Carotid stent trials: What are the unanswered questions (if any)?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Terumo, WL Gore
• Consulting Fees/Honoraria	• Abbott Vascular, Medtronic, Boston Scientific
• Major Stock Shareholder/Equity	• Silk Road Medical

All TCT 2017 faculty disclosures are listed online and on the app.

A lot of trials!

FDA IDE approval trials: 2000-2011

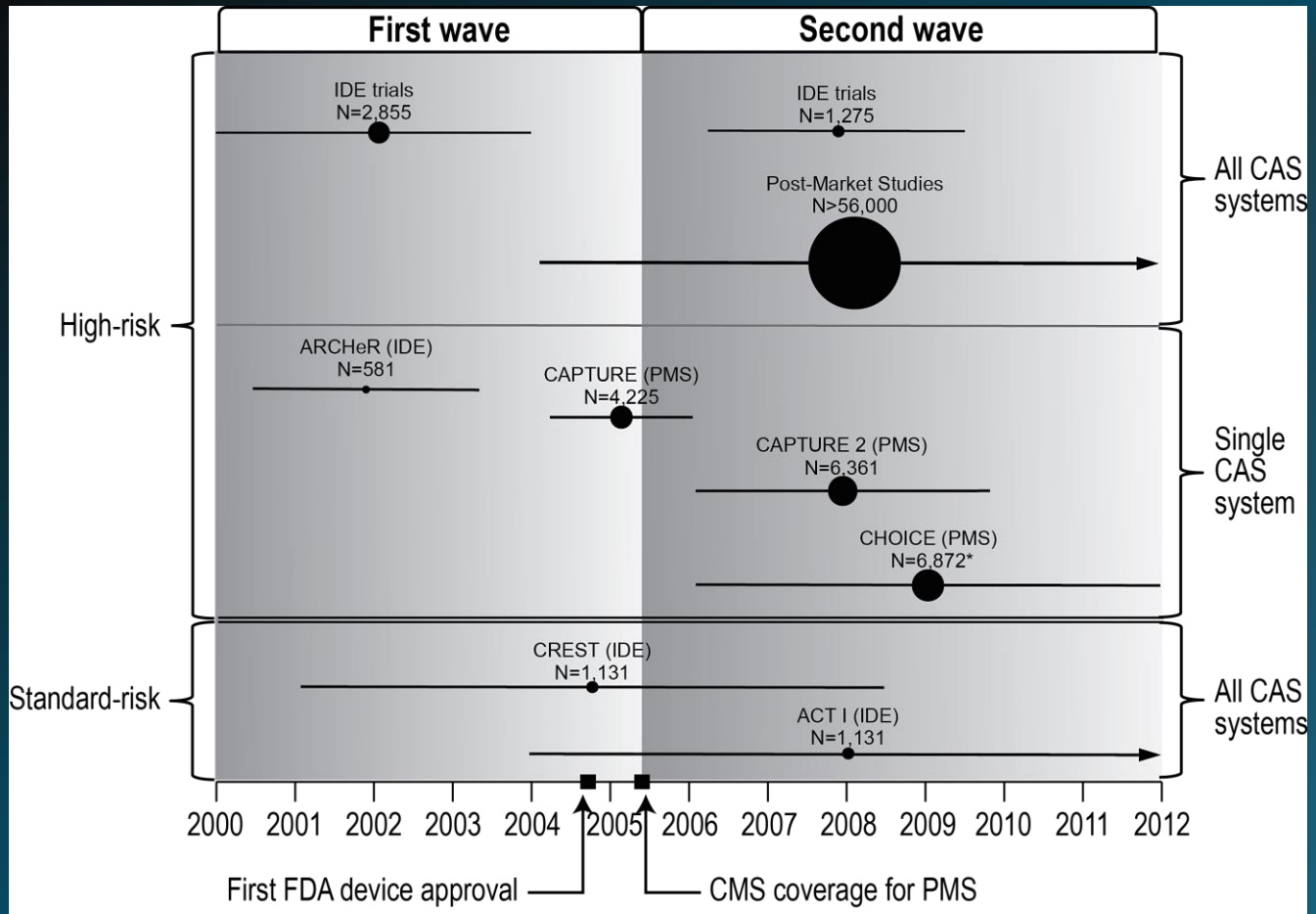
Largely in high-surgical risk patients

All device Systems approved as safe and effective

Nearly 6,000 patients

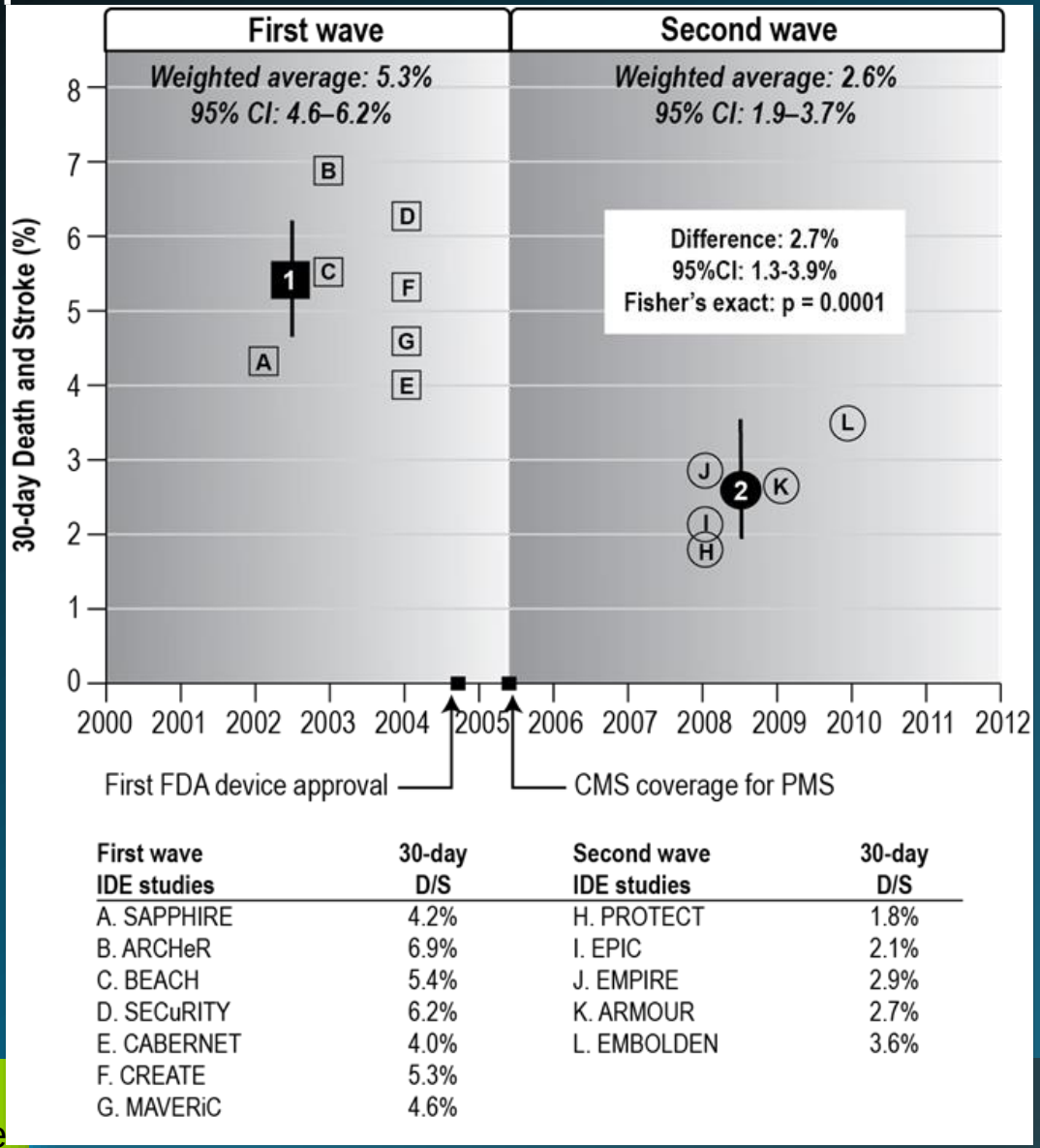
IDE Trial	N (CAS)	Year of FDA action	Stent System Approval/ EPD 510(k) Clearance	Postmarket Surveillance Study
ARCHeR	581	2004	Acculink PMA approval Accunet 510(k) clearance	CAPTURE (N=4,225) CAPTURE 2 (N=6,361) CHOICE (N=19,000)
SECURITY	305	2005	Xact PMA approval Emboshield 510(k) clearance	EXACT (N=2,145) CHOICE
SAPPHIRE	565	2006	Precise PMA approval Angioguard 510(k) clearance	CASES-PMS (N=1,493) SAPPHIRE WW (N=15,000)
CABERNET	488	2006	Nexstent PMA approval FilterWire Carotid 510(k) clearance	None
CREATE	419	2006 2007	Protégé Carotid PMA approval SpiderFX Carotid 510(k) clearance	CREATE PAS (N=3,500)
MAVErIC	449	2007	Exponent PMA approval GuardWire Carotid 510(k) clearance	None
PROTECT	320	2008	Emboshield NAV6 510(k) clearance	CHOICE
BEACH	480	2008	Wallstent Carotid PMA approval FilterWire EZ System clearance	CABANA (N=1,097)
EPIC	237	2008	Fibernet 510(k) clearance	None
EMBOLDEN	250	2009	GORE® Embolic Filter clearance	None
EMPIRE	245	2009	Gore Flow Reversal 510(k) clearance	FREEDOM (planned N=5,000)
ARMOUR	228	2009	Mo.ma 510(k) clearance	None
CREST	1,131	2011	Acculink PMA extension	CANOPY (planned N=1,200)

