stroke thereafter and found no significant difference between the CAS and the CEA group, respectively: 3.3% and 2.5%.[59]

Cognitive outcomes

Cognition was not included as an outcome in the AHRQ report. Three, small studies evaluating cognitive outcomes are reported here.

Mini-Mental State Examination (MMSE)

- Two small studies reported changes in MMSE scores in asymptomatic patients who underwent CAS or CEA.
- In one study, a significant decrease was seen in postoperative scores in CAS patients compared with CEA patients (change pre- to post-operative: -2.7 vs. -0.5; P = .03), with a decrease of greater than 5 points in seven (25%) versus one (3%) patient, respectively. However, by both the 6 and 12 month follow-up, MMSE scores were similar between the two groups.[50]
- Likewise, there were no significant differences between the CAS and CEA groups in MMSE change scores from baseline to follow-up at 3 months (-0.53 vs. -0.52) and 12 months (0.13 vs. -0.03) as reported by the second study.[69]

Trail-Making Test (TMT)

- Two studies evaluated results of the TMT and reported no significant differences in pre- to post-operative change scores between the two groups at any time point studied.
- One study reported the standardized change score of the combined TMT at a mean follow-up of 5.2 months: 0.63 (CAS) versus 0.74 (CEA).[113]
- The second study reported change scores for TMT part A (selective attention) and TMT part B (divided attention) separately at the 3 month (30.7 ± 65.2 vs. 12.7 ± 57.5 and -3.1 ± 122.0 vs. -3.2 ± 98.3) and 12 month follow-up visit (21.5 ± 59.1 vs. -0.1 ± 28.2 and -56.7 ± 72.5 vs. -49.3 ± 88.6) in the CAS and CEA groups, respectively.[69]

Controlled Oral Word Association (COWA)

- Two studies reported scores for the COWA test and reported no significant differences in pre- to post-operative change scores between the two groups at any time point studied.
- One study reported the standardized change score of the COWA at a mean follow-up of 5.2 months: 0.69 (CAS) versus 0.61 (CEA).[113]
- The second study reported change scores in the CAS and CEA groups, respectively, at the 3 month (0.9 ± 8.5 vs. 1.9 ± 10.8) and 12 month follow-up visit (3.6 ± 8.8 vs. 5.0 ± 8.1).[69]

Other cognitive outcomes

- The outcomes of various other cognitive tests (Babcock story recall, Rey's auditory verbal learning test immediate (Rey-IR) and delayed (Rey-DR) recall, category naming test, copy drawing test, Boston naming test, and Hopkins verbal learning test) were reported by one of two of the included studies with no significant differences between the two groups.[69,113]
- In one of these studies with a mean follow-up of 5.2 months, scores on the Processing Speed Index were significantly decreased in the CAS group compared with the CEA group (-0.32 vs. 0.58; P = .001) while scores on the Working Memory Index were significantly improved compared with the CEA (0.46 vs. -0.41; P = .001); however, the composite score for all seven cognitive tests evaluated (including these two tests) was not significantly different between groups.[113]

Activities of daily livings (ADLs) and Depression

- ADLs and depression were not included as outcomes in the AHRQ report. The following small study and these outcomes are unique to this report.
- One of the small nonrandomized studies evaluating cognition also looked at the basic ADL and instrumental ADL questionnaires and the Geriatric Depression Scale (GDS) at 3 months and 12 months following CAS and CEA and found no significant difference in either function or mood between the two groups.[69]
- At 3 months, basic ADL scores were -0.16 ± 0.51 and -0.15 ± 0.60 in the CAS and CEA groups respectively; at 12 months, -0.06 ± 0.5 versus -0.10 ± 0.47, respectively.
- Instrumental ADLs were 0.38 ± 2.1 versus -0.15 ± 2.2 at 3 months and 0.06 ± 2.0 versus 0.37 ± 2.0, respectively.
- GDS scores in the CAS and CEA groups at 3 months and 12 months, respectively, were -1.0 ±2.1 versus -0.6 ± 2.0 and -0.2 ± 3.9 versus -0.8 ± 1.7.

Table 8. Summary of cumulative rates of stroke, death, and MI *by longest follow-up* in asymptomatic patients from nonrandomized studies **reported in the AHRQ and those not included in the AHRQ report.**

Study, N	Outcome	Time Frame (mean)	Patients with outcome		Effect Size* RD % (95% CI)† RR/HR (95% CI)
			CAS % (n/N)	CEA % (n/N)	
Any stroke					
Zarins 2009 CaRESS cohort (Pro) N = 269	Any stroke	4 years	9.2 (7/76)‡	5.7 (9/158)‡	RD = -3.5 (-12.5 to 3.2)‡ RR = 1.62 (0.63–4.18)‡
Bangalore 2010§ REACH registry (Pro) N = 1672	Any stroke	1.5 years	3.8** (27/836)	2.6** (20/836)	Adjusted HR = 1.41 (0.79-2.51)
Wang 2011 Administrative data N = 10,958	Any stroke	1 year	5.3 (39/737)	4.1 (277/6724)	Unadjusted HR = 1.30 (0.93-1.82) Adjusted HR = 1.26 (0.89-1.78)
Death					
Zarins 2009 CaRESS cohort (Pro) N = 269	All-cause death	4 years	22.2 (19/86)‡	19.7 (24/122)‡	RD = -2.4 (-14.0 to 8.5)‡ RR = 1.12 (0.66–1.92)‡
Bangalore 2010§ REACH registry (Pro) N = 1672	Death	1.5 years	7.4** (40/828)	7.4** (57/830)	Adjusted HR = 0.73 (0.49-1.09)
Wang 2011 Administrative data N = 10,958	Death	1 year	9.9 (73/737)	6.1 (412/6724)	Unadjusted HR = 1.65 (1.29–2.12) Adjusted HR = 1.30 (1.01–1.69)
Stroke (any) or death					
Zarins 2009 CaRESS cohort (Pro) N = 269	Any stroke or death	4 years	25.8 (22/85)‡	23.2 (30/129)‡	RD = -2.6 (-14.7 to 8.8)‡ RR = 1.11 (0.69–1.79)‡
Bangalore 2010§ REACH registry (Pro) N = 1672	Stroke (nonfatal) or death	1.5 years	9.9** (58/828)	8.9** (68/830)	Adjusted HR = 0.89 (0.63–1.27)
Myocardial Infarction (MI)					
Zarins 2009 CaRESS cohort (Pro) N = 269	MI	4 years	7.9 (6/76)‡	10.1 (12/119)‡	RD = 2.2 (-7.1 to 10.1)‡ RR = 0.78 (0.31–2.00)‡
Bangalore 2010§ REACH registry (Pro) N = 1672	MI	1.5 years	3.2** (23/836)	4.8** (37/836)	Adjusted HR = 0.64 (0.38–1.08)
Wang 2011 Administrative data N = 10,958	MI	1 year	4.8 (35/737)	2.5 (165/6724)	Unadjusted HR = 1.97 (1.37–2.84) Adjusted HR = 1.56 (1.07-2.27)

Study, N	Outcome	Time Frame (mean)	Patients with outcome		Effect Size* RD % (95% CI)† RR/HR (95% CI)
			CAS % (n/N)	CEA % (n/N)	
Any stroke or transient ischemic attack (TIA)					
Bangalore 2010§ REACH registry (Pro) N = 1672	Any stroke (fatal or non-fatal) or TIA	1.5 years	5.5** (40/836)	5.0** (38/836)	Adjusted HR = 1.10 (0.71–1.72)
Any periprocedural stroke or death or post-procedural ipsilateral stroke					
De Rango 2011 Cohort study (Pro) N = 1518	Stroke or death up to 30 days or ipsilateral stroke thereafter	2.8 years	3.3††	2.5††	RR = 0.83 (0.49–1.39)‡‡

CAS: carotid artery stenting; CEA: carotid endarterectomy; HR: hazard ratio; Pro: prospective study design; RD: risk difference; RR: relative risk.

*As reported by authors unless otherwise stated.

†A positive risk difference favors CAS and negative risk difference favors CEA.

‡Given the percentages and counts (n's) provided by the authors, we back-calculated to determine the total N after loss-to-follow-up. A RR reflecting this change was also calculated as was a RD.

§Propensity-score matched analysis. The model included the following baseline characteristics: age, sex, race, documented transient ischemic attack, prior CABG, documented ischemic stroke, MI, nitrates, beta blockers, calcium channel blockers, statins, angiotensin-converting enzyme (ACE)-inhibitors, diuretics, insulin, smoking, unstable/stable angina, diabetes, congestive heart failure, ACE/angiotensin receptor blocker, hypercholesterolemia, history of atrial fibrillation, and history of treated hypertension.

**Kaplan Meier rate estimates and n/N as reported by the authors.

††5-year Kaplan Meier rate estimates as reported by the authors.

‡‡Calculated from raw data by the Agency for Healthcare Quality and Research (AHRQ).

Table 9. Summary of cognitive function, activities of daily living (ADLs) and depression outcomes in asymptomatic patients with carotid artery disease from three prospective cohort studies not included in the AHRQ report.

Study, N	Follow-up	Mean pre-op scores		Mean change scores (follow-up–preop)		*P*-value
		CAS	CEA	CAS	CAS	
Mini-Mental State Exam (MMSE)						
Feliziani 2010 N = 46	12 months	27.2 ± 1.9	27.8 ± 2.3	3 months: –0.53 ± 3.1 12 months: 0.13 ± 2.7	3 months: –0.52 ± 2.5 12 months: –0.03 ± 2.5	ns ns
Capoccia 2012 N = 60	12 months	25.6 ± 4.5	26.1 ± 3.5	Post-op: –2.7* 6 months: –1.9* 12 months: –1.5*	Post-op: –0.5* 6 months: –0.2* 12 months: –0.4*	ns ns ns
Trail Making Test (TMT)						
Feliziani 2010 N = 46	12 months	Part A 74.1 ± 37.7 Part B 135.4 ± 78.5	Part A 52.9 ± 24.4 Part B 162.5 ± 108.5	3 months: 30.7 ± 65.2 12 months: 21.5 ± 59.1 3 months: –3.0 ± 122.0 12 months: –56.7 ± 72.5	3 months: 12.7 ± 57.5 12 months: –0.1 ± 28.2 3 months: –3.2 ± 98.3 12 months: –49.3 ± 88.6	ns ns ns ns
Lal 2011 N = 46	5.2 months	Parts A & B 121 ± 22	Parts A & B 138 ± 26	5 months: 0.63†	5 months: 0.74†	ns
Controlled Oral Word Association (COWA)						
Feliziani 2010 N = 46	12 months	22.7 ± 7.8	22.4 ± 9.1	3 months: 0.9 ± 8.5 12 months: 3.6 ± 8.8	3 months: 1.9 ± 10.8 12 months: 5.0 ± 8.1	ns ns
Lal 2011 N = 46	5.2 months	38 ± 9	39 ± 11	5 months: 0.69†	5 months: 0.61†	ns

Study, N	Follow-up	Mean pre-op scores		Mean change scores (follow-up–preop)		*P*-value
		CAS	CEA	CAS	CAS	
Babcock story recall (Backcock-SR)						
Feliziani 2010 N = 46	12 months	9.0 ± 3.1	9.1 ± 3.1	3 months: –0.2 ± 4.5 12 months: –0.4 ± 3.3	3 months: 1.4 ± 3.9 12 months: 0.3 ± 5.0	ns ns
Rey's auditory verbal learning test immediate recall (Rey-IR)						
Feliziani 2010 N = 46	12 months	35.5 ± 8.9	33.5 ± 7.0	3 months: –0.5 ± 12.0 12 months: –1.5 ± 9.2	3 months: –1.5 ± 6.3 12 months: 1.6 ± 6.2	ns ns
Rey's auditory verbal learning test delayed recall (Rey-DR)						
Feliziani 2010 N = 46	12 months	7.4 ± 4.0	8.7 ± 3.8	3 months: –0.1 ± 2.6 12 months: –0.6 ± 2.4	3 months: –1.9 ± 4.8 12 months: –0.9 ± 4.6	ns ns
Category naming test (CNT)						
Feliziani 2010 N = 46	12 months	14.3 ± 4.0	14.3 ± 4.7	3 months: 0.8 ± 5.8 12 months: –1.9 ± 3.5	3 months: 1.2 ± 7.1 12 months: –1.4 ± 4.5	ns ns
Copy drawing test (CD)						
Feliziani 2010 N = 46	12 months	12.5 ± 2.0	12.5 ± 1.7	3 months: 0.8 ± 2.0 12 months: –0.7 ± 2.9	3 months: –0.5 ± 1.7 12 months: –1.3 ± 2.3	ns ns
Boston Naming Test						
Lal 2011 N = 46	5.2 months	52 ± 8	56 ± 10	5 months: 0.59†	5 months: 0.66†	ns
Hopkins Verbal Learning Test						
Lal 2011 N = 46	5.2 months	7.9 ± 2.0	8.1 ± 1.7	5 months: 0.77†	5 months: 0.86†	ns
Processing Speed Index						
Lal 2011 N = 46	5.2 months	107 ± 16	106 ± 13	5 months: –0.32†	5 months: 0.58†	.001
Working Memory Index						
Lal 2011 N = 46	5.2 months	100 ± 16	103 ± 15	5 months: 0.46†	5 months: –0.41†	.001
Basic activities of daily living (ADLs)						
Feliziani 2010 N = 46	12 months	5.7 ± 0.5	5.9 ± 0.4	3 months: –0.16 ± 0.51 12 months: –0.06 ± 0.5	3 months: –0.15 ± 0.60 12 months: –0.10 ± 0.47	ns ns
Instrumental activities of daily living (IADLs)						
Feliziani 2010 N = 46	12 months	5.9 ± 2.1	5.6 ± 1.7	3 months: 0.38 ± 2.1 12 months: 0.06 ± 2.0	3 months: –0.15 ± 2.2 12 months: 0.37 ± 2.0	ns ns
Geriatric Depression Scale (GDS)						
Feliziani 2010 N = 46	12 months	4.4 ± 2.4	3.0 ± 1.5	3 months: –1.0 ± 2.1 12 months: –0.2 ± 3.9	3 months: –0.6 ± 2.0 12 months: –0.8 ± 1.7	ns ns

CAS: carotid artery stenting; CEA: carotid endarterectomy; ns = not significant.

*Change scores were calculated by Spectrum Research using the postoperative scores provided at each time point.

†Standardized cognitive change score as reported by authors; a positive change score indicates improvement in cognitive function after procedure and a negative change score indicates deterioration.

4.1.2. Symptomatic

Summary regarding efficacy (RCT data)

CAS versus medical therapy alone: No RCT evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS compared with CEA: Ten reports from seven RCTs evaluated the efficacy of CAS and medical therapy versus CEA and medical therapy among symptomatic patients.[26,27,29,45,48,63,65,93,129,170] For the purposes of this HTA, short term outcomes were considered all outcomes occurring after 30 days and before 12 months, and longer-term outcomes were considered all outcomes occurring at or after 12 months. All seven RCTs evaluated long-term outcomes, and two RCTs evaluated short term outcomes.[65,128] One additional trial was conducted in high-risk patients (SAPPHIRE)[183] and is described in Key Question 4 on special populations.

CAS compared with CEA, Short term efficacy:

- **Any stroke (excluding periprocedural)**: There was no significant difference between treatments in risk of any stroke at 4 months in one large RCT.
- **Ipsilateral stroke (excluding periprocedural)**: There was no significant difference between treatments in risk of ipsilateral stroke at 4 months in one large RCT.
- **Death**: One RCT reported a significant increase in risk of death at 4 months for CAS compared with CEA (RD = 1.4, 95% CI: 0.3, 2.6).
- **Any stroke or death (including periprocedural)**: Across two RCTs, there was a significant increase in risk at 4 months in one large RCT (RD: 3.32, 95% CI 1.13, 5.52); however, no statistically significant difference between treatment arms was seen at 6 months.
- **Death or any periprocedural stroke or postprocedural ipsilateral stroke**: In one large RCT there was a significant increase in risks for CAS compared with CEA (RD=5.36%, 95% CI: 1.28, 9.42).
- **Cognitive function, blood pressure:** Two RCTs reported on cognitive function and blood pressure at 4 months. Overall, there were no statistical differences between treatment groups for change in measures of cognitive function or blood pressure.

CAS compared with CEA, Long term efficacy:

- **Any stroke (excluding periprocedural)**: No statistical differences between treatment groups were seen at two years (2 RCTs) or four years (2 RCTs). Risks ranged from 0% -3.8% in both treatment groups.
- **Ipsilateral stroke (excluding periprocedural**): No statistical differences were seen at two years (2 RCTs), or four years (2 RCTs) or 5.4 years (1 RCT). In the largest trials (CREST, SPACE, EVA-3s),[48,63,129] rates ranged from 1.5%-2.2% following CAS and 1.5% - 2.4%.
- **Death**: No statistical differences were seen at two years (2 RCTs), four years (2 RCTs) or 5.4 years (1 RCT).The pooled estimate across five studies failed to reach statistical significance.

- **Any stroke or death (including periprocedural)**: Lack of estimate stability across two small studies precludes the ability to draw meaningful conclusions.
- **Death or any periprocedural stroke or postprocedural ipsilateral stroke**: The pooled estimate across five studies reporting data for 2, 4 or 5.4 years failed to reach significance. Risks for this composite ranged from 0%-9.2% following CAS and 0%-10% for CEA.
- **Restenosis**: The pooled estimate for risk of restenosis (≥70%) across three studies reporting data for 2, 4 or 5.4 years failed to reach significance. Risks for restenosis ranged from 0% – 18.8% following CAS, and 0% – 4.6% for CEA.

Summary regarding effectiveness (nonrandomized comparative studies)

CAS versus medical therapy alone: No nonrandomized comparative studies evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS compared with CEA: Outcomes following CAS and medical therapy compared with CEA and medical therapy up to 4 years were reported by two nonrandomized prospective cohort studies included in this report.[59,189] Only any stroke or death at 4 years showed a statistically significant difference between groups as reported by one study, with lower rates following CAS compared with CEA.[189] All other outcomes (any stroke, all-cause death, MI, and any periprocedural stroke or death or post-procedural ipsilateral stroke), reported by one study each, did not differ statistically between treatment groups, although consistently lower rates were reported following CAS. Both studies were considered to be at moderately high risk of bias.

Detailed results:

Efficacy in symptomatic patients

CAS and medical therapy compared with medical therapy alone: No RCTs evaluated the efficacy of CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis.

CAS with medical therapy versus CEA with medical therapy: Ten reports from seven RCTs evaluated the efficacy of CAS and medical therapy versus CEA and medical therapy among symptomatic patients considered to be at "average" surgical risk.[26,27,29,45,48,63,65,93,129,170] Of these studies, four were large (N>500) multicenter[29,48,129,165] and multinational trials,[26,27,63] and three were smaller (N<150) single-center trials.[45,93,170] Four RCTs[26,27,65,128] reported on short-term outcomes comparing CAS versus CEA in

symptomatic patients, and seven RCTs[29,45,48,63,93,129,170] studies reported longer-term outcomes of CAS versus CEA in this population. As noted elsewhere, three of these RCTs were terminated early secondary to concerns regarding safety or futility[128,141,153] and two were stopped for other reasons.[93,170] Three studies did not use embolic protection devices.[45,141,170] In addition one RCT in patients who were considered high surgical risk was identified.[183] It was terminated due to slow recruitment and is discussed primarily in Key Question four.

For the purposes of this HTA, short-term outcomes were considered all outcomes occurring after 30 days and before 12 months, and longer-term outcomes were considered all outcomes occurring at or after 12 months. All seven RCTs evaluated long-term outcomes; however, two RCTs evaluated short term outcomes.[65,128]

Short-term efficacy in symptomatic patients:

Two RCTs reported the 4- and 6-month efficacy of CAS versus CEA in symptomatic patients.[65,128] There were statistically significant increases in risks of several short-term outcomes: death, periprocedural stroke or death or postprocedural stroke, and any periprocedural stroke or death or postprocedural ipsilateral stroke (Table 10). Both RCTs reported an increased risk of "any stroke or death" for CAS compared to CEA; however, it was only significant for the largest trial (RD: 3.32, 95% CI: 1.13, 5.52) (Table X). There were no differences in risks of any stroke, ipsilateral stroke, disabling stroke or death or MI between CAS and CEA treatment groups.

Table 10. Summary of risks of short-term outcomes reported by RCTs comparing CAS and CEA among symptomatic patients

Study	N	Follow-up	CAS		CEA		Effect Size	
			%	(n/N)	%	(n/N)	RD%* (95% CI)	RR (95% CI)
Any stroke (excluding periprocedural)†								
ICSS (2010)	1,710	4 months	0.8 %	(7/853)	0.9%	(8/857)	-0.11 (-0.99, 0.77)	0.88 (0.32, 2.42)
Death								
ICSS (2010)	1,710	4 months	2.3%	(19/853)	0.8%	(7/857)	1.37 (0.23, 2.51)	2.69 (1.14, 6.36)
Any stroke or death								
EVA-3S (2006)	527	6 months	11.8%	(31/262)	9.8%	(26/265)	1.65 (-3.17, 6.46)	1.18 (0.72, 1.94)
ICSS (2010)	1,710	4 months	8.5%	(72/853)	4.7%	(40/857)	3.32 (1.13, 5.52)	1.75 (1.20, 2.54)
Any periprocedural stroke or death or postprocedural stroke								
EVA-3S (2006)	527	6 months	10.9%	(29/262)	4.6%	(12/265)	5.63 (1.44, 9.83)	2.30 (1.20, 4.42)
Any periprocedural stroke or death or postprocedural ipsilateral stroke								
EVA-3S (2006)	527	6 months	10.2%	(27/262)	4.2%	(11/265)	5.36 (1.28, 9.43)	2.34 (1.19, 4.63)
Ipsilateral stroke (excluding periprocedural)†								
ICSS (2010)	1,710	4 months	0.7%	(6/853)	0.5%	(5/857)	0.12 (-0.63, 0.87)	1.20 (0.37, 3.93)
Disabling stroke or death								
ICSS (2010)	1,710	4 months	4.0%	(32/853)	3.2%	(27/857)	0.56 (-1.11, 2.23)	1.18 (0.72, 1.96)
MI								
ICSS (2010)	1,710	4 months	0.4%	(3/853)	0.5%	(4/857)	-0.11 (-0.72, 0.49)	0.75 (0.17, 3.36)

*Risk difference presented as percentage for ease of interpretation

†Data available to allow exclusion of periprocedural events

Cognition

One RCT evaluated 6-month change from baseline in cognition after CAS and CEA.[27] Changes in cognition scores (total or individual cognition subscores) were similar between CAS and CEA, and there were no statistically significant differences between treatment groups (Table 11).

Table 11. Summary of 6-month change in cognition comparing CAS and CEA among symptomatic patients

	CAS		CEA		Effect Size
	Δ	(sd)	Δ	(sd)	MD% (95% CI)
Change in cognition z scores					
Total Sum	-0.19	(0.38)	-0.02	(0.71)	-0.17 (-0.38, 0.03)
Abstract reasoning	-0.17	(0.48)	.04	(0.45)	-0.22 (-0.44, 0.00)
Attention	-0.09	(1.05)	-0.13	(1.60)	0.04 (-0.46, 0.53)
Executive functioning	0.13	(0.36)	0.17	(0.48)	-0.05 (-0.21, 0.12)
Language	-0.25	(0.68)	-0.18	(0.70)	-0.07 (-0.32, 0.18)
Verbal memory	-0.16	(0.76)	-0.09	(1.00)	-0.07 (-0.39, 0.26)
Visual memory	0.24	(0.72)	0.24	(0.66)	0.00 (-0.27, 0.26
Visual perception	-0.14	(0.54)	-0.17	(0.73)	-0.04 (-0.21, 0.28)
Neglect	-1.75	(1.70)	-0.61	(3.57)	-1.13 (-2.27, 0.01)

MD: mean difference

Blood pressure

One RCT evaluated 1-, 6-, and 12-month change from baseline in blood pressure after CAS and CEA.[26] Mean changes in systolic and diastolic blood pressure from baseline were similar between CAS and CEA, and there were no statistically significant differences between treatment groups (Table 12). In addition, mean differences in change in systolic and diastolic blood pressure between treatment groups were similar over time.

Table 12. Summary of 1-, 6-, and 12- month change in blood pressure comparing CAS and CEA among symptomatic patients

	CAS		CEA		Effect Size
	Δ	(95% CI)	Δ	(95% CI)	MD% (95% CI)
Change in blood pressure: 1-month					
Systolic blood pressure	-0.4	(-2.4, 1.7)	-1.6	(-3.4, 0.2)	-1.3 (-1.5, 4.0)
Diastolic blood pressure	-1.1	(0.0, 2.1)	0.8	(-0.2, 1.9)	0.2 (-1.3, 1.7)
Change in blood pressure: 6-months					
Systolic blood pressure	-2.5	(-4.7, -0.4)	-3.0	(-5.0, -0.9)	-0.4 (-2.5, 3.4)
Diastolic blood pressure	-0.9	(-2.1, 0.2)	-0.3	(-1.4, 0.9)	-0.7 (-2.3, 1.0)
Change in blood pressure: 12-months					
Systolic blood pressure	-2.1	(-4.3, 0.2)	-4.4	(-6.5, 2.2)	2.3 (-0.8, 5.4)
Diastolic blood pressure	-0.5	(-1.7, 0.6)	-0.7	(-1.9, 0.4)	0.2 (-1.4, 1.8)

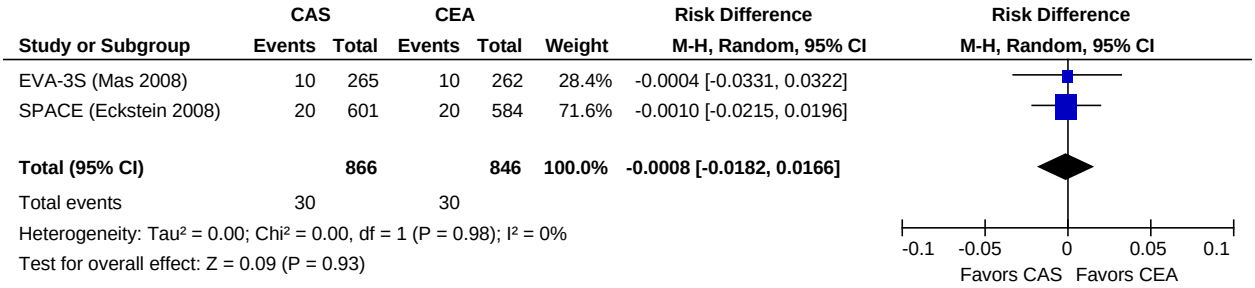
MD=Mean difference

Long-term efficacy in symptomatic patients:

Any stroke (excluding periprocedural)

Four out of seven RCTs examined long-term risk of any stroke.[48,63,93,129] Of these studies, two reported no post-periprocedural stroke events; thus, only 2 RCTs contribute data for this endpoint.[63,129] There were no differences in the risk of any stroke between CAS in CEA in any individual RCT (Table 13), nor when studies were combined in a pooled analysis (RD: -0.08%, 95%CI: -1.82, 1.66) (Figure 3).

Figure 3. Comparison of any stroke at last follow-up* (excluding periprocedural)



*Last follow-up: SPACE at 2 years, and EVA-3S at 4 years

Table 13. Summary of risks of any stroke reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			%	(n/N)	%	(n/N)	RD%* (95% CI)	RR (95% CI)
Any stroke (excluding periprocedural)								
SPACE (2008)	1,196	2 years	3.3%	(20/601)†	3.4%	(20/584)†	-0.10 (-2.15,1.96)	0.97 (0.53, 1.79)
Kentucky (2001)	104	2 years	0%	(0/53)†	0%	(0/50)†	NE	NE
EVA- 3S (2008)	527	4 years	3.8%	(10/265)	3.8%	(10/262)	-0.04 (-3.31, 3.22)	0.99 (0.42, 2.34)
BACASS (2008)	20	4 years	0%	(0/10)‡	0%	(0/10)‡	NE	NE
Pooled estimates							-0.08 (-1.82, 1.66)	.98 (0.59, 1.61)

NE = Not estimable

*Risk difference presented as percentage for ease of interpretation

† N's calculated by hand; periprocedural deaths were subtracted from total N

‡ n's calculated by hand

Similar results in symptomatic patients were seen in the SAPPHIRE trial of high surgical risk patients. Gurm et al (2008) No differences in three year stroke risk following treatment with either CAS or CEA, with a risk difference of -3% (95% CI, -13%, 8%) were found.[87] See Key Question 4 for additional details.

Ipsilateral stroke (excluding periprocedural)

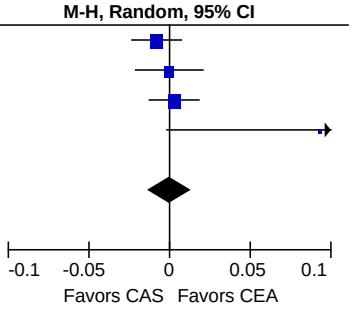
A total of five RCTs evaluated long-term risk of ipsilateral stroke (excluding periprocedural stroke) for CAS and CEA.[45,48,63,129,170] One small RCT reported no events in either treatment arm; therefore, only four RCTs contribute data for this endpoint.[48,63,129,170] There were no differences in risk of ipsilateral stroke between CAS and CEA in any individual RCT (Table 14), nor when studies were combined in the pooled analysis (RD: - 0.01%, 95%CI: -1.36, 1.34) (Figure 4). Estimates from sensitivity analysis excluding older studies, those with ≤ 10 patients per arm and those which did not use EPDdid not alter the conclusion. (RD: - 0.21%, 95% CI: -1.2%, 0.75%, p = 0.67; RR 0.67. 95% CI 0.31, 1.44).

Figure 4. Comparison of ipsilateral stroke at last follow-up* (excluding periprocedural)

	Favors CAS		CEA			Risk Difference	Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
CREST (Brott)	11	668	16	653	36.2%	-0.0080 [-0.0233, 0.0073]	
EVA-3S (Mas 2008)	4	265	4	262	25.8%	-0.0002 [-0.0211, 0.0207]	
SPACE (Eckstein 2008)	12	601	10	584	36.0%	0.0028 [-0.0125, 0.0182]	
Regensburg (Steinbauer)	4	43	0	44	2.0%	0.0930 [-0.0016, 0.1876]	
Total (95% CI)		**1577**		**1543**	**100.0%**	**-0.0001 [-0.0136, 0.0134]**	
Total events	31		30				

Heterogeneity: Tau² = 0.00; Chi² = 4.93, df = 3 (P = 0.18); I² = 39%

Test for overall effect: Z = 0.01 (P = 0.99)

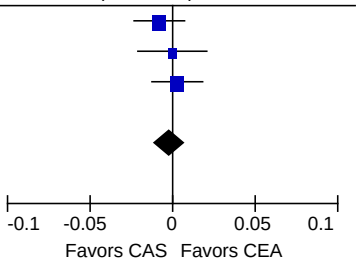


Sensitivity analysis

	Favors CAS		CEA			Risk Difference	Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
CREST (Brott)	11	668	16	653	39.6%	-0.0080 [-0.0233, 0.0073]	
EVA-3S (Mas 2008)	4	265	4	262	21.2%	-0.0002 [-0.0211, 0.0207]	
SPACE (Eckstein 2008)	12	601	10	584	39.2%	0.0028 [-0.0125, 0.0182]	
Total (95% CI)		**1534**		**1499**	**100.0%**	**-0.0021 [-0.0117, 0.0075]**	
Total events	27		30				

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.67)



***Last follow-up: SPACE and Kentucky at 2 years, EVA-3S and CREST at 4 years, and Regensburg at 5.4 years**

Table 14. Summary of risks of ipsilateral stroke reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			%	(n/N)	%	(n/N)	RD%* (95% CI)	RR (95% CI)
Ipsilateral stroke (excluding periprocedural)								
SPACE (2008)	1,196	2 years	2.2%	(12/601)†	1.9%	(10/584)†	0.28 (-01.25, 1.82)	1.17 (0.51, 2.68)
Kentucky (2001)	104	2 years	0%	(0/53)†	0%	(0/50)†	NE	NE
EVA- 3S (2008)	527	4 years	1.5%	(4/265) ‡	1.5%	(4/262)‡	-0.02 (-2.11, 2.07)	0.99 (0.25, 3.91)
CREST (2010)	1,321	4 years	1.6%	(11/668)‡	2.4%	(16/653)‡	-0.80 (-2.33, 0.73)	-0.00 (-0.01, 0.01)
Regensburg (2008)	87	5.4 years	9.5%	(4/43) §	0%	(0/44)§	9.30 (-0.16, 18.76)	9.20 (0.51, 165.96)
Pooled estimates							-0.01 (-1.36, 1.34)	0.97 (0.55, 1.73)

NE = Not estimable

*Risk difference presented as percentage for ease of interpretation

† N's calculated by hand; periprocedural deaths were subtracted from total N

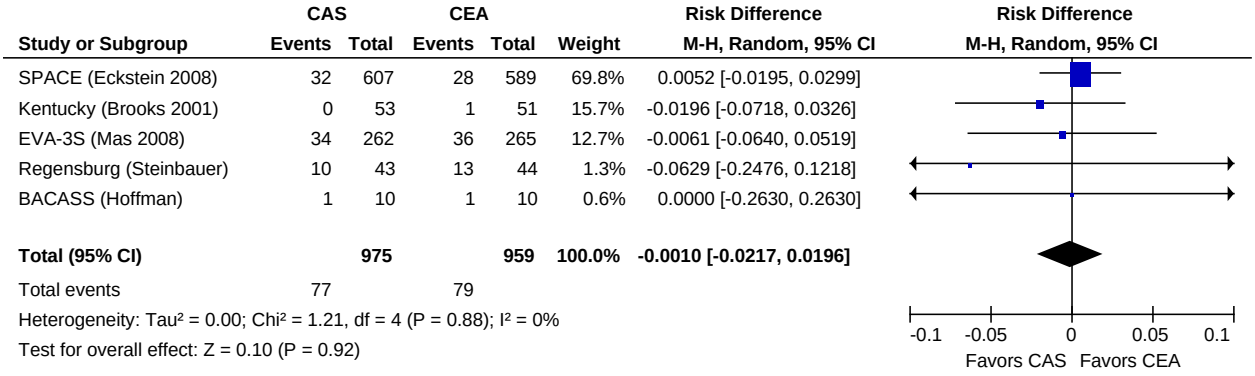
‡ n's calculated by hand

§ N's calculated by hand

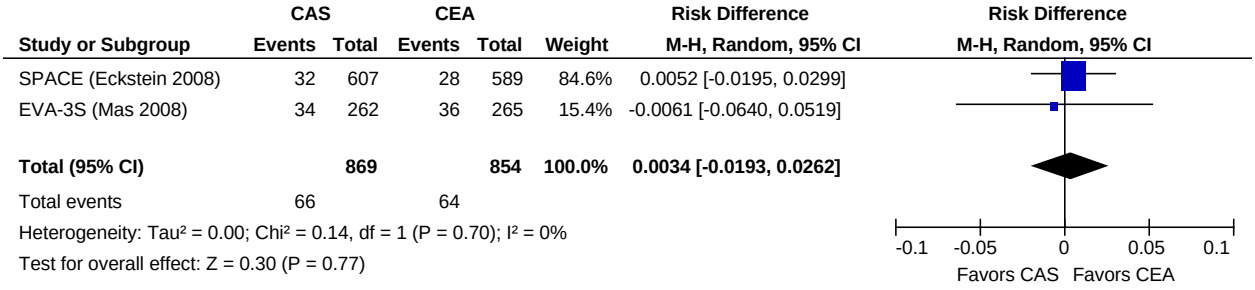
Death

Five RCTs evaluated long-term risk of death (including periprocedural events) for CAS and CEA.[45,63,93,129,170] were no differences in risk of death between CAS and CEA in any individual RCT (Table 15), nor when studies were combined in the pooled analysis (RD: -0.10%, 95%CI: -2.17, 1.96) (Figure 5). Three RCTs also provide data that allow the exclusion of periprocedural events to determine risk of post-procedural death.[45,93,129] In a pooled analysis excluding periprocedural deaths, there was no difference in risk of post-procedural death between CAS and CEA (RD: 0.38%, 95%CI: -1.87, 2.64).

Figure 5. Comparison of death at last follow-up* (including periprocedural)



Sensitivity analysis



*Last follow-up: SPACE and Kentucky at 2 years, EVA-3S and BACASS at 4 years, and Regensburg at 5.4 years

Table 15. Summary of risks of death reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
Death (including periprocedural)								
SPACE (2008)	1,196	2 years	(32/607)	6.3%	(28/589)	5.0%	0.52 (-1.95, 2.99)	1.11 (0.68, 1.82)
Kentucky (2001)	104	2 years	(0/53)	0.0%	(1/51)	1.9%	-1.96 (-7.18, 3.26)	0.32 (0.01, 7.70)
EVA- 3S (2008)	527	4 years	(34/262)	13.0%	(36/265)	13.6%	-0.61 (-6.40, 5.19)	0.96 (0.62, 1.48)
Regensburg (2008)	87	5.4 years	(10/43)	23.3%	(13/44)	29.5%	-6.29 (-24.76, 12.18)	0.79 (0.39, 1.60)
BACASS (2008)	20	4 years	(1/10)	10.0%	(1/10)	10.0%	0.0 (-26.30, 26.30)	1.00 (0.07, 13.87)
Pooled estimates							-0.10 (-2.17, 1.96)	0.97 (0.72, 1.30)
Death (excluding periprocedural)								
SPACE (2008)	1,196	2 years	(26/601)†	4.3%	(23/584)†	3.9%	0.39 (-1.88, 2.65)	1.10 (0.63, 1.90)
Kentucky (2001)	104	2 years	(0/53)†	0.0%	(0/50)†	0.0%	0.0 (-3.72, 3.72)	NE
BACASS (2008)	20	4 years	(1/10)†	10.0%	(1/10)†	10.0%	0.0 (-26.30, 26.30)	1.00 (0.07, 13.87)
Pooled estimates							0.38 (-1.87, 2.64)	1.09 (0.64, 1.87)

NE = Not estimable

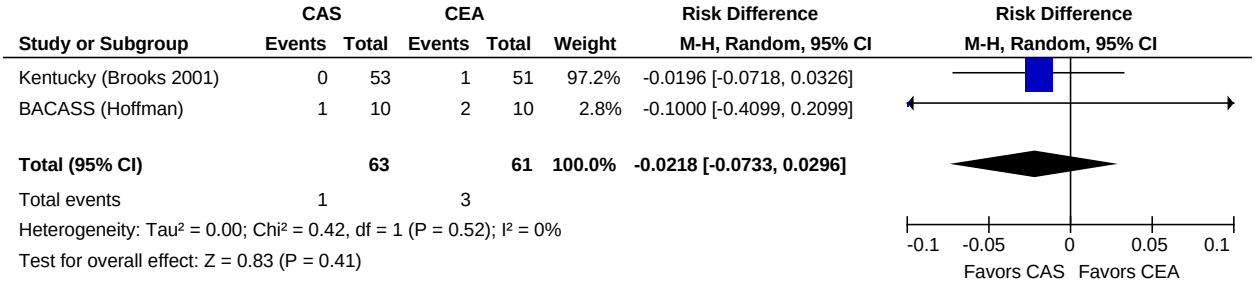
*Risk difference presented as percentage for ease of interpretation

† N's calculated by hand; periprocedural deaths were subtracted from total N

Death or any stroke (includes periprocedural)

Two small RCTs evaluated long-term risk of death or stroke (including periprocedural events) for CAS and CEA.[45,93] Risk of death or stroke at 2 and 4 years was lower for CAS compared to CEA; however, differences in risk between CAS and CEA were not significant for any individual RCT (Table 16), nor when studies were combined in the pooled analysis (RD: -2.18%, 95%CI: -7.33, 2.96) (Figure 6). It should be noted that these are small, older studies and embolic protection was not used.

Figure 6. Comparison of death or any stroke at last follow-up* (includes periprocedural)



*Last follow-up: Kentucky at 2 years, and BACASS at 4 years

Table 16. Summary of risks of death or any stroke reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
Death or any stroke (includes periprocedural)								
Kentucky (2001)	104	2 years	0%	(0/53)†,‡	2.0%	(1/51)†,‡	-1.96 (-7.18, 3.25)	0.32 (0.01, 7.70)
BACASS (2008)	20	4 years	12.5%	(1/10)†,**	22.2%	(2/10)†,**	-10.00 (-40.99, 20.99)	0.50 (0.05, 4.67)
Pooled estimates							-2.18 (-7.33, 2.96)	0.43 (0.07, 2.69)

NE = Not estimable

*Risk difference presented as percentage for ease of interpretation

† n's calculated by hand

‡ N's calculated by hand; periprocedural death data was not available

§ N's calculated by hand

Death or any periprocedural stroke or postprocedural ipsilateral stroke

A total of five RCTs evaluated long-term risk of death or any periprocedural stroke or postprocedural ipsilateral stroke for CAS and CEA.[45,48,63,93,170] There were no differences in risk of death, periprocedural stroke or postprocedural ipsilateral stroke at 2, 4 and 5.4 years for CAS compared to CEA in any individual RCT (Table 17). In a pooled analysis of these

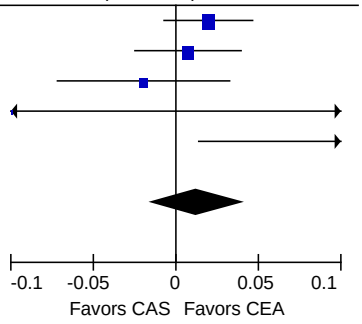
studies, risk of death or any periprocedural stroke or postprocedural ipsilateral stroke was similar for CAS and CEA treatment groups (Figure 7). Sensitivity analysis excluding older studies, those with ≤ 10 patients per arm and those which did not use EPD failed to reveal a statistically significant difference between groups.

Figure 7. Comparison of death or any periprocedural stroke or postprocedural ipsilateral stroke at last follow-up*

	CAS		CEA			Risk Difference	Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
CREST (Brott)	51	668	37	653	38.1%	0.0197 [-0.0071, 0.0465]	
SPACE (Eckstein 2008)	56	607	50	589	33.3%	0.0074 [-0.0248, 0.0396]	
Kentucky (Brooks 2001)	0	53	1	51	20.1%	-0.0196 [-0.0718, 0.0326]	
BACASS (Hoffman)	0	10	1	10	1.5%	-0.1000 [-0.3372, 0.1372]	
Regensburg (Steinbauer)	5	43	0	44	7.1%	0.1163 [0.0139, 0.2187]	
Total (95% CI)		**1381**		**1347**	**100.0%**	**0.0128 [-0.0164, 0.0419]**	
Total events	112		89				

Heterogeneity: Tau² = 0.00; Chi² = 6.68, df = 4 (P = 0.15); I² = 40%

Test for overall effect: Z = 0.86 (P = 0.39)

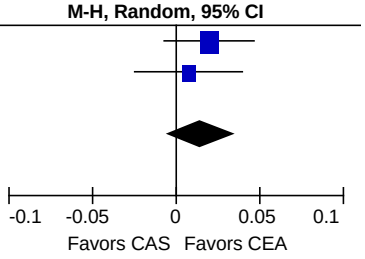


Sensitivity analysis

	CAS		CEA			Risk Difference	Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
CREST (Brott)	51	668	37	653	59.0%	0.0197 [-0.0071, 0.0465]	
SPACE (Eckstein 2008)	56	607	50	589	41.0%	0.0074 [-0.0248, 0.0396]	
Total (95% CI)		**1275**		**1242**	**100.0%**	**0.0146 [-0.0060, 0.0352]**	
Total events	107		87				

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%

Test for overall effect: Z = 1.39 (P = 0.16)



*Last follow-up: SPACE and Kentucky at 2 years, CREST and BACASS at 4 years, and Regensburg at 5.4 years

Table 17. Summary of risks of death or any periprocedural stroke or postprocedural ipsilateral stroke reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
Death or any periprocedural stroke or postprocedural ipsilateral stroke								
SPACE (2008)	1,196	2 years	9.2%	(56/607)†	8.5%	(50/589)†	0.01 (-2.48, 3.96)	1.09 (0.76, 1.56)
Kentucky (2001)	104	2 years	0%	(0/53)‡,§	2.0%	(1/51)‡**	-0.02 (-7.18, 4.65)	0.32 (0.01, 7.70)
CREST (2010)	1,321	4 years	8.0%	(51/668)†	3.2%	(37/653)†	0.02 (-0.71, 4.65)	1.35 (0.89, 2.03)
BACASS (2008)	20	4 years	0%	(0/10)‡,†	10.0%	(1/10)‡,†	-0.10 (-33.72, 13.72)	0.33 (0.02, 7.32)
Regensburg (2008)	87	5.4 years	11.6%	(5/43)†	0%	(0/44)†	0.12 (1.38, 21.87)	11.25 (0.64, 197.44)
Pooled estimates							1.28 (-1.64, 4.19)	1.20 (0.89, 1.62)

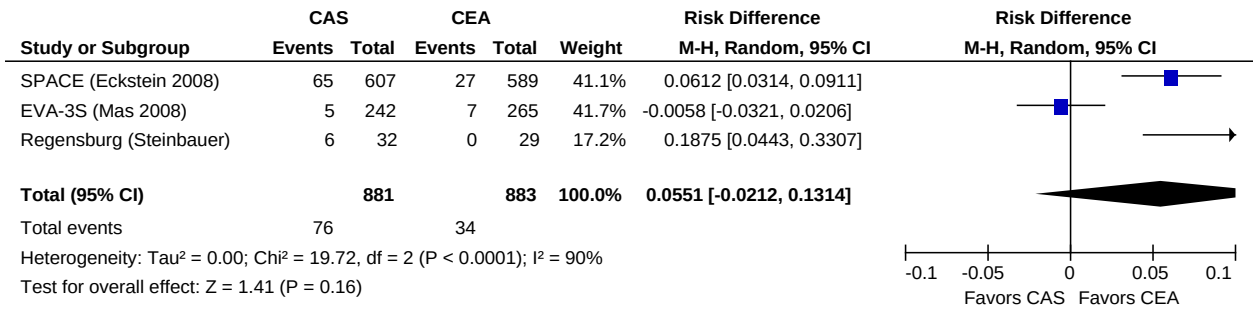
*Risk difference presented as percentage for ease of interpretation
† N's based on full sample
‡ n's calculated by hand
§ N's calculated by hand

Similarly, in symptomatic patients in the SAPPHIRE trial of high surgical risk patients, Gurm et al (2008) found no differences in three year death or ipsilateral stroke risk following treatment with either CAS or CEA, with a risk difference of 10% (95% CI, -7%, 28%).[87] See Key Question 4 for additional details.

