

Management Strategies for Asymptomatic Carotid Stenosis

A Systematic Review and Meta-analysis

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Background: Adults with asymptomatic carotid artery stenosis are at increased risk for ipsilateral carotid territory ischemic stroke.

Purpose: To examine comparative evidence on management strategies for asymptomatic carotid stenosis and the incidence of ipsilateral stroke with medical therapy alone.

Data Sources: MEDLINE, Cochrane Central Register of Controlled Trials, U.S. Food and Drug Administration documents, and review of references through 31 December 2012.

Study Selection: Randomized, controlled trials (RCTs) and prospective or retrospective nonrandomized, comparative studies of medical therapy alone, carotid endarterectomy (CEA) plus medical therapy, or carotid artery stenting (CAS) plus medical therapy for adults with asymptomatic carotid stenosis, as well as single-group prospective cohort studies of medical therapy, were reviewed.

Data Extraction: Two investigators extracted information on study and population characteristics, results, and risk of bias.

Data Synthesis: Forty-seven studies in 56 publications were eligible. The RCTs comparing CAS and CEA were clinically heteroge-

neous; 1 RCT reported more but not statistically significant ipsilateral stroke events (including any periprocedural stroke) in CAS compared with CEA, whereas another RCT, in a population at high surgical risk for CEA, did not. Three RCTs showed that CEA reduced the risk for ipsilateral stroke (including any periprocedural stroke) compared with medical therapy alone, but these results may no longer be applicable to contemporary clinical practice. No RCT compared CAS versus medical therapy alone. The summary incidence of ipsilateral stroke across 26 cohorts receiving medical therapy alone was 1.68% per year.

Limitations: Studies defined asymptomatic status heterogeneously. Participants in RCTs did not receive best-available medical therapy.

Conclusion: Future RCTs of asymptomatic carotid artery stenosis should explore whether revascularization interventions provide benefit to patients treated by best-available medical therapy.

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Ischemic stroke is a major public health problem in the United States, with nearly 700 000 events reported annually (1). Carotid artery stenosis is an important risk factor. Patients with vascular disease and several risk factors (such as diabetes, hypertension, hyperlipidemia, and smoking) have a greater probability of having carotid artery atherosclerosis. Because carotid atherosclerosis can proceed silently, the first manifestation can be a debilitating or fatal stroke. Asymptomatic carotid stenosis affects approximately 7% of women and more than 12% of men older than 70 years (2). Clinically important stenosis, at which point the risk for stroke is increased, is defined as stenosis greater than 50% or 60% (3). Adults with asymptomatic carotid stenosis are at increased annual risk (2% to 5%) for ipsilateral carotid territory ischemic stroke according to studies conducted before the introduction of modern medical therapy (4, 5).

Screening asymptomatic patients for carotid stenosis is not part of recommended clinical practice in the United States (3). However, asymptomatic Medicare beneficiaries

are increasingly being evaluated with noninvasive imaging studies for this indication (6). A substantial 27% increase in use of noninvasive carotid artery imaging occurred in the Medicare population from 2001 through 2006; approximately 124 studies per 1000 person-years were done in 2006 (7). Therapeutic options for patients with asymptomatic carotid stenosis include medical therapy alone, carotid endarterectomy (CEA) plus medical therapy, or carotid artery stenting (CAS) plus medical therapy. Approximately 124 000 carotid revascularization procedures (89% CEA and 11% CAS) are done each year in the United States (8). Carotid artery stenting is associated with greater median total hospital charges than CEA (\$33 500 vs. \$21 200, respectively) (9). Use of CAS has substantially increased, from 2.8% of all carotid revascularization procedures in 1998 to 12.6% in 2008 (10).

The goal of management of asymptomatic carotid stenosis is to decrease the risk for stroke and stroke-related deaths. However, the optimal therapeutic management strategy remains unclear. The primary objective of this systematic review was to compare management strategies for adults with asymptomatic carotid artery stenosis. Despite advances in the past decade, best-available medical therapy has not been evaluated in recent carotid artery revascularization trials. Therefore, a secondary objective was to evaluate contemporary stroke rates in studies evaluating medical therapy alone.

See also:

Web-Only
Supplement

METHODS

This article is based on a Technology Assessment report commissioned by the Coverage and Analysis Group at the Centers for Medicare & Medicaid Services through the Agency for Healthcare Research and Quality. We followed standard systematic review methods (11–13) to address the following questions: What is the comparative effectiveness of CAS plus medical therapy, CEA plus medical therapy, and medical therapy alone for adults with asymptomatic carotid artery stenosis for clinical outcomes, including ipsilateral stroke, any stroke, and death? What is the incidence rate of ipsilateral stroke in adults with asymptomatic carotid artery stenosis who receive medical therapy alone?

Data Sources and Searches

We searched MEDLINE and the Cochrane Central Register of Controlled Trials for English-language studies from inception through 31 December 2012 (**Supplement**, available at www.annals.org). We combined search terms and Medical Subject Headings for carotid artery diseases with terms relevant to the treatment strategies of interest (for example, carotid stenosis, stenting, and endarterectomy). We also hand searched bibliographies of systematic and narrative reviews, searched the U.S. Food and Drug Administration Web site, and contacted corresponding authors of eligible studies for unpublished data.

