Progress in CREST-2:
It will produce valuable results
Interesting findings to date

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- NIH Co-PI Management asymptomatic carotid stenosis (CREST-2)
- VA Merit PI Cognitive Impairment in Carotid Disease-1 (ACCOF-2)
- NIH/CSI/Industry PI National Carotid Registry (C2R)
- NIH (Admin Supp) PI Dental Carotid Cognitive Study (DCCS)
- NIH (Admin Supp) PI Carotid-LifeLine Screening Study (C-LLS)
- VA Merit PI Flow mediated thrombus resolution in DVT (EFFORT-2)
- MIPS-Maryland State PI Novel targeted imaging for PAD

Enrollment

- CREST-2 Enrollment
  - 1580 Number of CEA randomizations: 830
  - Number of CAS randomizations: 750 as of Nov 21, 2019

Site selection

- 120+ clinical sites in USA, Canada, Spain, Israel

Disclosures
No Conflicts

- NIH
- VA Merit
- NIH/CSI/Industry
- NIH (Admin Supp)
- NIH (Admin Supp)
- VA Merit
- MIPS-Maryland State

Study Selection

- Type
  - Private hospitals: 0.31, 1.52
  - VA Medical Centers: 0.27, 3.71
  - Academic Centers: 0.20, 1.00 (ref)

Progress with credentialing

<table>
<thead>
<tr>
<th>Surgical Management Committee</th>
<th>Intervventional Management Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>383 Total applications</td>
<td>332 Total Applications</td>
</tr>
<tr>
<td>12 Not Approved</td>
<td>45 Denied</td>
</tr>
<tr>
<td>371 (97%) Approved</td>
<td>118 Conditionally Approved</td>
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</tbody>
</table>

- 371 (97%) Approved
- 160 (48.2%) Approved

Credentialing of interventionists

- Specialty did not impact credentialing
- Only significant factor was recent case rate (~13/year)
As of Dec 31, 2018

- Enrolled >3000 patients overall
- 2141 symptomatic (45%) and asymptomatic (55%) patients ≤ 80 years of age with primary atherosclerosis

Lal BK et al JACC, In Press 2019

TCAR by CREST-2 investigators now > 500
TCAR rates have been increasing @ > 15% per year

Results are excellent, and currently being analyzed

Lal BK et al, ISC 2018

Percentage of patients in-target for risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Baseline</th>
<th>Last follow-up</th>
</tr>
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<tbody>
<tr>
<td>SBP &lt; 130 mmHg</td>
<td>47%</td>
<td>70%</td>
</tr>
<tr>
<td>LDL &lt; 70 mg/dL</td>
<td>45%</td>
<td>70%</td>
</tr>
<tr>
<td>Smoking stopped</td>
<td>79%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Lal BK et al, JACC, In Press 2019

Plaque morphologic features (>800 ultrasounds) correlate with baseline:
- Age
- Sex
- LDL levels
- Smoking (current or history-of)
- DBP

Encouraging news for the potential of risk-factor modification to modulate the plaque

Lal BK et al, ISC 2018

To determine whether a subset of CREST-2 patients with cerebral hemodynamic impairment and mild cognitive impairment will benefit from revascularization vs intensive medical management

Target enrollment 350
Current enrollment 118
**Cognitive function**

- CREST-2 patients demonstrate reduced cognitive function
  - Compared to 30,000 community-dwelling adults in the REGARDS study

![Graph showing cognitive function comparison](image)

Lazar R et al, ISC 2019

**Timeline for CREST family of studies**

- 2014: Start
- 2019: Complete enrollment
- 2022: CREST-H, CREST-L enrollment
- 2023: CREST-M enrollment
- 2024: CREST-T clinical study
- 2025: CREST-C clinical study
- 2027: CREST-L clinical study

- Efficacy of medical management
- Plaque features
- Features of high-quality CAS operators
- Features of high-enrolling centers

- C2R TF-CAS results
- C2R TCAR results
- Baseline cognitive function
- Baseline brain perfusion

- Potential protocol modifications
- CREST-3