Carotid Disease: Will ACT ONE Finally Tell Us the Best Options for Our Patients…Or are We on the CREST of a New Wave?

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Disclosures

• Consultant/Advisory Board Member:

Abbott Vascular, Abiomed, Boston Scientific, Cardiovascular Systems, Medtronic, Merck, and Spectranetics
Outline

• Rationale for Carotid Revascularization

• Treatment of Symptomatic Carotid Artery Disease

• Treatment of Asymptomatic Carotid Artery Disease

• Current Guidelines and Coverage For Carotid Stenting
Pathophysiology of Symptoms from Carotid Artery Stenosis

• Symptoms occur from embolism or low flow.

• Present as ipsilateral ocular and/or cerebral hemisphere ischemia.
  - Amaurosis fugax.

• Carotid atherosclerosis generally occurs at bifurcation or within 2 cm.
  - “Hourglass” appearance
Association Between Carotid Artery Stenosis and Stroke

- 696 patients with asymptomatic carotid artery stenosis.
- Mean follow up 41 months
- 75% of events were ipsilateral to stenosis

Carotid Artery Stenosis and Stroke Risk

Inzitari et al, NEJM 2000;342:1693-1700
Carotid Artery Stenosis and Stroke Risk – Asymptomatic Disease

Inzitari et al, NEJM 2000;342:1693-1700
5 Year Risk of Stroke

Barnett et al, JAMA 2000;283:1429-1436
Barnett et al, JAMA 2000;283:1429-1436
Treatment of Symptomatic Carotid Artery Stenosis

- Symptomatic carotid artery stenosis: defined as TIA or ipsilateral hemispheric stroke within the past six months.

- May present as amaurosis fugax.

- Benefit of early revascularization if significant stenosis present.
Early Benefit of Revascularization if Symptomatic

NASCET Trial, NEJM 1991;325:445-453
## Symptomatic Stenosis – Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Percent Stenosis</th>
<th>Patients</th>
<th>% Stroke Medical*</th>
<th>% Stroke Surgical*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST 70-99</td>
<td>778</td>
<td>17 (3 years)</td>
<td>10</td>
</tr>
<tr>
<td>NASCET 70-99</td>
<td>662</td>
<td>26 (2 years)</td>
<td>9</td>
</tr>
<tr>
<td>NASCET 50-69</td>
<td>858</td>
<td>22 (5 years)</td>
<td>16</td>
</tr>
<tr>
<td>VA 50-99</td>
<td>189</td>
<td>19 (1 year)</td>
<td>8</td>
</tr>
</tbody>
</table>

*Ipsilateral
Pooled Analysis - Symptomatic

- Re-analysis of ECST angiograms to match NASCET method.

- CEA beneficial for $\geq 70\%$ stenosis
  - NNT 6.3 for one stroke over five years, ARR 16%.

- No benefit in “String Sign” or Occlusion

- CEA beneficial for 50-69% stenosis
  - NNT 22 for one stroke over five years, ARR 4.6%
Carotid Artery Stenting For Symptomatic Disease

- Multiple trials of carotid artery stenting for patients with symptomatic carotid disease at average surgical risk
  - SPACE, EVA-3S, ICSS

- All three trials flawed
  - No consistent use of EPDs
  - Operator inexperience with stenting
## High Surgical Risk

**TABLE 1** Features Associated With High Risk of Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Medical Comorbidity</th>
<th>Anatomic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (&gt;75/80 yrs)</td>
<td>Surgically inaccessible lesions</td>
</tr>
<tr>
<td>Congestive heart failure (NYHA functional class III/IV)</td>
<td>At or above C2</td>
</tr>
<tr>
<td>Unstable angina (CCS III/IV)</td>
<td>Below the clavicle</td>
</tr>
<tr>
<td>CAD with ≥2 vessels ≥70% stenosis</td>
<td>Ipsilateral neck irradiation</td>
</tr>
<tr>
<td>Recent myocardial infarction (≤30 days)</td>
<td>Spinal immobility of the neck</td>
</tr>
<tr>
<td>Planned open heart surgery (≤30 days)</td>
<td>Contralateral carotid artery occlusion</td>
</tr>
<tr>
<td>Ejection fraction ≤30%</td>
<td>Laryngeal palsy</td>
</tr>
<tr>
<td>Severe pulmonary disease (COPD)</td>
<td>Tracheostoma</td>
</tr>
<tr>
<td>Severe renal disease</td>
<td>Previous ipsilateral CEA or neck surgery</td>
</tr>
</tbody>
</table>
SAPPHIRE Trial