Restenosis

Five RCTs evaluated long-term risk of severe restenosis (70% or greater) for CAS and CEA. One large RCT[48] did not present data stratified by symptomatic status, and in one small RCT[93] no events were reported in either treatment arm; therefore, only three RCTs contribute data for this endpoint. In two out of three RCTs risk of severe restenosis was significantly greater for CAS compared with CEA[129,170] however, in a pooled analysis of these studies, differences in risk between CAS and CEA were not statistically significant (Pooled RD: 5.51, 95% CI: -2.12, 13.14). (Figure 8, Table 18)

Figure 8. Comparison of risk of restenosis (≥ 70%) at last follow-up*



*Last follow-up: SPACE at 2 years, CREST, EVA-3S at 4 years, Regensburg at 5.4 years

Table 18. Summary of risk of restenosis reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
Restenosis ≥ 70%								
SPACE (2008)†	1,196	2 years	(65/607)	10.7%	(27/589)	4.6%	6.12 (3.14, 9.11)	2.34 (1.51, 3.61)
EVA- 3S (2011)	527	3 years	(5/242)	2.1%	(7/265)	2.8%	-0.58 (-3.21, 2.06)	0.78 (0.25, 2.43)
BACASS (2008)‡	20	4 years	(0/8)	0.0%	(0/9)	0.0%	0.0 (-20.00, 20.00)	NE
Regensburg (2008)§	87	5.4 years	(6/32)	18.8%	(0/29)	0.0%	18.75 (4.43, 33.07)	11.82 (0.69, 200.99)
Pooled estimates							5.51 (-2.12, 13.14)	1.90 (0.69, 5.20)

NE = Not estimable
*Risk difference presented as percentage for ease of interpretation
†Total number of patients with ultrasound follow-up not available; totals are numbers of randomized patients
‡Restenosis data was missing for 7.6% of patients
§Reported as restenosis >70%

Moderate stenosis (51%-69%) was described in three studies: For EVA-3S[29] an additional 23 events were reported for CAS and 5 for CEA; for BACASS,[93] 0 additional events were reported for CAS and 1 for CEA; and for Regensburg,[170] an additional 8 events were reported for CAS and 1 for CEA.

Other outcomes

TIA: Four RCTs evaluated long-term risk of TIA for CAS and CEA[45,93,128,170]; however, two RCTs reported no events in either treatment arm, thus only two RCTs contribute data for this endpoint.[128,170] There were no statistically significant differences in risk of TIA between CAS and CEA (Table 19).

Disease progression: One small RCT reported on risk of disease progression to a high-grade stenosis of the contralateral carotid artery.[170] The risk for CAS was 15.6% and for CEA was 10.3%. The difference in risk of disease progression between treatment arms was not statistically significant $P > 0.05$).

Reintervention rate: One small RCT reported a significant increase in risk of reintervention after CAS, compared with CEA[170]; however, no data were provided.

Table 19. Summary of risk of TIA reported by RCTs comparing CAS and CEA among symptomatic patients; by longest follow-up

Study	N	Follow-up	CAS		CEA		Effect Size	
			(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
TIA								
Kentucky (2001)	104	2 years	(1/53)	1.9%	(0/51)	0.0%	NE	NE
EVA-3S (2006)	520	3 years	(6/261)	2.3%	(2/259)	0.8%	1.48 (-0.59, 3.55)	2.93 (0.60, 14.40)
BACASS (2008)	20	3 years	(0/10)	0.0%	(0/10)	0.0%	NE	NE
Regensburg (2008)	87	5.4 years	(3/43)	7.0%	(2/44)	4.5%	2.17% (-7.1, 11.4)	1.5 (0.26, 8.56)

NE = Not estimable
*Risk difference presented as percentage for ease of interpretation

Effectiveness in symptomatic patients

CAS and medical therapy compared with medical therapy alone:
No nonrandomized comparative studies evaluating the efficacy of CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS and medical therapy compared with CEA and medical therapy:
Data from two nonrandomized, comparative studies describing the primary outcomes (e.g. stroke) were available. Both studies were prospective cohorts. One reported the 4-year results from the CaRESS study and included 128 symptomatic patients.[189] The second study analyzed results at a mean of 2.8 years from 684 symptomatic patients treated following a training phase.[59] Demographics were not reported separately for the symptomatic populations; however overall mean patient ages were similar across studies (~71 years) and males comprised 62% and 71% of the total populations. Both studies were considered to be at moderately high risk of bias. Data are summarized in Table 20.

A positive risk difference (RD) favors CAS and negative RD favors CEA.

Any stroke
The CaRESS cohort evaluated the risk of any stroke at 4 years of follow-up and found no significant difference following CAS (7.2%) compared with CEA (17.8%).[189]

Death
No statistically significant difference in the risk of all-cause death was seen in the CAS compared with the CEA group at 4 years as reported by the CaRESS study: CAS (10.4%) versus CEA (24.9%).[189]

Any stroke or death

The 4 year follow-up results of the CaRESS cohort showed a marginally significant decreased risk of any stroke or death following CAS compared with CEA: 12.4% versus 33.5%; RD = 20.8% (95% CI, 4.0%–34.5%) and relative risk (RR) = 0.38 (95% CI, 0.15–0.91).[189]

Myocardial infarction (MI)

No statistically significant difference in risk of MI was reported in the CAS compared with the CEA group at 4 years as reported by the CaRESS study: 7.1% versus 12.6%, respectively.[189]

Any periprocedural stroke or death or post-procedural ipsilateral stroke

A second clinical cohort study with a mean follow-up of 2.8 years reported 5-years Kaplan Meier estimates of stroke or death up to 30 days or ipsilateral stroke thereafter, with no statistically significant difference in risk between the CAS and the CEA group, although lower rates of this outcome were reported following CAS (4.9% vs. 8.7%, respectively).[59]

Table 20. Summary of cumulative rates of stroke, death, and MI *by longest follow-up* in patients with symptomatic carotid artery stenosis from clinical studies comparing CAS with CEA.

Study, N	Outcome	Time Frame (mean)	Patients with outcome		Effect Size RD % (95% CI)* RR (95% CI)
			CAS % (n/N)	CEA % (n/N)	
Any stroke					
Zarins 2009 CaRESS cohort (Pro) N = 128	Any stroke	4 years	7.2 (3/42)†	17.8 (13/73)†	RD = 10.7 (-3.2 to 22.0)† RR = 0.40 (0.12–1.33)†
Death					
Zarins 2009 CaRESS cohort (Pro) N = 128	All-cause death	4 years	10.4 (4/38)†	24.9 (15/60)†	RD = 14.5 (-2.0 to 28.3)† RR = 0.42 (0.15–1.17)†
Any stroke or death					
Zarins 2009 CaRESS cohort (Pro) N = 128	Any stroke or death	4 years	12.4 (5/40)†	33.5 (23/69)†	RD = 20.8 (4.0–34.5)† RR = 0.38 (0.15–0.91)†
Myocardial infarction (MI)					
Zarins 2009 CaRESS cohort (Pro) N = 128	MI	4 years	7.1 (2/28)†	12.6 (7/56)†	RD = 5.4 (-11.4 to 17.6)† RR = 0.57 (0.13–2.57)†
Any periprocedural stroke or death or post-procedural ipsilateral stroke					
De Rango 2011 Cohort study (Pro) N = 684	Stroke or death up to 30 days or ipsilateral stroke thereafter	2.8 years	4.9‡	8.7‡	NR, *P* = ns§

CAS: carotid artery stenting; CEA: carotid endarterectomy; NR: not reported; Pro: prospective study design; RD: risk difference; RR: relative risk.

*A positive risk difference favors CAS and negative risk difference favors CEA.

†Given the percentages and counts (n's) provided by the authors, we back-calculated to determine the total N after loss-to-follow-up. A RR reflecting this change was also calculated as was a RD.

‡Percentages are 5-year Kaplan Meier rate estimates as reported by the authors.
§As reported by authors, rates were similar between groups (*P* = 0.7).

4.2. Key question 2: Stenting in Intracranial Atherosclerotic Disease Efficacy, Effectiveness and Safety

In asymptomatic or symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is the evidence of short- and long-term comparative efficacy and effectiveness of intracranial artery stenting and medical therapy compared with medical therapy alone?

Results for comparative efficacy, effectiveness and safety of intracranial artery stenting are provided in this section for cohesiveness. For efficacy and effectiveness, outcomes beyond the 30 day periprocedural period are reported. For safety, outcomes within the periprocedural period as well as adverse events or complications beyond this period are reported.

4.2.1. Asymptomatic

No studies in asymptomatic patients meeting our inclusion criteria were found.

4.2.2. Symptomatic

Summary of RCT data: The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was the only RCT identified.[51]

- **Efficacy:** Based on Kaplan–Meier analysis, 1 year probabilities are summarized below:
  - **Any stroke**: Probabilities were significantly higher in patients assigned to receive stents (22.3%) than in those assigned to intensive medical care (14.9%)
  - **Death:** The probabilities were not statistically different between groups
  - **Any stroke or death:** Probabilities at 1 year were 23.4% and 17.5% respectively for the stenting and medical therapy arms, a marginally insignificant result.
  - **Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days:** This was the studies primary endpoint. Stenting was associated with a significantly higher probability of this composite outcome (20.0%) than medical therapy (12.2%), *P* = .009.
  - **Myocardial infarction:** The probabilities were not statistically different between treatment groups.

  - **Any major hemorrhage:** The probability of major hemorrhage was significantly greater in the stent group (9.0%) than in the medical treatment group (1.8%), p <0.001.
- **Safety:** This RCT was terminated early based on significantly higher risk of periprocedural (30 day) stroke or death in the stenting group (14.7%) compared with the medical management group (5.8%) and a futility analysis which demonstrated that no benefit in the stenting group would be shown had the trial been run to completion. The probability of any stroke was 14.7% for stenting and 5.3 % for medical therapy, (p = 0.03) RD of 9.4% (NNH 11), while there were no statistical differences in death between the groups.

Summary of nonrandomized studies: No nonrandomized comparative studies were found so no conclusions regarding comparative effectiveness or safety can be made. Five prospective case series met the inclusion criteria.[12,42,71,101,188] The longest follow-up was an average of 22 months.

- **Longer term effectiveness:** The risks of stroke and for any stroke or death by longest follow-up were lower than those reported in the RCT. Risk of in-stent restenosis ranged from 7.5%-32.3% with the majority reported as being asymptomatic.
- **Safety:**
  - For 30 day periprocedural safety outcomes, risks for stroke and any stroke or death were lower than those reported in the RCT and risk of death was similar.
  - Reported complications included access site complications (11.4%) stent thrombosis (0%-3.1%) and transient vasospasm (1.6% - 11.4%). Vessel dissection/perforation occurred in 0% -6.4% across four studies.

Detailed results:

Efficacy (RCT data)

Only one RCT that compared angioplasty and stenting of intracranial arteries with standard medical care was identified.[51] The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial enrolled a total of 451 patients from 50 sites in the United States; 224 were assigned to the angioplasty and stenting group and 227 to the medical-management group. The trial was terminated early as the 30-day risk of stroke or death was significantly higher in those who received stenting (14.7%) compared with the medical management group (5.8%) and a futility analysis demonstrated virtually no benefit in the stenting group would be shown had the trial been run to completion.

Eligible patients had a TIA or nondisabling stroke within 30 days before enrollment, attributed to angiographically verified stenosis of 70% to 99% of the diameter of a major intracranial artery (overall, mean stenosis 80% ± 7%). The location of the symptomatic qualify artery was the middle cerebral (~44%), basilar (~22%), internal carotid (~21%), and vertebral (~13%).

Kaplan-Meier analysis for cumulative probabilities was reported by the authors. Analysis curves were truncated at 15 months. Less than one half of the enrolled patients had been followed for longer than 1 year at the time of study publication and the maximum follow-up was 28.1 months in the stenting group and 28.9 months in the medical treatment group. Probabilities for the study's primary outcome at 1 year are summarized in Table 21

Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days

This was the study's primary endpoint. By 1 year, the probability of the primary end point was 20.0% compared with 12.2%, respectively; *P* = .009. A total of 46 patients in the stenting group and 26 in the medical group experienced an event. The proportion of patients experiencing an ischemic stroke in the territory of the qualifying artery between day 31 and up to 1 year was identical between groups, 5.8% and 5.7% (n = 13 each), respectively; thus, the statistically significant increased risk of the primary end point at 1 year is driven by the 30-day risk. The authors also conducted an as-treated analysis that excluded 11 patients in the stenting group who did not undergo angioplasty or have a stent placed (3 of whom had a stroke) and nine patients in the medical therapy group who underwent stenting during the follow-up period (3 of whom had a stroke after stenting) which showed the same results for the primary outcome at 1 year (P = 0.009).

Any stroke

Over the course of follow-up, 50 (22.3%) patients who underwent stenting and 32 (14.1%), a risk difference of 8.2%, (NNH 12) who received medical therapy only had a stroke. The probability of any stroke (ischemic stroke in territory of the qualify lesion or in other territory and symptomatic brain hemorrhage) was statistically greater in the stenting compared with the medical therapy group at 1 year, respectively: 22.3% versus 14.9%; P = .03. The number of patients with an event occurring after 30 days and up to 1 year was 17 (stenting) and 20 (medical only).

Death

No difference was seen in the probability of death by 1 year following stenting (3.4%) compared with the medical therapy only (4.1%). A total of seven deaths were reported in both groups over the course of follow-up; two (both non-stroke-related) occurred after 30 days in the stent group versus six (1 stroke-related/brain hemorrhage) in the medical group.

Any stroke or death
The probability of any stroke or death in the stenting compared with the medical therapy group at 1 year was 23.4% versus 17.5%, respectively (*P* = .06). A total of 52 stented patients and 37 medical patients had an event; after 30 days, any stroke or death was reported in 19 and 24 patients, respectively.

Disabling or fatal stroke
At 1 year, the probability of disabling or fatal stroke (ischemic stroke in territory of the qualify lesion or in other territory and symptomatic brain hemorrhage) was slightly higher following stenting compared with medical therapy: 9.0% versus 6.4% (*P* = ns). In the stent group 19 patients experienced an event compared with 13 in the medical group. The number of events was similar between groups for ischemic stroke (ipsilateral and contralateral) but was much higher following stenting for symptomatic brain hemorrhage following stenting (8 versus. 1 patient).

Myocardial infarction
The probability of MI was non-significantly lower in the stenting compared with the medical therapy group at 1 year: 2.2% versus 4.0%.

Major non-stroke-related hemorrhage
No significant differences were seen in the probability of a major non-stroke-related hemorrhage (to include subdural, gastrointestinal, ocular, lingual hematoma, and angiogram access site) following stenting and medical therapy only at 1 year: 3.6% versus 1.4%, respectively.

Any major hemorrhage
A significantly higher probability of any major hemorrhage (symptomatic, asymptomatic, non-stroke-related) at 1 year was reported following stenting as compared with medical therapy only: 9.0% versus 1.8%; *P* < .001. In total, 22 patients experienced a major hemorrhage in the stent group compared with only five patients in the medical therapy only group.

Table 21. Probability (95% CI) of outcomes at 1 year from the SAMMPRIS trial.

Outcome	Patients with events (%)		Probability (%) at 1 year (95% CI)		*P*-value*
	Stent	Medical	Stent	Medical	
Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days	46 (20.5)	26 (11.5)	20.0 (15.2–26.0)	12.2 (8.4–17.6)	.009
Any stroke or death	52 (23.2)	37 (16.3)	23.4 (18.1–29.8)	17.5 (12.8–23.6)	.06
Any stroke	50 (22.3)	32 (14.1)	22.3 (17.2–28.7)	14.9 (10.6–20.7)	.03
Ipsilateral ischemic stroke	36 (16.1)	23 (10.1)			
Ischemic stroke in other territory	4 (1.8)	8 (3.5)			
Symptomatic brain hemorrhage	10 (4.5)	1 (0.4)			
Death	7 (3.1)	7 (3.1)	3.4 (1.6–7.2)	4.1 (2.0–8.5)	.95
Stroke-related death	5 (2.2)	1 (0.4)			
Disabling or fatal stroke	19 (8.5)	13 (5.7)	9.0 (5.7–13.9)	6.4 (3.7–11.1)	.21
Ipsilateral ischemic stroke	8 (3.6)	7 (3.1)			
Ischemic stroke in other territory	3 (1.3)	5 (2.2)			
Symptomatic brain hemorrhage	8 (3.6)	1 (0.4)			
Myocardial infarction	5 (2.2)	7 (3.1)	2.2 (0.8–5.8)	4.0 (1.9–8.4)	.60
Major non-stroke related hemorrhage	10 (4.5)	4 (1.8)	3.6 (1.8–7.1)	1.4 (0.4–4.2)	.10
Subdural	0	1 (0.4)			
Gastrointestinal	4 (1.8)	3 (1.3)			
Ocular	1 (0.4)	0			
Lingual hematoma	1 (0.4)	0			
Angiogram access site	4 (1.8)	0			
Any major hemorrhage	22 (9.8)	5 (2.2)	9.0 (5.9–13.5)	1.8 (0.7–4.8)	< .001
Symptomatic brain hemorrhage	10 (4.5)	1 (0.4)			
Asymptomatic brain hemorrhage	2 (0.9)	0			
Major non-stroke-related hemorrhage	10 (4.5)	4 (1.8)			

*The p-value is for the comparison, with the use of the log-rank test, of the time-to-event curves for the two treatment groups for each of the specified adverse events.

Safety of intracranial stenting: RCT data

Probabilities for the study's primary outcome at 30 days are summarized in Table 22.

Any stroke
A significantly greater probability of any stroke (ischemic stroke in territory of the qualify lesion or in other territory and symptomatic brain hemorrhage) at 30 days was seen following stenting compared with medical therapy: 14.7% versus 5.3% a RD of 9.4% (NNH 11). A total of 33 strokes occurred following stenting compared with only 12 in those undergoing medical treatment only. In the stenting group, the types of stroke were as follows: ischemic stroke in the territory of the qualifying lesion (n = 23) and symptomatic brain hemorrhage (n = 10). In comparison, there were 10 ischemic strokes in the territory of the qualifying lesion and two in another territory, and no symptomatic brain hemorrhages in the medical group. Of the strokes, the difference in the number of symptomatic brain hemorrhages between groups at 30 days was statistically significant: 30.3% (10/33) after CAS versus 0% (0/12) with medical therapy; *P* = .04.

Death
No significant difference was seen in the probability of death at 30 days in the stenting group (2.2%) compared with the medical group (0.4%). There were five deaths in the stenting group, all as a result of stroke (1 ischemic stroke in the territory of the qualifying artery and 4 symptomatic brain hemorrhages), compared with only one non-stroke-related death in the medical group.

Any stroke or death within 30 days after enrollment
The probability of the primary outcome (any stroke or death) occurring at 30 days was significantly greater in the stenting versus the medical group: 14.7% versus 5.8%; P = .002.There were a total of 33 events following stenting and 13 events following medical therapy.

Disabling or fatal stroke
A higher probability of disabling or fatal stroke (ischemic stroke in territory of the qualify lesion or in other territory and symptomatic brain hemorrhage) was seen at 30 days in the stenting compared with the medical therapy group: 7.0% versus 1.8%. Details of stroke events are described above No symptomatic brain hemorrhages were reported in the medical group during the perioperative period.

MI
The probability of MI was lower (non-significantly) in the stenting compared with the medical therapy group at 30 days: 0.5% versus 1.3%.

Major non-stroke-related hemorrhage
No significant differences were seen in the probability of a major non-stroke-related hemorrhage (to include subdural, gastrointestinal, ocular, lingual hematoma, and angiogram access site) following stenting and medical therapy at 30 days, respectively: 2.7% versus 0.9%.

Any major hemorrhage
A significantly higher probability of any major hemorrhage (symptomatic, asymptomatic, or non-stroke-related) at 30 days was reported following stenting as compared with medical therapy only: 8.0% versus 0.9%.

Table 22. Probability (95% CI) of outcomes at 30 days from the SAMMPRIS trial.

Outcome	Patients with events (%)*		Probability (%) at 30 days (95% CI)		*P*-value†
	Stent	Medical	Stent	Medical	
Any stroke or death	33 (14.7)	13 (5.7)	14.7 (10.7–20.1)	5.8 (3.4–9.7)	.009
Any stroke	33 (14.7)	12 (5.3)	14.7 (10.7–20.1)	5.3 (3.1–9.2)	.03
Ipsilateral ischemic stroke	23 (10.3)	10 (4.4)			
Ischemic stroke in other territory	0	2 (0.9)			
Symptomatic brain hemorrhage	10 (4.5)	0			
Death	5 (2.2)	1 (0.4)	2.2 (0.9–5.3)	0.4 (0.1–3.1)	.95
Stroke-related death	5 (2.2)	0			
Disabling or fatal stroke	NR	NR	7.0 (4.3–11.4)	1.8 (0.7–4.8)	.21
Myocardial infarction	NR	NR	0.5 (0.1–3.2)	1.3 (0.4–4.1)	.60
Major non-stroke related hemorrhage	NR	NR	2.7 (1.2–5.9)	0.9 (0.2–3.5)	.10
Any major hemorrhage	NR	NR	8.0 (5.1–12.5)	0.9 (0.2–3.5)	<.001

*The numbers of cases for the outcomes of any stroke or death, any stroke, and death at 30 days were calculated using the information provided under the primary end point in table 3 of the article.
†The p-value is for the comparison, with the use of the log-rank test, of the time-to-event curves for the two treatment groups for each of the specified adverse events.

Data from nonrandomized studies

No comparative nonrandomized studies were identified. Five prospective case series (4 multicenter and 1 single-center) were found that reported outcomes following angioplasty and stenting for symptomatic intracranial atherosclerosis using FDA approved devices for this indication. Four studies investigated the Wingspan stent system in their populations. Two were clinical studies,[42,101] one of which was included in a FDA Summary of Safety and Probable Benefit report on the Wingspan stent system.[4,42] We used the data presented in both the FDA Summary report and in the published article for this assessment. The other two case series were from registries, one of which compiled data from the NIH registry for Wingspan which was created as a phase I trial prior to the SAMMPRIS study.[188] The other was a multicenter intention-to-treat registry (US Wingspan Registry) with one year follow-up data recently published.[71] For the purposes of this report, we used the publication that provided the longest follow-up and the greatest number of patients as the primary publication; two subsequent, earlier publications were also used which provided more detailed information on

periprocedural complications not reported in the newer publication[70] and restenosis.[25] The final study, the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA), was a clinical study investigating the Neurolink stent system and included both intracranial and extracranial indications.[12] This study was also used as the basis of the clinical information for a FDA Summary of Safety and Probable Benefit of the Neurolink stent system[3]; however all the data reported was for the combined extracranial and intracranial populations so we used only the intracranial data from the peer-reviewed article for this review.

Across these five series, sample sizes ranged from 43 to 158 patients. The mean patient ages were similar across four of the studies (63-66 years) with one study enrolling much younger patients (mean age 53 years).[101] The proportion of males varied from 55% to 87% across all studies. Mean follow-up periods ranged from 6 to 21.6 months with patient follow-up as high as 100% and as low as 70% as reported by the authors. Eligible patients had experienced a recent ischemic event (i.e. TIA or stroke) attributed to stenosis of 50% to 99% (4 studies) or 70% to 99% (phase I trial for SAMMPRIS) of the diameter of a major intracranial artery. Lesion locations were most commonly the internal carotid artery, the middle cerebral artery, the vertebral artery and the basilar artery. In all studies patients were treated with aspirin (81 to 325 mg) and clopidogrel (75 mg) for 2-3 days prior to the procedure (or given a therapeutic dose the day of the procedure) and were administered intravenous heparin during the procedure. All patients were discharged on a dual antiplatelet regimen (aspirin and clopidogrel); the prescribed length of the continued drug regimen varied slightly across the studies.

Data from these case series are presented in tables 23 and 24.

Effectiveness

Any stroke

Across all five studies, the proportion of patients experiencing any stroke after 30 days and up to the longest follow-up (21.6 months) ranged from 3.1% to 11.8%. In total, 23 ipsilateral strokes were reported after the periprocedural period.

Death

The incidence of death after 30 days and up 12 to 22 months of follow-up as reported by three studies ranged from 0% to 4.5%.[4,42,71,101] Four of the reported deaths were due to ipsilateral stroke and two were due to non-neurological causes.

Any stroke or death
Across three studies with follow-up ranging from 12 to 22 months, the proportion of patients experiencing any stroke or death after 30 days ranged from 4.0% to 13.6%.[4,42,71,101]

Transient ischemic attack (TIA)
The incidence of TIA after 30 days was 6.0% and 8.2% as reported by two studies with mean follow-up periods of 21.6 and 14.2 months, respectively.[71,101] All reported TIAs were ipsilateral or occurring in the territory of the stented artery.

Any stroke or death within 30 days or ipsilateral stroke thereafter
Three studies reported this composite measure as their primary end point and found incidences ranging from 7.3% to 15.7% in their populations.[71,101,188] Follow-up periods ranged from 6 months to 21.6 months.

Restenosis
All five studies reported the risk of in-stent restenosis which ranged from 7.5% to 32.3% across mean follow-up periods of 4.8 to 8.6 months.[4,12,25,42,101,188] The majority of restenoses were asymptomatic.

Safety – periprocedural/30 day outcomes (Table 23)

Any stroke
Across all five studies, the incidence of any stroke during the periprocedural period ranged from 4.5% to 9.3%.[4,12,42,71,101,188] Of the four studies that further classified the strokes (22 total cases), 11 were ipsilateral strokes and nine were intracranial or subarachnoid hemorrhages. In some studies, patients had more than one of these subcategories of stroke (i.e. a stroke was ipsilateral and hemorrhagic in nature). Also of note, in one study, one of the three ischemic strokes and both intracranial hemorrhages were due to vessel perforation/dissection cause by delivery of the Wingspan stent system.[101]

Death
Death occurred in 0% to 3.1% of patients within 30 days across all five studies. In total there were eight deaths due to stroke (including 3 that were hemorrhagic in nature) and one death due to unknown causes.

Any stroke or death
The risk of any stroke or death ranged from 4.5% to 9.6% across all five studies.[4,12,42,71,101,188]

Transient ischemic attack (TIA)

Only two studies reported TIAs during the periprocedural period with risks of 1.6% and 7.0%.[101,188]

Other complications (Table 24)

A number of other periprocedural complications were reported by four of the studies,[4,42,70,101,188] a few of which are briefly reported in this section. Vessel dissection/perforation was reported in 11 (3.1%) of the 351 total patients treated across all four studies; three were flow limiting requiring stenting, three resulted in stroke/hemorrhage, and five were asymptomatic or did not result in any serious sequelae. Among the individual studies, the risk of vessel dissection/perforation ranged from 0% to 6.4%. Two studies reported the incidences of stent thrombosis (3.1% and 0%) and transient vasospasm (1.6% and 11.4%).[4,42,188] In one study, seven access site complications occurred in five (11.4%) patients including three hematomas and one infection all requiring treatment.[4,42] No incidence of stent migration was reported by this same study. Transient visual symptoms completely resolving within 36 hours of procedure were reported in one (1.2%) patient in one study[70] and somnolence for 3 days with no infarct on MRI was seen in one (0.8%) patient in another study.[188] Other complications reported across the studies included hypertension, arrhythmia, fever, hypervolemia, hyperglycemia, nystagmus, emergency cerebral artery revascularization, and respiratory failure due to epiglottis edema.

Table 23. Periprocedural (30-day) outcomes

Study (year)	Demographics	No. of cases (%)			
		Any stroke	Death	Any stroke/death	TIA
Prospective case-series					
Fiorella (2011)	N = 158 Mean age: 62.7 years Male: 60.1%	9 (5.7)	4 (2.5)*	9 (5.7)	NR
Jiang (2011)	N = 100 Mean age: 53.2 years Male: 87%	5 (5.0)†	0 (0)	5 (5.0)	7 (7.0)
Zaidat (2008)	N = 129 Mean age: 64 years Male: 55%	11 (8.5)‡	4 (3.1)§	12 (9.6)	2 (1.6)
Bose (2007)/ FDA Summary (2004)	N = 45 Mean age: 66 years Male: 73.3%	2 (4.5)**	1 (2.3)	2 (4.5)	NR
SSYLVIA Investigators (2004)	N = 43 Mean age: 63.6 years†† Male: 82%††	4 (9.3)‡‡	0 (0)	4 (9.3)	NR

*All caused by stroke.
†3 ischemic strokes (1 due to severe distal vessel dissection) and 2 intracranial hemorrhages (both due to vessel perforation/hyperperfusion).
‡8 non-fatal (3 ischemic strokes in territory of the stented artery, 1 in and out of territory of the stented artery, 1 out of territory of the stented artery, 2 ischemic strokes in the territory and intracranial hemorrhage or subarachnoid hemorrhage, and 1 intracranial hemorrhage alone) and 3 fatal (2 intracranial hemorrhages and 1 ischemic stroke). §Intracranial hemorrhage (n = 2), ischemic stroke (n = 1), and unknown (n =1).
**Both were major ipsilateral strokes, one hemorrhagic in nature and resulted in death 10 days postop.
††Representative of the entire study population, to include the extracranial arteries (n = 18).
‡‡3 major ipsilateral strokes and 1 subarachnoid hemorrhage that resolved without residual deficits.

Table 24. Other complications

Study	Other periprocedural complications*
Prospective case-series	
Fiorella (2011) N = 158	• Not reported
Fiorella (2007)† N = 78 (82 lesions)	• Extra-cranial parent vessel dissection related to guide catheter manipulation, n = 5 (6.1%) ○ flow-limiting and requiring stenting, n = 2 • Flow-limiting intracranial dissection requiring stenting, n = 1 (1.2%) • Transient visual symptoms (completely resolved within 36 hours of procedure), n = 1 (1.2%)
Jiang (2011) N = 100	• Vessel dissection/perforation, n = 3 (3.0%) ○ Causing ischemic stroke (n = 1) and intracranial hemorrhage (n = 2) • Emergency cerebral artery revascularizations
Zaidat (2008) N = 129	• Asymptomatic vessel dissection, n = 2 (1.6%) • Stent thrombosis, n = 4 (3.1%) • Transient vasospasm, n = 2 (1.6%) • Cerebral infarct on MRI with neurological signs lasting < 24 hours, n = 2 (1.6%) • Somnolence for 3 days with no infarct on MRI, n = 1 (0.8%)
Bose (2007)/FDA Summary (2004) N = 44‡	• Access site complications, n = 5 (11.4%; 7 events) ○ requiring treatment, n = 4 (3 hematomas, 1 infection) • Parent vessel dissection/perforation, n = 0 • In-stent thrombosis, n = 0 • Stent migration, n = 0 • Vasospasm, n = 5 (11.4%) • Hematoma, n = 3 (6.8%)§ • Hypertension, n = 3 (6.8%) • Asymptomatic frontal medial branch occlusion in a small territory of the middle cerebral artery, n = 1 (2.3%) • Arrhythmia, n = 1 (2.3%) • Fever, n = 1 (2.3%) • Hypervolemia, n = 1 (2.3%) • Hyperglycemia, n = 1 (2.3%) • Nystagmus, n = 1 (2.3%) • Respiratory failure due to epiglottis edema, n = 1 (2.3%)
SSYLVIA investigators (2004) N = 43	• Not reported

*Unclear from the articles the extent to which patients could have more than one complication.

†Fiorella 2007 study focuses on the periprocedural outcomes primarily. Since they reported important safety data, and Fiorella 2011 did not, we chose to report the data for this earlier subset of patients.

‡ In total, 45 patients were enrolled; however, one patient was not treated due to tortuous anatomy so data are presented for the evaluable patient population through 30 days (n = 44).

§Unable to determine if these are the same 3 hematomas included under access site complications requiring treatment.

4.3. Key Question 3: Extracranial Carotid Artery Stenosis Stenting Safety

What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?

Key Question 3 focuses periprocedural safety outcomes. The definition of the periprocedural period varied slightly across trials. In the majority of studies, the periprocedural period included events occurring within 30 days of treatment; however, in analyses, some studies included events that occurred between randomization and treatment,[48,65,153] while others (EVA)[128] excluded these events. One RCT (ICSS)[65] analyzed periprocedural events occurring up to 120 days after randomization for all patients (regardless of whether they were treated or not), and three RCTs[45,46,170] provided no definition of periprocedural period. Adverse events outside of the periprocedural period are summarized.

For the nonrandomized studies, all but one of the included cohort and registry studies reported events occurring within 30 days of treatment. All administrative database studies and one large registry reported in-hospital outcomes only.

Safety data relating to intracranial artery disease is included under Key Question 2 for consistency.

4.3.1. Asymptomatic

Safety in Asymptomatic Patients

Summary of RCT data

CAS versus medical therapy alone: No RCTs evaluated adverse events and complications for CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis

CAS compared with CEA: Two RCTs provided data comparing CAS with medical therapy to CEA with medical therapy during the peri-procedural timeframe.[46,167]

- **Any periprocedural stroke:** Across two RCTs, risk of periprocedural stroke was slightly higher, though not statistically significant, for CAS compared to CEA; however, in one RCT no stroke events were reported in either treatment group.

- **Periprocedural death:** In 2 RCTs no deaths were reported during the periprocedural period.
- **Periprocedural stroke or death:** The risk of stroke or death was 2.5% for CAS and 1.4% for CEA based on the CREST study.[167] The difference was not statistically significant.
- **Periprocedural myocardial infarction (MI):** In one RCT (CREST) there was a statistically non-significant lower risk of periprocedural MI for CAS compared with CEA.
- **Periprocedural cranial nerve palsy:** Across both RCTs, risk of periprocedural cranial nerve palsy was significantly lower for CAS compared to CEA; although one RCT reported no events in either treatment arm (RD = -3.9%).
- **Periprocedural bleeding Complications:** In one RCT (CREST), there were no significant difference in risks of periprocedural bleeding complications (bleeding event requiring transfusion, hematoma requiring treatment, retroperitoneal hemorrhage, moderate or minor bleeding) between CAS and CEA; however, there was a statistically significant decrease in risks of surgical wound complications (hematoma requiring treatment and other complications) among CAS compared to CEA (RD = -1.8% and -2.0%, respectively).

Summary of nonrandomized comparative studies

CAS versus medical therapy alone: One small, retrospective, single-center cohort study, Bosiers et al. 2005,[43] reported 30-day stroke or death rates. No statistically significant difference was reported between those who received CAS versus medical therapy alone. This study was considered to be at a moderately high risk of bias.

CAS compared with CEA: Periprocedural outcomes following CAS and medical therapy compared with CEA and medical therapy were reported in a total of 21 nonrandomized comparative studies (7 cohorts,[43,49,59,96,108,125,189] 3 registries,[102,119,142] and 11 administrative[39,76,77,111,132,134,135,155,173,176,187]). All cohort studies were considered to be at moderately high risk of bias. For the registries, one was considered to be at a moderately low risk of bias and reported in-hospital data only,[142] one a moderately high risk of bias,[102] and the third at a high risk of bias.[119] All administrative studies were considered to be at a high risk of bias.

- **Any periprocedural stroke:** Across five small cohort studies (1 prospective and 4 retrospective), there were no statistical differences between treatment groups in the risk of periprocedural stroke. Confidence intervals were large and overlapped across studies. Across two large prospective registry studies, only one reported a statistically

significant difference favoring CEA at 30 days. Risks of stroke across 10 administrative studies were consistently higher following CAS compared with CEA.

- **Periprocedural death:** No statistical differences in risk of death were seen across four small cohort studies (1 prospective and 3 retrospective). One of the two included prospective registry studies reported a greater risk of death at 30 days following CAS compared with CEA while the second study, which reported in-hospital events, failed to reach statistical significance. Risk of death across 12 administrative studies provided mixed results; half of the studies reported a significantly increased risk following CAS compared with CEA and the other half did not reach statistical significance.

- **Periprocedural stroke or death:** Across six cohort studies (3 prospective and 3 retrospective), no statistical difference between groups was reported for this composite outcome. Wide confidence intervals suggest instability of estimates. One of two included registries reported an increased risk of periprocedural stroke or death at 30 days in persons receiving CAS compared with CEA (confidence intervals were large), while the other larger registry reported much lower in-hospital risks for both groups and failed find a statistical difference. The risk of periprocedural stroke or death following CAS was less than 3% in six of the eight studies. Risk of stroke or death was consistently higher following CAS in four administrative studies.

- **Periprocedural myocardial infarction (MI):** No statistical differences in MI risk were seen across five studies (1 prospective cohort, 2 retrospective cohorts and 2 prospective registries). One of two administrative studies reported a small increase in MI risk for CAS compared with CEA.

- **Periprocedural ipsilateral stroke:** No statistical difference between groups in the risk of in-hospital ipsilateral stroke was found as reported by one large prospective registry.

- **Periprocedural transient ischemic attack (TIA):** One small retrospective cohort study and one large prospective registry reported no significant differences in the risk of periprocedural TIA between CAS and CEA. One administrative database study reported an identical low risk (0.3%) in both treatment groups.

- **Periprocedural cranial nerve palsy:** Across two retrospective cohort studies and one large prospective registry (in-hospital data), no significant differences in the risk of cranial nerve palsy were reported following CAS compared with CEA. A

marginally significant decreased risk following CAS was reported by one administrative study.

- **Periprocedural bleeding complications:** The risk of hematoma was reported by two retrospective cohort studies with no significant differences between treatment groups; however, in the smaller of the two cohorts, the risk following CAS was twice that seen following CEA (RD = 4.1%). One administrative database study reported unspecified bleeding as a perioperative complication with similar risks seen in both groups.

- **Intracranial hemorrhage (ICH):** As reported by two administrative database studies, the incidence of ICH was rare in both groups; however, the risk was six times greater following CAS compared with CEA.

- **Other complications:** Unspecified cardiac complications were reported by three administrative database studies, two of which reported a marginally significant increased risk following CAS while the third administrative study found no difference between the treatment groups. The risk of venous thromboembolism was reported by one administrative study with no statistically significant difference between groups.

Detailed results: Asymptomatic patients

Results from RCTs

CAS and medical therapy versus medical therapy alone: No RCTs evaluated adverse events and complications for CAS and medical therapy versus medical therapy alone among patients with asymptomatic carotid stenosis

CAS and medical therapy versus CEA and medical therapy: Two RCTs provided data comparing CAS with medical therapy to CEA with medical therapy during the peri-procedural timeframe.[46,167] Results are summarized below and in Tables 25 and 26.

Any periprocedural stroke

Both RCTs (Kentucky, CREST)[46,167] reported on risk of any periprocedural stroke. In CREST the risk following CAS was 2.5% compared with 1.4% following CEA but the difference was not statistically meaningful; RD = 1.2%, 95% CI = -0.4, 2.7). In addition, the CREST[167] reported risks of major and minor stroke, both of which were slightly greater among patients undergoing CAS as compared to CEA (major stroke: 0.5% vs. 0.3%; minor

stroke: 2.0% vs. 1.0%, respectively), although the difference in risks was not statistically) (Table X). No cerebrovascular (stroke or TIA) events occurred in the Kentucky trial.[46]

Periprocedural death

One RCT (KENTUCKY) reported no deaths during the periprocedural period in either treatment group.[46]

Composite of periprocedural stroke or death

Both RCTs (CREST, Kentucky)[46,167] reported data for this composite endpoint; however one reported no events in either treatment group; therefore, only one RCT contributed data for this endpoint. In CREST there was a non-significant increase in the risk of stroke or death for CAS as compared to CEA (RD: 1.2%, 95% CI: -0.4, 2.7). The risk of any stroke or death was 2.5% following CEA and 1.4% following CAS in this study.

Periprocedural myocardial infarction (MI)

One RCT (CREST)[167] reported on risk of periprocedural MI. In CREST, risk of MI was 1.2% for the CAS group and 2.2% for the CEA group but there was no statistical difference between groups (RD: -1.0%, 95% CI: -2.5, 0.4) for asymptomatic patients. It should be noted that definitions of MI changed during the course of the trial. The influence of different definitions on event rates on published data is not known based.[2]

Cranial nerve palsy

Both RCTs (Kentucky, CREST)[46,167] reported on risk of periprocedural cranial nerve palsy. In CREST, CAS was associated with a significantly lower risk of cranial nerve palsies (RD: -3.9%, 95%CI: -2.2, -5.4) (Table 25). The Kentucky trial also reported on periprocedural cervical nerve injury; however, no events were reported in either treatment arm.

Table 25. Summary of major periprocedural adverse events and complications reported in RCTs comparing CAS and CEA among asymptomatic patients.

Study	CAS		CEA		Effect Size	
RCT	n/N	(%)	n/N	(%)	RD% (95% CI)	RR/HR (95% CI)
Any Stroke						
CREST	15/594	(2.5)	8/597	(1.4)	1.2% (-0.4,2.7)	1.88 (0.79, 4.42)
Kentucky	0/43	(0.0)	0/42	(0.0)	NE	NE
Major stroke						
CREST	3/594	(0.5)	2/597	(0.3)	0.2 (-0.6, 0.9)	1.50 (0.25, 9.95)
Minor stroke						
CREST	12/594	(2.0)	6/597	(1.0)	1.0 (-0.4, 2.4)	2.06 (0.77, 5.51)
Death						
Kentucky	0/43	(0.0)	0/43	(0.0)	NE	NE
Any stroke or death						
CREST	15/594	(2.5)	8/597	(1.4)	1.2% (-0.4,2.7)	1.88 (0.79, 4.42)
Kentucky	0/43	(0.0)	0/42	(0.0)	NE	NE

Study	CAS		CEA		Effect Size	
Myocardial infarction						
CREST	7/594	(1.2)	13/597	(2.2)	-1.0% (-2.5, 0.4)	0.55 (0.22, 1.38)
Cranial nerve palsy						
CREST	1/594	(0.2)	25/597	(4.2)	-3.9% (-2.2, -5.4)*	0.04 (0.01, 0.31)*
Kentucky	0/43	(0.0)	0/42	(0.0)	NE	NE
RD = risk difference; RR = relative risk; NE = Not estimable *Calculated by SRI						

Periprocedural Bleeding Complications

One RCT (CREST 2011)[167] reported data for several periprocedural bleeding complications which are listed below. Risks of surgical wound complications (hematoma requiring treatment, other complications) were significantly lower for CAS, compared to CEA (RD = -1.8%, 95%CI: =0.7, -2.9; RD = -2.0%, 95%CI: -0.8%, -2.0%, respectively). There were no significant differences in the risks of any bleeding events (need for transfusion, hematoma requiring treatment, retroperitoneal hemorrhage, moderate or minor bleeding) between CAS and CEA.

Table 26. Periprocedural bleeding complications reported by RCTs comparing CAS and CEA among asymptomatic patients in CREST

	CREST (Silver 2011)					
	CAS (n=594)		CEA (n=597)		RD (95% CI)	RR (95% CI)
	n	(%)	n	(%)		
Surgical Wound Complications						
Hematoma requiring treatment	0	(0)	11	(1.9)	-1.8% (-0.7, -2.9)*	NE
Other complications	0	(0)	12	(2.0)	-2. 0% (-0.8, -2.0)*	NE
Bleeding Complications						
Bleeding event requiring transfusion	8	(1.3)	7	(1.2)	0.2% (-1.1, 1.4)*	1.15 (0.42, 3.14)*
Hematoma requiring treatment	2	(0.3)	0	(0)	-0.3% (-0.1, 0.7)*	NE
Retroperitoneal hemorrhage	0	(0)	0	(0)	NE	NE
Moderate Bleeding	2	(0.3)	2	(0.3)	0.0 (-0.6, 0.6)*	1.01 (0.14, 7.11)*
Minor Bleeding	2	(0.3)	1	(0.2)	0.2% (-0.4, 0.7)*	2.01 (0.18, 22.1)*
RD = risk difference; RR = relative risk; NE = Not estimable *Calculated by Spectrum Research, Inc.						

