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Stroke prevention: carotid stenting versus carotid endarterectomy

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Abstract

Revascularization of the extracranial carotid arteries is a commonly performed surgical procedure to prevent stroke. Open surgery (i.e., carotid endarterectomy [CEA]) is a well-established stroke prevention procedure but is being 'challenged' by a less invasive percutaneous procedure (i.e., carotid artery stent [CAS] placement). Clinical trials comparing CAS and CEA for average-surgical-risk patients have demonstrated mixed results, whereas the data for CAS compared with CEA in high-surgical-risk patients have demonstrated non-inferiority. The impending Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) results will have a major impact on the utility of CAS relative to CEA in average-surgical-risk patients.

Introduction and context

Stroke is the third leading cause of death in the US after coronary artery disease and cancer and it is the leading cause of disability. There are two main types of stroke: ischemic and hemorrhagic. Ischemic stroke is most often caused by atherothrombotic emboli. Extracranial atherosclerotic carotid artery disease accounts for slightly more than half of the 731,000 strokes per year in the US. Hemorrhagic stroke includes primary cerebral hemorrhages or hemorrhage secondary to an ischemic event.

Cerebrovascular events are classified as transient ischemic attacks (TIAs) or as strokes. A TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction [1]. An ischemic stroke is defined as an infarction of central nervous system tissue [1]. The current definitions of TIA and stroke no longer include a duration requirement. Ischemic strokes may be either symptomatic or silent. Symptomatic ischemic strokes are manifested by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. Hemispheric or focal symptoms relate to a single carotid distribution, causing contralateral hemiparesis or hemiparesthesia, aphasia, and/or ipsilateral monocular blindness (amaurosis fugax). Non-hemispheric symptoms that often occur with vertebrobasilar insufficiency include dysarthria, diplopia, vertigo, syncope, and/or transient confusion. A silent stroke is a documented central nervous system infarction that was asymptomatic.

Carotid endarterectomy (CEA) is the currently established surgical procedure for stroke prevention in patients with extracranial carotid artery disease. Some of CEA's technical issues such as the benefits of an intraoperative shunt or of a patch closure versus primary repair continue to be debated. The comparability of data from highly selected patient populations enrolled in clinical trials of CEA with results obtained in everyday practice has been questioned [2]. There were markedly higher mortality rates in Medicare patients who underwent CEA at clinical trial hospitals than in the selected patients treated in clinical trials. Caution is advised in translating the efficacy of carefully controlled studies of CEA to effectiveness in everyday practice [2].

There has been significant variability or heterogeneity in the reporting of CEA outcomes in the literature, making comparison of studies difficult and confusing. In a meta-analysis of CEA in symptomatic patients (n = 51 studies), the strongest predictor of stroke or death was who (neurologist or surgeon) performed the post-operative

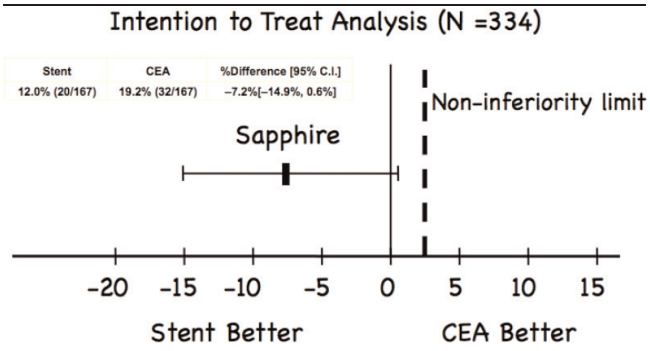
assessment [3]. When a neurologist evaluated post-operative patients, the risk of 30-day stroke and death was 7.7%, but when a single author who was a surgeon performed the evaluation, the reported risk was only 2.3%. There is a strong bias in favor of CEA in the current literature comparing Medicare or specialty outcomes data [4-6]. The bias is one of ascertainment; that is, independent neurological examination is mandated for reimbursement for most carotid artery stent (CAS) procedures but is rarely done for CEA. To obtain Medicare reimbursement, all but a very few CAS procedures must conform to US Food and Drug Administration (FDA) protocols, which require independent neurological examination. This independent neurological examination is not required for CEA reimbursement by Medicare. Performing an independent neurological examination markedly increases the number of events that are detected following a procedure. When comparing CEA and CAS, it is critical that the methodology for detecting events (the ascertainment of events) is similar, or the outcomes will be unfairly slanted.

Recent advances

High risk for carotid endarterectomy

Patients with high-surgical-risk features (Table 1) treated with CAS have been proven to have outcomes 'non-inferior' to CEA in SAPPHIRE (Stenting and Angioplasty with Protection of Patients with High Risk for Endarterectomy), a randomized controlled trial (Figure 1) [7]. Three-year outcomes have confirmed the durability of the CAS [8]. Additional supporting peer-reviewed and published evidence include a meta-analysis [9] and multiple pre-market [10-18] and post-market [19-23] surveillance trials. Additionally, a multi-specialty endorsed professional society document from the American College of Cardiology (ACC) is consistent with the conclusions of the randomized controlled trial (SAPPHIRE) and supports the benefit of CAS in patients with high-risk features for both symptomatic (>50% stenosis) and asymptomatic (>80% stenosis) patients [24].

