What's New In TAVR- Evolution of Valve Technology and Approaches

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Disclosures

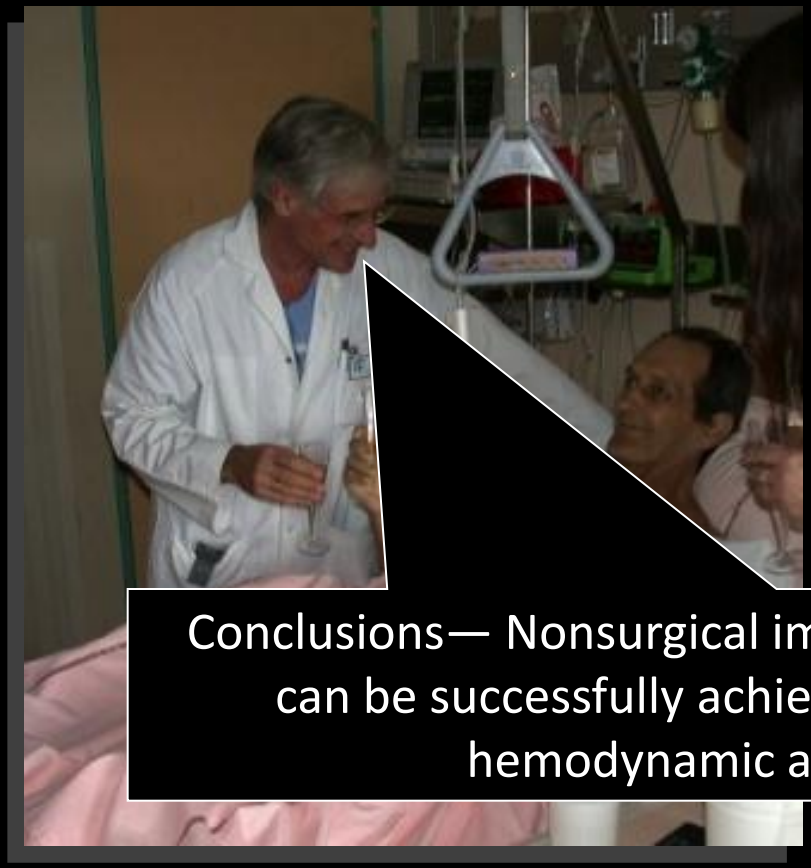
- Consultant:

Edwards Lifesciences Corporation

St. Jude Medical, Inc.

Medical City℠
Specialists. In life.

Dr. Alain Cribier
A Revolution Begins



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis

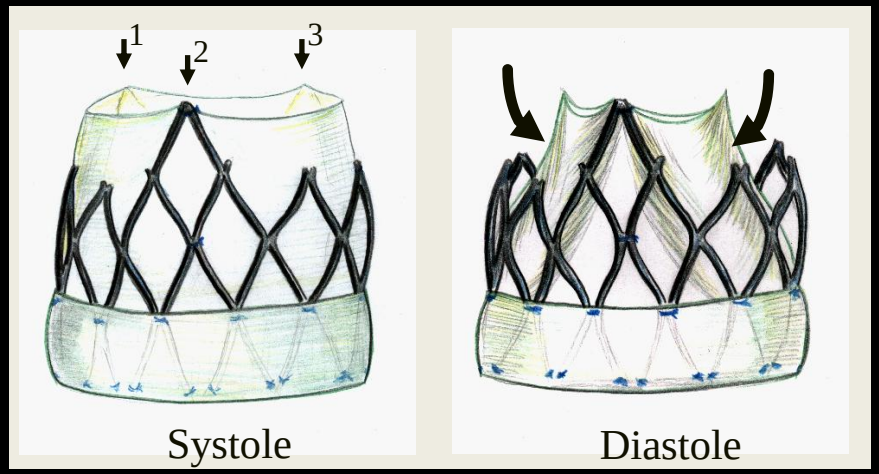
First Human Case Description

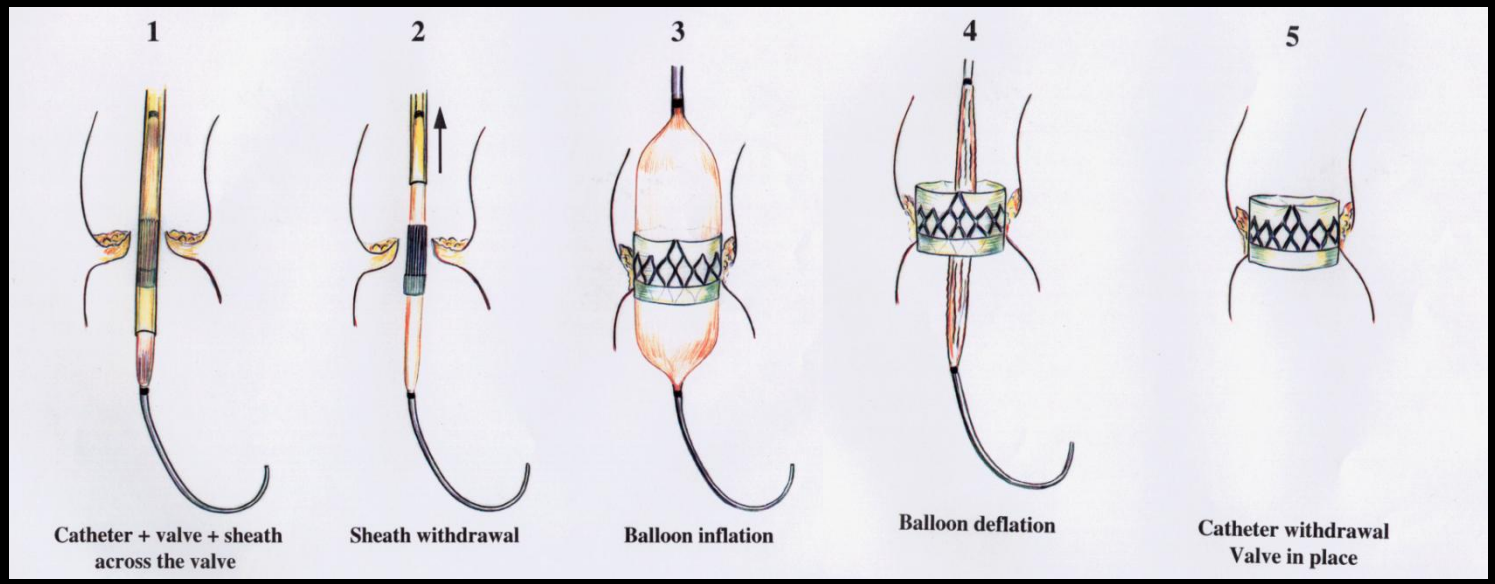
Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; François Laborde, MD; Martin B. Leon, MD

Conclusions— Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

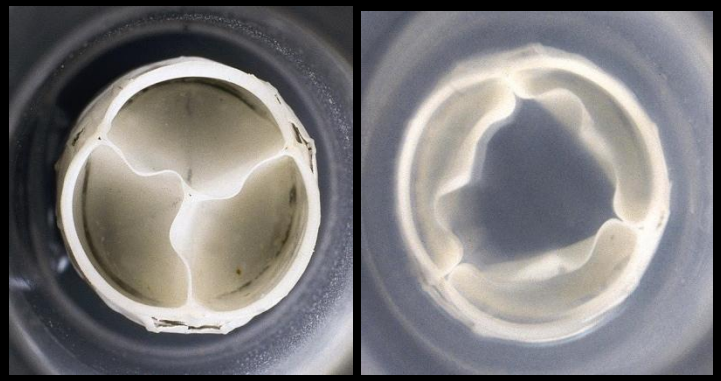
April 16, 2002

Alain Cribier Sketches (1990)

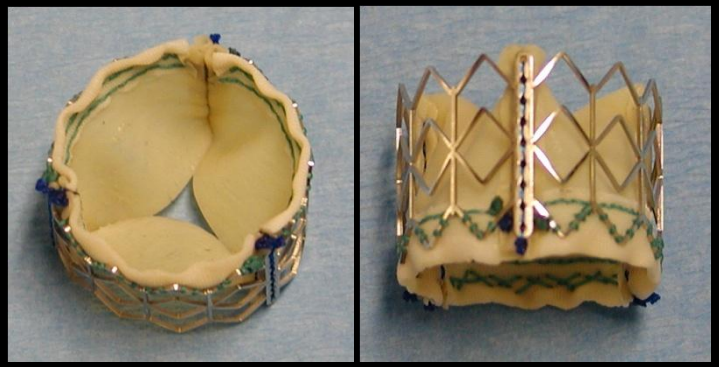




PVT-Edwards Percutaneous Heart Valve

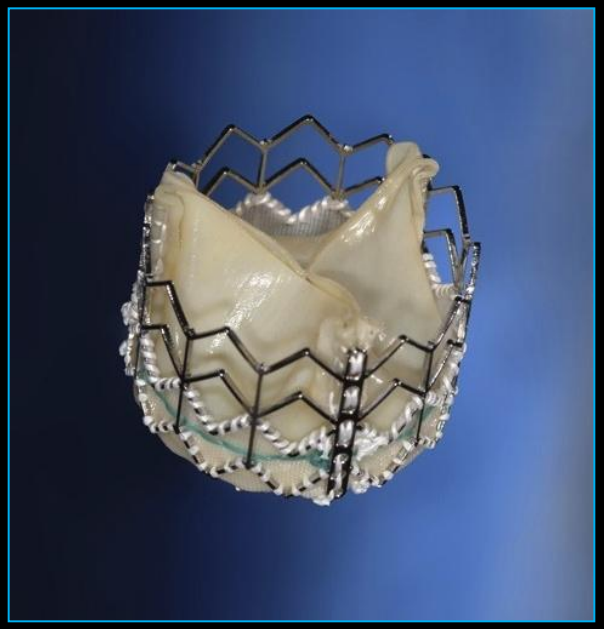


First generation – polyurethane



Second generation – bovine pericardium

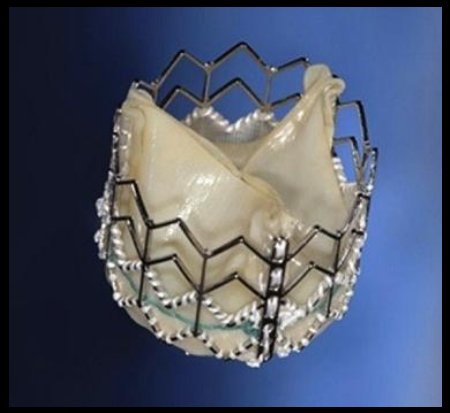
Cribier-Edwards Device



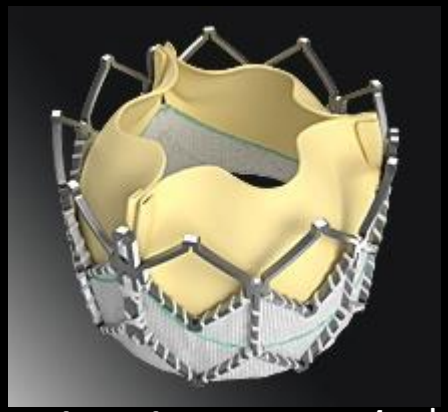
- ***equine pericardial valve***
- ***stainless steel stent***
- ***23mm and 26mm diameters***
- ***balloon-expandable***
- ***AVA = 1.7-1.9 cm^2***

What Have We Learned Since 2002?

