New Drugs and Technologies

Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel Meeting on the ACCULINK and ACCUNET Carotid Artery Stent System

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The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the US Food and Drug Administration (FDA) was convened on January 26, 2011, to review the application by Abbott Vascular (Santa Clara, CA) for a post–market approval supplement (PMA-s) to extend the indications for use of their ACCULINK Carotid Stent System. The stent system had received FDA approval in 2004 for patients at high risk for adverse events after carotid endarterectomy (CEA). Abbott Vascular was seeking to extend its approval to patients at standard risk for CEA on the basis of the data and outcomes derived from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST; ClinicalTrials.gov Identifier NCT00004732). Herein are presented the essential elements of that day-long meeting.

CREST Background

Study Conception and Timeline

The organizational work on the CREST project was initiated in 1996 by the project’s executive committee, which first published on its concept, rationale, and design in 1997.1 The experiential basis for the trial was chiefly 2 small stenting registries in high-surgical-risk, symptomatic patients totaling ≈200 procedures and reporting mortality rates of up to 3% and stroke rates of between 3% and 6%.2,3 The CREST executive committee recognized the novel nature and early stage of the technique, and in accordance with the tenets of clinical equipoise, as well as to provide reassurance to randomizing physicians that a reasonable safety of carotid artery stenting (CAS) had been established at an operator level and across sites, a rigorous credentialing phase was detailed for all participating centers. One of the stated secondary goals of CREST, to describe this experience in the lead-in phase of CREST, has been completed and published elsewhere.4 Although a 3-year enrollment period was originally anticipated for the main randomized trial, based on 50 sites recruiting 20 symptomatic patients per year, CREST ultimately required nearly 8 years and 120 centers to complete enrollment. Some of this delay can be ascribed to the pace of center certification given the aforementioned CAS credentialing requirements and the lack of qualified operators early in the course of the trial; although there were 47 centers selected to participate in CREST as of June 2001 (6 months after the initial patient was randomized), only 8 centers were approved to enroll lead-in CAS patients, and only a single center was qualified to randomize patients.5

National Institutes of Health Analysis Framework

CREST received its operational funding from the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NIH-NINDS) in January 1999 through an investigator-originated (R01) grant (NS 38384), which was subsequently converted to a cooperative agreement (U01) for the duration of the trial. Device support was provided by Guidant (now Abbott Vascular, Santa Clara, CA). Before trial initiation, the Healthcare Financing Administration was required to modify a longstanding national noncoverage policy for carotid angioplasty to allow reimbursement for the hospital and physician costs of the trial for participating Medicare and Medicaid beneficiaries, which became effective in July 2001. The primary NIH analysis has been published,6 along with several of the secondary analyses.7–9 Objectives, end points, and analyses for the NIH evaluation are compared below to those specified by the FDA for the post–market approval (PMA) analysis (see Methodological Differences Between NIH and PMA Analyses).

FDA Binding Agreement History

In 1997, during the initial CREST application review, NIH-NINDS recommended the use of a single stent device. In May 1999, Guidant Corporation (now Abbott Vascular), the manufacturer of the ACCULINK Carotid Stent System, agreed to participate in CREST as the sole supplier of the study device and initiated formal discussions with the FDA to support an indication for patients at standard risk for adverse events from CEA. These efforts resulted in a binding agreement between FDA and Guidant in July 1999. In this FDA binding agree-

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ment, the primary end point for device analysis was defined as stroke, myocardial infarction (MI), or death within 30 days, plus ipsilateral stroke to 1 year, which differed from the NIH-NINDS primary end-point follow-up of 4 years. To support product approval, the FDA requested a hypothesis test of noninferiority between the 2 procedures for the primary end-point analysis, with a margin of 2.6%. Importantly, this analysis was predefined as distinct from the NIH-NINDS superiority analysis and was in keeping with predicate and subsequent carotid stent device trials in terms of noninferiority hypothesis testing formulation, safety and effectiveness end-point definitions, and temporal duration of assessment.10

Although the potential for disparate outcomes between the NIH and FDA analyses was contemplated by the CREST executive committee, this probability was calculated to be <1/1000. Nevertheless, because the study had 2 separate goals—to assess differences in long-term efficacy of CEA versus CAS as treatment strategies (NIH-NINDS) and to evaluate the safety and efficacy of a stent system compared with CEA (FDA)—distinct data analyses were required, which created considerable complexity.

As industry funder, Guidant was initially responsible for holding the investigational device exemption. In February 2003, the investigational device exemption was transferred from Guidant to the principal investigator, Robert Hobson, MD (deceased, 2007), and then to Thomas Brott, MD, to streamline communications among the supervisory authorities within the trial.5 Guidant, and later Abbott Vascular, funded the transfer of the investigational device exemption responsibilities to the principal investigator, the monitoring of the trial by a clinical research organization, and expenses related to managing the trial, data management support, and incentives for sites to complete case report form data entry in a timely manner.

CREST initially included symptomatic patients with an ipsilateral ≥50% carotid bifurcation stenosis. Five years after the initiation of trial enrollment, the CREST protocol was modified to include asymptomatic subjects (reflecting new data from Europe regarding the efficacy of revascularizing asymptomatic patients,11 as well as to accelerate recruitment), which led to a revised binding agreement with the FDA in November 2005. The new agreement prespecified the nature of the primary and secondary analyses. In the 2005 FDA binding agreement, the power analysis was predicated on the assumption that enrollment would include nonoctogenarian patients; (2) rates of death, stroke, or MI (DSMI); (3) nonoc
togenarian patients; (4) rates of death, stroke, or MI (DSMI); and (5) primary end-point rates up to 4 years. No hypothesis of noninferiority was prespecified for octogenarian patients. Although octogenarians were included in the randomization phase of CREST, published outcome data in CEA were sparse (eg, octogenarians were excluded from landmark randomized CEA studies, including the North American Symptomatic Carotid Endarterectomy Trial and the Asymptom
tomatic Carotid Atherosclerosis Study) and outcomes in CAS patients identified octogenarian status as a predictor of adverse outcomes,12 which raised concerns regarding the lack of clinical equipoise between CAS and CEA for this patient population in CREST. Therefore, before data unblinding, a prespecified noninferiority analysis for nonoctogenarians was agreed on with the FDA and added to the Statistical and Analytic Plan.

### Populations to Be Studied in the FDA Analysis
Before data were unblinded, the FDA requested that the primary end-point analysis be conducted on 4 prespecified analysis populations: Intention to treat, as treated, modified as treated, and per protocol. Additionally, a propensity score adjusted per-protocol analysis was required. The prespecified study populations, as defined in the Statistical and Analytic Plan and agreed on with FDA, are summarized in the online-only Data Supplement (Figure I).

