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Annals of Internal Medicine | Review

Screening for Asymptomatic Carotid Artery Stenosis: A Systematic Review and Meta-analysis for the U.S. Preventive Services Task Force

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Background: Approximately 10% of ischemic strokes are caused by carotid artery stenosis (CAS). Estimated prevalence of asymptomatic CAS is 1%.

Purpose: To evaluate evidence on screening and treating asymptomatic adults for CAS.

Data Sources: MEDLINE, the Cochrane Library, EMBASE, and trial registries through September 2013; MEDLINE through March 2014 for trials.

Study Selection: Good- or fair-quality trials of screening, carotid endarterectomy (CEA), or stenting compared with medical therapy or of intensification of medical therapy; systematic reviews; multiinstitution studies reporting harms; and externally validated risk-stratification tools.

Data Extraction: Dual extraction and quality assessment.

Data Synthesis: No trials compared screening with no screening or stenting with medical therapy or assessed intensification of medical therapy, and no externally validated, reliable risk-stratification tools were found. Given the specificity of ultrasonography (range, 88% to 94% for CAS of ≥50% to ≥70%), its use in low-prevalence populations would yield many false-positive results. Absolute reduction of nonperioperative strokes was 5.5% (95% CI, 3.9% to 7.0%; 3 trials with 5223 participants) over approximately 5 years for CEA compared with medical therapy. The 30-day rates of stroke or death after CEA in trials and cohort studies were 2.4% (CI, 1.7% to 3.1%; 6 trials; $n = 3435$) and 3.3% (CI, 2.7% to 3.9%; 7 studies; $n = 17\,474$), respectively. Other harms of interventions include myocardial infarction, nerve injury, and hematoma.

Limitations: Trials may have overestimated benefits and used highly selected surgeons. Medical therapy used in trials was outdated, and stroke rates have declined in recent decades. Harms may have been underreported.

Conclusion: Current evidence does not establish incremental overall benefit of CEA, stenting, or intensification of medical therapy. Potential for overall benefit is limited by low prevalence and harms.

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Stroke is a leading cause of death and disability (1). An estimated 7 million U.S. adults have had a stroke, and roughly 75% were first attacks (2). Ischemic strokes account for nearly 90% of all strokes in the United States (3). Carotid artery stenosis (CAS) causes approximately 10% of ischemic strokes (4).

Carotid artery stenosis refers to atherosclerotic narrowing of the extracranial carotid arteries—specifically, the internal carotid arteries or the common and internal carotid arteries. The best available data for the prevalence of asymptomatic CAS from large U.S.-based studies of the general population were published in the 1990s and enrolled adults aged 65 years or older (5, 6). Data published in 1992 showed a prevalence of just more than 1% for CAS of 75% to 99% (6), and those published in 1998 suggested a prevalence of 0.5% for CAS of 70% to 99% (5).

Several studies have attempted to estimate the rate of progression of asymptomatic CAS and predict neurologic events (5, 7–11). The best available data from large U.S.-based studies of the general population revealed a 5-year risk for ipsilateral stroke of 5% for CAS of 70% or greater (5441 participants) (5).

The main purpose of this review is to evaluate the current evidence on whether screening asymptomatic adults for CAS reduces the risk for ipsilateral stroke and on harms associated with screening and interventions for CAS. We also evaluated evidence on the incremental benefit of medical therapy and on risk-stratification tools. Despite a D recommendation from the U.S. Preventive Services Task Force in 2007 (12), many surgeries or interventions for asymptomatic CAS continue to be performed, and free or "cash-on-the-barrel" screenings are offered in public locations across the country (13).

Methods

We developed an analytic framework (**Supplement 1**, available at www.annals.org) and key questions (**Table 1** of **Supplement 2**, available at www.annals.org) that guided the review. Detailed methods and additional results are publicly available in our full evidence report (www.uspreventiveservicestaskforce.org) (14).

Data Sources and Searches

We searched MEDLINE, the Cochrane Library, and EMBASE for English-language articles published through

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September 2013 (**Tables 2** and **3** of **Supplement 2**). We conducted a targeted update search of MEDLINE for trials published through 31 March 2014 and searched clinical trial registries for unpublished literature. To supplement electronic searches, we reviewed reference lists of included studies and literature suggested by reviewers.

Study Selection

Two investigators independently reviewed abstracts and full-text articles against prespecified eligibility criteria (**Table 4** of **Supplement 2**). We included studies that focused on asymptomatic adults with CAS and studies that analyzed the asymptomatic group separately. We included randomized, controlled trials (RCTs) of screening for CAS, RCTs and systematic reviews of treatment effectiveness, multi-institution trials or cohort studies that reported harms, and studies that attempted to externally validate risk-stratification tools. For evaluation of accuracy and reliability of ultrasonography, we focused on systematic reviews but also included primary studies that were published after the literature search cutoff of the most recent good-quality systematic review.

