Navigating CREST-2

Multispecialty Insights into Carotid Care

Sponsored by an educational grant from Medtronic

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Faculty Disclosures

- **Guillerme Dabus, MD, FAHA** has nothing to disclose in relation to this activity
- **William Gray, MD, FACC, MSCAI**
  Consultant: Contego Medical; Medtronic
- **Sean P. Lyden, MD, FACS**
  Consultant: Abbott; BD; Boston Scientific; Contego Medical; Cook; Cordis; Endologix; Inspire MD; Medtronic; Rapid Medical; Shockwave; Surmodics; Penumbra; Vivasure; Nectero; Reflow; Stock options: Inspire MD and Centerline Biomedical; Reflow; VIVA Physicians, Board Member; Research Studies: Abbott; Endologix; Cook; Surmodics; W.L. Gore; Terumo Aortic; NIH; Boston Scientific; Merit; Contego Medical; Inspire MD; Reva Medical; Penumbra; Medalliance; Nectero
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Disclosures

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Learning Objectives

- Review the evolution of carotid revascularization evidence
- Evaluate the design, outcomes, and limitations of CREST-2
- Assess results from the latest generation of carotid trials

CREST-2 = Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis.

Introduction: History of Landmark Carotid Trials

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Agenda

- History of carotid trials in the 90s looking at CEA vs medical management
- In the 2000s looking at CAS vs CEA
- Device, technique, and knowledge have continued to advance

Stroke

- Second leading cause of death globally
- Leading cause of disability
- 87% due to ischemic etiology (≈15%-20% related to carotid disease)

- Someone dies of a stroke every 3.7 minutes
- ≈390 deaths from stroke each day

- Heart Disease and Stroke Statistics
  2019 Update from the American Heart Association

65y Male with DM, CAD, and asymptomatic carotid bruit on good medical therapy. “Doc, what should I do, and what are my options?”

Proximal ICA - PSV 490 EDV 263

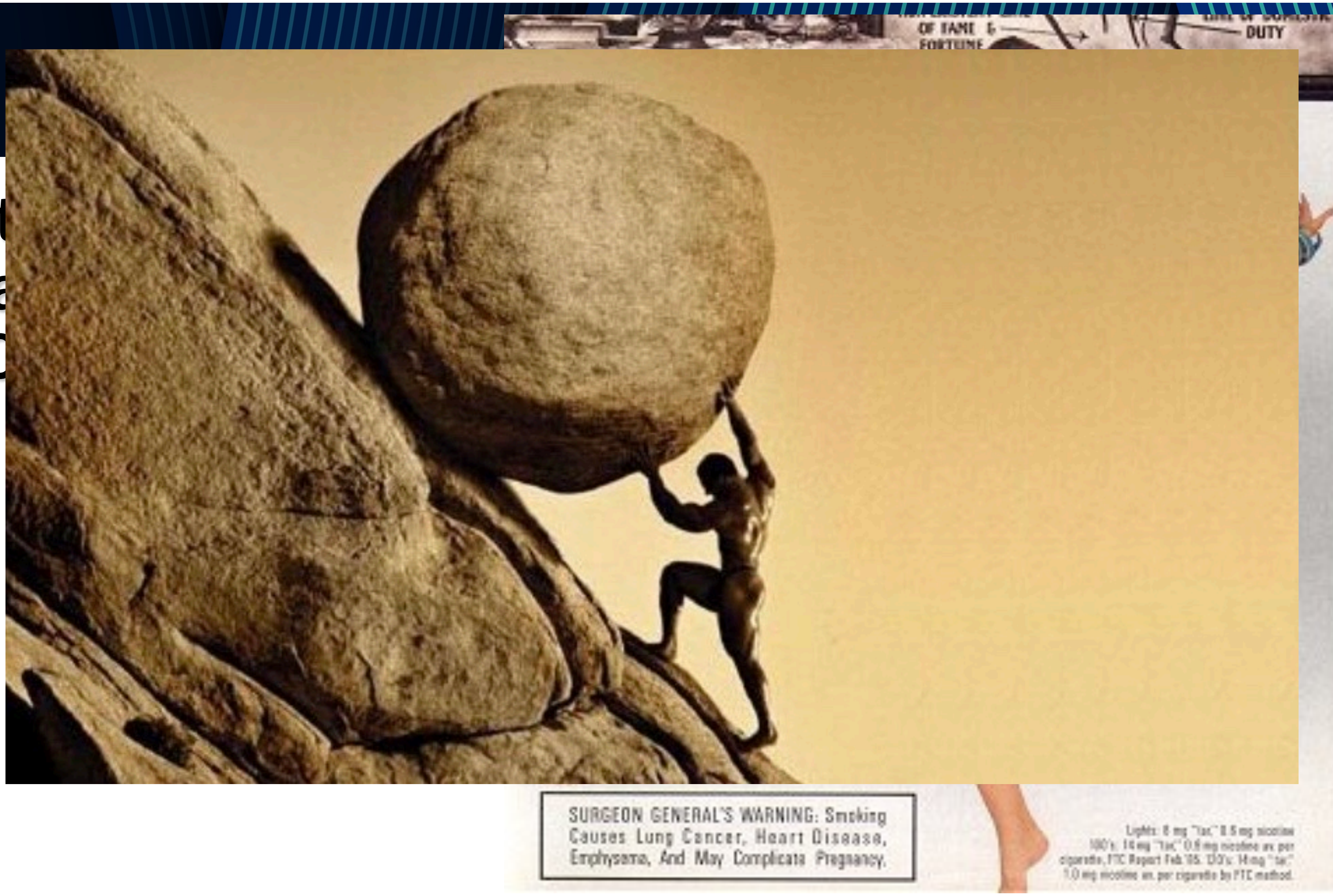
Carotid Artery Disease
Goal of Therapy

- Am I providing best therapy to prevent stroke, death, disability, and morbidity for my individual patient?
- Is this the therapeutic option my patient prefers?

- Answers to these questions are not always clear, and consensus has historically been lacking both within and across specialties

- More recent evidence may provide more clarity!

Carot
Disea
1990



Clinical Background: Status in Late 1980s-90s

Annual stroke rates with Carotid Stenosis (1990s)*

- Symptomatic 70%-99% 13%/yr
- Symptomatic 50%-69% 4.4%/yr
- Asymptomatic 60%-99% 2-2.5%/yr

**Recent data indicate much lower rate for Asymptomatic on OMT*

- ➢ **Carotid stenosis: Major cause of ischemic stroke**
- ➢ **CEA proposed to reduce embolic risk by plaque removal**
- ➢ **RCTs undertaken comparing CEA to medical therapy**

Therapy for Stroke Prevention RCTs: Revasc (CEA) vs Med Rx

Symptomatic High-risk **None**	Asymptomatic High-risk **None**
Symptomatic Standard-risk **NASCET** **ECST**	Asymptomatic Standard-risk **ACAS** **ACST 1**

VA Trial

NASCET: Symptomatic (TIA, Minor Stroke) Outcomes by Stenosis Severity

Stenosis	Medical Therapy	CEA	Absolute Benefit (Absolute Risk Reduction)
70%–99%	≈26% ipsilateral stroke	≈9%	≈17% ARR
50%–69%	≈22%	≈16%	≈6% ARR
<50%	Low	No benefit	—

CONCLUSIONS

- 70%–99% stenosis: Large absolute stroke risk reduction w/CEA
- 50%–69% stenosis: Moderate benefit
- <50% stenosis: No benefit or harm

CEA: Randomized Clinical Trials (Historical)

<u>Symptomatic</u>

- NASCET
- ECST
- VA Trial

<u>Asymptomatic</u>

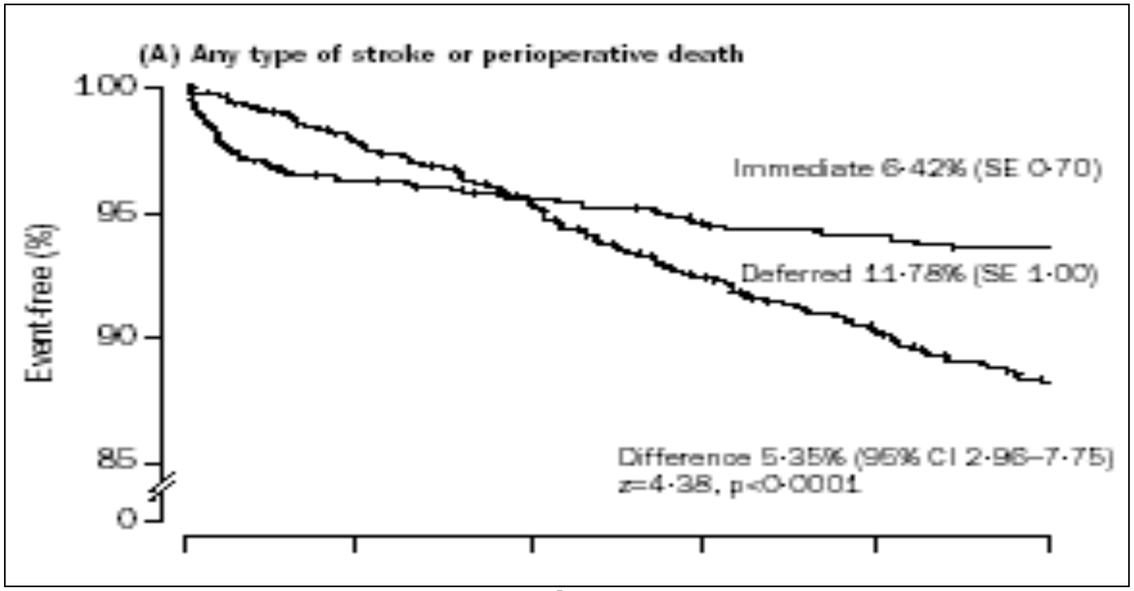
- Casanova/MACE
- VA Trial
- ACAS
- ACST

Table 1. Net Benefits of Carotid Endarterectomy Demonstrated in Randomized, Controlled Trials Involving More Than 500 Patients.

Trial*	Degree of Stenosis	Recent Symptoms†	Absolute Reduction in Risk‡		Rate of Surgical Complications§
			percent	P value	
	%				%
NASCET[4]	≥70	Yes	16.5 at 2 yr	<0.001	5.8
ECST[8]	≥60¶	Yes	11.6 at 3 yr	0.001	4.8
NASCET[6]	50–69	Yes	10.1 at 5 yr	0.005	6.7
NASCET[6]	<50	Yes	0.8 at 5 yr	0.97	6.7
ECST[9]	<40¶	Yes	Surgery group worse at 3 yr	<0.05	7.9
ACAS[5]	≥60	No	6.3 at 5 yr	0.08	2.3

ACAS and Asymptomatic Carotid Surgery Trials
(Stenosis ≥60%)

Benefit of immediate intervention with “CEA plus Med Rx” over strategy of “Best Med Rx” alone!



Time (years) →

Stroke/death

- Surgical 2.3% (periOP), 5.1% overall
- Medical 11% overall

NB:

- CEA + aspirin vs aspirin alone
- Absolute risk reduction ≈1% per year
- Benefit dependent on perioperative stroke/death <3%

Lancet. 2004;363

CEA Trials (1990s) Clinical Take-Home Points

- CEA provides clear benefit in symptomatic severe (≥70%) stenosis
- Moderate benefit in selected 50%–69% symptomatic patients
- Asymptomatic benefit is more modest and highly operator-dependent

NB: Results must be interpreted in context of modern medical therapy

Med Rx 1990s
- Aspirin as antiplatelet agent
- Minimal statin use
- Modest BP/lipid targets

→

Contemporary OMT
- Routine high-intensity statins
- Improved antihypertensive strategies
- Intensive risk-factor control (DM/smoking)

Lower baseline stroke risk → smaller absolute CEA benefit in asx disease

NASCET and ACAS Exclusions

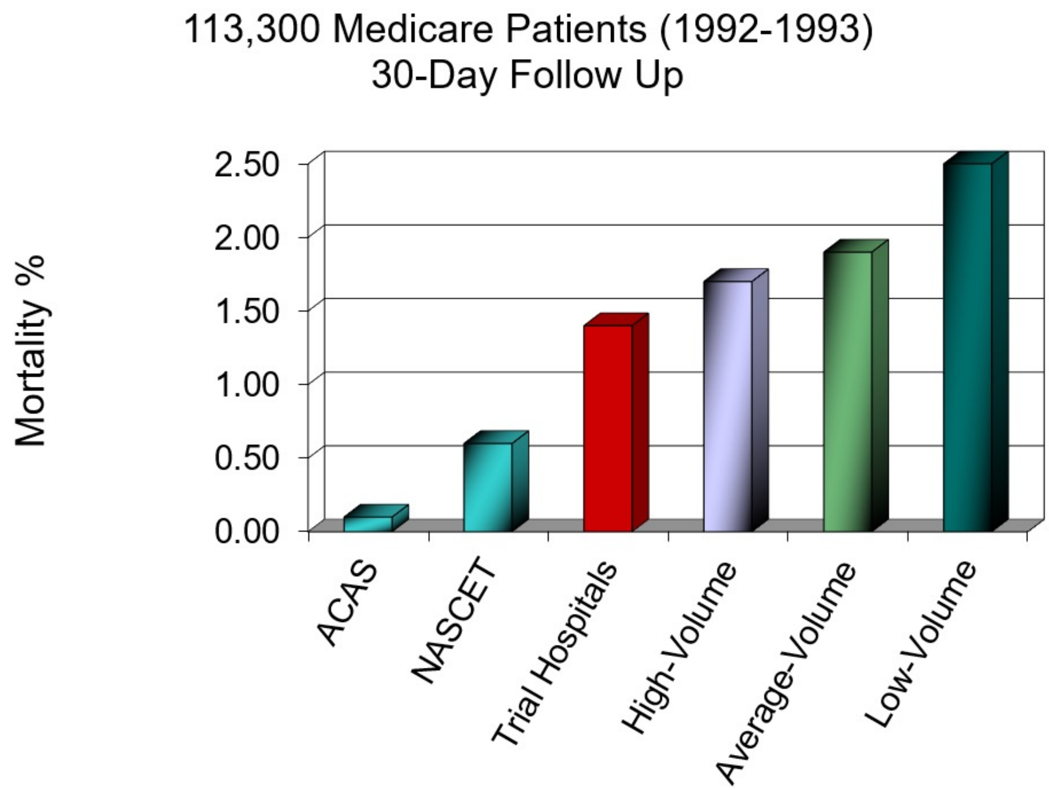
- Age >79
- Prior ipsilateral CEA
- Unstable coronary syndrome
- Myocardial infarct in previous 6 months
- Cardiac valvular or rhythm abnormality likely to cause embolic cerebrovascular symptoms
- Contralateral occlusion
- A more severe lesion cranial to the surgical lesion
- Contralateral CEA within previous 4 months
- Uncontrolled hypertension or diabetes
- Organ failure likely to cause death within 5 yrs
- Total occlusion
- Major surgical procedure in previous 30 days
- Prior severe CVA
- Progressing neurologic syndrome

Results of CEA Worse in High-Risk Groups
Stroke/Death @30 Days

- Age >75 yrs: 7%-10%
- Congestive heart failure: 8%-9%
- Co-existent CAD requiring bypass surgery: 8%-10%
- Contralateral carotid occlusion
  - ACAS: 2% increase over medical therapy
  - NASCET: 14.3%
- Prior CEA and recurrent stenosis: 8%-10%
- Renal insufficiency:
  - Cr >1.5 mg%: 8.2%
  - Cr >2.9 mg%: 43%

Daily PO, et al. *J Thor Cardiovasc Surg.* 1996:111(6):1185-1193. Goldstein LB, et al. *Stroke.* 1998:29(4):750-53. Wong JH, et al. *Stroke.* 1997;28(5):891-898.

CEA Mortality

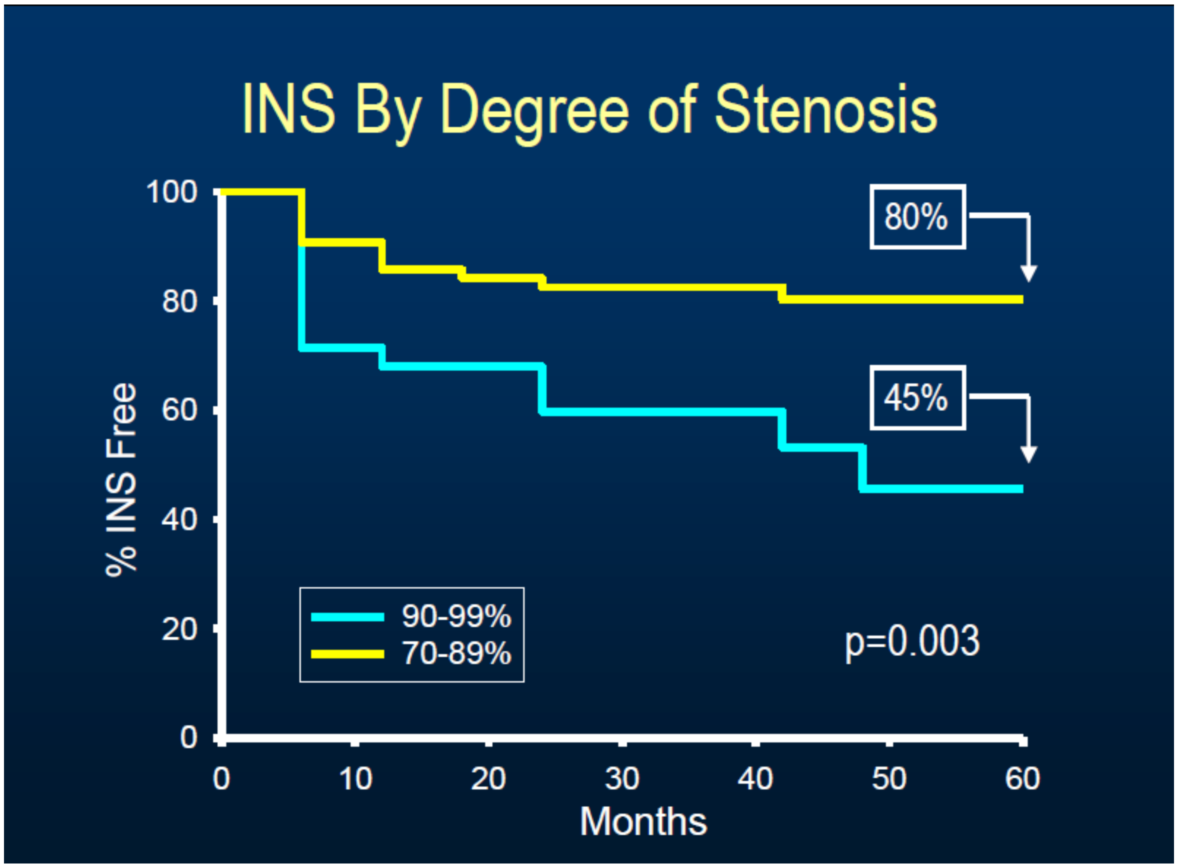


Wennberg, et al. *JAMA*. 1998;279:1278-1281.

