Objectives

- Understand the burden of carotid disease
- Understand the anatomy of the carotid arteries and aortic arch
- Be familiar with the trials involved with carotid artery stenting (CAS)
- Understand the pros and cons of CAS and carotid endarterectomy (CEA)

Why is this important?

- Each year, ≈795,000 people experience a new or recurrent stroke.
- Projections show that by 2030, an additional 3.4 million people aged ≥18 years will have had a stroke, a 20.5% increase in prevalence from 2012.
- Stroke is the 4th leading cause of death.
- Stroke is the leading cause of disability.
- The number of deaths with stroke as an underlying cause in 2010 was 129,476; any-mention mortality in 2010 was 217,621.
- Between 2012 and 2030, total direct medical stroke-related costs are projected to triple, from $71.6 billion to $184.1 billion.

*Heart Disease and Stroke Statistics – 2014 Update, American Heart Association*
**Suspicion for Extracranial Carotid Disease**

- Carotid Duplex Ultrasonography
- <50% Stenosis → Appropriate F/U DUS
- 50-99% Stenosis in Appropriate Clinical Scenario → MRA or CTA
- Occlusion → Appropriate F/U DUS
- DUS/MRA/CTA Agree? → YES (CAS) NO (Angio)
- Therapeutic Options:
  - Med Rx
  - Surgery
  - CAS

**Diagnosis and Treatment**

**Who Is a Candidate for Carotid Revascularization?**

- Any patient with hemispheric ischemic symptoms related to an ipsilateral internal carotid stenosis ≥50%
- Any asymptomatic patient with >70% internal carotid stenosis

**Treatment of Carotid Artery Disease**

CEA has been shown to be safe and effective in numerous randomized clinical studies:

- Superiority of CEA vs. best medical therapy:
  - NASCET\(^1\): Symptomatic >50% diameter stenosis
  - ACAS\(^2\): Asymptomatic >60% diameter stenosis
  - ECST\(^3\): Symptomatic >50% diameter stenosis
  - VA Cooperative Study\(^4\): Symptomatic >50% diameter stenosis

\(^1\) NEJM 325:445-453, 1991
\(^2\) JAMA 273:1421-1428, 1995
\(^3\) Stroke 34: 514-523, 2003
\(^4\) NEJM 328:221-227, 1993
NASCET Results >70% Stenosis Group

- CEA had a slightly higher perioperative stroke and death rate than medical therapy.
- CEA had a significantly lower 2 year ipsilateral stroke rate. An absolute risk reduction of 17%.

Acas Results: Lesions >60%

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

Carotid Artery Stenting

- A less-invasive, endovascular procedure
- Based on proven balloon angioplasty and stent placement procedures used for coronary and peripheral blockages
Candidates for Carotid Stenting (Historically)

- Symptomatic with >50% stenosis, OR
- Asymptomatic with >80% stenosis

AND

- At least one of the following anatomic or co-morbid risk factors placing them at high-risk for adverse events from CEA:
  
  **Anatomic**
  - Contralateral carotid occlusion
  - Contralateral laryngeal palsy
  - Post-radiation treatment
  - Previous CEA with recurrent stenosis
  - High cervical ICA lesions
  - CCA lesions below the clavicle
  - Severe tandem lesions

  **Co-morbid**
  - Congestive Heart Failure (Class III/IV), and/or known severe left ventricular dysfunction <30%
  - Open-heart surgery within 6 weeks
  - Recent myocardial infarction >24 hours and <4 weeks
  - Unstable angina (CCS class III/IV)
  - Synchronous severe cardiac and carotid disease requiring open heart surgery and carotid revascularization
  - Severe pulmonary disease to include any of the following:
    - Chronic oxygen therapy
    - Resting PO2 of < 60 mmHg
    - Baseline hematocrit > 50%
    - FEV1 or DLCO < 50% of normal
  - Abnormal stress test
Carotid Artery Stenting: Evidence

