Why CEA?

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

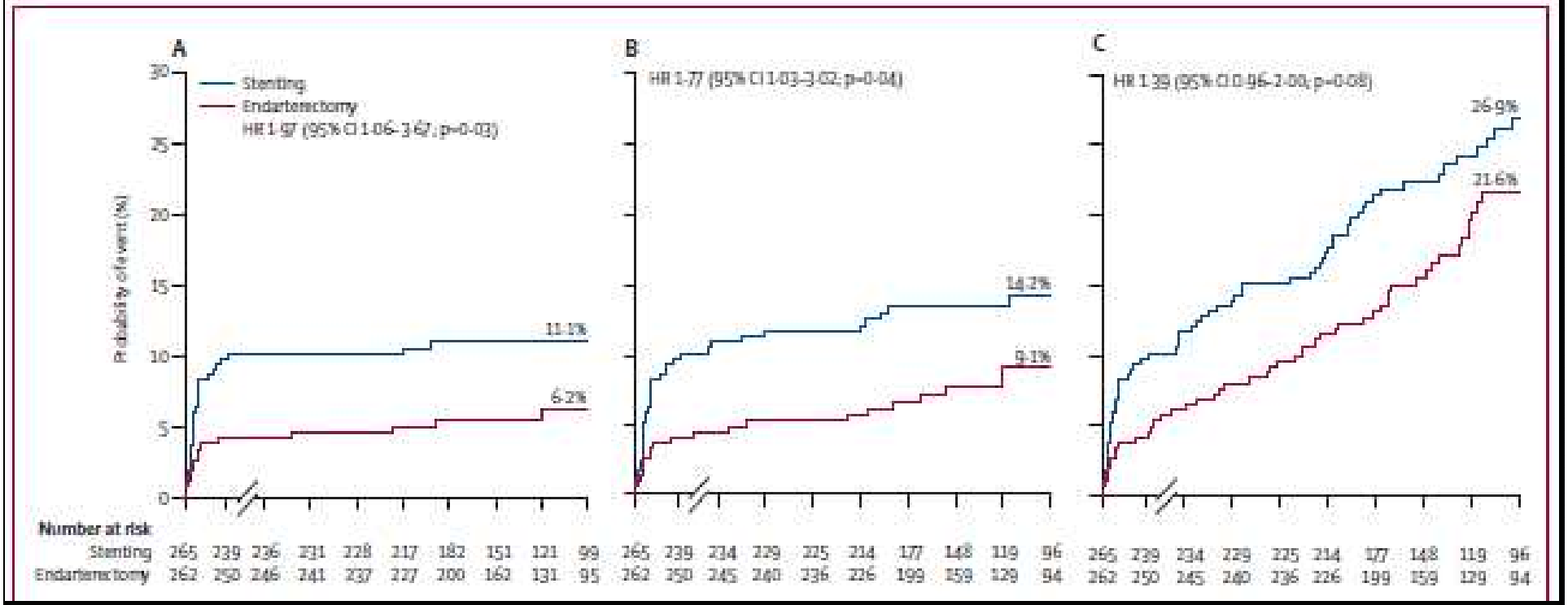
CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Stroke prevention efficacy equal between CEA and CAS

EVA-3S: 4-year outcomes

Any ipsilateral stroke | Any stroke | Any stroke or death

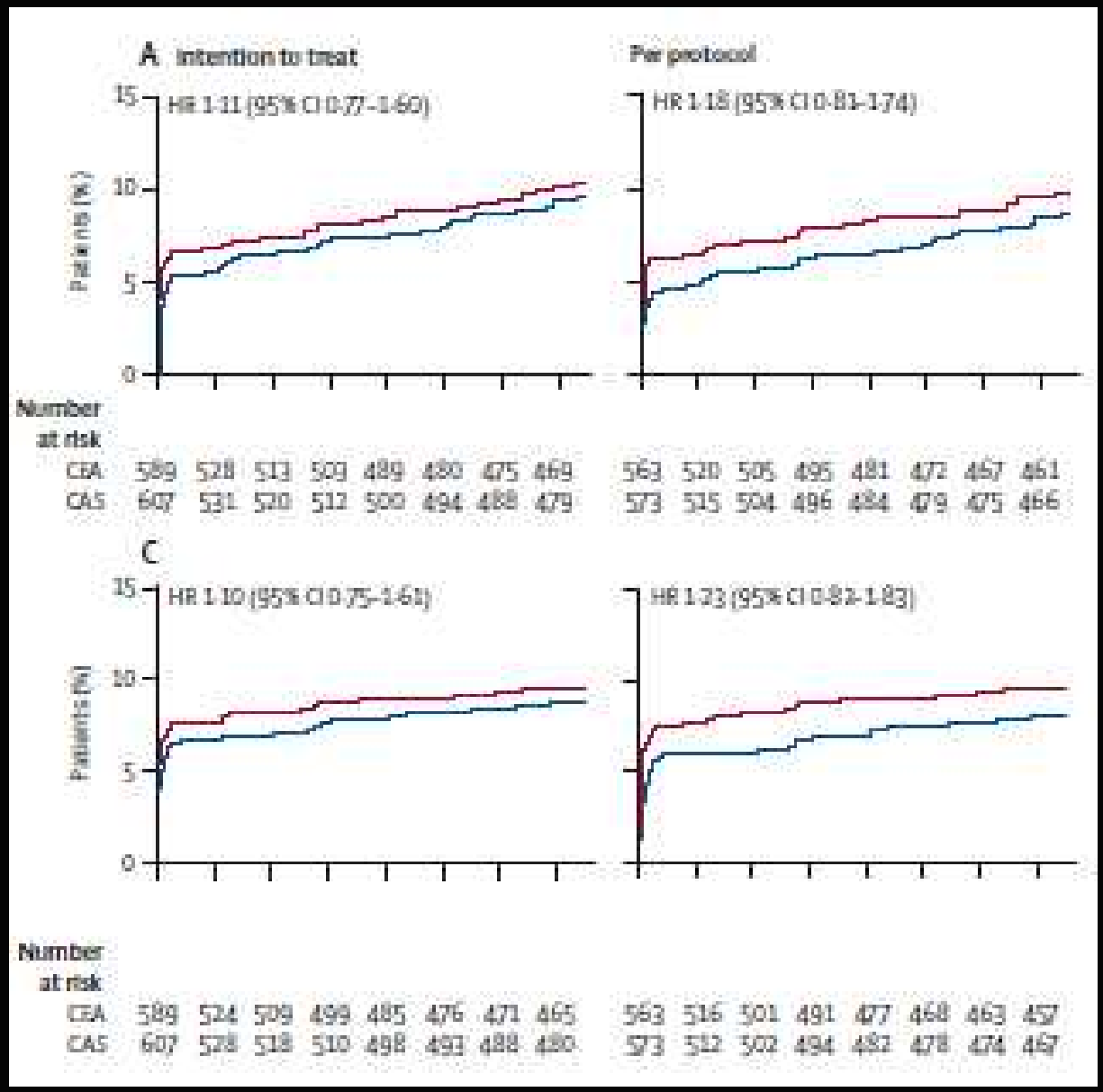


CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Stroke prevention efficacy equal between CEA and CAS