Results from nonrandomized comparative studies

CAS and medical therapy versus medical therapy alone: Only one retrospective, single-center cohort study, Bosiers et al. 2005, was found that compared CAS with medical therapy alone.[43] A total of 75 asymptomatic patients were included (59 CAS, 16 Medical); mean ages and sex distributions were not reported. This study was considered at high risk of bias due to various methodological shortcomings. The only outcome reported was the combined 30-day risk of stroke or death with no statistically significant difference seen between those

who received CAS and medical therapy compared with medical therapy alone: 1.7% versus 0%, respectively; RD = 1.7% (95% CI -9.0% to 17.7%).

CAS and medical therapy versus CEA and medical therapy: For the comparison of CAS and medical therapy with CEA and medical therapy in asymptomatic patients, data abstracted from the 2012 AHRQ report were combined with data from studies that were published after the AHRQ search or which appeared to have met the inclusion criteria but didn't appear to have been summarized in that report. Overall, this section includes data from seven comparative cohort studies,[43,49,59,96,108,125,189] four of which were included in the AHRQ report,[43,59,125,189] and three comparative registry studies,[102,119,142] one of which was included in the AHRQ report[119] and one which was a 2012 update to the Sideway et al. 2009 report on the SVS-VR registry included in the AHRQ report.[102] The study published in 2012 analyzed SVS-VR registry data stratified by Medicare age and included 3600 more patients than the earlier report; data were able to be calculate for the total asymptomatic population within each treatment group. These cohort and registry studies constitute the primary body of evidence for this section and report outcomes up to 30 days post-procedure, with the exception of one registry study that reported in-hospital data as stated previously.[142] In addition, 11 administrative data studies,[39,76,77,111,132,134,135,155,173,176,187] three of which were included in AHRQ,[76,134,135] are briefly described. All report in-hospital outcomes. Data are summarized in tables 27–32.

All cohort studies were considered to be at moderately high risk of bias. For the registries, one was considered to be at a moderately low risk of bias,[142] one a moderately high risk of bias,[102] and the third at a high risk of bias.[119] The administrative studies were all considered to be at high risk of bias. Concerns regarding such studies include questions of coding accuracy and variability of algorithms used to identify patients as previously described in the methods section of this report.

For purposes of this section, a positive risk difference favors CAS and negative risk difference favors CEA.

Any periprocedural stroke

Data were available from five small cohort studies (N range 87–269), one prospective and four retrospective,[49,96,108,125,189] and two prospective registry studies (N = 5268 and 5316).[102,142] In some studies, periprocedural stroke included fatal stroke. Across these studies, findings from the clinical cohorts showed no statistical differences between treatment groups. Confidence intervals were large and overlapped across studies. The risk of any stroke ranged from 0%–8.5% for CAS and 1.8 %–2.1% following CEA; in two studies risks were higher after CAS, but higher after CEA in three other studies. Of the two registry studies, one reached statistical significance favoring CEA with a risk of 1.7% versus 3.2%

with CAS (risk difference (RD) = -1.5%, 95% CI, -2.5% to -0.6% and relative risk (RR) = 1.9, 95% CI, 1.3–2.7), while the other, which analyzed in-hospital outcomes, reported identical risks between groups (0.7%), including both major and minor strokes. Data from 10 administrative database studies with sample sizes ranging from 8706 to 486,021,[39,76,77,111,134,135,155,173,176,187] seven of which analyzed National Inpatient Sample (NIS) data,[77,111,134,135,155,173,187] revealed consistently greater risks of any stroke following CAS, with eight of the studies reaching statistical significance. Risks ranged from 1.0%–2.1% for CAS and 0.6%–1.8% for CEA with a risk difference range of 0.3%–1.0%.

Periprocedural death

Four small cohort studies (N range 87–269), one prospective and three retrospective,[49,108,125,189] and two prospective registry studies (N = 5268 and 5316)[102,142] provided data for this outcome. Overall, the risk of perioperative death was relatively low for both treatment groups. No statistical differences in risk of death were seen across the cohort studies with risks ranging from 0%–1.1% following CAS and 0%–2.0% after CEA. One of the two registry studies reported a significantly greater risk of death following CAS (1.6%) compared with CEA (0.7%) with a RD of -0.8% (95% CI, -1.6% to -0.2%) and a RR of 2.1 (95% CI, 1.3–3.7), while the second study, which reported on in-hospital outcomes, failed to reach statistical significance (0.4% vs. 0.2%, respectively). Data were available from 11 administrative studies (N range 8706–486,021),[39,76,77,111,132,134,135,155,173,176,187] eight of which analyzed National Inpatient Sample (NIS) data.[77,111,132,134,135,155,173,187] Risk of death ranged from 0.4%–0.9% for CAS and 0.3%–0.6% for CEA with RDs ranging from 0.1%–0.4%. Results were mixed with half of the studies finding a significantly increased risk following CAS compared with CEA and the other half not reaching statistical significance.

Periprocedural stroke or death

Data were available for this composite from six cohort studies (N range, 87–1518),[43,49,59,108,125,189] three prospective and three retrospective, and two large prospective registries (N = 1416 and 5316).[119,142] Across the cohort studies, risks ranged from 0%–3.8% for CAS and 0%–4.0% for CEA, with no statistical difference between groups; in three of the studies risks were higher after CAS, but higher after CEA in the other three. Wide confidence intervals suggest instability of estimates. One of the two registries reported a statistically significant increased risk of periprocedural stroke or death in persons receiving CAS (10.9%) compared with CEA (4.0%) with a RD of -6.9% (95% CI, -14.5% to -2.0%) and a RR of 2.7 (95% CI, 1.46–5.01), while the other larger registry reported much lower in-hospital risks for both groups (0.7% and 0.9%, respectively) and failed to find a statistical difference. The risk of periprocedural stroke or death following CAS was < 3% in six of the eight studies. Data available from four administrative studies (2 using NIS data) with sample sizes ranging from 8706 to 486,021 showed that the risk of stroke or death was consistently

higher following CAS compared with CEA[39,76,77,187]; ranges were from 1.6%–2.5% and 0.9%–1.7%, respectively, with all but one study reporting a significant difference.

Periprocedural myocardial infarction (MI)

Three cohort studies (N range 87–269),[108,125,189] one prospective and two retrospective, and two prospective registries (N = 5268 and 5316)[102,142] reported data for this outcome. No statistical differences in MI risk were seen across all five studies (to include one registry that reported in-hospital outcomes). Risks ranged from 0%–1.1% following CAS and from 0%–1.4% following CEA; the majority of studies reported lower risks after CAS. The larger of two administrative studies (N = 238,389 and 52,588) reported a small increase in MI risk for CAS compared with CEA with a RD of 0.3% (95% CI, 0.1%–0.6%) and a RR of 1.2 (95% CI, 1.0%–1.4%).[134]

Periprocedural ipsilateral stroke

One large prospective registry study (N = 5316) which reported in-hospital data provided the only data for this outcome.[142] The risk of periprocedural ipsilateral stroke was low in both the CAS and CEA group, 0.4% and 0.6%, respectively, with no statistical difference between treatments.

Periprocedural transient ischemic attack (TIA)

One small retrospective cohort study (N = 129)[49] and one prospective registry (N = 5316)[142] reported no significant differences in the risk of TIA following CAS compared with CEA: 2.5% versus 0% and 0.5% versus 0.3% (in-hospital), respectively. One administrative database study (N = 8706)[76] reported an identical risk in both treatment groups (0.3%) using a propensity score matched analysis.

Periprocedural cranial nerve palsy

Data were available from two retrospective cohort studies (N = 87 and 238)[108,125] and one large prospective registry that reported in-hospital outcomes (N = 5316).[142] Across these three studies, no cases of cranial nerve palsy were reported following CAS compared with risks ranging from 0.9%–12.0% with CEA; however, the differences between groups were not significant in any instance and confidence intervals were large and overlapped across studies. A marginally significant decreased risk following CAS was reported by one administrative study (0.2% vs. 0.4%; RD = 0.3%, 95% CI, 0.0%–0.5%; Adjusted RR = 0.42, 95% CI, 0.18–0.96).[76]

Periprocedural bleeding complications

The risk of hematoma was reported by two retrospective cohort studies (N = 87 and 238) with no significant differences found between treatment groups[108,125]; however, in the smaller of the two cohorts, the risk following CAS was twice that seen following CEA (8.1% vs.

4.0%).[108] One administrative database study (N = 8706) reported unspecified bleeding as a perioperative complication with similar risks seen in both groups (3.4% and 3.8%, respectively).[76]

Intracranial hemorrhage (ICH)

Two administrative studies, both analyzing the NIS database (N = 136,077 and 217,596), provided data for this outcome.[132,173] The incidence of acute ICH was rare in both groups: 0.2% and 0.3% (CAS) versus 0.02% and 0.04% (CEA); however, a statistically significant, six-fold increased risk (adjusted odds ratios of 5.9 (95% CI, 3.1–11.1) and 6.1 (95% CI, 4.7–7.8)) was seen following CAS compared with CEA. Corresponding RDs were -0.13 (95% CI, -0.2 to -0.1) and -0.4 (95% CI, -0.5 to -0.3), respectively. One of the studies further reported on specific types of ICH and found significantly increased risks following CAS compared with CEA for subarachnoid hemorrhage (0.2% vs. 0.02%, respectively; RR = 9.7) and unspecified ICH (0.04% vs. 0.002%, respectively; RR = 12.2), although the confidence intervals were wide, but not for nontraumatic extradural hemorrhage.[132]

Other complications

Unspecified cardiac complications were reported by three administrative database studies (N range, 8706–495,331), two of which analyzed the NIS database and reported a marginally significant increased risk following CAS compared with CEA: 2.2% versus 1.9% (RD = -0.3%, 95% CI, -0.5% to -0.1%; RR = 1.2, 95% CI, 1.1–1.3) and 2.3% versus 1.9% (RD = -0.4%, 95% CI, -0.5% to -0.2%; RR = 1.2, 95% CI, 1.1–1.3).[111,187] The third administrative study which found no difference in unspecified cardiac complications between groups (CAS 4.9%; CEA 4.1%) conducted a propensity score matched analysis.[76] This same study also reported the risk of venous thromboembolism with no statistically significant difference seen following CAS (0.07%) compared with CEA (0.14%).

Table 27. Summary of periprocedural risks of any stroke from nonrandomized studies comparing CAS with CEA for asymptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 269	Any stroke	1.0 (1/99)	1.8 (3/170)	RD = 0.8 (-3.9 to 4.2) RR = 0.57 (0.06-5.42)‡
Iihara 2006 (Pro) N = 106	Any stroke	8.5 (5/59)§	2.1 (1/47)§	RD = -6.3 (-16.4 to 3.8) RR = 4.0 (0.48-32.94)
Marine 2006 (Retro) N = 238	Any stroke	1.1 (1/93)	2.1 (3/145)	RD = 1.0 (-4.0 to 4.9) RR = 0.52 (0.05-4.92)‡
Brown 2008 (Retro) N = 129	Any stroke	3.8 (3/79)	2.0 (1/50)	RD = -1.8 (-8.8 to 7.1) RR = 1.9 (0.20-17.75)
Kastrup 2003 (Retro) N = 87	Any stroke (major or minor)	0 (0/37)	2.0 (1/50)**	RD = 2.0 (-7.5 to 10.5) RR = not estimable
Registry studies				
Jim 2012 (SVS-VR) (Pro) N = 5268	Any stroke	3.2 (59/1850)	1.7 (58/3418)	RD = -1.5 (-2.5 to -0.6) RR = 1.88 (1.31-2.69)
Nolan 2012 (VSGNE) (Pro) N = 5316 (in-hospital data)	Any stroke	0.7 (2/273)	0.7 (35/5043)	RD = 0 (-1.9 to 0.6) RR = 1.06 (0.26-4.37)
	Major stroke	0.4 (1/273)	0.3 (15/5043)	RD = -0.1 (-1.8 to 0.3) RR = 1.23 (0.16-9.23)
	Minor stroke	0.4 (1/273)	0.4 (20/5043)	RD = 0 (-1.7 to 0.4) RR = 0.92 (0.12-6.9)
Administrative studies (in-hospital)				
McPhee 2008 (NIS) N = 122,986	Any stroke	1.6 (181/11,302)	0.9 (983/111,684)	RD = -0.7 (-1.0 to -0.5) RR = 1.82 (1.55-2.13)‡
McPhee 2007 (NIS) N = 238,389	Any stroke	1.8 (221/12,278)	0.9 (1945/226,111)	RD = -0.9 (-1.2 to -0.7) RR = 2.09 (1.82-2.40)‡
Giacovelli 2010 (NY & CA) †† N = 8706	Any stroke	2.0 (89/4353)	1.8 (76/4353)	RD = -0.3 (-0.9 to 0.3) Adjusted RR = 1.17 (0.86-1.58)‡
Giles 2010 (NIS) N = 486,021	Any stroke	1.0 (490/49,126)	0.6 (2628/436,895)	RD = -0.4 (-0.5 to -0.3) RR = 1.66 (1.51-1.83)
Rockman 2011 (NIS) N = 51,030	Any stroke	1.9 (52/2733)	0.9 (444/48,297)	RD = -1.0 (-1.6 to -0.5) RR = 2.07 (1.56-2.75)
Young 2011 (NIS) N = 249,592	Any stroke	1.3 (409/31,197)	0.9 (1922/218,395)	RD = -0.4 (-0.6 to -0.3) RR = 1.49 (1.34-1.66)
Khatri 2012 (NIS) N = 495,331	Any stroke	1.7 (989/57,626)	1.0 (4289/437,705)	RD = -0.7 (-0.8 to -0.6) RR = 1.75 (1.64-1.88)
Timaran 2009 (NIS) N = 125,350	Any stroke	1.8 (213/11,836)	1.0 (1135/113,514)	RD = -0.8 (-1.1 to -0.6) RR = 1.80 (1.56-2.08)
Bisdas 2012 (NY State Department of Health)‡‡ N = 52,588	Any stroke	2.1 (73/3546)	1.3 (622/49,042)	RD = -0.8 (-1.3 to -0.4) Adjusted RR = 1.62 (1.28-2.06)
Wang 2011 (CMS provider analysis) N = 10,958	Any stroke	1.9 (25/1323)	1.4 (132/9635)	RD = -0.5 (-1.4 to 0.1) RR = 1.38 (0.90-2.11)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; CMS: Centers for Medicare and Medicaid; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective

study design; RR = relative risk; SVS-VR: Society for Vascular Surgery Vascular Registry; VSGNE: Vascular Study Group of New England.

*Calculated from raw data by Spectrum Research unless otherwise indicated.

†A positive risk difference favors CAS and negative risk difference favors CEA.

‡Calculated from raw data by the Agency for Healthcare Research and Quality (AHRQ).

§All strokes were non-disabling.

**Minor stroke.

††Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.

‡‡Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of asymptomatic patients with the data provided.

Table 28. Summary of periprocedural risks of death from nonrandomized studies comparing CAS with CEA for asymptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 269	Death	0 (0/99)	0 (0/170)	RD = 0 (-3.7 to 2.2) RR = not estimable
Marine 2006 (Retro) N = 238	Death	1.1 (1/93)	0.7 (1/145)	RD = -0.4 (-5.2 to 2.9) RR = 1.56 (0.09-24.6)‡
Brown 2008 (Retro) N = 129	Death	0 (0/79)	2.0 (1/50)	RD = 2.0 (-2.9 to 10.5) RR = not estimable
Kastrup 2003 (Retro) N = 87	Death	0 (0/37)	0 (0/50)	RD = 0 (-9.4 to 7.1) RR = not estimable
Registry studies				
Jim 2012 (SVS-VR) (Pro) N = 5268	Death	1.6 (29/1850)	0.7 (25/3418)	RD = -0.8 (-1.6 to -0.2) RR = 2.14 (1.26-3.65)
Nolan 2012 (VSGNE) (Pro) N = 5316 (in-hospital data)	Death	0.4 (1/273)	0.2 (10/5043)	RD = -0.2 (-1.8 to 0.2) RR = 1.85 (0.24-14.38)
Administrative studies (in-hospital)				
McPhee 2008 (NIS) N = 122,986	Death	0.6 (64/11,302)	0.4 (424/111,684)	RD = -0.2 (-0.3 to -0.1) RR = 1.49 (1.14-1.93)‡
McPhee 2007 (NIS) N = 238,389	Death	0.4 (54/12,278)	0.3 (769/226,111)	RD = -0.1 (-0.2 to 0.0) RR = 1.29 (0.98-1.70)‡
Giacovelli 2010 (NY & CA)§ N = 8706	Death	0.6 (24/4353)	0.4 (17/4353)	RD = -0.2 (-0.5 to 0.1) Adjusted RR = 1.41 (0.75-2.62)‡
Giles 2010 (NIS) N = 486,021	Death	0.8 (398/49,126)	0.4 (1618/436,895)	RD = -0.4 (-0.5 to -0.4) RR = 2.19 (1.96-2.44)
Rockman 2011 (NIS) N = 51,030	Death	0.5 (14/2733)	0.4 (200/48,297)	RD = -0.1 (-0.4 to 0.1) RR = 1.24 (0.72-2.12)
Young 2011 (NIS) N = 249,592	Death	0.6 (178/31,197)	0.4 (852/218,395)	RD = -0.2 (-0.3 to -0.1) RR = 1.46 (1.24-1.72)
Khatri 2012 (NIS) N = 495,331	Death	0.6 (354/57,626)	0.4 (1756/437,705)	RD = -0.2 (-0.3 to -0.1) RR = 1.53 (1.37-1.72)
Timaran 2009 (NIS) N = 125,350	Death	0.7 (83/11,836)	0.5 (568/113,514)	RD = -0.2 (-0.4 to -0.1) RR = 1.40 (1.11-1.76)
McDonald 2011 (NIS) N = 217,596	Death	0.6 (76/12,633)	0.5 (1025/204,963)	RD = -0.1 (-0.3 to 0.0) RR = 1.20 (0.95-1.52)
Bisdas 2012 (NY State Department of Health)** N = 52,588	Death	0.8 (28/3546)	0.5 (233/49,042)	RD = -0.3 (-0.7 to -0.1) Adjusted RR = 1.66 (1.12-2.46)
Wang 2011 (CMS provider analysis) N = 10,958	Death	0.9 (12/1323)	0.6 (58/9635)	RD = -0.3 (-1.0 to 0.1) RR = 1.51 (0.81-2.80)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; CMS: Centers for Medicare and Medicaid; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; SVS-VR: Society for Vascular Surgery Vascular Registry; VSGNE: Vascular Study Group of New England.

*Calculated from raw data by Spectrum Research unless otherwise indicated.

†A positive risk difference favors CAS and negative risk difference favors CEA.

‡Calculated from raw data by the Agency for Healthcare Research and Quality (AHRQ).

§Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
**Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of asymptomatic patients with the data provided.

Table 29. Summary of periprocedural risks of any stroke or death from nonrandomized studies comparing CAS with CEA for asymptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 269	Any stroke or death	1.0 (1/99)	1.8 (3/170)	RD = 0.8 (-3.9 to 4.2) RR = 0.57 (0.06-5.42)‡
De Rango 2011 (Pro) N = 1518	Any stroke or death	2.3 (19/816)	1.6 (11/702)	RD = -0.8 (-2.2 to 0.7) RR = 1.49 (0.71-3.10)
Marine 2006 (Retro) N = 238	Any stroke or death	2.2 (2/93)	2.1 (3/145)	RD = -0.1 (-5.6 to 4.1) RR = 1.04 (0.17-6.10)‡
Bosiers 2005 (Retro) N = 79	Any stroke or death	1.7 (1/59)	0 (0/20)	RD = -1.7 (-9.0 to 14.5) RR = 1.02 (0.04-23.9)‡
Brown 2008 (Retro) N = 129	Any stroke or death	3.8 (3/79)	4.0 (2/50)	RD = 0.2 (-7.2 to 10.0) RR = 0.95 (0.16-5.48)
Kastrup 2003 (Retro) N = 87	Any stroke or death	0 (0/37)	2.0 (1/50)	RD = 2.0 (-7.5 to 10.5) RR = not estimable
Registry studies				
Lindstrom 2012 (Swedvasc) (Pro) N = 1416	Any stroke or death	10.9 (11/101)	4.0 (53/1315)	RD = -6.9 (-14.5 to -2.0) RR = 2.70 (1.46-5.01)‡
Nolan 2012 (VSGNE) (Pro) N = 5316 (in-hospital data)	Any stroke or death	0.7 (2/273)	0.9 (45/5043)	RD = 0.2 (-1.8 to 0.8) RR = 0.82 (0.20-3.37)
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)§ N = 8706	Any stroke or death	2.4 (104/4353)	1.9 (83/4353)	RD = -0.5 (-1.1 to 0.1) Adjusted RR = 1.25 (0.94-1.67)‡
Giles 2010 (NIS) N = 486,021	Any stroke or death	1.6 (807/49,126)	0.9 (3973/436,895)	RD = -0.7 (-0.9 to -0.6) RR = 1.81 (1.68-1.95)
Bisdas 2012 (NY State Department of Health)** N = 52,588	Any stroke or death	2.5 (90/3546)	1.7 (810/49,042)	RD = -0.9 (-1.5 to -0.4) Adjusted RR = 1.54 (1.24-1.91)
Young 2011 (NIS) N = 249,592	Any stroke or death	1.7 (527/31,197)	1.2 (2533/218,395)	RD = -0.5 (-0.7 to -0.4) RR = 1.46 (1.33-1.60) Adjusted OR = 1.28 (1.03–1.58)††

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; Swedvasc: Swedish Vascular Registry; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Calculated from raw data by the Agency for Healthcare Research and Quality (AHRQ).
§Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
**Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of asymptomatic patients with the data provided.
††Adjusted for comorbid conditions and demographics as reported by authors.

Table 30. Summary of periprocedural risks of myocardial infarction (MI) from nonrandomized studies comparing CAS with CEA for asymptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size*
		CAS % (n/N)	CEA % (n/N)	RD % (95% CI)† RR (95% CI)
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 269	MI	0 (0/99)	1.2 (2/170)	RD = 1.2 (-2.7 to 4.2) RR = 0.43 (0.01-9.42)‡
Marine 2006 (Retro) N = 238	MI	1.1 (1/93)	1.4 (2/145)	RD = 0.3 (-4.6 to 3.9) RR = 0.78 (0.07-8.47)‡
Kastrup 2003 (Retro) N = 87	MI	0 (0/37)	0 (0/50)	RD = 0 (-9.4 to 7.1) RR = not estimable
Registry studies				
Jim 2012 (SVS-VR) (Pro) N = 5268	MI	1.1 (20/1850)	1.0 (35/3418)	RD = -0.1 (-0.7 to 0.5) RR = 1.06 (0.61-1.82)
Nolan 2012 (VSGNE) (Pro) N = 5316 (in-hospital data)	MI	0.7 (2/273)	1.0 (50/5043)	RD = 0.3 (-1.7 to 0.9) RR = 0.74 (0.18-3.02)
Administrative studies (in-hospital)				
McPhee 2007 (NIS) N = 238,389	MI	2.0 (246/12,278)	1.7 (3844/226,111)	RD = -0.3 (-0.6 to -0.1) RR = 1.18 (1.04-1.35)‡
Bisdas 2012 (NY State Department of Health)§ N = 52,588	MI	0.6 (22/3546)	0.6 (309/49,042)	RD = 0 (-0.3 to 0.2) Adjusted RR = 0.98 (0.64-1.52)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; SVS-VR: Society for Vascular Surgery Vascular Registry; VSGNE: Vascular Study Group of New England.

*Calculated from raw data by Spectrum Research unless otherwise indicated.

†A positive risk difference favors CAS and negative risk difference favors CEA.

‡Calculated from raw data by the Agency for Healthcare Research and Quality (AHRQ).

§Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of asymptomatic patients with the data provided.

Table 31. Summary of periprocedural risks of ipsilateral stroke and transient ischemic attack (TIA) from nonrandomized studies comparing CAS with CEA for asymptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Ipsilateral stroke				
Registry studies				
Nolan 2012 (VSGNE) (Pro) N = 5316	Ipsilateral stroke	0.4 (1/273)	0.6 (30/5043)	RD = 0.2 (-1.5 to 0.6) RR = 0.62 (0.08-4.50)
Transient ischemic attack (TIA)				
Clinical studies				
Brown 2008 N = 129	TIA	2.5 (2/79)	0 (0/50)	RD = -2.5 (-8.8 to 4.8) RR = not estimable
Registry studies				
Nolan 2012 (VSGNE) (Pro) N = 5316 (In-hospital data)	TIA	0.5 (1/273)	0.3 (15/5043)	RD = -0.1 (-1.8 to 0.3) RR = 1.23 (0.16-9.29)
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)‡ N = 8706	TIA	0.3 (14/4353)	0.3 (13/4353)	RD = 0.0 (-0.3 to 0.2) Adjusted RR = 1.08 (0.51-2.29)§

CAS: carotid artery stenting; CEA: carotid endarterectomy; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
§Calculated from raw data by the Agency for Healthcare Research and Quality (AHRQ).

Table 32. Summary of periprocedural risks of other complications from nonrandomized studies comparing CAS with CEA for asymptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Cranial nerve injury or palsy				
Clinical studies				
Marine 2006 (Retro) N = 238	Cranial nerve palsy	0 (0/93)	2.8 (4/145)	RD = 2.8 (-1.5 to 6.9) RR = 0.17 (0.00-3.18)‡
Kastrup 2003 (Retro) N = 87	Cranial nerve injury (Mild and rapidly reversible)	0 (0/37)	12.0 (6/50)	RD = 12.0 (0.6-23.8) RR = not estimable
Registry studies				
Nolan 2012 (VSGNE) (Pro) N = 5316 (In-hospital data)	Cranial nerve injury (Persistent)	0 (0/273)	0.9 (45/5043)	RD = 0.9 (-0.5 to 1.2) RR = not estimable
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)§ N = 8706	Cranial nerve injury	0.2 (8/4353)	0.4 (19/4353)	RD = 0.3 (0.0-0.5) Adjusted RR = 0.42 (0.18-0.96)‡
Bleeding complications				
Clinical studies				
Marine 2006 (Retro) N = 238	Hematoma	5.4 (5/93)	4.1 (6/145)	RD = -1.2 (-8.2 to 4.3) RR = 1.30 (0.40-4.13)‡
Kastrup 2003 (Retro) N = 87	Hematoma	8.1 (3/37)	4.0 (2/50)	RD = -4.1 (-17.6 to 6.7) RR = 2.03 (0.36-11.53)
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)§ N = 8706	Unspecified bleeding	3.4 (148/4353)	3.8 (165/4353)	RD = 0.4 (-0.4 to 1.2) Adjusted RR = 0.90 (0.72-1.12)‡
Intracranial hemorrhage				
Administrative studies (in-hospital)				
Timaran 2009 (NIS) N = 136,077	Acute ICH	0.15 (19/13,093)	0.02 (20/122,984)	RD = -0.13 (-0.2 to -0.1) RR = 8.92 (4.76-16.72) Adjusted OR = 5.9 (3.1-11.1)**
McDonald 2011 (NIS) N = 217,596	Any ICH	0.5 (59/12,633)	0.07 (134/204,963)	RD = -0.4 (-0.5 to -0.3) RR = 7.14 (5.26-9.70)
	Acute ICH	0.3 (31/12,633)	0.04 (87/204,963)	RD = -0.2 (-0.3 to 0.1) RR = 5.78 (3.84-8.70)
	Subarachnoid hemorrhage	0.2 (25/12,633)	0.02 (42/204,963)	RD = -0.2 (-0.3 to -0.1) RR = 9.66 (5.89-15.84)
	Nontraumatic extradural hemorrhage	0 (0/12,633)	0.0005 (1/204,963)	RD = 0 (0.0-0.0) RR = not estimable
	Unspecified ICH	0.04 (3/12,633)	0.002 (4/204,963)	RD = 0 (-0.1 to 0.0) RR = 12.17 (2.72-54.36)
Other cardiac complications				
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)§ N = 8706	Cardiac complications, unspecified	4.92 (214/4353)	4.14 (180/4353)	RD = -0.8 (-1.7 to 0.1) Adjusted RR = 1.19 (0.98-1.44)
	Venous thromboembolism	0.07 (3/4353)	0.14 (6/4353)	RD = 0.1 (-0.1 to 0.2) Adjusted RR = 0.50

				(0.13-2.00)
Young 2011 (NIS) N = 249,592	Cardiac complications, not elsewhere classified	2.2 (671/31,197)	1.9 (4062/218,395)	RD = -0.3 (-0.5 to -0.1) RR = 1.16 (1.07-1.25)
Khatri 2012 (NIS) N = 495,331	Cardiac complications, not elsewhere classified	2.3 (1303/57,626)	1.9 (8268/437,705)	RD = -0.4 (-0.5 to -0.2) RR = 1.20 (1.13-1.27)

CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Calculated from raw data by the Agency for Healthcare Research and Quality (AHRQ).
§Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
**Odds ratio reported by authors; adjusted for age, sex, symptomatic status, comorbidity index, admission, hospital type.

4.3.2. Symptomatic

Safety in Symptomatic Patients

Summary of RCT data

CAS versus medical therapy alone: No RCTs comparing CAS and medical therapy with medical therapy alone in symptomatic patients were identified.

CAS compared with CEA: For the comparison of CAS and medical therapy with CEA and medical therapy, a total of ten studies from eight RCTs reported on various outcomes during the periprocedural period.[26,45,63,65,93,128,129,141,167,170]

- **Any periprocedural stroke:** Across six RCTs, risk of periprocedural stroke was significantly greater for CAS compared to CEA (Pooled RD: 3.39%, 95% CI .15%, 6.6%). This difference in risk suggests that for every 30 persons treated, there will be one additional stroke for CAS compared with CEA. Based on sensitivity analysis excluding older studies (which enrolled patients prior to 2000), studies with 10 or fewer patients per arm and studies that did not use embolic protection devices, pool risk difference remained significant favoring CEA (RD: 2.88%, 95% CI: 1.3, 4.44, NNH 35, 95% CI 23, 75)

- **Periprocedural death:** Across four RCTs, the rates of periprocedural death ranged from 0% to 1.3% for CAS and 0.5% to 2.0% for CEA. There was no difference in risk of periprocedural death between CAS and CEA in any individual RCT, nor when studies were combined in a pooled analysis.

- **Periprocedural stroke or death:** The risk of stroke or death was 7.1% for CAS and 4.1% for CEA based on pooled data across seven RCTs reporting this composite, neither of which fell below 6%. Three of the four largest RCTs reported significant increases in risk of stroke or death for CAS compared to CEA. In meta-analysis of seven RCTs, the RD of 2.75%, 95% CI -0.39%, 5.88% was not statistically significant; however, there was considerable heterogeneity in this analysis. To explore heterogeneity, older, small studies and those which did not use EPDs were excluded resulting in a pooled RD of 3.06%, 95% CI 1.43%, 4.69%); Number needed to harm was 33 (94% CI 21, 70).

- **Periprocedural myocardial infarction (MI):** Across four RCTs, periprocedural MI in individual studies ranged from 0.4% to 1.0% for CAS and 0.6% to 2.3% for CEA. There were no differences in risk between CAS and CEA in any individual study, nor when studies were combined in a pooled analysis.

- **Periprocedural ipsilateral stroke:** In pooled estimates across three studies, there was a suggestion of an increased risk of ipsilateral stroke for CAS compared to CEA (RD = 4.47% (`1.98%, 10.91%); however, it was not statistically significant and confidence intervals were wide.

- **Periprocedural fatal, major or disabling stroke:** Across five RCTs contributing data for this composite endpoint, the pooled risk difference between treatment groups and not statistically significant (RD: 0.88%, 95% CI -0.39%, 2.15%).

- **Periprocedural cranial nerve palsy:** In five RCTs, risk of cranial nerve injury or palsy was lower for CAS (0% to 1.1%) compared to CEA (2.3% to 7.8%). Three of the largest RCTs reported a significant reduction in risk for CAS compared with CEA. In pooled estimates risk of cranial nerve palsy was significantly lower among patients who received CAS compared with those having CEA (RD: -5.19%, 95% CI -4.14, -6.24).

- **Periprocedural hematoma:** In four RCTs, periprocedural rates of "severe hematoma requiring treatment" ranged from 0.4% to 5.7% for CAS, and from 0.8% to 2.0% for CEA treatment groups. There was no difference in risk between CAS and CEA treatment groups.

Summary of nonrandomized comparative studies

CAS versus medical therapy alone: No nonrandomized comparative studies evaluating periprocedural outcomes following CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS compared with CEA: Periprocedural outcomes following CAS and medical therapy compared with CEA and medical therapy were reported in a total of 18 nonrandomized comparative studies (7 cohorts,[43,49,59,96,107,108,189] 3 registries,[102,119,142] and 8 administrative[39,76,77,132,134,135,155,173]). All cohort studies were considered to be at moderately high risk of bias. For the registries, one was considered to be at a moderately low risk of bias and reported in-hospital outcomes only,[142] one a moderately high risk of bias,[102] and the third at a high risk of bias.[119] All administrative studies were considered to be at a high risk of bias.

- **Any periprocedural stroke:** No significant differences in the risk of any stroke between groups were reported across five cohort studies (2 prospective and 3 retrospective) whereas data from two large prospective registry studies (one reporting in-hospital events) consistently showed a statistical increased risk following CAS. Six of seven administrative studies reported that CAS was associated with an increased risk of any stroke compared with CEA.

- **Periprocedural death:** No statistical differences in risk of death were seen across three small cohort studies (1 prospective and 2 retrospective). Both of the included prospective registry studies reported a higher risk of death following CAS compared with CEA at 30 days and during the in-hospital period (wide confidence interval in the latter study suggests instability of the estimate). Across all eight administrative studies, risk of death was significantly increased following CAS.

- **Periprocedural stroke or death:** Across five cohort studies (2 prospective and 3 retrospective), no statistical difference between groups was reported for this composite outcome. Wide confidence intervals suggest instability of estimates. One of two included prospective registries reported an increased in-hospital risk of periprocedural stroke or death in persons receiving CAS compared with CEA, while the other larger registry reported similar risks for both groups at 30 days. The risk of periprocedural stroke or death following CAS was less than 6% in six of the seven studies. Risk of stroke or death was consistently significantly greater following CAS in three administrative studies.

- **Periprocedural myocardial infarction (MI):** No statistical differences in MI risk were seen across two cohort studies (1 prospective and 1 retrospective), two prospective registries, and two administrative data studies.

- **Periprocedural ipsilateral stroke:** CAS was associated with a three-fold greater risk of ipsilateral stroke compared with CEA during the in-hospital period as reported by one large prospective registry.

- **Transient ischemic attack (TIA):** No significant differences in the risk of TIA following CAS versus CEA were reported by one small retrospective cohort study and one large registry study. One administrative data study reported similar low risks (< 0.5%) in both treatment groups reporting in-hospital data only.

- **Periprocedural cranial nerve palsy:** Across one retrospective cohort study and one large prospective registry (in-hospital data), no significant differences in the risk of cranial nerve palsy were reported following CAS compared with CEA. One administrative data study reported similar low risks (< 0.5%) in both treatment groups.

- **Periprocedural bleeding complications:** The risk of hematoma was reported by one retrospective cohort study with no significant differences found in patients who undergone CAS compared with CEA. One administrative database study reported unspecified bleeding as a perioperative complication with no risk difference seen between groups.

- **Intracranial hemorrhage (ICH):** One administrative study analyzing the NIS database provided data for this outcome. The risk of any ICH was five and half times greater following CAS compared with CEA. Risks following CAS were also greater for the subcategories of acute ICH and subarachnoid hemorrhage, but were not significantly different between groups when considering nontraumatic extradural hemorrhage and unspecified hemorrhage.

- **Other complications:** Risk of unspecified cardiac complications and venous thromboembolism did not differ between CAS and CEA as reported by one administrative database study.

Detailed results: Symptomatic patients

Results from RCTs

CAS and medical therapy versus medical therapy alone: No RCTs comparing CAS and medical therapy with medical therapy alone in symptomatic patients were identified.

CAS and medical therapy versus CEA and medical therapy: A total of ten studies from eight RCTs comparing CAS with medical therapy to CEA with medical therapy reported on various outcomes during the periprocedural period.[26,45,63,65,93,128,129,141,167,170] Of these RCTs, four were large (N>500) multicenter and multinational trials,[65,128,129,167] and four were

smaller (N<150) single-center trials.[45,93,141,170] In the majority of studies, the periprocedural period included events occurring within 30 days of treatment; however, in analyses, some studies included events that occurred between randomization and treatment (CREST, SPACE, ICSS),[63,65,167] while others (EVA-3S)[124,128,129] excluded these events. One RCT (ICSS)[26,65] analyzed periprocedural events occurring up to 120 days after randomization for all patients (regardless of whether they were treated or not), and two RCTs(Kentucky, Regensburg)[45,141] provided no definition of periprocedural period.

Not all studies reported data for all periprocedural outcomes; therefore, only data published for by these trials were available for this report. Results are summarized in the text and tables below.

Any periprocedural stroke

A total of seven RCTs reported data on risk of any periprocedural stroke for CAS and CEA.[45,63,65,93,129,141,167] One RCT reported no periprocedural stroke events in either treatment arm[45]; therefore, only six RCTs contribute data for this endpoint. A statistically significant increase in risk of periprocedural stroke following CAS was seen in four of six individual RCTs. In pooled analysis of the six studies, the RD 3.39% (95% CI: 0.15, 6.64) was significant, favoring CEA. This corresponds to a number need to harm (NNH of 30 patients (95% CI: 15, 667). Thus, for every 30 patients treated with CAS and CEA, there is one additional stroke for patients treated with CAS compared to CEA. (Figure 9, Table 33).

The I^2 of 76% suggested the presence of considerable heterogeneity (Figure 9). To explore this, a sensitivity analysis was conducted excluding older studies (which enrolled patients prior to 2000), studies with 10 or fewer patients per arm and studies that did not use embolic protection devices. Studies included in sensitivity analysis were CREST , EVA -3S, ICSS and SPACE.[63,65,129,167] The pool risk difference remained significant favoring CEA (RD: 2.88%, 95% CI: 1.3, 4.44, NNH 35, 95% CI 23, 75) and heterogeneity was reduced (I^2 = 29%), Figure 10.

Table 33. Any periprocedural stroke reported by RCTs comparing CAS and CEA among symptomatic patients.

Study		CAS		CEA		Effect Size	
Any stroke	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
CREST (2011)	1,321	(37/668)	5.5%	(21/653)	3.2%	2.32 (0.12, 4.52)	1.72 (1.02, 2.91)
EVA- 3S (2008)	527	(24/265)	9.1%	(9/262)	3.4%	5.62 (1.52, 9.72)	2.64 (1.25, 5.56)
ICSS (2010)	1,649	(58/853)†	6.8%	(27/857)†	3.1%	3.65 (1.59, 5,70)	2.16 (1.38, 3.37)
SPACE (2008)	1,196	(44/607)	7.2%	(37/589)	6.3%	0.97 (-1.87, 3.81)	1.15 (0.76, 1.76)
Kentucky(2001)	104	(0/53)	0%	(0/51)	0%	NE	NE
BACASS (2008)	20	(0/10)	0%	(1/10)	10%	-10.00 (-33.72, 13.72)	0.33 (0.02, 7.32)
Leicester (1998)	17	(5/7)	71.4%	(0/10)	0%	71.43 (37.03, 105.83)	15.13 (0.97, 236.14)
Pooled estimates NNH						3.39 (0.15, 6.64) 30 (15, 667)	1.78 (1.21, 2.64)

NR = Not reported; NE = Not estimable; NNH = Number needed to harm
*Risk difference presented as percentage for ease or interpretation
† N based on the total population to estimate ITT analysis

Figure 9. Comparison of CAS versus CEA for periprocedural stroke

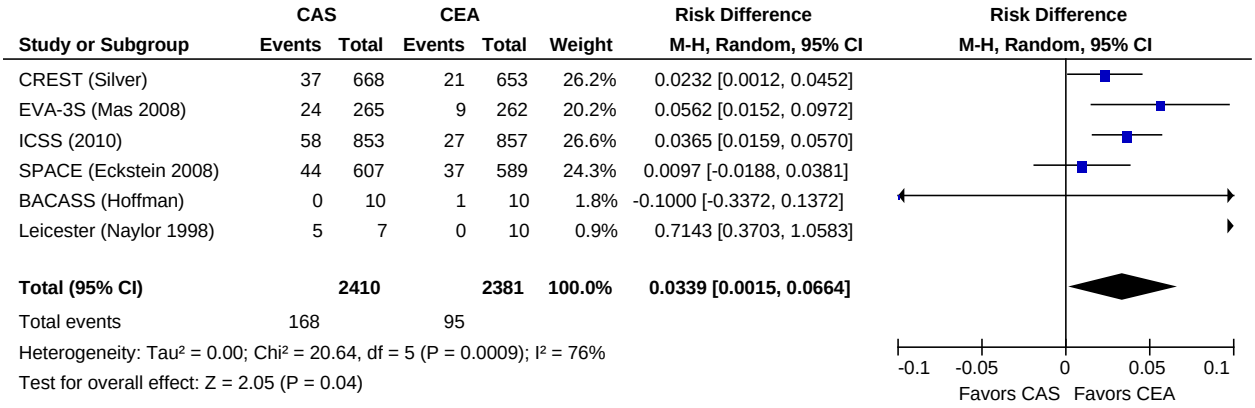
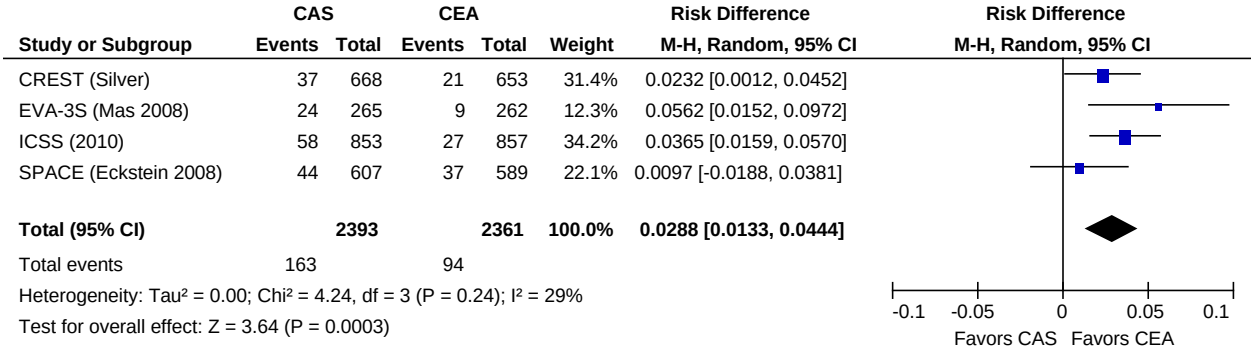


Figure 10. Sensitivity analysis: Comparison of CAS versus CEA for periprocedural stroke



Periprocedural death

A total of seven RCTs reported data on risk of periprocedural death for CAS and CEA.[45,63,65,93,129,141,170] In these studies, death was either reported separately or could be

determined from the data available. Three smaller RCTs reported no deaths in either treatment arm; therefore, only four RCTs contribute data for this endpoint. In individual RCTs, the rate of periprocedural death ranged from 0% to 1.3% for CAS and 0.5% to 2.0% for CEA. There was no difference in risk of periprocedural death between CAS and CEA in any individual RCT, nor when studies were combined in the pooled analysis (RD: 0.38, 95%CI: -0.25, 1.01) (Table 34, Figure 11). Exclusion of the Kentucky study which did not use EPDs did not appreciably alter the estimates and didn't affect the inference.

Table 34. Any periprocedural death reported by RCTs comparing CAS and CEA among symptomatic patients.

