MINI-FOCUS: PERIPHERAL VASCULAR
Clinical Research

Carotid Angioplasty With Stenting Versus Endarterectomy
10-Year Randomized Trial in a Community Hospital

William H. Brooks, MD,* Michael R. Jones, MD,* Paula Gisler, PhD,*
Rick R. McClure, MD,† Timothy C. Coleman, MD,* Linda Breathitt, RN,*
Cheryl Spear, RN*

*Lexington, Kentucky

Objectives This single-center, randomized, clinical trial was designed to determine the 10-year comparative efficacy and durability of carotid angioplasty and stenting (CAS) versus carotid endarterectomy (CEA) in preventing ipsilateral ischemic stroke in symptomatic and asymptomatic patients with high-grade carotid artery stenosis.

Background Modern clinical trials with short-term follow-up indicate CAS and CEA are equivalent in reducing the risk for ipsilateral ischemic stroke secondary to carotid stenosis. A paucity of data exists regarding long-term outcomes.

Methods Patients of all surgical risks with symptomatic and asymptomatic carotid stenosis (>70%) were randomly selected for CEA or CAS and followed a minimum of 10 years.

Results Long-term follow-up was achieved in 173 patients (91%). Eighty-seven (50.2%) died within this period, most commonly of nonvascular causes. No difference in the risk of stroke ipsilateral to the treated artery was noted among treatment groups (p > 0.05). Restenosis determined by sequential ultrasound was assessed only in the CAS group (3.3%) and remained asymptomatic. The combined risk of fatal or nonfatal heart attack over the 10-year period was highest in individuals with symptomatic versus asymptomatic stenosis (27.5% vs. 11.0%; hazard ratio [HR]: 2.32, 95% confidence interval [CI]: 1.298 to 4.146, p = 0.005) and was higher in all patients treated with CEA (HR: 2.27, 95% CI: 1.35 to 3.816, p = 0.002).

Conclusions Long-term protection against ipsilateral stroke provided by CAS and CEA did not differ in this trial. The 10-year risk of fatal/nonfatal myocardial infarction was highest in all patients harboring symptomatic carotid stenosis at enrollment. The risk of fatal/nonfatal heart attack was significantly more prevalent in those symptomatic or asymptomatic patients randomized to CEA. (J Am Coll Cardiol Intv 2014;7:163–8) © 2014 by the American College of Cardiology Foundation
The durability of carotid endarterectomy (CEA) for revascularization of high-grade carotid stenosis as defined by protection against ipsilateral stroke and absence of restenosis is well established through a series of randomized, controlled trials (1–5). The ECST (European Carotid Study Trial) observed the 10-year risk of stroke after CEA was approximately 2% per year. Less than one-half of these were related to residual or recurrent disease in the treated artery (5). The Mayo Clinic reported the restenosis rate following successful CEA was 0.1%, with no strokes at an average of 7 years of follow-up (6). Although CEA has long been considered the preferred intervention for carotid occlusive disease, recent randomized clinical trials (RCT) have indicated that carotid angioplasty and stenting (CAS) may serve as a minimally invasive alternative with equivalency in providing protection against ipsilateral stroke (7–11). Whereas these studies have reported favorable short- and mid-term (3 to 5 year) results, longer-term data, similar to that available for CEA, are lacking. Thus, despite the satisfactory early results, concern remains about the long-term durability of CAS.

The initial results of the Kentucky trial were presented over a decade ago (7,8). In this prospective, randomized trial, patients of all surgical risk categories with symptomatic or asymptomatic carotid artery stenosis were offered randomization into CEA versus CAS treatment groups. The results indicated that a clinical equipoise exists between the 2 revascularization strategies at 30 days and at 48 months. Extending our initial findings, the current report compares the long-term (>10 years) durability and consequences of CAS with CEA in this randomized cohort of symptomatic and asymptomatic individuals with carotid artery stenosis.