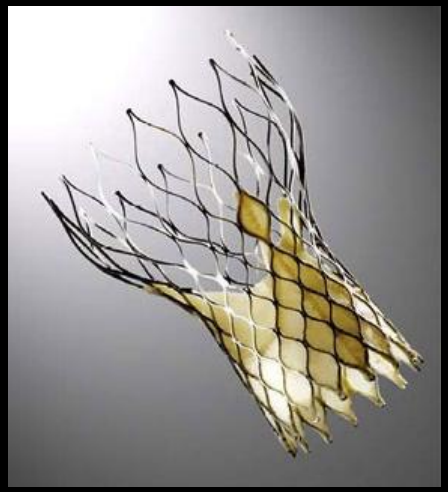
The Revolution Continues



Edwards Sapien THV (1st generation) 22/24 Fr with RetroFlex 3 delivery system



Edwards Sapien XT (2nd generation) 18/19 Fr with NovoFlex delivery system



Medtronic CoreValve

Medtronic Engager TA valve (Ventor Embracer)

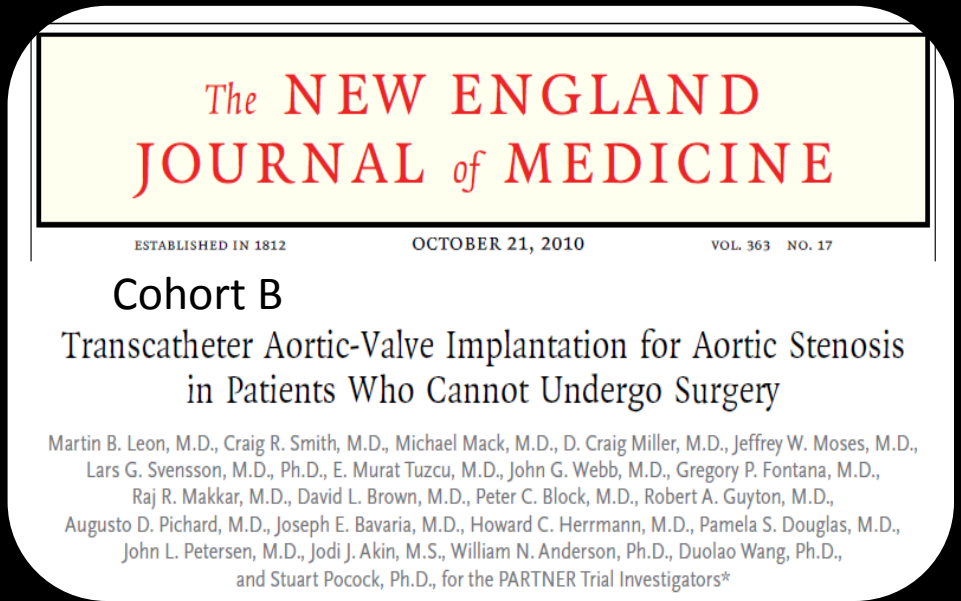
Boston Scientific Lotus self-exp valve (Sadra Lotus)

St. Jude Medical Portico valve

JenaValve

PARTNER I Trial Data

- In the PARTNER I randomized trials:
- "Inoperable" (Cohort B) patients had reduced mortality compared to standard therapy.
- Patients deemed high-risk for surgical AVR (Cohort A) that underwent TAVR had similar mortality compared to their surgical AVR counterparts.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Cohort B

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Cohort A

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

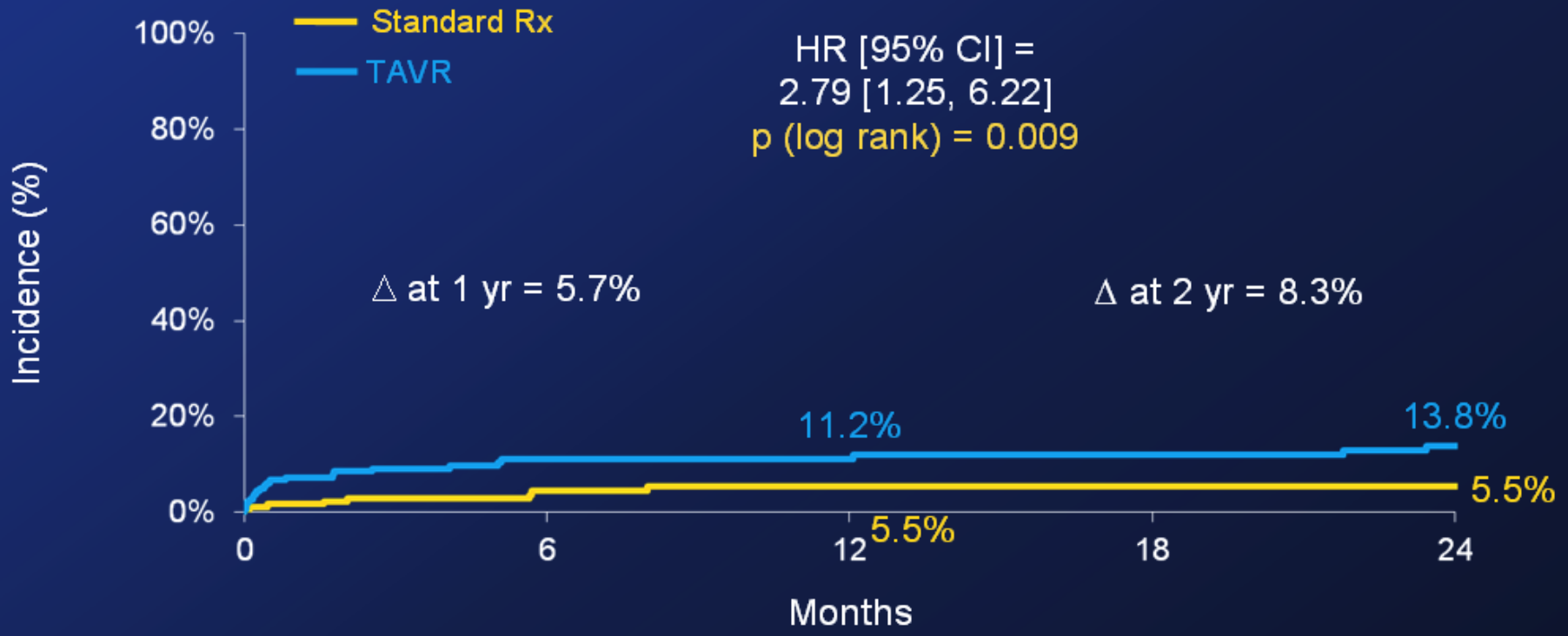
Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

Concerns From PARTNER I

PARTNER I Trial Peri-Procedural Concerns

- Strokes
- Vascular Complications
- Paravalvular Regurgitation

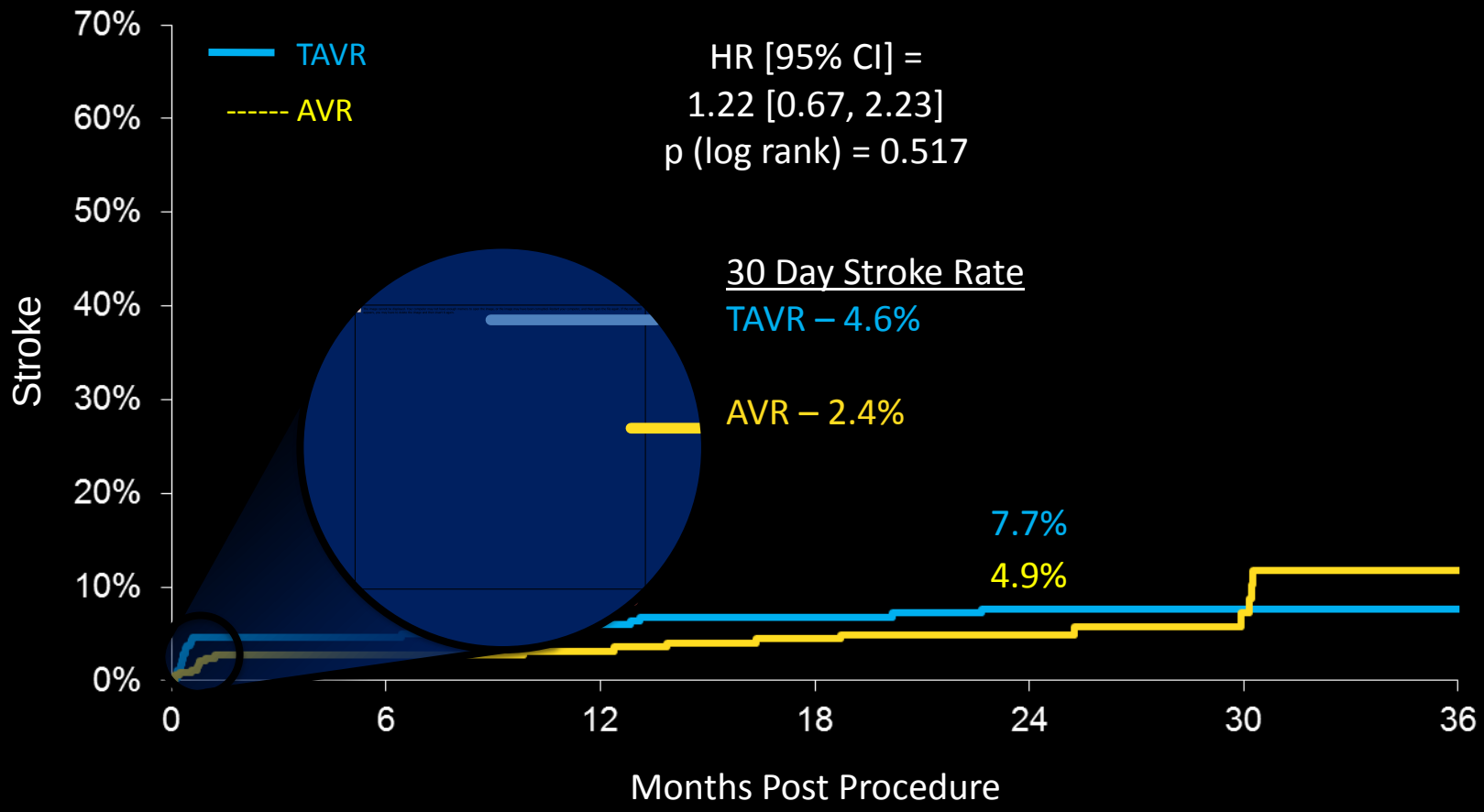
Cohort B Strokes



Numbers at Risk

TAVR	**179**	**128**	**116**	**105**	**79**
Standard Rx	**179**	**118**	**84**	**62**	**42**

