Achieving Optimal Clinical Results After Carotid Stenting:

The PROTECT Study and Beyond

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Disclosures

- Consultant
  - Abbott Vascular
  - Cordis/J&J
  - BSC
  - Medtronic
  - Contego
  - Silk Road

PROTECT STUDY:
PROTECTed Carotid Artery Stenting in Subjects at High Risk for Carotid Endarterectomy

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PROTECT: Purpose of the trial

- Sponsor: Abbott Vascular
- Purpose:
  - Pivotal IDE trial assessment of the Generation 5 Emboshield Pro Rapid Exchange Embolic Protection
  - Fulfill the long-term follow-up requirement of the Xact stent PMA conditions of approval: 3-year follow-up on at least 305 subjects
- Analysis Cohort:
  - Enrollment completed in 20 months (Nov 2006-June 2008); 274 patient cohort with 30 day follow-up analysis of embolic protection presented here.
  - 3 year Xact stent follow-up ongoing (n=322)

PROTECT: Design, conduct, and endpoints

- Design:
  - Prospective, single-arm registry for patients with carotid stenosis anatomic or physiologic high surgical risk features
  - Stenosis: Symptomatic >50% or asymptomatic >80%
- Study requirements:
  - Neurologic exam pre-enrollment, 24 hour, 30 day and annually (3 years) performed by an independent neurologist
  - Independent adjudication of neurological events by a CEC
  - Independent outcome monitoring by the DSMB
- 1º Endpoints: OPC based on 30-day MAE rates of SECuRITY, SAPPHIRE, ARCHeR, BEACH and MAVErIC
  - For Emboshield® Pro Rapid Exchange Embolic Protection System: 30-day composite rate of DSMI for first 220 consecutively enrolled subjects.
  - For Xact stent: Composite 30-day DSMI, plus ipsilateral strokes from 31-365 days and annually (3) years.

36 investigative sites in US

- Pinnacle Health Hospital, Harrisburg, PA
- Lenox Hill Hospital, New York, NY
- Washington Hospital, Fremont, CA
- Our Lady of Lourdes Medical Center, Camden, NJ
- Austin Heart P.A., Austin, TX
- Memorial Hospital Jacksonville, Jacksonville, FL
- St. Joseph's Medical Center, Wyomissing, PA
- Millard Fillmore Hospital-Kaleida Health Systems, Buffalo, NY
- El Camino Hospital, Mountain View, CA
- Stanford University Medical Center, Stanford, CA
- Chesapeake General Hospital, Norfolk, VA
- Hoag Memorial Hospital Presbyterian, Newport Beach, CA
- Massachusetts General Hospital, Boston, MA Parkview Hospital, Fort Wayne, IN
- St. John's Hospital, Springfield, IL Memorial Medical Center, Springfield, IL
- Baptist Hospital of East Tennessee, Knoxville, TN
- Washington Adventist Hospital, Takoma Park, MD
- Hawaii Permanente Medical Group-Kaiser Foundation Hospital, Honolulu, HI
- Greenville Memorial Medical Center, Greenville, SC
- St. Luke's Episcopal Hospital, Houston, TX
- Terrebonne General Medical Center, Houma, LA
- St. Luke's Medical Center, Milwaukee, WI
- Lakeland Regional Medical Center, Lakeland, FL
- Genesys Regional Medical Center, Grand Blanc, MI
- Oregon Health & Science University, Portland, OR
- St. Joseph's Mercy Hospital, Ann Arbor, MI
- University of Connecticut Health Center, Farmington, CT
- Northwestern University Memorial Hospital, Chicago, IL
- Bon Secours St. Mary's Hospital, Richmond, VA
- McLaren Regional Medical Center, Flint, MI
- St. Vincent Hospital and Health Care Center, Indianapolis, IN
- William Beaumont Hospital, Royal Oak, MI
- Presbyterian Hospital of Dallas, Dallas, TX
- Wake Medical Hospital, Raleigh, NC
- Holston Valley Medical Center, Kingsport, TN
- St. Michael's Medical Center, Newark, NJ
- Lehigh Valley Hospital, Allentown, PA

PROTECT: Patient Demographics

Characteristic	PROTECT N=274	SECuRITY N=305	ARCHeR N=581
Mean Age	72.3	74.5	72.6
Age ≥ 80	28.8	34	15.5%
% Symptomatic	12.1%	21%	23.8%
% Male	67.6%	64%	67.1%
Diabetes Mellitus	29.9%	31%	37.9%
Hypertension	87.2%	87%	83.8%
Hypercholesterolemia	86.5%	74%	72.6%
CHF	19.3%	6%	33.6%
Anatomic §	16.0%	NA	19.3%
Current Smoker	16.8%	NA	19.3%
PVD	38.0%	NA	36.6%
Renal Failure	3.3%	NA	2.9%

§ Excluding co-morbidities

PROTECT: Patient Demographics

Characteristic	CAPTURE N=4225	EXACT N=2232	CAPTURE 2 N=4356
Mean Age	72.7	72.5	72.5
Age ≥ 80	23.4%	23.9%	22.5%
% Symptomatic	13.8%	10.3%	13.2%
% Male	60.8%	63.2%	61.7%
Diabetes Mellitus	34.9%	34.7%	36.2%
Hypertension	88.4%	89.5%	89.7%
Hypercholesterolemia	78.0%	74.4%	88.6%
CHF	16.3%	18.3%	17.9%
Anatomic §	11.4%	10.6%	20.5%
Current Smoker	21.0%	19.6%	23.3%
PVD	37.4%	44.8%	46.2%
Renal Failure	8.2%	7.2%	3.0%

§ Excluding co-morbidities

PROTECT
Primary endpoint: 30-day major adverse events

EVENT	PROTECT (N=274)
Death, Stroke and MI*	1.8% (12% OPC)
Death#	0.4%
All Stroke#	1.5%
Major Stroke#	0.4%
Minor Stroke#	1.1%
MI#	0.4%
All Stroke and Death*	1.5%
Major Stroke and Death*	0.4%

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

#Non-hierarchical-represents each event even in patients with multiple events

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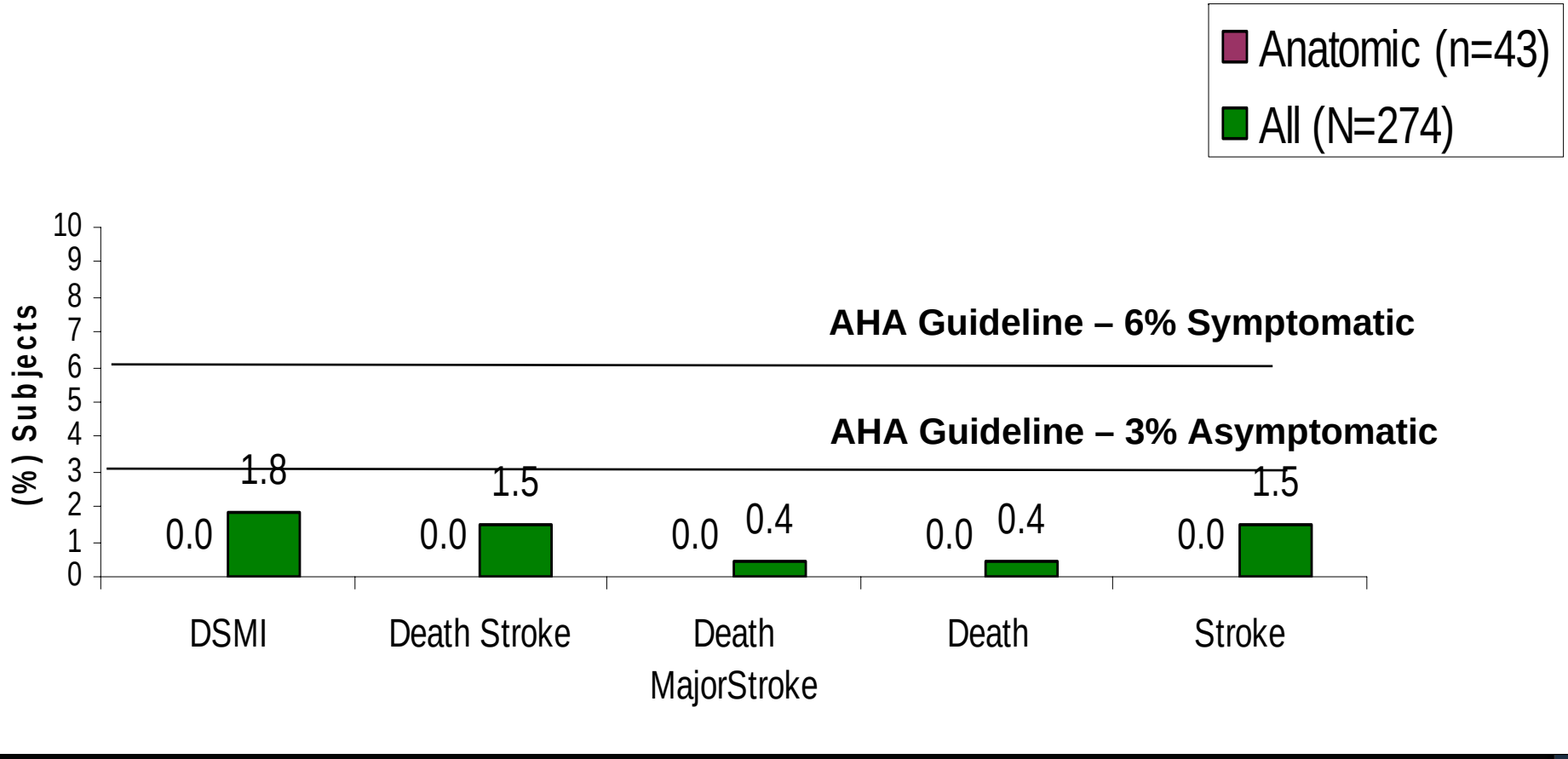
Total and anatomic subset vs. AHA guidelines for CEA



The anatomic subgroup does not include co-morbidities.

All age included.

