Differences in US vs. EU carotid artery stenting trial design: The differences explain the outcomes

William A. Gray MD
Director of Endovascular Services
Associate Professor of Clinical Medicine
Columbia University Medical Center
The Cardiovascular Research Foundation

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Faculty Disclosure

- William A. Gray, MD

- For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

- Honoraria received from and consulted for:
- Abbott Vascular
- Boston Scientific
- Cook
- Cordis/Johnson & Johnson
- Medtronic
- Medrad/Possis
- WL Gore

Faculty Disclosure (continued)

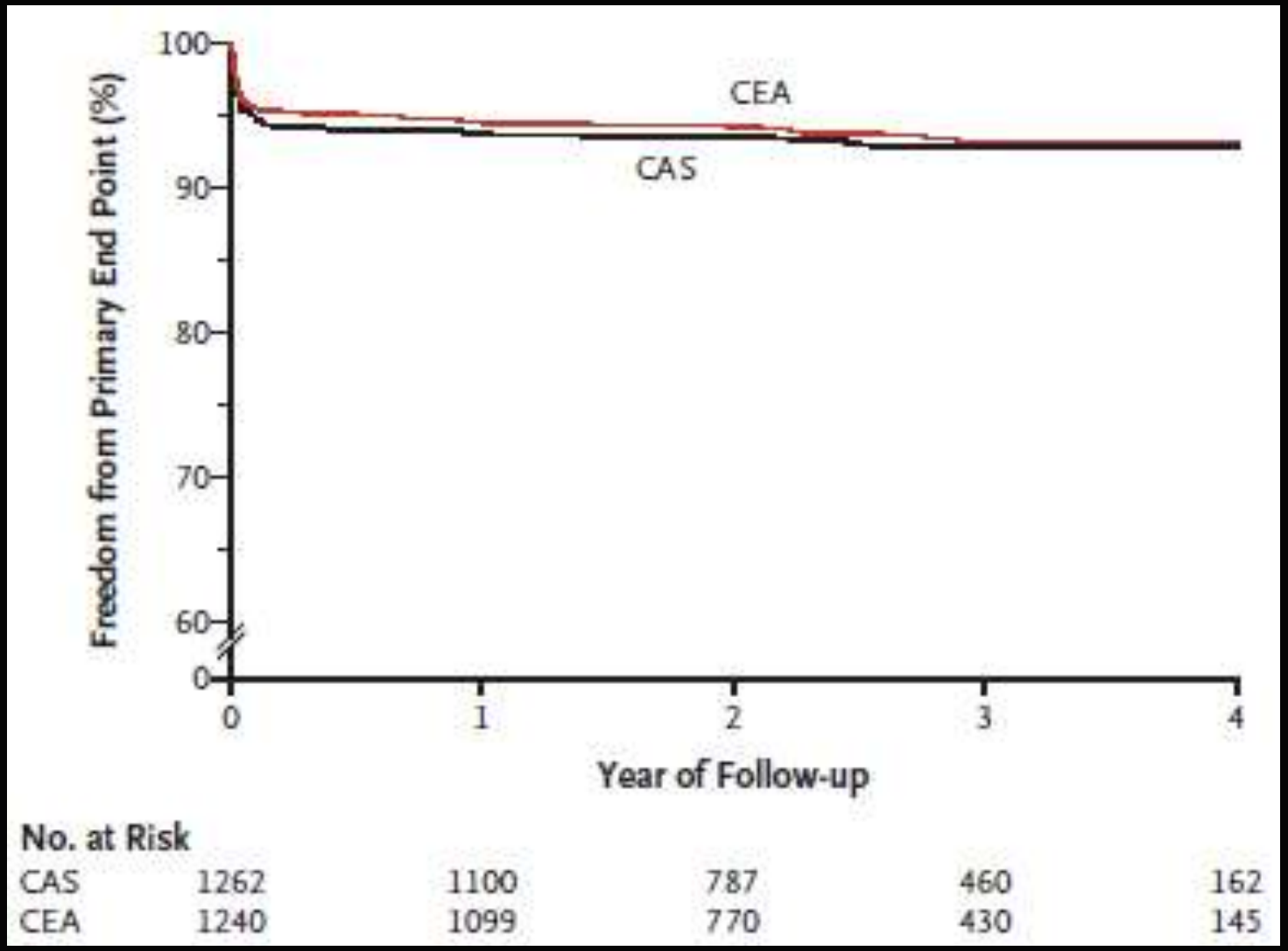
- William A. Gray, MD

- Held common stock in:
  - Biocardia
  - Contego

- Research, clinical trial, or drug study funds received from:
  - Abbott Vascular
  - Cordis/Johnson & Johnson
  - Medtronic

- I will be discussing products that are investigational or not labeled for use under discussion.

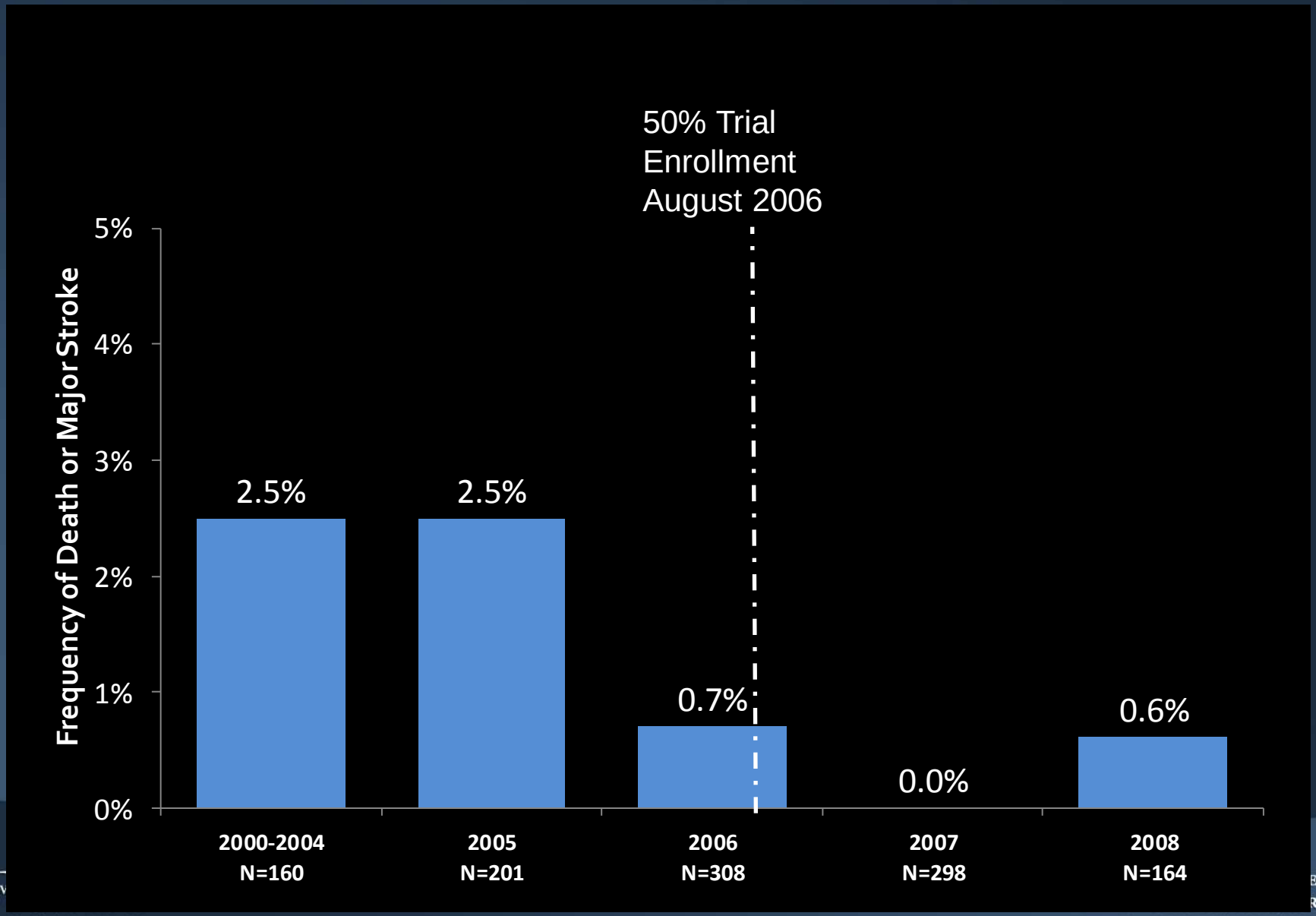
CREST:
CEA and CAS are no different for the primary endpoint



