Asymptomatic Carotid Disease - the CREST-2 trial

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Mayo Clinic Florida
October 3, 2015
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Grant Sponsorship:
NIH – US Public Health Service, NINDS – U01 NS080168
Learning Objectives

- Understand rationale for CREST-2 trial
- Become familiar with CREST-2 trial aims, design, eligibility criteria, and progress with recruitment
- Review 2014 AHA Guidelines recommendations regarding management of asymptomatic carotid stenosis
Population Trends in the Incidence and Outcomes of Acute Myocardial Infarction

Robert W. Yeh, M.D., Stephen Sidney, M.D., M.P.H., Malini Chandra, M.B.A., Michael Sorel, M.P.H., Joseph V. Selby, M.D., M.P.H., and Alan S. Go, M.D.

over the study period. The age- and sex-adjusted incidence of ST-segment elevation myocardial infarction decreased throughout the study period (from 133 cases per 100,000 person-years in 1999 to 50 cases per 100,000 person-years in 2008, P<0.001
Figure 1. Age- and Sex-Adjusted Incidence Rates of Acute Myocardial Infarction, 1999 to 2008.

Error bars represent 95% confidence intervals. MI denotes myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
The Problem
carotid artery disease

1. Cause of 5-10% of all strokes
2. But stroke mortality down by 41% since 2003 per CDC
Rationale for CREST-2
Endarterectomy for Asymptomatic Carotid Artery Stenosis

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study

Objective.—To determine whether the addition of carotid endarterectomy to aggressive medical management can reduce the incidence of cerebral infarction in patients with asymptomatic carotid artery stenosis.

Design.—Prospective, randomized, multicenter trial.

Setting.—Thirty-nine clinical sites across the United States and Canada.

Patients.—Between December 1987 and December 1993, a total of 1662 patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter were randomized; follow-up data are available on 1659. At baseline, recognized risk factors for stroke were similar between the two treatment groups.

Intervention.—Daily aspirin administration and medical risk factor management for all patients; carotid endarterectomy for patients randomized to receive surgery.

Main Outcome Measures.—Initially, transient ischemic attack or cerebral infarction occurring in the distribution of the study artery and any transient ischemic attack, stroke, or death occurring in the perioperative period. In March 1993, the primary outcome measures were changed to cerebral infarction occurring in the distribution of the study artery or any stroke or death occurring in the perioperative period.

Results.—After a median follow-up of 2.7 years, with 4657 patient-years of observation, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53% [95% confidence interval, 22% to 72%]).

Conclusion.—Patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors.

(JAMA. 1995;273:1421-1428)
Combined perioperative events and strokes:
- 6.9% vs. 10.9% at 5 years
- 13.4% vs. 17.9% at 10 years
Medical Management has improved markedly since ACAS and ACST
Medical Management in ACST

Lipid-lowering drug use

![Graph showing the percentage of lipid-lowering drug use over time, with two lines representing different years: one ending at 82% and the other at 80%, starting from 7% in 1991.]
Contemporary Studies
Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment
A Prospective, Population-Based Study

Lars Marquardt, MD; Olivia C. Geraghty, MRCP; Ziyah Mehta, PhD; Peter M. Rothwell, PhD

Stroke 2010;41:e11-e17; originally published online Nov 19, 2009
Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Colin P. Derdeyn, M.D., Tanya N. Turan, M.D., David Fiorella, M.D., Ph.D., Bethany F. Lane, R.N., L. Scott Janis, Ph.D., Helmi L. Lutsep, M.D., Stanley L. Barnwell, M.D., Ph.D., Michael F. Waters, M.D., Ph.D., Brian L. Hoh, M.D., J. Maurice Hourihane, M.D., Elad I. Levy, M.D., Andrei V. Alexandrov, M.D., Mark R. Harrigan, M.D., David Chiu, M.D., Richard P. Klucznik, M.D., Joni M. Clark, M.D., Cameron G. McDougall, M.D., Mark D. Johnson, M.D., G. Lee Pride, Jr., M.D., Michel T. Torbey, M.D., M.P.H., Osama O. Zaidat, M.D., Zoran Rumboldt, M.D., and Harry J. Cloft, M.D., Ph.D., for the SAMMPRIS Trial Investigators*
## Risk Factor Treatment in SAMMPRIS

