RESEARCH LETTER

Screening for Asymptomatic Carotid Artery Stenosis in the General Population: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Carotid artery stenosis is a known stroke risk factor and a cardiovascular disease marker. No population-based screening trials for carotid artery stenosis have been conducted. Optimal treatment for clinically significant asymptomatic carotid artery stenosis remains uncertain. Options include best medical therapy alone or in combination with revascularization (carotid endarterectomy or carotid artery stenting) to prevent stroke. Revascularization has been associated with small long-term benefits compared with best medical therapy alone in historic trials but can result in surgical harms.[1]

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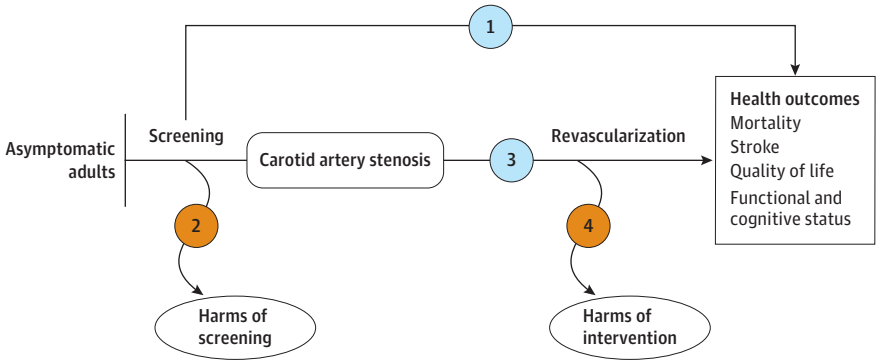
Since 2007, the US Preventive Services Task Force (USPSTF) has maintained a D recommendation against screening for asymptomatic carotid artery stenosis in the general adult population. This recommendation was based on a low prevalence of stroke attributable to asymptomatic carotid artery stenosis in the general population, the small benefit of surgery compared with medical therapy in older trials, and the potential for small to moderate surgical harms. This brief evidence update aimed to identify studies published since the previous 2014 review[1] to inform an updated USPSTF recommendation.

Methods | A literature search of MEDLINE, PubMed publisher-supplied records, and the Cochrane Central Register of Controlled Trials was conducted from January 1, 2014, to February 18, 2020. Ongoing surveillance in targeted publications was conducted through November 20, 2020. Two investigators independently evaluated articles that met inclusion criteria and summarized the data. The most recent comprehensive publication from each US national database or surgical registry reporting procedural harms was selected for review. The scope of this rapid review was limited to screening in the general population and did not address high-risk subpopulations. The results are limited to studies published since the previous review to support the 2014 recommendation.[2] An analytic framework and 4 key questions (KQs) guided the evidence update (**Figure**). Detailed methods and results of this systematic review are available in the full evidence report.[4]

Figure. Analytic Framework: Screening for Asymptomatic Carotid Artery Stenosis in the General Population



Key questions

1. Is there direct evidence that screening asymptomatic adults for carotid artery stenosis with duplex ulrasonography improves health outcomes?
2. What are the harms associated with screening or confirmatory testing for asymptomatic carotid 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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. Further details are available from the USPSTF procedure manual.[3]

Table. Comparison of Foundational and New Evidence: Screening for Asymptomatic Carotid Artery Stenosis in the General Population

	Rationale and foundational evidence[1]	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 Stroke after angiography: 0.4% and 1.2%	No new evidence	NA	NA
Incremental benefit of revascularization	CEA: 3 RCTs (n = 5226); 3.5% (95% CI, 1.8%-5.1%) absolute reduction in stroke/death at ≈5 y compared with best medical treatment (in 1990s) CAS: no studies	CEA: AMTEC trial (n = 55) reported a lower composite stroke/death risk after CEA at 3.3 median y (HR, 0.20 [95% CI, 0.06-0.65]) CAS: SPACE-2 trial (n = 316) reported no difference in stroke/death at 1 y (HR, 3.50 [95% CI, 0.42-29.11])	Underpowered, prematurely terminated trials	New trials have mixed results and do not definitively change previous conclusions
Harms of revascularization	CEA: Pooled estimates of 30-d postoperative stroke or death after CEA ranged from 2.41% in trials (n = 3436) to 3.32% in cohorts (n = 16 967) CAS: Estimates of 30-d postoperative stroke or death after CAS ranged from 3.1% in trials (n = 6152) to 3.8% in a credentialing cohort (n = 1151)	CEA: Estimates of 30-d postoperative stroke or death after CEA ranged from 1.4% to 3.5% (n = 1 903 761) CAS: Estimates of 30-d postoperative stroke or death after CAS ranged from 2.6% to 5.1% (n = 332 103)	Concerns of bias in harms estimates of registries and administrative data	Very large increase in sample size Similar or higher complication rates reported in contemporary observational and trial data

Abbreviations: AMTEC, Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis; CAS, carotid artery stenting; CEA, carotid endarterectomy; HR, hazard ratio; NA, not applicable; RCT, randomized clinical trial; SPACE-2, Stent Protected Angioplasty vs Carotid Endarterectomy.

