CAROTID ARTERY DISEASE
WHERE DO WE GO FROM HERE?

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UPMC HAMOT MEDICAL CENTER
LEARNING OBJECTIVES

• REVIEW THE RISK FACTORS FOR STROKE
• UNDERSTAND THE ROLE OF CAROTID ARTERY DISEASE AND STROKE
• EXAMINE MEDICAL THERAPIES FOR CAROTID DISEASE
• REVIEW CAROTID REVASCULARIZATION OPTIONS

THE GOLDEN RULE

WE TREAT CAROTID DISEASE WITH THE SAFEST AND MOST COST EFFECTIVE STRATEGIES TO REDUCE STROKE RISK
Stroke

- > 790,000 adults experience ischemic stroke each year in the United States, 185,000 are recurrent strokes
- 2nd most common cause of mortality and 3rd most common cause of disability
- 25% of patients will have mild and another 40% moderate to severe disability
- Approximately 240,000 will experience a TIA- focal neuro symptoms lasting <24 hours without imaging evidence of infarction.
- TIA increases risk for future stroke
- Annual risk for future stroke after initial is 3-4%.

Cumulative Mortality Over 5 Years After Ischemic Stroke

![Graph showing cumulative mortality over 5 years after ischemic stroke.](Hartmann%20A%20et%20al.%20Neurology%202001%3A57%3A2000-2005)
Long-Term Cause of Stroke Mortality Risk at 5 Years

Cerebrovascular Disease: Pathogenesis

Hemorrhagic Stroke (17%)
- Intracerebral Hemorrhage (59%)
- Subarachnoid Hemorrhage (41%)

Ischemic Stroke (83%)
- Atherosclerotic Cerebrovascular Disease (20%)
- Embolism (20%)
- Cryptogenic (30%)
- Lacunar (25%)

Risk Factors for Stroke

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Nonmodifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypertension</td>
<td>• Age</td>
</tr>
<tr>
<td>• Dyslipidemia</td>
<td>• Gender</td>
</tr>
<tr>
<td>• Diabetes</td>
<td>• Race/ethnicity</td>
</tr>
<tr>
<td>• Metabolic syndrome</td>
<td>• Heredity</td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
<td>• Cardiovascular Disease</td>
</tr>
<tr>
<td>• TIA/prior stroke</td>
<td></td>
</tr>
<tr>
<td>• Carotid stenosis</td>
<td></td>
</tr>
<tr>
<td>• Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>• Alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>• Obesity</td>
<td></td>
</tr>
<tr>
<td>• Physical inactivity</td>
<td></td>
</tr>
<tr>
<td>• Obstructive sleep apnea</td>
<td></td>
</tr>
</tbody>
</table>


Treating Hypertension to Prevent Stroke

• HTN is the single most important modifiable risk factor for stroke

• HTN contributes to 70% of all strokes
Benefits of Treating Hypertension

- Younger than 60 yrs
  - Reduces the risk of stroke by 42%
  - Reduces the risk of coronary event by 14%

- Older than 60yrs
  - Reduces overall mortality by 20%
  - Reduces cardiovascular mortality by 33%
  - Reduces incidence of stroke by 40%
  - Reduces coronary artery disease by 15%

Smoking

- Increases stroke risk by 3 to 4 fold
- Five years after smoking cessation - stroke risk is similar to that of a non-smoker
- Dose dependent risk factor
- It is never too late to quit!!!
Stroke Primary Prevention

• Physical Activity
  – Dose dependent effect with decreases in all stroke risk by 20 to 30%. Training to include aerobic, resistance and flexibility @ least 3x/week for 20-60 min/session.

