

AP Valve
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The Next Target of the Valvular Intervention: Future Perspective

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Disclosure Eberhard Grube, MD

Physician Name

Company/Relationship

Speaker Bureau/Advisory Board:

Medtronic: C, SB, AB, OF
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Boston Scientific: C, SB, AB
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Equity Interest:

InSeal Medical: E, AB,
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Key

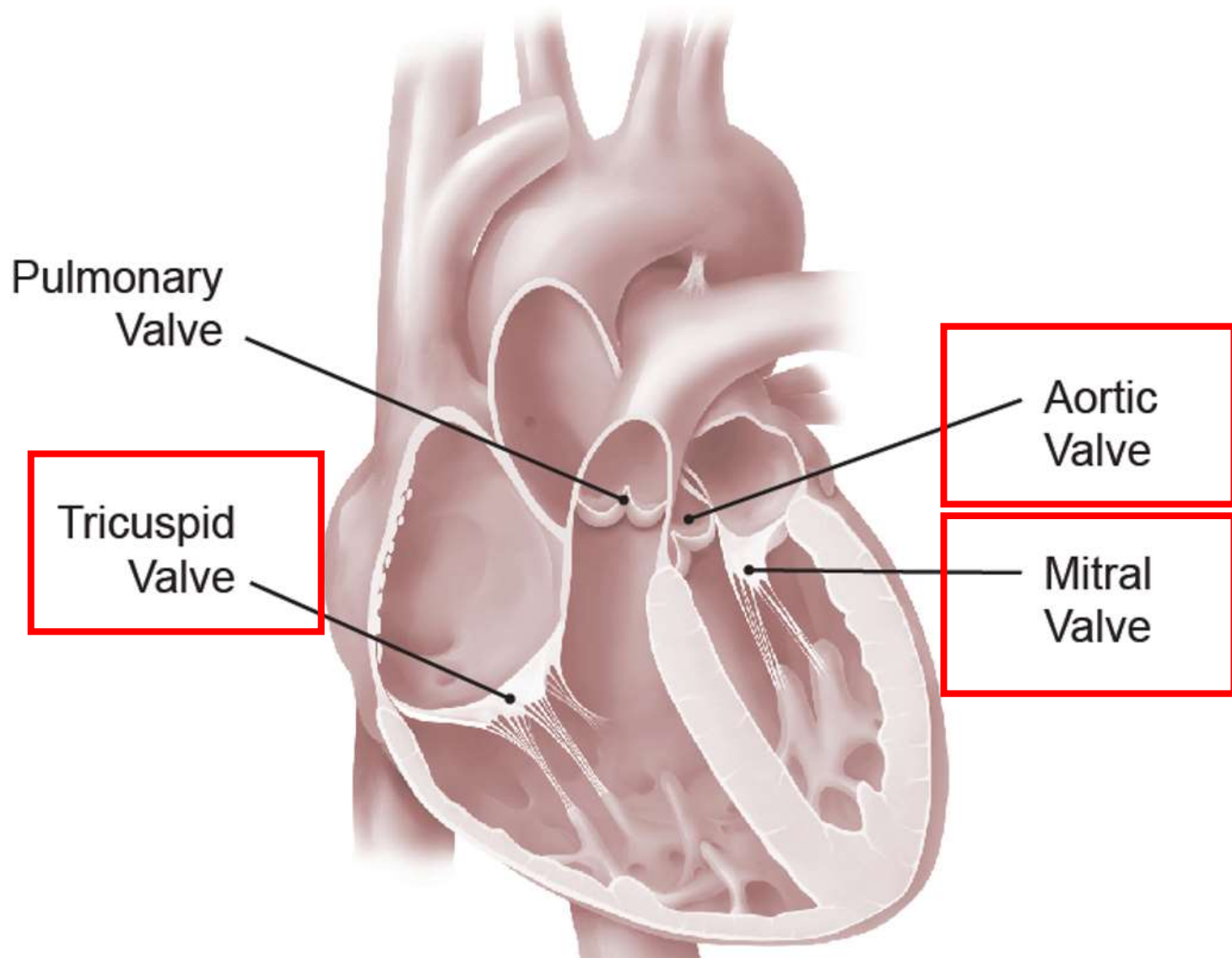
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Interventional Valve Therapy