FDA and CMS approvals (albeit limited) lead to volume expansion



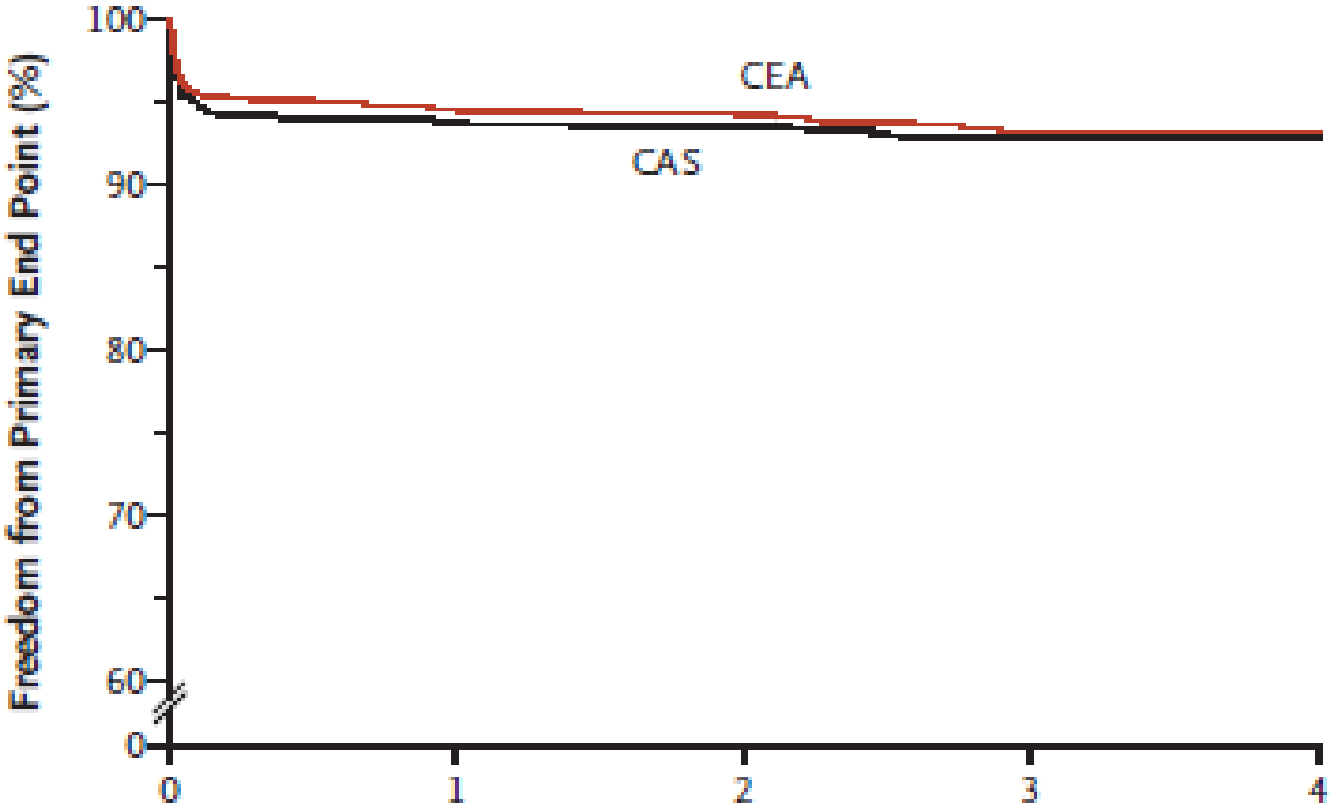
Size of black circles is proportional to number of patients enrolled.
Horizontal line length indicates dates of trial enrollment.
* Number includes only those patients who received an Acculink/Accunet stent system.
CAS, carotid artery stenting; CMS, Centers for Medicare & Medicaid Services;
IDE, investigational device exemption; PMS, post-marketing studies.

Volume expansion led to marked improvement in patient outcomes across devices



First wave IDE studies	30-day D/S	Second wave IDE studies	30-day D/S
A. SAPPHIRE	4.2%	H. PROTECT	1.8%
B. ARCHeR	6.9%	I. EPIC	2.1%
C. BEACH	5.4%	J. EMPIRE	2.9%
D. SECuRITY	6.2%	K. ARMOUR	2.7%
E. CABERNET	4.0%	L. EMBOLDEN	3.6%
F. CREATE	5.3%		
G. MAVERiC	4.6%		

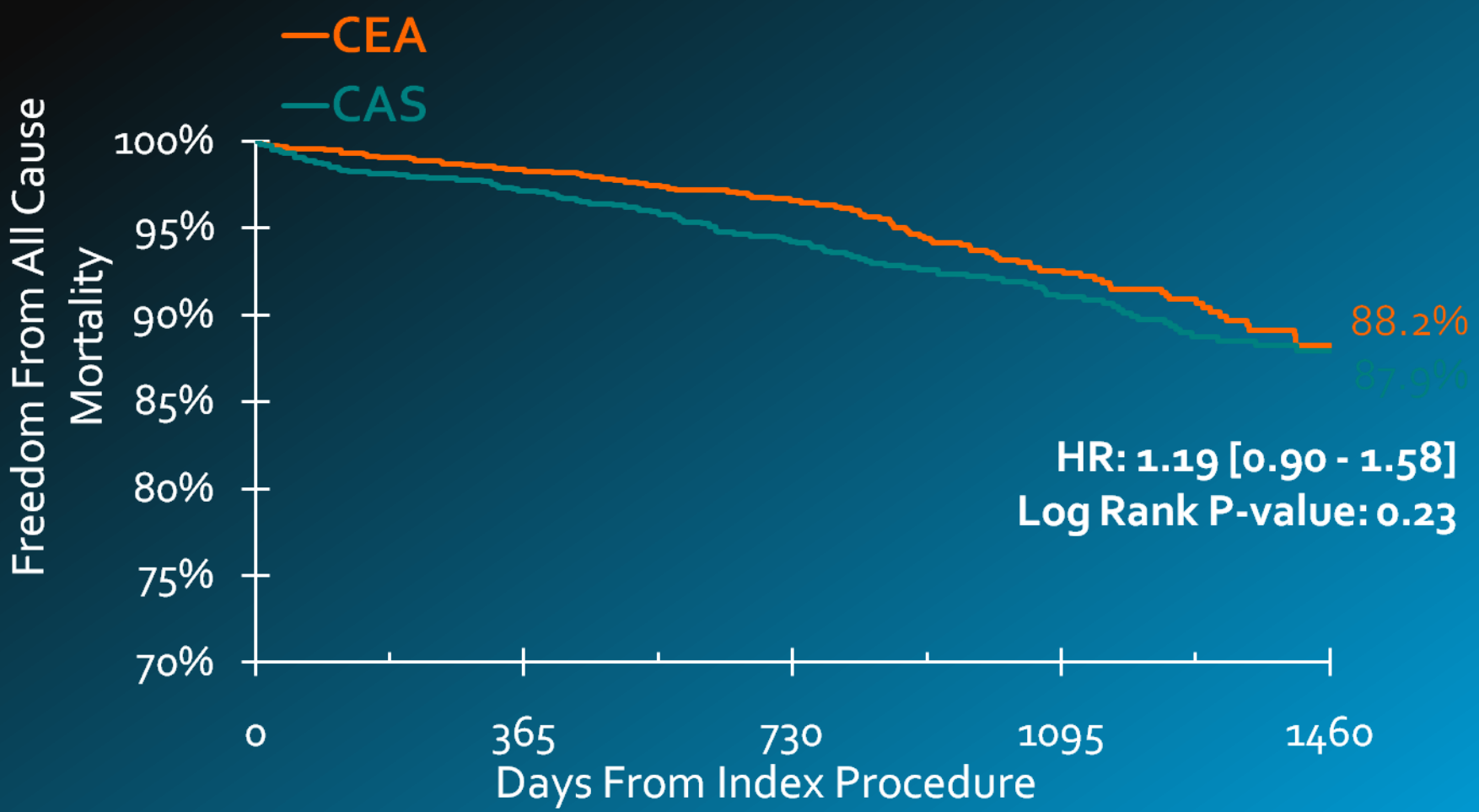
CREST outcome:
CEA and CAS are no different for the primary endpoint



