Complication Rates and Center Enrollment Volume in the Carotid Revascularization Endarterectomy Versus Stenting Trial

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Background and Purpose—Evidence indicates that center volume of cases affects outcomes for both carotid endarterectomy and stenting. We evaluated the effect of enrollment volume by site on complication rates in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).

Methods—The primary composite end point was any stroke, myocardial infarction, or death within 30 days or ipsilateral stroke in follow-up. The 477 approved surgeons performed >12 procedures per year with complication rates <3% for asymptomatic patients and <5% for symptomatic patients; 224 interventionists were certified after a rigorous 2 step credentialing process. CREST centers were divided into tertiles based on the number of patients enrolled into the study, with Group 1 sites enrolling <25 patients, Group 2 sites enrolling 25 to 51 patients, and Group 3 sites enrolling >51 patients. Differences in periprocedural event rates for the primary composite end point and its components were compared using logistic regression adjusting for age, sex, and symptomatic status within site-volume level.

Results—The safety of carotid angioplasty and stenting and carotid endarterectomy did not vary by site-volume during the periprocedural period as indicated by occurrence of the primary end point (P=0.54) or by stroke and death (P=0.87). A trend toward an inverse relationship between center enrollment volume and complications was mitigated by adjustment for known risk factors.

Conclusions—Complication rates were low in CREST and were not associated with center enrollment volume. The data are consistent with the value of rigorous training and credentialing in trials evaluating endovascular devices and surgical procedures.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00004732. (Stroke. 2014;45:3320-3324.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ randomized controlled trial ■ stenting ■ stroke ■ training

Carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) are technically demanding procedures associated with learning curves. For CEA, there is evidence that both surgeons’ cumulative experience and intensity of experience may contribute to successfully achieving satisfactorily low morbidity and mortality indices.1–3 Although the study was conducted during a period with higher periprocedural stroke and death rates from CEA, a combined periprocedural mortality and neurological morbidity <3% was not reached until after performance of >50 CEA operations per year and a cumulative experience of >325 CEA total.1 Existing literature suggests that it may be difficult to separate the effect of the intensity and the cumulative nature of the operative experience, but both are important.1 Studies also suggest that the effect of a learning curve related both to technical expertise and to patient selection may influence the outcomes of CAS.4 CAS operator volume to establish experience with CAS may be only 1 important factor in avoidance of complications. CAS complication rates may also be related to collective institutional proficiency and experience encompassing factors, such as patient selection, device selection, and adjunctive medical management, along with reviews of lessons learnt from collegial reviews of all cases.5

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Systematic review and meta-analysis data from primary studies on center volume–to–outcome relationships in CEA revealed that significantly lower mortality and stroke rates were achieved at hospitals providing a higher annual hospital volume of CEA. Likewise, important determinants of CAS outcomes include both site and operator CAS volume. In addition, for CAS, results demonstrated a reduction of inhospital stroke rates associated with increasing center experience. Finally, annual CAS procedure in-trial volume has also been associated with outcome. We sought to evaluate the effect of enrollment by site on complication rates in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). We hypothesized that there would be improved performance with increasing enrollment volume.

Methods

Study Design

The study design and primary results of CREST have been previously reported. CREST is a prospective, multicentered, randomized clinical trial with blinded end point adjudication comparing the efficacy of CEA and CAS in preventing stroke, myocardial infarction (MI), and death during a 30-day periprocedural period and stroke ipsilateral to the study artery over the follow-up period in patients with symptomatic or asymptomatic carotid stenosis. The protocol was approved by the institutional/ethics review boards at all participating sites, and all participants provided signed informed consent. Patients were enrolled between December 2000 and July 2008 at 117 clinical centers in the United States and Canada. Participants who had a stroke or transient ischemic attack in the distribution of the study artery within 180 days before randomization were considered asymptomatic and eligible if they had ipsilateral stenosis of ≥50% by angiography, ≥70% by ultrasound, or ≥70% by computed tomographic angiography or magnetic resonance angiography if ultrasound was 50% to 69%. Complete inclusion and exclusion criteria have been published elsewhere.

