ACC i2 Highlights @ TCTAP 2013: LAA Closure and TAVR for Extreme and High Risk Patients

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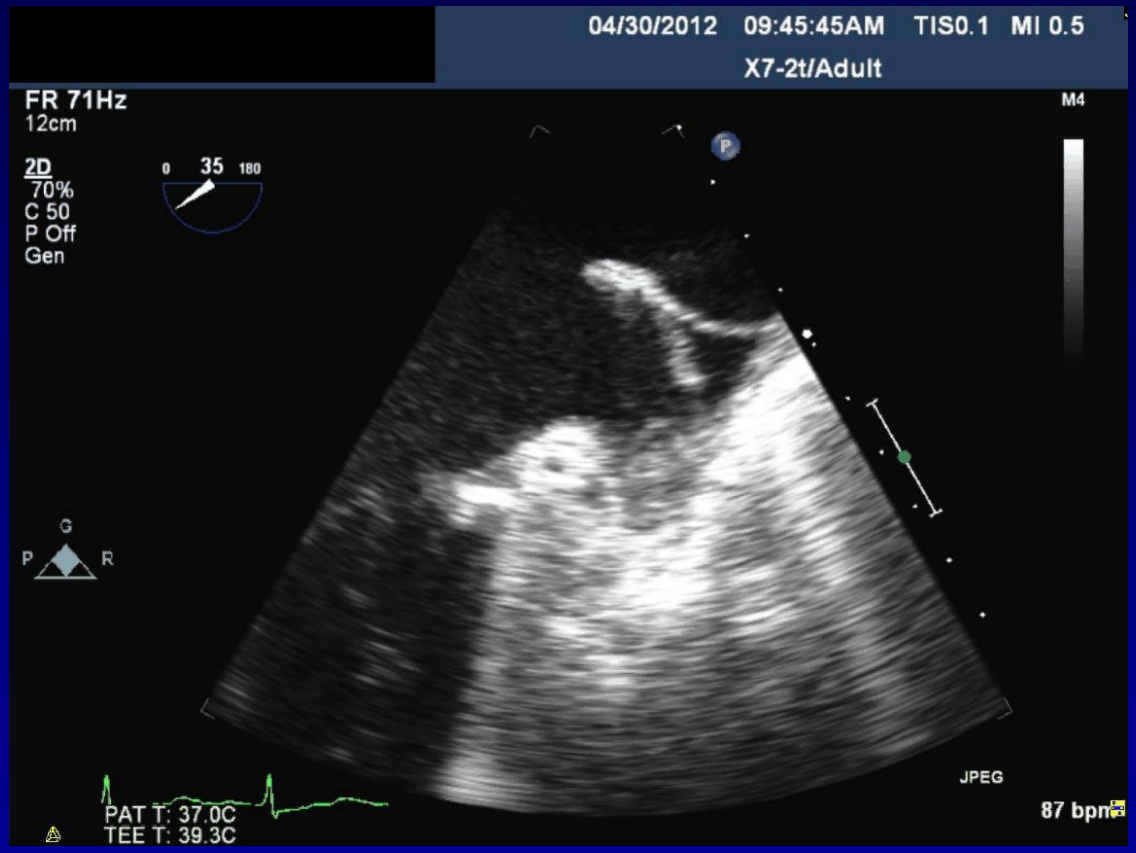
The Bad Actor in Atrial Fibrillation: The Left Atrial Appendage (LAA)

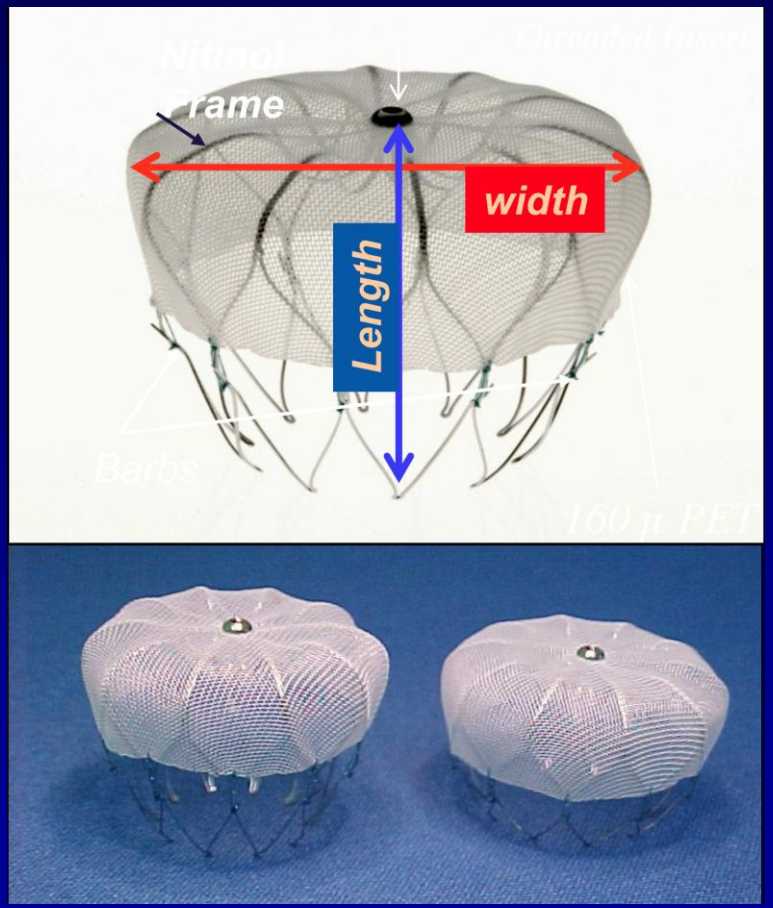


- 91% of thrombus originates in the LAA
- Thromboembolic stroke from AF more debilitating – due to size of clots

Blackshear J.L. Odell J.A., Annals of Thoracic Surgery, 1996;61:755-759

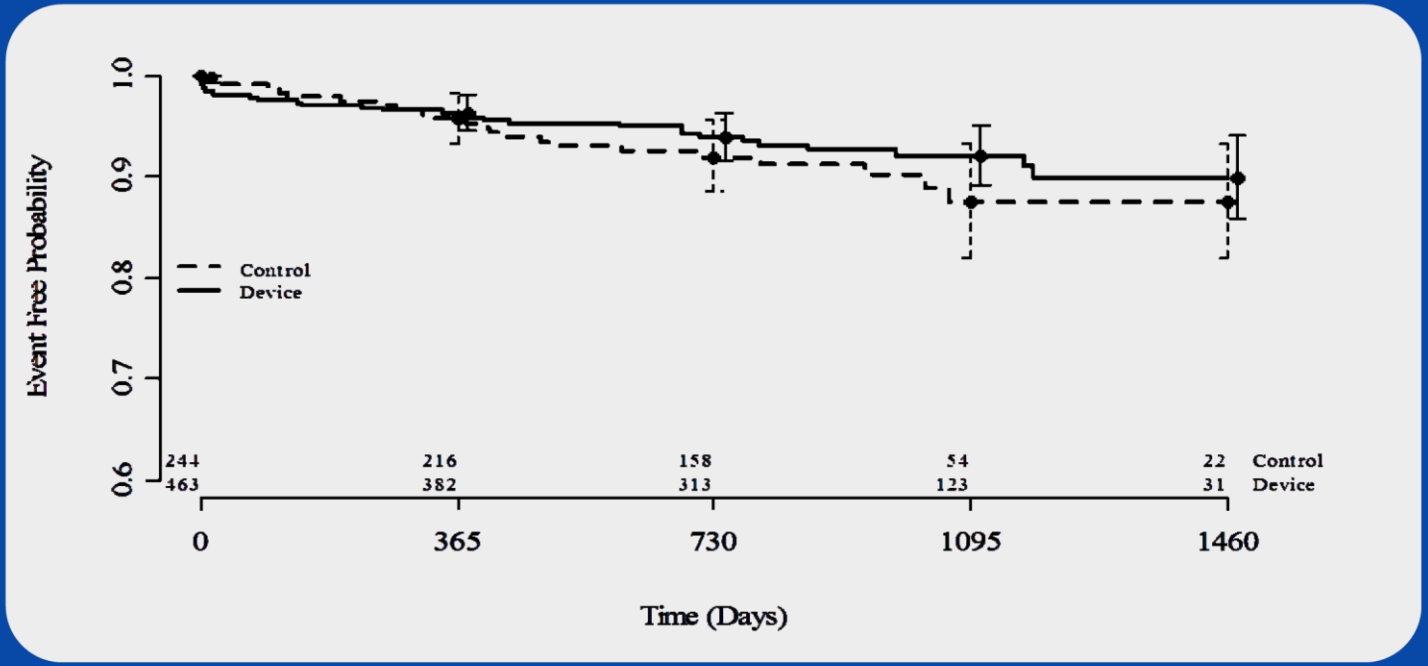
WATCHMAN Left Atrial Occluder Device

- Nitinol Frame
- PET Fabric Cap
- Barbs
- Threaded Insert
- Various Sizes (21, 24,27,30,33mm)
- *Length = width of device*



