Technology Assessment

Technology Assessment Program

Management of Asymptomatic Carotid Stenosis

Final Report
August 27, 2012

Prepared for:

Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, Maryland 20850

Management of Asymptomatic Carotid Stenosis

Technology Assessment Report

Project ID: CRDT0510

August 27, 2012

Tufts Evidence-based Practice Center

Gowri Raman, MD, MS
Georgios D. Kitsios, MD, PhD
Denish Moorthy, MBBS, MS
Nira Hadar, MS
Issa J. Dahabreh, MD, MS
Thomas F. O'Donnell, MD
David E. Thaler, MD, PhD, FAHA
Edward Feldmann, MD
Joseph Lau, MD

This report is based on research conducted by the Tufts Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290 2007 10055 1). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision-makers; patients and clinicians, health system leaders, and policymakers, make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Disclosure: None of the investigators has any affiliations or financial involvement related to the material presented in this report.

Acknowledgements

The authors of this report thank other members of the Tufts Evidence-based Practice Center (EPC), Ethan Balk MD MPH and Thomas A Trikalinos MD PhD, for helpful suggestions on a draft version of this report. We thank Jenny Lamont, MS, for editing a draft and final version of this report.

Table of Contents

List of Tables

List of Figures

Abbreviations and Acronyms

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACE-I	Angiotensin-converting enzyme inhibitor
ACR	American College of Radiology
ACST	Asymptomatic Carotid Surgery Trial
AHA	American Heart Association
ASA	American Stroke Association
CAD	Coronary artery disease
CaRESS	Carotid Revascularization Using Endarterectomy or Stenting Systems
CAS	Carotid angioplasty and stenting
CASANOVA	Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin
CEA	Carotid endarterectomy
CI	Confidence interval
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
CTA	Computed tomography angiography
CVD	Cardiovascular disease
DSA	Digital subtraction angiography
DUS	Doppler ultrasound
ECST	European Carotid Surgery Trial
HR	Hazard ratio
ICA	Internal carotid artery
ICAVL	Intersocietal Commission for the Accreditation of Vascular Laboratories
MI	Myocardial infarction
MRA	Magnetic resonance angiography
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OPG	Ocular pneumoplethysmography
RCT	Randomized controlled trial
RR	Relative risk
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SVS-VR	Society for Vascular Surgery–Vascular Registry
TIA	Transient ischemic attack
VA	Veterans Affairs

Executive Summary

Background

Carotid artery stenosis is an important cause of ischemic stroke and is increasingly prevalent from the fifth decade of life onward. Since carotid artery atherosclerosis can largely progress silently and unpredictably, the first manifestation can be a debilitating or fatal stroke. Asymptomatic carotid artery stenosis affects approximately 7 percent of women and over 12 percent of men, older than 70 years of age. Therapeutic options include carotid endarterectomy (CEA) and medical therapy, carotid angioplasty and stenting (CAS) and medical therapy, or medical therapy alone. However, the optimal therapeutic management strategy for patients with asymptomatic carotid stenosis is unclear. The Centers for Medicare and Medicaid Services (CMS) is interested in a systematic review of the literature on these three treatment strategies for patients with asymptomatic carotid stenosis. The Coverage and Analysis Group at the CMS requested this report from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Tufts Evidence-based Practice Center (Tufts EPC) (Contract number HSSA 290 2007 10055 I).

Methods

The present technology assessment provides a systematic review of the literature of treatment strategies for patients with asymptomatic carotid artery stenosis. The following key questions were formulated in consultation with CMS and AHRQ.

1. In asymptomatic patients with carotid artery stenosis, what is the evidence on long-term clinical outcomes (at least 12 months of followup) including stroke, death, myocardial infarction, 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 followup
   - 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?

Search strategy

A comprehensive search of the scientific literature was conducted in MEDLINE® and the Cochrane Central Register of Controlled Trials for English-language studies of adult human subjects from inception through May 2012. In addition, bibliographies of systematic reviews and selected narrative reviews were searched to identify additional citations. We also searched the Food and Drug Administration (FDA) Web site, and we contacted corresponding authors of eligible studies for unpublished data on outcomes of interest.

Study eligibility criteria

Population

Eligible studies included those of adults (≥ 18 years) with asymptomatic carotid artery stenosis. Eligible stenoses included atherosclerotic narrowing of the lumen of the carotid bifurcation or the extracranial part of the internal carotid artery between 50 to 99 percent. We accepted the definition of "asymptomatic" patients used in each study. We included studies with mixed cohorts of patients (symptomatic and asymptomatic carotid artery stenosis), provided that the results were stratified according to symptom status.

Intervention and comparator

We included studies of 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.

Outcomes

For Key Questions 1 and 2, we included studies that reported only major clinical outcomes: stroke, death, myocardial infarction (MI), and other cardiovascular events. For Key Question 3, we included studies that reported safety outcomes related to a procedure or therapy (referred to as complications) or clinical outcomes, including stroke, death, or MI (referred to as adverse events) occurring within 30 days of the procedures or within 30 days of followup in the medical therapy group.

Study designs

For Key Question 1a evaluating long-term clinical outcomes of medical therapy alone, we included prospective cohort studies and the medical therapy arm of eligible randomized controlled trials (RCTs) or prospective nonrandomized comparative studies.

Sample size and duration of followup

For Key Question 1a, studies with at least 30 patients with a minimum average followup of 12 months were included. For all other key questions comparing treatment strategies, we included at least 30 patients per intervention group and any duration of followup.

Data analysis

For studies of medical therapy alone where numerical data of events and average followup person-time were available, we calculated the incidence rate of events and its 95 percent exact

Poisson confidence interval (95 percent CI). Summary estimates of incidence rates were constructed by fitting a generalized linear random effects meta-analysis model and were expressed as percent per year (instead of number of events per 100 person-years). We performed meta-regression analyses with the last year of recruitment in each study to evaluate changes in the rates of events over time. We conducted further exploratory subgroup and meta-regression analyses based on a prespecified set of clinically relevant explanatory variables and only for the outcomes with at least five studies.

For comparative studies, we conducted meta-analysis using a random effects model and reported the results as summary relative risk (RR). RCTs and nonrandomized comparative studies were analyzed separately. When we identified discrepancies between published and unpublished data for a study, or extreme clinical heterogeneity between studies (i.e, inclusion of different patient groups), we refrained from conducting a meta-analysis but presented estimates of each study in forest plots. In RCTs comparing treatments, we also estimated summary incidence rates of ipsilateral stroke for each of the treatment arms.

Study quality and applicability

We used a three-level (A or low risk of bias, B or moderate risk of bias, and C or high risk of bias) system per the AHRQ methods guide to denote the methodological quality (risk of bias) of each study. Quality-A studies have the least bias and results are considered valid. Quality-B studies are susceptible to some bias, but it is not sufficient to invalidate the results. Quality-C studies have significant biases that may invalidate the study results.

Study applicability was described using study specific characteristics such as age groups of $\geq$ 65 years and $\geq$ 80 years, sex, other baseline clinical features including comorbid medical diseases, center characteristics, medical therapy at baseline, and clinical or anatomic features of carotid artery stenosis (> 70 percent or > 80 percent stenosis).

Strength of evidence

For each key question, grading of the strength of evidence provides an overall summary of risk of bias in individual studies, directness and precision of the evidence, and the consistency across studies. We used a four-category grading system per the AHRQ methods guide to grade the strength of evidence. For Key Question 1a, evaluating effectiveness of medical therapy alone, the strength of evidence was graded on the basis of individual studies (prospective cohort studies and trials with the medical therapy arms) rated quality-A or -B. For all other key questions comparing treatment strategies, the strength of evidence was graded on the basis of individual RCTs rated quality-A or -B. The quality-C studies were excluded from the strength-of-evidence assessment but are described in detail in full text of the report.

Grades were assigned according to our level of confidence that the evidence reflects the true effect for the interventions of interest and were defined as follows:

- High strength of evidence indicates that there is a high level of assurance that the findings of the literature are valid with respect to the relevant comparison and no important scientific disagreement exists across studies. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate strength of evidence indicates that there is a moderate level of assurance that the findings of the literature are valid with respect to the relevant comparison and little disagreement exists across studies. Further research may change our confidence in the estimates of effect and may change the estimate.

- Low strength of evidence indicates that there is a low level of assurance that the findings of the literature are valid with respect to the relevant comparison. Underlying studies may report conflicting results. Further research is likely to change our confidence in the estimate of effect and may change the estimate for this outcome.
- Insufficient strength of evidence indicates that evidence is either unavailable or does not permit estimation of an effect owing to a lack of data or sparse data. In general, when only one study has been published, the evidence was considered insufficient, unless the study was particularly large, robust, and of good quality.

These ratings provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they by necessity may oversimplify the many complex issues involved in the appraisal of a body of evidence. It is important to remember that the individual studies evaluated in formulating the composite rating differed in their design, reporting, and quality. The strengths and weaknesses of the individual reports, as described in detail in the text and tables, should also be taken into consideration.

Results

The literature search identified 60 eligible studies in 68 articles. In general, the definition of "asymptomatic" patients used in each study was heterogeneous. These included any of the following at enrollment: those without symptoms, those with symptoms present for > 6 months before their enrollment in the study but recently (within 6 months) asymptomatic, or those with symptoms in a vascular territory other than ipsilateral carotid (e.g., vertebrobasilar territory). All eligible studies are described in detail in full-text of the report. Only studies that contributed to grading the strength of evidence are described in the executive summary.

Key Question 1

Medical therapy alone (Key Question 1a)

There is 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.

In 20 quality-A and -B studies of (any) medical therapy alone, the summary incidence rate of ipsilateral stroke was 1.59 (95% CI = 1.21, 2.09) percent per year of followup. The summary incidence rate estimate of 13 studies reporting the combined outcome of ipsilateral stroke or transient ischemic attack (TIA) was 4.56 (95% CI = 3.79, 5.47) percent per year of followup. The summary incidence rate for any stroke in 12 studies was 3.18 (95% CI = 2.32, 4.35) and for any stroke or TIA in five studies was 5.71 (95% CI = 3.30, 9.90) percent per year of followup. The summary incidence rate of all-cause death across 11 studies was 4.38 (95% CI = 3.00, 6.41) percent per year of followup.

In subgroup analyses, use of statins by≥ 25 percent (vs. < 25 percent) of the study population and use of antiplatelet therapy by≥ 50 percent (vs. < 50 percent) of the study population was associated with significantly decreased rates of ipsilateral stroke.

Changes in outcome incidence over time across studies

Meta-regression analyses showed that the incidence rates of ipsilateral stroke was significantly decreased in studies with a recruitment closure year between 2000 and 2010 (recent studies) as compared with older studies (1.13 versus 2.38 percent per year, P for interaction =

0.0008). The summary incidence rate of ipsilateral stroke or TIA, any territory stroke, and death was also significantly decreased in recent studies as compared with older studies.

CEA and medical therapy versus medical therapy alone (Key Question 1b)

There is moderate strength of evidence (that is not applicable to contemporary medical treatment) among three quality-A RCTs (the Veterans Affairs Cooperative Study [VA], the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Atherosclerosis Trial [ACST]) that CEA and medical therapy can reduce the risk of ipsilateral stroke as compared with medical therapy alone, which was demonstrated by all three trials. The results from these trials are not applicable to contemporary clinical practice, as they do not compare CEA with current best medical therapy. Patients with asymptomatic carotid stenosis did not receive at randomization what is considered current best medical therapy, including the use of statins and targets for the treatment of blood pressure and diabetes. The meta-analyses of these RCTs showed no difference between the two treatment groups for the risk of any death, fatal stroke, or CVD death.

Ipsilateral stroke (including any stroke or death within 30 days)

All three RCTs contributed to the analysis of ipsilateral stroke (defined as any stroke or death within 30 days or subsequent ipsilateral stroke). In a meta-analysis, the CEA had a 31 percent significantly decreased risk of ipsilateral stroke (including perioperative stroke or death) compared with the medical therapy (summary RR = 0.69, 95% CI = 0.55, 0.87) without statistical heterogeneity (I^2 = 0.0%, P = 0.90).

Any stroke (including any death within 30 days)

All three RCTs reported the outcome of any stroke, defined as events of perioperative stroke or death or subsequent nonperioperative any territory stroke. In a meta-analysis, the CEA had a 32 percent significantly decreased risk of any stroke (including perioperative stroke or death) as compared with the medical therapy group (summary RR = 0.68, 95% CI = 0.56, 0.82) without statistical heterogeneity (I^2 = 17.7%, P=0.30).

Any stroke or death

All three RCTs reported that the CEA had a nonsignificantly decreased risk for the combined endpoint of any stroke or death compared with the medical therapy. A meta-analysis showed no significant difference between the two groups (summary RR = 0.94, 95% CI = 0.85, 1.03) without statistical heterogeneity (I^2 = 19%, P=0.29).

Death

A meta-analysis of the three RCTs showed no significant difference in death between the two intervention groups (summary RR = 1.05, 95% CI =0.97, 1.14) and no statistical heterogeneity (I^2 = 0.0%, P=0.60). When the meta-analysis was restricted to fatal stroke, the CEA had a nonsignificantly decreased risk by 21 percent as compared with the medical therapy (summary RR = 0.79, 95% CI =0.57, 1.08) and no statistical heterogeneity (I^2 = 0.0%, P=0.61).

CVD outcomes

A meta-analysis of three RCTs on cardiovascular deaths showed no significant difference between the two groups (summary RR = 1.01, 95% CI = 0.82, 1.25) with statistically nonsignificant heterogeneity (I^2 = 37.6%, P=0.20).

CAS and medical therapy versus medical therapy alone (Key Question 1c)

The strength of evidence was graded as insufficient because of a lack of RCTs.

CAS and medical therapy versus CEA and medical therapy (Key Question 1d)

No statistically significant difference in the risk of ipsilateral stroke or the risk of the composite endpoint of ipsilateral stroke was found between CAS and CEA in two RCTs (one quality-A and one quality-B). The strength of evidence is graded as insufficient because in these trials, the included population had extreme clinical heterogeneity (i.e., one study representing a population of low-to-average risk and the other representing a high-risk population). Therefore, these studies were not combined in meta-analyses. Furthermore, there was selective reporting of outcomes of interest.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial enrolled both symptomatic and asymptomatic patients who were assigned to treatments on the basis of stratified randomization according to symptom status. Thus, the treatment assignment was randomized among the subgroup of patients with asymptomatic carotid stenosis. However, among this subgroup, neither trial was powered to detect differences in the primary outcome (composite endpoint). Therefore, the failure to find statistically significant differences does not rule out the possibility that real differences exist between interventions. CREST was conducted as an equivalence trial but was analyzed as a noninferiority trial in the FDA submission and as a superiority trial in the published paper. The SAPPHIRE trial used group sequential design and was analyzed as a noninferiority trial in the published papers. In this trial (SAPPHIRE), there were differences in reporting between the published paper and unpublished data on the FDA Web site. One additional quality-B RCT (Brooks 2004) was a single-center trial and in this trial, no cerebrovascular outcomes occurred in either intervention group.

Ipsilateral stroke (including any stroke within 30 days)

Two RCTs (CREST and SAPPHIRE) reported data on ipsilateral stroke. CREST reported it as a composite of any periprocedural stroke (within 30 days) or postprocedural (> 30 days) stroke ipsilateral to the treated carotid artery at 4-year followup. CREST reported a nonsignificantly increased risk of ipsilateral stroke at the 4-year followup in CAS as compared with CEA (adjusted HR = 1.86; 95% CI = 0.95, 3.66). The SAPPHIRE trial defined it as ipsilateral stroke at 1 year, for which the data were obtained from the FDA Web site. The SAPPHIRE trial reported similar rates of ipsilateral stroke between CAS and CEA (5.2% vs. 5.3%).

Any stroke (including any death within 30 days)

The SAPPHIRE trial reported data on any stroke, with no statistical significance between groups (RR = 1.12, 95% CI = 0.51, 2.43)

Any stroke or TIA (including any death within 30 days)

One RCT (Brooks 2004) examined the outcome of any stroke or TIA but reported zero events for both treatment groups.

Any stroke or death

CREST reported a nonsignificantly increased risk of any stroke or death in CAS as compared with CEA (adjusted HR = 1.86; 95% CI = 0.95, 3.66). The SAPPHIRE trial did not report data for this outcome.

Death

The SAPPHIRE trial reported a nonsignificantly decrease in the risk of death in CAS as compared with CEA (RR = 0.47, 95% CI = 0.18, 1.20). CREST did not report data for this outcome.

CVD outcomes

No studies reported long-term data for CVD outcomes.

Composite endpoint including ipsilateral stroke

Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke

Two RCTs (CREST and SAPPHIRE) reported data on this composite outcome, which represented the primary outcome of CREST and SAPPHIRE trials over the 4-year and 3-year followup, respectively. Neither trial reported a statistically significant difference between CAS and CEA. The confidence interval of the RR estimate in each study was wide and the observed point estimates were in opposite directions (unfavorable for CAS in CREST [HR = 1.17, 95% CI = 0.69, 1.98] and favorable in the SAPPHIRE trial [RR = 0.73, 95% CI = 0.47, 1.14]). However, neither trial was powered to detect a significant difference in the primary outcome among subgroup of patients with asymptomatic carotid stenosis. Therefore, the failure to find statistically significant differences does not rule out the possibility that real differences exist between interventions.

Any periprocedural stroke, any death, or postprocedural ipsilateral stroke

Two RCTs (CREST and SAPPHIRE) reported data on this composite outcome. CREST reported a statistically nonsignificantly increased HR (adjusted for age and sex) with CAS as compared with CEA for this composite outcome (HR = 1.86, 95% CI = 0.95, 3.66). The SAPPHIRE trial reported that CAS had a statistically nonsignificantly decreased risk of this composite outcome as compared with CEA (RR = 0.54, 95% CI =0.28, 1.02). The observed point estimates in these two trials were extremely discordant. There were differences between published and unpublished data for the SAPPHIRE trial.

Summary incidence rate by treatment group

The summary incidence rate of quality-A and -B studies of medical therapy alone was 1.59 percent per year of followup. In a subgroup analysis, the summary incidence rate of ipsilateral stroke was 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 followup).

Five RCTs, namely the VA, ACAS, ACST, CREST, and SAPPHIRE trials, contributed to the incidence rate meta-analysis of the CEA and medical therapy arm. The summary incidence rate of ipsilateral stroke with CEA and medical therapy was 1.42 percent per year of followup. In a subgroup analysis of patients who had CEA and medical therapy, the summary incidence rate of ipsilateral stroke was significantly decreased in recent studies (recruitment closure year between 2000 and 2010) studies compared with older studies (recruitment closure year before

2000) studies (1.3 versus 1.6 percent per year of followup). For the two RCTs that reported long-term data, the summary incidence rate of ipsilateral stroke in the CAS and medical therapy arm was 1.61 percent per year of followup (in CREST) and 5.12 percent per year of followup (in SAPPHIRE). Both studies recruited patients after the year 2000.

Key Question 2 (Subgroups and treatment effect)

CEA and medical therapy versus medical therapy alone

The strength of evidence is graded as insufficient, because two quality-A RCTs (ACAS and ACST, in two publications) reported subgroup-specific data for three outcomes that cannot be combined. The outcomes evaluated for subgroups were ipsilateral stroke, including perioperative stroke or death, in the ACAS trial, nonperioperative carotid territory stroke in ACST with 5-year followup, and any territory stroke in ACST with 10-year followup. In addition, there was insufficient information on certain subgroups. The VA trial evaluated long-term outcomes and did not report any subgroup-specific data.

Demographic and other preoperative (baseline) features of studied patients

Age: Subgroup of patients ≥ 65 years

ACAS reported that patients < 68 years of age in the CEA group had a significantly decreased risk of ipsilateral stroke as compared with the medical therapy group but those ≥ 68 years of age had no difference between the two treatment groups. ACST reported that patients < 75 years of age had a significantly decreased risk of nonperioperative carotid territory stroke at 5 years or a significantly decreased risk of any territory stroke at 10 years with CEA and medical therapy as compared with medical therapy alone. But, patients ≥ 75 years of age had no significant difference between the two treatment groups.

Age: Subgroup of patients ≥ 80 years

No trials reported data for the subgroup of patients ≥ 80 years of age. ACAS excluded such patients. In the 10-year followup of ACST, both men and women < 75 years of age had significantly decreased annual rates of any stroke in the CEA group as compared with the medical therapy group. Similar benefit was not reported for the subgroup of men or women ≥ 75 years of age.

Sex

The VA trial included only men and the remaining two RCTs included a higher proportion of men than women. ACAS reported that during a projected 5-year followup, according to the Kaplan–Meier analysis, men had a significantly decreased risk of ipsilateral stroke (including perioperative stroke or death) in the CEA group than in the medical therapy group. During the 5- and 10-year followup of ACST, both men and women received greater benefits with CEA than with medical therapy for the outcome of nonperioperative carotid territory stroke or any stroke, respectively.

Clinical and anatomic features of carotid artery stenosis

Regardless of the degree of stenosis, in ACST, patients in the CEA group had a decreased risk of carotid territory stroke at 5 years as compared with patients in the medical therapy group, while in the 10-year followup, only a subgroup of patients with 70–89 percent stenosis had

decreased annual rates of any stroke in the CEA group as compared with the medical therapy group.

In ACAS, patients with prior symptoms due to contralateral carotid stenosis or prior contralateral CEA had a reduced risk of ipsilateral stroke (including perioperative stroke or death) in the CEA group as compared with the medical therapy group on the basis of 5-year projected estimates from the Kaplan–Meier analysis. However, over a median 2.7-year followup in ACAS, there were more events in the CEA group than in the medical therapy group among patients who had prior symptoms due to contralateral carotid stenosis or prior contralateral CEA. In ACST at the 10-year followup, patients with prior symptoms due to contralateral carotid stenosis or prior contralateral CEA had no difference between the two treatment groups.

Average or high risk for CEA owing to comorbid diseases

All three RCTs excluded the majority of patients who were believed to be at high risk for CEA owing to associated medical illnesses.

Concurrent and postoperative treatment

Only the 10-year followup of ACST evaluated any nonperioperative stroke stratified by concurrent use of medications (antihypertensive therapy, antithrombotic therapy, and lipid-lowering therapy) at study entry. Few patients in these trials were receiving lipid-lowering therapy at study entry. Regardless of the usage of antihypertensive or lipid-lowering therapy, as compared with the medical therapy group, the CEA group had a significantly decreased risk of carotid artery territory stroke at 5 years and decreased annual rates of any stroke at 10 years.

Length of followup

Overall estimates of ipsilateral stroke or any stroke after CEA decreased with followup, but estimates of death did not change regardless of whether 5- or 10-year data were used from ACST.

Methodological quality of studies

All three RCTs were rated quality A.

CAS and medical therapy versus medical therapy alone (Key Question 2)

The strength of evidence is graded as insufficient because of the lack of RCT data.

CAS versus CEA (Key Question 2)

The strength of evidence is graded as insufficient because there was insufficient information or only one of the three RCTs (CREST, SAPPHIRE, and Brooks 2004) reported data on subgroups of interest.

Demographic and other baseline features of studied patients

Age: Subgroup of patients ≥ 65 years

The average age of patients enrolled in RCTs ranged from 66.6 to 72.6 years. However, no study provided data for the age subgroups < 65 years or ≥ 65 years; thus, between these subgroups we could not evaluate whether the treatment effect of CAS was different from CEA.

Age: Subgroup of patients ≥ 80 years

No subgroup analysis by patient age was reported in asymptomatic carotid stenosis.

Sex

CREST reported data stratified by sex in asymptomatic patients. Both men and women had nonsignificantly increased hazard ratio for the primary composite endpoint, stroke, and stroke or death with CAS as compared with CEA.

Clinical and anatomic features of CAS

The SAPPHIRE trial included only patients with > 80 percent carotid stenosis and reported no significant differences between CAS and CEA for ipsilateral stroke, any stroke, death, or composite primary endpoint.

Average or high risk for CEA due to comorbid diseases

All patients included in the SAPPHIRE trial were considered to be at high risk for adverse events on the basis of the clinical and anatomic features specified in the trial eligibility criteria.

Types of stents used and use of embolic protection devices

Data on the type of stents and embolic protection devices were reported by three RCTs (CREST, SAPPHIRE, and Brooks 2004). The trials did not report subgroup data according to the specific type of stent used. The Brooks 2004 trial did not use embolic protection devices. The majority of patients in trials that reported long-term outcomes (CREST and SAPPHIRE) underwent CAS with embolic protection devices. These trials did not report subgroup-specific data for the patients that did not receive such devices. Therefore, the impact of the use of embolic protection devices on the treatment effect of CAS could not be evaluated.

Concurrent and postoperative treatments

The two RCTs (CREST and SAPPHIRE) employed similar medical treatment for perioperative management (dual antiplatelet therapy for the CAS group and single antiplatelet therapy for the CEA group) and long-term management of patients. Neither RCT reported data relevant to examination of the impact of various medical treatments on clinical outcomes.

Length of followup

Only the SAPPHIRE trial reported data for 1- and 3-year followup. The 1-year data showed a significant 53 percent reduction in the risk of the primary outcome of any periprocedural stroke, MI or death, or postprocedural ipsilateral stroke with CAS over CEA (RR = 0.47, 95% CI = 0.25, 0.89); this effect was no longer significant at 3 years (RR = 0.73, 95% CI = 0.47, 1.14).

Methodological quality of studies

Data for the long-term efficacy of CAS as compared with CEA were reported in one quality-A RCT (CREST) and one quality-B RCT (SAPPHIRE). The observed point estimates for outcomes were in opposite directions reflecting inclusion of different patient populations.

Key Question 3 (Outcomes occurring within 30 days)

CEA and medical therapy versus medical therapy alone

Two quality-A RCTs (VA and ACAS) showed an increased risk of adverse events including any stroke, death, or MI with CEA and medical therapy as compared with medical therapy alone

during a 30-day period. The strength of evidence is graded as moderate for periprocedural outcomes because these results may not translate to contemporary clinical practice. In these trials, patients with asymptomatic carotid stenosis did not receive at randomization what is currently considered the best medical therapy or contemporary postoperative medical management.

The periprocedural period for the medically treated patients was defined as 30 days and 42 days after randomization in the VA and ACAS, respectively. We did not include ACST in evaluating this outcome, as the definition of perioperative morbidity and mortality in the ACST medical therapy group differed considerably from the definitions used in the other two trials.

Any periprocedural stroke

Two RCTs (VA and ACAS) reported a significantly higher risk of any stroke during the periprocedural period in the CEA than during the corresponding followup period in the medical therapy (summary RR = 5.94, 95% CI = 2.06, 17.12). There was no statistical heterogeneity (I^2 = 0.0%, P=0.91).

Periprocedural death

Two RCTs (VA and ACAS) reported a nonsignificantly higher risk of death during periprocedural period in the CEA than during the corresponding followup period in the medical therapy (summary RR = 3.68, 95% CI = 0.77, 17.72). There was no statistical heterogeneity (I^2 = 0.0%, P=0.82).

Periprocedural MI

Two RCTs (VA and ACAS) reported a nonsignificantly higher risk of MI during periprocedural period with CEA than during the corresponding followup period in the medical therapy (summary RR = 8.39, 95% CI = 1.00, 70.33). There was no statistical heterogeneity (I^2 = 0.0%, P=0.39).

Periprocedural composite outcomes (*Stroke or death with or without MI during the periprocedural period)*

The VA and ACAS provided data on periprocedural composite outcomes. The risk of stroke or death without MI during periprocedural period was significantly higher with CEA than during the corresponding followup period with medical therapy (summary RR = 5.35, 95% CI = 2.24, 12.78), without statistical heterogeneity (I^2 = 0.0%, P=0.68). The risk of stroke or death with MI during periprocedural period was significantly increased in CEA than during the corresponding followup period in the medical therapy (summary RR = 6.14, 95% CI 2.60, 14.52) without statistical heterogeneity (I^2 = 0.0%, P=0.92).

Periprocedural cranial nerve palsy

One RCT reported cranial nerve palsy after CEA but no such events were reported during the corresponding followup period after medical therapy.

Periprocedural bleeding complications

RCTs reported no major bleeding events during the periprocedural period.

CAS and medical therapy versus medical therapy alone (Key Question 3)

The strength of evidence is graded as insufficient because of lack of RCT data.

CAS and medical therapy versus CEA and medical therapy (Key Question 3)

One quality-A RCT and two quality-B RCTs reported data on the risk of adverse events, including any periprocedural stroke, death, or MI (or combinations thereof) with CAS as compared with CEA. No statistically significant difference in the risk of periprocedural adverse events was found between the two interventions. The strength of evidence is graded as insufficient because between-trial comparisons were not possible, as there was extreme clinical heterogeneity. In addition, for clinical outcomes, the observed point estimates were in opposite directions (periprocedural stroke or death were nonsignificantly higher in the CAS group, and periprocedural MI events were nonsignificantly higher in the CEA group).

Any periprocedural stroke

CREST reported a statistically nonsignificant increase in the occurrence of any periprocedural stroke in CAS as compared with CEA (HR = 1.88, 95% CI = 0.79, 4.42). Similar results were reported in the SAPPHIRE trial, with a nonsignificant increase in the risk of any periprocedural stroke (RR = 1.54, 95% CI = 0.44, 5.31) or periprocedural ipsilateral stroke (RR = 1.71, 95% CI = 0.42, 6.99) with CAS as compared with CEA. No cerebrovascular events occurred in the Brooks 2004 trial.

Periprocedural death

Two RCTs (CREST and SAPPHIRE) reported this outcome. In CREST, there was no periprocedural death in the two treatment groups. The SAPPHIRE trial reported a nonsignificant increase in the risk of periprocedural death in CAS as compared with CEA (RR = 2.05, 95% CI = 0.18, 22.3), but the wide confidence interval indicates great uncertainty.

Periprocedural MI

Two RCTs (CREST and SAPPHIRE) reported a nonsignificantly reduced risk of periprocedural MI with CAS as compared with CEA. CREST reported a nonsignificantly decreased occurrence of periprocedural MI in CAS as compared with CEA (HR = 0.55, 95% CI = 0.22, 1.38). Similar results were reported in the SAPPHIRE trial, with a nonsignificant decrease in the risk of periprocedural MI (RR = 0.38, 95% CI = 0.10, 1.41).

Periprocedural composite outcome of any stroke, MI, or death

Two RCTs (CREST and SAPPHIRE) examined the composite outcome of any stroke, MI, or death. CREST found no difference in the risk of this composite outcome between CAS and CEA (adjusted HR = 1.02, 95% CI = 0.55, 1.86). According to the reported events in the published paper of the SAPPHIRE trial, there was a nonsignificantly decreased risk of the composite outcome with CAS as compared with CEA (RR = 0.51, 95% CI = 0.19, 1.32). We observed minor inconsistencies in the numbers of reported events for this outcome between the published paper and the data available from the FDA.

Periprocedural composite outcome of any stroke or death

Two RCTs (CREST and SAPPHIRE) examined the composite outcome of any stroke or death. CREST reported a nonsignificantly increased risk of this composite outcome in CAS as compared with CEA (adjusted HR = 1.88, 95% CI = 0.79, 4.42). On the basis of the reported numbers of events in the FDA report of the SAPPHIRE trial, a nonsignificantly increased risk of the composite outcome with CAS as compared with CEA was estimated (RR = 1.44, 95% CI = 0.47, 4.40).

Periprocedural cranial nerve palsy

In a meta-analysis of the two RCTs (CREST and Brooks 2004), a statistically significant reduction in the risk of cranial nerve palsy with CAS over CEA was found (summary RR = 0.06, 95% CI = 0.01, 0.31), without statistical heterogeneity (I^2=0.0%, P=0.48).

Periprocedural bleeding complications

CREST reported no differences in the risk of hematoma or bleeding between CAS and CEA.

Applicability

Studies of medical therapy alone, specifically studies with a recruitment closure year between 2000 and 2010, were deemed applicable to contemporary clinical practice. Data for subgroup analysis of baseline features such as contralateral CEA and clinical or anatomic features of carotid artery stenosis (> 70 percent) were available. However, no separate data for subgroup analysis according to the age categories (≥ 65 years or ≥ 80 years) were available. In addition, no separate subgroup data by sex or baseline comorbid medical conditions were available.

Trials comparing CEA with medical therapy alone provided specific data for all subgroups of interest. In these trials, at randomization, patients with asymptomatic carotid stenosis did not receive what is currently considered best medical therapy, including the use of statins and specific targets for the management of hypertension and diabetes. Thus the results of these older CEA trials may not be applicable or relevant to contemporary clinical practice. There were insufficient data reported for the comparison of CAS with medical therapy alone and therefore, the applicability was not assessed. At least one of the trials comparing CAS with CEA reported data relevant to all subgroups of interest. The patient-selection process in the SAPPHIRE trial, in which almost half of potentially eligible patients were not randomized but rather were included in a stenting registry, poses significant limitations in assessing the applicability of the study results. Similar patient-selection issues were reported in CREST prolonging the enrollment phase, in which eligible patients were enrolled into one of several stent registries. All trials were conducted at tertiary medical centers; thus, their results may not be generalizable to community settings.

Conclusions

The goal of management of asymptomatic carotid stenosis is to decrease the risk of stroke and stroke-related deaths. Our review of therapeutic strategies in patients with asymptomatic carotid stenosis indicates that there has been a significant reduction in the incidence of ipsilateral stroke over time with medical therapy alone. Our subgroup analysis shows that between the year 2000 and 2010, the current best medical therapy can reduce the risk of ipsilateral stroke to nearly 1 percent per year of followup. In addition, use of statins by ≥ 25 percent (vs. < 25 percent) of the study population and use of antiplatelet therapy by≥ 50 percent (vs. < 50 percent) of the study population was associated with significantly decreased rates of ipsilateral stroke in a few studies that reported this information.

Older trials comparing CEA with medical therapy demonstrate a reduction in the occurrence of stroke. This observed reduction reflects the low perioperative complication rate of < 3 percent achieved in ACAS and ACST. In these trials, surgeons were selected on the basis of their past operative experience and the surgeries were conducted in tertiary care centers. Thus, to reduce any future stroke-related events invasive procedures must carry an exceedingly low risk of

periprocedural adverse events, which may be difficult to achieve in routine clinical settings. In view of recent advances in medical therapy, the applicability or generalizability of the older CEA trial results to contemporary clinical practice requires careful interpretation. There is no randomized trial comparing CAS with medical therapy alone.

One recent large trial (CREST) reported higher rates of postprocedural ipsilateral stroke (including any periprocedural stroke) and its composite primary endpoint in the CAS, as compared with CEA, but this did not reach statistical significance in patients with asymptomatic carotid stenosis. The CREST and the SAPPHIRE trials randomized patients with symptomatic and asymptomatic carotid stenosis stratified according to symptom status. Therefore, the treatment assignment was randomized among the subgroup of patients with asymptomatic carotid stenosis. However, neither trial was powered to detect a significant difference in the primary composite endpoint among subgroups of patients with asymptomatic carotid stenosis. The failure to find a significant difference does not rule out the possibility that real difference exists between the intervention modalities tested.

In this review, we examined both older studies and more recent publications. Also in contrast to prior reviews, we examined nonrandomized studies conducted in real-world settings to evaluate the effectiveness of therapeutic strategies. Our review concludes that future trials should evaluate whether patients with asymptomatic carotid stenosis with >70 percent stenosis treated by current best medical therapy will derive additional benefit from invasive carotid revascularization procedures. Some limitations of this review directly reflect limitations of the data available in primary studies. The inclusion of populations in the studies was heterogeneous and reflects a lack of consensus in defining patients with asymptomatic carotid stenosis. The trials presented survival data for different outcomes, precluding us from conducting meta-analyses that would account for differential followup durations. The CAS trials included populations with extreme clinical heterogeneity and therefore were not combined in meta-analyses. Finally, our analyses and results were based on study-level data, but not patient-level data.

Patients with asymptomatic carotid stenosis are at an increased risk of future cerebrovascular events. Any expected benefits of an intervention depend on the reduction of the risk of future stroke-related events. Achieving this by medical therapy alone would allow patients to avoid the potential complications of invasive interventional procedures. Our review of medical cohort studies indicates that all patients with asymptomatic stenosis are likely to benefit from current best medical therapy alone. Recent observational studies suggest that there are methods to identify the high-risk group of patients with asymptomatic carotid stenosis who may benefit from invasive interventional procedures. Future trials should focus not only on whether CAS is equivalent or superior to CEA, but also on whether an invasive interventional procedure is likely to translate into any significant benefit to the patient treated with current best medical therapy.

Introduction

Background

Stroke is a leading cause of death in the United States. Although the number of deaths from stroke has declined in recent years, it continues to be a major public health problem in the United States, with an estimated $34.3 billion in direct cost and indirect cost of stroke in the year 2008.[1] Carotid artery stenosis represents an important risk factor for ischemic stroke, which accounts for nearly 90 percent of all strokes among U.S. men and women. Carotid artery stenosis is increasingly prevalent from the fifth decade of life onward. Patients with vascular disease and multiple risk factors (e.g., diabetes, hypertension, hyperlipidemia, and smoking) have a higher probability of having asymptomatic carotid stenosis. Since carotid artery atherosclerosis can largely proceed silently and unpredictably, the first manifestation can be a debilitating or fatal stroke. Asymptomatic carotid artery stenosis affects approximately 7 percent of women and over 12 percent of men, older than 70 years of age.[2] Clinically important stenosis, at which the risk of stroke is increased, is defined as stenosis of over 50 or 60 percent.[3] Natural history studies have reported that patients with asymptomatic carotid stenosis are at an increased risk of ipsilateral carotid territory ischemic stroke ranging from 5 to 17 percent.[4,5]

The goal of management of asymptomatic carotid stenosis is to decrease the risk of stroke and stroke-related deaths. However, screening asymptomatic patients for carotid stenosis is not part of common clinical practice as noted in a review by the U.S. Preventive Services Task Force from 1996, which concluded that evidence was insufficient to recommend either for or against screening.[3] As the general U.S. population ages, and with the availability of noninvasive imaging studies, asymptomatic carotid artery stenosis may be more frequently detected in the course of patient management. Auscultation of the carotid arteries to listen for bruits is by convention an initial means of clinical assessment of high-risk patients, but the presence of bruits is not necessarily indicative of significant stenosis.[6] Since carotid auscultation has limited sensitivity in detecting significant carotid stenosis,[7] additional imaging modalities including digital subtraction angiography (DSA), Doppler ultrasound (DUS), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) are being increasingly utilized.[8]

The most commonly used measurement method of carotid stenosis used in clinical trials or most common angiographic method was introduced in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[9] In the NASCET method, the stenosis is measured as the ratio of the linear luminal diameter of the narrowest portion of the artery's diseased segment divided by the diameter of the healthy distal carotid artery (above the post-stenotic dilation). An alternative method was used in the European Carotid Surgery Trial (ECST), which utilized the estimated carotid bulb at the site of maximal stenosis as the denominator.[10] The ECST method tends to yield higher degrees of stenosis, but measurements made by each method can be converted to those of the other using a simple arithmetic equation.[11] According to the 2003 Society of Radiologists in Ultrasound consensus criteria, a carotid stenosis is not quantified as an exact percentage of luminal stenosis but can be classified by range of stenoses that represent clinically relevant categories (normal, < 50 percent, 50-69 percent, ≥ 70 percent but less than near occlusion, near occlusion, or total occlusion).[8]

Therapeutic options in asymptomatic carotid stenosis include medical therapy alone, carotid endarterectomy (CEA) and medical therapy, or carotid angioplasty and stenting (CAS) and medical therapy. However, the optimal therapeutic management strategy for patients with

asymptomatic carotid stenosis is unclear. The Centers for Medicare and Medicaid Services (CMS) is interested in a systematic review of the literature on these three treatment strategies in patients with asymptomatic carotid stenosis. The Coverage and Analysis Group at the CMS requested the present report from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Tufts Evidence-based Practice Center (Tufts EPC) (Contract number, HSSA 290 2007 10055 I).

Therapeutic options in asymptomatic carotid stenosis

Medical therapy alone

The specifics of optimal medical management for asymptomatic carotid stenosis continue to evolve. Recent systematic reviews and their analyses of asymptomatic patients with medical therapy alone have shown decreased risk estimates for stroke.[12 13] Contemporary medical management of vascular diseases includes use of dual antiplatelet drugs, use of statins, blood-pressure targets in patients with hypertension, and newer classes of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers. Statin therapy, in particular, may have beneficial effects on carotid plaque morphology and attenuate the underlying inflammatory response.[14] Management of diabetes and lifestyle modifications (smoking cessation, physical activity, improved diet) may also be beneficial for the prevention of carotid stenosis-related stroke.[15] Primary prevention of stroke with aspirin remains to be of uncertain value, and other antiplatelet regimens (clopidogrel, ticlopidine, aspirin/extended-release dipyridamole, and cilostazol) have not been tested for primary prevention of stroke.

CEA and medical therapy

CEA was initially indicated in patients with symptomatic carotid stenosis, which was subsequently expanded to asymptomatic patients following the demonstrated modest benefit of CEA over medical therapy in RCTs of asymptomatic carotid stenosis.[16] The procedure involves surgical incision and removal of fatty plaque blockage. Different techniques of CEA have been developed, with the standard longitudinal arteriotomy modified to an 'eversion endarterectomy,' which allows full exposure of the plaque and removal through a transverse incision.

The perioperative antithrombotic management with heparin, low-molecular weight heparinoids, followed by antiplatelet drugs is routinely used. Antiplatelet treatment is an important element in the conduct of the procedure; more recently both aspirin and Clopidogrel are administered. In general, there are a wide range of practices in terms of the selection of technical and anesthesia modules for CEA. Additional techniques during CEA can include cerebral protection with the use of an in-line shunt to perfuse blood from the common carotid to the internal carotid and is applied on the operated side. The use of shunting varies widely. Selective shunting may be based on the surgeons' own observations (e.g. amount of 'back bleeding' or retrograde internal carotid artery flow following proximal common carotid artery occlusion) monitoring with electroencephalography, or transcranial ultrasound during CEA. There has also been a change in the management of the arteriotomy closure following CEA. Carotid patching is based on the creation of a wider internal carotid artery (ICA) diameter with improved flow dynamics associated with the patch.

