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Influence of Site and Operator Characteristics on Carotid Artery Stent Outcomes

Analysis of the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) Clinical Study

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Objectives The aim of this study was to analyze the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) study for physician- or site-related variables associated with differential outcomes for carotid artery stenting (CAS).

Background The CAPTURE 2 trial is an ongoing, prospective, nonrandomized, independently adjudicated, multicenter clinical study enrolling high-surgical-risk patients undergoing CAS.

Methods In this assessment of the CAPTURE 2 study, the American Heart Association carotid endarterectomy guideline limits were used to define acceptable site and physician CAS outcomes; therefore, the resulting population of nonoctogenarian, asymptomatic subjects in this analysis is confined to 3,388 (of the total 5,297) subjects treated at 180 U.S. hospitals by 459 operators between March 2006 and January 2009.

Results The rates of death, stroke, and myocardial infarction and death and stroke (DS) at 30 days were 3.5% and 3.3%, respectively, for the full CAPTURE 2 study cohort and 2.9% and 2.7%, respectively, for the asymptomatic, nonoctogenarian subgroup. In this subgroup, two-thirds of sites (118 of 180, 66%) had no DS events. Within the remaining sites, an inverse relationship between event rates and hospital patient volume as well as between event rates and individual operator volume was observed. The DS rates trended lower for interventional cardiologists compared with other specialties.

Conclusions Outcomes from the largest prospectively gathered, independently adjudicated, multicenter CAS study indicate that CAS can be safely performed in a variety of hospital settings by physicians with various specialties. The most important determinant of perioperative CAS outcomes was both site and operator CAS volume. A threshold of 72 cases was found to be necessary for consistently achieving a DS rate below 3% in this later-phase single arm study; background era and nonstudy operator experience will affect this determination. (Second Phase of "Carotid RX ACCULINK/RX ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events"; NCT00302237) (J Am Coll Cardiol Intv 2011;4:235–46) © 2011 by the American College of Cardiology Foundation

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In 2004, the U.S. Food and Drug Administration (FDA) approved the first endovascular device system for use in the U.S. for treatment of extracranial carotid artery disease in patients at high risk for adverse events from carotid endarterectomy (CEA). Since then, carotid artery stenting (CAS) has been performed with increasing numbers in a variety of hospital settings. After the initial adoption phase in CAS, there was a marked decrease in rates of adverse outcomes, possibly related to improved patient selection and increased operator experience (1). Because of this accumulating CAS experience, a better understanding of the factors associated with increased risk of adverse outcomes has been possible. Over the past 5 years it has been demonstrated that patient-related factors such as age (2–5), symptom status (2,3), timing of symptoms before CAS (3–5), patient comorbidities (4,6,7), concurrent medications (2), and smoking history (4) all might influence outcome. Carotid artery stenting outcomes are also impacted by physician-related factors, including training and experience, as well as hospital volume (2). Most of these factors are not yet well-characterized, although the progression in our understanding of risk predictors and the improvement of outcomes for CAS seems to mirror the experience previously demonstrated for CEA (8).

Abbreviations and Acronyms

AHA = American Heart Association

CAS = carotid artery stenting

CEA = carotid endarterectomy

DS = death and stroke

DSMI = death, stroke, and myocardial infarction

FDA = U.S. Food and Drug Administration

IC = interventional cardiology

Given the incomplete understanding of the patient- and physician-related features impacting CAS outcomes, continued efforts to better quantify these factors have led to further examination of patient selection and operator experience (2,9). Prompted by the observation that in multicenter studies many hospital sites were able to perform CAS with few or no adverse events—whereas others produced less favorable outcomes—there was a recognition of the need for a deeper understanding of what specific site and operator factors are associated with better CAS outcomes.

Accordingly, the aim of this study is to analyze the large (>5,000 patients) CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) study for physician- or site-related variables associated with differential outcomes, in an attempt to identify best practices.

Methods

Study design and current population. The CAPTURE 2 study is an ongoing, prospective, independently adjudicated, multicenter clinical study designed to record safety outcomes of CAS associated with the use of the RX Acculink Carotid Stent System and RX Accunet Embolic Protection System (Abbott Vascular Incorporated, Santa Clara, California) by physicians from a broad range of clinical practices in high-risk patients. Device certification has been previously described (10). The CAPTURE 2 study is a post-market clinical study, with a pre-specified protocol, informed consent, institutional review board approval and oversight, a pre-defined statistical and analytical plan containing pre-defined primary and secondary end points, pre-defined subgroup analyses, independent end point assessment, and independent adjudication of neurological events by an independent Clinical Event Committee, Harvard Clinical Research Institute, with site monitoring visits and annual reporting to the FDA (see details to follow). The CAPTURE 2 study was initiated in March 2006; the data in the current analysis include a subgroup of evaluable patients who had an attempted CAS procedure between March 2006 and January 2009 and who were asymptomatic and under the age of 80 years old. Asymptomatic patients had no ipsilateral hemispheric stroke, transient ischemic attack, or amaurosis fugax within 180 days before the procedure. Age was computed at the day of procedure. Patients were included if they completed their 30-day follow-up visits or had any end point event (i.e., death, stroke, or myocardial infarction within 30 days after the procedure). All study patients were identified by the operators to have had characteristics that made them high-risk for CEA and were asymptomatic with ≥80% stenosis of the common or internal carotid artery. Training requirements for physicians in this study have been described previously (10). Detailed descriptions of overall CAPTURE 2 study objective and rationale and selection of interventionists and patients were reported elsewhere (1).

Clinical sites, volume, and operators. The type and number of staffed hospital beds for the CAPTURE 2 clinical sites were manually annotated by reviewing the American Hospital Directory database. The number of beds among participating hospitals ranged from 30 to 2,236. Hospitals were classified on the basis of self-description into 3 major types: community, private, or academic (university). Facilities were categorized by geography, with 4 major geographic regions identified (Northeast, South, Midwest, and West), with the classification system used by the U.S. Census Bureau.

Volume was defined as number of CAS procedures performed in the CAPTURE 2 study at a single site or by a single operator, as of the time of the analysis.

Operator specialty was obtained from the training records and included: cardiology, vascular surgery, neurosurgery, neuroradiology, and interventional radiology. Analysis was presented on the first 2 (largest) groups, because the remaining 3 groups had insufficient numbers for analysis.

