Carotid revascularization outcomes comparing distal filters, flow reversal, and endarterectomy

Luke P. Brewster, MD, PhD,a Robert Beaulieu, BS,a Matthew A. Corriere, MD,a Ravi Veeraswamy, MD,b Khosrow A. Niazi, MD,b Gregory Robertson, MD,b Thomas F. Dodson, MD,a and Karthik Kasirajan, MD,a Atlanta, Ga

Introduction: Contradictory outcomes exist for different methods of carotid artery revascularization. Here we provide the comparative rates of adverse events in patients after carotid endarterectomy (CEA), carotid artery stenting (CAS) with a distal embolic protection device (EPD), and CAS with a proximal flow reversal system (FRS) from a single institution by various specialists treating carotid artery disease.

Methods: Procedural billing codes and the electronic medical records of patients undergoing revascularization for carotid artery stenosis from February 2007 through March 2010 were used for data collection. Primary outcome was the incidence of cerebrovascular accident (CVA), myocardial infarction (MI), or death after CEA and CAS. Each practitioner determined the choice of therapy, with five of the 14 specialists providing both CAS and CEA. Baseline characteristics were examined for effect on outcome. Planned comparisons between and within groups were analyzed using χ², t tests, and analysis of variance, as appropriate.

Results: A total of 495 procedures were documented, comprising 226 CEA, 216 CAS with EPD, and 53 CAS with FRS. Preoperative comparisons of patient comorbidities were similar among the cohorts. The carotid artery stenosis was symptomatic in 42% of these patients. Prior CEA was an indication for CAS rather than another CEA (P < .001). Significantly fewer patients undergoing CEA were receiving preoperative antiplatelet therapy (P < .001). The groups did not differ significantly in the overall composite end point of death, CVA, and MI (4%, 5.1%, 0%; P = .1) or any individual major adverse event. Overall, patients undergoing CAS with EPD had a statistically significant greater incidence of minor CVAs than CEA patients (P = .031), which was driven by the increased CVA risk for asymptomatic patients. Secondary end points occurred rarely (<2%). There have been no reoperations or interventions in these patients to date within this institution.

Conclusions: We have established a similar and low incidence of MI, CVA, and death among patients undergoing CEA and CAS, of whom approximately 40% were symptomatic. FRS provided superior results in this series; however, its use was limited to 20% of the CAS procedures. Still, zero adverse events in this cohort make FRS an exciting technology that warrants a large-scale prospective comparative study. (J Vasc Surg 2011;54:1000-5.)

Contradictory results and conclusions have recently been published with respect to carotid artery revascularization as a therapy for carotid artery stenosis. Surgical management of significant carotid artery disease, defined historically by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS), currently remains the gold standard for reducing the risk of a subsequent cerebrovascular accident (CVA).1,2 However, tradeoffs exist when deciding between carotid endarterectomy (CEA) or carotid artery stenting (CAS). Despite several large, multicenter trials that have been conducted to determine the risks and benefits of each procedure, the literature remains unclear about the absolute benefit of one procedure over the other.3-8

Recent data from the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) demonstrate an increased risk of CVA among patients undergoing CAS compared with CEA (4.1% vs 2.3%) and a decreased risk of myocardial infarction (MI) in CAS compared with CEA (1.1% vs 2.3%), leading to similar outcomes when combining death, MI, and CVA events.9 Further confounding broad consensus is the applicability of these superior results to practices outside the trial sites by physicians who prefer one mode of therapy rather than the other.

In addition, the technology used with CAS has advanced tremendously during the past decade, including increased familiarity of practitioners with the technique and the advent of new stents and distal protection devices making randomized controlled trials studies of the past, rather than present. CREST, in particular, used one distal protection device that has subsequently been modified. Hospital databases at high-volume institutions may provide more rapid dissemination of results as well as aligning results with physician behaviors to provide a real-world experience to more completely understand competing therapies.
The aim of this study was to investigate comparative rates of adverse events in patients after CEA, CAS with a distal embolic protection device (CAS + EPD), and CAS with a proximal flow reversal system (CAS + FRS) at a single institution by various specialists (vascular surgeons, cardiologists, and neurosurgeons) who treat carotid artery disease. Given the diversity of specialties represented, the large number of patients undergoing therapy, and the use of a new technology (ie, CAS + FRS), this study is unique in the literature and provides real-world insight into the expected benefits and limitations of both CAS and EPD and FRS, which will be useful to clinicians when they choose the therapy that is best suited to their patients.

