DWMRI Lesions, Cranial Nerve Injury & Neuropsychometric Testing: Is It Time To Incorporate These Outcomes In Carotid Trials As Primary Endpoints?

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Disclosure

Speaker name:

I have the following potential conflicts of interest to report:

- [ ] Consulting
- [x] Employment in industry
- [x] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest
Lecture Plan:

• Review choice of endpoints (surrogates)

• Assess impact of baseline DWMRI lesions on stroke, dementia, mortality & subsequent carotid intervention

• Compare relative incidence DWMRI lesions for various carotid interventional strategies

• Report clinical relevance of neuropsychometry after carotid intervention

• Present incidence & impact of CNI after carotid intervention
Important Characteristics Of Study Primary Endpoints; Surrogates:

• **Used as a substitute for a clinically meaningful endpoint**
  – Changes induced by the intervention on a surrogate are expected to reflect changes in a clinically meaningful endpoint
  – “A correlate does not a surrogate make”

• **Clinically meaningful:**
  – Any clinical event relevant to the patient
  – A direct measure of how the patient feels, functions or survives
Baseline White Matter Changes Predict Stroke, Dementia & Mortality (Supporting Their Use as An Intermediate Marker In A Research Setting):
The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis

46 longitudinal studies; general population & hospital based

**General population**
- Wong 2002\textsuperscript{w6}
- Vermeer 2003\textsuperscript{w1}
- Kuller 2004\textsuperscript{w7}
- Bokura 2006\textsuperscript{w2}
- Debette 2009\textsuperscript{w9}
- Buyck 2009\textsuperscript{w8}

Hazard ratio (95% CI): 3.1 (2.3 to 4.1)
Test for heterogeneity: P=0.55, I\(^2\)=0%

**High risk population**
- Yamauchi 2002\textsuperscript{w10}
- Gerdes 2006\textsuperscript{w3}
- Naka 2006\textsuperscript{w14}

Hazard ratio (95% CI): 7.4 (2.4 to 22.9)
Test for heterogeneity: P=0.12, I\(^2\)=53.4%

**Overall**

Hazard ratio (95% CI): 3.5 (2.5 to 4.9)
Test for heterogeneity: P=0.19, I\(^2\)=28.2%

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

Association WM lesions & incident stroke
### General population

- Kuller 2003\(^w17\)
- Prins 2004\(^w4\)
- Debette 2009\(^w9\)

Hazard ratio (95% CI): 2.9 (1.3 to 6.3)

Test for heterogeneity: \(P=0.001, I^2=85.1\%\)

### High risk population

- Geroldi 2006\(^w22\)
- Firbank 2007\(^w24\)
- Smith 2008\(^w25\)
- Bombois 2008\(^w27\)
- Kantarci 2009\(^w29\)
- Jokinen 2009\(^w30\)

Hazard ratio (95% CI): 1.4 (0.9 to 2.3)

Test for heterogeneity: \(P=0.04, I^2=57.7\%\)

### Overall

Hazard ratio (95% CI): 1.9 (1.3 to 2.8)

Test for heterogeneity: \(P<0.001, I^2=72.9\%\)

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**Association WM lesions & incident dementia**
Association WM lesions & mortality

**General population**
- Bokura 2006
- Kuller 2007
- Ikram 2008
- Debette 2009

Hazard ratio (95% CI): 2.3 (1.9 to 2.8)
Test for heterogeneity: $P=0.48$, $I^2=0\%$

**High risk population**
- Yamauchi 2002
- Levy 2003
- Kerber 2006
- Oksala 2009

Hazard ratio (95% CI): 1.6 (1.0 to 2.7)
Test for heterogeneity: $P=0.11$, $I^2=50.5\%$

**Overall**

Hazard ratio (95% CI): 2.0 (1.6 to 2.7)
Test for heterogeneity: $P=0.02$, $I^2=58.4\%$
The Impact of Baseline White Matter Changes on Subsequent Intervention:
ICSS: Baseline Age-Related White Matter Changes

ICSS: 30-day cumulative incidence of stroke by severity of white matter lesions
Influence of Carotid Interventional Strategy On DWMRI Findings: (Approach, EPD & stent design)
<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>ICSS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Transfemoral CAS</td>
<td>Distal filter (various)</td>
<td>51</td>
<td>73</td>
</tr>
<tr>
<td>ICSS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CEA</td>
<td>Clamp, backbleed</td>
<td>107</td>
<td>17</td>
</tr>
<tr>
<td>PROFI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Transfemoral CAS</td>
<td>Distal filter (Embosheild)</td>
<td>31</td>
<td>87</td>
</tr>
<tr>
<td>Leal&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Transfemoral</td>
<td>Distal Filter (FilterWire)</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>PROFI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Transfemoral CAS</td>
<td>Proximal occlusion (MoMA)</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>PROOF&lt;sup&gt;3&lt;/sup&gt;</td>
<td>TCAR</td>
<td>High flow rate flow reversal</td>
<td>48</td>
<td>16.7</td>
</tr>
<tr>
<td>Leal&lt;sup&gt;4&lt;/sup&gt;</td>
<td>TCAR</td>
<td>Flow Reversal</td>
<td>31</td>
<td>12.9</td>
</tr>
<tr>
<td>CARENET&lt;sup&gt;5&lt;/sup&gt; (CGuard stent)</td>
<td>Transfemoral</td>
<td>Distal filter (26 pts, MoMa 1 pt)</td>
<td>27</td>
<td>48%</td>
</tr>
</tbody>
</table>