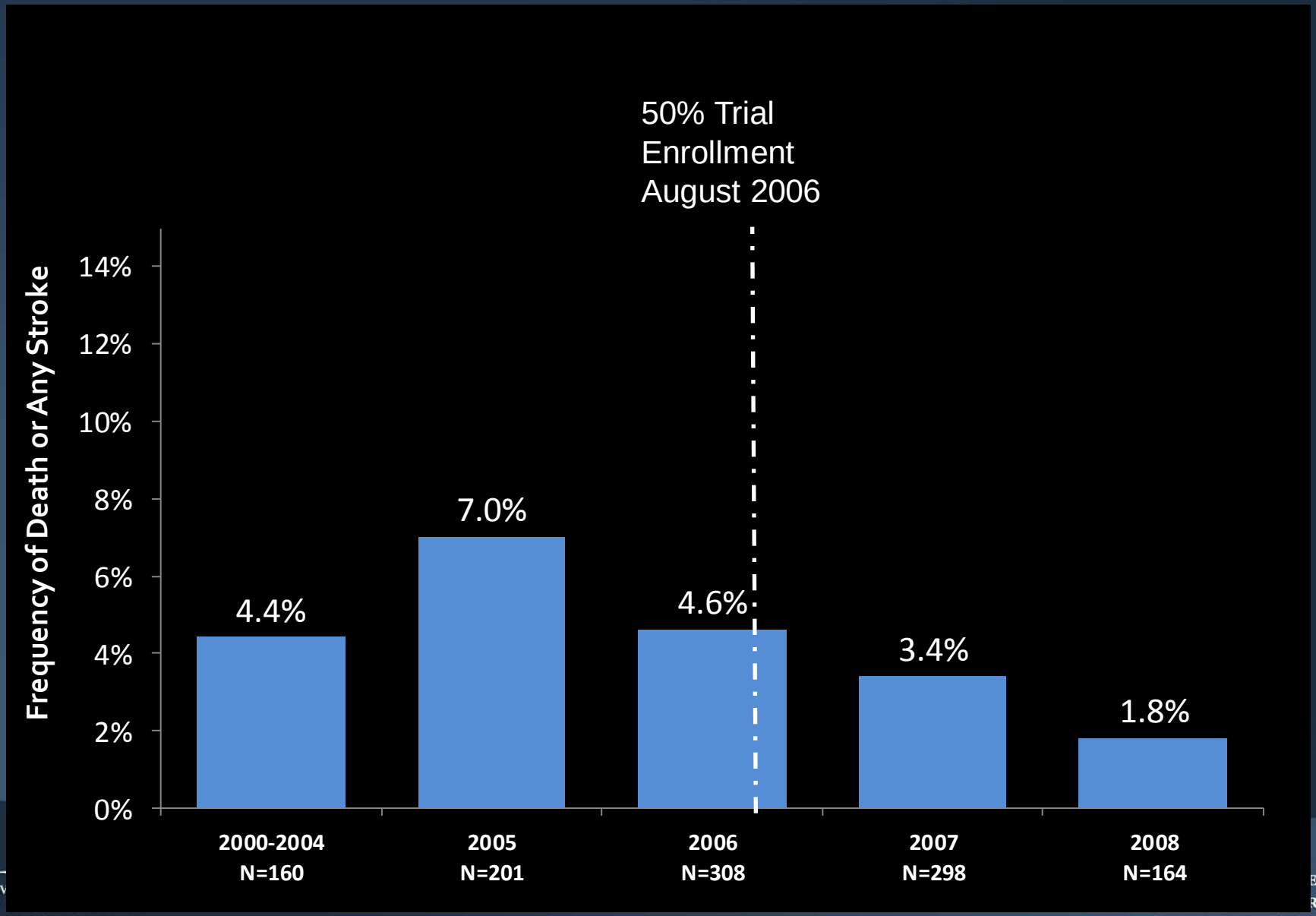
No. at Risk					
CAS	1262	1100	787	460	162
CEA	1240	1099	770	430	145

CREST in-trial learning curve

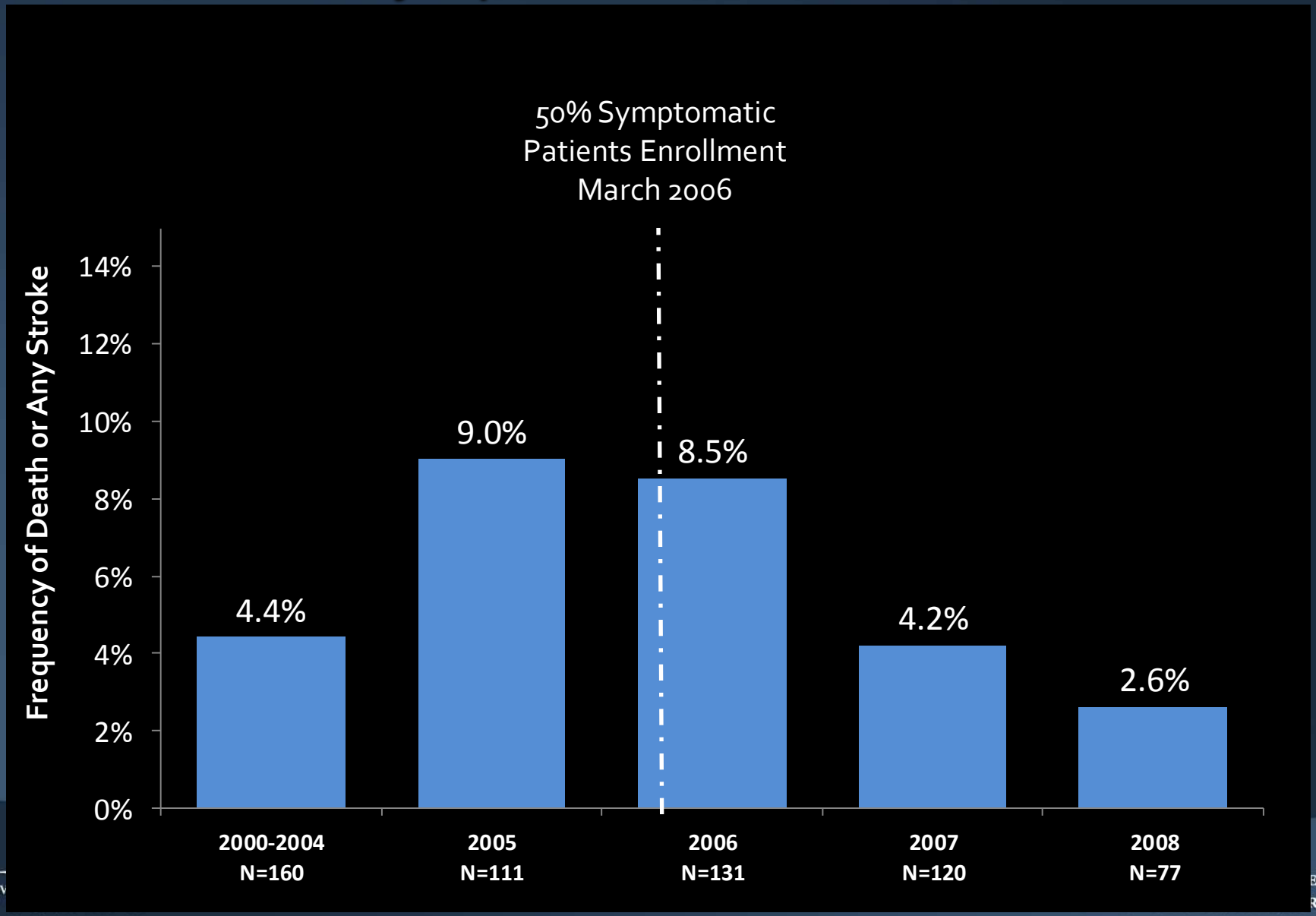
Death or Major Stroke Rates Decrease for CAS over the Period of CREST Enrollment



