CREST–2 Registry (C2R)
What is the Value?
What are we Learning?
What will it tell us?

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On behalf of...
Brajesh K. Lal, MD – C2R PI & CREST 2 Co-PI
Thomas G Brott, MD – CREST 2 PI
C2R Management Committee
C2R enrolers and C2 Investigators
In collaboration with NINDS-NIH, SVS-VQI and ACC-NCDR.

Kenneth Rosenfield, MD, MHCDS
Conflicts of Interest

- Consultant: Abbott Vascular, Access Vascular; Cardinal Health; SurModics; Cruzar Systems; Capture Vascular; Contego; Endospan; InspireMD; Magneto; Micell; Silk Road; Surmodics; Valcare; Volcano/Philips; Univ. of Maryland
- Grants/Contracts: Inari Medical; NIH
- Equity: Access Vascular; Contego; Emboitech; EXIMO; JanaCare, Inc; MD Insider; Micelle; PQ Bypass, Inc.; Primacea
- Board Member: VIVA Physicians, a not for profit 501c3 organization dedicated to advancing the field of vascular medicine and intervention through education and research (www.evapsrd.com)

CREST–2 Primary Aims
In patients with ≥70% asymptomatic stenosis, to assess:
- Outcome differences between intensive medical treatment (IMT) alone versus IMT with revascularization
- CEA
- CAS
Primary endpoint: any stroke or death within 44 days of randomization or ipsilateral ischemic stroke up to 4 years.

CREST–2 Summary

First patient enrolled Dec 2014
~ 150 enrolling centers; ~2,500 patients

Lal BK, Meschia J, Brott TG et al. Semin Vasc Surg 2017

CREST–2 Registry
How did this come into being?
- Disconnect between FDA approval and payer coverage...only pathway for CAS reimbursement for asymptomatic patients was PMA studies
- Absence of post-market surveillance studies → severe decline in CAS procedures → decreased operator experience ... an “operator-experience gap”
- Result: Conundrum for CAS arm of CREST–2

Carotid revasc rates plummeting

Lichtman J. JAMA 2017
Criteria established for credentialing of carotid stent operators in CREST-2
- 100 lifetime cases
- 25 cases in last 12 calendar months
- First 25 candidate operators reviewed - 0 credentialed
- First 50 - 2 credentialed

**Primary Objectives**
- Rapid enrollment in CREST-2 by credentialing high-quality operators
- Ensure that CAS is performed safely by adequately experienced operators

**Secondary Objectives**
- Allow for accrual of experience in existing and new operators
- Help operators acquire standardized techniques and eliminate large/inappropriate variances
- Acquire/analyze contemporary CAS outcomes from experienced operators
- Establish benchmarks for quality
- Develop systematic approach for evaluation/oversight of operators and outcomes

**C2R Operations**

**SITE & OPERATOR SELECTION**
- Data Collection
- Data Collation
- Data Analysis

**SVS-VQI Carotid Module**
(Chicago, IL & West Lebanon, NH)
PLUS C2R Supplementary Datasheet

**NCDR-PVI Carotid Module**
(Washington, DC)
PLUS C2R Supplementary Datasheet

**C2R Management Committee**
- Operator Credentialing
- Enrollment monitoring
- Outcomes monitoring

**Operator Credentialing**

<table>
<thead>
<tr>
<th>Surgical Management Committee</th>
<th>Interventional Management Committee</th>
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<tbody>
<tr>
<td>181 Total applications</td>
<td>332 Total Applications</td>
</tr>
<tr>
<td>12 Not Approved</td>
<td>45 Denied</td>
</tr>
<tr>
<td>169 Approved</td>
<td>118 Conditionally Approved</td>
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</tbody>
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As of October 2017