Outcome assessment and end points. Detailed descriptions of CAPTURE 2 study assessment and end points were

reported previously (1). Briefly, neurological evaluations were performed on patients within 14 days before the stenting procedure, within 24 h after the procedure, and at 30 days after the procedure by an independent neurologist. Baseline demographic data, comorbidities, lesion characteristics, treatment details, and information on adverse outcomes during the procedure and at follow-up visits were collected with electronic case report forms and entered into a centralized database. During the 24-h post-procedure and 30-day follow-up assessments, any occurrence of death, stroke, myocardial infarction, new neurologic events, or device-related adverse events was reported. Study subjects were evaluated for neurologic manifestations with the National Institutes of Health Stroke Scale by a non-operator independent neurologist. A clinical events adjudication committee, with pre-specified definitions, adjudicated all suspected and confirmed strokes. Major stroke was defined as any new neurologic deficit that resulted in an increase in the National Institutes of Health Stroke Scale of ≥5 points from the pre-procedure score and was still present at the 30-day follow-up visit. Strokes not meeting this definition were categorized as minor.

Analyses. For the purposes of this analysis, only data from nonoctogenarian, asymptomatic subjects in the CAPTURE 2 study were considered for the following reasons:

1. The selection of this patient population allows objective assessment of the operator and clinical site or hospital performance by excluding the 2 major known predictors of adverse events, specifically symptomatic and octogenarian patients (2,3) that would otherwise confound the analysis.
2. The analysis uses American Heart Association (AHA) guidelines for 30-day death/stroke outcomes for endarterectomy (having not been established for CAS) to define site and operator outliers. Those AHA recommendations were based on predicate data that largely excluded the octogenarian population. Because there are no accepted or established CEA thresholds for the octogenarian population (lacking adequate data), none could be used in this analysis.
3. Because operators and sites have a different mix of patient populations according to age and symptomatic status, head-to-head comparisons would have been unbalanced because there would be no way to establish a "blended" threshold to identify outliers, therefore justifying the subgroup analysis presented here.
4. A separate analysis of nonoctogenarian symptomatic patients was considered, because a threshold exists for this group. However, although the CAPTURE 2 study is the largest prospective, controlled carotid dataset ever assembled, there are not enough symptomatic nonoctogenarians to provide an adequately powered analysis. Specifically, 553 patients spread over 459 operators and 180 sites would not adequately distinguish sites and operators, due to the lack of precision in point estimates.

Baseline demographic, comorbidity, lesion, and procedural information were summarized with descriptive summary statistics. For variables involving proportions, counts, or percentages, the Clopper-Pearson exact 2-sided 95% confidence intervals were presented. The statistics for continuous variables included sample size, mean, median, SD, minimum, and maximum. For variables involving the differences between the 2 groups, asymptotic 95% confidence intervals were calculated. Linear regression modeling was conducted to analyze the relationship between the outcome event rate and potentially predictive variables from the clinical sites. Log transformation was performed on the number of subjects per site and per operator as well as on the 30-day death and stroke rates in the linear regression analyses. All statistical analyses were performed with the SAS software (version 9.1.3, SAS Institute, Cary, North Carolina).

Results

The 30-day rates of death, stroke, and myocardial infarction (DSMI) and death and stroke (DS) for the entire CAPTURE 2 cohort (n = 5,297) were 3.5% and 3.3%, respectively. The 30-day DSMI and DS rates were 3.0% and 2.8%, respectively, for asymptomatic subjects (n = 4,337) and 6.0% and 5.7%, respectively, for the symptomatic subjects (n = 721). The 30-day DSMI and DS rates were 2.9% and 2.7%, respectively, among asymptomatic nonoctogenarians (n = 3,388) and 4.5% and 4.2%, respectively, for symptomatic nonoctogenarians (n = 553). Among octogenarians, symptomatic subjects (n = 168) had higher 30-day DSMI (10.7% vs. 3.3%) and DS (10.7% vs. 3.2%) rates than asymptomatic subjects (n = 949). The 30-day major stroke rate for the entire cohort was 0.8% (44 of 5,297); for octogenarians and nonoctogenarians, it was 1.2% (14 of 1,166) and 0.7% (30 of 4,131), respectively.

The subset of asymptomatic nonoctogenarians including 3,388 patients treated at 180 U.S. hospitals by 459 operators is the focus of this analysis, as described in the Methods section. Baseline demographic data for this CAPTURE 2 subset are comparable (with the exception of age and symptom status) to those of the overall population (Table 1).

Patient characteristics. Sites were divided into 2 groups on the basis of 30-day DS rate > or <3%, corresponding to the AHA guidelines for acceptable 30-day DS rates for asymptomatic nonoctogenarians undergoing surgical revascularization (CEA) (11,12). The demographic characteristics of the <3% DS (group A, 127 sites and 2,072 patients) and ≥3% DS (group B, 53 sites and 1,316 patients) subsets were comparable in terms of mean patient age (69.3 vs. 69.3 years) and patient sex (62.3% vs. 60.3% male) distribution (Table 2). The medical histories of both cohorts were also comparable, with the exception of incidence of congestive

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Table 1. Baseline Demographic Data: All Evaluable Subjects Versus Asymptomatic and Nonoctogenarian Subjects

