Advances in Carotid Artery Disease

The Kentucky Trial, CREST, and Beyond

Southern Kentucky AHEC: Meeting the Challenges to Improve Cardiovascular Outcomes

Goals for This Presentation

• Review our approach to the diagnosis and management of carotid artery disease.
• Create an awareness of the groundbreaking single center and collaborative work that BHL has published over the last 15 years.
• Review our current strategy for the treatment of asymptomatic carotid artery disease... especially in reference to the CREST 2 TRIAL.

Stroke Facts

• Fourth Leading Cause Death in US
• Leading Cause of Long-Term Disability
• 20% are Related to Carotid Artery Disease
• 2/3 of These Affect Previously Asymptomatic Patients
Symptomatic Study Findings

- NASCET and ECST Trials ... mid-1980s.
- Pooled analysis of approximately 3200 patients.
- CEA beneficial for further stroke prevention over 5 years with AAR of 16% and NNT of 6.3
- Medical therapy was ASA!

Medical Therapy vs. Revascularization for Asymptomatic Carotid Disease

- European Asymptomatic Study (ACST)
  - 3120 Patients
  - 60-99% Stenosis
  - Published 2004
- North American Asymptomatic Study (ACAS)
  - 1662 Patients
  - 60-99% Stenosis
  - Published 1995
Asymptomatic Study Findings

- Absolute Reduction of Stroke Risk is About 1% per year for 5 years (versus BMT)
- Degree of CAS Did Not Significantly Affect Benefit from CEA
- Women (probably) Benefit less than Men
- Overall NNT to Prevent Stroke is 33

CLINICAL STUDIES

Carotid Angioplasty and Stenting vs. Carotid Endarterectomy: Randomized Trial in a Community Hospital
By William H. Barks, MD, Mark R. Mitcheel, MD, FACC; Michael E. Jones, MD, FACC; and Thomas C. Cudina, MD, Linda Berdin, RN, Louisville, Kentucky
JACC 38: 1589-1595, 2001

CAROTID ANGIOPLASTY AND STENTING VS CAROTID ENDARTERECTOMY FOR TREATMENT OF ASYMPTOMATIC CAROTID STENOSIS: A RANDOMIZED TRIAL IN A COMMUNITY HOSPITAL
Neurosurgery 54: 318-324, 2004

EDITORIAL COMMENT

Another Nail in the Coffin of Carotid Endarterectomy*

Christopher J. White, MD, FACC
New Orleans, Louisiana

*The randomized carotid stent vs. carotid surgery trial reported by Brooks et al. in this issue of the Journal is a notable accomplishment in several aspects. By reporting results in 101 patients, it becomes the largest randomized carotid artery stent vs. carotid endarterectomy published to date. It is also an excellent example of team building with a surgeon, cardiologist, and neurologist to optimize patient care.
Among Patients with Symptomatic or Asymptomatic Carotid Stenosis, the Risk of the Composite Primary Outcome of Stroke, MI, or Death, did not differ significantly between CAS and CEA.
CREST 10 Year Follow-up

N Engl J Med 2016; 374; 1021-1031

CREST LONG-TERM RESULTS

CONCLUSIONS
Over 10 years of follow-up, we did not find a significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of perioperative stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of perioperative (ipsilateral) stroke also did not differ between groups. Funded by the National Institutes of Health and Abbott Vascular Solutions, CREST Clinical Trials.gov number. NCT01004712.

CREST Primary End-Point Long Term

- Primary Composite End Point
- Stenting
- Endarterectomy

- Follow-up (yr)
- 0 1 2 3 4 5 6 7 8 9 10
- 0 10 20 30 40 50 60 70 80 90

- Events
- Stenting: 120 130 140 150 160 170 180 190 200 210
- Endarterectomy: 120 130 140 150 160 170 180 190 200 210
Revascularization Outcomes

- For short and long term outcomes, single center (The Kentucky Trial) and multicenter (CREST) trials suggest that revascularization with CEA vs CAS has reached an equipoise in validated centers.

- NOW, what about the “other” treatment option??

Results of BMT Alone for CAS

Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis
Results of a Systematic Review and Analysis
Ann L. Albers, PhD, MBBS, FRACP

Abstract: Significant advances in vascular disease medical interventions have led to large randomized trials for symptomatic severe carotid stenosis with failures and non-inferiority of a medical benefit. In this systematic review and meta-analysis of published data, it was found that type of antithrombotic and antiplatelet use significantly varied from the data collected, with results which overall suggests improvement in outcomes.” The 2010-2012 American Heart Association guidelines recommend that medical intervention alone is no longer a viable treatment strategy for symptomatic severe carotid stenosis, as medical intervention alone is now shown to confer a substantially lower risk of periinterventional death or major stroke benefit from additional carotid surgery.”

What is BMT?

- ACAS: Aspirin
- ACST: Evolved but Largely Aspirin
- Little use of
  - Theinopyrides
  - Statins
  - ACE Inhibitors
  - ARBs
Crest-2 Challenges

• ASYMPOMATIC patients make up 90% of the population undergoing CEA/CAS.
• Does revascularization offer any advantage over modern medical management in patients with carotid disease?