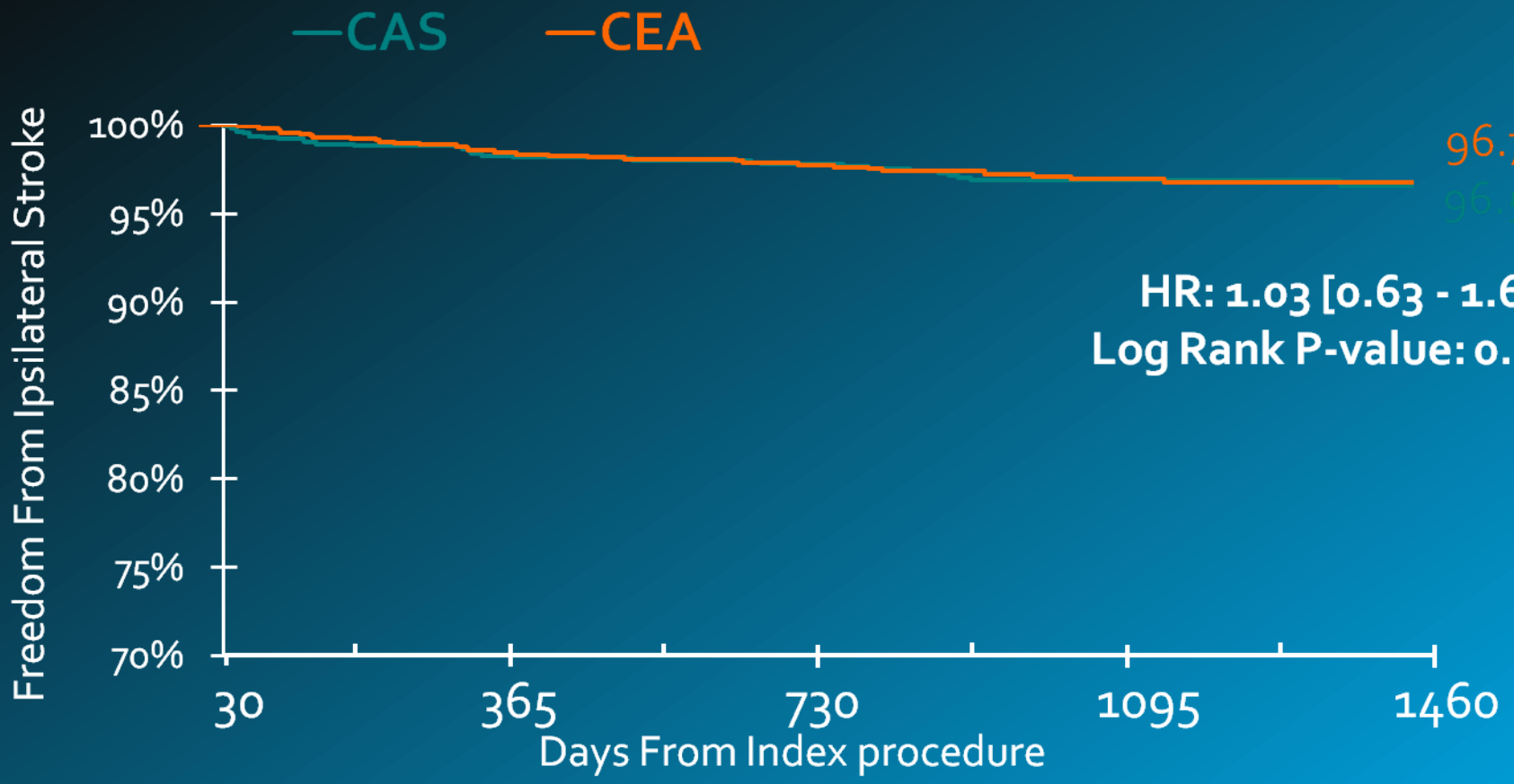
Intention-to treat analysis

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

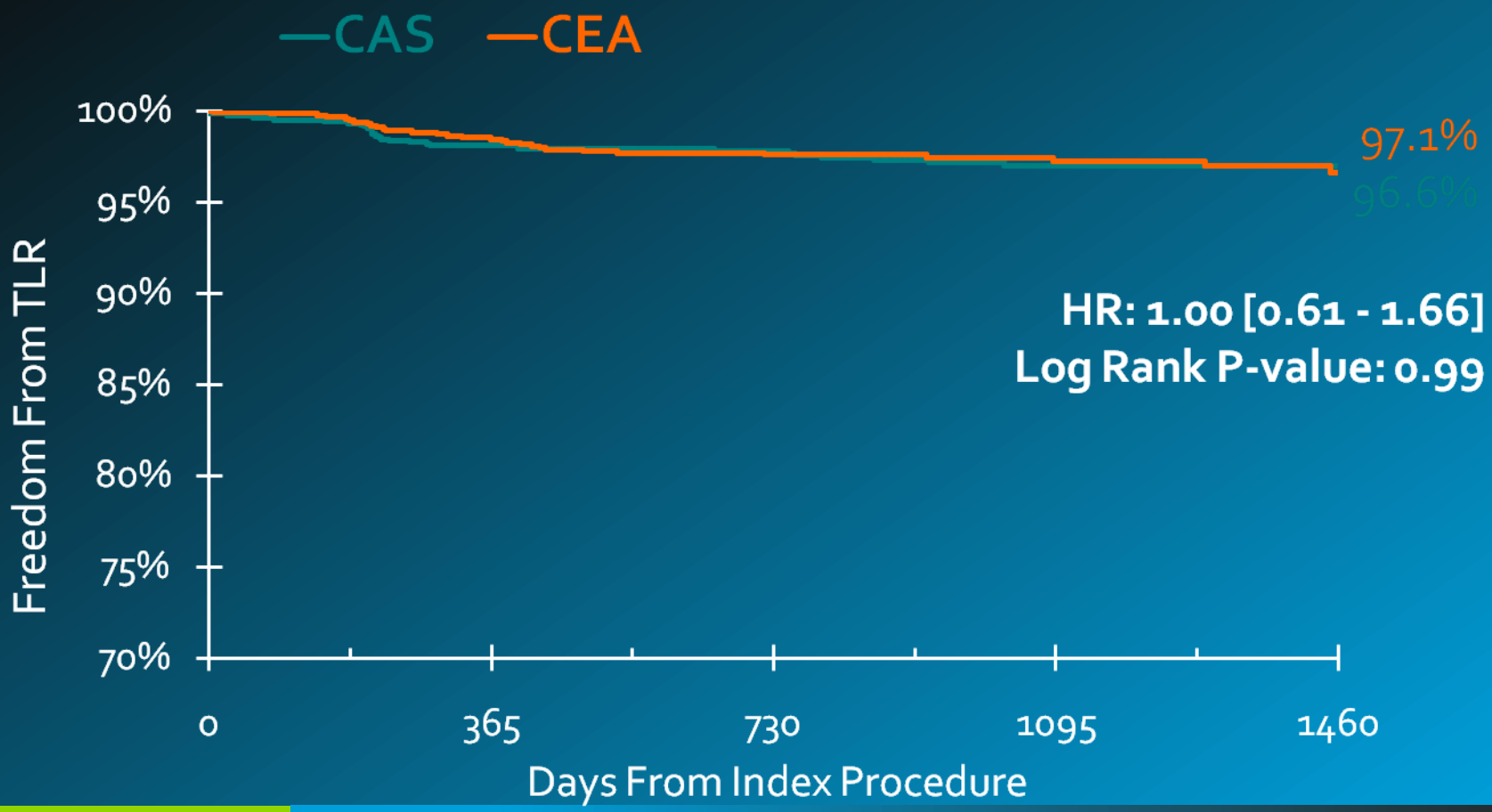
CREST: Similar mortality to 4 years



CREST: Similar freedom from ipsilateral stroke day 31 to 4 years



CREST: Similar freedom from TLR to 4 years



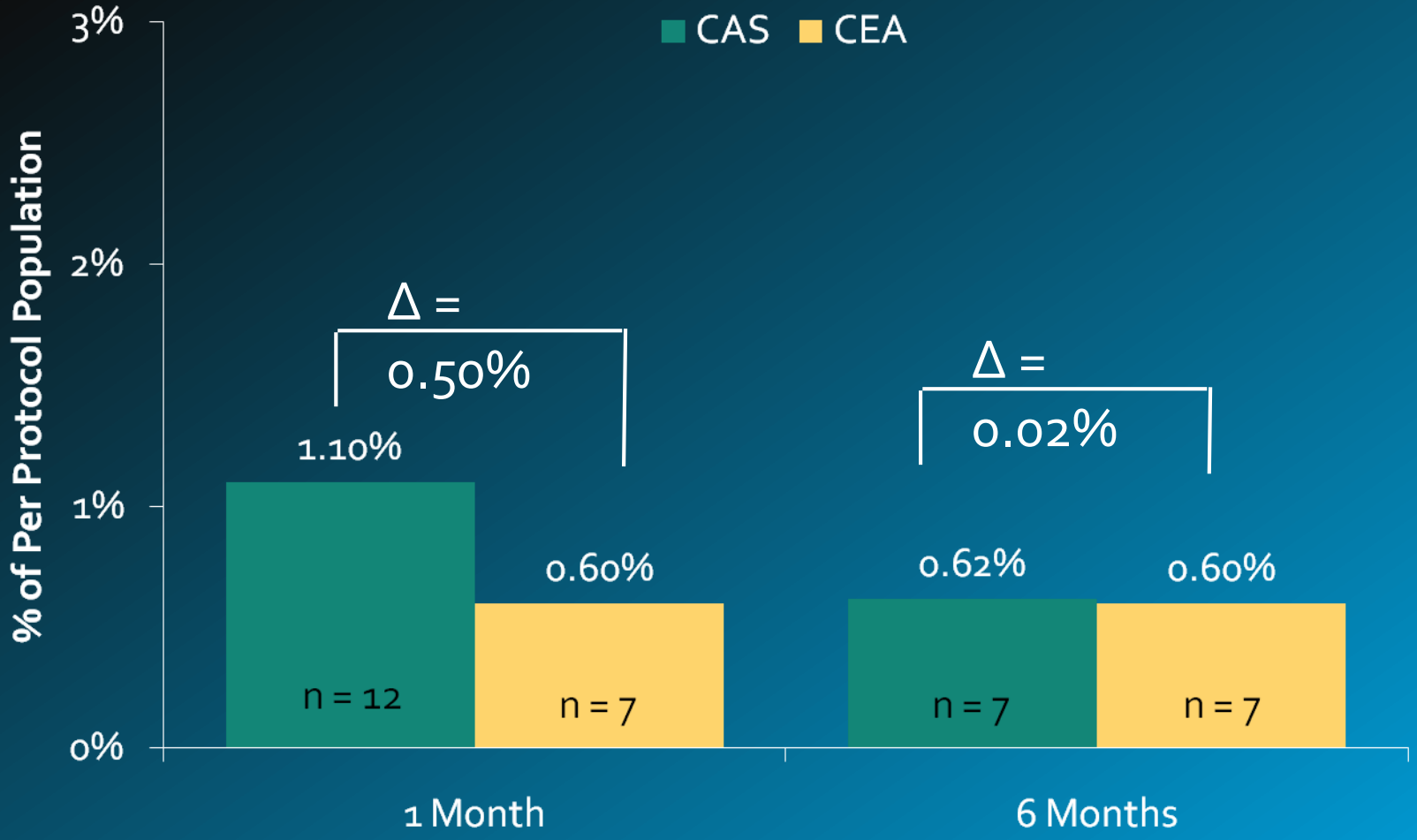
CREST: Death, Stroke and MI within 30 Days

