TAVI: Present and Future Perspective

Igor F. Palacios, M.D.
Director of Interventional Cardiology
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- For patients with symptomatic critical aortic stenosis, aortic valve replacement improves survival and quality of life.
- However, the risks of open heart surgery in high-risk surgical patients have prompted investigation of alternative therapies, including balloon aortic valvuloplasty and transcatheter aortic valve implantation (TAVI).

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Technological developments have been rapid in the field of percutaneous aortic valve intervention.
- Two devices have been approved for general use in Europe and USA: the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the CoreValve ReValving ® System (CoreValve ReValving® Technology Medtronic Inc., Minneapolis, MN).
- Both systems can be delivered via the transfemoral, transapical and the axillary/subclavian routes, depending upon patient characteristics, anatomy, and the device available to the operator.
- There are 15 potential new designs for percutaneous aortic valves in development around the world.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- At centers participating in the Society of Thoracic Surgery national database, the 30-day operative mortality in patients undergoing isolated aortic valve replacement is now 4%. This often-quoted risk, which includes young patients and those with bicuspid valves but excludes morbidity, may therefore represent only the floor of risk.
- In an older, but more inclusive, study from the National Medicare Database of patients 65 years of age, the average mortality was 8.8% and was as high as 13.0% in some centers.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Surgical AVR remains the gold standard for the treatment of severe, symptomatic aortic stenosis. However, percutaneous treatments are challenging this paradigm in high-risk surgical patients.
- In the past, high-risk and inoperable patients were offered balloon aortic valvuloplasty. This procedure remains an important palliative option but does not alter the natural history of aortic stenosis nor provide an improvement in survival.
- The current era of transcatheter aortic valve implantation built on this procedure and began with the first demonstration of feasibility in 2002.

PVT - The Foundation…

Percutaneous Valve Technologies
Aortic Heart Valve

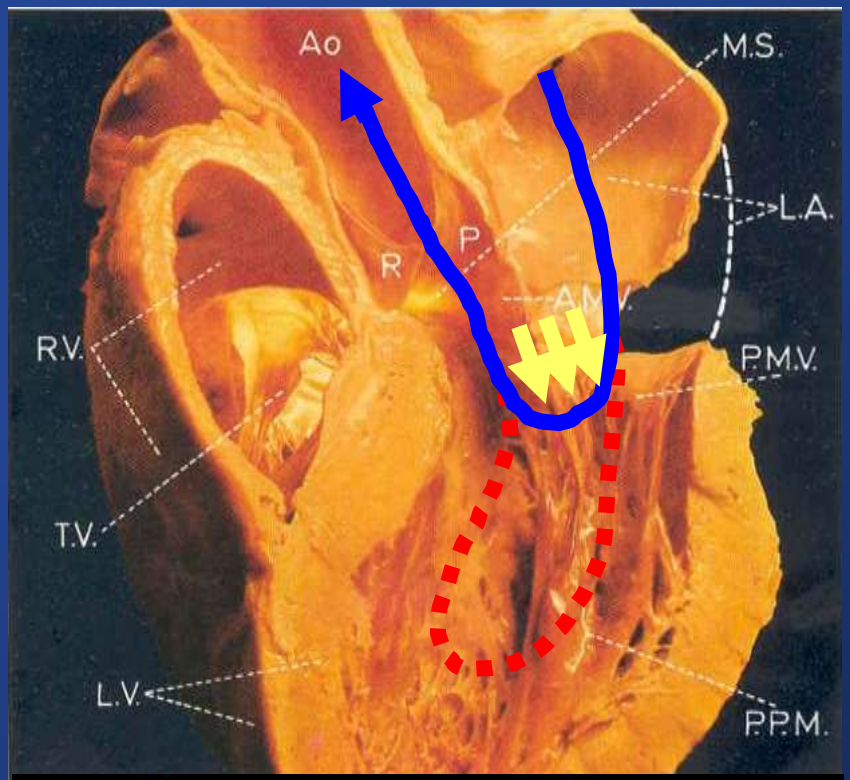
Polyurethane

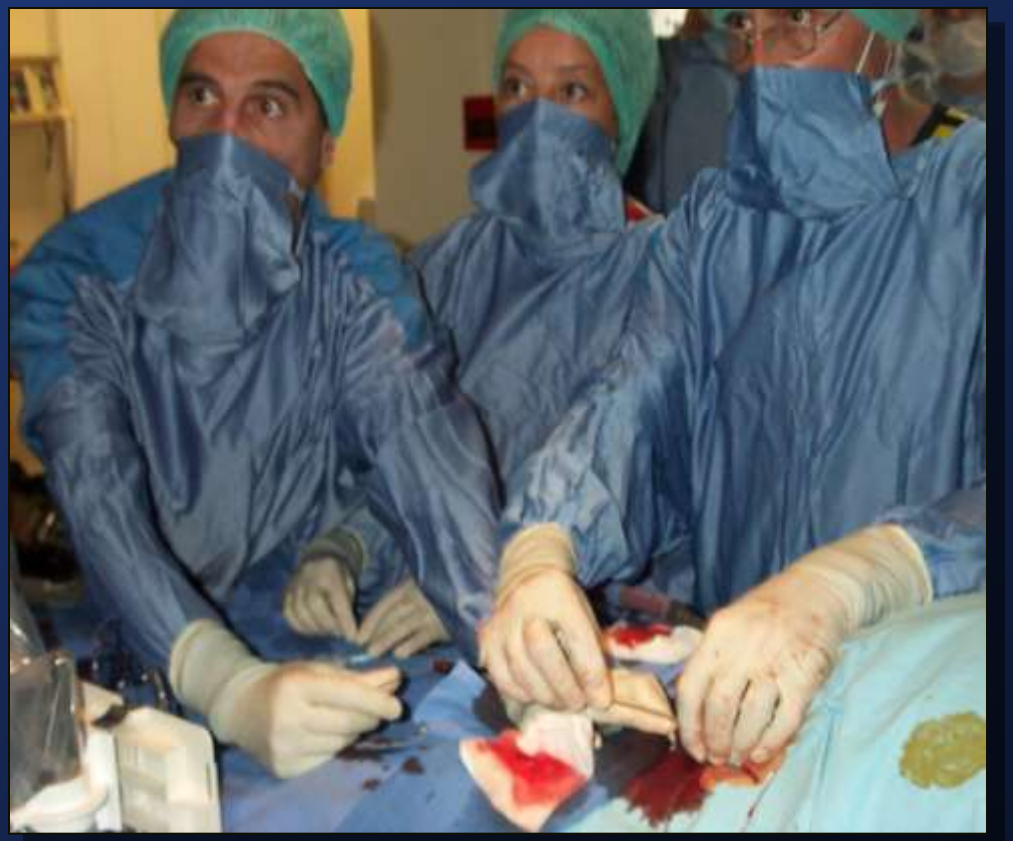
23mm max diameter

Bovine pericardium / Stainless steel stent

First Human Implant in 2002

Antegrade Approach: Guidewire Position in LV





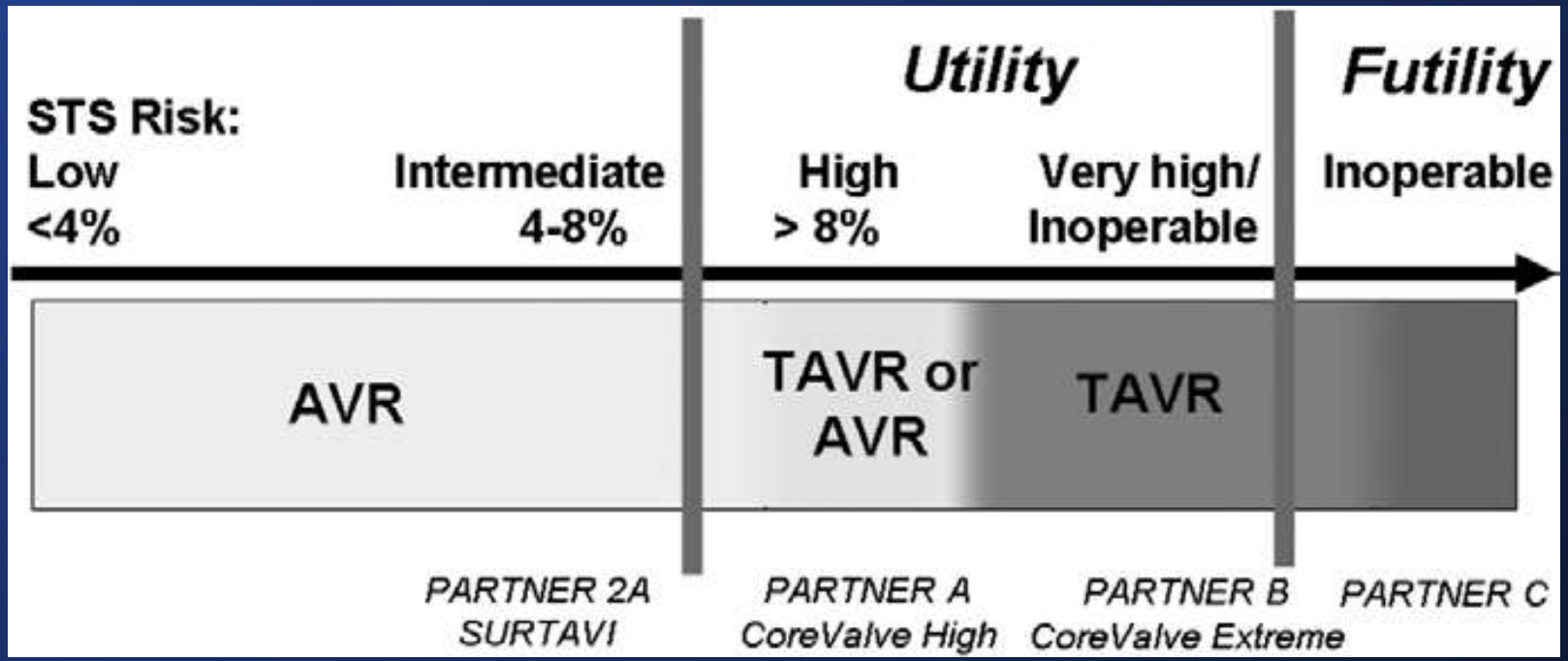
Collaboration across the seas….

Drs. John Webb and Alain Cribier

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Transcatheter aortic-valve implantation is becoming the standard of care for inoperable patients with severe aortic stenosis and a valid alternative for those at high surgical risk.
- Since the first percutaneous transcatheter aortic-valve implantation in humans in 2002, over 50,000 transcatheter aortic valves have been implanted in the last decade, with progressive improvement in the available devices.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective



Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Overall, there are two main families of transcatheter prosthesis: self-expandable and nonself-expandable.
- The self-expandable devices, for which CoreValve(®) (Medtronic CV Luxembourg S.a.r.l., Luxembourg) represents the prototype, are characterized by a structure composed of shape memory materials, usually nitinol, which acquire its final shape once released.
- By contrast, the non-self-expandable prostheses, mainly represented by the Edwards(®) valve (Edwards Life Sciences, Inc., CA, USA), require balloon dilatation to reach its final shape.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Although several publications have already provided positive data on both technologies, new clinical studies with improved systems are currently being conducted in order to provide more solid data and potentially expand the spectrum of patients who can benefit from this therapy.
- Thus, the aim of this presentation is to review the salient features of the two most used systems today (third-generation CoreValve and Edwards SAPIEN XT(®)) as well as to provide data on other emerging valves and future perspectives.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Careful selection of appropriate patients is essential to ensure a safe procedure.
- This necessitates a multidisciplinary approach (the Heart Team), with multiple imaging modalities used to fully delineate the peripheral vasculature, aortic anatomy and the valve itself.
- It is important to remember, however, that just because we can treat aortic valve disease percutaneously, it does not mean that we necessarily should do it.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- The gold standard treatment for aortic stenosis remains thoracotomy and surgical replacement of the valve.
- Thus, it is essential that cardiac surgeons play a central role in the decision-making processes for transcatheter aortic valve implantation and that they embrace this new and exciting technology, which promises to dramatically change the way their high-risk aortic valve patients are managed over the course of the next 10 years

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- The risk of aortic valve replacement increases with age and other comorbidities, including emergency and prior cardiac surgery, lung and renal disease, small body surface area, history of stroke, atrial fibrillation, heart failure, and the need for associated coronary revascularization.
- Some patients may be truly inoperable or denied surgery because of the presence of a porcelain aorta, prior radiation, cirrhosis, generalized frailty, or physician or patient preference. Therefore a nonsurgical alternative for these patients is both welcome and needed.

