TITLE: Carotid Artery Stenting versus Carotid Endarterectomy: A Review of the Clinical and Cost-Effectiveness

DATE: 22 September 2009

CONTEXT AND POLICY ISSUES:

A stroke is an interruption of blood supply and subsequently, oxygen, to any part of the brain. Common symptoms include: headache; change in alertness; difficulty in speaking, reading or writing; loss of coordination, balance, or vision; or weakness of a body part. Strokes can be caused by a blood clot in a blood vessel that blocks the flow of blood to the brain (also known as ischemic stroke) or by a rupture, causing a blood leak into the brain (also known as hemorrhagic stroke). If the brain lacks blood or oxygen supply for longer than a few seconds, it may cause permanent damage. In Canada, the 2005-06 age-standardized hospitalization rate for acute stroke was 94.9 per 100,000 individuals. The hospitalization rate was adjusted for differences in age for both males and females with strokes. Types of acute stroke include subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, and acute but ill-defined stroke. In 2004, 11,668 deaths in Canada were attributed to strokes. Since 1979, there has been a general decrease in the number of deaths due to strokes for men and women. Prevention approaches that help to control blood pressure, decrease smoking, and improve stroke care play a role in the reduced mortality rate.

Carotid endarterectomy (CEA) is the standard procedure for stroke prevention among symptomatic patients, where the surgeon removes plaque from the carotid artery. More specifically, it is recommended that CEA be performed on patients with symptomatic carotid artery disease of 70% to 99% stenosis (narrowing of the arteries) within two weeks of the incident stroke or transient ischemic attack (TIA). Stenosis is measured at angiography or by two concordant non-invasive imaging modalities. CEA is not recommended for patients with mild stenosis (less than 50%). Carotid artery stenting (CAS) is a less invasive percutaneous procedure compared with CEA. Patients receive local anaesthesia, and a fine wire is passed into the carotid artery through the femoral artery in the groin. CAS helps keep the artery open to maintain the blood flow and to prevent the recurrence of stenosis.
This report will review the evidence on the clinical and cost-effectiveness of carotid artery stenting compared with carotid endarterectomy for carotid artery stenosis.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of carotid artery stenting compared with carotid endarterectomy?

2. What is the cost-effectiveness of carotid artery stenting compared with carotid endarterectomy?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and August, 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies.

HTIS reports are organized so that the higher quality evidence is presented first. Systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials and economic evaluations.

SUMMARY OF FINDINGS:

The literature search identified one systematic review, two meta-analyses, one randomized controlled trial (RCT), and two economic evaluations. No health technology assessments were found.

Systematic review and meta-analyses

In 2009, Paraskevas et al. evaluated the available evidence in the management of symptomatic carotid artery stenosis using CAS compared with CEA. The literature search was conducted in The Cochrane Controlled Trials Register, PubMed/Medline and EMBASE databases until February 1, 2009 to identify randomized trials that compared CAS with CEA for symptomatic patients with carotid artery stenosis. One single-center and three multi-center trials met their selection criteria. According to the mean age, mean follow-up time, and mean carotid artery stenosis reported in some studies, the patient characteristics between both groups in each individual study were comparable, but they were not described in great detail in most studies. The clinical outcomes assessed include stroke, mortality and recurrent carotid stenosis rates.

Liu et al. conducted a meta-analysis in 2009 to assess the perioperative mortality and morbidity rates and other adverse between patients undergoing a CAS procedure compared with patients...
undergoing a CEA procedure. Eight studies published between 1998 and 2006 met the selection criteria and the total patient population was 2,972 (CAS=1,480 patients and CEA=1,462 patients). The clinical outcomes evaluated were stroke or death and mortality rates. The patient characteristics, such as mean age, gender, symptomatic compared with asymptomatic, history of stroke or TIA, and mean stenosis, were similar between both groups in the selected studies. The clinical outcomes were pooled to calculate the relative risk (RR) with 95% confidence intervals (CIs). The X² was used to measure the statistical heterogeneity among the studies in order to meta-analyze the clinical outcomes with a fixed-effects model. A P-value greater than or equal to 0.10 was the cutoff point for homogeneity. Appendix 2 presents pooled clinical outcomes measured. In the earlier RCTs included in the meta-analysis, CAS resulted in higher morbidity and mortality rates compared with CEA. Newer technologies and embolic protection devices (EPD) helped to improve the clinical outcomes and safety of CAS. The authors concluded that CAS and CEA may be viewed as complementary procedures instead of competing therapies, and optimal therapies for different patient populations. For instance, CAS with EPD may be the optimal choice for certain patients, but not ideal for symptomatic patients.