### Methods

The inclusion and exclusion criteria, methodology, and initial results of the Kentucky RCT comparing CEA with stenting have been published (7,8). Briefly, all patients presenting with symptomatic or asymptomatic carotid stenosis from 1998 through 2002 meeting the inclusion or exclusion criteria were offered enrollment. No anatomic risk factors or concurrent medical conditions other than those contained in the exclusionary criteria were considered in treatment assignment (7,8). Embolic protection devices were not available at the initiation of this trial and thus were not used. These RCT were approved by the institutional review board. A neurologist (T.C.C.) and research nurse coordinators (L.B., C.S.) provided independent oversight and neurological examination at specific prescribed intervals. Sequential independent neurological examinations and Rankin and Barthel scorings were performed concurrent with duplex scanning. This RCT was designed specifically to assess the initial (30 days), intermediate (48 months), and long-term (>10 years) safety and efficacy of CAS and CEA in a community hospital.

The presence of extracranial atherosclerosis was established by a combination of duplex ultrasound (DUS) and cerebral angiography (7,8). Carotid DUS was assessed within 24 h of the index procedure and at 1, 3, 6, 12, and 24 months and thereafter at 12-month intervals for >10 years. The protocol for DUS included B-mode and angle-adjusted Doppler spectral imaging as standardized in the core ultrasound laboratory at Central Baptist Hospital, consistent with guidelines of the CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) (9). Data were obtained from the treated and untreated carotid artery. Throughout this study, DUS accuracy and uniformity was confirmed by correlation with carotid angiography performed in individuals admitted to the stroke service but not enrolled in this RCT. Recurrent stenosis (>70%) was determined and defined as development of internal carotid artery peak velocities >300 cm/s and internal carotid artery/common carotid artery ratio of >3 subsequent to and compared with a previous ultrasound examination that showed no evidence of stenosis. All cases suspected of restenosis were confirmed by cerebral angiography.

A standardized pre-randomization assessment of risk factors and a post-procedural medical protocol were prescribed for all patients that included maintenance of systolic blood pressure at or below 140 mm Hg as recorded during each office visit; platelet inhibition with 325 mg of aspirin plus 75 mg of clopidogrel; encouragement for cessation of smoking, and prescribing statin therapy regardless of serum cholesterol levels. No specific pharmacological protocol for managing blood pressure was mandated. Post-procedural protocol compliance was based on patient and family self-report.

Adverse clinical events were defined as any stroke of any severity regardless of location, symptomatic ischemic heart disease, and/or death from any cause. The cause of death or morbidity was confirmed through family contact and review of medical records.

### Statistical analysis

Kaplan–Meier survival curves were generated for all asymptomatic and symptomatic CAS and CEA groups as well as for combined CAS and CEA asymptomatic and symptomatic cohorts. For each subject, person–time days at risk were calculated for all strokes, ipsilateral stroke, all myocardial infarctions, and all combined vascular adverse events. Each of these variables included both fatal and nonfatal events. Values were
censored if patients were known to have survived beyond the period of observation in the trial. No values were censored because of patients lost to follow-up or unknown outcomes. Differences in Kaplan-Meier survival curves were analyzed for significance using the log-rank test ($p < 0.05$).

The impact of risk factors for each adverse event group was analyzed using Cox proportional hazards analysis with the proportionality of survival curves visually assessed. Hazard ratios (HR) were evaluated for significance based on $p$ values of $<0.05$ as well as 95% confidence intervals (CI).

Before all analyses, all groups were assessed for differences using chi-square test for independence for categorical variables, including treatment of hypertension, smoking, use of statins, and platelet inhibition and presence of coronary vascular disease. Cramer V values were used to test differences between procedure and symptom status groups. Pearson chi-square with continuity correction was used to test for differences between the CEA and CAS groups. One-way between-groups analysis of variance with Tukey post hoc test was used to test for significant differences in the continuous variable of age. SPSS statistical software (version 19.0, SPSS, Inc., IBM, Armonk, New York) was used to evaluate the data (12).