• Hyperlipidemia
  – 4S trial - 28% reduction in stroke/TIA
  – Jupiter Trial – 48% reduction stroke

• Antiplatelet therapy
  – No conclusive data in primary prevention
Stroke Prevention

- Atrial Fibrillation
  - Stroke risk varies based on patients parameters (CHADS-VASC Score)
  - Anticoagulant therapy can dramatically reduce risk from as high as 15.2% to 1-2%
  - Watchman LAAC

Risk Reduction for Stroke or Death

<table>
<thead>
<tr>
<th>Pairwise Comparisons</th>
<th>Stroke</th>
<th>P value</th>
<th>Stroke or Death</th>
<th>P value</th>
<th>Death</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA vs placebo</td>
<td>18.1</td>
<td>0.013</td>
<td>13.2</td>
<td>0.016</td>
<td>10.9</td>
<td>NS</td>
</tr>
<tr>
<td>DP vs placebo</td>
<td>16.3</td>
<td>0.039</td>
<td>15.4</td>
<td>0.015</td>
<td>7.3</td>
<td>NS</td>
</tr>
<tr>
<td>DP + ASA vs placebo</td>
<td>37.0</td>
<td>&lt;0.001</td>
<td>24.4</td>
<td>&lt;0.001</td>
<td>8.5</td>
<td>NS</td>
</tr>
<tr>
<td>DP + ASA vs ASA</td>
<td>23.1</td>
<td>0.006</td>
<td>12.9</td>
<td>NS</td>
<td>-2.7</td>
<td>NS</td>
</tr>
<tr>
<td>DP + ASA vs DP</td>
<td>24.7</td>
<td>0.002</td>
<td>10.7</td>
<td>NS</td>
<td>1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

ASA = aspirin 25 mg bid, DP = modified-release dipyridamole 200 mg bid.

Adapted from Stroke 2013; 42: 1418-1424.
**Discontinuation Rates Due to Adverse Events**

- **Placebo** (n = 1649): 21% (4% due to headache)
- **Aspirin** (n = 1649): 19% (3% due to headache)
- **Aggrenox** (n = 1650): 25% (10% due to headache)

**Primary End Point: MI/Stroke/CV Death**

- Placebo + ASA
- Clopidogrel + ASA

20% Relative Risk Reduction

*Other standard therapies were used as appropriate.

* PLAWEY Prescribing Information

Adapted with permission (2002) from the Massachusetts Medical Society. The CURE Trial Investigators:

*N Engl J Med 2001;345:494-502*
CILOSTAZOL STROKE PREVENTION STUDIES

CSPS 1 – Cilostazol more effective than placebo for stroke reduction

CSPS 2 – 2757 noncardioembolic CVA pts.
  Rx 81mg ASA vs. 100mg BID CL.
  Cilostazol > 25% reduction CVA
  Cilostazol > 50% reduction CNS bleeds
CAROTID DISEASE AND STROKE

• Ischemic stroke accounts for 80% of all strokes
• Approximately 30% of new strokes are secondary to carotid atherosclerosis

CAROTID ATHEROSCLEROSIS

• Incidence
  - ≥50% carotid stenosis
    • 0.5% in 50’s years
    • 10% ≥ 80 years
• Annual risk of stroke for asymptomatic hemodynamically significant carotid stenosis is 2%
Carotid Disease

• Diagnosis
  – Physical examinations 75% of patients with lesions $\geq 60\%$ have bruits
  – Carotid duplex ultrasound
  – Magnetic resonance angiography
  – Angiography

Carotid Stent: Target Lesion Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA alone</td>
<td>3%</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>90%</td>
</tr>
<tr>
<td>CCA alone</td>
<td>5%</td>
</tr>
<tr>
<td>Multiple</td>
<td>2%</td>
</tr>
</tbody>
</table>
CAROTID ARTERY THERAPY

CAROTID ENDARTERECTOMY
CEA

CAROTID ARTERY STENTING
CAS

Carotid Endarterectomy (CEA)

• Goal
  – Reduce the risk of stroke

• Strategy to achieve goals
  – Surgically remove plaque

• Treatment
  – Arteriotomy at stenotic section
  – Plaque is removed
  – Closure of arteriotomy
LANDMARK CEA
CLINICAL TRIALS

• Asymptomatic Carotid Atherosclerosis Study (ASCAS)
• North American Symptomatic Carotid Endarterectomy Trial (NASCET)
• European Carotid Surgery Trial (ECST)

Carotid Endarterectomy

Summary

– Most useful in symptomatic patients with lesions > 70%
– Statistically beneficial in symptomatic patients with lesions 50-69% who have recent nondisabling hemispheric stroke.
– Asymptomatic male patients with lesions > 60% showed benefit from surgical therapy. Benefit unclear in women. Periop stroke/death rates should be approximately 2%.
Endovascular Carotid Therapy
CAS