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

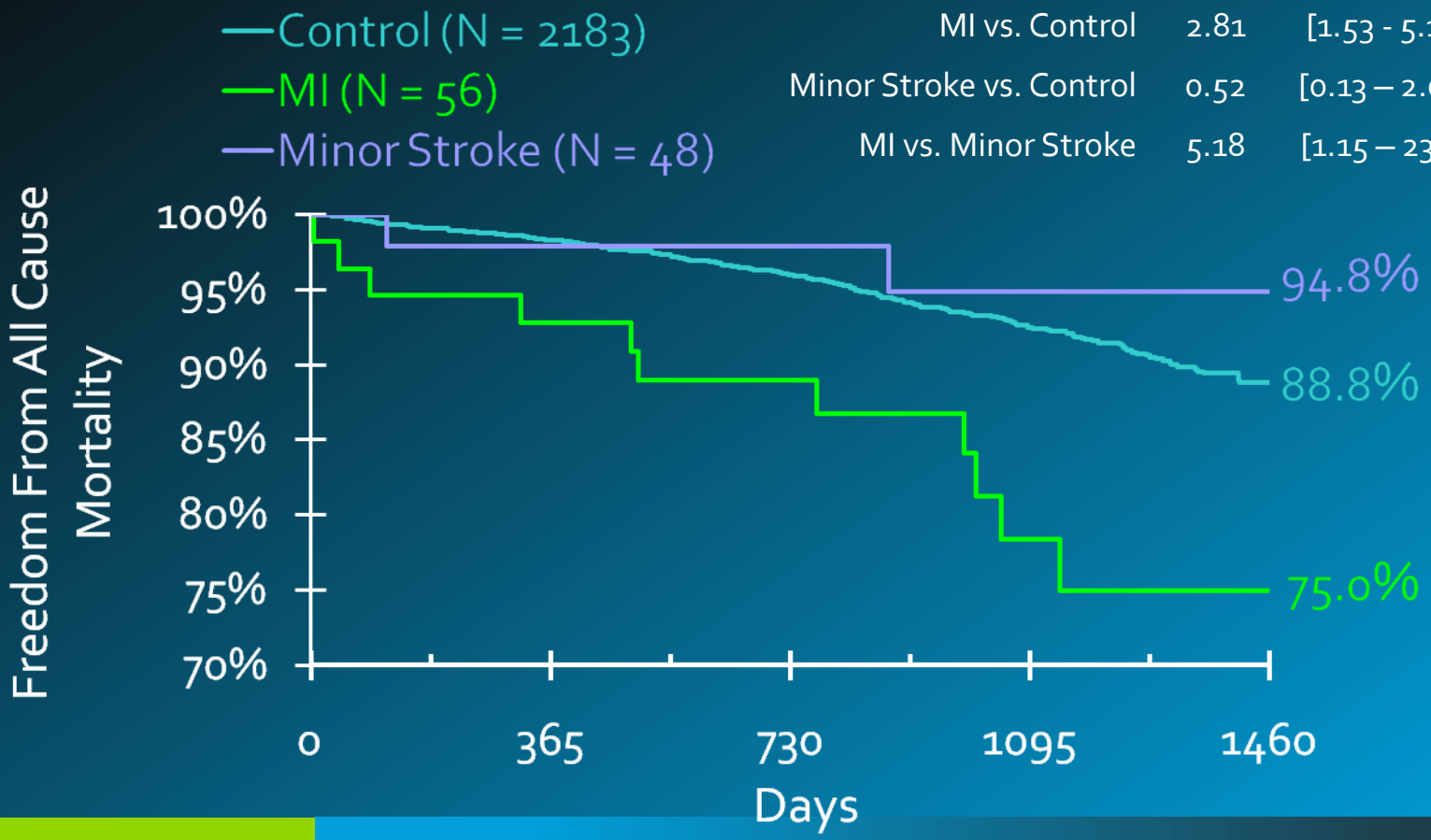
FDA PMA analysis:
Stroke and MI outcomes

Neurological residual deficit rates by NIHSS associated with minor strokes, equal at 6 months



Long-term mortality: No association with minor stroke but strong association with MI

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



Non-primary endpoint outcomes: Cranial nerve injury and access site complication

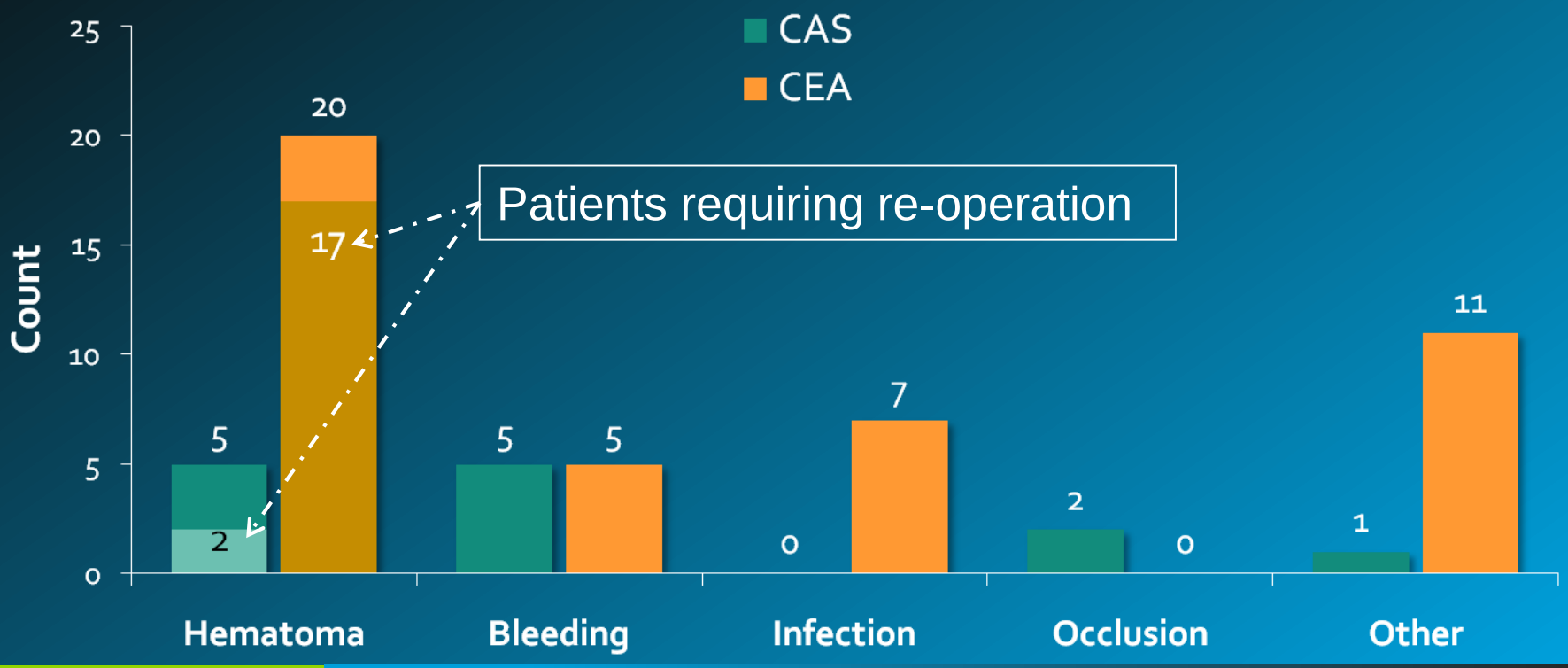
CREST:
No Observed CAS Related Cranial Nerve Injury and Fate of Cranial Nerve Injury in CEA

	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

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

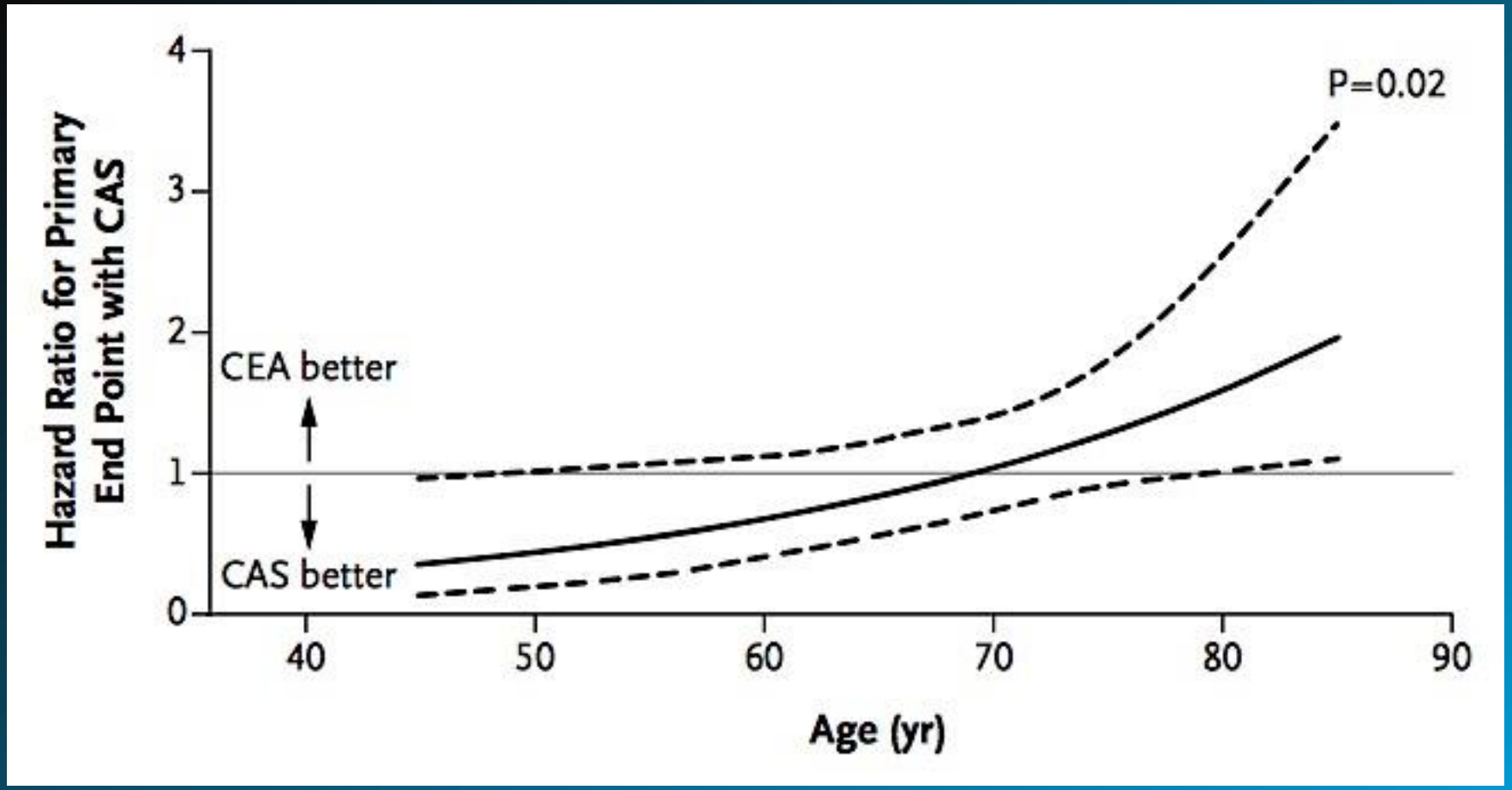
Less CAS Access Site Complications than CEA

