Abbott Vascular Statement to the MEDCAC Panel on Management of Carotid Atherosclerosis

MEDCAC Panel Meeting
January 25, 2012

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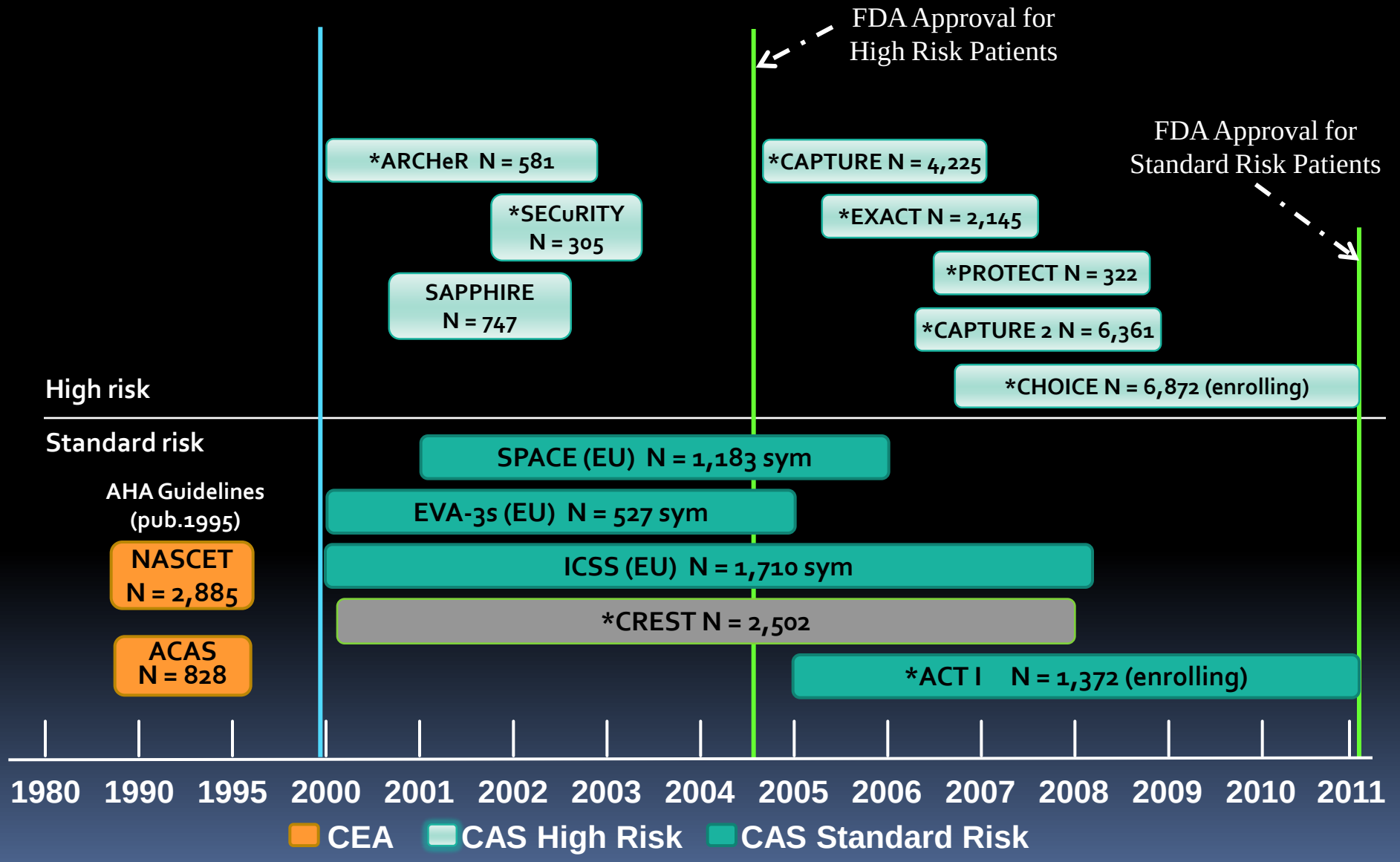
Treatments for Carotid Artery Disease

- 'Best Medical Therapy' (BMT) is a cornerstone treatment for all carotid artery disease patients
- Standard of care* supports revascularization for symptomatic and asymptomatic patients with hemodynamically significant stenosis
- Carotid artery stenting (CAS) and carotid endarterectomy (CEA) have similar net outcomes, and they are comparable alternatives
- A personalized approach for treating carotid artery disease is needed, and individual patient risk factors should dictate the "favored treatment strategy"
- The Panel should have high confidence that CAS and CEA are superior to BMT alone, and reasonable alternatives to one another
- New diagnostic tests and advanced imaging techniques show great promise to risk stratify asymptomatic patients. However, currently-available evidence does not support the broad (or mandated use) of these technologies.

* Per the multi-society guidelines, Class I evidence supports revascularization (CAS or CEA) of symptomatics with ≥50% stenosis. For asymptomatics with ≥70% stenosis, there is Class IIa and IIb evidence for CAS and CEA, respectively.

Carotid Stenting Clinical Research Programs
Abbott Vascular* Evaluating CAS Treatment > 20,000 patients



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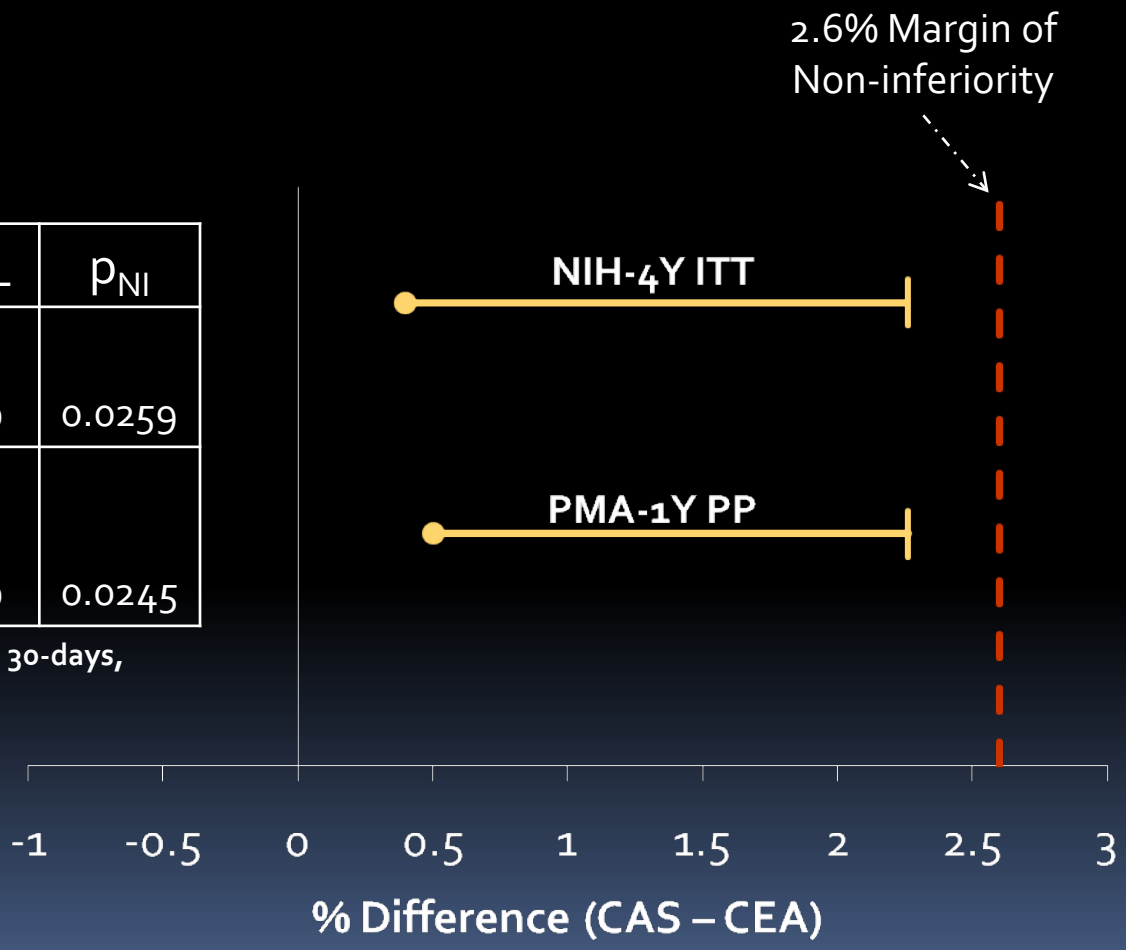
CREST Provided Best Available U.S. Evidence to Compare Carotid Revascularization Strategies

