Approach to Intervention in Carotid Artery Disease

Kenneth Rosenfield, M.D.
Section Head
Vascular Medicine and Intervention
MGH
Boston, MA
I am a Carotid Stentor, and do not perform CEA
Stenting or CEA or Medical Therapy? What is the role of each???

Remains a HOT topic
65 year old diabetic man with CAD and carotid bruit on good medical therapy. He asks- “Doc, what are my options?”

Proximal ICA PSV 490 EDV 263
Carotid Artery Disease

Goal of therapy

Am I providing best therapy to prevent stroke, death, disability, and morbidity for my individual patient, and is this the therapy my patient prefers?”

Answer to these questions are not always clear, and certainly consensus is lacking.
Optimal medical therapy – this is a given for ALL patients at risk (Consensus!)

MRC Asymptomatic Carotid Surgery Trial (ACST): Medical RX

...and we need to do better!
<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>Standard Risk</td>
<td>Standard Risk</td>
</tr>
</tbody>
</table>

MOST PATIENTS!
Natural Hx:
Annual Stroke Rates with Carotid Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi-risk</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Standard-risk</td>
<td><strong>Standard surgical risk patients</strong></td>
<td></td>
</tr>
<tr>
<td>70-99%</td>
<td>13%</td>
<td>60-99%</td>
</tr>
<tr>
<td>50-69%</td>
<td>4.4%</td>
<td>2-2.5%</td>
</tr>
</tbody>
</table>

...BUT, MOVING TARGET...

A) Probably different now, due to advances in medical therapy
B) Variability based on lesion severity, morphology, other factors
Revasc. In Asx Pts: which ones?

Relative Risk of Stroke by degree of stenosis

Asymptomatic Carotid Artery Stenosis

- Stroke Incidence (%)

- 0-19%
- 20-29%
- 30-39%
- 40-49%
- 50-59%
- 60-69%
- 70-79%
- 80-89%
- 90-99%

Norris Stroke. 22(12):1485-90, 1991
Mendelsohn & Yadav, Management of Atherosclerotic Carotid Disease, Remedica Publishing, 2000
Risk in Asymptomatic Stenosis

ACST: 3120 pt with carotid stenosis >60%, no symptoms, randomized to CEA vs. medical management

Any Stroke or Death

- CEA 6.4%
- Medical 11.8%

Major Stroke or Death

- CEA 3.5%
- Medical 6.1%
Consensus:

- Revasc indicated (on top of OMT) for symptomatic patients
- Asymptomatic patients – threshold for revasc now needs to be re-evaluated
- CEA has been existing standard

Where does CAS fit in?
Challenges in comparing carotid strategies: “moving targets”

- **Medical Rx** evolving - better drugs and increased understanding of pathophysiology

- **CAS** improving - better devices, increased experience, & better case selection

- **CEA** also improving - evolving techniques

- Event rates low - large number of patients required to detect difference (or equivalence)

- “noise” from other causes of stroke

- Physicians/patients - pre-conceived notions about best Rx; reluctance to accept change
Evidence base often derived from flawed trials, registries, databases – with variable methodologies:

- Comparisons made b/n patients who are fundamentally different (apples to oranges)
- Operators w/variable competency…differential skill level and procedural experience between those doing CAS vs. CEA
- Inconsistent neurologic assessment for stroke
- Utilization of equipment that is outdated for CAS
- Preponderance of Medicare age patients (commercial payors won’t allow investigational Rx)
Characteristics of patients referred for CAS differ markedly from those referred for CEA. Because of extreme clinical disparities between these patients, …comparative effectiveness analyses of observational data will be difficult.

