Carotid artery stenting in the US

Clinical outcomes and new data analysis

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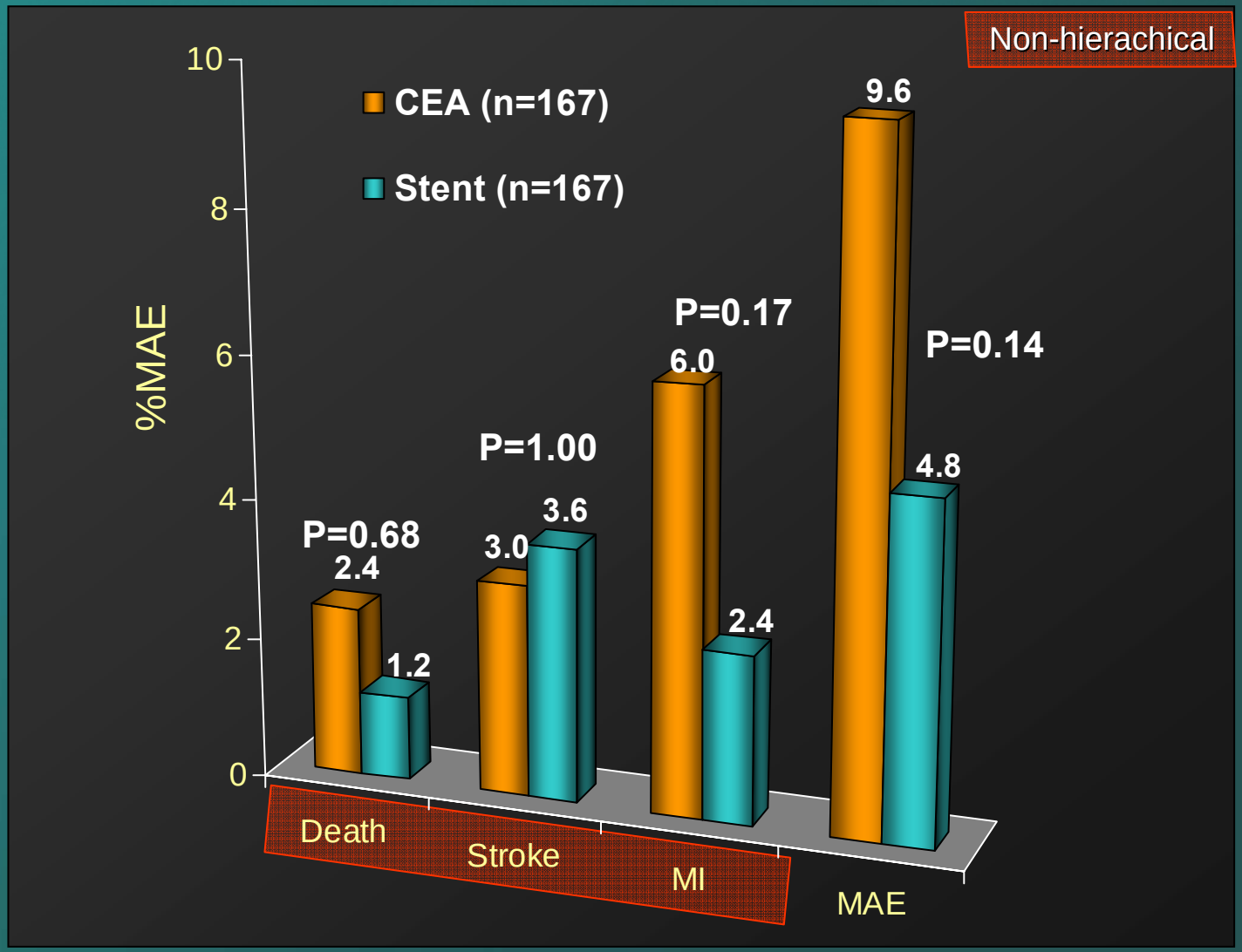
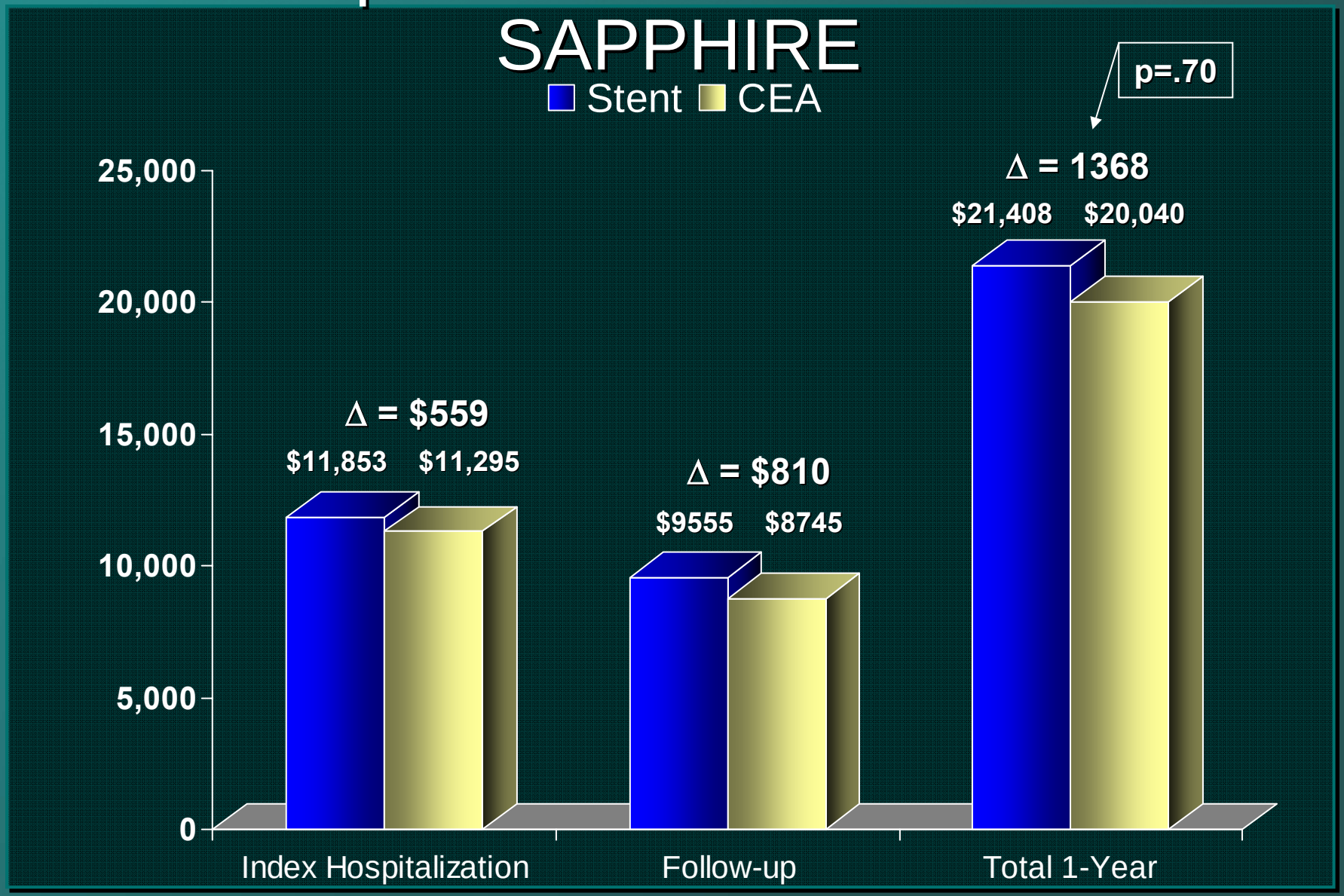
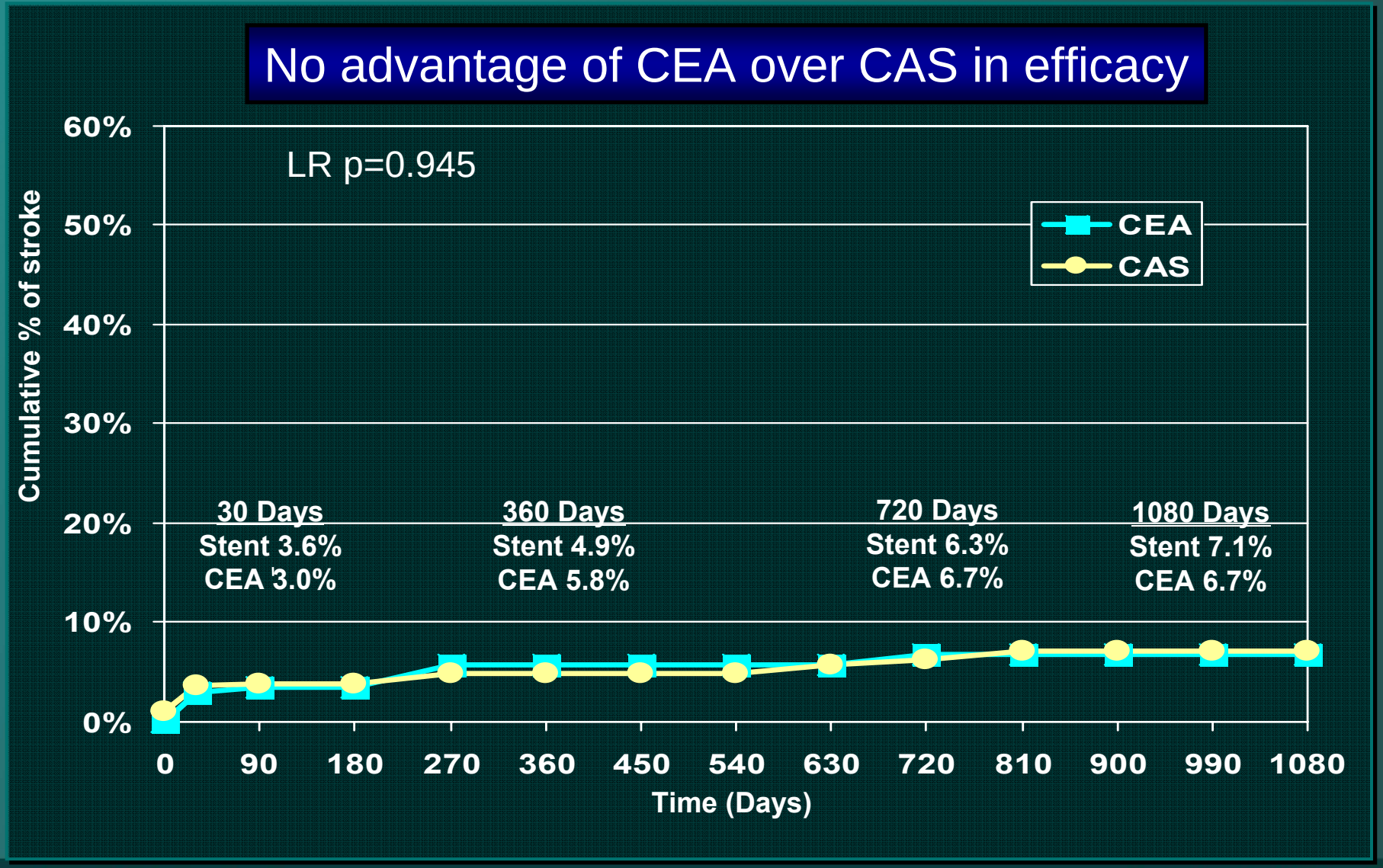
SAPPHIRE: randomized patients
30 day outcomes