Data Extraction and Quality Assessment

One investigator extracted pertinent information from each article. Another investigator reviewed extractions for completeness and accuracy. Two independent investigators assigned quality ratings (good, fair, or poor) for each study using predefined criteria (14, 15). Disagreements were resolved with team discussion. Poor-quality studies are described in the full report (14).

Data Synthesis and Analysis

We qualitatively synthesized findings for each key question by summarizing the characteristics and results of included studies in tabular or narrative format. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies following established guidance (16). We conducted meta-analysis of RCTs that compared carotid endarterectomy (CEA) with medical therapy for relevant outcomes reported by several studies. We used DerSimonian–Laird random-effects models to estimate pooled effects (17) and calculated risk differences between CEA and medical therapy to show the absolute differences between groups. Absolute measures are more easily interpreted, show more directly relevant information, and better allow decision makers to assess tradeoffs between benefits and harms (18–20). We calculated chi-squared and I^2 statistics to assess statistical heterogeneity in effects among studies (21, 22).

To allow the comparison of rates of perioperative harms reported in RCTs with those from sources that may be more representative of real-world clinical practice, we conducted meta-analyses of cohort studies that reported perioperative (30-day) stroke or death rates. We also conducted meta-analyses of such rates reported in trials that involved CEA or carotid angioplasty and stenting (CAAS), regardless of the comparator.

We conducted sensitivity analyses using profile likelihood random-effects methods when our meta-analyses included few studies (23–26). We did not include poor-quality studies in our analyses. Analyses were conducted using Stata, version 11.1 (StataCorp, College Station, Texas).

Role of the Funding Source

The Agency for Healthcare Research and Quality funded the review. Members of the U.S. Preventive Services Task Force and Agency for Healthcare Research and Quality assisted in developing the review's scope and reviewed draft manuscripts, but the authors are solely responsible for the content.

RESULTS

We included 78 published articles that reported on 56 studies (**Figure 1**).

Direct Evidence That Screening Reduces Ipsilateral Stroke

We found no eligible studies that provided evidence on whether screening reduced ipsilateral stroke.

Accuracy and Reliability of Duplex Ultrasonography

We included 3 meta-analyses (27–29) and 1 fair-quality primary study (30) (**Table 5** of **Supplement 2**). The most recent good-quality meta-analysis (28) included 47 studies published through 2003 that used digital subtraction angiography as the reference standard. It reported sensitivity and specificity for detecting stenosis of 50% or greater (1716 participants) of 98% (95% CI, 97% to 100%) and 88% (CI, 76% to 100%), respectively. Sensitivity and specificity for detecting stenosis of 70% or greater (2140 participants) were 90% (CI, 84% to 94%) and 94% (CI, 88% to 97%). Using data from this meta-analysis, the last evidence report for the U.S. Preventive Services Task Force estimated the sensitivity and specificity for detecting stenosis of 60% or greater as 94% and 92%, respectively (31). The meta-analysis reported wide, clinically important variation in measurement properties among laboratories (28). The findings of the other meta-analyses were generally consistent with these results, but specificity in the primary study was lower (66% for detecting CAS of 70% to 99% [95% CI, 63% to 71%]; 503 participants) (30). Additional results are provided in our full report (14).

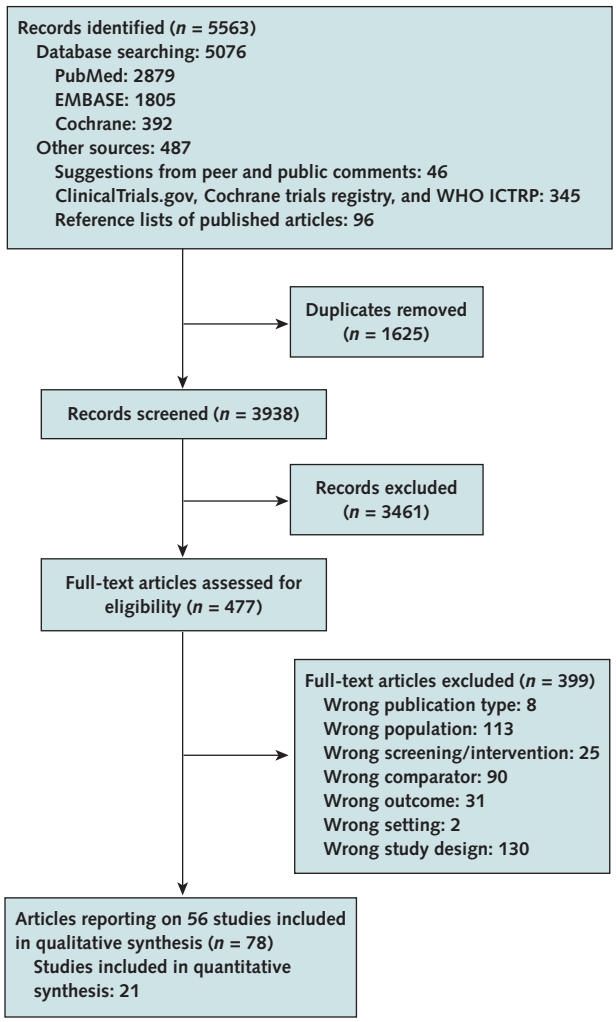
Benefits of CEA or CAAS Beyond Medical Therapy

We included 3 RCTs (**Table 1**) described in 12 publications (32–43) that compared CEA with medical therapy and 3 systematic reviews described in 5 publications (31, 44–47). We found no eligible studies that compared CAAS with medical therapy and no studies that compared CEA with current standard medical therapy.

