Update on Carotid Disease

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I disclose the following financial relationship(s):
President, Gates Vascular Institute
CEO, Jacobs Institute
Consultant/Honoraria - Abbott, BARD, Boston Scientific, Cordis, Toshiba, Gore, Medtronic

Financial Interest - Boston Scientific, Claret, Ostial, Vascular Dynamics, Silk Road
Director - Access Closure, Claret, Ostial

University Grants/Research Support - Boston Scientific, Cordis, Micrus Toshiba
Personal Experience

- CEA > 2000 (1979 - present)
- CAS > 2000 (1994 - present)
- UBNS > 3500 (1994-present)

- CREST: Neurosurgery PI, Executive Comm, National Endo Training Center

- Trial Experience as PI / Co PI / Steering Committee:
  - CREST
  - SAPPHIRE
  - VIVA
  - ACT I
  - EMPIRE
  - ARMOUR
  - CABERNET
  - CARESS
  - CABANNA
  - BEACH
  - CAPTURE
  - ARChEr
Carotid Stenosis…Therapeutic Options

Two Are Reimbursed

- Stent
  - >50% Sx
  - >75% Asx

- CEA
  - >50% Sx
  - >75% Asx

Best Medical Rx
Carotid Endarterectomy…

- Most studied operation in neuro
- WE KNOW WHO IS HIGH RISK
- What is it’s role today?

Carotid Stenting…

Why has it stagnated?
Is there definitive data?
What is it’s role…today & future?
Symptomatic Carotid Stenosis: What Do We Know?

- Carotid stenosis is an emergency
- CEA works well (Nascet, Naylor)
- Less minor strokes than CAS
- Best medical therapy is helpful

All studies - risk of stroke 3.5% at 2 days, 8% at 30 days

If only including studies with face-to-face follow up data (excluding studies using “administrative” data): 10% at 2 days and 13% at 30 days

Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis.
Wu CM, McLoughlin K, Lorenzetti DL, Hill MD, Manns BJ, Giali WA.
Department of Medicine, University of Calgary, Calgary, AB, Canada.
Asymptomatic Carotid Stenosis: What Do We Know?

CEA is better than medical Tx (ACAS & ACST)
• CEA prevents strokes in women (ACST)
• CEA prevents disabling strokes (ACST)
• CEA prevents fatal strokes (ACST)

Does CAS Do The Same?
Risk Factors for CEA vs Risk Factors for CAS

- Risk factors very different
- CEA risk factors well known
- CAS risk factors… we are still learning
- CREST design 1999 (5 yrs after 1st CAS)
- CREST trial 2000-2004 vs 2004-2008…
  learning curve… experience counts
CEA vs. CAS

• CREST: established clinical equipoise of CEA and CAS
  - More MI’s with CEA
  - More MINOR strokes with CAS

• Analysis of CREST data: stroke rate with CAS was significantly higher only on day 0 of procedure

*Circulation 2012;126:3054-3061*
Timing of Stroke After Carotid Revascularization: CAS vs. CEA

- **CAS**
  - Day 0: 30
  - Day 1-7: 9
  - Day 8-30: 3
- **CEA**
  - Day 0: 10
  - Day 1-7: 5
  - Day 8-30: 2

Significance:
- **CAS** vs. **CEA**: $P = 0.0008^{**}$

*Circulation* 2012;126:3054-3061
Evolution of CAS

*Overcoming the Barriers*

- Elderly pts (high need/increased Tx risk)
- Symptomatic pts (high need/increased Tx risk)
- Access issues (femoral – arch - carotid)
- Perioperative stroke
- Experience and judgment in current reimbursement climate

- *Today No choice for most patients!!*
CEA and CAS: High Risk Profiles

For CEA:
- Recurrent stenosis post CEA
- Previous neck surgery or radiation
- Tandem lesion
- Lesion above C2 or below clavicle
- Poor cardiac or pulmonary status

For CAS:
- Tortuous and diseased arch or common carotid artery access
- Elderly and symptomatic patients
- High risk for bleeding with dual antiplatelet therapy
- Severe dye allergy
Unanswered Questions

• Can we further reduce Risk for CAS?
• Should we treat elderly pts with CAS?
• Should we treat sx pts with CAS? If so, How??
• Are CEA and CAS complimentary?
• What is the future of CEA?
What About Elderly Patients (75-79) 

**NASCET Analysis**

- Absolute risk reduction (ARR) overall = 17%
- ARR in pts 75-79 = 30%

Elderly pts are at higher risk for stroke
At higher risk for CEA and CAS and...

