Innovations in Cardiac Devices

Andreas Baumbach

Consultant Cardiologist,

Professor of Interventional Cardiology

Bristol Heart Institute

University of Bristol

University of BRISTOL

Bristol Heart Institute

University Hospitals Bristol NHS

NHS Foundation Trust

Objectives

- To illustrate recent developments at the interface between cardiac surgery and interventional cardiology
- To provide an outlook for the near future of TAVI and device based enabling procedures

Structural Intervention

- Aortic Valves
  - –Status Quo
  - –Pipeline
- Enabling Devices
  - –Embolic Protection

TAVI

- Started with pioneering efforts in the aortic valve and in grown up congenital heart disease. In cooperation with Startup Companies

- Henning Andersen
- Alan Cribier
- Philipp Bonhöffer

FIRST GENERATION DEVICES

Sapien Edwards Valve

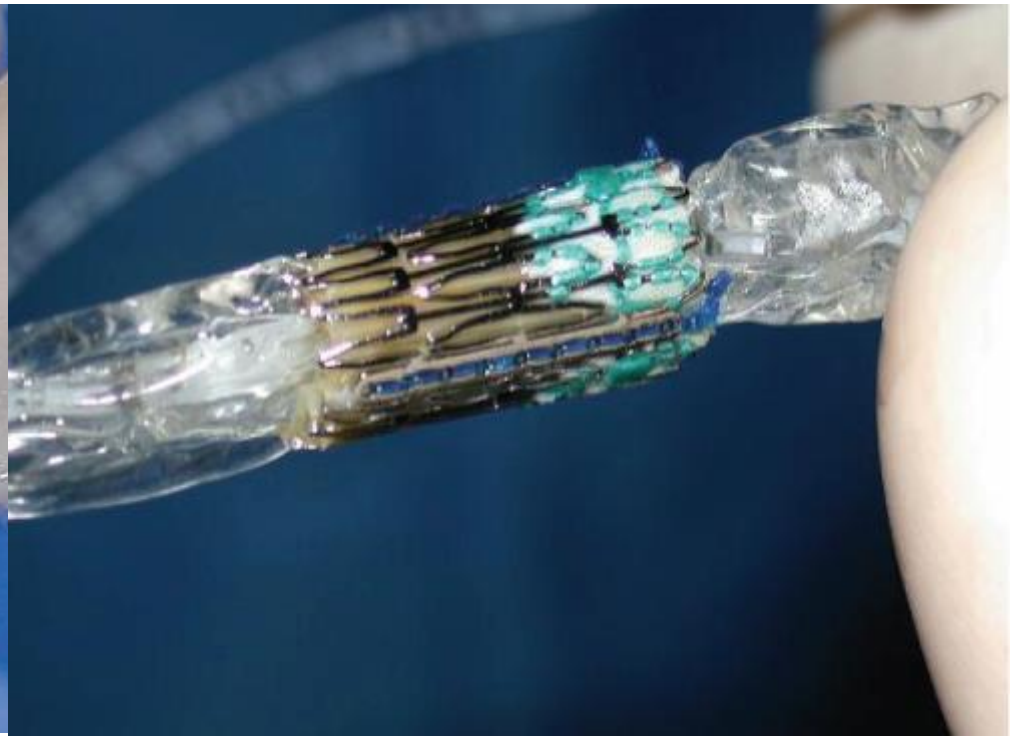
Tricuspid valve, equine pericardium

Stainless steel stent frame

22mm Numed ballon catheter

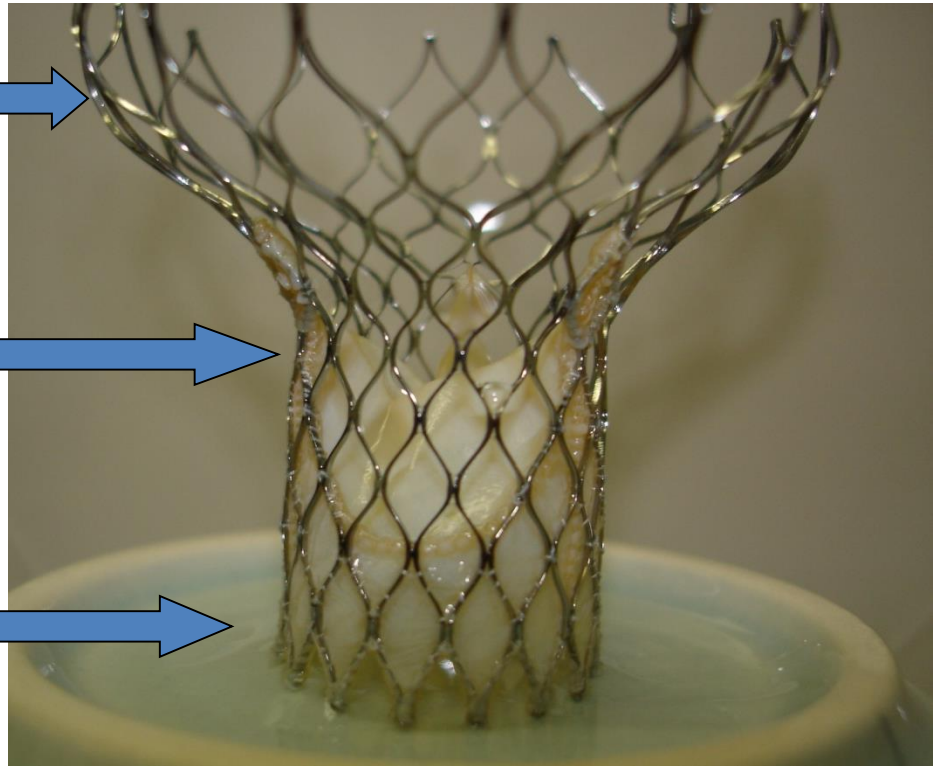
Original crimper device

Compatible with 24-Fr sheath



CoreValve: Self-Expanding Prosthesis

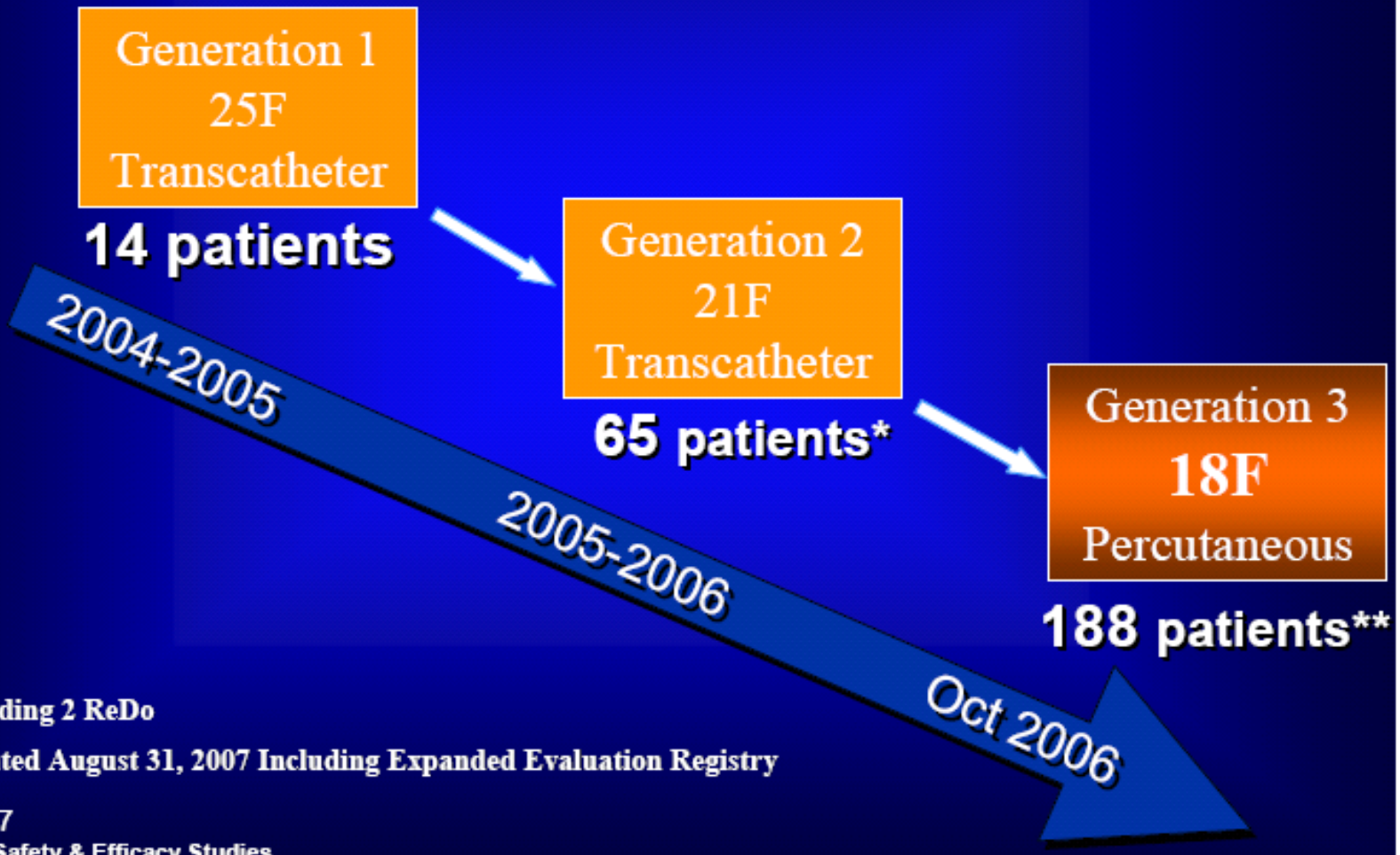
- **HIGHER PART** : increases quality of fixation and axes the system
- **MIDDLE PART :** is constrained to avoid coronaries and carries the valve
- **LOWER PART:** High radial force of the frame pushes aside the calcified leaflets and avoids recoil and para-valvular leaks



A pericardium porcine tissue valve

Fixed to the frame in a surgical manner with PTFE sutures

Technology Progress & Total Experience



* Including 2 ReDo

** Updated August 31, 2007 Including Expanded Evaluation Registry

ESC 2007

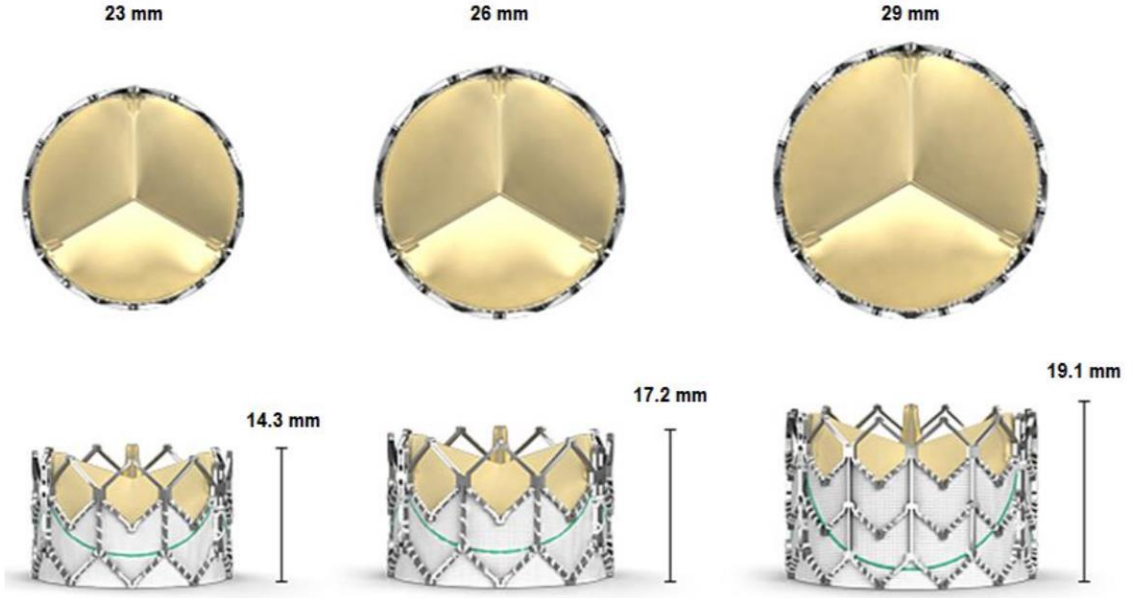
21F + 18F Safety & Efficacy Studies

The Work-Horse TAVI Devices

Medtronic CoreValve
Size 23, 26, 29, 31
Annulus: 18 -29mm

18F TF for all

Edward Sapien
Size 23, 26, 29
Annulus: 18-27mm



TF (16F eS) and TA

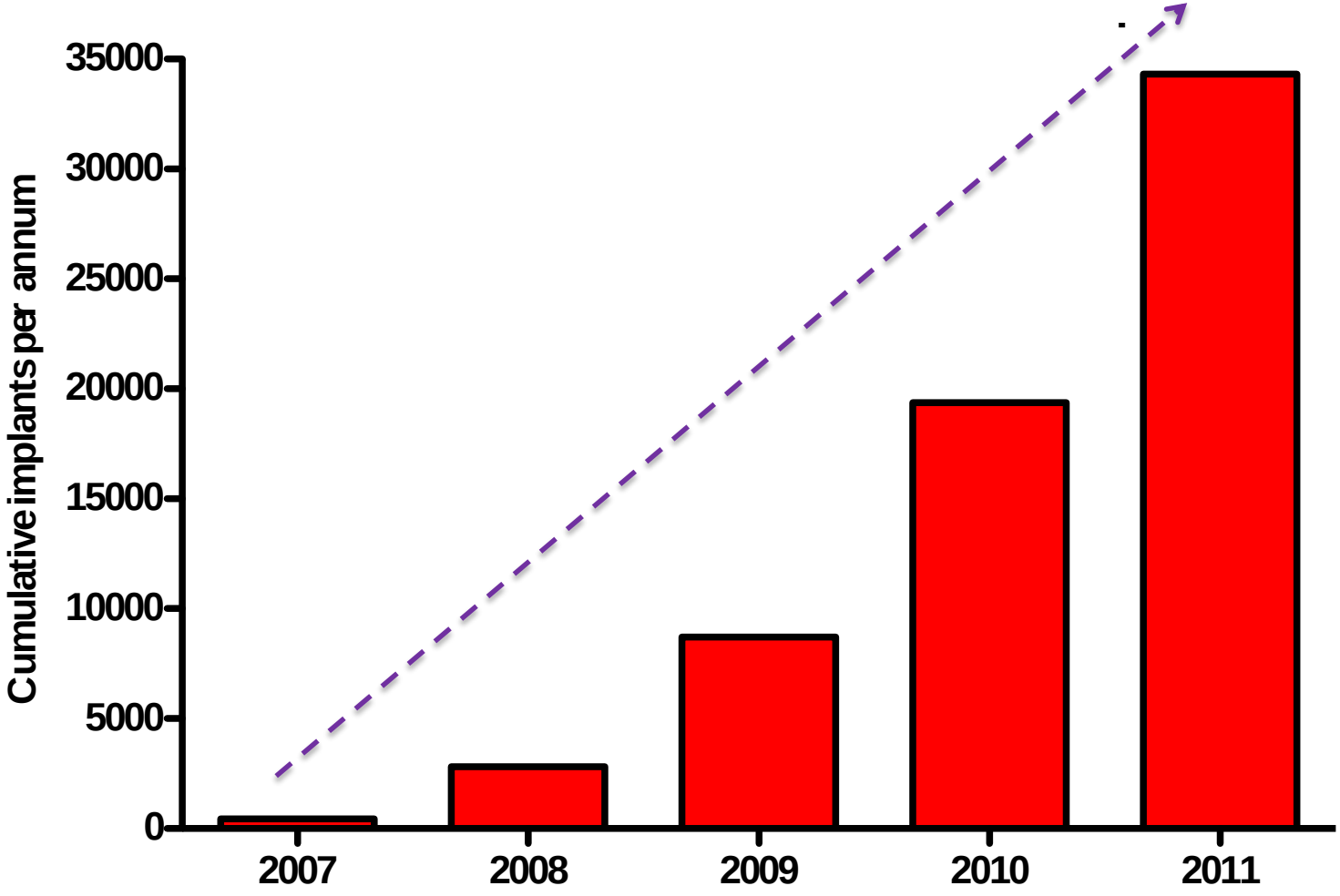
TF (18F eS) and TA

TF (20F eS) and TA

eS = e-Sheath

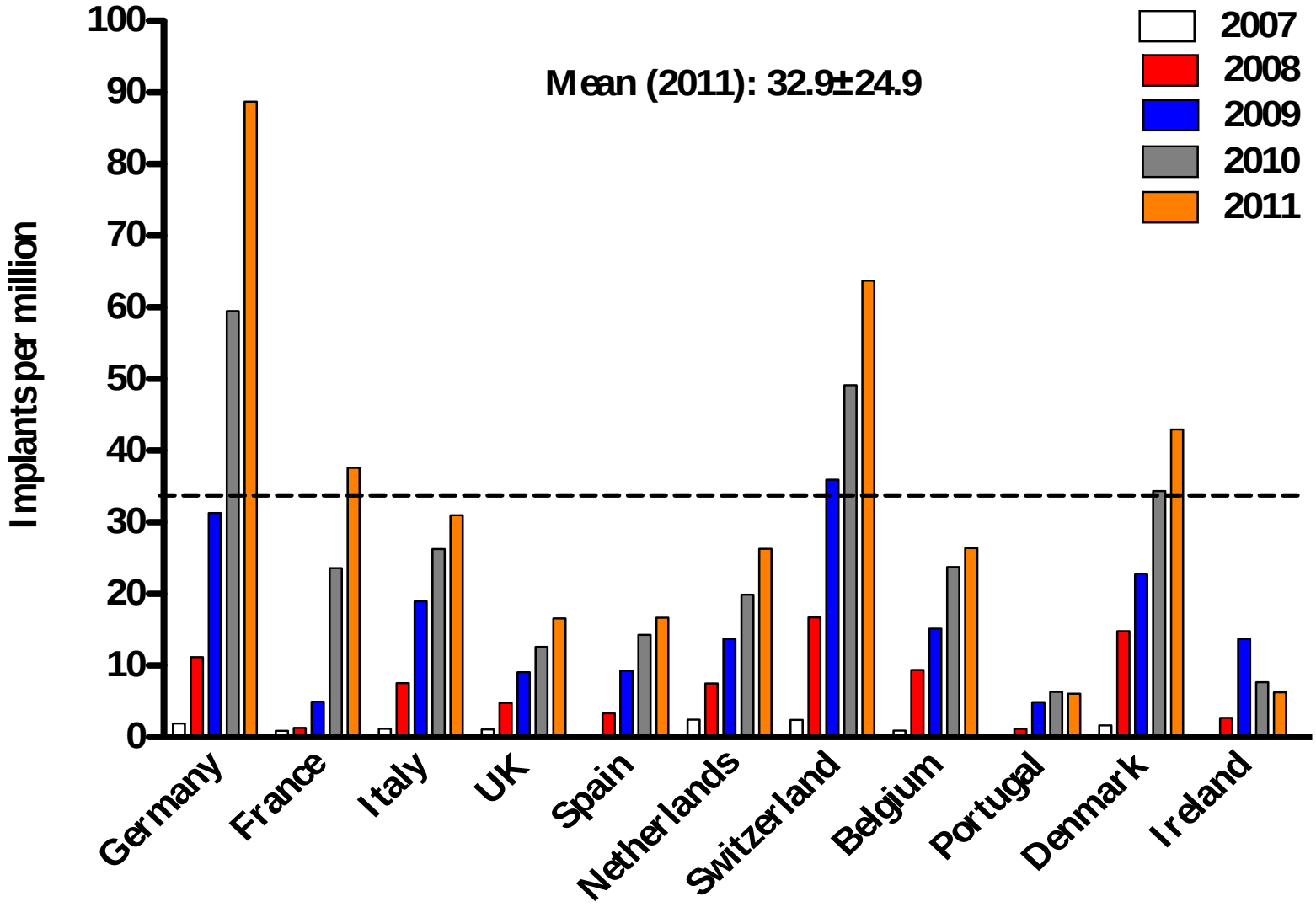
CUMULATIVE TAVI

2007 TO 2011



REGISTRY DATA

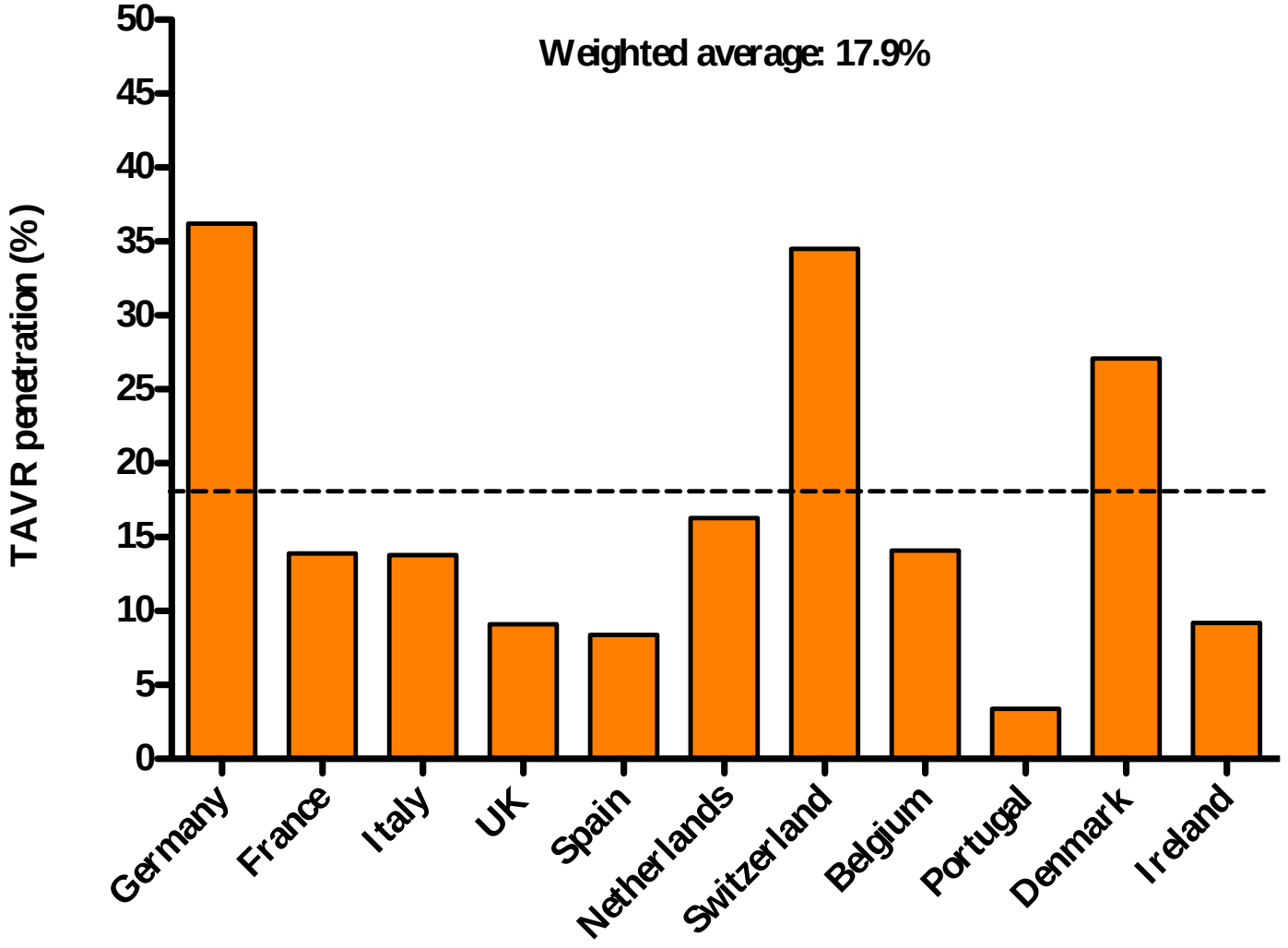
TAVI IMPLANTS PER MILLION



REGISTRY DATA

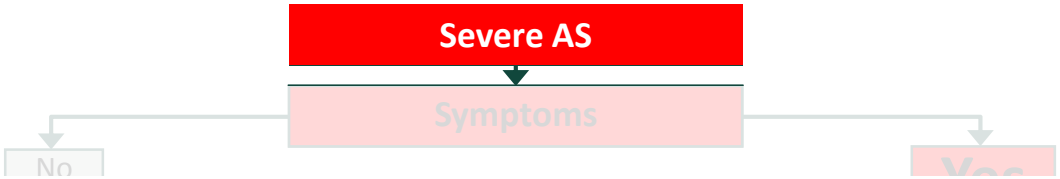
National TAVI Penetration

Year 2011



MANAGEMENT OF SEVERE AORTIC STENOSIS

ESC GUIDELINES ON VALVULAR HEART DISEASE 2012



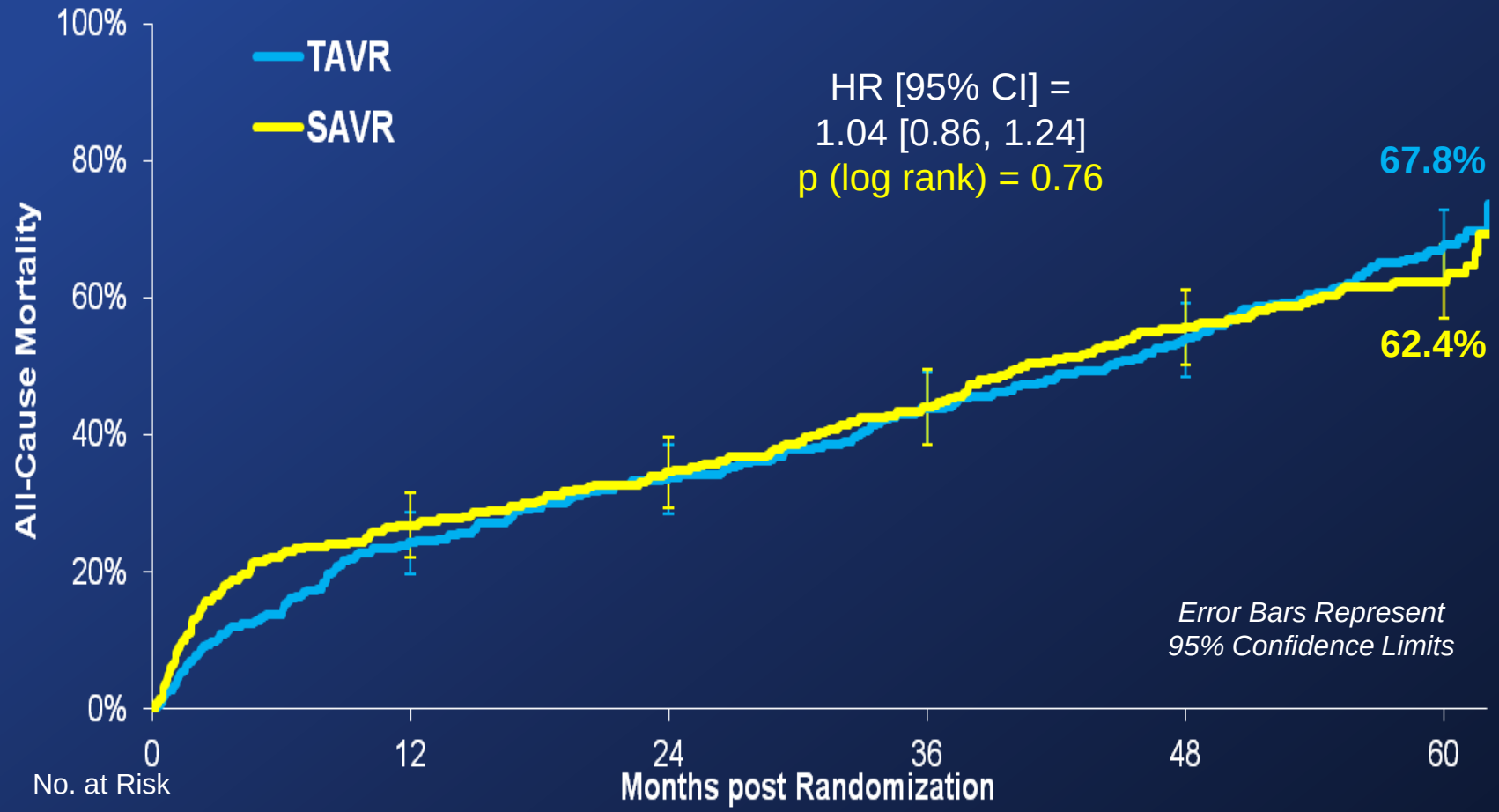
	Class	Level
TAVI should only be undertaken with a multidisciplinary "heart team" including cardiologists and cardiac surgeons and other specialists if necessary.	I	C
TAVI should only be performed in hospitals with cardiac surgery on-site.	I	C
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a " heart team" and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities.	I	B
TAVI should be considered in high risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a "heart team" based on the individual risk profile and anatomic suitability.	IIa	B

Eur Heart J 2012 - doi:10.1093/eurheartj/ehs109 & Eur J Cardiothorac Surg 2012 - doi:10.1093/ejcts/ezs455).

