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Screening for Asymptomatic Carotid Artery Stenosis in the General Population: An Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: To perform a targeted systematic review of evidence regarding the benefits and harms of screening for asymptomatic carotid artery stenosis in the general population to support the update of the USPSTF's 2014 D recommendation for this topic.

Data Sources: We conducted a literature search of MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2014, to February 14, 2020. In addition, we conducted ongoing surveillance of relevant literature through March 20, 2020.

Study Selection: We screened 2,373 abstracts and 143 full-text articles against *a priori* inclusion criteria. Retrospective analyses of vascular surgical registries were limited to data collected in the United States.

Data Analysis: Working independently, two investigators critically appraised each article that met inclusion criteria using design-specific criteria. We abstracted and narratively synthesized data from included studies. The results discussed in this report are limited to studies published since the previous review to support the 2014 recommendation.

Results: No eligible studies were identified that directly examined the benefits or harms of screening for asymptomatic carotid artery stenosis. Since the last USPSTF recommendation on this topic, two limited, fair-quality, prematurely terminated trials reported mixed results for the comparative effectiveness of carotid revascularization (carotid endarterectomy [CEA] or carotid artery stenting [CAS]) plus best medical treatment (BMT) compared with BMT alone. The SPACE-2 trial (N=316 reported no difference in composite outcome of stroke or death (30 days) or ipsilateral ischemic stroke (1 year) after CEA (unadjusted hazard ratio [HR] 2.82 [95% CI, 0.33 to 24.07]) or CAS (unadjusted HR 3.50 [95% CI, 0.42, 29.11]) compared with BMT in the 1-year interim publication. The smaller AMTEC trial (N=55) reported a statistically significantly lower composite risk of nonfatal ipsilateral stroke or death among the carotid endarterectomy (CEA) arm at 3.3 median years of followup (calculated unadjusted HR 0.20 [95% CI, 0.06 to 0.65]). Since the previous report, two fair-quality trials, two national datasets, and three surgical registries met our inclusion criteria reporting harms associated with CEA (N=1,903,761) or carotid artery stenting (CAS) (N=332,103). Overall, the rates of most postoperative adverse events were highest among analyses of national databases (Medicare data and National Inpatient Sample [NIS]), with lower rates reported in trials and surgical registries. Within the national databases and surgical registries, rates of 30-day postoperative stroke or death following CEA ranged from as low as 1.4 percent in the Vascular Quality Initiative (VQI) to as high as 3.5 percent in the Medicare database. Thirty-day postoperative mortality ranged from 0.5 percent in the Vascular Study Group of New England (VSGNE) to as high as 1.1 percent in the Medicare database for CEA. Thirty-day postoperative stroke rates following CEA ranged from 0.5 percent in the VSGNE to 1.5 percent in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). For the CAS procedure, 30-day stroke or death ranged from 2.6 percent in the VQI to 5.1 percent in Medicare. Thirty-day postoperative mortality after CAS ranged from 1.1 percent in the VQI to 3.1 percent in the Medicare database. Thirty-day postoperative stroke rates following CAS were only reported in the VQI at 1.8 percent. Rates of postoperative harms within the trials were generally underpowered to detect outcomes such as postoperative mortality. Within the SPACE-2 trial, the composite of 30-day postoperative stroke or death was reported at 2.5 percent following both CAS and CEA. Perioperative stroke was reported in one patient (3.2%) following CEA in the AMTEC trial. The other most common harms reported within trials included hematoma, facial nerve lesion, and contrast agent incompatibility.

Limitations: We identified no trials of screening versus no screening in unselected general populations or examining direct screening harms. There were few new trials, all with methodologic concerns, examining the important question of the comparative effectiveness and harms of revascularization plus best medical treatment compared with best medical treatment alone. Selection bias and measurement bias presented serious validity concerns for complication rates reported in the administrative databases and surgical registries. The procedural complication rates of patients categorized as "asymptomatic" in the harms studies may not be generalizable to the rates that may be expected in a population of screen-detected patients (who would be expected to have lower complication rates compared with populations with any neurologic symptoms or remote history of TIA or stroke) or procedures performed outside of trials by less-selected operators (who may be expected to have higher complication rates compared with highly selected operators at high volume centers).

Conclusions: There are no population-based screening trials addressing the benefits and harms of screening for carotid artery stenosis. Limited new evidence has emerged to determine the benefits of carotid revascularization over contemporary best medical management in asymptomatic patients. The ongoing CREST-2 and ECST-2 trials will be the largest trials to address this issue. Large national administrative databases and surgery registries suggest that postoperative 30-day stroke/death rates vary widely—1.4 to 3.5 percent for CEA and 2.6 to 5.1 percent for CAS—suggesting that there may be a wide variation in complication rates likely attributable to patient and operator selection.

Table of Contents

Chapter 1. Introduction.......... 1
Purpose.......... 1
Condition Background.......... 1
Condition Definition.......... 1
Prevalence and Burden.......... 1
Risk Factors.......... 2
Rationale for Screening and Screening Strategies.......... 2
Treatment Approaches.......... 3
Current Clinical Practice in the United States.......... 3
Recent Recommendations.......... 4
Previous USPSTF Recommendation.......... 4
Chapter 2. Methods.......... 5
Scope and Purpose.......... 5
Key Questions and Analytic Framework.......... 5
KQs.......... 5
Data Sources and Searches.......... 5
Study Selection.......... 5
Quality Assessment and Data Abstraction.......... 6
Data Synthesis and Analysis.......... 7
Expert Review and Public Comment.......... 7
USPSTF Involvement.......... 7
Chapter 3. Results.......... 8
Literature Search.......... 8
KQ1. Is There Direct Evidence That Screening Asymptomatic Adults for Carotid Artery Stenosis With Duplex Ultrasonography Improves Health Outcomes?.......... 8
KQ2. What Are the Harms Associated With Screening or Confirmatory Testing for Asymptomatic Carotid Artery Stenosis?.......... 8
KQ3. For Asymptomatic Persons With Carotid Artery Stenosis, Does Revascularization Provide Incremental Benefit Beyond Current Medical Treatment?.......... 8
Summary of Results.......... 8
Characteristics of Included Studies.......... 9
Study Quality and Applicability.......... 10
Detailed Results by Outcome.......... 11
KQ4. What Are the Harms Associated With Revascularization of Asymptomatic Carotid Artery Stenosis?.......... 12
Summary of Results.......... 12
Characteristics of Included Studies.......... 12
Study Quality and Applicability.......... 14
Detailed Results by Outcome in Asymptomatic Population.......... 15
Chapter 4. Discussion.......... 18
Summary of Findings and Comparison to Last Review.......... 18
Limitations.......... 19
Ongoing Studies.......... 21
Conclusions.......... 22

References **23**

Figure

Figure 1. Analytic Framework

Tables

Table 1. Summary of Recommendations for Screening for Asymptomatic Carotid Artery Stenosis
Table 2. Study Characteristics of Included Randomized, Controlled Trials of Revascularization vs. BMT, KQ 3
Table 3. Long-Term Health Outcomes Reported in Trials of CEA vs. BMT, KQ 3
Table 4. Long-Term Health Outcomes Reported in Trials of CAS vs. BMT, KQ 3
Table 5. Study Characteristics of Included Administrative Data and Vascular Registry Studies, KQ 4
Table 6. Postoperative Harms Reported in Trials of CEA vs. BMT, KQ 4
Table 7. Postoperative Adverse Composite Outcomes Reported in CEA Registries and Administrative Data, KQ 4
Table 8. Postoperative Mortality Reported in CEA Registries and Administrative Data, KQ 4
Table 9. Postoperative Stroke Reported in CEA Registries and Administrative Data, KQ 4
Table 10. Postoperative Cardiovascular Events Reported in CEA Registries and Administrative Data, KQ 4
Table 11. Other Postoperative Adverse Events Reported in CEA Registries and Administrative Data, KQ 4
Table 12. Postoperative Harms Reported in Trials of CAS vs. BMT, KQ 4
Table 13. Postoperative Adverse Composite Outcomes Reported in CAS Registries and Administrative Data, KQ 4
Table 14. Postoperative Mortality Reported in CAS Registries and Administrative Data, KQ 4
Table 15. Postoperative Stroke Reported in CAS Registries and Administrative Data, KQ 4
Table 16. Postoperative Cardiovascular Reported in CAS Registries and Administrative Data, KQ 4
Table 17. Summary of Previous 2014 USPSTF Review and New Evidence Identified in This Review

Appendixes

Appendix A. Detailed Methods
Appendix B. Literature Flow Diagram
Appendix C. Included Studies
Appendix D. Excluded Studies
Appendix E. Additional Evidence Tables
Appendix F. Ongoing Studies

Chapter 1. Introduction

Purpose

The Agency for Healthcare Research and Quality (AHRQ) has requested a targeted, rapid update focused on screening and treatment of asymptomatic carotid artery stenosis in the general population. This topic was last reviewed in 2014.[1, 2] The report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2014 recommendation on this topic.[3]

Condition Background

Condition Definition

Carotid artery stenosis is atherosclerotic systemic disease manifesting in the extracranial carotid arteries. Asymptomatic carotid atherosclerotic disease refers to the presence of stenosis in individuals without a history of ischemic stroke, transient ischemic attack (TIA), or other neurologic signs or symptoms.[4] The definition of "asymptomatic" status varies within trials of carotid artery stenosis treatment and generally includes those without a history of TIA, stroke, or symptoms in the previous 6 months. Severe narrowing of the carotid artery is clinically significant due to its correlation with stroke risk.[5] The clinically important degree of stenosis is considered the percentage of stenosis that corresponds to a substantial increased risk for stroke. The USPSTF recommendations[3] consider 60 to 99 percent stenosis to be clinically important. Some earlier trials of treatment considered a lower threshold of 50 to 99 percent stenosis to be clinically important.[2] The categories of stenosis severity which are historically based on duplex ultrasound estimates are as follows: moderate (50% to 69%) and severe (70% to 99%); severity estimation may vary by imaging modality with magnetic resonance angiography (MRA) leading to overestimates in degree of stenosis.[6] The USPSTF defines persons with asymptomatic carotid artery stenosis as those without a history of transient ischemic attack, stroke, or other neurologic signs or symptoms.[3]

Prevalence and Burden

The prevalence of asymptomatic carotid artery stenosis is low in the general population but increases with age. Population-based studies define asymptomatic carotid artery stenosis as a lack of history of TIA, stroke, or carotid revascularization, or do not clearly report how asymptomatic status was defined. As a result, the prevalence of asymptomatic carotid artery stenosis (60-99%) as defined above by the USPSTF may be lower than that published in population-based studies. A 2010 individual participant data meta-analysis (IPD-MA)[7] of four population-based studies of over 23,000 participants found the prevalence estimates of moderate asymptomatic carotid artery stenosis (defined as ≥50 percent stenosis) increased with age and was more common among men; the majority of participants in these cohorts were Caucasian. Among men, prevalence of carotid artery stenosis increased from 0.2 percent among those under age 50 years to 7.5 percent in men age 80 years and older. Similarly, among women the prevalence increased from essentially no cases to 5 percent after age 80 years. The prevalence of severe stenosis (defined as ≥70 percent stenosis) was even lower in this population but also increased with age to approximately 3 percent and 1 percent for men and women age 80 and older, respectively.[7] One U.S. study of self-referred individuals (n=3,291,382), found the prevalence of clinically significant carotid artery stenosis (≥50% stenosis) of 3.4 percent in women and 4.2 percent in men. These rates varied significantly by race, with Native American and white individuals having the highest prevalence and African American males and Asian females having the lowest. Prevalence trends remained the same in their analysis of more severe degrees of stenosis (≥80%).[8] There is limited data estimating the prevalence of asymptomatic carotid artery stenosis in nonwhite populations.

The most serious consequence of carotid artery stenosis is ischemic stroke; however, only 11% of strokes are attributable to asymptomatic carotid artery stenosis.[9] Furthermore, among patients who have at least 50 percent stenosis, one analysis estimates the risk of stroke is low at less than one percent annually, and about 5.5 percent of individuals in reasonably good health become symptomatic with stroke from the lesion during their lifetime. [10] The Asymptomatic Carotid Surgery Trial 1 (ACST-1) reports that 11.7 percent in the best medical therapy group required CEA for symptoms over 10 years.[11] These estimates are based on older studies and may overestimate the risk of individuals treated with current best medical management.

Risk Factors

Risk factors for the development of carotid artery stenosis are similar to those for coronary artery disease (CAD) and other peripheral vascular disease (e.g., advanced age, hypertension, smoking, diabetes, high cholesterol).[12, 13] Numerous individual risk factors can contribute to stroke risk but generally, major risk factors include hypertension, heart disease, smoking, diabetes, high cholesterol, advanced age, and male sex.[14] The current review solely addresses screening in the general asymptomatic population.

Rationale for Screening and Screening Strategies

Carotid artery stenosis is a known risk factor for stroke and a marker of increased risk for myocardial infarction (MI) and vascular death.[15-17] The potential benefit of screening for stenosis would be to reduce risk of these events in asymptomatic patients. Screening and confirmation testing using noninvasive imaging studies of the carotid artery can be accomplished with carotid duplex ultrasonography, magnetic resonance angiography (MRA) and computed tomography angiography (CTA). Auscultation for carotid bruits alone during physical examination has been found to be a poor predictor of underlying carotid stenosis or stroke risk in asymptomatic populations and is therefore not considered a reasonable screening approach. [18, 19]. Conventional cerebral angiography is the gold standard for imaging but is not recommended for screening as it is costly and invasive and has risk of stroke and morbidity. Studies have shown this procedure to have risk of permanent neurological complications (at approximately 1%).[20, 21]

Treatment Approaches

Uncertainty exists about the optimal treatment modality for clinically significant asymptomatic carotid artery stenosis in order to prevent future stroke. Both medical and revascularization options are available. Meta-analysis of three landmark trials (ACST, ACAS, VA) (N=5226) estimate that CEA is associated with a 3.5% (1.8 to 5.1%) absolute reduction in stroke or death at 5 years compared to BMT. (Jonas); however, currently, there are not consistent opinions on which management strategy is best.[10, 22] One approach to managing asymptomatic carotid stenosis centers on best medical therapy which involves statins, antiplatelets, treatment of hypertension or diabetes, and lifestyle modification counseling.[23] This approach aims to reduce not only future stroke but also overall CVD-related morbidity and mortality. The best medical therapy approach can be used alone or in combination with one of the revascularization techniques. Potential procedural options include revascularization with carotid endarterectomy (CEA) and carotid artery stenting (CAS). CEA can be performed under general or local anesthesia and involves open surgical exposure of the carotid artery and the removal of plaque to improve arterial patency. CAS is usually performed under local anesthesia and involves femoral or brachial arterial catheter approaches to carotid angiography, angioplasty, and stent placement. There is much debate about the comparative benefits and risks of CEA versus CAS.[23, 24] Additionally, transcarotid artery revascularization (TCAR) is a newer procedural approach in which stenting is performed via direct arterial access in the common carotid artery from a supraclavicular area.

Current Clinical Practice in the United States

Screening

Data from 2009 Medicare claims found that screening for asymptomatic carotid artery stenosis (defined as screening among those without a history of stroke, TIA, or focal neurological symptoms) occurred in 6.6 per 100 beneficiaries.[25] An analysis of Veterans Health Administration patients age 65 years and older undergoing carotid revascularization for asymptomatic carotid stenosis between 2005 and 2009 found that the rates of appropriate, uncertain, and inappropriate imaging were 5.4 percent, 83.4 percent, and 11.3 percent, respectively, based on expert opinion.[26] The most common indications listed for carotid imaging were carotid bruit (30.2% of indications) and followup of patients who had previously documented carotid stenosis (20.8% of indications).[26]

Surgical Repair

A recent report from the American Heart Association found that in 2014,[27] the most frequently performed surgical procedure to prevent stroke in the United States was CEA; an estimated 86,000 inpatient procedures were performed (tabulation of Healthcare Cost and Utilization Project, National Heart, Lung, and Blood Institute). This report also tabulated that trends of this procedure decreased annually between 1997 and 2014, while the use of CAS increased between 2004 and 2014.[27] Accurate data on current rates of CEA and CAS for asymptomatic patients in the general population are limited as symptomatic status is generally not detailed in large registries or administrative data sets. However, a recent study of Medicare claims data between

1999 and 2014 reported that 815,088 CEA procedures were performed, compared with 192,014 CAS procedures, in asymptomatic patients, defined as individuals without a principal discharge coding indicating cerebral infarction or a secondary diagnosis code indicating prior stroke, TIA, or amaurosis fugax.[28] Observations over 16 years showed a decline in CEA procedures performed in asymptomatic patients, while carotid artery stenting trends increased between 1999 and 2006 and decreased from 2007–2014.[28]

Recent Recommendations

No professional society recommends screening in the general population. National guidelines are not consistent regarding the role of screening in an asymptomatic population. The USPSTF and American Heart Association/American Stroke Association (AHA/ASA) recommend against routine screening of asymptomatic patients for carotid artery stenosis; however, the American Institute of Medicine and joint guidelines of multiple U.S. professional societies concluded that screening is indicated (or reasonable) for asymptomatic patients with a carotid bruit. While the Society for Vascular Surgery (SVS) and joint guidelines from multiple U.S. professional societies recommend consideration of screening in those with multiple risk factors and those with other known peripheral arterial disease or cardiovascular disease. (**Table 1**).

Previous USPSTF Recommendation

In 2014, the USPSTF recommended against screening for asymptomatic carotid artery stenosis in the general adult population (D recommendation). This recommendation was based on low prevalence of stroke related to asymptomatic carotid artery stenosis in the general population, the small benefit of CEA and/or CAS compared with medical therapy from older trials, and the potential for harms. The USPSTF did not issue a recommendation in 2014 for screening high risk populations. The USPSTF noted the need for valid and reliable tools to determine which people are at high risk for carotid artery stenosis or related stroke as well as modern studies comparing CEA or CAS with current standard medical therapy.

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence report to update its 2014 D recommendation on screening for asymptomatic carotid artery stenosis. Given that this topic was commissioned as a targeted, rapid update of screening in the general population, we only updating key questions for benefits and harms of screening and treatment.[29]

Key Questions and Analytic Framework

In consultation with members of the USPSTF, we developed an analytic framework (**Figure 1**) and four Key Questions (KQs) to guide our focused evidence update.

KQs

1. Is there direct evidence that screening asymptomatic adults for carotid artery stenosis with duplex ultrasonography improves health outcomes?
2. What are the harms associated with screening or confirmatory testing for asymptomatic carotid artery stenosis?
3. For asymptomatic persons with carotid artery stenosis, does revascularization provide incremental benefit beyond current medical treatment?
4. What are the harms associated with revascularization of asymptomatic carotid artery stenosis?

Data Sources and Searches

We conducted a literature search of MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2014, to February 14, 2020, to identify literature published since the previous review for the USPSTF. We worked with a research librarian to develop our search strategy, which was peer-reviewed by a second research librarian (**Appendix A**). We supplemented these searches by examining reference lists of recent reviews and primary studies. We limited our searches to articles published in English and managed search results using Endnote® version X7 (Thomson Reuters, New York, NY). Additionally, we conducted ongoing surveillance for relevant literature through March 20, 2020.

Study Selection

We developed specific inclusion criteria to guide study selection (**Appendix A Table 1**). Two reviewers independently reviewed the title and abstracts of all identified articles using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers then independently evaluated the full text of all potentially relevant articles, with differences reviewed by discussion.

For evidence on the benefits (KQ1) and potential harms (KQ2) of screening for asymptomatic carotid artery stenosis, we included randomized controlled trials of screening with carotid duplex ultrasonography compared with no screening. Ultrasound was the only screening modality considered for this review. Ideally, eligible populations would include unselected or community-dwelling adults without neurologic symptoms or a known history of stroke or TIA (at any time). However, the definition of "asymptomatic" status varied within trials and generally included those without a history of TIA, stroke, or symptoms in the previous 6 months. Likewise, observational studies for harms (KQ4) variably defined "asymptomatic."

For evidence on the incremental benefits of revascularization beyond current medical treatment (KQ3), we included randomized trials of revascularization versus medical management. Populations included in trials were required to be generally asymptomatic adults (>80% of participants were asymptomatic or outcomes were stratified based on asymptomatic status) with clinically important CAS (as defined by the trials). Eligible carotid interventions included carotid endarterectomy (CEA), carotid artery stenting (CAS), and transcarotid artery revascularization (TCAR). Eligible comparison groups were those that included best medical treatment or usual care. Studies of the comparative effectiveness of surgical treatments were excluded.

