

TAVI: FUTURE DEVELOPMENTS



DEUTSCHES HERZZENTRUM BERLIN
STIFTUNG DES BÜRGERLICHEN RECHTS

Volkmar Falk

Disclosure

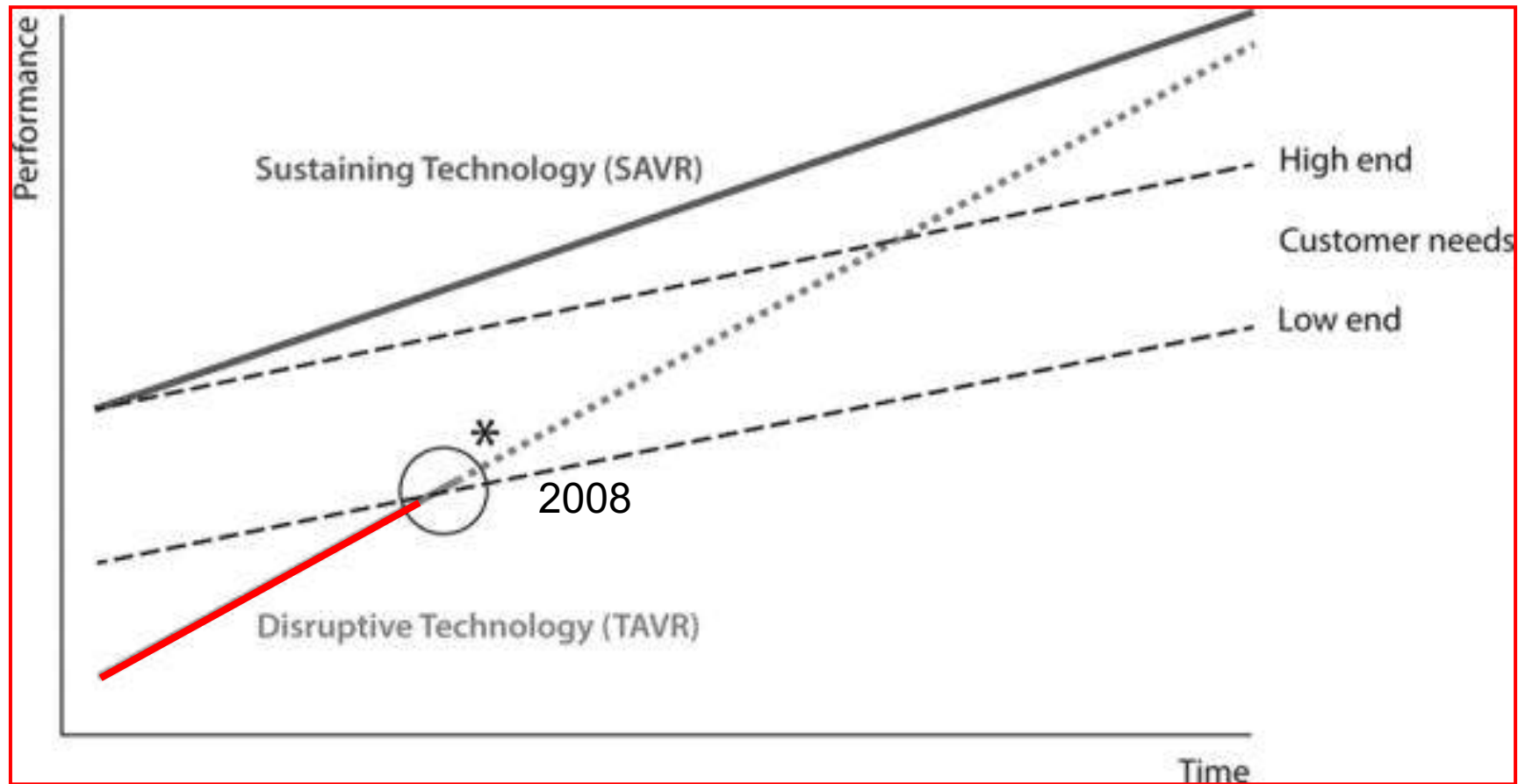
Speaker name:

Volkmar Falk.....

I have the following potential conflicts of interest to report:

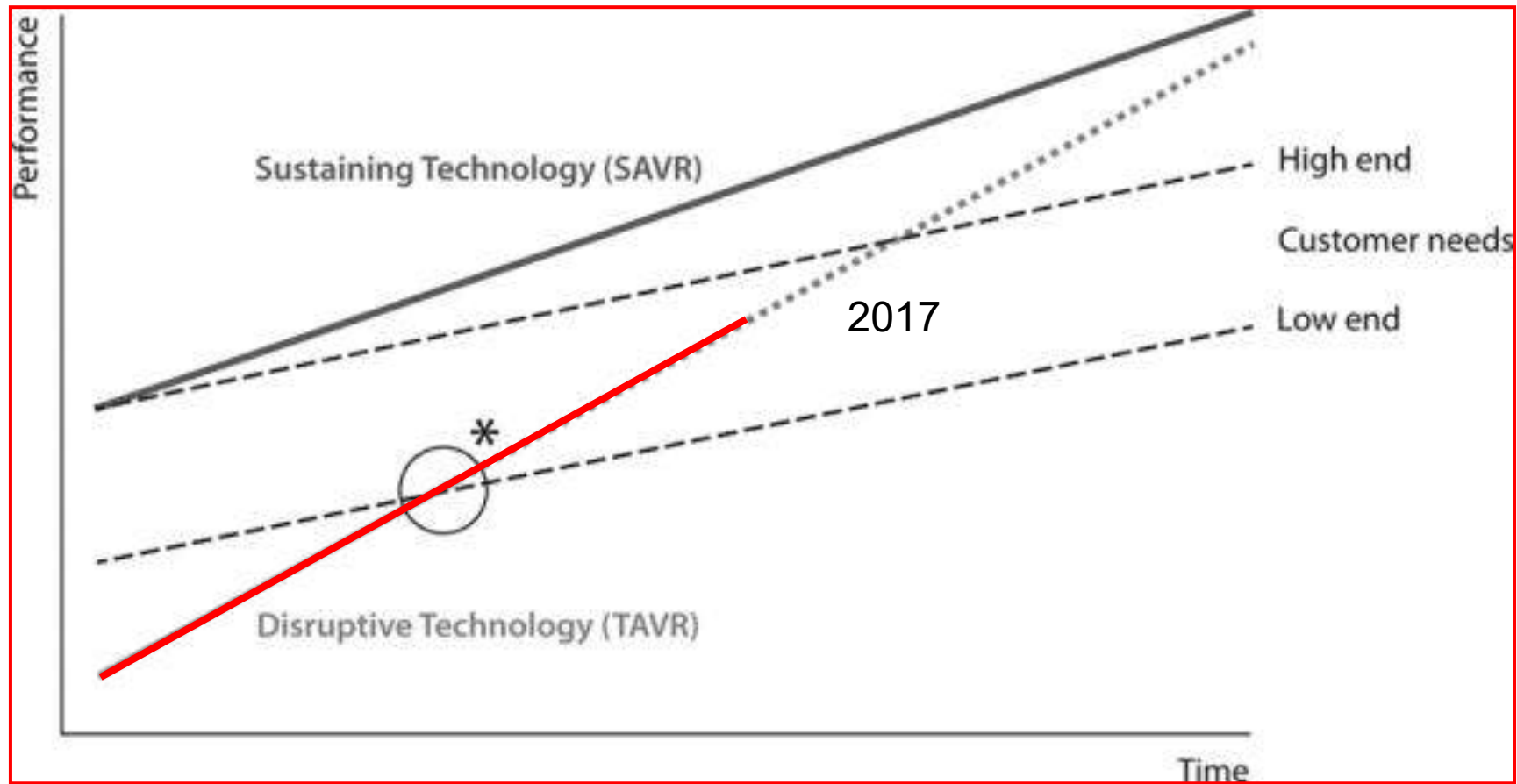
- ☒ Consulting: Aesculap
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☒ Other(s)
Departmental Research contracts: SJM, Phillips, Thoratec, Heartware
Speaker fees: Medtronic, SJM, Aesculap
PI: RESPOND Trial (Boston), DEDICATE,
- ☐ I do not have any potential conflict of interest

TAVI an example of disruptive technology



Initial target : "low-end" customers who do not need full product performance (very high-risk elderly patients) or target customers who have needs that were previously unserved by existing technologies. The latter applies to patients deemed inoperable by the existing "sustainable" technology (surgical aortic valve replacement [SAVR]) and represents a new market disruption

TAVI an example of disruptive technology





Imaging tools – planning and guidance

Additional technical solutions

Next generation TAVI devices

TAVI predictive modelling

Future TAVI indications



Imaging tools – planning and guidance

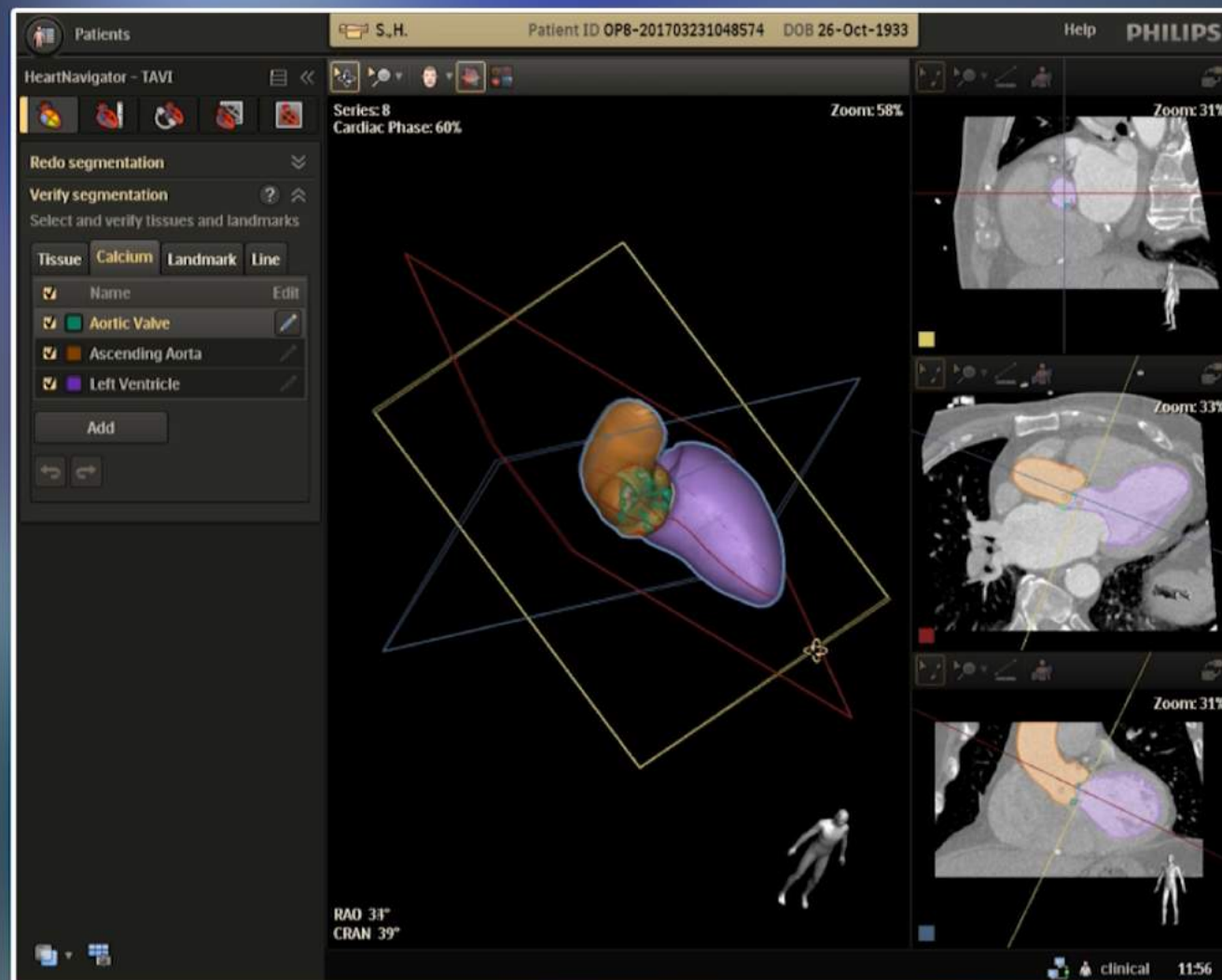
CT guided vascular access

VesselNavigator



CT based TAVI planning

HeartNavigator 3



CT guided TAVI

HeartNavigator 3

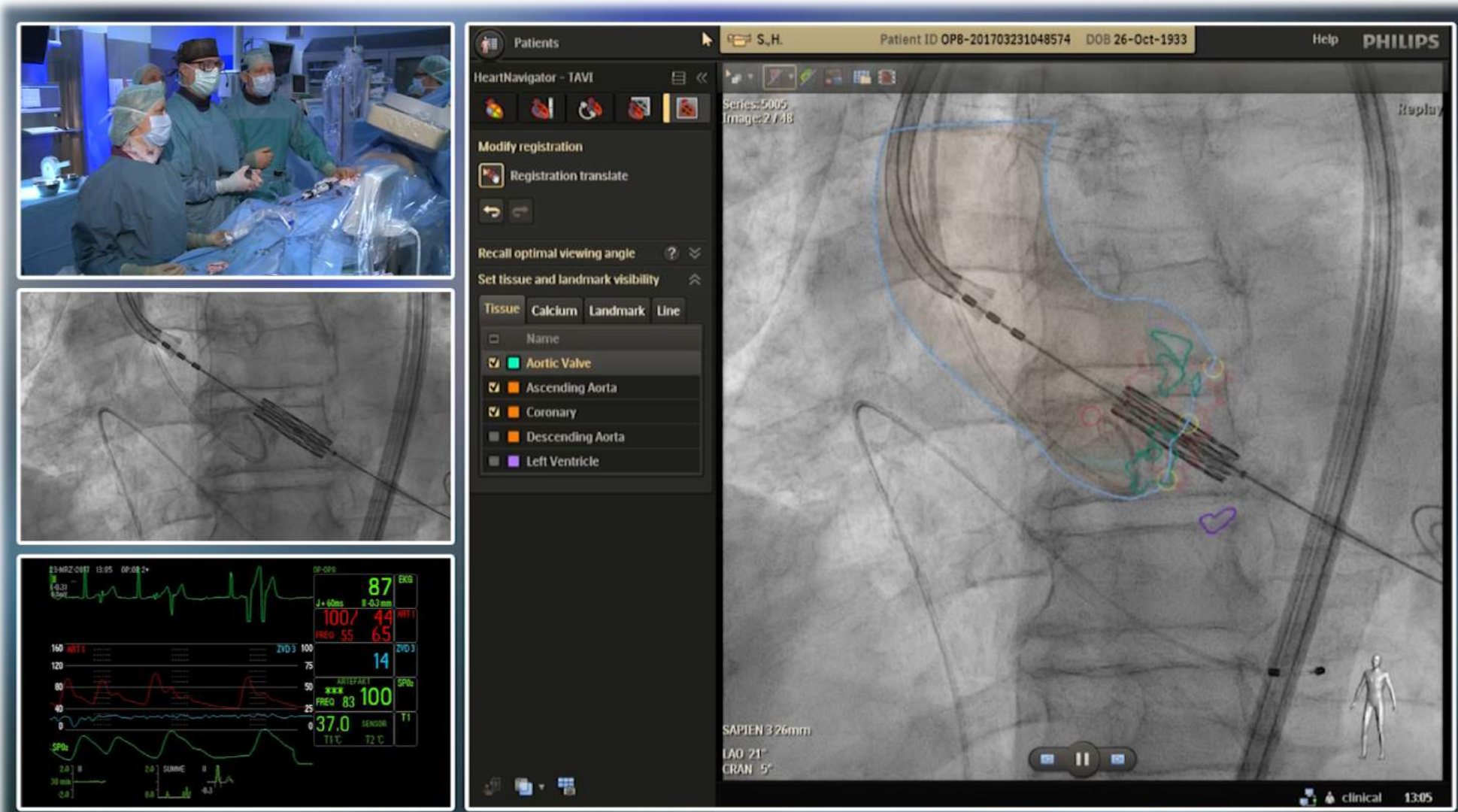


Image Guidance –VinV Mitral

M-ViV Implant – TEE-Fluoro-Fusion-Imaging

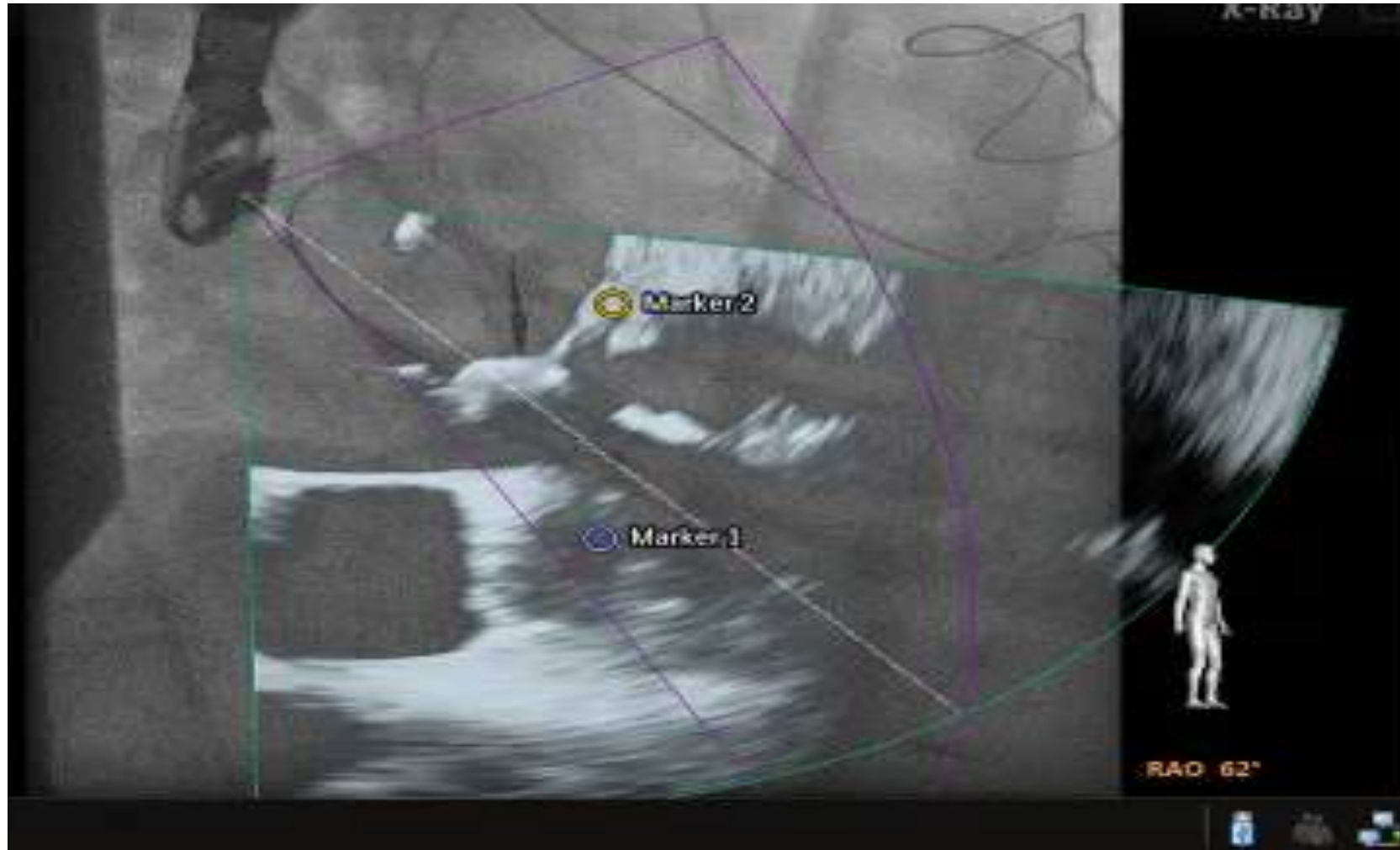
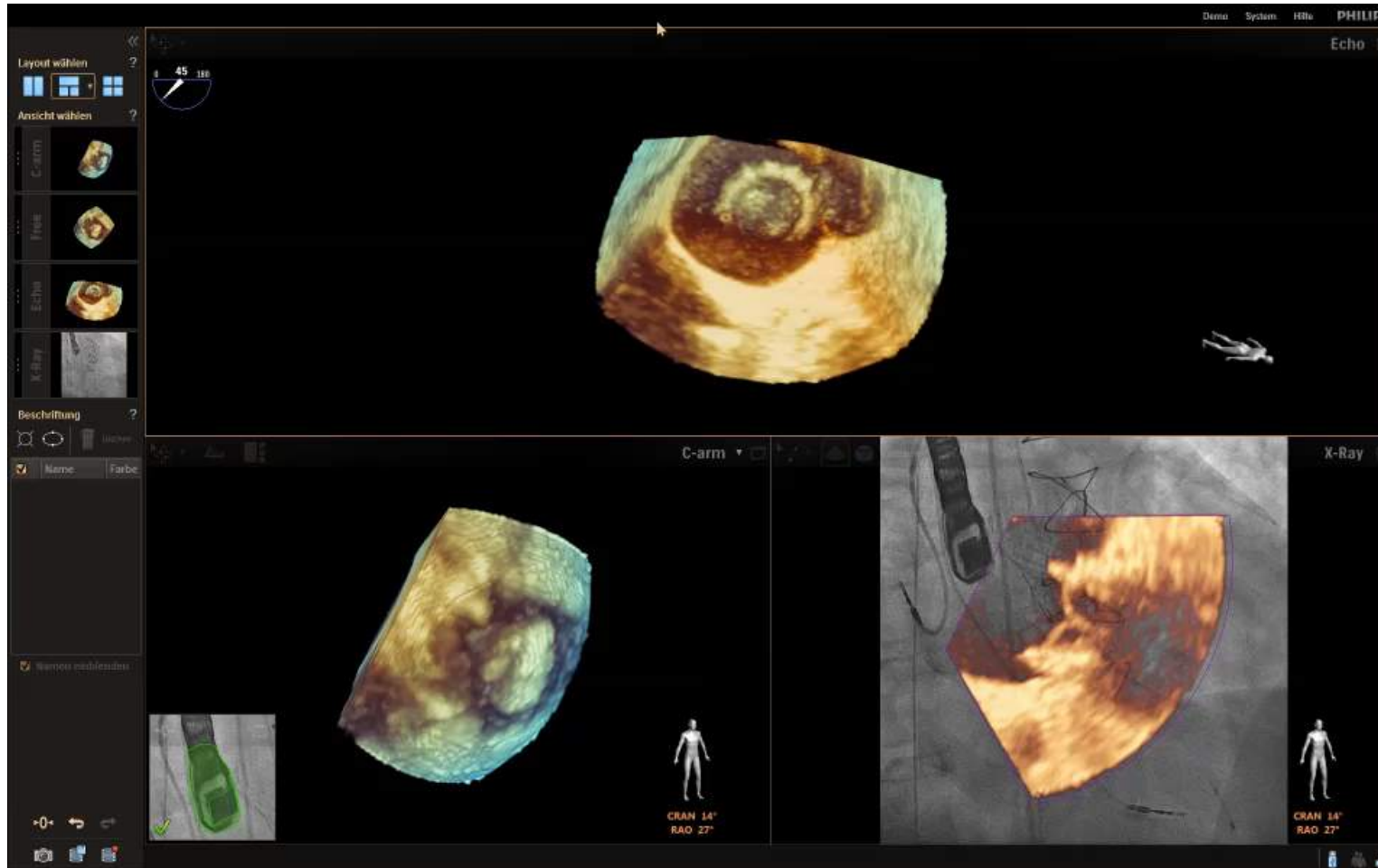