CAS and medical therapy

CAS is a less invasive carotid revascularization technique. CAS is performed intravascularly and does not involve a surgical incision. CAS does not require general anesthesia; the procedure is more commonly conducted under conscious sedation and local anesthesia. Antiplatelet treatment is an integral part of CAS, with dual antiplatelet regimens (aspirin plus clopidogrel), which are continued beyond the periprocedural period. The procedure involves a diagnostic arteriogram of both carotids, the advancement of a guide wire over the stenosis, optional pre dilation of the lesion with a balloon, and then deployment of a self-expandable stent (with varying diameters, lengths, and shapes) into the lesion. The stent selection is tailored to the optimal ICA diameter. Finally, a completion arteriogram of the bifurcation and intracranial carotid vessels is carried out to ensure that the stent is deployed correctly and to identify any potential dissection, vasospasm, or embolization. Because of the concerns regarding distal embolization related to catheter manipulation and stent deployment, embolic protection devices have been developed (e.g., distal balloon occlusion, flow reversal or filter trapping devices) with filter traps being the most commonly used.

Review of recent guidelines

The 2010 primary prevention guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend the use of aspirin only in conjunction with CEA, unless otherwise contraindicated (AHA/ASA rating: Class I, Level of Evidence C).[15] Recent recommendations from these guidelines state that prophylactic CEA performed with <3 percent combined operative morbidity/mortality can be useful in highly selected patients with asymptomatic carotid stenosis (AHA/ASA rating: Class IIa, Level of Evidence A).[15] These guidelines also recommend that prophylactic CAS might be considered in highly selected patients with an asymptomatic carotid stenosis, although the advantage of CAS over current medical therapy alone is not well established (AHA/ASA rating: Class IIb, Level of Evidence B). The usefulness of CAS as an alternative to CEA in asymptomatic patients at high risk for the surgical procedure is also uncertain (AHA/ASA rating: Class IIb, Level of Evidence C).[15]

The 2011 guidelines on the management of patients with extracranial carotid and vertebral artery disease was endorsed by multiple professional associations including the 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 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 NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography.[17] The recommendations vary in classes (size of treatment effect, ranging from I to III based on benefit from treatment is greater than risk) and differ by levels of supporting evidence (estimate of certainty or precision of treatment effect, ranging from A to C based on the hierarchy of study designs and data available in different subpopulations).

This guideline recommends that patients with asymptomatic carotid stenosis be treated with antihypertensive medication for those with hypertension to a target blood pressure below 140/90 mmHg (Class I, Level of Evidence A); counseling patients to quit tobacco smoking (Class I, Level of Evidence B); treating with statin medication alone (Class I, Level of Evidence B) to reduce low-density lipoprotein (LDL) cholesterol <100 mg/dL, and antiplatelet therapy with

aspirin, 75 to 325 mg daily (Class I, Level of Evidence A). Other suggestions include combination of statins with bile acid sequestrants or niacin (Class IIa, Level of Evidence B) to reduce LDL cholesterol < 100 mg/dL; treating with statin medication alone to reduce LDL levels < 70 mg/dL in patients with diabetes mellitus (Class IIa, Level of Evidence B); and managing diabetes mellitus with diet, exercise, and glucose-lowering drug to maintain a glycosylated hemoglobin A1c level < 7.0 percent (Class IIa, Level of Evidence A).

This guideline recommends that the selection of asymptomatic patients for carotid revascularization should be guided by assessment of comorbid conditions, life expectancy, and other individual factors. This decision should incorporate patient preferences achieved by a thorough discussion of the risks and benefits of the procedure (Class I, Level of Evidence C).

This guideline recommends that it is reasonable to perform CEA in patients with asymptomatic carotid stenosis who have >70 percent stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (Class IIa, Level of Evidence A). In particular, it recommends that the choice of CEA over CAS in patients with asymptomatic carotid stenosis is reasonably indicated in older patients with unfavorable pathoanatomy for CEA, patients of any age with unfavorable neck anatomy (Class IIa, Level of Evidence B). The guideline recommends prophylactic CAS may be considered in highly selected patients with asymptomatic carotid stenosis with ≥ 60 percent by angiography or ≥ 70 percent by DUS, but recognizes that the effectiveness of CAS has not been compared with medical therapy alone (Class IIb, Level of Evidence B).

The guideline also recognizes that in patients with asymptomatic carotid stenosis who are at high risk for carotid revascularization, neither CEA nor CAS has been evaluated for their effectiveness compared with medical therapy alone (Class IIb, Level of Evidence B). This guideline recommends against performing CEA or CAS in patients with < 50 percent stenosis, chronic total occlusion, and those with severe disability caused by cerebral infarction that precludes preservation of useful function.

Key Questions

Our objective was to answer the following key questions regarding the treatment strategies involved in the management of asymptomatic carotid stenosis. These key questions were formulated in consultation with CMS and AHRQ.

1. In asymptomatic patients with carotid artery stenosis, what is the evidence on long-term clinical outcomes (at least 12 months of followup), including stroke, death, myocardial infarction, and other cardiovascular events, for the following interventions and comparisons?

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 efficacy?

- Demographic and other baseline features of studied patients, including 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 in the studies
- Average or high risk for carotid endarterectomy due to comorbid diseases
- Types of the stents used and use of embolic protection devices
- Concurrent and postoperative treatments
- Length of followup
- 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?

Methods

This report on the effectiveness of three treatment strategies for asymptomatic carotid artery stenosis is based on a systematic review of the literature. The approach, methodology, and criteria used were agreed upon by consensus of the Tufts EPC, CMS, and AHRQ staff.

Search Strategy

We searched MEDLINE® and the Cochrane Central Register of Controlled Trials for English-language studies of adult human subjects to identify articles relevant to each key question from inception through May 2012. We searched the Food and Drug Administration (FDA) Web site, and we contacted corresponding authors of eligible studies for unpublished data on outcomes of interest. We also reviewed reference lists of systematic reviews and selected narrative reviews and primary articles. In electronic searches, we combined terms for carotid artery stenosis, endarterectomy, and stenting in the context of relevant research designs (see Appendix A for complete search strategy).

Study Selection

We assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Population

We included studies of adults (≥ 18 years) with asymptomatic carotid artery stenosis. Eligible stenoses included atherosclerotic narrowing of the lumen of the carotid bifurcation or the extracranial part of ICA between 50 to 99 percent, as defined by any invasive imaging modality (DSA) or noninvasive imaging modality (carotid DUS, CTA, or MRA). We included both unilateral and bilateral stenoses but excluded ipsilateral carotid occlusions (100 percent obstructions), since patients with carotid occlusions are not typically considered for revascularization.

In general, we accepted the definition of "asymptomatic" patients used in each study, which could include any of the following:

- Patients with eligible carotid stenoses and no history of any vascular territory symptoms or physical findings on neurological exam at enrollment (patients without symptoms).
- Patients with eligible carotid stenoses and a history of cerebrovascular symptoms or physical findings on neurological exam (either ipsilaterally or contralaterally, or in the vertebrobasilar territory) for > 6 months before their enrollment in the study but without any recent symptoms at enrollment (patients with remote symptoms).
- Patients with eligible carotid stenoses and a history of contralateral or vertebrobasilar symptoms and signs < 6 months before enrollment (patients with symptoms in a different vascular territory other than ipsilateral carotid).

We included studies with mixed cohorts of patients (symptomatic and asymptomatic carotid artery stenosis), provided that the results were stratified according to symptom status. We also included studies of mixed cohorts of patients who had either asymptomatic carotid artery

stenosis or who were asymptomatic but had a recurrence of carotid stenosis following prior carotid intervention (CEA or CAS).

Subgroups of interest included those stratified by the following characteristics: age≥ 65 years and ≥ 80 years, sex, other baseline features (including comorbid medical diseases), clinical or anatomic features of carotid artery stenosis of > 70 percent or > 80 percent, concurrent or postoperative treatments, length of followup, and methodological quality of studies. We were also interested in the subgroup of patients who are considered to be high risk for CEA. We systematically compiled a list of factors associated with an increased risk of periprocedural adverse events (death or stroke) in patients undergoing CEA: variables found to be statistically significant in multivariate analyses of published literature for predictive models, variables listed in the CMS decision memo,[18] predictors described in a published systematic review of the literature,[19] those included in the reference surgical risk classification tool,[20] and all study definitions for patients who were high risk for CEA (e.g., as in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy[SAPPHIRE] trial).[21] We created a list of these factors in three categories (angiographic, medical, and neurological), and we specifically sought data on these conditions in the included studies (Appendix B).

Interventions

The primary interventions of interest were medical therapy alone, CEA and medical therapy, and CAS and medical therapy. Medical therapy can range from use of antiplatelets, anticoagulants, antihypertensives, lipid-lowering drugs, control of diabetes, smoking cessation, exercise, diet, or any other standard of care measures. Optimal medical therapy has changed over time and recent studies may have used a different set of medical therapies. Consequently, we developed operational definitions of the type and intensity of medical interventions used in each study (e.g. use of dual or single antiplatelet treatment, use of statins). However, we did not exclude *a priori* any studies that did not report on the medical treatment used or that specifically did not use a certain type of treatment (e.g. aspirin). We also considered all natural history studies as medical therapy alone studies, since we assumed that patients included in natural history studies with active followup did not undergo revascularization intervention, and would have received the "standard medical care" available at the time.

CEA included all variations of the surgical technique (e.g. eversion CEA, patch, shunt etc.) or anesthetic procedure (local or general anesthesia). CAS included all carotid intravascular interventions that involved any type of stent placement (with or without prior balloon angioplasty or concurrent use of embolic protection device). We excluded studies with patients with asymptomatic carotid stenosis undergoing an additional revascularization procedure at a different vascular site (e.g. coronary artery bypass grafting).

Comparators

We considered the following comparisons of interest: CEA and medical therapy versus medical therapy alone, CAS and medical therapy versus medical therapy alone, and CAS and medical therapy versus CEA and medical therapy.

We excluded studies that compared different types of medical treatments. Also excluded were studies comparing different CAS techniques with each other (e.g., drug-eluting stents versus bare metal stents for CAS) and studies comparing different surgical techniques with each other (e.g., patch versus nonpatch) that did not examine a comparator of interest. We excluded studies that utilized comparisons of interventions with historical controls.

Outcomes

For Key Questions 1 and 2, we included studies that reported only major clinical outcomes: stroke, death, myocardial infarction (MI), or other cardiovascular events. For Key Question 3, we included studies that reported safety outcomes related to a procedure or therapy (referred to as complications) or clinical outcomes, including stroke, death, or MI (referred to as adverse events) occurring within 30 days of the procedures or within 30 days of followup in the medical therapy group. The specific outcomes of interest, and the key question they addressed, are as follows:

1. Cerebrovascular events (Key Questions 1, 2, and 3)
   A. Stroke (Key Questions 1, 2, and 3)
      - Ipsilateral or any vascular territory stroke
      - Ischemic or hemorrhagic stroke
      - Stroke of any severity (e.g., minor or major)
   B. Any cerebrovascular event (e.g., stroke plus TIA, including amaurosis fugax) or TIA based on either the tissue definition or the time definition (Key Questions 1 and 2)
2. Mortality (Key Questions 1, 2, and 3)
   A. All-cause death
   B. Cerebrovascular death
3. Composite cardiovascular outcomes (Key Questions 1, 2, and 3)
4. Other periprocedural adverse events and complications (Key Question 3)
   A. Periprocedural MI
   B. Periprocedural composite outcomes
   C. Cranial nerve palsy
   D. Bleeding complications at the surgical or the vascular access site.

Study designs

For Key Question 1a that addressed the long-term clinical outcomes of medical therapy alone, we included prospective cohort studies and the medical therapy arm of eligible randomized controlled trials (RCTs) or prospective nonrandomized comparative studies of patients that underwent CEA for ipsilateral asymptomatic or contralateral symptomatic carotid stenosis.

For all other Key Questions comparing treatment strategies, we included both RCTs and nonrandomized (retrospective or prospective) comparative studies. We included nonrandomized comparative studies that analyzed either clinical or administrative datasets, provided that outcome data for patients diagnosed and coded as having asymptomatic carotid stenosis were available. When percent stenosis was not clearly reported in studies based on administrative dataset analyses, we assumed that all patients had a carotid stenosis of at least 50 percent.

Sample size and duration of followup

Studies with at least 30 patients with a minimum average followup of 12 months were included to evaluate Key Question 1a (medical therapy alone). These criteria were chosen to both minimize the bias related to retrospective analyses and to set a minimum level of power and applicability.

For all other Key Questions comparing treatment strategies, we included studies with at least 30 patients per intervention group and any duration of followup.

Data Extraction

Items extracted from each study included first author, year, country, funding source, study design, inclusion and exclusion criteria, including study definitions of asymptomatic carotid stenosis, imaging modality used (and related diagnostic and quality assurance criteria) for determining degree of stenosis (see Appendix B for a sample data extraction form). For RCTs, we recorded the method of randomization, allocation concealment, patient and outcome assessor blinding, and whether results were reported on an intention-to-treat basis. For nonrandomized studies, we also recorded study design and analysis methods used to adjust potential confounders. Specific population characteristics for each treatment group included demographics such as age and sex, and percentage of octogenarians, patients with hypertension, diabetes, atrial arrhythmias, smoking, coronary artery disease, peripheral arterial disease, history of previous TIA or stroke, history of previous CEA or CAS, patients with severe carotid stenosis (>70 or >80 percent stenosis), and patients with contralateral occlusion. Details regarding stenting techniques (including type of stent, use of embolic protection device) surgical techniques (use of patch, shunt, eversion, and type of anesthesia), and/or medical interventions were also extracted.

For each outcome of interest, we recorded the exact study definitions used, the baseline screening methods, the frequency of followup, the duration of followup and the methodology for outcome ascertainment of stroke, including whether a neurologist was part of the team of outcome adjudication. In prospective cohort studies of medical treatment, we extracted or calculated incidence rates of the events of interest expressed in person-years of followup, based on raw data or Kaplan-Meier estimates. When available, data on incidence rates were extracted from published Kaplan-Meier curves, after digitization. For comparative studies, data on numbers of events and persons at risk were extracted in order to calculate relative effect size estimates. Adjusted relative risk estimates were also recorded, when available. Periprocedural safety and adverse event data were also extracted.

Quality Assessment

We used predefined criteria to grade study quality as A, B, or C to assess the risk of bias. This system defines a generic grading system that is applicable to varying study designs including RCTs, nonrandomized comparative studies, and observational studies.[22] A summary of the methodological aspects we considered as quality items is provided in the extraction form (Appendix B.2, Table L).

We also examined study quality items relating to the diagnostic methodologies for the determination of carotid stenosis, the interventions used, and the outcome ascertainment, whenever applicable. For the diagnostic methodology used to determine the extent of carotid artery stenosis, we recorded whether the authors reported on the following items: central, blinded reading of images, one or multiple readers, for ultrasound laboratories whether the lab used a technique that was validated previously against a gold-standard methodology (i.e. DSA), accreditation by the Intersocietal Commission for the Accreditation of the Vascular Laboratories (ICAVL) or the American College of Radiology (ACR), reporting of diagnostic accuracy metrics use of confirmatory, reference imaging technique (CTA, MRA, and DSA). For studies examining interventional techniques, we recorded whether certification requirements (for volume of procedures or performance standards) were reported for surgeons and interventionists. Additional considerations were given to evaluate the quality of the outcome ascertainment,

whether this was performed blinded to clinical status or treatment allocation and whether a neurologist assessed the outcome of stroke.

A (good)

Quality-A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias.

B (fair/moderate)

Quality-B studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria in quality-A studies because they have some deficiencies, but none likely to cause major bias. However, none of them introduce a significant bias.

C (poor)

Quality-C studies have significant biases that have significant flaws that imply biases of various types that may invalidate the study results. These studies introduce major errors in methods, analysis or discrepancies in reporting results.

Applicability

Applicability of study results was assessed on the basis of reporting of the following factors in stratified analyses: age groups of≥ 65 years and ≥ 80 years, sex, other baseline clinical characteristics including comorbid medical diseases, medical therapy at baseline, and clinical or anatomic features of carotid artery stenosis (> 70 percent or > 80 percent stenosis). In addition, studies had applicability graded on the basis of whether they were conducted in tertiary centers or community centers.

Data Analysis

Studies of medical therapy alone

We calculated the incidence rate of events —that is, the incidence density—as the ratio = number of events/average person-time of followup along with the 95 percent exact Poisson confidence interval (95 percent CI) in studies when numerical data of events and an average followup person-time were available.[23] For outcomes investigated in at least five studies, we obtained summary estimates of incidence rates by fitting a generalized linear random effects meta-analysis model for count data with the exact Poisson likelihood.[24] Studies that reported incidence rates with their 95 percent CIs, without providing the number of events or person-time, were included in sensitivity analyses using an inverse variance random effects meta-analysis model (DerSimonian–Laird).[25] In this report, we express the units as percent per year instead of the number of events per 100 person-years.

To examine trends in the incidence rates of outcomes over time, we performed meta-regression analyses with the last year of recruitment in each study (recruitment closure year) as a continuous covariate.[26] Because we were particularly interested in the incidence rates of events

occurring during contemporary medical treatment, we conducted a subgroup analysis for studies that reported recruitment year 2000 or after, based on the availability or an increased utilization of medications such as statins. We conducted further exploratory subgroup and meta-regression analyses based on a prespecified set of clinically relevant explanatory variables and only for the outcomes with adequate analyzable information ($\geq$ 5 studies). These restrictions were put in place in order to obtain precise estimates of subgroup-specific incidence rates and to minimize the risk of false-positive results,[27] These exploratory analyses included the quality of studies (A or B versus C), operational definitions on the intensity of reported treatment (stratification of studies by the reported proportion of patients under treatment with anti-thrombotic agents or statins), the extent of anatomical stenosis (> 70 percent versus 50–70 percent stenosis) and finally the inclusion of patients with contralateral CEA in the each study cohort versus never-operated patients. Statistically significant differences between subgroups were examined with meta-regression tests for interaction.

Comparative studies

For comparative studies, relative risk (RR) estimates were calculated from numerical event data. RCTs and nonrandomized comparative studies were analyzed separately and analyses were stratified by study designs (RCTs, nonrandomized comparative-clinical and nonrandomized comparative-administrative studies). We performed meta-analysis using a random effects model and reported the results as summary relative risks (RRs). Heterogeneity was tested with the Q-statistic and quantified with I^2. Statistical significance for all tests, other than those of heterogeneity, was defined as a two-sided P-value < 0.05. No adjustment for multiple comparisons was performed. When we identified discrepancies between published and unpublished data for a study, or when we identified extreme clinical heterogeneity, we refrained from conducting meta-analyses to synthesize data. In RCTs comparing treatments, when possible, we also estimated summary incidence rates of ipsilateral stroke for each of the treatment arms.

Grading the Strength of Evidence

We graded the strength of the body of evidence for each analysis within each key question per the AHRQ methods guide.[22] Risk of bias was defined as low, medium, or high on the basis of the corresponding quality rating A, B, or C, respectively, of individual studies. We assessed the consistency of the data, which was classified as either “no inconsistency” or “inconsistency present” (or “not applicable” if there was only one study). The direction, magnitude, and statistical significance of findings from all studies were evaluated in assessing consistency, and logical explanations were provided in the presence of equivocal results. We also assessed the directness of evidence and the precision of the evidence on the basis of the degree of certainty surrounding an effect estimate. A precise estimate was considered to be an estimate that would allow for a clinically useful conclusion. An imprecise estimate was one for which the confidence interval was wide enough to preclude a conclusion.

For Key Question 1a, evaluating effectiveness of medical therapy alone, the strength of evidence was graded on the basis of individual studies (prospective cohort studies and the medical therapy arms in eligible trials) rated quality-A or -B. For all other key questions comparing treatment strategies, the strength of evidence was graded on the basis of individual RCTs rated quality-A or -B. The quality-C studies were excluded from the strength-of-evidence assessment but are described in detail in the results section of this report.

Grades were assigned according to our level of confidence that the evidence reflects the true effect for the interventions of interest and were defined as follows:

High. There is a high level of assurance that the findings of the literature are valid with respect to the relevant comparison. No important scientific disagreement exists across studies. At least two quality-A studies are required for this rating. In addition, there must be evidence regarding important clinical outcomes. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate. There is a moderate level of assurance that the findings of the literature are valid with respect to the relevant comparison. Little disagreement exists across studies. Moderately rated bodies of evidence contain fewer than two quality-A or-B studies or such studies lack long-term outcomes of relevant populations. Further research may change our confidence in the estimates of effect and may change the estimate.

Low. There is a low level of assurance that the findings of the literature are valid with respect to the relevant comparison. Underlying studies may report conflicting results. Further research is likely to change our confidence in the estimate of effect and may change the estimate for this outcome.

Insufficient. Evidence is either unavailable or does not permit estimation of an effect due to a lack of data or sparse data. In general, when only one study has been published, the evidence was considered insufficient, unless the study was particularly large, robust, and of good quality.

Results

The literature search identified 7,571 abstracts. The abstract screening process identified a total of 375 full-text articles that were evaluated against the inclusion criteria. Of these, 60 studies published in 68 articles met the eligibility criteria (Appendix C, Figure 1).

Key Question 1 (Long-term outcomes)

In asymptomatic patients with carotid artery stenosis, what is the evidence on long-term clinical outcomes (at least 12 months) including stroke, death, myocardial infarction, and other cardiovascular events for the following interventions and comparisons?

Medical therapy alone (Key Question 1a)

A total of 41 studies assessed medical therapy and met our inclusion criteria (nine quality-A, 14 quality-B, and 18 quality-C studies). We evaluated the evidence on the absolute risk of long-term adverse clinical outcomes in patients with asymptomatic carotid stenosis and receiving medical therapy only (no revascularization procedure in the carotid artery of interest). We used the data from eligible single-arm prospective cohort studies of medical therapy, from the medical therapy groups of eligible RCTs and nonrandomized comparative studies and also followup data for the asymptomatic arteries of patients that underwent CEA to the contralateral carotid artery.

Table 1. Summary characteristics of studies of medical therapy that reported ipsilateral stroke

Study, Year, Country	Population	N subjects (followup yr)	Percent carotid stenosis	Contralateral status	Long-term outcomes
RCT*					
ACAS, 1995 USA[28]	Medical therapy group	834 (5.25)	60-99% DUS	9% occlusion; 19% CEA	Stroke, death, ipsilateral TIA
ECST, 1995 Europe[29]	Medical therapy group; contralateral to CEA	127 (3.5)	70-99% DSA	100% CEA in surgical group	Only ipsilateral stroke
Halliday, 2004, 2010 (ACST) Europe[30,31]	Medical therapy group	1560 (4.4)	60-99% DUS	9% occlusion, 24% CEA	Stroke, death
Hobson, 1993 (VA) USA[32]	Medical therapy group	233 (9)	50-99% DUS; DSA	33% occlusion	Stroke, death, ipsilateral TIA
Inzitari, Anderson, 2000, 2002 USA[33,34]	Contralateral asymptomatic artery in both groups	324 (2.4)	50-99% DSA	100% CEA in surgical group	Fatal stroke, death, ipsilateral TIA
AbuRahma, 2003 USA**[35]	Contralateral asymptomatic artery to CEA	101 (3.4)	50-99% DUS	100% CEA	Ipsilateral stroke and TIA

Table 1. Continued

Study, Year, Country	Population	N subjects (followup yr)	Percent carotid stenosis	Contralateral status	Long-term outcomes
Prospective studies					
Abbott, 2005 Australia[36]	Medical Cohort	202 (3)	60-99% DUS	5 % occlusion	Stroke, MI, ipsilateral TIA, non stroke death
AbuRahma, 2003 USA[37]	Medical Cohort	82 (5)	60-69% DUS	100 % occlusion	Stroke, death, ipsilateral TIA
Ballotta, 2007 Italy[38]	Medical Cohort	98 (2.7)	50-69% DUS / DSA	100% CEA	Ipsilateral stroke and TIA
Bogousslavsky, 1986 Switzerland[39]	Medical Cohort	38 (4.1)	90-99% DUS	0 % occlusion	Death, ipsilateral TIA
Goessens, 2007 The Netherlands[40]	Medical Cohort	221 (4.5)	50-99% DUS	nd	Stroke, MI, death
Gronholdt, 2001 Denmark[41]	Medical Cohort	111 (4)	50-99% DUS	nd	Death, ipsilateral TIA
Gur, 1996 Israel[42]	Medical Cohort	44 (3.6)	70-99% DUS / DSA	nd	Ipsilateral stroke and TIA
Johnson, 1985 USA[43]	Medical Cohort	121 (4)	75-99%; nd	nd	Ipsilateral stroke and TIA
Johnson, 1995 USA[44]	Medical Cohort	94 (2.9)	50-79% DUS	nd	Only ipsilateral stroke
Levien, 1984 South Africa[45]	Medical Cohort	50 (3)	50-99% DUS	nd	Ipsilateral stroke and TIA
Liapis, 2001 Greece[46]	Medical Cohort	136 (1.8)	50-99% DUS	nd	Ipsilateral stroke and TIA
Mackey, 1997 Canada[46,47]	Medical Cohort	357 (3.7)	50-99% DUS	nd	Stroke, ipsilateral TIA
Mansour, 1999 USA[48]	Medical Cohort	344 (5)	50-79% DUS	nd	Stroke, death; ipsilateral TIA
Markus, 2010 International[49]	Medical Cohort	467 (3.1)	70-99% DUS	nd***	Stroke, ipsilateral TIA
Marquardt, 2010 UK[50]	Medical Cohort	101 (2.1)	50-99% DUS	nd	Stroke, MI, ipsilateral TIA, death
Nicolaides, Kakkos, 2005 UK[51,52]	Medical Cohort	805 (3)	50-99% DUS	nd	Death, ipsilateral TIA
Silvestrini, 2000 Italy[53]	Medical Cohort	94 (2)	70-90% DUS	0 % occlusion	Stroke, MI, ipsilateral TIA
Spence, 2005, 2010 Canada[54,55]	Medical Cohort	468 (1.4)	60-99% DUS	nd	Stroke, MI, death
Takaya, 2006 USA[56]	Medical Cohort	154 (2)	50-79% DUS	nd	Ipsilateral stroke and TIA
Longstreth, 1998 USA[57]	Medical Cohort	184 (1.5)	50-99% DUS	0 % occlusion	Stroke, ipsilateral TIA
Zhang, 2009 China[58]	Medical Cohort	62 (1)	50-99% DUS	nd	Ipsilateral stroke and TIA, MI, death

DSA = digital subtraction angiography, DUS = duplex ultrasonography, MI = myocardial infarction, N= total number of patients analyzed, TIA = transient ischemic attack, nd = not documented

*All are RCTs of CEA versus medical therapy; **Included two trials of CEA; *** Included patients who had undergone CEA for the contralateral artery, but their proportion was unknown

Study characteristics

Eligibility criteria and diagnosis of asymptomatic carotid stenosis

The eligible studies included six RCTs comparing CEA with medical therapy, which reported results from the medical therapy group in eight publications.[28-34,59] Among the six RCTs, there were three studies that provided data from the medical therapy group of the RCT,[28,28,30-32] one study that provided data from the medical therapy group as well as additional data from the medical therapy group of the nonrandomized comparison of CEA and medical therapy[59], one study that provided data from the medical therapy group as well as from the contralateral artery in the CEA group,[29] a study of symptomatic patients that provided data from the asymptomatic contralateral artery of the CEA group, and the asymptomatic contralateral artery of the medical therapy group.[33,34] We also included a nonrandomized comparative study of CEA and medical therapy that provided data from the medical therapy group.[60] Additional data on medical therapy was obtained from a report on the events in the contralateral artery territory from two RCTs that compared CEA with primary closure and CEA with patching.[37] The remaining studies included 33 single-arm prospective cohort studies. One study reported data for two different cohorts, which contributed to two separate meta-analytic strata.[55]

DUS was used to assess the degree of carotid stenosis in 31 studies (75.5 percent) and a combination of DUS and DSA was used to assess stenosis in seven studies (17 percent).[32,38,42,59-62] DSA alone was used in two studies (5 percent) to assess carotid stenosis, [29,33,34] and one study did not provide information on the imaging modality used.[43] The characteristics of included studies that reported data on ipsilateral stroke are provided in Table 1.

Population

The studies included were conducted from 1978 through 2009. A total of 16,178 patients in 41 studies were followed for an average period of 3.4 years. The sample size of the studies ranged from 38 to 3,164, and the followup period ranged from 1 to 9 years. The average age of the participants across all studies was 68 years and ranged from 55 to 81 years. The proportion of octogenarians among the study populations ranged from zero to 40 percent, as reported in seven studies.[28,30,31,33,34,39,41,50,59] The proportion of males in each study ranged from 40 to100 percent, with a median of 63.5 percent (Interquartile range: 57.3 to 74 percent).

The majority of the studies (22 of 41 studies, 54 percent) included participants who had never previously undergone a CEA in the contralateral carotid artery; of those, one study included patients with contralateral carotid occlusion.[37] In 10 other studies (25 percent), a certain proportion of the included patients had undergone CEA in the contralateral carotid artery, ranging from 19 to 100 percent.[28-31,33-35,38,49,60,63,64] In 9 studies (22 percent), it was not specified whether patients that had undergone CEA in the contralateral carotid artery were excluded from the study population.

The proportion of participants with hypertension ranged from 12 to 90 percent and the proportion of participants with coronary artery disease ranged from 14 to 81 percent. The range of prevalence of peripheral vascular disease was from 15 to 71 percent, and prevalence of hyperlipidemia was 5 to 79 percent. The proportion of participants who currently smoked or had ever smoked ranged from 14 to 91 percent.

Description of medical therapy

Of all 41 studies, 29 (71 percent) had information on the medical treatment being given to the participants, and among them, 28 (68 percent) reported details of the anti-thrombotic treatment given to the participants, and only 13 (32 percent) reported details of lipid-lowering treatment. Among these studies reporting data on the actual medical therapy received, the use of anti-thrombotic medication (including both anti-platelet as well as anti-coagulant drugs) ranged from 0 to 100 percent with the median of the proportion of patients using anti-thrombotic drugs being 91.5 percent of the participants. Similarly, the range of usage of lipid-lowering medications such as statins was from 5 to 88 percent, with the median of the proportion of patients using statins and other lipid-lowering drugs being 62 percent. Two studies disallowed the participants from taking any anti-platelet drugs.[43,65] The details of the baseline characteristics are summarized in the Appendix E, Tables 1–2.

Incidence rates for cerebrovascular, mortality, and cardiovascular outcomes were calculated from 41 studies. Syntheses of these incidence rates were performed for outcomes of interest; results of these meta-analyses are shown below in Table 2.

Ipsilateral Stroke

The meta-analysis for ipsilateral stroke included 26 studies.[28-35,37-58] Ipsilateral stroke occurrence was 1.68 events per 100 person-years of followup with medical therapy alone or 1.68 percent per year (summary incidence rate = 0.017, 95% CI = 0.013, 0.021) (Figure 1). The median number of ipsilateral stroke occurring in each study was small (n=10).

Ipsilateral stroke or TIA

The summary estimate of 20 studies[28,32-35,37,38,42,43,45-52,56,58,62,63,66] reporting the combined outcome of ipsilateral stroke or TIA was 5.5 percent per year (Appendix D, Figure 1).

Any stroke

The summary incidence rates for any stroke in 17 studies [28,31,32,37,40,47-49,53,55,57,59,60,67-69] and any stroke or TIA in nine studies[47,48,53,64,67-71]) were 2.7 and 5.6 percent per year, respectively (Appendix D, Figures 2 and 3).

Mortality

The meta-analysis of all-cause death included 14 studies.[28,31,32,37,39-41,48,51,52,54,55,68,7258] The summary incidence rate of all-cause death was 4.6 percent per year (Appendix D, Figure 4). Patients with medical therapy alone had 4.1 percent per year cardiovascular deaths in a meta-analysis of six studies.[39,40,50-52,68,72]

Composite cardiovascular outcomes

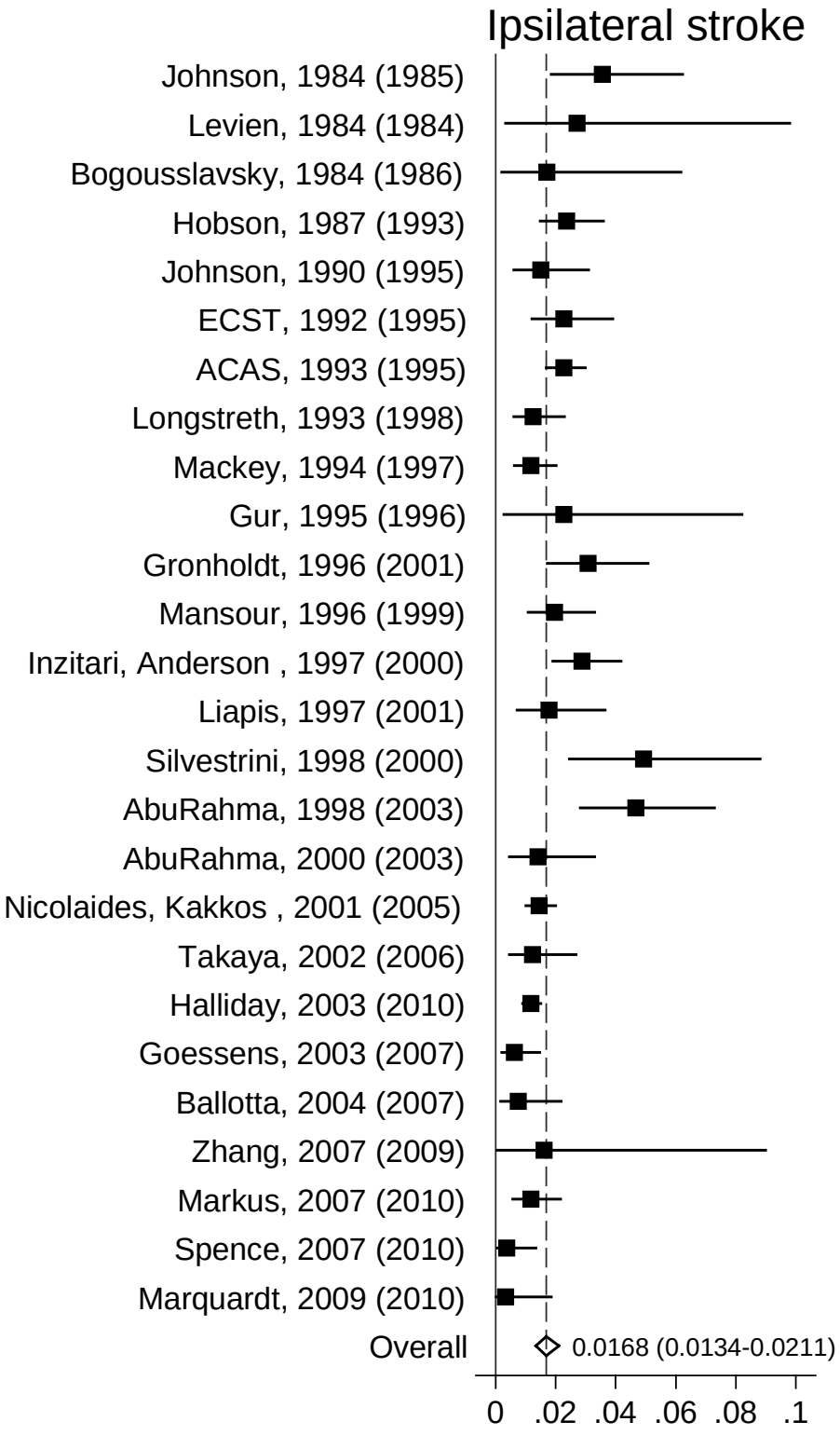
The analysis of composite outcomes included 15 studies.[33,34,36,37,40,41,47,49,50,57,59,61,65,68,71,72] Studies used various combinations of acute coronary syndrome, ischemic cerebrovascular events, referral to revascularization, and cardiovascular or all-cause death to report the composite endpoint. The clinical heterogeneity of the reported outcomes precluded any meaningful synthesis of incidence rates of events across these studies. Five studies that reported separate data for the outcome of MI were subjected to meta-analysis; the summary incidence rate was 2.3 percent per year.[40,50,53-55]

Table 2. Meta-analyses of incidence rates of events for all medical therapy studies

Outcome	N of studies	Summary incidence rate (95% CI)	Median number of events (IQR)	Median person-years of followup (IQR)
Ipsilateral stroke	26	0.0168 (0.0133 to 0.0211)	10 (3 - 15)	489.3 (337 – 851.9)
Ipsilateral stroke or TIA	20	0.0550 (0.0437 to 0.0690)	22 (8.5 – 49.5)	398.4 (109.15 – 889)
Ipsilateral TIA	9	0.0296 (0.0202 to 0.0435)	8 (5 - 14)	354.1 (223.3 – 406.6)
Any stroke	17	0.0267 (0.0195, 0.0366)	16 (7 - 27)	713.8 (386.65 - 930)
Any stroke or TIA	9	0.0557 (0.0398, 0.0781)	23 (16 - 64)	621.7 (223.25 - 1106.7)
Any TIA	5	0.0396 (0.0308, 0.0507)	7 (4 - 8)	108.5 (108.2 - 175)
Cardiovascular death	6	0.0409 (0.0323, 0.0518)	40 (23 - 91)	1069.2 (301 - 2269.2)
Death	14	0.0458 (0.0342 to 0.0613)	55 (14 - 103)	754.7 (406.6 - 2251.8)
MI	5	0.0234 (0.0124, 0.0440)	14 (2 - 14)	398 (301 - 538)

CI = confidence interval, IQR = interquartile range, MI = myocardial infarction, TIA = transient ischemic attack.

Figure 1. Forest plot of the incidence rates of ipsilateral stroke in medical therapy alone



The studies are ordered by the last year of recruitment in each study. Year of publication is provided in parentheses.

Meta-regression and subgroup analyses

To examine the impact of time on the incidence rates of events, we performed meta-regression analyses with the last year of recruitment in each study (recruitment closure year) as a continuous covariate. We conducted these meta-regression analyses for the four main ischemic cerebrovascular outcomes and for the outcome of all-cause death. Meta-regression analyses showed that the coefficient of the indicator variable "recruitment closure year" was statistically significantly different than zero for the ipsilateral territory outcomes, indicating that the incidence rates of ipsilateral stroke and ipsilateral stroke or TIA showed statistically significant reduction over time across studies (P<0.001). In contrast, no significant effect of time was detected for any territory cerebrovascular outcomes or the outcome of death (Table 3). The meta-regression plots (Figure 2) provide the log-transformed incidence rates of individual studies plotted against the recruitment closure year of each study and clearly depict a declining trend for the ipsilateral stroke and ipsilateral stroke or TIA outcomes.

We aimed to explore further why the reduction of incidence rates of ipsilateral events over time was statistically significant whereas the reductions of rates of any territory events or death were not. Given that different studies have been included in the meta-regression analyses for each outcome (depending on the availability of reported outcomes in each study), we performed sensitivity meta-regression analyses for the any territory outcomes and for the outcome of death, by considering only those studies that reported ipsilateral outcomes as well. With this approach, the same literature sample contributed data for the analyses of all outcomes, making the estimates of the coefficient of the indicator variable "recruitment closure year" comparable across analyses. The results are provided in Table 4, below. In these sensitivity analyses, there was evidence that the incidence rates of any stroke and death have shown statistically significant reduction over time (P=0.02 and 0.04, respectively). Thus, at least for those studies that provided data on ipsilateral events, there was significant reduction in the incidence rates of any stroke and death over time.

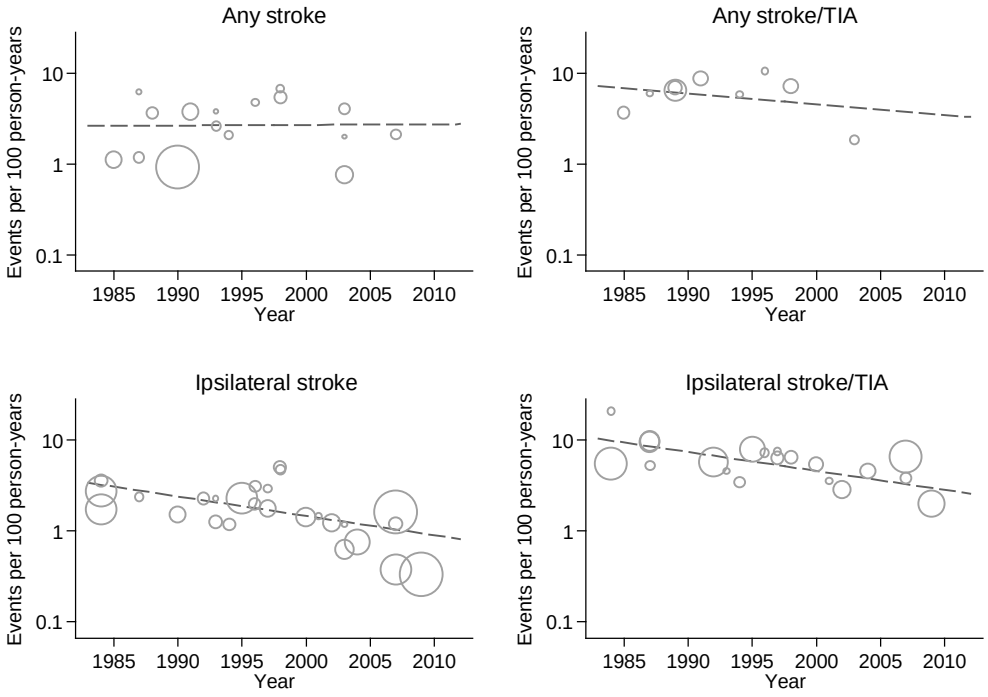
Table 3. Meta-regression analysis for the effect of the explanatory variable "recruitment closure year" on the incidence rate of events

Outcome	P-value for the coefficient of "recruitment closure year"	P-value in sensitivity analyses*
Ipsilateral stroke	0.001	NA
Ipsilateral stroke or TIA	<0.001	NA
Any stroke	0.947	0.020
Any stroke or TIA	0.352	NA (only 4 studies available)
Death	0.083	0.041

NA = not applicable; TIA = transient ischemic attack

*P-value for the coefficient of "recruitment closure year" in sensitivity analysis of studies reporting both ipsilateral and any territory outcomes

Figure 2. Meta-regression of the log-event rates by recruitment closure year for the four major ischemic cerebrovascular outcomes



Each study is depicted by a hollow circle with a size proportional to the number of observed events per outcome. The fitted line is derived from the meta-regression model.

In subgroup analysis, we further explored whether recent studies with recruitment closure years since 2000 compared with older studies with recruitment closure years before 2000 provide significantly different estimates of incidence rates of ipsilateral cerebrovascular events. Studies published with recruitment closure years since 2000 were considered to be more representative of contemporary medical therapies.