Are the patients who most need treatment
Decision Making for CAS

It’s Mostly About Anatomy and Pharmacoiology!

- **Anatomical factors**
  - Arch disease, tortuosity
  - Tortuosity of the Common Carotid
  - Contralateral carotid occlusion
  - High bifurcation
  - Ostial and tandem lesion
  - Hostile neck

- **Clinical factors**
  - Intolerance to anti platelet meds
  - Associated medical conditions(CHF etc)
European RPCT... CEA Looks Better??

- **EVA 3S** 9.6% vs 3.9*
- **SPACE** 6.8% vs 6.3
- **ICSS** 8.5% vs 5.2*

**What Have We Learned?**
- More minor strokes with CAS
- Experience counts
- Embolic Protection Helps
- MI not searchd for...does it matter?
Facility and Physician Experience Positively Correlated with Favorable Outcomes*

- 3,388 asymptomatic, non-octogenarian patients from 180 hospitals and 459 operators. 30-day DS rates were 2.7%. 82% of physicians had no DS events. The remaining 18% had at least 1 DS event; 92% of these operators had DS rates exceeding 3%.

- An inverse relationship between event rates and operator volume was observed. A threshold of **72 cases** was found to be necessary for consistently achieving a D/S rate below 3%.

Carotid Revascularization
Endarterectomy vs. Stenting Trial (CREST)
CREST Trial
2000-2008
First Gen Technology

Accunet
Embolic Protection System

Acculink
Carotid Stent System
Primary Endpoint ≤ 4 years
(any stroke, MI, or death within peri-procedural period plus ipsilateral stroke thereafter)

<table>
<thead>
<tr>
<th>CAS vs. CEA</th>
<th>Hazard Ratio, 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2 vs. 6.8%</td>
<td>HR = 1.11; 95% CI: 0.81-1.51</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Crest Take Home Points

1. **Best ever results for CEA and CAS !!**
   
   Overall Mortality 0.6%,  Major Stroke 0.85 %

2. CEA results outstanding… 60 year evolution
   CAS results outstanding… 15 year history

   **CAS early on learning and technology curve**
The Major Issue = Minor Strokes
Not Major Strokes

Message About Filters???

<table>
<thead>
<tr>
<th></th>
<th>30d Stroke/Death</th>
<th>30d Stroke</th>
<th>30d Major Stroke†</th>
<th>30d MI</th>
<th>EPDs Used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sx/Asx**</td>
<td>CAS</td>
<td>CEA</td>
<td>CAS</td>
<td>CEA</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>527/0</td>
<td>9.6%</td>
<td>3.9%</td>
<td>8.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>SPACE</td>
<td>1196/0</td>
<td>6.9%</td>
<td>6.5%</td>
<td>7.5%</td>
<td>6.2%</td>
</tr>
<tr>
<td>ICSS*</td>
<td>1713/0</td>
<td>7.4%</td>
<td>3.4%</td>
<td>7.0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>CREST#</td>
<td>1321/1181</td>
<td>Sx 6.0%</td>
<td>3.2%</td>
<td>5.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>Asx</td>
<td>2.5%</td>
<td>1.4%</td>
<td>2.5%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
History of Carotid Artery Stenting (CAS) Treatment

• 1994: First CAS
• 1998-2000: CREST planning - inclusion/ exclusion
  – 4 years after first CAS
• 2004: First FDA approval of CAS for patients at high risk of CEA (Acculink stent system)
• 2011: FDA Approval…low risk patients
Outcomes of CEA Over Time