The ACAS (Asymptomatic Carotid Atherosclerosis Study) and the VACS (Veterans Affairs Cooperative Study) were conducted in North America; the ACST (Asymptomatic Carotid Surgery Trial) involved 30 coun-

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Figure 1. **Summary of evidence search and selection.**



ICTRP = International Clinical Trials Registry Platform; WHO = World Health Organization.

tries, primarily in Europe. Medical therapy varied across trials and was often not clearly defined or standardized. Surgeons with a history of low complication rates were selected. They submitted records of their last 50 cases or previous 24 months of experience with CEA and were selected on the basis of review by a committee or morbidity and mortality rates less than 3%.

Our meta-analyses found that fewer persons treated with CEA had perioperative stroke or death or subsequent ipsilateral stroke, perioperative stroke or death or any subsequent stroke, any stroke or death, nonperioperative ipsilateral stroke, and any nonperioperative stroke than those in medical therapy groups (**Table 2** and **Figure 2**). For all-cause mortality, we found no significant difference. Results for sensitivity analyses using profile likelihood methods were very similar to those of our main analyses, with only minor variation in width of CIs (**Table 2**).

In the ACST, more than one half (57.8% [166 of 287]) of nonperioperative strokes were disabling or fatal, and the proportional reduction in disabling or fatal stroke (relative risk, 0.61 [CI, 0.41 to 0.92]) was similar to that for any stroke (relative risk, 0.54 [CI, 0.43 to 0.68]) (37). Subgroup analyses of the ACAS showed a statistically significant reduction for men (relative risk reduction, 66% [CI, 36% to 82%]) but not for women (relative risk reduction, 17% [−96% to 65%]) for estimated 5-year rate of perioperative stroke or death and subsequent ipsilateral stroke. In the ACST, reduction in first nonperioperative stroke rate was statistically significant for both sex subgroups.

Two of the 3 systematic reviews were conducted before the most recent ACST publication (37) and thus had preliminary ACST data (31, 44). The third review compared management strategies for asymptomatic CAS and included a meta-regression to evaluate the effect of time (to reflect improvements in medical therapy) on incidence rates of stroke (46). The investigators found that the incidence rate of ipsilateral stroke was lower in studies that completed recruitment from 2000 to 2010 than those that completed recruitment in earlier years (1.1% vs. 2.4% per year; $P < 0.001$) (46).

Incremental Benefit of Additional Medications Beyond Current Standard Medical Therapy

We found no eligible studies that assessed benefits of additional medications beyond current standard medical therapy.

Harms Associated With Screening

Potential harms of screening include harms associated with false-positive results and harms of any confirmatory work-up, such as angiography. We found no studies on anxiety or labeling among persons with false-positive results. Two RCTs reported strokes after angiography. In the ACAS (33), 1.2% of patients (5 of 414) who had angiography had strokes; 1 patient died subsequently. In the VACS (42), 0.4% of patients (3 of 714) had nonfatal strokes after angiography.

Harms Associated With CEA or CAAS

We included 3 RCTs that compared CEA with medical therapy and 24 additional good- or fair-quality multiinstitutional trials or cohort studies. Most studies reported perioperative death or stroke and did not report on other harms (such as nerve injuries, other postoperative harms, or psychological harms).

Trial Characteristics

Randomized, controlled trials that compared CEA with medical therapy have been described. Characteristics of other included trials, as well as threats to internal and external validity, are presented in **Table 6** of **Supplement 2** (48–56). In brief, these included 1 RCT that compared CEA with a control group (nearly one half of participants received CEA [48]), 1 RCT that compared CEA with low-

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Table 1. **Characteristics and Main Results of Included Fair- or Good-Quality Randomized, Controlled Trials of CEA Compared With MM for Asymptomatic CAS***