The summary incidence rate of ipsilateral stroke was significantly decreased in recent studies compared with older studies (0.011 versus 0.023, P for interaction <0.001). Similar results were obtained for the outcome of ipsilateral stroke or TIA (Table 4).

Table 4. Subgroup meta-analyses for the incidence rates of ipsilateral cerebrovascular outcomes for older studies and recent studies

	Studies with recruitment closure years before 2000		**Studies with recruitment closure years since 2000**		
Outcome	N of studies	Summary incidence rate (95% CI)	N of studies	Summary incidence rate (95% CI)	P-value (for interaction)
Ipsilateral stroke	16	0.0231 (0.0187, 0.0285)	10	0.0113 (0.0095 , 0.0134)	<0.001
Ipsilateral stroke or TIA	13	0.0677 (0.0520 , 0.0881)	7	0.0364 (0.0314, 0.0421)	<0.001

CI = confidence interval, TIA = transient ischemic stroke.

We conducted additional exploratory subgroup analyses by considering the following stratification factors: quality of studies (A or B versus C), operational definitions on the intensity of reported treatment (stratified by the reported proportion of patients under treatment with anti-thrombotic agents [50 percent threshold] or statins [25 percent threshold], extent of anatomical

stenosis (>70 percent versus 50-70 percent stenosis) and finally, inclusion of patients with contralateral CEA in the study cohort versus never-operated patients. The results of these analyses are shown in Table 5. For ipsilateral events, quality-A or -B studies resulted in lower point estimates of incidence rates compared with quality-C studies, but no formal statistical comparison was performed. [73] The subgroup of studies with populations with carotid stenosis >70 percent did not result in a significantly higher summary incidence rate of ipsilateral stroke compared with the subgroup of 50-70 percent stenosis (summary incidence rate = 0.024, 95% CI = 0.018, 0.032 vs. summary incidence rate = 0.0161, 95% CI = 0.011, 0.023; P-value for interaction = 0.431). However, severity of stenosis in medically-treated patients was associated with higher summary incidence rates for all other cerebrovascular outcomes, both ipsilateral (ipsilateral stroke or TIA, P = 0.028) or any territory (any stroke, P = 0.019, and any stroke or TIA, P<0.001). Use of statins by more than 25 percent of the study population was associated with significantly decreased rates of ipsilateral stroke compared with use of statins by less than 25 percent of the study population, but had no statistically significant difference in rates of any territory cerebrovascular events or death. Studies that allowed the inclusion of patients with contralateral CEA did not result in increased estimates of incidence rates of ipsilateral stroke and ipsilateral stroke or TIA (P-values for interaction = 0.504 and 0.879, respectively).

Table 5. Subgroup meta-analyses for the incidence rates of cerebrovascular events and death

		Summary incidence rate (95% CI), number of studies				
	Subgroup	**Ipsilateral stroke**	**Ipsilateral stroke or TIA**	**Any stroke**	**Any stroke or TIA]**	**Death**
Quality	A or B	0.0159 (0.0121, 0.0209), n=20	0.0455 (0.0379, 0.0547), n=13	0.0318 (0.0232, 0.0435), n=12	0.0571 (0.0330, 0.0990), n=5	0.0438 (0.03, 0.064), n=11
	C	0.0216 (0.0151, 0.0310), n=6	0.0881 (0.0596, 0.1304), n=7	0.0147 (0.0080, 0.0270), n=5	NA, n=4	NA, n=3
Stenosis	50-70%	0.0161 (0.0112, 0.0234), n=11	0.0476 (0.0370, 0.0612), n=10	0.0205 (0.0099, 0.0423), n=6	0.0550 (0.0392, 0.0773), n=6	NA, n=4
	>70%	0.0237 (0.0175, 0.0321), n=13	0.0828 (0.0537, 0.1277), n=12	0.0321 (0.0212, 0.0486), n=6	0.0775 (0.0645, 0.0932), n=7	NA, n=4
Statin use	<25%	0.0236 (0.0189, 0.0295), n=9	0.0579 (0.0489, 0.0686), n=8	0.0298 (0.0187, 0.0473), n=10	NA, n=4	0.0590 (0.0426, 0.0817), n=7
	>25%	0.0108 (0.0060, 0.0193), n=7	NA, n=3	0.0231 (0.0136, 0.0395), n=5	NA, n=2	0.0419 (0.0290, 0.0607), n=5
Anti-platelets use	<50%	NA, n=0	NA, n=0	NA, n=2	NA, n=2	NA, n=1
	>50%	0.0163 (0.0117, 0.0227), n=16	0.0492 (0.0403, 0.0599), n=11	0.0285 (0.0194, 0.0420), n=13	0.0529 (0.0277, 0.1009), n=4	0.0509 (0.0378, 0.0685), n=11
Contra-lateral CEA	None	0.0169 (0.0124, 0.0231), n=18	0.0552 (0.0398, 0.0765), n=13	0.0262 (0.017, 0.0400), n=13	0.0552 (0.0383, 0.0796), n=8	0.0466 (0.0324, 0.067), n=11
	Yes	0.0165 (0.0121-0.0226), n=7	0.0525 (0.0416, 0.0663), n=6	NA, n=4	NA, n=1	NA, n=2

CI = confidence interval, n = number, NA = not applicable.

In a sensitivity analysis, we considered only data derived from Kaplan-Meier analyses, either extracted from published figures following digitization or by using the reported incidence rates (95% CI) in each study. In a random-effects meta-analysis, the summary incidence rates obtained for each outcome were of similar magnitude to the summary estimates obtained in the main analysis of numerical data (summary incidence rate of ipsilateral stroke = 0.019, 95% CI =

0.010, 0.028, n=7 studies; summary incidence rate of ipsilateral stroke or TIA = 0.052, 95% CI = 0.029, 0.075, n=3 studies; summary incidence rate of any stroke = 0.041, 95% CI = 0.014, 0.067, n=3 studies; summary incidence rate of any stroke or TIA = 0.061, 95% CI = 0.054, 0.069, n=7 studies; summary incidence rate of death = 0.066, 95% CI = 0.037, 0.094, n=3 studies).

Sensitivity analyses

We conducted sensitivity analyses of quality-A and -B studies of medical therapy alone. In 20 quality-A and -B studies, the summary incidence rate of ipsilateral stroke in asymptomatic patients on (any) medical therapy alone was 1.59 (95% CI = 1.21, 2.09) percent per year of followup. The summary incidence rate estimate of 13 studies reporting the combined outcome of ipsilateral stroke or transient ischemic attack (TIA) was 4.56 (95% CI = 3.79, 5.47) percent per year of followup. The summary incidence rate for any stroke in 12 studies was 3.18 (95% CI = 2.32, 4.35) and for any stroke or TIA in five studies was 5.71 (95% CI = 3.30, 9.90) percent per year of followup. The summary incidence rate of all-cause death across 11 studies was 4.38 (95% CI = 3.00, 6.41) percent per year of followup. The summary incidence rate of ipsilateral stroke was significantly decreased in recent studies (recruitment closure between 2000 and 2010) as compared with older studies with recruitment closure before 2000 (1.13 versus 2.38 percent per year, P for interaction = 0.0008).

In contrast to our main analyses, a significant effect of time was detected for all cerebrovascular outcomes, including any stroke and any stroke or TIA.

Applicability

Medical therapy alone studies, specifically studies with recruitment closure year since 2000 were deemed applicable to contemporary clinical practice. However, no separate data were available by the age subgroups $\geq$ 65 years and $\geq$ 80 years. Furthermore, no separate subgroup data were available by sex and baseline comorbid medical conditions other than data for subgroup analysis by contralateral CEA, and clinical or anatomic features of carotid artery stenosis (>70 percent).

Summary of Key Question 1a (Effectiveness of medical therapy alone)

There is 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. Meta-regression analyses of quality-A and -B studies showed that the 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). The summary incidence rate of ipsilateral stroke was significantly decreased in recent studies compared with older studies (1.13 versus 2.38, P=0.0008). 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.

Key Question 1 (Comparison of Treatments and Long-term Outcomes)

CEA and medical therapy versus medical therapy alone

Data for the comparison of CEA and medical therapy with medical therapy alone for efficacy and safety endpoints (Key Questions 1–3) were contributed by three RCTs and seven nonrandomized comparative studies. In the following section, the design characteristics of these 10 studies are described in detail (Table 6). The results of these studies are then presented according to which key question is addressed by each study.

Table 6. Summary characteristics of studies comparing CEA versus medical therapy

Study	N subjects (followup yr)	Diagnosis of carotid stenosis	Percent carotid stenosis	Primary endpoint (long-term)	Perioperative outcome
RCT					
VA 1993[32]	444 (3.9)	DUS; OPG DSA	≥ 50% stenosis NASCET criteria	Composite of ipsilateral TIA, stroke, and death	TIA, stroke, MI, death, cranial nerve injuries
ACAS 1995[28]	1659 (2.7)	CEA: DSA Medical: DUS	≥ 60% stenosis NASCET criteria	Composite of ipsilateral stroke and death	Stroke, MI, death
ACST 2004, 2010*[30,31]	3120 (10)	DUS	≥ 60% stenosis ECST criteria	Composite: perioperative mortality, morbidity, and nonperioperative stroke	Stroke, MI, death
NRCS (Prospective)					
CASANOVA 1991[60]	233 (3)	DUS; DSA	50 – 90% stenosis; NASCET criteria	Composite: ipsilateral stroke and death	None
Mayo 1992[59]	158 (2)	DUS or DSA	≥ 50% stenosis NASCET criteria	Composite of TIA, stroke, and death	TIA, stroke, and death
NRCS (Retrospective)					
Libman 1992[74]	215 (5)	DUS	≥ 50% stenosis (criteria: nd)	Ipsilateral stroke or stroke free survival	Stroke
Hertzer 1986[75]	290 (~3)	DSA	≥ 50% stenosis (criteria: nd)	TIA, stroke, and death	Stroke, death
Poulias 1994[76]	134 (5.2)	No data	≥ 60% stenosis (criteria: nd)	Stroke or death	Stroke, death
Caracci 1989[77]	141 (~2)	DUS	≥ 75% stenosis (criteria: nd)	TIA, stroke, and death	Stroke, death
Bosiers 2005[78]	36 (30 d)	No data	≥ 80% stenosis (criteria: nd)	None	Stroke, death
Ogata 2012	93 (4.2)	DSA	≥ 80% stenosis (criteria: nd)	Stroke, MI, and death	Stroke, death

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial, DSA = digital subtraction angiography, DUS = duplex ultrasonography, ECST = European Carotid Surgery Trial, MI, myocardial infarction, NASCET = North American Symptomatic Carotid Endarterectomy Trial, nd = not documented, NRCS, nonrandomized comparative study, OPG = ocular pneumoplethysmography, RCT = randomized controlled trial, TIA = transient ischemic attack, VA = Veterans Affairs Cooperative Study.
* Includes patients with remote (>6 months) ipsilateral carotid territory symptoms.

Study characteristics

Randomized controlled trials

Three quality-A RCTs, the Veterans Affairs Cooperative Study (VA), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Atherosclerosis Trial (ACST), compared CEA with medical therapy and met our inclusion criteria.[28,30,32] A total of 5,223 patients were randomized to either CEA (2,659 patients) or to medical therapy (2,627 patients). While the VA trial compared CEA with medical therapy, ACAS and ACST compared immediate CEA with deferred CEA, in which the deferred CEA group was managed with "standard of care" medical therapy. Patients allocated to the deferred group did not undergo CEA unless they had subsequent ipsilateral or carotid territory symptoms of TIA or stroke (i.e. progressed from asymptomatic state to symptomatic state). All three trials were multicenter. The VA trial recruited adult men from 11 VA hospitals in the U.S. from 1983-1987. The VA trial recruited 444 eligible patients of the target sample of 500 patients, whereas ACAS and ACST achieved their target sample size. ACAS recruited adults (approximately two-thirds men and one-third women) between the ages of 40 and 79 years in the U.S. and Canada from 1987-1993. ACST recruited adults (approximately two-thirds men and one-third women) from 30 different countries from 1993–2003 and had two long-term (5 and 10 year) followup publications.[30,31]

Eligibility criteria and diagnosis of asymptomatic carotid stenosis

All three trials excluded patients who were at high medical risk for CEA due to associated medical illnesses or those who had contraindications to aspirin therapy. Both the VA trial and ACAS included patients without prior ipsilateral neurological symptoms, while ACST included patients with remote (> 6 months) ipsilateral carotid territory symptoms.

The methods to diagnose asymptomatic carotid stenosis as well as the degree of asymptomatic carotid stenosis as the inclusion criteria differed across three RCTs (Table 6). This included different diagnostic methods to evaluate the degree of carotid stenosis. ACST recruited 99 patients with stenosis < 60 percent based on their perceived need for an intervention or if they had a carotid stenosis with a soft plaque as defined by DUS.

Population

Baseline characteristics of the enrolled patients varied considerably in all three trials. All three RCTs included some proportion of patients with contralateral cerebrovascular symptoms. Both ACAS (20 percent) and ACST (24 percent) enrolled participants who had undergone CEA for contralateral carotid artery stenosis, while the VA trial excluded these patients. A higher percentage of participants had atrial fibrillation, contralateral carotid occlusions, and history of smoking in the VA trial compared with ACAS or ACST. Among included patients, contralateral carotid occlusions were present in 32 percent in the VA trial, but approximately 10 percent in both ACAS and ACST. In ACAS, almost 70 percent of participants had a history of CAD, which was much higher than in the VA trial (30 percent) or ACST (5 percent).

Interventions

All three trials required performance certification for the surgeons performing the CEA. In the VA trial each surgeon was required to provide performance records for the last 2 years. In ACAS surgeons were required to perform a minimum of 12 CEA per year with a mortality/morbidity < 3 percent in the last 50 CEAs. In the ACST trial, each surgeon was

required to submit a record of their last 50 CEAs, specifically the number of CEAs for asymptomatic carotid stenosis, and the events of morbidity/mortality occurring within 30 days. There was no report on the volume of each recruiting center. Across the many centers in each trial, there were no attempts to standardize surgical or anesthetic techniques. Details of surgical techniques lacked clear reporting. In ACAS, "selective shunt" to avoid cerebral hypoperfusion or technical variations, such as "patching of the endarterectomy site" or "eversion CEA" was used at the discretion of individual surgeons, while the other two trials did not report any technical data. Patients randomly assigned to CEA underwent surgery within 10 days in the VA trial or within 14 days in ACAS. In ACST, after randomization, no particular time frame for surgery was reported in the immediate CEA group, but participants underwent CEA surgery as soon as possible. In the same study, of those patients allocated to the immediate CEA group, 50 percent had ipsilateral CEA by 1 month, 88 percent by 1 year, and 91 percent by 5 years.

Comparators and co-medications

Across all three trials, medical treatments were left to the discretion of individual treating physicians with antiplatelet therapy being the most commonly prescribed medical therapy in both the intervention groups. Of note, the VA trial used a very high daily dose of aspirin (650 mg twice daily), while ACAS and ACST used a dosage of aspirin 325 mg daily. All studies reported the use of appropriate medical therapy for both groups, although ACST "optimized" and also standardized medical therapy for all patients using specific thresholds to control hypertension, lipid levels, and diabetes. Both ACAS and ACST provided additional information on the use of smoking cessation programs, and medications to control hypertension, lipid levels, and diabetes. Additionally, ACAS counseled participants against the use of alcohol or estrogen compounds. A recently published 10 year followup of ACST reported an increased use of lipid-lowering medications in the later years of followup up to 80 percent, compared to the use of these medications by only 10 percent of patients at study entry. Patients allocated to the medical therapy group crossed over to the surgical group and underwent CEA under the following conditions: if they had a TIA in the VA trial, if they had ipsilateral symptoms of TIA or stroke in ACAS, and if they had any carotid territory symptoms of TIA or stroke in ACST.

Outcomes

The average followup in the VA trial was 4 years, and the median followup in ACAS and ACST were 2.7 years and 9 years, respectively. The primary endpoint in each trial is listed in Table 6. Based on the results of the VA trial, the primary endpoint of ACAS was modified and TIA was excluded as an outcome of interest. In all three trials, neurologists assessed the stroke outcomes and stroke was classified based on location and etiology. The VA trial classified stroke outcomes as established by the Advisory Council of the National Institutes of Neurological and Communicative Disorders and Stroke and allowed patients with TIA to crossover to the CEA group. ACAS used the Glasgow Outcome scale (2 to 5) and ACST used a Rankin score 3 or greater for stroke severity classification; both trials allowed patients with stroke to crossover to the immediate CEA group.

Study quality

All were rated quality-A trials as they met most of our predefined methodological criteria. All three multicenter trials used central randomization. About 15 percent of recruited patients refused to participate in the VA trial and there was unclear reporting of patients with TIA that

crossed over to the CEA group. The proportion of patients who failed to undergo surgery in the CEA group after randomization ranged from 4 percent in the VA trial, 12 percent in ACAS, and 10 percent in ACST. All trials were evaluated using intention-to-treat analysis. ACAS reported interim benefit of CEA over medical therapy, so that the trial was stopped after a median of 2.7 years of the 5-year target followup. Other problems with the conduct of the trials were encountered: 1) the VA trial patients did not adhere to high dose of aspirin up to 650 mg twice daily (16 percent discontinued aspirin and 27 percent took aspirin 325 mg daily); and when ACAS was nearing its completion and patients had already undergone therapy, the trial authors had modified their primary outcome by excluding TIA from their primary endpoint after the VA trial was published.

Nonrandomized comparative studies

Two quality-B prospective and five quality-C retrospective nonrandomized comparative studies compared CEA versus medical therapy met our inclusion criteria.[59,60,74-78] All studies were conducted in the 1980's through the early 1990's except for one recently published study by Bosiers 2005, which retrospectively reviewed their 2003 data.[78]

Prospective studies

CASANOVA was a multicenter RCT among patients with asymptomatic carotid stenosis. By using a posthoc nonrandomized design, the authors reported the efficacy of CEA and medical therapy compared with medical therapy alone in patients with asymptomatic carotid stenosis. The trial was conducted in the Germany among 410 patients with asymptomatic carotid stenosis $\geq$ 50 percent.[60] The degree of stenosis was diagnosed by DUS and confirmed by angiography, both using NASCET criteria. Patients with > 90 percent stenosis were excluded and the trial used several treatment strategies including unilateral or bilateral CEA, and unilateral CEA or medical therapy. The medical therapy included daily doses of aspirin 300 mg plus dipyridamole 75 mg. CEA was performed frequently in patients with bilateral stenosis >50 percent who had been assigned to the medical therapy group. As high as 18 percent of randomized patients did not comply with the study protocol. The trial was stopped early when it became increasingly difficult to convince patients to undergo CEA.

The Mayo Clinic trial, a multicenter RCT conducted in the USA that compared CEA with aspirin (80 mg) was terminated early due to increased events of MI in the CEA group; but the trial continued to add eligible patients recruited through a nonrandomized design.[59] This RCT enrolled asymptomatic patients with > 50 percent stenosis diagnosed by DUS. The CEA group was not allowed to receive aspirin therapy, and only patients who were prescribed aspirin for prior cardiac disease were allowed to continue aspirin therapy. The trial excluded patients with atrial fibrillation, prior TIA or CEA, and contralateral occlusion. Higher rates of MI and TIA in the CEA group resulted in an early termination after only 71 patients were enrolled. The study added 87 eligible nonrandomized patients with addition of aspirin therapy in both groups and a total of 158 patients were followed for 2 years. The primary endpoint of the trial was TIA, any stroke or death. The study was inconclusive for the outcomes of interest.

Retrospective studies

Six retrospective studies evaluated CEA versus medical therapy in a total of 909 patients with asymptomatic carotid stenosis. All studies were conducted in the 1980's through the early 1990's except for two recently published studies.[78,79] Three studies included carotid stenosis >50

or > 60 percent stenosis as diagnosed by DSA[75] and DUS,[74,77] one included ≥80 percent stenosis as measured by DSA,[79] while one study did not report its method of diagnosis. The Bosiers 2005 study reported only perioperative outcomes and is further discussed in Key Question 3. The majority of patients included in the remaining four studies were ≥ 65 years of age. These studies provided no data or excluded patients who were at high risk for CEA.

Key question 1b (Long-term outcomes 12 months or greater)

Ipsilateral stroke (including any stroke or death within 30 days)

RCTs of CEA versus medical therapy

All three RCTs contributed to the analysis of ipsilateral stroke (defined as any stroke or death within 30 days or subsequent ipsilateral stroke). In individual trials, ipsilateral stroke were lower in the CEA compared the medical therapy, which reached statistical significance only in ACAS. In a meta-analysis (Figure 3), the CEA had a 31 percent significantly decreased risk of ipsilateral stroke (including perioperative stroke or death) as compared with the medical therapy (summary RR = 0.69, 95% CI = 0.55, 0.87) without statistical heterogeneity (I^2 = 0.0%, P =0.90).

Other comparative studies of CEA versus medical therapy

One quality-B prospective and two additional quality-C retrospective comparative studies contributed to the meta-analysis of ipsilateral stroke that showed no significant difference between CEA and medical treatment (summary RR = 0.78, 95% CI = 0.12, 4.87) with a very wide confidence interval and statistically significant heterogeneity (I^2 = 77%, P=0.01). Mayo 1992 with an average followup of 2 years reported that more patients in the CEA (who were precluded from aspirin therapy) had ipsilateral stroke than the medical therapy group (who were treated with a low dose of 80 mg/day aspirin). Libman 1994 followed 215 patients for an average of 3.8 years and the study had high periprocedural adverse events in the CEA group that resulted in higher risk of ipsilateral stroke compared to the medical therapy group (RR = 1.47, 95% CI = 0.48, 4.48). Caracci 1989 followed 141 patients for an average of 2 years and reported significantly decreased risk of ipsilateral stroke in the CEA group compared with the medical therapy group (RR = 0.13, 95% CI = 0.03, 0.55).

Any stroke (including any death within 30 days)

RCTs of CEA versus medical therapy

All three RCTs reported data on occurrence of any stroke, irrespective of location, cause, or type of stroke. The outcome of any stroke was defined as events of perioperative stroke or death or nonperioperative any territory stroke. Both ACAS and ACST reported statistically significant reduction in the risk of any stroke for CEA over medical therapy, while the VA trial did not. In a meta-analysis (Figure 4), the CEA had a 32 percent significantly decreased risk of any stroke (including perioperative stroke or death) as compared with the medical therapy (summary RR = 0.68, 95% CI = 0.56, 0.82) without statistical heterogeneity (I^2 = 17.7%, P=0.30).

Noncomparative studies of CEA versus medical therapy

Any stroke in nonrandomized comparative studies showed no significant difference between the treatment groups (summary RR = 1.01, 95% CI = 0.37, 2.73) with statistically nonsignificant heterogeneity (I^2 = 51.5%, P=0.13).

Any stroke or death

RCTs of CEA versus medical therapy

All three RCTs reported a nonsignificantly decreased risk for the combined endpoint of any stroke or death in the CEA as compared with the medical therapy. A meta-analysis (Figure 5) showed no significant difference between the two groups (summary RR = 0.94, 95% CI = 0.85, 1.03) without statistical heterogeneity (I^2 = 19%, P=0.29).

Nonrandomized comparative studies of CEA versus medical therapy

In nonrandomized comparative studies, a meta-analysis showed nonsignificant increase in the risk of any stroke or death in the CEA group over the medical therapy group (summary RR = 1.34, 95% CI = 0.34, 5.28). In view of heterogeneity (I^2 = 61%, P=0.11) even though it was not statistically significant, this requires cautious interpretation. CASANOVA 1991 was terminated when the endpoint of stroke or death was reached in 9.8 percent of 122 patients who had CEA compared with 12.6 percent of 111 patients who had medical therapy alone (P = 0.32).

Death

RCTs of CEA versus medical therapy

All three RCTs reported data on overall death. ACST with the longest followup of almost 10 years reported more deaths due to cancer and other related illnesses than the VA trial and ACAS, each with an average followup of 4 years and 2.7 years, respectively. A meta-analysis of the three RCTs showed no significant difference in death between the two intervention groups (summary RR = 1.05, 95% CI = 0.85, 1.03). There was no statistical heterogeneity (I^2 = 0.0%, P=0.60) (Figure 6). When the meta-analysis was restricted to fatal stroke (Figure 7) or by CVD related deaths (Figure 8), it resulted in similar results.

Nonrandomized comparative studies of CEA versus medical therapy

In contrast, three nonrandomized comparative studies assessed outcomes of death and all studies reported an increase in death in the medical therapy group compared to the CEA group.[59,76,77] Both Mayo 1992 and Poulias 1994 reported no events in the medical therapy group, while Caracci 1989 reported statistically significant increase in deaths in the medical therapy group over the CEA group (24 percent versus 9 percent, P <0.05) Ogata 2012 reported a nonsignificant increase in deaths in the medical therapy group over the CEA group (17 percent versus 37 percent, P = 0.20).

CVD outcomes

RCTs of CEA versus medical therapy

A meta-analysis using data from all three RCTs resulted in no significant difference in CVD deaths in the CEA as compared with the medical therapy (summary RR = 1.01, 95% CI = 0.82, 1.25) with statistically nonsignificant heterogeneity (I^2 = 37.6%, P=0.20)

Nonrandomized comparative studies of CEA versus medical therapy

Ogata 2012 reported a nonsignificant increase in MI in the medical therapy group over the CEA group (35 percent versus 20 percent, P = 0.75)..

Composite endpoint including ipsilateral stroke

RCTs of CEA versus medical therapy

All three RCTs reported composite endpoints of within 30-day stroke or death and subsequent ipsilateral stroke. In individual studies, ipsilateral stroke were decreased in the CEA group compared with the medical therapy group, which reached statistical significance only in ACAS trial. In a meta-analysis (Figure 9), the CEA had a 28 percent significantly decreased risk of ipsilateral stroke (including perioperative stroke or death) as compared with the medical therapy (summary RR = 0.72, 95% CI = 0.58, 0.90) without statistical heterogeneity (I^2 = 0.0%, P = 0.810).

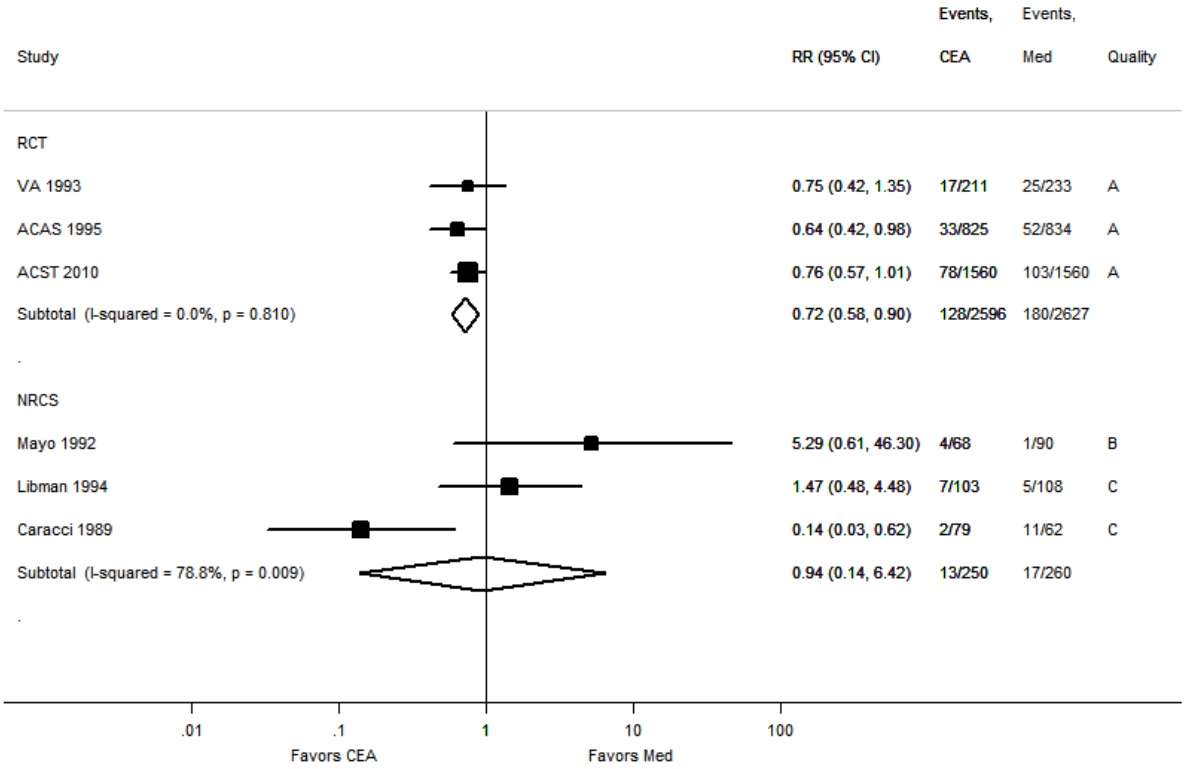
Nonrandomized comparative studies of CEA versus medical therapy

One quality-B prospective and two quality-C retrospective comparative studies found no significant differences between CEA and medical therapy for the risk of ipsilateral stroke (summary RR = 0.94, 95% CI = 0.14, 6.42), but with statistically significant heterogeneity (I^2 = 78.8%, P=0.009).

Summary of Key Question 1b (Effectiveness of CEA and medical therapy versus medical therapy alone on long-term outcomes)

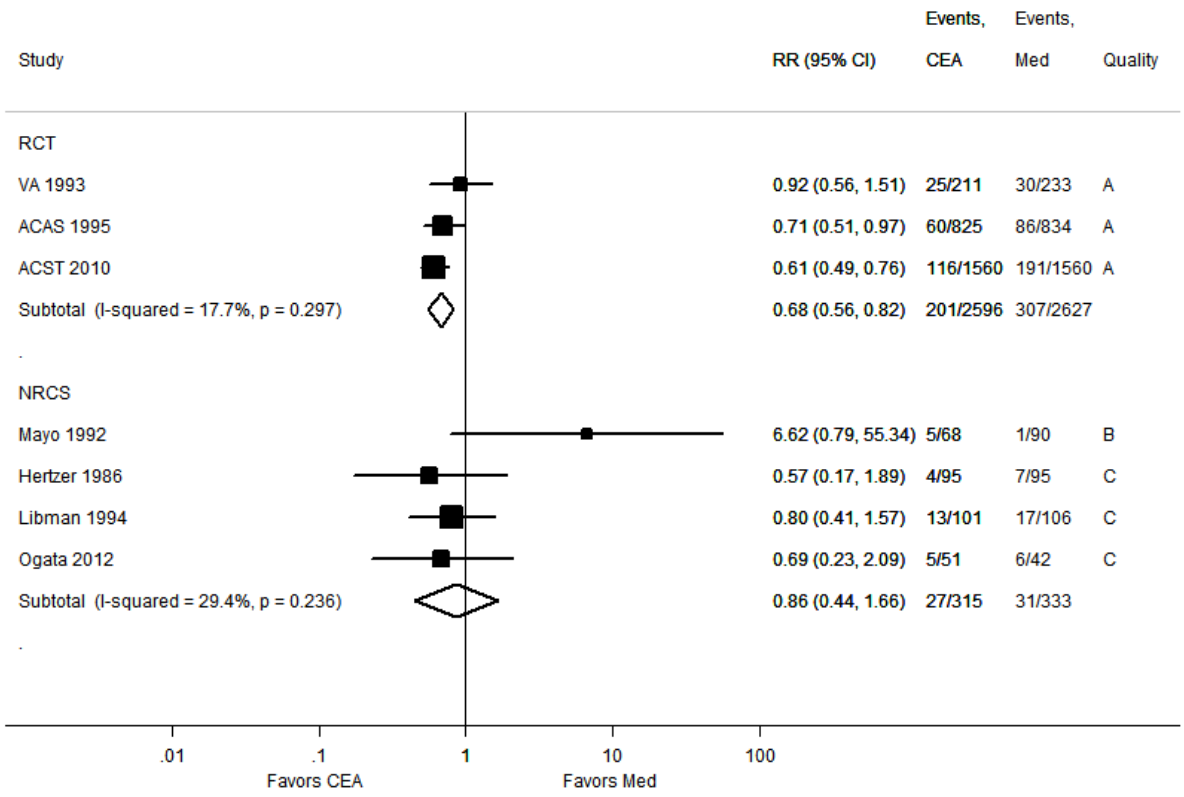
Three quality-A RCTs demonstrated a reduction in the risk of ipsilateral stroke with CEA and medical therapy compared with medical therapy alone. The strength of evidence is graded as moderate, but their results may not be applicable to contemporary clinical practice. In these trials, patients with asymptomatic carotid stenosis did not receive at randomization what is considered current best medical therapy, including healthy life-style habits and the use of optimized therapy such as statins and targets for the treatment of blood pressure and diabetes. The trials showed no difference between the two treatment groups for the risk of any death, fatal stroke, or CVD death. It is important to note that, all trials were conducted during 1990–2000 and used “standard of care” medical therapy that was considered appropriate for the management of patients with asymptomatic carotid stenosis during that period. Additionally, two prospective and six retrospective nonrandomized comparative studies compared CEA versus medical therapy. In contrast to the RCTs, nonrandomized comparative studies showed no significant difference in ipsilateral stroke between the two treatment groups. In view of wide confidence intervals of the summary estimate and statistically significant heterogeneity, the results of nonrandomized comparative studies need cautious interpretation.

Figure 3. Meta-analysis of ipsilateral stroke in studies of CEA versus medical therapy



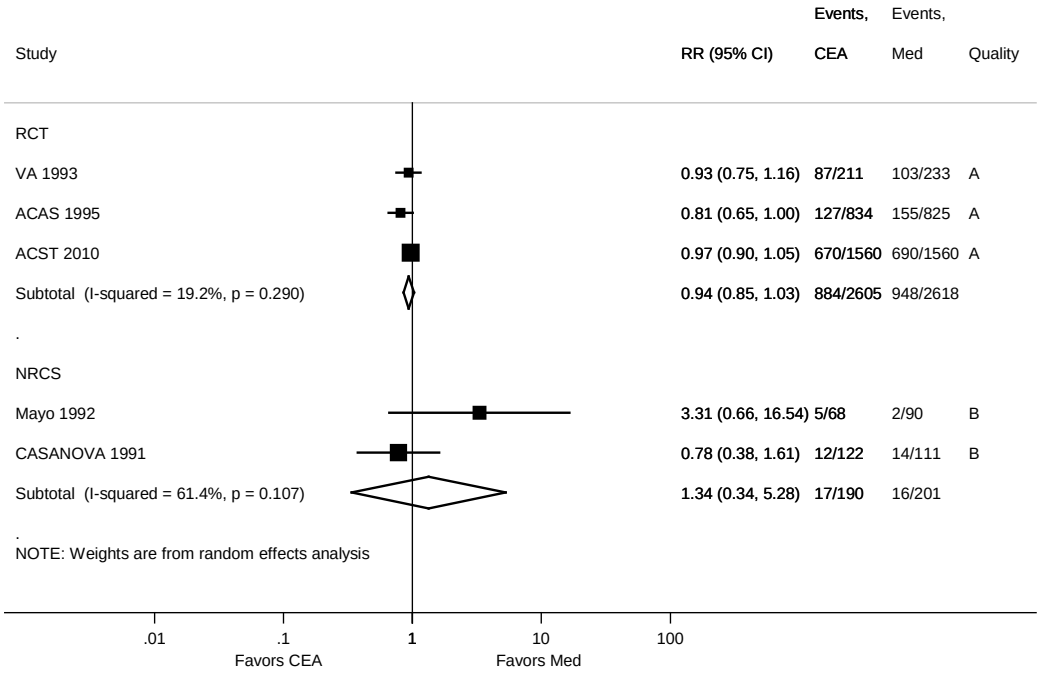
CEA = carotid endarterectomy; CI = confidence interval; Med = medical therapy; NRCS = nonrandomized comparative study; RCT = randomized controlled trial; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Figure 4. Meta-analysis of any stroke in studies of CEA versus medical therapy



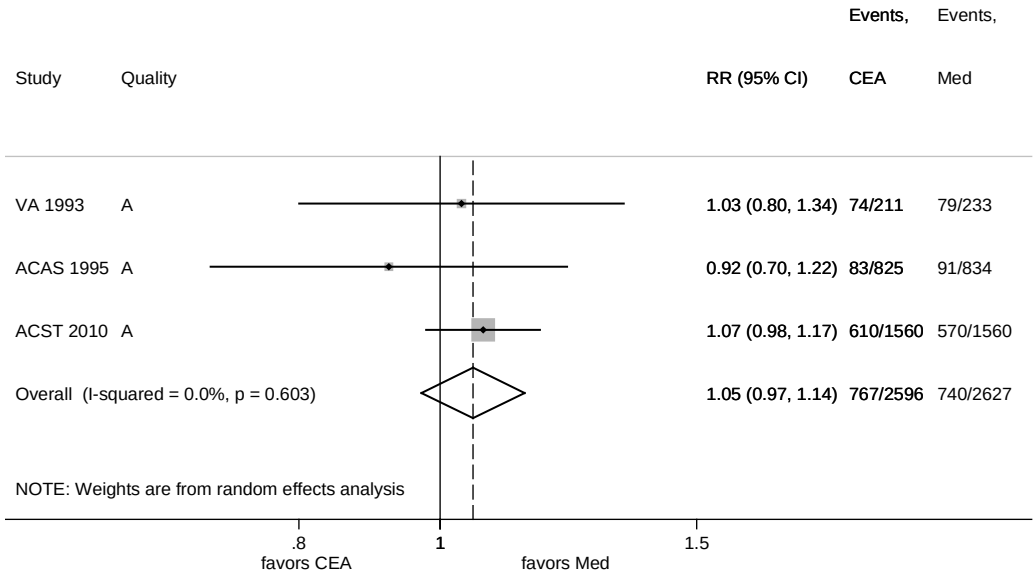
CEA = carotid endarterectomy; CI = confidence interval; Med = medical therapy; NRCS = nonrandomized comparative study; RCT = randomized controlled trial; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Figure 5. Meta-analysis of any stroke or death in studies of CEA versus medical therapy



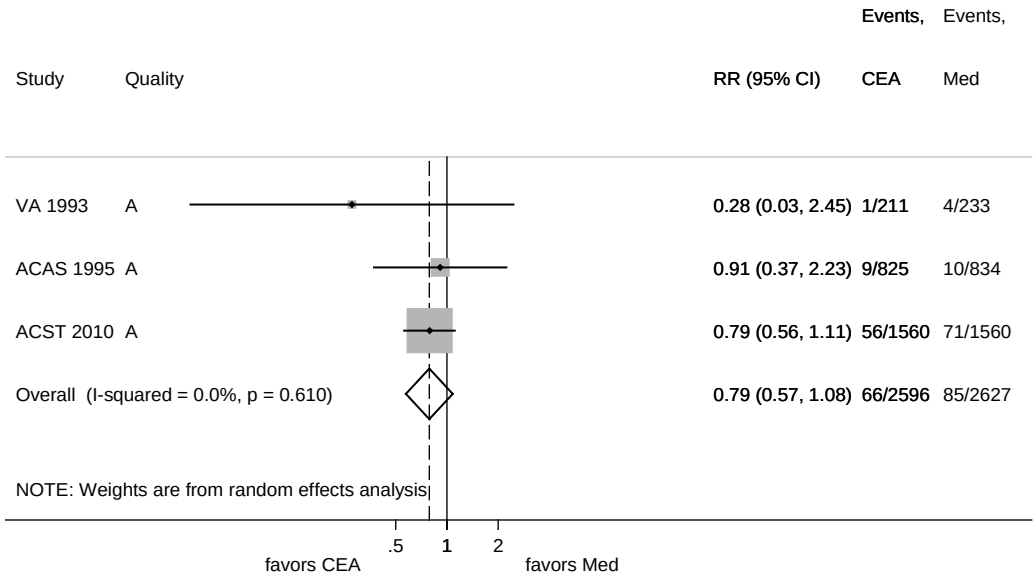
CEA = carotid endarterectomy; CI = confidence interval;Med = medical therapy; NRCS = nonrandomized comparative study; RCT = randomized controlled trial; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Figure 6. Meta-analysis of any death in studies of CEA versus medical therapy



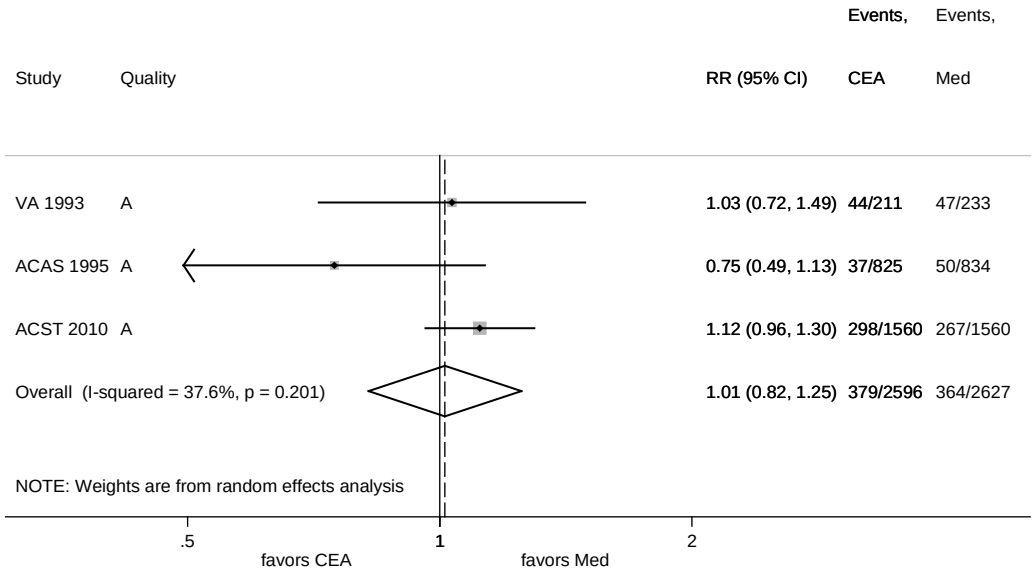
CEA = carotid endarterectomy; CI = confidence interval; Med = medical therapy; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Figure 7. Meta-analysis of fatal stroke in studies of CEA versus medical therapy



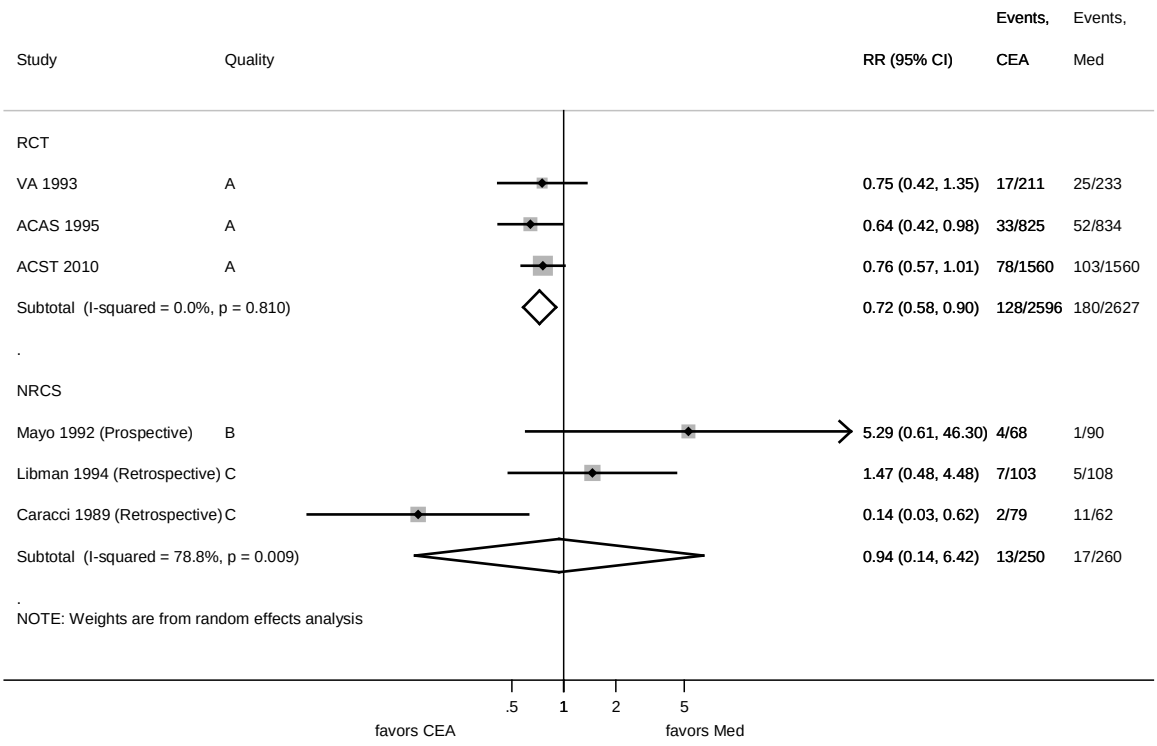
CEA = carotid endarterectomy; CI = confidence interval; Med = medical therapy; RCT = randomized controlled trial; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Figure 8. Meta-analysis of CVD deaths in studies of CEA versus medical therapy



CEA = carotid endarterectomy; CI = confidence interval; Med = medical therapy; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Figure 9. Meta-analysis of composite endpoint of within 30-day stroke or death and subsequent ipsilateral stroke in studies of CEA versus medical therapy



CEA = carotid endarterectomy; CI = confidence interval; Med = medical therapy; NRCS = nonrandomized comparative study; RCT = randomized controlled trial; RR = risk ratio
RR <1 favors CEA and medical therapy compared with medical therapy alone

Key Question 1 (Long-term outcomes) continued

CAS and medical therapy versus medical therapy alone

There were no eligible RCTs for the comparison of CAS and medical therapy with medical therapy alone. Two (one quality-B, one quality-C) nonrandomized comparative studies met our inclusion criteria.