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



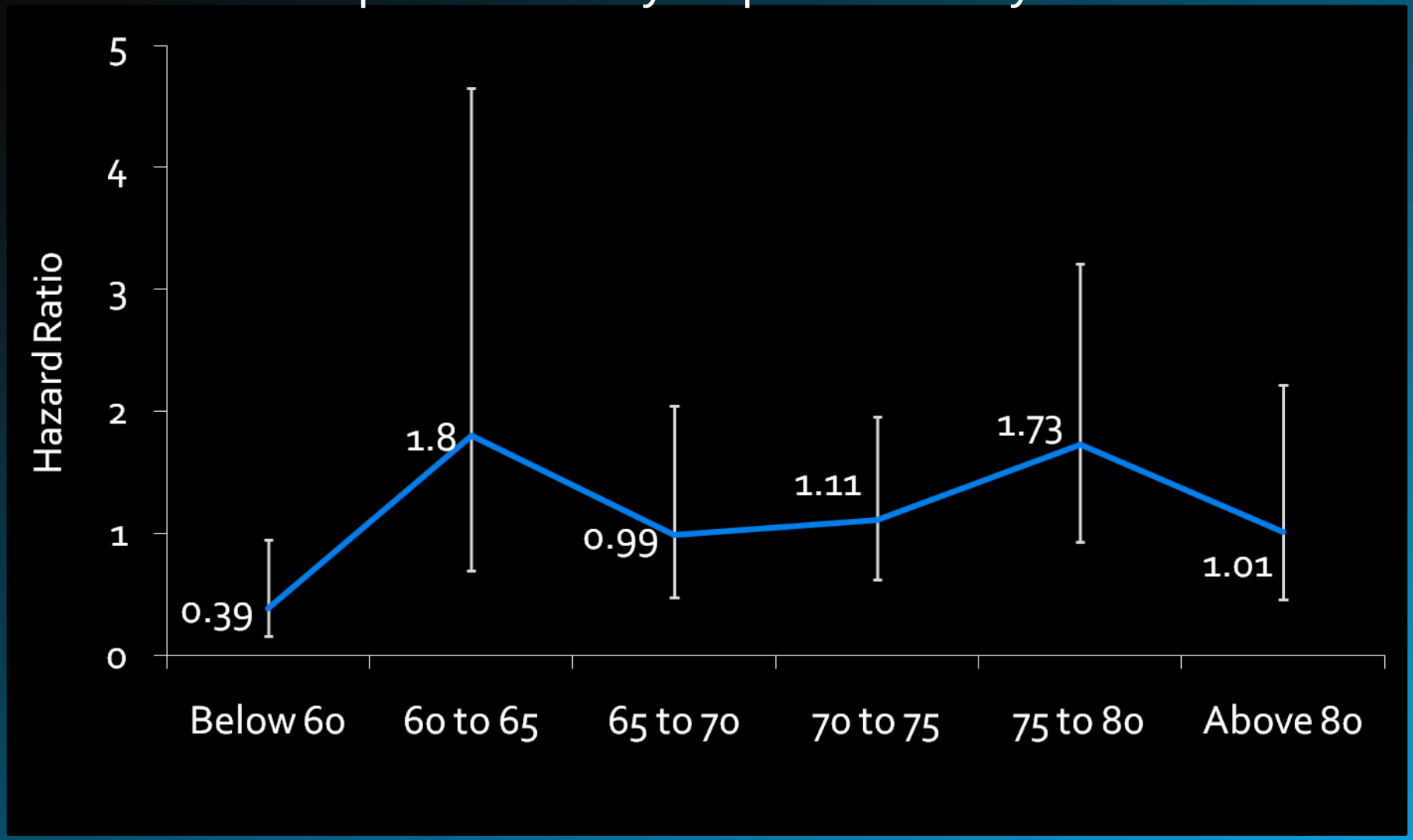
Events may occur more than once in the same patient.
Other includes pain requiring IV analgesics (5), incision complication (3), pseudoaneurysm (2), occlusion (1)

CAS and age

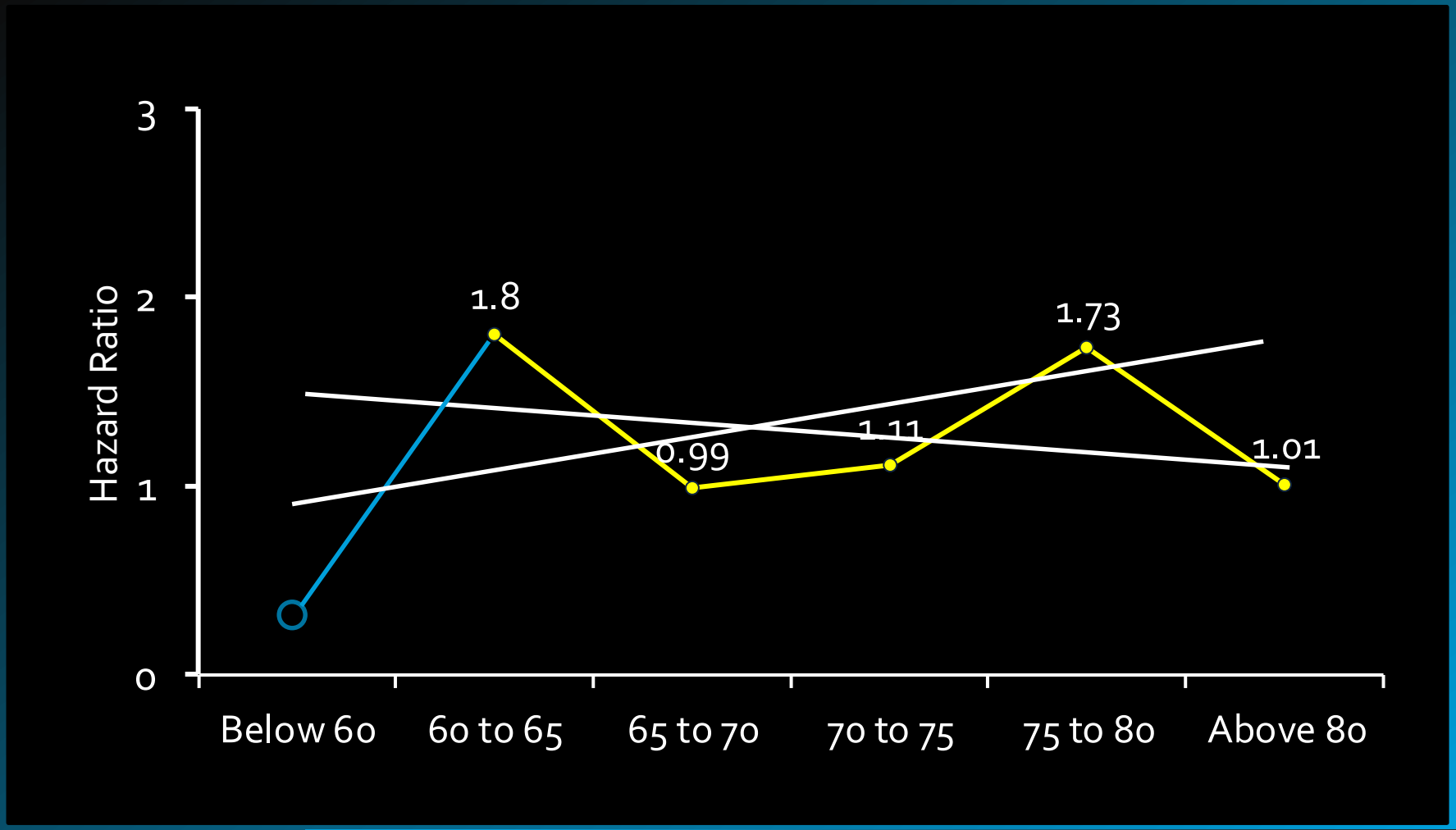

Hazard Ratio for Primary End Point with CAS
4
3
2
1
0
P=0.02
CEA better
CAS better
40
50
60
70
80
90
Age (yr)

Hazard Ratio by age group: no age trend

Per protocol analysis performed by FDA



“Best fit” line tipped by good CAS outcomes <60 years, *not* by poor outcomes in aged

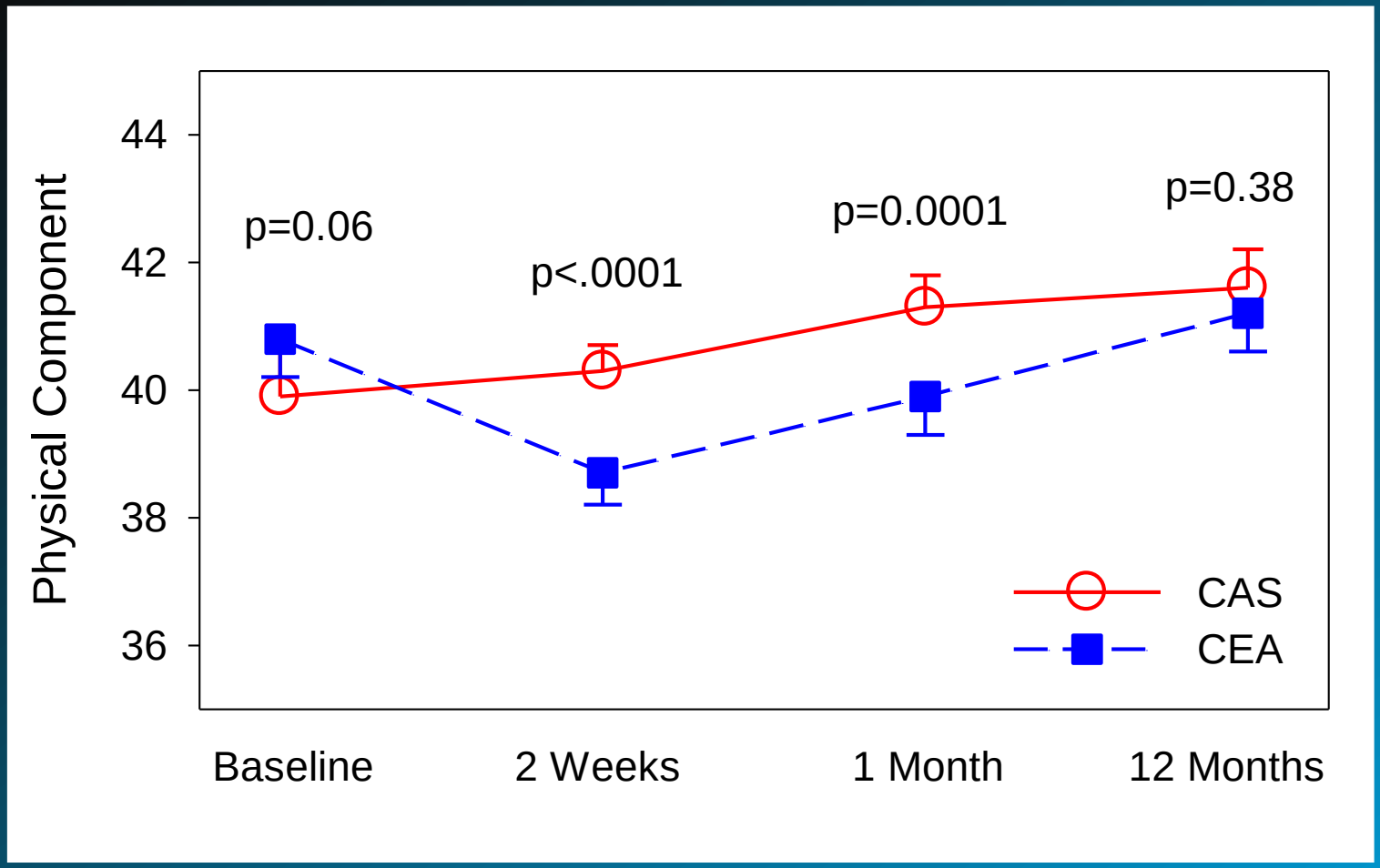


Main Line Health
Lankenau Heart Institute

Gray et al. Circulation. May 8 2012

Quality of life with CAS and CEA

CREST: SF-36 Physical Component *by treatment*



JACC; Vol. 58, No. 15 ; October 4, 2011:1557-65

CAS and cost

Prospective direct variable cost comparison: CREST

Table 3. One-Year Follow-Up Events and Costs (Modified ITT Population)