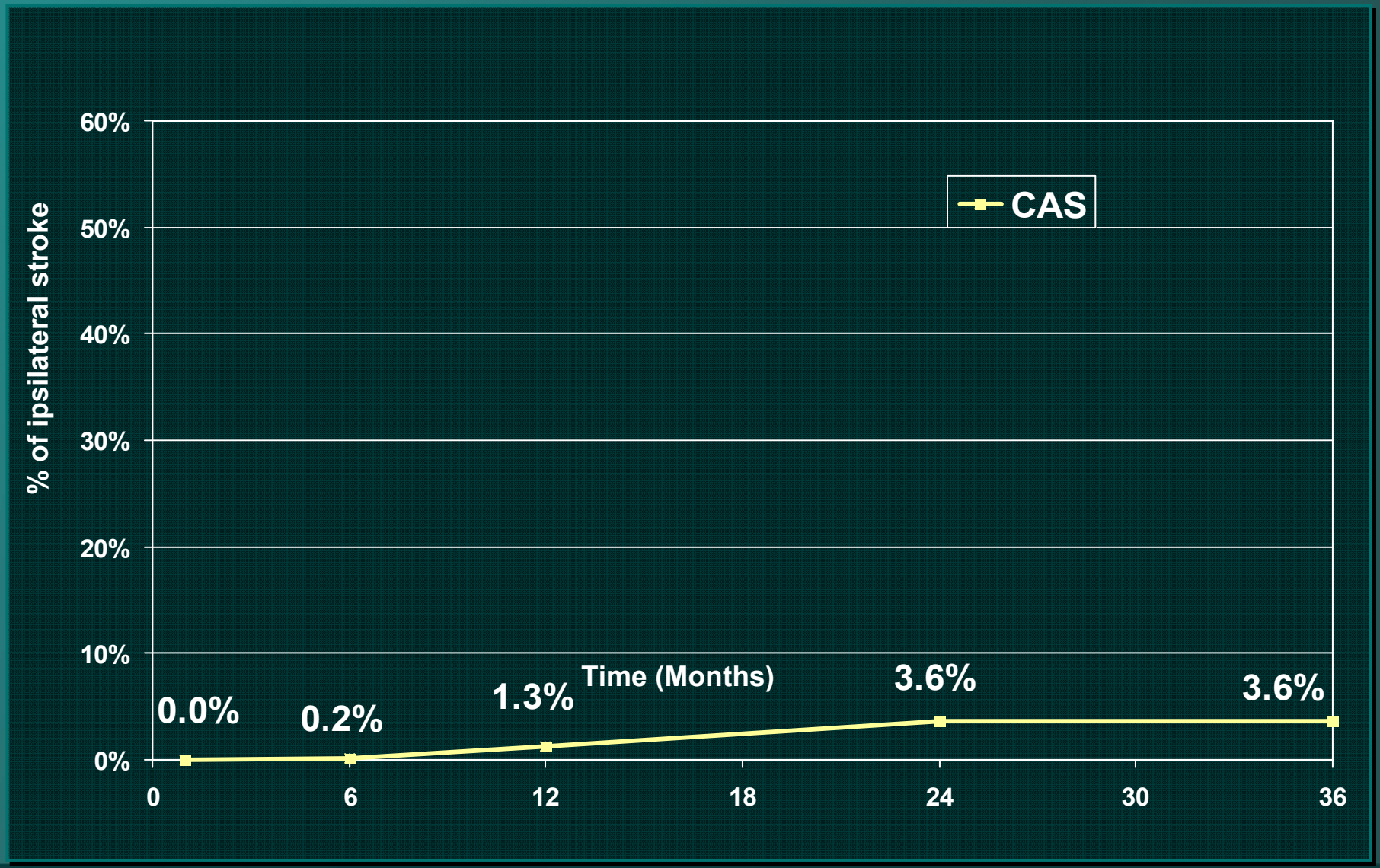
Cost equivalence of CAS and CEA



SAPPHIRE Randomized Cohorts: CEA and CAS
30 day stroke and ipsilateral stroke 31-1080 days



