Carotid Artery Stenting in Octogenarians
Periprocedural Stroke Risk Predictor Analysis From the Multicenter Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) Clinical Trial

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Background and Purpose—Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) is an ongoing prospective, nonrandomized, multicenter clinical trial enrolling patients undergoing carotid artery stenting. The aim of this analysis is to identify risk predictors for periprocedural stroke in patients ≥80 years old.

Methods—Symptomatic patients with ≥50% stenosis and asymptomatic patients with ≥80% stenosis were enrolled. Patients’ neurological status was assessed by an independent neurologist before as well as 24 hours and 30 days postprocedure. All strokes and suspected strokes were adjudicated by an independent committee. Logistic regression analysis was conducted to identify baseline demographic, lesion, procedural, or comorbidity parameters associated with outcomes in patients ≥80 years of age.

Results—As of January 10, 2009, 5297 patients underwent carotid artery stenting in 186 US CAPTURE 2 clinical centers and 1166 were ≥80 years old. Octogenarians were similar to nonoctogenarians in terms of gender and symptomatic status but had fewer of certain risk factors (prior myocardial infarction or carotid endarterectomy, diabetes, smoking history) and more cardiac arrhythmia and renal insufficiency. For the overall cohort, death/stroke rate was 3.3%; stroke rate was 2.7% (0.8% major, 1.9% minor). Death/stroke rates were significantly higher for octogenarians than nonoctogenarians (4.5% versus 3.0%) as were stroke rates (3.8% versus 2.4%). Symptomatic status, embolic protection device dwell time, and lesion length were risk predictors for periprocedural stroke in octogenarians.

Conclusions—Patients ≥80 years old have higher periprocedural event rates than nonoctogenarians. Age, symptomatic status, and lesion length should be considered when identifying appropriate candidates for the procedure. (Stroke. 2010; 41:757-764.)

Key Words: carotid artery stenting ■ octogenarians ■ outcome ■ risk predictors ■ stenosis ■ stroke

Stroke is the third leading cause of death in the United States with 795,000 new and recurrent incidences reported each year.1 A common etiology of stroke is arterial atherosclerotic disease leading to stenotic or occlusive disease of the carotid arteries and subsequent cerebral ischemia or infarction. Carotid endarterectomy (CEA) has been used extensively as an intervention to eliminate both hemodynamic stenosis as well as a source of cerebral atheroemboli, and to prevent stroke. Carotid artery stenting (CAS) has emerged as an alternative and less invasive treatment for patients considered at high risk for surgery.

Although the risk of stroke in octogenarians with significant carotid disease left untreated is not well understood, this group has been considered at higher risk for CEA and has been excluded from the landmark CEA randomized clinical trials North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS).2,3 CEA has been performed in older patients with mixed results. Elderly, symptomatic patients have been reported to benefit from CEA more than younger patients.4 On the other hand, asymptomatic patients >75 years did not have clear benefit in the Asymptomatic Carotid Surgery Trial.5 Also, previous Medicare analyses have shown increasing perioperative mortality after CEA with increasing age; the 30-day mortality in 1 study was 2.46% in patients 80 to 84 years of age and 3.6% in patients aged ≥85 years.6

CAS, a minimally invasive modality, represents an alternative for these higher-risk patients. However, some clinical trial data suggest that, similar to CEA, the rate of adverse outcomes increases when CAS is performed in older pa-
In both randomized controlled trials and postmarket clinical trials for CAS in high surgical risk patients such as Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE),\(^7\) the initial Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) lead-in phase,\(^7\) CAPTURE,\(^12\) and SAPPHIRE-WW,\(^13\) patients ≥80 years old were included; in these studies, age was identified as a risk factor for adverse perioperative outcomes, including death and stroke, compared with outcomes in younger patients. Paradoxically, several individual institutional studies specifically examining the role of age in CAS outcomes reported no significant difference in adverse outcome rates between octogenarians and nonoctogenarians.\(^14\)–\(^17\) Understandably, there remains uncertainty about both the safety of CAS in patients ≥80 years old and the possible unique factors contributing to adverse outcomes in this population. Octogenarians represent a fast-growing segment of the population for whom stroke is a major cause of mortality and morbidity. As such, there is a need to clarify the risk inherent in CAS for this population and to better understand what factors might influence success of the procedure.