- Pivotal NIH-sponsored, randomized comparative effectiveness trial compared CAS to CEA in standard surgical risk patients, included symptomatic and asymptomatic patients
- Collaborative design involved academic scientists, three government agencies [NIH, FDA, HCFA] and industry
- Largest randomized controlled trial (RCT) of CAS vs. CEA in standard risk population (2,500+ subjects)
- Sufficient procedural training allowed for an appropriate comparison between CAS and CEA

CREST NIH and Regulatory Analyses Are Consistent and Complementary

	CAS	CEA	95% CL	p_{NI}
NIH-4Yr **ITT**	7.2%	6.8%	2.26%	0.0259
PMA-1Yr **PP**	7.1%	6.6%	2.26%	0.0245

*** Primary Endpoint of Death, Stroke, or MI up to 30-days, plus ipsilateral stroke thereafter.**



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

No Statistical Difference for Components of Primary Endpoint (Death, Stroke and MI within 30 Days)

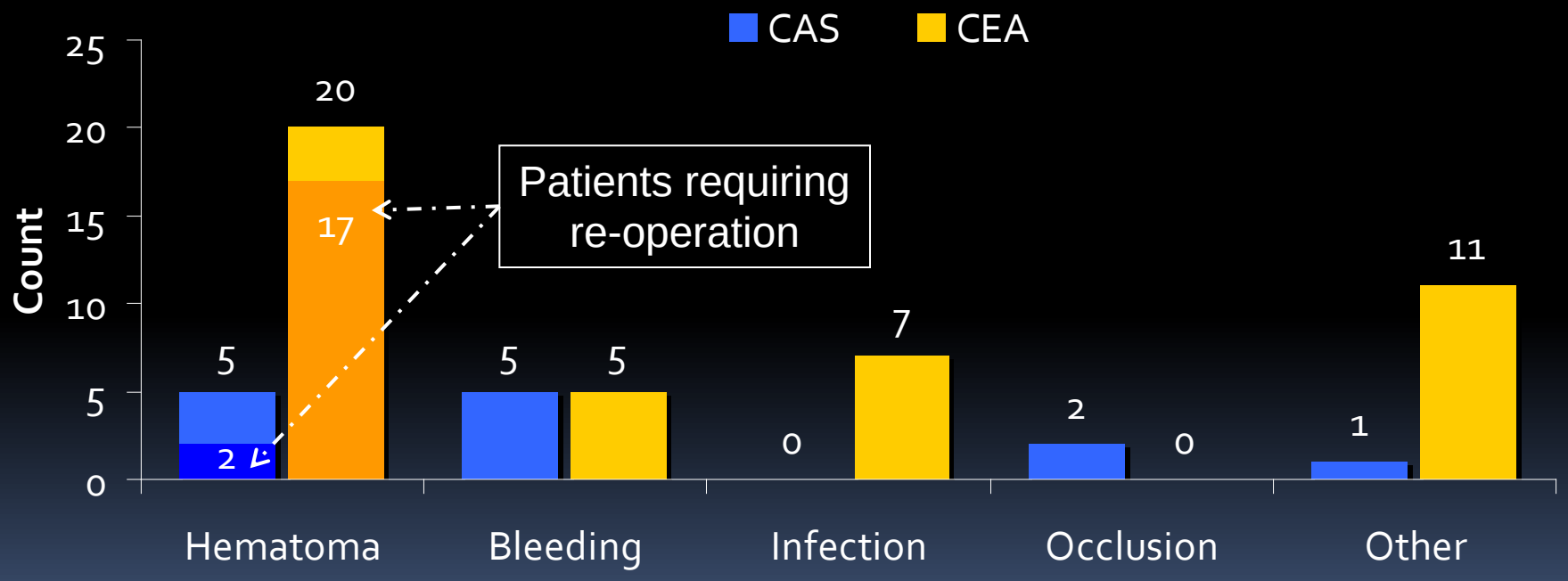
CREST Per Protocol	CAS N = 1,131	CEA N = 1,176	Difference	Unadjusted p-value*
All Death, Stroke, or MI	5.8% (65)	5.1% (60)	0.7%	0.5200
Death	0.53% (6)	0.26% (3)	0.27%	0.3335
Any Stroke	4.1% (46)	1.9% (22)	2.2%	0.0019
Major Stroke	0.9% (10)	0.4% (5)	0.5%	0.2005
Minor Stroke	3.2% (36)	1.5% (18)	1.7%	0.0088
MI	2.0% (22)	3.4% (40)	-1.5%	0.0387