All-Cause Mortality (ITT)

All Patients

THE PARTNER TRIAL



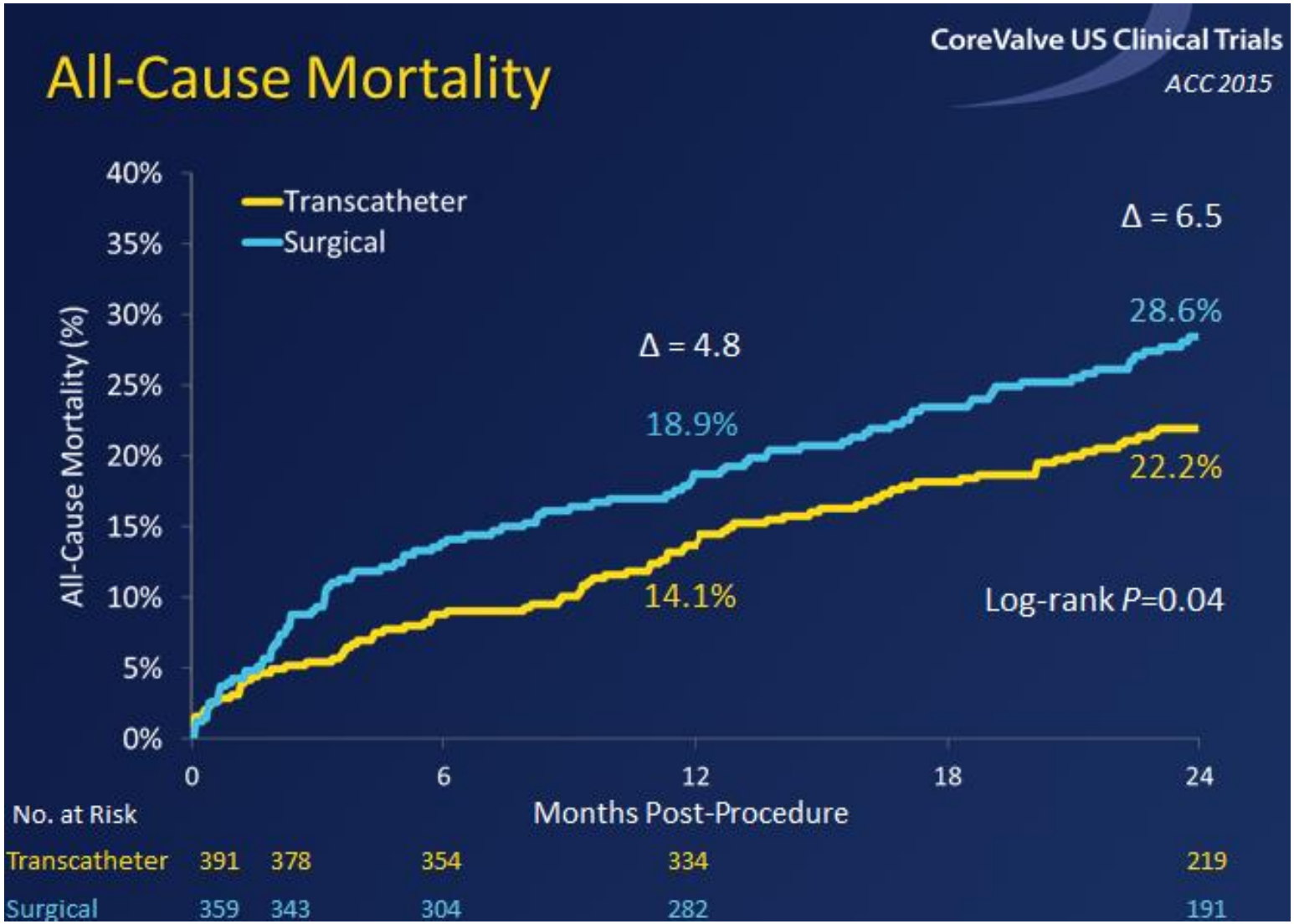
No. at Risk

TAVR	348	262	228	191	154	61
SAVR	351	236	210	174	131	64

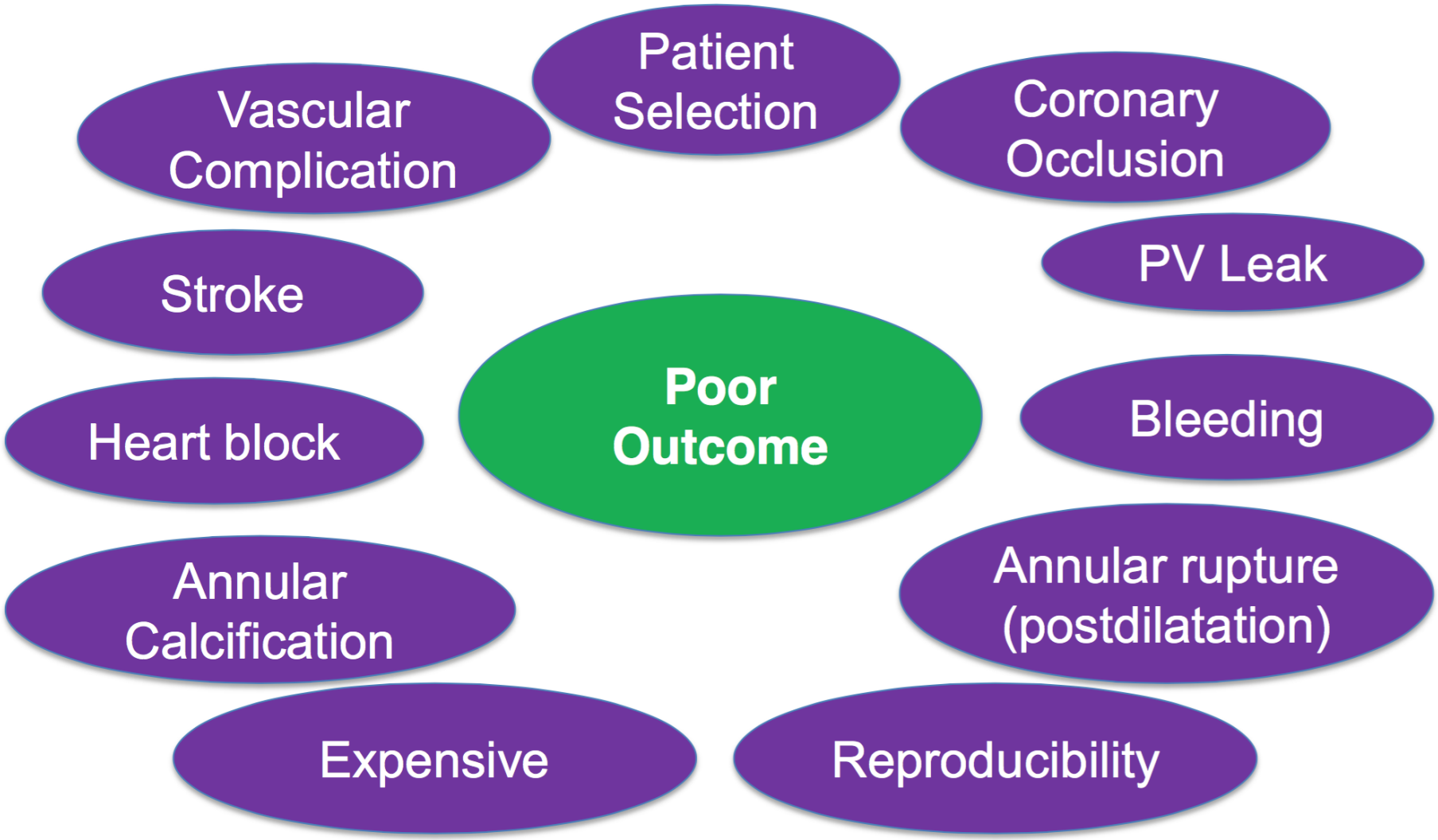
TAVI vs. SAVR

All-Cause Mortality in Intermediate Risk Patients

Adams DH et al. N Engl J Med. 2014 May 8;370(19):1790-8



What are the challenges with TAVI / current systems?



G Manoharan, Royal Victoria, Belfast

Evolution of Devices (2002 – 2015)

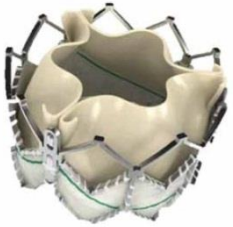
Prosthesis with CE – Mark Approval

2007 2010 2011 2012 2013 2014 2015

Edwards Sapien THV

TF, TA

Edwards Sapien XT



TF, TA

Symetis Acurate TA

TA

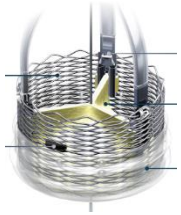
SJM Portico

TF

Direct Flow Medical

TF

BSC Lotus



TF

Edwards Sapien 3

TF, TA

Medtronic CoreValve

TF, TS, DA

JenaValve

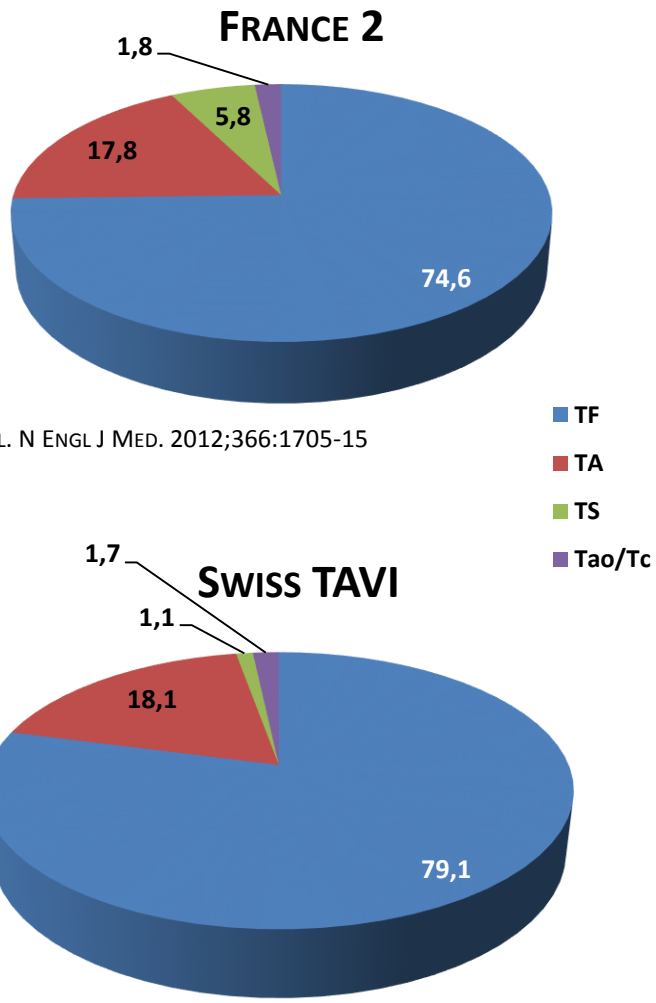
TA

Medtronic Engager

TA

Transcatheter Aortic Valve Implantation
Contemporary Clinical Practice

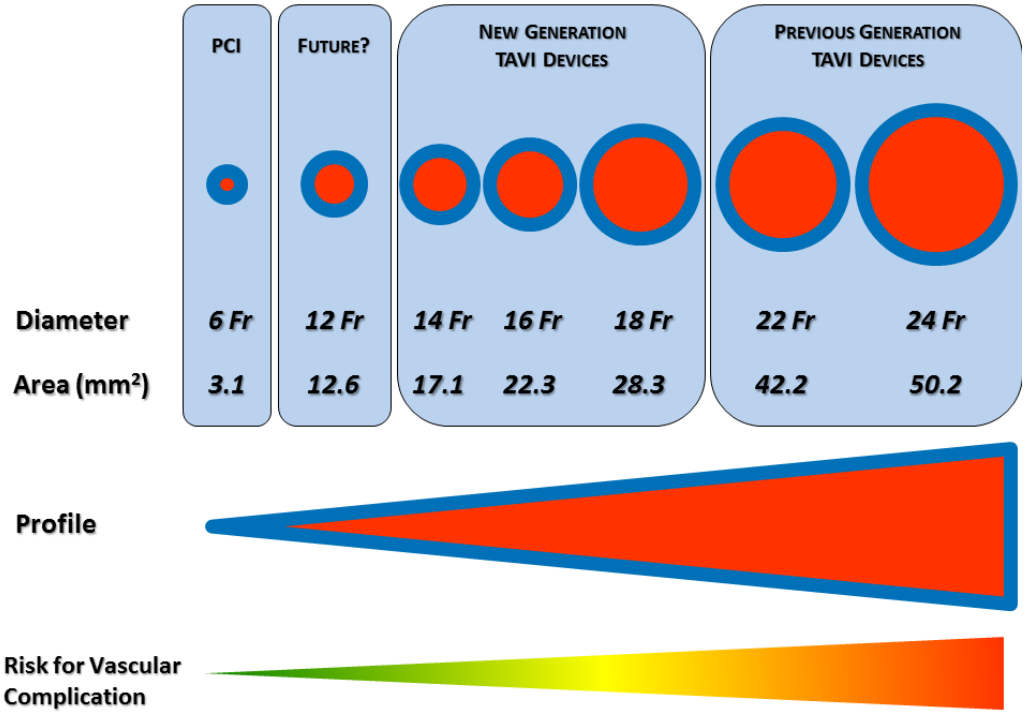
Access Route Selection



Gilard M et al. N Engl J Med. 2012;366:1705-15

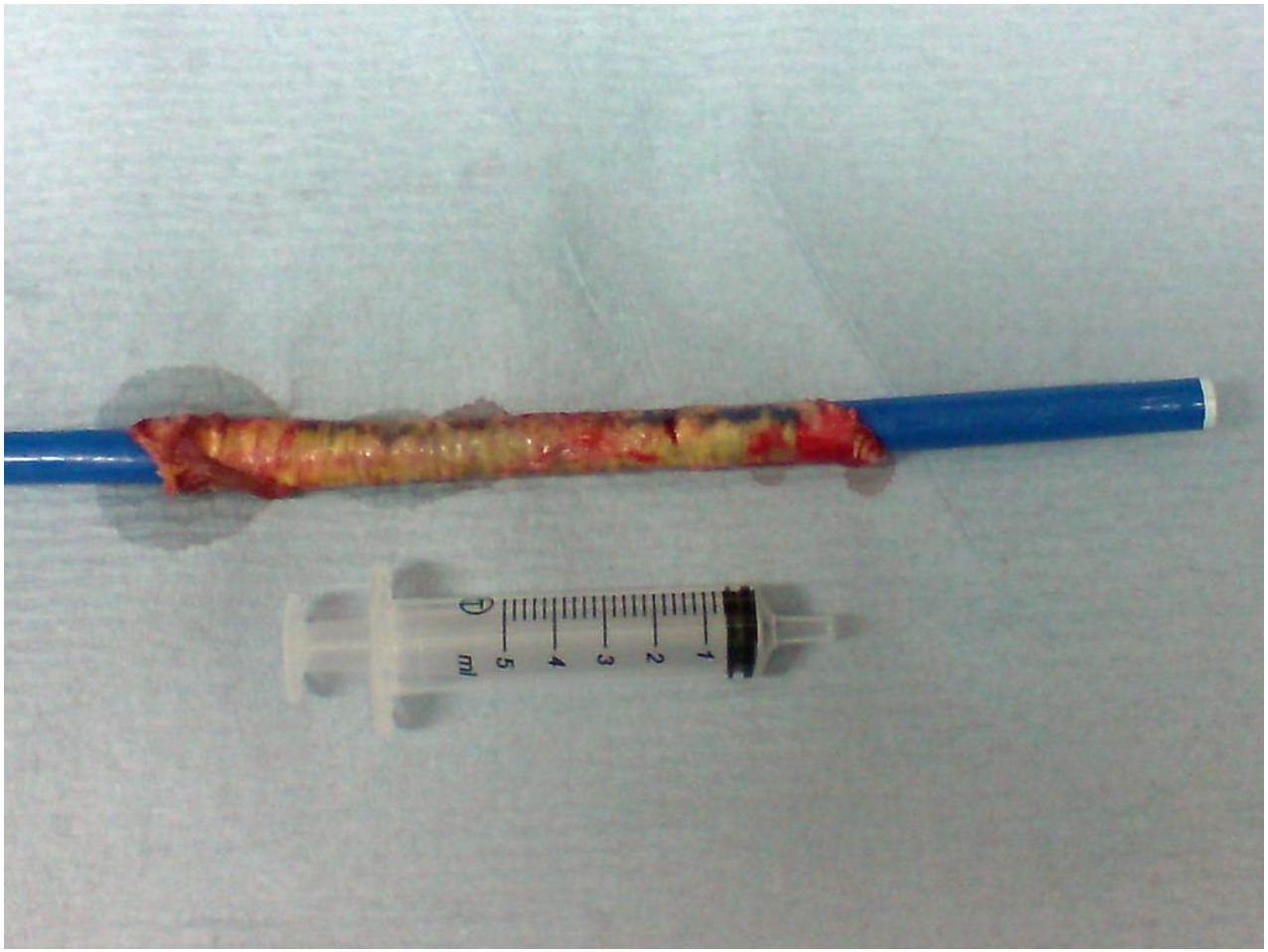
Wenaweser P et al. EuroIntervention 2014; 10:982-9

Transfemoral TAVI
A Fully Percutaneous Procedure



Toggweiler S et al. J Am Coll Cardiol. 2012;59:113-8

If the sheath does not want to move forward or back.....dont pull!!

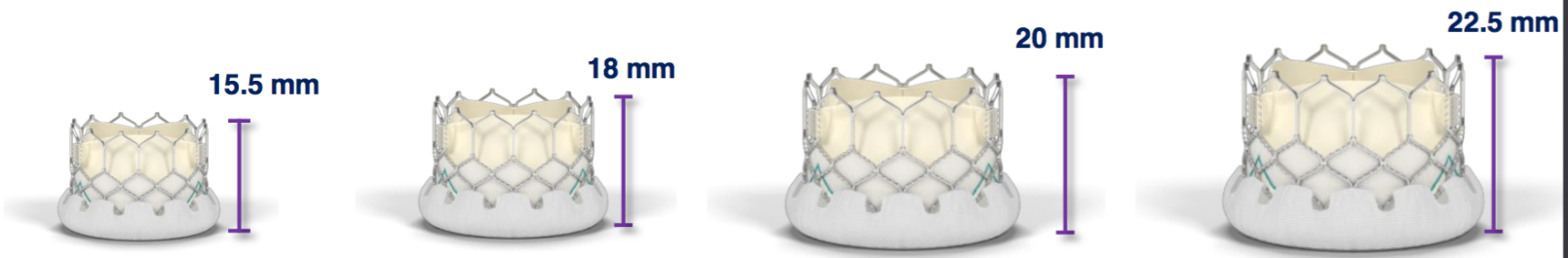


Sapien 3 System

Enhanced frame design
- New frame geometry
- High radial strength for circularity and optimal hemodynamics

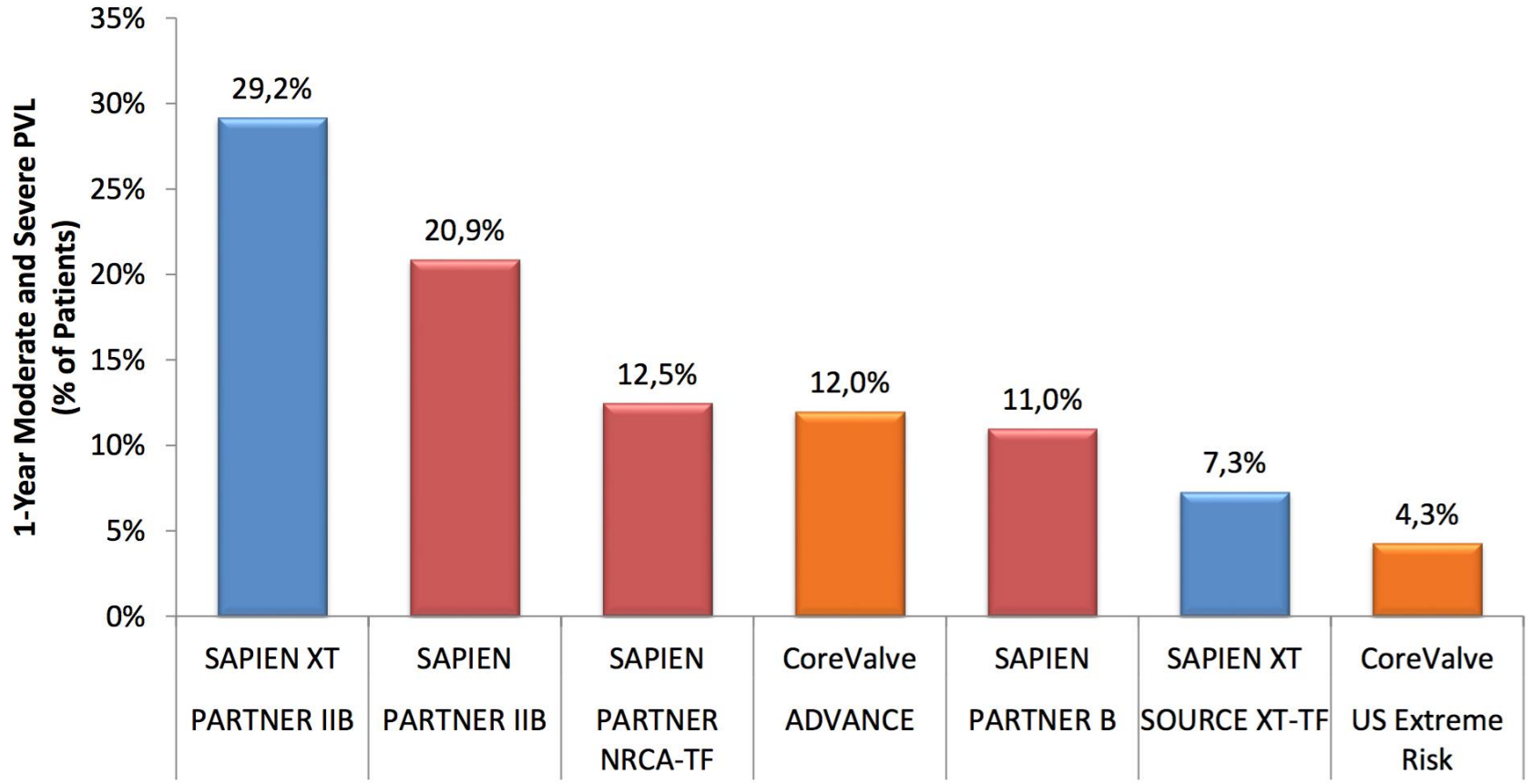
Bovine pericardial tissue
Optimized leaflet shape
Tissue treatment

New outer PET skirt



	20 mm	23 mm	26 mm	29 mm
eSheath size (Transfemoral)	14F	14F	14F	16F
Sheath size (Transapical, Transaortic)	18F	18F	18F	21F
Annulus size by TEE*	16-19 mm	18-22 mm	21-25 mm	24-28 mm

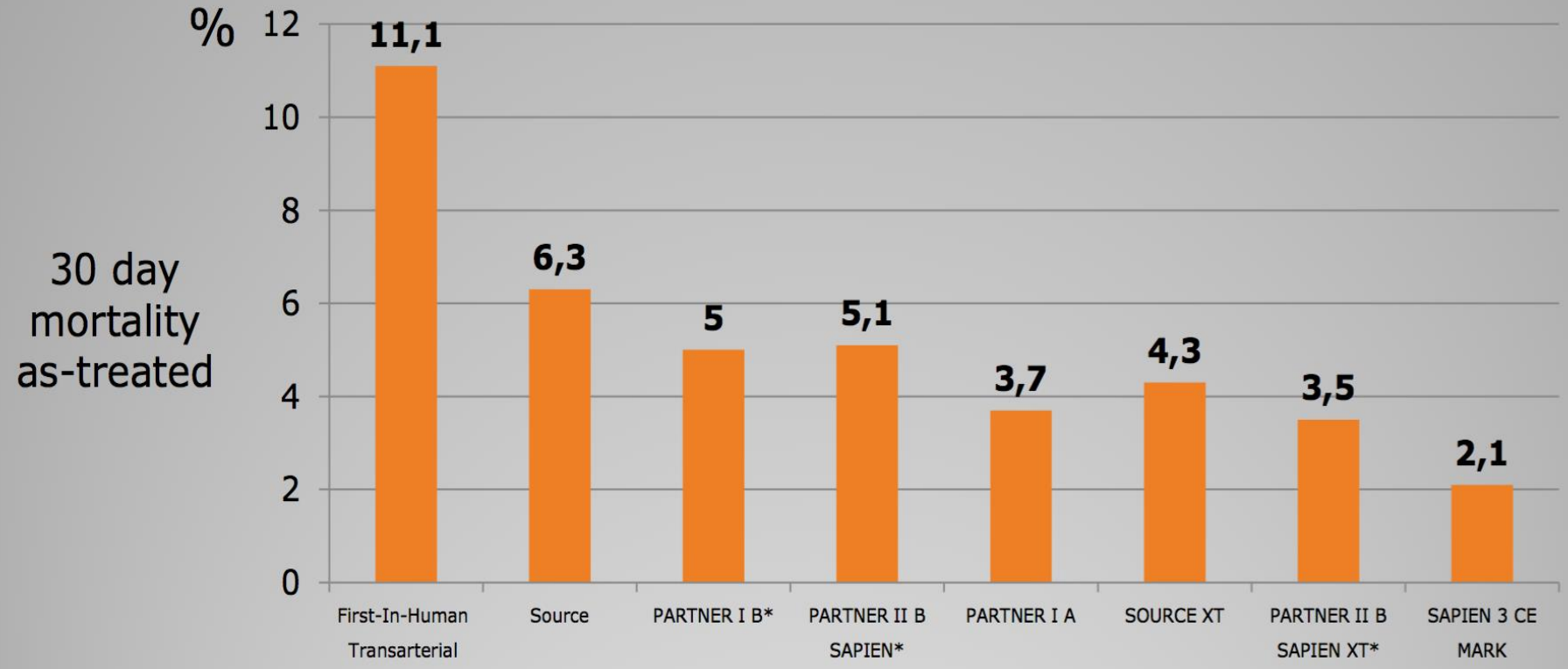
1-year moderate-severe PVL



[1]Leon, et. al. presented at ACC 2013; [2]Kodali, et al., presented at TCT 2012; [3]Linke, et. al. presented at EuroPCR 2013; [4]Leon, et al. *N Engl J Med* 2010; 363: 1597-1607; [5]Treede, et. al. presented at EuroPCR 2013; [6]Popma, et al., *J Am Coll Cardiol* 2014; epub

Evolution of Results

Studies: Mortality Rates are Falling



References

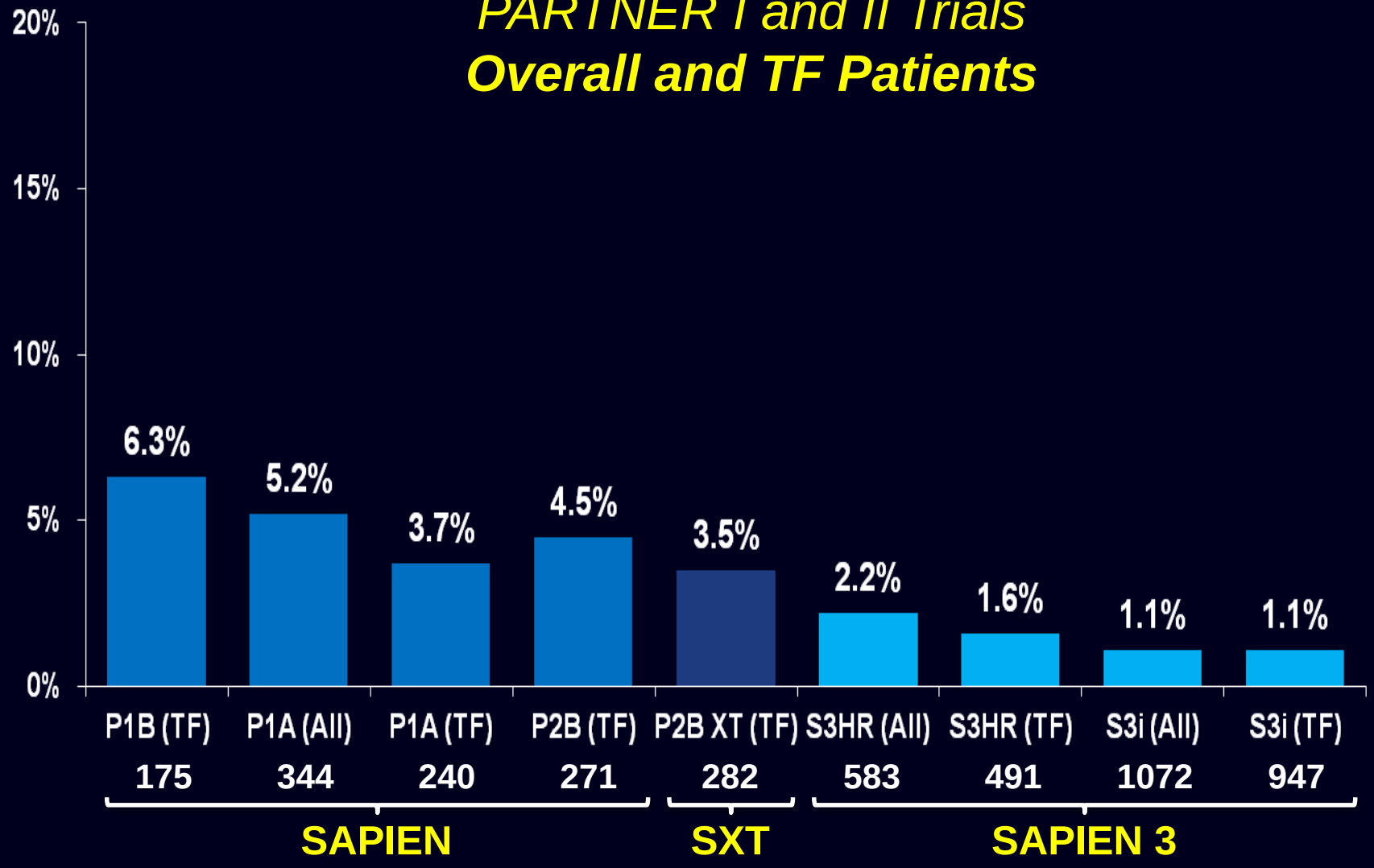
- **2005 Canadian Series:** Webb, J.G., et all., *Percutaneous Aortic Valve Implantation Retrograde from the Femoral Artery, Circulation, 2005. 113(6): 842-50.*
- **SOURCE:** Thomas, M., et al., *Thirty-Day Results of the Sapien Aortic Bioprosthesis European Outcome (SOURCE) Registry: A European Registry of Transcatheter Aortic Valve Implantation Using the Edwards Sapien Valve,* Circulation 2010. 122(1): 62-9.
- **PARTNER I Cohort B:** Leon, M.B., et al., *Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery,* NEJM, 2010. 363(17): 1597-607.
- **PARTNER II Cohort A:** Smith C.R., et al., *Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients,* NEJM 2010. 364(23): 2187-98.
- **SOURCE XT:** Wendler, O. *30 Day Outcomes from the SOURCE XT TAVI Post Approval Study.* Presented at EuroPCR 2012
- **PARTNER II:** Leon, M.B., et al., *A Randomized Evaluation of the Sapien XT Transcatheter Valve System in Patients with Aortic Stenosis Who Are Not Candidates for Surgery: PARTNER II, Inoperable Cohort.*