SPACE: K-M plots of 2-year outcomes

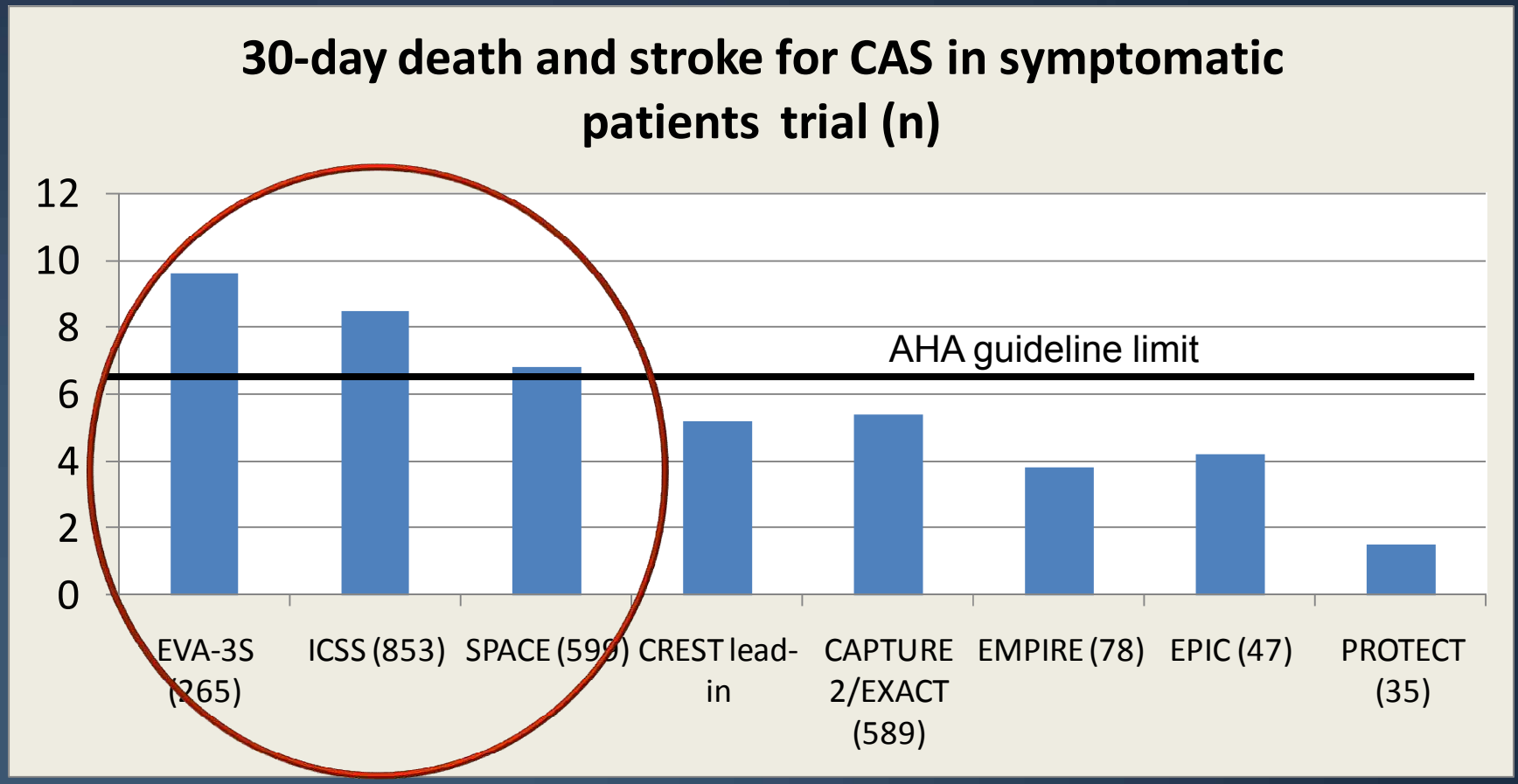


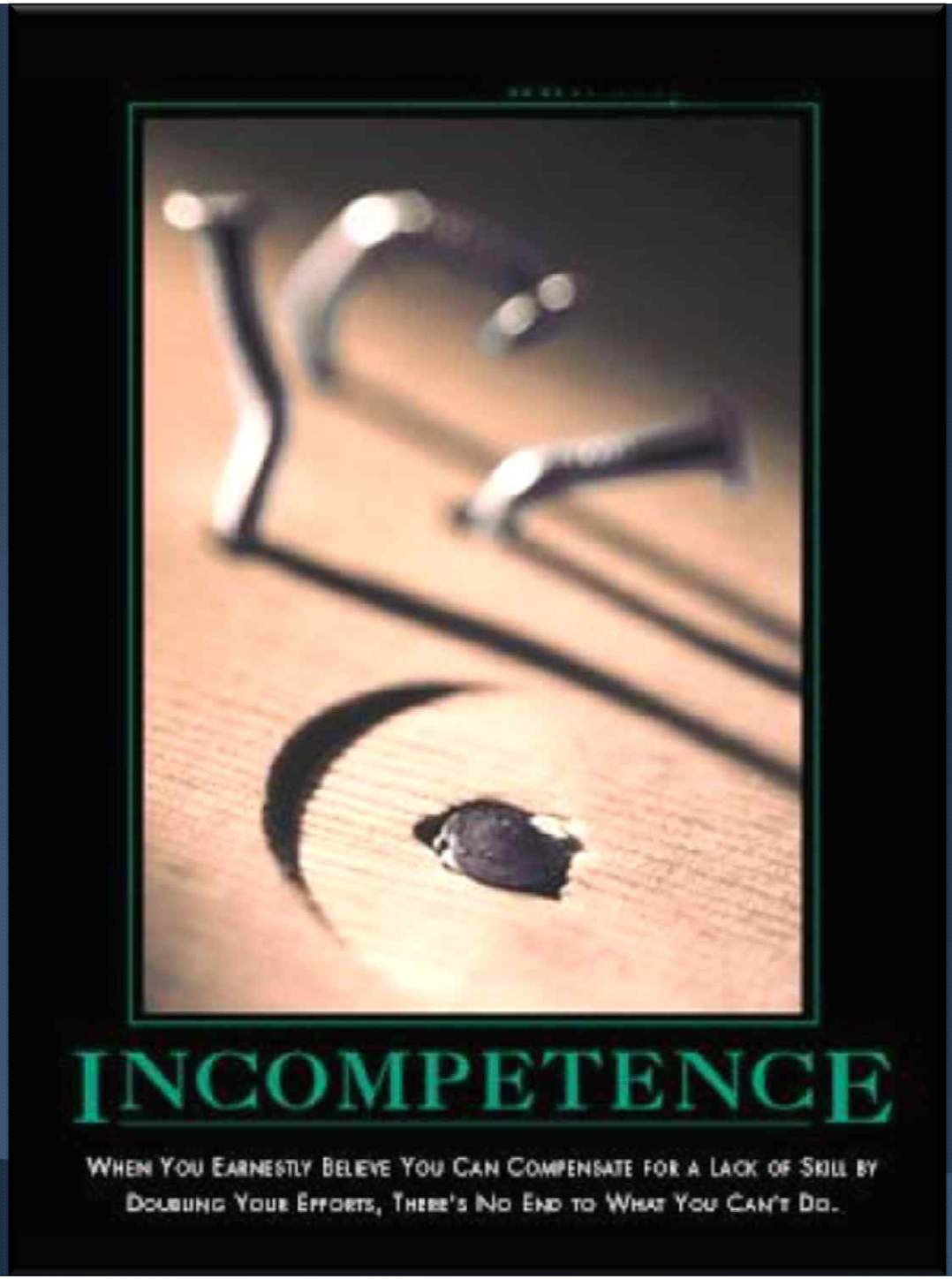
Ipsilateral stroke and vascular death

30-day stroke/death plus ipsilateral stroke to 2 years

Columbia University Medical Center

The evaluation of CAS in symptomatic patients: EVA-3S, SPACE, ICSS are outcome outliers

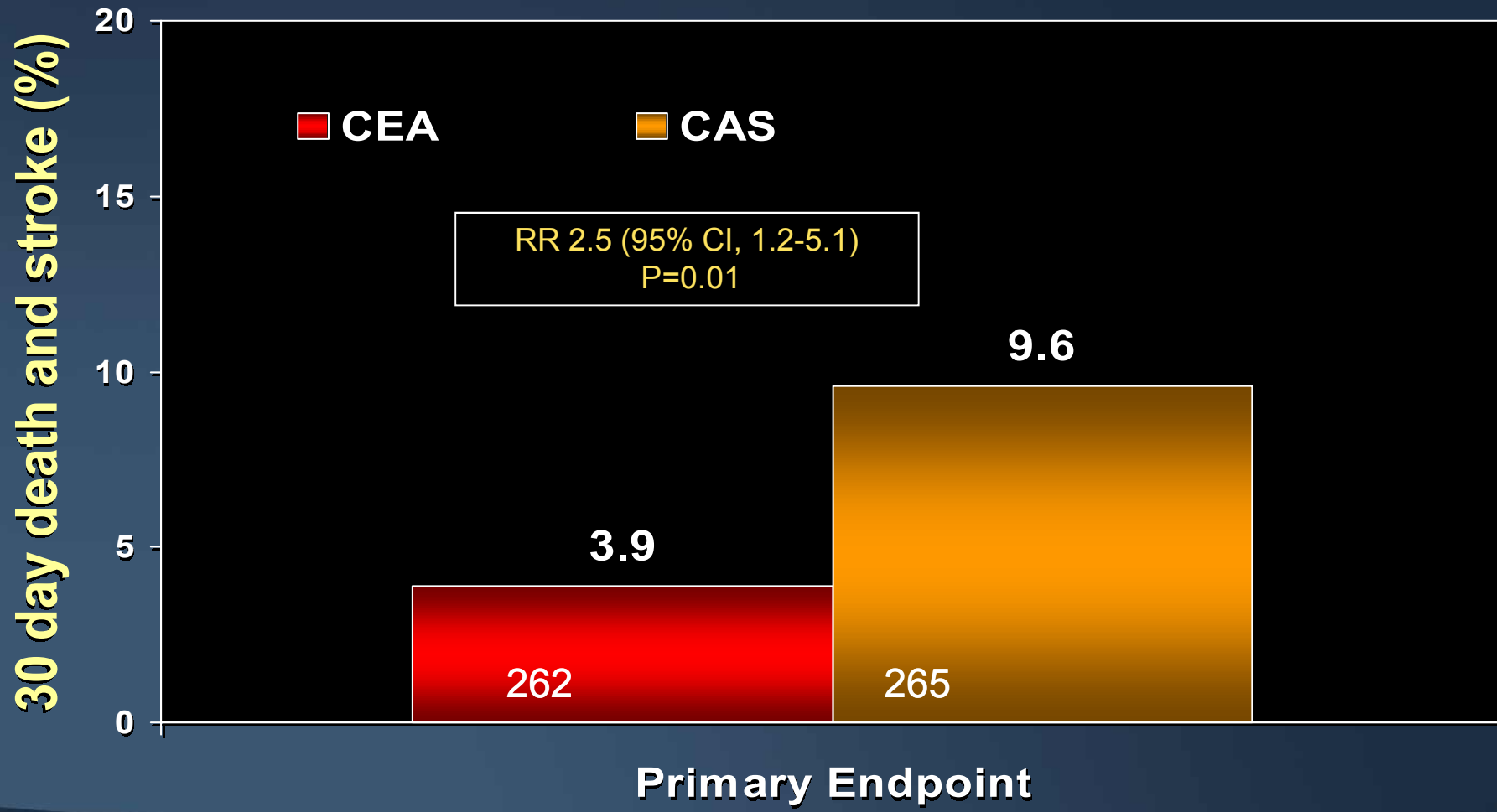




CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

EVA-3S: Randomized CEA vs. CAS



Mas JL et al. New Engl J Med 2006;355:1661-71

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

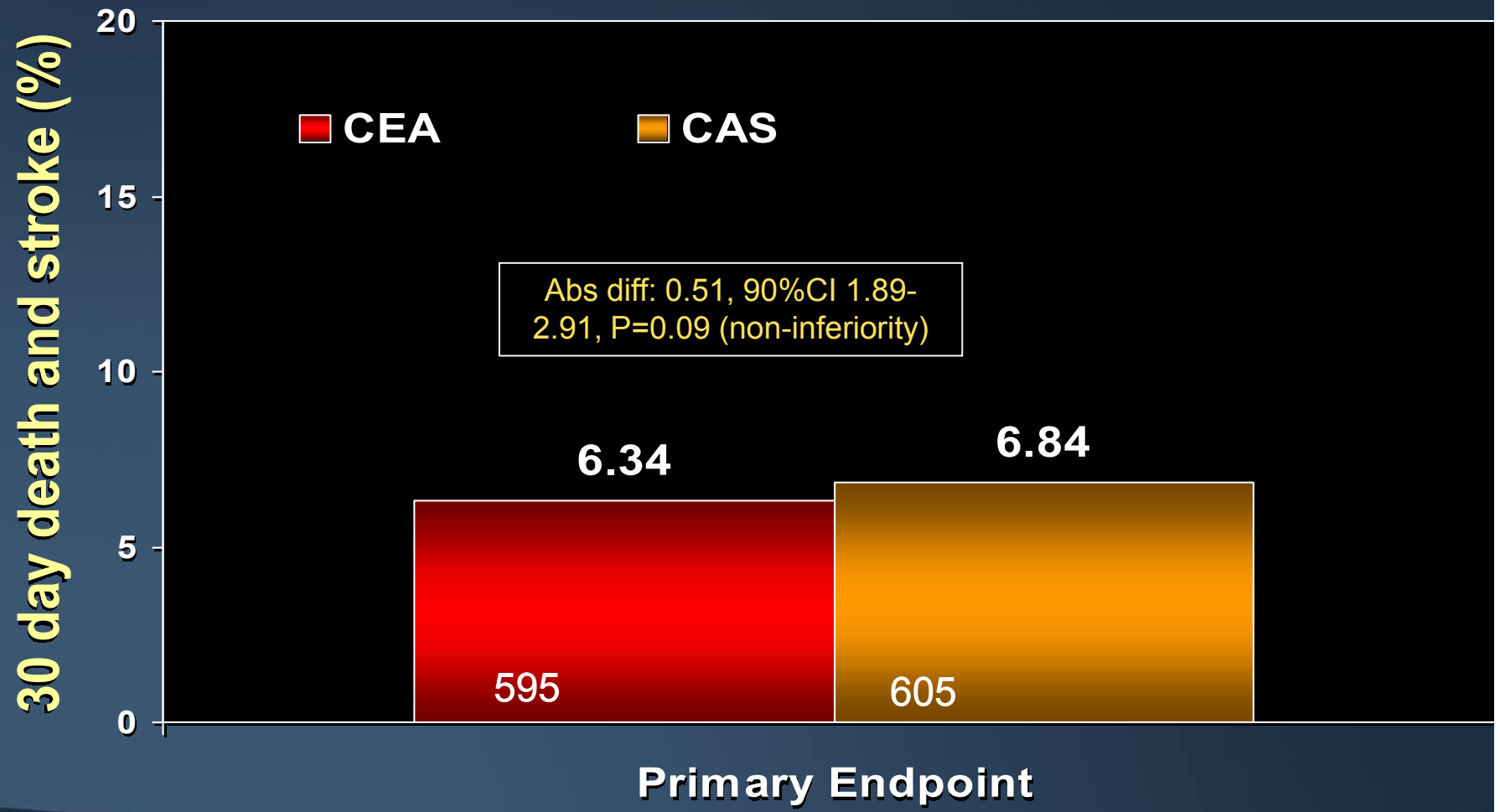
EVA-3S critique

- Slow enrollment/non-reimbursement resulted in limited investigator experience
  - 1.7 CAS patients/year/site
- Early and/or non-standard technique resulted in unnecessary morbidity
  - Use of EPD not widespread or familiar
    - Lack of use in the early phase of the trial associated with 4-5 excess strokes (~20% of all CAS strokes) with a rate of *>26% 30 day stroke!*
  - *5% stent procedure failure requiring emergency surgery* in this trial resulting in 2 strokes in the CAS group
    - Major pivotal trials in this country (e.g., SAPPHIRE, ARCHeR) have not reported *any* emergent surgical conversions
  - No pre-dilation in >80% of procedures (standard in US)
  - Significant (beyond local) anesthesia was employed in ~30% of procedures (estimated <5% in US)