**METHODS**

Institutional Review Board approval was obtained to retrospectively review our institution’s collective experience with CEA, CAS + EPD, and CAS + FRS between February 2007 and March 2010. Electronic medical records, procedural billing codes, and clinical visit documentation were analyzed and compiled into an Access database (Microsoft Corp, Redmond, Wash). Preoperative demographics collected included age, sex, renal function hypertension, diabetes mellitus, hyperlipidemia, smoking history, history of MI and CVA, preoperative antiplatelet regimen, and history of carotid revascularization. Disease-specific characteristics included presence of symptoms (as defined by NASCET criteria and physician judgment), degree of stenosis, methods of imaging, and postoperative follow-up course. In most patients, the degree of stenosis was quantified by a procedural arteriogram for CAS and by duplex ultrasound imaging for CEA. The individual practitioners chose the therapy, with five of the 14 specialists providing both CAS and CEA.

The primary outcome measure was a combined end point of CVA, MI, or death ≤30 days after the intervention. MI was defined as a clinically significant ischemic cardiac event. Secondary outcomes included length of stay (LOS), transient neurologic deficits, hyperperfusion syndrome, bradycardic/hypotensive sequela, and hematomas.

Patient cohorts were grouped by CAS and CEA. CAS was further divided into CAS + EPD and CAS + FRS. Admission records were used to identify patients who were transferred to an intensive care unit (ICU) after the procedure, their hospital LOS, and their likelihood of being discharged to home vs to a rehabilitation or subacute nursing facility.

Planned comparisons were analyzed between CEA and CAS cumulatively, between the two protection cohorts within CAS, and between asymptomatic and symptomatic patients in each group. Planned comparisons between and within groups were analyzed using Fisher exact, χ², t tests, and analysis of variance as appropriate.

**RESULTS**

During the 3-year study period, 495 procedures were performed at one institution by 14 physicians, consisting of 226 CEA and 269 CAS, of which 216 were CAS + EPD (80.1%) and the remaining 53 were CAS + FRS. Monitored anesthesia control was used for 35.8% of the CEAs, and 64.2% were completed under general anesthesia. There was no difference among the groups in the mode average percentage stenosis (80% to 99% in all three groups), the composite primary end points for CEA, CAS + EPD, and CAS + FRS (4%, 5.1%, 0%; P = 1), or among groups within any particular primary end point (Table I). No primary end point events occurred in the CAS + FRS cohort. Among practitioners performing both CEA and CAS, combined primary outcomes were also similar (P = .44). In 16 CEA patients and in 10 CAS patients, the procedure was done first with a combined cardiac surgical intervention.

All CVAs in these patients were ipsilateral and all but one occurred on postoperative day 0 or 1, with the exception being a CAS + EPD patient on postoperative day 3. Four CVAs (three major) occurred in patients after CEA, and all performed in symptomatic patients under general anesthesia. Seven CVAs occurred in the CAS + EPD group, four of which occurred in asymptomatic patients (all minor in prior asymptomatic patients). Of the three symptomatic patients who developed CVA after CAS, one CVA led to the patient’s death. Overall, the CAS + EPD patients had a greater incidence of minor CVAs compared with CEA patients, which was statistically significant (P = .049).

This significance was more obvious when only asymptomatic patients were compared (P = .032). However, when

**Table I. Primary events at 30 days**

<table>
<thead>
<tr>
<th>Event</th>
<th>CEA (n = 226)</th>
<th>CAS + EPD (n = 216)</th>
<th>CAS + FRS (n = 53)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse event</td>
<td>4.0 (8)</td>
<td>5.1 (9)</td>
<td>0.0 (0)</td>
<td>.100</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.0 (4)</td>
<td>4.0 (7)</td>
<td>0.0 (0)</td>
<td>.131</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>0.5 (1)</td>
<td>3.4 (6)</td>
<td>0.0 (0)</td>
<td>.070</td>
</tr>
<tr>
<td>Major stroke</td>
<td>1.5 (3)</td>
<td>0.6 (1)</td>
<td>0.0 (0)</td>
<td>.400</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Death (n = 425)</td>
<td>1.5 (3)</td>
<td>1.7 (3)</td>
<td>0.0 (0)</td>
<td>.464</td>
</tr>
</tbody>
</table>

CAS, Carotid artery stenting; CEA, carotid endarterectomy; EPD, embolic protection device; FRS, flow reversal system.

aData are presented as percentage (n).

bCEA/EPD: comparison of CEA vs CAS + EPD; CEA/FRS: comparison of CEA vs CAS + FRS.
patients who had FRS protection with EPD were included in the overall CAS group, this difference was no longer statistically significant \( (P = .06) \).

