RX Acculink® Carotid Stent System
Standard Surgical Risk Indication

PMA Supplement

Brian S. Kersten, Ph.D.
Divisional Vice President
Worldwide Regulatory Affairs
Abbott Vascular
Abbott Vascular’s Objective for the Advisory Committee Meeting

To demonstrate that sufficient scientific data have been collected that support the safety and effectiveness for the expanded indication of the RX Acculink Carotid Stent System to include patients at standard risk for adverse events from carotid endarterectomy.
Data Support the Safety and Effectiveness of the Acculink Carotid Stent System in High Risk Patients

- CE marked in Europe since 2002
- Approved in the United States in 2004
- Commercially available in over 85 countries
- Over 128,000 units have been distributed worldwide
- Well-established as safe and effective
# RX Acculink Carotid Stent System: Current vs. Proposed Indication

<table>
<thead>
<tr>
<th>Current Label Criteria</th>
<th>Proposed Label Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Reference diameter within 4.0 mm – 9.0 mm at the target lesion</td>
<td>No Change</td>
</tr>
<tr>
<td>Embolic Protection System: Accunet or Emboshield Family</td>
<td>Accunet Only</td>
</tr>
<tr>
<td>Surgical Risk: High Risk</td>
<td>Add</td>
</tr>
<tr>
<td><strong>Standard Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Reference diameter within 4.0 mm – 9.0 mm at the target lesion</td>
<td>Same as High Risk</td>
</tr>
<tr>
<td>Embolic Protection System: Accunet or Emboshield Family</td>
<td></td>
</tr>
<tr>
<td>Surgical Risk: High Risk</td>
<td></td>
</tr>
<tr>
<td>Current Label Criteria</td>
<td>High Risk</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>With neurological symptoms and ≥ 50% stenosis of the common or internal carotid artery</td>
<td>No Change</td>
</tr>
<tr>
<td>Without neurological symptoms and ≥ 80% stenosis of the common or internal carotid artery</td>
<td>No Change</td>
</tr>
</tbody>
</table>
# RX Acculink Carotid Stent System

**Acculink Carotid Stent**
- **Self-expanding Nitinol (nickel-titanium, super-elastic at body temperature) stent**
- **Straight Configuration**
  - Diameters: 5, 6, 7, 8, 9, 10 mm
  - Lengths: 20, 30, 40 mm
- **Tapered Configuration**
  - Diameters: 6-8, 7-10 mm
  - Lengths: 30, 40 mm

**Acculink Stent Delivery System**
- **Single-use device that uses a sheath to mechanically constrain the Acculink Carotid Stent at a small diameter for delivery to the treatment site**

**Accunet Embolic Protection System (EPS)**
- **Fixed-wire filter for carotid stenting interventions**
- **Flexible filter basket to conform to tortuosity**
- **Captures high volume; allows adequate blood flow**
RX Acculink: A Minimally Invasive Implanted Device For Revascularization
RX Acculink Carotid Stent System: Establishment of Safety and Effectiveness

IDE Study
- ARCHer
  N = 581

Post Approval Studies
- CAPTURE
  N = 4,225
- CAPTURE 2
  N = 6,361
- CHOICE
  N = 6,872

High risk

Standard risk

CREST
N = 2,502
Carotid Revascularization Endarterectomy vs. Stenting Trial

- Pivotal trial for standard risk patients

- Created in collaboration with the NIH and the University of Medicine and Dentistry of New Jersey

- Randomized 1:1 trial comparing carotid artery stenting (CAS) utilizing the Acculink stent to carotid endarterectomy (CEA) in patients at standard risk
## Regulatory History of RX Acculink Carotid System Provides Perspective

<table>
<thead>
<tr>
<th>Date</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 1999</td>
<td>Abbott Vascular* initiates formal discussions with FDA on CREST to support an indication for patients at standard risk of CEA</td>
</tr>
<tr>
<td></td>
<td>- Non-inferiority study comparing stenting to surgery</td>
</tr>
<tr>
<td></td>
<td>- Symptomatic standard risk patient population</td>
</tr>
<tr>
<td>Jul 1999</td>
<td>FDA and Abbott Vascular formalize binding agreement regarding analysis</td>
</tr>
<tr>
<td></td>
<td>- Analysis will include MI with Death and Stroke as Composite Primary Endpoint</td>
</tr>
</tbody>
</table>

* Guidant, acquired by Abbott Vascular, May 2006
Regulatory History of RX Acculink Carotid System Provides Perspective

<table>
<thead>
<tr>
<th>Date</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2005</td>
<td>CREST protocol modified for inclusion of asymptomatic standard risk patients</td>
</tr>
<tr>
<td></td>
<td>▪ To ensure validity of statistical analyses, enrollment restricted to range of 32% - 68% symptomatic patients</td>
</tr>
<tr>
<td>Dec 2005</td>
<td>Binding Agreement revised to incorporate inclusion of asymptomatic patients</td>
</tr>
</tbody>
</table>
# Regulatory Agreements for RX Acculink Carotid Stent System Solidifies Clinical Approach

<table>
<thead>
<tr>
<th>Date</th>
<th>Regulatory Agreement</th>
</tr>
</thead>
</table>
| Jul 1999, Dec 2005 | FDA and Abbott formalize binding agreement regarding analysis  
  ▪ Per-Protocol primary & secondary endpoint analyses, additional analysis performed |
| Apr 2010   | FDA recommends and Abbott agrees to 4 additional pre-specified analyses  
  ▪ Adjusted Per-Protocol  
  ▪ Intent-to-Treat  
  ▪ As-Treated  
  ▪ Modified As-Treated |
CREST Results Confirm Safety and Effectiveness in Standard Risk Patients