For evidence on harms of revascularization (KQ4), we included any adverse events reported in the trials included for KQ3. In addition, we considered retrospective analyses of the two largest U.S.-based nationally representative administrative databases (Medicare, National Inpatient Sample [NIS]) as well as surgical registries with at least 10,000 asymptomatic cases. Due to the limited scope of this targeted, rapid review, we used an auditing process to select the most recent comprehensive publication from each national database or registry (**Appendix A Table 2).**

Outcomes for studies of benefit (KQ1, KQ3) included stroke, mortality, quality of life, functional status, and cognitive status. For studies on potential screening harms (KQ2), we included adverse outcomes related to the screening test as well as any subsequent confirmatory testing. For studies of procedural harms (KQ4), we included perioperative complications occurring up to 30 days following the procedure.

For randomized trials we limited studies to those conducted in countries categorized as "very high" on the Human Development Index.[30] For surgical registries or hospital outcome data, we included studies in which the majority of individuals received treatment in the United States.

Quality Assessment and Data Abstraction

Two reviewers independently assessed the methodological quality of each included study using predefined criteria (**Appendix A Table 3**). We assigned each study a quality rating of "good," "fair," or "poor" according to the USPSTF's study design-specific criteria.[31] All studies identified in this review were rated as fair quality. We supplemented these criteria with modified questions from the Newcastle-Ottawa Scale.[32] Disagreements were resolved by discussion. We abstracted details on the study's design, patient characteristics, intervention characteristics, and outcomes specified in the inclusion criteria.

Data Synthesis and Analysis

This report is a rapid review to provide an overview of evidence published since the USPSTF last considered this topic in 2014. Therefore, it narratively describes the results of newly identified publications only. Results of studies included in previous evidence reviews are not pulled forward into the report, and no pooled analyses were conducted. Where necessary, results from included studies were recalculated so that they were comparable across studies (e.g., intervention and comparator groups were reversed to create comparable summary statistics). Any calculated outcomes are indicated in the evidence tables with footnotes. We included a summary table comparing the conclusions of this review to the previous review.[2]

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from August 15 through September 11, 2019. The draft Research Plan was additionally reviewed by USPSTF Federal Partners from the CDC and clarifications were made as appropriate.

USPSTF Involvement

This evidence update was funded by an AHRQ contract to support the USPSTF. We consulted with USPSTF members during the development of the research plan, including the analytic framework, KQs, and inclusion criteria. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the evidence update, and assisted with public comment on the research plan and draft report. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the evidence update.

Chapter 3. Results

Literature Search

Results of this search represent literature published since the previous review on this topic. We screened 2,373 abstracts and assessed 143 full-text articles for inclusion; no articles were reviewed for KQs 1–2, 20 were reviewed for KQ3, and 143 were reviewed for KQ4 (**Appendix B Figure 1**). After screening the full-text articles, we included two small trials (published in 6 articles)[33-38] for KQ3 and seven studies (in 17 articles)[28, 33-48] for KQ4. The full list of included studies and their ancillary articles is available in **Appendix C**. The list of excluded studies (with reasons for exclusion) is available in **Appendix D**.

KQ1. Is There Direct Evidence That Screening Asymptomatic Adults for Carotid Artery Stenosis With Duplex Ultrasonography Improves Health Outcomes?

No eligible studies were identified that directly examined the benefits of screening for asymptomatic carotid artery stenosis.

KQ2. What Are the Harms Associated With Screening or Confirmatory Testing for Asymptomatic Carotid Artery Stenosis?

No eligible studies were identified that directly examined the harms of screening for asymptomatic carotid artery stenosis.

KQ3. For Asymptomatic Persons With Carotid Artery Stenosis, Does Revascularization Provide Incremental Benefit Beyond Current Medical Treatment?

Summary of Results

Since the previous review for the USPSTF on this topic, two small fair-quality, prematurely terminated trials reported mixed results for the comparative effectiveness of carotid revascularization compared with best medical treatment (BMT).[33-38] The larger, European multinational SPACE-2 trial[37] (N=316 reported 1 year interim findings of no difference in composite outcome of stroke or death (30 days) or ipsilateral ischemic stroke (1 year) between the CEA and BMT groups (unadjusted hazard ratio [HR] 2.82 [95% CI, 0.33 to 24.07]), while the small Russian AMTEC trial[35] (N=55) reported a statistically significant lower composite risk of nonfatal ipsilateral stroke or death among the CEA arm at 3.3 median years of followup (calculated unadjusted HR 0.20 [95% CI, 0.06 to 0.65]). SPACE-2[37] (N=310) additionally reported no difference in the primary composite outcome (stroke or death [30 days] or ipsilateral ischemic stroke [1 year]) between the CAS and BMT groups (unadjusted HR 3.50 [95% CI, 0.42 to 29.11]). Both trials have risk of bias in important domains that limit validity or applicability of findings. Both trials were terminated early due to slow recruitment (SPACE-2) or apparent superiority of CEA over BMT (AMTEC).

Characteristics of Included Studies

Two fair-quality, prematurely terminated trials addressed the stroke and mortality effects of best medical therapy (BMT) compared with revascularization (**Table 2; Appendix E Table 1**). The SPACE-2 trial[37] (N=513) was designed as a three-arm study (CEA vs. CAS vs. BMT) but was converted to two separate trials (CEA vs. BMT and CAS vs. BMT) following low recruitment into the study. The trial was prematurely terminated in 2014 due to slow recruitment; specifically, a fraction of the numbers required for adequate power were recruited (513 enrolled vs. 3,550 planned). SPACE-2 recruited adults ages 50 to 85 years with asymptomatic carotid artery stenosis (≥70% stenosis) from 36 study centers in Germany, Switzerland, and Austria. The Russian AMTEC trial[35] (N=55) recruited high-risk individuals from surgical and medical clinics with 70 to 79 percent stenosis on ultrasound. AMTEC was prematurely terminated following an interim analysis of the first 55 individuals because the BMT group had an unexpectedly high ipsilateral stroke/death rate that was much higher than that of the CEA group; the data safety and monitoring board concluded that CEA had clear advantages over BMT in this trial population.[35]

Both trials excluded individuals with stroke or TIA in the previous 6 months/180 days, prior ipsilateral carotid procedures (CEA, CAS), or history of neck irradiation. SPACE 2 excluded individuals with a history of intracranial bleed within the previous 90 days or a life expectancy of less than 5 years. The AMTEC excluded people with “poor surgical risk” (e.g., due to recent MI), life expectancy of less than 6 months, or severe classes of heart failure, coronary disease, angina, lung and renal disease, and atrial fibrillation. The mean ages were 70 and 66.6 years in SPACE-2[37] and AMTEC,[35] respectively. In both trials, approximately three-quarters of the participants were male, and one-quarter had diabetes. Most participants in the SPACE-2 trial had hypertension (89.5%) and hypercholesterolemia (79.3%). Within the AMTEC trial, participant characteristics were less well reported. Smoking rates were much higher in AMTEC compared with SPACE-2 (58.2% ever-smokers compared with 19.5% current smokers), as were rates of coronary heart disease (70.9% compared with 35.5%). In addition, over half of AMTEC participants had had a previous coronary artery bypass grafting or percutaneous coronary intervention (52.7%). Only 3.5 percent of SPACE-2 participants had prior contralateral carotid occlusion. Median stenosis in SPACE 2 was 80 percent, and the vast majority were taking antiplatelet (96.5%), antihypertensive (87.3%) and lipid-lowering agents (81.5%) at baseline. In AMTEC, BMI was significantly lower in the BMT group compared with the CEA group (26.8 vs. 29.9, p=0.0008) and 16.4 percent had had a prior stroke. See **Appendix E Table 2** for detailed population characteristics of included trials.

In SPACE-2,[37] the revascularization groups received a CEA or CAS in addition to BMT within a median time of 14 days after randomization. The CEA group received aspirin or clopidogrel at least 3 days before surgery. The CAS group received dual antiplatelet therapy (aspirin and clopidogrel) for at least 3 days before the procedure and 6 weeks after CAS. In SPACE-2, surgeons were required to have conducted 40 consecutive procedures or 20 consecutive procedures with perisurgical complication rates of less than 6 percent in the SPACE-1 study.[38] In AMTEC,[35] the surgery group received a CEA in addition to BMT. Surgeries were conducted in five centers with a minimum of 150 procedures per year and less than 3 percent complications and death rates in asymptomatic carotid artery stenosis.[34]

In both trials, the intervention and control groups received BMT. In SPACE-2,[37] BMT was based on evidence-based guidelines current at that time in accordance with their individual risk-factor profile, including the treatment of risk factors (i.e., smoking cessation, weight reduction, blood pressure lowering, glycemic management, lipid lowering, and counseling about physical activity and alcohol consumption) and antiplatelet medication. In AMTEC,[35] BMT included lifestyle modification training (i.e., counseling about diet, exercise, and smoking cessation), obesity and diabetes mellitus management according to 2006 AHA/ACC guidelines,[49] and treatment with aspirin and aggressive lipid-lowering and antihypertensive therapy.

The planned primary outcome in SPACE-2 was the cumulative 30-day stroke or death plus ipsilateral ischemic stroke within 5 years, which the authors state will still be performed. Currently, only outcomes after 1 year of followup have been reported. The primary outcome in AMTEC was nonfatal ipsilateral stroke and death at study termination. Secondary outcome was a composite of nonfatal stroke, carotid revascularization and death.

Study Quality and Applicability

Both studies had some important limitations. The trials excluded those with recent stroke or TIA but did not exclude those with any history of these diagnoses. SPACE-2[37] recruited patients from surgery centers, so it is unclear if the participants were truly “screen-detected.” Individuals with a recent stroke or TIA were excluded; however, the trial did not exclude those with any history of these diagnoses. The SPACE-2 trial was limited by change in study design and early termination due to inadequate recruitment with short term 1 year results reported. The trial had protocol violations in 34 patients who received therapy different than randomized; however, the per-protocol and intention-to-treat analyses both showed similar results. Operators were carefully selected and requirements for participation included: at least 40 consecutive surgical or endovascular carotid procedures or at least 20 CEA or CAS with intervention complication rates of less than 6 percent in the prior SPACE-1 study.[50] Stroke was clinically defined and outcomes abstracted from medical records by separate but unblinded physicians.[37]

AMTEC[35] screened patients with high risk for CAS and selected participants with favorable perioperative risk and centers with less than 3 percent complication rates for asymptomatic carotid artery stenosis. As in the SPACE-2 trial, individuals with a recent stroke or TIA were excluded; but not those with any history of these diagnoses. This trial included participants with high prevalence of cardiovascular disease burden (half of participants had a previous coronary artery bypass grafting or percutaneous coronary intervention). This very small study presents concerns for selection bias: Less than 20 percent of those with stenosis of 70 to 79 percent based on ultrasound received confirmatory imaging required for consideration. The population is more selective for this trial, with an age range of 40 to 80 years and a narrower 70- to 79-percent stenosis window. The trial was conducted in highly selected centers, i.e., those with a less than 3 percent complication rate. In addition, the higher than expected mortality rate in the BMT group and small study size make result validity questionable. Early termination limited outcome reporting at planned followup time so reported results were short term. Blinded outcome adjudicators were used, and the study defined stroke as the presence of symptoms followed by a stroke-specific examination and confirmed with imaging.

Detailed Results by Outcome

CEA vs. BMT

In SPACE-2,[37] there was no statistically significant difference in the primary composite outcome (stroke or death [30 days] or ipsilateral ischemic stroke [1 year]) between the CEA (5/203 [2.5%]) and BMT arms (1/113 [0.9%]) (unadjusted HR 2.82 [95% CI, 0.33 to 24.07]) (**Table 3)**. In addition, no difference was found in the individual outcomes of stroke (unadjusted HR 4.51 [95% CI, 0.56 to 36.09] or ipsilateral stroke (unadjusted HR 2.24 [95% CI, 0.25 to 20.04]) for the CEA group compared with the BMT group. Mortality was reported as 2.5 percent (5/203) in the surgery group and 3.5 percent (4/113) in the best medical management group, with no hazard ratio reported.[37]

In AMTEC,[35] cumulative composite of nonfatal stroke or death at median 3.3 years' followup was lower in the CEA group (2/31 [6.5%]) compared with the BMT group (9/24 [37.5%]) (calculated unadjusted HR 0.20 [95% CI, 0.06 to 0.65]) (**Table 3**). The major adverse cardiac event rate at 3.3 median years was 12.9 percent and 58.3 percent in the CEA and BMT groups, respectively. The individual outcome of nonfatal stroke was lower in the CEA group compared with the BMT group (calculated unadjusted HR 0.20 [95% CI, 0.04 to 0.995). There was no statistically significant difference in mortality between the groups (calculated unadjusted HR 0.23 [95% CI, 0.04 to 1.35]).[35]

CAS vs. BMT

SPACE-2[37] additionally reported 1-year outcomes for CAS compared with BMT. No difference in the primary composite outcome (stroke or death [30 days] or ipsilateral ischemic stroke [1 year] was reported between the CAS (6/197 [3.05%]) and BMT groups (1/113 [0.9%]) (unadjusted HR 3.50 [95% CI, 0.42 to 29.11]) (**Table 4)**. In addition, there was no difference in the individual outcomes of stroke (HR 4.70 [95% CI, 0.59 to 37.61]) or ipsilateral stroke (HR 3.47, [0.42 to 28.84]). Mortality was reported as 1.0 percent (2/197) and 3.5 percent (4/113) in the CAS and BMT groups respectively, with no hazard ratio reported.[37]

KQ4. What Are the Harms Associated With Revascularization of Asymptomatic Carotid Artery Stenosis?

Summary of Results

Since the previous review for the USPSTF on this topic, two fair-quality trials (reported in 6 articles),[33-38] two national datasets,[28, 43] and three vascular registries (reported in 9 articles) [39-42, 44-48] reporting procedural harms from CEA (N= 1,903,761) or CAS (N= 332,103) met inclusion criteria. Overall, the highest rates of postoperative adverse events reported in analyses of national databases (Medicare data and NIS), with lower rates reported in trials and vascular surgical registries. Within the administrative databases and surgical registries, rates of 30-day postoperative stroke or death following CEA ranged from as low as 1.4 percent (Vascular Quality Initiative [VQI])[44] to as high as 3.5 percent (Medicare data).[28] Thirty-day postoperative mortality ranged from 0.5 percent in the VSGNE[39] to as high as 1.1 percent in the Medicare database.[28] Thirty-day postoperative stroke rates ranged from 0.5 percent in the VSGNE[39] to 1.5 percent in the ACS NSQIP.[40] Thirty-day postoperative cardiac events in ACS NSQIP publications ranged from 1.4 to 1.7 percent.[41, 46, 48]

For the CAS procedure, the rate of 30-day stroke or death was lowest in the VQI analysis[44] at 2.6 percent and highest in Medicare dataset at 5.1 percent.[28] Thirty-day postoperative mortality ranged from 1.1 percent in the VQI[44] to 3.1 percent in the Medicare database.[28] Thirty-day postoperative stroke rates following CAS were only reported in the VQI[44] at 1.8 percent.

Rates of postoperative harms within the trials were generally underpowered to detect outcomes such as postoperative mortality. Within the SPACE-2 trial, the composite outcome of 30-day postoperative stroke or death was reported at 2.5 percent following both CAS and CEA. Perioperative stroke was reported in one patient (3.2%) following CEA in the AMTEC trial. The other most common harms reported within trials included hematoma, facial nerve lesion, and contrast agent incompatibility.

Characteristics of Included Studies

In addition to the two trials from KQ3 (SPACE-2, AMTEC)[35, 37] (described above and in **Table 2 and Appendix E Table 1**), we identified data reported from two U.S. national databases (Medicare and NIS)[28, 43] and analyses of three U.S. surgery registries (the American College of Surgeons National Surgical Quality Improvement Program [ACS NSQIP], Vascular Quality Initiative [VQI], and the Vascular Study Group of New England [VSGNE])[39, 40, 44] (**Table 5, Appendix E Tables 3 and 4**). We selected the most contemporary and comprehensive publications from these national databases and registries.

The two largest sources of data were the national databases, which reported on both CEA and CAS. An analysis of Medicare data[28] (1999–2014; N=1,007,102 asymptomatic adults) reported claims for beneficiaries age 65 years and older enrolled in the fee-for-service Medicare who underwent either CEA or CAS during an index hospitalization without any concomitant major surgery. Asymptomatic status was determined if their International Classification of Disease

(ICD)-9 principal discharge codes for index hospitalization did not include precerebral/cerebral occlusion, cerebral infarction, TIA, or amaurosis fugax.[28] The NIS database[43] (2005–2015; N=1,101,704 asymptomatic adults) reported data for adults 18 years and older with ICD-9 diagnosis codes for carotid artery stenosis or a CEA or CAS procedure code. This analysis included all-payer inpatient health care services at participating institutions with unweighted data from more than 7 million hospital admissions each year. This dataset represents a 20 percent sample of hospitalizations from nonfederal U.S. community hospitals. In the analysis of NIS data, asymptomatic status was based on lack of diagnosis codes for stroke, TIA, amaurosis fugax.[43]

In addition to the two national administrative datasets, analyses related to revascularization harms were also included from three surgical registries. The VQI[44] (2005–2017; N=61,073 asymptomatic adults) is a prospective multicenter collaborative registry across the United States and Ontario, Canada, that includes patients ages 19 to 89 years undergoing CEA or CAS. Clinical professionals extract patient- and procedure-related information from medical charts and data are validated by comparing the registry data to claims data with corrections made for any errors. Mortality data is abstracted from the Social Security Death Index. Asymptomatic status was defined by the lack of ipsilateral symptoms before the procedure (timing not specified), including stroke, TIA, or amaurosis.[44] The VSGNE[39] (2002–2017; N=12,392 asymptomatic adults), a subset of the VQI located in New England, is a prospectively maintained quality improvement registry for patients undergoing vascular procedures including CEA with linkage to the Social Security Death Index Master file for mortality data.[39] The ACS NSQIP[40] (2008–2015; N=53,593 asymptomatic adults) is a national voluntary database for major surgical procedures, including CEA, in which ICD-9 codes identify patients undergoing CEA with trained clinical extractors responsible for data reporting. Within the ASC NSQIP, asymptomatic status is determined by lack of previous TIA or stroke (timing not specified).[40]

The baseline participant data in the two trials was previously discussed in Key Question 3 (**Appendix E Table 2**). See **Appendix E Table 5** for details on population characteristics of included administrative database and vascular registry studies. There was heterogeneity in the publications' reporting of population characteristics: The VSGNE and NSQIP reported baseline characteristics for those with asymptomatic carotid artery stenosis undergoing CEA; Medicare and VQI reported outcomes combining asymptomatic and symptomatic populations but stratified by type of revascularization (CEA and CAS combined); and NIS reported population characteristics for all patients without stratifying by symptomatology or type of revascularization.

In examining population characteristics contributing to high CAS or stroke risk, AMTEC had a high-risk population compared to SPACE-2 and the observational studies however, amongst the observational data, no single administrative database or registry clearly had higher or lower risk population compared to the others.

For the four administrative datasets and registries reporting characteristics of those under CEA,[28, 39, 40, 44] the reported mean ages ranged from 70.1[39] to 75.8 years[28] and the ACS NSQIP reported that 68.7 percent of individuals were between 60 and 80 years.[40] A little over one-half of participants were male, ranging from 57.3 percent[28] to 60.5[44] percent. Over 90 percent of participants were white (ranging from 91.2%[40] to 96.5%[39]). Among the studies, approximately one-third of participants had diabetes and over three-quarters had hypertension. Current smoking was reported as 27.8 percent in NSQIP[40] and ever-smoker as 75.6 and 79.2 percent in the VQI[44] and VSGNE,[39] respectively. Only VQI[44] and VSGNE[39] reported statin use; 80.3 and 84.1 percent of patients were taking statins preoperatively. Within the VSGNE, 62.8 percent had CAD, and history of congestive heart failure (CHF) was relatively rare at 10 percent or less across studies.[28, 39, 40, 44] The degree of stenosis or history of prior carotid revascularization was only reported within the VQI and VSGNE. Within the VQI, 61 percent had stenosis greater than 80 percent, while in VSGNE, 36.8 percent had at least 70 percent stenosis. A history of prior CEA or CAS was reported in VQI and VSGNE at approximately 15[44] and 9[39] percent, respectively.

Two of the administrative datasets (Medicare and VQI) provided baseline characteristics for individuals undergoing CAS; however, these characteristics pool together symptomatic and asymptomatic cases. Within the Medicare study[28] the mean age was 75.4 percent and the VQI analysis[44] was limited to those older than 65. Similar to the CEA population, over half of the participants were male (51–64%) and white (86–93%) with similar rates of diabetes and hypertension. Only the VQI[44] reported the percent of individuals with a history of ever smoking (75.8%), preoperative statin use (79.8%), history of CHF (15.2%), and history of prior carotid revascularization (15.4%).

The NIS administrative database provided baseline characteristics for all patients combined: asymptomatic and symptomatic patients undergoing CEA or CAS.[43] Mean age was 71.2 years, and over half were male (58.5%). NIS reported rates of diabetes (32.2%), hypertension (80.4%), hypercholesterolemia (58.0%), coronary artery disease (44.2%), heart failure (8.0%), COPD (18.0%), and chronic kidney disease (8.9%).[43]

Limited details were reported in these publications to further describe operative or operator characteristics (e.g., NSQIP[40, 41] and VSGNE[39] publications report surgical technique and time; VQI[45] reports surgeon volume).