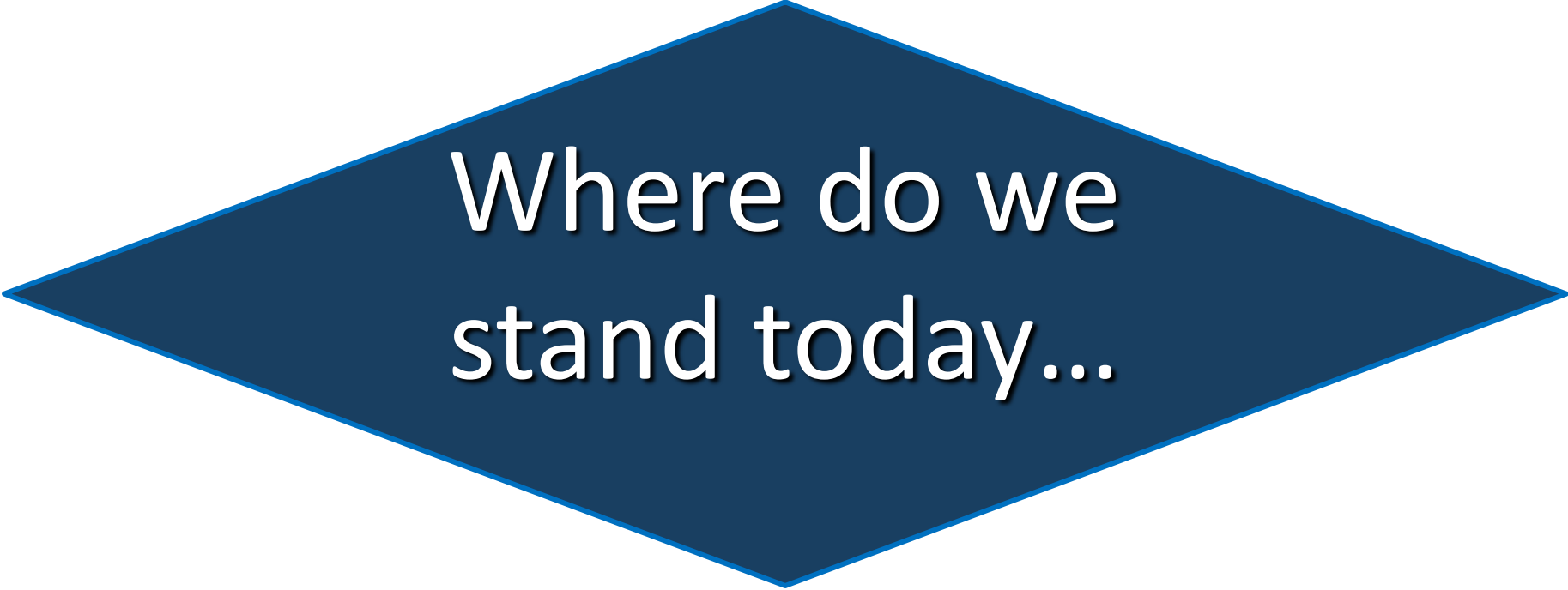
Overview

In recent years, treatment options for valvular disease have grown tremendously and have been truly disruptive.

This pace is likely to continue with future interventional therapies targeting aortic, mitral, and tricuspid valve diseases.



Interventional Valve Therapy - 2019



Where do we
stand today...

TAVR Current State

Clinical Trials with self-expanding and balloon-expandable TAVR devices have demonstrated excellent safety and device success in extreme, high, and intermediate surgical risk patients



