Carotid Artery Disease: Is there a New Gold Standard in Therapy?

RICHARD R. HEUSER, MD, FACC, FACP, FESC
Director Of Cardiology, St. Luke’s Medical Center, Phoenix, Arizona
Medical Director, Phoenix Heart Center, Phoenix, Arizona
Clinical Professor of Medicine Univ. of Arizona, College of Medicine, Tucson, Arizona
Stroke

- 731,000 strokes each year
- 160% increase in incidence by the year 2050
Carotid Endarterectomy

1st cases in 1953
by DeBakey and Eastcott
Surgical versus medical therapy

<table>
<thead>
<tr>
<th>ASYMPTOMATIC</th>
<th>% Risk reduction</th>
<th>SYMPTOMATIC</th>
<th>% Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>53%</td>
<td>NASCET</td>
<td>65%</td>
</tr>
<tr>
<td>VA Asymptomatic</td>
<td>30%</td>
<td>VA Symptomatic</td>
<td>60%</td>
</tr>
<tr>
<td>CASANOVA</td>
<td>5%</td>
<td>ECST</td>
<td>39%</td>
</tr>
</tbody>
</table>

NASCET: no advantage for stenosis <50%
disadvantage for stenosis <30%

_for symptomatic stenoses the periop. risk should be <6% (AHA)_

Recommendations:
- asymptomatic stenosis: >70%: recanalization
  <70: conservative, repeated
- follow-up
- symptomatic stenosis: >50%: recanalization
Recommendations applicable for PTA/Stent?

no trials comparing PTA vs medical therapy

is PTA equal to surgery (CEA)?
Carotid Stent types

Precise

NexStent

Exponent RX

Xact Carotid Stent

RX Acculink

ProtégéRX

Carotid Wallstent
Figure 6. Examples of Filter-Type Embolic Protection Devices
CEA: plaque removal
Stenting: Plaque containment
Let the battles begin
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>Asymptomatic Carotid Stenosis Stenting vs. Endarterectomy Trial</td>
</tr>
<tr>
<td>ARCHer</td>
<td>Acculink for Revascularization of Carotids in High-Risk Patients</td>
</tr>
<tr>
<td>BEACH</td>
<td>Boston Scientific EPI: A Carotid Stenting Trial for High Risk Surgical Patients</td>
</tr>
<tr>
<td>CABANA</td>
<td>Carotid Stenting Boston Scientific Surveillance Program</td>
</tr>
<tr>
<td>CABERNET</td>
<td>Carotid Artery Revascularization using Boston Scientific EPI Filterwire EX/EZ and the EndoTex NexStent</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>Carotid Acculink/Accunet Post Approval Trial to Uncover Rare Events</td>
</tr>
<tr>
<td>CeRESS</td>
<td>Carotid Revascularization using Endarterectomy or Stenting Systems</td>
</tr>
<tr>
<td>CASES-PMS</td>
<td>Carotid Stenting with Emboli Protection Surveillance-Post-Marketing Study</td>
</tr>
<tr>
<td>CREATE</td>
<td>Carotid Revascularization with ev3 Arterial Technology Evaluation</td>
</tr>
<tr>
<td>CREST</td>
<td>Carotid Revascularization: Endarterectomy versus Stent Trial</td>
</tr>
<tr>
<td>ELOCAS</td>
<td>European Long-term Carotid Artery Stenting Registry</td>
</tr>
<tr>
<td>EMPIRE</td>
<td>EMPIRE Embolic Protection with Reversed Flow</td>
</tr>
<tr>
<td>EVA-S3</td>
<td>Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis</td>
</tr>
<tr>
<td>ICSS</td>
<td>International Carotid Stenting Study (CAVATAS II)</td>
</tr>
<tr>
<td>MAVEIC</td>
<td>Evaluation of the Medtronic AVE Self-expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis</td>
</tr>
<tr>
<td>MO.MA</td>
<td>Multicenter Registry to Assess the Safety and Efficacy of the MO.MA Cerebral Protection Device During Carotid Stenting</td>
</tr>
<tr>
<td>PASCAL</td>
<td>Performance and Safety of the Medtronic AVE Self Expandable Stent in the Treatment of Carotid Artery Lesions</td>
</tr>
<tr>
<td>PRINCE</td>
<td>Prospective Investigation of Nitiol Carotid Stent with Embolic Filter</td>
</tr>
<tr>
<td>ProCAS</td>
<td>Prospective Registry of Carotid Angioplasty and Stenting</td>
</tr>
<tr>
<td>ProCAR</td>
<td>Proctigli Stent In the Treatment of Carotid Artery Stenosis with Adjunctive Use of a Filter Embolic Protection Device</td>
</tr>
<tr>
<td>RULE-Caratid</td>
<td>Rubicon Filter-Caratid</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy</td>
</tr>
<tr>
<td>SECURITY</td>
<td>Registry Study to Evaluate the NeuroShield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy</td>
</tr>
<tr>
<td>SHELTER</td>
<td>Stenting of High-risk Patients with Embolic Removal</td>
</tr>
<tr>
<td>SPACE</td>
<td>Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy</td>
</tr>
<tr>
<td>VIVA</td>
<td>ViveXx Carotid Revascularization Trial</td>
</tr>
<tr>
<td>XACT</td>
<td>Emboshield and Xact Post Approval Carotid Stent Trial</td>
</tr>
</tbody>
</table>
The CAVATAS Trial