* Fisher's exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

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

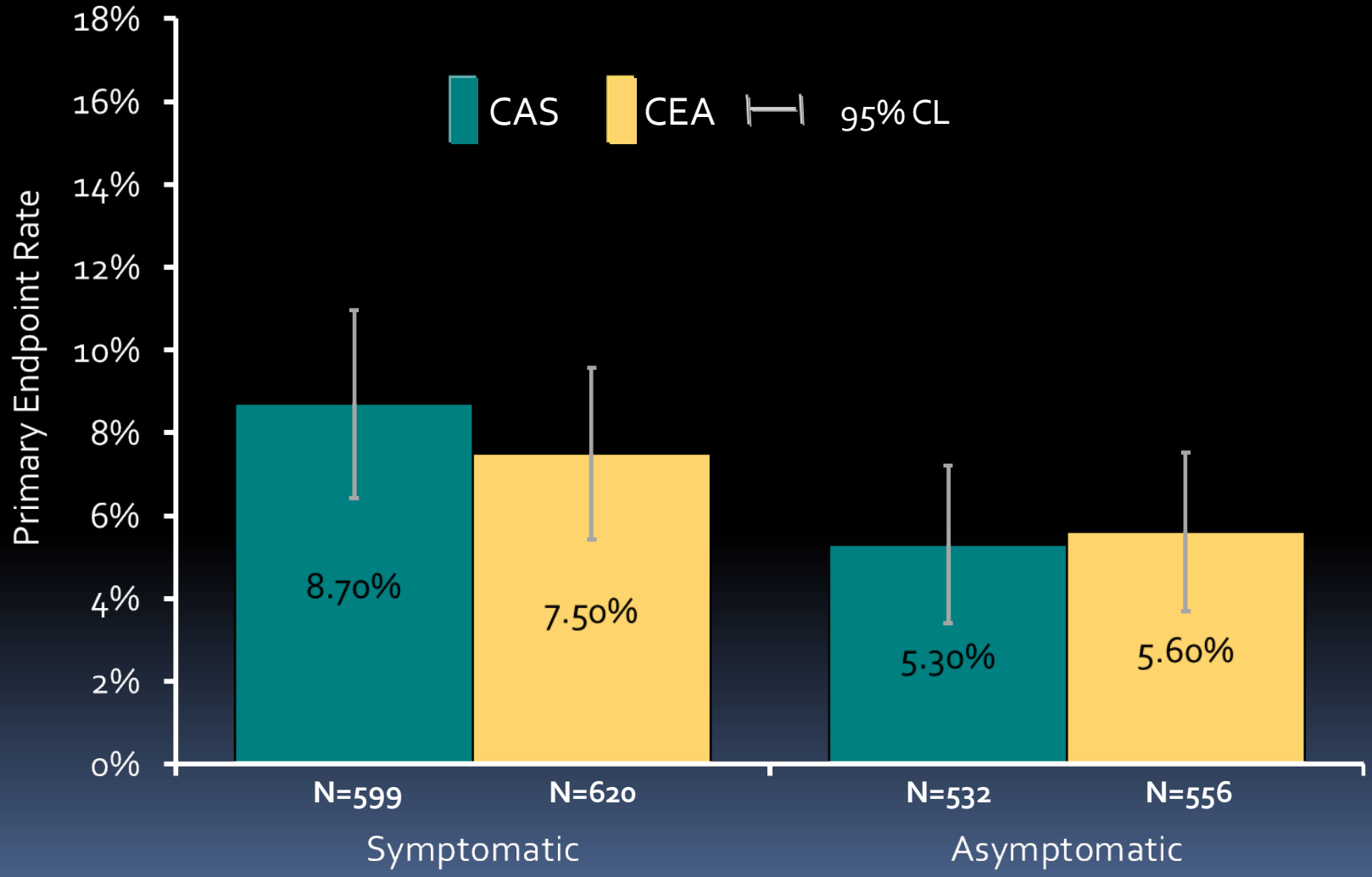
More Access Site Complications with CEA in CREST

	CAS N = 1,157	CEA N = 1,246	p-value
Access Site Complication Requiring Treatment	1.1%	3.5%	0.0001



Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247780.pdf.
*From FDA executive summary. Circle and text added for emphasis.

No Significant Difference for Primary Composite Endpoint by Symptomatic Status in CREST



Source:
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CREST All Stroke and Death Rates for CAS Are Low and Within AHA Guidelines

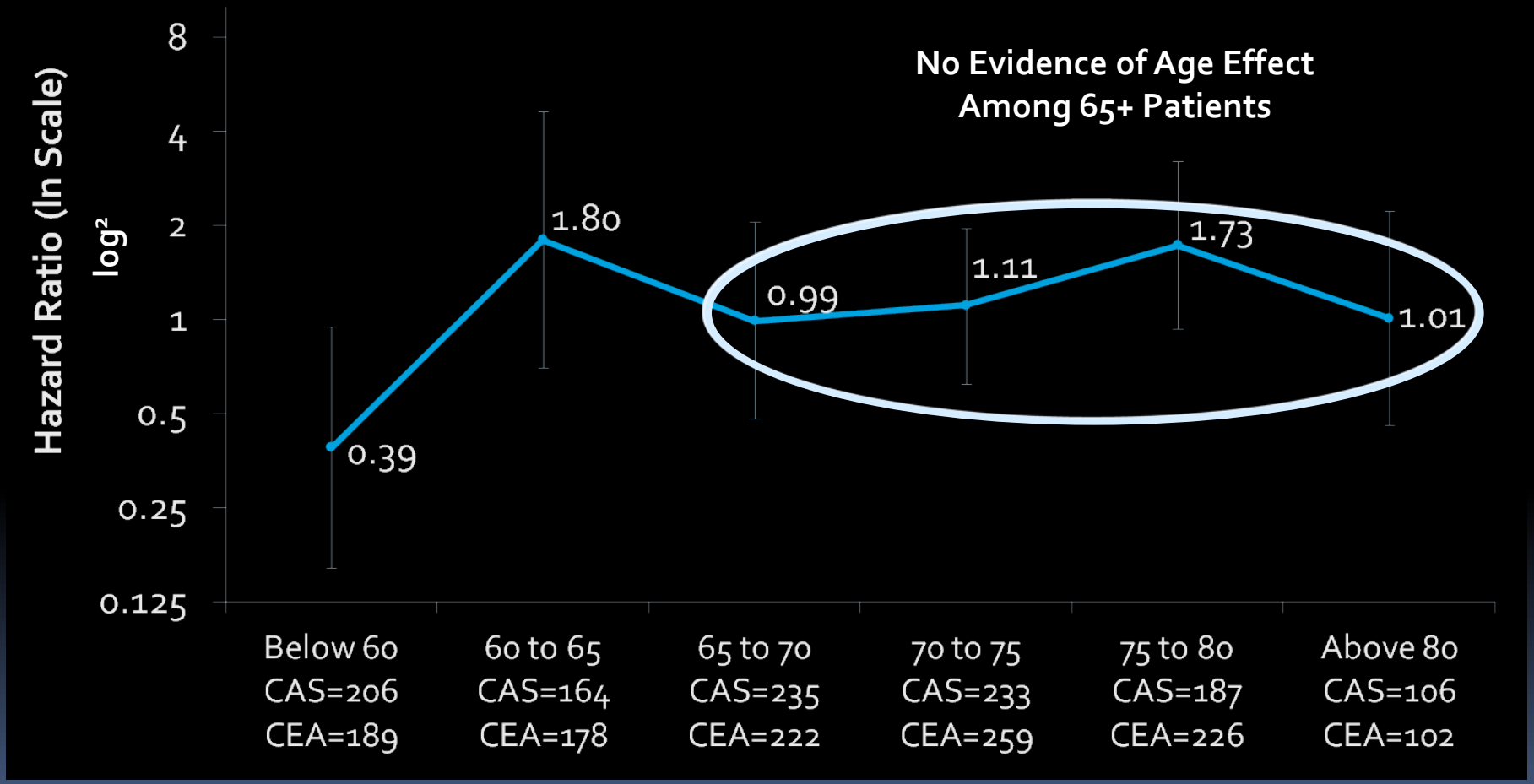
Subgroup	CAS	CEA	AHA Guidelines+
Symptomatic*	5.6%	2.6%	< 6.0%
Asymptomatic*	2.4%	1.5%	< 3.0%

* Octogenarians excluded (1,091 asymptomatic and 1,170 symptomatic patients).

+ AHA Guidelines based on *any* stroke (ipsilateral or contralateral) or death in peri-procedural period (30 days); figures from CREST calculated consistent with AHA Guidelines approach.

* Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, Goldstein LB, Meschia JF, Ferguson RD, Moore WS, Howard G, Brott TG, for the CREST Investigators. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;42:675-680.

No Difference in Outcomes by Age Among Elderly Subjects in CREST*



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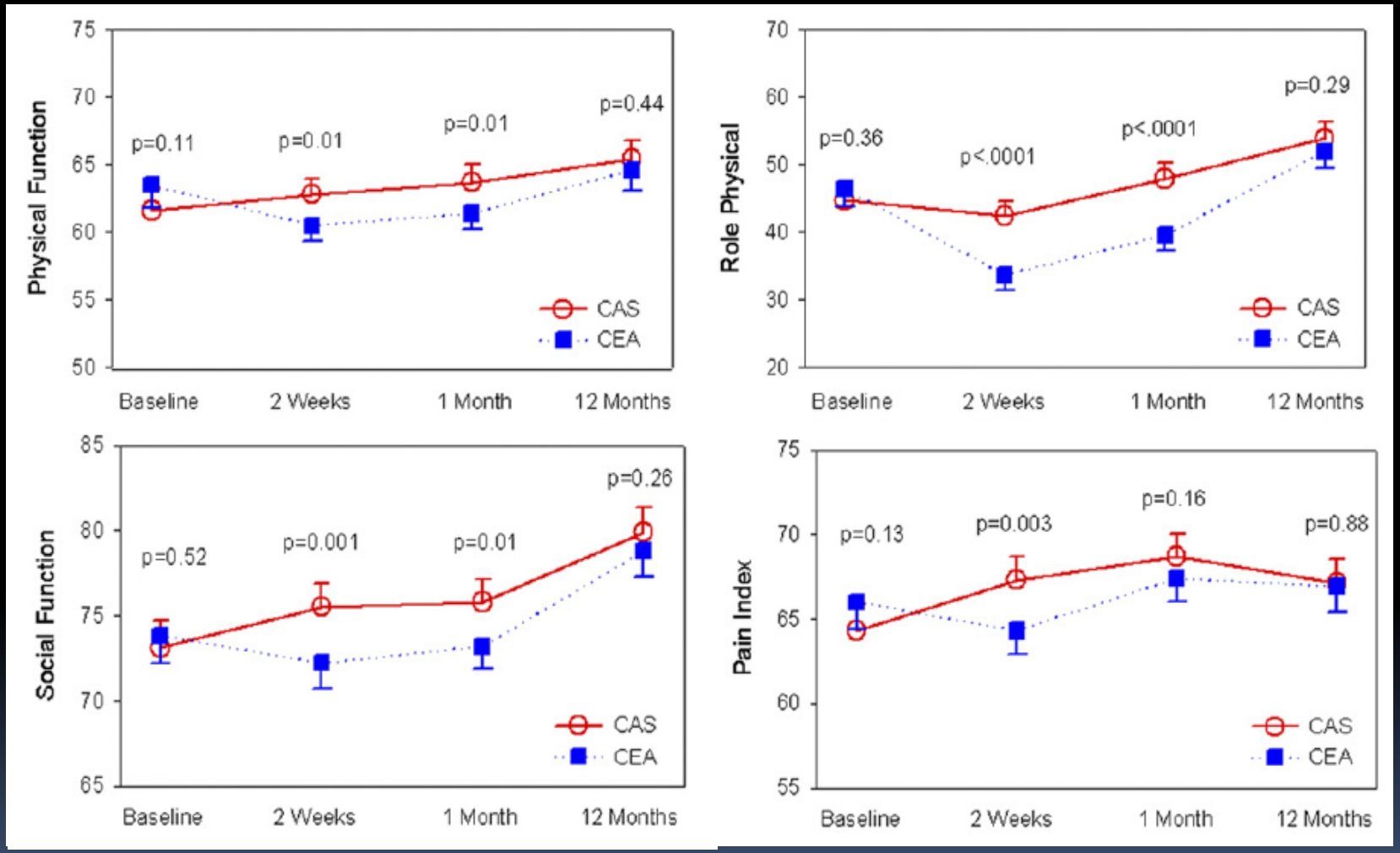
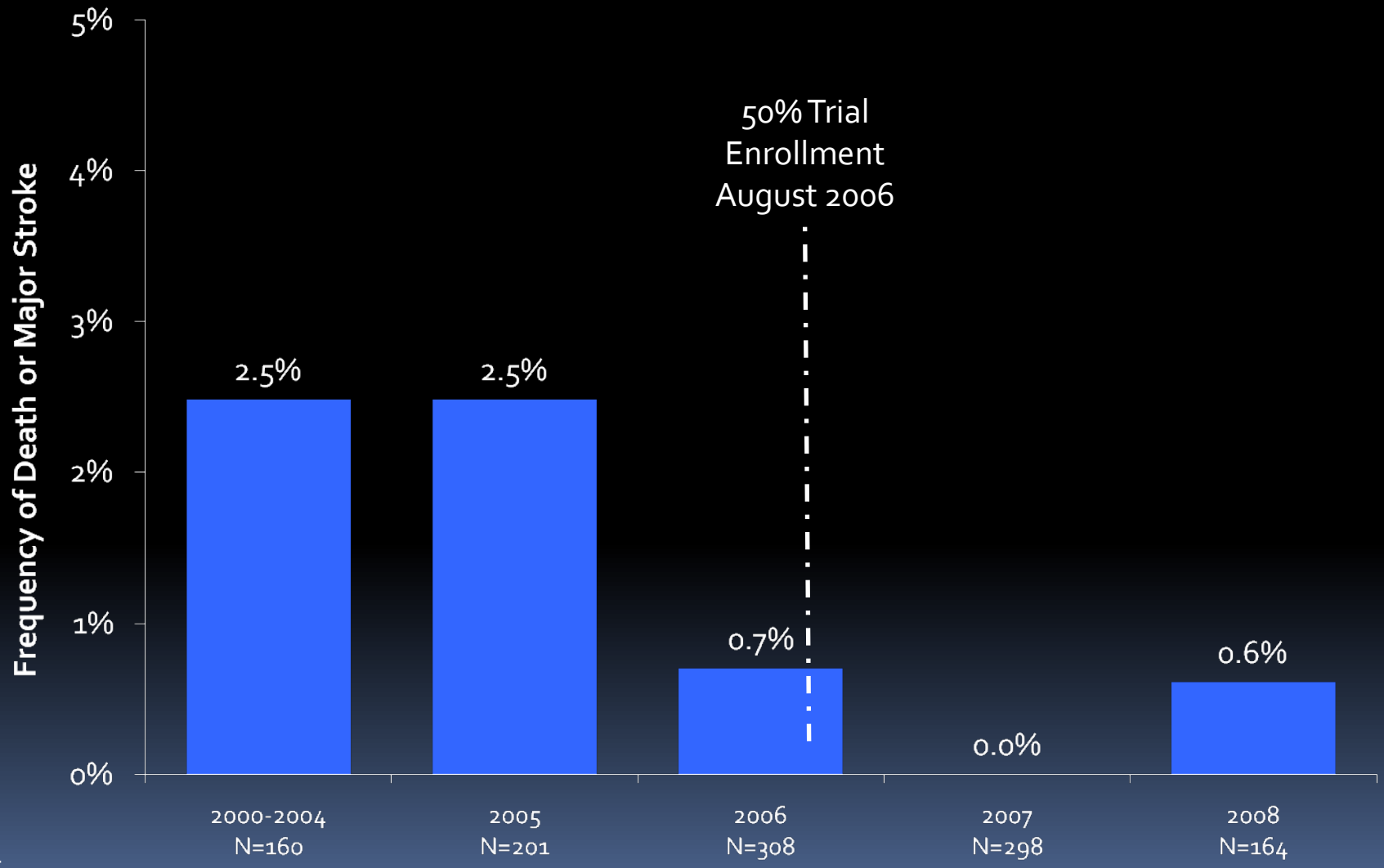
CREST Quality of Life Outcomes: CAS and CEA Equivalent at One Year



Source: Cohen DJ, et al. Health-Related Quality of Life after Carotid Stenting versus Carotid Endarterectomy: Results from CREST. *Circulation* 2011;58:1557-1565.

