Thirty-Day Outcomes for Carotid Artery Stenting in 6320 Patients From 2 Prospective, Multicenter, High-Surgical-Risk Registries

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Background—The American Heart Association has established guidelines for acceptable 30-day death and stroke rates for patients with severe carotid disease undergoing standard-risk carotid endarterectomy: <3% for asymptomatic lesions and <6% for symptomatic lesions. To date, carotid artery stenting has not demonstrated these outcomes in multicenter, prospective assessments of high-surgical-risk patients.

Methods and Results—Data from 2 prospective, multicenter (280 US sites, 672 operators), postmarket surveillance studies in high-surgical-risk patients were analyzed: 2145 patients from the Emboshield and Xact Post Approval Carotid Stent Trial (EX) and 4175 patients from the Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (C2). Both studies had pre- and postprocedure neurological evaluation and independent adjudication of neurological events. The overall 30-day death and stroke rate was 4.1% (95% CI, 3.3% to 5.0%) for EX and 3.4% (95% CI, 2.9% to 4.0%) for C2. In the population comparable with American Heart Association guidelines (<80 years), the combined 30-day death and stroke rate was 5.3% (95% CI, 3.6% to 7.4%) for symptomatic patients and 2.9% (95% CI, 2.4% to 3.4%) for asymptomatic patients, independent of unfavorable risk factors (anatomic or physiologic); in patients ≥80 years, this rate was 10.5% (95% CI, 6.3% to 16.0%) and 4.4% (95% CI, 3.3% to 5.7%), respectively. In subjects with anatomic features unfavorable for surgery, the 30-day death and stroke rates were 1.7% (95% CI, 0.0% to 8.9%) and 2.7% (95% CI, 1.3% to 4.9%) for symptomatic and asymptomatic cohorts, respectively, independent of age.

Conclusions—Outcomes for carotid artery stenting in nonoctogenarian high-surgical-risk patients have improved since the pivotal Food and Drug Administration approval trials, and have achieved American Heart Association standards in both symptomatic and asymptomatic lesions. (Circ Cardiovasc Intervent. 2009;2:159-166.)

Key Words: carotid arteries ■ stenosis ■ stroke ■ stents ■ outcomes

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To minimize potential confounding variables, the NASCET and ACAS studies excluded patients with significant medical or surgical comorbidities, including patients >79 years old (upper age limit was removed for the moderate stenosis portion of NASCET). The medical conditions included significant coronary artery disease, ventricular dysfunction, pulmonary disease, renal insufficiency, etc, and the surgical conditions included previous CEA, neck surgery, previous radiation therapy, tracheostomy, etc. In NASCET, contralateral occlusion was not excluded, but resulted in a 30-day risk of stroke and death of 14.3%, and in ACAS resulted in a 2% increase of stroke and death compared with medical therapy. Although following publication of these 2 trials there has been a broad use of CEA, including in high-surgical-risk patients as a result of the extrapolation of these study outcomes, there has never been a demonstration of significant benefit with CEA for patients with hemispheric ischemia and for men.
of CEA outcomes meeting the AHA recommendations for patients with high-surgical-risk factors in a rigorously conducted multicenter, prospective trial, with independent neurological assessment and independent event adjudication.

Carotid artery stenting (CAS) with embolic protection was originally introduced as a therapeutic alternative to surgery in these high-surgical-risk patients determined to require revascularization for stroke prevention. Initial randomized trial results demonstrated a nearly statistically significant improvement in outcomes at 1 year for the stent arm compared with CEA7 and good durability of the CAS result, matching the stroke prevention efficacy of CEA extending to 4 years.8–10 In this report, data are presented from 2 large, rigorously conducted, prospective, postmarket carotid stenting studies in patients at risk for surgery: final results from Emboshield and Xact Post Approval Carotid Stent Trial (EXACT) and interim data from Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2).