Image Guidance – D-VinV Mitral

M-ViV Implant; TEE-Fluouro-Fusion Imaging



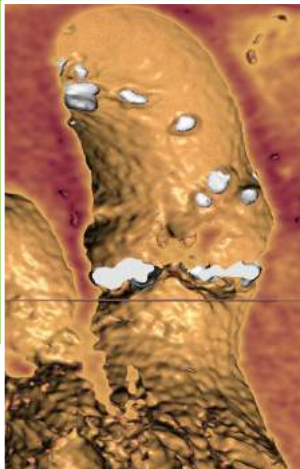
CT guided TAVI

Morphological risk assessment

Easy

almost all devices will work

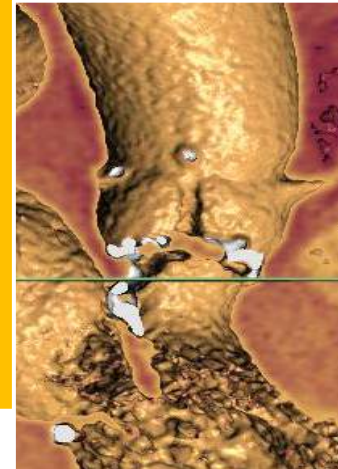
- No PVL
- No PPM
- No DLZ rupture
- No coronary occlusion



Intermediate

might favor one specific device or strategy to avoid

- PVL
- PPM
- DLZ rupture
- coronary occlusion

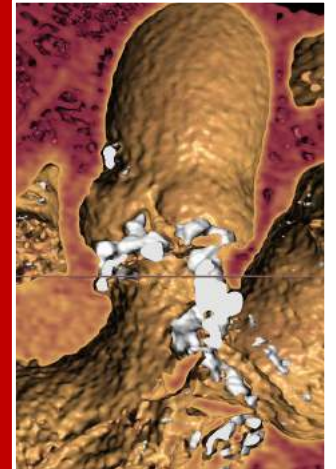


Hostile

TAVI might not be the best option

Risk for

- PVL
- PPM
- coronary occlusion
- DLZ rupture

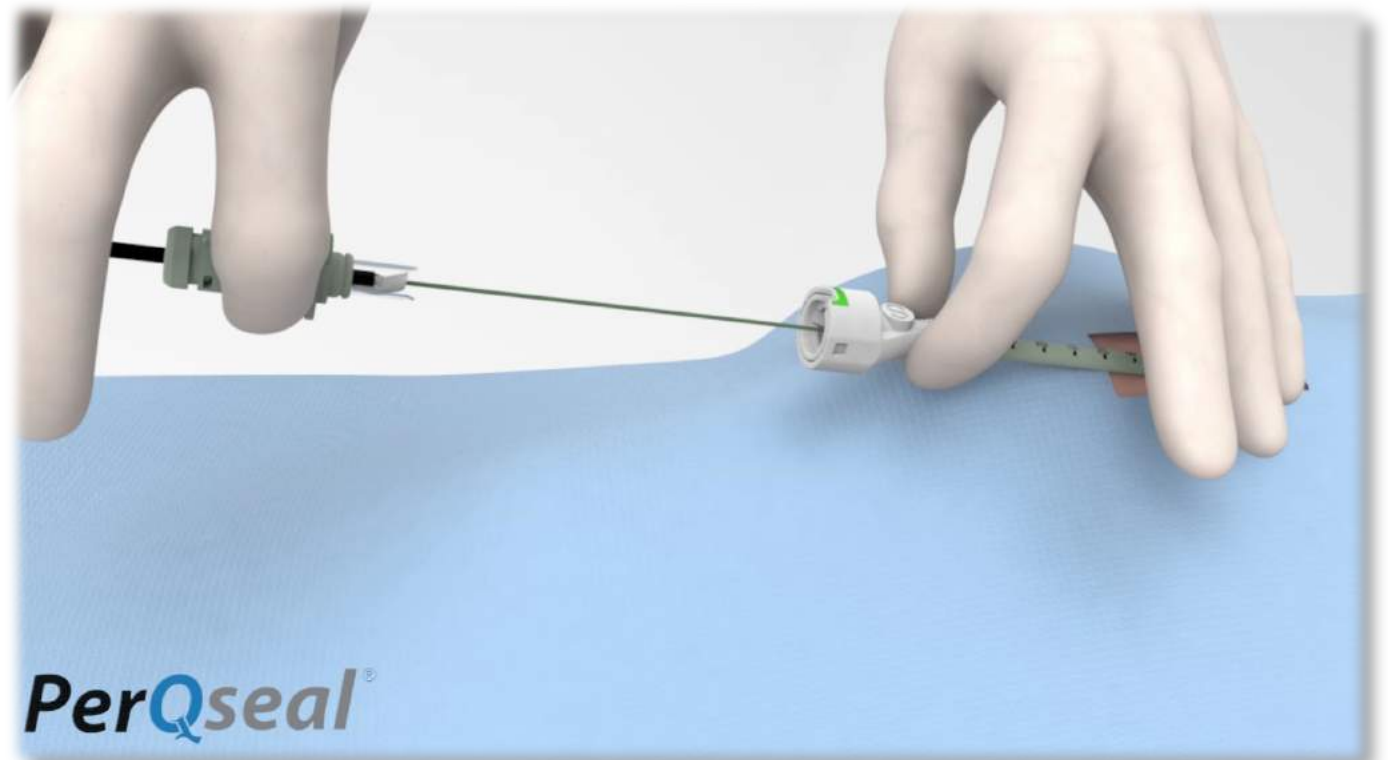
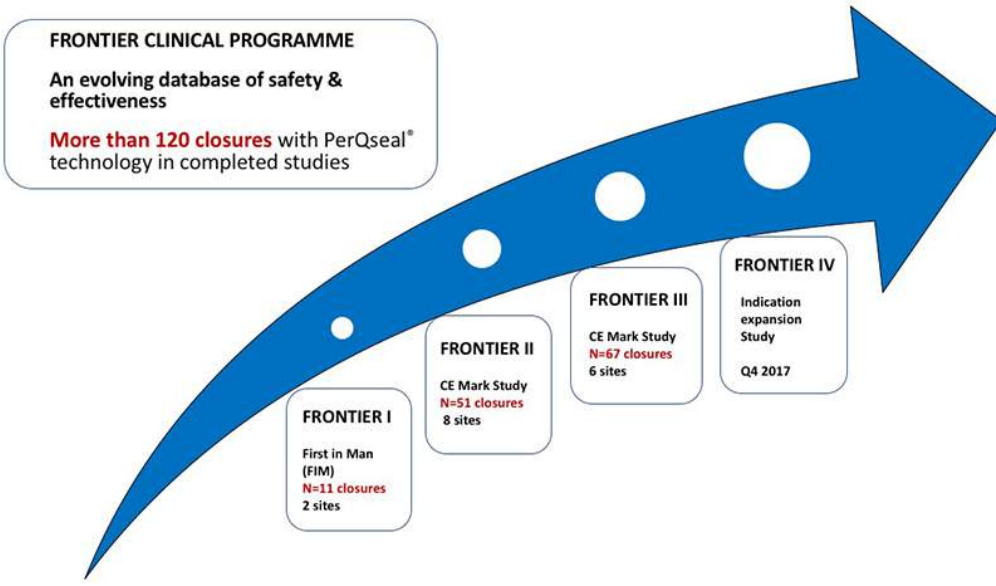




Additional technical solutions

Additional tools

PerQseal: percutaneous closure up to 24F, intravascular patch (resorbable synthetic polymer)



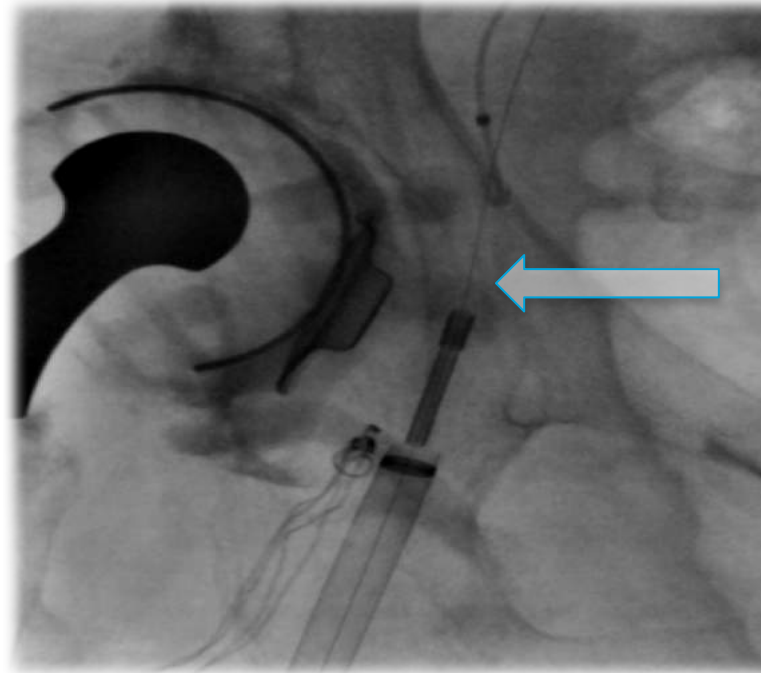
Additional tools

PerQseal: percutaneous closure up to 24F, intravascular patch (resorbable synthetic polymer)

Pre-implantation

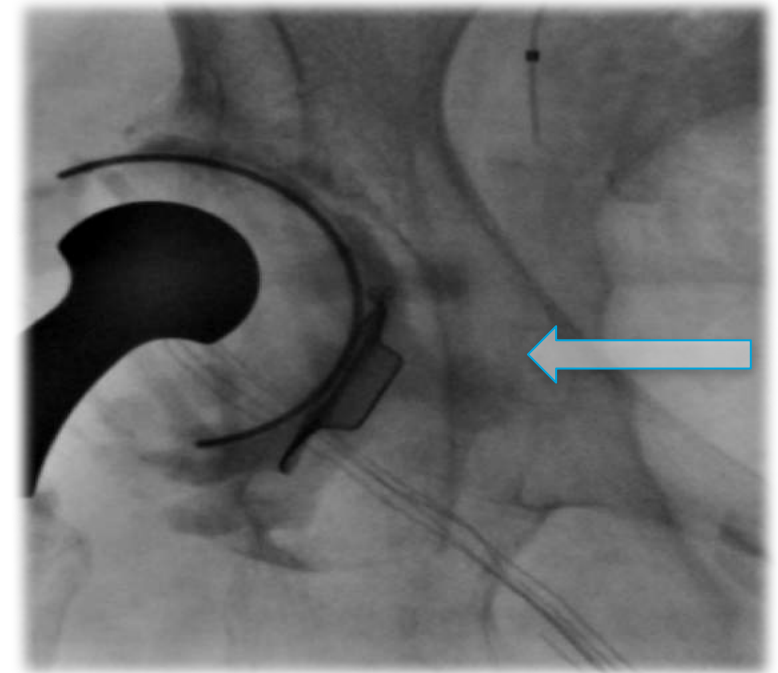


Tamponade peri-procedure



Control of bleeding during delivery

Post implantation

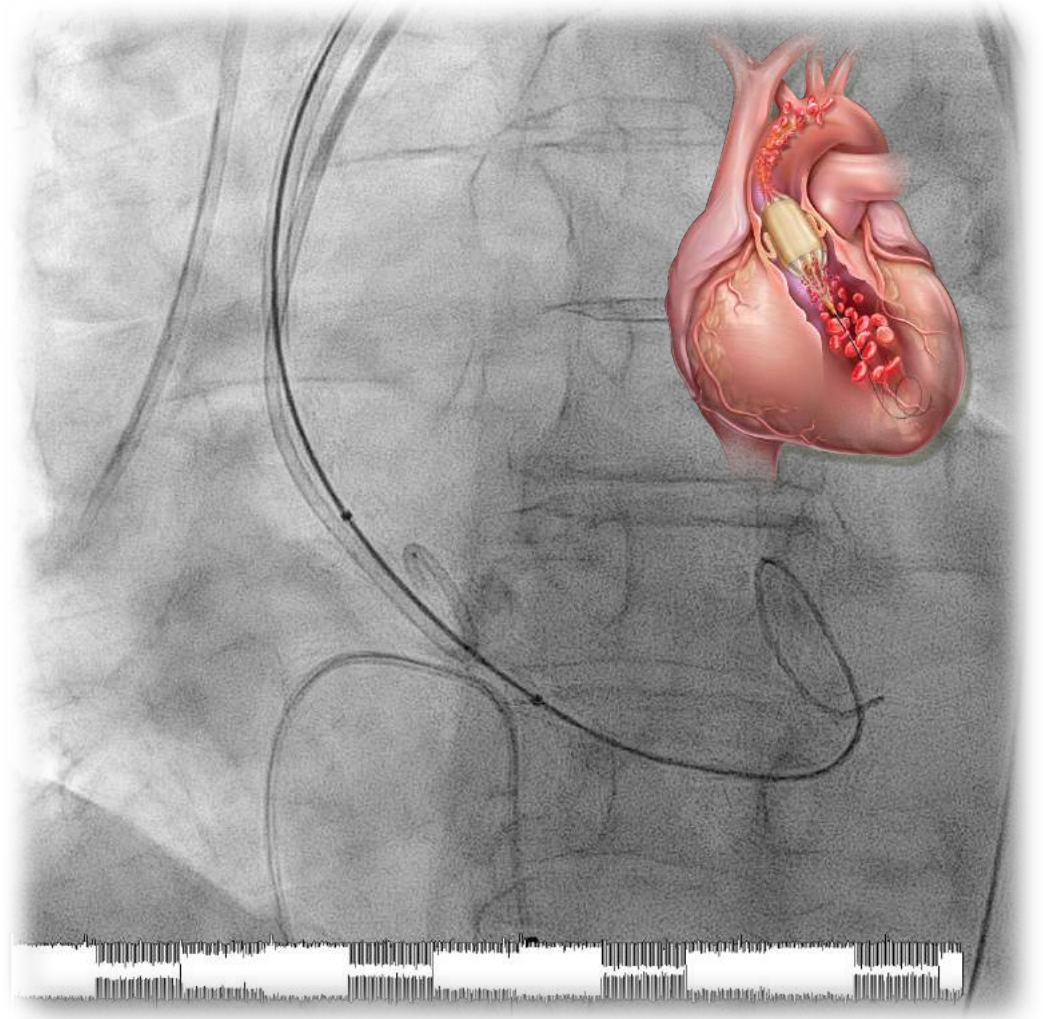


Complete haemostasis
No stenosis

← indicates site of implant

Additional tools

BARD True Flow balloon: continuous cardiac blood flow independent of the heart's rhythmic state



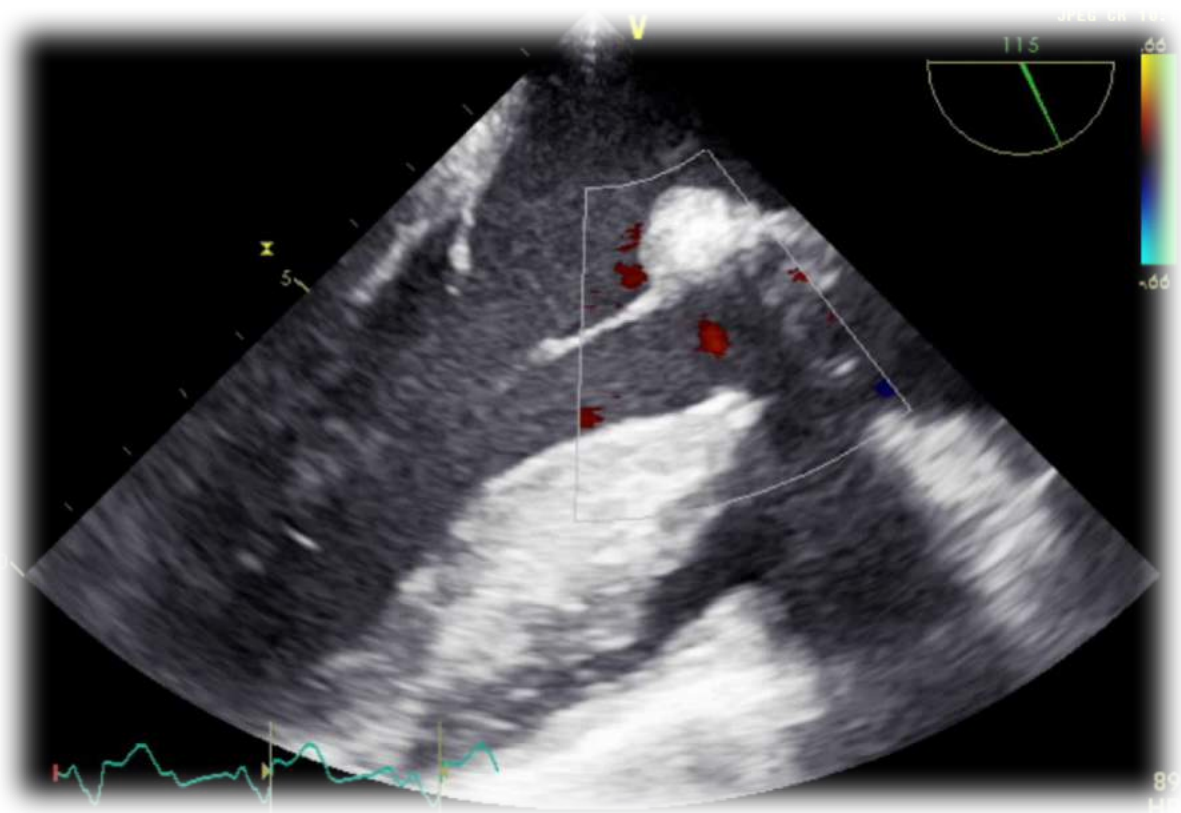
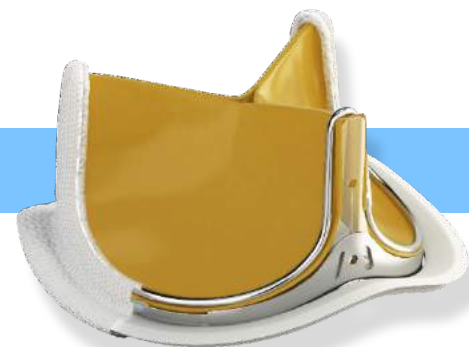
Additional tools

BARD True Flow balloon: continuous cardiac blood flow independent of the heart's rhythmic state



Additional tools

INSPIRIS: a platform for VinV



now



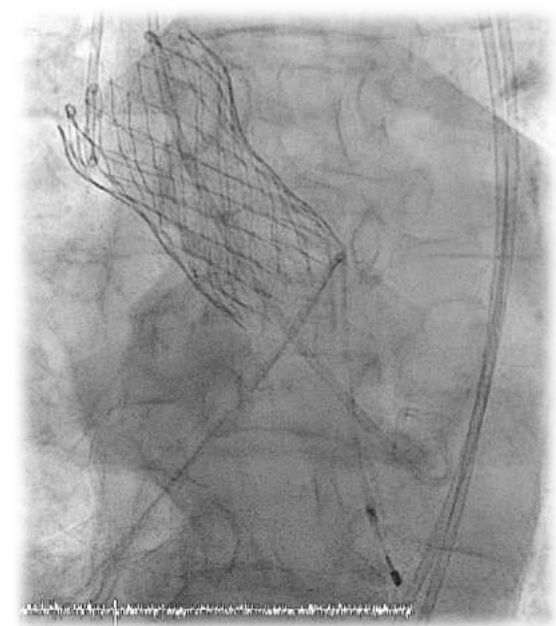
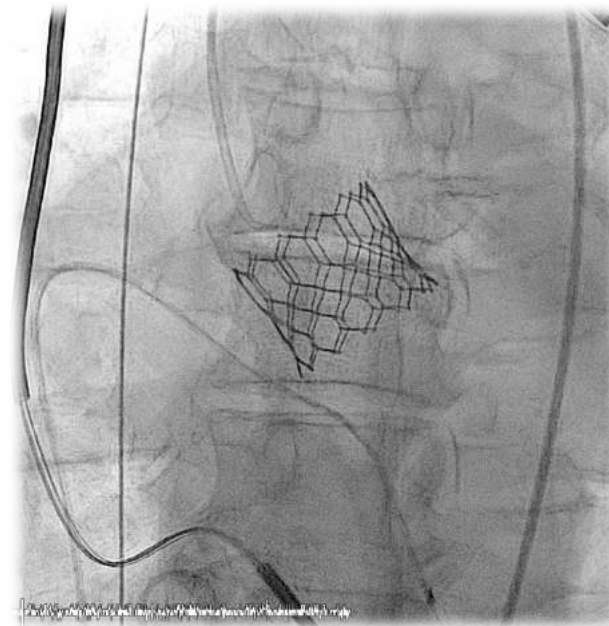
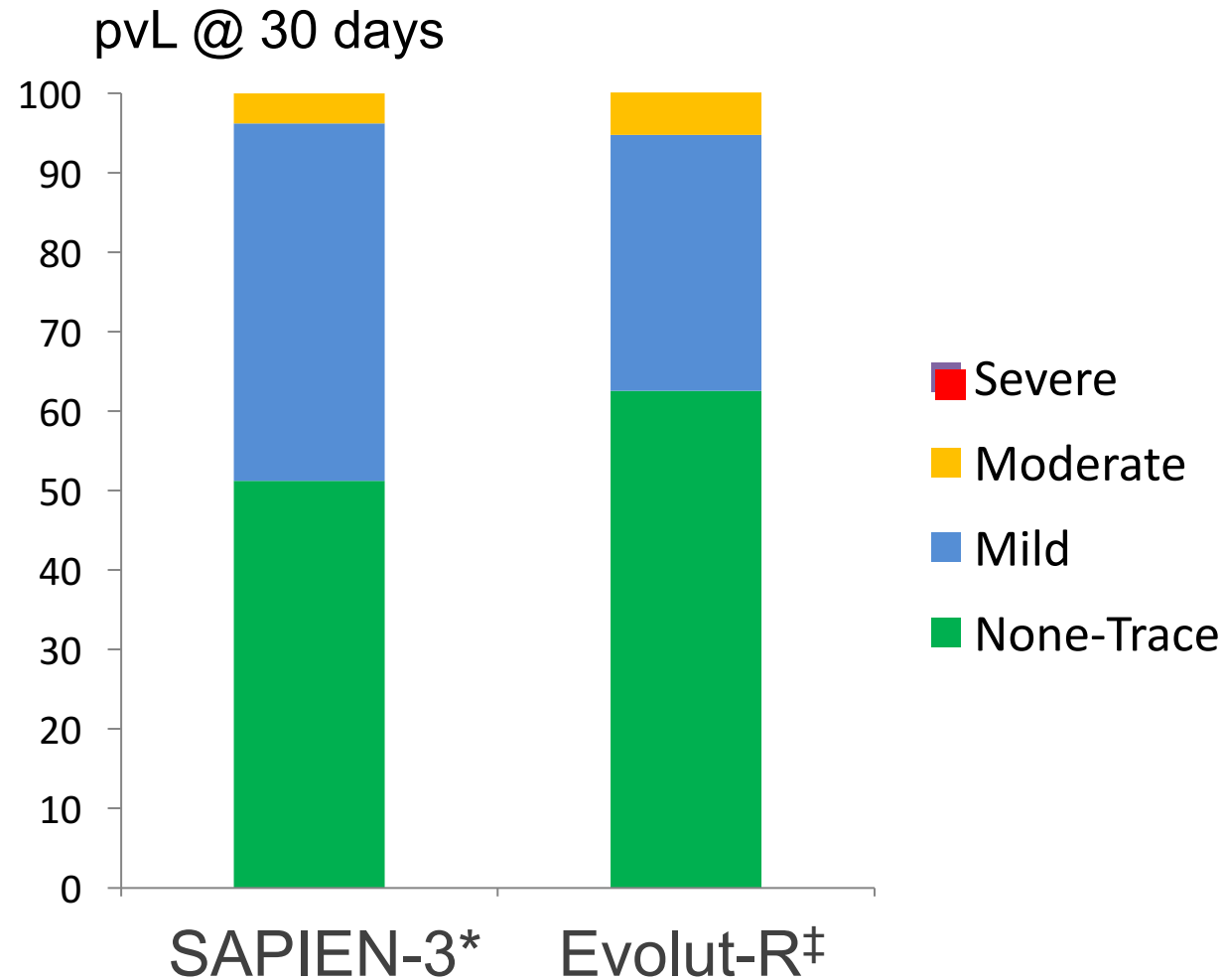
later



