RX Acculink® Carotid Stent System
Standard Surgical Risk Indication

P040012/S034

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Circulatory System

Devices Advisory Panel

Food and Drug Administration

RX Acculink® Carotid Stent System
Standard Surgical Risk Indication

PMA Supplement

Brian S. Kersten, Ph.D.
Divisional Vice President
Worldwide Regulatory Affairs
Abbott Vascular

Abbott Vascular's Objective for the Advisory Committee Meeting

To demonstrate that sufficient scientific data have been collected that support the safety and effectiveness for the expanded indication of the RX Acculink Carotid Stent System to include patients at standard risk for adverse events from carotid endarterectomy

Data Support the Safety and Effectiveness of the Acculink Carotid Stent System in High Risk Patients

- CE marked in Europe since 2002
- Approved in the United States in 2004
- Commercially available in over 85 countries
- Over 128,000 units have been distributed worldwide
- Well-established as safe and effective

RX Acculink Carotid Stent System: Current vs. Proposed Indication

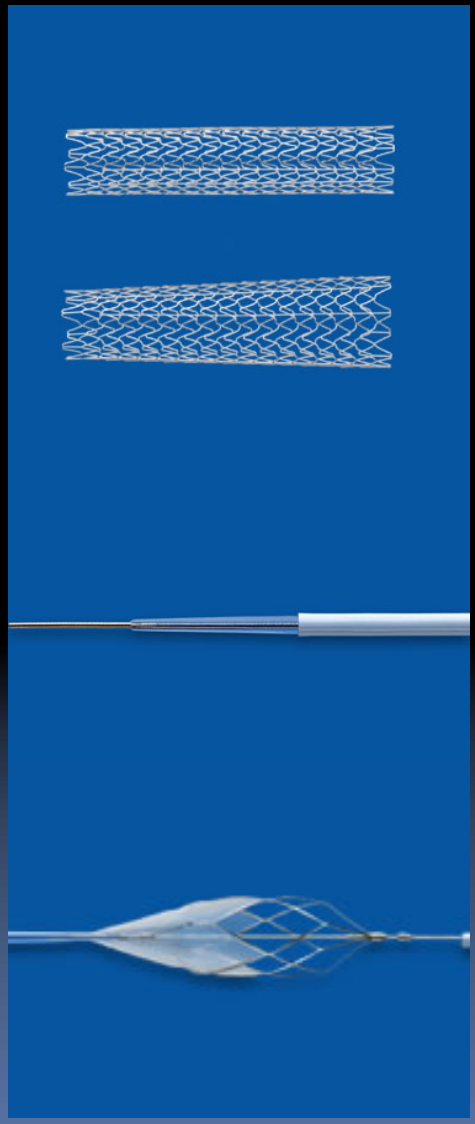
Current Label Criteria	Proposed Label Criteria	
	High Risk	Standard Risk
Reference diameter within 4.0 mm – 9.0 mm at the target lesion	No Change	Same as High Risk
Embolic Protection System: Accunet or Emboshield Family	No Change	Accunet Only
Surgical Risk: High Risk	No Change	Add

RX Acculink Carotid Stent System: Current vs. Proposed Indication

Current Label Criteria	Proposed Label Criteria	
	High Risk	Standard Risk
With neurological symptoms and ≥ 50% stenosis of the common or internal carotid artery	No Change	With neurological symptoms and ≥ 70% stenosis of the common or internal carotid artery by ultrasound or ≥ 50% stenosis of the common or internal carotid artery by angiogram
Without neurological symptoms and ≥ 80% stenosis of the common or internal carotid artery	No Change	Without neurological symptoms and ≥ 70% stenosis of the common or internal carotid artery by ultrasound or ≥ 60% stenosis of the common or internal carotid artery by angiogram

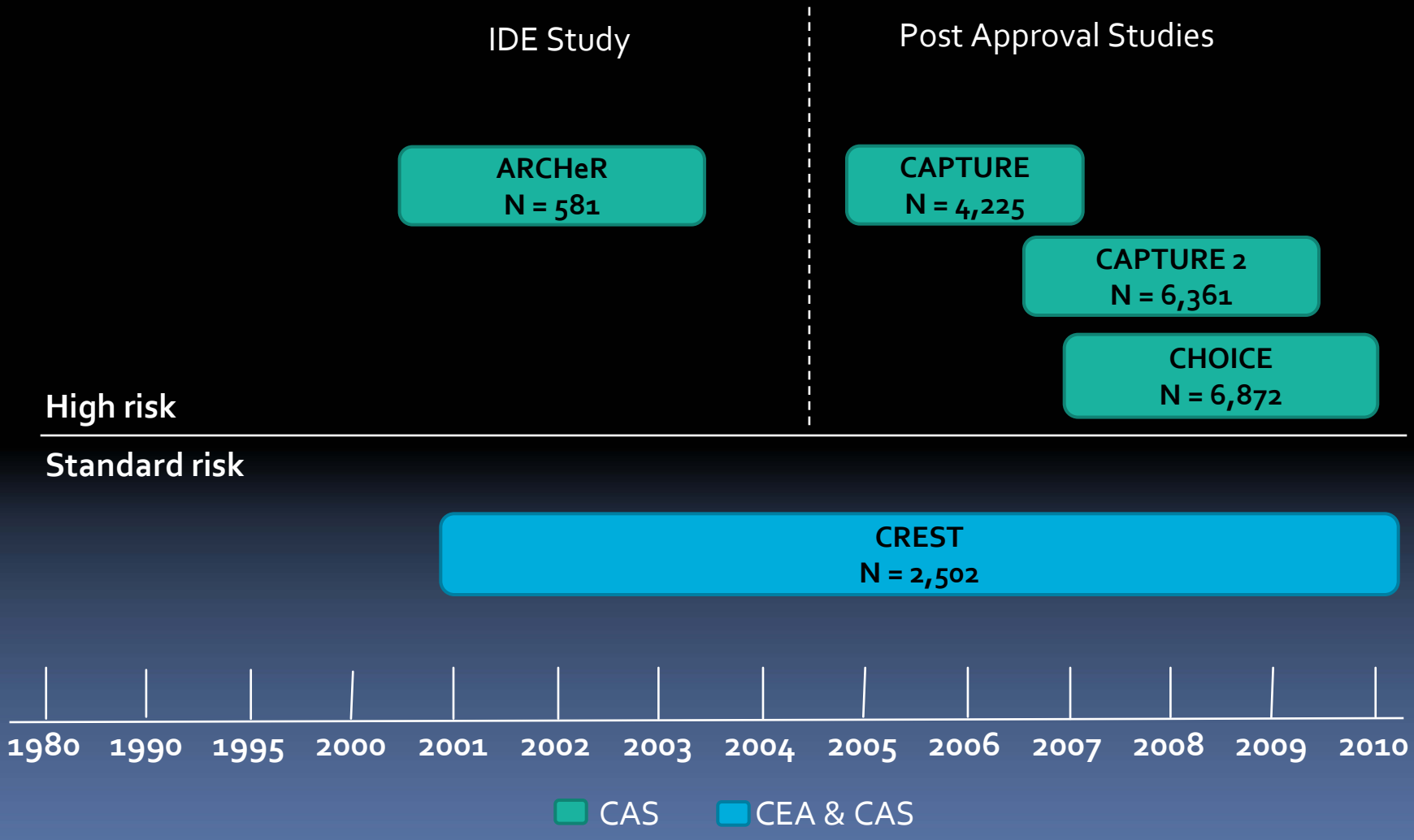
RX Acculink Carotid Stent System

Acculink Carotid Stent	▪ Self-expanding Nitinol (nickel-titanium, super-elastic at body temperature) stent ▪ Straight Configuration Diameters: 5, 6, 7, 8, 9, 10 mm Lengths: 20, 30, 40 mm ▪ Tapered Configuration Diameters: 6-8, 7-10 mm Lengths: 30, 40 mm
Acculink Stent Delivery System	▪ Single-use device that uses a sheath to mechanically constrain the Acculink Carotid Stent at a small diameter for delivery to the treatment site
Accunet Embolic Protection System (EPS)	▪ Fixed-wire filter for carotid stenting interventions ▪ Flexible filter basket to conform to tortuosity ▪ Captures high volume; allows adequate blood flow



RX Acculink: A Minimally Invasive Implanted Device For Revascularization

RX Acculink Carotid Stent System: Establishment of Safety and Effectiveness



Carotid Revascularization Endarterectomy
vs.
Stenting Trial

- Pivotal trial for standard risk patients
- Created in collaboration with the NIH and the University of Medicine and Dentistry of New Jersey
- Randomized 1:1 trial comparing carotid artery stenting (CAS) utilizing the Acculink stent to carotid endarterectomy (CEA) in patients at standard risk

Regulatory History of RX Acculink Carotid System Provides Perspective

Date	History
May 1999	Abbott Vascular* initiates formal discussions with FDA on CREST to support an indication for patients at standard risk of CEA ▪Non-inferiority study comparing stenting to surgery ▪Symptomatic standard risk patient population
Jul 1999	FDA and Abbott Vascular formalize binding agreement regarding analysis ▪Analysis will include MI with Death and Stroke as Composite Primary Endpoint

* Guidant, acquired by Abbott Vascular, May 2006

Regulatory History of RX Acculink Carotid System Provides Perspective

Date	History
Jan 2005	CREST protocol modified for inclusion of asymptomatic standard risk patients ▪To ensure validity of statistical analyses, enrollment restricted to range of 32% - 68% symptomatic patients
Dec 2005	Binding Agreement revised to incorporate inclusion of asymptomatic patients

Regulatory Agreements for RX Acculink Carotid Stent System Solidifies Clinical Approach

Date	Regulatory Agreement
Jul 1999, Dec 2005	FDA and Abbott formalize binding agreement regarding analysis ▪Per-Protocol primary & secondary endpoint analyses, additional analysis performed
Apr 2010	FDA recommends and Abbott agrees to 4 additional pre-specified analyses ▪Adjusted Per-Protocol ▪Intent-to-Treat ▪As-Treated ▪Modified As-Treated

CREST Results Confirm Safety and Effectiveness in Standard Risk Patients

CAS with RX Acculink Meets All Objectives

Primary	CAS with RX Acculink met the primary endpoint: ▪ CAS with RX Acculink is non-inferior to CEA in comparison of composite primary endpoint event rate: stroke, death, or MI at 30 days plus ipsilateral stroke up to 1 year

CREST Results Confirm Safety and Effectiveness in Standard Risk Patients

CAS with RX Acculink Meets All Objectives

Secondary	CAS with RX Acculink met all secondary objectives, including: ▪CAS with RX Acculink is non-inferior to CEA in asymptomatic and symptomatic patients at the 1-year composite endpoint ▪CAS with RX Acculink is non-inferior to CEA for the peri-procedural events

CREST Results Confirm Safety and Effectiveness in Standard Risk Patients

CAS with RX Acculink Meets All Objectives

Additional	CAS with RX Acculink met all additional objectives, including: ▪CAS with RX Acculink is non-inferior to CEA for the composite endpoint events out to 4 years, demonstrating long-term effectiveness

Objectives of Abbott Vascular PMA and NIH Analyses of CREST Data Are Different

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

Abbott Vascular PMA analysis of the CREST data is consistent with the NIH analysis and reveals similar outcomes

What Abbott Vascular Will Demonstrate Through the PMA Analysis of the CREST Data

- CAS with the Acculink Carotid Stent System demonstrates a reasonable assurance of safety and effectiveness compared to CEA
- Event rates are low for both CAS and CEA demonstrating an acceptable benefit-risk profile
- CAS with the Acculink Carotid Stent System is an appropriate treatment option for standard risk patients indicated for carotid revascularization

Agenda

- The Need for Additional Standard Risk Treatment Options
  - **L. N. Hopkins, MD**
    Professor and Chairman, Department of Neurosurgery, Professor of Radiology, State University of New York at Buffalo
- PMA and NIH Analysis of the CREST Data
  - **Chuck Simonton, MD**
    FACC, FSCAI, Chief Medical Officer, Abbott Vascular
  - **Thomas G. Brott, MD**
    Principal Investigator, IDE Sponsor, Mayo Clinic, Jacksonville, FL; James C. and Sarah K. Kennedy Dean of Research, Eugene and Marcia Applebaum Professor of Neurosciences
- Concluding Remarks
  - **Chuck Simonton, MD**
    FACC, FSCAI, Chief Medical Officer, Abbott Vascular

The Need for Additional Standard Risk Treatment Options

L. N. Hopkins, MD

Professor and Chairman, Department of Neurosurgery, Professor of Radiology

State University of New York at Buffalo

Financial Disclosure Relative to CREST

- Dr. Nick Hopkins, M. D.
  - NASCET investigator
  - Advisor and/or trial PI for various CAS studies with Abbott Vascular, Cordis, Boston Scientific, Gore and Medtronic Inc.
  - Grant Sponsorship
    - NIH – US Public Health Service, NINDS, R01 NS 038384 (CREST)
    - National Neurosurgery PI, Executive Committee, Training Center, Site PI

LN Hopkins, MD
Personal Experience

- CEA > 2000 (1979 - present)
- CAS > 2000 (1994 - present)

- Trial Experience as PI / Co PI / Steering Committee

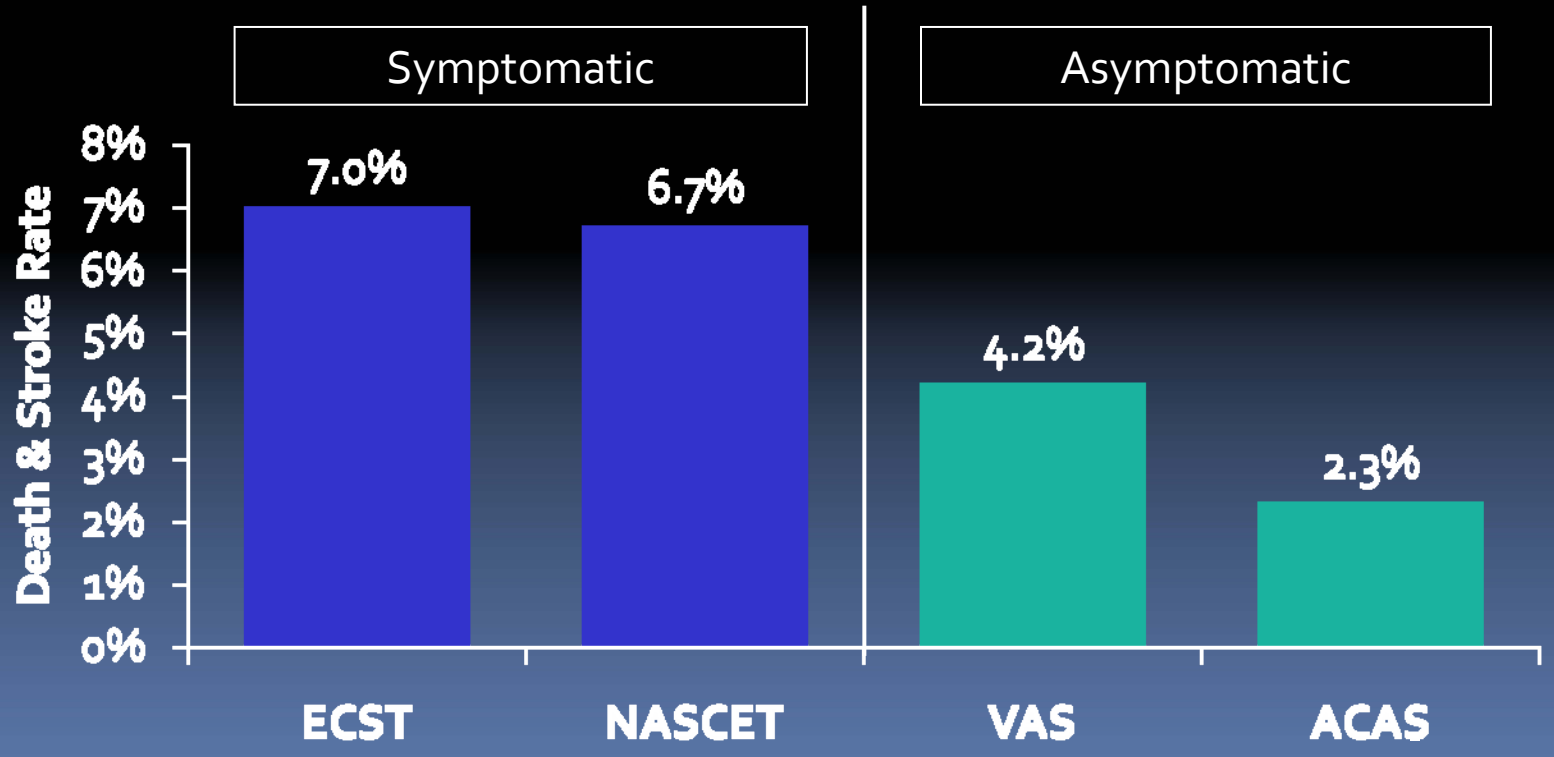
CREST	CABERNET
SAPPHIRE	CARESS
VIVA	CABANNA
ACT I	BEACH
EMPIRE	CAPTURE
ARMOUR	ARCHeR

History of Carotid Artery Stenting

- 1994: First CAS
- 1998-2000: CREST planning - inclusion/exclusion
  - 4 years after first CAS
- 2004: First FDA approval of CAS for patients at high risk of CEA (Acculink Stent System)
- 2011: CAS has become an effective alternative and important complement to CEA and should be available for patients at standard risk of CEA

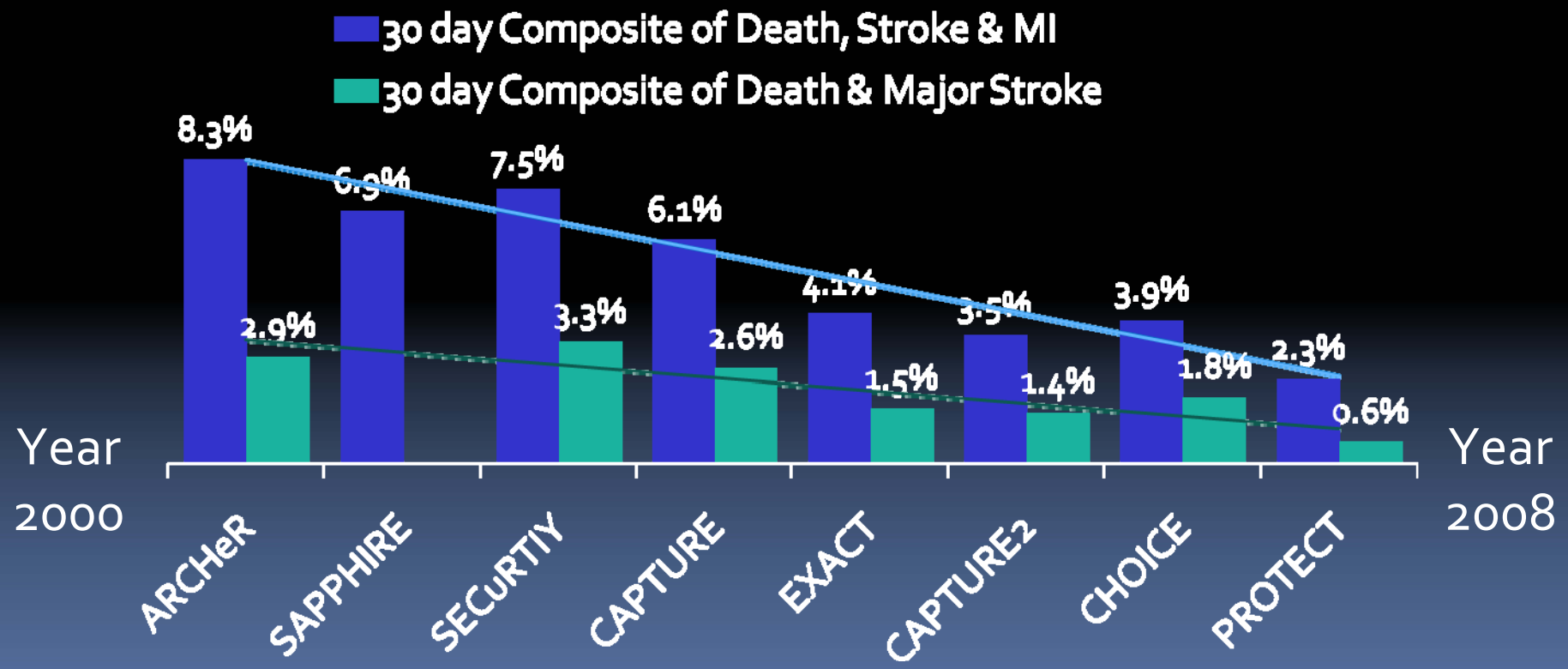
Outcome of CEA Trials Over Time

- In the 1980's: CEA risk up to 21% in some reports
- In the 1990s: death and stroke rates were 6%-7% for symptomatic patients and 3%-4% for asymptomatic patients
- Outcomes of CEA continue to improve over time