Study Selection

Using predefined criteria, we selected studies conducted in adults (aged 18 years or older) who had asymptomatic atherosclerotic narrowing of the lumen of the carotid bifurcation or the extracranial part of the internal carotid artery between 50% and 99%, but had no ipsilateral carotid territory symptoms within the preceding 6 months. We accepted definitions of asymptomatic carotid stenosis used in each study. We excluded studies reporting on mixed populations of symptomatic and asymptomatic persons when data were not available for each group separately (that is, by symptom status).

We included randomized, controlled trials (RCTs) and prospective or retrospective nonrandomized, comparative studies (NRCSs) comparing at least 2 of the following treatment strategies: CAS plus medical therapy, CEA plus medical therapy, and medical therapy alone. We required that comparative studies comprise at least 30 patients per intervention group, regardless of the duration of follow-up. We also included prospective single-group cohort studies of medical therapy alone (including medical therapy groups of RCTs and prospective NRCSs) that had at least 30 patients and a minimum average follow-up of 12 months (median follow-up was used when mean follow-up was not reported). We defined current “best” available medical therapy as the use of optimal targets for treatment of blood pressure and diabetes, statins, antiplatelets, and lifestyle modification (such as smoking cessation, exercise, and weight loss).

We reviewed information on ipsilateral stroke, any stroke, or death or their composite outcomes at 30 days and at last follow-up.

Data Extraction and Study Quality Assessment

One reviewer extracted data into structured forms that were reviewed by a second reviewer for completeness and accuracy. We collected information on study design, funding sources, settings, population characteristics, definition of carotid stenosis, imaging methods and related diagnostic and quality assurance criteria for determining degree of stenosis, details about stenting and endarterectomy techniques, medical therapies, and items relevant to outcome ascertainment.

We used standard methods to assess quality and applicability of individual studies (13). Risk of bias was categorized as low (“A”), medium (“B”), or high (“C”) (**Supplement**). The applicability of study findings to practice was evaluated on the basis of study and population characteristics, such as age (groups aged 65 years and older or 80 years and older), participant sex, comorbid conditions, medical therapy at baseline, and clinical or anatomical features of carotid stenosis (>70% or >80% stenosis), as well as setting of care (tertiary or community center). At least 2 reviewers did the quality and applicability assessment for each study.

Data Synthesis and Analysis

Two independent reviewers graded the overall strength of evidence for each question (or comparison), taking into account risk of bias in individual studies, directness and precision of evidence, and consistency of evidence across studies. We used a 4-category grading system (high, moderate, low, or insufficient) to grade the strength of evidence, using established criteria (13).

For comparative studies (RCTs and NRCSs), we conducted meta-analyses using an inverse-variance random-effects model and reported the results as summary relative risks (RRs) (14). We analyzed RCTs and NRCSs separately. When included populations varied markedly, we focused on describing the design, results, and limitations of individual studies and relied on qualitative synthesis rather than meta-analysis.

For each study of medical therapy alone that reported numerical data of events and average follow-up person-time, we calculated the incidence rate of events and its 95% CI. When raw data were not reported, data on incidence rates were extracted from published Kaplan–Meier curves (15) after digitization using open-source software (Engauge Digitizer, version 2.14, available at <http://digitizer.sourceforge.net>). Summary estimates of incidence rates were obtained by fitting a random-intercept generalized linear model (16) and were expressed as percentage per year instead of number of events per 100 person-years. To evaluate the effect of time (and, thus, possible improvements in medical therapy management) on the incidence rates of ipsilateral stroke, we conducted an exploratory meta-

Table 1. Summary Characteristics of RCTs Comparing Treatment Strategies in Asymptomatic Carotid Stenosis

Study, Year (Reference)	Study Location	Participants, n (Follow-up Time)	Diagnosis of Carotid Stenosis	Stenosis, %	Previous Symptoms, %*
CAS vs. CEA					
CREST, 2010, 2011 (17–19)	North America	1181 (4 y)	DSA, DUS, or MRAS	≥60	2.5
Brooks et al, 2004 (20)	United States	85 (4 y)	DSA	≥80	Not reported
SAPPHIRE, 2004, 2008 (21, 22)	United States	237 (3 y)	DUS	≥80	24
CEA vs. medical therapy					
VA, 1993 (23)	United States	444 (3.9 y)	DUS; OPG and DSA	≥50	32
ACAS, 1995 (24)	United States	1659 (2.7 y)	CEA: DSA Medical: DUS	≥60	5
ACST, 2004, 2010 (25, 26)	Europe	3120 (10 y)	DUS	≥60	24

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy Versus Stenting Trial; CTA = computed tomography angiography; DM = diabetes mellitus; DSA = digital subtraction angiography; DUS = duplex ultrasonography; MI = myocardial infarction; MRA = magnetic resonance angiography; OPG = ocular pneumoplethysmography; RCT = randomized, controlled trial; SAPPHIRE = Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy; TIA = transient ischemic attack; VA = Veterans Affairs.