Study (Reference)	CAS Percentage	Sample Demographic Characteristics	Sample Comorbid Conditions at Enrollment, %	Source of Patients	Follow-up, *y*
ACAS (32-35)	≥60%	Participants: 1662 Mean age: 67 y Men: 66% White: 95%	DM: 23 Hypertension: 64 Hypercholesterolemia: NR Smoke: 26 CAD: 69 Previous contralateral CEA: 20 Contralateral occlusion: 9 Contralateral TIA/stroke: 25	Ultrasonography laboratories; practitioners who found bruits or CAS during evaluation for peripheral vascular surgery or contralateral CEA	Median: 2.7
ACST (36-40)	≥60%	Participants: 3120 Mean age: 68 y Men: 66% White: NR	DM: 20 Hypertension: 65 Hypercholesterolemia: 27 Smoke: NR CAD, non-DM: 27 Previous contralateral CEA: 24 Contralateral occlusion: 9 Contralateral TIA/stroke: NR	Medical and surgical clinics	Median in survivors: 9
VACS (41-43)	≥50%	Participants: 444 Mean age: 65 y Men: 100% White: 87%	DM: 28 Hypertension: 64 Hypercholesterolemia: NR Smoke: 50 History of MI: 26 Previous contralateral CEA: NR Contralateral occlusion: NR Contralateral TIA/stroke: 32	11 VAMCs; patients scheduled for surgery with unilateral symptomatic lesions found to have contralateral asymptomatic stenosis or with incidental bruits and positive noninvasive screening test results	Mean: 4

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; ARR = absolute risk reduction; CAD = coronary artery disease; CAS = carotid artery stenosis; CEA = carotid endarterectomy; DM = diabetes mellitus; MI = myocardial infarction; MM = medical management; NR = not reported; RRR = relative risk; TIA = transient ischemic attack; VACS = Veterans Affairs Cooperative Study; VAMC = Veterans Administration Medical Center.

* Requirements for asymptomatic status differed slightly across the trials. For example, the ACST enrolled persons with no TIA or stroke attributable to the ipsilateral artery for the past 6 mo, and the ACAS enrolled those with no history of cerebrovascular events in the distribution of the ipsilateral carotid artery or the vertebrobasilar system and no symptoms referable to the contralateral artery for the past 45 d.

† During the perioperative period, 2.3% of surgical patients (n = 19) had a stroke or died (95% CI, 1.28%–3.32%) compared with 0.4% of patients in the medical group (CI, 0.0%–0.8%). It was estimated that if all 724 patients receiving CEA had arteriography as part of the ACAS (some had angiography in the 60 d before the study) that 2.7% of surgical patients would have had a stroke or died as a result of the procedure.

‡ At study entry, 17% of participants randomly assigned in 1993 to 1996 were receiving lipid-lowering therapy. That percentage increased to 58% in 2000 to 2003. At the last follow-up in 2002 to 2003, more than 90% of the survivors received antiplatelet therapy, 81% received antihypertensives, and 70% received lipid-lowering therapy. At follow-up in 2002 or 2003, mean blood pressure was 148/79 mm Hg in both groups (41).

§ 2.9% (44 of 1532 CEAs performed) was the rate of perioperative stroke or death for persons in the immediate CEA group; when those in the delayed group who had CEA were included, the rate was 3.0% (95% CI, 2.4%–3.9%).

dose aspirin (49), 2 RCTs that compared CEA with CAAS (50–52), 2 uncontrolled trials that used postmarketing surveillance data for CAAS (53, 54, 56), and 1 study that pooled data from 2 uncontrolled trials of CAAS (55). Further details are provided in our full report (14).

Observational Study Characteristics

Eight fair-quality, multi-institution cohorts reported perioperative (30-day) harms of CEA (**Table 6** of **Supplement 2**) (57–68). All 8 used Medicare claims or enrollment databases. Harms were identified using both claims data and medical chart review. Most studies were conducted among Medicare beneficiaries of single states (57–63, 66–68); 2 used data from 10 states (64, 65).

One cohort from the credentialing phase of CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) reported rates of harms after CAAS (1151 participants with asymptomatic CAS of ≥70%) (69).

An additional 8 fair-quality studies reported in-hospital (but not 30-day) perioperative events after CEA or CAAS from state discharge databases (70–72) or the Nationwide Inpatient Sample (**Table 6** of **Supplement 2**) (73–77). Results are provided in **Table 7** of **Supplement 2** but are not included in this article because they only capture in-hospital events.

CEA Compared With Medical Therapy

Our meta-analysis found that 1.9% (CI, 1.2% to 2.6%) more participants treated with CEA had perioperative (30-day) stroke or death than those in medical therapy groups (**Table 2** and **Figure 2**).

Two trials reported perioperative (30-day), nonfatal myocardial infarctions (MIs). The ACST found that 0.6% more participants treated with CEA had events than those treated with medical therapy (10 events vs. 1 event). The VACS reported 4 events in the CEA group and none in the medical therapy group.

Rates of Perioperative (30-Day) Death or Stroke

The main results of relevant studies are summarized in **Table 7** of **Supplement 2**. Our meta-analysis of 7 cohort