CAS with RX Acculink Meets All Objectives

<table>
<thead>
<tr>
<th>Primary Event</th>
<th>CAS with RX Acculink met the primary endpoint:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• CAS with RX Acculink is non-inferior to CEA in comparison of composite primary endpoint event rate: stroke, death, or MI at 30 days plus ipsilateral stroke up to 1 year</td>
</tr>
</tbody>
</table>
**CREST Results Confirm Safety and Effectiveness in Standard Risk Patients**

**CAS with RX Acculink Meets All Objectives**

<table>
<thead>
<tr>
<th>Secondary</th>
<th>CAS with RX Acculink met all secondary objectives, including:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>▪ CAS with RX Acculink is non-inferior to CEA in asymptomatic and symptomatic patients at the 1-year composite endpoint</td>
</tr>
<tr>
<td></td>
<td>▪ CAS with RX Acculink is non-inferior to CEA for the peri-procedural events</td>
</tr>
</tbody>
</table>
CREST Results Confirm Safety and Effectiveness in Standard Risk Patients

CAS with RX Acculink Meets All Objectives

<table>
<thead>
<tr>
<th>Additional</th>
<th>CAS with RX Acculink met all additional objectives, including:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAS with RX Acculink is non-inferior to CEA for the composite endpoint events out to 4 years, demonstrating long-term effectiveness</td>
</tr>
</tbody>
</table>
Objectives of Abbott Vascular PMA and NIH Analyses of CREST Data Are Different

<table>
<thead>
<tr>
<th>CREST PMA Analysis</th>
<th>CREST NIH Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To expand label indication to include Standard Risk patients for the RX Acculink Carotid Stent System</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>1 year</td>
</tr>
<tr>
<td>Primary Population</td>
<td>Per-Protocol</td>
</tr>
<tr>
<td>Primary Analysis</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>2,307</td>
</tr>
<tr>
<td>Median Follow-up</td>
<td>3 years</td>
</tr>
</tbody>
</table>

Abbott Vascular PMA analysis of the CREST data is consistent with the NIH analysis and reveals similar outcomes.
What Abbott Vascular Will Demonstrate Through the PMA Analysis of the CREST Data

- CAS with the Acculink Carotid Stent System demonstrates a reasonable assurance of safety and effectiveness compared to CEA

- Event rates are low for both CAS and CEA demonstrating an acceptable benefit-risk profile

- CAS with the Acculink Carotid Stent System is an appropriate treatment option for standard risk patients indicated for carotid revascularization
Agenda

- The Need for Additional Standard Risk Treatment Options
  - L. N. Hopkins, MD
    Professor and Chairman, Department of Neurosurgery, Professor of Radiology, State University of New York at Buffalo

- PMA and NIH Analysis of the CREST Data
  - Chuck Simonton, MD
    FACC, FSCAI, Chief Medical Officer, Abbott Vascular
  - Thomas G. Brott, MD
    Principal Investigator, IDE Sponsor, Mayo Clinic, Jacksonville, FL; James C. and Sarah K. Kennedy Dean of Research, Eugene and Marcia Applebaum Professor of Neurosciences

- Concluding Remarks
  - Chuck Simonton, MD
    FACC, FSCAI, Chief Medical Officer, Abbott Vascular
The Need for Additional Standard Risk Treatment Options

L. N. Hopkins, MD
Professor and Chairman, Department of Neurosurgery, Professor of Radiology
State University of New York at Buffalo
Financial Disclosure Relative to CREST

- Dr. Nick Hopkins, M. D.
  - NASCET investigator
  - Advisor and/or trial PI for various CAS studies with Abbott Vascular, Cordis, Boston Scientific, Gore and Medtronic Inc.
  - Grant Sponsorship
    - NIH – US Public Health Service, NINDS, R01 NS 038384 (CREST)
    - National Neurosurgery PI, Executive Committee, Training Center, Site PI
LN Hopkins, MD
Personal Experience

- CEA > 2000 (1979 - present)
- CAS > 2000 (1994 - present)

Trial Experience as PI / Co PI / Steering Committee
- CREST
- SAPPHIRE
- VIVA
- ACT I
- EMPIRE
- ARMOUR
- CABERNET
- CARESS
- CABANNA
- BEACH
- CAPTURE
- ARCHeR
History of Carotid Artery Stenting

- **1994**: First CAS
- **1998-2000**: CREST planning - inclusion/exclusion
  - 4 years after first CAS
- **2004**: First FDA approval of CAS for patients at high risk of CEA (Acculink Stent System)
- **2011**: CAS has become an effective alternative and important complement to CEA and should be available for patients at standard risk of CEA
Outcome of CEA Trials Over Time

- In the 1980’s: CEA risk up to 21% in some reports
- In the 1990s: death and stroke rates were 6%-7% for symptomatic patients and 3%-4% for asymptomatic patients
- Outcomes of CEA continue to improve over time
Outcomes of CAS Trials Over Time

- CAS results have vastly improved over time due to: (1) more experienced operators; (2) better patient selection and; (3) a wider spectrum of technology.
- CAS outcomes have evolved over time similarly to CEA.

