Carotid Artery Stenting

I. Description

Carotid artery angioplasty with stenting (CAS) is a treatment for carotid stenosis that is intended to prevent future stroke. It is an alternative to medical therapy and a less-invasive alternative to carotid endarterectomy (CEA).

A substantial body of randomized controlled trial (RCT) evidence compares outcomes of carotid artery angioplasty with stenting (CAS) with CEA for symptomatic and asymptomatic patients with carotid stenosis. The evidence does not support use of CAS in carotid artery disease for the average-risk patient, because early adverse events are higher with CAS and long-term outcomes are not better. Data from RCTs and large database studies establish that the risk of CAS exceeds the threshold set to indicate overall benefit from the procedure. Therefore, CAS is not covered for patients with carotid stenosis who are suitable candidates for CEA.

However, based on limited data, clinical input, an indirect chain of evidence, and unmet medical need, CAS may be considered a reasonable treatment option in recently symptomatic patients when CEA cannot be performed due to anatomic reasons. For this population, CAS may be considered medically necessary. It is considered investigational for all other indications, including carotid dissection.

II. Criteria/Guidelines

Carotid angioplasty with associated stenting and embolic protection is covered (subject to Limitations and Administrative Guidelines) for patients with:

A. 50% - 99% stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] measurement); AND
B. Symptoms of focal cerebral ischemia (transient ischemic attack or monocular blindness) in previous 120 days, symptom duration less than 24 hours, or nondisabling stroke; AND
C. Anatomic contraindication for carotid endarterectomy (such as prior radiation treatment or neck surgery, lesions surgically inaccessible, spinal immobility, or tracheostomy)

III. Limitations

Carotid angioplasty with or without associated stenting and embolic protection is not covered for all other indications, including but not limited to, patients with carotid stenosis who are suitable candidates for CEA and patients with carotid artery dissection.

IV. Administrative Guidelines

A. Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

B. The following documentation must be kept in the patient's medical records and be made available to HMSA upon request:

1. Clinical notes documenting the patient's symptoms of carotid artery stenosis and any high risk conditions for CEA.
2. Imaging studies documenting the degree of carotid stenosis as measured by a duplex Doppler ultrasound or carotid artery angiography.

C. Applicable codes:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>37215</td>
<td>Transcatheter placement of intravascular stent(s), cervical carotid artery, open or percutaneous, including angioplasty, when performed, and radiological supervision and interpretation; with distal embolic protection</td>
</tr>
<tr>
<td>37217</td>
<td>Transcatheter placement of an intravascular stent(s), intrathoracic common carotid artery or innominate artery by retrograde treatment, via open ipsilateral cervical carotid artery exposure, including angioplasty, when performed, and radiological supervision and interpretation</td>
</tr>
<tr>
<td>37218</td>
<td>Transcatheter placement of intravascular stent(s), intrathoracic common carotid artery or innominate artery, open or percutaneous antegrade approach, including angioplasty, when performed, and radiological supervision and interpretation (effective 01/01/2015)</td>
</tr>
<tr>
<td>0075T</td>
<td>Transcatheter placement of extracranial vertebral or intrathoracic carotid artery stent(s), including radiologic supervision and interpretation, percutaneous; initial vessel</td>
</tr>
<tr>
<td>0076T</td>
<td>each additional vessel</td>
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</table>

D. Code that does not Meet Payment Determination Criteria:
<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>37216</td>
<td>Transcatheter placement of intravascular stent(s), cervical carotid artery, open or percutaneous, including angioplasty, when performed, and radiological supervision and interpretation; without distal embolic protection</td>
</tr>
</tbody>
</table>

V. Background

Combined with optimal medical management carotid angioplasty with or without stenting has been evaluated as an alternative to CEA. Carotid angioplasty and stenting involves the introduction of coaxial systems of catheters, microcatheters, balloons, and other devices. The procedure is most often performed through the femoral artery, but a transcervical approach can also be used to avoid traversing the aortic arch. Interventionalists almost uniformly use an embolic protection device (EPD) designed to reduce the risk of stroke caused by thromboembolic material dislodged during CAS. EPDs can be deployed proximally (with flow reversal) or distally (using a filter). Carotid angioplasty rarely is performed without stent placement.

Proposed advantages of CAS over CEA include:

- General anesthesia is not required (although CEA can be performed under local/regional anesthesia).
- Cranial nerve palsy sequels are infrequent sequelae (although almost all following CEA resolve over time).
- Simultaneous procedures may be performed on the coronary and carotid arteries.

Regulatory Status

The U.S. Food and Drug Administration (FDA) has approved carotid artery stents and EPDs from various manufacturers. Examples include:

- Acculink and RX Acculink carotid stents and Accunet and RX Accunet cerebral protection filters, Guidant Corp. (approved August 2004)
- Xact RX carotid stent system and Emboshield embolic protection system, Abbott Vascular Devices (approved September 2005)
- Precise nitinol carotid stent system and AngioGuard XP and RX emboli capture guidewire systems, Cordis Corp. (approved September 2006)
- NexStent carotid stent over-the-wire and monorail delivery systems, Endotex Interventional Systems; and FilterWire EZ embolic protection system, Boston Scientific Corp. (approved October 2006)
- ProtégéRx and SpideRx, ev3 Inc, Arterial Evolution Technology, (approved January 2007)
- Carotid Wallstent, Boston Scientific Corp. (approved October 2008)
- GORE Flow Reversal System (clearance February 2009); GORE Embolic Filter (clearance May 2011)
- Mo.Ma Ultra Proximal Cerebral Protection Device, Invatec S.P.A. (clearance October 2009)
Each FDA-approved carotid stent is indicated for combined use with an EPD to reduce risk of stroke in patients considered to be at increased risk for periprocedural complications from CEA who are symptomatic with greater than 50% stenosis, or asymptomatic with greater than 80% stenosis—degree of stenosis being assessed by ultrasound or angiogram with computed tomography (CT) angiography also sometimes used. Patients are considered at increased risk for complications during CEA if affected by any item from a list of anatomic features and comorbid conditions included in each stent system’s Information for Prescribers.