PROTECT AF
Primary Efficacy Results

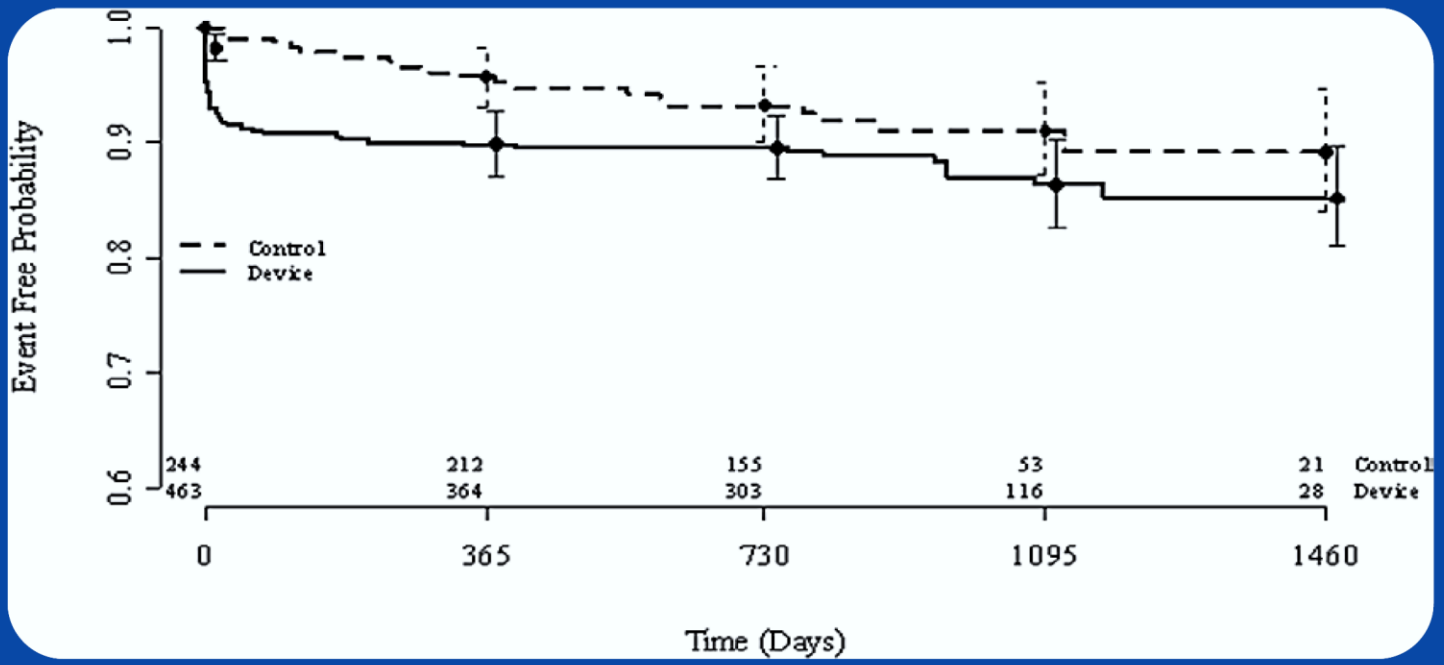
	Device	Control		Posterior Probabilities	
	Observed rate (events per 100 pt-yrs) (95% CrI)	Observed rate (events per 100 pt-yrs) (95% CrI)	Rate Ratio Intervention/Control (95% CrI)	Non-inferiority	Superiority
Primary Efficacy	3.0 (2.1, 4.3)	4.3 (2.6, 5.9)	0.71 (0.44, 1.30)	>0.99	0.88



Reddy, VY et al. Circulation. 2013;127:720-729;.

PROTECT AF
Primary Safety Results

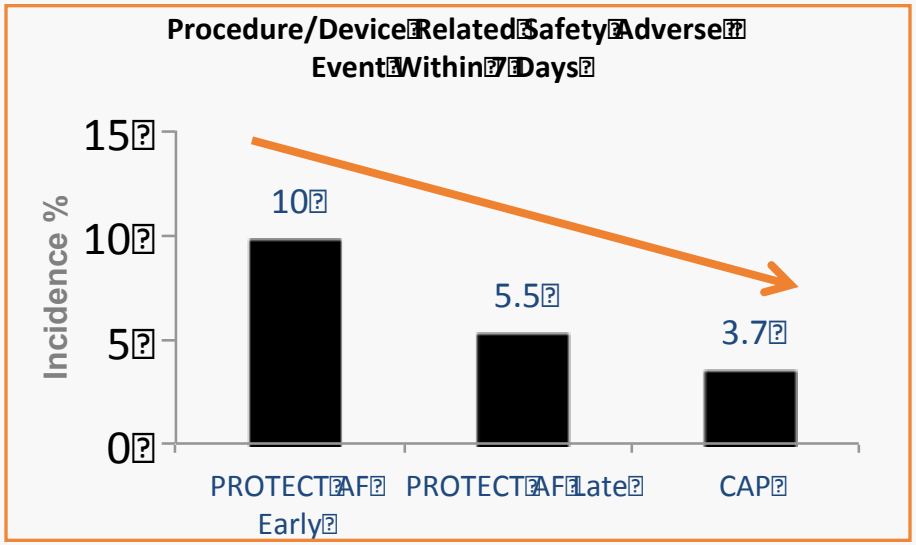
	Device	Control	
	Observed rate (events per 100 pt-yrs) (95% CrI)	Observed rate (events per 100 pt-yrs (95% CrI)	Rate Ratio Intervention/Control (95% CrI)
Primary Safety	5.5 (4.2, 7.1)	3.6 (2.2, 5.3)	1.53 (0.95, 2.70)

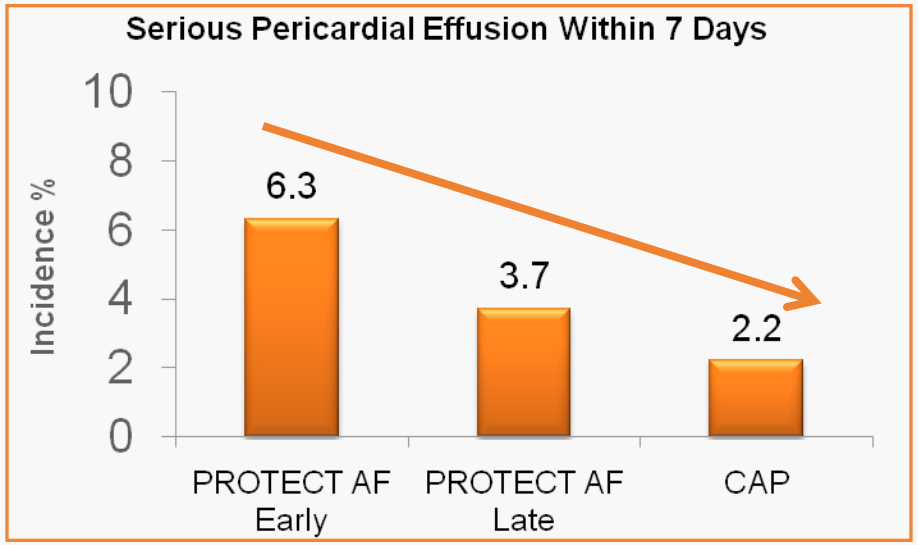


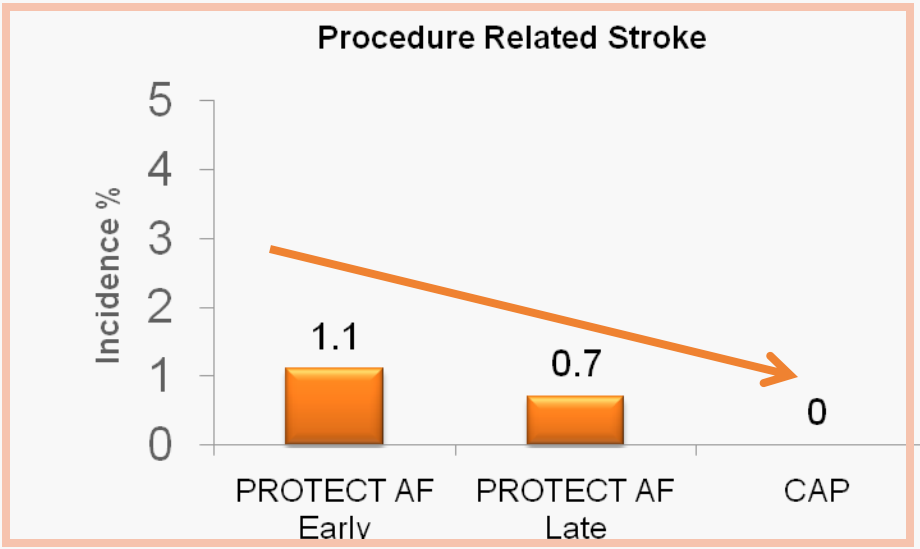
Reddy, VY et al. Circulation. 2013;127:720-729;.

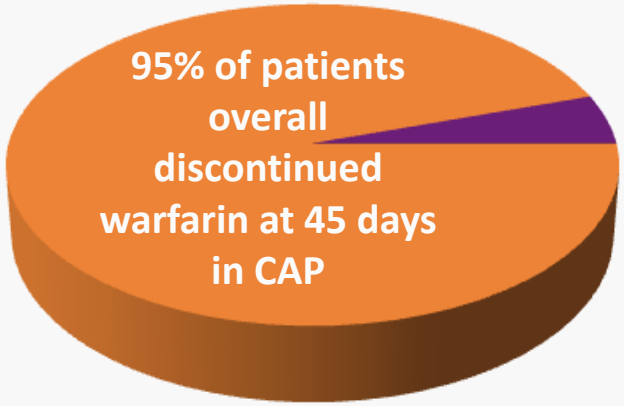
Caution: In the United States, WATCHMAN is an investigational device limited by Federal law and investigational use only. Not for sale in the US. Prior to use please review device indications, contraindications, warnings, precautions, adverse events, and operational instructions. Only available according to applicable local law.

