

Is CREST-2 a Worthwhile Use of Precious Resources?

***Another Failed NIH- Funded Study:
CREST-2 Is Coral Redux (or Worse)!***

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

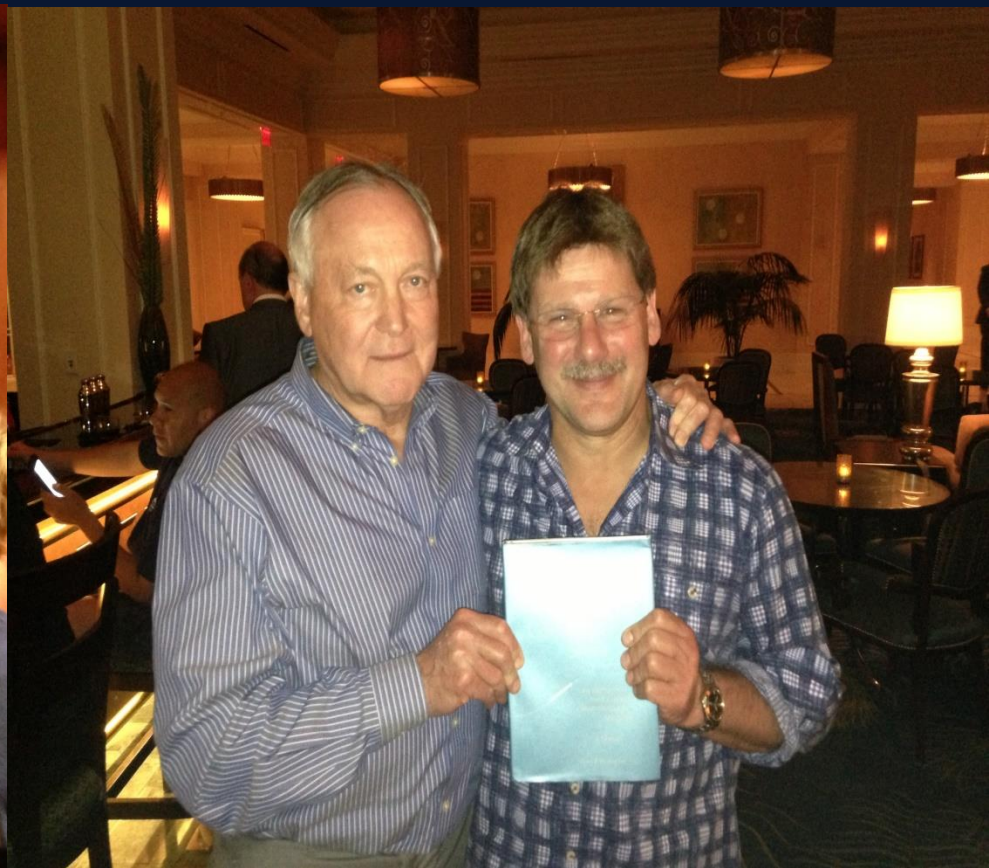
Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria
- Major Stock Shareholder/Equity
- Royalty Income
- Ownership/Founder
- Intellectual Property Rights
- Other Financial Benefit

Company

- None
- Abbott, Bard, TriVascular, CSI, Boston Scientific, Spectranetics
- None
- None
- None
- None
- VIVA Board Member

This Debate....







Questions as We Consider CREST-2

- Is there a good reason for this study?
- What is the existing evidence for CEA or CAS, & “evidence” for Medical Rx?
- Given existing evidence, should CREST-2 be the definitive/ONLY answer?
- C-2 unbiased; & answer “the question”?
- CAS operators treated fairly before C-2?
- Is C-2 “the CORAL of the Carotids”, and is this *intentional*?

CAS Facts/ Caveats

- CAS results continue to improve
- Excellent patency ($\geq 98\%$ @ 4 years)
- Excellent stroke prevention (98% 4yr)
- LOW ($<1\%$) peri-procedural major stroke rates
- Minor strokes: ~ all \leq NIHSS 1 @ 3 mon.
- 2 North American RCT's: CAS \approx CEA
- Results better with experienced operators & good case selection

CAS is WELL-STUDIED prospectively:

>50,000 patients with independent neurologic adjudication in IDE, Randomized, and Post-Marketing “Real World Trials” in patients with *obstructive* ($\geq 80\%$ Asx) carotid artery disease

What About CEA?