Three perioperative deaths occurred in each group. The three deaths in the CEA group occurred after subsequent cardiac surgery (two coronary artery bypass graft procedures, one valvuloplasty). Two of the three CEAs were completed under local anesthesia and all were done preemptively for asymptomatic disease; their deaths were not related directly to the CEA but rather due to complications after their cardiac operations. Of the three deaths that occurred after CAS, one was due to a major CVA. One was related to an aspiration in a patient who required a groin exploration for retroperitoneal hematoma related to an aspiration in a patient who required a groin exploration for retroperitoneal hematoma related to pneumonia. Because this work involves two hospitals, we queried practitioners to see if ICU or LOS was related to physician practice or not. After CEA, we found ICU stay was significantly more common at one of our hospitals (31 of 56 vs 43 of 218; \( P < .001 \)), but LOS was not significantly different (2.2 days vs 1.6 days; \( P = .11 \)).

CONCLUSIONS

We have established a similar and low incidence of MI, CVA, and death among patients undergoing CEA and CAS in 495 patients, of whom \(~40\%\) were symptomatic. No neurologic or other primary events occurred in the CAS + FRS group. Four CVAs occurred in symptomatic CEA patients, with three being major CVAs, whereas one of three CVAs were major CVAs in patients undergoing CAS + EPD. For asymptomatic patients, no CVAs occurred in patients undergoing CEA, and four minor CVAs occurred in patients undergoing CAS + EPD. The CREST trial demonstrated that even minor CVAs may have a more clinically relevant affect on patients’ quality of life than troponin leaks or non–ST-elevation MI. Thus, we agree with the CREST investigators that CAS + EPD for asymptomatic disease deserves scrutiny and that this population warrants further study. The reason for the increased prevalence of stroke in asymptomatic patients after CAS is not clear, and this experience was not powered to support this relationship; however, it is tempting to attribute these findings to the placement of the distal EPD.
Although the FRS provided perfect results in this series, its use was limited to 20% of the carotid artery CAS procedures and the prevalence of hyperlipidemia was less. Still, zero primary events in this cohort compared with the infrequent but not inconsequential adverse events in the CEA and CAS groups make this an exciting technology for the prevention of harm during carotid artery therapy. Logically, the decreased event rate may be due to not crossing carotid artery lesions to deploy the EPD. In support of this finding, the Embolic Protection with Flow Reversal (EMPIRE) trial did not find evidence of major ischemic stroke with the use of FRS.9 During a 3-year period, patients undergoing CAS were significantly less likely to be in the ICU postoperatively, had a significantly shorter LOS, and were more likely to be discharged home than patients undergoing CEA. These savings in hospital utilization are an interesting finding to be considered when deciding on a therapy for patients.

The limitations of this study include (1) the absence of a focused preoperative and postoperative neurologic examination by a neurologist, resulting in possible underrepresentation of neurologic events, (2) lack of standardized troponin levels and electrocardiogram tests in all patients, with the potential for missing silent MIs, (3) the differences in postoperative admission to the ICU after CEA between practitioners at the two hospitals, and (4) that all FRS were used at one hospital with one surgeon performing all but three of these cases. This surgeon had outcomes with CEA and CAS/FRS that were consistent with the cumulative results. However, these data are generated from a high-volume center with a number of practitioners directing carotid therapy according to their treatment plan, with accurate accounting for the complications that affected their patients’ hospitalization, which lends credibility of these data to patient care decisions in a manner that randomized controlled trials cannot. An interesting finding is that these results are similar to those of the CREST trial, which has been criticized for the expectation that such low complication rates will occur in all practices.

CVA morbidity continues to plague our population.10 Primary CVA prevention requires appropriate screening, medical therapy, and use of surgical therapies.11 The clinical quandary—most patients with asymptomatic carotid artery stenosis do not have CAVAs, yet most CAVAs occur in patients with asymptomatic disease—speaks to the prevalence of carotid disease in our population. Initiatives to stratify asymptomatic patients into groups more12 or less13 likely to benefit from surgical therapy, as well as determin-

