Strokes after TAVR: Perspectives from the PARTNER Trial

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Disclosure Statement of Financial Interest

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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	• Edwards Lifesciences
• Steering Committee	• Edwards Lifesciences, Claret Medical, Meril
• SAB (Equity)	• Thubrikar Aortic Valve, Inc

Perspective #1

Stroke following TAVR was an immediate concern and led to discussions about its role in surgical candidates

Controversy Raised

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Transcatheter Aortic-Valve Implantation — At What Price?

Hartzell V. Schaff, M.D.

In 2000, Bonhoeffer et al. described transvenous placement of a pulmonary-valve prosthesis and speculated that similar technology might be used in other cardiac valves, including the aortic position.[1] Two years later, the first transcatheter insertion of an aortic-valve prosthesis was performed by Cribier et al.[2] Transcatheter aortic-valve

patients who are eligible for transfemoral insertion and may decrease vascular injury.

But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith and colleagues report a 5.5% risk of stroke or transient ischemic attack within 30 days after

PARTNER Trial
Standardized Definitions

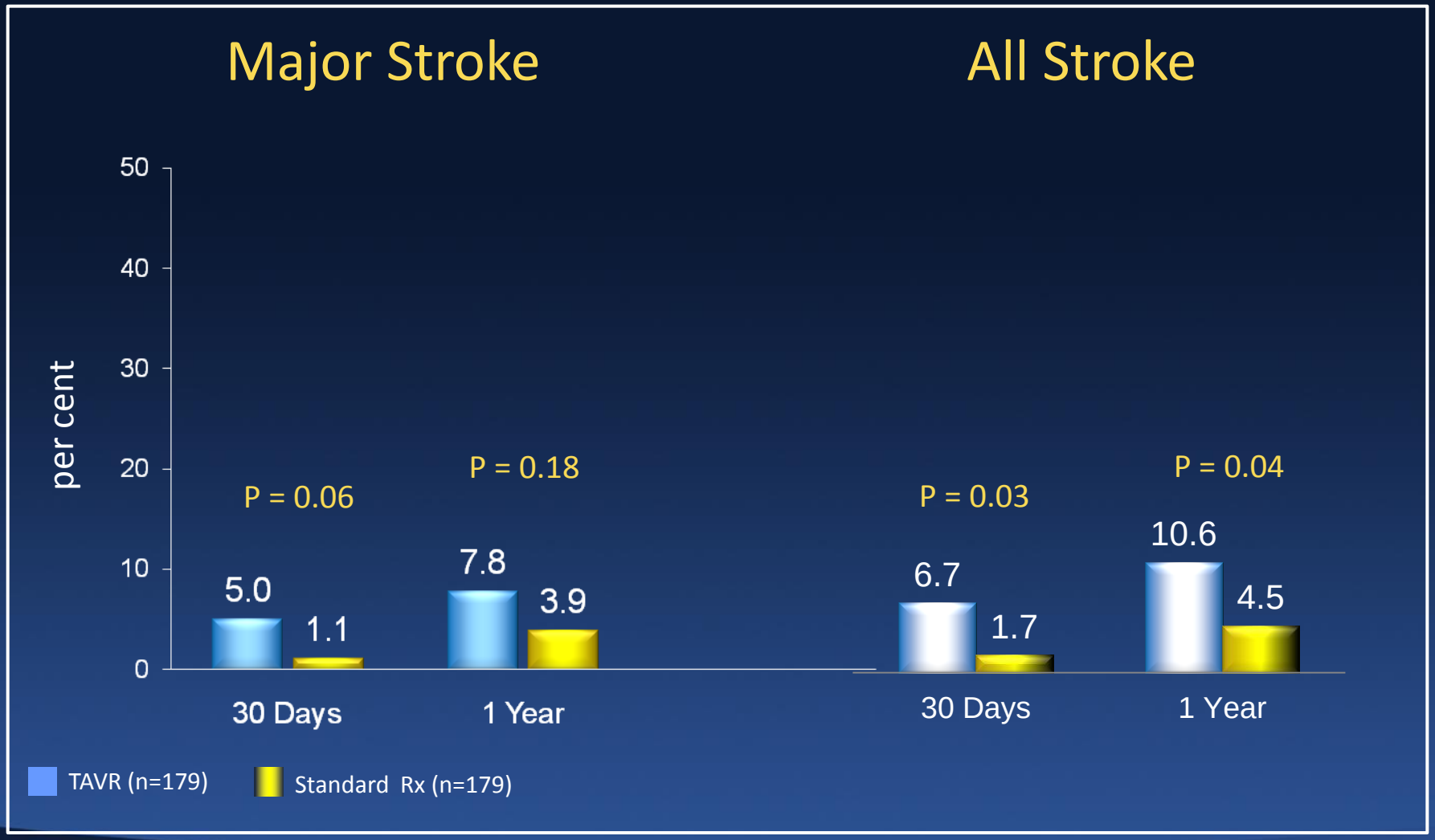
- All neurologic events were reviewed and adjudicated by an independent CEC
- Definitions
  - ***TIA***
    - **Focal neurologic event that was fully reversible in < 24 hours in the absence of any new imaging findings of infarction or other primary medical cause (hypoglycemia, hypoxia, etc).**
  - ***Stroke*** **:**
    - **Focal neurologic deficit lasting ≥ 24 hours OR**
    - **Focal neurologic deficit lasting < 24 hours with imaging findings of acute infarction or hemorrhage.**
    - **Stroke was further classified as ischemic, hemorrhagic (epidural, subdural, subarachnoid), or ischemic with hemorrhagic conversion.**

Why not TIA?

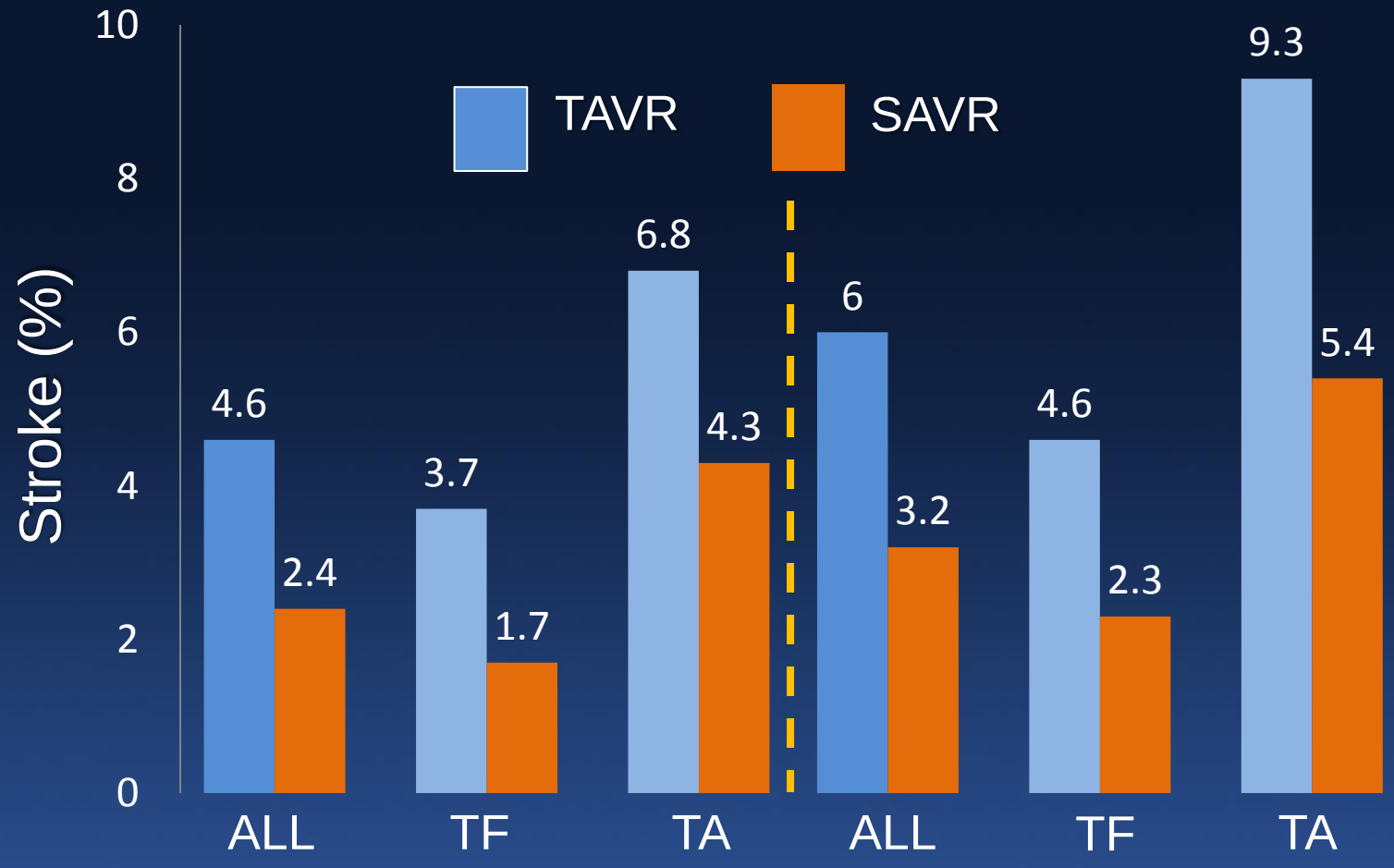
- Difficult to ascertain in this elderly population
- Clinical significance remains unclear
- Etiology may not be the same as stroke

Neuro events at 30 days and 1 year

Inoperable cohort B



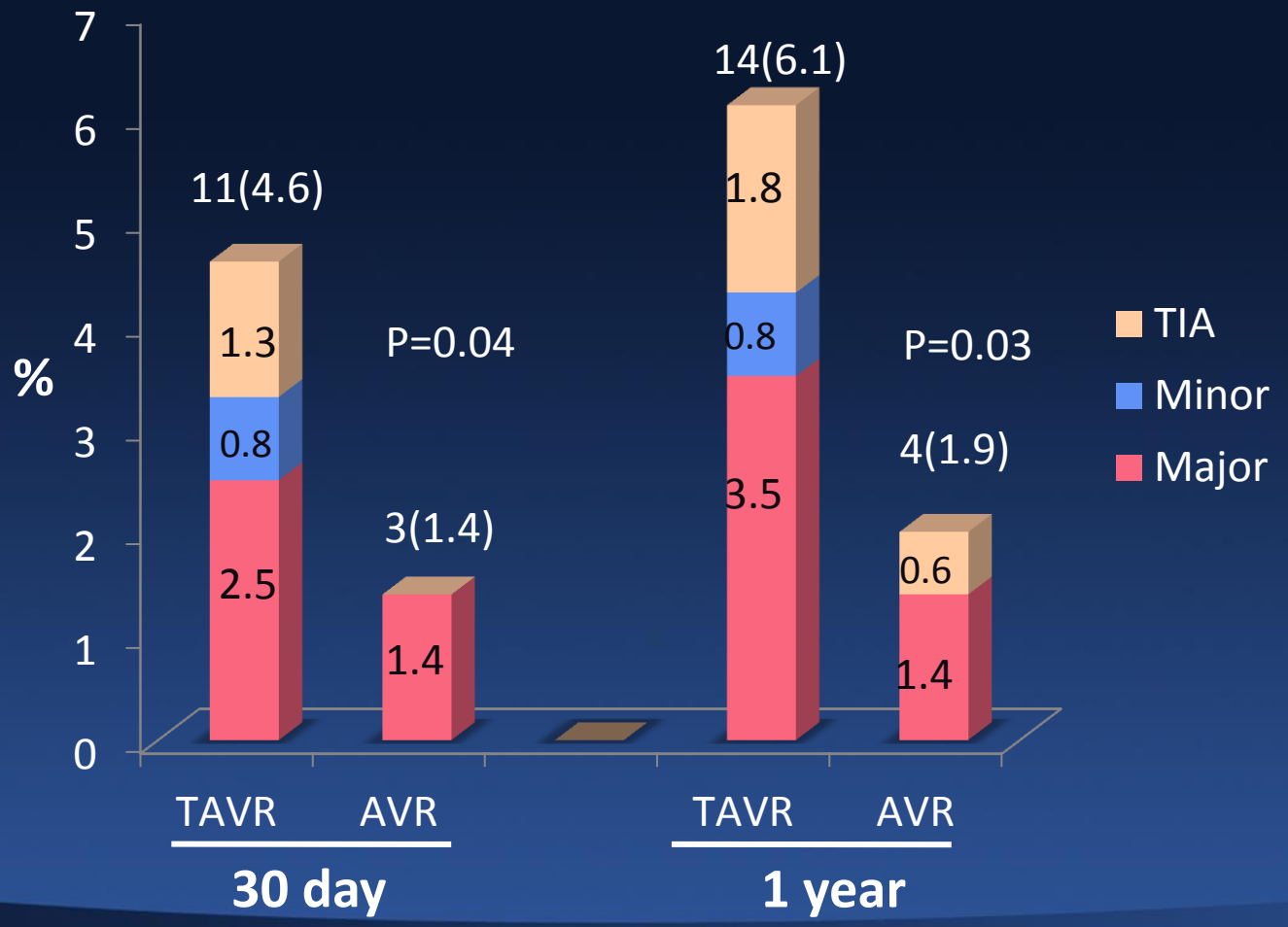
All Stroke : PARTNER A (ITT)