Carotid Angioplasty
Carotid and Vertebral Artery Angioplasty Study (CAVATAS)
- 504 patients with symptomatic carotid and vertebral artery disease
- Carotid Stenosis > 70%
- 253 patients treated with surgery
- 251 patients treated with angioplasty (1/4 stents)
- 3 year follow-up
CAVATAS

– Disabling stroke/death at 30 days
  • surgical 5.9%  \( p = \text{NS} \)
  • angioplasty 6.4%  \[ p = \text{NS} \]

– Total stroke
  • surgical 9.9%  \( p = \text{NS} \)
  • angioplasty 10%  \( p = \text{NS} \)

– Cranial nerve palsy
  • surgical 8.7%  \( p < .05 \)
  • angioplasty 0%  \( p = < .05 \)

– Hematoma requiring surgery/prolonged hospitalization
  • surgical 6.7%  \( p < .05 \)
  • angioplasty 1.2%  \( p < .05 \)

CAVATAS

• 3 Year Follow-up
  – Ultrasound restenosis ≥ 70%
    • PTA 21%
    • surgical 5%  \( p \leq .001 \)
  – No difference in
    • ipsilateral stroke
    • disabling stroke
    • death
  – No association between restenosis and recurrent symptoms
Mechanical Cerebral Protection

- Occlusive device with aspiration catheter
- Filter protection devices
- Flow Reversal
LANDMARK CAS CLINICAL TRIALS

• SAPPHIRE
• ACT I
• CREST I
• CREST II
Stenting and Angioplasty with protection in Patients at High Risk for Endarterectomy
(The SAPPHIRE Study)

Study Overview

• Randomized, multi-center trial comparing stenting with embolic protection to endarterectomy in high surgical risk patients
• 29 investigational sites
• First randomized trial ever in high risk CEA
SAPPHIRE TRIAL

- 29 US centers
- Asymptomatic patients with \(>80\%\) stenosis
- Symptomatic patients with \(\geq50\%\) stenosis
- High-risk anatomic and clinical criteria (CHF, severe COPD, previous CEA, severe CAD, radical neck surgery, radiation therapy)
- All patients were seen by a team composed of a neurologist, surgeon, and interventionalist

Primary endpoints

- 30-day death, stroke and MI
- 30 day MAE plus death and ipsilateral stroke between 31-days and 12-months
**SAPPHIRE design**

*Physician team*

- Neurologist, Surgeon, Interventionalist

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**CONSENSUS**

- Surgeon Refusal
- Interventionist Refusal

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**RANDOMIZED**

- Stent Registry: 406
  - Stenting: 159
  - CEA: 151
- Surgical Registry: 7

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**SAPPHIRE randomized patients**

*30-day events*

<table>
<thead>
<tr>
<th></th>
<th>STENT</th>
<th>CEA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death:</td>
<td>0.6%</td>
<td>2.0%</td>
<td>0.36</td>
</tr>
<tr>
<td>Stroke:</td>
<td>3.8%</td>
<td>5.3%</td>
<td>0.59</td>
</tr>
<tr>
<td>MI (Q or NQ)</td>
<td>2.6%</td>
<td>7.3%</td>
<td>0.07</td>
</tr>
<tr>
<td>Death/Stroke/MI</td>
<td>5.8%</td>
<td>12.6%</td>
<td>0.047</td>
</tr>
</tbody>
</table>
Cranial nerve injury: randomized arm

- CEA = 4.6% (7/151)
- Stent = 0.0% (0/159)
  p value = 0.006

SAPPHIRE RESULTS 3 YEARS

- Three year end point death, stroke, or MI within 30 days plus death and ipsilateral stroke between one and three years
- No significant difference in three year outcomes between CEA and Stent groups
CREST I

- NIH sponsored trial of CEA vs. CAS
- 117 centers in US and Canada
- 2502 patients {CAS 1262, CEA 1240}
- Randomized 1:1 CEA:CAS
- Primary end point :
  a. Death/CVA/MI @ 30 days
  b. Ipsilateral CVA @ 4 years

ACT I

Trial design: Asymptomatic subjects with carotid artery stenosis were randomized to carotid artery stenting with embolic protection (n = 1,089) vs. carotid endarterectomy (n = 394).