ARCHeR registry patients: CAS only
Ipsilateral stroke 31-1080 days



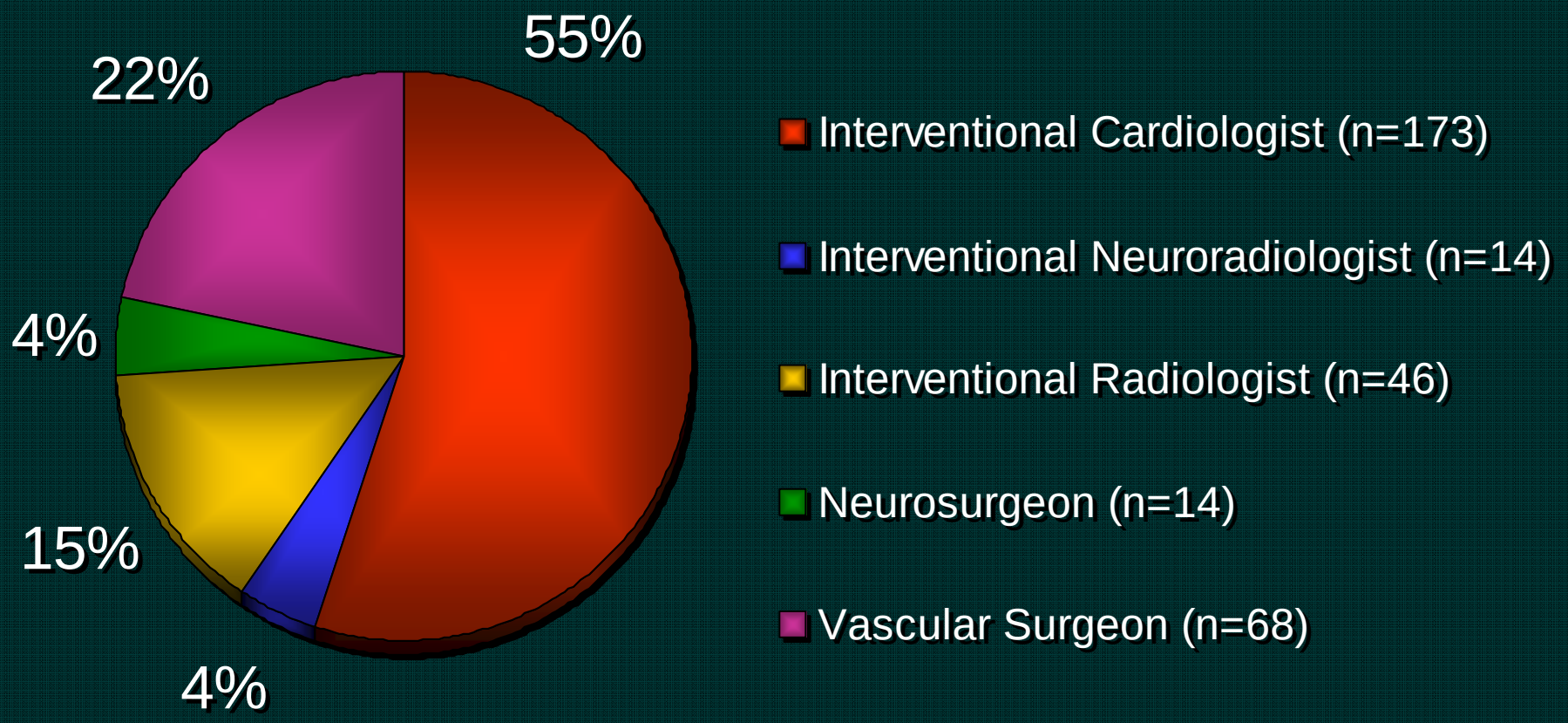
CAPTURE: Purpose of the trial

- FDA-mandated post-approval trial
- **Sponsor:** Guidant Corporation

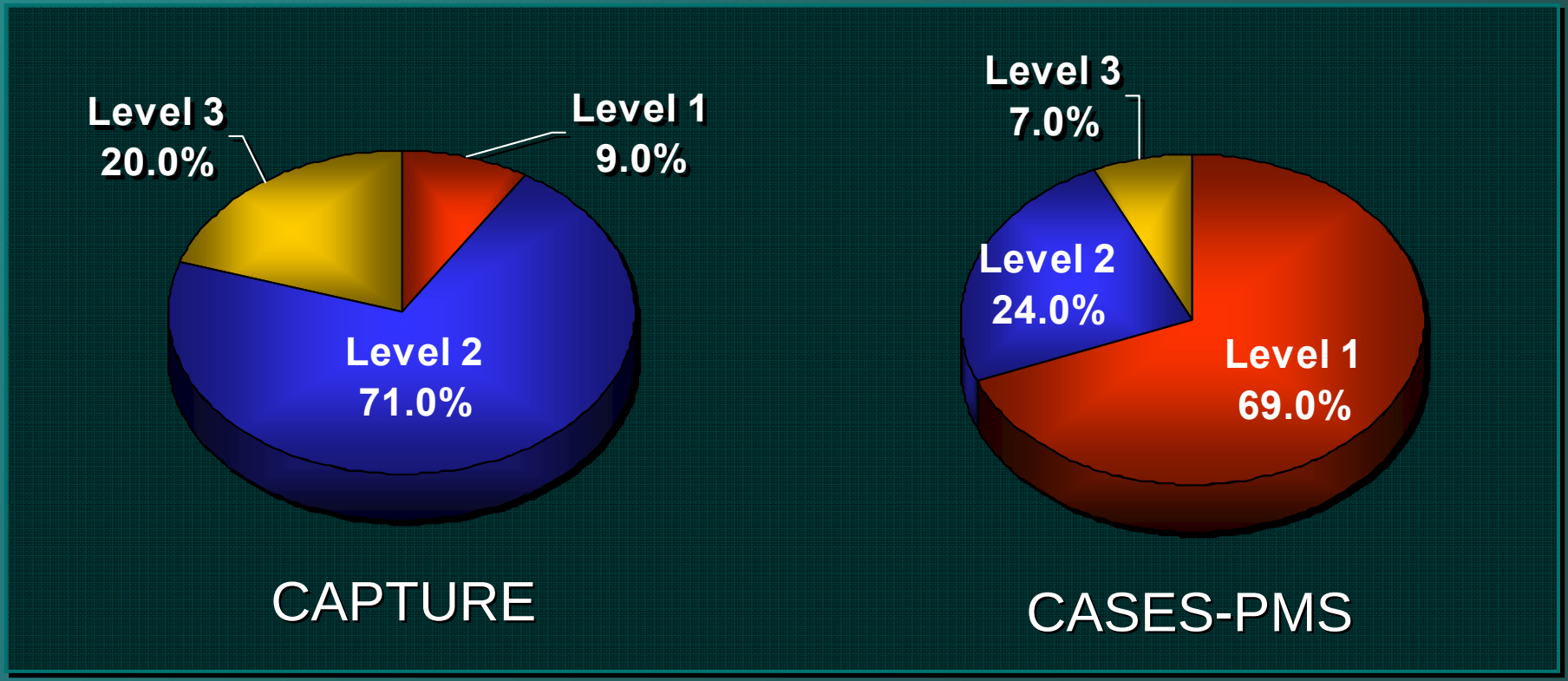
- **Purpose:**
  - Determine whether CAS can be performed safely by physicians with varying levels of experience
  - Identify rare or unanticipated device-related events
  - Evaluate the adequacy of Guidant's physician training program

- **Analysis Cohort:**
  - Enrollment and follow-up continues in CAPTURE
  - 3500 patient cohort analyzed
  - 137 hospitals participating