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.
Asymptomatic

- No stroke or stroke-like symptoms ipsilateral to the stenosis within 180 days of randomization.

≥ 70% Stenosis

- PSV ≥ 230 cm/second on DUS and:
  - EDV ≥ 100 cm/second on DUS, or
  - ICC PSW/CCC PSV ≥ 4.0 on DUS, or
  - ≥ 70% stenosis on MR angiogram, or
  - ≥ 70% stenosis on CT angiogram.

CREST-2 Parallel Study Design

(n = 1,340 in each trial)

- CAS + Medical
  - n = 620
- Medical
  - n = 620

- CEA + Medical
  - n = 620
- Medical
  - n = 620

Endpoint:

- All-cause death in first 30 days and (reversible) stroke/transient ischemic attack for 4 years.
Primary Outcome

Composite of all stroke and death within 30 days of randomization and ipsilateral stroke thereafter up to 4 years.

Cognitive Outcome

Is the change of cognitive function from baseline to 48 months no worse among those in the MEDICAL cohort compared to the CEA/CAS cohorts?

Is the change of cognitive function a surrogate for TIA's or small DWI infarcts?

Protocol

Observer-blinded endpoint.

5 year recruitment period.

Length of follow-up to at least 2 years after last patient is randomized.

~ 120 sites in North America (and beyond?).
Which trial? Which procedure?
Based on data from CREST:

- For ages 50-74, no favored procedure as HR for Stroke and Death = 1.03, 95% CI, 0.44 to 2.44.
- For ages < 60 years, CAS is the favored procedure.
- For ages > 74 years, CEA is the favored procedure.
- Caveat: in CREST, asymptomatic patients had few events, and so there were wide confidence intervals about the point estimates comparing CEA and CAS.

Accordingly, choice of CEA or CAS cannot be mandated -- individual patient characteristics and preferences may supersede guidelines based upon patient age.

Selected CAS Exclusion Criteria

- 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 and common carotid artery.
- Excessive or circumferential calcification of the stenotic lesion.
- Lesions > 20 mm in length, sequential lesions, and narrow-mouth ulcers.
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD).

Selected CEA Exclusion Criteria

- Radical neck dissection.
- Surgically inaccessible lesions.
- Adverse neck anatomy that limits surgical exposure.
- Presence of tracheostomy stoma.
- Laryngeal nerve palsy contralateral to target vessel.
**Medical Management:**

**SAMMPRIS model and Team**

- Patients in both trials will take aspirin 325 mg/day for the entire follow-up period (CAS patients will also take clopidogrel per protocol).

- Primary risk factors (systolic blood pressure and LDL) will be managed by the study neurologist according to predefined protocols targeting a systolic blood pressure < 140 mmHg (< 130 mmHg if diabetic) and LDL < 70.

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**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.

Recent BHL Carotid Imaging Studies, '12-'14
Intravascular Frequency-Domain Optical Coherence Tomography Assessment of Carotid Artery Disease in Symptomatic and Asymptomatic Patients

Michael R. Jones, MD; Guilherme F. Arismendi, MD; Carlo A. Corona II, MD; William H. Ericksen, MD; Stephen J. Garey, PhD; Christian K. Barrey, MD; Yousif Fajfar, MD; Moreno C. Buceri, MD, PhD; Marco A. Comi, MD, PhD

Results: Focus with intravascular ultrasound showed that visualized features were more common in symptomatic than in asymptomatic plaques (p = 0.001). There was a significant difference in the incidence of these features between plaque with rupture (1190 vs 582) and thrombus (167 vs 110, p < 0.001). Conversely, no plaque rupture was noted in patients with symptomatic plaques (10.84 vs 10.38, p = 0.28). The association between the degree of stenosis and plaque morphology was confirmed.

OCT Derived High Risk Plaque Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Stenosis area % measured.</td>
</tr>
<tr>
<td>B</td>
<td>Stenosis area % measured.</td>
</tr>
<tr>
<td>C</td>
<td>Stenosis area % measured.</td>
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<tr>
<td>D</td>
<td>Stenosis area % measured.</td>
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<tr>
<td>E</td>
<td>Stenosis area % measured.</td>
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<tr>
<td>F</td>
<td>Stenosis area % measured.</td>
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Whom do we Screen?

ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease


Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography

Class III: No Benefit

1. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. (Level of Evidence: C)

Class IIa

1. It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. (Level of Evidence: C)

Class IIb

2. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first-degree relative of atherothrombotic manifested before age 60 years, or a family history of ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (Level of Evidence: C)
CREST 2 INVESTIGATORS

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Why should I Refer to CREST 2 ?

• The study will define the management of asymptomatic carotid artery disease for the next 30 years
• Research initiatives of this sort are important in advancing “cutting-edge” neurovascular care at BHL
• It’s just the right thing to do

Why should I refer to CREST 2 ?

• You may need a carotid or heart procedure, so you REALLY want to stay on our good side.