The past,present and future of TAVI

- Further technological development such as smaller diameter TAVI devices and proof of safety and durability
- Other innovations include use of advanced imaging techniques, such as multi-slice CT scans and 3D echocardiography to determine aortic valve anatomy and calcification. The results help members of the Heart team to determine arterial access site (transfemoral, transapical, Axilary, Ascending Aorta)

Edwards Valve Innovation

THE PARTNER II TRIAL

Starr-Edwards
Mechanical
Heart Valve

Carpentier-Edwards PERIMOUNT
Bovine
Pericardial
Heart Valve

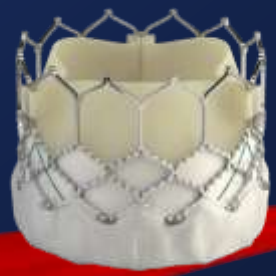
Carpentier-Edwards PERIMOUNT Magna Ease
Bovine Pericardial
Heart Valve

Cribier-Edwards
Transcatheter
Heart Valve

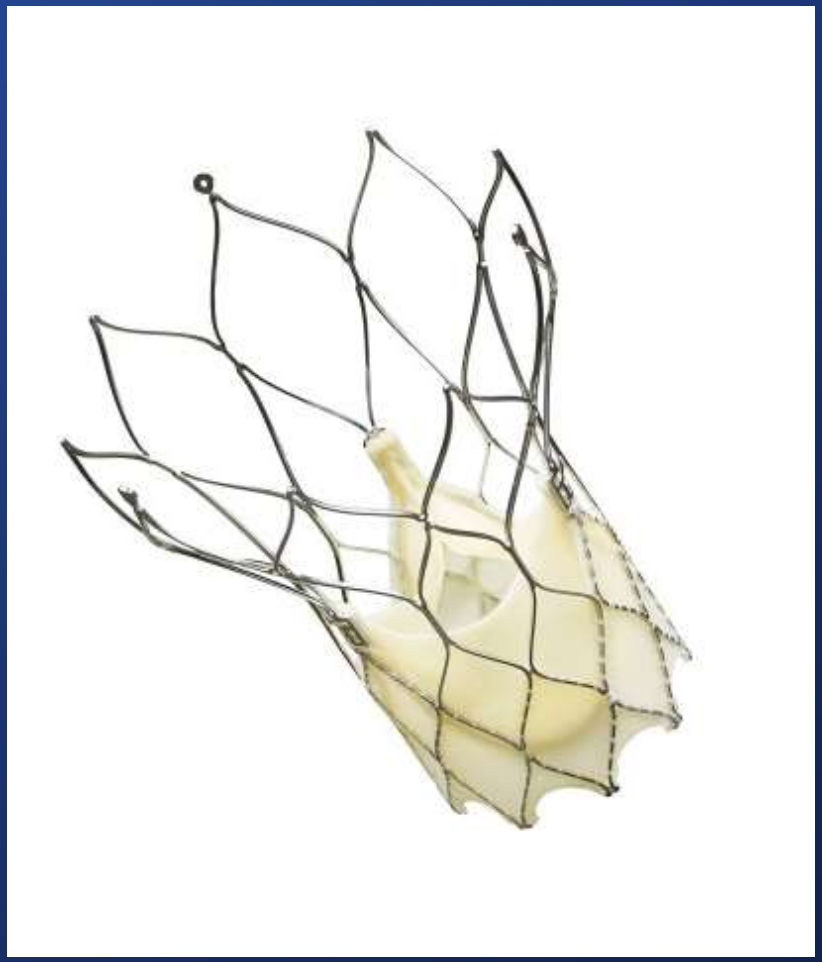
Edwards SAPIEN
Transcatheter
Heart Valve

Edwards SAPIEN XT
Transcatheter
Heart Valve

Edwards SAPIEN 3
Transcatheter
Heart Valve



The PORTICO St Jude TAVI

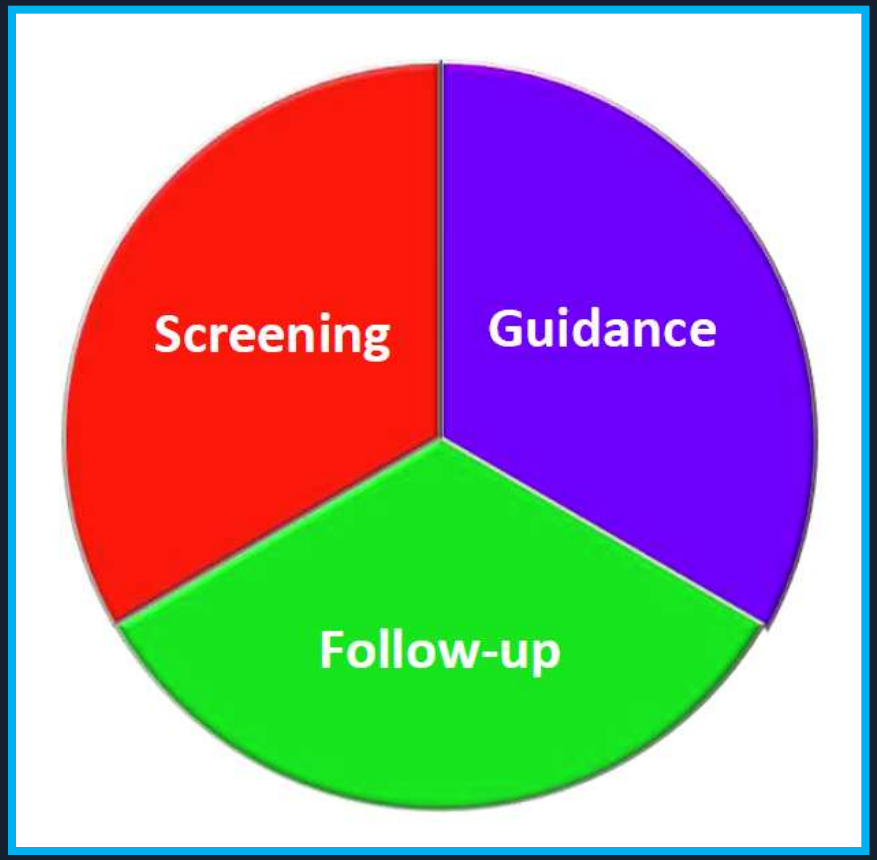


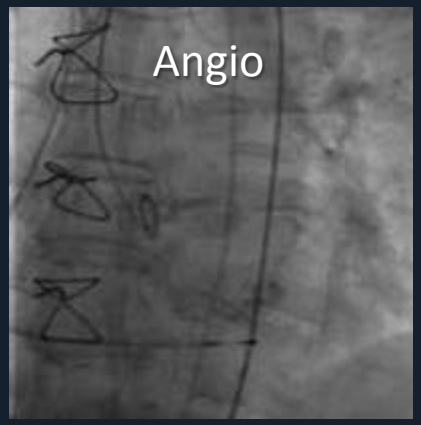
Ability to fully resheath and precisely reposition at the implant site prior to valve deployment help minimize procedural risk for the patient.

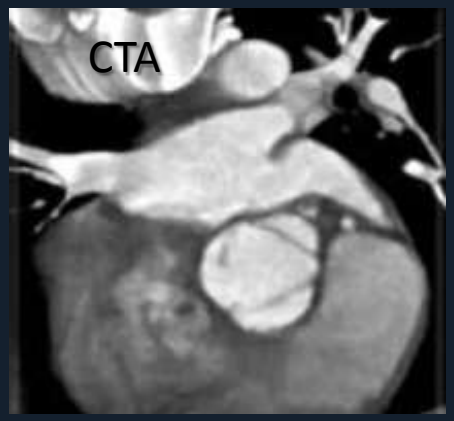
Is the first TAVI that can completely resheated into the delivery catheter and repositioned at the implant site or retrieved

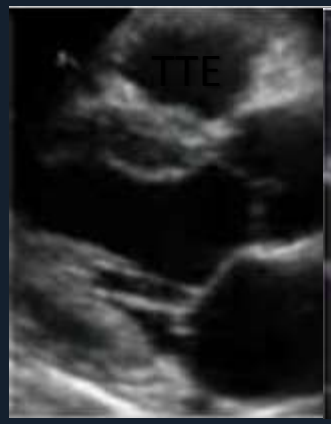
Adjunctive Imaging for TAVR

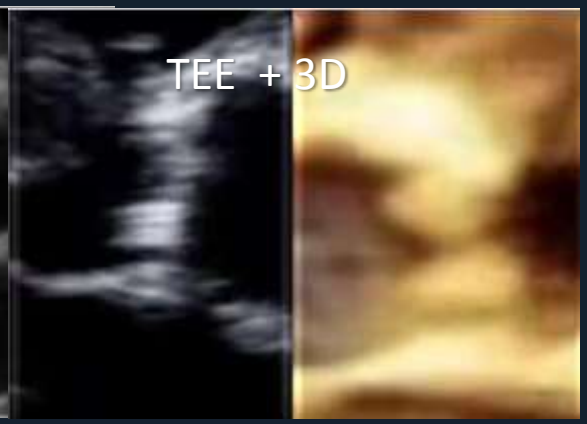
Multi-modality Imaging is the RULE









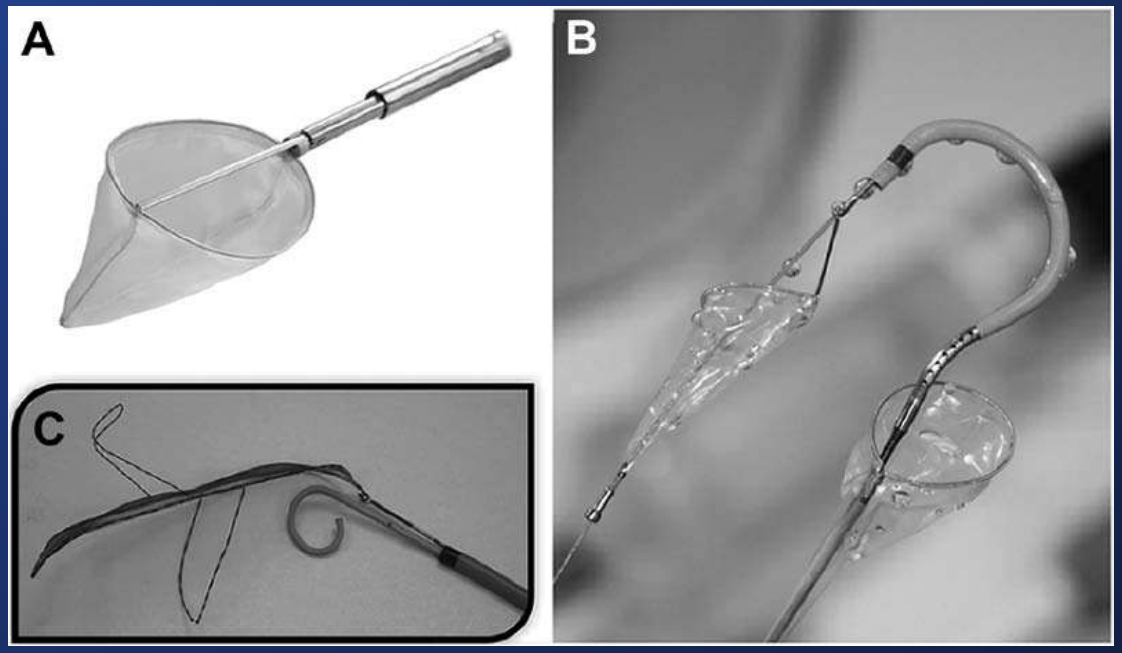


Adapted from: Lutz Buellesfeld

The past,present and future of TAVI

- Stroke, major vascular complication and post TAVI AR remain the most concerning risk of TAVI.
- New approaches to avoid embolic complications include the introduction of carotid filters and aortic deflectors.
- There appear to be two key times for stroke: The first- within 48 hours of the procedure – is likely to involve embolization- while the second one occurs 30 days later and is concern for thrombus formation around the valve. This raises important questions whether we should be routinely offering TAVI patients anticoagulation or antiplatelet therapy.