Next generation TAVI devices

Next generation TAVI devices

The present



*Thourani et al. Lancet 2016

†Williams et al. J Am Coll Cardiol 2016 (ACC.16)

Next generation TAVI devices

Evolut PRO: advanced sealing



Conformable Frame

Self-expanding nitinol frame conforms to annulus regardless of shape



CoreValve



Consistent Radial Force

Frame oversizing and cell geometry provide consistent radial force across treatable range

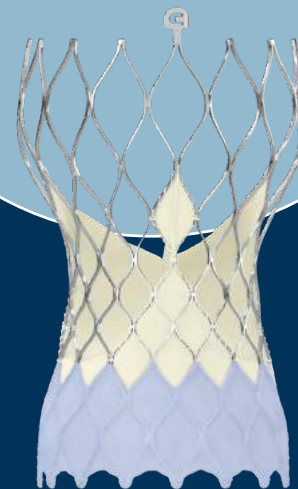


Evolut R



External Wrap

External wrap increases surface contact with native anatomy



Evolut PRO



Next generation TAVI devices

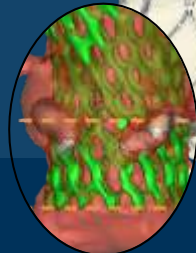
Evolut PRO: advanced sealing

Evolut™ R

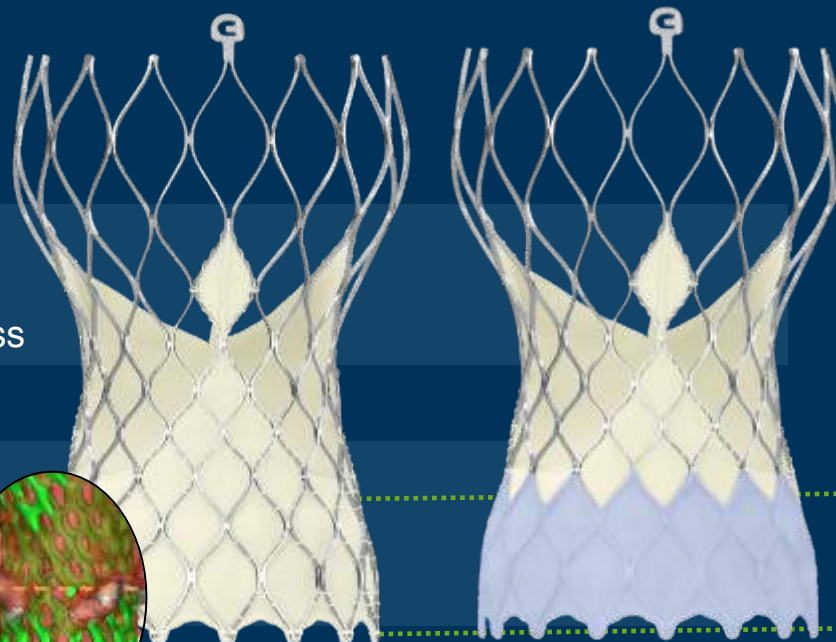
Evolut™ PRO

Supra-Annular Valve
Porcine Pericardial Tissue
Cell Size Enables Coronary Access

Self-Expanding Frame
Pericardial Skirt

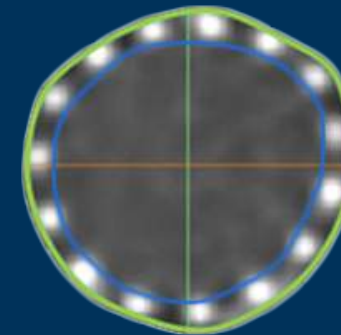


Sealing can occur at multiple levels;
including above and below calcification
with a self-expanding frame



Skirt
Height
13 mm

**Pericardial Wrap
Increases Surface Contact
with Native Anatomy**



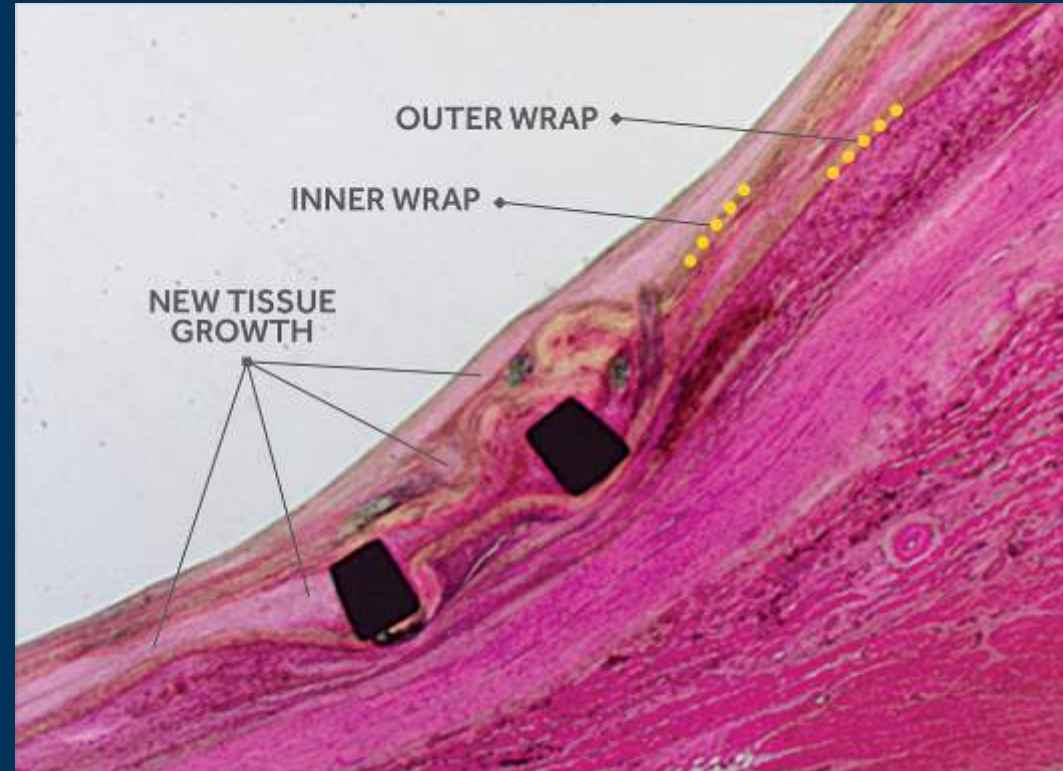
**Added Tissue Volume
between the TAV & native
anatomy to reduce gaps**

Next generation TAVI devices

Evolut PRO: advanced sealing

Animal Studies suggest favorable Response and Interaction with Native Tissue

- Low inflammatory response¹
- **Stable and mature tissue growth** observed at 90 days post implant¹
 - Thin and even layer of endothelial cells on inner lumen of device

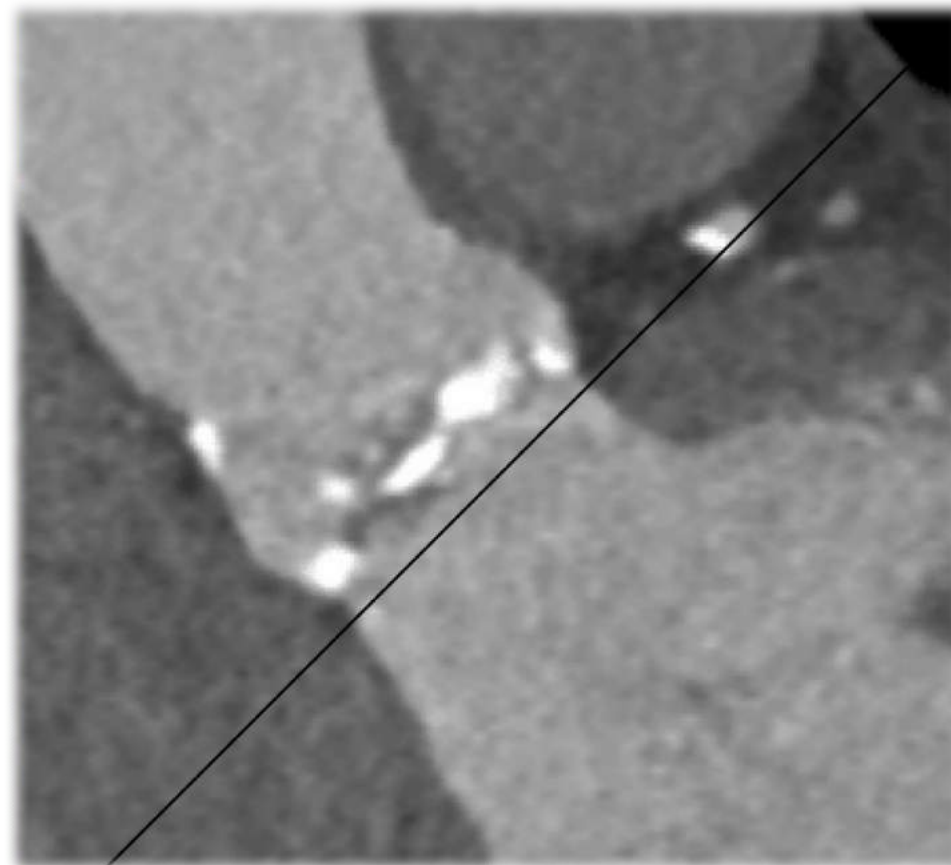
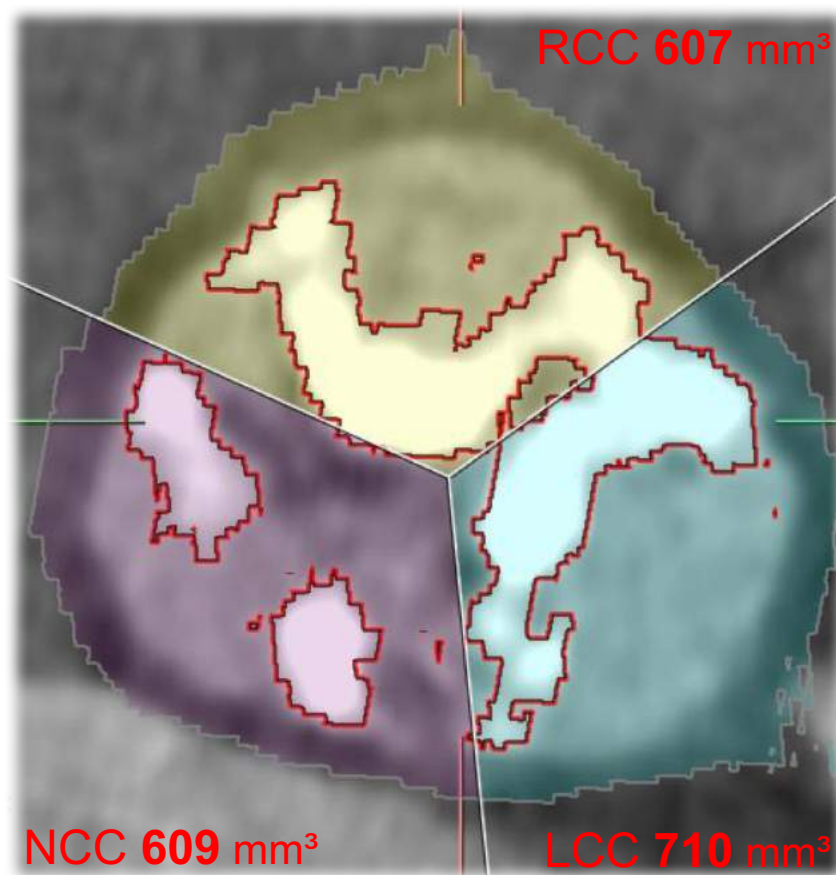
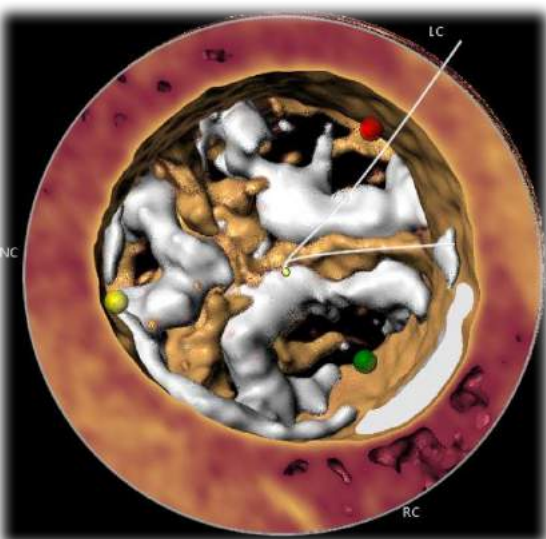


Evolut PRO explanted from Porcine Model at 60 Days, Cross Section between Nodes 1 and 2, example picture from MDT research study on file illustrating tissue interaction.²

1. Medtronic data on file. 90 day porcine GLP Evolut R study
2. Medtronic, data on file. 60 day porcine research study model,

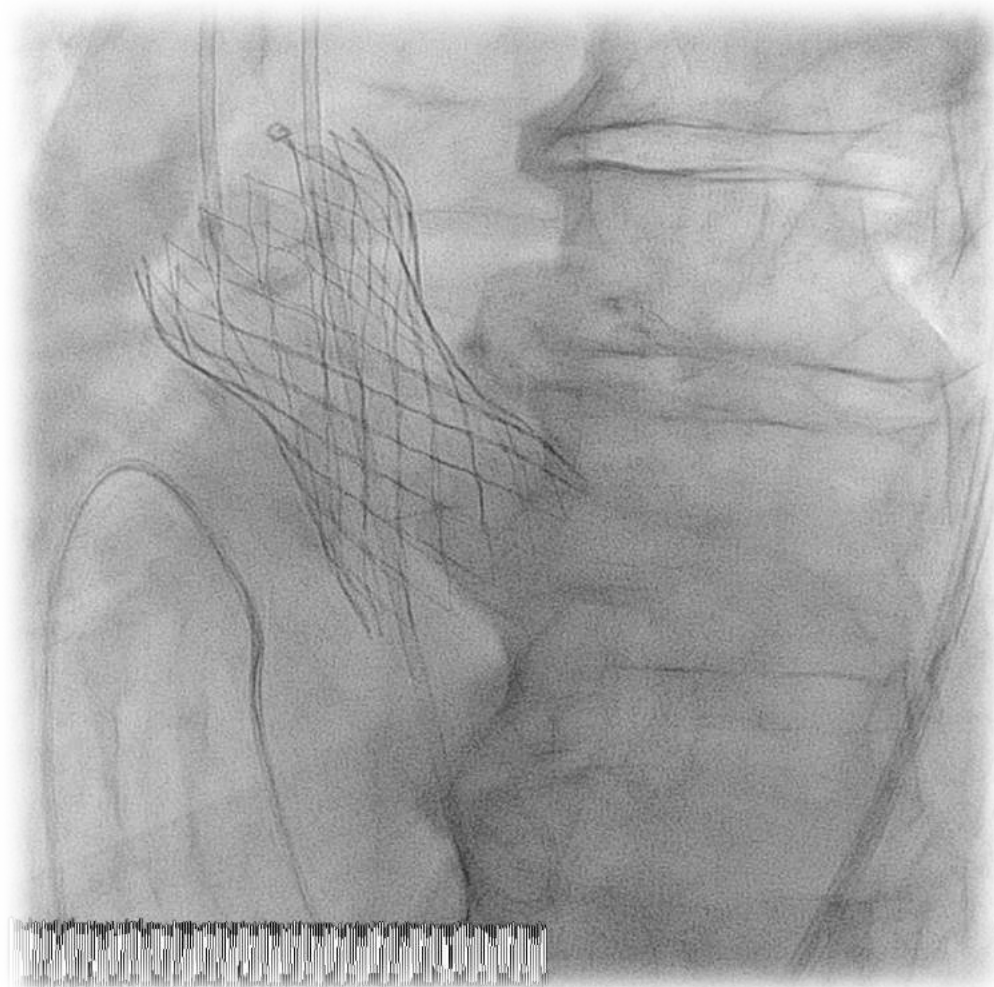
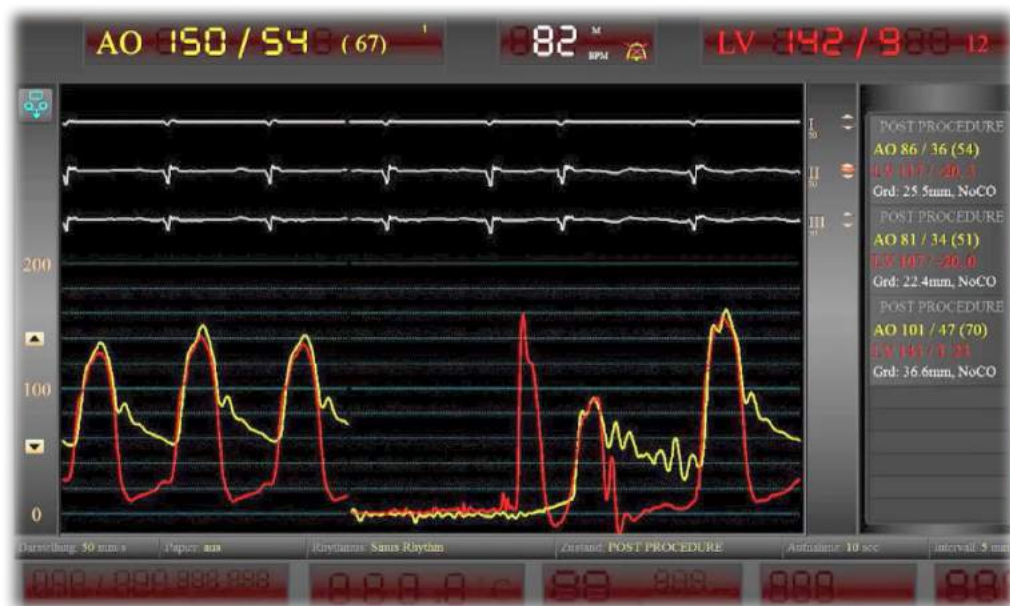
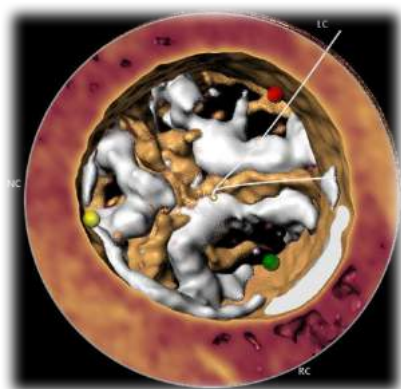
Next generation TAVI devices

Evolut PRO: advanced sealing



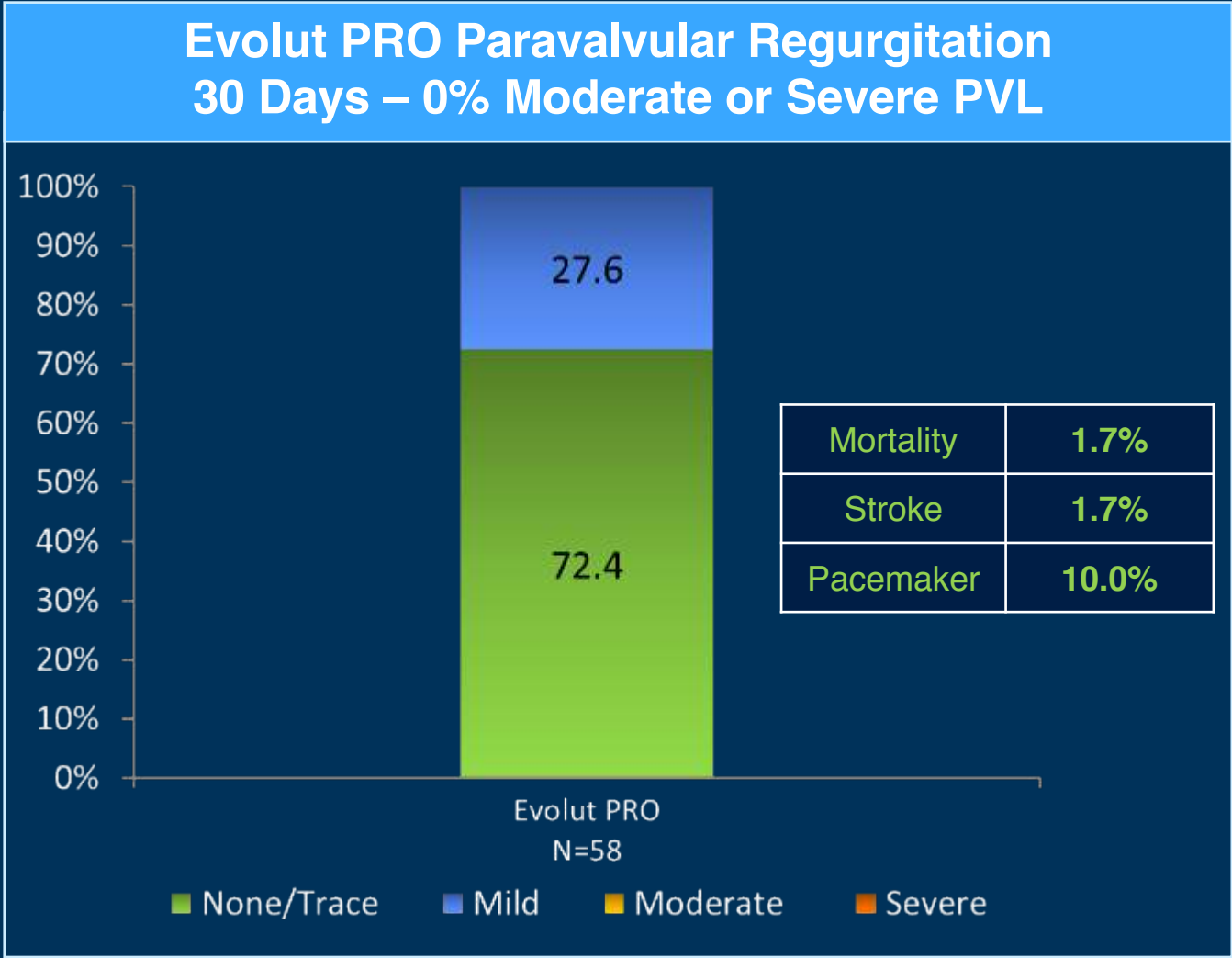
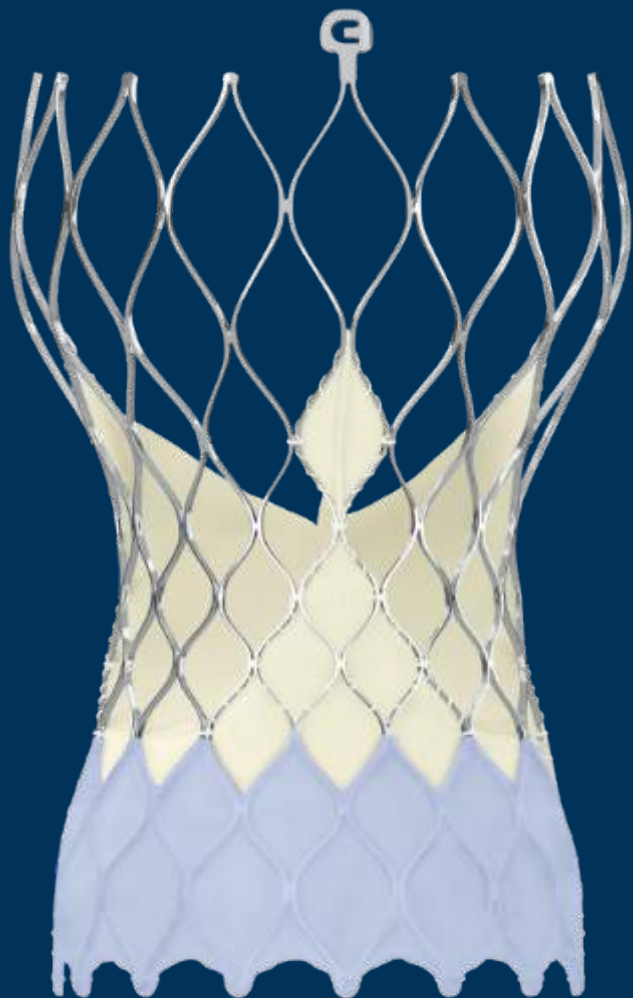
Next generation TAVI devices