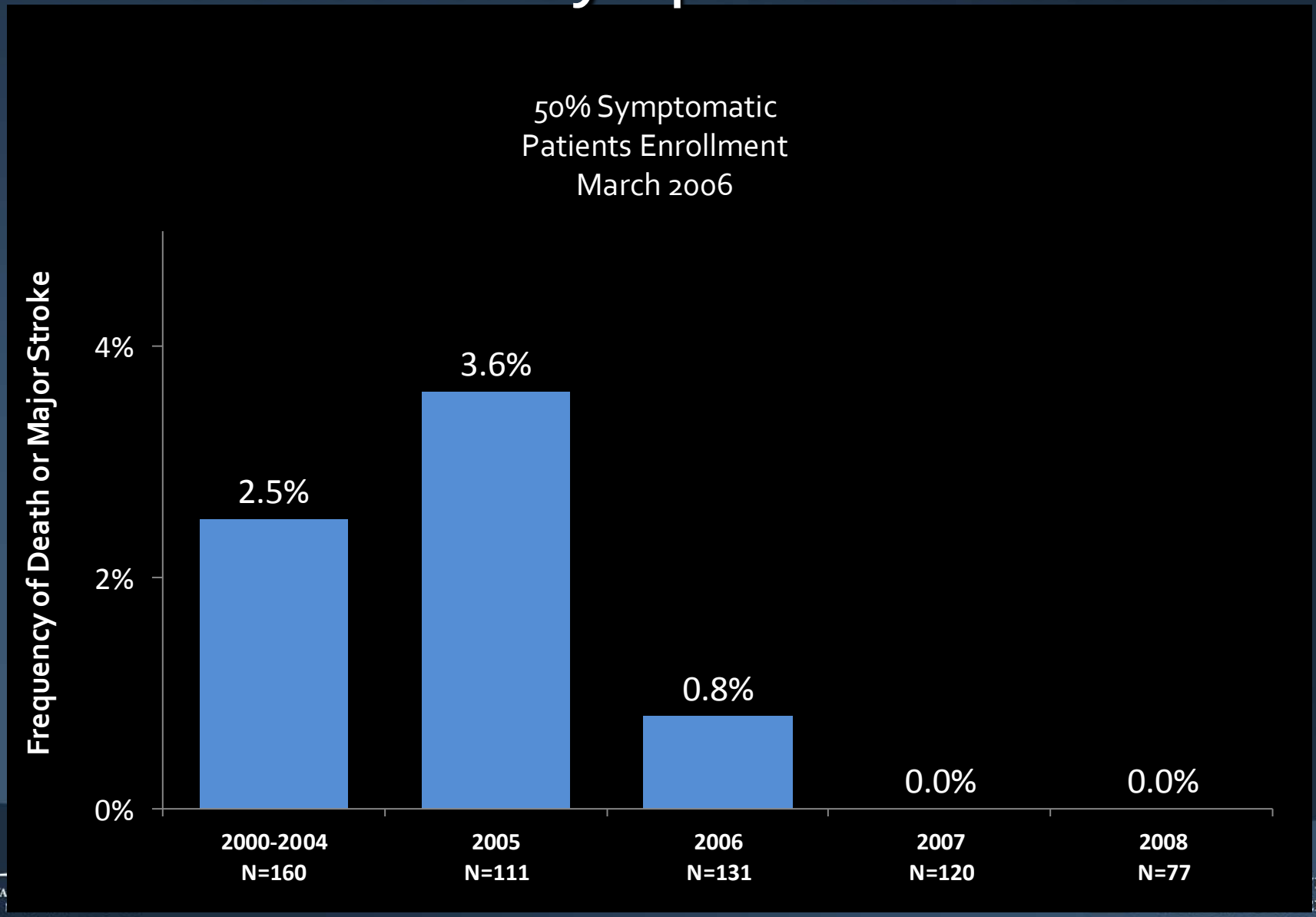
Death or Any Stroke Rates Decrease for CAS over the Period of CREST Enrollment



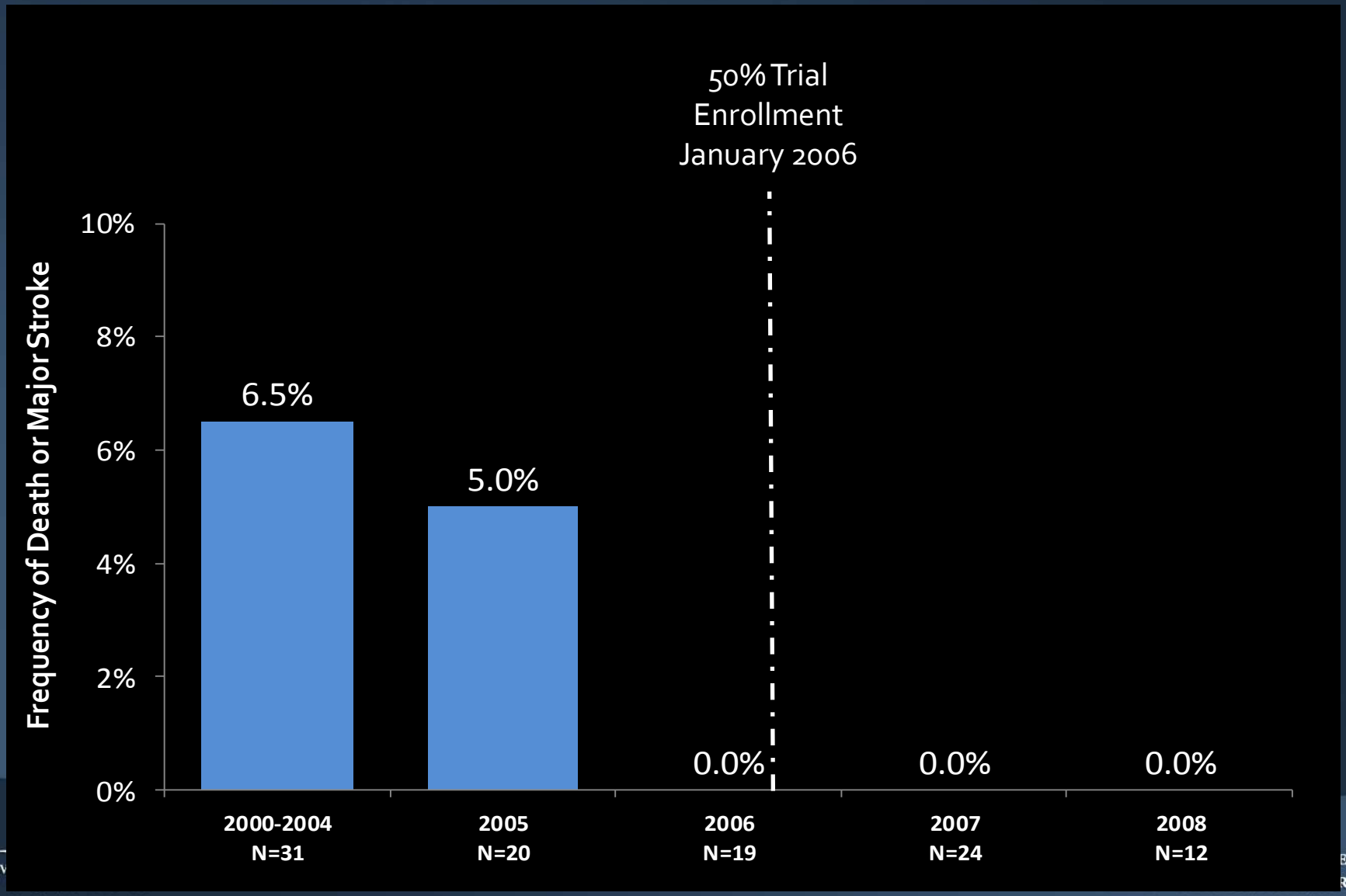
Death or Any Stroke Rates in CAS Decrease for Symptomatic Patients



