

Emerging Opportunities for Future TAVR Development: Stroke, Paravalvular Leaks and Beyond

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Disclosure Statement of Financial Interest TCT 2012; Miami, FL

Susheel K. Kodali, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Consulting Fees
- Medical Advisory Board - Equity

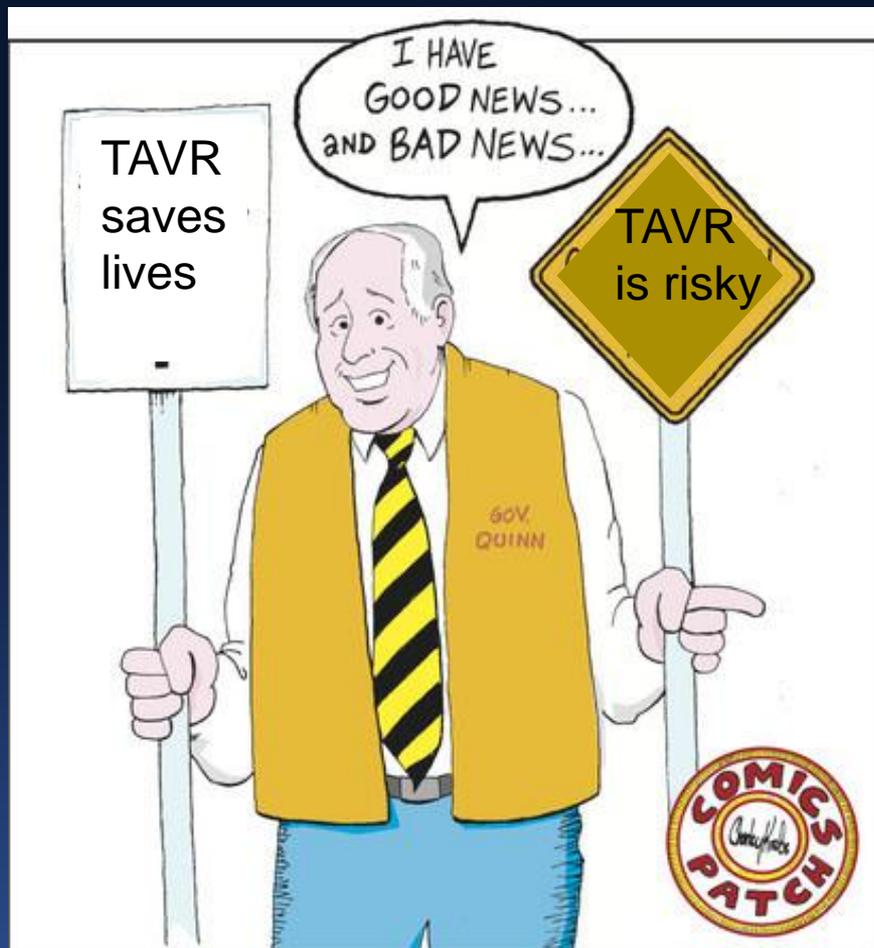
Company

- Edwards Lifesciences, St. Jude Medical
- Thubrikar Aortic Valve, Inc, VS Medtech

TAVR: Where are we now?

The Good News

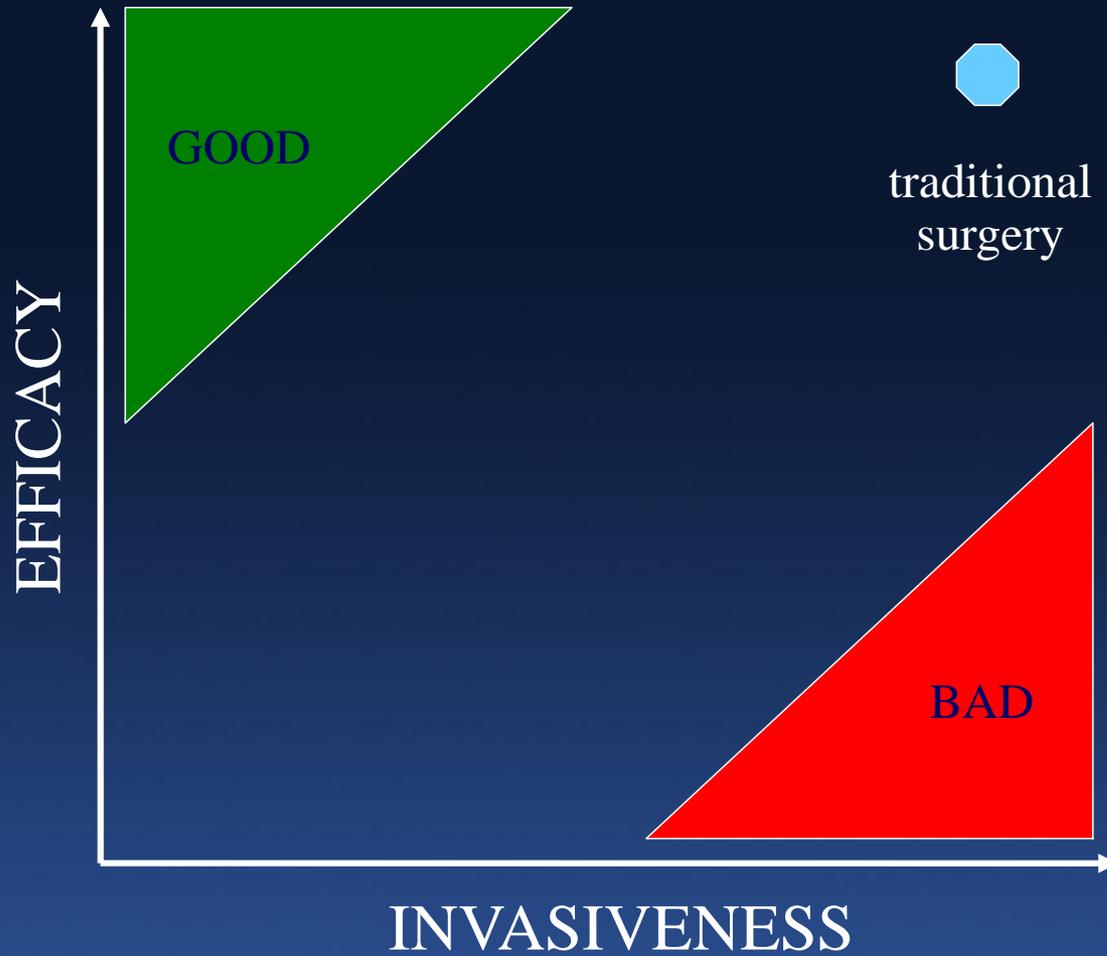
- **First generation devices have evolved to make TAVR a more predictable procedure**
- **Device profiles have come down making transfemoral approach safer and more feasible**
- **Randomized studies have proven role of TAVR in high risk and inoperable patients**
- **Mid term results have demonstrated valve durability (however, no long term results available)**

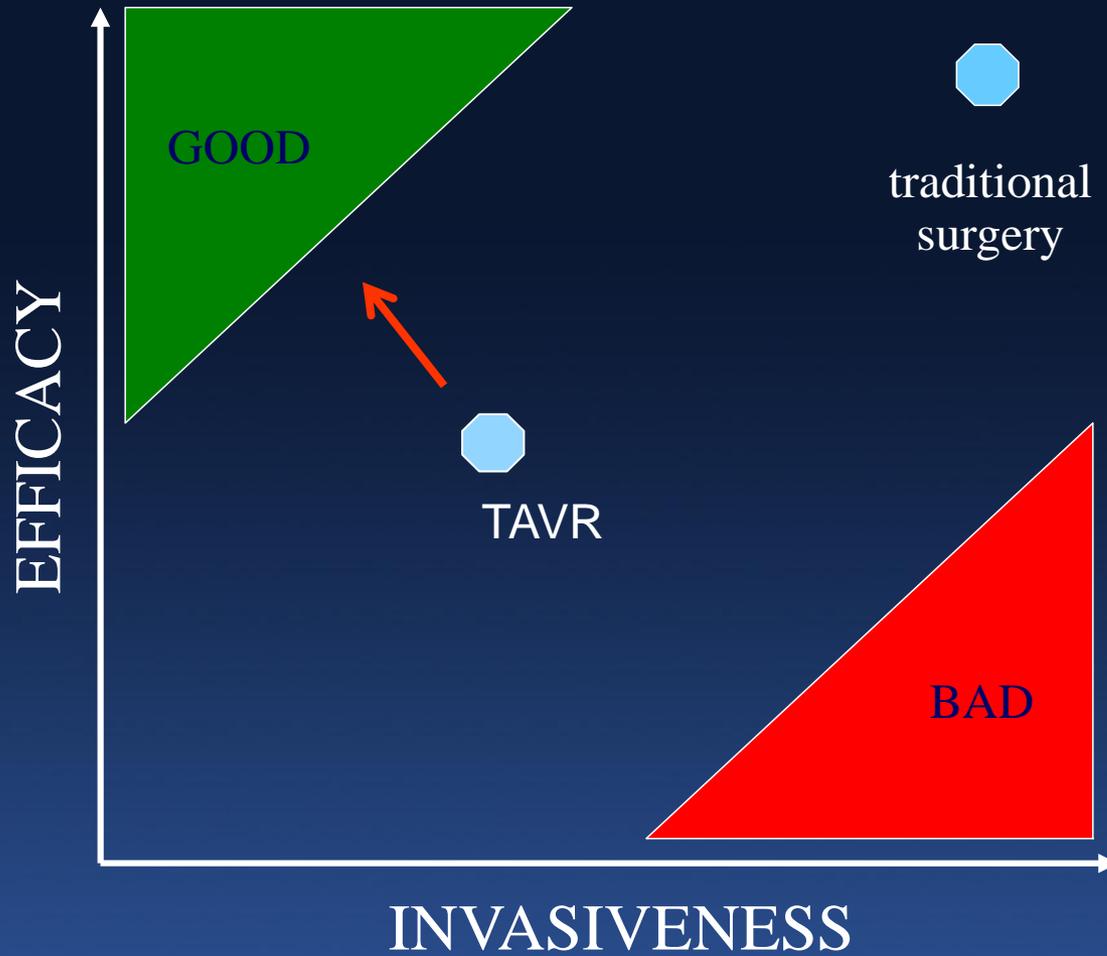


TAVR: Where are we now?

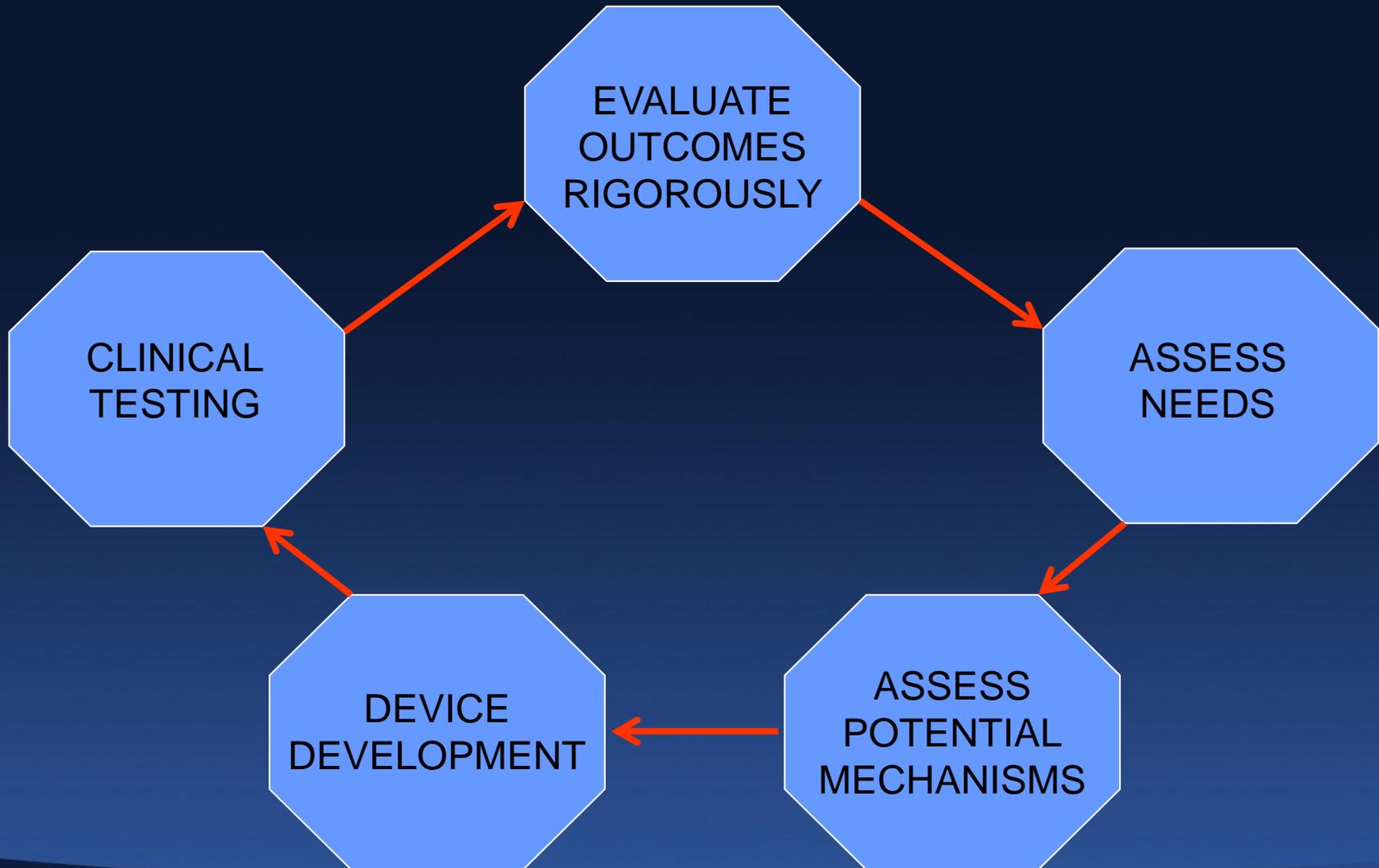
The Not So Good News

- Peri-procedural stroke remains a significant concern and may limit applicability of TAVR to lower risk populations
- Major bleeding and major vascular complications remain an issue and impact long term mortality
- Although rare (<1%), catastrophic procedural complications such as coronary occlusion, annular rupture and root injury still occur and are unpredictable





Device Development Lifecycle



TAVR

What are the Needs?

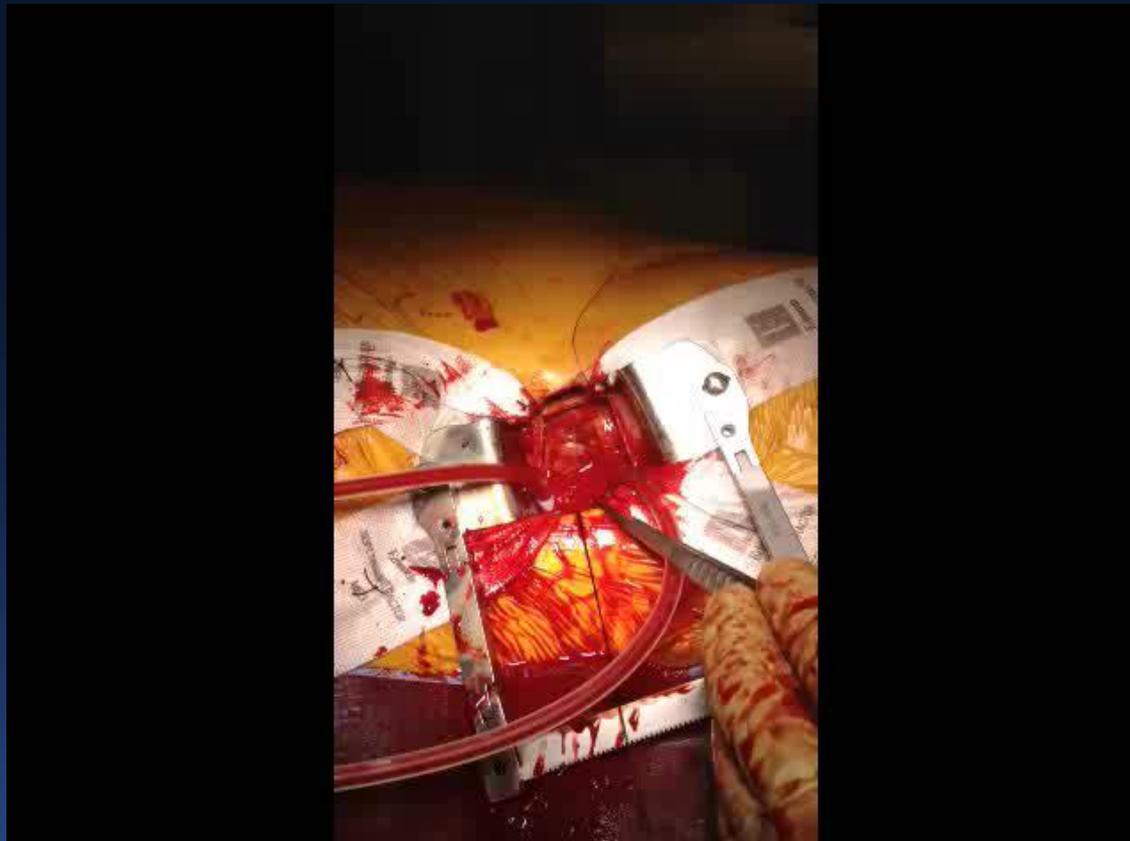
- **Access site management**
- **Embolic protection**
- **Management of Paravalvular Regurgitation**
- **Ability to predict complications**

TVAC - 2012

Transapical Access and Closure

Transapical Access and Closure

- **Advantages of TA approach**
 - **Most direct route to aortic valve**
 - **Provides a platform for other interventions – mitral valve, PVL closure, pulm vein ablation, etc**
- **Disadvantages**
 - **Unfamiliar to most surgeons**
 - **It is still an invasive approach**
 - **Bleeding complications can be catastrophic**



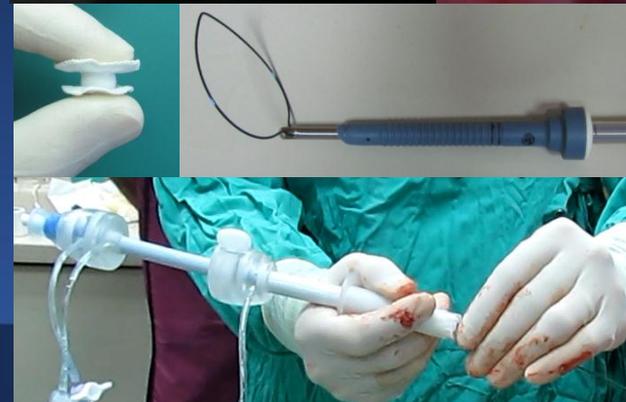
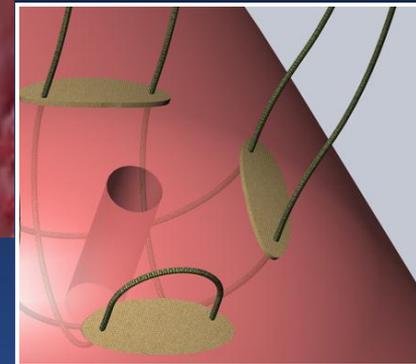
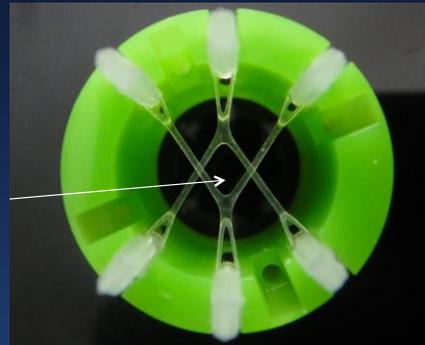
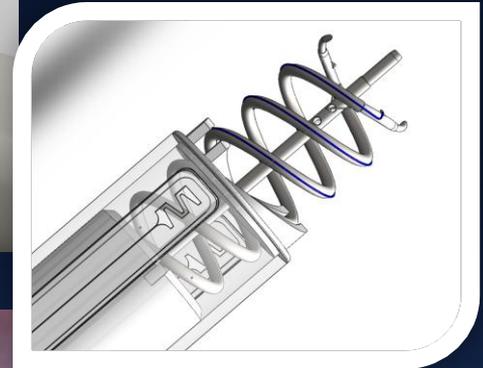
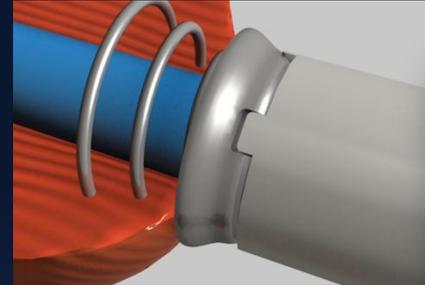
Surgeon's Worst Nightmare

Requirements of Transapical Closure System

- **Secure closure with a failsafe backup**
- **Biocompatible**
- **Works in all cases – reop chest, infarct, severe LVH, small LV, etc**
- **Small “footprint” – minimal material left behind with good healing response**
- **Easy to use – short learning curve**
- **Compatible with percutaneous access**

Transcutaneous Ventricular Access and Closure (TVAC)

- Apica ASC
- Entourage CardioClose
- MID Permaseal
- Novogate
- SpiRx
- Cardiapex



Apica ASC™ System

Titanium Access Coil

Closure Cap & Delivery Tool

Platform Technology Enables

- *TAVR*
- *MVR – Future Trans catheter Devices*
- *LVAD – Port Connector Variation*
- *TAA – Ascending Aorta*
- *Complex EP Ablation*

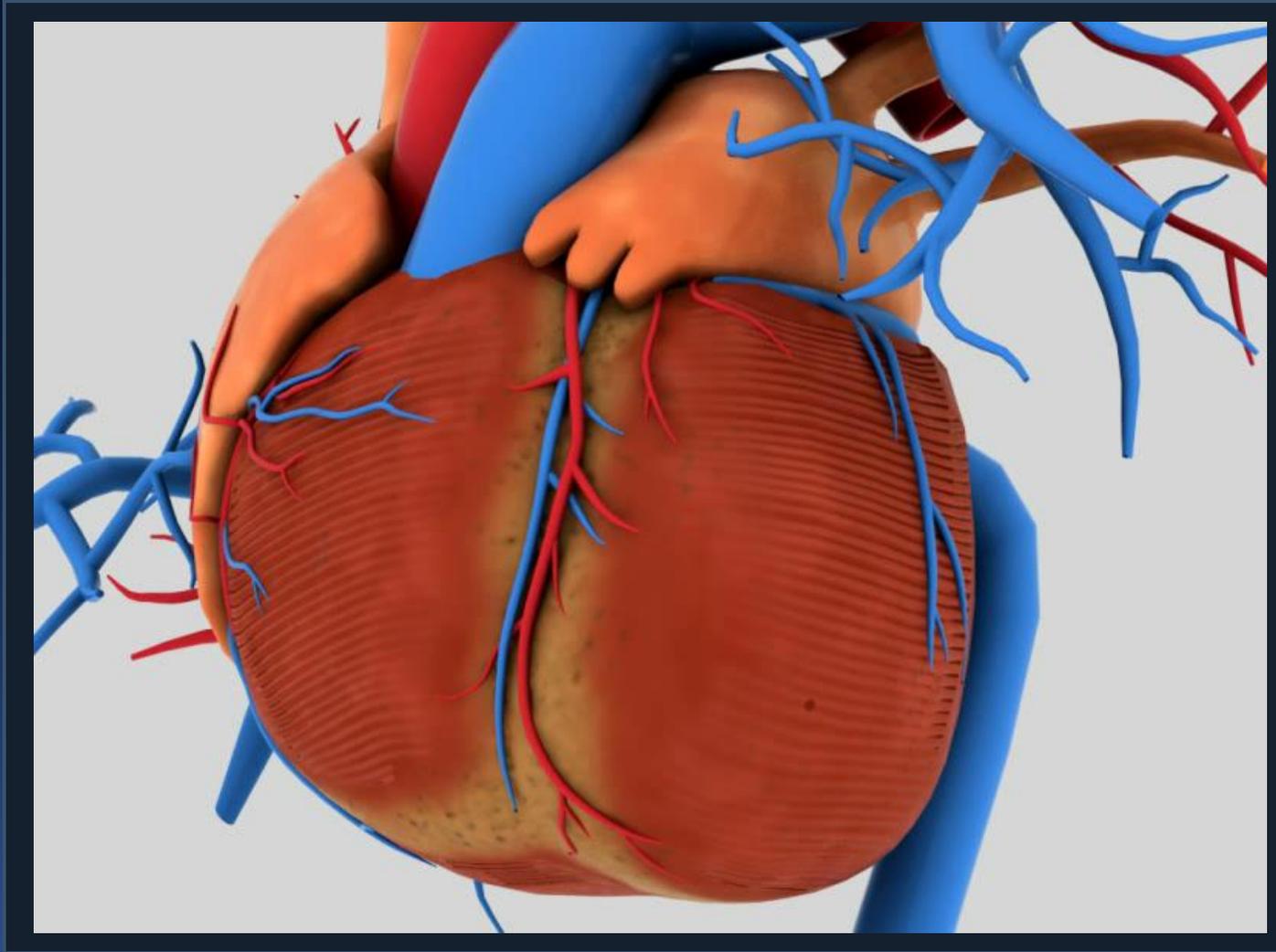
Apica ASC™ System

- **Titanium access coil attaches securely to ventricle and stabilizes sheath**
- **Durable Fatigue Profile**
- **Biocompatible**
 - **Surface modification promotes tissue adhesion**
 - **Long implant history**
- **Closure cap provides redundant mechanism**
- **Reaccessibile**