	CAS (n=1213)	CEA (n=1193)	Difference (95% CI)	*P* Value
Events after initial hospitalization				
Stroke, %	3.0	2.1	0.9 (−0.5 to 2.2)	0.173
Major, %	1.6	1.5	0.1 (−0.9, 1.0)	0.907
Minor, %	1.4	0.6	0.8 (−0.0 to −1.6)	0.044
MI,* %	0.3	0.5	−0.2 (−0.7 to 0.3)	0.545
Repeat revascularization, %	4.2	5.8	−1.6 (−3.3 to 0.2)	0.076
CAS, %	2.1	1.8	0.3 (−0.8 to 1.4)	0.598
CEA, %	2.1	3.9	−1.8 (−3.2 to −0.4)	0.010
Death, %	1.0	0.7	0.3 (−0.4 to 1.0)	0.388
TIA, %	0.9	0.5	0.4 (−0.3 to 1.1)	0.236
Costs to 1 y				
Total index hospitalization	$15 055±5539 [13 347]	$14 816±7709 [12 777]	$239 (−302 to 778)	0.185
Discharge to 1 y	$1321±4827 [0]	$1293±4502 [0]	$28 (−335 to 396)	0.441
Cumulative to 1 y	$16 375±7730 [13 637]	$16 108±9030 [13 112]	$267 (−366 to 961)	0.223

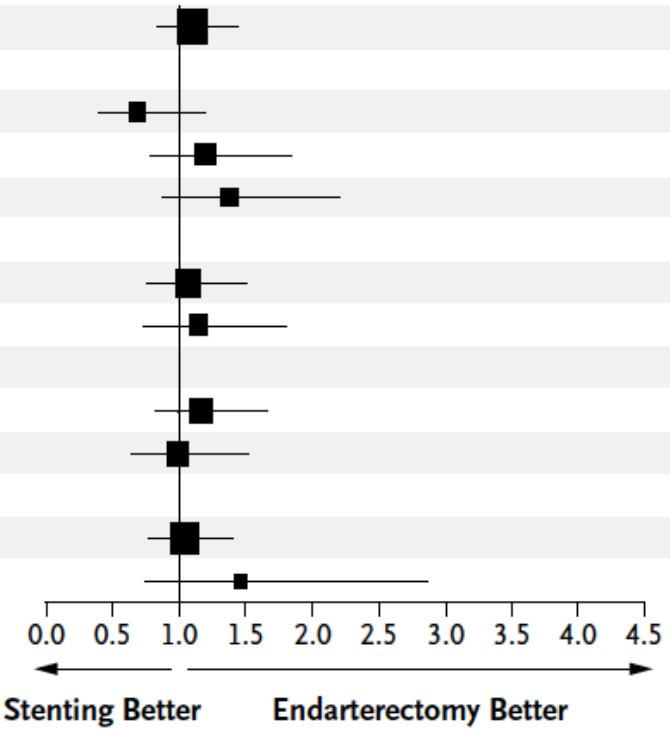
ORIGINAL ARTICLE

Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis

Thomas G. Brott, M.D., George Howard, Dr.P.H., Gary S. Roubin, M.D., Ph.D.,

A Primary Composite End Point

Subgroup	No. of Events/No. of Patients	P Value for Interaction
All patients	205/2502	
Age		0.10
39–64 yr	50/791	
65–74 yr	83/1025	
≥75 yr	72/686	
Sex		0.81
Male	130/1630	
Female	75/872	
Status		0.59
Symptomatic	122/1321	
Asymptomatic	83/1181	
Stenosis		0.30
Severe	171/2152	
Moderate	34/350	



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Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

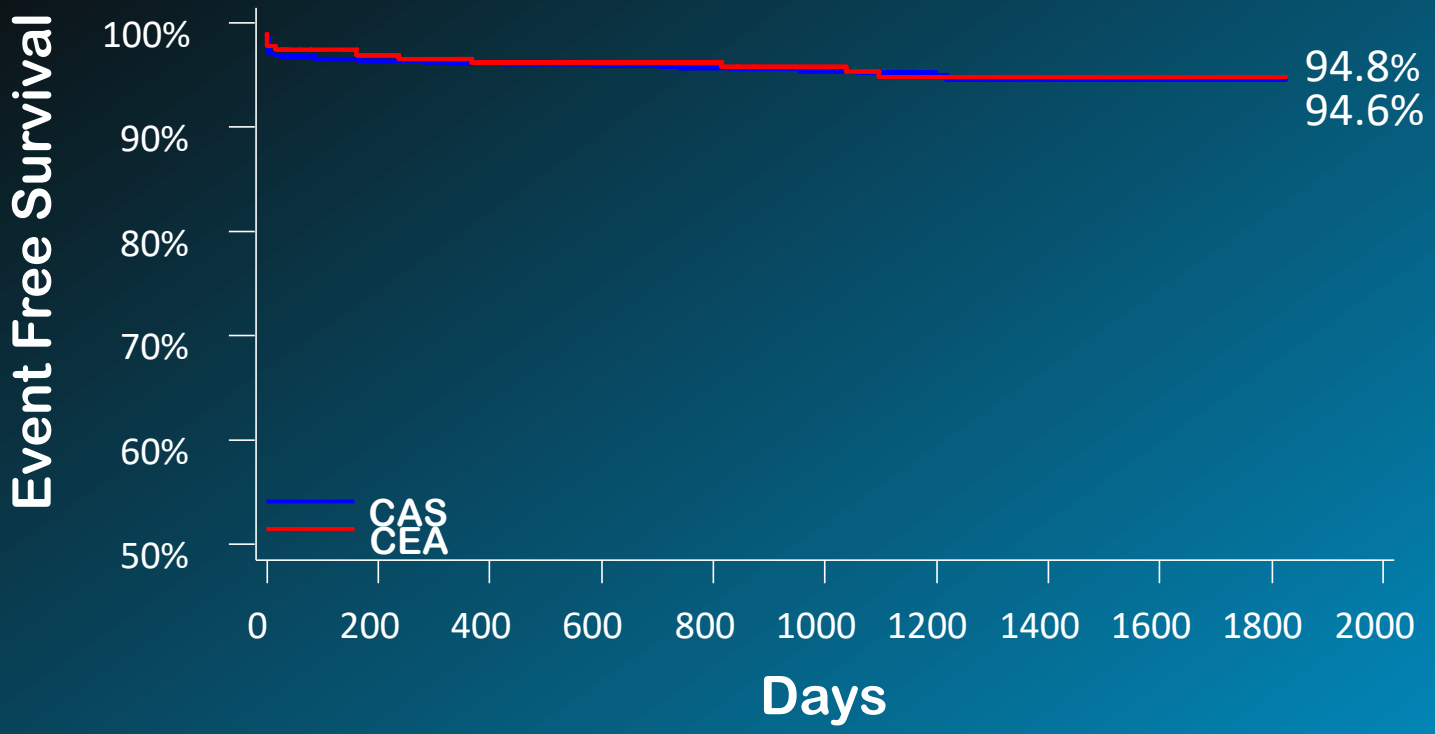
Kenneth Rosenfield, M.D., M.H.C.D.S., Jon S. Matsumura, M.D., Seemant Chaturvedi, M.D., Tom Riles, M.D., Gary M. Ansel, M.D., D. Chris Metzger, M.D., Lawrence Wechsler, M.D., Michael R. Jaff, D.O., and William Gray, M.D., for the ACT I Investigators*

ACT I: Primary Endpoint (ITT)

Stroke, MI, death within 30 days of procedure and ipsilateral stroke 31d – 1 year

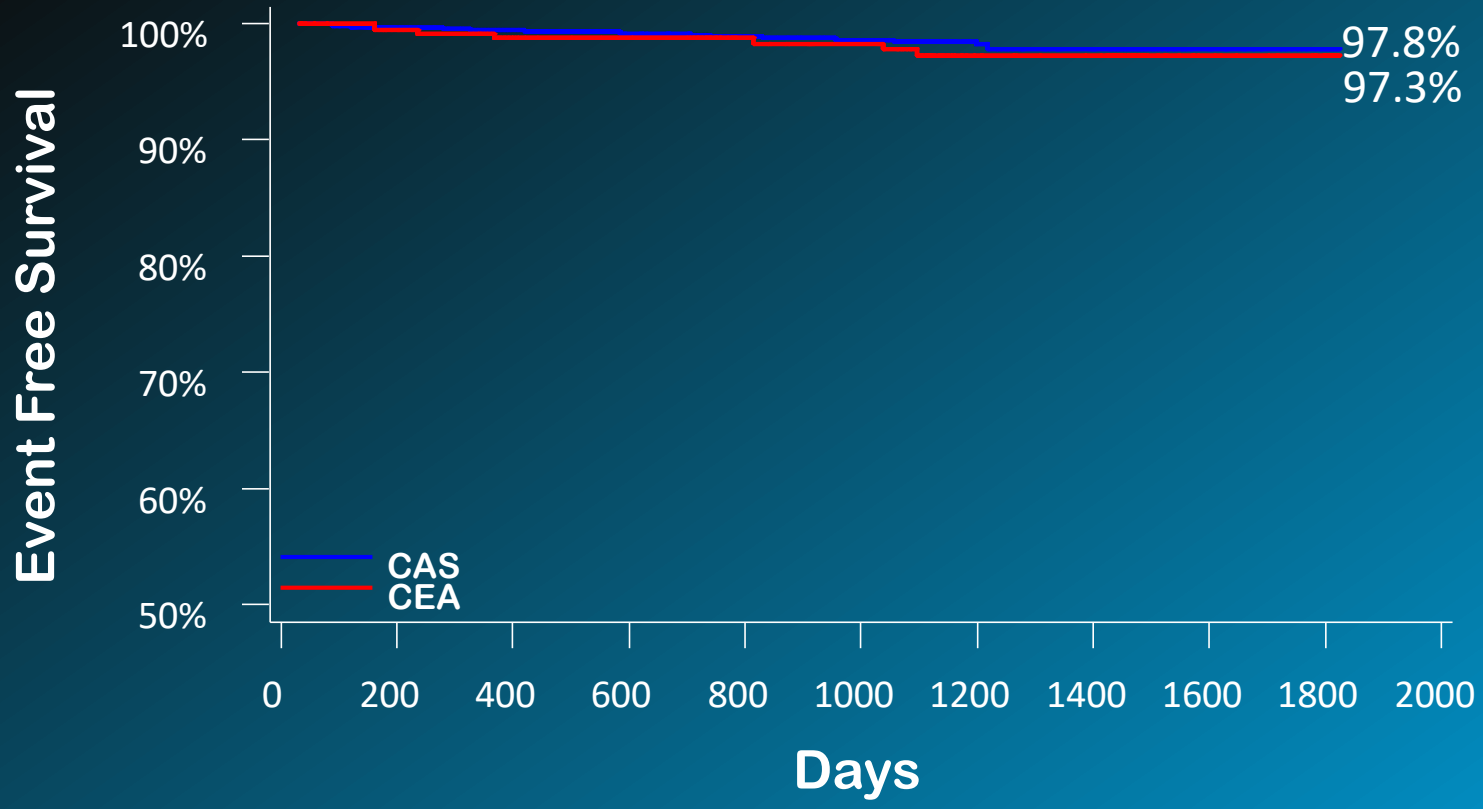
	CAS (N=1089)	CEA (N=364)	Diff	Upper Limit 95% CI	p Value NI
Primary Endpoint	3.8% ± 0.59%	3.4% ± 0.98%	0.4%	2.27 %	0.01