Carotid Endarterectomy (CEA)

- Established CEA as "gold standard" for intervention
- Major studies done in "standard-risk" patients
- *Studies done by experienced operators at high-volume centers many years after CEA introduced (refined procedure)*
- ***Results not duplicated for inexperienced operators OR high-risk patients***
- After the trials, scrutiny of CEA became local, and often "self reported" (no formal post-procedure neuro eval, NIHSS, cranial nerve eval)

For Asx Patients, Severity of Stenosis Matters!

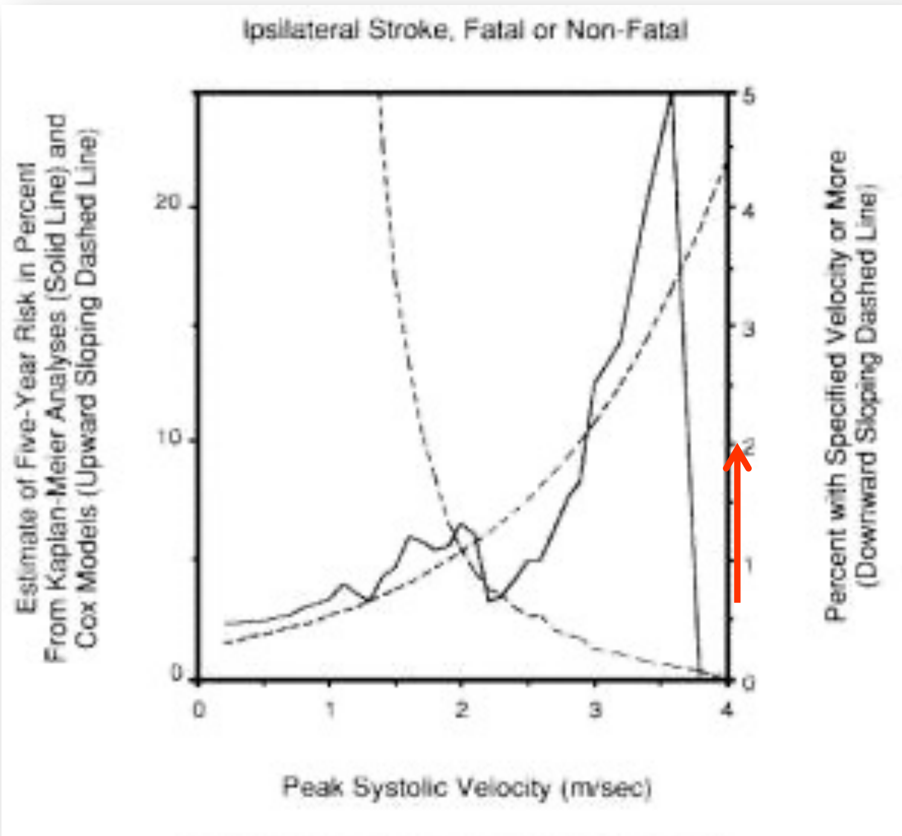


The natural history of asymptomatic severe carotid artery stenosis

Mark F. Conrad, MD, MMSc, Michael J. Michalczyk, BS, Arissa Opalacz, BS, Virendra I. Patel, MD, MPH, Glenn M. LaMuraglia, MD, and Richard P. Cambria, MD, *Boston, Mass*

Background: Although level 1 evidence supports carotid endarterectomy (CEA) for stroke prevention in patients with asymptomatic severe carotid artery stenosis (ASCAS; >70%), medical therapy alone has been promulgated by some as equally effective. The goal of this study was to determine the natural history of medically treated patients with ASCAS.
Methods: Patients with ASCAS from 2005 to 2006 were identified in a health network database. Patients were included if the initial therapeutic plan involved medical therapy alone (usually because of comorbidities or patient preference). Study end points included: ipsilateral neurologic symptoms (INS) of transient ischemic attack and/or stroke, death, and INS and/or death.
Results: There were 126 carotid arteries identified in 115 patients. Using standard duplex velocity criteria, 88 (70%) had severe (70%-89%) and 38 (30%) had very severe stenoses (VSS; 90%-99%). The average age was 73.5 years, demographic characteristics included: 66% hypertension, 64% coronary artery disease, 30% diabetes, 5% chronic kidney disease (CKD), and 86% were taking a statin drug (28% had a low-density lipoprotein level <100 mg/dL). There were 31 patients (24.6%) who developed INS during a mean follow-up of 27 months; most (23 of 31; 74%) occurred within 12 months of the initial duplex ultrasound examination; 14 (45%) were strokes. The 5-year actuarial freedom from INS was 70.1 ± 5%. Multivariate predictors of INS included: VSS (hazard ratio [HR], 3.23; 95% confidence interval [CI], 1.56-6.76; P = .002), CKD (HR, 6.25; 95% CI, 2.05-19.2; P = .001), and age (HR, 0.94; 95% CI, 0.91-0.98; P = .001). There were 41 patients (33%) who underwent eventual carotid revascularization (32 CEA, nine stent); 23 of 41 (56%) were performed for INS and 18 (44%) for plaque progression. Overall 5-year actuarial survival was 69.8% ± 4.1%. Multivariate predictors of death included: age (HR, 1.06; 95% CI, 1.03-1.1; P = .0001), chronic obstructive pulmonary disease (HR, 1.92; 95% CI, 1.08-3.41; P = .03), and diabetes (HR, 5.08; 95% CI, 2.86-9.01; P < .0001). The 5-year actuarial freedom from INS and/or death was 54 ± 4.4%. Multivariate predictors of INS and/or death were: VSS (HR, 1.98; 95% CI, 1.22-3.23; P = .006), CKD (HR, 5.46; 95% CI, 2.12-14.08; P = .0004), and diabetes (HR, 2.6; 95% CI, 1.59-4.24; P = .0001). Statin use was not protective against INS or death in this cohort.

Severity of Stenosis Matters!



5-yr risk of stroke
An inflection point
at a PSV >250

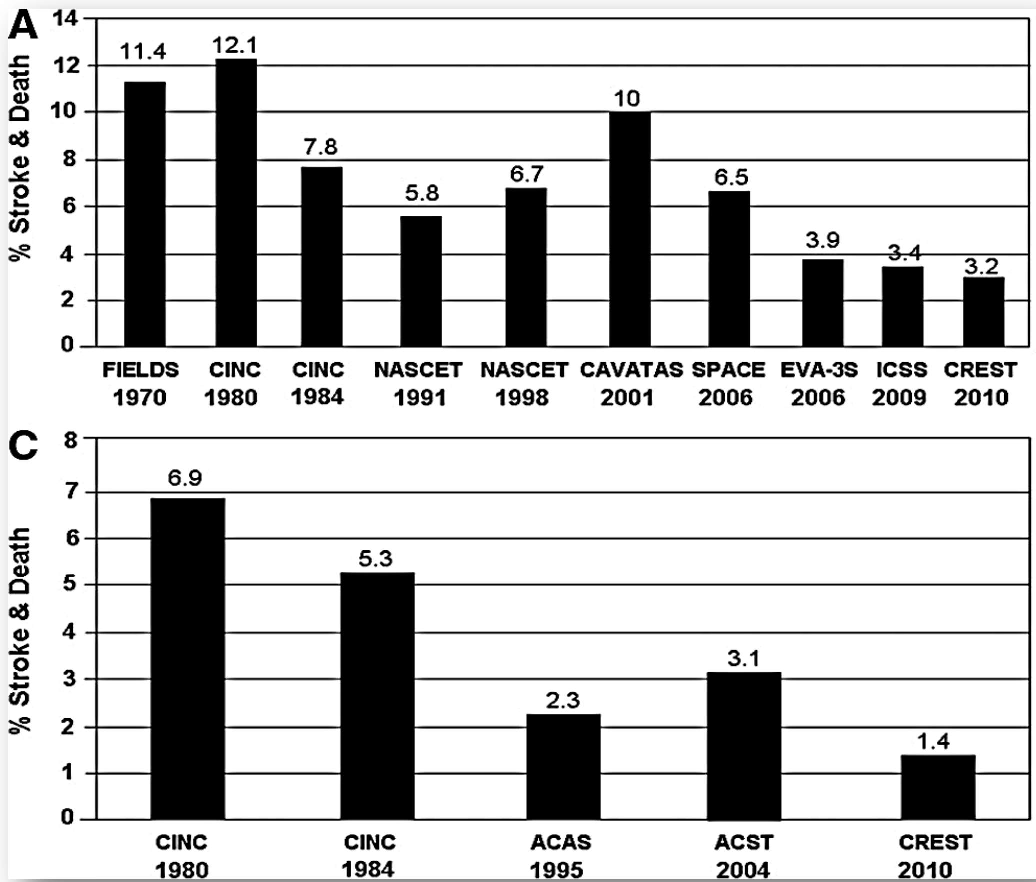
Asymptomatic Internal Carotid Artery Stenosis Defined by Ultrasound and the Risk of Subsequent Stroke in the Elderly: The Cardiovascular Health Study.
Longstreth, et al. *Stroke.* 29(11):2371-2376, November 1998.

Longstreth, et al. *Stroke*. 1998;29(11):2371-2376.

Evolution in CEA Outcomes over the Past 4 Decades

Symptomatic

Asymptomatic

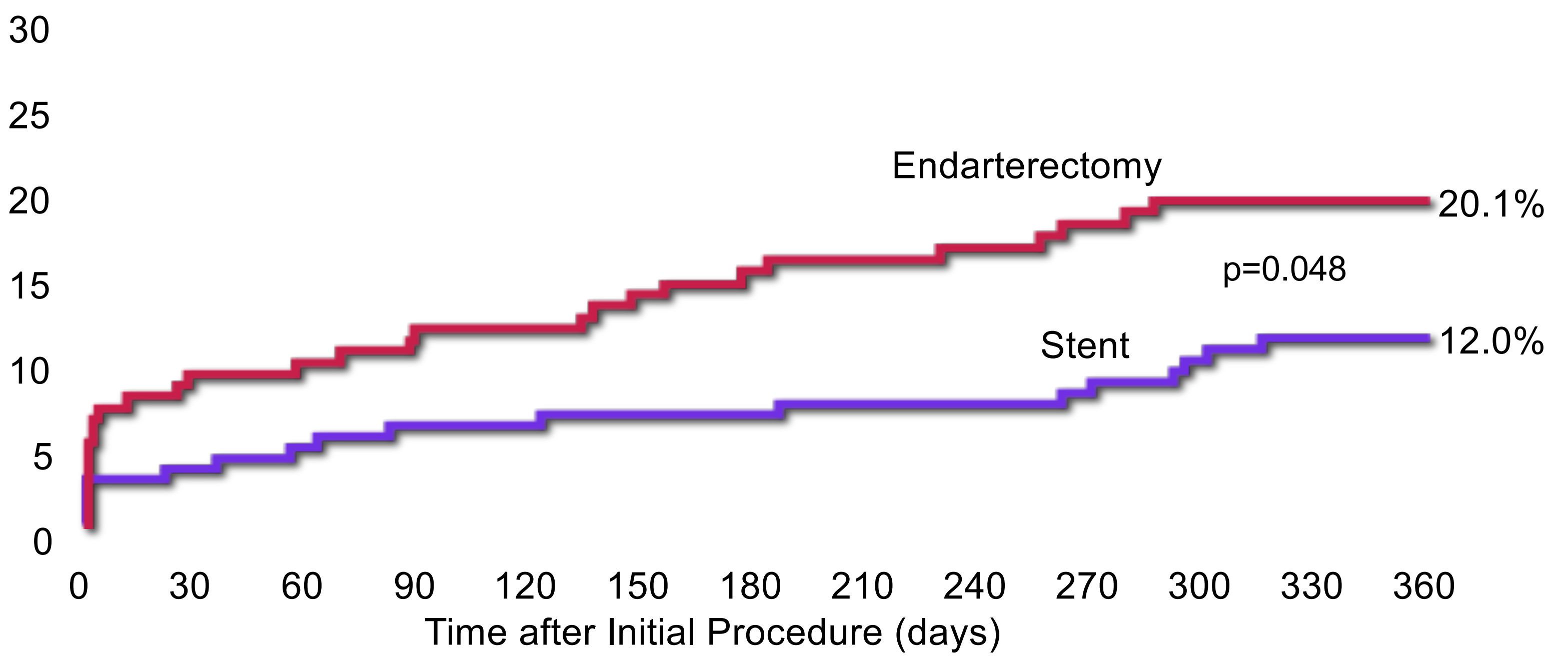


Summary 1

- Carotid artery disease accounts for a minority, but significant number of strokes
- Revascularization by CEA bests medical therapy in early trials, but benefit is less certain for high surgical risk patients
- Good outcomes in CEA require skilled /experienced surgeon
- Contemporary OMT may eliminate some relative benefit for revascularization in asymptomatic patients
- Aggressive medical management is essential in patients with carotid stenosis
- Stenosis often progresses despite OMT
- Higher grade stenoses → higher incidence of ipsilateral events

Along Comes Stenting: SAPPHIRE RCT
Sx and Asx High Surgical Risk Patients

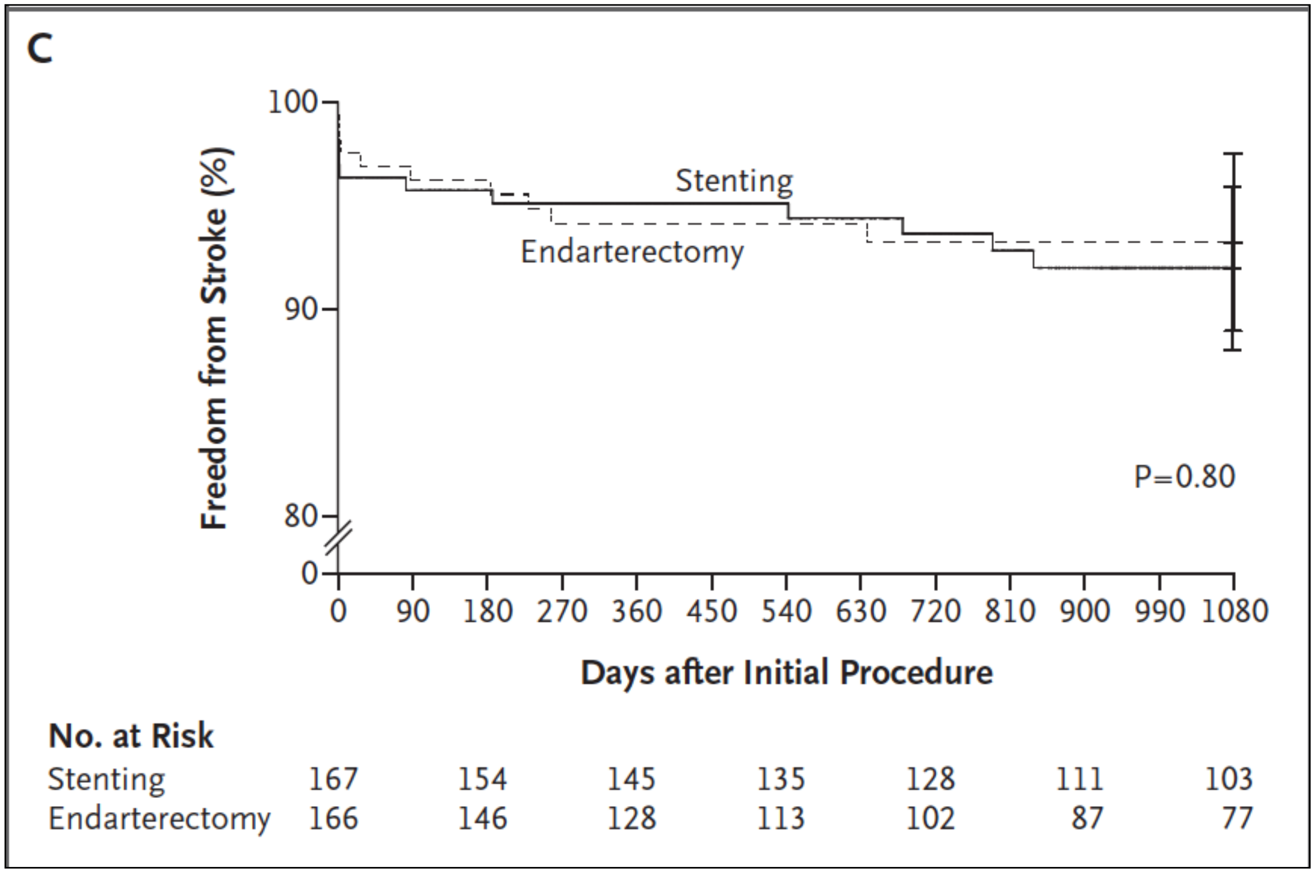
Cumulative Stroke, death, MI @ 1 yr



SAPPHIRE: Equivalent Stroke-Free Survival

SAPPHIRE 3-Yr Follow-Up

High Surgical Risk



Gurm H, et al. *N Engl J Med*. 2008;358:1572-1579.