- Enrollment 1992 to 1997
- 504 patients (96% symptomatic) randomized
- Randomized
  - 253 to CEA
  - 251 PTA (25% stent)
- Identical medical Rx in both arms
- High medical and surgical risk pts excluded
- 3 year follow up
- No EPD

Lancet 2001;357:1729
<table>
<thead>
<tr>
<th></th>
<th>PTA (n= 251)</th>
<th>CEA (n=253)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30d Death (%)</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>30d Disabl Stroke (%)</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>30d MI</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>30d Non-disabl stroke (%)</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>30d Death ± disabl stroke (%)</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>30d Death ± any stroke (%)</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>3-Yr Dth ± disabl stroke (%)</td>
<td>14</td>
<td>14</td>
<td>NS</td>
</tr>
</tbody>
</table>

Lancet 2001;357:1729
Attempted Right Carotid Endarterectomy
Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (The SAPPHIRE Study)

AHA Scientific Sessions
November 19, 2002
Device Specifications

ANGIOGUARD™

.014” Emboli Prevention Guidewire
Filter pore size 100 microns

Inventor of Device

PRECISE™

Nitinol Self-Expanding Stent
5.5 & 6 French Delivery Systems

Cordis
a johnson&johnson company
Equipoise and carotid therapy?

“The ethics of clinical research requires equipoise---a state of genuine uncertainty within the expert medical community regarding the comparative merits of each treatment arm in a trial.”

WHO WON?

5.8%  12.6%
SAPPHIRE
360-Day Primary Endpoint

*30 day MACE + death/ipsilateral stroke from 31-360 days post-procedure

Death: CEA (n=167) 13.5 vs Stent (n=167) 7.4, p=0.08
Stroke: CEA (n=167) 7.9 vs Stent (n=167) 6.2, p=0.60
MI: CEA (n=167) 7.5 vs Stent (n=167) 3.0, p=0.07
Primary Endpoint: CEA (n=167) 20.1 vs Stent (n=167) 12.2, p=0.05
SAPPHIRE
Other Outcomes at 360 Days

![Graph showing outcomes at 360 days for TLR and CN Palsy.]

- TLR: 4.3% (CEA) vs 0.6% (Stent), p=0.04
- CN Palsy: 4.9% (CEA) vs 0% (Stent), p=0.004
### 1 Year Data

**Randomized Patients (Per Protocol)**

<table>
<thead>
<tr>
<th>Events</th>
<th>Stent (159 pts)</th>
<th>CEA (151 pts)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death:</td>
<td>11 (6.9%)</td>
<td>19 (12.6%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Stroke:</td>
<td>9 (5.7%)</td>
<td>11 (7.3%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Major Ipsilateral:</td>
<td>0 (0.0%)</td>
<td>5 (3.3%)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Major Non-Ipsilateral:</td>
<td>1 (0.6%)</td>
<td>1 (0.7%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Minor Ipsilateral:</td>
<td>6 (3.8%)</td>
<td>3 (2.0%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Minor Non-Ipsilateral:</td>
<td>3 (1.9%)</td>
<td>3 (2.0%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>MI (Q or NQ)</td>
<td>4 (2.5%)</td>
<td>12 (7.9%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Q-Wave MI</td>
<td>0 (0.0%)</td>
<td>2 (1.3%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Non-Q Wave MI</td>
<td>4 (2.5%)</td>
<td>10 (6.6%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Yadav et al., NEJM 2004; 351: 1493