	All Evaluable Subjects (n = 5,297)	Asymptomatic, Nonoctogenarian Subjects (n = 3,388)
Age, yrs		
Mean ± SD (n)	72.3 ± 9.2 (5,297)	69.3 ± 7.4 (3,388)
Range (min–max)	(34.1–100.3)	(35.6–80.0)
(95% CI)*	(72.1–72.6)	(69.0–69.5)
Age ≥80 yrs	22.0% (1,166/5,297)	
(95% CI)†	(20.9%–23.2%)	
Sex		
Male	61.7% (3,266/5,297)	61.5% (2,083/3,388)
(95% CI)†	(60.3%–63.0%)	(59.8%–63.1%)
Medical history		
Symptomatic (ipsilateral stroke, TIA, amaurosis fugax ≤180 days)	14.3% (721/5,058)	
(95% CI)†	(13.3%–15.2%)	
Diabetes	36.5% (1,925/5,279)	38.7% (1,305/3,375)
(95% CI)†	(35.2%–37.8%)	(37.0%–40.3%)
Hypertension	89.2% (4,701/5,271)	89.1% (3,002/3,371)
(95% CI)†	(88.3%–90.0%)	(88.0%–90.1%)
Hypercholesterolemia	88.7% (4,609/5,198)	90.0% (3,008/3,343)
(95% CI)†	(87.8%–89.5%)	(88.9%–91.0%)
Current tobacco user	23.1% (1,177/5,085)	26.3% (862/3,279)
(95% CI)†	(22.0%–24.3%)	(24.8%–27.8%)
CHF	18.3% (958/5,240)	18.4% (616/3,352)
(95% CI)†	(17.2%–19.4%)	(17.1%–19.7%)
Prior MI	26.1% (1,306/5,008)	27.5% (888/3,232)
(95% CI)†	(24.9%–27.3%)	(25.9%–29.0%)
MI within 30 days	0.9% (45/5,008)	1.1% (34/3,232)
(95% CI)†	(0.7%–1.2%)	(0.7%–1.5%)
Needs CABG within 30 days	4.8% (239/4,995)	5.3% (170/3,226)
(95% CI)†	(4.2%–5.4%)	(4.5%–6.1%)
Arrhythmia	21.0% (1,098/5,221)	19.0% (635/3,349)
(95% CI)†	(19.9%–22.2%)	(17.6%–20.3%)
Coronary artery disease	73.2% (3,768/5,151)	74.4% (2,461/3,307)
(95% CI)†	(71.9%–74.4%)	(72.9%–75.9%)
Unstable angina	9.4% (485/5,150)	10.1% (333/3,307)
(95% CI)†	(8.6%–10.2%)	(9.1%–11.1%)
COPD	22.3% (1,160/5,204)	24.7% (824/3,336)
(95% CI)†	(21.2%–23.4%)	(23.2%–26.2%)
Renal insufficiency‡	18.7% (979/5,244)	17.9% (601/3,360)
(95% CI)†	(17.6%–19.8%)	(16.6%–19.2%)
Renal failure	3.3% (173/5,244)	3.4% (115/3,360)
(95% CI)†	(2.8%–3.8%)	(2.8%–4.1%)
Unfavorable anatomic conditions	21.8% (1,153/5,291)	22.0% (746/3,386)
(95% CI)†	(20.7%–22.9%)	(20.6%–23.5%)
Contralateral occlusion of ICA	16.9% (860/5,081)	18.1% (589/3,259)
(95% CI)†	(15.9%–18.0%)	(16.8%–19.4%)
Peripheral vascular disease	45.6% (2,299/5,037)	47.7% (1,550/3,248)
(95% CI)†	(44.3%–47.0%)	(46.0%–49.5%)
Prior CEA	16.8% (888/5,293)	18.3% (618/3,386)
(95% CI)†	(15.8%–17.8%)	(17.0%–19.6%)
Other significant disease	41.6% (2,202/5,297)	41.6% (1,410/3,388)
(95% CI)†	(40.2%–42.9%)	(40.0%–43.3%)

*By normal approximation. †Clopper-Pearson exact confidence interval (CI). ‡A subgroup of subjects with renal insufficiency were reported as having renal failure.

CABG = coronary artery bypass grafting; CEA = carotid endarterectomy; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ICA = internal carotid artery; MI = myocardial infarction; TIA = transient ischemic attack.

heart failure (CHF), which was significantly more frequent in group B (21.0%) than in group A (16.7%).

The site-reported vessel characteristics for the subject population are presented in Table 3. There was no evidence of any statistically significant difference between the 2 groups in terms of lesion location (left or right), percentage stenosis, plaque echogenocity, thrombus, or lesion length. However, higher DS rates (group B) were significantly associated with greater target lesion calcifications, more complex aortic arch anatomy, and atherosclerotic arch involvement.

Site characteristics. The 30-day periprocedural DS rate for each clinical site was plotted along with its respective patient volume (Fig. 1A). Event rates were calculated as percentages by dividing the number of DS events (left y axis) by the total number of patients (right y axis) at a given site. Two-thirds of sites (118 of 180, 66%) had no DS events and therefore had an event rate of 0%. One site is an outlier with 1 patient and 1 DS event (thus 100% DS rate) and was excluded from further analysis. Exclusion of this site does not change the results and conclusions of the analysis but improves the graphical representation of data. The remaining one-third, 61 sites, had at least 1 DS event, with the majority (52 of 61%, 85%) of these sites having DS rates exceeding 3%. Within the 61 sites with DS events, an inverse relationship

Table 2. Baseline Demographic Data for Nonoctogenarian Asymptomatic Subjects by Low and High Death/Stroke Rate Subgroups

	Low-Rate (<3%) Sites (n = 2,072)	High-Rate (≥3%) Sites (n = 1,316)	Difference (95% CI)*
Age			
Mean ± SD (n)	69.3 ± 7.4 (2,072)	69.3 ± 7.4 (1,316)	−0.07 (−0.58 to 0.44)
Range (min–max)	(35.6–80.0)	(43.8–80.0)	
(95% CI)*	(68.9–69.6)	(68.9–69.7)	
Sex			
Male	62.3% (1,290/2,072)	60.3% (793/1,316)	2.00% (−1.37% to 5.37%)
(95% CI)†	(60.1%–64.4%)	(57.6%–62.9%)	
Medical history			
Diabetes	38.0% (786/2,066)	39.6% (519/1,309)	−1.60% (−4.98% to 1.77%)
(95% CI)†	(35.9%–40.2%)	(37.0%–42.4%)	
Hypertension	89.3% (1,836/2,057)	88.7% (1,166/1,314)	0.52% (−1.65% to 2.69%)
(95% CI)†	(87.8%–90.6%)	(86.9%–90.4%)	
Hypercholesterolemia	90.8% (1,857/2,046)	88.7% (1,151/1,297)	2.02% (−0.11% to 4.15%)
(95% CI)†	(89.4%–92.0%)	(86.9%–90.4%)	
Current tobacco user	27.3% (548/2,009)	24.7% (314/1,270)	2.55% (−0.52% to 5.62%)
(95% CI)†	(25.3%–29.3%)	(22.4%–27.2%)	
CHF	16.7% (343/2,049)	21.0% (273/1,303)	−4.21%‡ (−6.95% to −1.47%)
(95% CI)†	(15.1%–18.4%)	(18.8%–23.3%)	
Prior MI	26.4% (522/1,977)	29.2% (366/1,255)	−2.76% (−5.94% to 0.42%)
(95% CI)†	(24.5%–28.4%)	(26.7%–31.8%)	
Arrhythmia	18.6% (380/2,045)	19.6% (255/1,304)	−0.97% (−3.71% to 1.76%)
(95% CI)†	(16.9%–20.3%)	(17.4%–21.8%)	
Coronary artery disease	75.0% (1,522/2,029)	73.5% (939/1,278)	1.54% (−1.53% to 4.61%)
(95% CI)†	(73.1%–76.9%)	(71.0%–75.9%)	
COPD	24.9% (509/2,046)	24.4% (315/1,290)	0.46% (−2.54% to 3.46%)
(95% CI)†	(23.0%–26.8%)	(22.1%–26.9%)	
Renal insufficiency	18.2% (374/2,050)	17.3% (227/1,310)	0.92% (−1.73% to 3.56%)
(95% CI)†	(16.6%–20.0%)	(15.3%–19.5%)	
Unfavorable anatomic conditions	22.8% (473/2,072)	20.8% (273/1,314)	2.05% (−0.79% to 4.89%)
(95% CI)†	(21.0%–24.7%)	(18.6%–23.1%)	
Contralateral occlusion of ICA	17.6% (354/2,009)	18.8% (235/1,250)	−1.18% (−3.91% to 1.55%)
(95% CI)†	(16.0%–19.4%)	(16.7%–21.1%)	
Peripheral vascular disease	47.2% (943/2,000)	48.6% (607/1,248)	−1.49% (−5.02% to 2.04%)
(95% CI)†	(44.9%–49.4%)	(45.8%–51.5%)	
Prior CEA	18.2% (376/2,071)	18.4% (242/1,315)	−0.25% (−2.92% to 2.43%)
(95% CI)†	(16.5%–19.9%)	(16.3%–20.6%)	

