

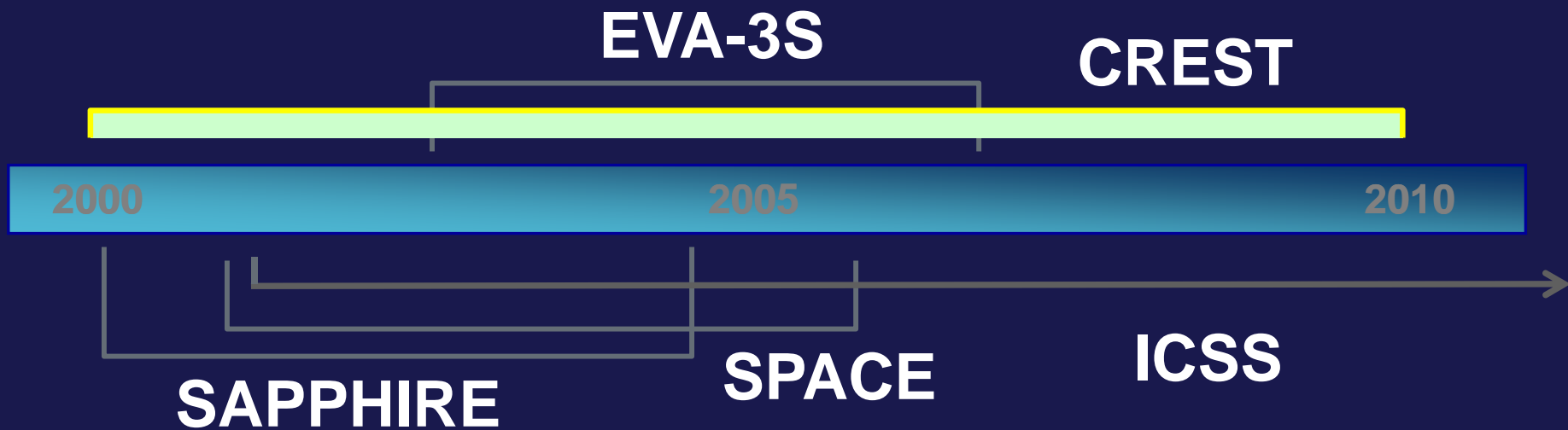


Normal Risk Symptomatic Patients: Ongoing Debate CAS vs CEA

John R. Laird, MD
Professor of Medicine
Medical Director of the Vascular Center
University of California, Davis

CLINICAL TIMELINE

Randomized Pivotal Trials



SAPPHIRE: Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients
EVA-3S: Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis
SPACE: Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy
CREST: Carotid Revascularization Endarterectomy vs. Stent Trial
ICSS (CAVATAS-2): International Carotid Stenting Study

Randomized Carotid Trials (RCTs)

	Study Size	Study Completed Enrollment	# of Centers	Lead-In/ Training Phase	Minimal Endovascular Experience Required (Lifetime)	% of Cases Where Cerebral Protection Devices were Used
SAPPHIRE ¹	334	No	29	No	CAS periprocedural death or stroke rate <6%	95%
EVA-3S ²	527	No	30	No	≥12 CAS or ≥5 CAS + ≥30 supra-aortic trunk stents	87%
SPACE ³	1214	No	35	No	≥25 successful CAS	27%
ICSS ⁴	1713	Yes	50	No	≥50 total stenting cases with ≥10 CAS	72%
CREST ⁵	2500	Yes	117	Yes	≥12 CAS/year; rates of death and complications <3% for asx and 5% for sx patients	96%

1. Yadav et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *New England Journal of Medicine*, October 7, 2004. 2. Jean-Louis Mas, et al. Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S). *New England Journal of Medicine*, October 19, 2006. 3. The SPACE Collaborative Group. 30 Day Results from the SPACE Trial of Stent-Protected Angioplasty versus Carotid Endarterectomy in Symptomatic Patients: A Randomized Non-inferiority Trial. *The Lancet*, October 7, 2006. 4. International Carotid Stenting Study Investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. 5. Brott, et al. Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis. *New England Journal of Medicine*, May 26, 2010.

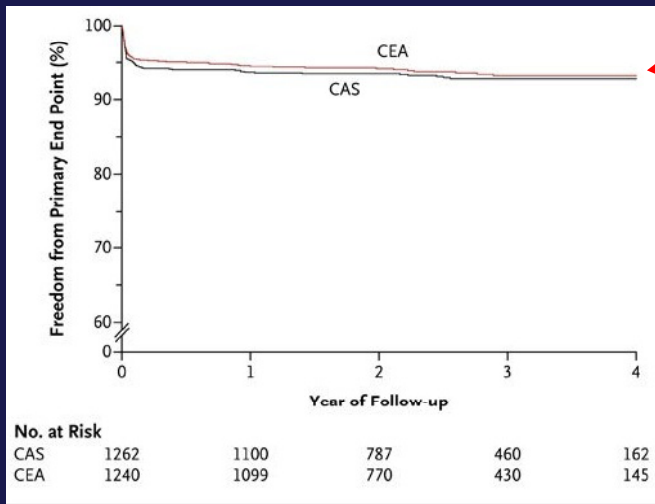
Make Sense of CREST

- Prospective, multicenter, randomized trial with blinded endpoint adjudication
- CAS vs. CEA in patients with symptomatic and asymptomatic carotid stenosis
 - Symptomatic >50%, Asymptomatic >70%
- 108 US and 9 Canadian sites
- Rigorous credentialing of surgeons (477) and interventionists (224)