Figure 1. SAPPHIRE randomized controlled trial, demonstrating non-inferiority for the stent compared with surgery in high-surgical-risk patients



CEA, carotid endarterectomy; C.I., confidence interval.

Recently, three very large, post-market surveillance trials evaluating CAS in a 'real-world' environment were published. The primary objective of the SAPPHIRE World-Wide (SAPPHIRE WW) post-market approval registry was to evaluate 30-day outcomes after CAS was performed in high-surgical-risk patients by CAS operators of varying experience [20]. Notably, independent neurological assessment was employed for outcomes assessment. The investigators reported 30-day safety and efficacy outcomes in 2,001 symptomatic and asymptomatic high-surgical-risk patients treated by carotid stent operators with varying clinical experience. The overall, independently adjudicated, 30-day stroke and death rate for CAS in 2,001 high-surgical-risk patients was 4.0% [20].

The results of more than 6,000 high-surgical-risk patients treated by CAS operators with varying levels of experience in two large prospective, multi-center, FDA-mandated post-market surveillance trials (Emboshield and Xact Post-Approval Carotid Stent Trial [EXACT] [n = 2,145] and Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events-2

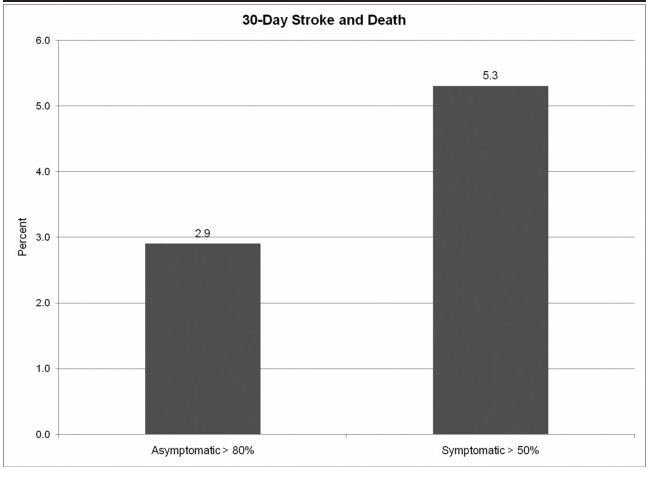
Table 1. Carotid artery stent high-surgical-risk features

Anatomic features	Comorbid conditions
Surgically inaccessible lesions at or above C2 spinal level or below the clavicle	Age of at least 75/80 years
Previous neck or head radiation therapy or surgery that included the area of stenosis/repair or ipsilateral radical neck dissection	Congestive heart failure (New York Heart Association class III/IV)
Spinal immobility of the neck due to cervical arthritis or other cervical disorders	Unstable angina (Canadian Cardiovascular System class III/IV)
Restenosis after a previous or unsuccessful attempt of carotid endarterectomy	Left main/at least two-vessel coronary disease
Contralateral laryngeal palsy	Recent heart attack (<30 days)
Presence of a tracheostoma	Left ventricular ejection fraction ≤30%
Contralateral carotid occlusion	Requirement for heart surgery within 30 days
	Severe lung disease
	Severe renal disease

[CAPTURE-2] [n = 4,175]) were recently published and demonstrated excellent outcomes [23]. Both trials included independent neurological assessment of outcomes to reinforce the rigor for ascertaining adverse events. The overall rates of incidence of 30-day stroke and death were 4.1% for the 2,145 EXACT patients and only 3.4% for the 4,175 CAPTURE-2 patients. Importantly, for patients who would have been comparable to patients included in the 2006 American Heart Association (AHA) published guidelines (<80 years of age) [25], the CAS results met the threshold recommendations for 30-day stroke and death rate at 5.3% (benchmark for CEA ≤6%) for symptomatic patients (i.e., those with ≥50% stenosis) and 2.9% (benchmark for CEA ≤3%) for asymptomatic patients (i.e., those with ≥80% stenosis) (Figure 2) [23]. These studies demonstrate equipoise for CAS and CEA in community settings on the basis of data collected during the decade of the 1990s with the large CEA versus best medical therapy trials, and the AHA expert consensus panel suggested that the perioperative risk of stroke and death should not exceed 3% for asymptomatic patients, 6% for symptomatic patients, or 10% for repeat CEA [25,26].

Published data have suggested that very old patients (≥75-80 years of age) are at increased risk for not only a higher complication rate of CEA [2,27,28] but also worse outcomes for CAS [11,23,29,30]. However, three peer-reviewed manuscripts published in the past year have reported excellent outcomes in high-surgical-risk patients ≥80 years of age undergoing CAS [31-33]. The very favorable overall 30-day stroke and death rates with independent neurological assessment in these octogenarians were 3.3%, 2.7%, and 0.8% [31-33]. The authors emphasized the importance of operator experience and careful case selection to avoid difficult aortic arch access, excessive lesion tortuosity, and heavy calcification [30]. The improved outcomes for octogenarians are consistent with the data reported in the CAPTURE-2 and EXACT trials demonstrating reduced CAS complications with expanding operator experience. The published peer-reviewed evidence does not support denying CAS to very old patients but does show that the best results are obtained with careful patient selection and experienced operators.