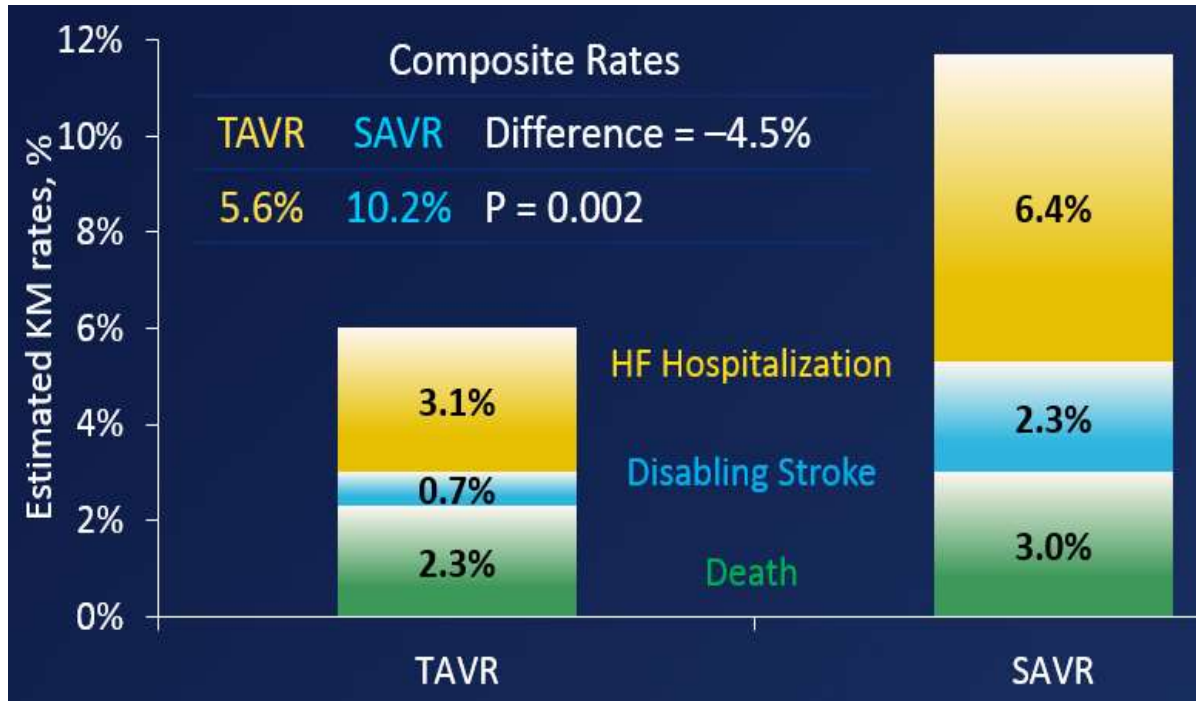
TAVR

Low Risk

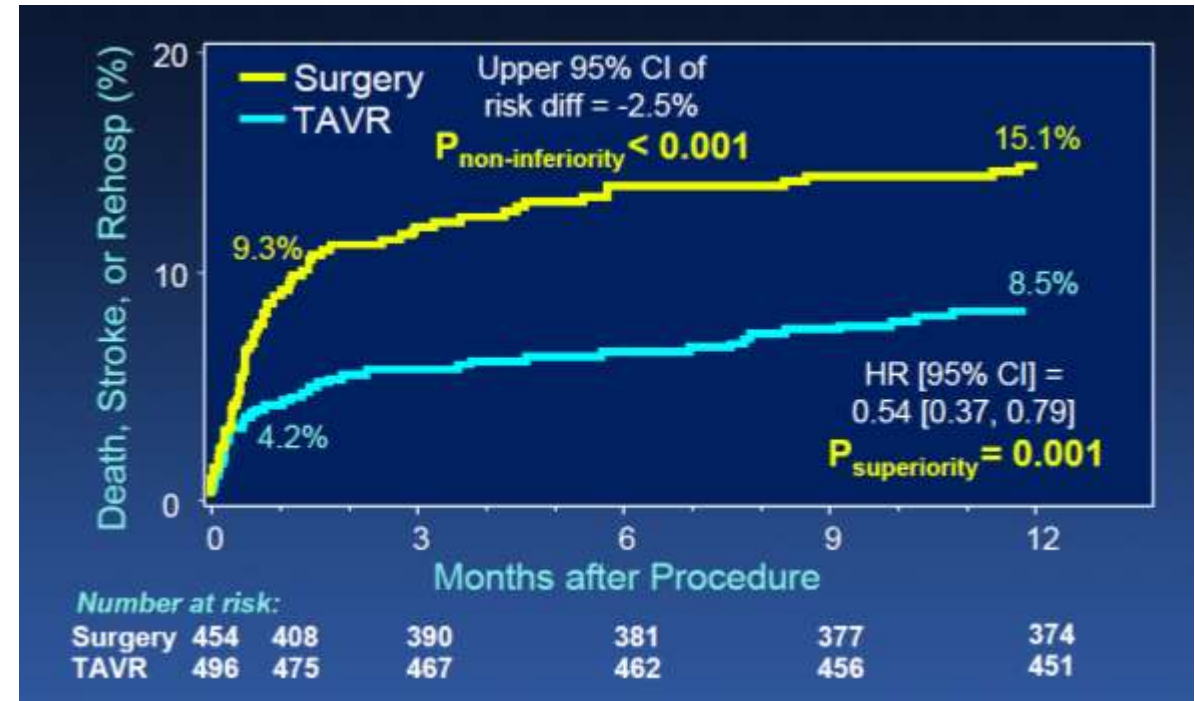
Results from the randomized Evolut Low-Risk and PARTNER 3 Trials demonstrated **success of the Evolut platform and SAPIEN 3 device in low surgical risk patients.**