EVA-3S critique (continued)

- Limited investigator experience and number of trained sites/operators
  - Experienced operators defined by 12 *lifetime* CAS procedures or 5 CAS procedure if 35 supra-aortic procedure
    - These operators were deemed experienced and allowed to tutor the non-experienced
  - No centralized training qualification process (local proctors pronounced the operators qualified)
  - Approximately 2/3 of sites were under tutelage at the beginning of their *randomized* participation.
- *Tutelage and randomization should be mutually exclusive terms*

SPACE
Randomized CEA vs. CAS symptomatic patients



SPACE collaborators. Lancet 2006;368:1239-47

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

SPACE: critique

- *EPD was used in only 27% of patients*
- Stopped due to lack of continued funding
  - Not safety or futility
  - But questionable ethics
- Stated conclusion: “SPACE failed to prove non-inferiority of carotid-artery stenting compared with carotid endarterectomy for the periprocedural complication rate.”
  - Should read *“SPACE failed to complete randomization, therefore no comparative assessment of the two therapies is possible”*
- Nevertheless, *prima facie* results appear to be comparable between stent and surgery

International Carotid Stent Study (ICSS)

- Randomized 1710 symptomatic patients to either CEA or CAS
  - 3 year primary endpoint: fatal or disabling stroke in any territory
  - Interim analysis published this week in Lancet
    - 120 day death, stroke, or MI
- CEA operators: >50 operations/>10 per year
- CAS operators: >50 stent procedures (anywhere), 10 lifetime CAS cases
  - Inexperienced operators had to complete 20 *randomized* cases satisfactorily to be released

ICSS

- Explanation offered for limited CAS training requirements in ICSS:
  - *"to use average operators to assess generalizability of the results"*
- This is unprecedented (surgeon qualification in NASCET/ACAS/ACST) and unacceptable:
  - From a trial construct perspective since it introduces a confounding factor likely to influence the assessment of the two variables being tested
  - From an ethical perspective (no explanation required)

ICSS: 120 day Outcomes

	CAS (853)	CEA (857)	HR	P value
Death, stroke, MI	**8.5%**	**5.2%**	**1.69**	**0.006**
Any stroke	**7.7%**	**4.1%**	**1.92**	**0.002**
Any stroke or death	**8.5%**	**4.7%**	**1.95**	**0.001**
Disabling stroke or death	4.0%	3.2%	1.28	0.34
All-cause death	**2.3%**	**0.8%**	**2.76**	**0.017**

ICSS: further observations

- Very low rate of MI in both groups suggests that they weren't routinely assessed (unclear from Methods)
- Embolic protection not mandated
  - Only documented in 72% of cases
- Major stroke was ~2% in each group, ~double what is seen in US outcomes
- *Poorly trained operators not using standard of care EPD in every case leading to poor results*
- *PS: DWI comparisons are similarly confounded by expertise, as well as being non-mandated/not pre-specified*

CREST: Study design

- Prospective, multicenter, randomized, controlled trial with blinded endpoint adjudication
- CAS vs. CEA in patients with symptomatic and asymptomatic stenosis
- 108 US and 9 Canadian sites
- *Rigorous credentialing for CAS operators*
  - *427 applicants/ 224 selected (52%) at 110 sites*
  - *~1500 patients in lead-in phase*

Primary Endpoint

- Peri-procedure
  - Composite of:
    - Any clinical stroke
    - Myocardial infarction
    - Death
- Post-procedural
  - Composite of
    - Peri-procedure events plus
    - Ipsilateral stroke up to 4 years

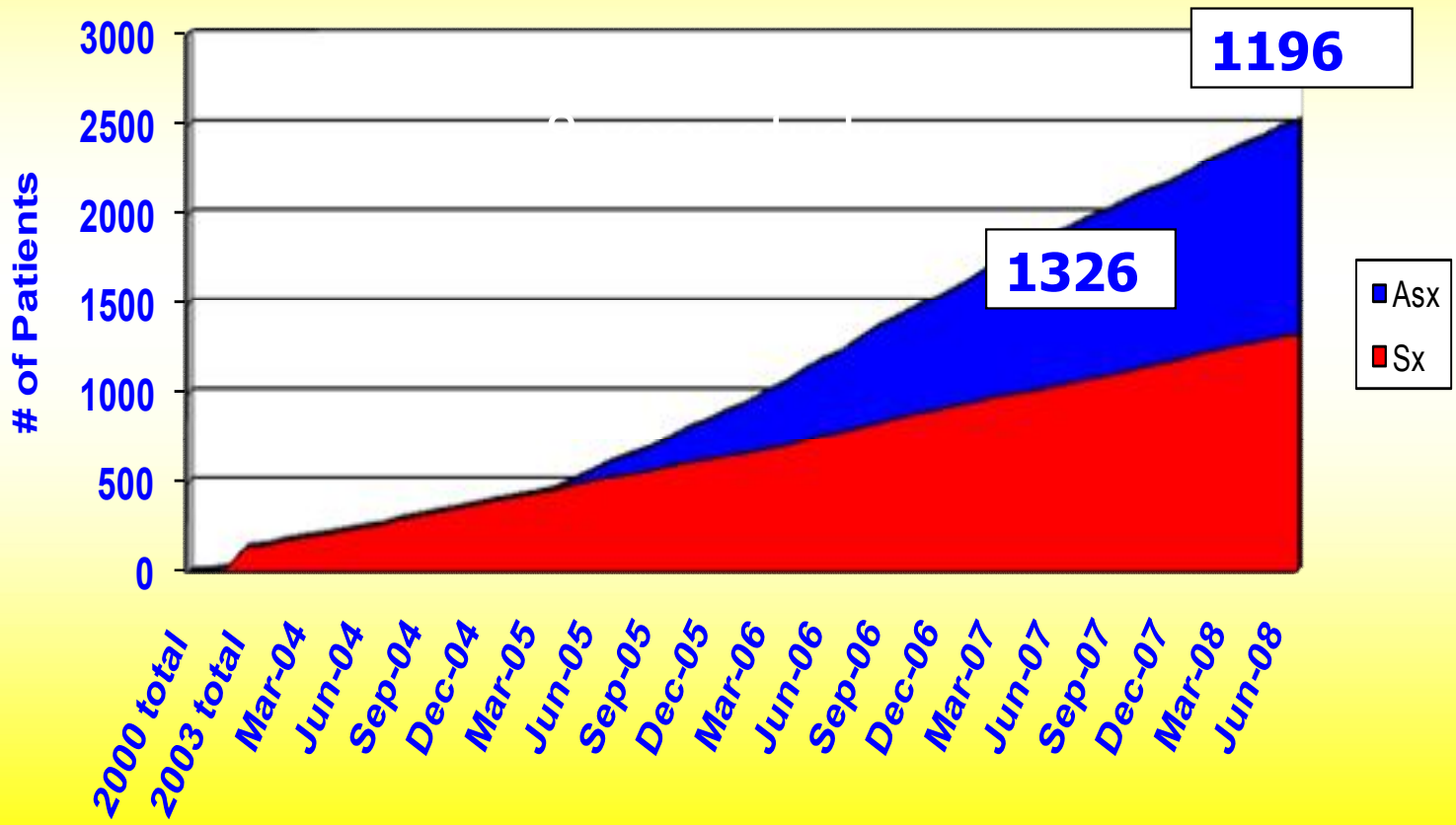
Myocardial infarction

- Combination
  - Cardiac enzyme (CK-MB or troponin) greater than 2 times individual center's ULN
  - Chest pain or equivalent symptoms c/w ischemia **or** ECG evidence of ischemia/infarction
- Not enzyme-only infarcts
- Adjudicated by 2 cardiologists blinded to treatment

Secondary analyses

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

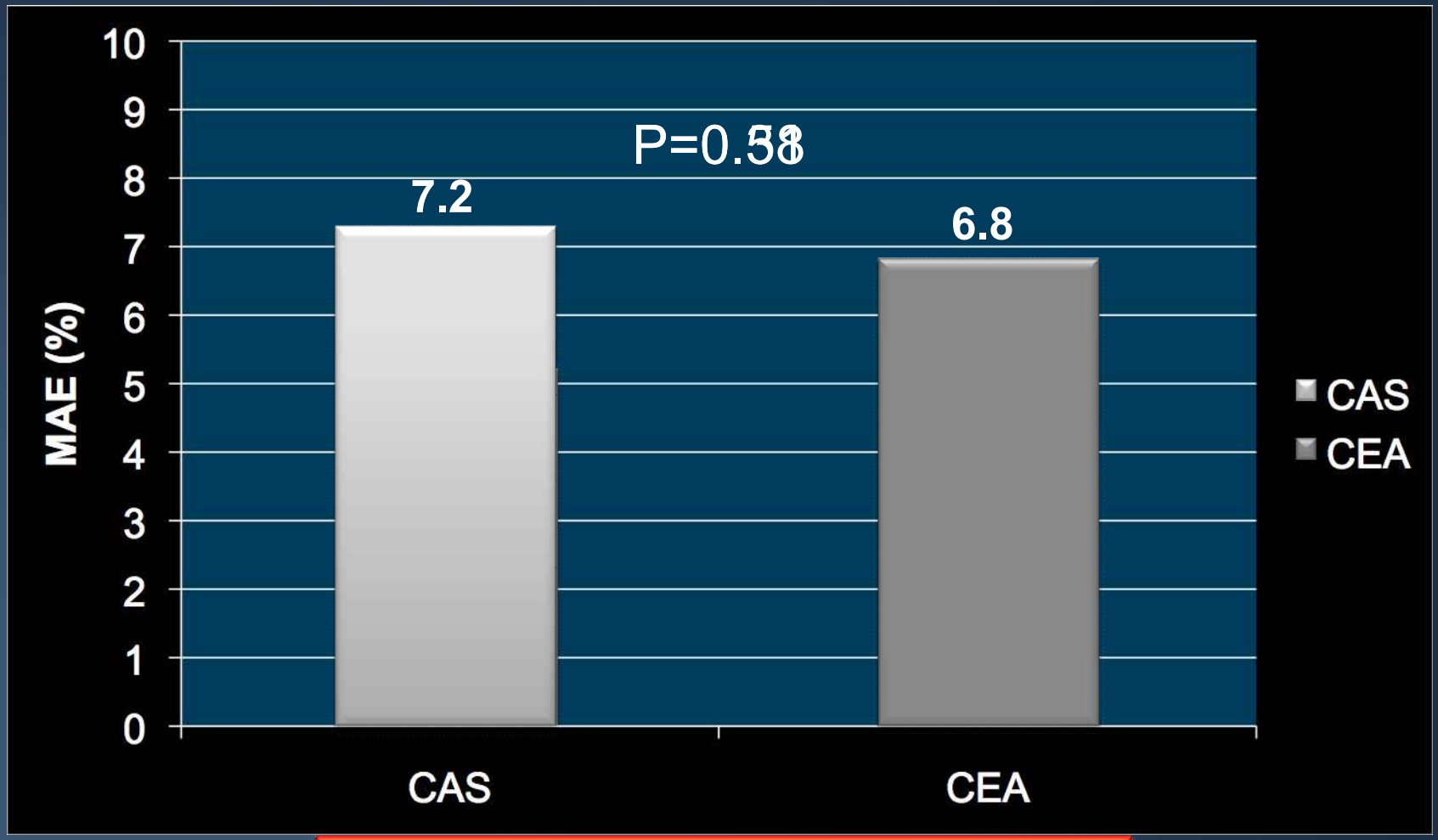
CREST: Final enrollment numbers
8 year study