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PROTECT: Conclusions

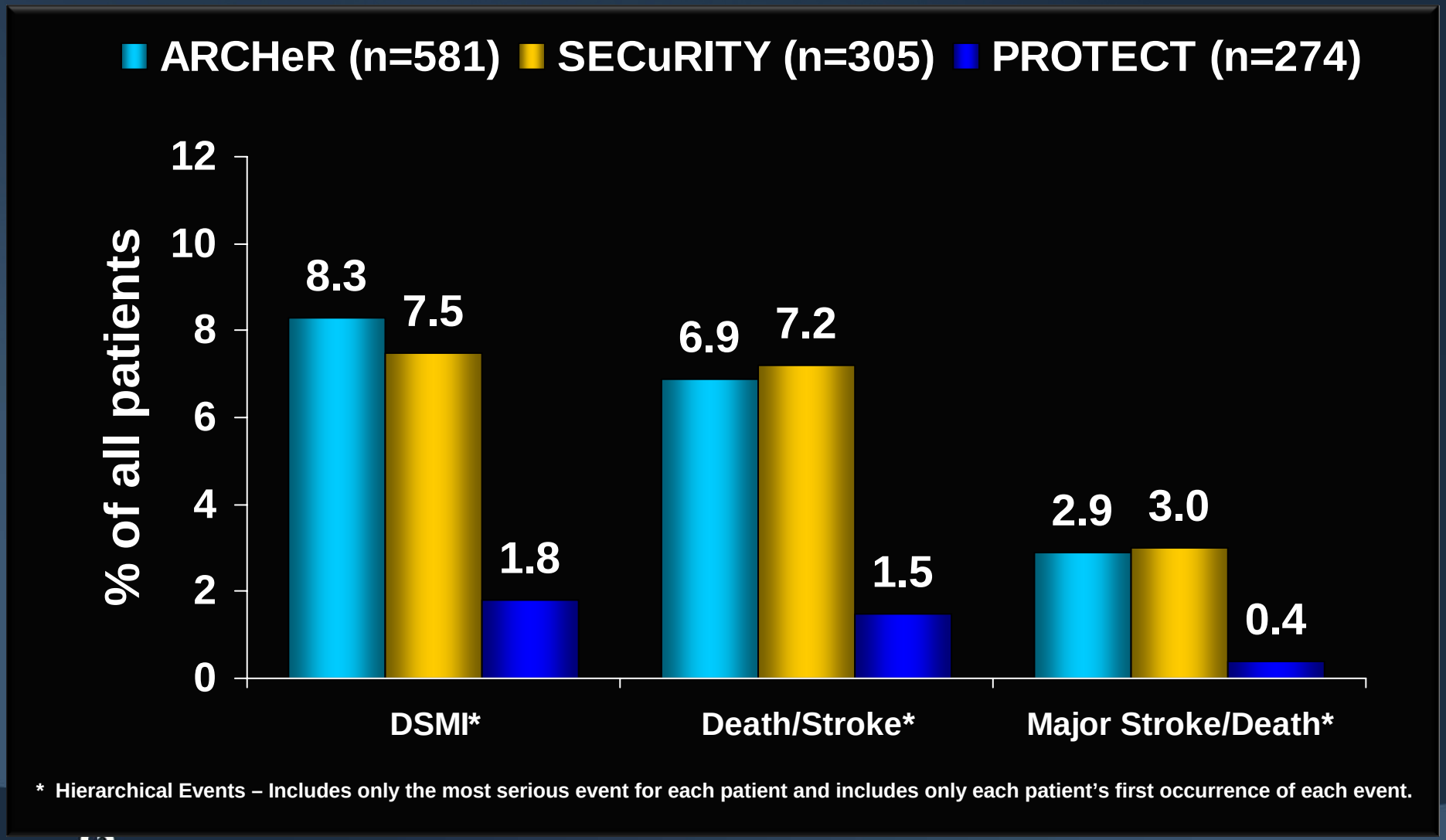
- 30 day primary outcome for PROTECT demonstrate non-inferiority with pre-specified OPC comparator
  - Next generation embolic protection proven safe and effective in preventing peri-procedural stroke
- Total, anatomic and physiologic subsets all achieved/exceeded AHA guidelines established for standard risk CEA

Overview

- What has the evolution in CAS data been?
- What predicts stroke in CAS?
- What are the data for outcomes as regards:
  - Experience
  - Devices
- Summary

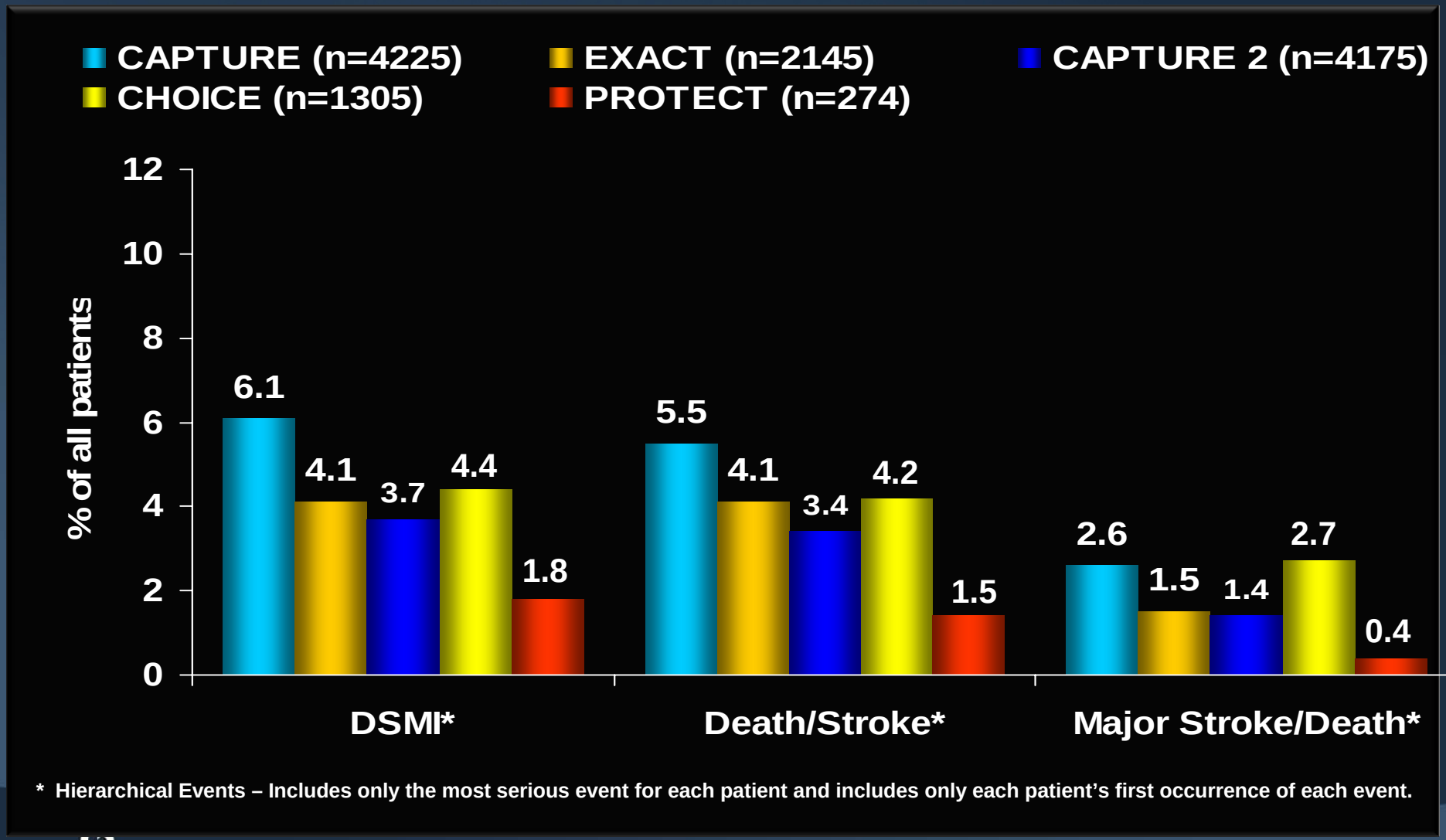
Evolution in CAS Outcomes

Pivotal (IDE) trial 30 day outcomes ARCHeR, SECuRITY, and PROTECT



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

Post-market approval studies vs. PROTECT: 30 day outcomes



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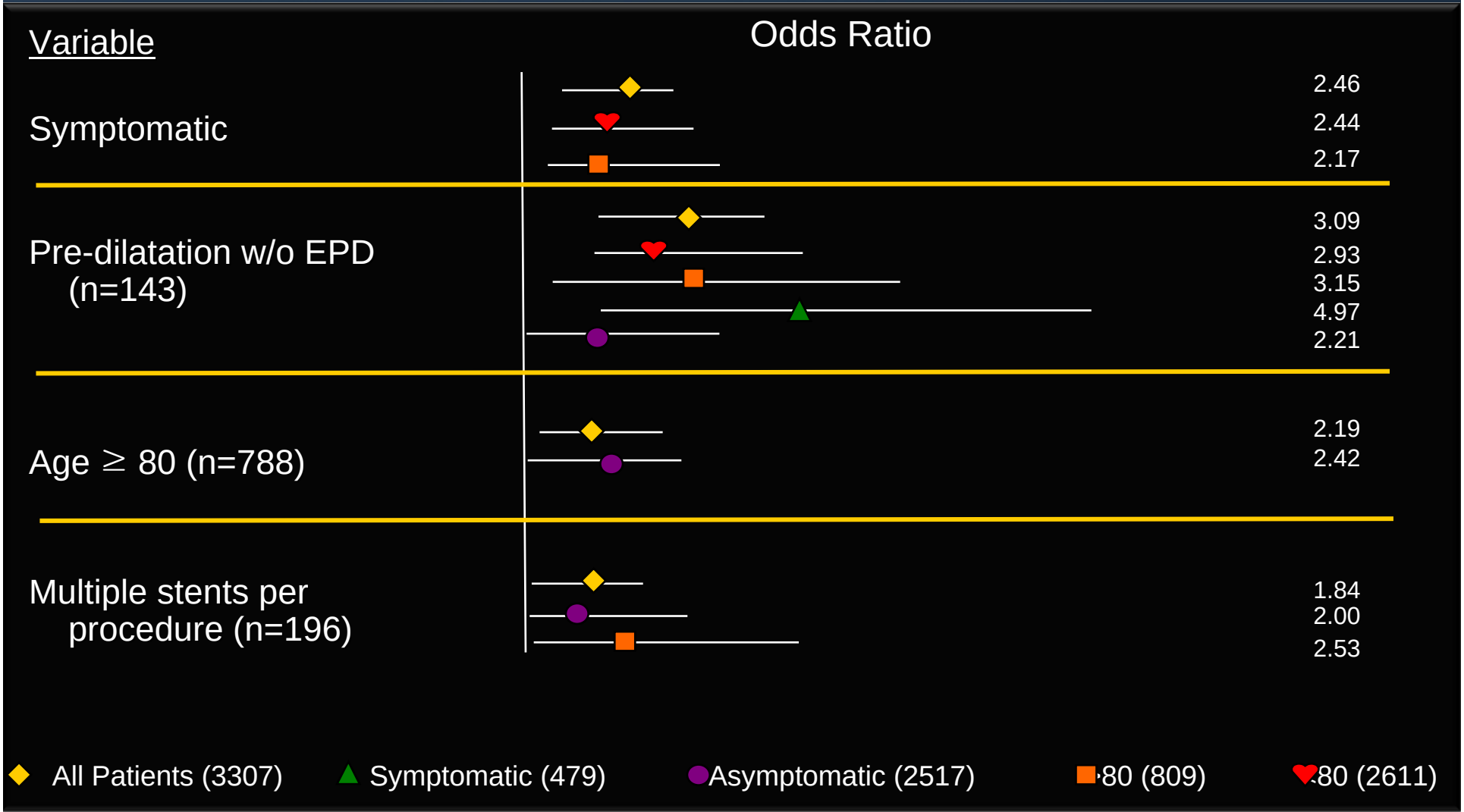
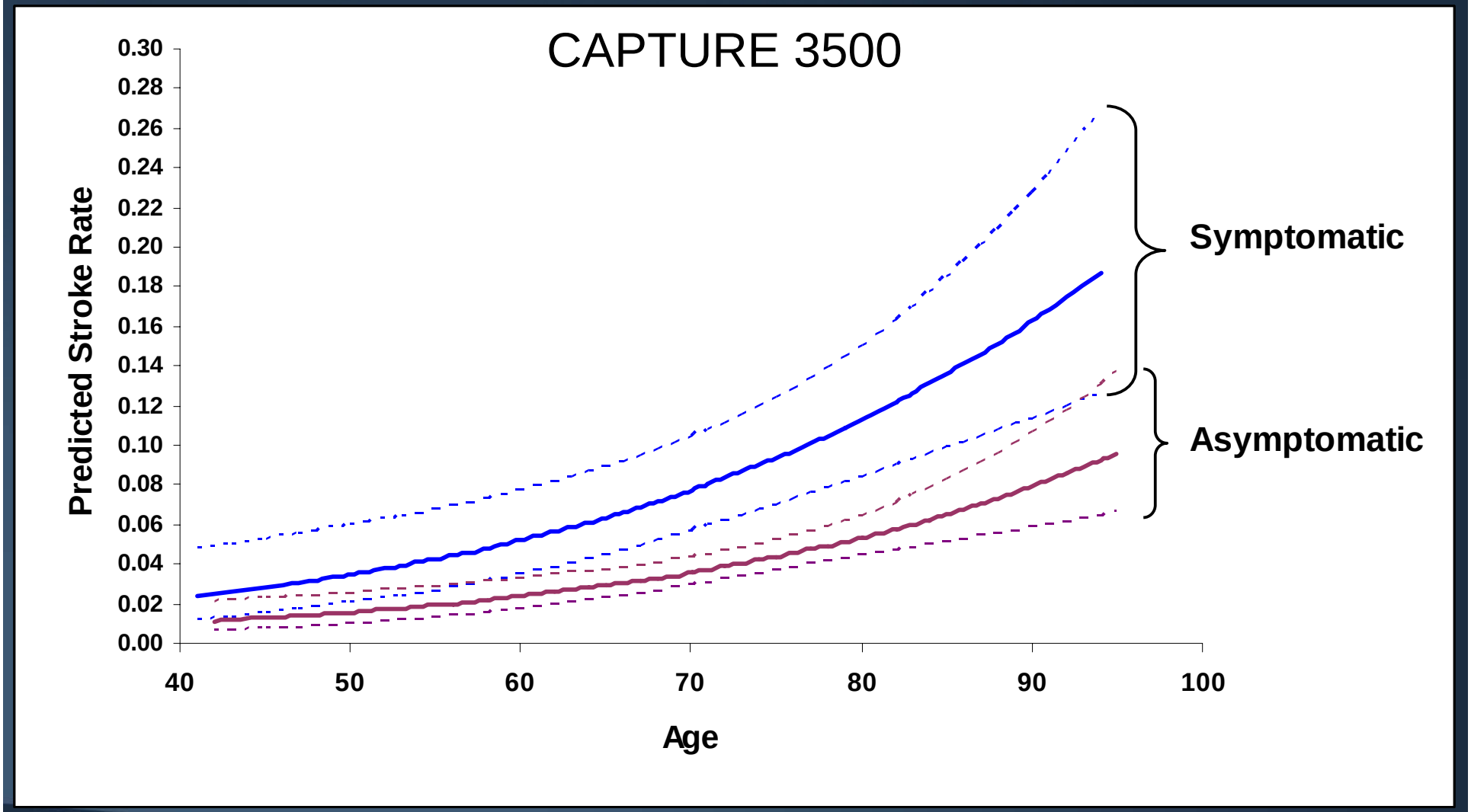
Predictors of Outcomes