Mortality at 30 Days

Edwards SAPIEN Valves (As Treated Patients)

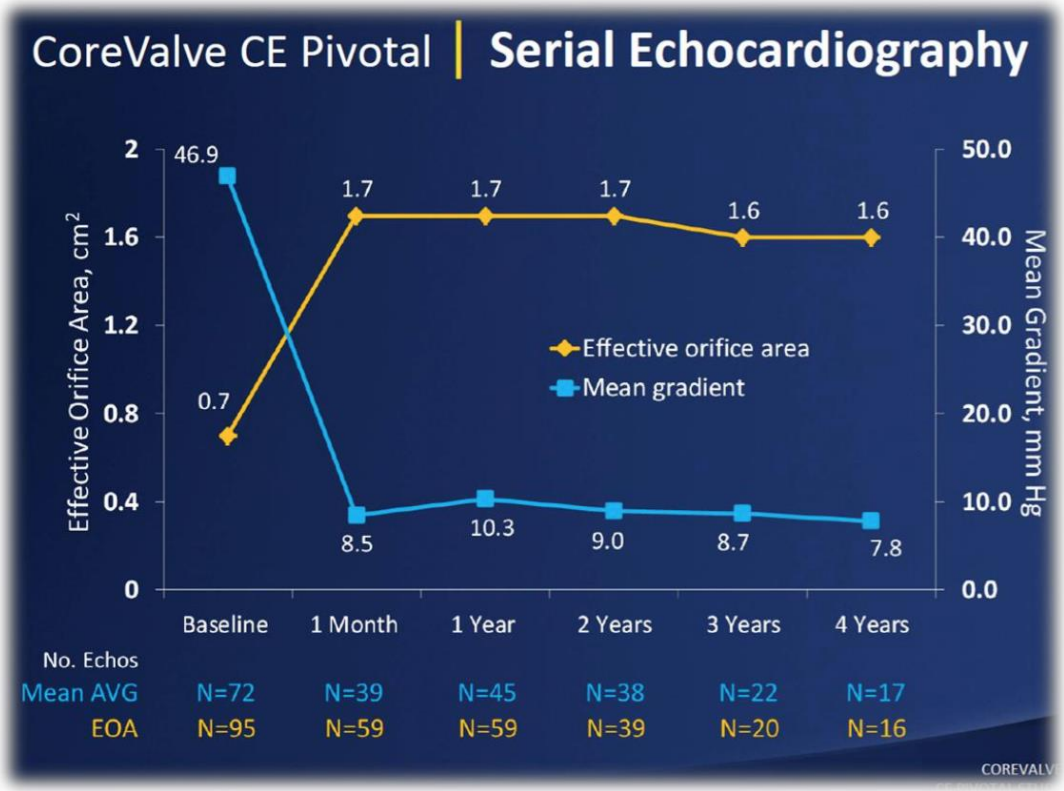
PARTNER I and II Trials

Overall and TF Patients

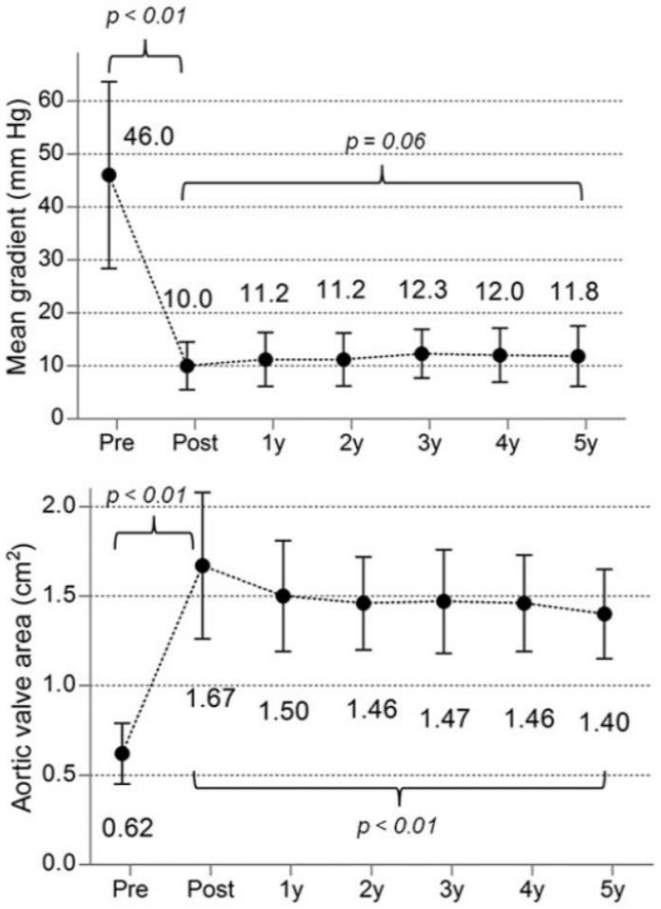


Long-term valve performance

CoreValve at 4 years[1]



Cribier-Edwards and SAPIEN at 5 years[2]

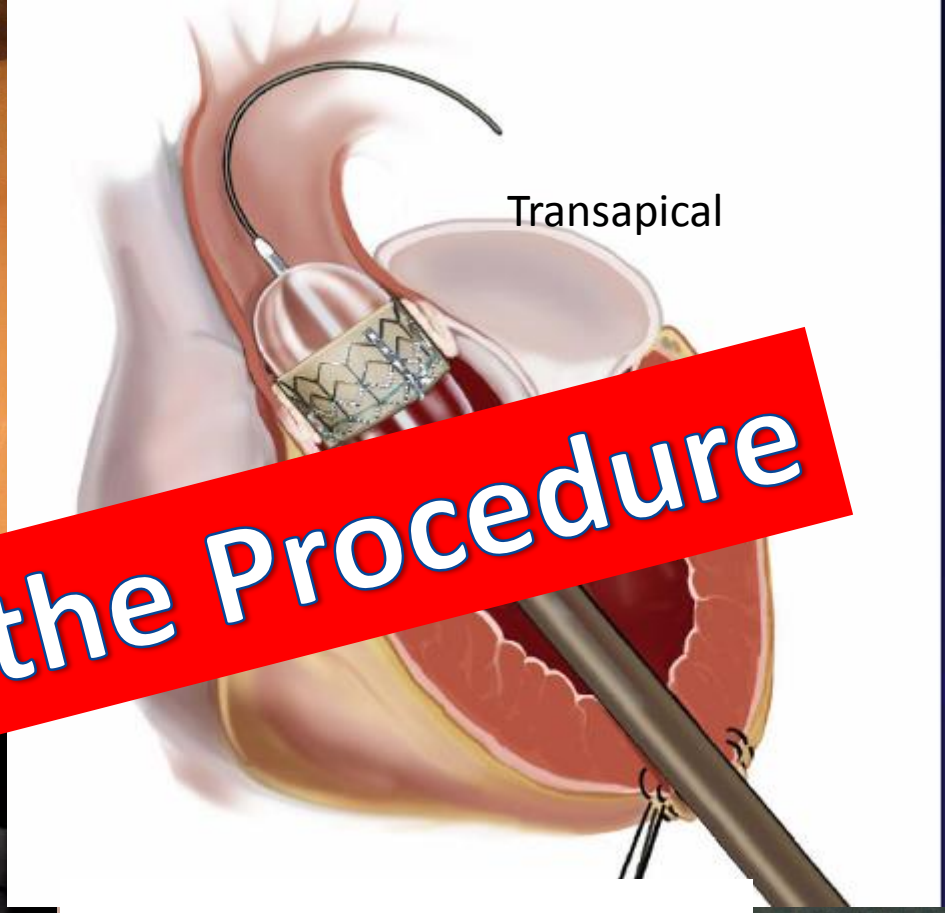


[1]Kovac, et al., presented at ACC 2014; [2]Tzagueiler, et al., *J Am Coll Card* 2013

Evolution of the Procedure

Transfemoral: Puncture

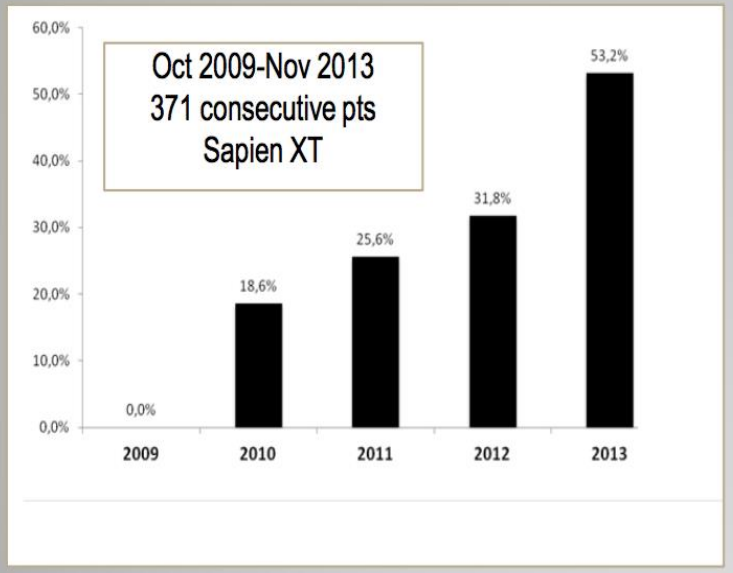
Transapical



Subclavia: cutdown

Change in Strategy: Minimalist TF-TAVI Approach

- Conscious sedation
- No TEE
- Percutaneous access
- Discharge: Day 1 to 3
- Back home



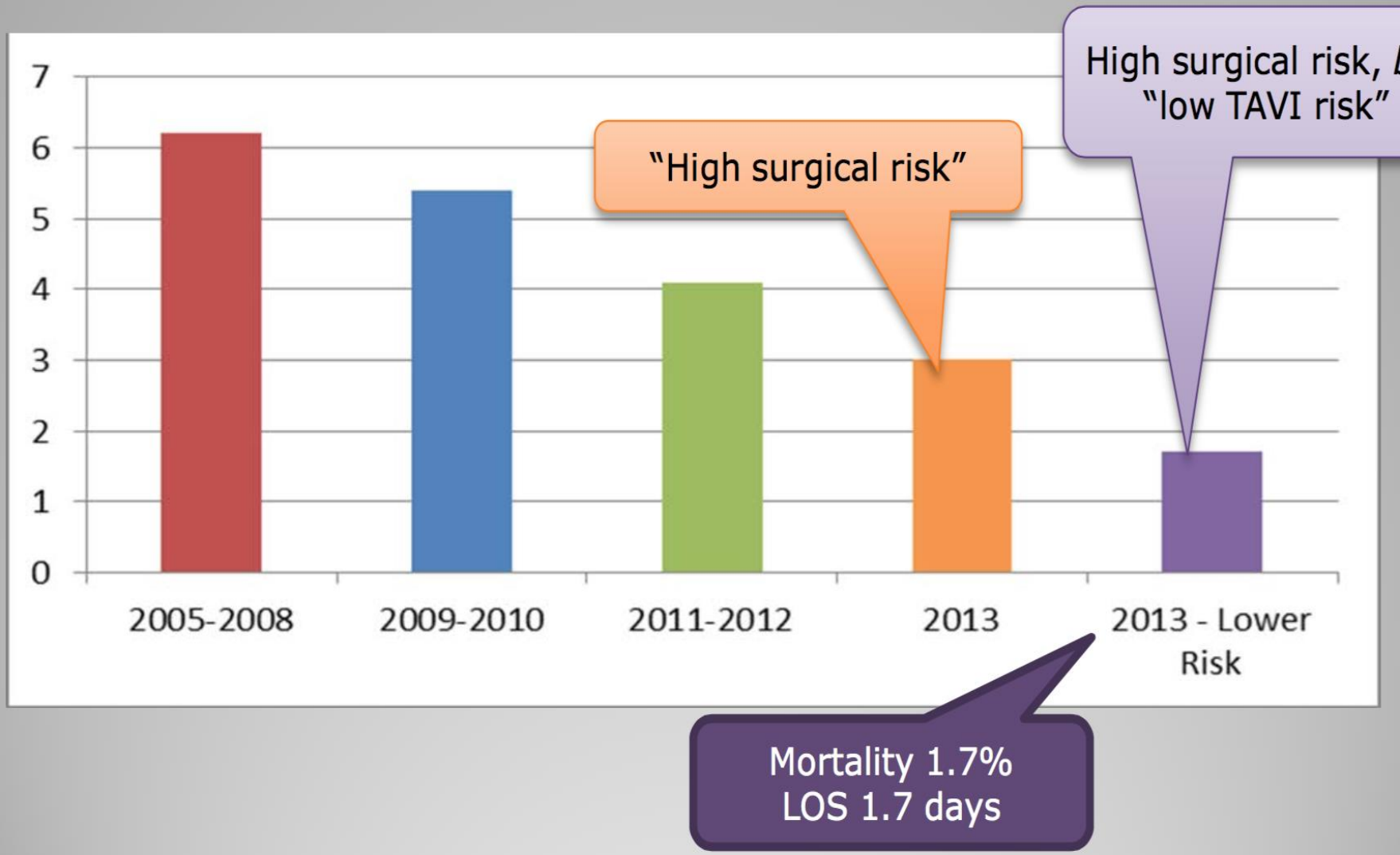
No death at 30-Day in the early discharge group

Since 2002 in our center

Durand, Eltchaninoff - JACC Cardiovasc Interv 2012
Bouzhame, Durand, Eltchaninoff – ESC 2014.

Reducing the Hospital Stay

Hospital Stay: Vancouver Transfemoral Program

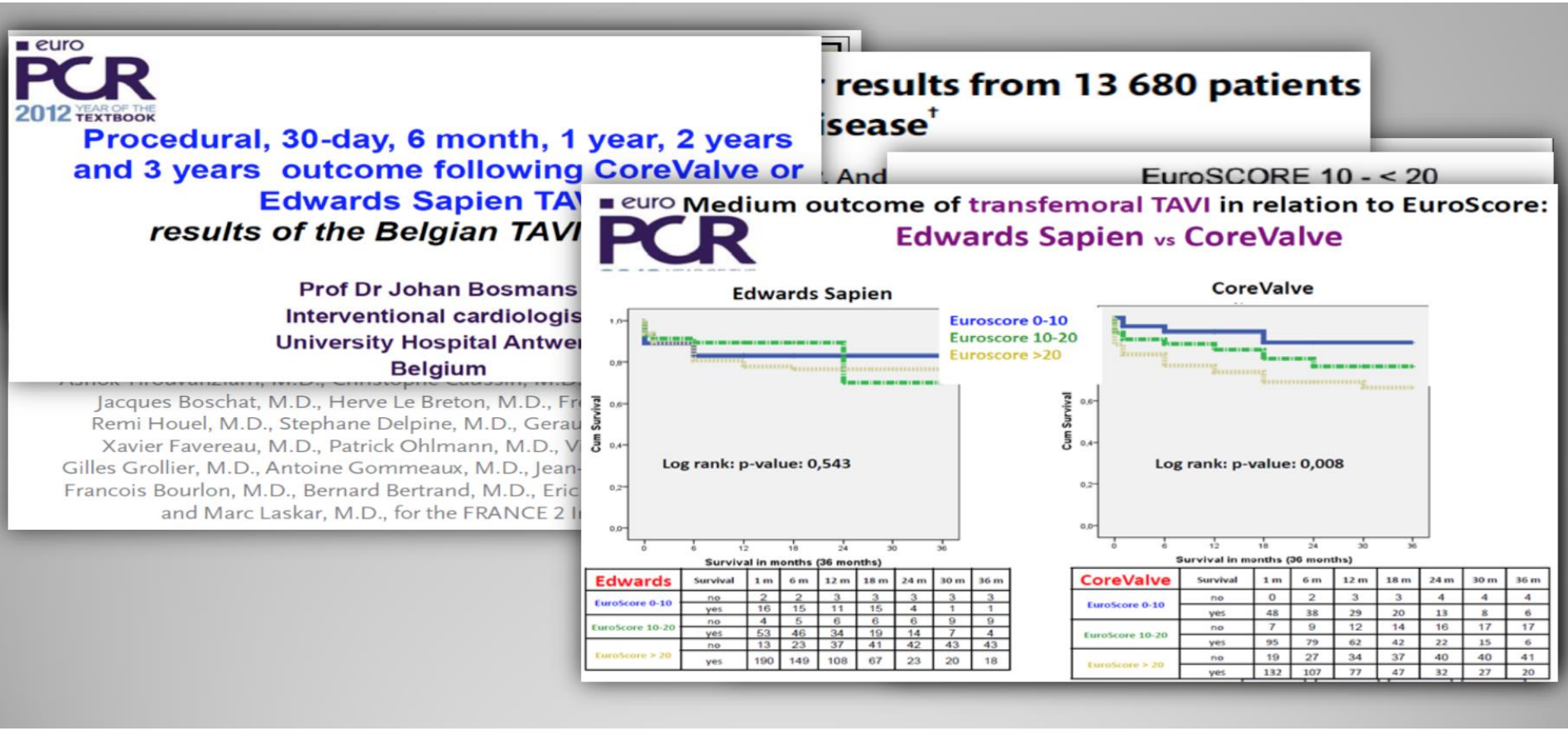


TAVI Length of Stay in Europe

Study (Country)	N	ICU LoS	Total LoS	Reference
[1]Observant (Italy)		2.4 ±2.6	8.1 ±5.1	D'Errigo IJC 2012. 167,1945-52
German TAVI Registry	697	2 (median)	17.2 ±9.2	Zahn EHJ 2011. 32, 198-204
[2]UK NHS TAVI (UK)	2071	NA	11.3	Internal UK HSCIS Data Analysis (2011 – 13)
Leuven (Belgium)	73	4 [3-6]	11 [7-18]	Dubois ICVTS 2013. 17, 492-500
FRANCE 2	3195	NA	11.1 ±8.0	Gillard M et al. NEJM 2012
Munich Grosshadern	461	2.83 ±2.84	16.21 ±8.5	Greif M. et al.. Heart 2013

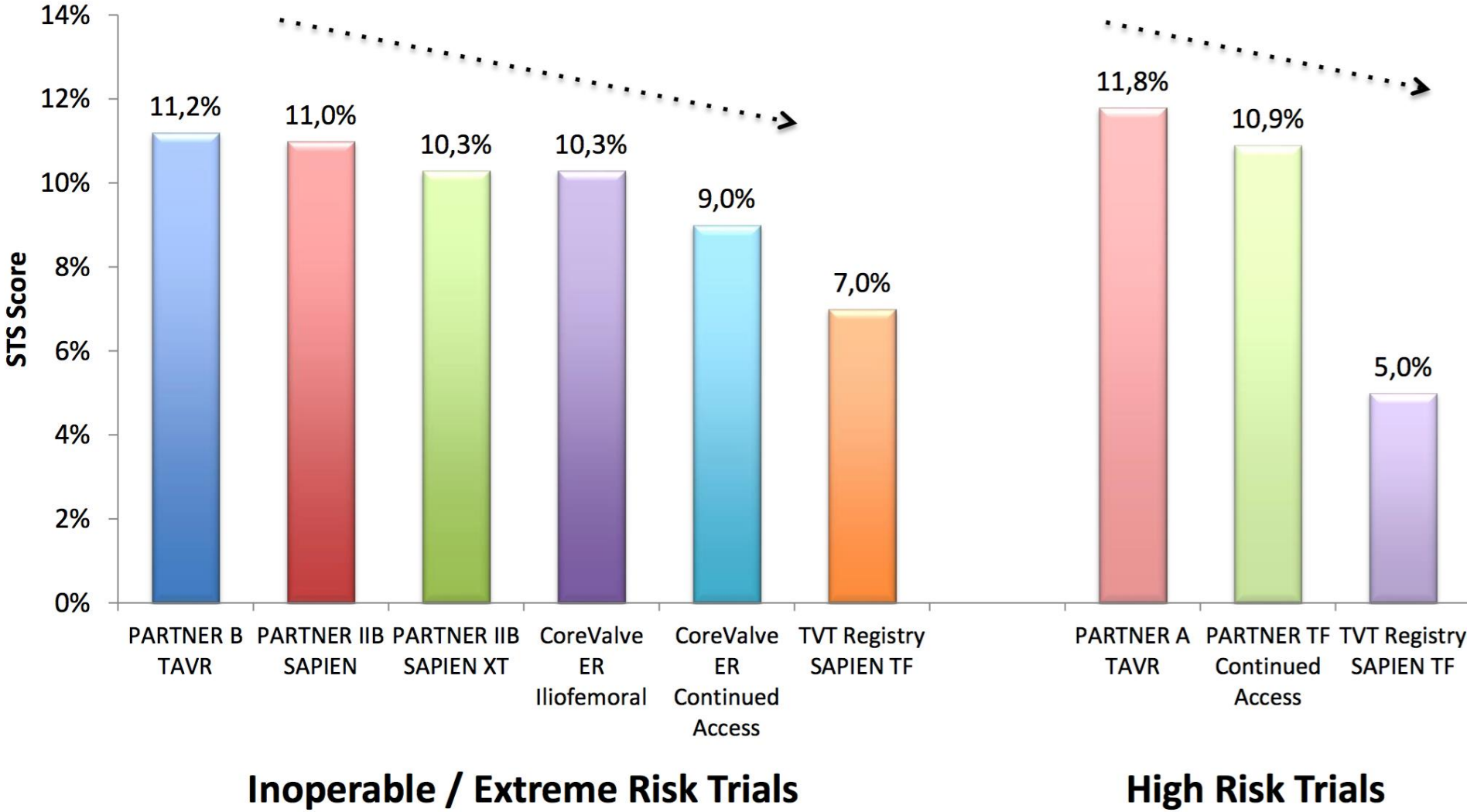
[1] Only the data on a matched pair subset of the Observant study have been published
[2] UK TAVI registry data not published, hospital data gives total admission NOT post-procedural LoS

Evolution of Indications
Intermediate Risk



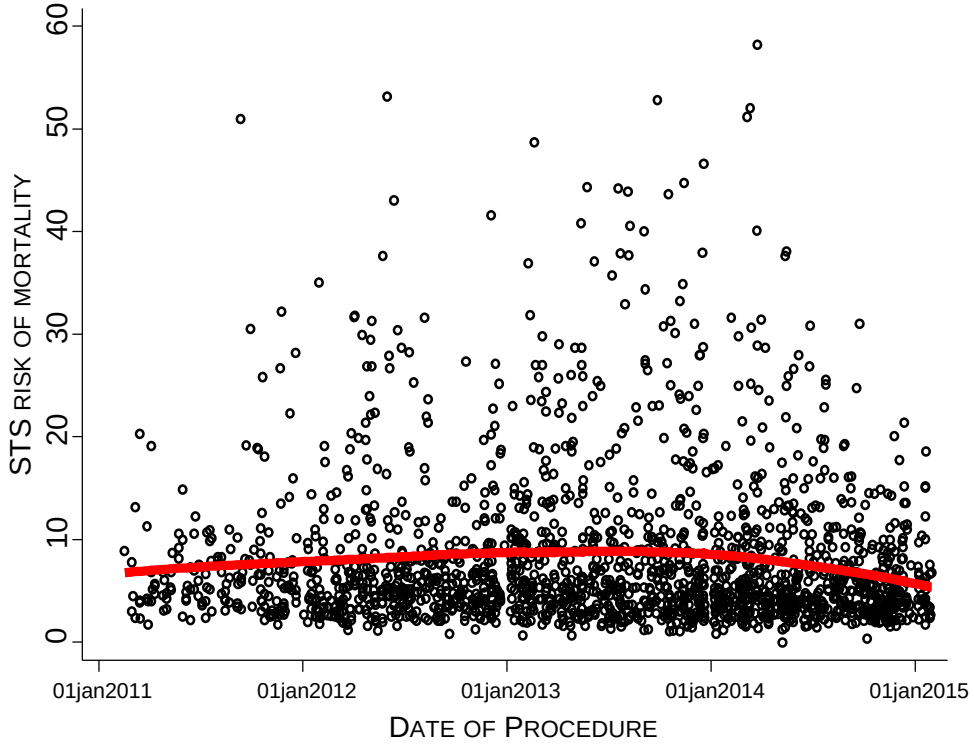
Risk classification

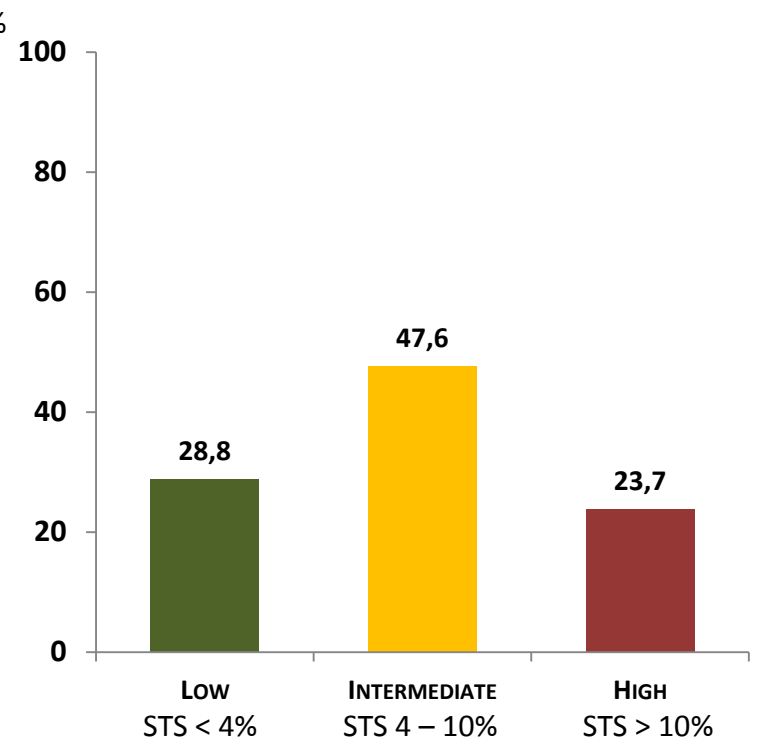
"Moving target"



Risk Distribution Among TAVI Patients
Nationwide SWISS TAVI Registry

Inclusion Period
February 1st 2011 – January 31st 2015
2158 patients at 14 Centers





Outcomes in lower risk

Clinical evidence suggests that patients in better condition at baseline have a better post-TAVI course than their sicker, comorbid counterparts.[1,2]

	Bern[1]		Munich[2]	
	Lower Risk (n=254)	Higher Risk (n=94)	Lower Risk (n=105)	Higher Risk (n=105)
STS (%)	5.1 ± 1.4	13.3 ± 7.1	4.8 ± 2.6	7.13 ± 5.4
Log EuroSCORE (%)	22.1 ± 11.9	35.1 ± 15.7	17.8 ± 12.0	25.44 ± 16.0
30 Day Mortality (%)	3.9	14.9	3.8	11.4
Total Vascular Complications (%)	17.7	20.3	14.7	28.6
Stroke / TIA (%)	5.0	3.4	1	6.7

[1]Wenaweser, et al., *Eur Heart J* 2013; 34: 1894-905; [2]Lange, et al., *J Am Coll Cardiol* 2012; 59: 280-7

Large Studies Proving Benefit

PARTNER II SAPIEN 3i Trial
~1,000 Patients

57 US & Canadian Participating Sites

SECOND GENERATION VALVES

Optimal TAVI device in 2014

✓ User friendly

↓ French size (14F)

✓ Precise positioning

✓ R^3

↓ gradients

⊘ paravalvular leak

↓ conduction abnormalities

Valve Durability

Overview: SJM Portico 23 and 25 mm Valve

General

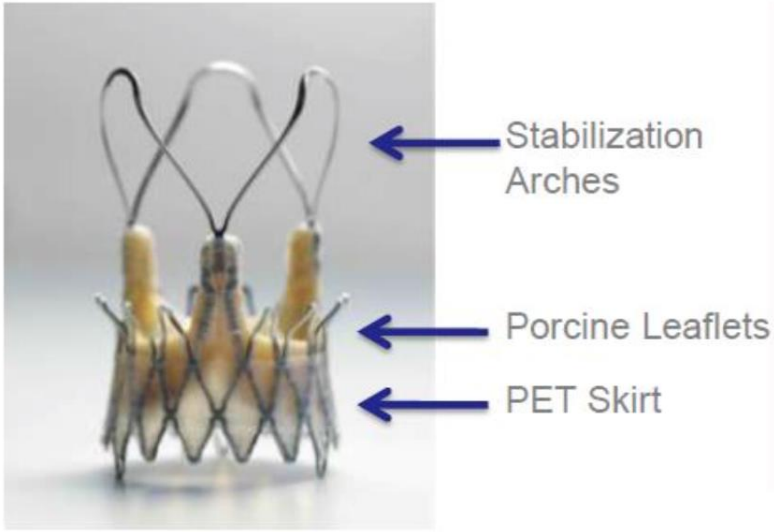
- 18F (TF) Nitinol self expanding valve designed to be:
  - Fully re-sheathable*
  - Repositionable* (antegrade and retrograde) at the implant site
  - Retrieveable*
- Bovine and porcine pericardial valve with Linx™ anti-calcification technology**
- For annulus range: 19 – 23 mm
- Cuff tissue and stent geometry designed to minimize PV leak

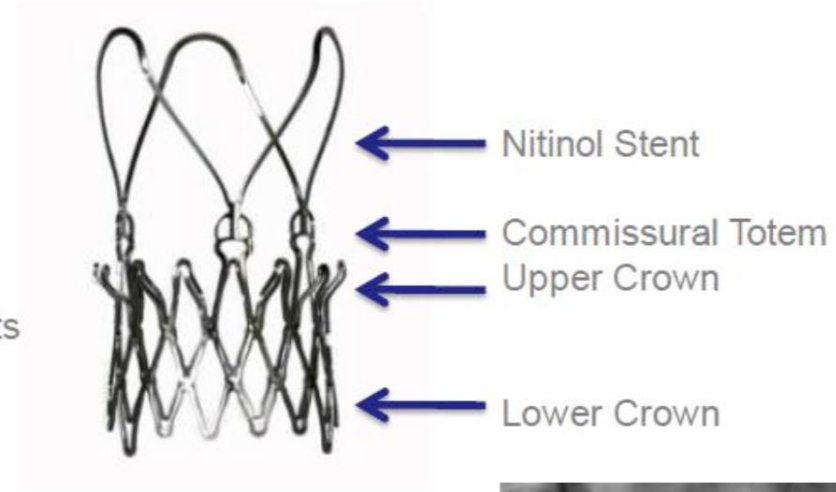
* Until fully deployed

** There is no clinical data currently available that evaluates the long-term impact of anti-calcification tissue treatment in humans.

