Are Distal Protection Devices ‘Protective’ During Carotid Angioplasty and Stenting?

Tiziano Tallarita, MD; Alejandro A. Rabinstein, MD; Harry Cloft, PhD; David Kallmes, MD; Gustavo S. Oderich, MD; Robert D. Brown, MD; Giuseppe Lanzino, MD

Background and Purpose—To evaluate the periprocedural outcome after carotid artery stenting with embolic brain protection (EBP+) versus without embolic brain protection (EBP−).

Methods—We retrospectively reviewed data from a prospective nonrandomized database of 357 patients who underwent carotid artery stenting in the neuroradiology division of our institution from 1999 to 2009. One hundred five patients underwent angioplasty and stenting without distal protection, whereas 252 were treated with distal protection. Patients were analyzed according to their EBP status (+ or −) for the primary end points of perioperative stroke, death, or myocardial infarction.

Results—Unprotected stenting was mostly performed in the early years of this study and this is reflected in significant baseline differences between the two groups. In our earlier experience, carotid artery stenting was used in patients with more significant comorbidities. Diabetes mellitus (P=0.04), previous coronary artery disease (P=0.02) and myocardial infarction (P=0.04), and symptomatic lesion (P=0.01) were significantly more common in the EBP− cohort. Despite these baseline differences, there were no significant differences in the primary end points (2% in the EBP+ group and 4.8% in the EBP−, P=0.15). The incidence of ipsilateral stroke in the EBP− and in the EBP+ group was 3.8% versus 0.8%, respectively (P=0.6). There were 2 perioperative deaths (1 in each group) and 4 myocardial infarctions (3 in the EBP+ arm and 1 in the EBP− arm, all non-Q infarcts; P=nonsignificant).

Conclusions—In accordance with recent literature, this series cast doubts as to the real effectiveness of distal embolic protection devices in reducing periprocedural complications. (Stroke. 2011;42:1962-1966.)

Key Words: carotid artery stenting ■ carotid stenosis ■ complications ■ distal protection devices ■ thromboembolic complications ■ carotid stenosis

Recent advances in endovascular techniques have added a feasible alternative to conventional surgical repair for the management of carotid diseases. Percutaneous carotid artery stenting (CAS) has the potential of being minimally invasive, less traumatic, and safer in patients with high surgical risk than carotid endarterectomy.1–3 The main limitation of CAS is the risk of distal cerebral embolization caused by mobilization and migration of plaque fragments. Although cerebral protection devices have been developed and are widely used to prevent periprocedural cerebral embolization, their application may result in additional complications.4 There are only 2 very small randomized studies that have evaluated the efficacy of such devices.5,6 These studies have suggested that protection devices may not be effective in reducing perioperative distal emboli and arguments have been formulated against their routine use.7,8 We reviewed our experience with >350 consecutive CASs and compared the incidence of perioperative complications in patients treated with and without distal protection.

Methods

We performed a retrospective review from a prospective database of consecutive CAS procedures done in the Neuroradiology Suite at the Mayo Clinic, Rochester, MN, from March 1999 to October 2009. Patient evaluation, intervention, and periprocedural evaluation were carried out by a team of radiologists, interventional neuroradiologists, neurosurgeons, and vascular surgeons. Patients with recurrent lesion after previous CAS were excluded. All CAS procedures were divided into 2 groups, protected embolic brain protection (EBP+) and nonprotected (EBP−) arms, on the basis of the use of the distal embolic brain protection device.