Smith et al, NEJM, June 2011

PARTNER-A Neurological Events (TF)

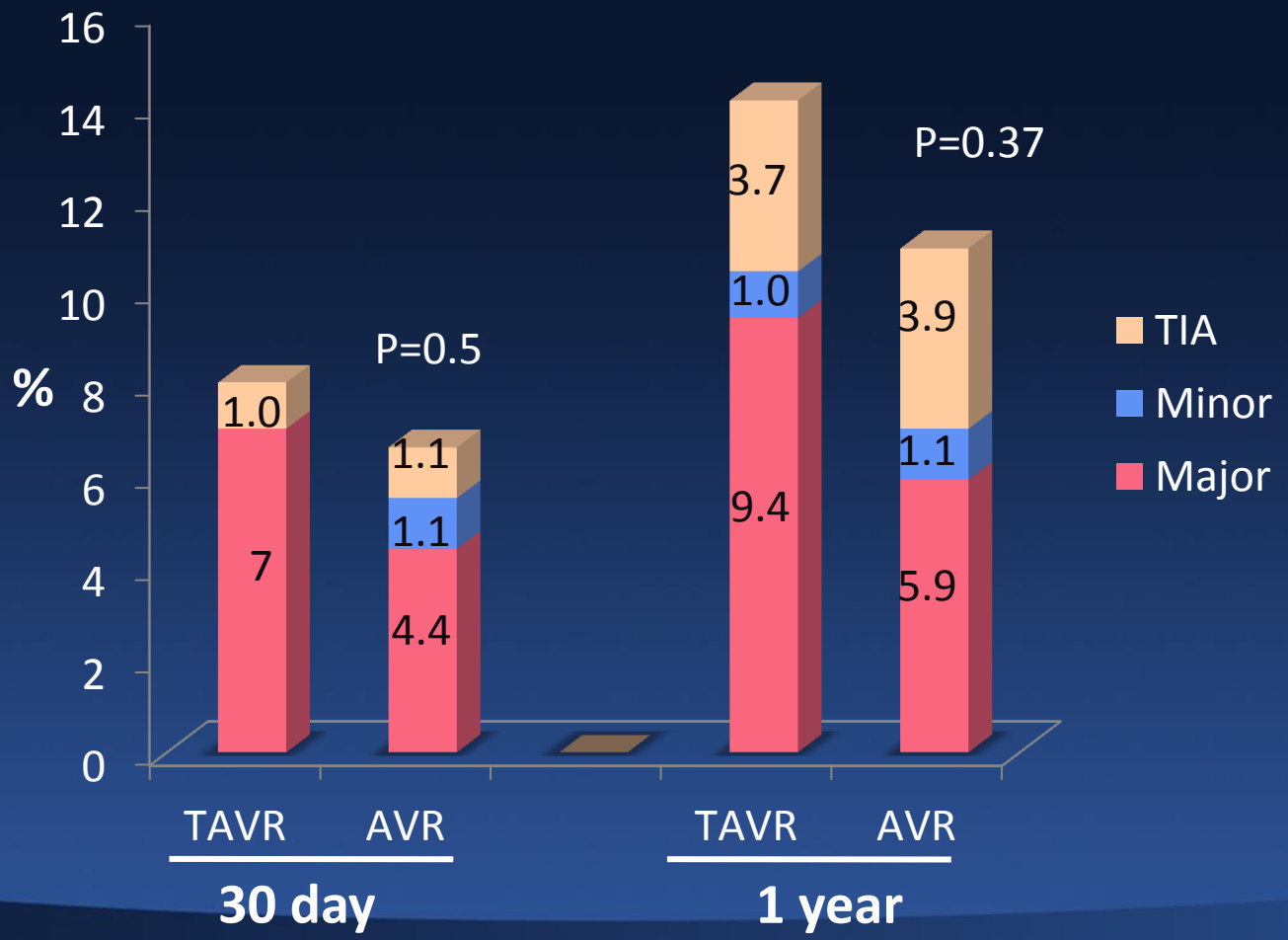
As Treated



Miller et al, J Thorac Cardiovasc Surg. 2012 Apr;143(4):832-843.

PARTNER-A Neurological Events (TA)

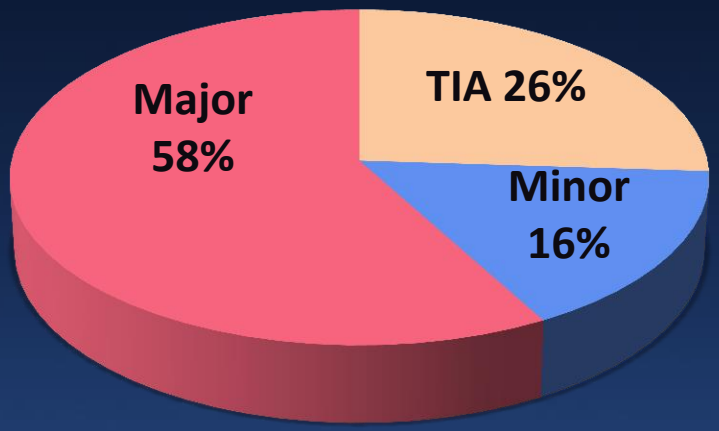
As Treated



Miller et al, J Thorac Cardiovasc Surg. 2012 Apr;143(4):832-843.

Neurologic Events in PARTNER-A

TAVR



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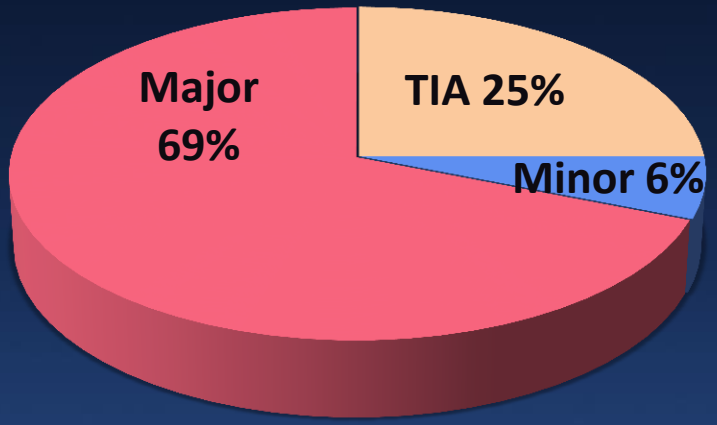
AVR



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47 patients, 49 events

- Ischemic- 72%, hemorrhagic- 0%, (ischemic → hemorrhagic- 4%), unknown- 24%

Miller et al, J Thorac Cardiovasc Surg. 2012 Apr;143(4):832-843.

Perspective #2

TAVR has increased risk of stroke compared to surgical AVR in initial experience

Risk Factors for Neurologic Events

Early high peaking hazard phase

Risk Factor	*Coefficient ± SD*	*P*	*R (%)*
Early hazard phase			
TAVR	2.21±0.68	.001	59
Smaller AVA index in TAVR group	-11.8±5.1	.02	57

Atrial fibrillation not significant in multivariable analysis

R(%) = bagging reliability

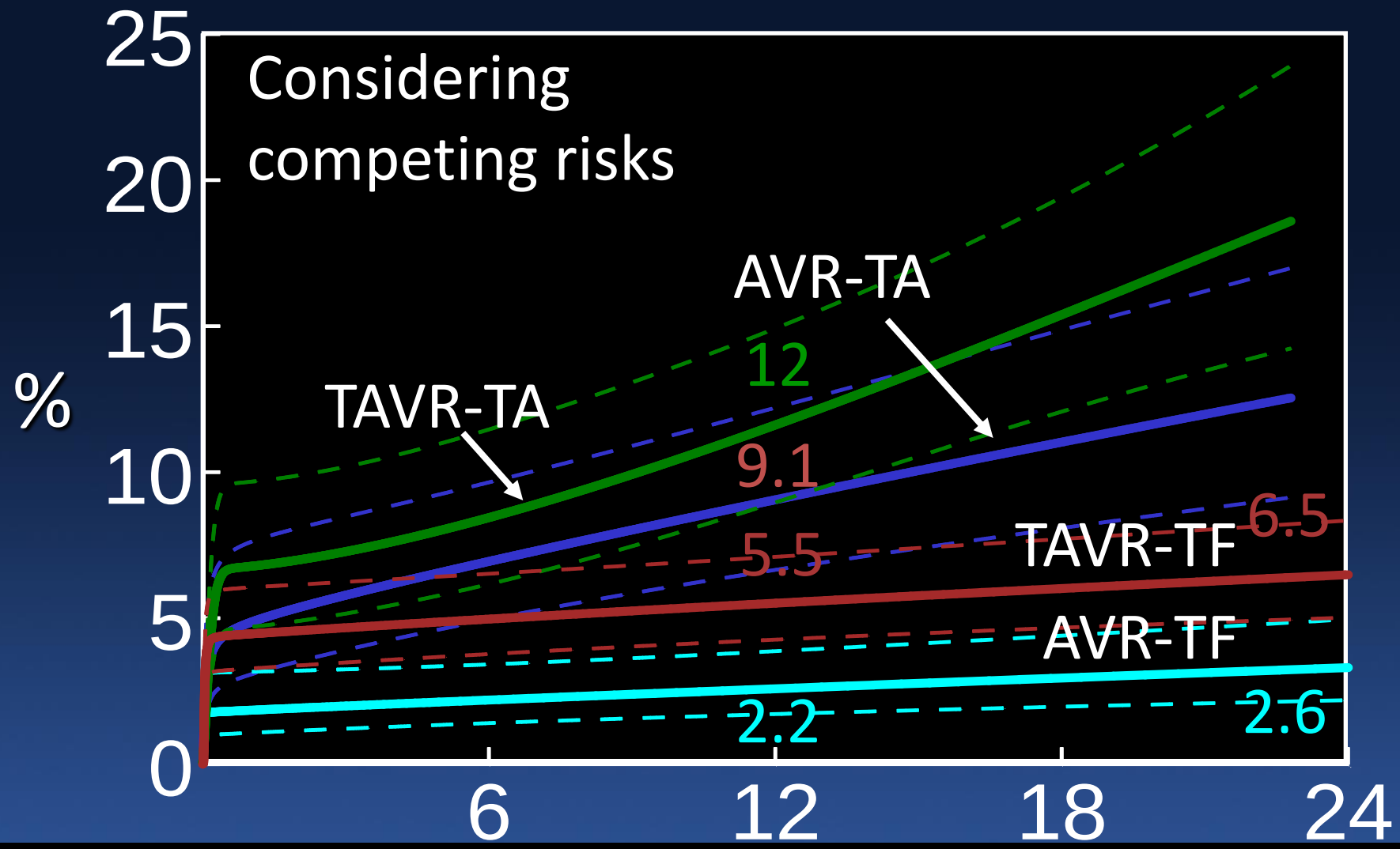
Risk Factors for Neurologic Events

Late constant hazard phase

Risk Factor	*Coefficient ± SD*	*P*	*R (%)*
Constant hazard phase			
TAVR	0.40±0.43	0.4	22
(Higher) NYHA	0.95±0.40	.02	75
Stroke or TIA within 6-12 mo	1.93±0.64	.002	60
Non-TF TAVR candidate	2.3±0.45	<.0001	96
History of PCI (less risk)	-1.60±0.63	.01	77
COPD (less risk)	-1.06±0.47	.03	79