#### Regulatory Perspective on Study Device
Preexisting FDA Approval and Experience for ACCULINK Carotid Stent System
Since 2002, the device has had regulatory approval in Europe and has been commercialized in >85 countries, with no

| Table 1. Pre-Specified Analyses in the FDA Binding Agreement and the SAP for CREST |
|---------------------------------|---------------------------------------------------------------|
| **Primary end point** | Composite of all death, any stroke or MI within 30 d of the procedure PLUS ipsilateral stroke from 31 to 365 d |
| **Secondary end points** | All death, any stroke, or MI at 30 d (perioperative) |
| | One year composite end point stratified by |
| | • Symptomatic status |
| | • Age by octogenarian status |
| | • Acute Success |
| | • Target Lesion Revascularization at 12 mo |
| | • Access site complications requiring treatment |
| | • Cranial nerve injury unresolved at 1 and 6 mo |
| | • Composite of all death, any stroke or MI within 30 d of the procedure PLUS ipsilateral stroke thereafter up to 4 y |
| **Interaction analyses** | Sex and symptomatic status (recently asymptomatic vs always asymptomatic) |
evidence of safety concerns. On the basis of the results of the ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR) pivotal trial,\(^1\) Guidant previously submitted the PMA to the FDA for the device system tested, which consisted of the ACCULINK carotid stent and the ACCUNET embolic filter. In August 2004, the FDA approved the ACCULINK Carotid Stent System for CAS in patients with severe carotid stenosis at high risk for adverse events from CEA, both with and without prior neurological symptoms. The CREST panel deliberations did not include this high-risk population; therefore, the outcome of the panel vote would not affect the existing indications for use\(^14\) in high-risk patients.

As a condition of the initial 2004 approval, the FDA required Guidant to conduct a postmarket study (ie, CAPTURE [Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events]) intended to assess both the incidence of rare and unanticipated events not captured in the pivotal study (ARCHeR, enrollment completed in 2002) and the adequacy of technology transfer from the trial setting to the clinical environment via physician training programs. The outcomes of CAPTURE (enrollment completed in 2006) and the subsequent study, CAPTURE 2 (performed to provide Centers for Medicare and Medicaid Services coverage with evidence development; enrollment completed in 2010) have been extensively published elsewhere.\(^12,15–18\) Since conduct-
ing ARCHeR, rates of 30-day DSMI with the ACCULINK/ACCUNET system have been noticeably reduced; specifically, 30-day DSMI rates for ARCHeR, CAPTURE, and CAPTURE 2 were 8.3%, 6.1%, and 3.5%, respectively. These studies, representing >180 sites and 450 operators in the United States, established the safety and effectiveness of the device for patients at high surgical risk in nontrial clinical settings. The clinical outcomes achieved in these postmarket studies of CAS in patients at high surgical risk met the American Heart Association guidelines threshold of adverse events set for CEA in patients at standard surgical risk; these AHA guideline thresholds were derived from outcomes of prior CEA trials in nonoctogenarian, standard-risk surgical patients.

Current Application for a PMA-s

In submitting the CREST PMA-s, the funder sought an extension to the current approved use of the ACCULINK Carotid Stent System (ie, in patients with carotid stenosis considered at high risk for adverse events from CEA) to include patients with carotid stenosis considered at standard risk, regardless of symptomatic status. The proposed changes to the indications for use are consistent with the population studied in CREST, specifically symptomatic standard-risk patients with carotid artery stenosis >70% stenosis by ultrasound or >50% stenosis by angiogram and asymptomatic standard-risk patients with >70% stenosis by ultrasound or >60% stenosis by angiogram.

Methodological Differences Between NIH and PMA Analyses

The results of the NIH analysis of the CREST data were published in the New England Journal of Medicine in 2010.\(^6\)

<table>
<thead>
<tr>
<th>Table 2. Differences Between CREST NIH-NINDS and PMA Analyses</th>
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<tr>
<td><strong>Trial component</strong></td>
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<tr>
<td><strong>Hypothesis</strong></td>
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<td><strong>Analysis population</strong></td>
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<tr>
<td><strong>Primary end point</strong></td>
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<tr>
<td><strong>Definition of “periprocedural”</strong></td>
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<tr>
<td><strong>Start of adverse event count</strong></td>
</tr>
<tr>
<td><strong>Adverse events included in analysis</strong></td>
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</tbody>
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*All patients as randomized.
†All patients as randomized minus those with a primary end point event before the procedure.

Although different in objectives and methodologies, these 2 analyses were nevertheless shown to be consistent and complementary (Table 2).

The objectives of the PMA analyses are device specific and meant to support FDA assessment and possible approval of the device, whereas the objectives of the NIH analyses are to provide academic and scientific evaluation of 2 carotid revascularization strategies. Because the mandate of the FDA is to provide reasonable assurance of safety and effectiveness of the device, these principles guide the statistical methodologies and analytic plan for the PMA. The PMA analyses used a noninferiority hypothesis test performed on a primary end point at 1 year, using the per-protocol population, whereas the NIH analyses used a superiority hypothesis test performed on a primary end point at 4 years, using the intent-to-treat population. The PMA analyses included an adverse event count that began on the day of procedure, whereas the NIH analyses tallied adverse events beginning on the day of randomization. Another key difference was that all adjudicated primary end points were used in the PMA analyses; for
every other prespecified analysis performed on the analysis populations consistently satisfied the noninferiority criteria (Figure 1B) for the stent system, therefore further supporting the robustness of the conclusion and interpretation.

Periprocedural Primary End-Point Outcome Measures

Rates of the periprocedural component of the composite end point (DSMI at 30 days) did not differ significantly for patients undergoing CAS (5.8%; 95% CI, 4.5% to 7.3%) or CEA (5.1%; 95% CI, 3.9% to 6.5%) and met the prespecified noninferiority hypothesis demonstrating that CAS was noninferior to CEA (Table 3). Rates of death and major stroke were very low compared with results from prior large randomized trials and were not significantly different between therapies. Minor strokes occurred more frequently in the CAS arm (3.2%; 95% CI, 2.2% to 4.4%) than in the CEA arm (1.5%; 95% CI, 0.9% to 2.4%). MI occurred more frequently in the CEA group (3.4%; 95% CI, 1.2% to 2.9%) than in the CAS arm (2.0%; 95% CI, 2.4% to 4.6%) and generally balanced the outcome event totals, which resulted in the equivalent composite end-point outcomes between groups for DSMI. The probability values listed in Table 3 are for descriptive purposes only, because CREST was neither designed nor powered to draw statistical inference in comparisons of components of the primary end point. No adjustments were made for multiple comparisons.

