TREATMENT FOR CAROTID STENOSIS

• Best medical management
  – Antiplatelet therapy
  – Antihypertensive therapy
  – Control of diabetes if present
  – Antilipid therapy if needed
  – Cessation of smoking

• Carotid endarterectomy (CEA)

• Carotid artery stenting (CAS)
NATURAL HISTORY

- Asymptomatic carotid stenosis: low stroke rate (2%/year), half of which are not disabling
- Moderate surgical benefit vs medical management for asymptomatic stenosis >60%
- Selection criteria: depend on patient’s age, gender, life expectancy, and perioperative complication rate

ASYMPTOMATIC CAROTID STENOSIS

• For patients with surgical risk <3% and life expectancy >5 years:
  CEA is beneficial for asymptomatic stenosis >60%
• ACST trial: 5 year stroke rate decreased by half with CEA. No benefit for patients >75 years
SYMPTOMATIC CAROTID STENOSIS

• NASCET:
  – CEA most beneficial for symptomatic stenosis 70-99%  
    (2 year stroke rate decreased from 26% to 9%)
  – Moderate benefit from CEA for symptomatic stenosis 50-69%  
    (5 year stroke rate decreased from 22% to 16%)
• Perioperative stroke or death risk must be <6%

NEJM 1991;15;325(7):445-453
CEA TRIALS

• CEA trials involved patients who had an average risk of perioperative stroke or death after surgery
• Patients who had a high surgical risk owing to severe CAD were excluded
### MORBIDITY AND MORTALITY FROM CEA (SUNDT CLASSIFICATION)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Risk factors</th>
<th>Risk (in 1,935 operations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Neurologically stable; no medical or angiographic risks; with unilateral or bilateral ulcerative-stenotic carotid disease</td>
<td>&lt;1% risk (5 RIND, 6 CVA)</td>
</tr>
<tr>
<td>II</td>
<td>Neurologically stable; no medical risks, but with angiographic risks (contralateral ICA occlusion most common)</td>
<td>1.8% risk (6 RIND, 7 CVA)</td>
</tr>
<tr>
<td>III</td>
<td>Neurologically stable; medical risks, with or without angiographic risks</td>
<td>4% risk (9 fatal MI, 10 RIND, 10 CVA (1 fatal))</td>
</tr>
<tr>
<td>IV</td>
<td>Neurologically unstable, with or without medical or angiographic risks</td>
<td>8.5% risk (27 CVA (8 fatal), 14 RIND, 2 fatal MI)</td>
</tr>
</tbody>
</table>

*Sundt TM: Occlusive cerebrovascular disease. W. B. Saunders, Philadelphia, 1987*
CURRENT STATUS OF CAS

• **FDA approval in 2004**: for high risk patients
  – with symptomatic carotid stenosis >50%
  – or asymptomatic carotid stenosis >80%  
    (based on SAPPHIRE data)

• **CMS approval in 2005**: for high risk patients
  – with symptomatic carotid stenosis >70%
  – with symptomatic carotid stenosis >50% or asymptomatic carotid stenosis >80% if enrolled in an IDE clinical trial
  – If they participate in an FDA-mandated postapproval study
High risk for CEA, Sym (7%)

High risk for CEA, Asym (18%)

Low risk for CEA, Asym (53%)

Low risk for CEA, Sym (22%)

Figure 2.—Symptoms of patients in the US receiving CEA.
Figure 3.—Review of carotid stent procedures in the US medicare system from 2005-2007.
HISTORY OF CAS

• The acceptable morbidity and mortality for CAS has not been clearly defined
  – Most patients are non-NASCET/non-ACAS eligible
  – CAS technology is continually improving
HISTORY OF CAS

• Early CAS studies without EPD had high rates of adverse events at 30 days
WALLSTENT TRIAL

• Prospective, randomized, multicenter study of 219 patients with symptomatic carotid stenosis >60%
• Stroke and death rate at one year was 12.1% in the CAS group and 3.6% in the CEA group (p = 0.022)

Stroke 2001;32:325-d
WALLSTENT TRIAL

• CAS was performed without EPD by inexperienced surgeons
• Stroke rate was 3.9 times higher among patients treated without EPD than among patients treated with EPD