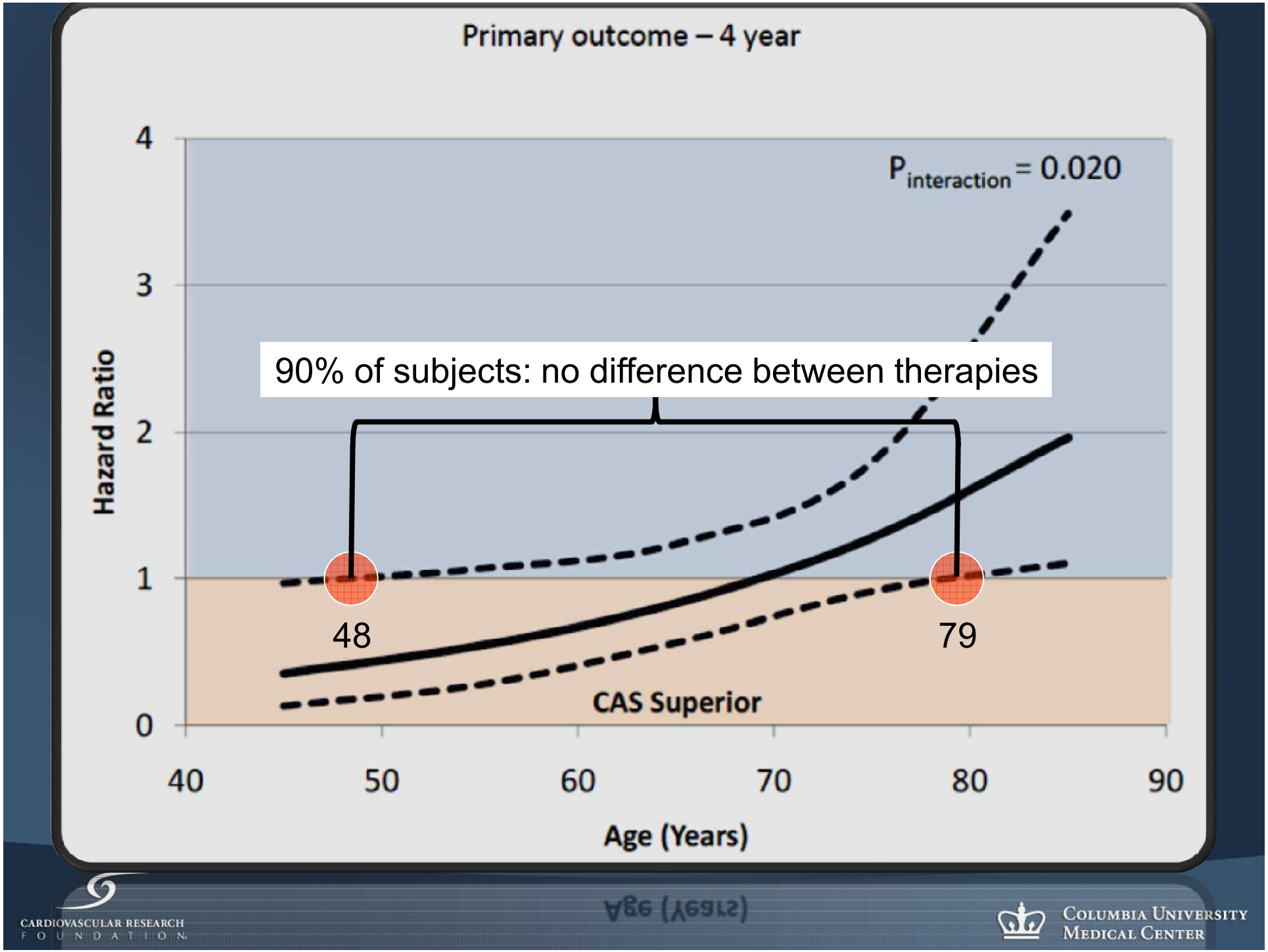
Interaction with the primary endpoint

- No effect detected:
  - Symptomatic status
  - Sex
- Interaction suggested for age

Periprocedural and 4-year results (DSMB)



HR 1.11 95% CI: 0.81-1.51


Primary outcome – 4 year
$P_{interaction}$ = 0.020
90% of subjects: no difference between therapies
48
79
CAS Superior
Hazard Ratio
0
1
2
3
4
40
50
60
70
80
90
Age (Years)

30-day endpoint components

	CAS	CEA	HR	95% CI	P value
Peri-procedural CVA	4.1%	2.3%	1.79	1.14-2.82	0.01
Peri-procedural MI	1.1%	2.3%	0.50	0.26-0.94	0.03
Peri-procedural Major CVA	0.9%	0.7%	1.35	0.54-3.36	0.52
Peri-procedural CN palsies	0.3%	4.8%	0.07	0.02-0.18	<0.0001
Ipsilateral CVA after peri-procedural period ≤4 years	2.0%	2.4%	0.94	0.50-1.76	0.85

Clinical impact of peri-procedural minor strokes

1 year neurological status in patients with minor stroke		
	NIHSS=0 or 1	**NIHSS>1**
ARCHeR 1 and 2	**100%**	**0%**

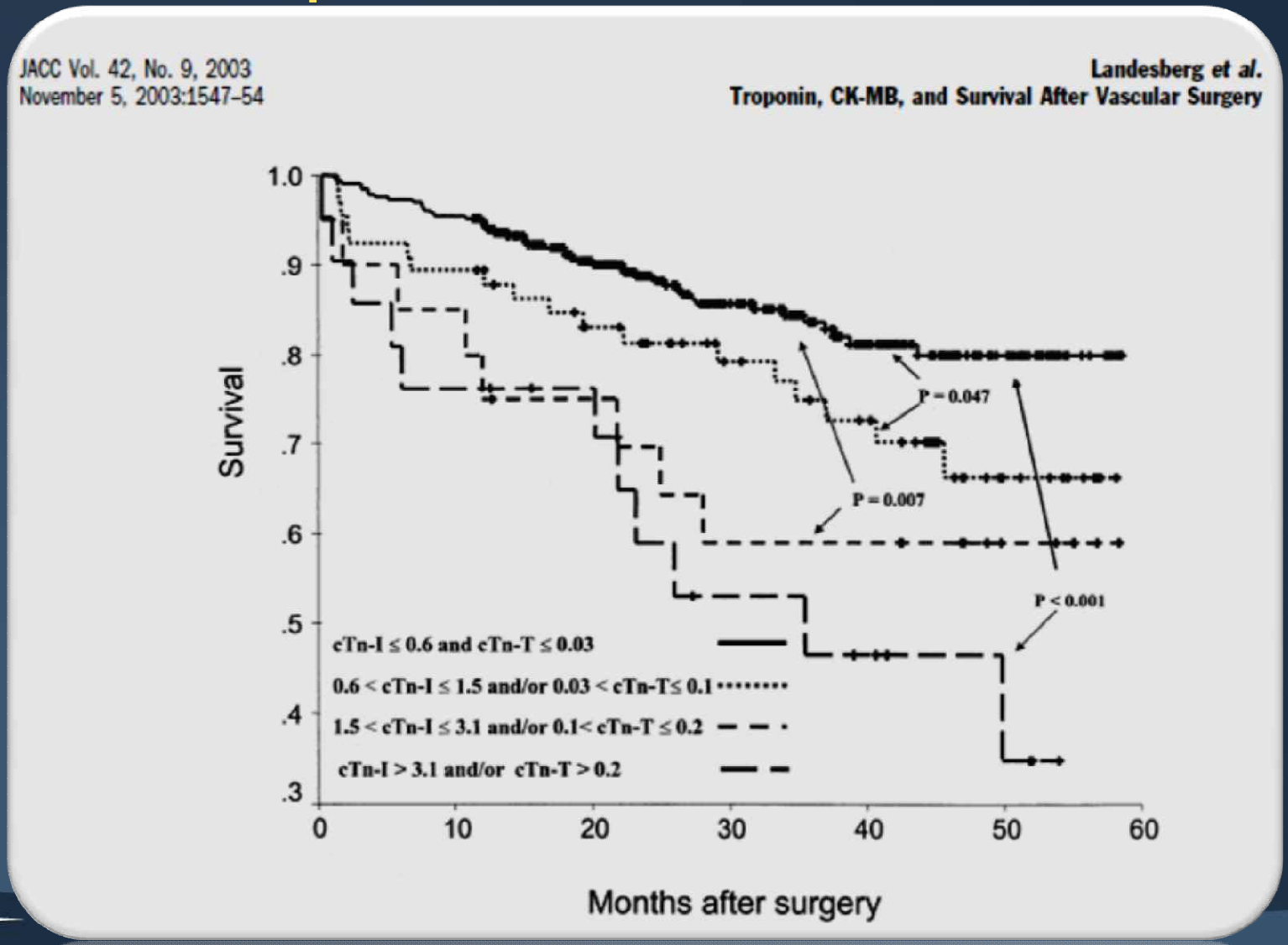
Minor strokes with a negligible clinical impact at 1 year

30-day endpoint components

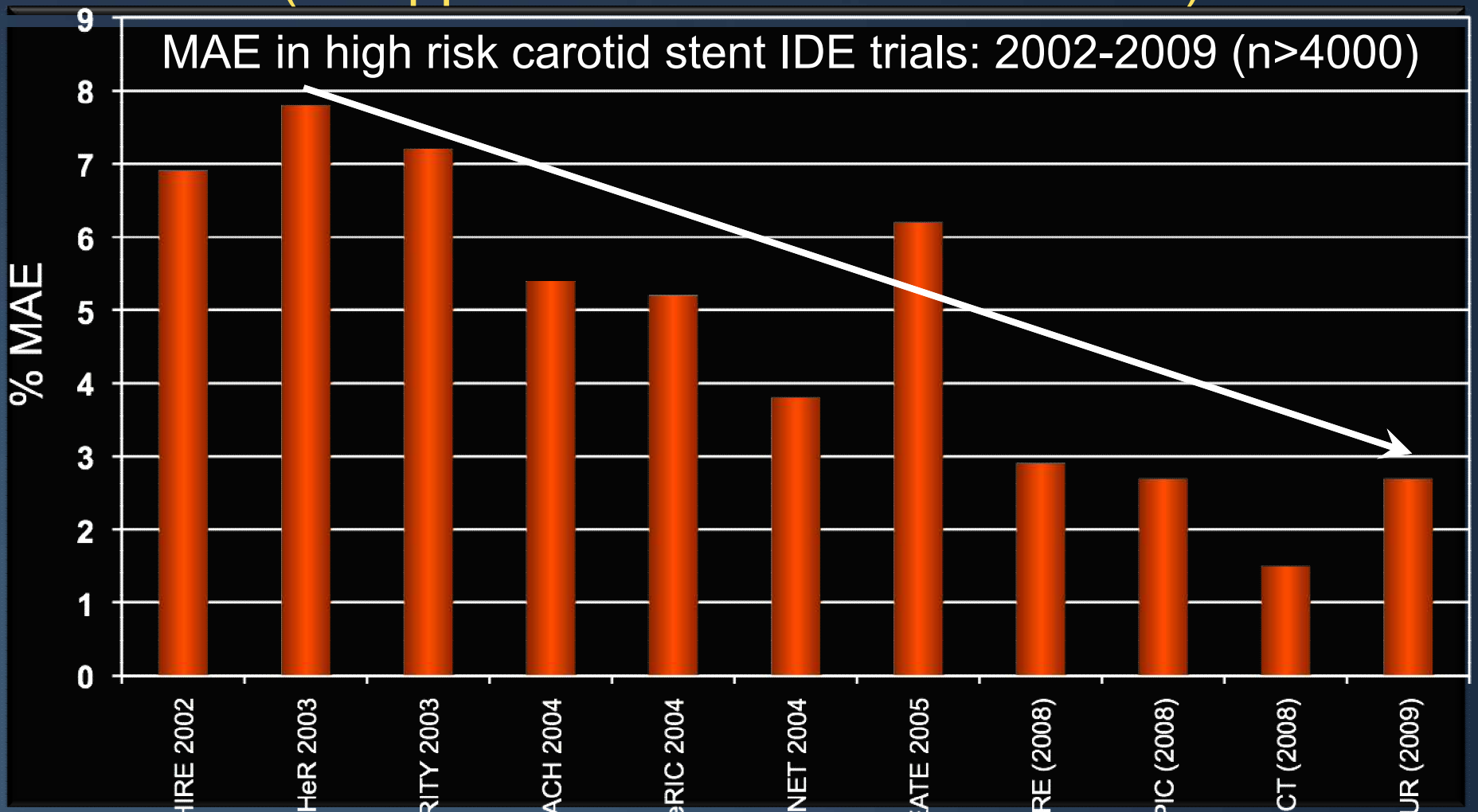
	CAS	CEA	HR	95% CI	P value
Peri-procedural CVA	4.1%	2.3%	1.79	1.14-2.8[illegible]	[illegible]1
Peri-procedural MI	1.1%	2.3%	0.[illegible]	[illegible]6-0.94	0.03
Peri-procedural Major CVA	0.9%		1.35	0.54-3.36	0.52
Peri-procedural CN palsi[illegible]	[illegible]%	4.8%	0.07	0.02-0.18	<0.0001
Ipsilateral [illegible] peri-proc[illegible]riod ≤4 years	2.0%	2.4%	0.94	0.50-1.76	0.85
Combined peri-procedural CN palsies and CVA	4.4%	7.1%			