Evolut PRO: advanced sealing



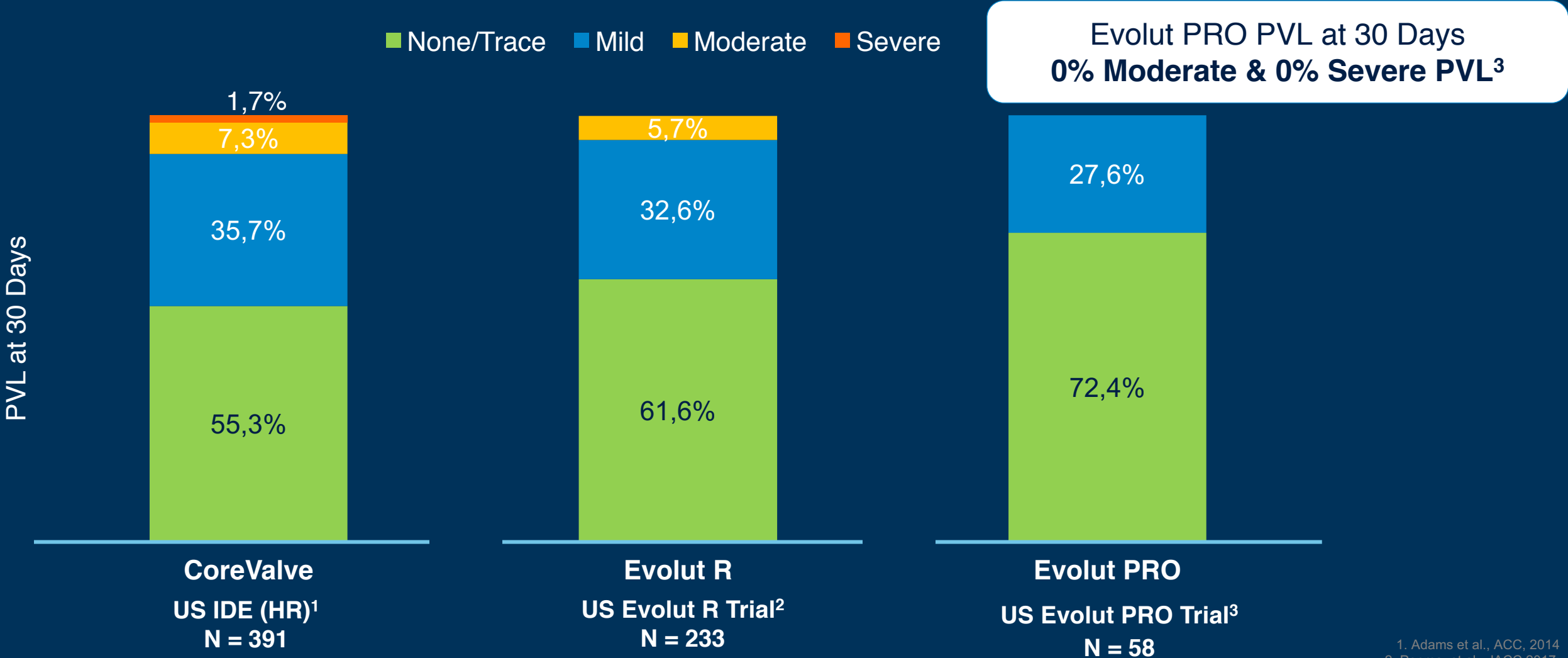
Next generation TAVI devices

Evolut PRO: advanced sealing



Next generation TAVI devices

Evolut PRO: advanced sealing

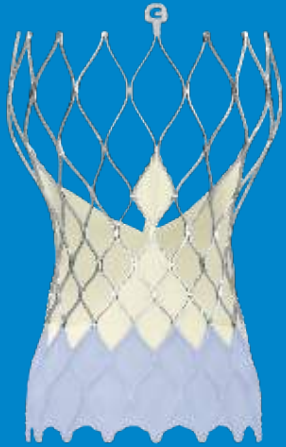


Next generation TAVI devices

Evolut PRO and beyond

Evolut™ PRO

- Advanced Sealing



**FDA & CE-Mark
Approved**

EnVeo™ PRO

- Seamless Tracking



**IN
DEVELOPMENT**

34 PRO

- PRO Performance:
Large Valve



**IN
DEVELOPMENT**

Next Gen Evolut™

- Superior Ease
of Use
- Positioning
Accuracy
- Low Profile

**IN
DEVELOPMENT**

Horizon

- Transformative
Aortic Platform
- Concentric
deployment



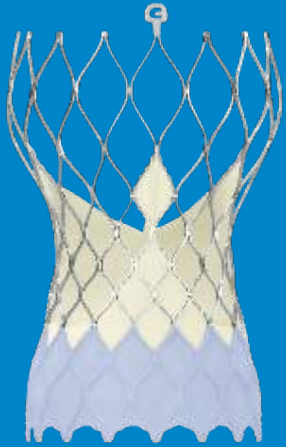
**IN
DEVELOPMENT**

Next generation TAVI devices

Evolut PRO and beyond

Evolut™ PRO

- Advanced Sealing



**FDA & CE-Mark
Approved**

EnVeo™ PRO

- Seamless Tracking



**IN
DEVELOPMENT**

34 PRO

- PRO Performance:
Large Valve



**IN
DEVELOPMENT**

Next Gen Evolut™

- Superior Ease of Use
- Positioning Accuracy
- Low Profile

**IN
DEVELOPMENT**

Horizon

- Transformative
Aortic Platform



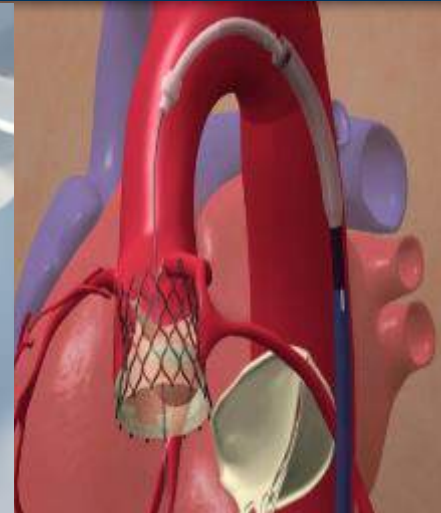
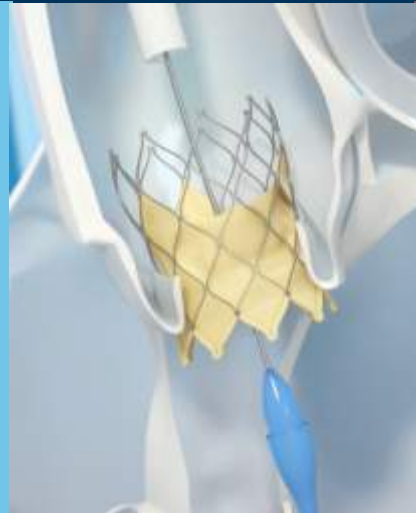
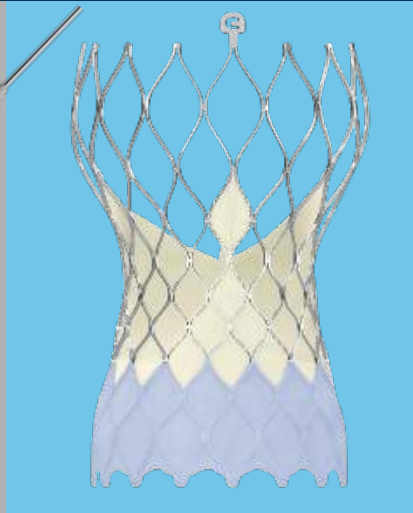
**IN
DEVELOPMENT**

Next generation TAVI devices

Future generations (MEDTRONIC)

Evolut NG

Horizon



Low
Profile

Controlled
Release

Concentric
Deployment

Superior
Hemodynamics

Improved
Visualization

Consistent
Implant Depth

Enhanced
Sealing

Complete
Control

Next generation TAVI devices

SAPIEN 3 Ultra System

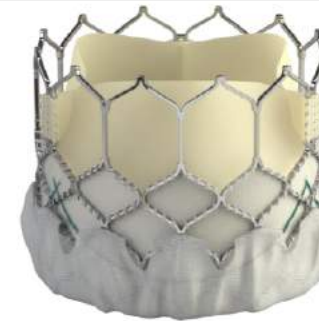
2016 | euro
PCR

Edwards SAPIEN 3 Ultra
Transcatheter Heart Valve System

John Webb, MD
St. Paul's Hospital, University of British Columbia
Vancouver, Canada



SAPIEN 3 Valve



1.1% 30-day All-cause mortality
(n=1077 PARTNER 2 S3i Trial)

0.9% 30-day All-cause mortality
(n=109 SAPIEN 3 EU Study)

SAPIEN 3 Ultra
Delivery System



Axela Sheath



On-balloon design removes the need for valve alignment

14F Axela Sheath for all valve sizes with **5.5 mm** vessel indication

Seamless sheath design allows for transient expansion and active contraction

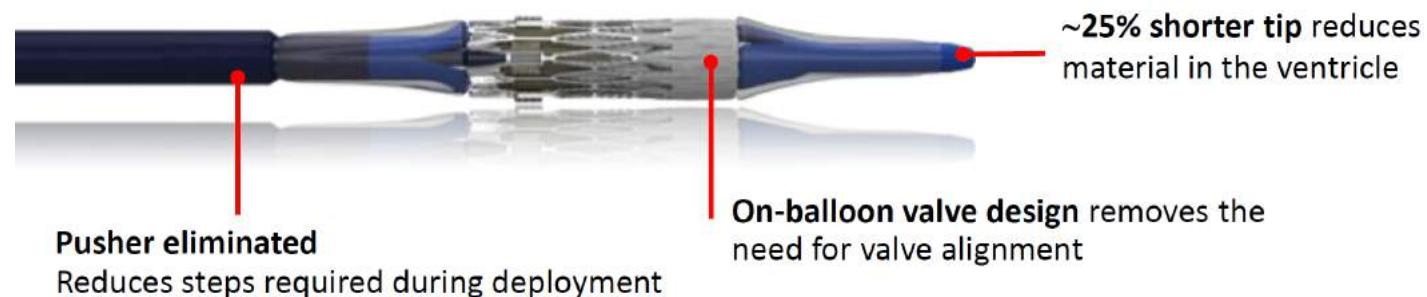
Next generation TAVI devices

On balloon design

2016 | euro
PCR

Edwards SAPIEN 3 Ultra
Transcatheter Heart Valve System

John Webb, MD
St. Paul's Hospital, University of British Columbia
Vancouver, Canada



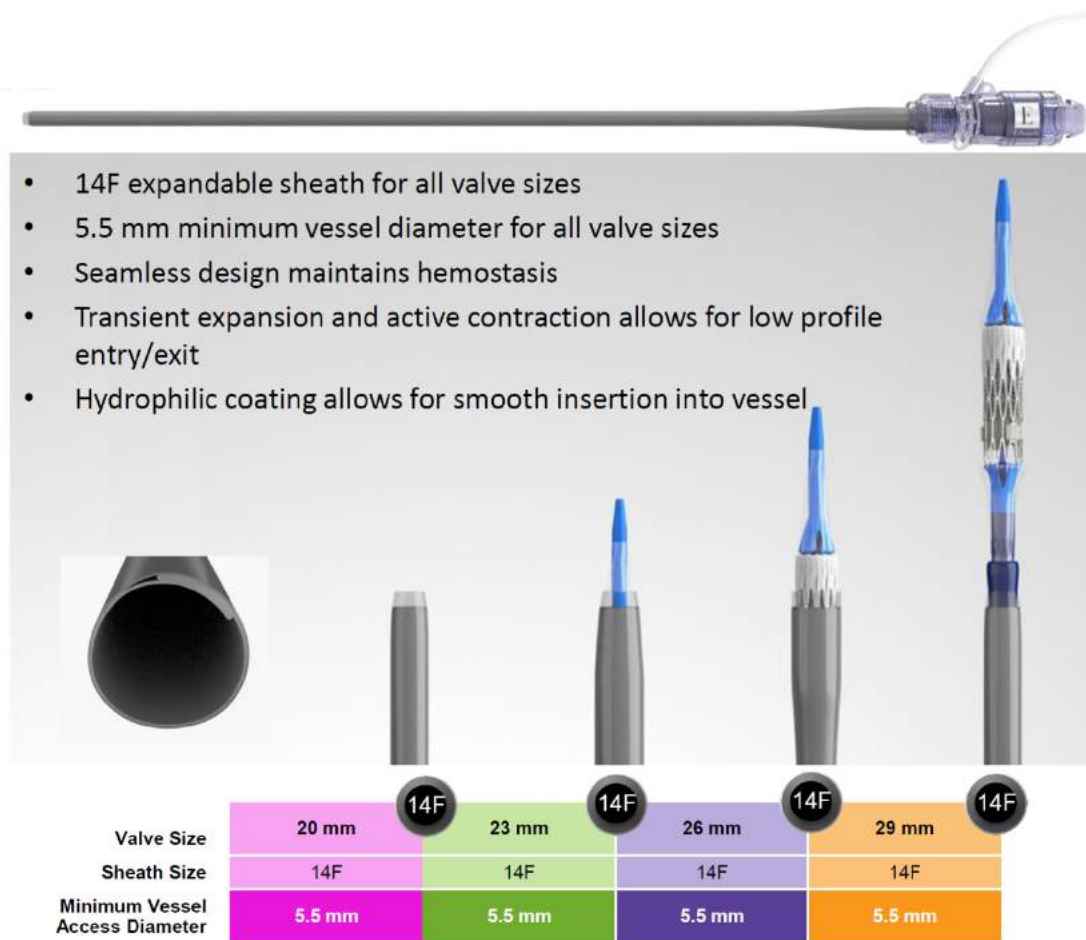
Next generation TAVI devices

Axela Sheath (14F, expandable)

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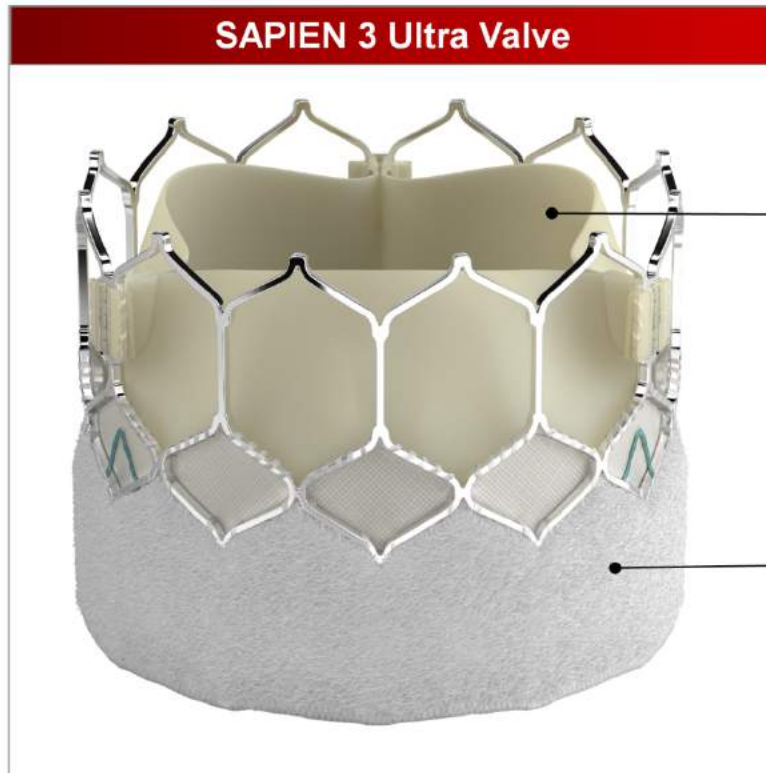
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Vancouver, Canada



Next generation TAVI devices

SAPIEN 3 Ultra Valve

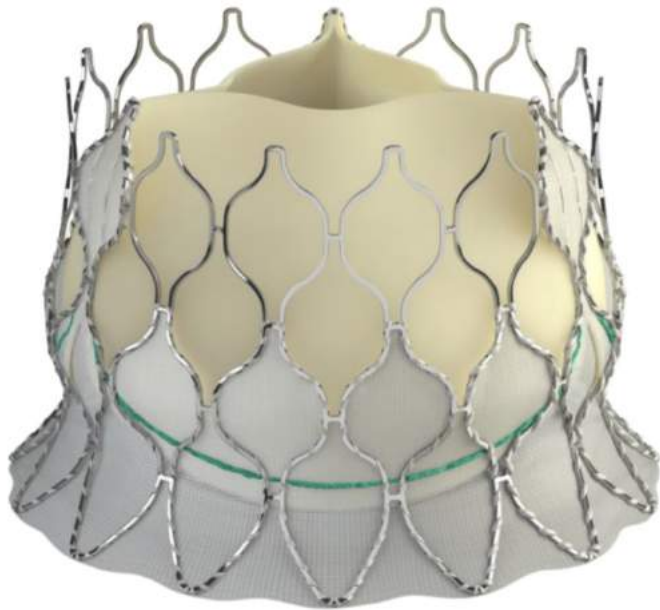


- Proven SAPIEN 3 leaflet and frame design

- Textured 3-dimensional PET skirt design
- 40% taller skirt - up to 50% more contact surface area with native anatomy
- 14F sheath compatible

Next generation TAVI devices

CENTERA

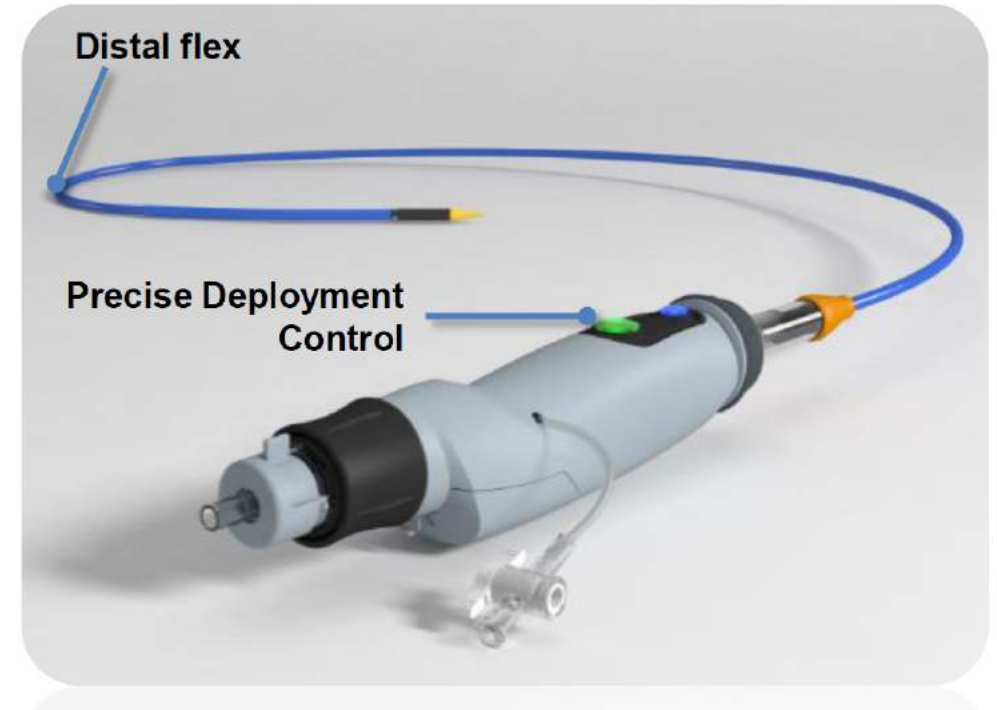


Nitinol frame

- self-expanding
- contoured

Pericardial leaflets

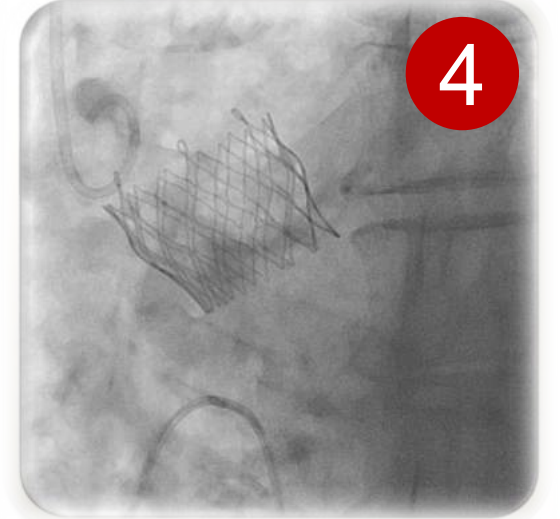
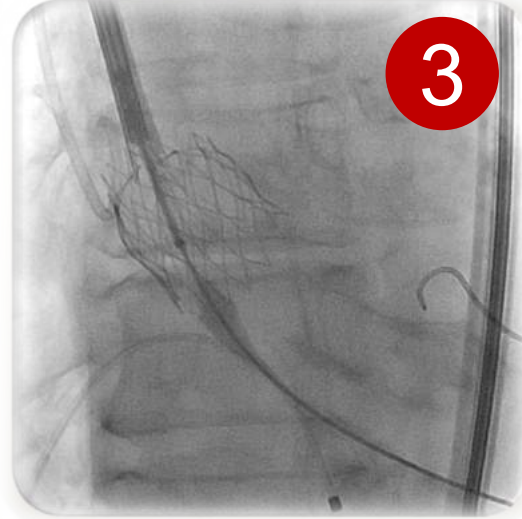
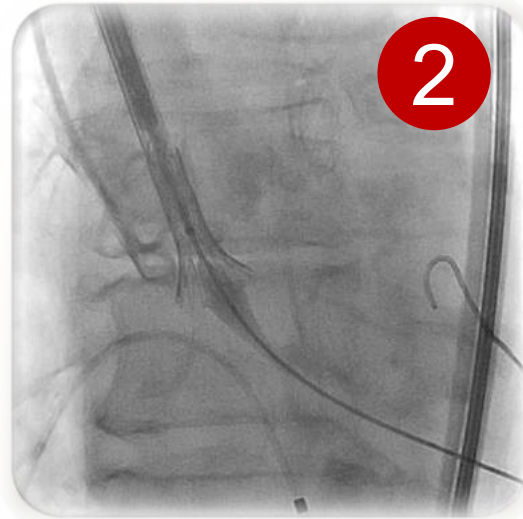
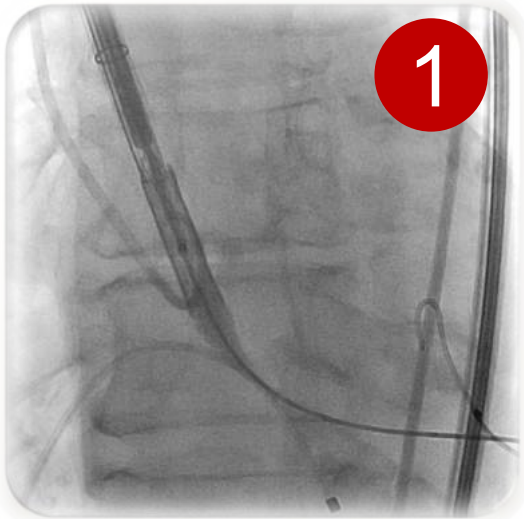
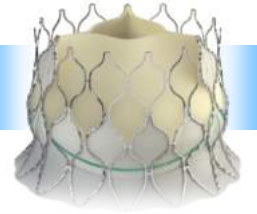
- bovine
- treated



14F eSheath compatible
motorized handle
repositionable and recapturable
flex mechanism (trackability, coaxial alignment)

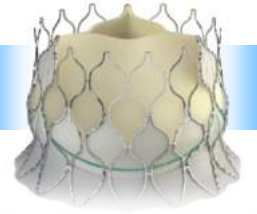
Next generation TAVI devices

CENTERA



Next generation TAVI devices

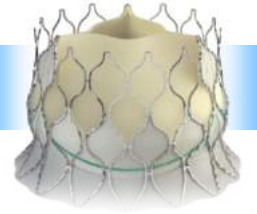
CENTERA: First results



Parameters	As treated (n = 203) %
Recapturing and repositioning	3.5%
Valve embolization	0.5%
Required CPB	2.0%
Technical success	97.5%
Device success	96.4%