Patients were considered symptomatic if they had an ipsilateral amaurosis fugax or transient or persistent focal symptoms felt to be caused by cerebral ischemia. Data were collected regarding various risk factors, including preoperative renal insufficiency defined as a serum creatinine value >1.3 mg/dL; coronary artery disease defined on the basis of an abnormal stress test, previous myocardial infarction on electrocardiography, or a history of coronary artery revascularization (open or percutaneous); chronic obstructive pulmonary disease identified on pulmonary function studies or ongoing need for an inhaler or steroid treatment. Diabetes, hyperlipidemia, hypertension, and congestive heart failure were identified in patients undergoing active medical or dietary treatment.
Pulmonary complications were defined as ventilator dependence for alteration on telemetry during the intensive care unit stay. Transient using North American Symptomatic Carotid Endarterectomy Trial age stenosis was based on the angiographic findings and calculated for distal protection in 24 cases. In the EBP arm, postdilatation alone and primary stenting were performed significantly more frequent than in the EBP+ arm (P=0.01 and P<0.001, respectively) reflecting different operators’ preference. The prestenting dilatation and pre- and poststenting dilations were used with similar frequency in the 2 groups. The percentage of residual stenosis after the procedure (divided into 3 levels, 1<20%; 2=20% to 40%; 3>40%) was not different between the 2 groups.

Morbidity and Mortality
Periprocedural ipsilateral stroke, MI, and mortality are presented in Tables 3 and 4. The overall stroke rate was 1.7% (patients with symptomatic carotid stenosis, 2.4%; patients with asymptomatic carotid stenosis, 1.1%). Two of the 6 strokes were related to acute in-stent thrombosis, and the others were considered to be the result of embolism. Among

### Table 1. Patients’ Demographics, Risk Factors, and Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>EPD+, No. (%)</th>
<th>EPD−, No. (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>71±9</td>
<td>70±10</td>
<td>0.3</td>
</tr>
<tr>
<td>Male</td>
<td>180 (71)</td>
<td>69 (66)</td>
<td>0.6</td>
</tr>
<tr>
<td>Female</td>
<td>72 (29)</td>
<td>36 (34)</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
<td>105 (42)</td>
<td>63 (60)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>220 (87)</td>
<td>90 (85)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>204 (81)</td>
<td>82 (78)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>69 (28)</td>
<td>40 (39)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoker</td>
<td>82 (32)</td>
<td>38 (36)</td>
<td>0.3</td>
</tr>
<tr>
<td>CHF</td>
<td>23 (9)</td>
<td>13 (12)</td>
<td>0.3</td>
</tr>
<tr>
<td>CAD</td>
<td>150 (60)</td>
<td>59 (55)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous MI</td>
<td>64 (25)</td>
<td>38 (36)</td>
<td>0.04</td>
</tr>
<tr>
<td>COPD</td>
<td>57 (23)</td>
<td>23 (22)</td>
<td>0.9</td>
</tr>
<tr>
<td>CRI</td>
<td>58 (23)</td>
<td>33 (31)</td>
<td>0.1</td>
</tr>
<tr>
<td>PAD</td>
<td>54 (21)</td>
<td>25 (24)</td>
<td>0.7</td>
</tr>
<tr>
<td>Tumors</td>
<td>69 (27)</td>
<td>36 (35)</td>
<td>0.2</td>
</tr>
<tr>
<td>Recurrent stenosis</td>
<td>57 (23)</td>
<td>23 (22)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

EPD+ indicates embolic protection device used; EPD−, embolic protection device not used; CHD, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; PAD, peripheral artery disease.

Significant stenosis requiring treatment was considered a stenotic lesion >50% in symptomatic patients or >80% in asymptomatic patients. Patient characteristics are summarized in Table 1.

### Primary and Secondary End Points

The primary study end points were periprocedural stroke, myocardial infarction, and death; secondary end points included acute carotid thrombosis, major renal, pulmonary, or cardiac complications, and intensive care unit and hospital length of stay. Stroke was diagnosed on the basis of new neurological deficit. Renal function impairment after stenting was defined as a serum creatinine concentration >1.3 mg/dL in patients with previous normal renal function or an increase >0.2 mg/dL in patients with preprocedural renal insufficiency, measured during the hospital period. Cardiac complications, which included myocardial infarction (MI) and arrhythmias, were defined by clinical symptoms associated with elevation of biochemical markers and electrocardiography findings. Arrhythmia was defined as pulse rate <60 beats/min or >100 beats/min or persistent rhythm alteration on telemetry during the intensive care unit stay. Transient arrhythmias occurring during the procedure were not considered. Pulmonary complications were defined as ventilator dependence for >6 hours after the procedure, need of postoperative intubation, clinical data or culture confirmation of pneumonia, or the need of tracheostomy. Abnormal SpO2 was defined as a value of oxygen saturation <90% measured with pulse oximeter.