"I tell my patients that they are at higher risk for stroke with CAS"

MI complicating major vascular surgery predicts late death.



What was happening in CAS during CREST?
11 US FDA approval trials with improving outcomes
(all approved as safe and effective)

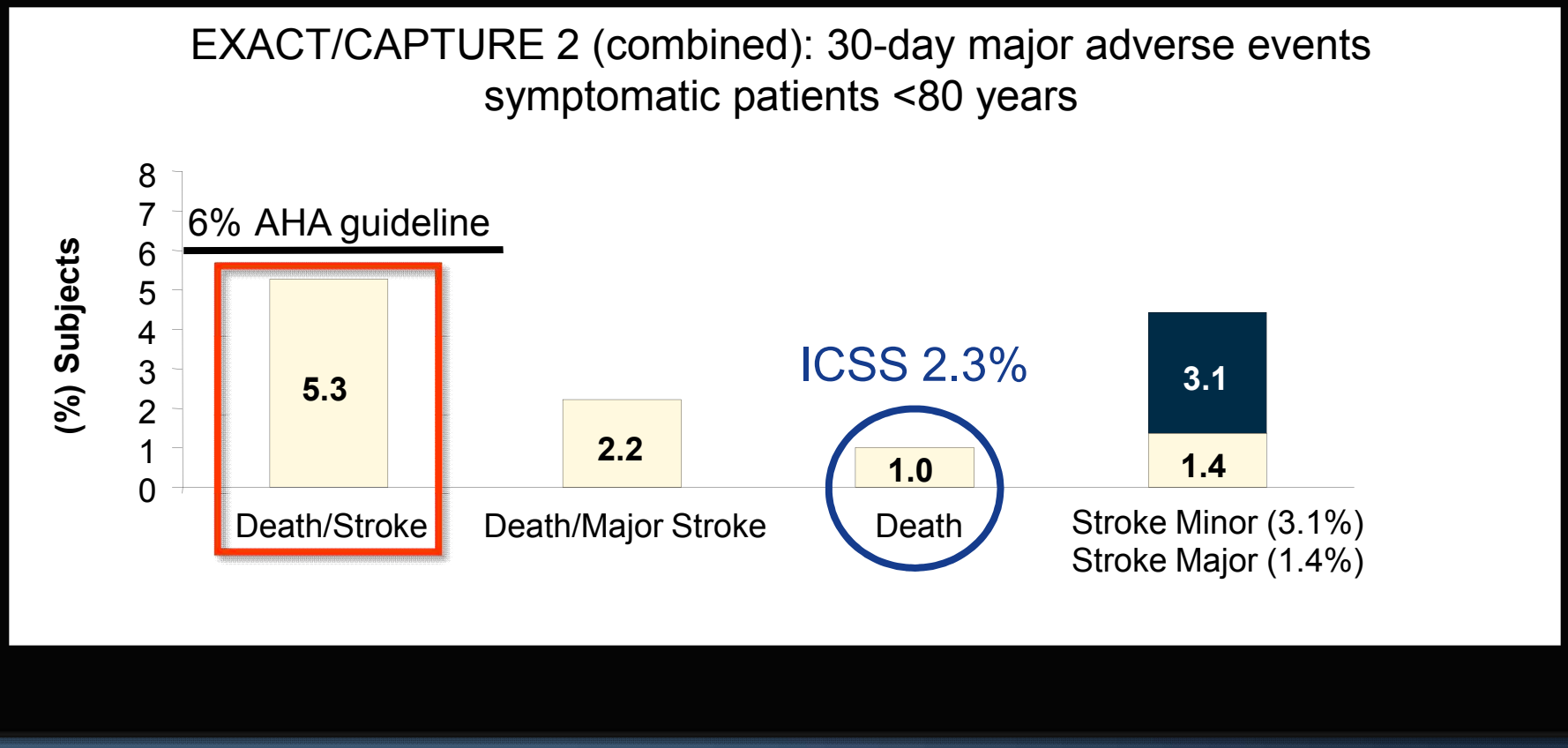


CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Real world outcomes for symptomatic high risk patients: AHA guidelines met or exceeded by >500 operators (not previously demonstrated by CEA)

N=589



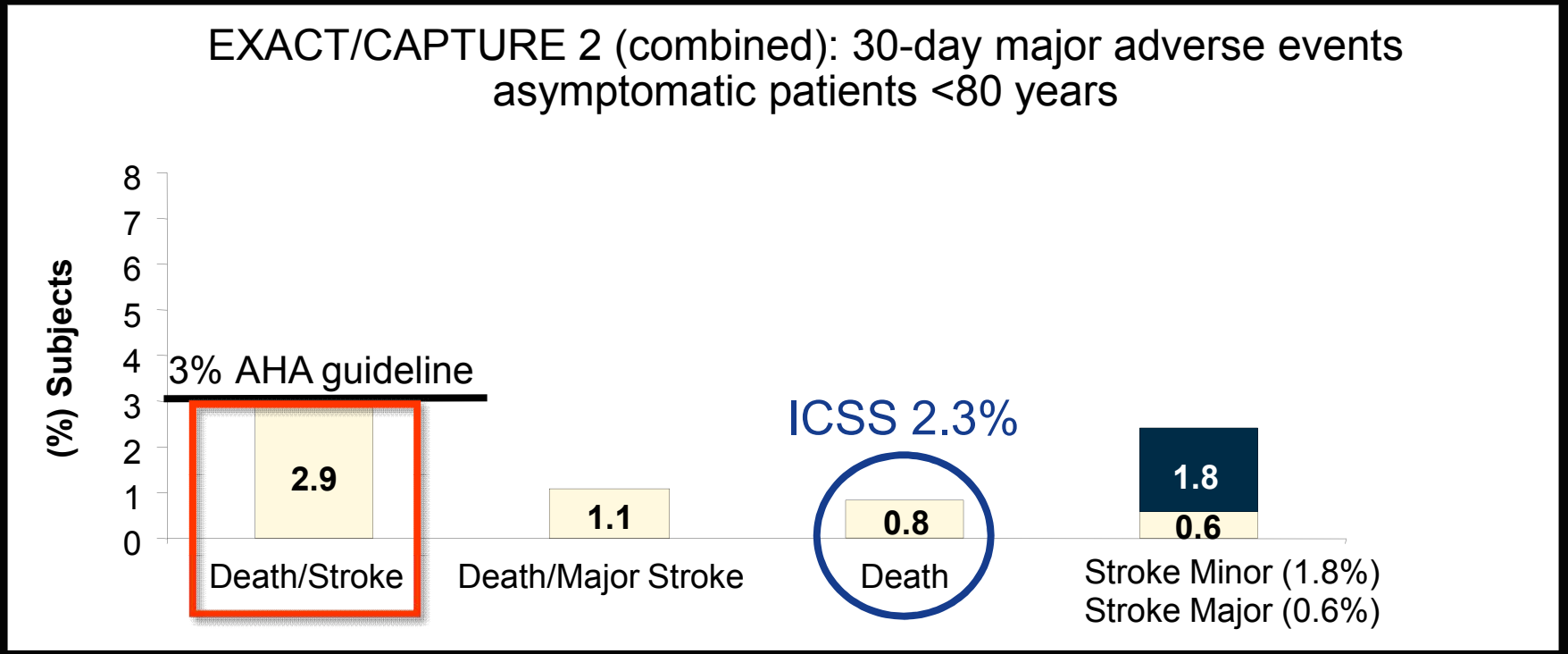
Hierarchical- Includes only the most serious event for each patient and includes only each patient first occurrence of each event.

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Real world outcomes for asymptomatic high risk patients: AHA guidelines met or exceeded by >500 operators (not previously demonstrated by CEA)

N=4282

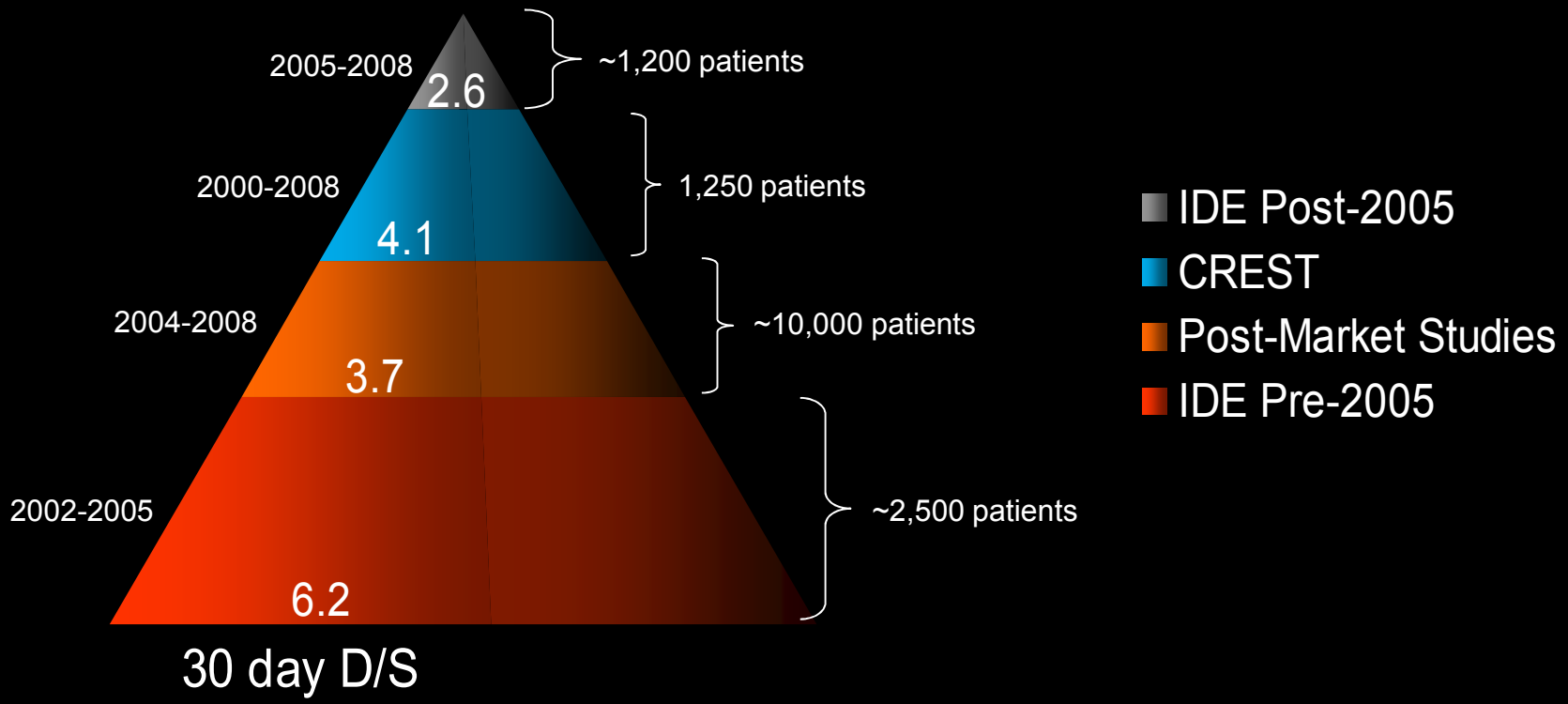


Hierarchical- Includes only the most serious event for each patient and includes only each patient first occurrence of each event.