Study characteristics

Nonrandomized comparative studies

Two (one quality-B, one quality-C) nonrandomized comparative studies met our inclusion criteria that compared CAS and medical therapy with medical therapy alone.[78,80] A total of 1,021 patients received either CAS (480 patients) or medical therapy (541 patients). Both of the studies were single center registries and analyzed retrospectively. The Sherif 2005 study attempted to balance the observed clinical characteristics in the two intervention groups by applying a propensity score-matched analysis, and was rated quality-B, while the Bosiers 2005 study, with no adjusted analyses, was rated quality-C.

The degree of carotid stenosis differed between the two studies. Sherif 2005study included patients with ≥ 70 percent asymptomatic carotid stenosis diagnosed by DUS, using the NASCET criteria. The ultrasound measurements were validated by angiography in an independent sample. Bosiers 2005 study included patients with≥ 80 percent asymptomatic carotid stenosis, but no information was documented on the diagnostic modality. Followup periods were also different between the two studies. The Sherif 2005 study followed patients for a median of 25 months (absolute range, 6 to 72 months), while Bosiers 2005 study followed patients for only 30 days.

In the Sherif 2005 study, medical therapy in both groups included antiplatelet therapy with aspirin or clopidogrel and recommended lipid-lowering therapy with statins for patients with hyperlipidemia. Data on medical therapy were not reported in the Bosiers 2005 study.

Baseline characteristics are shown in Appendix E, Table 8. The Sherif 2005 study included patients with an average age of 72.5 years, and the proportion of males was 68 percent. The percentages of patients with vascular risk factors were hypertension (76.5 percent), hyperlipidemia (76.5 percent), diabetes mellitus (35.5 percent), and current smoking status (18 percent). About 44.5 percent of patients had coronary artery disease. None of the patients in this study had a history of prior cerebrovascular events or previous CAS or CEA. Fifteen percent of the patients enrolled in the CAS group had contralateral carotid artery occlusion compared with 6 percent in the medical therapy group. During the followup period in the Sherif 2005 study, 17 percent (88 patients) of patients initially recruited into the medical therapy group crossed over to the CAS group.

No baseline characteristics were provided in the Bosiers 2005 study. Neither study reported data on patients above 80 years of age.

Study outcomes and outcome ascertainment

The primary endpoint in the Sherif 2005 study was any stroke or death using Kaplan-Meier estimates for a projected 5 years of followup. The primary endpoint for the Bosiers 2005 study was any stroke or death during periprocedural 30-day period. Neurologic evaluation was

performed at baseline in both studies. After intervention in the Bosiers 2005 study, a multi-disciplinary team managed the patients.

In the Sherif 2005 study, patients were followed clinically and by DUS at 6 and 12 months after their initial visit and then annually. A followup survey questionnaire was sent to all patients to assess the occurrence of study endpoints (stroke or death). Neurologic evaluation and mandatory cranial CT were done for all patients with events. Two observers who were unaware of the baseline laboratory data assessed outcomes independently. The Bosiers 2005 study did not provide information on outcome assessment.

Key Question 1c (Long-term outcomes 12 months or greater)

The outcome data are summarized in Appendix E, Table 9. The Sherif 2005 study was the only one reporting on long-term adverse clinical outcomes for this comparison of CAS and medical therapy with medical therapy alone. This study did not report outcomes of ipsilateral stroke outcomes.

Any stroke

The Sherif 2005 study reported an overall significantly decreased risk of any stroke in the CAS group compared with the medical therapy group (adjusted hazard ratio [HR] = 0.47, 95% CI = 0.24, 0.90).

Death

The Sherif 2005 study reported a significantly decreased risk of death in the CAS group compared with the medical therapy group (adjusted HR = 0.67, 95% CI = 0.46, 0.97).

Any stroke or death

The Sherif 2005 study followed 946 patients for an average of 5 years and reported a significantly decreased risk of any stroke or death in the CAS group compared with the medical therapy group (adjusted HR = 0.66, 95% CI = 0.47, 0.91).

Summary of Key Question 1c (Effectiveness of CAS versus medical therapy on long-term outcomes)

The strength of evidence is graded as insufficient because of a lack of RCTs. One available nonrandomized comparative study rated quality-B that showed a significantly decreased risk of any stroke or death with CAS and medical therapy over medical therapy alone. Although this study attempted to balance the observed clinical characteristics in the two intervention groups by applying a propensity score-matched analysis, this study did not report ipsilateral stroke.

CAS and medical therapy versus CEA and medical therapy (Key Question 1d)

Data for the comparison of CAS with CEA for efficacy and safety endpoints (Key Questions 1–3) were contributed by three RCTs and 10 nonrandomized comparative studies. In the following section, the design characteristics of these 13 studies are described in detail (Table 7). The results of these studies are then presented according to which key question is addressed by each study.

Table 7. Summary characteristics of studies comparing CAS versus CEA

Study, Yr	Percent carotid stenosis	Description of 'asymptomatic' status	N subjects (followup)	Primary outcome	Periprocedural events (safety)
RCT					
CREST[81,82,83]	≥ 60% on DSA ≥ 70% on DUS ≥ 80% on CTA or MRA (if stenosis on DUS was 50-69%)	No symptoms Remotely symptomatic (>6 months) Recent symptoms in a different territory	1181 (4yr)	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	Any stroke MI Any stroke, MI, or death Any stroke or death
SAPPHIRE[21,84]	≥ 80% on DUS	No symptoms (no further specification)	237 (3yr)	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	Any stroke, MI, or death
Brooks, 2004[85]	≥ 80% on DSA	No symptoms	85 (4yr)	Any stroke/TIA	Any stroke/TIA Cranial nerve palsy
NRCS					
CaRESS,[86,87], prospective	≥ 75% on DUS (confirmed by DSA when needed)	No symptoms remotely symptomatic (>6 months)	269 (4yr)	Any stroke or death*	Any stroke; Death; MI; Any stroke or death* Any stroke or death, or MI
Marine, 2006[88], retrospective	≥ 70% on DUS (MRA, CTA, DSA in selected patients)	No symptoms (no further specification)	238 (30d)	No long-term outcome data	Any stroke Death MI Any stroke or death Cranial nerve palsy Hematoma
Bosiers, 2005[78], retrospective	≥ 80% (no specification of diagnostic method)	No symptoms (no further specification)	122986 (<30d)	No long-term outcome data	Any stroke or death
McPhee, 2007,[89] retrospective*	nd	No symptomatic stenosis diagnosis codes present on admission	238389 (<30d)	No long-term outcome data	Any stroke Death MI

Table 7 continued

Study, Yr	Percent carotid stenosis	Description of 'asymptomatic' status	N subjects (followup)	Primary outcome	Periprocedural events (safety)
McPhee, 2008,[90] retrospective*	nd	No symptomatic stenosis diagnosis codes present on admission	1667 (30 d)	No long-term outcome data	Any stroke Death
Sidawy, 2009[91] retrospective*	nd	"Asymptomatic" coding in the SVS-Vascular Registry	8706 (<30 d)	No long-term outcome data	Any stroke TIA Death MI Any stroke or death or MI
Giacovelli, 2010,[92] retrospective*	nd	No symptomatic stenosis diagnosis codes present on admission	79 (30 d)	No long-term outcome data	Any stroke Death Any stroke or death Cranial nerve palsy Bleeding
De Rango, 2011, prospective[93]	>70% on angiography	No symptoms (no further specification)	1518 (5 y)	Any periprocedural stroke or death or postprocedural ipsilateral stroke	Any stroke or death
Bangalore, 2010, International Registry[94]	≥70% on color-coded DUS or angiography	No history of TIA or stroke	1672 (1.5 y)	Death or stroke	None
Lindstrom, 2012, Swedvasc Registry[95]	nd	No symptoms within the previous 6 months	(30 d)	No long-term outcome data	Any stroke Death MI Any stroke or death Any stroke or death or MI

CTA = computed tomography angiography, DSA = digital subtraction angiography, DUS = duplex ultrasonography, d= days, MI, myocardial infarction, MRA = magnetic resonance angiography, NRCS = nonrandomized comparative study, RCT = randomized controlled trial, nd = not documented, TIA = transient ischemic attack, y = year.
* Administrative dataset

Study characteristics

Randomized controlled trials

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST),[81,82] the SAPPHIRE[21,84] and the Brooks 2004 trial[85] met inclusion criteria for the comparison of CAS with CEA. CREST and the SAPPHIRE trial enrolled both symptomatic and asymptomatic patients with randomization stratified according to symptomatic status. Therefore, the treatments were randomly assigned among asymptomatic subgroup.

Although outcome data were reported separately for the asymptomatic populations enrolled in these trials, no power analyses for the primary outcome in the asymptomatic patient subgroups were conducted. Therefore, this requires a cautious interpretation of the asymptomatic subgroup data. The SAPPHIRE trial originally used group sequential design and was subsequently analyzed as a noninferiority trial in the published papers.[21,84] Given that only the asymptomatic

subgroup data were of interest to this report, we extracted the number of events in each treatment group from original publications of the SAPPHIRE trial and from data available at the FDA Web site. We calculated the relevant risk estimates without taking into account the noninferiority threshold originally used in this trial.[96]

CREST is the largest RCT published to date and enrolled asymptomatic patients from 108 U.S. centers and nine centers in Canada during the years 2005–2008. CREST was designed as an equivalence trial but, this was analyzed as a noninferiority trial in the FDA submission and as a superiority trial in the published paper.[97] However, since we considered only the data for the asymptomatic subgroup and we utilized the effect estimates from the published CREST data in our meta-analyses, we analyzed this study as a superiority trial. The SAPPHIRE trial enrolled asymptomatic patients from 29 U.S. centers during the years 2000–2002, and the Brooks 2004 trial enrolled 85 asymptomatic patients from a single U.S. center; a total of 1504 patients were randomized to either CAS (754 patients) or CEA (750 patients). In this trial, no cerebrovascular outcomes occurred in either intervention group.

Eligibility criteria and definition of asymptomatic carotid stenosis

CREST included asymptomatic patients with carotid stenosis diagnosed by the ICAVL or the ACR accredited ultrasound laboratories and determined by using the NASCET criteria. Patients were evaluated for clinical (e.g. no history of allergy to study medications) and anatomical (e.g. appropriate measurements of target vessel and lack of excessive tortuosity) suitability for either of the revascularization techniques. Those who were at high surgical risk (due to medical or anatomical conditions), previous severe stroke (confounding endpoint assessment), chronic or paroxysmal atrial fibrillation within the preceding 6 months or in need of anticoagulation therapy, MI within the previous 30 days, or unstable angina were excluded.

The SAPPHIRE trial also used the NASCET criteria for quantifying carotid stenosis, as measured by an ICAVL accredited vascular laboratory and required the presence of at least one of the following conditions conferring high surgical risk: clinically significant cardiac disease, 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. A patient was randomized only if all members of each participating center's team agreed that the patient was a suitable candidate for CEA or CAS. When team members disagreed, the patient was entered in a surgical or stenting registry according to the treating physicians' preference for treatment.

The Brooks 2004 trial included asymptomatic patients with an anticipated life expectancy of 5 years who were willing to complete treatment within 1 month of enrollment.

Interventions

In the CREST, both surgeons and interventionists had to have certification of technical competency. Certification was achieved by 477 surgeons (documenting more than 12 procedures annually and with adverse event rates < 3 percent in asymptomatic patients) and by 224 interventionists (after satisfactory evaluation of their endovascular experience, CAS results, and participation in hands-on and in a lead-in phase of training). The surgical technique involved the use of selective shunt in 53.6 percent and a patch in 68.5 percent of the cases. CEA was performed under general anesthesia in 87.5 percent of the cases. CAS involved the placement of the RX Acculink Carotid Stent System with the concomitant use of the RX Accunet® Embolic Protection device, whenever feasible (97.9 percent of the cases). Periprocedurally, the majority

of patients treated with CAS (88 percent) received dual antiplatelet therapy (aspirin plus thienopyridines), with 99 percent of patients in the CAS group being covered by at least one antiplatelet agent; the continuation of antiplatelet therapy beyond 30 days was recommended to all patients. Patients treated with CEA were under single agent antiplatelet treatment (aspirin or thienopyridines) or combination of aspirin and extended-release dipyridamole. The majority of patients (96.9 percent) continued to receive these regimens for a year or more. Patients in both groups received the contemporary standard of care medical treatment, including treatment of hypertension and hyperlipidemia, as considered by the study authors.

In the SAPPHIRE trial, certification of surgeons and interventionists required compliance with the AHA criteria for acceptable rates of adverse events with CEA and incidence of periprocedural stroke or death with CAS of less than 6 percent, respectively. Surgeons had a median annual volume of 30 CEA (range of 15-to-100 procedures), performed according to their customary techniques. Interventionists had a lifetime experience of CAS with a median of 64 procedures (range of 20 to 700). The stent used was a self-expanding, nitinol stent (S.M.A.R.T® or PRECISE®, both by Cordis Corporation) with an emboli-protection device (ANGIOGUARD® or ANGIOGUARD™ XP, Cordis). There were many modifications to the device design during the course of the SAPPHIRE trial. Patients on both groups received aspirin at a daily dose of 81 or 325mg before intervention, and continued indefinitely. Patients on the CAS group received 75mg of clopidogrel starting 24 hours before the procedure and continuing for 2-to-4 weeks.

In the single-center RCT by Brooks 2004, CEA was performed by standard techniques under general anesthesia with electroencephalographic monitoring, with no further information on surgeons' technical competency. CAS was performed without the use of embolic protection devices and two types of stents were placed: Carotid WALLSTENT® Endoprosthesis (Boston Scientific Corporation/Medi-tech Division, Natick, MA) or Dynalink (Guidant Corp., Indianapolis, IN). The Brooks 2004 trial differed from the other RCTs in that patients on both groups received dual antiplatelet therapy (325mg aspirin and 75mg clopidogrel) before intervention, but no data were available regarding continuation of antiplatelet therapy postprocedurally.

Study outcomes

The primary efficacy endpoint evaluated in CREST and in the SAPPHIRE trial was the composite of any periprocedural stroke, MI, or death, or postprocedural ipsilateral stroke within 4 years of randomization.

In CREST, neurologic evaluation was performed at baseline, 18 to 54 hours after the procedure, 1 month afterwards, and then every 6 months, which included the TIA-Stroke Questionnaire.[98] Study committees unaware of the treatment assignments adjudicated stroke and MI outcomes. MI was defined by a creatine kinase MB or troponin level that was twice the upper limit of the normal range or higher according to the center's laboratory, in addition to either chest pain or symptoms consistent with ischemia or ECG evidence of ischemia.

Outcome data from the SAPPHIRE trial were reported in two publications, including periprocedural and 1-year outcomes in the first paper and 3-year results in the second paper.[21,84] Followup visits were scheduled at 30 days, 6 and 12 months, and annually thereafter. Neurologic evaluation included the National Institutes of Health Stroke Scale, which was assessed daily after the intervention until discharge and at all followup visits. Outcomes adjudication was by a

committee composed of neurologists, surgeons, and cardiologists who were unaware of the treatment assignments.

The Brooks 2004 trial reported both periprocedural and long-term outcomes, evaluated by a neurologist at specified intervals.

Baseline characteristics

Baseline characteristics are shown in Appendix E, Table 10. The average ages of patients ranged from 66.6 to 72.6 years, and the proportion of males ranged from 63.8 to 67.5 percent. In terms of cardiovascular risk factors, the majority of patients had hypertension (85.1 to 91.0 percent); or hyperlipidemia (76.9 to 91.1 percent), except in the Brooks 2004 trial hyperlipidemia was present in only 21 percent. Diabetes mellitus was present in less than a third of patients. A minority of patients in CREST and the SAPPHIRE trial had current smoking habit, but a vast majority of patients in the Brooks 2004 trial were smokers (whether current or ex-smokers was not defined). In CREST, about 50 percent of patients had overt coronary artery disease in contrast to the SAPPHIRE trial in which about 81 percent had coronary artery disease. Regarding the severity of carotid stenosis, 91 percent of patients in CREST had a stenosis$\geq$ 70 percent whereas in the SAPPHIRE and Brooks 2004 trials, all patients had$\geq$ 80 percent stenosis. In the SAPPHIRE trial, 22.4 percent followed a prior CEA, and a small proportion of patients (3.4 percent) had a history of prior cerebrovascular event; no respective data were provided by the other two studies. Additionally, 25 percent of the patients enrolled in the SAPPHIRE trial had contralateral carotid artery occlusion.

Study quality

The CREST trial was rated quality-A. The SAPPHIRE and the Brooks 2004 trials were rated quality-B. Most of the methodological aspects evaluated as quality items (Appendix E, Table 11) were met by CREST and the SAPPHIRE trials, with the exception of "blinding" of patients and analyses accounting for center effects. The SAPPHIRE trial was rated as quality-B due to protocol violations observed in the conduct of this study and differences in reported results between published and unpublished reports. The SAPPHIRE trial was initially planned to demonstrate equivalence of two interventions, with a RCT sample size of 600–900 patients (symptomatic and asymptomatic). However, the trial was terminated early due to the slow pace of enrollment after a total of 334 patients (237 asymptomatic). Thus, data from the asymptomatic population were provided only by a subgroup with a small sample size. An additional potential limitation of the SAPPHIRE trial stems from its enrollment scheme requiring consensus of the team regarding the suitability of patients for revascularization; thus, the majority of patients enrolled were not finally randomized but were entered into the stenting registry. The Brooks 2004 trial was rated quality-B mainly due to its small sample size.

Nonrandomized comparative studies

Of the 10 eligible nonrandomized comparative studies (predominantly quality-C studies), four studies included clinical datasets,[78,86-88,93] and six studies analyzed administrative and registry datasets.[89-92,94,95] One study was prospective (quality-B) and the remaining six were retrospective in design (quality-C). The prospective trial, the Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) study, was a multicenter, nonrandomized study that included 269 patients.[86,87] The second prospective study included 1,518 patients with asymptomatic carotid stenosis from a single high-volume vascular center.[93] Of the retrospective

studies, two small single-center studies (nonrandomized comparative studies /clinical) evaluated asymptomatic patients treated with CAS (152 patients) and CEA (175 patients).[78,88] The remaining six studies (nonrandomized comparative studies /administrative) reported retrospective analyses of hospital discharge data from administrative databases or registry datasets. Two studies utilized data from the National Inpatient Sample database from different calendar years,[89,90] one study analyzed data from the Society for Vascular Surgery – Vascular Registry (SVS-VR),[91] one study collected data from New York and California state databases and applied a propensity score-matched analysis,[92] and two recent studies examined registry data (REACH registry[94] and Swedvasc registry[95]) In total, 30,275 patients treated with CAS and 346,177 patients treated with CEA were analyzed in these datasets.

Eligibility criteria and definition of asymptomatic carotid stenosis

About half of the patients enrolled in CaRESS were considered as high-risk for surgery, as defined by presence of contralateral stenosis, restenosis, advanced heart failure, prior coronary artery bypass grafting, age >80 years, or chronic obstructive pulmonary disease. Patients receiving CAS in the Marine 2006 study were also of high-surgical risk (mainly due to medical high-risk according to the SAPPHIRE criteria, restenosis, anatomically high lesion, or prior radiation to the neck). The Bosiers 2005 study included patients with > 80 percent stenosis, of which 26 percent were considered to be high-risk according to similar criteria. The studies on administrative datasets used the "International Classification of Diseases Ninth Revision, Clinical Modification" (ICD-9CM) procedural codes for CEA and CAS, and classified patients as asymptomatic when their discharge diagnoses did not include any codes indicative of stroke or TIA. In the SVS-VR, patients were analyzed as asymptomatic according to the data reported by providers of CAS and CEA through web-based entries. In these administrative datasets, no information on the degree of carotid stenosis was provided.

Interventions

In the CaRESS study, interventionists were required to have successfully deployed at least 20 carotid stents with < 6 percent rate of periprocedural stroke or death. The Carotid WALLSTENT® Monorail® Endoprosthesis was used with concurrent embolic protection device (GuardWire Plus, Medtronic USA, Inc.). Patients were on dual antiplatelet therapy for one month and were maintained on a daily dose of 325mg of aspirin indefinitely. Surgeons in CaRESS had an annual average of at least 50 CEA procedures and with a rate of stroke and death of less than 6 percent. Patients undergoing CEA were placed on aspirin, but no further data were provided regarding the surgical technique. In the Marine 2006 study, the surgeons met the ≤three percent stroke or death rate criterion as set by the AHA,[15] whereas for many of the participating interventionists the study cases represented their first experience. The stents used included WALLSTENT® or Acculink in the majority of cases, with the use of the FilterWire EX™ embolic protection device in more than 90 percent of the patients. Selective shunt was used in 46 percent, patch in 82 percent, and general anesthesia in 36 percent of the CEAs. In the SVS-VR, it was reported that 95 percent of the CAS interventions were conducted with an embolic protection device. No data regarding the revascularization techniques or medical treatment were provided in the remaining studies.

Study outcomes

Long-term efficacy outcomes over a followup period of 4 years were reported only by the CaRESS study. The remaining studies evaluated only periprocedural adverse events; three studies evaluated periprocedural outcomes over a 30-day followup period,[86-88,91] whereas the remaining three studies[89,90,92] included adverse events occurring within the in-hospital postprocedural period. Neurologic outcome ascertainment by a certified neurologist was reported by two studies. [86-88] For studies utilizing administrative datasets,[89,90,92] outcome ascertainment was based solely on information from hospital discharge data.

Baseline characteristics

Baseline characteristics of the populations included in the nonrandomized comparative studies of CAS with CEA are shown in Appendix E, Table 10. The average ages of patients ranged from 69.6 to 72.0 years, and the proportion of males ranged from 56.9 to 63.4 percent. In terms of cardiovascular risk factors, the majority of patients were suffering from hypertension (65.7 to 91.4 percent); hyperlipidemia was reported only by two studies and was present in 64.0 to 75.3 percent of patients. Data on frequency of diabetes mellitus were reported by most of the studies showing the presence of diabetes in about a quarter of the patient populations. Data on the severity of stenosis were provided only by three studies, which included predominantly [86,87] or exclusively[78,88] patients with an advanced >70 percent stenosis. The concomitant presence of coronary artery disease displayed variability in this sample of studies, with proportions of patients ranging from 11.0 to 74.2 percent; however, the exact definitions of the diagnosis of coronary artery disease were commonly unavailable.

Study quality

The CaRESS study was a prospective nonrandomized comparative study with pre-specified endpoints and followup protocol. This study was rated quality-B. The remaining clinical and administrative nonrandomized comparative studies were retrospective in design and were all rated quality-C. An important limitation in the administrative nonrandomized comparative studies was that the apparent asymptomatic baseline status of the patients and the outcome ascertainment were informed only by hospital discharge data or registry data entries and were not subjected to case-by-case adjudication. Two studies attempted to analytically control for observed confounders through propensity score-matched analyses.[92,94]

Key Question 1d (Long-term outcomes 12 months or greater)

Ipsilateral stroke (including any stroke within 30 days)

RCTs of CAS versus CEA

Two RCTs reported data on ipsilateral stroke (Figure 10). CREST reported it as a composite of any periprocedural stroke (within 30 days) or postprocedural (> 30 days) stroke ipsilateral to the treated carotid artery at 4-year followup. The SAPPHIRE trial defined it as ipsilateral stroke at 1 year, for which the data were obtained from the FDA Web site. At 4-year followup in CREST, CAS had a statistically nonsignificant increase in the occurrence of ipsilateral stroke as compared with CEA (HR = 1.86, 95% CI = 0.95, 3.66). The SAPPHIRE trial reported similar rates of ipsilateral stroke between CAS and CEA (5.2% vs. 5.3%). However, neither study was powered to detect differences in ipsilateral stroke among subgroups of asymptomatic carotid

stenosis. The failure to find statistically significant differences does not rule out the possibility that real differences exist between interventions. We observed a discrepancy between the reported number of events in the CEA arm of the SAPPHIRE trial between different tables of available data on the FDA Web site, we performed a sensitivity analysis by considering an alternative number of observed events in the CEA arm (six instead of eight ipsilateral stroke).[97]

Nonrandomized comparative studies of CAS versus CEA

The nonrandomized comparative studies did not report this outcome.

Any stroke (including any death within 30 days)

RCTs of CAS versus CEA

Both CREST and the SAPPHIRE trial reported data on any stroke. In a meta-analysis, there was no significant difference in the risk of any stroke between CAS and CEA (summary RR = 1.37, 95% CI = 1.00, 1.87). There was no statistical heterogeneity (I^2 = 0.0%, P=0.58).

Nonrandomized comparative studies of CAS versus CEA

One nonrandomized comparative study (CaRESS) reported data on any stroke (RR = 1.34, 95% CI = 0.51, 3.47). No significant difference between CAS and CEA was found (P=0.65) in an additional time-to-event analysis for the outcome of stroke-free survival by the study (unpublished data shared by the CaRESS study authors).

Any stroke or TIA

RCTs of CAS versus CEA

One RCT, the Brooks 2004 trial, examined the outcome of any stroke or TIA but reported zero events for both treatment groups; thus, no estimate of efficacy of CAS versus CEA could be deducted from this study.

Nonrandomized comparative studies of CAS versus CEA

One study examining REACH registry data reported no significant difference between CAS and CEA (HR = 0.91, 95% CI = 0.46, 1.80).

Any stroke or death

RCTs of CAS versus CEA

CREST reported a nonsignificantly increased risk of any stroke or death in CAS as compared with CEA (adjusted HR = 1.86; 95% CI 0.95, 3.66). The SAPPHIRE trial did not report data for this outcome.

Nonrandomized comparative studies of CAS versus CEA

In addition, one randomized comparative study reported data on any stroke or death. The CaRESS study reported no statistically significant difference between CAS and CEA (RR = 1.26, 95% CI = 0.77, 2.05). One study examining REACH registry data reported lower risk in the CAS group, but no significant difference between groups (HR = 0.67, 95% CI = 0.43, 1.05).

Any stroke or MI, or death

Nonrandomized comparative studies of CAS versus CEA

This composite outcome was examined in one nonrandomized comparative study (CaRESS) but no statistically significant effect of CAS versus CEA was found (RR = 1.18; 95% CI = 0.72, 1.91). One study examining REACH registry data reported significantly lower risk of this composite outcome with CAS, as compared with CEA (HR = 0.62, 95% CI = 0.42, 0.91).

Death

RCTs of CAS versus CEA

There was a nonsignificantly decreased risk of death with CAS as compared with CEA in the SAPPHIRE trial (RR = 0.47, 95% CI = 0.18, 1.20). The CREST trial did not report data for this outcome.

Nonrandomized comparative studies of CAS versus CEA

In contrast to the RCT data, the CaRESS study reported an increased risk that did not reach statistical significance (RR = 1.36, 95% CI = 0.78, 2.35). In an additional time-to-event analysis for the outcome of survival by the CaRESS study, no significant difference between CAS and CEA was found (P=0.38) (unpublished data shared by the study authors).

Composite endpoint including ipsilateral stroke

Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke

RCTs of CAS versus CEA

This composite outcome represented the primary outcome of CREST and the SAPPHIRE trial over the 4-year and 3-year followup, respectively. Neither trial found a statistically significant difference between CAS and CEA. The observed point estimates showed different directions of effects (unfavorable for CAS in CREST and favorable in the SAPPHIRE trial) and their confidence interval in each study was wide (Figure 11). However, neither trial was powered to detect differences in the primary outcome among subgroups of asymptomatic carotid stenosis. Therefore, the failure to find statistically significant differences does not rule out the possibility that real differences exist between interventions.

Nonrandomized comparative studies of CAS versus CEA

The nonrandomized comparative studies did not report this outcome.

Any periprocedural stroke or death or postprocedural ipsilateral stroke

RCTs of CAS versus CEA

CREST and the SAPPHIRE trial reported data on the composite outcome of any periprocedural stroke, or death and postprocedural ipsilateral stroke. CREST reported a statistically nonsignificantly increased HR (adjusted for age, sex, and symptom status) with CAS as compared with CEA for this composite outcome (HR = 1.86, 95% CI = 0.95, 3.66). The

SAPPHIRE trial reported a statistically nonsignificantly decreased risk of this composite outcome with CAS as compared with CEA (RR = 0.54, 95% CI =0.28, 1.02). As shown in Figure 12, the observed point estimates in these two studies were extremely discordant.

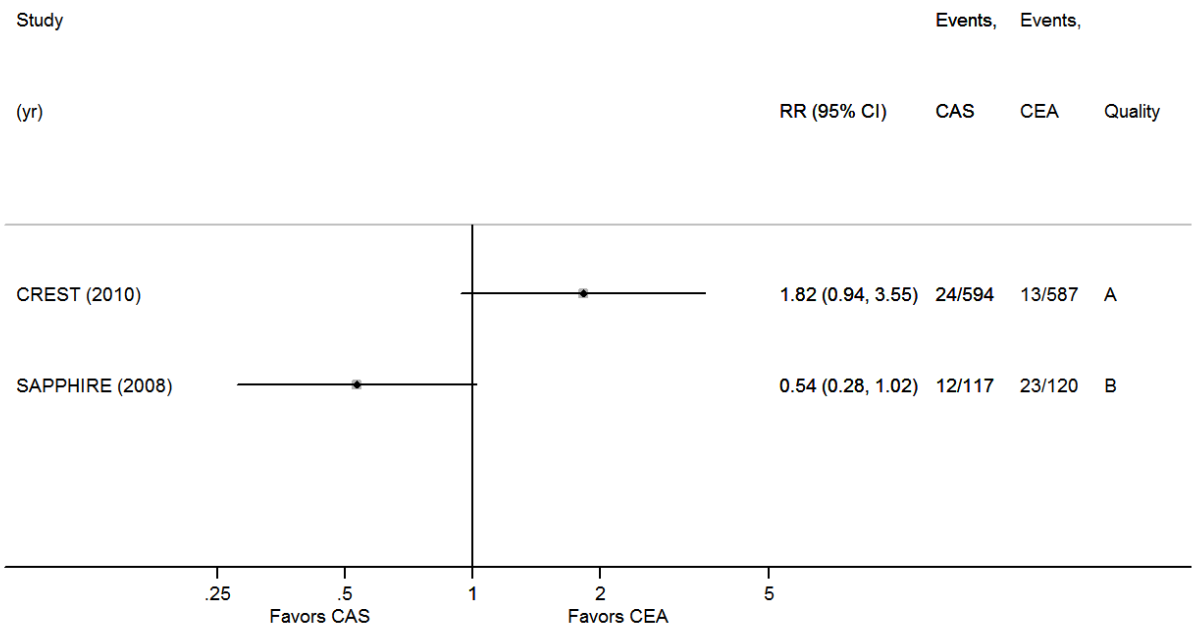
Nonrandomized comparative studies of CAS versus CEA

The nonrandomized comparative studies did not report this outcome.

Summary of Key Question 1d (Effectiveness of CAS versus CEA on long-term outcomes)

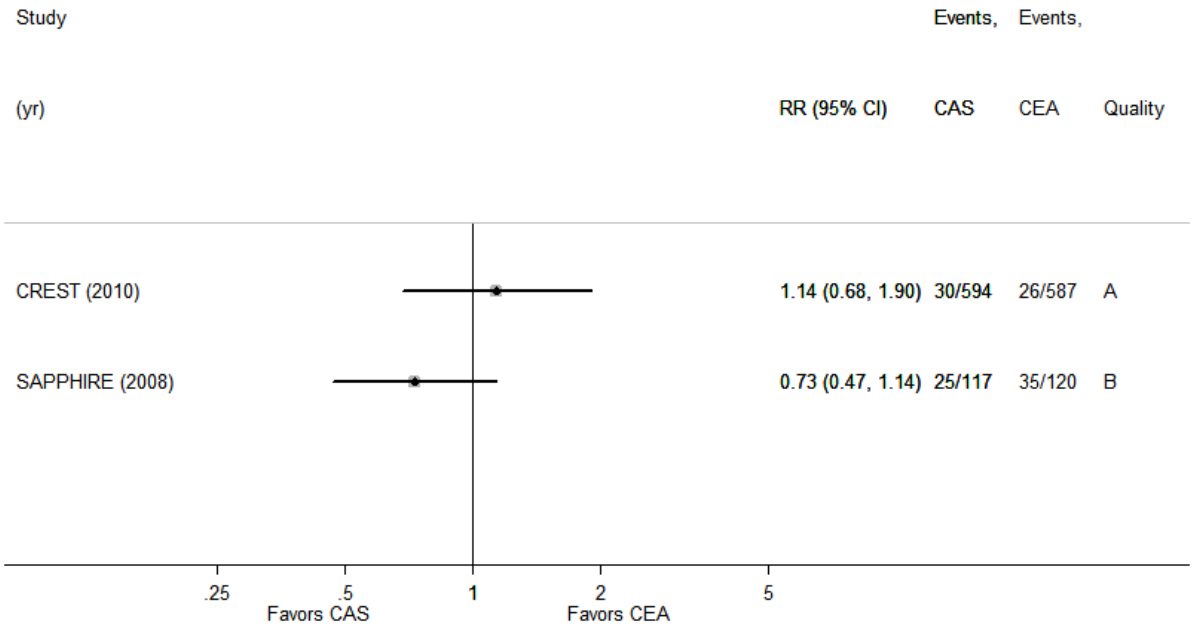
There were no statistically significant differences between the two interventional modalities. The strength of evidence is graded as insufficient because two RCTs (one quality-A and one quality-B) evaluated very different patient groups. For each of the outcome assessed (ipsilateral stroke and composite endpoint), the observed point estimates were in opposite directions across trials (as evidenced in forest plots). Furthermore, there was clinical heterogeneity and selective reporting of outcomes of interest. In one trial (SAPPHIRE), there were differences in reporting between the published paper and unpublished data on the FDA Web site. The nonrandomized comparative studies did not report long-term data for the outcome of ipsilateral stroke.

Figure 10. Forest plot of ipsilateral stroke in RCTs of CAS versus CEA



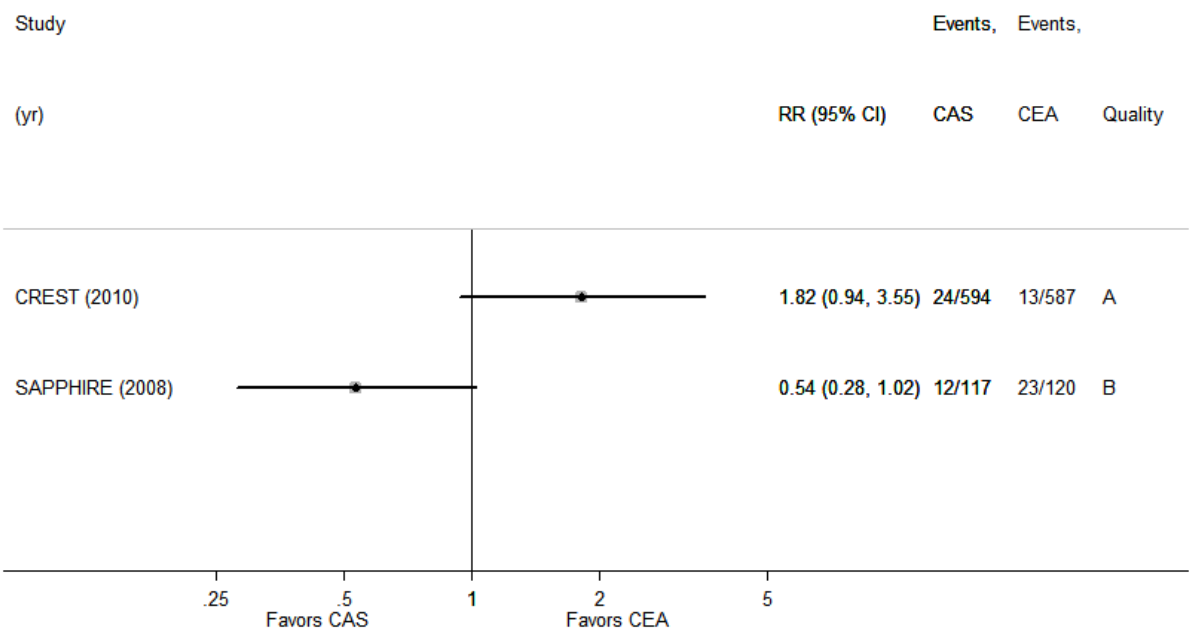
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 11. Forest plot of any periprocedural stroke, MI or death or postprocedural ipsilateral stroke in RCTs of CAS versus CEA



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 12. Forest plot of any periprocedural stroke or death or postprocedural ipsilateral stroke in RCTs of CAS versus CEA



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Summary incidence rate by treatment group

The summary incidence rate of medical therapy alone was 1.59 percent per year of followup quality-A and -B studies. In a subgroup analysis, the summary incidence rate of ipsilateral stroke was significantly decreased in recent studies (recruitment closure year between 2000 and 2010) as compared with studies in the previous years, recruitment closure year before 2000 (1.1 versus 2.3 percent per year of followup).

Five RCTs (the VA study, ACAS, ACST, CREST, and the SAPPHIRE trial) contributed to the incidence rate meta-analysis of CEA and medical therapy arm. We estimated that the summary incidence rate of ipsilateral stroke in patients with asymptomatic carotid stenosis who had CEA and medical therapy was 1.42 percent per year of followup. In a subgroup analysis of patients who had CEA and medical therapy, the summary incidence rate of ipsilateral stroke was significantly decreased in recent studies (recruitment closure year between 2000 and 2010) as compared with studies in the previous years, recruitment closure year before 2000 (1.3 versus 1.6 percent per year of followup). From two RCTs (CREST and SAPPHIRE) that reported long-term data, we estimated that the individual incidence rates of ipsilateral stroke in patients with asymptomatic carotid stenosis who had CAS with medical therapy. It is important to note that both studies recruited patients after 2000 (Table 8).

Table 8. Summary incidence rates of ipsilateral stroke by treatment groups

	Medical therapy alone	CEA with medical therapy	CAS with medical therapy
Number studies	26	5	2
Number subjects	7,210	3,303	711
Study quality	20 A or B	4 A; 1B*	1A; 1B**
Summary incidence rate of ipsilateral stroke (% per year of followup)	1.59 (95% CI = 1.21, 2.09)	1.42 (95% CI = 0.70, 2.91),	CREST: 1.61 (95% CI =1.03, 2.40) SAPPHIRE: 5.12 (95% CI = 1.88, 11.16)
Recent studies (recruitment closure since 2000)	1.13 (95% CI = 0.95, 1.34)	1.30 (95% CI =0.40, 4.50)	CREST: 1.61 (95% CI =1.03, 2.40) SAPPHIRE: 5.12 (95% CI = 1.88, 11.16)
Older studies (recruitment closure before 2000)	2.38 (95% CI = 1.87, 2.85)	1.60 (95% CI = 1.20, 2.10)	Not applicable

Detailed descriptions of medical therapy alone studies are provided in Table 1.
* CEA treatment groups from the following five RCTs: Veterans Affairs Cooperative (VA) Study; Asymptomatic Carotid Atherosclerosis Study (ACAS); Asymptomatic Carotid Surgery Trial (ACST); Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) trial; and Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)
** CAS treatment groups from the following two RCTs: CREST and SAPPHIRE
N = number; CEA = carotid endarterectomy; CAS = carotid angioplasty and stenting

Key Question 2 (Subgroups and treatment effect)

CEA and medical therapy versus medical therapy alone

Two quality-A rated RCTs (ACAS and the ACST) reported subgroup-specific data. The VA trial did not report subgroup-specific data. The outcomes evaluated for subgroups include ipsilateral stroke (including perioperative stroke or death) in ACAS, nonperioperative carotid territory stroke in the 5-year followup, and any stroke in the 10-year followup of ACST. Since these trials reported subgroup-specific data for three different outcomes, we did not conduct meta-analysis of these data subgroups, but presented data on at least four comparable subgroups as forest plots in Figure 13. No specific subgroup analyses were reported in nonrandomized comparative studies.