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Table 1—**Continued**

Medical Therapy Description	Rate of Perioperative Stroke/Death and Any Subsequent Stroke	Rate of Perioperative Stroke/Death and Subsequent Ipsilateral Stroke	Rate of Any Stroke or Death	Perioperative (30-Day) Stroke or Death, %
Aspirin 325 mg daily; also had risk factor discussion and modification at random assignment, subsequent interviews, and telephone follow-up	Observed events: MM: 10.3% CEA: 7.3% ARR: 3.0% 5-y estimate: MM: 17.5% CEA: 12.4% ARR: 5.1%	Observed events: MM: 6.2% CEA: 4.0% ARR: 2.2% 5-y estimate: MM: 11% CEA: 5.1% ARR: 5.9%	Observed events: MM: 18.6% CEA: 15.4% ARR: 3.2% 5-y estimate: MM: 31.9% CEA: 25.6% ARR: 6.3%	2.7†
Left to discretion of clinicians; usually included antiplatelet and antihypertensive therapy; in later years of the trial, lipid-lowering therapy was common‡	MM: 13.1% CEA: 9.2% RR: 0.7 (95% CI, 0.6–0.9) ARR: 3.9%	MM: 6.9% CEA: 5.3% RR: 0.8 (95% CI, 0.6–1.0) ARR: 1.6%	MM: 49.4% CEA: 47.2 % RR: 0.95 (95% CI, 0.89–1.03)	2.9§
Aspirin 650 mg twice daily, reduced to 325 mg daily if not tolerated	MM: 12.9% CEA: 10.4% RR: 0.8 (95% CI, 0.5–1.4) ARR: 2.5%	MM: 10.3% CEA: 6.6% RR: 0.64 (95% CI, 0.34–1.21) ARR: 3.7%	MM: 44.2% CEA: 41.2% RR: 0.9 (95% CI, 0.7–1.2)	4.7

studies (17 474 participants) using Medicare claims data and medical records found a rate of perioperative (30-day) death or stroke of 3.3% (CI, 2.7% to 3.9%) after CEA (**Table 2** and **Figure 3**). Among all trials that included a CEA group, regardless of the comparator, the rate was 2.4% (CI, 1.7% to 3.1%) (**Table 2** and **Figure 3**).

One cohort study (6932 participants from 150 hospitals in New York) reported rates by comorbid condition level after CEA; 7.1% of persons with high comorbid condition levels versus 2.7% of those with low levels had perioperative death or stroke (62). A high comorbid condition level was defined as any end-stage disease, severe disability, or 3 or more Revised Cardiac Risk Index risk factors.

Rates varied significantly across states and by hospital volume (**Table 7** of **Supplement 2**) (57, 58, 64, 65).

For CAAS, 1 cohort study (CREST credentialing phase) found a rate of 3.8% (CI, 2.9% to 5.1%) and higher rates for persons older than 75 years than for those

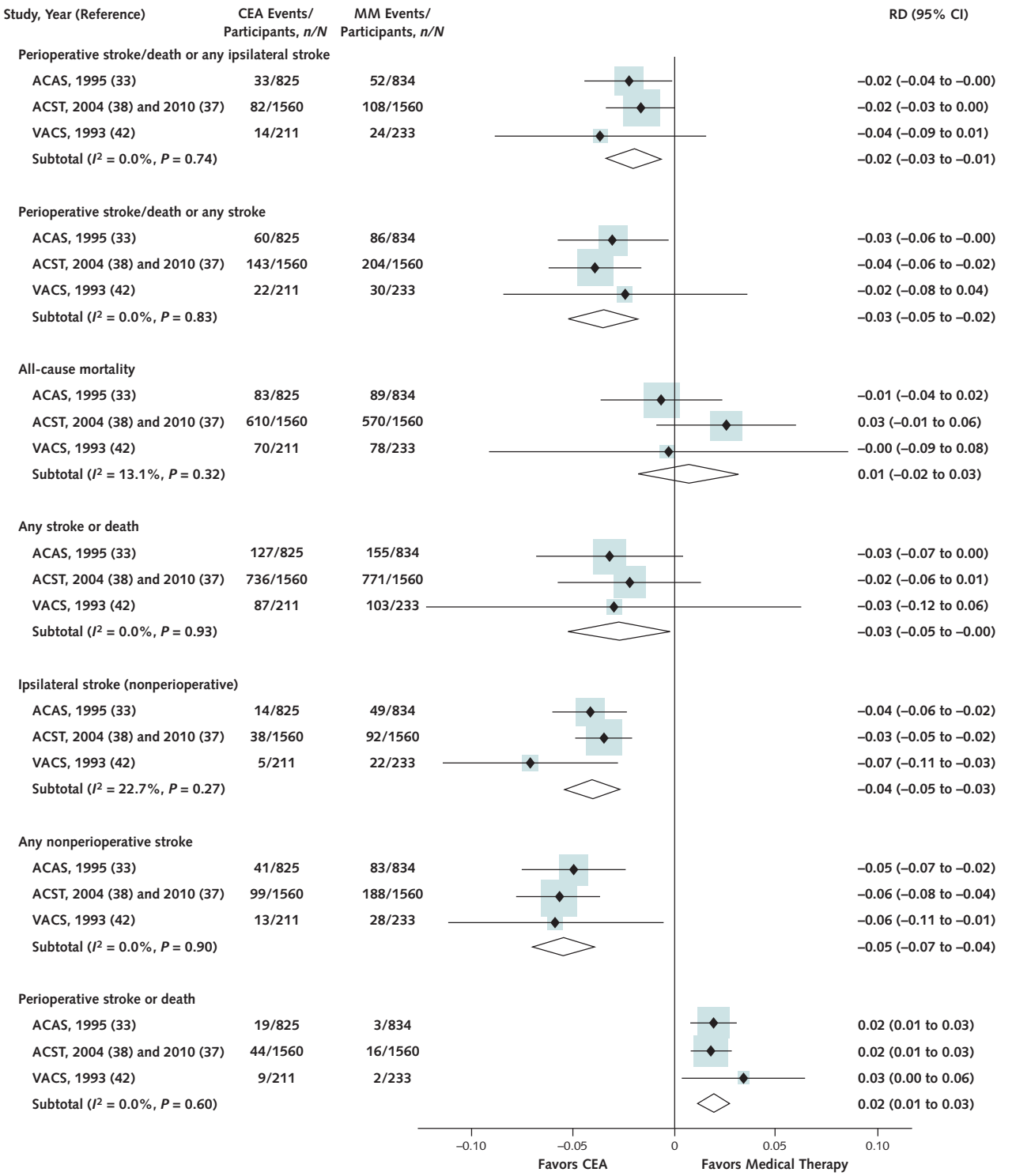
Table 2. **Summary of Main Results of Meta-Analyses**