Make Sense of CREST

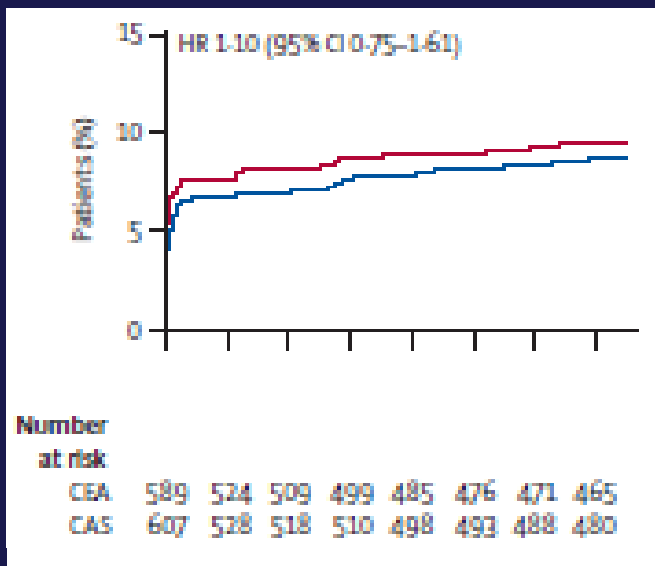
- Enrollment: December, 2000 to July, 2008
- Endpoints:
 - Death
 - Stroke: Neurologic deficit lasting >24 hours
 - MI: Cardiac enzymes increased to twice baseline plus anginal symptoms and/or ECG changes.
- Accunet/Acculink

Freedom from Primary Endpoint After Repair

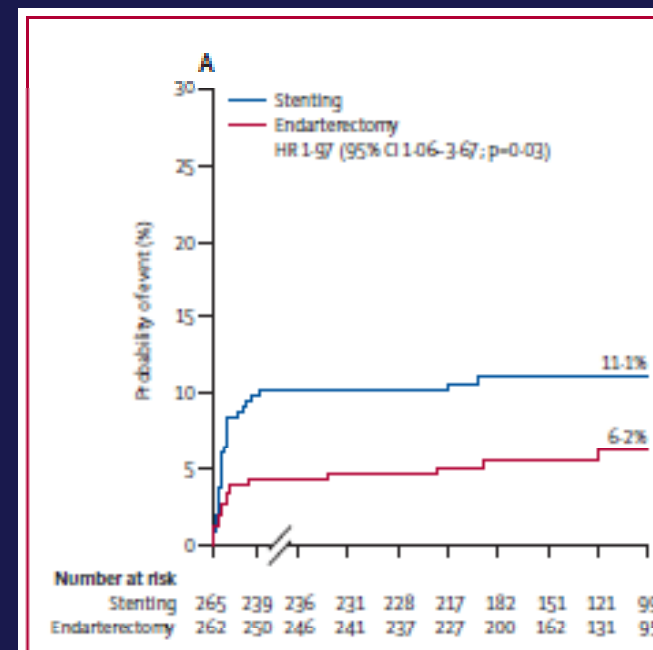


CREST N Engl J Med 2010

Both CEA and CAS are effective at long-term stroke prevention.



SPACE Lancet, 2008




EVA-3S N Engl J Med 2008

Make Sense of CREST

- The risk is in the first 30 days.
- The curves are parallel after that.

CREST Results

Peri-procedural period

	CAS	CEA	HR	P-value
Any Death, Stroke, or MI	5.2%	4.5%	HR = 1.18; 95% CI: 0.82-1.68	0.38
 Death	0.7%	0.3%	HR = 2.25; 95% CI: 0.69-7.30	0.18
All Stroke	4.1%	2.3%	HR = 1.79; 95% CI: 1.14-2.82	0.012
Major Stroke	0.9%	0.6%	HR = 1.35; 95% CI: 0.54-3.36	0.52
Minor Stroke	3.2%	1.7%	HR = 1.95; 95% CI: 1.15-3.30	0.01
MI	1.1%	2.3%	HR = 0.5; 95% CI: 0.26-0.94	0.03
Ipsilateral Stroke	2.0%	2.4%	HR = 0.94; 95% CI: 0.50-1.76	0.85
Cranial Nerve Palsy	0.3%	4.7%	HR = 0.07; 95% CI: 0.02-0.18	<0.0001



CAS

CEA

Any periprocedural stroke or
death or postprocedural
ipsilateral stroke

Asymptomatic patients	15 (2.5±0.6)	8 (1.4±0.5)
Symptomatic patients	40 (6.0±0.9)	21 (3.2±0.7)

Symptoms?	Stroke/Death Threshold Rate
Asymptomatic	3%
Symptomatic	6%

Make Sense of CREST

Areas of difference:

- Minor stroke: twice as many with CAS
- Myocardial infarction: twice as many with CEA
- Cranial nerve injury

What is the long term morbidity and quality of life after these events?