Post Hoc Analysis of the Temporal Trends of End-Point Outcomes

CREST enrolled subjects over an 8-year period, from 2000 to 2008. In 2004, the first FDA approval for CAS was granted (ACCULINK Stent System for high-surgical-risk patients based on the results of the ARCHER studies), and in 2005, the Centers for Medicare and Medicaid Services authorized reimbursement of the ACCULINK Stent System in high-risk surgical patients who were either symptomatic or participating in approved studies. As a condition of approval, the FDA mandated a postmarket study. During the same time frame, other devices were approved for the same indication, and in every case, a postmarket study was mandated; those studies (CAPTURE, CAPTURE 2, Emboshield and Xact Post-Approval Carotid Stent Trial [EXACT], Carotid Artery Stenting With Emboli Protection Surveillance Study [CASES]) enrolled >8000 patients by August 2006. As a result, a great

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**Table 3. Periprocedural Outcomes for the PMA Analysis**

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Unadjusted</th>
<th>Unadjusted</th>
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<tbody>
<tr>
<td></td>
<td>CAS N=1,176</td>
<td>CEA N=1,176</td>
</tr>
<tr>
<td><strong>All Death, Stroke or MI</strong></td>
<td>5.8% (65)</td>
<td>5.1% (60)</td>
</tr>
<tr>
<td>Death</td>
<td>0.53% (6)</td>
<td>0.26% (3)</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>4.1% (46)</td>
<td>1.9% (22)</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.9% (10)</td>
<td>0.4% (5)</td>
</tr>
<tr>
<td>Minor Stroke</td>
<td>3.2% (36)</td>
<td>1.5% (18)</td>
</tr>
<tr>
<td>MI</td>
<td>2.0% (22)</td>
<td>3.4% (40)</td>
</tr>
</tbody>
</table>

*Fisher’s exact P-values were not adjusted for multiple comparisons; P-values for descriptive purposes only.

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**Figure 1. Comparison of carotid artery stenting (CAS) and carotid endarterectomy (CEA) in the Carotid Revascularization Endarterectomy versus Stenting Trial for the primary end-point outcomes in the primary per-protocol population (A) and in additional prespecified analysis populations (B).** 95% CI indicates 95% confidence limit; pNI, probability of noninferiority; PP, per protocol; Adj, adjusted; ITT, intent-to-treat; AT, as treated; and MAT, modified intent-to-treat.

For a more detailed description of the distinct objectives of the 2 parallel primary end-point analyses (ie, NIH and PMA) and respective secondary and post hoc analyses, as well as the associated differences in end-point definitions, analysis populations, and statistical methodologies, please refer to the online-only Data Supplement Addendum to this panel report.

**PMA Analysis Results**

**Prespecified Primary End-Point Analyses**

Figure 1 is the graphical representation of the primary end point of CREST PMA analyses (ie, composite of all death, any stroke, or MI to 30 days plus ipsilateral stroke from 31–365 days) in the per-protocol analysis population. There is an absolute observed difference of 0.5% between the therapies, which, along with the accompanying 1-sided 95% confidence limit of 2.26%, is within the 2.6% margin of noninferiority (Figure 1A). Thus, CAS was demonstrated to be not inferior to CEA in standard-risk patients. In addition,
deal of experience, previously not available, was obtained by operators outside of CREST, roughly coincident with the addition of asymptomatic patients to CREST enrollment. In addition, the rates of 30-day DSMI in both FDA device approval and postmarket studies were observed to be declining at a significant pace.

With the non-CREST CAS case load increasing in the United States and the documented rates of complications associated with CAS decreasing, it was reasonable to query the CREST outcomes to assess any in-trial effects of these external factors; an analysis by year was therefore conducted. Given the slow pace of enrollment early in the trial, the first 4 years were grouped together in a single category (ie, 2000–2004), which led to 5 relatively balanced (numerically) groups: 2000 to 2004 (n=1160), 2005 (n=1201), 2006 (n=308), 2007 (n=298), and 2008 (n=164). A post hoc analysis of the composite of death and any stroke showed an initial increase in event rates from 4.4% in the first period (2000–2004) to 7.0% in 2005, then a steady decline thereafter to 4.6% in 2006, 3.4% in 2007, and 1.8% in 2008 (Figure 2A). The initial bump in event rates in 2005 may have been related to the sharp increase in new sites and CAS operators added to an already highly experienced initial group. The subsequent decline in rates may be the result of experience acquired by these newer operators (largely outside of CREST) or to the influence of more appropriate case selection, which for CAS was still evolving during the decade of CREST.

The symptomatic subgroup was likewise subjected to this post hoc analysis to determine whether the temporal effect on the composite of death and any stroke over time could be observed independent of the potential impact of asymptomatic patients on lowering event rates (Figure 2B). This analysis yielded different event rates but a similar trend; after an initial increase in event rates from 4.4% in the first period to 9.0% in 2005, there was a steady decline from 8.5% in 2006 to 4.2% in 2007 and finally to 2.6% in 2008. These findings confirm that the decline in event rates observed between 2006 and 2008 in CREST was not caused by the addition of asymptomatic patients in 2005 but was more likely related to the overall gain of experience in CAS both within and outside the trial after device approval in this country.

Another post hoc analysis conducted to determine the change in rate of the composite of death or major stroke yielded similar results. After an initial plateau in event rates at 2.5% in the first period and in 2005, there was a steady decline to 0.7% in 2006, 0% in 2007, and 0.6% in 2008 (Figure 2C). In the symptomatic subgroup, the effect was even more pronounced (Figure 2D). The initial increase in event rates from 2.5% in the first period to 3.6% in 2005 was followed by a sharp decline to 0.8% in 2006 and 0% in 2007 and 2008. Of note, there was not a single death or major stroke in symptomatic patients undergoing CAS in the second half of CREST. No change in event rates over time was observed in a similar temporal analysis of CEA outcomes. A comparison of baseline demographics between CAS and CEA in the second half of CREST did not show any major imbalance between arms. The decreasing rates of stroke and death for CAS over time and the similar rates of death and
major stroke for CAS and CEA in the second half of the study were among the key findings that led to a conclusion statement by Abbott Vascular that CAS and CEA had balanced outcomes.

Other Prespecified Secondary End Points

Outcomes by Symptomatic Status and Age According to Octogenarian Status

Although the primary composite end-point rates were higher in symptomatic and octogenarian patients than in their asymptomatic and nonoctogenarian counterparts, there was no evidence of a statistically significant difference between CEA and CAS in either subgroup, as depicted in Figure 3. Two noninferiority hypotheses were also prespecified in the 2005 binding agreement, 1 for symptomatic patients, and 1 for asymptomatic patients. In addition, a noninferiority hypothesis for nonoctogenarian patients was added to the Statistical and Analytic Plan, well in advance of data unblinding. For each of these subgroups (symptomatic, asymptomatic, and nonoctogenarian), CAS demonstrated noninferiority to CEA in outcome rates for the composite end point of periprocedural DSMI plus ipsilateral stroke to 1 year.