Cohort A Strokes



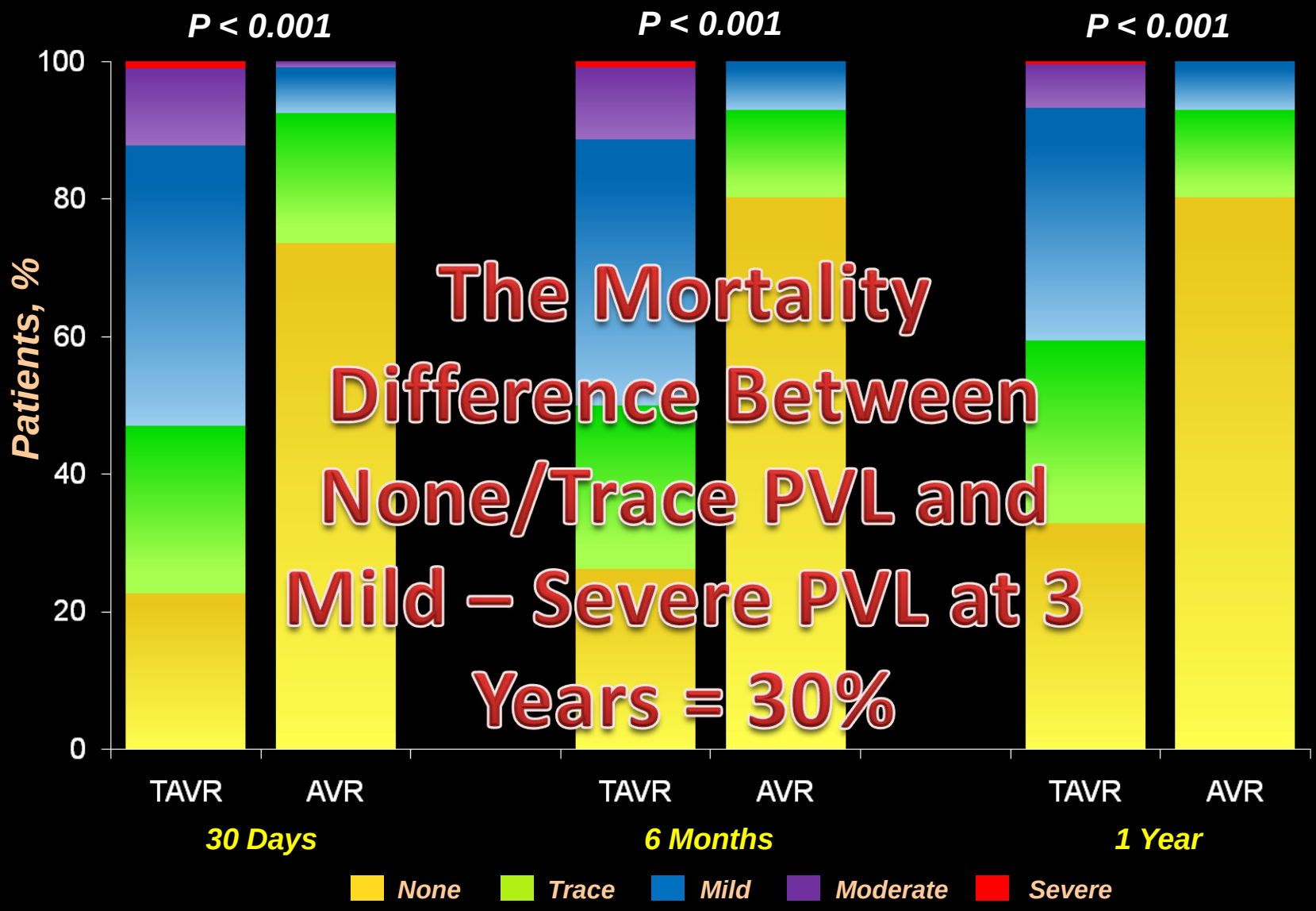
Numbers at Risk

TAVR	**348**	**287**	**249**	**224**	**162**	**65**	**28**
AVR	**351**	**246**	**230**	**211**	**160**	**62**	**31**

Complications Cohort B PARTNER I Trial

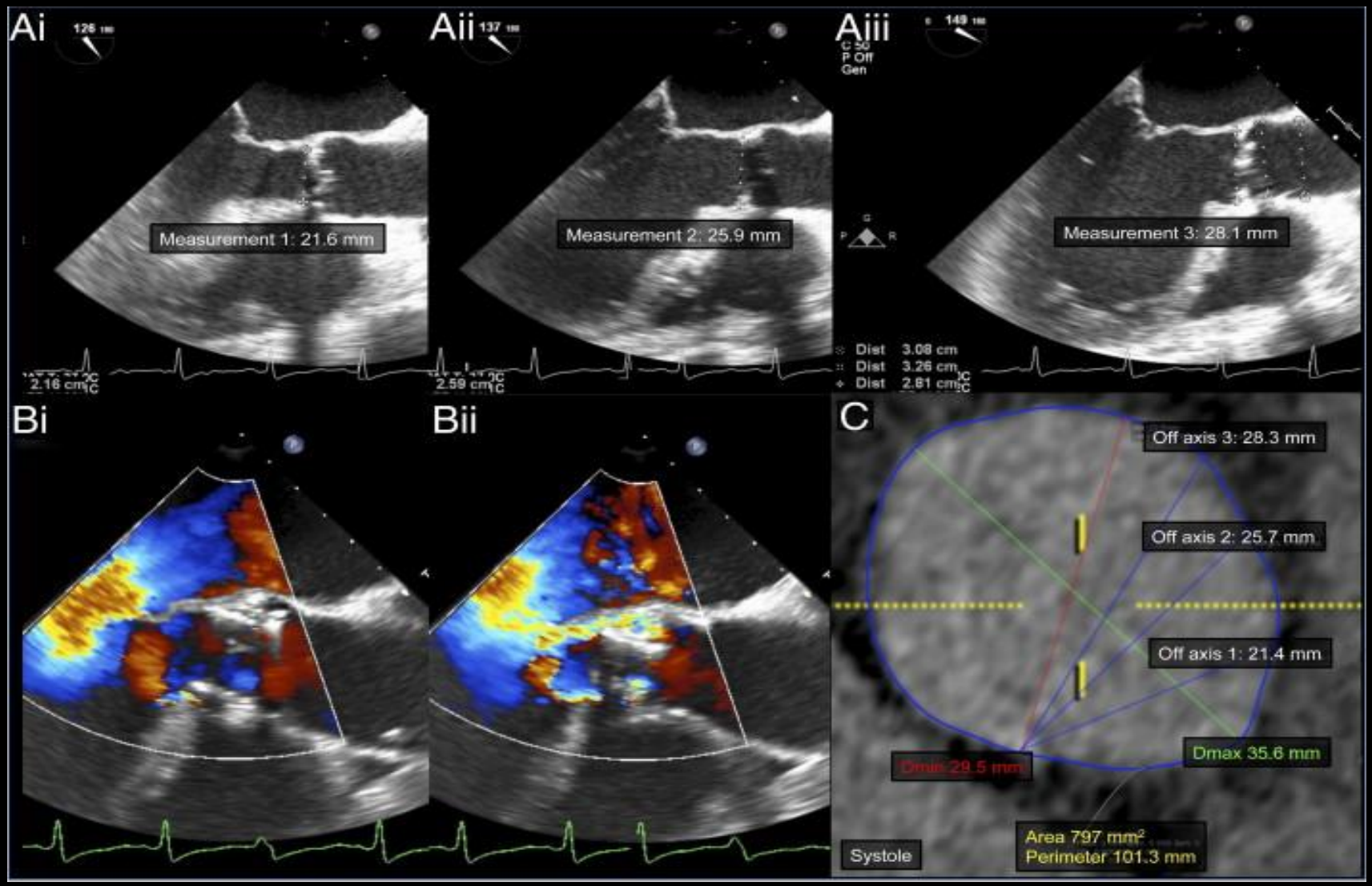
Outcome	30 Days n=179			1 Year n=179		
Vascular complications	**TAVI**	**Standard Rx**	**P-value**	**TAVI**	**Standard Rx**	**P-value**
All (%)	**30.7**	5.0	<.0001	32.4	7.3	<.0001
Major (%)	**17.5**	1.1	<.0001	17.8	2.2	<.0001
Acute kidney injury						
Creatinine >3 mg/dL (%)	0	1	1.00	1.1	2.8	0.45
RRT (%)	1.1	1.7	1.00	1.7	3.4	0.50
Bleeding - major (%)	16.8	3.9	<.0001	22.3	11.2	0.007
Cardiac re-intervention						
BAV (%)	0.6	1.1	1.0	0.6	36.9	<.0001
Re-TAVI (%)	1.7	na		1.7	na	
AVR (%)	0	1.7	0.25	1.1	9.5	<.0001
Endocarditis (%)	0	0	.	1.1	0.6	0.31
Arrhythmias						
New atrial fibrillation (%)	0.6	1.1	1.00	0.6	1.7	0.62
New pacemaker (%)	**3.4**	5.0	0.60	4.5	7.8	0.27

Paravalvular Leak PARTNER I Cohort A

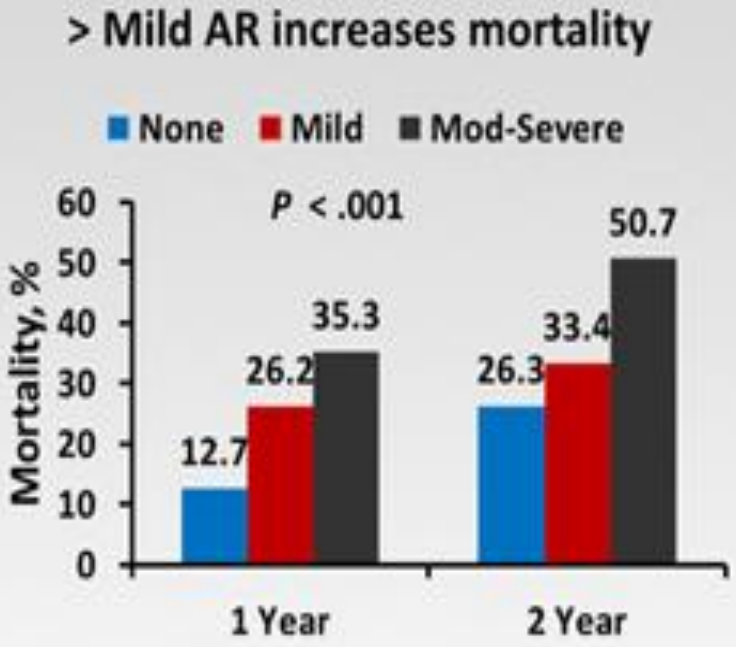


The Mortality Difference Between None/Trace PVL and Mild – Severe PVL at 3 Years = 30%

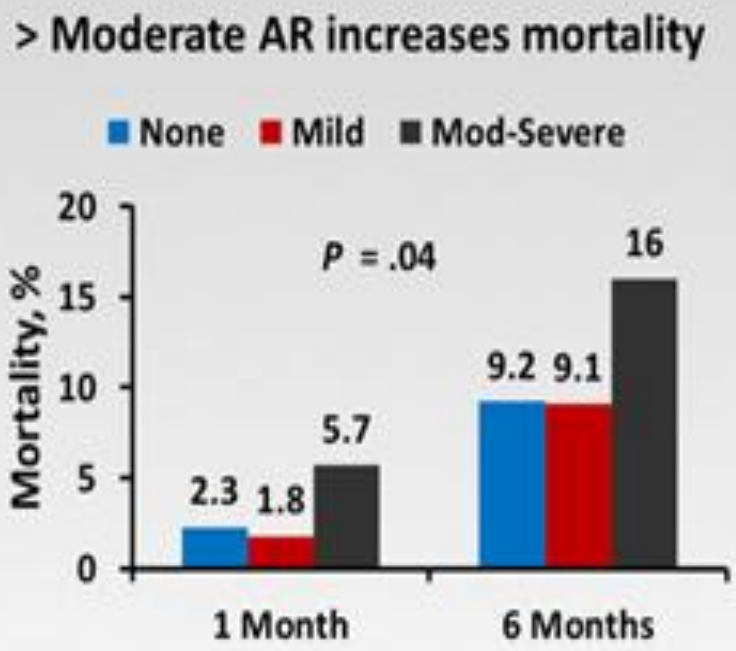
Paravalvular Leak: Aortic Annulus Assesment



CoreValve Vs. Sapien PVL



PARTNER Cohort A[a] Sapien valve
None/Trace (n = 135); Mild (n = 165);
Moderate-Severe (n = 34)

