Contemporary Prevention of Carotid Stroke

Learning objectives:

➢ Summarize 2014 AHA Guidelines recommendations regarding management of asymptomatic carotid stenosis.

➢ Understand rationale for the NINDS CREST-2 Trial.

➢ Describe the NINDS CREST-2 trial aims, design, eligibility criteria, and progress with recruitment.
Dr. Meschia serves on the Executive Committee of the CREST trial and is Co-Principal Investigator of the Clinical Coordinating Center of the CREST-2 trial, both of which are funded by the NINDS.
Patients with asymptomatic carotid stenosis should be prescribed daily ASA and a statin. Patients should be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted.

Class I, Level of Evidence C

In patients who are to undergo CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated.

Class I, Level of Evidence C

It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50%.

Class IIa, Level of Evidence C

It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established.

Class IIa, Level of Evidence A

Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.

Class IIb, Level of Evidence B

In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established.

Class IIb, Level of Evidence B

Screening low-risk populations for asymptomatic carotid artery stenosis is not recommended.

Class III, Level of Evidence C
Proportion operated at one year:
- 89.7% vs. 4.8%

Combined perioperative events and strokes:
- 6.9% vs. 10.9% at 5 years
- 13.4% vs. 17.9% at 10 years
Medical Management in ACST

Anticoagulant drug use

- Immediate
- Deferred

Antiplatelet drug use

- 91%
- 88%
- 89%
- 88%
Medical Management in ACST

Antihypertensive drug use & mean DBP

Lipid-lowering drug use

[Graphs showing trends in medical management from 1991 to 2007]
Rate of composite of death, myocardial infarction and stroke:
- 20.0% (PCI) vs. 19.5% (medical)
• Composite endpoint: death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy.

• Rate of primary composite endpoint: 
  • 35.1% (stenting) vs. 35.8% (medical)
Stopped early at 451 patients (764 planned)
32.4 months median follow-up
Primary endpoint = stroke and death within 30 days + target artery ischemic stroke thereafter
Absolute differences in primary endpoint were 7.1% at 1 year, 6.5% at 2 years and 9.0% at 3 years
Optimal risk factor control defined as 4/4 goals met:
- LDL <100 mg/dl
- SBP <140 mmHg
- Fasting blood glucose < 126 mg/dl
- Non-smoking

Optimal RF control went from 16.7% at entry to 36.2% (P<0.001)
Plus 
versus 
n=620

and

Plus 
versus 
n=620

only

only

n=620

4 Years
Primary Aims

- Assess in patients with high-grade asymptomatic stenosis:
  - The treatment differences between medical management and CEA
  - The treatment differences between medical management and CAS

- Primary endpoint:
  - The proportion of patients who experienced any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years.
Secondary Aims

To assess:

- Differences in cognitive function in patients randomized to intensive medical management compared to those randomized to CEA or CAS at 4 years of follow-up.

- Differences in major stroke events at 4-years.

- Treatment interactions by age, sex, severity of carotid stenosis, risk factor control status, and duration of asymptomatic period.
CREST-2 Coordinating Centers

- Imaging Core and Endpoint Adjudication and Cognitive Core
  Mayo Clinic, Rochester, MN
- Cognitive Core
  Columbia University, New York, NY
- Imaging Core and Safety Monitor
  University of Maryland, Baltimore, MD
- Medical Management Core
  Medical University of South Carolina, Charleston, SC
- Surgical Management Committee
  University of California, Los Angeles, CA
- Site Selection Committee
  Mayo Clinic Hospital, Phoenix, AZ
- Statistical and Data Coordinating Center (SDCC)
  University of Alabama, Birmingham AL
- Interventional Management Committee
  Brookwood Medical Center, Birmingham AL
- Clinical Coordinating Center (CCC)
  Mayo Clinic, Jacksonville, FL

08-13-2014
151 Sites
University of Florida Health at Shands

Close to Green-Light/Site Activation

CREST-2 Team

- **Anna Khanna, MD**
  Principal Investigator and Medical Management
- **Brian Hoh, MD**
  Interventionist and Vascular Surgeon
- **Siddharth Wayangankar, MD**
  Interventionist
- **Thomas Huber, MD**
  Vascular Surgeon
- **Teddy Youn, MD**
  Medical Management
- **Rosie Kizza**
  Coordinator
Percent of Target Enrollment by Procedure

As of March 7, 2017

CEA

- 19%
- 81%

CAS

- 22%
- 78%
Trial Definition of High-Grade Stenosis

➤ At least one of the following:
  • End diastolic velocity ≥100 cm/sec or
  • IC/CC peak systolic velocity ratio ≥4.0
  • ≥70% stenosis on MR angiogram or
  • ≥70% stenosis on CT angiogram
Informing clinical judgement

