The Role of CEA and CAS Post CREST and ICSS: What Have We Learned?

Wesley S. Moore, MD

OBJECTIONS

• Present the Design and Results of ICSS and CREST.
• Provide a Critique of Each
• Look at what (if anything) has changed
• Recommendation Regarding Indications for CEA and CAS at Present

RANDOMIZED TRIALS TO DATE

• 1. EVA-3S - FRENCH SYMPTOMATIC
• 2. SPACE - GERMAN SYMPTOMATIC
• 3. ICSS - INTERNATIONAL TRIAL
• 4. CREST - AMERICAN SYMPTOMATIC AND ASYMPOTMTIC

• EVA3S, SPACE, AND ICSS DEMONSTRATED CEA TO BE SUPERIOR TO CEA. WHAT ABOUT CREST?
INTERNATIONAL CAROTID STENTING STUDY (ICSS) DESIGN

- Prospective Randomized Trial Comparing CEA with CAS in Symptomatic Patients
- 50 Academic Centers in Europe, Australia, New Zealand, and Canada
- Primary Outcome in 120-day Interim Analysis included Death, Stroke, or Procedural Myocardial Infarction

SELECTION OF PARTICIPANTS IN ICSS

- Qualified Centers: Surgeon with >50 CEA (>10/Year); Interventionist with >50 cases of which >10 CAS
- Supervised Centers required proctors, promoted to Qualified after 20 cases if results were deemed acceptable
New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS)

Data are numbers (%). DWI, diffusion-weighted imaging. *Logistic regression analysis; †Unadjusted for intervals between treatment and post-treatment scans. ‡Events occurring between start of treatment and post-treatment scans only. No ischemic event occurred between the start of treatment and the post-treatment scan in patients without new DWI lesions.

Table 4: New DWI lesions on post-treatment scans
CREST TRIAL DESIGN

- PROSPECTIVE, RANDOMIZED TRIAL OF SYMPTOMATIC AND ASYMPTOMATIC PATIENTS
- PRIMARY ENDPOINTS ARE DEATH, STROKE, AND MYOCARDIAL INFARCTION
- 2500 patients provide a 90% power to detect a 1.2% absolute treatment difference/year
Lead-In Phase

- Specific training for interventionalists without previous experience with the ACCULINK™ or ACCUNET™ Systems
- Up to 20 lead-in cases per interventionalist

FINAL RANDOMIZATION

- CEA 1240 PATIENTS
- CAS 1262 PATIENTS
- TOTAL 2502 PATIENTS
- 47% Asymptomatic
- 53% Symptomatic
- MEDIAN FOLLOWUP 2.5 YEARS

OVERALL RESULTS

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>CEA</th>
<th>CAS</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEATH, ST, MI</td>
<td>56(4.5%)</td>
<td>66(5.2%)</td>
<td>0.38</td>
</tr>
<tr>
<td>DEATH</td>
<td>4(0.3%)</td>
<td>9(0.7%)</td>
<td>0.18</td>
</tr>
<tr>
<td>STROKE</td>
<td>29(2.3%)</td>
<td>52(4.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>DEATH+ST</td>
<td>29(2.3%)</td>
<td>55(4.4%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Impact of periprocedural events (stroke/MI) on SF-36 at 1 year adjusting age, sex, symptomatic cerebrovascular disease and baseline SF-36 measures – Growth Curve Modeling.

ICSS TRIAL STRENGTHS

- Trial limited to 1713 symptomatic patients
- A cohort was used to check pre and post procedure MRI for overt and silent brain infarcts

ICSS TRIAL WEEKNESSES

- Poor selection process for participants leading to sub-optimal CAS experience among participants
- Lack of stringent criteria for identifying MI
- Use of embolic protection devices recommended but not mandated
CREST TRIAL STRENGTHS

• Careful selection of interventionists with two stage evaluation including a lead in phase
• Included both symptomatic and asymptomatic patients reflecting practice in the United States
• Results of both CEA and CAS are the best reported to date

CREST INTERVENTIONIST APPROVAL PROCESS

• 427 Interventionists applied for approval.
• 227 Interventionists (52%) were approved.
• This highly selected group may not be representative of the community.
• The CREST results, in the short term, may not be re-producible community-wide.

