Contemporary Management of Carotid Disease
“What We Know So Far”

Ammar Safar, MD, FSCAI, FACC, FACP, RPVI

Interventional Cardiology & Endovascular Medicine
Disclosers

NONE
Epidemiology

• 80% of stroke are ischemic

• Approximately 25% of strokes are due to carotid artery disease

• Stroke is the third most common cause of death in the U.S. and the leading cause of serious long-term disability
Risk of Stroke and Carotid Stenosis

1986 NEJM:
500 patients with asymptomatic bruit plus abnormal ultraspund

Recorded TIA/Stroke rates

Study period 4 years
Mean follow up 26 months

Echogenicity

- <75% stenosis: 10%, 3%
- >75% stenosis: 49%, 12%
- Dense: 16%, 3%
- Echolucent: 48%, 15%
Risk of Stroke and Carotid Stenosis

- Patients with unilateral symptomatic carotid-artery stenosis
- Patients with asymptomatic contralateral stenosis
- The risk of stroke at five years after study entry in a total of 1820 patients increased with the severity of stenosis

Risk of Stroke and Carotid Stenosis

![Graph showing risk of ipsilateral stroke at 5 years for different degrees of stenosis on angiography. The graph indicates that the risk increases with increasing severity of stenosis. The categories include no disease, <50%, 50-59%, 60-74%, 75-94%, 95-99%, and occlusion. The risk for symptomatic cases is higher than for asymptomatic cases.](image)
Symptoms

• **Symptomatic patient**
  – Transient Ischemic Attack (TIA)
  – Amaurosis fugax (transient visual loss)
  – Minor non-disabling stroke
  – Cerebral infarction

**Fun Facts:**

– 35% of patients with a carotid *bruit* have >50% carotid stenosis
– Only 50% of patients with significant hemodynamic carotid stenosis have *a bruit* noted during physical examination
Evaluation

• *Physical Exam*
  – Noting cervical bruits

• *Carotid Duplex Ultrasonography*
  – Most frequent primary test today

• *CT Arteriography (CTA)*

• *MR Arteriography (MRA)*

• *Diagnostic angiography*
  – Considered highly accurate
  – Standard in clinical trials
Treatment Options

Medical therapy

Carotid Endarterectomy

Carotid artery Stenting
Medical Therapy

• Rationale:
  – Pathophysiology is thrombosis or atherosclerotic debris release from carotid artery plaque
  – Treatment directed toward risk factor reduction and thrombosis prevention, and should be a mainstay of treatment post procedure

• Optimal medical therapy includes:
  – Risk Factor Modification
  – Medications

• Medical therapy should be first course of therapy for:
  – Asymptomatic patients with <60% stenosis
  – Symptomatic patients with <50% stenosis
Medical Therapy

• Goals
  – Reduce the risk of future stroke
  – Control progression of carotid atherosclerosis

• Strategies to achieve goals
  – Antiplatelet or Anticoagulation therapy
  – Antihypertensive therapy
  – Statin therapy to lower serum cholesterol
  – Aggressive glycemic control
  – Quit smoking
  – Limit alcohol consumption
  – Diet and exercise
  – Duplex ultrasound monitoring for patients with stenosis of 50% or more
Carotid Endarterectomy (CEA)

Surgical procedure to *remove plaque* from the carotid artery

Goal: reduce future stroke risk

Gold standard therapy in patients at low surgical risk but who require reestablishment of blood supply and removal of plaque to prevent embolization

The superiority of CEA with medical therapy in comparison to medical therapy alone has been demonstrated in randomized prospective studies for two classes of Carotid Artery Disease patients:

- Symptomatic patients with stenosis >50%
- Asymptomatic patients with stenosis >75%
**CEA vs. Medical Therapy**  
NASCET: North American Symptomatic Carotid Endarterectomy Trial

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, Multicenter, Randomized Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratification</td>
<td>Endarterectomy + Medical Care (n=616) vs. Medical Care Alone (n=596)</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>To test the potential benefit of CEA in patients with moderate or severe stenosis; standard risk patients</td>
</tr>
</tbody>
</table>

| Subjects:                  | Randomized 1,212 |
| Sites:                     | 50 (US and Canada) |

**Primary Endpoint:** Ipsilateral stroke

**Follow-up:** 30 days, 1 year, & 2 years

- Patients stratified according to degree of stenosis:
  - moderate (<70%)
  - severe (70-99%)
- Trial demonstrated clear benefits from CEA relative to medical therapy with aspirin in symptomatic patients at standard risk for surgery.