R(%) = bagging reliability

Neurologic event



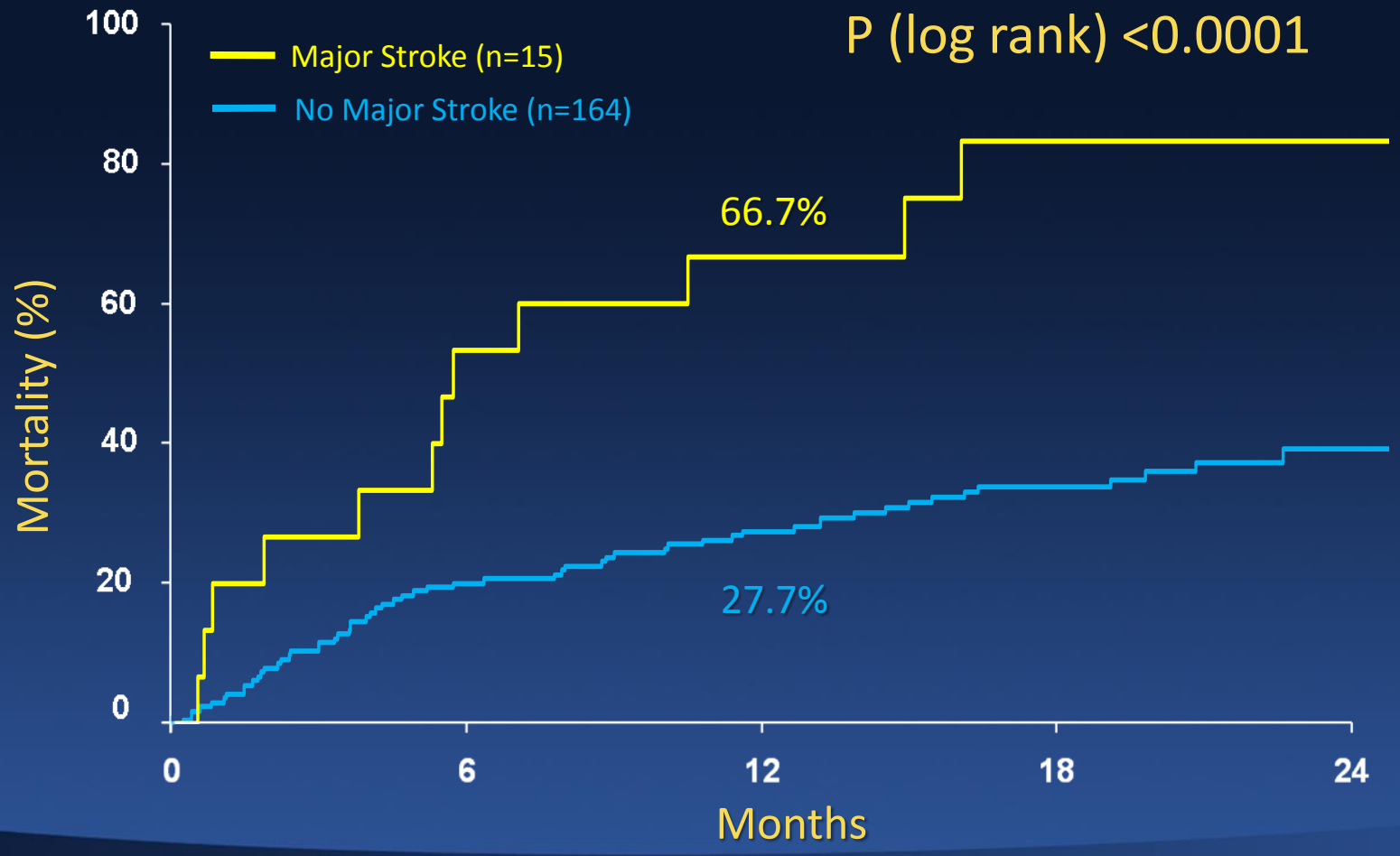
TAVR-TF	240	202	179	114	67
TAVR-TA	104	77	64	32	
AVR-TF	221	170	160	106	59
AVR-TA	92	67	62	18	

Perspective #3

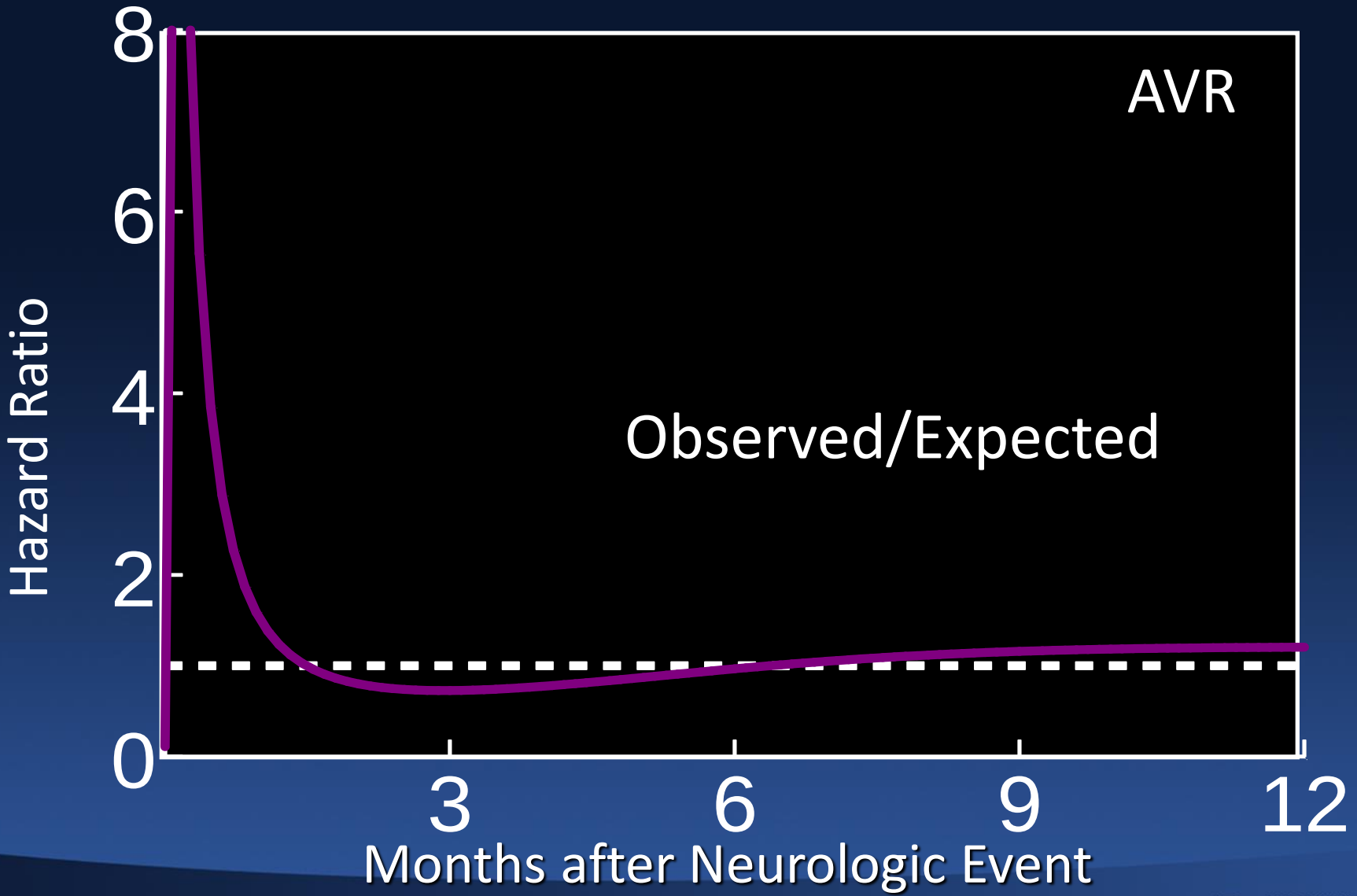
Neurologic complications lead to increased mortality in this elderly comorbid population

Mortality vs. Major Stroke (Cohort B)