Cranial Nerve Injury

Cranial nerve injury is a complication of CEA that tends to resolve in the first few months after surgery. The most common cranial nerves affected are V, VII, IX, X, and XII. The symptoms of cranial nerve injury can include lower jaw numbness, lower lip weakness, difficulty swallowing, hoarseness caused by vocal cord paralysis, and difficulty with speech because of tongue deviation. There were no cranial nerve injuries experienced in the CAS arm of CREST in the per-protocol population (online-only Data Supplement Table I). For the CEA arm, there was a 5.3% postoperative incidence of cranial nerve injury, which was reduced to 2.1% at 6 months. Of note, the majority of these (80%) involved a motor deficit.

Access Site Complications Requiring Treatment

Access site complications arising from either CEA or CAS are important secondary outcomes. For CAS, a bleeding complication can result in a retroperitoneal accumulation of blood and is potentially life-threatening. For CEA, bleeding at the surgical site is also potentially serious and may require reoperation to prevent or treat airway obstruction. In CREST, access site complications were significantly more frequent in the CEA group, with ~3 times the occurrence as with CAS (3.7% versus 1.1%, \( P=0.0001 \)). Bleeding that required reoperation was >8 times more frequent after CEA (\( n=17 \)) than after CAS (\( n=2 \); online-only Data Supplement Figure II).

Long-Term Outcomes and Predictors of Mortality

CAS and CEA did not differ in terms of long-term ipsilateral stroke prevention or requirement for target-lesion revascularization over the 4-year period (online-only Data Supplement Figures IIIA and IIIB). All-cause mortality was also comparable in the 2 treatment groups, as shown in the Kaplan-Meier 4-year plot (online-only Data Supplement Figure IIIC).

For periprocedural (ie, <30 days of procedure) stroke or MI, the presence of tobacco use, diabetes, ischemic heart disease/congestive heart failure, male sex, and advanced age were all associated with an increased risk of postprocedure death. The results of the Cox regression model for prediction of long-term mortality are shown in online-only Data Supplement Table II. Importantly, the 2 strongest predictors of mortality were stroke (hazard ratio [HR], 2.49; \( P=0.0011 \)) and MI (HR, 2.14; \( P=0.0079 \)). These results were consistent with the survival analysis that compared patients with periprocedural stroke or patients with periprocedural MI to patients without either periprocedural stroke or MI, defined as the control group (Figure 4A); however, a survival analysis comparing minor stroke with the 2 other subgroups showed that there was no impact of minor stroke on mortality (Figure 4B). These survival curves were important evidence for the panel to review considering the differential in event rates between CAS and CEA for MI and minor stroke (ie, twice as many periprocedural minor strokes after CAS than after CEA, and twice as many MIs after CEA than after CAS). In addition, Abbott Vascular presented data relative to the resolution of minor strokes over time (Figure 5) that showed that the vast majority of these events resolved completely and without any deficit at 6 months, as measured by the NIH Stroke Scale or the modified Rankin Scale. The number of patients left with residual deficits from minor strokes was equal or similar in both arms (CAS: \( n=7 \), CEA: \( n=7 \) by NIH Stroke Scale; CAS: \( n=9 \), CEA: \( n=6 \) by modified Rankin Scale).

Interactions

Subgroup Interaction Analysis

Prespecified interaction analyses using the primary end point and predefined subgroups found no interaction of symptomatic status, age (binary, \( \geq 80 \) or \( <80 \) years), or sex with treatment outcomes. A post hoc interaction analysis for diabetes also found no evidence of interaction for this clinical variable (online-only Data Supplement Figure IV).

Age

A closer examination of the comparative outcomes of CAS and CEA in patients by age subgroups is shown in Figure 6A; in this analysis, primary end-point rates up to 4 years are depicted for 5-year increments on a hazard scale. For patients...
≥80 years of age, the HR was 1.01 ($P = 0.988$), which indicates that primary end-point event rates were equivalent for octogenarians undergoing CAS or CEA. HRs stratified by age groups fluctuated and their 95% CI overlapped substantially, which indicates no clear trends.

Because of the apparent advantage for patients <60 years old who underwent CAS ($HR = 0.39; HR in favor of CAS: 1/0.39 = 2.56; 95\% CI, 0.16–0.95; P = 0.038$), the slope of a “best fit” curve (originally used in the CREST NIH analysis published in the *New England Journal of Medicine*) may be skewed, resulting in the appearance of a possible disadvantage for older patients undergoing CAS when in fact none exists. Exclusion of the group of patients <60 years old results in a leveling of the “best fit” line and the disappearance of any clear age effect, consistent with the aforementioned negative test for interaction.

The FDA independently also performed an age interaction analysis, finding a nonsignificant ($P = 0.20$) linear pattern and therefore no evidence of a statistically significant differential outcome by age between CAS and CEA. Later, the FDA confirmed that the original curvilinear pattern was driven by a regression equation that needed to take into account younger patients, in whom CAS was significantly superior to CEA.

**Use of Embolic Protection**

A total of 24 patients did not receive an embolic protection device: 5 patients were enrolled before the device was available, and 19 others did not have embolic protection devices placed for various reasons. These patients differed from those able to receive embolic protection devices (eg, they were older and more likely to have had symptoms before the procedure), and therefore, their outcomes were subject to selection bias. It is nevertheless noteworthy that there was a 20.8% rate of 30-day DSMI in the 24 patients without embolic protection devices. The exclusion of these patients resulted in an overall 30-day rate of DSMI for CAS patients of 5.3%, which more closely approximates the rate of 5.1% for CEA patients, and a primary end-point rate (6.6%) that was exactly equal for CAS and CEA ($P$ for noninferiority, 0.0080).