Carotid Artery Stenosis
What Is the Best Treatment?

STENTING!

CEA!

Medical Therapy!

The controversy rages…

CREST-1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 1, 2010 VOL. 363 NO. 1

Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis

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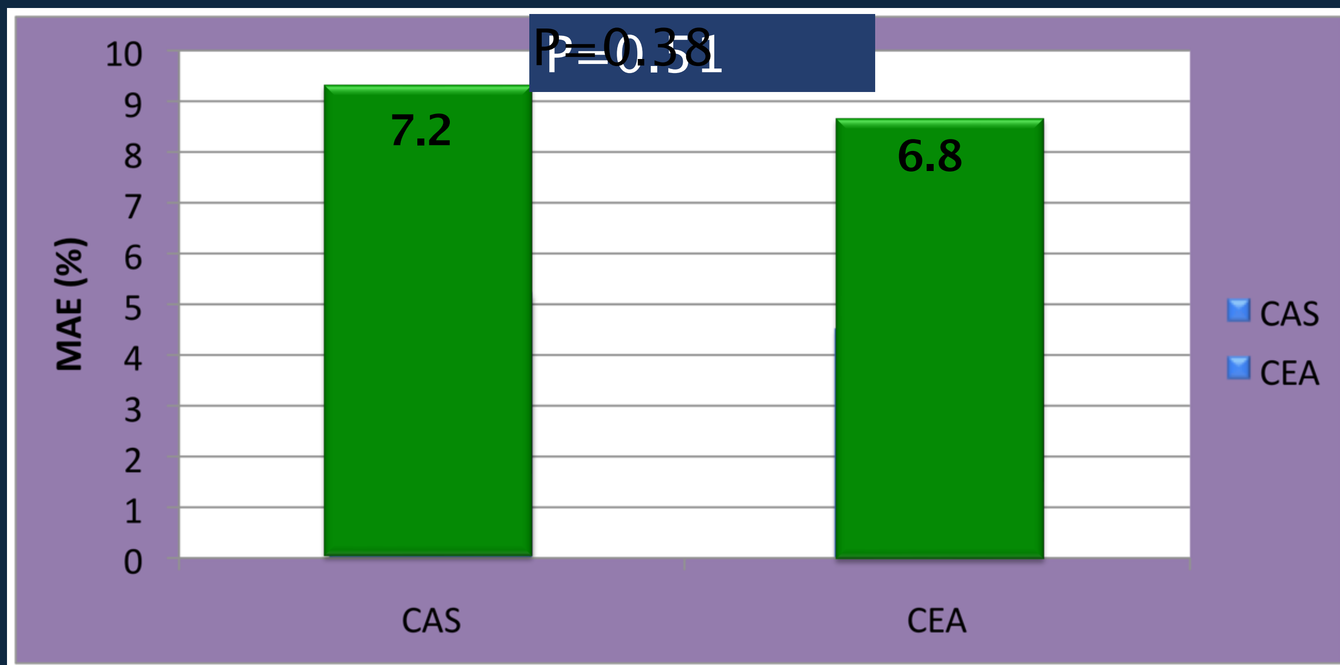
CREST = Carotid Revascularization Endarterectomy versus Stenting Trial.

CREST 1
Primary endpoint ≤4yrs (mean 2.5)

Peri-procedural outcomes

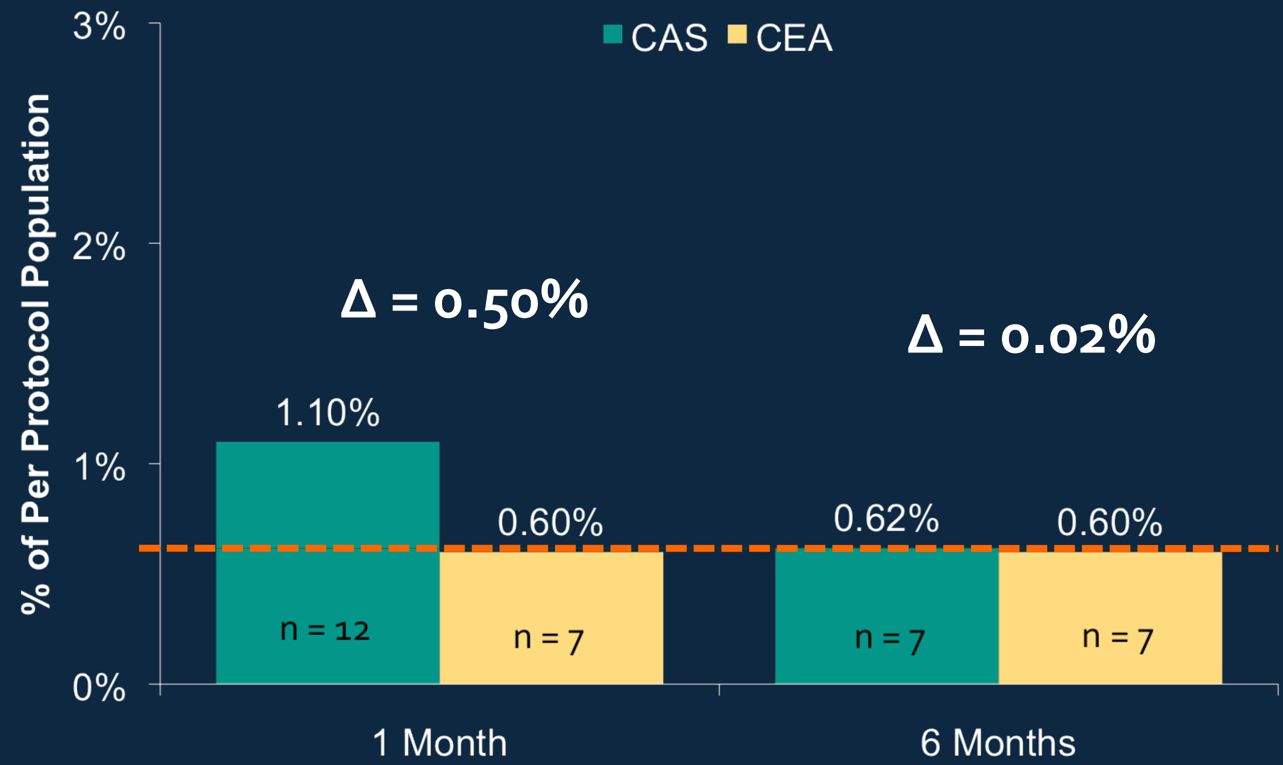


HR 1.11 95% CI: 0.81-1.51

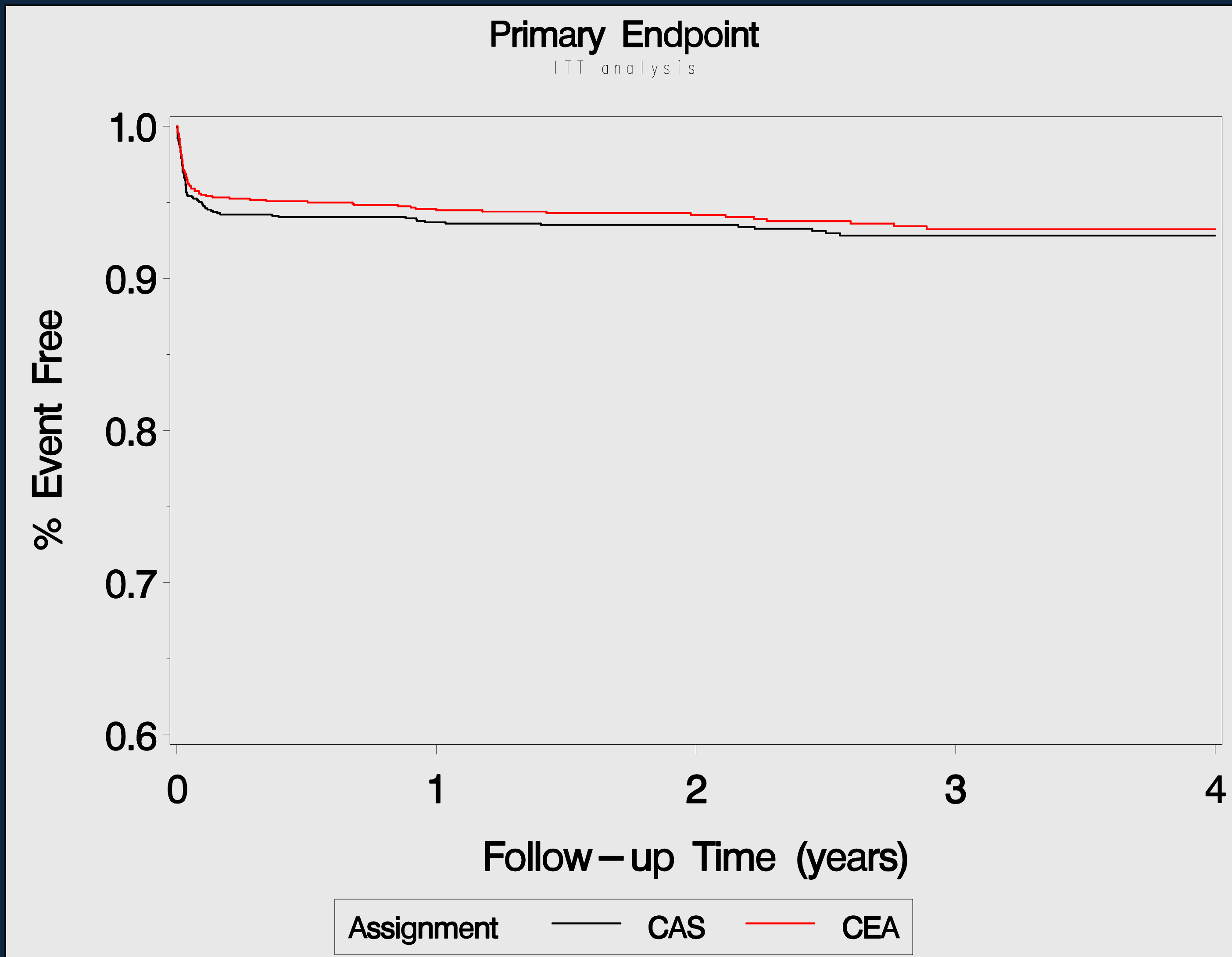
CREST: Peri-Procedural Stroke and MI

	CAS vs. CEA	Hazard Ratio 95% CI	*P*-Value
All Stroke	**4.1** vs. **2.3**%	HR = 1.79; 95% CI: 1.14-2.82	0.01
MI	**1.1** vs. **2.3**%	HR = 0.50; 95% CI: 0.26-0.94	0.03
Major Stroke	**0.9** vs. **0.6**%	HR = 1.35; 95% CI: 0.54-3.36	0.52

Neurological Residual Deficit Rates Associated with Minor Strokes @6 Months



CREST I

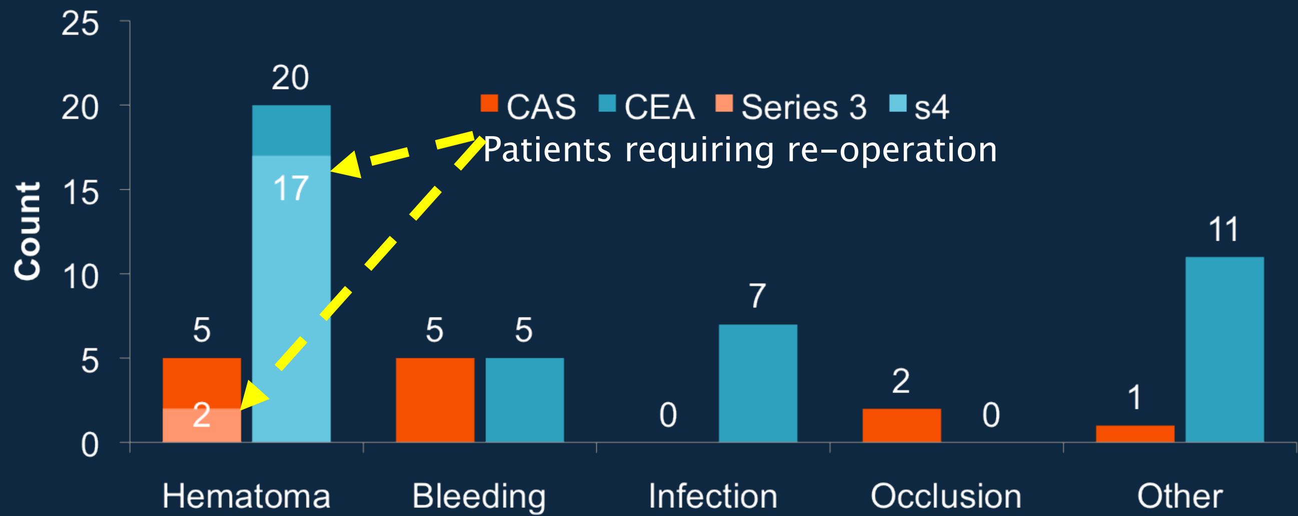

Primary Endpoint
ITT analysis
% Event Free
1.0
0.9
0.8
0.7
0.6
0
1
2
3
4
Follow-up Time (years)
Assignment
CAS
CEA

CREST: Cranial Nerve Injury

Patients with study procedure attempted/received	CAS N = 1,131	CEA N = 1,176	*p*-value
Procedure-related cranial nerve injury	0.0%	5.3% (62/1176)	<0.0001
Unresolved at 1 month	0.0%	3.6% (42/1176)	<0.0001
Unresolved at 6 months	0.0%	2.1% (25/1176)	<0.0001

Source:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247780.pdf

CREST: CEA vs CAS Access Site Cx

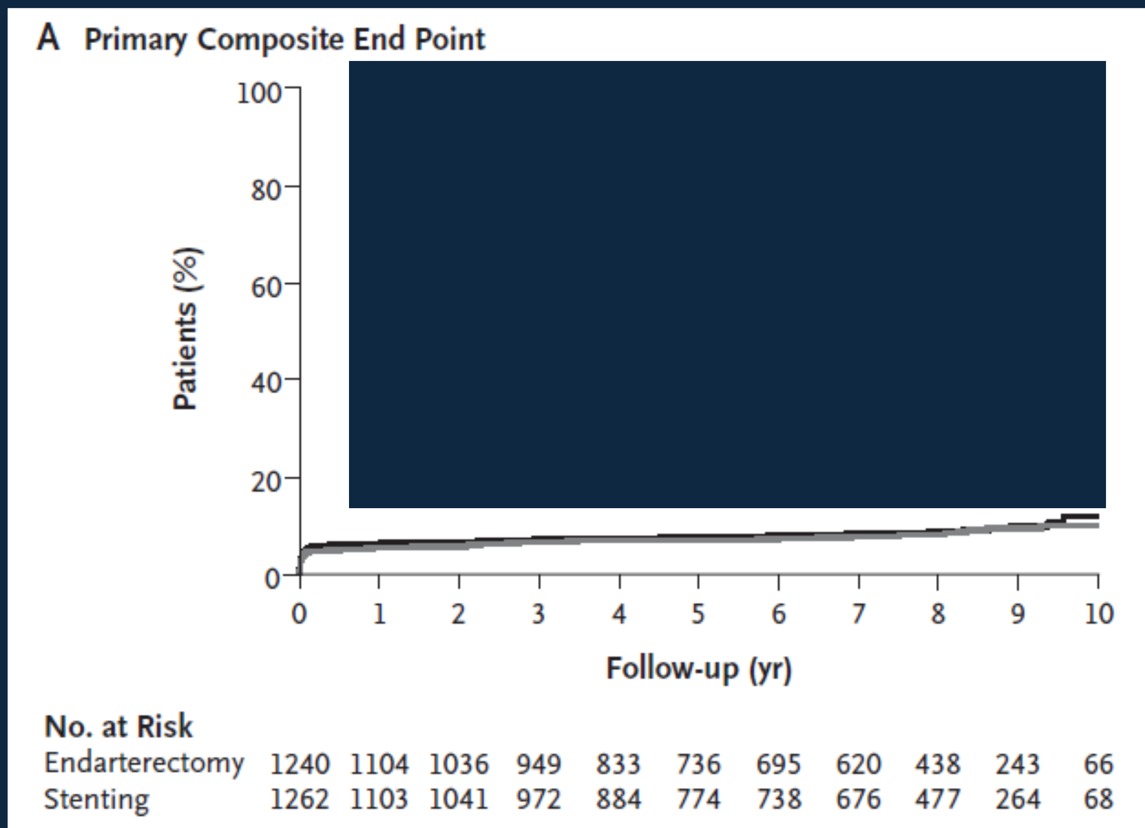


Per Protocol	CAS N = 1,131	CEA N = 1,176	p-value
Access Site Complication Requiring Treatment	1.1%	3.7%	0.0001

Events may occur more than once in the same patient. Other includes pain requiring IV analgesics (5), incision complication (3), pseudoaneurysm (2), occlusion (1)

Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247780.pdf

Long-Term Results CREST-1



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Conclusions

- Primary endpoint shows equivalence
- Lower minor stroke with CEA and lower MI with CAS
- Certain liabilities of CEA (access cx, CN palsy, etc.)
- Overall results of *both* are spectacular: Lowest event rates of any large RCT
- Issues
  - Included both sx and asx: not powered to analyze independently
  - No comparison to OMT alone

ACT 1 - Freedom from Death, Stroke and MI within

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Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

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CAS Number at Risk	1089	1067	1016	862	729	544	364
CEA Number at Risk	364	354	325	285	246	182	112

Asymptomatics: CREST 1 and ACT 1
TWO LARGE RCTs providing LEVEL 1 EVIDENCE

	CAS	CEA	p
ACT I – Primary Endpoint	3.8%	3.4%	0.01[1]
CREST – Primary Endpoint	5.6%	4.9%	0.56[2]
ACT I – 30 d Stroke, MI, Death	3.3%	2.6%	0.60
CREST – 30 d Stroke, MI, Death	3.5%	3.6%	0.96
ACT I – 30 d Stroke, Death	2.9%	1.7%	0.33
CREST – 30 d Stroke, Death	2.5%	1.4%	0.15

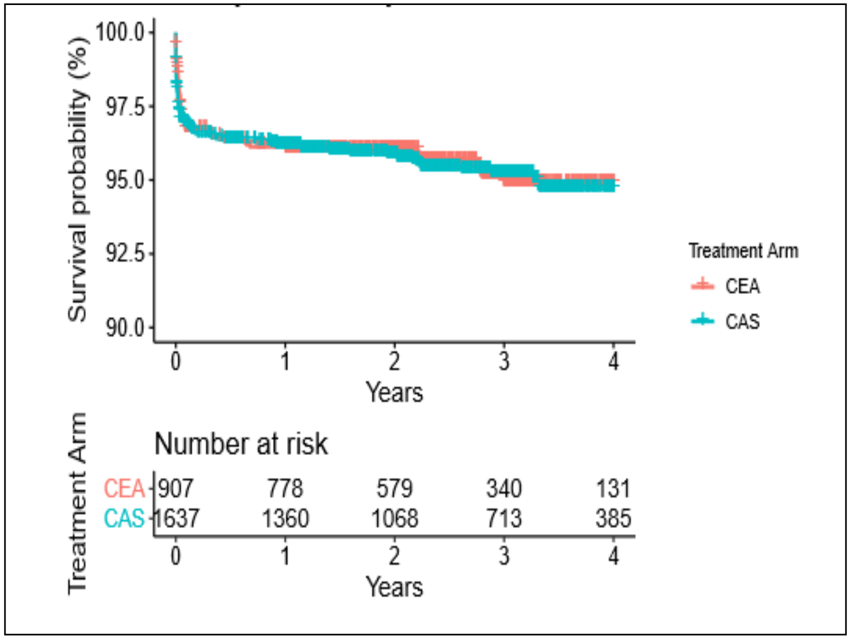
ACT I – 1453 Asx pts: 1089 CAS, 364 CEA
CREST – 1181 Asx pts: 594 CAS, 587 CEA

[1] 1-sided non-inferiority test
[2] 2-sided superiority test

CREST 1 and ACT 1 Combined Asx-Pooled Analysis
Results: Primary Endpoint

Composite of periprocedural death, stroke, myocardial infarction or 4-year ipsilateral stroke is similar

- CAS 5.3% vs CEA 5.1%
- Hazard ratio 1.02, 95% CI, 0.7 to 1.5, *P*=0.91

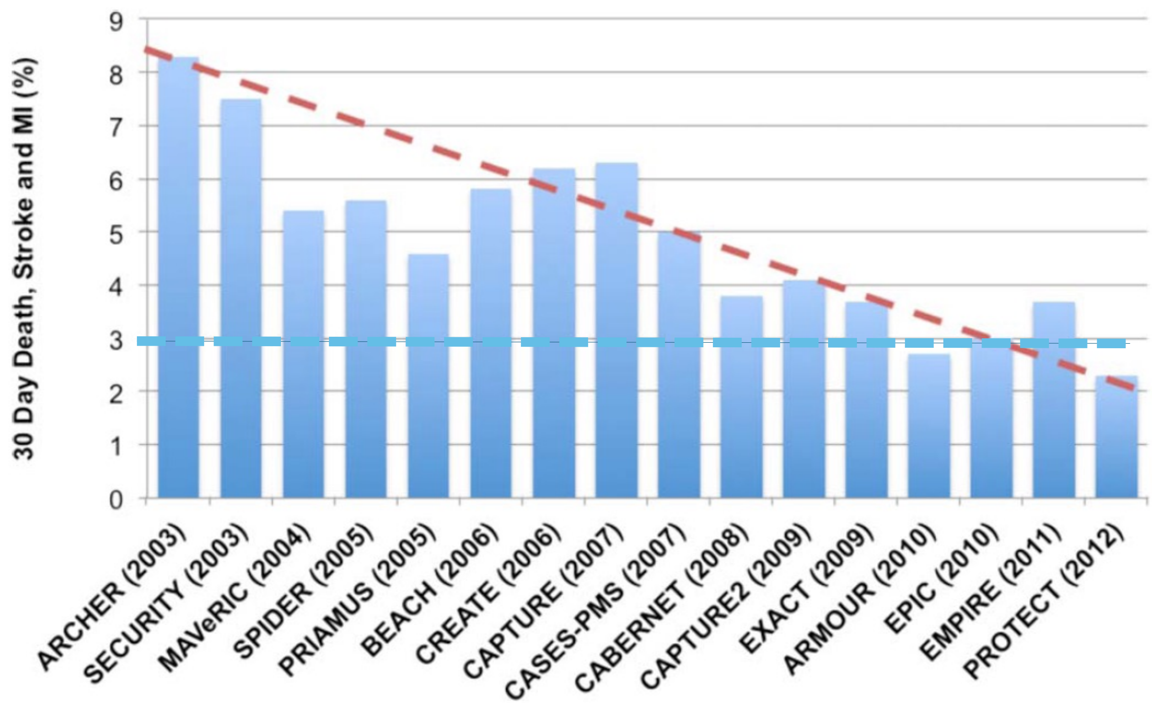


CREST 1 and ACT 1: Summary

- For asymptomatic, non-octogenarian, standard surgical and anatomic risk patients
  - CAS is non-inferior to CEA for 30-day DSMI and 1-yr ipsilateral stroke
  - CAS and CEA have similar 5-yr rates of stroke, survival, both extremely low
  - Repeat revascularization extremely low in both groups

CAS: An Evolving Procedure IDE and Registry Evidence

Declining Risk of Stroke, Death, and MI over Time



White CJ, et al. *Catheter Cardiovasc Interv*. 2013;82:715-726

Table III

Periprocedural Adverse Events for Carotid Stenting Procedures Performed in C2R for Primary Atherosclerosis

Characteristic, n (%)	All cases 2219 (100%)	Asymptomatic 1228 (55.3%)	Symptomatic 991 (44.7%)
Stroke or death	43 (1.9)	16 (1.3)	27 (2.7)
Any stroke, regardless of laterality	35 (1.6)	12 (1)	23 (2.3)
Stroke ipsilateral to the index artery	31 (1.4)	9 (0.7)	22 (2.2)
Stroke contralateral to the index artery	10 (0.5)	5 (0.4)	5 (0.5)
Death	8 (0.4)	4 (0.3)	4 (0.4)
Stroke, death, or myocardial infarction	47 (2.1)	18 (1.5)	29 (2.9)
Myocardial infarction	4 (0.2)	2 (0.2)	2 (0.2)
Stroke, death, MI, or access site complications	60 (2.7)	28 (2.3)	32 (3.2)
Major access site complications	14 (0.6)	10 (0.8)	4 (0.4)

Therapy for Carotid Artery Stenosis

TF Stenting or TCAR or CEA or OMT alone?

What is the role of each???

Remains a HOT topic

Perspectives on Carotid Revascularization Stakeholders

Physicians

- Vascular Surgeon
- Cardiologist
- Neurologist
- Radiologist
- Neurosurgeon
- Internist

Other Parties

- Industry
- FDA
- CMS
- Payors
- Patients

Carotid Artery Disease
The issue with this field

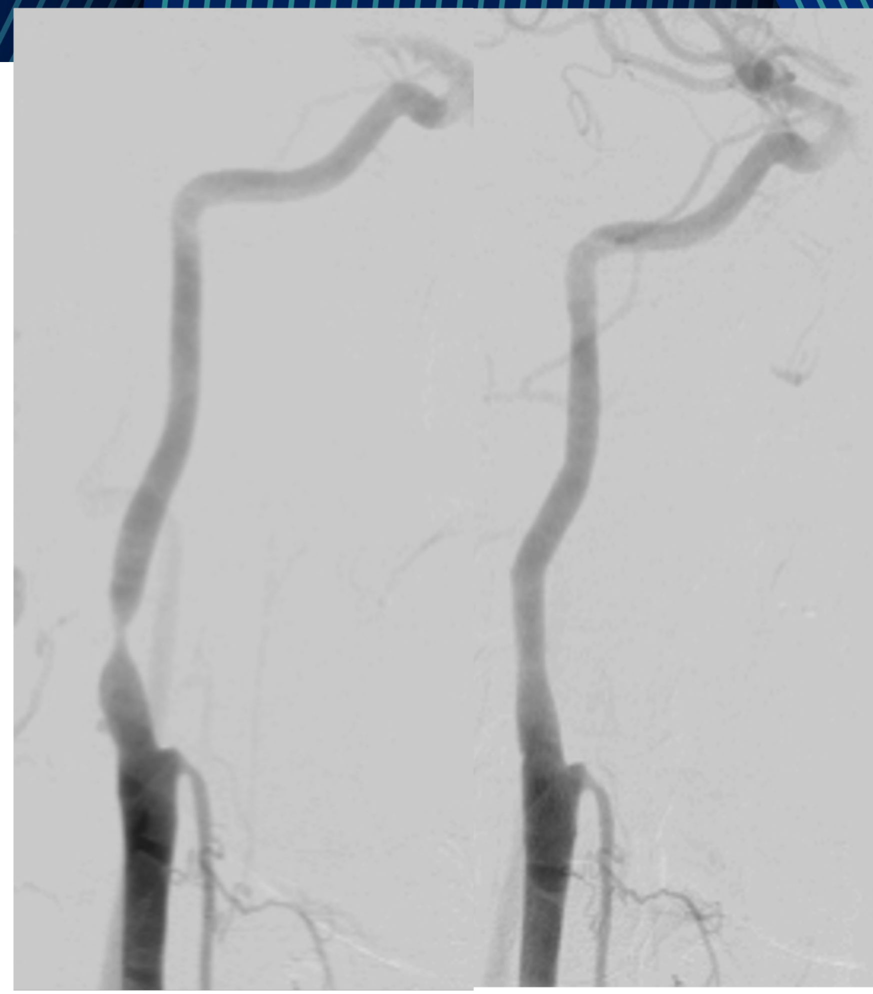
- Stakeholder interests extend beyond those of the patient…
  - Economics
  - Politics
  - “Control”
  - “Tradition”
- Many only “see” in the data what they want to see and use that to support their pre-conceived biases (or self-interests)

Perspectives: Interventionalist

- Differences between CEA and CAS outcomes…no longer lie in the procedure choice, but rather
  - Operator
  - Case selection
  - Equipment and technique
- Level I evidence and guidelines support offering CAS as (covered) option
- Operators need appropriate training, experience, and judgment
- Playing field should be level
  - All should have closer oversight, independent neuro eval

A Patient's Opinion

"Are the results similar?
If so, I want the choice…
I want a stent!"



Background and Outcomes of CREST-2

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Wynnewood, PA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Medical Management and Revascularization for Asymptomatic Carotid Stenosis

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Background and Outcomes of Crest-2

Outline

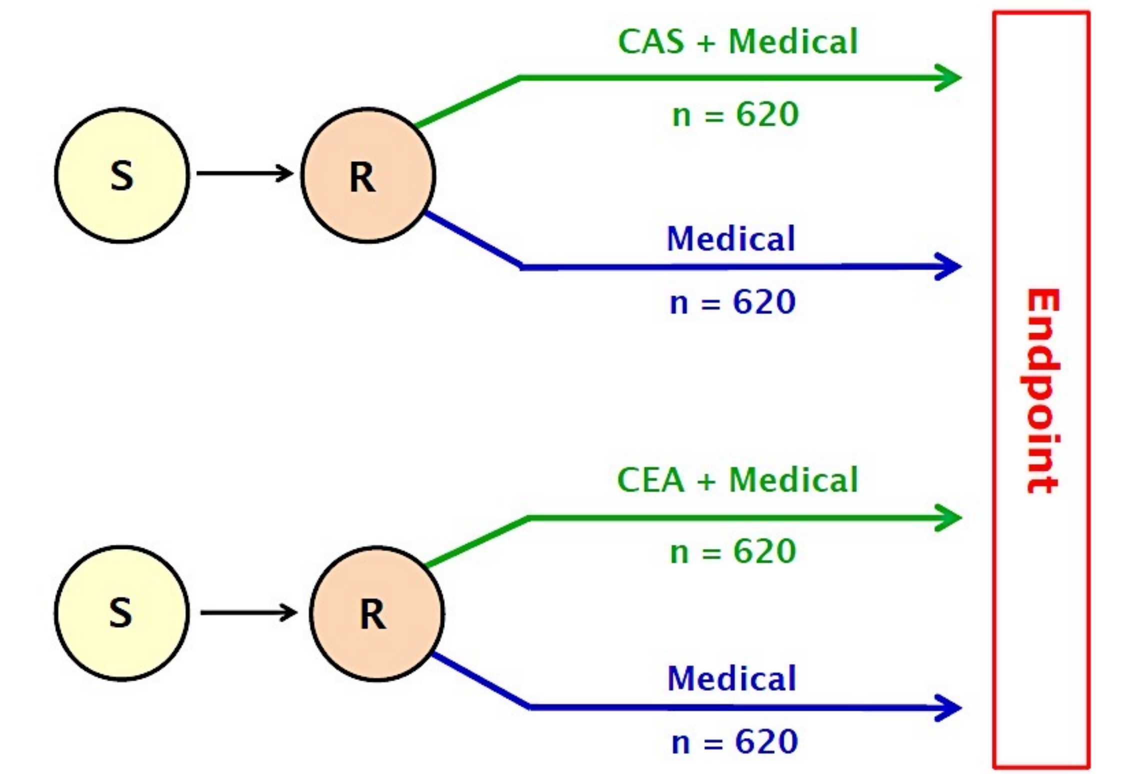
- What was the design and objective of CREST-2?
- What are the outcomes?
- What are the limitations and open questions regarding stenting, endarterectomy, and medical management?

The Rationale for the Crest-2 Study

- Although randomized data from the ACAS (1995) and ACST (2004) trials demonstrated superiority of immediate CEA over deferred in asymptomatic atherosclerotic bifurcation carotid stenosis, reasonable critiques of those trials noted
  - an absence of programmed medical therapy in the deferred arm
  - a marked improvement in the available medical therapies since those studies were done
- Systematic reviews and retrospective summary-level meta-analyses (methodologically limited) suggested that the natural history of stroke in carotid disease on modern medical therapy had materially declined, thus making the previous trials obsolete
- In addition, perioperative stroke and death had declined for CEA, and CAS had been shown equivalent to CEA in 2 RCT (CREST and ACT-1)
- Thus, a comparative evaluation of therapies would be valuable, hence CREST-2

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CEA = carotid endarterectomy; CAS = carotid artery stenting; ACT-1 = Carotid Angioplasty and Stenting versus Endarterectomy in Asymptomatic Subjects.

CREST-2: Parallel Study Design



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

CREST-2: Medical Therapy Arm

- Implemented by sites with central oversight and assistance
- Lifestyle management coach assigned to each patient

CEA Trial: aspirin 325mg/d

CAS Trial: Dual antiplatelet therapy for 1-3 months post-procedure, then aspirin

Primary Risk Factor Target Levels

- Systolic BP <140 mm Hg
- LDL cholesterol <70mg/dl

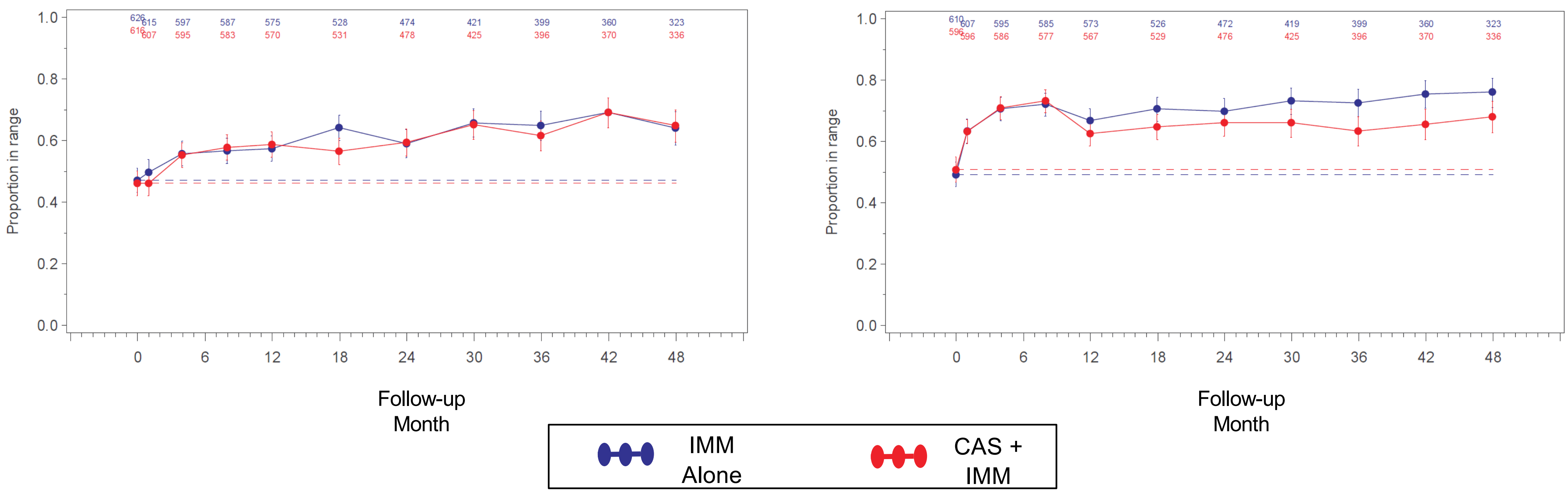
Secondary Risk Factor Target Levels

- Non-HDL cholesterol <100mg/dl
- Hemoglobin A1c <7.0%
- Tobacco smoking cessation
- Targeted weight management
- >30 min of moderate exercise 3x/wk

Turan TN, et al. *Stroke*. 2020;51(10):2960-2971. Whelton PK, et al. *Hypertension*. 2018;71(6):1269-1324. Erratum in: *Hypertension*. 2018;71(6):e136-e139. Erratum in: *Hypertension*. 2018;72(3):e33.