These data will drive an indication for low surgical risk patients in 2019. **Age, rather than risk, will become key in selecting patients for TAVI.**

Evolut Low-Risk Trial



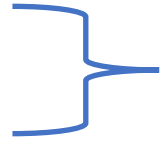
PARTNER 3 Low-Risk Trial



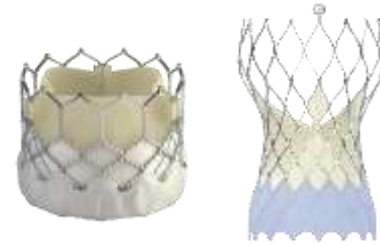
TAVI

Device Landscape

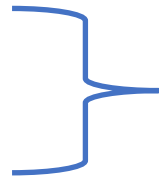
- Sapien 3/S3 Ultra
- Evolut R/PRO



Current Industry Standard



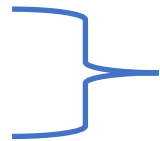
- Lotus/Lotus Edge
- Acurate Neo
- Portico



Next in Line/Increasing Clinical Use



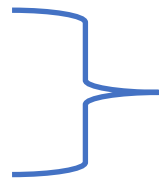
- Direct Flow
- Engager



Early or Later Demise



- Jena Valve
- Centera
- Venus A Valve



Rebooting and/or Increasing Momentum



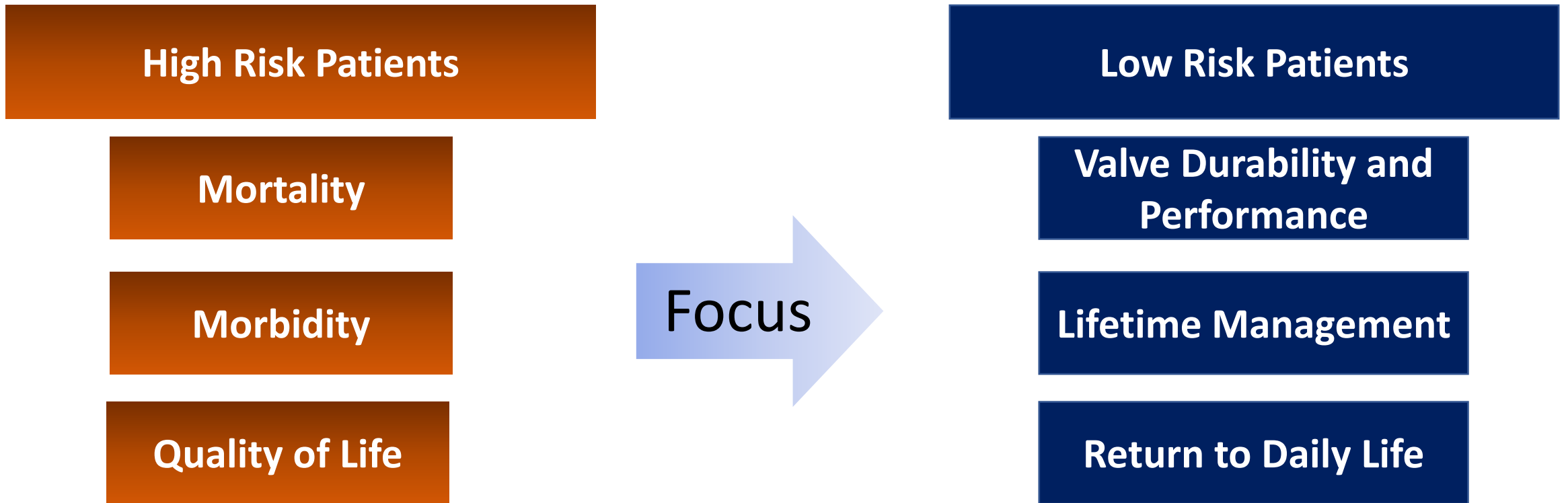
All of the Rest!