**Panel Discussion and Vote**

At the conclusion of the presentations and public deliberations, the panel was asked by the FDA to vote on 3 questions pertaining to use of the RX ACCULINK Carotid Stent System in patients at standard surgical risk who require carotid revascularization and who meet the criteria specified in the proposed indication:

1. Whether there is reasonable assurance that the system is safe
2. Whether there is reasonable assurance that it is effective
3. Whether the benefits outweigh the risks for use

On question 1, the panel voted 6-4-1 (yes, no, or abstained, respectively), agreeing that the data demonstrated that there is
reasonable assurance that the RX ACCULINK Carotid Stent System is safe for use in patients requiring carotid revascularization who meet the criteria specified in the proposed indication. Concerns were voiced by panel members regarding the safety of the stenting procedure, given the 2 times higher periprocedural stroke rate for CAS than for CEA; however, these concerns were believed to be mitigated by the improvements in adverse event rates during the second half of the trial (both composite end point and end-point components) in all patients undergoing CAS. There was a greater consensus (8-2-1) on the relative effectiveness of CAS and CEA procedures, with equivalent long-term stroke prevention benefits for both interventions over time. Finally, the panel agreed (7-3-1) that the benefits of the RX ACCULINK Carotid Stent System do outweigh the risks in the standard surgical risk patients as outlined in the proposed indication.

The panel also commented on the postapproval study outlined by the funder as a mechanism for ongoing surveillance of the safety and effectiveness of the stent system in symptomatic and asymptomatic patients and agreed this study should further elucidate any learning curve among participating physicians. The importance of proper training, patient selection, and strict observance of the specified indications was noted.

The industry representative, a nonvoting panel member, commented on the importance of this particular panel vote for the industry as a whole, in light of a very large, randomized controlled trial reaching a prespecified primary end point that was agreed on with the FDA. In a similar vein, an FDA official had previously acknowledged that “to do a device trial that size is extremely tough and arduous.” Furthermore, the FDA had determined, in consultation with clinical experts in the field, that (1) the noninferiority design was adequate, and (2) the trial, if successful, would provide robust evidence in support of approval.

Conclusions

In 2307 standard-risk patients with symptomatic and asymptomatic carotid artery disease, CAS demonstrated noninferiority to CEA for the primary composite end point of DSMI within 30 days of the procedure plus ipsilateral stroke from 31 to 365 days in the per-protocol analysis population. However, differences in individual components of the primary end point did occur, with more MIs reported in patients who underwent CEA, and with minor strokes reported more frequently in patients who underwent CAS. A significant number of minor strokes that occurred in CAS patients resolved by 6 months, which resulted in comparable unresolved minor stroke rates in the CAS and CEA arms at the 6-month time point. Survival analysis showed that MIs were associated with early and late mortality, whereas minor strokes were not. The separate and independent analysis of the CREST data using a superiority test hypothesis conducted on the NIH-NINDS intent-to-treat analysis population with 4-year follow-up yielded similar results. The achievement of comparable results from 2 independent analyses lends credibility to the finding that CAS using the ACCULINK/ACCUNET system is as safe and effective as CEA for standard-risk patients and is especially noteworthy in light of the numerous logistical and regulatory challenges faced by the CREST investigators. In the CREST PMA analysis, a lower primary end-point rate was observed in CAS patients who received the ACCUNET embolic protection system relative to those who did not, which indicates that the use of embolic protection was associated with better outcomes in this study.

There was a significant trend toward lower death and stroke rates in the latter half of the CREST trial, possibly because of improved technical proficiency, operator experience, and patient selection, which may require careful consideration. It is noteworthy that US approval of CAS in late 2004 roughly coincided with this improvement and may have contributed to an increased experience base for CAS outside of CREST and translated to improved outcomes within the trial. The improved CAS outcomes demonstrated...
over the 8-year course of the CREST trial correlate with the marked improvement in CAS outcomes seen in FDA investigational device exemption trials throughout the decade. This trend supports the hypothesis that increased operator experience and refined case selection should result in further improvement of CAS outcomes relative to CEA. The funder proposed a postapproval study to further investigate the ongoing risk of periprocedural death and stroke in symptomatic and asymptomatic standard risk patients, as well as to provide additional long-term follow-up data in real-world settings.

There was no evidence of a statistically significant age interaction with the primary end point for either intervention. The apparent trend toward worse outcomes in older relative to younger patients undergoing CAS was independently demonstrated by both the funder and the FDA to be an artifact of the best-fit methodology, driven by the better outcomes for CAS in patients <60 years of age and not by any differences in outcomes for older patients.

The FDA’s Circulatory System Devices Advisory Panel reviewed and considered the data and rendered a final vote recommending approval. On the basis of these data and the panel’s recommendation, the FDA subsequently granted the ACCULINK Carotid Stent System an extension for its indication to include patients at standard surgical risk, independent of symptomatic status, on May 6, 2011.

Acknowledgments
We thank the Abbott Vascular CREST team for their valuable contributions and Jane Bailly for editorial assistance.

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Dr Gray received research grant support as a CREST investigator.

Disclosures
Dr Gray is a member of the Scientific Advisory Board for Abbott Vascular. Drs Simonson and Verta are employees of Abbott Vascular and hold stock in Abbott Laboratories.

References
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ADDENDUM to Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel Meeting on the ACCULINK and ACCUNET Carotid Artery Stent System

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): A Description of the Two Separate Analyses Done for the National Institutes of Health and for the United States Food and Drug Administration

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¹Center for Interventional Vascular Therapy, Columbia University, New York, NY; and ²Abbott Vascular, Endovascular Global Clinical Science, Santa Clara, CA

Running title: Addendum to Panel Report on ACCULINK/ACCUNET CAS System

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Email: wg2131@columbia.edu

Word count: 3263

Subject codes: [49] carotid stenosis; [76] carotid endarterectomy; [78] angioplasty and stenting
I. Background

The recently completed Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) compared outcomes of carotid endarterectomy (CEA) with those of carotid-artery stenting (CAS) in approximately 2500 patients with symptomatic or asymptomatic extracranial carotid stenosis. Multiple comparisons of the two interventions in prior trials have produced conflicting results.\textsuperscript{1-4} Alternatively, CREST was conceived with elements (e.g., adequate sample size, review of ultrasound and angiography results in core laboratories, blinded endpoint adjudication, rigorous credentialing of the operators) intended to provide more definitive direction as to the appropriate choice of intervention for patients undergoing therapy for extracranial carotid stenosis. CREST was funded jointly by the US National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NINDS-NIH) through an investigator-originated (R01) grant and by Abbott Vascular (formerly Guidant Corporation). Although unified in the overarching goal — to compare two carotid artery interventions in terms of effectiveness and safety — the specific aims of the individual funders differed, as did the operating procedures associated with their respective regulatory environments. Therefore, from the outset of the trial, two distinct analyses were planned for the CREST dataset, one for the National Institutes of Health (NIH) and the other to obtain Premarket Approval (PMA) from the US FDA for the carotid artery stent system used in the trial. These analyses had different pre-specified endpoints and statistical analyses. The prior specification of two separate analyses for a single randomized, controlled trial is unusual and added a logistical burden to implementation of the trial. Nevertheless, CREST was successfully completed and produced complementary findings between the two analyses that have since been made public.\textsuperscript{5} The goal of this report is to articulate the distinct and separate objectives of the two parallel primary endpoint analyses.
and respective secondary and post-hoc analyses, and describe the associated differences in endpoint definitions, analysis populations, statistical methodologies and outcomes reported.