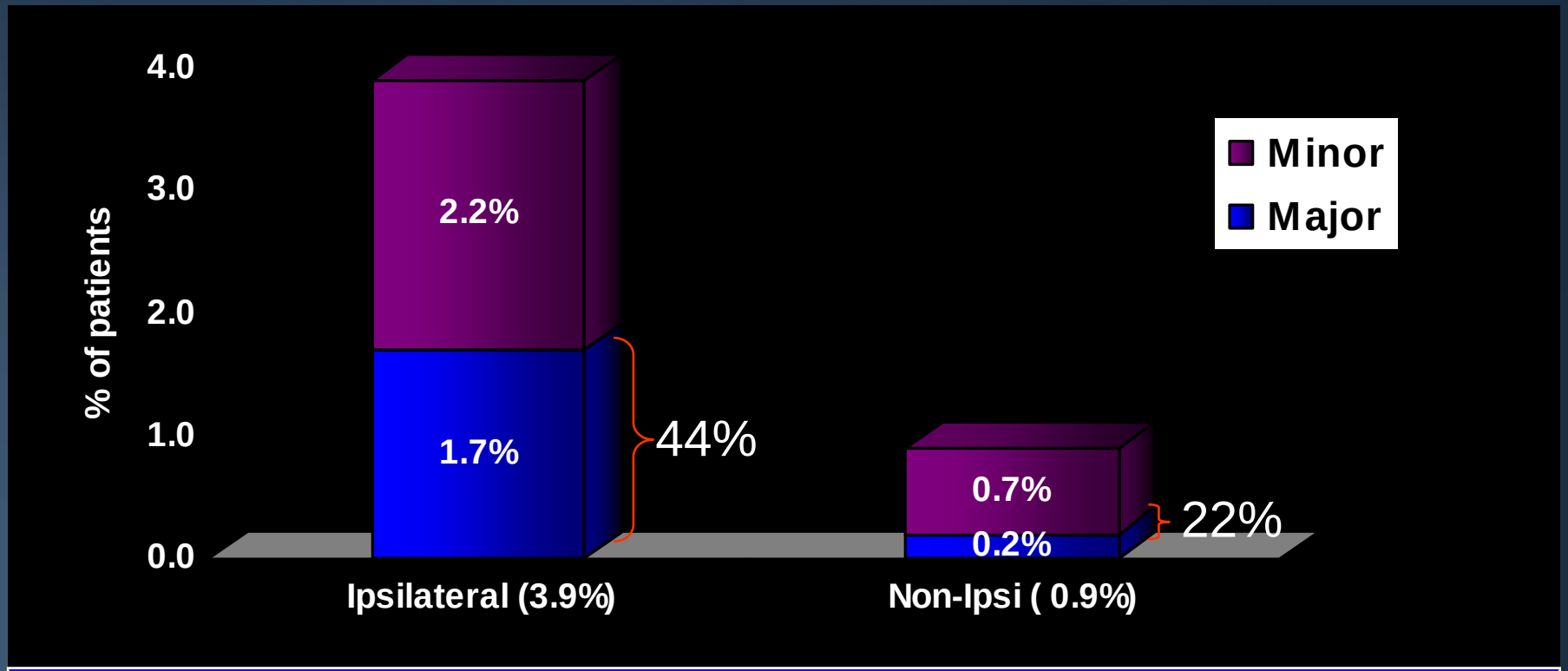
CAPTURE 3500: Predictors of CAS Outcomes



CAS Outcomes by age and symptoms



CAPTURE 3500: Stroke by Location



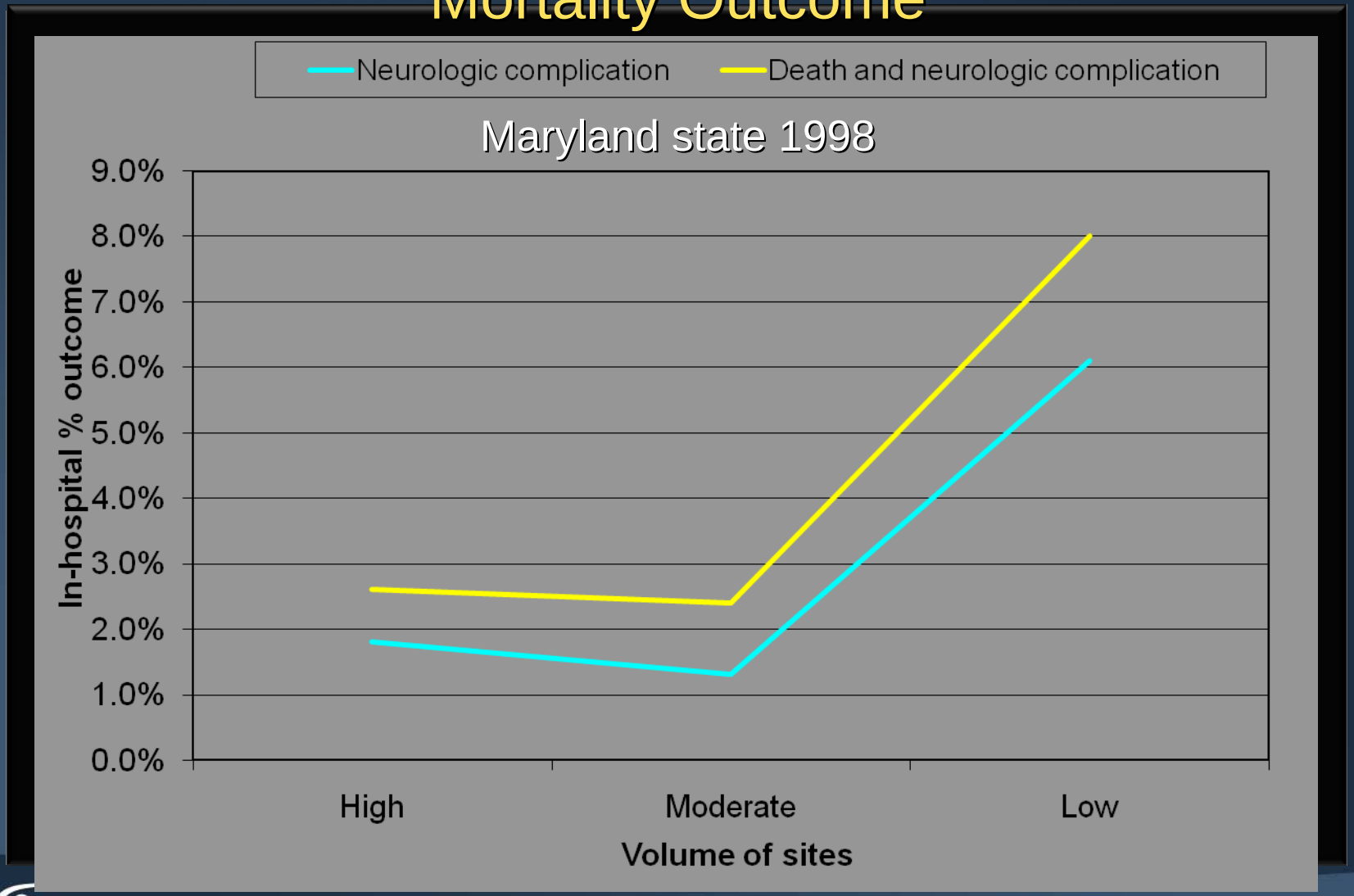
- 18% of all strokes in CAPTURE are non-ipsilateral
- More non-ipsilateral strokes were minor c/w ipsilateral