Outcome	Studies, *n*	Participants*, *n*	Effect Measure†	Estimate From Main Analysis (95% CI), %	I^2, %	PL Estimate From Sensitivity Analysis (95% CI), %
CEA vs. medical therapy						
Perioperative stroke/death or subsequent ipsilateral stroke	3	5223	RD	−2.0 (−3.3 to −0.7)	0	−2.0 (−3.6 to −0.7)
Perioperative stroke/death or any subsequent stroke	3	5223	RD	−3.5 (−5.1 to −1.8)	0	−3.5 (−5.2 to −1.5)
All-cause mortality	3	5223	RD	1.0 (−2.0 to 3.0)	13	0.7 (−2.4 to 3.8)
Any stroke or death	3	5223	RD	−2.7 (−5.1 to −0.3)	0	−2.7 (−5.4 to −0.1)
Ipsilateral stroke (nonperioperative)	3	5223	RD	−4.1 (−5.4 to −2.7)	23	−3.9 (−5.8 to −2.8)
Any nonperioperative stroke	3	5223	RD	−5.5 (−7.0 to −3.9)	0	−5.5 (−7.1 to −3.8)
Perioperative stroke/death	3	5223	RD	1.9 (1.2 to 2.6)	0	1.9 (1.2 to 2.8)
CEA						
Perioperative stroke/death rate from observational studies	7	17 474	Rate	3.3 (2.7 to 3.9)	68	NA‡
Perioperative stroke/death rate from trials	6	3435	Rate	2.4 (1.7 to 3.1)	30	NA‡
CAAS						
Perioperative stroke/death rate from trials	2	6152	Rate	3.1 (2.7 to 3.6)	0.1	3.1 (2.2 to 3.7)

CAAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; NA = not applicable; PL = profile likelihood; RD = risk difference.
* Participants who contributed to the meta-analysis.
† RDs represent absolute differences over approximately 5 y. Negative RDs favor CEA.
‡ Analyses did not have small numbers of studies.

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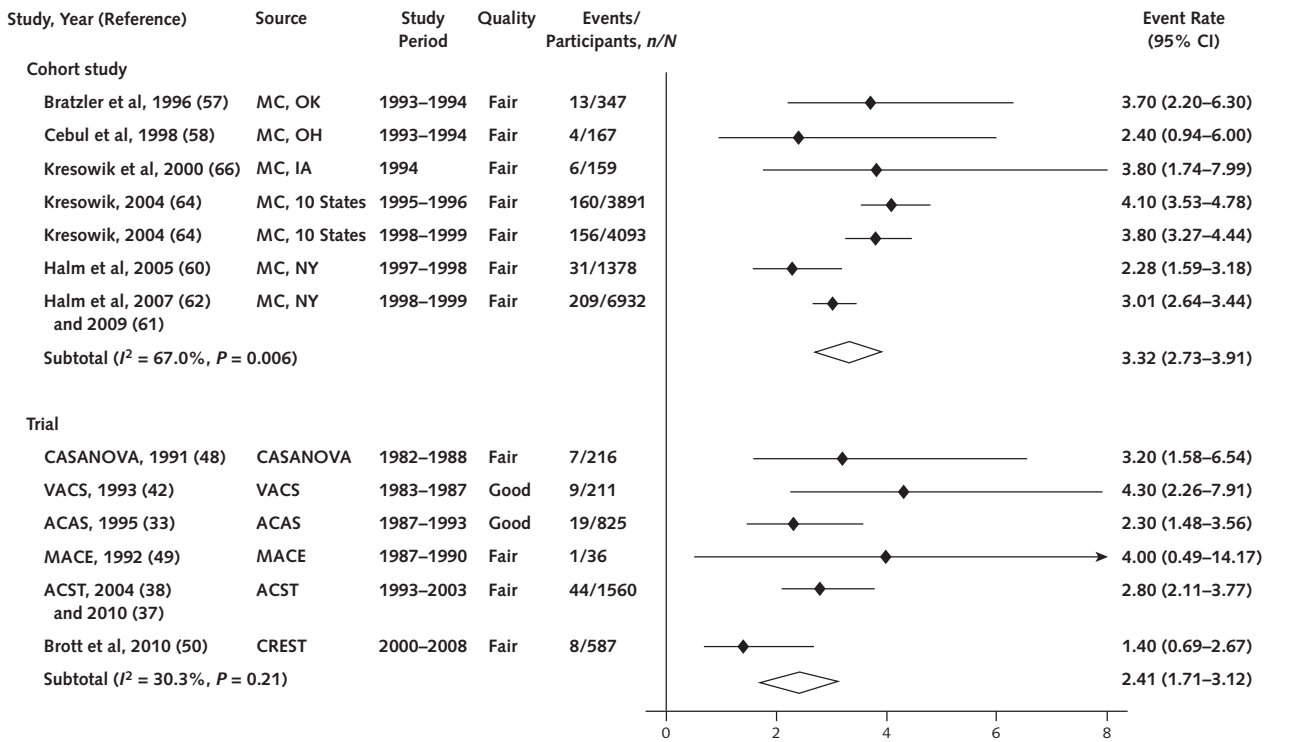
Figure 2. **Meta-analyses of randomized, controlled trials comparing CEA with medical therapy, by outcome.**



ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CEA = carotid endarterectomy; MM = medical management; RD = risk difference; VACS = Veterans Affairs Cooperative Study.

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Figure 3. **Rates of perioperative death or stroke after CEA, by study design.**



ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CASANOVA = Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy Versus Stenting Trial; IA = Iowa; MACE = Mayo Asymptomatic Carotid Endarterectomy; MC = Medicare; NY = New York; OH = Ohio; OK = Oklahoma.

aged 75 years or younger (7.5% vs. 2.4%) (69). Our meta-analysis of 2 trials found a rate of 3.1% (CI, 2.7% to 3.6%; 6152 participants) (**Table 2**).

Rates of Perioperative (30-Day) MIs

Studies of 1378 Medicare beneficiaries in New York (59) and 1002 in Georgia (63) conducted during the 1990s reported perioperative (30-day) rates of 0.9% for nonfatal MI and 0.8% for MI (0.6% for MI-related death) after CEA, respectively. One RCT (CREST) reported a 2.2% rate of any MI after CEA and 1.2% after CAAS (51).

Nerve Injuries, Infection, and Other Harms

In the VACS, 3.8% of persons who had CEA (8 of 211) had cranial nerve injuries with complete functional recovery. One multicenter trial conducted in Germany reported rates of 1.4% for pulmonary embolism, 4.2% for permanent cranial nerve damage, 1.4% for pneumonia, and 2.8% for local hematoma requiring surgery among 206 patients who were randomly assigned to the immediate surgical group (48). The total frequency of major complications (such as death, stroke, minor stroke, MI, or permanent cranial nerve damage) in that group was 7.9%. The Mayo Asymptomatic Carotid Endarterectomy study reported a 1.1% rate of minor cranial nerve injury after CEA (36 participants) (49).

Risk-Stratification Tools

For distinguishing persons more or less likely to have CAS, we found 1 study (78) that attempted to externally validate 2 tools using a cohort of 5449 participants from the Cardiovascular Health Study (78–80). We rated the quality of one of the attempted external validations as poor; thus, we focus on the other one here. The tool (79) assigned 1 point each for the presence of several risk factors (coronary artery disease, smoking, hypertension, and high cholesterol) to predict the likelihood of CAS of 50% or greater. The tool's overall discrimination (its ability to correctly assign those with CAS of ≥50% to a higher score than those with lesser CAS) was not much better than chance (c-statistic, 0.60 [CI, 0.56 to 0.64]) (78).

We found no eligible studies that distinguished persons at decreased or increased risk for stroke caused by CAS or for harms from CEA or CAAS. Some publications reported risk-stratification tools to predict increased risk for complications from CEA or CAAS, but those tools have not been externally validated (81–87).

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Discussion

Duplex ultrasonography is a widely available, noninvasive screening test. Reliability of ultrasonography is questionable because accuracy can vary considerably among laboratories. Its use in a low-prevalence population would result in many false-positive test results—for example, for a population of 100 000 adults with a prevalence of 1%, it would result in 940 true-positive results and 7920 false-positive results (using a specificity of 92%). If no confirmatory tests are done, many unnecessary interventions and harms would occur. If all positive tests were followed by angiography (which is not typically done in clinical practice), as many as 1.2% of persons would have a resulting stroke (33). If all positive test results were followed by magnetic resonance angiography (95% sensitivity and 90% specificity [29]), many patients would still be sent for unnecessary intervention—in the previous example, 792 false-positive results would still be sent for intervention.