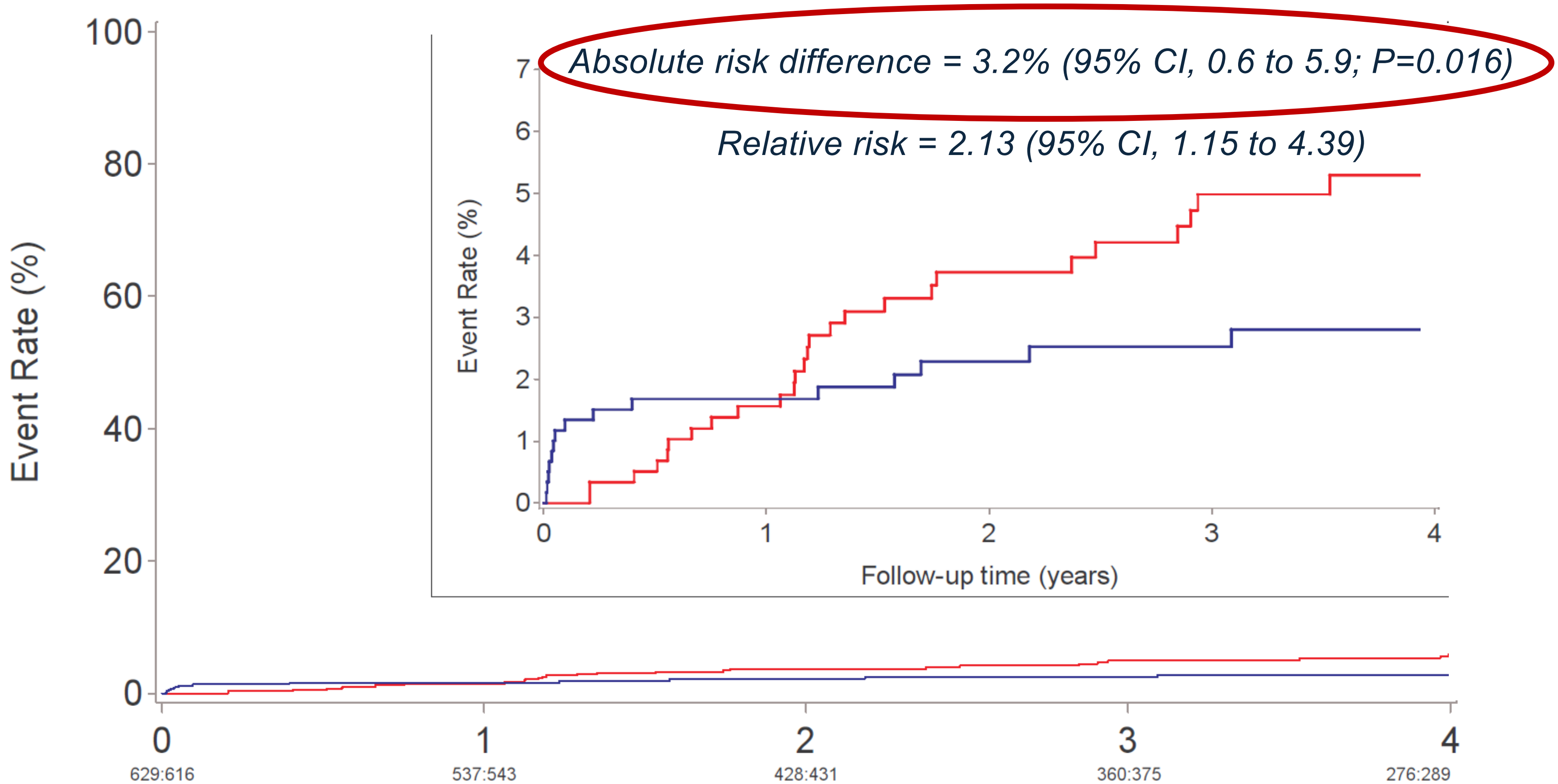
CREST-2: Risk Factor Control in Stent Arm

Proportion of systolic BP values in target | **Proportion of LDL values in target**



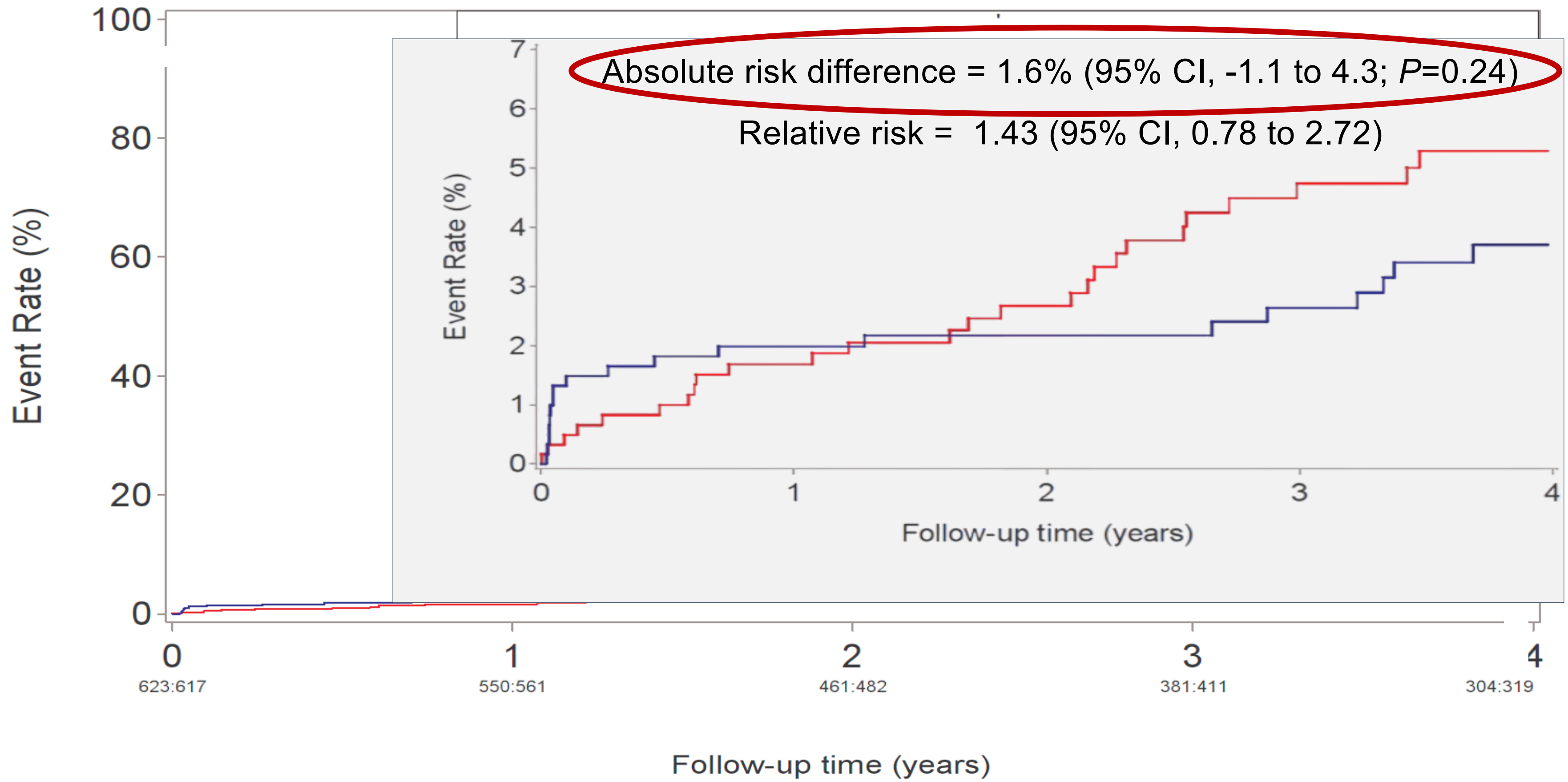
Brott TG, et al. *N Engl J Med*. 2026;394(3):219-231.

CAS Arm: Any Perioperative Stroke or Death Plus Ipsilateral Stroke Thereafter up to 4 Years



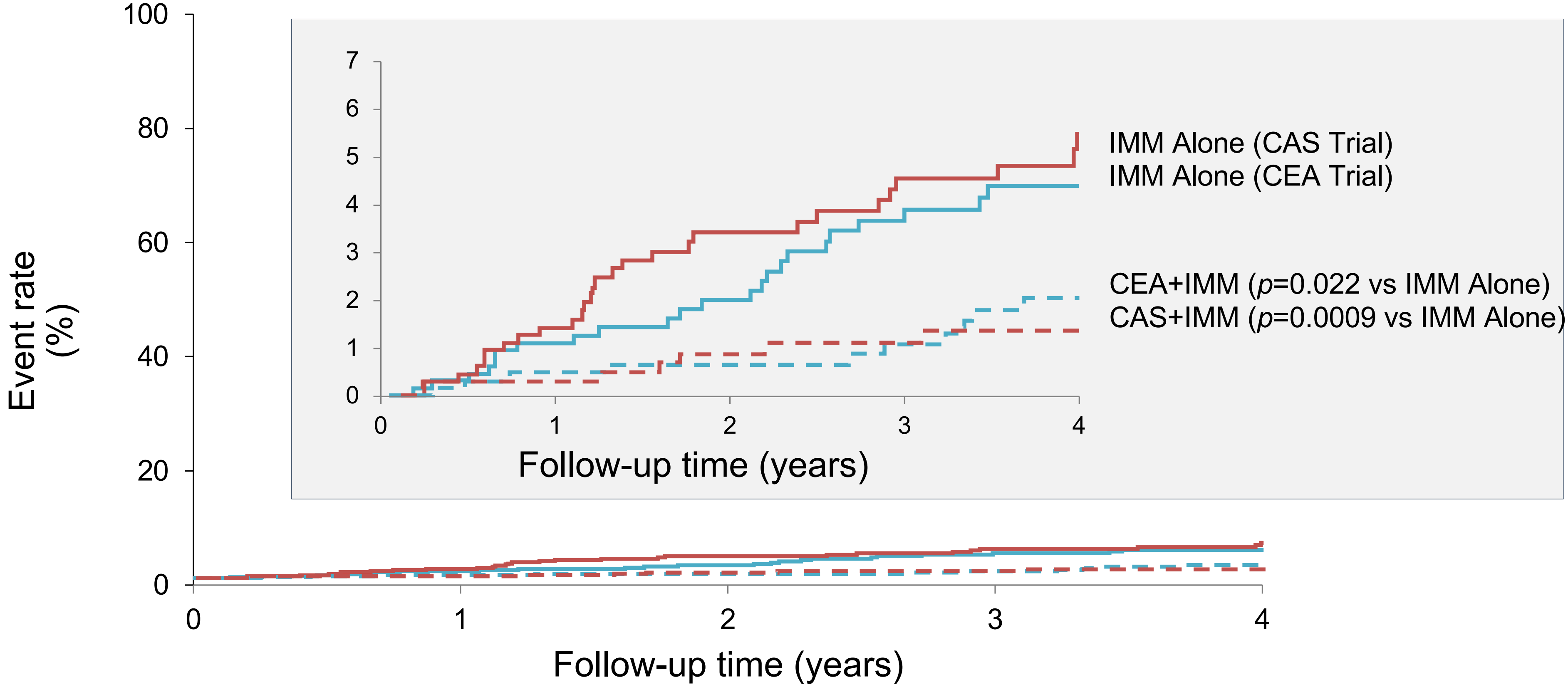
Brott TG, et al. *N Engl J Med.* 2026;394(3):219-231

CEA Arm: Any Perioperative Stroke or Death Plus Ipsilateral Stroke Thereafter up to 4 Years



Brott TG, et al. *N Engl J Med*. 2026;394(3):219-231

Kaplan-Meier Estimates of the Post-Procedural Component of the Primary Outcome



What are the limitations and open questions regarding stenting, endarterectomy, and medical management?

Regarding TF-CAS

- Limitations: The most recent generation of TF-CAS tools (Neuroguard IEP and CGUARDIANS stent) were not included in CREST-2. Compared with historical CAS outcomes (including those devices used in CREST-2), data suggests that they would increase the benefit seen with CAS vis-à-vis IMM

Regarding CEA

- Open questions: Would a larger or longer trial have demonstrated statistical benefit of CEA over IMM?
- Open questions: Given the protocol-driven intensity of IMM is not likely replicated in the clinical environment and therefore the benefit less than seen in CREST-2, is there any role at all for IMM as a sole approach to carotid stenosis in a suitable revascularization candidate?
- Would the inclusion of GLP-1 therapy have made a material difference in the CREST-2 results?
- Is IMM more effective in preventing a sub-critical lesion progressing to a critical lesion than preventing a critical lesion from becoming symptomatic?

Regarding TCAR

- Not included in CREST-2 — where does it stand in the management of asymptomatic patients?

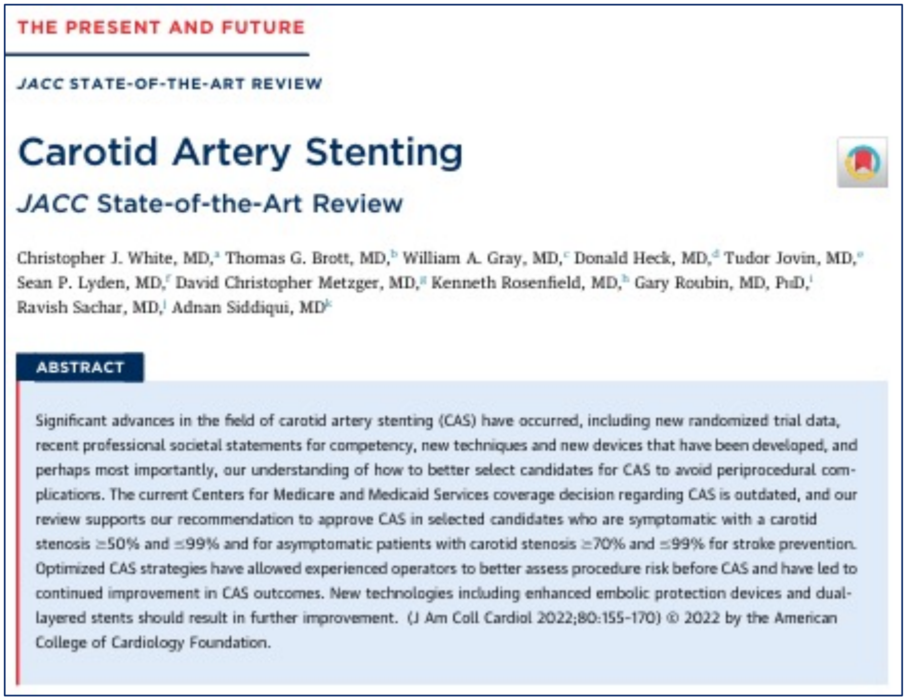
Summary: CREST-2

- Modern medical therapy appears to have improved outcomes in atherosclerotic bifurcation carotid stenosis compared with historical studies (ACAS and ACST)
- Both CAS and CEA perioperative outcomes have improved, with improvement CAS>CEA
- IMM likely improved long-term stroke rates even in the CAS and CEA
- Since rates of stroke are very low — ≈1%/year in IMM, 0.5%/year in CAS, CEA — any remaining open questions are unlikely to be investigated by an RCT since the size of the trial and the establishment of clinical equipoise would be difficult
- Based on the CREST-2 results, the task now is the development and acceptance of treatment algorithms and establishing associated lines of referral between specialties delivering carotid care

Latest Results from the New Generation of Carotid Trials

Sean P. Lyden, MD, FACS
Vascular Surgeon
Professor and Chairman, Cleveland Clinic
Cleveland, OH