Percutaneous transcatheter aortic valve implantation: Present and Future Perspective



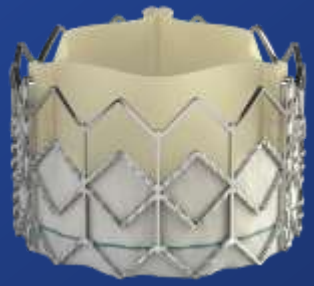
Embolic protection devices currently under investigation in transcatheter aortic valve replacement: Edwards Emboli-X filter (A), Claret CE Pro cerebral protection device (B), and TriGuard™ embolic deflection device (C).

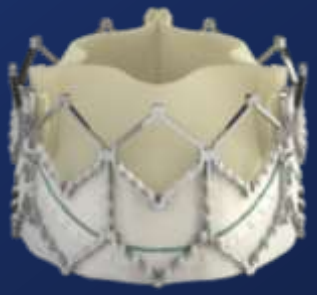
The past,present and future of TAVI

- Extending TAVI to intermediate risk patients is currently being explored in two ongoing trials: the SURTAVI trial for the Core Valve device and PARTNERS-2 for the Sapien valve. TAVI procedures to be widely acceptable to younger, lower risk patients.
- Looking to the future, it might be possible to use bioresorbable stent in TAVI. Instead of using animal valves, we might be using stem cells seeded on to structural supports.

Edwards SAPIEN XT THV Builds on the Proven Balloon Expandable Platform and Now Allows for a 16F TAVR Procedure*

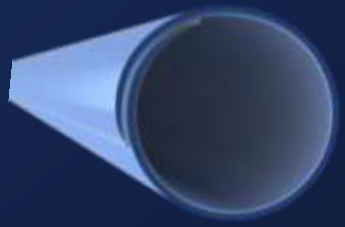
THE PARTNER II TRIAL





22F RetroFlex 3 Sheath
(Compatible with 23mm SAPIEN valve)

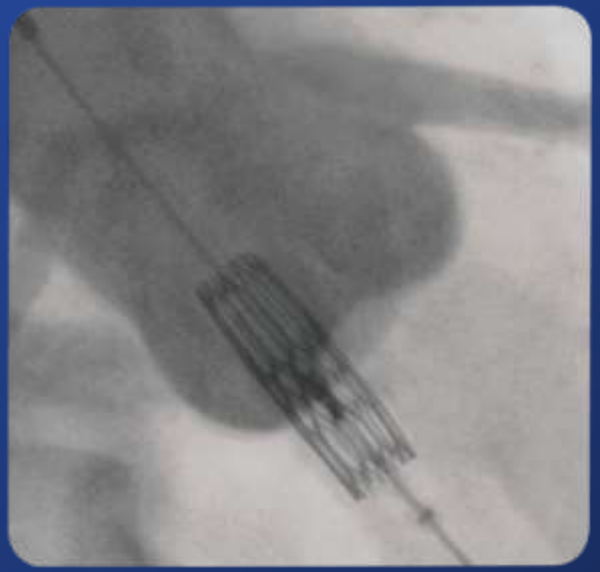
27%
Reduction
in Profile



16F eSheath
(Compatible with 23mm SAPIEN XT valve)

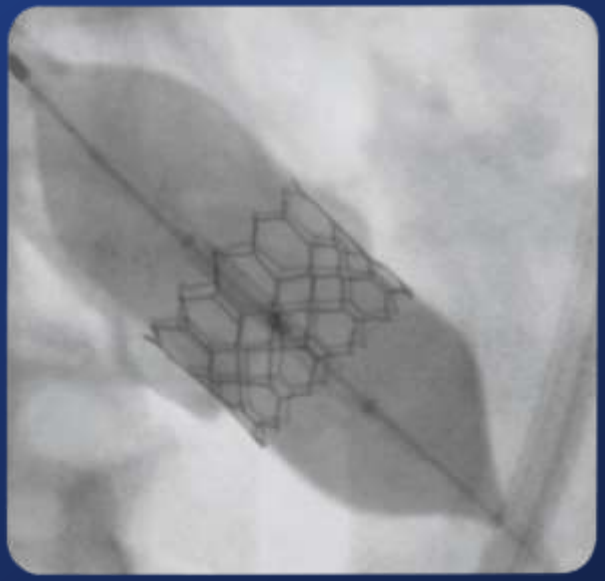
* For the 23mm SAPIEN XT valve

Balloon-Expandable Valves Designed for Predictable Results



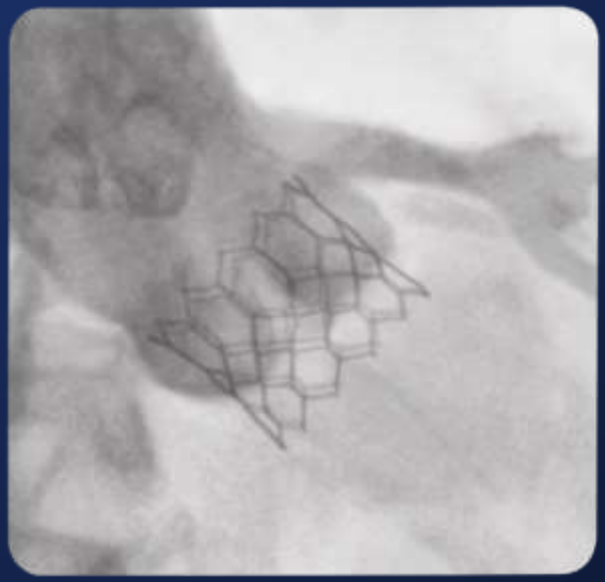
Initial Positioning

- Use Center Marker and fine positioning feature



Deployment

- Slow, controlled initial inflation using nominal volume



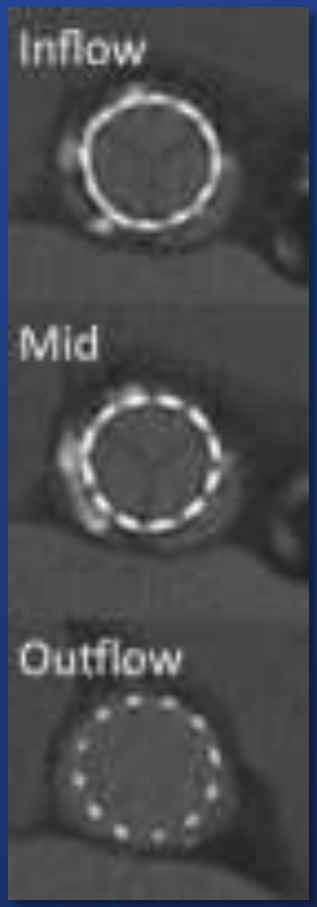
Final Placement

- Predictable results

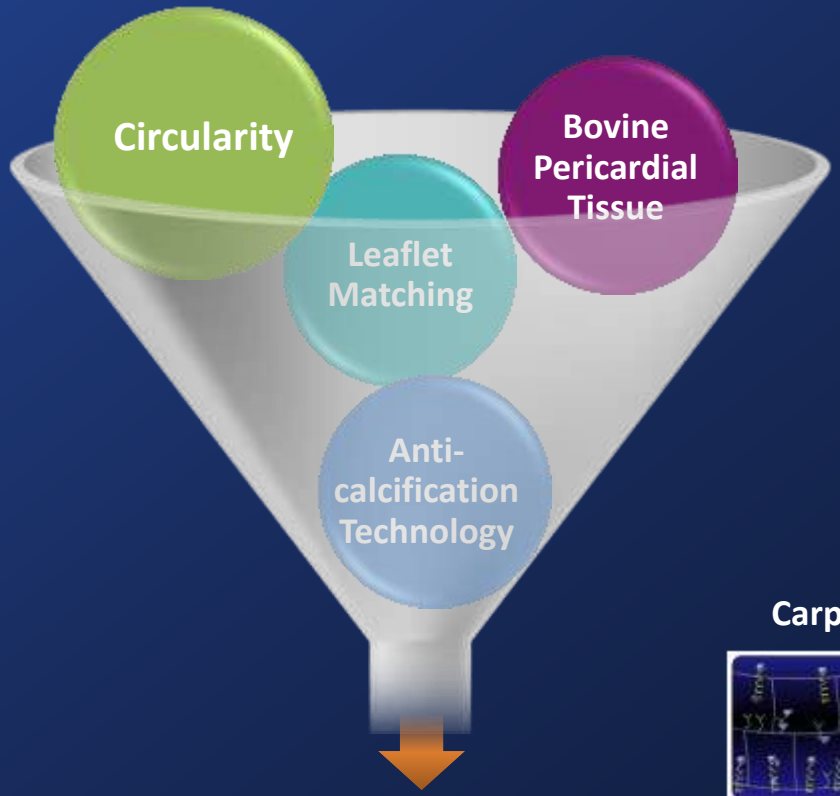
Critical Elements for Durability

THE PARTNER II TRIAL

Circularity



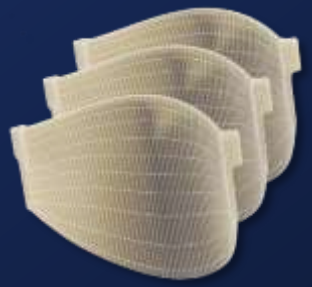
Binder R., et al. Transcatheter Aortic Valve Replacement with the SAPIEN 3: A New Balloon-Expandable Transcatheter Heart Valve. JACC Cardiovasc Intv Vol. 6, No. 3, 2013.



Durability

Bovine Tissue

Leaflet Matching



Carpentier-Edwards ThermaFix™ Process

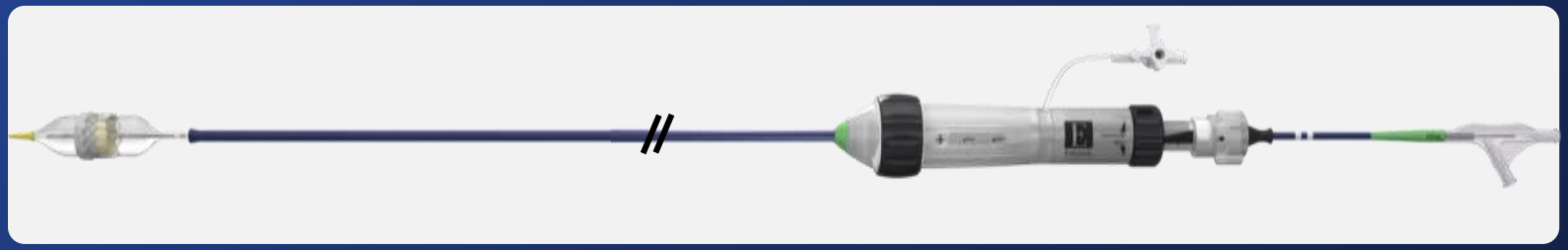
1. Heat treatment removes unstable glutaraldehyde molecules

2. Patented chemical treatment removes 98% of phospholipids

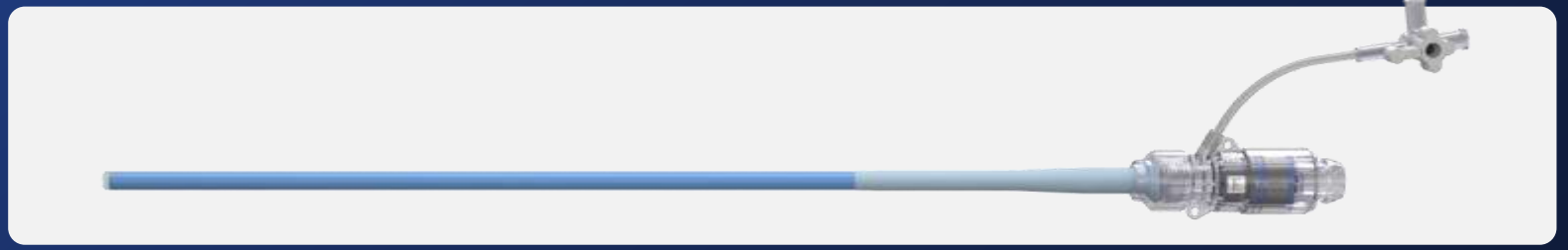
Edwards Commander Delivery System

THE PARTNER II TRIAL

- **Ultra-low profile 14F eSheath compatible***



- **Reduced minimum access vessel diameters**

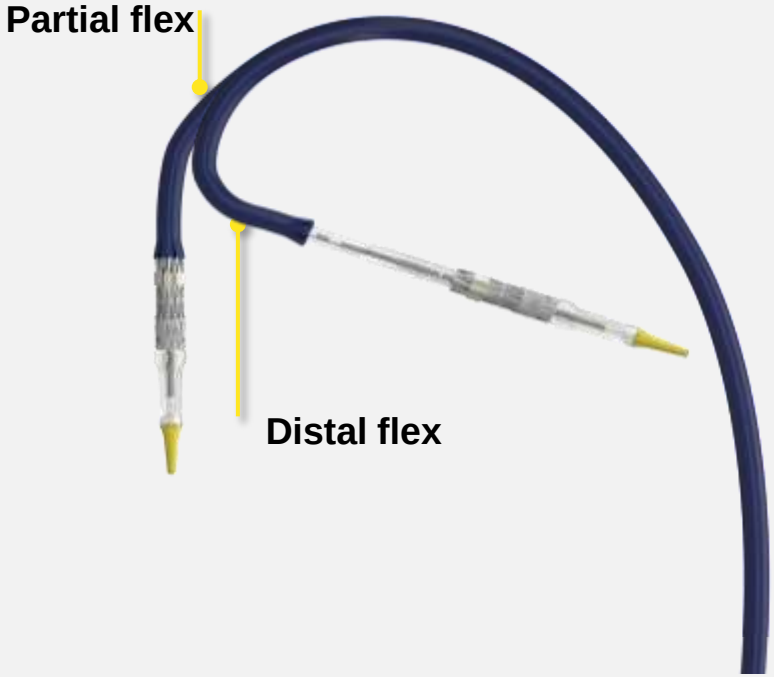


SAPIEN 3 Valve Size	23 mm	26 mm	29 mm
Edwards eSheath Introducer Set	14F	14F	16F
Minimum Access Vessel Diameter	5.5 mm	5.5 mm	6.0 mm