(Enrollment: 2000-2008) CREST – 5.7%
(Enrollment: 2000-2008) CREST – 1.1%
Today Many Patients at Standard Risk Are Clearly Better Served by CAS

- Anatomical features
- Clinical conditions
- Physician and patient choice
- Previous stroke
- C-spine disease
- Cosmetic reasons
- Personal preference – less invasive option
- Voice professionals
If a Patient Needs a Carotid Revascularization…

Its All About Decision Making and Judgment

Its All About Having Choices
Case Study: Asymptomatic Carotid Stenosis

62 year old male, standard risk for CEA, family history of stroke

CEA or CAS?

CAS Not YET Approved
Based on the data that will be presented today showing clinical equipoise between CAS and CEA, patients at standard risk for CEA need the treatment option of CAS for many reasons

- Many standard risk patients better served by CAS
- Patients and physicians need choices
PMA Analysis of the CREST Trial

Approvability of the RX Acculink Carotid Stent System for Revascularization of Carotid Artery Stenosis in Standard Surgical Risk Patients

Chuck Simonton, MD
FACC, FSACAI
Chief Medical Officer
Divisional Vice President
Abbott Vascular
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long Term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions
Clinical Trials Evaluating CAS Treatment

- **ARCHer N = 581**
- **SECURITY N = 305**
- **SAPPHIRE N = 747**
- **CAPTURE N = 4,225**
- **EXACT N = 2,145**
- **PROTECT N = 322**
- **CAPTURE 2 N = 6,361**
- **CHOICE N = 6,872 (enrolling)**

**High risk**

- **SPACE (EU) N = 1,183 sym**
- **EVA-3s (EU) N = 527 sym**
- **ICSS (EU) N = 1,710 sym**

**Standard risk**

- **NASCET N = 2,885**
- **ACAS N = 828**
- **CREST N = 2,502**
- **ACT I N = 1,372 (enrolling)**

*FDA Approval for High Risk Patients*

- **AHA Guidelines (pub.1995)**

Date range: 1980-2010

Legend:
- CEA
- CAS High Risk
- CAS Standard Risk
Trial Design

- Prospective, multicenter randomized trial
  - Compares carotid artery stenting (CAS) to surgical carotid artery endarterectomy (CEA)
  - RX Acculink Carotid Stent System for CAS
  - U.S. and Canada
- Enrollment
  - 2000: symptomatic patients only
  - 2005: asymptomatic patients approved for enrollment
- Randomization
  - Stratified by clinical site and symptomatic status
  - 1:1 randomization ratio
Sites included in this analysis
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
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- Conclusions
Trial Design – Primary Analyses

- Primary endpoint for the CREST PMA analysis is pre-specified in the binding agreement with FDA.

- Primary endpoint is composite of all death, any stroke or MI within 30 days of the procedure PLUS ipsilateral stroke from 31 to 365 days.

- There are four pre-specified analysis populations:
  - Intent-to-Treat (ITT)
  - As Treated (AT)
  - Modified As Treated (MAT)
  - Per Protocol (PP)
Trial Design – Secondary Analyses

- **Secondary endpoints:**
  - All death, any stroke, or MI at 30 days (peri-procedural)
  - One year composite endpoint stratified by
    - Symptomatic status
    - Age by octogenarian status
  - Acute Success
  - Target Lesion Revascularization at 12 months
  - Access site complications requiring treatment
  - Cranial nerve injury unresolved at 1 and 6 months

- **Pre-specified interaction analyses**
  - Sex and symptomatic status
Endpoint Definitions

- **Death**: All deaths to 30 days
- **Stroke**: Acute neurological ischemic event of at least 24 hours duration with focal signs and symptoms
  - Major stroke: NIHSS score of ≥9 at 3 months post stroke, or clinical judgment
  - Minor stroke: NIHSS score of <9 at 3 months post stroke
- **Myocardial Infarction (MI)**:
  - Cardiac biomarkers (CK-MB or troponin) > 2X ULN and/or
  - ECG evidence of >1mm ST elevation or depression in 2 contiguous leads and/or
  - Chest pain with either ECG or biomarker evidence

All endpoints adjudicated by CEAC
## Stroke Assessment Requirements

<table>
<thead>
<tr>
<th>Neurological Examination</th>
<th>Pre-procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-procedure 18 to 54 hours</td>
</tr>
<tr>
<td></td>
<td>1 month and 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke Scales (NIHSS, mRS)</th>
<th>Pre- and Post-procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 and 3 months</td>
</tr>
<tr>
<td></td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upon Stroke Occurrence</th>
<th>NIHSS 3 months after stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT or MRA per standard of care</td>
</tr>
</tbody>
</table>
## MI Assessment Requirements

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>Post-procedure 6 to 48 hours</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
</tr>
<tr>
<td>Cardiac Biomarkers</td>
<td>Post-procedure at 6-8 hours (if elevated, then checked every 8 hours for 3 consecutive draws)</td>
</tr>
<tr>
<td>(CK-MB or Troponin)</td>
<td></td>
</tr>
</tbody>
</table>

**ECG**

- Pre-procedure
- Post-procedure 6 to 48 hours
- 1 month

**Cardiac Biomarkers (CK-MB or Troponin)**

- Pre-procedure
- Post-procedure at 6-8 hours (if elevated, then checked every 8 hours for 3 consecutive draws)**
Definition of Standard Risk