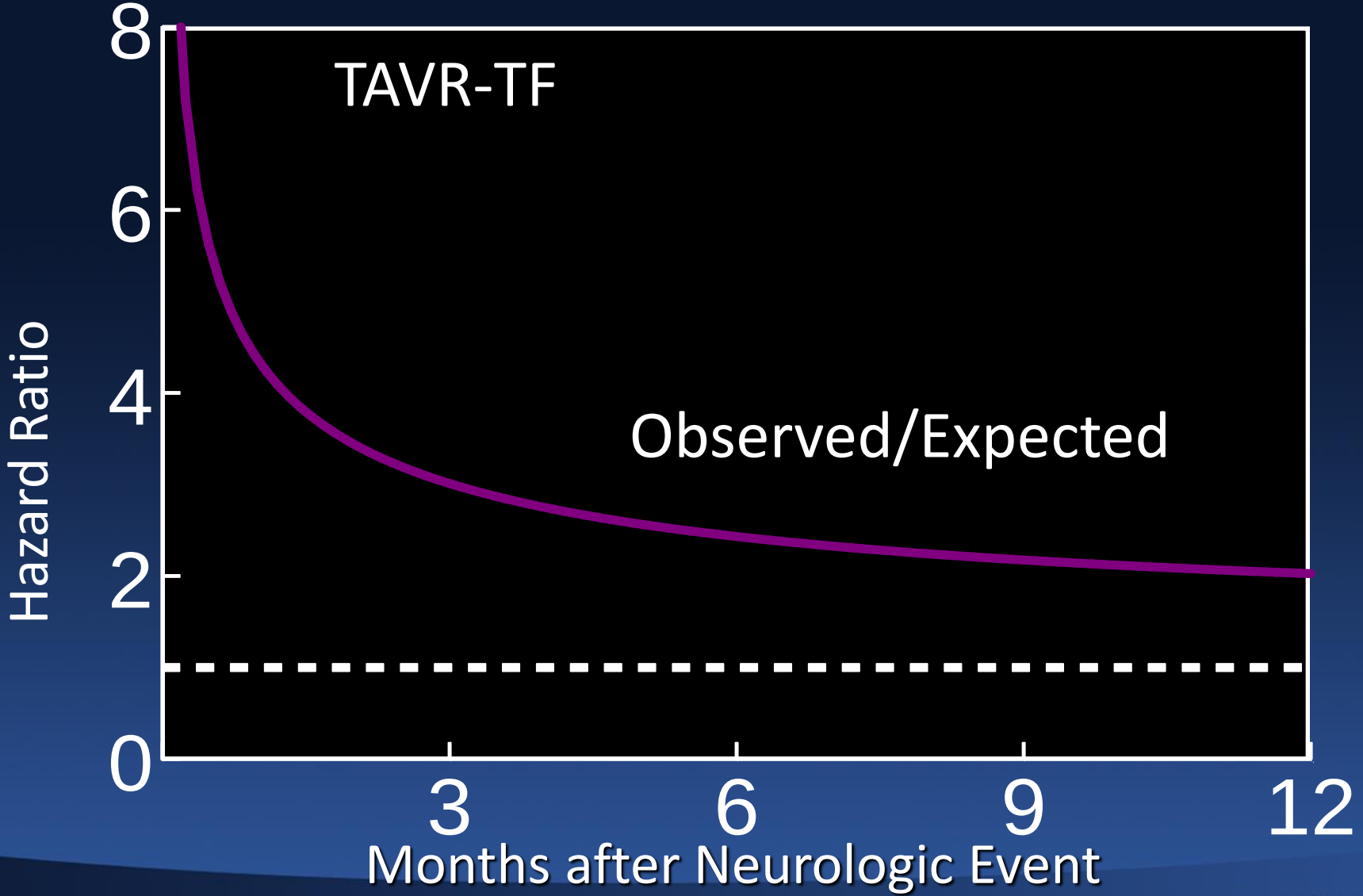
TAVR Patients



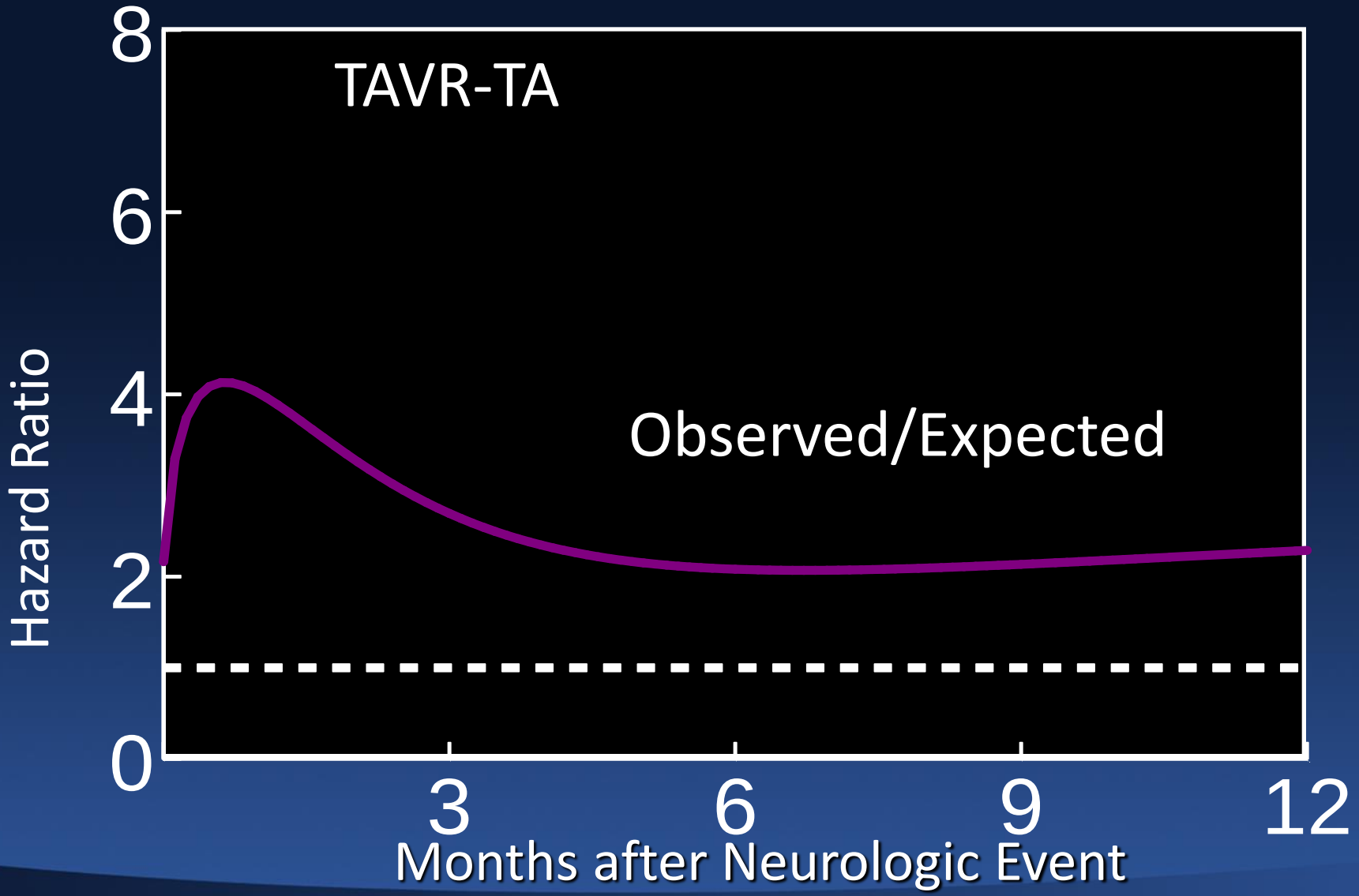
“Mortality Cost” of neuro event



“Mortality Cost” of neuro event



“Mortality Cost” of neuro event



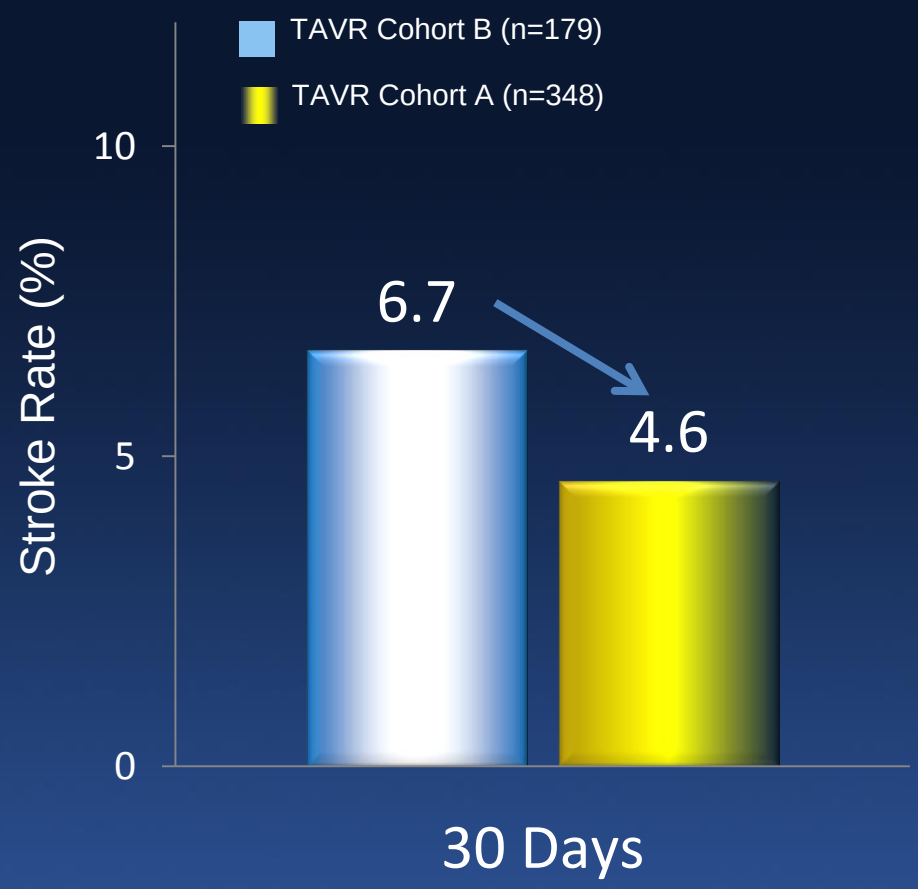
PARTNER-1A: Impact of Complications on Mortality

Complication	# Events (1 year)	# Deaths (1 year)
Major Stroke	18	9
Major Vascular	38	14
Major Bleeding	88	37

Perspective #4

With device iteration and increased operator experience, stroke rates decreased in PARTNER