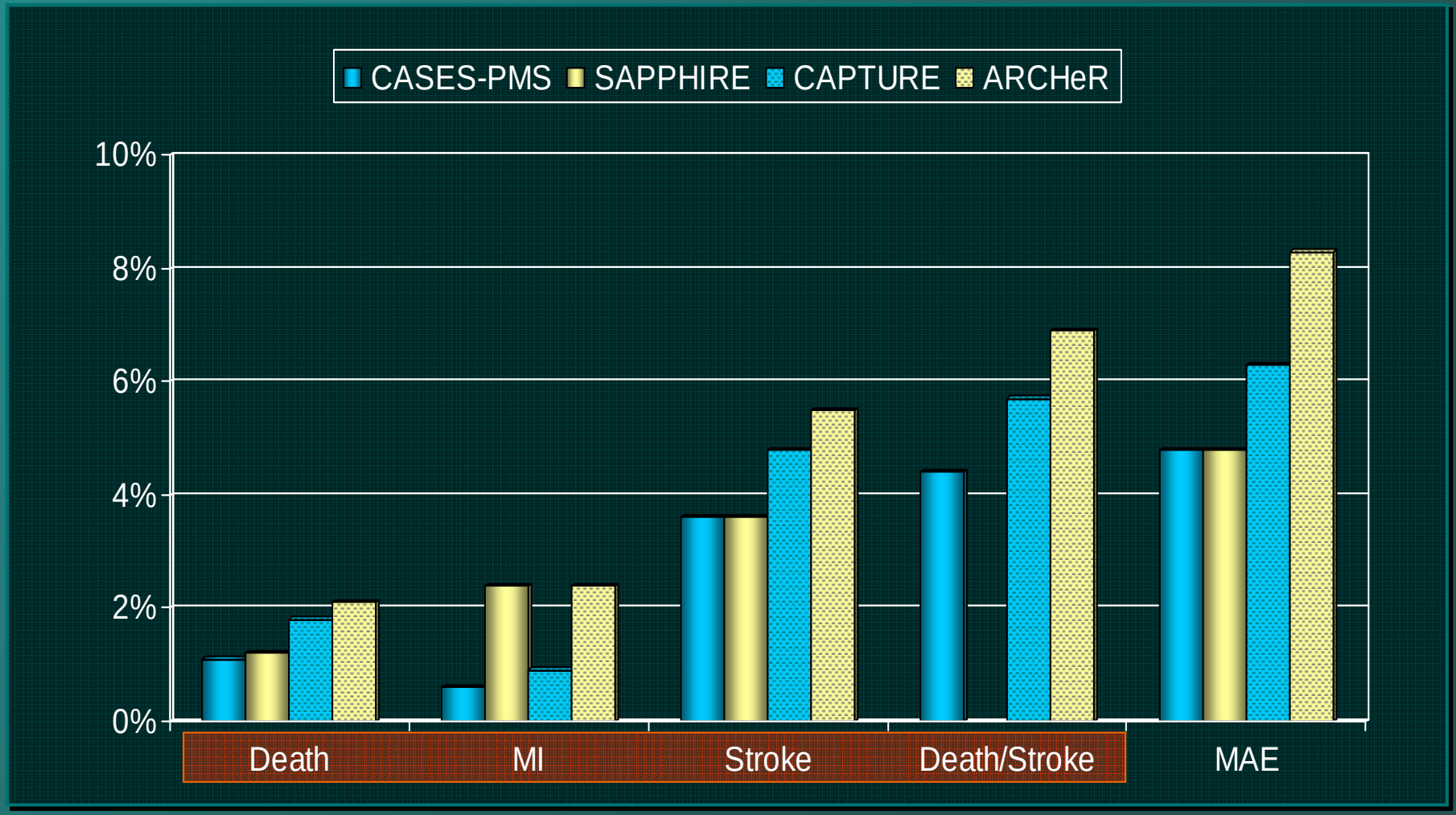
CAPTURE: Physician specialty mix



Physician prior experience

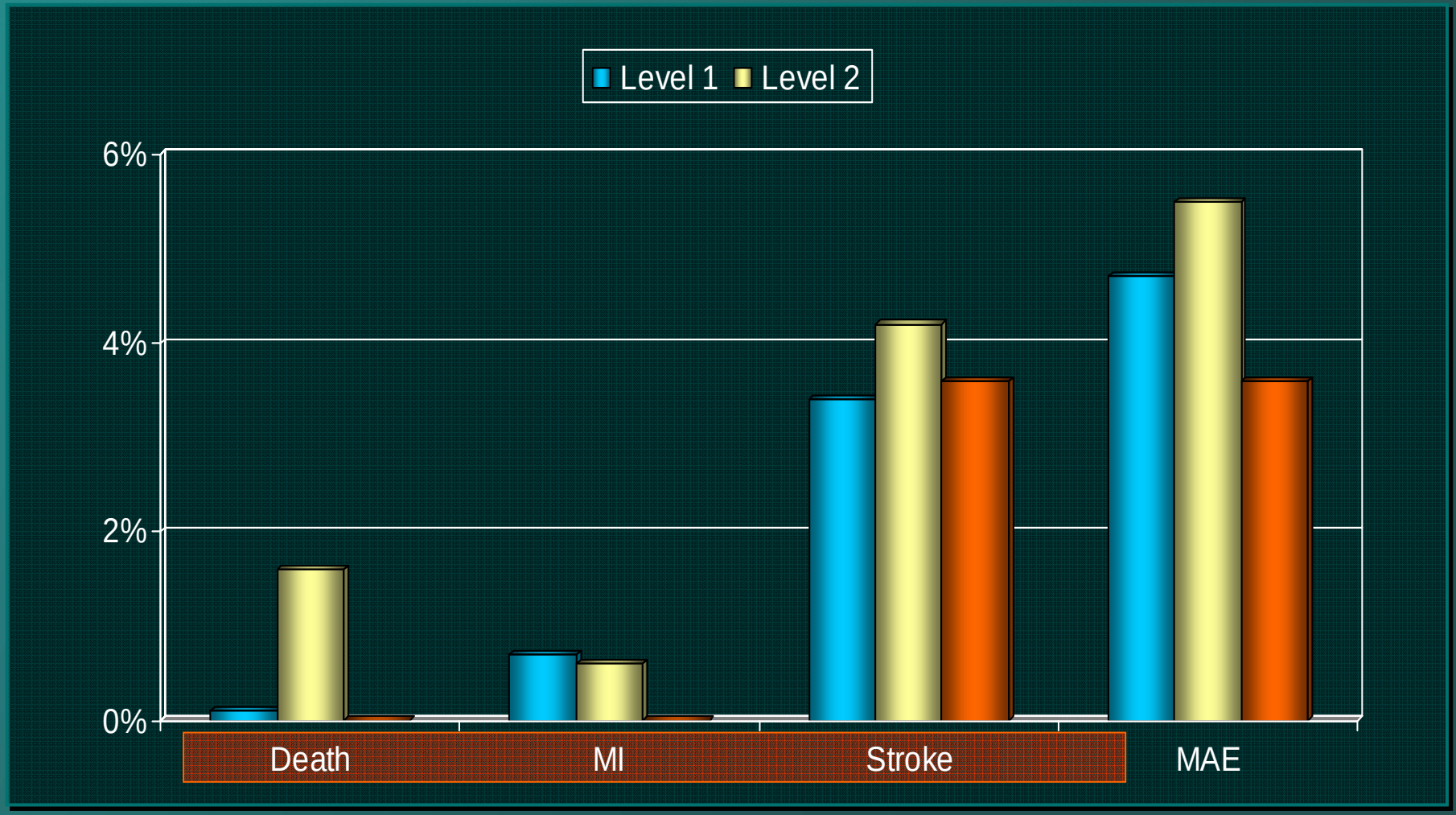


CASES-PMS and CAPTURE:
30 day outcomes compared to pivotal trials



Non-hierarchical

CASES-PMS:
30 day outcomes by operator status



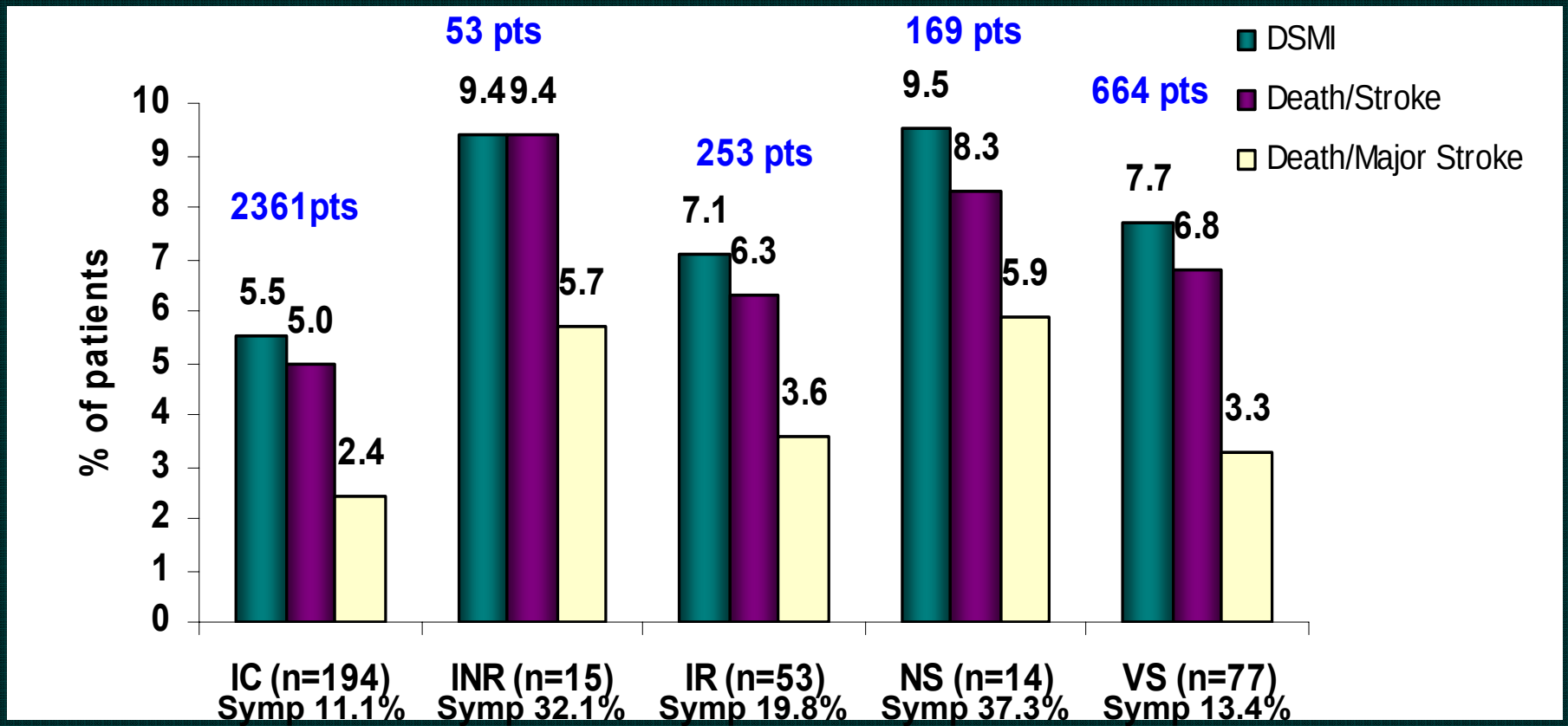
Non-hierarchical

CAPTURE 3500:
30 day outcomes by operator status

CAPTURE (N=3500)	High (n=282 pts)	Medium (n=2377 pts)	Low (n=841 pts)
Death, Stroke and MI*	5.3%	6.0%	7.4%
All Stroke and Death*	4.6%	5.4%	6.9%
Major Stroke and Death*	1.1%	2.9%	3.4%
Death	0.0%	1.8%	2.3%
All Stroke	4.6%	4.5%	5.7%
Major Stroke	1.1%	2.0%	2.3%
Minor Stroke	3.5%	2.6%	3.6%
MI	0.7%	1.0%	0.8%

* Hierarchical – Includes only the most serious event for each patient and includes only each patient's first occurrence of each event

CAPTURE 3500: Outcomes by physician specialty



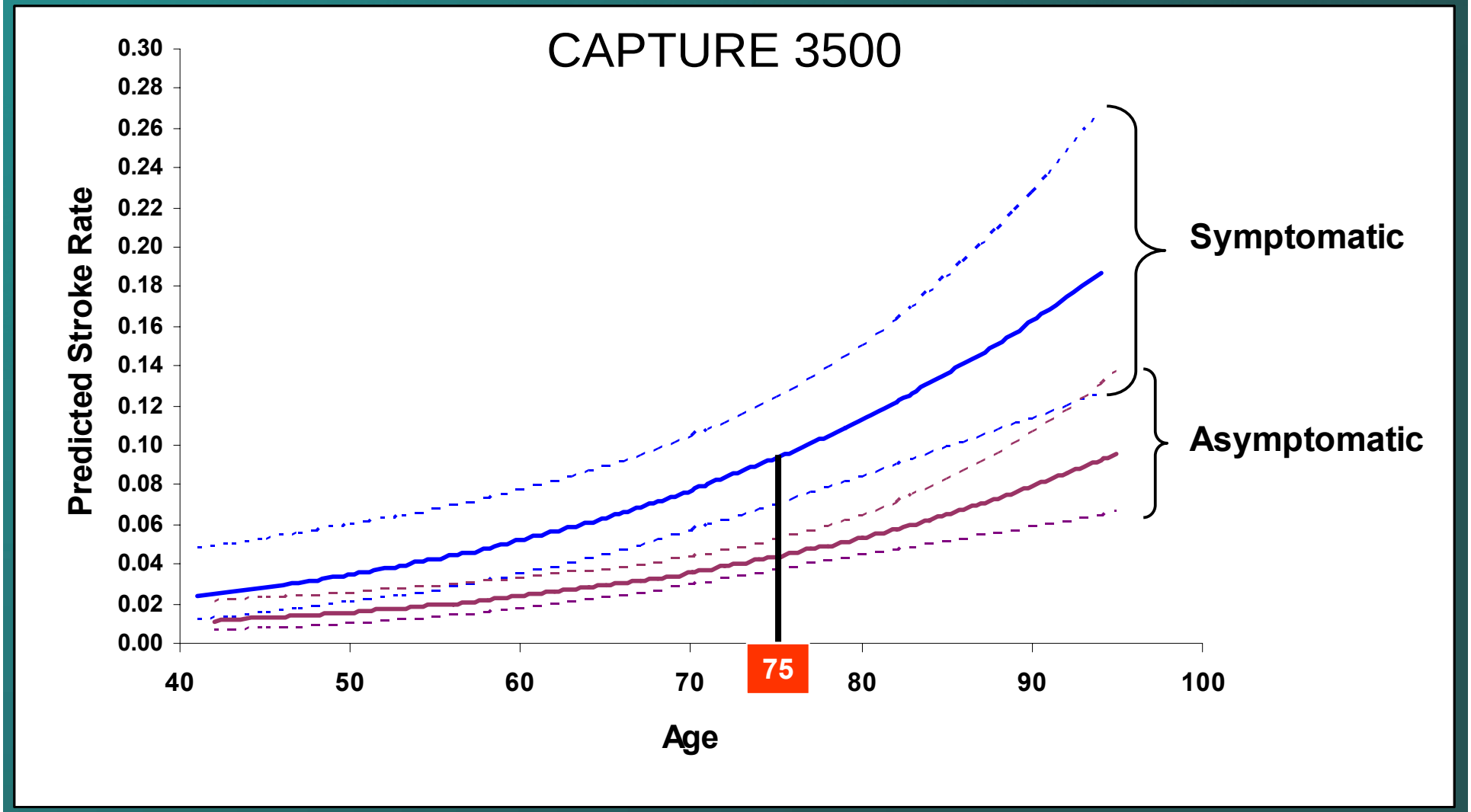
No differences were found in outcomes by physician specialty once the data are adjusted for age, symptomatic status and operator level.

Variable	P-value [1]	Odds Ratio [95% CI]
Site Level (2|3 vs 1)	0.3917	0.75 [0.39, 1.45]
Operator Level (3 vs 1|2)	0.1586	1.28 [0.91, 1.81]
Operator Level (2|3 vs 1)	0.8763	1.05 [0.59, 1.87]
Age = 76 Group (>=76 vs < 76)	< 0.0001	2.29 [1.67, 3.14]
Symptomatic (Yes vs No)	< 0.0001	2.24 [1.56, 3.23]
Gender (Female vs Male)	0.0613	1.35 [0.99, 1.84]
Diabetes (Yes vs No)	0.7520	0.95 [0.68, 1.32]
Hypertension (Yes vs No)	0.1187	1.58 [0.89, 2.81]
Hypercholesterolemia (Yes vs No)	0.4408	1.18 [0.77, 1.82]
Renal Failure (Yes vs No)	0.3534	1.28 [0.76, 2.14]
Contralateral Occlusion of ICA (Yes vs No)	0.4181	0.77 [0.41, 1.44]
CHF (Yes vs No)	0.3595	1.20 [0.81, 1.79]
Unstable Angina (Yes vs No)	0.8891	0.94 [0.41, 2.17]
Event After Second Procedure (Yes vs No)	0.9639	0.97 [0.23, 4.03]
Multiple Stents used within proc (No: 1 stent vs Yes: >1 stent)	0.0010	2.27 [1.39, 3.71]
Target Lesion Stenosis >= 90% (No vs Yes)	0.0829	1.32 [0.96, 1.80]
Target Lesion Calcification (Moderate to Heavy vs Little)	0.5790	1.10 [0.79, 1.51]
Thrombus at Site (Present vs Absent)	0.7932	0.87 [0.32, 2.41]
Medication History: Lipostatin (Yes vs No)	0.2711	0.82 [0.58, 1.16]
Pre-Dilatation without EPD (Yes vs No)	< 0.0001	4.04 [2.51, 6.49]
Post-Dilatation (No vs Yes)	0.2400	1.49 [0.77, 2.88]
Final Residual Stenosis < 10% (Yes vs No)	0.0951	1.30 [0.95, 1.78]
ACCULINK Success (No vs Yes)	0.2875	2.22 [0.51, 9.64]
ACCUNET Success (No vs Yes)	0.1650	1.93 [0.76, 4.91]
Smoking (Yes vs No)	0.0642	0.66 [0.43, 1.02]