*By normal approximation. †Clopper-Pearson exact CI. ‡Statistically significant.
Abbreviations as in Table 1.

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Table 3. Vessel Characteristics for Nonoctogenarian Asymptomatic Subjects by Low and High Death/Stroke Rate Subgroups

	Low-Rate (<3%) Sites (n = 2,072 Patients, 2,102 Lesions)	High-Rate (≥3%) Sites (n = 1,316 Patients, 1,326 Lesions)	Difference (95% CI)*
Lesion location			
Left internal carotid	45.1% (949/2,102)	45.2% (599/1,326)	−0.03% (−3.45% to 3.39%)
(95% CI)†	(43.0%–47.3%)	(42.5%–47.9%)	
Right internal carotid	44.2% (929/2,102)	44.2% (586/1,326)	0.00% (−3.41% to 3.42%)
(95% CI)†	(42.1%–46.3%)	(41.5%–46.9%)	
Left common carotid	4.7% (99/2,102)	4.4% (59/1,326)	0.26% (−1.17% to 1.69%)
(95% CI)†	(3.8%–5.7%)	(3.4%–5.7%)	
Right common carotid	3.7% (78/2,102)	3.2% (43/1,326)	0.47% (−0.78% to 1.72%)
(95% CI)†	(2.9%–4.6%)	(2.4%–4.3%)	
Left internal carotid/left common carotid	1.4% (29/2,102)	1.4% (19/1,326)	−0.05% (−0.86% to 0.76%)
(95% CI)†	(0.9%–2.0%)	(0.9%–2.2%)	
Right internal carotid/right common carotid	0.9% (18/2,102)	1.5% (20/1,326)	−0.65% (−1.42% to 0.11%)
(95% CI)†	(0.5%–1.4%)	(0.9%–2.3%)	
Target lesion stenosis (%)			
Mean ± SD (n)	85.9 ± 7.2 (2,102)	86.1 ± 7.7 (1,325)	−0.25 (−0.76 to 0.26)
Range (min–max)	(49.0–99.0)	(50.0–99.0)	
(95% CI)*	(85.5–86.2)	(85.7–86.5)	
Target lesion length (mm)			
Mean ± SD (n)	18.5 ± 8.5 (2,095)	18.1 ± 9.4 (1,324)	0.39 (−0.22 to 1.00)
Range (min–max)	(2.0–100.0)	(2.0–80.0)	
(95% CI)*	(18.1–18.9)	(17.6–18.6)	
Target site calcification			
None	25.9% (544/2,097)	21.7% (288/1,325)	4.21%‡ (1.30% to 7.11%)
(95% CI)†	(24.1%–27.9%)	(19.5%–24.1%)	
Mild	51.5% (1,080/2,097)	57.8% (766/1,325)	−6.31%‡ (−9.72% to −2.90%)
(95% CI)†	(49.3%–53.7%)	(55.1%–60.5%)	
Heavy	22.6% (473/2,097)	20.5% (271/1,325)	2.10% (−0.71% to 4.92%)
(95% CI)†	(20.8%–24.4%)	(18.3%–22.7%)	
Thrombus present at target site	3.0% (62/2,101)	2.5% (33/1,326)	0.46% (−0.65% to 1.57%)
(95% CI)†	(2.3%–3.8%)	(1.7%–3.5%)	
Aortic arch type			
I	49.3% (1,021/2,070)	44.9% (593/1,320)	4.40%‡ (0.96% to 7.84%)
(95% CI)†	(47.1%–51.5%)	(42.2%–47.7%)	
II	40.7% (842/2,070)	44.2% (583/1,320)	−3.49%‡ (−6.90% to −0.08%)
(95% CI)†	(38.6%–42.8%)	(41.5%–46.9%)	
III	10.0% (207/2,070)	10.9% (144/1,320)	−0.91% (−3.03% to 1.21%)
(95% CI)†	(8.7%–11.4%)	(9.3%–12.7%)	
Target lesion echogenicity			
Completely soft	24.2% (489/2,022)	22.2% (285/1,283)	1.97% (−0.97% to 4.91%)
(95% CI)†	(22.3%–26.1%)	(20.0%–24.6%)	
Completely calcified	7.5% (152/2,022)	8.6% (110/1,283)	−1.06% (−2.97% to 0.86%)
(95% CI)†	(6.4%–8.8%)	(7.1%–10.2%)	
Mixed	68.3% (1,381/2,022)	69.2% (888/1,283)	−0.91% (−4.15% to 2.33%)
(95% CI)†	(66.2%–70.3%)	(66.6%–71.7%)	
Aortic arch characteristic			
Diseased	44.9% (934/2,079)	51.1% (668/1,307)	−6.18%‡ (−9.64% to −2.73%)
(95% CI)†	(42.8%–47.1%)	(48.4%–53.9%)	
Nondiseased	55.1% (1,145/2,079)	48.9% (639/1,307)	6.18%‡ (2.73% to 9.64%)
(95% CI)†	(52.9%–57.2%)	(46.1%–51.6%)	

*By normal approximation. †Clopper-Pearson exact confidence interval (CI). ‡Statistically significant.

