Carotid Revascularization Endarterectomy and Stent Trial - Hemodynamics

(an ancillary study to CREST-2)
CREST-H Study Question

- Can revascularization (CEA or CAS) improve cognitive impairment among a subset of CREST-2 patients with cerebral hemodynamic impairment?
**Goal:** To determine whether the subset of CREST-2 patients with cerebral hemodynamic impairment (“flow failure”) and mild cognitive impairment benefit cognitively from revascularization.

**Background:** Prior studies show that patients with high-grade carotid stenosis may have cognitive impairment if they have low cerebral blood flow on the side of carotid occlusion. Case series suggest this may be reversible with revascularization.

**Objective:** CREST-H will assess cognitive outcomes in CREST-2 patients with cerebral hypoperfusion and cognitive impairment, comparing those who get revascularized (CEA or CAS) versus those who get Intensive Medical Management alone. The difference between treatment groups will be compared with a similar comparison among those without cerebral hypoperfusion.

**Primary Endpoint:** Cognition at 1 year

**Population:** Patients with asymptomatic high-grade carotid stenosis enrolled in the CREST-2 trial.
• **Enrollment goal:** 500 patients across 75 CREST-2 sites

• **Unique testing as part of CREST-H:**
  
  MRI perfusion (PWI) scan to look for hemodynamic flow failure at baseline. (We also acquire DWI, MRA, GRE, FLAIR, Hi-res T1)

  • 1.5 T or 3.0T MRI acceptable, but 3.0T preferred
  • Patients who have baseline flow failure will receive a 1 year follow up MRI scan
What is so important about CREST-H?

We have a chance to identify an alternative indication for revascularization of high grade asymptomatic carotid stenosis – namely reversing cognitive decline.

“You mean even if we don’t reduce the number of strokes our patients have, we might make ‘em smarter?”

-interventionist at CREST2 PI meeting in Chicago
### Prevalence of mild cognitive impairment in CREST-2

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean Z Score</th>
<th>Percentage &lt; 1SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CERAD Learning</td>
<td>0.33</td>
<td>2</td>
</tr>
<tr>
<td>2. Digit Span</td>
<td>0.12</td>
<td>14</td>
</tr>
<tr>
<td>3. Animal Naming</td>
<td>-0.27</td>
<td>31</td>
</tr>
<tr>
<td>4. COWA</td>
<td>-0.79</td>
<td>44</td>
</tr>
<tr>
<td>5. CERAD Memory</td>
<td>-1.17</td>
<td>57</td>
</tr>
<tr>
<td><strong>COMPOSITE Z (3 – 5)</strong></td>
<td><strong>-0.74</strong></td>
<td><strong>44</strong></td>
</tr>
</tbody>
</table>

Table 1. CREST-2 Baseline Cognitive Scores (n=207)
### Table 3

**Multiple regression on composite neurocognitive z scores, stratified by event type (TIA as qualifying event shown here, n = 32)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>95% confidence limits</th>
<th>Pr &gt;</th>
<th>t</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>−0.973</td>
<td>2.120</td>
<td>−5.370 to 3.424</td>
<td>0.651</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D scale</td>
<td>−0.008</td>
<td>0.012</td>
<td>−0.033 to 0.016</td>
<td>0.501</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PET ratio dichotomized (0 = abnormal, 1 = normal)</strong></td>
<td><strong>−1.100</strong></td>
<td><strong>0.503</strong></td>
<td><strong>−2.143 to −0.057</strong></td>
<td><strong>0.040</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.050</td>
<td>0.017</td>
<td>−0.085 to −0.014</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (1 for female, 0 for male)</td>
<td>0.196</td>
<td>0.307</td>
<td>−0.442 to 0.833</td>
<td>0.531</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (0 for 8th grade, 1 for high school, 2 for college)</td>
<td>0.489</td>
<td>0.289</td>
<td>−0.111 to 1.089</td>
<td>0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA side (1 for right, 0 for left)</td>
<td>−0.703</td>
<td>0.330</td>
<td>−1.387 to −0.019</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke (1 for yes, 0 for no)</td>
<td>−0.298</td>
<td>0.342</td>
<td>−1.007 to 0.412</td>
<td>0.394</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CES-D = Center for Epidemiological Studies-Depression; ICA = internal carotid artery.