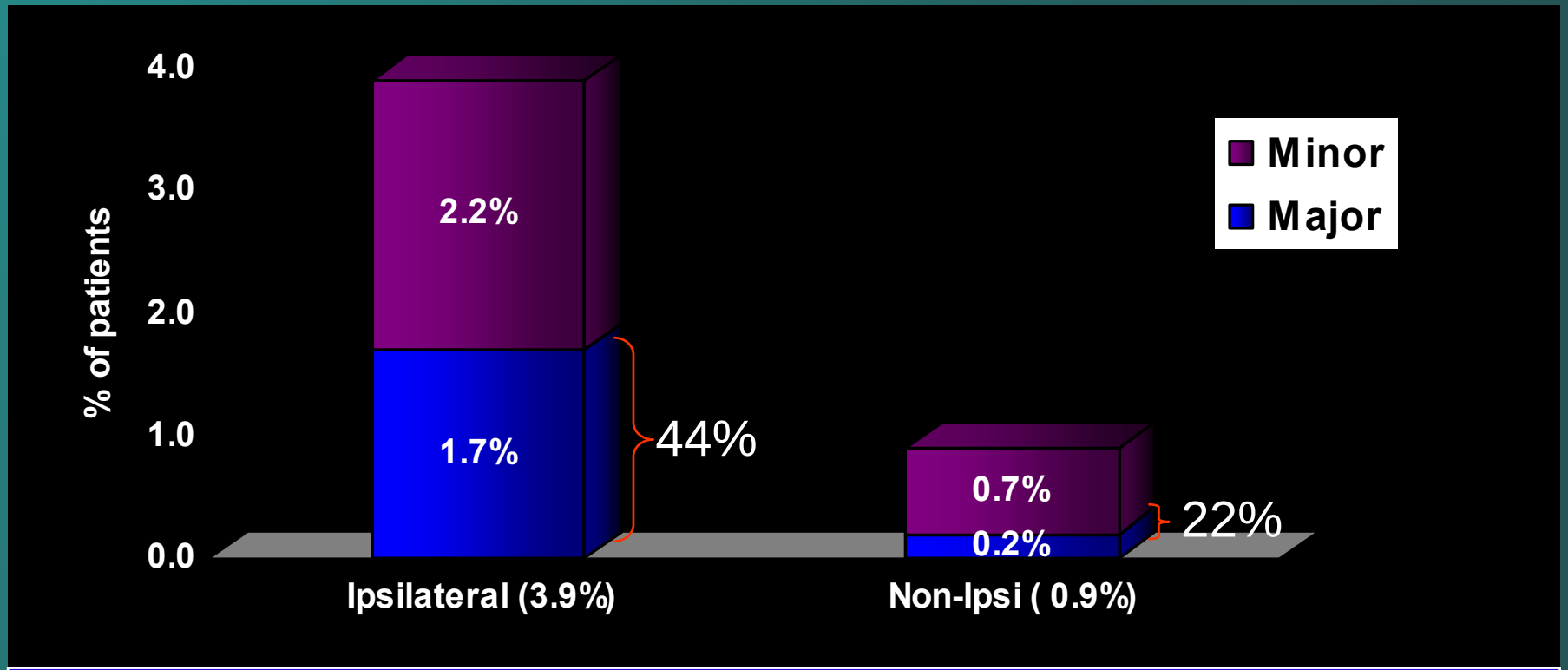
CAPTURE 3500: Multivariate analysis

Variables	DSMI		Death and Stroke		Stroke	
	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value
Pre-Dilitation without EPD	3.1 [1.94, 4.97]	<0.01	3.71 [2.28, 6.04]	<0.001	3.75 [2.30, 6.12]	<0.01
Symptomatic	2.44 [1.76, 3.39]	<0.01	2.15 [1.48, 3.12]	<0.01	2.14 [1.47, 3.11]	<0.001
Age ≥ 75	2.23 [1.67, 2.98]	<0.01	2.18 [1.58,3.01]	<0.001	2.24 [1.62,3.10]	<0.001
Multiple Stents per Procedure	1.82 [1.12, 2.97]	0.016	2.12 [1.27, 3.54]	0.004	2.27 [1.37, 3.76]	0.001

CAPTURE outcomes by age and symptoms



CAPTURE 3500: Stroke by Location



- 18% of all strokes in CAPTURE are non-ipsilateral
- More non-ipsilateral strokes were minor c/w ipsilateral

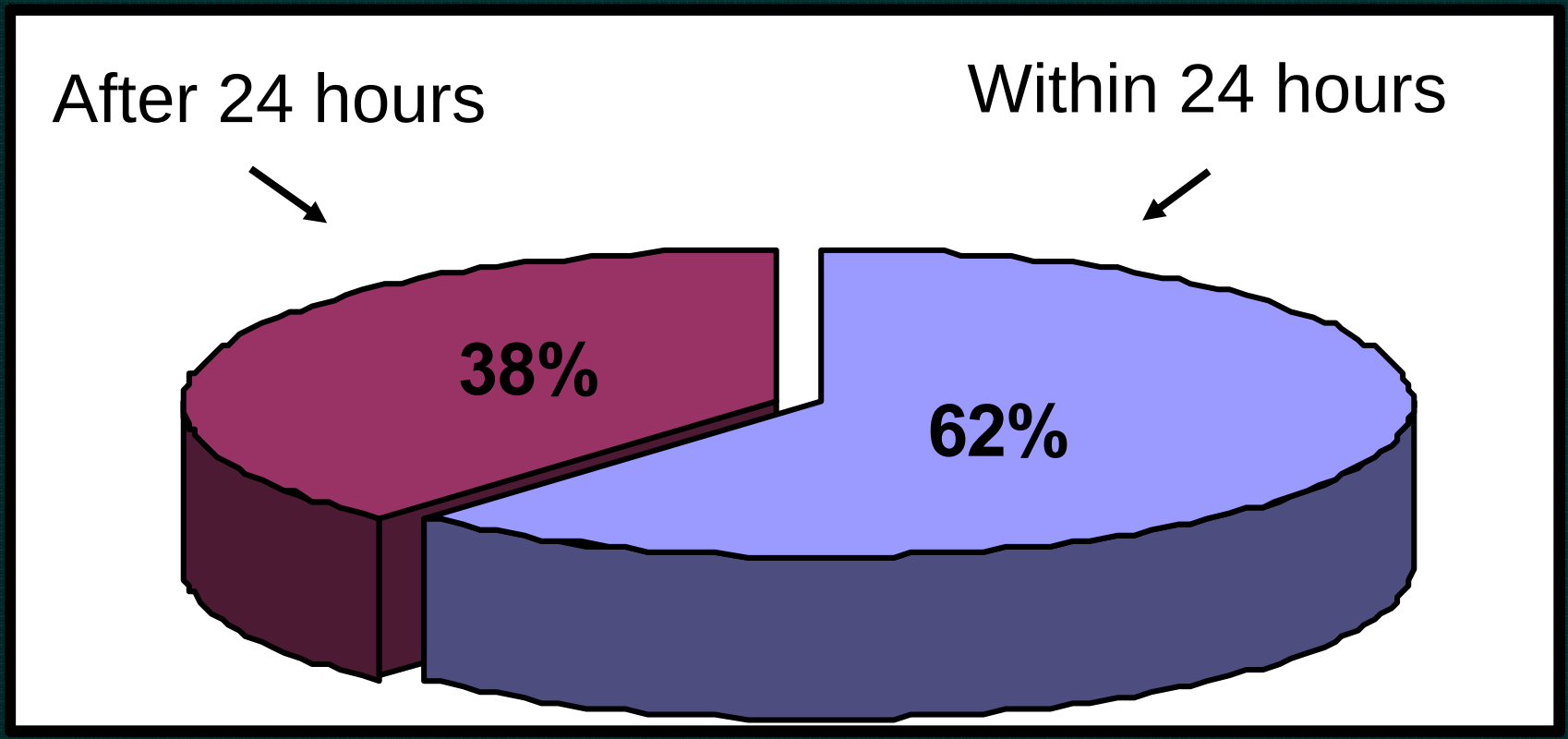
CAPTURE 3500:
Stroke Location by Symptoms, Age, Operator Level

	Ipsilateral	Non-ipsilateral	Proportion NI:I
Symptomatic status			
Symptomatic	7.9%	1.0%	13%
Asymptomatic	3.3%	0.9%	27%
Age			
≥80 years	6.2%	1.1%	18%
<80 years	3.3%	0.8%	24%
Operator experience			
High	3.5%	1.1%	31%
Medium	3.7%	0.8%	22%
Low	4.8%	1.1%	23%

Regardless of stroke potential of lesion/patient,
the absolute NI strokes do not vary

CAPTURE stroke timing:

38% strokes occur after 24 hours of procedure



This data was collected from source documents

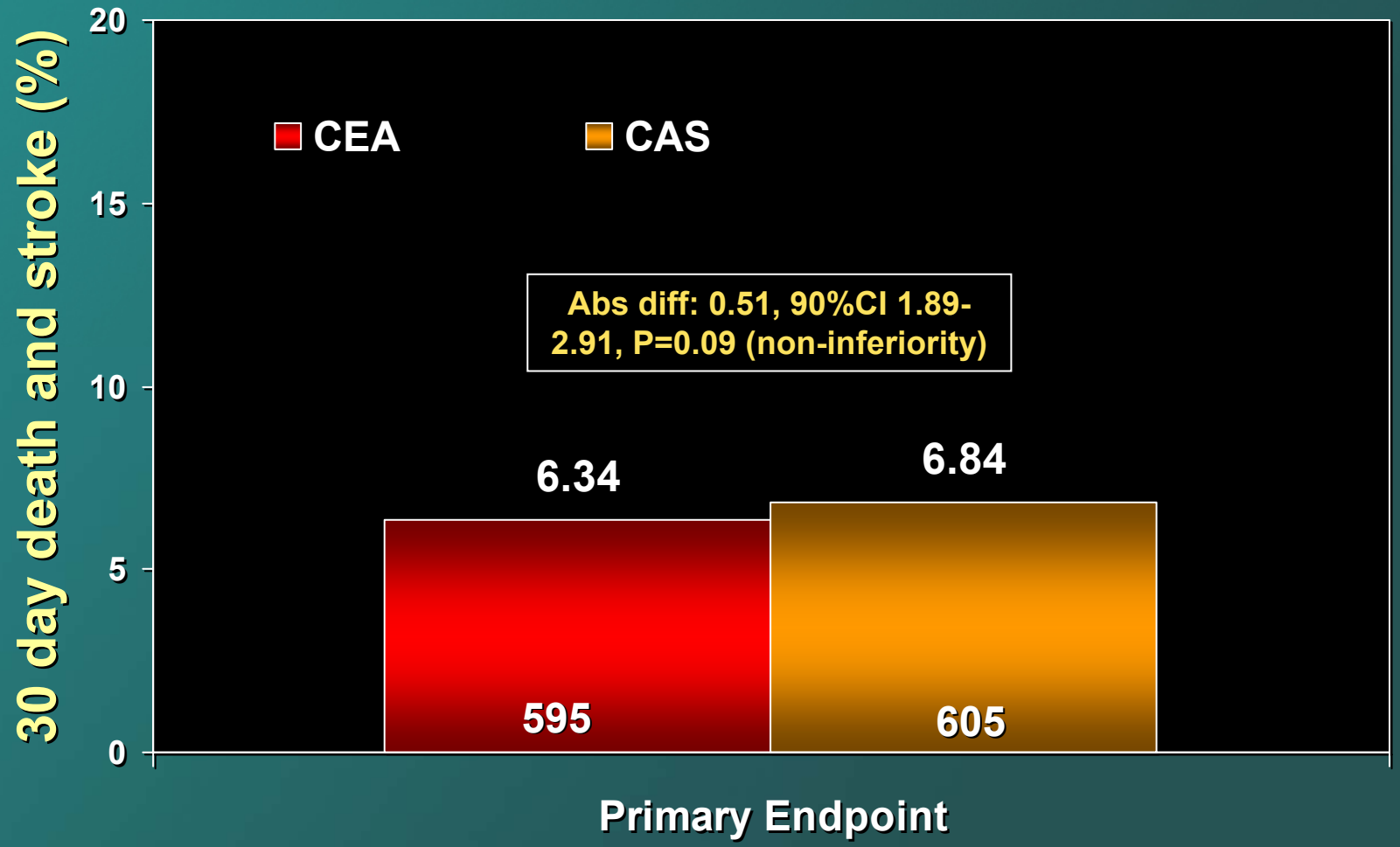
CAPTURE stroke cohort: Future Considerations/Conclusions

- Why do many strokes occur after the procedure (78%) or after 24 hours (38%)?
- How many late strokes are hemorrhagic?
- Why do 18 % occur in a vessel that has not been manipulated?
- Does the answer lie in?
  - Technical: Balloon sizing?
  - Arch type, calcification and overall plaque morphology
  - Improved technical equipment
  - Medical therapy before and after the procedure
- Potential to reduce stroke in an already safe procedure

SPACE

- 1183 patients randomized between stenting and surgery over 5 years/35 centers (3.4 CAS patients/year)
  - 98% of received stents
  - 27% EPD
  - 100% symptomatic
  - Mean age 68
  - Central selection committee
  - Moderate surgical risk
  - 77% thienopyridine use in endovascular Rx

SPACE
Randomized CEA vs. CAS symptomatic patients



SPACE collaborators. Lancet 2006;368:1239-47

SPACE: critique

- Stopped due to lack of continued funding after interim analysis
- Original power calculations→ 80% power achieved with N= 2x 950
- Second Interim analysis power calculations
  - Assuming original study assumption (no diff with average AE rate: 6.59%): 70% achieved with N= 2x 950
    - To reach 80% power →N needed= 2x 1250
  - Assuming observed 0.5% difference is “real”, 52% power achieved with N= 2x 950
    - To reach 80% power → N needed = 2 x 1980
- Did not achieve statistical endpoint of non-inferiority due to this early termination

SPACE: conclusion

- SPACE *failed to enroll enough patients* to show non-inferiority
  - With a 2.5% delta, the study was under-powered to show non-inferiority in the context of interim analyses, as shown by power simulations at the 2nd interim analysis:

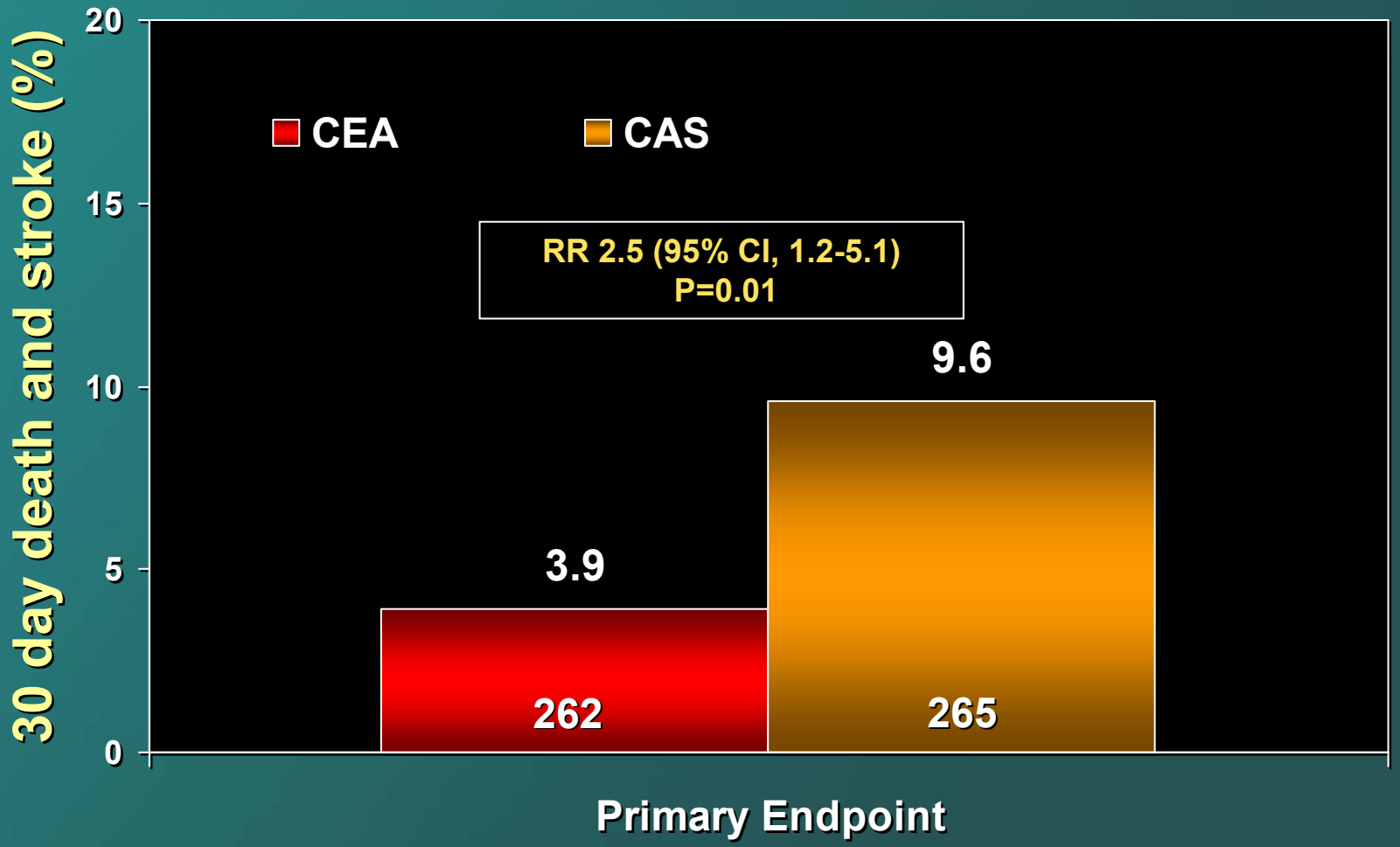
CEA	CAS	CAS - CEA	Power
5%	5.00%	0.00%	79%
5%	5.25%	0.25%	70%
5%	5.50%	0.50%	60%
5%	6.00%	1.00%	40%
5%	6.50%	1.50%	22%
5%	7.00%	2.00%	11%

Not achieving non-inferiority does not equal superiority

EVA-3S

- 527 patients randomized between CAS and surgery over 5 years/30 centers (1.7 patients/year)
  - 99% of received stents
  - 92% EPD (78% in first 58, 98% in last 169)
  - 100% symptomatic
  - Mean age 70 (36% over 75 years)
  - No central selection, proctor certified
  - Moderate surgical risk
  - 85% ASA and thienopyridine use in endovascular Rx