3. JVS 2011;54:1317-1323  
4. JVS 2012;56:1585-1590  
5. J Am Coll Cardiol Intv 2015;8:1229-1234
Lesion Volumes:

Individual lesion volume significantly smaller for CAS vs. CEA ($p < 0.001$)

Total lesion volume: Not significantly different ($p = 0.18$)
Periprocedural DWI lesions in the CAS group were more likely to occur in cortical or subjacent white matter areas supplied by leptomeningeal arteries than lesions occurring in the CEA group (OR, 4.2; 95% CI, 1.7–10.2; P=0.002). CAS lesions were, by trend, less often located in vascular border zone territories than CEA lesions (OR, 0.5; 95% CI, 0.2–1.1; P=0.092). There was no significant difference between treatment groups in the likelihood of DWI lesions occurring in the territory supplied by the contralateral carotid artery or the
Clinical Relevance Of Neuropsychometric Testing After Carotid Intervention:
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
DWMRI & Cognitive Function:

New white lesions:

17 in 34 CAS (50%)  
7 in 30 CEA (23%)  
RR 2.1; 95% CI 1.0 – 4.4,  
p = 0.041

Cognitive Function:

No significant difference
Neurocognitive Functioning after Carotid Revascularization: A Systematic Review

Maarten Plessers\textsuperscript{a}  Isabelle Van Herzeele\textsuperscript{b}  Frank Vermassen\textsuperscript{b}  Guy Vingerhoets\textsuperscript{a}

N = 37 studies (18 CEA, 12 CAS, 7 CEA vs. CAS)

“The available data seem to suggest that no obvious cognitive differences between CAS and CEA can be observed. Both improvement and deterioration in cognitive function occur. Methodological differences play an important role in explaining the…results”

Cerebrovascular Diseases Extra 2014;4:132-148
Cognitive changes after surgery vs stenting for carotid artery stenosis

Brajesh K. Lal, MD, a Maha Younes, PhD, b Gina Cruz, APN, c Indu Kapadia, PA, c Zafar Jamil, MD, c and Peter J. Pappas, MD, c Baltimore, Md; and Newark, NJ

N = 46

“CEA is associated with a reduction in memory function while CAS is associated with a reduction in psychomotor speed”

JVS 2011;54:691-698
Incidence & Impact of Cranial Nerve Injury After Carotid Interventions:
Carotid Stenting Trialists’ Collaboration:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CAS (n=1679)</th>
<th>CEA (n=1645)</th>
<th>Risk ratio* (95% CI)</th>
<th>p value†</th>
<th>Risk difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke or death</td>
<td>130 (7.7%)</td>
<td>73 (4.4%)</td>
<td>1.74 (1.32 to 2.30)</td>
<td>0.0001</td>
<td>3.4 (1.8 to 5.0)</td>
</tr>
<tr>
<td>Disabling stroke or death</td>
<td>65 (3.9%)</td>
<td>43 (2.6%)</td>
<td>1.48 (1.01 to 2.15)</td>
<td>0.04</td>
<td>1.2 (0.0 to 2.4)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>19 (1.1%)</td>
<td>10 (0.6%)</td>
<td>1.86 (0.87 to 4.00)</td>
<td>0.10</td>
<td>0.6 (-0.1 to 1.2)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>125 (7.4%)</td>
<td>70 (4.3%)</td>
<td>1.74 (1.31 to 2.32)</td>
<td>0.0001</td>
<td>3.3 (1.7 to 4.9)</td>
</tr>
<tr>
<td><strong>Stroke severity‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>12 (0.7%)</td>
<td>6 (0.4%)</td>
<td>1.97 (0.74 to 5.23)</td>
<td>0.16</td>
<td>0.4 (-0.1 to 0.8)</td>
</tr>
<tr>
<td>Disabling</td>
<td>47 (2.8%)</td>
<td>34 (2.1%)</td>
<td>1.35 (0.87 to 2.08)</td>
<td>0.18</td>
<td>0.6 (-0.4 to 1.6)</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>66 (3.9%)</td>
<td>31 (1.9%)</td>
<td>2.09 (1.37 to 3.19)</td>
<td>0.0004</td>
<td>2.0 (0.8 to 3.2)</td>
</tr>
<tr>
<td><strong>Stroke type§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>118 (7.0%)</td>
<td>57 (3.5%)</td>
<td>2.02 (1.48 to 2.75)</td>
<td>&lt;0.0001</td>
<td>37 (2.2 to 5.2)</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>7 (0.4%)</td>
<td>12 (0.7%)</td>
<td>0.57 (0.23 to 1.45)</td>
<td>0.23</td>
<td>-0.3 (-0.8 to 0.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.1%)</td>
<td>1 (0.1%)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td><strong>Stroke region§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral carotid</td>
<td>113 (6.7%)</td>
<td>66 (4.0%)</td>
<td>1.67 (1.24 to 2.25)</td>
<td>0.0005</td>
<td>2.8 (1.3 to 4.3)</td>
</tr>
<tr>
<td>Contralateral carotid or vertebrobasilar</td>
<td>10 (0.6%)</td>
<td>4 (0.2%)</td>
<td>2.45 (0.77 to 7.81)</td>
<td>0.11</td>
<td>0.4 (-0.1 to 0.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.1%)</td>
<td>0</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (0.2%)</td>
<td>7 (0.4%)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Non-fatal</td>
<td>1 (0.1%)</td>
<td>7 (0.4%)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Fatal</td>
<td>2 (0.1%)</td>
<td>0</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td><strong>Granual nerve palsy¶</strong></td>
<td>7 (0.4%)</td>
<td>99 (6.0%)</td>
<td>0.07 (0.03 to 0.15)</td>
<td>&lt;0.0001</td>
<td>-5.6 (-6.7 to -4.4)</td>
</tr>
<tr>
<td><strong>Severe haematoma¶¶</strong></td>
<td>12 (0.7%)</td>
<td>32 (1.9%)</td>
<td>0.37 (0.19 to 0.71)</td>
<td>0.0016</td>
<td>..</td>
</tr>
<tr>
<td><strong>Severe wound infection</strong> <strong>§§</strong></td>
<td>1 (0.1%)</td>
<td>4 (0.2%)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