- CEA has been proven beneficial over medical therapy
- Multiple clinical trials demonstrate the evidence for stenting patients at high risk for surgery:
  - Completed trials for high-risk patients:
    - SAPPHIRE
    - ArCHER
    - SECURITY
    - BEACH
    - CREST, sponsored by the NIH

ARChER Trials

- Objective
  - To demonstrate equivalence of carotid stent therapy with embolic filter protection using the RX Acculink® Carotid Stent System/RX Accunet™ Embolic Protection System in high-risk surgical patients, and a historical control in similar patients
- Design
  - Series of three single-arm, multi-center trials with identical inclusion/exclusion criteria using the same stent
- Sites
  - 48 Investigational Centers in US, Europe (4), and Argentina (1)

Devices Overview of ARChER Trials

<table>
<thead>
<tr>
<th></th>
<th>ARChER 1</th>
<th>ARChER 2</th>
<th>ARChER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>158 (+ 51 lead-ins)</td>
<td>278 (+ 25 lead-ins)</td>
<td>145</td>
</tr>
<tr>
<td>Stent</td>
<td>Acculink®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent Delivery System</td>
<td>Acculink® (OTW)</td>
<td>RX Acculink®</td>
<td></td>
</tr>
<tr>
<td>Embolic Protection Device</td>
<td>None</td>
<td>Accunet™ (OTW)</td>
<td>RX Accunet™</td>
</tr>
</tbody>
</table>
Design Across ARCHeR Trials

- Inclusion criteria
  - Stenosis severity
    - ≥ 50% by angiography (Symptomatic patients)
    - ≥ 80% by angiography (Asymptomatic patients)
  - Discrete ICA lesion ± / CCA
  - Vessel diameter ≥ 4mm and ≤ 9mm

- Key exclusion criteria
  - Recent (< 7 days) stroke
  - Previous major ipsilateral stroke
  - Neurological deficits not due to stroke

30-Day Endpoint Event Rates

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ARCHeR 1</th>
<th>ARCHeR 2</th>
<th>ARCHeR 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/Stroke**</td>
<td>6.3%</td>
<td>6.8%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Death/Stroke/MI**</td>
<td>7.6%</td>
<td>8.6%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Major + Fatal Strokes**</td>
<td>1.9%</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

ARCHeR: 1-Year Outcomes

- Composite endpoint
- Death/stroke/MI at 30 days plus ipsilateral stroke to 1 year*
- Comparative data
- 14.5% historical control

*Based on Kaplan-Meier estimates of all ARCHeR patients. Not all ARCHeR 3 patients have reached 1 year.
In surgical high-risk patients, carotid stenting with embolic protection using the RX Acculink® Carotid Stent System/RX Accunet™ Embolic Protection System compares favorably to control:

- Pre-specified non-inferiority hypothesis achieved
- Major/fatal strokes occur at a low rate, similar to previous landmark CEA trials
- Minor strokes in this trial had no significant clinical effects at 1-year

The results of carotid stenting with Acculink® are durable, as demonstrated by the low target lesion revascularization rate at 2.5 years and low rates of major/fatal ipsilateral stroke.

The results of carotid stenting with Acculink® are durable, as demonstrated by the low target lesion revascularization rate at 2.5 years and low rates of major/fatal ipsilateral stroke.

Carotid Artery Stenting: SAPPHIRE

SAPPHIRE – A Landmark Trial:

- Designed to test Non-inferiority hypothesis
- Multi-center
- Randomized
- High-risk surgical patients

SAPPHIRE - Stenting and Angioplasty with Protection In Patients at High Risk for Endarterectomy

- Study design
  - Prospective, randomized and registry, multi-center
  - Required surgical and interventional physician consensus to randomize
  - Subjects not randomized were entered into either a stent or surgical registry
  - Follow-up at 30–days and 6, 12, 24, 36 months
SAPPHIRE – Study Objectives