Methods

Postmarket Surveillance Study Rationale and Timelines

Following Food and Drug Administration (FDA) device approval of the Guidant Acculink stent and Accunet filter CAS system (subsequently acquired by Abbott Vascular, Santa Clara, Calif) in August 2004, the original CAPTURE study was established in October 2004 as a condition of approval to assess the occurrence of rare/unanticipated device-related events (standard for new device approvals) and to assess the adequacy of the technology transfer to the nontrial setting through training and operator selection. The study completed enrollment in December 2006, with 4225 subjects analyzed. The clinical study report was submitted to FDA and results were published in peer-review journals.11–13 The EXACT (EX) study was similarly initiated in November 2005, after FDA approval of the Xact stent and Emboshield filter system (Abbott Vascular). The study completed enrollment in April 2007, with 2145 subjects analyzed.

Continued assessment of CAS in this country was undertaken with both FDA oversight and the Centers for Medicare and Medicaid Services coverage in the form of the CAPTURE 2 (C2) study. which was initiated in March 2006, and enrollment is ongoing. This report includes the final results of EX and the interim results of C2.

Selection of Interventionalists and Patients

EX and C2 included physicians with an array of experience in carotid interventions, ranging from the most experienced (level 1) carotid interventionalists (eg, having participated in the pivotal carotid stenting studies) to the least experienced (level 3). As compared with the original CAPTURE operators these physicians tended to be more experienced, with 73% being either levels 1 or 2 (versus 65% in CAPTURE), and they gained further experience throughout the course of these studies. There were 253 investigators at 128 sites in EX and 519 investigators at 186 sites in C2. With 100 investigators and 34 sites overlapping between the studies, a total of 280 sites and 34 sites overlapping between the studies, a total of 34 sites the outcomes reported herein. The CAS operators represented a variety of medical subspecialties, including interventional cardiology, interventional radiology or neuroradiology, vascular surgery, and neurosurgery. Training requirements and device certification have been described previously.11 As the intent of these studies was observation of actual practice, no explicit patient inclusion and exclusion criteria were specified. However, training for both devices and studies emphasized patient selection criteria consistent with the FDA-approved device indications for use, which are high-surgical-risk patients who have symptomatic (≥50% stenosis) or asymptomatic (≥80% stenosis) lesions in the internal or common carotid artery. These FDA-approved indications for CAS include the following anatomic and physiological risk features: knowledge of 2 or more proximal or major diseased coronary arteries with ≥70% stenosis that have not, or cannot be revascularized, unstable angina defined as rest angina with ECG changes, myocardial infarction (MI) within the previous 30 days, and current need for carotid artery revascularization, concurrent requirement for aortocoronary bypass or cardiac valve surgery within 30 days, contralateral occlusion of the internal carotid artery, currently on a list for major organ transplantation (ie, heart, lung, liver, kidney) or is being evaluated for such, ejection fraction <30% or New York Heart Association functional class III or higher, forced expiratory volume in 1 second <30% (predicted), dialysis-dependent renal failure, uncontrolled diabetes defined as fasting glucose ≥400 mg/dl and ketones >2+, restenosis after previous CAS, patient is status/postradiation treatment to the neck, patient is status/postradical neck surgery, surgically inaccessible lesions (eg, lesions above the level of C2 or below the clavicle, lesions obstructed by tumors in the neck), spinal immobility (inability to flex neck beyond neutral or kyphotic deformity), presence of tracheostomy stoma, and contralateral laryngeal nerve paralysis. Of the patients presented in this analysis, only 9.7% did not have a high-risk feature defined by the site. Exclusion criteria used in the pivotal ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHER) study14 were not imposed in these studies: patients with other potential sources of stroke (prosthetic valves, atrial fibrillation, bilateral severe carotid artery stenosis, etc), and other surgical procedures within the first 30 days had access to treatment with CAS despite the potentially confounding nature of these conditions on outcomes. The EX and C2 study protocols were approved by the local institutional review boards at all participating sites, and patients provided written informed consent prior to study treatment.

Study Assessment and End Points

Investigators were to sequentially enroll all consenting patients appropriate for CAS revascularization in their practice into these studies according to approved FDA indications; once a patient was enrolled, the outcome of the procedure was included for evaluation in this report if the patient underwent 30-day follow-up or reached a study end point. The high-surgical-risk indication was recorded and, within 14 days previous to treatment, patients were interviewed and examined by an independent (nonoperator) study neurologist, including assessment according to the National Institutes of Health Stroke Scale (NIHSS). A neurological examination and NIHSS were completed 24 hours and 30 days after procedure to monitor for stroke and other adverse neurological clinical events. Because assessment of NIHSS by nonphysicians has been confirmed as a valid method of neurological evaluation,15–17 NIHSS certified personnel were also allowed to perform these independent evaluations.