**Results**

Among the 189 patients initially enrolled in the Kentucky trials, 53 symptomatic patients and 41 individuals with asymptomatic carotid stenosis were assigned to endarterectomy and 51 patients with symptomatic stenosis and 44 asymptomatic individuals were treated by CAS (7,8). Within the initial reporting period, 1 symptomatic patient in the CEA group died from an immediate post-operative myocardial infarction. One patient randomized to CAS experienced transient cerebral ischemia (National Institutes of Health Stroke Scale <4) during the procedure, which resolved within 30 min. Sixteen patients withdrew. The remaining 173 (91%) patients were monitored sequentially for a minimum of 10 years (range 10 to 13 years). All groups with symptomatic and asymptomatic carotid stenoses were similar in age, ischemic heart disease, tobacco abuse, and use of statin and antiplatelet therapy ($p > 0.05$).

Within the follow-up period, 87 (50.2%) initially enrolled patients died; the majority (47 of 87; 54%) of which resulted from nonvascular conditions, such as malignancy or pulmonary disease. Death related to all strokes was uncommon (6 of 173; 3.5%) but slightly more prevalent in the CAS group (5 of 90; 5.7%) than those undergoing CEA (1 of 83; 1.1%). However, only 1 of these, occurring 7 years after the indexed procedure, was ischemic and ipsilateral to the treated artery. All others (4) were hemorrhagic, contralateral to the treated artery, or vertebral-basilar in distribution, and hence, unrelated to the procedure (Table 1). Furthermore, although nonfatal ischemic strokes were observed only in those assigned to CAS, none occurred in the distribution of the indexed carotid artery.

Ischemic cardiac disease was implicated in 39% (34 of 87) of all observed deaths. The occurrence of fatal and nonfatal ischemic heart disease was more commonly associated with CEA (HR: 2.27; 95% CI: 1.35 to 3.815; $p = 0.002$) (Fig. 1) and those enrolled with symptomatic stenosis when compared with asymptomatic individuals (HR: 2.32; 95% CI: 1.298 to 4.146; $p = 0.005$) (Fig. 2). Both asymptomatic and symptomatic groups randomized to CAS fared far better for all myocardial events than those undergoing CEA in the context of time from the periprocedural period throughout the 10-year follow-up ($p = 0.001$) (Fig. 3).

Restenosis as defined by the DUS criteria of an internal carotid artery/common carotid artery ratio $>3.0$ and peak systolic velocity of $>300$ m/sec was remarkably infrequent (data not shown). Those that did occur ($n = 3$) were confirmed by angiography at 5, 8, and 9 years after intervention and were successfully treated with angioplasty without complication. All lesions were smooth without ulceration and asymptomatic. No stenosis of $>80\%$ was observed in the CEA group. No stenosis $>70\%$ as defined by DUS was noted to occur in the contralateral untreated artery of any group (data not shown).

In addition to sequential neurological examination and serial DUS determinations, protocols were designed to identify and modify risk factors associated with vascular disease. Age, at time of enrollment, was found not to be a risk factor for any adverse outcome ($p = 0.07$). The presence of hypertension (HR: 3.872; 95% CI: 1.196 to 12.537; $p = 0.02$) and cardiovascular disease (HR: 10.014; 95% CI: 2.435 to 41.178; $p = 0.001$) at time of enrollment were significant risk factors for all adverse advents in all groups. The attempt to aggressively modify these factors and use of statin therapy did not lessen the occurrence of restenosis or adverse events of any group ($p > 0.05$).