Performance Metrics
– Learning Curve Effect, PROTECT- AF vs. CAP









Reddy VY et al, Circulation. 2011;123:417-424

PREVAIL
Top 10 Participating Centers

Investigational Center	Location	Principal Investigator	Total Enrollment
Pacific Heart / St. Johns	Santa Monica, CA	*Shephal Doshi, MD*	45
Cedars-Sinai Medical Center	Los Angeles, CA	*Saibal Kar, MD*	32
Mercy Heart and Vascular	St. Louis, MO	*J. Mauricio Sanchez, MD*	32
Arizona Heart Rhythm Research Center	Phoenix, AZ	*Vijay Swarup, MD*	30
Intermountain Medical Center	Murray, UT	*Brian Whisenant, MD*	24
Methodist Hospital	Houston, TX	*Miguel Valderrabano, MD*	22
Scripps Green	La Jolla, CA	*Matthew Price, MD*	22
Central Baptist Hospital, Kentucky	Lexington, KY	*Gery Tomassoni, MD*	17
Fletcher Allen	Burlington, VT	*Daniel Lustgarten, MD*	17
St. Lukes Hospital, Kansas	Kansas City, MO	*Kenneth Huber, MD*	17

MAYO CLINIC

Study Goals and Design

- Similar design to PROTECT AF: prospective randomized 2:1 (device: control) trial
- 407 randomized patients from 41 US centers
- Confirm the results of PROTECT AF and demonstrate improved safety profile
- Inclusion of new centers and new operators to document that enhancements to the training program are effective
- Roll-in phase allowed new centers to implant 2 patients prior to randomization phase

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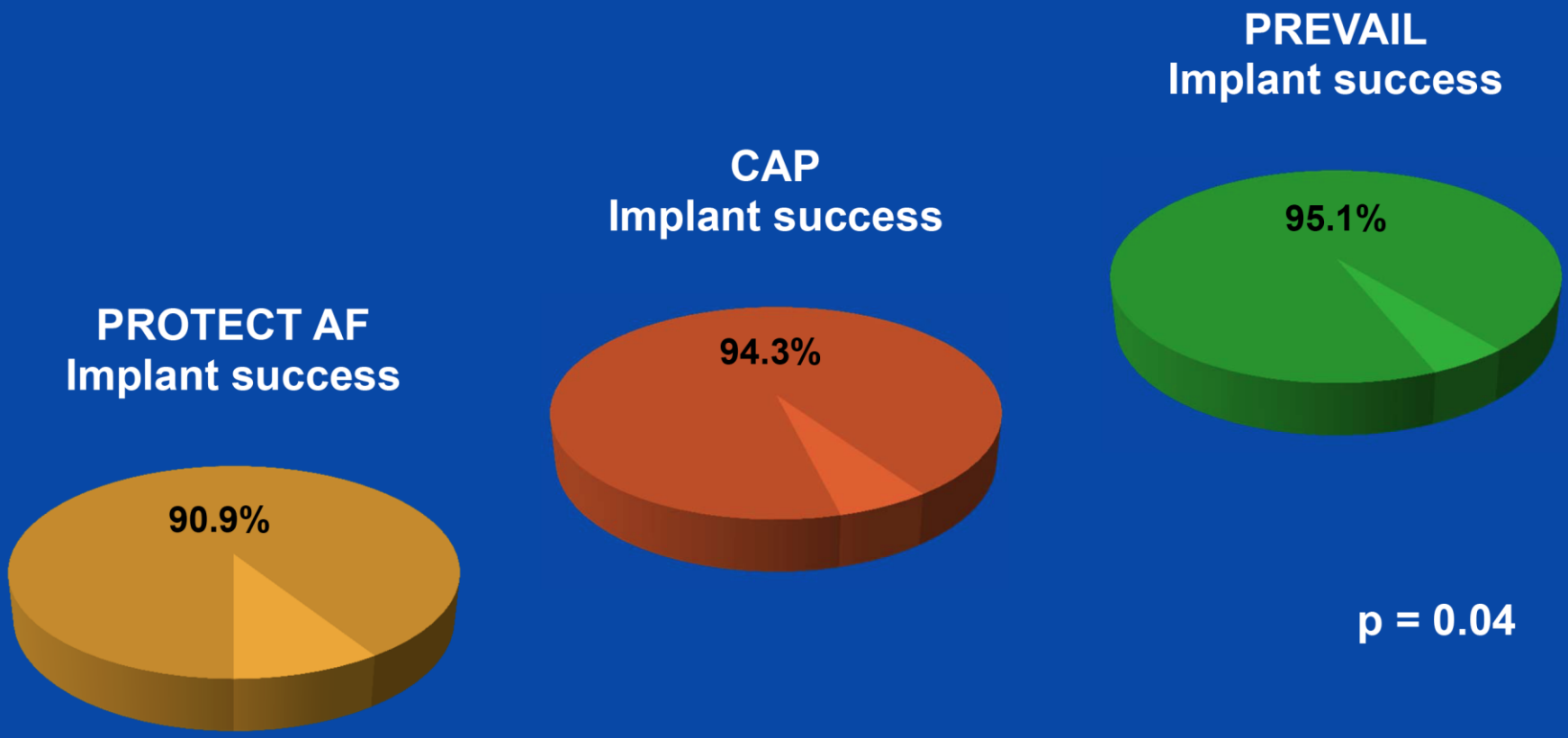
Procedure Implant Success



Implant success defined as deployment and release of the device into the left atrial appendage

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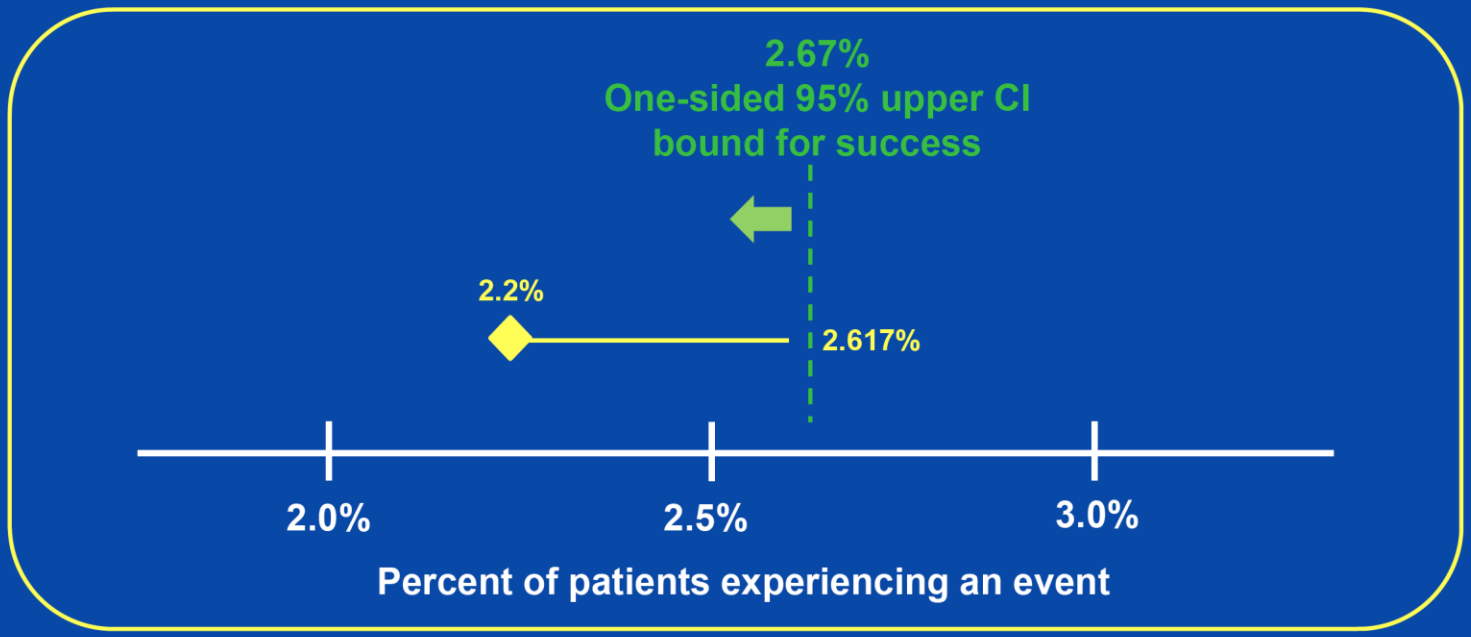
PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

First Primary Endpoint
Acute (7-day) Procedural Safety



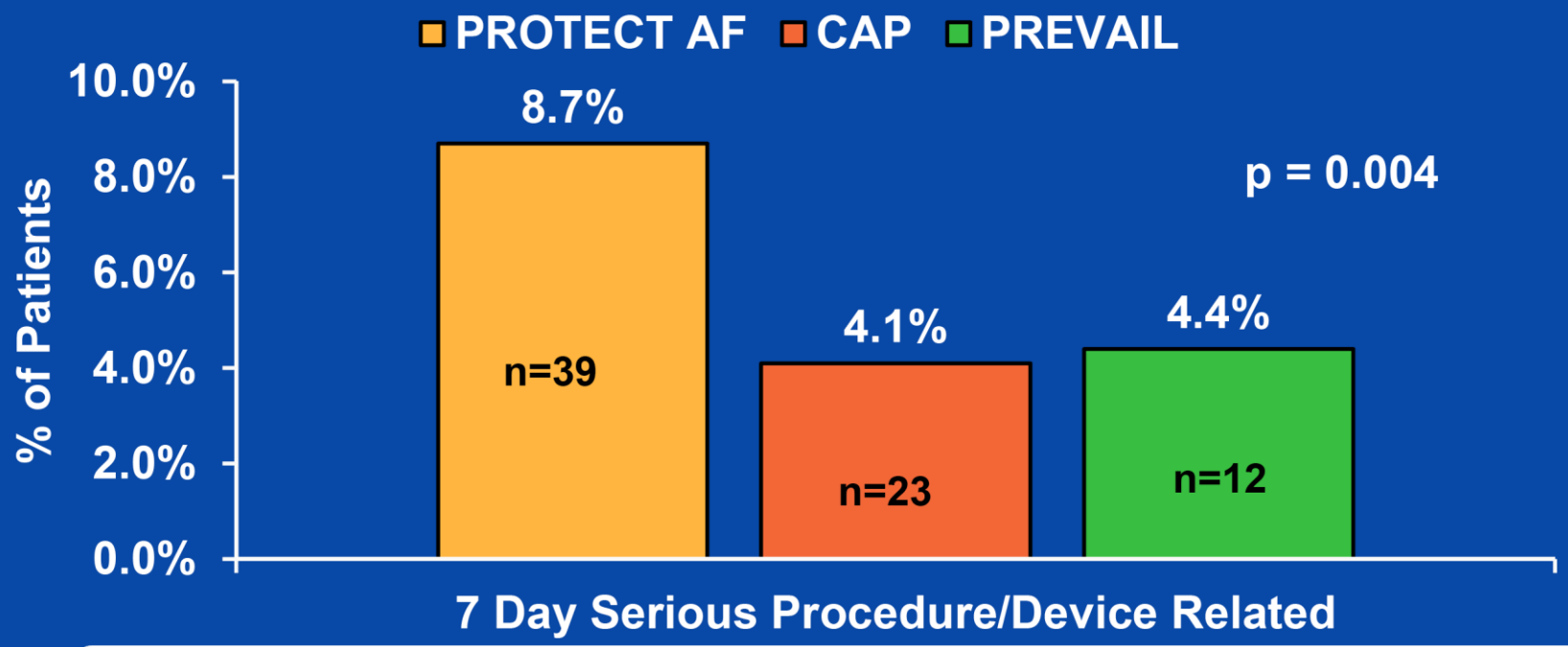
- 6 events in device group = 2.2% (6/269)
- Pre-specified criterion met for first primary endpoint (95% Upper confidence bound < 2.67%)
  - 95% CI = 2.618%