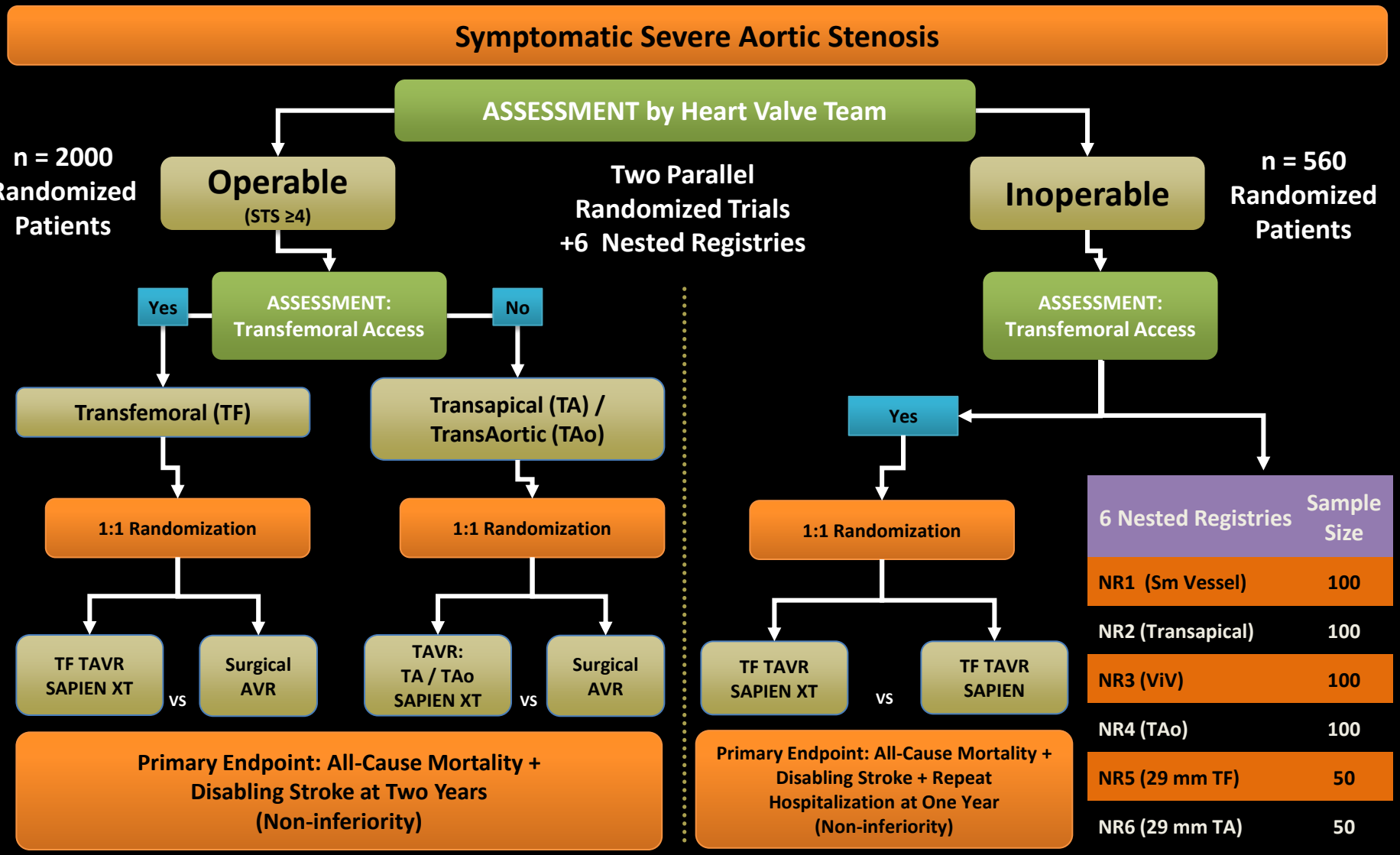


ADVANCE Registry[b] CoreValve*
None (n = 166); Mild (n = 551);
Moderate-Severe (n = 132)

What Does Second Generation Technology Change?

- The PARTNER II Trial

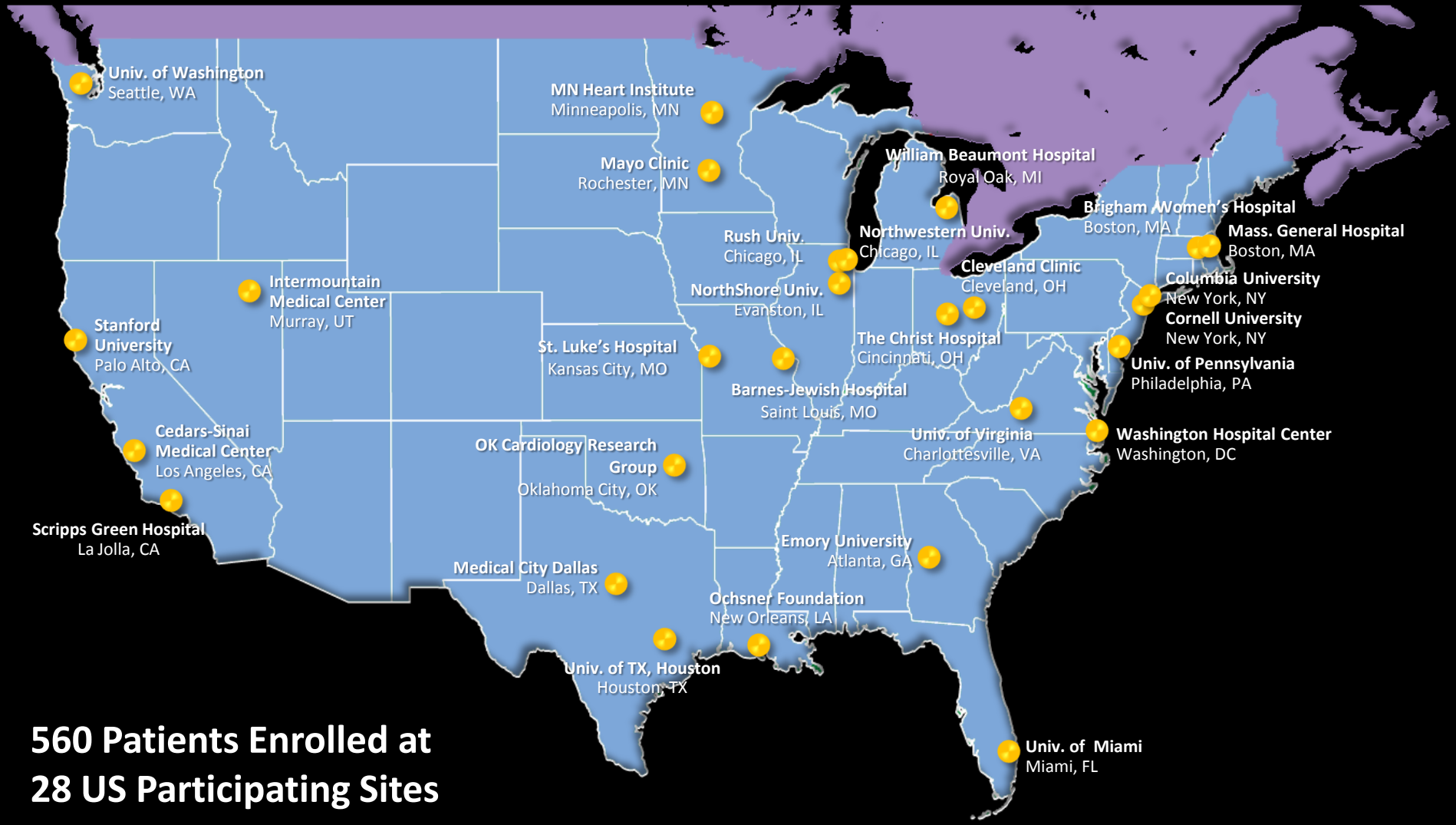
The PARTNER II Trial
Study Design



6 Nested Registries	Sample Size
NR1 (Sm Vessel)	100
NR2 (Transapical)	100
NR3 (ViV)	100
NR4 (TAo)	100
NR5 (29 mm TF)	50
NR6 (29 mm TA)	50

The PARTNER II Inoperable Cohort

Participating Sites



560 Patients Enrolled at
28 US Participating Sites

Other Important Endpoints

VARC 2 Definitions

SAFETY

- Cardiovascular mortality
- Major vascular complications
- All strokes and TIAs
- Peri-procedural MI
- Acute kidney injury
- Life-threatening or disabling bleeding
- No. of transfusions
- ***New permanent pacemakers***
- New onset atrial fibrillation
- ≥ 2 THV implants
- Repeat intervention

EFFICACY

- NYHA class
- QOL instruments
- 6-minute walk test
- Days alive out-of-hospital
- ICU and index hospital LOS

ECHO VALVE PERFORMANCE

- Mean and peak AV gradient
- Effective orifice area (and index)
- LV function (ejection fraction)
- Paravalvular and total AR
- Structural valve deterioration

Key Exclusion Criteria

Anatomic:

- Aortic annulus diameter (echo measurement) < 18 mm or > 25 mm
- Iliac-femoral anatomy precluding safe sheath insertion (vessel size ≥7 mm diameter)
- Severe LV dysfunction (LVEF < 20%)
- Untreated CAD requiring revascularization

Clinical:

- Serum Cr > 3.0 mg/dL or **dialysis dependent**
- Acute MI within 1 month
- CVA or TIA within 6 months
- Hemodynamic instability

