Barriers To Enrollment in CREST 2: How Can They Be Overcome?

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Primary Goal of CREST-2

• In patients with ≥70% asymptomatic stenosis, to assess:
  • The treatment differences between medical management and CEA
  • The treatment differences between medical management and CAS

Patient Selection

Based on CREST:
• For ages 50-74 years, no favored procedure
• For ages <50 years, CAS is the favored procedure
• For ages >74 years, CEA is the favored procedure
• BUT, in CREST asymptomatic patients had few events, so there were wide confidence intervals

So, the choice of CEA or CAS cannot be mandated in CREST-2...

...and individual patient characteristics and preferences may supersede guidelines

Objective

• The goal of this study was to assess our enrollment and randomization practices for CREST-2 in an effort to determine effects of exclusion criteria and treating physician specialty on screening and recruitment of asymptomatic patients with severe carotid stenosis.

Disclosures

Medtronic – consultant, member of CEC
Volcano – consultant, member DSMB
Bard – member of CEC
**Methods - Patients**

- Creation of Patient Cohort
- From 7/1/2015 to 12/31/2015, all carotid duplex ultrasound studies (CDUS) were reviewed.
- CDUS meeting CREST-2 criteria for ≥70% stenosis were identified.

**Duplex Criteria**

- PSV ≥ 230 cm/second on DUS
- plus one of the following 4 criteria:
  - EDV ≥ 100 cm/second on DUS
  - IC / CC PSV ≥ 4.0 on DUS
  - ≥ 70% stenosis on MR angiogram
  - ≥ 70% stenosis on CT angiogram

**Methods - Patients**

- Treating physicians were contacted by study nurses to determine why patients were excluded from the study
- Electronic medical records and institutional trial screening data were used to assess method of management and neurologic outcome.

**Results**

- 139 patients who had a ≥70% carotid stenosis by CDUS
- 17 presented with symptomatic disease
- 15 patients who had <70% stenosis on additional imaging.
- 107 patients in the cohort
  - 76 (71%) 70-89%
  - 31 (29%) 90-99%.

**Patient Characteristics**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>73 yrs</td>
</tr>
<tr>
<td>Male Gender</td>
<td>58%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38%</td>
</tr>
<tr>
<td>CAD</td>
<td>70%</td>
</tr>
<tr>
<td>Statin</td>
<td>88%</td>
</tr>
</tbody>
</table>

**Results**

- Primary Treating Provider
  - Vascular Surgeon | 73 (68%)
  - Cardiology/ Vascular Medicine | 20 (19%)
  - Neurologist | 14 (13%)
- 4 /107 (3.7%) patients randomized
  - 3 CAS arm
  - 1 CEA arm
Results

- 103 (96.3%) patients not randomized
- 64 (62%) had at least 1 exclusion criterion
  - Cardiac
  - Renal
  - Prior intervention

Exclusion Criteria

- Allergy to Study Medication
- GI Hemorrhage precluding antiplatelet therapy
- Prior major ipsilateral stroke with residual disability that will confound outcomes
- Severe dementia
- History of major symptomatic intracranial hemorrhage not related to anticoagulation
- Intracranial hemorrhage that is contraindication to anticoagulation or antiplatelet therapy
- Current neurologic illness that can not be distinguished from stroke
- Objection of blood transfusions
- Platelet count < 100,000/ul

Enrollment by Provider

<table>
<thead>
<tr>
<th>Provider</th>
<th>CREST Random</th>
<th>Comorbid Exclusion</th>
<th>Pt Refused/ Not Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeon (73)</td>
<td>0</td>
<td>40 (55%)</td>
<td>33 (45%)</td>
</tr>
<tr>
<td>Cardiology/VM (20)</td>
<td>1 CAS</td>
<td>16 (80%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Neurology (14)</td>
<td>2 CAS</td>
<td>8 (57%)</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

Surgeon Reluctance

- Patterns of Referral
  - CEA Expected
  - Not a CREST Surgeon
- Lack of clinical equipoise
  - 70%-89% - more likely to randomize
  - 90%-99% - less likely to randomize
### Treatment by Provider

<table>
<thead>
<tr>
<th>Provider</th>
<th>CAS</th>
<th>CEA</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeon (73)</td>
<td>8</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Cardiology/VM (19)</td>
<td>4</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Neurology (11)</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

### Summary

- Nearly 2/3 of patients with >70% asymptomatic carotid stenosis were not eligible for CREST-2
- Another 23% refused to participate
- Only 4% of those identified were randomized
- Enrollment and treatment dependent upon provider seen
- Neurologists most likely to enroll
- Surgeons least likely to enroll
- 75% of patients enrolled in CAS arm

### Conclusions

- Strict exclusion criteria and reluctance of surgeons to enroll patients suggest that completion of the CEA arm of the trial will be challenging
- Slow enrollment will make it difficult for CREST to answer the questions for which it was designed