Apica ASC System

Animation + FIM (Thomas Walther; May, 2012)



CardioClose™ Ventricular Closure Device

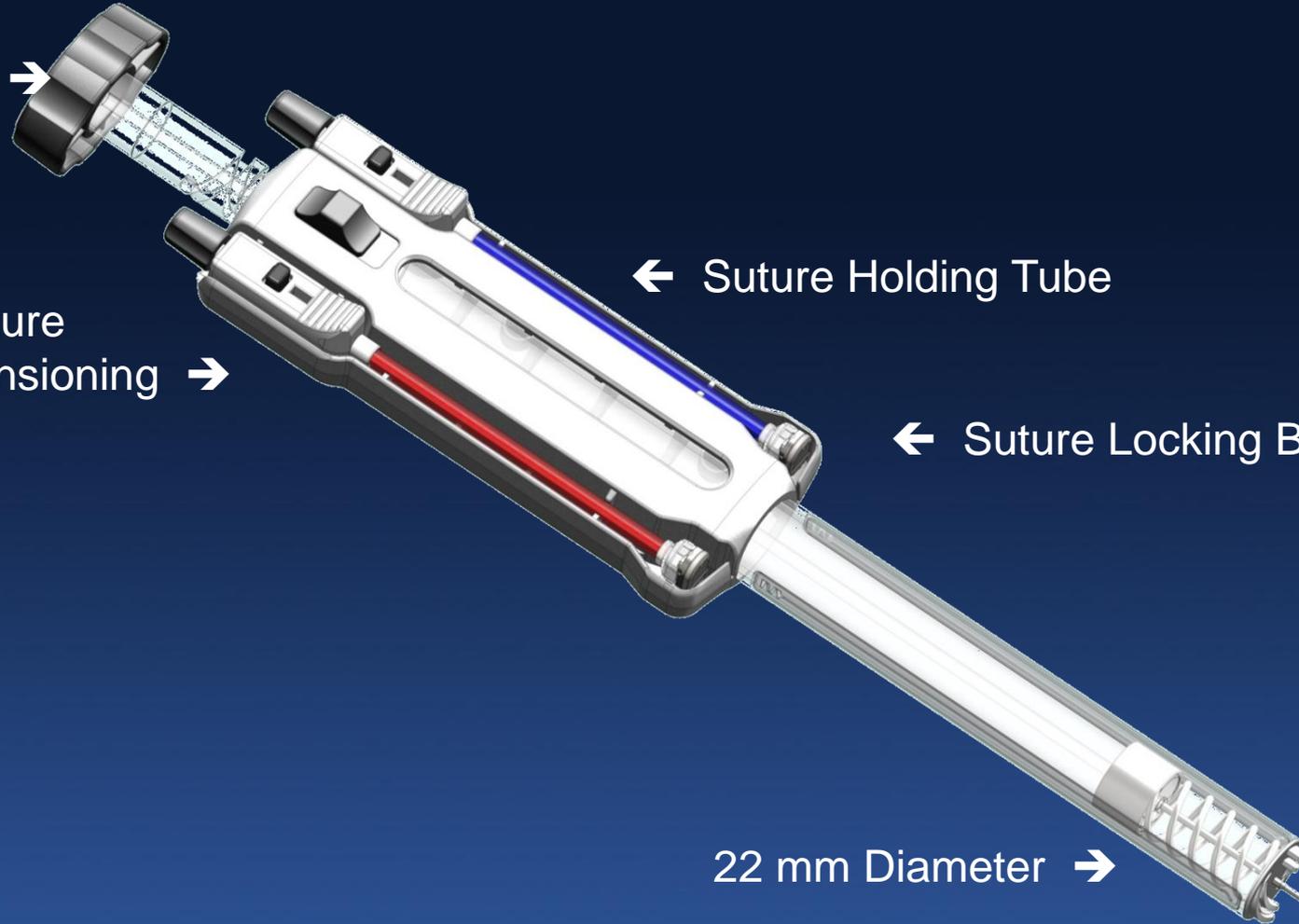
Screw
Driver →

Suture
Tensioning →

← Suture Holding Tube

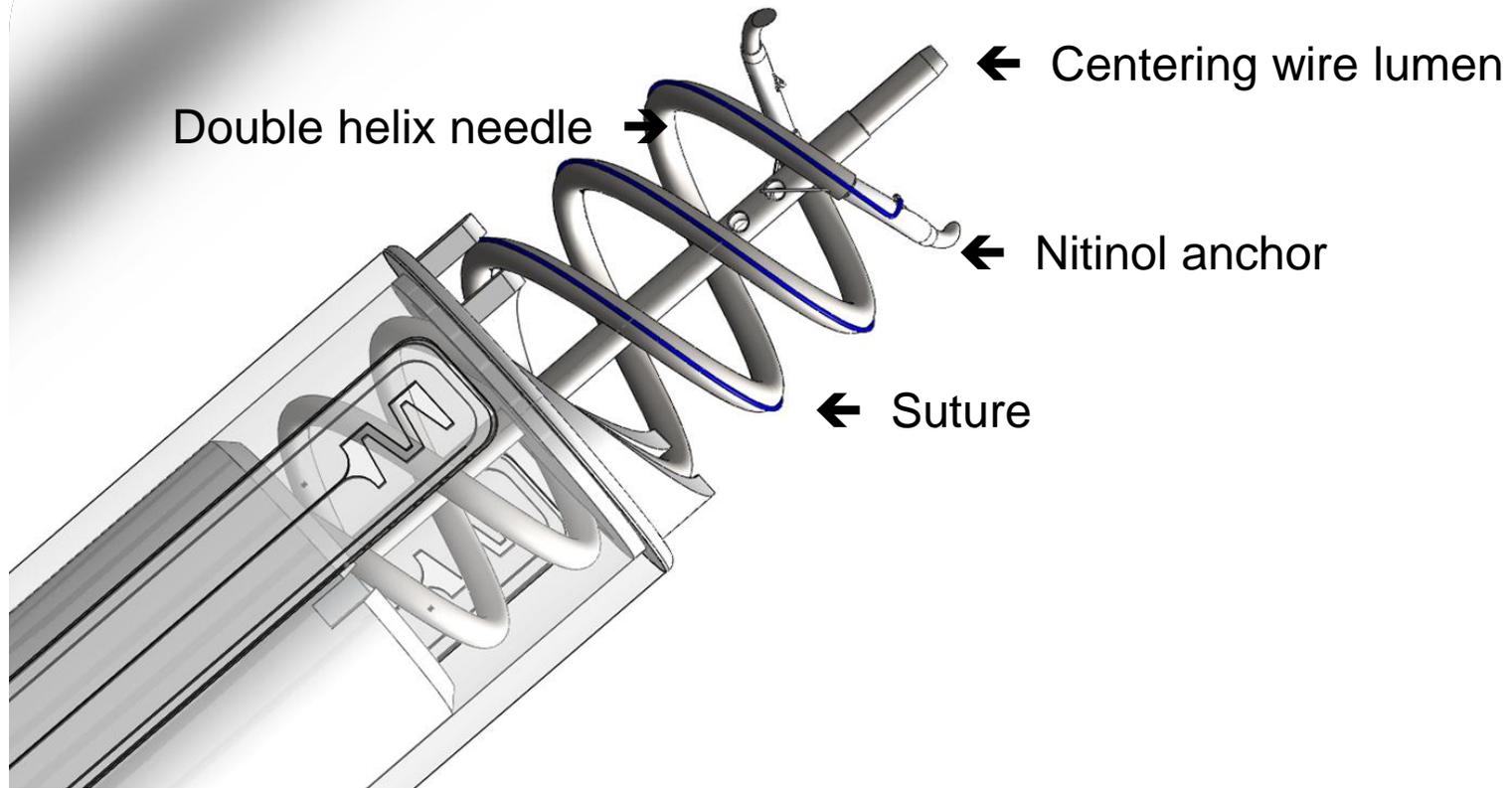
← Suture Locking Button

22 mm Diameter →

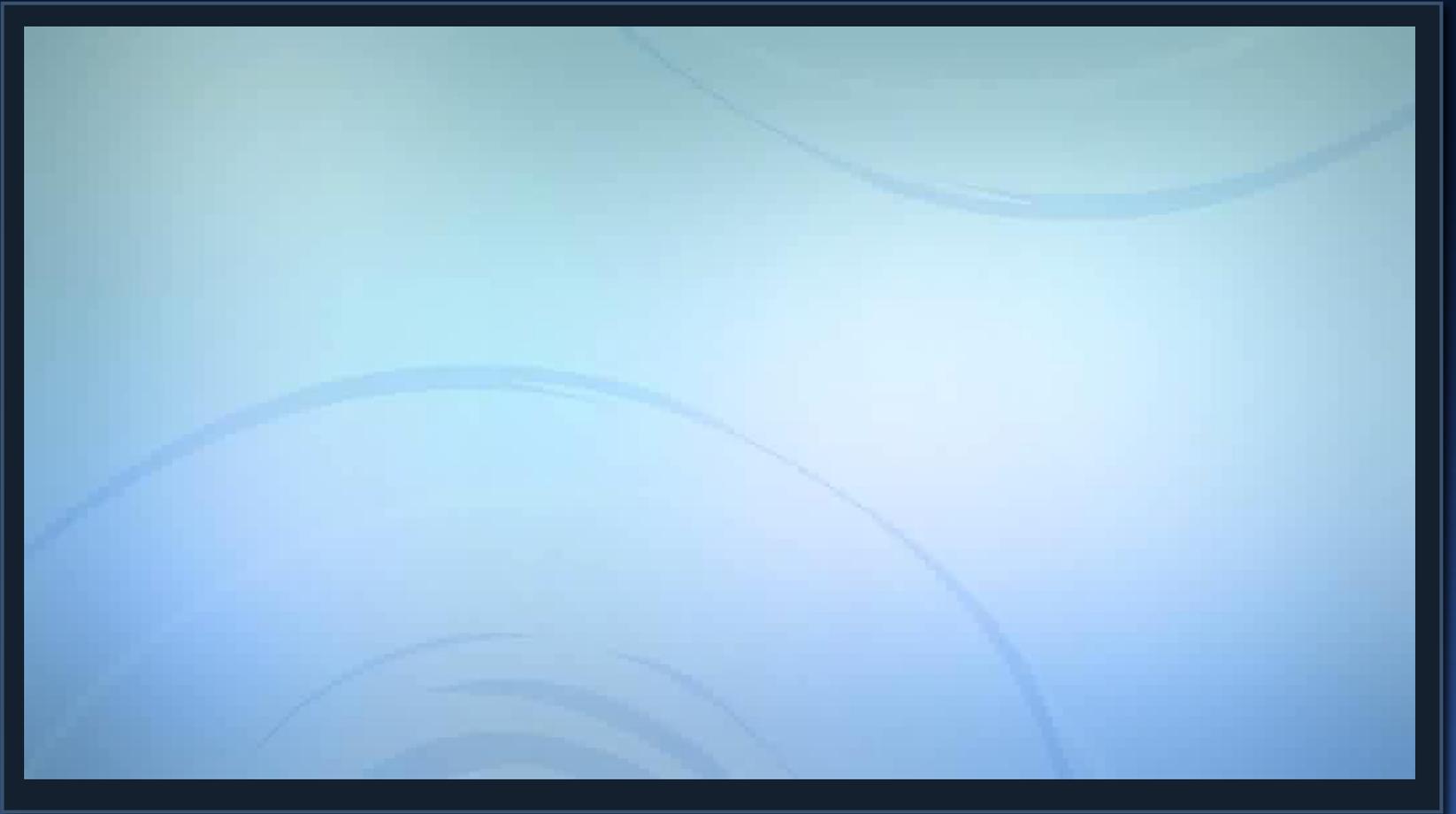


CardioClose™ : Distal End

26R01 CardioCl...

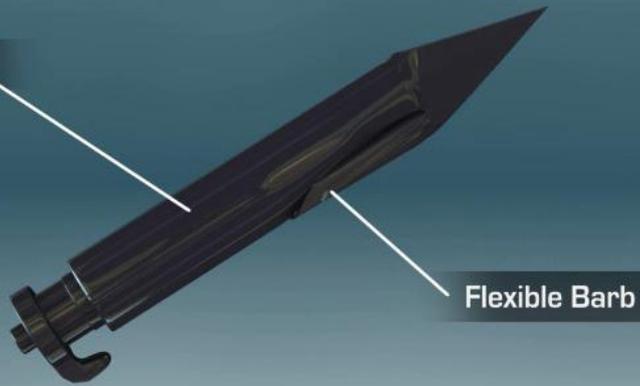


CardioClose™ Ventricular Closure Device



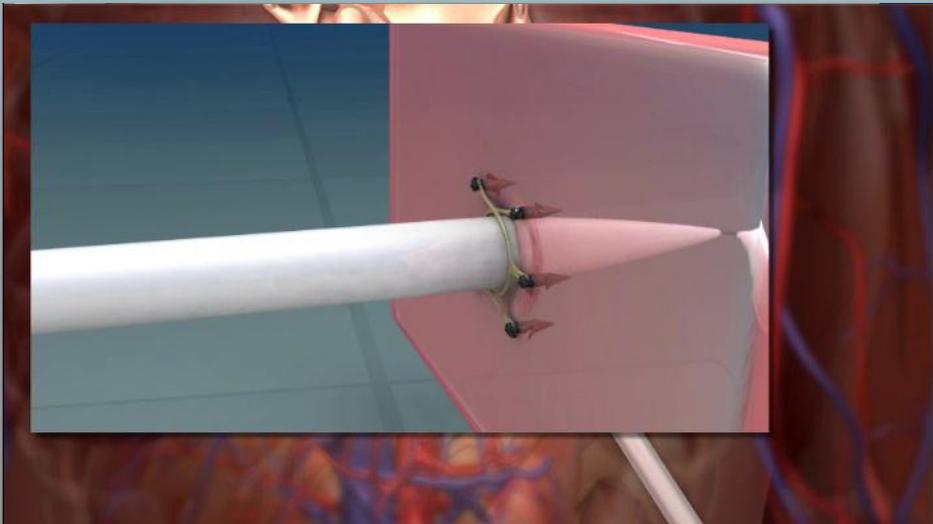
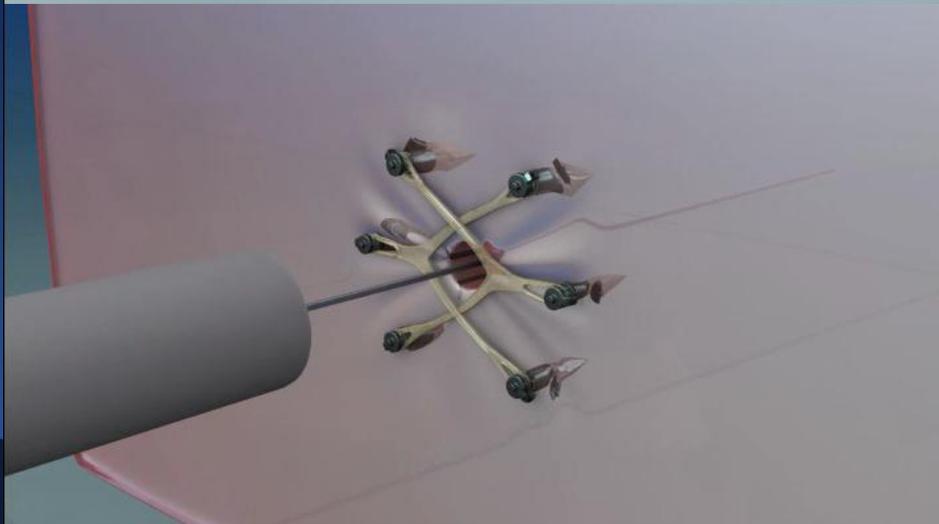
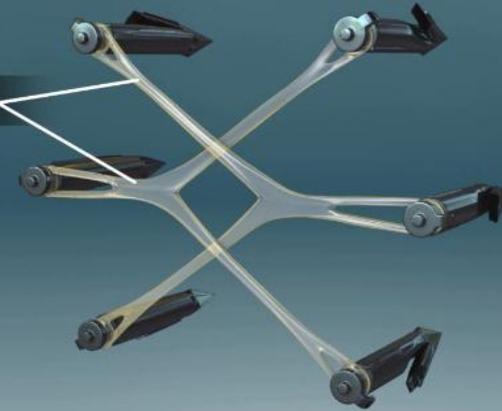
Permaseal™ Transmyocardial Access and Closure Device

Solid Core



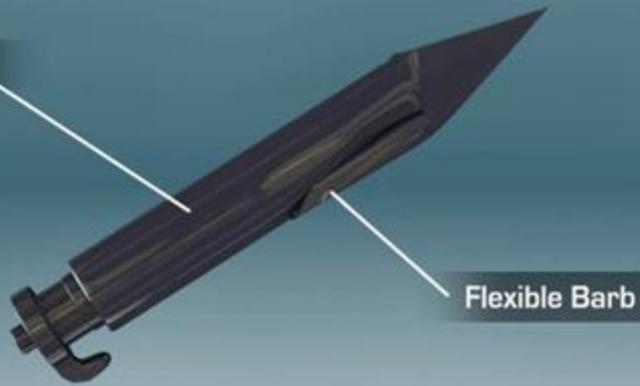
Flexible Barb

V-Stays

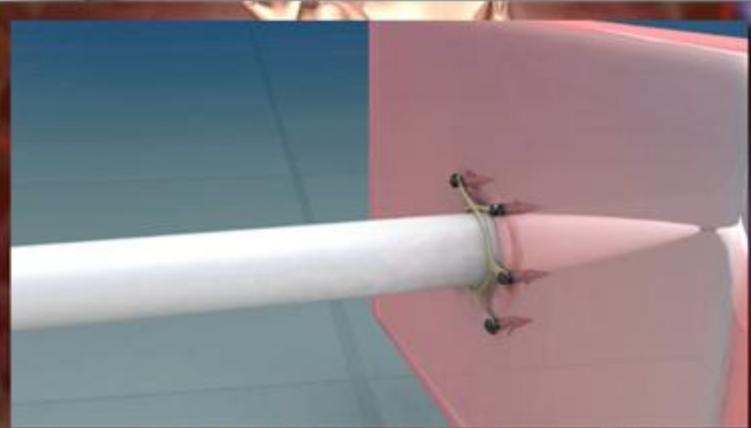
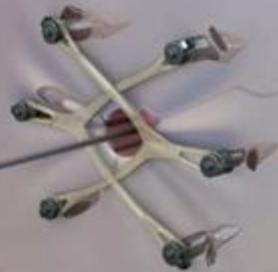
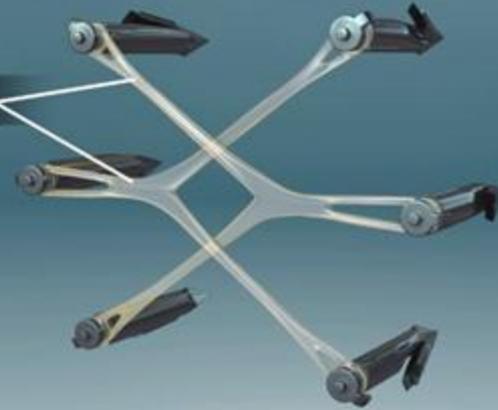


Permaseal™ Transmyocardial Access and Closure Device

Solid Core



V-Stays



PERMASEAL: TRANSMYOCARDIAL ACCESS AND CLOSURE DEVICE



TVAC - 2012

Large Vessel Closure

Large Vessel Closure

Is there a need?

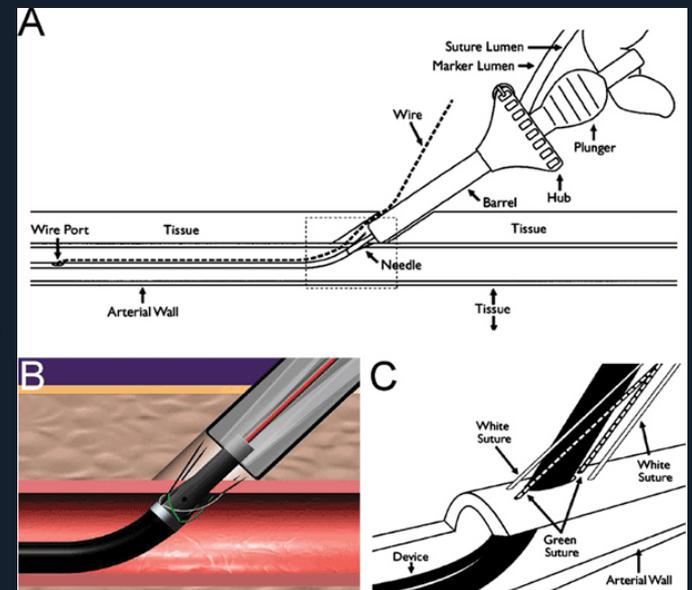
- **Goals of Closure**
 - Patient comfort
 - Facilitate early mobilization
 - Reduce infection risk?
- **Requirements of closure**
 - Accommodate varying size devices
 - Reliable
 - Reaccessible
 - Failure mode not catastrophic

Percutaneous Access & Closure

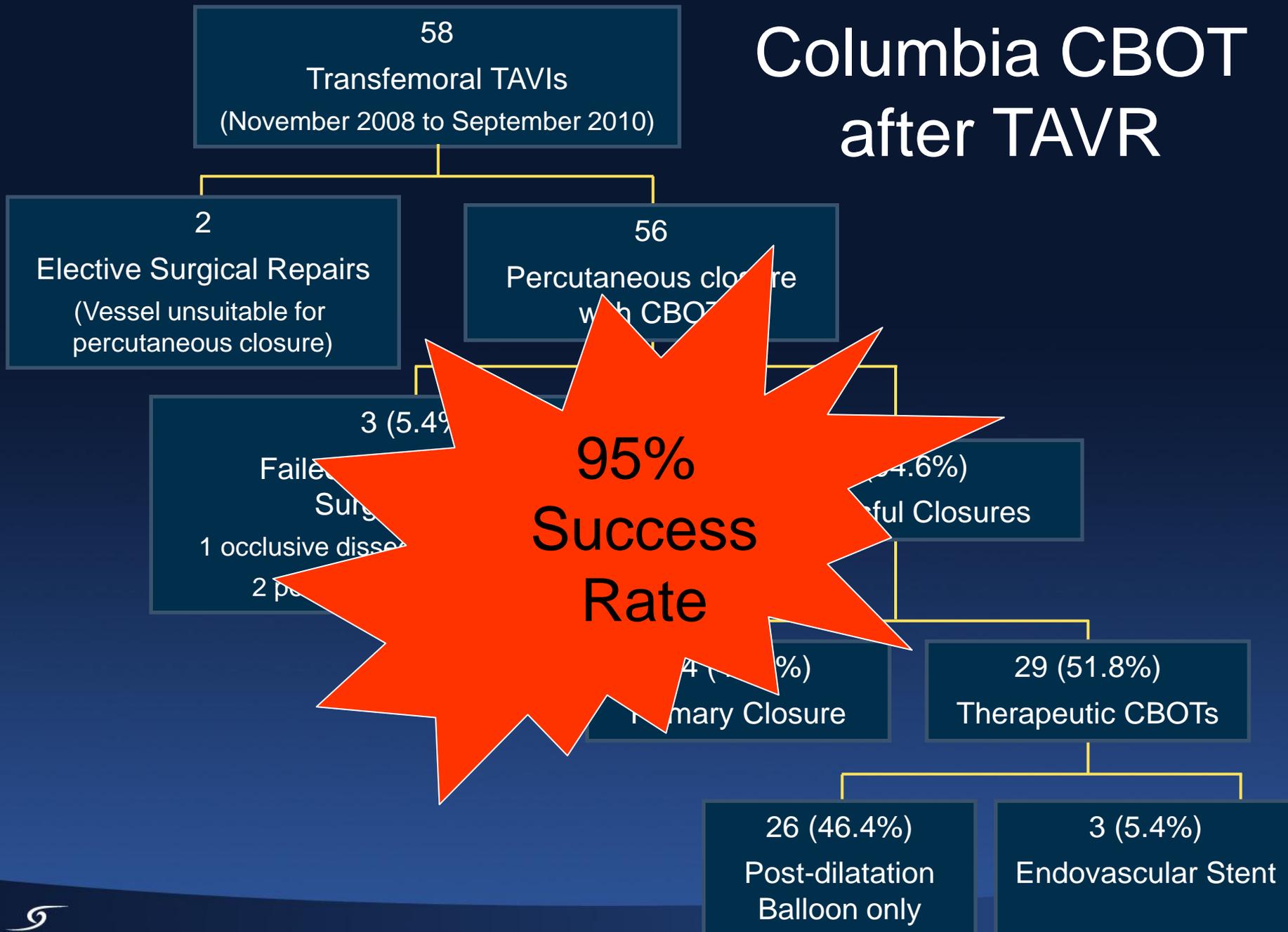
Current
CLOSURE

TAVR Vascular Closure Techniques (trans-femoral) *PERCUTANEOUS CLOSURE*

- Suture mediated
 - One Prostar
 - Two (or three) Proglides
- CE mark approval for up to 24F