Outcomes included stroke, death, MI, cardiac events in hospital and/or at 30 days. Other adverse events like blood transfusion, reoperation, readmission, wound infection, cranial nerve injuries were reported in the included contemporary NSQIP and VSGNE registries of asymptomatic patients.

Study Quality and Applicability

Measurement bias is a concern for all of the included administrative databases and registries for KQ4 (**Appendix E Table 4**). Because data from the national administrative databases (Medicare and NIS) are extracted from administrative data used primarily for billing, there is some concern about omission or coding errors. ACS NSQIP uses trained clinical reviewers, and VSGNE and VQI data abstraction is performed by clinical professionals (often the surgeons themselves), so while data abstraction comes from patient charts in addition to billing codes, there is a lack of blinding and concerns about potential measurement bias.

Selection bias is a major concern for all included studies for KQ4. Registry patient selection varied from 100 percent capture from voluntary physicians in VQI to “systematic sampling” in ACS NSQIP. While we abstracted outcomes solely for the asymptomatic population in this review, the designation of “asymptomatic” status was variably defined and, when reported, it was largely was based on history of TIA, stroke, or prior carotid procedures. The administrative databases are limited to diagnosis codes for stroke or TIA during the index admissions and may therefore miss prior neurologic events or symptoms. There remains some concern about selection bias when highly selected surgeons participate in the registries; these surgeons’ complication rates may or may not be representative of national rates. Furthermore, careful patient selection in these registries may contribute to the lower estimates seen in registries compared to the administrative databases.

Detailed Results by Outcome in Asymptomatic Population

CEA

30-Day Stroke or Death

One trial reported composite stroke or death outcomes (**Table 6**). Two studies of administrative data and three vascular registry studies reported composite outcomes of stroke or death (**Table 7**). The SPACE-2 trial reported that 5/203 (2.5%) individuals in the CEA arm met the composite endpoint of 30-day stroke or death rate.[37] A higher rate of 3.5 percent was reported by the large Medicare administrative database.[28] However, the vascular registries reported rates as low as 1.4[44] to 1.7[47] percent. The low rate in the primary VQI study is similar in other VQI publications at 1.1 percent to 1.6 percent.[42, 45, 48] One VQI analysis[42] reported no significant difference in adjusted risk of stroke or death based on degree of stenosis (severe [60-79%] vs. very severe stenosis [≥80%]). While the NIS did not report 30-day outcomes, the rate of major adverse events (including stroke, acute MI, or mortality) occurring in-hospital was 3.1 percent.[43]

30-Day Mortality

One trial reported results for 30-day mortality (**Table 6**). Two studies of administrative data and three vascular registry studies reported 30-day or in-hospital mortality (**Table 8**).There were no deaths reported at 30 days within the CEA arm of the SPACE-2 trial.[37] The highest rate of 30-day mortality was reported within the Medicare database at 1.1 percent.[28] Lower rates were reported within the three surgical registries and ranged from 0.5[39] to 0.7[40] percent. Thirty-day mortality rates were not reported by the NIS; however, the in-hospital mortality rate was 0.3 percent.[43]

30-Day Stroke

One trial reported 30-day stroke outcomes (**Table 6**). One study of administrative data and three vascular registry studies reported 30-day or in-hospital stroke outcomes (**Table 9**). In the SPACE-2 trial, 5/203 (2.5%) of individuals in the CEA arm had a stroke within 30 days of the procedure; the majority (4/5) of these strokes occurred on the day of the intervention.[37] The AMTEC trial did not report 30-day stroke rates; however, the trial did report one fatal stroke within 30 days of surgery.[35] Thirty-day stroke rates were reported in all three surgical registries and ranged from 0.5 percent in the VSGNE[39] to 1.5 percent in ACS NSQIP.[40] Three smaller ACS NSQIP publications showed similar 30-day stroke rates (1.2%[41] and 1.3%[46, 47]). Neither of the administrative databases reported 30-day stroke rates.[28, 43] The NIS study reported in-hospital stroke rate at 0.3 percent.[43]

Postoperative Cardiovascular Events

One trial reported postoperative cardiovascular events (**Table 6**). One study of administrative data and two vascular registry studies reported postoperative CV events (**Table 10**). There were no MIs reported within 30 days in the SPACE-2 trial.[37] The NIS reported in hospital acute MI or other cardiac complications of 2.7 percent[43]. Lower rates of cardiovascular events were reported in the vascular registries compared with NIS with in-hospital MIs reported in VSGNE as 0.8 percent[39] and 30-day cardiac events were reported in ACS NSQIP publications as 1.4[41] and 1.7[46, 47] percent. The primary ACS NSQIP study reported 30-day postoperative rate of MI, pneumonia, DVT/thrombophlebitis, PE, or renal failure of 2.0 percent.[40]

Other Adverse Events

Both included trials (**Table 6**) and two vascular registry studies (**Table 11**) reported additional adverse events. SPACE-2 reported the most common complication at 30 days to be wound hematoma (11.8%) followed by facial nerve lesion (6.9%).[37] Carotid dissections were reported in 1/203 (0.5%) individuals undergoing CEA. AMTEC reported one patient (3.2%) had cranial nerve palsy and two (6.5%) had >70% restenosis of the ICA (CAS was successfully performed in both patients), and an acute occlusion of the ICA was identified 12 hours after CEA in one patient (3.2%).[35] ACS NSQIP and VSGNE reported other complications: Cranial nerve injury rates were reported at 4.0 percent in the VSGNE[39] and 2.9 percent in an ACS NSQIP publication[46]; 30-day reoperations occurred in 3.2 percent of cases in the ACS NSQIP;[40] and in-hospital return to the operating room occurred in 1.4 percent of cases in the VSGNE.[39] The overall 30-day readmission rate in the ACS NSQIP was 5.2 percent.[40]

CAS

30-Day Stroke or Death

One trial, two administrative database studies, and one vascular registry study reported composite stroke or death outcomes (**Table 12 and Table 13**). Within the SPACE-2 trial stroke or death occurred within 30-days of stenting in 5/197 (2.5%) individuals[37]. The Medicare administrative database 30-day stroke or death rate of 5.1 percent was double that of the SPACE-2 trial .[28] Rates in the VQI were similar to the trial data; VQI reported 30 day stroke or death of at 2.6 percent.[44] One VQI analysis of only >60% stenosis showed a 30 day stroke or death rate of 1.9 percent.[42] Another VQI analysis[42] reported no significant difference in adjusted risk of stroke or death based on degree of stenosis (severe [60–79%] vs. very severe stenosis [≥80%]). A smaller, more contemporary analysis (2012-2017) found females experienced a higher rate of perioperative stroke/death (2.9% vs 1.9%) following CAS.[48] While 30-day outcomes were not reported in the NIS, rates of reported in-hospital acute MI, stroke, or death as were 3.6 percent.[43]

30-Day Mortality

One trial, one vascular registry study and two administrative database studies reported mortality outcomes (**Table 12 and Table 14**). There were no deaths within 30 days of stenting in the SPACE-2 trial.[37] 30-day mortality was reported as low as 1.1 percent[44] in VQI and as high as 3.1 percent[28] in Medicare data. In-hospital deaths were as low as 0.4 percent[43] in the NIS and as high as 1.5 percent[28] in Medicare administrative data.

30-Day Stroke

One trial, one administrative database study, and one vascular registry study reported ≤30-day stroke outcomes (**Table 12 and Table 15**). The 30-day stroke rate in SPACE-2 was 5/197 (2.5%); all of the strokes were ipsilateral.[37] VQI reported a 30-day stroke rate of 1.8 percent,[44] and the NIS reported the rate of in-hospital stroke of 0.4 percent.[43]

Postoperative Cardiac Events

One trial and one administrative database study reported postoperative cardiac events (**Table 12 and Table 16**). There were no MIs within 30 days of CAS in the SPACE-2 trial.[37] The NIS reported a rate of in-hospital acute MI and other cardiac complications of 3.1 percent.[43]

Other Adverse Events

One trial reported other postprocedural adverse events (**Table 12**). SPACE-2 reported the most common complication at 30 days to be femoral artery hematoma (2.0%) followed by contrast agent incompatibility (1.5%), hypotonia/vagal reaction (1.5%), and nerve injury (1.0%), and delirium (1.0%).[37] None of the surgical registries reported other adverse events for the CAS procedure.

Chapter 4. Discussion

Summary of Findings and Comparison to Last Review

Since the previous review on this topic, two new trials and five studies using administrative or surgical registry data were identified. The overall conclusions from this review are consistent with those of the previous review[2] (**Table 17**). No population based trials of screening versus no screening for carotid artery stenosis have ever been conducted. The two new trials that were identified addressed the comparison of revascularization with medical treatment for asymptomatic carotid artery stenosis; however, both trials were limited due to methodological concernss.[33-38] The SPACE-2 trial showed no difference in a composite outcome of stroke or death at 1 year in the revascularization (CEA or CAS) and BMT groups,[37] the 5 year outcomes have yet to be published. The small AMTEC trial specifically recruiting a high risk population showed statistically significant benefits in stroke or death at 3.3 year median followup in the CEA arm; however, AMTEC's conclusions are limited by validity and applicability issues.[35]

New evidence related to revascularization harms is available from contemporary analyses of national databases and surgical registries.[28, 35, 39-46] Rates of 30-day postoperative stroke or death for CEA were highest in the analyses of national databases (Medicare and NIS) compared with the trial data and surgical registries. Medicare and NIS reported rates of 3.5[28] and 3.1[43] percent, respectively. The SPACE-2 trial[37] reported 2.5 percent 30-day stroke or death rate, while the VQI and VSGNE reported lower rates of 1.1[44] to 1.8 percent.[39] For the CAS procedure, 30-day stroke or death was again highest in Medicare at 5.1 percent[28] and lowest in a VQI analysis of only individuals with less than 60 percent stenosis of 1.9 percent.[42] Previous analyses addressing the wide variations in estimates of vascular revascularization complications have cited concerns about administrative data's ability to categorize patients' symptomatic status and identify perioperative complications.[51, 52] Administrative data has shown poor concordance compared with surgical registries utilizing chart review (like the VQI and NSQIP) due to data collection methods and variable definitions for postoperative complications. However, these outcomes discrepancies are most apparent for postoperative complications other than distinct clinical outcomes such as death or MI.[53, 54] Others have suggested that participation in surgical registries may improve outcomes with active engagement in quality improvement initiatives.[55] While we presented administrative and registry data in an effort to reflect complication rates in real-world practice, selection and measurement bias from these data sources remain serious concerns.

The two new recent trials add little to the evidence base on effectiveness of revascularization compared with BMT (KQ3), which consists of the historical trials (ACAS, ACST, VACS) with larger study sizes and longer followup showing the long term benefits of CEA compared to BMT,[11, 56-58] included in the previous review. Estimates of surgical harms following CEA are also consistent with the previous review. The SPACE-2 trial[37] reported a 30-day stroke/death rate of 2.5 percent, which is similar to previous reviews'[2] meta-analysis of trials (2.4% [95% CI, 1.7 to 3.1%]). While our analysis did not pool the results of these trials, one recent network meta-analysis included the historical trials plus AMTEC and SPACE-2 reporting no differences in 30-day stroke and mortality, but lower rates of 30-day MI and higher rates of 30-day TIA in the CEA group compared with the BMT group.[59]

Contemporary national databases (NIS and Medicare) now represent a substantially larger population (over 1.7 million procedures) than in the previous review and showed similar stroke/death rates following CEA (3.1[43] [in-hospital stroke, MI, or death]) to 3.5[28]% [30-day ischemic stroke/death]) compared with previous MA of Medicare data (3.3% [95% CI, 2.6 to 3.9%]).[2] The rates reported in the national administrative databases remain higher than the recommended 3 percent threshold specified in expert guidelines as the acceptable rate of morbidity and mortality under which prophylactic CEA may be considered in those with at least a 3-5 year life expectancy.[60] The VSGNE and VQI report lower 30-day stroke/death rates ranging from 1.1[39] to 1.8[44] percent, perhaps reflecting select high-volume centers with experienced surgeons and highly selected surgical patients.

In addition, there is more evidence available related to the use of CAS in asymptomatic carotid artery stenosis than in the previous review. The previous review included no trials examining the effectiveness of CAS compared with medical therapy alone. New evidence from the SPACE-2 trial concluded that there was no difference in stroke between the CAS group compared with BMT group within one year.[37] The rate of 30-day stroke/death within the SPACE-2 trial was 2.5 percent, slightly lower than the rate found in trials in the previous review (3.1% [95% CI, 2.7 to 3.6%]).[2] However, the contemporary national databases (NIS and Medicare) including 300,000 procedures identified a rate of stroke/death of 3.6[28] to 5.1[43] percent. Rates were lower within the VQI at 2.6 percent (1.9% among those with >60% stenosis).[42, 44]

Limitations

The scope of this rapid review was limited to screening in the general population. Therefore, we did not address the benefits/harms of screening high-risk subpopulations, and the conclusions of this review may not necessarily apply to patients at high risk of asymptomatic carotid stenosis or who have had prior stroke or TIA contralateral to the asymptomatic stenosis. Such an analysis is highly clinically relevant and would require careful consideration of epidemiologic factors, ideally validated risk assessment pools alongside the results from ongoing trials.[61]

One salient argument against general population screening is that stroke caused by carotid artery stenosis has a low population attributable risk.[9, 62] Stroke remains a major cause of disability and death, and after more than four decades in decline, rates recently have stalled or reversed among some populations.[63] Approximately 12 percent of strokes are preceded by a TIA and 23 percent by a previous stroke.[64] One analysis estimated that about 34 percent of strokes are attributed to ICA thromboembolism and only 11 percent of strokes are associated with significant, previously asymptomatic stenosis.[9] Applying the absolute risk difference seen in the historical trials (ARD= 0.03 [0.05 to 0.00] in any stroke/death),[2] very few patients would realize benefit, particularly in light of perioperative complications and even with contemporary improvements in surgical techniques.[65] Many have argued that the historical trials have a more optimistic CEA benefit than would be expected with contemporary aggressive medical management of atherosclerotic risk factors,[66] as seen in the temporal decline in stroke risk in those with carotid artery stenosis. Thus, even if surgical operators and patients are carefully selected, few would benefit.[65]

A 2020 review analyzed data from 12 trials and observational studies of participants with asymptomatic carotid stenosis (N=3600) with 1.9 to 6.2 year mean or median followup.[10] They reported annual ipsilateral stroke risk of 0.3 to 3.1 percent for those with ≥50 percent stenosis and 0 to 3.3 percent risk for those with ≥60 or ≥75 percent stenosis. [10] Given the low risk of stroke overall in asymptomatic patients, one would ideally focus screening on those at high risk for stenosis and then identify those at high risk for progression to stroke. Among those asymptomatic patients with clinically significant carotid artery stenosis at higher risk of stroke, those with an acceptably low surgical risk profile could then be considered for CEA/CAS with operators who had favorable procedural complication rates.[6, 14] First, while there are some proposed risk models for carotid artery stenosis,[67] we are not aware of any externally validated risk models for identifying those at high risk for carotid artery stenosis, although one systematic review and external validation study is planned.[68] Second, there are no externally validated risk tools for stroke prediction in persons with carotid artery stenosis. In fact, the definition of 'clinically significant stenosis' is not entirely certain. Some models have been developed suggesting patient characteristics (e.g., age, systolic blood pressure) and radiographic characteristics (e.g., degree of stenosis, microemboli, plaque characteristics) that may predict risk of stroke in individuals with asymptomatic carotid artery stenosis however none have been externally validated. [69-71] Other models have been developed to estimate postoperative outcomes and 5-year survival following surgical repair.[72-74] To date, the SVS recommends consideration of CEA for asymptomatic patients with stenosis of 60 to 99 percent if perioperative stroke/death is less than 3 percent,[6] and the AHA/ASA[14] similarly recommends consideration of CEA in asymptomatic carotid artery stenosis of at least 70 percent stenosis on doppler ultrasound for highly selected patients if the risk of perioperative stroke, MI, and death is low. Implementation of these guidelines has been challenging due to limitations in the availability of risk-prediction tools.

Carotid artery stenosis is a manifestation of systemic atherosclerotic disease so identifying this condition may potentially lead to changes in medical management to prevent future CVD events in patients otherwise not known to have preexisting atherosclerotic disease. Because it was outside of the scope of this review, we did not explore use of carotid artery stenosis screening (degree of stenosis or carotid intima medial thickening) as a CVD risk-stratification tool to identify those with elevated 10-year CVD risk who are eligible for statin use. Many patients with clinically important CAS may already meet the 7.5 percent threshold in the Pooled Cohort Equation; however, the degree of overlap is uncertain.

There remain generalizability concerns about how the complication rates reported in these studies would translate to truly asymptomatic, screen-detected populations undergoing revascularization in low volume community hospitals (which may be expected to have higher complication rates compared with high volume academic centers).[75] Screen-detected cases would be expected to have lower complication rates compared with populations with any neurologic symptoms or remote history of TIA, stroke, or contralateral disease. The newer included and historical studies included patients with a history of these conditions. For KQ3, selection bias (asymptomatic case definition, patient/case selection, surgeon/operator selection) and measurement bias (omissions in data abstraction of postoperative complications) were serious concerns for the administrative databases and surgical registries. Nonetheless, these included studies represent the best-quality available evidence. Well-designed surgical registries with independent abstractors and data quality checks from geographically diverse regions would be ideal to capture real-practice complication rates for patients undergoing revascularization in community as well as academic centers in rural and urban centers in the United States.

The limited nature of this update also led to the exclusion of some studies related to revascularization harms. For example, no studies examining the benefits and harms of TCAR met inclusion criteria; however, a few publications from VQI and NSQIP registries of TCAR were excluded based on the size.[76-80] Likewise, smaller statewide[81] and multistate administrative databases[82, 83] were not included because CMS and NIS together contributed over 1 million asymptomatic patients and were considered more nationally representative. We also did not include non-US databases or registries as we sought to capture postoperative complication rates most representative of contemporary U.S. practice. We selected administrative databases and surgical registries with the most contemporary and largest datasets, therefore there may be older publications of these databases/registries that reported more details on adverse events; we focused on postoperative stroke and mortality. Finally, this review did not include harms from comparative effectiveness trials of CEA and CAS nor did it address the harms of BMT.

Ongoing Studies

For KQ1, we did not identify any published or ongoing trials of screening versus no screening in unselected general populations. For KQ3, there were few new trials examining the important question of the comparative effectiveness of revascularization compared with best medical treatment, although ongoing trials are imminent. We identified three important ongoing trials that address the effectiveness of revascularization compared with contemporary best medical treatment alone (**Appendix F**).[84-88] The CREST-2 trial (NCT02089217; N planned 2480) is being conducted as two parallel multicenter randomized clinical trials comparing best medical management alone to CEA or CAS plus best medical management. Participants will include individuals with at least 70 percent stenosis and no stroke or TIA within 180 of randomization. Medical management includes aggressive antihypertensive and anti-lipid treatment as well as lifestyle management programs for weight loss, smoking cessation, exercise, and diabetes management. The CREST-2 Registry is intended to credential interventionalists for the trial and optimize patient selection, procedural technique, and outcomes.[89] Primary outcomes will include composite endpoint of stroke/death within 44 days of randomization or ipsilateral stroke up to 4 years after randomization. Secondary outcomes include cognitive function, various severities and definitions of stroke; subgroup analyses are planned. The estimated primary enrollment completion date is December 2021.[85, 90] CREST-H (NCT03121209) is an add-on study to CREST-2 addressing whether cognitive impairment can be reversed by revascularization when cerebral blood flow is low on the side of a high-grade carotid stenosis.[91, 92]

The ECST-2 Trial (N planned 2000), an ongoing randomized trial comparing optimized medical management alone with CEA or CAS plus medical management. Participants have asymptomatic or symptomatic carotid artery stenosis with at least 50 percent stenosis and a 5-year ipsilateral stroke risk of less than 20 percent. Medical management in this trial includes antihypertensive and anti-lipid treatment as well as lifestyle counseling. Primary outcomes include any stroke during followup and nonstroke death within 30 days of revascularization. The trial will also measure longer-term outcomes including stroke, revascularization, and functional status/cognitive impairment, and a subset set of patients will have MRI followup to assess rates of new cerebral infarction, hemorrhage, or white matter changes. The estimated primary completion date is March 2022.[86, 87]

The Endarterectomy Combined With Optimal Medical Therapy (OMT) vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-Average Risk of Ipsilateral Stroke (ACTRIS) trial (N planned 700) will compare best medical management alone with CEA combined with best medical therapy. This trial intends to enroll 700 participants with 70 to 99 percent stenosis and at least one marker of increased stroke risk (e.g., silent brain infarction on MRI, rapid progression, history of contralateral stroke TIA or ischemic stroke). All participants will receive medical management with antiplatelet, antihypertensive, and antilipid treatment along with lifestyle counseling. Primary outcomes include ipsilateral stroke or procedural stroke or death. This trial is not planned to be completed until December 2025.[88]

Conclusions

Population-based screening trials addressing the benefits and harms of screening for carotid artery stenosis have never been conducted. Since the last review, little new indirect evidence has emerged that answers the critical question of whether carotid revascularization is superior to contemporary best medical management. The ongoing CREST-2 and ECST-2 trials will be the largest contemporary trials to address this issue. Large national administrative databases and vascular surgery registries suggest that postoperative 30-day stroke/death complication rates vary widely—1.4 to 3.5 percent for CEA and 2.6 to 5.1 percent for CAS—suggesting that careful surgeon/operator and patient selection is critical to realize benefits from screening and revascularization.