- In the 3 major *prospective, adjudicated* randomized trials of CEA vs. Medical Rx, CEA was superior to medical therapy in both symptomatic and asymptomatic patients with *obstructive* carotid artery disease
- CEA continues to perform well in CEA vs. CAS randomized trials, with CEA \approx CAS in North American RCT's

Medical Therapy & Risk Factor Modification for Carotid Disease

- Should be maximized for ALL patients!
- Med Rx alone is best for some patients
- Medical Rx and revascularization are *complimentary*, NOT *mutually exclusive*
 - Therapy should be *individualized* to each patient (especially those with \geq 80% stenosis)

Medical Therapy for Carotid Disease

- There is *NO* evidence demonstrating superiority of Medical Rx > intervention in patients with *obstructive* carotid dz.
- Existing “data” is in patients with nonobstructive disease and in observational studies w/o adjudication
- There are strong statements made regarding “success” of medical Rx without appropriate supporting data

2. BACKGROUND AND RATIONALE

2.1 Rationale

Carotid revascularization for asymptomatic carotid stenosis by CEA or CAS is common and costly. In 2007, there were an estimated 3.1 such procedures per 1,000 Medicare enrollees,¹ with the ratio of CEA to CAS of 4.2:1.0. Annual U.S. costs for CEA are about \$21 billion² and CAS are comparable in cost.³ The rationale for incurring large national costs for revascularization of asymptomatic patients is based on the results of ACAS⁴, ACST⁵, and CREST,⁶ all of which were done without comparison to modern intensive medical management. In ACAS and ACST primary event rates in the medical group were ~ 2% per year. More recently, (2002 to 2009) the population based Oxford Vascular Stroke Study followed 1,153 patients with at least 50% carotid stenosis and an average age of 75 years. With the incorporation of modern management of risk factors, the average annual ipsilateral stroke rate was only 0.34% (95% CI, 0.01 - 1.87).⁷ Two other large contemporary studies also reported stroke rates of ~ 1% per year on modern medical therapy.^{8,9} More recently, a trial in patients with atherosclerotic intracranial stenosis, SAMMPRIS,¹⁰ showed that the stroke rate for patients on intensive medical management was ~ 50% lower than similar patients in WASID who were treated with standard medical therapy.¹¹

2.2 Supporting Data

CREST-2 is needed to compare CEA and CAS to intensive medical management in

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Stroke

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Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic “Severe” Carotid Stenosis

Results of a Systematic Review and Analysis

Anne L. Abbott, PhD, MBBS, FRACP

(Stroke. 2009;40:e573-e583.)

Slide courtesy of Mehdi Shishehbor

Method

Method

Literature Search

A Medline literature search was performed for prospective studies of direct imaging identified nonoperated, angioplasty/stenting-free, asymptomatic severe (nonsubcategorized 50% to 75%+) proximal ICA stenosis with sufficient original data to calculate an average annual patient rate of stroke (fatal/nonfatal infarct/hemorrhage). To