Results are preliminary; final validation not yet complete

Death, ischemic stroke, SE and procedure or device related complications requiring major CV or endovasc intervention

Vascular Complications

- Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]



No procedure-related deaths reported in any of the trials

PROTECT-AF and CAP data from Reddy, VY et al. *Circulation.* 2011;123:417-424.

[11]Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

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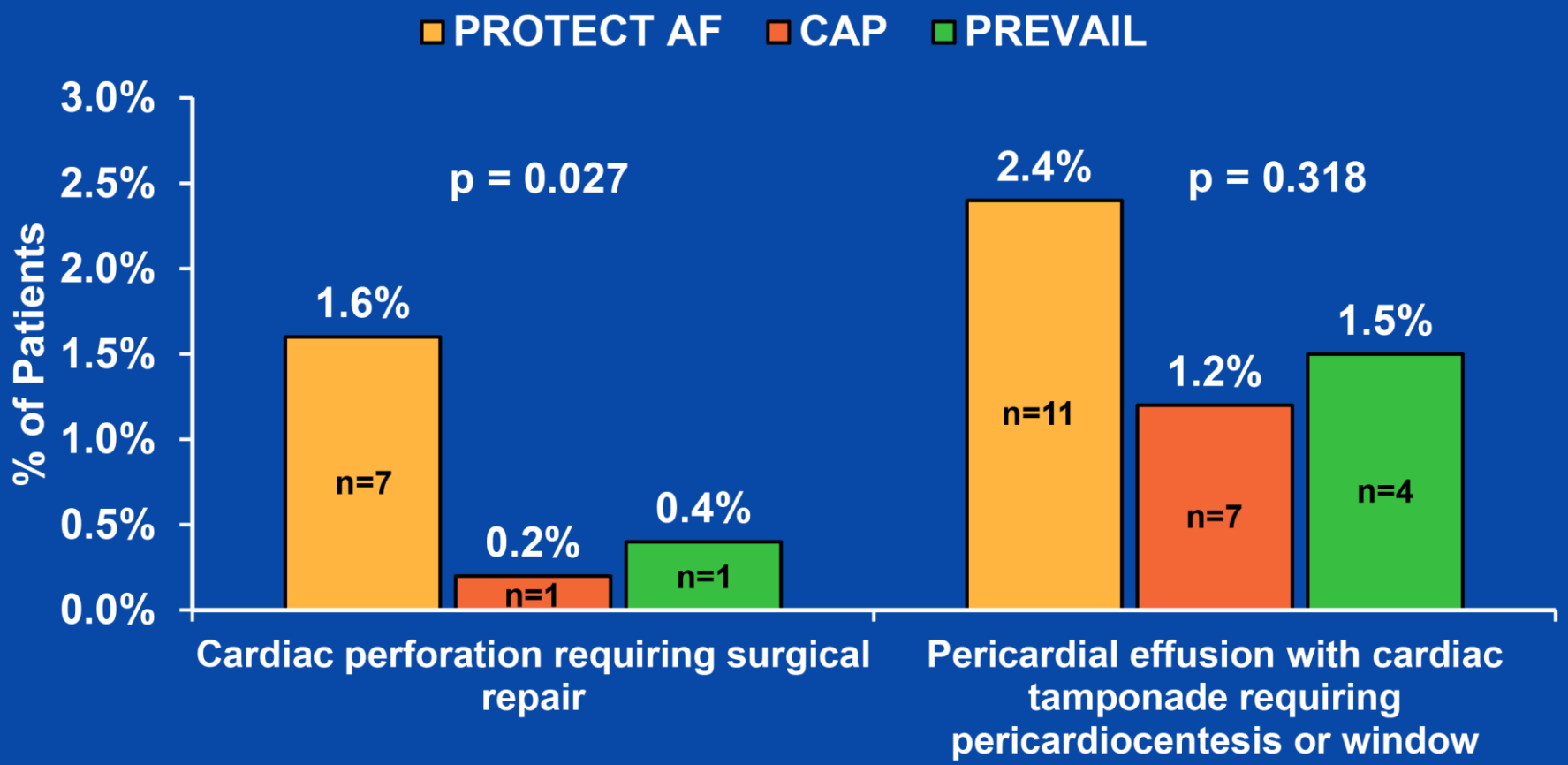
Pericardial Effusions Requiring Intervention



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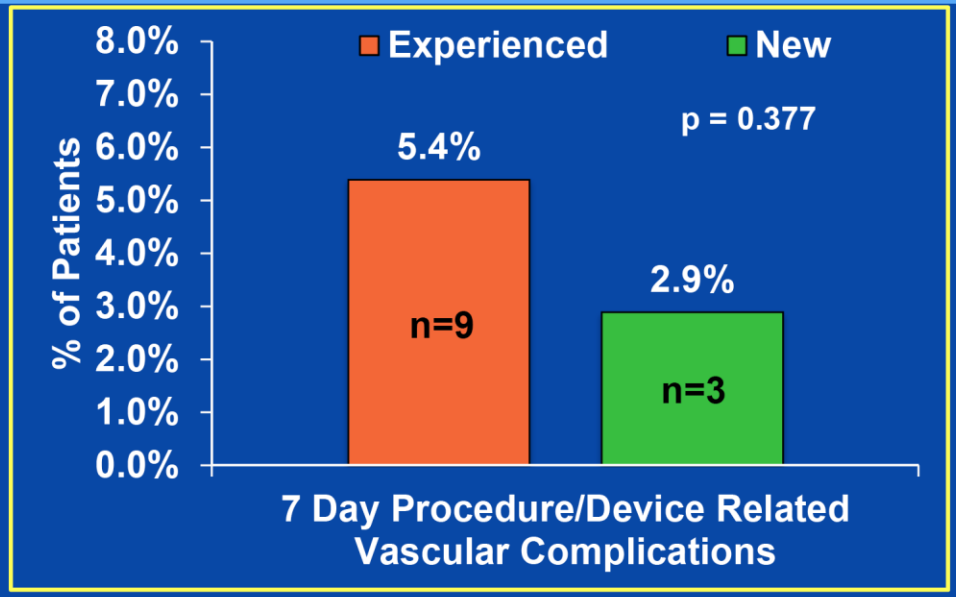
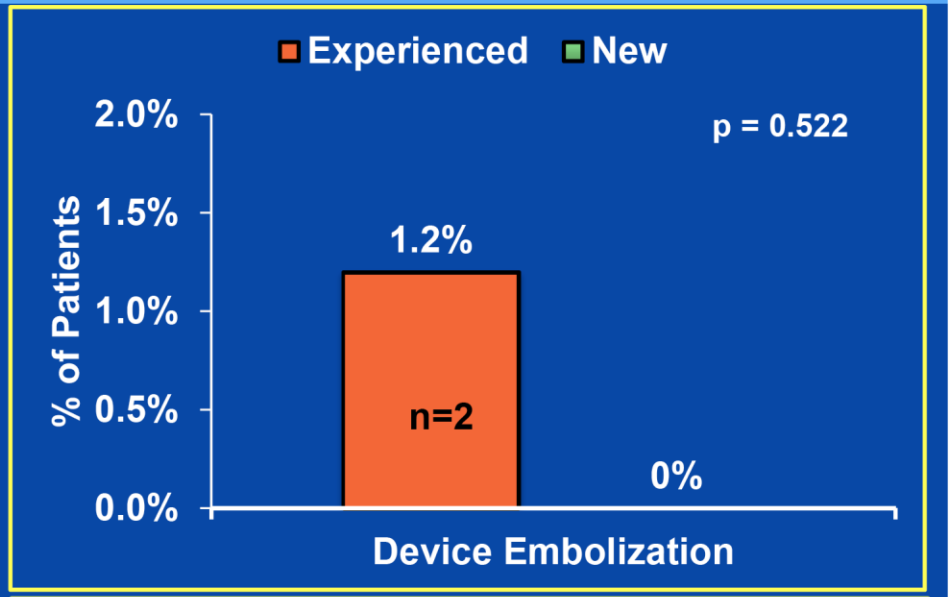
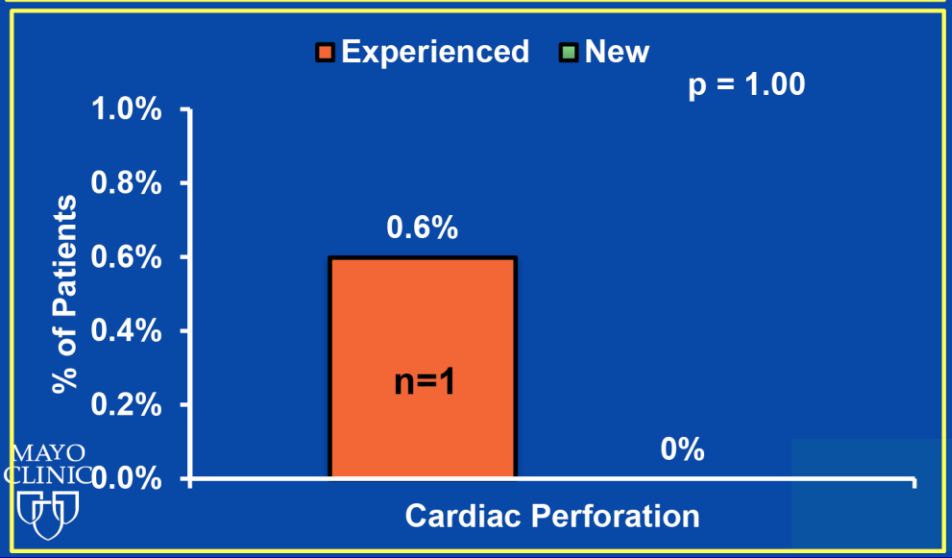
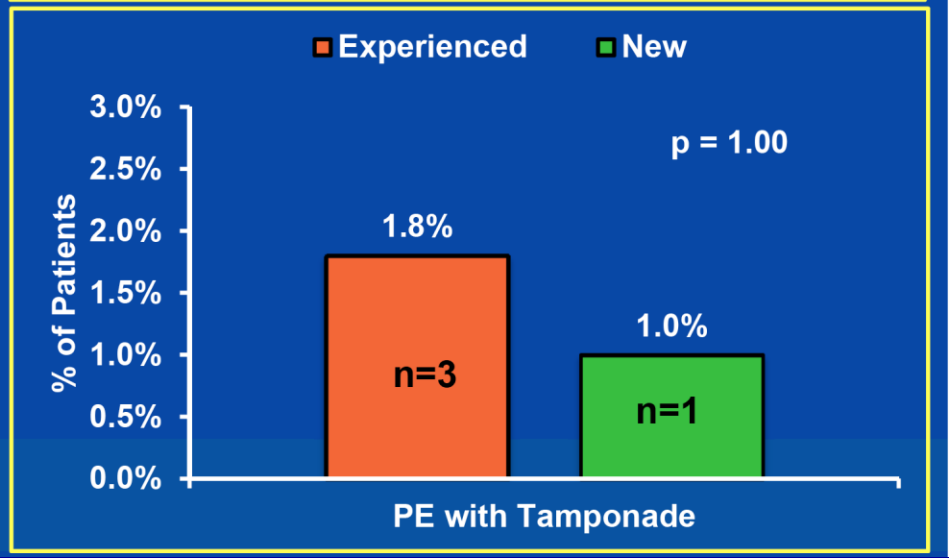
PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