  Stroke 2004;35:E18-E20

• DWI abnormalities with EPD have decreased from 29% to 7%

  AJNR 2001:1251-1259
CAVATAS
CAROTID AND VERTEBRAL ARTERY
TRANS-LUMINAL ANGIOPLASTY STUDY

• 504 patients randomized to CEA vs carotid angioplasty alone (25% also received stents)
• No difference in 30 day death or disabling stroke rates (6.3% for CEA, 6.4% for CAS)
• 30 day all stroke and death rate 10% in each group
• No substantial difference in the rate of ipsilateral stroke was noted with survival analysis up to 3 years after randomization
  (adjusted hazard ratio=1.04, 95% CI 0.63-1.70, p=0.9)

*Lancet 2001;357(9270):1729-37*
ELOCAS
EUROPEAN LONG TERM CAROTID ARTERY STENTING

- Largest retropective registry in 4 high volume European centers:
  - 2172 patients treated with CAS
    (>85% with EPD)
  - Combined stroke and death rate:
    • 4.1% at 1 year
    • 10.1% at 3 years
    • 15.5% at 5 years

HISTORY OF CAS

• Later studies using EPD (SAPPHIRE, CaRESS)
  – Similar morbidity and mortality rates after CAS compared with CEA in high risk patients
CAS TRIALS

- High risk registries
- Randomized clinical trials: CAS vs CEA
  - High risk: SAPPHIRE
  - Normal risk: CREST, ACT I, EVA-3S, SPACE
- Post market surveillance studies
High-Risk Carotid Registry Summary of Primary Endpoint Results

![Bar chart showing the summary of primary endpoint results for different stent systems.]

Source: SSEDs; PROTÉGÉ® RX Carotid Stent System IFU.
CAROTID STENTING (CAS) VS CAROTID ENDARTERECTOMY (CEA)?
SAPPHIRE TRIAL
STENTING AND ANGIOPLASTY WITH PROTECTION IN PATIENTS
AND HIGH RISK FOR ENDARTERECTOMY

• Randomized (CEA and CAS) multicenter trial of high risk patients, 167 patients in each arm
• Symptomatic carotid stenosis >50% (1/3 patients)
• Asymptomatic carotid stenosis >80% (2/3 patients)

NEJM 2004;351:1565-1567
## SAPPHIRE Trial Results:

<table>
<thead>
<tr>
<th>Event Categories</th>
<th>Randomized Stent (N = 167)</th>
<th>Randomized CEA (N = 167)</th>
<th>P-Value</th>
<th>Non-Randomized Stent (N = 406)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>MAE - Death, MI or stroke to 30-Days and death or ipsilateral stroke from 31-360 days</td>
<td>20/167 12.0</td>
<td>32/167 19.2</td>
<td>0.10</td>
<td>64/406 15.8</td>
</tr>
<tr>
<td>Death (All Cause)</td>
<td>12/167 7.2</td>
<td>21/167 12.6</td>
<td>0.14</td>
<td>41/406 10.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>10/167 6.0</td>
<td>12/167 7.2</td>
<td>0.83</td>
<td>37/406 9.1</td>
</tr>
<tr>
<td>Major Ipsilateral Stroke</td>
<td>1/167 0.6</td>
<td>5/167 3.0</td>
<td>0.21</td>
<td>13/406 3.2</td>
</tr>
<tr>
<td>Minor Ipsilateral Stroke</td>
<td>6/167 3.6</td>
<td>3/167 1.8</td>
<td>0.50</td>
<td>16/406 3.9</td>
</tr>
<tr>
<td>Myocardial Infarction Q or NQ</td>
<td>5/167 3.0</td>
<td>12/167 7.2</td>
<td>0.13</td>
<td>11/406 2.7</td>
</tr>
<tr>
<td>TIA</td>
<td>11/167 6.6</td>
<td>5/167 3.0</td>
<td>0.20</td>
<td>28/406 6.9</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>15/167 9.0</td>
<td>17/167 10.2</td>
<td>0.85</td>
<td>54/406 13.3</td>
</tr>
<tr>
<td>Cranial Nerve Injury</td>
<td>0/167 0.0</td>
<td>8/167 4.8</td>
<td>0.01</td>
<td>0/406 0.0</td>
</tr>
<tr>
<td>Severe Hypertension</td>
<td>29/167 17.4</td>
<td>5/167 3.0</td>
<td>&lt;0.01</td>
<td>63/406 15.5</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>14/167 8.4</td>
<td>5/167 3.0</td>
<td>0.06</td>
<td>14/406 3.4</td>
</tr>
<tr>
<td>Vascular Complications</td>
<td>9/167 5.4</td>
<td>N/A</td>
<td>N/A</td>
<td>10/406 2.5</td>
</tr>
<tr>
<td>Device/Procedure Related Events</td>
<td>0/167 0.0</td>
<td>0/167 0.0</td>
<td>-</td>
<td>0/406 0.0</td>
</tr>
<tr>
<td><strong>Efficacy Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion Success</td>
<td>145/158 91.8</td>
<td>N/A</td>
<td>N/A</td>
<td>368/407 90.4</td>
</tr>
<tr>
<td>Procedure Success</td>
<td>140/159 88.1</td>
<td>N/A</td>
<td>N/A</td>
<td>355/404 87.9</td>
</tr>
<tr>
<td>Device Success</td>
<td>145/159 91.2</td>
<td>N/A</td>
<td>N/A</td>
<td>363/405 89.6</td>
</tr>
<tr>
<td>ANGIOGUARD Success</td>
<td>152/159 95.6</td>
<td>N/A</td>
<td>N/A</td>
<td>372/406 91.6</td>
</tr>
<tr>
<td>Cumulative % of TLR at 360 Days</td>
<td>0.06</td>
<td>4.3</td>
<td>0.04</td>
<td>0.8</td>
</tr>
<tr>
<td>Cumulative % of MAE at 360 Days</td>
<td>12.2</td>
<td>20.1</td>
<td>0.05</td>
<td>16.0</td>
</tr>
</tbody>
</table>