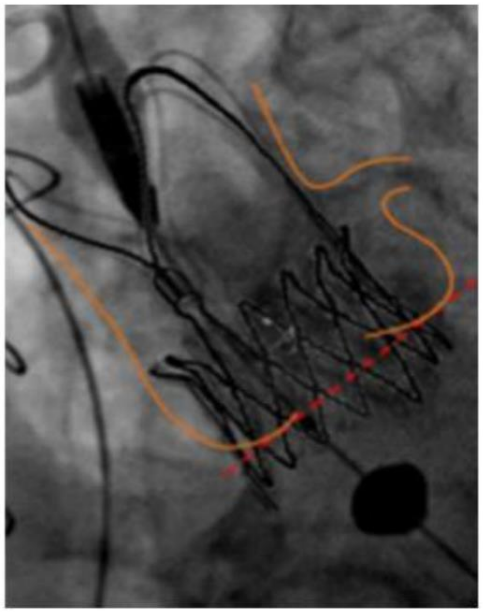
G Manoharan, Royal Victoria, Belfast

Symetis Acurate TA System



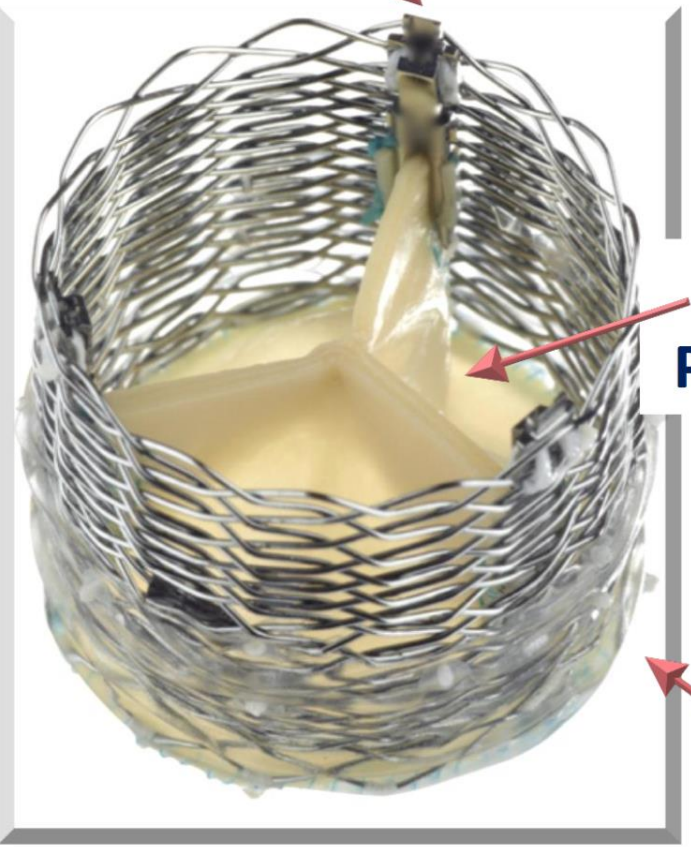


- Treats native annuli from 21mm to 27mm
- Repositionable, self-aligning
- Composed of:
  - Biologic porcine tissue valve for long term durability
  - Self-expandable nitinol stent = form fit
  - PET skirt for ↓ PV leak (inner and outer)

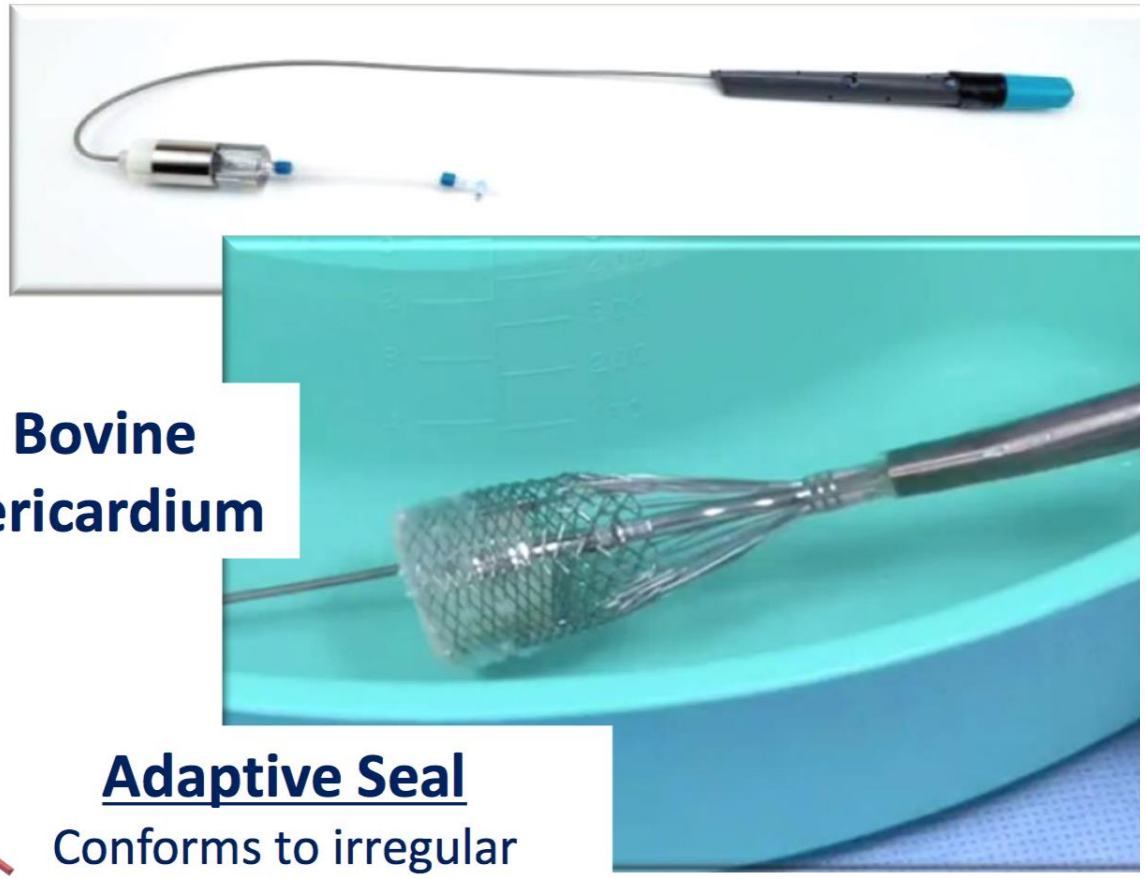


The Lotus™ Valve System
Preloaded Delivery System

Locking Mechanism



Bovine Pericardium

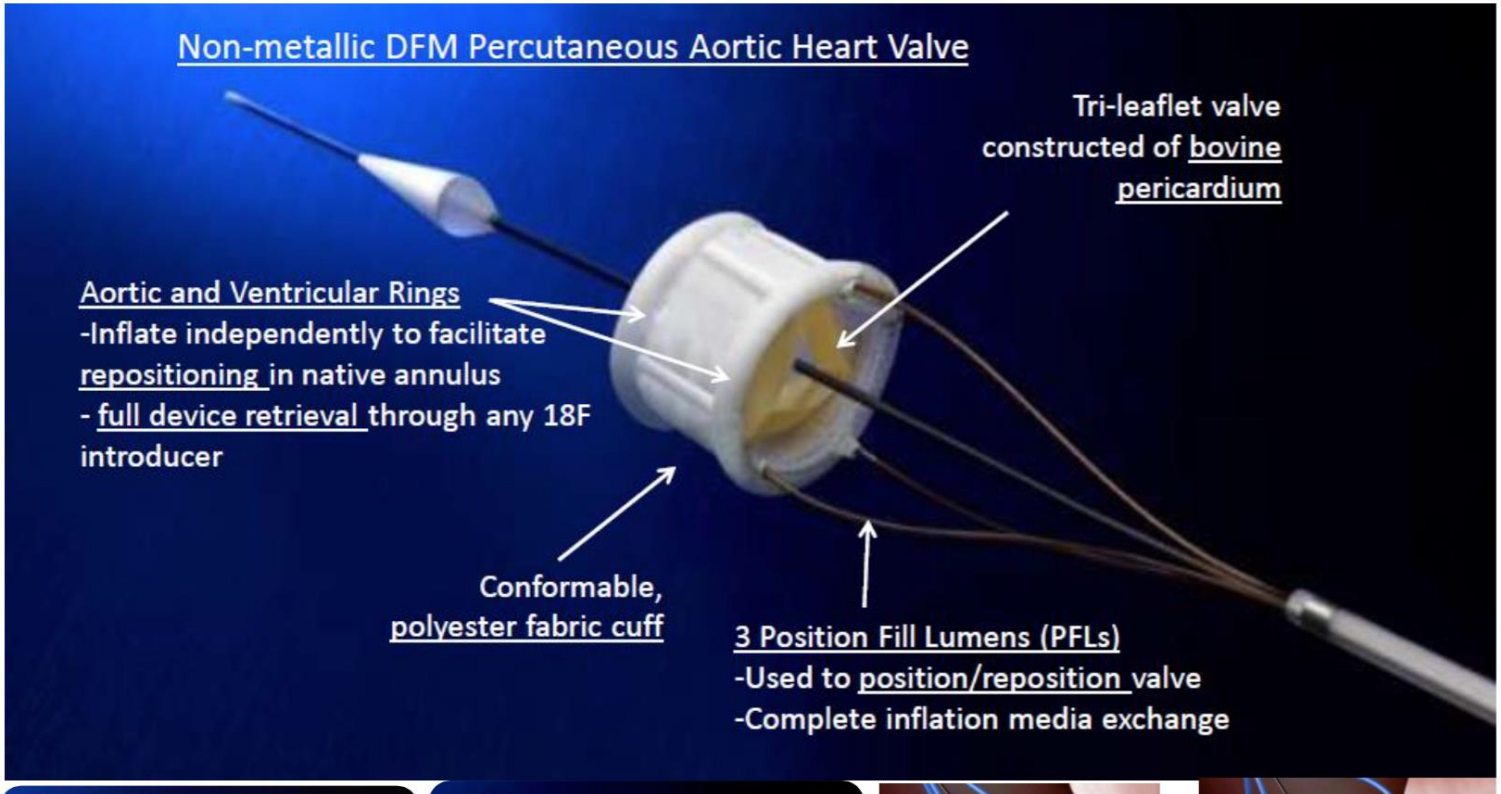


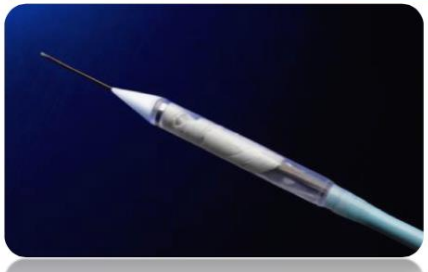
Adaptive Seal

Conforms to irregular anatomical surfaces and minimizes paravalvular leak

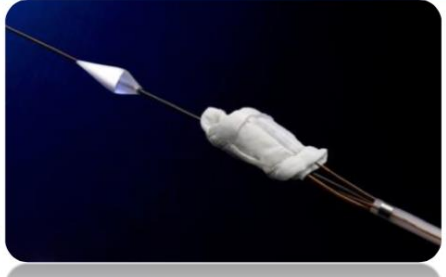
G Manoharan, Royal Victoria, Belfast

Direct Flow Medical Valve

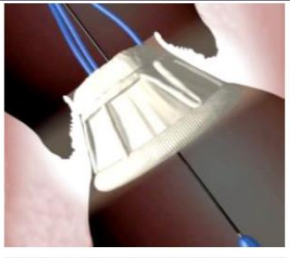




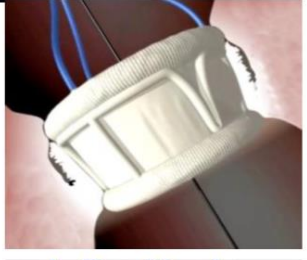
1.Valve loaded in the Delivery System



2. Valve unsheathed in the ventricle



3.Aortic Ring deflated during initial positioning



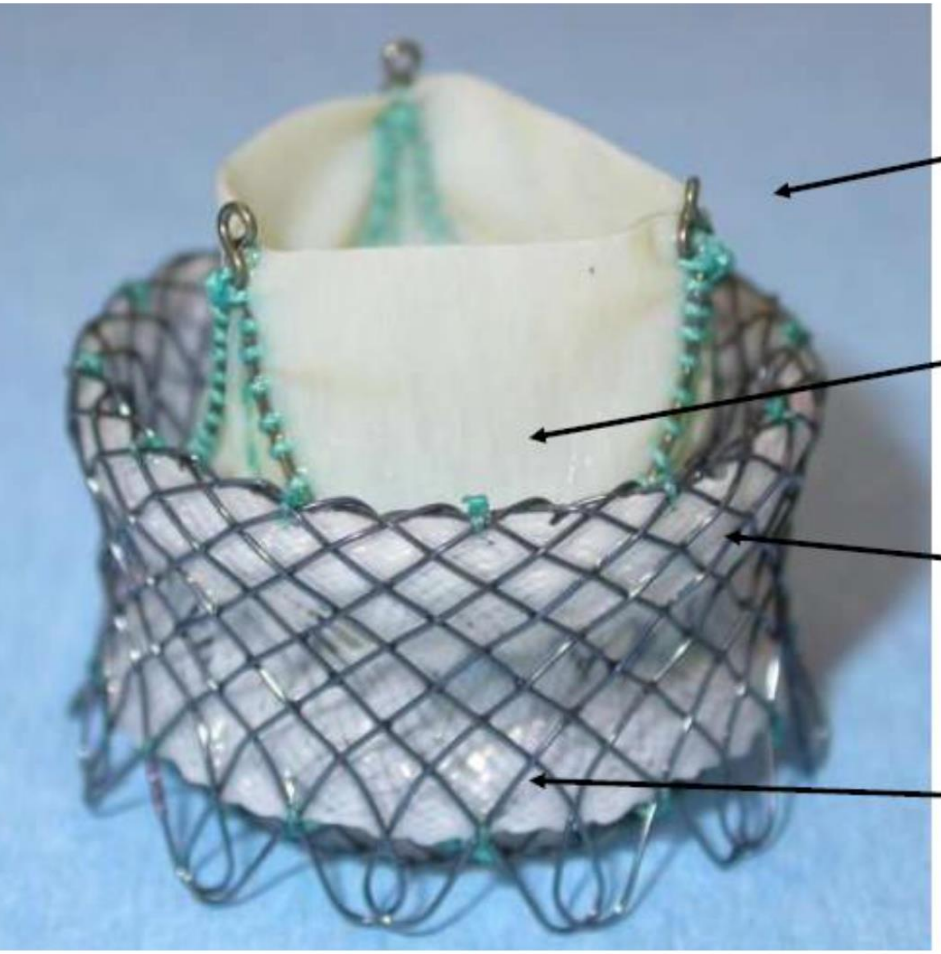
4. Positioning complete and Valve fully expanded

G Manoharan, Royal Victoria, Belfast

New Devices for Valvular Disease

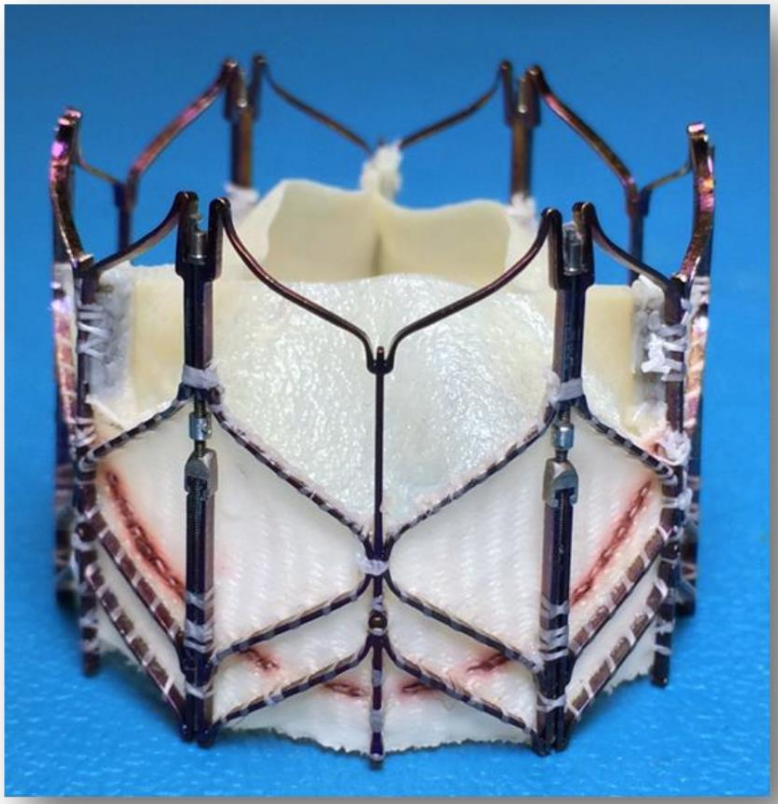
- Not all of these might work as intended..

Heart Leaflet Technology



G Manoharan, Royal Victoria, Belfast

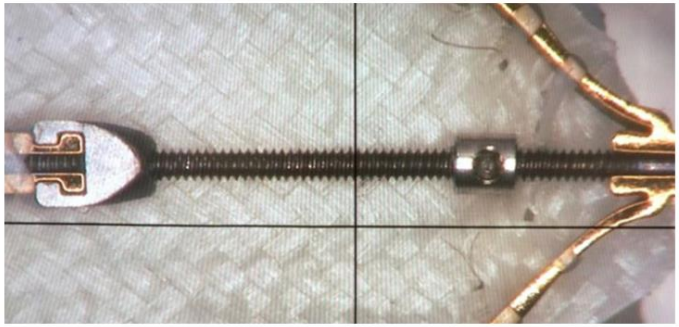
Syntheon Cardiology
Precision Actuated Framework

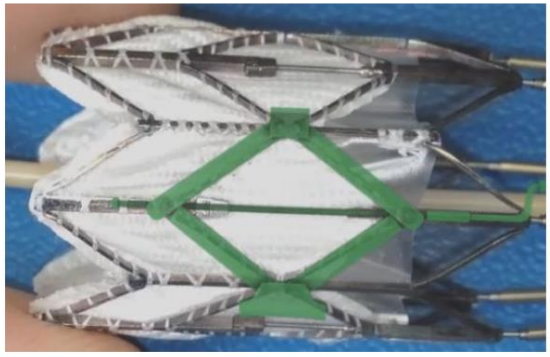


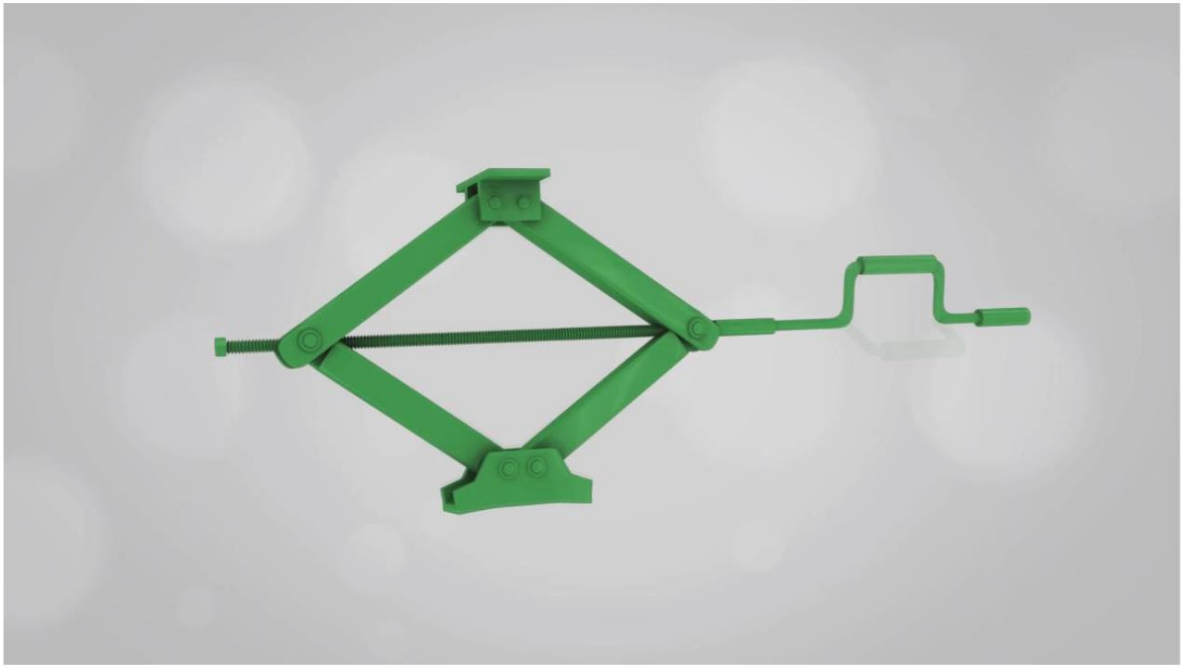
- Actuator Driven Expansion
- Microprocessor Controlled
- Constant Radial Force
- Fully Repositionable
- Fully Retrievable
- Full Verification of Valve Position and Seal Quality
- Simple Controls with Feedback

Syntheon Cardiology TAVR

- Nitinol Framework
- Micro Screw Actuators
- High Mechanical Advantage
- Exact and Reversible Control
- Continuous Feedback of Diameter and Radial Force
- Accurate Diameter Measurement
- Self-locking Screws Hold Position

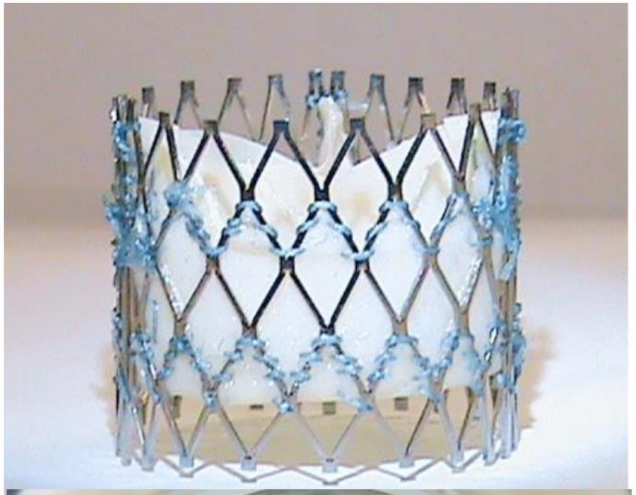


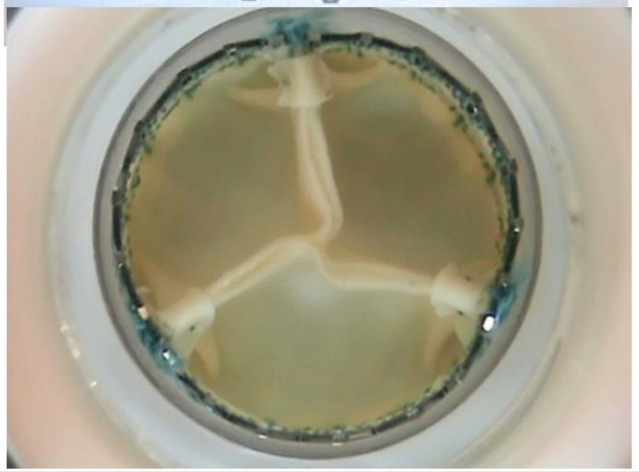




The Optimum Valve

- Single bovine pericardial cut-out used for all three leaflets
- The valve has commissure posts
  - Provides proper opening
  - Provides proper coaptation surface
- Valve design minimizes sutures
  - Total sutures – 274
  - No suture holes in moving leaflets (similar to surgical valves)
- 25mm OD Nitinol frame
  - Designed for up to 23mm annulus
  - Designed for stronger radial force
  - 19mm height





JenaValve Transfemoral TAVI System

- 18F delivery system TF
- Porcine pericardial valve
- Nitinol self-expanding stent
- Controlled 3 step valve deployment
- Anatomically correct positioning
- Leaflet “clipping” mechanism
- Available in 3 sizes: 23, 25 and 27
- Annuli coverage from 21mm to 27mm

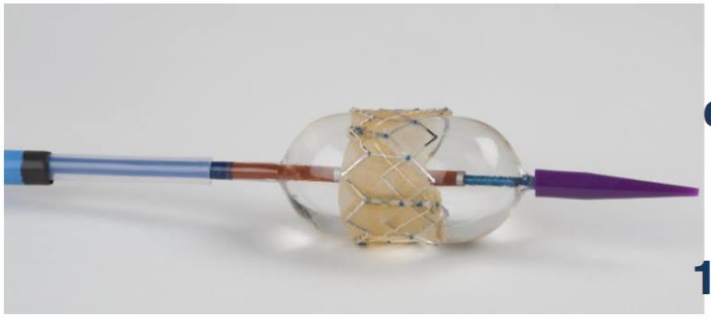
The Valve Medical System

Frame Module → ***Assembled Device*** ← **Valve Module**

1. Nitinol self-expanding frame module inserted in optimal annular location
2. Valve module is reconstituted in ascending Ao
3. Valve module is docked to frame
4. 12F delivery system

Colibri Heart Valve System

Colibri Valve
(21, 24 & 27 mm)

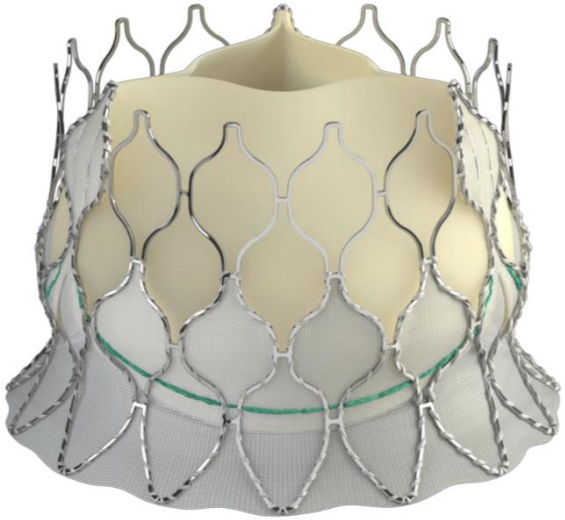


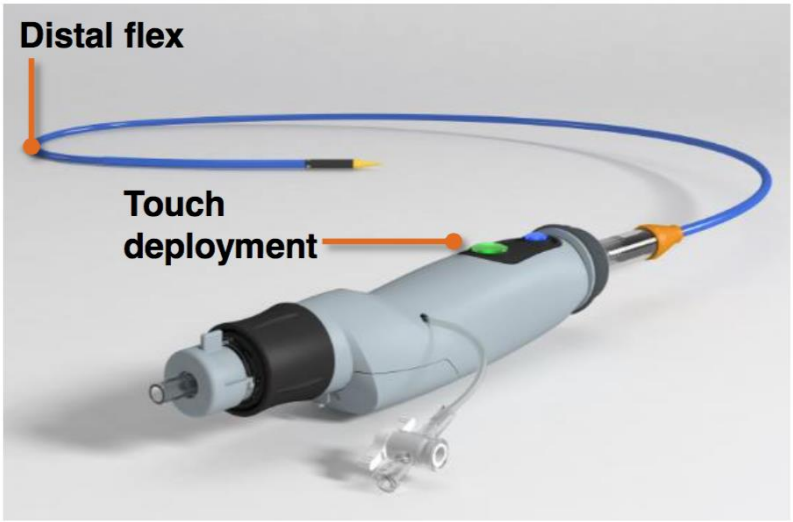
Balloon expandable delivery system in 14 Fr Sheath

- Pre-packaged, low profile, Ready-for-Use TAVI System
- Dry technology: Makes tissue thin, strong, durable
  - 70% reduction of mass compared to a « wet » membrane
- Positive preliminary FIH experience out to 15 months
- CE mark trial planned in 2014

Edwards CENTERA self expanding device

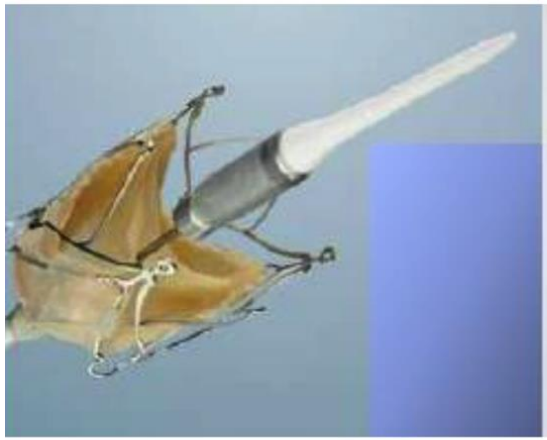
- Self-expanding Nitinol frame
- Treated bovine pericardium
- Contoured frame designed for optimal seating and sealing in the annulus
- Low frame height designed to minimize conduction disturbances
- Repositionable
- 23 mm, 26 mm, 29mm sizes