- J-Valve
- VitaFlow
- Taurus One
- Trinity
- Colibri
- Inovare
- Thubrikar
- Valve Medical
- Triskele
- BioValve
- MyVal
- HLT Meridian
- NVT
- Xeltis
- Zurich TEHV

TAVR

Shift in Focus

Device selection in younger patients will be driven by valve durability and performance of TAVI valves, lifetime management of patients, and getting patients back to their daily lives faster.



Future Perspective of TAVR:



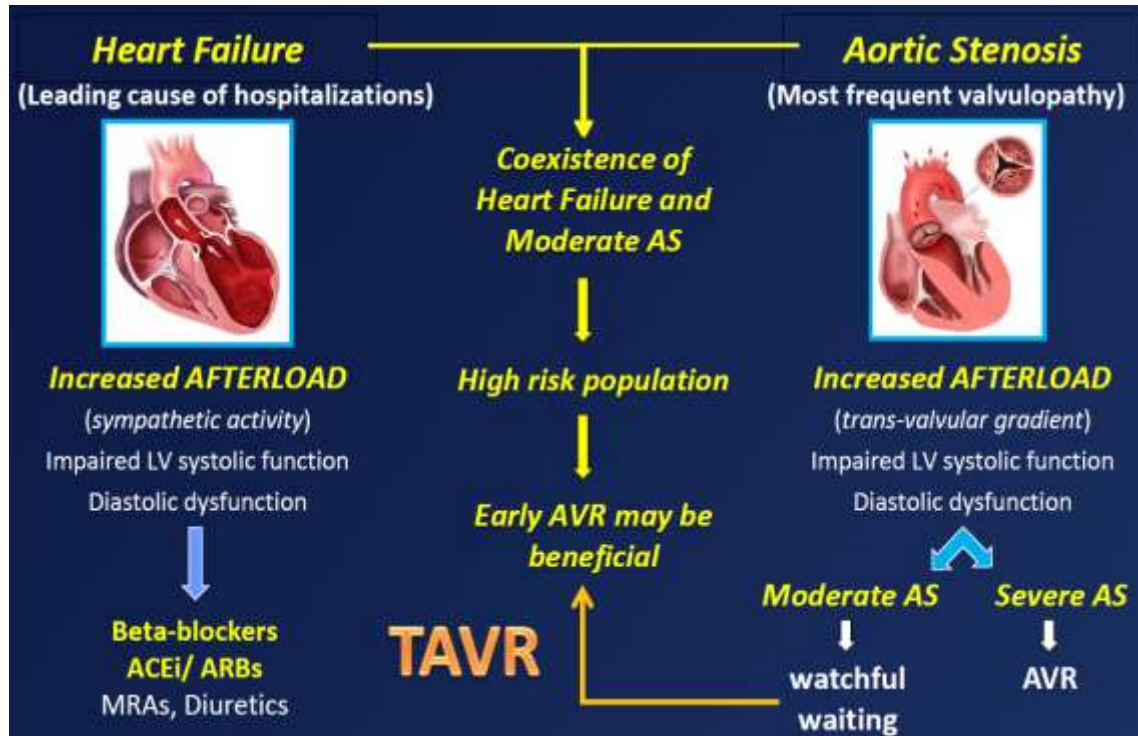
TAVR

Expanding Indications

Studies suggest early intervention for aortic stenosis may improve patient outcomes. The less-invasive TAVI therapy may be a good option for patients with few or no symptoms.