- 334 patients with symptomatic or asymptomatic carotid artery disease at high surgical risk for CEA
  - >50% stenosis if symptomatic
  - >80% stenosis if asymptomatic

- Consistent use of embolic protection, more experienced operators
SAPPHIRE Trial – Overall Results

12.2% vs. 20.1% (p=0.053 for superiority)

Yadav et al, NEJM 2004;351:1493-1501
SAPPHIRE Trial – Symptomatic Patients

Comparing CAS and CAE Results In High Surgical Risk Symptomatic Patients

- Red: Treated with Carotid Artery Stenting
- Blue: Treated with Carotid Endarterectomy

Risk of Death, Stroke or Myocardial Infarction (%)

- 0% at 0 days
- 5% at 30 days
- 10% at 60 days
- 15% at 90 days
- 20% at 120 days
- 25% at 180 days
- 30% at 270 days
- 35% at 360 days

P = 0.58

20% at 360 days
16.3% at 360 days
Decreasing Stroke Risk With Improved Techniques

CAS Results Show an Improving Trend in High Surgical Risk Patients (2003–2012)
Risk of Death, Stroke or Myocardial Infarction Within 30 Days of Procedure (%)
Proximal Embolic Protection for Symptomatic Carotid Artery Disease

• Initial crossing of carotid lesion is performed “unprotected”

• Possible benefit of proximal embolic protection

• Fewer carotid Doppler signals with proximal protection
Carotid Angiogram
MOMA Deployed

ECA balloon

CCA balloon

MOMA

4 X 30 MM BALLOON

CCA balloon
Stent Deployed

6-8 X 40 MM STENT
Post Dilation
Post Stent – MOMA Still In
Final Angiography
Prospective Registry of 1,300 Patients Treated with Proximal Embolic Protection
Treatment of Asymptomatic Carotid Artery Stenosis

- Data for benefit of asymptomatic carotid artery stenosis revascularization is based primarily on CEA vs. medical therapy data from the 1990’s.

- Early risk associated with revascularization, long-term benefit over five years.

- No definite benefit in women (under-representation?)
Short-Term Risk, Long-Term Benefit

ACST Trial, Lancet 2004;363:1491-1502
## Asymptomatic Stenosis: Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Percent Stenosis</th>
<th>Patients</th>
<th>% 5 year stroke, medical</th>
<th>% 5 year stroke, surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA &gt;50</td>
<td>444</td>
<td>9.4*</td>
<td>4.7*</td>
</tr>
<tr>
<td>ACAS &gt;60</td>
<td>1662</td>
<td>11.0*</td>
<td>5.1*</td>
</tr>
<tr>
<td>ACST &gt;60</td>
<td>3120</td>
<td>11.8**</td>
<td>6.4**</td>
</tr>
</tbody>
</table>

*Ipsilateral only  **Any stroke
CREST Trial

- 2,502 patients with symptomatic or asymptomatic carotid artery stenosis, enrolled from 2000-2008.
- Randomized to CEA or CAS.
- Primary composite endpoint of stroke, myocardial infarction, or death.
- Median follow up of 7.4 years.