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>Baseline</th>
<th>4 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Systolic BP</td>
<td>145</td>
<td>134</td>
</tr>
<tr>
<td>Lipids</td>
<td>LDL</td>
<td>97</td>
<td>74</td>
</tr>
<tr>
<td>Glycated hemoglobin in diabetics</td>
<td>Level - %</td>
<td>8.1</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Surgery and Stenting have also improved
Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis

Thomas G. Brott, M.D., Robert W. Hobson, II, M.D.,* George Howard, Dr.P.H., Gary S. Roubin, M.D., Ph.D., Wayne M. Clark, M.D., William Brooks, M.D., Ariane Mackey, M.D., Michael D. Hill, M.D., Pierre P. Leimgruber, M.D., Alice J. Sheffet, Ph.D., Virginia J. Howard, Ph.D., Wesley S. Moore, M.D., Jenifer H. Voeks, Ph.D., L. Nelson Hopkins, M.D., Donald E. Cutlip, M.D., David J. Cohen, M.D., Jeffrey J. Popma, M.D., Robert D. Ferguson, M.D., Stanley N. Cohen, M.D., Joseph L. Blackshear, M.D., Frank L. Silver, M.D., J.P. Mohr, M.D., Brajesh K. Lal, M.D., and James F. Meschia, M.D., for the CREST Investigators†
CREST Experience

30-day event rate for stroke, MI, and death (%)
Markers of Risk
Improving though need double digit HRs

- Silent infarction
- TCD microemboli: HR 2.5 (P=0.02) in ACES
- Ulceration on 3D ultrasound or OCT
- Plaque composition, roughness on ultrasound
- Neovascularization on ultrasound
- Intraplaque hemorrhage on MRI
- Plaque inflammation on PET/CT
The Centers for Medicare & Medicaid Services (CMS) has convened this meeting for the panel to review available evidence on various clinical strategies for the management of carotid atherosclerosis.”
MEDCAC Question #4

- “For persons with asymptomatic carotid atherosclerosis and carotid narrowing (≥ 60% by angiography or ≥ 70% by ultrasound)...

- How confident are you that there is adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy, as compared to BMT alone, to decrease stroke or death in the Medicare population?”

Confidence, Low = 1, Intermediate= 3, High= 5

Mean Score = 2 among 9 voting members
Novant Health is #1

CREST-2 Total Enrollment by Center
December 9, 2014 - September 30, 2015

Novant Health, Winston-Salem, NC
Baptist Health, Lexington, KY
Mercy Hospital, St. Louis, MO
Primary Aims

- In patients with ≥70% asymptomatic stenosis, to assess:
  - The treatment differences between medical management and CEA
  - The treatment differences between medical management and CAS

- Primary endpoint: proportion of patients who experienced any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years.
Definitions for ≥70% Stenosis

► Peak systolic velocity ≥230 cm/sec on Duplex ultrasound plus

► At least one of the following:
  ► End diastolic velocity ≥100 cm/sec or
  ► IC/CC peek systolic velocity ratio ≥4.0
  ► ≥70% stenosis on MR angiogram or
  ► ≥70% stenosis on CT angiogram
Numbers to consider

- Mean internal diameter of the ICA is 5.1 mm in men and 4.7 mm in women

- For the average man
  - 1.5 mm = 70%, the thickness of a penny
  - 1 mm = 80% stenosis
  - ~ 0.5 mm per 10% stenosis!!
Treatment by clinical judgement followed by randomization

S = screening
R = randomization

CAS n = 620
Med n = 620
CEA n = 620
Med n = 620
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

