Decreases in Mental Acuity, DWMRI Lesions & Cranial Nerve Injuries Should Be Outcome Measures (Endpoints) in Trials of CAS & CEA

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Important Characteristics Of Study
Primary Endpoints:

• Well defined & reliable
  • Reliable evidence about whether the intervention provides clinically meaningful benefit (or harm)
• Sensitive to the effects of the intervention
• Readily measureable
  • Onerous testing leads to missing data points & substantial bias


DWMRI Lesions:

Prospective DWMRI outcomes for various carotid interventional regimes:

ICSS Substudy: N = 231 (of a total of 1713)

New white lesions on DWI
73% transfemoral filter-protected CAS
35% unprotected CAS
(OR 1.28, 1.50-7.20; p = 0.003)

**Study Procedure Embolic Protection # subjects % w/ New DWI Lesions**

<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Embolic Protection</th>
<th># subjects</th>
<th>% w/ New DWI Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICSS1</td>
<td>Transfemoral CAS</td>
<td>Distal filter (Emboshield)</td>
<td>51</td>
<td>13</td>
</tr>
<tr>
<td>ICSS1</td>
<td>CEA</td>
<td>Clamp, backbleed</td>
<td>107</td>
<td>17</td>
</tr>
<tr>
<td>PROPF</td>
<td>Transfemoral CAS</td>
<td>Distal filter (EmboShield)</td>
<td>31</td>
<td>87</td>
</tr>
<tr>
<td>Leal5</td>
<td>Transfemoral</td>
<td>Distal filter (FilterWire)</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>PROPF</td>
<td>Transfemoral CAS</td>
<td>Proximal occlusion (MoMa)</td>
<td>127</td>
<td>45</td>
</tr>
<tr>
<td>DESERVE4</td>
<td>Transfemoral CAS</td>
<td>Proximal occlusion (MoMa)</td>
<td>48</td>
<td>16.7</td>
</tr>
<tr>
<td>PROOF3</td>
<td>Transcervical CAS</td>
<td>Flow Reversal</td>
<td>31</td>
<td>12.9</td>
</tr>
</tbody>
</table>

3. JVS 2011;54:1317-1323
5. JVS 2012;56:1585-1590

Debette S, Markus H. BMJ 2010;341:c3666

**Assessments of “Mental Acuity”: Neuropsychometric Testing**

71 studies, reporting 75 separate CAS treatment groups (4455 procedures) and 29 separate CEA treatment groups (1708 procedures)

Cognitive changes after surgery versus stenting for carotid artery stenosis

- Prospective non-randomized study
- N = 46
- Asymptomatic patients
- No difference in composite cognitive scores
- CEA resulted in reduction in working memory
- CAS resulted in reduction in psychomotor speed


BK Lal et al JVS 2011;54:691-698
Incidence & Impact of Cranial Nerve Injury After Carotid Interventions:

**CREST**

<table>
<thead>
<tr>
<th>Patients with study procedure attempted/received</th>
<th>CAS</th>
<th>CEA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Related Cranial Nerve Injury</td>
<td>0.6%</td>
<td>5.3%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><em>Unresolved at One Month</em></td>
<td>0.6%</td>
<td>2.1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><em>Unresolved at Six Months</em></td>
<td>0.6%</td>
<td>2.1%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*80% motor – hypoglossal & marginal mandibular branch of the facial overrepresented

**CREST: QoL**

At One Month:

CAS patients had better outcomes:

- Physical function, pain, physical function component summary (p < 0.01)
- Less difficulty driving, eating, swallowing, neck pain & headache but more difficulty walking & leg pain (p < 0.05)

**Lasting Impact of CNI:**

*Unclear:*

- Effects variable - range from complete facial palsy or inability to swallow (feeding tube) to mild paraesthesia of the face (shaving) or tongue
- SF36 may be insensitive to degree of disability & HRQoL impairment

**Conclusions:**

- Rationale to include DWMRI as a surrogate marker in carotid trials
- Specific QoL tools required to fully assess the lasting impact of CNI, however, whether the resulting injury is a "nuisance" or substantially disabling, they matter to the patient
- NP testing results in inconsistent findings in the world literature but when a spouse or close family member explains that their loved one is NOT RIGHT, they are PROBABLY RIGHT
Association WM lesions & incident dementia

Meta-Analysis Comparing DWMRI Lesions After CEA & CAS

Cognition after carotid endarterectomy or stenting
A randomized comparison

An ICSS Sub-Study:
N = 177 patients recruited in two Dutch centres
N = 140 Cognitive Function Assessment at baseline
N = 120 Cognitive Function Assessment at 6/12
10 Domains including executive function

Altinbas A et al Neurology 2011;77:1084 - 1090
**DWMRI & Cognitive Function:**

**New white lesions:**
- 17 in 34 CAS (50%)
- 7 in 30 CEA (23%)

**Cognitive Function:**
No significant difference

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**ICSS Primary Analysis CEA Vs. CAS in 1713 symptomatic patients**

**ICSS Substudy: N = 231**

**New white lesions on DWI**
- 62 of 124 (50%) transfemoral CAS
- 18 of 107 (17%) CEA

(OR 5.21, 2.78-9.79; \(p < 0.0001\))