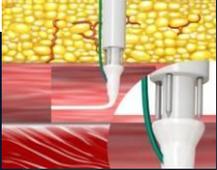
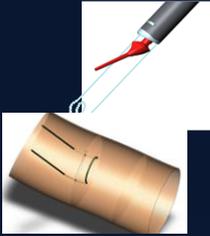
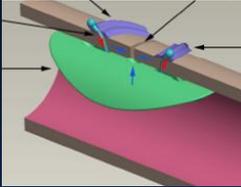
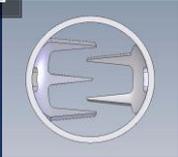
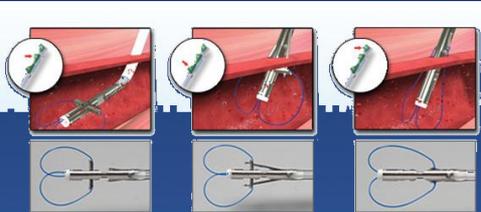
Columbia CBOT after TAVR



Percutaneous Access & Closure

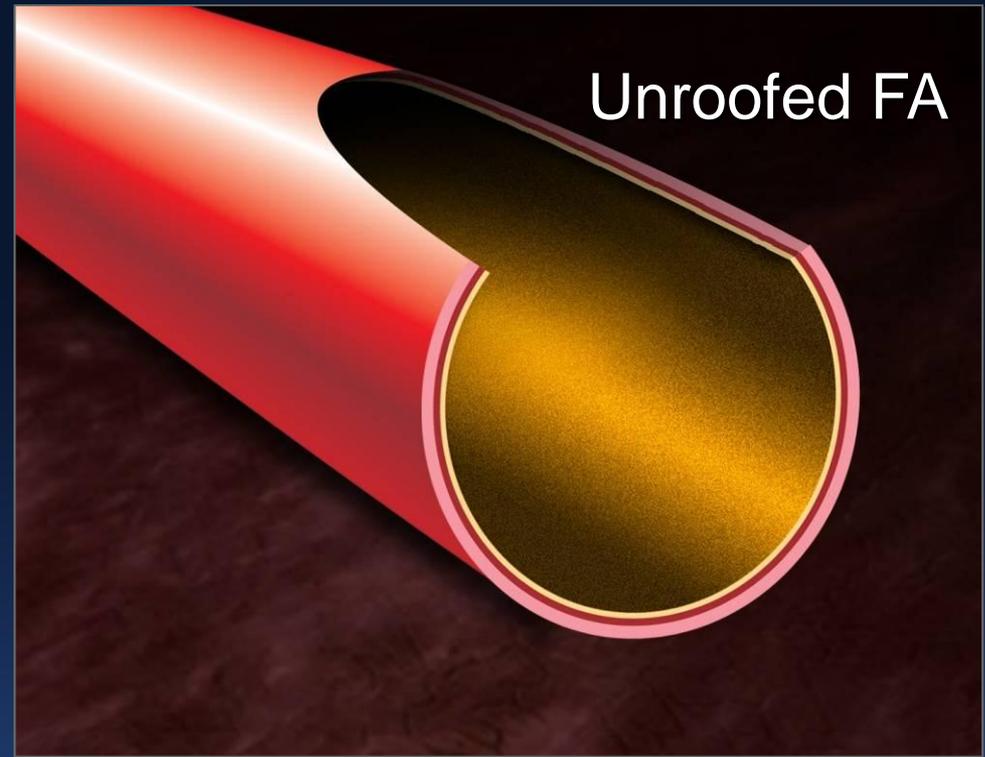
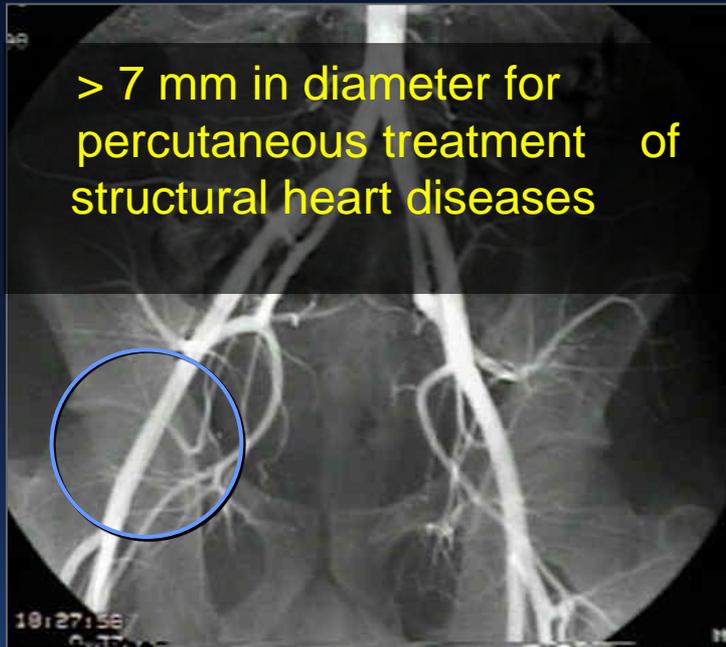
Novel
CLOSURE

Large Vessel Closure Landscape

Category	Company	Technology
Emerging Suture Based Technologies	Sutura Superstich	
	MediGlobe	
	SpiRx	
	Vasostich	
	Vivasure	
Emerging Patch or Plug Technologies	Access Closure-GRIP	
	InSeal	
	Promed	
Strategic Players	Medtronic, Inc.	
	Abbott Vascular	
	St. Jude Medical	
	Cook/Cardica	

Vascular Closure of Large Hole

Femoral Access



1. Suture-based
2. Suture + Plugs/Adhesives
3. Ipsi/contralateral Graft Placement

Sequential Step Indicator Window

Capture Handle

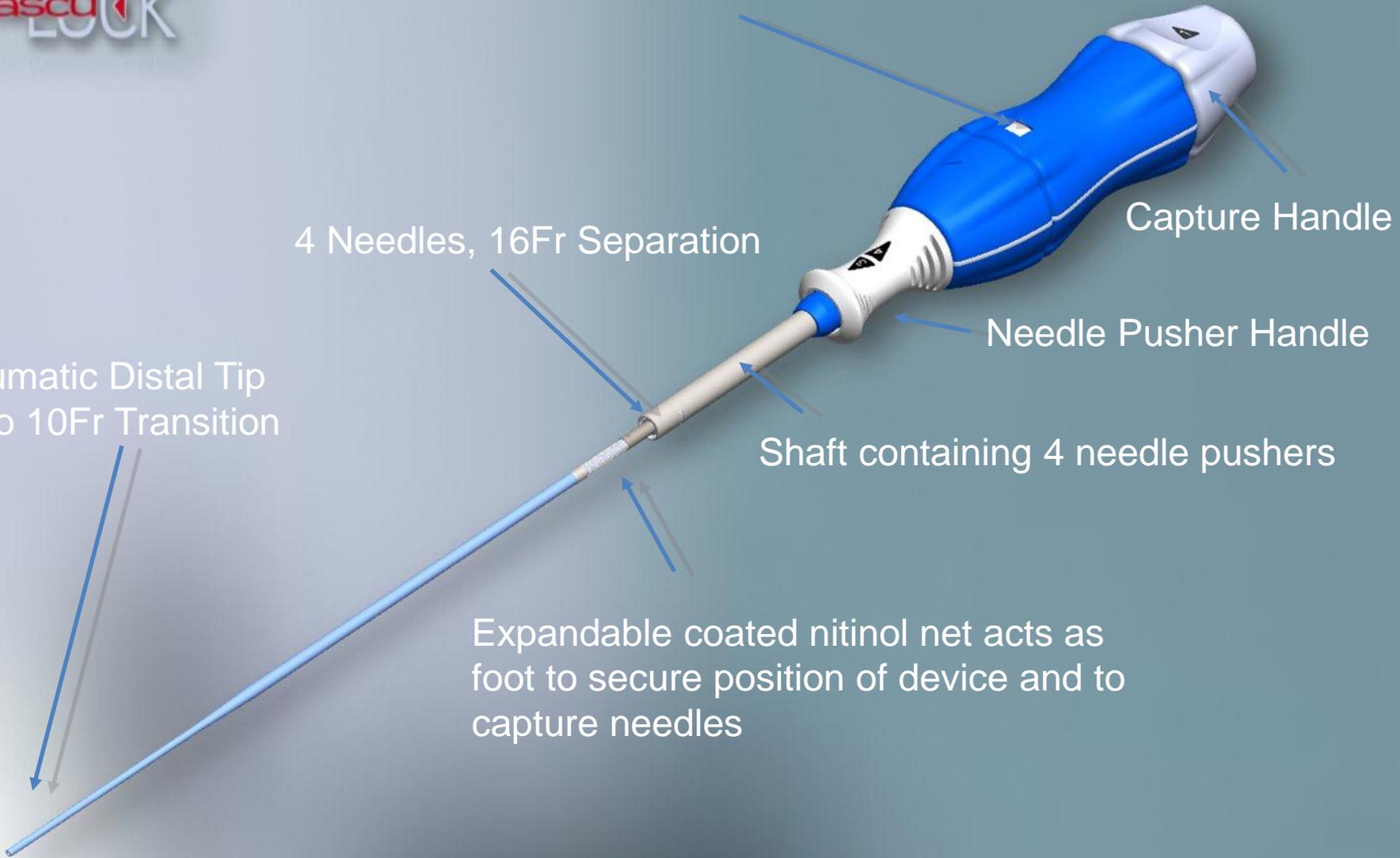
4 Needles, 16Fr Separation

Needle Pusher Handle

Atraumatic Distal Tip
6Fr to 10Fr Transition

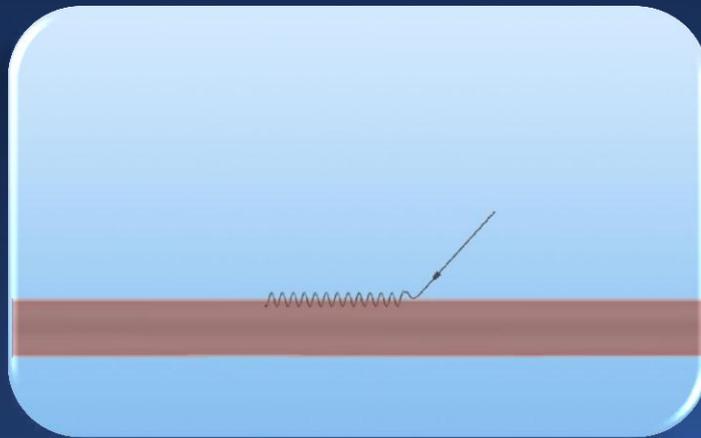
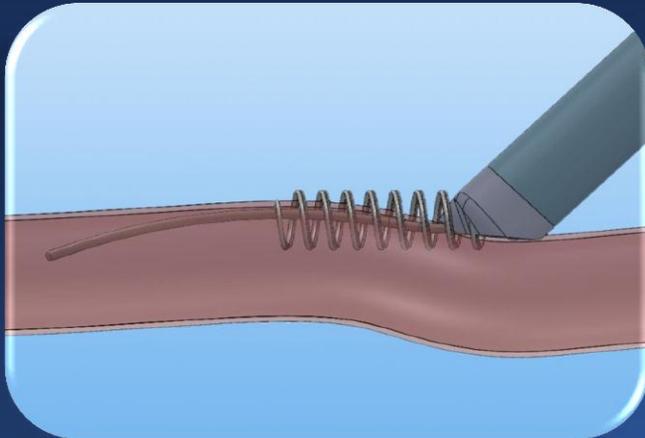
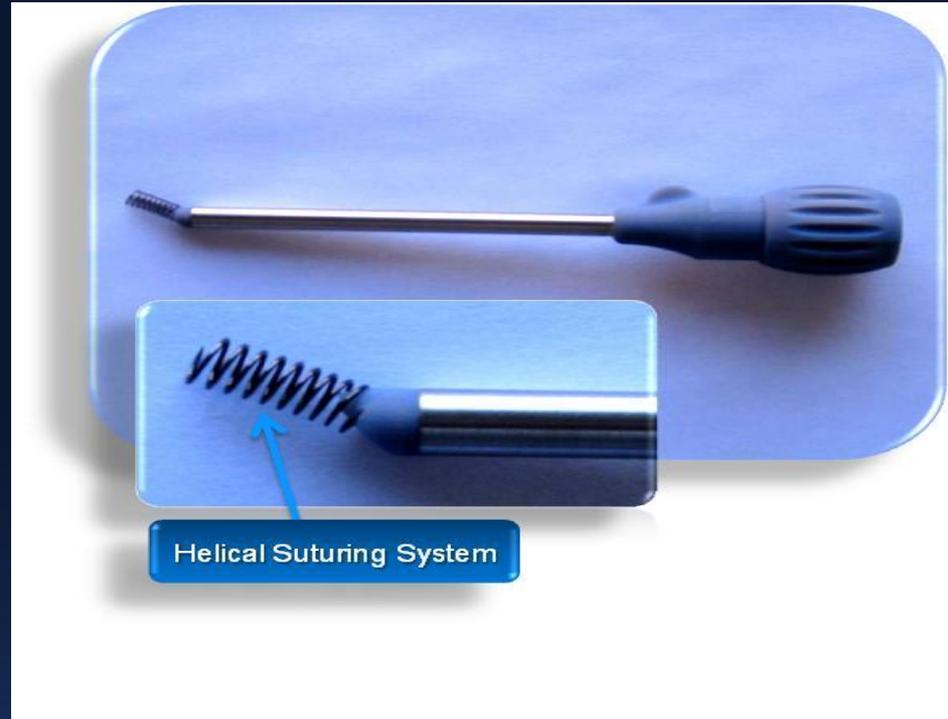
Shaft containing 4 needle pushers

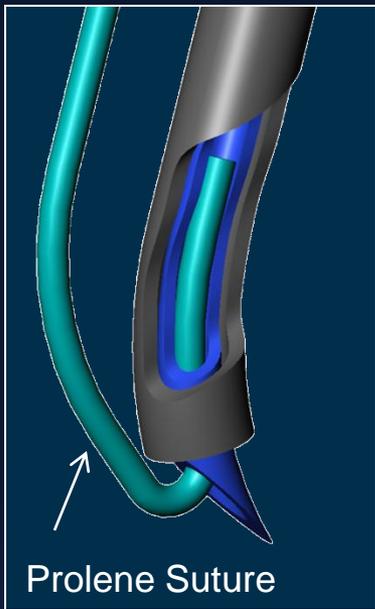
Expandable coated nitinol net acts as foot to secure position of device and to capture needles



VasoStitch

- Large bore vascular closure (12-24f)
- Suture mediated closure system delivered via coil inside artery
- Coil withdrawn to lay down suture and close access site
- Possible application for TA TAVR





Prolene Suture



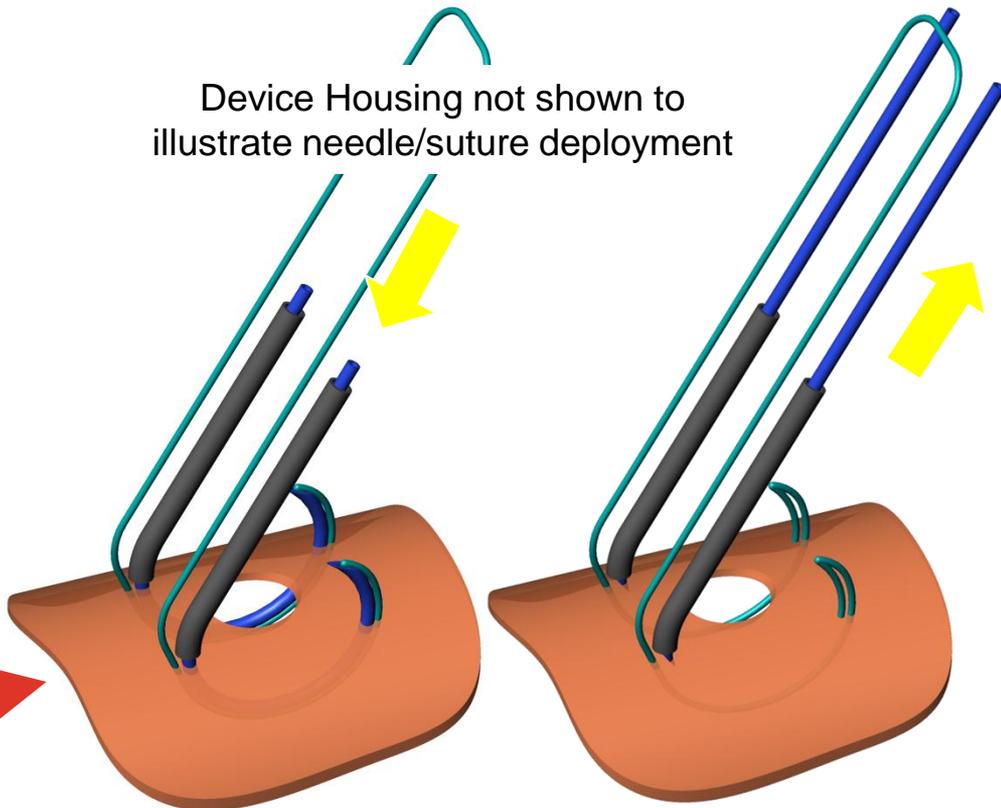
Nitinol Needle
(Free state)

(needle punctures in
direction of blood flow)

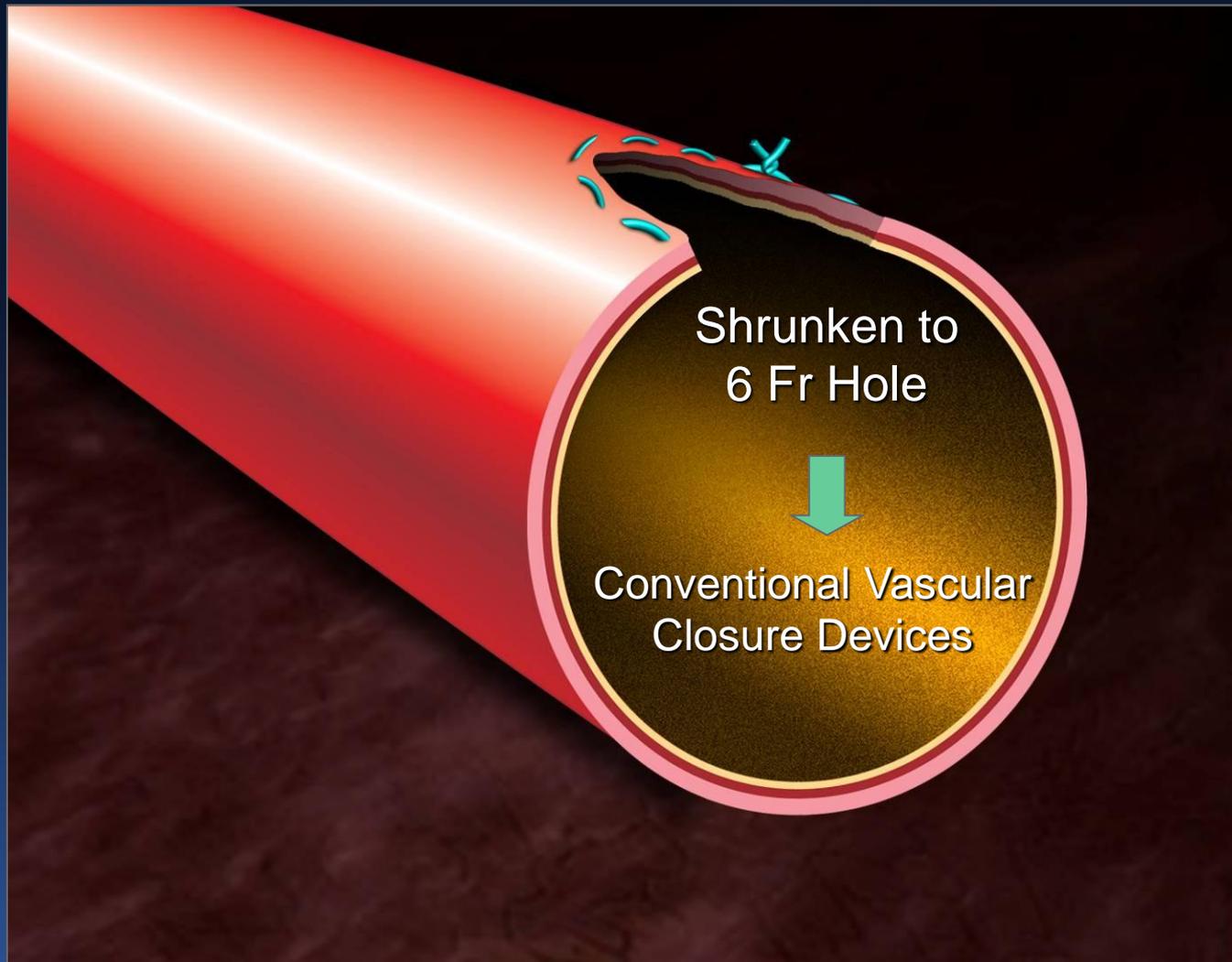
Blood flow



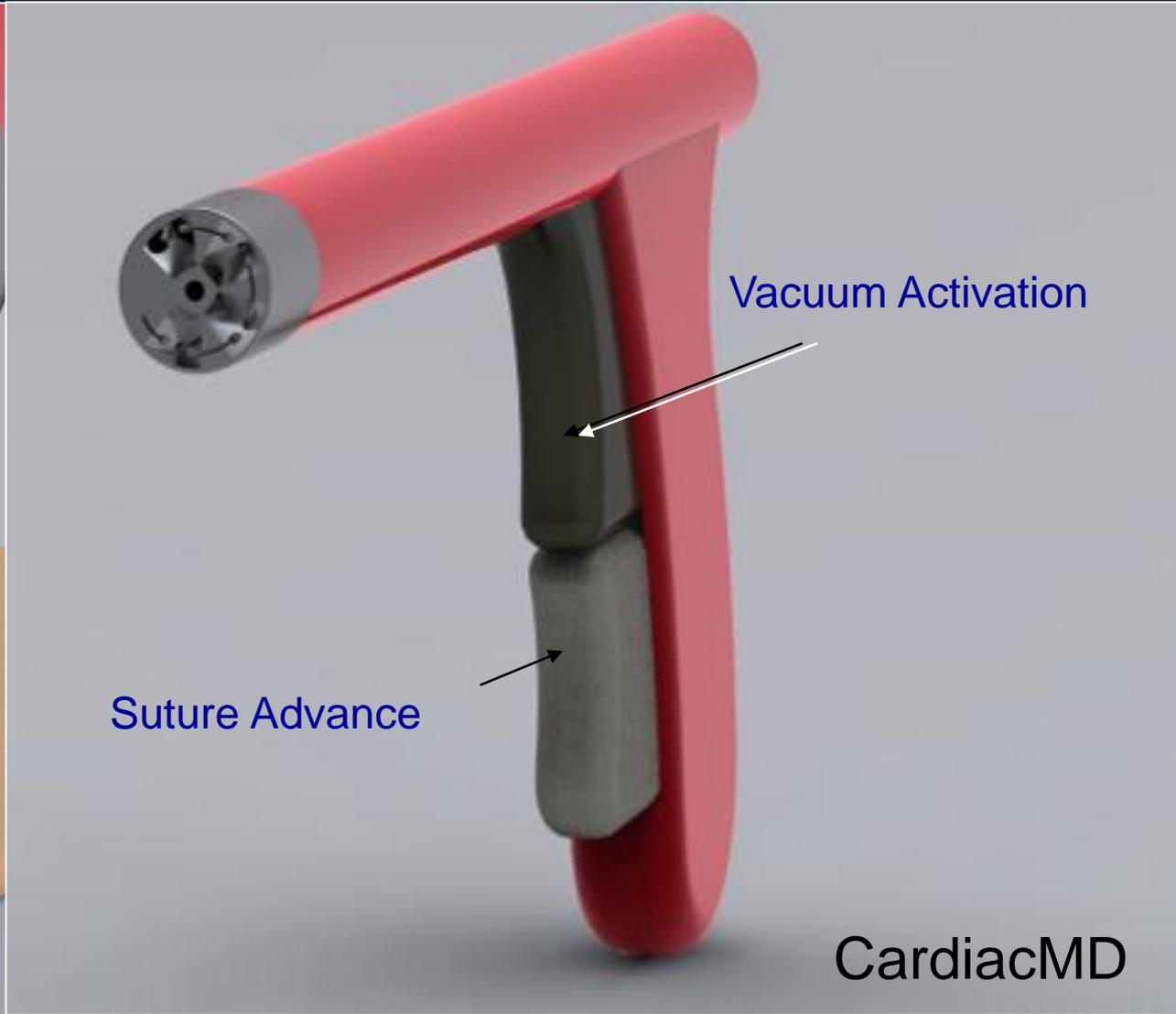
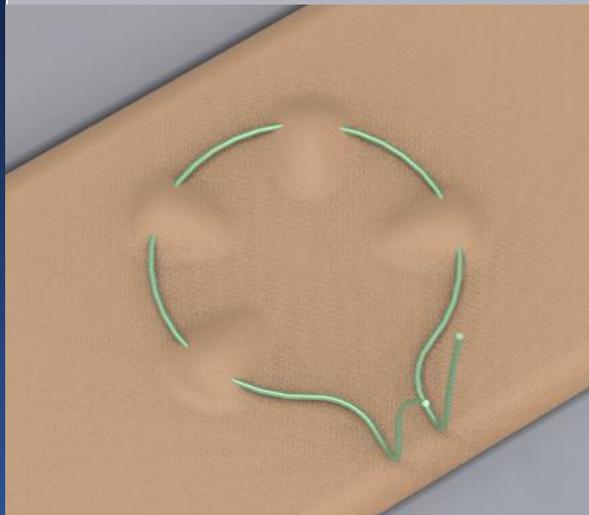
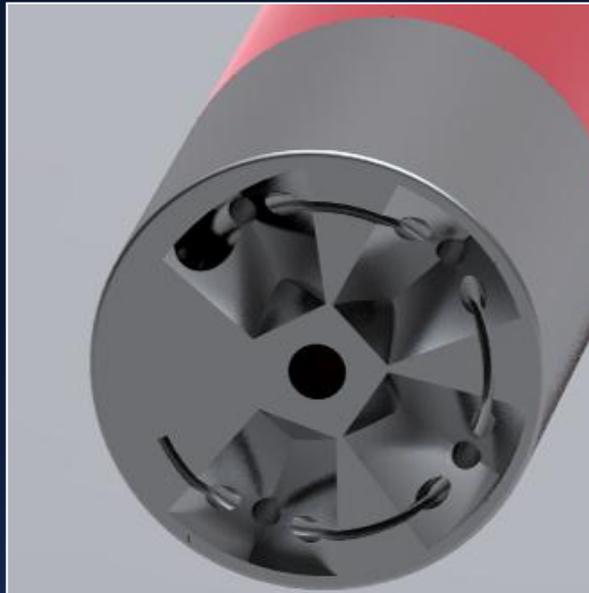
Device Housing not shown to
illustrate needle/suture deployment