Outcomes of CAS Trials Over Time

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



(Enrollment: 2000-2008) CREST – 5.7%

(Enrollment: 2000-2008) CREST – 1.1%

Today Many Patients at Standard Risk Are Clearly Better Served by CAS

- Anatomical features
- Clinical conditions
- Physician and patient choice
- Previous stroke
- C-spine disease
- Cosmetic reasons
- Personal preference – less invasive option
- Voice professionals

If a Patient Needs a Carotid Revascularization…

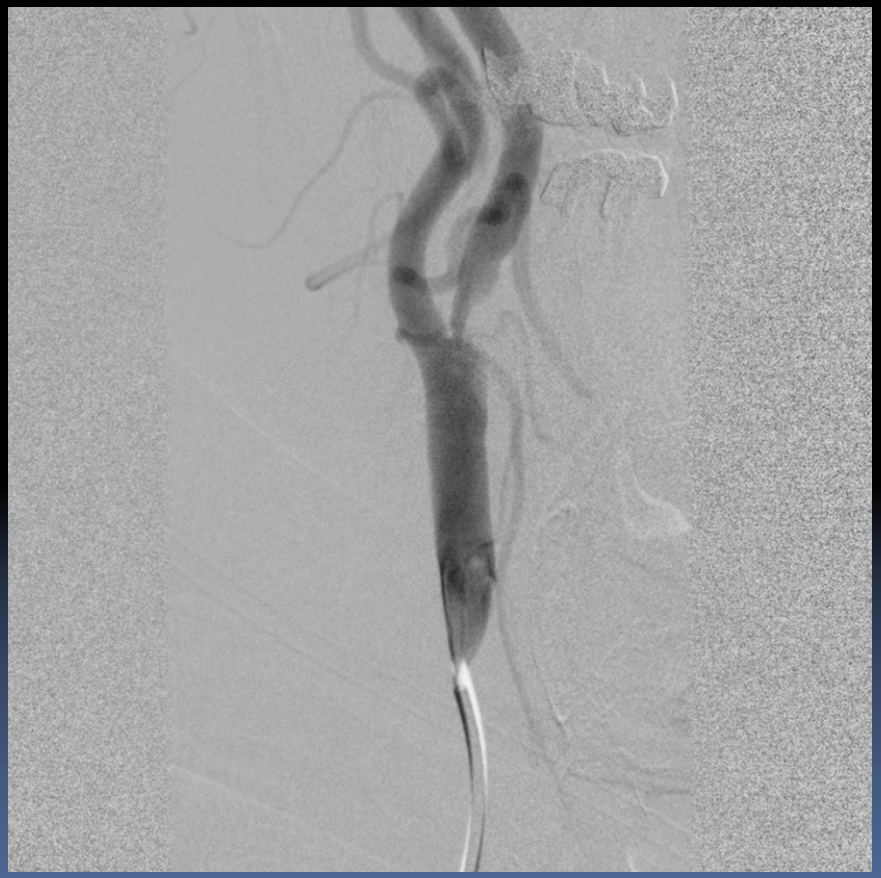
Its All About Decision Making and Judgment

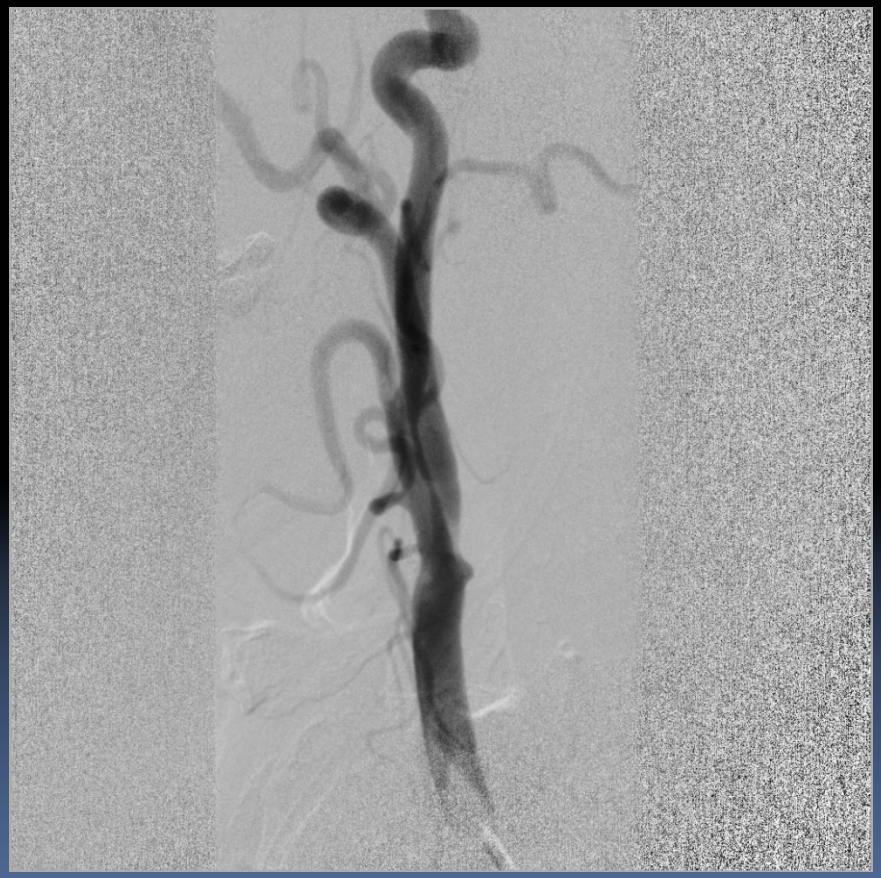
Its All About Having Choices

Case Study: Asymptomatic Carotid Stenosis

62 year old male, standard risk for CEA, family history of stroke

CEA or CAS?





CAS Not YET Approved

When Patients Need Carotid Revascularization…

Based on the data that will be presented today showing clinical equipoise between CAS and CEA, patients at standard risk for CEA need the treatment option of CAS for many reasons

- Many standard risk patients better served by CAS
- Patients and physicians need choices

PMA Analysis of the CREST Trial

Approvability of the RX Acculink Carotid Stent System for Revascularization of Carotid Artery Stenosis in Standard Surgical Risk Patients

Chuck Simonton, MD

FACC, FSCAI

Chief Medical Officer

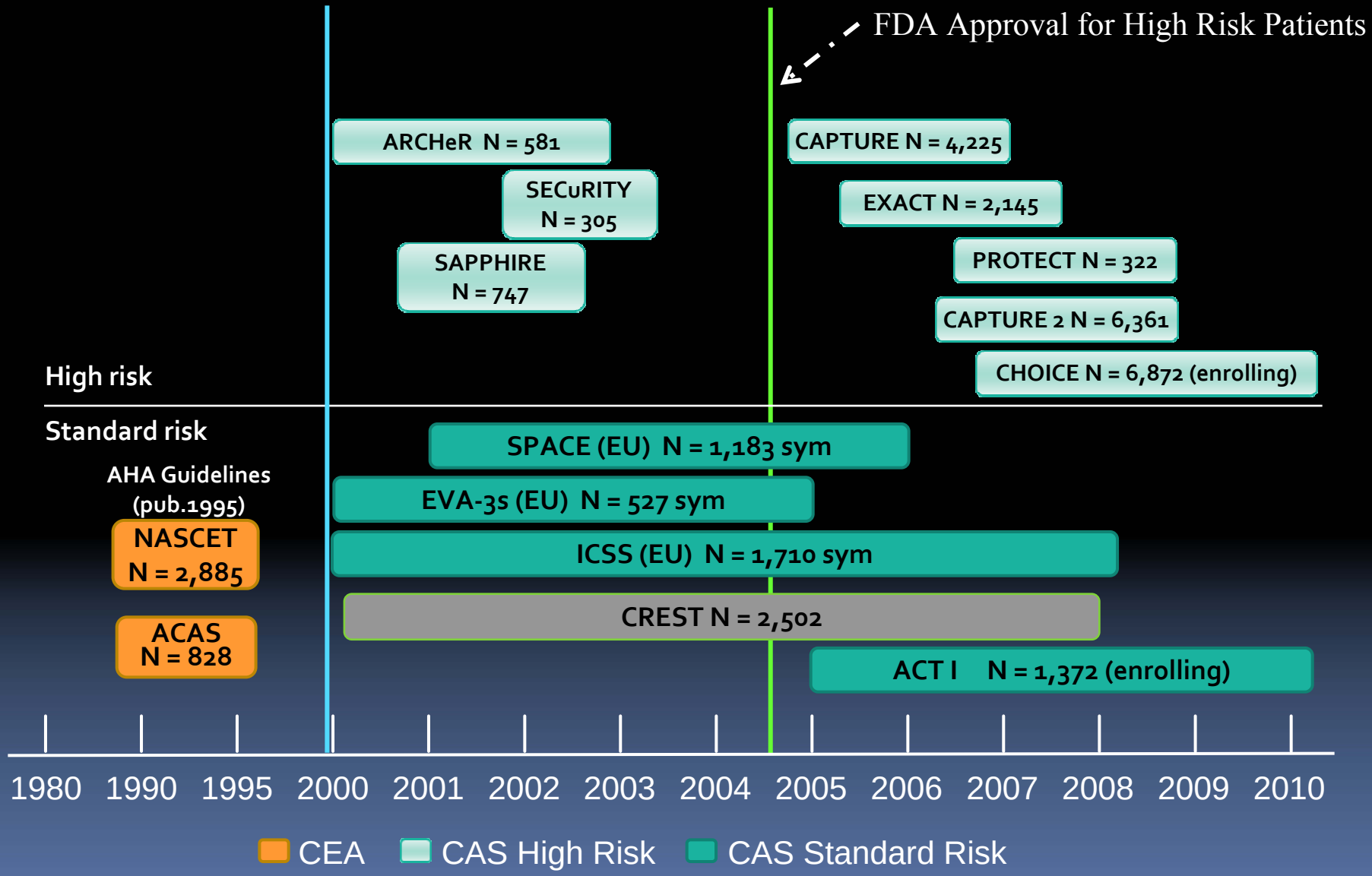
Divisional Vice President

Abbott Vascular

CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long Term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions

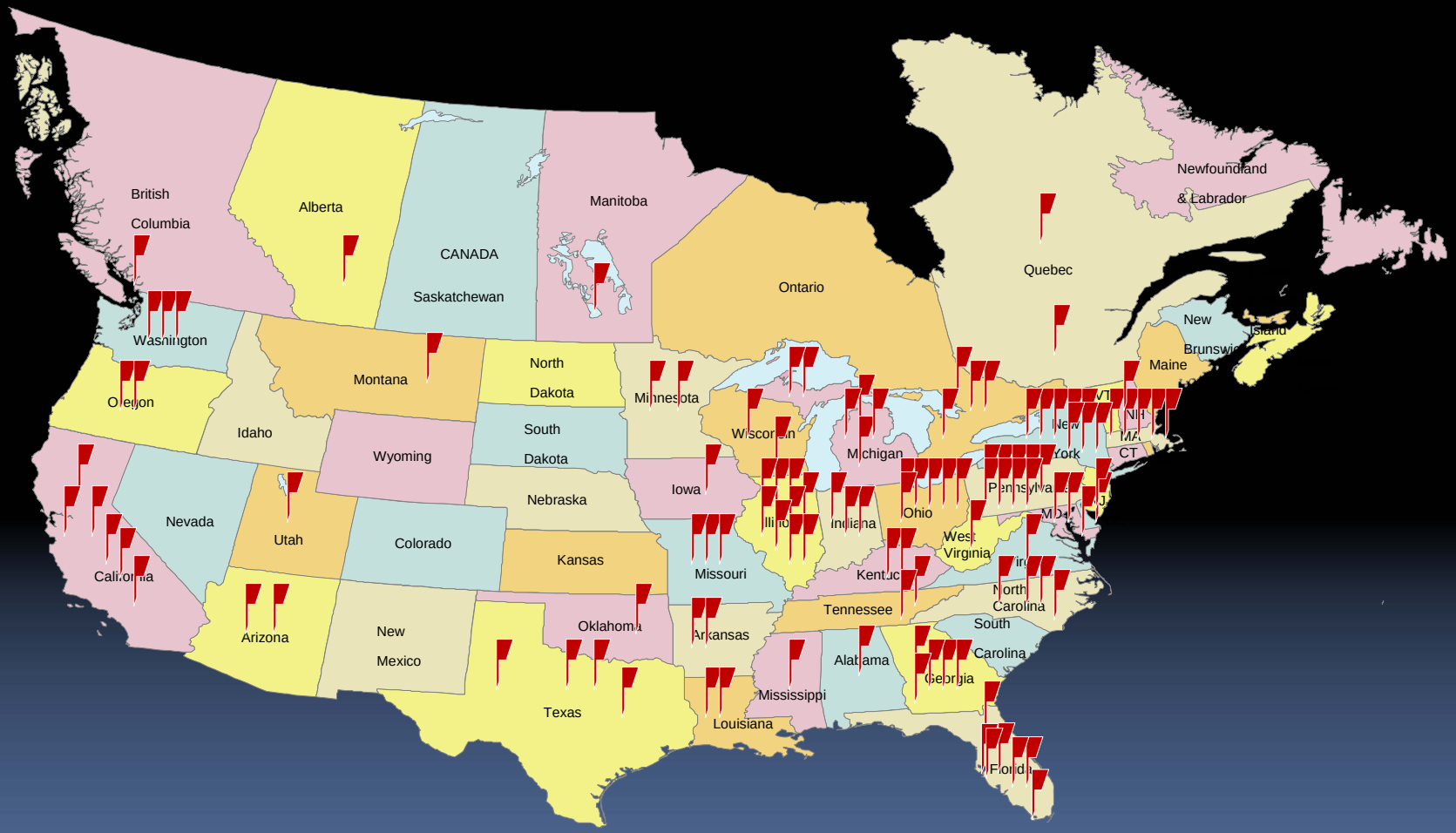
Clinical Trials Evaluating CAS Treatment



Trial Design

- Prospective, multicenter randomized trial
  - Compares carotid artery stenting (CAS) to surgical carotid artery endarterectomy (CEA)
  - RX Acculink Carotid Stent System for CAS
  - U.S. and Canada
- Enrollment
  - 2000: symptomatic patients only
  - 2005: asymptomatic patients approved for enrollment
- Randomization
  - Stratified by clinical site and symptomatic status
  - 1:1 randomization ratio

107 US and 9 Canadian Sites



Sites included in this analysis

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Trial Design – Primary Analyses

- Primary endpoint for the CREST PMA analysis is pre-specified in the binding agreement with FDA
- Primary endpoint is composite of all death, any stroke or MI within 30 days of the procedure PLUS ipsilateral stroke from 31 to 365 days
- There are four pre-specified analysis populations
  - Intent-to-Treat (ITT)
  - As Treated (AT)
  - Modified As Treated (MAT)
  - Per Protocol (PP)

Trial Design – Secondary Analyses

- Secondary endpoints:
  - All death, any stroke, or MI at 30 days (peri-procedural)
  - One year composite endpoint stratified by
    - Symptomatic status
    - Age by octogenarian status
  - Acute Success
  - Target Lesion Revascularization at 12 months
  - Access site complications requiring treatment
  - Cranial nerve injury unresolved at 1 and 6 months
- Pre-specified interaction analyses
  - Sex and symptomatic status

Endpoint Definitions

- Death: All deaths to 30 days
- Stroke: Acute neurological ischemic event of at least 24 hours duration with focal signs and symptoms
  - Major stroke: NIHSS score of ≥ 9 at 3 months post stroke, or clinical judgment
  - Minor stroke: NIHSS score of < 9 at 3 months post stroke
- Myocardial Infarction (MI):
  - Cardiac biomarkers (CK-MB or troponin) > 2X ULN and/or
  - ECG evidence of > 1mm ST elevation or depression in 2 contiguous leads and/or
  - Chest pain with either ECG or biomarker evidence

All endpoints adjudicated by CEAC

Stroke Assessment Requirements

Neurological Examination	▪ Pre-procedure ▪ Post-procedure 18 to 54 hours ▪ 1 month and 12 months
Stroke Scales (NIHSS, mRS)	▪ Pre- and Post-procedure ▪ 1 and 3 months ▪ Every 6 months
Upon Stroke Occurrence	▪ NIHSS 3 months after stroke ▪ CT or MRA per standard of care

MI Assessment Requirements

ECG	▪ Pre-procedure ▪ Post-procedure 6 to 48 hours ▪ 1 month
Cardiac Biomarkers (CK-MB or Troponin)	▪ Pre-procedure ▪ Post-procedure at 6-8 hours (if elevated, then checked every 8 hours for 3 consecutive draws)

Definition of Standard Risk

- Absence of anatomic or clinical conditions which make the patient at high risk for the surgical procedure

- For example, the absence of:
  - Anatomic: previous CEA, prior radiation treatment to the neck, surgically inaccessible lesions above C2
  - Clinical: left ventricular ejection fraction (LVEF) < 30%, unstable angina, recent MI

Patient Eligibility

- Discrete lesion in internal carotid artery (ICA) with or without involvement of common carotid artery (CCA)
- Symptomatic Patients
  - Age > 18 with TIA, amaurosis fugax, minor or non-disabling stroke within 6 months on the treated side
  - Carotid stenosis ≥ 50% by angiogram or ≥ 70% by ultrasound or ≥ 70% by MRA or CTA;
- Asymptomatic Patients
  - Age > 18, no symptoms within 6 months, and carotid stenosis ≥ 60% by angiogram or ≥ 70% by ultrasound or ≥ 80% by MRA or CTA

Statistical Methods: Primary Endpoint

- Non-inferiority analysis for the composite primary endpoint with the following assumptions
  - Composite end point rate of 7.48%
  - Non-inferiority margin of 2.6%
  - One-sided alpha of 0.05
  - 80% power

  Resulted in a population of 2,500 symptomatic patients

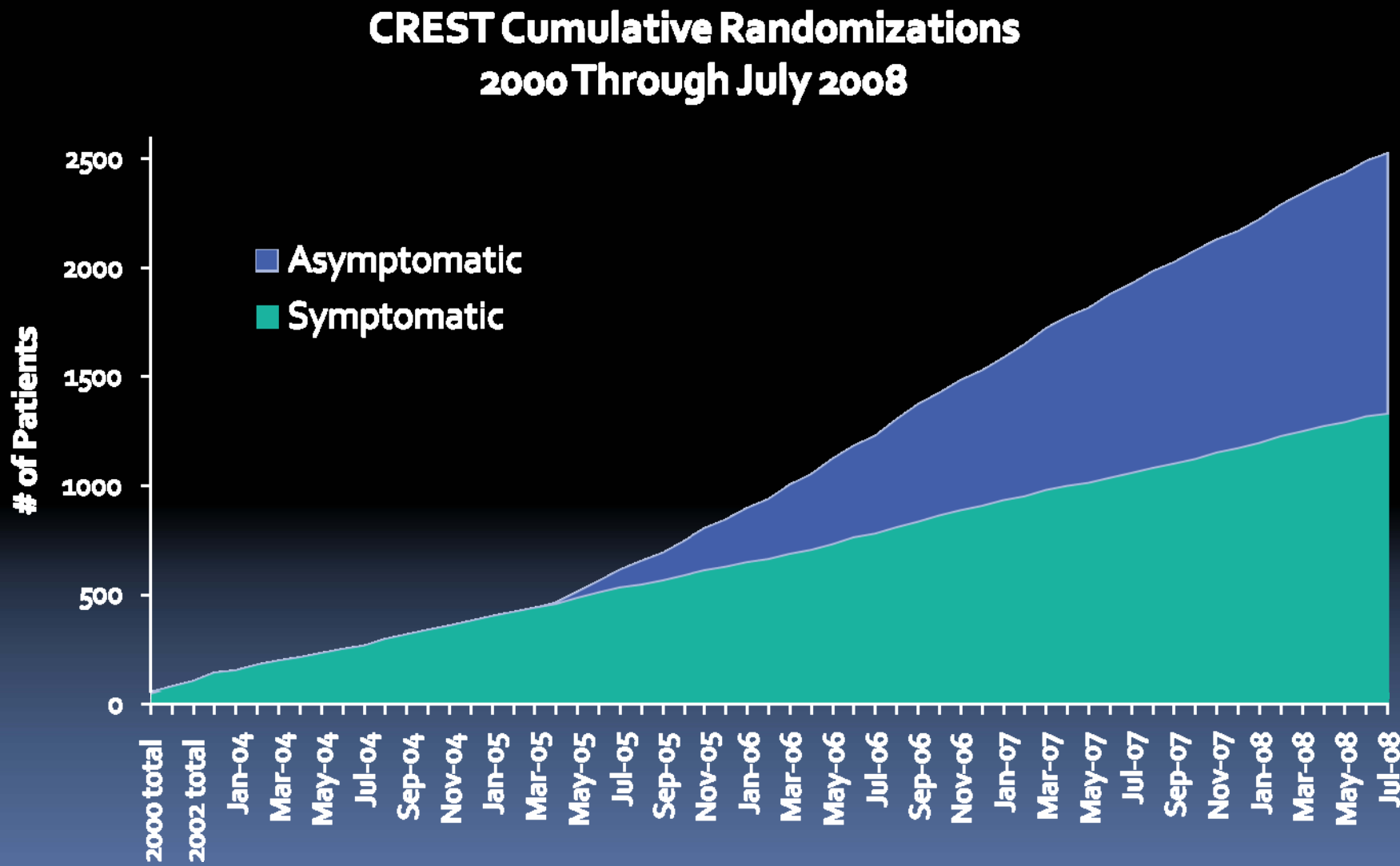
- Asymptomatic patients were added in 2005
  - Assumed 50% of the population would be asymptomatic
  - Assumed composite rate was revised to 6.76%
  - One-sided alpha of 0.05
  - Power of the study was increased to 82%