PREVAIL Complications
New vs Experienced Operator









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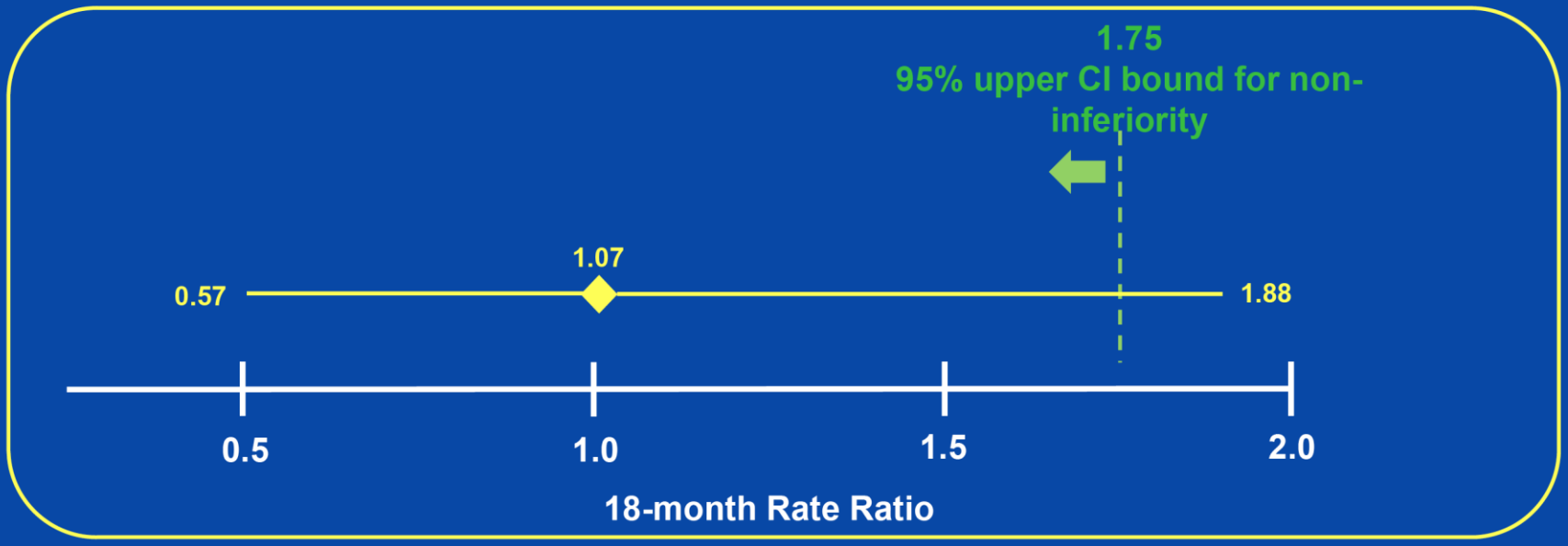
Second Primary Endpoint
Composite 18-month Efficacy



- Similar 18-month event rates in both control and device groups = 0.064
- Upper 95% CI bound slightly higher than allowed to meet success criterion (<1.75)
  - Limited number of patients with follow-up through 18 months thus far (Control = 30 pts, Device = 58 pts)

Results are preliminary; final validation not yet complete

MAYO CLINIC

PREVAIL
Control (Warfarin) Group Performance

- In spite of the high average $CHADS_2$ score of 2.6 in the control group, the observed rate of stroke in the PREVAIL Control group was lower than in other published warfarin studies
- PREVAIL control group rate = 0.7 (95% CI 0.1, 5.1)
  - Wide confidence bounds due to small number of patients with 18-months of follow-up

Trial	Control (Warfarin) Group Stroke, Systemic Embolism Rate (Per 100 PY)
PROTECT AF[1]	1.6
RE-LY (Dabigatran)[2]	1.7
ARISTOTLE (Apixaban)[3]	1.6
ROCKET AF (Rivaroxaban)[4]	2.2
PREVAIL	**0.7**

Results are preliminary; final validation not yet complete

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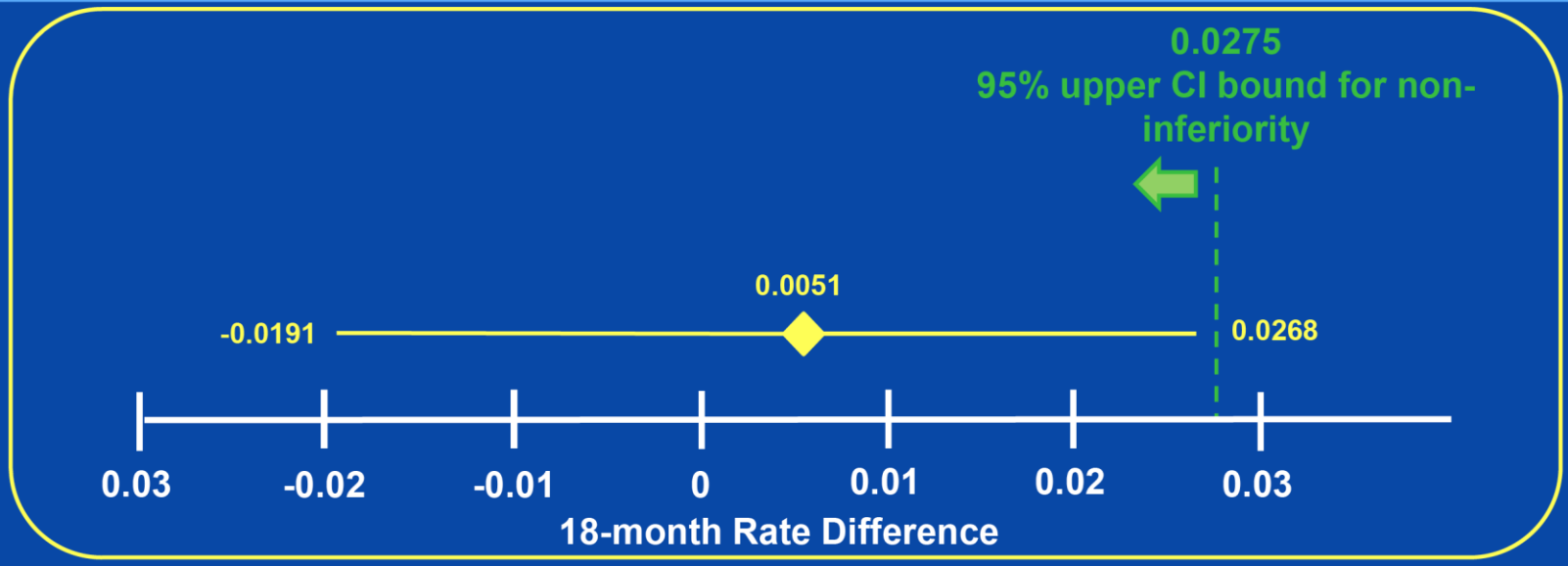
[1]Ischemic stroke rate from Holmes et al. *Lancet* 2009; 374:534-42
[2]Connolly et al. *N Engl J Med* 2009; 361:1139-51
[3]Granger et al. *N Engl J Med* 2011; 365:981-92
[4]Patel et al. *N Engl J Med* 2011; 365:883-91