### Table III. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>CEA (n = 226)</th>
<th>CAS + EPD (n = 216)</th>
<th>CAS + FRS (n = 53)</th>
<th>Overall</th>
<th>CEA/EPD</th>
<th>CEA/FRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>41</td>
<td>38</td>
<td>42</td>
<td>.80</td>
<td>.55</td>
<td>.91</td>
</tr>
<tr>
<td>Age</td>
<td>Median, years</td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>.62</td>
<td>.65</td>
</tr>
<tr>
<td>Average age ± SD</td>
<td>70 ± 9</td>
<td>70 ± 10</td>
<td>69 ± 11</td>
<td>.27</td>
<td>.43</td>
<td>.26</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>41</td>
<td>45</td>
<td>32.7</td>
<td>.068</td>
<td>.027</td>
<td>.051</td>
</tr>
<tr>
<td>Prior CEA</td>
<td>12</td>
<td>29</td>
<td>27</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.017</td>
</tr>
<tr>
<td>Contralateral</td>
<td>Stenosis</td>
<td>31.3</td>
<td>24.5</td>
<td>42.6</td>
<td>.45</td>
<td>.09</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Hypertension</td>
<td>94</td>
<td>92</td>
<td>86</td>
<td>.084</td>
<td>.04</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Hyperlipidemia</td>
<td>82</td>
<td>87</td>
<td>69</td>
<td>.014</td>
<td>.15</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Renal disease</td>
<td>9</td>
<td>11</td>
<td>2</td>
<td>.98</td>
<td>.46</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Prior cerebrovascular accident</td>
<td>29</td>
<td>22</td>
<td>17</td>
<td>.087</td>
<td>.09</td>
</tr>
<tr>
<td>Prior cerebrovascular accident</td>
<td>Prior transient ischemic attack</td>
<td>31</td>
<td>40</td>
<td>46</td>
<td>.067</td>
<td>.05</td>
</tr>
<tr>
<td>Prior transient ischemic attack</td>
<td>Diabetes</td>
<td>35</td>
<td>41</td>
<td>36</td>
<td>.44</td>
<td>.21</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Prior myocardial infarction</td>
<td>15</td>
<td>13</td>
<td>21</td>
<td>.42</td>
<td>.63</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>Drug therapy</td>
<td>Clopidogrel</td>
<td>35</td>
<td>96</td>
<td>96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>Acetylsalicylic acid</td>
<td>91</td>
<td>91</td>
<td>81</td>
<td>.104</td>
<td>.81</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Warfarin</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>.019</td>
<td>.97</td>
</tr>
</tbody>
</table>

CAS, Carotid artery stenting; CEA, carotid endarterectomy; EPD, embolic protection device; FRS, flow reversal system; MI, myocardial infarction. 
aData are presented as a percentage, unless otherwise indicated.

### Table IV. Postoperative hospitalization course and disposition at discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CEA</th>
<th>CAS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay (% in ICU)</td>
<td>41.6</td>
<td>27.7</td>
<td>.006</td>
</tr>
<tr>
<td>LOS, mean ± SD days</td>
<td>2.9 ± 3.4</td>
<td>1.6 ± 1.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Discharge to rehab</td>
<td>12/223</td>
<td>5/266</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CVA or MI in those discharged to rehab</td>
<td>4/11</td>
<td>4/5</td>
<td>.128</td>
</tr>
</tbody>
</table>

CAS, Carotid artery stenting; CEA, carotid endarterectomy; ICU, intensive care unit; LOS, length of stay; NS, not significant.
ing which surgical therapy has better outcomes for which asymptomatic patients, is critical as we enter the “century of the brain.”

To best stratify the expected risks and benefits of available therapies for carotid artery stenosis in contemporary times, patients would need to be prospectively randomized to CEA, CAS + EPD, or CAS + FRS for both symptomatic and asymptomatic disease. The latter would have to meet criteria for access vessels that the former choices would not. Further, asymptomatic patients should include a medical management arm. Finally, the trial would have to be completed in an expedited fashion with a shortened timeframe (maybe 30-day follow-up) among practitioners who perform all of these procedures with excellent results so that results could be compared while the technology is relatively stagnant. Because this may not be realistic, practitioners and referring physicians need to make decisions and educate their patients using randomized controlled trials, registry data, and institutional results in the manner that best represents what they can offer their patients. This study represents the first comparative study between treatment options using the FRS, and it certainly supports the hypothesis that proximal flow reversal may limit stroke during CAS.