FDA Panel

- Circulatory System Devices Panel of the FDA on January 26, 2011
- Voted 7-3 in favor of expanding use of carotid stents to standard risk patients.
- www.fda.gov/advisorycommittees/committees_meeting_materials/medical_devices

Cranial Nerve Injury

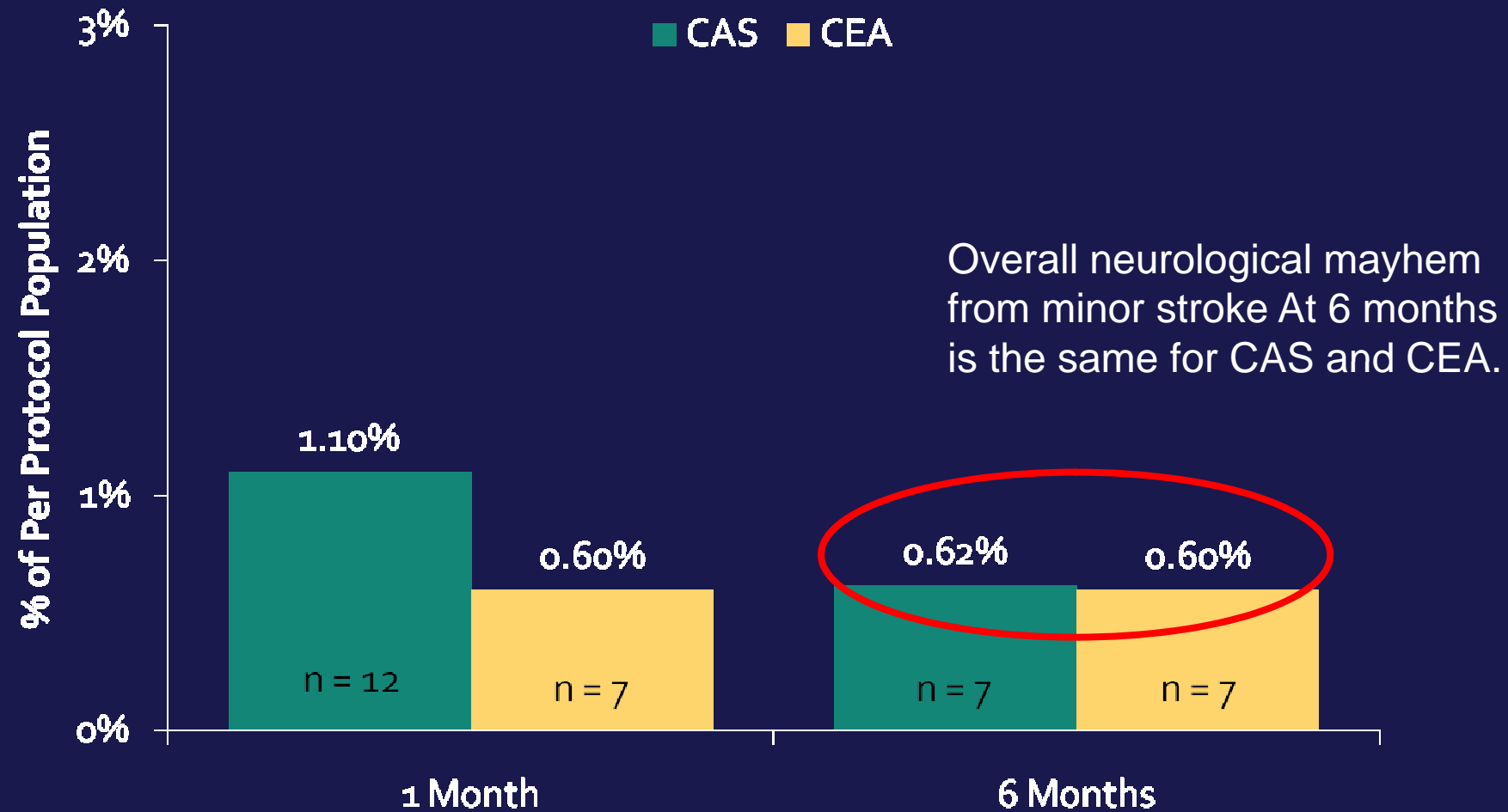
Cranial Nerve Injury 5.3% (62/1176)

Unresolved at Six Months 2.1% (25/1176)