The second phase of Carotid ACCULINK/ACQUUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) is a large prospective, multicenter, postmarket surveillance study currently evaluating the safety outcomes of CAS in the hands of physicians from diverse medical specialties in hospitals of broad clinical practice spectrum.\(^18\) As of January 10, 2009, CAS procedures were performed on and data were available for analysis from 5297 evaluable patients, including 1166 octogenarians. The large cohort of patients ≥80 years old in CAPTURE 2 represents a valuable source of outcome information in this population of interest. It also allows analysis of the variables potentially impacting CAS outcomes in octogenarians. Multiple patient-related\(^12\),\(^19\)–\(^21\) and procedure-related\(^15\),\(^19\) factors have been reported to predict perioperative stroke and/or mortality after CAS. Knowledge of the specific risk predictors for adverse outcomes after CAS in octogenarians could inform patient selection or impact clinical decision-making.

### Methods

#### Study Design and Patient Selection

CAPTURE 2 is an ongoing prospective, postmarket, multicenter clinical trial designed to document clinical outcomes and provide information on use of the RX Acculink Carotid Stent System and RX Accunet Embolic Protection System by a wide range of physicians under commercial conditions. The data in the current analysis includes all patients who had a CAS procedure by January 10, 2009. Both symptomatic and asymptomatic patients undergoing CAS were enrolled. Qualifying events for symptomatic patients were ipsilateral hemispheric stroke, transient ischemic attack, and/or amaurosis fugax within the previous 180 days. Patients who met inclusion criteria (high risk for CEA, symptomatic and ≥50% stenosis of the common or internal carotid artery, or asymptomatic and ≥80% stenosis) and signed a consent form were enrolled. Baseline demographics, comorbidities, lesion characteristics, treatment details, and information on adverse outcomes during the procedure and at follow-up visits were collected using electronic case report forms and were entered into the study database. Detailed descriptions of the study objective and rationale, primary end point, selection of patients and interventionalists, and study assessment were reported elsewhere.\(^18\)

#### Outcome Assessment and Adjudication

At baseline, procedure, and follow-up visits, data items were collected according to electronic case report forms and clinical end points of death, stroke, and myocardial infarction (MI) were documented. Study patients were evaluated for neurological manifestations using the National Institutes of Health Stroke Scale by a medical professional (nonoperator) who was certified in the administration of the National Institutes of Health Stroke Scale or by an independent neurologist (ie, nonoperator). These evaluations were performed at the following time points: (1) within 14 days before the stenting procedure; (2) within 24 hours postprocedure; and (3) at 30 days postprocedure. During the 24-hour postprocedure and 30-day follow-up assessments, any occurrence of death, stroke, MI; new neurological events; or device-related adverse events were reported.

All strokes and suspected strokes were adjudicated using prespecified definitions. Investigators were required to provide all source documents on the cases. All neurological complications were independently assessed by a nonoperator neurologist. Major stroke was defined as any new neurological deficit resulting in an increase in the National Institutes of Health Stroke Scale of >4 points from the preprocedure score that was also present at the 30-day follow-up visit. Strokes not meeting this definition were categorized as minor.

#### Statistical Analyses

Baseline demographic, comorbidities, lesion characteristics, and procedural information were summarized using descriptive summary statistics. For variables involving proportions, Clopper-Pearson exact 2-sided 95% CIs were given. The statistics for continuous variables included sample size, mean, median, SD, minimum, and maximum. Categorical variables were described using counts, percentages, and CIs (using either exact or normal approximation to the binomial distribution as appropriate). All probability values reported were rounded to 3 decimal places. Logistic regression analysis was used to analyze the association between the outcome variables (stroke) and the independent variables (patient demographics and angiographic vessel characteristics). Stroke was used as the outcome variable for this analysis because, in the current trial, stroke was the component of the end point that was independently adjudicated. First, univariate regression analysis was performed to evaluate the relationship between variables and the outcome. Multivariate stepwise modeling was then performed using those variables with a probability value ≤0.25 from the univariate analysis. A prespecified subgroup analysis was performed on the octogenarian and nonoctogenarian subgroups.

#### Results

##### Patient Demographic, Comorbidities, and Lesion Characteristics

As of January 2009, the CAPTURE 2 database contained 5297 evaluable patients enrolled from 186 clinical sites by 459 physicians in the United States. The demographic and medical history data are summarized in Table 1 for the subgroups of patients ≥80 years old (N=1166) and for patients <80 years old (N=4131).