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Figure 1. Analytic Framework

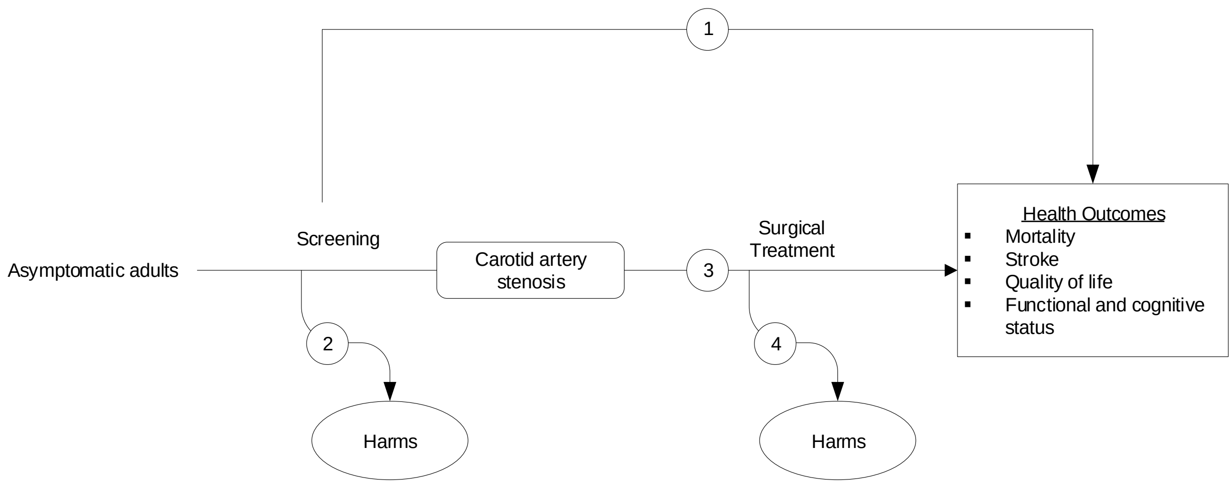


Table 1. Summary of Recommendations for Screening for Asymptomatic Carotid Artery Stenosis

Organization, Year	Summary of recommendation
United States Preventive Services Task Force, 2014[3]	The USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population. (D Recommendation)
American Heart Association / American Stroke Association, 2014[14]	Screening low-risk populations for asymptomatic carotid stenosis is not recommended.
	In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established
	It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established
American Institute of Ultrasound Medicine (AIUM), 2016[93]	Ultrasound examination of the extracranial cerebrovascular system is indicated in patients with a carotid bruit.
Joint guidelines from multiple US societies (ASA/ACCF/ AHA/AANN/AANS/ ACR/ASNR/CNS/SAIP/ SCAI/SIR/SNIS/SVM/SVS), 2011[60]	It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit.
	Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic peripheral arterial disease, coronary artery disease, or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of extracranial carotid and vertebral artery disease in those without carotid bruit would justify actions that affect clinical outcomes.
	Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have ≥2 of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, family history in a 1st-degree relative of atherosclerosis manifested before age 60 years, or family history of ischemic stroke. However, it's unclear whether establishing a diagnosis of extracranial carotid and vertebral artery disease would justify actions that affect clinical outcomes.
	Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis.
Society for Vascular Surgery, 2011[6]	Routine screening is not recommended to detect clinically asymptomatic carotid stenosis in the general population. Screening is not recommended for presence of a neck bruit alone without other risk factors.
	Screening for asymptomatic clinically significant carotid bifurcation stenosis should be considered in certain groups of patients with multiple risk factors that increase the incidence of disease as long as the patients are fit for and willing to consider carotid intervention if a significant stenosis is discovered. Such groups of patients include those with clinically significant peripheral vascular disease and those age ≥65 years with a history of ≥1 of the following atherosclerotic risk factors: coronary artery disease, smoking, or hypercholesterolemia.
	Carotid screening may be considered in patients prior to coronary artery bypass. Screening is most likely to be fruitful if the patient is age ≥65 years, has left main disease, or has a history of peripheral vascular disease. The strongest indication for screening these patients from the data available is to identify patients at high risk of perioperative stroke.

Abbreviations: AANN = American Association of Neuroscience Nurses; AANS = American Association of Neurological Surgeons; ACCF = American College of Cardiology Foundation; ACR = American College of Radiology; AHA = American Heart Association; ASA = American Stroke Association; ASNR = American Society of Neuroradiology; CAS = carotid artery stenting; CEA = carotid endarterectomy; CNS = Congress of Neurological Surgeons; SAIP = Society of Atherosclerosis Imaging and Prevention; SCAI = Society of Cardiovascular Angiography and Interventions; SIR = Society of Interventional Radiology; SNIS = Society of NeuroInterventional Surgery; SVM = Society of Vascular Medicine; SVS = Society for Vascular Surgery

Table 2. Study Characteristics of Included Randomized, Controlled Trials of Revascularization vs. BMT, KQ 3

Study Name Author, Year Quality	Country	N randomized	Study aim	Brief pop description	Recruitment setting	Pre-randomization evaluation & required stenosis	FU timepoints (Mean FU)	Early termination description
SPACE-2 Reiff, 2019[37] Fair	Germany, Switzerland, and Austria	513	To compare the stroke preventive effects of BMT alone with that of BMT in combination with CEA or CAS	Adults patients aged 50 to 85, with asymptomatic carotid artery stenosis (≥70%)	Hospital (multisite)	Carotid artery stenosis of ≥70% following ultrasound criteria	30-d, 1-yr (NR)	Originally designed as a 3 arm trial. Due to low recruitment it was changed to two separate trials (CEA vs BMT, CAS vs BMT). continuing low recruitment rates led to the premature termination of enrollment of the SPACE-2 study in 2014
AMTEC Kolos, 2015[35] Fair	Russia	55	To assess the value of BMT with and without CEA in patients with asymptomatic severe carotid artery stenosis*	Adults aged 40 to 80 years old, with asymptomatic CAS (70-79% stenosis)	Surgical & medical clinics	70–79% on ultrasonography and 60–79% on CTA, contrast MRA, or 60–79% on angiography in common carotid artery and/or internal carotid artery.†	3.3-yr cumulative (Median: 3.3 (range, 1.5-5.0-yr)	Data and Safety Monitoring Board voted to terminate trial: Given the clear advantages of CEA, all BMT patients were advised to undergo carotid revascularization after the study termination.

* CEA was preferred to CAS because of doubts concerning the quality of CAS in Russia at the beginning of the study.
† Patients with 70% to 79% stenosis were included because in 2009, CEA was strongly recommended (Class IA) in patients with severe carotid atherosclerosis, and the committee decided that BMT in patients with stenosis of >80% was unethical. Patients with stenosis of 60% to 70% were not included in the study because the committee considered that CEA would also be unethical.

Abbreviations: AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computerized tomography angiography; FU = followup; KQ = key question;; MRA = magnetic resonance angiography; NR = not reported; pop = population; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; vs = verse; yr = year

Table 3. Health Outcomes Reported in Trials of CEA vs. BMT, KQ 3

Study Name Author, Year Quality	Followup	Outcome	IG n analyzed	IG events (%)	CG n analyzed	CG events (%)	HR (95% CI)	P-value
SPACE-2 Reiff, 2019[37] Fair	1-yr	Composite (stroke or death (30-d) or ipsilateral ischemic stroke (1-yr))	203	5 (2.5%)	113	1 (0.9%)	2.82 (0.33, 24.07)	P=0.345
		Stroke*	203	8 (3.9%)	113	1 (0.9%)	4.51 (0.56, 36.09)	P=0.155
		Ipsilateral stroke	203	4 (2.0%)	113	1 (0.9%)	2.24 (0.25, 20.04)	P=0.471
		Mortality	203	5 (2.5%)	113	4 (3.5%)	NR	NR
		Disabling stroke†	203	2 (1.0%)	113	1 (0.9%)	NR	NR
		TIA	203	4 (2.0%)	113	6 (5.3%)	NR	NR
		Ipsilateral TIA	203	2 (1.0%)	113	6 (5.3%)	NR	NR
		MI	203	1 (0.5%)	113	0 (0%)	NR	NR
		Restenosis	203	4 (2.0%)	NA	NA	NA	NA
		Re- or progressive stenosis	203	4 (2.0%)	113	5 (4.4%)	NR	NR
AMTEC Kolos, 2015[35] Fair	3.3-yr (cumulative)‡	Nonfatal Stroke or death	31	2 (6.5%)	24	9 (37.5%)	0.20 (0.06, 0.65)§	P=0.008
		Nonfatal Stroke	31	1 (3.2%)	24	5 (20.8%)	0.20 (0.04, 0.995)§	P=0.0493
		Nonfatal stroke, carotid revascularization, and death	31	4 (12.9%)	24	12 (50.0%)	0.24 (0.09, 0.65)§	P=0.0048
		ACM‖	31	1 (3.3%)	24	4 (16.7%)	0.23 (0.04, 1.35)§	P=0.105
		Major adverse cardiac events#	31	4 (12.9%)	24	14 (58.3%)	0.21 (0.08, 0.54)§	P=0.0012

*Three strokes in the CEA arm and 1 stroke in the BMT arm occurred after day 30 (HR: 1.70 (0.18-16.37) p=0.645)
†Defined as mRS 30 days after stroke >2
‡The median follow-up period was 3.3 years (range, 1.5-5.0 years)
§Calculated unadjusted HRs. Study reported unadjusted HRs: Nonfatal stroke: 5.07 (1.005, 25.6); Nonfatal stroke or death: 5.1 (1.53, 16.79); Nonfatal stroke, carotid revascularization, and death: 4.2 (1.55, 11.53); ACM: 4.3 (0.74, 24.15)
‖Death in the CEA group was a fatal stroke 28 days after surgery; 4 sudden deaths in BMT group but exact cause of death was not established.
#Death, nonfatal MI, nonfatal stroke, carotid revascularization, and coronary revascularization

Abbreviations: ACM = all-cause mortality; AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BMT = best medical treatment; CEA = carotid endarterectomy; CG = control group; CI = confidence interval; IG = intervention group; HR = hazard ratio; KQ = key question; MI = myocardial infarction; mRS = modified Rankin Scale; NA = not applicable; NR = not reported; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; TIA = transient ischemic attack; vs = verse; yr = year

Table 4. Health Outcomes Reported in Trials of CAS vs. BMT, KQ 3

Study Name Author, Year Quality	Followup	Outcome	IG n analyzed	IG events (%)	CG n analyzed	CG events (%)	HR (95% CI)	P-value
SPACE-2 Reiff, 2019[37] Fair	1-yr	Composite (stroke or death (30-d) or ipsilateral ischemic stroke (1-yr))	197	6 (3.05%)	113	1 (0.9%)	3.50 (0.42, 29.11)	P=0.246
		Stroke*	197	8 (4.1%)	113	1 (0.9%)	4.70 (0.59, 37.61)	P=0.144
		Ipsilateral stroke	197	6 (3.0%)	113	1 (0.9%)	3.47 (0.42, 28.84)	P=0.249
		Mortality	197	2 (1.0%)	113	4 (3.5%)	NR	NR
		Disabling stroke†	197	1 (0.5%)	113	1 (0.9%)	NR	NR
		TIA	197	5 (2.5%)	113	6 (5.3%)	NR	NR
		Ipsilateral TIA	197	4 (2.0%)	113	6 (5.3%)	NR	NR
		MI	197	0 (0%)	113	0 (0%)	NR	NR
		Restenosis	197	11 (5.6%)	NA	NA	NA	NA
		Re- or progressive stenosis	197	11 (5.6%)	NA	NA	NA	NA

*Three strokes in the CAS arm and 1 stroke in the BMT arm occurred after day 30 (HR: 1.79 (0.19-17.24) p=0.613)
†Defined as mRS 30 days after stroke >2

Abbreviations: ACM = all-cause mortality; AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BMT = best medical treatment; CAS = carotid artery stenting; CG = control group; CI = confidence interval; IG = intervention group; HR = hazard ratio; KQ = key question; MI = myocardial infarction; mRS = modified Rankin Scale; NA = not applicable; NR = not reported; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; TIA = transient ischemic attack; vs = verse; yr = year

Table 5. Study Characteristics of Included Administrative Data and Vascular Registry Studies, KQ 4

Registry Author, Year Quality	Procedure type(s)	Years of data collection	Setting and source population	Total n	Total Asymptomatic n	Definition of symptomatic	Included stenosis* and determination method
ACS NSQIP Garcia, 2017[40] Fair	CEA	2008 to 2015	National voluntary database for major surgical procedures	53,593	53,593	Previous stroke or TIA	NR
Medicare Lichtman, 2017[28] Fair	CAS, CEA	1999 to 2014	Medicare data for beneficiaries aged 65 years or older enrolled in fee-for-service Medicare for 1 month or longer between January 1999 and December 2014.	1,168,188	1,007,102 (CAS: 192,014; CEA: 815,088)	Patients were considered symptomatic if they had an ICD-9-CM principal discharge diagnosis code indicating occlusion or stenosis of the precerebral or cerebral arteries with cerebral infarction or a secondary diagnosis code indicating prior stroke transient ischemic attack or amaurosis fugax	NR
NIS Mayor, 2019[43] Fair	CAS, CEA	2005 to 2015	NIS, an all-payer inpatient healthcare database in the US.	1,242,688 (CEA: 1,083,912 CAS: 158,776)	1,101,704 (CAS: 132,051; CEA: 969,653)†	Symptomatic carotid artery stenosis was differentiated from asymptomatic based on the presence of 1 or more diagnosis codes indicative of amaurosis fugax, transient ischemic attack, or stroke	NR
VSGNE Boitano, 2019[39] Fair	CEA	2003 to 2017†	The VSGNE CEA and long-term follow-up databases were queried to identify all patients undergoing CEA from 2011 to 2017.	18,832	12,392	Patients were considered symptomatic if they experienced ipsilateral cortical or eye symptoms before the procedure.	Preoperative carotid artery stenosis was dichotomized to ≥70% stenosis and <70% stenosis. The most severe stenosis documented on preoperative duplex ultrasound, computed tomography angiography, magnetic resonance angiography, or

Table 5. Study Characteristics of Included Administrative Data and Vascular Registry Studies, KQ 4

Registry Author, Year Quality	Procedure type(s)	Years of data collection	Setting and source population	Total n	Total Asymptomatic n	Definition of symptomatic	Included stenosis* and determination method
							angiography was used.
VQI Nejim, 2019[44] Fair	CAS, CEA	2005 to 2017	Prospective registry of multicenter collaboration across the United States and the Province of Ontario in Canada that captures various vascular interventions.	89,853	61,073 (CAS: 8038; CEA: 53,035)	Symptomatic status was defined as the presence of ipsilateral symptoms before the procedure: amaurosis fugax, transient ischemic attack, and minor or major stroke.	Degree of stenosis was defined as the most severe stenosis of each patient carotid artery measured by duplex ultrasound, magnetic resonance angiography, computed tomography angiography, or arteriogram.

*Percent stenosis to get into the analysis NR in included studies
†Per author communication

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CAS = carotid artery stenting; CEA = carotid endarterectomy; KQ = key question; NIS = National Inpatient Sample; NA = not applicable; NR = not reported; TIA = transient ischemic attack; VSGNE = Vascular Study Group of New England; US= United States; VQI = Vascular Quality Initiative

Table 6. Postoperative Harms Reported in Trials of CEA vs. BMT, KQ 4

Study Name Author, Year Quality	Outcome	Followup	N analyzed	N with outcome (%)
SPACE-2 Reiff, 2019[37] Fair	Stroke or death	30-d	203	5 (2.5%)
	Stroke	Day of intervention	203	4 (2.0%)
		30-d	203	5 (2.5%)
	Ipsilateral stroke	30-d	203	4 (2.0%)
	Mortality	30-d	203	0 (0%)
	MI	30-d	203	0 (0%)
	Other Peri/postoperative complications: *Lesion vagal nerve*	30-d	203	10 (4.9%)
	Lesion hypoglossal nerve	30-d	203	7 (3.4%)
	Lesion facial nerve	30-d	203	14 (6.9%)
	*Wound hematoma**	30-d	203	24 (11.8%)
	Facial hypesthesia	30-d	203	4 (2.0%)
	Dissection of carotid artery	30-d	203	1 (0.5%)
	Hypotonia/vasovagal reaction	30-d	203	1 (0.5%)
AMTEC Kolos, 2015[35] Fair	Fatal stroke	30-d	31	1 (3.2%)
	Other complications: *Cranial nerve palsy*	Perioperative§	31	1 (3.2%)
	>70% Restenosis of the ICA	Perioperative§	31	2 (6.5%)
	Acute occlusion of ICA	Perioperative§	31	1 (3.2%)

*Reoperation and hematoma evacuation in one patient
†Death, nonfatal MI, nonfatal stroke, carotid revascularization, and coronary revascularization
‡The median follow-up period was 3.3-yr (range, 1.5-5.0-yrs)
§ Timing not specified

Abbreviations: AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BMT = best medical treatment; CAS = carotid artery stenting; ICA = internal carotid artery KQ = key question; MI = myocardial infarction; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; vs = verse; yr = year

Table 7. Postoperative Adverse Composite Outcomes Reported in CEA Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Study reported outcome	Followup	N analyzed*	Events*	Event rates*
ACS NSQIP† Liang 2020[47]	Stroke/Death	30-d	14,756	225	1.7%
	MAE (composite of stroke, death, cardiac event)	30-d	14,756	478	3.2%
Medicare Lichtman, 2017[28] Fair	Ischemic stroke or death‡	30-d	815,088	28,212	3.5%
	Ischemic stroke, MI or death‡	30-d	815,088	30,564	3.7%
NIS Mayor, 2019[43] Fair	MAE (stroke, acute MI, in-hospital mortality)	In Hospital	969,653§	29,962	3.1%
VSGNE Boitano, 2019[39] Fair	MAE (Composite of stroke, MI, or death.)	30-d	12,392	228	1.8%
VQI Nejim, 2019[42, 44] Fair	Stroke/death	30-d	53,035	735	1.4%

*Data was calculated across subgroups for all studies except ACS NSQIP (Liang 2020)
†Data for stroke/death composite outcome taken from ancillary publication of ACS NSQIP, patients undergoing CEA from 2011-2017.
‡Ischemic stroke and MI events were determined from the date of hospital discharge for the index carotid procedure. Death was determined from the date of hospital admission for the index carotid procedure
§Asymptomatic n was provided by authors

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CEA = carotid endarterectomy; KQ = key question; MAE = major adverse event; NIS = National Inpatient Sample; VSGNE = Vascular Study Group of New England; VQI = Vascular Quality Initiative

Table 8. Postoperative Mortality Reported in CEA Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Followup	N analyzed*	Events*	Event rates*
ACS NSQIP Garcia, 2017[40] Fair	30-d	53,593	396	0.7%
Medicare Lichtman, 2017[28] Fair	30-d†	815,088	9144	1.1%
	In Hospital‡	815,088	4444	0.5%
NIS Mayor, 2019[43] Fair	In Hospital	969,653§	2,521	0.3%
VSGNE Boitano, 2019[39] Fair	30-d	12,392	58	0.5%
VQI Nejim, 2019[44] Fair	30-d	53035	320	0.6%

*Data was calculated across subgroups for all studies
†Death was determined from the date of hospital admission for the index carotid procedure
‡Death was determined from Discharge disposition
§Asymptomatic n was provided by authors

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CEA = carotid endarterectomy; KQ = key question; NIS = National Inpatient Sample; VSGNE = Vascular Study Group of New England; VQI = Vascular Quality Initiative

Table 9. Postoperative Stroke Reported in CEA Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Study reported outcome	Followup	N analyzed*	Events*	Event rates*
ACS NSQIP Garcia, 2017[40] Fair	Stroke	30-d	53,593	788†	1.5%
NIS Mayor, 2019[43] Fair	Stroke	In Hospital	969,653‡	2,909	0.3%
VSGNE Boitano, 2019[39] Fair	Stroke	30-d	12,392	57	0.5%
	Stroke or TIA	30-d	12,392	163	1.3%
	Ipsilateral Stroke	30-d	12,392	66	0.5%
VQI Nejim, 2019[44] Fair	Stroke	30-d	53035	416	0.8%