Carotid Artery Stenting: *JACC* State-of-the-Art Review



THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

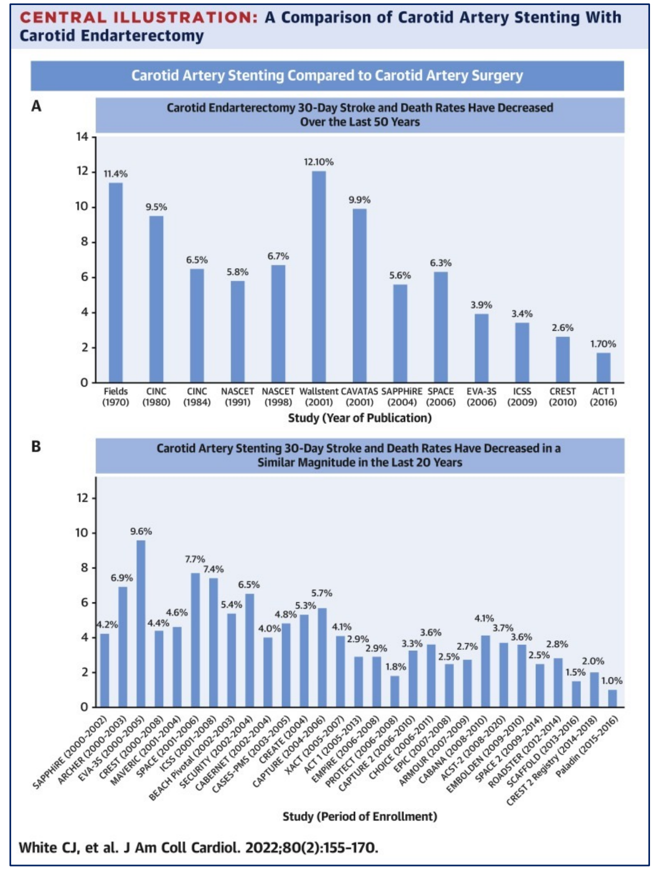
Carotid Artery Stenting

JACC State-of-the-Art Review

Christopher J. White, MD,[a] Thomas G. Brott, MD,[b] William A. Gray, MD,[c] Donald Heck, MD,[d] Tudor Jovin, MD,[e] Sean P. Lyden, MD,[f] David Christopher Metzger, MD,[g] Kenneth Rosenfield, MD,[h] Gary Roubin, MD, PhD,[i] Ravish Sachar, MD,[j] Adnan Siddiqui, MD[k]

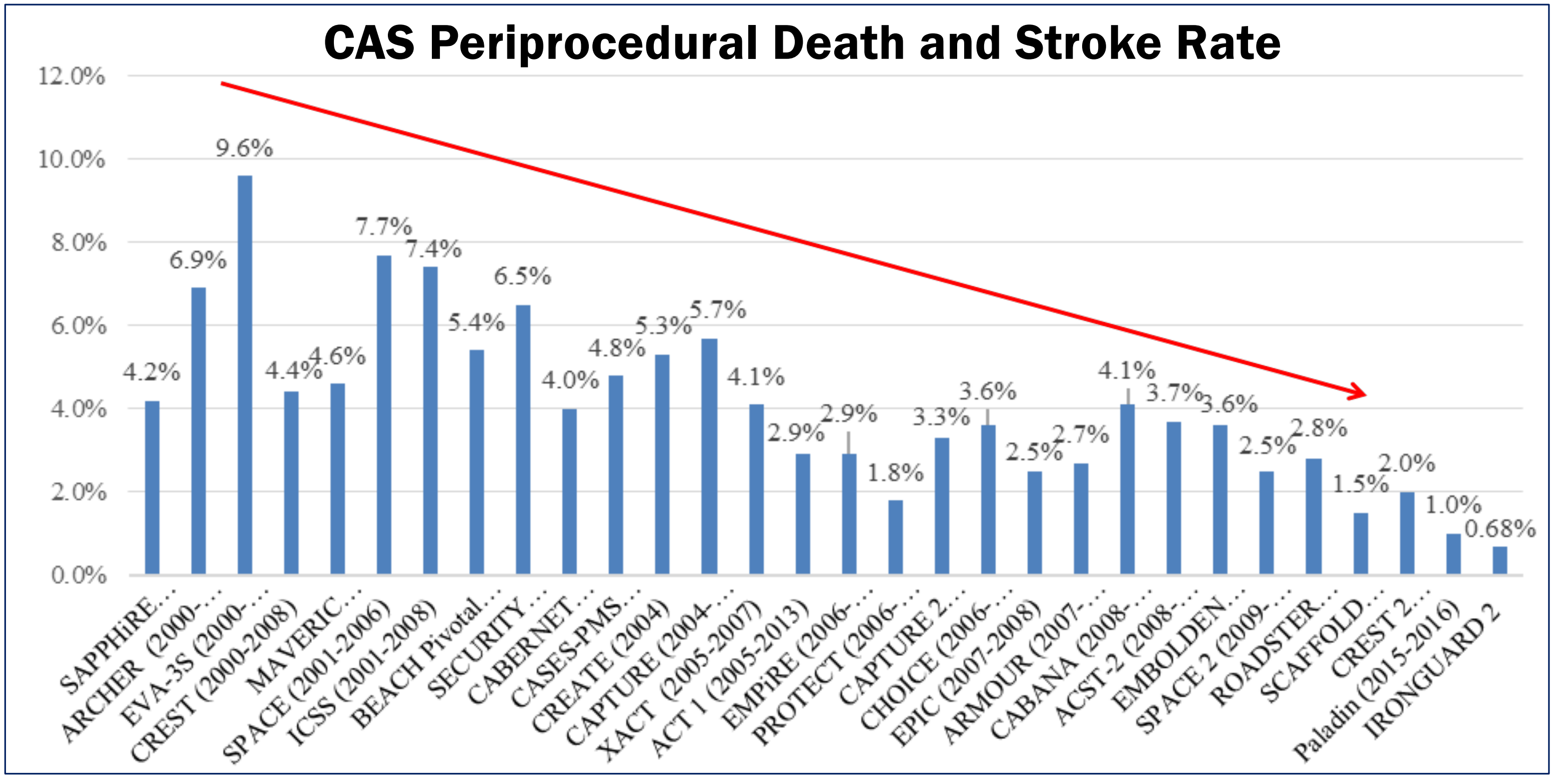
ABSTRACT

Significant advances in the field of carotid artery stenting (CAS) have occurred, including new randomized trial data, recent professional societal statements for competency, new techniques and new devices that have been developed, and perhaps most importantly, our understanding of how to better select candidates for CAS to avoid periprocedural complications. The current Centers for Medicare and Medicaid Services coverage decision regarding CAS is outdated, and our review supports our recommendation to approve CAS in selected candidates who are symptomatic with a carotid stenosis ≥50% and ≤99% and for asymptomatic patients with carotid stenosis ≥70% and ≤99% for stroke prevention. Optimized CAS strategies have allowed experienced operators to better assess procedure risk before CAS and have led to continued improvement in CAS outcomes. New technologies including enhanced embolic protection devices and dual-layered stents should result in further improvement. (J Am Coll Cardiol 2022;80:155-170) © 2022 by the American College of Cardiology Foundation.



White CJ, Brott TG, Gray WA, Heck D, Jovin T, Lyden SP, Metzger DC, Rosenfield K, Roubin G, Sachar R, Siddiqui A. *J Am Coll Cardiol.* 2022;80(2):155-170.

Improving Outcomes over Time



White CJ, Brott TG, Gray WA, Heck D, Jovin T, Lyden SP, Metzger DC, Rosenfield K, Roubin G, Sachar R, Siddiqui A. *J Am Coll Cardiol.* 2022;80(2):155-170.

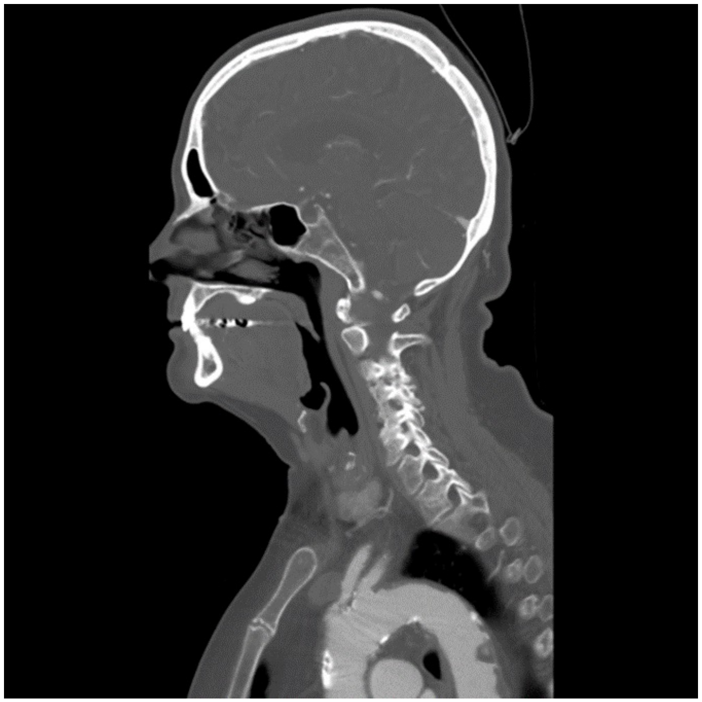
No Differences in Outcomes
Any Post-Procedural Stroke

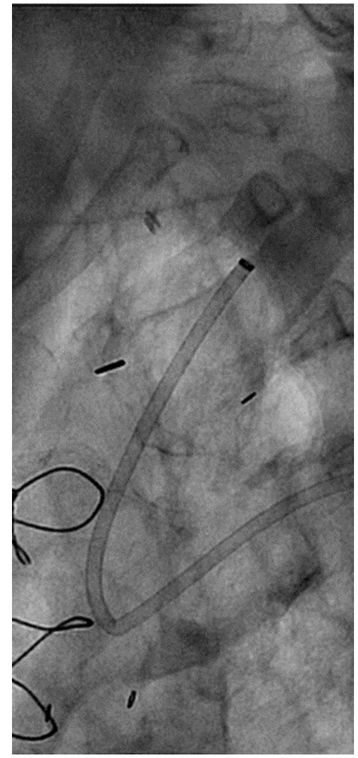
Trial/Study	Any Post-Procedural Stroke		
	CAS	CEA	p Value
ACT-1 Up to 5 years	6.9%	5.3%	0.44
Space-2 At 1 year	1.5%	1.5%	1
ACST-2 Mean f/u 5 years	5.3%	4.5%	0.33

ACT 1: Rosenfield K, et al. *N Engl J Med*, 2016;374(11):1011-1020.
SPACE 2: White CJ, et al. *Int J Stroke*. 2020;15:638-649.
ACST-2: Wang J, et al. *Lancet*. 2021;398:1065-1073

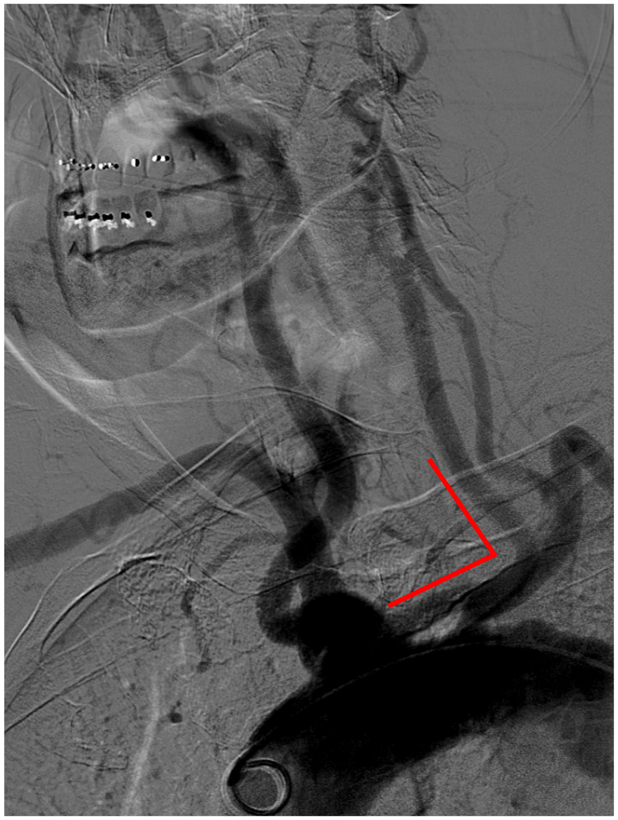
Procedure Selection: Aortic Arch

Bad Arches: Clot and Type





Higher Risk for CAS
More Examples



Severe CCA tortuosity

Severe innominate inflow disease

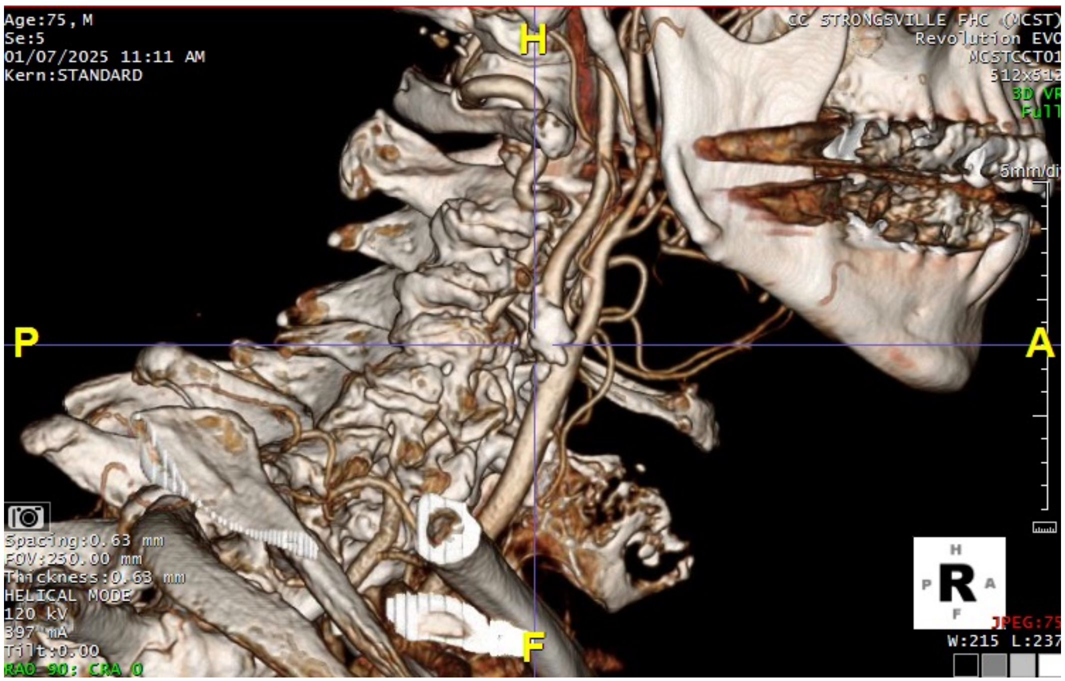
Severe CCA, ICA, ECA calcification

Bovine arch, severe CCA and ICA disease

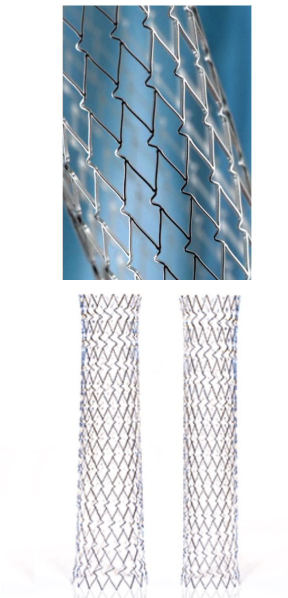
Protection Strategy:
Landing Zones and Vessel Tortuosity

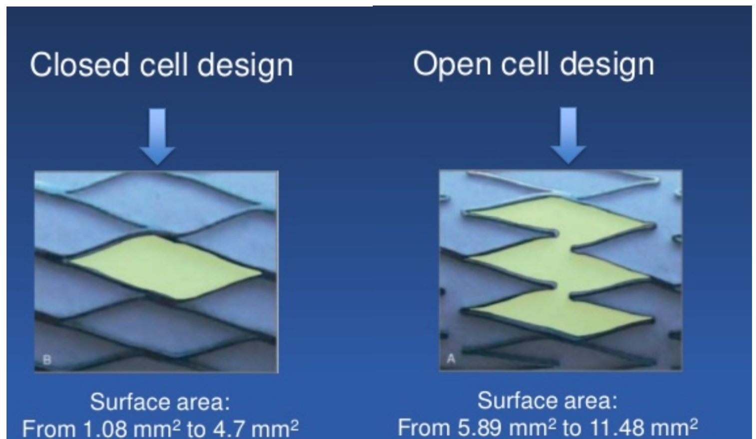
Lesion Findings: Calcium, Ulceration, or Degree of Stenosis

What’s Not a Good Candidate

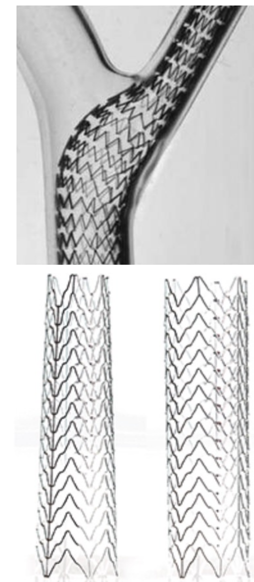


Stent Technology:
Closed Cell vs Open Cell



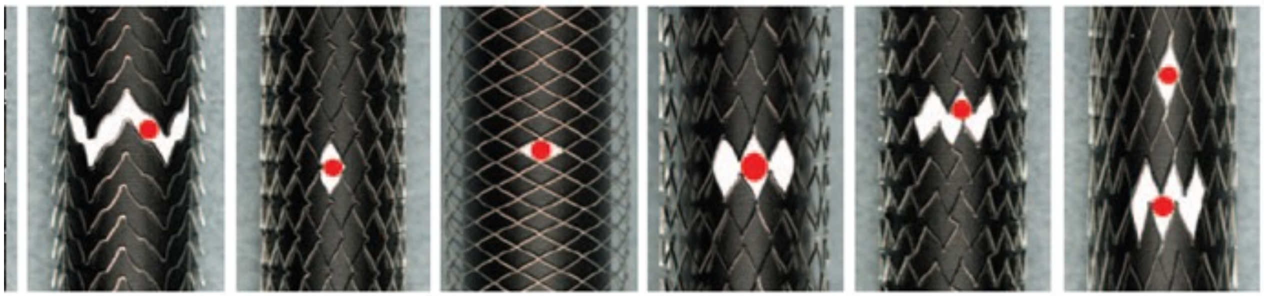


• All cells connected • Smaller Cells • Stiffer	• Some cells connected • Larger Cells • More Flexible