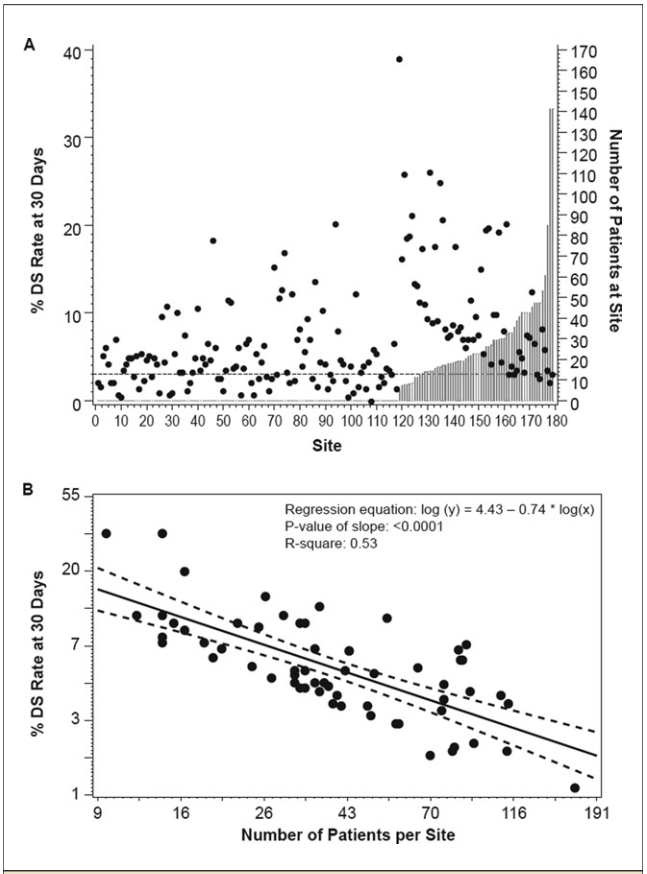

Figure 1. Patient DS Rate by Site and Patients/Site and Linear Regression of DS

(A) Death and stroke (DS) rate of nonoctogenarian asymptomatic patients by site and number of patients/site (**dotted horizontal line** indicates American Heart Association guideline of 3% event rate for asymptomatic patients). **(B)** Linear regression of DS on number of patients/site.

between event rates and patient volume was noted graphically (Fig. 1A) and represented quantitatively by a linear regression with log transformation of both variables to better reflect the nature of the observation. The result is given by the equation $\log(y) = 4.43 - 0.74^{*}\log(x)$, where y represents DS rates and x represents volume in number of patients/site, with p value for slope <0.0001, and $r^2 = 0.53$ (Fig. 1B).

Of the 118 sites without any DS events, patient volumes ranged widely. Low-volume sites (i.e., with less than 10 cases) have too small a sample size to accurately predict DS rates. In addition, adding a single event to a low-volume site would result in a high DS rate because of the smaller denominator, therefore confirming the inverse relationship observed with sites with DS events. In the same manner, a high-volume non-event site would have a low DS rate if their next case had an event, because of the larger denominator, therefore confirming again the inverse relationship observed. As a sensitivity analysis and to verify the validity of the methodology, 1 DS event was added to all sites with no events, then the plot was assessed, and a log-log regression analysis performed. A relationship similar to that seen in the sites with DS events was observed, and the regression showed lower p value and higher r^2, indirectly confirming and providing robustness to the original interpretation.

There was no evidence that hospital type or hospital geographic location had significant influence on outcomes at the $p = 0.05$ level (Table 4). Baseline demographic and lesion vessel characteristics of the patients were comparable across types of hospitals and hospital geographic regions. The DS rates were plotted against the number of staffed beds/hospital to evaluate whether outcomes were influenced by hospital size. No apparent relationship was observed (Fig. 2A). The lack of association was confirmed by a linear regression analysis, with p value for slope 0.4131, and $r^2 = 0.01$ (Fig. 2B).

Operator characteristics. To assess whether the inverse relationship between volume and DS rates was related not just to site volume but also to the individual operator volume, DS rates were plotted for each operator. Four of 5 operators (348 of 425, 82%) had no DS events and therefore had an event rate of 0%. The remaining 20%, 77 operators, had at least 1 DS event; 71 (92%) of these operators had DS rates exceeding 3% of their patient volume. An inverse relationship between event rates and operator volume was again observed (Fig. 3A). After log transformation of both variables, a simple linear regression was done to quantitatively assess the relationship. The result is given by the equation $\log(y) = 4.71 - 0.85^{*}\log(x)$, where y represents DS rates and x represents volume in number of patients/operator, with p value for slope <0.0001, and $r^2 = 0.81$ (Fig. 3B).

To further investigate whether the results were similar or discordant across the specialties of the operators, linear regression was performed for each of the 5 specialties. The results were consistent across all specialties, confirming that individual operator volume was a determinant of outcome, independent of the specialty of the operator; analyses were presented for the 2 largest groups (Figs. 4A to 4D).