84% asymptomatic high risk stenoses, what about symptomatic stenoses in normal risk patients?
CAS versus CEA - SAPPHIRE

1 Year Data
Randomized Patients (Per Protocol)

CEA: 30.3%
CAS: 25.5%

3 years

P = 0.048
Comparison of ACAS and NASCET to SAPHIRE

The Patients enrolled into the Sapphire Trial were at high risk for surgery – ACAS and NASCET Patients were carefully selected as low risk surgical candidates.

<table>
<thead>
<tr>
<th>ACAS</th>
<th>NASCET</th>
<th>SAPHIRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients were Excluded if they had any of the following High risk factors:</td>
<td>Patients were Excluded if they had any of the following High risk factors:</td>
<td>Patients were Included if they had one of the following high risk factors:</td>
</tr>
<tr>
<td>• Previous CEA</td>
<td>• Previous CEA</td>
<td>• Congestive Heart Failure</td>
</tr>
<tr>
<td>• Unstable Angina</td>
<td>• Unstable Angina</td>
<td>• Open Heart Surgery w/in 6 weeks</td>
</tr>
<tr>
<td>• Congestive Heart Failure</td>
<td>• MI (within 6 months)</td>
<td>• Recent MI (&gt; 24 hrs, &lt; 4 weeks)</td>
</tr>
<tr>
<td>• Previous Stroke</td>
<td>• Previous neck surgery</td>
<td>• Unstable Angina</td>
</tr>
<tr>
<td>• Renal Insufficiency</td>
<td>• Major surgery within past month</td>
<td>• Coexistent Severe Coronary Artery Disease</td>
</tr>
<tr>
<td>• Respiratory Insufficiency</td>
<td>• Age &gt; 79 years</td>
<td>• Severe Pulmonary Disease</td>
</tr>
<tr>
<td>• Previous neck surgery or radiation treatment</td>
<td>Also excluded:</td>
<td>• Contralateral Carotid Occlusion</td>
</tr>
<tr>
<td>• Major surgery within past month</td>
<td>• Asymptomatic Patients</td>
<td>• Contralateral Laryngeal Palsey</td>
</tr>
<tr>
<td>• Age &gt; 79 years</td>
<td></td>
<td>• Post Radiation Treatment</td>
</tr>
<tr>
<td>Also excluded:</td>
<td></td>
<td>• Previous CEA recurrent Stenosis</td>
</tr>
<tr>
<td>• Symptomatic Patients</td>
<td>Also excluded:</td>
<td>• High Cervical ICA Lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe Tandem Lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CCA Lesions below the Clavicle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 80 years of age</td>
</tr>
<tr>
<td></td>
<td>Also excluded:</td>
<td>Also excluded:</td>
</tr>
<tr>
<td></td>
<td>• Asymptomatic Patients</td>
<td>• Asymptomatic Patients</td>
</tr>
</tbody>
</table>

The published MAE rates for ACAS and NASCET were 30-day results – and did not include MI (SAPHIRE 30-day MAE results included patients with MI’s). At 30 days, the MAE rates were:

<table>
<thead>
<tr>
<th>ACAS</th>
<th>NASCET</th>
<th>SAPHIRE Stent</th>
<th>SAPHIRE CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3%</td>
<td>5.8%</td>
<td>4.4% - 3.8% without MI’s</td>
<td>9.9% - 4.6% without MI’s</td>
</tr>
</tbody>
</table>

Despite the fact that the SAPHIRE Patients were High Risk Patients, there is no significant difference in 30 day MAE rates when both the Stent and CEA cohorts are compared to both ACAS and NASCET.