More evidence: Balestrini series

- 326 pts with asymptomatic high grade carotid stenosis followed over 36 months
- MMSE declined faster in poor VMR group

**Table 2**: Multiple linear regression model predicting decrease in Mini-Mental State Examination score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>t</th>
<th>p Value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic breath-holding index</td>
<td>1.59</td>
<td>0.15</td>
<td>10.77</td>
<td>&lt;0.001</td>
<td>1.29 to 1.88</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01</td>
<td>0.15</td>
<td>-0.44</td>
<td>0.661</td>
<td>-0.04 to 0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.13</td>
<td>0.16</td>
<td>0.82</td>
<td>0.410</td>
<td>0.18 to 0.45</td>
</tr>
<tr>
<td>Education</td>
<td>-0.03</td>
<td>0.02</td>
<td>-1.56</td>
<td>0.120</td>
<td>-0.07 to 0.01</td>
</tr>
<tr>
<td>Constant</td>
<td>2.03</td>
<td>1.06</td>
<td>1.92</td>
<td>0.056</td>
<td>-0.05 to 4.10</td>
</tr>
</tbody>
</table>

Belestrini S et al *Neurology* 2013;80:2145-50
Can we restore hemispheral flow with revascularization? **YES!!**

Marshall RS et al *Stroke* 2003;34:945-9
Cognitive improvement after CAS? (case series data, N=579 pts, 552 ctls)

Table 2. MMSE and MoCA scores of CLI and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Before CAS</th>
<th>1 month</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.67 ± 1.72</td>
<td>27.79 ± 1.94</td>
<td>27.98 ± 2.15</td>
<td>28.38 ± 2.12</td>
<td>28.55 ± 1.98</td>
<td>28.53 ± 2.03</td>
<td>28.61 ± 1.89</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
</tr>
<tr>
<td><strong>MoCA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.91 ± 2.08</td>
<td>19.97 ± 2.17</td>
<td>19.91 ± 1.99</td>
<td>20.70 ± 2.31</td>
<td>20.82 ± 2.18</td>
<td>20.93 ± 2.41</td>
<td>20.89 ± 2.03</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
</tr>
<tr>
<td><strong>Alternating trial</strong></td>
<td>0.57 ± 0.43</td>
<td>0.59 ± 0.50</td>
<td>0.60 ± 0.59</td>
<td>0.63 ± 0.42</td>
<td>0.63 ± 0.51</td>
<td>0.65 ± 0.44</td>
<td>0.66 ± 0.48</td>
</tr>
<tr>
<td><strong>test</strong></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
</tr>
<tr>
<td><strong>Cube copying</strong></td>
<td>0.66 ± 0.38</td>
<td>0.57 ± 0.67</td>
<td>0.59 ± 0.87</td>
<td>0.60 ± 0.94</td>
<td>0.67 ± 0.85</td>
<td>0.65 ± 0.41</td>
<td>0.66 ± 0.38</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
</tr>
<tr>
<td><strong>Clock-drawing</strong></td>
<td>1.81 ± 0.57</td>
<td>1.64 ± 0.38</td>
<td>1.69 ± 0.45</td>
<td>1.70 ± 0.79</td>
<td>1.74 ± 0.74</td>
<td>1.75 ± 0.96</td>
<td>1.78 ± 0.83</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
</tr>
<tr>
<td><strong>Naming</strong></td>
<td>2.46 ± 0.61</td>
<td>2.39 ± 0.84</td>
<td>2.39 ± 0.71</td>
<td>2.41 ± 0.47</td>
<td>2.41 ± 0.53</td>
<td>2.41 ± 0.50</td>
<td>2.41 ± 0.63</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>4.31 ± 1.19</td>
<td>4.02 ± 1.48</td>
<td>4.15 ± 1.33</td>
<td>4.18 ± 1.16</td>
<td>4.28 ± 1.62</td>
<td>4.30 ± 1.54</td>
<td>4.34 ± 1.49</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
</tr>
<tr>
<td><strong>Sentence repeating</strong></td>
<td>1.41 ± 0.56</td>
<td>1.34 ± 0.64</td>
<td>1.35 ± 0.65</td>
<td>1.34 ± 0.68</td>
<td>1.38 ± 0.54</td>
<td>1.37 ± 0.69</td>
<td>1.38 ± 0.66</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td>0.35 ± 0.48</td>
<td>0.31 ± 0.39</td>
<td>0.32 ± 0.45</td>
<td>0.33 ± 0.51</td>
<td>0.34 ± 0.40</td>
<td>0.33 ± 0.38</td>
<td>0.34 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
</tr>
<tr>
<td><strong>Abstraction</strong></td>
<td>0.68 ± 0.54</td>
<td>0.61 ± 0.72</td>
<td>0.61 ± 0.71</td>
<td>0.62 ± 0.67</td>
<td>0.63 ± 0.48</td>
<td>0.63 ± 0.62</td>
<td>0.64 ± 0.69</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
</tr>
<tr>
<td><strong>AVLT-delayed recall</strong></td>
<td>3.34 ± 1.16</td>
<td>3.09 ± 1.22</td>
<td>3.16 ± 1.43</td>
<td>3.25 ± 1.29</td>
<td>3.29 ± 1.37</td>
<td>3.32 ± 1.51</td>
<td>3.32 ± 1.47</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>a*</td>
<td>b**</td>
<td>b**</td>
<td>b**</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>5.71 ± 0.59</td>
<td>5.64 ± 0.74</td>
<td>5.65 ± 0.65</td>
<td>5.64 ± 0.62</td>
<td>5.65 ± 0.48</td>
<td>5.67 ± 0.55</td>
<td>5.70 ± 0.41</td>
</tr>
</tbody>
</table>