CREST Peri-Procedural Outcomes

- Death: 0.7% stenting vs. 0.3% CEA (P=0.18)
- Stroke: 4.1% vs. 2.3% (P=0.01)
- Myocardial Infarction: 1.1% vs. 2.3% (P=0.03)
- Age interaction: Stenting better for patients <70 years of age, CEA better for >70 years of age

CREST Primary Endpoint

CREST 10 Year Outcomes

CREST 10 Year Outcomes

- Post-procedural ipsilateral stroke: 6.9% vs. 5.6%

- 5 year rates of post-procedural stroke by symptoms:
  - Asymptomatic: 2.5% stenting, 2.5% CEA
  - Symptomatic: 2.7% stenting, 2.7% CEA

Asymptomatic Carotid (ACT)-1 Trial

- Randomized trial of asymptomatic patients ≤ 79 years of age who were not high surgical risk.
- CEA or carotid stenting with embolic protection (Nav6) using closed cell stent (Xact).

Rosenfield et al, NEJM 2016 374:1011-1120
### ACT-1 Trial Characteristics

#### Lesion characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stenosis — % of vessel diameter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>73.7±8.8</td>
<td>73.9±10.2</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>33.8–98.6</td>
<td>34.7–96.0</td>
</tr>
<tr>
<td><strong>Lesion length — mm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>19.0±5.8</td>
<td>18.0±6.2</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>2.5–40.0</td>
<td>4.9–41.1</td>
</tr>
<tr>
<td><strong>Ulcerated — no./total no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>172/1062 (16.2)</td>
<td>37/255 (14.5)</td>
</tr>
<tr>
<td><strong>Thrombus — no./total no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10/1061 (0.9)</td>
<td>7/254 (2.8)</td>
</tr>
</tbody>
</table>

Rosenfield et al, NEJM 2016 374:1011-1120
93.1% stenting
94.7% CEA

Rosenfield et al, NEJM 2016 374:1011-1120
Rosenfield et al, NEJM 2016 374:1011-1120
2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease

• 80 pages
• 748 references
• Comprehensive review of the body of knowledge regarding extracranial carotid and vertebral artery disease
• Unprecedented collaboration between multiple societies
7.1. Recommendations for Selection of Patients for Carotid Revascularization*

**CLASS I**

1. Patients at average or low surgical risk who experience nondisabling ischemic stroke† or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the

2. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6% (360). *(Level of Evidence: B)*

3. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. *(Level of Evidence: C)*
**CLASS IIa**

1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (74, 76, 359, 361–363). *(Level of Evidence: A)*

2. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy.

3. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery (369–373). *(Level of Evidence: B)*

4. When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery (374). *(Level of Evidence: B)*
CLASS IIb

1. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (360). (Level of Evidence: B)

2. In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established (35,361,362,366, 369–372,375,376). (Level of Evidence: B)
Current Coverage for Carotid Artery Stenting

- CMS covers:
  - Symptomatic 70% stenosis
  - High risk for CEA
  - FDA-approved CAS system
  - Embolic protection device
  - CMS-approved institution
  - IDE trials or post-approval registries
CREST-2 Trial

- Asymptomatic patients with ≥70% asymptomatic stenosis.

- Two parallel arms
  - Medical management vs. CEA
  - Medical management vs. CAS
Trial Protocol

S -> R

CAS + Medical
n = 620

Medical
n = 620

CEA + Medical
n = 620

Medical
n = 620

Endpoint
Medical Management in CREST-2

- ASA 325 mg daily.
  - Clopidogrel after CAS

- Primary risk factor management
  - Directed by neurologist
  - Target SBP <140 mm Hg
  - Target LDL < 70 mg/dl

- Secondary risk factor management
  - HbA1C <7%, smoking cessation, weight management, moderate exercise
Decreasing Stroke Rates in Patients Managed Medically

Abbott, Stroke 2009;40:e573-e583
How Will CREST-2 Add to Our Knowledge of CEA?

• First trial to compare CEA + medical therapy to modern medical therapy in asymptomatic patients.

• Goal enrollment 2,480 patients (620 in each arm).
  ▪ 328 currently enrolled (October 2016)

• Includes patients with >70% stenosis.
Conclusions

• Robust data to support carotid artery revascularization for symptomatic stenosis.

• Most data on asymptomatic stenosis revascularization derived prior to modern medical therapy.

• Recent data demonstrate excellent long-term results of carotid artery stenting.