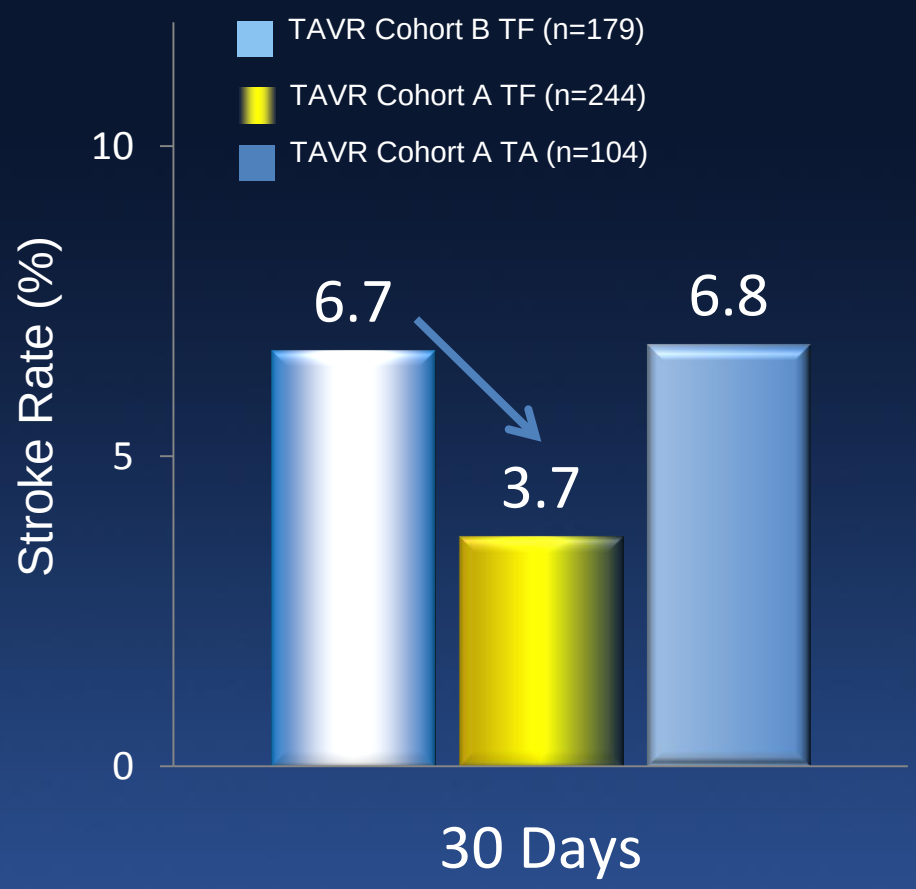
Stroke Rates Lower in Cohort A



Potential Reasons

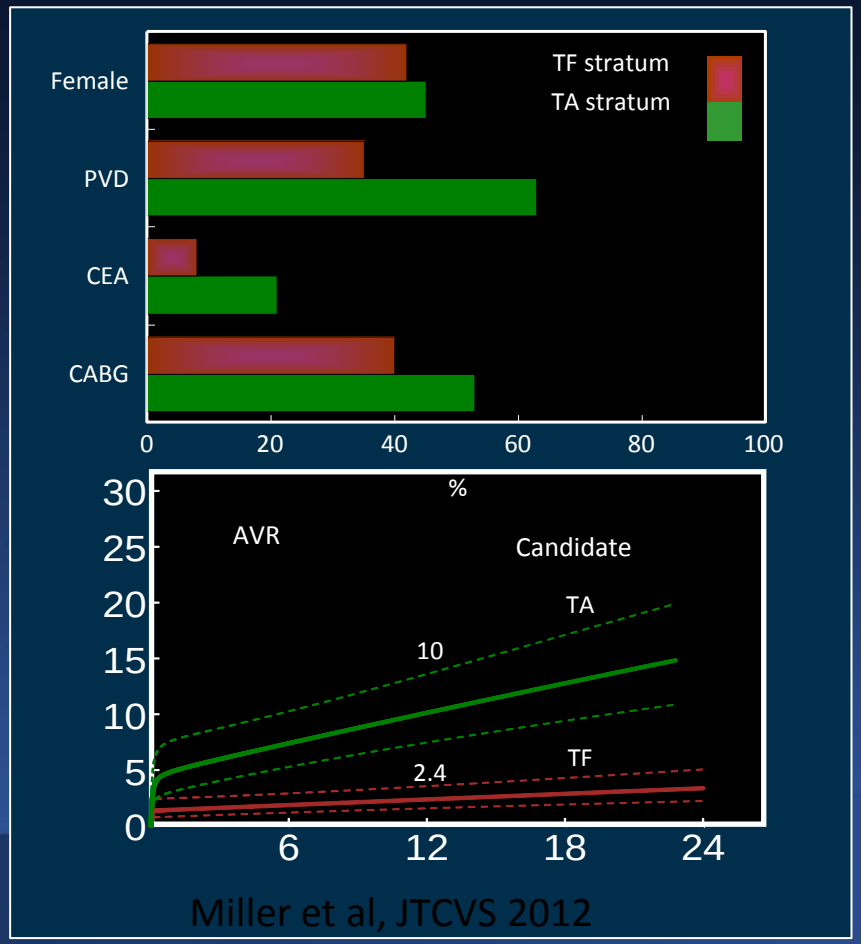
- Patients were healthier than the cohort B patients
- Cohort A enrolled later and therefore sites were further along on the learning curve
- Device iteration (Retroflex III catheter introduced during course of enrollment)

Lower Stroke Rate in TF Arm Only

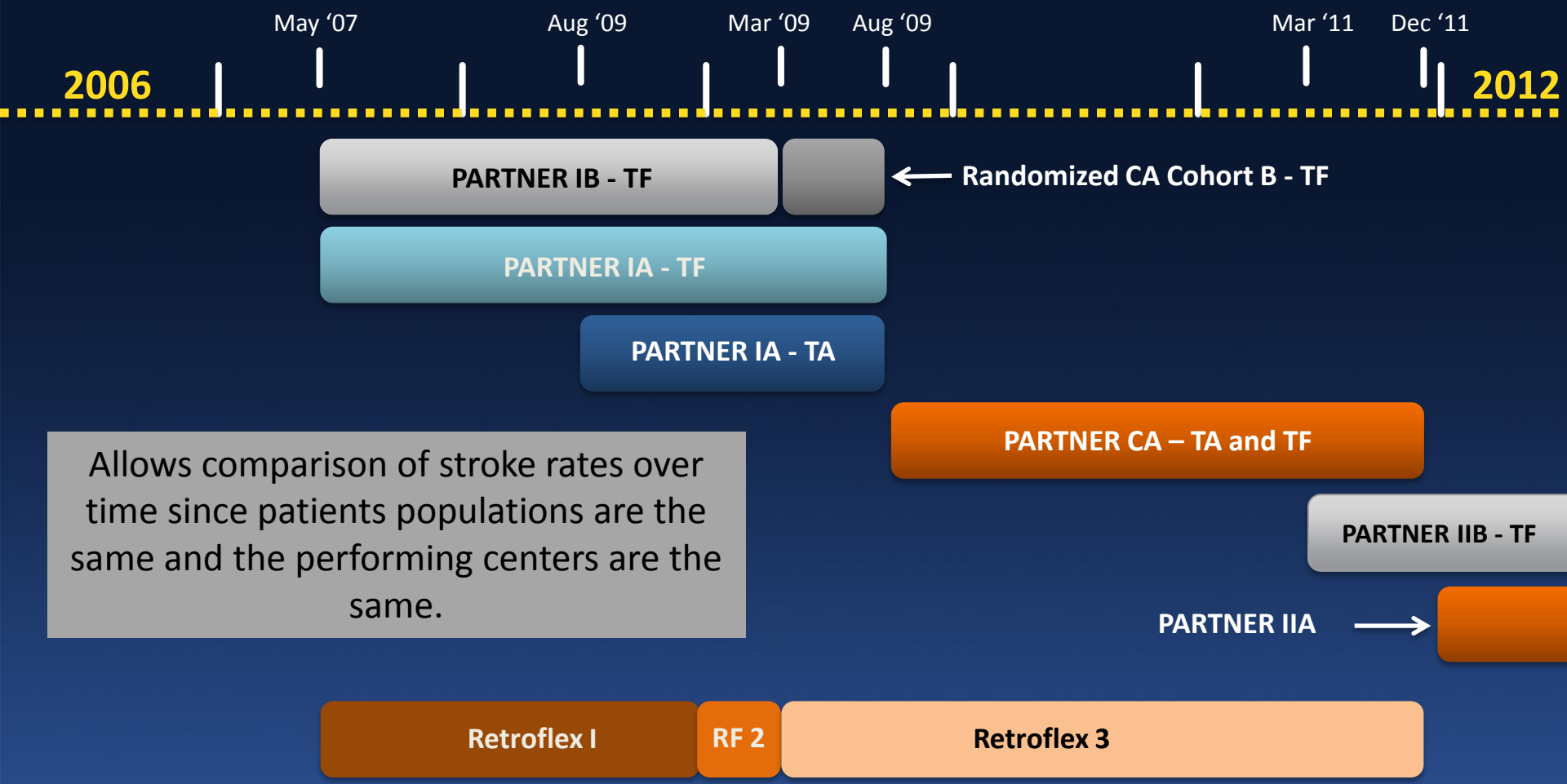


Potential Reasons

- TA population represented a sicker patient population with higher stroke risk

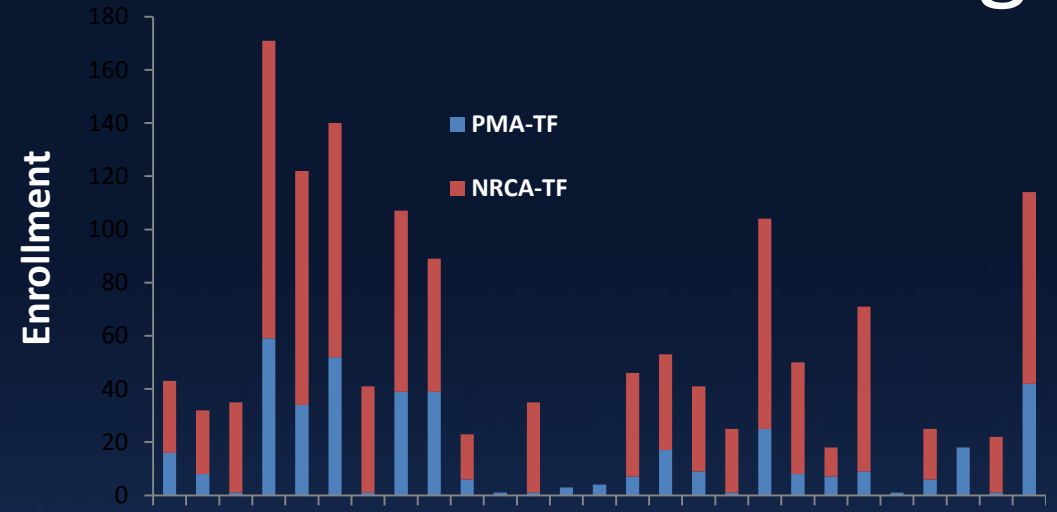


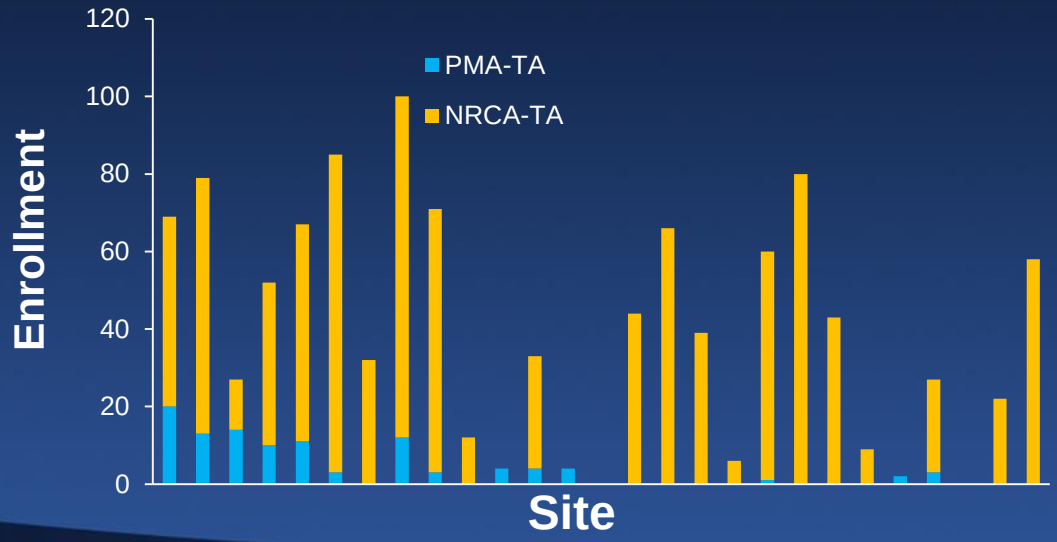
PARTNER Trial Timelines



Allows comparison of stroke rates over time since patients populations are the same and the performing centers are the same.

TAVR Volumes at Sites Increased with NRCA Registry





RCT-TF (27 sites)

Mean Enrollment: 15.4

NRCA-TF (27 sites)

Mean Enrollment: 37.7

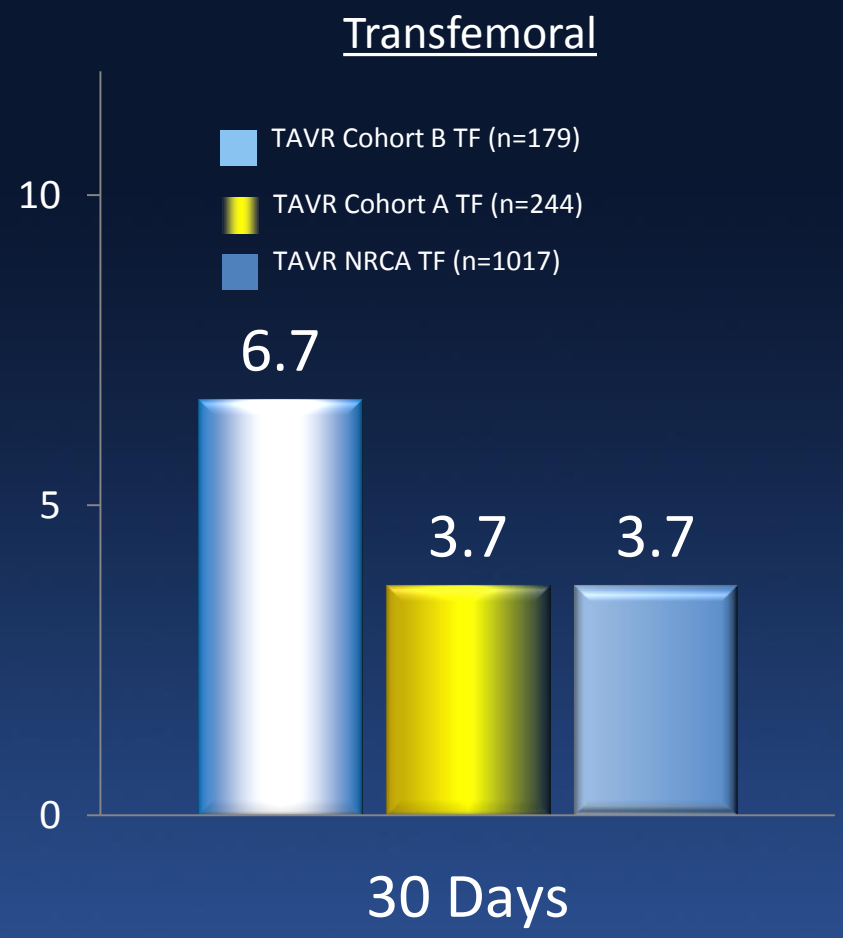
RCT-TA (14 sites)