A summary of periprocedural outcomes by physician specialty is presented in Table 5. The baseline demographic data, comorbidities, and site-reported carotid lesion characteristics of the patient population treated by each physician specialty were comparable, with the exception that vascular surgery patients had less reported target lesion calcification and aortic arch disease, fewer type III arches, more prior CEA, and more contralateral occlusion of the internal carotid artery. Interventional cardiology (IC) patients had more coronary artery disease, unstable angina, and peripheral artery disease than any other specialty. Patients treated by IC, which represented the largest proportion, tended to have lower DS rates than the other specialties, although these differences were not statistically significant at the 0.05 level. Of interest, among the only 2 specialties with sufficient patient volumes to allow for comparison, the ratio of

Table 4. Death and Stroke Events Within 30 Days by Hospital Type and Region for Asymptomatic Subjects <80 Years of Age

Events	Community Hospital (n = 433) (M = 24)	Private Hospital (n = 1,101) (M = 67)	Teaching Hospital (n = 1,854) (M = 89)	Midwest (n = 1,017) (M = 53)	Northeast (n = 675) (M = 29)	South (n = 1,338) (M = 71)	West (n = 358) (M = 27)
Death	0.0% (0/433)	0.8% (9/1,101)	1.0% (18/1,854)	0.8% (8/1,017)	0.6% (4/675)	1.1% (15/1,338)	0.0% (0/358)
(95% CI)*	(0.0%–0.8%)	(0.4%–1.5%)	(0.6%–1.5%)	(0.3%–1.5%)	(0.2%–1.5%)	(0.6%–1.8%)	(0.0%–1.0%)
All stroke	2.5% (11/433)	1.7% (19/1,101)	2.2% (41/1,854)	2.5% (25/1,017)	2.1% (14/675)	1.9% (26/1,338)	1.7% (6/358)
(95% CI)*	(1.3%–4.5%)	(1.0%–2.7%)	(1.6%–3.0%)	(1.6%–3.6%)	(1.1%–3.5%)	(1.3%–2.8%)	(0.6%–3.6%)
Major stroke	0.9% (4/433)	0.5% (6/1,101)	0.6% (12/1,854)	0.4% (4/1,017)	0.6% (4/675)	0.8% (11/1,338)	0.8% (3/358)
(95% CI)*	(0.3%–2.3%)	(0.2%–1.2%)	(0.3%–1.1%)	(0.1%–1.0%)	(0.2%–1.5%)	(0.4%–1.5%)	(0.2%–2.4%)
Minor stroke	1.8% (8/433)	1.2% (13/1,101)	1.6% (29/1,854)	2.1% (21/1,017)	1.5% (10/675)	1.1% (15/1,338)	1.1% (4/358)
(95% CI)*	(0.8%–3.6%)	(0.6%–2.0%)	(1.0%–2.2%)	(1.3%–3.1%)	(0.7%–2.7%)	(0.6%–1.8%)	(0.3%–2.8%)
Death–stroke†	2.5% (11/433)	2.4% (26/1,101)	2.9% (53/1,854)	3.2% (33/1,017)	2.4% (16/675)	2.6% (35/1,338)	1.7% (6/358)
(95% CI)*	(1.3%–4.5%)	(1.5%–3.4%)	(2.1%–3.7%)	(2.2%–4.5%)	(1.4%–3.8%)	(1.8%–3.6%)	(0.6%–3.6%)
Death–major stroke†	0.9% (4/433)	1.2% (13/1,101)	1.3% (24/1,854)	1.2% (12/1,017)	0.9% (6/675)	1.5% (20/1,338)	0.8% (3/358)
(95% CI)*	(0.3%–2.3%)	(0.6%–2.0%)	(0.8%–1.9%)	(0.6%–2.1%)	(0.3%–1.9%)	(0.9%–2.3%)	(0.2%–2.4%)

N = 3,388. *Clopper-Pearson exact confidence interval (CI). †Only includes each subject's first occurrence of the most serious event.
n = number of patients; M = number of hospitals.

minor/major strokes in patients treated by IC was approximately 2.5, compared with a ratio of approximately 1.25 for patients treated by vascular surgery, suggesting a potential difference in the mix of stroke severity between these 2 groups. No differences were observed between specialties in location of stroke (ipsilateral vs. non-ipsilateral) for either major or minor strokes.

Discussion

The CAPTURE 2 study represents the highest level of scientific inquiry for a post-market study and should be differentiated from a registry, which is characterized by self-reported events and no adjudication. This analysis of the CAPTURE 2 data was initiated by the observation that there were outcome disparities among participating sites and that, by identifying predictors of those differences, clinical results might further improve. The analysis was restricted to a large subgroup of patients to eliminate the influence of the 2 key predictors of outcome, symptomatic status and age (80 years and over). Site and individual operator case volume correlated most strongly with outcome, confirming other previous observations (2,13–16). Among the multiple patient factors assessed, congestive heart failure and certain anatomic features were more frequent in sites with DS higher than AHA guideline standards. Although specialty training of the operators did not influence the frequency of outcome events, the severity of stroke seemed to vary by operator specialty.

Improvement of CAS peri-procedural outcomes. The CAPTURE 2 study represents a valuable source of prospectively gathered, adjudicated CAS outcome data. It currently includes 5,279 evaluable patients treated at 184 hospitals and by 459 physicians from a variety of specialties at community, private, and teaching hospitals. The 30-day DS rate for the entire cohort of 5,297 patients was 3.5%, a significant improvement over that demonstrated in earlier CAS clinical trials with many fewer investigators and sites, where overall rates were 7% to 8% (SAPPHIRE [Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy], ARCHeR [ACCULINK for Revascularization of Carotids in High-Risk patients]) (17). For patients <80 years of age (nonoctogenarians), the DS rate for asymptomatic and symptomatic patients was 2.7% and 5.7%, respectively; both rates are well within the AHA guidelines defining acceptable risk of DS with carotid endarterectomy in asymptomatic (3%) and symptomatic (6%) patients. Importantly and to put the results from the CAPTURE 2 study in proper context, these AHA guidelines were developed on the basis of evidence from carotid endarterectomy in the population of patients for whom surgery was standard risk; because the CAPTURE 2 study enrolled only patients considered higher-risk for endarterectomy, the attainment of DS rates within the AHA guideline is notable. It should also be noted that improvements relative to earlier trials (10) are also observed in both the overall and subset (octogenarian, symptomatic, and so forth) populations.