Death or Major Stroke Rates Decrease for CAS over the Period of CREST Enrollment



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Evidence Now Supports CAS as an Appropriate Treatment Option for Carotid Artery Disease

- Current standard of care is revascularization (CAS or CEA) for symptomatic or asymptomatic patients with hemodynamically significant stenosis of the internal carotid artery
- CAS is now FDA approved for symptomatic and asymptomatic patients at standard surgical risk, based on rigorous evidence from CREST
- CREST represents the best evidence supporting CAS
  - Prospective randomized design
  - Robust sample size (2,500+ patients)
  - Proper physician training
  - Routine use of embolic protection devices
  - Appropriate screening for MI
- CAS represents a safe and effective treatment option for patients with obstructive carotid artery disease who are at standard surgical risk
- CAS should be available to Medicare beneficiaries

Appendix

CREST Study Leads to FDA Label Expansion in Standard Risk Patients

- FDA approved for high surgical risk patients in August 2004
- FDA advisory panel recommended approval for standard surgical risk patients on January 26, 2011, based on the NIH-sponsored CREST trial
- FDA approved for standard surgical risk patients in May 2011

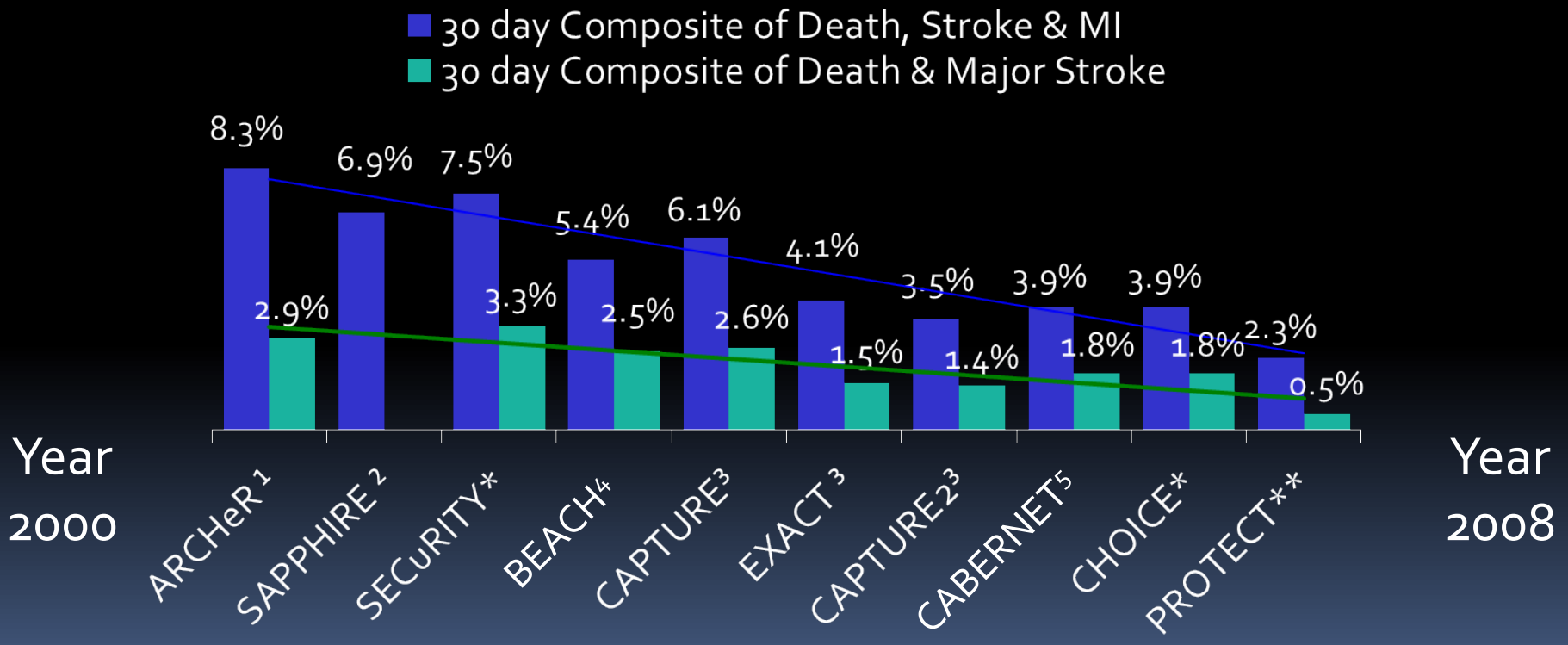
FDA Approved Indications – Acculink Carotid Stent System

Symptomatic Status	High Risk Approval Aug. 30, 2004	Standard Risk Approval May 6, 2011
Symptomatic	≥50% stenosis by ultrasound or angiogram	≥70% stenosis by ultrasound or ≥50% stenosis by angiogram
Asymptomatic	≥80% stenosis by ultrasound or angiogram	≥70% stenosis by ultrasound or ≥60% stenosis by angiogram

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

30 Day Stroke and Death Rates for CAS Are Low and Improving Over Time in High Risk Patients

- CAS results have vastly improved due to: (1) more experienced operators; (2) better patient selection; and (3) improved technology
- CAS outcomes have evolved over time similarly to CEA



[1] Gray et al, 2006; [2] Massop et al, 2009; [3] Gray et al, 2009; [4] White et al, 2006; [5] Hopkins et al, 2008
*Not yet published; **Matsumura et al, 2011 *accepted J Vasc Surgery*