Primary End Point

The primary end point for the 2 studies was identical: a composite of death, any stroke, or MI within 30 days of the procedure. In the event of death during the follow-up period, efforts were made to obtain relevant records from the hospital or the patient’s primary care physician, including death certificates and autopsy reports, to determine the cause of death.

For purposes of end point analysis, patients having 2 procedures within 30 days were considered as 1 patient: 8 patients were identified in EX and 38 patients in C2 as having procedures within 30 days, and therefore, were counted once in the denominator.

Independent Review of Safety Data

An independent Clinical Events Adjudication Committee (CEAC) using prespecified definitions reviewed strokes or suspected strokes, MI and death were not adjudicated and are entered as site reported. The CEAC composition in EX included 1 neurologist, 1 vascular surgeon, and 1 interventionalist (surgeon, radiologist, cardiologist); in C2, the CEAC included 2 neurologists and 1 interventionalist. In addition, an independent Data Safety Monitoring Board, consisting
of a neurologist, an interventional neuroradiologist, and a biostatistician, was responsible for monitoring cumulative safety data and to make recommendations regarding continuance of the study. Members of both the CEAC and the Data Safety Monitoring Board did not participate in the study as investigators.

Definitions

In both studies, patients were identified as symptomatic if they had experienced a transient ischemic attack, amaurosis fugax, or stroke in the territory supplied by the target vessel within 180 days previous to procedure. In both studies, procedural stroke and stroke severity were determined by the CEAC. Potential stroke events were reported to the CEAC if the local sites suspected a stroke based on clinical symptoms or a change in the NIHSS. Stroke included any acute neurological ischemic or hemorrhagic event lasting at least 24 hours in duration with focal signs and symptoms. A major stroke was defined in both studies as a new neurological deficit with an increase in the NIHSS of 4 points from the preprocedure score, which was present at the 30-day follow-up visit. In addition, EX included any patient with an increase in the Rankin score of 2 points or a raw score of >5, which persists to 30 days. A major stroke was also assigned if the extent of disability was undocumented. Data from strokes in either hemisphere up to 30 days was collected. Strokes affecting the cerebral hemisphere supplied by the study carotid artery were classified as ipsilateral.

Study Similarities

EX and C2 are concomitant, postmarket studies conducted by Abbott Vascular using 2 similar stent systems. Based on the identical nature of the inclusion criteria (which resulted in similar populations), the central adjudication of events using the same definitions by the same organization (Harvard Clinical Research Institute), the identical prespecified time intervals of neurological assessments, and the identical end points, these studies are combined to provide a larger sample size and a higher level of precision in outcome rates, in particular in subgroup analyses where samples are smaller.

Subsets

Two specific subsets of these studies were analyzed separately. First, the subsets of both symptomatic and asymptomatic nonoctogenarians were generated to allow for a rational comparison with the AHA guidelines, which were derived from the outcomes of the ACAS and NASCET studies that excluded octogenarians and used 30-day combined end point of death and stroke rate.

The second subset of subjects were those who, regardless of age, had an anatomic high-surgical-risk feature: history of CEA, radiation