The RX Acculink™ Carotid Stent System is also approved for use in conventional risk patients (not considered at increased risk for complications during CEA) with symptoms and ≥70% stenosis by ultrasound or ≥50% stenosis by angiogram, and asymptomatic patients with ≥70% stenosis by ultrasound or ≥60% stenosis by angiogram.

FDA-approved stents and EPDs differ in the deployment methods used once they reach the target lesion, with the RX (rapid exchange) devices designed for more rapid stent and filter expansion. The Precise and AngioGuard™ devices were studied in a randomized, controlled trial (RCT) (the SAPHIRE trial; see Rationale section). Other devices were approved based on uncontrolled, single-arm trials or registries and comparison to historical controls. The FDA has mandated postmarketing studies for these devices, including longer follow-up for patients already reported to the FDA and additional registry studies, primarily to compare outcomes as a function of clinician training and (e.g., facility experience. Each manufacturer’s system is available in various configurations straight or tapered) and sizes (diameters and lengths) to match the vessel lumen that will receive the stent.

In February 2015, FDA cleared for marketing the ENROUTE Transcarotid NPS (Silk Road Medical, Inc., Sunnyvale, CA), through the 510(k) process. The ENROUTE is a flow-reversal device designed to be placed via direct carotid access. Clearance was based on results of the Roadster trial (NCT01685567), a single-arm phase 3 pivotal trial to evaluate outcomes after CAS with the ENROUTE device among 283 subjects with symptomatic or asymptomatic carotid stenosis. Full results of the Roadster trial have not yet been published. The manufacturer has also submitted a premarket approval application for the ENROUTE transcarotid stent system, an optimized stent delivery system for use with the ENROUTE NPS.

V. Rationale

Risk/benefit Ratio of Invasive Carotid Procedures

Endovascular carotid angioplasty and stenting (CAS) or surgical endarterectomy (CEA) for carotid artery disease trades procedure-related harms of stroke and death for the benefit of reduced stroke risk over subsequent years—the balance determines whether either intervention will result in a net clinical benefit. That balance has been scrutinized for CEA although not for CAS; accordingly results from trials of CEA must be extrapolated to CAS.

A series of landmark clinical trials from the late 1980s through the 1990s compared the benefits and harms of CEA to best medical therapies then available in symptomatic and asymptomatic individuals with carotid artery stenosis. The trial results defined the magnitude of risk reduction for stroke, and periprocedural stroke and death rates that can be traded to achieve a net clinical
benefit or benefit outweighing harm—30-day rates less than 3% for asymptomatic (greater than 60% stenosis), and less than 6% for symptomatic patients (50–69% or 70–99% stenosis). Furthermore, because periprocedural harms are immediate but benefit is accrued over time, a net clinical benefit is obtained only in those patients surviving long enough to counterbalance the immediate harms. The necessary life expectancy was defined by the trial duration needed to demonstrate benefit—2 years for symptomatic patients with 70–99% stenosis, 5 years for symptomatic patients with 50–69% stenosis or asymptomatic patients with greater than 60% stenosis (summarized in the following table).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Stenosis (%)</th>
<th>Acceptable Periprocedural Death/Stroke Rate, %</th>
<th>Anticipated Life Expectancy, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>60–99</td>
<td>&lt;3%</td>
<td>5</td>
</tr>
<tr>
<td>Yes</td>
<td>50–69</td>
<td>&lt;6%</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>70–99</td>
<td>&lt;6%</td>
<td>2</td>
</tr>
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</table>

As an example of the fine line between benefit and harm, Arazi et al. performed a decision analysis of benefit for patients with asymptomatic stenosis using a base case derived from the Asymptomatic Carotid Surgery Trial (ACST) (periprocedural death/stroke rate of 1.8%). Over a 5-year time horizon, CEA provided 4 days of stroke-free survival and a net harm when periprocedural death/disabling stroke rates exceeded 2.1%.

Since the landmark trials were performed, there have been considerable improvements in medical care and evidence of substantial decline in stroke rates with medical care in asymptomatic carotid disease. Current medical therapies including aggressive lipid lowering were inconsistently used in the landmark trials. While indirect, evidence for impact of improved medical care supports a perspective that guidelines for periprocedural death/stroke rates reflect upper limits needed to obtain a net clinical benefit. Surgeons in contemporary clinical trials have also achieved CEA periprocedural death and stroke rates lower than those in pivotal trials. For example, in the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), the death/stroke rates for symptomatic patients was 3.2% and for asymptomatic patients was 1.4%. Accordingly, benchmarks established decades ago might no longer be appropriate. A recent consensus document suggests benchmarks of 2.0% for asymptomatic and 4.0% for symptomatic individuals.