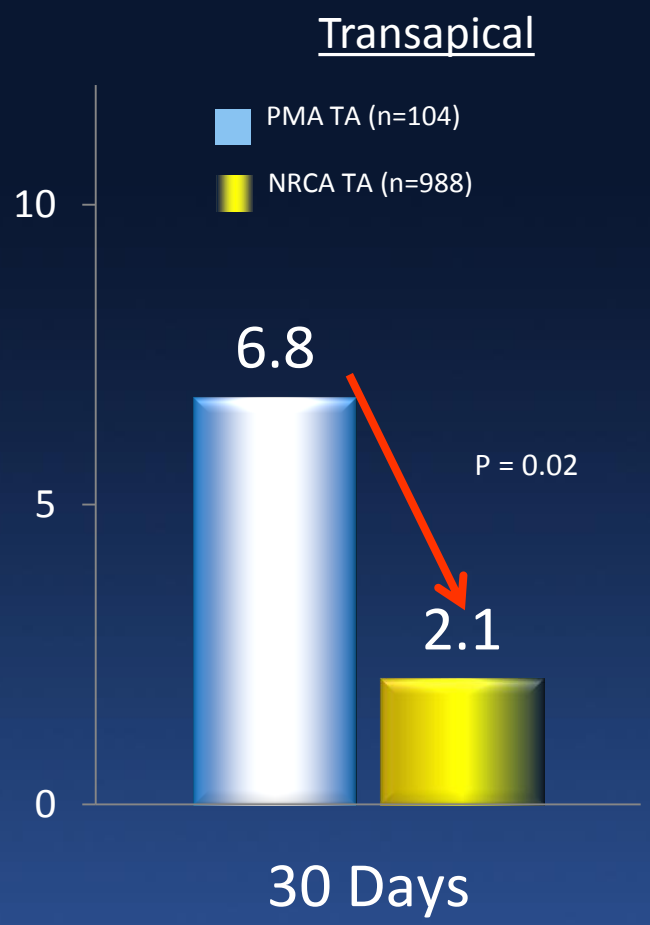
Mean Enrollment: 7.4

NRCA-TF (22 sites)

Mean Enrollment: 44.9

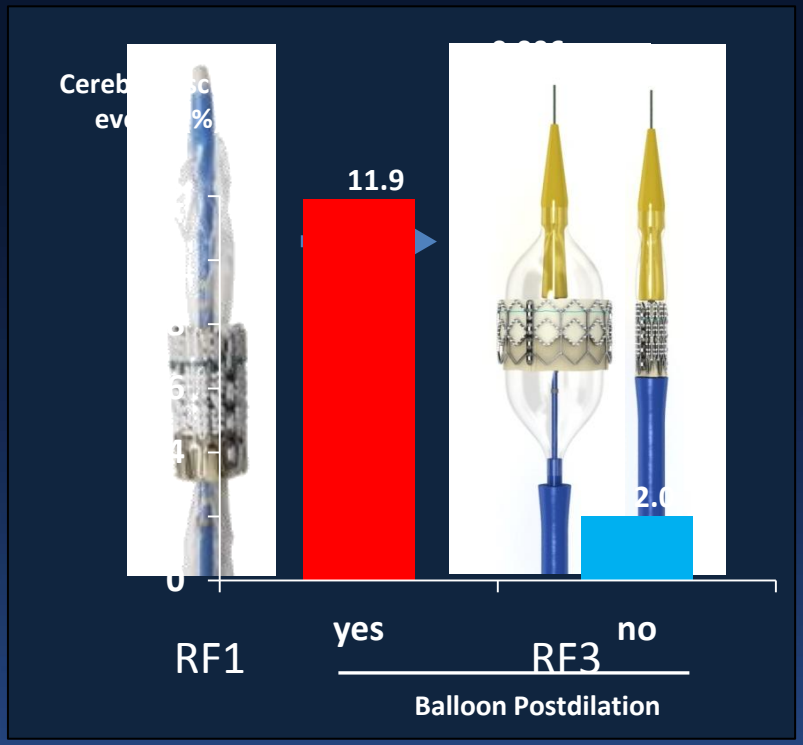
Lower Rates with Experience





Why would stroke rate decrease?

- Increased experience especially in TA arm
- Device improvement
  - Easier to cross ➔ less trauma to aortic valve
  - Fewer BAVs prior to valve
- Improved Procedural Technique
  - Better annular sizing
  - Less Post-Dilatation
    - PMA TF (36.7%) vs NRCA TF (9.4%)
- Better Patient Selection
  - Lower Risk
  - Aggressive Anti-Coagulation in high risk patients