Understanding factors that place patients at risk for perioperative complications facilitates continued improvement in CAS outcomes. Since the advent of CAS, efforts have been made to understand which patient and physician factors are associated with adverse outcomes in the periprocedural (≤30 days) period. Numerous studies (2–7,18–22) analyzing risk factors for CAS have identified patient-related factors, such as age and symptom status. Less is known about physician- and site-related variables that impact outcome. The current study illuminates the potential impact of these other factors. Interventionists with different

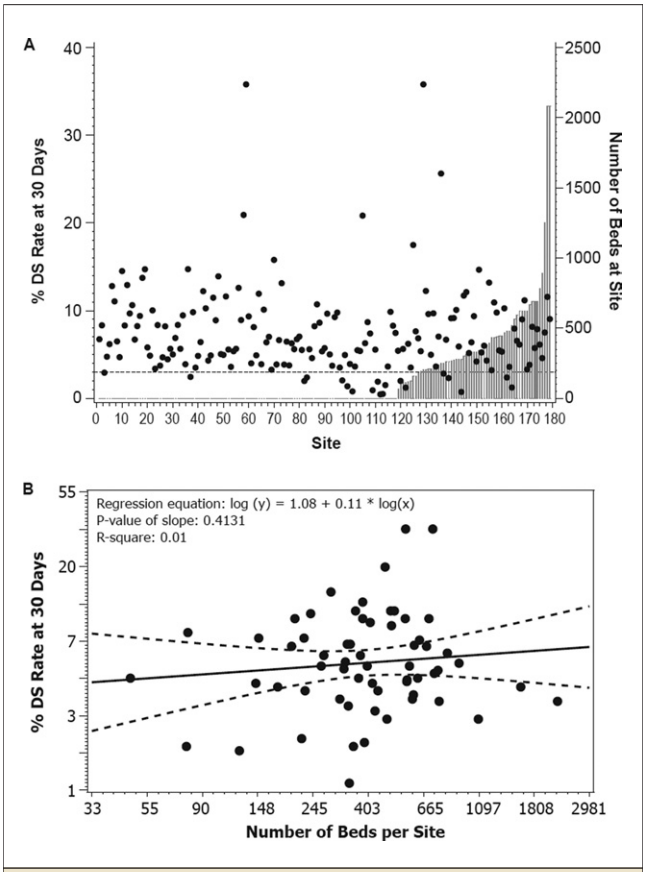

Figure 2. Patient DS Rate and Number of Staffed Beds/Hospital and Linear Regression of DS Rate on Number of Staffed Beds/Hospital

(A) Death and stroke (DS) rate of nonoctogenarian asymptomatic patients and number of staffed beds/hospital (**dotted horizontal line** indicates American Heart Association guideline of 3% event rate for asymptomatic patients). **(B)** Linear regression of DS rate on number of staffed beds/hospital.

specialty-training backgrounds and experience levels are performing CAS. Training, competency, and credentialing standards will continue to be developed and refined for CAS operators—as was the case with CEA (23,24)—and should be predicated on an understanding of the physician factors associated with successful CAS outcomes.

Influence of patient volume on periprocedural outcome. The availability of this large dataset of independently adjudicated CAS outcomes provides a unique opportunity to investigate physician-associated factors influencing outcomes, to help identify "best practice" guidelines for practitioners. It is noteworthy that most sites (118 of 180, 66%) did not report any events in the 30-day period after CAS. The remaining 61 sites reporting events become an important source of information regarding factors that influence outcome. A striking inverse relationship between DS rate and patient volume was identified at these sites: the more patients treated, the lower the event rate (r^2 = 0.53) (Fig. 1). This was even more pronounced when outcomes and patient numbers were stratified by individual physician volume (r^2 = 0.81) (Fig. 2). Notably, the relationship between higher operator and site patient volume and favorable outcomes has also been reported for CEA (13,15).

The regression model derived from the CAPTURE 2 study can be used to estimate the minimum number of carotid artery stenting procedures to achieve a DS rate below 3%. Replacing the value of 3% in the equation, log(rate) = 4.71 to 0.845 log(case), yields a minimum case number of 72. This value is higher than what has been suggested in the past or what has served as the threshold for enrolling patients in randomized trials like the CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) or ACT I (Carotid Stenting vs. Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients) trials.

Center volume was also found to be a significant predictor of peri-interventional death and stroke in a recent analysis of the Pro-CAS (Prospective Registry of Carotid Artery Stenting) data (2). Although individual operator experience was not captured in the Pro-CAS study, estimation of the appropriate individual physician learning curves (>15 interventions) was

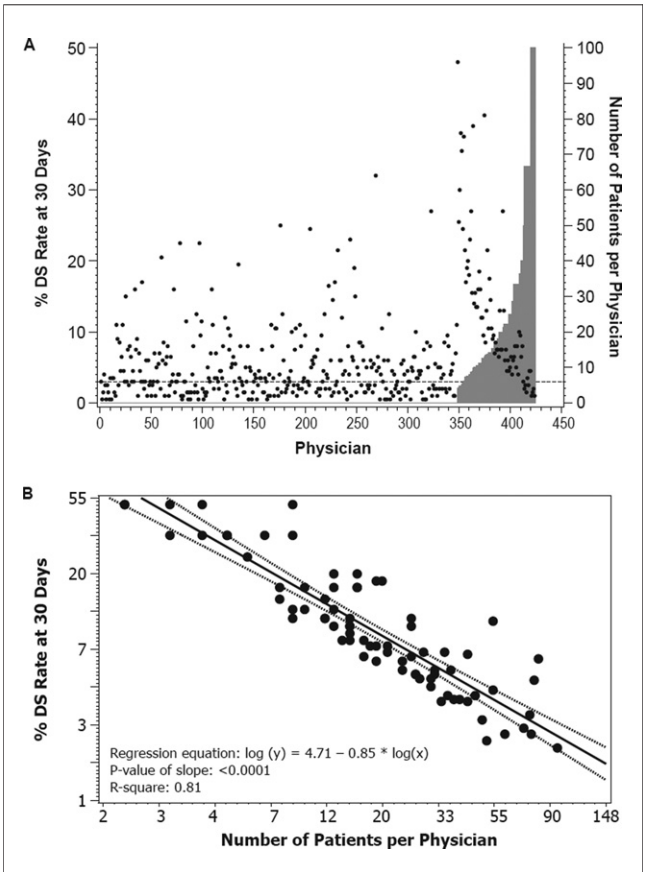

Figure 3. Patient DS Rate and Number of Patients/Physician and Linear Regression of DS Rate on Number of Patients/Physician

(A) Death and stroke (DS) rate of nonoctogenarian asymptomatic patients and number of patients/physician (**dotted horizontal line** indicates American Heart Association guideline of 3% event rate for asymptomatic patients). **(B)** Linear regression of DS rate on number of patients/physician.