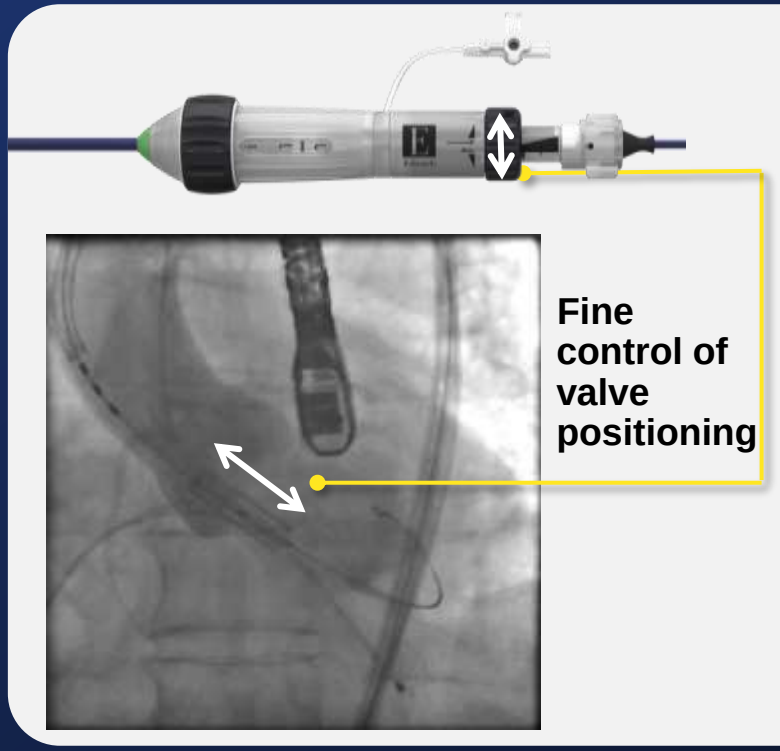
*14F eSheath compatible for 23 mm and 26 mm SAPIEN 3 valves. 16F eSheath compatible for 29 mm SAPIEN 3 valve.

Edwards Commander delivery system

- Dual articulation for coaxiality even in challenging anatomies; aids in crossing the native annulus

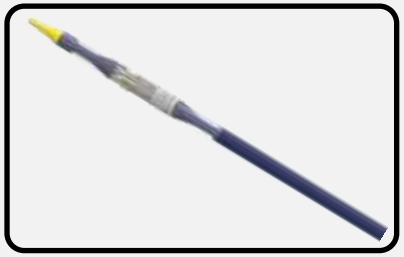


- Trusted balloon-expandable design with improved control of valve positioning



Edwards Certitude delivery system

- Ultra-low profile system – 18F Sheath compatible*
- Integrated pusher
- Articulation feature for ease of coaxial positioning
- Ergonomically designed handle



Integrated Pusher

Articulation Feature

Ergonomic Handle

SAPIEN 3 Valve Size	23 mm	26 mm	29 mm
Certitude Introducer Sheath	18F	18F	21F

Nov 2011
Oct 2012

FDA Approval (non-surgical and high risk surgical)

2008-09 — PARTNER US Pivotal

Since 2007 — Post market registries

2007 — CE mark commercialization

2005-07 — International TF and TA Feasibility Studies

2004 — Edwards Lifesciences

2002-03 — Feasibility Studies (antegrade)

2002 — F.I.M. THV implantation

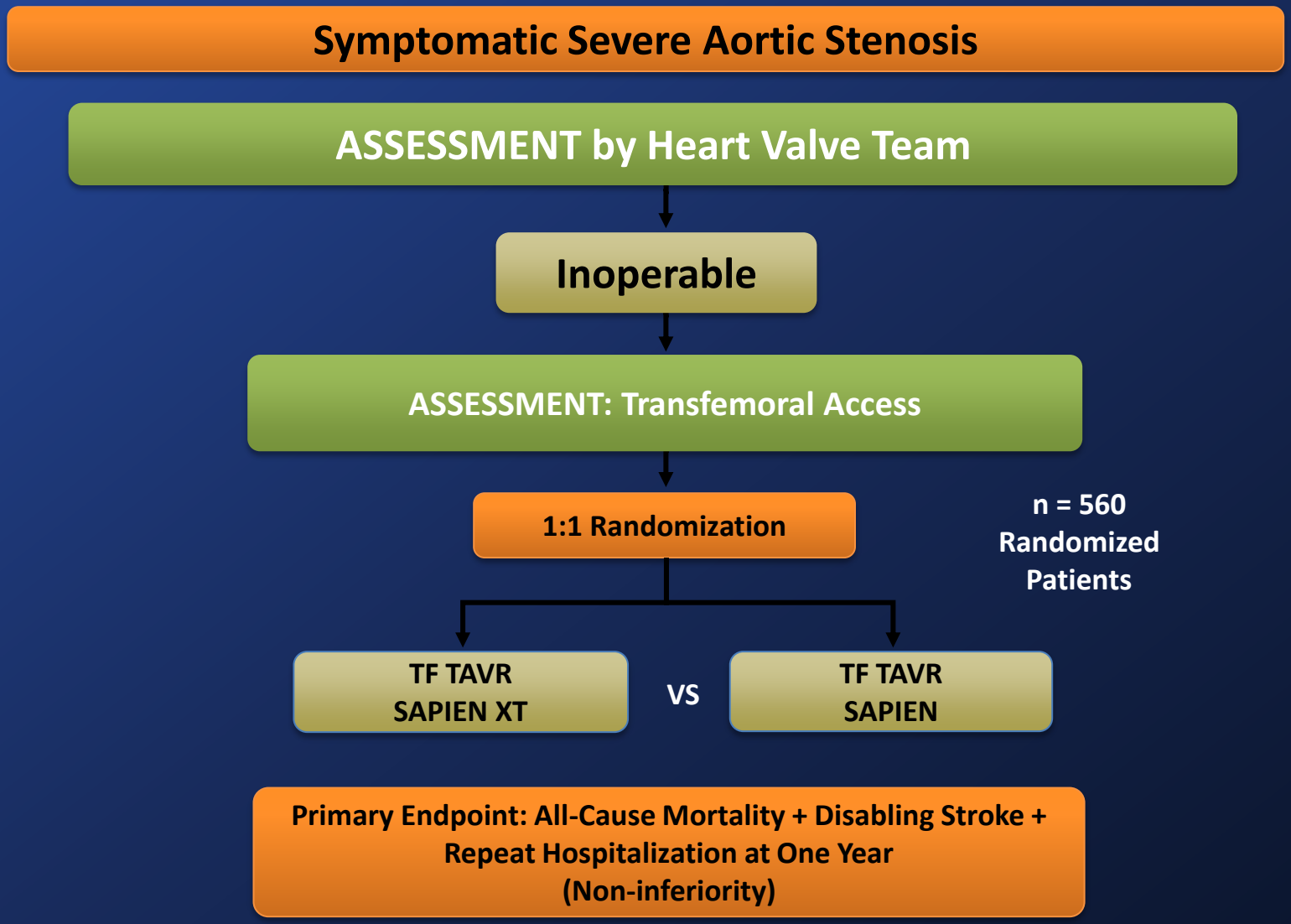
2000 — Animal implantations (sheep)

1999 — « Percutaneous Valve Technology » (prototypes)

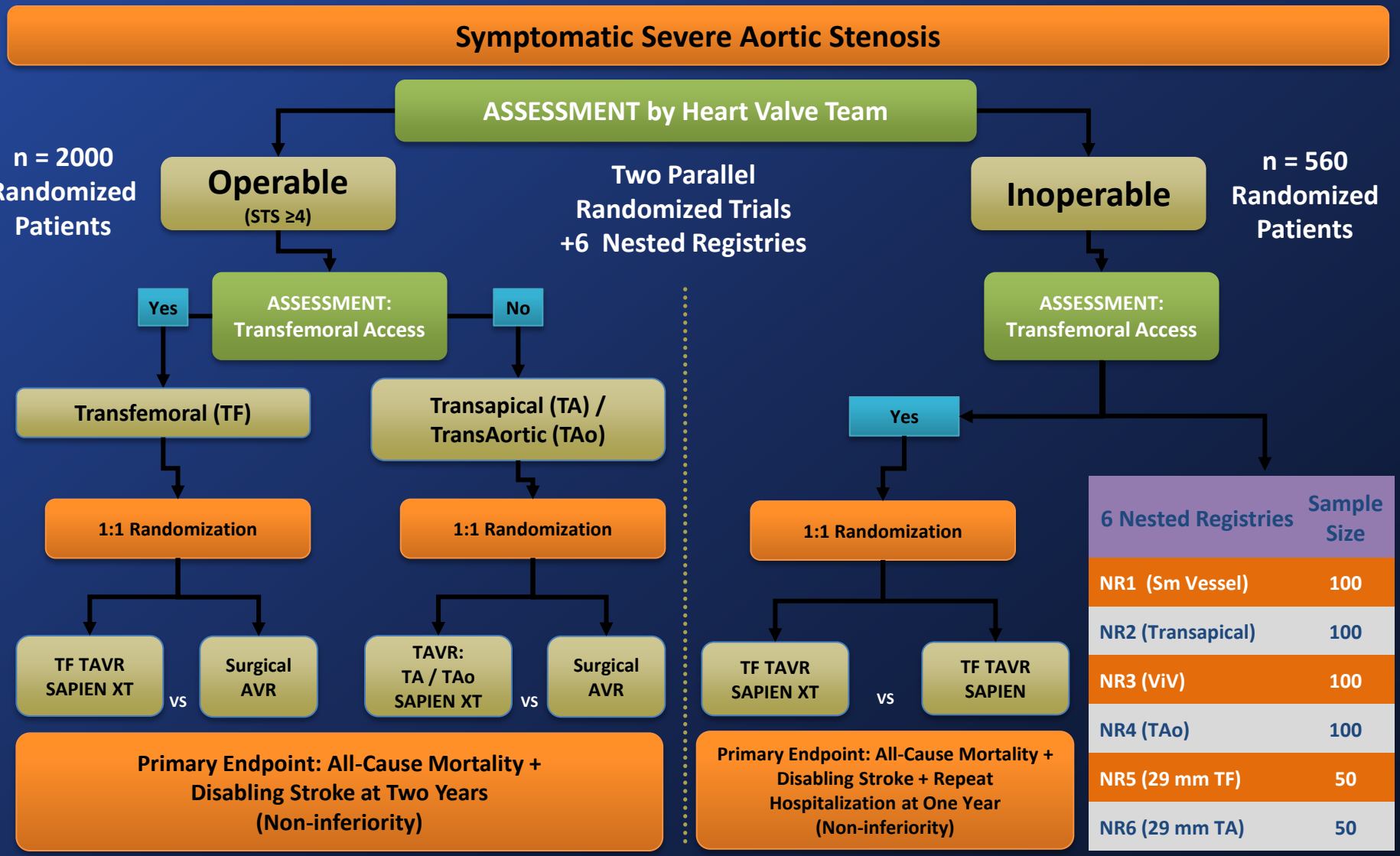
1993-1994 — Post-mortem studies of intra-valvular stenting