Source: Summary of Safety and Effectiveness Data. PMA: P030047. 22-Sep-06.
SAPPHIRE TRIAL

At 3 years, the incidence of stroke was virtually identical for CAS and CEA (7.1% for CAS and 6.7% for CEA, p = 0.945), indicating that CAS is non-inferior to CEA.

NEJM 2008;358:1572-1579
In high risk patients with severe carotid stenosis, no significant difference could be shown in long term outcomes between CAS and CEA.

NEJM 2008;358:1572-1579
SAPPHIRE TRIAL
CRITICISM

• >400 patients were excluded after initial inclusion
• 2/3 patients are asymptomatic and high risk
• In symptomatic patients, the primary endpoint did not differ
• 20% patients were treated for carotid restenosis
CaRESS TRIAL
CAROTID REVASCULARIZATION USING ENDARTERECTOMY OR STENTING SYSTEMS

• Multicenter non-randomized non-inferiority trial comparing CAS with CEA, 397 patients not all high risk
• Symptomatic patients with carotid stenosis >50% (1/3 patients)
• Asymptomatic patients with carotid stenosis >75% (2/3 patients)

CaRESS TRIAL

• Risk of stroke, death or MI:
  – 30 day results:
    2.1% for CAS and 4.4% for CEA, p=NS
  – 1 year results:
    10% for CAS and 13.6% for CEA, p=NS
EVA-3S TRIAL
ENDARTERECTOMY VS ANGIOPLASTY IN PATIENTS WITH
SYMPTOMATIC SEVERE CAROTID STENOSIS

• Multicenter randomized non-inferiority trial comparing CAS with CEA in 527 patients with symptomatic stenosis >60%, not high risk
• 30 day results: risk of stroke and death significantly higher in CAS group compared with CEA group (9.6% vs 3.9%; p=.01)
• No significant difference between the two groups in the 30 day incidence of MI

NEJM 2006;355:1660-1671
EVA-3S TRIAL

• 30 day incidence of disabling stroke or death was higher with CAS than CEA (3.4% vs 1.5%)
• No difference was seen between centers when the experience of the performing physician or the hospital workload was taken into account
EVA-3S TRIAL

• At 6 months, the incidence of stroke or death continues to be lower with CEA:
  6.1% after CEA vs 11.7% after CAS (p=.02)
• Study terminated in September 2005 for reasons of safety and futility
EVA-3S TRIAL
CRITICISM

• Lack of experience of investigators and number of trained site/operators in CAS
  – No centralized training qualification process
  – 2/3 of trial sites were under tutelage at the beginning of their randomized participation

• Lack of standardized techniques resulted in unnecessary morbidity
  – Use of EPDs was not widespread
  – No predilatation in >80% of procedures