• To compare safety and efficacy of stenting with embolic protection to CEA in high-risk patients
• To compare carotid artery stenting to CEA in order to demonstrate “non-inferiority” of stenting
• “Non-inferiority” defined as comparable or superior outcomes to CEA

SAPPHIRE

» Devices utilized
  - Cordis PRECISE™ Nitinol Self-Expanding Stent and ANGIOGUARD™ XP (OTW versions)

SAPPHIRE – Inclusion Criteria

» ICA/CCA stenosis
» >50% stenosis in symptomatic patients
» >80% stenosis in asymptomatic patients
» One or more co-morbidity which would make subject high-risk for CEA
» Registry enrollment completed February 2002
» Randomization halted June 2002
SAPPHIRE – Exclusion Criteria

- Acute ischemic stroke or within the past 48 hours
- Total occlusion of the target carotid artery
- Percutaneous or surgical intervention planned within 30 days of study procedure
- Ostial lesion of the CCA

SAPPHIRE

- Physician Consensus
- Interventional Refusal
- Surgical Refusal
- Stent Registry N=406
- Randomized N=334 (310 treated)
- CEA N=151
- Surgical Registry N=7

SAPPHIRE – Endpoints

- Primary endpoints
  - MAE at 30-days
  - Composite any death, stroke or MI
  - Death and ipsilateral stroke from day 31–365
- Secondary endpoints
  - Patency (<50% restenosis by ultrasound) at 48 hours, 6 months and 1, 2 and 3 years
  - Disabling stroke at 30-days and 6 months
  - Safety assessment of distal protection device
Overall, subjects randomized to CAS had lower 30-day events, although this was not statistically significant unless combined.

<table>
<thead>
<tr>
<th>Event</th>
<th>CAS 0.6%</th>
<th>CEA 2.0%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (any)</td>
<td>0.6%</td>
<td>2.0%</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke (any)</td>
<td>3.8%</td>
<td>5.3%</td>
<td>NS</td>
</tr>
<tr>
<td>MI (any)</td>
<td>2.6%</td>
<td>7.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Death/Stroke (any)</td>
<td>4.5%</td>
<td>6.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Combined death/stroke/MI (any)</td>
<td>5.8%</td>
<td>12.6%</td>
<td>P=0.047</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Event</th>
<th>Stenting 11.9%</th>
<th>CEA 19.9%</th>
<th>Stent Registry 15.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAE</td>
<td>11.9%</td>
<td>19.9%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Death</td>
<td>6.9%</td>
<td>12.6%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.7%</td>
<td>7.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td>MI</td>
<td>2.5%</td>
<td>7.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>TLR-clinically driven</td>
<td>0.6%</td>
<td>4.0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>


SAPPHIRE – 30-Day Outcomes

SAPPHIRE – 1-Year Outcomes

SAPPHIRE – 1-Year Ipsilateral Stroke Rate
Carotid Artery Stenting: SAPPHIRE

<table>
<thead>
<tr>
<th>Complications</th>
<th>Stent (n=167)</th>
<th>CEA (n=167)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Lesion Revascularization @ 1 year (TLR)</td>
<td>1 (0.6%)</td>
<td>6 (4.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Target Lesion Revascularization @ 2 year (TLR)</td>
<td>2 (1.4%)</td>
<td>10 (6.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Vessel Thrombosis</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>---</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>15 (9.0%)</td>
<td>17 (10.2%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Cranial Nerve Injury</td>
<td>0 (0.0%)</td>
<td>8 (4.8%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Clinically driven Target Lesion Revascularization based on results of duplex ultrasound and angiogram.

Conclusions

- Scientifically valid study with 700+ patients
  - 304 randomized patients
  - 406 registry patients
- Unbiased, rigorous data based on multidisciplinary team decisions (surgeon, neurologist, interventionalist)
- Carotid stenting non-inferior to CEA in high-risk patients
  - Observed Lower rates for stenting than CEA:
    - Cranial Nerve Injuries
    - TLR at 1 and 2 years

SAPPHIRE is the first randomized clinical trial of Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.