NASCET Results

- Results
  
  - *Symptomatic patients with* $\geq 70\%$ carotid stenosis derived substantial long term benefit from CEA
    - Medical event rate: close to 26%
    - CEA event rate 9%

  - *Symptomatic patients with moderate stenosis (50 – 69%),* benefitted much less ($p = 0.045$)

  - *Patients with* $<50\%$ stenosis showed no benefit from CEA

  - Safety monitoring committee stopped trial early for patients with 70 – 99% stenosis after *significant benefit* became apparent

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CEA vs. Medical Therapy
ACAS: Asymptomatic Carotid Atherosclerosis Study

**Design**
Prospective, Multicenter, Randomized Controlled Trial

**Stratification**
CEA + aspirin & risk factor reduction (n=825) vs. aspirin & risk factor reduction alone (n=834)

**Hypothesis**
To determine whether the addition of carotid endarterectomy to aggressive medical management can reduce the incidence of cerebral infarction in patients with asymptomatic carotid artery stenosis

**Subjects:**
Randomized 1,662 (follow-up on 1,659)

**Sites:**
39 (US and Canada)

**Enrollment End:**
1993

**Primary Endpoint:**
30-day perioperative stroke or death plus subsequent stroke ipsilateral to the treated carotid artery

**Follow-up:**
30 days, 1 year, & 2 years

**Trial demonstrated clear benefits from CEA relative to medical therapy with aspirin in symptomatic patients at standard risk for surgery.**

ACAS Results

- **30-day stroke and death** rate was higher in the CEA group: 2.3% vs. 0.4%
- Absolute risk reduction of 5-year ipsilateral stroke was 5.9%
- 1.2% stroke risk from pre-op angiogram

NASCET/ACAS Trials Summary

- NASCET/ACAS were key trials that set up *CEA as the standard of care* for carotid disease vs. Medical Management

- Established AHA recommendations for *perioperative stroke risk*
  - Symptomatic ≥ 70% stenosis < 6% (Peri-operative Stroke & Death risk)
  - Asymptomatic ≥ 60% stenosis <3% (Peri-operative Stroke & Death risk)

- *No Octogenarians* (80 years old) enrolled in these studies

- *30 day results* not as definitive as long term results for absolute risk reduction for stroke

- ACAS and NASCET are *NORMAL-RISK* trials and cannot be directly compared to the high-risk CAS trials

# Carotid Endarterectomy (CEA)

<table>
<thead>
<tr>
<th>Symptomatic stenosis</th>
<th>RECOMMENDATION</th>
<th>LEVEL OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade (≥ 70%)</td>
<td>Carotid endarterectomy performed by a surgeon with a perioperative morbidity rate &lt; 6%</td>
<td>Class I</td>
</tr>
<tr>
<td>Moderate (≥ 50% and &lt; 70%)</td>
<td>Carotid endarterectomy, depending on patient-specific factors such as age, sex, comorbidities, and severity of initial symptoms</td>
<td>Class I</td>
</tr>
<tr>
<td>Mild (&lt; 50%)</td>
<td>No indication for endarterectomy</td>
<td>Class I</td>
</tr>
<tr>
<td>Asymptomatic stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade (≥ 60%)</td>
<td>Endarterectomy performed by a surgeon with a perioperative morbidity and mortality rate &lt; 3%</td>
<td>Class I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Level of evidence A</td>
</tr>
</tbody>
</table>
Carotid Endarterectomy (CEA)

- Anatomical limitations for CEA

Not all people can be treated with endarterectomy.
Carotid Artery Stenting (CAS)

- Carotid artery stenting is a less invasive alternative to CEA
  - Goal to reduce future stroke risk
- Components of CAS include
  - Stent
    - Stabilizes and “traps” the plaque
    - Reduces the flow pressures on the plaque
    - Increases blood flow
  - Embolic Protection Device (EPD)
    - Designed to prevent embolization of debris released during a stenting procedure

Image courtesy of the NHLBI
Embolic Protection

• DEP devices
  – Filters
    • Porosity 100-150 µm
  – Distal occlusion
  – Flow reversal
Carotid Stenting
Carotid Stenting
CEA vs. CAS
CREST: Carotid Revascularization
Endarterectomy vs. Stenting Trial

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, Multicenter, Randomized Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent/EPD</td>
<td>CEA (n=1240) vs. CAS: (n=1262)</td>
</tr>
</tbody>
</table>
| Hypothesis      | 1. Superiority – Hazard Ratio for CAS vs. CEA with multi-year follow-up (NIH Analysis)  
                 | 2. Non-inferiority – CAS is not worse than CEA at 1 year follow-up (FDA analysis) |