Overall, the combined risk for and incidence of stroke ipsilateral to the treated artery and myocardial infarction was most common in symptomatic patients randomized

<table>
<thead>
<tr>
<th>Table 1. Mortality and Morbidity From Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths from stroke</strong></td>
</tr>
<tr>
<td>CEA ($n = 1$):</td>
</tr>
<tr>
<td>6 years from index procedure: hemorrhagic, contralateral</td>
</tr>
<tr>
<td>CAS ($n = 5$):</td>
</tr>
<tr>
<td>1. 7 years from index procedure: ischemic; ipsilateral</td>
</tr>
<tr>
<td>2. 8 years from the index procedure: ischemic; vertebral basilar</td>
</tr>
<tr>
<td>3. 9 years from index procedure: hemorrhagic; contralateral</td>
</tr>
<tr>
<td>4. 9 years from index procedure: ischemic; vertebral basilar</td>
</tr>
<tr>
<td>5. 10 years from index procedure: ischemic; contralateral</td>
</tr>
<tr>
<td><strong>Nonfatal strokes</strong></td>
</tr>
<tr>
<td>CEA: 0 of 83</td>
</tr>
<tr>
<td>CAS: 4 of 90</td>
</tr>
</tbody>
</table>

CAS = carotid angioplasty and stenting. CEA = carotid endarterectomy.
to CEA (HR: 5.702; 95% CI: 2.293 to 14.18; p = 0.001) followed by symptomatic individuals treated by CAS (HR: 3.996, 95% CI: 1.58 to 10.102, p = 0.003) (Fig. 4).

The risk and incidence of similar events was markedly less in asymptomatic individuals, yet still more prevalent in those randomized to CEA (HR: 2.27; 95% CI: 1.35 to 3.816; p = 0.002).

Discussion

Although RCT indicate that the early and intermediate-term safety and effectiveness of CAS is similar to CEA in restoring carotid artery patency and stroke prevention, the critical issues of long-term durability and efficacy of carotid artery stenting in the context of ipsilateral stroke prevention, patency, and consequences remain largely unknown. This trial provides the first long-term evidence that CAS and CEA are not only equally effective, but also durable in ipsilateral stroke prevention in individuals harboring high-grade stenoses (>70%). Overall, no significant differences were identified in the occurrence of ipsilateral stroke between those randomized to CEA or CAS (p > 0.05). Age, smoking, and statin use did not lessen the risk for an adverse event in any cohort. However, the risks and clinical outcomes in the context of both fatal/nonfatal stroke and ischemic heart disease are strongly associated with the presence of symptomatic carotid stenosis at the time of enrollment and intervention. Accordingly, individuals undergoing intervention for asymptomatic stenosis carry significantly less risk for late cerebral and/or cardiac adverse events when compared with those presenting with symptoms of carotid stenosis. Furthermore, the risk for the occurrence of any adverse event was less in those individuals randomized to CAS than in those treated by CEA (HR: 1.649, 95% CI: 1.025 to 2.653, p = 0.039).

Shorter-term trials comparing stenting with endarterectomy have shown that troponin and/or other cardiac biomarker release, consistent with procedurally related myocardial injury, is more common during endarterectomy than with stenting (9,13). Although largely asymptomatic and unassociated with diagnostic electrocardiographic changes, these markers have been shown to be a negative prognostic indicator in terms of increased risk for subsequent ischemic heart disease (14,15). Although cardiac biomarkers were not assessed in this trial, both asymptomatic and symptomatic groups randomized to CAS fared better than their cohort undergoing CEA in the context of lessened incidence and risk for myocardial infarction, thereby suggesting that cardiac biomarker “leak” associated with CEA may indeed carry long-term clinical significance. Indeed, the increased risk for myocardial ischemia subsequent to CEA extended throughout the 10 years of this trial. The increased risk for myocardial infarction in symptomatic versus asymptomatic patients is poorly understood, but it is likely consistent with
the concept that atherosclerosis may be present as a generalized, inflammatory disorder (16, 17).