Remarkable data for latest trials: *high-risk patients*
N>1000

- Lumen/Invatec Fibernet (2008)
  - 30 day MAE: ***3.0%***
- WL Gore Flow Reversal System (2008)
  - 30 day MAE: ***2.9%***
- Abbott Vascular Gen V Emboshield (2008)
  - 30 day MAE: ***1.8%***
- Invatec ARMOUR (2009)
  - 30 day MAE: ***2.7%***

CREST results fit well into the progression of CAS outcome improvement in past decade



CREST summary

- 10 year, 80 million dollar NINDS/NIH study examining an important public health question: stroke prevention therapy
  - The essence of “evidenced-based medicine”
- Two very safe and effective therapies for stroke prevention in carotid bifurcation disease
  - Lowest CEA event rate ever seen in a prospective multicenter trial, matched by CAS
- Any differences in the subsets of the composite endpoint are balanced and represent opportunities for improvement, and do not otherwise differentiate the therapies
  - Morbidity of procedures is captured by both the composite endpoint as well as the CN injury

CREST summary (continued)

- The results of CREST establish both CAS and CEA as very safe and effective choices for patients and their physicians
  - The CREST outcomes represent a midpoint on the continuum of CAS outcomes, with multiple recent IDE trial data demonstrating even better outcomes.
- Given the trial conduct and operator inexperience that characterize much of the European data, CREST represents the largest, most rigorous and complete examination of the two therapies to date
- *Ultimately, these are not mutually exclusive therapies, but complimentary. The wise physician will advise patients accordingly.*

Stroke

- Acute neurologic ischemic event of at least 24 hours duration with focal signs and symptoms
- Adjudicated by at least 2 neurologists blinded to treatment

Major eligibility criteria

- Conventional (not low surgical risk) patients with carotid stenosis
  - Symptomatic
    - ≥50% by angiography
    - ≥70% by ultrasound, or
    - >70% by CTA/MRA if U/S is 50%-69%
  - Asymptomatic
    - ≥60% by angiography
    - ≥70% by ultrasound, or
    - >80% by CTA/MRA if ultrasound is 50-69%

Major eligibility criteria: selected exclusions

- Evolving stroke or major stroke likely to confound study endpoints
- Chronic atrial fibrillation
- MI within the previous 30 days
- Unstable angina

Baseline patient characteristics

	CAS (N=1262)	CEA (N=1240)
Age	69	69
Female (%)	36	34
Asymptomatic (%)	47	47
Hypertension (%)	86	86
Diabetes (%)	30	30
Dyslipidemia (%)	82	85
Current smoker (%)	26	26
Cardiovascular disease (%)	41	43
Systolic BP (mean, mmHG)	142	141
% stenosis ≥70%	85	87
Days from qualifying event (for symptomatic subjects)	20	25

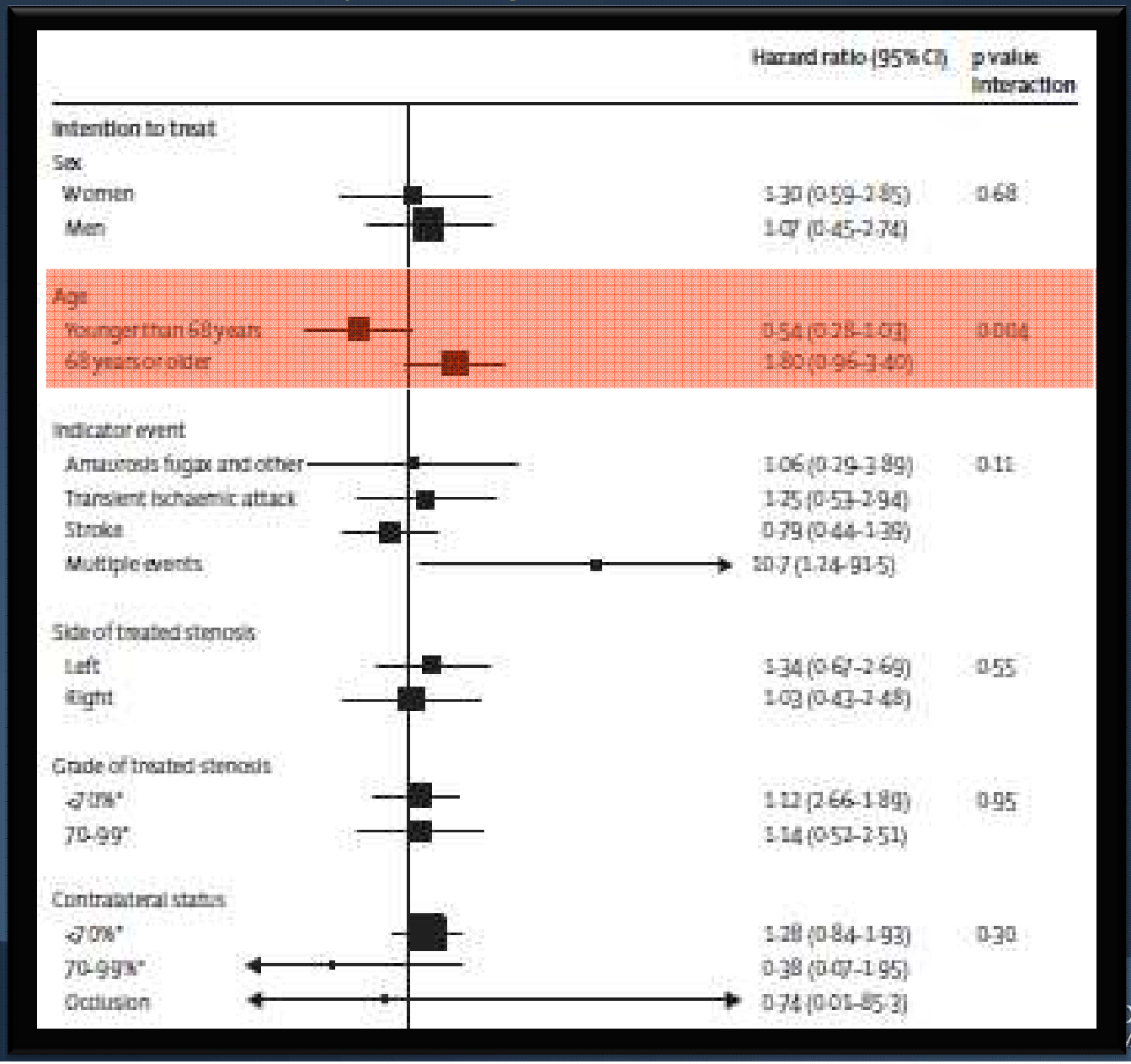
SPACE shows CAS better than CEA in younger patients

	CAS			CEA		
	n	Events (rate)*	p†	n	Events (rate)*	p†
Age (years)						
≤62	138	3 (2·2%)	0·001 (trend 0·0003)	135	11 (8·1%)	0·417 (trend 0·401)
>62–68	141	4 (2·8%)		141	6 (4·3%)	
>68–75	167	18 (10·8%)		127	5 (3·9%)	
>75	127	14 (11·0%)		160	9 (5·6%)	
Sex						
Female	157	13 (8·3%)	0·457	162	9 (5·6%)	1·0
Male	416	26 (6·3%)		401	22 (5·5%)	
Qualifying event						
Ocular	91	3 (3·3%)	0·57	87	3 (3·4%)	0·358
TIA	169	14 (8·3%)		173	9 (5·2%)	
Stroke	257	17 (6·6%)		241	18 (7·5%)	
Other	15	1 (6·7%)		7	0 (0·0%)	
Multiple	41	4 (9·8%)		55	1 (1·8%)	
Contralateral stenosis						
No	535	38 (7·1%)	0·503	524	26 (5·0%)	0·072
Yes	38	1 (2·6%)		39	5 (12·8%)	
Side of intervention						
Left	300	18 (6·0%)	0·507	297	18 (6·1%)	0·583
Right	273	21 (7·7%)		266	13 (4·9%)	
Stenosis grade						
<60%	91	8 (8·8%)	0·20 (trend 0·897)	95	2 (2·1%)	0·377 (trend 0·050)
60–69%	123	4 (3·3%)		124	5 (4·0%)	
70–79%	57	7 (12·3%)		57	4 (7·0%)	
80–89%	195	14 (7·2%)		183	12 (6·6%)	