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; AVLT, Auditory–Verbal Learning Test; CLI, cerebral lacunar infarction; CAS, carotid artery stenting.

a, Compared with the controls.

b, Compared with the CLI patients before CAS.

*P < 0.05 and ** P < 0.01.

Study Design

CREST-2 enrolled patients

Flow failure

- yes 100
  - yes 70
  - no 30

- no 400
  - yes 150
  - no 250

MCI

- yes
  - revasc 35*
  - med 35*

- no
  - revasc 15*
  - med 15*

Treatment

- *get 1-year follow up MRI*

Compare cognitive improvement diffs at 1 year
H1: red diff > black diff
1. Randomization into CREST-2 (all CREST-2 inclusion criteria apply)

2. Specific CREST-H inclusion criteria:
   - Age 35 to 86 years (no cognitive norms are available over age 90)
   - Patient agrees to complete a baseline MRI scan and another MRI scan at one year if needed.
Unique CREST-H Exclusion Criteria

- Unable to have MRI (e.g. metal implants)
- Allergy to gadolinium contrast dye
- Renal failure: either creatinine ≥ 2.5 mg/dl or GFR < 30cc/min
- >70% stenosis on the side opposite the target vessel as assessed by MRA, CTA or Doppler ultrasound
- Pre-existing diagnosis of dementia
- History of severe head trauma (loss of consciousness >30 minutes, or seizure at the time of trauma)
- Current major depression
- Education <8 years
WHAT WE NEED:

• To participate as a CREST-H site you must have:
  – 1.5T or 3T MRI scanner (3T preferred)
  – The capability to do gado-based MR perfusion on your CREST-2 patients before they get their procedure or within a week of enrollment if randomized to medical therapy alone. Other standard MRI images will also be obtained.
  – A designated, independent co-investigator who can upload de-identified images to the CREST-2 imaging site at U Maryland.
CREST-H Data Flow