Third Primary Endpoint
18-month Thrombolic Events



- **Endpoint success in the presence of an over performing control group**

Device 18-Month Rate	Control 18-Month Rate
0.0253	0.0201

- **Pre-specified non-inferiority criterion met for third primary endpoint (95% CI Upper Bound < 0.0275%)**

Results are preliminary; final validation not yet complete

Ischemic stroke or SE> 7days post procedure

Conclusions

- Improved procedural success and less complications than PROTECT-AF, despite 40% of cases performed by new operators
- Non-inferior to warfarin with regard to post-procedure stroke and systemic embolism (despite overperforming control group)
- Non-inferiority not met for 18-month efficacy (CV death, any stroke, SE) – observed rates identical in both arms and few patients actually reached end of FU, resulting in wide confidence bounds

Edwards SAPIEN vs SAPIEN XT Transcatheter Heart Valves

THE PARTNER II TRIAL

NEW FRAME GEOMETRY
- Less metal content
- Lower crimp profile

NEW FRAME MATERIAL
- Cobalt-chromium
- Greater tensile and yield strength

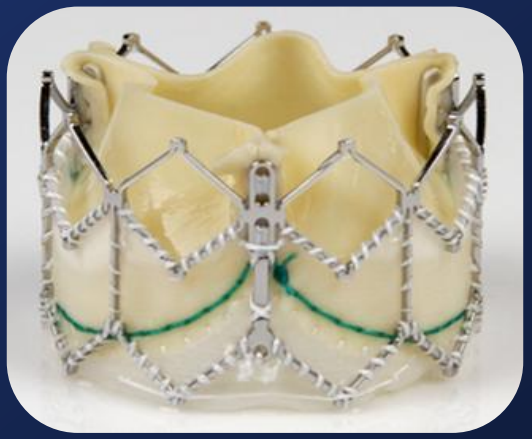
NEW LEAFLET GEOMETRY
- Partially closed

SAPIEN THV

Stainless Steel

SAPIEN XT THV

Cobalt-chromium



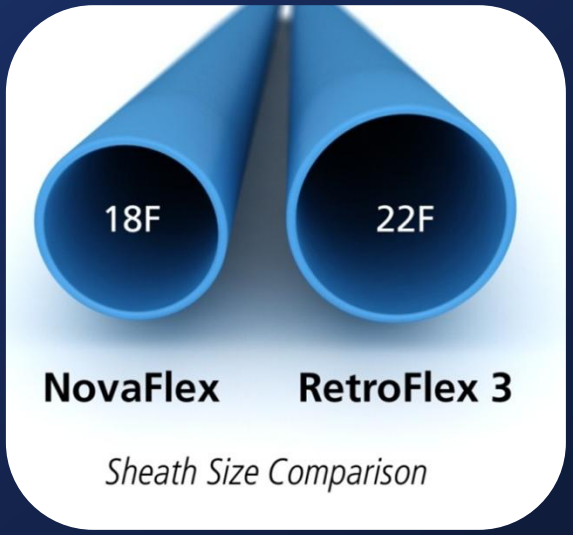
RetroFlex 3

NovaFlex

Sheath Size Comparison

THE PARTNER II TRIAL

Valve	Valve Size	Sheath ID	Sheath OD	Minimum Vessel Diameter
SAPIEN THV	23mm	22F	25F (8.4mm)	7.0mm
SAPIEN XT THV	23mm	18F	22F (7.2mm)	6.0mm
SAPIEN THV	26mm	24F	28F (9.2mm)	8.0mm
SAPIEN XT THV	26mm	19F	23F (7.5mm)	6.5mm



33% reduction in CSA

Purpose of PARTNER II
Inoperable Cohort

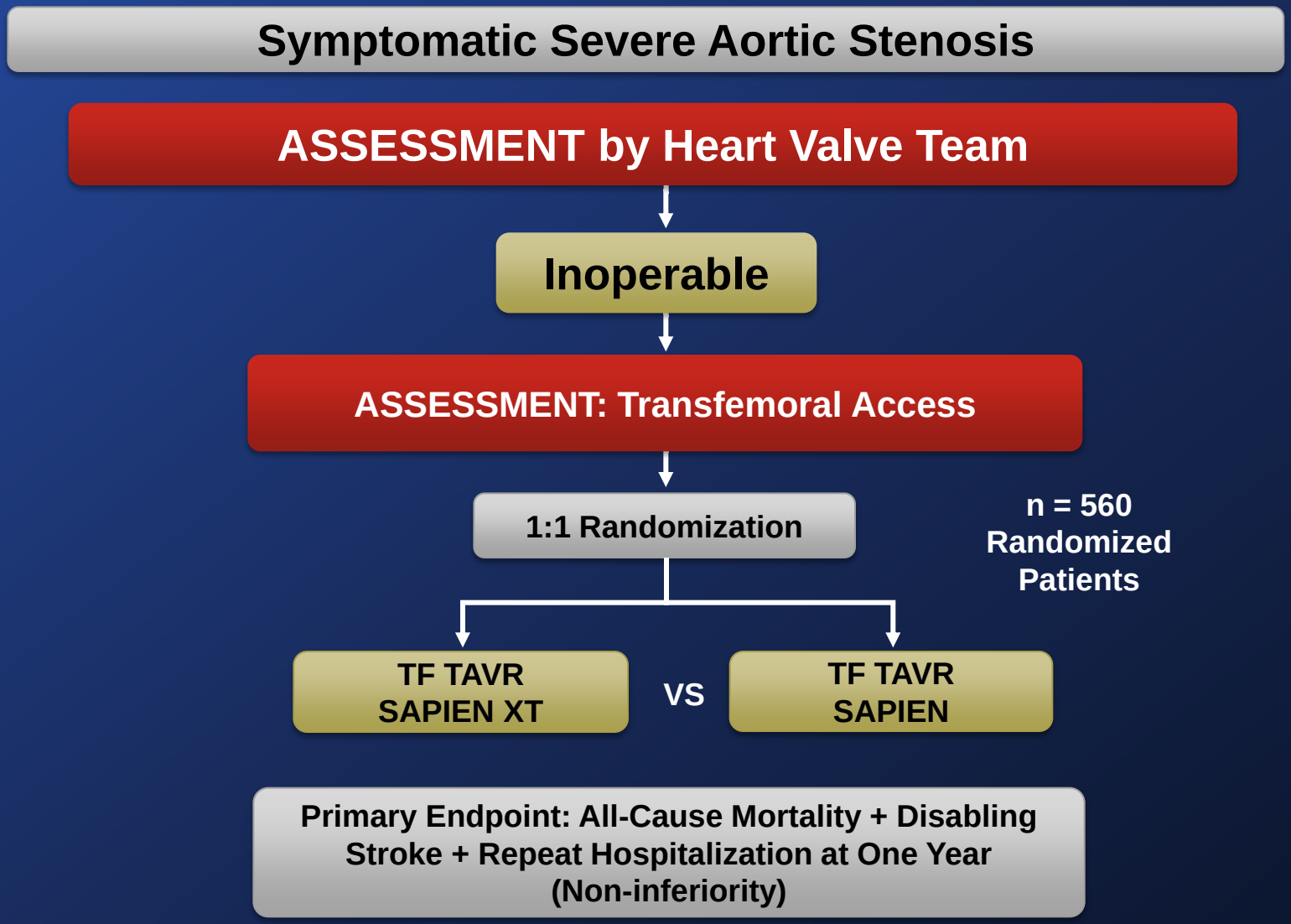
- To compare the safety and effectiveness of the new SAPIEN XT versus the FDA-approved SAPIEN in a randomized controlled trial for patients with symptomatic severe aortic stenosis who cannot have surgery (“inoperable”).

- To apply rigorous clinical trial methodologies including systematic serial neurologic assessments and VARC 2 definitions* for clinical outcomes.

* Kappetein AP, et al. J Am Coll Cardiol 2012;60:1438-54

The PARTNER II Inoperable Cohort

Study Design



Procedural Factors (AT)

THE PARTNER II TRIAL

Events	SAPIEN (n=271)		SAPIEN XT (n=282)		
	n		n		p-value
Procedure time (mins)	271	109.6 ± 57.2	282	101.0 ± 43.2	0.18
Anesthesia time (mins)	266	212.0 ± 75.7	277	197.6 ± 60.8	0.02
≥ 2 valves implanted	10	3.7	3	1.1	0.05
Valve embolization	0	0	0	0	NA
Aborted procedure	8	3.0	2	0.7	0.06
Aortic rupture	2	0.7	1	0.4	0.62
Aortic dissection	1	0.4	1	0.4	0.99
IABP during procedure	6	2.2	1	0.4	0.06
Cardiopulmonary Bypass	5	1.8	5	1.8	0.99

Vascular and Bleeding Events:
At 30 Days (AT)

THE PARTNER II TRIAL

	SAPIEN (n=271)		SAPIEN XT (n=282)		
Events	**n**	**%**	**n**	**%**	**p-value**
Vascular:					
Major	42	15.5	27	9.6	0.04
Minor	20	7.4	14	5.0	0.23
Bleeding:					
Disabling	34	12.6	22	7.8	0.06
Major	44	16.4	44	15.7	0.84
Patients with transfusions	80	29.5	73	25.9	0.40