- In addition to the four analysis populations, a propensity score adjusted analysis was performed for the primary endpoint

Trial Management

- Study Principal Investigators
  - Dr. Robert Hobson (deceased)
  - Dr. Thomas G. Brott
- Trial Management
  - University of Medicine and Dentistry of New Jersey
- Core Labs
  - Ultrasound: Univ. Of Washington; Dr. Kirk Beach
  - Angiographic: Beth Israel Deaconess Hospital; Dr. Jeff Popma
  - ECG: Wake Forest Univ. School of Medicine; Dr. Ronald Prineas
- Clinical Events Adjudication Committees (CEAC)
  - MI: Independent cardiologists, Chairman: Dr. Joseph Blackshear
  - Stroke: Independent neurologists, Chairman: Dr. Stanley Cohen
- Statistical and Data Management
  - University of Alabama at Birmingham (UAB)
  - Abbott Vascular
- DSMB
  - NIH

CREST Trial Enrollment



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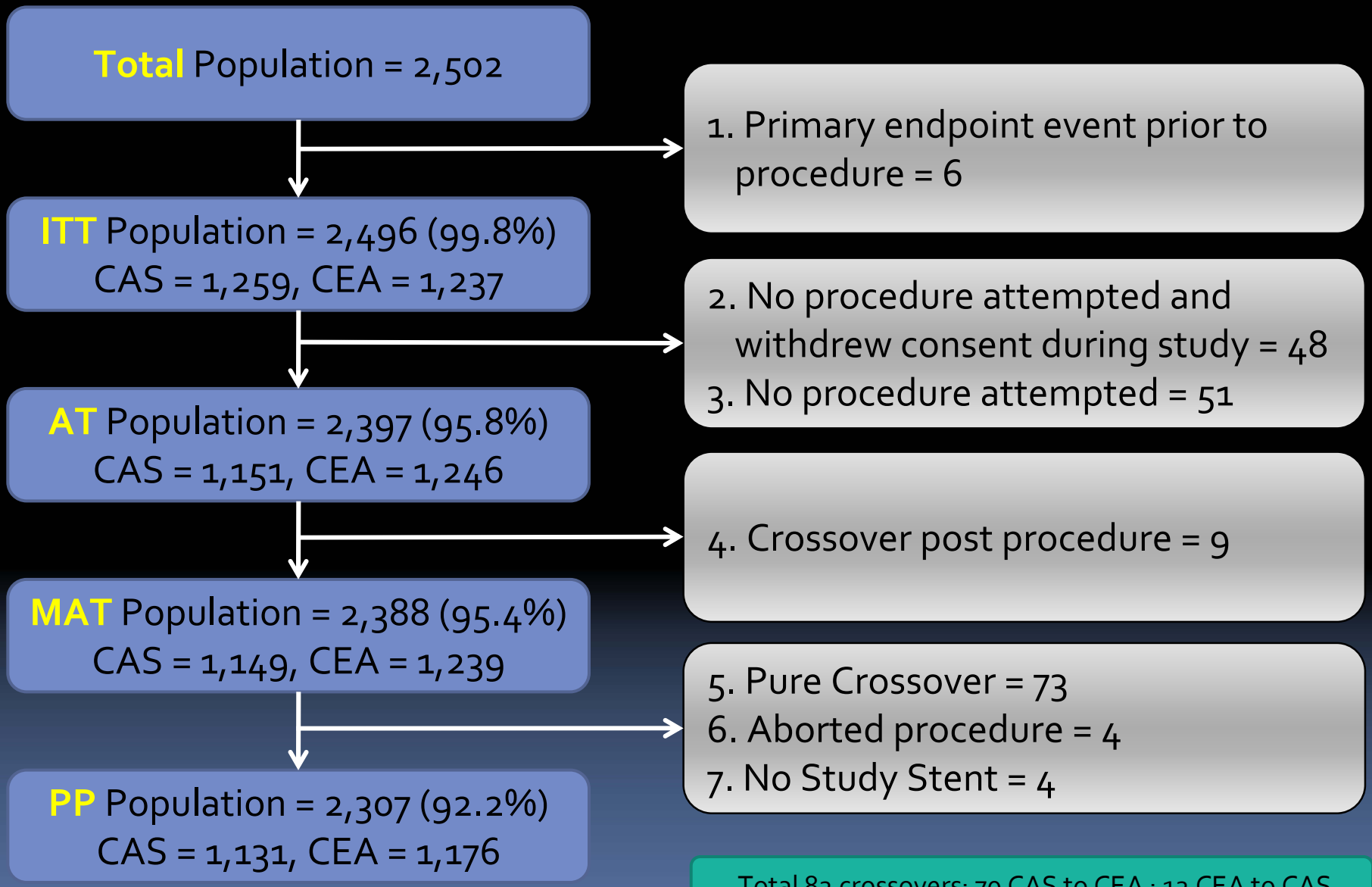
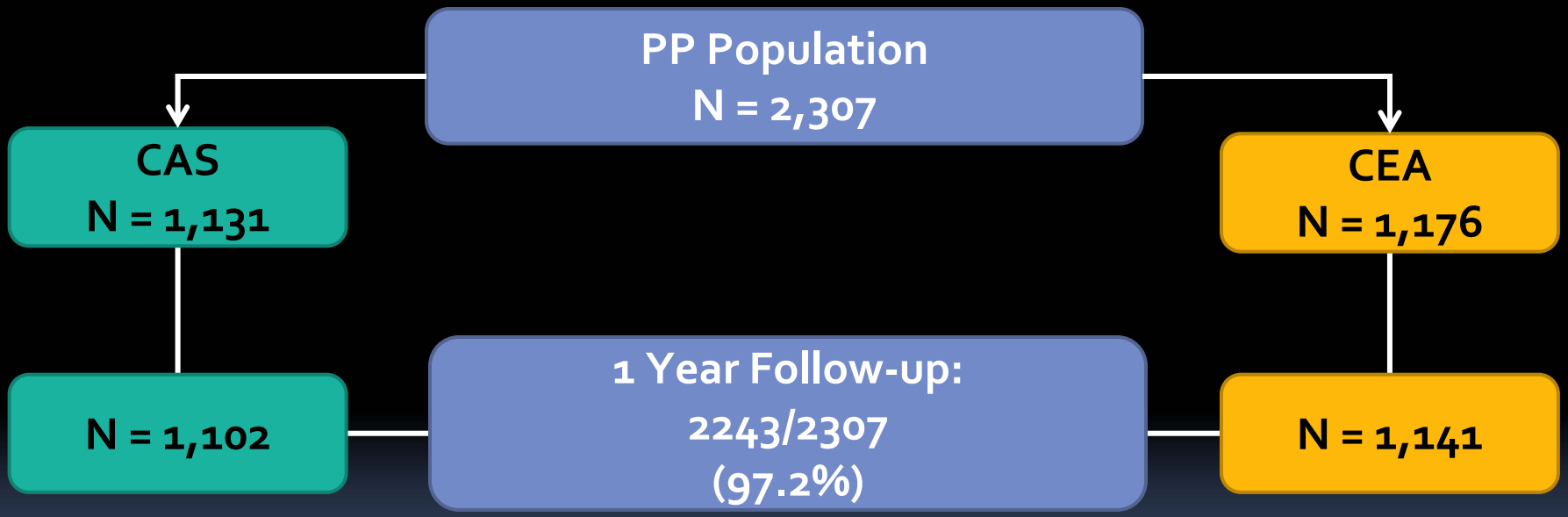
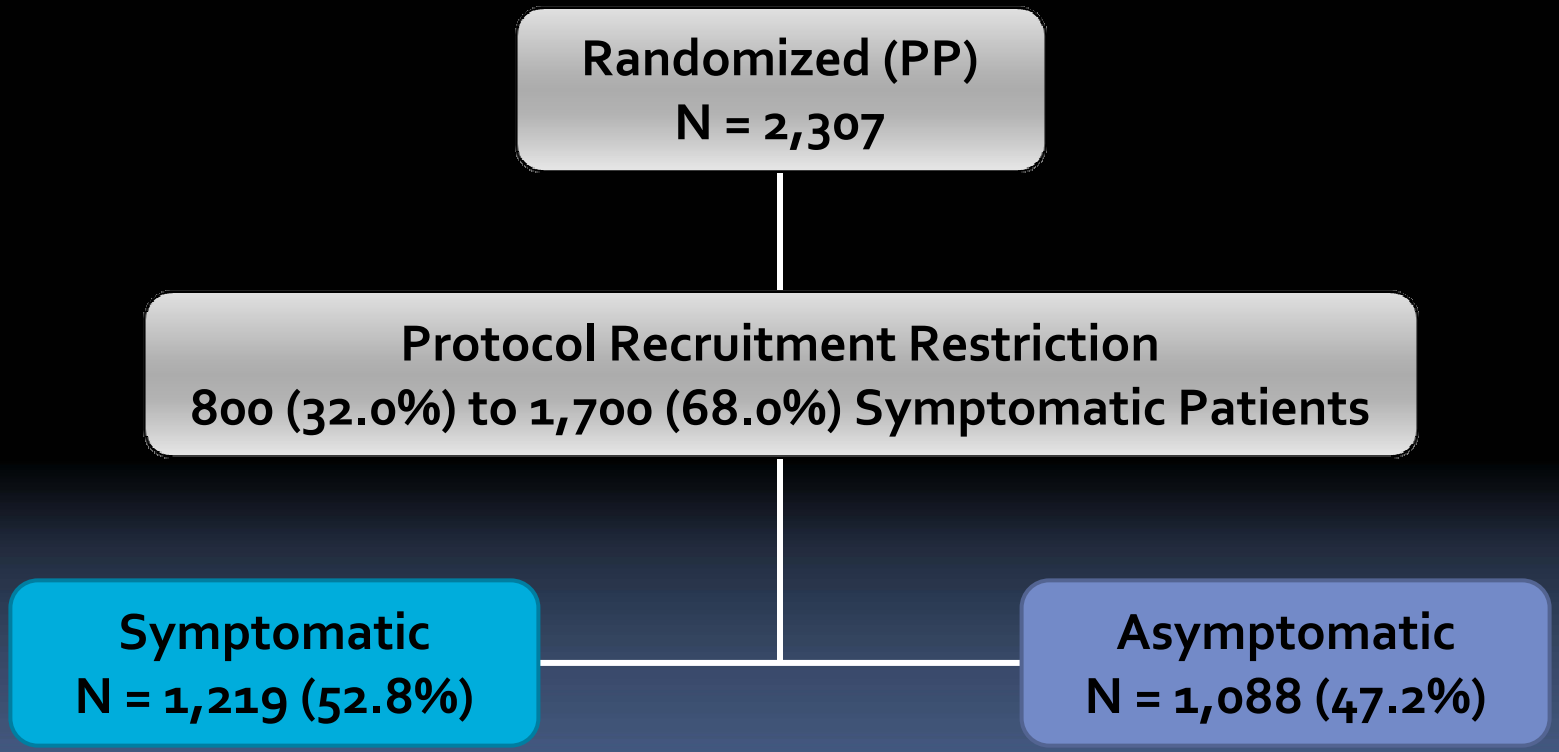
Pre-specified Analysis Populations



High Follow-up Rate for the Primary Endpoint



Randomization by Symptomatic Status



Baseline Characteristics

Per Protocol	CAS N = 1,131	CEA N = 1,176	Unadjusted p-value*
Mean Age	68.7	69.1	0.20
Age ≥ 80 years	9.4%	8.8%	0.61
Male	64.6%	66.7%	0.30
Symptomatic	53.0%	52.7%	0.91
Hypertension	84.8%	86.4%	0.27
Diabetes Mellitus	30.0%	30.9%	0.62
Dyslipidemia	83.8%	85.8%	0.18
Current smoker	27.6%	26.0%	0.38
Cardiovascular disease	43.2%	44.9%	0.41
CABG	20.7%	21.8%	0.52
Contralateral CEA	4.2%	5.2%	0.24

* p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

Balanced Target Lesion Stenosis at Enrollment

Per Protocol		CAS N = 1,131	CEA N = 1,176	Unadjusted p-value*
Target Lesion	*Right*	50.0%	47.9%	0.297
	Left	50.0%	52.1%	0.297
Angiography	*Mean ± SD*	75.8 ± 11.0	73.6 ± 10.7	0.002
Ultrasound	*< 50*	0.5%	1.5%	0.031
	50 - 69	11.4%	10.5%	0.514
	70 - 99	87.8%	88.0%	0.913
	Occluded	0.3%	0.1%	0.366**

* p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

** Fisher's Exact Test

PMA Primary Endpoint

Composite of all death, any stroke, or MI to 30 days

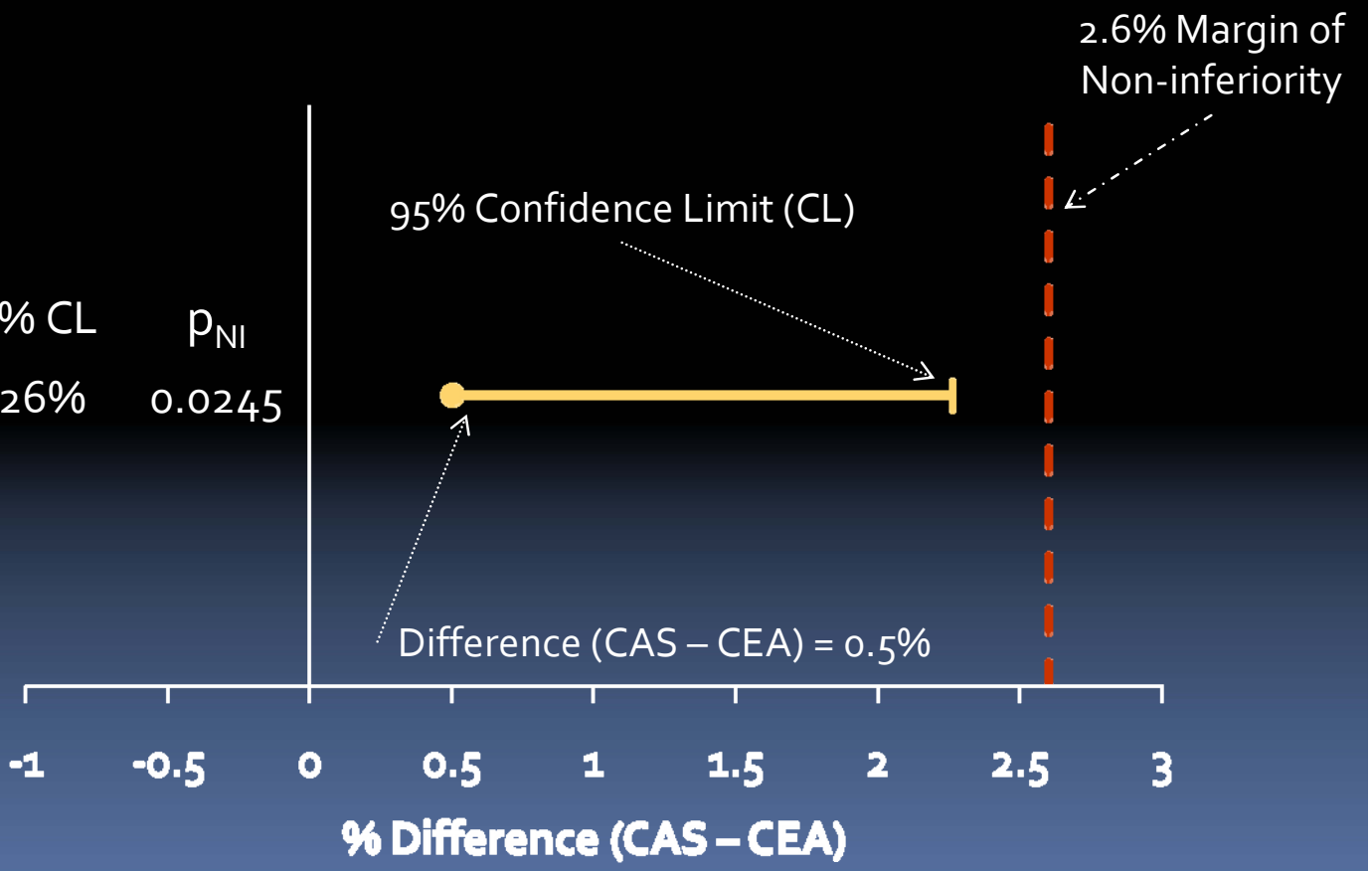
Plus

Ipsilateral stroke from 31 to 365 days

The RX Acculink Carotid Stent System Met the Primary Endpoint of the Trial

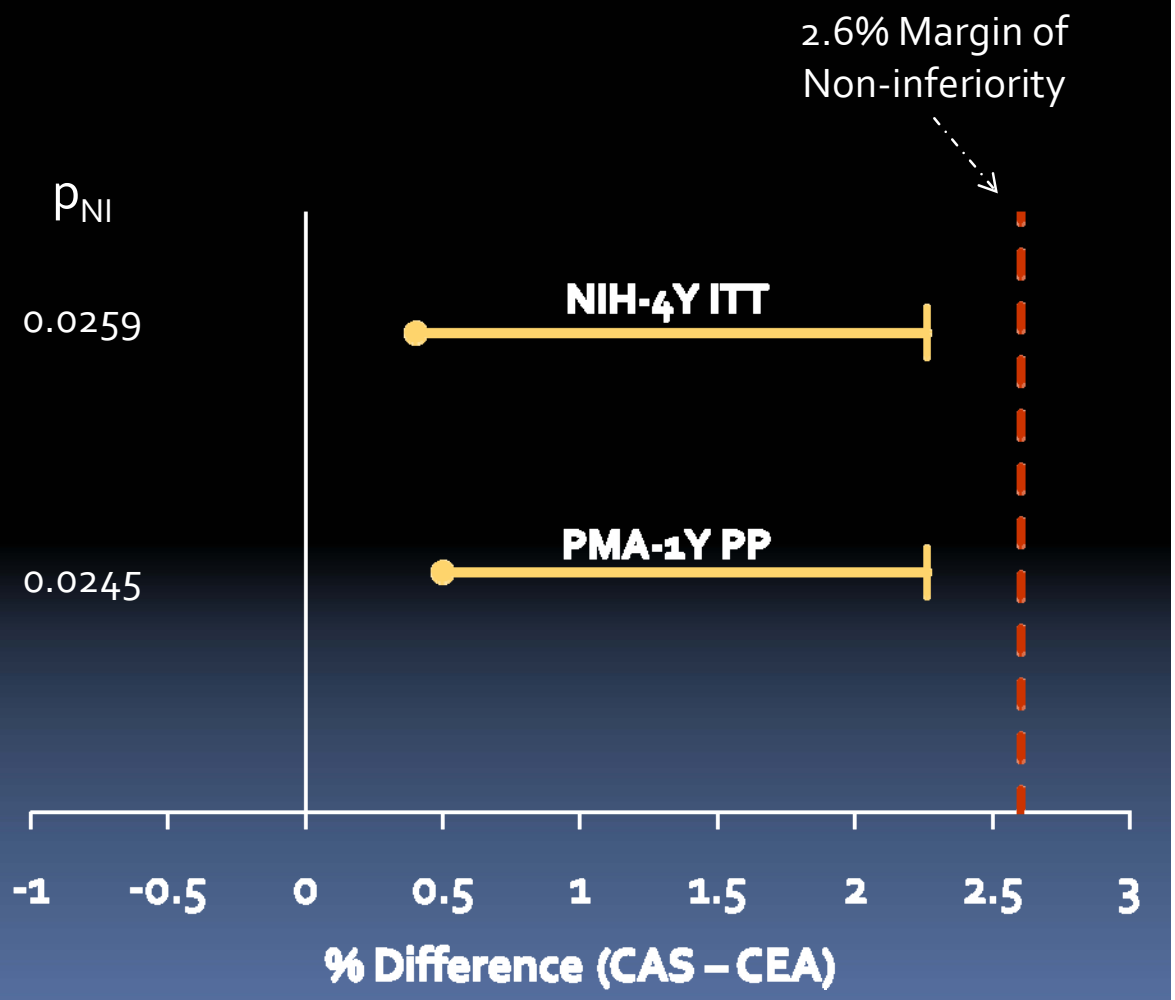
CAS is non-inferior to CEA in **Per Protocol** analysis