CARDIOVASCULA
FOUND

UNIVERSITY
CENTER

SPACE shows CAS better than CEA in younger patients

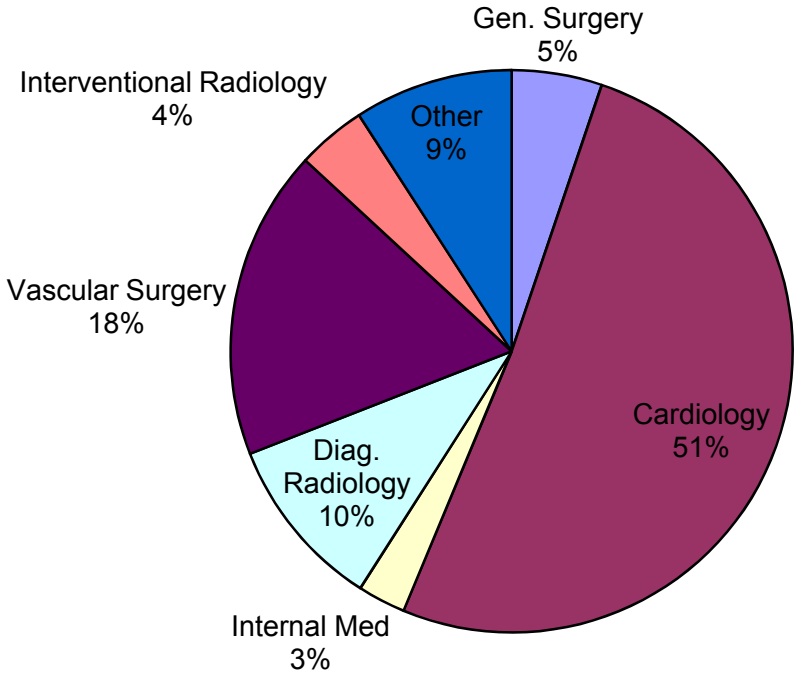


CARDIOVASCULAR RESEARCH FOUNDATION

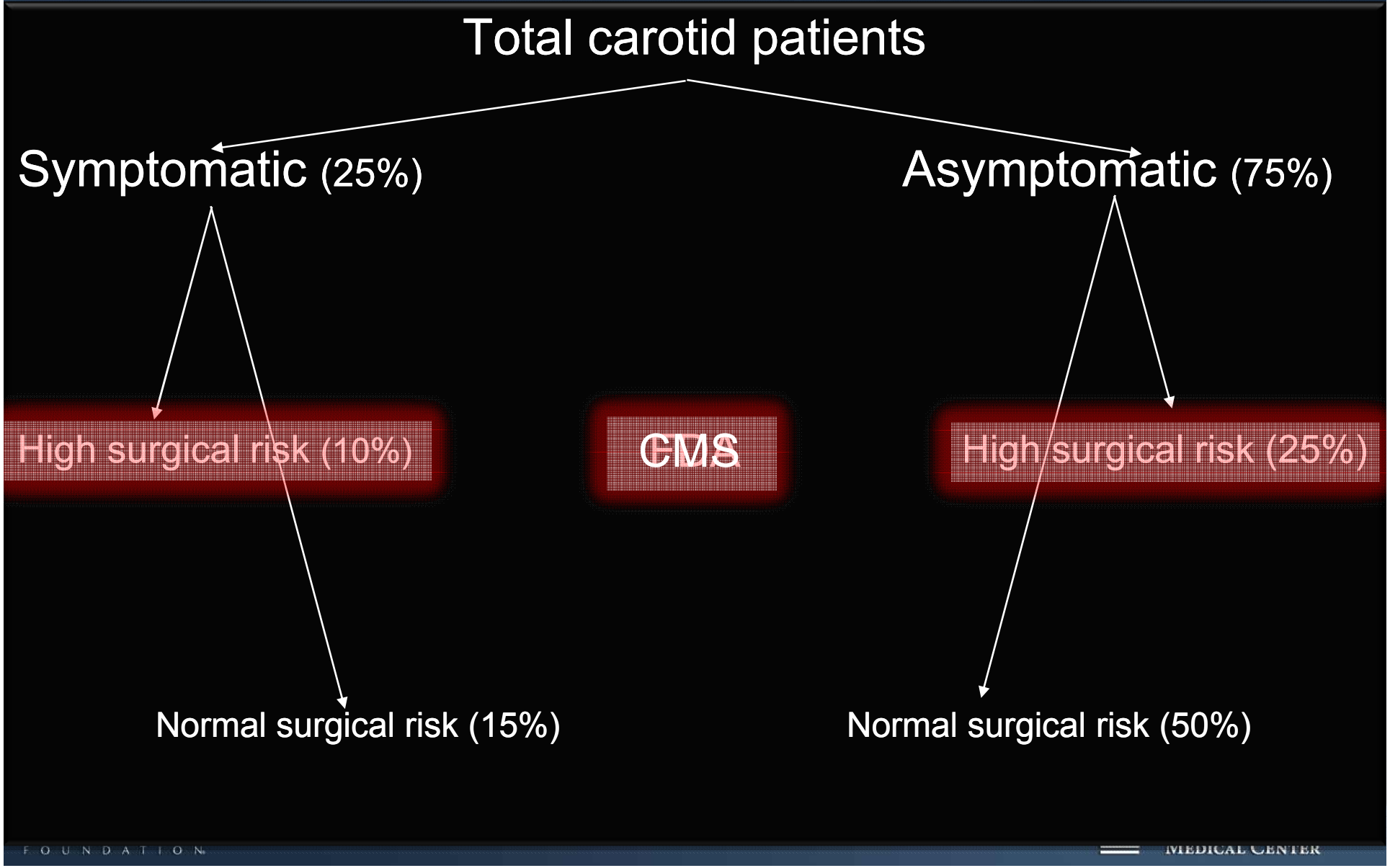
COLUMBIA UNIVERSITY MEDICAL CENTER

Specialty activity in CAS

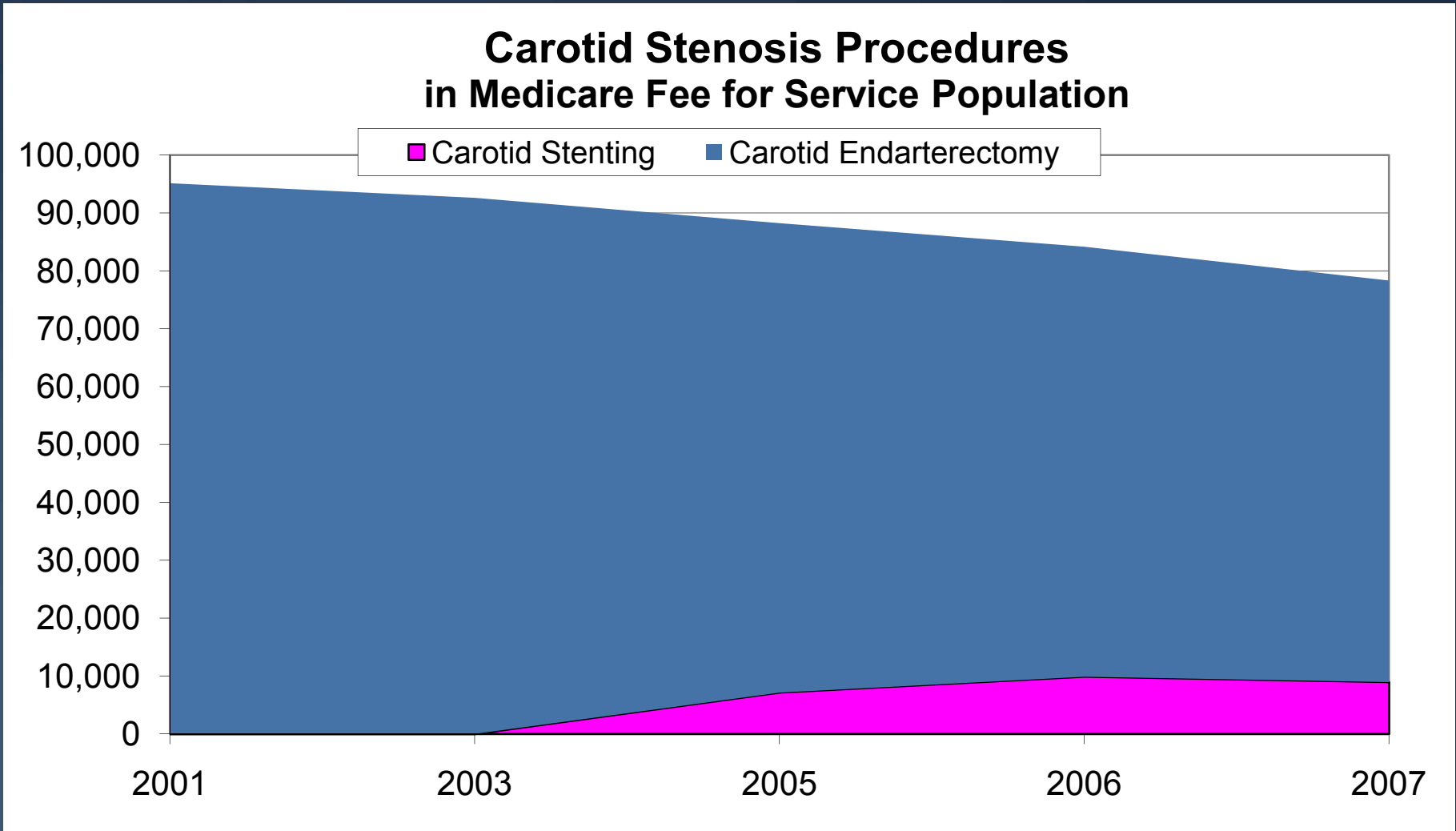
Medicare Allowed Procedures for Carotid Stenting in 2007 (CPT Code 37215)



CMS limits patient access to high risk carotid stenting



US CAS volumes flat to declining

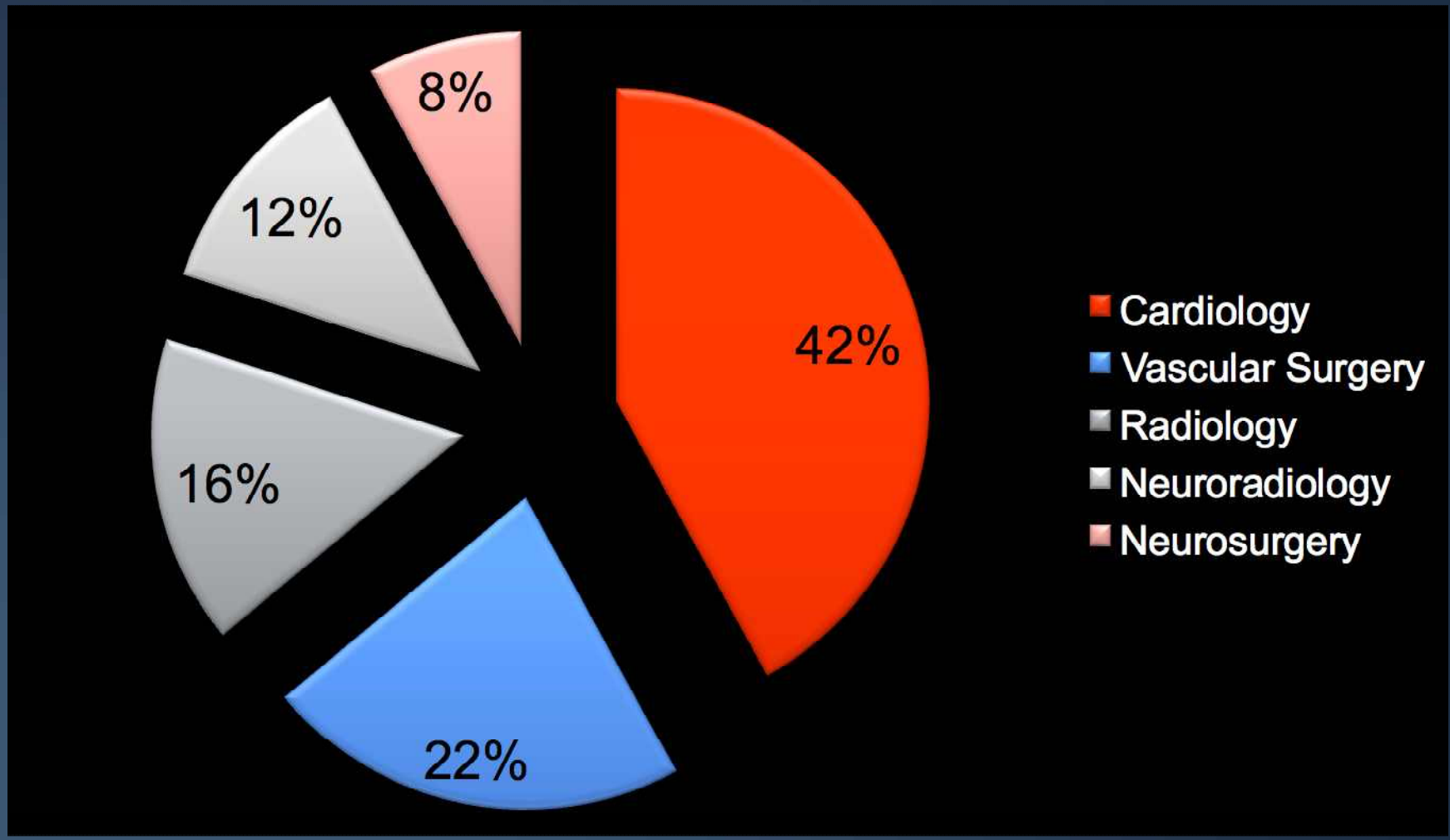


So what ***is*** the current reality?