### Technique

Patients were premedicated with 75 mg clopidogrel per day and 325 mg aspirin per day starting 5 days before the procedure or given a loading dose immediately before the procedure and continued for a minimum of 4 weeks. The procedure was performed under local anesthesia and this permitted careful clinical assessment during each step. However, general anesthesia was preferred in a few cases of uncooperative patients or when difficult and tortuous proximal anatomy made catheterization challenging. Brachiocephalic angiography with intracranial views always preceded stenting. The percentage stenosis was based on the angiographic findings and calculated using North American Symptomatic Carotid Endarterectomy Trial (NASCET) method in all cases. When the distal protection tech-
patients who experienced embolic stroke, 3 were treated with pre- (before stenting) dilatation alone (1 in protected CAS and 2 in nonprotected CAS) and 1 underwent postdilatation alone (nonprotected group) and the difference was not significant (P=0.09).

Stroke rate was higher in patients with symptomatic carotid disease in both groups (EBP+: symptomatic, 1.0%; asymptomatic, 0.7%; EBP−: symptomatic, 4.75%; asymptomatic, 2.4%), but these differences were again not statistically significant.

Overall mortality was 0.6% (symptomatic, 0.6%; asymptomatic, 0.5%). The difference in mortality between the EBP+ group (0.4%) and EBP− group (0.95%) was not significant. The low event rate (n=2) did not allow further statistical analysis of predictors of postoperative death. Four myocardial infarctions were observed (all non-Q wave). Three (1.2%) occurred in the EBP+ and 1 (1.0%) in the EBP− group (P=nonsignificant).

When only patients treated with distal filter devices were considered (n=228), the stroke rate was 0.8% versus 3.8% in the nonprotected CAS group (P=0.08). There were 3 MIs (1 less than in all protected CASs) and the overall stroke/death/MI was 1.7% (2% in all protected CASs). When compared with the nonprotected (EPD−) group, the primary combined end point of stroke/death/MI was not statistically significant (P=0.15). Temporary or permanent increases of serum creatinine concentration were seen in 6 patients in the EBP+ arm and in 9 patients in the EBP− arm (P=nonsignificant). The incidence of restenosis after the procedure was mildly higher in the EBP+ than in the EBP− (P=0.054). Hospital length of stay was 2.1±2.5 days and 2.3±2.6 days (P=nonsignificant) in protected and unprotected arms, respectively. Finally, intensive care unit stay was longer in the unprotected group than in the EBP+ group (Table 5). Other minor adverse events included groin hematoma (EBP+: 2% versus EBP−: 2.9%; P=nonsignificant), confusion after procedure (EBP+: 1.6% versus EBP−: 6%; P=0.027), arrhythmia (EBP+: 3.7% versus EBP−: 6.1%; P=nonsignificant), and abnormal Spo2 (EBP+: 29.6% versus EBP−: 48.6%; P=0.003).

Clinical Predictors
Age ≥70 years was significantly associated with 2.1-fold increase in stroke when considering all cases combined. We found no other variable to be associated with the risk of stroke.

Discussion
Distal protection devices have become “standard of care” during angioplasty and stenting for carotid artery stenosis. These devices “… appear seductively simple, elegant, and beneficial to both physician and patients,”10 yet there is no strong evidence that distal protection is effective in reducing the incidence of thromboembolic complications during CAS.6,11–17 We found no significant differences in the incidence.
idence of perioperative stroke, MI, and death rates between patients treated with or without distal protection. There was a slightly higher incidence of perioperative strokes in the nonprotected group, which did not reach statistical significance. The EBP+ group reflected mostly our early experience (including the very first cases) with devices not specifically designed for use in the carotid system and less operator experience (1999 to 2003; Figure). Moreover, symptomatic status (a known risk factor for periprocedural ischemic complications18,19) was significantly more common in the EBP+ group (60% versus 42%, \( P < 0.01 \)).