The average age±SD for the overall cohort was 72.3±9.2 years old and 22.2% were octogenarians. A majority (61.7%) of the patients was male and 14.3% was symptomatic. Consistent with known risk factors for atherosclerotic disease, a majority of the patients had hypertension (89.2%) and hypercholesterolemia (88.7%). More than one third (36.5%) had diabetes and approximately one fourth (23.1%) were current tobacco users.
Higher Event Rates in Octogenarians and Symptomatic Patients

Event rates for the overall CAPTURE 2 cohort as well as octogenarian and nonoctogenarian subgroups are presented hierarchically and nonhierarchically (Table 3). In the overall cohort of 5297 patients, the composite event rate of death, stroke, MI was 3.5%; the death/stroke rate was 3.3%; and the death/major stroke rate was 1.4%. Octogenarians showed higher event rates than nonoctogenarians: death, stroke, MI (4.5% versus 3.3%; death/stroke (4.5% versus 3.0%); death/major stroke (1.9% versus 1.3%); all stroke (3.8% versus 2.4%); major stroke (1.2% versus 0.7%); and minor stroke (2.6% versus 1.7%). Some of the differences reached statistical significance at the 0.05 level (death and stroke, all events). The prespecified subgroup analysis by age showed that the patient demographics were similar in terms of gender and symptomatic status. Nonoctogenarian and octogenarian subgroups included 61.8% and 61.1% males, respectively. Among nonoctogenarians, 14.0% were symptomatic, whereas octogenarians included 15.0% symptomatic patients. The average age ± SD for nonoctogenarian and octogenarian patients was 69.0 ± 7.6 years and 83.9 ± 3.0 years, respectively.

A greater proportion of the nonoctogenarian patients had prior medical conditions compared with the octogenarians (Table 1). The differences between nonoctogenians and octogenians were statistically significant at the 0.05 level for the following conditions: diabetes mellitus (38.5% versus 29.4%), current tobacco use (27.5% versus 7.3%), prior MI (26.8% versus 23.5%), unstable angina (10.2% versus 6.7%), chronic obstructive pulmonary disease (24.2% versus 15.6%), unfavorable anatomic conditions (23.1% versus 17.1%), contralateral occlusion of the internal carotid artery (18.1% versus 12.7%), peripheral vascular disease (46.7% versus 41.9%), and prior CEA (17.8% versus 13.1%). However, significantly more octogenarians than nonoctogenarians had arrhythmias (28.3% versus 19.0%) and renal insufficiency (22.2% versus 17.7%). Overall, nonoctogenians had more cardiovascular disease (except for cardiac arrhythmia), metabolic disease, and other medical conditions (except for renal insufficiency) at baseline than did octogenarians.

Table 2 summarizes the baseline patient lesion characteristics assessed by angiography for the different age groups. Most of the features were similar between the octogenarian and nonoctogenarian subgroups. The diseased lesion was on the left side of the internal carotid territory in approximately 50% of the patients in each subgroup. The 2 subgroups had comparable mean lesion stenosis (approximately 86%) and length (approximately 18 mm), but octogenarians had statistically significantly more heavily calcified lesion sites (26.9% versus 23.5%), more Type III arch (19.8% versus 10.1%), and greater prevalence of diseased arch (60.7% versus 46.7%).
Event rates calculated for subgroups classified by symptomatic status rather than age showed that symptomatic patients had approximately twice as many events (death, stroke, MI; death/stroke; or death/major stroke) as asymptomatic patients (Supplemental Table I; available http://stroke.ahajournals.org).

### Risk Predictor Logistic Regression Analysis

Univariate regression analysis on the periprocedural stroke outcome was performed on the subgroup of octogenarians using a variety of patient variables (eg, demographic, baseline medical conditions, lesion/anatomic characteristics) as potential predictors (Table 4). Multivariate stepwise regression was performed using the variables that were selected from the univariate analysis using 0.25 as a cutoff for the probability value. The following 10 variables were selected: age (years) as a continuous variable, gender (female versus male), symptomatic status (yes versus no), hypercholesterolemia requiring medication (yes versus no), unfavorable anatomic condition (yes versus no), target lesion length (millimeters) as a continuous variable, aortic arch type (III versus I and II), anticoagulant usage (yes versus no), embolic protection device (EPD) dwell time (minutes) as a continuous variable, and final residual stenosis (percent) as a continuous variable.

The multivariate analysis revealed that symptomatic status, EPD dwell time, and target lesion length were predictors for stroke in the octogenarian subgroup (Table 5).

### Discussion

The large number of octogenarians in the CAPTURE 2 clinical trial population provides a unique opportunity to both accurately measure death and stroke rates and to collect valuable information on factors associated with adverse outcomes. In CAPTURE 2, 30-day death/stroke rates were significantly higher for octogenarians (4.5%) than for nonoctogenarians (3.0%). The higher rate was not unexpected given that age has been identified as a risk factor for adverse outcomes in the periprocedural period in numerous studies. However, the CAPTURE 2 outcomes represent an improvement over rates for octogenarians observed in the first CAPTURE trial. According to the US Census Bureau, there are currently >9 million octogenarians in the United States. This population will increase in the near future. With the potential increase in the frequency of carotid revascularization intervention in octogenarians, the safety of performing CAS in octogenarians and the specific factors placing them at risk for adverse outcomes become pivotal issues.