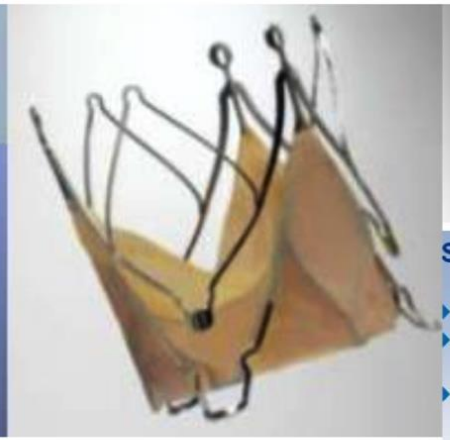


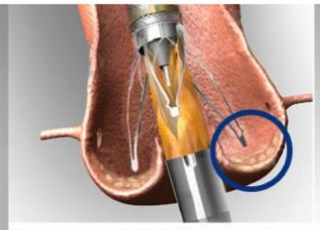


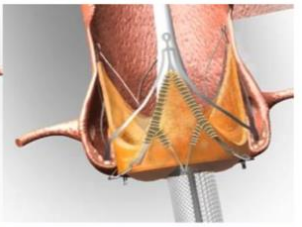
G Manoharan, Royal Victoria, Belfast

Jena Valve (TA)









Step 1 Position

- Feeler guided
- Implantation height defined by native valve
- Commissural alignment and anatomically alignment

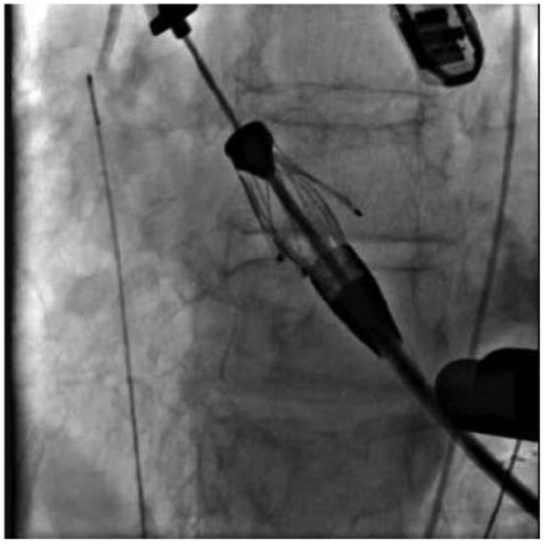
Step 2 Clip

- Fixates itself on the native valve cusp
- Works for calcified and uncalcified aortic valve pathology

Step 3 Release

- Low profile stent design
- Unobstructed coronary ostia

- **Self-expanding Nitinol stent**
- **Size: 23, 25 and 27mm**
- **Feeler guided, commissural and anatomical alignment**
- **Valve active fixation to native leaflet**



The Trinity TA System

- Transapical aortic valve system
- Self-expanding Nitinol frame
- Bovine pericardial valve leaflets
- Sealing of the lower crown
- Detachable catheter tip with pre-mounted valve
- Repositionable and retrievable
- Zero pressure crimping

Detachable tip with pre-mounted **TRINITY** valve prosthesis

Catheter (w/o tip)

Engager™ Design

- Self-expanding nitinol + polyester skirt to conform and seal
- Supra annular valve function
- Bovine pericardial tissue

Design Goals:

- Precise Valve Positioning: Control arms provide tactile feedback and stabilize bioprosthesis during deployment
- Minimal Paravalvular Leak: Control arms capture the native leaflets and the self-expanding frame conforms to the annulus

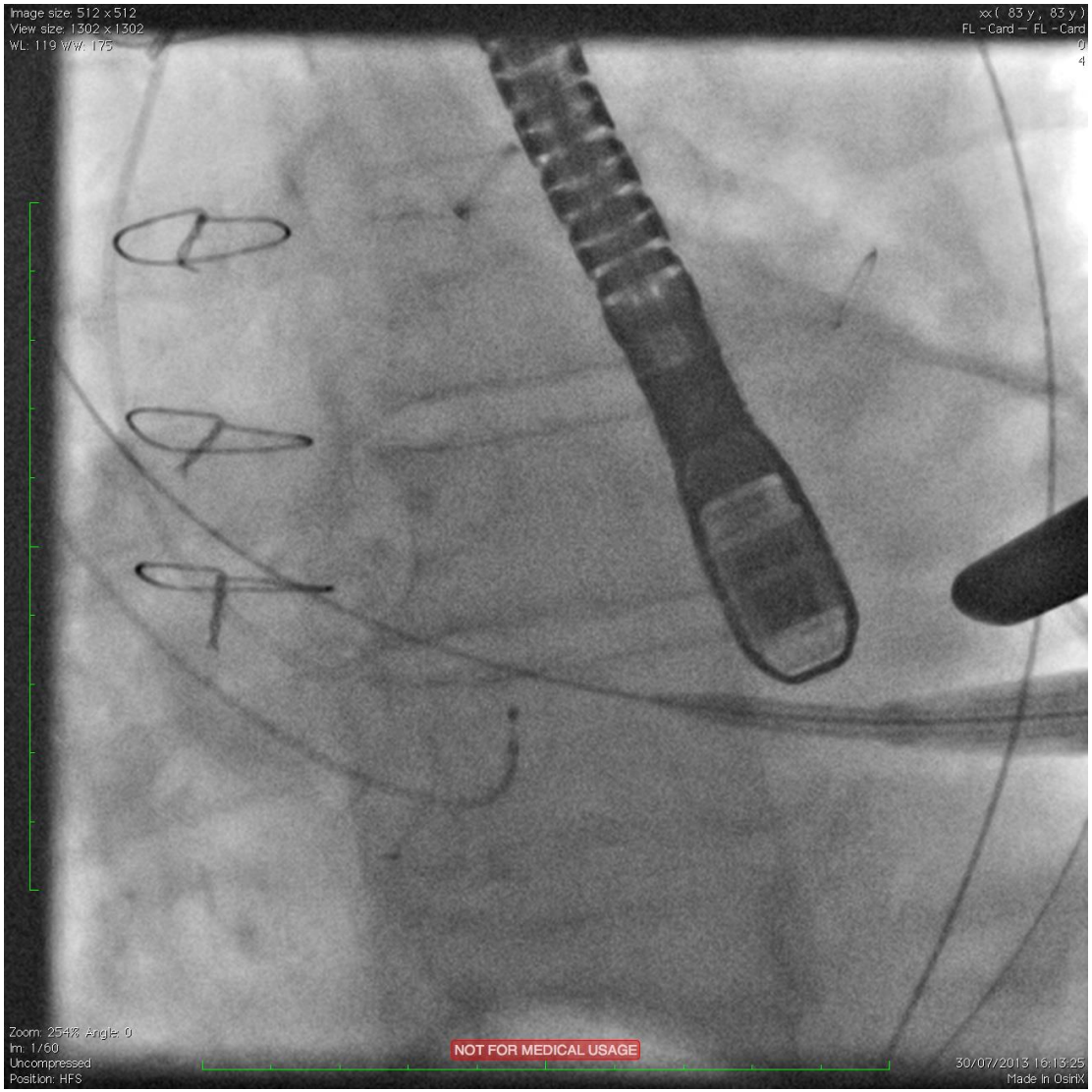


Image size: 512 x 512
View size: 1302 x 1302
WL: 119 WW: 175
xx (83 y , 83 y)
FL - Card — FL - Card
0
4
Zoom: 254% Angle: 0
Im: 1/60
Uncompressed
Position: HFS
NOT FOR MEDICAL USAGE
30/07/2013 16:13:25
Made in OsiriX

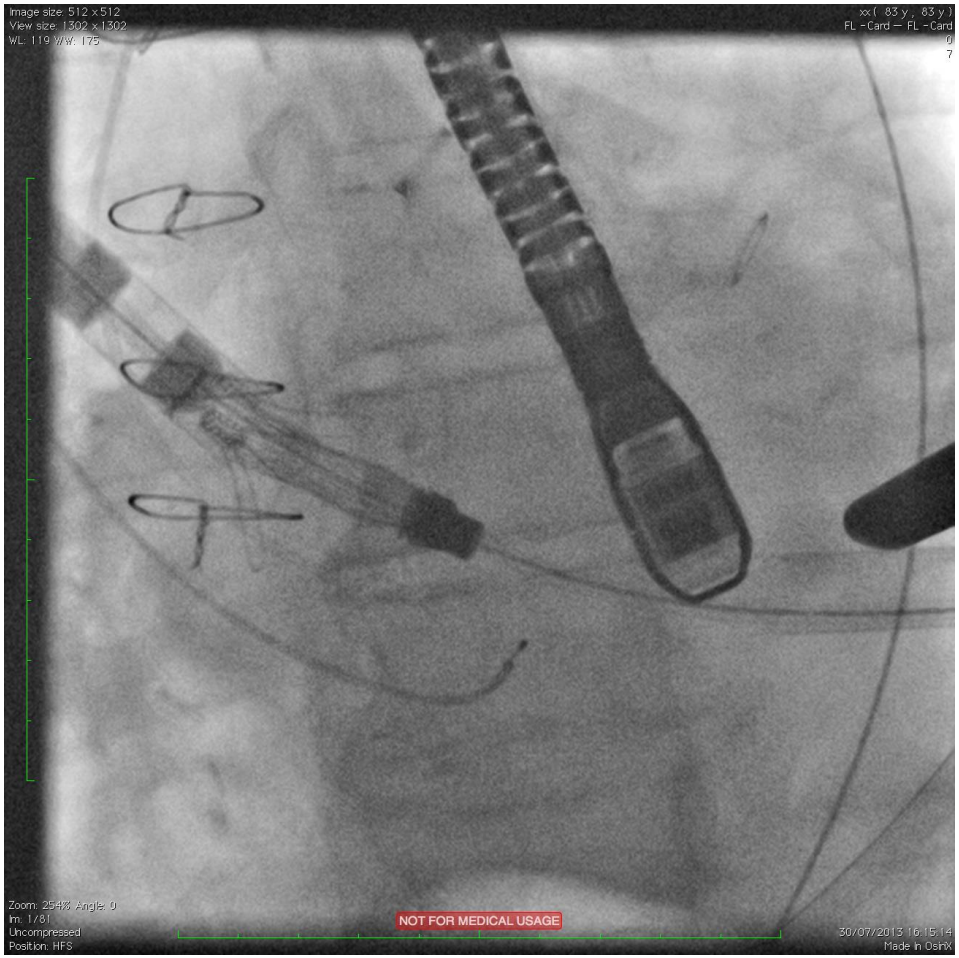


Image size: 512 x 512
View size: 1302 x 1302
WL: 119 WW: 175
xx(83 y , 83 y)
FL - Card — FL - Card
0
7
Zoom: 254% Angle: 0
Im: 1/81
Uncompressed
Position: HFS
NOT FOR MEDICAL USAGE
30/07/2013 16:15:14
Made in OsiriX

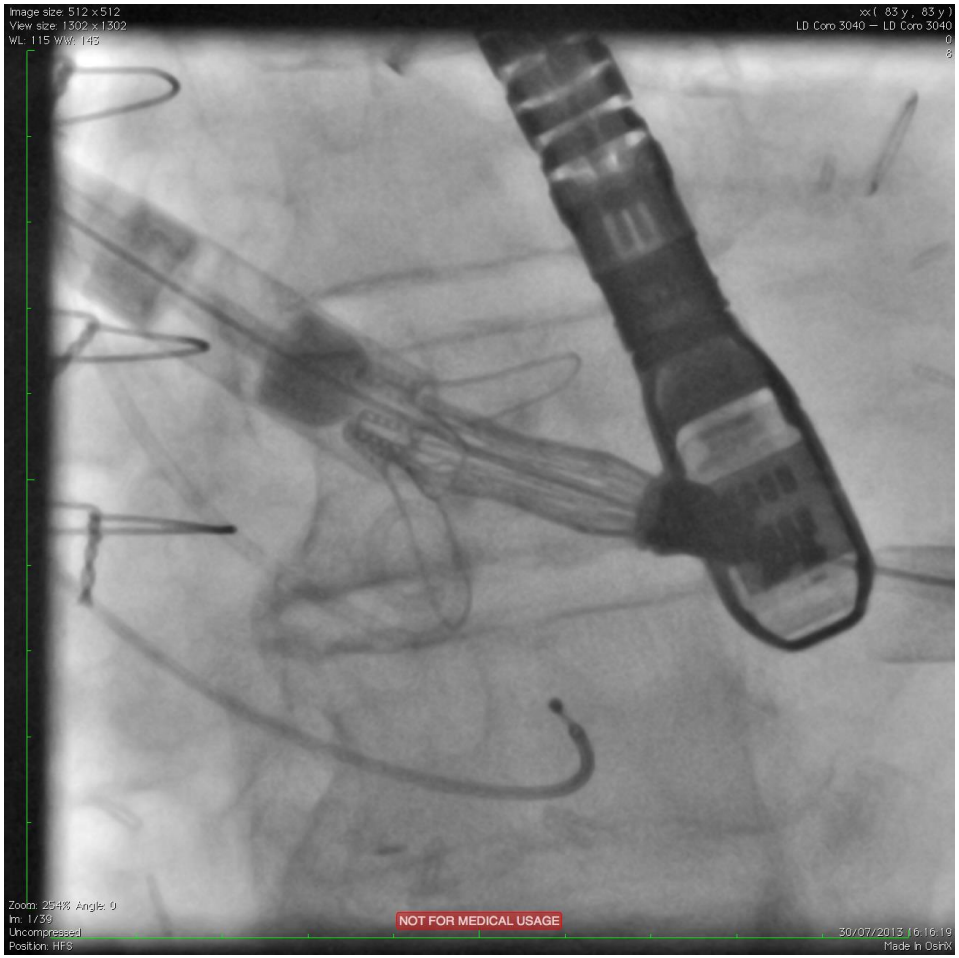


Image size: 512 x 512
View size: 1302 x 1302
WL: 115 WW: 143
xx(83 y, 83 y)
LD Coro 3040 — LD Coro 3040
0
8
Zoom: 254% Angle: 0
Im: 1/39
Uncompressed
Position: HFS
NOT FOR MEDICAL USAGE
30/07/2013 16:16:19
Made in OsiriX

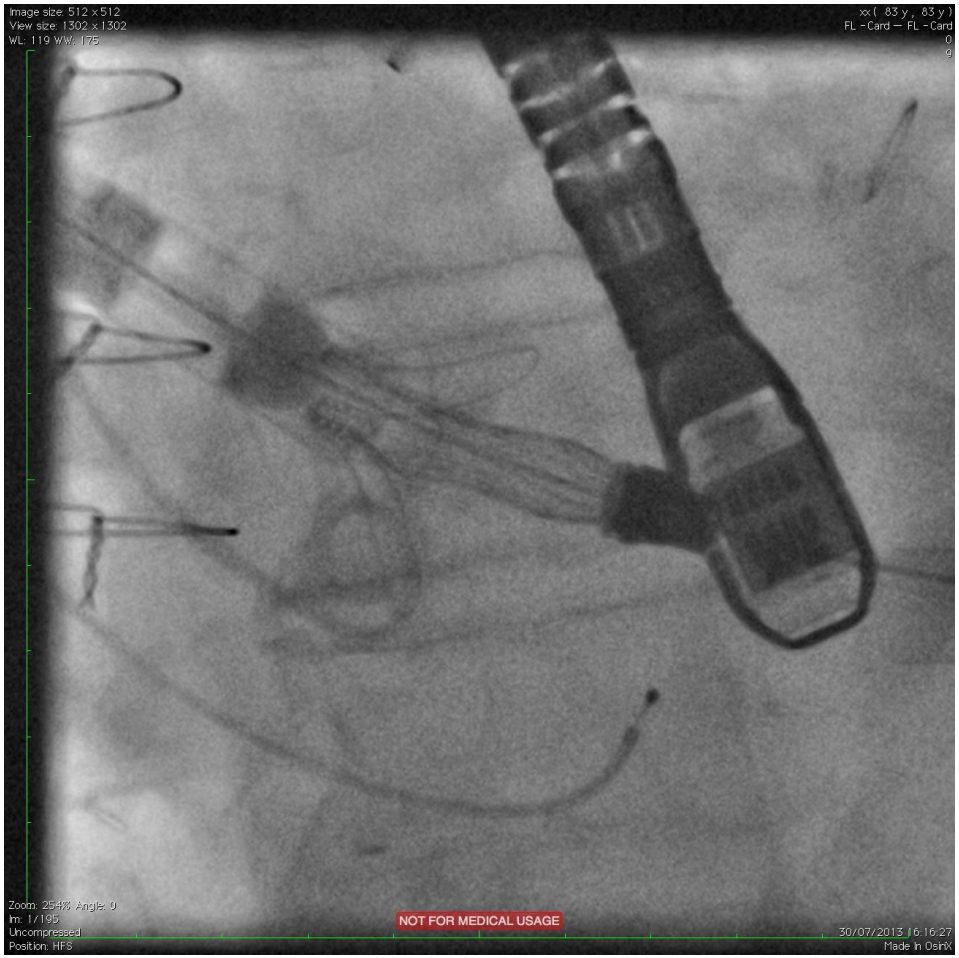


Image size: 512 x 512
View size: 1302 x 1302
WL: 119 WW: 175
xx (83 y , 83 y)
FL - Card — FL - Card
0
0
Zoom: 254% Angle: 0
Im: 1/195
Uncompressed
Position: HFS
NOT FOR MEDICAL USAGE
30/07/2013 16:16:27
Made in OsiriX

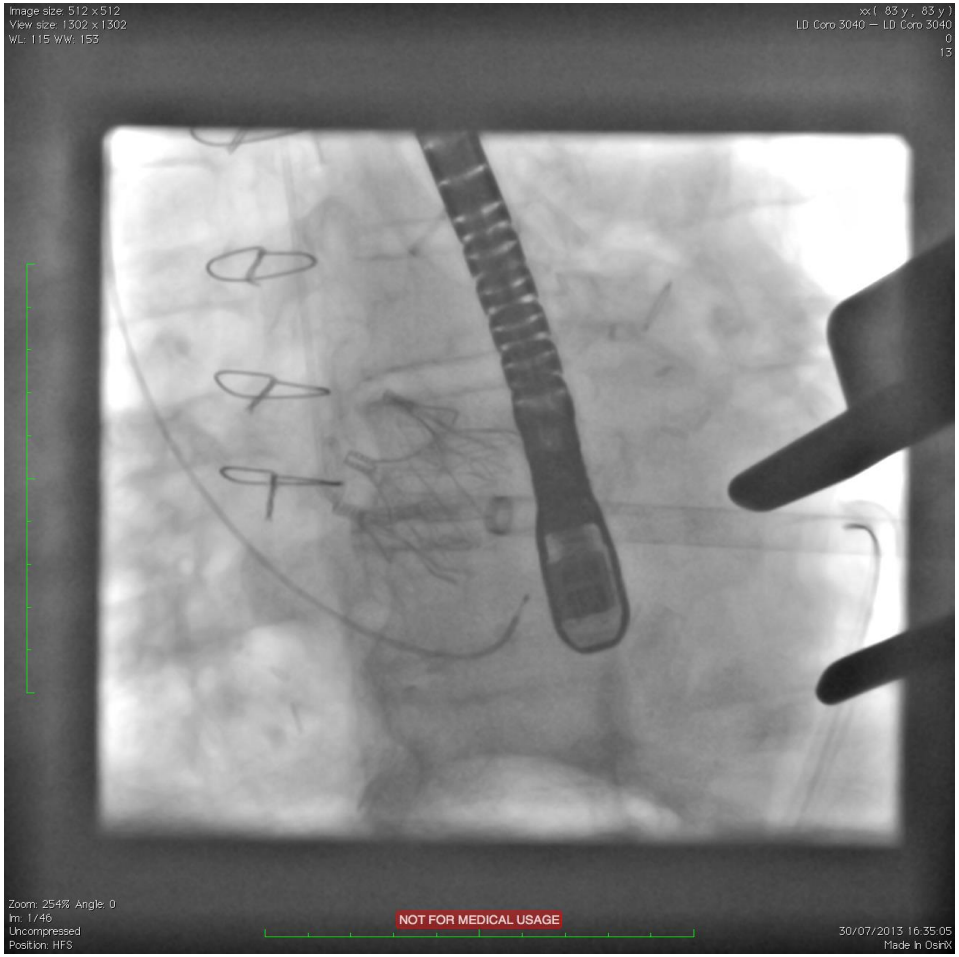


Image size: 512 x 512
View size: 1302 x 1302
WL: 115 WW: 153
xx (83 y , 83 y)
LD Coro 3040 — LD Coro 3040
0
13
Zoom: 254% Angle: 0
Im: 1/46
Uncompressed
Position: HFS
NOT FOR MEDICAL USAGE
30/07/2013 16:35:05
Made in OsiriX

Overview when compared to 1st Generation (30D)

	Portico	Direct Flow	Lotus	Sapien 3 (TF)	CoreValve (Advance Registry)	CoreValve (Extreme Risk, IDE)	CoreValve (High risk, IDE)	Sapien (Partner)	Sapien (Partner 2 inop.)
Death	3.6%	1.3%	1.7%	2.1%	4.5%	7.3%	3.3%	5.2%*	5.1 ; 3.5%
Stroke (Disabling)	2.4%	4%	3.4%	0%	1.2%	2.4%	3.1%	3.8%	3 ; 3.2%
New PPM	10.8%	17%	29.3%	12.5%	26.3%	22.2%	19.8%	3.8%	5.9 ; 6.4%
MI	1.2%	1.3%	1.7%	2.1%	0.2%	1.3%	NA	0%	0.7 ; 1.8%
Major Vascular Comp.	6%	2.7%	5.1%	5.2%	10.9%	8.3%	5.9%	11%	15.5 ; 9.6%
Disabling bleeding	2.4%	2.7%	8.5%	2.1%	4%	11.7%	13.6%	9.3%	12.6 ; 7.8%
Mean Gradient post TAVI	8.7	14.4	11.3	10.9	9.3	8.5	8.8%	10	10.4 ; 10
PVL (Mod/sev)	5%	2%	1.9%	2.6%	13%	11.5%	9%	12%	16.9 ; 24.2%

- Actually treated patients
- Partner2: Sapien vs XT

G Manoharan, Royal Victoria, Belfast

TAVI Summary

- 2 Systems established the technology
- Careful device iterations lead to increasing
  - Feasibility
  - Predictability of Success
  - Reduced Complications
  - Expansion of the indication
- TAVI will become the procedure of choice for treatment of AS

Outlook to the future . . .

TAV will no longer be done for patients who are bad candidates for surgery
TAVI will be done for patients who are good candidates for TAVI

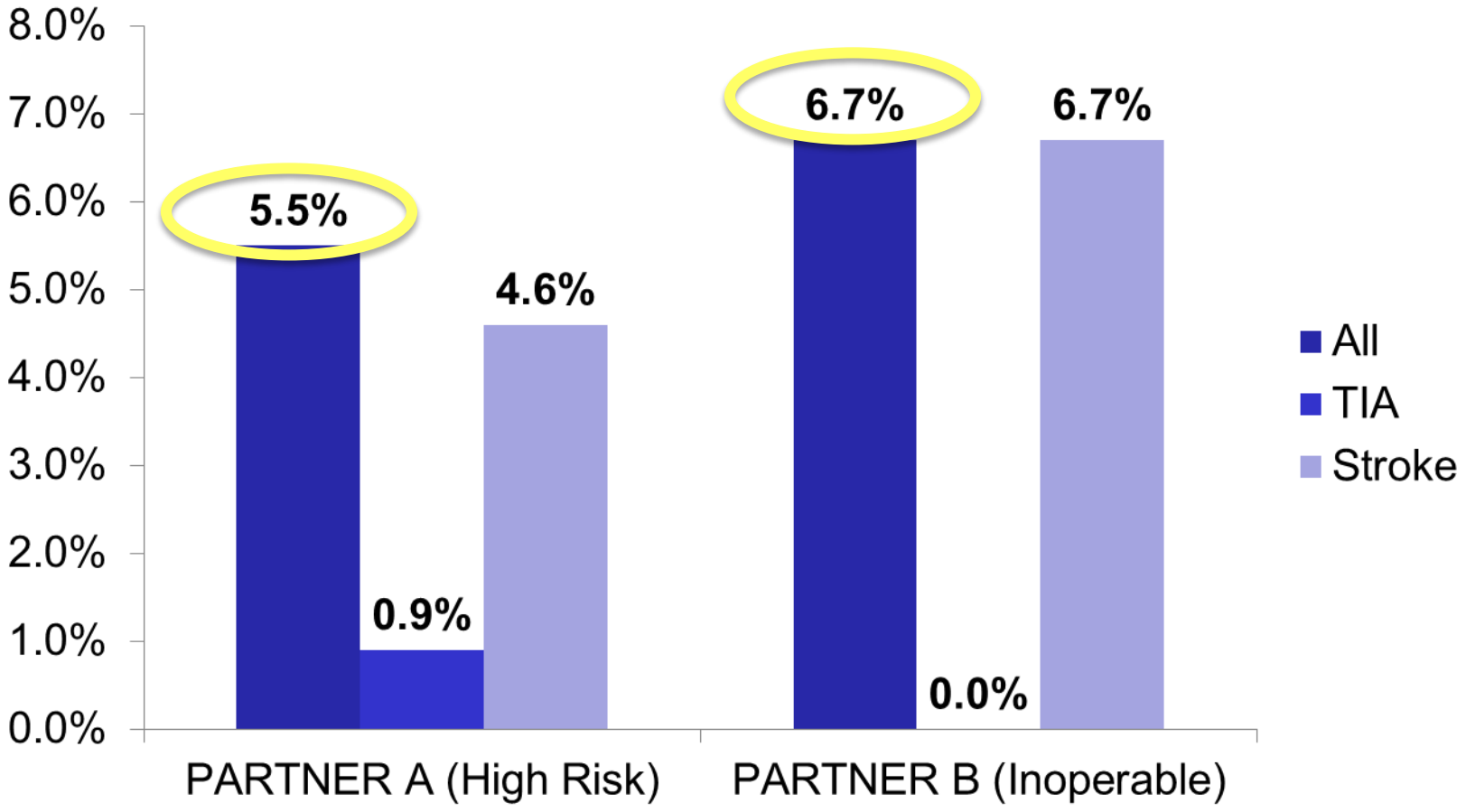
Surgery will be reserved for selected patients who are contraindicated for TAVI

STROKE

EMBOLIC PROTECTION DEVICES

Clinical Manifestations

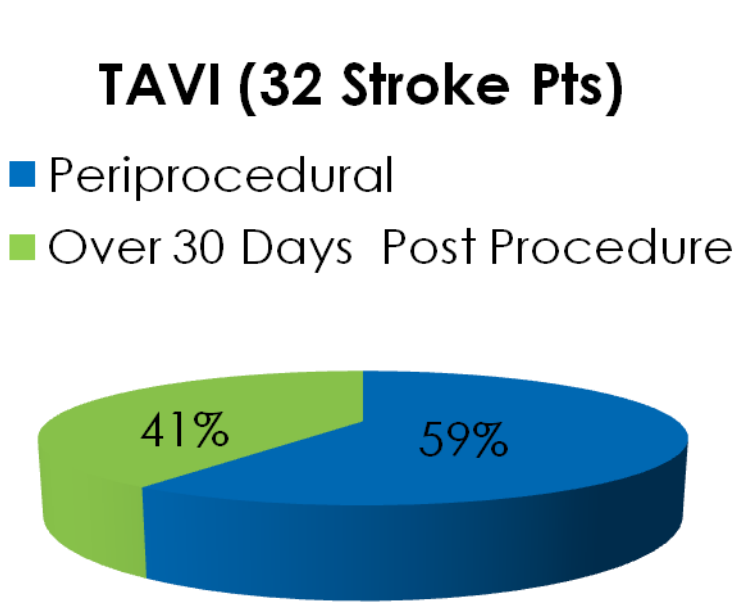
Acute Manifestations: PARTNER A and B (30-Day Events)

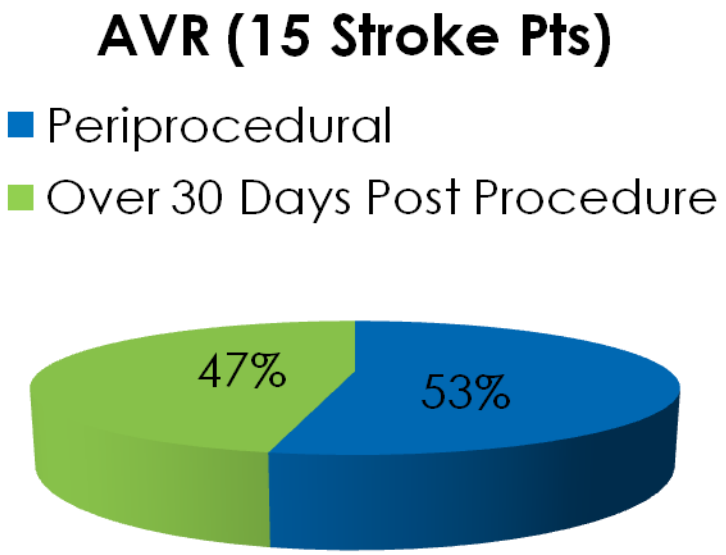


Smith et al. N Engl J Med 2011;364:2187-98. Leon et al. N Engl J Med 2010;363:1597-1607.

Timing of Neurological Events

PARTNER (Cohort A)





FRANCE 2

- N 3191 pts undergoing TAVI
- 3.98% reported CVE
  - 55% major strokes
  - 14.5% minor strokes
  - 30.5 % TIA
- Predictors: advanced age, multiple valves

Tchetche et al. J Am Coll Cardiol Intv 2014;7: epub ahead of print

FRANCE 2: Timing of CVE

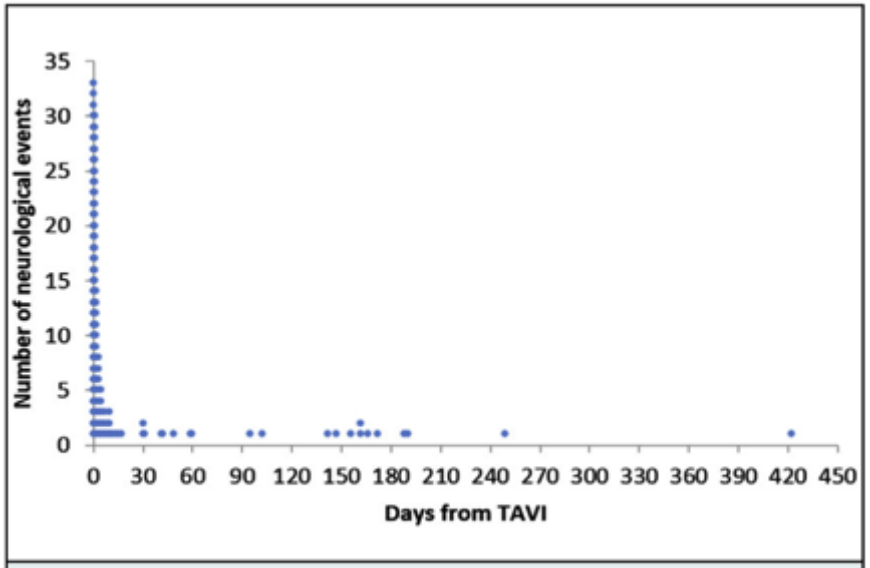


FIGURE 1 Timing of Cerebrovascular Events

50% periprocedural
Majority of major strokes on day 1 !