A 2009 meta-analysis by Usman et al. compared the periprocedural (30-day) myocardial infection (MI), stroke, and death rates for CAS with CEA in patients of 80 years or older. Forty-one studies (CAS=8 and CEA=33) published from 1997 to 2007 that compared CAS with CEA in octogenarians (80 years and older) were selected for inclusion. The authors measured the effect size of each individual study to determine its weight on the meta-analysis and a pooled effect size and variance were calculated for each clinical outcome. A random effects model was used for the meta-analysis to account for the within and between study variance. In total, there were 826 patients in the CAS group compared with 7,017 patients who underwent CEA. There were minimal differences between both groups in terms of patient demographics. Demographics compared were mean age, asymptomatic compared with symptomatic, diabetes, smoking status, previous MI, and hypertension. For comparative purposes, each study in the meta-analysis was paired with a theoretical control. The pooled clinical outcomes showed that the MI rate (CAS=0.95% compared with 2.20%; P=0.083; 95% CI was not reported) and mortality rate (CAS=1.98% compared with 1.11%; P=0.253; 95% CI was not reported) were not statistically significantly different between both groups. The relative risk of MI using the 1% MI rate as the cutoff was also performed, and the results should no significant difference between both groups (RR not reported). There was a statistically significant difference in the stroke rate between the CAS and CEA groups (CAS=7.04% compared with CEA=1.91%; P<0.01; 95% CI was not reported). The relative risk (RR) of stroke was calculated according to the acceptable stroke rate of 3%. The RR of a stroke in the CAS group was 2.18 (95% CI: 1.31 to 3.63) compared with 0.63 (95% CI: 0.46 to 0.87) in the CEA group. The absolute risk for stroke in the CAS group was 3.46 times greater than in the CEA group. In this case, the absolute risk represents the probability of a stroke for the octogenarians. Given the greater risk of stroke for octogenarians associated with CAS, the authors recommended that this patient population undergo treatment with CEA.

**Randomized controlled trials**

Howard et al. conducted one RCT in 2009, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), to compare CAS with CEA in stroke prevention, MI and death a 30-day periprocedural period and stroke ipsilateral to the study artery over the follow-up period of up to one year in patients with symptomatic and asymptomatic extracranial carotid stenosis. A lead-in phase was incorporated into the study design to allow eligible interventionalists interested in participating in the clinical trial phase the opportunity to perform up to 20 CAS
procedures and submit data to the CREST Interventional Management Committee for review and approval to proceed to the clinical trial phase. In the lead-in phase, Howard et al. reported results of the 30-day complication rate between women and men and between symptomatic and asymptomatic patients. Patients with amaurosis fugax, transient ischemic attack (TIA) or stroke in the distribution of the study artery with the previous 180 days were defined as symptomatic and had to have at least 50% or greater stenosis by angiography as indicated by the American Symptomatic Carotid Endarterectomy Trial criteria. Patients without cerebrovascular symptoms relative to the study artery and with at least 70% stenosis or greater by angiography were considered to be asymptomatic.

In the lead-in phase, 1,564 participants from 97 study sites were enrolled from December 2000 to February 2008. Each site had a CREST-approved interventionalist and neurologist. CAS procedures were performed by CREST-certified interventionalist using local anesthesia and following a standard protocol. Patients took an aspirin and clopidogrel 48 hours before and for 30 days after the intervention. Patients were also treated with the RX ACCULINK Carotid Stent System and the RX ACCNET Embolic Protection System. Both devices are manufactured by Abbott Vascular Corporation, Abbott Park, Ill, USA.