Facial droop (VII)	8
Hoarseness (x)	7
Dysphagia (IX)	3
Tongue deviation (XII)	3
Facial numbness (V)	2
Unknown	2

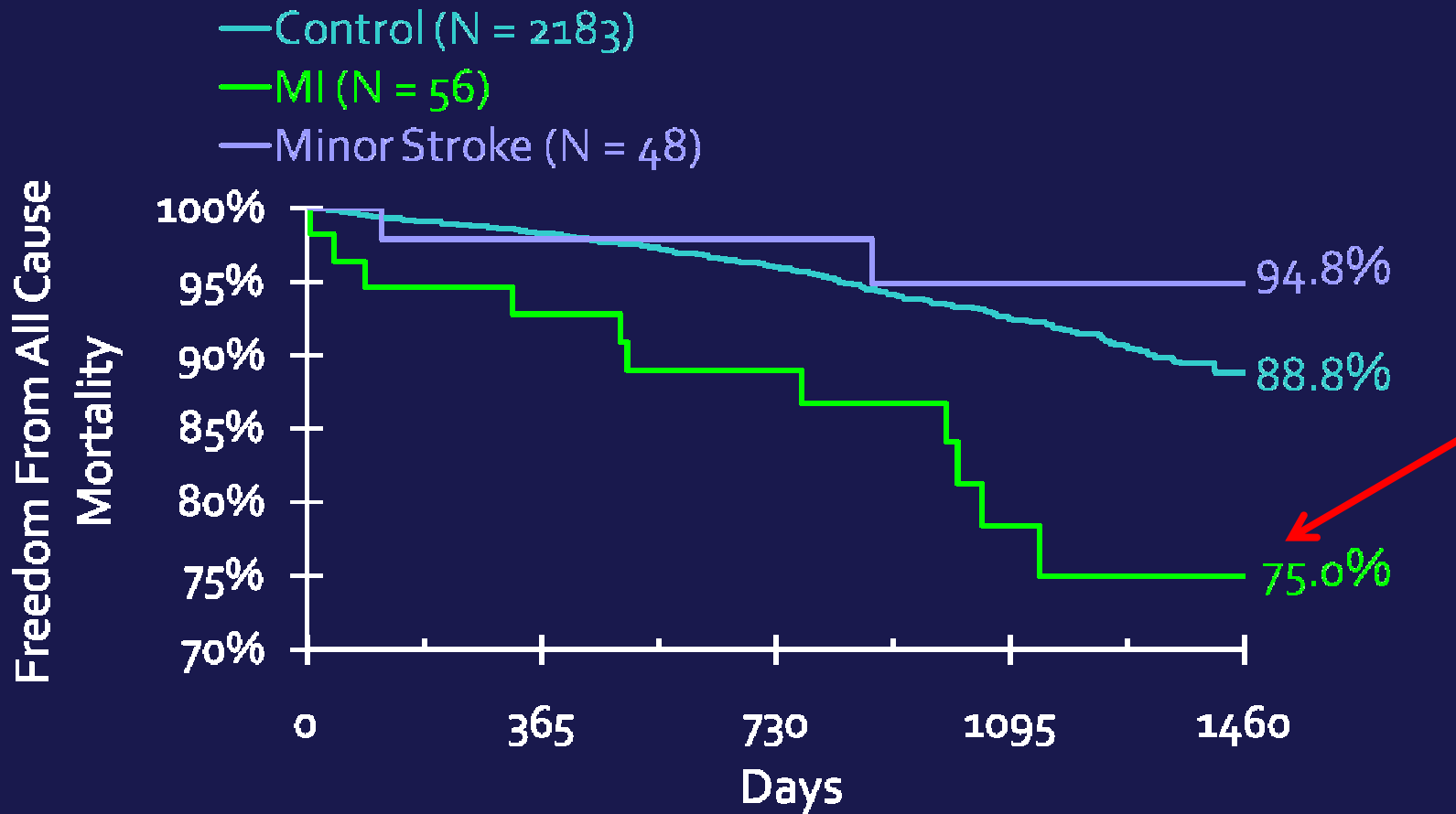
FDA Panel Presentation
Jan. 26, 2011

Minor Stroke Neurological Deficit Assessed by NIH Stroke Scale