1985 — F.I.M. Balloon Aortic Valvuloplasty

The PARTNER II Inoperable Cohort
Study Design



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

Primary Endpoint Events:
At 30 Days (ITT)

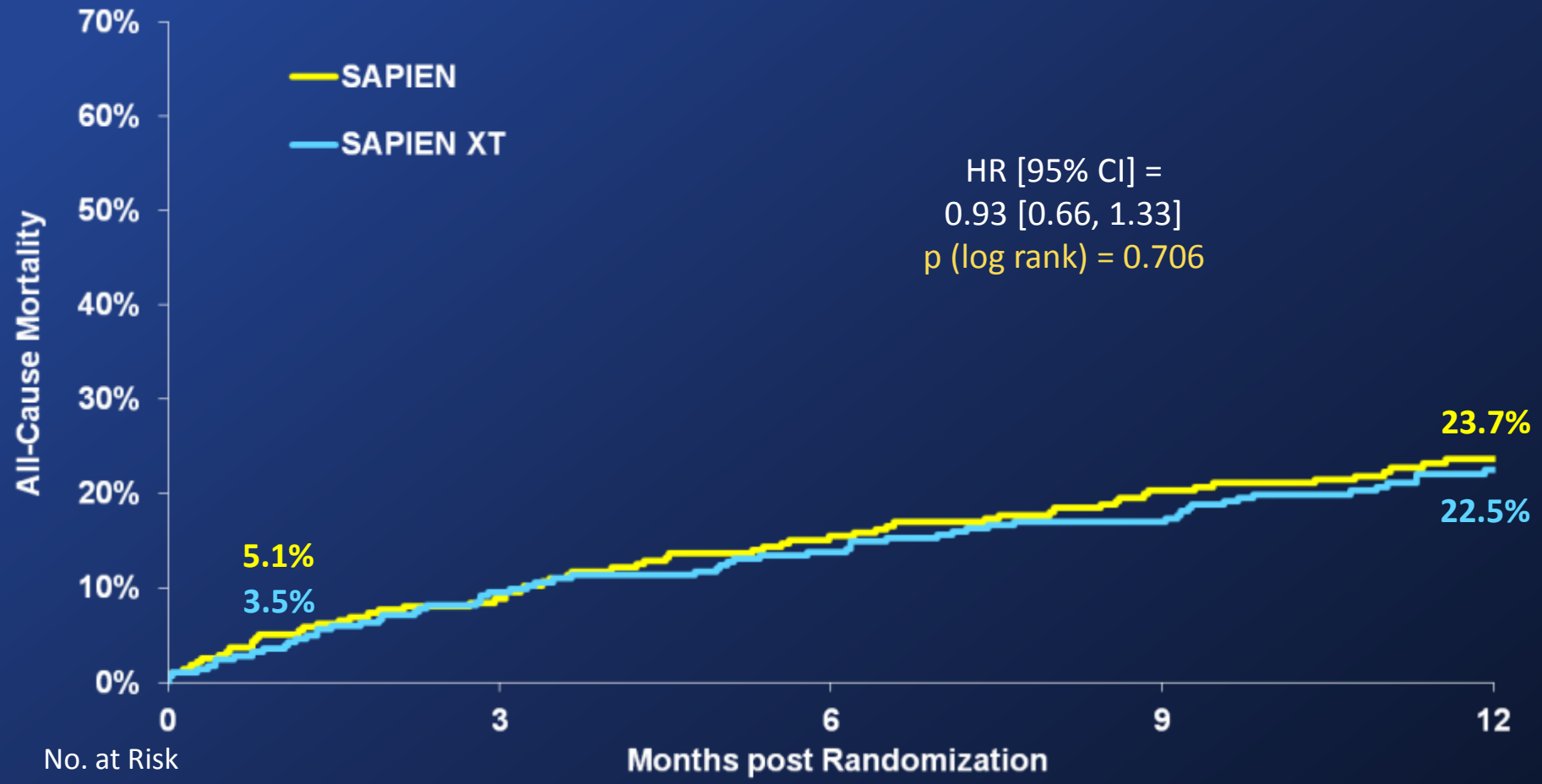
Events	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value*
Death:					
All-Cause	14	5.1	10	3.5	0.36
Cardiovascular	9	3.3	5	1.8	0.26
Stroke:					
Disabling	8	3.0	9	3.2	0.85
All	11	4.1	12	4.3	0.88
All + TIA	13	4.8	12	4.3	0.78
Death (all-cause) and Stroke (disabling)	19	6.9	18	6.4	0.80
Re-hospitalizations	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 Complication Categories:
At 30 Days (AT)

	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

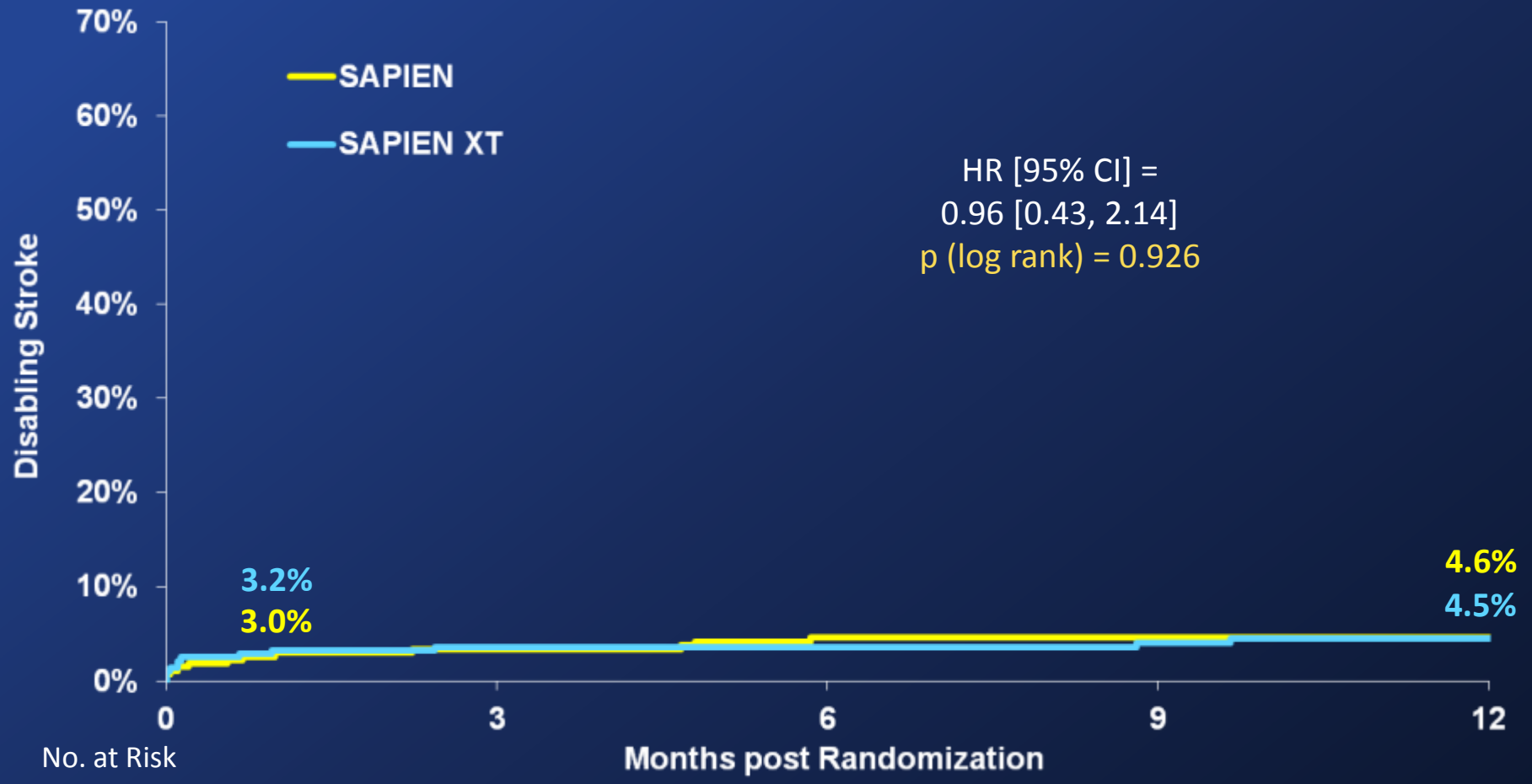
All-Cause Mortality (ITT)



No. at Risk

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

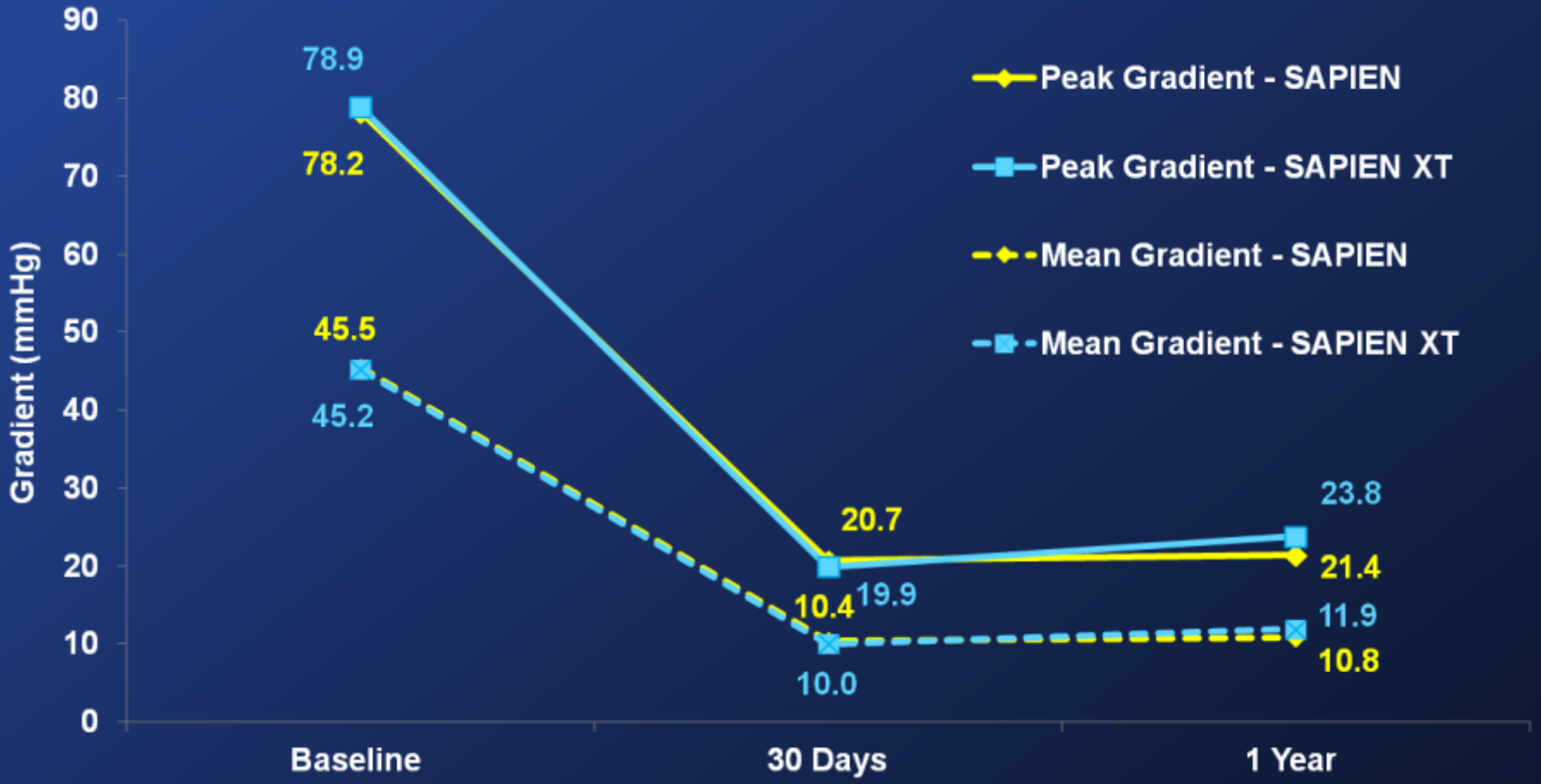
Disabling Stroke (ITT)