Demographic and other preoperative (baseline) features of studied patients in RCTs

Age: Subgroup of patients ≥ 65 years

Both ACAS and ACST stratified their analyses on the basis of age categories (Figure 9). ACAS reported that patients aged < 68 years with asymptomatic carotid stenosis in the CEA group had a significantly decreased risk of ipsilateral stroke compared to the medical therapy group, but those ≥ 68 years of age had no difference between the two treatment groups. ACST reported that patients < 65 and 65–74 years of age had a significantly decreased risk of nonperioperative carotid territory stroke at 5 years and a significantly decreased risk of any stroke at 10 years with CEA as compared with medical therapy alone, but patients ≥ 75 years of age had no significant difference between the two treatment groups.

Age: Subgroup of patients ≥ 80 years

There was no evidence available in the evaluated studies, as they did not specifically report on the subgroup of patients ≥ 80 years of age with asymptomatic carotid stenosis. In fact, ACAS excluded these patients. In the 10-year followup of ACST, both men and women < 75 years of age had significantly decreased annual rates of any stroke in the CEA group as compared with the medical therapy group. Similar reduction was not reported for the subgroup of men or women ≥ 75 years of age.

Sex

The VA trial included only men and the remaining two RCTs included a higher proportion of men than women. In ACAS, men in the CEA group had lower numbers of observed ipsilateral strokes than men in the medical therapy group after 2.7 years of followup; no similar reduction was reported for women. ACAS reported that during a projected 5-year followup, according to Kaplan–Meier analysis, men had a significantly decreased risk of ipsilateral stroke (including perioperative stroke or death) in the CEA group than in the medical therapy group. During the 5- and 10-year followups of ACST, both men and women received greater benefits with CEA than with medical therapy for the outcome of nonperioperative carotid territory stroke or any stroke, respectively.

Clinical and anatomic features of carotid artery stenosis

In ACAS, patients with prior symptoms due to contralateral stenosis or prior contralateral CEA had a reduced risk of ipsilateral stroke (including perioperative stroke or death) in the CEA group as compared with the medical therapy group on the basis of 5-year projected estimates from the Kaplan–Meier analysis. However, at the median 2.7-year followup in ACAS, there were more events in the CEA group than in the medical therapy group among patients who had prior symptoms due to contralateral stenosis or prior contralateral CEA. In ACST at the 10-year followup, patients with prior symptoms due to contralateral stenosis or prior contralateral CEA had no difference between the two treatment groups. Regardless of the degree of stenosis, in ACST, patients in the CEA group had a significantly decreased risk of carotid territory stroke at 5 years as compared with patients in the medical therapy group, while in the 10-year followup, only a subgroup of patients with 70–89 percent stenosis had significantly decreased annual rates of any stroke in the CEA group as compared with the medical therapy group.

Average or high risk for CEA due to comorbid diseases

All three RCTs excluded the majority of patients who were believed to be at high risk for CEA owing to associated medical illnesses. ACST reported a subgroup analysis of a small number of patients who had diabetes or ischemic heart disease at study entry; there was no difference in the risk of nonperioperative ipsilateral stroke between the CEA and medical treatment groups.

Concurrent and postoperative treatments

Only the 10-year followup of ACST evaluated any nonperioperative stroke stratified by concurrent use of medications (antihypertensive therapy, antithrombotic therapy, and lipid-lowering therapy) at study entry. An additional analysis was conducted for the ipsilateral stroke outcome stratified by concurrent use of medications at the time of outcome assessment. Less than 55 percent of patients were using antihypertensive therapy, and approximately 11 percent were using lipid-lowering therapies, at randomization. The medical therapy usage continued to increase in the later years of followup in both the CEA and medical therapy groups, with up to 89 percent of patients using antihypertensive therapy and 82 percent using lipid-lowering therapy. Regardless of the usage of antihypertensive or lipid-lowering therapy, as compared with the medical therapy group, the CEA group had a significantly decreased risk of carotid artery territory stroke at 5 years and significantly decreased annual rates of any stroke at 10 years.

Length of followup

Overall estimates of ipsilateral stroke or any stroke after CEA decreased with followup, but estimates of death did not change regardless of whether 5- or 10-year data were used from ACST.

Methodological quality of studies

All three RCTs were rated quality A.

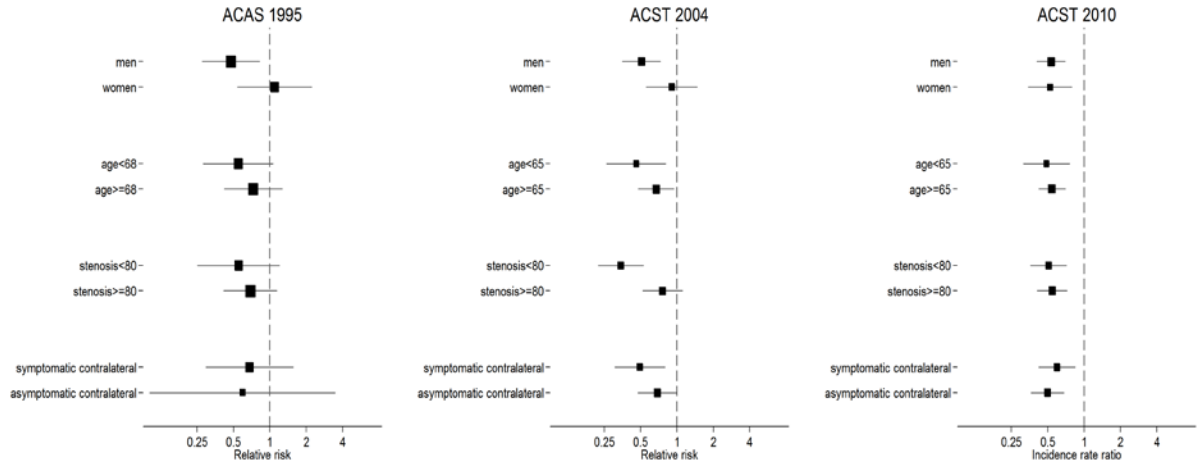
Demographic and other preoperative (baseline) features of studied patients in comparative studies of CEA versus medical therapy

Four nonrandomized comparative studies included patients with an average age of ≥ 65 years that reported heterogeneous and inconclusive results for the comparison of CEA and medical therapy with medical therapy alone. Two retrospective nonrandomized comparative studies evaluated patients with > 75 percent stenosis and one study reported 2.5 percent perioperative

events in the CEA group, while the other reported no events in both groups. No specific subgroup analyses were conducted in these studies.

All nonrandomized comparative studies were rated either quality-B or -C, had considerable heterogeneity and reported variable results in outcomes of ipsilateral stroke, any stroke, and the combined endpoint of any stroke or death.

Figure 13. Forest plot of ipsilateral stroke, and any stroke by subgroups* comparing CEA and medical therapy with medical therapy alone



*ACAS 1995 evaluates relative risk of ipsilateral stroke by subgroups; ACST 2004 evaluates relative risk of carotid territory stroke by subgroups; and ACST 2010 evaluates incidence rates of any stroke. Published paper of ACST 2010 estimates annual rates by subgroups, while the figure here evaluates incidence rates.
Relative risk or incidence rate ratio <1 favors CEA over medical therapy.

Key Question 2 (Subgroups and treatment effect)

CAS and medical therapy versus medical therapy alone

The noncomparative study (Sherif 2005) included patients with > 70 percent asymptomatic carotid stenosis and reported data on long-term adverse clinical outcomes. This study did not report outcomes of ipsilateral stroke outcomes. This study did not evaluate any subgroups as predictors of outcomes. In addition, the Bosiers 2005 study did not report any subgroup analyses.

CAS versus CEA

Two trials (CREST and SAPPHIRE) reported some subgroup-specific data. No specific subgroup analyses were reported in nonrandomized comparative studies.

Demographic and other baseline features of studied patients in RCTs

Age: Subgroup of patients ≥ 65 years

The average age of patients enrolled in RCTs ranged from 66.6 to 72.6 years; among patients included in nonrandomized comparative studies, age ranged from 69.6 to 72.0 years. However, no study provided data for the age subgroups < 65 years or ≥ 65 years; thus, we could not evaluate whether the treatment effect of CAS as compared with CEA was different between these patient populations. Given that the majority of patients included in the analyzed studies were aged ≥ 65 years, the results of these studies can be considered applicable to those ≥ 65 years of age with asymptomatic carotid artery stenosis.

Age: Subgroup of patients ≥ 80 years

No subgroup analysis by patient age was reported in asymptomatic carotid stenosis.

Sex

CREST reported data stratified by sex in asymptomatic patients, on the basis of a prespecified secondary analysis.[83] Both men and women had nonsignificantly increased hazard ratios for the primary composite endpoint, stroke, and stroke or death with CAS as compared with CEA.

Clinical, and anatomic features of CAS

The SAPPHIRE trial included only patients with > 80 percent carotid stenosis and found no significant differences between CAS and CEA for ipsilateral or any stroke, death, or the composite primary endpoint.

Average or high risk for CEA due to comorbid diseases

All patients included in the SAPPHIRE trial were considered to be at high risk for adverse events on the basis of the clinical and anatomic features specified in the trial eligibility criteria. No significant differences between CAS and CEA were found for ipsilateral or any stroke, death, or the composite primary endpoint.

Types of stents used and use of embolic protection devices

Data on the specific type of stents and embolic protection devices were provided by three RCTs (CREST, SAPPHIRE, and Brooks 2004) that examined long-term clinical outcomes. CREST and the SAPPHIRE trial, each used different types of stents. The trials did not report subgroup data according to the specific type of stents used.

All trials had a high rate of embolic protection device utilization (> 90 percent). The Brooks 2004 study did not use embolic protection devices. The majority of patients in trials that reported long-term outcomes (CREST and SAPPHIRE) underwent CAS with embolic protection devices. These trials did not report subgroup-specific data for the patients that did not receive such devices. Therefore, the impact of the use of embolic protection devices on the treatment effect of CAS could not be evaluated.

Concurrent and postoperative treatments

CREST and the SAPPHIRE trial employed similar medical treatment for perioperative management (dual antiplatelet therapy for the CAS group and single antiplatelet therapy for the CEA group) and long-term management of patients, and thus, no relevant data are available to examine the impact of various medical treatments on clinical outcomes.

Length of followup

The SAPPHIRE trial reported data in two different publications, with 1-year followup data given in 2004 and 3-year followup data in 2008. The 1-year data showed a significant 53 percent reduction in the risk of the primary outcome with CAS over CEA (RR = 0.47, 95% CI = 0.25, 0.89); this effect was no longer significant at 3 years (RR = 0.73, 95% CI = 0.47, 1.14).

Methodological quality of studies

Data for the long-term efficacy of CAS as compared with CEA were reported in one quality-A RCT (CREST) and one quality-B RCT (SAPPHIRE). The observed point estimates for outcomes were in opposite directions. However, there were no significant differences in the risk of ipsilateral stroke or composite primary endpoint between the two intervention groups.

Demographic and other baseline features of studied patients in nonrandomized comparisons of CAS versus CEA

One nonrandomized comparative study (CaRESS) reported data on the specific type of stents and the use of embolic protection devices. The impact of the use of embolic protection devices on the treatment effect of CAS could not be evaluated because no subgroup-specific data for the patients that did not receive such devices were provided. This study was rated as quality-B and reported no significant difference in the risk of stroke or composite outcomes between the two intervention groups.

Summary of Key Question 2 (Subgroups and treatment effect for all treatment comparisons)

For the comparisons of CEA and medical therapy with medical therapy alone, two quality-A RCTs (ACAS and ACST) reported subgroup-specific data. The strength of evidence is graded as insufficient, because these trials reported subgroup-specific data for three outcomes that cannot be combined. The outcomes evaluated for subgroups were ipsilateral stroke, including perioperative stroke or death, in the ACAS, nonperioperative carotid territory stroke in the 5-year followup of ACST, and any territory stroke in the 10-year followup of ACST. In addition, there

was insufficient information on certain subgroups. The nonrandomized comparative studies comparing of CEA and medical therapy with medical therapy alone provided insufficient information on the subgroup-specific data.

The strength of evidence is graded as insufficient on the basis of a lack of RCT data for the comparison of CAS and medical therapy with medical therapy alone. No specific subgroup analyses were reported in the nonrandomized comparative studies.

The strength of evidence is graded as insufficient for the comparison of CAS with CEA because there was insufficient information or only one of the three RCTs (CREST, SAPPHIRE, and Brooks 2004) reported data for subgroups of interest. No subgroup analyses were reported by one nonrandomized comparative study that reported long-term outcomes.

Key Question 3 (Outcomes occurring within 30 days)

CEA and medical therapy versus medical therapy alone

Two RCTs (VA and ACAS) and three nonrandomized comparative studies reported data on adverse events and complications within 30 days. All studies were conducted in the early 1990s except for one more recent retrospective nonrandomized comparative study by Bosiers 2005, which retrospectively reviewed their 2003 data.[78]

Patients randomly assigned to CEA underwent surgery within 10 days in the VA trial or within 14 days in ACAS. The periprocedural period for the medically treated patients was defined as 30 days and 42 days after randomization in the VA trial and ACAS, respectively. We did not include ACST in evaluating this outcome, as the definition of perioperative morbidity and mortality in the ACST medical therapy group differed considerably from the definitions used in the other two trials. ACST compared the rate of periprocedural events between the immediate CEA group and the deferred CEA group after they were operated on.

The retrospective nonrandomized comparative study, Bosiers 2005, included all patients with > 80 percent asymptomatic carotid stenosis. In general, there was incomplete reporting of baseline and surgical characteristics in this study (Appendix E, Table 2). The study also included in the analysis 25 percent of patients who were at high risk for CEA.

Any periprocedural stroke

RCTs of CEA versus medical therapy

Two RCTs (VA and ACAS) reported a significantly higher risk of any stroke during periprocedural period in the CEA compared with the corresponding followup period in the medical therapy alone (summary RR = 5.94, 95% CI = 2.06, 17.12). There was no statistical heterogeneity (I^2 = 0.0%, P=0.91).

Nonrandomized comparative studies of CEA versus medical therapy

Two nonrandomized comparative studies reported periprocedural events occurring in CEA, but there were no events reported during corresponding followup period in the medical therapy.

Periprocedural death

RCTs of CEA versus medical therapy

Two RCTs (VA and ACAS) reported a nonsignificantly higher risk of death during periprocedural period with CEA than during the corresponding followup period in the medical therapy (summary RR = 3.68, 95% CI = 0.77, 17.72). There was no statistical heterogeneity (I^2 = 0.0%, P=0.82).

Nonrandomized comparative studies of CEA versus medical therapy

The nonrandomized comparative studies did not report this outcome.

Periprocedural MI

RCTs of CEA versus medical therapy

Two RCTs reported a nonsignificantly higher risk of MI during periprocedural period with CEA than during the corresponding followup period in the medical therapy alone (summary RR = 8.39, 95% CI = 1.00, 70.33). There was no statistical heterogeneity (I^2 = 0.0%, P=0.39).

Nonrandomized comparative studies of CEA versus medical therapy

The nonrandomized comparative studies did not report this outcome.

Periprocedural composite outcomes

Stroke or death during the periprocedural period or within 30 days followup

RCTs of CEA versus medical therapy

The risk of stroke or death with or without MI during the periprocedural period was significantly higher with CEA than with medical therapy alone, according to data from the analysis of two trials (VA and ACAS) (Figures 14–15). The estimates of outcomes during periprocedural period did not change considerably with or without the addition of stroke or death attributable to the selective use of arteriography in ACAS.

Nonrandomized comparative studies of CEA versus medical therapy

In contrast to the RCTs, three nonrandomized comparative studies (Bosiers 2005, Mayo 1992, and Hertzer 1986) reported periprocedural events occurring in the CEA groups, whereas no events occurred during the corresponding followup period in the medical therapy groups.

Periprocedural cranial nerve palsy

RCTs of CEA versus medical therapy

One RCT reported cranial nerve palsy after CEA but no such events occurred during the corresponding followup period in the medical therapy.

Nonrandomized comparative studies of CEA versus medical therapy

One nonrandomized comparative study reported cranial nerve palsy after CEA but no such events during the corresponding followup period in the medical therapy.

Periprocedural bleeding complications

RCTs of CEA versus medical therapy

No trial reported major bleeding events.

Nonrandomized comparative studies of CEA versus medical therapy

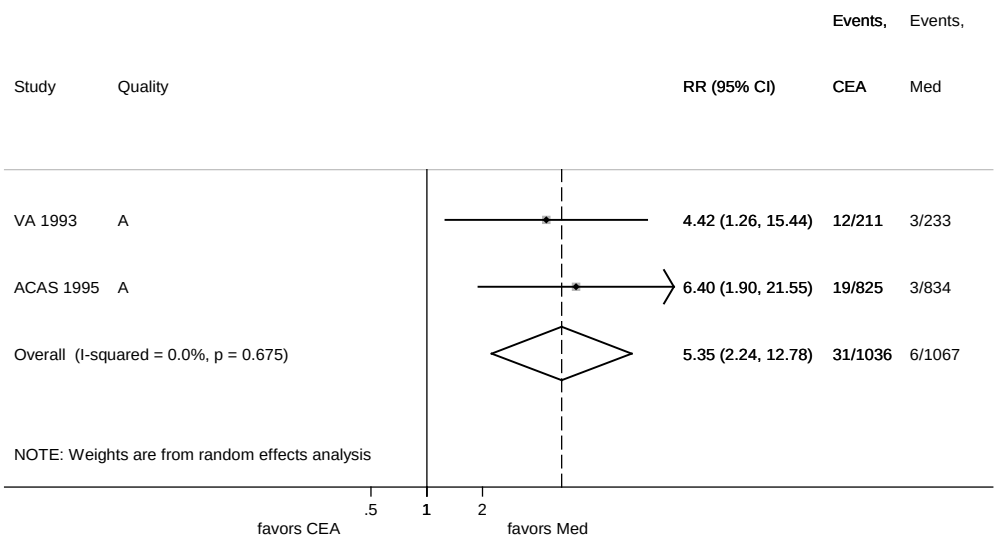
One nonrandomized comparative study reported no major bleeding events in the CEA group.

Summary of Key Question 3 (CEA versus medical therapy: outcomes within 30 days)

The strength of evidence is graded as moderate, but may not translate to contemporary clinical practice for periprocedural outcomes of RCTs of CEA and medical therapy as compared

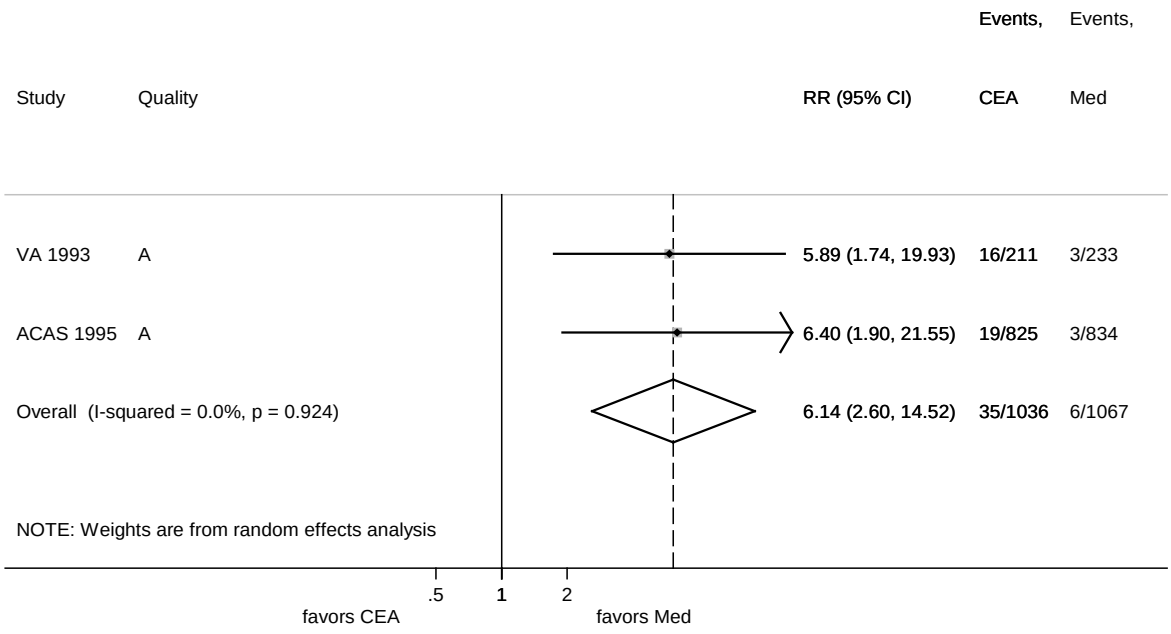
with medical therapy alone. At randomization, patients with asymptomatic carotid stenosis were not receiving what is currently considered the best medical therapy or contemporary postoperative medical management. Two quality-A RCTs in patients with asymptomatic carotid stenosis showed an increase in the risk of adverse events including any stroke, death, or MI with CEA and medical therapy over medical therapy alone.

Figure 14. Meta-analysis of stroke and death during 30-day period in RCTs of CEA versus medical therapy



CEA = carotid endarterectomy; Med = medical therapy; RR = risk ratio
RR >1 favors medical therapy alone over CEA and medical therapy

Figure 15. Meta-analysis of stroke, MI, and death during 30-day period in RCTs CEA versus medical therapy



CEA = carotid endarterectomy; Med = medical therapy; RR = risk ratio
RR >1 favors medical therapy alone over CEA and medical therapy

Key Question 3 (Outcomes occurring within 30 days) continued

CAS and medical therapy versus medical therapy alone

A single nonrandomized comparative study (Bosiers 2005) provided data for the endpoint of any stroke or death during the periprocedural 30-day period and reported no significant differences between the CAS and medical therapy compared with medical therapy alone (Appendix E, Table 9).

Any stroke or death

The risk of stroke or death was reported during the periprocedural 30-day period between the CAS group (1.7 percent) and the medical therapy group (0.0 percent).

Summary

The strength of evidence is graded as insufficient based on lack of RCTs.

CAS and medical therapy versus CEA and medical therapy

Data for the comparison of periprocedural adverse events of CAS and CEA were provided by all available 10 studies (three RCTs and seven nonrandomized comparative studies). Periprocedural outcomes were considered all outcomes occurring within 30 days from the intervention or in the case of the administrative nonrandomized comparative studies, all outcomes occurring within the period of hospitalization. Detailed descriptions are summarized in Appendix E, Tables 17–22.

Any periprocedural stroke

RCTs of CAS versus CEA

All RCTs reported this outcome (Figure 16). CREST reported a statistically nonsignificant increase in the occurrence of any periprocedural stroke in CAS as compared with CEA (adjusted HR = 1.88, 95% CI = 0.79, 4.42). Similar results were reported in the SAPPHIRE trial, with a statistically nonsignificant increase in the risk of any periprocedural stroke (RR = 1.54, 95% CI = 0.44, 5.31) or ipsilateral stroke (RR = 1.71, 95% CI = 0.42, 6.99) with CAS as compared with CEA. . No cerebrovascular events occurred in the Brooks 2004 trial.

Nonrandomized comparative studies of CAS versus CEA

Six nonrandomized comparative studies reported this outcome. The meta-analysis of two nonrandomized comparative studies with clinical datasets (one quality-B and one quality-C) showed a nonsignificant decrease in the risk of periprocedural stroke with CAS, thus favoring CAS over CEA (summary RR = 0.55, 95% CI = 0.11, 2.67), without statistical heterogeneity (I^2 = 0.0%, P=0.95) (Figure 17).

On the contrary, meta-analysis of the four nonrandomized comparative studies with administrative data (all quality-C) resulted in a significant summary estimate showing a 71 percent increased risk for periprocedural stroke with CAS compared with CEA (summary RR = 1.71, 95% CI = 1.34, 2.26), with statistically significant heterogeneity (I^2=75%; P=0.007) (Figure 18).

Although these nonrandomized comparisons included much larger sample sizes than the RCTs, these studies are observational in nature and are prone to biases, such as confounding by indication. The single study (Giacovelli 2010) that attempted to address observed confounders with propensity score-matched analyses showed no significant increase in the risk of stroke (RR = 1.17, 95% CI = 0.86, 1.59).

Periprocedural death

RCTs of CAS versus CEA

Two RCTs (CREST and SAPPHIRE) reported this outcome. In CREST, there was no periprocedural death in the two treatment groups. The SAPPHIRE trial reported a statistically nonsignificant increase in the risk of periprocedural death between CAS and CEA (RR = 2.05, 95% CI = 0.18, 22.3), but the wide CI indicates great uncertainty.

Nonrandomized comparative studies of CAS versus CEA

Five nonrandomized comparative reported this outcome. Single nonrandomized comparative study (Marine 2006) based on clinical dataset reported no statistical difference between CAS and CEA (RR = 1.56, 95% CI = 0.10, 24.6). In a meta-analysis of four nonrandomized comparative studies based on administrative datasets, there was a significant increase in the risk of periprocedural death with CAS (summary RR = 1.43, 95% CI = 1.20, 1.71), without statistical heterogeneity (I^2 = 0.0%, P=0.44) (Figure 19).

Periprocedural MI

RCTs of CAS versus CEA

Two RCTs (CREST and SAPPHIRE) reported nonsignificant reductions in the risk of periprocedural MI, favoring CAS over CEA (Figure 20).

Nonrandomized comparative studies of CAS versus CEA

Four nonrandomized comparative studies reported this outcome. In a meta-analysis of two nonrandomized comparative studies based on clinical data (one quality-B and one quality-C), there was a nonsignificant decrease in the risk of MI with CAS compared with CEA (summary RR = 0.57, 95% CI = 0.09, 3.70), without statistical heterogeneity (I^2 = 0.0%, P=0.67) (Figure 21).

Data from two available quality-C rated studies based on administrative data were not synthesized due to variability in the outcome rates. The estimate of the larger study reported a statistically significant 18 percent increased risk of MI in CAS compared with CEA (RR = 1.18, 95% CI = 1.04, 1.34). The smaller study reported a nonsignificantly increased risk of MI with CAS over CEA (RR = 2.36, 95% CI = 0.82, 6.75).

Periprocedural composite outcome of any stroke, MI, or death

RCTs of CAS versus CEA

Two RCTs (CREST and SAPPHIRE) examined this periprocedural composite endpoint. CREST reported no difference in the risk of this composite outcome between CAS and CEA (adjusted HR = 1.02, 95% CI = 0.55, 1.86). According to the reported events in the published

paper of the SAPPHIRE trial, there was a nonsignificant decrease in the risk of the composite outcome with CAS compared with CEA (RR = 0.51, 95% CI = 0.19, 1.32).[21] We observed some inconsistencies in the numbers of reported events for this outcome between the published paper and the data available from the FDA.

Nonrandomized comparative studies of CAS versus CEA

Among two nonrandomized comparative studies, the CaRESS study reported a nonsignificantly decreased risk of this composite endpoint with CAS compared with CEA (RR = 0.34, 95% CI = 0.03, 2.92). The second nonrandomized comparative study based on administrative data for this outcome showed opposing results, a statistically significant increased risk with CAS over CEA (RR = 2.33, 95% CI = 1.32, 4.10).

Periprocedural composite outcome of any stroke or death

RCTs of CAS versus CEA

Two RCTs (CREST and SAPPHIRE) examined this periprocedural composite endpoint. CREST reported a nonsignificant increase in the risk of this composite outcome with CAS as compared with CEA (adjusted HR = 1.88, 95% CI 0.79, 4.42). On the basis of the reported numbers of events in the FDA report of the SAPPHIRE trial, a nonsignificant increase in the risk of the composite outcome with CAS as compared with CEA was estimated (RR = 1.44, 95% CI = 0.47, 4.40).

Nonrandomized comparative studies of CAS versus CEA

Five nonrandomized comparative studies examined this periprocedural composite endpoint in a total of 2,014 patients with asymptomatic carotid stenosis. In a meta-analysis of four nonrandomized comparative studies based on clinical data, there was no significant difference between CAS and CEA (summary RR = 1.30, 95% CI = 0.69, 2.45), and there was no statistical heterogeneity (I^2=0.0%, P = 0.87) (Figure 22).

Periprocedural cranial nerve palsy

RCTs of CAS versus CEA

In a meta-analysis of CREST and the Brooks 2004 trial, there was a statistically significant reduction in the risk of cranial nerve palsy with CAS over CEA (summary RR = 0.06, 95% CI = 0.01, 0.31), and there was no statistical heterogeneity (I^2=0.0%, P = 0.48) (Figure 23).

Nonrandomized comparative studies of CAS versus CEA

Two nonrandomized comparative studies that examined cranial nerve palsy did not report significant reductions with CAS.

Periprocedural bleeding complications

RCTs of CAS versus CEA

One RCT (CREST) showed no significant differences in the risk of hematoma or bleeding between CAS and CEA.

Nonrandomized comparative studies of CAS versus CEA

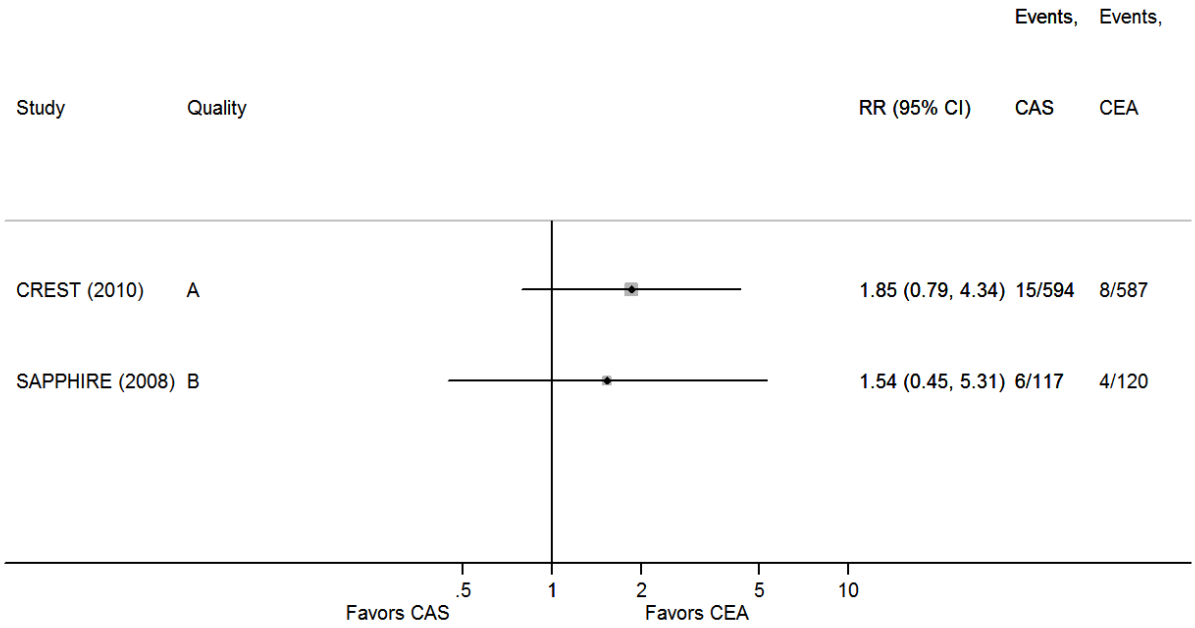
Two nonrandomized comparative studies showed no significant differences in the risk of hematoma or bleeding between CAS and CEA.

Summary of Key Question 3 (CAS versus CEA - outcomes within 30 days)

The strength of evidence is graded as insufficient because between-trial comparisons were not possible, as there was extreme clinical heterogeneity. In addition, clinical trial outcomes were in opposite directions (periprocedural stroke or death were nonsignificantly higher in the CAS, and periprocedural MI events were nonsignificantly higher in the CEA). There were differences between published and unpublished data in one RCT. One quality-A RCT and two quality-B RCTs showed no statistically significant differences in the risk of adverse events, including any periprocedural stroke, death, or MI (or combinations thereof), in patients undergoing CAS as compared with those undergoing CEA.

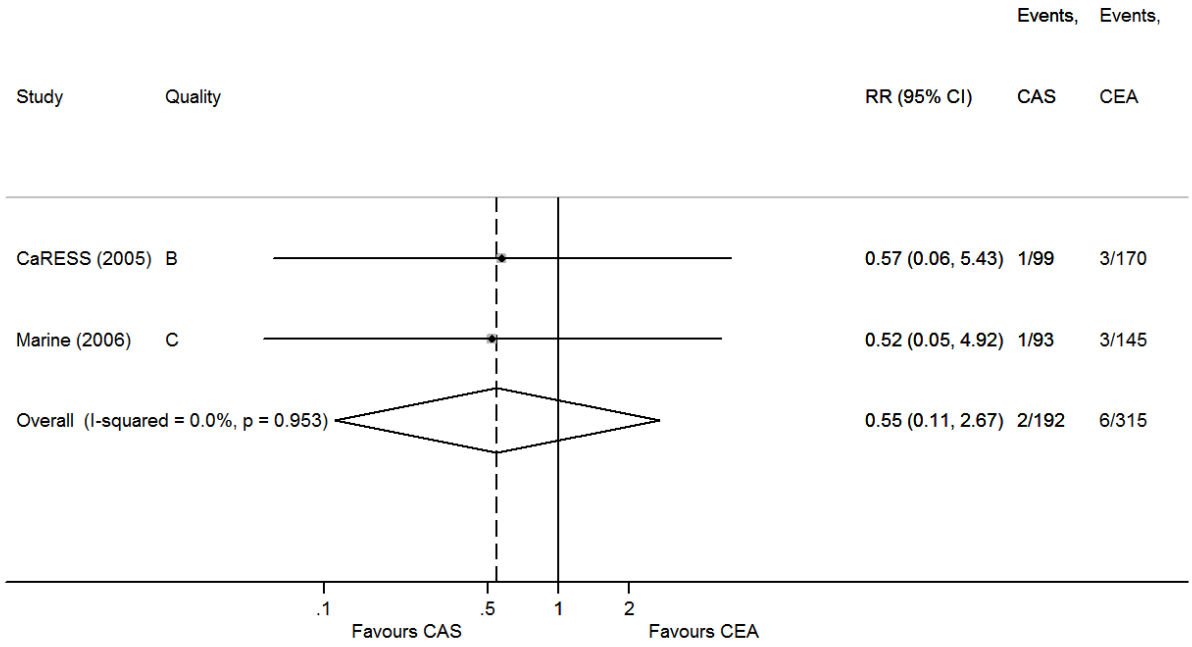
The results of nonrandomized comparative studies based on clinical datasets concurred with the results of RCTs. In contrast, the nonrandomized comparative studies based on administrative datasets showed a significantly greater risk of periprocedural stroke, death, or MI in the CAS than in the CEA.

Figure 16. Forest plot of any periprocedural stroke in RCTs of CAS versus CEA



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

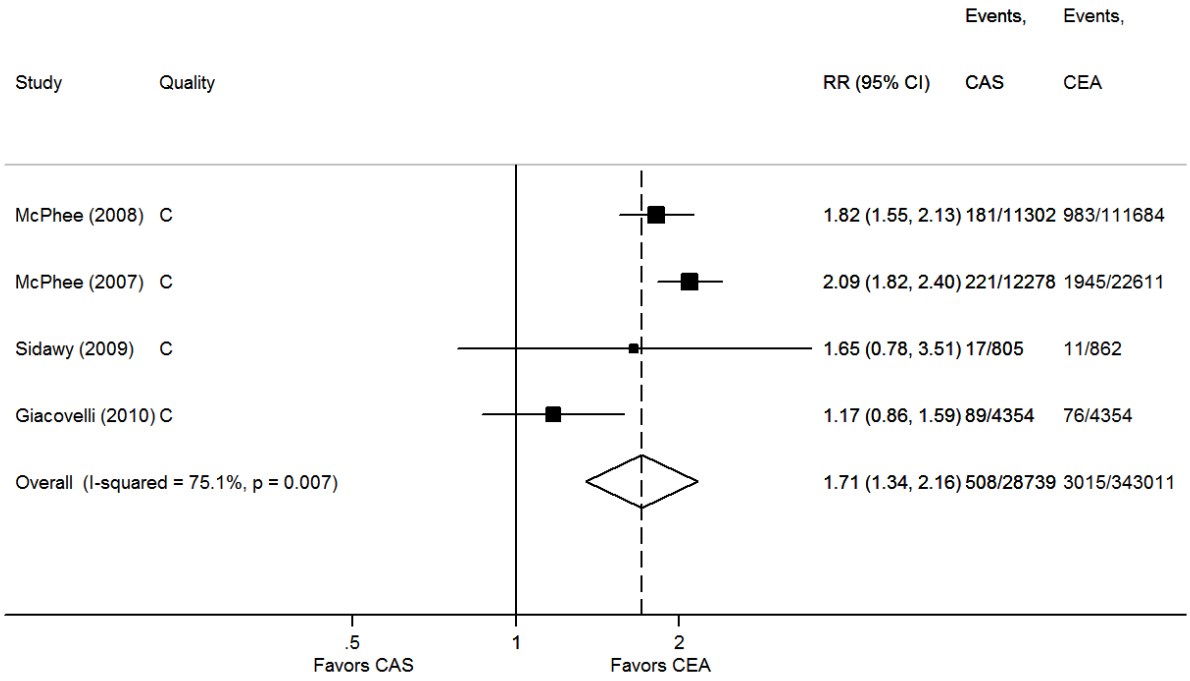
Figure 17. Meta-analysis of any periprocedural stroke in nonrandomized comparative studies of CAS versus CEA



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio

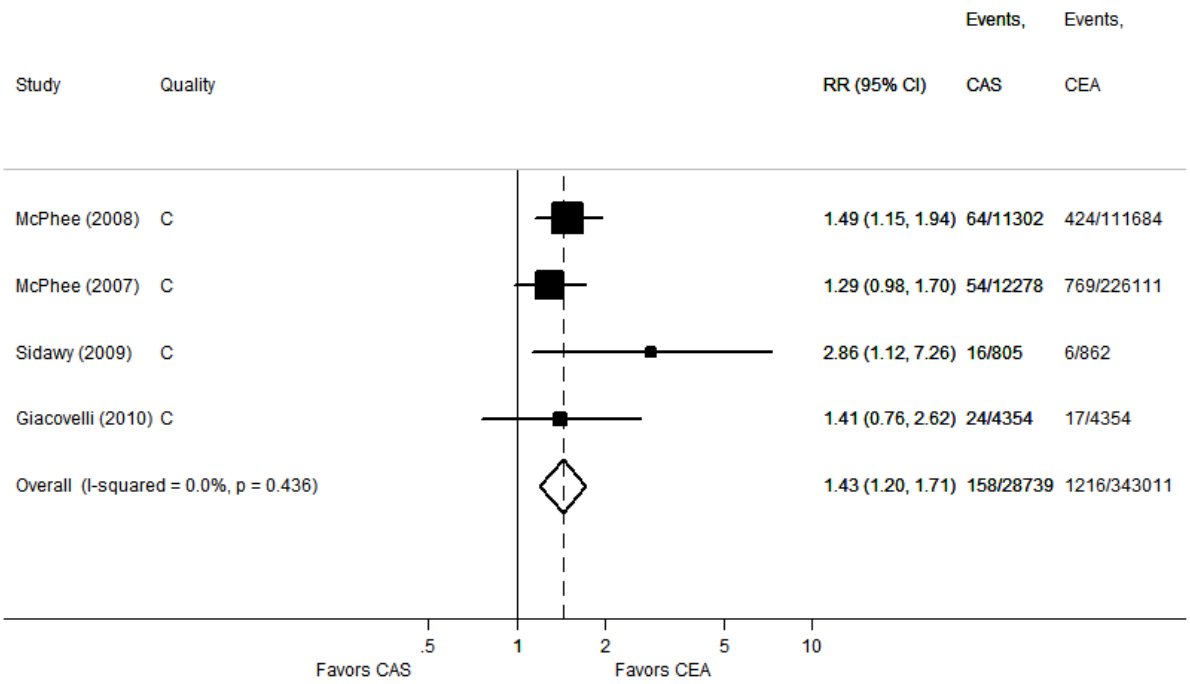
RR < 1 favors CAS over CEA

Figure 18. Meta-analysis of any periprocedural stroke in nonrandomized comparative studies (administrative datasets) of CAS versus CEA



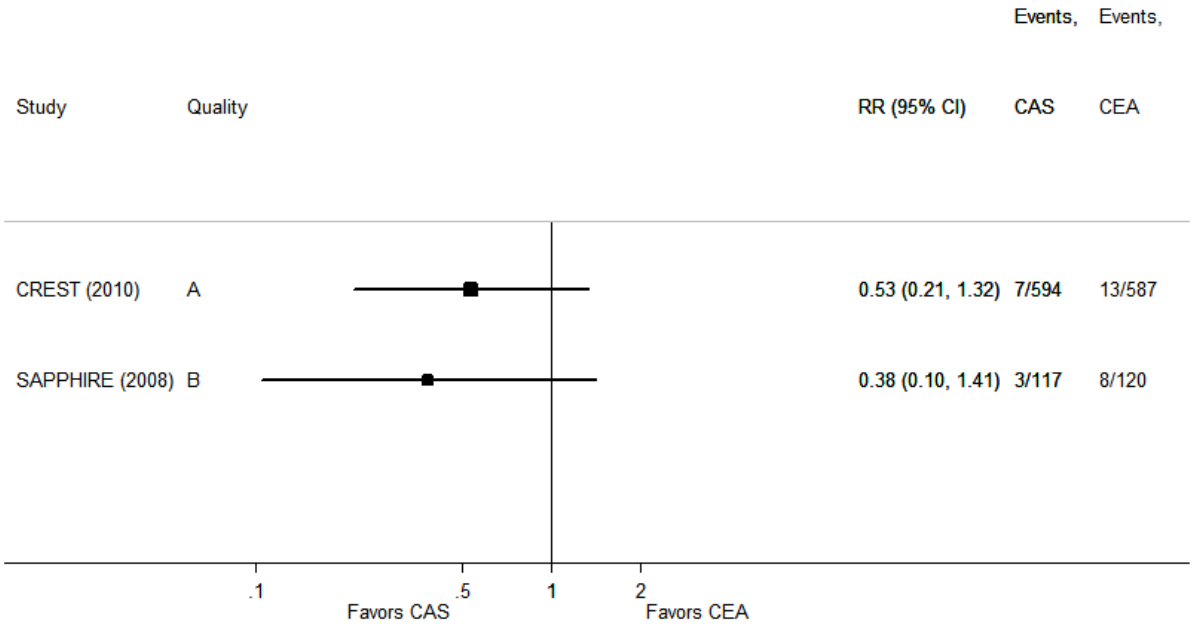
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 19. Meta-analysis of periprocedural death in nonrandomized comparative studies (administrative datasets) of CAS versus CEA