“Suture or Reducer Plus” Approach

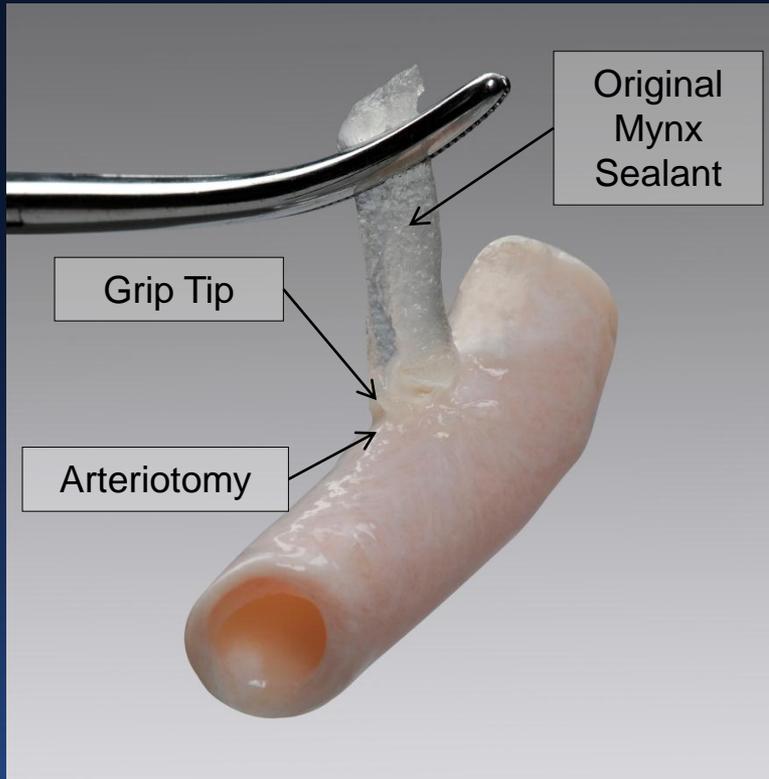


Circumferential Tightening



CardiacMD

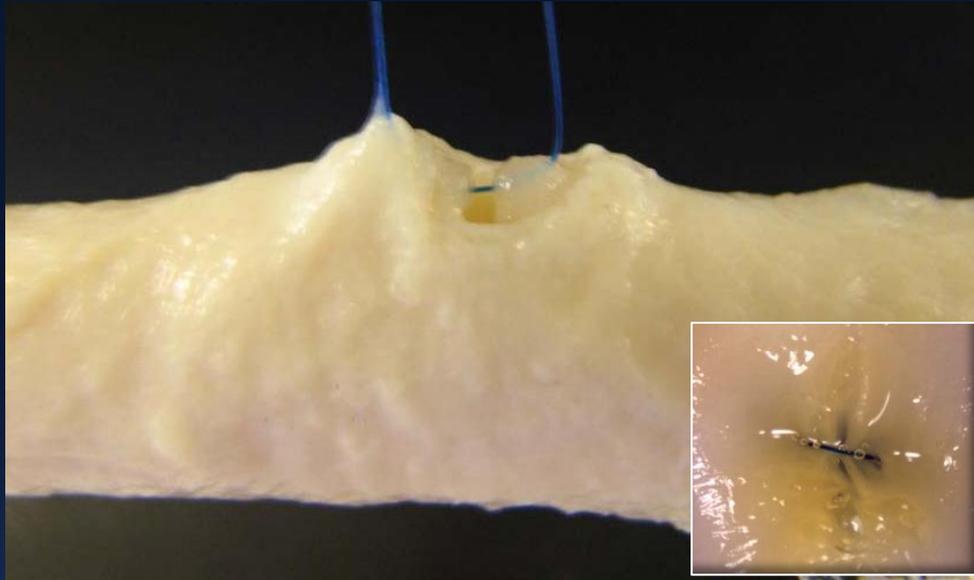
Grip Technology: *New Sealant for Vascular Closure*



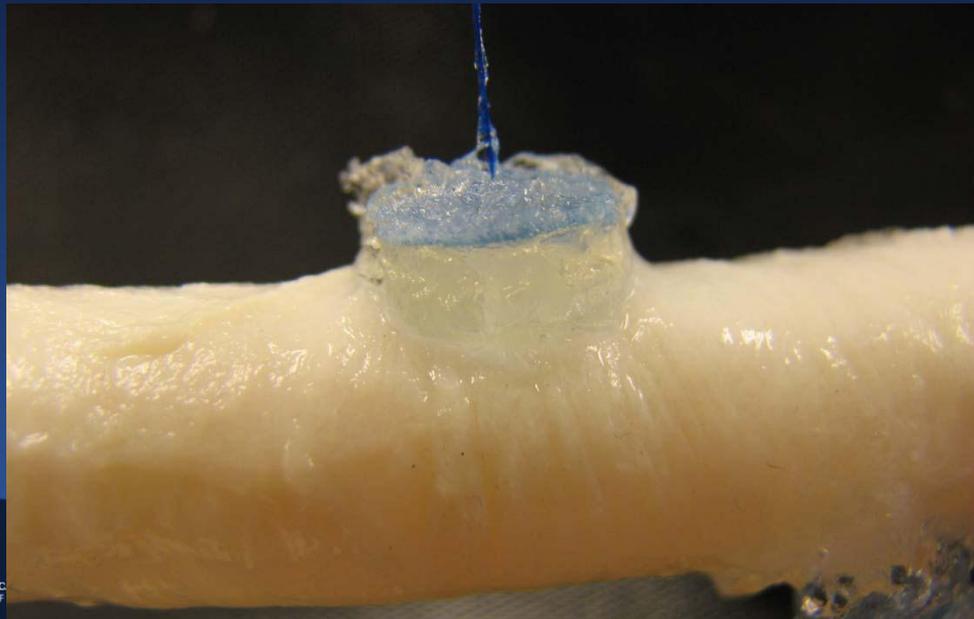
MynxGrip deployment on a porcine, carotid vessel

- Grip Technology is a new formulation of polyethylene glycol
- The Grip Tip portion of the MynxGrip sealant actively grips the artery
- MynxGrip achieves active extravascular closure
- Bioabsorbable sealant dissolves in <30 days, leaving nothing behind

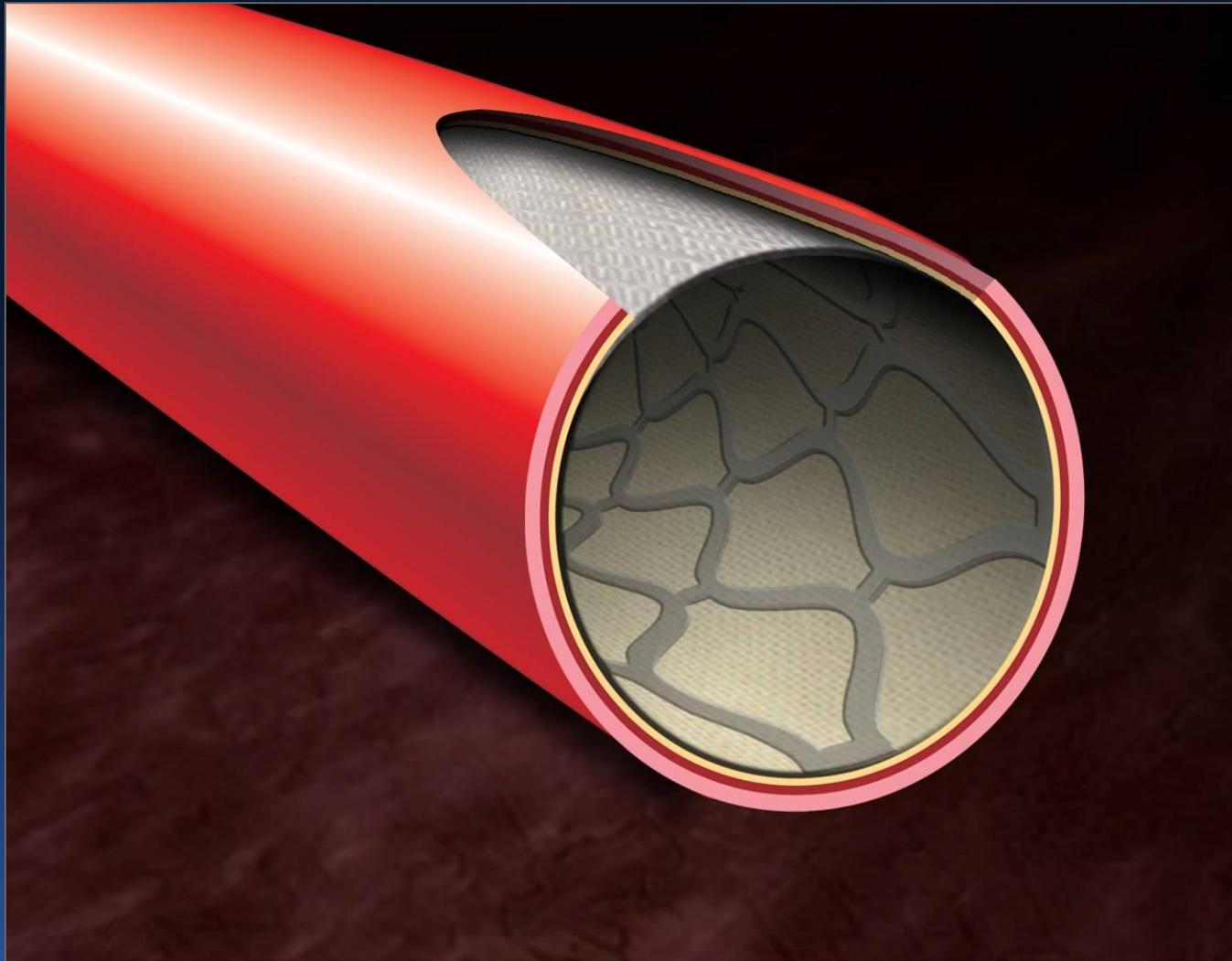
Grip Technology for Large Hole Closure



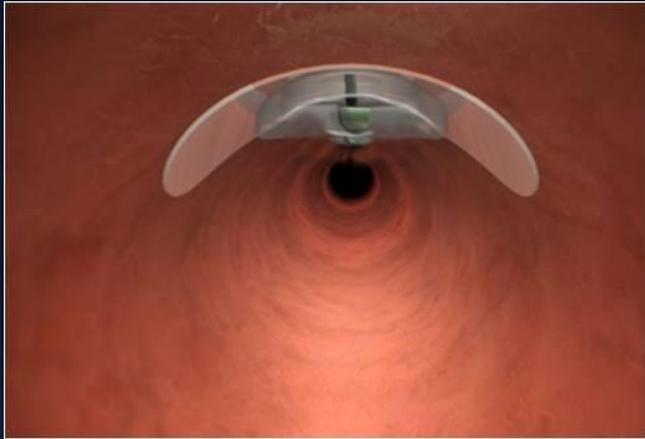
- *Single suture for approximation of arterial wound*
- *Grip provides seal over arteriotomy*
- *Certain Closure, minimum intravascular components*



Ipsi/Contralateral Graft Approach

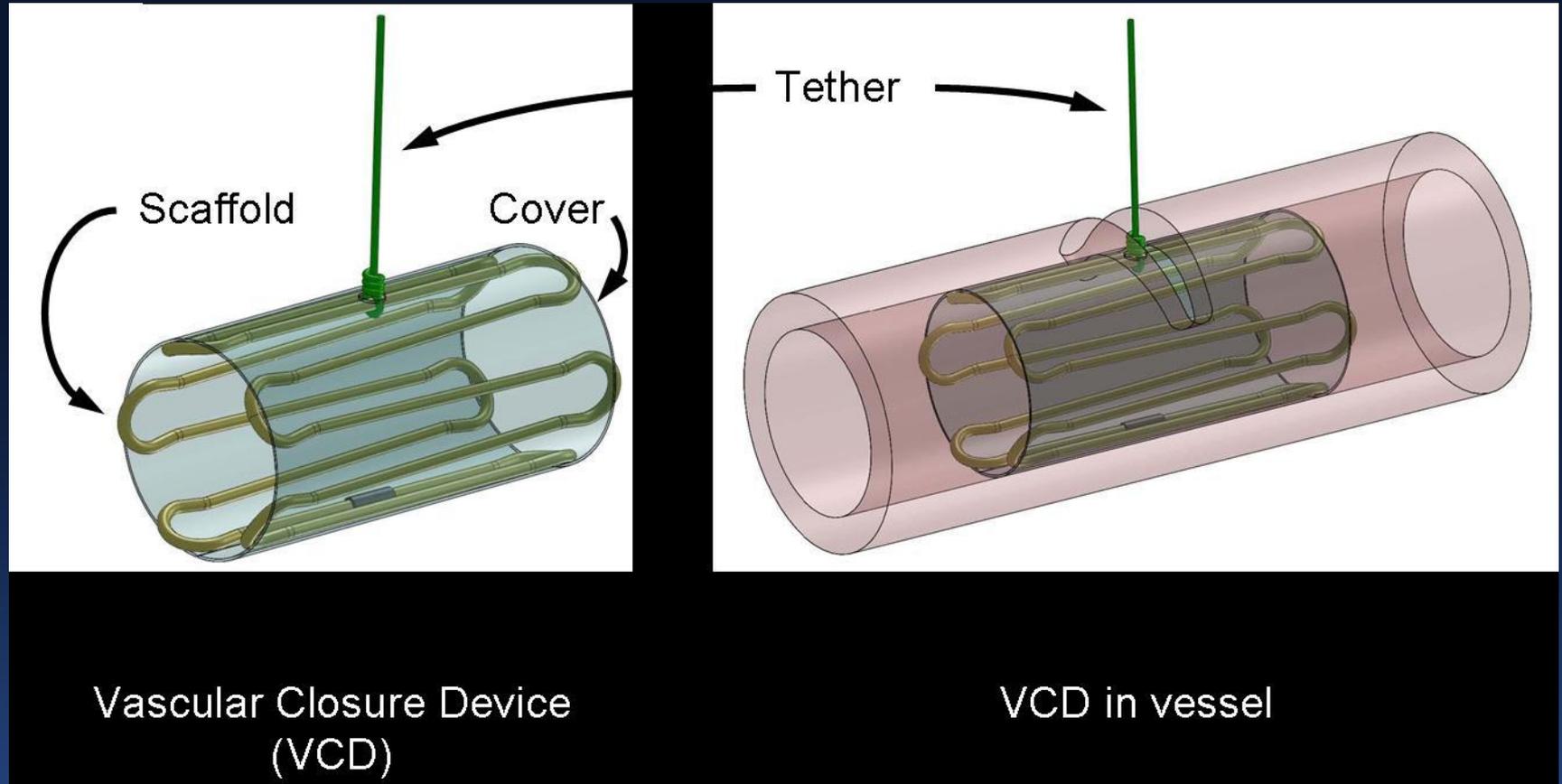


Frontier Vascular Closure Device



- Easy-to-use device, designed specifically for percutaneous Large Hole Closure
- Immediate secure closure for arteriotomies between 12 and 24F
- Over-the Wire System which utilises the Procedural Sheath
- Controls blood loss during deployment
- Fully Bioabsorbable, low profile, conforming Patch Graft design
- Simplifies and shortens procedure for both patient and physician

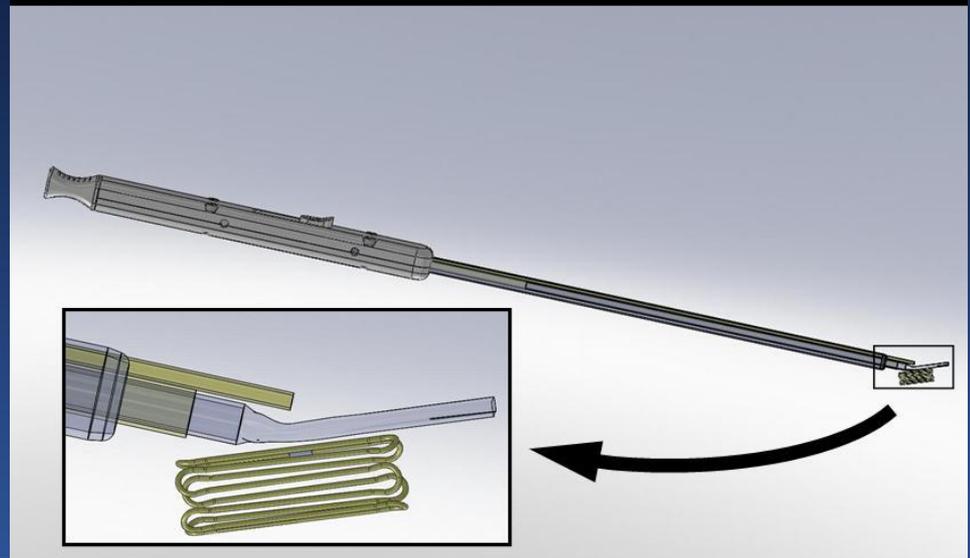
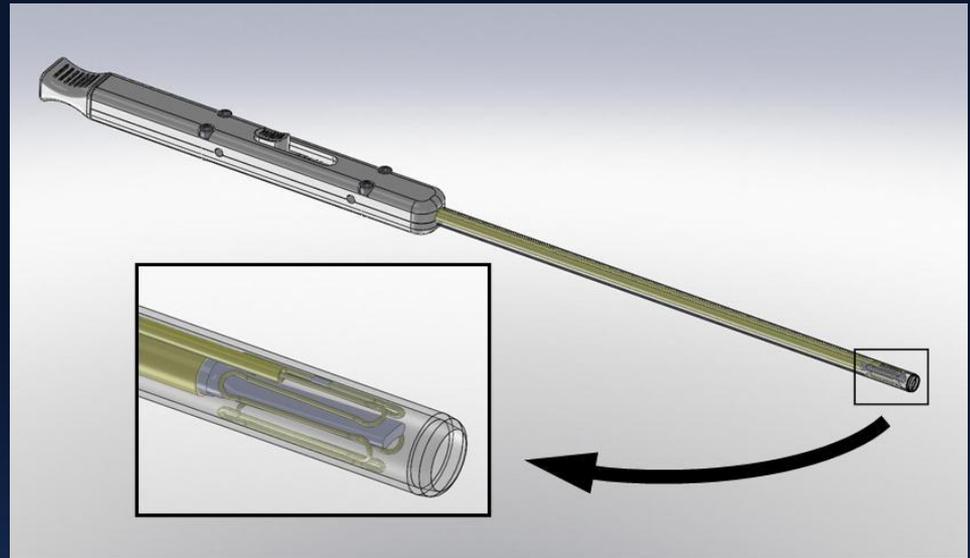
ProMed Device



**Bioabsorbable cover over thin frame
nitinol scaffold (ipsilateral)**

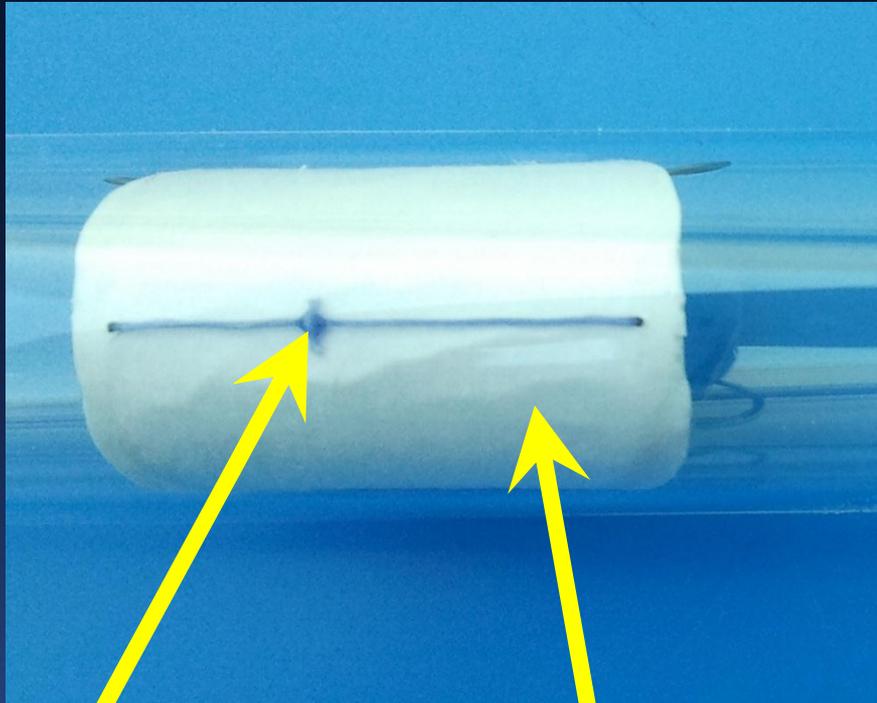
ProMed Device

- Facilitates standard interventional approach to closure
- Compatible with existing 18-24 F sheaths
- Utilizes a bioabsorbable covered scaffold that is fully protected by sheath until ready to deploy
- Minimal signature implant allows for re-intervention



InSeal Intravascular Closure Device

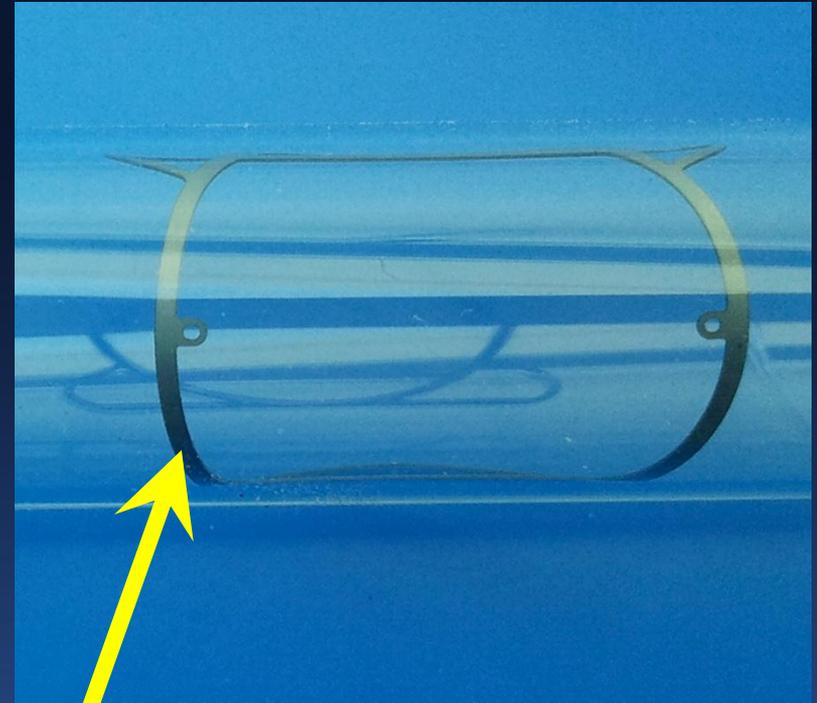
Acute



Tether
(biodegradable)

Sealing membrane
(biodegradable)

After
biodegradation



Nitinol frame

Stroke

Published on-line June 5, 2011
@ NEJM.org and print June 9, 2011

Editorial Response

EDITORIALS



Transcatheter Aortic-Valve Implantation — At What Price?