Trials are currently underway to determine the safety and effectiveness of TAVI in moderate and asymptomatic AS patients. If successful, TAVI may become the treatment of choice for these patient populations.

Moderate AS



Asymptomatic AS

Sudden Death	Peri-operative Mortality
Severe Asymptomatic AS	SAVR
~1-2%/year	~1-5%
TAVR may be a better option for Asymptomatic patients	
30-day Mortality	
SURTAIVI Intermediate risk	PARTNER trial 2A Intermediate PM
Core Valve TAVR	SAPVR
2.2%	1.7%
Sapien 3 TAVR	SAPVR
1.1%	4.0%

TAVR

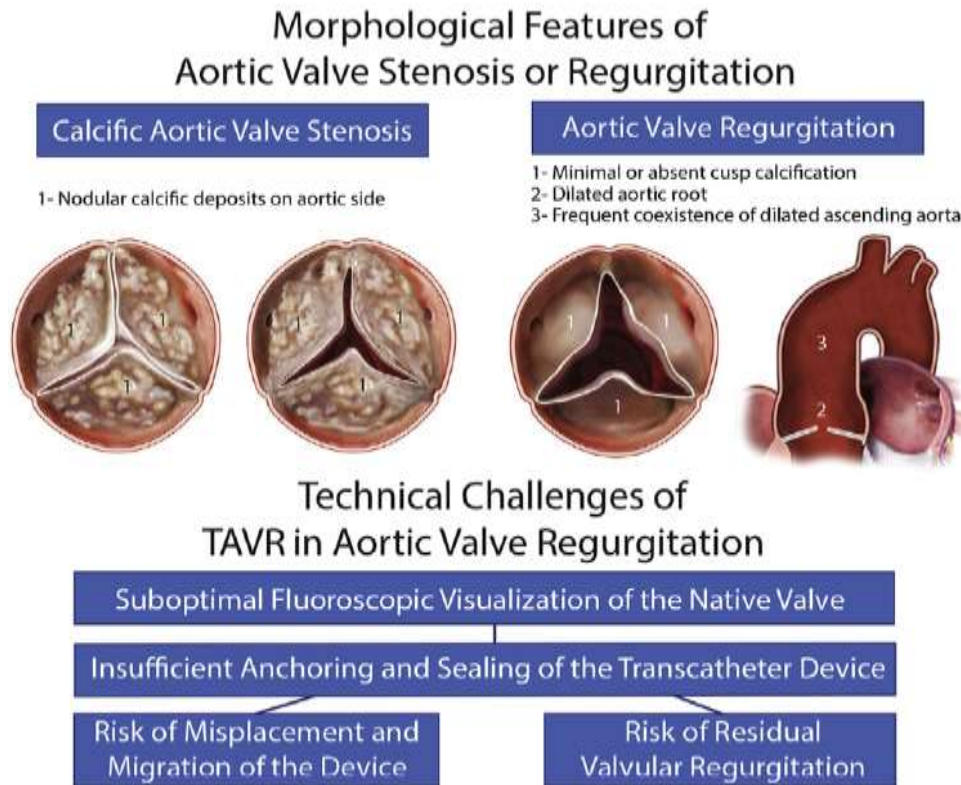
Expanding Indications

In addition to treating aortic stenosis, interventional cardiology will be used to treat patients with bicuspid aortic valves and patients with pure aortic regurgitation.

However, these patients present new challenges that are currently being studied

Pure AR Challenges

Bicuspid Aortic Valve Challenges



POTENTIAL ANATOMIC FEATURE	PROCEDURAL CONCERNS
Elliptical annulus	Impairs positioning and sealing
Large annulus	May be out of TAV size range
Assymetric leaflets and / or assymetric leaflet calcification	Impedes expansion, leads to gradients or PVL
Fused commissures (raphe)	Risk of rupture (during BAV or valve deployment)
Aortopathy	Risk of aortic dissection during the procedure, and as a late complication Difficulty anchoring

TAVR

Accessory Devices

Devices that will make the TAVI procedure safer are currently under development. Future TAVI procedures may include a number of these devices.