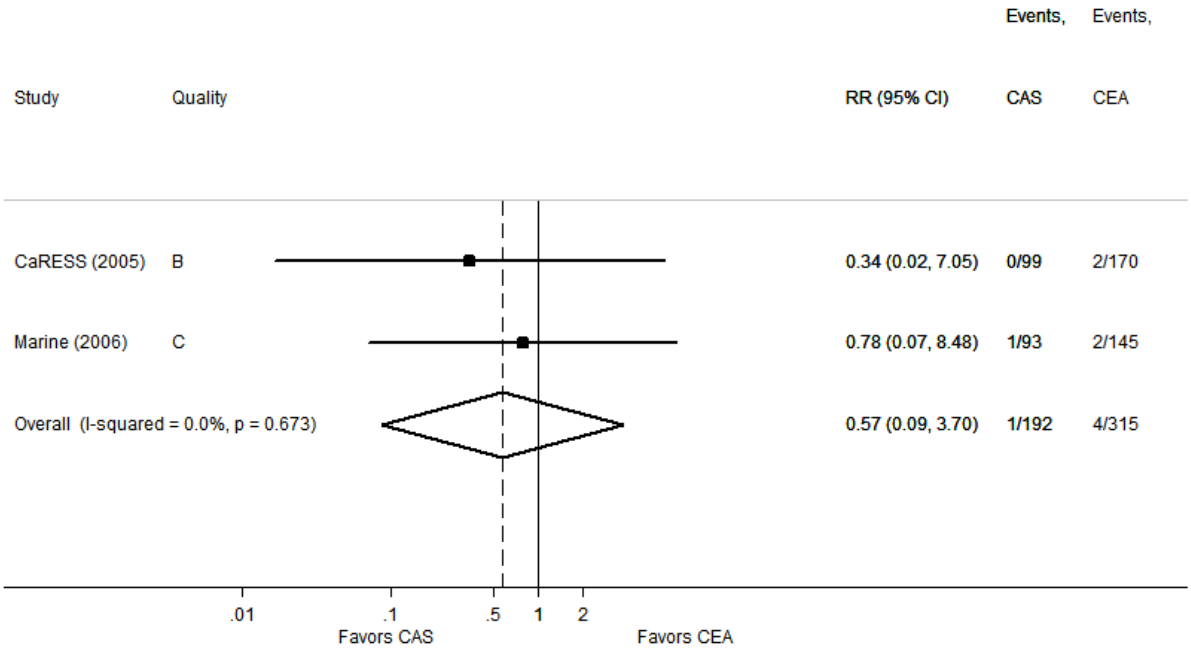
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 20. Forest plot of periprocedural MI in RCTs of CAS versus CEA



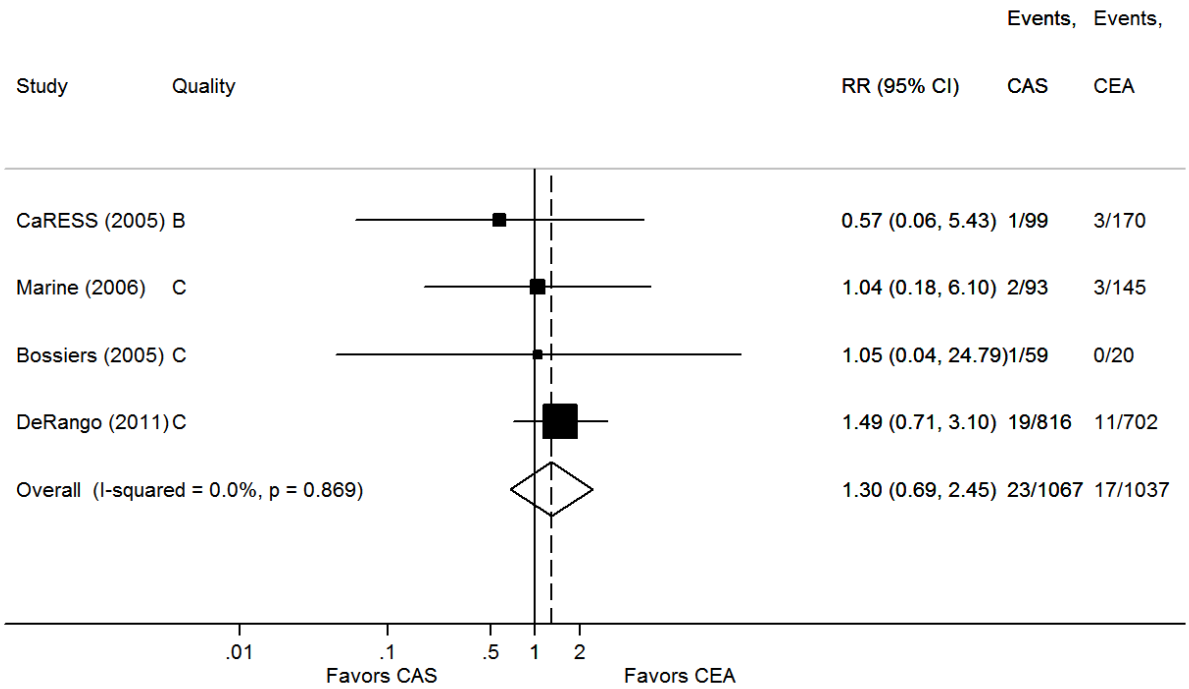
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 21. Meta-analysis of periprocedural MI in nonrandomized comparative studies of CAS versus CEA



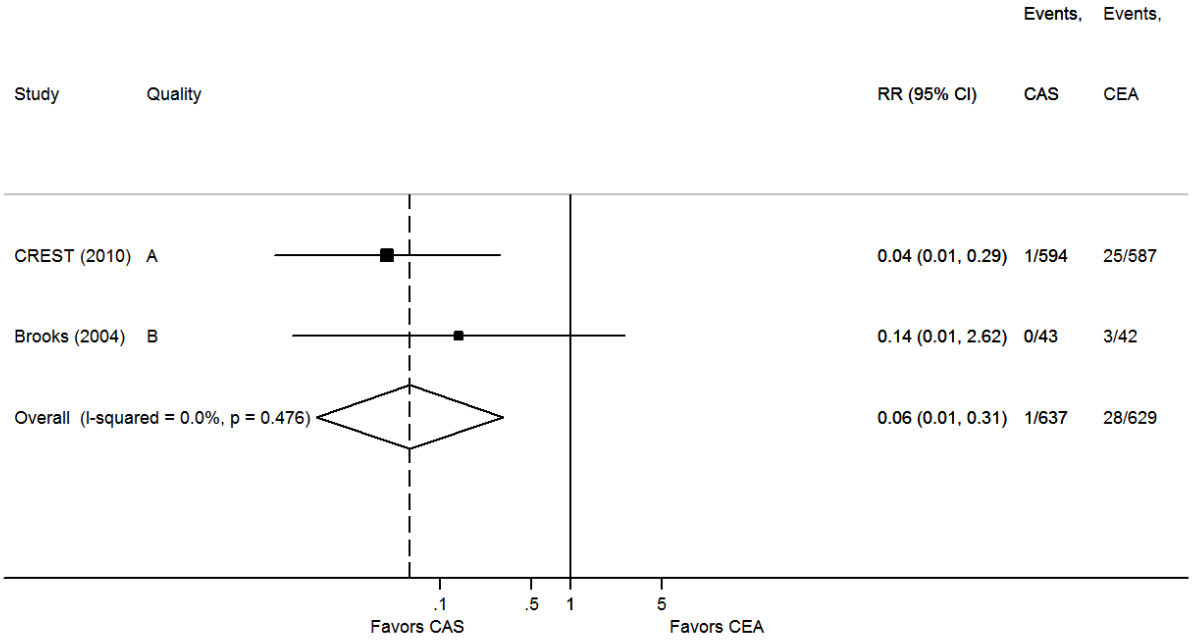
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 22. Meta-analysis of any periprocedural stroke or death in nonrandomized comparative studies of CAS versus CEA



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Figure 23. Meta-analysis of cranial nerve palsy in RCTs of CAS versus CEA



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CI = confidence interval; RR = risk ratio
RR < 1 favors CAS over CEA

Applicability

The trials comparing CEA and medical therapy with medical therapy alone reported using standard medical therapy available at that period, but did not report the use of optimized therapy (e.g., specific target levels to manage comorbid conditions such as diabetes or hypertension or hyperlipidemia). Furthermore, at randomization, patients with asymptomatic carotid stenosis were not receiving what is considered current best medical therapy, including the use of statins. Thus the medical therapy used in these trials may not reflect those that are used in contemporary clinical practice. All trials were conducted at tertiary centers and the results may not be generalizable to community settings.

There were insufficient data comparing CAS and medical therapy with medical therapy alone and therefore, the applicability was not assessed. At least one of the trials of CAS and medical therapy compared with CEA and medical therapy included patients for all the subgroups of interest. The patient selection process applied in the SAPPHIRE trial, in which almost half of potentially eligible patients were not randomized but rather were included in a stenting registry, poses significant limitations in assessing the applicability of the study results. Patient-selection issues were also reported in CREST prolonging the enrollment phase, in which eligible patients were enrolled into one of several stent registries. Both trials were conducted at tertiary medical centers, thus the results may not be generalizable to community settings.

Discussion

Summary of findings

Our systematic review indicates that the summary incidence rate of ipsilateral stroke was 1.59 percent per year in quality-A and -B studies among patients with asymptomatic carotid stenosis who were treated with medical therapy alone. There is moderate strength of evidence that medical therapy alone can reduce the incidence rate of ipsilateral stroke over time. Our review of RCTs demonstrates a significant reduction in the risk of ipsilateral stroke or any stroke with CEA and medical therapy compared with medical therapy alone. However, the strength of the available evidence is graded as moderate for this comparison because these trials were conducted from the 1990's through early 2000 and thus, their results may not translate to contemporary clinical practice. The strength of evidence is graded as insufficient because of lack of RCTs comparing CAS and medical therapy with medical therapy alone. Our review of RCTs comparing CAS and medical therapy with CEA and medical therapy found no statistically significant differences between the two interventional modalities. However, across two trials, the clinical heterogeneity and the observed effect estimates were in opposite directions (as evidenced in individual forest plots) and the summary estimates were in opposite directions across periprocedural outcomes. Therefore, the strength of evidence is graded as insufficient.

Medical therapy alone

Our meta-analysis of quality-A and quality-B prospective studies involving medical therapy alone for the ipsilateral asymptomatic carotid artery of interest showed that the summary incidence rate of ipsilateral stroke was relatively low, which suggests that asymptomatic patients can benefit from either CEA or CAS in addition to medical therapy only if these interventions are performed with very low periprocedural risk. It is important to note that in the majority of the older studies included in this analysis the enrolled patients did not receive what is currently considered intensive medical therapy, which may involve the use of vascular protective agents, such as dual antiplatelet agents, ACE-inhibitors, and statins as is evidenced in the treatment of hypertension, diabetes, and hyperlipidemia – all of which have aggressive treatment goals. When the analysis was restricted to the more recent studies (with recruitment of patients between 2000 and 2010), the summary incidence rate of ipsilateral stroke was 1.1 percent per year, much lower than published event rates before 2000 (2.3 percent per year). In a subgroup meta-analysis stratified by the reported use of statins in each study, it was shown that studies in statins were used by more than 25 percent of the study population had a significantly decreased rate of ipsilateral stroke compared with use of statins by less than 25 percent of the study population. Additional evidence from meta-regression analyses indicates a reduction in the rates of ipsilateral stroke, which showed that there is a statistically significant reduction in the incidence rate of ipsilateral stroke (and ipsilateral stroke or TIA) over time.

This significant reduction in the rate of ipsilateral events is in agreement with a recent systematic review that examined a smaller number of studies (n=11) by using a weighted linear regression model analysis.[13] In comparison to this review, which excluded studies with <100 participants, our review used a threshold of at least 30 participants in each study resulting in more heterogeneous, but larger number of studies (n=41 studies in total). Furthermore, for the analysis of these data we employed a formal meta-regression model with the Poisson likelihood, which is more appropriate for the analysis of such rare events.

In contrast, we found no significant effect of time for any territory cerebrovascular outcomes (any stroke and any stroke or TIA). This finding contradicts to a previous analysis conducted by a recent systematic review, which reported significant reduction in the published rates of any stroke and any stroke or TIA.[13] This apparent discrepancy between our results and the analysis by the previous systematic review may stem from differences in our inclusion criteria. The previous systematic review included studies reporting any territory outcomes only if these studies provided data on ipsilateral stroke events as well, whereas our review included studies with any territory outcome data, irrespective of whether ipsilateral outcomes were provided. Thus, the two systematic reviews are not directly comparable. When we conducted a sensitivity analysis of any territory stroke by including only those studies that reported ipsilateral events, then this demonstrated a significant reduction of the incidence rates of any stroke. Our all-inclusive analysis of studies for any stroke events did not show the same reduction pattern, which may be due to potential differences in the ascertainment of outcomes between studies that did and did not report ipsilateral stroke, e.g. ascertainment of any territory stroke being more sensitive in studies that reported the outcome of ipsilateral stroke as well. Furthermore, limiting our analyses to quality-A and -B studies, significant effect of time (older vs. newer studies) was detected for any territory stroke and any stroke or TIA.

In this review, subgroup analysis of medically treated patients by degree of stenosis showed that the populations with >70 percent carotid stenosis did not have a significantly higher summary incidence rate of ipsilateral stroke compared with the subgroup of 50-70 percent stenosis. Nevertheless, severity of stenosis in medically-treated patients was associated with higher summary incidence rates for all other cerebrovascular outcomes (ipsilateral stroke or TIA, any stroke, and any stroke or TIA) indicating that severity of stenosis may be a surrogate marker of cerebrovascular disease.

In summary, there is moderate strength of evidence that the use of intensive systemic medical therapy in the context of vascular diseases can reduce ipsilateral stroke, any stroke, and death.

CEA and medical therapy versus medical therapy alone

It is important to note that three RCTs were conducted during the 1990s through early 2000. These trials used ‘standard of care’ medical therapy that was considered appropriate for management of patients with asymptomatic carotid stenosis during that period. The medical therapy group at randomization did not receive what is currently considered as optimal medical therapy, including the use of statins. Thus, their stroke event rate may be higher than currently seen in optimally treated medical patients. The reduction of ipsilateral stroke with CEA and medical therapy observed in these RCTs mostly reflects the low perioperative adverse event rate (< 3 percent) in the ACAS and the ACST trials. The surgeons in these trials were selected based on their past operative experience and the surgeries were conducted in tertiary care centers. Such a low rate of adverse events may be difficult to achieve in routine clinical settings.[99] Given the recent advances in medical therapy of vascular diseases, the findings of these RCTs may not be generalizable to contemporary clinical practice. The ACAS trial showed significant reduction in the risk of ipsilateral stroke (including perioperative stroke or death), while ACST at 10-year followup showed a reduction in the risk of any nonperioperative stroke on either carotid artery territory. The use of lipid-lowering therapy was much more prevalent during the later years of followup in ACST trial; the absolute benefits achieved from successful CEA were much smaller in those patients on lipid-lowering therapy as compared with those who were not on lipid-

lowering therapy. In contrast to the RCTs, the nonrandomized comparative studies showed heterogeneous results without significant difference between the two interventions.

CAS and medical therapy versus medical therapy alone

There was paucity of randomized data for the comparison of CAS and medical therapy with medical therapy alone. Of the two eligible studies that were reviewed, only one nonrandomized comparative study reported long-term adverse clinical outcomes comparing patients receiving CAS and medical therapy with medical therapy alone. This study did not report the outcome of ipsilateral stroke, but reported a significantly decreased risk of any stroke or death in the CAS group compared with medical therapy group.

CAS and medical therapy versus CEA and medical therapy

Despite showing no significant differences in the efficacy of CAS and medical therapy compared with CEA and medical therapy for the long-term adverse outcomes by two RCTs, the effect estimates for long-term data were in opposite directions, as evidenced in forest plots, and were in opposite directions across trials for periprocedural outcomes..

The medical and vascular interventions used in the CREST and SAPPHIRE trials were similar; the majority of patients received antiplatelet regimens and underwent stent implantation with the use of embolic protection devices. However, there was considerable clinical heterogeneity in the patients enrolled in these trials. The SAPPHIRE included patients with anatomically more advanced stenosis and those at high-risk for complications with CEA. About 20 percent of patients included in this trial also had a history of a prior CEA in their carotid artery of interest, and were thus undergoing intervention in previously operated arteries. In contrast, CREST included low-risk patients with moderate stenosis. The clinical differences between these two trial populations may account for the opposite direction in terms of the point estimates of relative risks of ipsilateral stroke, favoring CAS in the SAPPHIRE trial and favoring CEA in the CREST. In addition, different types of stents were used in these trials.

The CREST and SAPPHIRE trials enrolled both symptomatic and asymptomatic patients with randomization stratified according to symptomatic status. Therefore, the interventions were randomly assigned among asymptomatic subgroup. However, neither trial was powered to detect differences in the primary composite endpoint among subgroups of patients with asymptomatic carotid stenosis. The failure to find statistically significant differences does not rule out the possibility that real differences exist between the interventions. In addition to the inadequately powered asymptomatic subgroups, no significant differences between CAS and CEA demonstrated in these two RCTs may also be a reflection of including MIs in the composite primary endpoint. In both trials, dual antiplatelet therapy was offered only to the CAS group. However, in the CREST, patients in the CEA group experienced more MIs in the periprocedural period compared to the CAS group, but an increased occurrence of more stroke events in the CAS group. In a secondary outcome analysis excluding MIs, the CAS group had 86 percent increase in the relative hazards of periprocedural stroke or death or postprocedural ipsilateral stroke, although this increase did not reach statistical significance (P=0.07). The use of dual antiplatelet therapy during CEA is an area of ongoing research that may further reduce adverse event rates with CEA. Finally, the patient selection process applied in the SAPPHIRE trial, in which almost half of potentially eligible patients were not randomized but were included in a stenting registry, poses significant limitations in assessing the applicability of the study results

with respect to identifying patients in clinical practice who would be similar to the ones that underwent randomization.

Regarding within 30-day outcomes, in individual trials, there was no statistically significant difference in periprocedural cardiovascular adverse event rates between CAS and CEA. On the contrary, synthesis of results from nonrandomized studies using administrative or clinical datasets showed that CAS was associated with significantly increased risk of periprocedural stroke and periprocedural death as compared with CEA. These estimates of increased risk are derived from large sample sizes and thus have robust statistical support. However, inferences drawn from administrative datasets need caution. These studies are vulnerable to selection bias, ascertainment bias, and confounding. Of particular concern is confounding by indication, that is, patients who are selected to undergo CAS may be based on the perceived surgical risks. Thus, in these observational studies, patients who undergo CAS may not be comparable with patients who undergo CEA, in particular for the outcome of periprocedural adverse events.

Context of findings (Comparison with recent reviews)

A published meta-analysis of RCTs evaluated patients with both symptomatic and asymptomatic carotid stenosis and found no significant differences in ipsilateral stroke or composite endpoints of ipsilateral stroke between the two interventions in a stratified analysis of the two RCTs in patients with asymptomatic carotid stenosis (CREST and SAPPHIRE).[100] However, to the best of our knowledge, observational data for the efficacy of CAS compared with CEA have not been considered in previous systematic reviews.

Recent guidelines state that it is reasonable to perform prophylactive CEA or CAS in the select group of patients with asymptomatic carotid stenosis with >70 percent stenosis. They recommend that such a decision should incorporate patient preferences, ascertained by a thorough discussion of the risks and benefits of the procedure.

In this review, we examine both older studies and more recent publications. Also in contrast to prior reviews, we examined nonrandomized studies conducted in real-world settings to evaluate the effectiveness of therapeutic strategies. Our review concludes that future trials should evaluate whether patients with asymptomatic carotid stenosis with >70 percent stenosis treated by current best medical therapy will derive additional benefit from invasive carotid revascularization procedures.

Limitations

The limitations of this review directly reflect limitations of the data available in primary studies. The inclusion of populations in the studies was heterogeneous and reflects a lack of consensus in defining patients with asymptomatic carotid stenosis. The trials presented survival data for different outcomes, precluding us from conducting meta-analyses that would account for differential followup durations. The CAS trials included populations with extreme clinical heterogeneity and therefore were not combined in meta-analyses.

Conclusions

The goal of management of asymptomatic carotid stenosis is to decrease the risk of stroke and stroke-related deaths. Our review of therapeutic strategies in patients with asymptomatic carotid stenosis indicates that there has been a significant reduction in the incidence of ipsilateral stroke over time with medical therapy alone. Our subgroup analysis shows that between the year 2000 and 2010, the current best medical therapy can reduce the risk of ipsilateral stroke to nearly 1 percent per year of followup. Older trials comparing CEA with medical therapy demonstrate a reduction in the occurrence of stroke. This observed reduction reflects the low perioperative adverse event rate of < 3 percent achieved in ACAS and ACST. In these trials, surgeons were selected on the basis of their past operative experience and the surgeries were conducted in tertiary care centers. Thus, to reduce any future stroke-related events invasive procedures must carry an exceedingly low risk of periprocedural adverse events, which may be difficult to achieve in routine clinical settings. In view of recent advances in medical therapy, the applicability or generalizability of the older CEA trial results to contemporary clinical practice requires careful interpretation. There is no randomized trial comparing CAS with medical therapy alone. One recent large trial (CREST) reported higher rates of postprocedural ipsilateral stroke (including any periprocedural stroke) and its composite primary endpoint in the CAS, as compared with CEA, but this did not reach statistical significance in patients with asymptomatic carotid stenosis. The CREST and SAPPHIRE trials randomized patients with symptomatic and asymptomatic carotid stenosis stratified according to symptom status. Therefore, the treatment assignment was randomized among the subgroup of patients with asymptomatic carotid stenosis. However, neither trial was powered to detect a significant difference in the primary composite endpoint among subgroups of patients with asymptomatic carotid stenosis. The failure to find a significant difference does not rule out the possibility that real difference exists between the intervention modalities tested. Patients with asymptomatic carotid stenosis are at an increased risk of future cerebrovascular events. Any expected benefits of an intervention depend on the reduction of the risk of future stroke-related events. Achieving this by medical therapy alone would allow patients to avoid the potential complications of invasive interventional procedures. Our review indicates that all patients with asymptomatic stenosis are likely to benefit from current best medical therapy alone. Recent observational studies suggest that there are methods to identify the high-risk group of patients with asymptomatic carotid stenosis who may benefit from invasive interventional procedures.[49,54,101] Future trials should focus not only on whether CAS is equivalent or superior to CEA, but also on whether an invasive interventional procedure is likely to translate into any significant benefit to the patient treated by current best medical therapy.

Future research

- In patients with asymptomatic carotid stenosis, trials evaluating current best medical therapy with or without invasive interventional approaches are needed.
- Proper analyses of nonrandomized comparative studies using either propensity score-matched analyses or instrumental variable analyses are needed.
- Collaborative individual patient-level meta-analyses identifying subpopulations that will benefit from different treatment strategies are needed.
- Future research is needed to evaluate the functional significance of periprocedural MI in the long-term prognosis of those undergoing invasive interventional approaches, which are aimed to reduce stroke outcomes.
- Creation of registries to include quality observational data of medically managed patients with asymptomatic carotid stenosis is needed. This will aid in risk stratification of patients who will benefit from medical therapy alone.
- Explorative analysis of large prospectively collected data is needed to aid in risk stratification of patients, who will benefit from medical therapy alone.
- Explorative analysis of large administrative data sets is needed to aid in risk stratification of patients who will have reduced periprocedural events in those undergoing interventional procedures.
- Evaluation of the role of predictive effects of the following imaging parameters are needed: a) silent infarction on baseline computed tomography or magnetic resonance imaging (MRI), b) spontaneous embolization on transcranial Doppler, c) computerized ultrasound plaque analysis, and d) evidence of intraplaque haemorrhage on MRI.
- Conducting value of information analysis with an aim to reduce uncertainty in a decision context is needed.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012 Jan 3;125(1):e2-e220. PM:22179539

2. de WM, Greving JP, de Jong AW, et al. Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. Stroke 2009 Apr;40(4):1105-13. PM:19246704

3. Wolff T, Guirguis-Blake J, Miller T GM, et al. Screening for Carotid Artery Stenosis: An Update of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2007 Dec 18;147(12):860-70. PM:18087056

4. Kartchner MM, McRae LP. Noninvasive evaluation and management of the "asymptomatic" carotid bruit. Surgery 1977 Dec;82(6):840-47. PM:929374

5. Thompson JE, Patman RD, Talkington CM. Asymptomatic carotid bruit: long term outcome of patients having endarterectomy compared with unoperated controls. Annals of Surgery 1978 Sep;188(3):308-16. PM:686896

6. Aronson L, Landefeld CS. Examining Older People for Carotid Bruits. J Gen Intern Med 1998 Feb;13(2):140-41. PM:9502377

7. Sonecha TN, Delis KT, Henein MY. Predictive value of asymptomatic cervical bruit for carotid artery disease in coronary artery surgery revisited. Int J Cardiol 2006 Feb 15;107(2):225-29. PM:16412801

8. Muto PM, Welch HJ, Mackey WC, et al. Evaluation of carotid artery stenosis: is duplex ultrasonography sufficient? J Vasc Surg 1996 Jul;24(1):17-22. PM:8691519

9. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. Stroke 1999 Sep;30(9):1751-58. PM:10471419

10. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998 May 9;351(9113):1379-87. PM:9593407

11. Rothwell PM, Gibson RJ, Slattery J, et al. Equivalence of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke 1994 Dec;25(12):2435-39. PM:7974586

12. Rothwell PM. Carotid stenting: more risky than endarterectomy and often no better than medical treatment alone. Lancet 2010 Mar 20;375(9719):957-59. PM:20304225

13. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009 Oct;40(10):e573-e583. PM:19696421

14. Makris GC, Lavida A, Nicolaides AN, et al. The effect of statins on carotid plaque morphology: a LDL-associated action or one more pleiotropic effect of statins? Atherosclerosis 2010 Nov;213(1):8-20. PM:20494361

15. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the Primary Prevention of Stroke. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2010 Dec 6 PM:21127304

16. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database of Systematic Reviews 2005(4):CD001923. PM:16235289

17. Brott TG, Halperin JL, Abbara S, et al. ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the 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 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 NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation 2011 Jul;124 PM:21282504

18. Decision Memo for Percutaneous Transluminal Angiolasty (PTA) of the Carotid Artery Concurrent with Stenting (CAG-00085R7). 2010. Available at: PM:None.

19. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. BMJ 1997 Dec 13;315(7122):1571-77. PM:9437274

20. Sundt TM, Sandok BA, Whisnant JP. Carotid endarterectomy. Complications and preoperative assessment of risk. Mayo Clin Proc 1975 Jun;50(6):301-06. PM:1127994

21. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. New England Journal of Medicine 2004 Oct 7;351(15):1493-501. PM:15470212

22. Methods Guide for Effectiveness and Comparative Effectiveness Review. Agency for Healthcare Research and Quality.; 2011. Available at: http://effectivehealthcare.ahrq.gov/.

23. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990 Feb;131(2):373-75. PM:2296988

24. Bagos P, Nikolopoulos GK. Mixed-Effects Poisson Regression Models for Meta-Analysis of Follow-Up Studies with Constant or Varying Durations. Int J Biostat 2009;5(1):Article 21. PM:None

25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-88. PM:3802833

26. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002 Jun 15;21(11):1559-73. PM:12111920

27. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004 Jun 15;23(11):1663-82. PM:15160401

28. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995 May 10;273(18):1421-28. PM: 7723155

29. Risk of stroke in the distribution of an asymptomatic carotid artery. The European Carotid Surgery Trialists Collaborative Group. Lancet 1995 Jan 28;345(8944):209-12. PM:7823712

30. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004 May 8;363(9420):1491-502. PM:15135594

31. Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010 Sep 25;376(9746):1074-84. PM:20870099

32. Hobson RW, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. New England Journal of Medicine 1993 Jan 28;328(4):221-27. PM:8418401

33. Anderson DC, Kappelle LJ, Eliasziw M, et al. Occurrence of hemispheric and retinal ischemia in atrial fibrillation compared with carotid stenosis. Stroke 2002 Aug;33(8):1963-67. PM:12154246

34. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. New England Journal of Medicine 2000 Jun 8;342(23):1693-700. PM:10841871

35. AbuRahma AF, Cook CC, Metz MJ, et al. Natural history of carotid artery stenosis contralateral to endarterectomy: results from two randomized prospective trials. Journal of Vascular Surgery 2003 Dec;38(6):1154-61.

36. Abbott AL, Chambers BR, Stork JL, et al. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. Stroke 2005 Jun;36(6):1128-33. PM:15879327

37. AbuRahma AF, Metz MJ, Robinson PA. Natural history of > or =60% asymptomatic carotid stenosis in patients with contralateral carotid occlusion. Annals of Surgery 2003;238(4):551-61.

38. Ballotta E, Da GG, Meneghetti G, et al. Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: a 10-year prospective study. Journal of Vascular Surgery 2007 Mar;45(3):516-22. PM: 17275244

39. Bogousslavsky J, Despland PA, Regli F. Asymptomatic tight stenosis of the internal carotid artery: long-term prognosis. Neurology 1986 Jun;36(6):861-63. PM:3703297

40. Goessens BM, Visseren FL, Kappelle LJ, et al. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. Stroke 2007 May;38(5):1470-75. PM:17363718

41. Gronholdt ML, Nordestgaard BG, Schroeder TV, et al. Ultrasonic echolucent carotid plaques predict future strokes. Circulation 2001 Jul 3;104(1):68-73. PM:11435340

42. Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive factor of stroke in asymptomatic patients? Stroke 1996 Dec;27(12):2188-90. PM:8969778

43. Johnson JM, Kennelly MM, DeCesare D, et al. Natural history of asymptomatic carotid plaque. Archives of Surgery 1985 Sep;120(9):1010-12. PM:3896195

44. Johnson BF, Verlato F, Bergelin RO, et al. Clinical outcome in patients with mild and moderate carotid artery stenosis. Journal of Vascular Surgery 1995 Jan;21(1):120-26. PM:7823350

45. Levien LJ, Fritz VU, Lithgow-Jolly P. The natural history of asymptomatic carotid disease. A preliminary report. S Afr J Surg 1984 Nov;22(4):249-53. PM:6523303

46. Liapis CD, Kakisis JD, Kostakis AG. Carotid stenosis: factors affecting symptomatology. Stroke 2001 Dec 1;32(12):2782-86. PM:11739973

47. Mackey AE, Abrahamowicz M, Langlois Y, et al. Outcome of asymptomatic patients with carotid disease. Asymptomatic Cervical Bruit Study Group. Neurology 1997 Apr;48(4):896-903. PM:9109874

48. Mansour MA, Littooy FN, Watson WC, et al. Outcome of moderate carotid artery stenosis in patients who are asymptomatic. J Vasc Surg 1999 Feb;29(2):217-25. PM:9950980

49. Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010 Jul;9(7):663-71. PM:20554250

50. Marquardt L, Geraghty OC, Mehta Z, et al. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke 2010 Jan;41(1):e11-e17. PM:19926843

51. Kakkos SK, Nicolaides A, Griffin M, et al. Factors associated with mortality in patients with asymptomatic carotid stenosis: results from the ACSRS Study. International Angiology 2005 Sep;24(3):221-30. PM:16158030

52. Nicolaides AN, Kakkos SK, Griffin M, et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. European Journal of Vascular & Endovascular Surgery 2005 Sep;30(3):275-84.

53. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000 Apr 26;283(16):2122-27. PM:10791504

54. Spence JD, Tamayo A, Lownie SP, et al. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. Stroke 2005 Nov;36(11):2373-78. PM:16224084

55. Spence JD, Coates V, Li H, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Archives of Neurology 2010 Feb;67(2):180-86. PM:20008646

56. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke 2006 Mar;37(3):818-23. PM:16469957

57. Longstreth WT, Jr., Shemanski L, Lefkowitz D, et al. Asymptomatic internal carotid artery stenosis defined by ultrasound and the risk of subsequent stroke in the elderly. The Cardiovascular Health Study. Stroke 1998 Nov;29(11):2371-76. PM:9804651

58. Zhang C, Qu S, Li H, et al. Microembolic signals and carotid plaque characteristics in patients with asymptomatic carotid stenosis. Scand Cardiovasc J 2009;43(5):345-51. PM:19863395

59. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Asymptomatic Carotid Endarterectomy Study Group. Mayo Clin Proc 1992 Jun;67(6):513-18. PM:1434877

60. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. The CASANOVA Study Group. Stroke 1991 Oct;22(10):1229-35. PM: 1926232

61. Aichner FT, Topakian R, Alberts MJ, et al. High cardiovascular event rates in patients with asymptomatic carotid stenosis: the REACH Registry. European Journal of Neurology 2009 Aug;16(8):902-08.

62. Satiani B, Porter RM, Jr. The influence of contralateral disease on the natural history of nonoperated significant carotid stenosis. Ann Vasc Surg 1990 Jul;4(4):313-17. PM:2364044

63. Langsfeld M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. Journal of Vascular Surgery 1989 Apr;9(4):548-57. PM:2651727

64. Satiani B, Chen TY, Shook L, et al. Contralateral disease progression after carotid endarterectomy. Surgery 1993 Jul;114(1):46-51. PM:8356526

65. Takahashi W, Ohnuki T, Ide M, et al. Stroke risk of asymptomatic intra- and extracranial large-artery disease in apparently healthy adults. Cerebrovasc Dis 2006;22(4):263-70. PM:16788300

66. Siebler M, Nachtmann A, Sitzer M, et al. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. Stroke 1995 Nov;26(11):2184-86. PM:7482670

67. Hennerici M, Hulsbomer HB, Hefter H, et al. Natural history of asymptomatic extracranial arterial disease. Results of a long-term prospective study. Brain 1987 Jun;110(Pt 3):777-91. PM:3580834

68. Norris JW, Zhu CZ, Bornstein NM, et al. Vascular risks of asymptomatic carotid stenosis. Stroke 1991 Dec;22(12):1485-90. PM:1962321

69. Bock RW, Gray-Weale AC, Mock PA, et al. The natural history of asymptomatic carotid artery disease. J Vasc Surg 1993 Jan;17(1):160-69. PM:8421333

70. Ellis MR, Franks PJ, Cuming R, et al. Prevalence, progression and natural history of asymptomatic carotid stenosis: is there a place for carotid endarterectomy? European Journal of Vascular Surgery 1992 Mar;6(2):172-77. PM:1572457

71. Sabeti S, Schlager O, Exner M, et al. Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. Stroke 2007 Nov;38(11):2887-94. PM:17885257

72. Dick P, Sherif C, Sabeti S, et al. Gender differences in outcome of conservatively treated patients with asymptomatic high grade carotid stenosis. Stroke 2005 Jun;36(6):1178-83. PM:15890998

73. Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics 2001 Dec;2(4):463-71. PM:12933636

74. Libman RB, Sacco RL, Shi T, et al. Outcome after carotid endarterectomy for asymptomatic carotid stenosis. Surgical Neurology 1994 Jun;41(6):443-49. PM:8059320

75. Hertzer NR, Flanagan RA, Jr., Beven EG, et al. Surgical versus nonoperative treatment of asymptomatic carotid stenosis. 290 patients documented by intravenous angiography. Annals of Surgery 1986 Aug;204(2):163-71. PM:3527089

76. Poulias GE, Doundoulakis N, Skoutas B, et al. Carotid artery surgery and the principle of prophylaxis: recurrence in operated and nonoperated patients. Cardiovascular Surgery 1994 Oct;2(5):586-91. PM:7820518

77. Caracci BF, Zukowski AJ, Hurley JJ, et al. Asymptomatic severe carotid stenosis. Journal of Vascular Surgery 1989 Feb;9(2):361-66. PM:2645445

78. Bosiers M, Peeters P, Deloose K, et al. Selection of treatment for patients with carotid artery disease: medication, carotid endarterectomy, or carotid artery stenting. Vascular 2005 Mar;13(2):92-97. PM:15996363

79. Ogata T, Yasaka M, Wakugawa Y, et al. Long-term results of medical and surgical therapy for Japanese patients with moderate carotid stenosis. J Stroke Cerebrovasc Dis 2012 Jan;21(1):24-29. PM:20851631

80. Sherif C, Dick P, Sabeti S, et al. Neurological outcome of conservative versus endovascular treatment of patients with asymptomatic high-grade carotid artery stenosis: a propensity score-adjusted analysis. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists 2005 Apr;12(2):145-55. PM:15823061

81. Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. New England Journal of Medicine 2010 Jul 1;363(1):11-23. PM:20505173

82. Silver FL, Mackey A, Clark WM, et al. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2011 Mar;42(3):675-80. PM:21307169

83. Howard VJ, Lutsep HL, Mackey A, et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol 2011 Jun;10(6):530-37. PM:21550314

84. Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. New England Journal of Medicine 2008 Apr 10;358(15):1572-79. PM:18403765

85. Brooks WH, McClure RR, Jones MR, et al. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. Neurosurgery 2004 May;54(2):318-24. PM:14744277

86. CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. Journal of Vascular Surgery 2005 Aug;42(2):213-19. PM:16102616

87. Zarins CK, White RA, Diethrich EB, et al. Carotid revascularization using endarterectomy or stenting systems (CaRESS): 4-year outcomes. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists 2009 Aug;16(4):397-409. PM:19702339

88. Marine LA, Rubin BG, Reddy R, et al. Treatment of asymptomatic carotid artery disease: similar early outcomes after carotid stenting for high-risk patients and endarterectomy for standard-risk patients. Journal of Vascular Surgery 2006 May;43(5):953-58. PM:16678689

89. McPhee JT, Hill JS, Ciocca RG, et al. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. Journal of Vascular Surgery 2007 Dec;46(6):1112-18. PM:18154987

90. McPhee JT, Schanzer A, Messina LM, et al. Carotid artery stenting has increased rates of postprocedure stroke, death, and resource utilization than does carotid endarterectomy in the United States, 2005. Journal of Vascular Surgery 2008 Dec;48(6):1442-50. PM:18829236

91. Sidawy AN, Zwolak RM, White RA, et al. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. Journal of Vascular Surgery 2009 Jan;49(1):71-79. PM:19028045

92. Giacovelli JK, Egorova N, Dayal R, et al. Outcomes of carotid stenting compared with endarterectomy are equivalent in asymptomatic patients and inferior in symptomatic patients. J Vasc Surg 2010 Oct;52(4):906-13, 913. PM:20620010

93. De RP, Parlani G, Verzini F, et al. Long-term prevention of stroke: a modern comparison of current carotid stenting and carotid endarterectomy. Journal of the American College of Cardiology 2011 Feb 8;57(6):664-71. PM:21292127

94. Bangalore S, Bhatt DL, Rother J, et al. Late outcomes after carotid artery stenting versus carotid endarterectomy: insights from a propensity-matched analysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2010 Sep 14;122(11):1091-100. PM:20805431

95. Lindstrom D, Jonsson M, Formgren J, et al. Outcome after 7 years of carotid artery stenting and endarterectomy in Sweden - single centre and national results. Eur J Vasc Endovasc Surg 2012 May;43(5):499-503. PM:22342694

96. Soonawala D, Middelburg RA, Egger M, et al. Efficacy of experimental treatments compared with standard treatments in non-inferiority trials: a meta-analysis of randomized controlled trials. Int J Epidemiol 2010 Dec;39(6):1567-81. PM:20837637

97. FDA Presentation. Circulatory System Devices Panel Meeting. 2004. Accessed on June 14, 2012. Available at: www.fda.gov/ohrms/dockets/ac/04/briefing/4033b1.htm

98. Meschia JF, Brott TG, Chukwudelunzu FE, et al. Verifying the stroke-free phenotype by structured telephone interview. Stroke 2000 May;31(5):1076-80. PM:10797168

99. Rothwell PM. Can overall results of clinical trials be applied to all patients? Lancet 1995 Jun 24;345(8965):1616-19. PM:7783541

100. Bangalore S, Kumar S, Wetterslev J, et al. Carotid Artery Stenting vs Carotid Endarterectomy: Meta-analysis and Diversity-Adjusted Trial Sequential Analysis of Randomized Trials. Arch Neurol 2010 Oct 11 PM:20937941

101. Hirt LS. Progression Rate and Ipsilateral Neurological Events in Asymptomatic Carotid Stenosis. Stroke 2011 Jul 28 PM:21799164

Appendix A. Search Strategy

Searches	Results
exp cohort studies/ or exp prospective studies/ or exp retrospective studies/ or exp epidemiologic studies/ or exp case-control studies/	1330225
(cohort or retrospective or prospective or longitudinal or observational or follow-up or followup or registry).af.	1597416
case-control.af. or (case adj10 control).tw.	150635
ep.fs.	950004
randomized controlled trial.pt.	572821
controlled clinical trial.pt.	160840
randomized controlled trials/	73473
Random Allocation/	89432
Double-blind Method/	196453
Single-Blind Method/	23183
clinical trial.pt.	737920
Clinical Trials.mp. or exp Clinical Trials/	275390
(clinic$ adj25 trial$).tw.	228819
((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.	221671
Placebos/	48502
placebo$.tw.	233236
random$.tw.	762140
trial$.tw.	592575
(randomized control trial or clinical control trial).sd.	233432
(latin adj square).tw.	3570
Comparative Study.tw. or Comparative Study.pt.	1632454
exp Evaluation studies/	137267
Follow-Up Studies/	440231
Prospective Studies/	336648
(control$ or prospectiv$ or volunteer$).tw.	2488706
Cross-Over Studies/	46589
or/5-26	4945677
carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis.mp. [mp=ti, ot, ab, nm, hw, ui, sh, kw]	28040
carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/	40463
constriction, pathologic/	16579
29 and 30	793
(carotid adj5 (stenosis or thrombo$ or disease$ or narrow$ or plaque$ or arterioscler$ or atheroscler$ or narrowing$ or bruit or asymptomatic or silent or lesion$)).tw.	17408
28 or 31 or 32	33069

angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/	18077
Balloon Dilatation/	13112
Stents/	38010
(angioplasty or stent$ or endovascular).tw.	80476
(balloon adj5 (dilat$ or catheter$)).tw.	12185
((endoluminal or transluminal or percutaneous) adj5 (repair$ or intervention)).tw.	11054
34 or 35 or 36 or 37 or 38 or 39	110461
endarterectomy/	5915
endarterectomy, carotid/	5760
(carotid adj5 endarterectomy).tw.	7671
1 or 2 or 3 or 4	2400448
33 and 44	10313
limit 45 to yr="2008 -Current"	1773
remove duplicates from 46	1610
41 or 42 or 43	13458
40 or 48	121379
33 and 49	10357
27 and 50	5298
47 or 51	6475
remove duplicates from 51	4876
47 or 53	6053

Appendix B. Carotid stenosis data extraction form

Appendix B.1. Medical therapy alone extraction form

Author, Year		**Study Name**		**Intervention 1**	
PMID*		**RefID**			
Key Question(s)					
Design †					
Extractor				**Comments**	

* or Cochrane number

† RCT; Randomized; NRCS, prospective; NRCS, retrospective; Cohort, prospective; Cohort, retrospective

B. ELIGIBILITY CRITERIA AND OTHER CHARACTERISTICS

Inclusion	Exclusion	Did patients refuse and were considered ineligible for other Tx? (If yes, list the other Tx)	Enrollment Years	Multicenter?	Country	Funding source	Definition of asymptomatic disease *	Description of the diagnostic modality#	Comments

***** Describe 1) % stenosis 2) how stenosis was diagnosed (imaging modality, measurement method NASCET - ECST) 3) Whether patients were stroke free or not (if not, what was the duration since stroke)

Describe: ICAVL lab, central reading of imaging, 1 or multiple readers, prevalidated Ultrasound lab, reported diagnostic accuracy, confirmatory imaging technique (CTA, MRA, angiography)

C. DESCRIPTION OF INTERVENTIONS (per study protocol) *

Medical Tx										
Anti-PLTs	**Dual Anti-PLT**	**Statins (or other antilipids)**	**Anti-HT**	**Anti-coagulants**	**Lifestyle modification**	**Smoking cessation**	**Exercise**	**Diet**	**Other**	**Comments**

***** Please provide summary statistics for each intervention. If the intervention is mentioned but no summary statistics are provided, then only list intervention. If intervention is not mentioned, use "nd"

D. BASELINE CHARACTERISTICS:

AuthorYear Country PMID	N enrolled (analyzed)	Male, %	Age, y	% age >80 y	HTN, %	AFib/AFlutter, %	% hyper-lipidemia	DM, %	Smokers, % (define)	% CAD	% PVD	% previous TIA	% previous CEA	%≥70% stenosis	% contralateral occlusion	% previous CAS

* Mean±SD. If median, SE, range, IQR, or other, specify these.