SAPPHIRE – Conclusions

- Symptomatic and asymptomatic patients randomized to stenting had better outcomes overall
- Stenting with protection had more favorable event-free survival at 1-year compared to CEA
- Stenting with protection had significantly lower rates than CEA for MI, major ipsilateral stroke and cranial nerve injury
- Lower rates of TLR with stenting may support the durability of the procedure
Some trials have shown unfavorable results for CAS but have serious limitations

**EVA-3S Trial: Design**

- Prospective, Multicentered, Randomized
- Sponsored by French Ministry of Health
- Inclusion:
  - Symptomatic Carotid Stenosis > 60%
  - Patients equal candidate for either option
- Primary endpoint:
  - Any stroke or death within 30 days - (Not MI)
- Stopped prematurely by safety monitoring committee after 527 patients were enrolled

**EVA-3S Trial: Results**

- 30 Day rate of any stroke or death
  - Endarterectomy = 3.9%
  - Carotid Stent = 9.6%
  - Relative Risk of 2.5 (95% CI 1.2 to 5.1)

- 30 Day rate of disabling stroke or death
  - Endarterectomy = 1.5%
  - Carotid Stent = 3.4%
  - Relative Risk of 2.2 (95% CI 0.7 to 7.2)**
    - Not statistically significant
**EVA-3S Trial: Limitations**

- Distal protection was only “[strongly] recommended” after February 2003 (50% trial duration)
  - 30 day stroke or death
    - Without DEP = 25% (5 of 20)
    - With DEP = 7.9% (18 of 227)
- If 7.9% rather than 9.6% is used:
  - Relative Risk = 2.0 (p = 0.07)

**EVA-3S Trial: Limitations**

- Experience bias
  - Vascular surgeons:
    - Required 25 CEAs in the year prior to study entry
  - Endovascular physicians:
    - Required 12 carotid stents or 35 “supra-aortic stents” with at least 5 carotid stents
    - Or, Allowed to receive training and credentialing “under supervision” as they enrolled patients in the trial
    - Allowed to use new stents after only two cases

**EVA - 3S Trial: Limitations**

- Unexperienced centers
  - 1.7 pts/year

- Aspirin + Plavix was not mandatory
  - Not prescribed in 15%!

- Patients with high surgical risk were excluded
  - But patients with high stent risk not!
Many centers/investigators had problems to fulfill the entrance criteria
- Only 25 carotid stent procedures!

Limited availability of embolic protection devices (only few were allowed)
- Some operators had limited experience with those embolic protection devices allowed in the trial

71% of CAS performed without embolic protection

The Next Frontier: Standard risk patients

CREST: Study Overview
Carotid Revascularization Endarterectomy vs. Stenting Trial
- Design: Prospective, Multicenter, Randomized 1:1 CEA vs CAS
- Stent/EPD: RX-Acculink / RX-Accunet
- EPD use required whenever feasible; 96.1% CAS patients had an EPD
- Randomization phase: from 2001 - 2003
- 94% patients randomized to CAS prior to addition
- NIH Analysis
- First Lead-in period: 2000 - 2001
- Lead-in Phase completed Feb 2002
- Hardening Phase completed Apr 2003
- 1 year follow-up completed

Conventional-risk (not low risk) patients with symptomatic carotid stenosis:
- $\geq 50\%$ by angiography
- $\geq 70\%$ by ultrasound, or
- $>70\%$ by CTA/MRA if ultrasound is $50-69\%$
Major Eligibility Criteria: Asymptomatic

- Asymptomatic carotid stenosis
  - ≥60% by angiography
  - ≥70% by ultrasound, or
  - >80% by CTA/MRA if ultrasound is 50–69%

Major Eligibility Criteria: selected exclusion

- Evolving stroke or major stroke likely to confound study endpoints
- Chronic atrial fibrillation
- MI within the previous 30 days
- Unstable angina