During CAS, there is a real risk of dislodging microemboli after each stage of the procedure (crossing the lesion, prestent angioplasty, stenting, and poststent angioplasty).20 Protection devices have been designed in an attempt to reduce the risk of distal microemboli. The concept is theoretically very appealing, but in practice, there are several factors limiting the true efficacy of distal protection. The first is the need to cross the lesion before protection is achieved. The second drawback is related to the stiffness of these devices, which makes navigation through the stenosis challenging, especially in the presence of proximal and/or distal (to the stenosis) tortuosity (very common in patients with atherosclerotic disease). The filter “recatch” phase is another potential generator of distal emboli.21 Despite adequate restoration of carotid lumen after CAS, it is possible that the “bulky” protection device may dislodge plaque debris protruding through the stent struts during the retrieval phase.

In the absence of Class I evidence, indirect observational studies—often with historical controls—initially supported the use and suggested potential efficacy of distal protection during CAS.12,22 However, more recent and stronger data have questioned the effectiveness of distal protection. A subanalysis of pooled data from multicenter trials of CAS for symptomatic stenosis (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis [EVA-3S], Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy [SPACE]) failed to show a clear benefit of “protected” versus unprotected CAS in reducing periprocedural ipsilateral ischemic events.16,23 Similarly, in the recent International Carotid Stenting Study (ICSS),17 the rate of stroke in the group treated with protection devices was higher (5.1%) than in the group in which no protection was used (2.4%). In this same study, the rate of MRI diffusion-weighted abnormalities after CAS was also higher in the protected group. Finally, Tietke et al24 retrospectively analyzed 358 unprotected CAS, reporting a very low (2%) rate of periprocedural stroke suggesting that “safe” CAS can be performed without such adjuncts. Our observation is in line with the conclusions of these studies questioning the efficacy of these devices.

To avoid some of the problems encountered with “filter-type” protection devices, other concepts have been proposed to reduce the incidence of distal emboli. Flow reversal can be achieved with a triple lumen-guiding balloon catheter with an additional distal occlusion balloon. Flow is arrested through the common carotid artery by inflating the balloon catheter and reversed by occluding the external carotid with the distal balloon. The reversed flow is directed through the guiding catheter, which is externally connected to a blood-filtered femoral vein line.25 Although appealing, superiority of flow-reversal devices over “filter types” has not been tested in a randomized study.

Among patients with asymptomatic carotid stenosis, the risk of stroke or death was 1.3% with EBP and 2.4% without EBP, which could be higher than with modern intensive medical therapy alone. However, our asymptomatic patients undergoing the intervention were a selected population and these often had progression of plaques despite aggressive medical treatment. Whether stenting or endarterectomy can be justified for patients with asymptomatic stenosis is currently a matter of debate.26,27 Future studies of endarterectomy or stenting in asymptomatic stenosis should have a medical arm.

Our study has several limitations. Nonprotected stenting was mainly performed in the first phase of the institutional experience with operators having different backgrounds, techniques, and levels of experience. However, in theory, these differences should have been an advantage for the protected group because distal protection was used almost
routinely in the most recent part of the experience when operators had already acquired greater expertise in CAS and patients undergoing CAS were not as complicated (in terms of significant comorbidities) as was commonly the case in the early years of CAS. Moreover, this is the largest single-center study comparing protected and unprotected CAS to our knowledge with precise criteria of data collection and independent vascular neurologist assessment of most patients, resulting in high-quality and a large spectrum of information for each patient.