Edwards SAPIEN vs SAPIEN XT Transcatheter Heart Valves

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

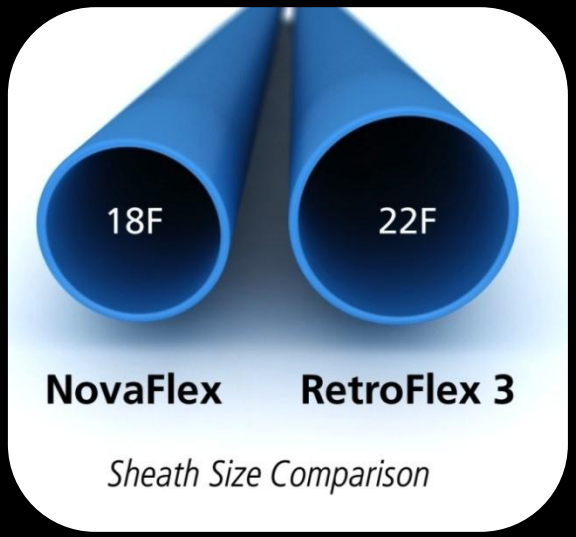
Cobalt-chromium

RetroFlex 3

NovaFlex

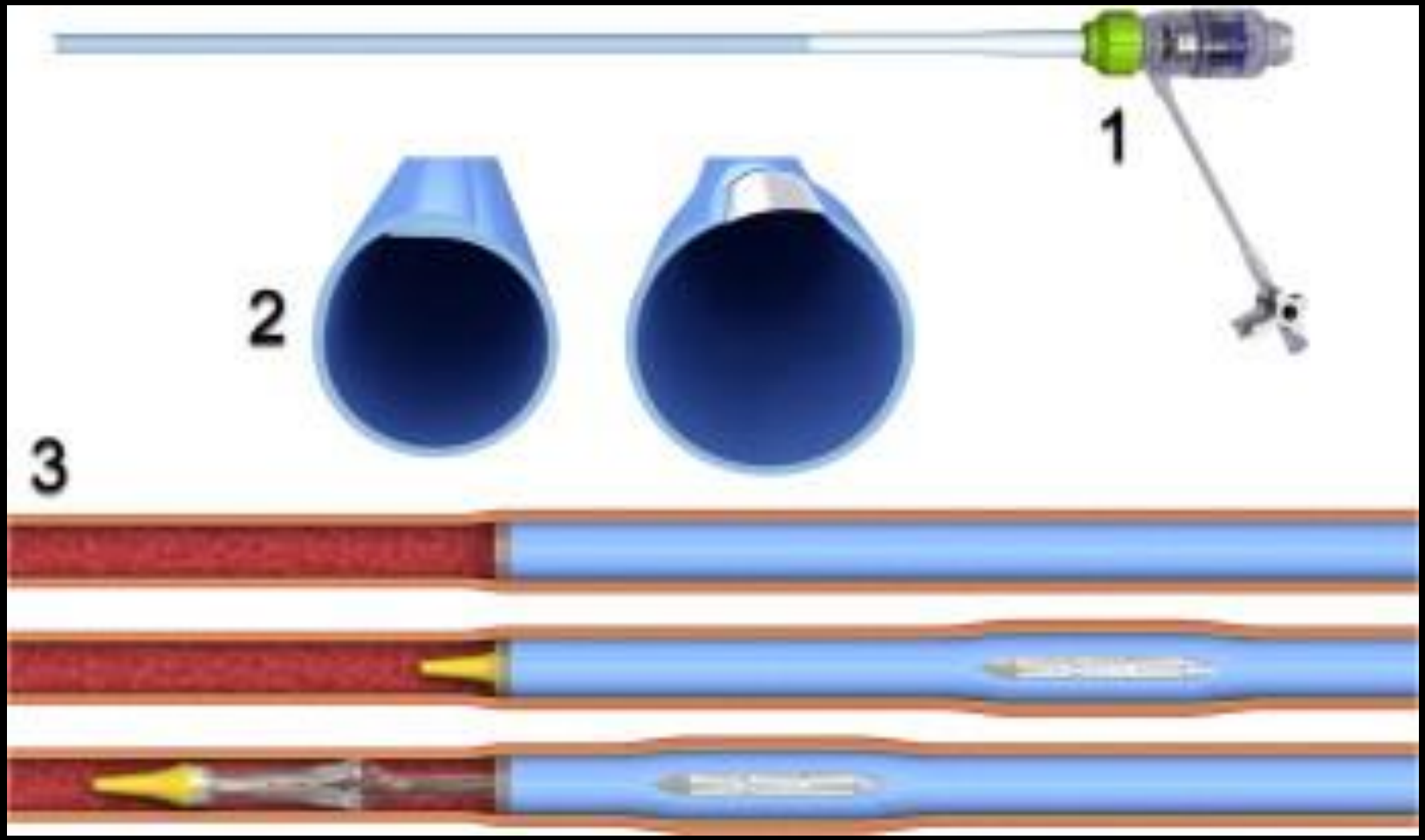
Sheath Size Comparison

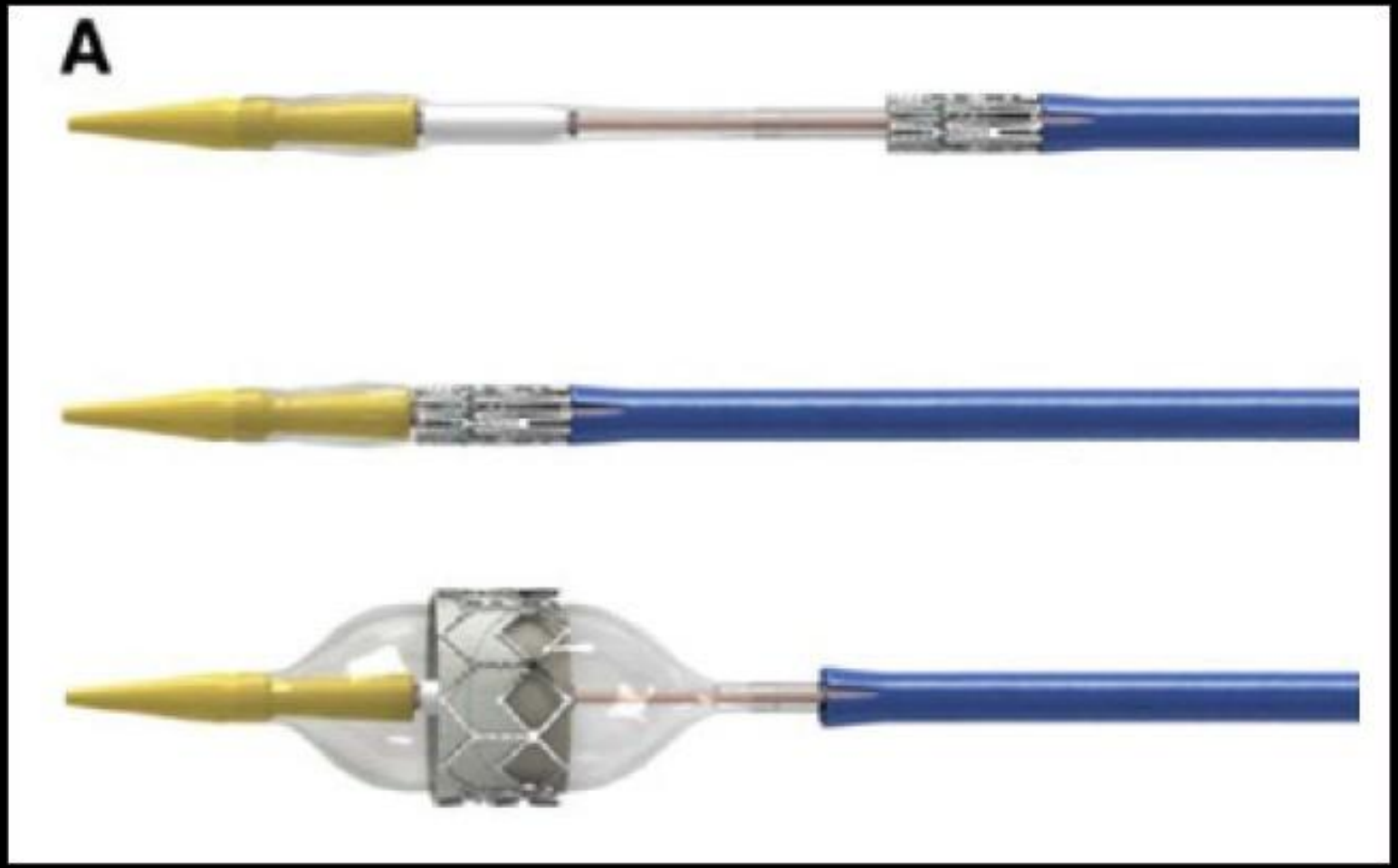
Valve	Valve Size	Sheath ID	Sheath OD	Minimum Vessel Diameter
SAPIEN THV	23mm	22F	25F (8.4mm)	7.0mm
SAPIEN XT THV	23mm	18F	22F (7.2mm)	6.0mm
SAPIEN THV	26mm	24F	28F (9.2mm)	8.0mm
SAPIEN XT THV	26mm	19F	23F (7.5mm)	6.5mm



