

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.

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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 perioperative 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.⁶ Likewise, important determinants of CAS outcomes include both site and operator CAS volume.⁷ In addition, for CAS, results demonstrated a reduction of in-hospital stroke rates associated with increasing center experience.^{8,9} Finally, annual CAS procedure in-trial volume has also been associated with outcome.¹⁰ 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.^{11,12} 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 symptomatic and eligible if they had ipsilateral stenosis of $\geq 50\%$ by angiography, $\geq 70\%$ by ultrasound, or $\geq 70\%$ by computed tomographic angiography or magnetic resonance angiography if ultrasound was 50% to 69%. Patients who had not had a stroke or transient ischemic attack associated with the study artery within the previous 180 days were considered asymptomatic and eligible if the ipsilateral stenosis was $\geq 60\%$ by angiography, $\geq 70\%$ by ultrasound, or $\geq 80\%$ by computed tomographic angiography or magnetic resonance angiography

if ultrasound was 50% to 69%. Complete inclusion and exclusion criteria have been published elsewhere.^{11,12}

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.¹¹⁻¹⁴ The Interventional Management Committee, consisting of a multidisciplinary group of physicians, was responsible for the rigorous 2-step credentialing process of the interventionalists applying for CREST. Candidates were required to submit case studies of up to 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, interventionalists 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 inserviced 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,¹⁵ where candidates submitted ≈ 50 CEA procedures for review before approval for participation in the trial.¹⁶ 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

Variable	Group 1, <25 Patients (n=853 Patients)	Group 2, 25–51 Patients (n=848 Patients)	Group 3, >51 Patients (n=801 Patients)	P Value
Age, y, mean (SD)	69.6 \pm 8.7	69.6 \pm 8.9	67.8 \pm 8.9	<0.0001
Male, %	61.3	65.5	68.9	0.005
White race, %	93.9	88.8	97.1	<0.0001
Symptomatic, n (%)	44.7	54.4	59.8	<0.0001
Risk factor, n (%)				
Hypertension	87.3	84.4	86.0	0.22
Diabetes mellitus	33.0	29.2	29.2	0.15
Dyslipidemia	85.9	83.2	83.9	0.28
Prior cardiovascular disease or CABG	47.1	45.2	42.4	0.17
Current smoker	23.0	24.2	32.0	<0.0001
Days from randomization to treatment, median (IQR)	7 (9)	7 (9)	6 (8)	0.002
Mean number of interventionalists who performed ≥ 1 procedure per center*	1.3	1.9	2.5	<0.0001
Mean number of surgeons who performed ≥ 1 procedure per center*	1.8	2.6	3.0	<0.0001

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

	Group 1, <25 Patients; No. of Events/No. of Subjects (Rate±SE)	Group 2, 25–51 Patients; No. of Events/No. of Subjects (Rate±SE)	Group 3, >51 Patients; No. of Events/No. of Subjects (Rate±SE)	OR (95% CI)*	P Value
MI (any MI during peri-procedural period)	5/429 (1.2±0.5)	3/432 (0.7±0.4)	6/401 (1.5±0.6)	1.26 (0.65–2.45)	0.49
OR (95% CI)	Reference	0.62 (0.15–2.62)	1.53 (0.46–5.13)		0.44
Stroke and death end point (any stroke or death within peri-procedural period)	18/429 (4.2±1.0)	13/432 (3.0±0.8)	24/401 (6.0±1.2)	1.25 (0.89–1.77)	0.20
OR (95% CI)	Reference	0.67 (0.32–1.39)	1.49 (0.79–2.84)		0.07
Primary end point (any stroke, MI or death within peri-procedural period)	22/429 (5.1±1.1)	16/432 (3.7±0.9)	28/401 (7.0±1.3)	1.24 (0.90–1.70)	0.19
OR (95% CI)	Reference	0.68 (0.35–1.33)	1.47 (0.82–2.66)		0.06

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.

and Safety Monitoring Board appointed by the National Institutes of Health met about twice yearly for additional oversight of the study. There were no operators with >2 events. No sites, surgeons, or interventionalists were withdrawn because of untoward complications.

Treatment

Participants were randomly assigned to receive either CAS or CEA. Patients randomized to CAS were treated with aspirin and clopidogrel 48 hours before and for 30 days after the procedure. Patients were treated with the RX Acculink Carotid Stent System and, whenever feasible, the RX Accunet Embolic Protection System (Abbott Vascular, Inc, Abbott Park, IL). Patients randomized to CEA received aspirin at least 48 hours before and continued for a year or more. Full details of the protocol have been reported elsewhere.^{11,12} Procedures were performed only by CREST-certified interventionalists and surgeons.

Outcomes

In CREST, the primary composite end point was any stroke, MI, or death during the periprocedural period or ipsilateral stroke in follow-up. For the purposes of this analysis, CREST centers were divided into tertiles based on the number of patients enrolled into the study, with Group 1 composed of sites each enrolling <25 patients, Group 2 with sites enrolling 25 to 51 patients, and Group 3 with sites enrolling >51 patients. Baseline demographic information for patients in each group was recorded. The number of interventionalists and surgeons was recorded.