Only one of the two rows (CEA or CAS) will be filled for each of these variables.

E. OUTCOMES (all outcomes listed should match one-for-one with outcomes in results sections)

	Specific Outcome	Composite?	Primary outcome?	Definition of Outcome	FU duration	Baseline screening	FU screening, Timepoints	Assessment by Neurologist (Y/N?)
1								
2								
3								
4								

Specific outcomes:
Composite outcomes: **(any stroke, MI, death: <30 days; ipsilateral stroke >31 days), (any stroke: <30 days; ipsilateral stroke >31 days), (any stroke, death: <30 days; ipsilateral stroke >31 days), (any adverse event:<30 days), (any stroke, MI, death: <30 days), (any stroke, death: <30 days).**
Separate outcomes: **Major stroke, Major ipsilateral stroke, Major nonipsilateral stroke, Minor stroke, Minor ipsilateral stroke, Minor nonipsilateral stroke, Death, Cardiac Death, Neurological Death, Other cause of Death, Referral to CEA or CAS, MI, STEMI, Non-STEMI, Fatal MI,**

E2. Definitions of components of outcomes:

Stroke	
TIA (time or tissue based definition?)	
major stroke	
MI	
Referral to CEA or CAS	
Restenosis	
other	

F. RESULTS (other reporting)

Author, Year Country PMID	Outcome	Intervention	Follow-up in person-years (raw data)	Events (raw data)	Annual Rate as per Raw Data *	Follow-up in person-years (Kaplan Meier estimates)	Events (Kaplan Meier estimates)	Annual Rate as per Kaplan Meier estimates	Quality	Quality issues

* Annualized rate of (No of events/ person-years of follow-up)

Comments on Results	

Author, Year Country PMID	Subgroup	Outcome	Intervention	Follow-up in person-years (raw data)	Events (raw data)	Annual Rate as per Raw Data *	Follow-up in person-years (Kaplan Meier estimates)	Events (Kaplan Meier estimates)	Annual Rate as per Kaplan Meier estimates	Quality	Quality issues

G. QUALITY

Study objectives and hypothesis clearly stated? (y/n)	Were inclusion / exclusion Criteria Clear? (y/n)	Consecutive Patients? (y/n/nd)	Was Selection Bias Likely (if yes, explain below)? * (y/n)	Were Interventions Adequately Described? (y/n)	Were the Outcomes Fully Defined? (y/n)	Power calculations described? (y/n/NA)	Dropout rate / Crossover to CEA rate >20%? (y/n/nd/NA)	Outcome ascertainment by neurologist (y/n) (if no, explain below)?	Diagnostic imaging quality characteristics present? (Y/n/nd)	Clear population Description with No Discrepancies (y/n)	Clear Reporting of Results with No Discrepancies (y/n)
Other Issues:											
Overall Quality (A, B, C)											

* Common source of selection bias: non consecutive patients, population of patients deemed eligible for CEA or CAS, population of patients self-selected for medical Tx

H. SUMMARY OF THE STUDY IN NARRATIVE FORM

Appendix B.2. Comparative studies extraction form.

Author, Year		**Study Name**		**Intervention 1**	
PMID*		**RefID**		**Intervention 2**	
Key Question(s)				**Intervention 3**	
Design †				**Control**	
Extractor				**Comments**	

* or Cochrane number

† RCT; Randomized; NRCS, prospective; NRCS, retrospective; Cohort, prospective; Cohort, retrospective

B. ELIGIBILITY CRITERIA AND OTHER CHARACTERISTICS

Inclusion	**Exclusion**	**Eligibility criteria same for both arms? (describe differences)**	**Was risk for CEA determined by study? (Y/N/nd/NA)**	**High Risk for CEA? (Y/N/nd/NA)**	**Angiographic/ Medical / Neurologic high risk?**	**Definition of asymptomatic disease***	**Description of the diagnostic modality#**	**Enrollment Years**	**Multicenter?**	**Country**
Funding source	**Certification of Surgeons**	**Certification of Interventionists**	**High volume center (y/n/nd/NA)**	Comments						

***** Describe 1) % stenosis 2) how stenosis was diagnosed (imaging modality, measurement method NASCET - ECST) 3) Whether patients were stroke free or not (if not, what was the duration since stroke)

Describe: ICAVL lab, central reading of imaging, 1 or multiple readers, prevalidated Ultrasound lab, reported diagnostic accuracy, confirmatory imaging technique (CTA, MRA, angiography)

C. DESCRIPTION OF INTERVENTIONS (per study protocol)

CEA										
Selective shunt?	Patch?	Eversion CEA?	Conc Medical Tx before	Conc Medical Tx during	General Anesthesia?	Conc Medical Tx after	Continuation of medical Tx for >30 days?	Any Anti-PLT (Y/N)	Dual Anti-PLT (Y/N)	Comments
CAS										
Commercial Name	Stent Description (Material, Covered vs noncovered?, Drug-eluting?, Diameter?, Length?)	Embolic-Protection Device Y/N (Commercial Name)	Conc Medical Tx before	Conc Medical Tx during		Conc Medical Tx after	Continuation of medical Tx for >30 days?	Any Anti-PLT (Y/N)	Dual Anti-PLT (Y/N)	Comments
Medical Tx										
Anti-PLTs	Dual Anti-PLT	Statins (or other LLT)	Anti-HT	Anti-coagulants	Lifestyle modification	Smoking cessation	Exercise	Diet	Other	Comments

D. OUTCOMES (all outcomes listed should match one-for-one with outcomes in results sections)

	Outcome Category*	Specific Outcome	Composite?	Primary outcome?	Definition of outcome (if needed)	FU duration	Baseline screening	FU screening, Timepoints	Assessment by Neurologist (Y/N?)
1									
2									
3									
4									

* **peri-procedural** (<30 days from intervention); **efficacy** (>31 days from intervention), **other adverse event or complication** (>31 days from intervention or anytime in medical Tx arm)

Specific outcomes:

Composite outcomes: **(any stroke, MI, death: <30 days; ipsilateral stroke >31 days), (any stroke: <30 days; ipsilateral stroke >31 days), (any stroke, death: <30 days; ipsilateral stroke >31 days), (any adverse event:<30 days), (any stroke, MI, death: <30 days), (any stroke, death: <30 days), (vascular death, stroke, MI)**

Separate outcomes: **Major stroke, Major ipsilateral stroke, Major nonipsilateral stroke, Minor stroke, Minor ipsilateral stroke, Minor nonipsilateral stroke, Death, Cardiac Death, Neurological Death, Other cause of Death, Target vessel revascularization, MI, STEMI, Non-STEMI, Fatal MI, Cranial Nerve Palsy, Complications at the surgical site or the vascular access site, Hyperperfusion syndrome**

Please add a footnote when an outcome is specifically defined (e.g. MI, major stroke, time-or tissue based TIA definition)

E. BASELINE CHARACTERISTICS:

Author Year Country PMID	Group	N enrolled (analyzed)	Male, %	Age, y	% age >80 y	HTN, %	AFib/AFlutter, %	% hyper-lipidemia	DM, %	Smokers, % (define)	% CAD	% PVD	% previous TIA	% previous CEA	%≥70% stenosis	% contralateral occlusion	% previous CAS

* Mean±SD. If median, SE, range, IQR, or other, specify these.

F. RESULTS (dichotomized or categorical outcomes) **If a value is calculated by us (not reported), highlight yellow**

Leave an empty row between outcomes data

Author, Year Country PMID	Outcome	Tx	Cx	N_Tx	N_Cx	Follow-up (y)	n Event_Tx	n Event_Cx	Unadjusted (reported)						Adjusted (reported)					
									Metric*	Result	LCL	UCL	SE	P btw	Result	LCL	UCL	SE	P btw	Adjusted for:

* RR, OR, HR, RD

G. RESULTS (other reporting)

Author, Year Country PMID	Outcome		Intervention	Follow-up	Results

H. RESULTS FOR ANNUAL RATE OF EVENTS IN MEDICAL ARMS ONLY

Author, Year Country PMID	Outcome	Intervention	Follow-up in person-years (raw data)	Events (raw data)	Annual Rate as per Raw Data *	Follow-up in person-years (Kaplan Meier estimates)	Events (Kaplan Meier estimates)	Annual Rate as per Kaplan Meier estimates	Quality	Quality issues

Comments on Results	

I. REASONS FOR TREATMENT DISCONTINUATION or DROPOUT or LACK OF COMPLIANCE

Intervention	% Dropout	Reasons

SUBGROUPS: Eg, Subgroups = male/female; age group (<50, 50-70, >70); ….

J. SUBGROUP RESULTS (dichotomized or categorical outcomes)

Author, Year Country PMID	Subgroup	Outcome	Tx	Cx	N_Tx	N_Cx	Follow-up (y)	n Event_Tx	n Event_Cx	Unadjusted (reported)						Adjusted (reported)					
										Metric*	Result	LCL	UCL	SE	P btw	Result	LCL	UCL	SE	P btw	Adjusted for:

* RR, OR, HR, RD

K. ADVERSE EVENTS (Any)

Author, Year Country UI	Adverse Event	Follow-up	Intervention	Intervention	Intervention	Intervention

L. QUALITY (y/n/nd/NA)

RCT (y/n)	Appropriate Randomization Technique (y/n/nd/NA) By symptoms?	Allocation Concealment (y/n/nd/NA)	Dropout Rate <20% (y/n)	Blinded Patient (y/n/nd)	Blinded Outcome Assessment (y/n/nd)	Intention to Treat Analysis (y/n/nd)	Appropriate Statistical Analysis (y/n)	If Multicenter, Was this accounted for in analysis? (y/n/NA)	Were Potential Confounders Properly Accounted For? (y/n/nd/NA)	Clear Reporting with No Discrepancies (y/n)

	Were Eligibility Criteria Clear? (y/n)	Was Selection Bias Likely (if yes, explain below)? (y/n)	Were Interventions Adequately Described? (y/n)	Were the Outcomes Fully Defined? (y/n)	Did the Analyses Account for Compliance? (y/n/NA)	Any cross-over before start of intervention?	Any cross-over during intervention?	Training/certification well outlined	Baseline imbalance between groups	Device/surgical modifications?

Reasons for drop-outs:	
Other Issues:	
Overall Quality (A, B, C)	?

*nonrandomized cannot be A, retrospective study is always C

M. SPECIFIC COMMENTS CONCERNING THE STUDY

Comments

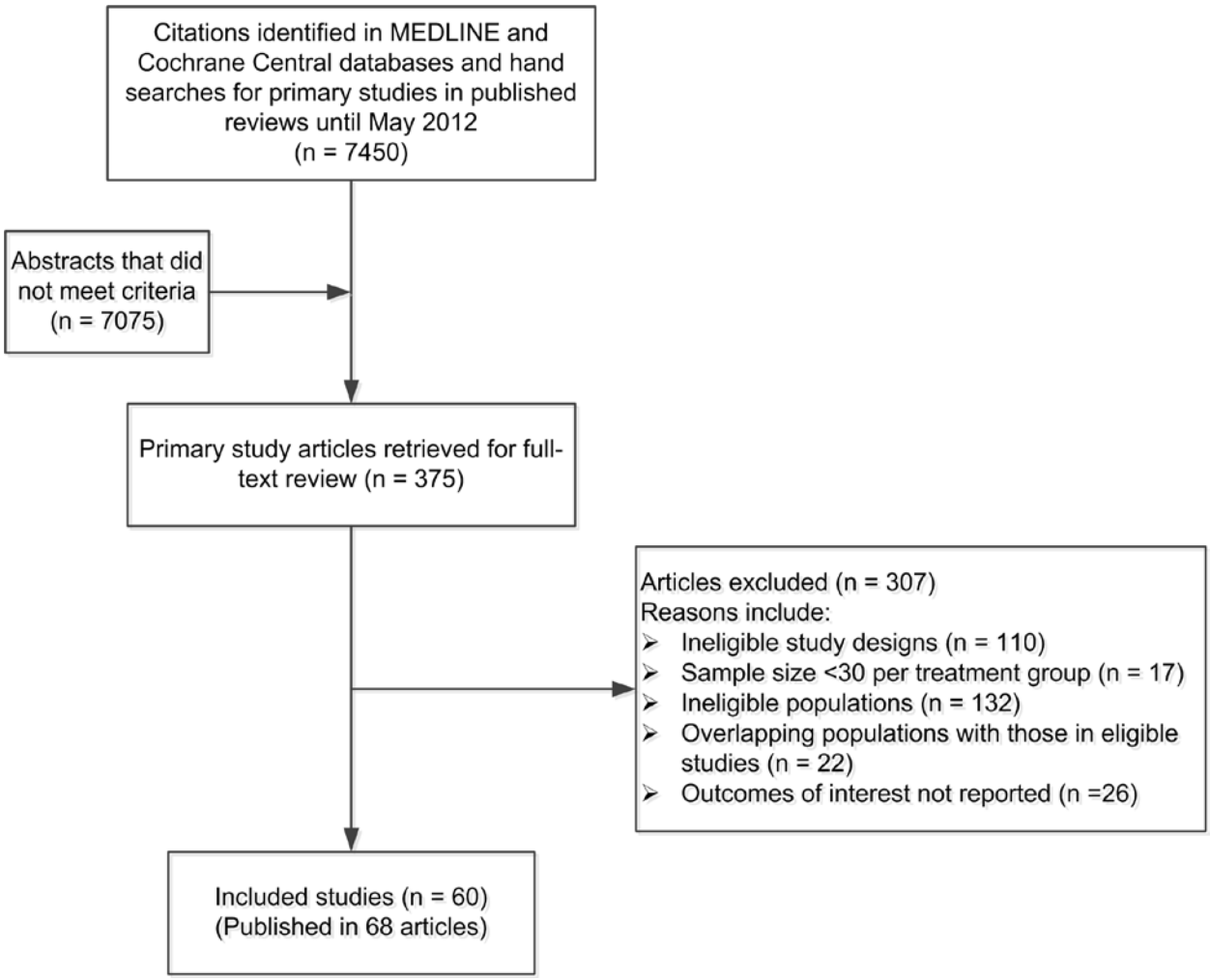
N. Summary Table (Intervention _____ vs. Control ____)

Author, Year Country PMID	Total (n)	Intervention (n)	Control (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥70% stenosis	Followup (y)	Outcome	Metric*	Result	95% CI	P btw	Study quality

Table O. Conditions potentially associated with increased risk for periprocedural adverse events from CEA

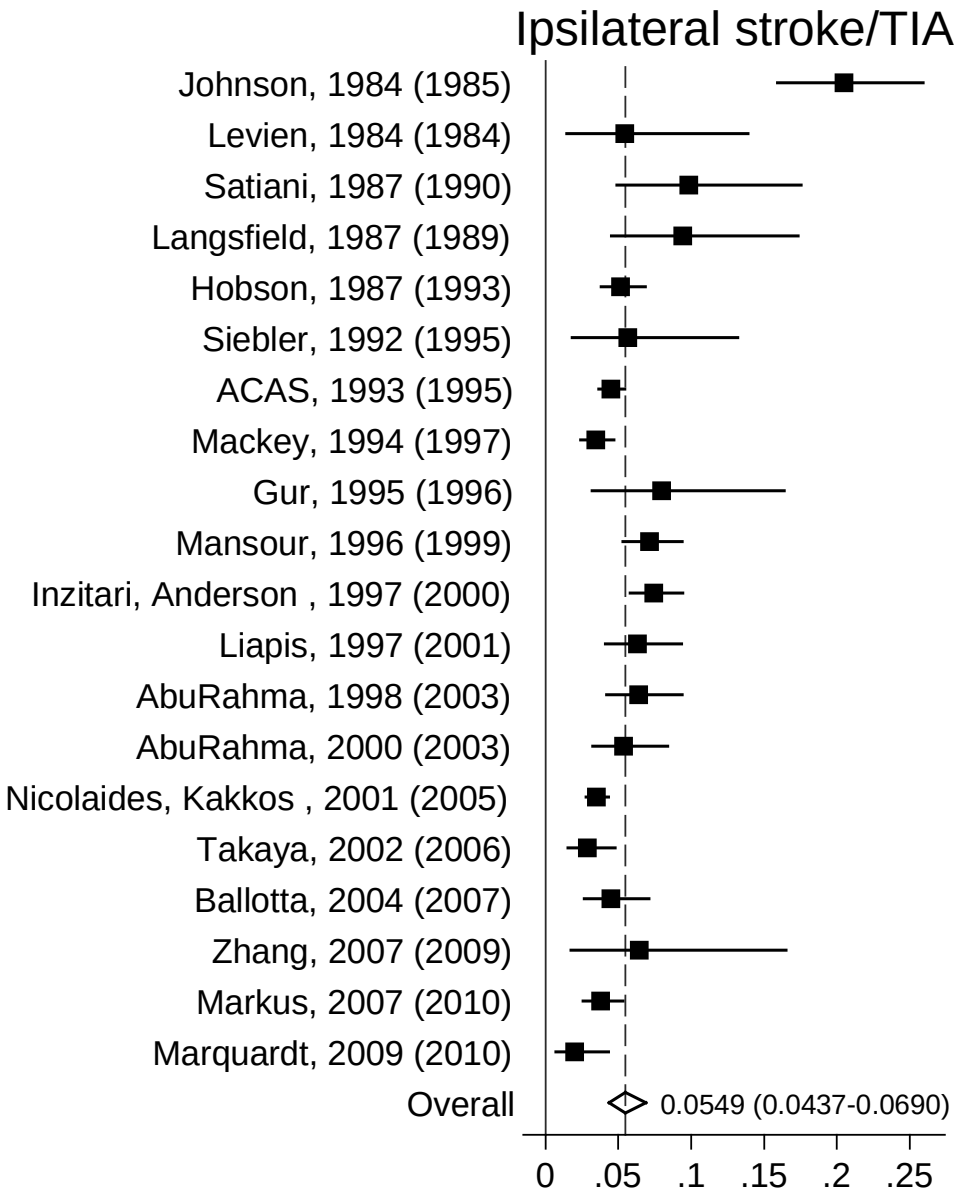
Condition	Type of Condition
Contralateral occlusion	Angiographic
Contralateral stenosis >50percent	Angiographic
Stenosis of ipsilateral internal carotid siphon	Angiographic
Previous CEA with recurrent stenosis	Angiographic
Prior radiation treatment to the neck	Angiographic
Bifurcation of carotid artery at the level of C2 in conjunction with short neck	Angiographic
Atrial fibrillation	Medical
Age >80 years old	Medical
Left ventricular ejection fraction<30 percent	Medical
Unstable angina	Medical
Recent MI	Medical
Severe obesity	Medical
Emergency CEA	Neurologic
Preoperative ipsilateral stroke	Neurologic
Stroke as an indication for CEA	Neurologic
Crescendo transient ischemic attack /stroke	Neurologic
Cerebral events *versus* ocular events	Neurologic
History of transient ischemic attack /stroke in the prior 6 months (contralaterally)	Neurologic

Appendix C. Study Flow Diagram

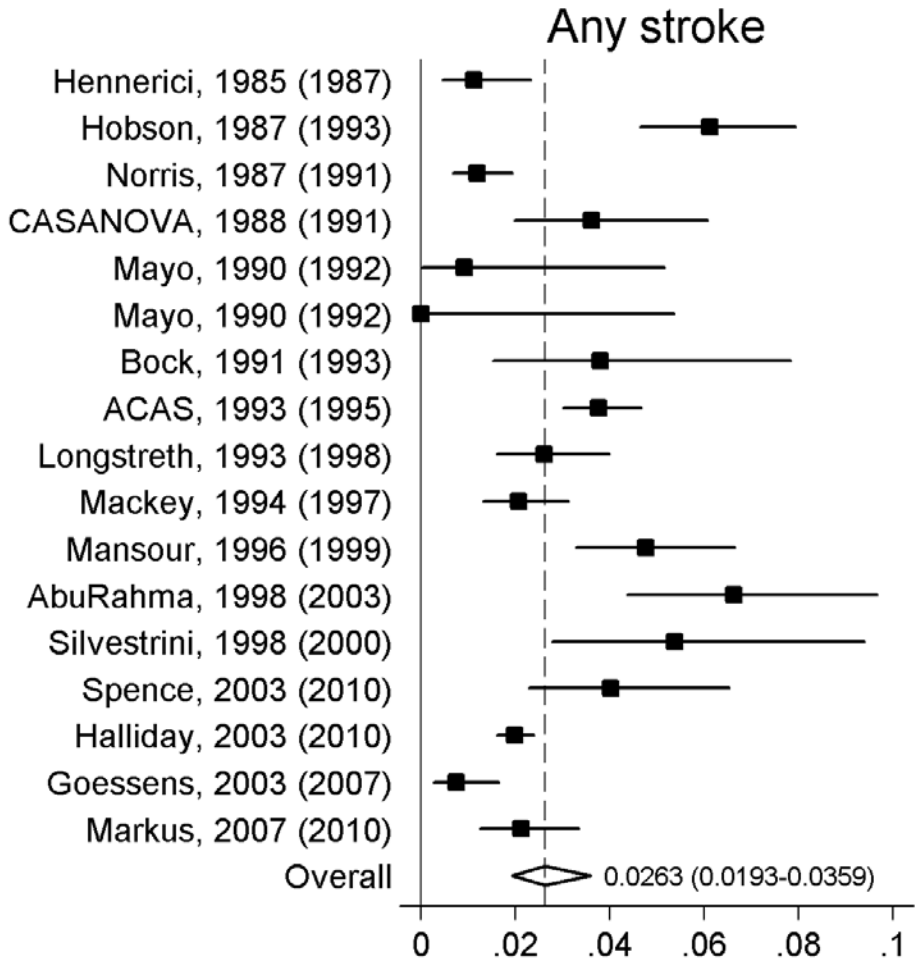


Appendix D. Forest plot of medical therapy alone studies

Appendix D. Figure 1. Forest plot of the meta-analysis of incidence rates of ipsilateral stroke or TIA in medical treatment studies.
The studies are ordered by the last year of recruitment in each study. Year of publication is provided in parentheses.

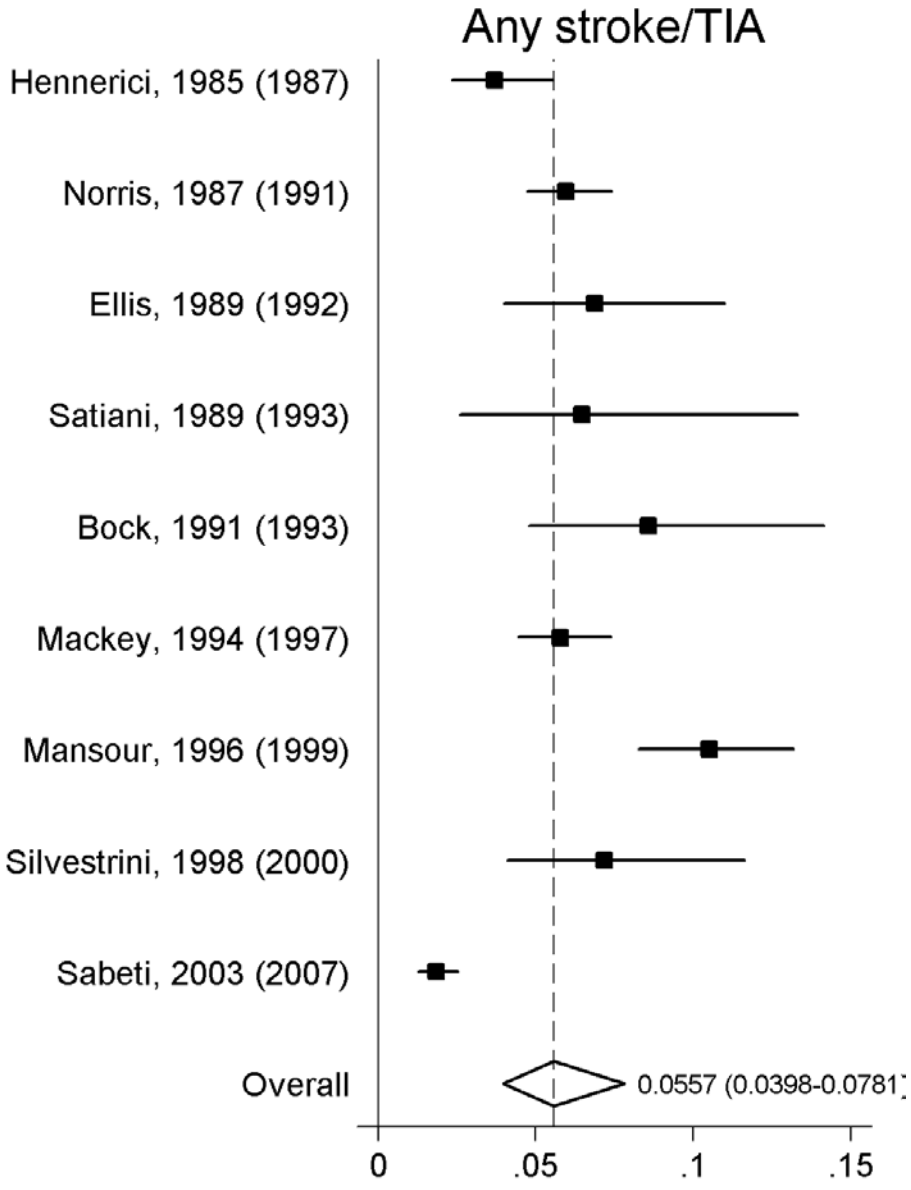


Appendix D. Figure 2. Forest plot of the meta-analysis of incidence rates of any stroke in medical treatment studies.



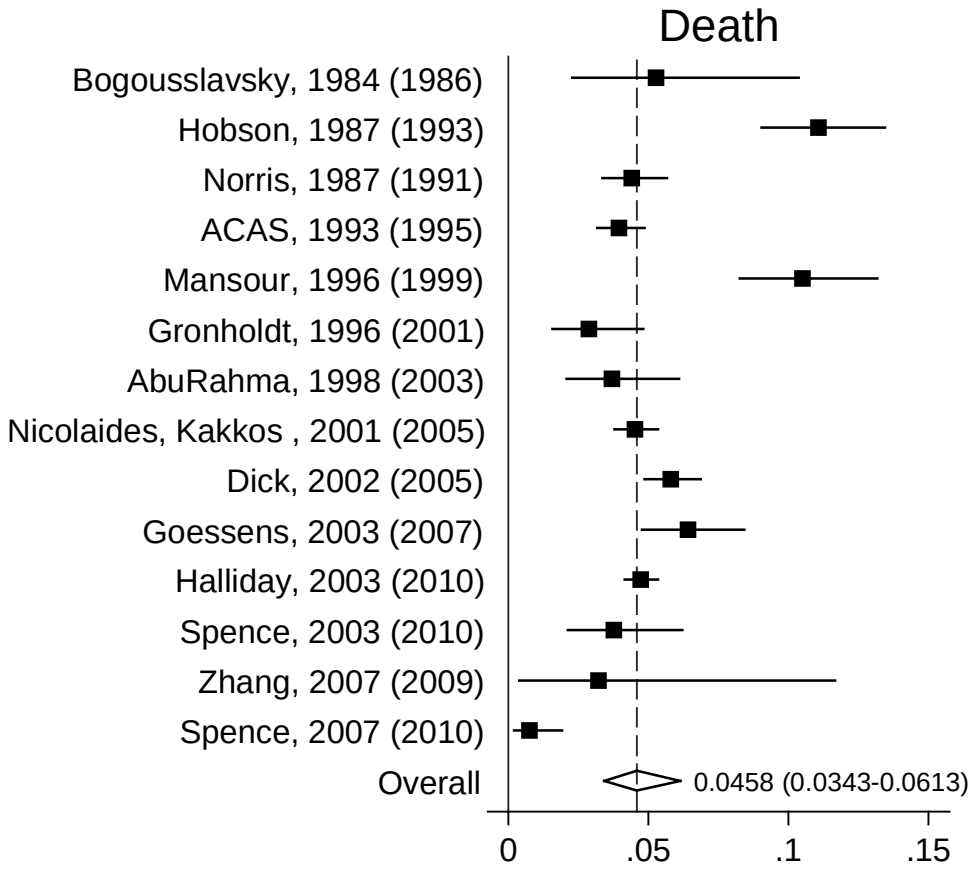
The studies are ordered by the last year of recruitment in each study. Year of publication is provided in parentheses.

Appendix D. Figure 3. Forest plot of the meta-analysis of incidence rates of any stroke or TIA in medical treatment studies.



The studies are ordered by the last year of recruitment in each study. Year of publication is provided in parentheses.

Appendix D. Figure 4. Forest plot of the meta-analysis of incidence rates of death in medical treatment studies.



The studies are ordered by the last year of recruitment in each study. Year of publication is provided in parentheses.

Appendix E. Baseline characteristics and results of included studies

Table 1. Baseline characteristics of studies of medical therapy alone

Author, Year Country PMID	Enroll yr	N	f/u (y)	% Male	Age (yr)	Degree of stenosis	Imaging	HTN (%)	Hyper - lipidemia (%)	DM (%)	Smoker * (%)	CHD (%)	Prev CEA (%)	>70% stenosis (%)	Anti-thrombotic (%)	LLT (%)	Quality
RCT																	
ACAS, 1995 USA 7723155	1987-1993	834	5.25	66	67	60-99%	DUS	64		21	24	69	19	29	100	Y; nd on coverage	A
Abbott, 2005 Australia 15879327	1996-2000	202	3	68	74	60-99%	DUS	72	67	17	14	52	0	49	93	75	A
ECST, 1995 Europe 7823712	Before 1992	127	3.5	71	64	70-99%	DSA	nd	nd	14.2	50	33	0	100	100	nd	B
Halliday, 2004, 2010 (ACST) Multicenter 15135594, 20870099	1993-2003	1560	4.4	66	68	60-99%	DUS	65	nd	nd	nd	nd	24	nd	100	82	A
Hobson, 1993 (VA) USA 8418401	1983-1987	233	9	100	64.7	50-99%	DUS DSA	64	nd	nd	91	25	0	nd	84	nd	A
Inzitari, Anderson, 2000, 2002 USA 10841871, 12154246	1988-1997	324	2.4	68	66	50-99%	DSA	60	32	22	33	36	~50%	32	95	nd	A
Prospective studies																	
AbuRahma, 2003 USA 14681599	1991-2000 (2 RCTs)	101	3.4	nd	nd	50-99%	DUS	nd	nd	nd	nd	nd	100	36[##]	nd	nd	B
AbuRahma, 2003 USA 14530726	nd	82	5	55	66	60-69%	DUS	71	49	38	59	46	0	0	100	nd	B
Aichner, 2009 Austria 19473362	nd	3164	3.2	64	71	70-99%	DUS DSA	87	74.2	37.1	18.5	54.8	0	100	90	71	C
Ballotta, 2007 Italy 17275244	1995-2004	98	2.7	62.1	71	50-69%	DUS DSA	57.1	43.1	33	67.6	44.6	100	0	100	nd	B
Bock, 1993 Australia 8421333	1985-1991	74	1	78	68.1	50-99%	DUS	59	nd	23	35	57	0	13.7[##]	27	nd	B

Author, Year Country PMID	Enroll yr	N	f/u (y)	% Male	Age (yr)	Degree of stenosis	Imaging	HTN (%)	Hyper - lipidemia (%)	DM (%)	Smoker * (%)	CHD (%)	Prev CEA (%)	>70% stenosis (%)	Anti-thrombotic (%)	LLT (%)	Quality
Bogousslavsky, 1986 Switzerland 3703297	1980-1984	38	4.1	55	60	90-99%	DUS	52.6	nd	21.1	73.7	79	0	100	100	0	C
CASANOVA, 1991 Germany 1926232	1982-1988	111	6	82.5	64.1	50-90%	DUS DSA	62	52	33	24	42	26	54	100	nd	C
Dick, 2005 Austria 15890998	1997-2002	525	4	62	73 (median)	70-99%	DUS	75	76	34	19	43	0	100	37	62	C
Ellis, 1992 UK 1572457	1985-1989	164	3.2	nd	nd	50-99%	DUS	nd	nd	nd	nd	nd	nd	nd	nd	nd	C
Goessens, 2007 The Netherlands 17363718	1996	221	4.5	73	64.5	50-99%	DUS	nd	nd	21	90	59	0	nd	63	45	A
Gronholdt, 2001 Denmark 11435340	1994-1996	111	4	53	64	50-99%	DUS	38	nd	9	56	nd	0	27[##]	nd	nd	B
Gur, 1996 Israel 8969778	1995	44	3.6	50	69	70-99%	DUS DSA	66	23	41	25	nd	nd	100	100	nd	C
Hennerici, 1987 Germany 3580834 [#]	1978-1985	235	2	59	61.8	50-99%	DUS	54	38	23		81	0	15[##]	31	0	C
Johnson, 1985 USA 7823350	1981-1984	121	4	nd		75-99%	nd	nd	nd	nd	nd	nd	0	100	0	nd	C
Johnson, 1995 USA 7823350	nd	94	2.9	62		50-79%	DUS	nd	nd	nd	nd	nd	0	nd	nd	nd	C
Langsfeld, 1989 Australia 2651727 [#]	1983-1987	225	7	83	66.5	50-99%	DUS	51	nd	nd	81	41	100	1.3[###]	nd	nd	C
Levien, 1984 South Africa 6523303	1984	50	3	nd	nd	nd	DUS	nd	nd	nd	nd	nd	0	nd	nd	nd	C
Liapis, 2001 Greece 11739973	1988-1997	136	1.8	nd	nd	nd	DUS	nd	nd	nd	nd	nd	0	31.6	nd	nd	C
Longstreth, 1998 USA 9804651	nd	184	1.5	nd	73	50-99%	DUS	nd	nd	nd	nd	nd	0	27	nd	nd	B
Mackey, 1997 Canada 9109874 [#]	1988-1994	357	3.7	40	65	50-99%	DUS	47	50	20	35	39	0	42[##]	nd	nd	B
Mansour, 1999 USA 9950980	1992-1996	344	5	100	70.6	50-79%	DUS	78	27	36	67	61	0	nd	62	nd	B

Author, Year Country PMID	Enroll yr	N	f/u (y)	% Male	Age (yr)	Degree of stenosis	Imaging	HTN (%)	Hyper - lipidemia (%)	DM (%)	Smoker [*] (%)	CHD (%)	Prev CEA (%)	>70% stenosis (%)	Anti-thrombotic (%)	LLT (%)	Quality
Markus, 2010 International 20554250	nd	467	3.1	74	71.5	70-99%	DUS	90	nd	21	61	36.9	nd [^]	40[##]	95.9	64	A
Marquardt, 2010 UK 19926843	2002-2009	101	2.1	61	71.5	50-99%	DUS	68	nd	16	75	14	nd	32	96	88	A
Mayo, 1992 USA 1434877	~1990	90	2	57.3	nd	50-99%	DUS DSA	72	62	18	73.5	40	0	nd	100	nd	B
Nicolaides, Kakkos, 2005 UK 16130207, 16158030	nd	805	3	61	70	50-99%	DUS	63	60	21	71	34	0	56	84	25	B
Norris, 1991 Canada 1962321	nd	393	2	54	65.6	50-100%	DUS	50	30	15	77	37	nd	45[###]	54	nd	C
Sabeti, 2007 Austria 17885257 [#]	2002-2003	613	3.1	63	71.8	50-99%	DUS	72	73	24.5	27	43	nd	nd	56	59	B
Satiani, 1990 USA 2364044 [#]	nd	57	3.2	44	67.6	50-99%	DUS DSA	49	nd	24	56	54	0	27[##]	nd	nd	C
Satiani, 1993 USA 8356526 [#]	nd	127	3.4	50	67.5	50-99%	DUS	nd	nd	nd	nd	nd	100	0.4[##]	nd	nd	C
Siebler, 1995 Germany 7482670	nd	64	3.6	75	65.5	70-90%	DUS	60.9		17.2	57.8	46.9	0	100	78.2		C
Silvestrini, 2000 Italy 10791504	1996-1998	94	2	79	71	70-90%	DUS	70	32	30	37	nd	0	100	100	32	B
Spence, 2005, 2010 Canada 20008646, 16224084	2000-2007	468	1.4	57.8	69.8	60-99%	DUS	75.4	50.8	18.6	18.1	33.2	nd	nd	81	13.6	A
Takahashi, 2006 Japan 16788300	1994-2001	2924	2.3	65	55	50-99%	DUS	12	5	3	nd	nd	nd	nd	0	5	C
Takaya, 2006 USA 16469957	nd	154	2	82	71.1	50-79%	DUS	75	79	25	87	44	nd	nd		64	B
Zhang, 2009 China 19863395	nd	62	1	nd	65.5	50-99%	DUS	nd	nd	nd	nd	nd	nd	30.6	nd	nd	B

[*] - Current or past smoker; [#] - Baseline values are for the overall population sample from which patients with >50% stenosis were selected; [##] - ≥ 80% stenosis; [###] - ≥ 75% stenosis; f/u = followup; HTN = Hypertension; DM = Diabetes mellitus; CHD = Coronary heart disease; PVD = Peripheral vascular disease; CEA = Carotid endarterectomy; LLT = Lipid lowring therapy, which includes statins and other drugs; [^] - In Markus 2010, the population included patients who had undergone CEA for the contralateral artery, but their numbers or proportion was not known.