Results | We screened 2373 titles and abstracts and 144 full-text articles. No eligible studies were identified that directly examined the benefits or harms of screening for asymptomatic carotid artery stenosis (KQ1, KQ2). Two limited, prematurely terminated trials reported mixed results for the comparative effectiveness of carotid revascularization plus best medical therapy compared with best medical therapy alone (KQ3). The SPACE-2 trial[5] (n = 316) reported no significant difference in composite outcome of stroke or death (30 days) or ipsilateral ischemic stroke (1 year) after carotid endarterectomy (unadjusted hazard ratio [HR], 2.82 [95% CI, 0.33-24.07]) or carotid artery stenting (unadjusted HR, 3.50 [95% CI, 0.42-29.11]) compared with best medical therapy at 1 year. The smaller AMTEC trial[6] (n = 55) reported a statistically significantly lower composite risk of nonfatal ipsilateral stroke or death among the carotid endarterectomy group at a median of 3.3 years (calculated unadjusted HR, 0.20 [95% CI, 0.06-0.65]). The 2 trials, 2 national data sets, and 3 surgical registries reported procedural harms associated with carotid endarterectomy (n = 1 903 761) or carotid artery stenting (n = 332 103) (KQ4). These data estimated that postoperative 30-day rates of stroke or death varied from 1.4% to 3.5% for carotid endarterectomy and from 2.6% to 5.1% for carotid artery stenting.

Discussion | The conclusions of this review are consistent with those of the previous review (**Table**).[1] There was no direct evidence examining the benefits or harms of screening. The 2 new trials added little to the evidence base on effectiveness of revascularization compared with best medical therapy. New evidence related to procedural harms from contemporary national databases and surgical registries reported complication rates; however, their selection and measurement biases remain serious concerns. The reported wide variation in complication rates may be attributable to patient and surgeon/operator selection.

While there were few new trials examining the comparative effectiveness of revascularization compared with contemporary best medical treatment alone, the ongoing CREST-2 (NCT02089217, estimated completion date of December 2022), ECST-2 (ISRCTN97744893, estimated completion date of March 2022), and ACTRIS (NCT02841098, estimated completion date of December 2025) trials will add to this treatment evidence base for asymptomatic carotid artery stenosis in the future.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Guirguis-Blake.
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Additional Information: A draft version of this evidence report underwent external peer review from 5 content experts (Ethan Halm, MD, MPH [University of Texas Southwestern Medical Center]; James F. Meschia, MD [Mayo Clinic Hospital, Jacksonville, Florida]; John J. Ricotta, MD [George Washington School of Medicine and Health Sciences]; Nicholas J. Swerdlow, MD [Beth Israel Deaconess Medical Center]) and 1 federal partner: National Institutes of Health, National Institute of Neurological Disorders and Stroke. Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional peer review after submission to *JAMA*.

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Asymptomatic SARS-CoV-2 Infections Among Persons Entering China From April 16 to October 12, 2020

The magnitude of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a question of global concern. Individuals who test positive for SARS-CoV-2 infection via a polymerase chain reaction (PCR) test but lack coronavirus disease 2019 (COVID-19)–like symptoms must be followed up through the incubation period to distinguish individuals with asymptomatic infection from those with presymptomatic infection.[1]

China successfully controlled its initial COVID-19 epidemic in March 2020[2] and has since focused on preventing importation of SARS-CoV-2 infection. Beginning April 1, 2020, persons entering China via air, sea, or land have been mandatorily tested for SARS-CoV-2 infection by PCR test at border checkpoints. Individuals who have tested positive have been hospitalized in isolation and those who have tested negative have been quarantined for 14 days at centralized facilities and then retested on day 13. We assessed the proportion of international entrants to China with asymptomatic SARS-CoV-2 infection.

Methods | This retrospective cohort study was approved by the institutional review board of the Chinese Center for Disease Control and Prevention; informed consent was not required. All international entrants found to have SARS-CoV-2 infection via a positive PCR test result at China's border checkpoints from April 16 to October 12 were included in this study. This allowed 15 days for full policy implementation (April 1-15) and 13 days of follow-up for the last enrolled participant (October 13-25).

Participants were categorized as either confirmed COVID-19 cases (ie, positive test results for SARS-CoV-2 infection plus being symptomatic or presymptomatic) or asymptomatic SARS-CoV-2 infection cases (ie, positive test results for SARS-CoV-2 infection but having no symptoms throughout the 14-day quarantine).[1] Although different from the that of the World Health Organization,[3] this case definition is standard in China.[1] Fifteen-day intervals during the study were used to investigate changes over time.

The χ^2, Cochran-Mantel-Haenszel, and Jonckheere-Terpstra nonparametric trend tests were used. A 2-sided $P < .05$ was considered statistically significant. All analyses were performed using SAS software version 9.2 (SAS Institute Inc).

Results | Of the 19 398 384 international travelers who entered China during the study period, 3103 had SARS-CoV-2 infection. Most were male (75.5%) and were aged 20 to 49 years (80.8%) (**Table**). Among all SARS-CoV-2–positive entrants, 1354 (43.6%) had symptoms at entry (symptomatic) and 137 (4.4%) developed symptoms (presymptomatic; median time to symptom onset, 1 day; interquartile range [IQR], 0-5 days; 95th percentile, 10 days) and were categorized as confirmed COVID-19 cases, whereas 1612 (51.9%) never developed symptoms through day 13 and were considered to have asymptomatic SARS-CoV-2 infection.

Among all international entrants (part A in the **Figure**), the proportion of SARS-CoV-2–positive persons screened remained stable at 0.01% to 0.03% (part B), but the proportion of individuals with symptomatic, presymptomatic, and asymptomatic SARS-CoV-2 infection did not remain stable (part C). Among all SARS-CoV-2–positive entrants, the proportion of asymptomatic infections increased significantly over time from 27.8% during April 16 to April 30 to 59.4% during September 28 to October 12 ($P < .001$) (Table).