Based on CREST:

- For ages 50-74 years, no favored procedure
- For ages <50 years, CAS is the favored procedure
- For ages >74 years, CEA is the favored procedure
- In CREST asymptomatic patients had few events, so there were wide confidence intervals

*So, the choice of CEA or CAS cannot be mandated in CREST-2.*

Individual patient characteristics and preferences may supersede guidelines.
Selected CEA Exclusions

- Radical neck dissection
- Surgically inaccessible lesions
- Neck anatomy limiting surgical exposure
- Tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel
Selected CAS Exclusions

- Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries
- Type III, calcified aortic arch anatomy
- Angulation or tortuosity (≥90°) of the innominate, common or internal carotid artery
Selected CAS Exclusions

- Excessive or circumferential calcification of the stenotic lesion
- Lesions >30 mm in length, sequential lesions, and narrow-mouth ulcers
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD)
Surgeons given latitude on approach to endarterectomy
## Stenters given some latitude on devices

<table>
<thead>
<tr>
<th>Company</th>
<th>Stent</th>
<th>Embolic Protection Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>RX Acculink®</td>
<td>RX Accunet®</td>
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<tr>
<td></td>
<td>Xact Stent</td>
<td>Emboshield Nav⁶</td>
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<tr>
<td>Boston Scientific</td>
<td>Carotid WALLSTENT™</td>
<td>FilterWire EZ™</td>
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<tr>
<td>Cordis-a Cardinal Health Company</td>
<td>PRECISE PRO RX® Nitinol Stent</td>
<td>ANGIOGUARD® RX Emboli Capture Guidewire</td>
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<tr>
<td>Medtronic/Covidien</td>
<td>Protege® RX</td>
<td>SpiderFX®</td>
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<tr>
<td></td>
<td></td>
<td>MO.MA® Ultra</td>
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</table>
Medical Management

- Patients in both trials will take aspirin 325mg/d for the entire follow-up period (CAS patients will be on DAP pre- and 1 month post-procedure).

- Primary risk factors: systolic blood pressure and LDL cholesterol
  - Target systolic BP <140 mm Hg
  - Target LDL <70 mg/dl
  - Managed by the study neurologist or internist
Medical Management

Secondary risk factor targets:

- <100 mg/dl non-HDL cholesterol
- <7.0% hemoglobin A1C
- >30 min. moderate exercise 3x/week
- Smoking cessation
- Targeted weight management
Covered Medications

- Antiplatelet agents
  - Clopidogrel

- Statin
  - Atorvastatin

- Anti-hypertensive Rx
  - One drug from each major class will be available: diuretic, ACE inhibitor, potassium-sparing diuretic, angiotensin receptor blocker, beta blocker, vasodilator, central alpha agonist, long-acting calcium channel antagonist
BP Management Algorithm

Check BP
Adjust medications as needed

Check BP
Adjust medications as needed

Check BP
Adjust medications as needed

+ atenolol, felodipine, or spironolactone based on $k^+$ and HR

+ chlorthalidone 12.5 mg

lisinopril 10 – 40 mg

No medications
CREST-2
Surgical Management Committee

Committee Members:
- Wesley Moore, Chair
- Thomas Brott
- Richard Cambria
- Peter Henke
- Brajesh K. Lal
- Bruce Perler
- Joseph Rapp
- Robert Hye (deceased)

As of March 7, 2017

361 Total applications

12 Pending
12 Not Approved

337 Approved
CREST-2
Interventional Management Committee

318 Total Applications

- 41 Denied
- 9 Deferred
- 2 Pending
- 123 Conditionally Approved

143 Approved

As of March 7, 2017

Committee Members:
Gary Roubin, Chair
Thomas Brott
Guilherme Dabus
William Gray
Donald Heck
Nick Hopkins
Brian Jankowitz
Tudor Jovin
Barry Katzen
Brajesh K. Lal
Sothear Luke
Jon Matsumura
James F. Meschia
Kenneth Rosenfield
Chris White
Lifestyle Coaching in CREST-2

- Lifestyle management and cardiovascular disease risk reduction will be done using INTERVENT.

- Incorporates SAMMPRIS targets and national guidelines.

- Provides individualized risk factor counseling telephone sessions at regular intervals:
  - twice a month for 12 weeks.
  - monthly thereafter.