The patient population included 579 women (37%) and 985 men. Most patient baseline characteristics between both groups were comparable, except that 20.9% of women compared with 16.7% of men were smokers (P=0.038; 95% CI was not reported). The 30-day stroke or death rate was 4.3% (24 of 414) compared with 3.7% (43 of 1,150) in asymptomatic patients (measures of variation not reported). The 30-day stroke or death rate was 4.5% [26 of 579; 95% CI: 3.0% to 6.5%] for women compared with 4.2% (41 of 985; 95% CI: 3.0% to 5.6%) for men. The MI rate for symptomatic patients was 1.2% (14 of 414) compared with 0.2% (1 of 1,150) for asymptomatic patients. For women, the MI rate was 1.6% (9 of 579) compared with 0.6% (6 of 985) for men (measures of variation not reported). The difference in the stroke, death, and MI rate between symptomatic and asymptomatic women (6.3% compared with 5.5% for a 0.8% difference) compared with symptomatic and asymptomatic men (5.9% compared with 4.4% for a 1.5% difference). The clinical outcomes indicate higher stroke or death and MI rates in symptomatic patients compared with asymptomatic patients for both women and men. The results of a univariate analysis demonstrated a slightly higher risk of a stroke or death for women compared with men [odds ratio (OR): 1.08; 95% CI: 0.66 to 1.79]. The analysis was stratified separately by age and race to measure their impact on risk. The risk was impacted by an increasing age (OR_{10-year increment}: 2.31; 95% CI: 1.65 to 3.25) but race did not affect the risk level (OR: 1.07; 95% CI: 0.38 to 3.05). When the analysis was stratified by age (younger than or equal to 70 years compared with older than 70 years) and was adjusted for race, the difference in risk between women and men was greater for the younger group (OR: 1.93%; 95% CI: 0.42 to 8.88) compared with the older group (OR: 0.76; 95% CI: 0.18 to 3.23). The difference in either stratification was not significant. Compared with men, the study results showed that women do not have a greater risk of carotid artery stenting stroke or death. The authors did not indicate the publication date of the trial results.

**Economic evaluations**

Janssen et al. used a Markov model to evaluate the cost-effectiveness of CAS compared with CEA. The study perspective was not specified. Patient survival rate was measured using data on endarterectomy patients with a stenosis greater than 70% in the European Carotid Surgery Trial and a 2007 Cochrane systematic review on percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Data on symptomatic patients only were extracted from the Cochrane review. Procedural costs of CAS and CEA were based on the resources used and
procedures conducted at two hospitals in the Netherlands. Cost associated with acute major and minor strokes and hospital stay were based on Dutch published literature.\textsuperscript{9} The costs for rehabilitation, nursing home, and physical therapy were taken from the published literature, and all costs were adjusted to the 2003 price index.\textsuperscript{9} A four percent annual rate was used to discount costs and clinical outcomes. The authors varied complication rates and procedural costs to assess their impact on cost-effectiveness in different scenarios and changes in costs and effects as a function of peri-operative complication and re-operation rates were evaluated in the sensitivity analyses.\textsuperscript{9}

Patient characteristics were not reported in the economic evaluation. The study results indicated that the average cost of a CAS procedure is €1,488 greater than a CEA procedure.\textsuperscript{9} The length of stay in a hospital accounts for a large part of CEA costs, and the costs directly related to the stenting procedure, such as stents, catheters, and cerebral protection devices, is a major driver of CAS costs.\textsuperscript{9} The findings from the sensitivity analyses suggested that the cost-effectiveness of CAS is impacted primarily by major peri-operative stroke rates. A one percent increase in a major stroke rate raised the cost by €1,051 and reduced quality adjusted life years (QALYs) by 0.059.\textsuperscript{9} One co-author received research grants from the European Union, Sanofil-Synthélabo, the Stroke Association and the Medical Research Council in the UK.\textsuperscript{9}

Pawaskar \textit{et al.} conducted a retrospective cost analysis to compare the reimbursement and costs of CAS compared with CEA for the treatment of procedural and nonprocedural carotid artery stenosis.\textsuperscript{10} Patients undergoing CAS were pair-matched with those undergoing CEA based on age, gender, race, disease-related group (DRG) classification, length of stay, comorbidities as measured by the Charlson index, and preoperative and postoperative adverse events.\textsuperscript{10} The total direct costs related directly to the procedure [e.g., operating room or catheterization laboratory, central supplies, intensive care unit (ICU), etc.] and non-procedure (e.g., nursing, pharmacy, laboratory, and radiology services) were included. Thirty-one patients in each intervention who were classified to DRG 533 (extracranial procedures with comorbidities or complications) and DRG 534 (extracranial procedures without comorbidities or complications) formed part of the study population.\textsuperscript{10} Costs were expressed in US dollars. The patient baseline characteristics were similar between both groups, with the exception of age. Patients in the CAS group had a mean age of 69.10 years (±1.60 years) compared with 67.77 years (±1.84 years) in the CEA group. The total mean cost for CAS was $8,219.71 (±$2,958.55) compared with $3,765.12 (±$2,170.82) for CEA. Patients in the CAS group incurred higher procedure costs compared with those in the CEA group: central supplies [CAS=$4,548 (±$1,658.99); CEA=$338.39 (±$134.11)] and room and board and ICU [CAS=$835.91 (±$1,091.55); CEA=166.29 (±$582.55)]. Nursing costs were lower for CAS [CAS=$90.48 (±$189.61); CEA=$538.12 (±$652.44)].\textsuperscript{10} Other remaining procedural and non-procedural costs were comparable between both groups.