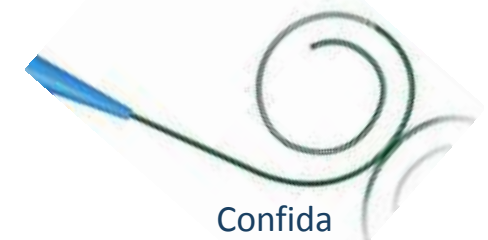
Neuroprotection devices



Expandable in-line sheath



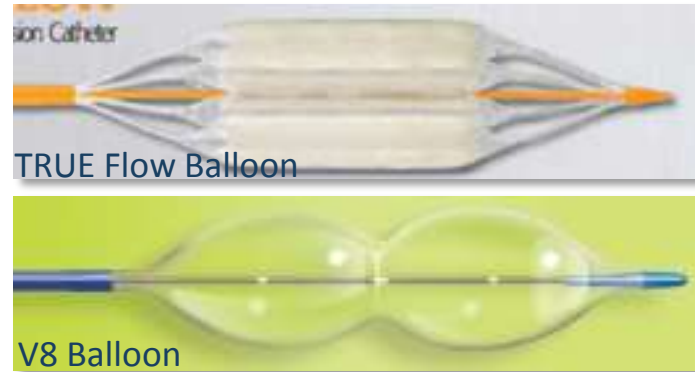
Dedicated wires and pacing leads



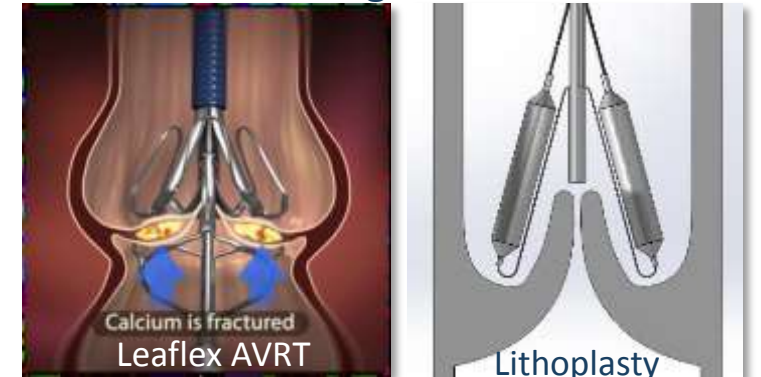
Large-hole closure devices



Balloon Aortic Valvuloplasty



Calcium Management Tools



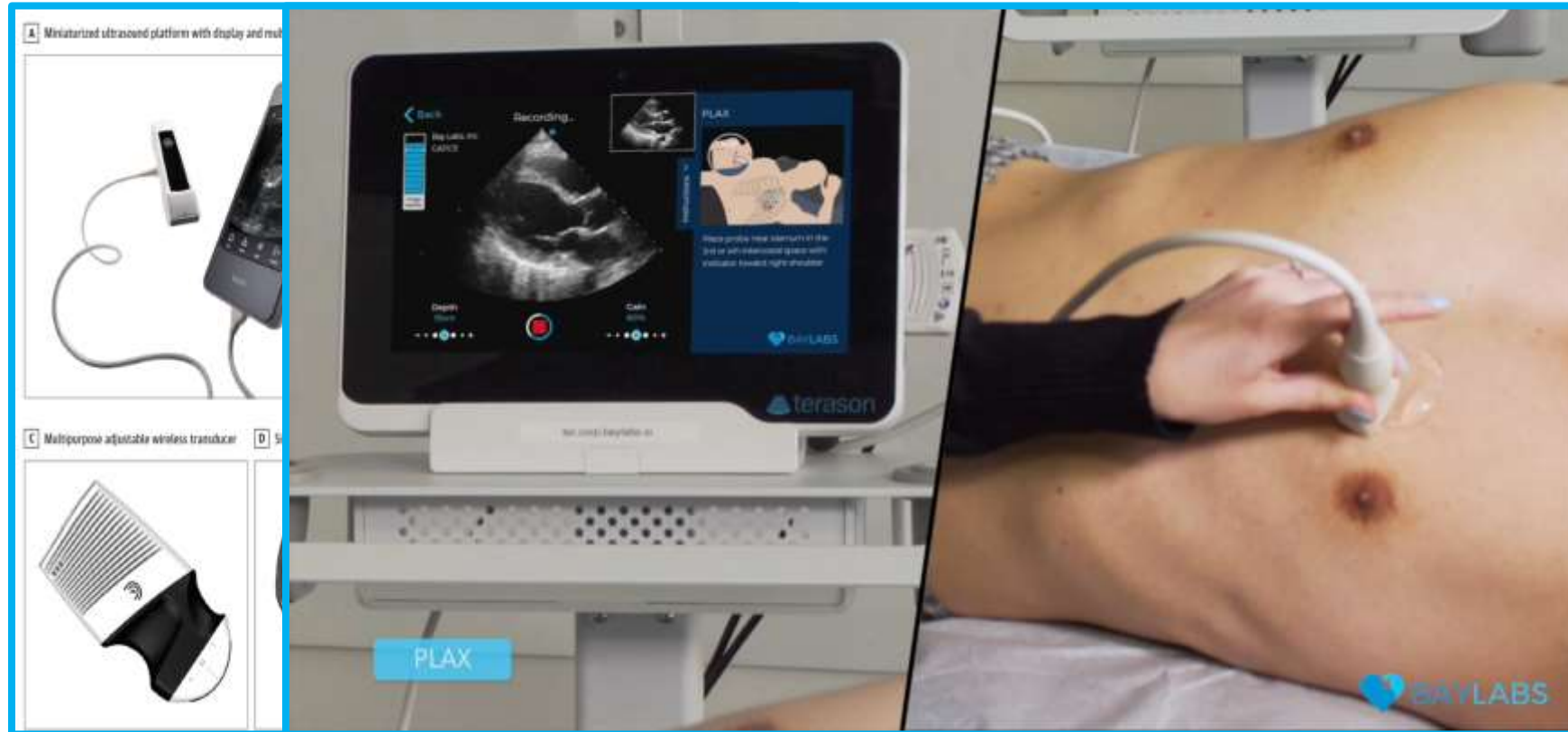
TAVR