- Case Managers at INTERVENT call center, Savannah, GA.
Cognitive Outcomes in CREST-2

**Secondary Aim**
- To compare the changes of cognitive function from baseline to 48 mo. among those in the revascularized cohort with those in the non-revascularized cohort.

**Testing**
- Word list learning
- SF-12
- Word list learning (recall)
- Letter fluency
- Animal naming
- Digit span – forward and backward
- CES-D-4 Depression scale

**Timeline Schedule**
- Base
- 44 day
- 12 mo
- 24 mo
- 36 mo
- 48 mo
Sites are encouraged to evaluate all patients with possible stroke or TIA endpoint with brain MRI unless contraindicated, in which case CT is acceptable.

Brain imaging should be done as close to symptom onset as possible, preferably within the first 2-7 days.

Brain imaging should be completed even if symptoms resolve within 24 hours.

Stroke evaluation should also include a NIHSS.

Common MRI Contraindications

- Metal implant
- Surgical/aneurysm clip
- Deep brain stimulator wire
- Cardiac pacemaker
- Cochlear implant
- Claustrophobia
Sites will send digital copies of CT and/or MRI and any relevant medical records.

- Admission note; Neurology consult; ED admission/triage; ECG; echocardiogram; NIHSS; discharge summary, laboratory reports; physical, occupational and speech therapy notes

- Studies will be centrally read by neuroradiologist at Mayo Clinic Rochester blinded to treatment group assignment.
Stroke Adjudication

- Centralized (Mayo Clinic Rochester).
- Blinded to treatment assignment.
- Uses modern definitions of ischemic stroke and TIA.
- Classifies subtypes of stroke by inferred mechanism.
- Abstraction of information related to stroke severity and in-hospital outcomes.
CMS will include CREST-2 and C2R on the list of Medicare approved facilities/trials/registries posted to the CMS website to ensure facilities and providers are aware that Medicare beneficiaries participating in the study and/or registry are covered by Medicare.

This website is available at:

http://www.cms.gov/Medicare/Medicare-General-Information/MedicareApprovedFacilities/
Actual & Projected Cumulative Enrollment

As of March 7, 2017
## Top CREST-2 Sites

<table>
<thead>
<tr>
<th>Site Name</th>
<th># Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baptist Health, Lexington, KY</td>
<td>33</td>
</tr>
<tr>
<td>Novant Health, Winston-Salem, NC</td>
<td>27</td>
</tr>
<tr>
<td>Cardiovas Assoc/Brookwood, Birmingham, AL</td>
<td>19</td>
</tr>
<tr>
<td>Johns Hopkins Medical Institution, Baltimore, MD</td>
<td>18</td>
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<tr>
<td>Tennova Healthcare, Knoxville, TN</td>
<td>17</td>
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<tr>
<td>Mercy Hospital, St. Louis, MO</td>
<td>17</td>
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<tr>
<td>UPMC Presbyterian, Pittsburgh, PA</td>
<td>16</td>
</tr>
<tr>
<td>Ochsner Health System, New Orleans, LA</td>
<td>15</td>
</tr>
<tr>
<td>Columbia University Medical Center, New York, NY</td>
<td>14</td>
</tr>
<tr>
<td>Washington Adventist Hospital, Takoma Park, MD</td>
<td>14</td>
</tr>
<tr>
<td>North Carolina Heart and Vascular, Raleigh, NC</td>
<td>12</td>
</tr>
<tr>
<td>Prairie Heart/St. John’s Hospital, Springfield, IL</td>
<td>12</td>
</tr>
<tr>
<td>Maine Medical Center, Portland, ME</td>
<td>11</td>
</tr>
<tr>
<td>Massachusetts General Hospital, Boston, MA</td>
<td>10</td>
</tr>
</tbody>
</table>

As of March 7, 2017
% of patients meeting PRIMARY risk factor targets in CREST-2

% of patients in target

Month

SBP
LDL
% of patients meeting SECONDARY risk factor targets in CREST-2

- Smoking
- Physical activity
- HgA1c (diabetics only)
- Weight
• Embolic signals detected in 77/467 (16.5%)
• Absolute annual risk of ipsilateral stroke was 3.62% for those with embolic signals vs. 0.70% for those without embolic signals
Summary

- 2014 guidelines still consider endarterectomy indicated for patients with high degree stenosis and low risk of complications.

- 2014 guidelines consider stenting as only worth considering in patients too high risk for surgery.

- Intensive medical management has proven superiority for symptomatic intracranial stenosis.

- CREST-2 will establish whether it is justified to consider intensive medical management as the preferred treatment for asymptomatic carotid stenosis.
Want to refer a patient?

crest2trial.org

844-956-1826 (toll free)