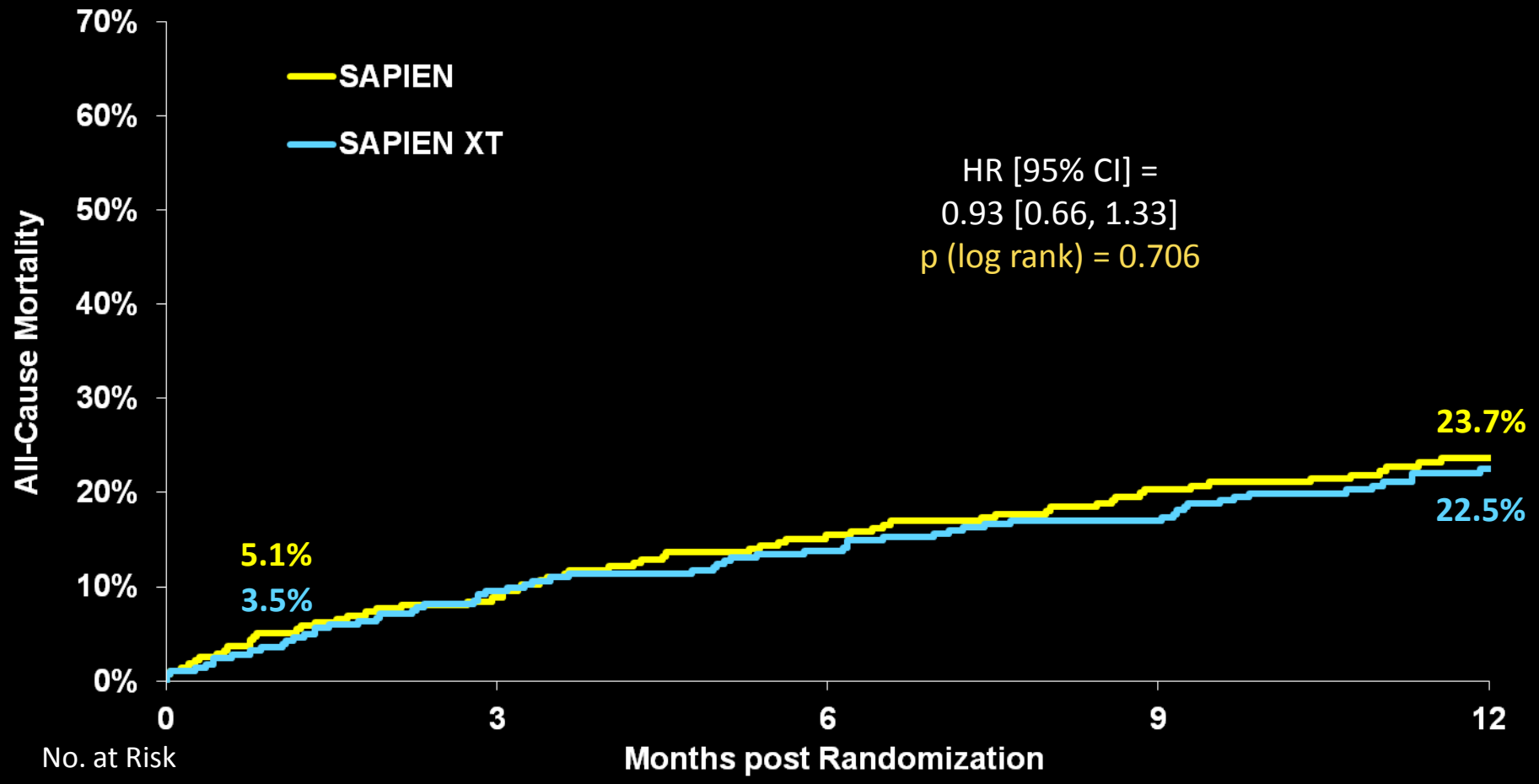
33% reduction in CSA

16Fr and 18Fr Expandable Sheaths



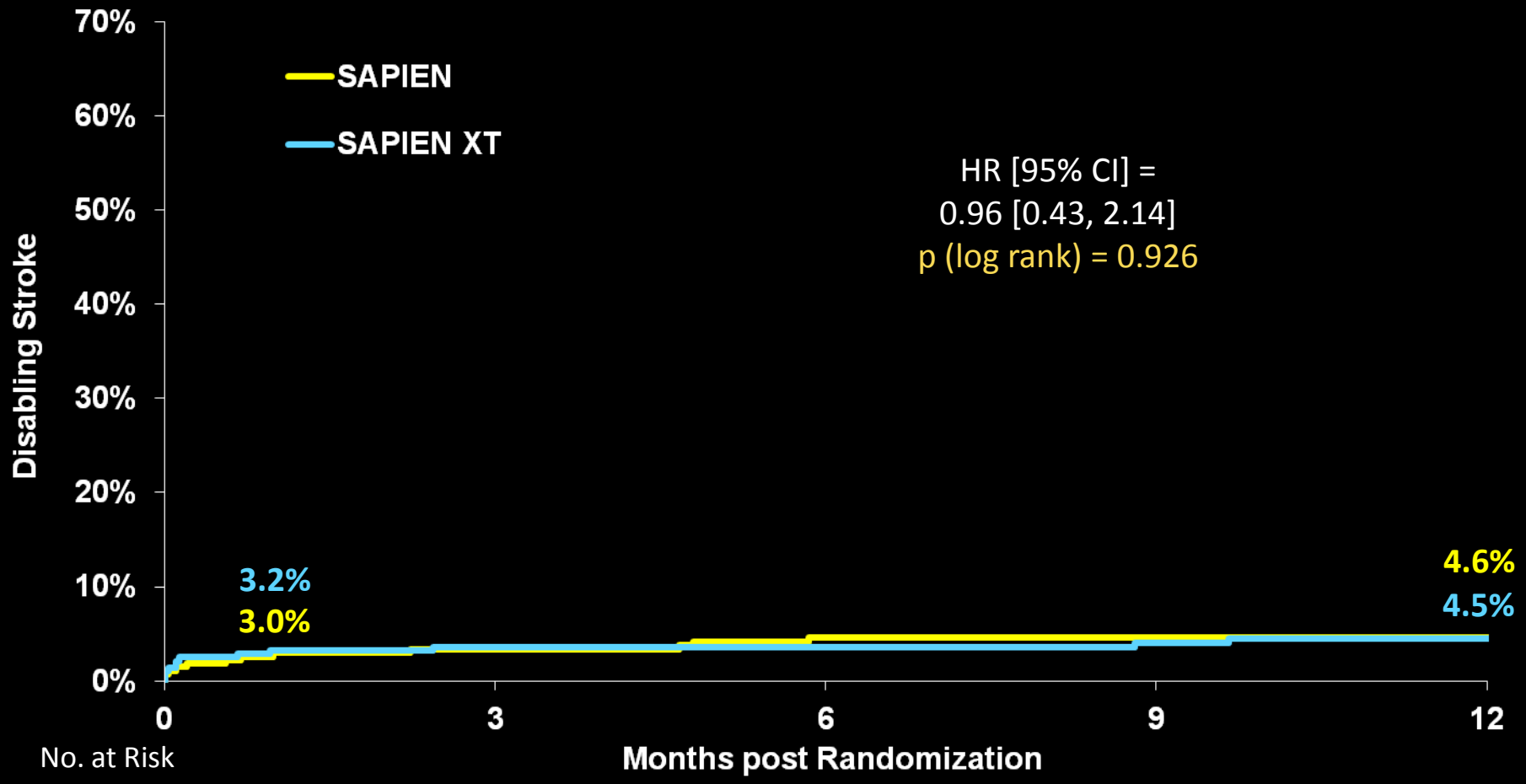

A

PARTNER II Mortality Cohort B



No. at Risk					
SAPIEN	276	246	227	213	137
SAPIEN XT	284	255	242	232	147

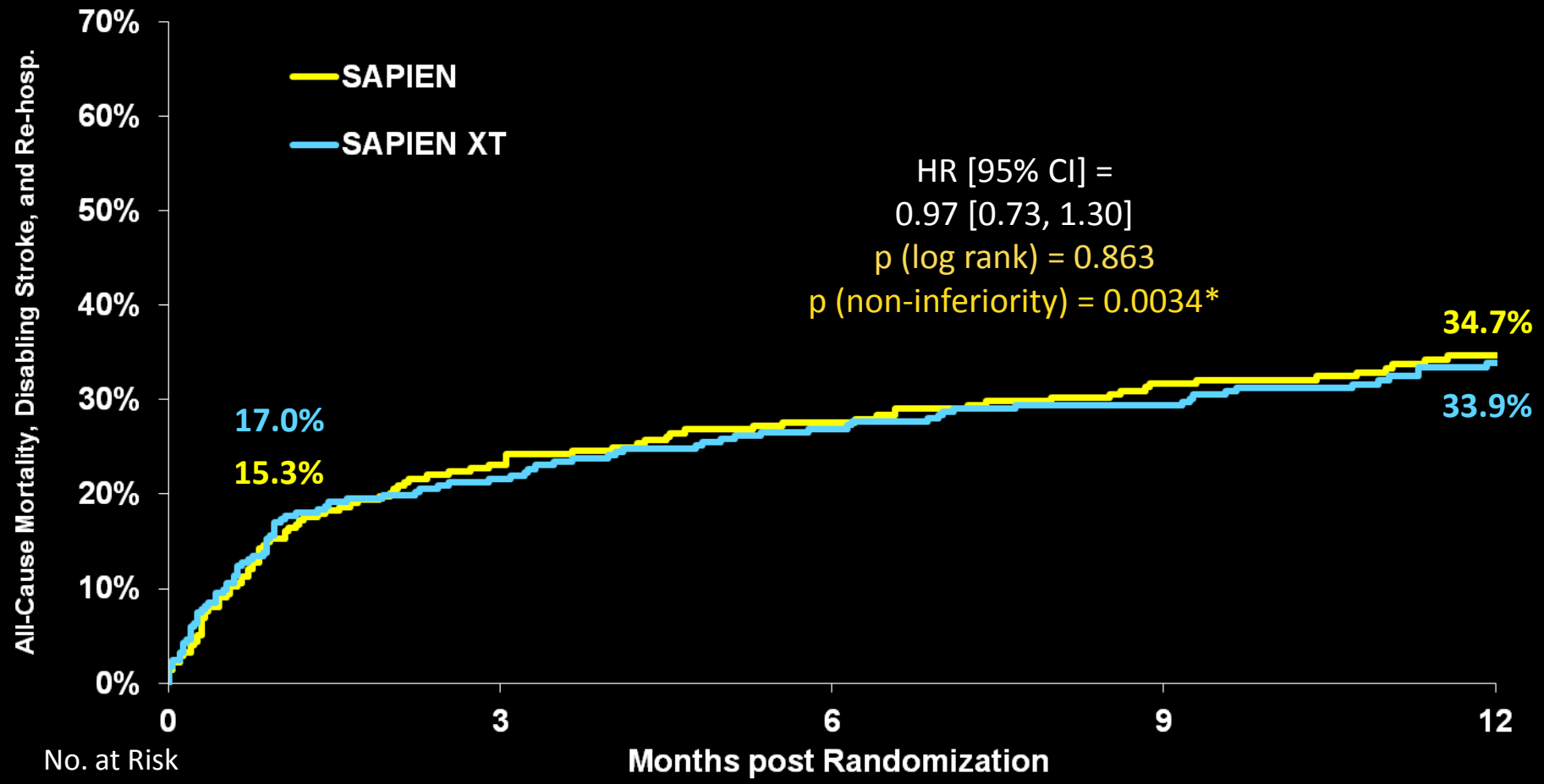
PARTNER II Cohort B Strokes



No. at Risk

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

All-Cause Mortality, Disabling Stroke, and Re-Hospitalization
PARTNER II



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.

Procedural Factors PARTNER II Cohort B

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
IABP during procedure	6	2.2	1	0.4	0.06

Primary Endpoint Events PARTNER II Cohort B 30 Days:

Events	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value*
Death:					
All-Cause	14	5.1	10	3.5	0.36
Cardiovascular	9	3.3	5	1.8	0.26
Stroke:					
Disabling	8	3.0	9	3.2	0.85
All	11	4.1	12	4.3	0.88
All + TIA	13	4.8	12	4.3	0.78
Death (all-cause) and Stroke (disabling)	19	6.9	18	6.4	0.80
Re-hospitalizations	27	10.2	32	11.6	0.59
Death (all-cause),Stroke (disabling), and Re-hosp	42	15.3	48	17.0	0.60

*p-values are KM - Log Rank

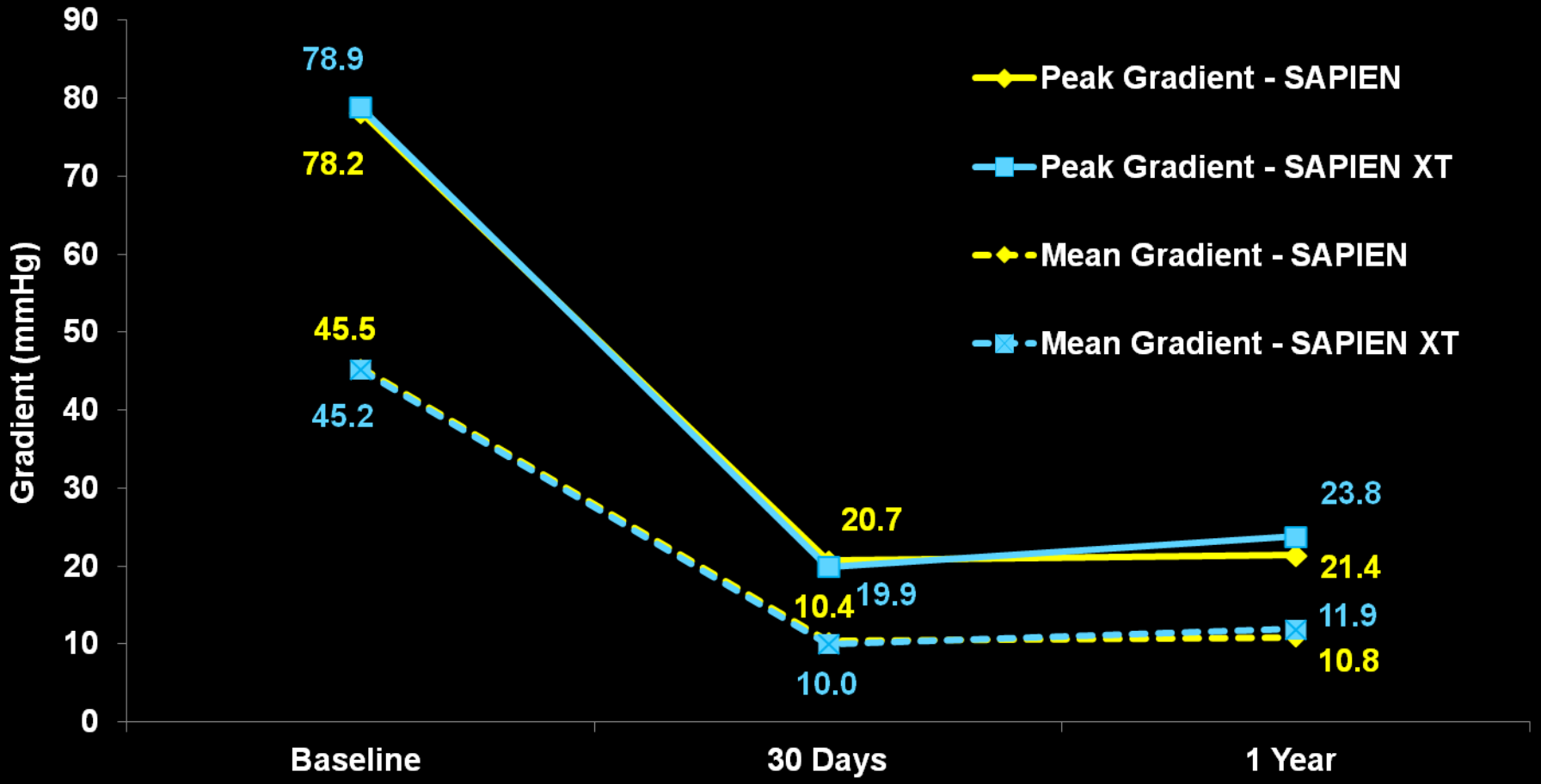
Vascular and Bleeding Events:
At 30 Days