Study		CAS		CEA		Effect Size	
Death	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
EVA- 3S (2008)	520	(2/261)†	0.8%	(3/259)†	1.2%	-0.39 (-2.07, 1.29)	0.66 (0.11, 3.93)
ICSS (2010)	1,649	(11/853)‡	1.3%	(4/857)‡	0.5%	0.82 (-0.06, 01.71)	2.76 (0.88, 8.64)
SPACE (2008)	1,196	(6/607)	1.0%	(5/589)	0.9%	0.14 (-0.94, 1.22)	1.16 (0.36, 3.79)
Kentucky (2001)	104	(0/53)	0%	(1/51)	2.0%	-1.96 (-7.18, 3.26)	0.32 (0.01, 7.70)
BACASS (2008)	20	(0/10)	0%	(0/10)	0%	NE	NE
Leicester (1998)	17	(0/7)	0%	(0/10)	0%	NE	NE
Regensburg (2008)	87	(0/43)§	0%	(0/44)§	0%	NE	NE
Pooled estimates						0.38 (-0.25, 1.01)	1.41 (0.68, 2.91)

NR = Not reported; NE = Not estimable

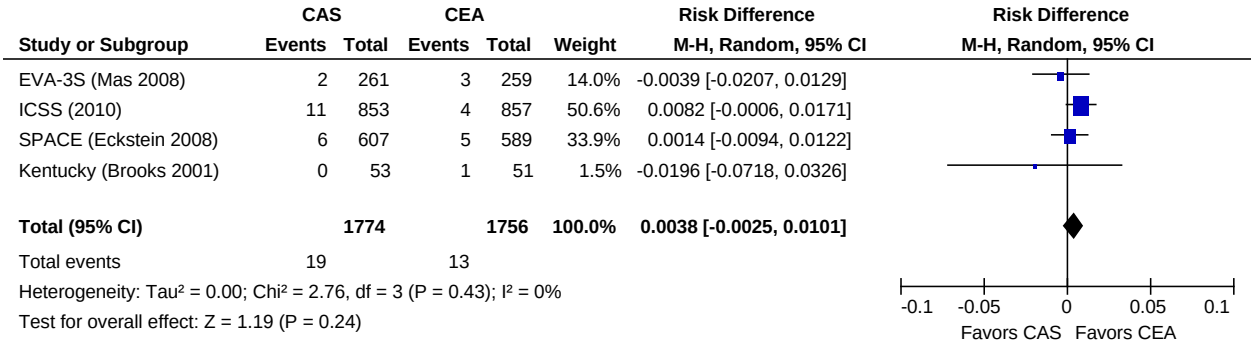
* Risk difference presented as percentage for ease or interpretation

† N based on Mas 2006; N's reported in Mas 2006 differ from N's reported in Mas 2008

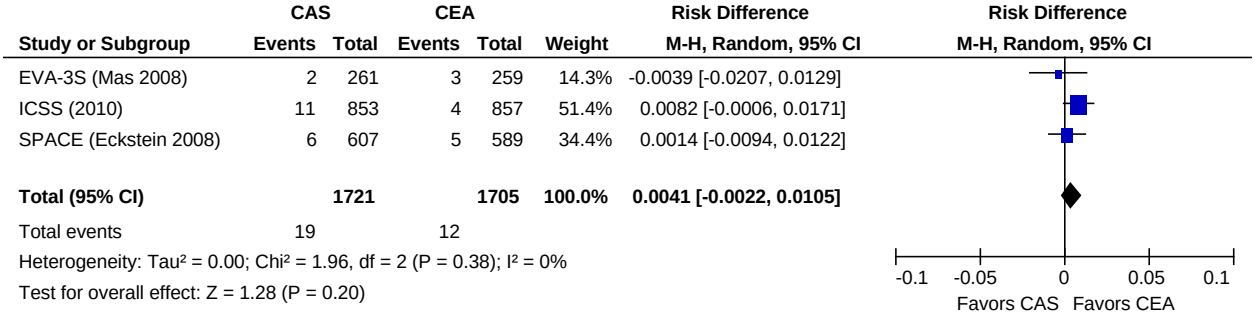
‡ N based on the total population to estimate ITT analysis

§ n calculated by hand

Figure 11. Comparison of CAS versus CEA for periprocedural death: Meta-analysis and sensitivity analysis



Sensitivity Analysis



Periprocedural stroke or death

The composite of death or any stroke during the periprocedural period was reported in seven RCTs (Table 35).[45,63,65,93,129,141,167] Given the small number of periprocedural deaths in these RCTs, the composite risk of any stroke or death is primarily influenced by the overall higher rates of stroke across studies.

Combining data from all seven RCTs, the risk of death or any stroke during the periprocedural period was 7.1% (176/2,463) for CAS compared with 4.1% (100/2,432) for CEA. Four individual RCTs reported a statistically significant increase in risk of death or any stroke following CAS. Meta-analysis across all seven studies, tended to favor CEA, suggesting increased risk of periprocedural stroke or death for CAS compared to CEA (RD: 2.75%, 95%CI: -0.39, 5.88); however, the confidence intervals are wide, and the result was not statistically significant (Figure 12).

The I^2 of 75% suggested there was considerable heterogeneity between studies. Thus, sensitivity analysis excluding older studies (which enrolled patients prior to 2000), studies with 10 or fewer patients per arm, and studies that did not use embolic protection devices was done. Studies included in sensitivity analysis were CREST,[167] EVA -3S (Mas 2008),[129]

ICSS,[65] and SPACE.[63] This reduced the heterogeneity to moderate (I^2 =32%) and the variability of the pooled RD estimate from the sensitivity analysis (RD: 3.06%, 95%CI: 1.43, 4.69) improved. This difference in risk corresponds to a number need to harm (NNH) of 33 patients (95% CI: 21, 70). Thus, for every 33 patients treated with CAS and CEA, there is one additional stroke for CAS compared with CEA. The risk of stroke or death remained stable, 7.1% (171/2393) for CAS and 4.1% (98/2361) for CEA based on pooled estimates in this sensitivity analysis (Figure 13).

Table 35. Any periprocedural stroke or death reported by RCTs comparing CAS and CEA among symptomatic patients.

Study		CAS		CEA		Effect Size	
Stroke or Death	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
CREST (2011)	1,321	(40/668)	6.0%	(21/653)	3.2%	2.77 (0.52, 5.02)	1.86 (1.11, 3.12)
EVA- 3S (2008)	527	(25/265)	9.4%	(10/262)	3.8%	5.62 (1.40, 9.83)	2.47 (1.21, 5.04)
ICSS (2010)	1,649	(61/853)†	7.4%	(28/857)†	3.4%	3.88 (1.78, 5.98)	2.19 (1.41, 3.39)
SPACE (2008)	1,196	(45/607)	7.4%	(39/589)	6.6%	0.79 (-2.10, 3.69)	1.12 (0.74, 1.69)
Kentucky (2001)	104	(0/53)	0%	(1/51)	2.0%	-1.96 (-7.18, 3.26)	0.32 (0.01, 7.70)
BACASS (2008)	20	(0/10)§	0%	(1/10)§	10.0%	-10.00 (-33.72, 13.72)	0.33 (0.02, 7.32)
Leicester (1998)	17	(5/7)§	71.4%	(0/10)§	0%	71.43 (37.03, 105.83)	15.13 (0.97, 236.14)
Pooled estimates						2.75 (-0.39, 5.88)	1.75 (1.18, 2.60)

NR = Not reported; NE = Not estimable

* Risk difference presented as percentage for ease or interpretation

† N based on the total population to estimate ITT analysis

Figure 12. Comparison of CAS versus CEA for any periprocedural stroke or death

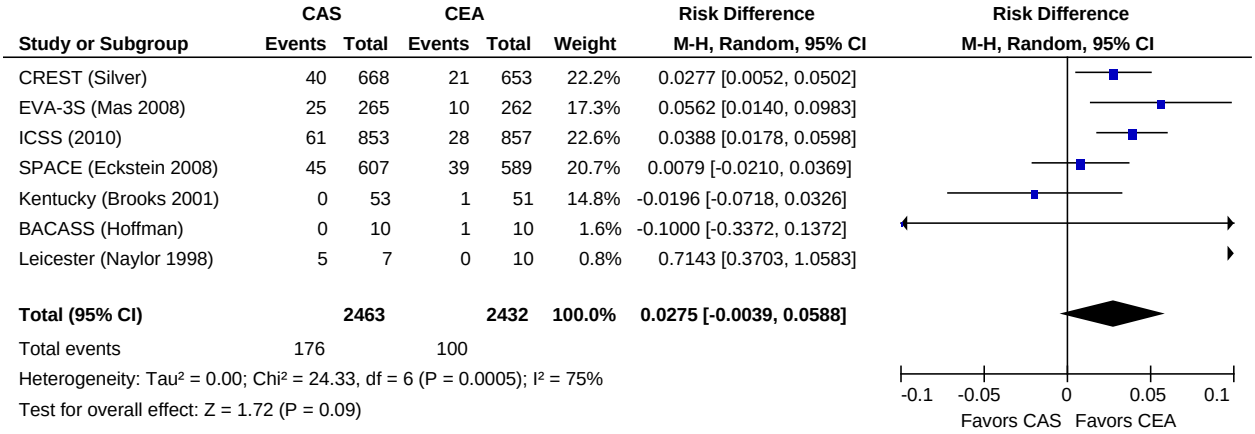
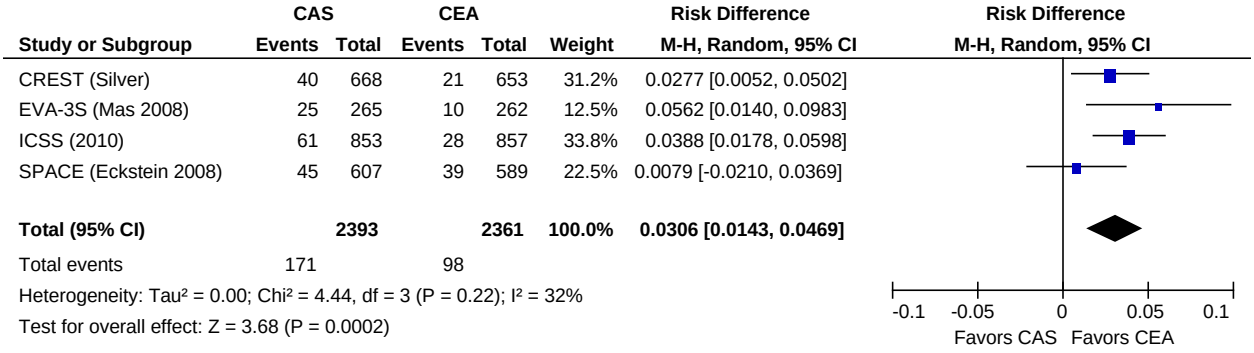


Figure 13. Sensitivity analysis: Comparison of CAS versus CEA for any periprocedural stroke or death



Periprocedural myocardial infarction (MI)

A total of five RCTs reported data on risk of periprocedural myocardial infarction.[45,65,93,129,167] The three largest trials (CREST, EVA-3S and ICSS)[65,129,167] used very similar definitions of myocardial infarction, which were based on a combination of symptoms, elevations in cardiac enzymes and electrocardiogram abnormalities; however, myocardial infarction was not defined in two smaller.[45,93] The definition of MI changed during the course of the CREST trial.[2] One of the smallest RCTs reported no MI events in either treatment arm[93]; therefore, only four studies contribute data to this endpoint in meta-analysis. Rates of periprocedural MI in individual studies ranged from 0.4% to 1.0% for CAS and 0.6% to 2.3% for CEA. There were no differences in risk of periprocedural myocardial infarction between CAS and CEA in any individual study, nor when studies were combined in the pooled analysis (Table 36, Figure 14). Exclusion of the BACASS and Kentucky studies had no appreciable effect on the estimates and no influence on the inference.

Table 36. Periprocedural myocardial infarction (MI) reported by RCTs comparing CAS and CEA among symptomatic patients

Study		CAS		CEA		Effect Size	
MI	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
CREST (2011)	1,321	(7/668)	1.0%	(15/653)	2.3%	-1.25 (-2.63, 0.14)	0.46 (0.19, 1.11)
EVA- 3S (2008)	527	(1/265)†	0.4%	(2/262)†	0.8%	-0.39 (-1.67, 0.90)	0.49 (0.05, 5.42)
ICSS (2010)	1,649	(3/853)‡	0.4%	(5/857)‡	0.6%	-0.25 (-0.92, 0.42)	0.59 (0.14, 2.48)
Kentucky (2001)	104	(0/53)	0%	(1/51)	2.0%	-1.96 (-7.20, 3.28)	0.48 (0.24, 0.97)
BACASS (2008)	20	0/10	0%	(0/10)	0%	NE	NE
Pooled estimates						-0.44 (-0.99, 0.10)	0.49 (0.24, 1.01)

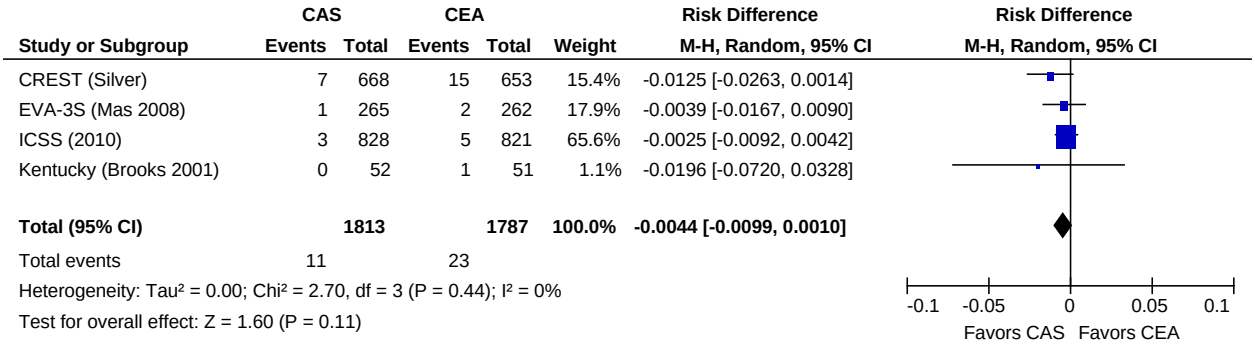
NR = Not reported; NE = Not estimable

* Risk difference presented as percentage for ease or interpretation

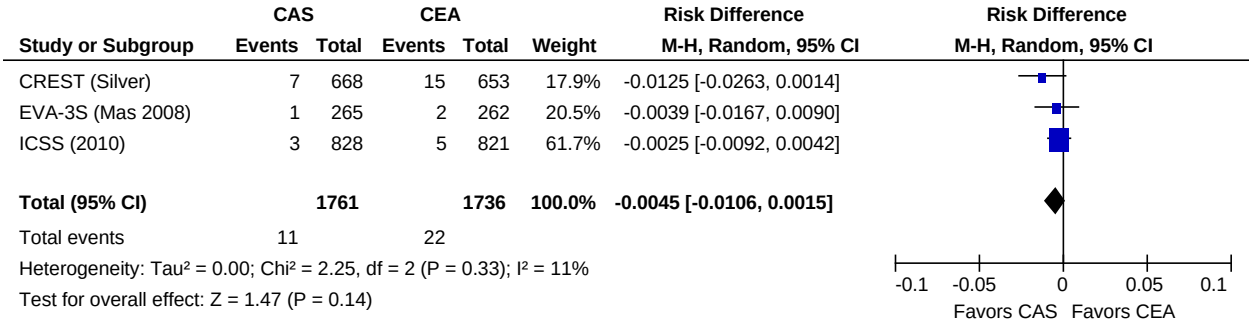
† N based on Mas 2008; N's reported in Mas 2006 differ from N's reported in Mas 2008

‡ N based on the total population to estimate ITT analysis

Figure 14. Comparison of CAS versus CEA for periprocedural myocardial infarction: Meta-analysis and sensitivity analysis



Sensitivity analysis



Periprocedural ipsilateral stroke

Three RCTs reported data on risk of periprocedural ipsilateral stroke (Table 37).[63,65,141] In these studies, ipsilateral stroke was either reported separately or could be determined from the data available. A statistically significant increase in risk of ipsilateral stroke following CAS was seen in two individual RCTs.[65,141] Combining data from all three RCTs, the total event rate of periprocedural ipsilateral stroke was 6.5% (96/1,467) for CAS compared with 4.2% (56/1,456) for CEA. In a pooled meta-analysis of these studies, there was a suggestion of an increased risk of ipsilateral stroke for CAS compared to CEA; however, it failed to reach statistical significance (RD = 4.47, 95%CI -1.98, 10.91) The small sample size and result variability of the Leicester study[141] is likely to strongly influences the heterogeneity (Figure 15) which was verified in the related sensitivity analysis below. This study did not use embolic protection whereas the others did. The risk difference of 2.37% (95% CI 0.42%, 4.3%) corresponds to a NNH of 42.

Table 37. Periprocedural ipsilateral stroke reported by RCTs comparing CAS and CEA among symptomatic patients.

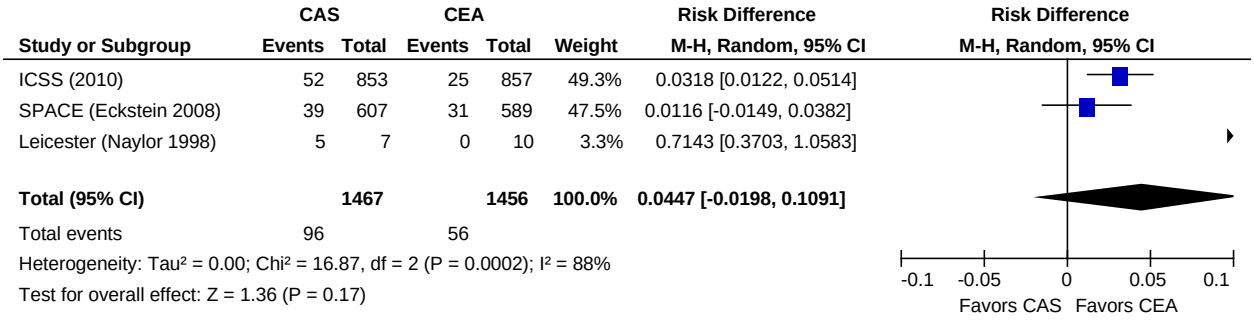
Study		CAS		CEA		Effect Size	
Ipsilateral stroke	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
ICSS (2010)	1,649	(52/853)†	6.1%	25/857)†	2.9%	0.03 (0.01, 0.05)	2.09 (1.31, 3.34)
SPACE (2008)	1,196	(39/607)	6.4%	(31/589)	5.3%	0.01 (-0.01, 0.04)	1.22 (0.77, 1.93)
Leicester (1998)	17	(5/7)	71.4%	(0/10)	0%	0.71 (0.37, 1.06)	15.13 (0.97, 236.14)
Pooled estimates						4.47 (-1.98, 10.91)	1.79 (0.94, 3.40)

NR = Not reported; NE = Not estimable

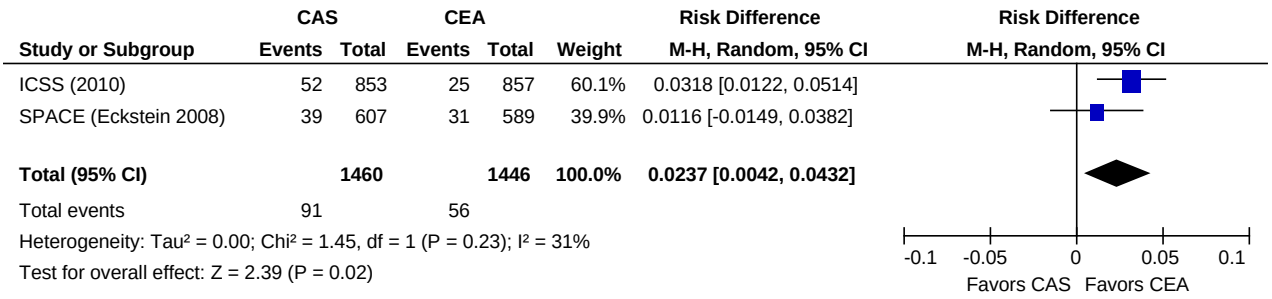
* Risk difference presented as percentage for ease or interpretation

† N based on the total population to estimate ITT analysis

Figure 15. Comparison of CAS versus CEA for periprocedural ipsilateral stroke and related sensitivity analysis.



Sensitivity analysis:



Periprocedural fatal, major or disabling stroke

A total of six RCTs reported data on risk of periprocedural fatal, major or disabling stroke (CREST, EVA-3S, ICSS, SPACE, Leicester, Kentucky).[45,63,65,128,141,167] Definitions of fatal, major or disabling stroke differed considerably across every study: CREST[167] reported Major stroke only, EVA-3S[128] reported any disabling stroke requiring treatment or death, ICSS[65] reported fatal or disabling stroke, SPACE[63] reported any disabling stroke or death and Leicester[141] reported disabling ipsilateral stroke. One small RCT reported no periprocedural

strokes in either treatment group[45]; therefore, only five RCTs contribute data for this composite endpoint in meta-analysis.

Although all studies tended to show higher risk of fatal, major or disabling stroke following CAS, the difference in risk between treatment groups was statistically significant in only one small RCT.[141] Combining data from these five RCTs, the total event rate of periprocedural fatal, major or disabling stroke was 3.0% (73/2,396) for CAS compared with 2.1% (49/2,368) for CEA. Pooled estimates of the difference in risk of fatal, major or disabling stroke between CAS and CEA treatment groups was not statistically different (RD: 0.88, 95% CI: -0.39, 2.15 (Figure 16); the relative risk of this composite outcome was marginally significant for CAS compared to CEA (RR: 1.45, 95% CI: 1.01, 2.07), Table 38.

A moderate amount of heterogeneity between studies (I^2 = 47%) was noted for this analysis. Thus, sensitivity analysis excluding older studies (which enrolled patients prior to 2000), studies with 10 or fewer patients per arm, and studies that did not use embolic protection devices was done. Studies included in sensitivity analysis were CREST,[167] EVA -3S,[128] ICSS[65] and SPACE.[63] In sensitivity analysis, heterogeneity was reduced (I^2 = 0%) and the difference between groups was not significant, RD: 0.64%, 95%CI: -0.14, 1.41 (Figure 17).

Table 38. Periprocedural fatal, major or disabling stroke or death reported in RCTs comparing CAS and CEA among symptomatic patients.

Study		CAS		CEA		Effect Size	
Fatal, major or disabling stroke	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
CREST (2011)†	1,321	(8/668)	1.2%	(6/653)	0.9%	0.00 (-0.01, 0.01)	1.30 (0.45, 3.74)
EVA- 3S (2006)‡	527	(9/261)§	3.4%	(4/259)§	1.5%	0.02 (-0.01, 0.05)	2.23 (0.70, 7.16)
ICSS (2010)**	1,649	(22/853)††	2.6%	(17/857)††	2.0%	0.01 (-0.01, 0.02)	1.30 (0.70, 2.43)
SPACE (2008)‡‡	1,196	(31/607)	5.1%	(22/589)	3.9%	0.01 (-0.01, 0.04)	1.37 (0.80, 2.33)
Kentucky (2001)	104	(0/53)	0%	(0/51)	0%	NE	NE
Leicester (1998)§§	27	(3/7)	42.9%	(0/10)	0%	0.43 (0.06, 0.79)	9.63 (0.57, 161.44)
Pooled estimates						0.88 (-0.39, 2.15)	1.45 (1.01, 2.07)

NR = Not reported; NE = Not estimable

* Risk difference presented as percentage for ease or interpretation

† Major stroke only

‡ Any disabling stroke requiring treatment or death

§ N's based on Mas 2006, N's reported in Mas 2006 differ from N's reported in Mas 2008

** Fatal or disabling stroke

†† N based on the total population to estimate ITT analysis

‡‡ Any disabling stroke or death

§§ Disabling ipsilateral stroke

Figure 16. Comparison of CAS versus CEA for periprocedural fatal, major or disabling stroke

Study or Subgroup	CAS Events	CAS Total	CEA Events	CEA Total	Weight	Risk Difference M-H, Random, 95% CI
CREST (Silver)	8	668	6	653	35.6%	0.0028 [-0.0082, 0.0138]
EVA-3S (Mas 2008)	9	261	4	259	15.4%	0.0190 [-0.0077, 0.0458]
ICSS (2010)	22	853	17	857	30.3%	0.0060 [-0.0082, 0.0201]
SPACE (Eckstein 2008)	31	607	22	589	18.5%	0.0137 [-0.0095, 0.0370]
Leicester (Naylor 1998)	3	7	0	10	0.1%	0.4286 [0.0634, 0.7937]
Total (95% CI)		**2396**		**2368**	**100.0%**	**0.0088 [-0.0039, 0.0215]**
Total events	73		49			

Heterogeneity: Tau² = 0.00; Chi² = 7.51, df = 4 (P = 0.11); I² = 47%

Test for overall effect: Z = 1.36 (P = 0.18)

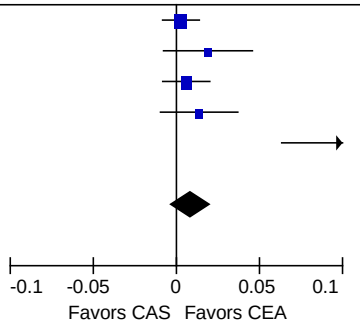
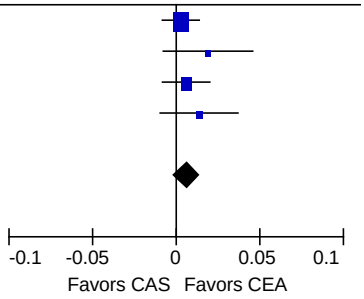


Figure 17. Sensitivity analysis: Comparison of CAS versus CEA for periprocedural fatal, major or disabling stroke

Study or Subgroup	CAS Events	CAS Total	CEA Events	CEA Total	Weight	Risk Difference M-H, Random, 95% CI
CREST (Silver)	8	668	6	653	50.0%	0.0028 [-0.0082, 0.0138]
EVA-3S (Mas 2008)	9	261	4	259	8.5%	0.0190 [-0.0077, 0.0458]
ICSS (2010)	22	853	17	857	30.3%	0.0060 [-0.0082, 0.0201]
SPACE (Eckstein 2008)	31	607	22	589	11.2%	0.0137 [-0.0095, 0.0370]
Total (95% CI)		**2389**		**2358**	**100.0%**	**0.0064 [-0.0014, 0.0141]**
Total events	70		49			

Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%

Test for overall effect: Z = 1.60 (P = 0.11)



Periprocedural cranial nerve palsy

A total of seven RCTs reported data on risk of periprocedural cranial nerve injuries.[45,65,93,128,141,167,170] Definitions of cranial nerve injuries differed across studies: two large trials (CREST, and EVA-3S)[128,167] report cranial nerve palsy, one large ICSS[65] and two smaller (Leicester and Regensburg)[141,170] report cranial nerve injury, one small study reported cervical or cranial nerve injury (Kentucky),[45] and one small study reported cranial nerve paralysis. No studies mentioned data on duration of cranial nerve injuries. In addition, two of the smallest RCTs reported no cranial nerve injury events in either treatment arm[93,141]; therefore, only five studies contribute data to this endpoint.

Across individual RCTs, risk of cranial nerve injury or palsy was significantly less common among persons receiving CAS (frequencies range from 0% to 1.1%) compared with those receiving CEA (frequencies range from 2.3% to 7.8%), with the three largest RCTs[65,128,167]

reporting a statistically significant reduction in risk for CAS. In a pooled meta-analysis of these studies, risk of cranial nerve palsy was a 5.19% lower among patients who received CAS compared with those having CEA (RD: -5.19%, 95%CI: -6.24, -4.14% and RR: 0.07, 95%CI: 0.02, 0.24) (Table 39).

Table 39. Periprocedural cranial nerve injuries reported by RCTs comparing CAS and CEA among symptomatic patients.

Study		CAS		CEA		Effect Size	
Cranial nerve injuries	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
CREST (2011)†	1,321	(0/668)	0.4%	(33/653)	5.1%	-0.05 (-0.07, -0.03)	0.01 (0.00, 0.24)
EVA- 3S (2006)†	527	(3/261)‡	1.1%	20/259)‡	7.7%	-0.07 (-0.10, -0.03)	0.15 (0.04, 0.49)
ICSS (2010)†	1,649	(1/853)	0.1%	(45/857)	5.3%	-0.05 (-0.07, -0.04)	0.02 (0.00, 0.16)
Kentucky (2001)§	104	(0/53)	0%	(4/51)	7.8%	-0.08 (-0.16, 0.00)	0.11 (0.01, 1.94)
BACASS (2008)**	20	(0/10)	0%	(0/10)	0%	NE	NE
Leicester (1998)††	17	(0/7)	0%	(0/10)	0%	NE	NE
Regensburg (2008)	87	(0/43)	0%	(1/44)	2.3%	-0.02 (-0.08, 0.04)	0.34 (0.01, 8.14)
Pooled estimates						-5.19 (-6.24, -4.14)	0.07 (0.02, 0.24)

NR = Not reported; NE = Not estimable

* Risk difference presented as percentage for ease or interpretation

† Cranial nerve palsy

‡ N's reported in Mas 2006 differ from N's reported in Mas 2008

§ Cranial or cervical nerve injury

** Cranial nerve paralysis

†† Cranial nerve injury

Periprocedural Bleeding Complications

Six RCTs reported data on risk of periprocedural bleeding complications.[45,65,93,128,167,170] Definitions of bleeding complications varied across studies: four studies report "any hematoma", three studies report "severe hematoma requiring treatment", and one RCT reports "severe cervical or groin hematoma requiring treatment". A total of four studies contribute data to the both the "any hematoma" and "severe hematoma requiring treatment" endpoints. One small RCT reported data on both outcomes; however, no events occurred in either treatment arm so this study was excluded from pooled analyses.[93]

Three RCTs reported statistically significant decreases in risk of "any hematoma" following CAS (frequencies range from 0% to 3.5%) compared to CEA (frequencies range from 1.2% to 13.6%). In a pooled analysis of these studies, risk of "any" periprocedural hematoma was -2.13% (95% CI: -4.57, 0.31) lower for CAS compared to CEA; although this difference in risk was not statistically significant (Table 40).

In three RCTs, rates of "severe hematoma requiring treatment" ranged from 0.4% to 5.7% for CAS, and from 0.8% to 2.0% for CEA treatment groups. Only one out of three RCTs reported a statistically significant decrease in risk of "severe" hematoma requiring treatment among patients who received CAS; however, when studies were combined in the pooled analysis, there was no difference in risk between CAS and CEA treatment groups (RD = -0.99%, 95%CI: -3.08, 1.10 and RR = 0.56, 95%CI: 0.15, 2.13) The numbers of events were small and resulting in reduced the ability to detect significant associations (Table 40).

Table 40. Periprocedural bleeding complications reported in RCTs comparing CAS and CEA among symptomatic patients.

Study		CAS		CEA		Effect Size	
Any Hematoma	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
CREST (2011)	1,321	(0/668)	0%	(8/653)	1.2%	-0.01 (-0.02, -0.00)	0.06 (0.00, 0.99)
ICSS (2010)	1,649	(30/853)	3.5%	50/857)	5.8%	-0.02 (-0.04, -0.00)	0.60 (0.39, 0.94)
BACASS (2008)	20	(0/10)	0%	(0/10)	0%	NE	NE
Regensburg (2008)	87	(1/43)	2.3%	(6/44)	13.6%	-0.11 (-0.22, -0.00)	0.17 (0.02, 1.36)
Pooled estimates						-2.13 (-4.57, 0.31)	0.30 (0.08, 1.15)
Severe Hematoma requiring treatment	N	(n/N)	%	(n/N)	%	RD%* (95% CI)	RR (95% CI)
EVA- 3S (2006)†	527	(1/261)†	0.4%	(2/259)†	0.8%	-0.00 (-0.02, 0.01)	0.50 (0.05, 5.44)
ICSS (2010)	1,649	(8/853)	0.9%	(28/857)	3.3%	-0.02 (-0.04, -0.01)	0.29 (0.13, 0.63)
Kentucky (2001)	104	(3/53)	5.7%	(1/51)	2.0%	0.04 (-0.04, 0.11)	2.89 (0.31, 26.85)
BACASS (2008)	20	(0/10)‡	0%	(0/10)‡	0%	NE	NE
Pooled estimates						-0.99 (-3.08, 1.10)	0.56 (0.15, 2.13)

NE = Not estimable

* Risk difference presented as percentage for ease or interpretation

† Severe cervical or groin hematoma requiring treatment

‡ Calculated by hand

Other Outcomes

Other periprocedural outcomes reported by various studies include hypertension, bradycardia, hypotension, treatment failure, length of hospital stay, pain, and cerebral events. Hypotension and brachycardia events occurred more frequently and hypertension occurred less frequently among persons treated by CAS as compared to CEA; however, for all other periprocedural outcomes reported, rates of events were similar for CAS and CEA (Table 41).

Table 41. Other periprocedural outcomes reported on RCTs comparing CAS and CEA among symptomatic patients

Outcome Study	N	CAS		CEA		Effect Size
Length of hospital stay		Mean ± SD (days)		Mean ± SD (days)		
BACASS (2008)	20	3.5 ± 1.8		7.8 ± 3.3		NR
Kentucky (2001)	104	5.2 ± 11/4		3.7 ± 3.1		NR
Pain at 1 month		Mean (range 0-10)		Mean ± SD (range 0-10)		
Kentucky (2001)	104	<1.0 (0-4)		<1.0 (0-4)		NR
Hypertension		(n/N)	%	(n/N)	%	
CREST (2011)	1,321	(8/668)	1.1%	(32/653)	4.9%	NR
Hypotension						
CREST (2011)	1,321	(30/668)	4.5%	(13/653)	2.0%	NR
Kentucky (2001)	104	(12/53)	22.6%	(3/51)	5.9%	NR
Bradycardia						
CREST (2011)	20	(20/668)	3.0%	(4/653)	0.6%	NR
Kentucky (2001)	104	(7/53)	13.2%	(0/51)	0%	NR
EVA-3S (2006	527	(11/261)	4.2%	(0/259)	0%	P<0.001
Ipsilateral intracerebral bleeding						
SPACE (2008)	1,196	(2/607)	0.3%	(5/589)	0.9%	HR: 0.39 (0.09, 1.73)
Arterial thrombosis/amputation						
Kentucky (2001)	104	(1/53)	1.9%	(0/51)	0%	NR
Femoral Artery Complications						
CREST (2011)	1,321	(6/668)	0.9%	(2/653)	0.3%	NR
Infection requiring treatment						
EVA-3S (2006)	527	(1/261)	0.4%	(1/259)	0.4%	NR
Procedural failure						
SPACE (2008)	1,196	(21/607)	3.5%	(15/589)	2.6%	OR: 1.36 (0.72, 2.58)

NR = Not reported

Comparison to other meta-analyses

Several other systematic reviews have evaluated rates of periprocedural events comparing CAS and medical therapy with CEA and medical therapy. The most recent and complete meta-analysis was conducted by Bonati et al.[41] However, Bonati included RCTs that were either excluded from this review[11,24,67,120,191] or were included only in the section on special populations. [87,183] (See key question 4). In addition, Bonati had access to patient level data for multiple studies. Thus, we could not directly compare the results of our meta-analysis with the results reported in Bonati et al. In order to provide a more meaningful comparison of our results, we conducted a separate meta-analysis, which we call "Bonati Comparison" that omits the studies excluded in our review and uses the data reported by Bonati et al. for the studies included in our review (see Table 42). For all major periprocedural outcomes, the results of our meta-analyses are similar to those for "Bonati Comparison"; however, there are

several instances (for example, periprocedural MI) where the results for "Bonati Comparison" are statistically significant, and ours are not. This is most likely related to sample size, as Bonati had access to patient level data for several RCTs, and in many instances, had more cases reported for outcomes in these trials.

Table 42. Comparison of Spectrum meta-analysis of periprocedural endpoints to "Bonati-lite" meta-analysis.

	Spectrum Meta-analysis		Bonati Comparison* Meta-analysis		
Periprocedural endpoints					
	RD% (95% CI) RR (95% CI)	Studies included	RD% (95% CI)† RR (95% CI)†	Studies Included	Comments
Any Stroke	RD: 3.39 (0.15, 6.64) RR: 1.78 (1.21, 2.62)	CREST EVA-3S ICSS SPACE Kentucky BACASS Leicester	RD: 3.46 (0.53, 6.39) RR: 1.73 (1.36, 2.20)	CREST EVA-3S ICSS SPACE Kentucky BACASS Leicester Beijing	Pooled RR's for SRI and Bonati are comparable Discrepancies: SPACE: Bonati uses N=689 for CEA; however, all tables report N=589. When the correct N is used, OR=1.69 (1.24, 2.30) EVA-3S & ICSS: Bonati reports slightly different n's; he had patient level data for these studies
Death	RD: 0.38 (-0.25, 1.01) RR: 1.41 (0.68, 2.91)	EVA-3S ICSS SPACE Kentucky BACASS Leicester Regensburg	RD:0.35 (-0.06, 0.77) RR: 1.33 (0.66, 2.68)	CREST EVA-3S ICSS SPACE Kentucky BACASS Leicester Regensburg TESCAS-C Beijing	Pooled RR's for SRI and OR's for Bonati are comparable Discrepancies: CREST: Bonati reported data for total study population (asymptomatic and symptomatic combined). CREST did not report n's/N's for symptomatic only. SPACE: Bonati uses N=689 for CEA; however, all tables report N=589. When the correct N is used, OR=1.23 (0.63, 2.42)
Stroke (any) or death	RD: 2.75 (-0.39, 5.88) RR: 1.75 (1.18, 2.59)	CREST EVA-3S ICSS SPACE Kentucky BACASS Leicester	RD: 2.74 (0.03 5.46) RR: 1.71 (1.26, 2.31)	CREST EVA-3S ICSS SPACE Kentucky BACASS Leicester Wallstent TESCAS Beijing	Pooled RR's for SRI and Bonati are comparable Discrepancies: EVA-3S & ICSS: Bonati uses slightly different n's; he had patient level data for these studies Regensburg: Bonati uses n's reported as "Risk of stroke or death or other treatment-related outcome 1 year after carotid artery stenting or carotid endarterectomy". Since these events were not specified to be peri-

	Spectrum Meta-analysis		Bonati Comparison* Meta-analysis		
Periprocedural endpoints					
					procedural, we do not consider these events as periprocedural.
MI	RD:-0.44 (-0.99, 0.10) RR: 0.49 (0.24, 1.01)	CREST EVA-3S ICSS SPACE BACASS	RD: -0.43 (-0.96, 0.10) RR: 0.48 (0.24, 0.95)	CREST EVA-3S ICSS SPACE BACASS Regensburg Beijing	Pooled RR's for SRI and Bonati are comparable; only significant for Bonati Lite Discrepancies: Regensburg: Bonati uses n's reported as "Risk of stroke or death or other treatment-related outcome 1 year after carotid artery stenting or carotid endarterectomy". Since MI events were not specified to be peri-procedural, we do not consider this event as periprocedural.
Fatal, Major or Disabling stroke	RD: 0.88 (-0.39, 2.15) RR: 1.45 (1.01, 2.07)	CREST EVA-3S ICSS SPACE Kentucky Leicester	RD: 0.75 (-0.49, 1.95) RR: 1.37 (0.97, 1.94)	CREST EVA-3S ICSS SPACE BACASS Leicester Kentucky	Pooled RR's for SRI and Bonati are in the same direction; only significant for SRI Discrepancies: EVA-3S, ICSS, SPACE & BACASS: Bonati reports slightly different n's; he had patient level data for these studies study
Ipsilateral stroke	RD: 4.47 (-1.98, 10.91) RR: 1.79 (0.94, 3.40)	ICSS SPACE Leicester	NR	NR	
Cranial nerve injury or palsy	RD: -5.19 (-6.24, -4.14) RR: 0.07 (0.02, 0.24)	CREST EVA-3S ICSS Kentucky BACASS Leicester Regensburg	RD: -5.17 (-6.10, -4.25) RR: 0.47 (0.21, 1.08)	CREST EVA-3S ICSS SPACE Kentucky BACASS Leicester Regensburg	Pooled RR's are larger and statistically significant for SRI, compared to Bonati Discrepancies: SPACE: Bonati reports n's which are not reported in the manuscript; he had patient level data for this study
Hematoma (any)	RD: -2.13 (-4.57, 0.31) RR: 0.30 (0.08, 1.15)	CREST ICSS BACASS Regensburg	NR	NR	
Hematoma requiring treatment	RD:-0.99 (-3.08, 1.10) RR: 0.56 (0.15, 2.13)	EVA-3S ICSS Kentucky BACASS	RD: -1.03 (-3.07, 1.02) RR: 0.47 (0.21, 1.08)	EVA-3S ICSS SPACE Kentucky BACASS Regensburg Beijing	Pooled RR's for SRI and Bonati are comparable Discrepancies: SPACE: Bonati reports n's which are not reported in the manuscript; he had patient level data for this study Regensburg: Bonati used

	Spectrum Meta-analysis		Bonati Comparison* Meta-analysis		
Periprocedural endpoints					
					data reported as "Any hematoma" by Regensburg for this outcome

*For "Bonati Comparison", we performed a met-analysis using a subset of the studies reported by Bonati, which were similar to those included in this HTA (excludes CAVATAS, and SAPPHIRE)

Results from nonrandomized comparative studies

CAS versus medical therapy alone: No nonrandomized comparative studies evaluating periprocedural outcomes following CAS and medical therapy versus medical therapy alone among patients with symptomatic carotid stenosis were found.

CAS and medical therapy versus CEA and medical therapy:
Overall, this section includes data from seven comparative cohort studies[43,49,59,96,107,108,189] and three comparative registry studies.[102,119,142] These studies constitute the primary body of evidence for this section and report outcomes up to 30 days post-procedure, with the exception of one registry study that reported in-hospital data as stated previously.[142] In addition, eight administrative studies are briefly described.[39,76,77,132,134,135,155,173] All report in-hospital data. Data are summarized in Tables 43–48.

All cohort studies were considered to be at moderately high risk of bias. For the registries, one was considered to be at a moderately low risk of bias,[142] one a moderately high risk of bias,[102] and the third at a high risk of bias.[119] All administrative studies were considered to be at a high risk of bias. Concerns regarding such studies include questions of coding accuracy and variability of algorithms used to identify patients as previously described in the methods section of this report.

For purposes of this section, a positive risk difference favors CAS and negative risk difference favors CEA.

Any periprocedural stroke
Data were available for this primary outcome from five cohort studies (N range, 75–155),[49,96,107,108,189] two prospective and three retrospective, and two large prospective registries (N = 2761 and 3645).[102,142] In some studies, periprocedural stroke included fatal stroke. Across the cohort studies, no significant differences in the risk of any stroke following CAS versus CEA were reported. Risks ranged from 2.9%–10.0% and 2.4%–7.2%, respectively, and were higher after CAS in three studies, but higher after CEA in two other studies. (Of note, one of the studies was conducted in patients aged 75 years or older and

reported the highest rate of stroke in the CAS group, 10.0%, primarily driven by the risk of minor stroke.[107]) Two studies further reported the risk of major and minor stroke, with no significant differences in either outcome between groups.[107,108] Significantly increased risks following CAS were reported by the two registry studies; one reported outcomes through 30 days (6.1% vs. 4.1%) and one reported in-hospital outcomes (5.1% vs. 1.4%). Respective relative risks (RRs) were 1.5 (95% CI, 1.1–2.0) and 3.6 (95% CI, 1.7–7.6), with risk differences (RDs) of -2.1% (95% CI, -3.6% to -0.7%) and -3.7% (95% CI, -8.4% to -1.1%). The registry that analyzed in-hospital outcomes also reported the risk of major and minor stroke separately, both of which were significantly increased in the CAS group: 2.6% vs. 0.6% and 2.6% vs. 0.8%, respectively.[142] Across seven administrative database studies, six reported that CAS was associated with an increased risk of any stroke compared with CEA; ranges were 4.1%–8.1% for CAS and 1.1%–4.6% for CEA (range of RDs = -3.5% to -1.6%; range of RRs = 1.7–3.8) with only study controlling for confounding factors using a propensity score matched analysis.[39,77,134,135,155,173]

Periprocedural death

Three small cohort studies (N range 75–155), one prospective and two retrospective,[49,108,189] and two large prospective registry studies, (N = 2761 and 3645)[102,142] provided data for this outcome. Risk of death was similar across the cohort studies, with risks ranging from 0%–1.6% following CAS and 0%–1.3% after CEA. Both of the included registry studies reported a higher risk of death following CAS: 2.0% vs. 1.1% at 30 days in one study (RD = -0.9%; RR = 1.8, 95% CI, 1.1–3.1) and 1.3% vs. 0.2% during the in-hospital period in the other (RD = -1.1%; RR = 6.7, 95% CI, 1.3–34.2). The wide confidence intervals in the second study suggest instability of the estimate. Data were available from eight administrative studies (N range 1086–52,937),[39,76,77,132,134,135,155,173] six of which analyzed National Inpatient Sample (NIS) data. Risk of death was significantly greater following CAS compared with CEA across all studies, ranging from 3.7%–7.5% and 0.9%–4.0%, respectively, with RDs ranging from -6.5% to -2.2% and RRs from 1.6–7.5.