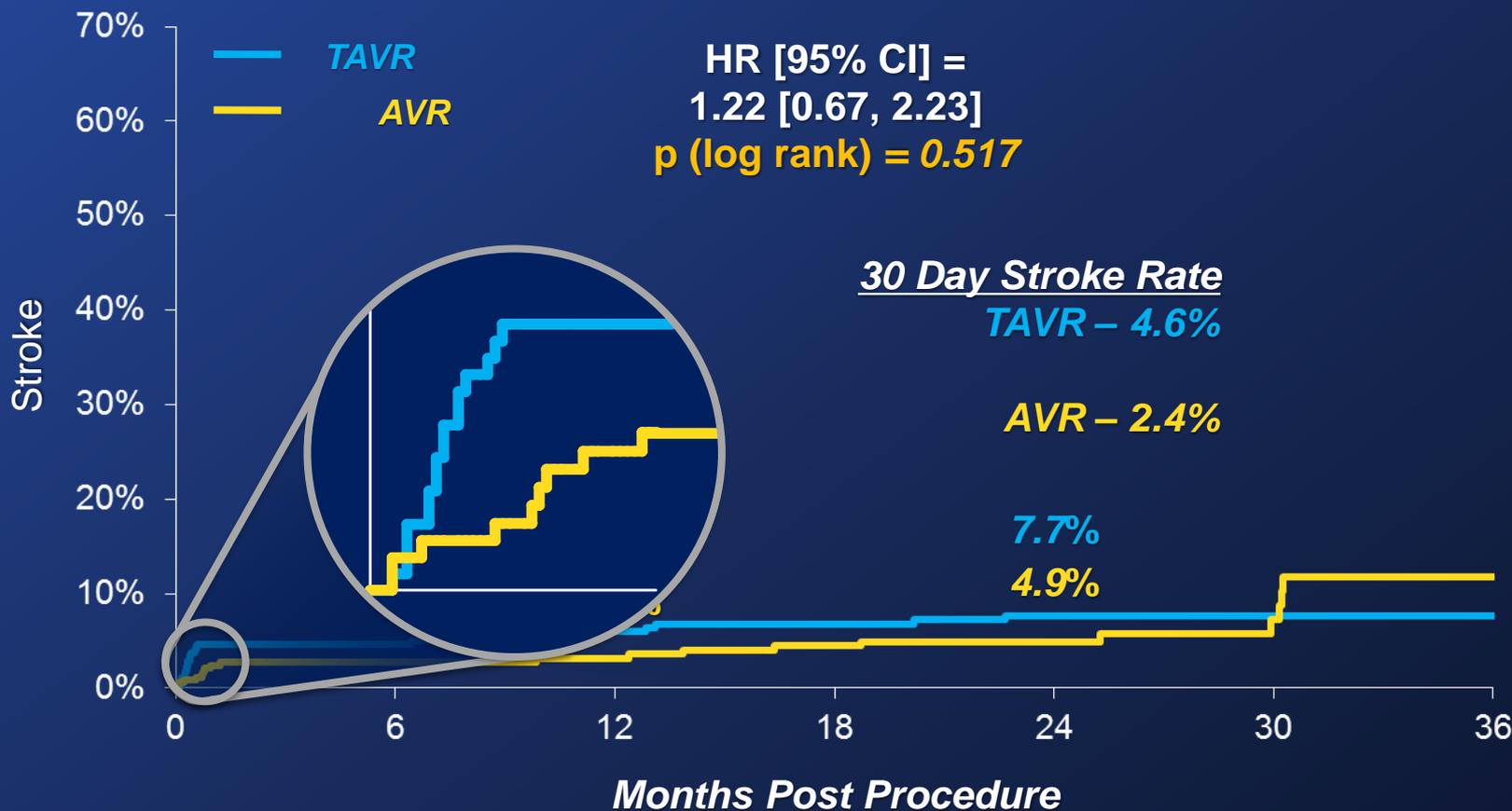
Hartzell V. Schaff, M.D.

In 2000, Bonhoeffer et al. described transvenous placement of a pulmonary-valve prosthesis and speculated that similar technology might be used in other cardiac valves, including the aortic position.¹ Two years later, the first transcatheter in-

patients who are eligible for transfemoral insertion and may decrease vascular injury.

But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith

Strokes (ITT) High Risk Cohort



Numbers at Risk

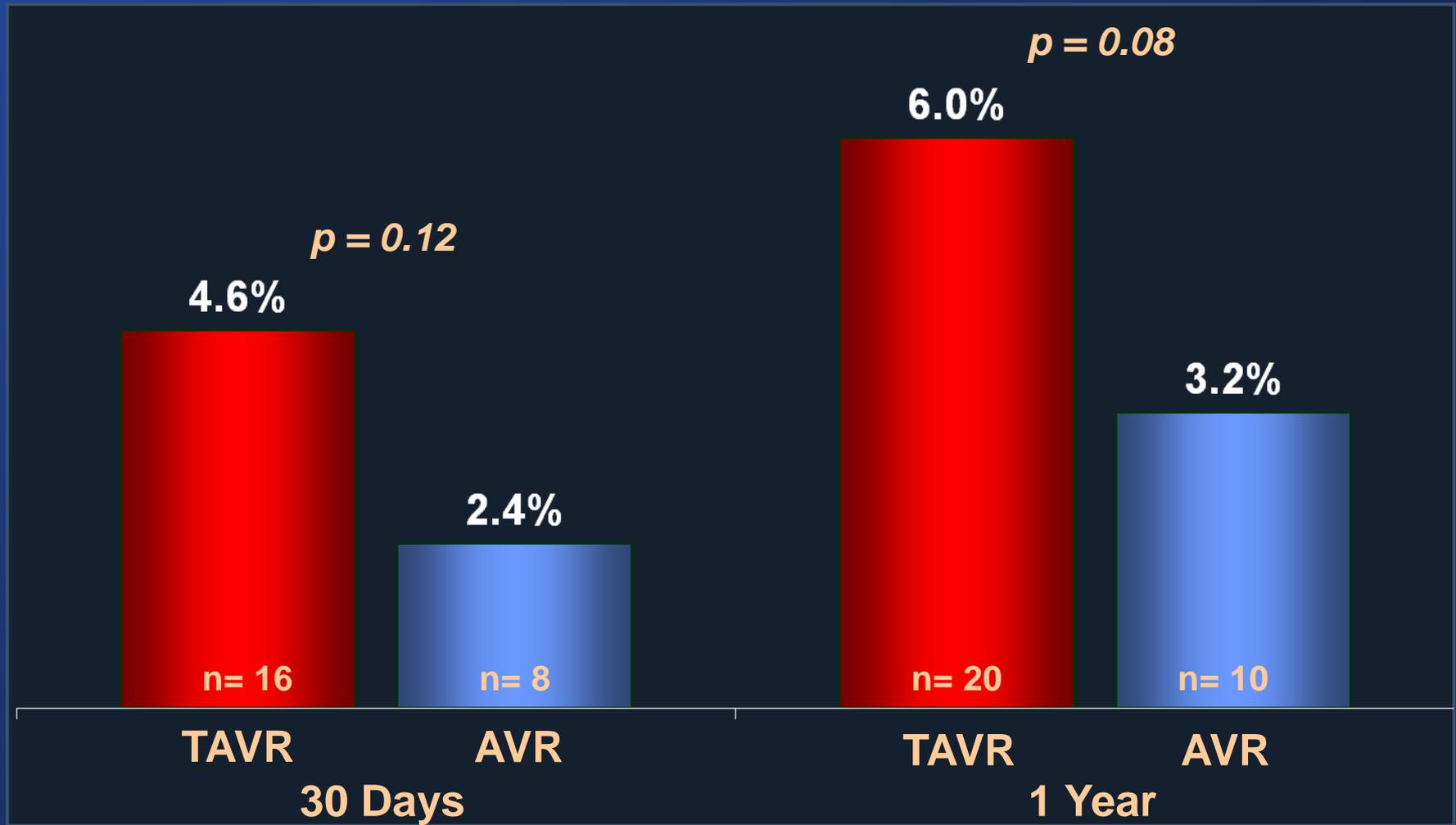
TAVR	348	287	249	224	162	65	28
AVR	351	246	230	211	160	62	31

Procedural Predictors of Mortality

High Risk Cohort



All Strokes (major and minor) at 30 Days & 1 Year



ITT Population

Diffusion-Weighted MRI Study

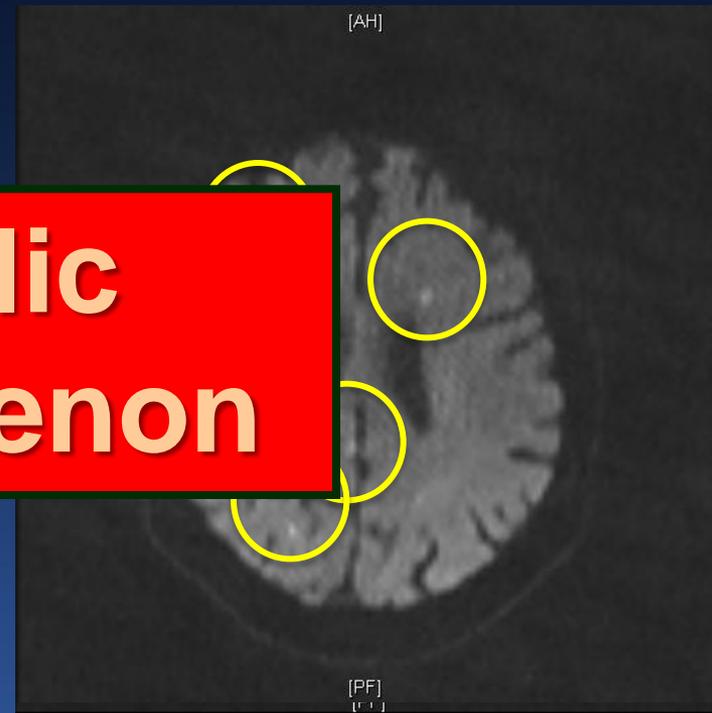
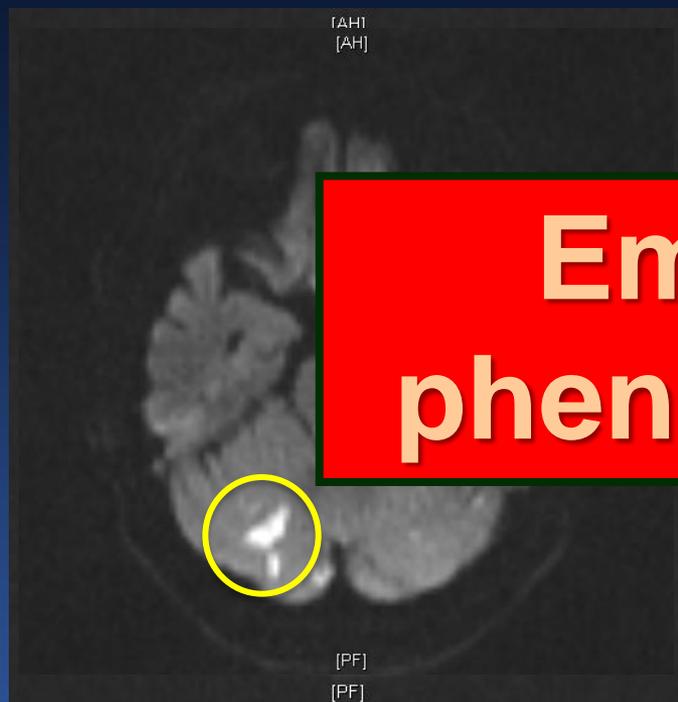
Philipp Kahlert, MD

West German Heart Center Essen

Pre-TAVI

Post-TAVI

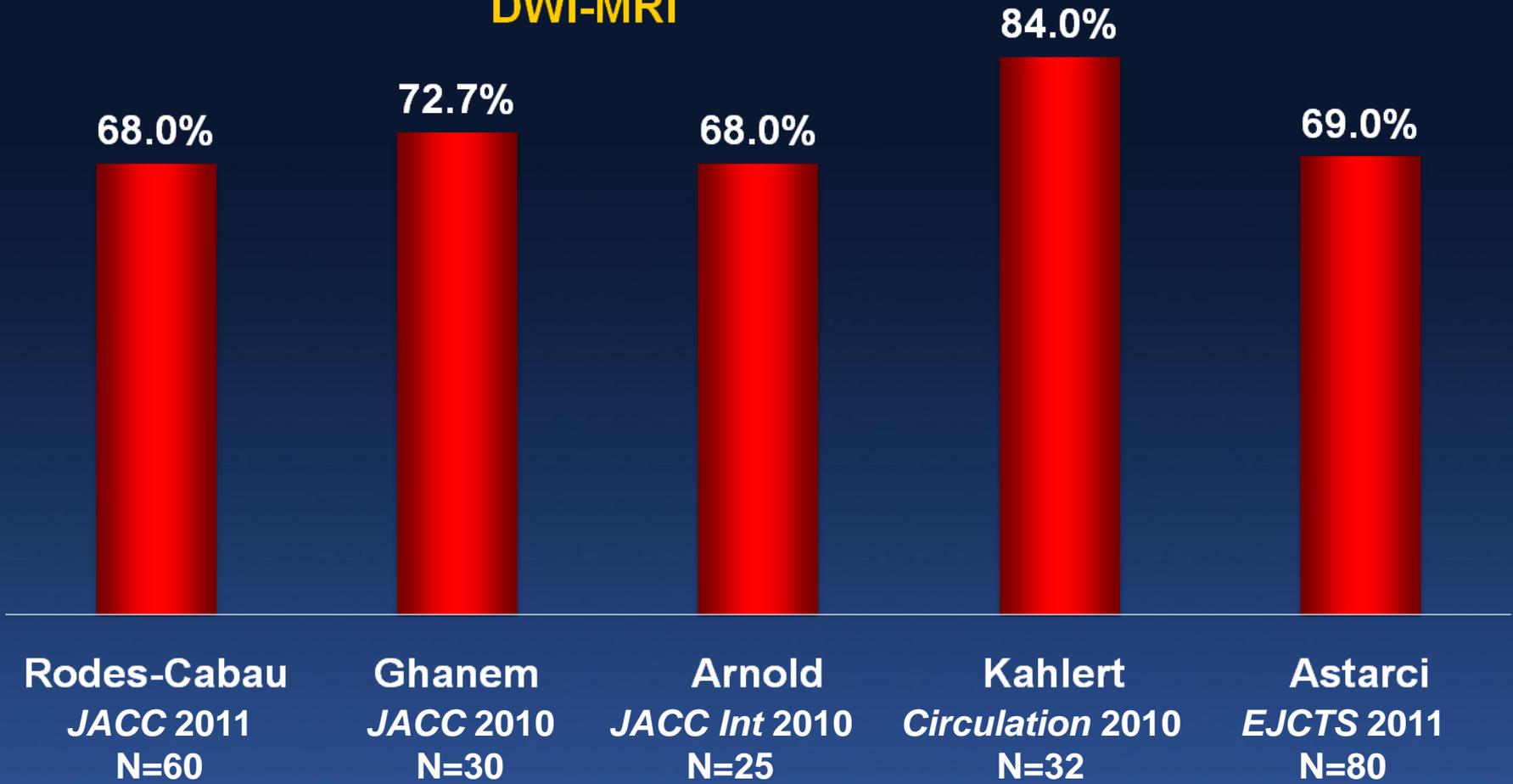
Example of an 82-year-old patient two days after successful TAVI



**Embolic
phenomenon**

Neuro-imaging with TAVR

**% of patient with new ischemic lesions on
DWI-MRI**



Embolic Protection

Unanswered Questions

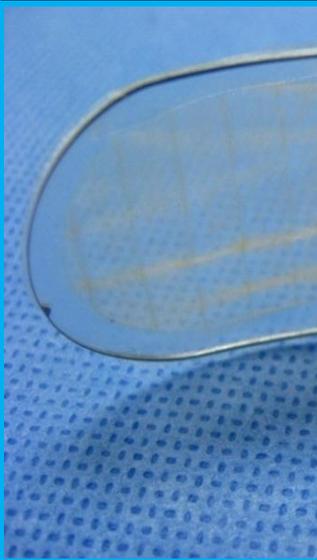
- **Questions**
 - Does it need to protect all head vessels?
 - Does it need to capture material?
 - Is it necessary in every patient?
 - What endpoints should be used in studies?
- **Requirements**
 - Easy to use and low profile
 - Shouldn't complicate access site management
 - Should not require excessive arch manipulation

Cerebral Embolic Protection Devices

Deflectors and Filters



SMT
(15 pts)

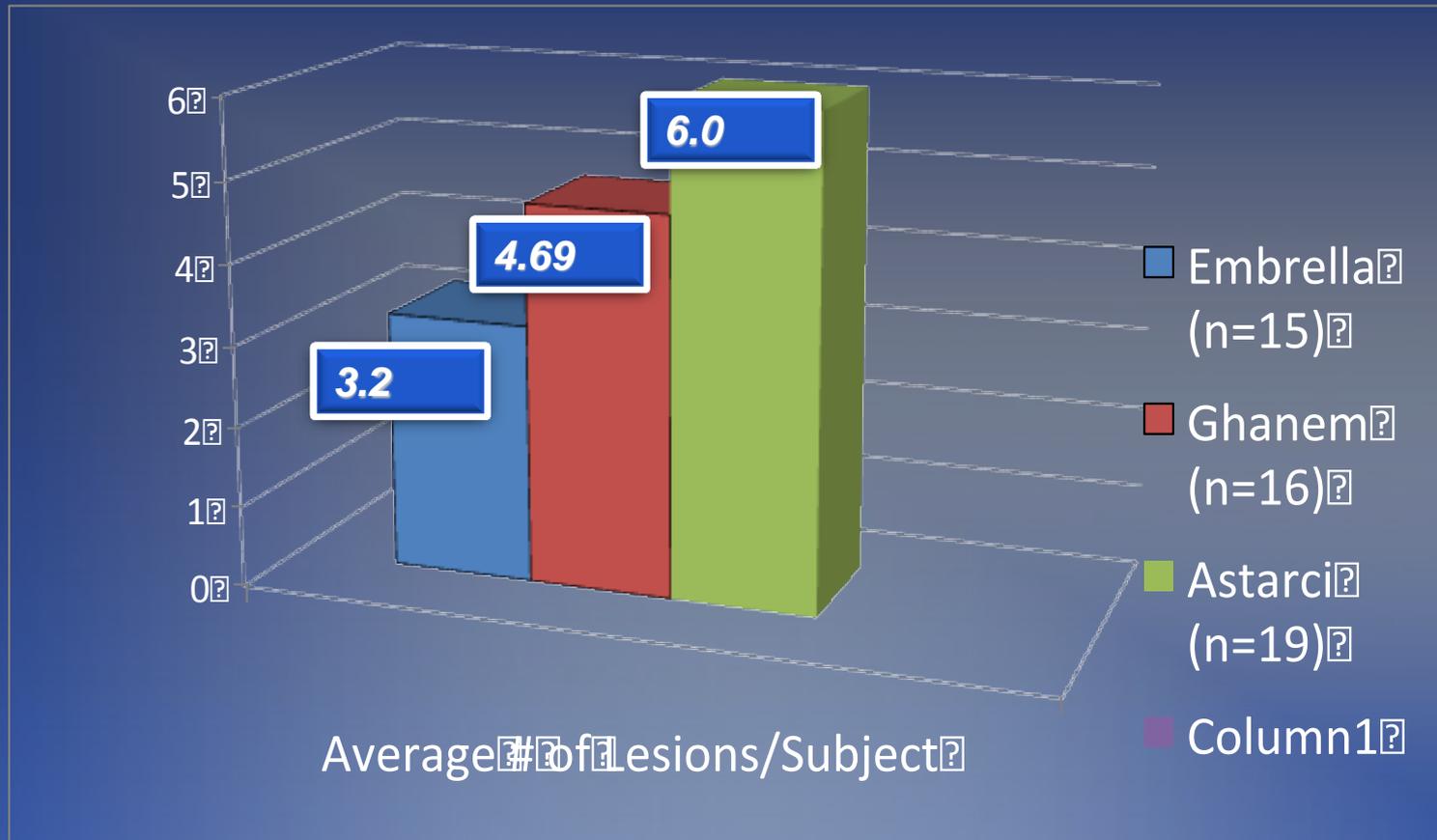


Embrella
(20 pts)



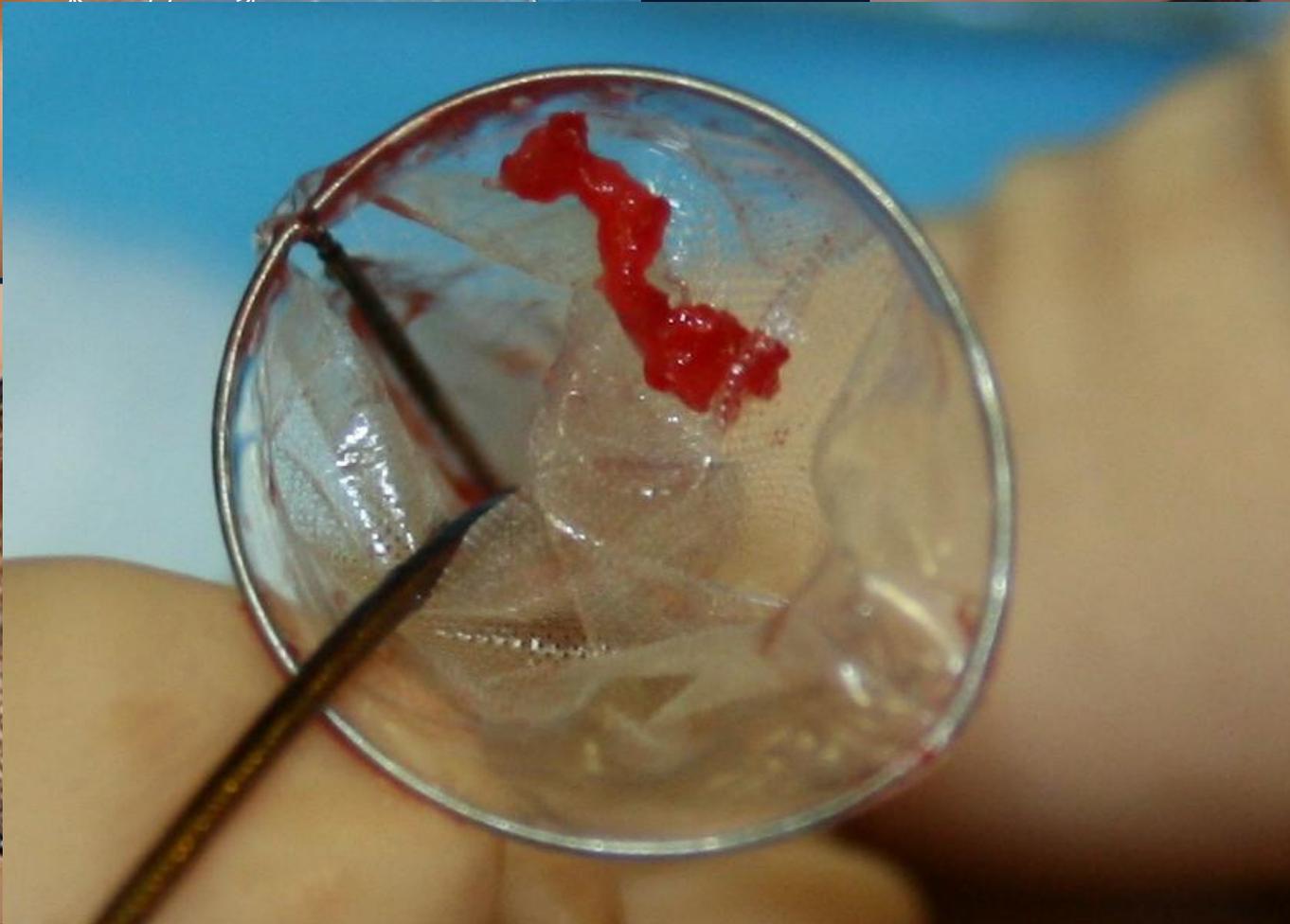
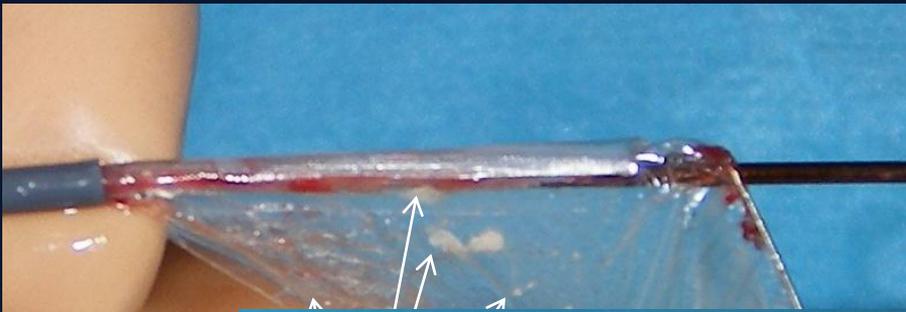
Claret
(40 pts)

Embololic Protection in TAVR



Ghanem et al, J Am Coll Cardiol 2010;55:1427–32
Astarci et al, Abstract presentation EACTS 2010

Embololic Material after TAVR



PROTAVI - C

Severe AS + Symptoms
Case selection: Heart Team (high-risk)