* Can include any 1 or more of the following: symptoms related to contralateral carotid or other vascular territory or endarterectomy in the contralateral carotid artery.

† RCTs did not provide details about standard medical therapy.

‡ CAS features include stent name, design, and embolic protection device. CEA approach includes details about selective shunt and patch.

§ ≥60% on DSA, ≥70% on DUS, and ≥80% on CTA or MRA.

|| CAS received dual-antiplatelet and CEA received single-antiplatelet treatment.

¶ RX Acculink stent; 96% of patients received RX Accunet embolic protection device.

** Wallstent, Dyalink stents and no embolic protection device.

†† Smart or Precise Cordis stents, self-expanding nitinol stent, and 96% of patients received Angioguard or Angioguard XP Cordis embolic protection device.

regression analysis by adding the covariate of “last year of study enrollment” to the model. We compared the incidence rates of ipsilateral stroke in studies with enrollment closure between 2000 and 2010 versus earlier years. Statistical analyses were conducted using Stata, version 11.2/ Special Edition (StataCorp, College Station, Texas).

Role of the Funding Source

The Agency for Healthcare Research and Quality funded the Technology Assessment report and provided input in the formulation of research questions but had no role in study selection; quality assessment; data synthesis, analysis, or interpretation; or the decision to prepare and submit the manuscript for publication.

RESULTS

The search identified 8004 citations. We evaluated the full text of the 379 citations that were considered potentially relevant and found 47 studies described in 56 articles that met eligibility criteria (Appendix Figure, available at www.annals.org). Table 1 shows characteristics of the relevant RCTs, and Table 2 summarizes overall findings and strength evidence. Of 3 RCTs that compared CAS plus medical therapy versus CEA plus medical therapy, 1 (17–19) was of low risk and 2 (20–22) were of medium risk of bias. Three RCTs (23–26), all of low risk of bias, com-

pared CEA plus medical therapy with medical therapy alone. The Supplement includes information on NRCSS and single-group cohorts of medical therapy. Definitions of “asymptomatic status” in each study were generally heterogeneous.

Comparison of Management Strategies

CAS Plus Medical Therapy Versus CEA Plus Medical Therapy

Three RCTs described in 6 publications (17–22) and 10 NRCSS described in 11 publications (27–37), which were predominantly of high risk of bias, evaluated CAS plus medical therapy versus CEA plus medical therapy. Evidence was insufficient to clearly support 1 interventional strategy over another in adults with asymptomatic carotid stenosis (Table 2).

Two RCTs, CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) (17) and SAPPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy) (22), included both symptomatic and asymptomatic patients. Randomization was stratified by symptom status in both trials; the data we present pertain to the asymptomatic subgroups. Two RCTs (17, 20) excluded patients with arrhythmia or other acute cardiac diseases (Table 1). The CAS group in the RCTs received dual antiplatelet therapy (aspirin plus thienopyridines), with the continuation of at least 1 antiplatelet

Table 1—Continued

Excluded Medical Condition	Description of Medical Therapy†	Definition of Asymptomatic Status	CAS Features and CEA Approach‡	Composite Primary End Point
Atrial fibrillation; MI <30 d; unstable angina	Antiplatelet‡; standard medical therapy	No symptoms or ipsilateral symptoms (>6 mo) or recent symptoms in a different territory	CAS: Stent; design; embolic protection¶ CEA: Shunt, 54%; patch, 69%	Periprocedural stroke, MI, or death or postprocedural ipsilateral stroke
Cardiac arrhythmia	Dual antiplatelet	No symptoms	CAS: Stent** CEA: Not reported	Any stroke or TIA
Ischemic stroke <48 h	Antiplatelet‡; standard medical therapy	No symptoms	CAS: Stent; design; embolic protection†† CEA: Not reported	Periprocedural stroke, MI, or death or postprocedural ipsilateral stroke
High surgical risk	High-dose aspirin; standard medical therapy	No symptoms	None	Ipsilateral TIA, stroke, and death
Atrial fibrillation; MI; unstable angina; severe DM or hypertension	Antiplatelet; standard medical therapy and lifestyle modification	No symptoms or contralateral symptoms (>1.5 mo) or recent symptoms in a different territory	Not reported	Ipsilateral stroke and death
Recent MI; cardiac source of emboli; CEA and CABG	Antiplatelet; antihypertensive; lipid-lowering therapy in later years of follow-up	No symptoms or ipsilateral symptoms (>6 mo)	Shunt or patch used at the discretion of surgeon	Perioperative death, illness, and nonperioperative stroke

therapy beyond 30 days after the procedure. The CEA group received single-agent antiplatelet treatment (aspirin or thienopyridines) or a combination of aspirin and extended-release dipyridamole for at least 1 year. Both groups received contemporary standard medical therapy prescribed by individual treating physicians.

Periprocedural and 30-Day Outcomes. Ten studies, including 3 RCTs and 7 NRCSs (2 clinical data sets, 4 administrative data sets, and 1 study based on registry data), evaluated 30-day outcomes (17, 20, 22, 28–31, 33–37). Characteristics of study participants varied markedly in 2 of the 3 RCTs (17, 22). Although the difference in the risk for periprocedural adverse events between treatment groups did not reach statistical significance in these 2 RCTs, the rate of the periprocedural composite outcome of stroke or death was greater with CAS and the rate of periprocedural myocardial infarction was greater with CEA in both RCTs (Supplement). The third RCT reported no periprocedural cerebrovascular events (20).