Periprocedural stroke or death

Data were available for this composite from five cohort studies (N range, 75–684),[43,49,59,108,189] two prospective and three retrospective, and two large prospective registries (N = 2761 and 5149).[119,142] Across the cohort studies, risks ranged from 2.6%–7.9% for CAS and 2.4%–7.2% for CEA, with no statistical difference between groups; in three studies risks were higher after CAS, but higher after CEA in two other studies. Wide confidence intervals suggest instability of estimates. One of the two registries reported an increased risk of periprocedural stroke or death during the in-hospital period in persons receiving CAS (5.1%) compared with CEA (1.6%) with a RD of -3.5% (95% CI, -8.2% to -0.9%), and a RR of 3.2 (95% CI, 1.5–6.7), while the other larger registry reported similar risks for both groups (4.9%

and 4.4%, respectively). The risk of periprocedural stroke or death following CAS was < 6% in six of the seven studies. Data available from three administrative studies with sample sizes ranging from 1086 to 52,937, showed that the risk of stroke or death was consistently higher following CAS compared with CEA; ranges were from 8.3%–13.1% and 4.3%–5.9%, respectively, with all reporting a significant difference.[39,76,77]

Periprocedural myocardial infarction (MI)

Two cohort studies (N = 128, 155),[108,189] one prospective and one retrospective, and two prospective registries (N = 2761, 3645)[102,142] reported data for this outcome. No statistical differences in MI risk were seen across all four studies. In the cohorts, no MIs were reported in either treatment group and risks were similar for both groups (~1.3%) in both registries (to include one that used in-hospital data). Similarly, no statistical differences in MI risk were reported in two administrative studies (N = 4834, 20,691); risks were 2.2% for both CAS groups and 1.1% and 2.0% for the CEA groups.[39,134]

Periprocedural ipsilateral stroke

One large prospective registry study (N = 2671) that analyzed in-hospital events provided the only data for this outcome.[142] The risk of periprocedural ipsilateral stroke was 3-fold greater following CAS compared with CEA: 3.9% versus 1.2% (RD = -2.7%, 95% CI, -7.0% to -0.5; RR = 3.2, 95% CI, 1.4–7.6).

Periprocedural transient ischemic attack (TIA)

One small retrospective cohort study (N = 75)[49] and one large prospective registry (N = 2761)[142] analyzing in-hospital outcomes reported no significant differences in the risk of TIA following CAS versus CEA (2.9% vs. 2.4% and 0.7% vs. 0.6%, respectively) One administrative database study (N = 1086) reported similar low risks in both treatment groups (CAS 0.4%; CEA 0.3%) using a propensity score matched analysis.[76]

Periprocedural cranial nerve palsy

Data were available from one retrospective cohort study (N = 155)[108] and one large prospective registry that reported in-hospital events (N = 2761).[142] In the cohort study, all palsies were defined as mild/rapidly reversible, whereas the registry study defined them as persistent in nature. Across these two studies, no cases of cranial nerve palsy were reported following CAS compared with risks after CEA of 13.0% in the cohort and 1.1% in the registry; however, the differences between groups were not significant in any instance and confidence intervals were large. Similarly, no significant differences were reported between

groups in one administrative study analyzing 1086 patients (0.2% vs. 0%, respectively) using a propensity score matched analysis.[76]

Periprocedural bleeding complications

The risk of hematoma (requiring surgery) was reported by one retrospective cohort study (N = 155) with no significant differences found following CAS (0%) compared with CEA (1.1%).[108] One administrative database study (N = 1086) reported unspecified bleeding as a perioperative complication with no significant difference seen between groups, 3.3% versus 4.4%, respectively.[76]

Intracranial hemorrhage (ICH)

One administrative study analyzing the NIS database (N = 11,300) provided data for this outcome.[132] The incidence of any ICH was five and half times greater following CAS (4.4%) compared with CEA (0.8%) (RD = -3.6%, 95% CI, -4.9% to -2.6%; RR = 5.5, 95% CI, 3.9–7.6). When considering subcategories of ICH, the risk of both acute ICH and subarachnoid hemorrhage remained statistically significant between groups, 1.7% versus 0.4% (RD = -1.2%, 95% CI, -2.1% to -0.6%; RR = 3.8, 95% CI, 2.3–6.4) and 2.8% versus 0.3% (RD = -2.5%, 95% CI, -3.5% to -1.7%; RR = 8.3; 95% CI, 5.2–13.2), respectively, while risks of non-traumatic extradural hemorrhage and unspecified hemorrhage did not differ between groups.

Other complications

Unspecified cardiac complications were reported by one administrative database study (N = 1086) using a propensity score adjusted analysis and found no difference in risk between groups (CAS 5.5%; CEA 6.1%).[76] This same study also reported the risk of venous thromboembolism with no statistically significant difference seen following CAS (0.4%) compared with CEA (0 %).

Table 43. Summary of periprocedural risks of any stroke from nonrandomized studies comparing CAS with CEA for symptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 128	Any stroke	4.7 (2/44)	7.2 (6/84)	RD = 2.6 (-8.7 to 10.9) RR = 0.64 (0.13-3.02)
Iihara 2006 (Pro) N = 103	Any stroke	6.7 (2/30)‡	4.1 (3/73)‡	RD = -2.6 (-17.5 to 6.2) RR = 1.62 (0.29-9.22)
Brown 2008 (Retro) N = 75	Any stroke	2.9 (1/34)	2.4 (1/41)	RD = -0.5 (-12.6 to 9.9) RR = 1.21 (0.08-18.57)
Kastrup 2003 (Retro) N = 155	Any stroke	6.3 (4/63)	6.5 (6/92)	RD = 0.2 (-9.4 to 8.1) RR = 0.97 (0.29-3.31)
	Major stroke	3.2 (2/63)	3.3 (3/92)	RD = 0.1 (-7.9 to 6.4) RR = 0.97 (0.17-5.66)
	Minor stroke	3.2 (2/63)	3.3 (3/92)	RD = 0.1 (-7.9 to 6.4) RR = 0.97 (0.17-5.66)
Kastrup 2004§ (Retro) N = 99	Any stroke	10.0 (3/30)	2.9 (2/69)	RD = -7.1 (-22.9 to 2.5) RR = 3.45 (0.61-19.60)
	Major stroke	3.3 (1/30)	2.9 (2/69)	RD = -0.4 (-13.9 to 7.1) RR = 1.15 (0.11-12.20)
	Minor stroke	6.6 (2/30)	0 (0/69)	RD = -6.7 (-21.3 to 0.5) RR = not estimable
	Fatal stroke	0 (0/30)	0 (0/69)	RD = 0 (-11.4 to 5.3) RR = not estimable
Registry studies				
Jim 2012 (SVS-VR) (Pro) N = 3645	Any stroke	6.1 (95/1547)	4.1 (85/2098)	RD = -2.1 (-3.6 to -0.7) RR = 1.52 (1.14-2.02)
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital data)	Any stroke	5.1 (8/156)	1.4 (37/2605)	RD = -3.7 (-8.4 to -1.1) RR = 3.61 (1.71-7.62)
	Major stroke	2.6 (4/156)	0.6 (16/2605)	RD = -1.9 (-5.8 to -0.3) RR = 4.17 (1.41-12.33)
	Minor stroke	2.6 (4/156)	0.8 (21/2605)	RD = -1.8 (-5.6 to -0.1) RR = 3.18 (1.11-9.15)
Administrative data studies (in-hospital)				
McPhee 2008 (NIS) N = 10,496	Any stroke	4.1 (46/1116)	2.5 (235/9380)	RD = -1.6 (-3.0 to -0.5) RR = 1.65 (1.21-2.24)
McPhee 2007 (NIS) N = 20,691	Any stroke	4.2 (74/1757)	1.1 (208/18,934)	RD = -3.1 (-4.2 to -2.3) RR = 3.83 (2.95-4.98)
Giacovelli 2010 (NY & CA)** N = 1086	Any stroke	5.7 (31/543)	4.1 (22/543)	RD = -1.7 (-4.3 to 0.9) Adjusted RR = 1.41 (0.83-2.40)
Timaran 2009 (NIS) N = 10,727	Any stroke	5.0 (63/1257)	2.6 (246/9470)	RD = -2.4 (-3.8 to -1.3) RR = 1.93 (1.47-2.53)
Giles 2010 (NIS) N = 52,937	Any stroke	8.1 (603/7438)	4.6 (2099/45,499)	RD = -3.5 (-4.2 to -2.9) RR = 1.76 (1.61-1.92)
Rockman 2011 (NIS) N = 2844	Any stroke	5.0 (18/358)	2.6 (65/2486)	RD = -2.4 (-5.2 to -0.5) RR = 1.92 (1.15-3.20)
Bisdas 2012 (NY Department of Health)†† N = 4834	Any stroke	6.9 (32/466)	3.8 (167/4368)	RD = -3.0 (-5.8 to -1.0) Adjusted RR = 1.79 (1.25-2.59)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; SVS-VR: Society for Vascular Surgery Vascular Registry; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡All were non-disabling strokes.
§Study was in elderly patients aged ≥ 75 years.
**Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
††Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of symptomatic patients with the data provided.

Table 44. Summary of periprocedural risks of death from nonrandomized studies comparing CAS with CEA for symptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 128	All-cause death	0 (0/44)	1.3 (1/84)	RD = 1.2 (-6.9 to 6.4) RR = not estimable
Brown 2008 (Retro) N = 75	Death	0 (0/34)	0 (0/41)	RD = 0 (-10.2 to 8.6) RR = not estimable
Kastrup 2003 (Retro) N = 155	Death	1.6 (1/63)	0 (0/92)	RD = -1.6 (-8.5 to 2.6) RR = not estimable
Registry studies				
Jim 2012 (SVS-VR) (Pro) N = 3645	Death	2.0 (31/1547)	1.1 (23/2098)	RD = -0.9 (-1.8 to -0.1) RR = 1.83 (1.07-3.12)
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital data)	Death	1.3 (2/156)	0.2 (5/2605)	RD = -1.1 (-4.4 to -0.1) RR = 6.68 (1.31-34.15)
Administrative data studies (in-hospital)				
McPhee 2008 (NIS) N = 10,496	Death	4.6 (51/1116)	1.4 (131/9380)	RD = -3.2 (-4.6 to -2.1) RR = 3.27 (2.38-4.49)
McPhee 2007 (NIS) N = 20,691	Death	7.5 (132/1757)	1.0 (189/18,934)	RD = -6.5 (-7.8 to -5.4) RR = 7.53 (6.06-9.35)
Giacovelli 2010 (NY & CA)‡ N = 1086	Death	3.7 (20/543)	1.3 (7/543)	RD = -2.4 (-4.4 to -0.5) Adjusted RR = 2.86 (1.22-6.70)
Timaran 2009 (NIS) N = 10,727	Death	4.6 (58/1257)	1.4 (133/9470)	RD = -3.2 (-4.5 to -2.2) RR = 3.29 (2.43-4.45)
McDonald 2011 (NIS) N = 11,300	Death	6.2 (78/1251)	4.0 (402/10,049)	RD = -2.2 (-3.8 to -1.0) RR = 1.56 (1.23-1.97)
Giles 2010 (NIS) N = 52,937	Death	6.0 (448/7438)	1.8 (814/45,499)	RD = -4.2 (-4.8 to -3.7) RR = 3.37 (3.01-3.77)
Rockman 2011 (NIS) N = 2844	Death	6.1 (22/358)	2.5 (61/2486)	RD = -3.7 (-6.7 to -1.5) RR = 2.50 (1.56-4.03)
Bisdas 2012 (NY Department of Health)§ N = 4834	Death	4.1 (19/466)	0.89 (39/4368)	RD = -3.2 (-5.4 to -1.7) Adjusted RR = 4.57 (2.66-7.84)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; SVS-VR: Society for Vascular Surgery Vascular Registry; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.

‡Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
§Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of symptomatic patients with the data provided.

Table 45. Summary of periprocedural risks of any stroke or death from nonrandomized studies comparing CAS with CEA for symptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) Prospective N = 128	Any stroke or death	4.7 (2/44)	7.2 (6/84)	RD = 2.6 (-8.7 to 10.9) RR = 0.64 (0.13-3.02)
De Rango 2011 (Pro) N = 684	Any stroke or death	4.5 (12/268)	2.9 (12/416)	RD = -1.6 (-5.0 to 1.2) RR = 1.55 (0.71-3.40)
Bosiers 2005 (Retro) N = 213	Any stroke or death	2.6 (4/153)	3.3 (2/60)	RD = 0.7 (-3.9 to 8.9) RR = 0.78 (0.15-4.17)
Brown 2008 (Retro) N = 75	Any stroke or death	2.9 (1/34)	2.4 (1/41)	RD = -0.5 (-12.6 to 9.9) RR = 1.21 (0.08-18.57)
Kastrup 2003 (Retro) N = 155	Any stroke or death	7.9 (5/63)	6.5 (6/92)	RD = -1.4 (-11.4 to 6.9) RR = 1.22 (0.39-3.82)
Registry studies				
Lindstrom 2012 (Swedvasc) (Pro) N = 5149	Any stroke or death	4.9 (7/142)	4.4 (220/5007)	RD = -0.5 (-5.5 to 2.1) RR = 1.12 (0.54-2.34)
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital data)	Any stroke or death	5.1 (8/156)	1.6 (42/2605)	RD = -3.5 (-8.2 to-0.9) RR = 3.18 (1.52-6.66)
Administrative data studies (in-hospital)				
Giacovelli 2010 (NY & CA)‡ N = 1086	Any stroke or death	8.3 (45/543)	4.6 (25/543)	RD = -3.7 (-6.7 to -0.8) Adjusted RR = 1.80 (1.12-2.89)
Giles 2010 (NIS) N = 52,937	Any stroke or death	13.1 (973/7438)	5.9 (2698/45,499)	RD = -7.2 (-8.0 to -6.4) RR = 2.21 (2.06-2.36) Adjusted OR = 2.6 (2.1-3.2)§
Bisdas 2012 (NY Department of Health)** N = 4834	Any stroke or death	9.7 (45/466)	4.3 (187/4368)	RD = -5.4 (-8.4 to -2.9) Adjusted RR = 2.26 (1.65-3.08)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; Swedvasc: Swedish Vascular Registry; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.
§Adjusted for age and sex; odds ratio as reported by authors.
**Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of symptomatic patients with the data provided.

Table 46. Summary of periprocedural risks of myocardial infarction (MI) from nonrandomized studies comparing CAS with CEA for symptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Clinical studies				
Zarins 2009 (CaRESS) (Pro) N = 128	MI	0 (0/44)	0 (0/84)	RD = 0 (-8.0 to 4.4) RR = not estimable
Kastrup 2003 (Retro) N = 155	MI	0 (0/63)	0 (0/92)	RD = 0 (-5.7 to 4.0) RR = not estimable
Registry studies				
Jim 2012 (SVS-VR) (Pro) N = 3645	MI	1.4 (21/1547)	1.3 (27/2098)	RD = -0.1 (-0.9 to 0.7) RR = 1.05 (0.60-1.86)
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital data)	MI	1.3 (2/156)	1.3 (34/2605)	RD = 0 (-3.3 to 1.1) RR = 0.98 (0.24-4.05)
Administrative data studies (in-hospital)				
McPhee 2007 (NIS) N = 20,691	MI	2.2 (39/1757)	2.0 (379/18,934)	RD = -0.2 (-1.0 to 0.4) RR = 1.11 (0.80-1.54)
Bisdas 2012 (NY Department of Health)‡ N = 4834	MI	2.2 (10/466)	1.1 (49/4368)	RD = -1.0 (-2.8 to 0.0) Adjusted RR = 1.91 (0.98-3.75)

CaRESS: Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; SVS-VR: Society for Vascular Surgery Vascular Registry; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Propensity score matched analysis. Outcomes were adjusted for patients' demographics, co-morbidities and hospital annual volume in CAS and CEA. The primary focus of the article was on sex difference so the results were reported stratified by symptom status and sex (males + females matched by propensity score). We were able to calculate risk for each outcome for the total population of symptomatic patients with the data provided.

Table 47. Summary of periprocedural risks of ipsilateral stroke and transient ischemic attack (TIA) from nonrandomized studies comparing CAS with CEA for symptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size* RD % (95% CI)† RR (95% CI)
		CAS % (n/N)	CEA % (n/N)	
Ipsilateral stroke				
Registry studies				
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital data)	Ipsilateral stroke	3.9 (6/156)	1.2 (31/2605)	RD = -2.7 (-7.0 to -0.5) RR = 3.23 (1.37-7.63)
TIA				
Clinical studies				
Brown 2008 (Retro) N = 75	TIA	2.9 (1/34)	2.4 (1/41)	RD = -0.5 (-12.6 to 9.9) RR = 1.21 (0.08-18.57)
Registry studies				
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital data)	TIA	0.7 (1/156)	0.6 (16/2605)	RD = 0 (-2.9 to 0.6) RR = 1.04 (0.14-7.82)
Administrative data studies (in-hospital)				
Giacovelli 2010 (NY & CA)‡ N = 1086	TIA	0.41 (2/543)	0.26 (1/543)	RD = -0.2 (-1.2 to 0.7) Adjusted RR = 2.00 (0.18 to 21.99)

CAS: carotid artery stenting; CEA: carotid endarterectomy; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.

Table 48. Summary of periprocedural (30-day) risks of other complications from nonrandomized studies comparing CAS with CEA for symptomatic carotid stenosis.

Study (N)	Outcome	Patients with outcome		Effect Size*
		CAS % (n/N)	CEA % (n/N)	RD % (95% CI)† RR (95% CI)
Cranial nerve injury or palsy				
Clinical studies				
Kastrup 2003 (Retro) N = 155	Cranial nerve palsy (mild and rapidly reversible)	0 (0/63)	13.0 (12/92)	RD = 13.0 (5.1-21.4) RR = not estimable
Registry studies				
Nolan 2012 (VSGNE) (Pro) N = 2761 (in-hospital)	Cranial nerve palsy (persistent)	0 (0/156)	1.1 (29/2605)	RD = 1.1 (-1.3 to 1.6) RR = not estimable
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)‡ N = 1086	Cranial nerve palsy	0.18 (1/543)	0 (0/543)	RD = -0.2 (-1.0 to 0.5) Adjusted RR = not estimable
Bleeding complications				
Clinical studies				
Kastrup 2003 (Retro) N = 155	Hematoma (requiring surgery)	0 (0/63)	1.1 (1/92)	RD = 1.1 (-4.7 to 5.9) RR = not estimable
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)‡ N = 1086	Unspecified bleeding	3.3 (18/543)	4.4 (24/543)	RD = 1.1 (-1.2 to 3.5) Adjusted RR = 0.75 (0.53-1.90)
Intracranial hemorrhage				
Administrative studies (in-hospital)				
McDonald 2011 (NIS) N = 217,596	Any ICH	4.4 (55/1251)	0.8 (81/10,049)	RD = -3.6 (-4.9 to -2.6) RR = 5.45 (3.89-7.64)
	Acute ICH	1.7 (21/1251)	0.4 (44/10,049)	RD = -1.2 (-2.1 to -0.6) RR = 3.83 (2.29-6.43)
	Subarachnoid hemorrhage	2.8 (35/1251)	0.3 (34/10,049)	RD = -2.5 (-3.5 to -1.7) RR = 8.27 (5.18-13.21)
	Nontraumatic extradural hemorrhage	0 (0/1251)	0 (0/10,049)	RD = 0 (-0.3 to 0) RR = not estimable
	Unspecified ICH	0.1 (1/1251)	0.03 (3/10,049)	RD = -0.1 (-0.4 to 0) RR = 2.68 (0.28-25.72)
Other cardiac complications				
Administrative studies (in-hospital)				
Giacovelli 2010 (NY & CA)‡ N = 1086	Cardiac complication, not otherwise classified	5.5 (30/543)	6.1 (33/543)	RD = 0.6 (-2.3 to 3.4) Adjusted RR = 0.91 (0.56-1.47)
	Venous thromboembolism	0.37 (2/543)	0 (0/543)	RD = -0.4 (-1.3 to 0.4) Adjusted RR = not estimable

CAS: carotid artery stenting; CEA: carotid endarterectomy; NIS: National Inpatient Sample; NY & CA: New York and California discharge data; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR = relative risk; VSGNE: Vascular Study Group of New England.
*Calculated from raw data by Spectrum Research unless otherwise indicated.
†A positive risk difference favors CAS and negative risk difference favors CEA.
‡Propensity score-matched analysis. Outcomes adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity.

4.4. Key Question 4: Differential Efficacy, Effectiveness and Safety in Special Populations

Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other comorbidities, ethnicity, or disability)?

4.4.1. Asymptomatic

Summary results: Asymptomatic patients

CAS versus medical therapy alone: No RCT data were available. Differential effectiveness was evaluated in one retrospective cohort study which explored the severity of ipsilateral stenosis as a potential factor.[163]

- **Severity of ipsilateral stenosis:** One retrospective cohort study of 946 asymptomatic patients may suggest that stroke risk be (through a median of 25 months follow-up) increased with the degree of stenosis in the medical therapy group but remained stable in those treated with CAS, however no formal statistical evaluation was provided

CAS compared with CEA: Differential efficacy, effectiveness and safety were evaluated. One RCT (CREST) was available to evaluate differential safety outcomes.[94] In addition, one prospective cohort study,[96] one registry study[102] and five administrative database studies[39,77,111,132,187] are included in this report. Data from one trial (SAPPHIRE)[87,183] of asymptomatic high surgical risk patients were also included, however, no direct comparison with standard surgical risk patients could be made.

- **Age:** No RCT data were available. Data from one registry study of 5268 asymptomatic patients suggested that age (< 65 versus ≥ 65) did not modify the treatment effect of CEA versus CAS in terms of periprocedural death, stroke, or MI, or the composite outcome of periprocedural death, stroke, or MI. Data from three administrative database studies are also provided for additional context, some of which find that age may modify treatment effect.

- **Sex:** One RCT was available (CREST) and showed that patient sex did not modify treatment effect in terms of various periprocedural or four-year outcomes as evaluated in 1321 asymptomatic patients. Data from administrative database studies suggested that sex did not modify the treatment effect of CEA versus CAS in terms of in-hospital death, stroke, or MI, or the composite outcome of periprocedural death or stroke in asymptomatic patients.

- **Surgical risk:** Efficacy data from the SAPPHIRE trial of 237 asymptomatic high surgical patients undergoing CAS versus CEA suggested these patients had similar risks of stroke through 3 years or the composite outcome ipsilateral stroke or death through 3 years regardless of treatment received. Efficacy data from the same trial suggested that high surgical risk patients had lower rates of ipsilateral stroke or death through 1 year follow-up when they had been randomized to receive CAS. Safety data from the same trial suggested these patients had similar risks of the composite outcome of periprocedural death, stroke, or MI regardless of treatment received. Data from one prospective cohort study and one administrative database study are also provided. As this trial did not compare treatment outcomes between high surgical risk patients and standard/average risk patients, no conclusions regarding the extent to which surgical risk differentially influences outcomes can be made.

Detailed results: Asymptomatic patients

CAS versus medical therapy alone: No RCT data were available. Differential effectiveness was evaluated in one retrospective cohort study.[163]

Severity of ipsilateral stenosis

Data from one retrospective cohort study of 946 asymptomatic patients may suggest that stroke risk through a median of 25 months follow-up increased with the degree of stenosis in the medical therapy group but remained stable in those treated with CAS. Sherif et al (2005)[163] found (after adjusting for potentially confounding variables) that CAS patients had a similar stroke risk irrespective of the severity of ipsilateral stenosis (i.e., 70-79%, 80-89%, or 90-99%). In contrast, patients who received conservative medical therapy and had 80-89% or 90-99% stenosis were found to have a significantly higher risk of stroke than those with 70-79% stenosis. The authors concluded that stroke risk increased with the degree of stenosis in the medical therapy group but remained stable in those treated with CAS. No formal

evaluation of statistical interaction was presented, however and raw data were not available. See Table 1 in Appendix G that summarizes findings from the study.

CAS compared with CEA: Differential efficacy, effectiveness and safety were evaluated. One RCT (CREST) was available to evaluate differential safety outcomes.[94] In addition, one prospective cohort study,[96] one registry study[102] and five administrative database studies[39,77,111,132,187] are included in this report. Data from one trial of asymptomatic high risk patients were also included, however, no direct comparison with average risk patients could be made.[87,183]

Age: No RCT data were available. Data from one registry study of 5268 asymptomatic patients suggested that age (< 65 versus ≥ 65) did not modify the treatment effect of CEA versus CAS in terms of periprocedural death, stroke, or MI, or the composite outcome of periprocedural death, stroke, or MI. Data from three administrative database studies are also provided for additional context, some of which find that age does modify treatment effect. Tables 3-4 in the Appendix G summarize findings from individual studies.

Registry studies (1 study). Analyses from one registry study for periprocedural outcomes were available. Jim et al reported data from a registry study of 5268 asymptomatic patients, and the test for interaction between subgroups showed that age (< 65 years versus ≥ 65 years) did not modify treatment effect for death, stroke, MI or the composite of death, stroke or MI.[102] It is noted that for MI, effects for the groups tend toward the opposite directions and there is less overlap of confidence intervals. Small numbers of events in the <65 year old group may contribute to lack of statistical significance for tests of interaction. Detailed data are found in Appendix G, Table 3.

30-day Death	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	1.4% (6/428)	0.8% (6/762)	1.78 (0.58, 5.49) P=0.32	NS	*P* = 0.71
≥ 65 years of age	1.6% (23/1422)	0.7% (19/2656)	2.26 (1.24, 4.14) P=0.008	CEA	

30-day Stroke	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	2.3% (10/428)	1.3% (10/762)	1.78 (0.75, 4.24) P=0.19	NS	*P* = 0.89
≥ 65 years of age	3.5% (49/1422)	1.8% (48/2656)	1.91 (1.29, 2.82) P=0.001	CEA	

30-day MI	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	1.2% (5/428)	0.4% (3/762)	2.97 (0.71, 12.36) P=0.14	NS	*P* = 0.12
≥ 65 years of age	1.1% (15/1422)	1.2% (32/2656)	0.88 (0.48, 1.61) P=0.67	NS	

30-day Death, stroke, or MI	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	4.4% (19/428)	2.1% (16/762)	2.11 (1.10, 4.07) P=0.02	CEA	*P* = 0.44
≥ 65 years of age	5.3% (75/1422)	3.3% (88/2656)	1.59 (1.18, 2.15) P=0.002	CEA	

Administrative database studies (3 studies). Two administrative database studies evaluated whether age modified the treatment effect for the individual outcomes of in-hospital stroke or in-hospital death.[111,132] One administrative database study assessed whether age modified the outcome of in-hospital cardiac complications.[111] Three administrative database studies reported the effects of age on the composite outcome of in-hospital death, stroke, or cardiac complications.[111,187] Detailed data are available in Appendix G, Table 4.

- *In-hospital death.* Khatri et al (2012)[111] reported that regarding in-hospital death, in patients aged less than 70 years CEA was favored and those who were 70 years or older had no difference in their risk of in-hospital death between treatment groups. In contrast, McDonald et al (2011)[132] found that age (< 70 years versus ≥ 70 years) did not modify treatment effect in terms of in-hospital death.
- *In-hospital stroke.* Khatri et al (2012)[111] reported that regarding in-hospital stroke, that both age subgroups (< 70 years versus ≥ 70 years) favored CEA, however, age was found to modify treatment effect in terms such that patients aged 70 years or older had a greater magnitude of benefit with CEA compared with those under 70 years of age. In contrast, McDonald et al (2011)[133] found that age (< 70 years versus ≥ 70 years) did not modify treatment effect in terms of in-hospital stroke.
- *In-hospital cardiac complications.* Khatri et al (2012)[111] reported that regarding in-hospital cardiac complications, that both age subgroups (< 70 years versus ≥ 70 years) favored CEA, however, age was found to modify treatment effect in terms such that patients aged 70 years or older had a greater magnitude of benefit with CEA compared with those under 70 years of age.

- *In-hospital composite outcome.* Neither Khatri et al (2012)[111] nor Young et al (2011)[187] found that age modified treatment effect in terms of in-hospital death, stroke, or cardiac complications (Khatri: < 70 years versus ≥ 70 years; Young: ≤ 79 years versus ≥ 80 years).

Sex: One RCT was available (CREST)[94] and showed that patient sex did not modify treatment effect in terms of various periprocedural or four-year outcomes as evaluated in 1321 asymptomatic patients. Data from administrative database studies suggested that sex did not modify the treatment effect of CEA versus CAS in terms of in-hospital death, stroke, or MI, or the composite outcome of periprocedural death or stroke in asymptomatic patients.

Analyses from RCTs

4-years (1 RCT). As part of the CREST trial, sex was prespecified for subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke or the composite outcome of 4-year stroke or death following CAS (n = 594) compared with CEA (n = 587) in asymptomatic patients. Raw data were not provided, however the study provided hazard ratios and interaction p-values. In all cases, the results suggested that sex did not modify treatment outcome.[94]

4-year Ipsilateral Stroke*	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.08 (0.45, 2.62)	NS	*P* = 0.83
Male	NR	NR	1.24 (0.65, 2.39)	NS	

* includes any stroke, death, or MI during the periprocedural period

4-year Ipsilateral Stroke*	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.59 (0.53, 4.75)	NS	*P* = 0.71
Male	NR	NR	2.16 (0.91, 5.10)	NS	

* includes any stroke during the periprocedural period

4-year Any stroke or death	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.59 (0.53, 4.75)	NS	*P* = 0.71
Male	NR	NR	2.16 (0.91, 5.10)	NS	

* includes any stroke or death during the periprocedural period

Periprocedural outcomes (1 RCT). As part of the CREST trial, sex was prespecified for subgroup analyses to determine whether it modified the following outcomes: periprocedural stroke; periprocedural MI; the composite outcome of stroke or death; or the composite outcome of periprocedural stroke, death, or MI following CAS (n = 594) compared with CEA (n = 587) in asymptomatic patients. Raw data were not provided,

however the study provided hazard ratios and interaction p-values. In all cases, the results suggested that sex did not modify treatment outcome.[94]

Periprocedural Any Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	2.11 (0.55, 8.15)	NS	*P* = 0.82
Male	NR	NR	1.75 (0.57, 5.37)	NS	

Periprocedural Any Stroke or Death	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	2.11 (0.55, 8.15)	NS	*P* = 0.82
Male	NR	NR	1.75 (0.57, 5.37)	NS	

Periprocedural MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	0.67 (0.15, 3.01)	NS	*P* = 0.74
Male	NR	NR	0.48 (0.15, 1.56)	NS	

Periprocedural Any Stroke, Death, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.18 (0.44, 3.16)	NS	*P* = 0.72
Male	NR	NR	0.93 (0.43, 2.01)	NS	

Analyses from nonrandomized studies

Administrative database studies (2 studies). Two administrative database studies evaluated whether sex modified the treatment effect for the individual outcomes of in-hospital death or in-hospital stroke. [39,187] One administrative database study assessed whether sex modified the outcome of in-hospital cardiac complications or the composite outcome of in-hospital death or stroke.[39] In no case did sex significantly modify treatment effect. Further details are available in Appendix G, Table 4.

Surgical risk: Efficacy data from the SAPPHIRE trial of 237 asymptomatic high surgical patients undergoing CAS versus CEA suggested these patients had similar risks of stroke through 3 years or the composite outcome ipsilateral stroke or death through 3 years regardless of treatment received. Efficacy data from the same trial suggested that high surgical risk patients had lower rates of ipsilateral stroke or death through 1 year follow-up when they had been randomized to receive CAS. Safety data from the same trial suggested these patients had similar risks of the composite outcome of periprocedural death, stroke, or MI regardless of treatment received. Data from one prospective cohort study and one

administrative database study are also provided. Detailed data are available in Appendix G, Tables 5-7.

Analyses from RCTs

The SAPPHIRE trial[87,183] evaluated CAS versus CEA for 237 asymptomatic high surgical risk patients, which included at least one of the following characteristics: clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery); severe pulmonary disease; contralateral carotid occlusion; contralateral laryngeal-nerve palsy; previous radical neck surgery or radiation therapy to the neck; recurrent stenosis after endarterectomy; or age > 80 years. The study did not include any patients considered to be at average surgical risk, thus we cannot directly compare outcomes for high- versus average surgical risk within this study. However, the results will be placed in context with those from KQ1 and KQ3, as appropriate. Details are available in Appendix G, Table 7.

3-year stroke. Grum et al (2008) found that asymptomatic high surgical risk patients had no differences in three year stroke risk following treatment with either CAS or CEA.[87]

3-year Stroke	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	10.3% (12/117)	9.2% (11/120)	-2% (-9%, 4%) 0.74 (0.34, 1.62)	NS

Regarding similar results found in studies of asymptomatic average risk patients, two RCTs (CREST and Kentucky) reported stroke at 4 years follow-up. The CREST trial[48] reported no difference in the risk of ipsilateral stroke through four years for CAS versus CEA, with a risk difference of 1.9% (95% CI, -0.5%, 4.3%). The Kentucky RCT reported zero events for both treatment groups.[46] See Key Question 1 for additional details.

3-year ipsilateral stroke or death. Grum et al (2008) also reported that asymptomatic high surgical risk patients treated with CAS versus CEA had similar risks of the composite outcome of ipsilateral stroke or death at three years.[87]

3-year Ipsilateral stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	21.4% (25/117)	29.2% (35/120)	-8% (-19%, 3%) 0.73 (0.47, 1.14)	NS

Regarding similar results found in studies of asymptomatic average risk patients, one RCT (CREST) evaluated stroke or death through 4 years following CAS versus CEA and found no difference between treatment groups in this outcome, with a risk difference of 1.9% (95% CI, -0.5%, 4.3%).[48] See Key Question 1 for additional details.

1-year ipsilateral stroke or death. Data from the Yadav et al (2004) study of the SAPPHIRE trial suggest that asymptomatic patients treated with CAS had a significantly lower risk of ipsilateral stroke or death at one year follow-up compared with patients who received CEA.[183]

1-year Ipsilateral stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	9.9% (12/117)	21.5% (26/120)	-11% (-21%, -2%) 0.47 (0.25, 0.89)	CAS

No 1-year efficacy data were found for asymptomatic average surgical risk patients. See Key Question 1 for additional details.

Periprocedural (1 RCT). Yadav et al found similar rates of periprocedural death, stroke, or MI following CAS and CEA in asymptomatic patients.[183]

Periprocedural Death, Stroke, or MI	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	5.4% (6/117)	10.2% (12/120)	-5% (-12%, 2%) 0.51 (0.20, 1.32)	NS

No safety data for periprocedural death, stroke, or MI were found for asymptomatic average surgical risk patients. See Key Question 3 for additional details.

Analyses from nonrandomized studies

Cohort studies (1 study). Iihara et al. (2006)[96] conducted a prospective cohort study and found that CEA risk grades (I, II, or III) did not significantly modify treatment effect following CAS versus CEA in terms of periprocedural non-disabling stroke in 106 asymptomatic patients. (Appendix G, Table 5)

Administrative database studies (1 study). One administrative database suggested that surgical risk modified the treatment effect for in-hospital stroke, in-hospital death, or the composite outcome of in-hospital death or stroke in 486,021 asymptomatic patients.

Giles et al (2010)[77] In terms of in-hospital death, patients at low surgical risk had a statistically lower rate of in-hospital death following CEA while those at high surgical risk didn't favor either treatment group. For in-hospital stroke or the composite outcome of in-hospital death or stroke, the study found that both treatment groups favored CEA, though patients in the low surgical risk group favored CEA to a greater magnitude than high surgical risk patients. Further details are available in Appendix G, Table 6.

4.4.2. Symptomatic

Summary: Symptomatic patients

CAS versus medical therapy only: No studies found.

CAS compared with CEA: Differential efficacy, effectiveness and safety were evaluated. Patient-level data were available for age and sex for six trials (Leicester, EVA-3S, SPACE, BACASS, ICSS, and CREST) as reported in the Bonati systematic review.[41] Otherwise, four trials were included (EVA-3S, SPACE, ICSS, and CREST).[63,65,91,94,129,171] In addition, one prospective cohort study,[96] one registry study[102] and four administrative database studies[39,77,132,155] were included in this report. Data from one trial of symptomatic high risk patients were also included, however, no direct comparison with average risk patients could be made.[87,183]

- **Age:** A meta-analysis of patient-level safety data from five RCTs suggested that age (< 70 versus ≥ 70 years) may modify treatment outcome in terms of the composite outcome of periprocedural stroke or death such that patients 70 years of age and older favor CEA while those under 70 years of age had similar results regardless of treatment group. Pooled estimates and test for subgroup differences from sensitivity analysis (which excluded older studies, those with ≤ 10 per treatment arm and those that did not use EPDs as previously described, leaving EVA-3S, SPACE and ICSS in the analysis), indicate that age modifies the effect of treatment. With regard to risk of periprocedural death or stroke, CEA is favored in those age ≥ 70 years old. Efficacy data from the three trials above were also available. While data from two trials suggested that age (< 70 versus ≥ 70 years) did not modify treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ICSS) or in terms of ipsilateral stroke through four years (EVA-3S), data from one trial suggested that age (< 68 versus ≥ 68 years) significantly modified treatment outcome in terms of the composite outcome of ipsilateral stroke or death through 2 years (SPACE) such that patients 68 years of age and older had significantly better outcomes following

CEA, while those under 68 years of age had similar outcomes regardless of treatment received. Safety data from one registry study reported that age did not modify treatment effect in terms of periprocedural death, stroke, MI, or in terms of the composite outcome of periprocedural death, stroke, or MI. Data from one administrative database study are included to provide additional context.

- **Sex:** A meta-analysis of patient-level safety data from six RCTs suggested that sex did not significantly modify treatment outcome in terms of the composite outcome of periprocedural stroke or death. Pooled estimates and test for subgroup differences from sensitivity analysis reaffirms that there is no modification of treatment effect by sex for the outcome of periprocedural death or stroke. One RCT reported similar outcomes for periprocedural stroke or periprocedural MI but found that sex did modify treatment outcome in terms of the composite outcome of periprocedural stroke, death, or MI such that females had significantly better results following CEA while males had similar results regardless of treatment received. Efficacy data from four trials were also available. Results suggested that sex did not modify treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ICSS) or for the composite outcome of death or ipsilateral stroke through two years (SPACE). Similarly, combined efficacy data from two trials suggested that sex did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S, CREST). Data from the CREST trial also suggested that sex did not modify treatment outcome in terms of the composite outcome of 4-year stroke or death. Data from two administrative database studies are included to provide additional context.

- **Diabetes:** Efficacy data from two trials were available, and both suggested that diabetes status did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S) or for the composite outcome of death, stroke, or MI through 120 days (ICSS).

- **Type of symptomatic qualifying event:** Efficacy data from two trials were available and suggested that type of symptomatic qualifying event (i.e., stroke, transient ischemic attack, ocular, or multiple events) did not modify treatment outcome in terms of ipsilateral stroke through four years (EVA-3S) or for the composite outcome of death or ipsilateral stroke through two years (SPACE). Safety data from one trial suggested that type of symptomatic qualifying event not modify treatment outcome in terms of periprocedural stroke or the composite outcome of periprocedural ipsilateral stroke or death (CREST).

- **Severity of ipsilateral stenosis:** Efficacy data from three trials were available, and results suggested that severity of stenosis in the ipsilateral artery did not modify

treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ipsilateral stenosis of 50-69% versus 70-99%), the composite outcome of death or ipsilateral stroke through two years (ipsilateral stenosis of < 70% versus ≥ 70%) (SPACE), ipsilateral stroke through 4 years (ipsilateral stenosis of < 90% versus ≥ 90%) (EVA-3S).

- **Severity of contralateral stenosis:** Safety data from one trial suggested severity of stenosis in the contralateral artery did not modify treatment outcome in terms of the composite outcome of periprocedural ipsilateral stroke or death (SPACE). Efficacy data from three trials were available, and results suggested that severity of stenosis in the contralateral artery did not modify treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ICSS), the composite outcome of death or ipsilateral stroke through two years (ipsilateral stenosis of < 70% versus 70-99% versus 100%) (SPACE), or for ipsilateral stroke through 4 years (contralateral stenosis of < 70% versus 70-100%) (EVA-3S).

- **Time to treatment:** Efficacy data from two trials were available, and results suggested that time to treatment (< 14 days versus ≥ 14 days) did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S) or for the composite outcome of death, stroke, or MI through 120 days (ICSS).

- **Hypertension:** Efficacy data from two trials were available. Data from the ICSS trial suggested that hypertensive status at baseline does modify the treatment effect in terms of the composite outcome of 120 day death, stroke or MI, such that patients without treated hypertension favor CEA while those without treated hypertension have similar outcomes regardless of treatment group. Data from the EVA-3S trial suggested that baseline hypertensive status did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S).

- **Smoking status:** Efficacy data from one trial were available, and results suggested baseline smoking status did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S).

- **Surgical risk:** Efficacy data from the SAPPHIRE trial of 96 symptomatic high surgical risk patients undergoing CAS versus CEA suggested these patients had similar risks of stroke through 3 years, the composite outcome ipsilateral stroke or death through 3 years, and ipsilateral stroke or death through 1 year regardless of treatment received. Safety data from the same trial suggested these patients had similar risks of the composite outcome of periprocedural death, stroke, or MI regardless of treatment received. As stated previously, since this trial did not include

and compare treatment outcomes from standard/average risk patients, direct comparisons cannot be made. Safety data from one prospective cohort study and one administrative database study are provided in the detailed results, and in general demonstrated that surgical risk did not modify treatment outcomes. Data from one cohort study also suggested that CEA risk grades did not modify outcome in terms of periprocedural non-disabling stroke.

Detailed results: Symptomatic patients

Differential efficacy, effectiveness and safety were evaluated. Patient-level data were available for age and sex for six trials (Leicester, EVA-3S, SPACE, BACASS, ICSS, and CREST) as reported in the Bonati systematic review.[41] Otherwise, four trials were included (EVA-3S, SPACE, ICSS, and CREST).[63,65,91,94,129,171] In addition, one prospective cohort study,[96] one registry study[102] and four administrative database studies[39,77,132,155] were included in this report. Data from one trial of symptomatic high risk patients were also included, however, no direct comparison with average risk patients could be made.[87,183]

CAS versus CEA

Age: A meta-analysis of patient-level safety data from 5 RCTs suggested that age (< 70 versus ≥ 70 years) may modify treatment outcome in terms of the composite outcome of periprocedural stroke or death such that patients 70 years of age and older favor CEA while those under 70 years of age had similar results regardless of treatment group. To explore heterogeneity, sensitivity analyses which excluded studies older studies that enrolled patients prior to 2000, those with ≤ 10 patients per arm and/or did not use embolic protection devices was done, leaving trials in the analysis (EVA-3S, SPACE and ICSS). Pooled estimates and test for subgroup differences from sensitivity analysis (which excluded older studies, those with ≤ 10 per treatment arm and those that did not use EPDs as previously described), indicate that age modifies the effect of treatment. With regard to risk of periprocedural death or stroke, CEA is favored in those age ≥ 70 years old. Efficacy data from the three trials as published were also available. While data from two trials suggested that age (< 70 versus ≥ 70 years) did not modify treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ICSS) or in terms of ipsilateral stroke through four years (EVA-3S), data from one trial suggested that age (< 68 versus ≥ 68 years) significantly modified treatment outcome in terms of the composite outcome of ipsilateral stroke or death through 2 years (SPACE) such that patients 68 years of age and older had significantly better outcomes following CEA, while those under 68 years of age had similar outcomes regardless of treatment received. Safety data from one registry study reported that age did not modify treatment effect in terms of periprocedural death, stroke, MI, or in terms of the composite

outcome of periprocedural death, stroke, or MI. Data from one administrative database study are included to provide additional context.

Analyses from RCTs.

Periprocedural (meta-analysis of 5 RCTs and sensitivity analysis of 3): For the composite outcome of periprocedural stroke or death, age may modify the treatment effect such that patients 70 years of age and older favor CEA while those under 70 years of age had similar results regardless of treatment group. The Cochrane systematic review provided patient level data for periprocedural death or any stroke according to age for four trials (EVA-3S 2006, SPACE 2006, BACASS 2008, and ICSS 2010) and also included published data on the Leicester trial.[41] Overall, the test for subgroup differences suggests that age may significantly modify treatment outcomes in terms of 30 day death or stroke rates. Although there was no difference in treatment outcomes for patients under the age of 70, patients 70 years of age and older tended towards a higher 30 day death or stroke risk when treated with CAS, although there was some overlap in the 95% confidence intervals between treatment groups regardless of whether risk difference (test for subgroup differences: $P = 0.07$) or risk ratio risk difference (test for subgroup differences: $P = 0.04$) was calculated (Figure 18). No data were available from RCTs to evaluate whether there was differential efficacy based on age for other periprocedural (e.g. death or stroke separately) outcomes.

Periprocedural Death or Stroke	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Age: < 70 years	5.5% (48/876)	4.9% (42/852)	0.56% (-1.55%, 2.6%) 1.14 (0.70, 1.84)	NS NS	*P* = 0.07 (RD) *P* = 0.04 (RR)
Age: ≥70 years	10.9% (94/866)	4.9% (43/876)	8.28% (0.14%, 16.4%) 2.14 (1.47, 3.10)	CEA CEA	

Figure 18. Results of meta-analysis and sensitivity analysis of CAS versus CEA for symptomatic carotid stenosis: periprocedural death or any stroke according to age.