30-day outcomes (per protocol evaluation)
**CREST**

<table>
<thead>
<tr>
<th>Patients with study procedure attempted/received</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Related Cranial Nerve Injury</td>
<td>0.0%</td>
<td>5.3% (62/1176)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>* Unresolved at One Month</td>
<td>0.0%</td>
<td>3.6% (42/1176)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>* Unresolved at Six Months</td>
<td>0.0%</td>
<td>2.1% (25/1176)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*80% motor – hypoglossal overrepresented*
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)
# Health-Related Quality of Life After Carotid Stenting Versus Carotid Endarterectomy

Results From CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial)

<table>
<thead>
<tr>
<th>SF-36 Subscale</th>
<th>Mean Difference* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>1.5 (−4.7 to 7.6)</td>
<td>0.643</td>
</tr>
<tr>
<td>Role—physical</td>
<td>3.9 (−6.7 to 14.6)</td>
<td>0.471</td>
</tr>
<tr>
<td>Vitality</td>
<td>4.6 (−0.5 to 9.7)</td>
<td>0.075</td>
</tr>
<tr>
<td>Pain index</td>
<td>−1.3 (−7.5 to 5.0)</td>
<td>0.692</td>
</tr>
<tr>
<td>General health</td>
<td>1.9 (−2.7 to 6.5)</td>
<td>0.429</td>
</tr>
<tr>
<td>Social function</td>
<td>3.2 (−3.0 to 9.4)</td>
<td>0.307</td>
</tr>
<tr>
<td>Role—emotional</td>
<td>0.8 (−9.1 to 10.6)</td>
<td>0.881</td>
</tr>
<tr>
<td>Mental health</td>
<td>3.0 (−1.1 to 7.1)</td>
<td>0.157</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>0.1 (−2.4 to 2.6)</td>
<td>0.939</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>1.4 (−1.0 to 3.7)</td>
<td>0.263</td>
</tr>
</tbody>
</table>

1 year outcomes
“On the basis of these findings, we conclude that CNI is not a trivial consequence of CEA but rarely results in significant long-term disability.”

Incidence, outcomes, and effect on quality of life of cranial nerve injury in the Carotid Revascularization Endarterectomy versus Stenting Trial.
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 OR co-primary endpoint in carotid trials, supported by traditional clinical outcomes

• Specific QoL tools required to fully assess the lasting impact of **CNI** & before CNI can be suggested as a co-primary endpoint but ought to be a secondary endpoint

• **NP** testing results in inconsistent findings in the world literature post carotid intervention & is onerous, requiring significant effort on the part of patient & researcher alike & should only be utilized as a surrogate alongside DWMRI endpoints *

*Dependent on absolute incidence of microembolic burden*
DWMRI Lesions, Cranial Nerve Injury & Neuropsychometric Testing: Is It Time To Incorporate These Outcomes In Carotid Trials As Primary Endpoints?

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