Excluded from landmark CEA trials were patients with significant comorbidities such as those judged likely to cause death within 5 years that might also increase periprocedural and anesthetic risk for complications. Therefore, CAS has appeal as a treatment option for patients with potentially higher periprocedural risk due to medical or anatomic reasons (e.g., medical factors include severe cardiac dysfunction, requirement for combined coronary and carotid revascularization, severe renal or pulmonary dysfunction, and other characteristics associated with increased surgical risk; anatomic factors include surgically inaccessible stenosis, prior radiation, prior neck surgery, spinal immobility, prior laryngeal nerve palsy, contralateral occlusion, prior ipsilateral CEA, restenosis after CEA).
Although general anesthetic risk is considered a potential reason to use CAS, CEA can typically be safely performed under local or regional anesthesia, as confirmed in the 95-center General Anesthesia versus Local Anesthesia (GALA) trial. Investigators randomized 3,526 patients undergoing CEA to general or local anesthesia and found no difference in 30-day death/stroke/myocardial infarction (MI) rates according to anesthetic approach (risk ratio [RR]: 0.94; 95% confidence interval [CI]: 0.70 to 1.3).

Randomized Controlled Trials of CAS versus CEA

SAPPHIRE Trial

The first major RCT of CAS versus CEA was the Stenting and Angioplasty, with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. The relevant conclusions are summarized as follows:

- SAPPHIRE included few patients with symptomatic stenosis at increased risk for periprocedural complications from CEA (n=96), which resulted in wide confidence intervals; differences between arms in 30-day and 1-year outcomes were not statistically significant.
- For patients with asymptomatic stenosis at increased risk for periprocedural complications from CEA, differences in 30-day outcomes also had wide confidence intervals and were not statistically significant.
- Early study closure resulted in fewer study patients than planned, which compromised the evaluation of noninferiority.
- Variance in differential complication rates for the two treatments across sites may have influenced results, since 5 of 34 sites contributed 64% of randomized patients, and data were unavailable for comparison.
- Direct comparative evidence was lacking for optimal medical management alone as an alternative to adding CAS with EPD or CEA for patients with increased risk of surgical complications.

Long-term follow-up of SAPPHIRE was reported at 3 years. For asymptomatic and symptomatic patients combined, ipsilateral strokes from day 31 to 1,080 days were observed in 4.4% of patients undergoing CAS and 3.6% with CEA (from digitized figure). Cumulative 3-year repeat target vessel revascularization (a proxy for restenosis) was more common after CEA, but the difference was not statistically significant (7.1% vs 3.0%; p=0.26).

SPACE Trial

In 2006, the Stent-supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was published. This trial randomized 1,200 patients within 180 days of neurologic symptoms, transient ischemic attack, or moderate (non-disabling) stroke, and with ≥50% stenosis of the ipsilateral carotid artery, to CAS (N=605) with or without EPD (73% of procedures performed without), or CEA (N=595). (18) The analysis (N=1,183) failed to conclude that CAS was noninferior to CEA by a margin of 2.5% for the primary outcome of ipsilateral ischemic stroke or death by 30 days after randomization. Periprocedural (30-day) event rates were 6.8% for the CAS group and 6.3% for the CEA group. The absolute between-group difference favored CEA and was 0.5% (90% CI: -1.9% to 2.9%) by intent-to-treat (ITT) analysis and 1.3% (90% CI: -1.1 to 3.8) in per-protocol analysis.
Editorialists pointed to some methodologic issues raised with SPACE, including the high rate of rejection for potential participating collaborators (approximately 25%, based on their prior outcomes records, but review criteria were not reported), and the trial did not require use of an EPD with CAS (although 30-day event rates were 7.3% with vs. 6.7% without EPD).

Long-term follow-up of the SPACE study was reported at 2-years. Approximate annual ipsilateral stroke rates from day 31 through longest follow-up for CAS and CEA, respectively, were 0.4% and 0.4%. These results support a conclusion that following the periprocedural period (i.e., 31 days to longest follow-up), stroke risk reduction in symptomatic patients not selected for medical or anatomic comorbidities is similar with either CAS or CEA. Recurrent stenosis greater than 70% was more frequent 2 years following CAS versus CEA (10.7% vs. 4.6%, respectively; p=0.001).

EVA-3S Trial

The Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was a noninferiority comparison of CAS (with EPD in 92%) versus CEA in symptomatic patients at average risk for complications from CEA with ≥60% stenosis of the ipsilateral carotid artery. (21) The trial was terminated prematurely (N=527 enrolled; original target N=872), based on interim analysis of 30-day outcomes. The incidence of any stroke or death through 30 days was 3.9% (95% CI: 2.0% to 7.2%) after CEA and 9.6% (95% CI: 6.4% to 14%) after CAS (RR: 2.5; 95% CI: 1.2% to 5.1%; p=0.01).

Over a mean follow-up of 2.1 years, restenosis (≥50%) was more frequent following CAS than CEA (12.5% vs 5.0%). Long-term follow-up of EVA-3S was reported at 4 years. Approximate annual ipsilateral stroke rates from day 31 through longest follow-up for CAS and CEA, respectively, were 1.1% and 0.9%. These results support a conclusion that following the periprocedural period (i.e., 31 days to longest follow-up) stroke risk reduction in symptomatic patients not selected for medical or anatomic comorbidities is similar with either CAS or CEA.

Editorialists criticized EVA-3S for recommending but not requiring, antiplatelet premedication (3 days of aspirin plus either ticlopidine or clopidogrel) and for not requiring interventionalists to be adequately experienced with the specific stent and EPD devices they used to treat trial subjects. Participating interventionalists were required to have successfully completed 12 or more CAS procedures, compared with 25 or more CEAs for vascular surgeons. EVA-3S also permitted use of 5 different stents and 7 different EPDs but required only 2 prior procedures with a new device before an investigator could use that device on a patient randomized to CAS.