AUTHOR CONTRIBUTIONS
Conception and design: LB, RB, KK
Analysis and interpretation: LB, RB, KK
Data collection: LB, RB, MC, KK, RV, KN, GR, TD
Writing the article: LB, RB, KK
Critical revision of the article: LB, RB, KK, RV, KN, GR, TD
Final approval of the article: LB, RB, KK, RV, KN, GR, TD
Statistical analysis: LB, RB, KK
Obtained funding: KK
Overall responsibility: KK

REFERENCES

DISCUSSION
Dr Carlos H. Timaran (Dallas, Tex). Dr Beaulieu & colleagues have presented a retrospective observational study about their contemporaneous results of all carotid interventions performed at their institution. As shown in this study, all carotid interventions may offer excellent outcomes when these are applied to the appropriate patients. Because carotid artery stenting (CAS) is currently reserved primarily for high-risk patients, the excellent outcomes observed in this study clearly confirm its role in the treatment of carotid stenosis. Moreover, the “zero” stroke and death rate with CAS under flow reversal is indeed intriguing and probably the way to improve neurologic outcomes with this intervention. Based on the results of the current study, I have the following comments and questions:

1. Although reporting overall results for carotid interventions is important in terms of quality improvement, interpretation of observational studies like this one is difficult, particularly because CAS is currently used primarily for high-risk patients. To avoid comparing apples and oranges, reporting outcomes using propensity scores and multivariate analyses for risk-adjustment is advisable when treatment groups with different risk-profile are assessed, as in the current study. In addition to the results reported in the manuscript, did you analyze the data using any type of risk-stratification? If so, what type of risk-adjustment did you use and which were the results?
2. We all are aware of your excellent outcomes with CEA under local anesthesia, which could be used for high-risk patients. It would be of particular interest to report the outcomes of carotid endarterectomy (CEA) and CAS among patients at high-risk because of comorbidities. Do you have these specific results? By the way, I see that most of your endarterectomies are now performed under general anesthesia? Why have you changed the type of anesthesia used for CEA?
3. Another major problem with observational studies is the selection bias introduced to choose between therapies. It is remark-
able that more than half the patients at your institution undergo CAS, which in the U.S. is still reserved for high-risk patients. Did you offer CAS to conventional-risk patients during the study period? I understand that several of the patients undergoing CAS under flow reversal were enrolled in the EMPIRE trial. Apart from this, how did you choose between therapies? Were patients offered all treatments? Again, because CAS is currently reserved for high-risk patients, this is probably unlikely, unless you offered CAS to all comers or you enrolled patients in trials that included conventional-risk patients. Did you enroll patients in any of these trials?

4. Most octogenarians at your institution undergo CAS. The excellent outcomes observed in those patients with CAS under flow reversal clearly indicate that this is the method of choice for embolic protection for the elderly. Do you use flow reversal in all octogenarians undergoing CAS? How do you plan these procedures?

5. Finally, and based on the results of your study and the current regulatory restrictions, how do you choose between therapies for carotid stenosis today?

I want to thank the authors for sending me their manuscript in advance and the Association for the honor of discussing this important study and the privilege of the floor.

Dr Robert Beaulieu. Thank you very much for your comments, and thank you to the Southern Association Vascular Surgery for allowing us to present this work. Both patients in the carotid endarterectomy and carotid artery stenting cohort had similar incidences of comorbidities and physiological risk factors. The majority of patients undergoing carotid artery stenting did so for anatomical risk factors. We did not subdivide stented patients according to anatomical and physiologic risk, as our aim was to present results from physician-driven treatment decisions for patients with carotid artery stenosis.

Regarding the CEA under local anesthesia, the CEA was performed under local versus general anesthesia at the surgeon’s preference. Several publications have had difficulty finding differences in outcomes between patients undergoing local or general anesthesia. Also, Emory’s current outcomes are comparable to those under Dr Robert B. Smith II, who preferentially utilized local anesthesia. Since there was no difference between the number of medical high risk patients in the carotid endarterectomy and the carotid artery stenting groups, it is not surprising that their outcomes were also similar.

Further, looking at who was offered carotid artery stenting, only high-risk patients were offered stenting, with the exception of a small number of patients who participated in the CREST trial. Many patients are referred to us for stenting, and this may explain the percentage of carotid artery stents performed.

Regarding octogenarians and flow reversal, currently our flow reversal is used only for high risk symptomatic patients, due to the lack of reimbursement and the lack of post-market study. Good results in octogenarians may be due to correct patient selection, namely identifying hostile aortic arches or highly calcified or thrombus-laden vessels that would probably benefit from CEA more so than flow reversal.

Finally, looking at our algorithm for treating patients with either carotid endarterectomy or carotid artery stenting, standard risk patients are all offered CEA. Anatomically high-risk patients, whether they are symptomatic or asymptomatic, are offered carotid artery stenting. And, physiologically high-risk patients that are symptomatic are offered carotid artery stenting, and those that are asymptomatic are given medical management.