NOTE: This represents investigational data. Carotid Stenting is not an FDA approved procedure.
"BETWEEN YOU AND ME, I'M FED UP BEING A GUINEA PIG!"
Trial data

- Total multi-center US carotid stent trial data reported (to date):
  - 3338

- Total multi-center US endarterectomy data (NASCET and ACAS):
  - 3179
Why embolic protection?
Protection or not?

**German CAS Registry**

Participating Centers 36
Interventions 2,147 (100.0 %)

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>no CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>minor stroke</td>
<td>1.3 %</td>
<td>1.5 %</td>
</tr>
<tr>
<td>major stroke</td>
<td>0.7 %</td>
<td>1.3 %</td>
</tr>
<tr>
<td>total</td>
<td>2.0 %</td>
<td>2.8 %</td>
</tr>
</tbody>
</table>

Risk reduction 30%
We now have evidence-based clinical data on patients who are high-risk with severe carotid disease...
Patient History

• 55 yo male
  – No carotid symptoms
  – Prior neck radiation for unknown carcinoma
  – Surveillance CT initially performed 2/2006 showed severe bilateral carotid disease; repeat CT performed 2/2007 showed no significant changes
CTA Feb 2007

- Bilateral occluded ICA’s
- Patent circle of Willis
- 85% stenosis distal right CCA with 90% ECA stenosis
- Occluded right vertebral artery at origin
- Patent small left vertebral artery
- Collateral circulation thought to derive from external carotid arteries
Left vertebral
Strategy

• Medical therapy
• Endarterectomy
• Six-pack and a fishing pole
• Scratch your head
• PTA/Stent
  – Embolic protection?
  – Consent / risks?
Carotid stenting is inferior to carotid endarterectomy

Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S)

Guidelines & Trials

EVA-3S

Trial Design: EVA-3S was a randomized trial of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) in patients with symptomatic carotid artery stenosis ≥80%. Primary endpoint was death or stroke within 30 days of treatment.

Results
- Trial stopped early after hazard observed with carotid stenting over endarterectomy
- Death or stroke more than double in CAS group vs. CEA group (Figure), regardless of use of cerebral protection with stenting or physician experience
- Death or stroke remained higher in CAS group at 6 months (11.7% vs. 6.1%, p = 0.002)
- Nonfatal stroke in CAS group (8.6% vs. 2.7%, RR 3.3, 95% CI 1.4-7.5, p = 0.004), including disabling stroke (Figure)

Conclusions
- Among patients with symptomatic carotid artery stenosis, treatment with CAS was associated with 2.5 times higher rate of death or stroke by 30 days vs. CEA
- For every 17 patients treated with stenting rather than endarterectomy, 1 additional stroke or death occurred
- Based on these findings and other recent large randomized trials, CEA, and not CAS, should be considered optimal treatment for carotid artery stenosis
EVA 3-S

Unprotected CAS – trial suspended

Trial restarted with protected CAS

Trial suspended October 2005 (527 patients enrolled)

Procedural stroke risk 9.6% (CAS) vs. 3.9% (CEA) (primary endpoint)


Concerns: complication rate very high (unusual)

some interventionalists performed their first CAS during trial under coaching
EVA-3S

- 1.8 patients enrolled per center in the 5 years the study took
- 2.4% didn’t even receive Heparin or similar agents during the procedure.
- Most of the operators were vascular surgeons with no previous interventional experience
Same procedure again!!

Randomized Study of Carotid Angioplasty and Stenting versus Carotid Endarterectomy: A Stopped Trial
Naylor AR; J Vasc Surg 1998;28:326-34

- Endarterectomy 10 pts
  No complications

- Carotid Angioplasty 7 pts
  5 strokes (3 disabling)

- Trial stopped, first stent implantations of trialists
What did we learn from EVA-3S?

Three years into the trial... the investigators thought embolic protection might be important.
What did we learn from EVA-3S?

Three years into the trial the investigators thought ASA/Plavix should be begun 3 days before.
What did we learn from EVA-3S?

They felt 5 cases done investigators was adequate training.
What did we learn from EVA-3S?

Some sites randomized patients with the 1st enrollment of treatment.
What did we learn from EVA-3S?