Time From Date of Valve Placement (in Calendar Days)	No.	Mean	SD	Median	Range
Overall	131	22.9	59.5	2	0–422
Major stroke	72	21.3	52.8	1	0–249
Minor stroke	19	28.2	96.3	2	0–422
Transient ischemic attack	40	23.1	48.8	2	0–188

Tchetche et al. J Am Coll Cardiol Intv 2014;7: epub ahead of print

Reporting Stroke: What if we ask Neurologists ?

Stroke After Aortic Valve Surgery: Results From a Prospective Cohort

Steven R. Messé, Michael A. Acker, Scott E. Kasner, Molly Fanning, Tania Giovannetti, Sarah J. Ratcliffe, Michel Bilello, Wilson Y. Szeto, Joseph E. Bavaria, W. Clark Hargrove, III,, Emile R. Mohler, III, and Thomas F. Floyd
for the Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators

Circulation. 2014;129:2253-2261; originally published online April 1, 2014;

- Prospective evaluation of pts undergoing surgical AVR
- Pre and post assessment and DW MRI

- Clinical strokes in hospital: 17%
- Moderate/severe: 4%
- TIA 2%
- Silent infarcts on MRI: 54%

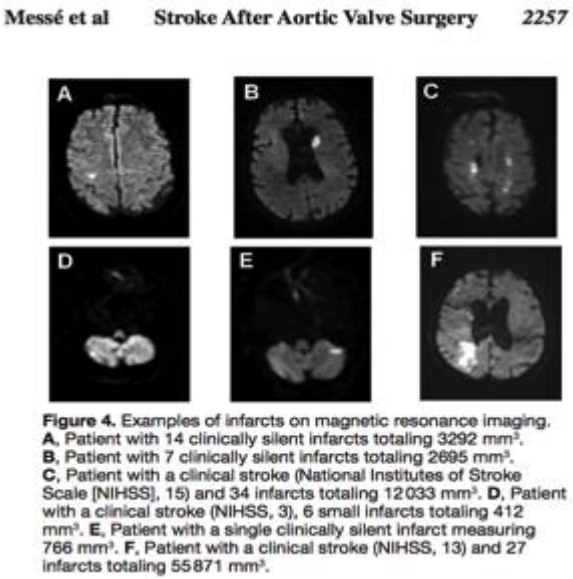
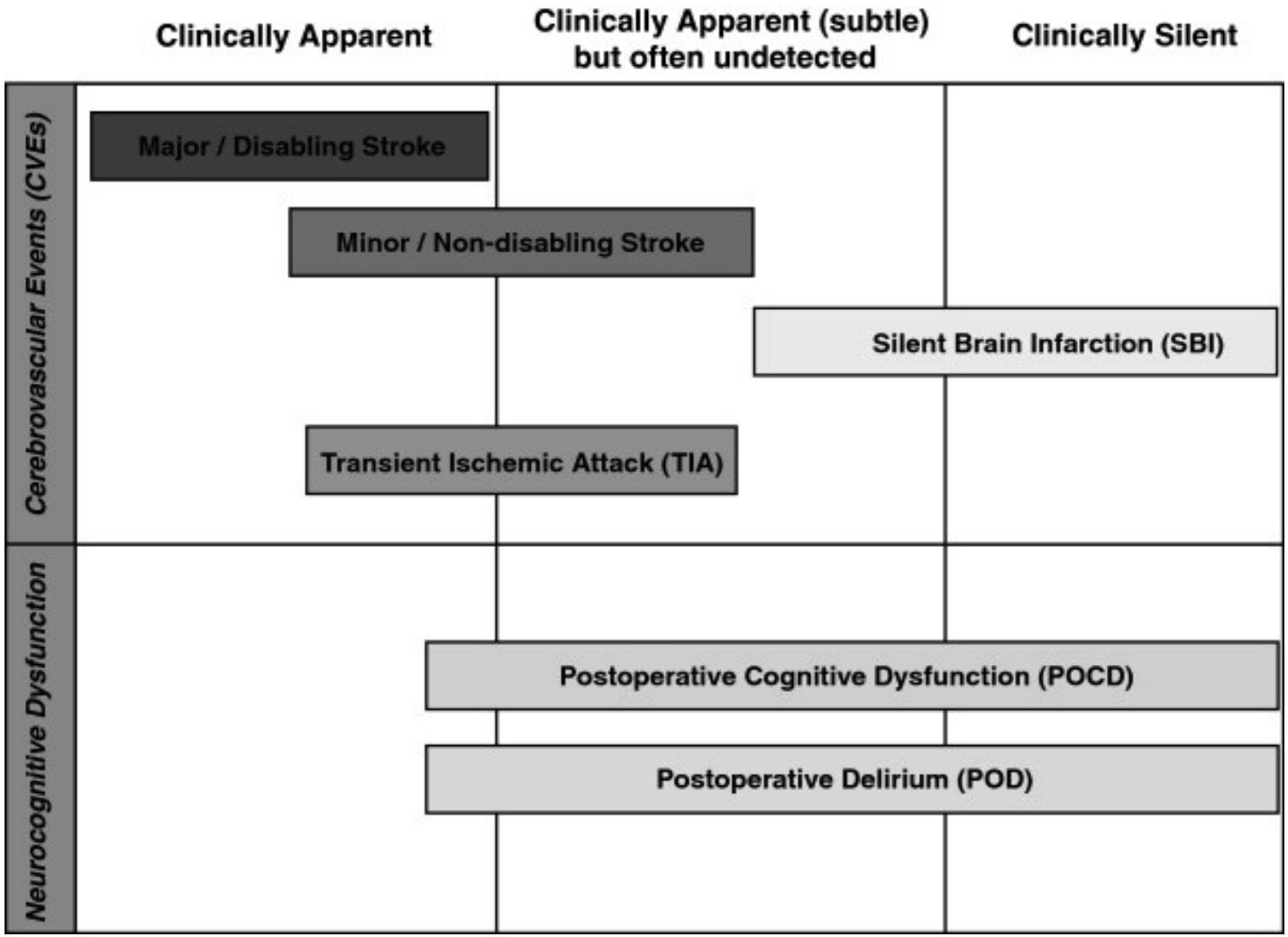


Figure 4. Examples of infarcts on magnetic resonance imaging. **A**, Patient with 14 clinically silent infarcts totaling 3292 mm³. **B**, Patient with 7 clinically silent infarcts totaling 2695 mm³. **C**, Patient with a clinical stroke (National Institutes of Stroke Scale [NIHSS], 15) and 34 infarcts totaling 12033 mm³. **D**, Patient with a clinical stroke (NIHSS, 3), 6 small infarcts totaling 412 mm³. **E**, Patient with a single clinically silent infarct measuring 766 mm³. **F**, Patient with a clinical stroke (NIHSS, 13) and 27 infarcts totaling 55871 mm³.

Stroke

- Periprocedural Stroke remains a relevant clinical problem
- Numbers are likely to be higher
  - When evaluated by neurologists
  - Outside clinical trials
  - In higher risk environment

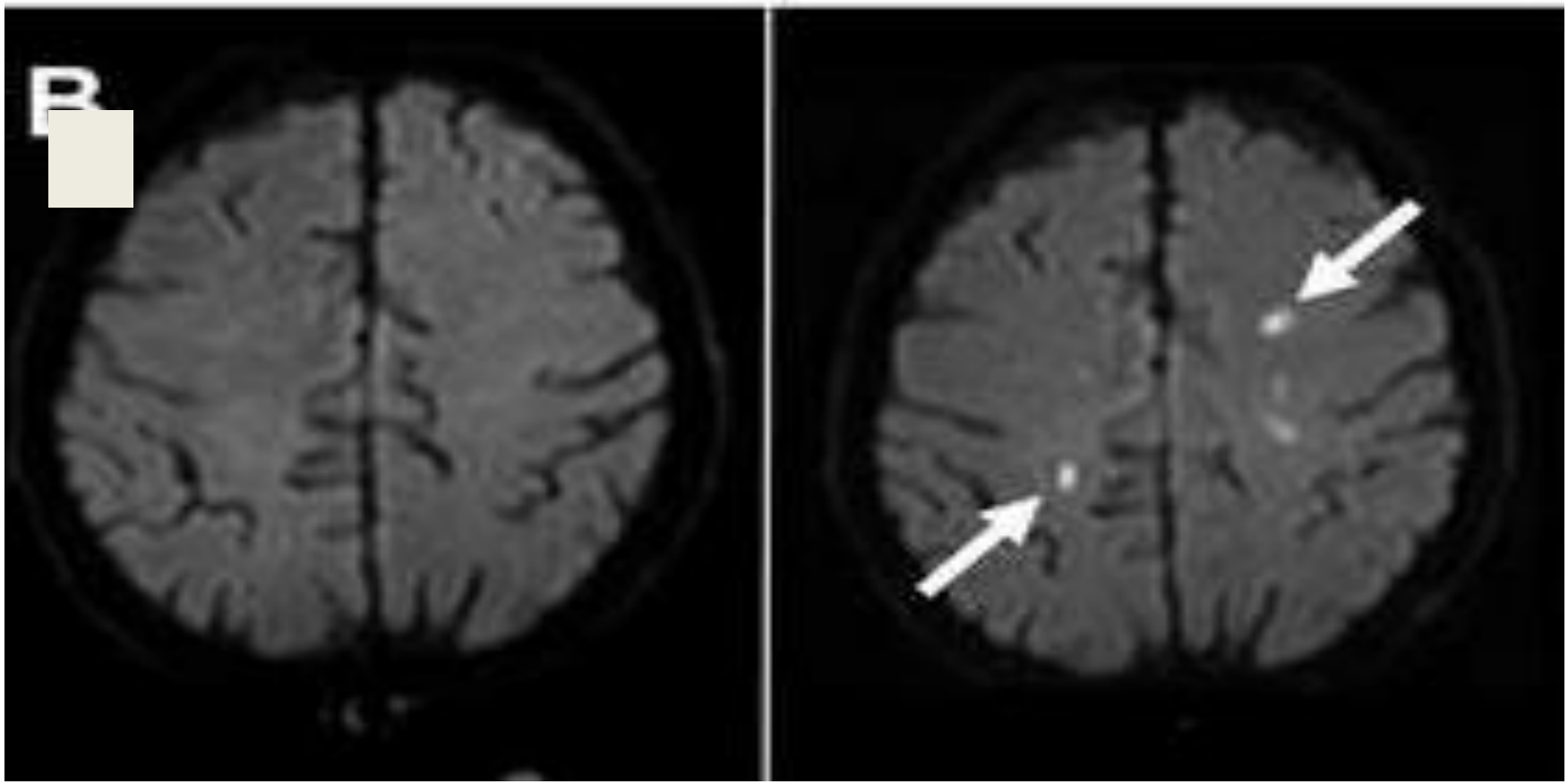
Spectrum of Cerebrovascular Events



Postoperative cognitive capacity

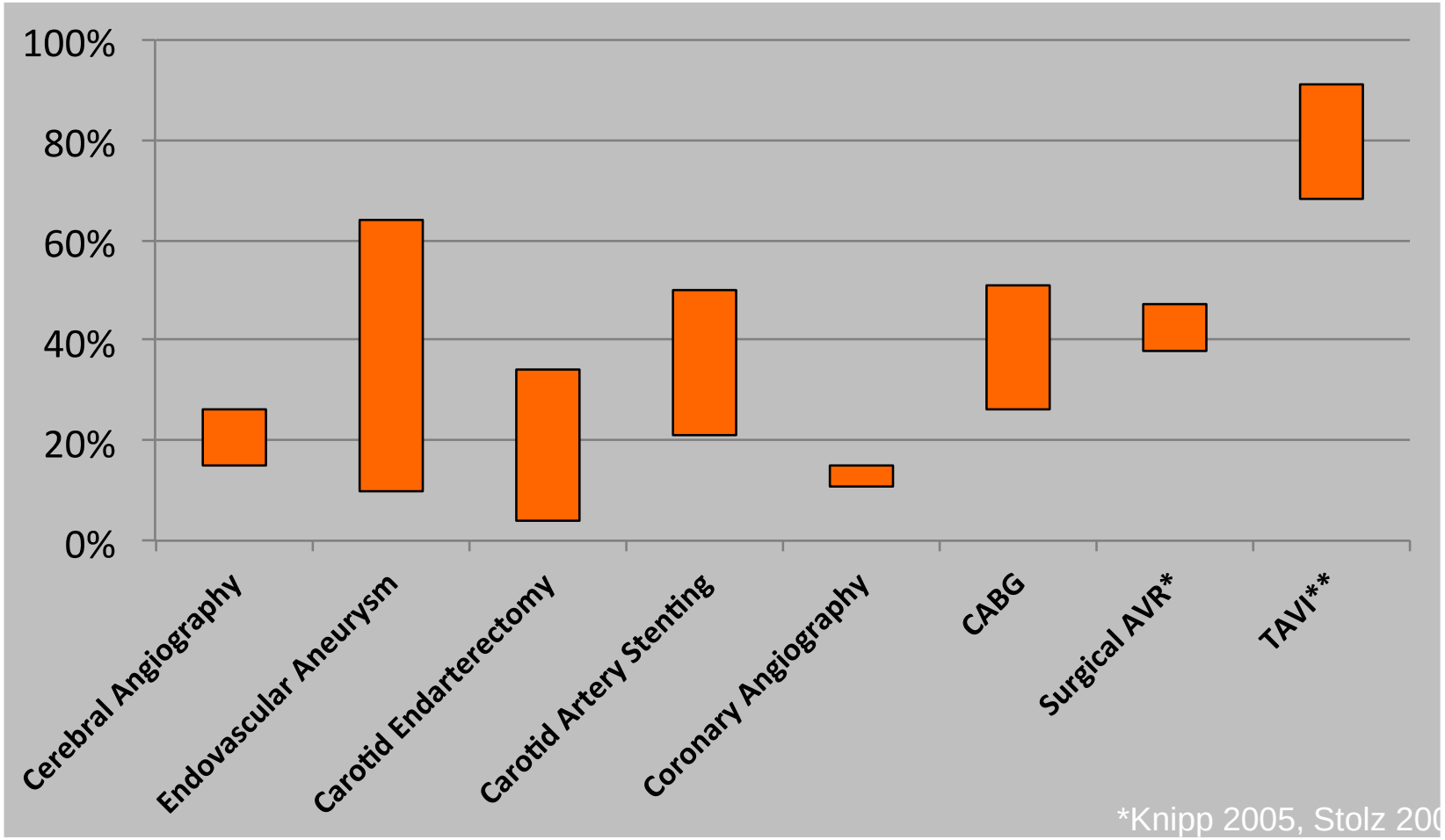
cognitive decline
memory
mood disturbances
psychomotor speed
personality changes

Silent cerebral embolic events are common
New DW-MRI lesions post TAVI



DW-MRI: sensitivity 94%; specificity 97% for detecting stroke considered procedure of choice to detect acute neurologic deficits

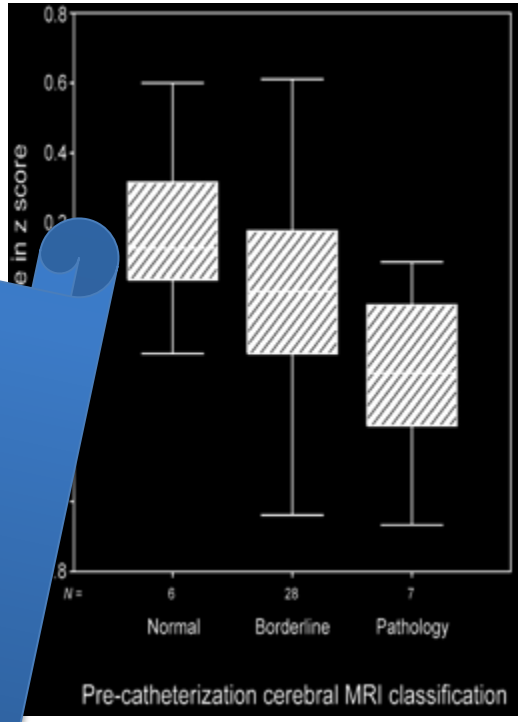
Incidence of New Brain Lesions



Neurocognitive Decline
and New Lesions

- Pre-existing and new lesions on DW-MRI after catheterization is relate decline
- Patie post neu cog patients with stable

The link between DWMRI lesions and decline in cognitive function has yet to be established in the TAVI cohort



Lund et al, 2005 Restrepo et al Stroke 2002

PREVENTION OF STROKE WITH DEVICES

Pathophysiology

Potential Paths of Cerebral Embolism

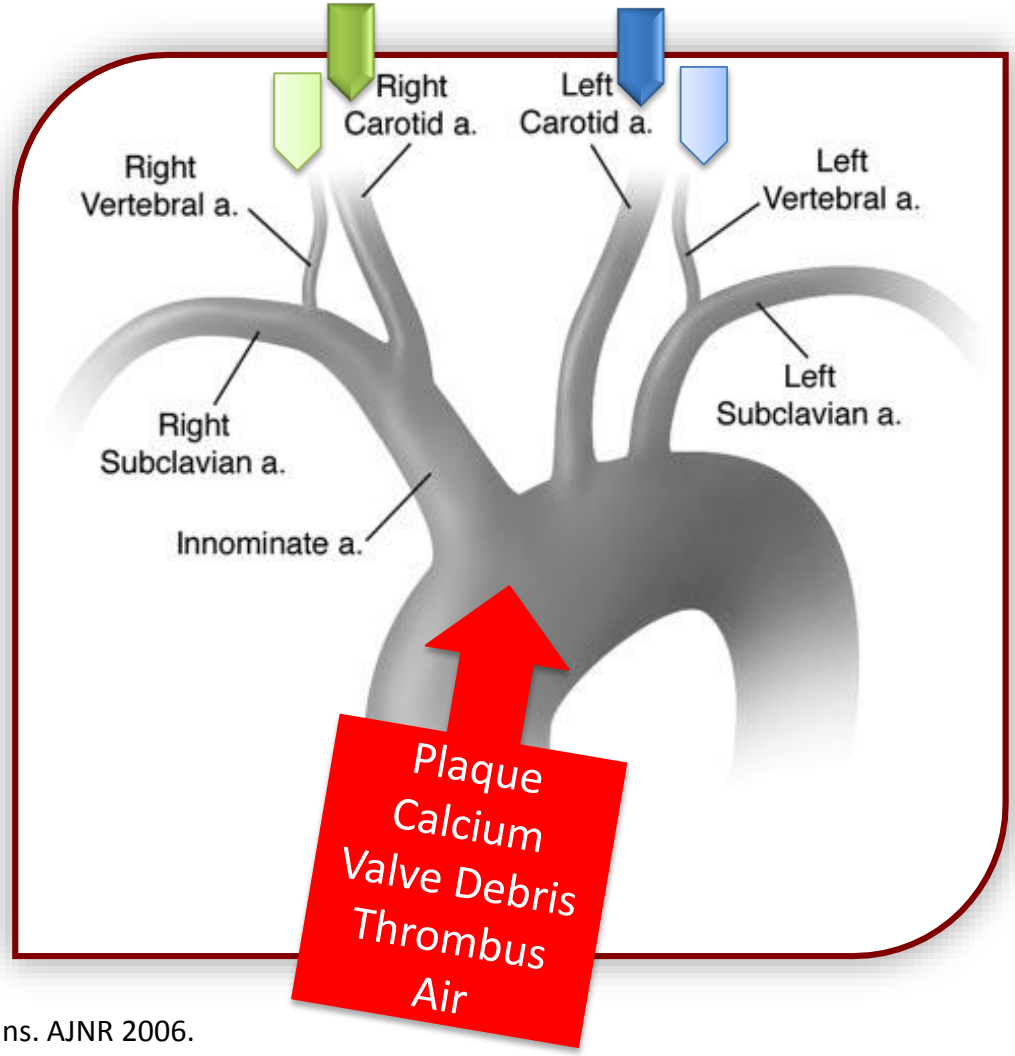
Typical aortic arch anatomy

Right Carotid

Right Vertebral

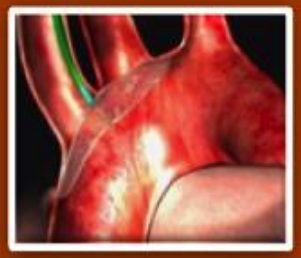
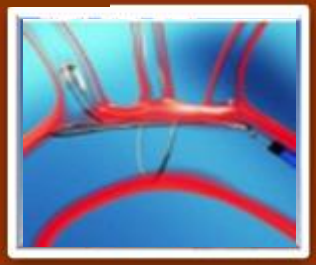
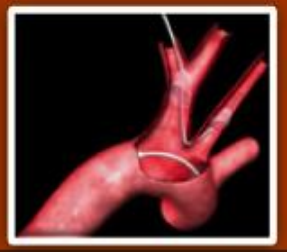
Left Carotid

Left Vertebral

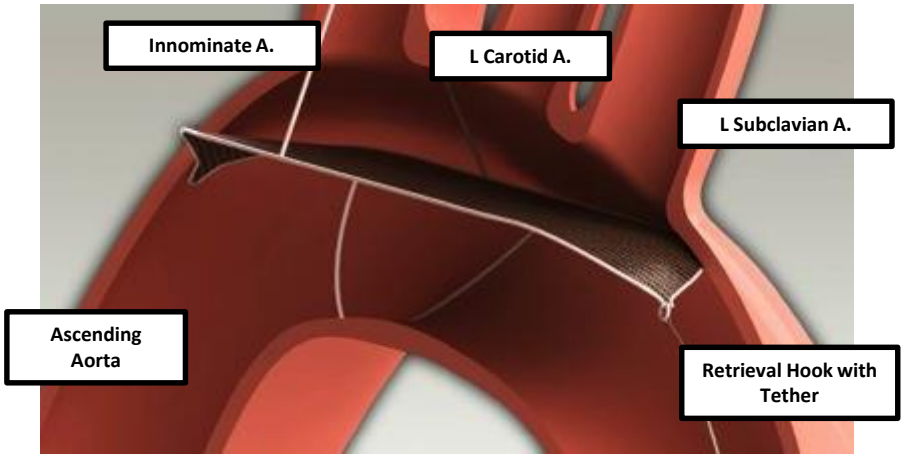


Layton KF et al. Bovine Aortic Arch Variant in Humans. AJNR 2006.

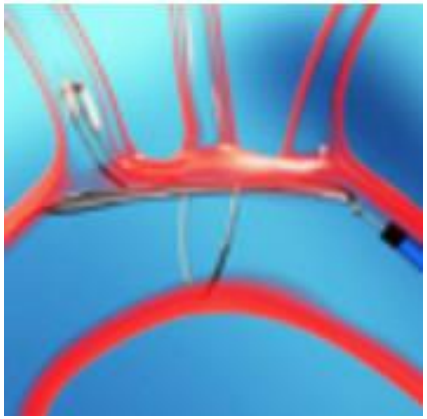
EMBOLIC PROTECTION DEVICES

Feature	Embrella	Triguard	Claret Medical
			
Access	Radial	Femoral	Radial
Position	Aorta	Aorta	Brachiocephalic Left Common Carotid
Coverage Area	Brachiocephalic & LCC	Brachiocephalic & LCC & LSC	Brachiocephalic & LCC
Mechanism	Deflection	Deflection	Capture
Size	6F	9F	6F
Pore Size	100 microns	~200 microns	140 microns

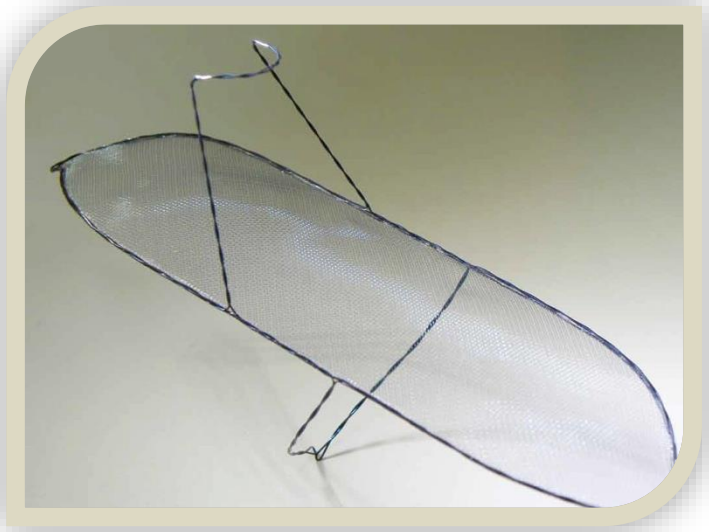
2: Keystone Heart Embolic Deflection Device Triguard



Designed for Coverage of All 3 Take-Offs



Simple, Fast, Familiar through Femoral access to reduce procedural complexity



Nitinol Frame and Mesh
Self-positioning, with stabilizing atraumatic arms to avoid migration/embolization

Keystone Heart Overall Clinical Program Completed

- **DEFLECT I (N=37)**
  - Gen 1.0 TriGuard device
  - Observational, compared to historical controls
  - Reduction in lesion volume and total ischemic burden
  - CE Mark in 2013
  - PIs: M Mullen, MD

- **DEFLECT II (N=15)**
  - FIM to assess the next generation TriGuard 1.5 device (EU)
    - Steerable
    - Pore size 120 micron with radiopaque markers for good visibility
  - Data being analyzed
  - PI: P Stella

DW-MRI Results

Lesion Volume Reduction vs. Historic Controls

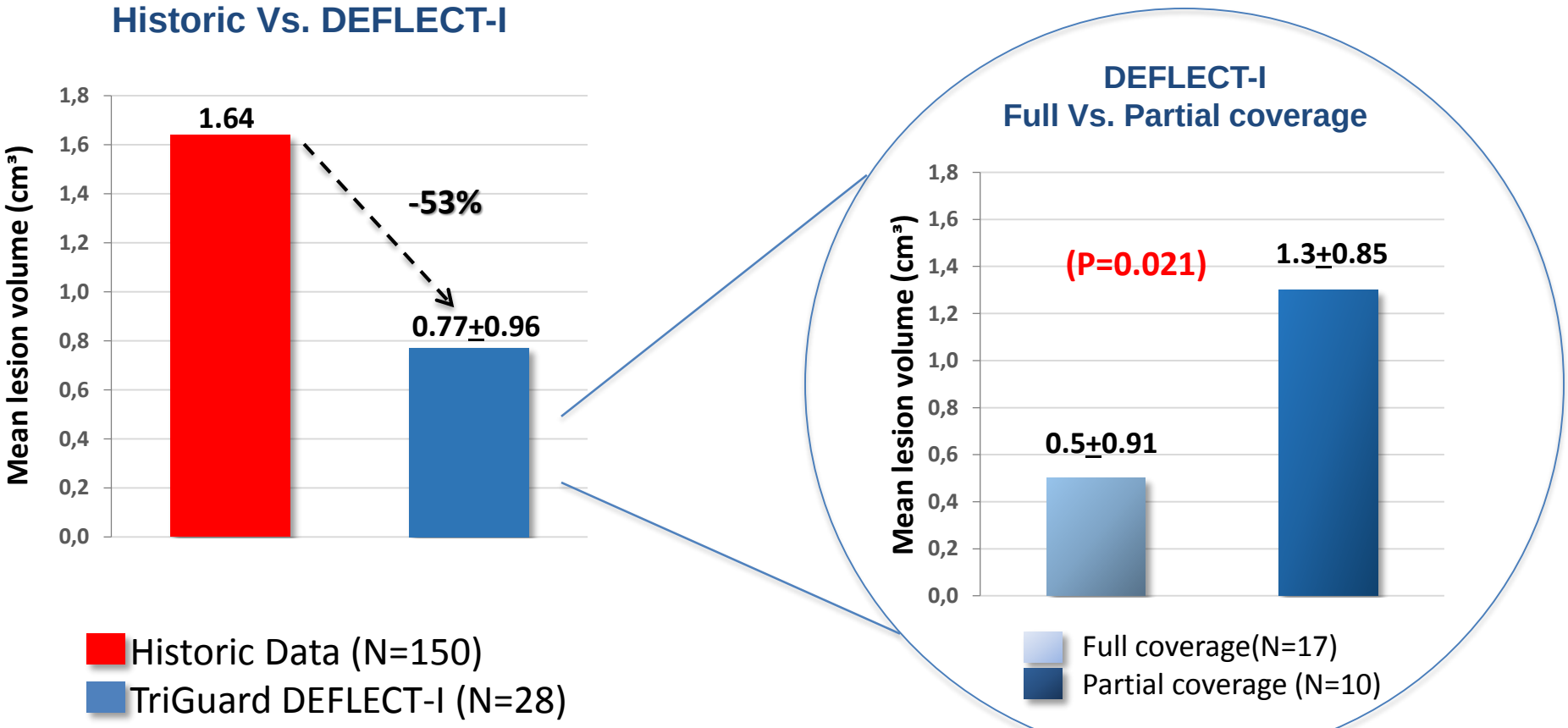
(Kahlert 2010, Ghanem 2011, Astarci 2011, Stolz 2004, Rodes Cabau 2011)

28 Paired DW-MRI

Parameter	DEFLECT-I N=28	Historical Data N=150
Proportion of Patients with New Lesions	78.6%	77%
Number of New Lesions	5.14± 6.10 (0 - 28)	4.60 (0 -36)
Average New Lesion Volume	0.13±0.13 cm^3 (0 – 0.47)	0.33 cm^3
Total New Lesion Volume	0.77±0.96 cm^3 (0 – 3.94)	2.18±4.5 cm^3 (1.65 – 4.3)