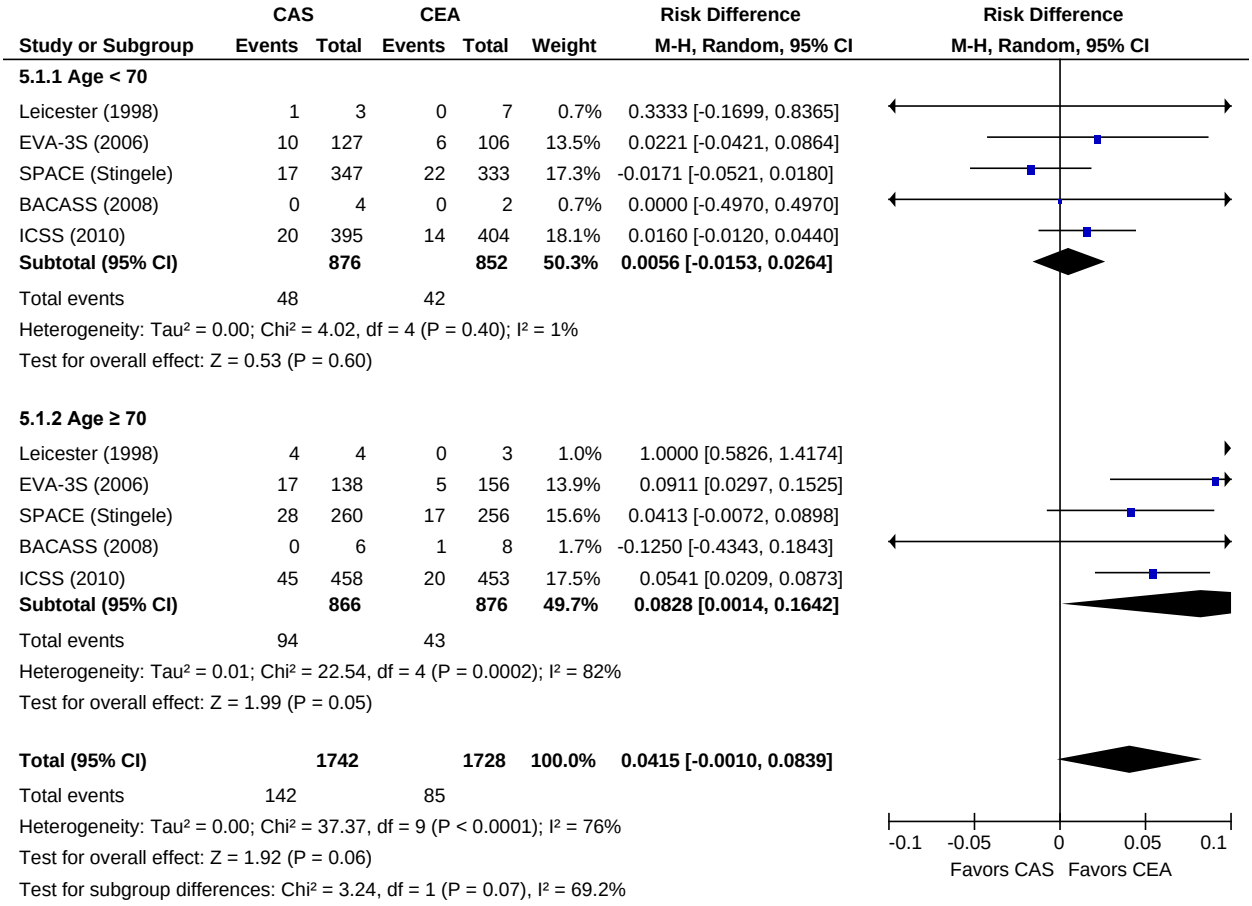
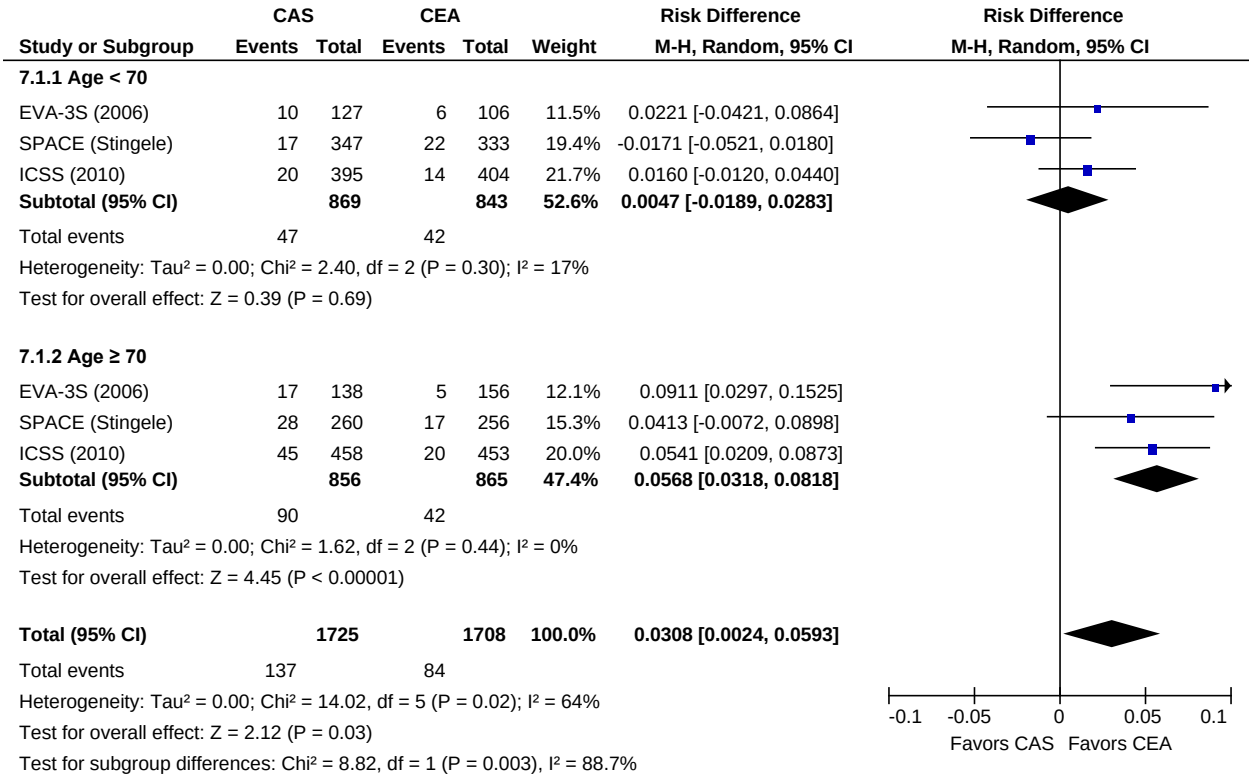


Figure 18 cont.
Sensitivity analysis



120 days (1 RCT): As part of the ICSS trial of 1713 symptomatic patients, age was predefined as a subgroup for which exploratory analysis would be conducted.[65] Overall, Ederle et al. (2010) found that age (< 70 versus ≥ 70 years) does not modify the treatment effect in terms of 120 day death, stroke, or MI. Additional details are available in Appendix G, Table 10.

120-day Death, Stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-value
Age: < 70 years	NR	NR	1.46 (0.75, 2.84)	NS	*P* = 0.62
Age: ≥70 years	NR	NR	1.79 (1.14, 2.83)	NS	

2-years (1 RCT). The SPACE trial of 1214 symptomatic patients prespecified a few subgroup analyses, and a follow-up paper reported subgroup analyses of 2-year ipsilateral stroke or death.[63] Overall, the subgroup analysis reported by Eckstein et al. (2008) suggested that age may significantly modify the treatment effect ($P \leq .006$) such that patients 68 years of age and older had significantly better outcomes following CEA, while those under 68 years of age had similar outcomes regardless of treatment received.

2-year Ipsilateral Stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Age: < 68 years	5.0% (14/293)	9.0% (25/284)	-4% (-8%, 0%) 0.54 (0.29, 1.02)	NS	*P* = 0.005 (RD) *P* = 0.006 (RR)
Age: ≥68 years	13.7% (42/314)	8.6% (25/305)	5% (0%, 1%) 1.63 (1.02, 2.61)	CEA*	

* *P* = .04 for both RD and RR

4-years (1 RCT). As part of the EVA-3S trial age was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients.[129] Mas et al (2008) found that age (< 70 versus ≥ 70 years) was not a significant modifier of the treatment effect in terms of 120 day death, stroke, or MI.

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Age: < 70 years	NR	NR	~1.10 (0.45, 2.70)*	NS	*P* = 0.08
Age: ≥70 years	NR	NR	~3.40 (1.40, 8.10)*	CEA	

* data estimated from Forest plot.

Analyses from nonrandomized studies

Registry studies (1 study). Analyses from one registry study for periprocedural outcomes were available. Jim et al reported data from a registry study of 3655 symptomatic patients, and the test for interaction between subgroups showed that age (< 65 years versus ≥ 65 years) did not modify treatment effect for death, stroke, MI or the composite of death, stroke or MI.[102] It is noted that for MI, effects for the groups tend toward the opposite directions and there is less overlap of confidence intervals. Small numbers of events and sample size in the <65 year old group may contribute to lack of statistical significance for tests of interaction. Detailed data are found in Appendix G, Table 8.

30-day Death	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	0.9% (4/443)	0.7% (4/585)	1.32 (0.33,5.25) P=0.69	NS	*P* = 0.62
≥ 65 years of age	2.4% (27/1114)	1.3% (19/1513)	1.93 (1.08,3.45) P=0.03	CEA	

30-day Stroke	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	4.6% (20/443)	4.8% (28/585)	0.94 (0.54, 1.65) P=0.84	NS	*P* = 0.06
≥ 65 years of age	6.7% (75/1114)	3.8% (57/1513)	0.94 (0.54, 1.65) P=0.001	CEA	

30-day MI	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	0.7% (3/443)	0.2% (1/585)	3.96 (0.41, 37.96) 0.23	NS	*P* = 0.23
≥ 65 years of age	1.6% (18/1114)	1.7% (26/1513)	0.94 (0.52, 1.71) P=0.84	NS	

30-day Death, stroke, or MI	CAS % (n/N)	CEA % (n/N)	RR (95% CI)	Favors	Interaction p-values
< 65 years of age	6.0% (26/443)	5.5% (32/585)	1.07 (0.65, 1.77) P=0.78	NS	*P* = 0.17
≥ 65 years of age	9.5% (106/1114)	6.0% (90/1513)	1.60 (1.22, 2.10) P=0.0007	CEA	

Administrative database studies (1 study). In a study of 11,300 symptomatic patients, McDonald et al (2011) reported that age (< 70 years versus ≥ 70 years) did not modify treatment effect for in hospital death.[132] However, results suggested that for in-hospital death, patients under the age of 70 favored CEA to a greater extent than did those aged 70 or older. Detailed data are found in Appendix G, Table 9.

Sex: Efficacy data from three trials were available. Results suggested that sex did not modify treatment outcome in terms of the composite outcome of death or ipsilateral stroke through two years (SPACE) or for the composite outcome of death, stroke, or MI through 120 days (ICSS). Similarly, combined efficacy data from two trials suggested that sex did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S, CREST). A meta-analysis of patient-level safety data from 6 RCTs suggested that sex did not significantly modify treatment outcome in terms of the composite outcome of periprocedural stroke or death. In terms of periprocedural outcomes, one follow-up study to the CREST trial found that while sex did not significantly modify periprocedural stroke or MI, that it did have an effect on the composite outcome of periprocedural stroke, death or MI such that females had a significantly lower risk of this outcome following CEA, while males had similar outcomes regardless of treatment group.

Safety data from two administrative database studies were also included in the detailed results, and provided similar conclusions.

Analyses from RCTs.

Periprocedural safety outcomes (meta-analysis of 6 RCTs and sensitivity analysis of 4 RCTs): For the composite outcome of periprocedural stroke or death, sex did not

modify the treatment effect. The Cochrane systematic review provided patient level data for periprocedural death or any stroke according to age for four trials (EVA-3S 2006, SPACE 2006, BACASS 2008, and ICSS 2010); similar data were also included from two published trials (Leicester and CREST).[41] Overall, the test for subgroup differences suggests that sex did not significantly modify treatment outcomes in terms of periprocedural death or stroke rates ($P \geq .51$). As described for age, sensitivity analysis was done. Pooled estimates and test for subgroup differences from this sensitivity analysis reaffirms that there is no modification of treatment effect by sex for the outcome of periprocedural death or stroke (Figure 19).

Periprocedural Death or Stroke	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Sex: Female	7.8% (58/739)	5.1% (36/709)	2.6% (-2.1%, 7.2%) 1.5 (1.0, 2.3)	NS	*P* = 0.66 (RD) *P* = 0.51 (RR)
Sex: Male	7.5% (124/1663)	4.1% (69/1663)	4.0% (-0.1%, 8.1%) 1.9 (1.1, 3.1)	CEA*	

***** p-values hover around statistical significance (RD: 0.06; RR; 0.04).

Figure 19. Results of meta-analysis and sensitivity analysis of CAS versus CEA for symptomatic carotid stenosis: periprocedural death or any stroke according to sex.

Study or Subgroup	CAS Events	CAS Total	CEA Events	CEA Total	Weight	Risk Difference M-H, Random, 95% CI
5.3.1 Male						
Leicester (1998)	4	5	0	4	0.4%	0.8000 [0.3650, 1.2350]
EVA-3S (2006)	21	193	7	204	11.4%	0.0745 [0.0240, 0.1250]
SPACE (Stingele)	31	436	29	422	14.2%	0.0024 [-0.0317, 0.0365]
BACASS (2008)	0	8	0	9		Not estimable
ICSS (2010)	46	601	18	606	15.6%	0.0468 [0.0216, 0.0720]
CREST (2010)	22	428	15	427	15.3%	0.0163 [-0.0110, 0.0435]
Subtotal (95% CI)		**1663**		**1663**	**56.9%**	**0.0398 [-0.0010, 0.0806]**
Total events	124		69			
Heterogeneity: Tau² = 0.00; Chi² = 20.23, df = 4 (P = 0.0005); I² = 80%						
Test for overall effect: Z = 1.91 (P = 0.06)						
5.3.2 Female						
Leicester (1998)	1	2	0	6	0.2%	0.5000 [-0.0971, 1.0971]
EVA-3S (2006)	6	72	4	58	6.3%	0.0144 [-0.0769, 0.1056]
SPACE (Stingele)	14	171	10	167	10.7%	0.0220 [-0.0326, 0.0766]
BACASS (2008)	0	2	1	1	0.1%	-1.0000 [-1.7335, -0.2665]
ICSS (2010)	19	252	15	251	12.5%	0.0156 [-0.0282, 0.0595]
CREST (2010)	18	240	6	226	13.3%	0.0485 [0.0091, 0.0878]
Subtotal (95% CI)		**739**		**709**	**43.1%**	**0.0257 [-0.0209, 0.0724]**
Total events	58		36			
Heterogeneity: Tau² = 0.00; Chi² = 11.43, df = 5 (P = 0.04); I² = 56%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**2402**		**2372**	**100.0%**	**0.0332 [0.0048, 0.0616]**
Total events	182		105			
Heterogeneity: Tau² = 0.00; Chi² = 31.62, df = 10 (P = 0.0005); I² = 68%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						

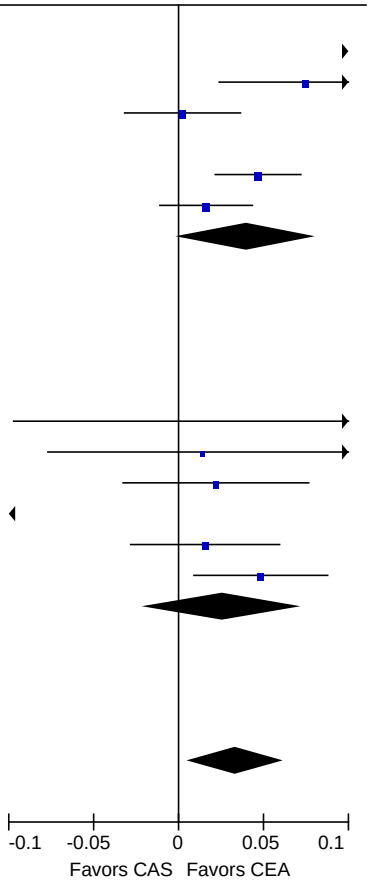
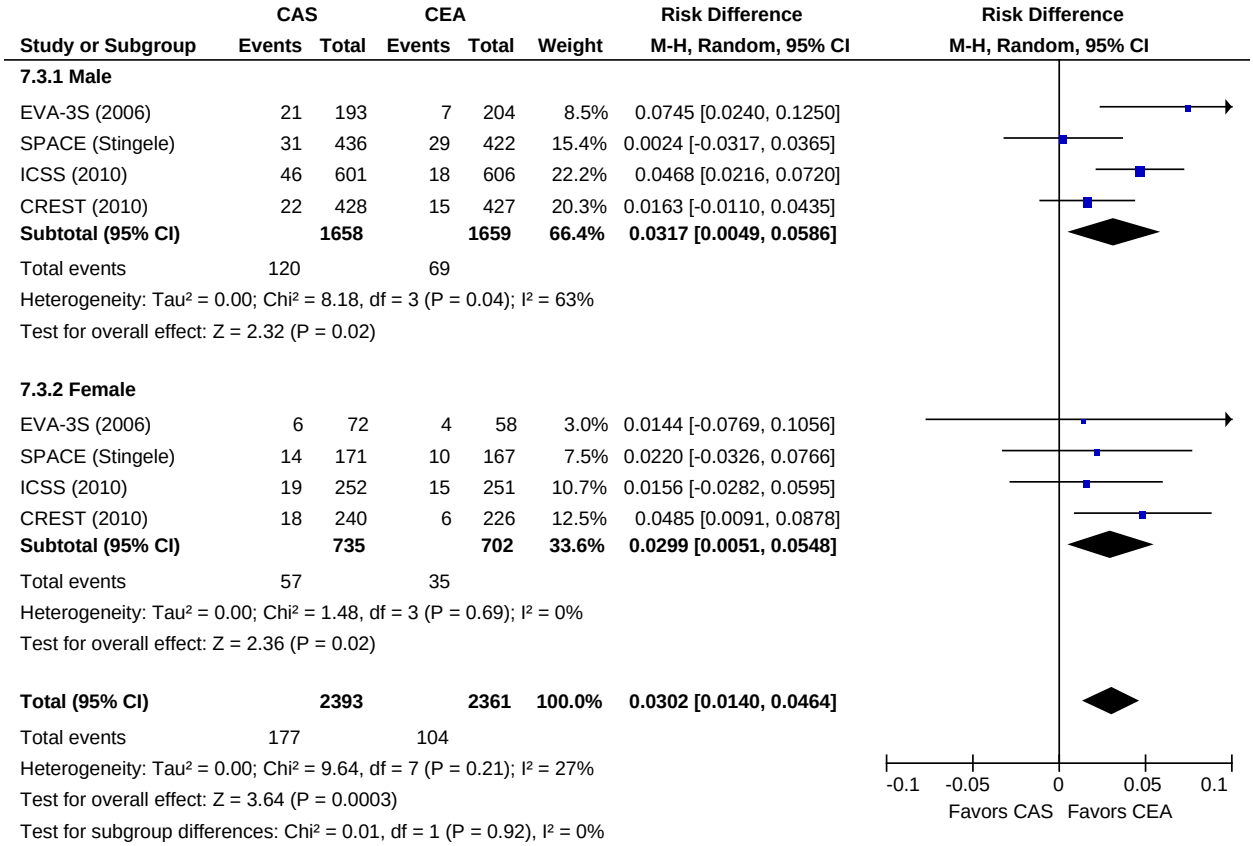


Figure 19 cont.
Sensitivity analysis



In addition, a follow-up study of the CREST trial evaluated whether patient sex modified treatment outcome.[94] This subgroup analysis was prespecified.

In terms of periprocedural outcomes, Howard et al (2011) found that while sex did not significantly modify periprocedural stroke or MI, that it did have an effect on the composite outcome of periprocedural stroke, death or MI such that females had a significantly lower risk of this outcome following CEA, while males had similar outcomes regardless of treatment group.[94]

Periprocedural Any Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	2.80 (1.11, 7.07)	CEA	*P* = 0.17
Male	NR	NR	1.28 (0.65, 2.52)	NS	

Periprocedural MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.26 (0.28, 5.63)	NS	*P* = 0.11
Male	NR	NR	0.25 (0.07, 0.88)	CAS	

Periprocedural Any Stroke, Death, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	2.33 (1.07, 5.07)	CEA	*P* = 0.04
Male	NR	NR	0.88 (0.50, 1.55)	NS	

120 days (1 RCT): As part of the ICSS trial of 1713 symptomatic patients, sex was predefined as a subgroup for which exploratory analysis would be conducted.[65] Overall, Ederle et al. (2010) found that the differences between females and males in treatment outcome of 120 day death, stroke, or MI was not statistically significant ($P \geq .07$), therefore sex does not modify the treatment effect. Additional details are available in Appendix G, Table 10.

120-day Death, Stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-value
Sex: Female	NR	NR	2.17 (1.35, 3.50)	NS	*P* = .071
Sex: Male	NR	NR	1.05 (0.56, 1.97)	NS	

2-years (1 RCT). The SPACE trial of 1214 symptomatic patients prespecified a few subgroup analyses, and a follow-up paper reported subgroup analyses of 2-year ipsilateral stroke or death.[63] Overall, the subgroup analysis reported by Eckstein et al. (2008) suggested that sex does not significantly modify the treatment effect ($P \geq .69$).

2-year Ipsilateral Stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Sex: Female	8.3% (14/171)	6.7% (11/167)	2% (-4%, 7%) 1.24 (0.58, 2.66)	NS	*P* = 0.73 (RD) *P* = 0.69 (RR)
Sex: Male	9.9% (42/436)	9.6% (39/422)	0% (-4%, 4%) 1.04 (0.69, 1.58)	NS	

4-years (2 RCTs). Analysis of differential efficacy based on sex for longer term effectiveness was done in two RCTs (EVA-3S and CREST).

Regarding four-year ipsilateral stroke, overall, combined data from the EVA-3S and CREST studies suggest that sex does not modify treatment effect.

The EVA 3S evaluated whether patient sex modified treatment outcome using post-hoc subgroup analyses.[129] The interaction p-values calculated from hazard ratios suggested that sex significantly modified treatment outcome ($P = .03$), although there was some overlap in the 95% confidence intervals between treatment groups. The results suggest that males are at greater risk of periprocedural death or stroke following CAS versus CEA, while females had similar outcomes regardless of treatment group. The authors

noted that because the number of events was low, the confidence intervals were relatively large.

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Sex: Female	NR	NR	~0.65 (0.25, 2.10)*	NS	*P* = 0.03
Sex: Male	NR	NR	~3.30 (1.50, 7.40)*	CEA	

* data estimated from a Forest plot.

As part of a follow-up study of the CREST trial, Howard et al (2011) evaluated whether patient sex modified treatment outcome.[94] This subgroup analysis was prespecified. In terms of 4-year outcomes, the authors found that sex did not significantly modify any outcome evaluated: ipsilateral stroke or any stroke or death.

4-year Ipsilateral Stroke*	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.49 (0.81, 2.74)	NS	*P* = 0.19
Male	NR	NR	0.87 (0.53, 1.44)	NS	

* includes any stroke, death, or MI during the periprocedural period

4-year Ipsilateral Stroke*	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.58 (0.81, 3.08)	NS	*P* = 0.41
Male	NR	NR	1.10 (0.62, 1.94)	NS	

* includes any stroke during the periprocedural period

4-year Any stroke or death	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Female	NR	NR	1.58 (0.81, 3.08)	NS	*P* = 0.56
Male	NR	NR	1.23 (0.71, 2.14)	NS	

* includes any stroke or death during the periprocedural period

Analyses from nonrandomized studies

Administrative database studies (2 studies). Two administrative database studies evaluated whether sex modified the treatment effect for in-hospital stroke and in-hospital death.[39,155]

- *In-hospital death.* Bisdas et al (2011)[39] reported that sex modified treatment effect in terms of in-hospital death such that while females had a statistically lower rate of in-hospital death following CAS, males had a statistically lower rate of in-hospital death following CEA. In contrast, Rockman et al (2011)[155] reported that sex did not modify treatment effect in terms of in-hospital death. See Appendix G, Table 9 for additional details.

- *In-hospital stroke.* Bisdas et al (2011)[39] reported that sex modified treatment effect in terms of in-hospital stroke; both groups had significantly lower rates of in-hospital stroke following CEA versus CAS though the magnitude of effect was greater in males than females. In contrast, Rockman et al (2011)[155] reported that sex did not modify treatment effect in terms of in-hospital death. See Appendix G, Table 9 for additional details.
- *In-hospital MI; composite outcome.* One administrative study found that sex did not modify the treatment effect of either in-hospital MI or the composite of stroke or death.[39] See Appendix G, Table 9 for additional details.

Diabetes: Efficacy data from two RCTs were available, and both suggested that diabetes status did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S) or for the composite outcome of death, stroke, or MI through 120 days (ICSS).

120-days (1 RCT): As part of the ICSS trial of 1713 symptomatic patients, diabetes status was predefined as a subgroup for which exploratory analysis would be conducted.[65] Overall, Ederle et al. (2010) found that the presence of diabetes does not modify the treatment effect. Additional details are available in Appendix G, Table 10.

120-day Death, Stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-value
Diabetes: Yes	NR	NR	1.67 (0.81, 3.43)	NS	*P* = 0.97
Diabetes: No	NR	NR	1.64 (1.05, 2.55)	CEA	

4-years (1 RCT): Analysis of differential efficacy based on diabetes status for longer term effectiveness was done in one RCT (EVA-3S), in which diabetes status was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients. Diabetes status did not modify treatment effect in terms of 4 year ipsilateral stroke rates (*P* = .27).[129]

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Diabetes: Yes	NR	NR	~1.20 (0.30, 3.75)*	NS	*P* = 0.27
Diabetes: No	NR	NR	~2.60 (1.20, 5.60)*	CEA	

* data estimated from a Forest plot.

Type of symptomatic qualifying event: Safety data from one RCT suggested that type of symptomatic qualifying event not modify treatment outcome in terms of periprocedural stroke or the composite outcome of periprocedural ipsilateral stroke or death (CREST). Efficacy data from two RCTs were available and suggested that type of symptomatic qualifying event (i.e., stroke, transient ischemic attack, ocular, or multiple events) did not modify treatment outcome in terms of ipsilateral stroke through four years (EVA-3S) or for the composite outcome of death or ipsilateral stroke through two years (SPACE).

Periprocedural stroke (1 RCT): As part of the CREST trial, Hill et al. conducted post hoc subgroup analysis as to whether the type of indicating event in symptomatic patients affected outcomes following CAS versus CEA. Tests for interaction suggested that the type of qualifying event (i.e., stroke, transient ischemic attack, or Amaurosis Fugax/ocular) did not modify the treatment effect ($P \geq .46$).[91]

Periprocedural Stroke (any)	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Qualifying event: Stroke	6.2% (16/257)	1.9% (5/262)	4% (1%, 8%) 3.26 (1.21, 8.77)	CEA	*P* = 0.46 (RD) *P* = 0.53 (RR)
Qualifying event: TIA	6.0% (15/252)	2.8% (7/250)	3% (0%, 7%) 2.13 (0.88, 5.12)	NS	
Qualifying event: Ocular	3% (3/87)	3.0% (3/100)	0% (-5%, 6%) 1.15 (0.24, 5.55)	NS	

Periprocedural ipsilateral stroke or death (1 RCT): The SPACE trial prespecified type of symptomatic indicating event for subgroup analyses of 30 day ipsilateral stroke or death. Stingele et al (2008) found that the type of qualifying event (i.e., stroke, transient ischemic attack, Amaurosis Fugax/ocular, multiple events, or other) did not modify the treatment effect ($P \geq .48$).[171]

Periprocedural Ipsilateral stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Qualifying event: Stroke	7.0% (19/270)	8.3% (21/252)	-1% (-6%, 3%) 0.84 (0.47, 1.53)	NS	*P* = 0.48 (RD) *P* = 0.55 (RR)
Qualifying event: TIA	8.3% (15/180)	6.6% (12/183)	2% (-4%, 7%) 1.27 (0.61, 2.64)	NS	
Qualifying event: Ocular	3% (3/95)	4% (4/90)	-1% (-7%, 4%) 0.71 (0.16, 3.09)	NS	
Qualifying event: Multiple events	9% (4/47)	2% (1/56)	7% (-2%, 15%) 4.77 (0.55, 41.19)	NS	
Qualifying event: Other	7% (1/15)	0% (0/8)	7% (-14%, 27%) 1.69 (0.08, 37.26)	NS	

2-years (1 RCT): The SPACE trial prespecified a few subgroup analyses, and a 2-year follow-up paper reported subgroup analyses of 2-year ipsilateral stroke or death.[63] Overall, the subgroup analysis reported by Eckstein et al. (2008) suggested that the type of qualifying event (i.e., stroke, transient ischemic attack, Amaurosis Fugax/ocular, or multiple events) did not modify the treatment effect ($P \geq .13$).

2-year Ipsilateral Stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Qualifying event: Stroke	8.7% (23/270)	11.0% (27/252)	4% (-2%, 9%) 1.56 (0.84, 2.93)	NS	$P = 0.13$ (RD) $P = 0.25$ (RR)
Qualifying event: TIA	9.6% (19/180)	10.8% (17/183)	1% (-5%, 7%) 1.14 (0.61, 2.11)	NS	
Qualifying event: Ocular OR Other	5.5% (6/110)	5% (5/98)	0% (-6%, 6%) 1.07 (0.34, 3.39)	NS	
Qualifying event: Multiple events	19% (8/47)	2% (1/56)	15% (4%, 27%) 9.53 (1.24, 73.48)	CEA	

4-years (1 RCT): Analysis of differential efficacy based on type of symptomatic qualifying event for longer term effectiveness was done in one RCT (EVA 3S), in which diabetes status was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients.[129] Mas et al. 2008 found that type of symptomatic qualifying event (i.e., stroke, transient ischemic attack (TIA), or Amaurosis Fugax/ocular symptoms) did not significantly modify treatment effect ($P \geq 0.16$).

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Qualifying event: Stroke	NR	NR	~3.00 (1.60, 6.80)*	CEA	$P \geq 0.16$
Qualifying event: TIA	NR	NR	~1.50 (0.45, 5.15)*	NS	
Qualifying event: Ocular	NR	NR	~2.00 (0.10, 4.30)*	NS	

* data estimated from a graph.

Severity of ipsilateral stenosis: Efficacy data from three RCTs were available, and results suggested that severity of stenosis in the ipsilateral artery did not modify treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ipsilateral stenosis of 50-69% versus 70-99%), the composite outcome of death or ipsilateral stroke through two years (ipsilateral stenosis of < 70% versus ≥ 70%) (SPACE), ipsilateral stroke through 4 years (ipsilateral stenosis of < 90% versus ≥ 90%) (EVA-3S).

120-days (1 RCT): As part of the ICSS trial of 1713 symptomatic patients, severity of stenosis in the ipsilateral artery was predefined as a subgroup for which exploratory analysis would be conducted.[65] Overall, Ederle et al. (2010) found that stenosis severity (50-69% versus 70-99%) does not modify the treatment effect. Additional details are available in Appendix G, Table 10.

120-day Death, Stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-value
Ipsilateral stenosis 50-69%	NR	NR	1.13 (0.25, 5.04)	NS	*P* = 0.584
Ipsilateral stenosis 70-99%	NR	NR	1.75 (1.19, 2.58)	CEA	

2-years (1 RCT): The SPACE trial prespecified a few subgroup analyses, and a 2-year follow-up paper reported subgroup analyses of 2-year ipsilateral stroke or death.[63] Overall, the subgroup analysis reported by Eckstein et al. (2008) suggested that the severity of ipsilateral stenosis (i.e., <70% versus 70 – 99%) did not modify treatment effect in terms of 2 year ipsilateral stroke or death ($P \geq .49$)

2-year Ipsilateral Stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Ipsilateral stenosis < 70%	8.2% (18/225)	6.3% (14/230)	2% (-3%, 7%) 1.31 (0.67, 2.58)	NS	*P* = 0.54 (RD) *P* = 0.49 (RR)
Ipsilateral stenosis ≥ 70%	10.2% (38/382)	10.3% (36/359)	0% (-4%, 4%) 0.99 (0.64, 1.52)	NS	

4-years (1 RCT): Analysis of differential efficacy based on type of symptomatic qualifying event for longer term effectiveness was done in one RCT (EVA 3S), in which diabetes status was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients.[129] Mas et al. 2008 reported that ipsilateral stenosis severity (i.e., < 90% versus ≥ 90%) did not modify treatment effect in terms of 4 year ipsilateral stroke rates ($P = .61$).

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Ipsilateral stenosis < 90%	NR	NR	~2.30 (1.00, 5.40)*	NS	*P* = 0.61
Ipsilateral stenosis ≥ 90%	NR	NR	~1.65 (0.60, 4.30)*	NS	

* data estimated from a Forest plot.

Severity of contralateral stenosis: Safety data from one RCT suggested severity of stenosis in the contralateral artery did not modify treatment outcome in terms of the composite outcome of periprocedural ipsilateral stroke or death (SPACE). Efficacy data from three RCTs were available, and results suggested that severity of stenosis in the contralateral artery did not modify treatment outcome in terms of the composite outcome of death, stroke, or MI through 120 days (ICSS), the composite outcome of death or ipsilateral stroke through two years (ipsilateral stenosis of < 70% versus 70-99% versus 100%) (SPACE), or for ipsilateral stroke through 4 years (contralateral stenosis of < 70% versus 70-100%) (EVA-3S).

Periprocedural (1 RCT): The SPACE trial prespecified severity of contralateral stenosis for subgroup analyses of 30 day ipsilateral stroke or death. Stingele et al. 2008 found that the severity of contralateral stenosis at baseline did not modify the effect of treatment in terms of 30 day ipsilateral stroke or death.[171]

Periprocedural Ipsilateral Stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Contralateral stenosis < 70%	7.1% (40/567)	5.9% (32/543)	1% (-2%, 4%) 1.20 (0.76, 1.88)	NS	*P* = 0.14 (RD) *P* = 0.16 (RR)
Contralateral stenosis 70-99%	5% (2/40)	13% (6/46)	-8% (-20%, 4%) 0.38 (0.08, 1.79)	NS	

120 days (1 RCT): As part of the ICSS trial of symptomatic patients, severity of contralateral stenosis was predefined as a subgroup for which exploratory analysis would be conducted. Ederle et al. (2010) reported that severity of contralateral stenosis at baseline (i.e., 0-49%, 50-69%, 70 – 99%, or 100%) did not modify the effect of treatment in terms of 120 death, stroke, or MI risk following CAS versus CEA.[65]

120-day Death, stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Contralateral stenosis 0-49%	NR	NR	1.70 (1.05, 2.73)	CEA	*P* = 0.741
Contralateral stenosis 50-69%	NR	NR	2.04 (0.85, 4.85)	NS	
Contralateral stenosis 70-99%	NR	NR	1.37 (0.51, 3.68)	NS	
Contralateral stenosis 100%	NR	NR	1.51 (0.14, 16.61)	NS	

2-years (1 RCT): The SPACE trial prespecified a few subgroup analyses, and a 2-year follow-up paper reported subgroup analyses of 2-year ipsilateral stroke or death. The severity of contralateral stenosis (i.e., <70%, 70 – 99%, or 100%) did not modify treatment effect regarding 2 year ipsilateral stroke or death.[63]

2-year Ipsilateral Stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors	Interaction p-values
Contralateral stenosis < 70%	9.4% (52/567)	16.2% (41/253)	-7% (-12%, -2%) 0.57 (0.39, 0.83)	CAS	*P* = 0.82 (RD) *P* = 0.89 (RR)
Contralateral stenosis 70-99%	9% (2/22)	22% (6/27)	-13% (-33%, 7%) 0.41 (0.09, 1.83)	NS	
Contralateral stenosis 100%	11% (2/18)	16% (3/19)	-5% (-27%, 17%) 0.70 (0.13, 3.73)	NS	

4-years (1 RCT): As part of the EVA-3S trial (Mas 2008), severity of stenosis of the contralateral artery was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients. Contralateral stenosis severity (i.e., < 70% versus 70 – 100%) did not modify treatment effect in terms of 4 year ipsilateral stroke rates.[129]

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Contralateral stenosis < 70%	NR	NR	~2.20 (1.10, 4.30)*	CEA	*P* = 0.65
Contralateral stenosis 70-100%	NR	NR	~1.45 (0.30, 6.50)*	NS	

* data estimated from a Forest plot.

Time to treatment: Efficacy data from two RCTs were available, and results suggested that time to treatment (< 14 days versus ≥ 14 days) did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S) or for the composite outcome of death, stroke, or MI through 120 days (ICSS).

120 days (1 RCT): As part of the ICSS trial of symptomatic patients, time to treatment was predefined as a subgroup for which exploratory analysis would be conducted. Overall, time from the most recent ipsilateral event (prior to randomization) to treatment did not modify the treatment effect in terms of 120 day risk of stroke, death, or MI following CAS versus CEA.[65]

120-day Death, stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Time to treatment: < 14 days	NR	NR	2.21 (0.82, 5.95)	NS	*P* = 0.68
Time to treatment: ≥ 14 days	NR	NR	1.76 (1.12, 2.78)	CEA	

4 years (1 RCT): As part of the EVA-3S trial (Mas 2008), time to treatment was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients. Time to treatment (i.e., < 14 days versus ≥ 14 days) did not modify treatment effect in terms of 4 year ipsilateral stroke rates.[129]

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Time to treatment: < 14 days	NR	NR	~6.75 (0.80, ≥8)*	NS	*P* = 0.40
Time to treatment: ≥ 14 days	NR	NR	~1.70 (0.80, 3.45)*	NS	

* data estimated from a Forest plot.

Hypertension: Efficacy data from two RCTs were available. Data from the ICSS trial suggested that hypertensive status at baseline does modify the treatment effect in terms of the composite outcome of 120 day death, stroke or MI, such that patients without treated hypertension favor CEA while those without treated hypertension have similar outcomes regardless of treatment group. Data from the EVA-3S trial suggested that baseline hypertensive status did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S).

120 days (1 RCT): As part of the ICSS trial of symptomatic patients, treated hypertension status at baseline was predefined as a subgroup for which exploratory analysis would be conducted. Overall, the results suggest that hypertensive status at baseline does modify the treatment effect, such that patients without treated hypertension favor CEA while those without treated hypertension have similar outcomes regardless of treatment group.[65]

120-day Death, stroke, or MI	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Treated hypertension: Yes	NR	NR	1.29 (0.83, 2.00)	NS	*P* = 0.039
Treated hypertension: No	NR	NR	3.25 (1.46, 7.20)	CEA	

4-years (1 RCT): As part of the EVA-3S trial (Mas 2008), hypertension status was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA

(n = 262) symptomatic patients. Hypertensive status at baseline did not modify treatment effect in terms of 4 year ipsilateral stroke rates (*P* = .62).[129]

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Hypertension: Yes	NR	NR	~1.80 (0.85, 3.65)*	NS	*P* = 0.62
Hypertension: No	NR	NR	~2.90 (0.75, ≥8)*	NS	

* data estimated from a Forest plot.

Smoking status: Efficacy data from one RCT were available, and results suggested baseline smoking status did not modify treatment outcome in terms of ipsilateral stroke through 4 years (EVA-3S).

4-years (1 RCT): As part of the EVA-3S trial (Mas 2008), baseline smoking status was evaluated using post-hoc subgroup analyses to determine whether it modified the outcome of 4 year ipsilateral stroke rates following CAS (n = 265) compared with CEA (n = 262) symptomatic patients. Smoking status at baseline did not modify treatment effect in terms of 4 year ipsilateral stroke rates.[129]

4-year Ipsilateral Stroke	CAS % (n/N)	CEA % (n/N)	HR (95% CI)	Favors	Interaction p-values
Smoking: Yes	NR	NR	~1.75 (0.5, 6.1)*	NS	*P* = 0.81
Smoking: No	NR	NR	~2.10 (1.00, 4.40)*	NS	

* data estimated from a Forest plot.

Surgical risk: Efficacy data from the SAPPHIRE trial of 96 symptomatic high surgical patients undergoing CAS versus CEA suggested these patients had similar risks of stroke through 3 years, the composite outcome ipsilateral stroke or death through 3 years, and ipsilateral stroke or death through 1 year regardless of treatment received. Safety data from the same trial suggested these patients had similar risks of the composite outcome of periprocedural death, stroke, or MI regardless of treatment received. Safety data from one prospective cohort study and one administrative database study are provided in the detailed results, and in general demonstrated that surgical risk did not modify treatment outcomes. Data from one cohort study also suggested that CEA risk grades did not modify outcome in terms of periprocedural non-disabling stroke.

Analyses from RCTs.

The SAPPHIRE trial[87,183] evaluated CAS versus CEA in 96 symptomatic high surgical risk patients, which included at least one of the following characteristics: clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery); severe pulmonary disease; contralateral carotid occlusion; contralateral laryngeal-nerve palsy; previous radical neck surgery or radiation therapy to the neck; recurrent stenosis after endarterectomy; or age > 80 years. The study did not include any patients considered to be at average surgical risk, thus we cannot directly compare outcomes for high- versus average surgical risk within this study. However, the results will be placed in context with those from KQ1 and KQ3, as appropriate.

3-year stroke: Grum et al (2008) found that symptomatic high surgical risk patients had no differences in three year stroke risk following treatment with either CAS or CEA.[87]

3-year Stroke	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	6% (3/50)	9% (4/46)	-3% (-13%, 8%) 0.69 (0.16, 2.92)	NS

Regarding similar results found in studies of symptomatic average risk patients, two RCTs (SPACE and EVA-3S) reported stroke at 2 and 4 years follow-up, respectively.[63,129] There was no difference in the cumulative 2- or 4-year stroke risk (excluding periprocedural) between CAS and CEA treatment groups, with a pooled risk difference of -0.1% (95% CI, -1.8%, 1.7%). See Key Question 1 for additional details.

3-year ipsilateral stroke or death. Grum et al (2008) also reported that symptomatic high surgical risk patients treated with CAS versus CEA had similar risks of the composite outcome of ipsilateral stroke or death at three years.[87]

3-year Ipsilateral stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	32% (16/50)	22% (10/46)	10% (-7%, 28%) 1.47 (0.74, 2.91)	NS

Regarding similar results found in studies of symptomatic average risk patients, five RCTs (SPACE & Kentucky (2 years), CREST and BACASS (4 years), and Regensburg (5.4 years)) reported death or ipsilateral stroke at 2, 4, or 5.4 years follow-up, as noted.[45,48,63,93,170] There was no difference in this outcome between CAS and CEA treatment groups, with a pooled risk difference of 1.3% (95% CI, -1.6%, 4.2%). See Key Question 1 for additional details.

1-year ipsilateral stroke or death. Data from the Yadav et al (2004) study of the SAPPHIRE trial suggest that symptomatic patients treated with CAS had a similar risk of ipsilateral stroke or death at one year follow-up compared with patients who received CEA.[183]

1-year Ipsilateral stroke or Death	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	16.8% (8/50)	16.5% (8/46)	-1% (-16%, 14%) 0.92 (0.38, 2.25)	NS

Regarding similar results found in studies of symptomatic average risk patients, no RCTs reported this outcome between 6 months and 2 years. See Key Question 1 for additional details.

Periprocedural safety outcomes. Yadav et al found similar rates of periprocedural death, stroke, or MI following CAS and CEA in symptomatic patients.[183]

Periprocedural Death, Stroke, or MI	CAS % (n/N)	CEA % (n/N)	RD (95% CI) RR (95% CI)	Favors
High surgical risk	2.1% (1/50)	9.3% (4/46)	-7% (-16%, 2%) 0.23 (0.03, 1.98)	NS

Regarding similar results found in studies of symptomatic average risk patients, no RCTs reported this periprocedural outcome. See Key Question 3 for additional details.

Analyses from nonrandomized studies

Cohort study (1 study). Iihara et al. (2006)[96] conducted a prospective cohort study and found that CEA risk grades (I, II, or III) did not significantly modify treatment effect following CAS versus CEA in terms of periprocedural non-disabling stroke as evaluated in 103 symptomatic patients. See Appendix G, Table 12 for additional details.

Administrative database studies (1 study). One administrative database study evaluated whether surgical risk modified the treatment effect for in-hospital stroke, in-hospital death, or the composite outcome of in-hospital death or stroke in 52,937 symptomatic patients.[77] See Appendix G, Table 13 for additional details, including how high surgical risk was defined.

- *In-hospital death:* Giles et al (2010)[77] found that surgical risk may modify treatment effect in terms of in-hospital death. Although both high and surgical risk patients had significantly better outcomes following CEA, the magnitude of this effect was significantly greater in low surgical risk patients. See Appendix G, Table 13 for additional details.
- *In-hospital stroke or composite outcome:* Giles et al (2010) found that surgical risk did not modify treatment effect in terms of in-hospital stroke or in terms of the composite outcome of in-hospital death or stroke. Both high surgical risk and average surgical risk patients favored CEA.