Meta-analysis of 2 NRCSs of clinical data sets (1 of medium risk and 1 of high risk of bias) found a lower incidence of periprocedural stroke with CAS than with CEA (29, 34), although the difference was not statistically significant. Meta-analysis of 4 NRCSs of high risk of bias based on administrative data found a statistically significantly increased risk for periprocedural stroke and death with CAS compared with CEA (Appendix Table 1, available at www.annals.org) (31, 35–37). Outcome ascertainment in studies using administrative data sets was based solely on information from hospital discharge records.

Long-Term Outcomes. Six studies (3 RCTs and 3 NRCSs) reported long-term outcomes (17, 20, 21, 27, 29, 30). Of 3 RCTs, 1 reported no cerebrovascular events (20). There was no statistically significant difference in the risk

for outcomes of ipsilateral stroke (including the periprocedural composite outcome of stroke or death), any stroke (including periprocedural death), or a composite end point (including ipsilateral stroke between patients treated with CAS or CEA) (Appendix Table 1). Greater incidences of postprocedural ipsilateral stroke (including any periprocedural stroke) in the CAS than in the CEA group were reported in 1 RCT of low risk of bias, but the difference between groups did not reach statistical significance in adults with asymptomatic carotid stenosis (Figure 1). Findings from 3 NRCSs, 1 of medium risk and 2 of high risk of bias, were consistent with RCTs for the composite outcome of stroke or death (27, 29, 30) and for the outcome of ipsilateral stroke (30).

CEA Plus Medical Therapy Versus Medical Therapy Alone

Carotid endarterectomy was compared with medical therapy alone in 11 studies (3 RCTs and 8 NRCSs) (23–25, 28, 38–44). All 3 RCTs recruited patients before the year 2000 (23–25). Although all RCTs reported use of appropriate medical therapy as prescribed by individual treating physicians, at randomization adults with asymptomatic carotid stenosis did not receive what is currently considered “best”-available medical therapy (Table 1). Therefore, evidence supporting the use of CEA rather than medical therapy alone may have limited applicability to contemporary management of adults with asymptomatic carotid stenosis.

Periprocedural and 30-Day Outcomes. Two RCTs showed an increased risk for periprocedural stroke, death, and myocardial infarction with CEA and medical therapy versus medical therapy alone (23, 24). The periprocedural period for the medically treated patients was defined as 30

Table 2. Summary Assessment of Strength of Evidence for Comparisons Among Interventions

Outcomes, by Comparator	Strength of Evidence	Studies (Participants), n	Risk-of-Bias Rating	Consistency	Precision	Applicability	Findings
Ipsilateral stroke*							
CAS vs. CEA	Insufficient	RCT: 2 (1418) NRCS: 0	RCT: 1 low, 1 medium NRCS: NA	Inconsistent	Imprecise	Applicable†	No statistically significant difference; CAS group had greater event rate in 1 RCT and lower in another
CEA vs. medical therapy alone	Moderate	RCT: 3 (5223) NRCS: 3 (510)	RCT: 3 low NRCS: 1 medium, 2 high	Consistent	Precise	Limited applicability‡	Evidence to support the use of CEA may no longer be applicable to contemporary clinical practice
CAS vs. medical therapy alone	Insufficient	RCT: 0 NRCS: 0	Not graded	Unknown	Unknown	Unknown	
Any strokes§							
CAS vs. CEA	Insufficient	RCT: 2 (1418) NRCS: 1 (269)	RCT: 1 low, 1 medium NRCS: 1 medium	Consistent	Imprecise	Applicable†	No statistically significant difference; CAS group had greater event rate
CEA vs. medical therapy alone	Moderate	RCT: 3 (5223) NRCS: 4 (648)	RCT: 3 low NRCS: 1 medium, 3 high	Consistent	Precise	Limited applicability‡	Evidence to support the use of CEA may no longer be applicable to contemporary clinical practice
CAS vs. medical therapy alone	Insufficient	RCT: 0 NRCS: 1 (946)	NRCS: 1 medium	Unknown	Precise	Limited applicability‡	Insufficient evidence; only a single retrospective study was available
Death							
CAS vs. CEA	Insufficient	RCT: 1 (237) NRCS: 1 (269)	RCT: 1 medium NRCS: 1 medium	Inconsistent	Imprecise	Applicable to patients at high risk for CEA complications	No statistically significant difference between groups
CEA vs. medical therapy alone	Moderate	RCT: 3 (5223) NRCS: 2 (234)	RCT: 3 low NRCS: 2 high	Consistent	Precise	Limited applicability†	No statistically significant difference; CEA group had greater event rate
CAS vs. medical therapy alone	Insufficient	RCT: 0 NRCS: 1 (946)	RCT: NA NRCS: 1 medium	Unknown	Precise	Limited applicability‡	Insufficient evidence; only a single retrospective study was available