*Data was calculated across subgroups for all studies
†Number of events confirmed by author communication
‡Asymptomatic n was provided by authors

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CEA = carotid endarterectomy; KQ = key question; NIS = National Inpatient Sample; TIA = transient ischemic attack; VSGNE = Vascular Study Group of New England; VQI = Vascular Quality Initiative

Table 10. Postoperative Cardiovascular Events Reported in CEA Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Study reported outcome	Followup	N analyzed*	Events*	Event rates*
ACS NSQIP Garcia, 2017 [40] Fair	MI, PNA, DVT/thrombophlebitis, PE, renal failure	30-d†	53,593	1063	2.0%
NIS Mayor, 2019[43] Fair	MI‡	In Hospital	969,653§	26,084	2.7%
VSGNE Boitano, 2019[39] Fair	MI	In Hospital	12,392	101	0.8%

*Data was calculated across subgroups for all studies
†Outcome assessment timing confirmed by author
‡Postoperative MI included both acute MI and other cardiac complications
§Asymptomatic n was provided by authors

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CEA = carotid endarterectomy; DVT = deep venous thrombosis; KQ = key question; MI = Myocardial infarction; NIS = National Inpatient Sample; PE = pulmonary embolism; PNA = pneumonia; VSGNE = Vascular Study Group of New England

Table 11. Other Postoperative Adverse Events Reported in CEA Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Study reported outcome	Followup	N analyzed*	Events*	Event rates*
ACS NSQIP Garcia, 2017[40] Fair	Blood transfusion	Operative/ Postoperative (timing not specified)	53,593	954	1.8%
	Reoperation	30-d	53,593	1727	3.2%
	Readmission	30-d	53,593	2798	5.2%
	SSI	Postoperative (timing not specified)	53,593	209	0.4%
VSGNE Boitano, 2019[39] Fair	Return to OR	In Hospital	12,392	174	1.4%
	Dysrhythmia	In Hospital	12,392	174	1.4%
	Reperfusion syndrome	In Hospital	12,392	20	0.2%
	Wound infection	In Hospital	12,392	7	0.06%
	Cranial nerve injury	In Hospital	12,392	494	4.0%

*Data was calculated across subgroups for all studies
†Outcome assessment timing confirmed by author
‡Postoperative MI included both acute MI and other cardiac complications
§Asymptomatic n was provided by authors

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CEA = carotid endarterectomy; KQ = key question; MI = myocardial infarction; OR = operating room; SSI = surgical-site infection VSGNE = Vascular Study Group of New England

Table 12. Postoperative Harms Reported in Trials of CAS vs. BMT, KQ 4

Study Name Author, Year Quality	Outcome	Followup	N analyzed	N with outcome (%)
SPACE-2 Reiff, 2019[37] Fair	Stroke or death	30-d	197	5 (2.5%)
	Stroke	Day of intervention	197	3 (1.5%)
		30-d	197	5 (2.5%)
	Ipsilateral stroke	30-d	197	5 (2.5%)
	MI	30-d	197	0 (0%)
	Mortality	30-d	197	0 (0%)
	Other peri/postoperative complications: *Aneurysm of femoral artery*	*30-d*	*197*	*2 (1.0%)*
	Nerve injury	*30-d*	*197*	*1 (1.0%)*
	Incompatibility of contrast agent	*30-d*	*197*	*3 (1.5%)*
	Hematoma of femoral artery	*30-d*	*197*	*4 (2.0%)*
	Hypotonia/ vasovagal reaction	*30-d*	*197*	*2 (1.5%)*
	Delirium	*30-d*	*197*	*2 (1.0%)*

Abbreviations: BMT = best medical treatment; CAS = carotid artery stenting; KQ = key question; MI = myocardial infarction; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; vs = verse;

Table 13. Postoperative Adverse Composite Outcomes Reported in CAS Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Study reported outcome	Followup	N analyzed*	Events*	Event rates*
Medicare Lichtman, 2017[28] Fair	Ischemic stroke or death†	30-d	192,014	9711	5.1%
	Ischemic stroke, MI or death†	30-d	192,014	10,369	5.4%
NIS Mayor, 2019[43] Fair	MAE‡	In Hospital	132,051§	4,807	3.6%
VQI Nejim, 2019[44] Fair	Stroke/death	30-d	8038	212	2.6%

*Data was calculated across subgroups for all studies
†Ischemic stroke and MI events were determined from the date of hospital discharge for the index carotid procedure. Death was determined from the date of hospital admission for the index carotid procedure
‡A major adverse event constituted a composite variable reflecting one or more of the other outcomes (stroke, acute MI, in-hospital mortality)
§Asymptomatic n was provided by authors

Abbreviations: CAS = carotid artery stenting; KQ = key question; MAE = major adverse event; MI = myocardial infarction; NIS = National Inpatient Sample; VQI = Vascular Quality Initiative

Table 14. Postoperative Mortality Reported in CAS Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Followup	N analyzed*	Events*	Event rates*
Medicare Lichtman, 2017[28] Fair	30-d†	192,014	5910	3.1%
	In Hospital‡	192,014	2920	1.5%
NIS Mayor, 2019[43] Fair	In Hospital	132,051§	475	0.4%
VQI Nejim, 2019[44] Fair	30-d	8038	87	1.1%

*Data was calculated across subgroups for all studies
†Death was determined from the date of hospital admission for the index carotid procedure
‡Death was determined from discharge disposition
§Asymptomatic n was provided by authors

Abbreviations: CAS = carotid artery stenting; KQ = key question; NIS = National Inpatient Sample; VQI = Vascular Quality Initiative

Table 15. Postoperative Stroke Reported in CAS Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Followup	N analyzed*	Events*	Event rates*
NIS Mayor, 2019[43] Fair	In Hospital	132,051†	581	0.4%
VQI Nejim, 2019[44] Fair	30-d	8038	143	1.8%

*Data was calculated across subgroups for all studies
†Asymptomatic n was provided by authors

Abbreviations: CAS = carotid artery stenting; KQ = key question; NIS = National Inpatient Sample; VQI = Vascular Quality Initiative

Table 16. Postoperative Cardiovascular Outcomes Reported in CAS Registries and Administrative Data, KQ 4

Registry Author, Year Quality	Study reported outcome	Followup	N analyzed*	Events*	Event rates*
NIS Mayor, 2019[43] Fair	MI†	In Hospital	132,051‡	4,146	3.1%

*Data was calculated across subgroups for all studies
†Postoperative MI included both acute MI and other cardiac complications
‡Asymptomatic n was provided by authors

Abbreviations: CAS = carotid artery stenting; KQ = key question; MI = myocardial infarction; NIS = National Inpatient Sample

Table 17. Summary of Previous 2014 USPSTF Review and New Evidence Identified in This Review

	Rationale and foundational evidence	New evidence findings	Limitations of new evidence	Consistency of new evidence with foundational evidence and current understanding
Benefits of screening	No direct evidence	No new evidence.	NA	NA
Harms of screening	No studies examined direct harms of screening. Two trials reported 0.4% and 1.2% of patients had a stroke following angiography.	No new evidence.	NA	NA
Incremental benefit of revascularization	Pooled results from 3 RCTs (N= 5226) found CEA resulted in a 3.5% (95% CI 1.8% to 5.1%) absolute reduction of perioperative stroke or death at approximately 5 years compared with medical management available at the time of these trials (1990's). No studies compared CAS with medical management.	Two contemporary, prematurely terminated trials comparing revascularization plus BMT to BMT alone report mixed results. The larger but underpowered SPACE-2 trial (N=513) reported no difference in the composite outcome of stroke or death between the two groups. The small AMTEC trial (N=55) in high risk patients reported a statistically significantly lower composite outcome of stroke or death in the CEA group. SPACE-2 reported no difference in the primary composite outcome (stroke or death [30-d] or ipsilateral ischemic stroke [1-yr]) between the CAS and BMT groups.	Underpowered, prematurely terminated trials.	New trials have mixed results and do not definitively change previous conclusions.
Harms of revascularization	Pooled results from 8 cohorts (N=16,967) estimated a 30-day perioperative stroke/death rate of 3.32% (95% CI, 2.73% to 3.91%). Pooled results of 6 trials (N= 3,436) estimated a 30-d perioperative stroke/death rate of 2.41% (95% CI, 1.71% to 3.12%). One cohort study on harms from CAS (N= 1,151) found a 30-day stroke or death rate of 3.8% (95% CI, 2.9% to 5.1%). A meta-analysis of 2 trials (n = 6,152) found a stroke or death rate of 3.1% (95% CI, 2.7% to 3.6%) after CAS.	30-d postoperative stroke or death for CEA were highest in the national databases (Medicare and NIS) compared to the trial data and vascular surgery registries: Medicare and NIS reported 30-d postoperative stroke or death rates of 3.5% and 3.09%, respectively, the SPACE-2 trial reported 2.5% while VQI and VSGNE reported lower rates of 1.4 to 1.8%. For the CAS procedure, 30-d stroke or death was again highest in	Wide variation in 30-d stroke/death rates reported in trial and registries compared to national administrative Medicare and NIS databases.	Single additional trial SPACE-2 showed 30-d stroke/death of 2.5% which is similar to previous reviews MA of trials. Contemporary national databases (NIS and Medicare) showing similar 30-d stroke/death rates compared to previous MA of cohorts.

Table 17. Summary of Previous 2014 USPSTF Review and New Evidence Identified in This Review

	Rationale and foundational evidence	New evidence findings	Limitations of new evidence	Consistency of new evidence with foundational evidence and current understanding
	Other important potential harms of CEA or CAS include nonfatal perioperative myocardial infarction, cranial nerve injury, pulmonary embolism, pneumonia, local hematoma requiring surgery, and psychological harms.	Medicare at 5.1% and lowest in a VQI analysis at 2.6%.		CAS 30-d stroke/death in Medicare registry higher than previous meta-analysis of 2 trials. However contemporary vascular registries showing lower complication rates.

Abbreviations: AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy; MA = meta-analysis; NA = not applicable; NIS = National Inpatient Sample; RCT = randomized controlled trial; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; vs = verse; VSGNE = Vascular Study Group of New England; VQI = Vascular Quality Initiative; yr = year

Appendix A. Detailed Methods

Literature search strategy

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword

(revise this list as needed)

MEDLINE
Bridge and modified search:
Database: Ovid MEDLINE(R) <1946 to January February 1 2020>, Ovid MEDLINE(R) Daily Update <February 14, 2020>
Search Strategy:
----
1 Carotid Stenosis/ or Carotid Artery Diseases/ (36561)
2 (carotid adj3 stenos$).ti. (3714)
3 (carotid adj3 stenos$).ti,ab. (9926)
4 limit 3 to ("in data review" or in process or publisher or "pubmed not medline") (0)
5 carotid Atheroscléro$.ti. (2123)
6 carotid Atheroscléro$.ti,ab. (4300)
7 limit 6 to ("in data review" or in process or publisher or "pubmed not medline") (0)
8 1 or 2 or 4 or 5 or 7 (36749)
9 Mass screening/ (101017)
10 screen$.ti,ab. (619754)
11 test$.ti. (368769)
12 confirmatory test$.ti,ab. (3238)
13 ultrasonography/ or ultraso$.ti,ab. (380599)
14 or/9-13 (1342469)
15 8 and 14 (9130)
16 Endarterectomy, Carotid/ (8641)
17 endarterectom$.ti,ab. (13414)
18 Angioplasty/ (7147)
19 Angioplasty, Balloon/ (17309)
20 angioplasty.ti,ab. (39163)
21 (Balloon$ or Transluminal Arterial Dilation).ti,ab. (61103)
22 Stents/ (65623)
23 (stent or stents or stenting or stented).ti,ab. (83162)
24 (Revasculari?ation or Recanali?ation or Percutaneous).ti,ab. (167061)
25 or/16-24 (299073)
26 8 and 25 (13577)
27 Carotid Stenosis/su or Carotid Artery Diseases/su [Surgery] (11437)
28 26 or 27 (16739)
29 15 or 28 (23334)

30 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (321250)
31 meta-analysis as topic/ (17589)
32 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt. (938072)
33 random$.ti,ab. (937349)
34 control groups/ or double-blind method/ or single-blind method/ (184785)
35 clinical trial$.ti,ab. (300236)
36 controlled trial$.ti,ab. (185776)
37 (metaanaly$ or meta analy$).ti,ab. (131986)
38 (dummy or placebo).ti,ab. (193650)
39 trial.ti. (182540)
40 or/30-39 (1808812)
41 29 and 40 (3415)
42 Long Term Adverse Effects/ (527)
43 Postoperative Complications/ or Intraoperative Complications/ (379698)
44 (harm or harms or harmful or harmed).ti,ab. (92224)
45 Endarterectomy, Carotid/ae [Adverse Effects] (2477)
46 Angioplasty, Balloon/ae [Adverse Effects] (3983)
47 Stents/ae [Adverse Effects] (8591)
48 Mortality/ (43069)
49 Morbidity/ (29686)
50 death/ (17388)
51 (death or deaths).ti,ab. (696577)
52 adverse*.ti,ab. (442084)
53 complication$.ti,ab. (761472)
54 side effect$.ti,ab. (211943)
55 safety.ti,ab. (405799)
56 postoperative event$.ti,ab. (608)
57 Risk factors/ or Risk assessment/ (985343)
58 risk$.ti. (412304)
59 (MACEs or myocardial infarction or arrhythmia or ipsilateral stroke or transient ischemic attack).ti,ab. (197182)
60 or/42-59 (3479126)
61 28 and 60 (8819)
62 exp cohort studies/ (1955143)
63 evaluation studies/ or evaluation study/ (249661)
64 (cohort adj (study or studies)).ti,ab. (160529)
65 cohort analy*.ti,ab. (6379)
66 (follow up adj (study or studies)).ti,ab. (44447)
67 treatment group$.ti,ab. (83001)
68 subgroup$.ti,ab. (190396)
69 retrospective.ti,ab. (425951)
70 longitudinal.ti,ab. (197093)
71 prospective.ti,ab. (481670)
72 retrospective.ti,ab. (425951)
73 or/62-72 (2644879)
74 40 or 73 (3984551)

75 61 and 74 (5018)
76 41 or 75 (6572)
77 limit 76 to (english language and yr="2014 -Current") (1473)
78 exp Databases as Topic/ or Multilevel Analysis/ or Registries/ or Comparative Study.pt. or (multivar$ or Univar$ or Vascular Quality Initiative or Logistic regression or registr$).ti,ab. (2614182)
79 ("Healthcare Cost and Utilization Project" or HCUP or National Inpatient Sample or Nationwide Inpatient Sample or State Inpatient Database* or National Hospital Discharge Survey or NHDS or National Hospital Care Survey or NHCS or Medicare Claims Data or Military Health System Tricare Encounter Data or Veterans Affairs Surgical Quality Improvement Program or VASQIP or National Surgical Quality Improvement Program or NSQIP or Vascular Study Group of Northern New England or VSGNE or VSGNNE or Vascular Quality Initiative or VQI or University Health System Consortium or Private analytics database* or PearlDiver or MarketScan or Premier or Vizient or large administrative or administrative data$).ti,ab. (25366)
80 78 or 79 (2625707)
81 61 and 80 (2269)
82 limit 81 to (english language and yr="2014 -Current") (648)
83 29 and 79 (153)
84 limit 83 to (english language and yr="2014 -Current") (105)
85 82 or 84 (656)
86 85 not 77 (130)
87 (201908* or 201909* or 201910*).ed. (249714)
88 77 and 87 (58)
89 86 or 88 (188)
90 carotid.ti,ab. (106005)
91 25 and 90 (22932)
92 27 or 91 (26449)
93 79 and 92 (269)
94 limit 93 to (english language and yr="2014 -Current") (152)
95 89 or 94 (307)
96 (201910* or 201911* or 201912* or 2020*).ed. (346582)
97 77 or 86 or 94 (1651)
98 96 and 97 (145)

Bridge Indexed Feb 2020:
Database: Ovid MEDLINE(R) Epub Ahead of Print <February 14, 2020>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to February 14, 2020>
Search Strategy:
----
1 Carotid Stenosis/ or Carotid Artery Diseases/ (0)
2 (carotid adj3 stenos$).ti. (418)
3 (carotid adj3 stenos$).ti,ab. (1071)
4 limit 3 to ("in data review" or in process or publisher or "pubmed not medline") (1063)
5 carotid Atherosclero$.ti. (226)
6 carotid Atherosclero$.ti,ab. (480)
7 limit 6 to ("in data review" or in process or publisher or "pubmed not medline") (478)
8 1 or 2 or 4 or 5 or 7 (1480)
9 Mass screening/ (0)
10 screen$.ti,ab. (104859)

11 test$.ti. (40650)
12 confirmatory test$.ti,ab. (511)
13 ultrasonography/ or ultraso$.ti,ab. (54286)
14 or/9-13 (193238)
15 8 and 14 (398)
16 Endarterectomy, Carotid/ (0)
17 endarterectom$.ti,ab. (1188)
18 Angioplasty/ (0)
19 Angioplasty, Balloon/ (0)
20 angioplasty.ti,ab. (3150)
21 (Balloon$ or Transluminal Arterial Dilation).ti,ab. (7677)
22 Stents/ (0)
23 (stent or stents or stenting or stented).ti,ab. (13697)
24 (Revasculari?ation or Recanali?ation or Percutaneous).ti,ab. (22510)
25 or/16-24 (38558)
26 8 and 25 (670)
27 Carotid Stenosis/su or Carotid Artery Diseases/su [Surgery] (0)
28 26 or 27 (670)
29 15 or 28 (960)
30 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (0)
31 meta-analysis as topic/ (0)
32 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt. (529)
33 random$.ti,ab. (172485)
34 control groups/ or double-blind method/ or single-blind method/ (0)
35 clinical trial$.ti,ab. (54968)
36 controlled trial$.ti,ab. (36725)
37 (metaanaly$ or meta analy$).ti,ab. (34315)
38 (dummy or placebo).ti,ab. (21174)
39 trial.ti. (31135)
40 or/30-39 (235497)
41 29 and 40 (153)
42 Long Term Adverse Effects/ (0)
43 Postoperative Complications/ or Intraoperative Complications/ (0)
44 (harm or harms or harmful or harmed).ti,ab. (19521)
45 Endarterectomy, Carotid/ae [Adverse Effects] (0)
46 Angioplasty, Balloon/ae [Adverse Effects] (0)
47 Stents/ae [Adverse Effects] (0)
48 Mortality/ (0)
49 Morbidity/ (0)
50 death/ (0)
51 (death or deaths).ti,ab. (92977)
52 adverse*.ti,ab. (78743)
53 complication$.ti,ab. (119417)
54 side effect$.ti,ab. (30106)
55 safety.ti,ab. (78542)
56 postoperative event$.ti,ab. (106)

57 Risk factors/ or Risk assessment/ (0)
58 risk$.ti. (63073)
59 (MACEs or myocardial infarction or arrhythmia or ipsilateral stroke or transient ischemic attack).ti,ab. (21781)
60 or/42-59 (416687)
61 28 and 60 (354)
62 exp cohort studies/ (1)
63 evaluation studies/ or evaluation study/ (26)
64 (cohort adj (study or studies)).ti,ab. (35733)
65 cohort analy*.ti,ab. (1342)
66 (follow up adj (study or studies)).ti,ab. (4044)
67 treatment group$.ti,ab. (10773)
68 subgroup$.ti,ab. (31209)
69 retrospective.ti,ab. (84803)
70 longitudinal.ti,ab. (40344)
71 prospective.ti,ab. (72828)
72 retrospective.ti,ab. (84803)
73 or/62-72 (234615)
74 40 or 73 (428577)
75 61 and 74 (146)
76 41 or 75 (215)
77 limit 76 to (english language and yr="2014 -Current") (150)
78 exp Databases as Topic/ or Multilevel Analysis/ or Registries/ or Comparative Study.pt. or (multivar$ or Univar$ or Vascular Quality Initiative or Logistic regression or registr$).ti,ab. (133118)
79 ("Healthcare Cost and Utilization Project" or HCUP or National Inpatient Sample or Nationwide Inpatient Sample or State Inpatient Database* or National Hospital Discharge Survey or NHDS or National Hospital Care Survey or NHCS or Medicare Claims Data or Military Health System Tricare Encounter Data or Veterans Affairs Surgical Quality Improvement Program or VASQIP or National Surgical Quality Improvement Program or NSQIP or Vascular Study Group of Northern New England or VSGNE or VSGNNE or Vascular Quality Initiative or VQI or University Health System Consortium or Private analytics database* or PearlDiver or MarketScan or Premier or Vizient or large administrative or administrative data$).ti,ab. (6737)
80 78 or 79 (137740)
81 61 and 80 (66)
82 limit 81 to (english language and yr="2014 -Current") (55)
83 29 and 79 (10)
84 limit 83 to (english language and yr="2014 -Current") (10)
85 82 or 84 (58)
86 85 not 77 (25)
87 (201908* or 201909* or 201910*).ed. (11298)
88 77 and 87 (0)
89 86 or 88 (25)
90 carotid.ti,ab. (10209)
91 25 and 90 (2477)
92 27 or 91 (2477)
93 79 and 92 (44)
94 limit 93 to (english language and yr="2014 -Current") (43)
95 89 or 94 (62)