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CAS (n=1262)</th>
<th>CEA (n=1240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female - %</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Asymptomatic - %</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Hypertension - %</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Diabetes - %</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Dyslipidemia - %</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>Current smoker - %</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Cardiovascular disease - %</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Systolic BP, mean mmHg</td>
<td>142</td>
<td>141</td>
</tr>
<tr>
<td>% stenosis ≥70%</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>Days from qualifying event (for symptomatic subjects)</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

No significant differences between groups
Stroke Definition

- An acute neurological ischemic event of at least 24 hours duration with focal signs and symptoms
- Adjudicated by at least two neurologists blinded to treatment

Source: CREST Presentation at International Stroke Conference on February 26, 2010

Myocardial Infarction (MI) Definition

- Combination
  - Elevation of cardiac enzymes (CK-MB or troponin) to a value 2 or more times the individual clinical center’s laboratory upper limit of normal. **Plus**
  - Chest pain or equivalent symptoms consistent with myocardial ischemia, or, ECG evidence of ischemia including new ST segment depression or elevation > 1 mm in 2 or more contiguous leads
- Not enzyme-only
- Adjudicated by two cardiologist blinded to treatment

Source: CREST Presentation at International Stroke Conference on February 26, 2010
Primary Endpoint:
Both stenting and surgery are equally safe and effective
Any death, stroke or MI within the peri-procedural period
plus ipsilateral stroke out to 4 years

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<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>

Peri-procedural period defined per protocol as 30 days post-procedure for all patients receiving assigned therapy within 30 days from randomization.

Any death, stroke or MI within the peri-procedural period
plus ipsilateral stroke out to 4 years

Peri-procedural period defined per protocol as 30 days post-procedure for all patients receiving assigned therapy within 30 days from randomization. The lower 36 days after randomization for all patients not receiving assigned treatment within 30 days.

Primary Endpoint Components:
Peri-procedural period

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2%</td>
<td>4.5%</td>
<td>HR = 1.18, 95% CI: 0.82-1.68</td>
<td>0.38</td>
</tr>
<tr>
<td>0.7%</td>
<td>0.3%</td>
<td>HR = 2.26, 95% CI: 0.89-7.30</td>
<td>0.18</td>
</tr>
<tr>
<td>4.1%</td>
<td>2.3%</td>
<td>HR = 1.79, 95% CI: 1.14-2.82</td>
<td>0.012</td>
</tr>
<tr>
<td>0.9%</td>
<td>0.6%</td>
<td>HR = 1.35, 95% CI: 0.54-3.38</td>
<td>0.52</td>
</tr>
<tr>
<td>3.2%</td>
<td>1.7%</td>
<td>HR = 1.95, 95% CI: 1.15-3.30</td>
<td>0.01</td>
</tr>
<tr>
<td>1.7%</td>
<td>2.3%</td>
<td>HR = 0.82, 95% CI: 0.28-2.84</td>
<td>0.63</td>
</tr>
</tbody>
</table>

- The Primary Endpoint shows no evidence of a difference for either treatment
- Similarity in the Primary Endpoint driven by differences in peri-procedural minor stroke and MI
  - More MI’s after CEA. More minor strokes after CAS
- Both therapies showed best reported peri-procedural outcomes with a very low stroke rate

Post-hoc Analysis by Symptomatic Status
Peri-procedural period plus ipsilateral stroke out to 4 years

Death, Stroke, MI

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<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>0.8%</td>
<td>0.4%</td>
<td>HR = 1.08, 95% CI: 0.74-1.50</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Death, Stroke

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<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>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.
Post-hoc 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: 0.65-1.66</td>
<td>0.96</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>6.7%</td>
<td>5.4%</td>
<td>HR = 1.28; 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>8.0%</td>
<td>3.2%</td>
<td>HR = 1.88; 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.

In CREST, both therapies showed best reported peri-procedural outcomes for symptomatic patients.
Both therapy groups met AHA Guidelines for symptomatic patients.