No. at Risk

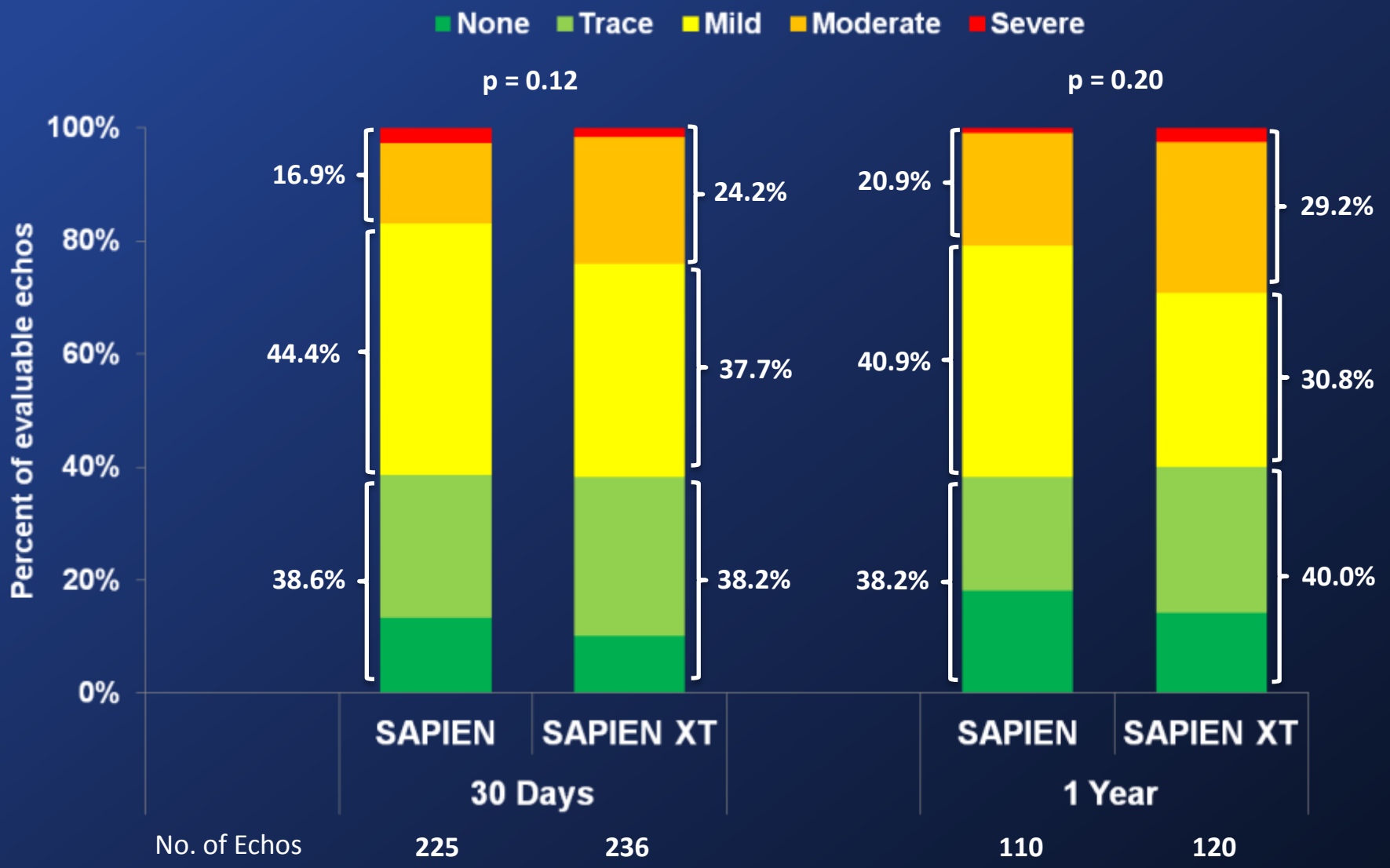
SAPIEN	276	241	223	209	134
SAPIEN XT	284	250	238	227	145

Echocardiographic Findings:
Mean & Peak Gradients (AT, Valve Implant)



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

Paravalvular Aortic Regurgitation (Valve Implant)



PARTNERS II - Results

- SAPIENT XT treatment was associated with reductions in anesthesia time (p = 0.02), multiple valve implants (p = 0.05), aborted procedures (p = 0.06), and the need for IABP hemodynamic support (p = 0.06).
- At 30 days,
  - All-cause mortality and disabling strokes were similar (Mortality: SAPIEN 5.1% vs. SAPIEN XT 3.5%; Strokes: SAPIEN 3.0% vs. SAPIEN XT 3.2%)
  - Major vascular complications were reduced after SAPIENT XT (from 15.5% to 9.6%, p = 0.04), including perforations, dissections, and hematomas
  - All other clinical endpoints were similar

PARTNERS II - Results

- At 1 year,
  - All-cause mortality, disabling strokes, and re-hospitalizations were similar, including the non-hierarchical composite primary endpoint (SAPIEN XT 33.9% vs. SAPIEN 34.7%, non-inferiority p-value = 0.0034)
  - Improvement in NYHA class was similar
  - Echo valve performance (EOA and gradients) was similar

Implications

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.

Edwards THV Evolution

- *Stainless Steel Frame*
- *Equine Pericardial Tissue*

2004

Cribier-Edwards™ THV
23mm

- *Stainless Steel Frame*
- *Bovine Pericardial Tissue*

2007

Edwards SAPIEN™ THV
23 mm and 26 mm

- *Cobalt-Chromium Frame*
- *Bovine Pericardial Tissue*
- *Semi-closed leaflets*
- *Reduced crimped profile*

2010

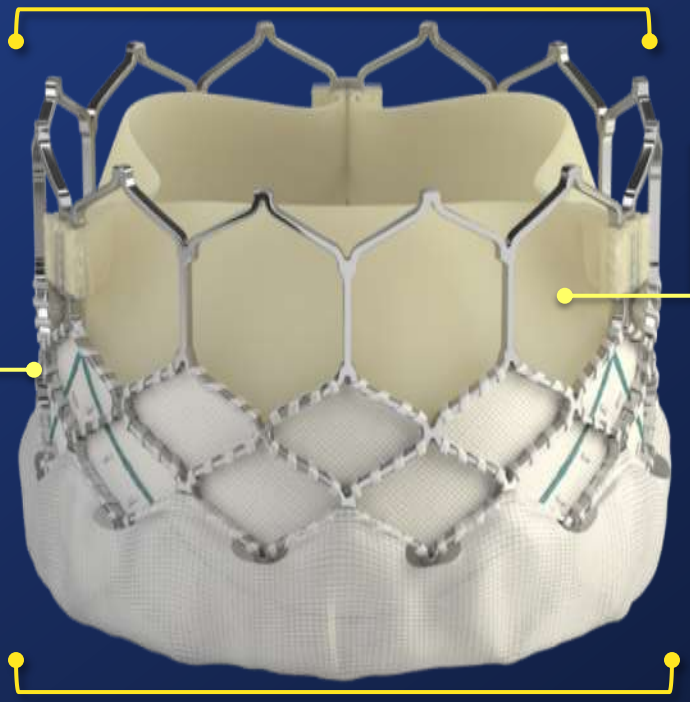
Edwards SAPIEN XT ™ THV
23 mm, 26 mm, and 29mm

Edwards SAPIEN 3 THV

THE PARTNER II TRIAL

Frame design
- Enhanced frame geometry for ultra-low delivery profile
- High radial strength for circularity and optimal hemodynamics

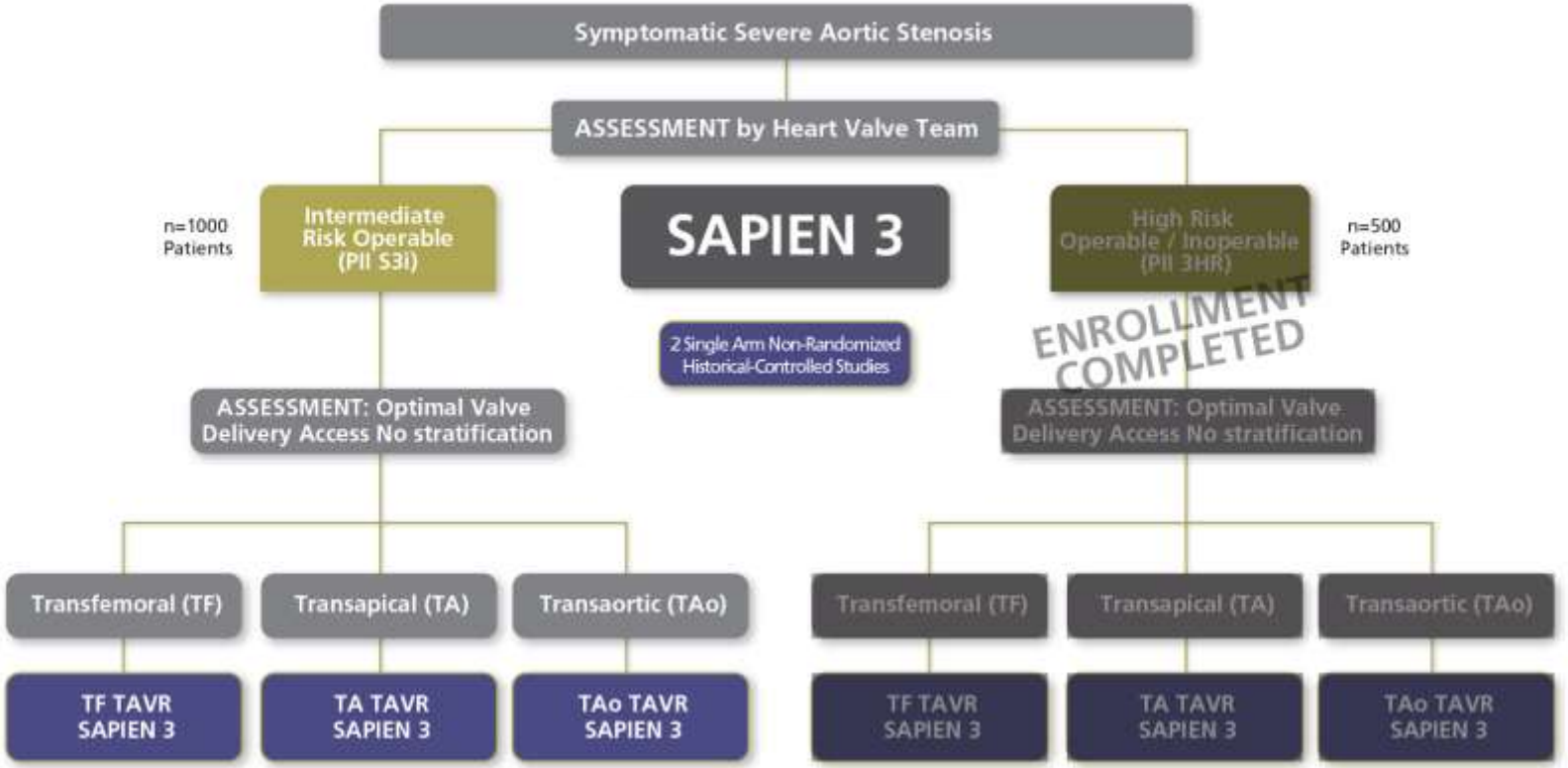
Low frame height
- Respects the cardiac anatomy



Bovine pericardial tissue
- Optimized leaflet shape
- Carpentier-Edwards ThermaFix* process for anti-calcification

Outer skirt
- Designed to minimize paravalvular leak

The PARTNER II Trial: SAPIEN 3i Study Design – Intermediate Risk



Baseline Characteristics (1)

Operability Risk Assessment	AT* PATIENTS (N = 150)
Age (Years)	83.6 ± 5.0
Female	81 (54.0%)
NYHA III/IV	130 (86.7%)
Severe Pulmonary Hypertension	10 (6.7%)
Severely Impaired Pulmonary Function Contradicting Surgery	8 (5.3%)
Hostile Chest	3 (2.0%)
Severe Liver Disease / Cirrhosis	2 (1.3%)
Frailty Index VARC-2 (continuous)	1.3 ± 0.9
Patients with 1 or More Risk Factors	147 (98.0%)

Non-Cardiac Conditions	AT* PATIENTS (N = 150)
Renal Insufficiency	60 (40.0%)
Diabetes	48 (32.0%)
Anemia	46 (30.7%)
Pulmonary Disease – COPD	40 (26.7%)
Cancer	32 (21.3%)

Echo Parameters	AT* PATIENTS (N = 150)
Effective Orifice Area (cm^2)	0.6 ± 0.2
Mean Gradient (mm Hg)	45.3 ± 14.3
LV Ejection Fraction (LVEF) (%)	56.3 ± 9.2
Mitral Regurgitation (Moderate to Severe)	26 (22.4%)
Annular Diameter (TEE - mean) (mm)	23.2 ± 2.3

* AT, as-treated.