Closed Cell Designs: Good for plaque coverage in straight anatomy
Open Cell Designs: Better apposition in tortuosity

Carotid Stent Design: Comparing Largest Inscribed Circle

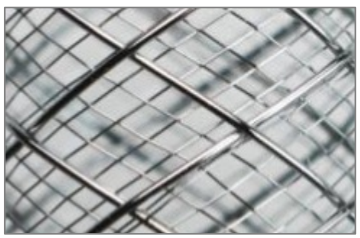


Manufacturer	Abbott Laboratories	Abbott Laboratories	Boston Scientific Corporation	ev3 Inc./ Covidien	Cordis Corporation	Medtronic, Inc./ Invatec
Device	ACCULINK® RX DEVICE	XACT® DEVICE	WALLSTENT® MONORAIL® DEVICE	PROTÉGÉ RX® DEVICE	PRECISE® DEVICE	CRISTALLO IDEALE DEVICE

No significant difference between open cell and closed cell stents for largest inscribed circle Range: 0.8 mm^2 – 1.1 mm^2

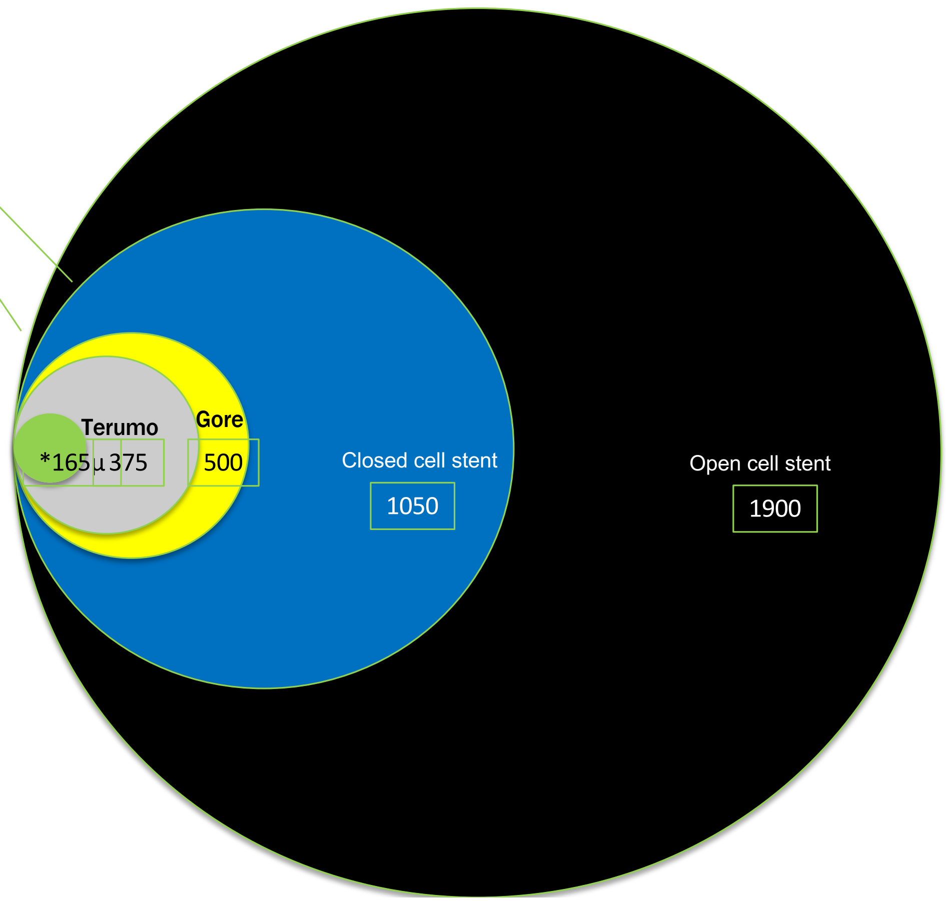
Can We Make TF-CAS Even Better? Micromesh Stents

Inspire MD CGUARD

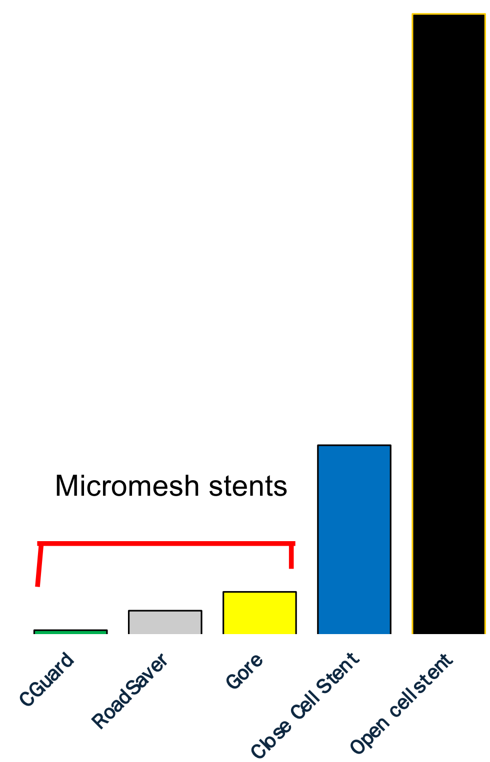


TERUMO Roadsaver

GORE carotid stent



Area Comparison (mm^2)



C-GUARDIANS: 30-Day Major Adverse Events

Event rate in % (n)	ITT (N=316)	Per Protocol^
Death, Stroke or MI*	0.95% (3)	0.63% (2)
Death#	0.32% (1)	0.00% (0)
Any stroke#	0.95% (3)	0.63% (2)
Major Stroke#	0.63% (1)	0.32% (1)
Minor Stroke#	0.32% (2)	0.32% (1)
MI#	0.00% (0)	0.00% (0)
Death or any stroke*	0.95% (3)	0.63% (2)
Death or major stroke*	0.63% (2)	0.32% (1)

30-day S/D/MI

** Hierarchical: patient count (each patient first occurrence of the most serious event). # Non-hierarchical: event count (multiple events in each patient are counted individually).*
^ Per Protocol Analysis excludes 1 patient (did not take dual antiplatelet therapy; had a major stroke and died).

The CEC independently adjudicated all neurological, cardiac events:

- 1 major fatal stroke on post procedural day 10 after all DAPT stopped contrary to protocol requirements.
- 1 minor stroke. (NIHSS 2, post procedure). NIHSS 1, CDU patent 30 days, NIHSS 0 at 6 and 12 months
- 1 retinal infarct in a patient presenting with amaurosis fugax, adjudicated as a minor stroke. (NIHSS 1). NIHSS 0, CDU patent 30 days

The VIVA Foundation. 2023 Late Breakers. Published Nov 1, 2023. Accessed Feb 8, 2026. https://viva-foundation.org/news-article?id=178081

C-GUARDIANS Trial
1-Year Primary Endpoint Results

Kaplan-Meier estimate for all 1-yr endpoints ** Per Protocol Analysis excludes 15 patients with Major Protocol Deviations

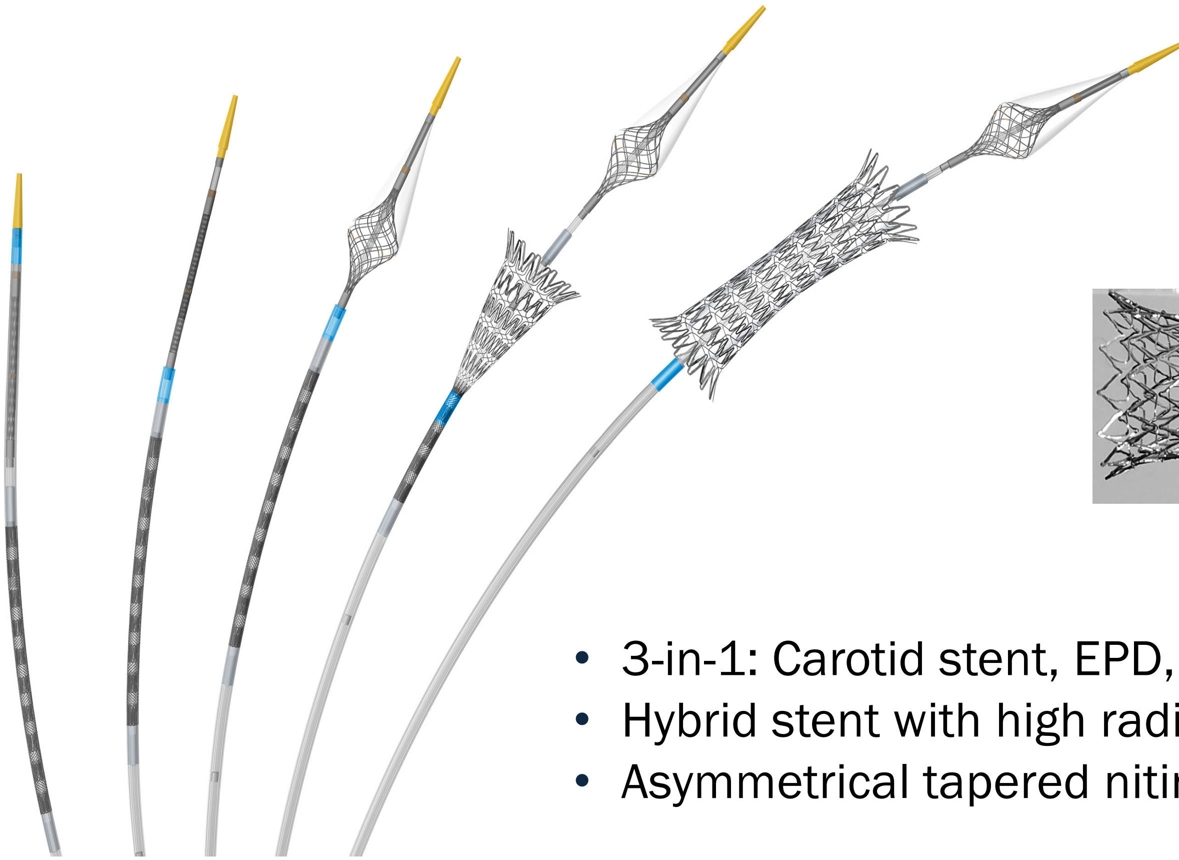
Event*	ITT	Per Protocol**
30-day DSMI + Ipsilateral stroke between 31 and 365 days	1.95 % (6)	1.70% (5)
30-day DSMI	0.95% (3)	0.63% (2)
Ipsilateral stroke between 31 and 365 days	**1.00% (3)**	**1.04% (3)**
TLR	0.98% (3)	1.01% (3)

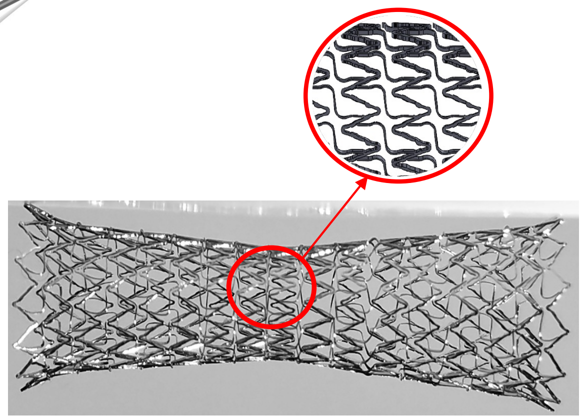
CEC independently adjudicated all neurological, cardiac events:

- 1 minor stroke (retinal) on POD 189
- 1 major stroke on POD 280: Prostatectomy (Antiplatelet therapy stopped)
- 1 major stroke on POD 307: Stent patent; A Fib discovered

The VIVA Foundation. 2024 Late Breaker. Published Nov 4, 2024. Accessed Feb 8, 2026. https://viva-foundation.org/news-article?id=191501

Neuroguard IEP Carotid Stent





- 3-in-1: Carotid stent, EPD, and post-dilation balloon
- Hybrid stent with high radial force and flexibility
- Asymmetrical tapered nitinol stent with flared ends

Integrated Embolic Protection to Address Microembolization during CAS

• Outcomes Through 30 Days and 1 Yr		Paladin IEP[1]	PERFORMANCE	
		N=106	PI (N=67)[2]	PII (N=305)[3]
30-day Outcomes	Major adverse events (DSMI)	1 (1/105)	1.5 (1/67)	2.3 (7/305)
	Death	0 (0/105)	0 (0/67)	0.3 (1/305)
	Stroke (all)	1 (1/105)	0 (0/67)	1.3 (4/305)
	Minor	1 (1/105)	0 (0/67)	1.3 (4/305)
	Major	0 (0/105)	0 (0/67)	0.0 (0/305)
	Myocardial infarction	0 (0/105)	1.5 (1/67)	0.7 (2/305)
1-yr Outcomes	Ipsilateral stroke (all; day 31-365)	--	0 (1/67)	0.4 (1/282)
	Minor	--	0 (1/67)	0.4 (1/282)
	Major	--	0 (1/67)	0 (0/282)

1. Langhoff R, et al. *JACC Cardiovasc Interv*. 2019;12(4):395-403.
2. Langhoff R, et al. *Catheter Cardiovasc Interv*. 2022;100(6):1090-1099.
3. Gray WA, et al. *JACC Cardiovasc Interv*. 2025;18(3):367-376.

PERFORMANCE Trials

Outcomes Through 30 Days and 1 Yr		Paladin IEP[1] N=106	PERFORMANCE PI (N=67)[2]	PII (N=305)[3]	PIII (N=146)
30-day Outcomes	Major adverse events (DSMI)	1 (1/105)	1.5 (1/67)	2.3 (7/305)	0.69 (1/145)
	Death	0 (0/105)	0 (0/67)	0.3 (1/305)	0.69 (1/145)
	Stroke (all)	1 (1/105)	0 (0/67)	1.3 (4/305)	0 (0/145)
	Minor	1 (1/105)	0 (0/67)	1.3 (4/305)	0 (0/145)
	Major	0 (0/105)	0 (0/67)	0.0 (0/305)	0 (0/145)
	Myocardial infarction	0 (0/105)	1.5 (1/67)	0.7 (2/305)	0 (0/145)
1-yr Outcomes	Ipsilateral stroke (all; day 31-365)	--	0 (1/67)	0.4 (1/282)	--
	Minor	--	0 (1/67)	0.4 (1/282)	--
	Major	--	0 (1/67)	0 (0/282)	--

1. Langhoff R, et al. *JACC Cardiovasc Interv*. 2019;12(4):395-403.
2. Langhoff R, et al. *Catheter Cardiovasc Interv*. 2022;100(6):1090-1099.
3. Gray WA, et al. *JACC Cardiovasc Interv*. 2025;18(3):367-376.

PERFORMANCE II: 2-Year Outcomes

	Intention-to-Treat	Per-Protocol[1]
Neurological Death	0.0% (0)	0.0% (0)
Stent Thrombosis	0.0% (0)	0.0% (0)
Clinically-driven Target Lesion Revascularization (CD-TLR)[2]	0.4% (1/260)	0.4% (1/259)
Target Lesion Revascularization (TLR)[3]	2.7% (7/260)	2.7% (7/259)
In-Stent Restenosis (ISR)[4]	3.9% (10/260)	3.9% (10/259)

The VIVA Foundation. 2024 Late Breaker. Published Nov 4, 2024. Accessed Feb 8, 2026. https://viva-foundation.org/news-article?id=191501

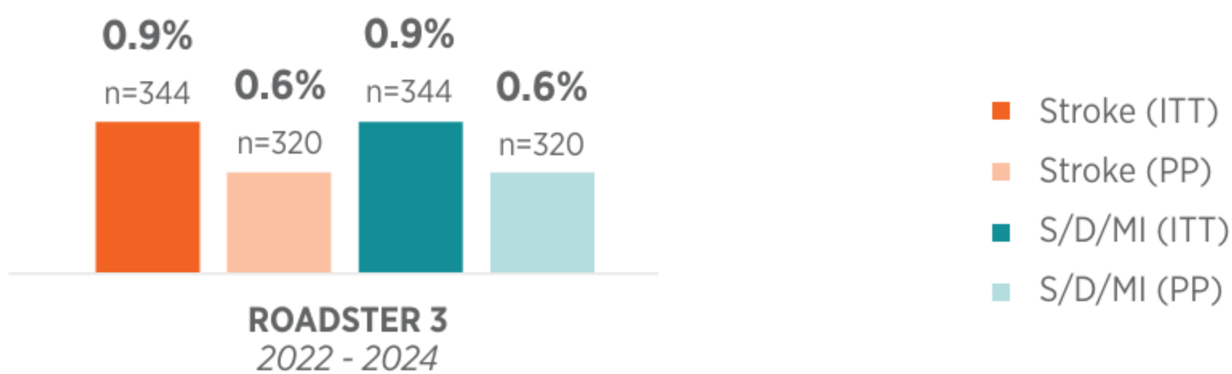
TCAR

Trial	Population	*N*	30-Day Stroke	30-Day Stroke/ Death/MI	Notes
ROADSTER	High surgical risk	~208	1.4%	3,5%	First pivotal TCAR trial; independent neurologic assessment
ROADSTER 2	Real-world high-risk	~1,600+	1,9%	2,3%	Broad operator expericιece
ROADSTER 3	Standard surgical risk	344 ITT/ 319 PP	0.9% (ITT) 0,6% (PP)	0.6% all resolved	First prospective standard-risk TCAR dat- a very low 1-yr ipsi- lateral stroke (0,7%)
			0,9% (ITT) 0,6% (PP)	0.6% all resolved	

Roadster 3 Trial

	ITT Population		PP Population	
Parameter	**Symptomatic** n=56	**Asymptomatic** n=288	**Symptomatic** n=49	**Asymptomatic** n=271
Death/Stroke/MI	0	1.0% (3)	0	0.7% (2)
Stroke	0	1.0% (3)	0	0.7% (2)

No significant difference based on symptomatic status.