Experience and Outcomes

Experience

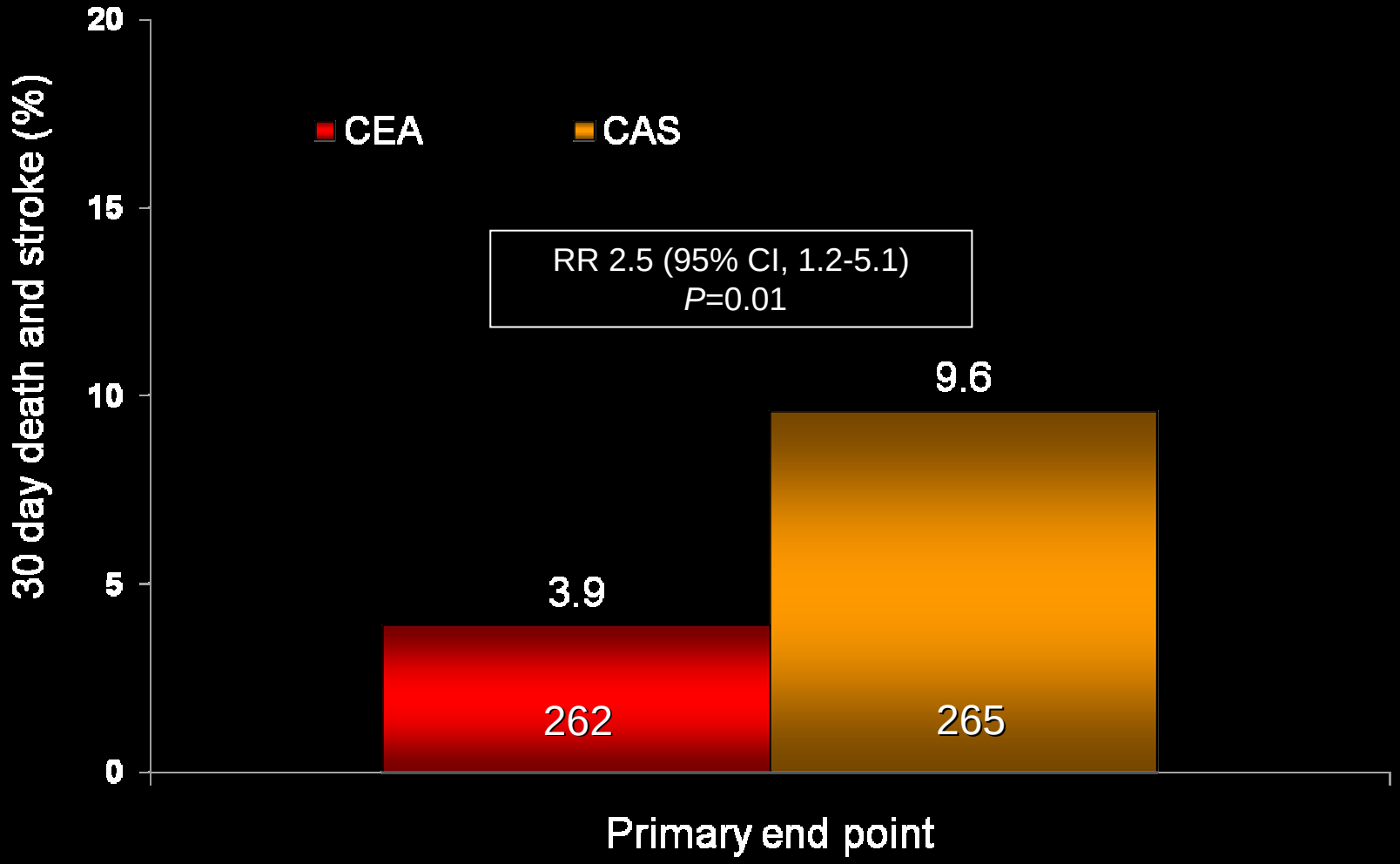
- Assumption: volume equals experience
- Trial-based outcome data supporting experience as a determinant of outcomes
  - Surgical
  - EVA-3S
  - SPACE
  - Pro-CAS
  - PMS registries

Retrospective CEA Survey Demonstrates Inverse Relationship between Volume and Neurologic and Mortality Outcome



EVA-3S

Randomized CEA vs CAS



Mas JL, et al. New Engl J Med. 2006;355:1661-1671

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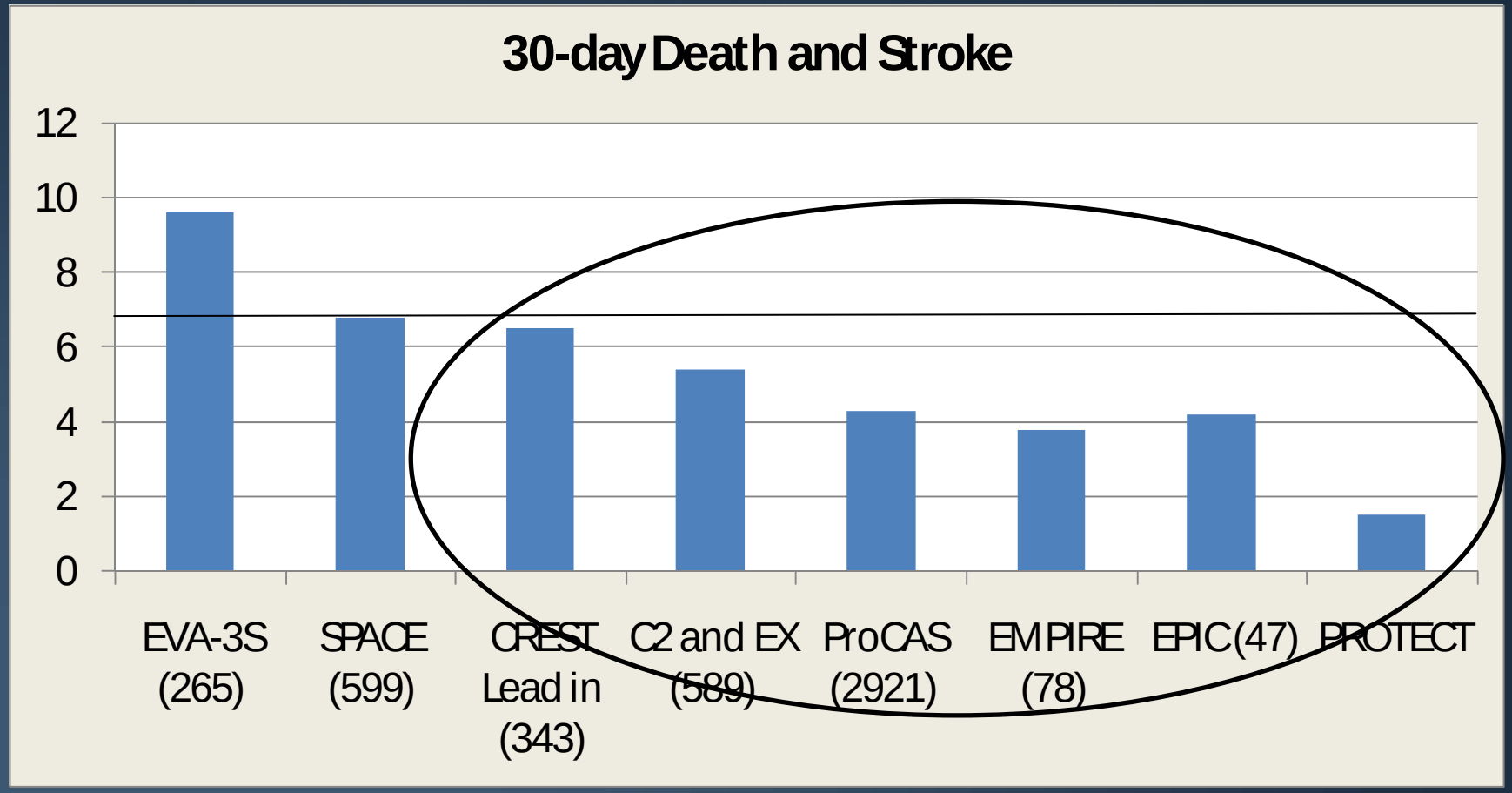
The evolution of CAS in symptomatic patients: EVA-3S vs. the world



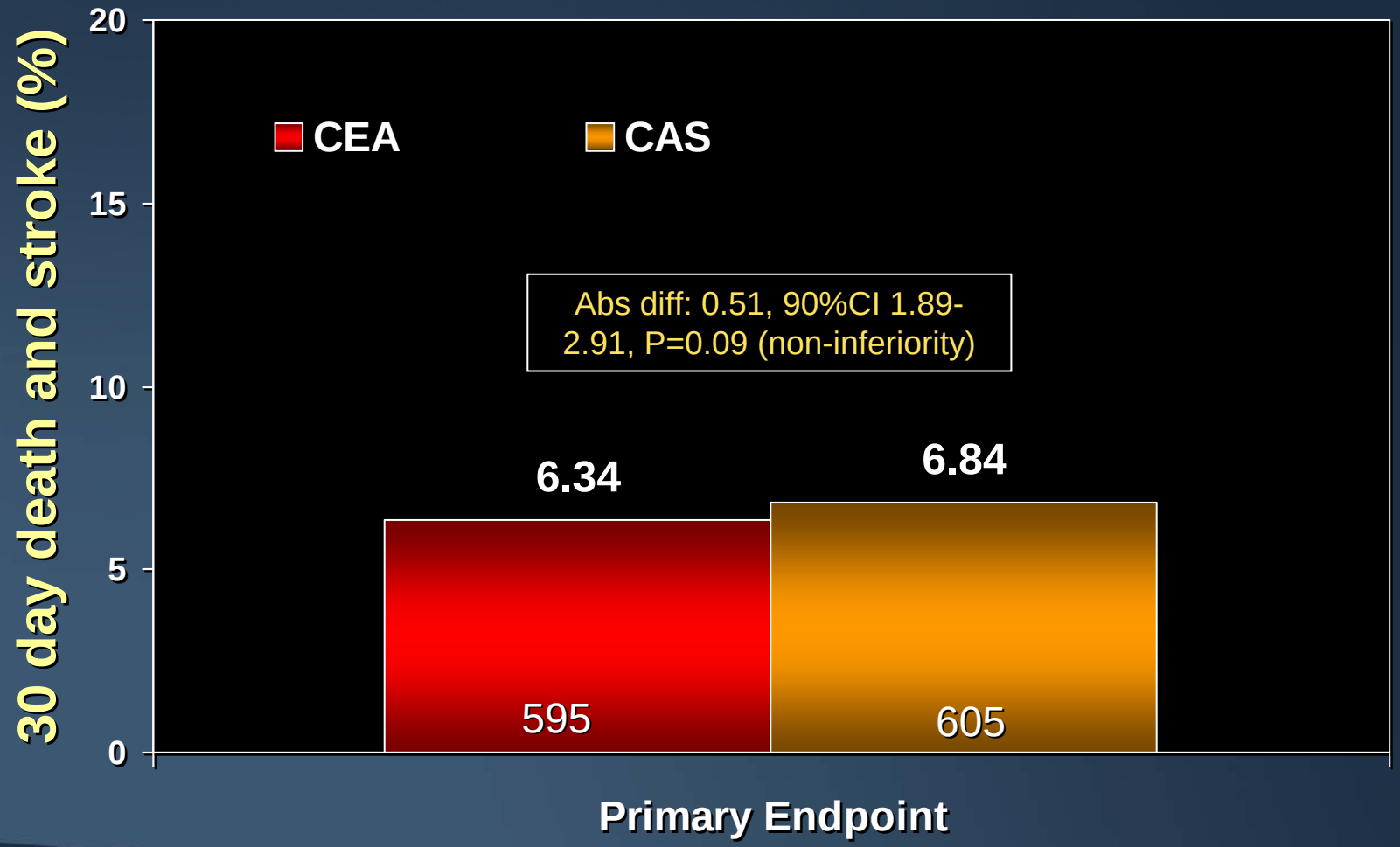
EVA 3S: conclusion

- Prototypical low operator experience multi-center trial
- Outcomes for CAS in EVA-3S for symptomatic standard risk patients are higher than the contemporary cohorts