<table>
<thead>
<tr>
<th>Subjects:</th>
<th>Lead-in 1,564</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized 2,522</td>
</tr>
<tr>
<td>Sites:</td>
<td>117 (108 US, 9 Canada)</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>1 mo, 6 mos, every 6 mos for 4 years</td>
</tr>
<tr>
<td>Enrollment:</td>
<td>First Patient Dec 00</td>
</tr>
<tr>
<td></td>
<td>Lead-in completed Apr 08</td>
</tr>
<tr>
<td></td>
<td>Randomized completed Jul 08</td>
</tr>
<tr>
<td></td>
<td>First data presented Feb 10</td>
</tr>
</tbody>
</table>

- CREST represents the largest, most rigorous, prospective randomized trial to show both stenting and surgery are safe and effective.
- Both CAS and CEA treatment groups had very low event rates confirming safety and effectiveness.
- CAS was proven non-inferior to CEA for the primary endpoint, and death, stroke, or MI at 30 days

CREST Primary Endpoint:
Stenting and Surgery Found to be Equally Durable

Any death, stroke or MI within the perioperative period
plus ipsilateral stroke out to 4 years

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.2%</td>
<td>6.8%</td>
<td>HR = 1.11; 95% CI: 0.81-1.51</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Clark, CREST Presentation at International Stroke Conference on February 26, 2010
## CREST
### Peri-procedural Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CEA %</th>
<th>CAS %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural stroke+MI+death</td>
<td>4.5</td>
<td>5.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Periprocedural stroke</td>
<td>2.3</td>
<td>4.1</td>
<td>0.01</td>
</tr>
<tr>
<td>- Major ipsilateral stroke</td>
<td>0.3</td>
<td>0.9</td>
<td>0.09</td>
</tr>
<tr>
<td>- Minor ipsilateral stroke</td>
<td>1.4</td>
<td>2.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Periprocedural MI</td>
<td>2.3</td>
<td>1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Periprocedural death</td>
<td>0.3</td>
<td>0.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Periprocedural cranial nerve injury</td>
<td>4.8</td>
<td>0.3</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Thomas G. Brott N Eng Journal of Med 2010*
Pre-specified Secondary Analysis by **Symptomatic Status: Peri-procedural period**

**Death, Stroke, MI**

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>3.5%</td>
<td>3.6%</td>
<td>HR = 1.02; 95% CI: 0.55-1.86</td>
<td>0.96</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>6.7%</td>
<td>5.4%</td>
<td>HR = 1.26; 95% CI: 0.81-1.96</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**Death, Stroke**

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>2.5%</td>
<td>1.4%</td>
<td>HR = 1.88; 95% CI: 0.79-4.42</td>
<td>0.15</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>6.0%</td>
<td>3.2%</td>
<td>HR = 1.89; 95% CI: 1.11-3.21</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Peri-procedural death, stroke rates for both CAS and CEA meet AHA guidelines in both asymptomatic and symptomatic patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CEA %</th>
<th>CAS %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 years stroke+MI+death</td>
<td>6.8</td>
<td>7.2</td>
<td>0.51</td>
</tr>
<tr>
<td>4 years stroke</td>
<td>2.3</td>
<td>2</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Thomas G. Brott N Eng Journal of Med 2010
Pre-specified Secondary Analysis by Symptomatic Status:  
*Peri-procedural period plus ipsilateral stroke out to 4 years*

### Death, Stroke, MI

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>5.6%</td>
<td>4.9%</td>
<td>HR = 1.17; 95% CI: 0.69-1.98</td>
<td>0.56</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>8.6%</td>
<td>8.4%</td>
<td>HR = 1.08; 95% CI: 0.74-1.59</td>
<td>0.69</td>
</tr>
</tbody>
</table>

### Death, Stroke

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>4.5%</td>
<td>2.7%</td>
<td>HR = 1.86; 95% CI: 0.95-3.66</td>
<td>0.54</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>8.0%</td>
<td>6.4%</td>
<td>HR = 1.37; 95% CI: 0.90-2.09</td>
<td>0.14</td>
</tr>
</tbody>
</table>

No evidence of a difference for either treatment by symptomatic status

CREST Findings

Age

Younger patients have better outcome with CAS while older patients have better outcome with CEA

Thomas G. Brott N Eng Journal of Med 2010

120 days *stroke and death risk*

<table>
<thead>
<tr>
<th>Age</th>
<th>CAS (%)</th>
<th>CEA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 yrs</td>
<td>5.8</td>
<td>5.7</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>12</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Arterial tortuosity and calcification in elderly prone to catheter provoked cerebral emboli

Bonati LH Lancet 2010
# CEA vs. CAS

<table>
<thead>
<tr>
<th>Carotid Endarterectomy (CEA)</th>
<th>Carotid Artery Stenting (CAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>↓ Periprocedural stroke</td>
<td>↑ MI</td>
</tr>
<tr>
<td>↑ Cranial nerve injury</td>
<td>No cranial nerve injury</td>
</tr>
<tr>
<td>↑ Wound infection</td>
<td>↓ Wound infection</td>
</tr>
<tr>
<td>Required GA</td>
<td>No GA required</td>
</tr>
<tr>
<td>Longer recovery</td>
<td>Minimally invasive</td>
</tr>
</tbody>
</table>
So, What is the Optimal Strategy?
Matching Patient to Intervention

Treatment decisions depend on patient-specific factors.