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Figure 4. Patient DS by Specialty

(A) Death and stroke (DS) rate by number of patients/physician for interventional cardiologists (**dotted horizontal line** indicates American Heart Association guideline of 3% event rate for asymptomatic patients). **(B)** Linear regression of DS rate by number of patients for interventional cardiologists. **(C)** The DS rate by number of patients for vascular surgeons (**dotted horizontal line** indicates American Heart Association guideline of 3% event rate for asymptomatic patients). **(D)** Linear regression of DS rate by number of patients for vascular surgeons.

based on a mean number of cases/operator/site. In the current analysis, data regarding individual operator volume were available, allowing a more precise examination of the relationship between physician caseload and outcome. The association of higher adverse outcome rates with low patient volume underscores the importance of experience. Although various early credentialing documents have recommended minimum numbers of proctored procedures, (25) the number of CAS interventions (both observed and proctored) required for an operator to become competent has not yet been established in the published reports on the basis of outcome data.

Impact of physician training. It should be noted that the CAPTURE 2 study was neither designed nor powered to show outcome differences for physician specialties. There seemed to be trends in volume according to operator specialty: the mean number of patients treated per surgeon was 6.5 (725 patients treated by 112 physicians) and per cardiologists was 9.1 (2,312 patients treated by 255 physicians). The inverse relationship of patient volume and periprocedural outcomes was independent of physician specialty, suggesting that highly experienced operators from any of the specialties achieve better outcomes. Although we found no evidence of significant differences in outcome rates by specialty, there seem to be disparities in ratios of minor to major strokes for the different specialties.

Reflections on current processes and future trials. This analysis confirms the value of FDA-mandated, post-market approval surveillance studies in data-collection and possible process improvements. This is especially relevant in a technically demanding procedure such as CAS. Furthermore, the finding of volume/experience as predictor of outcome is important not only for the analysis of prior studies and their results but also to establish the experience and training requirements for future trials as a way to eliminate unqualified operators as potential confounders of outcomes.

Study limitations and strengths. The analyses presented in this report were not pre-specified at the start of the study or in the protocol; however, they were pre-defined at the concept stage of the report and are based on a large subgroup of asymptomatic nonoctogenarian patients. Therefore, we should caution the reader about making strong inferential statements, because most of the analyses should be interpreted as exploratory. However, given the large cohort explored, these analyses have value and add to the weight of evidence that experience matters in technical procedures.

Table 5. Death and Stroke Events Within 30 Days by Physician Specialty for Asymptomatic Subjects <80 Years of Age

	Interventional Cardiologist (n = 255 inv) (N = 2,312 pts)	Interventional Neuroradiologist (n = 19 inv) (N = 132 pts)	Interventional Radiologist (n = 34 inv) (N = 208 pts)	Neurosurgeon (n = 10 inv) (N = 51 pts)	Vascular Surgeon (n = 102 inv) (N = 674 pts)
Hierarchical events*					
All death, stroke, and MI	2.7% (63/2,312)	3.0% (4/132)	2.9% (6/208)	3.9% (2/51)	3.3% (22/674)
(95% CI)†	(2.1%–3.5%)	(0.8%–7.6%)	(1.1%–6.2%)	(0.5%–13.5%)	(2.1%–4.9%)
All stroke, death	2.5% (58/2,312)	3.0% (4/132)	2.4% (5/208)	3.9% (2/51)	3.1% (21/674)
(95% CI)†	(1.9%–3.2%)	(0.8%–7.6%)	(0.8%–5.5%)	(0.5%–13.5%)	(1.9%–4.7%)
Major stroke, death	1.1% (26/2,312)	1.5% (2/132)	0.5% (1/208)	2.0% (1/51)	1.6% (11/674)
(95% CI)†	(0.7%–1.6%)	(0.2%–5.4%)	(0.0%–2.6%)	(0.0%–10.4%)	(0.8%–2.9%)
Nonhierarchical events*					
Death	0.6% (15/2,312)	1.5% (2/132)	0.5% (1/208)	0.0% (0/51)	1.3% (9/674)
(95% CI)†	(0.4%–1.1%)	(0.2%–5.4%)	(0.0%–2.6%)	(0.0%–7.0%)	(0.6%–2.5%)
All stroke	1.9% (45/2,312)	1.5% (2/132)	1.9% (4/208)	3.9% (2/51)	2.7% (18/674)
(95% CI)†	(1.4%–2.6%)	(0.2%–5.4%)	(0.5%–4.9%)	(0.5%–13.5%)	(1.6%–4.2%)
Major stroke	0.6% (13/2,312)	0.0% (0/132)	0.0% (0/208)	2.0% (1/51)	1.2% (8/674)
(95% CI)†	(0.3%–1.0%)	(0.0%–2.8%)	(0.0%–1.8%)	(0.0%–10.4%)	(0.5%–2.3%)
Minor stroke	1.4% (33/2,312)	1.5% (2/132)	1.9% (4/208)	2.0% (1/51)	1.5% (10/674)
(95% CI)†	(1.0%–2.0%)	(0.2%–5.4%)	(0.5%–4.9%)	(0.0%–10.4%)	(0.7%–2.7%)
MI	0.4% (9/2,312)	0.0% (0/132)	0.5% (1/208)	0.0% (0/51)	0.3% (2/674)
(95% CI)†	(0.2%–0.7%)	(0.0%–2.8%)	(0.0%–2.6%)	(0.0%–7.0%)	(0.0%–1.1%)

*Only includes the first occurrence of the most serious event for each subject. †Clopper-Pearson exact confidence interval (CI).
MI = myocardial infarction; N = number of patients; n = number of investigators (inv).

Another limitation of the current analysis is the lack of information about the true CAS volume of both operators and sites. This analysis only includes CAPTURE 2 patients and ignores the overall site or operator volume performed outside of the study. For much of the course of enrollment in the CAPTURE 2 study, availability of CAS outside of the study at these sites and for these operators was limited. Despite the absence of data regarding overall CAS volumes, the strength of the relationships associating CAS volume to outcome in the CAPTURE 2 study alone is evidenced by high values of the coefficient of determination r^2.

Lastly, although data on the angiographic and lesion characteristics were analyzed and seemed to yield outcome predictors (e.g., aortic arch type), the lack of an angiographic or ultrasound core laboratory limits the strength of these findings.

Conclusions

Outcomes from the largest prospectively gathered, independently adjudicated, multicenter CAS study indicate that CAS can be safely performed in a variety of hospital settings by physicians with various specialties. The most important determinant of perioperative CAS outcomes was both site and operator CAS volume. A threshold of 72 cases was found to be necessary for consistently achieving a DS rate below 3%.

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Key Words: angioplasty ■ carotid ■ risk factors ■ stenosis ■ stents ■ stroke.