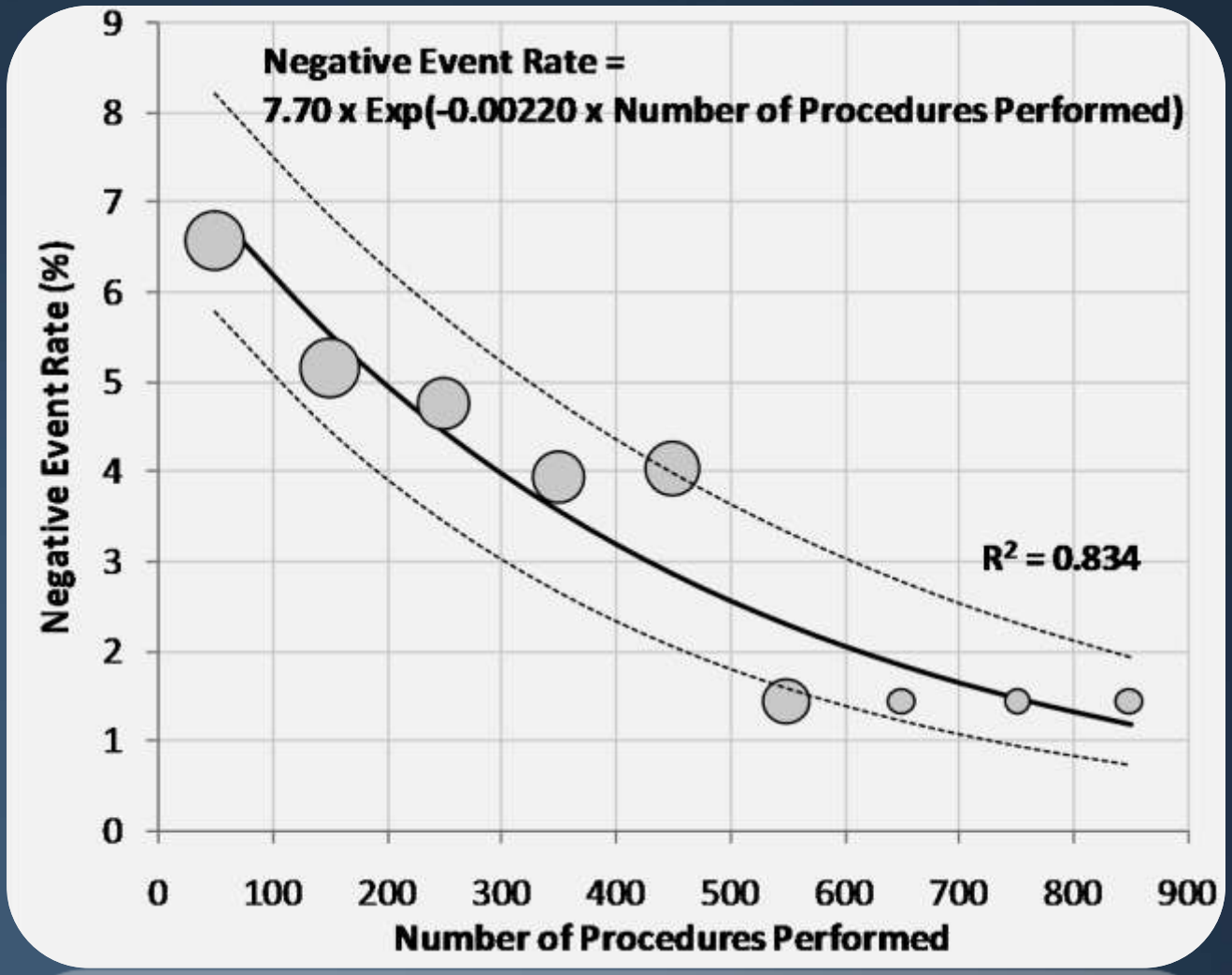
Death or Major Stroke Rates in CAS Decrease for Symptomatic Patients



Death or Major Stroke Rates in CAS Decrease for Octogenarian Patients



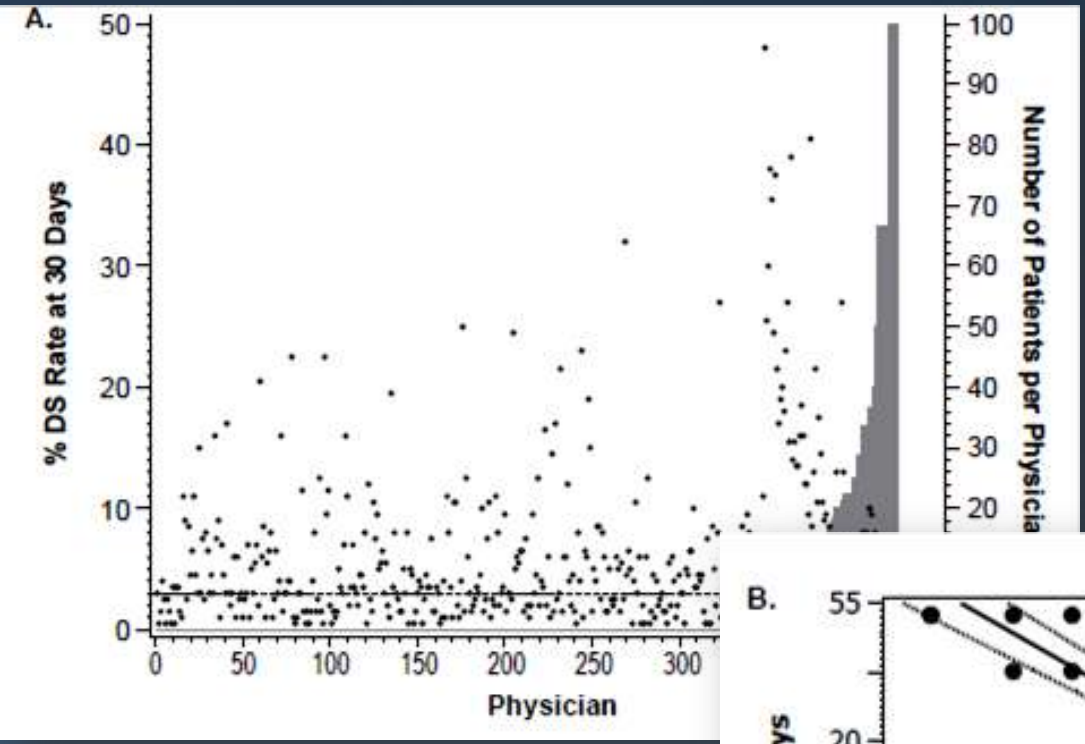
CAS learning curve: practice makes perfect

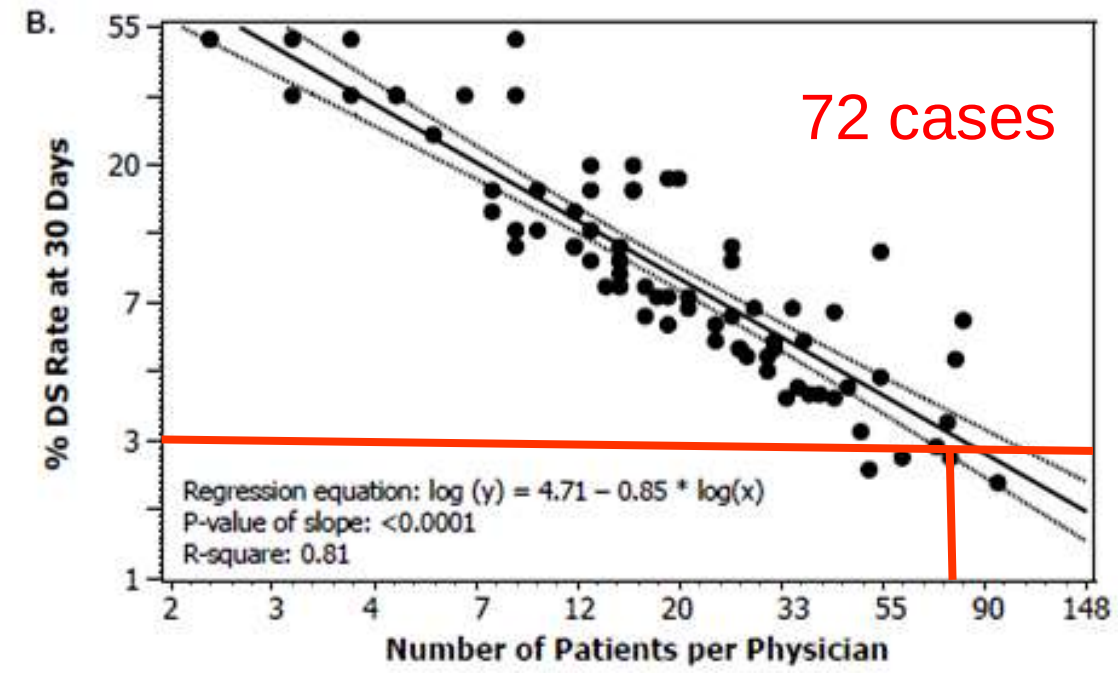


Smout J, Macdonald S, Stansby G International Journal of Stroke. Vol5, Dec 2010; 477-482