- In the 1970’s: CEA risk up to 21% in some reports
  - Easton and Sherman
- In the 1990s: death and stroke rates were 6%-7% for symptomatic patients and 3%-4% for asymptomatic patients
- Outcomes of CEA continue to improve over time

### Death & Stroke Rate

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST</td>
<td>7.0%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nascet</td>
<td>6.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACAS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:

- ECST
- Nascet
- VAS
- ACAS
Outcomes of CAS Trials Over Time

- CAS results have vastly improved over time due to:
  - (1) more experienced operators; (2) better patient selection
  - (3) a wider spectrum of technology
- CAS outcomes have evolved over time similarly to CEA

(Enrollment: 2000-2004) CREST – 5.7%
(Enrollment: 2005-2008) CREST – 1.1%
Why are Recent CAS Results Better?

CREST CAS Specific Exclusion Criteria Asx Patients
Randomization Often Based on Ultrasound Alone

- 1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement.
- 2. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath.

- Criteria based on operator discretion

CREST CEA Specific Exclusions = 22
Today We Have a Better Understanding…

Stenting Exclusion Criteria Proposed for CREST II

- Occlusive or critical ilio-femoral disease that precludes safe femoral access to the aortic arch.
- Angiographic, C.T., M.R. or ultrasound evidence of severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries.
- Type III, calcified aortic arch anatomy in patients > 75 years that may preclude safe and expeditious sheath access to the common carotid arteries.
- Angulation or tortuosity (>90 degree) of the innominate, right common carotid artery or left common carotid artery that precludes safe, expeditious sheath placement or will transmit a severe loop to the internal carotid after sheath placement.
- Severe angulation or tortuosity of the internal carotid artery (including calyeal origin from the carotid bifurcation) that precludes safe embolic protection device or stent placement. Severe tortuosity is defined as 2 or more >90 degree bend points within 3cm of the target Stenosis.
- Excessive circumferential calcification of the stenotic lesion defined as > 3mm of calcification seen in orthogonal views on fluoroscopy.
- Elderly subjects (>75 years) with any 2 or more of the following (including advanced age)
  - Unfavorable arch anatomy or tortuosity as defined in exclusions 3, 4 & 5.
  - Excessive calcification.
  - Decreased Cerebral Reserve. Defined as prior (remote) large stroke, multiple lacunar infarcts, or dementia. Prior large stroke was defined by ≥ 1/3 middle cerebral artery territory infarction on CT brain; multiple lacunar infarcts was defined by diffuse lacunes associated with encephalomalacia and/or cerebral atrophy on CT brain; dementia was assessed by a mini-mental state examination if indicated by clinical suspicion.
  - Stenosis of the carotid bifurcation (common carotid) and/or ipsilateral external carotid artery in combination with a hostile arch-type III, heavily calcified or atherosclerotic that precludes safe sheath placement into the common carotid artery.
  - Stenosis that contain visible thrombus.
  - Occlusion (TIMI0 flow) or “string sign of the ipsilateral common or internal carotid artery.
  - Stenotic lesions (normal appearing vessel to normal appearing vessel) greater than 25mm in length.
PMA Analysis of the CREST Trial

FDA Analysis of the RX Acculink Carotid Stent System for Revascularization of Carotid Artery Stenosis in Standard Surgical Risk Patients

PMA Analysis = Per Protocol
PMA Primary Endpoint

Composite of all death, any stroke, or MI to 30 days

Plus

Ipsilateral stroke from 31 to 365 days
CAS is Non-inferior to CEA for Peri-Procedural DSMI

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>( p_{NI} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>5.8%</td>
<td>5.1%</td>
<td>2.20%</td>
<td>0.0401</td>
</tr>
<tr>
<td>ITT</td>
<td>5.8%</td>
<td>5.5%</td>
<td>1.83%</td>
<td>0.0155</td>
</tr>
</tbody>
</table>