Randomization 1:1

Standard TAVR

Standard TAVR + Deflection

Primary Endpoint: Volume of
DW-MRI brain lesions @ 1 wk

Re-Randomization 1:1

ASA alone
for 3 months

ASA + clopidogrel for
3 months

2nd Primary Endpoint: composite
stroke/TIA + bleeding @ 1 year

Co-PIs: Profs Vahanian
and Beversdorf

Paravalvular Regurgitation

PVL after TAVR Predicts Increased Mortality

Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results

from the German transcatheter aortic valve

inter

Moham

Tran

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Michae

Alfried

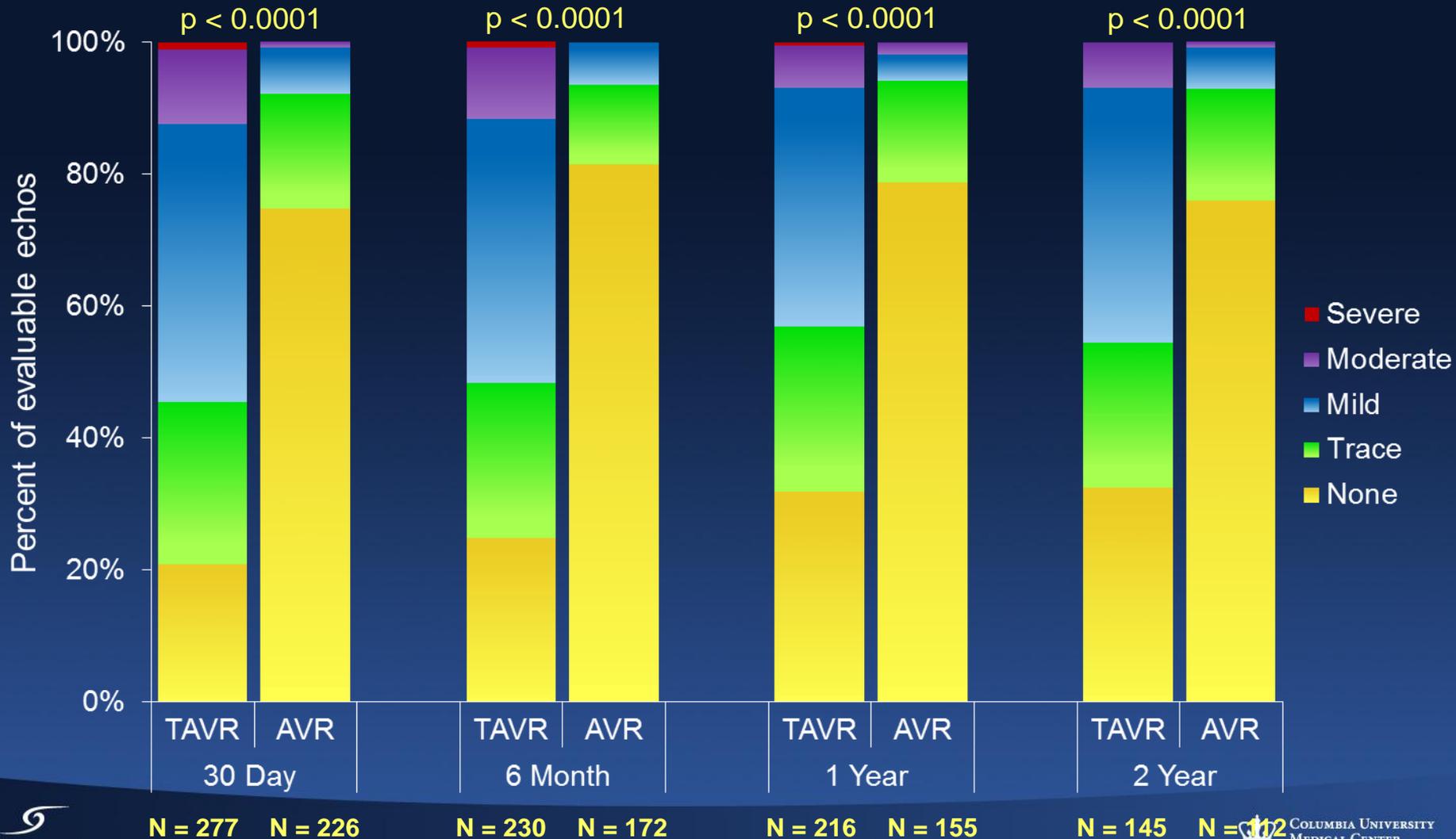
Long-Term Outcomes After Transcatheter Aortic Valve Implantation in High-Risk Patients With Severe Aortic Stenosis

The U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry

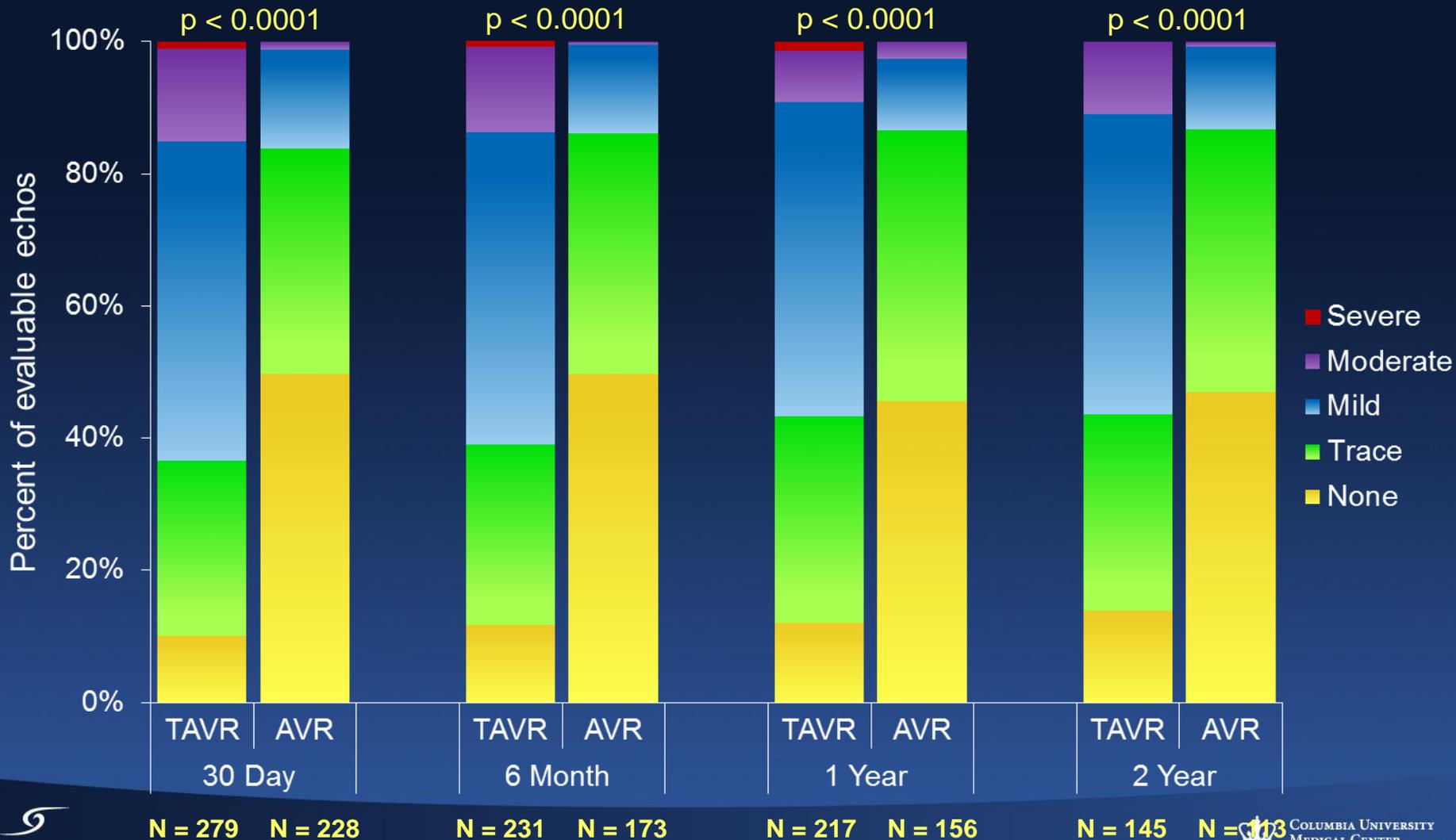
Neil E. Moat, MBBS, MS,* Peter Ludman, MA, MD,† Mark A. de Belder, MA, MD,‡ Ben Bridgewater, PhD,§ Andrew D. Cunningham, PhD,|| Christopher P. Young, MD,¶ Martyn Thomas, MD,¶ Jan Kovac, MD,# Tom Spyt, MD,# Philip A. MacCarthy, BS, PhD,** Olaf Wendler, MD, PhD,** David Hildick-Smith, MD,†† Simon W. Davies, MBBS, MD,* Uday Trivedi, MBBS,†† Daniel J. Blackman, MD,‡‡ Richard D. Levy, MD,§ Stephen J. D. Brecker, MD,§§ Andreas Baumbach, MD,|| Tim Daniel, MB, ChB,¶¶ Huon Gray, MD,## Michael J. Mullen, MBBS, MD***

with
of

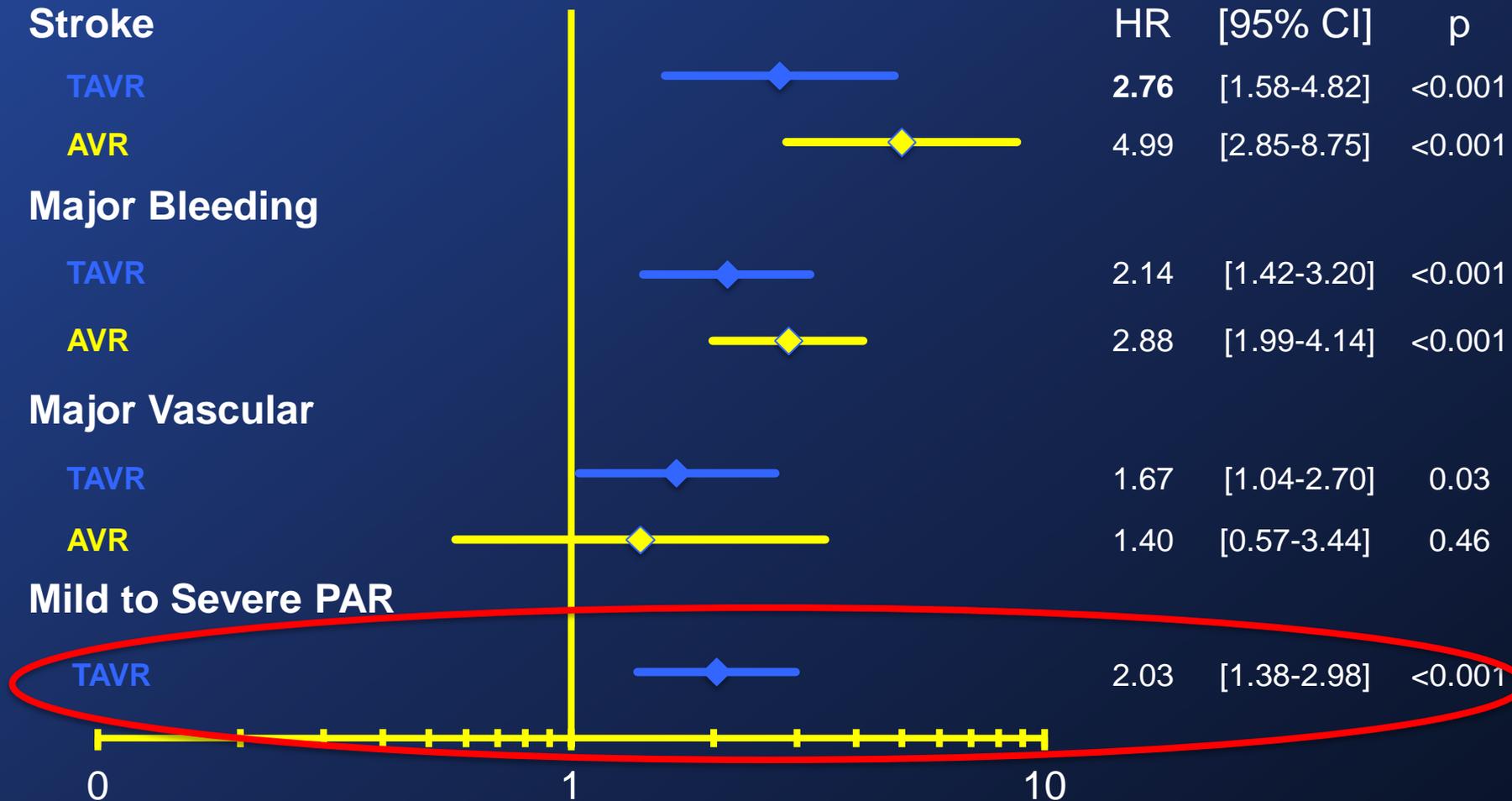
Paravalvular Aortic Regurgitation (AT)



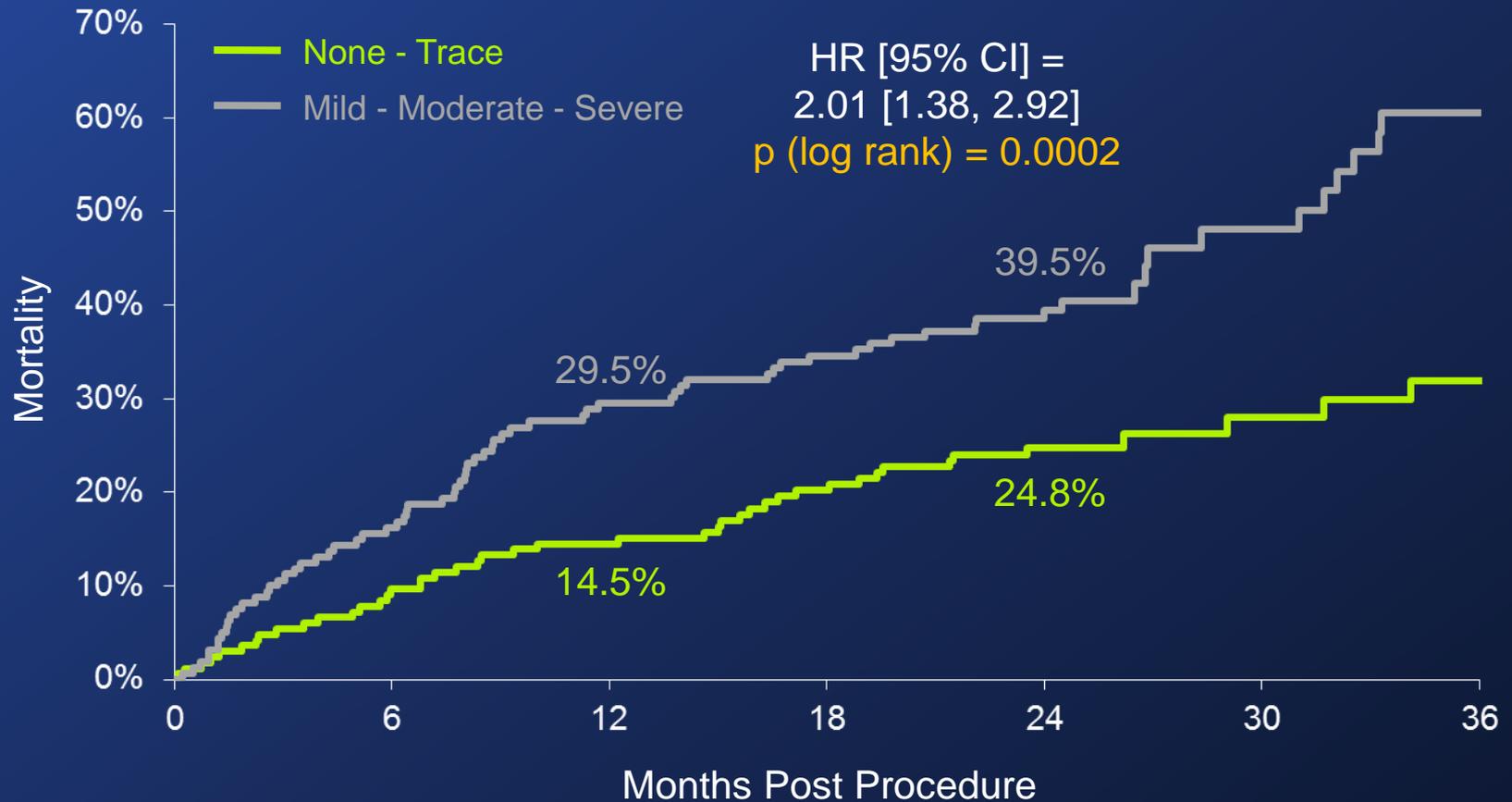
Aortic Regurgitation (AT)



Procedural Predictors of Mortality



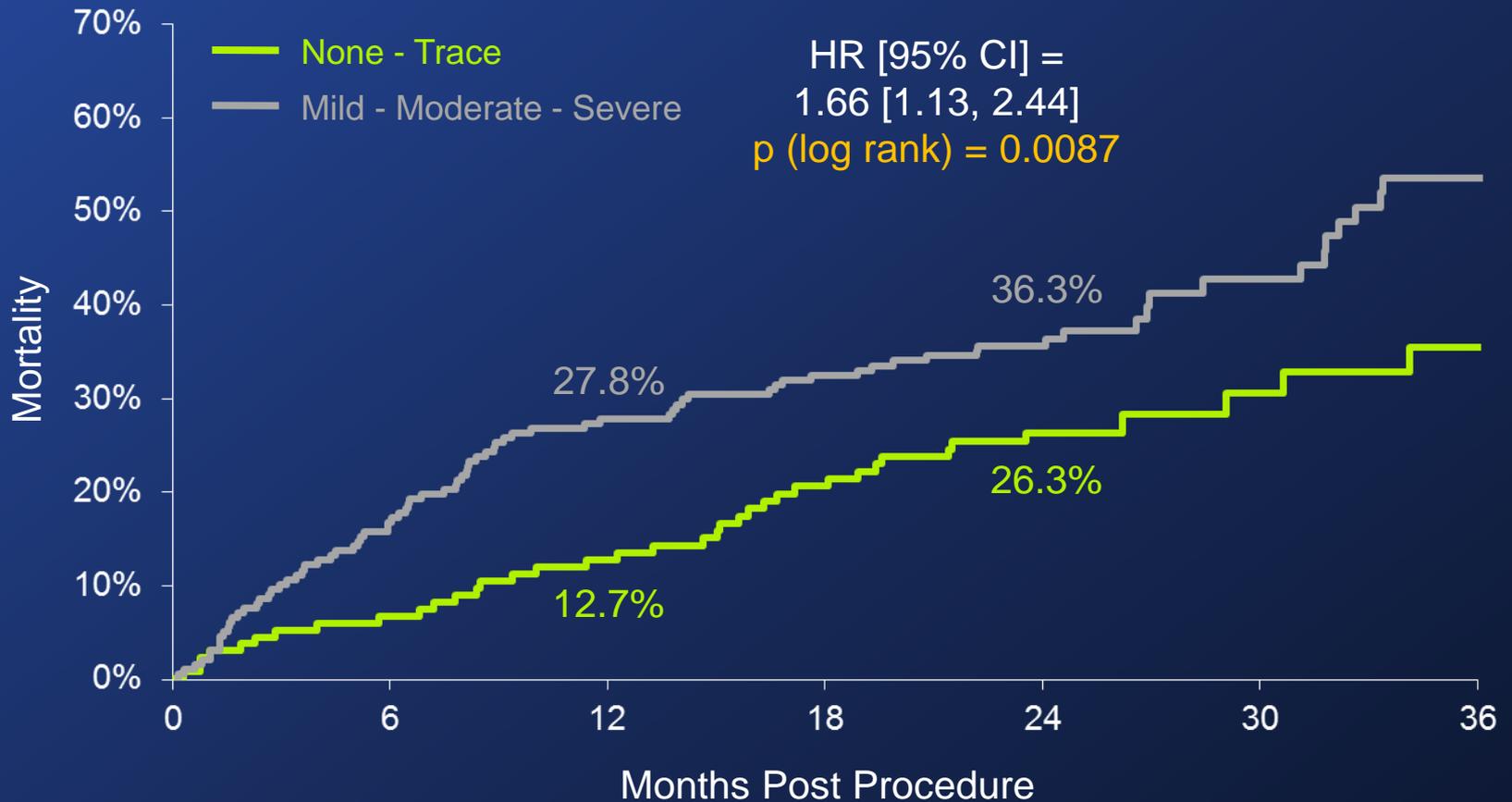
Paravalvular AR and Mortality TAVR Patients (AT)



Numbers at Risk

	0	6	12	18	24	30	36
None-Tr	167	149	140	126	87	41	16
Mild-Mod-Sev	160	134	112	101	64	26	12

Total AR and Mortality TAVR Patients (AT)



Numbers at Risk

	0	6	12	18	24	30	36
None-Tr	135	125	115	101	68	31	11
Mild-Mod-Sev	199	164	143	130	86	39	18

Prevention and Treatment of AR Depends on Etiology

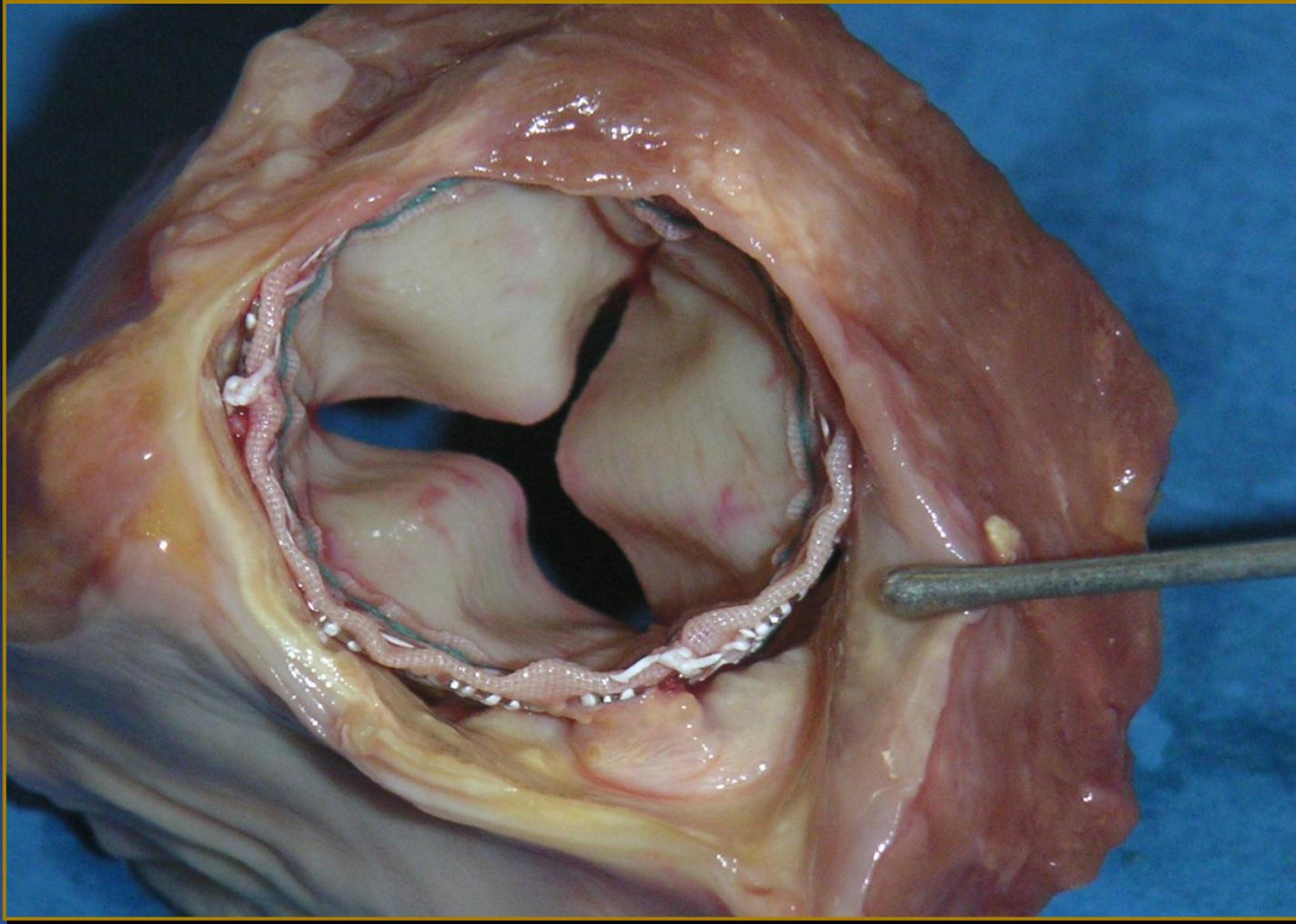
- **Native Aortic valve morphology**
 - Number of cusps
 - Symmetry/severity of calcification
- **Undersizing of the THV**
 - Annular measurement
- **Malpositioning of the THV**
 - Aortic root morphology
 - Mitral valve calcification
 - Sigmoid septum

Circularity of THV

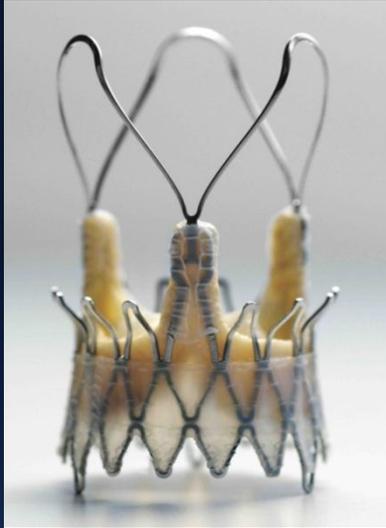
THV “seal”

Position of THV
influenced by “AV
complex”

