CURRENT STATUS OF CAROTID ARTERY STENTING
TRIALS, REGISTRIES, AND CMS

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OUTLINE
• Historic perspective: CEA and CAS
• Results of recent trials
• Ongoing trials
• CMS and carotid stenting

WHICH OF THE FOLLOWING DESCRIBES RANDOMIZED CLINICAL TRIAL DATA ON CAS AND CEA FOR PATIENTS WITH ASYMPTOMATIC CAROTID STENOSIS?

1. Large trials show that CEA is better.
2. Large trials show that CAS and CEA have similar outcomes
3. Large trials show that CAS is better
4. Few trials have been reported showing similar outcomes
5. Few trials have been reported showing CEA is better
WHICH OF THE FOLLOWING IS NOT A RISK FACTOR FOR STROKE WITH CAS?

1. Smaller (vs larger) filter pores
2. Symptomatic (vs asymptomatic) carotid stenosis
3. Beginning investigators (vs experienced) in symptomatic patients
4. Octogenarian (vs younger) patient

CAS

- CAS process of care is in progress and less mature than CEA
- Study data is difficult to compare because of differences in
  - Symptom status
  - Subject enrollment criteria, high or standard risk for CEA
  - Investigator experience (measured many ways)
  - Medical adjuncts
  - Device development
  - Procedure techniques (routine EP)
  - Outcome assessment (independent exam, biochemical screening)
- Contemporary randomized trials must be supported

CAROTID ENDARTERECTOMY SUPERIOR TO MEDICAL THERAPY

Symptomatic

- NASCET:
  - 2226 patients
  - 65% lower ipsilateral events when stenosis > 70%
  - Surgery was superior in 50-69% stenosis
- ECST:
  - 2024 patients
  - >80% stenosis surgery was superior

Both groups excluded high risk patients

?? Results if current aggressive medical management
CAROTID ENDARTERECTOMY SUPERIOR TO MEDICAL THERAPY

Asymptomatic Trials
- ACAS:
  - 1662 patients
  - 53% risk reduction for stenosis >60%
- ACST
  - 3120 patients
  - Surgery beneficial for >80% stenosis

RECOMMENDATIONS ON CAROTID ENDARTERECTOMY FOR CAROTID STENOSIS

<table>
<thead>
<tr>
<th>Symptomatic stenosis</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade (≥ 70%)</td>
<td>Carotid endarterectomy performed by a surgeon with a perioperative morbidity rate &lt; 6%</td>
</tr>
<tr>
<td>Moderate (50% and &lt; 70%)</td>
<td>Carotid endarterectomy depending on patient-specific factors such as age, sex, comorbidities, and severity of initial symptoms</td>
</tr>
<tr>
<td>Mild (&lt; 50%)</td>
<td>No indication for endarterectomy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asymptomatic stenosis</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade (≥ 60%)</td>
<td>Endarterectomy performed by a surgeon with a perioperative morbidity and mortality rate &lt; 3%</td>
</tr>
</tbody>
</table>

EARLY CAS IN A US MULTICENTER RCT

ALBERTS, STROKE 2001

- 219 patients with symptomatic 60%-90% stenosis were randomized to CEA or CAS
- 7Fr system, no embolic protection
- Results at 1yr:
  - CAS 12.2% Ipsilateral Stroke
  - CEA 3.6% Ipsilateral Stroke
  - P=0.022

Trial was stopped before reaching 700 subjects

CAVATAS INTERVENTIONALIST CRITERIA

- Radiologist with training in neuroradiology and angioplasty
- 88% of patients symptomatic
- 74% PTA/26% stent
- 0% EPD
CAVATAS: CAROTID AND VERTEBRAL ARTERY TRANSLUMINAL ANGIOPLASTY STUDY

Lancet 2001

<table>
<thead>
<tr>
<th>Major outcome events</th>
<th>Endovascular group (n=251)</th>
<th>Surgical group (n=253)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7 (3%)</td>
<td>4 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>9 (4%)</td>
<td>11 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-disabling stroke</td>
<td>9 (4%)</td>
<td>10 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Death or disabling stroke</td>
<td>16 (6%)</td>
<td>15 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Death or any stroke</td>
<td>25 (10%)</td>
<td>25 (10%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Other outcome events:
- Cranial nerve palsy: 0 vs 22 (9%), p < 0.0001
- Peripheral nerve palsy: 0 vs 2 (1%), NS
- Haematoma (requiring surgery or extending hospital stay): 3 (1%) vs 17 (7%), p < 0.0015
- Nystagmus (non-fatal): 0 vs 3 (1%), NS
- Pulmonary embolus: 0 vs 2 (1%), NS

Patients were analysed by intention to treat. Values are numbers (%). NS = non-significant. *Fatal in one patient and analysed as a death.