The hospital received a similar mean reimbursement for DRGs 533 and 534 from Medicare and private insurers [health maintenance organizations (HMOs) and preferred provider organizations (PPOs)]. For instance, the mean total reimbursements received from Medicare were (CAS=$9,717.50; CEA=$9,854.50) and (CAS=$13,024.50; CEA=$13,456.00) from HMOs/PPOs.\textsuperscript{10} Conversely, the hospital had a greater cost savings for CEA compared with CAS [Medicare: (CAS=$1,497.79; CEA=$6,089.37) and HMOs/PPOs: (CAS=$4,804.79; CEA=$9,690.87)].\textsuperscript{10} CAS had a greater total mean cost compared with CEA, and the hospital received a higher costs savings with CEA for both DRG classifications and all insurers. The authors suggested new financial strategies and infrastructure for CAS should be developed to ensure that it becomes feasible option for patients with carotid artery stenosis. One author received a grant from industry (Zonare Inc, Mountain View, CA, USA).\textsuperscript{10}
Limitations

None of the studies in the meta-analysis by Usman et al. were direct comparisons between CAS and CEA procedures. Most study designs were retrospective cohort or case series reports, potentially increasing the risk of confounding or bias, such as selection or retrospective bias.⁷

The results from the CREST study were based on the lead-in phase of the trial and not from the randomized phase. As a result, the patient population may not be representative of all patients undergoing a CAS procedure at the study sites.⁸ Also, additional data related to clinical and angiographic risk factors were collected in the randomized phase but were not captured in the lead-in phase.⁸ CREST and the International Carotid Stenting Study (ICSS) trials are in progress and are expected to provide greater insight on the clinical effectiveness of CAS compared with CEA.

The literature search did not identify any economic evaluations conducted in Canada, so the relevance of the economic evaluations from other countries to the Canadian health care system may be limited.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The results of the clinical outcomes in the selected studies varied. One meta-analysis found similar rates of MI and mortality, but higher stroke rates for octogenarians in the CAS group compared with the CEA group.⁹ CAS was associated with a greater recurrent carotid stenosis and re-stenosis rates compared with CEA across all studies included in one systematic review,⁵ and a positive correlation between women and risk of carotid artery stenting or stroke was not identified in one RCT.⁸ One meta-analysis reported differences in the stroke or death rate between both groups.⁶ The relative risk of patient adverse events and MI rate were significantly higher for CAS compared with CEA.⁶ The economic evaluations suggested that CAS had a higher average cost compared with CEA.⁹,¹⁰

According to the current literature, CAS is associated with an increased risk of stroke, MI, recurrent carotid stenosis, and re-stenosis and patient adverse events and higher average costs compared with CEA. Two large RCTs are on-going, and their results have not been published. It is a challenge to draw solid conclusions on the clinical effectiveness of CAS compared with CEA for carotid artery stenting based on the available evidence and limited experience with the CAS procedure.¹¹

PREPARED BY:
Julie Polisena, MSc, Research Officer
Raymond Banks, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