Interventionalist and Surgeon Certification

Patients could not be randomly assigned to a treatment group until the interventionalists performing CAS and surgeons performing CEA had been certified. The details of certification have been previously described. The Interventional Management Committee, consisting of a multidisciplinary group of physicians, was responsible for the rigorous 2-step credentialing process of the interventionists applying for CREST. Candidates were required to submit case studies of at least 30 previous CAS cases, and selection of interventionalists was based on the demonstration of mandatory clinical and technical skills. After approval to join CREST and before enrolling patients in the lead-in phase, interventionists without previous experience with the study devices were required to participate in a specially designed Carotid Stent Operator Certification Program. The Carotid Stent Operator Certification Program was an intensive didactic program consisting of an overview of the CREST protocol, with strong emphasis on carotid stenting. Training included diagnostic angiography, complex anatomy, postprocedure care, and management of carotid complexities. The participants were instructed on the trial devices and given the opportunity to work with bench models. There was at least one case observation using the trial devices.

For surgeons, the Surgical Management Committee used approaches proven successful in the Asymptomatic Carotid Atherosclerosis Study, where candidates submitted ≥50 CEA procedures for review before approval for participation in the trial. Criteria for approval included performance of ≥12 CEA procedures per year with complication rates <3% for asymptomatic patients and <5% for symptomatic patients.

There was ongoing monitoring of complications in CREST. Per protocol, the Statistical and Data Management Center informed the CREST Principal Investigator and the Surgical Management Committee or Interventional Management Committee the first time a stroke or death occurred at a clinical site, which initiated a watch status. A second death or stroke triggered a potential audit of the site and the individual operator by the appropriate committee. A site visit or additional proctoring might be required. According to the severity and number of events, an individual operator or clinical site could be terminated from participating in the trial. An independent Data

Table 1. Baseline Demographics, Clinical Characteristics, and Interventionalist/Surgeon Information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1, &lt;25 Patients</th>
<th>Group 2, 25–51 Patients</th>
<th>Group 3, &gt;51 Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>69.6±8.7</td>
<td>69.6±8.9</td>
<td>67.8±8.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>61.3</td>
<td>65.5</td>
<td>68.9</td>
<td>0.005</td>
</tr>
<tr>
<td>White race, %</td>
<td>93.9</td>
<td>88.8</td>
<td>97.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
<td>44.7</td>
<td>54.4</td>
<td>59.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk factor, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>87.3</td>
<td>84.4</td>
<td>86.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33.0</td>
<td>29.2</td>
<td>29.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>85.9</td>
<td>83.2</td>
<td>83.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Prior cardiovascular disease or CABG</td>
<td>47.1</td>
<td>45.2</td>
<td>42.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Current smoker</td>
<td>23.0</td>
<td>24.2</td>
<td>32.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days from randomization to treatment, median (IQR)</td>
<td>7 (9)</td>
<td>7 (9)</td>
<td>6 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean number of interventionalists who performed ≥1 procedure per center*</td>
<td>1.3</td>
<td>1.9</td>
<td>2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean number of surgeons who performed ≥1 procedure per center*</td>
<td>1.8</td>
<td>2.6</td>
<td>3.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; and IQR, interquartile range.

*Counted as an interventionalist if performed CAS procedure; counted as surgeon if performed CEA.
Table 2. Event Rates by Center Enrollment Volume for CAS