• Significant anesthesia in 30% of procedures
EVA-3S TRIAL

• At 4 years: Cumulative probability of periprocedural stroke or death and nonprocedural ipsilateral stroke was higher with CAS than with CEA (11.1% vs 6.2%, p=0.03)
• Periprocedural risk (within 30 days) is higher with CAS
• After the periprocedural period, the risk of ipsilateral stroke was low and similar in both treatment groups
• Probability of restenosis >50% at 3 years was more evident with CAS than with CEA
SPACE TRIAL
STENT-SUPPORTED PERCUTANEOUS ANGIOPLASTY OF THE CAROTID ARTERY VS ENDARTERECTOMY

• Multicenter randomized non-inferiority trial comparing CAS with CEA in patients with symptomatic stenosis >50%, not high risk
• 37 centers in Germany, Austria and Switzerland
• Use of EPDs was at the discretion of the participating center
• 1214 patients were randomized (613 in CAS group; 601 in CEA group)
• Non inferiority threshold was set at 2.5%

*Lancet 2006;368:1239-1247*
SPACE TRIAL

- 30 day results: stroke and death rate 6.8% in CAS group, 6.3% in CEA group
- Absolute difference 0.51% (-1.9% vs 2.9%, 95% CI; p=.09))
- This exceeded the threshold of 2.5%
- Patient recruitment was stopped after 1214 patients
- 73% patients received a stent without an EPD
SPACE TRIAL

- At 2 years: no difference in clinical outcome between CAS and CEA (5% vs 6.3% mortality, hazard ratio 1.11)
- Restenosis >70% more common after CAS (10.7% vs 4.6%, p<0.01)
- Patients >68 years had a significantly lower risk of primary endpoint after CEA compared with CAS
- CEA remains the preferred treatment for symptomatic carotid stenosis
SPACE TRIAL

• Outcome event (ipsilateral stroke or death) was not related to the use of EPD
• 25% procedures were performed with EPD
• Only half of complications occurred during the actual stent and angioplasty procedure
ICSS TRIAL
INTERNATIONAL CAROTID STENTING STUDY

• Symptomatic carotid stenosis >50% within 6 months of randomization
• 1710 patients were included from 49 centers in the ITT analysis: 853 CAS and 857 CEA
• 30 day rate of stroke, MI or death: 5.1% for CEA vs 8.5% for CAS (p=0.004)

XVIII European Stroke Conference 2009
CREST TRIAL
CAROTID REVASCULARIZATION ENDARTECTOMY VS STENT

- NIH/NINDS sponsored multicenter randomized trial comparing CAS with CEA in patients with asymptomatic stenosis >60% and symptomatic stenosis >50%
- 30 day-4 yr rate of stroke, MI or death
- Recruitment of 2522 patients in 118 sites in North America was completed in July 2008
- 53% patients symptomatic and 47% patients asymptomatic
CREST TRIAL

• Analyses based on the pool of these patients will provide 90% power to detect treatment differences in the two groups
• One year follow-up was scheduled in July 2009
• Publication of one year data in March 2010
• Follow-up will last for 4 years
CREST TRIAL
New Data on Risk of CAS in Octogenarians

- 749 lead-in patients undergoing CAS (31% symptomatic, 69% asymptomatic)
- Patients were separated into 4 age categories (<60, 60-69, 70-79, >80 years)
- An increasing proportion of patients suffered stroke and death with increasing age (p= .0006)
  - 1.7% under age 60
  - 1.3% aged 60-69
  - 5.3% aged 70-79
  - 12.1% age >80
ONGOING CAS TRIALS

- High risk registries:
  - CHOICE (Guidant/Abbott)
  - VIVA (BARD VIVEXX stent and Abbott Emboshield)
  - EMPIRE (Gore NPS and any approved stent)
  - Fibernet (Lumen BioMedical and any approved stent)
  - ARMOUR (mo.Ma and any approved stent)
  - SAPPHIRE PMS (Cordis Angioguard and Precise stent)
ONGOING CAS TRIALS

• Standard risk registries:
  – CREST (Guidant/Abbott system)
  – ACT I
  – TACIT
CONCLUSION

• CAS has outcomes that are inferior to CEA for treatment of symptomatic carotid stenosis
• CAS technology and expertise of operators are improving
LESSONS LEARNED

• Experience counts!
• Patient selection for CAS is crucial
• Participation in clinical trials
• Until CREST data are published, limit CAS to high risk patients who meet criteria for revascularization