ACT I:
Freedom from death, stroke and MI within 30 days and ipsilateral stroke 31 days to 5 years



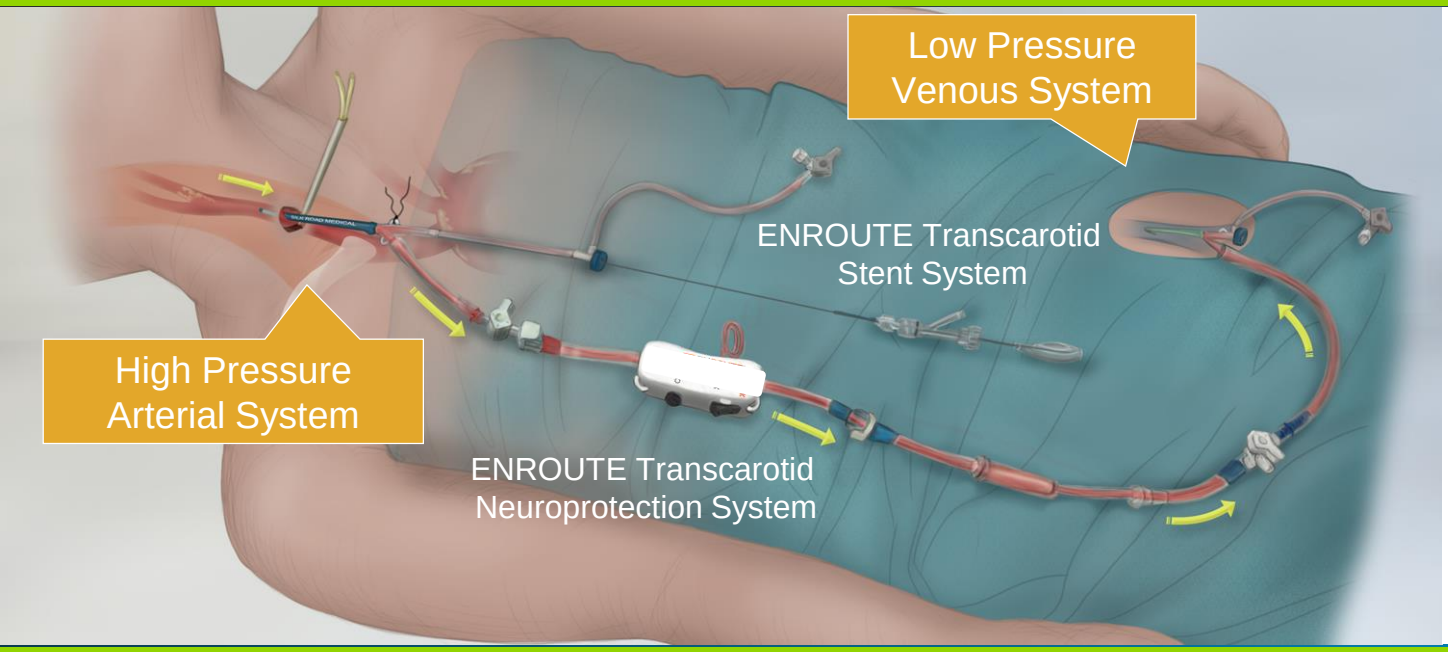
Days	0	(0, 30]	(30, 365]	(365, 730]	(730, 1095]	(1095, 1460]	(1460, 1825]
CAS Number at Risk	1089	1067	1016	862	729	544	364
CEA Number at Risk	364	354	325	285	246	182	112

ACT I:
Freedom from ipsilateral stroke from 31 days to 5 years



Days	31	(31, 365]	(365, 730]	(730, 1095]	(1095, 1460]	(1460, 1825]
CAS Number at Risk	1049	1045	887	751	561	375
CEA Number at Risk	333	333	291	251	185	115

New technology:
Direct Carotid Access with High Rate Flow Reversal



- Avoid the arch
- "CEA-like" neuroprotection
- Less manipulation
- Predictable, efficient

Silk Road Medical, Inc.

ROADSTER Outcomes
Intention to Treat, Per Protocol

High Surgical Risk	Pivotal Group, ITT (n=141)		Pivotal Group, PP (n=136)	
S/D/MI*	5	3.5%	4	2.9%
Major Stroke	0	0%	0	0%
Minor Stroke	2	1.4%	1	0.7%
Death	2	1.4%	2	1.5%
MI	1	0.7%	1	0.7%
Stroke & Death	4	2.8%	3	2.2%
Cranial Nerve Injury (CNI)	1	0.7%	1	0.7%
CNI Unresolved at 6 Mos	0	0%	0	0%

*Hierarchical

Per Protocol excludes major protocol deviations

All FDA-approved carotid stent systems were used per site preference (Acculink, Xact, Precise, Protégé, Wallstent)

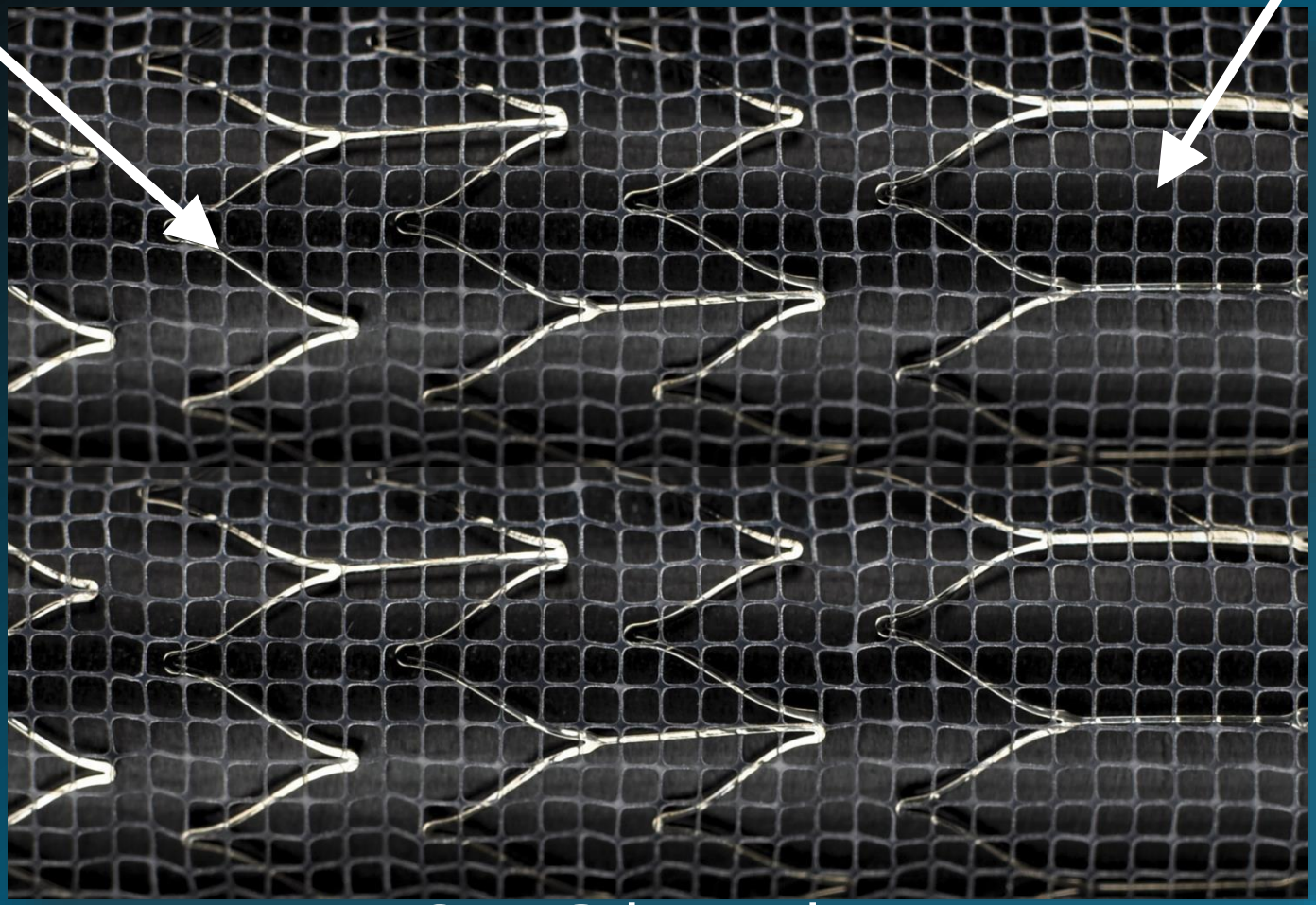
ROADSTER Subgroup Outcomes

High Surgical Risk Pivotal Intention to Treat	Age ≥75	Symptomatic
n	n=66 (47%)	n=36 (26%)
S/D/MI	3 (4.5%)	1 (2.8%)
Major Stroke	0%	0%
Minor Stroke	0%	0%
Death	3.0%	2.8%
MI	1.5%	0%
Stroke & Death	3.0%	2.8%