2.3% Margin of Non-inferiority
### Key Differences…

*Death, Stroke and MI within 30 Days*

<table>
<thead>
<tr>
<th>Per protocol</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>Difference</th>
<th>Unadjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Death, Stroke, or MI</td>
<td>5.8% (65)</td>
<td>5.1% (60)</td>
<td>0.7%</td>
<td>0.5200</td>
</tr>
<tr>
<td>Death</td>
<td>0.53% (6)</td>
<td>0.26% (3)</td>
<td>0.27%</td>
<td>0.3335</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>4.1% (46)</td>
<td>1.9% (22)</td>
<td>2.2%</td>
<td>0.0019</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.9% (10)</td>
<td>0.4% (5)</td>
<td>0.5%</td>
<td>0.2005</td>
</tr>
<tr>
<td>Minor Stroke</td>
<td>3.2% (36)</td>
<td>1.5% (18)</td>
<td>1.7%</td>
<td>0.0088</td>
</tr>
<tr>
<td>MI</td>
<td>2.0% (22)</td>
<td>3.4% (40)</td>
<td>-1.5%</td>
<td>0.0387</td>
</tr>
</tbody>
</table>

* Fisher’s exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only.
Why MI as a Primary Endpoint?

**Long Term Mortality: Minor Stroke vs MI**

<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>

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- Control (N = 2183)
- MI (N = 56)
- Minor Stroke (N = 48)
Outcomes Balance for CAS and CEA

- **Death or Major Stroke**
  - Low rates for both CAS and CEA
  - Decreasing MAE rates for CAS over time
  - Similar rates for CAS and CEA in the second half of the study

- **Minor stroke**
  - More frequent with CAS at 30 days (absolute difference 1.7%)
  - Decreasing rates for CAS over time
  - By 6 months, CAS and CEA show similar low rates of residual neurological disability (0.80% vs 0.50% for overall population)

- **Peri-procedural MI**
  - More frequent with CEA at 30 days (absolute difference 1.5%)
  - Shows a significant relationship to mortality
What Have We Really Learned From CREST?

Politics have killed expanded reimbursement

More data needed
What is Clear From CAS Trials…

CAS Compliments CEA

- Medical Co morbidities… esp cardiac
- Surgical high risk… esp recurrent stenosis
- Poor collateral circulation/tandem lesions
- Neurologic instability
- Anatomical considerations
CEA or CAS

CEA AND CAS
Barriers to CAS

• Reimbursement: <10% covered by CMS
  - Experience factor
  - Industry turn off thwarting new technology

• Competing specialties
  - VS leadership against CAS
  - Neurology against all Carotid surgery
  - Cardiology vested interest

• Higher incidence of preoperative stroke
<table>
<thead>
<tr>
<th>Factors Adverse for CAS and Favoring CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age greater than 80…?? anatomy</td>
</tr>
<tr>
<td>• Female gender</td>
</tr>
<tr>
<td>• Compromised arterial access</td>
</tr>
<tr>
<td>• Tortuous aortic arch or severe atherosclerosis</td>
</tr>
<tr>
<td>• Carotid artery tortuosity</td>
</tr>
<tr>
<td>• Elongated plaque of the internal carotid artery</td>
</tr>
<tr>
<td>• Carotid plaque ulceration</td>
</tr>
<tr>
<td>• Severe carotid plaque calcification</td>
</tr>
</tbody>
</table>
Important Risk Factors for CAS
Remaining Obstacles …
*From All the Trial Data*

• Symptomatic Patients
  “Hot Lesions”

• Octogenarians
  - Tortuosity
The Issues:

Anatomy & Case selection
Experience
Which type EP to use?