**C2R Progress as of Dec 2017**

- Total applications: 2198
- Number of operators: 332
- As of Jan 1, 2015
C2R Patients as of 9/30/18
- CAS procedures performed by C2R interventionists: n=4064
- C2R ineligible: n=855
- C2R eligible: n=3209
  - Symptomatic: n=1400
  - Asymptomatic: n=1809
- CREST-2 ineligible: n=1656
- CREST-2 eligible: n=153
- 98 sites in US
- 184 interventionalists
- Patients (C2R eligible):
  - Mean Age 67.8 (+/- 7.9 yrs)
  - Female: 34.1%
  - Caucasian: 92.5%
  - Smoker: 75.8%
  - Diabetes: 38.6%
  - CAD: 45.8%
  - HTN: 87.4%
- Full range of FDA-approved stents and EPDs represented
  - Filter: 86.3%
  - Flow reversal: 13.7%

C2R Data through 9/30/18
- Full range of FDA-approved stents and EPDs represented
  - Filter: 86.3%
  - Flow reversal: 13.7%
- Outcomes...to be presented at International Stroke Conference in Feb 2019

CREST-2 Enrollment
- 2014: 41%
- 2015: 51.4%
- 2016: 48%
- 2017: 2018
- Declining carotid revascularization rates
  - Declining procedures for asymptomatic disease
- People still need carotid revascularization
  - Developing a generation of operators with adequate expertise
  - Maintaining this expertise over time
- Maintaining rapid enrollment in CREST-2
  - We do need an answer for whether revascularization is beneficial for asymptomatic disease!

C2R – What have we learned?
- Great variation in experience and technique still exists
- Significant deviations from “standard of care” and “standard technique” remain
- C2R can provide platform from which to educate, inform, and train operators in positive, non-threatening way

C2R Future Plans
- Maintain the Registry until C2 is completed, and then some...
  - All patients eligible after Randomization completed, at least until trial results published
  - Analyze and Publish the Data
    - Measure of success of the C2R goals: rate of trial enrollment, # interventionists approved/denied
    - Report Contemporary Outcomes for CAS
    - Analyze variations in procedural technique and outcomes
    - Device use off IFU (i.e. “mixed” stent/EPD combinations, “unapproved devices”)
C2R – Prospective Data Analyses

- Stroke & death rates among symptomatic vs asymptomatic patients among C2R eligible cases
- C2R-eligible vs. C2R-ineligible
- C2-eligible vs. C2-ineligible (among asymptomatic cases)
- Revision of recommended threshold for stroke rate among asymptomatic & symptomatic cases
- Outcomes stratified by stent type: Closed-cell vs open-cell stent
- Outcomes stratified by platelet inhibition: No platelet inhibition vs P2Y12 inhibitors
- Outcomes stratified by Angioplasty balloon size
- Outcomes stratified by type of embolic protection device: Flow reversal vs distal filter
- Outcomes stratified by type of embolic protection device: Pre-procedure vs post-procedure
- Outcome stratified by type of antiplatelet therapy: Dual antiplatelet vs single antiplatelet
- Outcomes stratified by SCAR scores (sex, contralateral occlusion, age, restenosis)
- Sex- & age-related outcomes
- Outcomes stratified by CHADS2 score
- Outcomes stratified by pre-procedural statin therapy
- Outcomes stratified by Renal function (creatinine & GFR)

CREST–2 Registry
Segue to a new NCD?

- C2R provides template for the role of a "monitored registry" to enhance high quality clinical care
- Sets stage for new approach
  - "Managed coverage" (form of CED)
  - Modest procedure oversight and peer review
  - Requirement for data submission
  - Operator credentialing based on experience, outcomes

Objectives

- Promote enrollment in NINDS-NIH funded CREST 2 Trial while optimizing procedural safety
- Collaboration between CREST 2 Leadership, Investigators, CMS, FDA, NIH, Industry Partners
- Eligible patients include high–grade asymptomatic or symptomatic carotid stenosis at standard or high–risk for carotid endarterectomy (CEA)
- Operators credentialed by multi–specialty committee
  - Information collected and analyzed centrally
    - Demographics, clinical features, procedural technique and outcomes
- Safety and outcomes are assessed to ensure high quality CAS, and to guide the selection of operators for CREST–2