“Characteristics of patients referred for CAS differ markedly from those referred for CEA. Because of extreme clinical disparities between these patients, …comparative effectiveness analyses of observational data will be difficult.”
## European trials: ICSS—RCT of Symptomatic Standard Risk

**Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CAS (853)</th>
<th>CEA (857)</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, stroke, MI</td>
<td>8.5%</td>
<td>5.2%</td>
<td>1.69</td>
<td>0.006</td>
</tr>
<tr>
<td>Any stroke</td>
<td>7.7%</td>
<td>4.1%</td>
<td>1.92</td>
<td>0.002</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>8.5%</td>
<td>4.7%</td>
<td>1.95</td>
<td>0.001</td>
</tr>
<tr>
<td>Disabling stroke or death</td>
<td>4.0%</td>
<td>3.2%</td>
<td>1.28</td>
<td>0.34</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.3%</td>
<td>0.8%</td>
<td>2.76</td>
<td>0.017</td>
</tr>
</tbody>
</table>
A minimum of 50 total stenting procedures, of which at least ten should be in the carotid artery; tutor-assisted procedures allowed for interventionalists with insufficient experience.

Metzger: “Are-You-Kidding-Me” Trial?
Ken Rosenfield in his first NASCAR race!
Physician Experience Dictates Outcomes

Data from CAPTURE 2

Source: JACC Interv 2011 ;Gray et al:

72 cases

Regression equation: \( \log(y) = 4.71 - 0.85 \times \log(x) \)

P-value of slope: <0.0001

R-square: 0.81
## Operator Experience in RCT’s

<table>
<thead>
<tr>
<th>Trial</th>
<th>Operator Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA-3S</td>
<td>Poor (12 lifetime CAS or 35 supra-aortics with 5 CAS)</td>
</tr>
<tr>
<td>SPACE</td>
<td>Adequate for era <em>(but not comparable to CEA)</em></td>
</tr>
<tr>
<td>ICSS</td>
<td>Poor (50 stents anywhere, 10 lifetime CAS…or supervised)</td>
</tr>
<tr>
<td>CREST</td>
<td>Adequate for era <em>(but not comparable to CEA)</em></td>
</tr>
</tbody>
</table>

Source: William A. Gray MD, Presented at Oxford University, England
NASCET and ACAS Exclusions

- Age > 79
- Prior ipsilateral CEA
- Unstable coronary syndrome
- MI in previous 6 months
- Cardiac valvular or rhythm abnormality likely to cause embolic cerebrovascular symptoms
- Contralateral occlusion
- A more severe lesion cranial to the surgical lesion

- Contralateral CEA within previous 4 months
- Uncontrolled hypertension or diabetes
- Organ failure likely to cause death within 5 years
- Total occlusion
- Major surgical procedure in previous 30 days
- Prior severe CVA
- Progressing neurologic syndrome
RCT’s: CAS vs. CEA

**SAPPHIRE** *
- Symptomatic High-risk None
- Asymptomatic High-risk None

**EVA3s, SPACE 1** *
- Symptomatic Standard-risk
- Asymptomatic Standard-risk

**CREST** *

**ACT 1, SPACE 2**
- Symptomatic Standard-risk
- Asymptomatic Standard-risk

CREST* completed

SAPPHIRE* ongoing
SAPPHIRE RCT: 1-Year Outcome
Sx and Asx high surgical risk

Cumulative Percentage of MAE – Stroke, death, MI

Endarterectomy

Stent

Time after Initial Procedure (days)

0 30 60 90 120 150 180 210 240 270 300 330 360

0 5 10 15 20 25 30

Endarterectomy
20.1%
p=0.048

Stent
12.0%
SAPPHIRE 3-Year Outcomes

Freedom from MAE

A

Freedom from Major Adverse Event (%)

Stenting

Endarterectomy

P=0.27

Days after Initial Procedure

No. at Risk

Stenting

Endarterectomy

167

155

146

135

129

111

103

166

142

123

109

100

85

75

Declining Risk of Stroke, Death and MI with CAS

Catheterization and Cardiovascular Interventions 82:715-726 (2013)
Conditions qualifying pt at high surgical risk