SPACE: Predictors of outcomes

- Randomized, multicenter non-inferiority study of CEA vs. CAS in standard surgical risk symptomatic patients with 70% carotid stenosis
  - Primary endpoint 30-day ipsilateral stroke and death
  - Only 27% EPD use
  - Pre-specified secondary analyses include:
    - Age
    - Sex
    - Type of event
    - Side of intervention
    - Degree of stenosis
    - High-grade contralateral stenosis

SPACE
Randomized CEA vs. CAS symptomatic patients

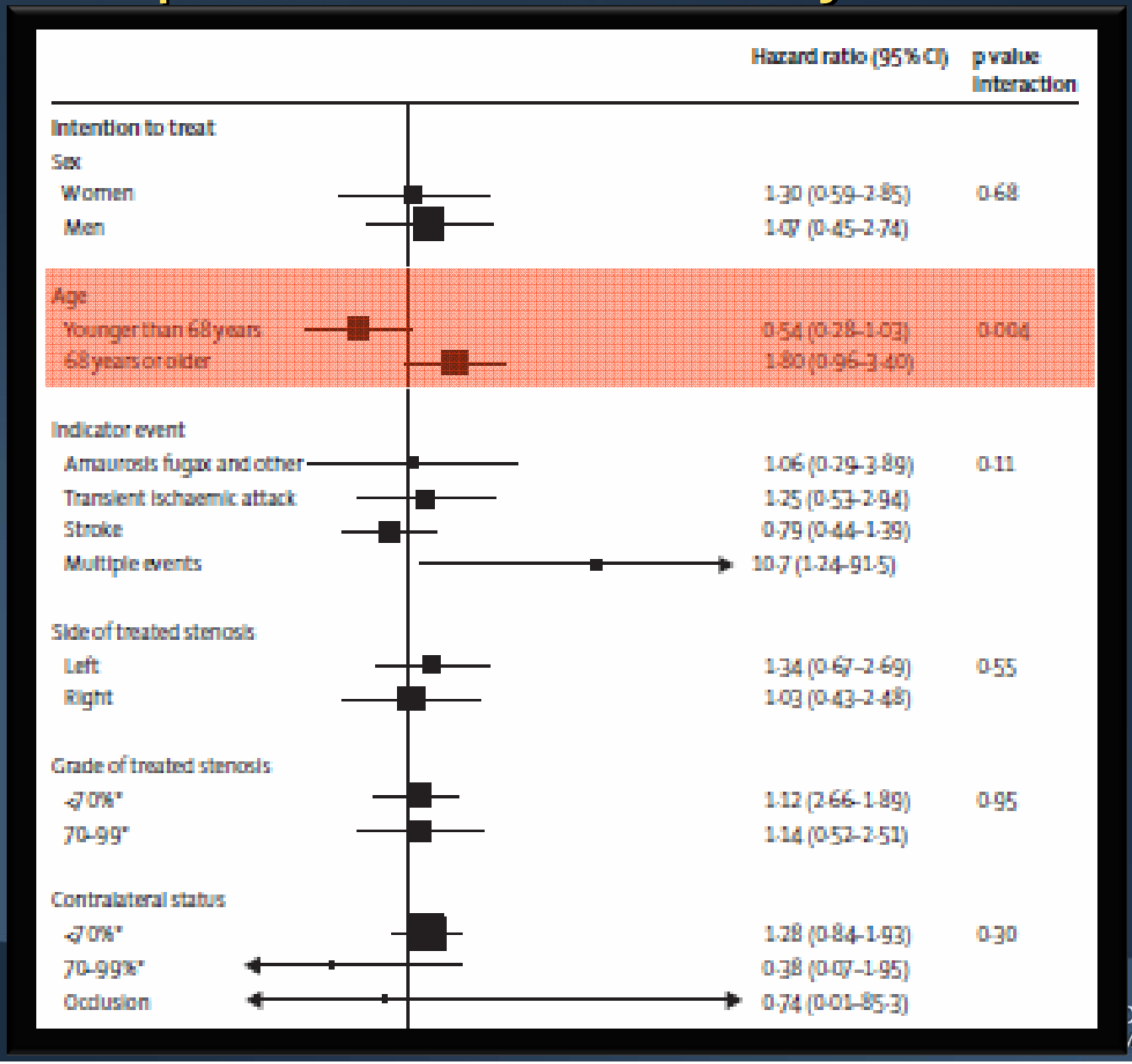


SPACE collaborators. Lancet 2006;368:1239-47

SPACE: Effect of volumes on outcome

Class		Centres (*n*)	Outcome event (*n*)	Total (*n*)	pOE rate (95% CI) in %
CAS (ITT, pOE)	≥25 patients	9	18	370	4.9 (2.9–7.6)
	10–<25 patients	10	16	171	9.4 (5.4–14.7)
	<10 patients	15	8	66	12.1 (5.4–22.5)
CEA (ITT, pOE)	≥25 patients	8	21	337	6.2 (3.9–9.4)
	10–<25 patients	11	16	192	8.3 (4.8–13.2)
	<10 patients	15	1	60	1.7 (0.0–8.9)

SPACE: Hazard ratio for 30-day MAE plus ipsilateral stroke to 2 years



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SPACE: conclusions

- No difference between CAS and CEA after 1200 normal risk patients randomized
  - In spite of only 27% EPD use
  - Advantage to stenting in the under 68 age group
  - Experience (volumes) dictated outcome rates

Pro-CAS: Prospective registry of CAS

- Prospective, multi-center German registry
  - 25 sites/6 year enrollment (July 1999-June 2005)
  - 5341 interventions (outcomes of first 3267 published 2004)
    - Median # of center CAS before enrollment: 38 (0-1200)
    - Median # of center CAS SPACE enrollment: 140 (10-806)
    - No learning curve data available
  - No defined inclusions or exclusions, or procedural methods
  - No angiographic core lab
  - Voluntary independent neurologic assessment (no stroke scales or CEC)
  - Primary endpoint: in-hospital death and stroke

Stroke 2008;39;2325-2330;

Pro-CAS: Overall outcomes

- Median age: 70 years (32-96)
- In-hospital stoke and death: 3.6%

Pro-CAS: effect of symptom status*

Symptomatic status			0.0019
Symptomatic	2921/5333	4.3%	
Asymptomatic	2412/5333	2.7%	
Type of symptoms leading to CAS‡			0.1007
Transient monocular blindness	381/2884	2.6%	
Transient ischemic stroke	1359/2884	4.4%	
Stroke	1144/2884	4.5%	
Interval between symptoms and CAS‡			0.7821
≤2 weeks	609/2344	3.6%	
2–4 weeks	326/2344	4.3%	
2–12 weeks	763/2344	4.6%	
>12 weeks	646/2344	3.9%	

***Univariate analysis**

Pro-CAS: Effect of experience*

Variable	No. Variables/Total	Periprocedural Stroke or Death	*P*
Year			0.0294
July 1, 1999, to June 30, 2000	461/5341	6.1%	
July 1, 2000, to June 30, 2001	705/5341	3.8%	
July 1, 2001, to June 30, 2002	793/5341	3.8%	
July 1, 2002, to June 30, 2003	995/5341	2.6%	
July 1, 2003, to June 30, 2004	1130/5341	3.7%	
July 1, 2004, to June 30, 2005	1257/5341	3.0%	
Center experience			0.0010
Interventions 1 to 50	471/5341	5.9%	
Interventions 51 to 150	1089/5341	4.5%	
Interventions 151 and higher	3781/5341	3.0%	
Patient volume			0.0014
≤50 interventions/year	2067/5341	4.6%	
>50 interventions/year	3274/5341	2.9%	

*Univariate analysis

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Pro-CAS: effect of age and gender*

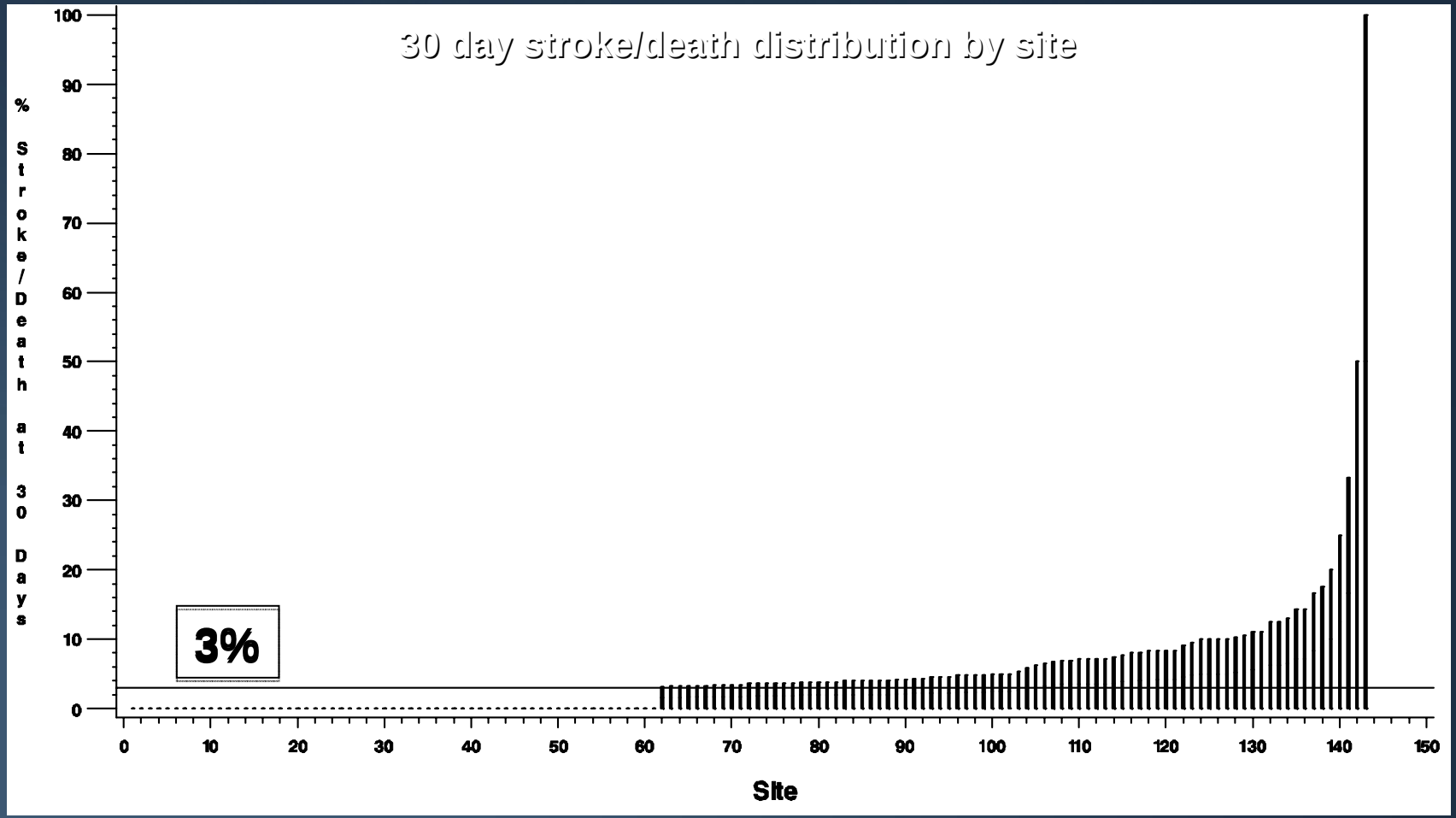
Age			<0.0001
<60 years	679/5341	1.3%	
60–69 years	1811/5341	3.0%	
70–79 years	2133/5341	3.8%	
≥80 years	718/5341	6.3%	
Gender†			0.4158
Male	3421/4834	3.5%	
Female	1413/4834	3.0%	