- Absence of anatomic or clinical conditions which make the patient at high risk for the surgical procedure

- For example, the absence of:
  - Anatomic: previous CEA, prior radiation treatment to the neck, surgically inaccessible lesions above C2
  - Clinical: left ventricular ejection fraction (LVEF) < 30%, unstable angina, recent MI
Patient Eligibility

- Discrete lesion in internal carotid artery (ICA) with or without involvement of common carotid artery (CCA)

- Symptomatic Patients
  - Age > 18 with TIA, amaurosis fugax, minor or non-disabling stroke within 6 months on the treated side
  - Carotid stenosis ≥ 50% by angiogram or ≥ 70% by ultrasound or ≥ 70% by MRA or CTA;

- Asymptomatic Patients
  - Age > 18, no symptoms within 6 months, and carotid stenosis ≥ 60% by angiogram or ≥ 70% by ultrasound or ≥ 80% by MRA or CTA
Statistical Methods: Primary Endpoint

- **Non-inferiority analysis** for the composite primary endpoint with the following assumptions
  - Composite end point rate of 7.48%
  - Non-inferiority margin of 2.6%
  - One-sided alpha of 0.05
  - 80% power

  Resulted in a population of 2,500 symptomatic patients

- Asymptomatic patients were added in 2005
  - Assumed 50% of the population would be asymptomatic
  - Assumed composite rate was revised to 6.76%
  - One-sided alpha of 0.05
  - Power of the study was increased to 82%

- In addition to the four analysis populations, a propensity score adjusted analysis was performed for the primary endpoint
Trial Management

- Study Principal Investigators
  - Dr. Robert Hobson (deceased)
  - Dr. Thomas G. Brott

- Trial Management
  - University of Medicine and Dentistry of New Jersey

- Core Labs
  - Ultrasound: Univ. Of Washington; Dr. Kirk Beach
  - Angiographic: Beth Israel Deaconess Hospital; Dr. Jeff Popma
  - ECG: Wake Forest Univ. School of Medicine; Dr. Ronald Prineas

- Clinical Events Adjudication Committees (CEAC)
  - MI: Independent cardiologists, Chairman: Dr. Joseph Blackshear
  - Stroke: Independent neurologists, Chairman: Dr. Stanley Cohen

- Statistical and Data Management
  - University of Alabama at Birmingham (UAB)
  - Abbott Vascular

- DSMB
  - NIH
CREST Trial Enrollment

CREST Cumulative Randomizations
2000 Through July 2008

# of Patients

- Asymptomatic
- Symptomatic

2000 total
2002 total

Jan-04
Mar-04
May-04
Jul-04
Sep-04
Nov-04
Jan-05
Mar-05
May-05
Jul-05
Sep-05
Nov-05
Jan-06
Mar-06
May-06
Jul-06
Sep-06
Nov-06
Jan-07
Mar-07
May-07
Jul-07
Sep-07
Nov-07
Jan-08
Mar-08
May-08
Jul-08
CREST PMA Analysis

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- Conclusions
Pre-specified Analysis Populations

**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
2. No procedure attempted and withdrew consent during study = 48
3. No procedure attempted = 51
4. Crossover post procedure = 9
5. Pure Crossover = 73
6. Aborted procedure = 4
7. No Study Stent = 4

Total 82 crossovers; 70 CAS to CEA; 12 CEA to CAS
High Follow-up Rate for the Primary Endpoint

PP Population
N = 2,307

1 Year Follow-up:
2243/2307 (97.2%)

CAS
N = 1,131

N = 1,102

CEA
N = 1,176

N = 1,141
Randomization by Symptomatic Status

Randomized (PP)  
N = 2,307

Protocol Recruitment Restriction
800 (32.0%) to 1,700 (68.0%) Symptomatic Patients

Symptomatic  
N = 1,219 (52.8%)

Asymptomatic  
N = 1,088 (47.2%)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>Unadjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>68.7</td>
<td>69.1</td>
<td>0.20</td>
</tr>
<tr>
<td>Age ≥ 80 years</td>
<td>9.4%</td>
<td>8.8%</td>
<td>0.61</td>
</tr>
<tr>
<td>Male</td>
<td>64.6%</td>
<td>66.7%</td>
<td>0.30</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>53.0%</td>
<td>52.7%</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84.8%</td>
<td>86.4%</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>30.0%</td>
<td>30.9%</td>
<td>0.62</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>83.8%</td>
<td>85.8%</td>
<td>0.18</td>
</tr>
<tr>
<td>Current smoker</td>
<td>27.6%</td>
<td>26.0%</td>
<td>0.38</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>43.2%</td>
<td>44.9%</td>
<td>0.41</td>
</tr>
<tr>
<td>CABG</td>
<td>20.7%</td>
<td>21.8%</td>
<td>0.52</td>
</tr>
<tr>
<td>Contralateral CEA</td>
<td>4.2%</td>
<td>5.2%</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only.
## Balanced Target Lesion Stenosis at Enrollment