<table>
<thead>
<tr>
<th>Category</th>
<th>Group 1, &lt;25 Patients; No. of Events/No. of Subjects (Rate±SE)</th>
<th>Group 2, 25–51 Patients; No. of Events/No. of Subjects (Rate±SE)</th>
<th>Group 3, &gt;51 Patients; No. of Events/No. of Subjects (Rate±SE)</th>
<th>OR (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (any MI during peri-procedural period)</td>
<td>5/429 (1.2±0.5)</td>
<td>3/432 (0.7±0.4)</td>
<td>6/401 (1.5±0.6)</td>
<td>1.26 (0.65–2.45)</td>
<td>0.49</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>0.62 (0.15–2.62)</td>
<td>1.53 (0.46–5.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke and death end point (any stroke or death within peri-procedural period)</td>
<td>18/429 (4.2±1.0)</td>
<td>13/432 (3.0±0.8)</td>
<td>24/401 (6.0±1.2)</td>
<td>1.25 (0.89–1.77)</td>
<td>0.20</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>0.67 (0.32–1.39)</td>
<td>1.49 (0.79–2.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point (any stroke, MI or death within peri-procedural period)</td>
<td>22/429 (5.1±1.1)</td>
<td>16/432 (3.7±0.9)</td>
<td>28/401 (7.0±1.3)</td>
<td>1.24 (0.90–1.70)</td>
<td>0.19</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>0.68 (0.35–1.33)</td>
<td>1.47 (0.82–2.66)</td>
<td></td>
<td>0.06</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stent; CI, confidence interval; MI, myocardial infarction; and OR, odds ratio.
*OR (95% CI) adjusted for age, sex, and symptomatic status.

Table 3. Event Rates by Center Enrollment Volume for CEA

<table>
<thead>
<tr>
<th>Category</th>
<th>Group 1, &lt;25 Patients; No. of Events/No. of Subjects (Rate±SE)</th>
<th>Group 2, 25–51 Patients; No. of Events/No. of Subjects (Rate±SE)</th>
<th>Group 3, &gt;51 Patients; No. of Events/No. of Subjects (Rate±SE)</th>
<th>OR (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (any MI during peri-procedural period)</td>
<td>13/424 (3.1±0.8)</td>
<td>9/416 (2.2±0.7)</td>
<td>6/400 (1.5±0.6)</td>
<td>0.68 (0.42–1.11)</td>
<td>0.12</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>0.66 (0.28–1.58)</td>
<td>0.47 (0.17–1.27)</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Stroke and death end point (any stroke or death within peri-procedural period)</td>
<td>8/424 (1.9±0.7)</td>
<td>8/416 (1.9±0.7)</td>
<td>13/400 (3.3±0.9)</td>
<td>1.29 (0.81–2.07)</td>
<td>0.29</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>0.92 (0.34–2.49)</td>
<td>1.59 (0.64–3.94)</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Primary end point (any stroke, MI or death within peri-procedural period)</td>
<td>20/424 (4.7±1.0)</td>
<td>17/416 (4.1±1.0)</td>
<td>19/400 (4.8±1.1)</td>
<td>0.97 (0.70–1.36)</td>
<td>0.87</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>0.80 (0.41–1.83)</td>
<td>0.95 (0.49–1.83)</td>
<td></td>
<td>0.79</td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; and OR, odds ratio.
*OR (95% CI) adjusted for age, sex, and symptomatic status.
Table 4: Differences in Periprocedural Event Rates for the Primary Composite End Point and Its Components by Volume and Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>CAS, No. of Events/No. of Subjects (Rate±SE)</th>
<th>CEA, No. of Events/No. of Subjects (Rate±SE)</th>
<th>CAS-to-CEA, OR (95% CI)*</th>
<th>Treatment by Site-Size Interaction P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI end point (any MI within peri-procedural period)</td>
<td>5/429 (1.2±0.5)</td>
<td>13/424 (3.1±0.8)</td>
<td>0.37 (0.13–1.05)</td>
<td>0.34</td>
</tr>
<tr>
<td>Stroke and death end point (any stroke or death within peri-procedural period)</td>
<td>6/401 (1.5±0.6)</td>
<td>6/400 (1.5±0.6)</td>
<td>1.01 (0.32–3.16)</td>
<td>0.87</td>
</tr>
<tr>
<td>Primary end point (any stroke, MI, or death within peri-procedural)</td>
<td>12/401 (3.0±0.8)</td>
<td>12/400 (3.0±0.9)</td>
<td>1.0 (0.94–1.37)</td>
<td>0.54</td>
</tr>
<tr>
<td>Primary end point</td>
<td>17/401 (4.2±1.0)</td>
<td>17/400 (4.1±1.0)</td>
<td>0.92 (0.46–1.85)</td>
<td>0.58</td>
</tr>
</tbody>
</table>
| CAS indicates carotid artery stent; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; and OR, odds ratio. *Adjusted for age, sex, and symptomatic status.