	CAS	CEA	95% CL	p_{NI}
PP	7.1%	6.6%	2.26%	0.0245



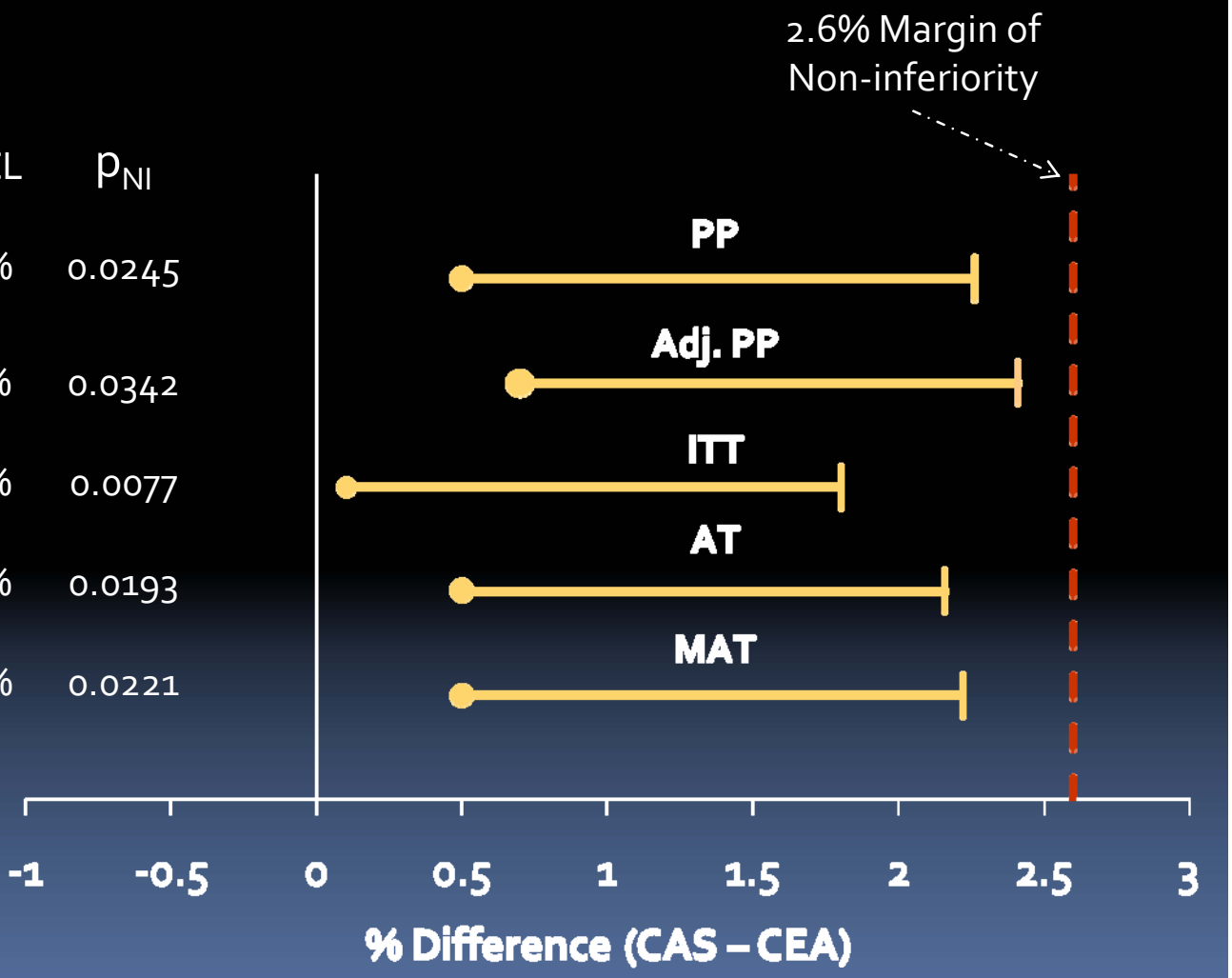
PMA and NIH Analyses Are Consistent and Complementary

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



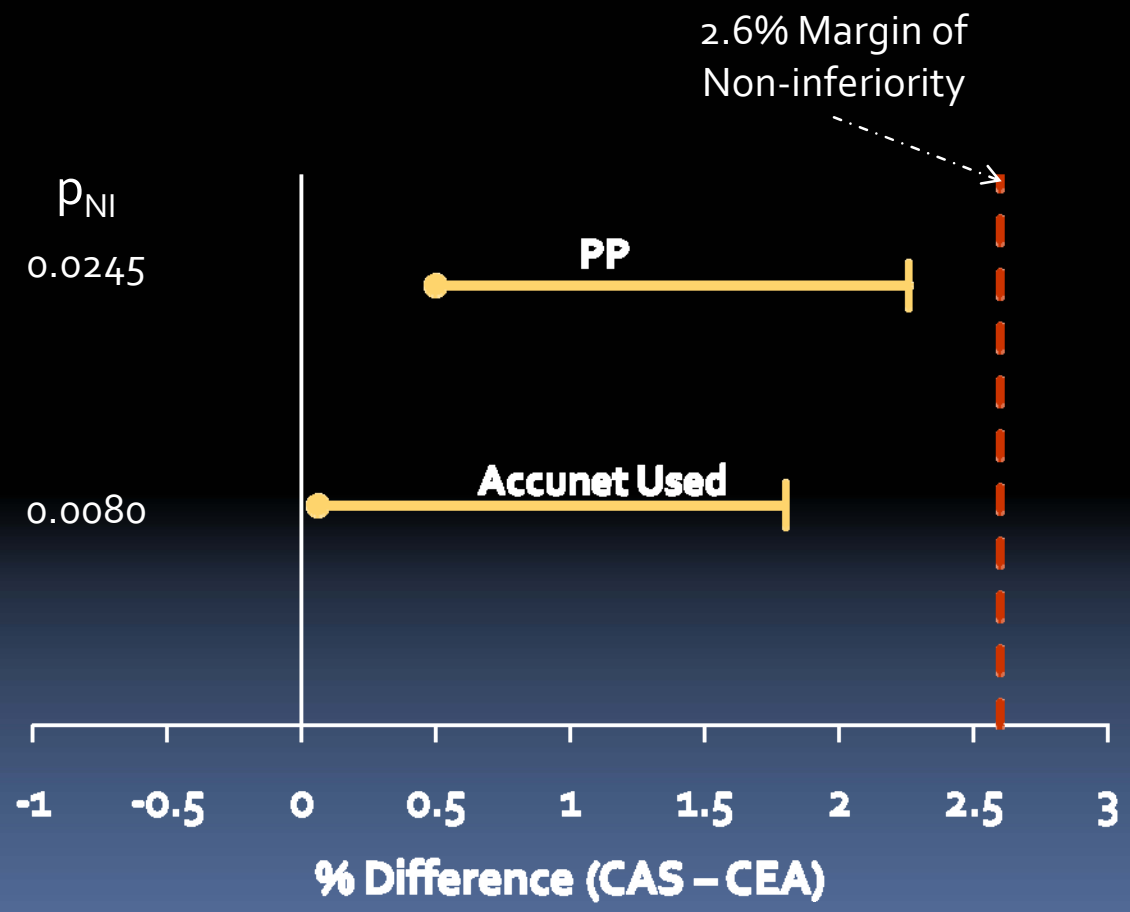
CAS is Non-inferior to CEA in <u>All</u> PMA Analysis Populations

	CAS	CEA	95% CL	p_{NI}
PP	7.1%	6.6%	2.26%	0.0245
Adj. PP	7.2%	6.5%	2.41%	0.0342
ITT	7.0%	6.9%	1.80%	0.0077
AT	7.2%	6.7%	2.16%	0.0193
MAT	7.2%	6.7%	2.22%	0.0221



A Lower Primary Endpoint Rate was Observed in CAS Patients Treated with the Accunet EPS

	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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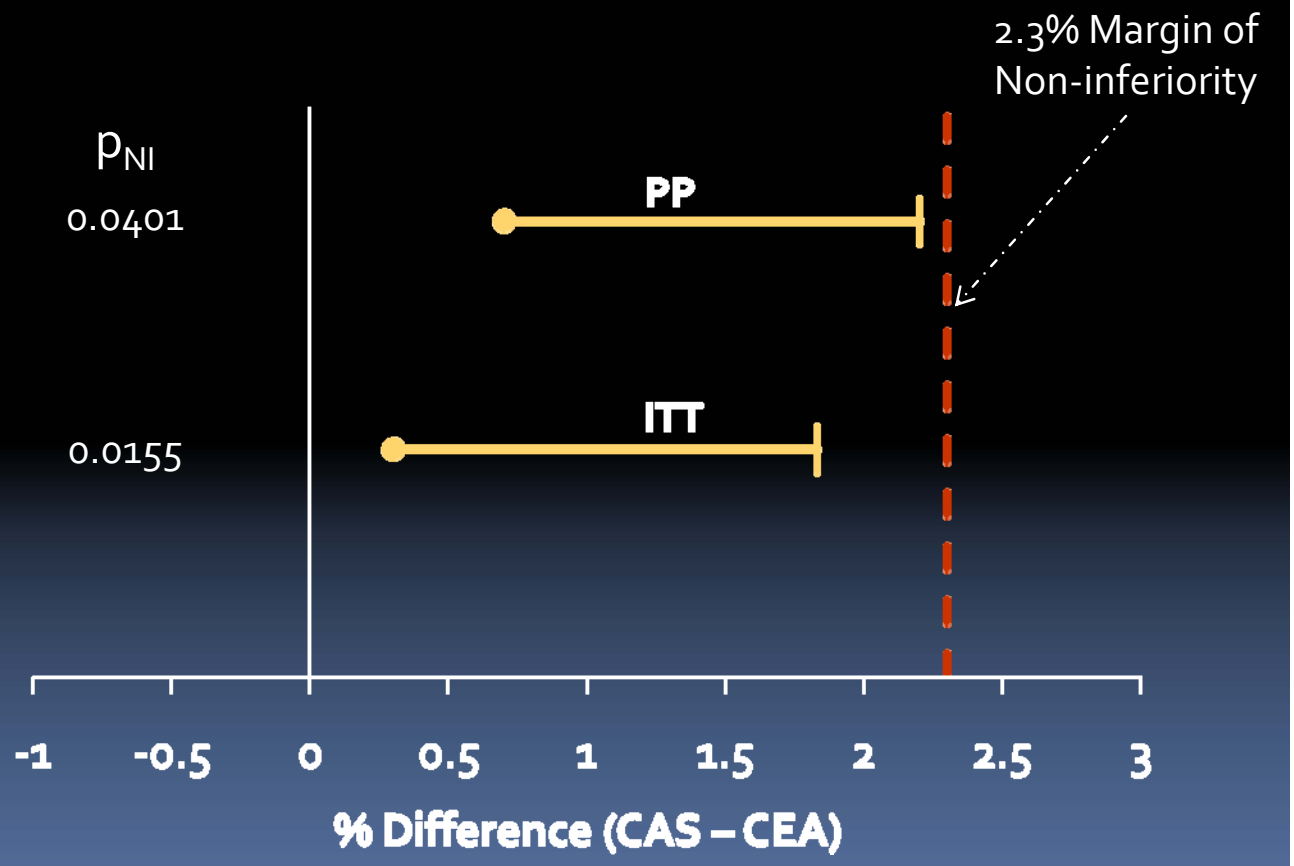
Peri-Procedural Composite Endpoint

All death, any stroke or MI
at 30 days post-procedure

CAS is Non-inferior to CEA for Peri-Procedural DSMI

	CAS	CEA	95% CL	p_{NI}
PP	5.8%	5.1%	2.20%	0.0401
ITT	5.8%	5.5%	1.83%	0.0155



Death, Stroke and MI within 30 Days

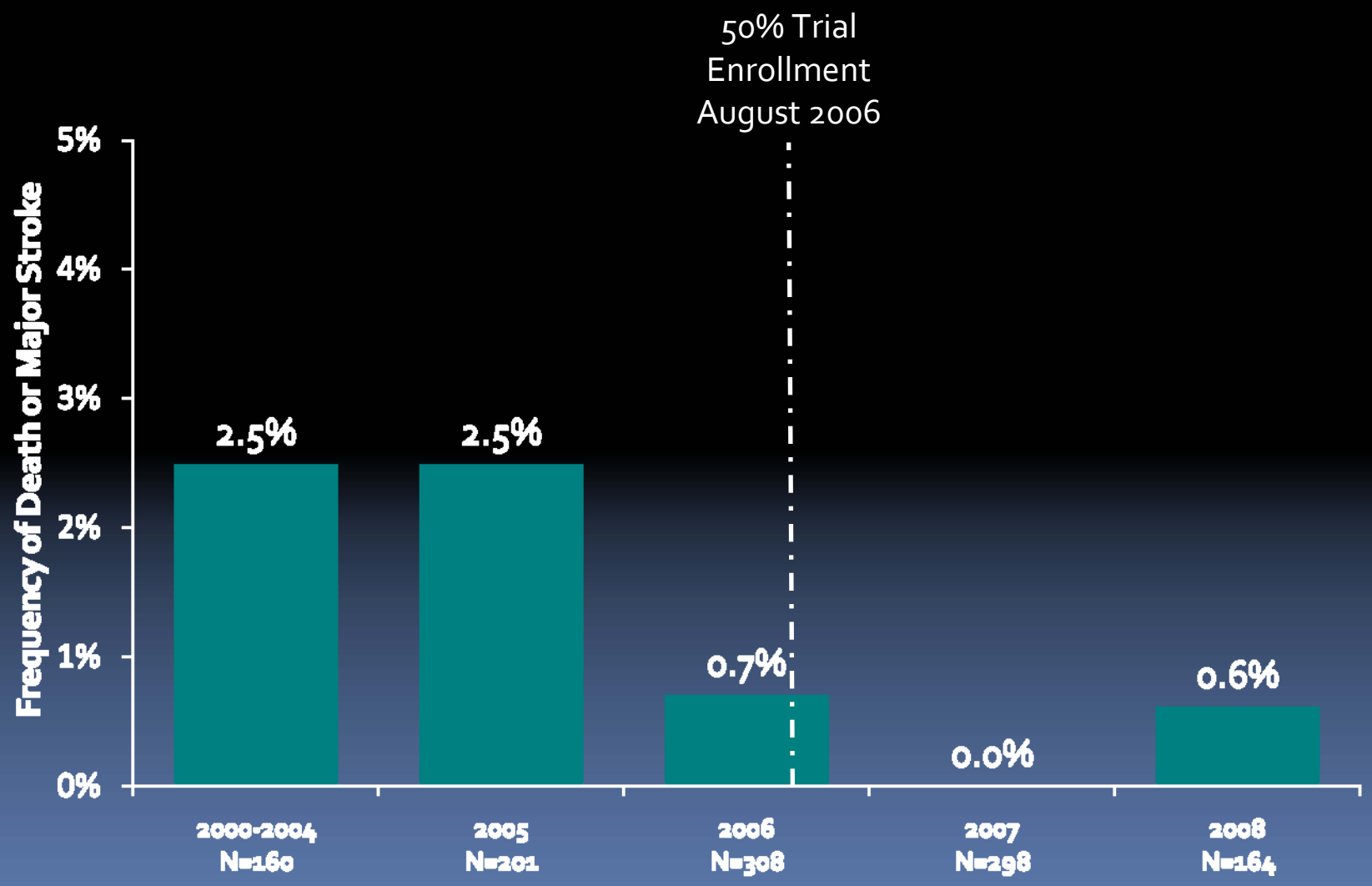
Per protocol	CAS N = 1,131	CEA N = 1,176	Difference	Unadjusted p-value*
All Death, Stroke, or MI	5.8% (65)	5.1% (60)	0.7%	0.5200
Death	0.53% (6)	0.26% (3)	0.27%	0.3335
Any Stroke	4.1% (46)	1.9% (22)	2.2%	0.0019
Major Stroke	0.9% (10)	0.4% (5)	0.5%	0.2005
Minor Stroke	3.2% (36)	1.5% (18)	1.7%	0.0088
MI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

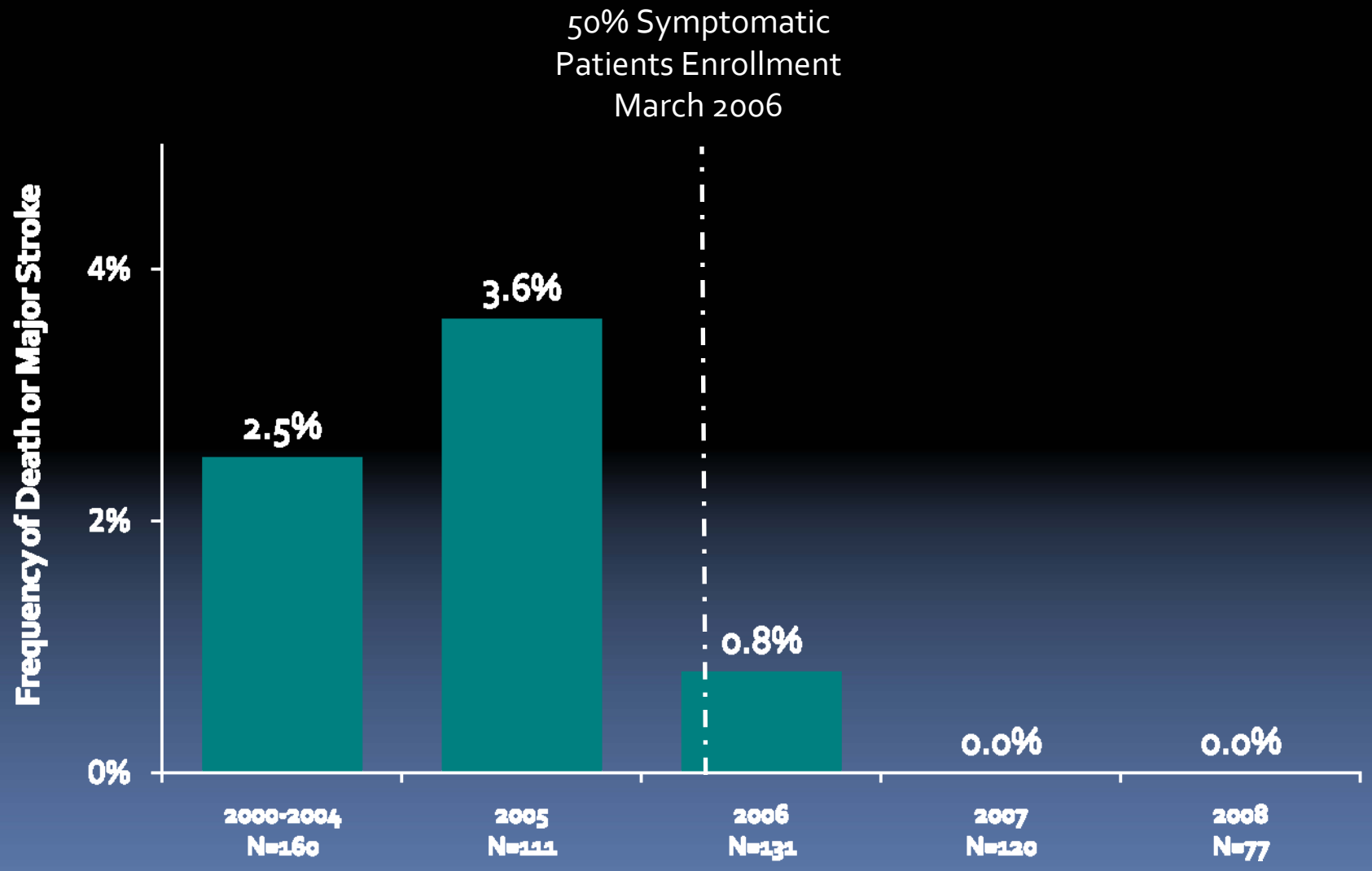
Despite these directional differences for the stroke and MI components of the primary composite endpoint:

The CREST PMA analysis shows *very low event rates* for **both** CAS and CEA, lower than historical rates and within the AHA guidelines for 30-day event rates.