Physician experience dictates outcomes

Data from CAPTURE 2

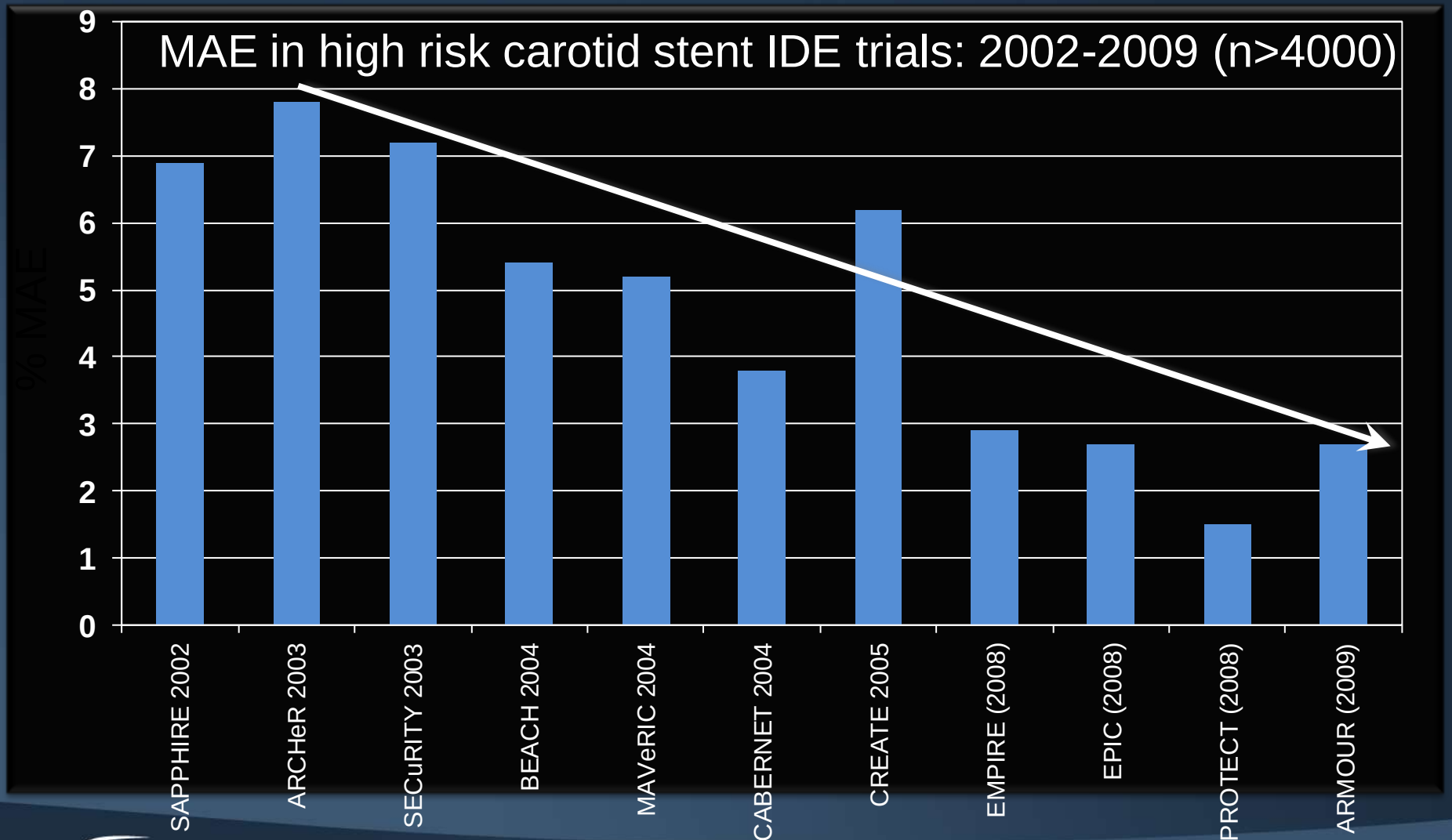




Gray et al.
J Am Coll Cardiol Intv 2011;4:235–46

CARDIOVASCULAR RESEARCH FOUNDATION

Rapid improvement in outcomes over the past decade

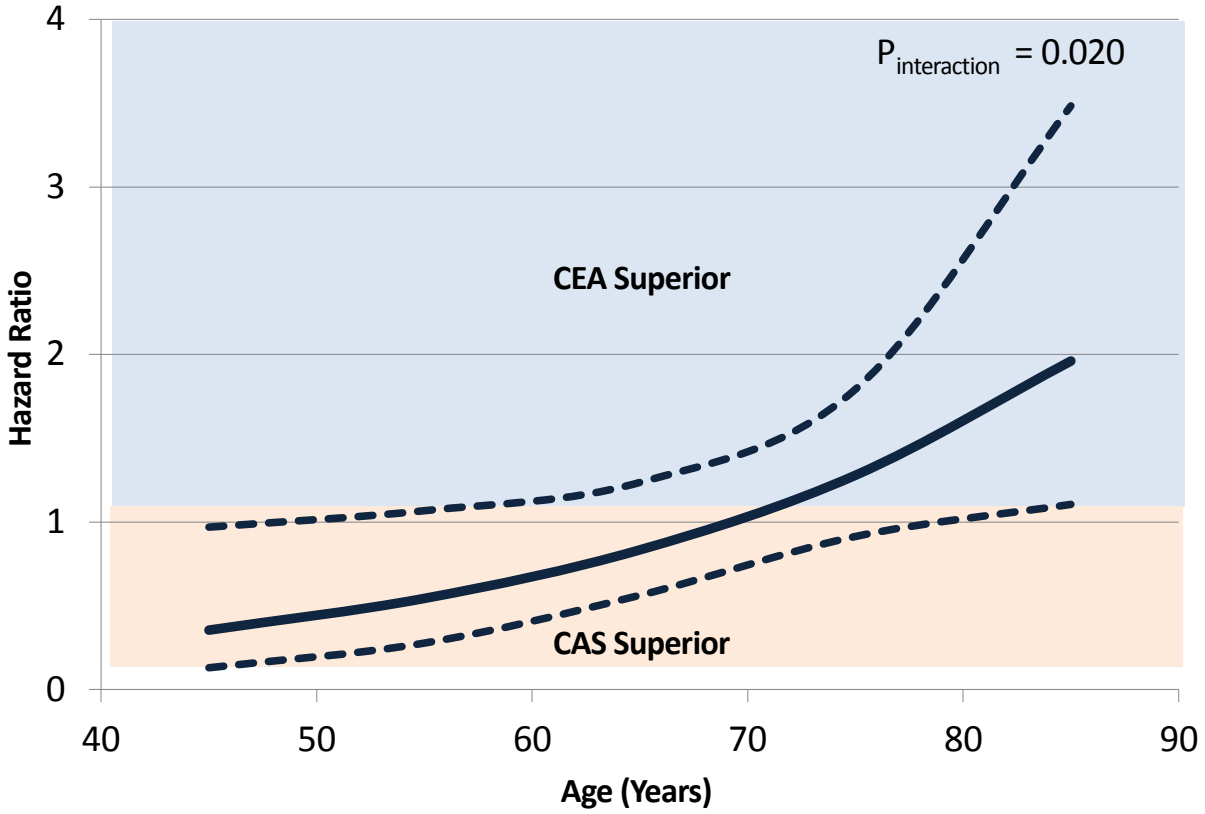


30-Day DS Rate for the 2nd Half of Symptomatic Patients and 2nd Half of Asymptomatic Patients