- Risk factors for CEA
- Risk factors for CAS

Medical
Surgical / Anatomical

WE CARE ABOUT YOU
Risk Factors for CEA

Medical Risk Factors

- CHF and left ventricular dysfunction
- Unstable angina or recent MI (<30 days)
- Coronary artery disease (CAD)
- Open heart surgery needed within 6 weeks
- Severe pulmonary dysfunction

- Risk of worse outcome
- Similar stroke and death rate between low and high risk patient

Mozes J Vasc Surg 2004
Risk factors for CEA

*Surgical / Anatomical risk factors*

**Surgical Factors**
- Restenosis after prior CEA
- Previous ablative neck surgery (e.g. radical neck dissection, laryngectomy)
- Previous neck irradiation
- Contralateral vocal cord paralysis
- Tracheostomy

**Local complications**
- Infection
- Nerve injury
- Cervical haematoma
- Wound dehiscence
Risk Factors for CEA

Surgical / Anatomical risk factors

Anatomical Factors
- High carotid bifurcation (above C2)
- Extension of atherosclerotic lesion into intracranial ICA or proximal CCA below clavicle

↑ Intraoperative or Peri-operative stroke
Risk Factors for CAS

- Heavily Calcified Target Lesion
- Marked Carotid Tortuosity
- Heavily Calcified Aortic Arch
- Angulated (“type 3”) Aortic Arch
- Severe Vascular Disease Precluding Femoral Access

Target Vessel Arch Access
Individualized Management

Optimal treatment selection specific for each patient

*Lowest morbidity rate*

*Most favorable outcomes*
What’s on the Horizon?
Plaque Imaging
Do All Plaques Behave the Same?

Vulnerable plaque with hemorrhage
Understanding Peri-Procedural Strokes

*Not all strokes appear on the day of the procedure*
## Understanding Peri-Procedural Strokes

Delayed neurologic Events 1-30 days
Open vs. Closed Cell design

<table>
<thead>
<tr>
<th>Total population</th>
<th>Patients</th>
<th>All events</th>
<th>Post-procedural events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open cell</td>
<td>937</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>Closed cell</td>
<td>2242</td>
<td>51</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>3179</td>
<td>90</td>
<td>61</td>
</tr>
</tbody>
</table>

Cell type
- Open cell: 4.2% All events, 3.4% Post-procedural events
- Closed cell: 2.3% All events, 1.3% Post-procedural events

2/3 of neuro events were delayed (1-30d)
Stent Design
Open vs. Closed cell
What is The Optimal Carotid Stent?

• Needs to offer:
  – Scaffolding
  – Lesion Containment
  – Conformability
  – Visibility
  – Ease of use
  – Low profile
New Mesh Stent Design

- Gore
- Terumo
- InspireMD
New Mesh Stents

A Novel CAS Design
– Closed cell structure with flexible Nitinol weave
– Dual layer micromesh design for sustained embolic prevention
– Retrievable and repositionable
Plaque Protrusion - OCT

Mesh vs Closed cell stent
Direct Carotid Access
High Rate Flow Reversal-TCAR

- Avoid the arch
- “CEA-like” neuroprotection
- Less manipulation
## Roadster Outcomes

<table>
<thead>
<tr>
<th>High Surgical Risk</th>
<th>Pivotal Group, ITT (n=141)</th>
<th>Pivotal Group, PP (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/D/MI*</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor Stroke</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke &amp; Death</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cranial Nerve Injury (CNI)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CNI Unresolved at 6 Mos</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
New Technologies in CAS

• Mesh-covered carotid stents likely to add benefit in terms of reducing not only clinical events but also surrogate DWI lesions

• Double-filtration and TCAR is already showing benefit both clinically (TCAR), and using DWI surrogates

• Patient CAS outcomes—already good—should improve further
Asymptomatic carotid disease

Examining CAS and CEA in the context of intensive medical therapy

Figure 1. CREST-2 parallel study design. Endpoint = stroke and death in first 30 days and ipsilateral stroke thereafter up to 4 years. S, screening; R, randomization.
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Congestive Heart Failure
Turning Failure into Success

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Sinclair Community College
Building 12, Conference Center

Keynote Speaker: Javed Butler, MD, MPH, MBA
Heart Failure 2018: Where Are We and Where Are We Going!

Registration Fee:
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