*Univariate analysis

Pro-CAS: conclusions

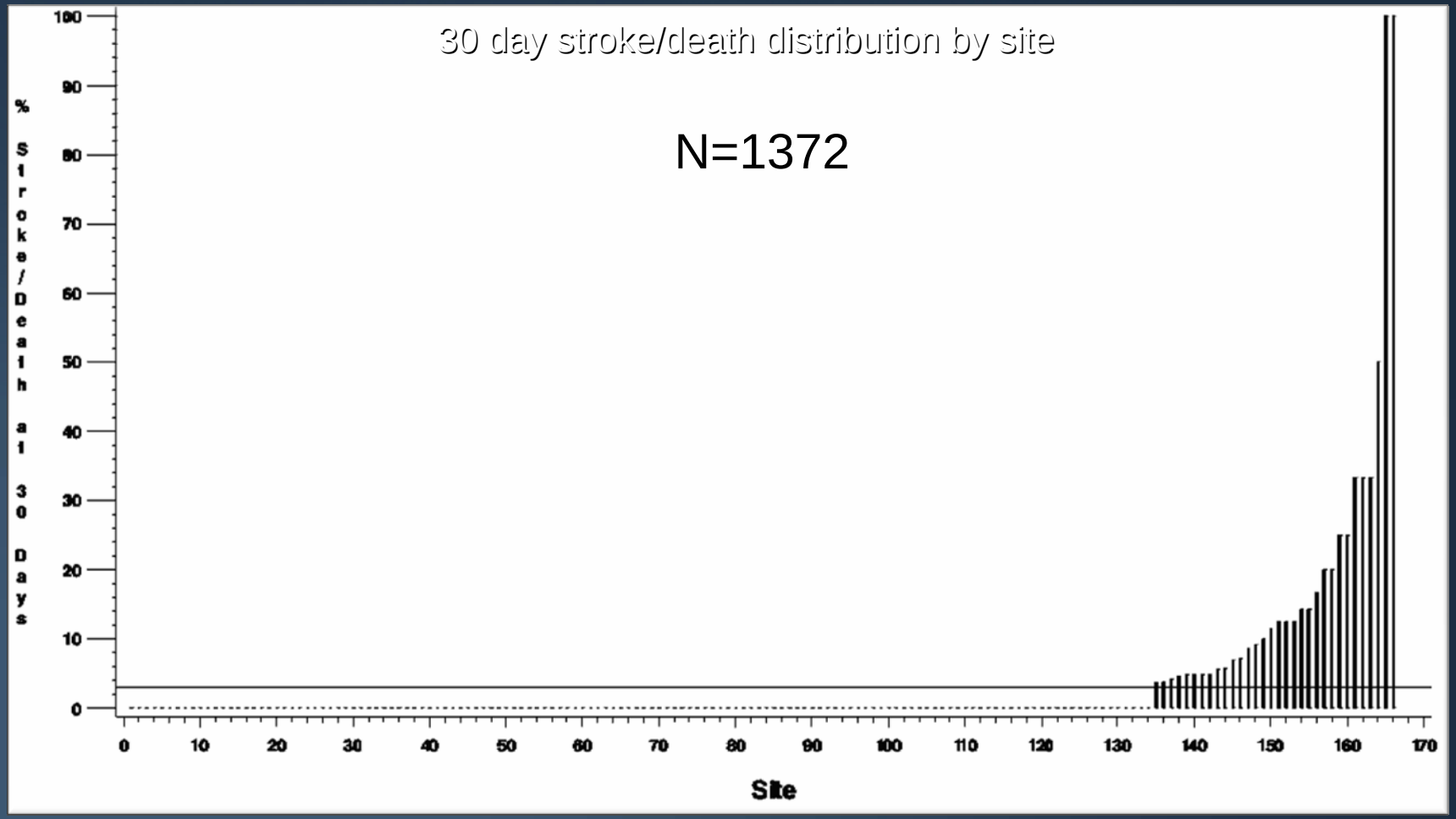
- Improving CAS outcomes with greater experience
- Similar age related gradient seen in SPACE, CAPTURE

CAPTURE:
Asymptomatic Patients <80 Years



No stroke/death at 43% (61/143) of sites

CAPTURE 2:
Asymptomatic <80 Patients



No stroke or death in 81% (134/166) of sites

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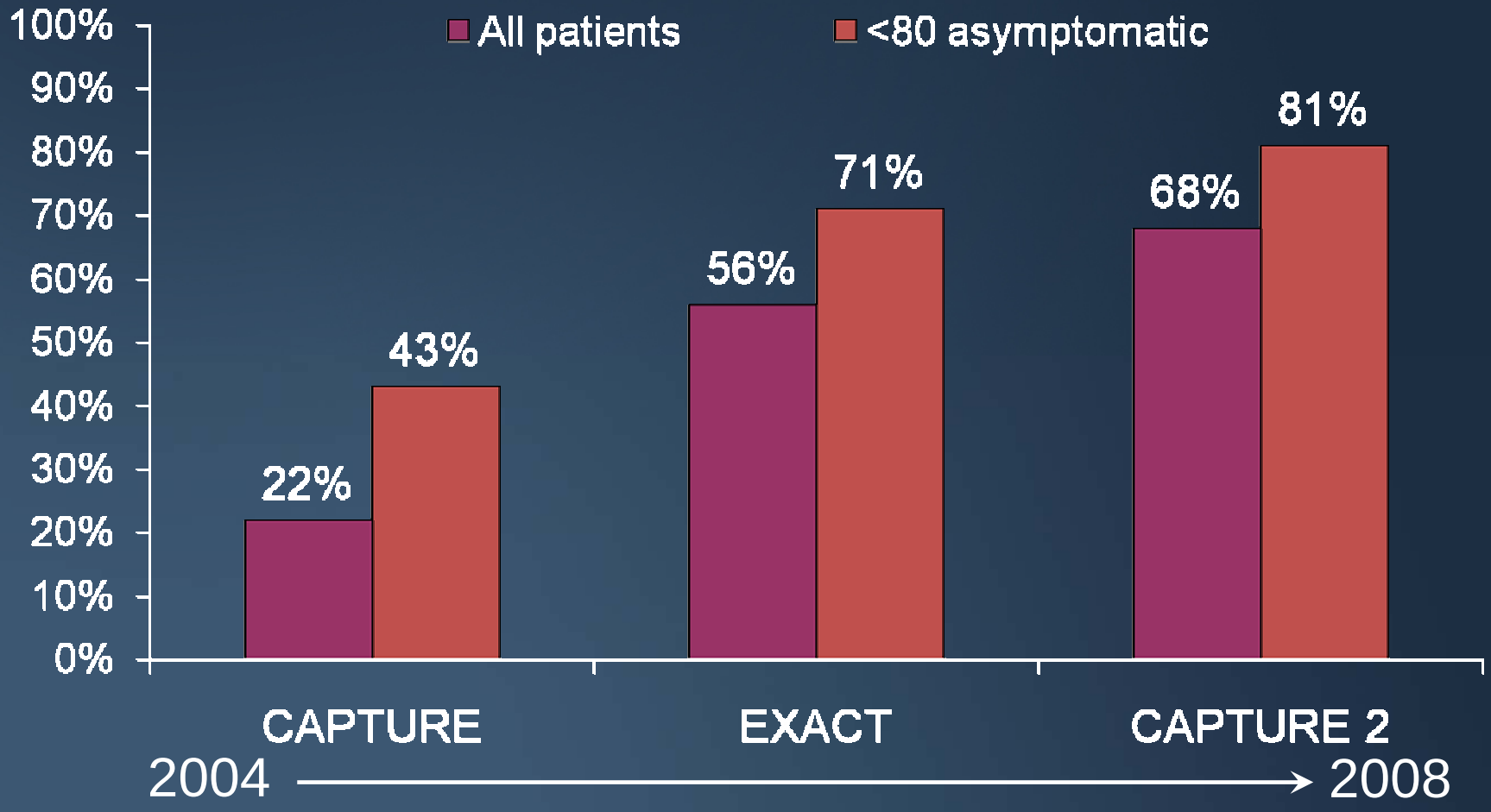
Outcome Improvements with Increasing Volumes