CAS = carotid artery stenting; CEA = carotid endarterectomy; NA = not applicable; NRCS = nonrandomized, comparative study; RCT = randomized, controlled trial.
 * Includes any stroke within 30 d or the composite end point of ipsilateral stroke, including any stroke or death within 30 d.
 † Applicable to low to medium risk for CEA (1 RCT); high risk for CEA (1 RCT).
 ‡ Not applicable to contemporary clinical practice because the available studies did not use what is currently considered best medical therapy.
 § Includes any death within 30 d.

days (23) and 42 days (24) after randomization in these RCTs. They showed a statistically significantly greater risk for any stroke and a nonstatistically significantly greater risk for death during the perioperative period in the CEA

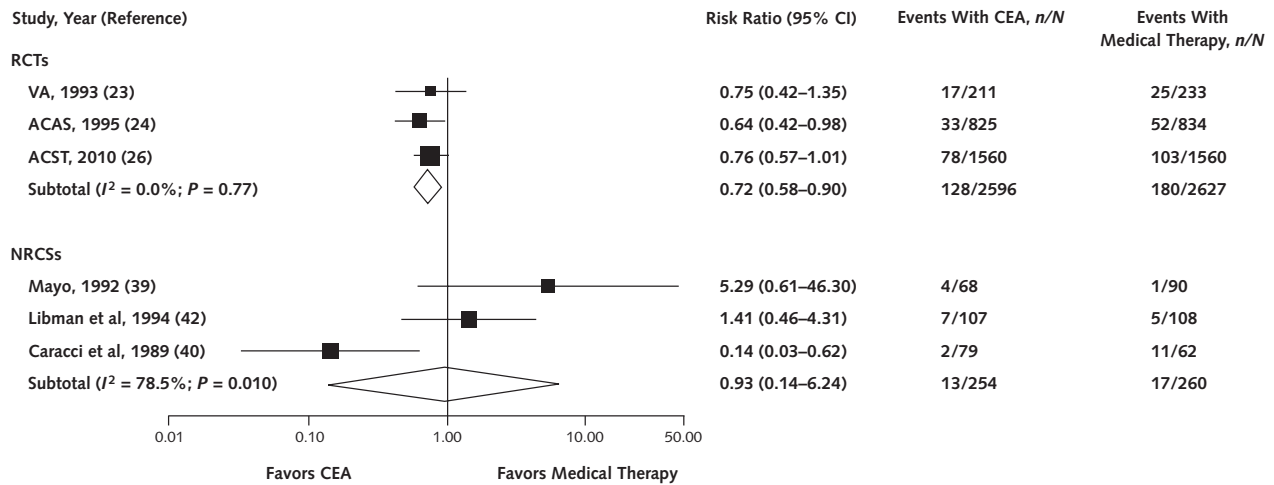
group than in the medical therapy group during the corresponding follow-up (Appendix Table 2, available at www.annals.org). The third RCT used a definition of 30-day illness and mortality rates in the medical therapy group

Figure 1. Forest plot of ipsilateral stroke (including any stroke within 30 days) in RCTs of CAS versus CEA.



CAS = carotid artery stenting; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy Versus Stenting Trial; RCT = randomized, controlled trial; SAPHIRE = Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy.

Figure 2. Meta-analysis of ipsilateral stroke (including any stroke within 30 days) in RCTs and NRCSs of CEA versus medical therapy.



ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CEA = carotid endarterectomy; NRCS = nonrandomized, comparative study; RCT = randomized, controlled trial; VA = Veterans Affairs.

after they had a CEA surgery during follow-up (25). This definition differed considerably from the definitions used in the other 2 RCTs (23, 24). In contrast, 3 NRCSs, 1 of medium risk and 2 of high risk of bias, reported that differences between groups were not statistically significant for the outcomes of stroke or death (28, 39, 41).

Long-Term Outcomes. Three RCTs (all of low risk of bias) and 7 NRCSs (2 of medium risk and 5 of high risk of bias) compared the effect of CEA and medical therapy on long-term outcomes (23–25, 38–44). The risk for ipsilateral stroke and any stroke was statistically significantly lower with CEA than with medical therapy alone in RCTs (Appendix Table 2). Meta-analyses of these RCTs did not show statistically significant differences between treatment groups for the risk for fatal stroke, death from any cause, or death from cardiovascular causes. Meta-analysis of NRCSs did not show a statistically significant difference in the risk for ipsilateral stroke with CEA compared with medical therapy alone (Figure 2). For other outcomes, findings from NRCS were consistent with RCT findings.

CAS Plus Medical Therapy Versus Medical Therapy Alone

No RCT compared CAS versus medical therapy. Of the 2 NRCSs reporting on this comparison, 1 reported data on periprocedural outcomes and the other on long-term outcomes (28, 45). Available evidence was insufficient to reach conclusions on the relative effectiveness of the treatments.

Periprocedural and 30-Day Outcomes. A single NRCS of high risk of bias provided data for the composite end point of any stroke or death during the 30-day period and reported no statistically significant difference between CAS and medical therapy versus medical therapy alone (28).