New technology:
Gore Carotid Stent (GCS)

Stent Frame

Stent Lattice



CBAS heparin-bonded coating

SCAFFOLD 30 day outcomes: Per Protocol (PP) N=264

Subjects with one or more MAE at 30 d	8 (3.0%)
Death	1 (0.4%)
Myocardial infarction	4 (1.5%)
Q-wave myocardial infarction	0 (0%)
Stroke	3 (1.1%)
Major stroke	3(1.1%)
Ipsilateral	2 (0.8%)
Non-ipsilateral	0 (0%)
Hemorrhagic (ipsilateral)	1(0.4%)
Minor stroke	0 (0%)

SCAFFOLD:
Per Protocol Subgroup analysis:
N=264

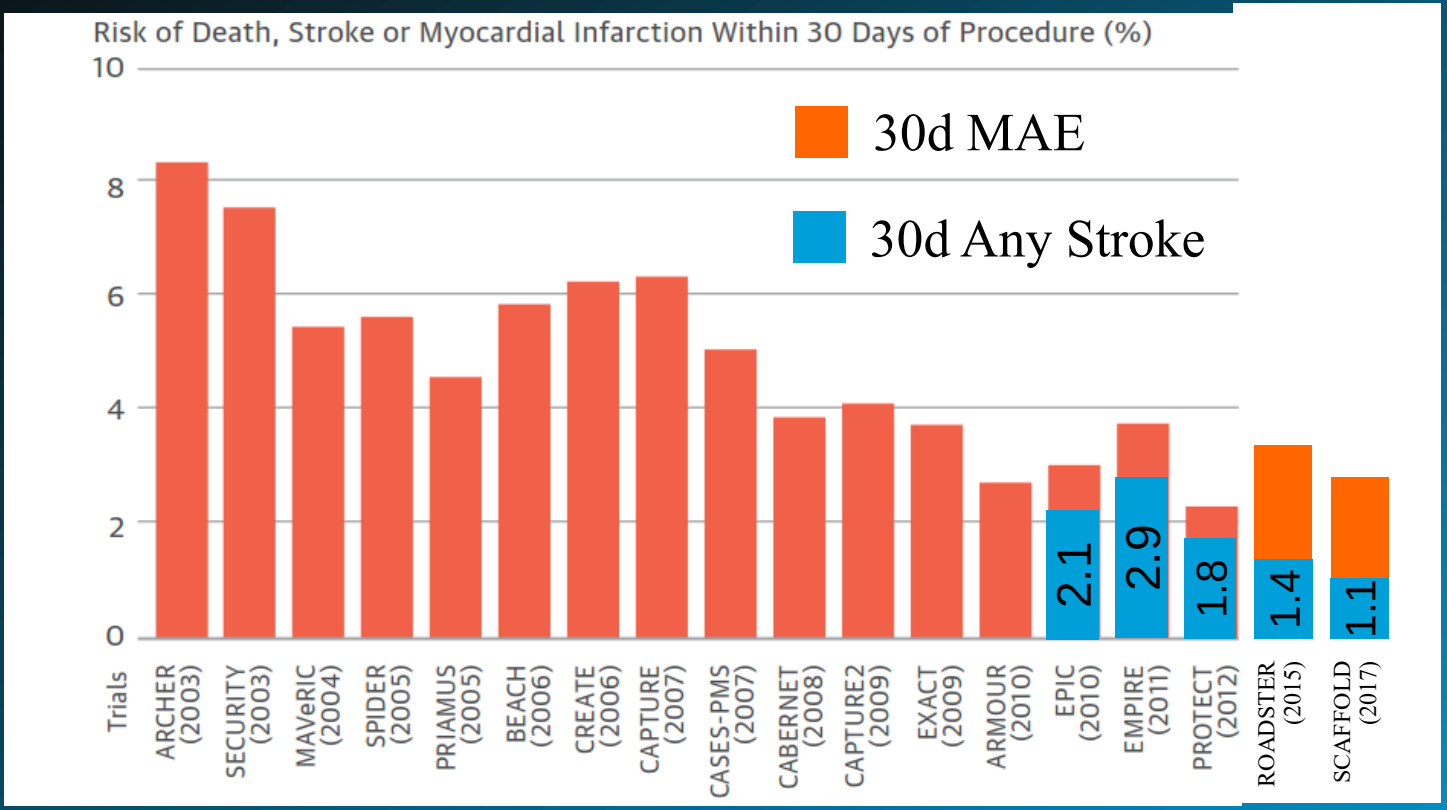
	30-Day MAE				
All Per-Protocol Subjects (N=264)	**N**	**Death**	**Stroke**	**MI**	**MAE**
Overall Evaluable[1]	263	1 (0.4%)	3 (1.1%)	4 (1.5%)	8 (3.0%)
Symptomatology	N=263				
Symptomatic	33 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asymptomatic	230 (87.5%)	1 (0.4%)	3 (1.3%)	4 (1.7%)	8 (3.5%)
High-Risk Subgroup	N=263				
Anatomic	79 (30.0%)	0 (0.0%)	1 (1.3%)	1 (1.3%)	2 (2.5%)
Comorbid	184 (70.0%)	1 (0.5%)	2 (1.1%)	3 (1.6%)	6 (3.3%)
Comorbid Age Status	N=263				
Age 75+ years	124 (47.1%)	1 (0.8%)	2 (1.6%)	2 (1.6%)	5 (4.0%)
Age <75 years	139 (52.9%)	0 (0.0%)	1 (0.7%)	2 (1.4%)	3 (2.2%)
Octogenarian Status	N=263				
Age 80+ years	61 (23.2%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	2 (3.3%)
Age <80 years	202 (76.8%)	1 (0.5%)	2 (1.0%)	3 (1.5%)	6 (3.0%)

Summary of trial results

	D/S/MI (peri-procedure)	CNI	Access site complication	Long-term outcomes	Cost	QoL
CEA	=	-	-	=	=	=
CAS	=	+	+	=	=	(+)

Since the comparative trials in standard surgical risk trials, newer technology in high surgical risk patients with improved outcomes

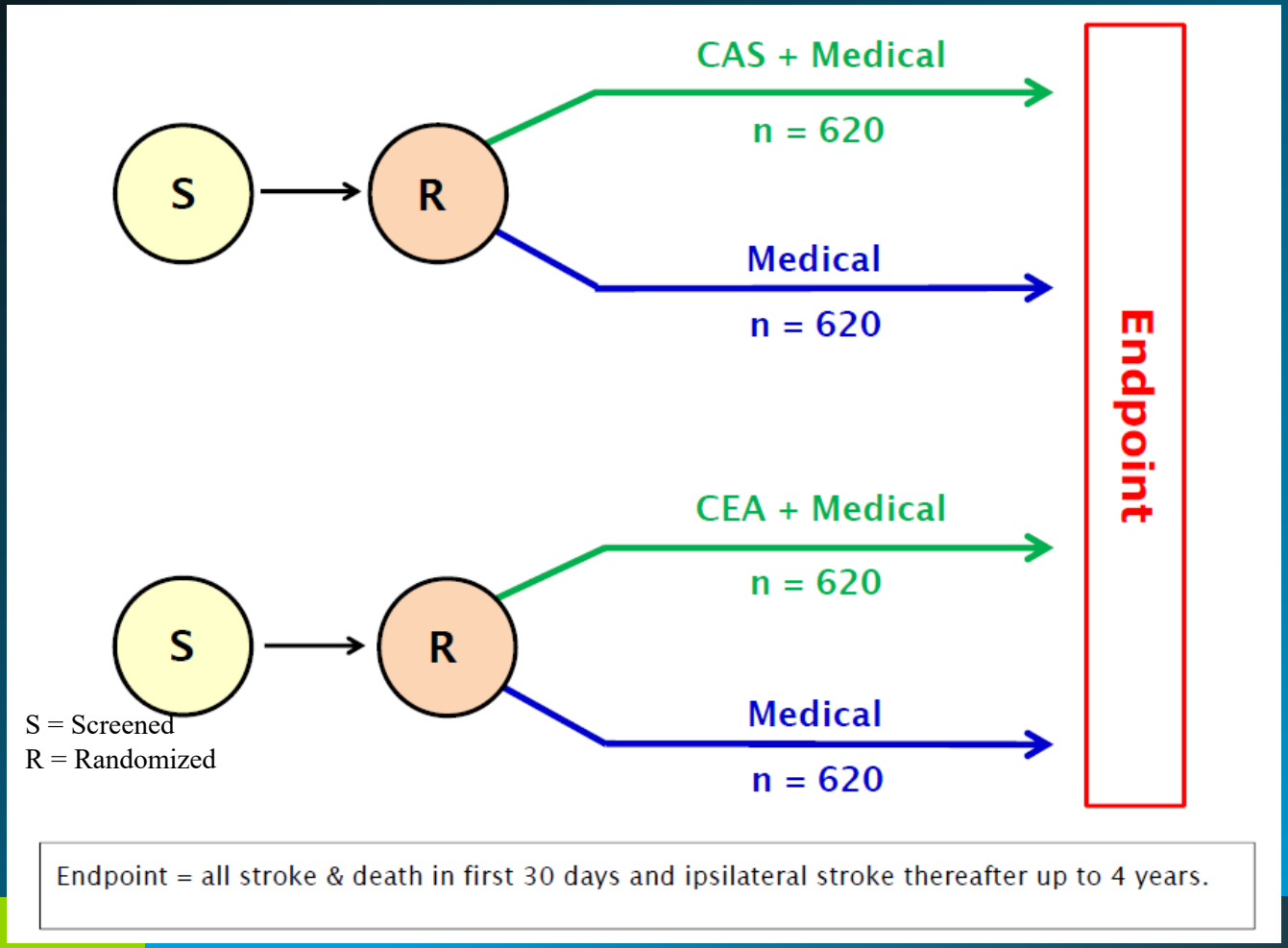
Improving results



J Am Coll Cardiol. 2014 Aug 19;64(7):722-31

Question 1: what is the best path for asymptomatic patients in the era of modern medical management

CREST-2



Question 2:
Why is there still limited access to carotid stenting?