### Table 1. Baseline Patient Characteristics for EXACT and CAPTURE 2

<table>
<thead>
<tr>
<th></th>
<th>EXACT (n=2145 Patients)</th>
<th>95% CI</th>
<th>CAPTURE 2 (n=4175 Patients)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD (n)</td>
<td>72.9±8.9 (2145)</td>
<td></td>
<td>72.5±9.2 (4175)</td>
<td></td>
</tr>
<tr>
<td>Range (minimum, maximum)</td>
<td>36.2, 96.2</td>
<td>72.5 to 73.3*</td>
<td>34.2, 100.3</td>
<td>72.3 to 72.8*</td>
</tr>
<tr>
<td>≥80</td>
<td>23.8% (511/2145)</td>
<td>22.0% to 25.7%†</td>
<td>22.5% (938/4175)</td>
<td>21.2% to 23.8%†</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63.1% (1354/2145)</td>
<td>61.0% to 65.2%‡</td>
<td>61.7% (2575/4175)</td>
<td>60.2% to 63.2%‡</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>34.6% (739/2135)</td>
<td>32.6% to 36.7%†</td>
<td>36.1% (1502/4159)</td>
<td>34.7% to 37.6%‡</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89.7% (1912/2132)</td>
<td>88.3% to 90.9%†</td>
<td>89.7% (3723/4151)</td>
<td>88.7% to 90.6%†</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>74.0% (1263/1706)</td>
<td>71.9% to 76.1%†</td>
<td>88.6% (3620/4086)</td>
<td>87.6% to 89.6%†</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19.2% (404/2099)</td>
<td>17.6% to 21.0%</td>
<td>23.1% (924/3997)</td>
<td>21.8% to 24.5%†</td>
</tr>
<tr>
<td>Symptomatic (stroke, TIA, amaurosis fugax ≤180 d, ipsilateral to the treated side)</td>
<td>9.9% (213/2144)</td>
<td>8.7% to 11.3%†</td>
<td>13.1% (548/4175)</td>
<td>12.1% to 14.2%†</td>
</tr>
<tr>
<td><strong>Cardiac risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>18.3% (388/2122)</td>
<td>16.7% to 20.0%‡</td>
<td>18.0% (741/4125)</td>
<td>16.8% to 19.2%†</td>
</tr>
<tr>
<td>Prior MI</td>
<td>25.1% (520/2069)</td>
<td>23.3% to 27.1%†</td>
<td>26.0% (1019/3916)</td>
<td>24.7% to 27.4%†</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>19.8% (418/2108)</td>
<td>18.1% to 21.6%†</td>
<td>21.3% (875/4103)</td>
<td>20.1% to 22.6%†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>70.7% (1480/2094)</td>
<td>68.7% to 72.6%†</td>
<td>73.2% (2965/4051)</td>
<td>71.8% to 74.6%†</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8.6% (182/2109)</td>
<td>7.5% to 9.9%‡</td>
<td>9.4% (382/4051)</td>
<td>8.5% to 10.4%‡</td>
</tr>
<tr>
<td><strong>Noncardiac risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>16.8% (359/2131)</td>
<td>15.3% to 18.5%‡</td>
<td>22.0% (903/4096)</td>
<td>20.8% to 23.3%‡</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>NA</td>
<td></td>
<td>19.4% (801/4124)</td>
<td>18.2% to 20.7%†</td>
</tr>
<tr>
<td>Renal failure</td>
<td>7.2% (153/2132)</td>
<td>6.1% to 8.4%†</td>
<td>3.0% (122/4124)</td>
<td>2.5% to 3.5%†</td>
</tr>
<tr>
<td>Unfavorable anatomic conditions including previous CEA‡</td>
<td>4.4% (94/2145)§</td>
<td>3.6% to 5.3%†</td>
<td>8.1% (337/4170)</td>
<td>7.3% to 9.0%†</td>
</tr>
<tr>
<td>On a list for a major organ transplant</td>
<td>0.9% (19/2126)</td>
<td>0.5% to 1.4%†</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Contralateral occlusion of ICA</td>
<td>11.2% (234/2081)</td>
<td>9.9% to 12.7%†</td>
<td>17.5% (659/3848)</td>
<td>16.4% to 18.8%†</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>44.9% (904/2013)</td>
<td>42.7% to 47.1%†</td>
<td>46.0% (1812/3943)</td>
<td>44.4% to 47.5%†</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; CHF, congestive heart failure; ICA, internal carotid artery.