Next generation TAVI devices

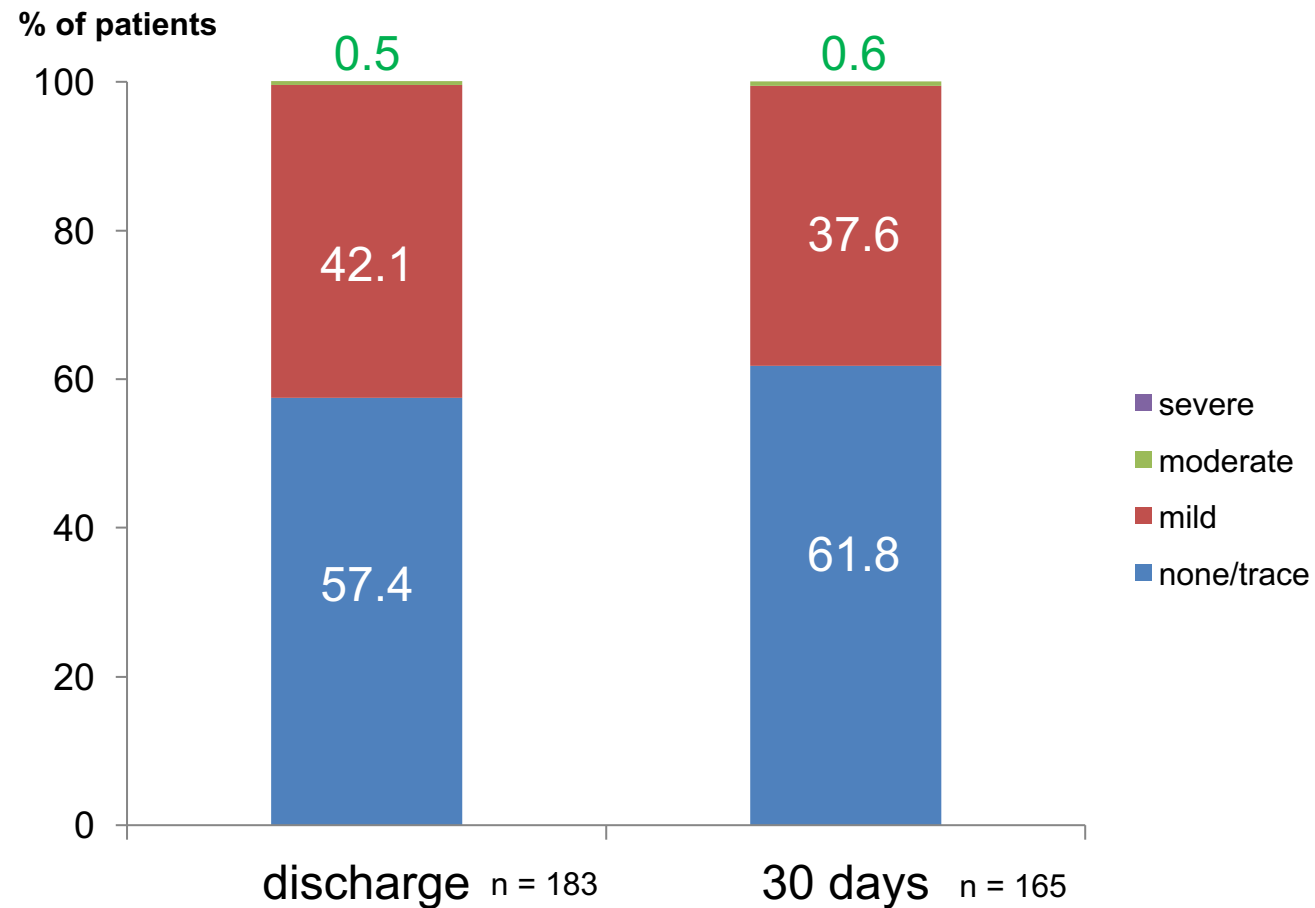
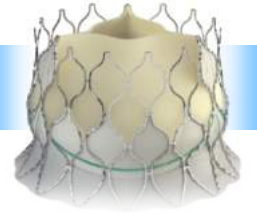
CENTERA: Clinical outcomes at 30-days



Safety endpoints	As treated (n = 203) %
Mortality	1.0%
Stroke	4.0%
Disabling stroke	2.5%
Myocardial infarction	1.5%
Major vascular complication	6.4%
Life-threatening/disabling bleeding	4.9%
New permanent pacemaker	4.9%

Next generation TAVI devices

CENTERA: aortic regurgitation



no severe AR

Next generation TAVI devices

SYMETIS ACURATE neo Advanced Seal



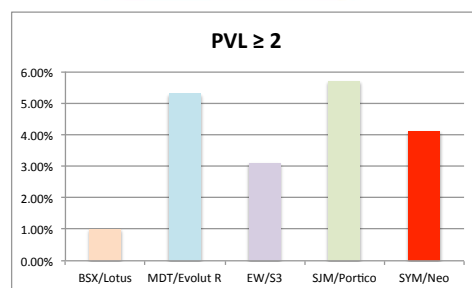
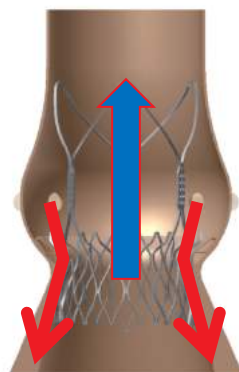
2017 **euroPCR**

ACURATE neo AS

Advanced Sealing technology –
First Data Presentation



Paravalvular leak PVL

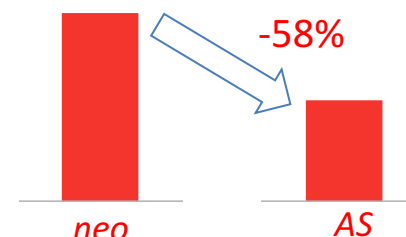


BSX: Meredith2014 (N=120)/ REPRIS II
MDT: Williams2016 (N=241)
EW: Wendler2016 (N=1695) / SOURCE 3

ACURATE *neo*



ACURATE *AS*



In-vitro Simulated PVL
Regurgitant Fraction (%)

SJM: Manoharan2016 (N=222)
SYM: Möllmann2016 (N=1000)

ACURATE *neo AS*

- Incremental development
- Same stent
- Same valve
- Same delivery system
- Modified skirt material
- Reduced PVL expected
- First 30/120 patients already enrolled in CE mark trial

Next generation TAVI devices



SYMETIS ACURATE neo Advanced Seal

2017 euro
PCR

ACURATE neo AS

Advanced Sealing technology –
First Data Presentation



PERFORMANCE	Post-implant (n=30)	7D (n=28*)	30D (n=22**)
<i>Days post-procedure</i> [days \pm SD]	-	6 \pm 1	35 \pm 11
Mean ∂ P gradient [mmHg, mean \pm SD]	6.6 \pm 3.1	9.3 \pm 3.2	8.3 \pm 2.7
Mean EOA [cm ² , mean \pm SD]	1.6 \pm 0.4	1.7 \pm 0.4	1.7 \pm 0.3
PVL Grade	n=28	n=28	n=22
Grade 0 (none/trace) [n,%]	21 / 75.0	19 / 67.9	17 / 77.3
Grade 1 (mild) [n,%]	7 / 25.0	9 / 32.1	5 / 22.7
\geq Grade 2 [n,%]	-	-	-

Next generation TAVI devices



SYMETIS ACURATE neo Advanced Seal

2017 euro
PCR

ACURATE neo AS

Advanced Sealing technology –
First Data Presentation

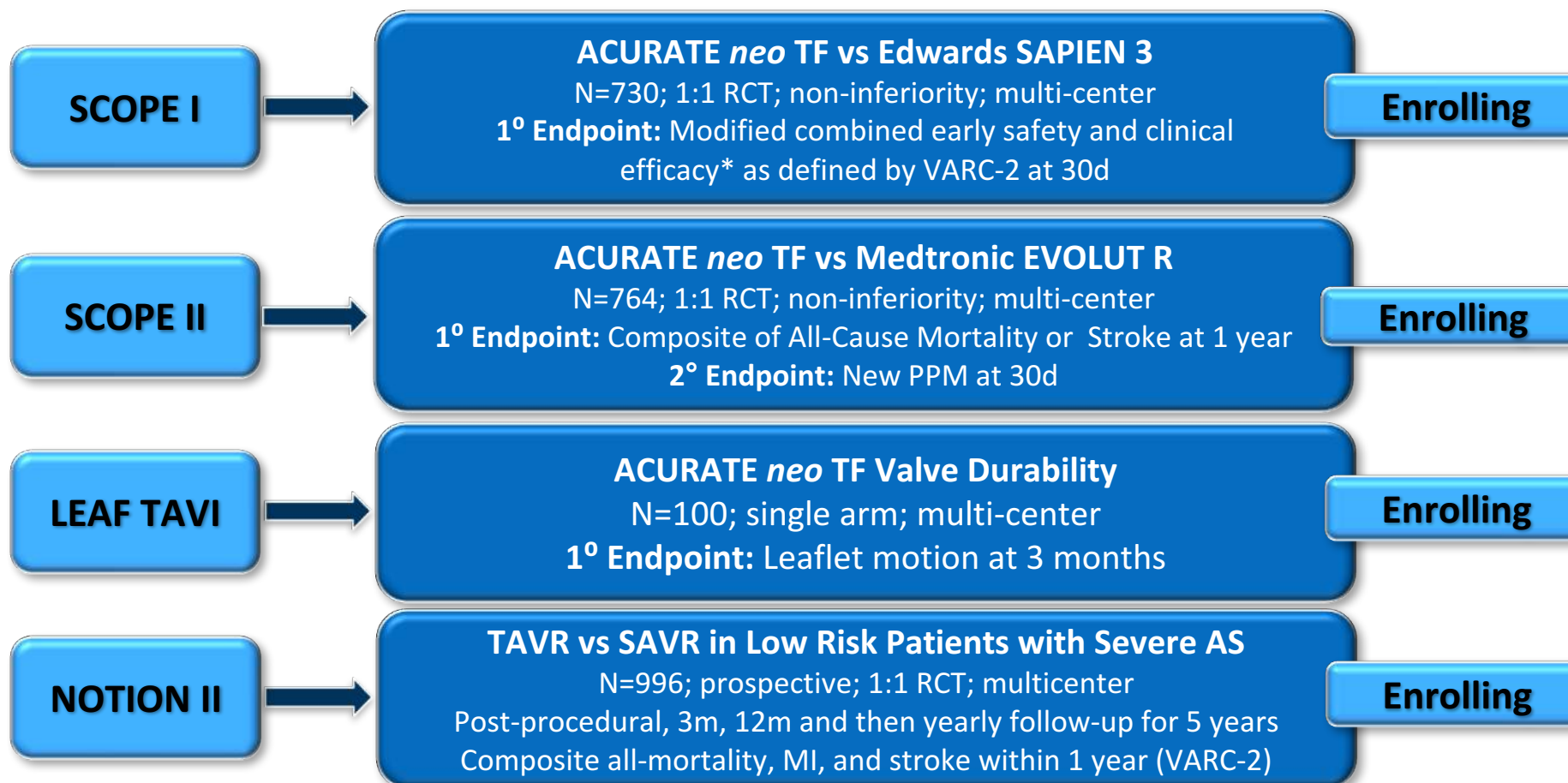


VARC 2 COMBINED SAFETY	30D
Population [n]	30
All-cause mortality [n,%]	0 / 0.0
Stroke [n,%]	1 / 3.3
Life-threatening bleeding [n,%]	0 / 0.0
Coronary artery obstruction requiring intervention [n,%]	0 / 0.0
Major vascular complications [n,%]	0 / 0.0
AKI stage 2 or 3 [n,%]	0 / 0.0
Repeat procedure for valve-related dysfunction [n,%]	0 / 0.0
Patients with at least one VARC 2 event [n,%]	1 / 3.3
Freedom from VARC 2 events [n,%]	29 / 96.7

Next generation TAVI devices



ACURATE neo ISRs



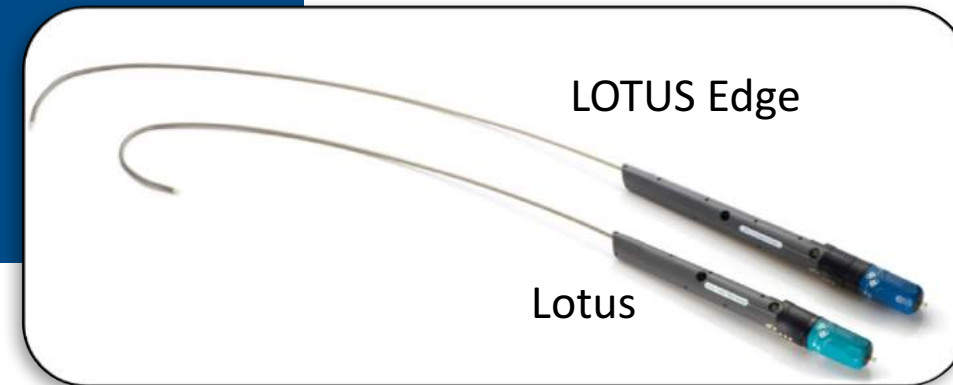
Next generation TAVI devices

LOTUS Edge Valve System



Design Goals

- Maintain benefits of first generation Lotus
 - Adaptive seal to minimize PVL
 - Complete repositionability
 - Early valve function
- Improve delivery
 - Lower profile system
 - More flexible catheter
- Optimize deployment
 - Depth Guard™ limits depth of implant
 - One-view locking with additional RO Markers



Next generation TAVI devices

LOTUS Edge Valve System

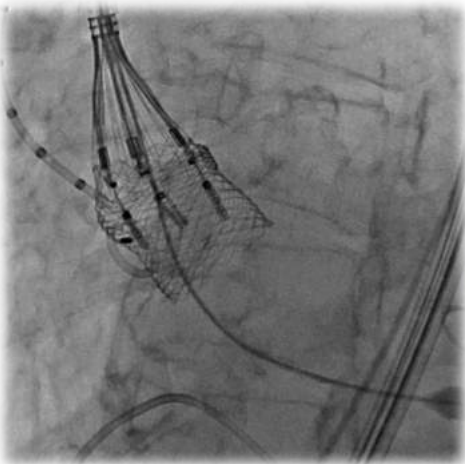


LOTUS Edge



LOTUS Edge Catheter

- Increased flexibility
- Exceptional coaxial alignment with optimized pre-shape curve
- Proximal catheter profile reduction (3F – 4F)



LOTUS Edge Valve Modifications

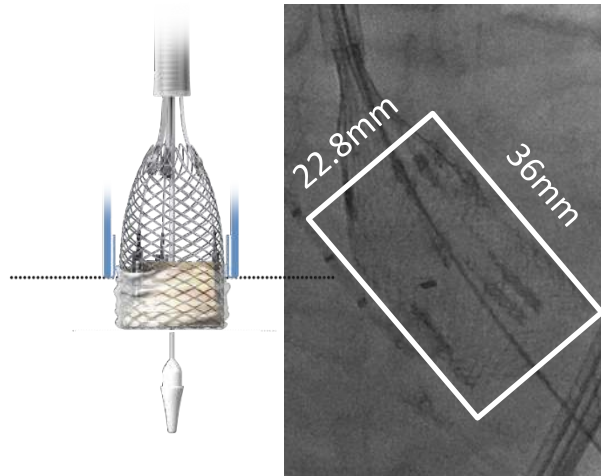
- One-view locking with RO markers
- Limited depth of implant with Depth Guard™ technology

Next generation TAVI devices

LOTUS Edge Valve System



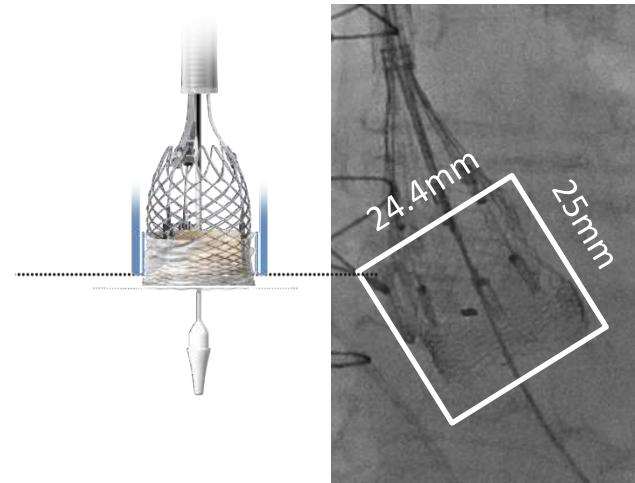
Controlled Mechanical Expansion



The Lotus Valve System

- Frame elongates during deployment before anchoring

Controlled Mechanical Expansion with Depth Guard



Lotus with Depth Guard & LOTUS Edge

- Anchors early during deployment with less elongation
- Minimizes depth of valve frame reducing LVOT interaction

Next generation TAVI devices



LOTUS Edge Valve System

Design Feature	Lotus	Lotus with Depth Guard	LOTUS Edge
Adaptive Seal	✓	✓	✓
Braided NiTi Frame	✓	✓	✓
Early Valve Function	✓	✓	✓
23mm, 25mm, & 27mm Sizes	✓	✓	✓ + 21mm & 29mm
Depth Guard		✓	✓
One-View Locking			✓
Sheath	18F ID	18F ID	14F / 15F ID
Delivery System	Pre-shaped	Pre-shaped	Flexible, less outward radial force

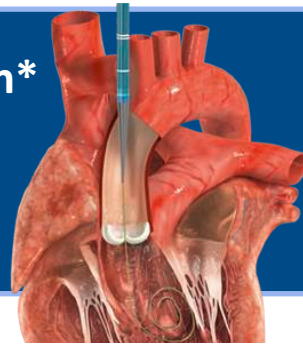
Next generation TAVI devices

LOTUS Edge Valve System



iSleeve™ Expandable Sheath*

14F /15F ID design
Improved vessel access



BOLT™ Direct Access Sheath

Reduced length
Uncoated with multiple markers

LOTUS Edge™ Valve System

Enhanced flexibility
Optimizing valve deployment
One-view locking with RO markers
Limited depth of implant with Depth Guard

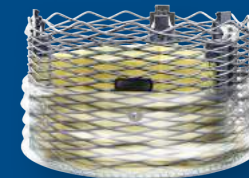
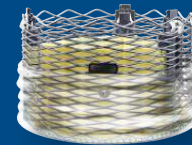


Five Valve Sizes

21mm*

New

29mm*

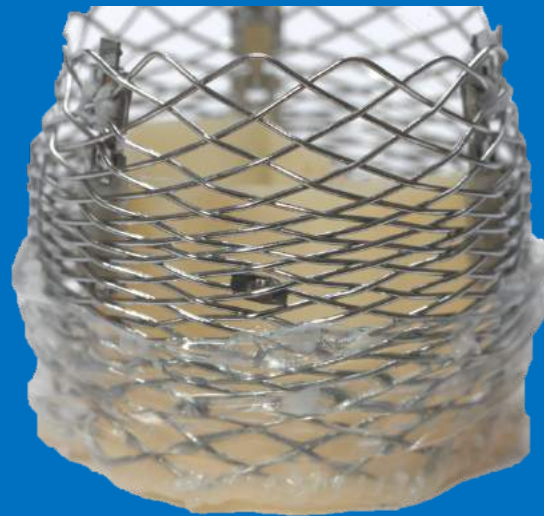
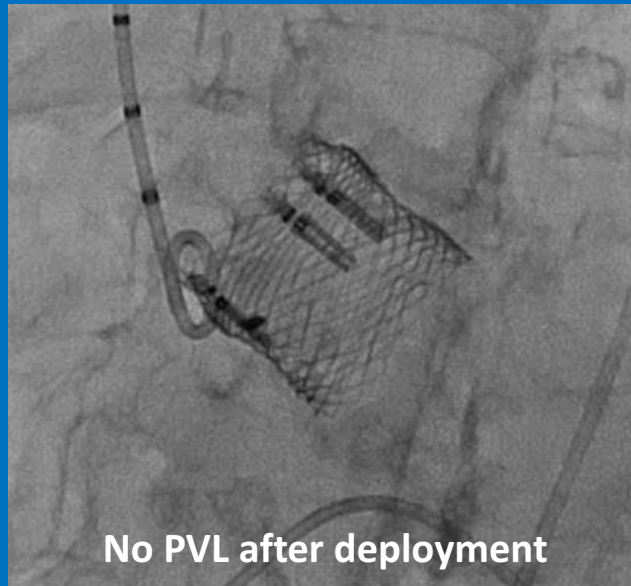


18mm – 29mm
Annulus Size

Next generation TAVI devices

LOTUS Edge Valve System

The adaptive seal conforms to irregular anatomical surfaces to minimize paravalvular leak



Adaptive Seal



Moderate / Severe PVL with Lotus & LOTUS Edge at 30 days:

- **0.3%** in RESPOND (N=996)¹
- **0.6%** in REPRISE III (N=511)²
- **0%** in LOTUS Edge Feasibility (N=21)³

case example courtesy of Meredith, IT

¹Falk, PCR 2016

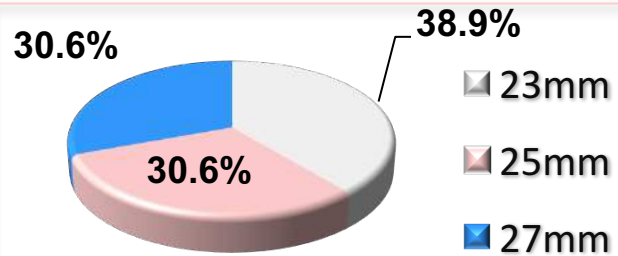
²Feldman, PCR 2017

³Walters, ACC 2017

Next generation TAVI devices



LOTUS Edge Feasibility Study & REPRISE Edge 30-d Results

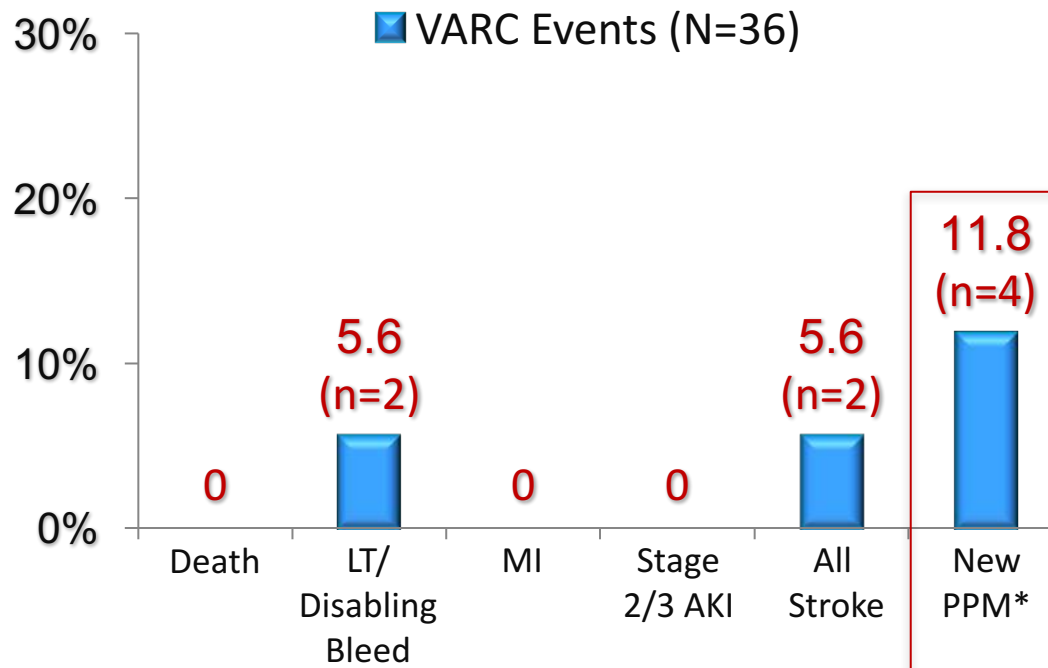


64% Female, Mean Age 84 years
STS Score 4.4 ± 1.9
NYHA Class III or IV 61.1%

100% Technical Success

100% None –Mild PVL

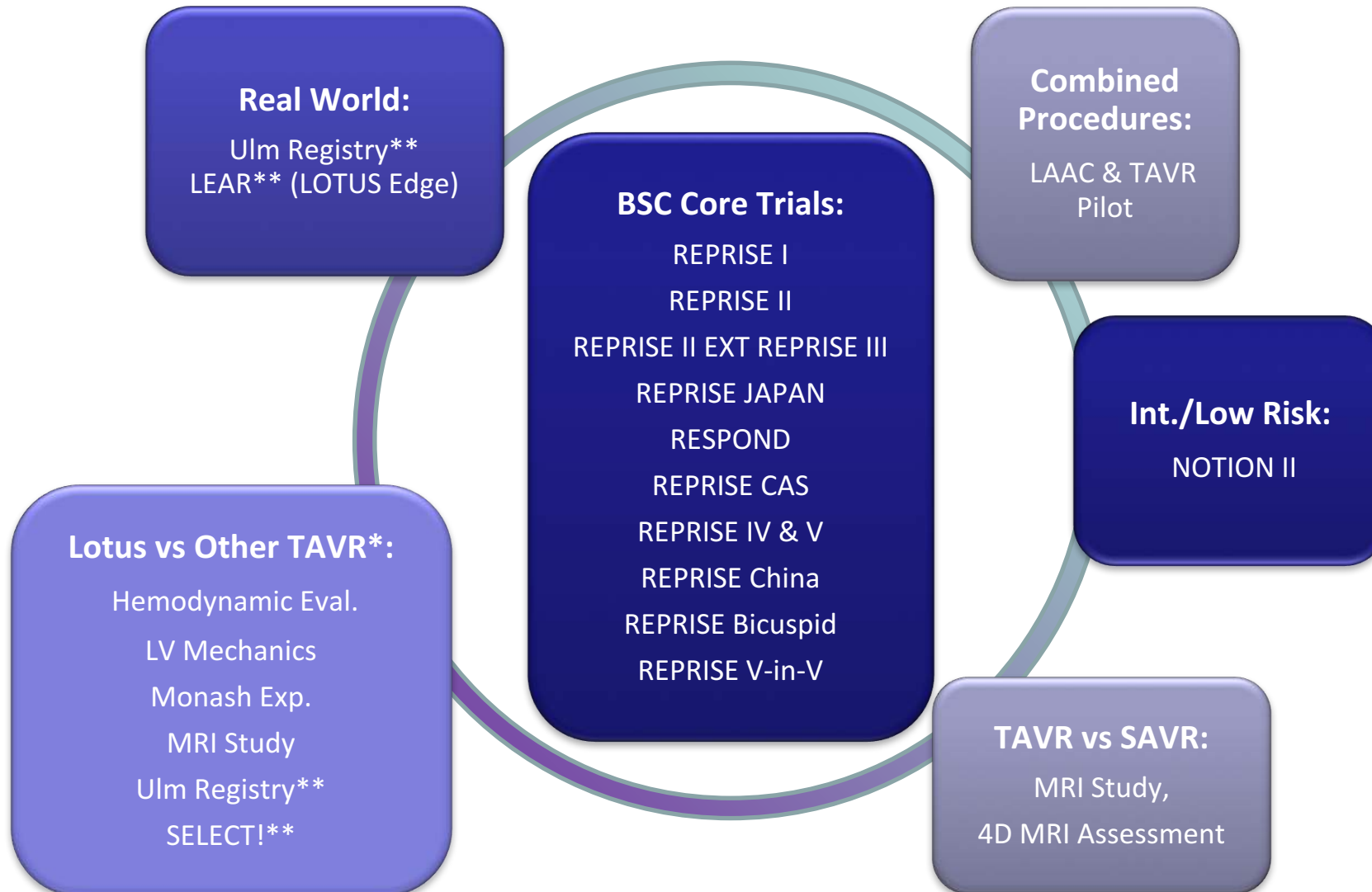
0% Repeat Procedures



- Advantages of the first-generation Lotus Valve System are conserved with the next generation LOTUS Edge Valve System

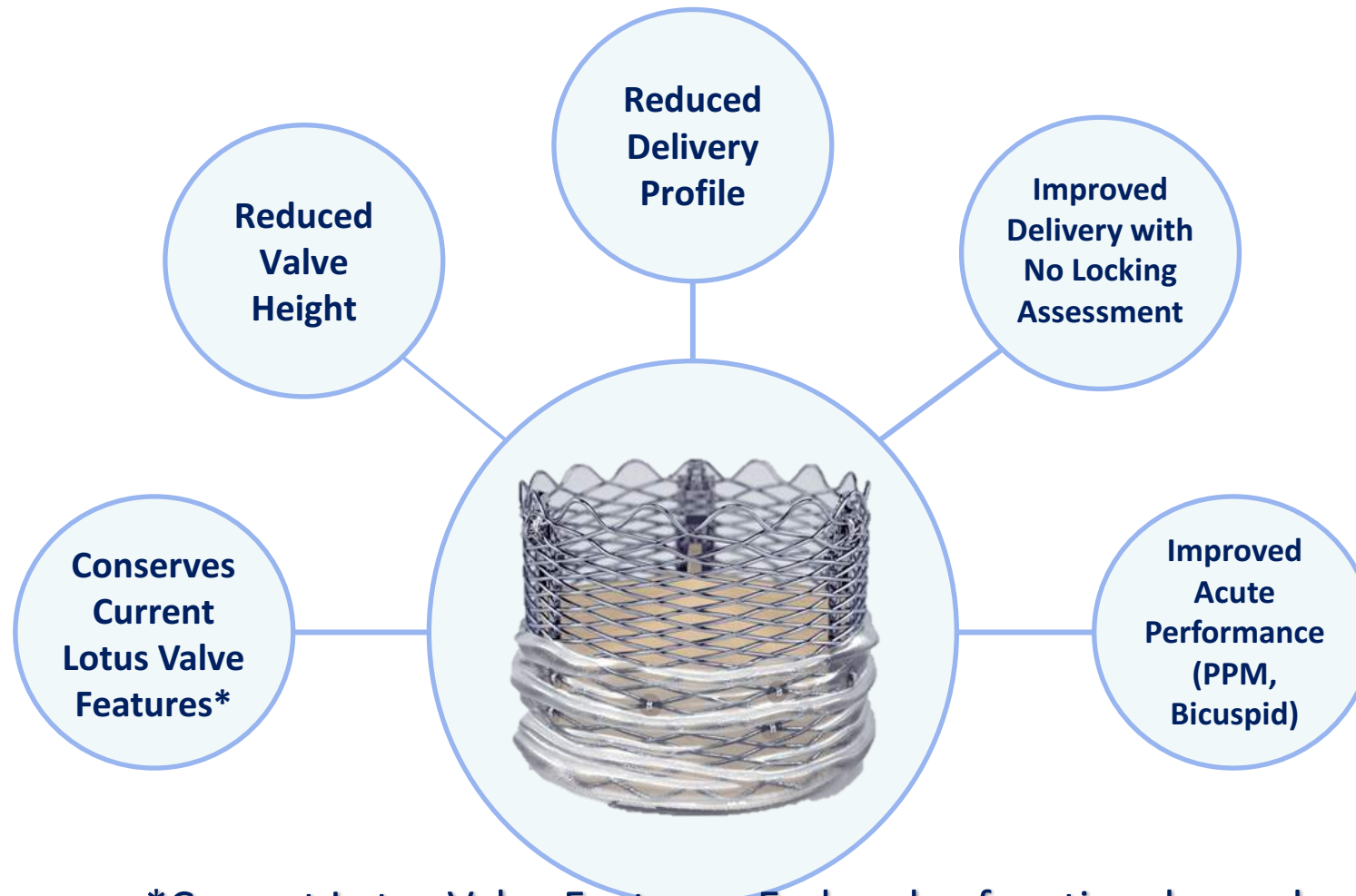
Next generation TAVI devices

LOTUS Ongoing and Upcoming Core Trials and ISRs for the Lotus Valve



Next generation TAVI devices

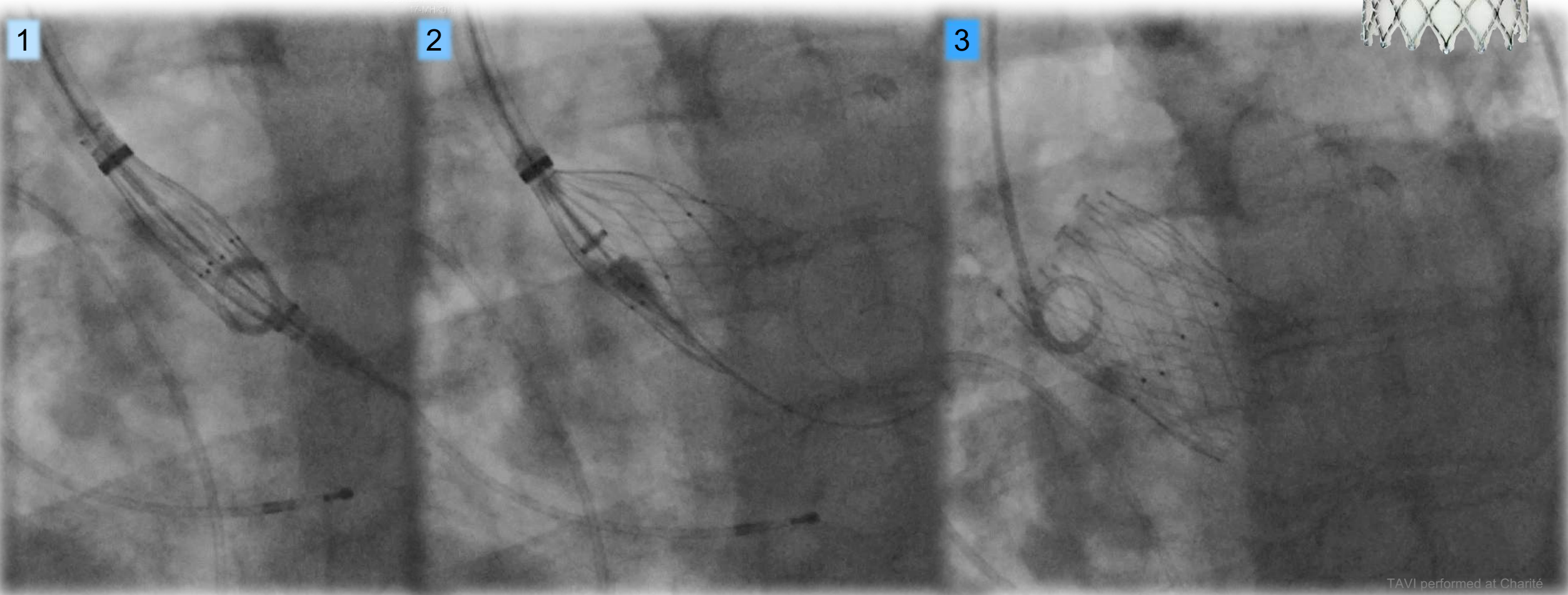
Future generation: LOTUS Mantra Valve



*Current Lotus Valve Features: Early valve function, hemodynamic stability, no rapid pacing, precise placement, negligible PVL, fully repositionable & retrievable

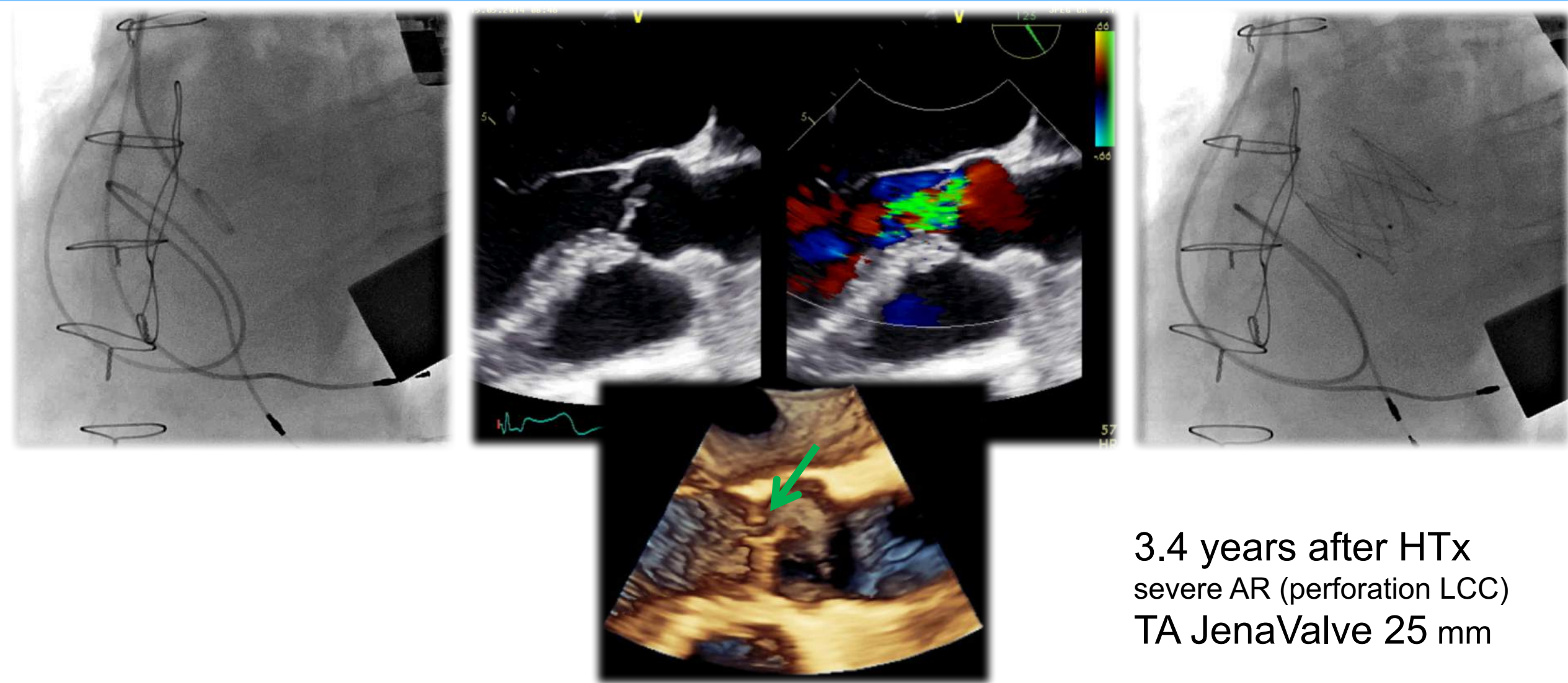
Next generation TAVI devices

nvt ALLEGRA



Next generation TAVI devices

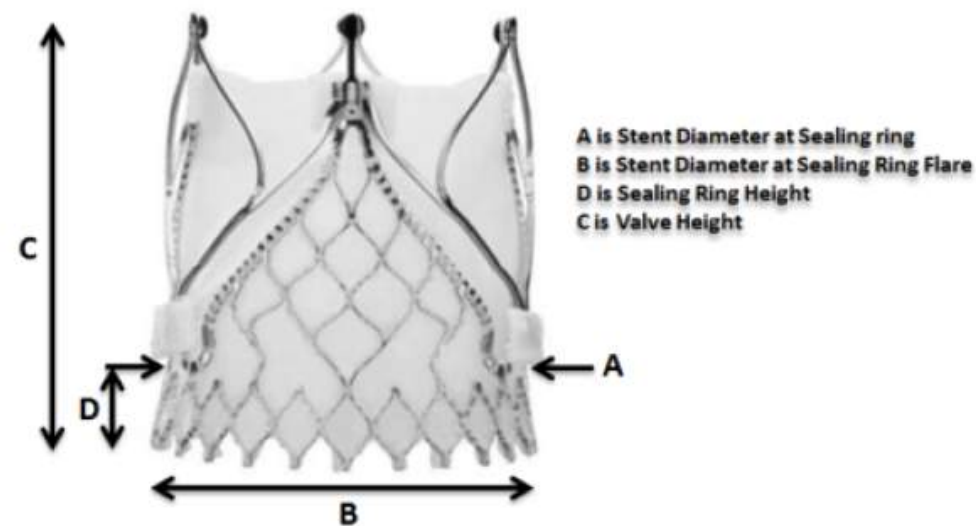
JenaValve (previous device)



Next generation TAVI devices

JenaValve (next generation device)

TF access
treatment of **pure aortic regurgitation**



THV Model Number	A mm	B mm	C mm	D mm
JV-2000-PY23	26	28	31.3	5
JV-2000-PY25	28	30	33.7	5.2
JV-2000-PY27	30	32.4	35.7	5.8

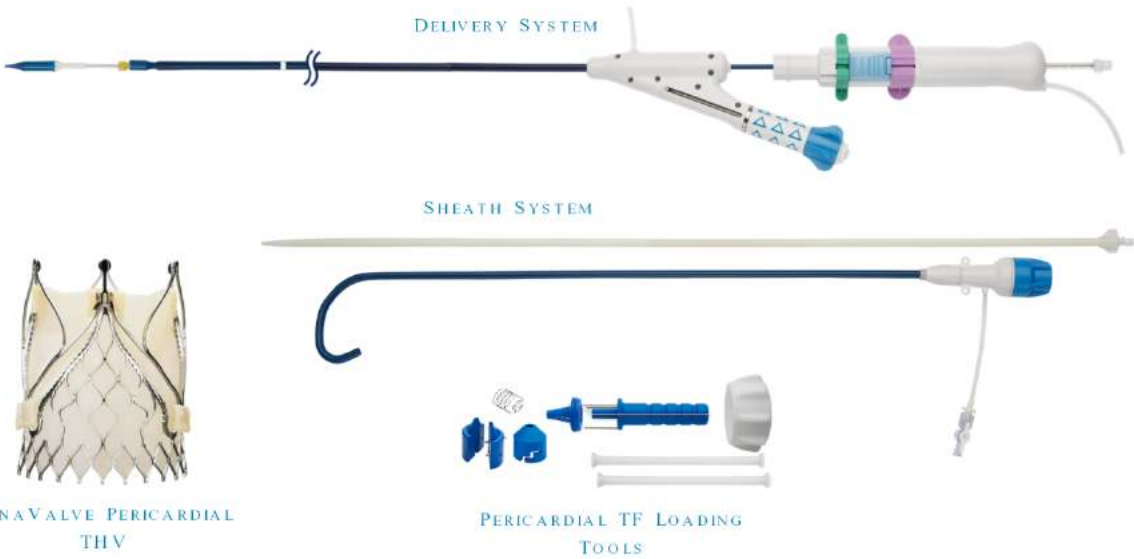
Next generation TAVI devices

JenaValve (next generation device)