Statistical Analysis

Baseline demographics, comorbidities, and procedural information were summarized with descriptive summary statistics. Differences in periprocedural event rates by center enrollment volume for the primary composite end point and its components were compared using logistic regression adjusting for age, sex, and symptomatic status. Comparisons in event rates by center enrollment volume were made separately for each treatment. Tests for linear trend across all 3 volume groups were conducted to assess the significance of the increase in risk per category of change. Clinically, a hazard ratio between 2 and 3 was considered to be important to patients and their physicians. Comparisons within site-volume level by treatment group were then performed, and tests for treatment by volume interactions were conducted.

Results

As previously reported,¹⁴ 158 interventionalists and 477 surgeons were credentialed in CREST; 2502 patients were randomized, and there was no difference between CAS and CEA in the estimated 4-year rates of the primary outcome (7.2% and 6.8%, respectively; hazard ratio, 1.11; 95% confidence interval [CI], 0.81–1.51; $P=0.51$).¹¹

Group 1 (853 patients) included 82 sites each enrolling <25 patients; Group 2 (848 patients) included 24 sites enrolling 25 to 51 patients; and Group 3 (801 patients) included 10 sites enrolling >51 patients. Baseline demographic information for each of the 3 groups is listed in Table 1. Patients at centers with higher enrollment volume tended to be older, more likely

Table 3. Event Rates by Center Enrollment Volume for CEA

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

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

		CAS, No. of Events/No. of Subjects (Rate \pm SE)	CEA, No. of Events/No. of Subjects (Rate \pm SE)	CAS-to-CEA, OR (95% CI)*	Treatment by Site-Size Interaction <i>P</i> Value*
MI end point (any MI within peri-procedural period)	Group 1	5/429 (1.2 \pm 0.5)	13/424 (3.1 \pm 0.8)	0.37 (0.13–1.05)	0.34
	Group 2	3/432 (0.7 \pm 0.4)	9/416 (2.2 \pm 0.7)	0.32 (0.09–1.20)	
	Group 3	6/401 (1.5 \pm 0.6)	6/400 (1.5 \pm 0.6)	1.01 (0.32–3.16)	
Stroke and death end point (any stroke or death within peri-procedural period)	Group 1	18/429 (4.2 \pm 1.0)	8/424 (1.9 \pm 0.7)	2.25 (0.96–5.25)	0.87
	Group 2	13/432 (3.0 \pm 0.8)	8/416 (1.9 \pm 0.7)	1.62 (0.66–3.95)	
	Group 3	24/401 (6.0 \pm 1.2)	13/400 (3.3 \pm 0.9)	1.89 (0.94–3.79)	
Primary end point (any stroke, MI, or death within peri-procedural)	Group 1	22/429 (5.1 \pm 1.1)	20/424 (4.7 \pm 1.0)	1.08 (0.58–2.01)	0.54
	Group 2	16/432 (3.7 \pm 0.9)	17/416 (4.1 \pm 1.0)	0.92 (0.46–1.85)	
	Group 3	28/401 (7.0 \pm 1.3)	19/400 (4.8 \pm 1.1)	1.51 (0.83–2.76)	

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.

men, more likely white, and more likely to be symptomatic ($P<0.005$). There were no other significant differences in baseline risk factors between the groups, except for smoking status ($P<0.0001$) and days from randomization to treatment ($P=0.002$; Table 1). In parallel with patient volumes, the number of surgeons and interventionists increased, with nearly double the number of each in Group 3 compared with Group 1 ($P<0.001$; Table 1).

Event rates by center enrollment volume, adjusted for age, sex, and symptomatic status were compared for CAS (Table 2) and CEA (Table 3) separately. For the CAS group, on average, there was a 24% increase (odds ratio [OR]=1.24; 95% CI, 0.90–1.70) in the odds of a primary end point per category of patient volume as we contrast the small, medium, and large volume groups; however, the increase was not significant. Similar results were found for the MI, stroke, and death end points. Within the CEA group, there was a slight reduction in risk (OR=0.97; 95% CI, 0.70–1.36) in the odds of a primary end point per category of patient volume moving from small to large. There was a reduced risk of MI (OR=0.68; 95% CI, 0.42–1.11) and an increase in odds of stroke and death (OR=1.29; 95% CI, 0.81–2.07) as you moved from small to large volume, but none of these differences were significant.

Table 4 provides details of event rates for complications of CAS and CEA by site-volume, with adjustment for age, sex, and symptomatic status. The safety of CAS and CEA did not vary by site-volume during the periprocedural period as indicated by nonsignificant ORs for each treatment comparison within center enrollment volume level. The overall test for treatment by volume interactions were nonsignificant for all end points (primary end point [$P=0.54$], MI [$P=0.34$], or by stroke and death [$P=0.87$]).

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.^{1,4} 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 safety⁵ nor for maintenance of competency.²¹ Moreover, different specialty societies have different elements which define competency.^{21–23} 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, and Consultant in Covidien. The other authors report no conflicts.

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