EVA-3S: Randomized CEA vs. CAS



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

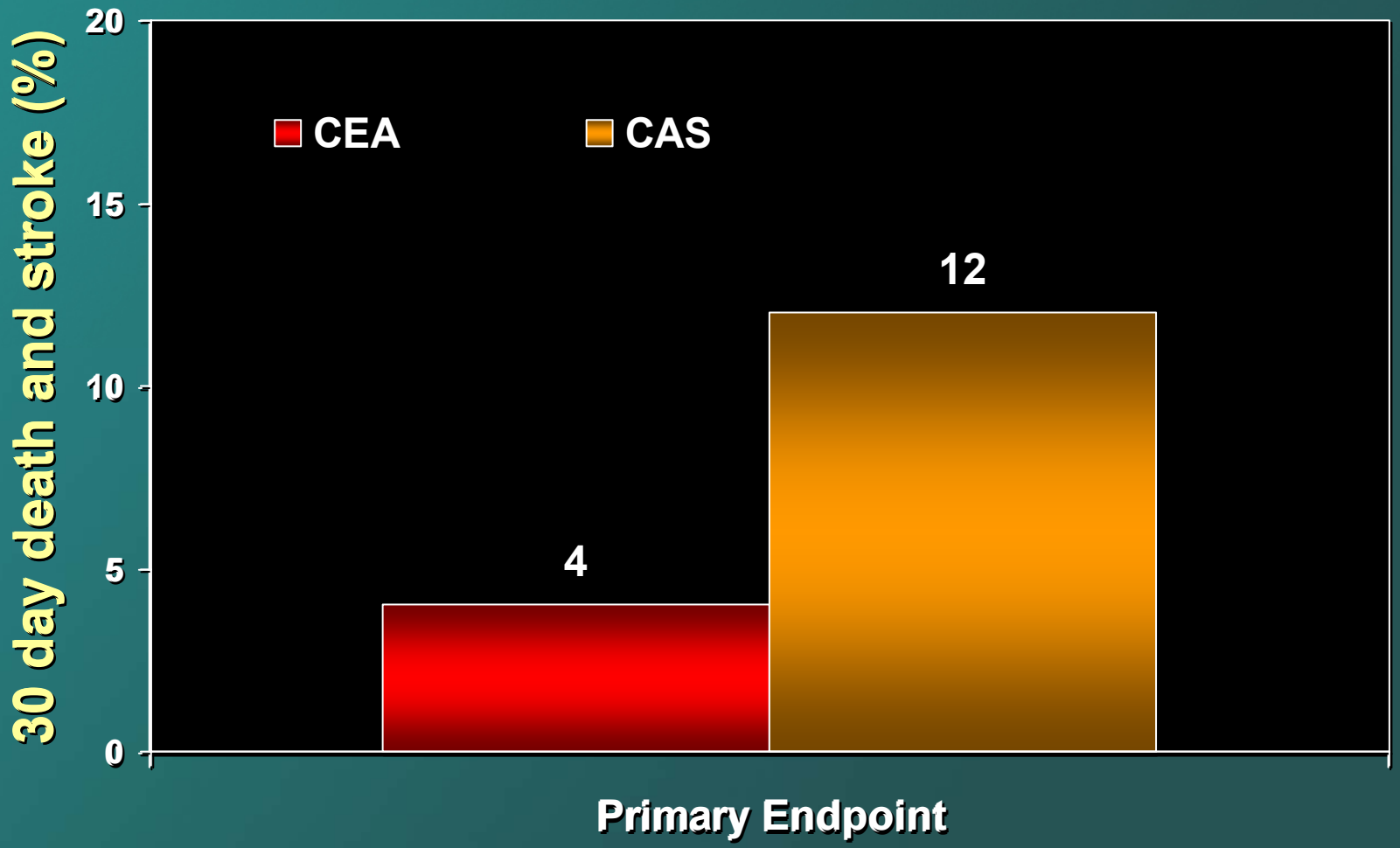
EVA-3S critique

- 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
    - No outcomes criteria documented for these physicians!!!
    - No documentation of EPD use
    - 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.
- Slow enrollment compounded limited investigator experience
  - 1.7 CAS patients/year/site

EVA-3S critique

- Early/non-standard technique and equipment resulted in unnecessary morbidity
  - 5 different EPD, 7 different stents used in this trial
  - Use of EPD not widespread or familiar at start of trial
    - Lack of use in the early phase of the trial likely responsible for 4-5 excess strokes (~20% of all strokes in the CAS arm)
  - *5%* stent procedure failure requiring emergency surgery in this trial resulting in 2 strokes in the CAS group
    - Major pivotal trials in the US (e.g., SAPPHIRE, ARCHeR) have not reported *any* emergent surgical conversions
    - Cranial nerve palsy in 1.1% of CAS patients
  - No pre-dilation in >80% of procedures (standard in US)
  - Significant (beyond local) anesthesia was employed in ~30% of procedures (estimated <5% in US)

Carotid Wall Stent Trial (1997-1999)



Important factors in analysis of CAS outcomes

- Operator expertise (and the judging mechanism)
  - Pace of recruitment
- Proportion symptomatic/asymptomatic patients
- Age distribution of patients
- Use of EPD (and stents)
- High surgical risk patient features
- Anti-platelet regimen
- Definitions and adjudication (i.e., CEC)

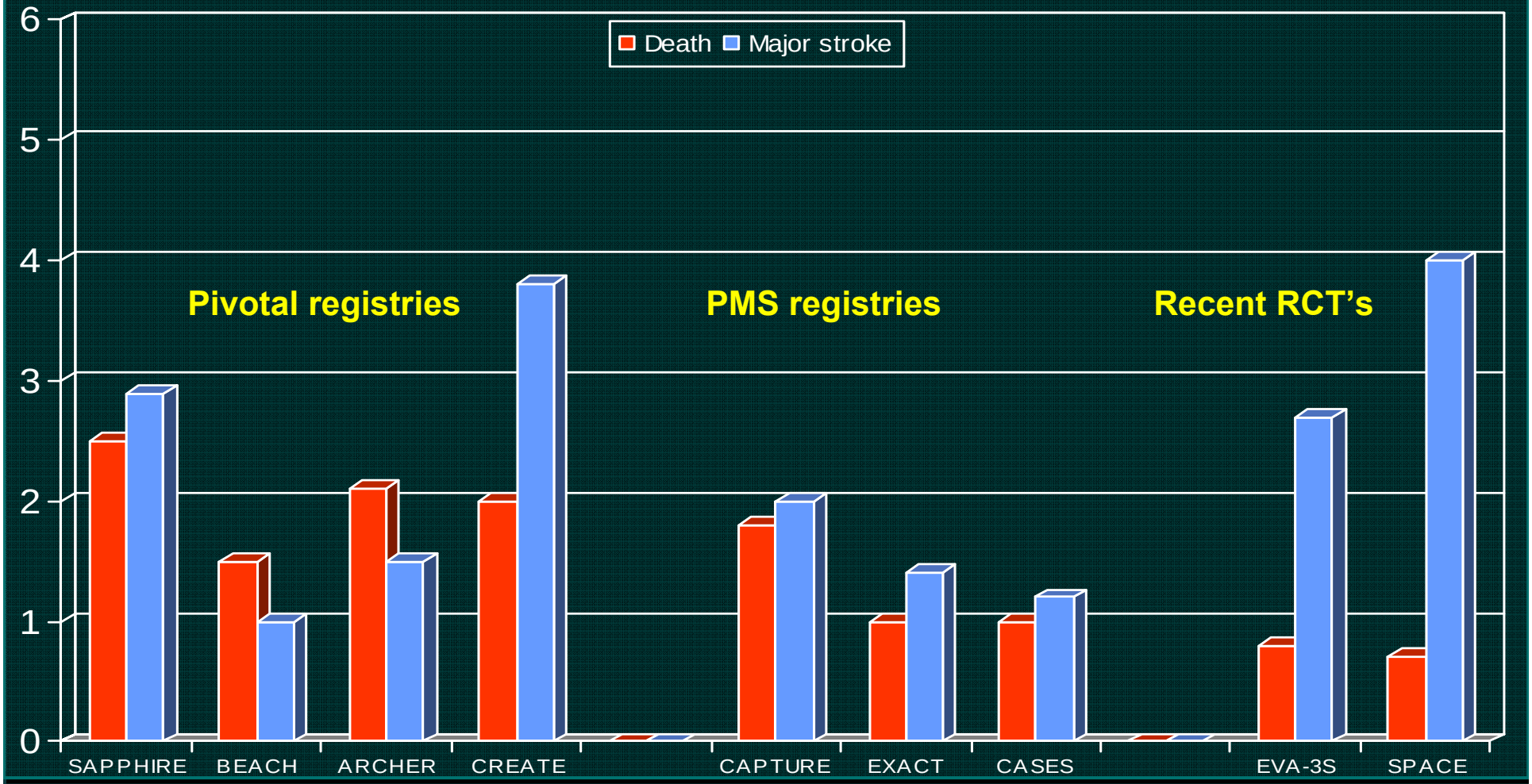
Understand the pitfalls in comparing trials

- *Endpoints, definitions, and adjudication differ between these seemingly similar trials*

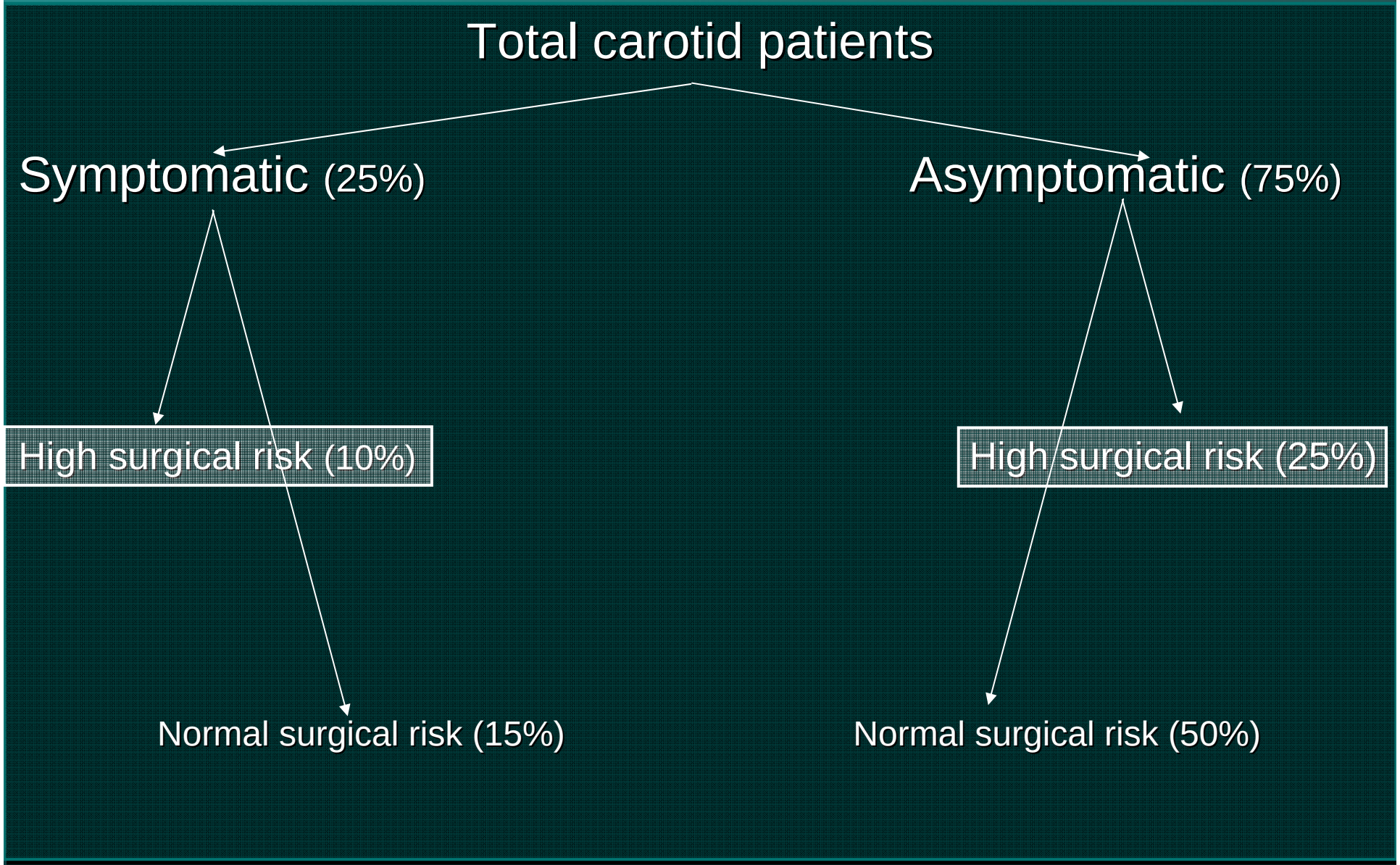
Company/Device	Trial	Primary Endpoint	
Guidant / Acculink	ARCHeR 1, 2, 3	Death, stroke, MI within 30 days, plus, ipsilateral stroke within day 31-365	
Abbott / Xact	SECuRITY	Death, stroke, MI within 30 days, plus, ipsilateral stroke within day 31-365	
Cordis / Precise	SAPPHIRE	Death, stroke, MI within 30 days, plus, **death** and ipsilateral stroke within day 31-360	
Boston Scientific/ EndoTex/ NexStent	CABERNET	**All** death, stroke and MI at 365 days	