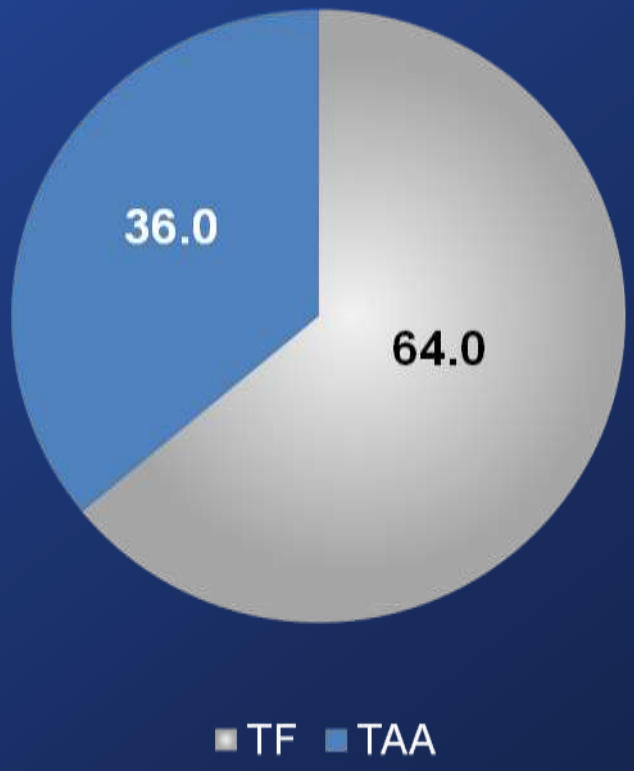
THE SAPIEN 3 TRIAL

Baseline Characteristics (2)

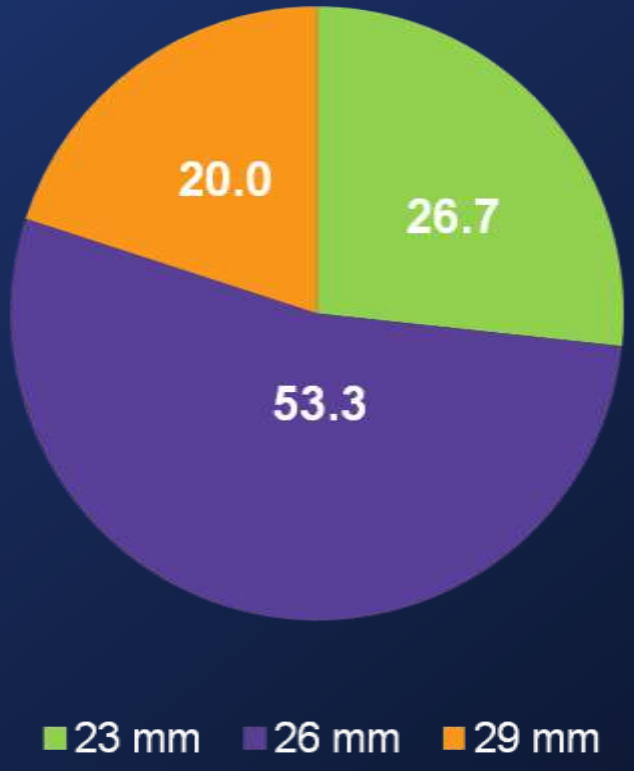
Baseline Characteristics (%)	TF PATIENTS (N = 96)	TAA PATIENTS (N = 54)	P-VALUE
STS PROM Score	7.5 ± 4.26	7.3 ± 4.94	0.813
Logistic EuroSCORE (%)	**19.8 ± 10.9**	**24.9 ± 14.0**	**0.022**
Peripheral Vascular Disease	**16.7**	**38.9**	**0.003**
Previous Myocardial Infarction	**11.5**	**27.8**	**0.014**
Previous CABG	**14.6**	**27.8**	0.056
Atrial Fibrillation	22.9	35.8	0.125
Previous Aortic Valvuloplasty	10.4	3.7	0.213
Previous Pacemaker Implantation	13.5	16.7	0.635
Carotid Disease	25.0	25.9	1.000
Porcelain Aorta	1.0	1.9	1.000
Prior Stroke	7.3	7.4	1.000

Procedural Characteristics (1)

ACCESS APPROACH (%)



VALVE SIZE (%)



Note: Limited14F eSheath availability during initial patient enrollment period.
The 29 mm valve was introduced later in the trial.
Due to a low rate of paravalvular leak a strategy of minimal oversizing evolved.

THE SAPIEN 3 TRIAL

Procedural Characteristics (2)

Variable	TF PATIENTS (N = 96)
Femoral Access/Anesthesia	
General	63.5%
Conscious Sedation	36.5%
Femoral Access/Closure	
Percutaneous/Closure Device	95.8%
Surgical	4.2%

Variable	ALL PATIENTS (N = 150)
Procedural Outcomes	
Correct Placement at Intended Site	**149 (99.3%)**
Post-dilatation	**5 (3.3%)**
Technical Success*	94.0%
Procedural Events	
Conversion to Conventional Surgery	1 (0.7%)
Patient Required ECMO	1 (0.7%)
Coronary Obstruction	**0 (0.0%)**
Valve-in-Valve	**0 (0.0%)**

* No procedural mortality, correct positioning, and only one valve implanted.

THE SAPIEN 3 TRIAL

Clinical Outcomes at 30 Days (1)

Clinical Outcome	EVENT RATE IN THE AT POPULATION # PATIENTS (KM %)		
	TF (N = 96)	TAA (N = 54)	Overall (N = 150)
All-Cause Mortality	2 (2.1%)	6 (11.1%)	8 (5.3%)
Cardiac Mortality	2 (2.1%)	5 (9.3%)	7 (4.7%)
All-Stroke*	1 (1.0%)	3 (5.6%)	4 (2.7%)
Disabling Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)
Major Vascular Complication	5 (5.2%)	4 (7.4%)	9 (6.0%)
Major Bleeding	19 (19.8%)	11 (20.4%)	30 (20.0%)
Life-Threatening Bleeding	2 (2.1%)	3 (5.6%)	5 (3.3%)
Rehospitalization†	0 (0.0%)	0 (0.0%)	0 (0.0%)

Primary Endpoint	EVENT RATE IN THE VI POPULATION # PATIENTS (KM %)		
	TF (N = 95)	TAA (N = 54)	Overall (N = 149)
All-Cause Mortality	1 (1.1%)	6 (11.1%)	7 (4.7%)

VI, valve implant = all enrolled patients who received a SAPIEN 3 implant, and retain the valve upon leaving the cath lab
* Severity of the one TF stroke unknown.
† Rehospitalization for for valve-related symptom or worsening of congestive heart failure.

THE SAPIEN 3 TRIAL

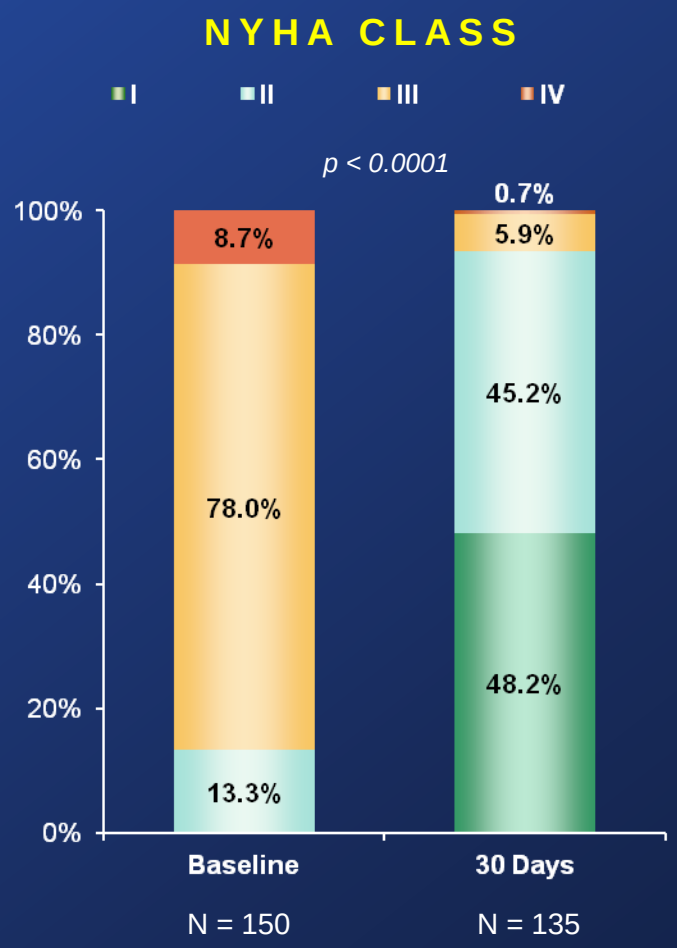
Clinical Outcomes at 30 Days (2)

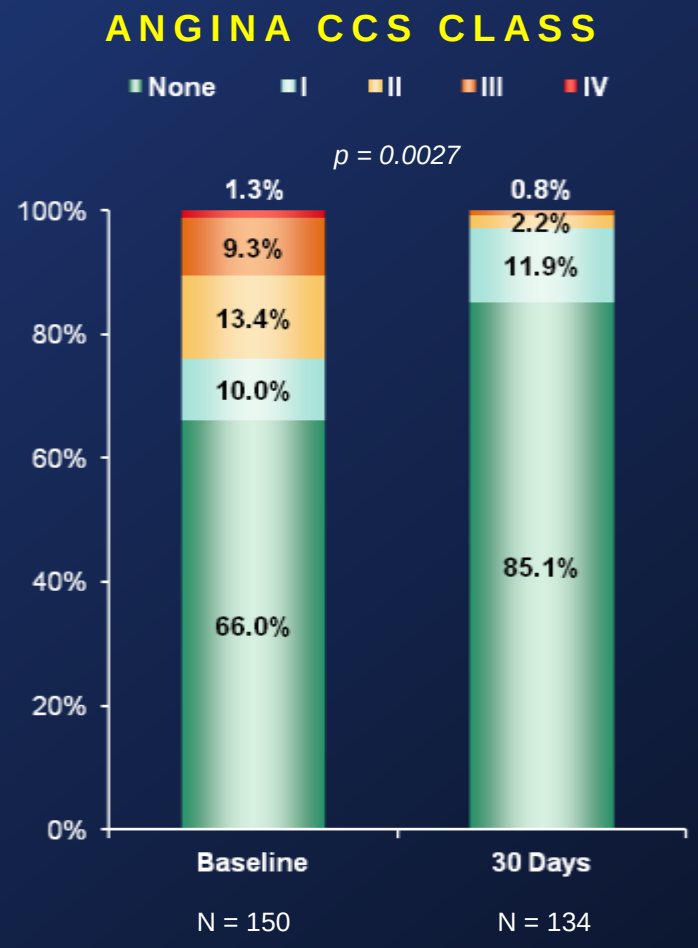
Clinical Outcome	EVENT RATE IN THE AT POPULATION # PATIENTS (KM %)		
	TF (N = 96)	TAA (N = 54)	Overall (N = 150)
Acute Kidney Injury (Stage II/III)	1 (1.0%)	3 (5.6%)	4 (2.7%)
Myocardial Infarction	2 (2.1%)	0 (0.0%)	2 (1.3%)
Reintervention*	1 (1.0%)	0 (0.0%)	1 (0.7%)
Endocarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Valve Thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)
New-Onset Atrial Fibrillation	7 (7.3%)	11 (20.4%)	18 (12.0%)
New Permanent Pacemaker Implanted	12 (12.5%)	8 (14.8%)	20 (13.3%)