Baseline

Consent at Site/MRI → Patient Info Entered at UAB

Image Received at MD

Image Received at UCLA/Analyzed

Image Received at Mayo/Analyzed

No Repeat MRI

Image Analysis to UAB

Perf Image + → Enrolled for Repeat MRI

Repeat MRI at Site

Image Received at MD

Image Received at UCLA/Analyzed

Image Received at Mayo/Analyzed

Image Analysis to UAB

1-year follow up
## MRI Sequences

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Orientation</th>
<th>Slice (mm)</th>
<th>Gap</th>
<th>Slices</th>
<th>TR</th>
<th>TE</th>
<th>TI</th>
<th>FOV(cm)</th>
<th>Freq</th>
<th>Phase</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Res T1</td>
<td>Sagittal</td>
<td>1.2</td>
<td>0</td>
<td>160</td>
<td>NA</td>
<td>Full Min</td>
<td>900</td>
<td>24</td>
<td>192</td>
<td>192</td>
<td>3D</td>
</tr>
<tr>
<td>MRA</td>
<td>Axial</td>
<td>1.4 (0.7)</td>
<td>0</td>
<td>3 x 32</td>
<td>Min</td>
<td>Min</td>
<td>NA</td>
<td>18</td>
<td>384</td>
<td>224</td>
<td>3D</td>
</tr>
<tr>
<td>T2 FLAIR</td>
<td>Axial</td>
<td>4</td>
<td>0</td>
<td>36</td>
<td>11000</td>
<td>147</td>
<td>2460</td>
<td>22</td>
<td>256</td>
<td>192</td>
<td>2D</td>
</tr>
<tr>
<td>Perfusion*</td>
<td>Axial</td>
<td>5</td>
<td>0</td>
<td>Max for TR</td>
<td>2225</td>
<td>60</td>
<td>NA</td>
<td>24</td>
<td>128</td>
<td>96</td>
<td>2D</td>
</tr>
<tr>
<td>DWI/ADC</td>
<td>Axial</td>
<td>4</td>
<td>0</td>
<td>36</td>
<td>10000</td>
<td>Min</td>
<td>NA</td>
<td>22</td>
<td>128</td>
<td>256</td>
<td>2D</td>
</tr>
<tr>
<td>GRE</td>
<td>Axial</td>
<td>4</td>
<td>0</td>
<td>36</td>
<td>1700</td>
<td>Full Min</td>
<td>NA</td>
<td>22</td>
<td>128</td>
<td>128</td>
<td>2D</td>
</tr>
</tbody>
</table>

*FOR THE PERFUSION SEQUENCE:
1. Antecubital vein IV catheter of 18 gauge is required.
2. A test injection will be performed with approximately 10 ml of normal saline solution.
3. Cover the indicated area with maximum number of slices for TR from the vertex inferiorly.
4. Load the power injector with 20cc contrast and 50cc saline flush.
5. Using the power injector, inject 20cc contrast at 4cc/sec and a 25cc saline flush at 4cc/sec.
6. Do an AUTOPRESCAN
7. CHOOSE SCAN
8. Inject contrast when there is 1:18 remaining in scan (11 SEC DELAY). Make sure the sequence is producing mages before you inject.
CREST-H Image Transfer

- Images will be transferred from sites to the Vascular Imaging Core Lab at the University of Maryland (https://VIBE.umaryland.edu/VIC)

- University of Maryland will send images to:
  - UCLA (MRP, MRA) for perfusion (flow failure) analysis
  - Mayo Clinic Rochester (DWI/ADC, FLAIR, GRE, HiRes-T1) for structural analysis
Site Check-list

1. Site subcontract for CREST-H in place.
2. Confirm with your own Radiology department how de-identification and uploading of image files is done.
3. Upload a de-identified test PWI scan to U Maryland.
4. Obtain any local IRB approvals needed.
5. Decide who will be the MD designated UI to handle perfusion images and any “safety read” information.
6. Make sure the treatment team remains blinded to any PWI results.
In addition to CREST-2 payments, sites will receive the following:

- $1,000 in start-up to cover regulatory/IRB costs
- Up to $1,725 per patient to cover imaging and CRF completion

**Note:** for CREST-H sites with 3.0T MRI scanners, an additional reimbursement will be provided for a “plaque imaging” MRI scan, which would be done as part of the same MRI session as the CREST-H baseline MRI (combined MRI protocol).
# Contact Information

**Protocol/Eligibility/Follow-up:**
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