Figure 2. Outcomes for CAPTURE and EXACT clinical trials in patients younger than 80 years of age



CAPTURE, Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events; EXACT, Emboshield and Xact Post-Approval Carotid Stent Trial.

Low- or average-surgical-risk patients

The EVA-3S (Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) trial randomly assigned 527 symptomatic (≥60%) low- or average-surgical risk patients to CAS or CEA [34]. The 30-day incidence rates of stroke or death were 3.9% for CEA and 9.6% for CAS. Early in the trial, the use of embolic protection devices (EPDs) was not required and this generated a stroke rate of 25% (5 of 20). This caused the trial to be stopped and restarted with EPD use required. The inexperience of the interventionalists, particularly the surgical operators, is a significant limitation of this study. The patients in EVA-3S had risk profiles similar to those of CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) roll-in patients, but CREST required at least 20 cases of carotid stent experience with audited results and mandated the use of an EPD. In contrast to the high rate of stroke and death in EVA-3S, the most recent report of 1,246 lead-in patients demonstrated a 30-day stroke and death rate of 5.6% for symptomatic CREST lead-in registry patients [35].

Physician specialty-specific data from CREST were presented by Donald V Heck at the 2009 Society of NeuroInterventional Surgery meeting. He reported 30-day stroke and death by subspecialty during the lead-in phase of the CREST trial. Subspecialty training in catheter-based techniques – cardiology, radiology, and neuroradiology – had a statistically lower event rate than did the non-catheter-based specialty of vascular surgery. Vascular surgeons had a statistically significant, twofold increase in their complication rate (stroke and death) compared with the physicians trained in catheter-based techniques.

The SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy) trial showed no difference between CEA and CAS in average surgical risk in symptomatic patients with optional use of EPDs [36]. The 30-day stroke and death rates were

6.8% for CAS and 6.3% for CEA and were not clinically or statistically different. One drawback of the study was the lack of EPD use in 73% of the study subjects. After 2 years of follow-up, there continued to be no difference in outcomes between CEA and CAS; however, for patients who were younger than 69 years of age at randomization, CAS was significantly better (30-day stroke and death and ipsilateral stroke for 2 years; 4.8%) compared with CEA (8.0%; $P < 0.005$) [37,38].

A major impact on the field has been made with proximal embolic occlusion (PEO) devices by lowering post-procedural complication rates [39]. These PEO devices have an advantage in that when the carotid lesion is crossed with a guidewire for the entire procedure, no antegrade flow occurs, thus the patient is protected against procedure-related emboli. A recent trial reported a 1.4% 30-day stroke and death rate with a PEO in 1,288 consecutive patients [40]. The risks of 30-day stroke and death were less than 1% in asymptomatic patients and near 3% in symptomatic patients [40].

Implications for clinical practice

High risk for surgery

There now exists the highest level of evidence (AHA/ACC class I, level of evidence A) that there is clinical equipoise between CAS and CEA for patients at increased surgical risk for CEA. This applies to both symptomatic and asymptomatic patients with anatomic or comorbid features that place them at increased risk for CEA. This conclusion is supported and reinforced by the three recently published post-market surveillance trials (CAPTURE-2, EXACT, and SAPPHIRE WW) [20,23]. In these patients at high risk for CEA (both symptomatic and asymptomatic patients) younger than 80 years of age, the AHA benchmark levels were met. The current recommendation for patients at increased risk for CEA is that CAS should be considered a reasonable alternative for stroke prevention.

Usual or average risk for surgery

There is no consensus regarding the relative outcomes of CAS versus CEA in average-risk patients. Clinical trials in this patient population over the past 2 years have ranged from EVA-3S, which strongly favored CAS over CEA, to the most recently reported PEO system with extremely low stroke and death rates in both symptomatic and asymptomatic patients. The SPACE trial split the difference, showing a benefit for CAS in patients younger than 69 years old and an advantage for CEA in older patients. The results of CREST, a large randomized controlled trial in average-surgical-risk patients, will be reported within the next few months and will go a very long way toward informing our recommendations in the low- or usual-surgical-risk population.

Abbreviations

ACC, American College of Cardiology; AHA, American Heart Association; CAPTURE-2, Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events-2; CAS, carotid artery stent; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial; EPD, embolic protection device; EVA-3S, Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; EXACT, Emboshield and Xact Post-Approval Carotid Stent Trial; FDA, US Food and Drug Administration; PEO, proximal embolic occlusion; SAPPHIRE (WW), Stenting and Angioplasty with Protection of Patients with High Risk for Endarterectomy (World-Wide); SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy; TIA, transient ischemic attack.

Competing interests

The author is the national principal investigator for the CABANA (Carotid Stenting Boston Scientific Surveillance Program) trial, a carotid stent trial sponsored by Boston Scientific (Natick, MA, USA).

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