96 77 or 86 or 94 (209)

Bridge and modified search: Oct 2019

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 23, 2019>

Search Strategy:

----

1 Carotid Stenosis/ or Carotid Artery Diseases/ (36134)
2 (carotid adj3 stenos$).ti. (4058)
3 (carotid adj3 stenos$).ti,ab. (10797)
4 limit 3 to ("in data review" or in process or publisher or "pubmed not medline") (1002)
5 carotid Atherosclero$.ti. (2305)
6 carotid Atherosclero$.ti,ab. (4696)
7 limit 6 to ("in data review" or in process or publisher or "pubmed not medline") (464)
8 1 or 2 or 4 or 5 or 7 (37728)
9 Mass screening/ (99767)
10 screen$.ti,ab. (705651)
11 test$.ti. (403988)
12 confirmatory test$.ti,ab. (3661)
13 ultrasonography/ or ultraso$.ti,ab. (426422)
14 or/9-13 (1503805)
15 8 and 14 (9403)
16 Endarterectomy, Carotid/ (8513)
17 endarterectom$.ti,ab. (14388)
18 Angioplasty/ (7057)
19 Angioplasty, Balloon/ (17150)
20 angioplasty.ti,ab. (41951)
21 (Balloon$ or Transluminal Arterial Dilation).ti,ab. (67614)
22 Stents/ (64537)
23 (stent or stents or stenting or stented).ti,ab. (94574)
24 (Revasculari?ation or Recanali?ation or Percutaneous).ti,ab. (185716)
25 or/16-24 (331040)
26 8 and 25 (14017)
27 Carotid Stenosis/su or Carotid Artery Diseases/su [Surgery] (11304)
28 26 or 27 (17158)
29 15 or 28 (23951)
30 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (318080)
31 meta-analysis as topic/ (17321)
32 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt. (925795)
33 random$.ti,ab. (1082326)
34 control groups/ or double-blind method/ or single-blind method/ (182479)
35 clinical trial$.ti,ab. (345233)
36 controlled trial$.ti,ab. (215083)
37 (metaanaly$ or meta analy$).ti,ab. (158011)
38 (dummy or placebo).ti,ab. (211662)
39 trial.ti. (206780)

40 or/30-39 (2001318)
41 29 and 40 (3520)
42 Long Term Adverse Effects/ (497)
43 Postoperative Complications/ or Intraoperative Complications/ (374478)
44 (harm or harms or harmful or harmed).ti,ab. (107892)
45 Endarterectomy, Carotid/ae [Adverse Effects] (2427)
46 Angioplasty, Balloon/ae [Adverse Effects] (3916)
47 Stents/ae [Adverse Effects] (8483)
48 Mortality/ (42384)
49 Morbidity/ (29356)
50 death/ (17231)
51 (death or deaths).ti,ab. (772153)
52 adverse*.ti,ab. (505358)
53 complication$.ti,ab. (860315)
54 side effect$.ti,ab. (237346)
55 safety.ti,ab. (468930)
56 postoperative event$.ti,ab. (690)
57 Risk factors/ or Risk assessment/ (967587)
58 risk$.ti. (462348)
59 (MACEs or myocardial infarction or arrhythmia or ipsilateral stroke or transient ischemic attack).ti,ab. (215153)
60 or/42-59 (3809621)
61 28 and 60 (9004)
62 exp cohort studies/ (1914283)
63 evaluation studies/ (246756)
64 (cohort adj (study or studies)).ti,ab. (186835)
65 cohort analy*.ti,ab. (7346)
66 (follow up adj (study or studies)).ti,ab. (47718)
67 treatment group$.ti,ab. (91905)
68 subgroup$.ti,ab. (215039)
69 retrospective.ti,ab. (491318)
70 longitudinal.ti,ab. (230247)
71 prospective.ti,ab. (540111)
72 retrospective.ti,ab. (491318)
73 or/62-72 (2811985)
74 40 or 73 (4313965)
75 61 and 74 (5043)
76 41 or 75 (6651)
77 limit 76 to (english language and yr="2014 -Current") (1498)
78 exp Databases as Topic/ or Multilevel Analysis/ or Registries/ or Comparative Study.pt. or (multivar$ or Univar$ or Vascular Quality Initiative or Logistic regression or registr$).ti,ab. (2705425)
79 ("Healthcare Cost and Utilization Project" or HCUP or National Inpatient Sample or Nationwide Inpatient Sample or State Inpatient Database* or National Hospital Discharge Survey or NHDS or National Hospital Care Survey or NHCS or Medicare Claims Data or Military Health System Tricare Encounter Data or Veterans Affairs Surgical Quality Improvement Program or VASQIP or National Surgical Quality Improvement Program or NSQIP or Vascular Study Group of Northern New England or VSGNE or VSGNNE or Vascular Quality Initiative or VQI or University Health System Consortium or

Private analytics database* or PearlDiver or MarketScan or Premier or Vizient or large administrative or administrative data$).ti,ab. (30541)
80 78 or 79 (2720814)
81 61 and 80 (2275)
82 limit 81 to (english language and yr="2014 -Current") (644)
83 29 and 79 (150)
84 limit 83 to (english language and yr="2014 -Current") (102)
85 82 or 84 (654)
86 85 not 77 (144)
87 (201908* or 201909* or 201910*).ed. (235118)
88 77 and 87 (50)
89 86 or 88 (194)
90 carotid.ti,ab. (114442)
91 25 and 90 (24957)
92 27 or 91 (28451)
93 79 and 92 (296)
94 limit 93 to (english language and yr="2014 -Current") (178)
95 89 or 94 (335)

Original search:
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 01, 2019>
Search Strategy:
----
1 Carotid Stenosis/ or Carotid Artery Diseases/ (35865)
2 (carotid adj3 stenos$).ti. (4020)
3 (carotid adj3 stenos$).ti,ab. (10699)
4 limit 3 to ("in data review" or in process or publisher or "pubmed not medline") (995)
5 carotid Atheroscleros$.ti. (2287)
6 carotid Atheroscleros$.ti,ab. (4654)
7 limit 6 to ("in data review" or in process or publisher or "pubmed not medline") (470)
8 1 or 2 or 4 or 5 or 7 (37452)
9 Mass screening/ (98406)
10 screen$.ti,ab. (694500)
11 test$.ti. (400788)
12 confirmatory test$.ti,ab. (3587)
13 ultrasonography/ or ultraso$.ti,ab. (421694)
14 or/9-13 (1485202)
15 8 and 14 (9343)
16 Endarterectomy, Carotid/ (8434)
17 endarterectom$.ti,ab. (14286)
18 Angioplasty/ (6994)
19 Angioplasty, Balloon/ (17068)
20 angioplasty.ti,ab. (41755)
21 (Balloon$ or Transluminal Arterial Dilation).ti,ab. (67067)
22 Stents/ (63757)
23 (stent or stents or stenting or stented).ti,ab. (93545)
24 (Revasculari?ation or Recanali?ation or Percutaneous).ti,ab. (183770)

25 or/16-24 (327733)
26 8 and 25 (13881)
27 Carotid Stenosis/su or Carotid Artery Diseases/su [Surgery] (11226)
28 26 or 27 (17012)
29 15 or 28 (23758)
30 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (314090)
31 meta-analysis as topic/ (17115)
32 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt. (913982)
33 random$.ti,ab. (1065326)
34 control groups/ or double-blind method/ or single-blind method/ (180260)
35 clinical trial$.ti,ab. (338856)
36 controlled trial$.ti,ab. (209876)
37 (metaanaly$ or meta analy$).ti,ab. (153046)
38 (dummy or placebo).ti,ab. (209115)
39 trial.ti. (202838)
40 or/30-39 (1974179)
41 29 and 40 (3488)
42 Long Term Adverse Effects/ (480)
43 Postoperative Complications/ or Intraoperative Complications/ (370637)
44 (harm or harms or harmful or harmed).ti,ab. (105554)
45 Endarterectomy, Carotid/ae [Adverse Effects] (2404)
46 Angioplasty, Balloon/ae [Adverse Effects] (3892)
47 Stents/ae [Adverse Effects] (8393)
48 Mortality/ (41848)
49 Morbidity/ (29024)
50 death/ (17065)
51 (death or deaths).ti,ab. (761575)
52 adverse*.ti,ab. (495899)
53 complication$.ti,ab. (849195)
54 side effect$.ti,ab. (234610)
55 safety.ti,ab. (460269)
56 postoperative event$.ti,ab. (675)
57 Risk factors/ or Risk assessment/ (952588)
58 risk$.ti. (454985)
59 (MACEs or myocardial infarction or arrhythmia or ipsilateral stroke or transient ischemic attack).ti,ab. (212877)
60 or/42-59 (3757473)
61 28 and 60 (8907)
62 exp cohort studies/ (1881908)
63 evaluation studies/ (244805)
64 (cohort adj (study or studies)).ti,ab. (181586)
65 cohort analy*.ti,ab. (7171)
66 (follow up adj (study or studies)).ti,ab. (47307)
67 treatment group$.ti,ab. (90750)
68 subgroup$.ti,ab. (211156)
69 retrospective.ti,ab. (481085)

70 longitudinal.ti,ab. (226145)
71 prospective.ti,ab. (532052)
72 retrospective.ti,ab. (481085)
73 or/62-72 (2769621)
74 40 or 73 (4251917)
75 61 and 74 (4992)
76 41 or 75 (6591)
77 limit 76 to (english language and yr="2014 -Current") (1444)

PUBMED – no changes for Bridges
#1: (carotid[tiab] AND (stenos*[tiab] OR Atherosclero*[tiab]))
#2: ((screen*[tiab] OR ultrason*[tiab])
#3: (endarterectom*[tiab] OR angioplasty[tiab] OR Balloon*[tiab] OR Transluminal Arterial Dilation[tiab] OR stent[tiab] OR stents[tiab] OR stenting[tiab] OR stented[tiab] OR Revascularization[tiab] OR recanalisation[tiab] OR Percutaneous[tiab]))
#4: #2 OR #3
#5: #1 AND #4
#6: #5 AND publisher[sb] AND eng[la]

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)
#1 (carotid near/3 stenosis):ti,ab,kw 1467
#2 (carotid near/3 atherosclero*):ti,ab,kw 895
#3 #1 or #2 2201
#4 screen*:ti,ab,kw 63474
#5 test:ti 10453
#6 (confirmatory next test*):ti,ab,kw 172
#7 (ultrasonog* or untrasound*):ti,ab,kw 15280
#8 endarterectom*:ti,ab,kw 1936
#9 (angioplasty or balloon or Transluminal Arterial Dilation):ti,ab,kw 13417
#10 (stent or stents or stenting or stented):ti,ab,kw 14232
#11 (Revasculari?ation or Recanali?ation or Percutaneous):ti,ab,kw 26028
#12 {or #4-#11} 124050
#13 #3 AND #12 with Publication Year from 2014 to 2019, in Trials 426
#14 #3 AND #12 with Cochrane Library publication date Between Jan 2014 and Aug 2019, in Cochrane Reviews 3

Cochrane Bridge: Oct 2019
ID Search Hits
#1 (carotid near/3 stenosis):ti,ab,kw 1496
#2 (carotid near/3 atherosclero*):ti,ab,kw 913
#3 #1 or #2 2243
#4 screen*:ti,ab,kw 65252
#5 test:ti 10696
#6 (confirmatory next test*):ti,ab,kw 181
#7 (ultrasonog* or untrasound*):ti,ab,kw 15589
#8 endarterectom*:ti,ab,kw 1954
#9 (angioplasty or balloon or Transluminal Arterial Dilation):ti,ab,kw 13582
#10 (stent or stents or stenting or stented):ti,ab,kw 14472

#11 (Revasculari?ation or Recanali?ation or Percutaneous):ti,ab,kw 26504
#12 {or #4-#11} 126989
#13 #3 AND #12 with Publication Year from 2014 to 2019, in Trials 454
#14 #3 AND #12 with Cochrane Library publication date Between Jan 2014 and Aug 2019, in Cochrane Reviews 3
#15 #3 AND #12 with Cochrane Library publication date Between Aug 2019 and Oct 2019, in Trials

Cochrane Bridge: Feb 2020
#1 (carotid near/3 stenosis):ti,ab,kw 1564
#2 (carotid near/3 atherosclero*):ti,ab,kw 954
#3 #1 or #2 2340
#4 screen*:ti,ab,kw 70418
#5 test:ti 11010
#6 (confirmatory next test*):ti,ab,kw 189
#7 (ultrasonog* or untrasound*):ti,ab,kw 16054
#8 endarterectom*:ti,ab,kw 2024
#9 (angioplasty or balloon or Transluminal Arterial Dilation):ti,ab,kw 14186
#10 (stent or stents or stenting or stented):ti,ab,kw 15546
#11 (Revasculari?ation or Recanali?ation or Percutaneous):ti,ab,kw 28120
#12 {or #4-#11} 135078
#13 #3 AND #12 with Publication Year from 2014 to 2019, in Trials 500
#14 #3 AND #12 with Cochrane Library publication date Between Jan 2014 and Aug 2019, in Cochrane Reviews 3
#15 #3 AND #12 with Publication Year from 2014 to 2020, with Cochrane Library publication date Between Oct 2019 and Feb 2020, in Trials 45

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Populations	**KQs 1, 2:** Unselected or community-dwelling, generally asymptomatic adults (i.e., without neurologic symptoms referable to the carotid artery or a history of a stroke or transient ischemic attack) **KQs 3, 4:** Unselected or community-dwelling, generally asymptomatic adults with clinically important CAS (defined as 60% to 99% stenosis)	**All KQs:** Children and adolescents; **symptomatic adults with CAS;** adults with history of stroke or transient ischemic attacks **KQs 1, 2:** People with known carotid occlusion; with known CVD; who are undergo CAS testing for pre-operative planning; or have had CEA or CAAS and are undergoing surveillance for restenosis
Interventions	**KQs 1, 2:** Screening with carotid duplex ultrasonography **KQs 3, 4:** Surgical repair including carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS), transcarotid artery revascularization (TCAR)	**KQs 1, 2:** Physical examination for carotid bruit; CIMT for CVD risk prediction
Comparisons	**KQs 1, 2:** No screening **KQ 3:** Medical treatment/usual care (e.g., statins, antiplatelet medications) **KQ 4:** Medical treatment/usual care or noncomparative studies reporting rates of harms	**KQs 3, 4:** Comparative studies of CEA versus CAS
Outcomes	**KQs 1, 3:** CAS-related stroke, mortality, quality of life, functional status, cognitive status **KQ 2:** Adverse outcomes related to screening tests or subsequent confirmatory testing (i.e., angiography) **KQ 4:** Perioperative complications (e.g., stroke, mortality, myocardial infarction, cranial nerve injuries)	**KQs 1, 2:** Diagnostic accuracy, CVD risk prediction
Study designs	**KQs 1-3:** Randomized, controlled trials **KQ 4:** Randomized, controlled trials; large cohort studies or registries	**All KQs:** Cost-effectiveness analyses **KQs 1-3:** All designs other than randomized, controlled trials **KQ 4:** Case reports, small observational studies
Countries	Studies conducted in countries categorized as “very high” on the Human Development Index (as defined by the United Nations Development Programme)	
Language	English only	Non-English languages
Years	2014-present	Publications prior to 2014

Abbreviations: CAS = carotid artery stenting; CEA = carotid endarterectomy; CIMT = carotid intima-media thickness test; CVD = cardiovascular disease; KQ = key question

Appendix A Table 2. Audit Criteria

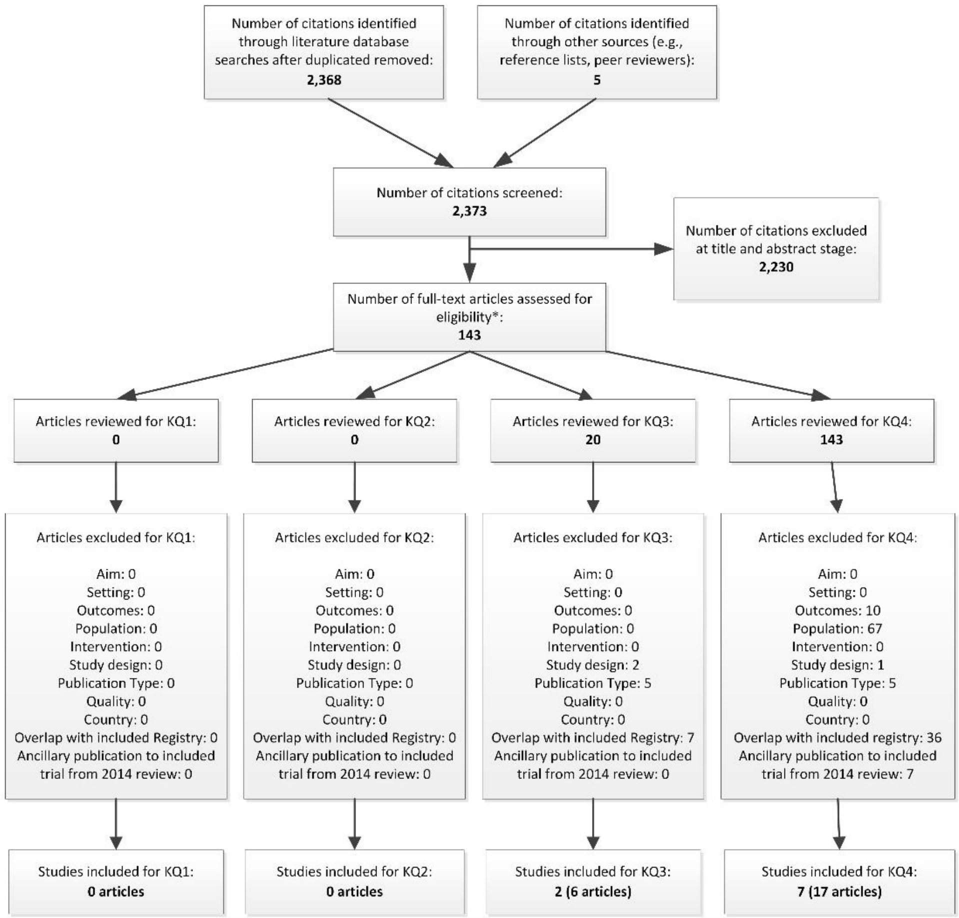
Topic	Criteria
Initial eligibility criteria for Key Question 4 audit	• ≥ 10,000 asymptomatic surgeries • U.S. data • Large national administrative databases or smaller surgical registries
Audit prioritization criteria for each vascular registry	• Primary study was the largest, most recent population study ○ If a more recent but smaller study was available, it was included as an ancillary article to compare similarities or changes in trends • Results were stratified by symptomatic status • If no studies stratified by symptomatic status, we selected studies with >80 percent asymptomatic cases

Appendix A Table 3. Quality Assessment Criteria*

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[31]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • Controlled Clinical Trial only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported
Registry studies, adapted from the Newcastle-Ottawa Scale[32]	• Does the cohort appear to be valid? • Is the cohort representative of the average-risk patient? • Did the study adjust for prognostic variables? • Can we be confident in the assessment of the presence or absence of prognostic factors? • Can we be confident in the assessment of outcomes?

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.