4.4.3. Intracranial

No studies were found that evaluated differential efficacy or safety for special populations undergoing treatment for intracranial artery stenosis.

4.5. Key question 5: Economic Evaluation

What is the evidence of cost-effectiveness of CAS compared with other treatment options (medical therapy, CEA) in the short-term and the long term?

No full economic studies comparing the cost effectiveness of CAS with medical therapy versus medical therapy alone were found.

To investigate the cost-effectiveness of carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA), full economic analyses were considered for inclusion. Searches yielded 34 potentially relevant citations. Review at the title and abstract level identified 11 studies for full text appraisal. Five cost-utility studies meeting the inclusion criteria were identified.[99,124,130,175,186] Quality of Health Economic Studies (QHES)[144] scores ranged from 84-100, which primarily reflects the quality of reporting on specific factors that are important in economic analyses. It does not provide for evaluation of quality with respect to modeling assumptions or extensive consideration of data quality and included outcomes measures relevant to a specific topic. In general, the quality of the individual studies was considered moderate to high. One study considered only asymptomatic patients,[130] two studies concentrated on symptomatic patients[99,186] and two studies provided a subgroup analysis for both symptomatic statuses.[124,175] Based on studies included in key questions 1 and 4, the longest-term follow- up was 4 years.

No full economic studies evaluating the cost effectiveness of intracranial vessel stenting and alternative treatments were found.

Table 49 summarizes characteristics and findings from included economic studies.

4.5.1. Asymptomatic

Summary of full economic analysis studies for asymptomatic patients (overall strength of evidence, low)

CAS compared with CEA: Of the five included cost-utility studies comparing CAS with CEA, three provided data for asymptomatic patients (one study that considered only asymptomatic patients[130] and two that provided a subgroup analysis stratified by symptom status[124,175]).

- Across two cost utility studies, the evidence suggested CAS to be a plausible, but not verifiably superior treatment for high surgical risk patients. Over 1-year time horizon studies reported ICERs of $49,514 and $67,891. Primary limitations of these studies should, however, be considered and relate to methods for parameter estimation and concerns regarding the reliability extrapolating beyond the last follow-up of the SAPPHIRE trial should be noted. Variation in methodology for determining patient utility levels across studies contributed to potential discrepancy in the results between the studies and validity of the utilities used.
- When focusing on patients with standard surgical risk, CEA was found to be slightly less expensive and provided slightly more quality-adjusted life years (QALYs) in one study. In that sense, it CEA was the preferred treatment given commonly assumed cost-effectiveness thresholds.

Detailed results: full economic analysis studies of asymptomatic patients

CAS compared with CEA: Three cost-utility studies provided information on asymptomatic patients and the results were varied. Two used outcomes data from the SAPPHIRE trial of patients considered being at high risk for CEA based on anatomical characteristics or comorbid conditions that increased surgical risks.[124,130] Different cost data and time horizons were assumed in each. Sub-analysis of asymptomatic patients was done in a third study based on outcomes from the CREST trial among patients considered to be at average surgical risk.[175]

Maud (2010)[130] and Mahoney (2011)[124] performed a cost-utility analysis of CAS versus CEA for asymptomatic patients using the SAPPHIRE trial data. Both studies applied simulation methods to estimate ICERs for the two treatments. Outcomes were measured for a 1-year post-procedure window. At the 1-year follow-up, Maud and colleagues estimated the cost per QALY to be $67,891/QALY and interpreted their results to indicate a non-inferiority of CAS when considering 1-year outcomes. However, the 95% confidence interval was very dispersed around the mean ICER and ranged from -$129,327/QALY to $379,661/QALY. Mahoney et al. relied on prospectively collected individual patient resource use and forecasted estimates over the remaining lifetime of a hypothetical cohort of 72-year-olds. In their analysis, Mahoney and colleagues reported an economically more attractive ICER of $49,514 over the same time horizon of 1-year. When projected over the patients' lifetime, the ICER decreased further to $2,667/QALY for asymptomatic patients. Overall, authors caution against generalizing the results beyond the population described by the SAPPHIRE trial. It should be noted that this trial was terminated early for slow recruitment and the length of follow up was 3 years.

Vilain (2012)[175] considered patients of both symptomatic statuses separately. The study was designed to be an economic evaluation conducted alongside the CREST trial. The CREST trial was different from the SAPPHIRE trial both in patient population (specifically surgical risk attributes) and in corresponding clinical outcomes. CREST had more closely correlated outcomes across treatment groups and very little difference in survival rates. Due to a lack of notable outcome differences and a sensitivity analysis suggestive of equal likelihood of cost-effectiveness for each treatment, the authors concluded that the preferred procedure should be determined according to factors other than a cost-effectiveness measure alone such as individual patient characteristics. As a point of comparison, another economic analysis using CREST data was conducted by Khan et al.[109] This study was not eligible for formal inclusion, as results for asymptomatic and symptomatic patients were not analyzed separately. In this study, patients of both symptomatic statuses were pooled together and the resulting ICER was $229,429/QALY. Khan and colleagues argue that although CAS is similar in effectiveness to CEA for patients at average surgical risk suffering from severe carotid artery stenosis, the higher cost of CAS makes it a less attractive alternative.

The overall strength of evidence was considered low. Many of the results had a high degree of variability and were unstable when evaluated through sensitivity analyses even though QHES scores ranged from 84-99. Concern about the reliability of the SAPPHIRE follow-up data was a notable limitation of the two studies that relied on it. The short follow up time was especially problematic considering the role long-term outcomes play in determining cost-effectiveness. Overall, for asymptomatic patients the evidence suggested CAS to be a plausible, but not verifiably superior treatment for high surgical risk patients. The higher upfront procedural cost of CAS was consistently an influential factor driving the cost-effectiveness. When focusing on average risk patients CEA was found to be slightly less

expensive and provided slightly more quality-adjusted life years (QALYs). In that sense, it CEA dominated CAS as the cost-effective alternative.

Study Synopsis: Maud et al. 2010

Overview:
Maud et al.[130] performed a cost-utility analysis of CAS and CEA based on data from the SAPPHIRE trial in high surgical risk asymptomatic patients. The cost-effectiveness of the treatments was then expressed as an ICER.

Costs were considered from a US Healthcare perspective. Expenses and quality of life measures were adjusted to 2006 units using yearly inflation increments taken from the Medical Care component of the Consumer Price Index (CPI). Monte Carlo methods were used to simulate the results. The model iterated 10,000 data points using specified distributions for different clinical outcome rates. ICERs were calculated for a 1-year post-procedure period.

Assumptions:
The sample population used was that of SAPPHIRE trial. The trial consisted of 70% asymptomatic patients with an average age of 72 years (range: 46-91) considered to be at a high risk for CEA. SAPPHIRE outcome rates served as approximations for treatment effectiveness. Cost information was acquired from the Healthcare Cost and Utilization Project (H-CUP). Utility estimates were obtained from published literature. To approximate QALYs, the authors consulted a study done by Nyman,[143] which relied on self-reported health statuses. Good health, with no adverse events, was assigned 0.815 out of 1 QALYs. MI was given a weight of 0.744, and strokes a weight of 0.718. See below for discussion of potential limitations.

The total cost for each intervention was taken to be the sum of procedural costs, potential cost of MI, the annual cost of moderate disability after stroke, and the cost of death. Hospital expenses for CAS were $11,220 and $6,802 for CEA. The cost of care for minor MI, major MI, and all strokes was $8,404, $5,890, and $6,876 respectively. Costs were measured for a 1-year post-procedure period. Disability costs for minor stroke, major stroke, and all MI were estimated to be $2,808, $10,400 and $4,200. Death was assumed to cost $5,000.

Referencing the SAPPHIRE trial data, 1-year clinical outcome rates were used. CAS had a mortality rate of 7% while CEA was nearly double at 13%. Minor and major strokes occurred at a rate of 4% and 1% respectively in the CAS treatment arm, and 2% and 4% in the CEA patients. Non-Q-wave MI was assumed to be 2% for CAS and 5% for CEA.

Results:
Maud and colleagues found CAS had a cost of $12,782 and a QALY of 0.753. CEA was less expensive, costing an estimated $8,916 with a QALY of 0.701. Taking the ratio of the differences yielded an ICER of $67,891/QALY for the first year post-procedure.

There was however, a large degree of uncertainty associated with these estimates. The 95% confidence interval was very dispersed around the mean ICER and ranged from minus (-) $129,327/QALY to $379,661/QALY. Despite such variability, closer analysis of the simulation revealed that all trials had an incremental cost greater than zero. This indicated that the marginal benefit produced by CAS was insufficient to offset its higher cost. Assuming a willingness to pay equal to $67,891 (the median ICER), the probability of CAS being cost-effective was less than 40%, which suggests that approximately 60% of the time the estimated cost of producing an additional quality-adjusted year to the patient's life using CAS would exceed $67,891.

Conclusions and limitations:
Maud et al.[130] estimated CAS to be more costly than CEA and only slightly more effective- finding an incremental cost of $3,867 and incremental QALY of 0.052. The authors propose that in order for CAS to become more reasonably cost-effective the procedural cost should be no more than those associated with CEA.

There are several potential limitations. First, the SAPPHIRE trial was prematurely terminated due to slow recruitment. The authors argue that the relatively small sample size possibly worked against the ICER for CAS. Maud and colleagues provided little discussion concerning how the utilities used were derived. The study cited in the text by Nyman et al.[143] relied on EQ-5D in the Medical Expenditure Panel Survey with no distinction between varying stroke severity. Furthermore, the utility level for healthy patients was selected for patient's age 65-74-years-old. However, the condition utility value in the study was for the whole population in all health-states. Also of concern, was the short follow-up time of 1-year, which may not capture the long-term effects associated with the two interventions (specifically the durability of CAS). While uncertainty was partially addressed, a more detailed sensitivity analysis would help to enrich the overall conclusions. Lastly, no secondary outcomes were considered such as cranial nerve palsy or complications at the surgical site.

Funding and disclosures:
No funding information was provided. The authors stated that there exists no commercial, proprietary or financial interest in any of the products or companies described in the study.

Study Synopsis: Mahoney et al. 2011

Overview:
Mahoney et al.[124] conducted an economic analysis considering the cost-effectiveness of CAS and CEA for high surgical risk patients. The study used the SAPPHIRE trial results and looked primarily at asymptomatic individuals; subgroup results were also presented for symptomatic patients. Base case ICERs were computed and were followed by a detailed sensitivity analysis.

Bootstrap approximation methods were used to model the results. Estimates were resampled 5,000 times to build a statistical sense of their distributions. The model forecasted costs and utility values over the expected lifetime of the patients. Events during the trial year were used to determine outcome rates, to which the authors applied a life expectancy, calculated using the Saskatchewan data. To that life expectancy Mahoney and colleagues then applied the associated annual costs.

Cost-effectiveness was examined from the perspective of the healthcare system, including nursing home costs and patient reported costs. Future costs and quality of life measures were discounted to 2002 levels at an annual rate of 3%.

Assumptions:
The principal data source for outcomes of the study was the SAPPHIRE trial results. The trial included 70% asymptomatic patients, however, separate results were computed for symptomatic patients. The average age was 72 years and ranged from 46 to 91. All patients were considered to be at a high risk for CEA due to comorbid conditions or anatomical characteristics. Cost estimates were obtained from a combination of hospital billing data and resource-based costs. Utility estimates were acquired using societal weights taken from the EQ-5D.

The initial procedural cost of CAS was $7,084 and $3,003 for CEA. Annualized costs incorporated post-procedural hospital care, and recurrent hospitalizations. Baseline costs were assumed to be $5,817 per year. MI incurred a cost of $10,176 per year and major strokes cost $18,515 per year.

Relying on the SAPPHIRE trial data, 1-year clinical outcome rates were given. CAS had a mortality rate of 7% while CEA was nearly double at 13%. Minor and major strokes occurred at a rate of 4% and 1% in the CAS treatment arm, and 2% and 4% in the CEA patients. MI was assumed to 2.5% and 7.9% for CAS and CEA respectively. Life expectancy was estimated by applying the occurrence of adverse outcomes to life expectancy approximations derived from the Saskatchewan Health Database (consisting of 31,006 similarly high-risk patients). With no adverse events, males were expected to live 8.22 years and females 9.34 years.

Using EQ-5D no adverse events received a utility level of 0.841. MI was given a weight of 0.737, major strokes a weight of 0.436 and minor strokes a weight of 0.729.

Results:
Mahoney and colleagues found that for asymptomatic patients CAS had a post-procedure remaining lifetime cost of $60,700. CEA was estimated to cost $58,798. CAS yielded 0.71 more QALYs implying an ICER of $2,667/QALY based on the lifetime horizon. However, if the scope of the model is reduced to a 1-year time horizon, the cost-effectiveness the ICER became $49,514/QALY.

The authors followed their base case results with a sensitivity analysis that varied several of the assumptions made in the model. Considering both symptomatic and asymptomatic patients, if the cost of stents and embolic protection devices were reduced by a half, the ICER for stenting would fall to $2,373/QALY, suggesting that CAS would be cost effective based on this time horizon. If loss of life expectancy related to death, MI and stroke were reduced by 50% (resulting in longer lives), the ICER increased to $10,623

Conclusions and limitations:
Mahoney et al.[124] interpreted their findings to suggest that for patients at a high risk of adverse outcomes from CEA, CAS is a potentially cost-effective alternative treatment from the perspective of the US healthcare system. The authors caution that these results are not necessarily generalizable to populations outside of those described by the SAPPHIRE trial (specifically patients at low surgical risk). Further limitations relating to using SAPPHIRE as a data source are described above for the Maud et al. study. Regarding the estimation of patient utilities, the values used were derived from EQ-5D for all times within the trial. However, when forecasting beyond 1-year Beaver Dam based utilizes were assigned, which have a tendency to underestimated differences in utilities when compared to EQ-5D. The Beaver Dam study relies on SF-36 to predict utilities, whereas EQ-5D uses time trade-off estimated and references a British study by Dolan et al.[61] Given the impact of different methodologies in determining utility weights, it can be problematic to use multiple approaches and ultimately may confound the end results. Attention was also drawn to difficulties approximating life expectancy parameters. The impact of this variability was addressed in the sensitivity analysis where the loss of life expectance was cut in half and CEA still failed to dominate CAS. Compared with the Maud study, different rates of stroke, types of stroke and weights were used, contributing in the differences in findings between the two studies.

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inventor of the Angioguard emboli-protection device used in the SAPPHIRE trial and was a shareholder in Angioguard, Inc. at the time of its purchase by Johnson & Johnson in 1999. He receives recurring payments from Johnson & Johnson as a former shareholder of Angioguard, Inc. He does not own any shares of stock in Johnson & Johnson. Dr. Cohen has received research support from and serves as a consultant to Cordis, Inc. Dr. Wholey was a shareholder in Angioguard at the time of its purchase by Johnson & Johnson in 1999. He receives recurrent payments by Johnson & Johnson as a former shareholder of Angioguard, Inc. He was also on the advisory board for Cordis at that time. Dr. Gray has served as a consultant to Cordis/Johnson & Johnson."

Study Synopsis: Vilain et al. 2012

Overview:
Vilain et al.[175] compared the cost-utility of CAS and CEA. The study was designed as a compliment to the CREST trial, which included both symptomatic and asymptomatic subgroups. ICERs were computed for both groups.

A Markov disease-simulation model was implemented to evaluate the costs and patient outcomes over time. 10-year forecasts were projected and the model's calibration was confirmed through back-testing (i.e. using the model to predict observable outcomes to verify its performance).

The US healthcare system was the assumed perspective of the analysis. All future values were discounted by 3% annually to 2008 levels.

Assumptions:
The model was calibrated to the CREST results, which consisted of 2,502 patients, 53% of which were classified as symptomatic. Resource use for each procedure was multiplied with unit costs to estimate procedural cost where acquisition costs were approximated from a sample of study centers. Hospital billing records were used to estimate costs over the first year. SF-36 scores were used to estimate utility levels. From the 1-year observed outcomes, the model forecasted 10-year estimates.

The index hospitalization cost of a CAS procedure was estimated to be $15,055, while CEA was $14,816. At the one-year follow up, taking into consideration adverse events and their associated costs, the cumulative costs were $16,375 and $16,108 for CAS and CEA respectively (not statistically significant different, p-value=0.223).

From CREST, there was assumed to be death rate and major stroke rate of 0.3% and 0.5% respectively for CAS patients. The corresponding CEA rates were 0.2% and 0.3% (both with p-values testing for difference across treatments greater than 0.5). Minor strokes and MI had

an incidence rate of 2.5% and 1.5% in CAS and 1.0% and 2.9% in CEA (both p-values less than 0.05 for comparison between treatments).

Utility weights were derived from SF-36. First raw SF-36 scores were converted to utility weights based on the methodology used by Brazier and colleagues and appear to reflect the British population.[44] Linear regression was then used to estimate the influence of adverse outcomes on patient utility levels. Major stroke was shown to have the largest impact on the utility level of surviving patients, and was given a disutility weight of 0.10 for the first month, and 0.06 after 12-months. Minors strokes weighted the patients' utility by a factor of 0.02 after 1-month, and 0.03 after 12-months. Neither MI nor cranial nerve injury influenced utility levels differently across treatment types.

Results:
Separate results were presented depending on symptom status. For asymptomatic patients, the expected costs were $80,314 and $79,705 while the expected QALYs were 4.862 and 4.859. Computing the ratio of the differences yields an ICER of $277,249/QALY. Similar results were found for symptomatic patients as well.

To test the robustness of the results, the uncertainty of parameters was assessed using a probabilistic sensitivity analysis, which sampled all of the estimates from their specified distributions. This was iterated 1,000 times and performed for each subgroup. Assuming a willingness to pay of $50,000/QALY, the simulation found CEA to be preferred 54% of the time for asymptomatic patients. Therefore, if society is only willing to pay $50,000 for each quality-adjusted year of the patient's life approximately 54% of the time CEA will be preferred.

Conclusions and limitations:
Vilain and colleagues found CAS to be slightly more expensive both in with respect to initial procedural costs and over a 10-year projected time horizon. Comparing the quality-of-life effects of the two treatments revealed insignificant long-term differences. The sensitivity analysis suggested that there was approximately a 50% chance of each treatment being economically preferred. The authors concluded that for populations similar to that used in this study, there was insufficient evidence to recommend one procedure over the other.

The authors caution generalizing the results outside of the assumptions made explicit in the analysis. They also note that both fixed and variable costs were used to estimate resource use when in the short-term pure variable costs might be more accurate (though more difficult to approximate). The results using estimates for utility weights taken from Brazier et al.[44] tend to yield more conservative estimates than studies referencing EQ-5D and the approach used by Post and colleagues.[148] A more detailed sensitivity analysis would be helpful to show the dynamics of the cost-effectiveness relationship between the two treatments. Lastly, the

authors discuss a potential bias in site and operators used in the CREST data, which may not be representative of typical clinical practice due to extensive training and adequate volumes.

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4.5.2. Symptomatic

Summary of full economic analysis studies for symptomatic patients (overall strength of evidence, low)

CAS compared with CEA: Of the five included cost-utility studies comparing CAS with CEA, four provided data for symptomatic patients (two studies that considered only symptomatic patients[99,186] and two that provided a subgroup analysis stratified by symptom status[124,175]).

- Evidence across four cost-utility studies indicated that CEA tended to be more cost-effective than CAS in symptomatic patients. Two out of the four studies examining symptomatic patients found there to be insufficient evidence to strongly favor one treatment method over the other.
- In two studies focused on symptomatic patients, one concluded that CAS was at best non-inferior in terms of clinical outcomes, however, its long-run cost savings failed to compensate for the greater upfront procedural costs. The second study found CEA to be both more effective and less costly for symptomatic patients (CEA dominated CAS). The first study authors chose not to report a specific ICER due to variability in models when different data sources were used.
- In the two studies that presented sub-group results for symptomatic patients, CAS was not found to be an economically attractive alternative. CEA dominated CAS in one and was preferred in the other.

Detailed results: full economic analysis studies of symptomatic patients

CAS compared with CEA: Evidence across four full economic, cost-utility studies indicated that CEA tended to outperform CAS in symptomatic patients as well.[99,124,175,186]

The results were even less favorable for CAS in this population. Studies done by Janssen (2008)[99] and Young (2010)[186] examined the cost-effectiveness of CAS and CEA in symptomatic patients. When compared to the studies that considered high-risk patients described by the SAPPHIRE trial data, these studies produced less economically attractive results for CAS. The two symptomatic patient focused studies both implemented long-term Markov disease-simulation models one considered 10-year outcomes and the project the patients remaining lifetime outcomes. Young and colleagues found CAS to be dominated by CEA (i.e. more expensive and fewer QALYs). Janssen and colleagues concluded that CAS is at best, a non-inferior treatment to CEA; however, because of a wide range in variability, an accurate ICER was unavailable. Both studies indicated a strong positive correlation between the incidence rate of major peri-procedural stroke and the cost-effectiveness of CAS. The death rate after CAS was also a major contributor to the difference in costs and effects. Janssen goes on to note that the reduction in the length of hospital stay is offset by the higher initial procedural costs of CAS.

Vilain (2012)[175] and Mahoney (2011)[124] considered patients of both symptomatic statuses separately. The Vilain study was designed to be an economic evaluation conducted alongside the CREST trial. The CREST trial was different from the SAPPHIRE trial both in patient population and in corresponding clinical outcomes. CREST had more similar outcomes across treatments and very little difference in survival rates. Due to a lack of notable outcome differences and a sensitivity analysis suggestive of equal likelihood of cost-effectiveness for each treatment, the authors conclude that the preferred procedure should be determined according to factors other than a cost-effectiveness measure alone such as individual patient characteristics. Lastly, Mahoney (2011)[124] considered a sub-group of symptomatic patients at high surgical risk found the SAPPHIRE trial. The study found CAS to be the more expensive treatment option with negligible QALY improvement, which produced an extreme ICER of $204,229/QALY.

The overall strength of evidence was again considered low. Two out of the four studies examining symptomatic patients found there to be insufficient evidence to strongly favor one treatment method over the other. However, results were consistently less favorable for CAS. QHES scores ranged from 94-100. Primary limitations across studies were similar for both symptomatic statuses- notably there was insufficient follow-up evidence.

Study Synopsis: Janssen et al. 2008

Overview:
Janssen et al.[99] evaluated the cost-effectiveness of CAS compared to CEA in symptomatic patients. Their results and subsequent discussion explored key factors determining cost-effectiveness through a comparison of ICERs across different data sources and outcome rates.

A multi-state Markov decision model was implemented for the analysis. Hypothetical patients moved between mutually exclusive health states allowing estimates of relevant costs and treatment effectiveness to be determined over a ten-year time horizon. Health states included healthy, minor stroke, major stroke, and death. Different scenarios were considered to test the models' robustness and provide insight to significant variables.

The study was carried out in the Netherlands. Costs were considered from the hospital's perspective. Expenses and quality of life measures were adjusted to 2003 levels using a discount rate of 4% and appropriate purchase power parities.

Assumptions:
A hypothetical cohort was designed to reflect a target population of symptomatic patients suffering from carotid artery stenosis. All treatment costs were based on procedures performed successfully, while the costs of complications were derived from published literature. Effectiveness for CEA was modeled using peri-operative survival rates from the European Carotid Stenosis Trial (ECST)[10] trial with greater than 70% stenosis. A review by Wholey was referenced for CAS effectiveness, which surveyed data from the Global Artery Stent Registry.[179] Further comparisons were made using data from a 2007 Cochrane Review by Ederle.[66]

Procedural costs were found to be €5,500 and €4,012 ($6,510 and $4,749) for CAS and CEA respectively. The cost of MI was estimated to be €15,000 ($17,575) and the cost of an acute major stroke was €25,769/event ($30,505). The projected expenditure for a major stroke within six-months of treatment was €18,789/6 months and €5,556/6 months ($22,242 and $6,577) for minor strokes. After a six-month window, the associated costs were reduced to €8,017 and €4,146 ($9,490 and $4,908). Procedural costs were derived from hospital records. The costs of adverse outcomes were obtained from published literature.

The likelihood of complications was given as annual percentages. Re-operations rates were 0.68% and 0.09% for CAS and CEA respectively. Minor and major strokes occurred at a rate of 0.66% and 0.43% per year. MI was assumed to affect patients at a rate of 1.59% annually. The probability of technical failure during CAS was 1.11%, where technical success was

defined as less than 30% residual stenosis that covers an area smaller than the original lesion without any decreased or abnormal intracranial arterial anatomy.

To approximate QALYs, the authors consulted published literature to find utility parameters. Healthy individuals were assigned a QALY of 1 per year. Patients experiencing from MI, minor strokes, major strokes and death received a QALY per year of 0.88, 0.65, 0.15 and 0.00 for their respective health state.

Results:
Due to the wide variability induced by certain model parameters, specifically the peri-operative major stroke rate, the authors concluded that there was insufficient evidence to estimate an ICER.

This variability was explored with sensitivity analysis. Simulations showed that when using the Cochrane data, CEA was the preferred treatment 99.7% of the time (assuming a cost-effectiveness threshold of €25,000/QALY ($29,595/QALY). However, modeling with the Wholey data, which reported significantly lower complication rates, CAS was the preferred treatment 93.3% of the time. To better explain this discrepancy Janssen et al.[99] provided the change in costs and effects per percentage increase in complications. Most notably, they found increasing the risk of peri-operative major stroke resulted in increased costs of €1,051 ($1,244). The length of hospital stay was another influential parameter, which if reduced by 3-days caused an additional €740 ($876) in savings for CEA. Overall, if the complication rates for CAS, especially for peri-operative major stroke, were shown to be as low as reported by Wholey and colleagues then CAS would be a cost-effective alternative.

Conclusions and limitations:
Janssen and colleagues[99] found CAS to be at best a non-inferior alternative to CEA in terms of clinical outcome. They go on to conclude that the cost savings due to shorter hospital stays are offset by more expensive procedural costs. Furthermore, the authors stress that their analysis relied solely on short-term outcomes and that additional evidence is needed to yield insights into long-term cost-effectiveness. Similarly, inherent in any modeling study is estimation error, which the authors highlight in their sensitivity analysis, however the sensitivity analysis was limited (restricted to model parameters) and not well reported. Given the impact complication rates had in determining the cost-effectiveness, verifying these parameters across the multiple studies would be essential to arrive at an accurate ICER. Overall, the presentation of the results was limited in scope. Lastly, the economic analysis was designed and conducted in the Netherlands with cost associated with Dutch healthcare. Therefore, consideration should be taken when generalizing the results outside of that context.

Funding and disclosures:
Funding was provided by the Netherlands Organization for Health Research and Development. Disclosed potential conflicting of interest included two authors have served advisory roles for industry companies and have received research grants for other work

Study Synopsis: Young et al. 2010

Overview:
Young et al.[186] investigated the cost-effectiveness of CAS compared to CEA in symptomatic patients. Through a modeling approach, incremental costs and QALYs were compared.

The authors designed a Markov model to evaluate the treatments over time. Hypothetical patients transitioned between states of being well, suffering a major stroke, minor stroke, or death at specified probabilities. The model used one-month cycles over the remaining lifetime of the patients, based on a cohort of 70 year olds.

The analysis assumes a perspective that includes US Medicare costs. 2007 is used as the base year and costs and future utilities were discounted at a rate of 3%.

Assumptions:
The target population consisted of symptomatic 70-year-old patients suffering from carotid artery stenosis who were medically suitable for either intervention. Probability data beyond 30-days was obtained as a weighted average of the 2-year SPACE, 3-year SAPPHIRE and 4-year EVA-3S studies (weighted by trial size). Short-term outcomes were derived from a meta-analysis of 30-day outcomes.

The cost of a CAS procedure was estimated to be $10,400, while CEA was $9,170. The cost of care for each adverse health states was assumed to be equivalent for both treatment arms. The cost per year of MI, minor stroke and major stroke was $4,500, $7,500, and 33,900 with initial hospitalization cost of $9,100, $9,800, and $10,500 respectively.

Transition rates for short-term outcomes with CAS were 0.64%, 3.81%, 3.21% and 0.62% for MI, minor stroke, major stroke and death. CEA was assumed to have associated rates of 1.31%, 2.66%, 2.02% and 1.26% for the same events. Over a long-term time horizon death rates of CAS exceeded those so CEA averaging 1.5% per year compared to 0.96%. The risk of stroke for CAS patients was nearly double that of CEA patients at 4% versus 2.1% (with 30% being major strokes).

The baseline quality of life for being well was 1, and 0 for death. MI was weighted by a factor of 0.88, minor strokes received a weight of 0.65, and major strokes a weight of 0.15.

Quality of life measures were derived from the EQ-5D database with stroke risks matched according to Rankin scores.

Results:
Applying their model, Young et al.[186] found CAS had lifetime costs of $52,900 and a QALY gain of 8.97. CEA was estimated to cost $35,200 with total QALYs of 9.64. Therefore, CAS was dominated by CEA because it was provided fewer QALYs and was more expensive.

One one-way deterministic sensitivity analyses was used to investigate the model's assumptions. Increasing the long-term stroke rate of CEA from 2.1% per year to 6.3% per year resulted in CAS dominating CEA. Varying post-30-day mortality rates for CEA or CAS shows it to be a highly influential parameter and driver of cost-effectiveness. Varying the proportion of those starting in the "well" or "minor stroke" branches and the 30-day peri-procedural risks did not affect the dominance of CEA. None of the procedural costs, or utility parameters altered the conclusions of the base case analysis.

The authors also performed a two-way sensitivity analysis to explore the influence of stroke rates after 30-days. Assuming equivalent rates of stroke, CEA remained more cost-effective.

A probabilistic sensitivity analysis found CEA to be the preferred treatment 59% of the time over a wide range of economic values for each QALY and a willingness to pay of more than $200,000. This suggests that supposing society was willing to pay more than $200,000, CEA would remain the optimal treatment 59% of the time when allowing for variations in the model's parameters.

Conclusions and limitations:
Given the assumptions of their model, Young and colleagues determined CEA dominates CAS. From the study's sensitivity analysis, the authors note the importance of long-term strokes and risk of mortality in determining the cost effective treatment. When equal rates of stroke were assumed beyond the first 30-days CEA was still the preferred treatment at a willingness to pay of $100,000.

When performing the meta-analysis to estimate outcome rates, the authors note both high-risk and standard-risk patients for CEA were pooled together. The data used only consisted of 2 to 4 years of follow-up observations. Lastly, only major adverse outcomes were considered, for a more complete understanding of the cost effectiveness of the CAS compared to CEA a more detailed analysis is needed.

Funding and disclosures:
Funding was provided by The National Center for Research and Resources, and the NIC Roadmap for Medical Research. A portion of author's salary is from the NIH and has also received a clinical research grant for ACT-1 and CREST.

Study Synopsis: Vilain et al. 2012[175] (symptomatic patients only)
(See asymptomatic section above for further details concerning study design, limitations and disclosures)

Results for symptomatic patients:
For symptomatic patients CAS was dominated by CEA with expected costs of $79,988 and $79,540 and expected QALYs of 4.823 and 4.840. In the asymptomatic subgroup, the results were similar, however, CAS slightly increased the number of QALYs.

Assuming a willingness to pay of $50,000/QALY, the simulation found CEA to be preferred 57% for symptomatic patients. Therefore, if society is only willing to pay $50,000 for each quality-adjusted year of the patient's life approximately 57% of the time CEA will be preferred.

Study Synopsis: Mahoney et al. 2011[124] (symptomatic patients only)
(See asymptomatic section above for further details concerning study design, limitations and disclosures)

Results for symptomatic patients:
Restricting the analysis to symptomatic patients resulted in a lifetime cost of $60,131 and $53,141 for CAS and CEA respectively. With a much smaller incremental difference in QALYs of only 0.03 favoring CAS. The resulting ICER was found to be $204,229/QALY.

Mahoney et al.[124] discussed the results according to symptomatic status and reported that after one year there was a significant clinical benefit for asymptomatic patients treated with CAS (9.9 vs. 21.5%, p=0.02). However, the symptomatic patients did not experience the same benefit (16.8 vs. 16.5%, p=0.95). This lack of effectiveness in symptomatic patients was the cause of the small incremental change in QALY, which ultimately produced the high ICER.

Table 49. Summary of Included Economic Studies

Study (year) QHES Funding	Design Perspective Population	Primary Findings (ICER; dominance, range of ICERs)	Limitations	Comments
Asymptomatic				
Maud (2010) QHES = 84 NR	• Monte Carlo simulation using SAPPHIRE trial data with one-year follow up. • Health system perspective • Asymptomatic patients at high surgical risk, average age of 72	Results: • CAS cost = $12,782 • CEA cost = $8,916 • CAS QALY = 0.712 • CEA QALY = 0.753 • CAS vs. CEA ICER: $67,891 Notes: • 1- year results	• The SAPPHIRE trial was prematurely terminated due to slow recruitment. • Short follow-up time of 1-year • No secondary outcomes were considered • Broad assumptions made in gathering utility weights, no sensitivity analysis on QoL.given	• Authors suggest that the procedural costs of CAS needs to be reduced to that of CEA to make it C/E • The target population of the SAPPHIRE trial is patients are high surgical risk
Mahoney (2011) QHES = 99 Funding source not disclosed, though funding agreement stipulated that the authors reserved the right to publish regardless of their findings.	• Bootstrap approximation methods using SAPPHIRE trial data with lifetime horizon. • US Healthcare perspective • Primarily asymptomatic patients with sub-group results for symptomatic patients (See below for results) • High surgical risk patients	Results: • 1-year ICER: $49,514/QALY • CAS: lifetime cost = $60,700 • CEA: lifetime cost = $58,798 • Incremental QALY (CAS-CEA): 0.71 • Lifetime CAS vs. CEA ICER: $2,667/QALY Notes: • Remaining lifetime results (expected life: male = 8.22 yrs, female = 9.34 yrs)	• Uses SAPPHIRE trial results. Similar limitations to Maud et al. above • Concern due to the variability in life expectancy estimates. • Multiple methodologies used to estimate utility weights. Possible confounding.	• Though modeled over a lifetime horizon, only had access to 1-year follow up outcomes, resource use, costs and QoL. •
Vilain (2012) QHES = 94 National Institute of Neurological Disorders and Stroke and the National Institutes of Health	• Markov model • US Healthcare system perspective • Provides results for both asymptomatic and symptomatic patients (see below)	Results: • CAS: cost = $80,314 • CEA: cost = $79,705 • CAS: QALY = 4.862 • CEA: QALY = 4.859 • ICER: $277,249/QALY Notes: • 10-year time horizon	• Used both variable and fixed costs for resource use when strictly variably may have been more accurate • Potential bias in site and operators used in sample	Conclude that for populations similar to that used in this study, there is insufficient evidence to recommend one procedure over the other.
Symptomatic				
Janssen (2008) QHES = 96 Netherlands Organization for Health Research and Development	• Markov model • Hospital specific cost in the Netherlands • Symptomatic patients	Results: • CAS procedural costs: €5,500 ($6,510) • CEA procedural costs: €4,012 ($4,749) • Inconclusive ICER (due to data variability) Notes: • 10-year time horizon	• Only short-term data • Dutch specific costs	• Found major stroke rate to be a key factor in determining CE • Reducing hospital stay time causes CEA to become more cost effective
Young (2010) QHES = 100 The National Center for Research and Resources	• Markov model • Medicare costs perspective • 70-year-old symptomatic patients suitable for either procedure	Results: • CAS: Cost = $52,900 • CEA: Cost = $35,200 • CAS QALY = 8.97 • CEA QALY = 9.64 • CAS dominated by CEA • Simulation showed CEA to remain optimal treatment 59% of the time Notes: • Remaining lifetime results	• Follow-up data limited to 4-years • Pooled all risk-level patients for CEA in meta-analysis for event probability	• Found long-term stroke rate and mortality to be a key factor in determining CE • Tripling the risk of stroke after CEA from 2.1% to 6.3 caused CAS to dominate

Study (year) QHES Funding	Design Perspective Population	Primary Findings (ICER; dominance, range of ICERs)	Limitations	Comments
Mahoney (2011) (See above)	• (See above)	Results: • CAS: cost = $60,131 • CEA: cost = $58,798 • Incremental QALY (CAS-CEA): 0.03 • CAS vs. CEA ICER: $204,229/QALY Notes: • Remaining lifetime results (expected life: male = 8.22 years, female = 9.34 years)	• (See above)	• (See above) • The high ICER is driven primarily by the small difference in QALYs between treatments.
Vilain (2012) (See above)	• (See above)	Results: • CAS: cost = $79,988 • CEA: cost = $79,540 • CAS: QALY = 4.823 • CEA: QALY = 4.840 • CAS is dominated by CEA Notes: • 10-year time horizon	• (See above)	• See above)

Glossary of Economic Terminology

Term/Abbreviation	Definition
CAS	Carotid Angioplasty and Stenting
CEA	Carotid Endarterectomy
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio defined to be the difference in cost divided by the difference in QALY. A generalized measure of cost per unit of improvement.
MI	Myocardial Infarction
QALY	Quality Adjusted Life Years. A utility weighted measure of patients' duration and quality of life.
QHES	Quality of Health Economics Score
QoL	Quality of Life
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy

4.5.3. Intracranial

No formal economic evaluations were found analyzing the cost-effectiveness of CAS compared with medical therapy for stenting of intracranial atherosclerotic disease.

5. Summary by Key Question – Strength of Evidence

The overall quality (strength) of the body of evidence for the primary outcomes for each key question is provided in the tables below. The summaries below are based on the highest quality evidence available. Additional information on other outcomes and lower quality studies is available in the report. Strength of evidence (SoE) considers study design, elements that may influence the risk of bias in a study and factors that increase or decrease the confidence in the effect estimates when looking across a body of evidence. (See appendices for additional detail). Interpretation of the strength of evidence categories, based on the AHRQ Methods Guide[22] are as follows:

High – Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.

Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.

Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or the estimate is close to the true effect.

Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; No available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Key Question 1: What is the evidence for efficacy and effectiveness?

Asymptomatic

Randomized controlled trials

Quality of evidence summary for Key Question 1: In asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)** RR (95% CI)**	**Favors**
Any stroke	4 years 1 RCT N = 85	Serious risk of bias*	Unknown	No serious indirectness	Serious risk of imprecision ‡	Undetected	Low	0.0% (0/43)	0/0% (0/42)	Not estimable	NA
Ipsilateral stroke	4 years 2 RCTs N = 1181 N = 85	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low	1.5% (9/584) 0.0% (0/43)	0.9% (5/582) 0.0% (0/43)	RD = 0.7 (-0.57, 1.9) RR = 1.78 (0.60, 5.28) Not estimable	NS NA
Any periprocedural stroke or death or post-procedural ipsilateral stroke	4 years 1 RCTs N = 1181	Serious risk of bias*	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	4.5% (24/594)	2.7% (13/587)	RD = 1.9 (-0.5, 4.3) HR = 1.9 (0.95, 3.7)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; NS: not statistically significant; RD: risk difference; RR: risk ratio.
NOTE: A total of 2 RCTs are represented in the table.
** A negative risk difference favors CAS and positive risk difference favors CEA

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Nonrandomized comparative studies

Quality of evidence summary for Key Question 1: In asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative effectiveness of extracranial CAS and medical therapy compared with medical therapy alone.

KQ1:CAS vs. medical therapy only								Treatment groups		Effect size	
Outcome	**Studies N Follow-up (median)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)***	**Medical (%)***	**Adjusted HR (95% CI)***	**Favors**
Any stroke	1 retrospective registry N = 946 2.1 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	9	11	0.5 (0.2, 0.9)	CAS
Death	1 retrospective registry N = 946 2.1 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	20	32	0.7 (0.5, 0.9)	CAS
Any stroke or death	1 retrospective registry N = 946 2.1 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	29	38	0.7 (0.5, 0.9)	CAS

CAS: carotid artery stenting; CI: confidence interval; HR: hazard ratio.
NOTE: A total of 1 nonrandomized study is represented in the table.
*Kaplan-Meier estimates for projected 5 years of follow-up. Authors conducted a propensity-score adjusted analysis with the following baseline clinical characteristics were entered into a multivariate probit model to define a propensity score: age, gender, body mass index, degree of carotid stenosis, diabetes, hypertension, hyperlipidemia, smoking, congestive heart failure, coronary artery disease, history of myocardial infarction, peripheral artery disease, concomitant malignancy, American Society of Anesthesiologists classification (I to IV), Asymptomatic Carotid Atherosclerosis Study eligibility, and the date of CAS to account for temporal trends during the study period.

Reasons for downgrading quality of evidence:
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Quality of evidence summary for Key Question 1: In asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative effectiveness of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)* RR/HR (95% CI)**	**Favors**
Any stroke	1 prospective cohort N = 269 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	9.2	5.7	RD = -3.5 (-12.5, 3.2) RR = 1.6 (0.6, 4.2)	NS
	1 prospective registry† N = 1672 1.5 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	3.8‡	2.6‡	Adjusted HR = 1.4 (0.8, 2.5)	NS
Death	1 prospective cohort N = 269 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	22.2	19.7	RD = -2.4 (-14.0, 8.5) RR = 1.1 (0.7, 1.9)	NS
	1 prospective registry† N = 1672 1.5 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	7.4‡	7.4‡	Adjusted HR = 0.7 (0.5, 1.1)	NS
Any stroke or death	1 prospective cohort N = 269 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	25.8	23.2	RD = -2.6 (-14.7, 8.8) RR = 1.1 (0.7, 1.8)	NS
	1 prospective registry† N = 1672 1.5 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	9.9‡	8.9‡	Adjusted HR = 0.9 (0.6, 1.3)	NS

KQ1: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)* RR/HR (95% CI)**	**Favors**
MI	1 prospective cohort N = 269 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	7.9	10.1	RD = 2.2 (-7.1, 10.1) RR = 0.8 (0.3, 2.0)	NS
	1 prospective registry† N = 1672 1.5 years	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	3.2‡	4.8‡	Adjusted HR = 0.6 (0.4, 1.1)	NS
Any periprocedural stroke or death or post-procedural ipsilateral stroke	1 prospective cohort N = 1518 2.8 years	Serious risk of bias††	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	3.3§	2.5§	RR = 0.8 (0.5, 1.4)**	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NS: not statistically significant; RD: risk difference; RR: risk ratio.
NOTE: A total of 3 nonrandomized studies are represented in the table.
*A positive risk difference favors CAS and negative risk difference favors CEA.
†Propensity score-matched analysis. The model included the following baseline characteristics: age, sex, race, documented transient ischemic attack, prior coronary artery bypass grafting, documented ischemic stroke, myocardial infarction, nitrates, beta blockers, calcium channel blockers, statins, angiotensin-converting enzyme (ACE)-inhibitors, diuretics, insulin, smoking, unstable/stable angina, diabetes, congestive heart failure, ACE/angiotensin receptor blocker, hypercholesterolemia, history of atrial fibrillation, and history of treated hypertension.
‡Kaplan Meier rate estimates as reported by the authors.
§5 year Kaplan Meier rate estimates as reported by the authors.
**Calculated from raw data by the Agency for Healthcare Quality and Research (AHRQ).