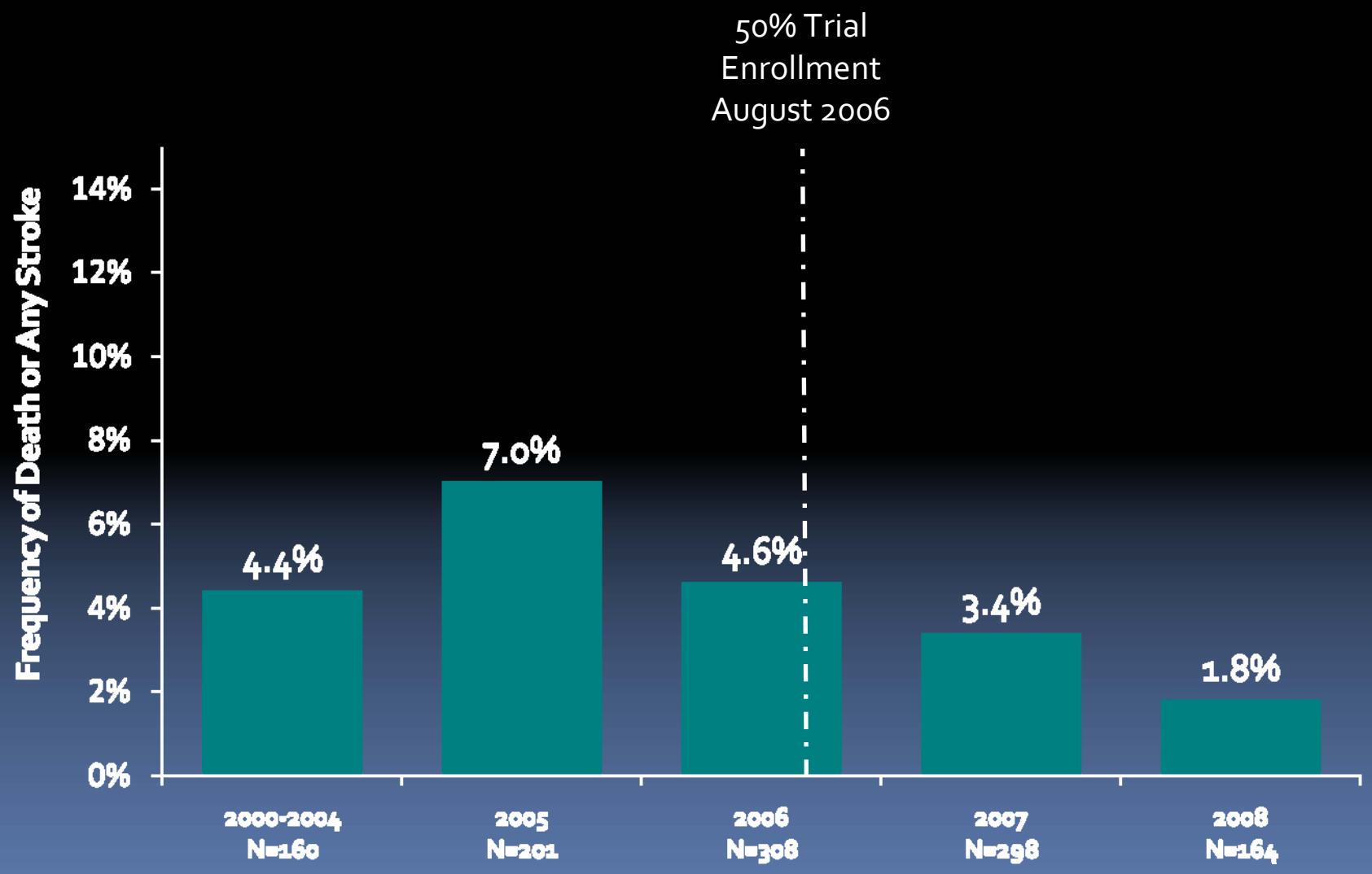
Death or Major Stroke Rates Decrease for CAS over the Period of CREST Enrollment



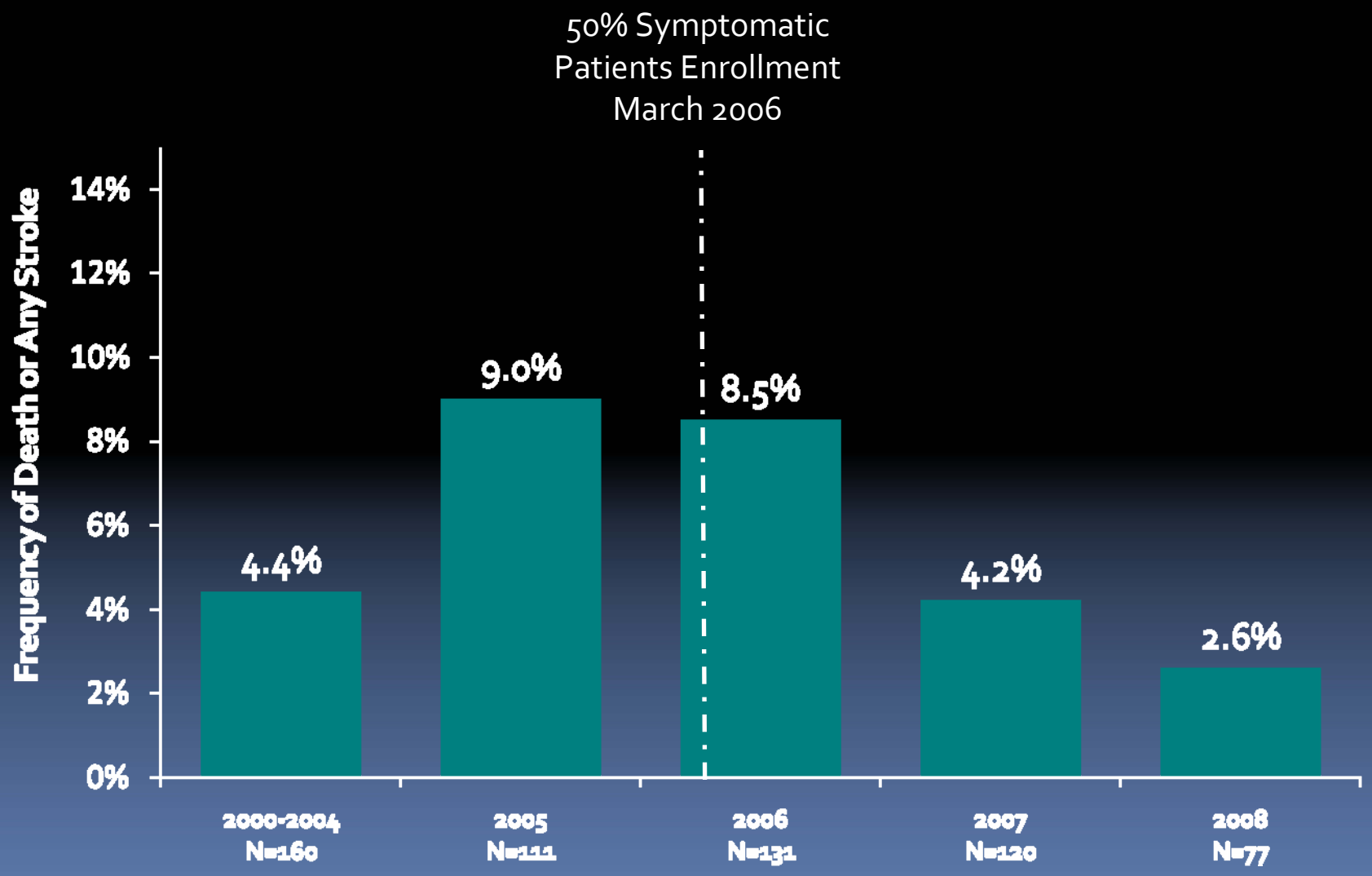
Death or Major Stroke Rates in CAS Decrease for Symptomatic Patients



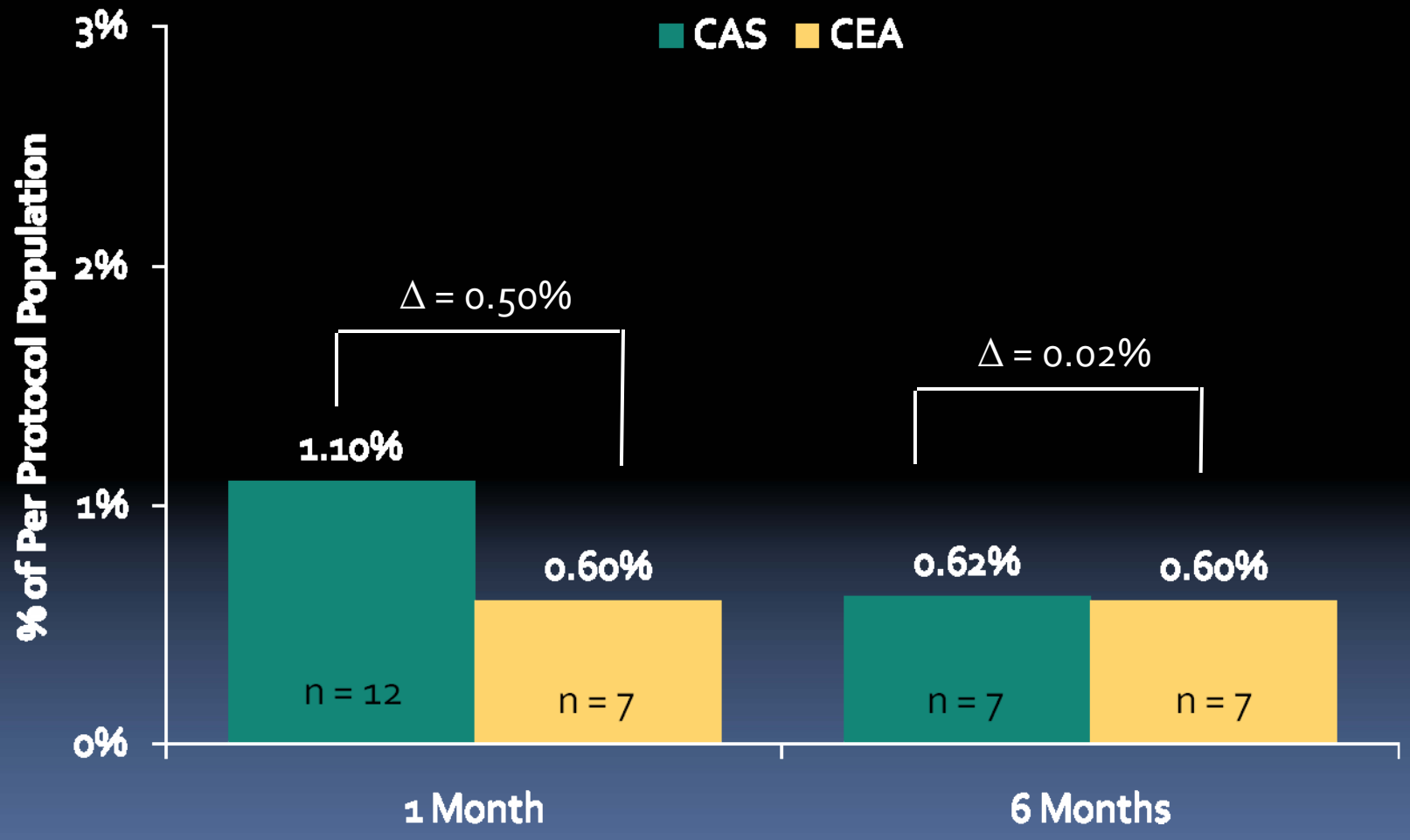
Death or Any Stroke Rates Decrease for CAS over the Period of CREST Enrollment



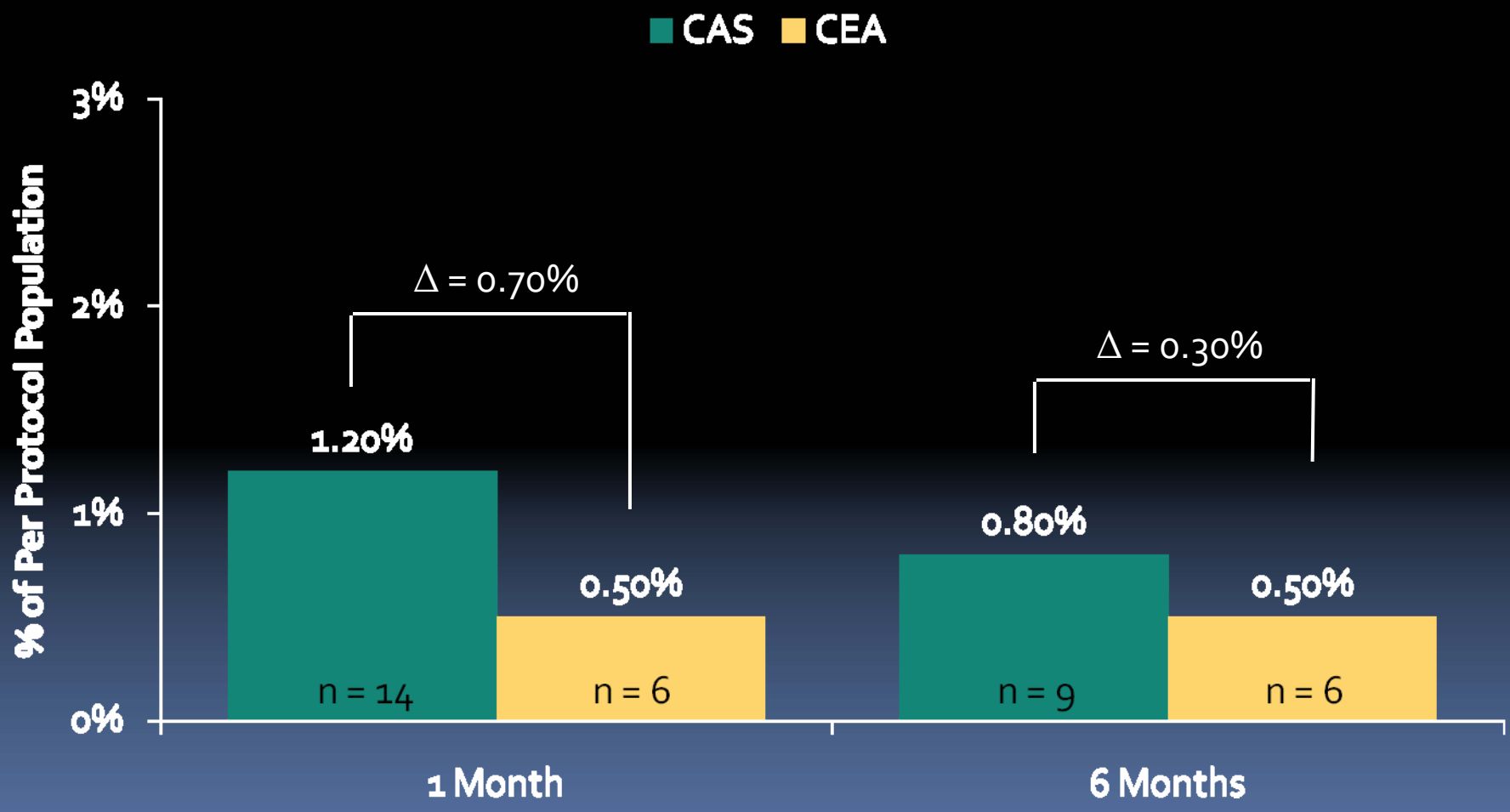
Death or Any Stroke Rates in CAS Decrease for Symptomatic Patients



Neurological Residual Deficit Rates by NIHSS Associated with Minor Strokes, Equal at 6 Months

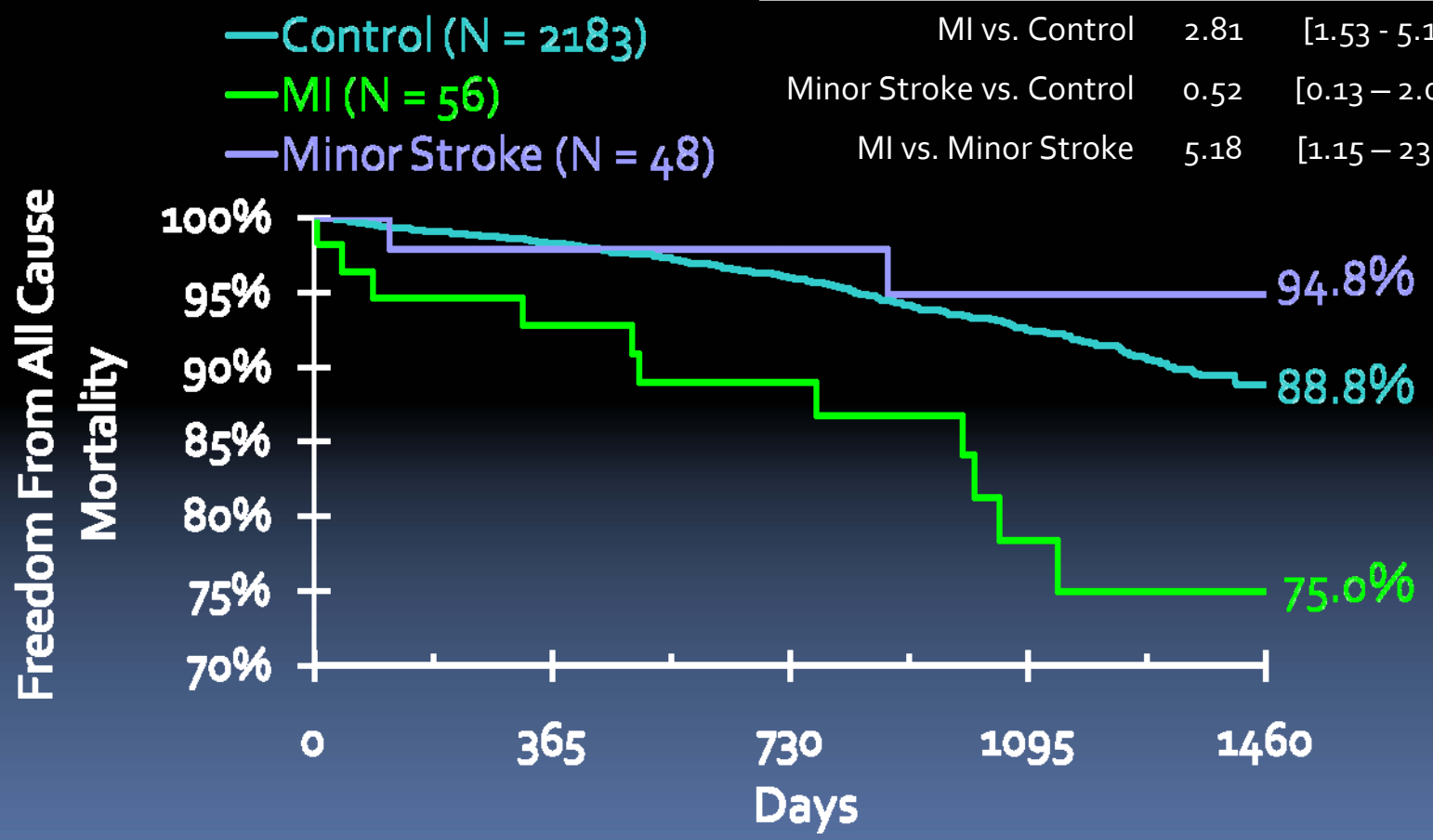


Neurological Residual Deficit Rates by mRS Associated with Minor Strokes, Similar at 6 Months