CEA VS CAS

• 259,080 Patients underwent carotid Rx
• 245,045 CEA (94.6%)
• 14,035 CAS (5.4%)
• 92% Asymptomatic
• 8% symptomatic
CEA was performed with lower stroke and death rates than CAS

<table>
<thead>
<tr>
<th>EVENT</th>
<th>OVERALL CAS</th>
<th>OVERALL CEA</th>
<th>ASYMPT CAS</th>
<th>ASYMPT CEA</th>
<th>SYMPT CAS</th>
<th>SYMPT CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>STROKE</td>
<td>2.1%</td>
<td>0.88%</td>
<td>1.88%</td>
<td>0.86%</td>
<td>4.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>DEATH</td>
<td>1.3%</td>
<td>0.39%</td>
<td>0.44%</td>
<td>0.36%</td>
<td>7.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>COMB</td>
<td>3.4%</td>
<td>1.17%</td>
<td>2.24%</td>
<td>1.22%</td>
<td>11.7%</td>
<td>2.16%</td>
</tr>
<tr>
<td>MI</td>
<td>-</td>
<td>-</td>
<td>2%</td>
<td>1.7%</td>
<td>2.2%</td>
<td>2.0%</td>
</tr>
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</tr>
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NATIONAL HOSPITAL DISCHARGE DATA 2005 EVENT RATES

<table>
<thead>
<tr>
<th>EVENT</th>
<th>M/M %</th>
<th>LOS/Days</th>
<th>Charges $</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA/ASYM</td>
<td>1.16%</td>
<td>2.25</td>
<td>$21,700.00</td>
</tr>
<tr>
<td>CAS/ASYM</td>
<td>1.9%</td>
<td>2.05</td>
<td>$32,400.00</td>
</tr>
<tr>
<td>CEA/SYMP</td>
<td>3.14%</td>
<td>5.4</td>
<td>$37,000.00</td>
</tr>
<tr>
<td>CAS/SYMP</td>
<td>7.7%</td>
<td>6.8</td>
<td>$63,000.00</td>
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</tbody>
</table>
CMS has mandated all hospitals who wish to perform carotid stenting to submit their data to a registry. SVS has established an approved registry that tracks results on not only CAS but also CEA. This registry provides a unique opportunity to compare, side by side, the results of both techniques.

### 30 Day Outcome in Symptomatic Patients

<table>
<thead>
<tr>
<th></th>
<th>CAS N=645</th>
<th>CEA N=506</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.17%</td>
<td>0.79%</td>
<td>0.091</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.27%</td>
<td>2.37%</td>
<td>0.015</td>
</tr>
<tr>
<td>MI</td>
<td>0.93%</td>
<td>0.59%</td>
<td>0.739</td>
</tr>
<tr>
<td>Combined</td>
<td>7.13%</td>
<td>3.75%</td>
<td>0.014</td>
</tr>
</tbody>
</table>

### 30 Day Outcome in Asymptomatic Patients

<table>
<thead>
<tr>
<th></th>
<th>CAS N=805</th>
<th>CEA N=606</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.99%</td>
<td>0.7%</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.11%</td>
<td>1.28%</td>
<td>0.252</td>
</tr>
<tr>
<td>MI</td>
<td>1.37%</td>
<td>0.58%</td>
<td>0.135</td>
</tr>
<tr>
<td>Combined</td>
<td>4.6%</td>
<td>1.97%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### CREST Trial Weaknesses

- Lack of pre and post procedure brain imaging making it impossible to detect silent brain infarction
- Powered appropriately (90%) for 2500 patients overall, but perhaps inadequately powered for 53% symptomatic and 47% asymptomatic sub-group analysis
AREA OF ICSS AND CREST AGREEMENT

- For symptomatic patients, the incidence of peri-procedural death and stroke was twice as great with CAS compared to CEA
- Patients over the age of 70 did better with CEA

AREA OF ICSS AND CREST DISAGREEMENT

- MI rate after CEA higher in CREST than ICSS

WHAT IS THE IMPACT OF A HIGHER MI RATE WITH CEA?

- In other trials, a Troponin elevation is associated with compromise in life expectancy.
- In CREST, survival among CEA and CAS patients was identical due to the surprise finding that stroke, even minor, compromised survival similar to MI.

WHY WAS THERE A HIGHER MI RATE WITH CEA?

- 10 years ago best medical management did NOT include Statins and Beta blockers pre-op.
- CAS patients were on dual anti-platlet agents (ASA and Plavix); CEA patients were on ASA alone.
WHAT HAVE WE LEARNED

• Not Much
• We now know that CEA does better in reducing stroke risk but at the expense of a higher MI rate
• We now know that patients over the age of 70 do better with CEA
• We now know that in the hands of highly selected interventionists and qualified surgeons, the results of CEA and CAS are the best reported to date
• The results of CAS are likely to improve with time
• The Challenge to CEA is to reduce the risk of MI

WHEN CEA, WHEN CAS

• Asymptomatic average risk-CEA
• Asymptomatic high medical risk-no intervention, medical management
• Asymptomatic high anatomic risk-CAS
• Symptomatic average risk-CEA
• Symptomatic high risk-CAS

CONCLUSIONS

• If the objective of treating lesions of the carotid artery is to prevent death and disability from stroke, CEA wins over CAS, but at the expense of an increased rate of non-fatal MI.
• From the patients perspective, stroke is far more disabling than MI.
• The longer term survival in CEA and CAS patients was identical in spite of a higher MI rate in CEA.
• Patients over the age of 70 do better with CEA