*Per CMS (3/05), based on hi-risk studies*

<table>
<thead>
<tr>
<th>A. Anatomical Conditions</th>
<th>B. Co-morbid Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CCA lesion(s) below clavicle</td>
<td>• Clinically significant cardiac disease</td>
</tr>
<tr>
<td>• High cervical Internal Carotid Artery (ICA)</td>
<td>• Recent Myocardial Infarction (MI)</td>
</tr>
<tr>
<td>• Previous neck radiation</td>
<td>• LVEF &lt; 30%</td>
</tr>
<tr>
<td>• Prior neck surgery/radical neck dissection</td>
<td>• CHF NYHA Class III or IV</td>
</tr>
<tr>
<td>• Restenosis of prior CEA</td>
<td>• Abnormal stress test</td>
</tr>
<tr>
<td>• Tracheostomy</td>
<td>• Need for open-heart surgery</td>
</tr>
<tr>
<td>• Contralateral carotid occlusion</td>
<td>• Unstable angina: CCS III/IV</td>
</tr>
<tr>
<td>• Contralateral laryngeal nerve palsy</td>
<td>• Severe pulmonary disease</td>
</tr>
<tr>
<td>• Age ≥80</td>
<td>• ESRD on dialysis</td>
</tr>
<tr>
<td>• ESRD on dialysis</td>
<td></td>
</tr>
</tbody>
</table>
CAS and CEA

What is the LEVEL I evidence?

- **RCT:**
  - **CEA bests medical Rx** in standard surgical risk patients (NASCET, ACAS, ACST)
  - **CAS equals CEA** in high surgical risk patients (SAPPHIRE, registries)

**NOW:**

- **CAS equals CEA** in standard surgical risk patients
CREST
Primary endpoint ≤4 years (mean 2.5)

Peri-procedural outcomes

HR 1.11  95% CI: 0.81-1.51
CREST: Peri-procedural Stroke and MI

<table>
<thead>
<tr>
<th></th>
<th>CAS vs. CEA</th>
<th>Hazard Ratio 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Stroke</strong></td>
<td>4.1 vs. 2.3%</td>
<td>HR = 1.79; 95% CI: 1.14-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>1.1 vs. 2.3%</td>
<td>HR = 0.50; 95% CI: 0.26-0.94</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Major Stroke</strong></td>
<td>0.9 vs. 0.6%</td>
<td>HR = 1.35; 95% CI: 0.54-3.36</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Neurological Residual Deficit Rates Associated with Minor Strokes @ 6 Months

Δ = 0.50%

Δ = 0.02%

% of Per Protocol Population

Δ = 0.50%

Δ = 0.02%

n = 12

n = 7

n = 7

n = 7
Association of Minor Stroke and MI with Long Term Mortality

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>Confidence Interval</th>
<th>Log Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI vs. Control</td>
<td>2.81</td>
<td>[1.53 - 5.17]</td>
<td>0.0005</td>
</tr>
<tr>
<td>Minor Stroke vs. Control</td>
<td>0.52</td>
<td>[0.13 - 2.09]</td>
<td>0.34</td>
</tr>
<tr>
<td>MI vs. Minor Stroke</td>
<td>5.18</td>
<td>[1.15 - 23.4]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Control (N = 2183)
- MI (N = 56)
- Minor Stroke (N = 48)
Death or **Major** Stroke for CAS over CREST Enrollment (all pts)

Frequency of Death or Major Stroke

- 2000-2004: 2.5% (N=160)
- 2005: 2.5% (N=201)
- 2006: 0.7% (N=308)
- 2007: 0.0% (N=298)
- 2008: 0.6% (N=164)

50% Trial Enrollment August 2006
Patients requiring re-operation

<table>
<thead>
<tr>
<th>Access Site Complication</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>20</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>5</td>
<td>2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Events may occur more than once in the same patient. Other includes pain requiring IV analgesics (5), incision complication (3), pseudoaneurysm (2), occlusion (1).
Conclusions

- Primary endpoint shows equivalence
- lower minor stroke with CEA and lower MI with CAS
- Significant liabilities of CEA (access cx, CN palsy, etc.) not captured in endpt
- Overall results of both are spectacular: Event rates lowest of any large RCT
- Issues:
  - Included both sx and asx: not powered to analyze independently
  - No Comparison to OMT alone
### ECVD Guidelines 2011 - Recommendations of 14 Specialties re: revascularization