DW-MRI Results

Mean Total New Lesion Volume (cm^3)

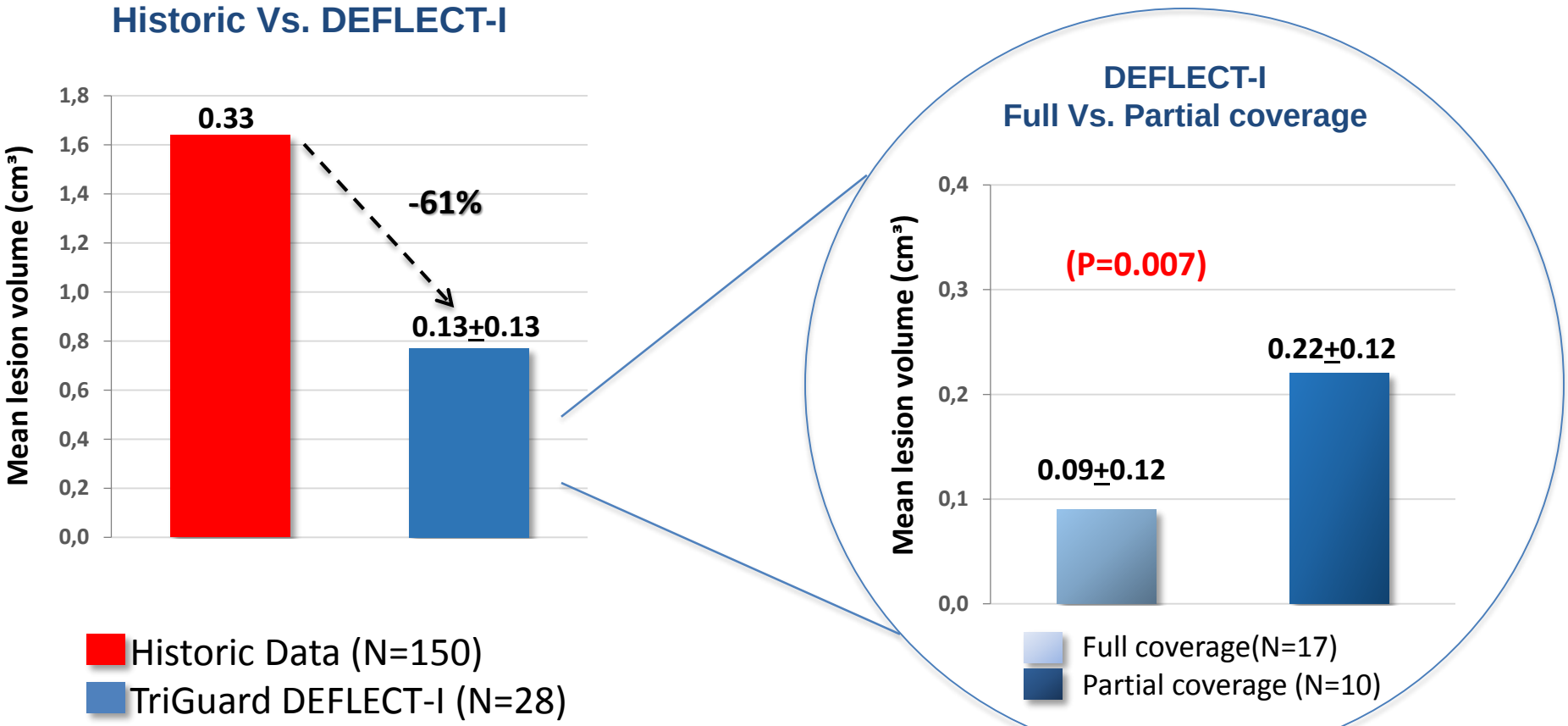


Historical Data: Astarci 2010, Ghanem 2010, Kahlert 2010, Fairbarn 2011, Knipp 2012

Baumbach,.., Lanksy Eurointervention 2015, epub ahead of print

DW-MRI Results

Mean Single New Lesion Volume (cm^3)



Historical Data: Astarci 2010, Ghanem 2010, Kahlert 2010, Fairbarn 2011, Knipp 2012

Baumbach,.., Lanksy Eurointervention 2015, epub ahead of print

Overall Clinical Program Enrolling

- **TransAortic (N=20)**
  - Observational, compared to single center data without protection (Canada)
  - PI J Rhodes-Cabau
- **NeuroTAVR (N=60)**
  - Observational multicenter study of contemporary TAVR (US)
  - PI: A Lansky
- **DEFLECT III (N=86)**
  - Multicenter, randomized 1:1 (EU)
  - PI: A Baumbach and A Lansky

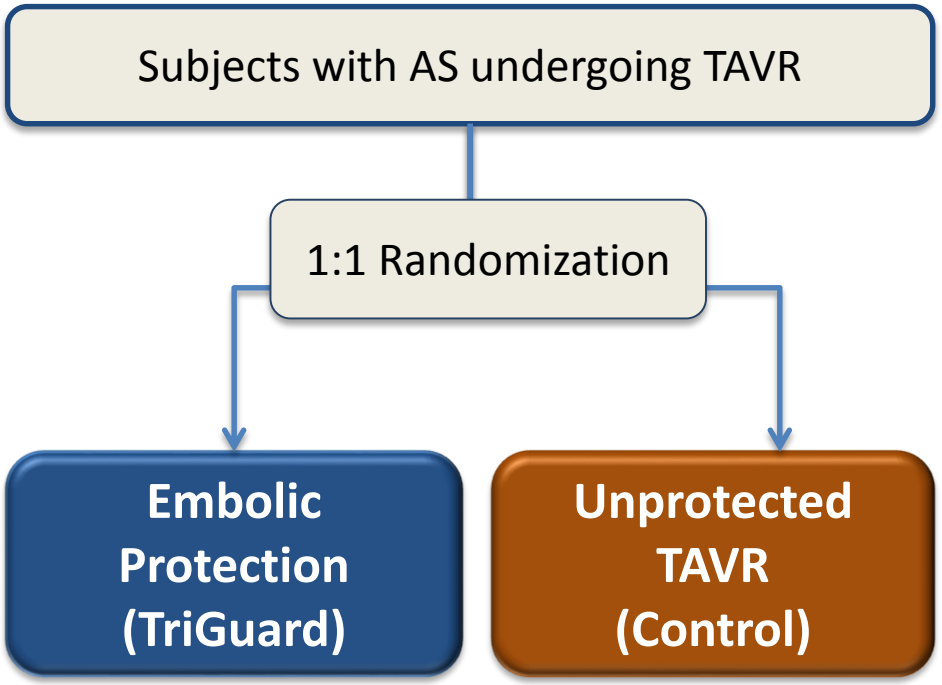
DEFLECT III Study Overview

Design: Multicenter prospective single-blind randomized controlled trial at 13 sites (EU/IL)

Objective: To evaluate the safety, efficacy and performance of TriGuard protection compared with unprotected TAVR.

Sample Size: Exploratory study with no formal hypothesis testing.

86 patients selected to benchmark events for the design of a pivotal RCT.



Lansky,..Baumbach EHJ 2015 accepted for publication

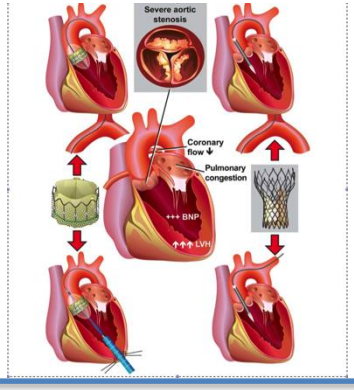
DEFLECT III

- Pre Procedure

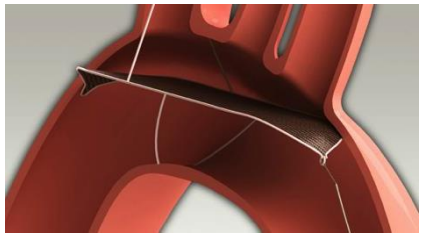
Neurocognitive Assessment

N: 86

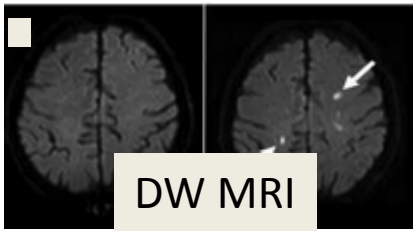
Procedure



+/-

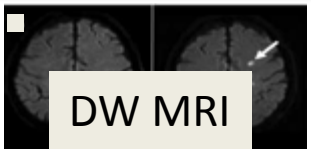


Post Procedure



Neurocognitive Assessment

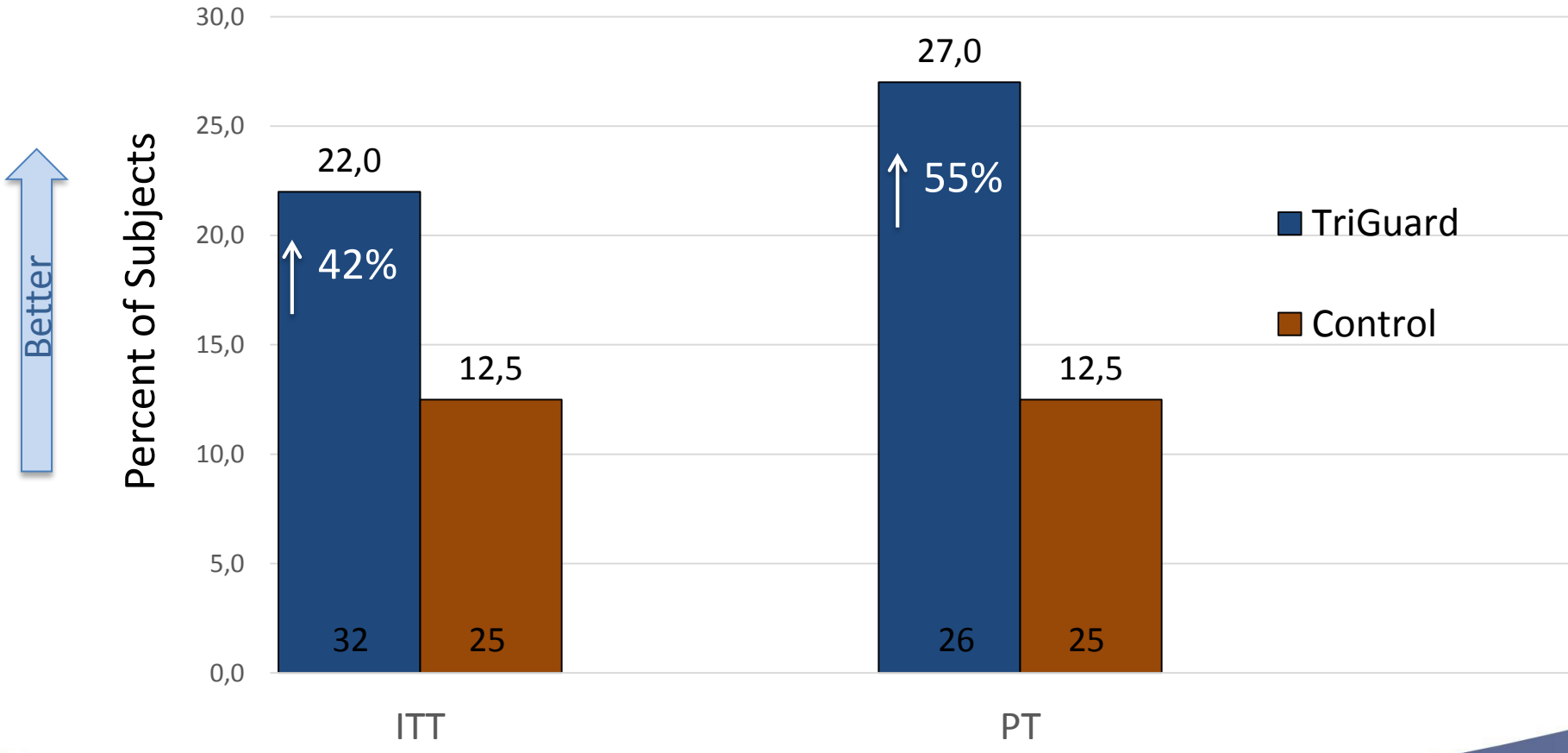
30 Day Follow-up



Neurocognitive Assessment

DW-MRI Results – Patients with No Ischemic Brain Lesions

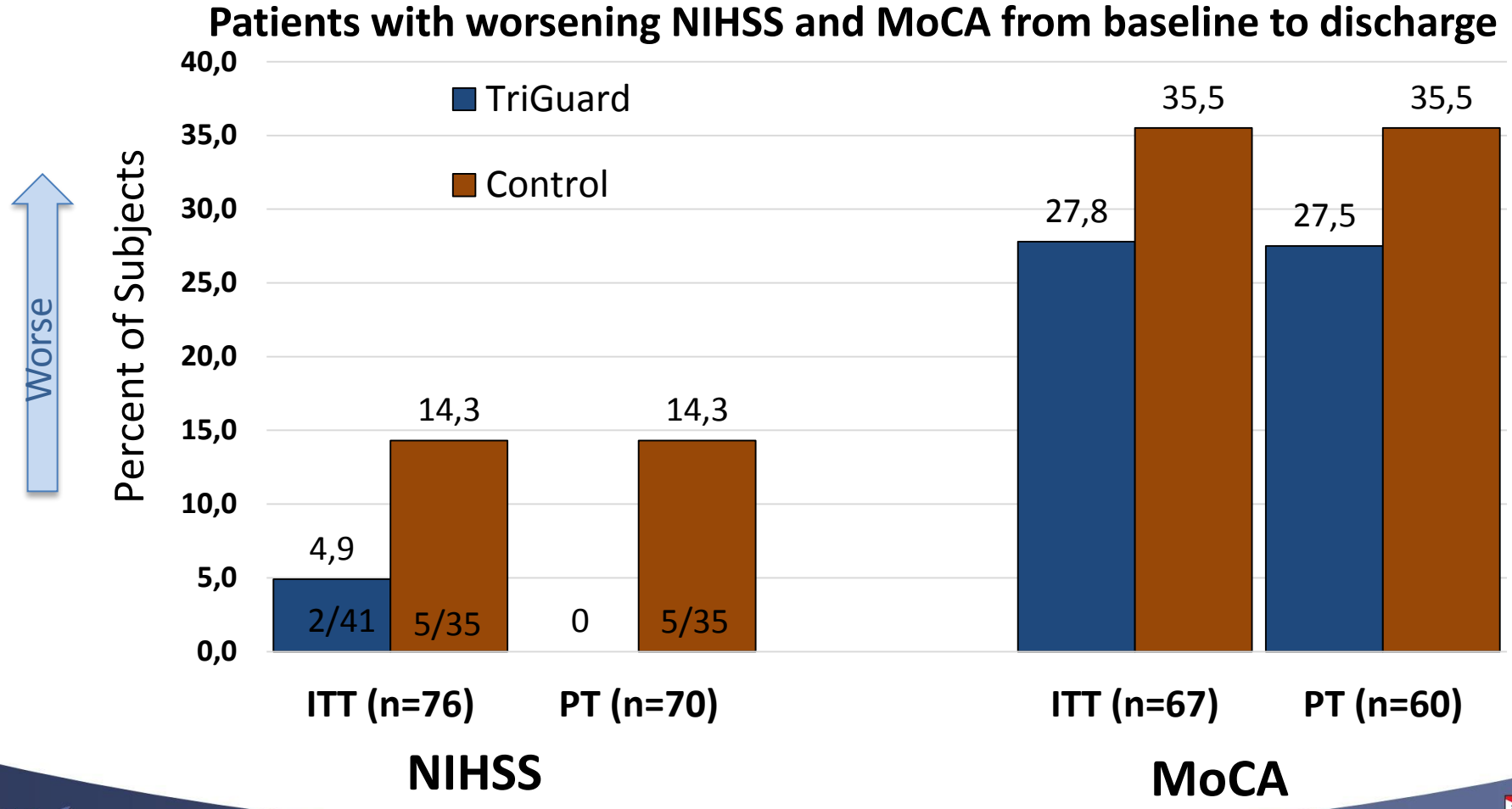
Protection has more freedom from ischemic lesions



Lansky,..Baumbach EHJ 2015 accepted for publication

Clinical Efficacy Outcomes – NIHSS and MoCA

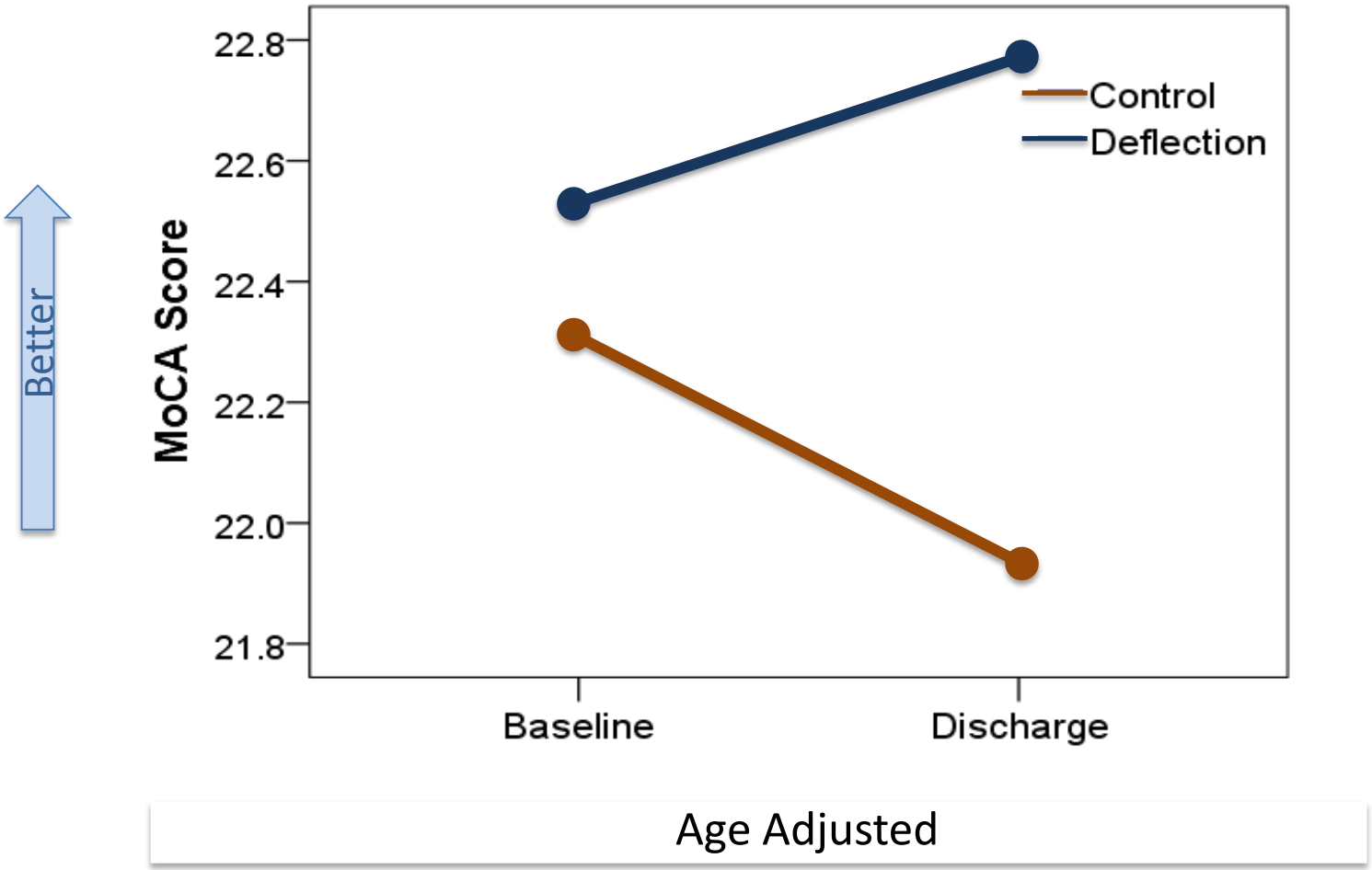
Protection had fewer strokes and better cognitive outcomes



Lansky,..Baumbach EHJ 2015 accepted for publication

MoCA Score –Change from Baseline to Discharge (ITT)

Protection prevents a decline in cognition at discharge



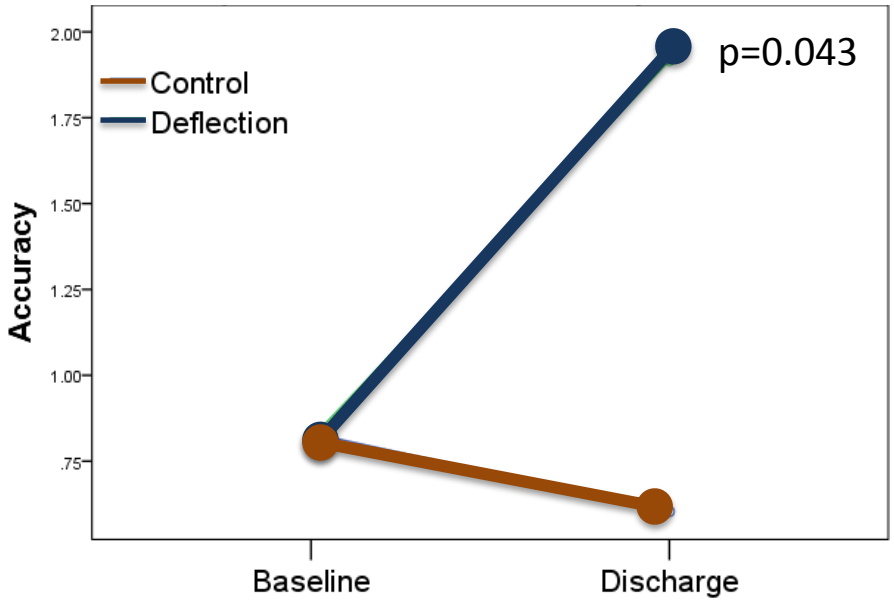
Age Adjusted

Lansky,..Baumbach EHJ 2015 accepted for publication

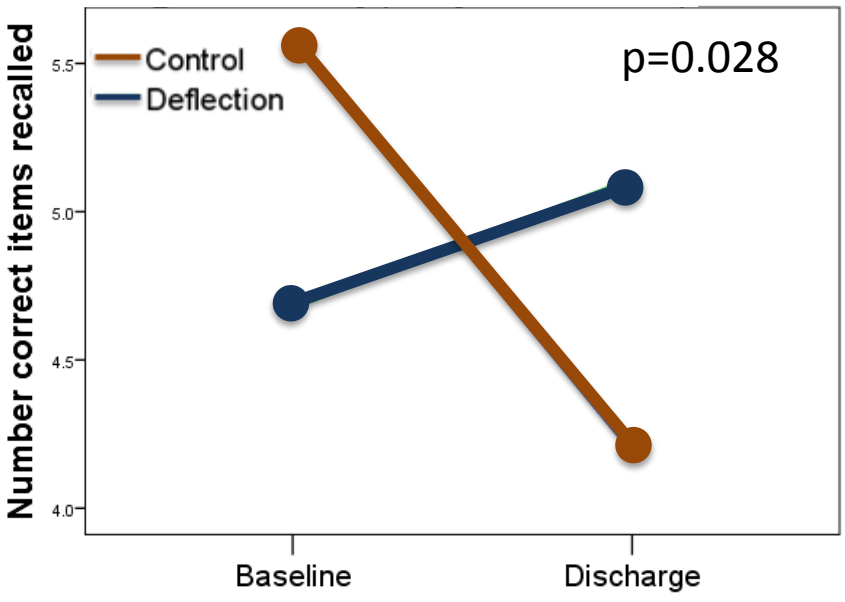
Clinical Efficacy: CogState-Test Results (PT)

Protection is associated with improved short and delayed memory at discharge

Short term memory test



Delayed memory test



Age Adjusted

Lansky,..Baumbach EHJ 2015 accepted for publication

Planned: REFLECT

- A prospective multicenter randomized trial of TriGuard™ neuro protection vs no protection in patients undergoing TAVR
- FDA IDE study (EU and US)
- Randomized 1:1
- Chair J Moses, PIs A Lansky and A Baumbach

Summary

- Stroke continues to be a clinically relevant problem
- ‘Silent’ cerebral infarcts are frequent and are likely to impact on cognitive function
- Initial results with cerebral protection devices are promising
- This technology might improve outcomes in surgical and other interventional procedures

The Ultimate Goal

of

Device Based Treatment

Our Patients:

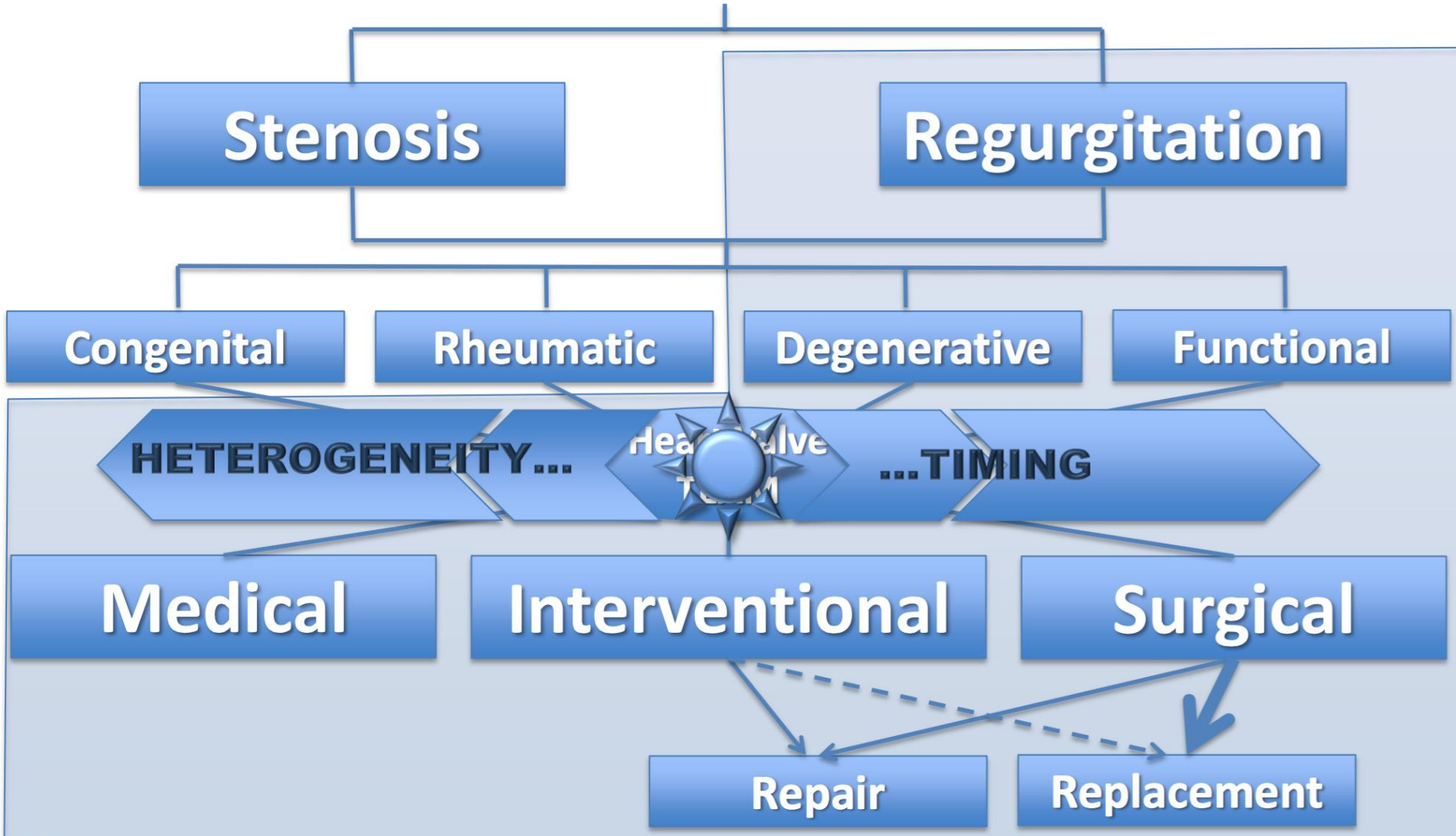
Old

And

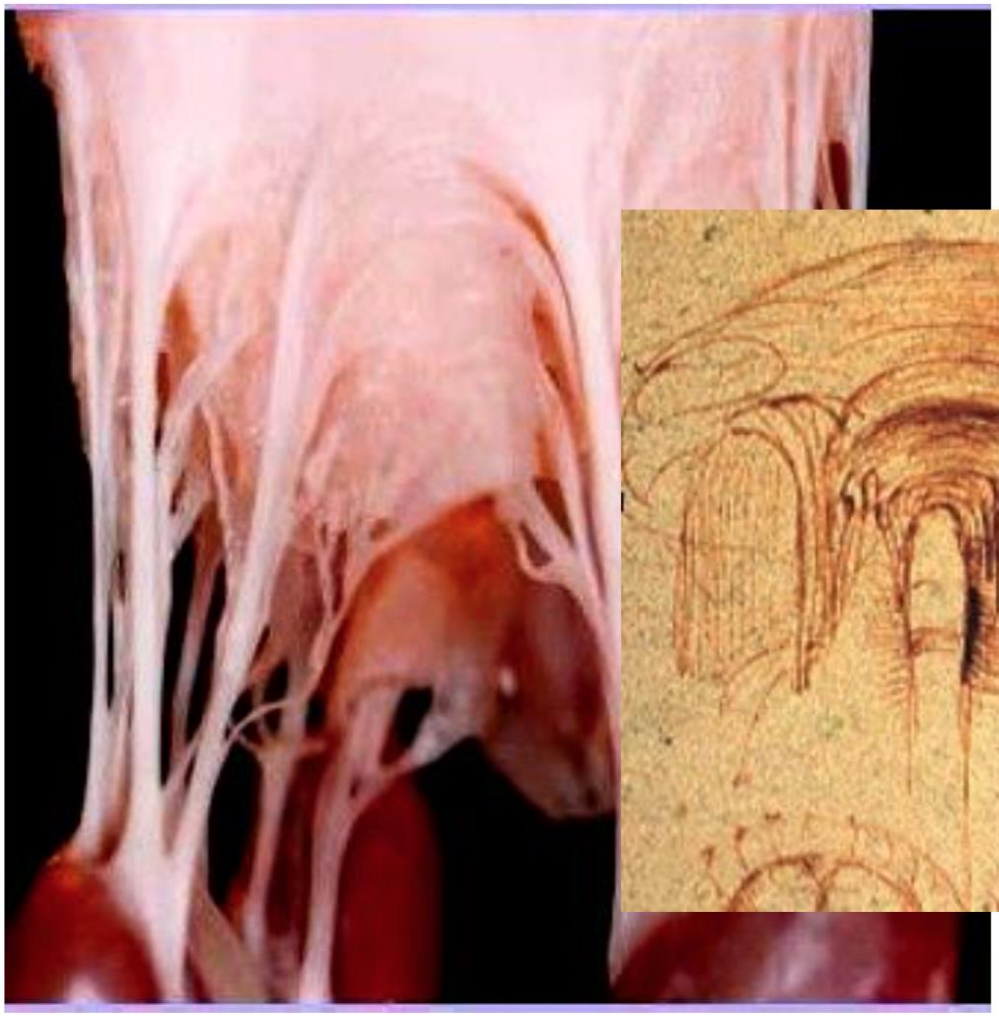
Happy

MITRAL DEVICES

Therapies for Mitral Valve Pathology
Unresolved Issues



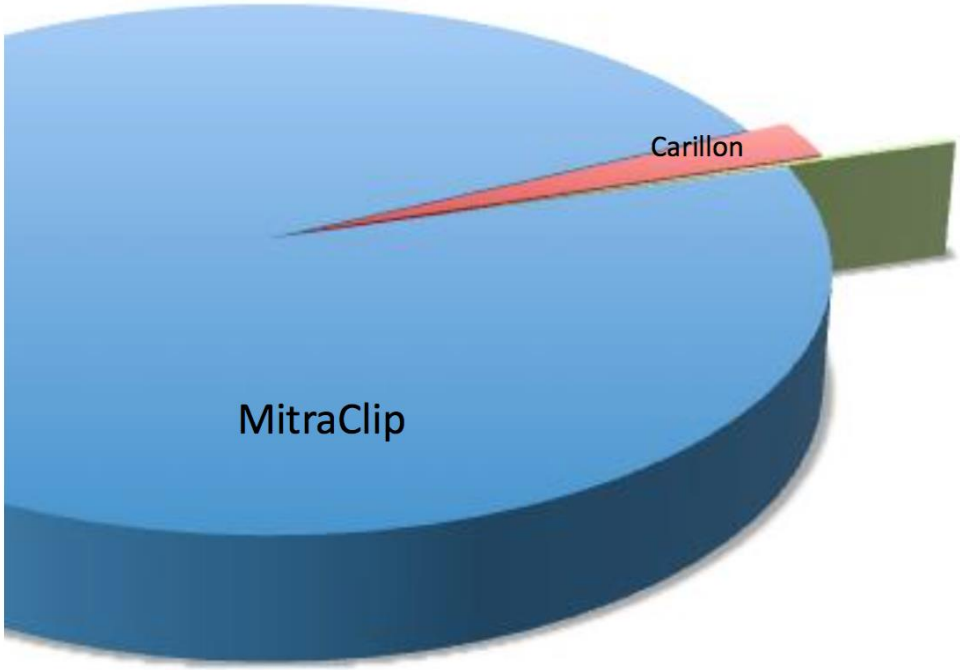
The mitro-ventricular architecture



New Techniques on the Horizon

- **Repair**
  - Direct and adjustable annuloplasty
  - Chordal implants
- **Replacement**
  - Valve support
  - TMVR
  - Docking concept