**Enumeration of the Key Stakeholders in CREST**

CREST originated in 1996 as a proposal by a group of clinicians to NIH-NINDS for a comparison of two treatment strategies, CEA vs. CAS using multiple stent systems in symptomatic patients. This proposal was subsequently modified in 1998 to limit the comparison to CAS using one stent system. In 1999, in order to satisfy this NIH mandate to have a sole device in the trial, Guidant agreed to supply the ACCULINK® Carotid Stent System and assist in the training of investigators. As the industry funder, Guidant was originally responsible for holding the investigational device exemption (IDE) required by the FDA allowing the stent system to be used in the study. In February 2003, the IDE was transferred from Guidant to the Principal Investigator. In 2005, asymptomatic patients were included in the CREST study, based on promising data in patients undergoing CEA without prior neurological symptoms. The resulting CREST population included symptomatic and asymptomatic patients at standard risk for adverse events from CEA. In May 2011, CREST data led to the expansion of the pre-existing indication for the ACCULINK system (i.e., use in patients at high risk for adverse events following CEA) to standard risk patients having severe carotid stenosis both with and without prior symptoms via submission of a PMA supplement to the FDA. The key “stakeholders” in CREST thus included the clinical investigators, the funders (NIH-NINDS and Abbott Vascular), the Center for Medicare and Medicaid Services (who agreed to support the clinical costs of care for the study patients where appropriate) and the FDA.
Different Objectives of the Two Funders

The NIH-NINDS and industry funders follow distinct regulatory processes governing clinical trial development, conduct and oversight. They also have different objectives. The NIH-NINDS’s goal was to compare two strategies for carotid revascularization, while the PMA’s objective was to evaluate the safety and effectiveness of a particular device (the ACCULINK stent system) compared to surgery. The NIH-NINDS analysis was therefore focused on comparing the long-term safety and effectiveness of CEA and CAS in the standard-risk patient population, and on detecting a difference, if one existed. For their part, the goal of the regulatory analysis was to demonstrate that the new product (the ACCULINK System) was as safe and effective as the established intervention (CEA) or, at least not inferior (by a margin of non-inferiority, or $\Delta$) following the process dictated by the FDA for scientific and regulatory review of medical devices. Therefore, CREST evolved as both a superiority trial (NIH-NINDS analysis) and a non-inferiority trial (PMA analysis) with similar participants and outcomes measured but distinct frameworks for hypothesis-testing and data analysis. The possibility of obtaining discordant results from the two analyses was considered, but, in consultation with the CREST Data and Safety Monitoring Board, was determined to be minimal (<1/1000).\textsuperscript{8,9}

II. Key Differences in Design of the Two Primary Analyses

a. Populations Studied

The nature of the trial hypotheses (superiority or non-inferiority) impacted the treatment populations used for the NIH-NINDS and PMA analyses. In a superiority trial, the null hypothesis is that the two study treatments are equivalent; the alternative hypothesis is that the treatments differ. To minimize known and unknown biases, the appropriate analysis population for such a trial is the intent-to-treat (ITT) population (i.e., all patients regardless of
whether they completed allocated treatment). Therefore the NIH-NINDS analysis was based on the ITT population (n=2502; 1262 CAS, 1240 CEA). In contrast, for a non-inferiority trial, the inclusion of noncompliant patients that did not fully satisfy entry criteria, crossed over to the other arm, or dropped out may result in a bias towards making the two treatments appear similar. To reduce the potential impact of such bias, (i.e., a true difference in treatment effect masked by aspects of trial conduct), the PMA analysis focused on those patients who received the allocated treatment as specified by the protocol— i.e., the “per-protocol” (PP) population, resulting in a reduction in overall subject numbers by 195 (n=2307; 1131 CAS; 1176 CEA) compared to the NIH analysis. However, other analysis populations were also pre-specified by the FDA for the PMA analysis prior to un-blinding of the data, including the ITT, as-treated (AT), and modified as treated (MAT) populations, to ensure a complete evaluation of all available data.

b. Endpoints

Two distinct primary analyses were pre-specified for CREST according to the funding sources. Both analyses shared a similar composite primary endpoint that included the safety component of death, stroke and myocardial infarction (MI) during the peri-procedural period, but differed in the duration of the effectiveness portion of the combined endpoint reporting ipsilateral stroke to one year (PMA analysis, in accordance with the FDA precedent for medical devices) or 4 years (NIH-NINDS analysis). Secondary analyses planned for the NIH-NINDS analyses and pre-specified for the PMA pathway are summarized in Table 1. Planned NIH-NINDS secondary analyses were listed in the protocol and its appendices. Pre-specified PMA secondary analyses were also listed in the protocol and its appendices but were further described in detail in the Statistical and Analytical Plan (SAP). The SAP was submitted to the FDA.
for approval prior to the data being unblinded to Abbott Vascular. The objective of the SAP is to minimize bias by describing in detail the analyses to be performed in advance of data unblinding. Deviations from the SAP are typically not accepted by the FDA. In accordance with the FDA/International Conference on Harmonisation guidance on Statistical Principles for Clinical Trials\textsuperscript{11} which states that “statisticians or other staff involved in unblinded interim analysis should not participate in the blind review or in making modifications to the SAP”, Abbott Vascular personnel were not present at review meetings of unblinded interim analyses.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Planned NIH-NINDS Secondary Analyses</th>
<th>Pre-specified PMA Secondary Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-procedural event rates</td>
<td>Differences in peri-procedural event rates for CAS and CEA</td>
<td>Differences in peri-procedural event rates for CAS and CEA</td>
</tr>
<tr>
<td>Symptomatic status</td>
<td>Differences in peri-procedural event rates by symptomatic status</td>
<td>• Differences in the primary endpoint event rates by symptomatic strata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Assessment of poolability of symptomatic and asymptomatic patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Differential effectiveness by asymptomatic status</td>
</tr>
<tr>
<td>Effectiveness beyond peri-procedural period</td>
<td>Differences in the post-procedural event rates</td>
<td>Primary endpoint up to 4 years</td>
</tr>
<tr>
<td>Acute success</td>
<td>Devices success for CAS; procedural and clinical success for each intervention</td>
<td></td>
</tr>
<tr>
<td>Non-primary endpoint</td>
<td>Differences in other (non-primary endpoint) major and minor complications</td>
<td>• Cranial nerve injuries unresolved at 1 and 6 months</td>
</tr>
<tr>
<td>Restenosis/revascularization</td>
<td>Assessments of differences in the degree of stenosis at the lesion site between treatment groups at 6 and 12 months</td>
<td>• Target lesion revascularization at 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Evaluation of the treated segment by ultrasound at 6 and 12 months</td>
</tr>
<tr>
<td>Procedure</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Difference in the primary endpoint event rates for non-octogenarians</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>Comparison of health-related quality of life (QOL) for CAS and CEA</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Relative cost-effectiveness of treatment strategies, measured as cost per quality-adjusted year of life gained</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Differential effectiveness by gender</td>
<td></td>
</tr>
<tr>
<td>Learning curve</td>
<td>Comparison of event rates for lead-in versus randomized CAS patients</td>
<td></td>
</tr>
<tr>
<td>Risk factor assessment</td>
<td>Identification of factors that may influence the relative effectiveness of CAS and CEA</td>
<td></td>
</tr>
</tbody>
</table>