Para-valvular Regurgitation

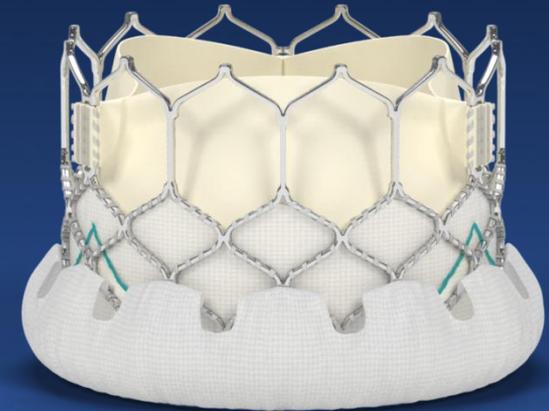


Devices with Reduced Paravalvular AR



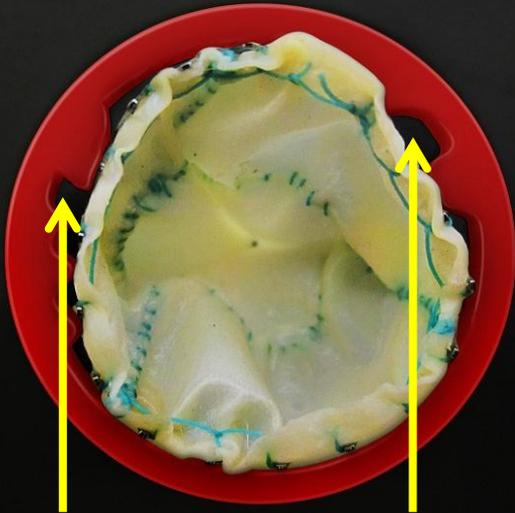
Subannular
Fixation

Space
Fillers



Endoluminal Sciences

current gen tissue skirts

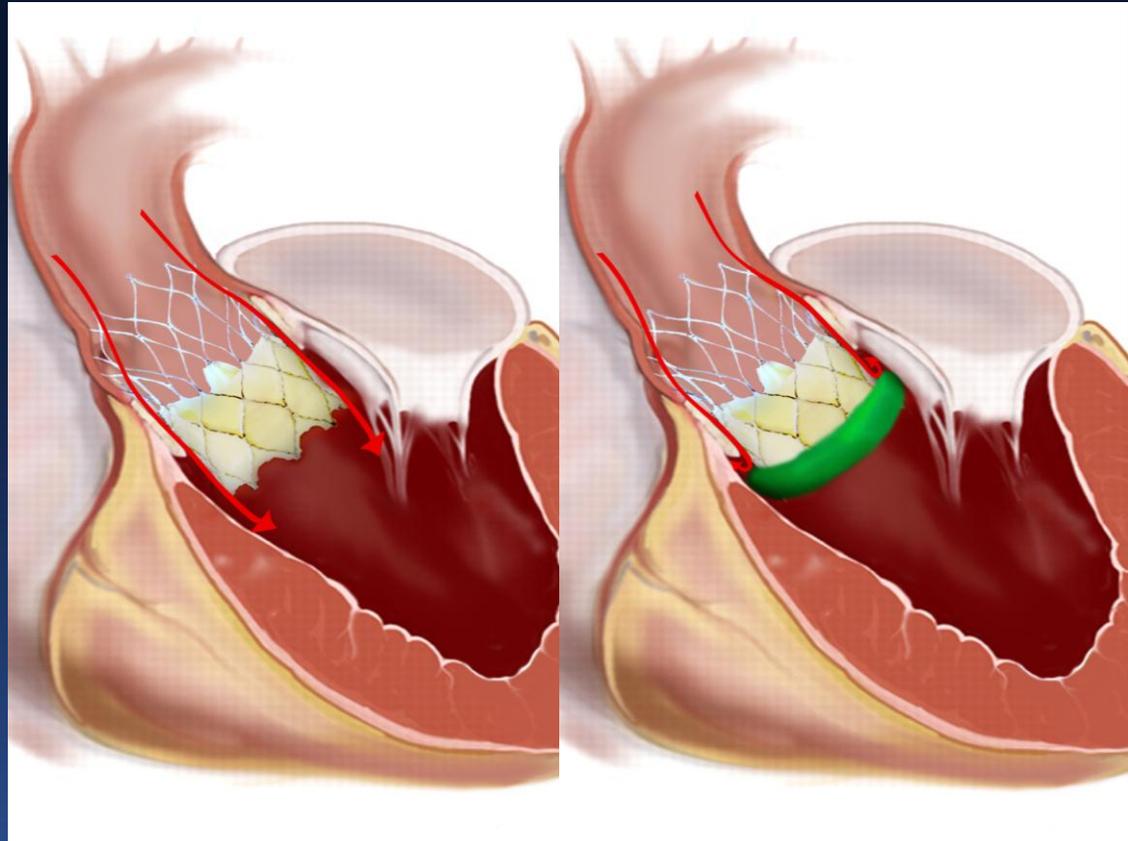


paravalvular leak sites

next gen "expandable" skirts



paravalvular leak sites sealed

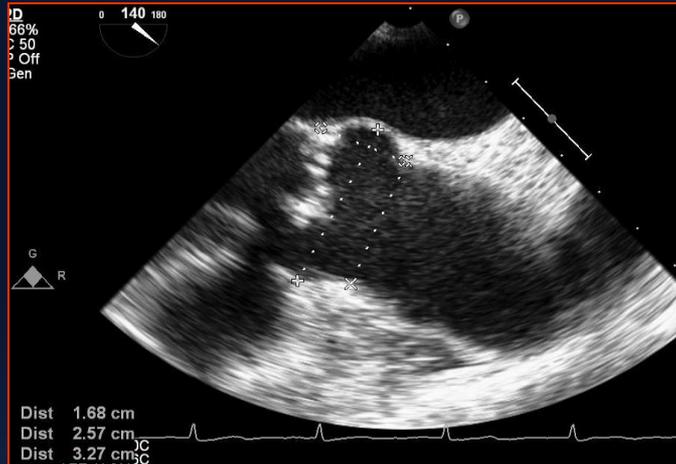


Predicting Complications

Predicting Complications

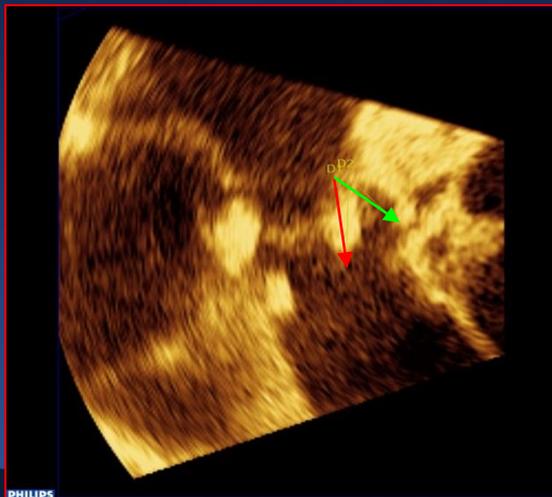
- **Complications such as annular rupture and coronary obstruction are low frequency events**
- **However, when they occur, they are often catastrophic**
- **Predictability of these complications is poor**
- **Ideally, these patients would be screened out or a different valve would be chosen**

Risk of Coronary Occlusion



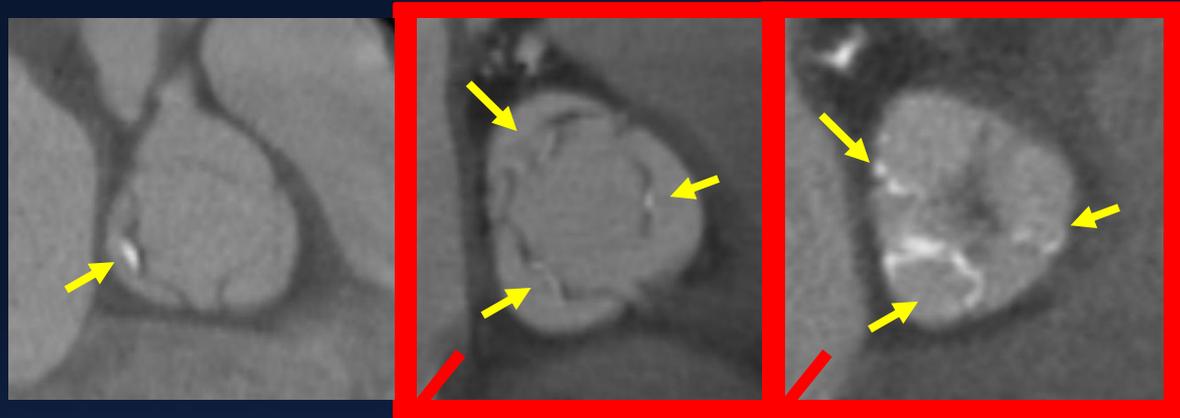
Annulus → LM = 1.1 cm

LCC length = 1.4 cm

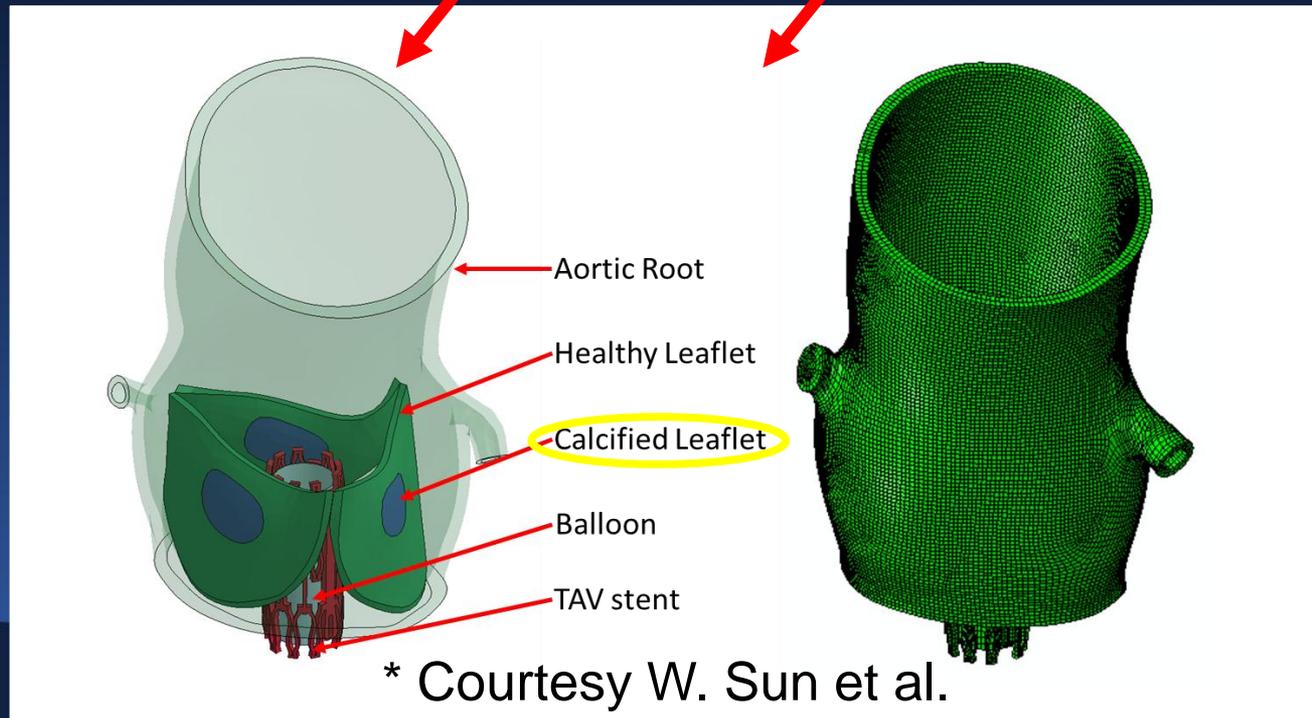


- Due to native leaflets obstructing LM
- Not solely dependent on LM height
- Other factors include:
 - Height of the Sinuses
 - Width of the Sinuses
 - Diameter and calcification of the sino-tubular junction (STJ)
 - Length of LCC

TAVR – Modeling Deployment

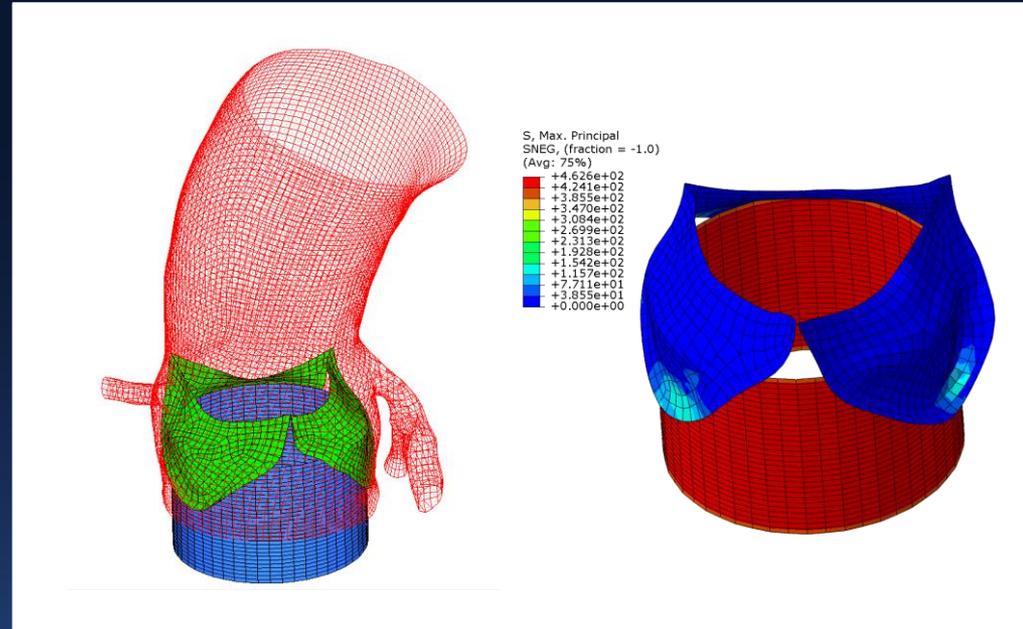
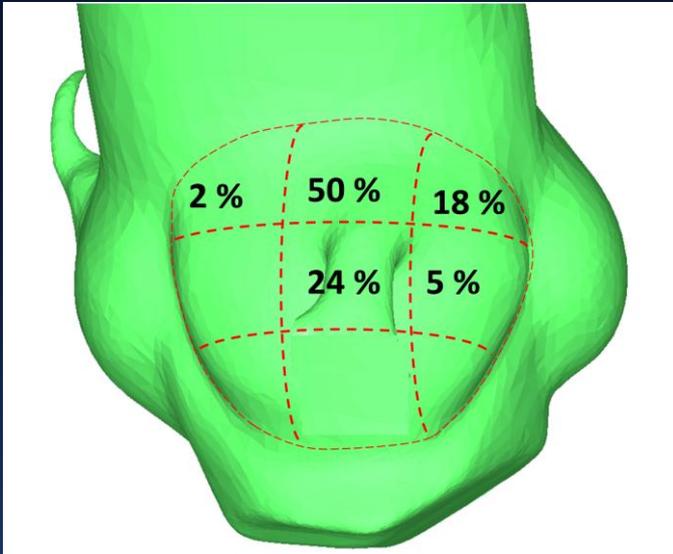


Yellow arrows show calcification



Coronary Artery Occlusion

Can we predict?

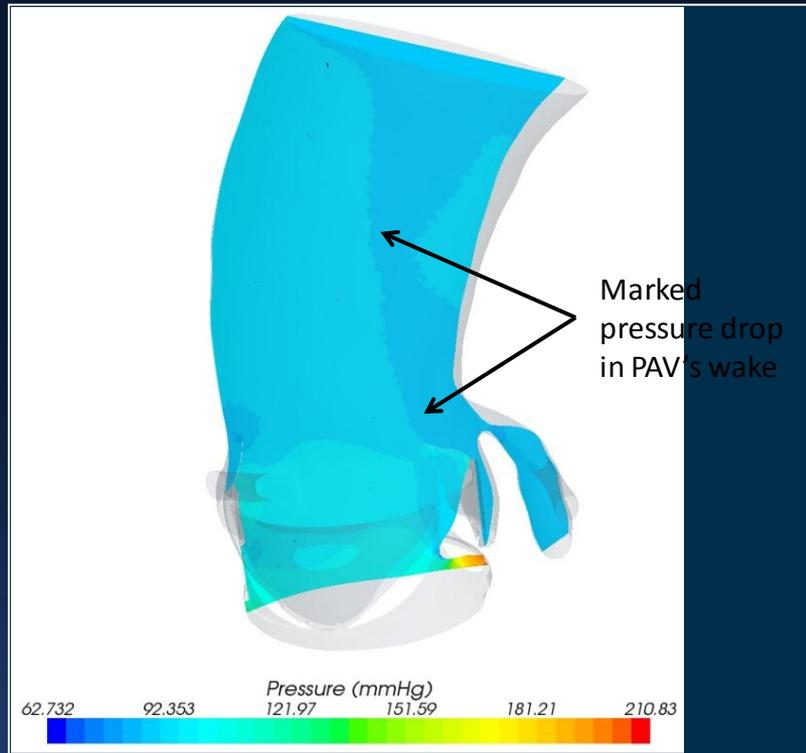


Coronary Artery
Position Variable

* Courtesy W. Sun et al.

Coronary Artery Flow

Can we predict?

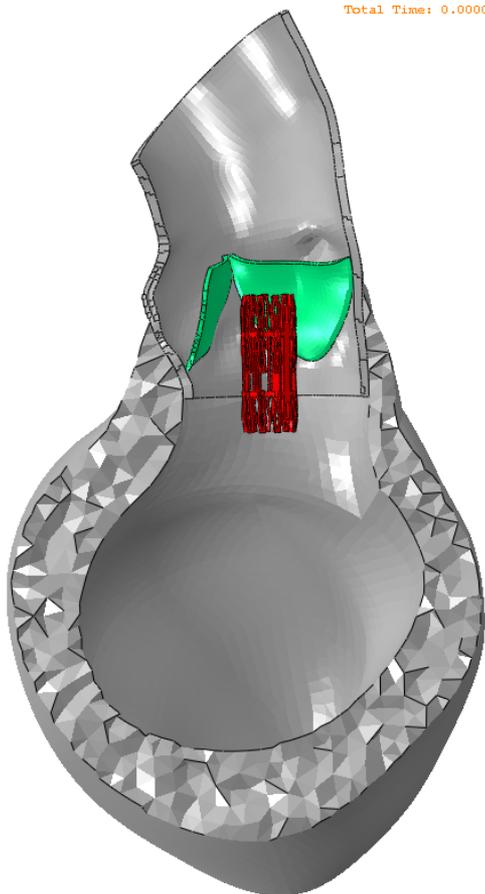


- Pressure drop induced in TAV's wake (left)
 - Drop in coronary flow per stroke
 - Reduced percentage of cardiac output to coronary arteries
 - 5.14% down to 4.07%

SIMULATED VALVE DEPLOYMENT

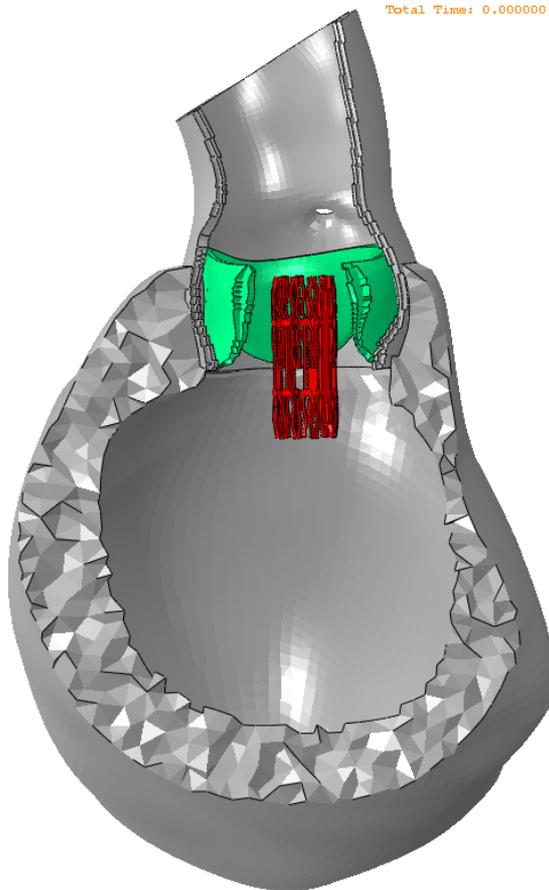
Viewport: 3 ODB: Y:/Simulations/abaqus/r_...olid_MH60_AS2_LV_mesh.odb

Step: Step-1 Frame: 0
Total Time: 0.000000



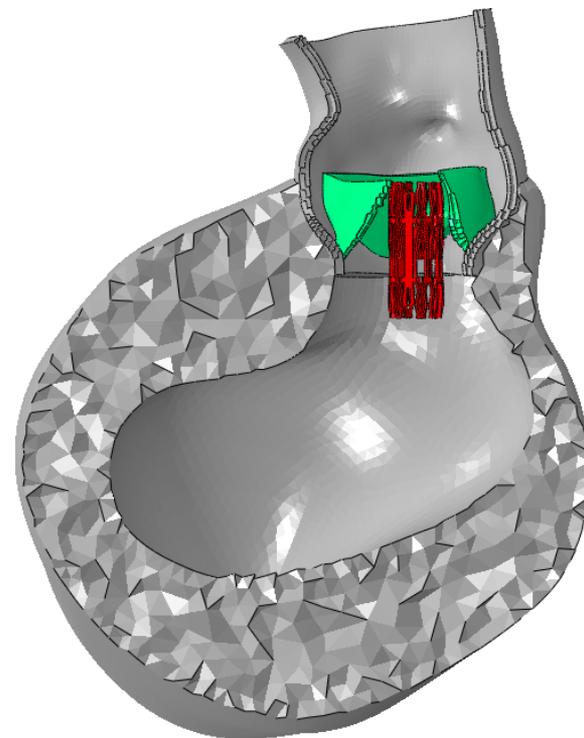
Viewport: 4 ODB: Y:/Simulations/abaqus/r_...olid_MH60_AS2_LV_mesh.odb

Step: Step-1 Frame: 0
Total Time: 0.000000



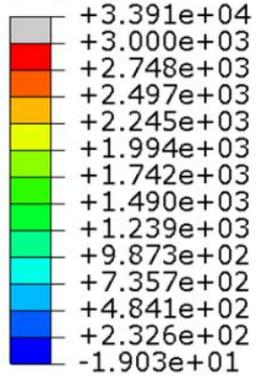
Viewport: 5 ODB: Y:/Simulations/abaqus/r_...olid_MH60_AS2_LV_mesh.odb

Step: Step-1 Frame: 0
Total Time: 0.000000

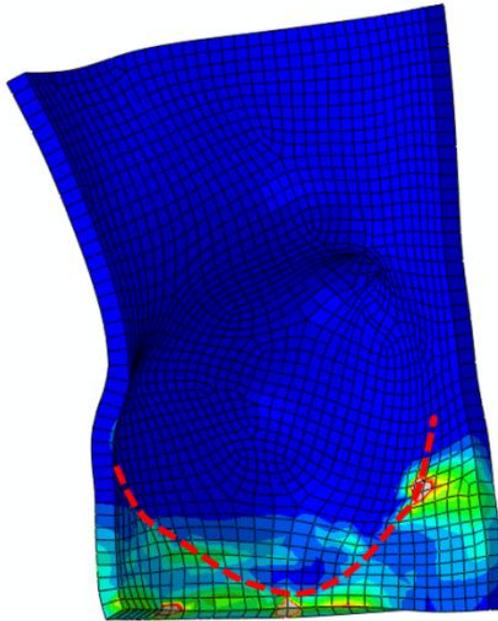


Predicting Wall Stress

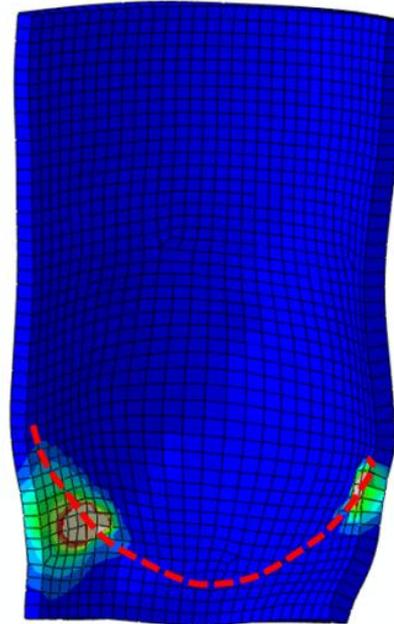
S, Max. Principal
(Avg: 75%)



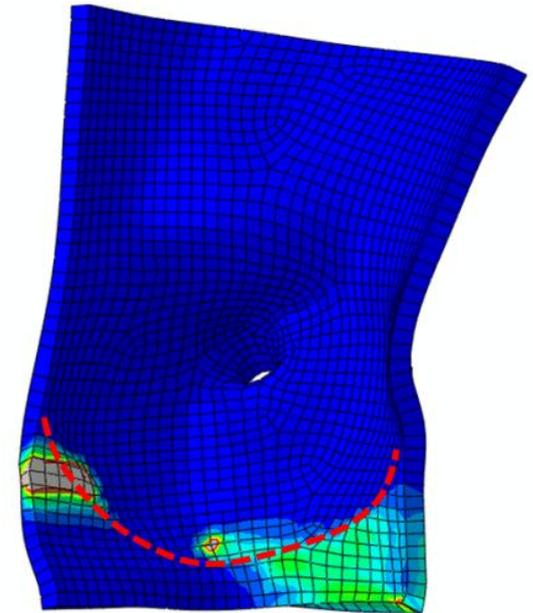
LCS



NCS



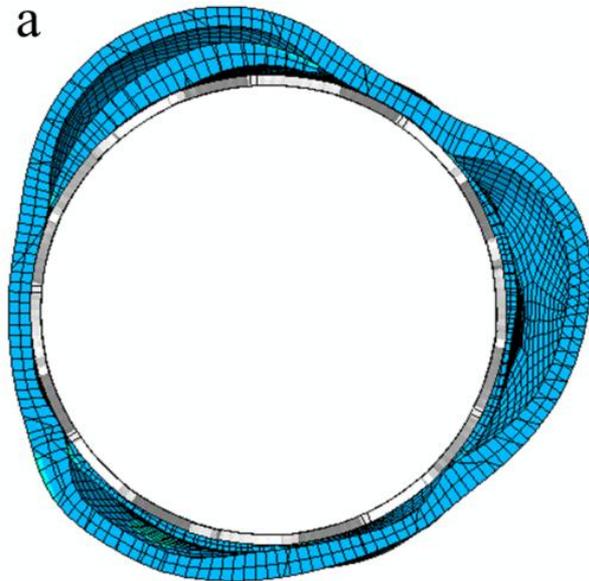
RCS



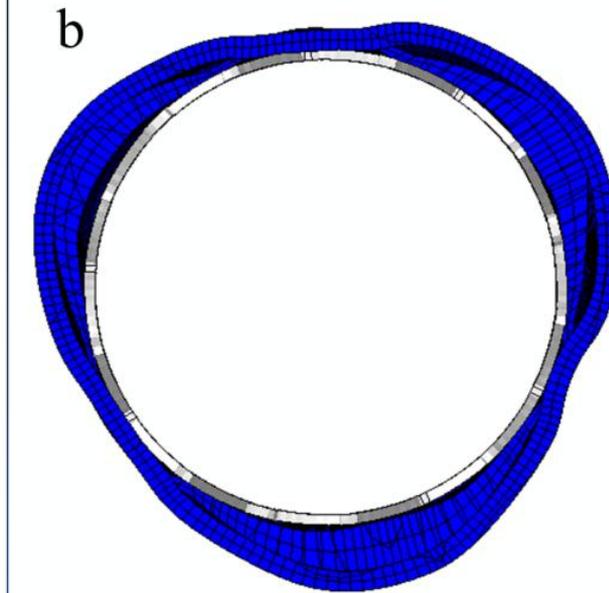
Modeling TAVR

Can we predict AR?