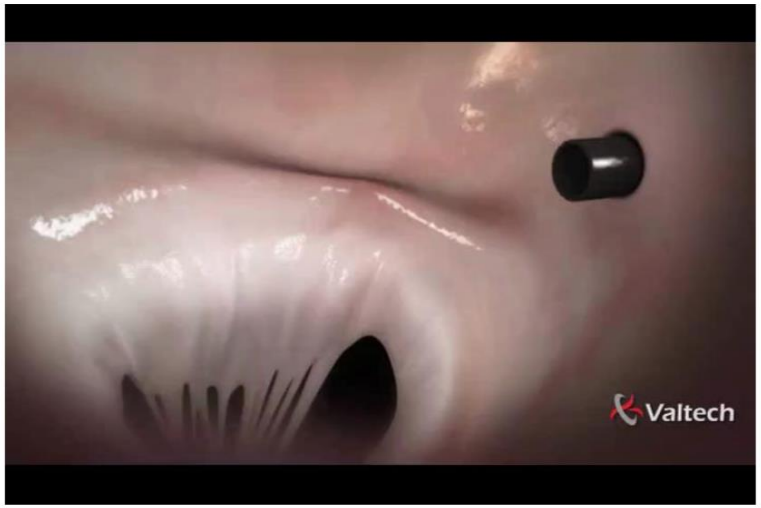
Less Invasive Therapies:
Treated Patients



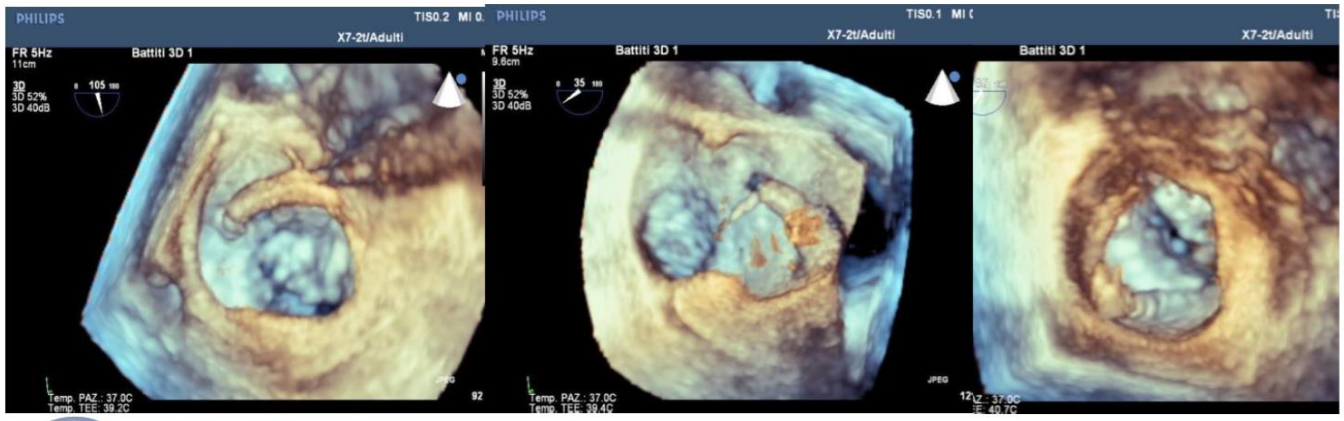
MitraClip	>14,000
Carillon	300
Mitralign	40
Cardioband	20
Replacement	5

(Courtesy of Dr. T. Feldman)

Percutaneous Direct Annuloplasty with the Adjustable Cardioband



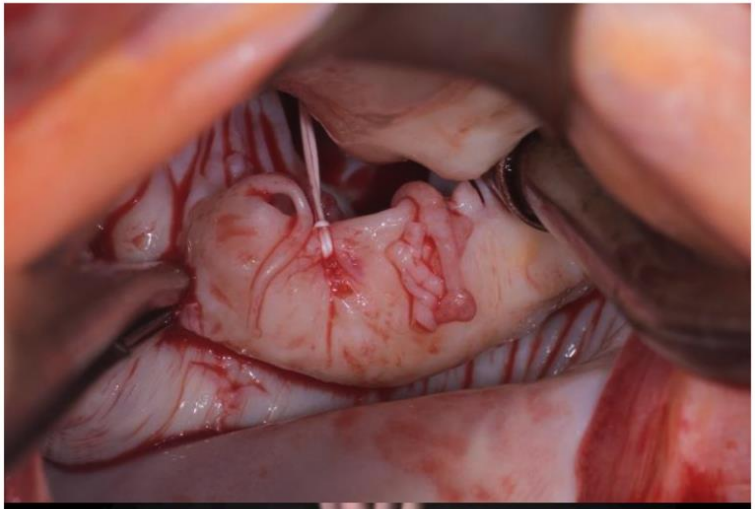
- Surgical band delivered via transfemoral venous access
- Implanted on the supra-annular position, similar to the surgical treatment
- Bi-lateral controlled adjustment of the posterior annulus for optimal hemodynamic results

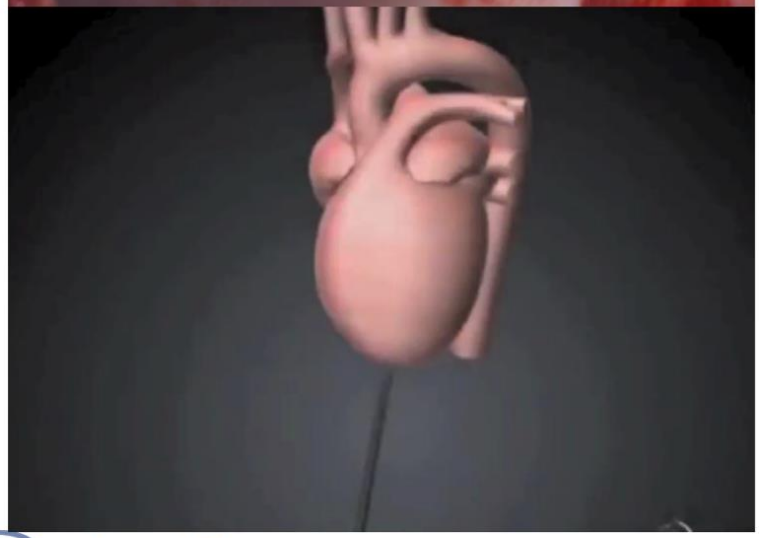


FIM procedure (F. Maisano)

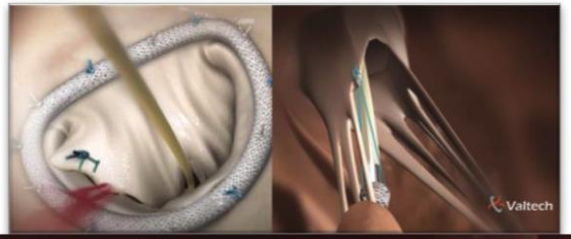
Chordal Implants

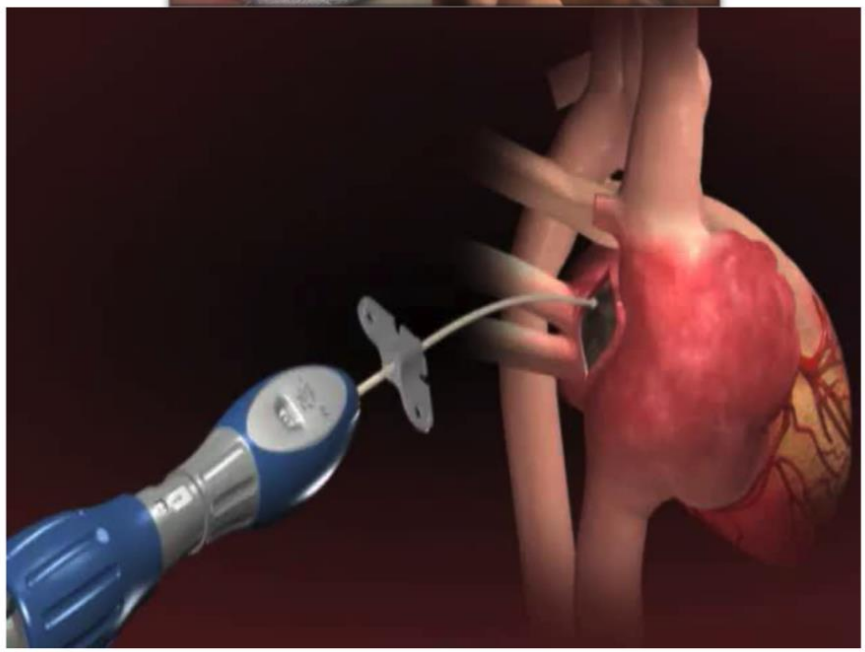
NeoChord





V-Chordal Valtech



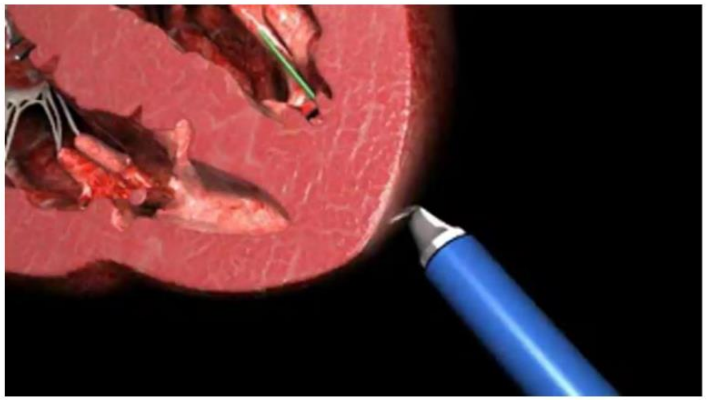


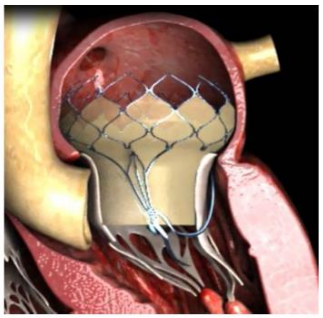
FIM trial completed
TF platform under development

MitrAssist

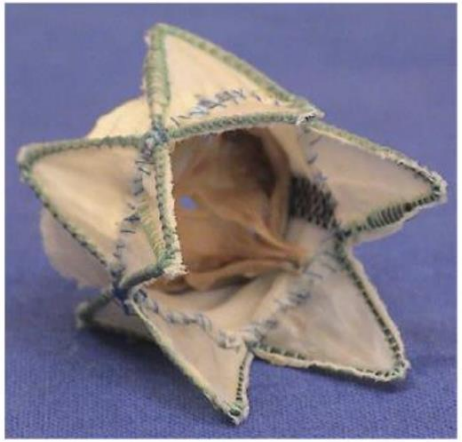
A valve that ASSISTS the native valve

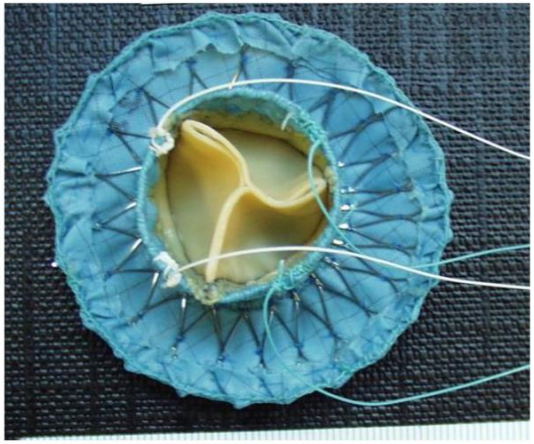
- Nitinol construction with Pericardium tissue
- Supports native valve functionality
- Reduces risk of LVOT Obstruction
- Low Profile (18Fr.)
- Asymmetrical bi-leaflet design (AL & PL)
  - > 90% of closure distance is promoted by native leaflets
  - > 70% of LV pressure is acting on native valve apparatus





Tendyne MV

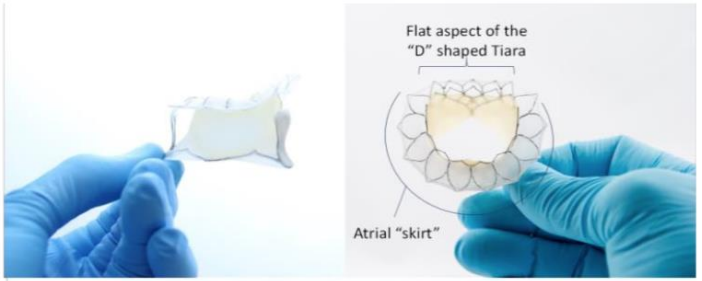


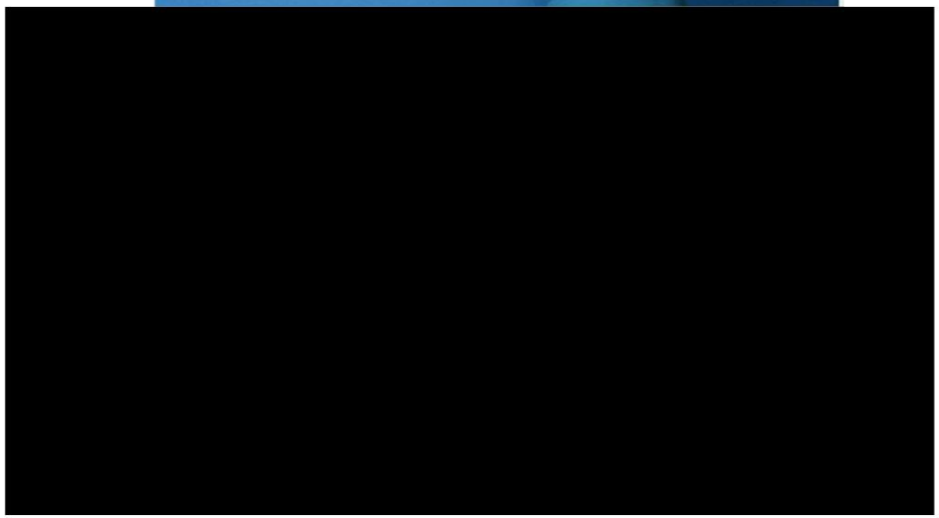


- NiTi Stent with porcine pericardium
- Fully Retrievable and repositionable
- Left ventricular apical tether
- Simple, controlled deployment
- Requires no rapid pacing or CPB support
- FIM – temporary implants done in Paraguay
  - Eduardo de Marchena MD
  - Georg Lutter MD

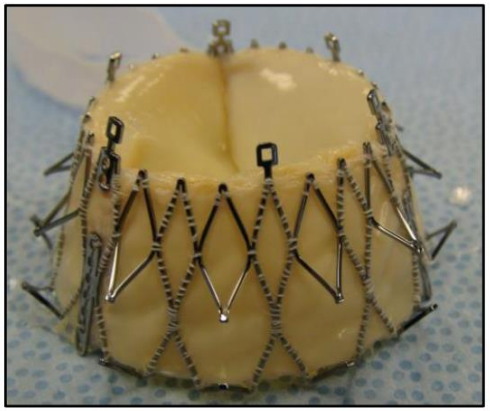
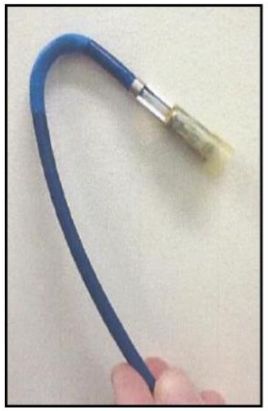
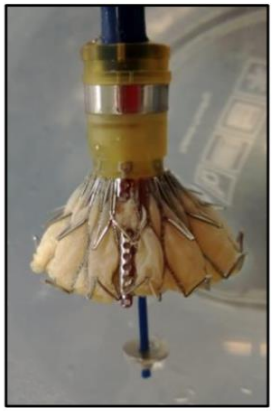
TIARA Prosthesis - TMVR

- Self-expanding D-shape Nitinol frame with a tri-leaflet bovine pericardium bioprosthesis,
- Fit into the asymmetric and multiplanar MV annulus
- Spare chordal structure
- Leave adjacent myocardium intact
- Avoid obstruction of the LV outflow tract
- Avoid impingement of the coronary arteries and veins





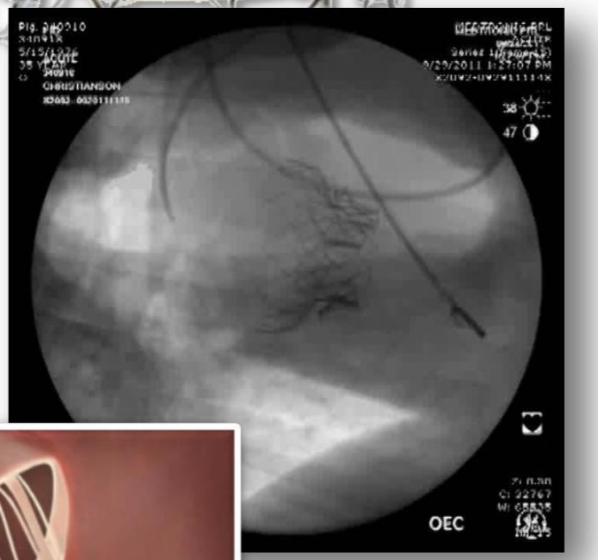
NaviGate Mitral Valve

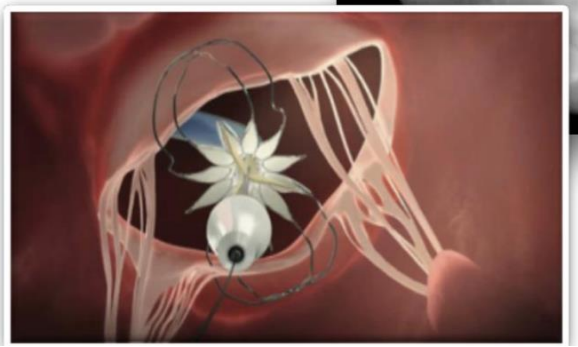





- NiTinol Stent-frame with a 21 mm height truncated-cone shape (*Inflow=30mm/Outflow=40mm*)
- Chemically Preserved Xenogeneic Pericardium
- Annular winglets anchoring structures of annulus and mitral valve leaflet
- Delivery system 30F profile distal capsule and 18F catheter shaft
- Four degrees of motion at tip with 135° Articulation
- Controlled Valve Release
- Transatrial, transseptal and transapica delivery available

Medtronic TMVR Program

- Self expanding nitinol
- Fixation with the native mitral apparatus
- Preserves native mitral apparatus
- Cylindrical, trileaflet pericardial valve
- Large, flexible inflow
- Minimal extension into LV
- Recapturable
- Chronic animal studies



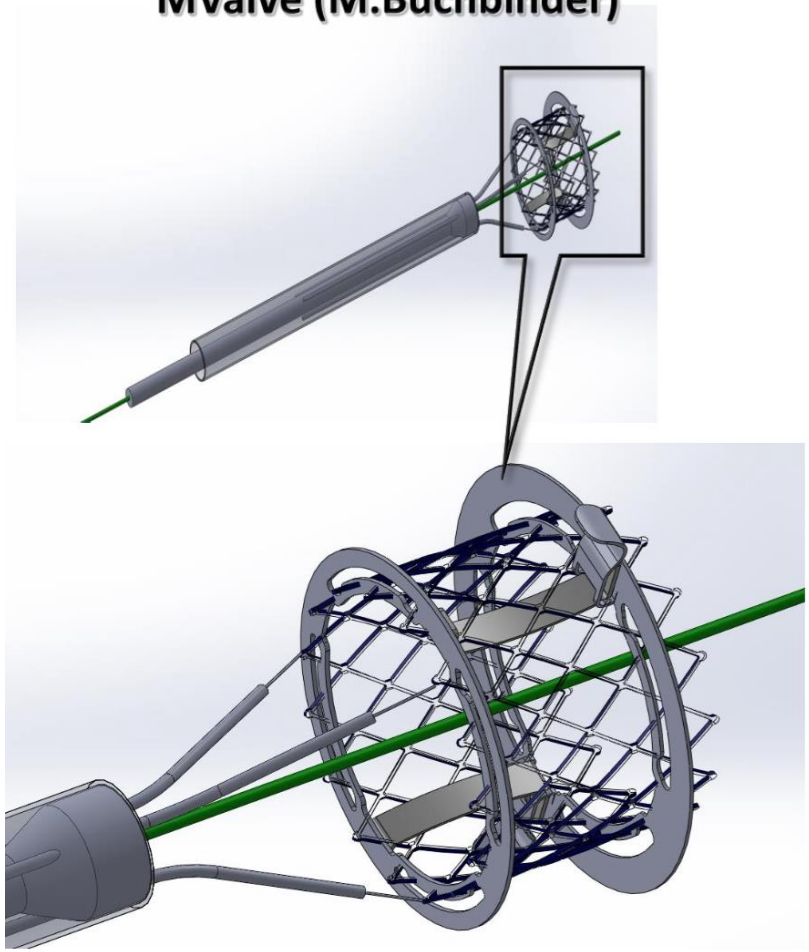


Valtech Transcatheter Mitral Valve

- Self-expanding Nitinol
- Pre-Clinical being completed
- FIM trial under development

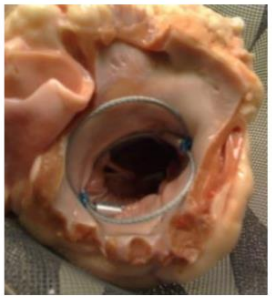
Docking Mitral Devices

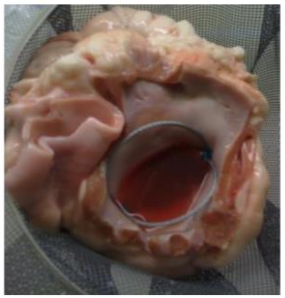
MValve (M.Buchbinder)



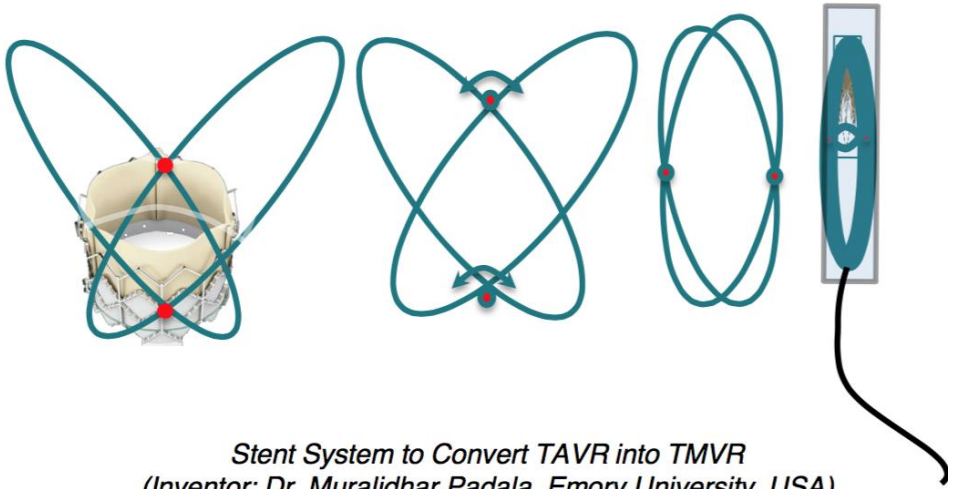
M.Padala (Emory University)

Implant in the D- shaped Mitral Orifice



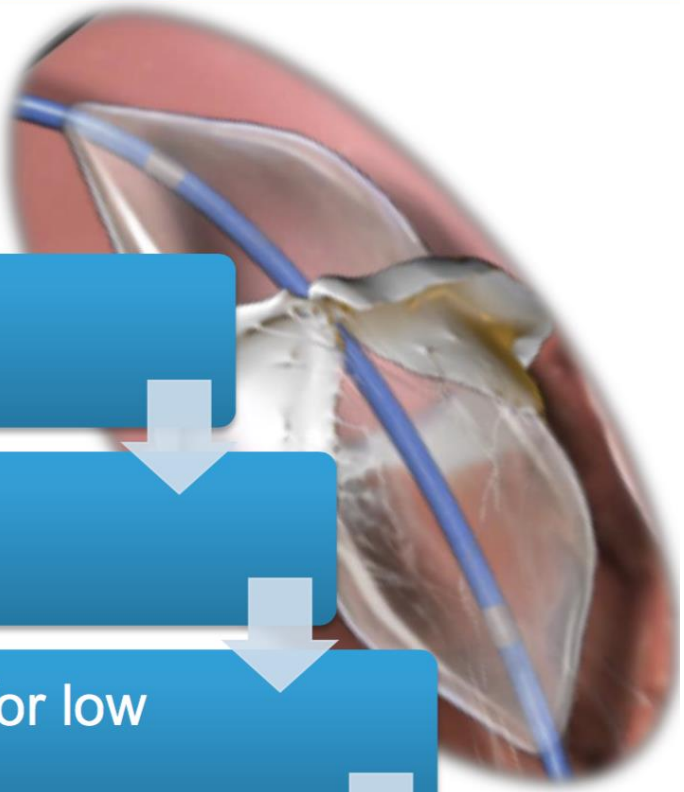


Dual Ring System Allows Collapsibility



Stent System to Convert TAVR into TMVR
(Inventor: Dr. Muralidhar Padala, Emory University, USA)

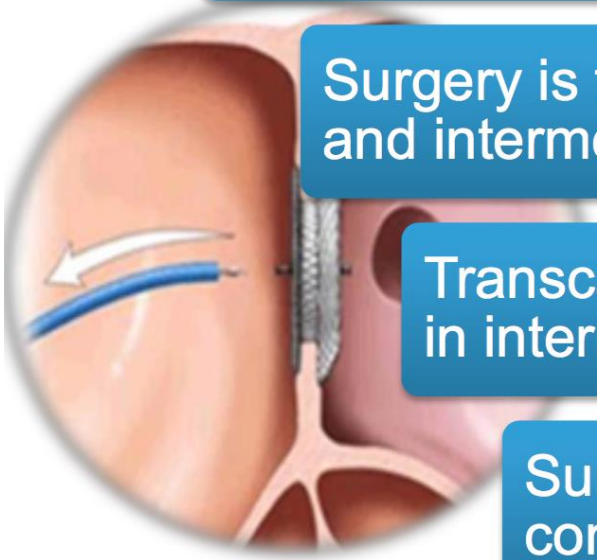
Evolution of interventions



Surgery is the only treatment

Surgery is the gold standard treatment

Surgery is the preferred treatment for low and intermediate risk patients



Transcatheter interventions are performed in intermediate risk patients

Surgery is performed in patients with contraindication to transcatheter approach