They treated 85.4% of the enrolled patients with ASA/Plavix.
What did we learn from EVA-3S?

5 % of patients had failure of carotid stenting and had to have CEA.
What did we learn from EVA-3S?

The median carotid stenting time was 70 minutes.
SPACE The Final Frontier???
SPACE-Trial

- Prospective multicenter trial
- Inclusion criteria: >70% symptomatic stenosis
- Primary endpoints: stroke & death in 30 days
- Secondary endpoints: stroke & death after 1 year
- Trial powered to 1,900 patients – stopped after 1,200
- Non-inferiority trial – margin set at 2.5%
Guidelines & Trials

Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE)

**SPACE**

**Trial Design:** SPACE was a randomized trial of carotid artery stenting (CAS) (n=396) or carotid endarterectomy (CEA) (n=395) in patients with symptomatic carotid artery stenosis. Primary endpoint was ipsilateral ischemic stroke or death through 30 days, evaluated for non-inferiority.

**Results**
- Primary endpoint failed to meet non-inferiority criteria in both ITT analysis (Figure: absolute difference 0.51%, 90% CI 1.86%–2.91%) and per protocol analysis (0.90% for CAS vs 0.64% for CEA, absolute difference 1.26%)
- All secondary endpoints fell in favor of CEA, including disabling ipsilateral stroke or death (4.07% for CAS vs 0.77% for CEA, OR 1.50), disabling ipsilateral stroke (Figure, OR 1.30), any stroke (7.51% for CAS vs 6.16% for CEA, OR 1.24), and procedural failure (3.17% for CAS vs 2.55% for CEA, OR 1.25)
- Results similar in subgroup of patients treated with embolic protection devices in CAS group

**Conclusions**
- Among patients with symptomatic carotid artery stenosis, treatment with carotid artery stenting failed to demonstrate non-inferiority compared to carotid endarterectomy at 30 day follow-up
- Given these findings and those of other recent trials, carotid endarterectomy – not carotid artery stenting – should be considered optimal treatment for carotid artery stenosis
SPACE

• No MI Endpoint.
• No contralateral CVA endpoint.
• Procedure failure 3%?
• Why antiplatelet agents in only 79%?
• Why EPD’s in only 27%?
• Why are no Cardiologists involved?
• Lots of low volume centers.
Why would a patient select a more invasive procedure for symptomatic carotid therapy if the outcomes were the same?
Conclusion From the Two Studies

- Failure to adequately treat patients with dual agents is unacceptable.
- The procedure needs to be performed by an experienced operator.
- The use of embolic protection is mandatory and if the use of embolic protection is not possible because of anatomy, the patient might be better off with CEA or other medical therapy.
CEA: plaque removal
Facts on carotid Stenting

• ASA/Plavix should be given for 5 days prior.
• Embolic Protection is essential
• In 2007 the interventionist should have done a minimum of 100 carotid angio’s and 25 carotid interventions before performing a CAS procedure.
• The filter time should be less than 20 minutes.
FUTURE CAROTID THERAPY
- From The Pharmaceutical Perspective -

• recently developed statins and anti-platelet agents are a start
• why only treat focal areas of disease when atherosclerosis is known to be a systemic disease?
• we need to look beneath the surface of plaque and address the underlying pathophysiology of atherosclerosis & inflammation
Perhaps there is a new battle brewing.
Carotid Artery Disease: Is there a New Gold Standard in Therapy?
Carotid Artery Disease: Is there a New Gold Standard in Therapy?

Conclusion

• **We do know high risk patients are helped with CAS and EPD compared to CEA.**
• **What about > 80 year old patients?**
• **Experience, use of EPD, use of antiplatelet agents, and technique are crucial in CAS (and CEA).**
• **We don’t know about low risk patients... CEA or CAS.**
• **If CAS is found to be equivalent to CEA in low risk patients it will be the patient preferred procedure of choice.**
Conclusion

- CREST, ICSS, and ACT I need to be completed.
- These low risk trials will give us direction to determine whether the treatment of carotid disease has truly changed.
- Perhaps there is a role for a trial of aggressive medical therapy compared to CEA and CAS similar to the COURAGE trial.