*By normal approximation.
†Clopper-Pearson exact CI.
‡Excluding patients with comorbidities.
§Lower percentage as compared with CAPTURE 2 because of the absence of specific question regarding “prior CEA” on CRF of EXACT.
therapy to the neck or radical neck surgery, surgically inaccessible
lesion at or above the C2 vertebra or below the clavicle, lesions
obstructed by tumors in the neck, spinal immobility/inability to flex
neck beyond neutral or kyphotic deformity, the presence of a
tracheostomy stoma, and contralateral laryngeal nerve palsy. This
anatomic high-surgical-risk group was analyzed to determine
whether a significant differential in outcomes was apparent based on
the indications for the procedure, with the comparison group defined
as patients with physiological high-surgical-risk features. For the
purposes of this analysis, the physiological group had as one of the
inclusion criteria age
\[
80 \text{ years, resulting in an unequal frequency of this known predictor of outcomes: 15.1\% octogenarians in the}
\]
anatomic subset and 26.7\% in the physiological subset. The anatomic
inclusions accounted for 431 patients (C2: 292 asymptomatic, 45
symptomatic; EX: 79 asymptomatic, 15 symptomatic), 16% of the
combined total of both studies.

### Data Collection and Statistical Analysis

Relevant patient demographic, clinical, and procedural data as well as
information pertinent to postprocedural complications, in-hospital
events, and postdischarge adverse events were prospectively
documented on standardized case report forms. All data were submitted to
the study sponsor (Abbott Vascular) who performed the primary
analysis, in concert with the Executive Committee overseeing the
study. For variables involving proportions, Clopper-Pearson Exact
2-sided 95\% CIs are given. Means, SDs, ranges, and 2-sided 95\% CIs based on the normal distribution are displayed for the appropriate
continuous variables. No prespecified hypotheses were performed in
these studies, and subsequently no probability values were com-
puted. Subgroup analyses by age and symptomatic status were
prespecified; results are presented with CIs. Subset analyses by
anatomic risk factors were ad hoc analyses; results are presented with
CIs. SAS statistical software (release 9.1 TS1M3, SAS Institute,
Cary, NC) was used.

### Results

A total of 2145 patients in EX and 4175 patients in C2 were
evaluable for outcome analysis; 5\% of all enrolled patients were
missing outcome data or lost to follow-up and are not
included in this report. The baseline characteristics for each
study are listed in Table 1 and are largely comparable as a
result of the similarities in enrollment criteria between the 2
studies. The mean age of the patients was 72 years, with
almost 1 in 4 over the age of 79 years. The number of
symptomatic patients was relatively small in both studies, 10\% and 13\%, likely owing to the reimbursed availability of
CAS in this population. Of note, the subset of patients for

### Table 2. Baseline Angiographic and Lesion Characteristics

<table>
<thead>
<tr>
<th>Angiographic Characteristics</th>
<th>EXACT (n=2145 Patients, 2206 Lesions*)</th>
<th>95% CI</th>
<th>CAPTURE 2 (n=4175 Patients, 4218 Lesions*)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left carotid</td>
<td>51% (1133/2206)</td>
<td>49% to 53%†</td>
<td>51% (2156/4218)</td>
<td>50% to 53%†</td>
</tr>
<tr>
<td>Right carotid</td>
<td>49% (1073/2206)</td>
<td>47% to 51%†</td>
<td>49% (2062/4218)</td>
<td>47% to 50%†</td>
</tr>
<tr>
<td>Target lesion stenosis, %*</td>
<td>Mean:±SD (n)</td>
<td>86±8 (2206)</td>
<td>86±8 (4218)</td>
<td>86±8 (4218)</td>
</tr>
<tr>
<td>Target lesion length (mm)</td>
<td>Mean:±SD (n)</td>
<td>17±9 (2202)</td>
<td>18±9 (4189)</td>
<td>18±9 (4189)</td>
</tr>
<tr>
<td>Target site calcification</td>
<td>None</td>
<td>NA</td>
<td>23% (849/4211)</td>
<td>21% to 24%†</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>NA</td>
<td>54% (2278/4211)</td>
<td>53% to 56%†</td>
</tr>
<tr>
<td></td>
<td>Heavy</td>
<td>NA</td>
<td>23% (884/4211)</td>
<td>22% to 25%†</td>
</tr>
<tr>
<td></td>
<td>Little or none</td>
<td>46% (1010/2206)</td>
<td>44% to 48%†</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Moderate to heavy</td>
<td>54% (1196/2206)</td>
<td>52% to 56%†</td>
<td>NA</td>
</tr>
<tr>
<td>Thrombus present at target site</td>
<td>2% (52/2206)</td>
<td>2% to 3%†</td>
<td>3% (126/4215)</td>
<td>2% to 4%†</td>
</tr>
<tr>
<td>Aortic arch type</td>
<td>I</td>
<td>NA</td>
<td>44% (1803/4144)</td>
<td>42% to 45%†</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>NA</td>
<td>45% (1845/4144)</td>
<td>43% to 46%†</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>NA</td>
<td>12% (496/4144)</td>
<td>11% to 13%†</td>
</tr>
<tr>
<td>Target lesion echogenicity</td>
<td>Completely soft</td>
<td>NA</td>
<td>22% (876/4057)</td>
<td>20% to 23%†</td>
</tr>
<tr>
<td></td>
<td>Completely calcified</td>
<td>NA</td>
<td>9% (365/4057)</td>
<td>8% to 10%†</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>NA</td>
<td>69% (2816/4057)</td>
<td>68% to 71%†</td>
</tr>
<tr>
<td>Aortic arch characteristic</td>
<td>Diseased</td>
<td>NA</td>
<td>49% (2048/4144)</td>
<td>48% to 51%†</td>
</tr>
<tr>
<td></td>
<td>Nondiseased</td>
<td>NA</td>
<td>51% (2096/4144)</td>
<td>49% to 52%†</td>
</tr>
</tbody>
</table>