Conclusions

In line with recent experience, our observation questions the real efficacy of routine distal protection during CAS. It is likely that improved technology and the design of refined distal protection devices in the near future may overcome some of the current limitations. Given the large number of CAS procedures already being performed in North America and the likely increase in the use of this revascularization technique after the publication of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) results, these observations call for a well-designed multicenter study to determine the value of distal protection in CAS.

Disclosures

None.

References


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Stroke. 2011;42:1962-1966; originally published online May 12, 2011;
doi: 10.1161/STROKEAHA.110.607820

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Abstract 3

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Key Words: carotid artery stenting ■ carotid stenosis ■ complications ■ distal protection devices ■ thromboembolic complications ■ carotid stenosis

Background and Objectives

The use of distal protection devices in endovascular carotid artery stenting (CAS) for the prevention of stroke and death has been a matter of controversy. The effectiveness of these devices has not been rigorously established. In this study, we compared the safety and effectiveness of a mechanical distal protection device versus balloon occlusion plus embolic protection.

Methods

We performed a randomized, multicenter, single-blind, noninferiority trial in 3,400 patients with a 90% power to detect a 0.05absolute difference in the noninferiority margin. All patients were intended to undergo CAS. The primary end point was stroke or death during CAS. The primary end point was stroke or death during CAS. We used a 1:1 randomization scheme to assign patients to one of two groups: either carotid artery stenting plus mechanical distal protection device (Group D, n = 1,700) or carotid artery stenting plus balloon occlusion plus embolic protection (Group E, n = 1,700).

Results

There were no significant differences between the two groups with respect to the primary end point (95% confidence interval: -0.04 to 0.09; P < 0.001). The rate of stroke or death during CAS was lower in Group D than in Group E (0.08% vs 0.12%; P = 0.73). The rate of ipsilateral stroke or death during CAS was lower in Group D than in Group E (0.08% vs 0.12%; P = 0.73). The rate of contralateral stroke or death during CAS was lower in Group D than in Group E (0.08% vs 0.12%; P = 0.73).

Conclusion

The results of this trial suggest that mechanical distal protection devices during CAS may be as safe and effective as balloon occlusion plus embolic protection. Further studies are needed to confirm these findings.
### Table 3. Major Adverse Events After Carotid Artery Stenting for Patients Who Underwent Protected CAS Compared With Nonprotected CAS

<table>
<thead>
<tr>
<th>Event</th>
<th>EPD+ (N=252, %)</th>
<th>EPD− (N=105, %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/death/MI</td>
<td>5 (2)</td>
<td>5 (4.8)</td>
<td>0.2*</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4)</td>
<td>1 (0.95)</td>
<td>0.5*</td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>2 (0.8)</td>
<td>4 (3.8)</td>
<td>0.06*</td>
</tr>
<tr>
<td>MI</td>
<td>3 (1.2)</td>
<td>1 (0.95)</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

EPD+ indicates embolic protection device used; EPD−, embolic protection device not used; MI, myocardial infarction.

*Fisher exact test used.

### Table 4. Major Outcomes in Symptomatic and Asymptomatic Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Asymptomatic No. (%)</th>
<th>Symptomatic No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPD− (n=147)</td>
<td>EPD− (n=42)</td>
</tr>
<tr>
<td>Stroke/death/MI</td>
<td>3 (2.1)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.7)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>MI</td>
<td>2 (1.4)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

| Event             | EPD+ (n=105)          | EPD− (n=63)         | P      |
| Stroke/death/MI   | 2 (1.9)               | 3 (4.75)            | 0.4*   |
| Stroke            | 1 (0.95)              | 3 (4.75)            | 0.2*   |
| MI                | 1 (0.95)              | 0 (0)               | 1.0*   |
| Death             | 1 (1.6)               | 1 (1.6)             | 0.4*   |

EPD+ indicates embolic protection device used; EPD−, embolic protection device not used; MI, myocardial infarction.

*Fisher exact test.

### Figure
Distribution of carotid artery stenting (CAS) according to the use of an embolic brain protection device.