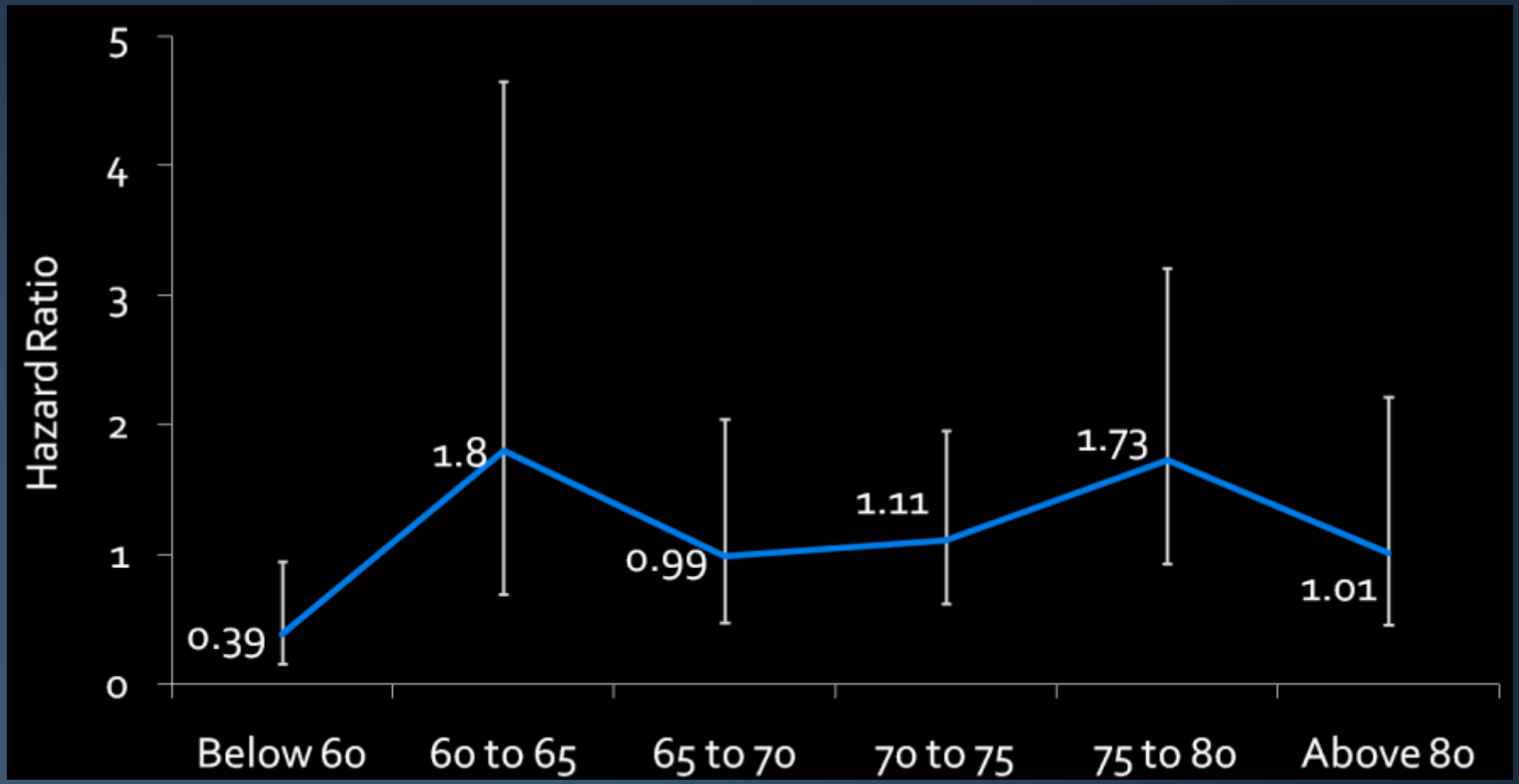
	Event Rate SE (N)		Difference
	CAS	CEA	95% CL
2nd Half of Patients	3.73% (21/563)	2.38% (14/588)	1.35% [-0.64%, 3.34%]

Age related outcomes in CAS and CEA

Age related outcomes: NIH analysis



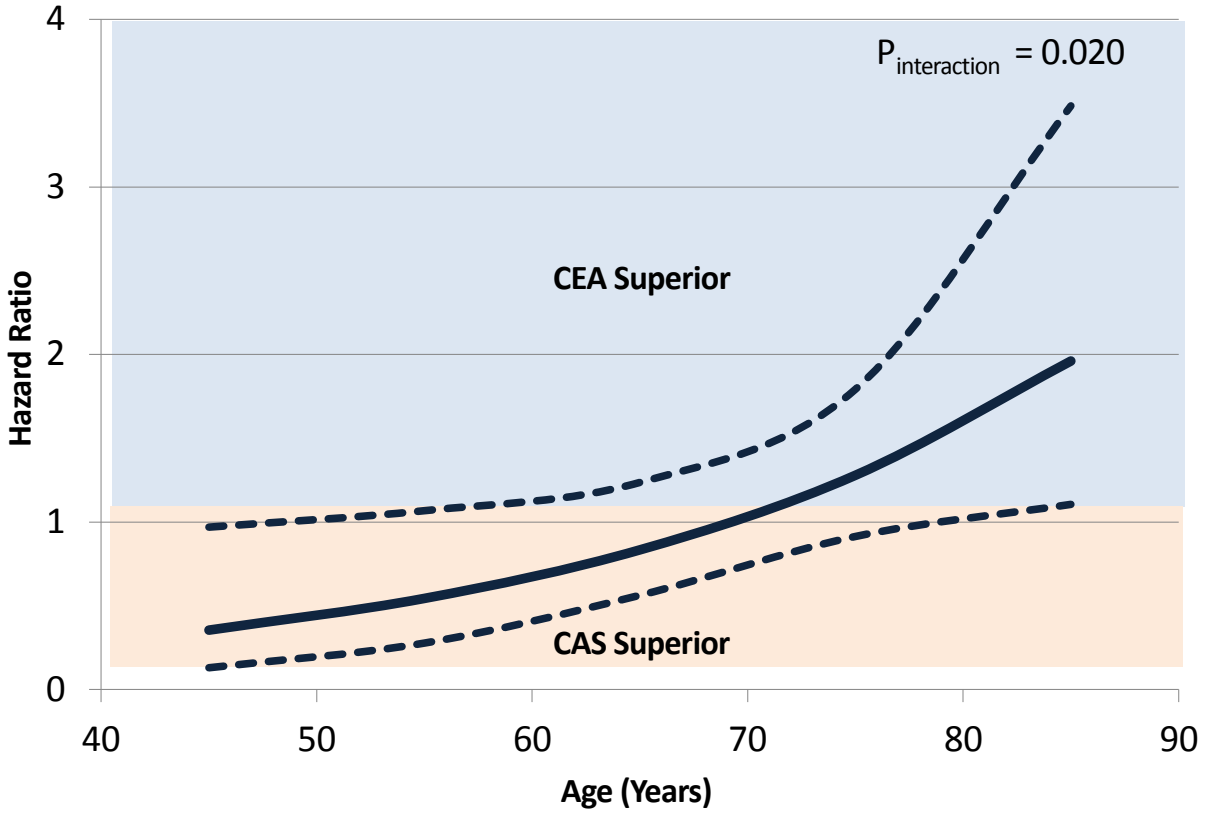
Changes in Hazard Ratio by Age Group Per Protocol: FDA analysis



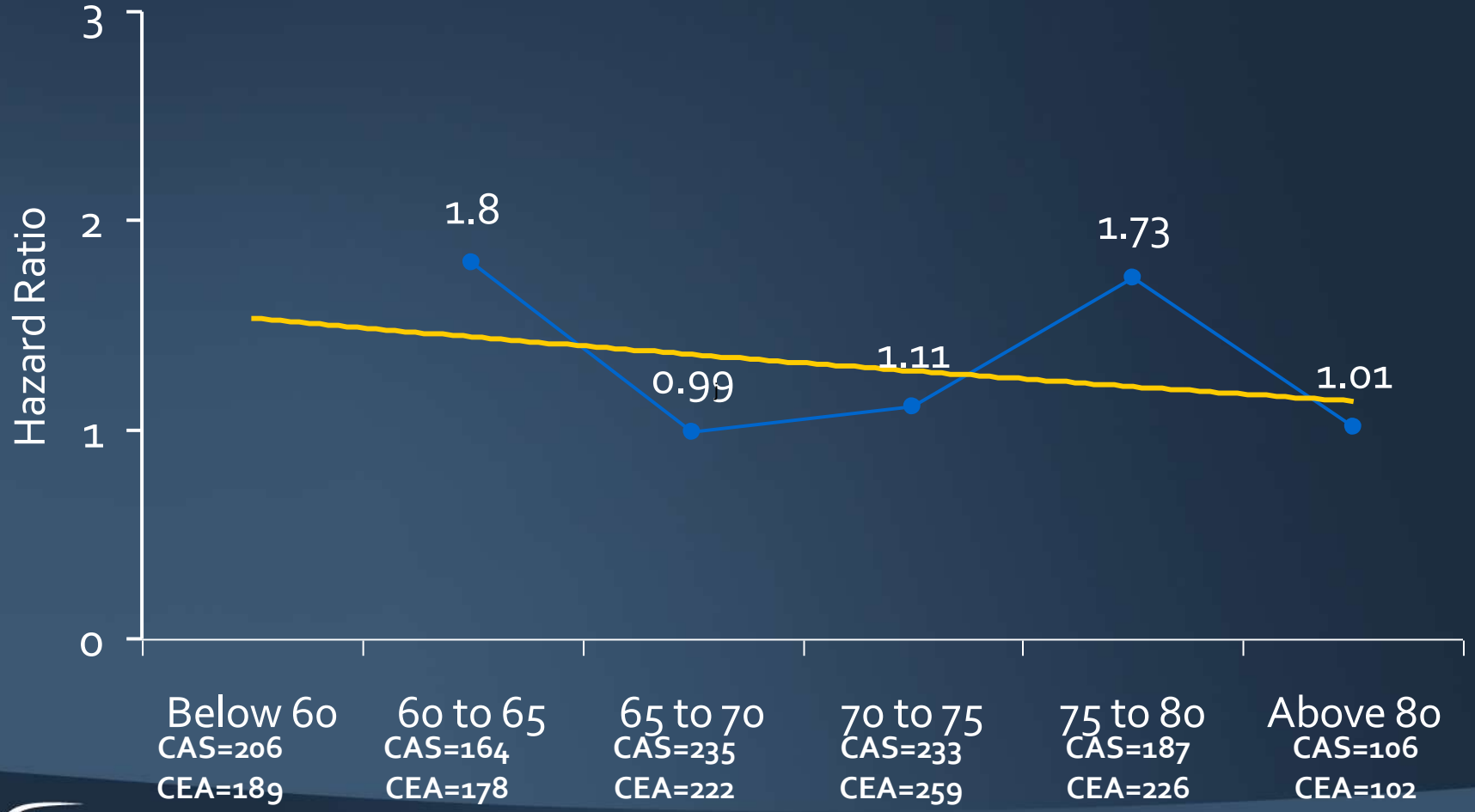
Below 60	60 to 65	65 to 70	70 to 75	75 to 80	Above 80
CAS=206	CAS=164	CAS=235	CAS=233	CAS=187	CAS=106
CEA=189	CEA=178	CEA=222	CEA=259	CEA=226	CEA=102

*From FDA executive summary

Age related outcomes: NIH analysis



Changes in Hazard Ratio by Age Group (PP)*: Model Sensitive to Removal of Below 60 HR



*From EDA executive summary; Exponential trend line added by sponsor.