The VIVA Foundation. 2024 Late Breaker. Published Nov 4, 2024. Accessed Feb 8, 2026. https://viva-foundation.org/news-article?id=191501

Performance III TCAR with Neuroguard Direct IEP

Secondary Endpoints	N=146 (ITT)
Acute success **Ability to insert the Neuroguard IEP Direct System, deliver the stent, and remove the stent delivery catheter**	**98.63% (144/146)**
Technical Success **Ability to utilize the accessories provided in the Neuroguard Direct Access Kit to establish flow reversal, defined as visualization of blood in the collection tubing**	**99.32% (145/146)**
Procedural Success **Acute Success and Technical Success in the absence of device-related MAEs (defined as the cumulative incidence of stroke, MI and death) prior to discharge**	**98.63% (144/146)**
Cranial nerve injury In the vicinity of the treated carotid artery present at discharge that has not resolved by the 30-day follow-up visit	0.00% (0/146)
Volume of contrast media used during the index procedure, mL	46.42 ± 24.28 (146)
Blood volume collected in the external bag at the end of the procedure, mL	139.34 ± 80.77 (145)
Blood transfusion from procedure through discharge	0.00% (0/146)

PERFORMANCE III
Primary Endpoint: Outcomes through 30 Days

30-day Outcomes†	ITT N=146	PP N=144
Major adverse events through 30 days	0.69% (1/145)	0.00% (0/143)
Death	0.69% (1/145)	0.00% (0/143)
All stroke	0.00% (0/145)	0.00% (0/143)
Minor	0.00% (0/145)	0.00% (0/143)
Major	0.00% (0/145)	0.00% (0/143)
Myocardial infarction	0.00% (0/145)	0.00% (0/143)

Performance III TCAR

- Primary outcome was met
  - 30-day composite of major adverse events (DSMI) of 0.69% (1/145)
  - The upper confidence interval bound of 3.78% is lower than performance goal of 11.0%
- Mean flow reversal time was 7.42 ± 3.45 minutes
- Acute, technical, and procedural success all 99%
- No blood transfusions required
- No cranial nerve injury (CNI)
- No strokes or neurological deaths through 30 days

Regional variation in patient selection, practice patterns, and outcomes based on techniques for carotid artery revascularization in the Vascular Quality Initiative

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- VQU CEA and CAS databases 2016-2021
  - 88,367 CEA 30 Day stroke and death 1.5%
    - 87% conventional 12% eversion
    - 85% prosthetic patch 1% vein
    - Routine shunting 40% selective 8% EEG 30%
    - Completion imaging 60% doppler, 30% duplex, 5% angio
  - 16,298 CAS 30-Day stroke and death 2.9%
  - 22,103 TCAR 30-Day stroke and death 1.6%

Dakour-Aridi H, et al. *J Vasc Surg*. 2022;76(4):e54-e55.

Clinical Data from CREST-2 Registry

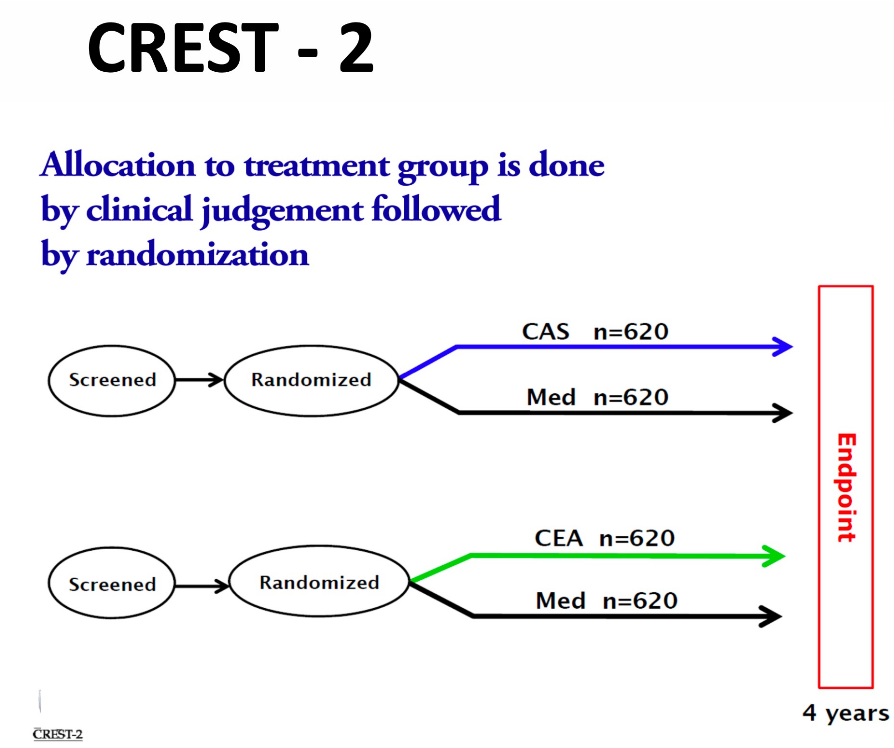
- CAS achieved low 30-day stroke/death rates for both asymptomatic and symptomatic patients with operator experience and patient selection

	All Patients (N = 2,141*; 100%)	Asymptomatic (n = 1,180; 55.1%)	Symptomatic (n = 961; 44.9%)
Stroke or death	43 (2.0)	16 (1.4)	27 (2.8)
Any stroke, regardless of laterality	35 (1.6)	12 (1.0)	23 (2.4)
Stroke ipsilateral to the index artery	31 (1.5)	9 (0.8)	22 (2.3)
Stroke contralateral to the index artery	10 (0.5)	5 (0.4)	5 (0.5)
Death	8 (0.4)	4 (0.3)	4 (0.4)
Stroke, death, or MI	47 (2.2)	18 (1.5)	29 (3.0)
MI	4 (0.2)	2 (0.2)	2 (0.2)
Stroke, death, MI, or major† access site complications	59 (2.8)	27 (2.3)	32 (3.3)
Major access site complications	13 (0.6)	9 (0.8)	4 (0.4)

Lal BK, et al. *JACC*. 2019;74(25):3071-3079.

CREST-2

- CREST-2: Parallel RCT of CAS vs OMT and CEA vs OMT in pts with ≥70% asymptomatic disease
- 1° endpoint: The proportion of patients who experienced any stroke or death *within 44 days of randomization* **<u>or</u>** ipsilateral ischemic stroke thereafter up to 4 yrs (estimated by Kaplan-Meier survival function)



OMT = optimized medical therapy.

ALL Carotid Patients Need Concomitant OMT
OMT Is a Big Reach in the *Real World*

Treatment	Details
Life style modification	Smoking cessation, moderation of alcohol intake, moderate intensity exercise 4 to 7 days per week, at least 150 min per week, Mediterranean diet
Antithrombotic therapy	Aspirin 75-325 mg/day Clopidogrel 75 mg per day Ticagrelor 90 mg BD (if intolerant or allergic to Aspirin)
Lipid-lowering therapy	LDL target <70 mg/dL High-dose statin If not controlled - add ezetimibe, PCSK9 inhibitor
Antihypertensive therapy	Target <130/80 mm Hg
Glucose-lowering therapy	Target HbA1c <7.0%

LDL=Low-density lipoprotein







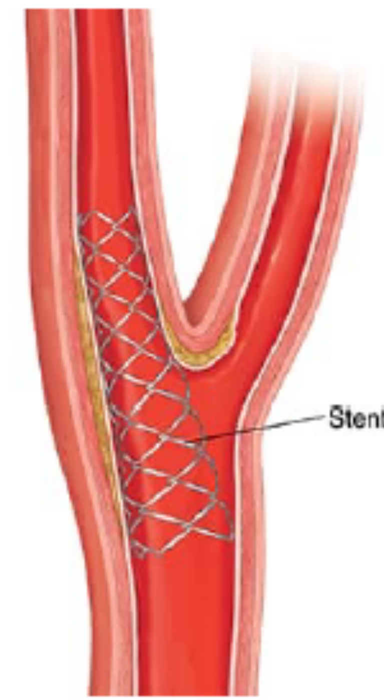

CREST-2 had a third-party risk factor management program (INTERVENT) to manage and ***direct OMT to GOAL, not just be on the right medications***

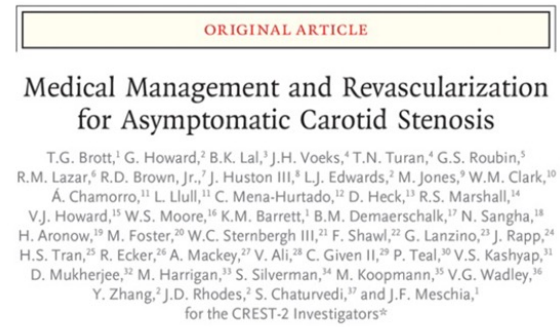
Kleindorfer D, et al. *Stroke*. 2021;52(7):e364-e467.

CREST-2

Key CAS Details

- Credentialing criteria: ≥100 lifetime cases + ≥25 cases in last 12 months
- ≈50% of interventionists who applied were accepted
- Key exclusions
  - Lesions >2cm
  - Circumferential calcification
  - Severe tortuosity
  - Type III aortic arch




ORIGINAL ARTICLE

Medical Management and Revascularization for Asymptomatic Carotid Stenosis

T.G. Brott,[1] G. Howard,[2] B.K. Lal,[3] J.H. Voeks,[4] T.N. Turan,[4] G.S. Roubin,[5] R.M. Lazar,[6] R.D. Brown, Jr.,[7] J. Huston III,[8] L.J. Edwards,[2] M. Jones,[9] W.M. Clark,[10] Á. Chamorro,[11] L. Llull,[11] C. Mena-Hurtado,[12] D. Heck,[13] R.S. Marshall,[14] V.J. Howard,[15] W.S. Moore,[16] K.M. Barrett,[1] B.M. Demaerschalk,[17] N. Sangha,[18] H. Aronow,[19] M. Foster,[20] W.C. Sternbergh III,[21] F. Shawl,[22] G. Lanzino,[23] J. Rapp,[24] H.S. Tran,[25] R. Ecker,[26] A. Mackey,[27] V. Ali,[28] C. Given II,[29] P. Teal,[30] V.S. Kashyap,[31] D. Mukherjee,[32] M. Harrigan,[33] S. Silverman,[34] M. Koopmann,[35] V.G. Wadley,[36] Y. Zhang,[2] J.D. Rhodes,[2] S. Chaturvedi,[37] and J.F. Meschia,[1] for the CREST-2 Investigators*

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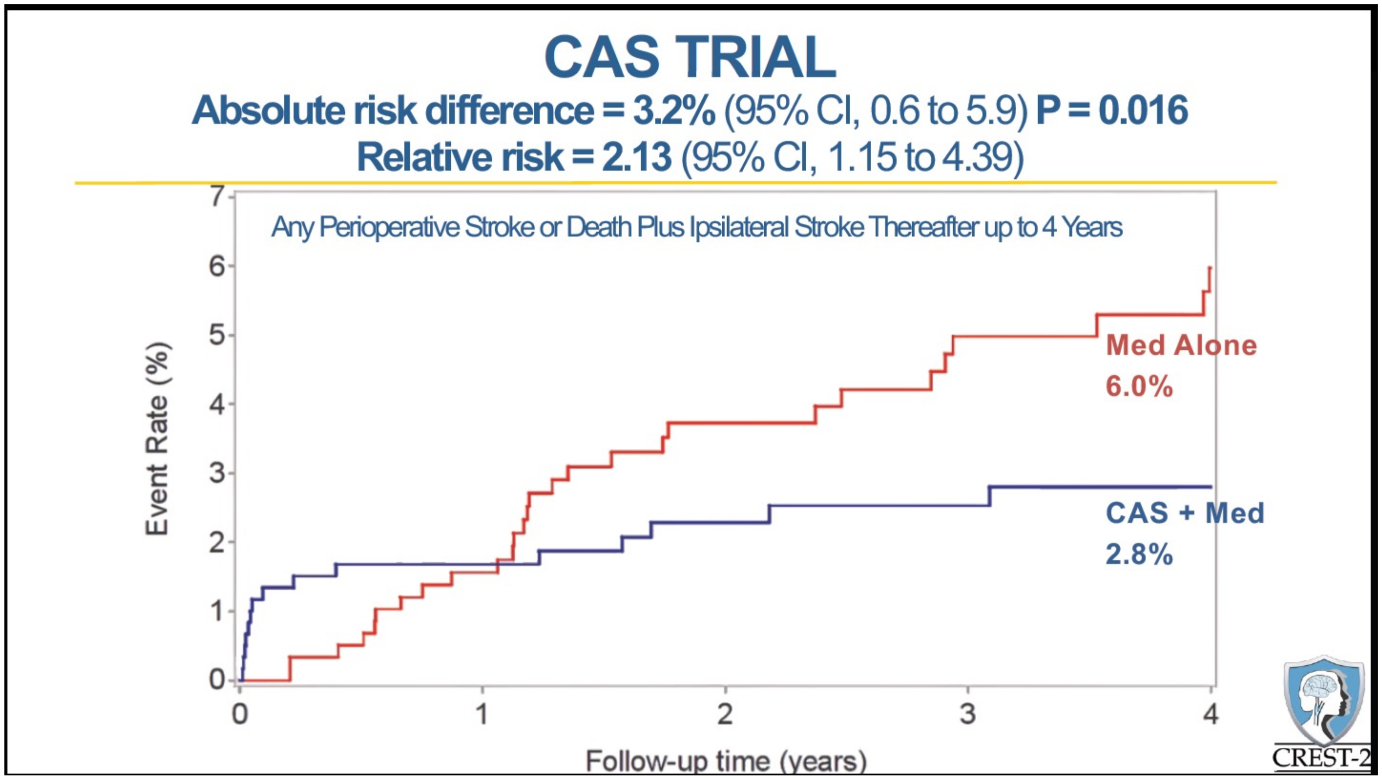
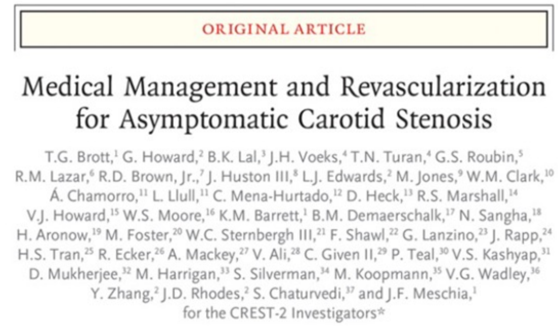
CREST-2





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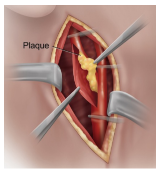
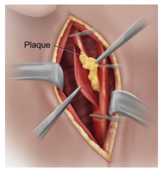
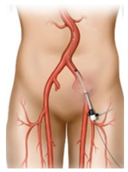
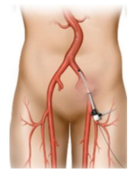
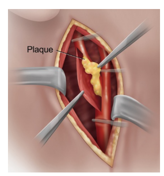
Potential Treatment Approach Based on Patient Characteristics

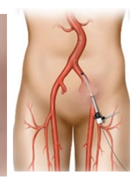
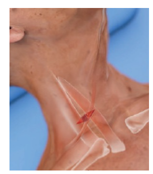





CEA	CEA/TFCAS	TFCAS	TFCAS/TCAR	TCAR
Low Surgical Risk Complex Access/Arch/CCA Short/Diseased CCA Recently Symptomatic	Low Surgical Risk Good Femoral/Radial Acc Complex Access/Arch/CCA Short/Diseased CCA	High Surgical Risk (Anatomic/Comorbidities) Good Femoral/Radial Acc Young (<75)	High Surgical Risk (Anatomic/Comorbidities) Good Femoral/Radial Acc Young (<75)	High Surgical Risk (Anatomic/Comorbidities) Difficult Femoral Access Recently Symptomatic



CEA/TFCAS/TCAR: Low Surgical Risk, Good Femoral/Radial/CCA Access, Young (<75), Recently Symptomatic

CMS Requirement
Formal Patient-Physician Shared Decision-Making Interaction

- Requirement established due to the importance of individual patient anatomy, pathophysiology, and preferences, and since CAS and CEA come with different procedural risk
- **The shared decision-making interaction must include:**

- Discussion of all treatment options, including carotid endarterectomy (CEA), CAS (which includes transcarotid artery revascularization [TCAR] and optimal medical therapy [OMT])
- Explanation of risks and benefits for each option specific to the beneficiary's clinical condition
- Integration of clinical guidelines (eg, patient comorbidities and concomitant treatments)
- Discussion and incorporation of the beneficiary's personal preferences and priorities in choosing a treatment plan

Conclusions

- Newer data supports stenting as equivalent therapy
- Long-term outcomes equivalent to CEA
- Newest devices have had lowest event rates ever

Discussion

- Guillerme Dabus, MD, FAHA
  William Gray, MD, FACC, MSCAI
  Sean P. Lyden, MD, FACS
  Kenneth Rosenfield, MD, MHCDS, FACC, FAHA, MSCAI

Thank You