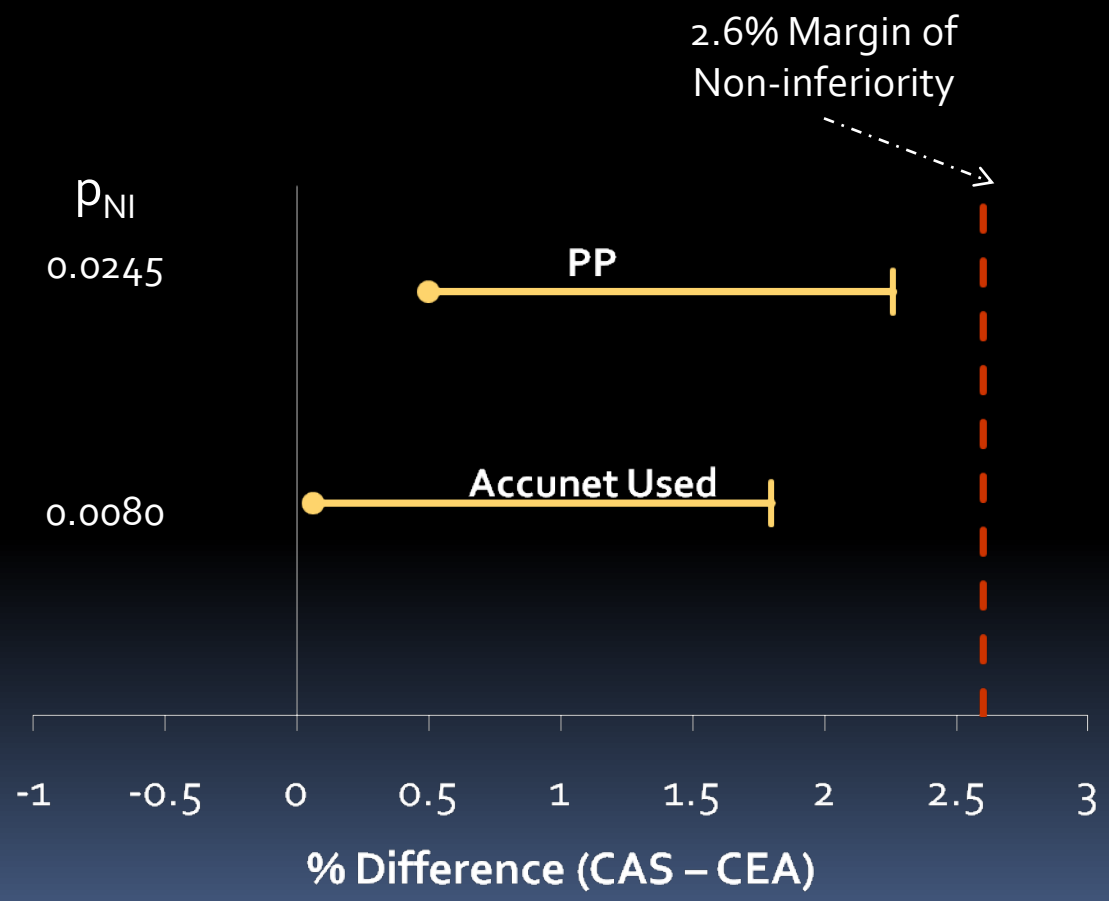
CREST was Designed to Involve Two Separate Analyses for NIH and FDA Regulatory Approval

	CREST NIH Analysis	CREST FDA Analysis
Objective	To provide scientific and academic evaluation of two carotid revascularization strategies	To expand label indication to include Standard Risk patients for the Acculink Carotid Stent System
Primary Endpoint	Stroke, MI or death in 30 days, ipsilateral stroke thereafter	
	4 years	1 year
Primary Population	Intent-to-Treat	Per-Protocol
Primary Analysis	Superiority	Non-inferiority
Number of Patients	2,502	2,307
Median Follow-up	2.5 years	3 years

Source: Hobson, Howard, Brott, Howard, Rubin, Furgeson. Organizing CREST: NIH, HCFA and industry funding. *Current Controlled Trials in Cardiovascular Medicine*. 2001

A Lower Primary Endpoint Rate Was Observed in CAS Patients Treated with the Accunet EPD

	CAS	CEA	95% CL	p_{NI}
PP	7.1%	6.6%	2.26%	0.0245
Accunet Used	6.6%	6.6%	1.80%	0.0080



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NIH CREST Analysis Confirms Independent Importance of MI in Predicting Late Mortality

	Hazard Ratio Unadjusted p-value	Hazard Ratio Risk-adjusted p-value
Confirmed MI N = 42	3.40 p < 0.001	3.67 p = 0.001
Biomarker-only MI N = 20	3.57 p < 0.001	2.87 p = 0.023

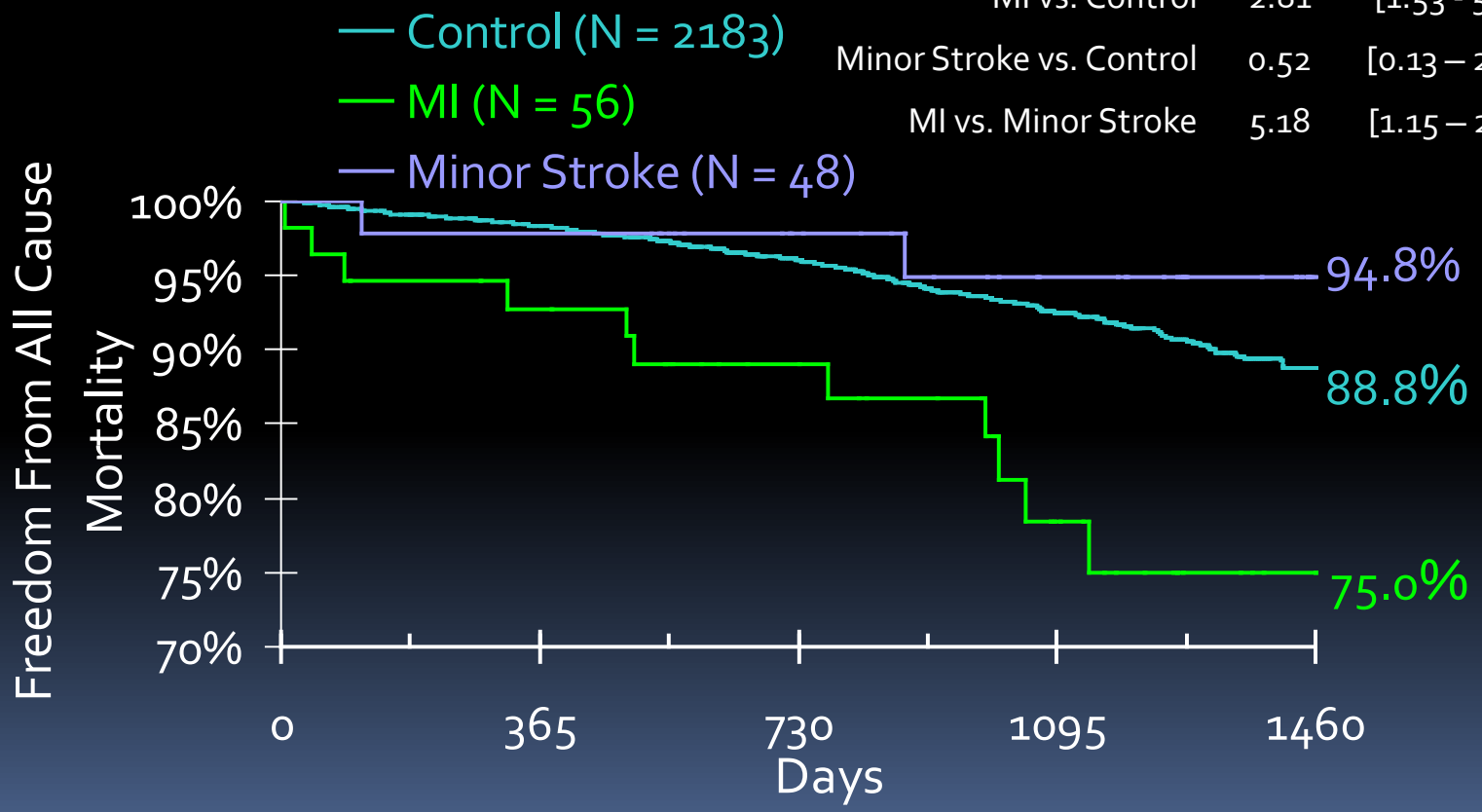
Multivariate model adjusted for age, prior CV disease, diabetes, previous CABG, and baseline creatinine clearance (No MI: N = 2440)

- **Periprocedural MI after carotid revascularization yields a three-fold higher risk of long-term mortality**
- **Increased long-term mortality from peri-procedural MIs should be considered when comparing revascularization techniques, CAS versus CEA.**

Blackshear JL, Cutlip DE, Roubin GS, et al. for the CREST Investigators. Myocardial Infarction following Carotid Stenting and Endarterectomy: Results from CREST. *Circulation* 2011.