STENTING VS ENDARTERECTOMY FOR TREATMENT OF CAROTID ARTERY STENOSIS

(crest)
- 117 Centers
- 2502 patients
- 43% Asymptomatic
- Median f/u 2.5 years

STENTING VS ENDARTERECTOMY FOR TREATMENT OF CAROTID ARTERY STENOSIS

(crest)

OTHER SYMPTOMATIC CAROTID TRIALS

- Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis: (EVA-3S) 927 patients French study
  - death and stroke at 1 and 6 months were lower with endarterectomy than with stenting.
  - Stroke or death: 9.6; 3.9
- International Carotis Stenting Study (ICSS): 50 centers, 1713 patients
  - carotid endarterectomy should remain the treatment of choice for patients suitable for surgery.
  - Stroke death or MI: 8.5 vs 5.2 (most event with in 30 days)
  - Diff persisted at 5 years
  - 3X more patients in stent group had findings on DWI

• Registries
EPIC STUDY DESIGN

Patients at High-Risk for CEA
Prospective, Multi-center, Non Randomized Trial
Evaluating the FiberNet® Embolic Protection System for Use During Carotid Artery Stenting Procedures (26 Sites)

Follow Up - 30 Days
Primary Endpoints Adjudicated by Independent Clinical Events Committee

EPIC STUDY 30 DAY EVENT RATES

Endpoint
- All death = 0.4%
- All stroke = 2.1%
  - Major Stroke = 1.3%
  - Minor Stroke = 0.8%
- All MI = 0.9%

30 Day Composite Primary Endpoint = 3.0%

PROTECT: PURPOSE OF THE TRIAL

- Sponsor: Abbott Vascular

- Purpose:
  - Pivotal IDE trial assessment of the Generation 5 Emboshield Pro Rapid Exchange Embolic Protection
  - Fulfill the long-term follow-up requirement of the Xact stent PMA conditions of approval: 3-year follow-up on at least 305 high risk for CEA subjects

- Analysis Cohort:
  - Enrollment completed in 20 months (Nov 2006-June 2008); 322 patient cohort with 30 day follow-up analysis of embolic protection.
  - 3 year Xact stent follow-up ongoing (n=372)
PROTECT PRIMARY ENDPOINT: 30-DAY MAJOR ADVERSE EVENTS

<table>
<thead>
<tr>
<th>EVENT</th>
<th>PROTECT (N=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, Stroke and MI*</td>
<td>3.1%</td>
</tr>
<tr>
<td>Death*</td>
<td>0.3%</td>
</tr>
<tr>
<td>All Stroke*</td>
<td>2.2%</td>
</tr>
<tr>
<td>Major Stroke*</td>
<td>0.3%</td>
</tr>
<tr>
<td>Minor Stroke*</td>
<td>1.9%</td>
</tr>
<tr>
<td>MI*</td>
<td>0.9%</td>
</tr>
<tr>
<td>All Stroke and Death*</td>
<td>2.2%</td>
</tr>
<tr>
<td>Major Stroke and Death*</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

*Hierarchical- Includes only the most serious event for each patient and includes only each patient first occurrence of each event.*Non-hierarchical-represents each event even in patients with multiple events

SUMMARY OF RESULTS

- Met Study Primary Endpoint
  - Low death rate of 0.8%
  - Low stroke rate of 2.8%
  - Low MAE rate of 4.0%
  - Low MAE Rate of 5.4% for Octogenarians
  - Low MAE Rate of 5.4% for Symptomatic Subjects
  - High Technical Success Rate of 96.4%
  - Demonstrated compatibility with FDA approved stents used in the trial

ACT 1

STUDY DESIGN

- Prospective, randomized trial of asymptomatic, non-octogenarian patients
  - Exclude anatomy high risk for CAS and CEA
- Lead-in enrollment of up to 400 subjects
- Strict investigator criteria by SMC and IMC
- Maximum of 1658 pivotal subjects
- Prescribed contemporary medical therapy guidelines for all patients
ACT I: PATIENT DEMOGRAPHICS
LEAD IN PATIENTS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=160</th>
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</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>68.3</td>
</tr>
<tr>
<td>% Male</td>
<td>58.1%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>36.3%</td>
</tr>
<tr>
<td>Hypertension requiring medication</td>
<td>81.3%</td>
</tr>
<tr>
<td>Hyperlipidemia requiring medication</td>
<td>84.4%</td>
</tr>
<tr>
<td>CAD</td>
<td>53.8%</td>
</tr>
<tr>
<td>History of cardiac arrhythmia</td>
<td>13.1%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>21.3%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>28.8%</td>
</tr>
<tr>
<td>Current contralateral disease</td>
<td>48.8%</td>
</tr>
<tr>
<td>Previous coronary stenting or angioplasty</td>
<td>30.6%</td>
</tr>
<tr>
<td>History of renal impairment</td>
<td>10.0%</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>23.1%</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>29.4%</td>
</tr>
</tbody>
</table>