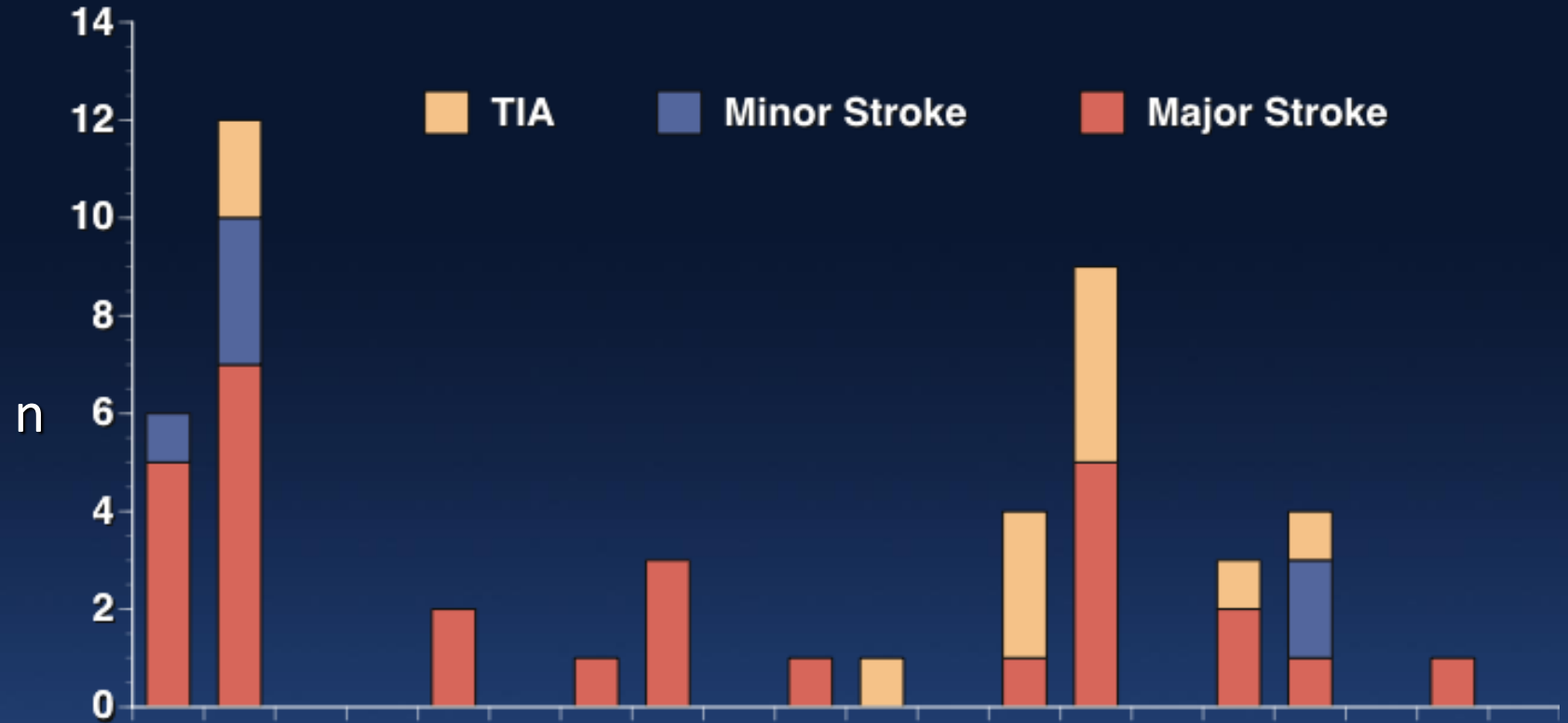


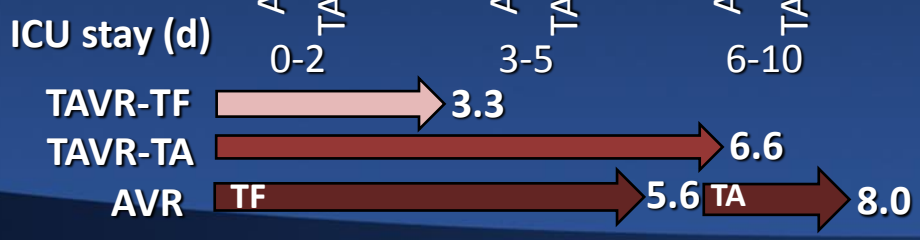
Nombela-Franco et al. JACC Intv 2012

Perspective #5

Timing of strokes suggest multiple etiologies for increased embolic risk

PARTNER-1A: Timing of Neurological Events



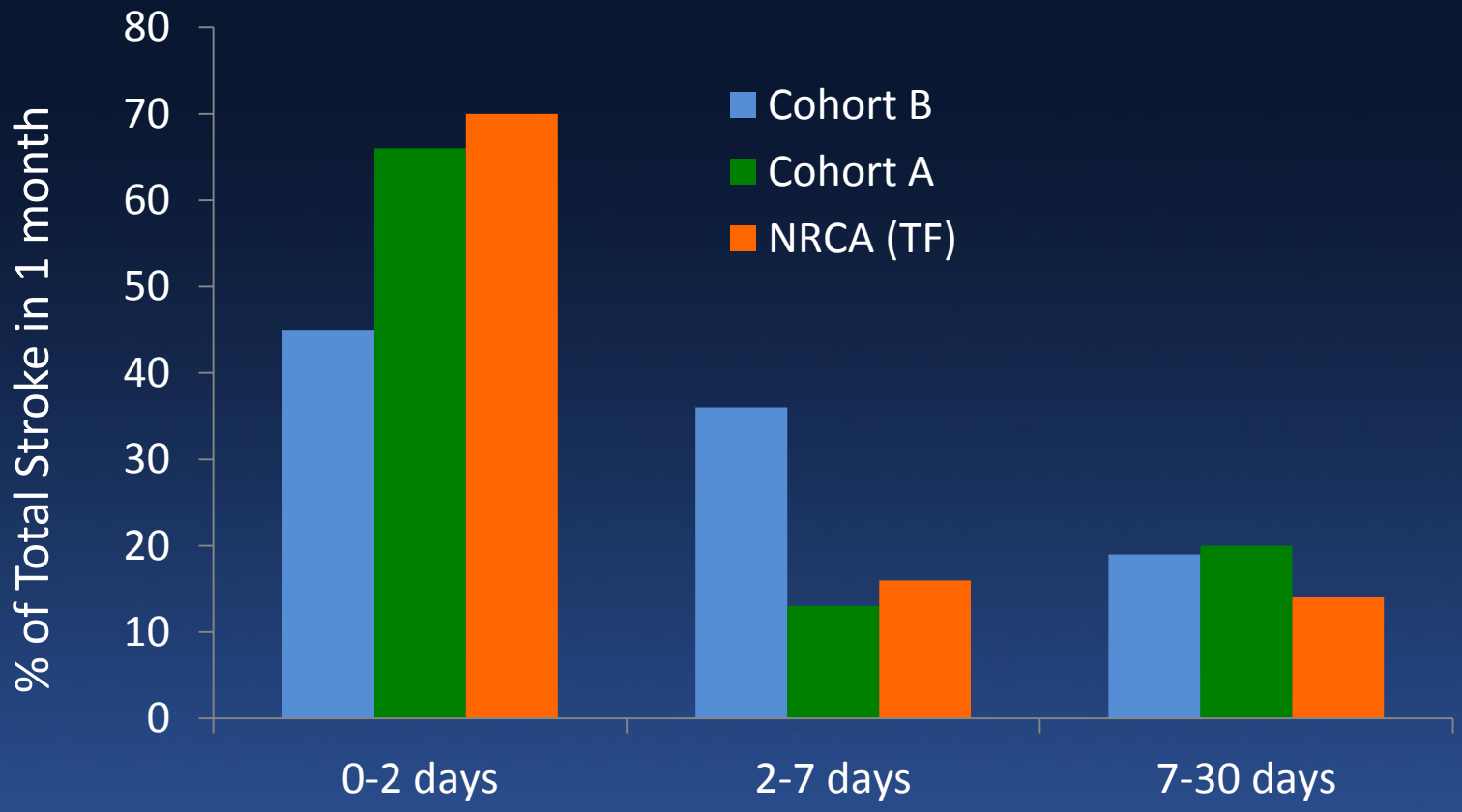


* Adapted from DC Miler and S Kapadia

Etiology of “Delayed” Events

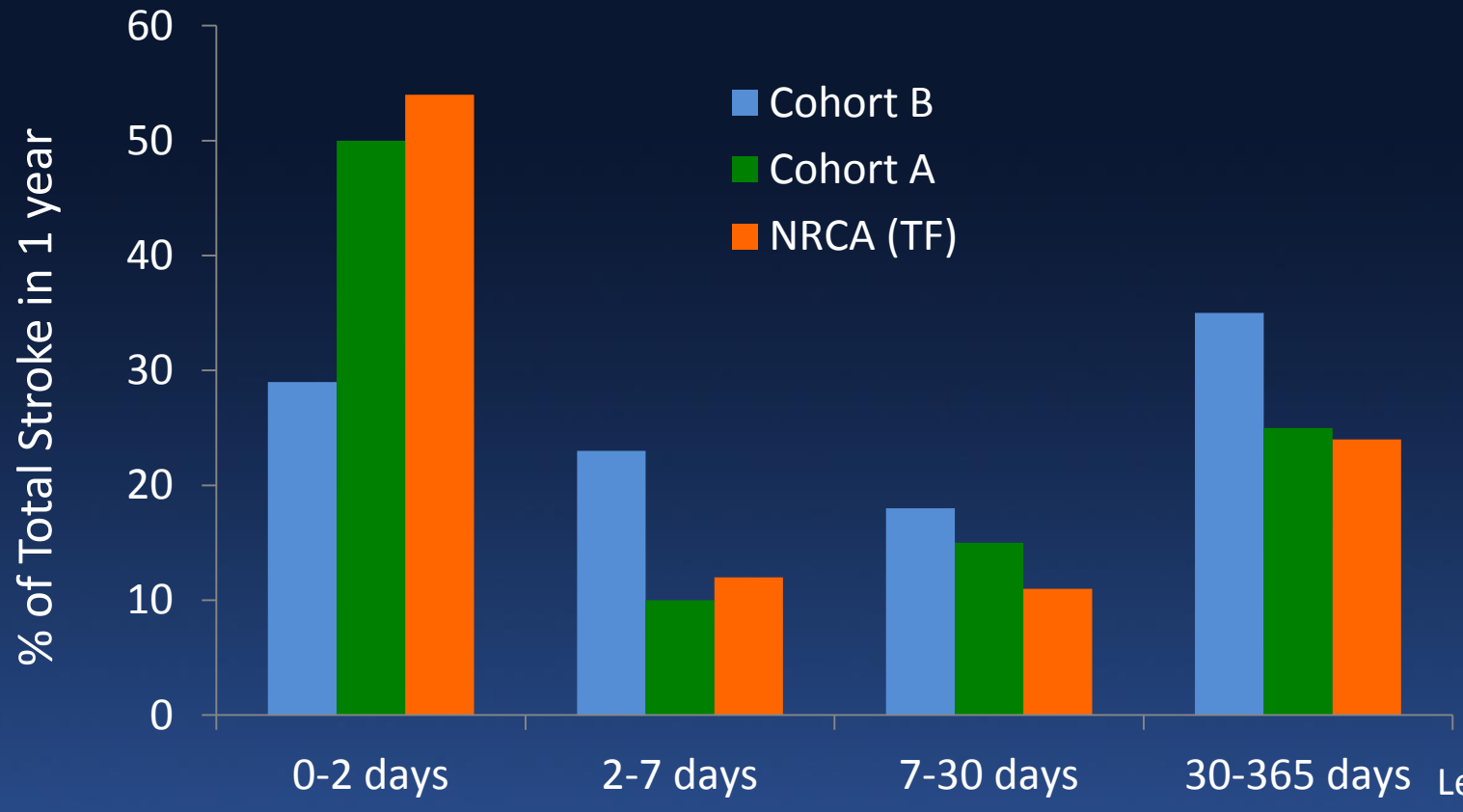
- Late embolization of debris liberated during during procedure
- Atrial arrhythmias
- Bleeding events related to pharmacology

Distribution of Stroke within 30 days



* courtesy Samir Kapadia

Stroke Timing within 1 year



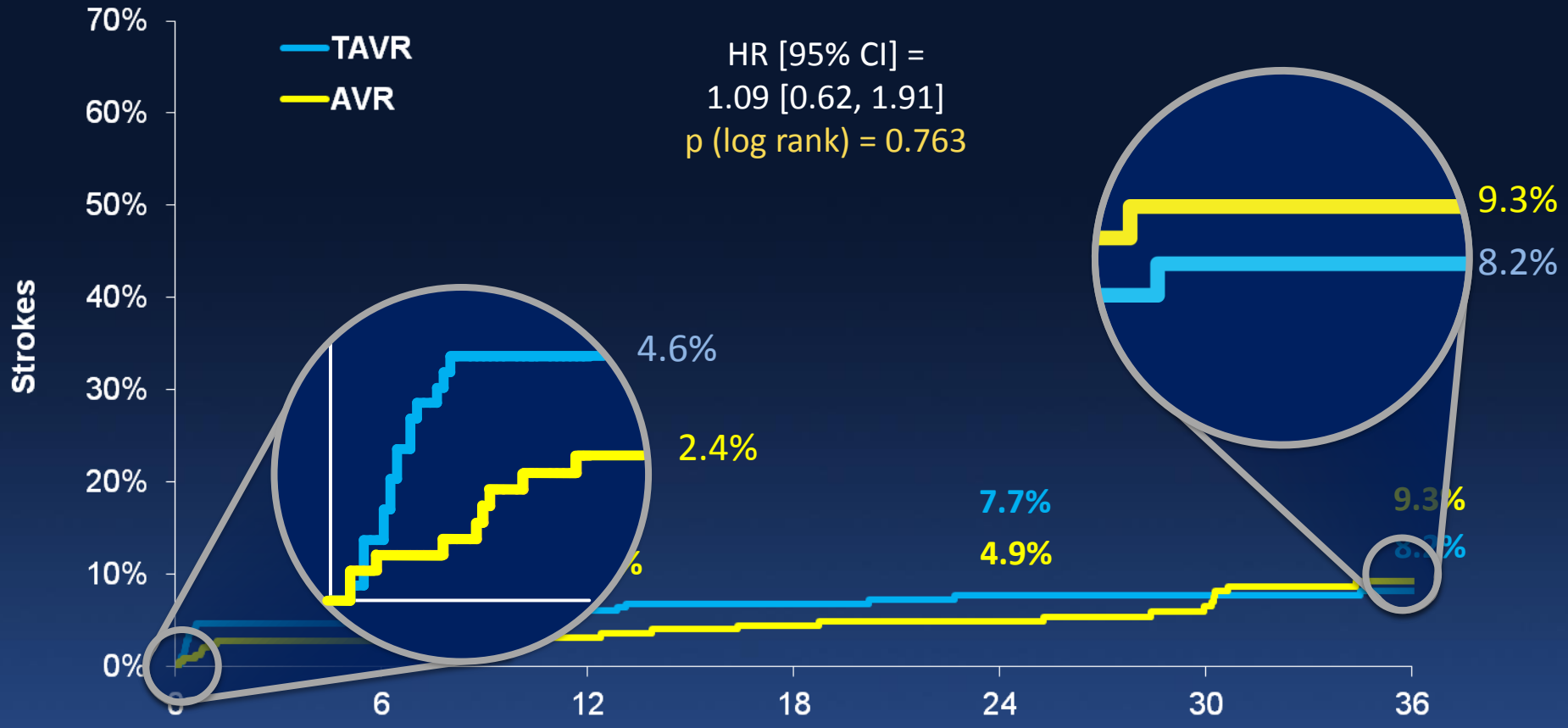
Leon et al, NEJM
Smith et al, NEJM
Kodali et al, ACC 2013

* courtesy Samir Kapadia

Perspective #6

There does not appear to late hazard for embolic events after TAVR

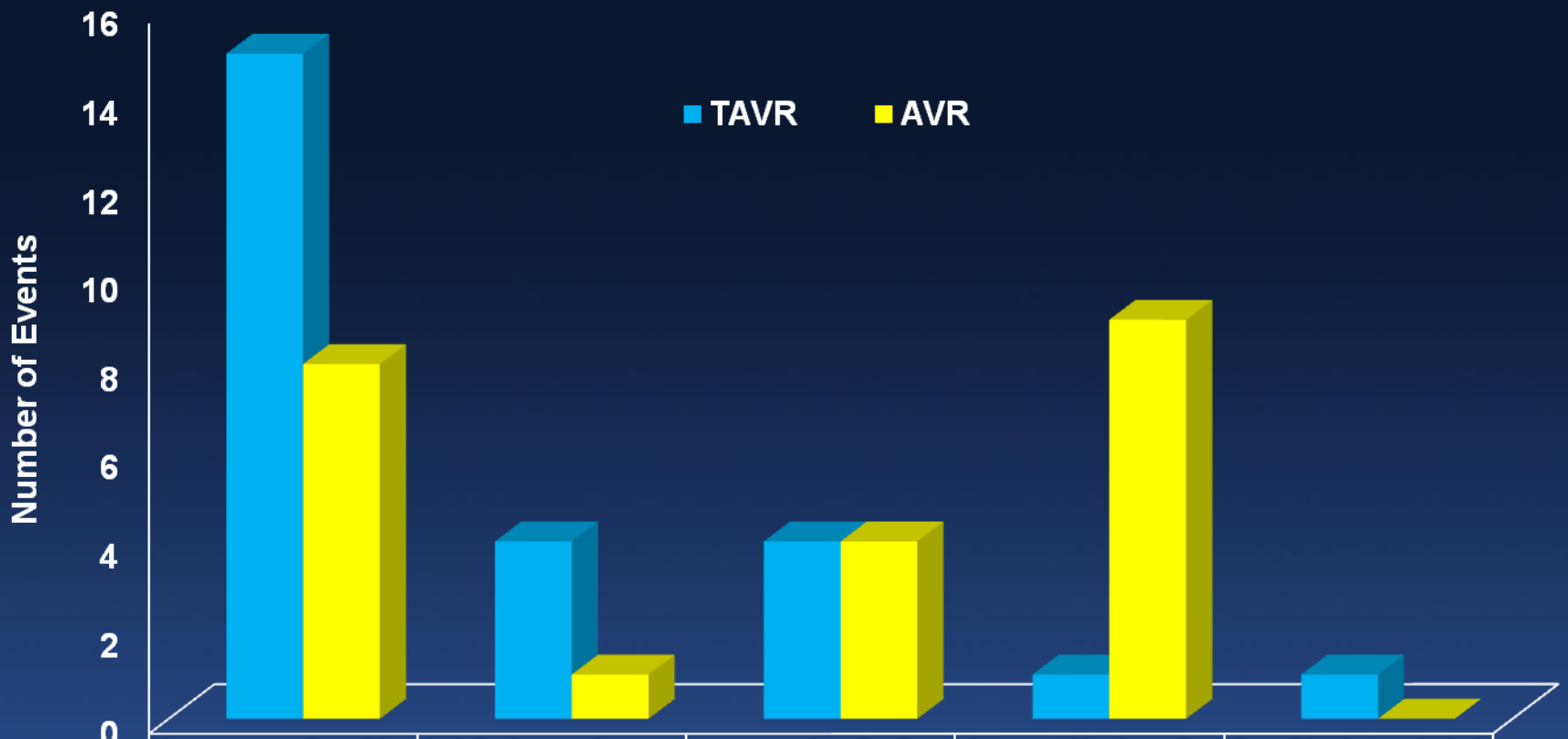
PARTNER 1 A - Stroke (ITT)