c. **Adverse Event Counting**

Adverse event counting for the peri-procedural term and the longer-term follow-up period also differed for the two primary analyses. The analysis for NIH-NINDS began event counting in one of two ways. Either counting started at procedure for patients who underwent the assigned procedure within 30 days after randomization, or at randomization for patients who did not receive the assigned procedure (i.e., either no procedure, or the non-assigned procedure) or received it more than 30 days post-randomization. In the PMA analysis, counts
started at procedure for all revascularized patients, irrespective of whether they received the
assigned or non-assigned procedure. The PMA primary analysis was linked to the specific
relationship between intervention and adverse events which dictated adverse event reporting
beginning at the time of procedure to determine causality, if present.

Both NIH-NINDS and PMA analyses used blinded endpoint adjudication for MIs and
strokes. However, the NIH-NINDS analysis included MIs specifically defined by elevated enzyme
(creatine kinase MB or troponin) levels along with chest pain or symptoms consistent with
ischemia or ECG evidence of ischemia, (biomarkers elevation alone, irrespective of levels, was
necessary but not sufficient alone to qualify the event as MI) whereas the PMA analysis more
conservatively included both “possible” and “definite” MI (i.e., as labeled by the Myocardial
Infarction Adjudication Committee) in its event count, in keeping with the evolving diagnostic
definition of MI which reflects advances in assay sensitivity and specificity. This resulted in 20
fewer MI events in the NIH analysis as compared to the PMA analysis: 8 in the CAS group and 12
in the CEA group.

d. Trial Conduct

Trial conduct was also regulated differently for the two analyses with different protocol-
approval pathways, procedures for clinical monitoring and interpretation of trial results.12 The
regulatory pathway was bound by the typical standards imposed by the FDA in PMA studies
including good clinical practice (GCP) standards for the design, conduct, performance and
reporting of clinical trials,13 including biomedical research (BiMo) audits — on-site inspections
and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated
research for credibility and accuracy.
III. Outcomes Reported in the Two Analyses

a. Results of the Hypothesis Tests for the Primary Endpoint

Outcomes of the hypothesis tests conducted in the NIH-NINDS and PMA analyses on the respective primary endpoints are shown in Table 2. In the PMA analysis, non-inferiority between CEA and CAS in terms of the primary endpoint (peri-procedural death/stroke/MI plus ipsilateral stroke to one year) was demonstrated. In the NIH-NINDS analysis, superiority of CEA to CAS was not shown, as indicated by the non-significant p-value, and in the PMA analysis non-inferiority was demonstrated by virtue of a significant p-value.
Table 2. Summary of the Results of the Hypotheses Tests for the Primary Endpoint

<table>
<thead>
<tr>
<th>Analyses</th>
<th>PMA</th>
<th>CAS</th>
<th>CEA</th>
<th>Difference</th>
<th>Non-inferiority test margin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol</td>
<td>7.1% ± 0.8% (1131)</td>
<td>6.6% ± 0.7% (1176)</td>
<td>0.5%</td>
<td>2.6%</td>
<td>[-, 2.26%]</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

NIH

<table>
<thead>
<tr>
<th>Analyses</th>
<th>NIH</th>
<th>CAS</th>
<th>CEA</th>
<th>Difference</th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat</td>
<td>7.2% ± 0.8% (85)</td>
<td>6.8% ± 0.7% (76)</td>
<td>0.4%</td>
<td>1.1 (0.8 to 1.5)</td>
<td>[-1.8, 2.6%]</td>
<td>0.51†</td>
</tr>
</tbody>
</table>

* significant p-value demonstrates non-inferiority
† non-significant p-value accepts absence of superiority

Figure 1 is the graphical representation of the difference in primary endpoint outcomes of patients undergoing CEA versus those undergoing CAS using the relevant analysis populations (i.e., ITT and PP, respectively). If the non-inferiority margin is applied to the NIH-NINDS ITT population, the outcome, conclusion and interpretation of the analysis are not changed, concluding non-inferiority of the two interventions. Conversely, if the superiority design parameters are applied to the PMA PP population, the absence of superiority is also shown.

Outcomes for components of the peri-procedural primary endpoint for each analysis are shown in Table 3.
Figure 1. Differences (%) in the primary endpoint rates between CAS and CEA (95% one-sided confidence limit)

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>P_{NI}</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH-4Y ITT</td>
<td>7.2%</td>
<td>6.8%</td>
<td>2.26%</td>
<td>0.0259</td>
</tr>
<tr>
<td>PMA-1Y PP</td>
<td>7.1%</td>
<td>6.6%</td>
<td>2.26%</td>
<td>0.0245</td>
</tr>
</tbody>
</table>

2.6% Margin of Non-inferiority
Table 3. Primary Endpoint Components for NIH and PMA Analyses

<table>
<thead>
<tr>
<th></th>
<th>PMA Analysis (within 30-day)</th>
<th>NIH Analysis (Peri-procedural)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAS</td>
<td>CEA</td>
</tr>
<tr>
<td></td>
<td>N = 1131</td>
<td>N = 1176</td>
</tr>
<tr>
<td>Death, Stroke or MI</td>
<td>5.8% (65)</td>
<td>5.1% (60)</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>4.1% (46)</td>
<td>1.9% (22)</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.9% (10)</td>
<td>0.4% (5)</td>
</tr>
<tr>
<td>Minor Stroke</td>
<td>3.2% (36)</td>
<td>1.5% (18)</td>
</tr>
<tr>
<td>MI</td>
<td>2.0% (22)</td>
<td>3.4% (40)</td>
</tr>
<tr>
<td>Death</td>
<td>0.53% (6)</td>
<td>0.26% (3)</td>
</tr>
</tbody>
</table>