APPENDIX 1: Key Clinical Findings of Randomized Trials

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Design</th>
<th>Patients Characteristics</th>
<th>Clinical Findings</th>
</tr>
</thead>
</table>
| CAVATAS (2005) | Multi-center randomized trial | ● CAS=251 patients* and CEA or patients who received endovascular treatment =253 patients
● Number of symptomatic patients: CAS = 246 patients (97%) compared with CEA = 242 patients (96%)
● Mean carotid artery stenosis: CAS = 86.4% ± 9.1% compared with CEA = 85.1% ± 10.2%
● Mean follow-up (IQR): CAS = 1.95 (1.0 to 2.2) years compared with CEA = 1.98 (1.0 to 2.8) years | ● Death or disabling stroke in any vascular territory or ipsilateral stroke rate: CAS=14.3% compared with CEA=14.2% (number of events per group not reported)
● Severe (70% to 99%) of recurrent stenosis on ultrasonography at one year: CAS= 14% (n=25 patients) compared with 4% (n=7 patients) |
| Steinbauer et al. (2008) | Single-center randomized trial | ● CAS=43 patients and CEA=44 patients with >70% symptomatic carotid artery stenosis
● Mean follow-up: CAS = 66 ± 14.2 months compared with CEA = 64 ± 12.1 months | ● Ipsilateral stroke rate: [CAS=9.5% (4 of 42) compared with CEA= 0% (0 of 42)]
● Recurrent carotid stenosis (> 70%): [CAS=19% (6 of 32) compared with CEA=0% (0 of 29)]
● Reintervention rates for restenosis (> 70%): [CAS=16% (5 of 32) compared with CEA=0% (0 of 29)] |
| EVA-3S (2008) | Multi-center randomized trial | ● CAS=265 patients and CEA=262 patients
● All patients had a hemispheric or retinal TIA, retinal infarct, or nondisabling stroke within 120 days before enrolment | ● Rate of stroke or death within 30 days of procedure: Hazard ratio (HR)=1.97 (95% CI: 1.06 to 3.67) for CAS compared with CEA
● Rate of stroke or periprocedural death: HR=1.77 (95% CI: 1.03 to 3.02)
● Rate of any stroke or death: HR=1.39 (95% CI: 0.96 to 2.00) |
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Design</th>
<th>Patients Characteristics</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPACE (2008)</td>
<td>Multi-center randomized trial</td>
<td>• CAS=613 patients and CEA=601 patients with symptomatic carotid artery stenosis</td>
<td>Incidence of ≥70% recurrent carotid stenosis at two years:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intention-to-treat: (CAS=10.7% compared with CEA=4.6% (number of events per group not reported)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Per-protocol=(CAS=11.1% compared with CEA=4.6% (number of events per group not reported)</td>
</tr>
</tbody>
</table>

CAS=Carotid artery stenting; CI=Confident interval; IQR=Interquartile range; TIA=Transient ischemic attack

*Stents were used in approximately 25% of patients receiving endovascular treatment and 75% of these patients received balloon angioplasty alone.
APPENDIX 2: Relative Risk of Clinical Outcomes between CAS and CEA Procedures

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td><strong>Clinical outcomes measured in all selected trials</strong></td>
<td></td>
</tr>
<tr>
<td>Stroke or death rate 30 days after procedure</td>
<td>0.69 (0.45 to 1.07)</td>
</tr>
<tr>
<td>Stroke or death rate one year after procedure</td>
<td>0.88 (0.43 to 1.09)</td>
</tr>
<tr>
<td>Stroke or death rate 30 days after procedure among previously symptomatic patients</td>
<td>0.53 (0.30 to 0.95)</td>
</tr>
<tr>
<td>Mortality rate 30 days after procedure</td>
<td>0.79 (0.55 to 1.13)</td>
</tr>
<tr>
<td>Disabling stroke incidence 30 days after procedure</td>
<td>0.73 (0.47 to 1.14)</td>
</tr>
<tr>
<td>Non-disabling stroke incidence 30 days after procedure</td>
<td>0.65 (0.465 to 1.04)</td>
</tr>
<tr>
<td>Disabling stroke incidence 30 days after procedure with EPD</td>
<td>0.84 (0.55 to 1.13)</td>
</tr>
<tr>
<td>Disabling stroke incidence 30 days after procedure without EPD</td>
<td>0.70 (0.45 to 1.07)</td>
</tr>
<tr>
<td><strong>Clinical outcomes measures according to available data</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>4.96 (0.24 to 102.81)</td>
</tr>
<tr>
<td>Cervical or groin hematoma</td>
<td>5.13 (0.35 to 10.37)</td>
</tr>
<tr>
<td>Ipsilateral intracerebral bleeding</td>
<td>5.13 (0.60 to 43.77)</td>
</tr>
<tr>
<td>MI within 30 days of procedure</td>
<td>3.69 (1.28 to 10.67)</td>
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<tr>
<td>MI within one year of procedure</td>
<td>3.16 (1.04 to 9.58)</td>
</tr>
<tr>
<td>Cervical or peripheral nerve injury within 30 days of procedure</td>
<td>12.70 (4.82 to 33.48)</td>
</tr>
<tr>
<td>Bradycardial or hypotension within 30 days of procedure</td>
<td>0.08 (0.03 to 0.22)</td>
</tr>
<tr>
<td>Restenosis rate one year after procedure</td>
<td>0.28 (0.28 to 063)</td>
</tr>
</tbody>
</table>

CI=Confident interval; EPD=Embolic protection devices; MI=Myocardial infarction.