Long-Term Outcomes. One NRCS of medium risk of bias found a statistically significantly decreased risk for stroke, death, and a composite of these 2 end points with CAS versus medical therapy alone (45), using a propensity score-matched analysis. The study did not report information on the outcome of ipsilateral stroke.

Rate of Ipsilateral Stroke With Medical Therapy Alone

Meta-analysis for ipsilateral stroke included 26 studies in 30 articles (23–26, 46–71). The incidence rate of ipsilateral stroke was 1.68% (CI, 1.34% to 2.11%) per year of follow-up. The incidence rate of ipsilateral stroke in a subgroup analysis of studies of low or medium risk of bias was similar: 1.59% (CI, 1.21% to 2.09%) per year of follow-up. Meta-regression analyses showed that the incidence rate of ipsilateral stroke was statistically significantly lower in studies that completed recruitment between 2000 and 2010 than in those that completed recruitment earlier (1.13% vs. 2.38% per year, respectively; $P < 0.001$).

DISCUSSION

Evidence was neither sufficiently robust (for CAS) nor applicable to current clinical practice (for CEA) to determine the comparative effectiveness of management approaches for adults with asymptomatic carotid stenosis. Because recent RCTs of interventional strategies (CAS vs. CEA) did not evaluate adequate numbers of persons with asymptomatic carotid stenosis and recruited heterogeneous groups of patients (across studies), definitive conclusions about the superiority of 1 interventional strategy over another could not be reached. Evidence from comparisons of CEA plus medical therapy versus medical therapy alone

showed a reduction in the risk for ipsilateral stroke or any stroke with the combined approach. However, RCTs comparing CEA plus medical therapy with medical therapy alone recruited participants from the 1990s through early 2000. Medical therapy was suboptimal in these older RCTs by current standards, and findings of the RCTs may not be applicable to contemporary clinical practice. No RCT compared CAS with medical therapy alone.

Meta-analysis of incidence rate data from prospective single-group cohorts of medical therapy alone for asymptomatic carotid stenosis showed that the incidence rate of ipsilateral stroke was low (1.68% per year), particularly in studies conducted in the past decade (1.13% per year). Being at relatively low risk for ipsilateral stroke, asymptomatic patients receiving best-available medical therapy may benefit from either revascularization procedure only if periprocedural complications can be minimized. Most adults with asymptomatic stenosis are likely to benefit from best-available medical therapy alone (72). At the same time, there are certain high-risk groups of patients for whom medical therapy may not be sufficient who may be at an increased risk for stroke. Recent studies suggest methods (for example, the detection of microemboli, ulceration, or intraplaque hemorrhage) that can help identify high-risk patients with asymptomatic carotid stenosis who may benefit from invasive interventional procedures (67, 68, 73).

In older RCTs that compared CEA and medical therapy alone, the composite primary end point of ipsilateral stroke included the periprocedural outcome of stroke or death, whereas in recent RCTs comparing CAS with CEA, the composite periprocedural outcome also included myocardial infarction. Recent RCTs showed that the CEA group had more periprocedural myocardial infarctions, whereas the CAS group had more periprocedural strokes. In 1 RCT, even a minor periprocedural stroke had a greater effect on physical and mental health status at 1 year, as measured by the 36-Item Short Form Health Survey, than did periprocedural myocardial infarction (17). Further research is needed to evaluate the effect of periprocedural myocardial infarction in the long-term prognosis of patients having invasive carotid artery procedures.

According to recent guidelines, **prophylactic CEA** is reasonable (class IIa recommendation, as designated by the American Heart Association) in persons with **stenosis greater than 70% who are at low risk for perioperative complications** and that CAS rather than CEA should be used when revascularization is indicated but neck anatomy is unfavorable for arterial surgery (74). Across the guidelines published in 2011, the strength of the recommendations for revascularization in asymptomatic carotid stenosis varies considerably (74–76). The lack of concordance on the strength of the recommendation among these guidelines may relate to insufficient evidence. The absence of contemporary evidence (for CEA) and the paucity of direct evidence (for CAS) comparing best medical therapy to these interventions emphasize the need for a large trial in

asymptomatic persons that defines the role of revascularization techniques to reduce stroke due to atherosclerotic plaque compared with current best medical therapy.

To put our findings in context, we searched MEDLINE for recent (published since 2010) reviews on this topic. Our searches identified 7 systematic reviews including 3 to 7 RCTs each (**Supplement**). Six reviews compared CAS versus CEA (77–82), and 1 compared CEA versus medical therapy alone (83). Our findings and those of the other reviews were consistent, even though most other reviews combined symptomatic and asymptomatic populations and excluded NRCSs. Our meta-analysis of single-group cohorts for medical therapy alone concurred with a previous analysis that examined only 11 selected studies (72). In addition, through application of advanced statistical methods, our findings emphasize the reduced incidence of ipsilateral stroke in recent years, among asymptomatic populations managed with medical therapy alone.