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

Individual patient characteristics and preferences may supersede guidelines.
Selected General 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)
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>Acculink</td>
<td>RX Accunet OR</td>
</tr>
<tr>
<td></td>
<td>Xact Stent</td>
<td>Emboshield Nav6</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Carotid Wallstent</td>
<td>FilterWire EZ</td>
</tr>
<tr>
<td>Covidien</td>
<td>Protege® RX</td>
<td>SpiderFX®</td>
</tr>
<tr>
<td>Medtronic</td>
<td></td>
<td>MOMA</td>
</tr>
<tr>
<td>Cordis</td>
<td>PRECISE® Nitinol Stent</td>
<td>ANGIOGUARD™ Emboli Capture Guidewire</td>
</tr>
</tbody>
</table>
Crest-2 Interventional Management Committee

249 Total Applications

27 Denied
8 Deferred
4 Pending
137 Conditionally Approved

73 Approved

As of September 8, 2015

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

- **Total applications**: 249
- **Pending**: 11
- **Not Approved**: 8
- **Approved**: 230

Committee Members:
- Wesley Moore, Chair
- Thomas Brott
- Richard Cambria
- Robert Hye
- Brajesh K. Lal
- Bruce Perler

As of September 8, 2015
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)
Medical Management

- Patients in both trials will take aspirin 325mg/d for the entire follow-up period (CAS patients will be on dual antiplatelet therapy for 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:

- Non-HDL cholesterol <100 mg/dl
- Hemoglobin A1c <7.0%
- Smoking cessation
- Targeted weight management
- >30 minutes of moderate exercise
- 3 times a week
BP Management Algorithm

At Enrollment: Is SBP <140?

- **YES**
  - IN TARGET
  - Return for Study visit and BP check in 44 days

- **NO**
  - NOT IN TARGET
  - Adjust meds per protocol
  - Return for BP check in 30 days

At 44 day visit Is SBP <140?

- **YES**
  - IN TARGET
  - Return for BP check at required 4-month visit

- **NO**
  - NOT IN TARGET
  - Adjust meds per protocol
  - Return for BP check in 30 days

At repeat 30 day blood pressure checks or at any study follow-up visit: Is SBP <140?

- **YES**
  - IN TARGET
  - Return for BP check at required 4-month visit

- **NO**
  - NOT IN TARGET
  - Adjust meds per protocol
  - Return for BP check in 30 days
Managing LDL

At enrollment:
1. If LDL ≥70, start Atorvastatin 40 mg (if not already on a statin) or increase dose of patient’s current statin, or switch from current statin to atorvastatin.
2. If LDL <70, leave on current statin at current dose.
3. Check AST, ALT & CK.

CAS and CEA patients: Extra dose of atorvastatin 80 mg or maximum dose of patient’s current statin night before procedure.

At 44 days recheck LDL if enrollment LDL ≥70:
- If LDL <70, no change.
- If LDL still ≥70, increase atorvastatin to 80 mg (40 mg in Asians) or increase dose of patient’s other statin to maximum dose.

LDL values within 90 days of enrollment are acceptable.

Next visit at day 44.
# Equivalent Doses of Statins

## Relative LDL-lowering Efficacy of Statin-based Therapies (mg)

<table>
<thead>
<tr>
<th>Atorva</th>
<th>Fluva</th>
<th>Pitava</th>
<th>Lova</th>
<th>Prava</th>
<th>Rosuva</th>
<th>Vytorin</th>
<th>Simva</th>
<th>LDL lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>1</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
<td>10</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>80</td>
<td>80</td>
<td>5</td>
<td>10/10</td>
<td>40</td>
<td></td>
<td>41%</td>
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<tr>
<td>40</td>
<td></td>
<td>10</td>
<td>10/20</td>
<td>80</td>
<td>10/40</td>
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<td>47%</td>
</tr>
<tr>
<td>80</td>
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<td></td>
<td></td>
<td>40</td>
<td>10/80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63%</td>
</tr>
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</table>
Lifestyle Coaching in CREST-2

- INTERVENT provides risk factor counseling telephone sessions:
  - twice a month for 12 weeks
  - monthly thereafter
CMS will include CREST-2 and C2R on the list of Medicare approved facilities/trials/registries posted to the CMS website.

Because CREST-2 is covered under a national coverage determination, the process does not require study sites to get approval from the Medicare Administrative Contractors.
Registry Take-Home Points

- The C2R has been designed as a quality control activity, to enhance enrollment and safety of CREST-2.