Discussion

Complication rates were low in CREST and were not associated with center enrollment volume. Historically, a learning curve has been present with both methods of revascularization.14 Outcomes have been shown to be related to both surgeon volume and hospital volume for CEA,2,3,6,17 and similar data have been reported for CAS.7,8,18 Our data did not demonstrate an association with outcome and enrollment volume by site of patients entered into CREST, most likely because the interventionalists and surgeons were selected based on demonstration of experience with the procedures and devices, as well as upon event rates within an accepted standard combined with on-going monitoring for complications throughout the study. We suggest that these results underscore the value of rigorous training and credentialing in trials evaluating endovascular devices and surgical procedures. The certification requirements in CREST likely minimized the variability in outcomes because of operator experience.

Our results are similar to those reported in the Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study where complication rates did not differ by center enrollment rates.19 In contrast, the results reported in the Stent-Protected Angioplasty Versus Endarterectomy (SPACE) study showed an association between complication rate and patient volume for CAS but not for CEA.9 Standardization for the interventionalists in SPACE differed from CREST. Interventionalists in SPACE could be credentialed if they had performed 25 stents or angioplasties in any vascular location. For credentialing in CREST, interventionalists had to submit documents for ≥10 to 20 carotid stents and then had to participate in a Lead-In registry with up to 20 carotid stents (n=1565). In addition, 3 stent devices and 5 embolic protection devices were approved for use in SPACE.20 Only one CAS system and embolic protection device was used in CREST, which helps to avoid confounding because of external factors related to different devices, but limits the generalizability of our results.

There are several limitations to our analysis. We categorized centers into tertiles; however, a low-enrolling site in CREST does not equate to a low-volume site because we do not have data on the number of patients who underwent revascularization outside CREST at each center. Similarly, because of ongoing entry of new interventionalists and surgeons into CREST, operator experience independent of center enrollment volume cannot be addressed. Overall, event rates in this analysis were similar to the periprocedural rates reported in the CREST primary analysis for CAS and CEA (5.2% and 4.5%, respectively; HR for CAS, 1.18; 95% CI, 0.82–1.68; P=0.38);
however, in addition to event rates being low, CREST was not powered to detect differences in outcome based on center enrollment volume. Our observations are specific to the CREST trial, and so these results may not be generalizable and should be interpreted with caution.

Regarding CAS, there is no consensus on the minimum number of CAS procedures required to define safety or for maintenance of competency. Moreover, different specialty societies have different elements which define competency. This issue is further complicated by other factors, such as patient comorbidities and hospital volume, which are also associated with safety. CREST included interventionalists and operators from multiple specialties. Our results strongly suggest that careful selection of interventionalists and operators ensures that confounding of results because of experience and device is minimized.

Summary
Complication rates in CREST were not associated with center enrollment volume. Rigorous credentialing requirements may overcome the learning curve and provide a more accurate approximation of the safety of revascularization procedures for carotid artery stenosis.

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Disclosures
Dr Clair is Consultant at Arsenal Medical, Confluent, Endologix, Vessix Vascular, Volcano Corp; Data and Safety Monitoring Board member at Bard; and in Advisory Board at Boston Scientific, Medtronic. Dr Barr is a Shareholder at Boston Scientific, Medtronic, Vessix Vascular, Volcano Corp; Data and Safety Monitoring Board member at Bard; and in Advisory Board at Boston Scientific, Medtronic, and Consultant in Cvidien. The other authors report no conflicts.

References
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