In 2014, Mas et al published long-term follow up (median 7.2 years) from the EVA-3S trial. Complete follow-up until death or the final telephone interview was obtained in 493 patients (94%). At the 5-year follow-up point, the main composite end point (ipsilateral stroke after randomization or procedural stroke or death) occurred in 29/265 subjects in the CAS group and 16/262 subjects in the CEA group (cumulative probability 11% vs 6.3%; 5-year absolute risk reduction 4.7%). The HR for CAS versus CEA was 1.85 (95% CI, 1.0 to 3.40; p=0.04). At the 10-year follow-up point, the HR for the main composite end point for CAS versus CEA was 1.70 (95% CI, 0.95 to 3.06; p=0.07).
ICSS. The International Carotid Stenting Study enrolled 1,713 symptomatic patients at 50 academic medical centers across Europe, Australia, New Zealand, and Canada between May 2001 and October 2008. EPDs were recommended but not required (utilized in 72% of procedures), and a number of different stents and EPD types were used. Based on plausible event rates, a target study sample size of 1,500 was estimated able to define a between-group difference less than 3.3% in disabling stroke or death, but also a 3.0% difference in 30-day stroke, death, or MI. Only interim 30- and 120-day results were included in the initial report. From a per-protocol analysis, the 7.1% periprocedural death/stroke death rates accompanying CAS both exceed the rate established to provide a net clinical benefit and was more than twice that following CEA (3.4%). In a substudy of 231 ICSS participants, new ischemic brain lesions were approximately 3-fold more frequent following CAS protection devices did not appear to mitigate their occurrence. While follow-up of the sample for the primary endpoint is ongoing, interim results are consistent with the accompanying editorialist’s conclusion that “routine stenting in symptomatic patients must now be difficult to justify....”

In 2014, Bonati et al published longer term follow-up results from the International Carotid Stenting Study (ICSS). The cumulative 5-year risk of fatal or disabling stroke did not differ significantly between the CAS and CEA groups (6.4% for CAS vs 6.5% for CEA; hazard ratio (HR), 1.06; 95% CI, 0.72 to 1.57; p=0.77). The risk of any stroke was higher in the CAS group compared with the CEA group (5-year cumulative risk 15.2% vs 9.45; HR, 1.71; 95% CI, 1.28 to 2.3; p<0.001). The authors note that the difference between CEA and CAS groups in stroke risk after the procedural period was mainly attributable to strokes occurring in the contralateral carotid or vertebrobasilar territory in the CAS group. Functional outcomes, measured by modified Rankin scale scores, did not differ significantly between groups.

Also in 2014, Altinbas et al reported that periprocedural rates of hemodynamic instability in the ICSS study differed between CEA and CAS groups. Hemodynamic depression occurred more commonly in CAS patients (13.8% vs 7.2%; RR, 1.9; 95% CI, 1.4 to 2.6; p<0.000), while hypertension requiring treatment occurred less commonly in CAS patients (RR, 0.2; 95% CI, 0.1 to 0.4; p<0.000). Hemodynamic instability was not associated with the ICSS study’s primary composite outcome.

CREST Trial

The Carotid Revascularization Endarterectomy vs. Stenting Trial was conducted between December 2000 and July 2008, enrolling 2,522 patients at 117 centers across the U.S. and Canada. Of 427 interventionalists who applied to participate in CREST, only 224 (52%) were ultimately approved. Inclusion was initially restricted to recently symptomatic patients; due to slow enrollment, the protocol was amended to include asymptomatic patients. A March 2004 protocol amendment excluded further enrollment of patients 80 years and older due to poor outcomes. Of the 1,271 patients randomized to CAS, 65 underwent CEA and 54 neither procedure; of the 1,251 patients randomized to CEA, 13 underwent CAS and 44 neither procedure. There were 20 patients excluded from one site due to reported data fabrication. A sample size of 2,500 was targeted to detect a 46% reduction in the hazard ratio for the primary endpoint of any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization.

In the entire sample (symptomatic and asymptomatic patients), investigators reported no difference between CAS and CEA for the primary outcome of any periprocedural stroke, MI, or
death or postprocedural ipsilateral stroke. Stroke was more frequent following CAS, MI after CEA. The periprocedural MI rate after CEA (2.3%) was considerably higher in CREST than any comparable trial (e.g., in EVA-3S 0.8%, SPACE 0%, ICSS 0.6%). This may be attributable to a somewhat higher prevalence of coronary artery disease among participants and routine cardiac enzyme assays, but the relative difference was large. Periprocedural CAS death/stroke rates were the lowest reported in any trial. Although participating interventionalists performing CAS were highly selected, periprocedural death/stroke rates following CAS exceeded those for CEA: in symptomatic patients 5.6% versus 2.4%, respectively (the lowest rate for CAS reported in any trial); in asymptomatic patients 2.6% versus 1.4%, respectively. The RR for periprocedural death/stroke in the symptomatic group was 1.89 (95% CI: 1.11 to 3.21) in the asymptomatic group 1.85 (95% CI: 0.79 to 4.34). The trial had limited power to detect a difference between procedures in the asymptomatic group. In CREST, 2-year restenosis (>70%) or reocclusion rates were similar following either CEA (6.3%) or CAS (6.0%)—2-year restenosis alone 5.8% with either procedure.