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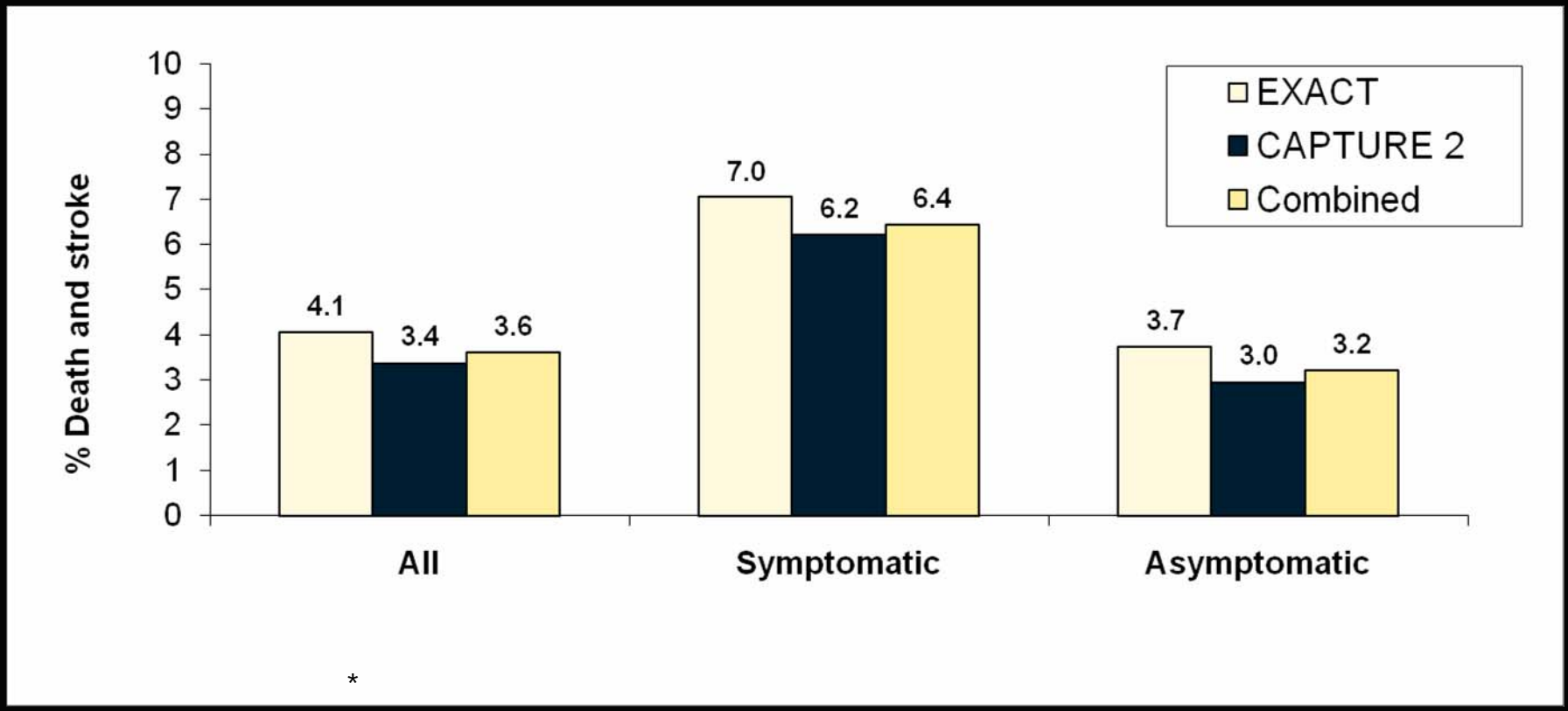
EXACT and CAPTURE 2
30-day Composite Endpoint of Death and Stroke



*

EXACT (N=2145)*	EXACT (N=213)	EXACT (N=1931)
CAPTURE 2 (N=4175)	CAPTURE 2 (N=548)	CAPTURE 2 (N=3627)
Combined (N=6320)	Combined (N=761)	Combined (N=5558)

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

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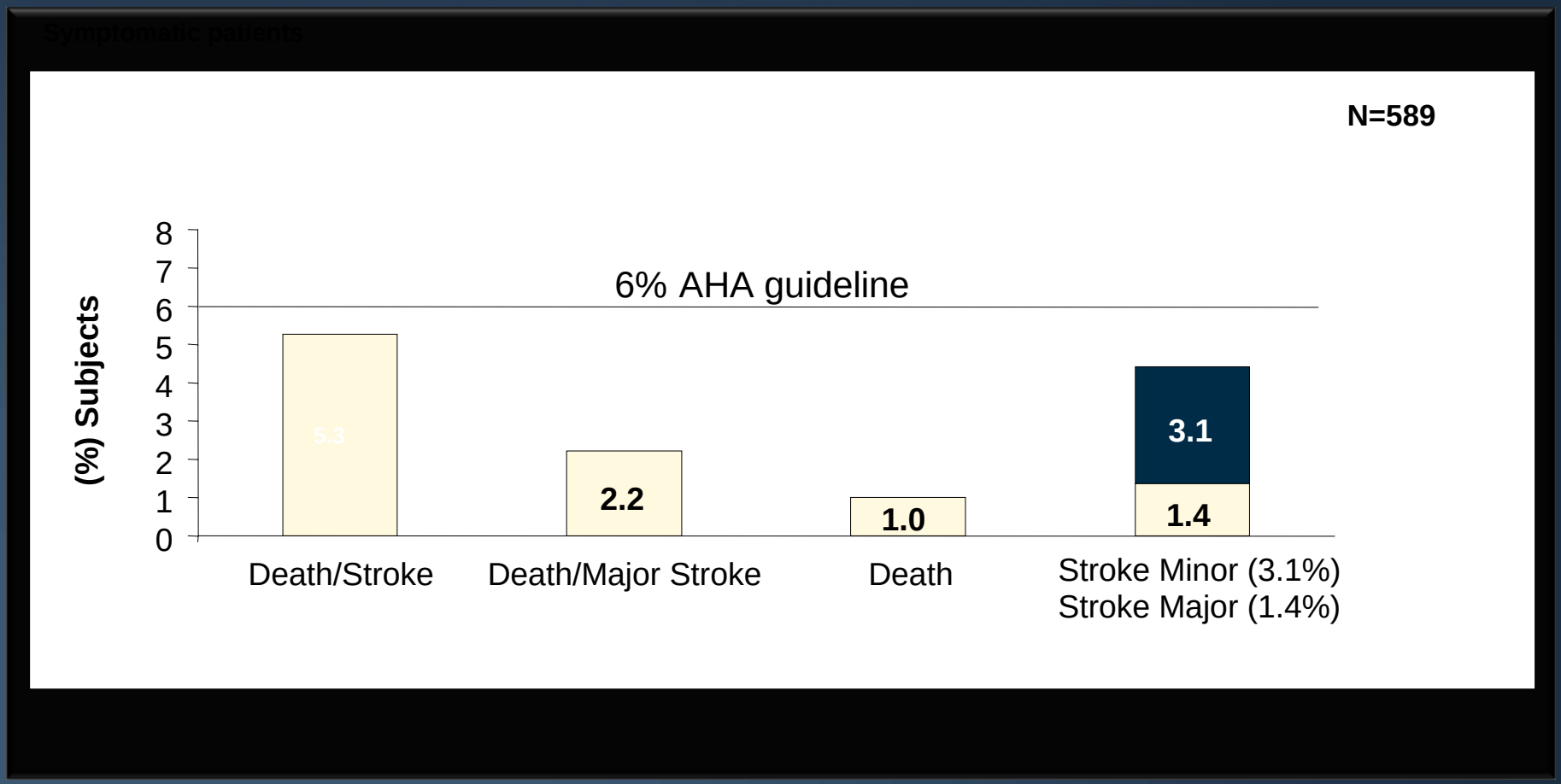
EXACT/CAPTURE 2 (combined): 30-day major adverse events symptomatic patients <80 years



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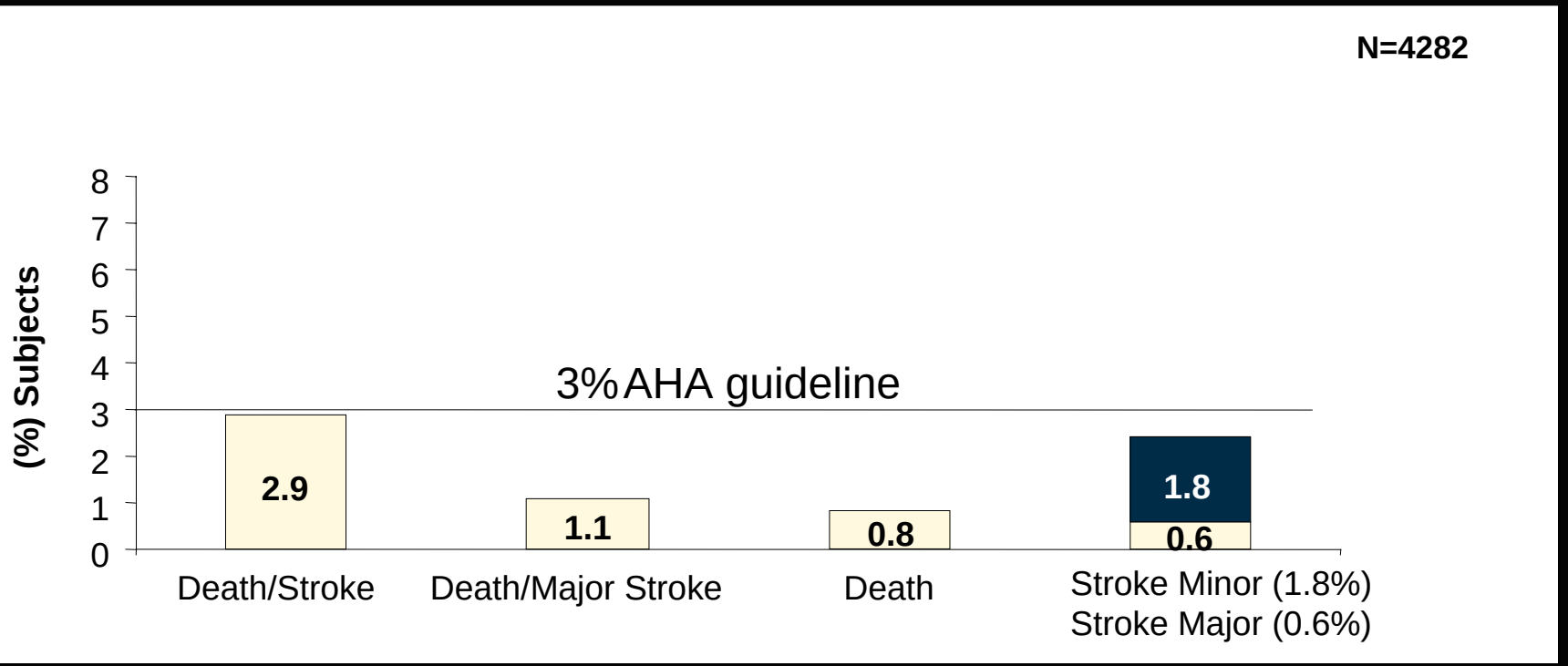
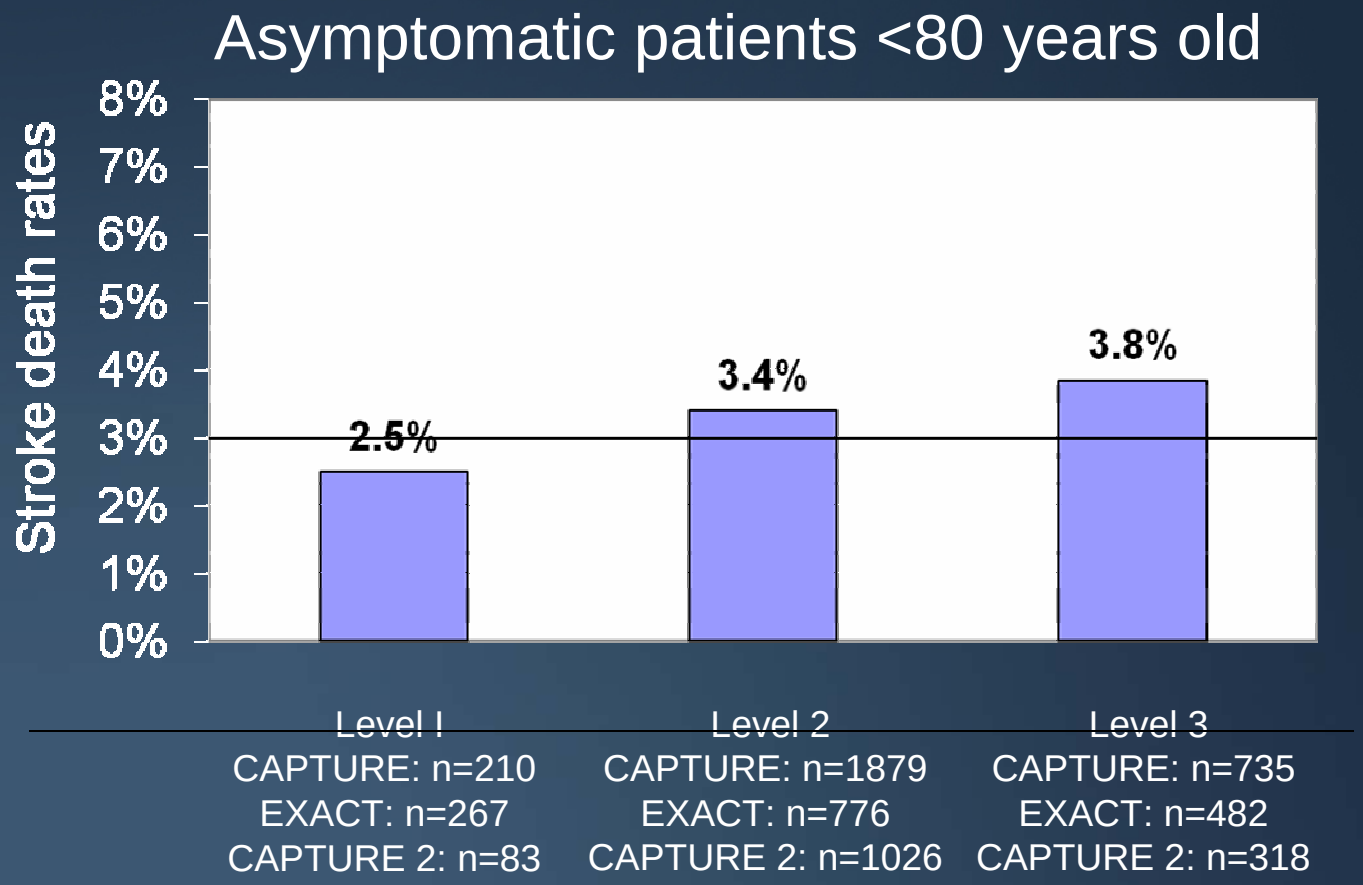
EXACT/CAPTURE 2 (combined): 30-day major adverse events asymptomatic patients <80 years