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>Unadjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>50.0%</td>
<td>47.9%</td>
<td>0.297</td>
</tr>
<tr>
<td>Left</td>
<td>50.0%</td>
<td>52.1%</td>
<td>0.297</td>
</tr>
<tr>
<td><strong>Angiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>75.8 ± 11.0</td>
<td>73.6 ± 10.7</td>
<td>0.002</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.031</td>
</tr>
<tr>
<td>50 - 69</td>
<td>11.4%</td>
<td>10.5%</td>
<td>0.514</td>
</tr>
<tr>
<td>70 - 99</td>
<td>87.8%</td>
<td>88.0%</td>
<td>0.913</td>
</tr>
<tr>
<td>Occluded</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.366**</td>
</tr>
</tbody>
</table>

* p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

** Fisher’s Exact Test
PMA Primary Endpoint

Composite of all death, any stroke, or MI to 30 days

Plus

Ipsilateral stroke from 31 to 365 days
The RX Acculink Carotid Stent System Met the Primary Endpoint of the Trial

CAS is non-inferior to CEA in **Per Protocol** analysis

<table>
<thead>
<tr>
<th>PP</th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>p&lt;sub&gt;NI&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>7.1%</td>
<td>6.6%</td>
<td>2.26%</td>
<td>0.0245</td>
</tr>
</tbody>
</table>

95% Confidence Limit (CL)

Difference (CAS – CEA) = 0.5%

2.6% Margin of Non-inferiority
PMA and NIH Analyses Are Consistent and Complementary

<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
CAS is Non-inferior to CEA in All PMA Analysis Populations

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>( p_{NI} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>7.1%</td>
<td>6.6%</td>
<td>2.26%</td>
<td>0.0245</td>
</tr>
<tr>
<td>Adj. PP</td>
<td>7.2%</td>
<td>6.5%</td>
<td>2.41%</td>
<td>0.0342</td>
</tr>
<tr>
<td>ITT</td>
<td>7.0%</td>
<td>6.9%</td>
<td>1.80%</td>
<td>0.0077</td>
</tr>
<tr>
<td>AT</td>
<td>7.2%</td>
<td>6.7%</td>
<td>2.16%</td>
<td>0.0193</td>
</tr>
<tr>
<td>MAT</td>
<td>7.2%</td>
<td>6.7%</td>
<td>2.22%</td>
<td>0.0221</td>
</tr>
</tbody>
</table>

2.6% Margin of Non-inferiority
A Lower Primary Endpoint Rate was Observed in CAS Patients Treated with the Accunet EPS

<table>
<thead>
<tr>
<th>PP</th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>P_{NI}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.1%</td>
<td>6.6%</td>
<td>2.26%</td>
<td>0.0245</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accunet Used</th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>P_{NI}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6%</td>
<td>6.6%</td>
<td>1.80%</td>
<td>0.0080</td>
</tr>
</tbody>
</table>

2.6% Margin of Non-inferiority
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions
Peri-Procedural Composite Endpoint

All death, any stroke or MI
at 30 days post-procedure
CAS is Non-inferior to CEA for Peri-Procedural DSMI

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>$P_{NI}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>5.8%</td>
<td>5.1%</td>
<td>2.20%</td>
<td>0.0401</td>
</tr>
<tr>
<td>ITT</td>
<td>5.8%</td>
<td>5.5%</td>
<td>1.83%</td>
<td>0.0155</td>
</tr>
</tbody>
</table>

2.3% Margin of Non-inferiority
## Death, Stroke and MI within 30 Days

<table>
<thead>
<tr>
<th>Per protocol</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>Difference</th>
<th>Unadjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Death, Stroke, or MI</td>
<td>5.8% (65)</td>
<td>5.1% (60)</td>
<td>0.7%</td>
<td>0.5200</td>
</tr>
<tr>
<td>Death</td>
<td>0.53% (6)</td>
<td>0.26% (3)</td>
<td>0.27%</td>
<td>0.3335</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>4.1% (46)</td>
<td>1.9% (22)</td>
<td>2.2%</td>
<td>0.0019</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.9% (10)</td>
<td>0.4% (5)</td>
<td>0.5%</td>
<td>0.2005</td>
</tr>
<tr>
<td>Minor Stroke</td>
<td>3.2% (36)</td>
<td>1.5% (18)</td>
<td>1.7%</td>
<td>0.0088</td>
</tr>
<tr>
<td>MI</td>
<td>2.0% (22)</td>
<td>3.4% (40)</td>
<td>-1.5%</td>
<td>0.0387</td>
</tr>
</tbody>
</table>

* Fisher’s exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only.
Despite these directional differences for the stroke and MI components of the primary composite endpoint:

The CREST PMA analysis shows very low event rates for both CAS and CEA, lower than historical rates and within the AHA guidelines for 30-day event rates.
Death or Major Stroke Rates Decrease for CAS over the Period of CREST Enrollment

Frequency of Death or Major Stroke

- 2000-2004: 2.5% (N=160)
- 2005: 2.5% (N=201)
- 2006: 0.7% (N=308)
- 2007: 0.0% (N=298)
- 2008: 0.6% (N=164)

50% Trial Enrollment August 2006
Death or Major Stroke Rates in CAS Decrease for Symptomatic Patients

50% Symptomatic Patients Enrollment
March 2006

Frequency of Death or Major Stroke

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-04</td>
<td>2.5%</td>
<td>160</td>
</tr>
<tr>
<td>2005</td>
<td>3.6%</td>
<td>111</td>
</tr>
<tr>
<td>2006</td>
<td>0.8%</td>
<td>131</td>
</tr>
<tr>
<td>2007</td>
<td>0.0%</td>
<td>120</td>
</tr>
<tr>
<td>2008</td>
<td>0.0%</td>
<td>77</td>
</tr>
</tbody>
</table>
Death or Any Stroke Rates Decrease for CAS over the Period of CREST Enrollment