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic patients</th>
<th>Symptomatic patients</th>
<th>Asymptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECVD Guidelines</strong></td>
<td>50-69% stenosis</td>
<td>70-99% stenosis</td>
<td>70-99% stenosis</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>Class I LOE: B</td>
<td>Class I LOE: A</td>
<td>Class IIa LOE: A</td>
</tr>
<tr>
<td><strong>Stent</strong></td>
<td>Class I LOE: B</td>
<td>Class I LOE: B</td>
<td>Class IIb LOE: B</td>
</tr>
</tbody>
</table>
Differences between CEA and CAS outcomes…no longer lies in the procedure choice, but rather:

- Operator
- Case selection
- Equipment and technique

Level I evidence and guidelines support offering CAS as (covered) option

Operators need appropriate training, experience, and judgement

Playing field should be level

- all patients with Carotid disease medical Rx or undergoing revascularization should have closer oversight, independent neuro eval
Moving targets…
Medical Treatments That *Did Not Exist* During Revascularization Trials

- **Modulators of Renin Angiotensin System**
  - ACE inhibitors
    - Hope
  - Angiotensin Receptor Blockers
    - Life
- **Statins**
  - HPS
  - CARDS
- **Advanced antipltlt therapies**
Medical Treatment for Asymptomatic Carotid Stenosis


Asymptomatic Carotid Stenosis Clinical Trials
"The great majority of patients won't get a benefit from stents or surgery," said Australian neurologist Anne L. Abbott, who has led a pushback against high rates of carotid surgery and stents. About 125,000 Americans now get carotid surgery or carotid stents each year.

Her findings focus on the majority of people who haven't had mini-strokes, or temporary symptoms. Those with symptoms are regarded as higher risk, and more likely to benefit from invasive treatment.

Her research has concluded that stroke rates have plummeted in recent years in patients with neck-artery blockage and no symptoms, largely because of the advent of modern antiplatelet drugs like Plavix, blood-pressure drugs and cholesterol medicines. She and other proponents of drug therapy point out that $21,200 carotid operations and $33,500 carotid-stent placements are costing the U.S. taxpayer up to eight times what drug treatment would cost.
• Improved medical Rx may make revascularization obsolete
• “Need more data”
Which Trial?  
Which Procedure?

Based on CREST:

- For ages 50-74 years, no favored procedure
- For ages <50 years, CAS is the favored procedure
- For ages >74 years, CEA is the favored procedure
- **BUT**, in CREST asymptomatic patients had few events, so there were wide confidence intervals

**So, the choice of CEA or CAS cannot be mandated in CREST-2...**

...**and** individual patient characteristics and preferences may supersede guidelines
The C2R CAS Registry (C2R) will promote rapid initiation and completion of enrollment in the CREST−2 trial.
C2R Steps to Participation

1. Each Operator/Site selects and joins a registry
   - Must be one of 2 options:
     - Society for Vascular Surgery’s Vascular Quality Initiative (SVS VQI)
       http://www.vascularqualityinitiative.org
     - American College of Cardiology’s National Cardiovascular Data Registry (ACC NCDR)
       https://www.ncdr.com
CAROTID STENTING
Case Selection and Technical considerations

• Access to lesion – Arch type
• Tortuosity
• Lesion morphology
• EPD suitability
• Brain “reserve”
• Overall patient “protoplasm”
Aortic Arch Type I - Ideal

~70%-75% of patients
Aortic arch Type III – suboptimal
Likely not good candidates for CAS
XS Tortuosity - Higher Risk for CAS

Tortuous ICA:
- 90 degree take-off
- 120 degree prox. turn
“Look before you jump!”
Select appropriate patients to avoid this!
CAS: Is Embolic Protection Valuable?