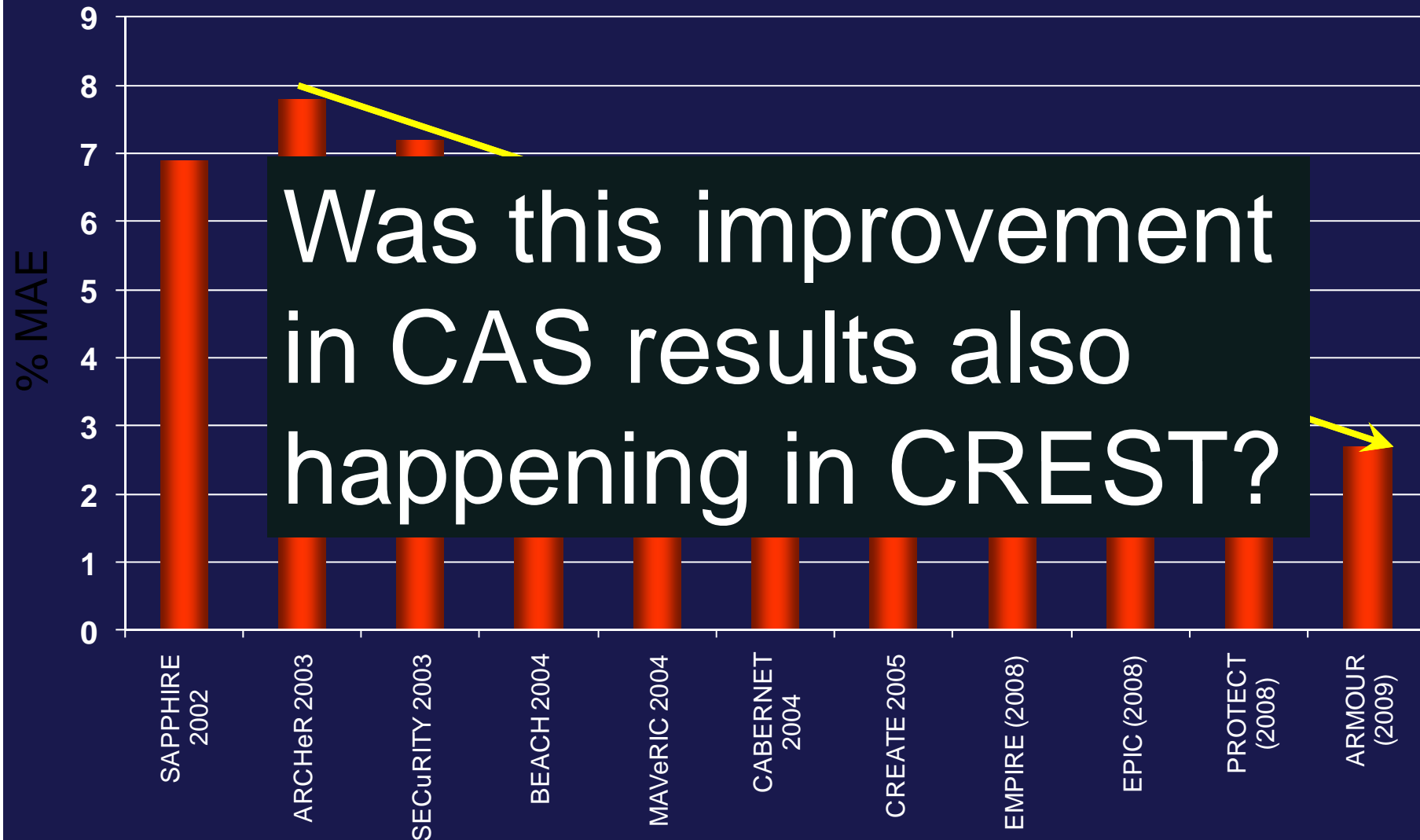
FDA Panel Presentation
Jan. 26, 2011

Minor Stroke and MI

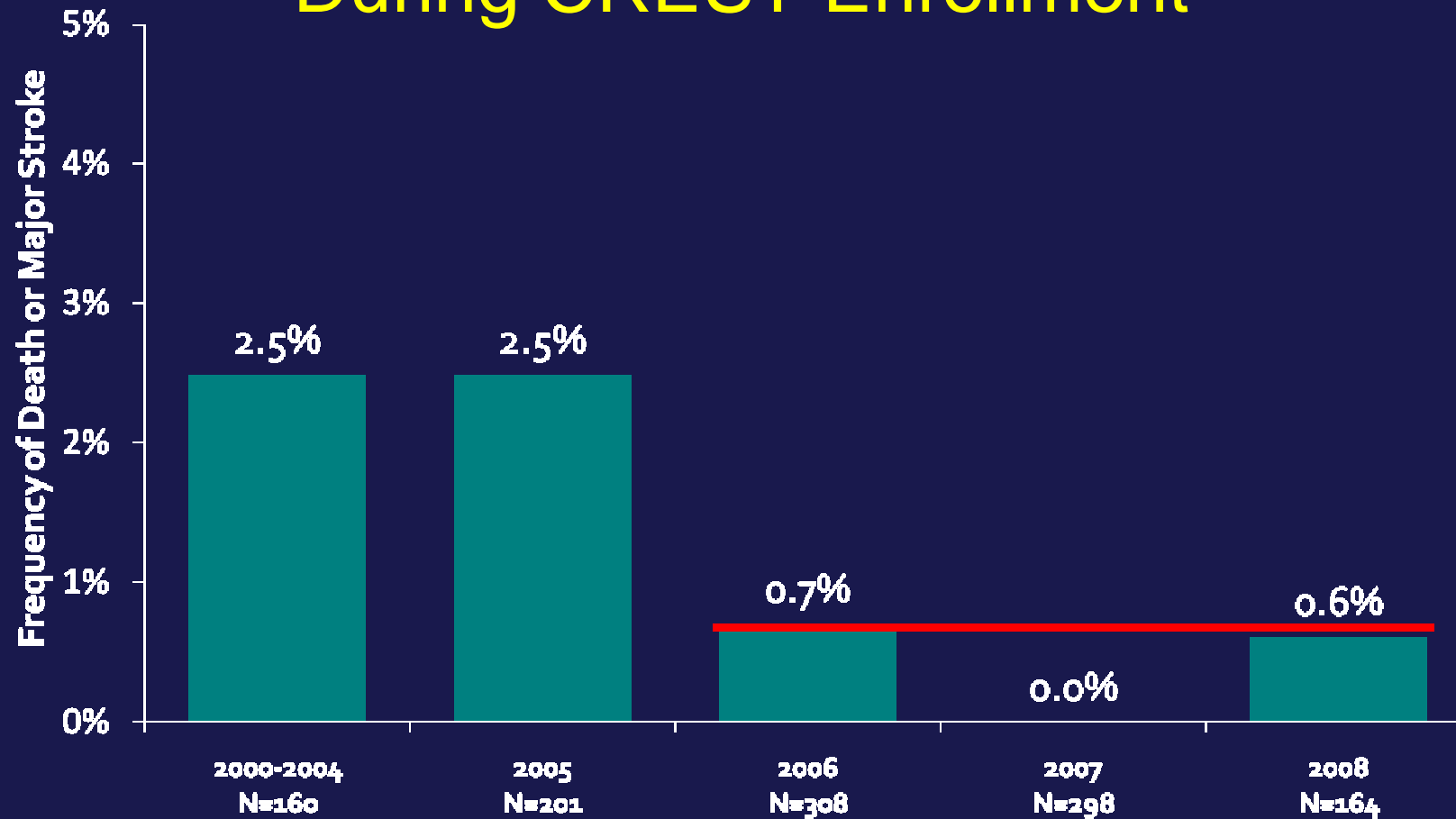


FDA Panel Presentation
Jan. 26, 2011

During the eight years that CREST enrolled, we were learning how to make CAS safer.