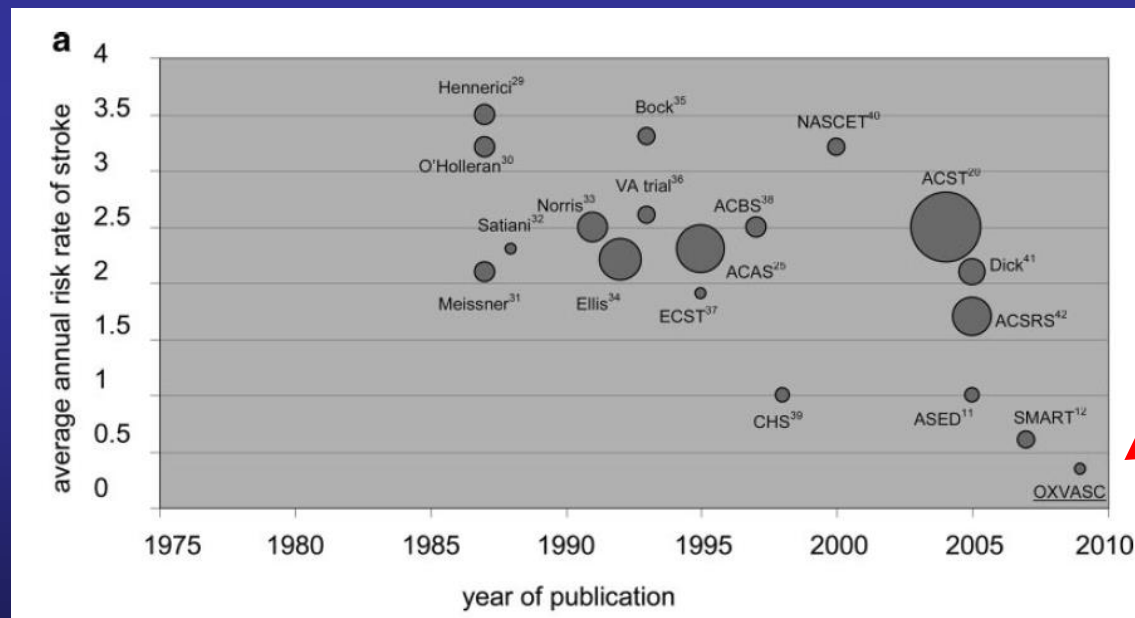
.....asymptomatic severe (nonsubcategorized 50% to 75% +).....



Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment : A Prospective, Population-Based Study

Lars Marquardt, Olivia C. Geraghty, Ziyah Mehta and Peter M. Rothwell

Conclusions—In the first study of the prognosis of $\geq 50\%$ asymptomatic carotid stenosis to be initiated in the last 10 years, the risk of stroke on intensive contemporary medical treatment was low. Larger studies are required to determine whether this apparent improvement in prognosis is generalizable. (*Stroke*. 2010;41:e11-e17.)



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Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis
on Best Medical Treatment : A Prospective, Population-Based Study
Lars Marquardt, Olivia C. Geisler, et al. **Rothwell**

Of the 1153 imaged patients, 33 patients had $\geq 50\%$ stenosis of
at least 1 carotid artery. Of these 33 patients, 10% asymptomatic carotid stenosis, 75 present-
symptomatic carotid stenosis, and 15% asymptomatic carotid stenosis.

..... the majority of patients had only 50% to 69%
stenosis, with about a third of our patients having an asymp-
tomatic carotid stenosis of 70% to 99%.

What has Happened with CAS Before CREST- 2?

- There are NO ongoing postmarketing CAS registries (CMS denials to cont.)
- CAS remains severely restricted by CMS (despite FDA approval > 12 years)
- CAS operators now have MUCH less experience and maintenance of skills, AND may be more likely enroll (inappropriately?) to have access
- All “while we wait for CREST -2”

Is CREST-2 a Fair Study?