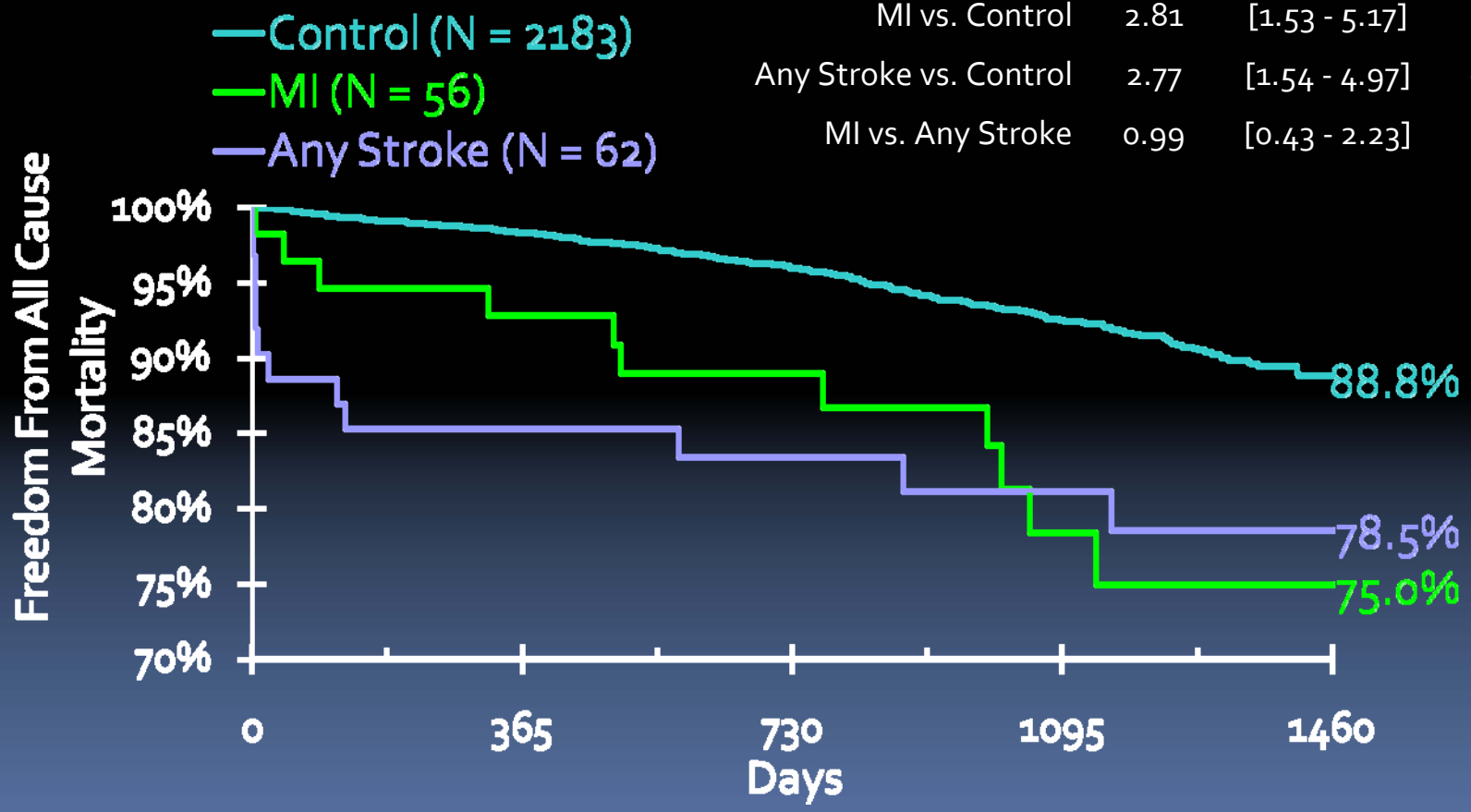
Lack of Association of Minor Stroke with Long Term Mortality

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



Similar Association of Any Stroke or MI on Long Term Mortality

Comparison	HR	HR Confidence Interval	Log Rank P-value
MI vs. Control	2.81	[1.53 - 5.17]	0.0005
Any Stroke vs. Control	2.77	[1.54 - 4.97]	0.0004
MI vs. Any Stroke	0.99	[0.43 - 2.23]	0.97



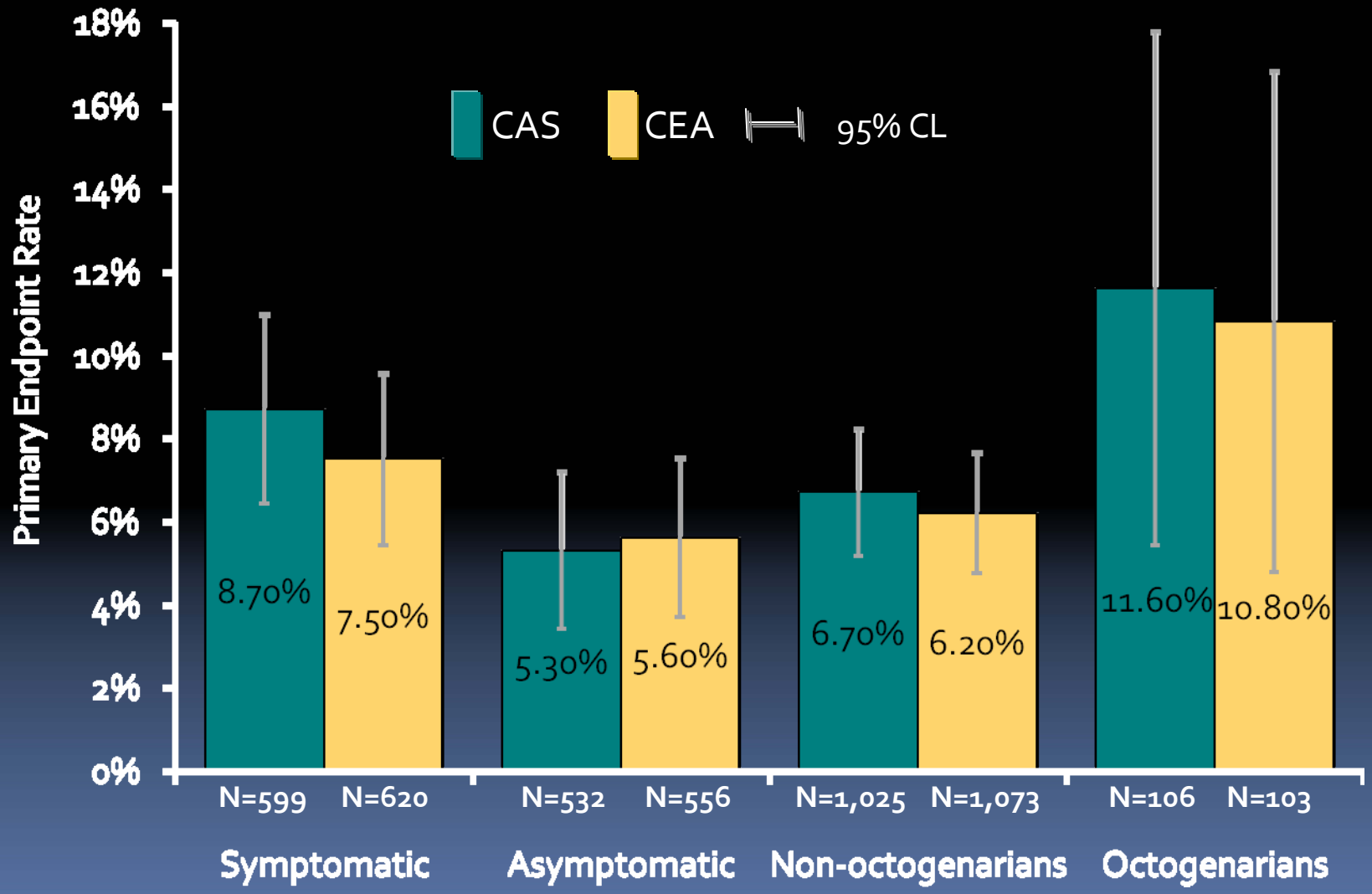
Outcomes Balance for CAS and CEA

- Death or Major Stroke
  - Low rates for both CAS and CEA
  - Decreasing rates for CAS over time
  - Similar rates for CAS and CEA in the second half of the study
- Minor stroke
  - More frequent with CAS at 30 days (absolute difference 1.7%)
  - Decreasing rates for CAS over time
  - By 6 months, CAS and CEA show similar low rates of residual neurological disability (0.80% vs 0.50% for overall population)
- Peri-procedural MI
  - More frequent with CEA at 30 days (absolute difference 1.5%)
  - Shows a significant relationship to mortality

Other Pre-Specified Secondary Endpoints

- Primary Composite Endpoint
  - Symptomatic status
  - Age by octogenarian status
- Acute Success
- Target Lesion Revascularization (TLR) at 1 year
- Access Site Complications Requiring Treatment
- Cranial Nerve Injury at 1 and 6 months

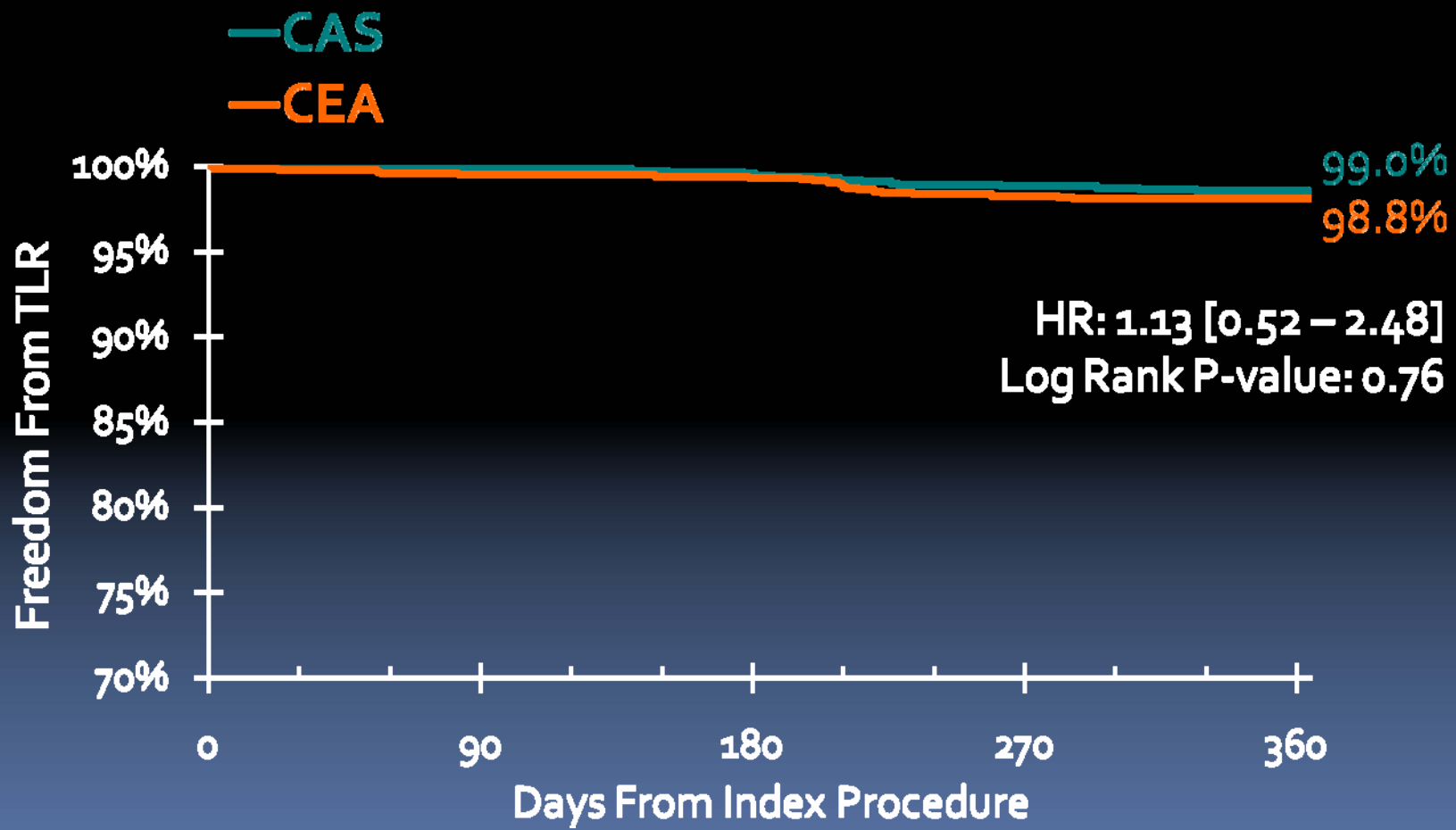
Primary Composite Endpoint by Symptomatic or Octogenarian Status



Comparable Procedure and Clinical Success

	CAS N = 1,131	CEA N = 1,176
Procedure Success [95% Conf. Interval]	97.5% [96.4%, 98.3%]	93. 6% [92.1%, 94.9%]
Clinical Success [95% Conf. Interval]	91.9% [90.2%, 93.4%]	89.8% [87.9%, 91.5%]

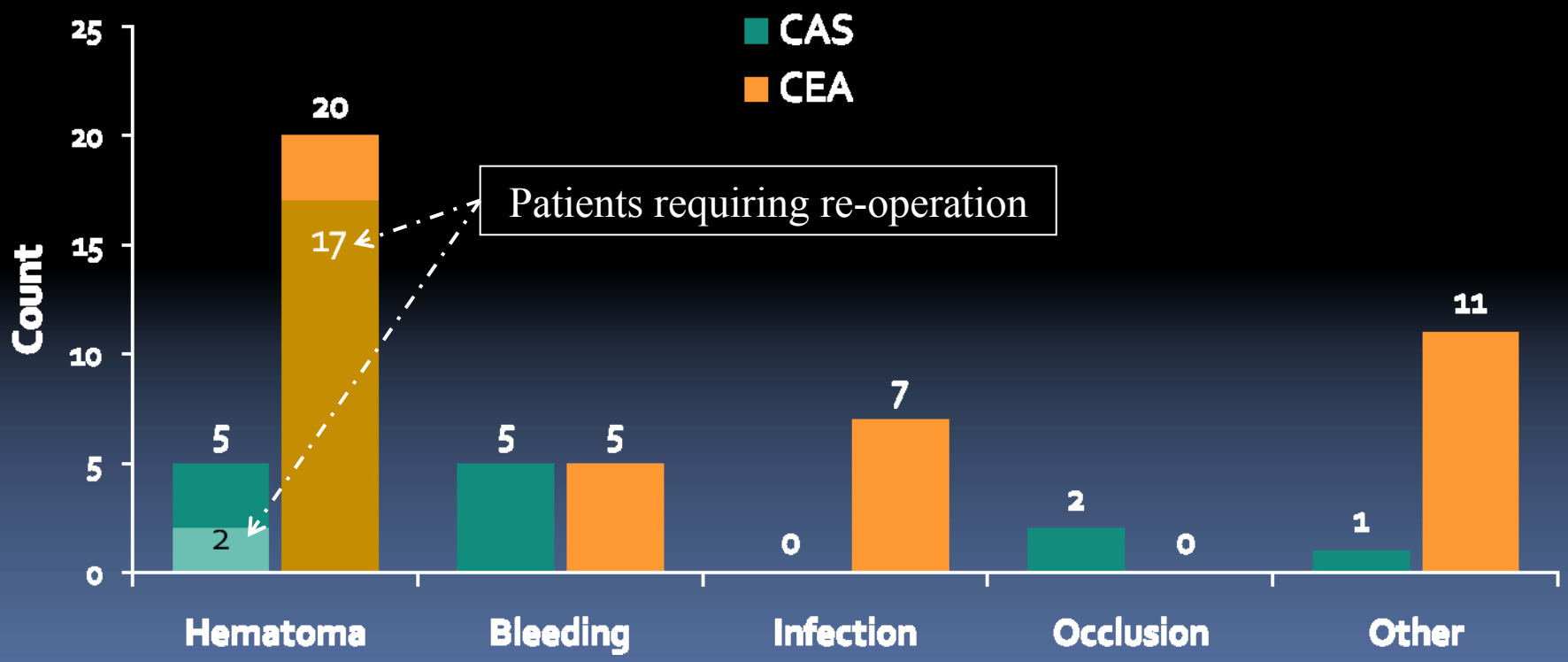
Freedom from Target Lesion Revascularization up to One Year



per protocol

Lower CAS Access Site Complications

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)

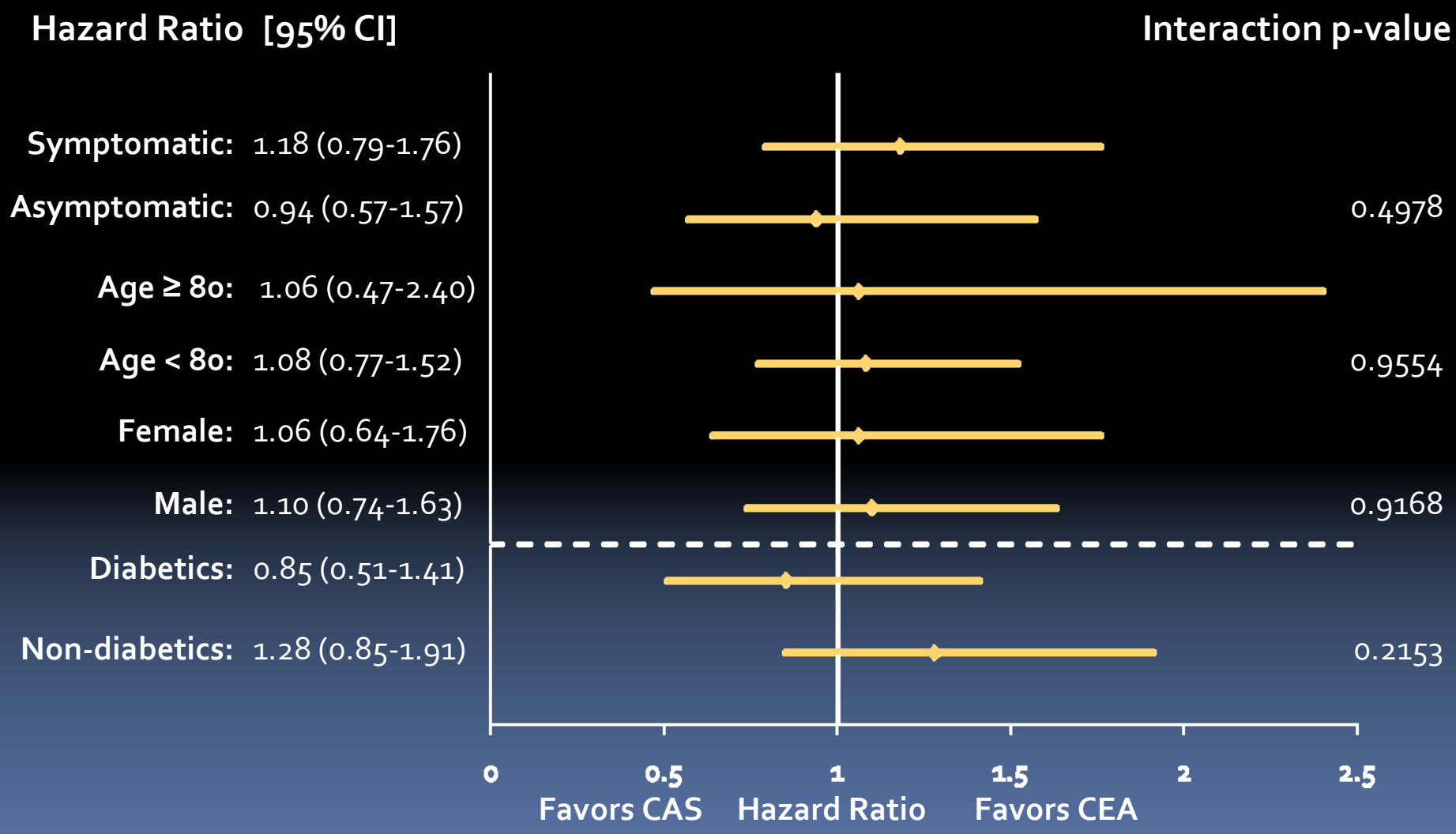
No Observed CAS Related Cranial Nerve Injury

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 One Month	0.0%	3.6% (42/1176)	< 0.0001
Unresolved at Six Months	0.0%	2.1% (25/1176)	< 0.0001

CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions

No Interaction by Subgroup for Primary Endpoint



CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
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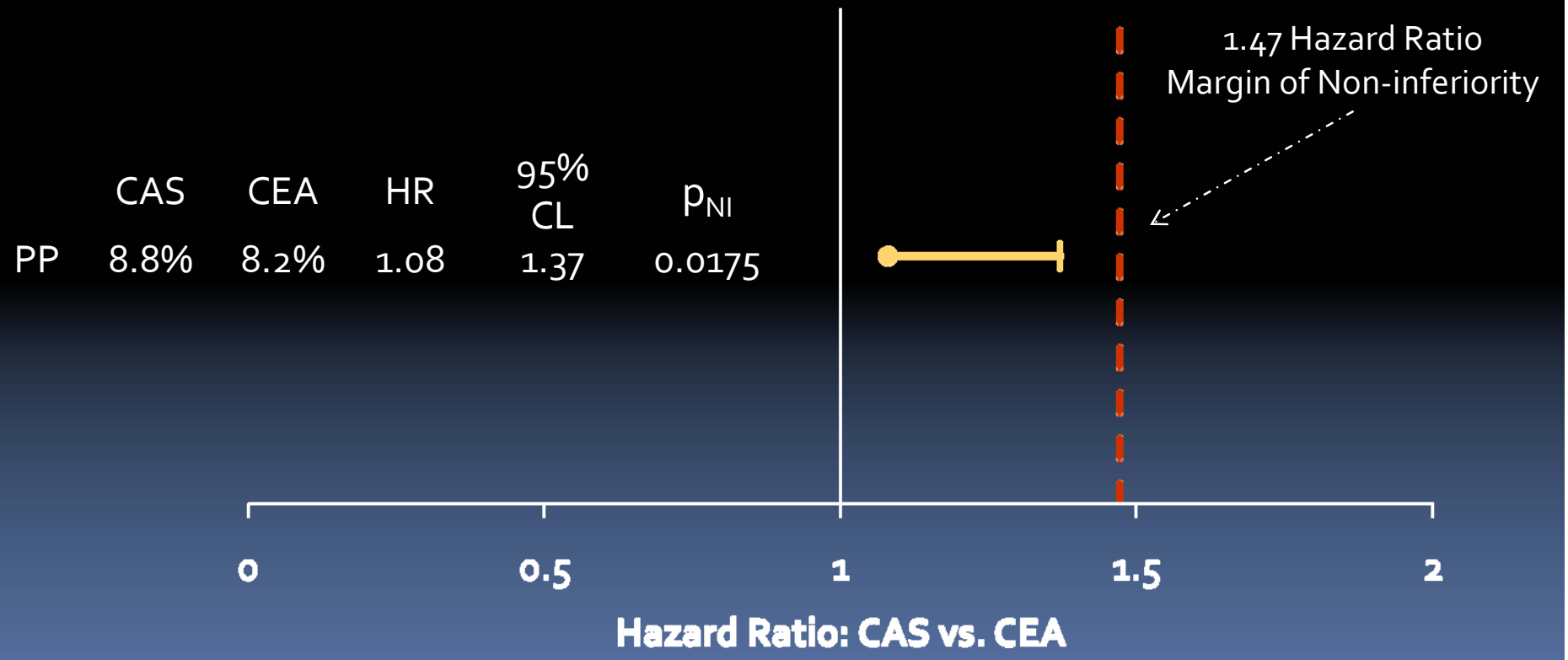
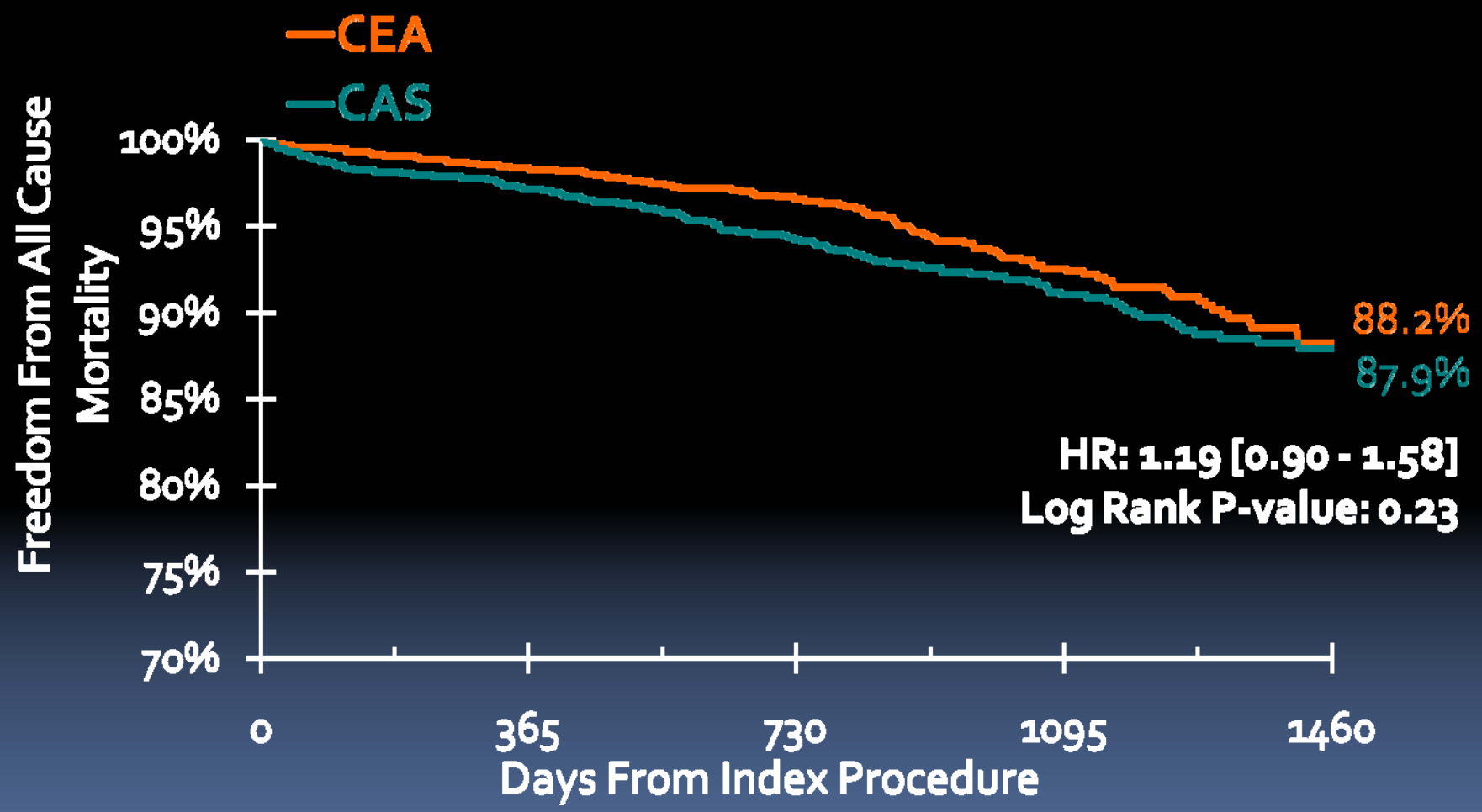
  - Multivariable Predictors of Mortality
- Conclusions

CAS Demonstrates Long Term Effectiveness to 4 Years

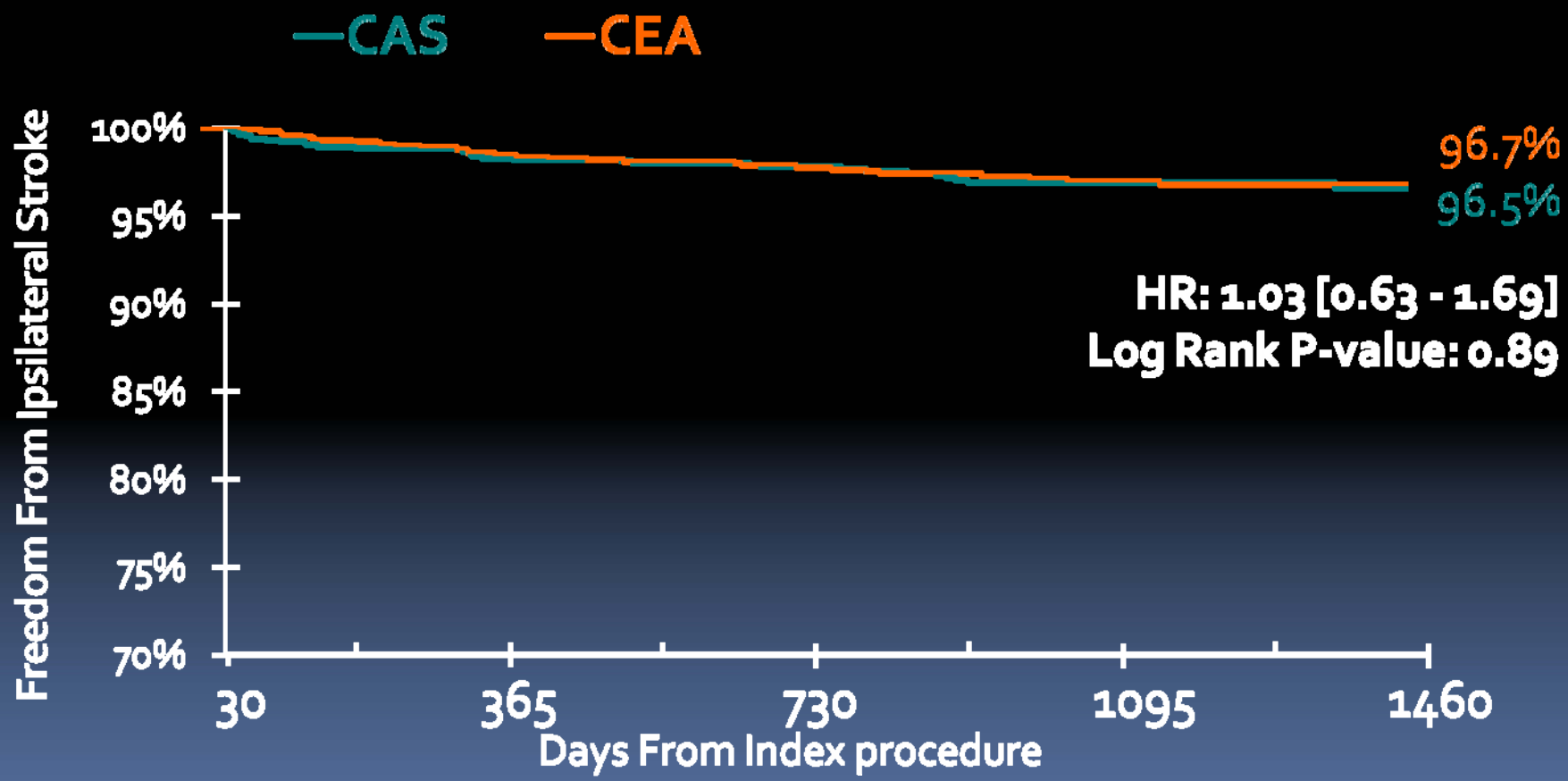
Primary Composite Endpoint (Median Follow-up 3 Years)



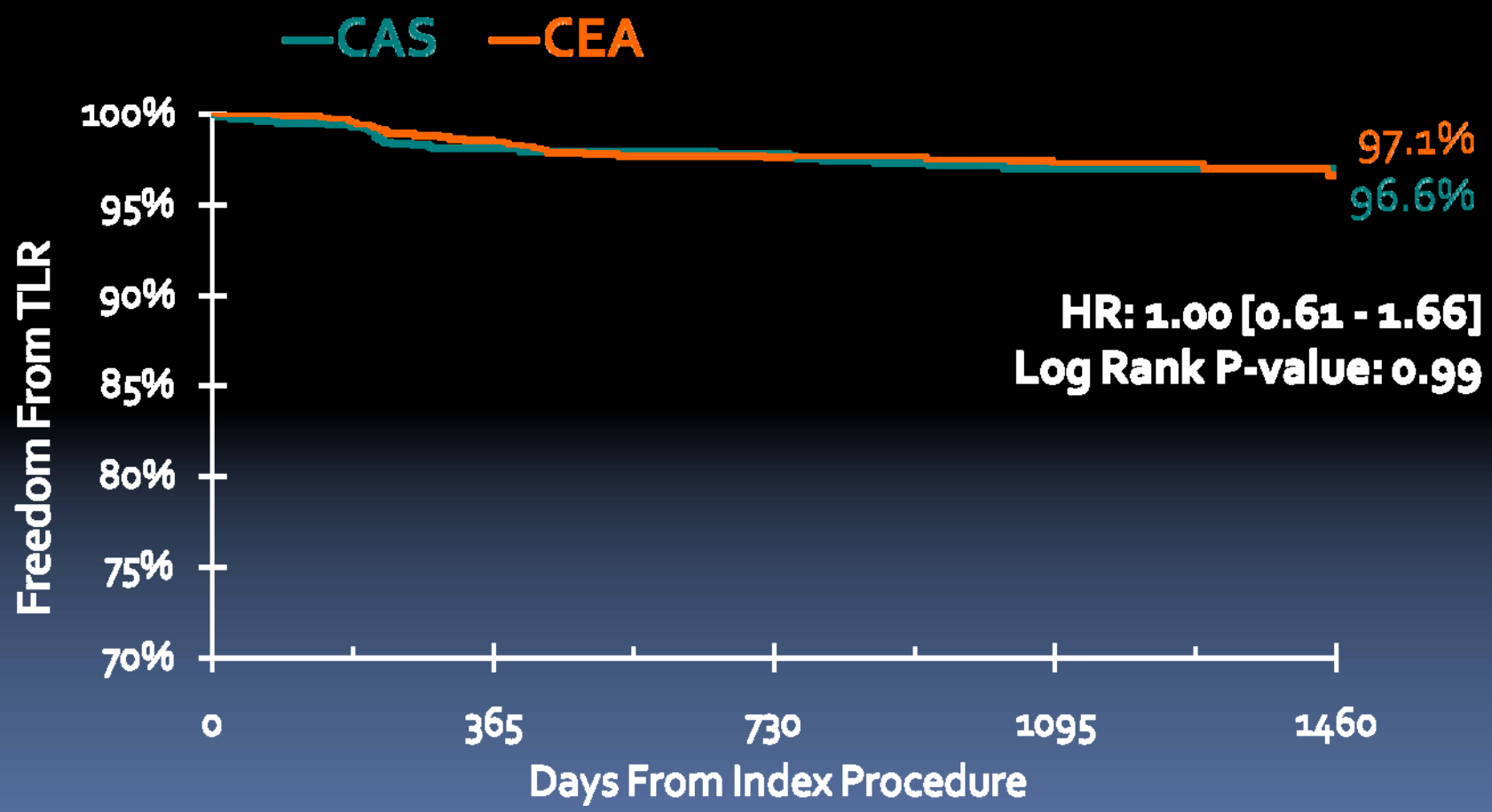
Similar Mortality to 4 Years



Similar Freedom from Ipsilateral Stroke Day 31 to 4 Years



Similar Freedom from TLR to 4 Years



CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions

Independent Predictors of Mortality

Variable	HR	95% CI	p-value
Any stroke within 30 days (yes vs. no)	2.49	1.44 - 4.32	0.0011
MI within 30 days (yes vs. no)	2.14	1.23 - 3.86	0.0079
Current Smoker (yes vs. no)	1.69	1.19 - 2.39	0.0034
Diabetes (yes vs. no)	1.57	1.16 - 2.12	0.0032
Sex (male vs. female)	1.50	1.08 - 2.08	0.0150
Ischemic Heart Disease/ Congestive Heart Failure (yes vs. no)	1.48	1.10 - 2.00	0.0097
Age (in Years)	1.06	1.04 - 1.08	< 0.0001

p-values from Cox regression model, for descriptive purposes only

CREST PMA Analysis

- Background
- Methods
- Results
  - Primary Composite Endpoint
  - Secondary Endpoints
  - Pre-specified Interaction Analyses
  - Long term Effectiveness and Durability
  - Multivariable Predictors of Mortality
- Conclusions

Conclusions

- The PMA analysis of the CREST study demonstrates:
  - CAS is non-inferior to CEA for:
    - the primary endpoint in all analysis populations
    - death, stroke or MI at 30 days
  - CAS shows similar durability to CEA by freedom from the primary endpoint, mortality, ipsilateral stroke, and TLR to 4 years
  - The primary endpoint rates were similar for CAS and CEA for symptomatic or octogenarian status

Final Interpretation

- CREST PMA analysis supports the proposed expanded indication to treat patients at standard surgical risk with CAS using the Acculink Stent System
- CAS with the Acculink Carotid Stent System demonstrates a reasonable assurance of safety and effectiveness compared to CEA
- Treatment with CAS or CEA should be determined by physicians and patients based on the clinical profile of each patient

NIH Analysis of the CREST Data

Thomas G. Brott, MD
Principal Investigator, IDE Sponsor

Mayo Clinic
Jacksonville, FL

James C. and Sarah K. Kennedy Dean of Research

Eugene and Marcia Applebaum Professor of Neurosciences

Financial Disclosure

- Dr. Thomas G. Brott, M. D.
  - No financial relationship with Abbott Vascular, Inc.
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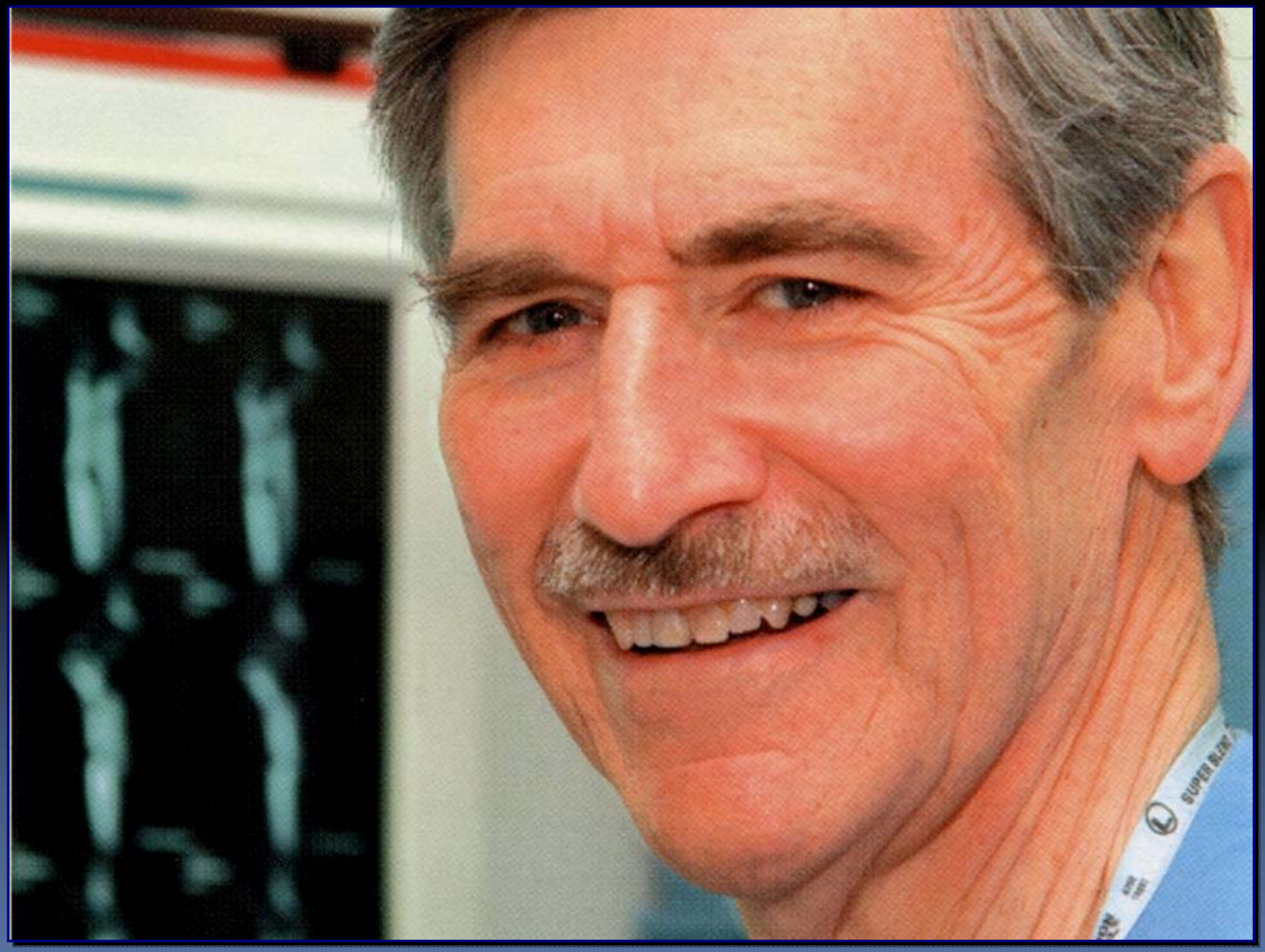
    - NIH – US Public Health Service, NINDS, R01 NS 038384

Acknowledgements

- 1,565 credentialing and 2,502 randomized patients
- More than 117 Site Principal Investigators
- More than 200 Site Coordinators
- University of Medicine and Dentistry of New Jersey (UMDNJ)
- University of Alabama at Birmingham (UAB)
- 3 Core Labs and the QOL/Cost group
- Adjudication Committees, the DSMB, NINDS, and Abbott Vascular, Inc.