Interventionalists in CREST were the most carefully selected in any trial, and the lack of similar careful selection has been a critique expressed concerning the other trials. However, analyses of CAS in Medicare patients between 2005 and 2007 found that few CAS operators had the experience of CREST investigators. Among the 11,846 procedures where operator experience was documented, 68% were performed by operators having performed fewer than 12 procedures.

In a follow-up analysis of the CREST trial data, Gonzalez et al reported no differences in outcomes for subjects treated in high-, medium-, or low-volume centers.

Additional RCTs

Several additional smaller trials have compared CEA with CAS. In 2014, Li et al published a study that reported to randomize 130 subjects at high risk of stroke due to angiographically confirmed carotid stenosis (≥50%) to CEA (n=65) or CAS (n=65). The authors report a 3-month post-operative risk of mortality of 1.5% with CAS, compared with 9.2% with CEA. However, “existence of complete follow-up data” is an inclusion criterion, and insufficient details are provided about enrollment and randomization procedures to allow conclusions to be drawn about the study.

In 2015, Kuliha et al published results of an RCT which randomized 150 subjects with at least 70% ICA stenosis to CEA (n=73) or CAS (n=77). New infarctions on magnetic resonance imaging (MRI) were found more frequently after CAS (49% vs 25%; p=0.002).

Section Summary

RCTs comparing CEA with CAS enrolled a mix of symptomatic and asymptomatic patients and and employed different selection criteria for participating centers. Periprocedural stroke and death rates following CAS exceeded those after CEA. Following the early perioperative period, the subsequent rate of ipsilateral and/or transient ischemic attack (TIA) appears to be similar for the 2 procedures. While some trials found higher restenosis rates after CAS (SAPPHIRE, SPACE, EVA-3S), restenosis in CREST occurred with similar frequency following either procedure. The rates of early complications in these trials exceed the threshold that has been set to denote overall benefit. There is some variability in the results of these trials. For example, results from CREST were more favorable for CAS than those reported from the SPACE, EVA-3S, or ICSS. Periprocedural death/stroke rates with CAS were lower than 6% in symptomatic and 3% in asymptomatic patients.
Interventionalists in CREST were the most carefully selected in any trial and the criteria used to credential in other trials has been a focus of criticisms, along with the inconsistent use of embolic protection devices.

There are no RCTs of CAS versus medical therapy. Since the pivotal CEA versus medical therapy trials, there have been marked improvements in medical therapy and declining stroke rates in asymptomatic patients with carotid stenosis. In 1993 the Asymptomatic Carotid Artery Stenosis trial reported that the annual ipsilateral stroke rate was approximately 2.0% with medical therapy. A recent estimate in 2009 described a contemporary annual ipsilateral stroke or transient ischemic attack (TIA) rate of 0.34% among asymptomatic patients with asymptomatic carotid stenosis equal to or greater than 50%; a rate less than the 0.51% estimated by Arazi et al. needed justify the periprocedural risk of death and disabling stroke. This evidence can be used to argue that medical therapy in asymptomatic patients is preferable to intervention. Therefore, it is not possible to determine whether CAS is superior to medical therapy.

Systematic Reviews and Meta-analysis of RCTs

Several TEC Assessments and meta-analyses have been published with similar findings. In average risk symptomatic patients the body of evidence demonstrates worse periprocedural outcomes with CAS compared to CEA. While data show secular improvement in periprocedural outcomes following CAS there is evidence of a net harm compared to CEA. The individual patient data meta-analysis of SPACE, EVA-3S, and ICSS indicates some uncertainty in comparative periprocedural death/stroke rates for younger symptomatic patients. Still, that subgroup result must be considered carefully given the larger body of evidence, lack of stratified randomization, as well as the evidence on restenosis. Meta-analyses have generally found that restenosis is more common following CAS than CEA. In a meta-analysis of 13 trials, among those reporting restenosis rates, Bangalore et al. reported pooled relative odds for restenosis following CAS compared to CEA of 2.8 (95% CI: 2.0 to 4.0; \( I^2 = 0\% \)).

Of note was the individual patient data meta-analysis (n=3,433) of SPACE, EVA-3S and ICSS. In these symptomatic patients the 30-day death/stroke risk (per-protocol analyses) with CAS was 7.7% versus 4.4% following CEA (RR 1.74; 95% CI: 1.32 to 2.30). However, in the subgroup younger than 70 years of age, comparative 30-day death/stroke rates were 5.1% (CAS) and 4.5% (CEA) (RR: 1.11; 95% CI: 0.73 to 1.71); for patients 70 years or older 10.5% (CAS) and 4.4% (CEA) (RR: 2.41; 95% CI: 1.65 to 3.51). However, randomization was not stratified by age in these trials.

Paraskavas et al conducted a systematic review of studies comparing cognitive outcomes after CEA with those after CAS. Thirteen studies were included, with heterogeneity in the types of cognitive outcome measures reported. In qualitative analysis, the authors report that most studies did not report a significant difference between CEA and CAS in terms of cognitive outcomes but that the heterogeneity in outcomes reported precluded more definitive conclusions.

Galyfos et al reported results of a systematic review that included 9 trials (n=5959) with a focus on risk of periprocedural symptomatic or asymptomatic myocardial ischemia or MI. Four studies did not report their definition used for myocardial ischemia, and other studies varied in their definitions. In pooled analysis, compared with CEA, CAS was associated with decreased risk for cardiac damage (pooled RR, 0.37; 95% CI, 0.22 to 0.61; \( p < 0.000 \)). However, the study provides
incomplete information about selection of studies for inclusion, which limits conclusions that can be drawn.