Primary Endpoint



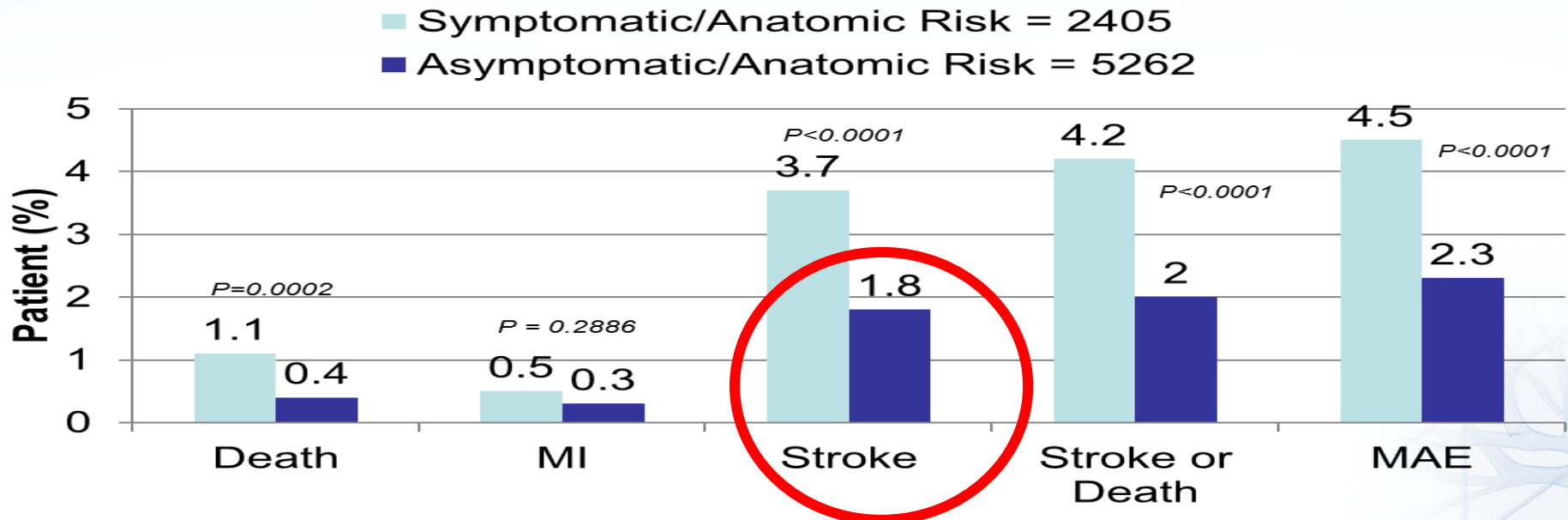
- ▶ The Primary Endpoint of CREST-2 is the proportion of patients who experienced any stroke (WHO definition) or death within 44 days of randomization OR ipsilateral ischemic stroke thereafter up to 4 years (estimated by Kaplan-Meier survival function).

Which group of asymptomatic patients w/ 70% is likely to have more small strokes within 30 days of randomization, AND is an NIHSS=2 after procedure the same as late stroke?

Is CREST-2 a Fair Study?-2

- Asymptomatic patients with anatomic risk FOR CEA are EXCLUDED from CAS!

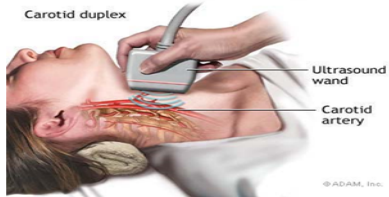
Major Adverse Events to 30 Days: By Symptom Status and Anatomic Risk



Is CREST-2 Balanced? -3

Patient Inclusion

CREST-2 criteria for $\geq 70\%$ 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 peak systolic velocity ratio ≥ 4.0
- $\geq 70\%$ stenosis on MR angiogram or
- $\geq 70\%$ stenosis on CT angiogram
- $\geq 70\%$ stenosis by angiography

Q: Any Risk that many low risk patients may be enrolled?

Q2: Do we think equal % of $>90\%$ stenosis will be enrolled?

SO... For CAS, CREST- 2:

- Excludes patients best suited for CAS
- Comes at a time of *forced* reduction in operator experience (~ONLY in CREST2)
- Does not measure cranial nerve injuries
- Includes 1^o low event risk patients
- Counts early small post-procedure events the same as future major strokes
- Has FEW CAS leaders participating
- Is mandated despite flawed rationale & ↑↑ CAS & CEA true data, ~NONE Med Rx

Predictions for CREST -2

- It will enroll slowly; with ↑ “crossovers”
- There will be significantly more patients with 70-80% lesions than 80-99%
- Will have poor “buy in” from true leaders in the field
- ~Performed by low volume operators, in a study which appears biased against CAS
- Holds CAS “hostage” while showing what CMS and CREST2 organizers want it to show

CREST- 2



**BAAAD,
BAAAAAD
STUDY!!**

CREST 2 may supply additional data, but should not stop access to or alone define carotid revascularization.

Thank You for Your Attention!