Appendix B Figure 1. Literature Flow Diagram



*Articles may appear under more than one Key Question

Appendix C. Included Studies Lists

Included trials for KQ1, by author

Ancillary publication(s) indented under primary article

No studies included

Included trials for KQ2, by author

Ancillary publication(s) indented under primary article

No studies included

Included Trials for KQ3 and KQ4, by Trial

Ancillary publication(s) indented under primary article

The Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial (AMTEC)

Kolos I, Troitskiy A, Balakhonova T, et al. Modern medical treatment with or without carotid endarterectomy for severe asymptomatic carotid atherosclerosis. J Vasc Surg. 2015;62(4):914-22. PMID: 26410046. https://dx.doi.org/10.1016/j.jvs.2015.05.005

> Kolos I, Loukianov M, Dupik N, et al. Optimal medical treatment versus carotid endarterectomy: the rationale and design of the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis (AMTEC) study. Int j. 2015;10(2):269-74. PMID: 23490405. https://dx.doi.org/10.1111/ijs.12019

Stent Protected Angioplasty versus Carotid Endarterectomy trial (SPACE-2)

Reiff T, Eckstein HH, Mansmann U, et al. Angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy compared to best medical treatment: One-year interim results of SPACE-2. Int j. 2019:1747493019833017. PMID: 30873912. https://dx.doi.org/10.1177/1747493019833017

> Eckstein HH, Reiff T, Ringleb P, et al. SPACE-2: A Missed Opportunity to Compare Carotid Endarterectomy, Carotid Stenting, and Best Medical Treatment in Patients with Asymptomatic Carotid Stenoses. Eur J Vasc Endovasc Surg. 2016;51(6):761-5. PMID: 27085660. https://dx.doi.org/10.1016/j.ejvs.2016.02.005

> Reiff T, Eckstein HH, Amiri H, et al. Modification of SPACE-2 study design. Int j. 2014;9(3):E12-3. PMID: 24636584. https://dx.doi.org/10.1111/ijs.12253

> Reiff T, Stingele R, Eckstein HH, et al. Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy: SPACE2 - a three-arm randomised-controlled clinical trial. Int J Stroke. 2009;4(4):294-9. PMID: 19689759. https://doi.org/10.1111/j.1747-4949.2009.00290.x

Appendix C. Included Studies Lists

Included Registry Studies for KQ4, by Registry

Ancillary publication(s) indented under primary article

American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP)

Garcia RM, Yoon S, Cage T, et al. Ethnicity, Race, and Postoperative Stroke Risk Among 53,593 Patients with Asymptomatic Carotid Stenosis Undergoing Revascularization. World Neurosurg. 2017;108:246-53. PMID: 28890012. https://dx.doi.org/10.1016/j.wneu.2017.08.184

> Glousman BN, Sebastian R, Macsata R, et al. Carotid endarterectomy for asymptomatic carotid stenosis is safe in octogenarians. J Vasc Surg. 2019;27:27. PMID: 31471235. https://dx.doi.org/10.1016/j.jvs.2019.05.054
>
> Liang P, Solomon Y, Swerdlow NJ, et al. In-hospital outcomes alone underestimate rates of 30-day major adverse events after carotid artery stenting. J Vasc Surg. 2020. PMID: 32063441. https://doi.org/10.1016/j.jvs.2019.06.201
>
> Rao V, Liang P, Swerdlow N, et al. Contemporary outcomes after carotid endarterectomy in high-risk anatomic and physiologic patients. J Vasc Surg. 2019;20:20. PMID: 31443978. https://dx.doi.org/10.1016/j.jvs.2019.05.041

Medicare

Lichtman JH, Jones MR, Leifheit EC, et al. Carotid Endarterectomy and Carotid Artery Stenting in the US Medicare Population, 1999-2014. Jama. 2017;318(11):1035-46. PMID: 28975306. https://dx.doi.org/10.1001/jama.2017.12882

National Inpatient Sample (NIS)

Mayor JM, Salemi JL, Dongarwar D, et al. Sex-Based Differences in Ten-Year Nationwide Outcomes of Carotid Revascularization. J Am Coll Surg. 2019;229(1):38-46.e4. PMID: 30922980. https://dx.doi.org/10.1016/j.jamcollsurg.2019.02.054

Vascular Study Group of New England (VSGNE)

Boitano LT, Ergul EA, Tanious A, et al. A Regional Experience with Carotid Endarterectomy in Patients with a History of Neck Radiation. Ann Vasc Surg. 2019;54:12-21. PMID: 30223012. https://dx.doi.org/10.1016/j.avsg.2018.08.069

Vascular Quality Initiative (VQI)

Nejim B, Alshwaily W, Dakour-Aridi H, et al. Age modifies the efficacy and safety of carotid artery revascularization procedures. J Vasc Surg. 2019;69(5):1490-503.e3. PMID: 31010514. https://dx.doi.org/10.1016/j.jvs.2018.07.062

> Dansey KD, Pothof AB, Zettervall SL, et al. Clinical impact of sex on carotid revascularization. J Vasc Surg. 2020;31:31. PMID: 32014286. https://dx.doi.org/10.1016/j.jvs.2019.07.088

Hicks CW, Nejim B, Aridi HD, et al. Transfemoral Carotid Artery Stents Should Be Used with Caution in Patients with Asymptomatic Carotid Artery Stenosis. Ann Vasc Surg. 2019;54:1-11. PMID: 30339900. https://dx.doi.org/10.1016/j.avsg.2018.10.001

O'Donnell TFX, Schermerhorn ML, Liang P, et al. Weekend Effect in Carotid Endarterectomy. Stroke. 2018;49(12):2945-52. PMID: 30571415. https://dx.doi.org/10.1161/STROKEAHA.118.022305

Appendix D. Excluded Studies List

Exclusion Code	Definition
E1	Aim not relevant
E2	Study design
E3	Population (general)
E3a	Asymptomatic n is <10,000
E3b	Population not stratified by number symptomatic or percent asymptomatic not reported
E3c	Population is ≤80 percent asymptomatic and not stratified
E3d	Smaller administrative databases
E4	No relevant outcomes; or outcomes not reported as absolute rates
E4a	Reported only cost and/or utilization outcomes
E5	Setting not in “very-high” HDI country
E6	Poor Quality
E7	Publication Type (Abstract only)
E8	Publication overlasps with a more recent (and/or complete) registry publication
E9	A more recent analysis of a previously included trial

1. Adegbala O, Martin KD, Otuada D, et al. Diabetes mellitus with chronic complications in relation to carotid endarterectomy and carotid artery stenting outcomes. *J Stroke Cerebrovasc Dis*. 2017;26(1):217-24. PMID: 27810149. https://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.09.012 **KQ4E8.**

2. Al-Damluji MS, Dharmarajan K, Zhang W, et al. Readmissions after carotid artery revascularization in the Medicare population. *J Am Coll Cardiol*. 2015;65(14):1398-408. PMID: 25857904. https://dx.doi.org/10.1016/j.jacc.2015.01.048 **KQ4E8.**

3. Alhaidar M, Algaeed M, Amdur R, et al. Early outcomes after carotid endarterectomy and carotid artery stenting for carotid stenosis in the ACS-NSQIP database. *J Vasc Interv Neurol*. 2018;10(1):52-6. PMID: 29922406. **KQ4E3c.**

4. Arhuidese IJ, Faateh M, Nejim BJ, et al. Risks associated with primary and redo carotid endarterectomy in the endovascular era. *JAMA Surg*. 2018;153(3):252-9. PMID: 29117272. https://dx.doi.org/10.1001/jamasurg.2017.4477 **KQ4E8.**

5. Arous EJ, Simons JP, Flahive JM, et al. National variation in preoperative imaging, carotid duplex ultrasound criteria, and threshold for surgery for asymptomatic carotid artery stenosis. *J Vasc Surg*. 2015;62(4):937-44. PMID: 26067201. https://dx.doi.org/10.1016/j.jvs.2015.04.438 **KQ4E4.**

6. Aziz F, Lehman EB, Reed AB. Increased duration of operating time for carotid endarterectomy is associated with increased mortality. *Ann Vasc Surg*. 2016;36:166-74. PMID: 27395809. https://dx.doi.org/10.1016/j.avsg.2016.02.043 **KQ4E3b.**

7. Badheka AO, Chothani A, Panaich SS, et al. Impact of symptoms, gender, co-morbidities, and operator volume on outcome of carotid artery stenting (from the Nationwide Inpatient Sample [2006 to 2010]). *Am J Cardiol*. 2014;114(6):933-41. PMID: 25208563. https://dx.doi.org/10.1016/j.amjcard.2014.06.030 **KQ4E3b.**

8. Boitano LT, DeCarlo C, Schwartz MR, et al. Surgeon specialty significantly affects outcome of asymptomatic patients after carotid endarterectomy. *J Vasc Surg*. 2019;09:09. PMID: 31831310. https://dx.doi.org/10.1016/j.jvs.2019.04.489 **KQ4E8.**

9. Brinjikji W, El-Sayed AM, Kallmes DF, et al. Racial and insurance based disparities in the treatment of carotid artery stenosis: a study of the Nationwide Inpatient Sample. *J Neurointerv Surg*. 2015;7(9):695-702. PMID: 25015114. https://dx.doi.org/10.1136/neurintsurg-2014-011294 **KQ4E4.**

10. Brinjikji W, Kallmes DF, Lanzino G, et al. Carotid revascularization treatment is shifting to low volume centers. *J Neurointerv Surg*. 2015;7(5):336-40. PMID: 24714610. https://dx.doi.org/10.1136/neurintsurg-2014-011180 **KQ4E8.**

11. Burton BN, Finneran Iv JJ, Harris KK, et al. Association of primary anesthesia type with postoperative adverse events after transcarotid artery revascularization. *J Cardiothorac Vasc Anesth*. 2019;31:31. PMID: 31445834. https://dx.doi.org/10.1053/j.jvca.2019.07.142 **KQ4E3a.**

12. Chandler JV, George BP, Kelly AG, et al. For-profit hospital status and carotid artery stent utilization in US hospitals performing carotid revascularization. *Stroke*. 2017;48(11):3161-4. PMID: 28939675. https://dx.doi.org/10.1161/STROKEAHA.117.017556 **KQ4E4.**

13. Chaudhry SA, Afzal MR, Kassab A, et al. A new risk index for predicting outcomes among patients undergoing carotid endarterectomy in large administrative data sets. *J Stroke Cerebrovasc Dis*. 2016;25(8):1978-83. PMID: 27216378. https://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.01.023 **KQ4E3b.**

14. Cheng TW, Farber A, Kalish JA, et al. Carotid endarterectomy performed before the weekend is associated with increased length of stay. *Ann Vasc Surg*. 2018;48:119-26. PMID: 29217437. https://dx.doi.org/10.1016/j.avsg.2017.09.028 **KQ4E8.**

15. Choi JC, Johnston SC, Kim AS. Early outcomes after carotid artery stenting compared with endarterectomy for asymptomatic carotid stenosis. *Stroke*. 2015;46(1):120-5. PMID: 25424479. https://dx.doi.org/10.1161/STROKEAHA.114.006209 **KQ4E3d.**

16. Choi JH, Pile-Spellman J, Brisman JL. US Nationwide trends in carotid revascularization: is there a clinical opportunity cost associated with the introduction of novel medical devices? *Acta Neurol Scand*. 2014;129(2):94-101. PMID: 23772989. https://dx.doi.org/10.1111/ane.12152 **KQ4E3b.**

17. Choi JH, Pile-Spellman J, Brisman JL. US Nationwide trends in carotid revascularization: hospital outcome and predictors of outcome from 1998 to 2007. *Acta Neurol Scand*. 2014;129(2):85-93. PMID: 23834476. https://dx.doi.org/10.1111/ane.12163 **KQ4E3b.**

18. Chou EL, Sgroi MD, Chen SL, et al. Influence of gender and use of regional anesthesia on carotid endarterectomy outcomes. *J Vasc Surg*. 2016;64(1):9-14. PMID: 27183853. https://dx.doi.org/10.1016/j.jvs.2016.03.406 **KQ4E3c.**

19. Clouse WD, Boitano LT, Ergul EA, et al. Contralateral occlusion and concomitant procedures drive risk of non-ipsilateral stroke after carotid endarterectomy. *Eur J Vasc Endovasc Surg*. 2019;57(5):619-25. PMID: 30940430. https://dx.doi.org/10.1016/j.ejvs.2018.11.009 **KQ4E8.**

20. Clouse WD, Ergul EA, Patel VI, et al. Characterization of perioperative contralateral stroke after carotid endarterectomy. *J Vasc Surg*. 2017;66(5):1450-6. PMID: 28697940. https://dx.doi.org/10.1016/j.jvs.2017.04.059 **KQ4E3a.**

21. Columbo JA, Martinez-Camblor P, MacKenzie TA, et al. A comparative analysis of long-term mortality after carotid endarterectomy and carotid stenting. *J Vasc Surg*. 2019;69(1):104-9. PMID: 29914828. https://dx.doi.org/10.1016/j.jvs.2018.03.432 **KQ4E8.**

22. Columbo JA, Martinez-Camblor P, MacKenzie TA, et al. Comparing long-term mortality after carotid endarterectomy vs carotid stenting using a novel instrumental variable method for risk adjustment in observational time-to-event data. *JAMA Netw Open*. 2018;1(5):e181676. PMID: 30646140. https://dx.doi.org/10.1001/jamanetworkopen.2018.1676 **KQ4E8.**

23. Dakour Aridi H, Locham S, Nejim B, et al. Comparison of 30-day readmission rates and risk factors between carotid artery stenting and endarterectomy. *J Vasc Surg*. 2017;66(5):1432-44.e7. PMID: 28865979. https://dx.doi.org/10.1016/j.jvs.2017.05.097 **KQ4E3d.**

24. Dakour Aridi H, Paracha N, Nejim B, et al. Anesthetic type and hospital outcomes after carotid endarterectomy from the Vascular Quality Initiative database. *J Vasc Surg*. 2018;67(5):1419-28. PMID: 29242070. https://dx.doi.org/10.1016/j.jvs.2017.09.028 **KQ4E3c.**

25. Dakour-Aridi H, Faateh M, Kuo PL, et al. The Vascular Quality Initiative 30-day stroke/death risk score calculator after transfemoral carotid artery stenting. *J Vasc Surg*. 2019;13:13. PMID: 31526692. https://dx.doi.org/10.1016/j.jvs.2019.05.051 **KQ4E3a.**

26. Dakour-Aridi H, Gaber MG, Khalid M, et al. Examination of the interaction between method of anesthesia and shunting with carotid endarterectomy. *J Vasc Surg*. 2019;04:04. PMID: 31699512. https://dx.doi.org/10.1016/j.jvs.2019.08.248 **KQ4E8.**

27. Dakour-Aridi H, Kashyap VS, Wang GJ, et al. The impact of age on in-hospital outcomes after transcarotid artery revascularization, transfemoral carotid artery stenting, and carotid endarterectomy. *J Vasc Surg*. 2020. PMID: 32035784. https://doi.org/10.1016/j.jvs.2019.11.037 **KQ4E3c.**

28. Dakour-Aridi H, Nejim B, Locham S, et al. Complication-specific in-hospital costs after carotid endarterectomy vs carotid artery stenting. *J Endovasc Ther*. 2018;25(4):514-21. PMID: 29893167. https://dx.doi.org/10.1177/1526602818781580 **KQ4E3d.**

29. Dakour-Aridi H, Ou M, Locham S, et al. Outcomes following eversion vs. conventional endarterectomy in the Vascular Quality Initiative Database. *Ann Vasc Surg*. 2019;15:15. PMID: 31626932. https://dx.doi.org/10.1016/j.avsg.2019.07.021 **KQ4E3c.**

30. Dakour-Aridi H, Rizwan M, Nejim B, et al. Association between the choice of anesthesia and in-hospital outcomes after carotid artery stenting. *J Vasc Surg*. 2019;69(5):1461-70.e4. PMID: 31010512. https://dx.doi.org/10.1016/j.jvs.2018.07.064 **KQ4E3a.**

32. de Waard DD, de Borst GJ, Bulbulia R, et al. Diastolic blood pressure is a risk factor for peri-procedural stroke following carotid endarterectomy in asymptomatic patients. *Eur J Vasc Endovasc Surg*. 2017;53(5):626-31. PMID: 28318997. https://dx.doi.org/10.1016/j.ejvs.2017.02.004 **KQ3E9, KQ4E9.**

33. DeMartino RR, Brooke BS, Neal D, et al. Development of a validated model to predict 30-day stroke and 1-year survival after carotid endarterectomy for asymptomatic stenosis using the Vascular Quality Initiative. *J Vasc Surg*. 2017;66(2):433-44.e2. PMID: 28583737. https://dx.doi.org/10.1016/j.jvs.2017.03.427 **KQ4E8.**

34. Dhillon AS, Li S, Lewinger JP, et al. Comparison of devices used in carotid artery stenting: a vascular quality initiative analysis of commonly used carotid stents and embolic protection devices. *Catheter Cardiovasc Interv*. 2018;92(4):743-9. PMID: 30019819. https://dx.doi.org/10.1002/ccd.27646 **KQ4E3b.**

35. Dua A, Desai SS, Seabrook GR, et al. The effect of Surgical Care Improvement Project measures on national trends on surgical site infections in open vascular procedures. *J Vasc Surg*. 2014;60(6):1635-9. PMID: 25454105. https://dx.doi.org/10.1016/j.jvs.2014.08.072 **KQ4E3b.**

36. Dua A, Romanelli M, Upchurch GR Jr, et al. Predictors of poor outcome after carotid intervention. *J Vasc Surg*. 2016;64(3):663-70. PMID: 27209401. https://dx.doi.org/10.1016/j.jvs.2016.03.428 **KQ4E8.**

37. Edenfield L, Blazick E, Eldrup-Jorgensen J, et al. Outcomes of carotid endarterectomy in the Vascular Quality Initiative based on patch type. *J Vasc Surg*. 2019;03:03. PMID: 31492613. https://dx.doi.org/10.1016/j.jvs.2019.05.063 **KQ4E4.**

38. Edenfield L, Blazick E, Healey C, et al. Long-term impact of the Vascular Study Group of New England carotid patch quality initiative. *J Vasc Surg*. 2019;69(6):1801-6. PMID: 31159983. https://dx.doi.org/10.1016/j.jvs.2018.07.078 **KQ4E3c.**

39. Enomoto LM, Hill DC, Dillon PW, et al. Surgical specialty and outcomes for carotid endarterectomy: evidence from the National Surgical Quality Improvement Program. *J Surg Res*. 2014;188(1):339-48. PMID: 24480081. https://dx.doi.org/10.1016/j.jss.2013.11.1119 **KQ4E3b.**

40. Epstein AJ, Yang L, Yang F, et al. A comparison of clinical outcomes from carotid artery stenting among US hospitals. *Circ Cardiovasc Qual Outcomes*. 2014;7(4):574-80. PMID: 24895452. https://dx.doi.org/10.1161/CIRCOUTCOMES.113.000819 **KQ4E3b.**

41. Eslami MH, Reitz KM, Rybin DV, et al. Improved access to health care in Massachusetts after 2006 Massachusetts Healthcare Reform Law is associated with a significant decrease in mortality among vascular surgery patients. *J Vasc Surg*. 2018;68(4):1193-202.e1. PMID: 29615354. https://dx.doi.org/10.1016/j.jvs.2017.12.066 **KQ4E3b.**

42. Eslami MH, Rybin D, Doros G, et al. Care of patients undergoing vascular surgery at safety net public hospitals is associated with higher cost but similar mortality to nonsafety net hospitals. *J Vasc Surg*. 2014;60(6):1627-34. PMID: 25441012. https://dx.doi.org/10.1016/j.jvs.2014.08.055 **KQ4E3b.**

43. Eslami MH, Rybin D, Doros G, et al. An externally validated robust risk predictive model of adverse outcomes after carotid endarterectomy. *J Vasc Surg*. 2016;63(2):345-54. PMID: 26804216. https://dx.doi.org/10.1016/j.jvs.2015.09.003 **KQ4E3a.**

44. Eslami MH, Rybin DV, Doros G, et al. The association of publication of Center for Medicaid and Medicare Services guidelines for carotid artery angioplasty and stenting (CAS) and CREST Results on the utilization of CAS in carotid revascularization. *Ann Vasc Surg*. 2015;29(8):1606-13. PMID: 26315795. https://dx.doi.org/10.1016/j.avsg.2015.06.091 **KQ4E8.**

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Appendix E Table 1. Inclusion and Exclusion Criteria for Included Randomized, Controlled Trials, KQ3

Study Name Author, Year Quality	Country	Inclusion criteria	Exclusion criteria	Intervention description	Surgeon selection
SPACE-2 Reiff, 2019[37] Fair	Germany, Switzerland, and Austria	Carotid artery stenosis of ≥70% following ultrasound criteria with no stroke or stroke-like symptoms within the last 180 days, stenosis treatable with CEA and CAS, available for follow-up examinations, informed consent, adequate contraception among women with childbearing potential	Stroke or stroke-like symptoms due to the stenosis within the last 180 days, nonatherosclerotic stenosis (e.g. dissection, floating thrombus, fibromuscular dysplasia), stenosis following radiotherapy, previous CEA or CAS in the artery to be randomized, additional higher grade intracranial or intrathoracic stenosis (tandem stenosis), intracranial bleeding within the last 90 days, known intracranial angioma or aneurysms, preexisting disability (modified Rankin scale >1), contraindications for heparin, aspirin, clopidogrel or contrast media, indication for anticoagulation with phenprocoumon or warfarin, life expectancy of <5 years, recent history of a malignant tumor, major surgery (with the exception of trial-related procedures) planned within 8 weeks after randomization, previously enrollment in SPACE-2 Trial.	All patients received BMT according to current evidence based guidelines in accordance with their individual risk factor profile including the treatment of risk factors, lipid-lowering and anti-platelet medication. CEA: Aspirin (ASA) or clopidogrel (but not dual antiplatelet therapy) had to be administered for at least 3 days before CEA, as well as during and after surgery. 67% of cases were performed with general anesthesia. Median time from randomization to treatment was 14 days. CAS: All patients had to receive dual antiplatelet therapy (ASA and clopidogrel) for at least 3 days before and for at least 6 weeks after CAS. Cerebral protection devices were used in 36% of cases based on the discretion of the endovascular specialist. Median time from randomization to treatment was 14 days.	All participating interventionalists have to achieve the following standards: at least 40 CAS procedures within 24 months, evaluated by an independent neurologist, or at least 20 CAS procedures with a perinterventional complication rate below 6% within the SPACE-1 study.