No. at Risk

TAVR	348	287	250	228	211	176	139
AVR	351	246	230	217	197	169	139

PARTNER 1A Strokes (AT)

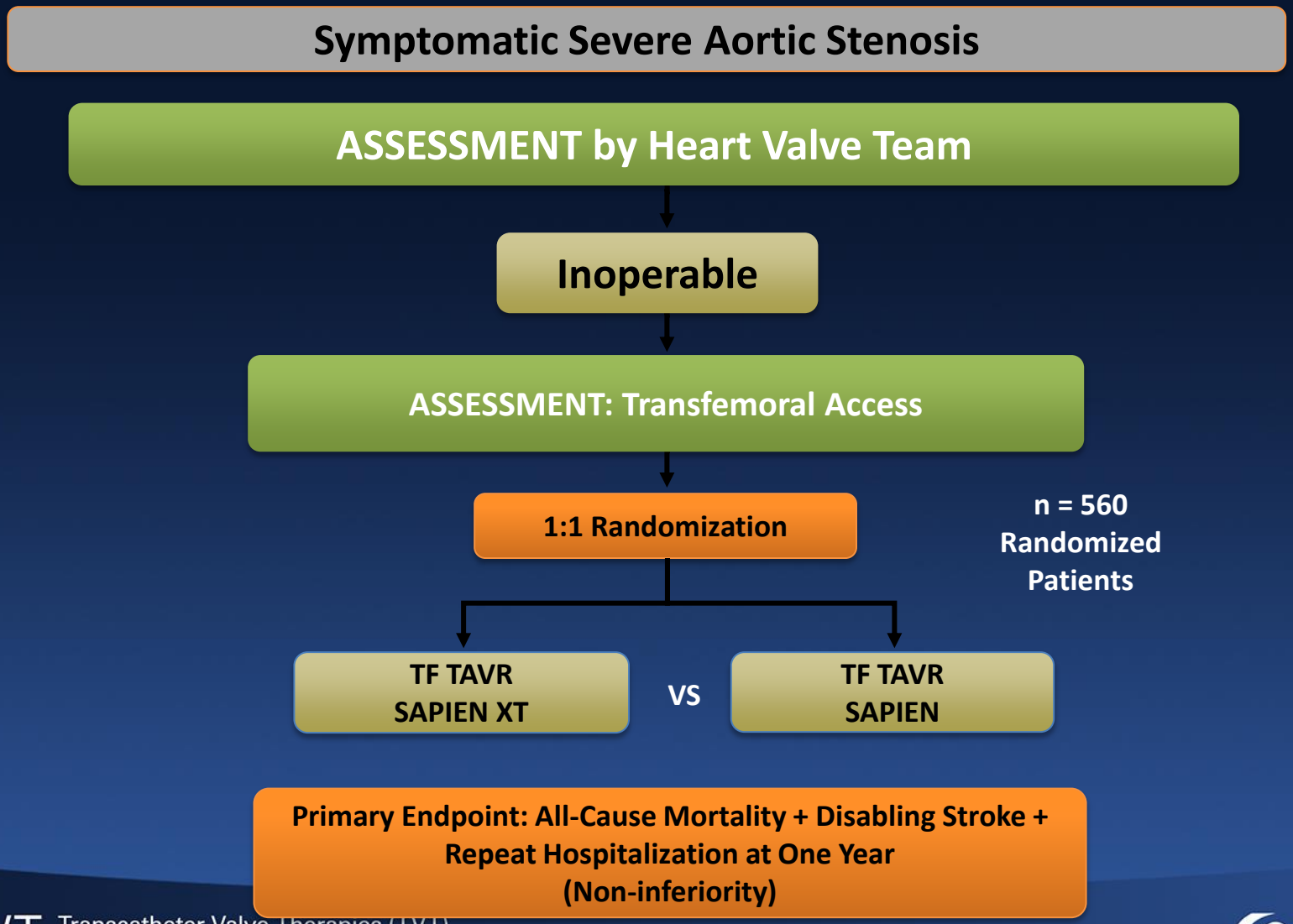


	≤ 30 Days	30 Days - 1 Year	1 - 2 Years	2 - 3 Years	> 3 Years
TAVR	15	4	4	1	1
AVR	8	1	4	9	0

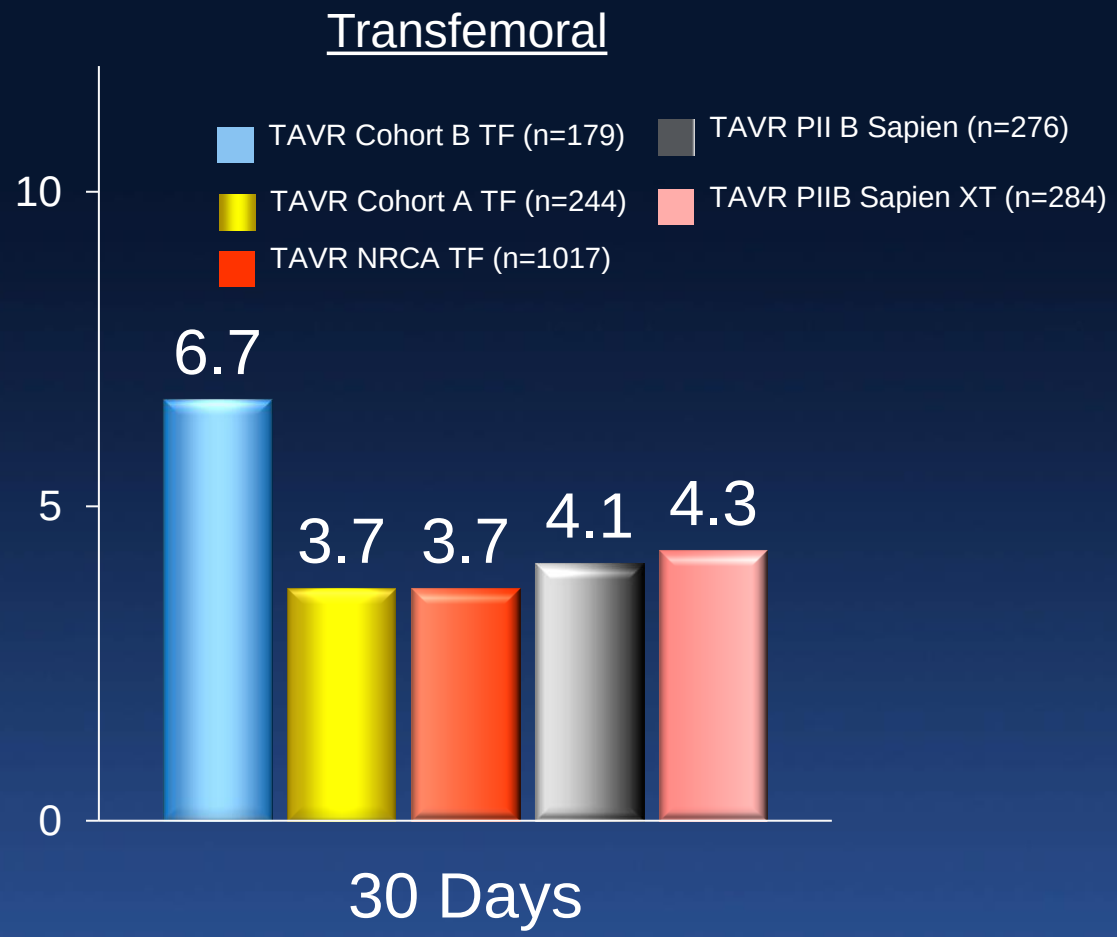
Perspective #7

Next Generation devices have not significantly reduced the risk of stroke following TAVR

The PARTNER II Inoperable Cohort
Study Design



PARTNER II Trial with Sapien XT valve demonstrated stable stroke rates

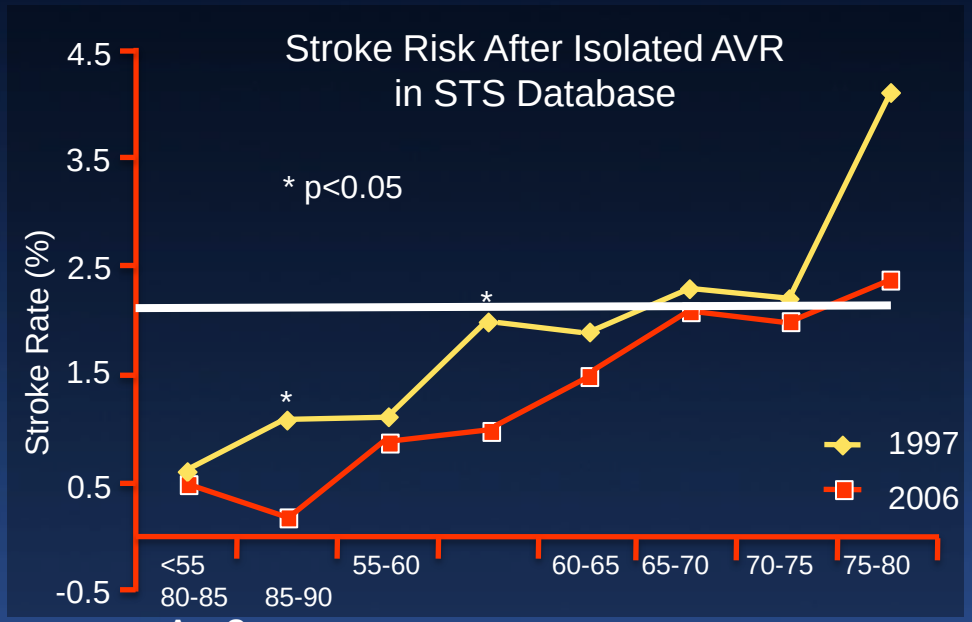


PARTNER II Trial

- Randomized trial of Sapien vs Sapien XT
- Inoperable patients only
- Patients assessed at baseline and follow-up by neurologists

Final Thoughts

- Device iteration and improvements in procedural technique have helped decrease 30 day stroke rates after TAVR
- Comparisons between trials difficult despite standardization of definitions due to differences in patient characteristics as well as rigor of neurologic assessment
- Embolic phenomenon will always be an issue with TAVR
- Goal should be to reduce the clinical impact to an acceptable level
- Continued iteration in devices as well as accessory devices such as filters and deflectors will potential help achieve this goal



Brown et al, JTCVS 2009