Appendix E. Table 2. Baseline characteristics of RCTs of CEA versus medical therapy

Author, Year Country PMID	Group	N enrolled (analyzed)	Male, %	Age, yr	% age >80yr	HTN %	Afib/ AFlutter %	Hyper lipid emia (%)	DM %	Smokers % (define)	CAD %	PVD %	Previous TIA %	Previous CEA %	%≥70% stenosis	Contralateral occlusion %	previous CAS %
VA, 1993 US 8418401	Medical	233 (233)	100	64.7 (6.7)	nd	64	14	nd	27	49 (daily) 42 (former)	25	59	26	0	nd	33	0
	CEA+ medical	211 (211)[1]	100	64.1 (6.8)	nd	63	17	nd	30	52 (daily) 43 (former)	30	61	26	0	nd	32	0
ACAS, 1995 USA 7723155	CEA	825	66	67	0	64	nd	nd	25	28 (current)	69	nd	22	20	58 (29)[2]	10	0
	Medical	834	66	67	0	64	nd	nd	21	24 (current)	69	nd	27	19	58 (29)	9	0
ACST, 2004, 2010, Multicenter 15135594 20870099	Both (Immediate CEA vs Deferred CEA)	3120 (3120)	66	68 (40-91)	21	65	0	nd	20	nd	nd	nd	nd[3]	24	nd	9	NA

[1] 8 patients declined surgery after randomization, but were treated as ITT
[2] 29% had above 80% stenosis
[3] 12% had ipsilateral symptoms

Appendix E. Table 3. Baseline characteristics of prospective nonrandomized comparative studies of CEA vs medical therapy

Author, Year Country Design	Group	N enrolled (analyzed)	Male, %	Age yr	% age >80yr	HTN %	AFib/ Aflutter %	Hyper-lipid Emia %	DM %	Smokers % (define)	CAD %	PVD %	Previous TIA %	Previous CEA %	%≥70% stenosis	Contralateral occlusion %	Previous CAS %
CASANOVA, 1991 Germany Prospective[4]	CEA	122	83.2	64.4	nd	59	nd	48	26	29 (nd)	44	56	0	27	50	0	0
	medical	111	82.5	64.1	nd	62	nd	52	33	24 (nd)	42	50	0	26	54	0	0
Mayo, 1992 USA 1434877	CEA (RCT)	36	55.6	nd	0	64	0	44.4	19.4	66.7 (ever)	41.6	22.2	0	0	nd	0	0
	Medical (RCT)	35	60	nd	0	63	0	65.7	14.3	74.3 (ever)	40.0	22.9	0	0	nd	0	0
	CEA (NRCS)	32	81.2	nd	0	84.4	0	59.4	18.8	81.3	43.7	46.9	0	0	nd	0	0
	Medical (NRCS)	55	54.6	nd	0	80	0	58.2	21.8	72.7	40	36.4	0	0	nd	0	0

[4] Proportion applies to a larger sample

Appendix E. Table 4. Baseline characteristics of retrospective comparative studies of CEA versus medical therapy

Author, Year Country PMID	Group	N enrolled (analyzed)	Male %	Age yr	% age >80 yr	HTN %	AFib %	Hyper-lipid Emia %	DM %	Smokers % (define)	CAD %	PVD %	Previous TIA %	Previous CEA %	%≥70% stenosis	Contralateral occlusion %	Previous CAS %
Hertzer, 1986 3527089	CEA	95	66	64	nd	71	nd	nd	20	nd	nd	nd	0	nd	nd	nd	NA
	MEDICAL	195	64	67	nd	62	nd	nd	19	nd	nd	nd	0	nd	nd	nd	NA
Libman, 1994 USA 8059320	CEA	107(101)	63	66.7	nd	69	nd	20	15	75 (ever smoked)	MI = 23, angina = 20	nd	nd	36[5]	76%[6]	nd	NA
	Med	108 (106)	51	69.3	nd	52	nd	43	23	56 (ever smoked)	MI = 11, angina = 27	nd	nd	12[7]	68%[8]	nd	NA
Poulias 1994 Greece 7820518	Both	134[9]	86	58 (28 – 42)	0	23.4[10]	nd	nd	nd	nd	nd	nd	nd	nd	nd	141[11]	NA
Bosiers, 2005 15996363 Belgium	CEA	20	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	100	nd	Nd
	medical	16	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	100	nd	Nd
Caracci, 1989 USA	CEA	79	49	65	nd	49	nd	nd	nd	57	32	nd	0	0	nd	nd	NA
	Medical	62	65	60	nd	65	nd	nd	nd	65	32	nd	0	0	nd	nd	NA

[5] For the contralateral artery
[6] >80% stenosis
[7] For the contralateral artery
[8] >80% stenosis
[9] 100 operated patients and 34 unoperated patients in the asymptomatic group
[10] For the whole cohort of patients with and without symptoms (n=700)
[11] For the whole cohort of patients with and without symptoms (n=700)

Appendix E. Table 5. Results of RCTs of CEA versus medical therapy

Author, Year Country PMID	Total (n)	Intervention (n)	Control (n)	Age (yr)	Male %	CAD %	DM %	%≥70% stenosis	Followup (yr)	Outcome	Metric*	Result	95% CI	P btw	Study quality
Ipsilateral stroke															
VA, 1993 US 8418401	444	211	233	63	100	28	29	nd	3.9	Any stroke or death (30 d); ipsilateral stroke >30 d	RR	0.75	0.42, 1.35	NS	**A**
ACAS, 1995 USA, Canada 7723155	1659	825	834	67	66	69	23	58	2.7	Any stroke or death (30 d); ipsilateral stroke >30 d	RR	0.64	0.42, 0.98	0.041	A
ACST, 2004, Multicenter 15135594	3120	1560	1560	68	66	nd	20	nd	5	Any stroke or death (30 d); ipsilateral stroke >30 d	RR	0.73	0.51, 1.03	NS	A
ACST, 2010, Multicenter 20870099	3120	1560	1560	68	66	nd	20	nd	10	Any stroke or death (30 d); ipsilateral stroke >30 d	RR	0.76	0.57, 1.01	NS	A
Any stroke															
VA, 1993 US 8418401	444	211	233	63	100	28	29	nd	3.9	Any stroke or death (30 d); any stroke >30 d	RR	0.92	0.56, 1.51	NS	A
ACAS, 1995 USA, Canada 7723155	1659	825	834	67	66	69	23	58	2.7	Any stroke or death (30 d); any stroke >30 d	RR	0.71	0.51, 0.97	0.03	A
ACST, 2004, Multicenter 15135594	3120	1560	1560	68	66	nd	20	nd	5	Any stroke or death (30 d); any stroke >30 d	RR	0.63	0.48, 0.82	<0.05	A
ACST, 2010, Multicenter 20870099	3120	1560	1560	68	66	nd	20	nd	10	Any stroke or death (30 d); any stroke >30 d	RR	0.61	0.49, 0.76	<0.05	A
Any stroke or death															
VA, 1993 US 8418401	444	211	233	63	100	28	29	nd	3.9	Any stroke or death	RR	0.93	0.75, 1.16	NS	A
ACAS, 1995 USA, Canada 7723155	1659	825	834	67	66	69	23	58	2.7	any stroke or death	RR	0.81	0.65, 1.00	0.084	A
ACST, 2004, Multicenter 15135594	3120	1560	1560	68	66	nd	20	nd	5	Any stroke or death	RR	0.95	0.83, 1.09	NS	A
ACST, 2010, Multicenter 20870099	3120	1560	1560	68	66	nd	20	nd	10	Any stroke or death	RR	0.97	0.90, 1.05	NS	A
Any death															
VA, 1993 US 8418401	444	211	233	63	100	28	29	nd	3.9	Any death	RR	1.03	0.80, 1.34	NS	A
ACAS, 1995 USA, Canada 7723155	1659	825	834	67	66	69	23	58	2.7	Any death	RR	0.92	0.70, 1.22	NS	A

Author, Year Country PMID	Total (n)	Intervention (n)	Control (n)	Age (yr)	Male %	CAD %	DM %	%≥70% stenosis	Followup (yr)	Outcome	Metric*	Result	95% CI	P btw	Study quality
ACST, 2010, Multicenter 20870099	3120	1560	1560	68	66	nd	20	nd	10	Any death	RR	1.07	0.98, 1.17	NS	A
Events within 30 d randomization															
VA, 1993 US 8418401	444	211	233	63	100	28	29	nd	30 d	Stroke or death (30 d)	RR	3.68	1.03, 13.2	0.045	A
ACAS, 1995 USA, Canada 7723155	1659	825	834	67	66	69	23	58	30 d	any stroke, death: <30 days	RR	6.40	1.90, 21.55	0.003	A
Halliday, 2004, 2010, Multicenter 15135594 20870099	3120	1560	1560	68	66	nd	20	nd	30 d	Periprocedural stroke death	RR	5.03	1.10, 22.98	0.04	A

Appendix E. Table 6. Results characteristics of prospective nonrandomized studies of CEA versus medical therapy

Author, Year Country PMID	Total (n)	Intervention (n)	Control (n)	Age (yr)	Male %	CAD %	DM %	%≥70% stenosis	Followup (yr)	Outcome	Metric*	Result	95% CI	P btw	Study quality
CASANOVA, 1991 Germany 1926232	233	122	111	64.1	82.5	43	30	52	3	Any stroke and death due to surgery or stroke	RR	0.78	0.38, 1.61	0.503	B
Mayo, 1992 USA 1434877 (RCT)	71	36	35	nd	57	41	17	nd	1.96	Any stroke, TIA, death	OR	0.97	0.26, 3.58	0.966	B
										Any stroke	OR	5.83	0.30, 112.	0.243	
Mayo, 1992 USA 1434877 (NRCS)	87	32	55	nd	68.3	41.5	21	nd	1.96	Any stroke, TIA, death	OR	3.44	0.92, 12.8	0.066	B
										Any stroke	OR	6.88	0.80, 58.8	0.078	

Appendix E. Table 7. Results of retrospective nonrandomized studies of CEA versus medical therapy

Author, Year Country PMID	Total (n)	Intervention (n)	Control (n)	Age (yr)	Male %	CAD (%	DM (%)	%≥70% stenosis		Follow up (yr)	Outcome	Metric*	Result	95% CI	P btw	Study quality
Libman, 1994 USA 8059320	215	107	108	68y	57 %	MI:17%, Angina: 24%	19 %	72% [12]		0.083	Peri-procedural ipsilateral Stroke	OR	11.1	0.62, 198.33	0.102	C
											Ipsilateral stroke	OR	1.47	0.48, 4.48	0.499	
											Any stroke	OR	0.80	0.41, 1.57	0.519	
											Stroke - free survival	OR	1.17	0.98, 1.39	0.076	
Poulias 1994 Greece 7820518	134 [13]	100	34	58 (28 – 42)	86	ND	ND	ND		5.2 (0.3 – 10)	Neurological deficit	OR	0.02	0, 0.39	0.01	C
											Death	OR	0.01	0, 0.20	0.002	
Bosiers, 2005 15996363 Belgium	NRCS, retro	20	16	nd	nd	nd	nd	nd		30 days	Any stroke or death	OR	Non-estimable			C
Ogata 2012 20851631 Japan	NRCS, retro	51	42	70	nd	nd	nd	nd		nd	Any stroke	RR	0.69	0.23, 2.09		C

[12] >80% stenosis

[13] 100 operated patients and 34 unoperated patients in the asymptomatic group

Appendix E. Table 8. Baseline Characteristics of CAS versus medical therapy

Author, Year Country PMID	Group	N enrolled (analyzed)	Male %	Age yr	% age >80 yr	HTN %	AFib/ AFlutter %	Hyper-lipidemia %	DM %	Smokers, % (define)	CAD %	PVD %	Previous TIA %	Previous CEA %	%≥70% stenosis	Contralateral occlusion %	Previous CAS %
Sherif, 2005 Austria 15823061	CAS	499 (421)	68	72	nd	78	nd	77	37	17 (current)	46	49	0	0	100	15	0
	medical	616 (525)	68	73	nd	75	nd	76	34	19 (current)	43	41	0	0	100	6	0
Bosiers, 2005 15996363 Belgium	CAS	59	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	100	nd	nd
	medical	16	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	100	nd	nd

Appendix E. Table 9. Results of CAS versus Medical therapy

Study PMID	Design	Total (n)	Intervention (n)	Control (n)	Age (yr)	Male %	CAD %	DM %	%≥70% stenosis	Followup (yr)	Outcome	Metric*	Result	95% CI	P btw	Study quality
Sherif, 2005 Austria 15823061	NRCS, retro	946	421	525	73	64	44	35	100	5	Any stroke or death	HR*	0.66	0.49,0.91	0.012	B
											Any stroke	HR*	0.47	0.24,0.90	0.023	B
											Death	HR*	0.67	0.46,0.97	0.035	B
Bosiers, 2005 Belgium 15996363	NRCS, retro	75	59	16	nd	nd	nd	nd	100	30 days	Any stroke or death		Not estimable			C

CI = confidence interval, HR = hazard ratio, NRCS = non randomized comparative study, nd = no data, RR = relative risk.

* Adjusted for age (in quartiles), sex, body mass index, arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, baseline degree of stenosis, (70% to 79%, 80% to 89%, 90% to 99%), history of MI, congestive heart failure (NYHA), peripheral artery disease (Fontaine), presence of a malignancy, surgical risk assessed by the American Society of Anesthesiologists score (I to IV), use of statins and clopidogrel, and the propensity for carotid stenting.

NRCS with propensity score matching, all pts >70 percent stenosis, available subgroup results by categories of stenosis in KM curves, single CAS interventionist, robust methods of outcome ascertainment, diagnostic modality validated.

Appendix E. Table 10. Baseline characteristics of patients in the CAS versus CEA.

Author, Year Country PMID	Study Design	Group	N	Male %	Age yr	% age >80y	HTN %	AFib/ Aflutter %	% hyperlipidemia	DM, %	Smokers, % (define)	% CAD	% PVD	% previous Stroke/TIA	% previous CEA	%≥70% stenosis	% contralateral occlusion	% previous CAS
CREST 2010; 2011 USA 20505173; 21307169 21550314	RCT	CAS	594	63.8	69	nd	88.2	nd	89.7	32.6	26.1 (current)	48.6	nd	nd	nd	92.8	2.3	nd
		CEA	587	67.5	69.6	nd	87.9	nd	91.1	33.7	22.2 (current)	50.9	nd	nd	nd	91.8	2.7	nd
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	CAS	117	66.9*	72.5*	19.3*	85.5*	Nd	78.5*	25.3*	16.9* (current)	85.8*	Nd	2.8	22.6*	100	23.6*	Nd
		CEA	121	67.1*	72.6*	20.5*	85.1*	nd	76.9*	27.5*	16.4* (current)	75.5*	nd	3.9	22.2*	100	25.3*	Nd
Brooks, 2004 USA 14744277	RCT	CAS	43	Nd	66.6	Nd	82	Nd	21	16	93	81.4	Nd	Nd	Nd	100	Nd	Nd
		CEA	42	nd	69.9	nd	98	nd	21	12	88	47.6	nd	nd	nd	100	nd	Nd
CaRESS, 2005 2009, USA, 16102616 ;19702339	NRCS, prosp	CAS	99	60*	71.2*	19*	81*	Nd	64*	29*	77* (ever)	66*	45*	nd	nd	94*	nd	6*
		CEA	170	63*	71.4*	19*	81*	Nd	70*	24*	77* (ever)	61*	41*	Nd	Nd	89*	Nd	0
De Rango, 2011, Italy 21292127[s]	NRCS, prosp	CAS	816	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
		CEA	702	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Marine, 2006 1434877 USA	NRCS, retro	CAS	93	63.4	69.8	20	77.2	nd	66.9	30.3	54.5 (ever)	57.9	37.9	nd	nd	100	nd	nd
		CEA	145	61.4	69.6	18.3	91.4	nd	75.3	37.6	58.1 (ever)	74.2	33.3	nd	nd	100	nd	nd
Bosiers, 2005 15996363 Belgium	NRCS, retro	CAS	59	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	100	nd	Nd
		CEA	20	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	100	nd	Nd
McPhee, 2008 USA 18829236	NRCS, retro[†]	CAS	11302	62.9	71.6	Nd	65.7	nd	nd	26.5	nd	11.8	nd	0	nd	nd	nd	nd
		CEA	111684	57.2	71.1	nd	71.9	nd	nd	26.6	nd	11.0	nd	0	nd	nd	nd	nd
McPhee, 2007 USA 18154987	NRCS, retro[†]	CAS	12278	59.3	70.5	nd	66.7	nd	nd	25.8	nd	11.7	nd	0	nd	nd	nd	nd
		CEA	226111	56.9	71.2	nd	70.8	nd	nd	25.4	nd	11.8	nd	0	nd	nd	nd	nd
Sidawy, 2009 USA	NRCS,	CAS	1404 (805)	59.5*	70.8*	nd	81.6*	13.8*	nd	33.0*	59.3	61.4*	38.3*	nd	24.3*	nd	nd	nd

Author, Year Country PMID	Study Design	Group	N	Male %	Age yr	% age >80y	HTN %	AFib/ Aflutter %	% hyperlipidemia	DM, %	Smokers, % (define)	% CAD	% PVD	% previous Stroke/TIA	% previous CEA	%≥70% stenosis	% contralateral occlusion	% previous CAS
19028045	retro†	CEA	1877 (862)	59.7*	71.2*	nd	71.8*	11.1*	nd	26.1*	55.6*	45.7*	46.1*	nd	1.1*	nd	nd	nd
Giacovelli, 2010 USA 20620010	NRCS, retro†	CAS	4354	59.9	71.4	nd	73.8	13.7	49.4	28.5	nd	47.3	nd	nd	nd	nd	nd	nd
		CEA	4354	60.2	72.0	nd	74.3	14.3	50.5	29.8	nd	49.2	nd	nd	nd	nd	nd	Nd
Bangalore, 2010, International, 20805431	Registry, prosp	CAS	836	68.1	70	nd	86.0	13.6	78.3	41	64.0	49.5	nd	19.5	nd	nd	nd	nd
		CEA	836	66.6	69	nd	86.8	14.1	78.3	44	65.4	47.6	nd	20.0	nd	nd	nd	nd
Lindstrom, 2012, Sweden, 22342694	Registry	CAS	101	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
		CEA	1315	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; AFib/Aflutter, atrial fibrillation/ atrial flutter; PVD, peripheral vascular disease; TIA, transient ischemic attack.; nd, no data

* Proportion applies to a larger sample of patients

† Administrative dataset

§ Baseline data not available for patients with asymptomatic carotid stenosis

Appendix E. Table 11. Comparison of CAS versus CEA for the outcome of cerebrovascular events

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup	Outcome	Metric	Result	95% CI	P btw	Study quality
CREST, 2010, 2011 USA 20505173, 21307169, 21550314	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	4y	Any periprocedural stroke or postprocedural ipsilateral stroke	HR*	1.86	0.95, 3.66	0.07	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	1y	Any periprocedural stroke or ipsilateral stroke	RR†	0.77	0.27 - 2.14	0.617	B
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	3y	Any stroke	RR†	1.12	0.51 - 2.43	0.777	B
Brooks, 2004 USA 14744277	RCT	85	43	42	68.2	nd	64.5	14	100	4y	Any stroke/TIA	RR	Non-estimable‡			B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	4y	Any stroke	RR†	1.34	0.51 - 3.47	0.553	B
Bangalore, 2010, International, 20805431	Registry, prosp	1672	836	836	70	67	49	43	100	1.5y	Any stroke	HR	1.41	0.79-2.51	0.25	C
											Any Stroke/TIA	HR	1.10	0.71-1.72	0.67	

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Adjusted for age and sex
† Calculated from raw data
‡ RR cannot be estimated because no events occurred in any of the treatment arms

Appendix E. Table 12. Comparison of CAS versus CEA for the outcome of mortality

Author, Year Country PMID	Study Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup (y)	Outcome	Metric	Result	95% CI	P btw	Study quality
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	1y	Death	RR	0.47	0.18 - 1.20	0.116	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	4y	Death	RR*	1.36	0.78 - 2.35	0.273	B
Bangalore, 2010, International, 20805431	Registry, prosp	1672	836	836	70	67	49	43	100	1.5y	Death	HR	0.73	0.49 – 1.09	0.13	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Calculated from raw data

Appendix E. Table 13. Comparison of CAS versus CEA for the composite outcomes.

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
CREST, 2010 USA 20505173	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	4y	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	HR*	1.17	0.69 - 1.98	0.56	A
CREST, 2010 USA 20505173	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	4y	Any periprocedural stroke or death or postprocedural ipsilateral stroke	HR*	1.86	0.95 - 3.66	0.07	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	3y	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	RR†	0.73	0.46 - 1.14	0.171	B
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	1y	Any periprocedural stroke or death or postprocedural ipsilateral stroke	RR‡	0.54	0.28-1.02	0.059	B
De Rango, 2011, Italy 21292127	NRCS, prosp	1518	816	702	nd	nd	nd	nd	nd	2.8y	Any periprocedural stroke or death or postprocedural ipsilateral stroke	RR†	0.83	0.49-1.39	0.48	C
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	4y	Any stroke or death	RR†	1.26	0.77 - 2.05	0.358	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	4y	Any stroke or death or MI	RR†	1.18	0.72 - 1.91	0.501	B
Bangalore, 2010, International, 20805431	Registry, prosp	1672	836	836	70	67	49	43	100	1.5y	Any stroke or death	HR	0.89	0.63 – 1.27	0.53	C
											Any stroke or death or MI	HR	0.79	0.58 – 1.08	0.14	

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Adjusted for age and sex

† Calculated from raw data

‡ Calculated from raw data as provided in the FDA website

Appendix E. Table 14. Comparison of CAS versus CEA for the high-surgical risk population

Author, Year Country PMID	Subgroup	Design	Total (n)	CAS (n)	CEA (n)	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Yadav 2004, Gurm 2008, USA 15470212; 18403765	High surgical risk	RCT	237	117	120	3y	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	RR*	0.73	0.46 - 1.14	0.171	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	High surgical risk	RCT	237	117	120	3y	Any stroke	RR*	1.12	0.51, 2.43	0.777	A

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Calculated from raw events

Appendix E. Table 15. Comparison of CAS versus CEA for the patients with anatomically advanced disease (>80% stenosis).

Author, Year Country PMID	Subgroup	Design	Total (n)	CAS (n)	CEA (n)	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Yadav 2004, Gurm 2008, USA 15470212; 18403765	>80%	RCT	237	117	120	3y	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	RR*	0.73	0.46, 1.14	0.171	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	>80%	RCT	237	117	120	30 days	Any stroke, MI, or death	RR*	0.51	0.19, 1.32	0.167	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	>80%	RCT	237	117	120	3y	Any stroke	RR*	1.12	0.51, 2.43	0.777	A
Brooks, 2004 USA 14744277	>80%	RCT	85	43	42	4y	Any stroke/TIA	RR	Non-estimable†			B

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Calculated from raw events

† RR cannot be estimated since no events occurred in both arms.

Appendix E. Table 16. Comparison of CAS versus CEA for different durations of follow-up.

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	1y	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	RR*	0.47	0.25 - 0.89	0.021	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	3y	Any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke	RR*	0.73	0.46 - 1.14	0.171	A

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Calculated from raw events

Appendix E. Table 17. Comparison of CAS versus CEA for the outcome of periprocedural cerebrovascular events

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
CREST, 2010; 2011 USA 20505173; 21307169	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	Any stroke	HR*	1.88	0.79,4.42	0.15	A
Brooks, 2004 USA 14744277	RCT	85	43	42	68.2	nd	64.5	14	100	30 days	Any stroke / TIA	RR	Non-estimable†			B
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	30 days	Any stroke	RR‡	1.54	0.44 - 5.31	0.496	B
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	30 days	Ipsilateral stroke	RR‡	1.71	0.42-6.99	0.456	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	30 days	Any stroke	RR‡	0.57	0.06, 5.42	0.627	B
De Rango, 2011, Italy 21292127	NRCS, prosp	1518	816	702	nd	nd	nd	nd	nd	2.8y	Any periprocedural stroke or death	OR	1.5	0.71-3.17	0.36	C
Marine, 2006 1434877 USA	NRCS, retro	238	93	145	69.7	61.9	68.2	35.5	100%	30 days	Any stroke	RR‡	0.52	0.05, 4.92	0.568	C
McPhee, 2008 USA 18829236	NRCS, retro§	122,986	11,302	111,684	71.1	57.7	11.1	26.6	nd	in-hospital (<30 days)	Any stroke	RR‡	1.82	1.55, 2.12	<0.0001	C
McPhee, 2007 USA 18154987	NRCS, retro§	238,389	12278	226111	71.2	57	11.8	25.4	nd	in-hospital (<30 days)	Any stroke	RR ‡	2.09	1.82, 2.40	<0.0001	C
Sidawy, 2009 USA 19028045	NRCS, retro§	1667	805	862	71	59.6	54	30	nd	30 days	Any stroke	RR‡	1.65	0.77, 3.51	0.189	C
Sidawy, 2009 USA 19028045	NRCS, retro§	1667	805	862	71	59.6	54	30	nd	30 days	TIA	RR‡	3.21	1.04, 9.91	0.042	C
Giacovelli, 2010 USA 20620010	NRCS, retro§	8706	4354	4354	71.7	60.1	48.1	29.2	nd	<30 days	Any stroke	RR‡	1.17	0.86, 1.58	0.307	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Adjusted for age and sex

† RR cannot be estimated since no events occurred in both arms.

‡ Calculated from raw data; § Administrative dataset

Appendix E. Table 18. Comparison of CAS versus CEA for the outcome of periprocedural mortality

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	30 days	Death	RR†	2.05	0.18 - 22.3	0.555	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	30 days	Death	RR	Non-estimable			B
Marine, 2006 1434877 USA	NRCS, retro	238	93	145	69.7	61.9	68.2	35.5	100%	30 days	Death	RR†	1.56	0.09, 24.6	0.752	C
McPhee, 2008 USA 18829236	NRCS, retro*	122,986	11,302	111,684	71.1	57.7	11.1	26.6	nd	in-hospital (<30 days)	Death	RR†	1.49	1.14, 1.93	0.003‡	C
McPhee, 2007 USA 18154987	NRCS, retro*	238,389	12278	226111	71.2	57	11.8	25.4	nd	in-hospital (<30 days)	Death	RR†	1.29	0.98, 1.70	0.067	C
Sidawy, 2009 USA 19028045	NRCS, retro*	1667	805	862	71	59.6	54	30	nd	30 days	Death	RR†	2.86	1.12, 7.26	0.028	C
Giacovelli, 2010 USA 20620010	NRCS, retro*	8706	4354	4354	71.7	60.1	48.1	29.2	nd	<30 days	Death	RR§	1.41	0.75, 2.62	0.276	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

*Administrative dataset

†Calculated from raw data

‡Contrary to the reported p-value in the paper, our calculations showed statistical significance

§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

Appendix E. Table 19. Comparison of CAS versus CEA for the outcome of periprocedural MI

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Brott, 2010 USA 20505173	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	MI	HR*	0.55	0.22,1.38	0.2	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	30 days	MI	RR†	0.38	0.10 - 1.41	0.150	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	30 days	MI	RR†	0.43	0.01, 9.42	0.592	B
Marine, 2006 1434877 USA	NRCS, retro	238	93	145	69.7	61.9	68.2	35.5	100	30 days	MI	RR†	0.78	0.07, 8.47	0.838	C
McPhee, 2007 USA 18154987	NRCS, retro‡	238,389	12278	226111	71.2	57	11.8	25.4	nd	in-hospital (<30 days)	MI	RR†	1.18	1.04, 1.35	0.012	C
Sidawy, 2009 USA 19028045	NRCS, retro‡	1667	805	862	71	59.6	54	30	nd	30 days	MI	RR†	2.36	0.82, 6.75	0.111	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Adjusted for age and sex

† Calculated from raw data

‡ Administrative dataset

Appendix E. Table 20. Comparison of CAS versus CEA for periprocedural composite outcomes

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Brott, 2010 USA 20505173	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	Any stroke, MI, or death	HR*	1.02	0.55,1.86	0.96	A
Brott, 2010 USA 20505173	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	Any stroke or death	HR*	1.88	0.79,4.42	0.15	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	30 days	Any stroke, MI, or death	RR†	0.51	0.19, 1.32	0.167	A
Yadav 2004, Gurm 2008, USA 15470212; 18403765	RCT	237	117	120	72.5	67	80.0	26.0	100	**30 days**	Any stroke or death	RR§	1.44	0.47-4.40	0.526	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	30 days	Any stroke or death	RR†	0.57	0.06, 5.42	0.627	B
CaRESS, 2005 2009, USA, 16102616;19702339	NRCS, prosp	269	99	170	71.3	62	63	26	91	30 days	Any stroke or death or MI	RR†	0.34	0.03, 2.92	0.324	B
Marine, 2006 1434877 USA	NRCS, retro	238	93	145	69.7	61.9	68.2	35.5	100	30 days	Any stroke or death	RR†	1.04	0.17, 6.10	0.966	C
Bosiers, 2005 15996363 Belgium	NRCS, retro	79	59	20	nd	nd	nd	nd	100	30 days	Any stroke or death	RR†	1.02	0.04, 23.9	0.992	C
Sidawy, 2009 USA 19028045	NRCS, retro‡	1667	805	862	71	59.6	54	30	nd	30 days	Any stroke, death or MI	RR†	2.33	1.32, 4.10	0.003	C
Giacovelli, 2010 USA 20620010	NRCS, retro‡	8706	4354	4354	71.7	60.1	48.1	29.2	nd	<30 days	Any stroke or death	RR†	1.23	0.92, 1.63	0.161	C
Lindstrom, 2012, Sweden, 22342694	NRCS, retro‡	1416	101	1315	nd	nd	nd	nd	nd	30 day	Any stroke or death	RR†	2.70	1.46, 5.01	0.002	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Adjusted for age and sex

† Calculated from raw data

‡ Administrative dataset

§Calculated from raw data as provided in the FDA website

Appendix E. Table 21. Comparison of CAS versus CEA for the outcome of periprocedural cranial nerve palsy.

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥ 70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Brott, 2010; Silver 2011 USA 20505173; 21307169	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	Cranial Nerve Palsy	RR*	0.04	0.00, 0.29	0.002	A
Brooks, 2004 USA 14744277	RCT	85	43	42	68.2	nd	64.5	14	100	30 days	Cranial Nerve Palsy	RR*	0.14	0.00, 2.61	0.188	B
Marine, 2006 1434877 USA	NRCS, retro	238	93	145	69.7	61.9	68.2	35.5	100%	30 days	Cranial nerve palsy	RR*	0.17	0.00, 3.18	0.238	C
Giacovelli, 2010 USA 20620010	NRCS, retro†	8706	4354	4354	71.7	60.1	48.1	29.2	nd	<30 days	Cranial Nerve Palsy	RR	0.47	0.21 - 1.04	0.064	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Calculated from raw data

† Administrative dataset

Appendix E. Table 22. Comparison of CAS versus CEA for periprocedural bleeding complications.

Author, Year Country PMID	Design	Total (n)	CAS (n)	CEA (n)	Age (y)	male (%)	CAD (%)	DM (%)	%≥70% stenosis	Followup	Outcome	Metric*	Result	95% CI	P btw	Study quality
Brott, 2010; Silver 2011 USA 20505173; 21307169	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	Bleeding (requiring transfusion)	RR*	1.13	0.41 - 3.09	0.813	A
Brott, 2010; Silver 2011 USA 20505173; 21307169	RCT	1181	594	587	69.3	65.6	49.7	33.1	92.3	30 days	Hematoma	RR*	4.94	0.23 - 102.	0.302	A
Marine, 2006 1434877 USA	NRCS, retro	238	93	145	69.7	61.9	68.2	35.5	100%	30 days	Hematoma	RR*	1.30	0.40, 4.13	0.658	C
Giacovelli, 2010 USA 20620010	NRCS, retro†	8706	4354	4354	71.7	60.1	48.1	29.2	nd	<30 days	Bleeding	RR*	0.90	0.72, 1.12	0.357	C

RCT, randomized controlled trial; NRCS, nonrandomized comparative study; retro, retrospective; prosp, prospective; CEA, carotid endarterectomy; CAS, carotid artery stenting; CAD, coronary artery disease; DM, diabetes mellitus; TIA, transient ischemic attack; nd, no data; HR, hazard ratio; RR, relative risk

* Calculated from raw data

† Administrative dataset

Appendix F. List of included studies

1) No Authors listed. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. The CASANOVA Study Group. Stroke. 1991;22:1229-35. PM: 1926232

2) No Authors listed. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Asymptomatic Carotid Endarterectomy Study Group. Mayo Clinic Proceedings. 1992;67:513-18. PM:1434877

3) No Authors listed. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995;273:1421-28. PM: 7723155

4) No Authors listed. Risk of stroke in the distribution of an asymptomatic carotid artery. The European Carotid Surgery Trialists Collaborative Group. Lancet. 1995;345:209-12. PM:7823712

5) Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. Stroke. 2005;36:1128-33. PM:15879327

6) AbuRahma AF, Metz MJ, Robinson PA. Natural history of >or =60% asymptomatic carotid stenosis in patients with contralateral carotid occlusion. Annals of Surgery. 2003;238:551-61. PM:14530726

7) AbuRahma AF, Cook CC, Metz MJ, Wulu JT, Jr., Bartolucci A. Natural history of carotid artery stenosis contralateral to endarterectomy: results from two randomized prospective trials. Journal of Vascular Surgery. 2003;38:1154-61. PM:14681599

8) Aichner FT, Topakian R, Alberts MJ, Bhatt DL, Haring HP, Hill MD et al. High cardiovascular event rates in patients with asymptomatic carotid stenosis: the REACH Registry. European Journal of Neurology. 2009;16:902-8. PM:19473362

9) Anderson DC, Kappelle LJ, Eliasziw M, Babikian VL, Pearce LA, Barnett HJ. Occurrence of hemispheric and retinal ischemia in atrial fibrillation compared with carotid stenosis. Stroke. 2002;33:1963-67. PM:12154246

10) Ballotta E, Da GG, Meneghetti G, Barbon B, Militello C, Baracchini C. Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: a 10-year prospective study. Journal of Vascular Surgery. 2007;45:516-22. PM: 17275244

11) Bock RW, Gray-Weale AC, Mock PA, App SM, Robinson DA, Irwig L et al. The natural history of asymptomatic carotid artery disease. Journal of Vascular Surgery. 1993;17:160-169. PM:8421333

12) Bogousslavsky J, Despland PA, Regli F. Asymptomatic tight stenosis of the internal carotid artery: long-term prognosis. Neurology. 1986;36:861-63. PM:3703297

13) Dick P, Sherif C, Sabeti S, Amighi J, Minar E, Schillinger M. Gender differences in outcome of conservatively treated patients with asymptomatic high grade carotid stenosis. Stroke. 2005;36:1178-83. PM:15890998

14) Ellis MR, Franks PJ, Cuming R, Powell JT, Greenhalgh RM. Prevalence, progression and natural history of asymptomatic carotid stenosis: is there a place for carotid endarterectomy? European Journal of Vascular Surgery. 1992;6:172-77. PM:1572457

15) Goessens BM, Visseren FL, Kappelle LJ, Algra A, van der GY. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. Stroke. 2007;38:1470-1475. PM:17363718

16) Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. Circulation. 2001;104:68-73. PM:11435340

17) Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive factor of stroke in asymptomatic patients? Stroke. 1996;27:2188-90. PM:8969778

18) Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004;363:1491-502. PM:15135594

19) Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet. 2010;376:1074-84. PM:20870099

20) Hennerici M, Hulsbomer HB, Hefter H, Lammerts D, Rautenberg W. Natural history of asymptomatic extracranial arterial disease. Results of a long-term prospective study. Brain. 1987;110:777-91. PM:3580834

21) Hobson RW, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. New England Journal of Medicine. 1993;328:221-27. PM:8418401

22) Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. New England Journal of Medicine. 2000;342:1693-700. PM:10841871

23) Johnson BF, Verlato F, Bergelin RO, Primozich JF, Strandness E Jr. Clinical outcome in patients with mild and moderate carotid artery stenosis. Journal of Vascular Surgery. 1995;21:120-126. PM:7823350

24) Johnson JM, Kennelly MM, DeCesare D, Morgan S, Sparrow A. Natural history of asymptomatic carotid plaque. Archives of Surgery. 1985;120:1010-1012. PM:3896195

25) Kakkos SK, Nicolaides A, Griffin M, Sabetai M, Dhanjil S, Thomas DJ et al. Factors associated with mortality in patients with asymptomatic carotid stenosis: results from the ACSRS Study. International Angiology. 2005;24:221-30. PM:16158030

26) Langsfeld M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. Journal of Vascular Surgery. 1989;9:548-57. PM:2651727

27) Levien LJ, Fritz VU, Lithgow-Jolly P. The natural history of asymptomatic carotid disease. A preliminary report. South African Journal of Surgery. 1984;22:249-53. PM:6523303

28) Liapis CD, Kakisis JD, Kostakis AG. Carotid stenosis: factors affecting symptomatology. Stroke. 2001;32:2782-86. PM:11739973

29) Longstreth WT, Jr., Shemanski L, Lefkowitz D, O'Leary DH, Polak JF, Wolfson SK, Jr. Asymptomatic internal carotid artery stenosis defined by ultrasound and the risk of subsequent stroke in the elderly. The Cardiovascular Health Study. Stroke. 1998;29:2371-76. PM:9804651

30) Mackey AE, Abrahamowicz M, Langlois Y, Battista R, Simard D, Bourque F et al. Outcome of asymptomatic patients with carotid disease. Asymptomatic Cervical Bruit Study Group. Neurology. 1997;48:896-903. PM:9109874

31) Mansour MA, Littooy FN, Watson WC, Blumofe KA, Heilizer TJ, Steffen GF et al. Outcome of moderate carotid artery stenosis in patients who are asymptomatic. Journal of Vascular Surgery. 1999;29:217-25. PM:9950980

32) Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol. 2010;9:663-71. PM:20554250

33) Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke. 2010;41:e11-e17. PM:19926843

34) Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. European Journal of Vascular & Endovascular Surgery. 2005;30:275-84. PM:16130207

35) Norris JW, Zhu CZ, Bornstein NM, Chambers BR. Vascular risks of asymptomatic carotid stenosis. Stroke. 1991;22:1485-90. PM:1962321

36) Sabeti S, Schlager O, Exner M, Mlekusch W, Amighi J, Dick P et al. Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. Stroke. 2007;38:2887-94. PM:17885257

37) Satiani B, Porter RM, Jr. The influence of contralateral disease on the natural history of nonoperated significant carotid stenosis. Annals of Vascular Surgery. 1990;4:313-17. PM:2364044

38) Satiani B, Chen TY, Shook L, Finnie K. Contralateral disease progression after carotid endarterectomy. Surgery. 1993;114:46-51. PM:8356526

39) Siebler M, Nachtmann A, Sitzer M, Rose G, Kleinschmidt A, Rademacher J et al. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. Stroke. 1995;26:2184-86. PM:7482670

40) Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA. 2000;283:2122-27. PM:10791504

41) Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. Stroke. 2005;36:2373-78. PM:16224084

42) Spence JD, Coates V, Li H, Tamayo A, Munoz C, Hackam DG et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Archives of Neurology. 2010;67:180-186. PM:20008646

43) Takahashi W, Ohnuki T, Ide M, Takagi S, Shinohara Y. Stroke risk of asymptomatic intra- and extracranial large-artery disease in apparently healthy adults. Cerebrovascular Diseases. 2006;22:263-70. PM:16788300

44) Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke. 2006;37:818-23. PM:16469957

45) Bosiers M, Peeters P, Deloose K, Verbist J, Sprouse RL. Selection of treatment for patients with carotid artery disease: medication, carotid endarterectomy, or carotid artery stenting. Vascular. 2005;13:92-97. PM: 15996363

46) Caracci BF, Zukowski AJ, Hurley JJ, Naunheim KS, Auer AI. Asymptomatic severe carotid stenosis. Journal of Vascular Surgery. 1989;9:361-66. PM: 2645445

47) Hertzer NR, Flanagan RA, Jr., Beven EG, O'Hara PJ. Surgical versus nonoperative treatment of asymptomatic carotid stenosis. 290 patients documented by intravenous angiography. Annals of Surgery. 1986;204:163-71. PM: 3527089

48) Libman RB, Sacco RL, Shi T, Correll JW, Mohr JP. Outcome after carotid endarterectomy for asymptomatic carotid stenosis. Surgical Neurology. 1994;41:443-49. PM: 8059320

49) Poulias GE, Doundoulakis N, Skoutas B, Haddad H, Karkanias G, Papadakis E. Carotid artery surgery and the principle of prophylaxis: recurrence in operated and nonoperated patients. Cardiovascular Surgery. 1994;2:586-91. PM: 7820518

50) Sherif C, Dick P, Sabeti S, Mlekusch W, Amighi J, Ahmadi R et al. Neurological outcome of conservative versus endovascular treatment of patients with asymptomatic high-grade carotid artery stenosis: a propensity score-adjusted analysis. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 2005;12:145-55. PM: 15823061

51) Brott TG, Hobson RW, Howard G, Roubin GS, Clark WM, Brooks W et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. New England Journal of Medicine. 2010;363:11-23. PM: 20505173

52) Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. New England Journal of Medicine. 2008;358:1572-79. PM: 18403765

53) Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. New England Journal of Medicine. 2004;351:1493-501. PM: 15470212

54) Brooks WH, McClure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. Neurosurgery. 2004;54:318-24. PM: 14744277

55) CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. Journal of Vascular Surgery. 2005;42:213-19. PM: 16102616

56) Zarins CK, White RA, Diethrich EB, Shackelton RJ, Siami FS, CaRESS Steering Committee and CaRESS Investigators. Carotid revascularization using endarterectomy or stenting systems (CaRESS): 4-year outcomes. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 2009;16:397-409. PM: 19702339

57) Marine LA, Rubin BG, Reddy R, Sanchez LA, Parodi JC, Sicard GA. Treatment of asymptomatic carotid artery disease: similar early outcomes after carotid stenting for high-risk patients and endarterectomy for standard-risk patients. Journal of Vascular Surgery. 2006;43:953-58. PM: 1434877

58) McPhee JT, Hill JS, Ciocca RG, Messina LM, Eslami MH. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. Journal of Vascular Surgery. 2007;46:1112-18. PM: 18154987

59) McPhee JT, Schanzer A, Messina LM, Eslami MH. Carotid artery stenting has increased rates of postprocedure stroke, death, and resource utilization than does carotid

endarterectomy in the United States, 2005. Journal of Vascular Surgery. 2008;48:1442-50. PM: 18829236

60) Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA et al. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. Journal of Vascular Surgery. 2009;49:71-79. PM: 19028045

61) Giacovelli JK, Egorova N, Dayal R, Gelijns A, McKinsey J, Kent KC. Outcomes of carotid stenting compared with endarterectomy are equivalent in asymptomatic patients and inferior in symptomatic patients. Journal of Vascular Surgery. 2010;52:906-13, 913. PM: 20620010

62) Silver FL, Mackey A, Clark WM et al. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2011 March;42(3):675-80. PM: 21307169

63) Howard VJ, Lutsep HL, Mackey A et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurology 2011 June;10(6):530-7. PM: 21550314

64) Zhang C, Qu S, Li H, et al. Microembolic signals and carotid plaque characteristics in patients with asymptomatic carotid stenosis. Scand Cardiovasc J 2009;43(5):345-51. PM:19863395

65) Ogata T, Yasaka M, Wakugawa Y, et al. Long-term results of medical and surgical therapy for Japanese patients with moderate carotid stenosis. J Stroke Cerebrovasc Dis 2012 Jan;21(1):24-29. PM:20851631

66) De RP, Parlani G, Verzini F, et al. Long-term prevention of stroke: a modern comparison of current carotid stenting and carotid endarterectomy. Journal of the American College of Cardiology 2011 Feb 8;57(6):664-71. PM:21292127

67) Bangalore S, Bhatt DL, Rother J, et al. Late outcomes after carotid artery stenting versus carotid endarterectomy: insights from a propensity-matched analysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2010 Sep 14;122(11):1091-100. PM:20805431

68) Lindstrom D, Jonsson M, Formgren J, et al. Outcome after 7 years of carotid artery stenting and endarterectomy in Sweden - single centre and national results. Eur J Vasc Endovasc Surg 2012 May;43(5):499-503. PM:22342694