Reasons for downgrading quality of evidence:
†† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)
‡‡Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§§Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Symptomatic

Randomized controlled trials

Quality of evidence summary for Key Question 1: In symptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Symptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)** RR (95% CI)**	**Favors**
Any stroke (excluding periprocedural	4 months 1 RCT N = 1710	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	0.8% (7/853)	0.9% (8/857)	RD = -0.11 (-0.99, 0.77) RR = 0.88 (0.32, 2.42)	NS
	2-4 years 2 RCTs	Serious risk of bias*	No serious inconsistency.	No serious indirectness	No serious imprecision	Undetected	Moderate	3.5% (30/866)	3.5% (30/846)	RD†† = -0.08 (-1.82, 1.66) RR†† = 0.98 (0.59, 1.61)	NS
Ipsilateral stroke (excluding periprocedural)	4 months 1 RCT N = 1710	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	0.7% (6/853)	0.5% (5/857)	RD = 0.12 (-0.63, 0.87) RR = 1.20 (0.37, 3.93)	NS
	2-5.4 years 4 RCTs	Serious risk of bias¶	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	2.0% (31/1577)	1.9% (30/1543)	RD†† = -0.01 (-1.36, 1.34) RR†† = 0.97 (0.55, 1.73)	NS
Death	4 months 1 RCT N = 1710	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	2.3% (19/853)	0.8% (7/857)	RD = 1.37 (0.23, 2.51) RR = 2.69 (1.14, 6.36)	CEA

KQ1: Symptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)** RR (95% CI)**	**Favors**
	2-5.4 years 5 RCTs (including periprocedural)	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	7.9% (77/975)	8.2% (79/959)	RD†† = -0.10 (-2.17, 1.96) RR†† = 0.97 (0.72, 1.30)	NS
	2-5.4 years 2 RCTs (excluding periprocedural)	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	4.1% (27/664)	3.7% (24/644)	RR†† = 0.38 (-1.87, 2.64) RR†† = 1.09 (0.64, 1.87)	NS
Any stroke or death (including periprocedural)	4-6 months 2 RCTs N = 527 N =1710	Serious risk of bias¶	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	11.8% (31/262) 8.5% (72/853)	9.8% (26/265) 4.7% (40/857)	RD = 1.65 (-3.17, 6.46) RR = 1.18 (0.72, 1.94) RD = 3.32 (1.13, 5.52) RR = 1.75 (1.20, 2.54)	NS CEA
	2-4 years 2 RCTs	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡	Undetected	Low	1.6% (1/63)	4.9% (3/61)	RD††= -2.18 (-7.33, 2.96) RR†† = 0.43 (0.07, 2.69)	NS
Any periprocedural stroke or death or post-procedural ipsilateral stroke	6 months 1 RCT N = 527	Serious risk of bias¶	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	10.2% (27//262)	4.2% (11/265)	RD = 5.36 (1.28, 9.43) RR = 2.34 (1.19, 4.63)	CEA
	2-5.4 years 5 RCTs	Serious risk of bias¶*	Serious inconsistency	No serious indirectness	Serious risk of imprecision ‡	Undetected	Low	8.1% (112/1381)	6.6% (89/1347)	RD†† = 1.28 (-1.64, 4.19) RR†† = 1.20 (0.89, 1.62)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NR: not reported; NS: not statistically significant; RD: risk difference; RR: risk ratio.
NOTE: A total of 7 RCTs are represented in the table.
** A negative risk difference favors CAS and positive risk difference favors CEA
†† Effect size estimates from pooled meta-analysis with weighting based on sample size; data for n/N are numbers of total events/total number of patients
¶ CAS and CEA patients received different anti-platelet interventions in two trials (EVA, SPACE)

Reasons for downgrading quality of evidence (general):
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Nonrandomized comparative studies

Quality of evidence summary for Key Question 1: In symptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative effectiveness of extracranial CAS and medical therapy compared with CEA and medical therapy.

KQ1: Symptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**CEA (%)**	**RD % (95% CI)* RR (95% CI)**	**Favors**
Any stroke	1 prospective cohort N = 128 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	7.2	17.8	RD = 10.7 (-3.2, 22.0) RR = 0.4 (0.1, 1.3)	NS
Death	1 prospective cohort N = 128 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	10.4	24.9	RD = 14.5 (-2.0, 28.3) RR = 0.4 (0.2, 1.2)	NS
Any stroke or death	1 prospective cohort N = 128 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	12.4	33.5	RD = 20.8 (4.0, 34.5) RR = 0.4 (0.2, 0.9)	CAS
MI	1 prospective cohort N = 128 4 years	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	7.1	12.6	RD = 5.4 (-11.4, 17.6) RR = 0.6 (0.1, 2.6)	NS
Any periprocedural stroke or death or post-procedural ipsilateral stroke	1 prospective cohort N = 684 2.8 years	Serious risk of bias††	Unknown	No serious indirectness	Precision Unknown	Undetected	Low	4.9†	8.7†	NR	NS‡

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NR: not reported; NS: not statistically significant; RD: risk difference; RR: risk ratio.

NOTE: A total of 2 nonrandomized studies are represented in the table.
*A positive risk difference favors CAS and negative risk difference favors CEA.
†5 year Kaplan Meier rate estimates as reported by the authors.
‡As reported by the authors, "rates were similar between groups" (*P* = .07).

Reasons for downgrading quality of evidence:
†† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)
‡‡Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§§Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Key Question 2: What is the evidence of short- and long-term comparative efficacy and of safety (peri-procedural, 30-day outcomes) in persons with atherosclerotic intracranial artery stenosis?

Asymptomatic

No studies were found.

Symptomatic

Efficacy

Quality of evidence summary for Key Question 2: In persons with atherosclerotic intracranial artery stenosis what is the evidence of short- and long-term comparative efficacy of CAS and aggressive medical therapy compared with medical therapy alone.

KQ2: Efficacy of intracranial artery stenting versus medical therapy								Treatment groups Probability (%) 1 year (95% CI) Patient Events (n/N)		Effect size**	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS**	**Medical**	***P*-value†**	**Favors**
Any stroke	1 RCT N = 451 1 year	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	22.3 (17.2–28.7) (50/224)	14.9 (10.6–20.7) (32/227)	.03	Medical RD 7.4% NNH 13

KQ2: Efficacy of intracranial artery stenting versus medical therapy								Treatment groups Probability (%) 1 year (95% CI) Patient Events (n/N)		Effect size**	
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS**	**Medical**	***P*-value†**	**Favors**
Death	1 RCT N = 451 1 year	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	3.4 (1.6–7.2) (7/224)	4.1 (2.0–8.5) (7/227)	.95	NS
Any stroke or death	1 RCT N = 451 1 year	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	23.4 (18.1–29.8) (52/224)	17.5 (12.8–23.6) (37/227)	.06	NS
Study's Primary Outcome: Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days	1 RCT N = 451 1 year	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	20.0 (15.2–26.0) (46/224)	12.2 (8.4–17.6) (26/227)	.009	Medical RD 7.8% NNH 13
Myocardial infarction	1 RCT N = 451 1 year	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	2.2 (0.8–5.8) (5/224)	4.0 (1.9–8.4) (7/227)	.60	NS
Any major hemorrhage	1 RCT N = 451 1 year	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	9.0 (5.9–13.5) (22/224)	1.8 (0.7–4.8) (5/227)	< .001	Medical RD 7.2% NNH 14

CAS: carotid artery stenting; CI: confidence interval; NS: not statistically significant.

NOTE: Only 1 RCT (SAMMPRIS trial) is represented in the table.

**Authors do not report effect size; probabilities and p-values are provided.

†The p-value is for the comparison, with the use of the log-rank test, of the time-to-event curves for the two treatment groups for each of the specified adverse events.

Reasons for downgrading quality of evidence (general):

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)

‡Consistency across multiple studies cannot be evaluated

Safety

Table X. Quality of evidence summary for Key Question 2: In persons with atherosclerotic intracranial artery stenosis what is the evidence of the safety (peri-procedural, 30 day outcomes) of CAS and aggressive medical therapy compared with medical therapy alone.

KQ1: Asymptomatic CAS vs. CEA								Treatment groups Probability (%) 1 year (95% CI) Patient Events (n/N)		Effect size**	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS**	**Medical**	***P*-value†**	**Favors**
Any stroke	1 RCT N = 451	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	14.7 (10.7–20.1) (33/224)	5.3 (3.1–9.2) (12/227)	.03	Medical RD 9.4% NNH 11
Death	1 RCT N = 451	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	2.2 (0.9–5.3) (5/224)	0.4 (0.1–3.1) (1/227)	.95	NS
Any stroke or death	1 RCT N = 451	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	14.7 (10.7–20.1) (33/224)	5.8 (3.4–9.7) (13/227)	.009	Medical RD 8.9% NNH 11
Myocardial infarction	1 RCT N = 451	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	0.5 (0.1–3.2) (NR)	1.3 (0.4–4.1) (NR)	.60	NS
Any major hemorrhage	1 RCT N = 451	Serious risk of bias*	Unknown‡	No serious indirectness	No serious imprecision	Undetected	Low	8.0 (5.1–12.5) (NR)	0.9 (0.2–3.5) (NR)	< .001	Medical RD 7.9% NNH 13

CAS: carotid artery stenting; CI: confidence interval; NS: not statistically significant.
NOTE: Only 1 RCT (SAMMPRIS trial) is represented in the table.
**Authors do not report effect size; probabilities and p-values are provided.

†The p-value is for the comparison, with the use of the log-rank test, of the time-to-event curves for the two treatment groups for each of the specified adverse events.

Reasons for downgrading quality of evidence (general):
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)
‡Consistency across multiple studies cannot be evaluated

Key Question 3: What is the evidence for safety (peri-procedural, 30-day outcomes)?

Asymptomatic

Randomized controlled trials

Quality of evidence summary for Key Question 3: In asymptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)** RR range (95% CI)**	**Favors**
Any stroke	2 RCTs N = 1191 N = 85	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	2.5% (15/594) 0.0% (0/43)	1.4% (8/597) 0.0% (0.42)	RD = 1.2 (-0.4,2.7) RR = 1.9 (0.8, 4.4) Not estimable	NS
Death	1 RCT N = 85	Serious risk of bias*	Unknown	No serious indirectness	Serious risk of imprecision ‡	Undetected	Low	0.0% (0/43)	0.0% (0/42)	Not estimable	NA
Any stroke or death	2 RCTs N = 1191 N = 85	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	2.5% (15/594) 0.0% (0/43)	1.4% (8/597) 0.0% (0/42)	RD = 1.2 (-0.4,2.7) RR = 1.9 (0.8, 4.4) Not estimable	NS NA
MI	1 RCT N = 1191	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Moderate	1.2% (7/594)	2.2% (13/597)	RD = -1.0 (-2.5, 0.4) RR = 0.6 (0.2, 1.4)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; RD: risk difference; RR: risk ratio.

NOTE: A total of 2 RCTs are represented in the table.

**A negative risk difference favors CAS and positive risk difference favors CEA.

Reasons for downgrading quality of evidence (general):

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Nonrandomized comparative studies

Quality of evidence summary for Key Question 3: In asymptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS compared with medical therapy alone.

KQ3: Asymptomatic CAS vs. medical therapy only								Treatment groups		Effect size	
Outcome	**Studies N**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (%)**	**Medical (%)**	**RD % (95% CI)* RR (95% CI)**	**Favors**
Any stroke or death	1 retrospective cohort N = 75	Serious risk of bias††	Unknown	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	1.7	0	RD = 1.7 (-9.0, 17.7) RR = not estimable	NS

CAS: carotid artery stenting; CI: confidence interval; NS: not statistically significant; RD: risk difference; RR: risk ratio.

*A positive risk difference favors CAS and negative risk difference favors CEA.

Quality of evidence summary for Key Question 3: In asymptomatic patients with atherosclerotic carotid artery stenosis , what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
Any stroke	5 cohorts (2 pro, 3 retro) N, 87–269	Serious risk of bias††	Serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	0–8.5	1.8–2.1	RD = -6.3 to 2.0 CI low range (-16.4, -3.9) CI high range (3.8, 10.5) 4 studies RR = 0.5–4.0 CI low range (0.1, 0.5) CI high range (4.9, 32.9) 1 study RR = not estimable	NS
	2 prospective registries N = 5268, 30 Day)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	3.2 (59/1850)	1.7 (58/3418)	RD = -1.5 (-2.5 to -0.6) RR = 1.88 (1.31-2.69	1 CEA
	N = 5316 (in hospital)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	0.7 (2/273)	0.7 (35/5043)	RD = 0 (-1.9 to 0.6) RR = 1.06 (0.26-4.37)	1 NS (in hospital)
Death	4 cohorts (1 pro, 3 retro) N, 87–269	Serious risk of bias††	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	0–1.1	0–2.0	RD = -0.4 to 2.0 CI low range (-9.4, -2.9) CI high range (2.2, 10.5) 1 study RR = 1.6 (0.1, 24.6) 3 studies RR = not estimable	NS

KQ3: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
	2 prospective registries N = 5268 (30 day)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	1.6 (29/1850)	0.7 (25/3418)	RD = -0.8 (-1.6 to -0.2) RR = 2.14 (1.26-3.65)	1 CEA
	N = 5316 (in hospital)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	0.4 (1/273)	0.2 (10/5043)	RD = -0.2 (-1.8 to 0.2) RR = 1.85 (0.24-14.38)	1 NS (in hospital
Any stroke or death	6 cohorts (3 pro, 3 retro) N, 87–1518	Serious risk of bias††	Serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	0–3.8	0–4.0	RD = -1.7 to 2.0 CI low range (-9.0, -2.2) CI high range (0.7, 14.5) <u>5 studies</u> RR = 0.6–1.5 CI low range (0.04, 0.71) CI high range (3.1, 23.9) <u>1 study</u> RR = not estimable	NS
	2 prospective registries N = 1416 (30 days)	Serious risk of bias††	Unknown	No serious indirectness	No serious imprecision	Undetected	Insufficient	10.9 (11/101)	4.0 (53/1315)	RD = -6.9 (-14.5 to -2.0) RR = 2.70 (1.46-5.01)	1 CEA
	N = 5316 (in hospital	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	0.7 (2/273)	0.9 (45/5043)	RD = 0.2 (-1.8 to 0.8) RR = 0.82 (0.20-3.37)	1 NS (in hospital)
Ipsilateral stroke	1 prospective registry N = 5316 (in hospital)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	0.4	0.6	RD = 0.2 (-1.5 to 0.6) RR = 0.6 (0.1-4.5)	NS
MI	3 cohorts (1 pro, 2 retro) N, 87–269	Serious risk of bias††	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	0–1.1	0–1.4	RD = 0 to 1.2 CI low range (-9.4, -2.7) CI high range (3.9, 7.1) <u>2 studies</u>	NS

KQ3: Asymptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
										RR = 0.3–1.2 CI low range (0.01, 0.07) CI high range (8.5, 9.4) 1 study RR = not estimable	
	2 prospective registries N = 5268 (30 day) N = 5316 (in hospital)	No serious risk of bias No serious risk of bias	Unknown Unknown	No serious indirectness No serious indirectness	No serious imprecision No serious imprecision	Undetected Undetected	Low Low	1.1 (20/1850) 0.7 (2/273)	1.0 (35/3418) 1.0 (50/5043)	RD = -0.1 (-0.7 to 0.5) RR = 1.06 (0.61-1.82) RD = 0.3 (-1.7 to 0.9) RR = 0.74 (0.18-3.02)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR: risk ratio.

NOTE: A total of 9 nonrandomized studies are represented in the table.

*A positive risk difference favors CAS and negative risk difference favors CEA.

Reasons for downgrading quality of evidence:

†† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort or registry (see Appendix for details)

‡‡Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§§Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Symptomatic

Randomized controlled trials

Quality of evidence summary for Key Question 3: In symptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Symptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS † (% range)**	**CEA† (% range)**	**RD range, % (95% CI)** RR range (95% CI)**	**Favors**
Any stroke	4 RCTs‡‡ N = 4754	Serious risk of bias¶	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	6.8% (163/2393)	4.0% (94/2361)	RD = 2.9 (1.3, 4.4) NNH = 35 (22, 75) RR = 1.7 (1.2, 2.5)	CEA
Death	4 RCTs N = 3530	Serious risk of bias¶*	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low	1.1% (19/1774)	0.7% (13/1756)	RD = 0.4 (-0.3, 1.0) RR = 1.4 (0.7, 2.9)	NS
Any stroke or death	4 RCTs‡‡ N = 4754	Serious risk of bias¶	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	7.1% (171/2393)	4.1% (98/2361)	RD = 3.1 (1.4, 4.7) NNH = 33 (2, 70) RR = 1.8 (1.2, 2.6)	CEA
Ipsilateral stroke	3 RCTs N = 2923	Serious risk of bias¶*	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Moderate	6.5% (96/1467)	3.8% (56/1456)	RD = 4.5 (-1.9, 10.9) RR = 1.8 (0.9, 3.4)	NS
Fatal, major or disabling stroke	5 RCTs N = 4764	Serious risk of bias¶*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	3.0% (73/2396)	2.1% (49/2368)	RD = 0.9 (-0.4, 2.2) RR = 1.5 (1.0, 2.1)	NS
MI	4 RCTs N = 3600	Serious risk of bias¶*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	0.6% (11/1813)	1.3% (23/1787)	RD = -0.4 (-1.0, 0.1) RR = 0.5 (0.2, 1.0)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; RD: risk difference; RR: risk ratio.

NOTE: A total of 6 RCTs are represented in the table.

**A negative risk difference favors CAS and positive risk difference favors CEA. Significance based on evaluation of risk difference

† Effect size estimates from pooled meta-analysis with weighting based on sample size; data for n/N are numbers of total events/total number of patients

‡‡ Based on sensitivity analysis which excluded older, small studies and those which did not use embolic protection

¶ CAS and CEA patients received different anti-platelet interventions in two trials (EVA, SPACE

Reasons for downgrading quality of evidence (general):

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Nonrandomized comparative studies

Quality of evidence summary for Key Question 3: In symptomatic patients with atherosclerotic carotid artery stenosis, what is the evidence regarding adverse events and complications, particularly during the periprocedural period, and longer term for CAS and medical therapy compared with CEA medical therapy.

KQ3: Symptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
Any stroke	5 cohorts (2 pro, 3 retro) N, 75–155	Serious risk of bias††	Serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	2.9–10.0	2.4–7.2	RD = -7.1 to 2.6 CI low range (-22.9, -8.7) CI high range (2.5, 10.9) RR = 0.6–3.5 CI low range (0.1, 0.6) CI high range (3.0, 19.6)	NS
	2 prospective registries N = 3645 (30 day)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	6.1 (95/1547)	4.1 (85/2098)	RD = -2.1 (-3.6 to -0.7) RR = 1.52 (1.14-2.02)	CEA
	N = 2761 (in hospital)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	5.1 (8/156)	1.4 (37/2605)	RD = -3.7 (-8.4 to -1.1) RR = 3.61 (1.71-7.62)	
Death	3 cohorts (1 pro, 2 retro) N, 75–155	Serious risk of bias††	Serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	0–1.6	0–1.3	RD = -1.6 to 0 CI low range (-10.2, -6.9) CI high range (6.4, 8.6) RR = not estimable for all studies	NS
	2 prospective registries N = 3645 (30 day)	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	2.0 (31/1547)	1.1 (23/2098)	RD = -0.9 (-1.8 to -0.1) RR = 1.83 (1.07-3.12)	CEA
	N = 2761 (in	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	1.3 (2/156)	0.2 (5/2605)	RD = -1.1 (-4.4 to -0.1) RR = 6.68 (1.31-34.15)	

KQ3: Symptomatic CAS vs. CEA								Treatment groups		Effect size	
Outcome	**Studies N range**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**CAS (% range)**	**CEA (% range)**	**RD range, % (95% CI)* RR range (95% CI)**	**Favors**
	hospital)										
Any stroke or death	5 cohorts (2 pro, 3 retro) N, 75–684	Serious risk of bias††	Serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	2.6–7.9	2.4–7.2	RD = -1.6 to 2.6 CI low range (-12.6, -3.9) CI high range (1.2, 10.9) RR = 0.6–1.6 CI low range (0.1, 0.7) CI high range (3.0, 18.6)	NS
	2 prospective registries N = 5149 (30 day) N = 2761 (in hospital)	Serious risk of bias†† No serious risk of bias	Unknown Unknown	No serious indirectness No serious indirectness	No serious imprecision No serious imprecision	Undetected Undetected	Insufficient Low	4.9 (7/142) 5.1 (8/156)	4.4 (220/5007) 1.6 (42/2605)	RD = -0.5 (-5.5 to 2.1) RR = 1.12 (0.54-2.34) RD = -3.5 (-8.2 to-0.9) RR = 3.18 (1.52-6.66)	1 NS 1 CEA (in hospital)
Ipsilateral stroke	1 prospective registry N = 2761	No serious risk of bias	Unknown	No serious indirectness	No serious imprecision	Undetected	Low	3.9	1.2	RD = -2.7 (-7.0 to -0.5) RR = 3.2 (1.4, 7.6)	CEA
MI	2 cohorts (1 pro, 1 retro) N = 128, 155	Serious risk of bias††	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡‡	Undetected	Insufficient	0	0	RD = 0 CI low range (-8.0, -5.7) CI high range (4.0, 4.4) RR = not estimable	NS
	2 prospective registries N = 3645 (30 day) N = 2761 (in hospital)	No serious risk of bias No serious risk of bias	Unknown Unknown	No serious indirectness No serious indirectness	No serious imprecision No serious imprecision	Undetected Undetected	Low Low	1.4 (21/1547) 1.3 (2/156)	1.3 (27/2098) 1.3 (34/2605)	RD = -0.1 (-0.9 to 0.7) RR = 1.05 (0.60-1.86) RD = 0 (-3.3 to 1.1) RR = 0.98 (0.24-4.05)	NS

CAS: carotid artery stenting; CEA: carotid endarterectomy; CI: confidence interval; MI: myocardial infarction; NS: not statistically significant; Pro: prospective study design; RD: risk difference; Retro: retrospective study design; RR: risk ratio.

NOTE: A total of 9 nonrandomized studies are represented in the table.

*A positive risk difference favors CAS and negative risk difference favors CEA.

Reasons for downgrading quality of evidence:

†† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort or registry (see Appendix for details)

‡‡Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§§Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Key Question 4: What is the evidence on of differential efficacy or safety for special populations?

Asymptomatic

Table X. Quality of evidence summary for Key Question 4: Is there evidence of differential efficacy or safety for special populations?

KQ4: Asymptomatic CAS vs. Medical Therapy												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**CAS* HR (95% CI)**	**Medical Therapy** HR (95% CI)**	**Interaction p-values**
Subgroup: Ipsilateral stenosis (IS)												
Stroke	1 retro cohort study N = 946 25 mos. (median)	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡	Undetected	No	Insufficient	IS: 70-79% (n = 307)	aHR: 1.32 (0.43)	aHR: 1.0	NR
									IS: 80-89% (n = 366)	aHR: 0.91 (0.33, 2.49)	aHR: 2.36 (1.02, 5.44)	
									IS: 90-99% (n = 273)	aHR: 0.98 (0.27, 3.61)	aHR: 3.17 (1.15, 4.11)	

aHR: adjusted hazard ratios; n/a: not applicable; NR: not reported; NS: not statistically significant
NOTE. A positive risk difference favors CAS and negative risk difference favors CEA; a HR > 1 favors CEA and a HR < 1 favors CAS.
**n/N for each outcome not reported

Reasons for downgrading quality of evidence:

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendix for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Subgroup analysis not done a priori

Table X. Quality of evidence summary for Key Question 4: Is there evidence of differential efficacy or safety for special populations?

KQ4: Asymptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
Subgroup: Age												
Death	1 registry N = 5268 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Insufficient	Age: < 65 yrs	RR: 1.78 (0.58, 5.49)	NS	P = 0.71
									Age: ≥65 yrs	RR: 2.26 (1.24, 4.14)	CEA	
Stroke	1 registry N = 5268 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Insufficient	Age: < 65 yrs	RR: 1.78 (0.75, 4.24)	NS	P = 0.89
									Age: ≥65 yrs	RR: 1.91 (1.29, 2.82)	CEA	
MI	1 registry N = 5268 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Insufficient	Age: < 65 yrs	RR: 2.97 (0.71, 12.36)	NS	P = 0.12
									Age: ≥65 yrs	RR: 0.88 (0.48, 1.61)	NS	
Subgroup: Sex												
Ipsi-lateral stroke	1 RCT N = 1181 4 yrs.	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Low	Female	HR: 1.59 (0.53, 4.75)	NS	*P* = 0.71
									Male	HR: 2.16 (0.91, 5.10)	NS	
Stroke or Death	1 RCT N = 1181 4 yrs.	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 1.59 (0.53, 4.75)	NS	*P* = 0.71

KQ4: Asymptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
									Male	HR: 2.16 (0.91, 5.10)	NS	
Stroke	1 RCT N = 1181 Periprocedural	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 2.11 (0.55, 8.15)	NS	P = 0.82
									Male	HR: 1.75 (0.57, 5.37)	NS	
Stroke or Death	1 RCT N = 1181 Periprocedural	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 2.11 (0.55, 8.15)	NS	P = 0.82
									Male	HR: 1.75 (0.57, 5.37)	NS	
MI	1 RCT N = 1181 Periprocedural	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 0.67 (0.15, 3.01)	NS	P = 0.74
									Male	HR: 0.48 (0.15, 1.56)	NS	
Subgroup: Surgical risk												
Stroke (non-dis-abling)	1 prosp. cohort study N = 106 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	Yes	Insufficient	CEA Risk Grade I **	RR: 3.68 (0.16, 85.98)	NS	*P* < 0.72
									CEA Risk Grade II **	RR: 1.88 (0.09, 37.63)	NS	
									CEA Risk	RR:	NS	

KQ4: Asymptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI) RR (95% CI)**	**Favors**	**Interaction p-values**
									Grade III **	1.65 (0.19, 14.62)		

n/a: not applicable; HR: hazard ratio; NR: not reported; NS: not statistically significant; RR: risk ratio

NOTE. A positive risk difference favors CAS and negative risk difference favors CEA; a HR > 1 favors CEA and a HR < 1 favors CAS.

NOTE: A total of 3 studies are represented in this table.

Reasons for downgrading quality of evidence:

* Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality RCT (see Appendix for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Subgroup analysis not done a priori

** CEA Risk Grades: I, neurologically stable patients with no major medical or angiographically defined risks but with unilateral or bilateral ulcerative/stenotic CA disease; II, neurologically stable patients with no major medical risks but with significant angiographically defined risks; III, neurologically stable patients with no major medical risks and with or without significant angiographically defined risks.

Symptomatic

Table X. Quality of evidence summary for Key Question 4: Is there evidence of differential efficacy or safety for special populations?

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
Subgroup: Age												
Stroke or Death	Meta-analysis 5 RCTs N = 3470 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Age: < 70 yrs	0.56% (-1.55%, 2.6%) 1.14 (0.70, 1.84)	NS	*P* = 0.07 (RD) *P* = 0.04 (RR)
									Age: ≥ 70 yrs	8.28% (0.14%, 16.4%) 2.14 (1.47, 3.10)	CEA	
	Meta-analysis-Sensitivity analysis: 3 of the 5 RCTs N = 3433	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Age: < 70 yrs	0.47% (-1.89%, 2.83%) 1.08 (0.68, 1.72)	NS	*P* = 0.003 (RD) *P* = 0.03 (RR)
									Age: ≥ 70 yrs	5.68% (3.18%, 8.18%) 2.14 (1.45, 3.17)	CEA	
Ipsi-lateral Stroke or Death	1 RCT N = 1214 2 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Age: < 68 yrs	-4% (-8%, 0%) 0.54 (0.29, 1.02)	NS	*P* = 0.005 (RD) *P* = 0.006 (RR)
									Age: ≥ 68 yrs	5% (0%, 1%) 1.63 (1.02, 2.61)	CEA	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Low	Age: < 68 yrs	HR: ~1.10 (0.45, 2.70)	NS	*P* = 0.08
									Age: ≥ 68 yrs	HR: ~3.40 (1.40, 8.10)	CEA	

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
Subgroup: Sex												
Stroke or Death	Meta-analysis 6 RCTs N = 4774 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	2.6% (-2.1%, 7.2%) 1.5 (1.0, 2.3)	NS	*P* = 0.66 (RD) *P* = 0.51 (RR)
									Male	4.0% (-0.1%, 8.1%) 1.9 (1.1, 3.1)	CEA	
Stroke	1 RCT N = 1321 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 2.80 (1.11, 7.07)	CEA	*P* = 0.17
									Male	HR: 1.28 (0.65, 2.52)	NS	
MI	1 RCT N = 1321 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 1.26 (0.28, 5.63)	NS	*P* = 0.11
									Male	HR: 0.25 (0.07, 0.88)	CAS	
Ipsi-lateral Stroke or Death	1 RCT N = 1214 2 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	2% (-4%, 7%) 1.24 (0.58, 2.66)	NS	*P* = 0.73 (RD) *P* = 0.69 (RR)
									Male	0% (-4%, 4%) 1.04 (0.69, 1.58)	NS	
Ipsi-lateral stroke	2 RCTs N = 1848 4 yrs.	Serious risk of bias†	Serious inconsistency* *	No serious indirectness	No serious imprecision	Undetected	Yes (1 RCT) No (1 RCT)	Low	Female	HR: ~0.65-1.58 (0.25, 3.08)	NS	*P* ≥ 0.05

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
									Male	HR: ~1.10-3.30 (0.62, 7.40)	NS	
Stroke or Death	1 RCT N = 1321 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Female	HR: 1.58 (0.81, 3.08)	NS	*P* = 0.56
									Male	HR: 1.23 (0.71, 2.14)	NS	
Subgroup: Diabetes												
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Low	Diabetes: Yes	HR: ~1.20 (0.30, 3.75)	NS	*P* = 0.27
									Diabetes: No	HR: ~2.60 (1.20, 5.60)	CEA	
Subgroup: Type of symptomatic qualifying event												
Stroke	1 RCT N = 1208 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	No	Insufficient	Qualifying event: Stroke	4% (1%, 8%) 3.26 (1.21, 8.77)	CEA	*P* = 0.46 (RD) *P* = 0.53 (RR)
									Qualifying event: TIA	3% (0%, 7%) 2.13 (0.88, 5.12)	NS	
									Qualifying event: Ocular	0% (-5%, 6%) 1.15 (0.24, 5.55)	NS	
Ipsi-lateral stroke or Death	1 RCT N = 1196 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	Yes	Low	Qualifying event: Stroke	-1% (-6%, 3%) 0.84 (0.47, 1.53)	NS	*P* = 0.48 (RD) *P* = 0.55 (RR)

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
									Qualifying event: TIA	2% (-4%, 7%) 1.27 (0.61, 2.64)	NS	
									Qualifying event: Ocular	-1% (-7%, 4%) 0.71 (0.16, 3.09)	NS	
									Qualifying event: Multiple events	7% (-2%, 15%) 4.77 (0.55, 41.19)	NS	
									Qualifying event: Other	7% (-14%, 27%) 1.69 (0.08, 37.26)	NS	
Ipsi-lateral stroke or Death	1 RCT N = 1196 2 yr.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	Yes	Low	Qualifying event: Stroke	4% (-2%, 9%) 1.56 (0.84, 2.93)	NS	*P* = 0.13 (RD) *P* = 0.25 (RR)
									Qualifying event: TIA	1% (-5%, 7%) 1.14 (0.61, 2.11)	NS	
									Qualifying event: Ocular OR Other	0% (-6%, 6%) 1.07 (0.34, 3.39)	NS	
									Qualifying event: Multiple events	15% (4%, 27%) 9.53 (1.24, 73.48)	CEA	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡	Undetected	No	Insufficient	Qualifying event: Stroke	HR: ~3.00 (1.60, 6.80)	CEA	*P* ≥ 0.16

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
									Qualifying event: TIA	HR: ~1.50 (0.45, 5.15)	NS	
									Qualifying event: Ocular	HR: ~2.00 (0.10, 4.30)	NS	
Subgroup: Severity of Ipsilateral Stenosis												
Ipsi-lateral stroke or Death	1 RCT N = 1196 2 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Yes	Moderate	Ipsilateral stenosis < 70%	2% (-3%, 7%) 1.31 (0.67, 2.58)	NS	*P* = 0.54 (RD) *P* = 0.49 (RR)
									Ipsilateral stenosis ≥ 70%	0% (-4%, 4%) 0.99 (0.64, 1.52)	NS	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Low	Ipsilateral stenosis < 90%	HR: ~2.30 (1.00, 5.40)	NS	*P* = 0.61
									Ipsilateral stenosis ≥ 90%	HR: ~1.65 (0.60, 4.30)	NS	
Subgroup: Severity of Contralateral Stenosis												
Ipsi-lateral stroke or Death	1 RCT N = 1196 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	Yes	Low	Contra-lateral stenosis < 70%	1% (-2%, 4%) 1.20 (0.76, 1.88)	NS	*P* = 0.14 (RD) *P* = 0.16 (RR)
									Contra-lateral stenosis 70-99%	-8% (-20%, 4%) 0.38 (0.08, 1.79)	NS	

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
Ipsi-lateral stroke or Death	1 RCT N = 1196 2 yr.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	Yes	Low	Contra-lateral stenosis < 70%	-7% (-12%, -2%) 0.57 (0.39, 0.83)	CAS	*P* = 0.82 (RD) *P* = 0.89 (RR)
									Contra-lateral stenosis 70-99%	-13% (-33%, 7%) 0.41 (0.09, 1.83)	NS	
									Contra-lateral stenosis 100%	-5% (-27%, 17%) 0.70 (0.13, 3.73)	NS	
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Low	Contra-lateral stenosis < 70%	HR: ~2.20 (1.10, 4.30)	CEA	*P* = 0.65
									Contra-lateral stenosis 70-100%	HR: ~1.45 (0.30, 6.50)	NS	
Subgroup: Time to Treatment												
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision §	Undetected	No	Insufficient	Time to treatment: < 14 days	HR: ~6.75 (0.80, ≥8)	NS	*P* = 0.40
									Time to treatment: ≥ 14 days	HR: ~1.70 (0.80, 3.45)	NS	
Subgroup: Hypertension												
Ipsi-lateral	1 RCT N = 527	Serious risk	No serious inconsistency	No serious indirectness	Serious risk of imprecision	Undetected	No	Insufficient	Hyper-tension:	HR: ~1.80 (0.85, 3.65)	NS	*P* = 0.62

KQ4: Symptomatic CAS vs. CEA												
Outcome	**Studies N range Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	***a priori* subgroup analysis**	**Overall quality of evidence**	**Subgroup**	**RD (95% CI)* RR (95% CI)**	**Favors**	**Interaction p-values**
Stroke	4 yrs.	of bias†			§				Yes			
									Hyper-tension: No	HR: ~2.90 (0.75, ≥8)	NS	
Subgroup: Smoking Status												
Ipsi-lateral Stroke	1 RCT N = 527 4 yrs.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	No	Low	Smoking: Yes	HR: ~1.75 (0.5, 6.1)*	NS	*P* = 0.81
									Smoking: No	HR: ~2.10 (1.00, 4.40)*	NS	
Subgroup: Surgical Risk												
Stroke (non-dis-abling)	1 prosp. cohort study N = 106 Periprocedural	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious risk of imprecision ‡§	Undetected	Yes	Insufficient	CEA Risk Grade I ††	RR: Not Estimable	n/a	Not Estimable
									CEA Risk Grade II ††	RR: Not Estimable	NS	
									CEA Risk Grade III ††	RR: 3.43 (0.28, 41.32)	NS	

n/a: not applicable; HR: hazard ratio; NR: not reported; NS: not statistically significant; RD: risk difference; RR: risk ratio

NOTE. A positive risk difference favors CAS and negative risk difference favors CEA; a HR > 1 favors CEA and a HR < 1 favors CAS.

NOTE: A total of 7 studies are represented in this table.

Reasons for downgrading quality of evidence:

* Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality RCT (see Appendix for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendix for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Subgroup analysis not done a priori

** Serious risk of inconsistency: one RCT showed that sex modified the interaction in terms of ipsilateral stroke through four years (N = 527), while the other RCT (N = 1321) showed that sex did not modify the interaction.

†† CEA Risk Grades: I, neurologically stable patients with no major medical or angiographically defined risks but with unilateral or bilateral ulcerative/stenotic CA disease; II, neurologically stable patients with no major medical risks but with significant angiographically defined risks; III, neurologically stable patients with no major medical risks and with or without significant angiographically defined risks.

Key Question 5: What is the evidence of cost-effectiveness?

Note: GRADE has not been developed to evaluate the quality of cost-effectiveness evidence.

KQ5: Stenting compared with other treatment options (medical therapy, CEA)					
Population	**Studies**	**Countries**	**QHES Range***	**Overall quality of evidence**	**Conclusions**
Asymptomatic Atherosclerotic Stenosis	3 cost-utility analyses	USA	84-99	Low	• Two studies based on data from the SAPPHIRE trial in high surgical risk patients reported ICERs of $49,514 and $67,891 for a 1-year time horizon, suggesting that CAS may be plausible but not verifiably superior treatment. One study reported that over a life-time horizon CAS may be more cost-effective, however, methodological concerns regarding extrapolation of data for life-time time horizon and determination of utilities were noted • In one evaluation in patients with standard surgical risk, CEA was the preferred treatment given commonly assumed cost-effectiveness thresholds
Symptomatic Atherosclerotic Stenosis	4 cost-utility analyses	USA Sweden	94-100	Low	• Evidence across four cost-utility studies indicated that CEA tended to be more cost-effective than CAS in symptomatic patients. Two out of the four studies examining symptomatic patients found there to be insufficient evidence to strongly favor one treatment method over the other. • Subanalysis of patients from the SAPPHIRE trial of high surgical risk patients found CAS to be the more expensive treatment option with negligible QALY improvement leading to extremely high ICERs.
Intracranial Atherosclerotic Stenosis	No studies identified			No Evidence	N/A

CAS: carotid artery stenting; CEA: carotid endarterectomy; ICER: incremental cost-effectiveness ratio; N/A: not applicable; QALY: quality-adjusted life years; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.

NOTE: A total of 5 studies are represented in the table.

*Quality of Health Economic Studies (QHES) scores ranged from 84-100, which primarily reflects the quality of reporting on specific factors that are important in economic analyses. It does not provide for evaluation of quality with respect to modeling assumptions or extensive consideration of data quality and included outcomes measures relevant to a specific topic.

6. Synopsis and remaining questions

Synopsis of highest evidence for primary outcomes: Asymptomatic patients with extracranial carotid atherosclerotic stenosis

- **CAS versus current best medical therapy**: Efficacy cannot be assessed as no RCTs were found. Evidence from one retrospective registry study suggests that CAS was favored over medical therapy and was graded as insufficient.
- **Short- and long-term efficacy CAS versus. CEA**: The overall strength (quality) of evidence was considered low regarding short and long-term efficacy data from two RCTs (CREST and Kentucky 2004) comparing CAS with CEA for outcomes past the periprocedural period. Event rates were similar and no statistical differences between treatments were seen for stroke, ipsilateral stroke and vessel patency up to 4 years. The rate of the composite of any periprocedural stroke or death or post-procedural ipsilateral stroke was 4.5% for CAS and 2.7% for CEA at 4 years. The difference was not statistically significant. Small sample sizes likely contributed to lack of statistical significance for some outcomes.
- **Safety CAS versus CEA**: The overall strength (quality) of evidence was moderate that there were no statistical differences between treatment groups for safety outcomes (30-day peri-procedural period) including stroke, the composite of death or stroke and myocardial infarction, primarily based on analysis of asymptomatic patients in the CREST trial. The risk of stroke and for the composite of death or stroke was 2.5% for CAS and 1.4% for CEA, but the difference (1.2%) failed to reach statistical difference.
- **No differential treatment or safety effects** in special populations were identified, however, the data were limited and the overall strength of evidence grades were as follows:
    - Insufficient with respect to percent of ipsilateral stenosis for the comparison of CAS with medical therapy (cohort data only);
    - Insufficient with respect to age and surgical risk for the comparison of CAS with CEA (registry data)
    - Moderate with respect to sex (1 RCT).
- **Full economic evaluations**: One study suggests that CAS may be plausible but not verifiably superior for a one year time horizon in high risk patients; another reported CAS may be more cost effective given a life-time horizon and a third CEA as preferred. The overall strength of evidence was low.

Synopsis of highest evidence for primary outcomes: Symptomatic patients with extracranial carotid atherosclerotic stenosis

- **CAS with best medical therapy**: No comparative studies were found.
- **Short- and long-term efficacy CAS versus CEA**: The overall strength (quality) of evidence was considered moderate to low regarding short and long-term efficacy.
    - Short term: There is moderate evidence for the following:

        - When periprocedural strokes were excluded, risk of any stroke and risk of ipsilateral stroke were similar between treatment groups at 4 months (1RCT);
        - Risk of any stroke or death was significantly higher in patients receiving CAS at 4-6 months across two RCTs when periprocedural events were included. Risk of any periprocedural stroke or death or postprocedural ipsilateral stroke was significantly higher up to 6 months (1RCT)
        - Risk of death at 4 months was signigicantly higher following CAS (1RCT).
    - Longer term: Length of follow-up ranged from 2-5.4 years across 5 RCTs, 3 of which used embolic protection. Longest follow-up in these 3 RCTs was 4 years.
        - There is moderate evidence that risk of death was similar between treatment groups regardless of whether periprocedural death was included across 5 RCTs at up to 5.4 years follow-up.
        - There is low evidence that there were no signicant differences between treatments for he composite of death or any stroke (including periprocedural) or the composite of any periprocedural stroke or death or postprocedural ipsilateral stroke at follow-up to 5.4 years across 5 RCTs.
- **Safety of CAS versus CEA:**
    - Based on meta-analyses of the four more recent RCTs which employed embolic protection, there is moderate evidence that the risk of stroke and the composite of any stroke or death are significantly higher in symptomatic persons who received CAS compared with CEA. The risk of any stroke or death was 7.1% for CAS and 4.1% for CEA, RD 3.1% (1.4%, 4.7%), NNH = 35. These risks are primarily influenced by stroke risk.
    - There is moderate evidence that no significant risk differences between treatments for the following outcomes: death, ipsilateral stroke, fatal, major or disabling stroke or MI.
- **Differential treatment efficacy or safety effects for special populations**
    - Age: There is moderate evidence from meta-analysis of more RCTs (using embolic protection) that age modifies the effect of treatment. In symptomatic persons with regard to risk of periprocedural death or stroke, CEA is favored in those age $\geq$ 70 years old while those under 70 years of age had similar results regardless of treatment group.
    - Sex: there is moderate evidence from meta-analysis of RCTs that sex does not modify treatment effect or safety.
    - Surgical risk: There is insufficient evidence from RCTs. Efficacy data from the SAPPHIRE trial of 96 symptomatic high surgical patients undergoing CAS versus CEA suggested these patients had similar risks for efficacy and safety outcomes.

  - There is moderate evidence from 1 RCT and low evidence from another RCT that severity of ipsilateral stenosis does not modify treatment or safety effects. This trial did not include and compare treatment outcomes from standard/average risk patients thus direct comparisons and conclusions cannot be made.
  - There is insufficient to low evidence from individual RCTs that treatment or safety effects are not modified by diabetes, type of symptomatic qualifying event, severity of contralateral stenosis, time to treatment, hypertension or smoking.
- **Full economic evaluations**: Low evidence across four cost-utility studies indicated that CEA tended to be cost effective than CAS. Subanalysis of the SAPPIRE trial found CAS to be more expensive with negligible improvement in QALY.

Synopsis of highest evidence primary outcomes: Intracranial stenting for atherosclerotic disease

- No studies in asymptomatic persons were found.
- The overall strength of evidence is low for efficacy and safety based on one study in symptomatic persons. The one available RCT was terminated because of safety concerns. Stenting was associated with a significantly higher probability (20.0%) of stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days compared with medical therapy (12.2%).
- No studies evaluating differential effectiveness in special populations were found.
- No economic studies were found.

Limitations of the literature and remaining questions

This report synthesizes studies comparing stenting with other treatment options for the treatment of atherosclerotic disease in the carotid arteries and intracranial arteries, with a focus on the highest quality, least biased evidence available in the peer reviewed literature. There are a number of questions that remain.

- In order to weigh whether or not to recommend an invasive procedure with serious risks in a healthy asymptomatic person, there should be clear evidence that benefits outweigh the risks. Benefits of CAS compared with current medical therapy have not been shown. There are no high quality data comparing stenting with current best medical practices in asymptomatic patients and limited data from randomized controlled trials in asymptomatic, low-risk patients comparing CAS with CEA. Although statistical significance was not reached, risk of stroke or death was lower following CEA in asymptomatic patients, but trials lacked a medical treatment comparator.
- Do any long-term benefits (>5 years) of CAS outweigh risks associated with periprocedural events (e.g. stroke)? The longest follow-up reported in more contemporary studies using embolic protection devices was 4 years. The number of individuals with available data at longer follow-up times was not uniformly reported across studies and in some studies although statistical projection of longer term outcomes was reported, actual data are needed. Long-term data for implanted devices is essential.

- It is important to study the impact of improvements in stent technology and techniques (e.g. different embolic protection mechanisms), operator experience, surgical technique and medical therapy (including more active lifestyle counseling) on the bigger context of comparative effectiveness of CAS, medical therapy and CEA for the treatment of atherosclerotic carotid stenosis in not known. Although there is potential for improvements in devices to decrease risk of stroke and death with CAS, no published studies have included treatment arms for CAS, medical therapy and CEA in the same underlying population to allow for direct comparisons of current best treatments. For asymptomatic patients in particular, this is an important question. In addition, data on the risks and benefits of CAS and CEA from methodologically rigorous studies outside of high volume centers participating in RCTs is essential to understand what the risks and benefits would be in actual use.
- Based on available evidence, intracranial artery stenting in the treatment of intracranial atherosclerotic disease has substantial risk of harm. The only comparative study available was terminated early based on due to increased risk of stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery. The extent to which intracranial stenting is an effective treatment for primary treatment or in patients failed medical therapy, thrombectomy or PTA is not clear.
- Is CAS efficacious and safe in "high risk" patients? There does not appear to be a standard definition of "high risk" and many factors are considered when determining a patient's surgical risk. Although one RCT (SAPPHIRE) explicitly sought to evaluate the efficacy of CAS in "high risk" patients compared with CEA, because there was no direct comparison with a group of "standard" risk patients, firm conclusions cannot be drawn.
- The extent to which there is differential efficacy and safety in some special populations is not clear. Overall, studies were underpowered to detect modification of treatment.
- The cost-effectiveness of CAS is not established based on published studies. Although full economic analyses were available and based on data from RCTs, methodological concerns and potential for bias limit the usefulness of these analyses firm conclusions.

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