*For multiple lesions on the same side treated on the same day, only the target lesion with the highest preprocedure stenosis is included.
†Clopper-Pearson exact CI.
‡By normal approximation.
whom the procedure was performed on the basis of an anatomic feature that made them high risk for surgery varied between 4% and 8%, with some undeclared CEA restenosis in EX due to the lack of a specific question on the report form. Angiographic and lesion characteristics are listed in Table 2, showing comparable values between studies, with the mean lesion stenosis of $86\%$, and the mean lesion length of 18 mm. Owing to differences in reporting requirements, some features (eg, calcification, arch type, etc) are either reported by the studies using different descriptors, or not at all.

### Thirty-Day Outcomes

The nonhierarchical tally of all events is shown in Table 3 for both studies separately, and in combination. Noteworthy in these data are the findings of nonipsilateral stroke comprising $14\%$ of all strokes. The 30-day primary composite end point (hierarchical) of death, stroke, and MI for EX was 4.1% (95% CI, 3.3% to 5.1%), for C2 was 3.7% (95% CI, 3.1% to 4.3%), and for the combined studies was 3.8% (95% CI, 3.4% to 4.3%).

The 30-day combined end point of death and stroke rate for EX was 4.1% (95% CI, 3.3% to 5.0%), 3.4% (95% CI, 2.9% to 4.0%) for C2, and 3.6% (95% CI, 3.2% to 4.1%) for the combined population. For the combined symptomatic population the rate of 30-day death and stroke was 6.4% (95% CI, 4.8% to 8.4%), and for the combined asymptomatic population it was 3.2% (95% CI, 2.8% to 3.7%). Thirty-day death and major stroke was 1.5% (95% CI 1.2% to 1.8%) for the combined population and 2.6% (95% CI, 1.6% to 4.0%) and 1.3% (95% CI, 1.0% to 1.6%) for the combined symptomatic and asymptomatic groups, respectively (Figure 1).

For patients less than 80 years, the combined outcomes of both studies are shown in Figure 2. The composite end point of death and stroke is included to allow comparison of outcomes with the AHA recommendations, which do not include MI as a component. The 30-day rate of death and stroke for the nonoctogenarian symptomatic group ($n=589$)
was 5.3% (95% CI, 3.6% to 7.4%) and most (69%) of the strokes were minor. The 30-day rate of death and stroke for the nonoctogenarian asymptomatic group (n=4282) was 2.9% (95% CI, 2.4% to 3.4%); again, most (75%) of the strokes were minor. Both results fall within the AHA guidelines. Over the age of 80 years, the combined outcomes of both studies for 30-day death and stroke rate was 10.5% (95% CI, 6.3% to 16.0%) for the symptomatic group and 4.4% (95% CI, 3.3% to 5.7%) for the asymptomatic group.