The limitations of this review reflect, to a large extent, the limitations of the data in primary studies. The populations in the studies we reviewed were heterogeneous, reflecting a lack of consensus in defining persons with asymptomatic carotid stenosis. Researchers should consider how to better standardize definitions of asymptomatic carotid stenosis and methods for assessing its severity. Published RCTs did not present survival data for the outcomes of interest in asymptomatic subgroups, thereby precluding us from conducting meta-analyses of time-to-event data. No studies provided data beyond 10-year follow-up to evaluate long-term effects of revascularization interventions. Observational data could be misleading due to population selection and outcome ascertainment bias (84).

We searched for ongoing studies indexed in clinical trial registries (ClinicalTrials.gov and Current Clinical Trials) and identified 7 ongoing RCTs (4 comparing revascularization vs. medical therapy alone [NCT00805311, NCT00497094, ISRCTN78592017, and ISRCTN97744893] and 3 comparing CAS vs. CEA [NCT00772278, NCT00883402, and NCT00106938]) that had planned sample sizes ranging from 500 to 5000 participants (**Supplement**). Based on our meta-analyses of the current incidence rate of ipsilateral stroke with medical therapy alone (1.13% per year) and the effectiveness of revascularization (RR, 0.72, for the comparison of CEA vs. medical therapy), we estimate that a trial needs to enroll approximately 3000 participants per group to have 80% power to demonstrate superiority of revascularization versus medical therapy alone over 5 years of follow-up, at the 2-sided significance level of 0.05. This requirement is not being met by any of the 4 ongoing RCTs comparing revascularization with medical therapy alone.

The approach to primary stroke prevention in persons with asymptomatic extracranial carotid stenosis has been controversial, in part because the benefits of surgery have been known to be modest. The possibility of substantial iatrogenic harm (stroke or death) in patients who are, by

definition, without symptoms is real and counterbalances enthusiasm for interventional treatments. This review emphasizes the uncertainty that remains in this area. Our findings also highlight that event rates in patients treated with medical therapy have decreased over time. A similar effect was illustrated recently in a study of stroke prevention in medically managed patients with intracranial arterial stenosis (85). Future RCTs of asymptomatic carotid stenosis should focus not only on whether CAS is equal or superior to CEA but also on whether these invasive interventional procedures provide incremental benefits over best-available medical therapy.

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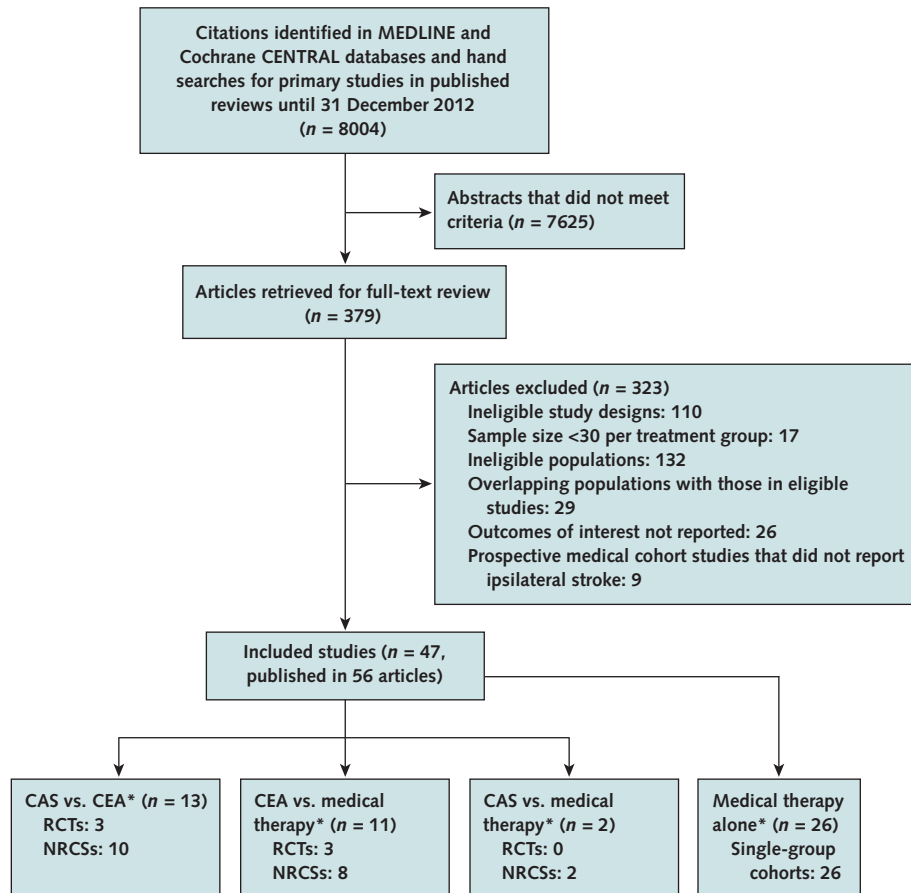
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Appendix Figure. Summary of evidence search and selection.



CAS = carotid artery stenting; CEA = carotid endarterectomy; CENTRAL = Central Register of Controlled Trials; NRCS = nonrandomized, comparative study; RCT = randomized, controlled trial.

* Indicates overlap of studies.