If externally validated, reliable risk-stratification tools were available to distinguish subgroups of persons who were more likely to have CAS, then the ratio of true-positive results to false-positive results would improve. However, the only study that attempted external validation of such a tool found inadequate discrimination.

An accurate estimate of potential benefit for the current primary care population is difficult to obtain. Although our meta-analyses of RCTs that compared CEA with medical therapy found a reduction in perioperative stroke or death or any subsequent stroke (and other outcomes), the applicability of the evidence to current practice is substantially limited. Medical therapy was often not clearly defined or standardized; was not kept constant during the study; and would not have included treatments now considered to be current standard medical therapy, including aggressive management of blood pressure and lipids. Current standard therapy to reduce stroke risk includes use of statins, antihypertensives (including newer classes, such as angiotensin-converting enzyme inhibitors), glycemic control for persons with diabetes, and use of antiplatelet drugs for vascular diseases and risk reduction.

To address some applicability limitations of previous studies, the new CREST-2 trial (88) (to begin later this year) will compare both CAAS plus medical therapy versus medical therapy alone and CEA plus medical therapy versus medical therapy alone. None of the trials we identified focused on a population identified by screening in primary care. Definitions of asymptomatic status varied across the trials and included persons with a history of contralateral stroke or TIA (25% in the ACAS and 32% in the VACS), ipsilateral symptoms that were not recent, and previous contralateral CEA.

The trials that compared CEA with medical therapy used highly selected surgeons, requiring low rates of complications to allow participation. A relatively low perioperative stroke or death rate of less than 3% is required for CEA to have a reasonable likelihood of resulting in more benefit than harm for persons with asymptomatic CAS. Although our meta-analyses of trial data found rates less than 3%, observational data show higher rates and reveal a wide range of rates across states (more than 6% in some states) (65).

The potential benefits of CEA or CAAS depend on the risk for an asymptomatic lesion eventually resulting in a stroke. Evidence suggests that this risk has decreased in recent decades, most likely due to advances in medical therapy (46, 89). The best recent evidence suggests that the incidence rate of ipsilateral stroke is nearing 1% per year (46), approaching the rate achieved in the surgical groups of trials that compared CEA with medical therapy. This would significantly reduce the potential benefits of surgery. Medical intervention has also been estimated to be 3 to 8 times more cost-effective (89).

In theory, patients at greater risk for ipsilateral stroke may be more likely to benefit from surgery or intervention. However, no externally validated, reliable risk-stratification tools are available that can distinguish persons with asymptomatic CAS who are at decreased or increased risk for stroke caused by CAS despite current standard medical therapy or those who are at decreased or increased risk for harms from CEA or CAAS. One may expect that persons with greater reduction of the carotid diameter would have greater potential for benefit, but subgroup analyses from trials that compared CEA with medical therapy found no significant difference by CAS percentage (33, 37).

Of note, the main estimates of overall benefit from the trials that compared CEA with medical therapy do not include some important harms, such as nonfatal MI, permanent cranial nerve damage, pulmonary embolism, pneumonia, wound infection, acute renal failure, deep venous thrombosis, and local hematoma requiring surgery. The CAS screening cascade also has potential psychological harms (14). Most studies we reviewed did not report on harms other than perioperative stroke or death. Thus, lack of reporting or underreporting of some harms is possible.

Timing of events and life expectancy are also important considerations when assessing the potential for benefit. The consolidation of all stroke and death events together into one composite outcome does not reflect different values that patients may have for a stroke or death caused by surgery than for one caused by natural progression. Based on the data from RCTs, a life expectancy of at least 5 to 10 years would be needed to have a reasonable chance of benefit from CEA. Potential for benefit decreases with advanced age (older than 75 years) because of competing hazards. The mean age of patients in trials that compared CEA with medical therapy was 65 to 68 years. However, the mean age of Medicare patients who have CEA is 75 years (90), raising the question of whether many persons who have surgical intervention are likely too old to benefit.

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The limitations of this review primarily reflect the published literature, and most key issues limiting applicability of the evidence have been described. Changes in technology, standard medical therapy, surgical procedures, and stroke rates may not be reflected in the included literature (because much of the data is from the 1990s). Our review did not evaluate the use of carotid intima–media thickness in assessing coronary heart disease risk, but a previous review for the U.S. Preventive Services Task Force concluded that evidence does not support its use (91).

Asymptomatic CAS has low prevalence in the general adult population. Noninvasive screening with ultrasonography would result in many false-positive results. Externally validated, reliable risk-stratification tools to distinguish persons who are more likely to have CAS are not available.

Current evidence does not sufficiently establish incremental overall benefit of CEA beyond current standard medical therapy, primarily because medical therapy for trials was ill-defined, varying, and often lacked treatments that are now standard and have reduced the rate of stroke in persons with asymptomatic CAS in recent decades. Externally validated, reliable risk-stratification tools that can distinguish persons with asymptomatic CAS who have increased or decreased risk for ipsilateral stroke or harms after CEA or CAAS are not available.

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