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

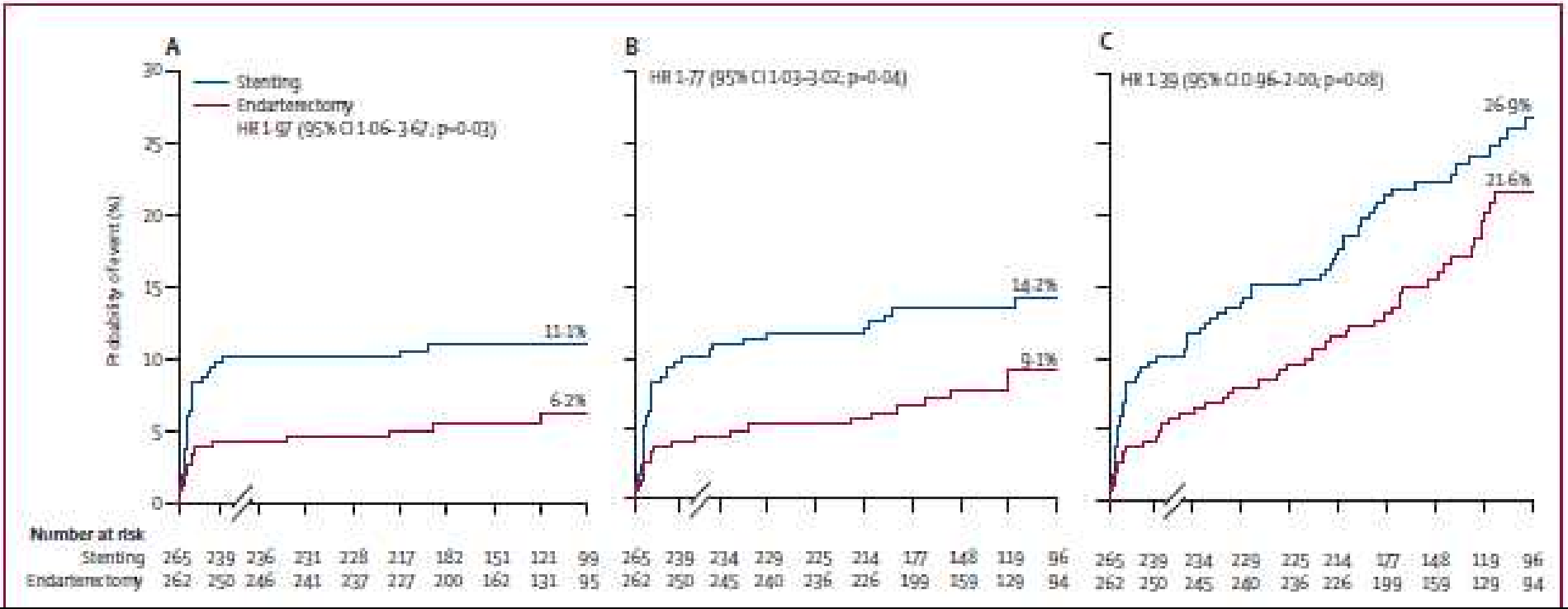
CREST lead-in enrollment by specialty



Stroke prevention efficacy equal between CEA and CAS

EVA-3S: 4-year outcomes

Any ipsilateral stroke | Any stroke | Any stroke or death

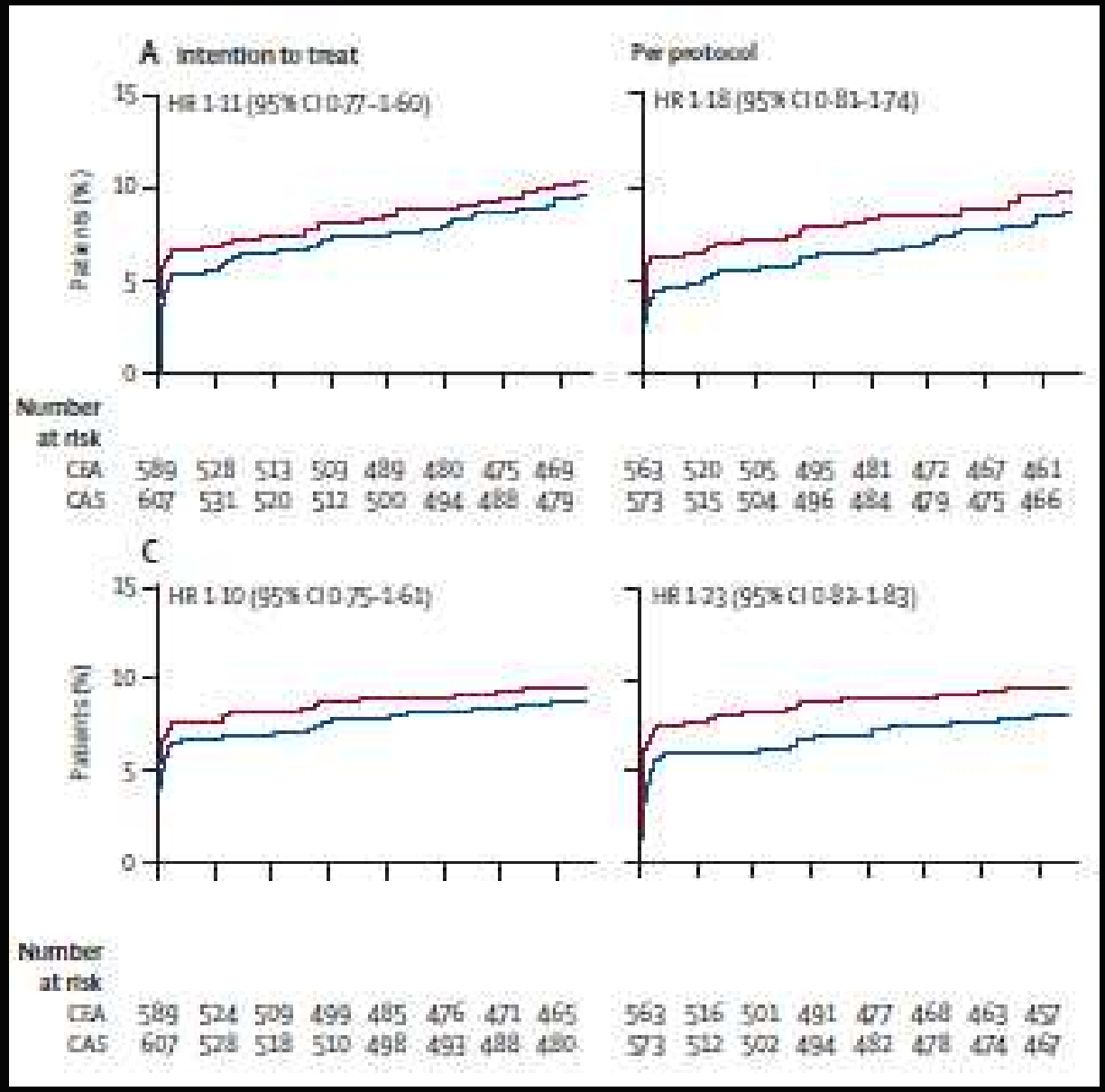


CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Stroke prevention efficacy equal between CEA and CAS

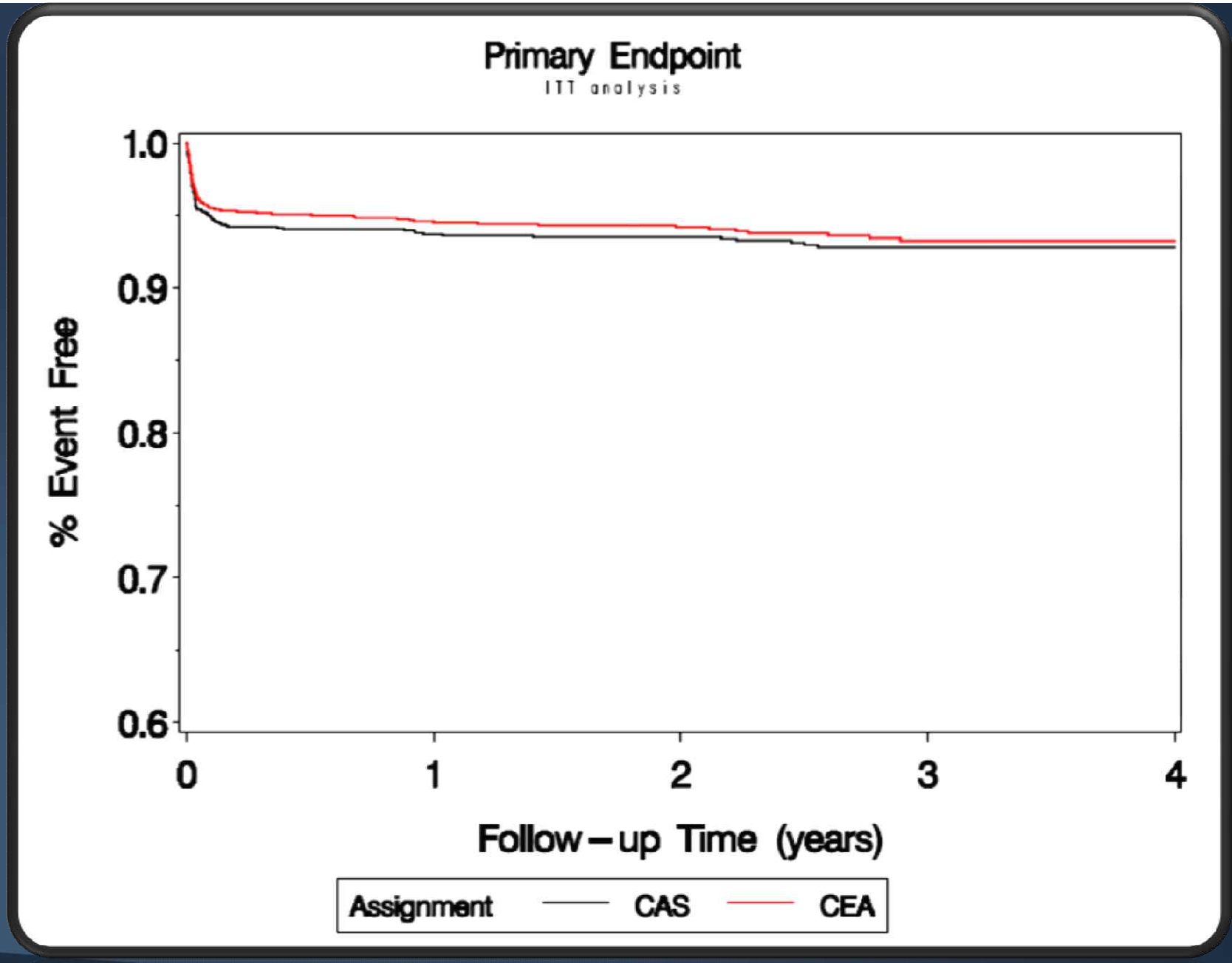
SPACE: K-M plots of 2-year outcomes



Ipsilateral stroke and vascular death

30-day stroke/death plus ipsilateral stroke to 2 years

Columbia University Medical Center


Primary Endpoint
ITT analysis
1.0
0.9
0.8
0.7
0.6
% Event Free
0
1
2
3
4
Follow – up Time (years)
Assignment
CAS
CEA