Appendix Table 1. Results Comparing CAS Plus Medical Therapy With CEA Plus Medical Therapy for Asymptomatic Carotid Stenosis

Results	RCTs			NRCSs			<i>I</i> ² Heterogeneity (P Value)
	Design (Study Reference)	Studies (Participants), n	CAS vs. CEA Estimate (95% CI)	Design (Study Reference)	Studies (Participants), n	CAS vs. CEA Summary Risk Ratio (95% CI)	
Long-term outcomes							
Ipsilateral stroke (including any stroke within 30 d)	RCTs (17, 21)	2 (1418)	CREST: Adjusted HR, 1.86 (0.95–3.66) SAPPHIRE: RR, 0.54 (0.28–1.02)	Not reported			
Composite end point of ipsilateral stroke*	RCTs (17, 21)	2 (1418)	CREST: Adjusted HR, 1.17 (0.69–1.98) SAPPHIRE: RR, 0.73 (0.47–1.14)	NRCS (30)	1 (1518)	RR, 1.29 (0.72–2.32)	NA
Any stroke (including any death within 30 d)	RCTs (17, 21)	2 (1418)	CREST: Adjusted HR, 1.17 (0.69–1.98) SAPPHIRE: RR, 1.12 (0.51–2.43)	NRCS (29)	1 (269)	RR, 1.34 (0.51–3.47)	NA
Any stroke or death	RCT (17)	1 (1181)	CREST: RR, 1.86 (0.95–3.66)	NRCS (27, 29)	1 (269)† 1 (1672)‡	RR, 1.26 (0.77–2.05) Adjusted HR, 0.62 (0.42–0.91)	NA
Death	RCT (21)	1 (237)	SAPPHIRE: RR, 0.47 (0.18–1.20)	NRCS (29)	1 (269)†	RR, 1.36 (0.78–2.35)	
Periprocedural or 30-d outcomes							
Any stroke	RCTs (19, 22)	2 (1418)	CREST: RR, 1.64 (0.68–3.97) SAPPHIRE: RR, 2.05 (0.18–22.30)	NRCS (29–32, 35, 36)	2 (507)† 4 (375 351)‡	RR, 0.55 (0.11–2.67) RR, 1.74 (1.41–2.16)	0% (0.95); 75% (0.008)
Death	RCTs (19, 22)	2 (1418)	CREST: No events SAPPHIRE: RR, 2.05 (0.18–22.30)	NRCS (31, 32, 35, 36)	4 (375 353)‡	RR, 1.43 (1.20–1.71)	0% (0.44)

CAS = carotid artery stenting; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy Versus Stenting Trial; HR = hazard ratio; NA = not applicable; NRCS = nonrandomized, comparative study; RCT = randomized, controlled trial; RR = relative risk; SAPPHIRE = Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy.

* Including any stroke or myocardial infarction or death within 30 d.

† Clinical data set.

‡ Administrative data set or registry.

Appendix Table 2. Results Comparing CEA Plus Medical Therapy With Medical Therapy Alone in Asymptomatic Carotid Stenosis

Results	RCTs				NRCSS			
	Design (Study Reference)	Studies (Participants), n	CEA vs. Medical Therapy Alone Summary RR (95% CI)	I ² Heterogeneity (P Value)	Design (Study Reference)	Studies (Participants), n	CEA vs. Medical Therapy Alone Summary RR (95% CI)	I ² Heterogeneity (P Value)
Long-term outcomes								
Ipsilateral stroke (including any stroke within 30 d)	RCT (23, 24, 26)	3 (5223)	0.72 (0.58–0.90)	0.0% (0.77)	NRCS (39, 40, 42)	3 (514)	0.93 (0.14–6.42)	78% (0.010)
Composite end point of ipsilateral stroke*	RCT (23, 24, 26)	3 (5223)	0.69 (0.55–0.87)	0% (0.90)	NRCS (39, 40, 42)	3 (514)	0.78 (0.12–4.87)	77% (0.009)
Any stroke (including any death within 30 d)	RCT (23, 24, 26)	3 (5223)	0.68 (0.56–0.82)	17.7% (0.30)	NRCS (39, 40, 42, 43)	4 (648)	0.86 (0.44–1.66)	29.4% (0.24)
Any stroke or death	RCT (23, 24, 26)	3 (5223)	0.94 (0.85–1.03)	19% (0.29)	NRCS (38, 39)	2 (391)	1.34 (0.34–5.28)	61.4% (0.110)
Death	RCT (23, 24, 26)	3 (5223)	1.05 (0.97–1.14)	0% (0.60)	NRCS (40, 43)	2 (234)	2.81 (1.99–3.98)	22.3% (<0.010)
Periprocedural or 30-d outcomes								
Any stroke	RCT (23, 24)	2 (1036)	5.94 (2.06–17.12)	0% (0.91)	NRCS (40, 43)	2† (234)	NA	NA
Death	RCT (23, 24)	2 (1036)	3.68 (0.77–17.72)	0% (0.82)	None	NA	NA	NA

CEA = carotid endarterectomy; NA = not applicable; NRCS = nonrandomized, comparative study; RCT = randomized, controlled trial; RR = risk ratio.

* Including any stroke or death within 30 d.

† Reported 0 events.