ACT I: OUTCOMES
LEAD IN PATIENTS

<table>
<thead>
<tr>
<th>Event</th>
<th>30 days, N=160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, Stroke and MI</td>
<td>1.3% (2/160)</td>
</tr>
<tr>
<td>All Stroke and Death</td>
<td>1.3%</td>
</tr>
<tr>
<td>Major Stroke and Death</td>
<td>0.0%</td>
</tr>
<tr>
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<td>All Stroke</td>
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<tr>
<td>MI</td>
<td>0.0%</td>
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Ipsilateral Stroke 31-365 days, N=146 0.0%

NEW TRIALS

SPACE 2

Asymptomatic (no ipsilateral symptoms within previous 180 days)
Carotid artery stenosis $\geq 70\%$ Ultrasound proven by certified study personal

Informed consent
Randomisation

CEA
n=1550
Procedure within 30 days

CAS
n=1550
Procedure within 30 days

conservative
n=540

Optimal medical treatment up to 5 years
STENT-PROTECTED ANGIOPLASTY IN SYMPTOMATIC CAROTID ARTERY STENOSIS VS. ENDARTERECTOMY A THREE-ARM CLINICAL TRIAL

Objective:

Safety endpoint
Rate of any stroke (ischemic or hemorrhagic) and all-cause death within 30 days.

The primary efficacy endpoint
Cumulative rate of any stroke (ischemic or hemorrhagic) and all-cause death within 30 days plus ipsilateral stroke within 5 years of follow-up.

Secondary endpoints
Individual components of the common endpoint, cardiac events, serious stroke, any stroke in the long-term observation to 5 years, vascular deaths, technical failure, restenosis.

Tertiary endpoints
The above endpoint events after one and three years.

ASYMPTOMATIC CAROTID SURGERY TRIAL-2 (ACST-2)

- ACST-2 is a randomized trial comparing CEA and CAS that was designed to be easily integrated routine health care.
- Sites are screened for track records (signed by neurologist) of interventionalists and surgeons, with a blended stroke/death rate of <=4% for asymptomatic patients and <=8% for symptomatic patients.
- CEA and CAS techniques and equipment must be appropriate for routine clinical practice, and EP is optional.

ROADSTER Trial

Design: a prospective Multicenter, single arm trial

Patient Population: Asymptomatic and Symptomatic patients with carotid stenosis considered high risk for surgery

Primary end point: Composite incidence of any stroke, MI, or Death

Procedure:
Direct access through a cut down under local anesthesia

Other similar studies in Europe:
PROOF: in Germany reported on 65 patients with no primary endpoints at 30 days
LOTUS study in the UK

ASYMPTOMATIC CAROTID SURGERY TRIAL-2 (ACST-2)

- Largest study: aim 5000 patients
- Objective: Compare CEA to CAS in patients who have severe asymptomatic stenosis.
- Update interim report:
  - 986 patients
  - 96% patients with 70-90% stenosis
  - At 1 month follow up Rankin score @6 months for any stroke, overall serious cardiovascular: 1%
RISK FACTORS FOR CAS

- Advanced age
- Recent symptoms < 2 weeks
- Poor access—arch and iliofemoral
- Tortuosity—unable to use EPD
- Severe calcification
- Free-floating thrombus
- String sign
- Experience level of interventionalist

SVS AND CAS

- Survey showed 78% vascular surgery practices offer CAS
- Typical VS offers all three treatment options
- Anatomic high risk criteria
  - Previous CEA
  - Radiation to the neck
  - High lesion
  - Bifurcation below Clavicle
  - Contralateral Vocal cord palsy
  - Contralateral ICA occlusion
  - Presence of Tracheostomy

CMS DECISIONS ABOUT COVERAGE

- Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis ≥70%. Coverage is limited to procedures performed using FDA-approved carotid artery stenting systems and FDA-approved or cleared embolic protection devices. If deployment of the embolic protection device is not technically possible, and not performed, then the procedure is not covered by Medicare.
- Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 79%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the NCD on carotid artery stenting (CAS) post-approval studies (Medicare NCD Manual 26.70);
- Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥80%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the NCD on CAS post-approval studies (Medicare NCD Manual 26.70).

Catch-22: Carotid Stenting is Safe and Effective (Food and Drug Administration) But Is it Reasonable and Necessary (Centers for Medicare and Medicaid Services)?