	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 Complications PARTNER II Cohort B:

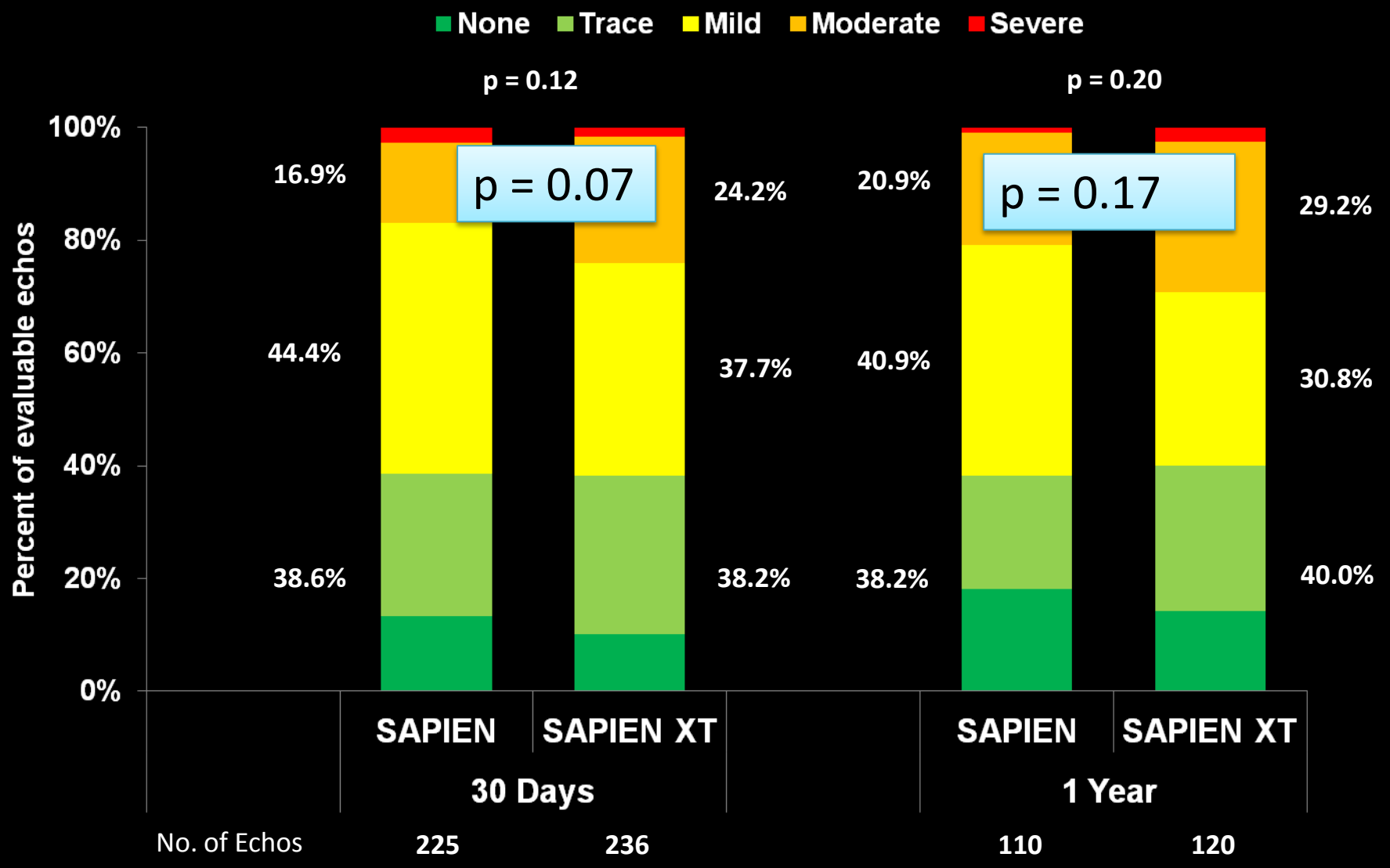
	SAPIEN (n=271)		SAPIEN XT (n=282)		
Events	n	%	n	%	p-value
Perforation	13	4.8	2	0.4	0.003
Dissection	25	9.2	12	4.3	0.03
Hematoma	16	5.9	10	3.6	0.23

Echocardiographic Findings:
Mean & Peak Gradients



No. of Echos			
SAPIEN	237	224	113
SAPIEN XT	263	237	118

Paravalvular Aortic Regurgitation (Valve Implant)



Clinical Gains From PARTNER II

- Decreased Anesthesia Time (p=0.02)
- Decreased Vascular Complications (p=0.03)
- Decreased Multiple Valve Implants (p=0.06)
- Decreased Aborted Procedures (p=0.06)
- Decreased Need For IABP (p=0.06)

PARTNER II- Inoperables
What Did Not Change…

- Mortality:

  Sapien XT 3.5%

  Sapien 5.1%

- Stroke:

  Sapien XT 3.2%

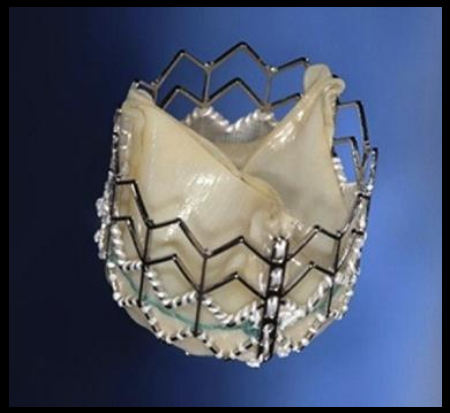
  Sapien 3.0%

- Paravalvular Leak Similar at 1 year

Future Challenges to Be Addressed by Next Generation Technology

- Low Profile Systems
- Retrievable and Repositionable
- Reduction of Paravalvular Leak
- Ability to Deliver Through Alternative Access
- Reduce Conduction System Disturbances
- Integrate with Embolic Protection Systems
- Keep The Surgeon Engaged !

Challenges Addressed



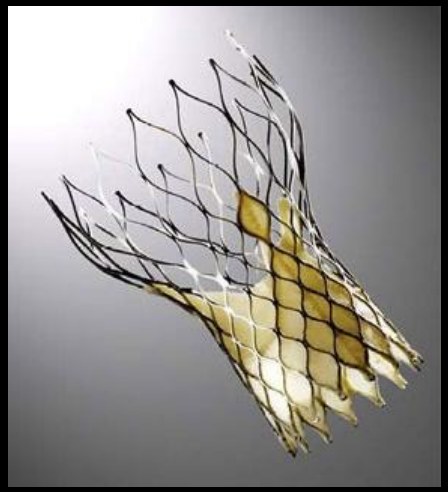
Edwards Sapien THV (1st generation) 22/24 Fr delivery system

Edwards Sapien 3

(14 Fr delivery system)

Medtronic Engager TA valve (Ventor Embracer)

St. Jude Medical Portico valve



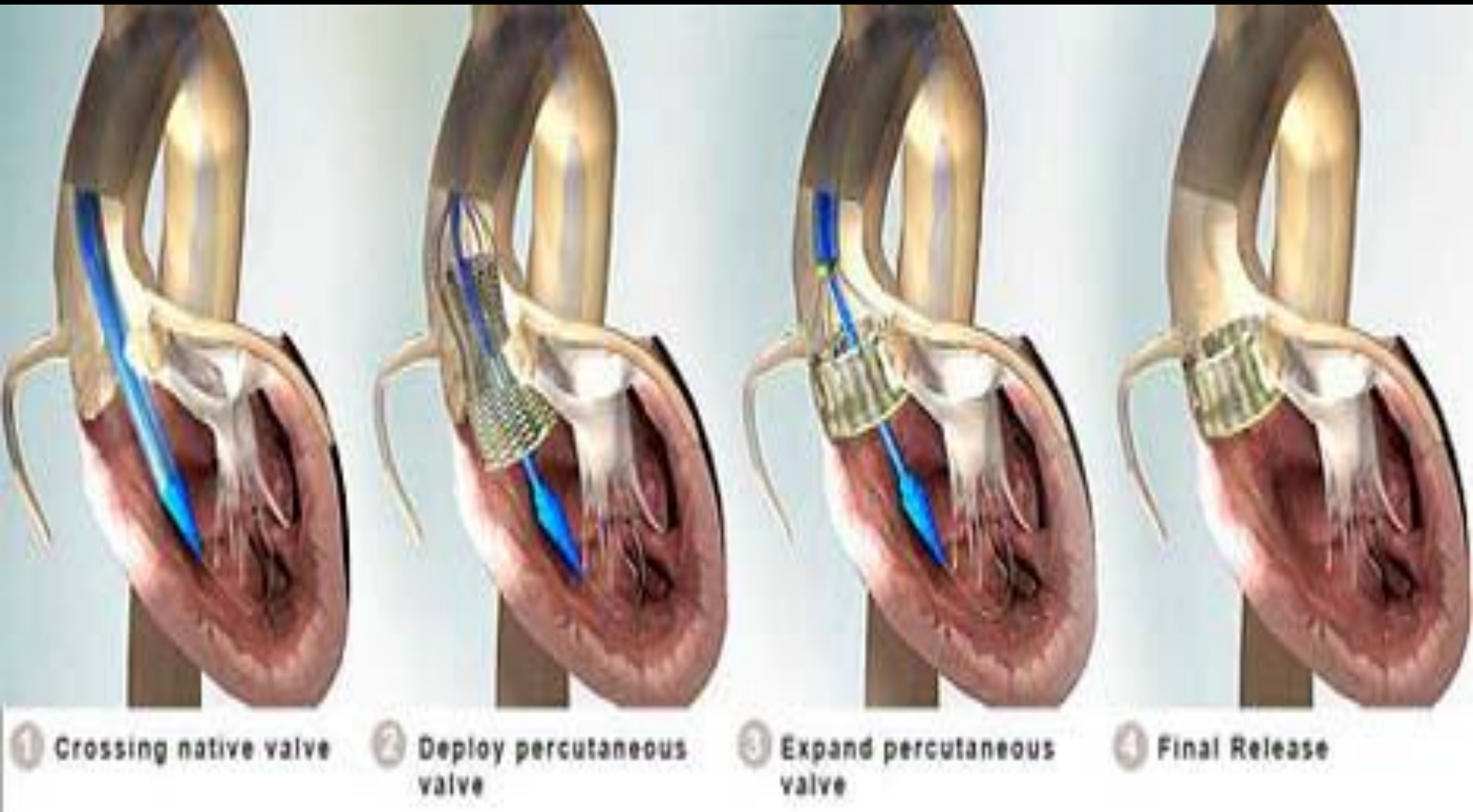
Medtronic CoreValve

Boston Scientific Lotus self-exp valve (Sadra Lotus)