Appendix E Table 1. Inclusion and Exclusion Criteria for Included Randomized, Controlled Trials, KQ3

Study Name Author, Year Quality	Country	Inclusion criteria	Exclusion criteria	Intervention description	Surgeon selection
AMTEC Kolos, 2015[35] Fair	Russia	Unilateral or bilateral carotid artery stenosis that was considered to be severe (carotid artery diameter reduction 70–79% on ultrasound and 60–79% on computed tomographic angiography/ magnetic resonance angiography (CTA/MRA), if the risk of perioperative stroke or death is less than 3%; this stenosis had not caused any stroke, transient cerebral ischemia, or other relevant neurological symptoms in the last six-months; arterial hypertension: systolic blood pressure (BP) >140 mmHg and diastolic BP >90 mmHg at office visit or regular antihypertensive treatment; age from 40 to 80 years; Both the physician and the surgeon were substantially uncertain on whether to choose immediate CEA or deferral of any CEA; and the patient had no known circumstance or condition likely to preclude long-term follow-up	Stroke/transient cerebral ischemia in the last 6 months, restenosis after prior carotid artery stenting (CAS) or CEA, high surgical risk, assessed as a lesion at C2 or higher, a lesion below the clavicle, prior radical neck surgery or radiotherapy, contralateral carotid occlusion, prior ipsilateral CEA, contralateral laryngeal nerve palsy, tracheostoma, age >=80 years, New York Heart Association Functional Class III/IV congestive heart failure, class III/IV angina pectoris, left main or coronary disease in two or more vessels, urgent (<30 days) heart surgery, left ventricular ejection fraction <=30%, recent (<30 days) myocardial infarction, severe chronic lung disease, severe renal disease, and atrial fibrillation.	All patients received lifestyle modification training: Mediterranean diet, regular exercise, smoking cessation consult, obesity and diabetes mellitus management according to the current guidelines (2006 AHA/ACC cited) All patients received antiplatelet therapy with aspirin at a dose of 81 to 325 mg/d, aggressive therapy to lower low-density lipoprotein (LDL) cholesterol levels with atorvastatin (10-80 mg/d), with a target LDL level of <2.6 mmol/L (ideally <2.0 mmol/L), and antihypertensive therapy with amlodipine (5-10 mg/d) and losartan (50-100 mg/d) to lower the blood pressure (BP) to a target level of <140/90 mm Hg, and hydrochlorothiazide (12.5 mg/d) was added if the target BP was not achieved. (2006 AHA/ACC cited)	Selected five centers that perform more than 150 CEA per year, with the rates of complications and death less than 3% among patients with asymptomatic carotid atherosclerosis.

Abbreviations: AHA = American Heart Association; ACC = American College of Cardiology; AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BMT = best medical treatment; BP = blood pressure; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computerized tomography angiography; FU = followup; KQ = key question; mm Hg = millimeters of Mercury; MMT = modern medical treatment; MRA = magnetic resonance angiography; NR = not reported; pop = population; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; vs = verse; yr = year

Appendix E Table 2. Baseline Population Characteristics of Included Randomized, Controlled Trials, KQ3

Study Name Author, Year Quality	Mean age (range)	Male, n (%)	White ethnicity, n (%)	DM, n (%)	HTN, n (%)	High chol, n %)	Smoker, n (%)	Statin use, n (%)	CHD, n (%)	Prior contralateral CEA, TIA/stroke	Contralateral occlusion	Additional BL characteristics or comorbidities
SPACE-2 Reiff, 2019[37] Fair	70* (50 to 80)	381 (74.3%)	NR (NR)	151 (29.4%)	459 (89.5%)	407 (79.3%)	100 (19.5%)†	397 (77.4%)‡	182 (35.5%)	NR§	18 (3.5%)	Grade of stenosis (Median (IQR)): 80 (75-85) Number of vascular risk factors (median): 3 BMI (median (IQR)): 27 (25, 30) Medications at baseline: antiplatelet: 495 (96.5%); anticoagulants 12 (2.3%); antihypertensive: 448 (87.3%); lipid lowering: 418 (81.5%); antidiabetic: 134 (26.1%)
AMTEC Kolos, 2015[35] Fair	66.6 (40 to 80)	40 (72.7%)	NR (NR)	14 (25.5%)	Duration of arterial HTN, yrs: 13.7	NR	32 (58.2%)	NR	39 (70.9%)	NR	NR	BMI: 28.5 kg/m2 (BMI significantly lower in MMT group (26.8) than CEA group (29.9) (p=0.0008) Previous PCI/CABG: 29 (52.7%) Prior MI: 17 (30.9%) Prior stroke: 9

Appendix E Table 2. Baseline Population Characteristics of Included Randomized, Controlled Trials, KQ3

Study Name Author, Year Quality	Mean age (range)	Male, n (%)	White ethnicity, n (%)	DM, n (%)	HTN, n (%)	High chol, n %)	Smoker, n (%)	Statin use, n (%)	CHD, n (%)	Prior contralateral CEA, TIA/stroke	Contralateral occlusion	Additional BL characteristics or comorbidities
												(16.4%) CKD: 1 (1.8%)

*Median
†Current smoker
‡35 (6.8%) on other lipid lowering drugs
§Ipsilateral symptoms >180 days on side of randomized artery: 29 (5.7%)

Abbreviations: AMTEC = the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis trial; BL = baseline; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CHD = coronary heart disease; chol = cholesterol; CKD = chronic kidney disease; DM = diabetes mellitus; FU = followup; HTN = hypertension; IQR = interquartile range; KQ = key question; MI = myocardial infarction; mm Hg = millimeters of Mercury; MMT = modern medical treatment; NR = not reported; PCI = percutaneous coronary intervention; SPACE-2: Stent Protected Angioplasty versus Carotid Endarterectomy trial; TIA = transient ischemic attack

Appendix E Table 3. Additional Study Details of Included Administrative Database and Vascular Registry Studies Reporting Outcomes for Asymptomatic Patients, KQ 4

Registry Author, Year Quality	Database or registry methods	Inclusion Criteria	Exclusion criteria	Urgency of procedure
ACS NSQIP Garcia, 2017[40] Fair	Trained clinical extractors	Patients undergoing CEA	Patients were excluded if assigned a postoperative single ICD-9 diagnosis unrelated to carotid stenosis, had previous history of stroke or transient ischemic attack, or underwent carotid stenting	Elective, Emergency, Urgent
Medicare Lichtman, 2017[28] Fair	For patients undergoing multiple carotid procedures during the study period, the first procedure was selected as the index admission.	Age 65 years or older, enrolled in fee-for-service Medicare for 1 month or longer between January 1999 and December 2014, undergoing carotid endarterectomy or carotid artery stenting in US acute care hospitals.	Patients were excluded if they underwent both carotid endarterectomy and carotid artery stenting during the index hospitalization or received any other concomitant major interventions (eg, coronary artery bypass grafting) during the index admission	Elective, Emergency, Urgent
NIS Mayor, 2019[43] Fair	Unweighted data from more than 7 million hospital admissions each year (20% sample of hospitalizations from non-federal US community hospitals).*	All adult (18 years of age and older) admissions for carotid revascularization between January 1, 2005 and September 30, 2015.	NR	Elective, Emergency, Urgent
VSGNE Boitano, 2019[39] Fair	Prospectively maintained quality improvement registry which includes patients undergoing vascular operative procedures across New England. Linkage of the registry with the Social Security Death Index Master File allows accurate mortality and survival analysis	Patients undergoing CEA within the VSGNE cohort from 2011-2017.	Patients were excluded if they had a prior ipsilateral CEA; underwent a concomitant procedure including CABG, proximal angioplasty, stenting of the carotid artery, carotid-carotid bypass, carotid subclavian bypass, or carotid axillary bypass, if they did not have a surgical side (right or left) denoted or documentation regarding previous neck radiation	Elective, Emergency, Urgent
VQI Nejim, 2019[44] Fair	Clinical professionals extract patient- and procedure-related information from medical charts of the participating centers. Data validation is accomplished by comparing the data entered in the VQI registry with claims data provided from the participating center on an annual basis and rectifies any inconsistency if found. Mortality data in the VQI are obtained from the Social Security Death Index	All patients between 19 and 89 years old were included. Patients of age 90 or older were coded as 89 years to avoid identification	Prospective registry of multicenter collaboration across the United States and the Province of Ontario in Canada that captures various vascular interventions.	Elective, Emergency, Urgent

*The fourth quarter of 2015 was excluded to remove extraneous influence on study findings due to the transition ICD-9-CM to ICD-10-CM, which occurred October 1, 2015.

Appendix E Table 3. Additional Study Details of Included Administrative Database and Vascular Registry Studies Reporting Outcomes for Asymptomatic Patients, KQ 4

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; KQ = key question; MAE = major adverse event; NIS = National Inpatient Sample; NA = not applicable; NR = not reported; VSGNE = Vascular Study Group of New England; US= United States; US = United States; VQI = Vascular Quality Initiative

Appendix E Table 4. Assessment of Patient Characteristics and Outcomes in Trials, Administrative Database, and Vascular Registries, KQ4

Study/Registry	Assessment of stenosis	Assessment of asymptomatic status	Assessment of outcomes	Sampling frame
SPACE-2[37]	Trial inclusion criteria: >70% stenosis (ECST criteria) on ultrasound (equivalent to >50% NASCET criteria)	Trial inclusion criteria: No stroke or stroke-like symptoms due to stenosis within 180 days	Review of medical records	NA
AMTEC[35]	Trial inclusion criteria: 70–79% stenosis (NASCET criteria) on ultrasound and 60–79% on CTA/MRA confirmation	Trial inclusion criteria: No stroke, transient cerebral ischemia, or relevant neurological symptoms in previous 6 months	Review of medical records; nonfatal strokes confirmed with CT/MRI	NA
ACS NSQIP[40]	NR	Patients considered asymptomatic if they had a previous history of stroke or transient ischemic attack (timing not specified)	Assessment by trained Surgical Clinical Reviewer based on patient medical charts	Randomly assigned patients (details NR)
Medicare[28]	NR	Considered symptomatic if they had an ICD-9-CM principal discharge diagnosis code indicating occlusion or stenosis of the precerebral or cerebral arteries with cerebral infarction or a secondary diagnosis code indicating prior stroke, transient ischemic attack, or amaurosis fugax.	ICD-9 codes	All Medicare beneficiaries with inpatient claims for CEA and CAS (based on ICD-9 codes)
NIS[43]	NR	Symptomatic status based on the presence of 1 or more diagnosis codes indicative of amaurosis fugax, transient ischemic attack, or stroke.	ICD-9 codes	Sample of hospitalizations selected from all hospitals participating in HCUP
VSGNE[39, 94]	NR	Patients considered symptomatic if they experienced ipsilateral cortical or eye symptoms before the procedure (timing not specified).	Data input completed by nurses, research personnel, surgeons, or chart abstractors. Linked to Social Security Death Index.	All patients undergoing CEA at participating institutions
VQI[44, 95]	Most severe stenosis of each patient measured by duplex ultrasound, MRA, CTA, or arteriogram (criteria NR)	Symptomatic status was defined as the occurrence of pre-procedural amaurosis fugax, transient ischemic attack, and minor or major stroke (timing not specified).	Clinical abstraction from medical chart and linked to Social Security Death Index.	All eligible procedures at participating institute

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computerized tomography angiography; ECST = the European Carotid Surgery Trial; HCUP = the Healthcare Cost and Utilization Project; ICD-9 = The International Classification of Diseases, ninth revision; KQ = key question; MRA = magnetic resonance angiography; NASCET = the

Appendix E Table 4. Assessment of Patient Characteristics and Outcomes in Trials, Administrative Database, and Vascular Registries, KQ4

North American Symptomatic Carotid Endarterectomy Trial; NIS = National Inpatient Sample; NA = not applicable; NR = not reported; VSGNE = Vascular Study Group of New England; US= United States; US = United States; VQI = Vascular Quality Initiative

Appendix E Table 5. Baseline Population Characteristics of Included Administrative Database and Vascular Registry Studies, KQ 4

Registry Author, Year Quality	Cohort (n)	Mean age (Range)	Male, n (%)	White ethnicity, n (%) Black ethnicity, n (%)	DM, n (%)	HTN, n (%)	High chol, n (%)	Smoker, n (%)	Statin use, n (%)	CAD, n (%)	CHD, n (%)	CHF, n (%)	COPD, n (%)	CKD, n (%)	BMI	Additional characteristic or comorbidities
ACS NSQIP Garcia, 2017[40] Fair	CEA (n=53,593)*	NR†	31,996 (59.7%)	48,875 (91.2%) 2428 (4.5%)	15,842 (29.6%)	45,522 (84.9%)‡	NR	14,893 (27.8%) §	NR	NR	NR	Hx of CHF: 648 (1.2%)	Severe COPD: 6089 (11.4%)	Hx of dialysis: 566 (1.1%)	BMI >30: 18,551 (34.6%)	NR
Medicare Lichtman, 2017[28] Fair	CEA (n=937,111)‖#	75.8 (≥65)	536,617 (57.3%)	877,925 (93.7%) 31,833 (3.4%)	294,295 (31.4%)	704,146 (75.1%)	NR	NR	NR	NR	NR	69,251 (7.4%)	192,313 (20.5%)	Kidney failure: 45,587 (4.9%)	NR	Chronic atheroscler-osis (53.7%), prior MI (4.5%), prior Stroke (6.1%), PVD (21.9%)
	CAS (n=231,077)**	75.4 (≥65)	118,476 (51.3%)	198,648 (86.0%) 21,890 (9.5%)	85,493 (37.0%)	159,837 (69.2%)	NR	NR	NR	NR	NR	37,215 (16.1%)	55,800 (24.1%)	Kidney failure 33,216 (14.4%)	NR	Chronic atheroscler-osis (46.5%), prior MI (2.5%), prior Stroke (9.7%), PVD (7.9%)
NIS Mayor, 2019[43] Fair	CEA and CAS cohort (n=1,242,688) ††	71.2‡‡ (IQR 64.3 to 77.4)	726,972 (58.5%)	NR (NR) NR (NR)	400,146 (32.2%)	999,121 (80.4%)	720,759 (58.0%)	NR	NR	549,268 (44.2%)	NR	99,415 (8.0%)	223,684 (18.0%)	110,59 9 (8.9%)	NR	NR
VSGNE Boitano, 2019[39] Fair	CEA (12,392)§§	70.1 (NR)	7433 (60.0%)	11,954 (96.5%) NR (NR)	4056 (32.7%)	11,002 (88.8%)	NR	9820 (79.2%)‖‖	10,419 (84.1%)##	7782 (62.8%) †††	NR	1049 (8.5%)	2673 (21.6%)	3737 (30.1%)	28.3	Stenosis ≥70%: 4,565 (36.8%))††† Prior CEA: 1124 (9.1%) Prior CAS: 42 (0.3%)
VQI Nejim, 2019[44]	CEA (n=76,081) ‡‡‡	NR (>65)	46,026 (60.55)	Non-white:	DM on Rx:	67,580 (88.8%)	NR	Ever smoker:	Preop statin:	NR	NR	7784 (10.2%)	16,890 (22.2%)	Hemo-dialysis:	NR	Prior CEA or CAS:

Appendix E Table 5. Baseline Population Characteristics of Included Administrative Database and Vascular Registry Studies, KQ 4

Registry Author, Year Quality	Cohort (n)	Mean age (Range)	Male, n (%)	White ethnicity, n (%) Black ethnicity, n (%)	DM, n (%)	HTN, n (%)	High chol, n (%)	Smoker, n (%)	Statin use, n (%)	CAD, n (%)	CHD, n (%)	CHF, n (%)	COPD, n (%)	CKD, n (%)	BMI	Additional characteristic or comorbidities
Fair				4416 (5.8%)	23,221 (30.5%)			57,550 (75.6%)	61,130 (80.3%)					818 (1.1%)		11,690 (15.4%) Degree of stenosis >80%: 46,403 (61.0%),
	CAS (n=13,772) ‡‡‡	NR (>65)	8764 (63.6%)	Non-white: 1004 (7.3%)	DM on Rx: 4465 (32.4%)	12,259 (89.0%)	NR	Ever smoker: 10,440 (75.8%)	Preop statin: 10,997 (79.8%)	NR	NR	2097 (15.2%)	3548 (25.8%)	Hemo-dialysis: 182 (1.3%)	NR	Prior CEA or CAS: 11,690 (15.4%) Degree of stenosis >80%: 8993 (65.3%)

* Baseline characteristics calculated across race/ethnicity groups
†<60 years (11.5%), 60-80 years (68.7%), >80 years (19.8%)]
‡ HTN requiring medication
§Current smoker
‖Baseline characteristics calculated across time spans.
#Demographics only reported for entire CEA cohort, including symptomatic pts (n=122,023 (13.0%))
**Demographics only reported for entire CAS sample, including symptomatic (n=1,168,188)
††Demographics and comorbidities For entire cohort, including Symptomatic 140,424 (11.3%) and both procedure types (CEA: 87.2%) and CAS: 12.8%)
‡‡Median
§§Baseline characteristics calculated across subgroups
‖‖Any smoking history
##Preop meds
***Additional co-morbidities reported: Contralateral carotid occlusion: 340 (2.7%); ASA class 4 or 5: 885 (7.1%); CABG/PCI: 2214 (17.9%); Arterial Bypass (Non-Cardiac): 801 (6.5%); PTA/stent (NonCardiac)t: 1020 (8.2%); Aneurysm repair: 350 (2.8%); Prior CEA: 1124 (9.1%); Prior CAS: 42 (0.3%)
†††These absolute numbers and percentages are shown as published in the study. Denominators that authors used to calculate these percentages were not reported.
‡‡‡ Baseline characteristics calculated across groups and includes 30% symptomatic

Appendix E Table 5. Baseline Population Characteristics of Included Administrative Database and Vascular Registry Studies, KQ 4

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; BMI = body mass index; CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disorder; DM = diabetes mellitus; KQ = key question; MI = myocardial infarction; NIS = National Inpatient Sample; NR = not reported; PVD = peripheral vascular disease; Rx = prescription; VSGNE = Vascular Study Group of New England; US= United States; VQI = Vascular Quality Initiative

Appendix F Table 1. Ongoing Studies Table

Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	2020 status (January 2020)
NCT00883402 Alison Halliday	Carotid Endarterectomy Versus Carotid Artery Stenting in Asymptomatic Patients (ACST-2)	UK	3600	2-arm trial comparing 1) carotid artery stenting with 2) carotid endarterectomy	Stroke and death MI Quality of life	Recruiting: Est. study completion date December 2020
NCT02089217 Thomas G. Brott	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)	USA	2480	2-arm treatment trial comparing 1) carotid revascularization and intensive medical management, 2) medical management alone	Stroke and death Cognitive function	Recruiting: Est. completion date December 2021 per author communication
NCT03121209 Randolph S. Marshall	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial - Hemodynamics (CREST-H) (CREST-H)	USA	500	Cohort study addressing whether cognitive impairment can be reversed when it arises from abnormal cerebral hemodynamic perfusion in a hemodynamically impaired subset of the CREST-2 - randomized patients	Cognitive function	Recruiting: Est. completion date 2022
ISRCTN97744893 Ekaterina Biggs	European Carotid Surgery Trial 2 (ECST-2)	UK	200	2-arm treatment trial comparing 1) immediate endartorectomy to 2) medical treatment alone.	Stroke and death Functional status (mRS)	Recruiting: Est. completion date March 2022
NCT02841098 Jean-Louis MAS	Endarterectomy Combined With Optimal Medical Therapy Versus Optimal Medical Therapy Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-average Risk of Ipsilateral Stroke (ACTRIS)	France	700	2-arm treatment trial comparing 1) carotid endarterectomy (CEA) combined with optimal medical therapy (OMT), 2) optimal medical therapy.	Stroke and death MI Other AEs including haematoma and cranial nerve palsy	Not yet recruiting: Est. completion date December 2025

Appendix F Table 1. Ongoing Studies Table

Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	2020 status (January 2020)
NCT00772278 Dallit Manheim	Comparing Carotid Stenting With Endarterectomy in Severe Asymptomatic Carotid Stenosis	Israel	137	2-arm trial comparing 1) carotid artery stenting with 2) carotid endarterectomy	Mortality Morbidity Cranial nerves damage	Recruitment completed: Est. study completion date September 2015 No results published