Outcomes of the CAS:CEA “mega-trials”

TRIAL	30-120 -day outcome Death/stroke		
EVA-3S (2006)	CEA: 3.9%	CAS: 9.6%	p=0.01
SPACE (2006)	CEA: 6.3%	CAS: 6.8%	p=0.09
ICSS (2010)	CEA: 4.7%	CAS: 8.5%	p=0.001
CREST (2010)	CEA: 4.5%	CAS: 5.2%	p=0.38

Examine the elements

- Embolic protection device use
- Myocardial infarction as a component of the endpoint
- Disparities in operator experience
  - Between surgeons and interventionalists
  - Between trials

Use of embolic protection device (EPD)

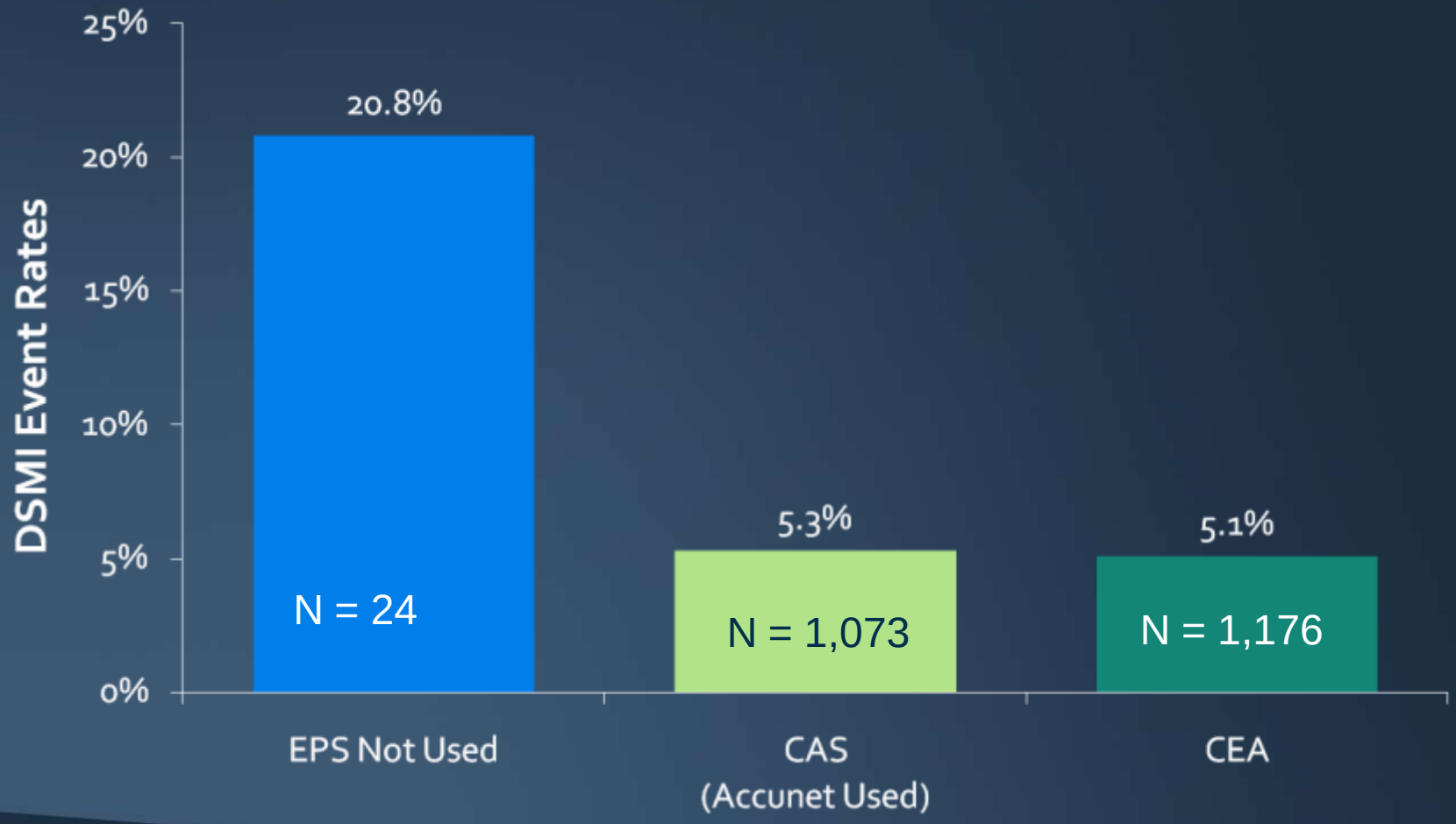
- No randomized trials assessing impact of EPD on clinical outcomes
- However, multiple comparative retrospective analysis* confirm utility of EPD in lowering rates of complication
- This may be especially true for the recently symptomatic plaque