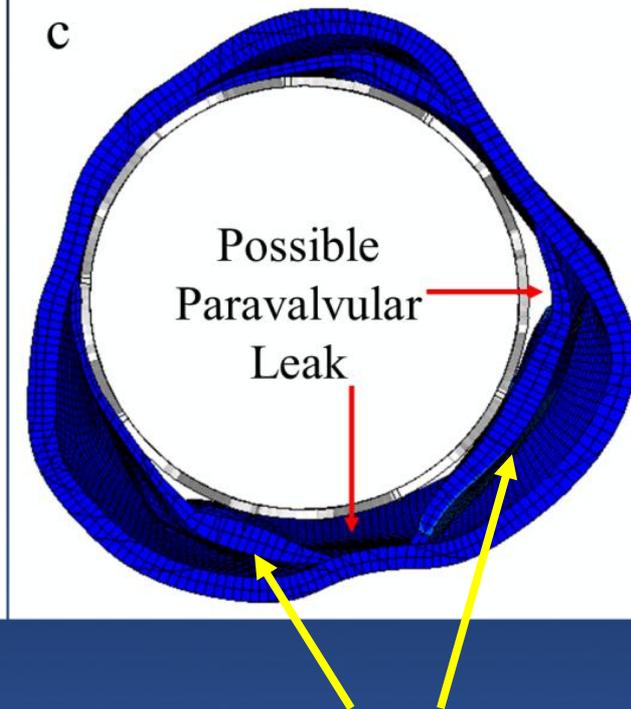
Patient 1



Patient 2



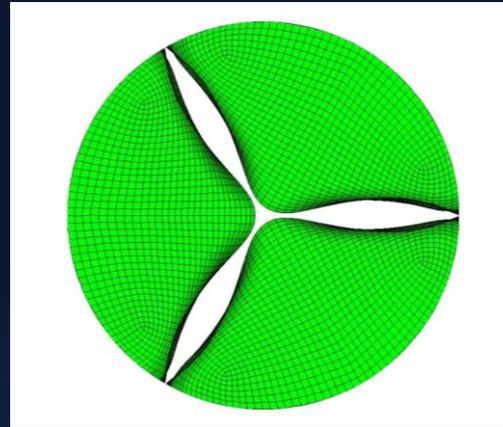
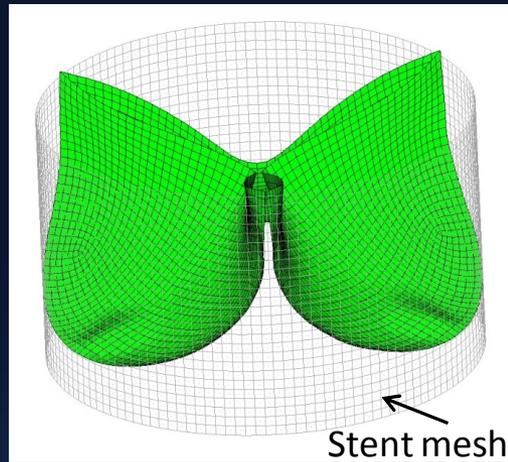
Patient 3



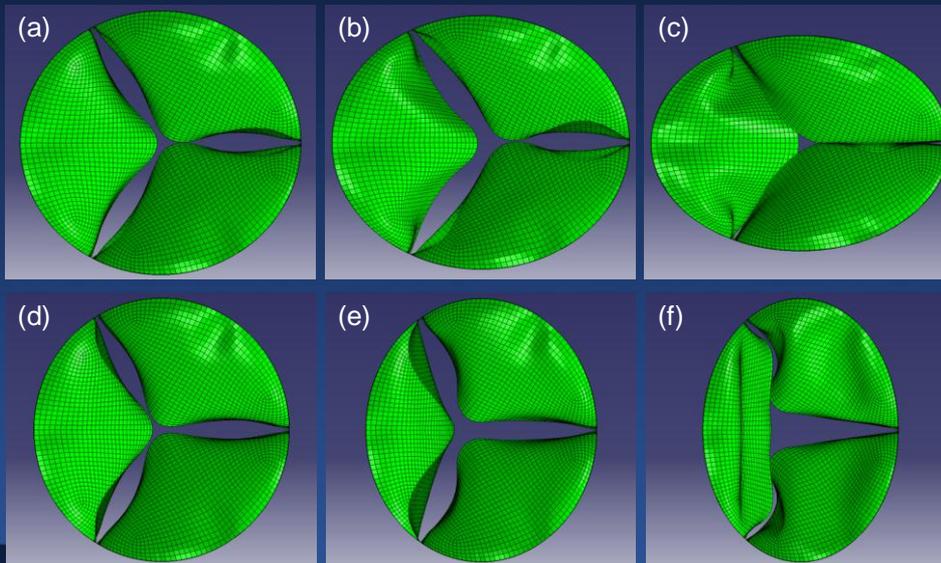
Possible
Paravalvular
Leak

Leaflet
calcification

Simulated Deformations of a “Generic” TAV

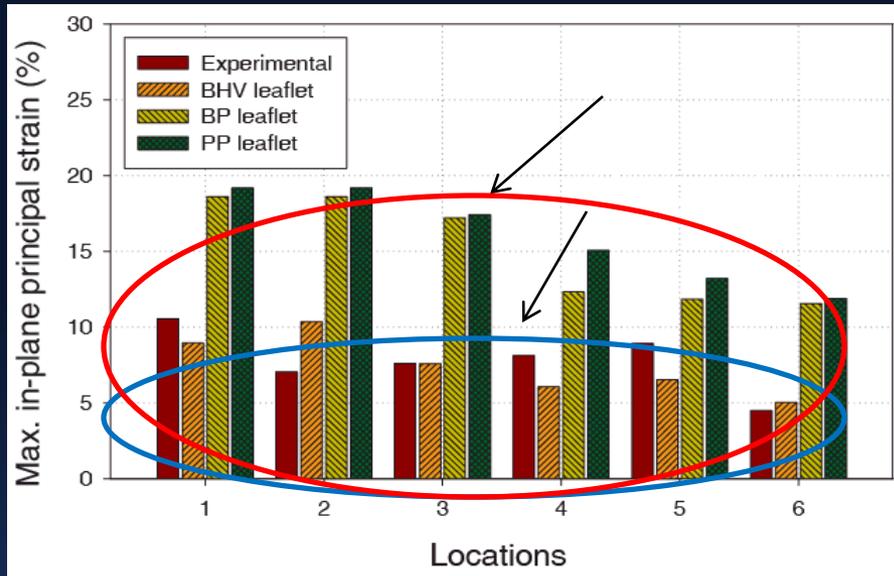


1. No stent-tip deflection ⁽¹⁾
2. Thin leaflet – Thin bovine and porcine pericardium of ~ 0.20 mm, modeled with nonlinear, anisotropic Fung model.

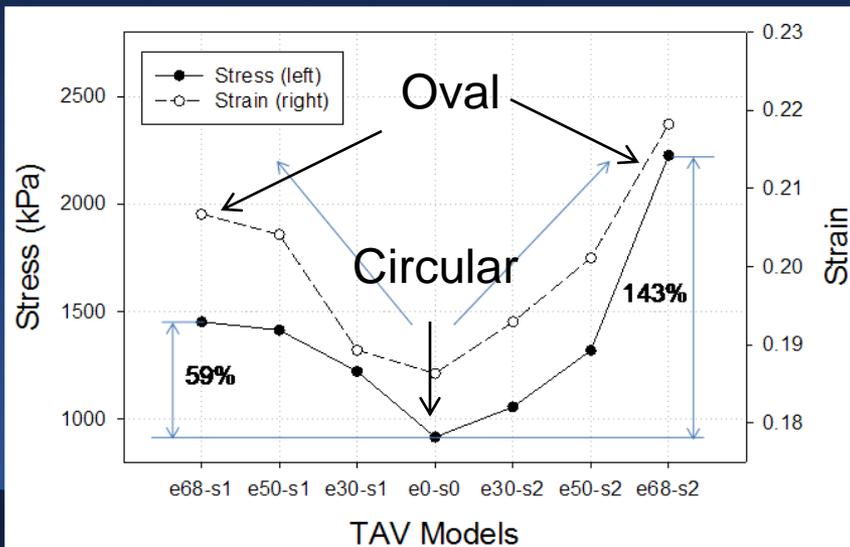


3. Asymmetric valve deployment
→ leaflet mal-coaptation ⁽²⁾

Simulations of a TAV device deformation



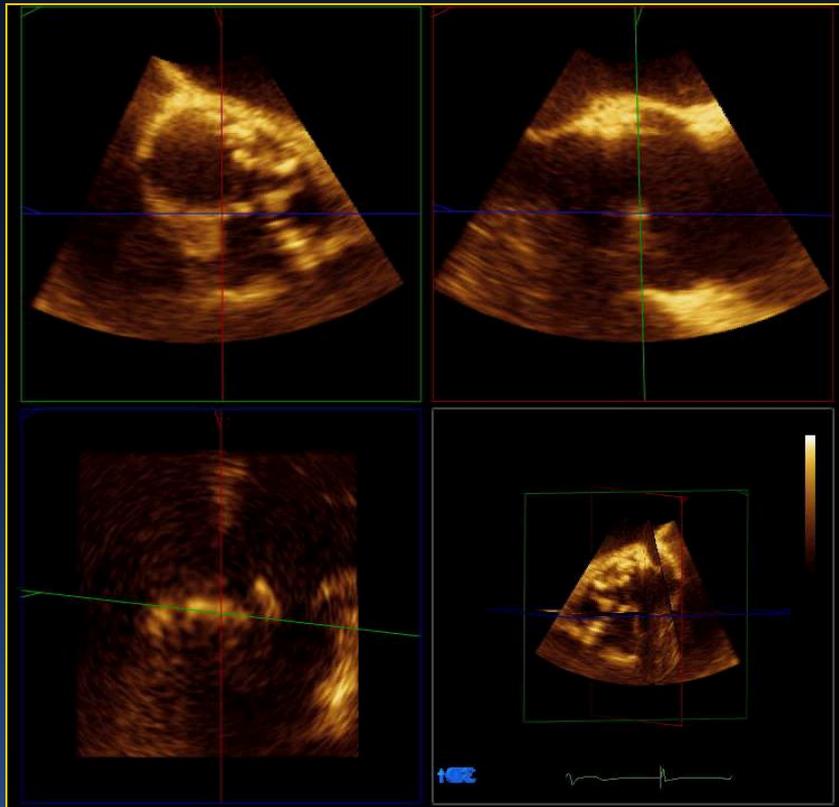
TAV with thin pericardial leaflets and rigid stent has higher strain than surgical pericardial valve



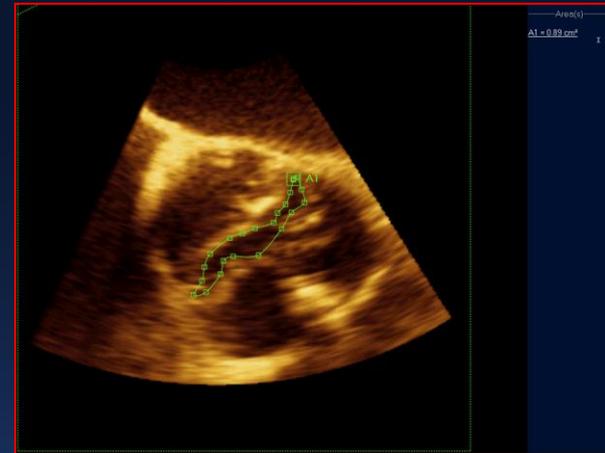
Asymmetric TAV deployment has higher stress/strain than nominal circular TAV deployment

These high stresses/strains will have an impact on TAV device durability!

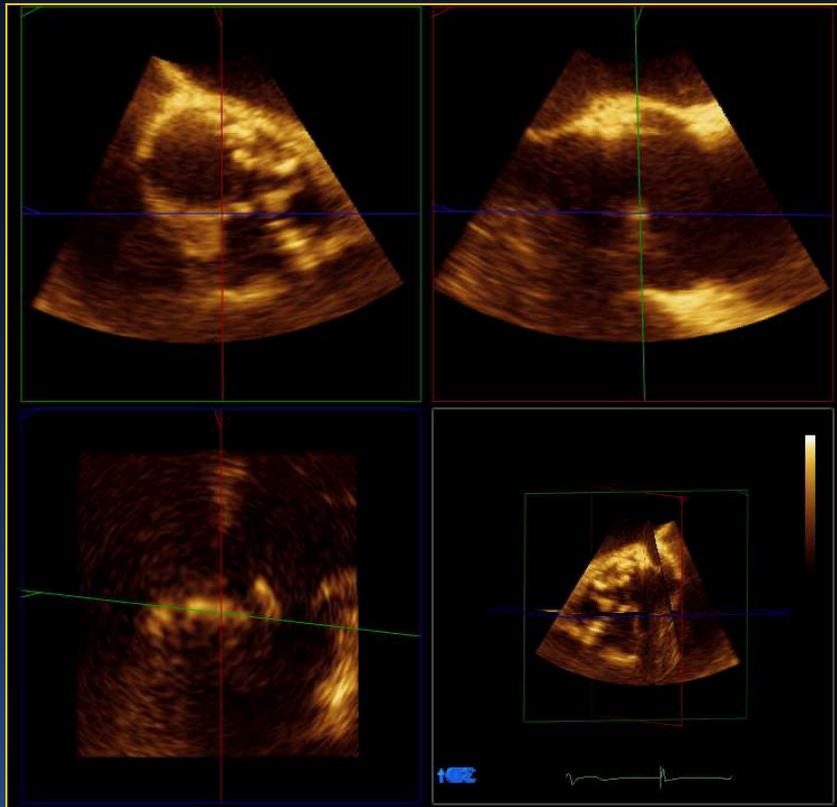
Impact of Asymmetric Deployment



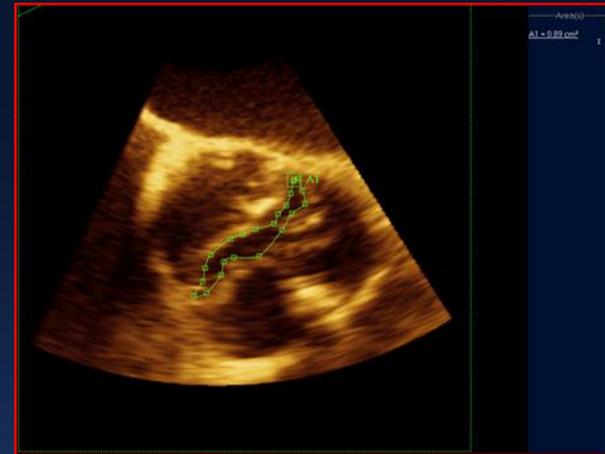
Planimetered area = 0.9 cm²



Impact of Asymmetric Deployment



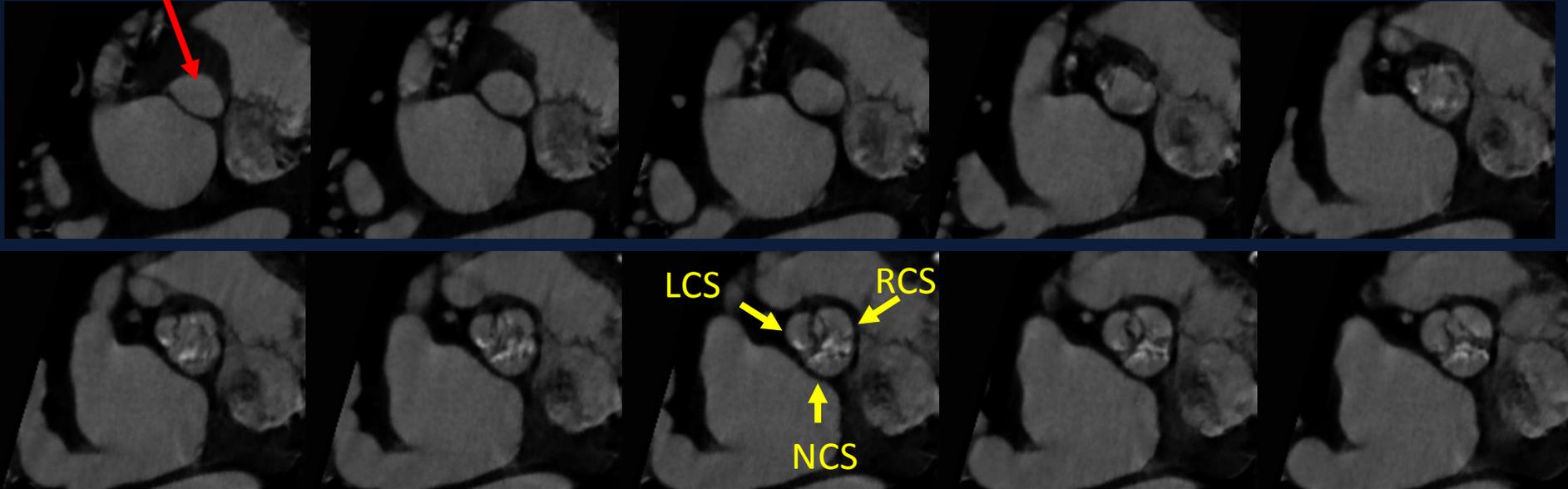
Planimetered area = 0.9 cm²



Modeling of TAVR : A Case Study

Aortic annulus

From 320-slice CT scanner



Patient Information and Clinical Observations

- 94-yo female with annulus size of 19.6mm
- Only the left coronary leaflet opens
- Calcification concentrates in right and non-coronary leaflets

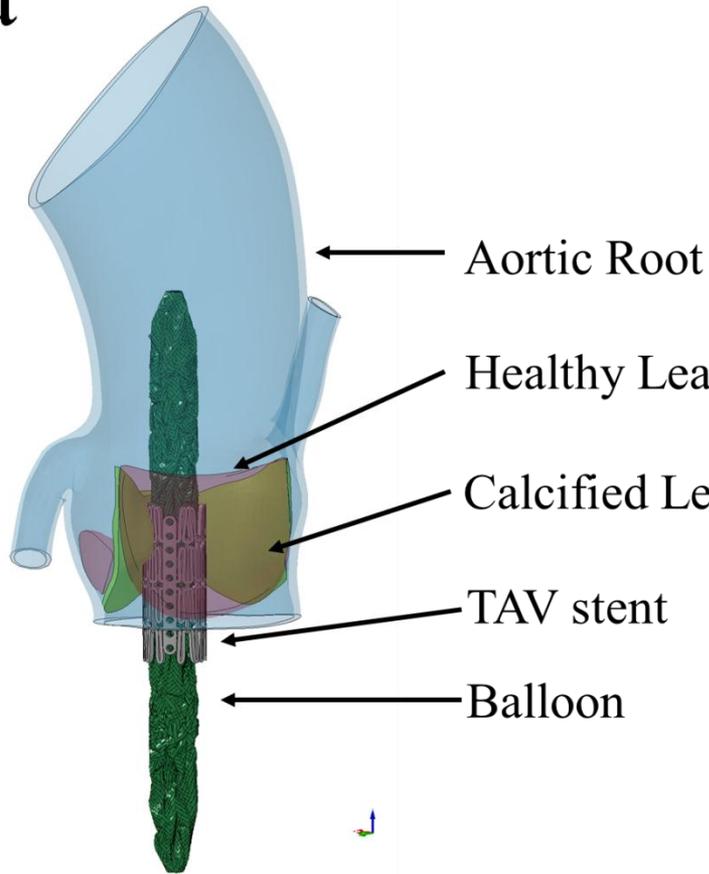
TAVR RESULTS : A CASE STUDY

A size 23 Edwards SAPIEN valve was used. During TAVI procedure:

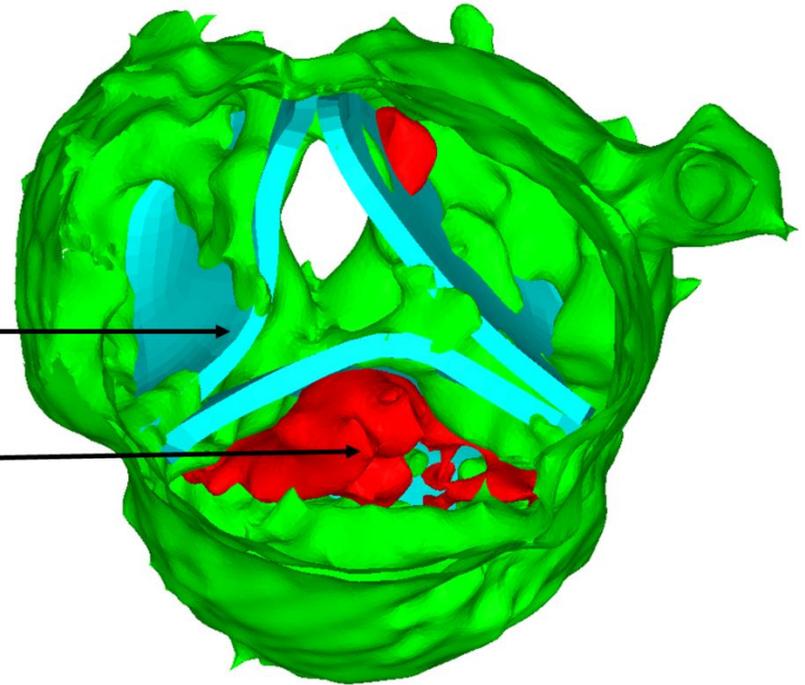
- Aortic root tearing happened and visualized below the left main coronary artery
- Open-heart valve surgery was performed

Finite Element Model Reconstructed from MSCT

a

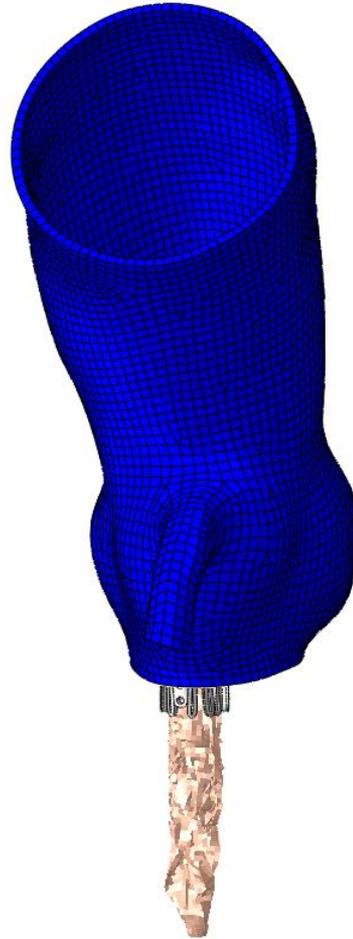


b



Modeling of TAVR Deployment

Step: Step-1 Frame: 0
Total Time: 0.000000



Conclusions (1)

- Although TAVR procedural results have improved with acceptable outcomes, complications are still common and occasionally catastrophic
- Advances in access management (TA or TF) will simplify procedure and make it more generalizable -- However, careful studies will need to be done with these devices to determine if there are any long term implications with them
- Embolic protection is mandatory before we can expand indications for TAVR to a lower risk population – Studies to evaluate these devices will likely use surrogate endpoints

Conclusions (2)

- In the future, patient anatomy will be modeled pre-procedure to predict and likelihood of complications and choose appropriate device for patients
- In addition, long term follow-up will be needed to determine durability of these valves – Given deployment is often asymmetric and there are unknown forces on these leaflets, patients must be followed long term.