Both therapies showed best reported peri-procedural outcomes for asymptomatics.
Both therapy groups met AHA Guidelines for asymptomatic patients.
The Ipsilateral Stroke Endpoint shows excellent durability up to 4 years for either treatment.

<table>
<thead>
<tr>
<th>Ipsilateral Stroke</th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0%</td>
<td>2.4%</td>
<td>HR = 0.94, 95% CI: 0.50-1.76</td>
<td>0.85</td>
</tr>
</tbody>
</table>

After the peri-procedural timepoint out to 4 years.


### Quality of Life

Impact of peri-procedural events (stroke/MI) on SF-36 at 1 year adjusting for age, sex, symptomatic extracranial disease and baseline SF-36 measures – Growth Curve Modeling.

- Major strokes have the largest impact on quality of life.
- There is no difference in major stroke rates between CAS and CEA.
- Minor stroke seem to have a slightly higher impact than MI on patient’s quality of life.

### Peri-procedural Cranial Nerve Palsies

<table>
<thead>
<tr>
<th>Cranial Nerve Palsies</th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3%</td>
<td>4.7%</td>
<td>HR = 0.07, 95% CI: 0.02-0.18</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Signs and symptoms of cranial nerve palsy include:
  - Difficulty in swallowing
  - Vocal cord paralysis
  - Facial weakness
  - Nummerness of face or tongue
  - Hoarseness of the voice

* Represents patients randomized to CAS but crossed over to CEA.

Source: CREST Presentation at International Stroke Conference on February 26, 2010
There is no evidence of difference between therapies in ~90% of patients treated in CREST.

- Patients ≥ 80 are higher risk for carotid artery stenting.
- Risk factors in elderly include anatomical limitations such as vascular tortuosity, severe calcification, and diseased aortic arch.
- Patient selection remains an important consideration.
- Patients ≤ 48 are at higher risk for CEA.

Largest, most rigorous, prospective randomized trial and shows the two therapies are safe and effective.

CREST is the standard by which these therapies should be measured.

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th># of Patients</th>
<th># of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST</td>
<td>2,602</td>
<td>117</td>
</tr>
<tr>
<td>ICSS</td>
<td>1,710</td>
<td>53</td>
</tr>
<tr>
<td>SPACE*</td>
<td>1,183</td>
<td>35</td>
</tr>
<tr>
<td>EVA-3S*</td>
<td>520</td>
<td>30</td>
</tr>
<tr>
<td>SAPPHIRE*</td>
<td>334</td>
<td>29</td>
</tr>
</tbody>
</table>

* Trials stopped prematurely.

CREST represents the largest, most rigorous prospective randomized trial examining these two methods of revascularization therapies.

The results establish both CAS and CEA as safe and effective choices for patients and their physicians.

Patient selection remains an important factor; anatomical limitations more likely observed in the very elderly.
Patients were followed for a median of 4.2 years.

The number of fatal or disabling strokes (52 vs 49) and cumulative 5-year risk did not differ significantly between the stenting and endarterectomy groups (6.4% vs 6.5%; hazard ratio [HR] 1.06, 95% CI 0.72–1.57, p=0.77).

Any stroke was more frequent in the stenting group than in the endarterectomy group (119 vs 72 events; ITT population, 5-year cumulative risk 15.2% vs 9.4%, HR 1.71, 95% CI 1.28–2.30, p<0.001; per-protocol population, 5-year cumulative risk 8.9% vs 5.8%, 1.53, 1.02–2.31, p=0.04), but were mainly non-disabling strokes.

The distribution of modified Rankin scale scores at 1 year, 5 years, or final follow-up did not differ significantly between treatment groups.

Conclusion: Long-term functional outcome and risk of fatal or disabling stroke are similar for stenting and endarterectomy for symptomatic carotid stenosis.

What is “modern” carotid stenting?

Consecutive patients (71% men, mean age 71.3 years) treated by CEA (n = 1,118) or CAS (n = 1,084) after a training phase were reviewed. Selection of treatment was based on better-suitability characteristics (morphology and clinical).