Whereas CEA has been associated with an increased risk for subsequent cardiac ischemia, CAS is correlated with an increased risk of procedurally related strokes (9, 10) and an increased number of ischemic alterations in the brain demonstrated by magnetic resonance imaging (18). No differences between the procedures in the risk and/or incidence of ipsilateral stroke were found in this composite trial. Nevertheless, the overall occurrence of any cerebrovascular event was more prevalent in the CAS group. The link between late hemorrhagic and vertebral-basilar stroke and CAS was not attributable to enrollment risk factors or specific anatomic factors noted at the time or subsequent to the procedure and, thus, remains problematic. The initial report of this trial indicated that no differences in the generation of ischemic changes were observed on fluid-attenuated inversion recovery sequence magnetic resonance imaging of individuals in either group (7). However, the relevance and importance of an increase in asymptomatic ischemic changes in the brain subsequent to CAS in other studies using more sensitive diffusion-weighted magnetic resonance imaging should not be dismissed (19). Despite initial observations that these alterations may be asymptomatic, the long-term sequelae of silent ischemia of the brain are not known. Thus, whereas this RCT has shown the long-term efficacies of CAS and CEA in preventing ipsilateral stroke are similar, the even longer-term, more subtle consequences of these procedures on brain function or manifestations of ischemic heart disease, respectively, remain problematic. These collective observations are particularly cogent when considering intervention for individuals who harbor asymptomatic carotid stenosis, given the results of contemporary medical management of occlusive vascular disease and where the risk of ipsilateral cerebral ischemic events are predicted to occur with a very low frequency (20, 21).

Prevention of ipsilateral stroke is the ultimate goal of any treatment for critical carotid stenosis. However, durability, defined as patency determined by DUS, may also serve to define therapeutic utility. Accordingly, it is inferred that progressive stenosis carries increased risk for ipsilateral stroke. Durability associated with CEA is well documented, although the direct association of restenosis and incipient stroke remains unknown. Restenosis of the carotid artery following CEA ranges from 8.8% to up to 19%, yet only 0.6% to 3.6% of these become symptomatic (22, 23). Indeed, it is suggested that long-term surveillance of CEA using DUS is unnecessary (24). In view of our observation that the risk of restenosis is very small and remained asymptomatic, occurring at a rate of 0.3% per year, sequential DUS also may not be necessary for CAS. This finding is consistent with shorter studies of CAS in which a low frequency of in-stent stenosis is reported, and all individuals remained asymptomatic (25–28).
Study limitations. The small sample size—particularly with regard to the incidence of fatal and nonfatal stroke—is a limitation. Though the data for stroke were statistically analyzed and showed no difference across procedure, symptom status, or modification of risk factors, the single-digit stroke sample size impairs the validity of the statistical analysis. However, this does not detract from the overall implications supported by ipsilateral stroke data. Finally, because the study was confined to 1 center where the same small number of highly experienced physicians performed all aspects of the protocol, this study lacks the skill variability seen in multicenter studies that marks more-typical practice. Thus, this may limit this study’s external validity.

The strengths of the study are that there were remarkably little patient attrition (91%) over the 10 years. Similarly, the same physicians and research coordinator were present throughout the 10-year study, enhancing data reliability and integrity. Finally, this is the first RCT designed to compare the long-term (10-year) efficacy and durability of carotid stenting and endarterectomy.

Conclusions

The collective data from this long-term trial clearly suggest that CAS and CEA are equally effective in long-term prevention of ipsilateral ischemic stroke. Furthermore, these observations suggest CAS may be superior in the context of overall, long-term event-free survival.

Reprint requests and correspondence: Dr. William H. Brooks, Neurosurgical Associates, Baptist Health Lexington, 1780 Nicholasville Road, Lexington, Kentucky 40503. E-mail: william.brooks@bhsi.com.

REFERENCES


Key Words: carotid endarterectomy n carotid stenting n prevention of stroke n 10-year randomized trial.