Section Summary

The systematic reviews corroborate the results of individual RCTs in reporting that early adverse events are higher with CAS compared to CEA that long-term stroke rates following the perioperative period are similar, and that restenosis is higher with CAS. These data indicate that for the average risk patient with carotid stenosis, CAS is associated with a net harm compared to CEA.

Periprocedural Death/Stroke Rates following CAS

This question was assessed in BCBSA October 2009 TEC Assessment. Noting again that CAS (like CEA) trades procedure-related risk of stroke and death for a reduced risk of stroke over subsequent years, and limits for periprocedural stroke and death rates that can be traded to achieve a net clinical benefit outlined in current guidelines are less than 3% for asymptomatic and less than 6% for symptomatic patients, the Assessment sought evidence to address the following questions:

1. Is the periprocedural death/stroke rate with CAS less than 3% for asymptomatic and less than 6% for symptomatic patients?

Eighteen multicenter prospective registries collectively enrolling 20,194 patients were identified. Eleven enrolled patients in accordance with FDA labeling and 30-day outcomes were available for analysis according to symptomatic status (13,783 asymptomatic and 3,353 symptomatic). For 9 registries, 30-day death/stroke rates were either reported or obtained from investigators; in the remaining 2, death/stroke rates were estimated from 30-day death/stroke/MI and MI rates. An independent assessment of neurological outcomes was required in all but one registry. For asymptomatic patients, the pooled periprocedural death/stroke rate was 3.9% (95% CI: 3.3%–4.4%); for symptomatic patients 7.4% (95% CI: 6.0%–9.0%).

A subsequent systematic review, without consideration to FDA labeling, reported results consistent with the TEC Assessment (pooled periprocedural death/stroke rates in asymptomatic patients of 3.3% [95% CI: 2.6% to 4.1%; 23 studies; 8,504 patients] and in symptomatic patients of 7.6% [95% CI: 6.3% to 9.1%; 42 studies; 4,910 patients]).

2. For those subgroups defined by a) medical comorbidities or b) unfavorable anatomy, are periprocedural death/stroke rates with CAS less than 3% for asymptomatic and less than 6% for symptomatic patients?

Combined data from 2 registries reported periprocedural death/stroke rates for patients with unfavorable anatomy but included only 371 asymptomatic and 60 symptomatic patients. No other registry reported results by symptomatic status for those subgroups.

Since the publication of the 2009 TEC Assessment, some additional evidence has been published related to rates of periprocedural stroke/death following CAS, particularly related to subgroups defined by medical comorbidities. Spangler et al evaluated patients treated with isolated primary CEA (n=11,336) or primary CAS (n=544) at 29 centers between 2003 and 2013 to assess periprocedural mortality and stroke risks for patients considered medically high risk. A Cox
proportional hazards model was used to generate predicted 5-year mortality, and patients in the highest risk score quartile were considered high risk. For asymptomatic patients, there were no significant differences between CEA and CAS for major periprocedural outcomes (major or minor stroke, MI, death) for either high- or low-risk patients. Periprocedural death/stroke rates with CAS were 1.1% for low-risk patients and 1.6% for high-risk patients. For symptomatic patients, periprocedural death/stroke rates were higher with CAS than CEA for both low- and high-risk groups. For low-risk symptomatic patients, periprocedural death/stroke rates were 6.0% for CAS, compared with 2.2% for CEA (p<0.01). For high-risk symptomatic patients, periprocedural death/stroke rates were 9.3% for CAS, compared with 2.5% for CEA (p<0.01).

CAS for Carotid Dissection

Carotid dissection is uncommon (incidence approximately 2 per 100,000/year) and occurs generally in younger individuals. With a frequently favorable prognosis, conservative therapy with anticoagulants to restore blood flow is typically employed while surgical intervention reserved for patients whose symptoms fail to respond to conservative care. Some have described CAS as a potential treatment in those instances however, there are no clinical trials comparing alternative strategies and interventions. Current guidelines (detailed below) rate CAS in for this indication as a class IIb (Level of Evidence: C) recommendation.

Ongoing Clinical Trials

There are 2 large ongoing randomized trials comparing CEA and CAS (ACT I, enrolling asymptomatic patients at average risk for complications from CEA, was terminated), which are summarized in Table 2.

Table 2: Ongoing RCTs Comparing CEA and CAS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Estimated Study</th>
<th>Planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPACE 2: Stent-protected angioplasty in asymptomatic</td>
<td>RCT comparing CAS, CEA, and best medical therapy in</td>
<td>January 2020</td>
<td>3523 (1636 in CEA vs best medical)</td>
</tr>
<tr>
<td>ACST-2: Carotid Endarterectomy Versus Carotid Artery Stenting in asymptomatic</td>
<td>RCT comparing CEA and CAS in asymptomatic</td>
<td>January 2019</td>
<td>5000</td>
</tr>
</tbody>
</table>

SPACE 2 was originally planned as a 3-arm clinical trial to compare CAS, CEA, and best medical therapy. In January 2013, due to insufficient enrollment, the study protocol was changed two 2-arm superiority trials. Patients are allocated to 1 of the 2 substudies based on the decision of the including physician and the patient's preference: either CEA compared with best medical management (SPACE2 a substudy) or CAS compared with best medical management (SPACE2b substudy).