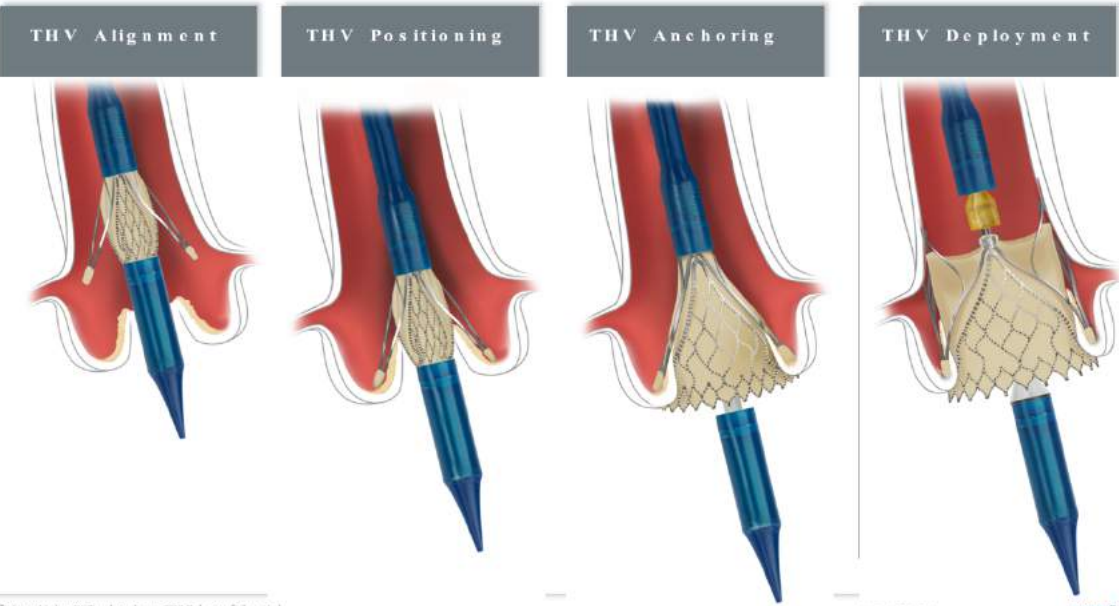
Next Generation Pericardial TAVR

CLINICAL STUDY SYSTEM COMPONENTS



System Deployment

Implantation Sequence



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MKT-2777777

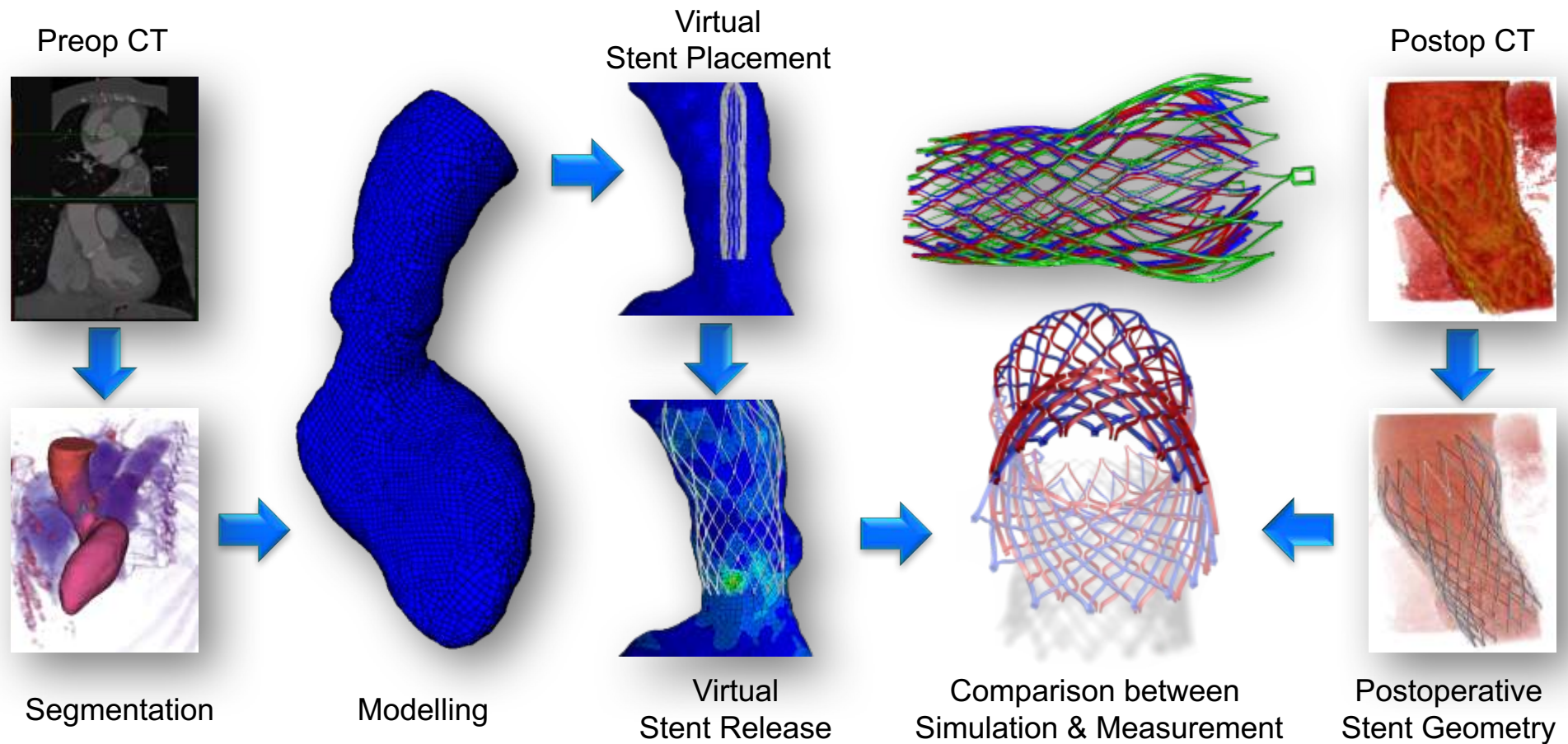
page 7



TAVI predictive modelling

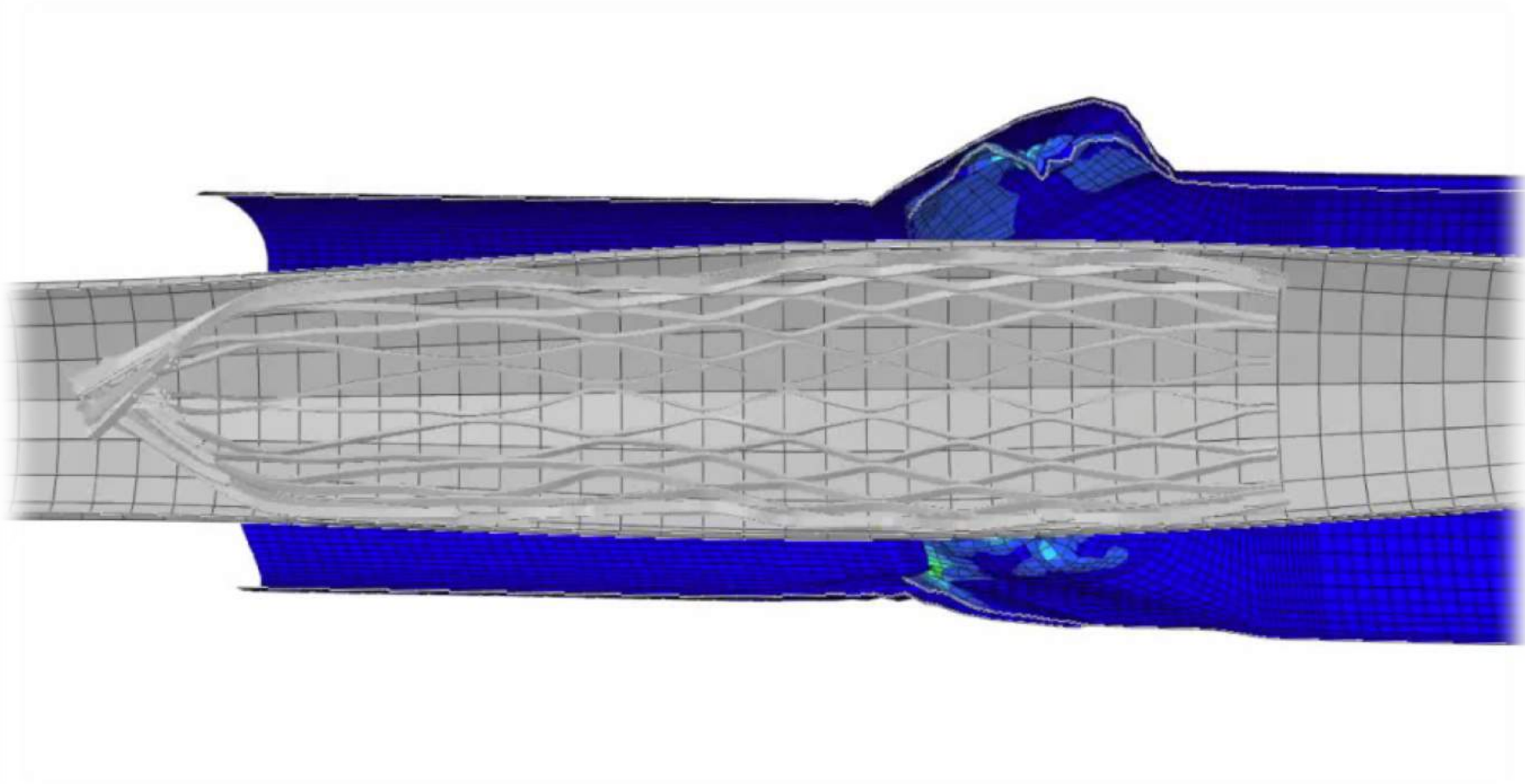
TAVI predictive modelling

Result validation with post-procedural data



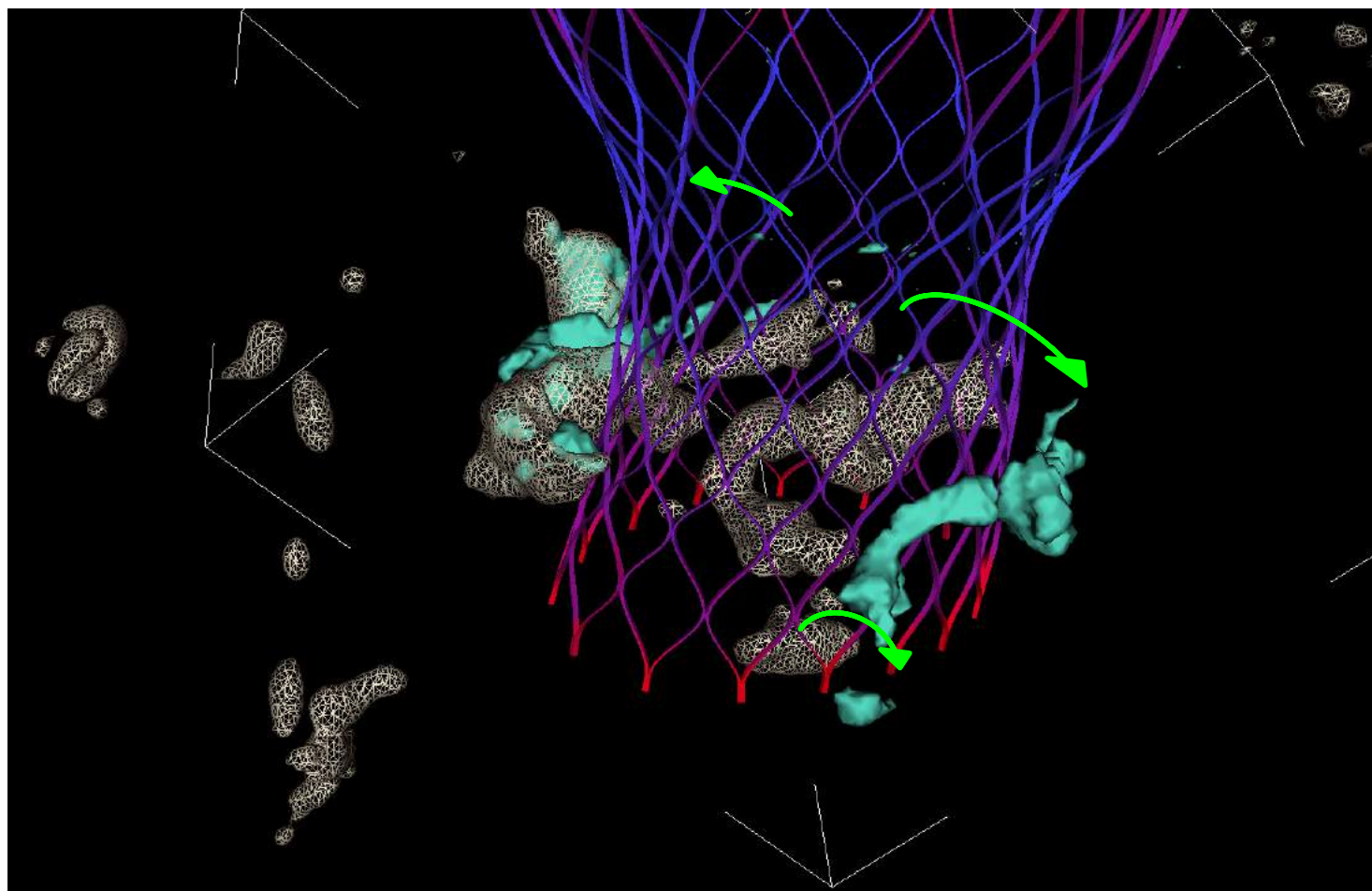
TAVI predictive modelling

Virtual stent release



TAVI modelling and forecasting

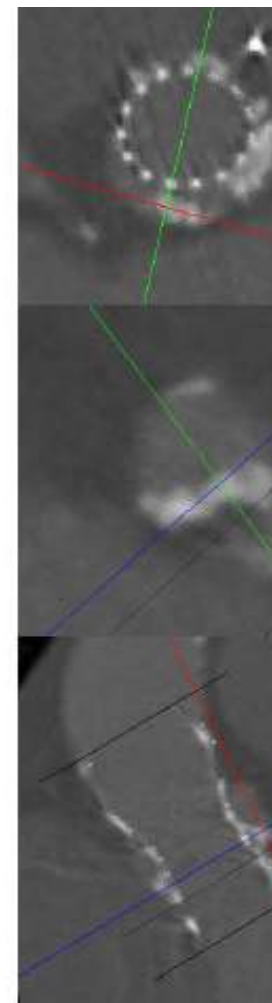
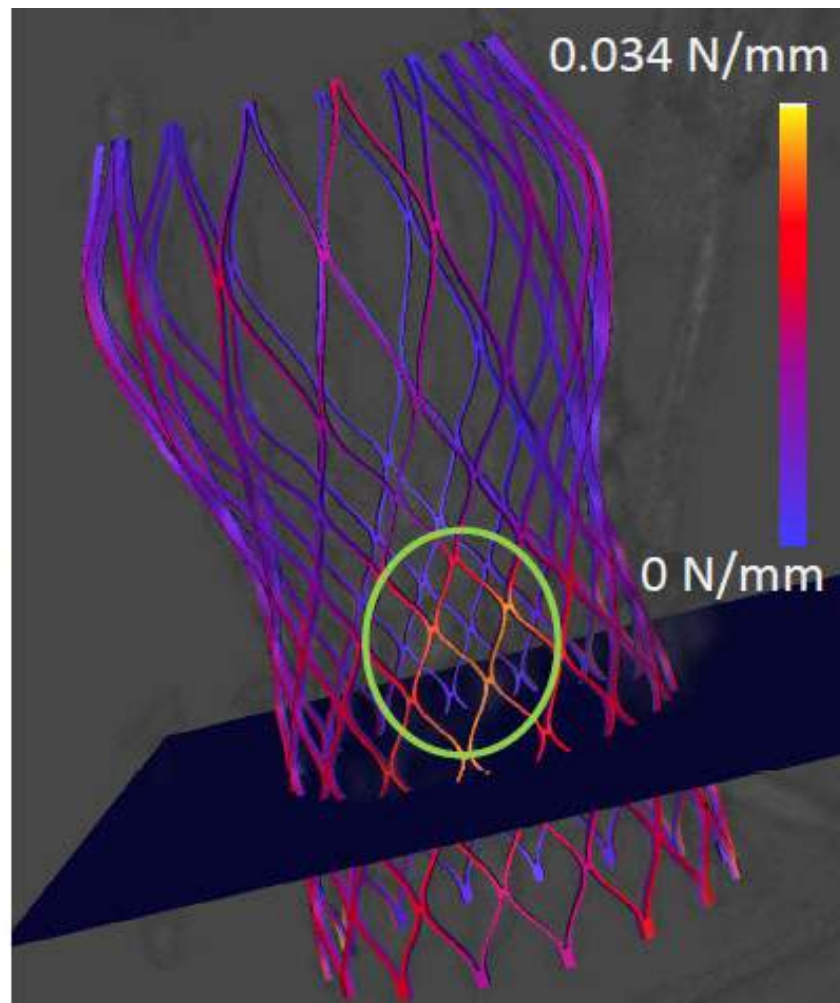
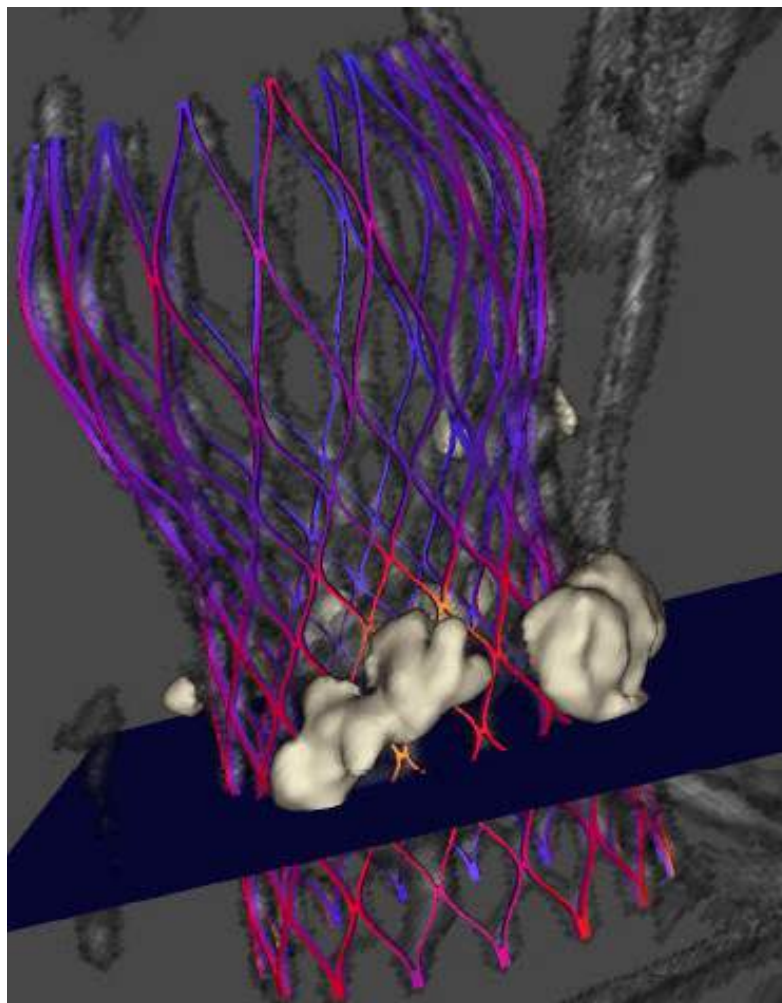
Analysis of calcium displacement and loss



Preoperative Calcium (white) and postoperative calcium (green)

TAVI modelling and forecasting

Analysis of local stress/strain and valve deformation



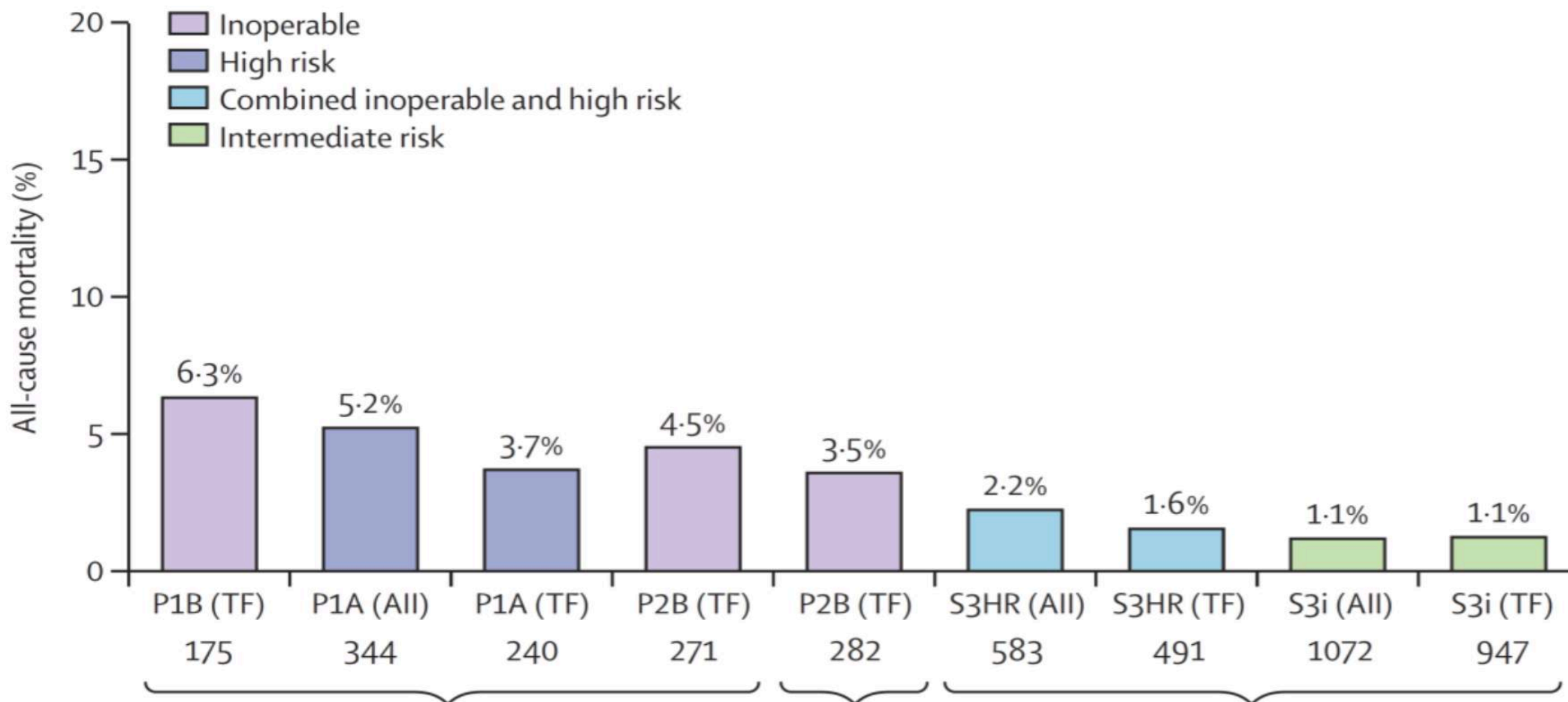


Future TAVI indications

RATIONALE FOR TAVI IN LOW-RISK PATIENTS

BONOW ET AL. LANCET 2016 387:1312-23

All-cause Mortality at 30 Days

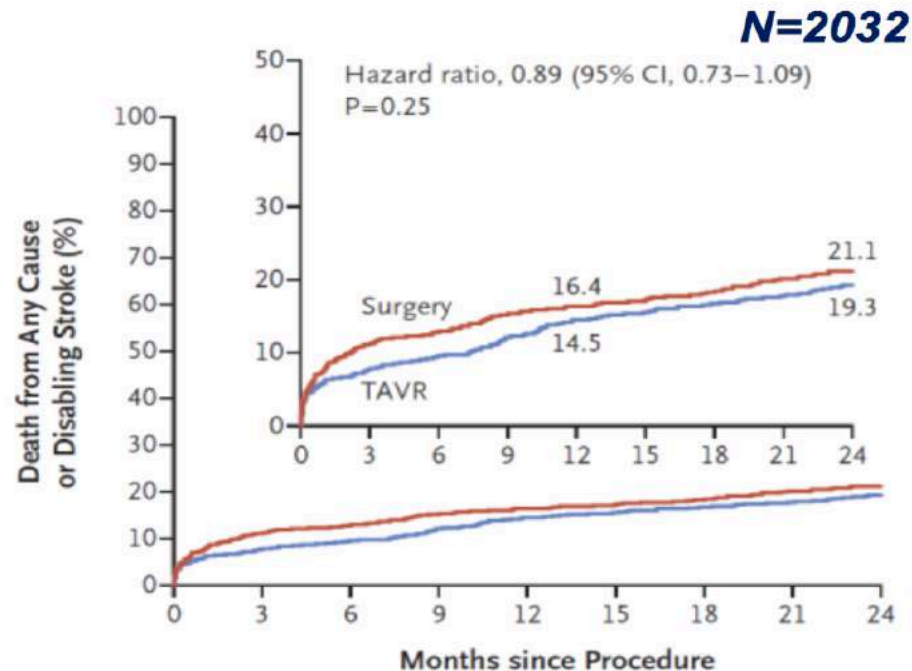


TAVI vs SURGICAL AORTIC VALVE REPLACEMENT: INTERMEDIATE-RISK AND ALL-COMERS PATIENTS

PARTNER 2A: 2-Year Follow-Up

Leon MB et al. *N Engl J Med* 2016

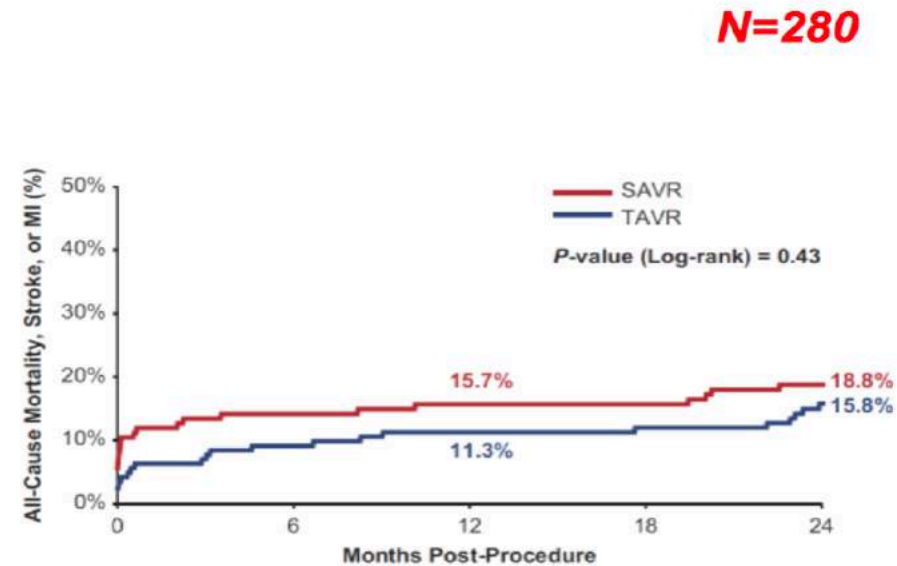
All-cause Mortality or Stroke



NOTION: 2-Year Follow-Up

Søndergaard L et al. *Circ Cardiovasc Interv* 2016

All-cause Mortality, Stroke, or MI



Future TAVI indication



The present



2017 ESC/EACTS Guidelines for the management of valvular heart disease

The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Helmut Baumgartner* (ESC Chairperson) (Germany), Volkmar Falk*¹ (EACTS Chairperson) (Germany), Jeroen J. Bax (The Netherlands), Michele De Bonis¹ (Italy), Christian Hamm (Germany), Per Johan Holm (Sweden), Bernard Iung (France), Patrizio Lancellotti (Belgium), Emmanuel Lansac¹ (France), Daniel Rodriguez Muñoz (Spain), Raphael Rosenhek (Austria), Johan Sjögren¹ (Sweden), Pilar Tornos Mas (Spain), Alec Vahanian (France), Thomas Walther¹ (Germany), Olaf Wendler¹ (UK), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain)

Document Reviewers: Marco Roffi (CPG Review Coordinator) (Switzerland), Ottavio Alfieri¹ (EACTS Review Coordinator) (Italy), Stefan Agewall (Norway), Anders Ahlsson¹ (Sweden), Emanuele Barbato (Italy), Héctor Bueno (Spain), Jean-Philippe Collet (France), Ioan Mircea Coman (Romania), Martin Czerny (Germany), Victoria Delgado (The Netherlands), Donna Fitzsimons (UK), Thierry Folliquet¹ (France),

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE II <4% (logistic EuroSCORE I <10%) ^a		+
STS/EuroSCORE II ≥4% (logistic EuroSCORE I ≥10%) ^a	+	
Presence of severe comorbidity (not adequately reflected by scores)	+	
Age <75 years		+
Age ≥75 years	+	
Previous cardiac surgery	+	
Frailty ^b	+	
Restricted mobility and conditions that may affect the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+

Future TAVI indication

DEDICATE Trial design



DZHK

DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

STS-PROM 2-6%

SAVR
n=800

1 : 1

TAVI
n=800

- ✓ Severe symptomatic aortic valve stenosis
- ✓ Intermediate and lower risk (STS-PROM 2-6%)
- ✓ Heart team consensus that isolated TAVI and SAVR are both feasible

- ✗ Congenital bicuspid/unicuspid or non-calcified aortic valve, endocarditis
- ✗ Untreated relevant CAD, PCI w/in 1 month
- ✗ Severe mitral/tricuspid VD
- ✗ Severe cardiomyopathy (LVEF <20%)
- ✗ Stroke/ICB w/in 1 month
- ✗ Life expectancy <12 months