- **2000-2004**: 4.4% (N=160)
- **2005**: 7.0% (N=201)
- **2006**: 4.6% (N=308)
- **2007**: 3.4% (N=298)
- **2008**: 1.8% (N=164)

The period of CREST Enrollment was in August 2006.
Death or Any Stroke Rates in CAS Decrease for Symptomatic Patients

50% Symptomatic Patients Enrollment
March 2006

Frequency of Death or Any Stroke

- 2000-2004: 4.4% (N=160)
- 2005: 9.0% (N=131)
- 2006: 8.5% (N=131)
- 2007: 4.2% (N=120)
- 2008: 2.6% (N=77)
Neurological Residual Deficit Rates by NIHSS Associated with Minor Strokes, Equal at 6 Months

\[ \Delta = 0.50\% \]

\[ \Delta = 0.02\% \]

1 Month:
- CAS: 1.10%, n = 12
- CEA: 0.60%, n = 7

6 Months:
- CAS: 0.62%, n = 7
- CEA: 0.60%, n = 7
Neurological Residual Deficit Rates by mRS Associated with Minor Strokes, Similar at 6 Months

Δ = 0.70%

Δ = 0.30%

% of Per Protocol Population

1.20%
0.50%
0.80%
0.50%

n = 14
n = 6
n = 9
n = 6

1 Month
6 Months
Lack of Association of Minor Stroke with Long Term Mortality

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>Confidence Interval</th>
<th>Log Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI vs. Control</td>
<td>2.81</td>
<td>[1.53 - 5.17]</td>
<td>0.0005</td>
</tr>
<tr>
<td>Minor Stroke vs. Control</td>
<td>0.52</td>
<td>[0.13 – 2.09]</td>
<td>0.34</td>
</tr>
<tr>
<td>MI vs. Minor Stroke</td>
<td>5.18</td>
<td>[1.15 – 23.4]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Freedom From All Cause Mortality

- Control (N = 2183)
- MI (N = 56)
- Minor Stroke (N = 48)
### Similar Association of Any Stroke or MI on Long Term Mortality

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>Confidence Interval</th>
<th>Log Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI vs. Control</td>
<td>2.81</td>
<td>[1.53 - 5.17]</td>
<td>0.0005</td>
</tr>
<tr>
<td>Any Stroke vs. Control</td>
<td>2.77</td>
<td>[1.54 - 4.97]</td>
<td>0.0004</td>
</tr>
<tr>
<td>MI vs. Any Stroke</td>
<td>0.99</td>
<td>[0.43 - 2.23]</td>
<td>0.97</td>
</tr>
</tbody>
</table>

#### Graph

- **Control (N = 2183)**
- **MI (N = 56)**
- **Any Stroke (N = 62)**

Freedom From All Cause Mortality (%): 88.8%

Days: 0, 365, 730, 1095, 1460

Mortality:

- 78.5%
- 75.0%
Clinical Equipoise for CAS and CEA

- Death or Major Stroke
  - Low rates for both CAS and CEA
  - Rates decreased over time for CAS
  - Rates are the same for CAS and CEA in the second half of enrollment

- Minor stroke
  - More frequent with CAS at 30 days
  - CAS and CEA demonstrated similar rates of residual disability by 6 months

- Peri-procedural MI
  - More frequent with CEA at 30 days
  - Shows a significant relationship to mortality
Other Pre-Specified Secondary Endpoints

- Primary Composite Endpoint
  - Symptomatic status
  - Age by octogenarian status
- Acute Success
- Target Lesion Revascularization (TLR) at 1 year
- Access Site Complications Requiring Treatment
- Cranial Nerve Injury at 1 and 6 months
Primary Composite Endpoint by Symptomatic or Octogenarian Status

- Symptomatic
  - CAS: 8.70%
  - CEA: 7.50%
  - N = 599
- Asymptomatic
  - CAS: 5.30%
  - CEA: 5.60%
  - N = 532
- Non-octogenarians
  - CAS: 6.70%
  - CEA: 6.20%
  - N = 1,025
- Octogenarians
  - CAS: 11.60%
  - CEA: 10.80%
  - N = 106
## Comparable Procedure and Clinical Success

<table>
<thead>
<tr>
<th></th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Success</td>
<td>97.5%</td>
<td>93.6%</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[96.4%, 98.3%]</td>
<td>[92.1%, 94.9%]</td>
</tr>
<tr>
<td>Clinical Success</td>
<td>91.9%</td>
<td>89.8%</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[90.2%, 93.4%]</td>
<td>[87.9%, 91.5%]</td>
</tr>
</tbody>
</table>
Freedom from Target Lesion Revascularization up to One Year

- CAS
- CEA

HR: 1.13 [0.52 – 2.48]
Log Rank P-value: 0.76

per protocol
Lower CAS Access Site Complications

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>CAS</th>
<th>CEA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1,131</td>
<td>1.1%</td>
<td>3.7%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Access Site Complication Requiring Treatment

Events may occur more than once in the same patient.
Other includes pain requiring IV analgesics (5), incision complication (3), pseudoaneurysm (2), occlusion (1)
**No Observed CAS Related Cranial Nerve Injury**