Results
- Death, stroke, or MI within 30 days or ipsilateral stroke within 1 year: 3.8% of the carotid stent group vs. 3.4% of the carotid endarterectomy group (p for noninferiority = 0.01)
- Death or major stroke: 0.6% vs. 0.6%

Conclusions
- Among asymptomatic patients with carotid artery stenosis, carotid artery stenting with embolic protection was noninferior to carotid endarterectomy
- Long-term outcomes were similar between the groups

# CREST 1

Primary End Points @ 30 Days

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>CAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVA/D/MI</td>
<td>4.5%</td>
<td>5.2%</td>
<td>ns</td>
</tr>
<tr>
<td>Major CVA</td>
<td>0.7%</td>
<td>0.9%</td>
<td>ns</td>
</tr>
<tr>
<td>Minor CVA</td>
<td>1.5%</td>
<td>2.7%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>MI</td>
<td>2.3%</td>
<td>1.1%</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Cranial N. Palsy</td>
<td>4.8%</td>
<td>0.3%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

![Figure 1](image-url)
## CRANIAL NERVE INJURY RESOLUTION

<table>
<thead>
<tr>
<th>Type of injury</th>
<th>Present Immediately Post-op n (%)</th>
<th>Present at 1-month n (%)</th>
<th>Present at 12-months n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglossal (XII)</td>
<td>13 (24.5)</td>
<td>6 (11.3)</td>
<td>0 (0) a,b</td>
</tr>
<tr>
<td>Facial (VII)</td>
<td>16 (30.2)</td>
<td>10 (18.9)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Dysphagia/hoarseness (IX, X)</td>
<td>22 (41.5)</td>
<td>18 (33.9)</td>
<td>6 (11.5)c</td>
</tr>
<tr>
<td>Horner Syndrome</td>
<td>2 (3.8)</td>
<td>1 (1.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Any CNI</td>
<td>53 (100)</td>
<td>35 (66)</td>
<td>10 (19.2)d</td>
</tr>
</tbody>
</table>

## CREST I

Stroke 30 days to 4 years

- **CEA** 2.0%
  
  \( p = .85 \)

- **CAS** 2.4%
CREST I

Primary End Point @ 4 Years
{ 30 day S/D/MI + ipsilateral CVA > 1 month}

CAS 7.2%
ns
CEA 6.8%

CREST I

10 YEAR STROKE RATES

<table>
<thead>
<tr>
<th>Total Stroke</th>
<th># Events</th>
<th>Rate (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting</td>
<td>42</td>
<td>6.9% (4.4 - 9.7)</td>
<td>0.99 (0.64 - 1.52)</td>
<td>0.96</td>
</tr>
<tr>
<td>Surgery</td>
<td>41</td>
<td>5.6% (3.7 - 7.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carotid Revascularization for Primary Prevention of Stroke Trial (CREST-2)

CREST 2
OBJECTIVE

- In patients with ≥70% asymptomatic stenosis, to assess: Medical management vs. Endarterectomy and Medical management vs. Stenting
CREST 2
SECONDARY OBJECTIVES

- Cognitive functional differences at 4 years
- Incidence of ‘stroke events’ at 4 years
- Are differences in primary outcomes affected by patient age, sex, severity of carotid stenosis, risk factor level, and duration of asymptomatic period?

Which trial? Which procedure?

Endpoints = stroke & death in first 30 days and ipsilateral stroke thereafter up to 4
What factor matters the most to reduce complications with carotid revascularization?

The effect of surgeon’s specialty and volume on the perioperative outcome of carotid endarterectomy
J Vasc Surgery Sept 2013

- 953 patients treated by CEA
- 24 Surgeons General (GS), Cardiac, Vascular
- Surgeons grouped by low, intermediate, or high volume (<10, 10-30,>30/year)
- Primary end point (PEP) was 30 day Death/Stroke
- PEP GS 4.1%, CV 2.9%, V 1.4%
- PEP Low Vol 4.3%, I Vol 4.1%, High Vol 1.3%
CEA in OHIO
7/1/1993-6/30/99

• Retrospective review with sample of 678/4120 patients
• Primary end point Death plus Stroke @ 30 Days