In the current study, octogenarians and nonoctogenarians were comparable in terms of gender and proportion of symptomatic patients; however, they presented with different frequencies and types of comorbidities with the nonoctogenarian group showing more cardiovascular and metabolic disease burden. Apart from symptomatic status, no comorbidity factors were identified as predictors of periprocedural stroke outcomes among the octogenarians. A separate analysis of the CAPTURE 2 data revealed no evidence that comorbidity burden impacted event rates (Matsumura et al, unpublished data).

In CAPTURE 2, octogenarians had more calcified lesions and a greater prevalence of diseased and Type III arch lesions. Anatomic changes are known to occur with aging,
including increased tortuosity and calcification of the arch and supra-arch vessels, increased prevalence of Type III arch as well as aortic arch elongation, distortion, and stenosis.\textsuperscript{14,26}

The prevalence of these anatomic challenges in the octogenarian population and their potential effect on CAS outcomes should be acknowledged. However, they do not preclude successful stenting of patients 80 years old as shown by the outcomes from both the current and previous studies.\textsuperscript{14–18,27}

Clinical predictors of adverse outcomes in octogenarians are not well characterized. In the current analysis, symptomatic status was identified as a risk factor for death/stroke in octogenarian patients. Symptomatic status is a known predictor of adverse outcomes post-CAS in patients of all ages.\textsuperscript{12,19}

The effect of symptomatic status as a predictor was greater in patients 80 years old than in younger patients; the OR for stroke for symptomatic patients was 3.31 in the octogenarian subgroup, whereas it was 2.32 in the overall CAPTURE 2 cohort.

Lesion length was also identified as a predictor in CAPTURE 2 octogenarians. Lesion characteristics such as length,

<table>
<thead>
<tr>
<th>Table 3. Primary Safety Events Within 30 Days: Hierarchical and Nonhierarchical Events by Patient Age Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchical events*</td>
</tr>
<tr>
<td>Death, stroke, and MI</td>
</tr>
<tr>
<td>Death, stroke</td>
</tr>
<tr>
<td>Death, major stroke</td>
</tr>
<tr>
<td>Nonhierarchical events‡</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>All stroke</td>
</tr>
<tr>
<td>Major stroke</td>
</tr>
<tr>
<td>Ipsilateral to treated hemisphere</td>
</tr>
<tr>
<td>Nonipsilateral to treated hemisphere</td>
</tr>
<tr>
<td>Minor stroke</td>
</tr>
<tr>
<td>Ipsilateral to treated hemisphere</td>
</tr>
<tr>
<td>Nonipsilateral to treated hemisphere</td>
</tr>
<tr>
<td>MI</td>
</tr>
</tbody>
</table>

*Only includes the first occurrence of the most serious event for each patient.
†Clopper-Pearson exact CI.
‡Only includes each patient’s first occurrence of the event.