<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% (62/1176)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Unresolved at One Month</td>
<td>0.0%</td>
<td>3.6% (42/1176)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Unresolved at Six Months</td>
<td>0.0%</td>
<td>2.1% (25/1176)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions
No Interaction by Subgroup for Primary Endpoint

<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></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.94 (0.57-1.57)</td>
<td>0.4978</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></td>
</tr>
<tr>
<td>Male</td>
<td>1.10 (0.74-1.63)</td>
<td>0.9168</td>
</tr>
<tr>
<td>Diabetics</td>
<td>0.85 (0.51-1.41)</td>
<td></td>
</tr>
<tr>
<td>Non-diabetics</td>
<td>1.28 (0.85-1.91)</td>
<td>0.2153</td>
</tr>
</tbody>
</table>
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions
CAS Demonstrates Long Term Effectiveness to 4 Years

Primary Composite Endpoint (Median Follow-up 3 Years)

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>95% CL</th>
<th>P_{NI}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>8.8%</td>
<td>8.2%</td>
<td>1.08</td>
<td>1.37</td>
<td>0.0175</td>
</tr>
</tbody>
</table>

1.47 Hazard Ratio Margin of Non-inferiority

Hazard Ratio: CAS vs. CEA
Similar Mortality to 4 Years

Freedom From All Cause Mortality

- CEA
- CAS

Days From Index Procedure

HR: 1.19 [0.90 - 1.58]
Log Rank P-value: 0.23

88.2%
87.9%
Similar Freedom from Ipsilateral Stroke
Day 31 to 4 Years

CAS

CEA

HR: 1.03 [0.63 - 1.69]
Log Rank P-value: 0.89

Freedom From Ipsilateral Stroke

Days From Index procedure
Similar Freedom from TLR to 4 Years

HR: 1.00 [0.61 - 1.66]
Log Rank P-value: 0.99
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions
# Independent Predictors of Mortality

<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 days (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 (male vs. female)</td>
<td>1.50</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
CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions
Conclusions

- The PMA analysis of the CREST study demonstrates:
  - CAS is non-inferior to CEA for the primary endpoint in all analysis populations
  - CAS is non-inferior to CEA for death, stroke or MI at 30 days
  - CAS shows similar durability to CEA by freedom from the primary endpoint, mortality, ipsilateral stroke, and TLR to 4 years
  - The primary endpoint rates were similar for CAS and CEA for symptomatic or octogenarian status
Final Interpretation

- CREST PMA analysis supports the proposed expanded indication to treat patients at standard surgical risk with CAS using the Acculink Stent System.

- CAS with the Acculink Carotid Stent System demonstrates a reasonable assurance of safety and effectiveness compared to CEA.

- Treatment with CAS or CEA should be determined by physicians and patients based on the clinical profile of each patient.
NIH Analysis of the CREST Data

Thomas G. Brott, MD
Principal Investigator, IDE Sponsor
Mayo Clinic
Jacksonville, FL

James C. and Sarah K. Kennedy Dean of Research
Eugene and Marcia Applebaum Professor of Neurosciences
Financial Disclosure

- Dr. Thomas G. Brott, M. D.
  - No financial relationship with Abbott Vascular, Inc.
  - Grant Sponsorship
    - NIH – US Public Health Service, NINDS, R01 NS 038384
Acknowledgements

- 1,565 credentialing and 2,502 randomized patients
- More than 117 Site Principal Investigators
- More than 200 Site Coordinators
- University of Medicine and Dentistry of New Jersey (UMDNJ)
- University of Alabama at Birmingham (UAB)
- 3 Core Labs and the QOL/Cost group
- Adjudication Committees, the DSMB, NINDS, and Abbott Vascular, Inc.
Robert Hobson II, M. D.
PI, 1999 - 2007
Study Design

- Randomized, controlled trial with blinded endpoint adjudication
- Comparing CAS and CEA
- Symptomatic and asymptomatic patients
- Intent-to-treat superiority design with sample size of 2,500 to detect an annual difference of 1.2%, based upon the ACAS results which changed practice (corresponding to a hazard ratio of 1.48)
Primary Endpoint

- Peri-procedural, a composite of:
  - Any Clinical Stroke
  - Myocardial Infarction (not enzyme only)
  - Death

- Post-procedural
  - Ipsilateral stroke up to 4 years
Key Secondary Aims

- Differential efficacy by symptomatic status, sex, and age
- Differential restenosis
- Quality of Life and cost effectiveness
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1,262</td>
<td>1,240</td>
</tr>
<tr>
<td>Age</td>
<td>68.9 ± 9.0</td>
<td>69.2 ± 8.7</td>
</tr>
<tr>
<td>Cardiovascular disease - %</td>
<td>42.4</td>
<td>45</td>
</tr>
<tr>
<td>Systolic BP, mean mmHg</td>
<td>142</td>
<td>141</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>30.6</td>
<td>30.4</td>
</tr>
<tr>
<td>Dyslipidemia %</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>% stenosis ≥ 70%</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>Days from qualifying event</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>(for symptomatic subjects)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Results
Primary Endpoint ≤ 4 Years

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>7.2%</td>
</tr>
<tr>
<td>CEA</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

Hazard Ratio: 1.11
95% Confidence Interval: 0.81 – 1.51
p-value: 0.51

(any stroke, MI, or death within peri-procedural period plus ipsilateral stroke thereafter)
Primary Endpoint
ITT Analysis
Multiple Imputation in the NIH Analysis