There are no ongoing or direct comparisons of CAS versus CEA in patients at increased risk for CEA complications. Particularly problematic is the lack of adequate data, from either randomized or non-randomized studies, to separately compare outcomes of the alternatives (CAS vs. CEA vs.
current optimal medical management) in symptomatic and asymptomatic increased-risk subgroups.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 4 physician specialty societies (6 reviewers) and 4 academic medical centers while this policy was under review in 2009. (In addition, one unsolicited response from a specialty society was also received.) This clinical input strongly supported use of CAS in recently symptomatic patients where CEA cannot be performed due to anatomic reasons, although acknowledging the limited evidence pertaining to this subgroup. The lack of alternative treatments for recently symptomatic patients and the established increased risk of stroke were factors supporting this opinion.

Summary of Evidence

A substantial body of RCT evidence compares outcomes of CAS with CEA for symptomatic and asymptomatic patients with carotid stenosis. The evidence does not support use of CAS in carotid artery disease for the average risk patient, since early adverse events are higher with CAS and long-term outcomes are not better. Data from RCTs and large database studies establish that the risk of CAS exceeds the threshold set to indicate overall benefit from the procedure. Therefore, for patients with carotid stenosis who are suitable candidates for CEA, CAS is not covered.

However, based on limited data, clinical input, an indirect chain of evidence, and unmet medical need, CAS may be considered a reasonable treatment option in recently symptomatic patients when CEA cannot be performed due to anatomic reasons. For this population, CAS may be considered medically necessary. It is not covered for all other indications, including carotid dissection.

Practice Guidelines and Position Statements

In 2011, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines, American Stroke Association (ASA), American Association of Neuroscience Nurses (AANN), American Association of Neurological Surgeons (AANS), American College of Radiology (ACR), American Society of Neuroradiology (ASNR), Congress of Neurological Surgeons (CNS), Society of Atherosclerosis Imaging and Prevention (SAIP), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), Society for Vascular Medicine (SVM), and Society for Vascular Surgery (SVS) issued guidelines on the management of patients with extracranial carotid and vertebral artery diseases, which are summarized in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL OF EVIDENCE</td>
</tr>
<tr>
<td>CLASS I Benefit &gt;&gt;&gt; Risk</td>
</tr>
</tbody>
</table>

Level of Evidence
CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6% (360).

<table>
<thead>
<tr>
<th>CLASS IIa Benefit &gt;&gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention.</td>
</tr>
<tr>
<td>It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.</td>
</tr>
<tr>
<td>When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IIb Benefit ≥ Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.</td>
</tr>
<tr>
<td>In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established.</td>
</tr>
<tr>
<td>Carotid angioplasty and stenting might be considered when ischemic neurological symptoms have not responded to antithrombotic therapy after acute carotid dissection.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS III: NO BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Except in extraordinary circumstances, carotid revascularization by either CEA or CAS is not recommended when atherosclerosis narrows the lumen by less than 50%.</td>
</tr>
<tr>
<td>Carotid revascularization is not recommended for patients with chronic total occlusion of the targeted carotid artery.</td>
</tr>
<tr>
<td>Carotid revascularization is not recommended for patients with severe disability caused by cerebral infarction that precludes preservation of useful function.</td>
</tr>
</tbody>
</table>

Levels of Evidence:
A—data derived from multiple randomized controlled trials or meta-analyses; multiple populations evaluated.
B—Data derived from a single randomized controlled trial or non-randomized studies; limited populations evaluated.
C—Only consensus opinion of experts, case studies, or standard of care; very limited populations evaluated.

Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease

Table 4

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAGE I &quot;benefit clearly outweighs risk&quot;</td>
<td></td>
</tr>
<tr>
<td>In most patients with carotid stenosis who are candidates for intervention, CEA is preferred to CAS for reduction of all-cause and periprocedural death</td>
<td>B</td>
</tr>
<tr>
<td>GRAGE II &quot;benefits and risks are more closely matched and are more dependent on specific clinical scenarios&quot;</td>
<td></td>
</tr>
<tr>
<td>CAS is preferred over CEA in symptomatic patients with &gt;50% stenosis and tracheal stoma, situations where local tissues are scarred and fibrotic from prior ipsilateral surgery or external beam radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body</td>
<td>B</td>
</tr>
<tr>
<td>CAS is preferred over CEA in symptomatic patients with &gt;50% stenosis and severe uncorrectable coronary artery disease, congestive heart failure, or chronic obstructive pulmonary disease</td>
<td>C</td>
</tr>
<tr>
<td>There are insufficient data to recommend CAS as primary therapy for neurologically asymptomatic patients with 70% to 99% diameter stenosis. In properly selected asymptomatic patients, CAS is equivalent to CEA in the hands of experienced interventionalists with a combined stroke and death rate &lt;3%</td>
<td>B</td>
</tr>
</tbody>
</table>

Levels of Evidence: A (high quality); B (moderate quality); C (low quality)

In 2011, the European Society of Cardiology issued guidelines on the diagnosis and treatment of peripheral artery diseases, which included recommendations regarding carotid revascularization, summarized in Table 5.