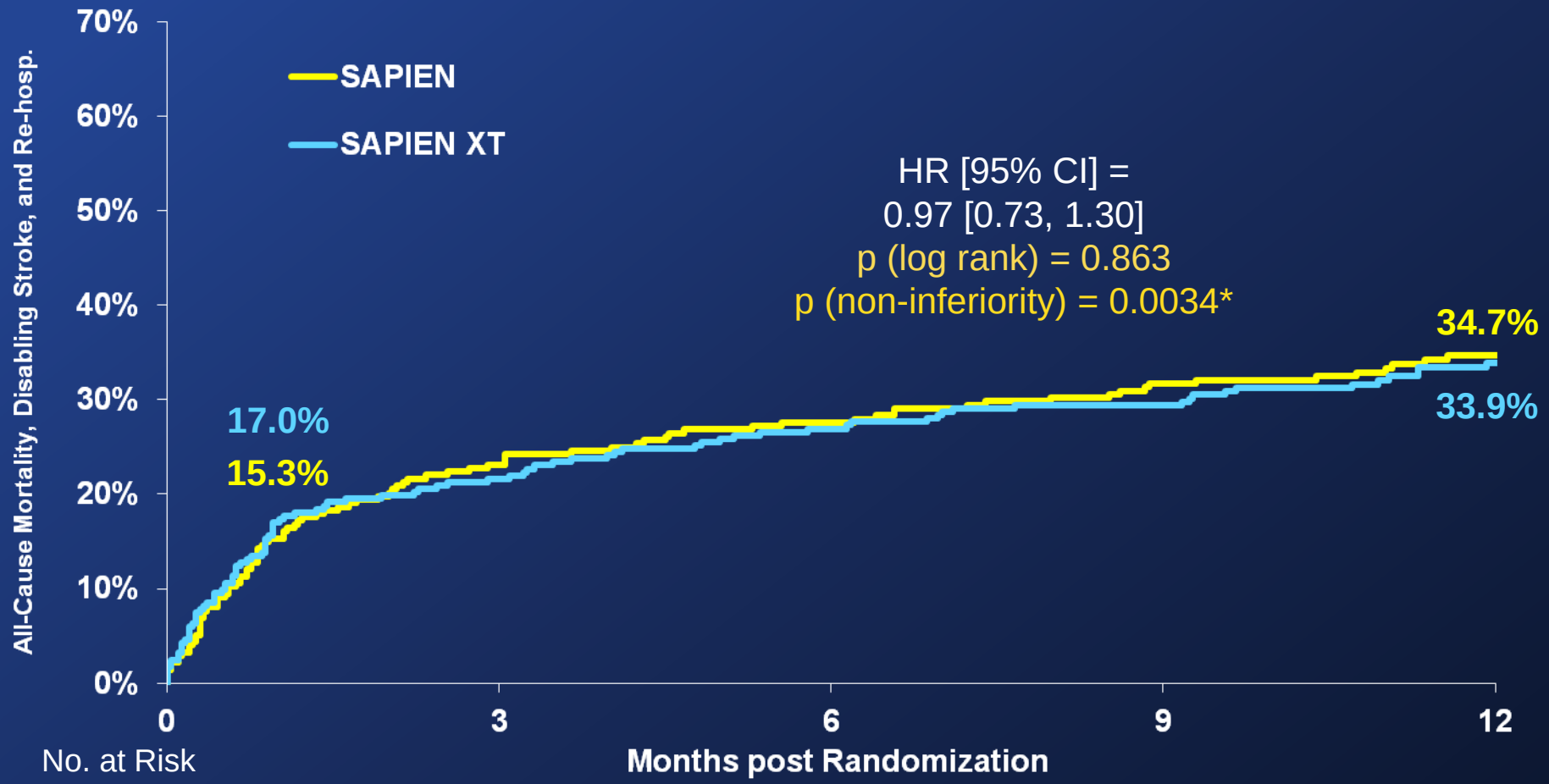
Vascular Complication Categories:
At 30 Days (AT)

THE PARTNER II TRIAL

	SAPIEN (n=271)		SAPIEN XT (n=282)		
Events	n	%	n	%	p-value
Perforation	13	4.8	2	0.4	0.003
Dissection	25	9.2	12	4.3	0.03
Hematoma	16	5.9	10	3.6	0.23

All-Cause Mortality, Disabling Stroke, and Re-hospitalization (ITT)

THE PARTNER II TRIAL



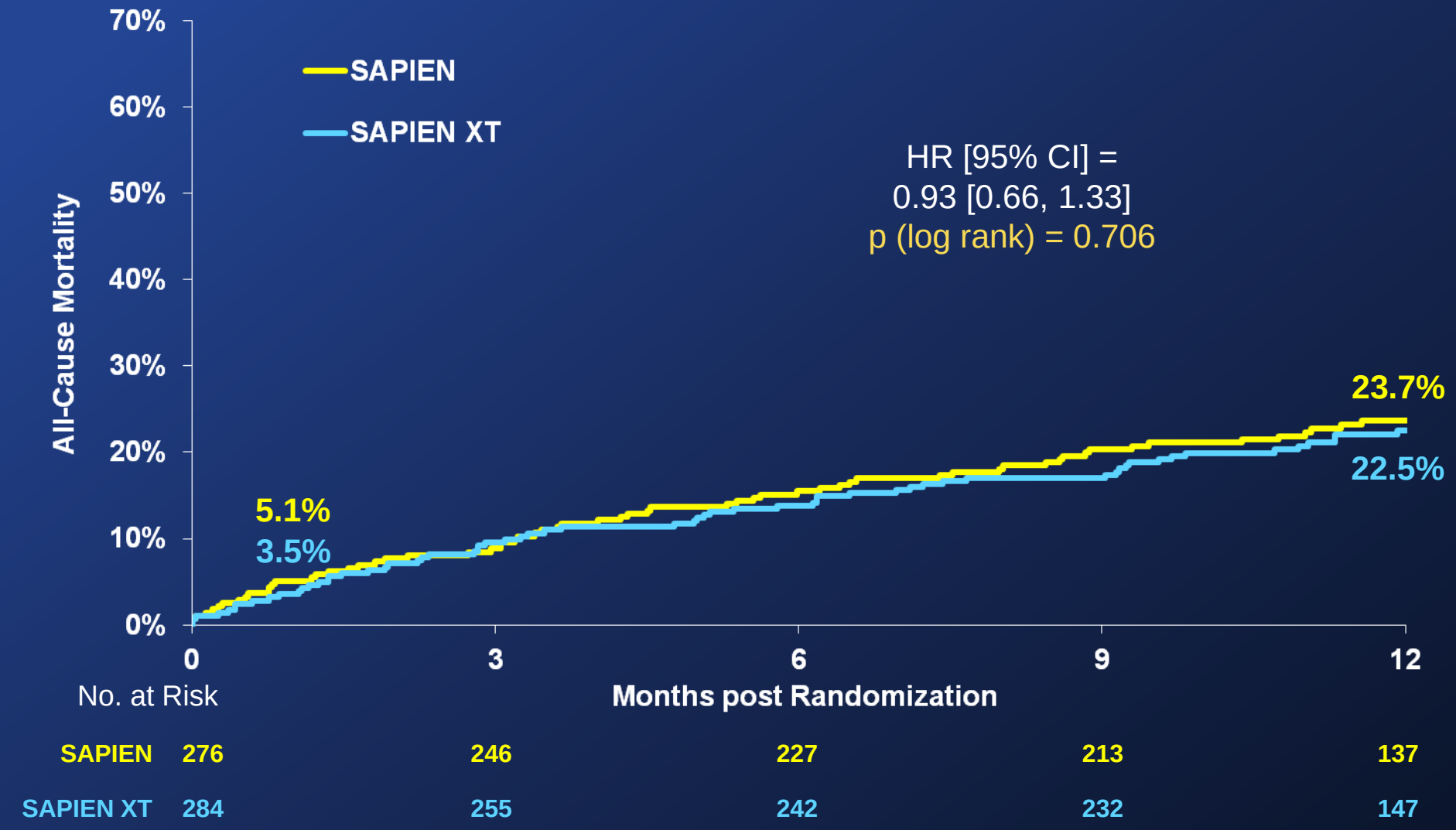
No. at Risk

SAPIEN	276	207	194	182	118
SAPIEN XT	284	221	205	197	122

*Preliminary based upon 100% CEC adjudication at 30 days and 89% CEC adjudication at 1 year.

All-Cause Mortality (ITT)