* Valve Malposition requiring a second valve on Day 0

THE SAPIEN 3 TRIAL

Clinical Improvement at 30 Days

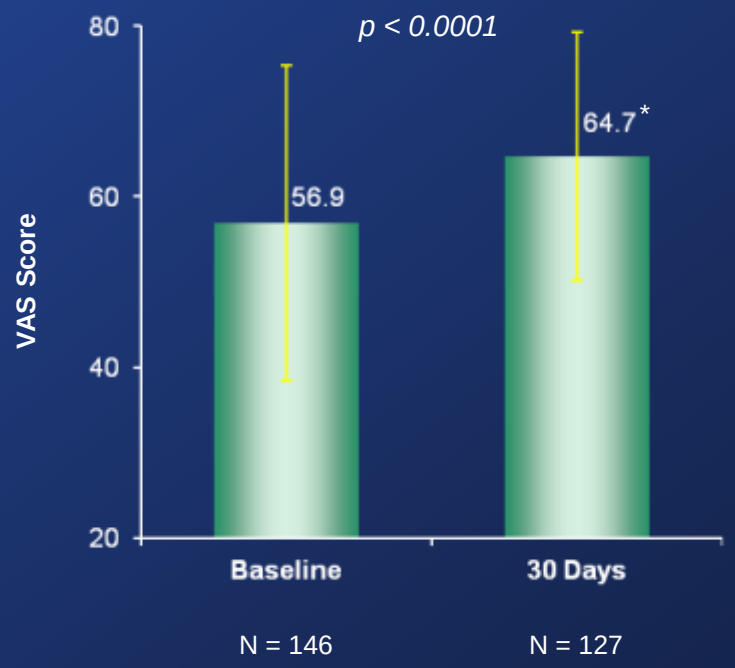




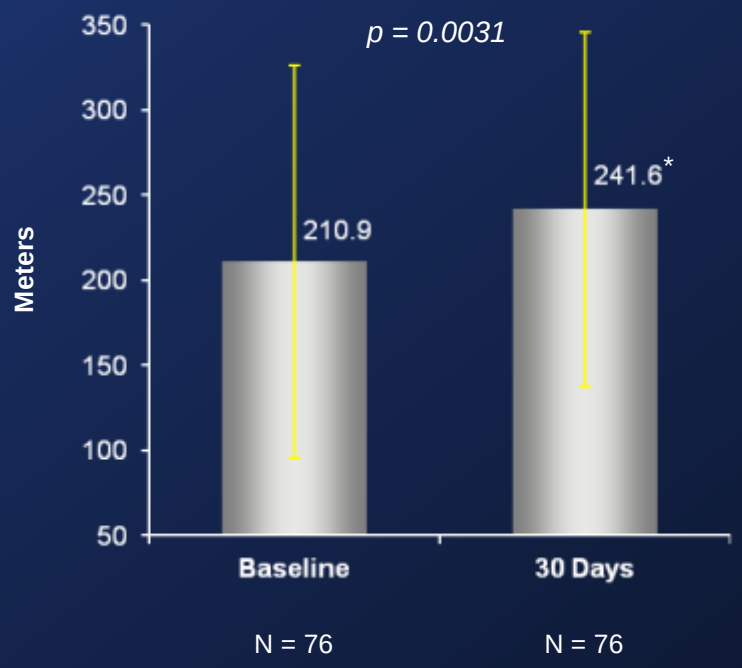
THE SAPIEN 3 TRIAL

Improvement in Quality of Life at 30 Days

VAS EQ-5D



6-MINUTE WALK TEST

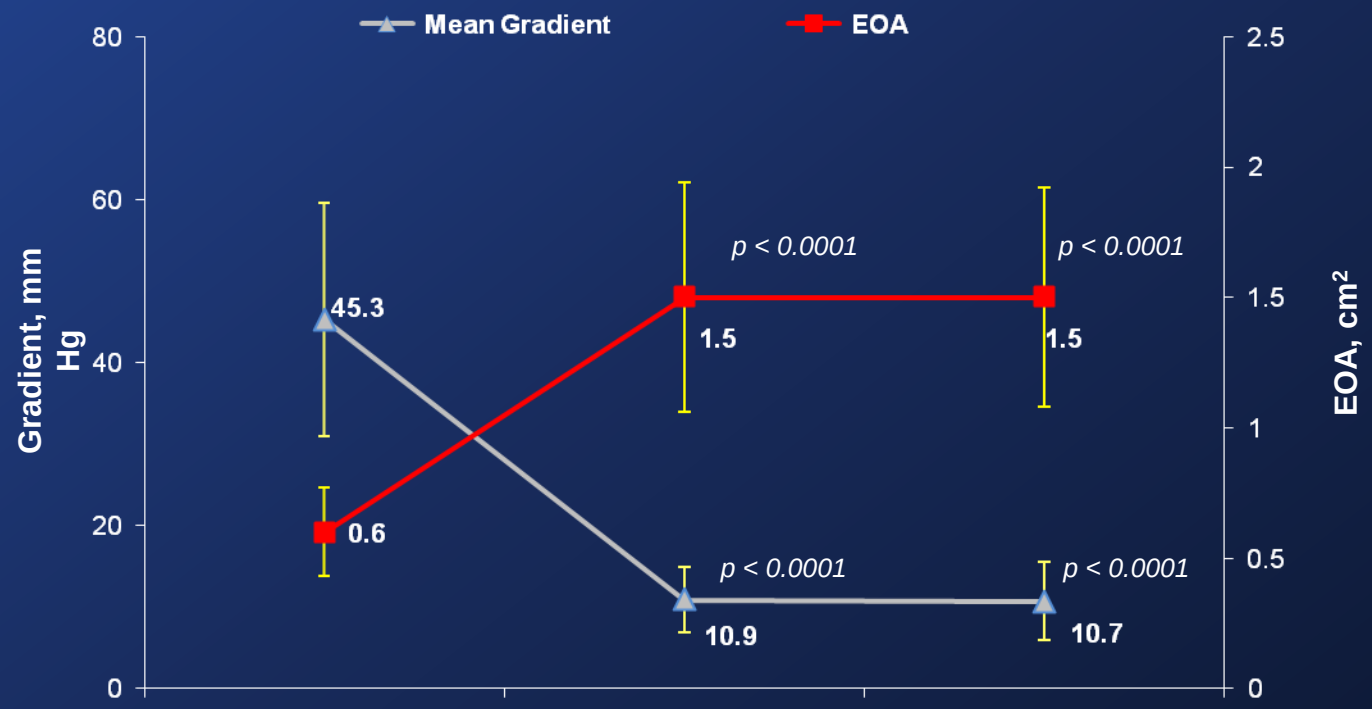


VAS, Visual Analogue Scale.
* p-values from paired t-test baseline vs follow-up.

THE SAPIEN 3 TRIAL

Echocardiographic Data

MEAN GRADIENT & EFFECTIVE ORIFICE AREA (EOA)*

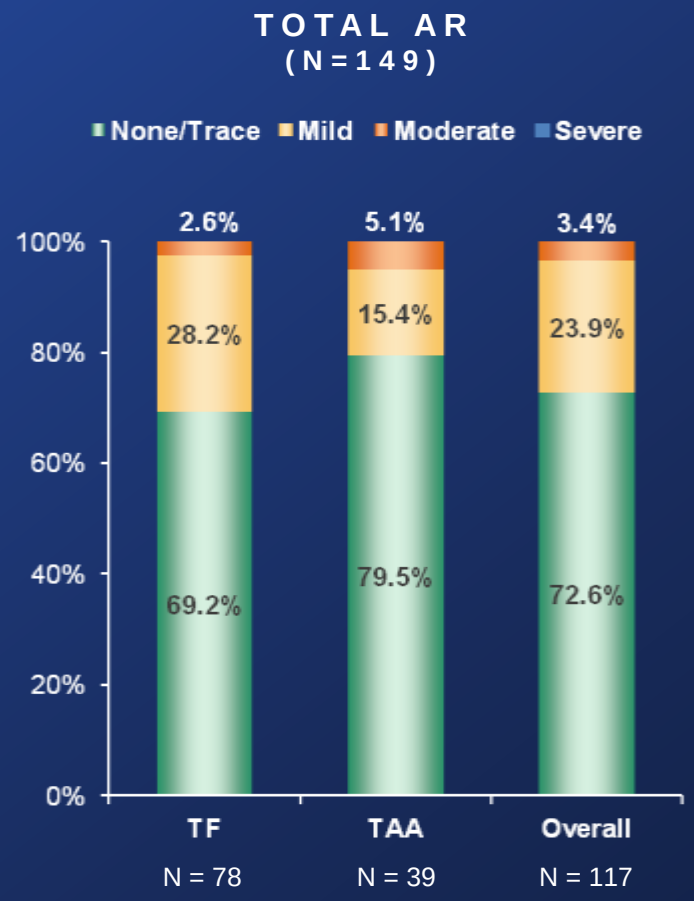


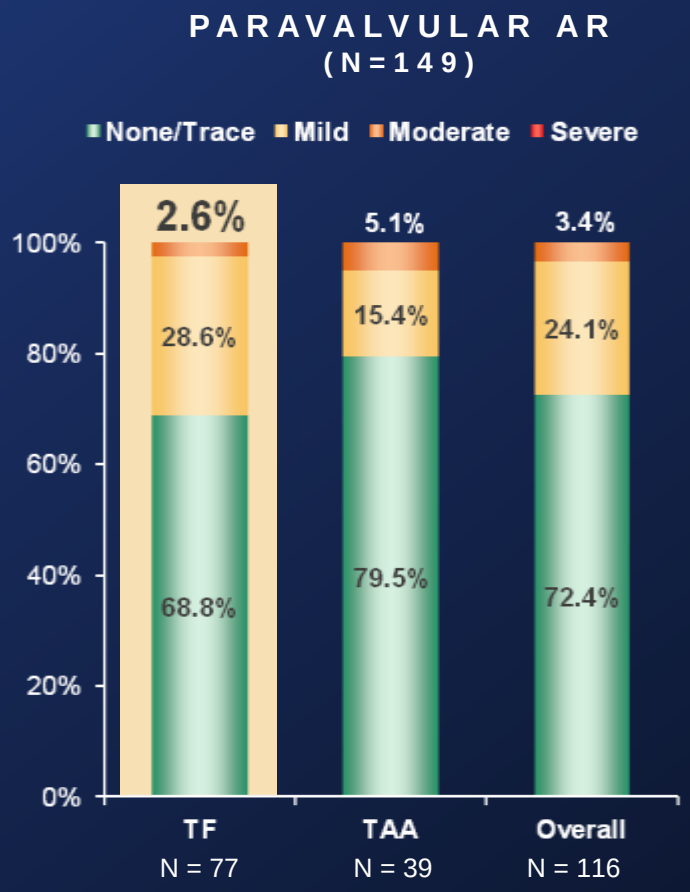
No. of Patients			
EOA	110	99	100
Mean Gradient	125	116	122

* mVI population (Overall, N = 149; TF, N=95). The modified valve implant (mVI) population consists of all VI patients who retained the study valve at the time of assessment.

THE SAPIEN 3 TRIAL

Echocardiographic Data at 30 Days





THE SAPIEN 3 TRIAL

Conclusions – The SAPIEN 3 Trial

- Outcomes at 30 days were excellent
- TF SAPIEN 3 implantation was associated with a very low mortality of 2.1%, stroke of 1.0%, and very few access-site complications
- TF implantation was associated with a very low mortality of 1.1% in the valve implant population
- 99.3% of valves were implanted at the intended location - due to precise SAPIEN 3 positioning
- 96.6% of patients had ≤ mild PVL. There was no severe PVL
- Post-implant maneuvers were rarely needed despite reduced oversizing – procedural post-dilatation (3.3%), valve-in-valve implants (0%)
- The SAPIEN 3 THV may enable treatment of intermediate-risk patients with aortic stenosis

THE SAPIEN 3 TRIAL

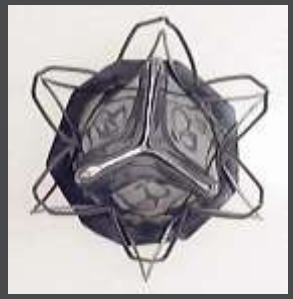
New TAVI Systems - *Transfemoral*

- Direct Flow
- Sadra
- St. Jude
- AorTx
- HLT
- EndoTech
- ABPS PercValve







New TAVI Systems - *Transapical*

- Jena Valve

- MDT (Engager)

- Symetis

(73 pts, + CE approval)

(40 pts)

(90 pts, + CE approval)

New Edwards Sapien 3 Valve Platform