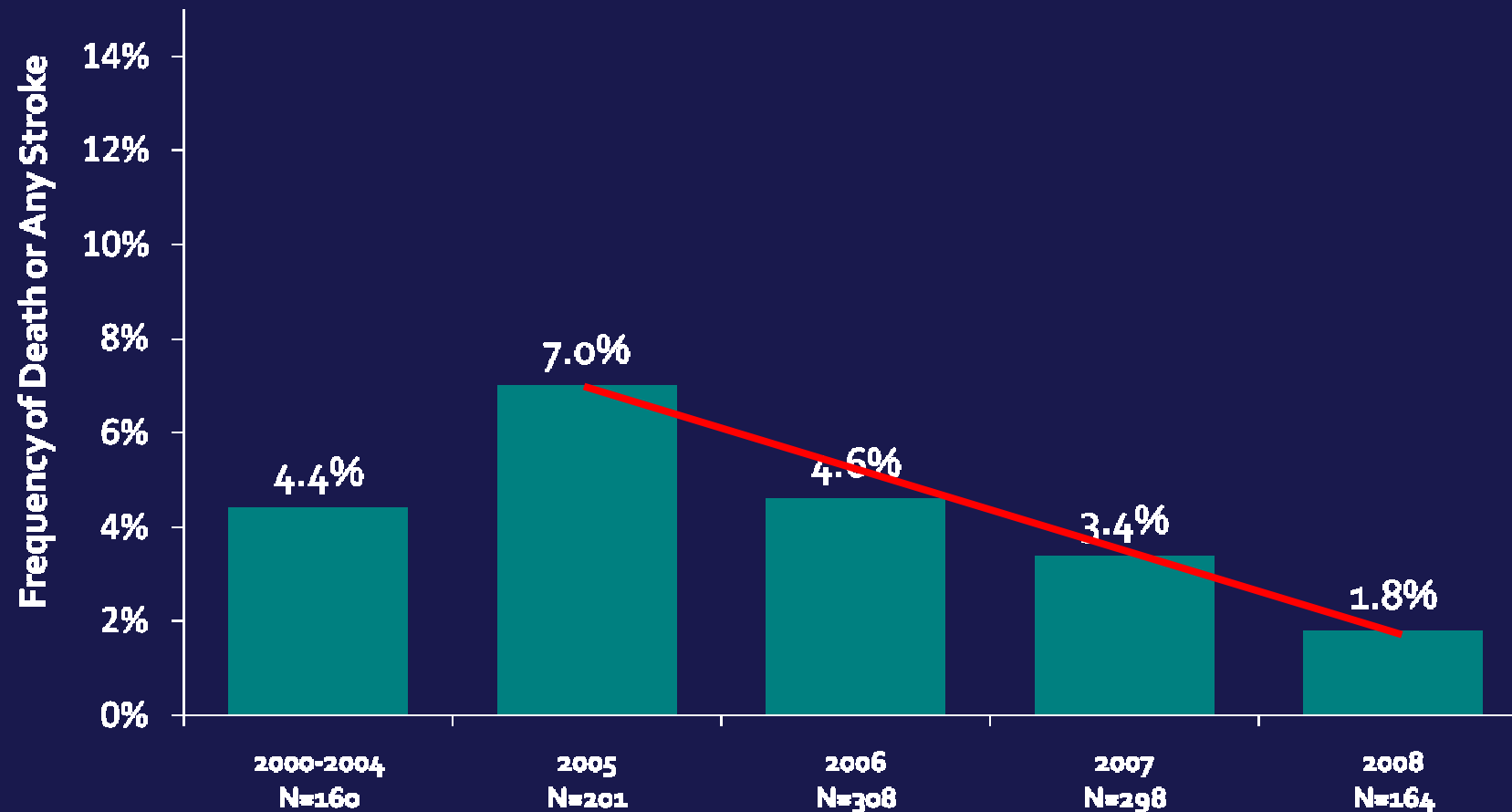


Death and Major Stroke for CAS During CREST Enrollment



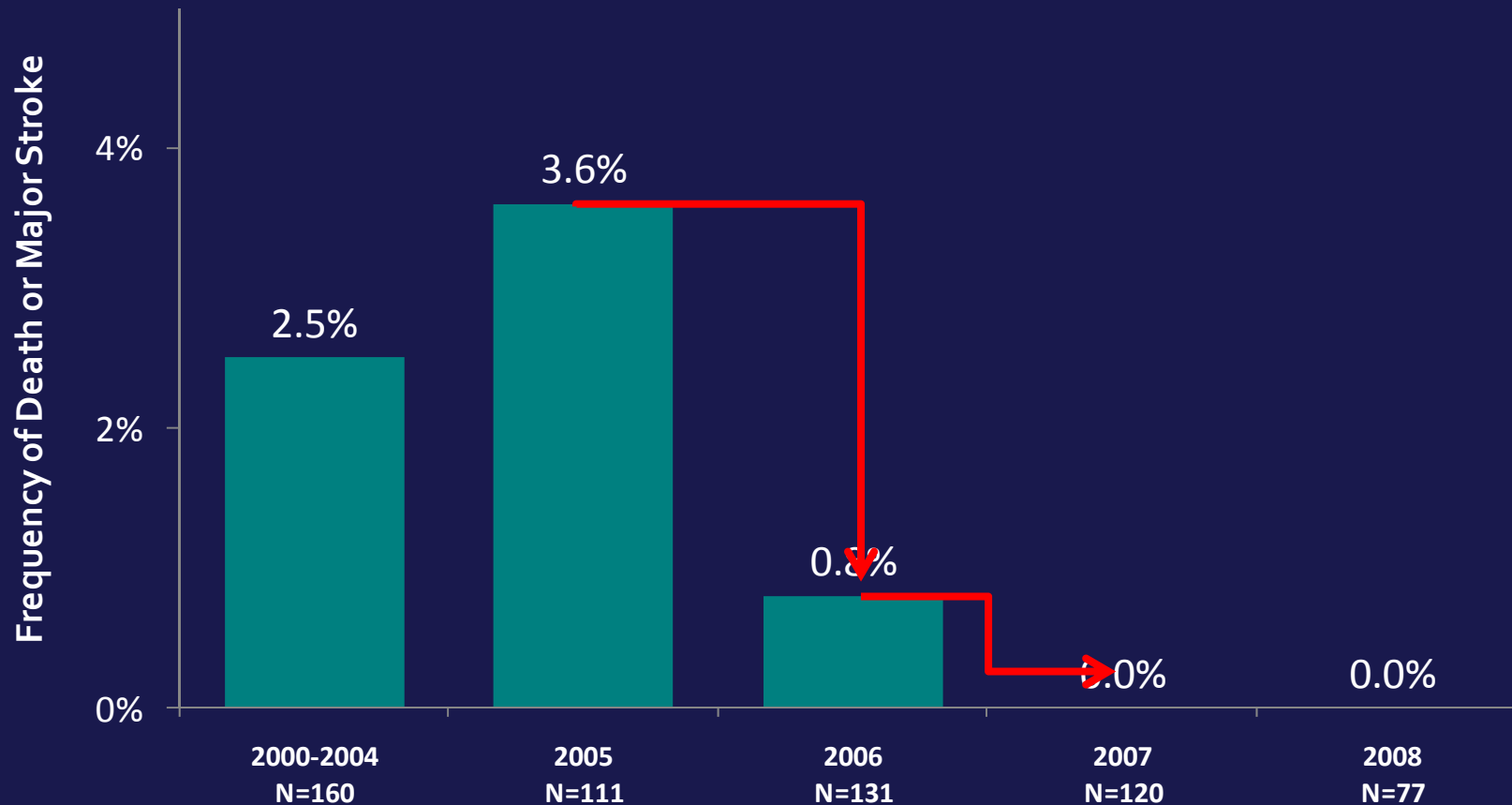
FDA Panel Presentation
Jan. 26, 2011

Death and Stroke for CAS During CREST Enrollment



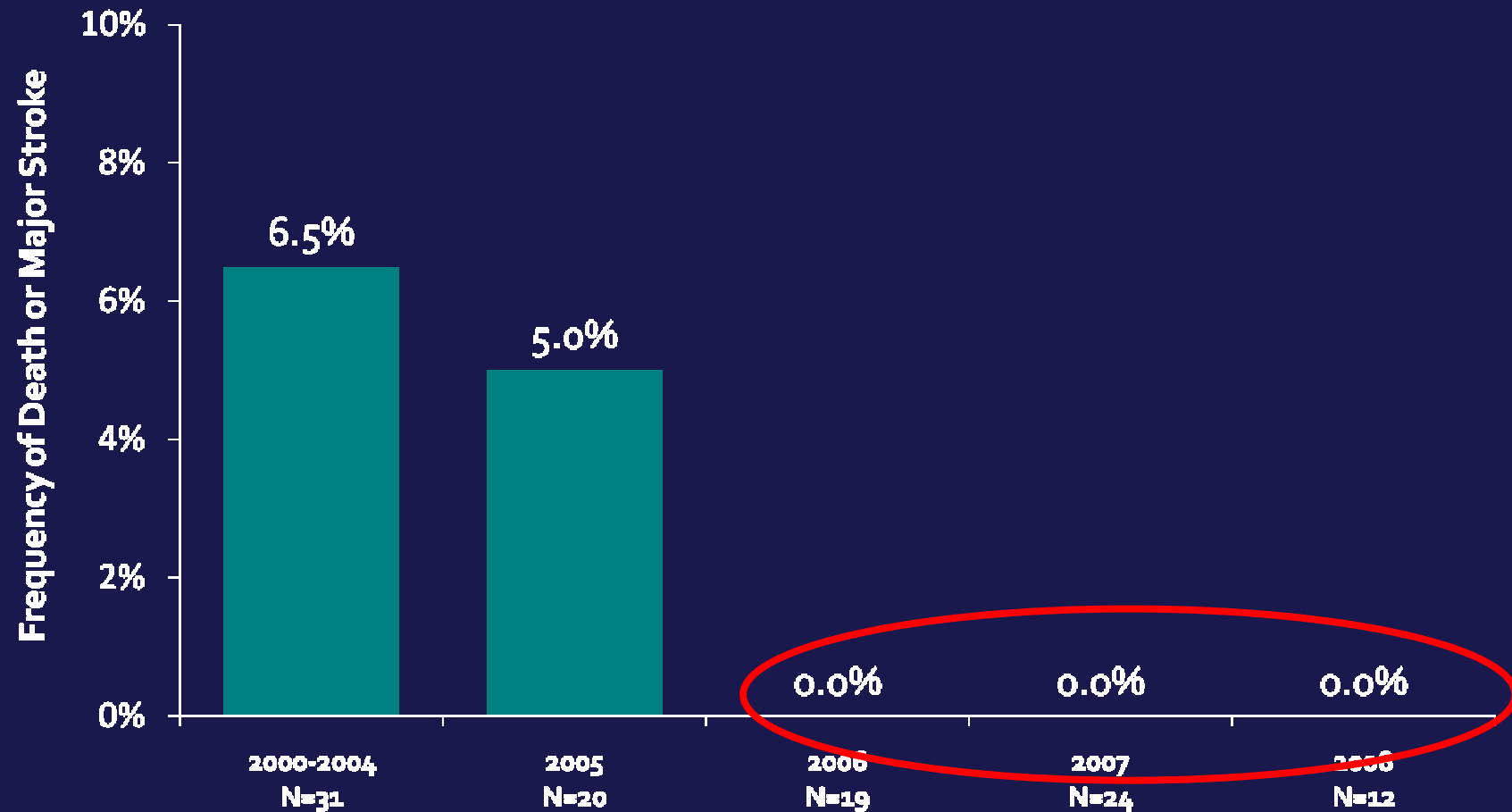
FDA Panel Presentation
Jan. 26, 2011

Death and Major Stroke for CAS Symptomatic Patients



FDA Panel Presentation
Jan. 26, 2011

Death and Major Stroke for CAS Octogenarians



FDA Panel Presentation
Jan. 26, 2011

Conclusions

- CAS and CEA were equivalent with regards to primary endpoint in CREST
- CREST used obsolete technology – despite this, excellent results achieved
- Significant learning curve for CAS again demonstrated – remarkably better outcomes in last 3 years of trial

Conclusions

- While there were fewer minor strokes with CEA, there was no difference in neuro deficits at 6 months
- Cranial nerve injuries and MI's are extremely morbid.