CEA Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>43.4%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>24.6%</td>
</tr>
<tr>
<td>Nonspecific Sx</td>
<td>22.9%</td>
</tr>
<tr>
<td>CVA</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

CEA in OHIO

• 81% of hospitals performed 62 or < CEA/Yr
• 88% Surgeons performed 21 or < CEA/Yr
• Hospital volumes and outcomes (S+D)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Low Volume</th>
<th>High Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asym</td>
<td>4.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Nonspec</td>
<td>4.6%</td>
<td>0%</td>
</tr>
<tr>
<td>TIA</td>
<td>9.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>CVA</td>
<td>7.7%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
CAS EXPERIENCE & OUTCOMES

A. Annual operator volume

- 30-Day mortality
- Failure to use EPD

B. Operator experience

- 30-Day mortality
- Failure to use EPD
### UPMC HAMOT CARDIOLOGY CAROTID STENT REGISTRY

12/31/2017

<table>
<thead>
<tr>
<th></th>
<th>HMC</th>
<th>SAPH/A1/CR1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>940</td>
<td>162 /1089/1262</td>
</tr>
<tr>
<td>Death</td>
<td>0.1%</td>
<td>/---/ 0.7 %</td>
</tr>
<tr>
<td>MI</td>
<td>0.1%</td>
<td>/---/ 1.1 %</td>
</tr>
<tr>
<td>Major CVA</td>
<td>0.3%</td>
<td>/---/ 0.9 %</td>
</tr>
<tr>
<td>Minor CVA</td>
<td>1.6%</td>
<td>/---/ 2.9 %</td>
</tr>
<tr>
<td>TIA</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>30 Day Death</td>
<td>0.3%{SCD}</td>
<td>1.2 /0.1/ 0.7%</td>
</tr>
<tr>
<td>30 Day MCVA</td>
<td>0.1%</td>
<td>1.2 /0.5/ 0.9%</td>
</tr>
<tr>
<td>TMACE @ 30 Days</td>
<td>3.8%</td>
<td>4.8 /3.3/ 5.2 %</td>
</tr>
</tbody>
</table>
Carotid Solution
Safety Net with Greater Plaque Protection

CGuard™ Embolic Prevention System
Combines stent and embolic protection in a single device

- Stent platform provides revascularization benefits
- MicroNet acts as safety net by offering greater plaque scaffolding to prevent prolapse related to late embolization
- Allows perfusion to vessel wall, does not inhibit endothelialization

- CE marked
- Self-expanding nitinol stent
- Global market valued at $500M*
- Strong CARENET FIM data released 9/14 and 1/15
- First commercial orders (LMR) received 04/2014

* Health Research International, 2011

Filter-protected CAS procedures
CARENET vs PROFI: DW-MRI analysis

DW-MRI analysis @ 48 hours

\[
\begin{array}{c|c|c|c}
& CGuard & Conventional Carotid stent (hybrid) \\
\hline
VOLUME of new ipsilateral lesions (mL) & 0.04 & 0.39 \\
\hline
n=27 & n=31
\end{array}
\]
CONCLUSION

1. Large randomized US trials of CEA vs. CAS have shown equivalence in both short and long term outcomes.

2. Certain patient subgroups may have different risk vs. benefits with each procedure i.e. a higher risk of minor cva with CAS in octogenarians and higher risk of myocardial infarction and permanent cranial nerve injuries with CEA.

3. The results of the CREST 2 trial will hopefully elucidate the best treatment strategy for usual risk asymptomatic patients.
CONCLUSION

4. The clinical outcomes for UPMC Hamot CAS patients over the last 15 years are comparable to those achieved in the landmark CAS trials

5. With operator experience and technological advancements CAS outcomes have and I expect will continue to improve over time

Advantages of CAS VS CEA

– Can treat larger area than the cervical portion of carotid arteries
– No general anesthesia
– Little to no cranial nerve palsy and lower MI risk, but a higher minor cva rates in patients >75 years. Neurologic symptoms usually resolve by 30 days.
– Useful for CEA restenotic lesions
– Simultaneous procedures on carotid, vertebral and coronary arteries {CARDIOLOGY OPERATORS}
– Patients would rather have their necks look like???
POST CEA SCAR

NECK AFTER STENTING ?