Risk of Stroke

RR of STROKE 0.59 favoring EPD use
Filter/Frame Length and Landing Zones

Need enough parking space…

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Device Name</th>
<th>Frame Length (mm)</th>
<th>Frame and Filter Length (mm)</th>
<th>Filter Size Shown and Measured (Vessel Range) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. L. Gore &amp; Associates</td>
<td>GORE® Embolic Filter</td>
<td>9</td>
<td>20.5</td>
<td>7.5 (4.0 – 5.5)</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>RX ACCUNET® Device</td>
<td>20.5</td>
<td>31.5</td>
<td>7.5 (6.0 – 7.0)</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>EMBOSHIELD NAV® Device</td>
<td>12.5</td>
<td>18.0</td>
<td>7.2 (6.0 – 7.0)</td>
</tr>
<tr>
<td>Boston Scientific Corporation</td>
<td>FILTERWIRE EZ Device</td>
<td>13.5</td>
<td>23.5</td>
<td>3.5 – 5.5 (3.5 – 5.5)</td>
</tr>
<tr>
<td>ev3 Inc. / Covidien</td>
<td>SPIDERFX® Device</td>
<td>10.0</td>
<td>26.0</td>
<td>6.0 (4.5 – 6.0)</td>
</tr>
<tr>
<td>Cordis Corporation</td>
<td>ANGIOGUARD® RX Device</td>
<td>11.0</td>
<td>16.5</td>
<td>6.0 (5.5 – 6.5)</td>
</tr>
<tr>
<td>Medtronic, Inc. / Invatec</td>
<td>FIBERNET® Device</td>
<td>5.5</td>
<td>7.0</td>
<td>3.5 – 5.0 (3.5 – 5.0)</td>
</tr>
</tbody>
</table>

Ref: WLGore Website
CAS will only get better...

- Potential reduction in HITS and silent but worrisome (?) MRI defects seen in ICSS
- Extends capability of CAS
# Carotid Mesh Stent Designs

<table>
<thead>
<tr>
<th>Design</th>
<th>Gore</th>
<th>Terumo</th>
<th>CGuard™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aperture Size</td>
<td>500µ</td>
<td>375-500µ</td>
<td>150-180µ</td>
</tr>
<tr>
<td>Materials</td>
<td>PTFE mesh (Heparin coated) on nitinol stent</td>
<td>nitinol on nitinol</td>
<td>PET MicroNet™ on nitinol stent</td>
</tr>
<tr>
<td>(Min Guide Sheath/ Min Guide Cath)</td>
<td>5F/7F</td>
<td>5F/7F</td>
<td>6F/8F</td>
</tr>
</tbody>
</table>
| Details | • Launched SCAFFOLD trial in Sept 2013  
• PI: Bill Gray, MD  
• Target 351 pts  
• Has enrolled 100 pts. FDA has stopped trial requesting 6 mo F/U on these 100 before proceeding | • Data on first 11 pts presented at LINC (Max Amor, MD)  
• Flexibility, plaque coverage and ability to conform to any anatomy mentioned as key benefits  
• Easy to recross (tapered ends) | • Initial placements promising  
• 11 of 11 KOL’s (LINC) felt our aperture size a benefit over larger  
• Data on MGuard MicroNet a “plus” for CGuard  
• Ability to dilate MicroNet at external bifurcation a potential benefit |
Summary: Perspective on CAS

- Widely divergent and strongly held opinions re: role and efficacy of CAS.
- Well-conducted trials show CAS performed by experienced operators utilizing proper technique in appropriately selected pts is an excellent procedure.
- Say “no” to high-risk CAS cases.
- Prox. protection may extend utility to more patients.
- CAS does NOT replace optimal medical Rx.
- CAS does NOT replace CEA (ALL high-CAS risk, low CEA-risk pts best w CEA or med Rx).
Role of the patient in decision-making…

Principles of “patient-centered care”

- Encourage shared decision-making with patients
- Allow patients to choose b/n two therapies that have similar benefit and risk profile
- Ask the *PATIENT* what *HE/SHE* wants!
The Most Important Perspective *The PATIENT!*

- 50 year old male anesthesiologist
  - 1996  XRT for nasopharyngeal carcinoma
  - 2004  radical neck dissection and addl XRT
  - 2009  normal DUS
  - 2011  new severe RICA stenosis - asx

**Duplex**

**CTA**

-Duplex PSV 314 EDV 141-

-Green arrow head pointing to the vessel/area of interest-

-Renal artery showing stenosis-
What would you tell this man?

Additional Info
- Lt SCA occlusion; Rt → Lt SC steal
- Lt vocal cord paralysis

Vasc Surg. Opinion
“You need an Endarterectomy!”
“CAS has much higher incidence of stroke!”
Patient’s opinion

“Are the results similar? If so, I want the choice ...I want a stent!”