MI Is Associated With Long Term Mortality, While Minor Stroke Is Not

Comparison	HR	HR Confidence Interval	Log Rank P-value
MI vs. Control	2.81	[1.53 - 5.17]	0.0005
Minor Stroke vs. Control	0.52	[0.13 – 2.09]	0.34
MI vs. Minor Stroke	5.18	[1.15 – 23.4]	0.02



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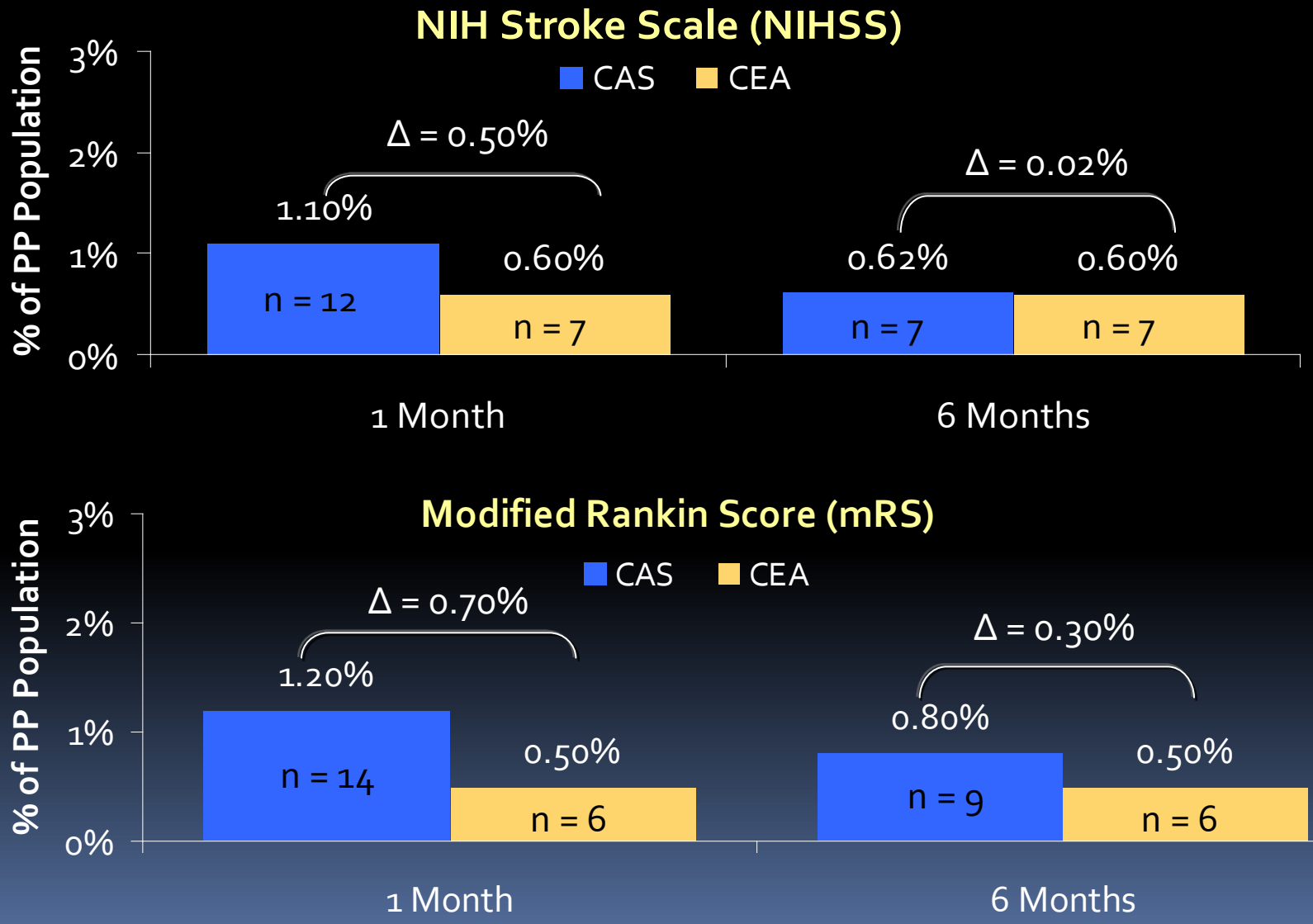
Neurological Residual Deficits Associated with Minor Strokes, Equal at 6 Months



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Death, Stroke and MI within 30 Days by EPD Usage (PP) in CREST

Per Protocol	Accunet® EPD Used N = 1,073	EPD Not Used N = 24	Difference [95% CI][1]
All Death, Stroke, and MI[2]	5.3%	20.8%	-15.5% [-31.8%, 0.8%]
Death[2]	0.4%	8.3%	-8.0% ANM
All Stroke[2]	3.8%	8.3%	-4.5% ANM
Major Stroke	0.7%	4.2%	-3.4% ANM
Minor Stroke	3.1%	4.2%	-1.1% ANM
MI[2]	1.9%	8.3%	-6.5% ANM

Note: Only includes each subject's first occurrence of the event.

[1] By normal approximation

[2] Hierarchical event in first row, all other are non-hierarchical events

[3] ANM: Assumptions Not Met

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

PROTECT: Best CAS Event Rates to Date Among High Surgical Risk Patients

30-day Major Event	Rate (N=220)
Death, Stroke and MI*	2.3%
Death	0.5%
All Stroke	1.8%
Major Stroke	0.5%
Minor Stroke	1.4%
MI	0.5%
Death and All Stroke*	1.8%
Death and Major Stroke*	0.5%

* Hierarchical - Includes only the most serious event for each patient and includes only first occurrence of each event.
[#] Accepted for publication to *J Vasc Surg*, Oct. 2011.

