Carotid Revascularization, Endarterectomy versus Stent Trial

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Disclosures
None

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CREST Organizational Chart

CREST Primary Aim

• To compare the efficacy of CAS vs. CEA
  – In preventing any stroke, MI, and all-cause mortality during a 30-day peri-procedural period, and
  – In preventing ipsilateral stroke over the follow-up period (extending up to 4 years)

Ensure that the study compared the best surgical to best stenting ability possible
CREST Secondary Aims

- To describe the
  - Differential efficacy of CAS and CEA in male and female patients
  - Differences in restenosis rates
  - Differences in health related quality of life
  - Differences in cost effectiveness
  - Subgroups of participants at differential risk for CAS and CEA

CREST Lead-in (Credentialing) Phase Specific Aims

- To ensure that the study compared the best surgical to best stenting ability possible
- Non-randomized phase, where procedural indications, technique, and results would be intensely scrutinized
- To objectively
  - Guide site credentialing/selection
  - Train stent operators
  - Guide stent operator credentialing/selection

CREST Procedural details

- Surgery
  - Details per surgeon preference
- Stenting
  - Rapid-exchange, 0.014 system, Acculink stents, Accunet embolic protection system

CREST Historical Perspective

- CREST funded by the National Institutes of Health
- CREST Lead-in begins
- Medicare implementation of Clinton order
- FDA approval of modified protection device
- Inclusion of asymptomatic patients
CREST Lead-in Phase

Inclusion Criteria

• Symptomatic CS ≥50%
• Asymptomatic CS ≥60%
• High and Normal Risk patients
  – Post-CEA restenosis
  – Radiation-induced stenosis
  – Primary atherosclerosis
  – Cardiac, pulmonary or other co-morbidities
• Age
  – Octogenarians excluded later because of safety

Credentialing and Training of Interventionalists

A three-step credentialing process for stent operators was designed to minimize learning curve effects upon outcomes

Credentialing and Training Step 1

1. Potential sites evaluated by a Site Selection Committee for:
   – Substantial case-load of CEA (≥ 50 CEA/yr)
   – Established low CEA complication rates
   – Presence of an experienced clinical team
Credentialing and Training

Step 2

2a. Stent data on the 10-30 most recent consecutive cases submitted by prospective interventionalists to the Interventional Management Committee (IMC)
   – Admission notes, Procedural reports, Discharge summaries, Peri-procedural events, 30-day post-procedural events

2b. Based on evaluation, operators were:
   – Approved for the CREST Randomized study based on prior experience with the study devices
   – Approved for the CREST Lead-In credentialing study
   – Requested to submit additional cases for re-review or
   – Not granted approval

Credentialing and Training

Step 3

3a. Upon committee approval operators underwent training for Lead-In
   – Carotid Stent Operator Certification Program (CSOCP)
   – Animal training
   – CREST protocol training
   – Device training and first case observation by Abbott Vascular

3b. Perform stent cases in Lead-In
   – N=5 for experienced operators; n=10 for less experienced
   – Outcome data reviewed by CREST Clinical Events Committee

3c. Review of all data and recommendation by committee to:
   – Advance to CREST randomization phase
   – Perform more cases in Lead-In
   – Not granted approval

Credentialing Outcomes

426 operators applied

240 committee-approved for Lead-in Phase
   • 17 did not meet regulatory or training requirements
   • 28 from sites not participating or operator no longer at site

70 committee-approved for Randomization Phase
   • 6 did not meet regulatory or training requirements
   • 1 from site not participating or operator no longer at site

116 did not receive committee approval
   • 17 did not meet regulatory or training requirements
   • 26 from sites not participating or operator no longer at site

223 approved for Randomization

Stent-Credentialed Specialties

Interventional NeuroRadiology 23%
Interventional Radiology 11%
Cardiology 40%
Vascular Surgery 16%
Neurosurgery 7%
Neurology 3%
What Else Have We Learned?

Stroke or Death Outcomes

<table>
<thead>
<tr>
<th>Stroke or Death</th>
<th>n</th>
<th>Total %</th>
<th>Symptomatic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST Lead-in</td>
<td>409</td>
<td>4.4 ± 0.6</td>
<td>6.0 ± 1.2</td>
</tr>
<tr>
<td>SAPPHIRE (CAS)</td>
<td>4.8</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>EVA-3S (CAS)</td>
<td>247</td>
<td>-</td>
<td>9.6</td>
</tr>
<tr>
<td>SPACE (CAS)</td>
<td>535</td>
<td>-</td>
<td>6.8</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>482</td>
<td>5.7</td>
<td>10.6</td>
</tr>
</tbody>
</table>

What Else Have We Learned?

Stroke or Death Outcomes

<table>
<thead>
<tr>
<th>Stroke or Death</th>
<th>n</th>
<th>Total %</th>
<th>Asymptomatic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST</td>
<td>1131</td>
<td>4.4 ± 0.6</td>
<td>3.4 ± 0.6</td>
</tr>
<tr>
<td>SAPPHIRE (CAS)</td>
<td>4.8</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>CAPTURE</td>
<td>3018</td>
<td>5.7</td>
<td>4.9</td>
</tr>
</tbody>
</table>

What Else Have We Learned?

Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>Stroke and Death Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 yrs</td>
<td>174</td>
<td>6.5</td>
</tr>
<tr>
<td>60-69 yrs</td>
<td>390</td>
<td>2.6</td>
</tr>
<tr>
<td>70-79 yrs</td>
<td>594</td>
<td>13.2</td>
</tr>
<tr>
<td>≥80 yrs</td>
<td>145</td>
<td>12.8</td>
</tr>
</tbody>
</table>

p=0.0005

What Else Have We Learned?

Hemodynamics

- Stroke/death associated with hemodynamic adverse events occurring within 7 days of CAS:
  - Hypotension (n=71) vs. normal BP
    - 11.4% vs. 4.1% (p=0.004)
  - Hemorrhage (groin or retroperitoneal, n=21) vs. no bleed
    - 19.6% vs. 4.3% (p=0.002)
What Else Have We Learned?

Multiple Stents

- 30-day stroke rate in patients with
  - 1 stent vs. 2-3 stents to cover the lesion
  - 4.0% vs. 13.2% (p=0.0002, HR 2.78)

- Cohort of 1,303 patients
  - 83.6% of all strokes occurred in patients with 1 stent
  vs. 16.4% of strokes in those with 2 (n=8) or 3 stents
  (n=1) stents

What Else Have We Learned?

Gender

- ACAS: Men had a 66% RR reduction in stroke/MI vs. 17% in women
- NASCET I: No differential gender effects with >70% stenosis
- NASCET II: Men with 50-69% stenosis had greater benefit after CEA
- EVA-3S men had more complications after CAS vs. women (p=0.03)
- SPACE: No differences based on gender

- CREST Lead-in cohort: Women 37%
- 30-day stroke and death rate:
  - Women 4.5% (26/579) vs. Men 4.2% (41/985)
  - p=ns after adjustment for age, anatomic features, or risk factors

What Else Have We Learned?

Restenosis

- SPACE: Restenosis >70% in 10.7% of patients at 2 years
- SAPPHIRE: Restenosis >50% in 19% of patients at 1 year

- CREST Lead-in, n=643
- Restenosis ≥50% in 182 patients: 28%
- Occlusion in 2 patients: 0.3%
- Repeat revascularization (all endovascular) 1.2%

CREST Randomized Study
CREST Inclusion Criteria

- Similar to the previous NIH CEA RCTs:
  - NASCET
  - ACAS
- Normal-risk patients with symptomatic CS
  - ≥50% by angiography
  - ≥70% by ultrasound, or
  - >70% by CTA/MRA if ultrasound is 50-69%
- Normal risk patients with asymptomatic CS
  - ≥60% by angiography
  - ≥70% by ultrasound, or
  - >80% by CTA/MRA if ultrasound is 50-69%

Clinical Sites for CREST

- Originally specified 40 sites
- Increased to 80, then 120

CREST Completes Enrollment

CREST Cohort Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>1</td>
<td>7</td>
<td>0.3%</td>
</tr>
<tr>
<td>Asian</td>
<td>12</td>
<td>20</td>
<td>1.3%</td>
</tr>
<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>2</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>Black (AA)</td>
<td>52</td>
<td>57</td>
<td>4.3%</td>
</tr>
<tr>
<td>White</td>
<td>812</td>
<td>1538</td>
<td>93%</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>35%</strong></td>
<td><strong>65%</strong></td>
<td></td>
</tr>
</tbody>
</table>
CREST Cohort
Demographics

Mean Age 69.1 yrs
Diabetes 30%
Hypertension 85%
Dyslipidemia 83%
Current smoker 25%
Previous CABG 21%

CREST Anticipated Timeline of Results

Patient #2,522 enrolled 7/18/2008

Late 2009 30-day adjudicated randomized data submitted to AVS
End 2009

1-year data presented to investigators & AVS at Data Retreat

Late 2010 FDA Panel meeting

Early 2010 Primary results paper submitted

CREST 1-year data published Mid 2010

Conclusions
CREST Randomized Study

• Recruitment completed on one of the largest randomized carotid revascularization trials

• Follow-up on-going; last person recruited to be followed for at least one year
  – Average follow-up approaching three years

• 90% power to detect an annual absolute difference of 1.2% in the primary endpoints between CAS and CEA

• 80% power to detect a difference for symptomatic and asymptomatic patients separately

Conclusions
CREST Lead-in Phase

• Recruitment completed on one of the largest supervised credentialing efforts leading in to a randomized trial ever conducted by the NIH

• The credentialing process has resulted in interventionalists that have matched or exceeded outcomes achieved in other CAS procedural registries/trials

• Their outcomes can be relied upon in the randomized phase of the trial
Conclusions
CREST Lead-in Phase

- Additional knowledge gained:
  - Adverse impact of age on CAS outcomes
  - Importance of hemodynamic monitoring and aggressive management of hemodynamic events during CAS
  - Importance of sizing of the lesion and accurate deployment of the stent to ensure that only a single stent is utilized to cover the lesion
  - Importance of restenosis as an endpoint, since early periprocedural benefit with one procedure may be offset by a higher recurrence and re-intervention rate in the long-term