Figure. Periprocedural death/stroke rates with 95% CI by age groups.
### Table 4. Predictors of Stroke Within 30 Days From Univariate Logistic Regression for Octogenarian Patients (N = 1166)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>P Value*</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.06</td>
<td>0.2031</td>
<td>1.06 [0.97, 1.16]</td>
</tr>
<tr>
<td>Gender, female versus male</td>
<td>-0.43</td>
<td>0.1960</td>
<td>0.65 [0.34, 1.25]</td>
</tr>
<tr>
<td>Symptomatic, yes versus no</td>
<td>1.13</td>
<td>0.0009</td>
<td>3.10 [1.59, 6.05]</td>
</tr>
<tr>
<td>Current tobacco user, yes versus no</td>
<td>0.57</td>
<td>0.2421</td>
<td>1.78 [0.68, 4.66]</td>
</tr>
<tr>
<td>Diabetes, yes versus no</td>
<td>-0.23</td>
<td>0.5164</td>
<td>0.79 [0.40, 1.59]</td>
</tr>
<tr>
<td>Hypertension, yes versus no</td>
<td>-0.39</td>
<td>0.3897</td>
<td>0.68 [0.28, 1.64]</td>
</tr>
<tr>
<td>Hypercholesterolemia, yes versus no</td>
<td>0.68</td>
<td>0.2633</td>
<td>1.97 [0.60, 6.46]</td>
</tr>
<tr>
<td>Hypercholesterolemia requiring medication—lipostatin, yes versus no</td>
<td>0.61</td>
<td>0.1444</td>
<td>1.85 [0.81, 4.20]</td>
</tr>
<tr>
<td>Renal insufficiency, yes versus no</td>
<td>0.06</td>
<td>0.8606</td>
<td>1.07 [0.52, 2.20]</td>
</tr>
<tr>
<td>Renal failure, yes versus no</td>
<td>-0.09</td>
<td>0.9305</td>
<td>0.91 [0.12, 6.88]</td>
</tr>
<tr>
<td>Contralateral occlusion of ICA, yes versus no</td>
<td>-0.08</td>
<td>0.8715</td>
<td>0.92 [0.36, 2.39]</td>
</tr>
<tr>
<td>Needs CABG within 30 days, yes versus no</td>
<td>Complete separation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF, yes versus no</td>
<td>-0.21</td>
<td>0.6130</td>
<td>0.81 [0.36, 1.84]</td>
</tr>
<tr>
<td>Peripheral vascular disease, yes versus no</td>
<td>0.29</td>
<td>0.3517</td>
<td>1.34 [0.73, 2.46]</td>
</tr>
<tr>
<td>Arrhythmia, yes versus no</td>
<td>-0.38</td>
<td>0.3175</td>
<td>0.68 [0.32, 1.44]</td>
</tr>
<tr>
<td>Atrial fibrillation, yes versus no</td>
<td>-0.02</td>
<td>0.9576</td>
<td>0.98 [0.43, 2.23]</td>
</tr>
<tr>
<td>Coronary artery disease, yes versus no</td>
<td>0.07</td>
<td>0.8544</td>
<td>1.07 [0.53, 2.15]</td>
</tr>
<tr>
<td>Unstable angina, yes versus no</td>
<td>0.36</td>
<td>0.4986</td>
<td>1.44 [0.50, 4.14]</td>
</tr>
<tr>
<td>Pulmonary, yes versus no</td>
<td>0.37</td>
<td>0.3336</td>
<td>1.45 [0.68, 3.08]</td>
</tr>
<tr>
<td>Unfavorable anatomic condition, yes versus no</td>
<td>-0.75</td>
<td>0.1596</td>
<td>0.47 [0.17, 1.34]</td>
</tr>
<tr>
<td>Previous carotid endarterectomy, yes versus no</td>
<td>-0.43</td>
<td>0.4218</td>
<td>0.65 [0.23, 1.85]</td>
</tr>
<tr>
<td>Lesion length ≥20 mm, yes versus no</td>
<td>0.76</td>
<td>0.0184</td>
<td>2.14 [1.14, 4.04]</td>
</tr>
<tr>
<td>Target lesion stenosis ≥90%, yes versus no</td>
<td>-0.05</td>
<td>0.8801</td>
<td>0.95 [0.52, 1.74]</td>
</tr>
<tr>
<td>Target lesion calcification, heavy–mild versus none</td>
<td>0.29</td>
<td>0.5087</td>
<td>1.34 [0.56, 3.22]</td>
</tr>
<tr>
<td>Target lesion calcification, heavy versus mild–none</td>
<td>0.14</td>
<td>0.6857</td>
<td>1.15 [0.59, 2.22]</td>
</tr>
</tbody>
</table>

*(From the Wald $\chi^2$ test.
ICA indicates internal carotid artery; CABG, coronary artery bypass grafting; CHF, congestive heart failure.

ulcerated stenosis, and ostial location have previously been identified as risk factors in several smaller stenting studies.28–30 It follows that the anatomic characteristics particular to aging mentioned previously (eg, carotid artery tortuosity, arch calcification, Type III arch, etc) and increased lesion length would confer greater challenge to the stenting procedure, thereby impacting outcomes in octogenarians.

The logistic regression modeling showed that EPD dwell time was a predictor of stroke in octogenarians. Further analysis indicated that EPD dwell time was related to several anatomic and lesion parameters such as arch type, lesion site calcification, and multiple stents per treated side. These characteristics are directly associated with the duration of the placement of the embolic protection filter. For example, patients with Type I arch showed lower complication rates likely related to the ease by which the carotid arteries are accessed resulting in a shorter overall procedure duration. It is reasonable to consider dwell time as a surrogate marker for both operator experience and procedure difficulty related to the accessibility and nature of the lesion and not necessarily causative of adverse outcomes.

Age is a well-known risk factor for adverse outcomes post-CAS.12,19–21 As expected, in the overall CAPTURE 2 trial, age was a predictor of periprocedural death and stroke.
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### References


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