SVIN: Update on CREST-2 Trial

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October 25, 2013
Disclosures

- Edwards Lifesciences Corporation – Consultant
- Daiichi-Sankyo – Honorarium
Outline

- CREST-2 Research Plan
- FDA
- NINDS
- CMS
- CED
- Input from audience
Intensive Medical Management

compared to

Carotid Endarterectomy or Carotid Stenting plus

Intensive Medical Management

Grant # U01 NS080168 – Clinical Coordinating Center
Grant # U01 NS080165 – Statistical and Data Management
~ 140,000 carotid revascularizations (CEA and CAS) yearly in the US.

Annual US costs for CEA ~ $21 Billion
- CAS costs are comparable on a per case basis.

“Do the benefits of these two procedures persist?”
Background

- For 1181 asymptomatic CREST patients, the primary endpoint was similar in CAS compared to CEA (5.6% vs. 4.9%).

- Perioperative stroke and death rates were low, within the AHA Guideline-recommended range of < 3% for asymptomatic patients (2.5% for CAS and 1.4% for CEA).

“RCT needed to compare CAS and CEA to intensive medical management.”
Primary Aims

In patients with $\geq 70\%$ 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 PSV/CCC PSV ≥ 4.0 on DUS, or
  - ≥ 70% stenosis on MR angiogram, or
  - ≥ 70% stenosis on CT angiogram.
Primary Outcome

- Composite of all stroke and death within 30 days of randomization and ipsilateral stroke thereafter up to 4 years.
CREST-2 Parallel Study Design

(n = 1,240 in each trial)

S → R → CAS + Medical
n = 620

S → R → Medical
n = 620

S → R → CEA + Medical
n = 620

Endpoint

Endpoint = all stroke & death in first 30 days and ipsilateral stroke thereafter up to 4 years.
Primary Statistical Analysis

- Intention-to-treat.
- Superiority assessment of differences in event rate at 4-years.
- 85% power to detect differences in either trial:
  - 3.6% CEA/CAS versus 8.4% medical (1.2% per year)
  - 3.6% CEA/CAS versus 0.8% medical
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 < 50 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 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.
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 ($\geq 90^\circ$) 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).
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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.
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.
Covered Medications

- **Antiplatelet agents**
  (clopidogrel)

- **Anti-hypertensive Rx**
  (one drug from each major class will be made available: diuretic, ACE inhibitor, potassium-sparing diuretic, angiotensin receptor blocker, beta blocker, vasodilator, central alpha agonist, long-acting calcium channel antagonist)

- **Statin**
  (atorvastatin)
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 TIAs or small DWI infarcts?
Credentialing

Criteria for procedural (CEA/CAS) credentialing include:

- Low complication rate.
- Use of standard techniques.
- Avoidance of erroneous techniques.
- Submit 50 consecutive cases (CEA or CAS).
CEA and CAS must have been performed in asymptomatic patients with combined rate of stroke and death <3%.

Can seek credentialing in EITHER or BOTH procedures.
Interventional Management Committee

Draft Roster

➢ Thomas G. Brott, MD – ExOfficio
➢ James Meschia, MD
➢ Gary S. Roubin, MD, PhD – Chair
➢ William Gray, MD
➢ Ricardo Hanel, MD
➢ Kenneth Rosenfield, MD
Surgical Management Committee
Draft Roster

- Thomas G. Brott, MD – ExOfficio
- Wesley S. Moore, MD – Chair
- B.K. Lal, MD
- Two CREST-2 site investigators who rotate on 2-year basis
Site Selection Committee
Draft Roster

- Thomas G. Brott, MD – ExOfficio
- Bart Demaerschalk, MD – Chair
- Virginia Howard, PhD
- Frank Veith, MD
- Nils Wahlgen, MD
Ideally, we should incorporate advances into the protocol as they become feasible, and when the data available support safety and effectiveness.

*Potential examples include:* 
- Proximal occlusion with flow reversal as an embolic protection strategy independent of type of stent 
- Mini incision CEA 
- Filtered stents 
- Hybrid stents (combined open and closed cell designs)
Conclusion

- CEA, CAS, and medical treatments have all improved since ACAS and ACST.

- CREST-2 will test these 3 options for patients with asymptomatic carotid artery disease.

- The results will change practice for the coming decade.
traffic at 2:30 PM, Washington, D.C., day 2 of the Federal Government shutdown 2013
IDE application submitted 9/25

Abbott: Acculink and Xact stents

Boston Scientific: Wallstent

Medtronic: MoMA

Opportunity to mix and match

Up to $5M to maintain IDE at 120 ctrs
NINDS

- NOGA (Notice of Grant Award) cannot be issued until the IDE is approved

  (and when NINDS has the dollars?)
CAS for conventional risk patients is not re-imbursed

CREST-2 interventionist-leadership concerned with decline in operator experience

CED (Coverage under Evidence Development) – hybrid RCT/registry
CMS, NINDS, FDA, AHRQ, FDA, Industry, physician stake-holders engaged

“...with the goal of carefully expanding coverage for stenting in a way that supports CREST-2...The aim is for the coverage decision to be open for reconsideration by the end of the year”

Sean Tunis, Center for Medical Technology Policy, October 26, 2013
CED: *points of contention*

- Asymptomatics and symptomatics?
- High risk too?
- CREST-2 eligibles outside CREST-2?
- If yes, how many?
- Oversight
Input from audience

➢ Load of atorvastatin for CEA?
➢ Load of atorvastatin and clopidogrel for CAS?
LA peak systolic velocity ≥230 cm/second on DUS,

**plus** confirmatory findings of an end diastolic velocity of ≥100 cm/second or internal carotid/common carotid ratio of PSV ≥4.0 on DUS or ≥70% stenosis observed on MRA or on CTA will be required, or

**Or**, conventional angiography documenting ≥70% stenosis.
Thanks to our CREST partners...and to those who will be participating in CREST-2

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