Significant Benefits of Revascularization vs. Best Medical Therapy in Two RCTs

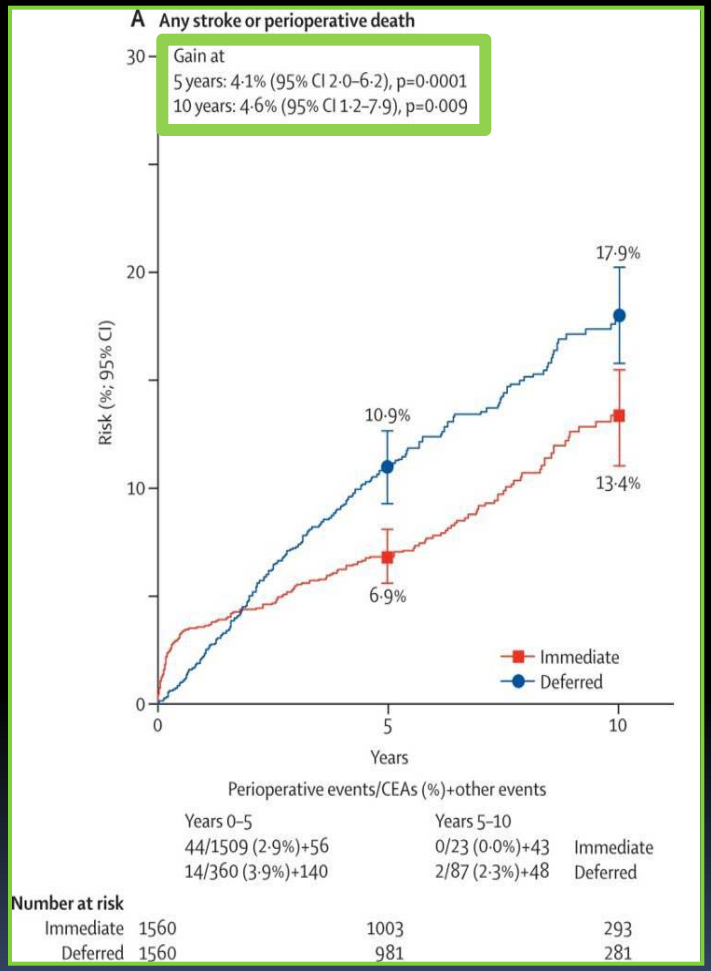
Revascularization Lowers Stroke and Death Rates in Asymptomatic Patients

Study	Treatment Arm	Perioperative Stroke and Death	5 Yr Ipsilateral Stroke and Death	5 Yr All Stroke and Death
ACAS (1987-1993)	CEA + BMT	2.3%	5.1%	-
	BMT	NA	11.0%	-
ACST* (1999-2003)	CEA + BMT	3.1%	-	6.9%
	BMT	NA	-	10.9%

CEA = Carotid endarterectomy
BMT = Best Medical Therapy
* Note: ACST treatment arms involved immediate CEA vs. deferred CEA. Immediate CEA labeled *CEA + BMT* above and deferred CEA labeled *BMT*.

Sources: Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *J Am Med Assoc* 1995;273:1421–1428; and Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: an RCT. *Lancet* 2004; 363: 1491–1502.

ACST 10-year Follow-up Results Provide Most Rigorous Comparison of Revascularization and BMT

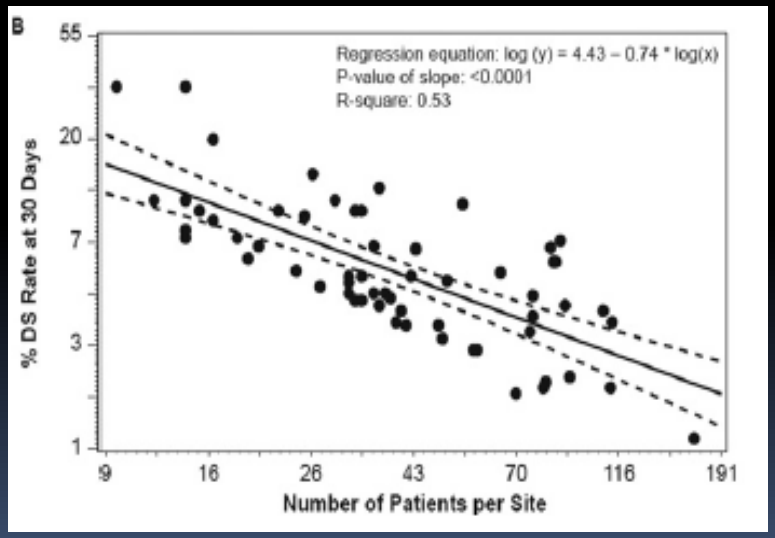


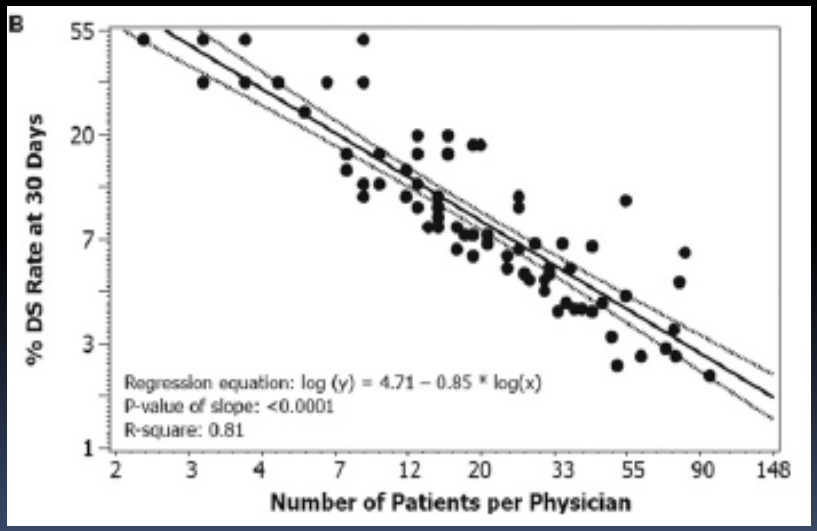
- Revascularization continues to show statistically significant benefit at 5- and 10-year follow up
- Patients followed up to 2009
- Patients received intensive medical therapy
  - 80% of subjects on lipid lowering drugs
  - 88% of subjects on anti-hypertensives
  - 88-89% of subjects on anti-platelets
- Post-hoc analysis found CEA benefit was clearest for patients on lipid-lowering medication or under age 75 years

* Halliday A, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial. *Lancet* 2010;376:1074-84.

Facility and Physician Experience Positively Correlated with Favorable Outcomes*

- Recent Capture 2 data adds to growing body of literature demonstrating that as hospitals and physicians gain experience with CAS, patient outcomes improve
- 3,388 asymptomatic, non-octogenarian patients from 180 hospitals and 459 operators reported 30-day DS rates of 2.7%





*Gray WM, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P. Influence of Site and Operator Characteristics on Carotid Artery Stent Outcomes Analysis of the CAPTURE2 Clinical Study. *JACC: Cardiol Intv* 2011;4:235-46.

Assuring Quality Outcomes with Expanded Medicare Standard Risk Coverage

- CREST demonstrates CAS and CEA have similar net patient outcomes
- Medicare Coverage can be expanded via "Rational Dispersion"[1] in controlled clinical settings, closely resembling CREST requirements
- Mandatory accreditation of all CAS facilities
  - ICACSF and ACE programs endorsed by 15 national societies
- Use existing national registries to collect data for all patients undergoing CAS
  - ACCF NCDR® and SVS

[1] Mack MJ, Holmes DR Jr. Rational Dispersion for the Introduction of Transcatheter Valve Therapy. *JAMA* 2011; 306(19):2149-50.