*Garg N et al. J Endovasc Ther. 2009 Aug;16(4):412-27

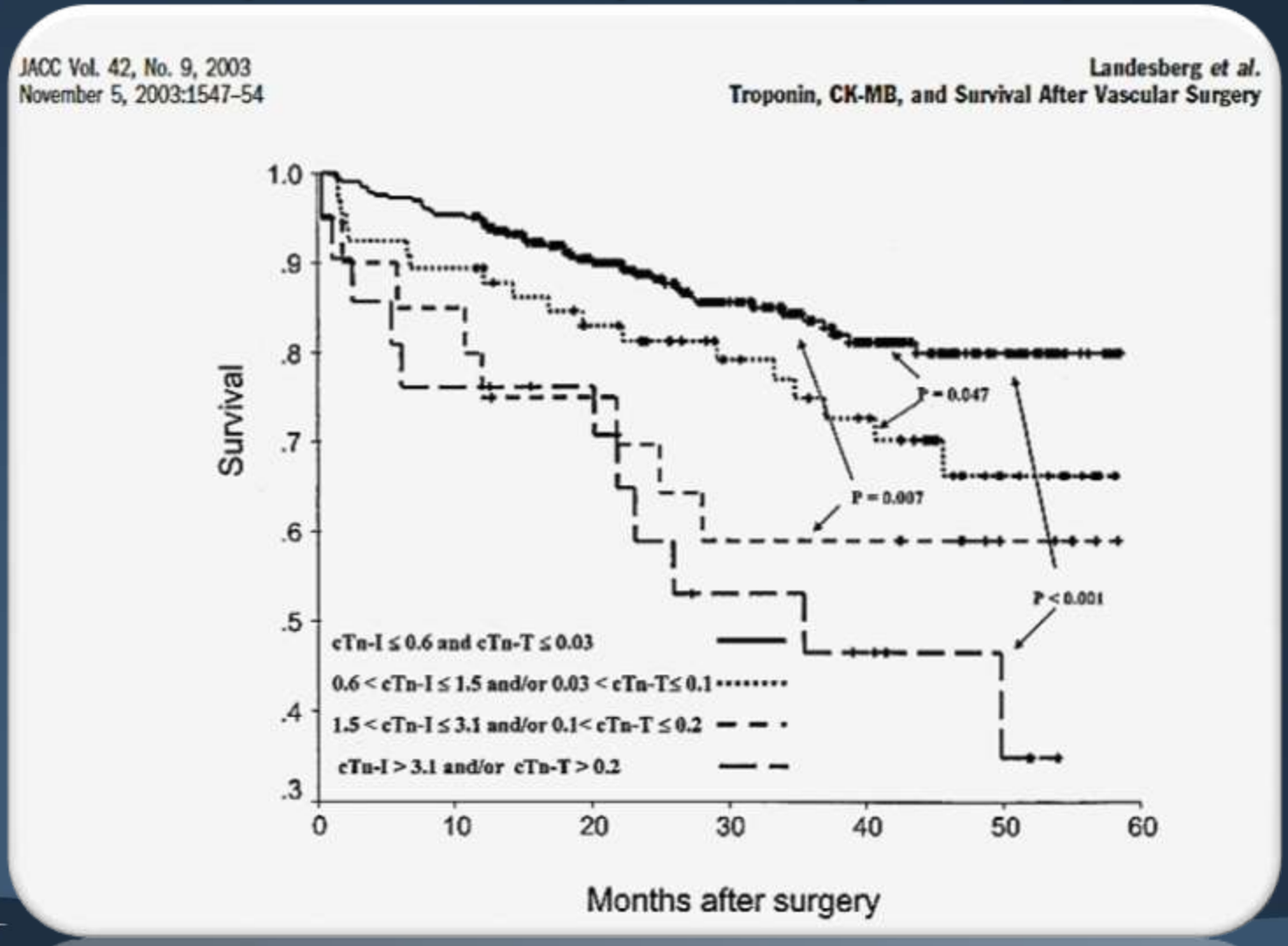
Rates of use of EPD

TRIAL	EPD use
EVA-3S	Not mandated until after the first 80 patients treated. ~20% of all CAS strokes
SPACE	27%
ICSS	72% (“known to receive EPD”)
CREST	>95%

Death, Stroke and MI within 30 Days by EPS Usage (PP)



Inclusion and ascertainment of MI as a component of primary endpoint

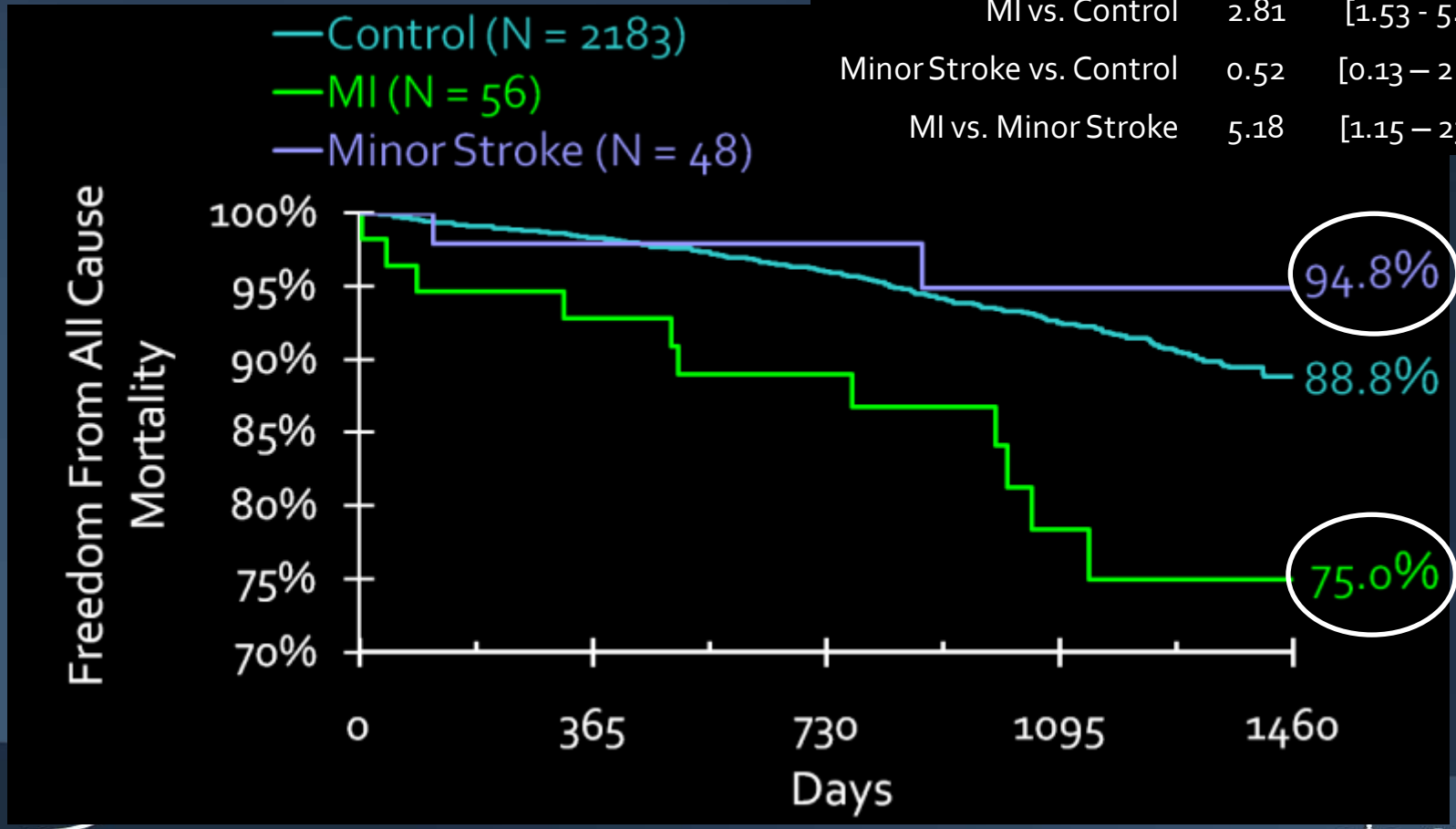


Management of MI as an endpoint

TRIAL	MI ascertainment and rates
EVA-3S	Not a primary endpoint. Ascertainment not described. CAS-0.4% CEA-0.8%
SPACE	Not a primary or secondary endpoint. No routine ascertainment. No MI's reported.
ICSS	Not a primary endpoint. No routine ascertainment. CAS-0.4% CEA-0.5%
CREST	Part of the primary endpoint. Routine surveillance. CAS-1.1% CEA-2.3%

Effect of minor stroke and myocardial infarction 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



Minor stroke and MI finding in CREST consistent with prior experience

TABLE I. Summary of Assumptions and Data Sources for Long-Term Cost and Life Expectancy Projections

	Annual cost	Life expectancy[a]	Utility	QALYs	Lost life years[b]	Lost QALYs[b]
Males						
No event	$5817 [10]	8.22	0.841	6.91	0	0
MI	$10,176 [10,12]	3.85	0.737	2.84	4.37	4.07
Major stroke	$18,515 [11]	5.28	0.436	2.30	2.94	4.61
MI + major stroke	$18,515 [11]	3.85	0.436	1.68	4.37	5.23
Minor stroke	$5817 [10]	8.22	0.729	5.99	0	0.92
Females						
No event	$5817 [10]	9.34	0.833	7.78	0	0
MI	$10,176 [10,12]	4.22	0.733	3.09	5.12	4.69
Major stroke	$18,515 [11]	5.73	0.433	2.48	3.61	5.30
MI + major stroke	$18,515 [11]	4.22	0.433	1.83	5.12	5.95
Minor stroke	$5817 [10]	9.34	0.725	6.77	0	1.01

[a]Life expectancy estimates for a subject 72 years of age at baseline (median age in SAPPHIRE), obtained using the Saskatchewan Health Database

Operator experience and clinical equipoise

- Clinical equipoise pre-supposes an equal preparation of the safety and effectiveness of the treatment options: timely availability, equivalent operator characteristics, tested devices, etc.

- Without these assurances:
  - Ethical basis of the trial is in serious question
  - The interpretation of trial results will be seriously limited due to outcome differences that can be ascribed not to the treatment *per se* but potentially to one or more confounding factors involved with the treatment

Operator experience and outcomes

TRIAL	Operator experience
EVA-3S	Poor (12 lifetime CAS or 35 supra-aortics with 5 CAS)
SPACE	Adequate for era
ICSS	Poor (50 stents anywhere, 10 lifetime CAS)
CREST	Adequate for era

Summary of critical trial attributes

TRIAL	EPD use	MI ascertainment	Operator experience
EVA-3S	+	0	0
SPACE	1/2+	0	++
ICSS	+	0	0
CREST	++	++	++

Explaining the differences

- CREST trial design and conduct distinguishes it from “historic” European trials, and gives its results the imprimatur of credibility
- The CREST outcomes therefore allow an assessment of the comparative “truth” between CAS and CEA, at least for this era

Conclusion

- The differences in outcomes among trials are readily explained by design elements
- The stringent CAS operator requirements imposed in CREST (only ~50% applicants admitted to trial) “bought time” for technique, operator experience and patient selection to be improved enough to balance outcomes between CAS and CEA

Thank you