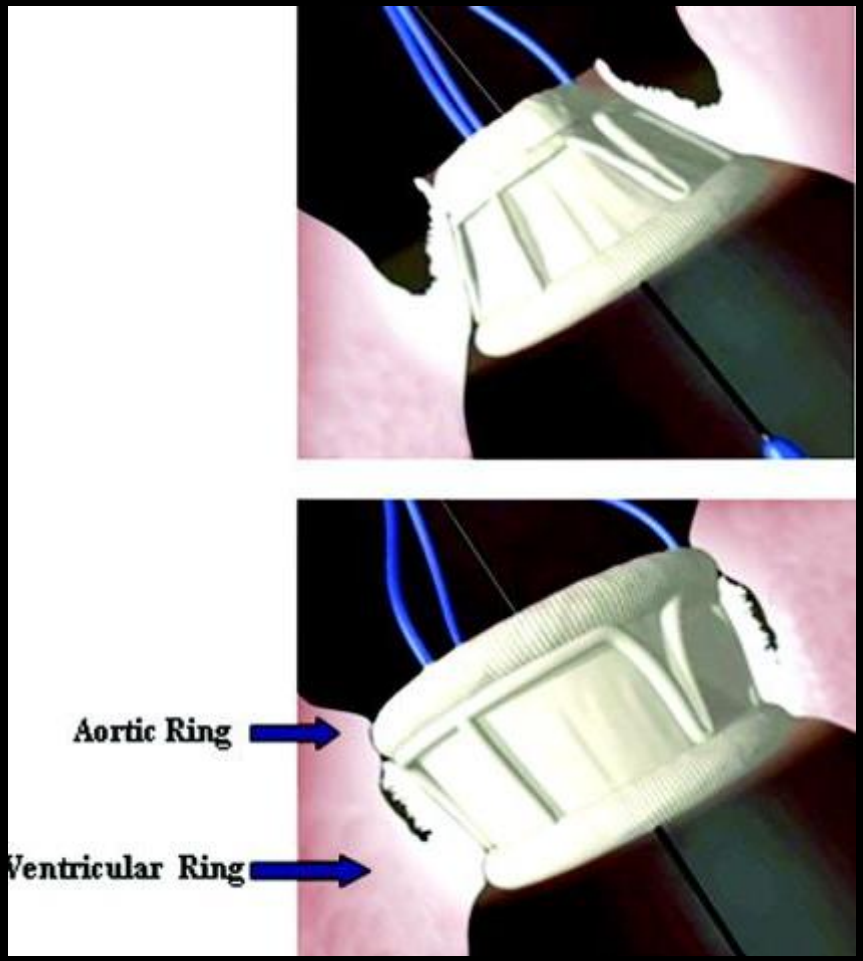
JenaValve

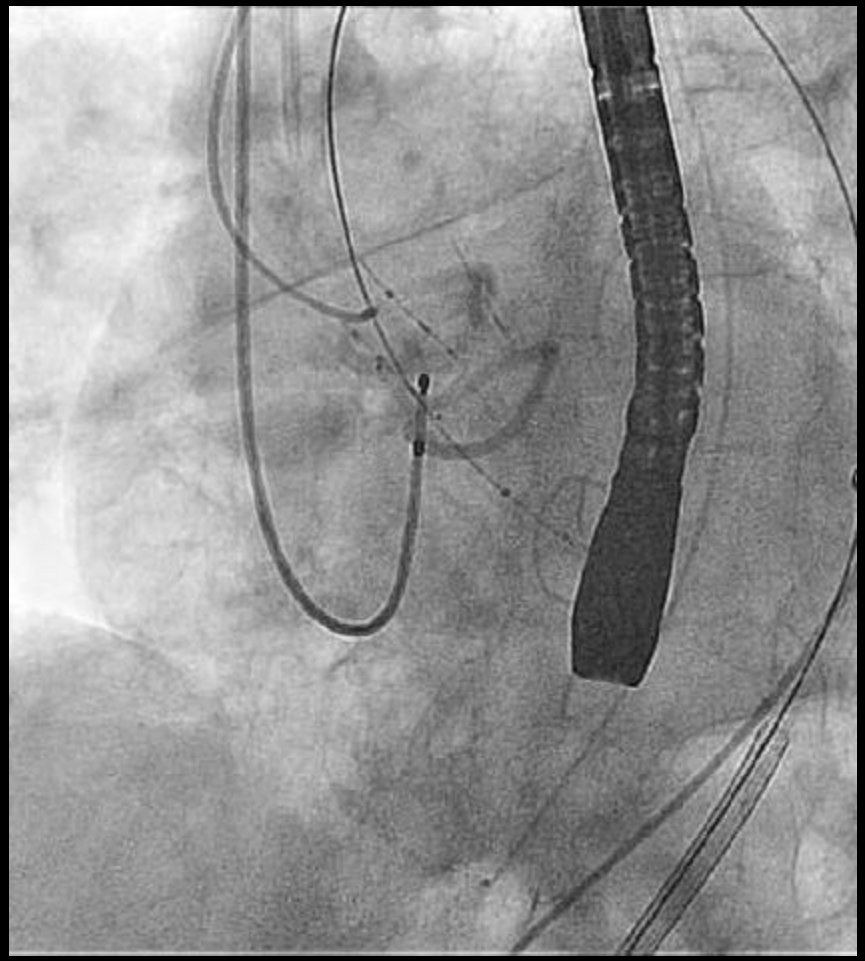
Lotus Valve Reposition Recapture

At this point valve can be fully recaptured and returned to position 1

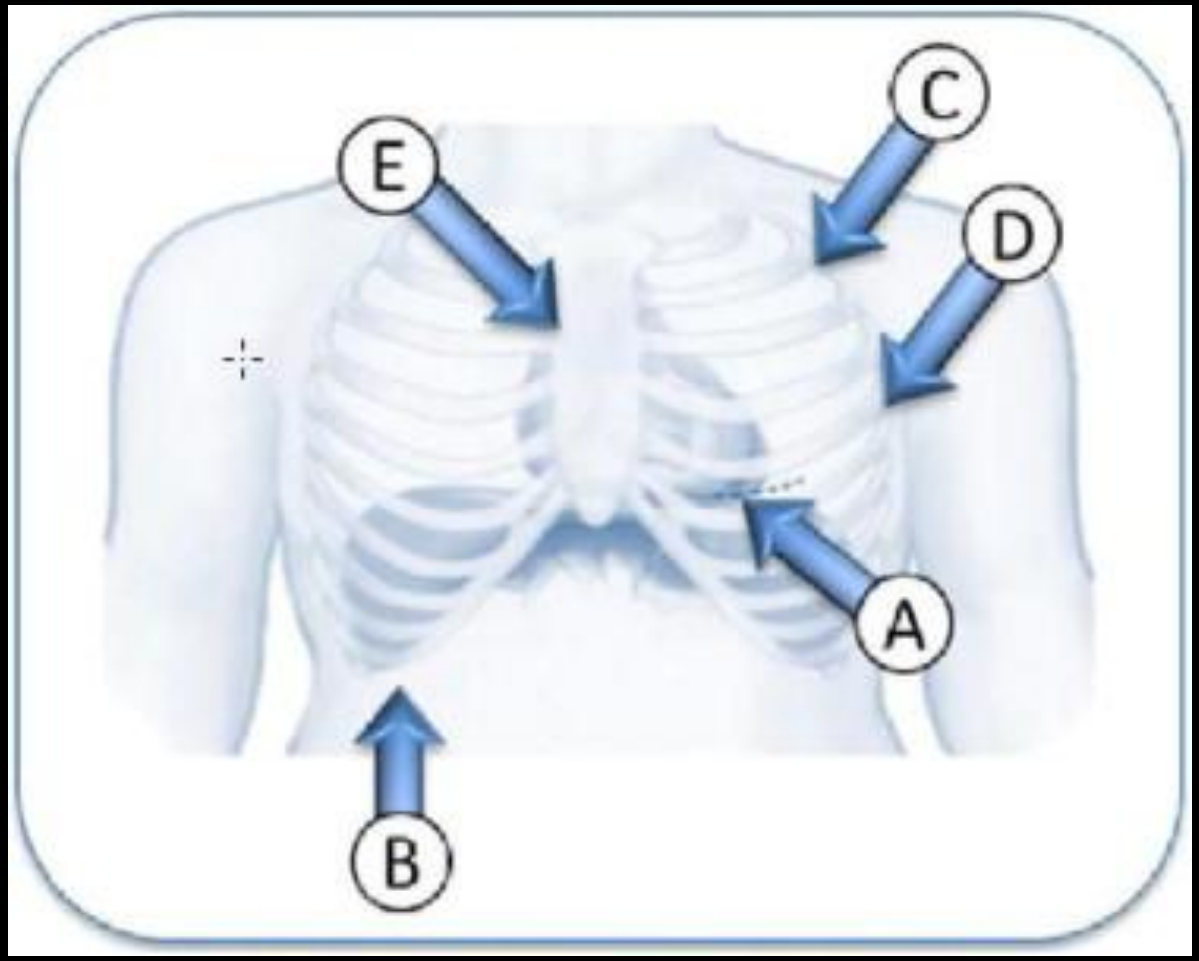


Direct Flow Valve- Novel Design to Impact PVL





Alternative Access



FDA NEWS RELEASE

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FDA Approval Expands Access to Artificial Heart Valve for Inoperable Patients

The U.S. Food and Drug Administration today approved revised labeling for the Sapien Transcatheter Heart Valve (THV), making the device available to an expanded group of patients who have inoperable aortic valve stenosis, a disease of the heart valves that causes narrowing of the aortic valve, restricting blood flow from the heart.

People with severe aortic valve stenosis must have a heart valve replacement to restore normal blood flow. Those who are in good enough health to tolerate surgery usually undergo aortic valve replacement during open-heart surgery using a heart-lung machine to take over the function of the heart and lungs during the surgical procedure. Because of the overall risks and extended recovery time associated with open-heart surgery, about 30 percent of patients are considered inoperable or at high risk for surgical complications and are not referred for this surgery.

The Sapien THV is implanted without opening the chest or heart and does not require a heart-lung machine. The device is compressed into a thin, flexible delivery catheter, inserted into an access point in the body and threaded to the site of the diseased valve.

The FDA previously approved the valve for insertion through the femoral artery (transfemoral approach), through the leg or through the lower tip of the heart (transapical approach). The new labeling removes references to specific access points now making it available for inoperable patients who need an alternate access point.

To support the labeling change, Edwards Lifesciences Corp. submitted data from the Transcatheter Valve Therapy Registry (TVTR) in the United States and THV device registries in Europe, along with data from FDA-approved clinical studies, and peer-reviewed medical journals. The TVTR data came from several thousand procedures performed on patients using an alternative access point and showed no evidence that the device performs differently or has a different benefit-risk profile based on the access point.The manufacturer will continue to use data from the TVTR to study short- and long-term patient outcomes of THV procedures using alternative access sites.

The TVTR, launched in 2012, collects clinical data on all transcatheter aortic valve replacements performed in the United States in order to study the short- and long-term outcomes of the procedure. The data is also an important source of clinical safety and effectiveness information once THVs are on the market. The TVTR is managed by the American College of Cardiology (ACC) and the Society of Thoracic Surgeons (STS).

“Just two years after the THV entered the market for a specific patient population, data from the TVTR was used to support FDA approval that expands patient access to a life-saving therapy,” said Jeffrey Shuren, M.D., director of the FDA’s Center for Devices and Radiological Health. “Medical device registries like the TVTR, not only play an important role in the FDA’s post market surveillance system, they also collect robust and timely data that can be used to identify additional patient populations that benefit from the therapy. “

“Leveraging clinical research inside the framework of a device registry to expand access to therapy for more patients is a new paradigm for the FDA, researchers, registry sponsors and the medical device industry,” said Shuren. “We believe this approach can be used with future well-designed device registries to speed patient access to important, well-evaluated therapies.”

The Sapien Transcatheter Heart Valve (THV) is made by Edwards Lifesciences Corp., headquartered in Irvine, Calif.

Thank You