For patients identified with anatomic factors unfavorable for surgery, the combined outcomes are shown in Figure 3. The 30-day rate of death and stroke for the 60 symptomatic patients with anatomic factors was 1.7% (95% CI, 0.0% to 8.9%); the single stroke was adjudicated as major. The 30-day rate of death and stroke for the 371 asymptomatic patients with anatomic high-risk features was 2.7% (95% CI, 1.3% to 4.9%), of which 78% were minor. Both results fall within the AHA guidelines. In the cohort of patients identified with physiological factors unfavorable for surgery, the combined 30-day rate of death and stroke for 574 symptomatic patients was 6.4% (95% CI, 4.6% to 8.8%), and for the 4603 asymptomatic patients was 3.3% (95% CI, 2.8% to 3.9%).

**Discussion**

The combined results of the EX and C2 studies demonstrate 30-day outcomes for CAS on nonoctogenarians that meet or exceed the AHA guidelines previously established to define acceptable endarterectomy risk in both symptomatic and asymptomatic patients. This was true not only for patients under the age of 80, but also for patients of any age with anatomic surgical risks. These multicenter data were rigorously developed, largest, prospective set of information ever gathered, including the largest, multi-institutional data of clinical outcomes in an endovascular setting. The results include both the symptomatic and asymptomatic populations. In the combined outcomes, both studies for 30-day death and stroke rate was 10.5% (95% CI, 6.3% to 16.0%) for the symptomatic group and 4.4% (95% CI, 3.3% to 5.7%) for the asymptomatic group.

At least 2 analyses have confirmed the need for prospective neurological evaluation before and after CEA to best estimate outcomes, with a 3-fold increase in events with neurology assessment compared with outcomes that were otherwise self-reported; this is especially relevant because the NASCET and ACAS trials used such evaluations and are the basis for the AHA guidelines. It is also noteworthy that in the original CAPTURE study, CEAC adjudication resulted in the identification of ≈50% more 30-day adverse outcomes events compared with site reporting of events alone, thus confirming the importance of both prospective data gathering and the adjudication process in providing full reporting of the outcomes.

Although there continues to be debate in some circles regarding the actual definition of high surgical risk, recent randomized data validate the concept given the increase in stroke and death outcomes in a predefined surgical population with both physiological and anatomic surgical risks. However, in the 10 years since the publication of the AHA guidelines there has not been a similarly rigorous demonstration of fulfillment of the guidelines in the high-surgical-risk population undergoing CEA. Although there have been a number of single center and statewide reports of surgical experiences with CEA since the NASCET and ACAS publications, some specifically examining outcomes in high-surgical-risk patients, the outcomes from these studies are neither valid comparators to the results presented herein nor the AHA standard, given their retrospective nature, the lack of independent neurological assessment, and the absence of standardization of clinical outcome event reporting by a CEAC.

Several features of the data from EX and C2 are notable. First, these results represent a robust, substantial, and broad US population undergoing CAS and are the most rigorously collected, largest, prospective set of information ever gath-
ered specific to any therapy for severe carotid stenosis. Second, the results seem to be independent of devices used and are likely to be generic to the procedure, because the EX and C2 studies used different CAS systems (bare wire filter/closed cell stent and fixed wire filter/open cell stent, respectively). Third, there seems to be a substantial and continuous improvement in CAS outcomes since the initial introduction of these devices in US trials; compared with outcomes in the pivotal ARCHeR and the original CAPTURE registry the results for the entire group improved considerably (30-day death and stroke: 6.9% versus 5.7% versus 3.6%, respectively). These observed improvements have translated to all the subset analyses and ultimately resulted in the achievement of AHA guidelines. It seems the documented increase in operator experience in EX and C2 (presumably leading to both operator skill and better patient selection) compared with the earlier experiences are resulting in improved outcomes. This phenomenon was recently confirmed when an analysis of the SPACE and Pro-CAS studies demonstrated improvement of CAS, but not CEA outcomes, both during the course of those trials and at high-volume sites.27,28 Last, two thirds of the strokes noted in both EX and C2 were minor; in the analysis of the minor strokes in the pivotal ARCHeR study, complete recovery (NIHSS 0 or 1) was seen in all cases by 1 year, with most of this recovery occurring within 30 days. Major stroke and death rates were very low in EX and C2, and likely to be more comparable with the retrospective reports of CEA lacking careful prospective neurological assessment of outcomes referenced earlier.