Future TAVI indication

Low surgical risk: active trials randomizing TAVI vs SAVR

Medtronic Low Risk¹



N = ~1200

Up to 80 centers
Evolut R, all routes

Industry-sponsored
10-year follow-up

PARTNER 3²



N = 1228

Up to 64 centers
SAPIEN 3,
transfemoral

Industry-sponsored
10-year follow-up

UK TAVI³

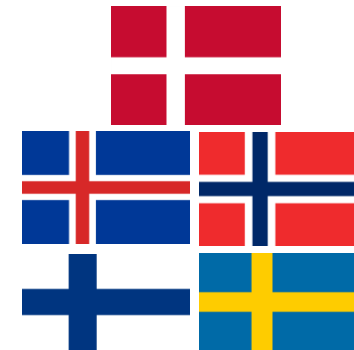


N = 808

All UK TAVI centers
All valves, all routes

Publically funded
5-year follow-up

NOTION-2⁴



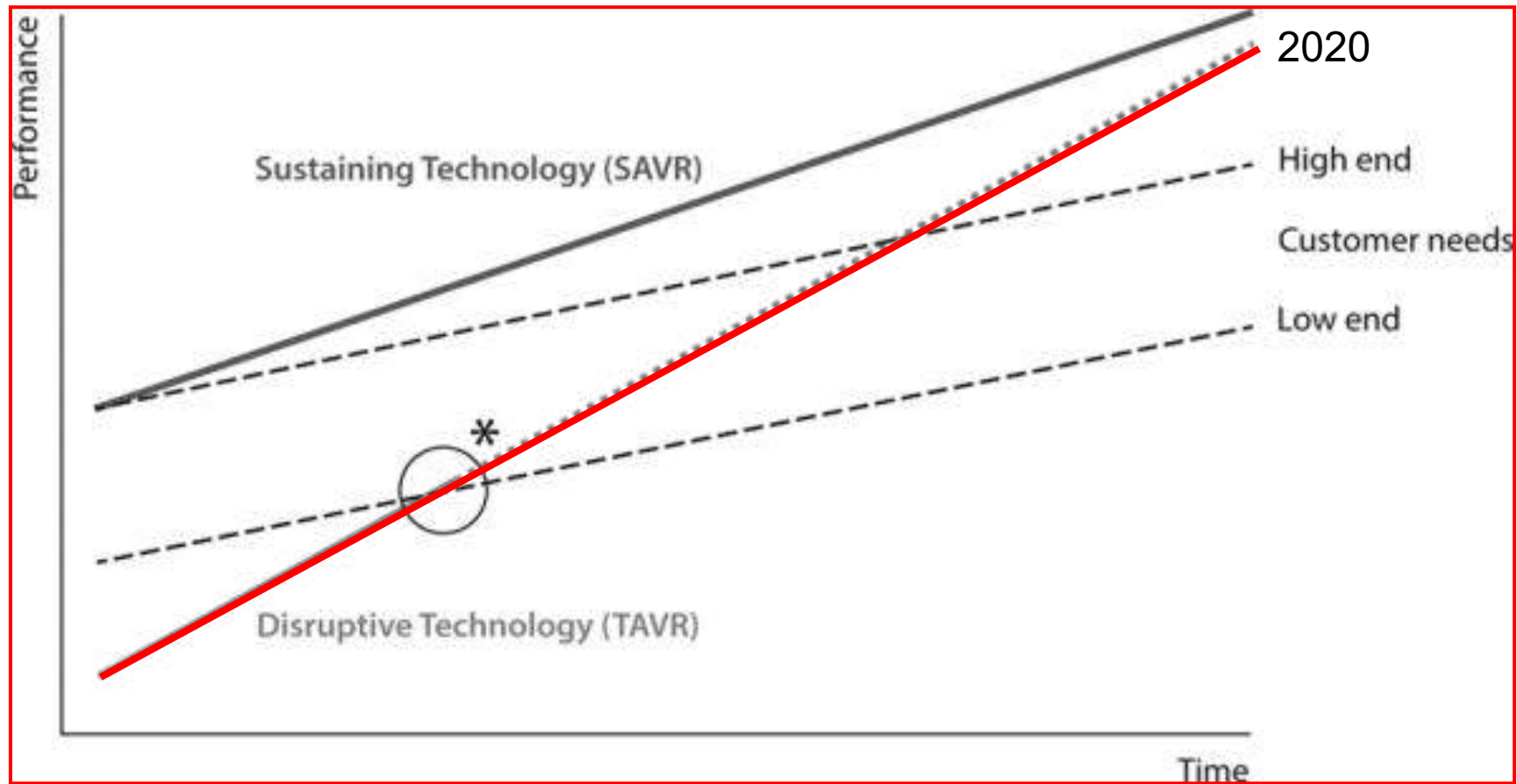
N = 992

All Nordic countries
All valves,
transfemoral

Physician and
industry-sponsored
5-year follow-up

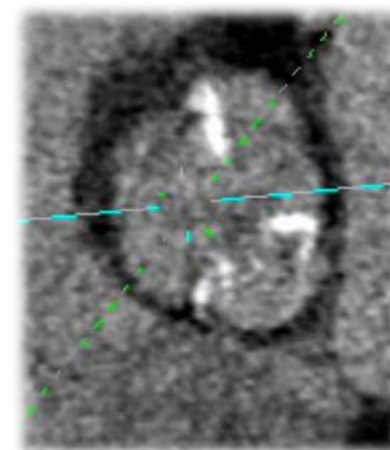
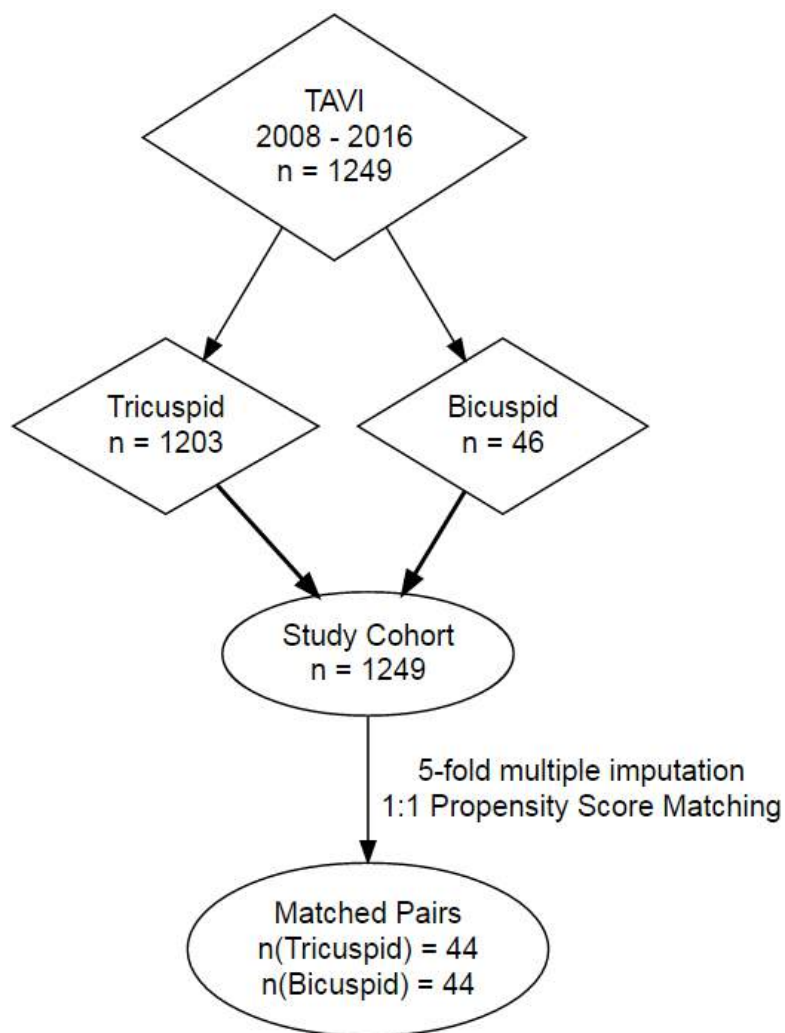
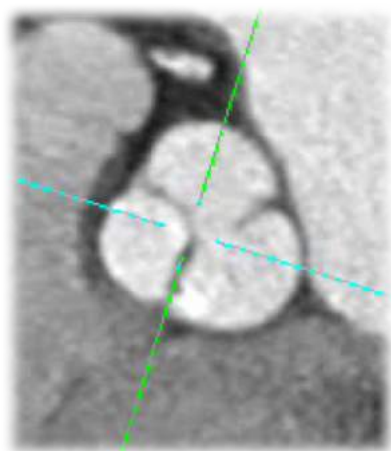
¹Popma, et al. TCT 2016; ²Mack, et al. TCT 2016; ³Moat, et al. TCT 2016; ⁴Sondergaard, et al. TCT 2016 (summary from Grube E)

TAVI an example of disruptive technology



Future TAVI indication

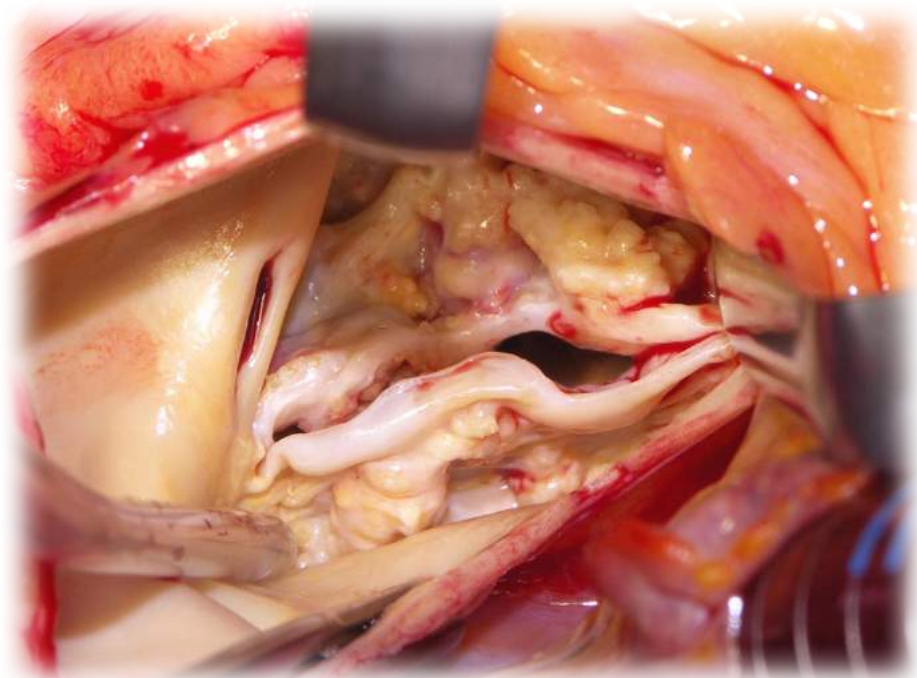
Bicuspid morphology



Inclusion criteria:
Exclusion criteria:

TA or TF access
Valve-in-Valve

Future TAVI indication: bicuspid morphology



5/44 **11.4%**

Type 0
No raphe



31/44 **70.5%**

Type 1
One raphe



1/44 **2.3%**

Type 2
Two raphe



R - N

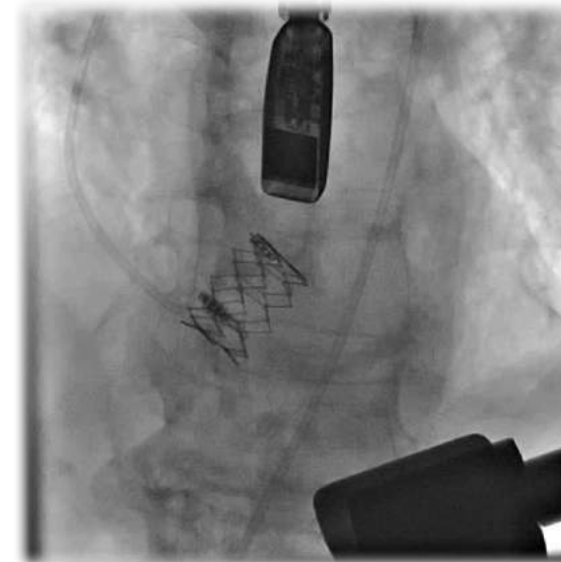
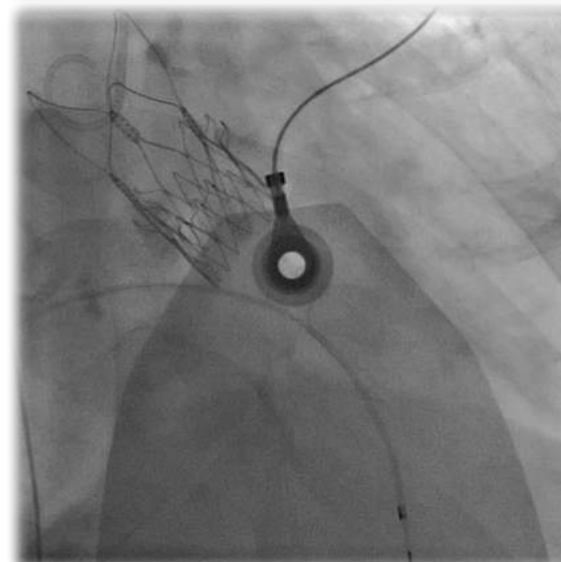
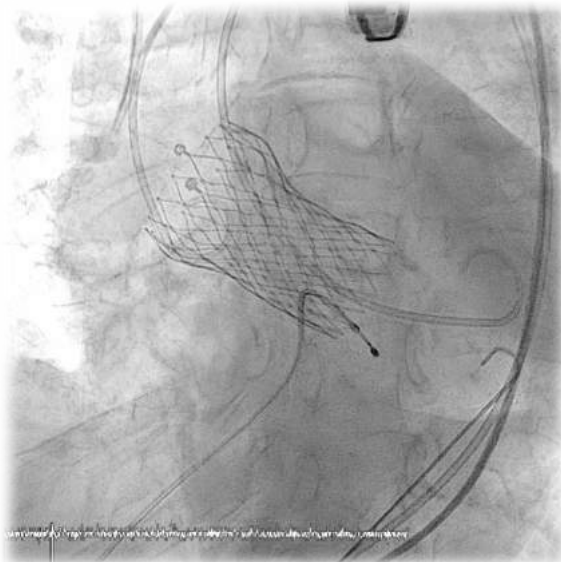
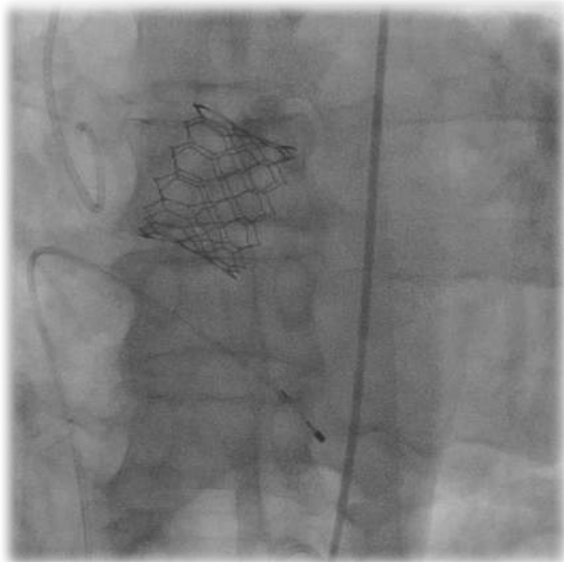
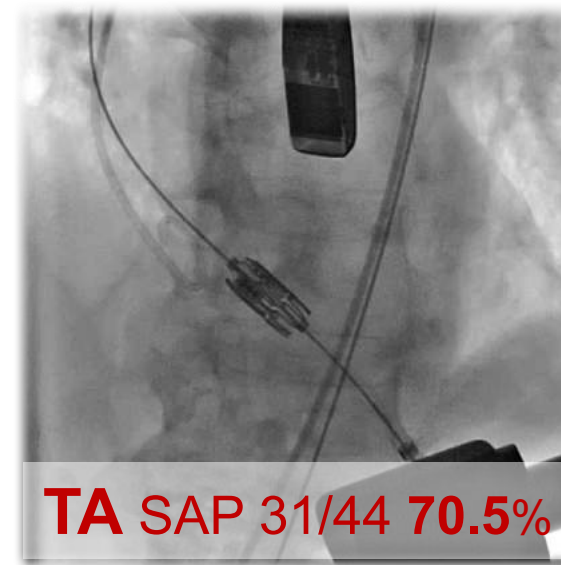
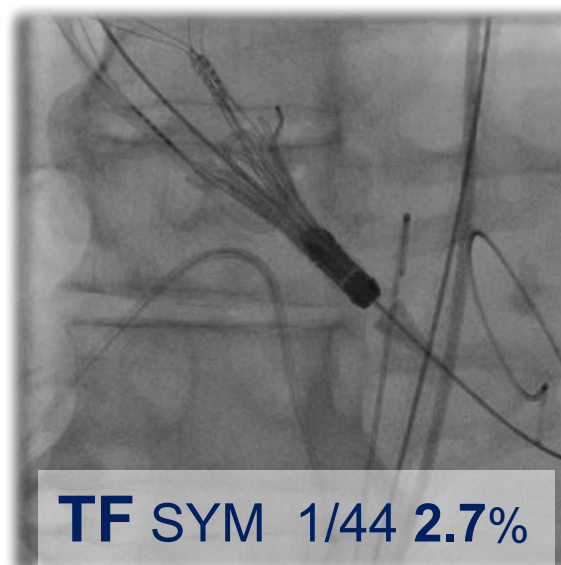
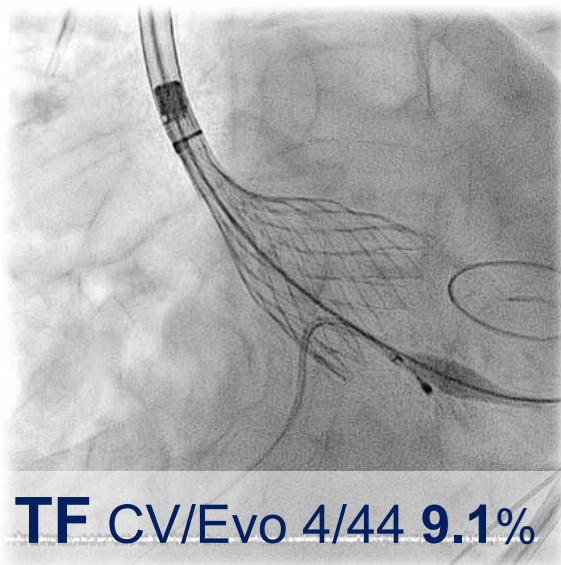
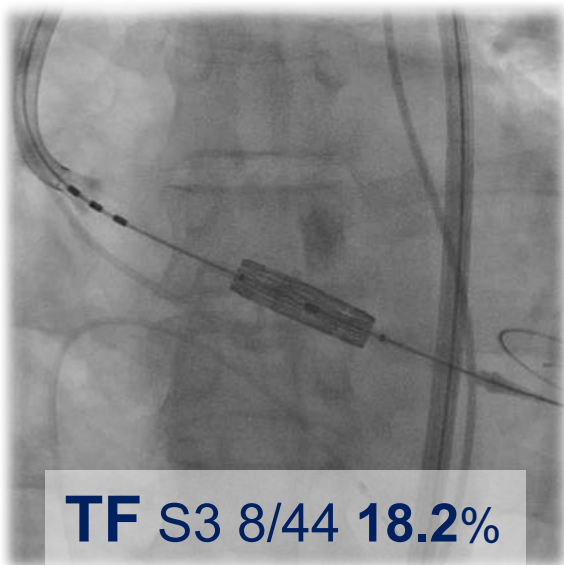
5/44 **11.4%**



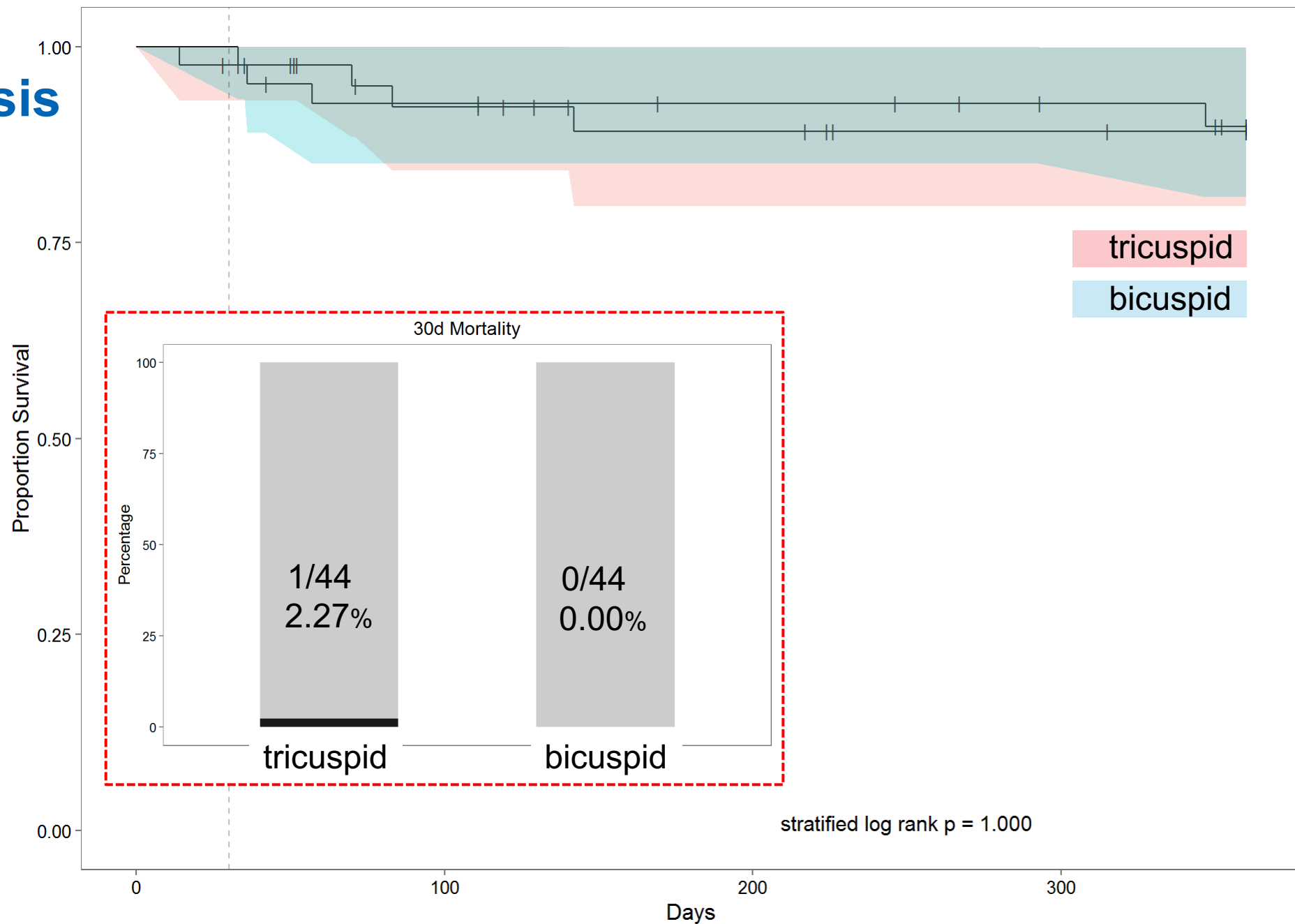
L - N

2/44 **4.5%**

Future TAVI indication: bicuspid morphology



Survival analysis



Conclusions

TAVI: future developments

TAVI – a disruptive technology.

Technical evolution in imaging simplifies pre-procedural planning and intra-procedural guidance.

Next generation devices will minimize the limitations of TAVI:

- paravalvular regurgitation
- heart block and conductance disturbances
- vascular complications

The Indication shift towards lower risk patients will continue.

TAVI: future developments

Thank You!



DEUTSCHES HERZZENTRUM BERLIN
STIFTUNG DES BÜRGERLICHEN RECHTS