Table 5

<table>
<thead>
<tr>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIa &quot;Should be considered&quot;</td>
<td></td>
</tr>
<tr>
<td>In symptomatic patients at high surgical risk requiring revascularization, CAS should be considered as an alternative to CEA</td>
<td>B</td>
</tr>
<tr>
<td>Class IIb &quot;May be considered&quot;</td>
<td></td>
</tr>
<tr>
<td>In symptomatic patients requiring carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate &lt;6%</td>
<td>B</td>
</tr>
</tbody>
</table>

Levels of Evidence: A (Data derived from multiple randomized clinical trials or meta-analyses.); B (Data derived from a single randomized clinical trial or large non-randomized studies); C (Consensus of opinion of the experts and/or small studies, retrospective studies, registries)

NICE

“Current evidence on the safety of CAS placement for asymptomatic extracranial carotid stenosis shows well documented risks, in particular, the risk of stroke. The evidence on efficacy is
inadequate in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.”

Australasian Carotid Stenting Guidelines Committee

“CAS may be considered as a treatment option for patients with symptomatic severe carotid stenosis who are at high risk of stroke, but are surgically unsuitable for CEA, namely postradiation therapy, block dissection of the neck, in situ tracheostomy, recurrent stenosis following previous CEA, severe cervical spine arthritis, surgically inaccessible carotid stenosis (e.g., obesity, high carotid bifurcation), contralateral recurrent laryngeal nerve injury, and contralateral internal carotid occlusion.”

“The overall results of randomized controlled trials indicate that CAS is not as safe as CEA for treatment of symptomatic carotid stenosis for prevention of ipsilateral stroke.”

“There is currently no evidence to support CAS as a treatment for asymptomatic carotid stenosis.”

Medicare National Coverage

From March 2001, Medicare’s national coverage policy restricted coverage for carotid angioplasty and stenting to patients participating in a clinical trial with Category B Investigational Device Exemption (IDE) designation from the FDA. Percutaneous transluminal angioplasty (PTA) of the vertebral and cerebral arteries remained noncovered.

When FDA approved the first (Guidant) devices, Medicare coverage under the IDE trial policy was no longer available for that manufacturer’s devices and was not applicable to FDA-required post-approval studies. Thus, on October 12, 2004, Medicare broadened its national coverage policy and “determined that the evidence is adequate to conclude that percutaneous transluminal angioplasty (PTA) with carotid stent placement is reasonable and necessary when performed consistent with FDA approval of the carotid stent device and in an FDA required post-approval study.” For unapproved stents and EPD devices, the prior policy remained in effect and restricted coverage to patients participating in an FDA-approved Category B IDE trial of stent placement in the cervical carotid artery.

While the Medicare decision differed from the conclusions of this policy, Medicare made a public policy decision “that making available new, effective therapies aimed at addressing treatment and prevention of cerebrovascular disease was important to Medicare beneficiaries.” Medicare also noted that it recognized value in supporting post-approval studies as “the collected data may provide an opportunity for practitioners to determine which patients are most appropriate for carotid artery stenting and to reinforce IDE trial data on health outcomes and adverse events.”

CMS provides a continually updated listing of facilities eligible for Medicare reimbursement that met CMS's minimum facility standards for performing carotid artery stenting for high-risk patients.

On March 17, 2005, CMS determined that CAS with EPD is reasonable and necessary for patients at high risk for CEA who also have symptomatic carotid artery stenosis equal to or greater than 70%. CMS limited coverage for these patients to procedures performed using FDA-approved devices. CMS also limited coverage for patients at high risk for CEA with symptomatic carotid artery stenosis between 50% and 70%, and for patients at high risk for CEA with asymptomatic stenosis equal to or
greater than 80%, to FDA-approved Category B IDE clinical trials for unapproved devices, or to FDA-required post-approval studies for approved devices. CMS defined patients at high risk for CEA as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection) who would be poor candidates for CEA in the opinion of a surgeon.

The paragraph below provides CMS’ reasoning for this change in coverage policy:

“Considering the evidence and clinical situation, there appears to be sufficient evidence to infer that CAS with embolic protection can improve health outcomes for patients with severe symptomatic stenosis >70% who are also at high risk for CEA, if performed with the same expertise and rate of adverse events as demonstrated in the published clinical trials. Since patients with severe symptomatic stenosis ≥70% are at high risk for stroke, carotid interventions to reduce the risk of stroke should be considered. Although the published studies on CAS have various potential biases, we feel that the need for an alternative treatment to CEA for patients who are truly at high risk for CEA should be factored into the coverage decision, unlike the BCBS TEC report, which did not consider this circumstance. By not covering this group, symptomatic patients who also are at high risk for surgery may be left with no other treatment options. The risk benefit consideration may be similarly influenced. However, having mentioned this situation, the high risk CAS studies compared CAS to CEA and found that CEA can be performed as well as CAS in a group classified as high risk. Therefore, two comparable options exist for patients with symptomatic stenosis ≥70% who are at high risk.”

On April 30, 2007, a decision memo reaffirmed CMS’s previous decision following a request to expand coverage while clarifying that “CAS is only covered when used with an embolic protection device and is, therefore, not covered if deployment of the distal embolic protection device is not technically possible.” On October 14, 2008 in the sixth reconsideration, and on December 9, 2009 in the seventh reconsideration, CMS reaffirmed their prior coverage decisions.

On January 25, 2012 CMS convened a MEDCAC panel to consider “Management of Carotid Atherosclerosis.” Panel members voted on specific questions using a scale of 1 (low confidence) to 5 (high confidence). For symptomatic patients not considered at high-risk, the mean scores to the question of whether CAS is the favored treatment strategy in this population was 1.85 and for CEA 3.6. For asymptomatic patients not considered high-risk the evidence was not judged to reach a level of certainty to provide allow determining a favored treatment.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA consider the application of this Medical Policy to the case at issue.

VII. References

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