Robert Hobson II, M. D.
PI, 1999 - 2007



Study Design

- Randomized, controlled trial with blinded endpoint adjudication
- Comparing CAS and CEA
- Symptomatic and asymptomatic patients
- Intent-to-treat superiority design with sample size of 2,500 to detect an annual difference of 1.2%, based upon the ACAS results which changed practice (corresponding to a hazard ratio of 1.48)

Primary Endpoint

- Peri-procedural, a composite of:
  - Any Clinical Stroke
  - Myocardial Infarction (not enzyme only)
  - Death
- Post-procedural
  - Ipsilateral stroke up to 4 years

Key Secondary Aims

- Differential efficacy by symptomatic status, sex, and age
- Differential restenosis
- Quality of Life and cost effectiveness

Patient Characteristics

	CAS N = 1,262	CEA N = 1,240
Age	68.9 ± 9.0	69.2 ± 8.7
Cardiovascular disease - %	42.4	45
Systolic BP, mean mmHg	142	141
Diabetes %	30.6	30.4
Dyslipidemia %	82	85
% stenosis ≥ 70%	85	87
Days from qualifying event (for symptomatic subjects)	20	25

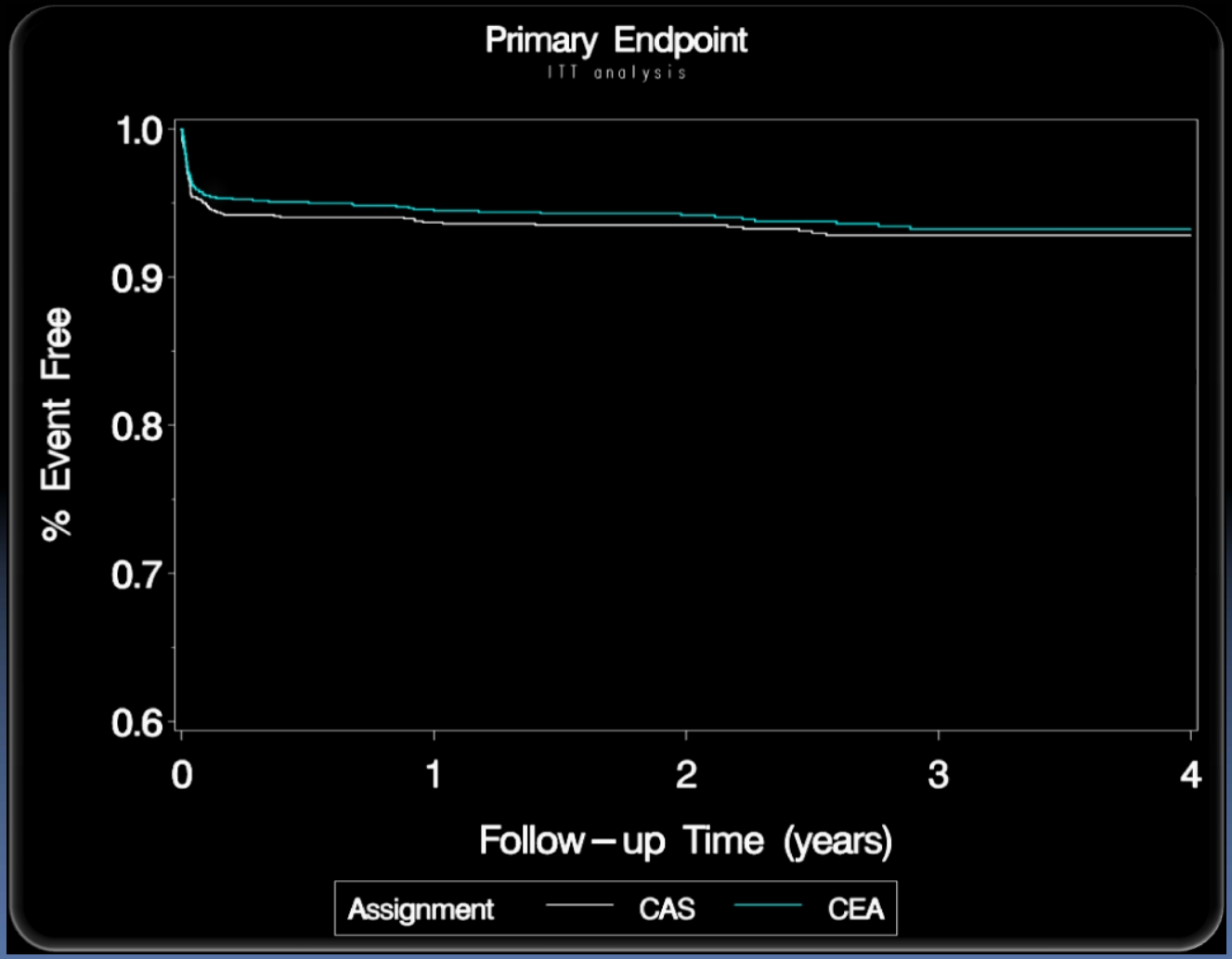
Primary Results

Primary Endpoint ≤ 4 Years

CAS	7.2%
CEA	6.8%
Hazard Ratio	1.11
95% Conf. Int.	0.81 – 1.51
p-value	0.51

(any stroke, MI, or death within peri-procedural period plus ipsilateral stroke thereafter)

Primary Endpoint
ITT Analysis



Multiple Imputation in the NIH Analysis

- Differential withdrawal (censoring) between treatment group could introduce bias
- Multiple imputation using a method similar to Taylor* was employed to assess potential differences
  - Outcomes of censored individuals were replaced with randomly selected outcomes of non-censored individuals
  - Procedure repeated 10 times
  - Analyzed using standard multiple imputation approaches
- Findings were strikingly similar to analysis without imputation (identical to the second decimal), suggesting the absence of bias from this source

* Statistics and Probability Letters, 2002, 58: 221-232

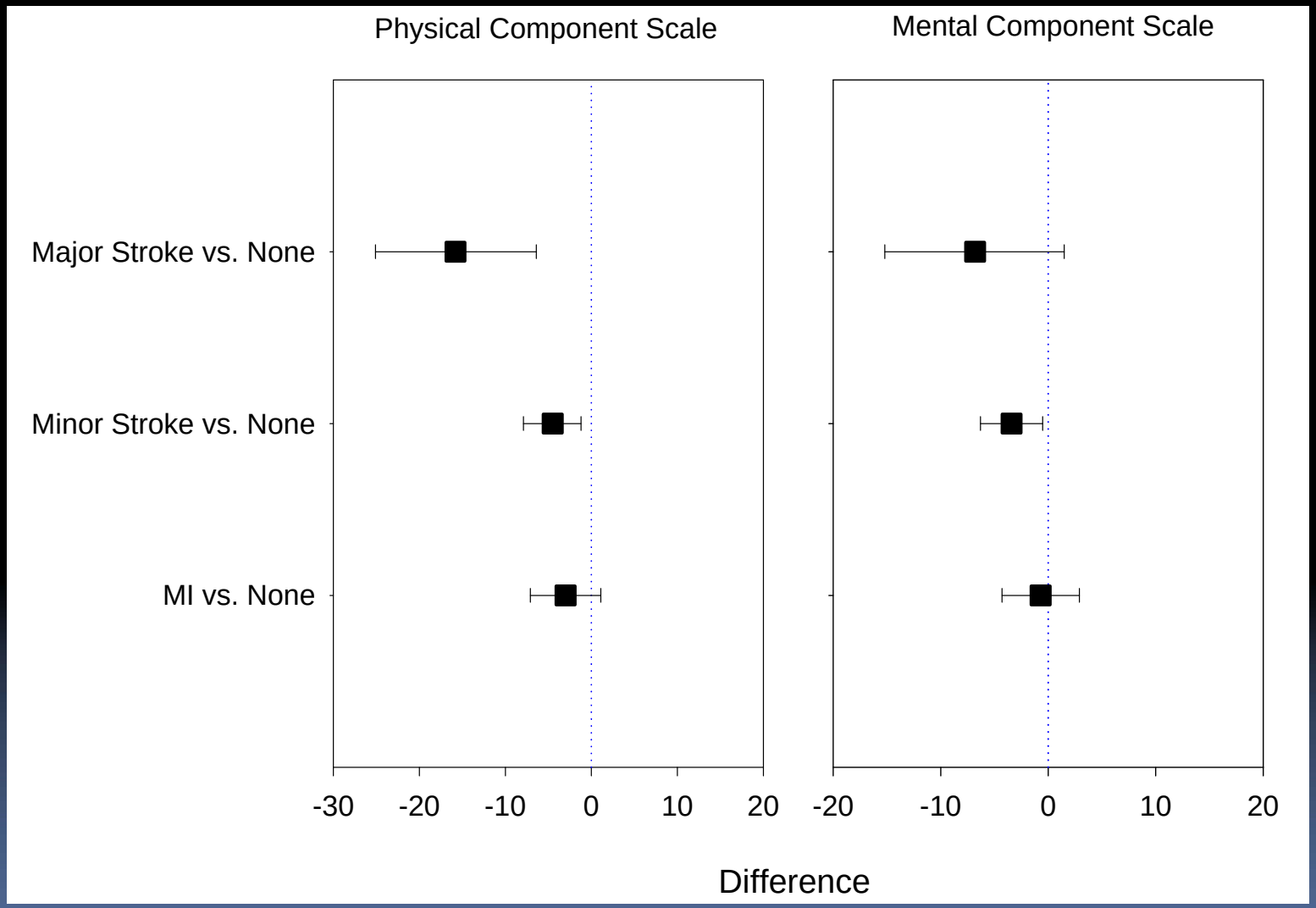
Peri-procedural Stroke & MI

	Stroke	MI
CAS	4.1%	1.1%
CEA	2.3%	2.3%
Hazard Ratio 95% Conf. Int.	1.79 1.14 – 2.82	0.50 0.26 – 0.94
p-value	0.01	0.03

Peri-procedural Stroke

	Stroke	Major Stroke
CAS	4.1%	0.9%
CEA	2.3%	0.7%
Hazard Ratio 95% Conf. Int.	1.79 1.14 – 2.82	1.35 0.54 – 3.36
p-value	0.01	0.52

Quality of Life Measures



Impact of peri-procedural events (stroke/MI) on SF-36 at 1 year adjusting age, sex, symptomatic cerebrovascular disease and baseline SF-36 measures – Growth Curve Modeling

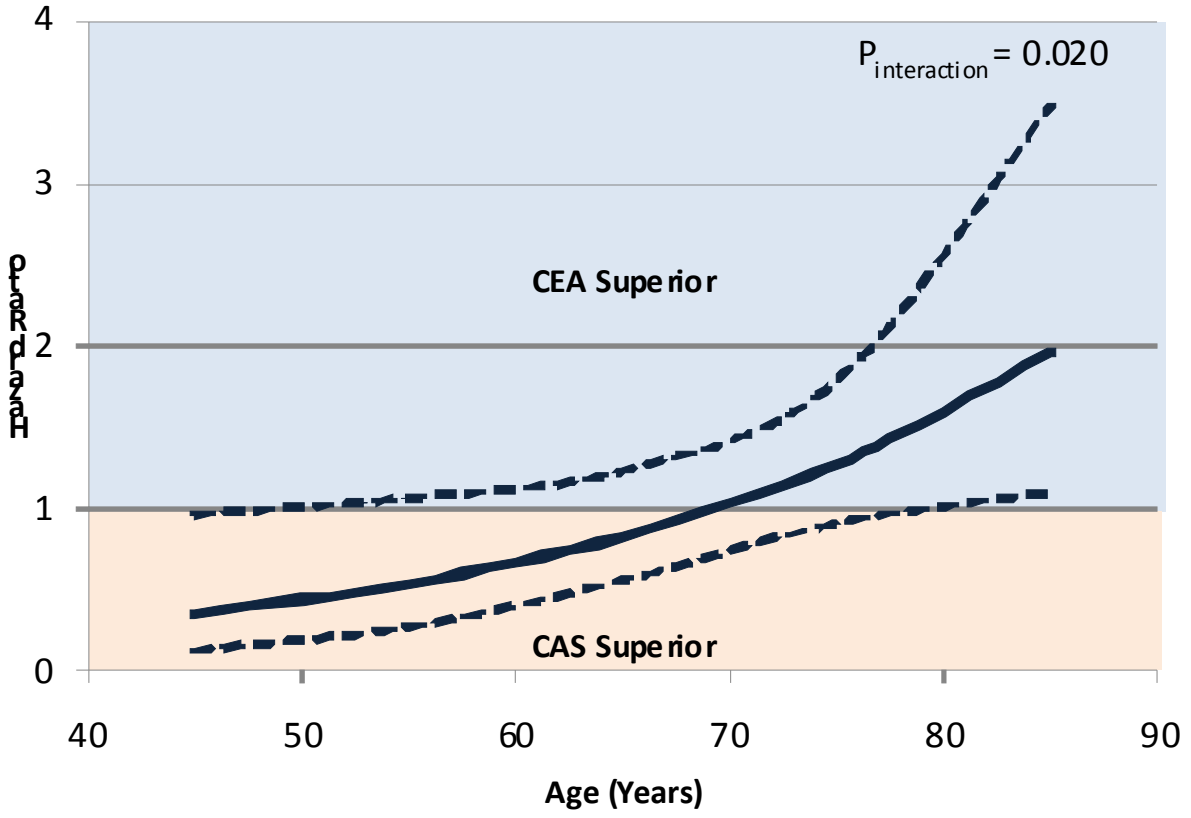
Ipsilateral Stroke After Peri-procedural Period

	Stroke
CAS	2.0%
CEA	2.4%
Hazard Ratio 95% Conf. Int.	0.94 0.50 – 1.76
p-value	0.85

Interaction with Primary Endpoint

- No effect detected for symptomatic status or sex
- Interaction suggested for Age, $p = 0.02$

Primary Outcome – 4 Year



Relationship Between Medical Specialty and Risk of Primary Outcome

Specialty	HR (95% CI) adjusted for age, sex, symptomatic status
Cardiology	reference
Neuroradiology/ Neurointerventionalist	1.27 (0.63-2.54)
Interventional Radiology	0.72 (0.32-1.63)
Vascular Surgery	1.18 (0.60-2.31)
Neurosurgery	1.49 (0.76-2.89)
p-value for difference	0.505

CREST NIH Results at 1 Year

- Intent-to-Treat population and NIH methodology
- Primary endpoint
  - CAS: 6.30 ± 0.69%
  - CEA: 5.52 ± 0.66%
- Non-inferiority met for NIH analysis
  - One-sided 95% CI for the difference between CAS and CEA is 2.36%, p = 0.03

Conclusions

- CEA and CAS have similar net outcomes
  - CAS: Lower MI rate
  - CEA: Lower Stroke rate
- Younger patients may have improved efficacy with CAS and older patients have improved efficacy with CEA

Conclusion

- At experienced centers both CEA and CAS appear to have low peri-procedural complications and excellent longer-term results
- Both treatments are viable options for standard risk patients

Concluding Remarks

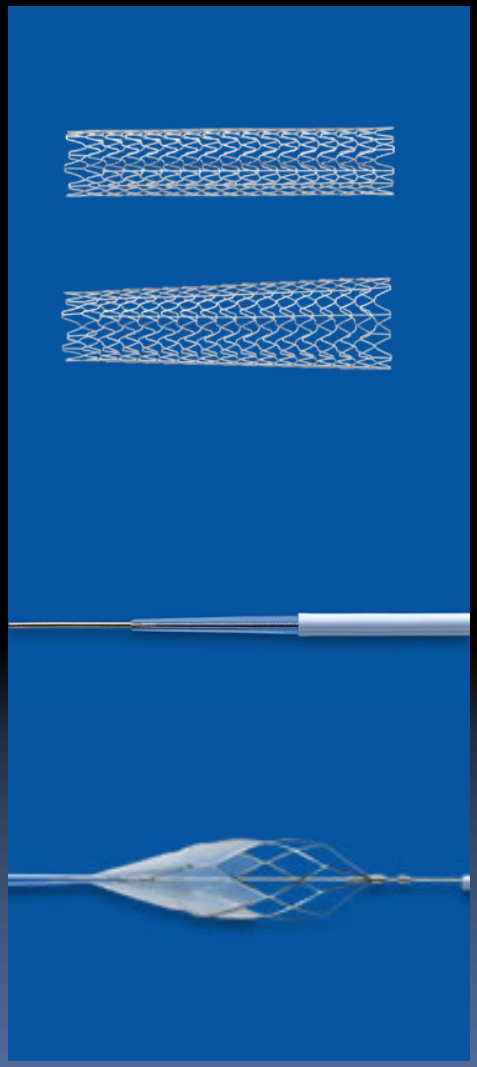
Chuck Simonton, MD
FACC, FSCAI
Chief Medical Officer
Divisional Vice President
Abbott Vascular

Abbott Vascular Post-Approval Study Commitment

- Abbott Vascular has extensive experience with post approval studies for carotid stenting in high-risk patients (> 17,000)
- This experience will be leveraged to conduct a timely and robust post-approval study of patients at standard risk of CEA
  - Collect post-approval data on a broad group of physicians under commercial use
  - 3 year follow-up
  - Follow safety and effectiveness outcomes

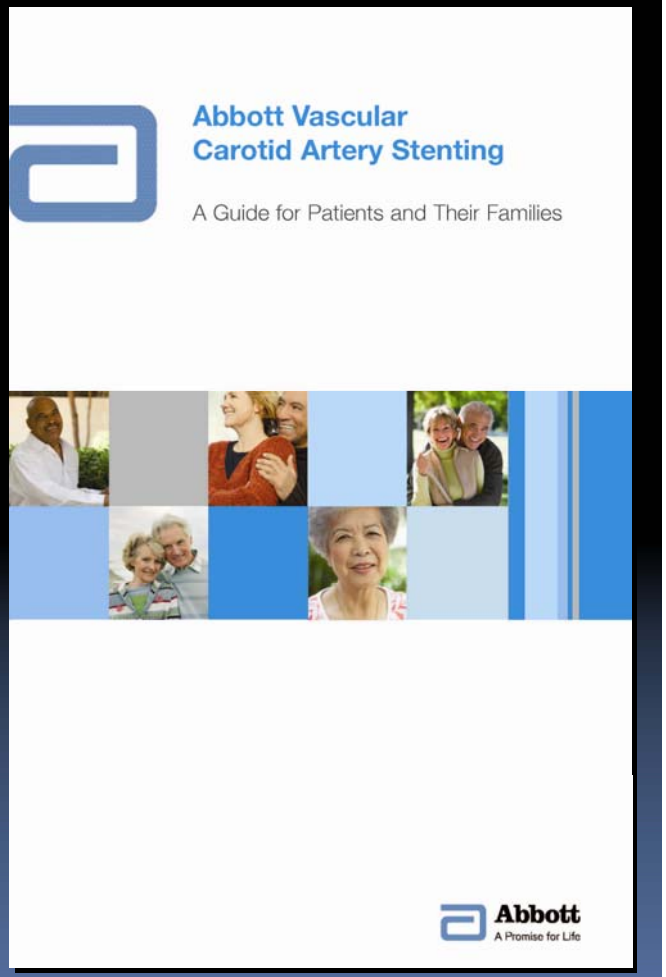
Physician Education Programs to Ensure Safe Use

- Comprehensive Physician Education Program
  - In place since 2004 for high risk patients
  - No changes required for standard risk patients
- Certification Pathways
  - Based on previous carotid stent or endovascular experience
- Embolic Protection System Training Program



Patient Guide with Comprehensive Information

- Helping health-care providers educate their patients
- Treatment options
- Procedure preparation
- Post procedure follow-up
- Lifestyle management



Safety and Effectiveness of CAS Demonstrated in Standard Surgical Risk Patients

- Non-inferior to CEA for the primary composite endpoint at 1 year and for DSMI at 30 days
- Death or any stroke rate for CAS decreased over the time of enrollment
  - Death or major stroke rate became essentially equivalent to CEA for symptomatic patients
- Comparable outcomes to CEA by symptomatic status and age
- Similar durability as CEA for up to 4 years

Benefits Outweigh the Risks for the RX Acculink Carotid Stent System

- Benefits
  - Comparable outcomes to CEA
  - Lower MI rate compared to CEA
  - Long term effectiveness confirmed out to 4 years
  - Less invasive with fewer access site complications and lack of cranial nerve injury
- Risks
  - Higher rate of minor stroke at 30 days compared to CEA
    - Declining rates of minor stroke over time for CAS
    - Similar residual neurological deficits at 6 months

Subject Matter Experts

Abbott Vascular Consultants

Kirk W. Beach, MD, Ph.D.

Duplex Ultrasound Core Laboratory, University of Washington School of Medicine

David Cohen, MD

QOL, Director of Cardiovascular Research, St. Luke's Mid America Heart Institute

William A. Gray, M.D.

Director of Endovascular Services, New York-Presbyterian Hospital / Columbia University Medical Center

Kerry Lee, Ph.D

Dept. of Biostats & Bioinform., Duke University School of Medicine

Abbott Vascular

Nora Hadding, JD

Director, Regulatory Affairs

Lugene Keene

Director, Clinical Research

Bjorn Svensson

Director, Research and Development

Brian Tyser

Manager, Physician Education and Training

Roseann White, MA

Director, Biostatistics

RX Acculink® Carotid Stent System
Standard Surgical Risk Indication

P040012/S034

January 26, 2011

Circulatory System
Devices Advisory Panel
Food and Drug Administration