A single, high volume cardiovascular center in Italy.
Thirty-day stroke/death rates were similar: 2.8% in CAS and 2.0% in CEA (p = 0.27).

The risk was higher in symptomatic (3.5%) versus asymptomatic (2.0%) patients (p = 0.04) but without significant difference between CAS and CEA groups.

Five-year survival rates were 82.0% in CAS and 87.7% in CEA (p = 0.05).

Composite of any peri-procedural stroke/death and ipsilateral stroke at 5 years after the procedure were similar in all patients (4.7% vs. 3.7%; p = 0.4) and the subgroups of symptomatic (8.7% vs. 4.9%; p = 0.7) and asymptomatic (2.5% vs. 3.3%; p = 0.2) patients in CEA versus CAS, respectively.
A Modern Comparison of Current Carotid Stenting and Carotid Endarterectomy

Conclusions:
- When physicians use their clinical judgment to select the appropriate technique for carotid revascularization CAS can offer efficacy and durability comparable to CEA with benefits persisting at 5 years.
- Favors CEA:
  - Unfavorable aortic arch anatomy
  - Extreme tortuous carotid anatomy
  - Severe peripheral vascular disease precluding femoral access
  - Known allergies to aspirin or clopidogrel
- Favors CAS:
  - Severe coronary disease
  - High-neck carotid bifurcation
  - Obesity
Anatomical factors that are less favorable for carotid stenting
- String sign
- Extensive or circumferential calcification
- More than one 90 degree bend either above or below the lesion
- Very long lesions (> 20 mm)
- Unfavorable arch anatomy (Type III, calcified)
- Lack of suitable vascular access
- Inability to deploy an FDA-approved embolic protection device

Anatomical factors that are less favorable for carotid endarterectomy
- Radical neck dissection
- Surgically inaccessible lesions
- Adverse neck anatomy that limits surgical exposure
- Presence of tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel

In the periprocedural phase, patients allocated to stenting have a significant excess of minor strokes, whereas patients undergoing endarterectomy have significantly more myocardial infarctions and cranial nerve injuries.

In patients younger than 70 years, 30-day rates of stroke and death are similar after stenting and endarterectomy.

In the long term, the rates of death or disabling stroke are similar for the two procedures at all ages.
Based on data from CREST:
- For ages 50–74, no favored procedure as HR for stroke and death = 1.03, 95% CI, 0.44 to 2.44.
- For ages < 50 years, CAS is the favored procedure.
- For ages > 74 years, CEA is the favored procedure.
- Caveat: In CREST, asymptomatic patients had few events, and so there are wide confidence intervals about the point estimates comparing CEA and CAS.
- Accordingly, choice of CEA or CAS cannot be mandated—individual patient characteristics and preferences may supersede guidelines based upon patient age.

CREST-T (Transcarotid artery revascularization): A trial comparing traditional stenting vs. the new TCAR procedure.

CREST-P (Plaque): Studying the structure of the plaque and the forces acting on the plaque, to try to identify those patients at higher risk for stroke.

CREST-B (Bio-banking): Plaque from surgical patients will be collected and evaluated chemically, biochemically and histologically, to try to determine what mechanisms cause the plaque to rupture and cause a stroke. The team will also do genetic testing to look for stroke risk factors.

CREST-H (Hemodynamics): Looking for how brain perfusion is impacted by carotid stenosis and how brain function also is affected by the reduced perfusion. A total of 150 CREST-2 patients will undergo a perfusion MRI scan both before and after surgery; brain function also will be tested.
Where are we now?

- CAS results have vastly improved over time, driven by more experienced operators, better patient selection, and a wider spectrum of technology.
- Physicians have two (or three?) safe choices for revascularizing their patients.
- Physicians now have more information to tailor treatment options for their patients with carotid artery disease.
- CAS and CEA should be viewed as complementary, not competing, procedures.
- And don’t forget about a thing called medical therapy...

Cases

Thank you