THE PARTNER II TRIAL

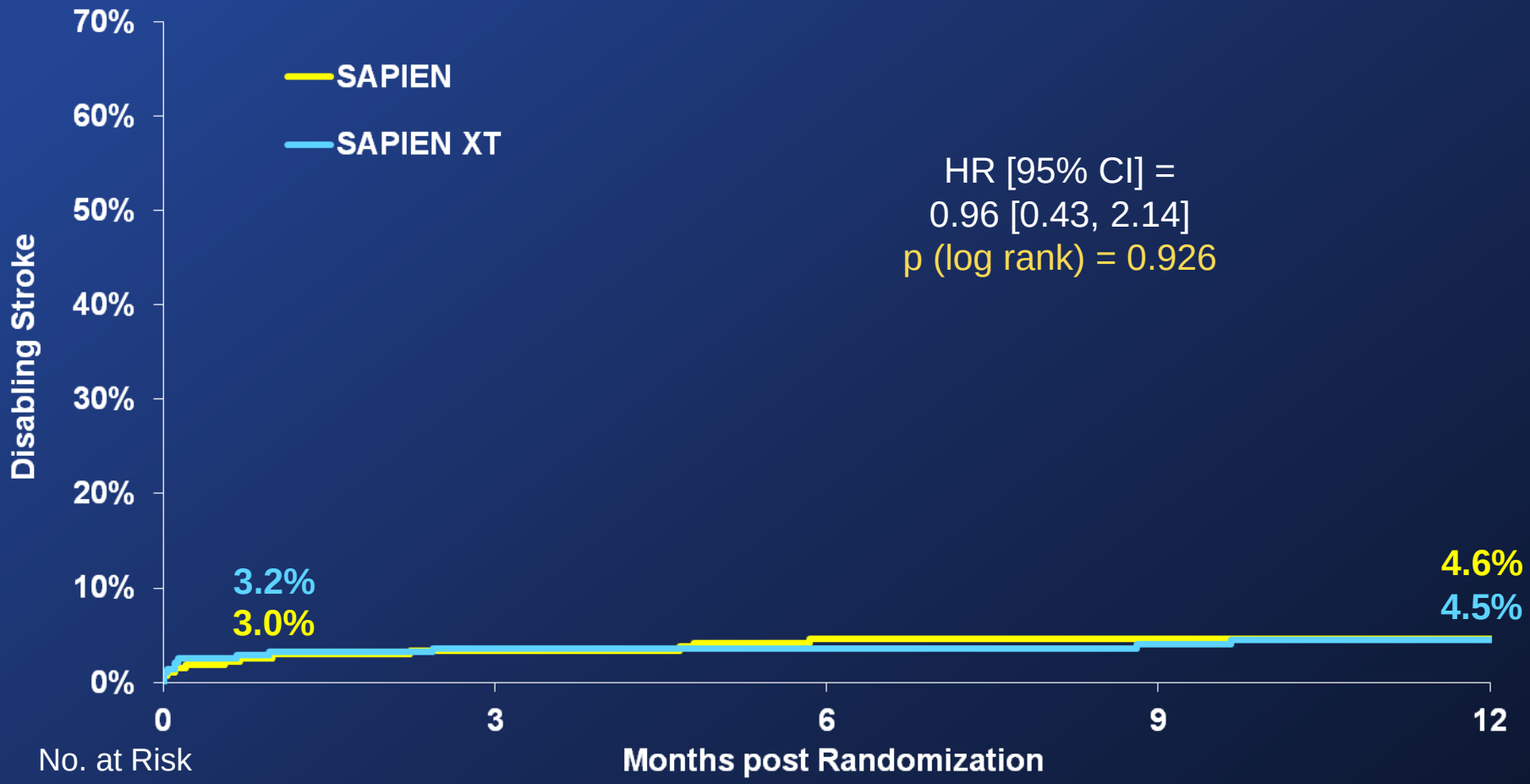


No. at Risk

SAPIEN	276	246	227	213	137
SAPIEN XT	284	255	242	232	147

Disabling Stroke (ITT)

THE PARTNER II TRIAL

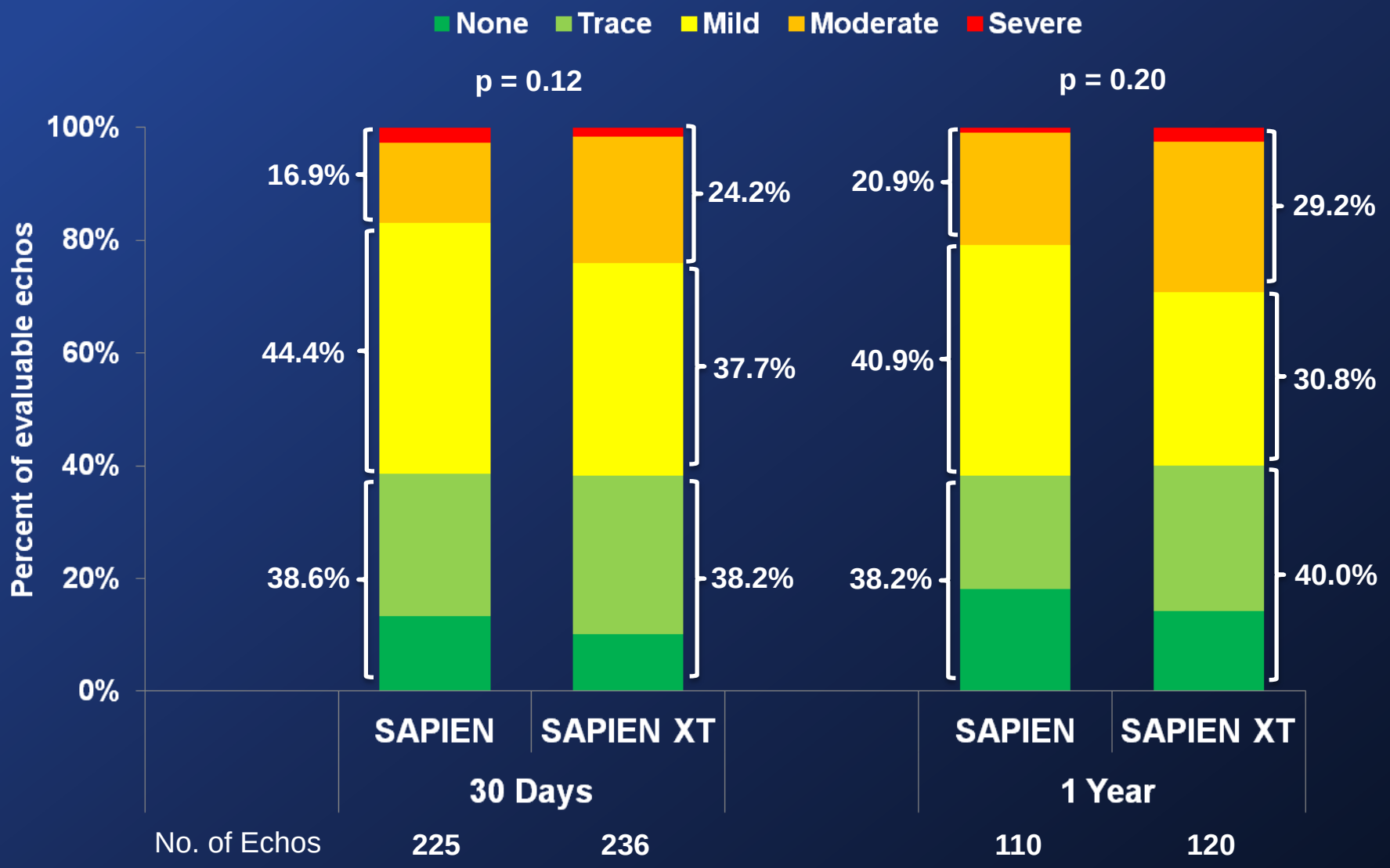


No. at Risk

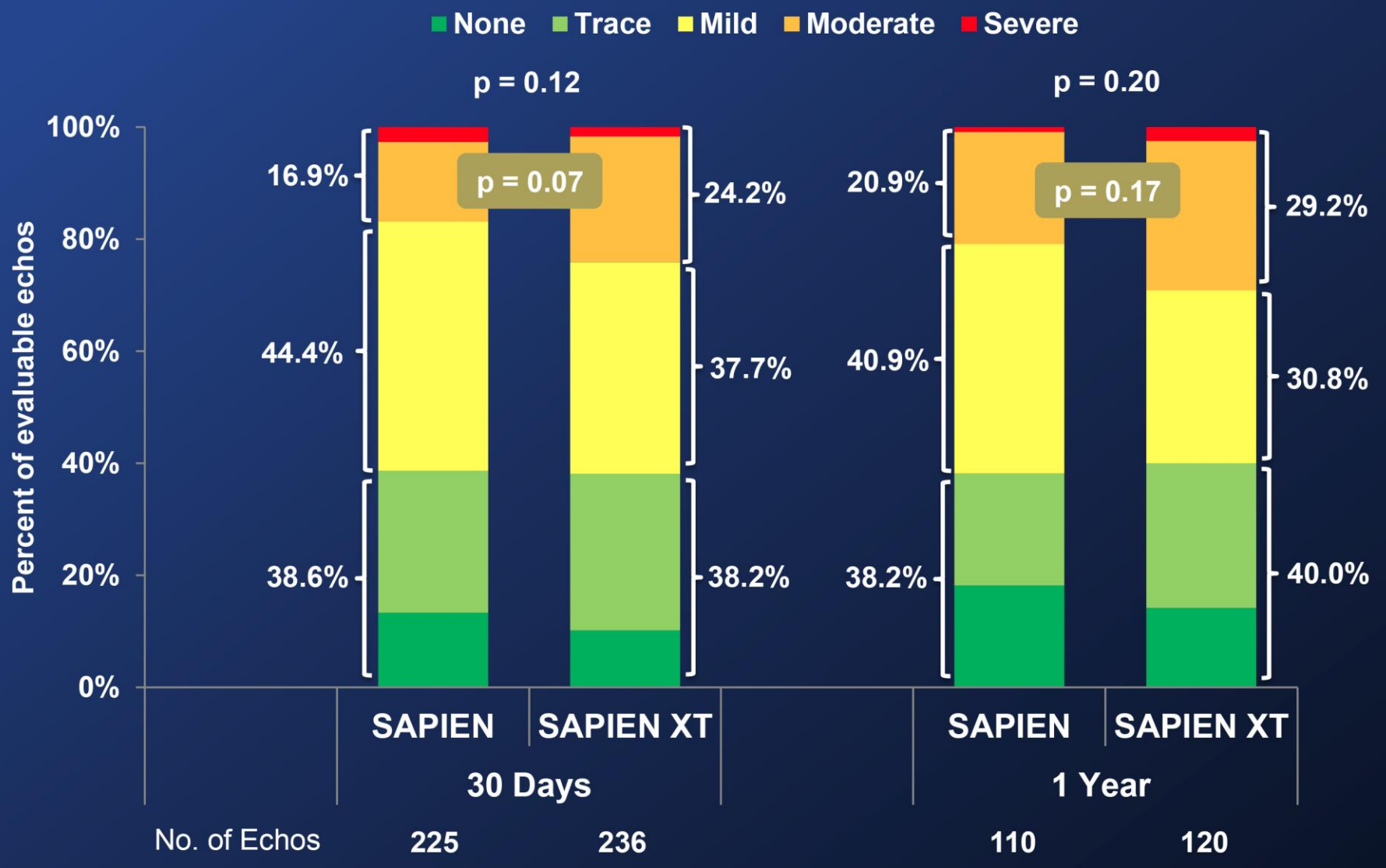
SAPIEN	276	241	223	209	134
SAPIEN XT	284	250	238	227	145

Paravalvular Aortic Regurgitation (Valve Implant)

THE PARTNER II TRIAL



Paravalvular Aortic Regurgitation (Valve Implant)



Implications

THE PARTNER II TRIAL

In the inoperable cohort of The PARTNER II Trial, the new lower profile SAPIEN XT THV system was associated with…

- Improved procedural outcomes
- Similar low 30-day mortality and strokes
- Reduced vascular complications
- Similar 1-year major clinical events and valve performance

Therefore, SAPIEN XT represents a worthwhile advance with incremental clinical value and is the preferred balloon-expandable THV system.