- Differential withdrawal (censoring) between treatment group could introduce bias
- Multiple imputation using a method similar to Taylor* was employed to assess potential differences
  - Outcomes of censored individuals were replaced with randomly selected outcomes of non-censored individuals
  - Procedure repeated 10 times
  - Analyzed using standard multiple imputation approaches
- Findings were strikingly similar to analysis without imputation (identical to the second decimal), suggesting the absence of bias from this source

## Peri-procedural Stroke & MI

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>4.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>CEA</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.79</td>
<td>0.50</td>
</tr>
<tr>
<td>95% Conf. Int.</td>
<td>1.14 – 2.82</td>
<td>0.26 – 0.94</td>
</tr>
<tr>
<td>p-value</td>
<td>0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>
## Peri-procedural Stroke

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>Major Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>4.1%</td>
<td>0.9%</td>
</tr>
<tr>
<td>CEA</td>
<td>2.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.79</td>
<td>1.35</td>
</tr>
<tr>
<td>95% Conf. Int.</td>
<td>1.14 – 2.82</td>
<td>0.54 – 3.36</td>
</tr>
<tr>
<td>p-value</td>
<td>0.01</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Impact of peri-procedural events (stroke/MI) on SF-36 at 1 year adjusting age, sex, symptomatic cerebrovascular disease and baseline SF-36 measures – Growth Curve Modeling
# Ipsilateral Stroke After Peri-procedural Period

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>2.0%</td>
</tr>
<tr>
<td>CEA</td>
<td>2.4%</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.94</td>
</tr>
<tr>
<td>95% Conf. Int.</td>
<td>0.50 – 1.76</td>
</tr>
<tr>
<td>p-value</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Interaction with Primary Endpoint

- No effect detected for symptomatic status or sex
- Interaction suggested for Age, $p = 0.02$
Primary Outcome – 4 Year

\[ P_{\text{interaction}} = 0.020 \]

CEA Superior

CAS Superior
# Relationship Between Medical Specialty and Risk of Primary Outcome

<table>
<thead>
<tr>
<th>Specialty</th>
<th>HR (95% CI) adjusted for age, sex, symptomatic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>reference</td>
</tr>
<tr>
<td>Neuroradiology/Neurointerventionalist</td>
<td>1.27 (0.63-2.54)</td>
</tr>
<tr>
<td>Interventional Radiology</td>
<td>0.72 (0.32-1.63)</td>
</tr>
<tr>
<td>Vascular Surgery</td>
<td>1.18 (0.60-2.31)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1.49 (0.76-2.89)</td>
</tr>
<tr>
<td>p-value for difference</td>
<td>0.505</td>
</tr>
</tbody>
</table>
CREST NIH Results at 1 Year

- Intent-to-Treat population and NIH methodology

- Primary endpoint
  - CAS: 6.30 ± 0.69%
  - CEA: 5.52 ± 0.66%

- Non-inferiority met for NIH analysis
  - One-sided 95% CI for the difference between CAS and CEA is 2.36%, p = 0.03
Conclusions

- CEA and CAS have similar net outcomes
  - CAS: Lower MI rate
  - CEA: Lower Stroke rate

- Younger patients may have improved efficacy with CAS
  and older patients have improved efficacy with CEA
Conclusion

- At experienced centers both CEA and CAS appear to have low peri-procedural complications and excellent longer-term results

- Both treatments are viable options for standard risk patients
Concluding Remarks

Chuck Simonton, MD
FACC, FSCAI
Chief Medical Officer
Divisional Vice President
Abbott Vascular
Abbott Vascular Post-Approval Study Commitment

- Abbott Vascular has extensive experience with post approval studies for carotid stenting in high-risk patients
- This experience will be leveraged to conduct a timely and robust post-approval study of patients at standard risk of CEA
  - Collect post-approval data on a broad group of physicians under commercial use
  - 3 year follow-up
  - Follow safety and effectiveness outcomes
Physician Education Programs to Ensure Safe Use

- **Comprehensive Physician Education Program**
  - In place since 2004 for high risk patients
  - No changes required for standard risk patients

- **Certification Pathways**
  - Based on previous carotid stent or endovascular experience

- **Embolic Protection System Training Program**
Patient Guide with Comprehensive Information

- Helping health-care providers educate their patients
- Treatment options
- Procedure preparation
- Post procedure follow-up
- Lifestyle management
Safety and Effectiveness Demonstrated for the RX Acculink Carotid Stent System

- Non-inferior to CEA for the primary composite endpoint in all analysis populations

- Non-inferior to CEA for DSMI at 30 days

- The primary endpoint rates were similar for CAS and CEA for symptomatic or octogenarian status

- CAS shows similar durability to CEA by freedom from the primary endpoint, mortality, ipsilateral stroke, and TLR to 4 years
Benefits Outweigh the Risks for the RX Acculink Carotid Stent System

- **Benefits**
  - Non-inferior to CEA
  - Lower MI rate compared to CEA
  - Long term effectiveness confirmed out to 4 years
  - Less invasive with fewer access site complications and lack of cranial nerve injury

- **Risks**
  - Higher rate of minor stroke at 30 days compared to CEA, but similar residual neurological deficits at 6 months
Subject Matter Experts

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Standard Surgical Risk Indication

P040012/S034

January 26, 2011

Circulatory System
Devices Advisory Panel
Food and Drug Administration