* The peri-procedural period was defined as the 30-day period after the procedure (for all patients who underwent the assigned procedure within 30 days after randomization) or the 36-day period after randomization (for all patients who did not undergo the assigned procedure within 30 days after randomization).
b. Secondary Analyses

Secondary analyses were planned for the NIH-NINDS analysis and pre-specified in the PMA’s SAP. NIH-NINDS secondary analyses reported treatment effect by symptomatic status, sex and quality of life assessments. Secondary analyses pre-specified in the SAP for the PMA were also conducted and the results were reported to FDA and at the Circulatory Panel.

c. Exploratory/Post-hoc Analyses to Date

Exploratory and post-hoc analyses (i.e., analyses that are hypothesis-generating or trend-assessing with potential for clinical relevance) have been generated from both the NIH-NINDS and the PMA analyses. NIH-NINDS post-hoc analyses to date have included effect of peri-procedural stroke and myocardial infarction on health status at 1 year (SF-36 physical and mental health scales) and the effect of age on the primary endpoint. The impact of revascularization on cranial nerve palsies for the peri-procedural period, the effect of interventionalist medical specialty on primary endpoint rates, and the association of MI after CAS or CEA with 4-year mortality were also examined. PMA post-hoc analyses thus far have included predictors of death, prognostic value of strokes and MI, temporal trends in treatment outcomes, impact of ACCUNET use on primary endpoint and sensitivity analysis of differential treatment effect by age.

IV. Conclusions

CREST was successfully completed with the design, logistical, and communication challenges inherent in two different, pre-specified primary analyses. Despite the many differences between NIH-NINDS and PMA analyses — including distinct objectives, endpoints, populations studied, AE counting practice, and trial conduct — fundamentally similar
conclusions were reached in both: that carotid revascularization by CAS or CEA is effective and safe in standard-risk patients and that neither intervention was found to be superior. Post-hoc analyses of these data will likely continue, and an in-depth understanding of the differences between the groups will be important to the critical reader of these and subsequent results.

Acknowledgments

We thank the Abbott Vascular CREST team and Jane Bailly for editorial assistance.

Funding Sources

Dr. Gray received institutional research grant support as a CREST Investigator.

Disclosures

Dr. Gray is a member of the Scientific Advisory Board for Abbott Vascular. Dr. Simonton and Dr. Verta are employees of Abbott Vascular and hold stock in Abbott Laboratories.
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11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical Principles for Clinical Trials. Available at:


Appendix

Supplement to: Gray et al., Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel Meeting on the ACCULINK and ACCUNET Carotid Artery Stent System

Figure 1. Pre-specified analysis populations in CREST

- **Total** Population = 2,502
- **ITT** Population = 2,496 (99.8%)
  - CAS = 1,259, CEA = 1,237
- **AT** Population = 2,397 (95.8%)
  - CAS = 1,151, CEA = 1,246
- **MAT** Population = 2,388 (95.4%
  - CAS = 1,149, CEA = 1,239
- **PP** Population = 2,307 (92.2%)
  - CAS = 1,131, CEA = 1,176

1. Primary endpoint event prior to procedure = 6 (CAS:3, CEA:3)
2. No procedure attempted and withdrew consent during study = 48 (CAS:22, CEA:26)
3. No procedure attempted = 51 (CAS:28, CEA:23)
4. Crossover post procedure = 9 (CAS:7, CEA:2)
5. Pure Crossover = 73 (CAS:63, CEA:10)
6. Aborted procedure = 4 (CAS:4, CEA:0)
Table 1. Rates of cranial nerve injury in patients undergoing CAS or CEA in CREST

<table>
<thead>
<tr>
<th>Patients With Study Procedure Attempted/Received</th>
<th>CAS N= 1, 131</th>
<th>CEA N = 1,176</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure-related cranial nerve injury</td>
<td>0.0%</td>
<td>5.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unresolved at 1 month</td>
<td>0.0%</td>
<td>3.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unresolved at 6 months</td>
<td>0.0%</td>
<td>2.1%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Figure 2. Access site complications in CREST

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>CAS N = 1,131</th>
<th>CAS N = 1,176</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access Site Complication Requiring Treatment</td>
<td>1.1%</td>
<td>3.7%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

![Bar chart showing access site complications in CREST](chart.png)

- **Patients requiring re-operation**
  - Hematoma: 20 (CAS) vs. 2 (CEA)
  - Bleeding: 17 (CAS) vs. 5 (CEA)
  - Infection: 7 (CAS) vs. 0 (CEA)
  - Occlusion: 2 (CAS) vs. 0 (CEA)
  - Other: 11 (CAS) vs. 1 (CEA)
Figure 3. Comparison of 4-year outcomes in patients undergoing CAS or CEA for long-term ipsilateral stroke prevention (A), requirement for target lesion revascularization (B), and all-cause mortality (C)
Table 2. Independent predictors of mortality in patients undergoing CAS or CEA in CREST

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke within 30 day (yes vs. no)</td>
<td>2.49</td>
<td>1.44-4.32</td>
<td>0.0011</td>
</tr>
<tr>
<td>MI within 30 days (yes vs. no)</td>
<td>2.14</td>
<td>1.23-3.86</td>
<td>0.0079</td>
</tr>
<tr>
<td>Current smoker (yes vs. no)</td>
<td>1.69</td>
<td>1.19-2.39</td>
<td>0.0034</td>
</tr>
<tr>
<td>Diabetes (yes vs. no)</td>
<td>1.57</td>
<td>1.16-2.12</td>
<td>0.0032</td>
</tr>
<tr>
<td>Sex (yes vs. no)</td>
<td>1.5</td>
<td>1.08-2.08</td>
<td>0.0150</td>
</tr>
<tr>
<td>Ischemic heart disease/congestive heart failure (yes vs. no)</td>
<td>1.48</td>
<td>1.10-2.00</td>
<td>0.0097</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>1.06</td>
<td>1.04-1.08</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

p-values from Cox regression model, for descriptive purposes only
Figure 4. Per protocol interaction analysis by subgroup in CREST

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio [95% CI]</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>1.18 (0.79–1.76)</td>
<td>0.4978</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.94 (0.57–1.57)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>1.06 (0.47–2.40)</td>
<td>0.9554</td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>1.08 (0.77–1.52)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.06 (0.64–1.76)</td>
<td>0.9168</td>
</tr>
<tr>
<td>Male</td>
<td>1.10 (0.74–1.63)</td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>0.85 (0.51–1.41)</td>
<td>0.2153</td>
</tr>
<tr>
<td>Non-diabetics</td>
<td>1.28 (0.85–1.91)</td>
<td></td>
</tr>
</tbody>
</table>