Major endpoints are best used for comparisons between trials

Death and major stroke are not as subject to definition or adjudication



Carotid stenting: incomplete access



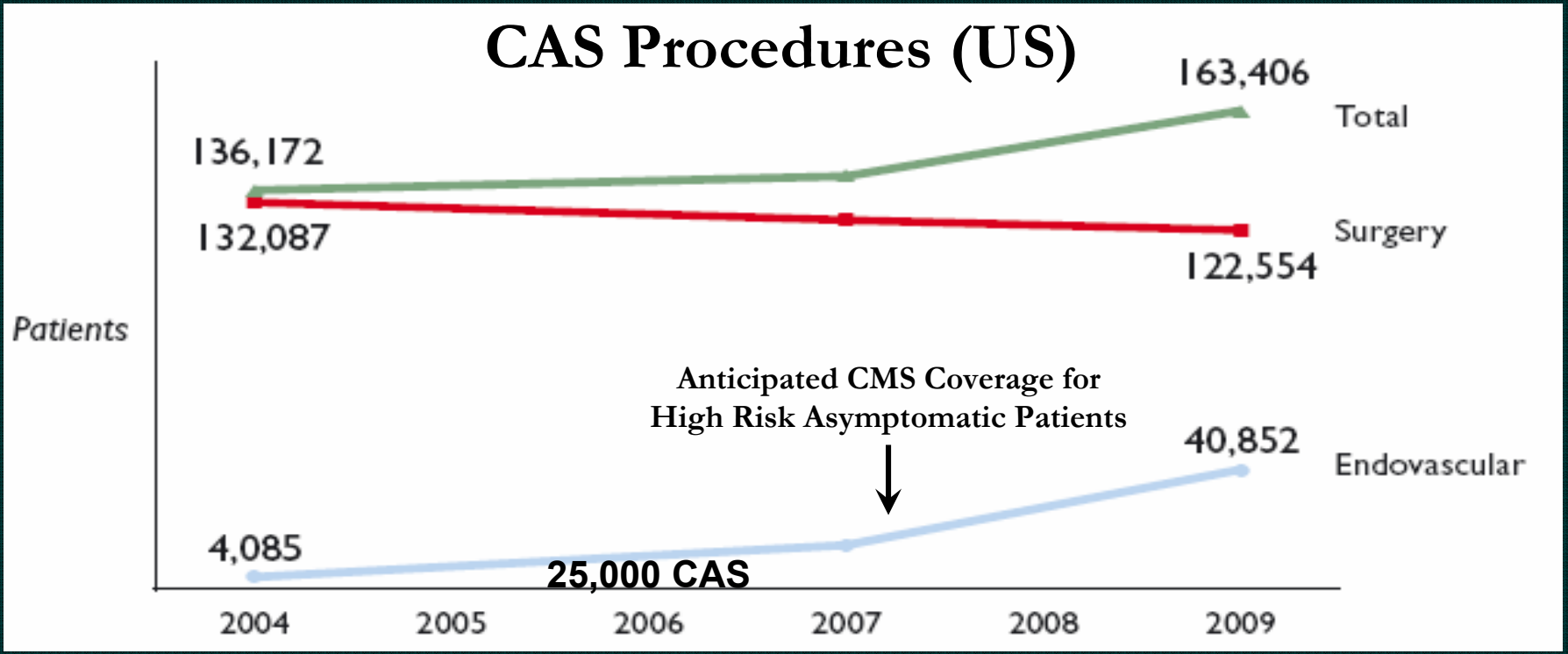
Carotid Stenting: Current Key Trials

- For high-risk patients, FDA registries currently completing enrollment
- The normal risk patient cohorts are now being evaluated:
  - NIH CREST
  - ACT I

Carotid stenting: Conclusions

- With the advent of CAS, the management of the patient with carotid disease is in evolution, as are the specialties involved
- No new data is anticipated for 4-5 years that would expand FDA-approved indications
- Much of the current clinical decision-making is based on coverage and reimbursement decisions by CMS, which may expand partially
- As carotid stenting becomes more proven in broader patient subsets, as selection for therapy improves based on individual patient characteristics, and as more physicians from all specialties become trained, the majority of carotid therapy will shift to CAS

Carotid revascularization: projected volume



2006 Snapshot
Est. 750 MDs
> 600 Centers

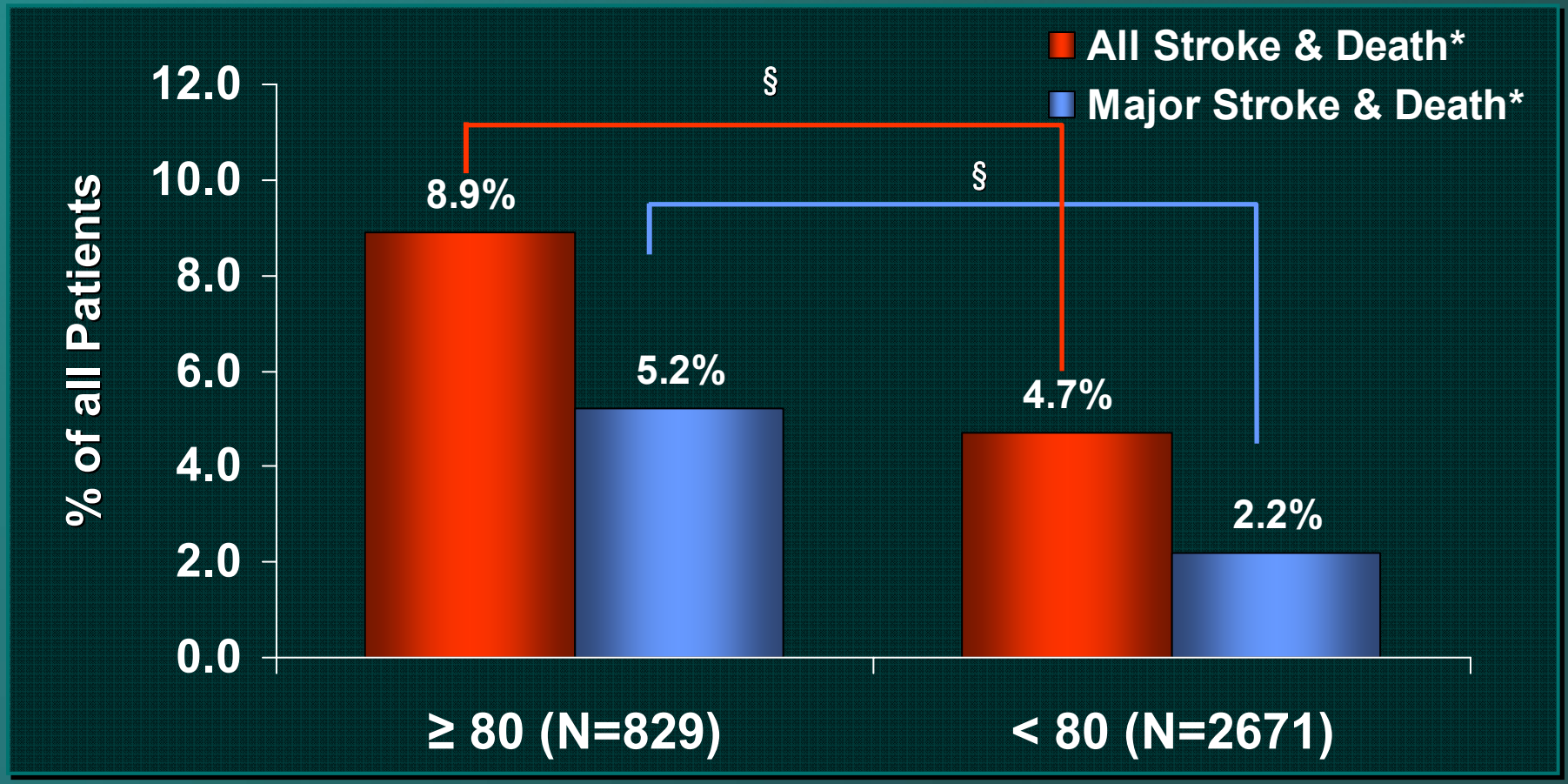
2009 Snapshot

Cardiology	**50 %**
Vascular Surg.	**35 %**
Radiology	**15 %**

Driver of carotid stenting volume in US

The proof and approval of patients with asymptomatic stenosis

CAPTURE 3500:
30 Day Outcomes by Octogenarian Status



§ Denotes statistically significant difference at the 0.05 level

* Hierarchical Events – Includes only the most serious event for each patient and includes only each patient's first occurrence of each event