- Approval of the C2R has been obtained by NINDS and CMS.

- The C2R provides a pathway for CAS in conventional-risk and selected high-risk symptomatic and asymptomatic patients (until the primary results of CREST-2 are published)
CREST-2 Centers Approved to Enroll
First patient enrolled December 9, 2014.
Want to refer a patient?

www.crest2trial.org

844-956-1826 (toll free)
Current randomized trials

- ACT-1
- ACST-2
- SPACE-2
- ECST-2
- CREST-2
Join us in exploring a potential new option for carotid artery disease

ACT I is a new clinical study in carotid artery disease. The ACT I study will compare carotid artery stenting (CAS) to carotid endarterectomy (CEA) surgery for the treatment of patients who are symptom-free and at standard risk for surgery.

Enrollment for the ACT I study is now underway. Up to 2,058 patients will be enrolled in at least 50 sites throughout North America. More information about ACT I can be found on this Web site.

Click the buttons below to find more information about the ACT I study.

Patients and Public
- Learn more about ACT I and carotid artery disease

Healthcare Professionals
- ACT I background, rationale, trial sites, and resources

Investigators
- ACT I trial updates, news, information, and enrollment materials
- Password-protected resources

1454 Patients
The Asymptomatic Carotid Surgery Trial 2

Background and aims of the ACST-2 study.

BY SUMAIRA MACDONALD, MBChB (COMM.), FRCP, FRCR, PhD,
AND ALISON W. HALLIDAY, MS, FRCS

1921 Patients
Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy: SPACE2 – a three-arm randomised-controlled clinical trial

T. Reiff¹, R. Stinke³, H. H. Eckstein³, G. Fraedrich⁴, O. Jansen⁵, H. Mudra⁶, U. Mansmann⁷, W. Hacke¹*, P. Ringleb¹, and for the SPACE2-Study Group


Halted because of poor enrollment
The new ECST-2 is a randomized clinical trial that will compare medical therapy alone with CEA or CAS for patients with asymptomatic and symptomatic carotid artery stenosis using a new measure called the Carotid Artery Risk Score.

BY ROLAND L. FEATHERSTONE, PHD, AND MARTIN M. BROWN, MA, MD, FRCP

103 Patients
...and what will happen in the future?
The SPRINT trial: A major advance in treating high blood pressure

POSTED SEPTEMBER 16, 2015, 11:53 AM

Deepak Bhatt, MD, MPH, Editor in Chief, Harvard Heart Letter
Gore Hybrid Stent

*CAUTION: Investigational Device. Limited by United States Law to Investigational Use only.
Transcarotid Stenting with Dynamic Flow Reversal

The new Silk Road procedure draws upon proven surgical techniques to protect the brain from stroke risk during carotid artery stenting. It allows physicians to deliver a stent directly from the neck, which is intended to avoid complications associated with starting from the femoral artery in the groin, which is typically used in carotid artery stenting procedures. To provide protection for the patient’s brain during the entire procedure, the ENROUTE® Transcarotid Neuroprotection System temporarily reverses blood flow in order to move any debris away from the brain.

*Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician.

IT’S ALL ABOUT STROKE
A potential complication of stenting for carotid artery disease is a stroke during the procedure itself. A stroke can be caused by plaque that is inadvertently dislodged. There are two ways plaque can dislodge. ...+

MICROEMBOLISM MATTERS
The Silk Road Procedure is designed to protect the brain from most sizes and types of emboli. Small emboli, not large enough to cause a major stroke, can still cause a small brain infarction and impact cognitive function. ...+

ENDOVASCULAR ADVANTAGE
The Silk Road procedure requires a smaller incision than traditional carotid artery surgery (CEA) and can be performed using local anesthesia. Local anesthesia only requires medicating the local area of treatment. ...+
Classification of Recommendations

- Class I: … evidence, general agreement, or both that a given procedure or treatment is useful and effective.

- Class II: …there is conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment.

- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

- Class III: …evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful.
Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials
- Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies
- Level of Evidence C: Consensus opinion of experts
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 compare 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
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.
Thanks for your attention
And hope the weather behaves!