3 main types
- distal occlusion balloons
- distal filters
- proximal protection devices
<table>
<thead>
<tr>
<th>Factors Adverse for CEA and Favoring CAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of congestive heart failure</td>
</tr>
<tr>
<td>• Unstable angina pectoris</td>
</tr>
<tr>
<td>• Un-reconstructable triple vessel coronary disease</td>
</tr>
<tr>
<td>• Need for combined coronary and carotid revascularization</td>
</tr>
<tr>
<td>• Severe pulmonary dysfunction</td>
</tr>
<tr>
<td>• Dialysis dependent renal failure</td>
</tr>
<tr>
<td>• Hostile neck anatomy</td>
</tr>
<tr>
<td>• Prior cervical radiation with skin damage</td>
</tr>
<tr>
<td>• Lesion of internal carotid artery extending above C-2</td>
</tr>
<tr>
<td>• Recurrent carotid stenosis after prior CEA</td>
</tr>
<tr>
<td>• Contra-lateral carotid occlusion</td>
</tr>
</tbody>
</table>
DWI and TCD Studies Post CEA & CAS

• More hits post CAS
• More hits with filters vs proximal EP
• No definite clinical correlation
• Significance of concern
Solving CAS Problems
Proximal Versus Distal Protection

- Distal protection – filters
- Proximal protection – flow arrest or reversal
- Outstanding FDA trial results with proximal EP (Gore, Invatec)
- Direct Carotid Approach (ROADSTER)
Solving CAS Problems

- **Proximal protection devices**
  - Complete flow arrest/reversal
  - **Advantages**
    - Protection before traversing the lesion
    - Valuable with tight irregular stenosis
    - Allows capture of all size particles
    - **Trial results are excellent**
      - EMPIRE, ARMOUR
- Better results with symptomatic patients
Increased incidence of perioperative complications in patients with unfavorable aortic arch anatomy

Excellent results in elderly pts with favorable anatomy
Understanding risk factors for perioperative ischemic events with carotid stenting: is it patient age over 80 years or is it unfavorable arch anatomy to blame?

Consecutive series, mean age 71.6, N=240

**Difficult arch:** 7.9% M&M (TIA or minor stroke)
- 52% age>80, female, < CAD, L side lesions

**Normal arch:** 0.7% M&M (TIA or minor stroke)
- 29% > age 80

**It’s NOT the age, It’s the Anatomy!**

Dumont et al: In Press
Access Obstacles for CAS

Arch Issues …Especially in Elderly Patients

- Arch Anatomy
- Arch Tortuosity
- Arch disease
- Ostial disease
- Prox CCA kinks
Prevention
Direct Carotid Access and CAS
Procedural Stroke

New Tools

Timing from Procedure for Ischemic Stroke

1. Avoid High Risk Anatomy
2. Proximal Protection
3. Direct Carotid Access
Delayed Stroke

- 78-year old WM
- Visual difficulties ?TMB Right
- PMH: Cardiac stents x5
- Carotid dopplers: Rt 80-99% stenosis
- Dx Angio: Right ICA stenosis 81% left < 50%
Pre-stent angioplasty followed by exact stent deployment.

Stent placed
Good flow
IVUS detected thrombus

Repeated aspiration and flow reversal did not dislodge the clot.
Second Stent placed

IVUS still showed thrombus
In stent Angioplasty

- Intraluminal thrombus disappeared
Procedural Stroke

New Tools

Timing from Procedure for Ischemic Stroke

- CAS-Ischemia
- CEA-Ischemia

“Covered Stent”

# of Strokes

Day 0
Day 1-7
Day 8-30
Delayed Stroke

- Peri Procedural Strokes Post Procedure
- The Next CAS Frontier?
- Gore Scaffold

Open Cell NiTi Frame
- Closed Cell 500 µm lattice on outside of NiTi Frame
- Permanently Bound CBAS Heparin on all device surfaces
Future

- Patient individualization
- Plaque interrogation for Asx patients
  - TCD, MRI, CTA
- Vascular inflammation markers (Lp-Pla2)
- Optimal medical management
- **Peri Procedural Strokes Post Procedure**
  - The Next CAS Frontier?
Conclusions

CAS and CEA are Complimentary

- CAS is NOT going away
- More minor strokes with CAS... Must be fixed!
- More MI’s after CEA... MI is BAD!
- CAS improving with experience + technology
- Patient selection and technology are KEY!
- We must prove Asx pts will benefit from CAS
Come Innovate With Us