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

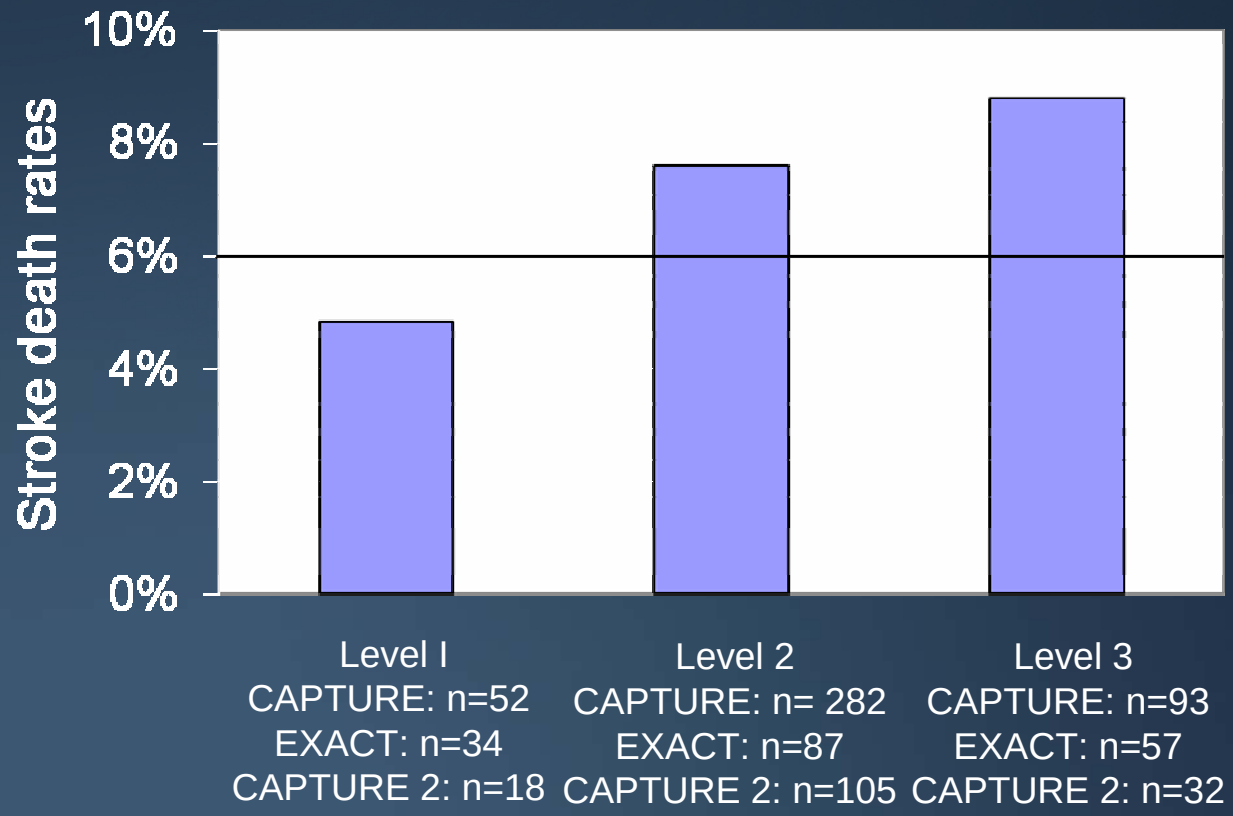
The Influence of Experience: PMS Outcomes



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

The Influence of Experience: PMS Outcomes

Symptomatic patients <80 years old

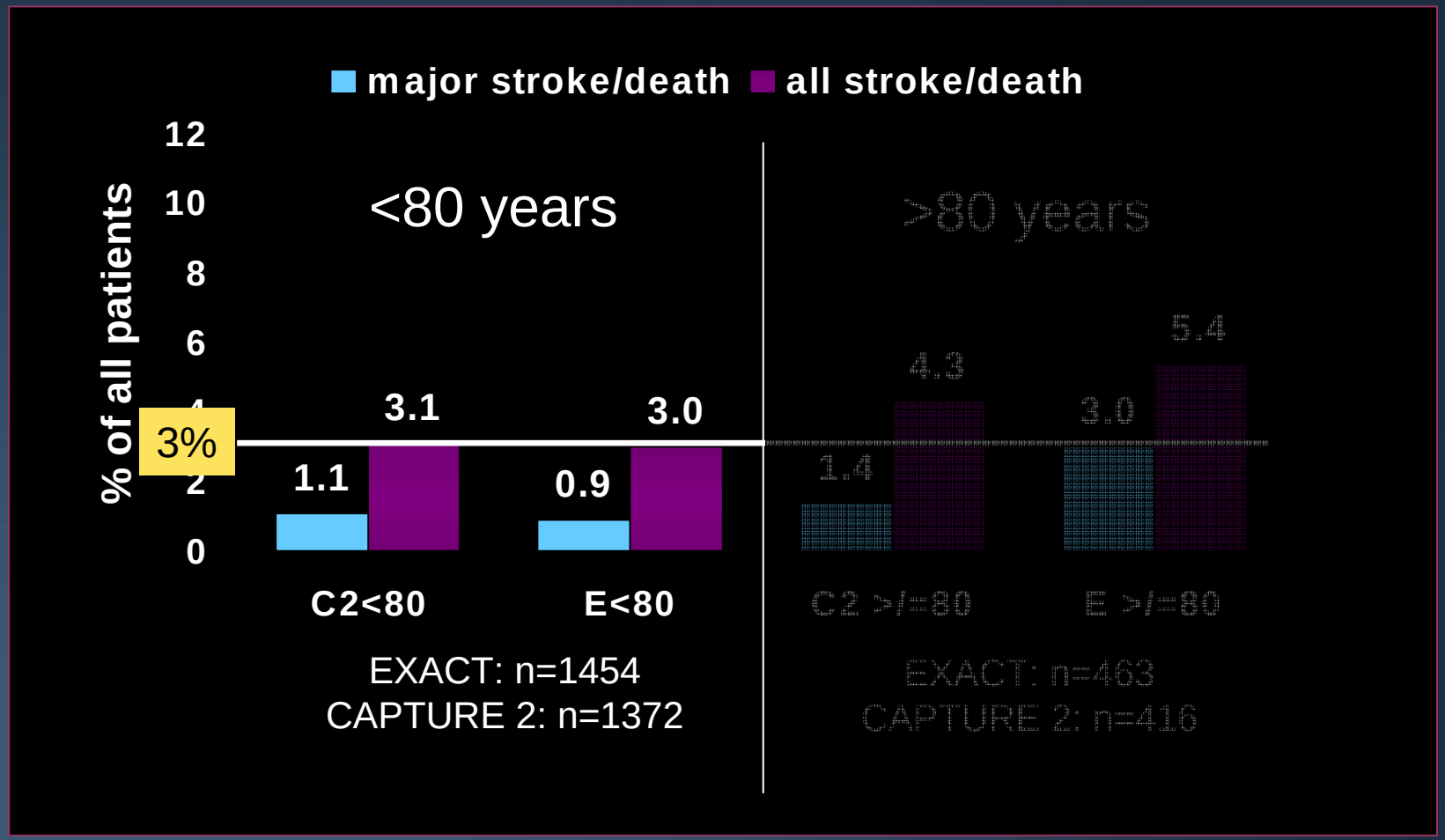


* Hierarchical events – Includes only the most serious event for each patient and includes only each patient's first occurrence of each event.

Devices and Outcomes

CAS outcomes: No differences by stent

30 day Outcomes



- Hierarchical Events – Includes only the most serious event for each patient and includes only each patient's first occurrence of each event
- Clinical Studies are not directly comparable by methodology presented. -Data from respective studies are presented for educational purposes

Future Data Sets

- CREST: 2009-2010
- ACT I: Lead-in phase

Event	30 days, N=118
Death, Stroke, and MI*	1.7%
All Stroke and Death*	1.7%
Major Stroke and Death*	0.0%
Death	0.0%
All Stroke	1.7%
Major Stroke	0.0%
Minor Stroke	1.7%
MI	0.0%

Conclusions

- A relationship of experience to outcomes in CAS appears to be present based on indirect evidence:
  - Generally improving outcomes for the field
  - Operator disparity
- …and direct evidence
  - EVA-3S vs. “the world”
  - IDE and PMS registries
- No convincing evidence of device influence
- Future trials will deliver more prospective, and likely confirmatory, data