Limitations of this study include the absence of an angiographic core laboratory; accordingly, no analysis of angiographic predictors or associations with outcomes is offered. Also, a small percentage of patients (<10%) did not have a high-surgical-risk feature defined by the site, but the inclusion of those patients is not likely to have affected the overall results or conclusions in any meaningful way. Although no explicit inclusion/exclusion criteria were imposed on the investigators, a review of the patient demographics finds this patient population was comparable with the predicate high-surgical-risk pivotal trial (ie, ARCHeR27) and had more complexity than patients in the standard-surgical-risk ACST, ACAS, or NASCET trials. Importantly, additional procedures (eg, coronary artery bypass grafting, abdominal aortic aneurysm repair) were allowed in this study during the follow-up period, although no data on the frequency of a second, noncarotid, procedure within the first 30 days is available. Such second procedures have been demonstrated to result in additional major adverse events as seen in the pivotal ARCHeR trial, where 18 patients had coronary artery bypass grafting within 30 days, with death/stroke rate of 39%, a 5-fold increase over the entire cohort; when excluding these patients, the major adverse event rate was reduced for the entire cohort by \( \approx 13\% \) of the total. In addition, these results do not prove that CAS is beneficial compared with medical therapy as there was not a medically treated control group. This study also carries the limitations of any registry analysis, including limited follow-up duration and the potential for bias in end point detection. Given that any prophylactic procedure requires the patient to survive long enough to reap the benefit of reduced end point events to justify procedural or surgical risk (as per the AHA guidelines document stipulation of an expected 5-year survival), no definitive statements regarding the ultimate benefit of CAS can be made absent long-term follow-up in this population. Last, the separation of patients between high-risk anatomic and physiological features is complex because of the need to rank order the risk factors for categorization (ie, a patient may have both an anatomic and physiological risk), resulting in almost twice the number of octogenarians in the physiological group, and potentially contributing to an increase in outcome events in this cohort.

In conclusion, CAS has demonstrated real-world outcomes consistent with established AHA guidelines for CEA in both symptomatic and asymptomatic nonoctogenarian patients. This represents a significant achievement not only for the practice of CAS but also for patients with severe carotid stenosis at risk for CEA, for whom large-scale prospective data on their outcomes with CEA continues to be lacking, but who are being considered for revascularization.

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References
Carotid stenting with embolic protection (carotid artery stenting) was approved by the Food and Drug Administration in 2004 for treatment of carotid artery stenosis in patients at high risk for complications from carotid endarterectomy. Carotid artery stenting is increasingly being used as an alternative treatment modality in high-surgical-risk patients requiring revascularization for stroke prevention. Data are presented from 2 large, rigorously conducted, prospective, Food and Drug Administration–audited, postmarket carotid stenting studies in patients at risk for surgery, treated by a broad group of physicians under commercial use conditions. In total, data on 6320 patients from 280 US sites and 672 operators are included in this analysis. In patients <80 years old, the combined 30-day rate of death and stroke was 5.3% for symptomatic patients and 2.9% for asymptomatic patients, independent of unfavorable risk factors (anatomic or physiologic). These outcomes meet the guideline standards established by the American Heart Association for acceptable 30-day death and stroke rates for patients undergoing standard-surgical-risk carotid endarterectomy: <6% risk of perioperative stroke and death within 30 days with previous symptoms of nondisabling stroke or transitory ischemic attack, or <3% risk without previous symptoms. The data reported have not been described previously in a multicenter, prospective assessment of high-surgical-risk patients. The outcomes represent a significant achievement for the practice of carotid artery stenting in real-world conditions and provide an important addition to the data available to physicians weighing the benefits of different treatment modalities.
Thirty-Day Outcomes for Carotid Artery Stenting in 6320 Patients From 2 Prospective, Multicenter, High-Surgical-Risk Registries
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on behalf of the Investigators and the Executive Committees

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