Accessory Devices/**Imaging Technologies**

Bay Labs – Echo acquisition

Available hand-held POCUS devices

Prompts for BL echo acquisition

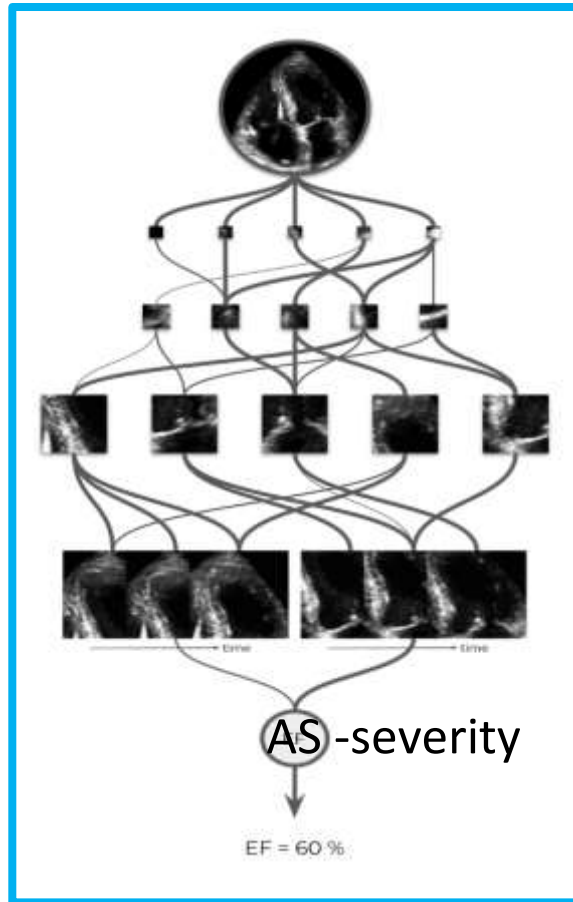


POCUS = point-of-care ultrasound

TAVR

Accessory Devices/**Imaging Technologies**

Bay Labs – Echo interpretation



Training: > 25,000 complete AS echo studies

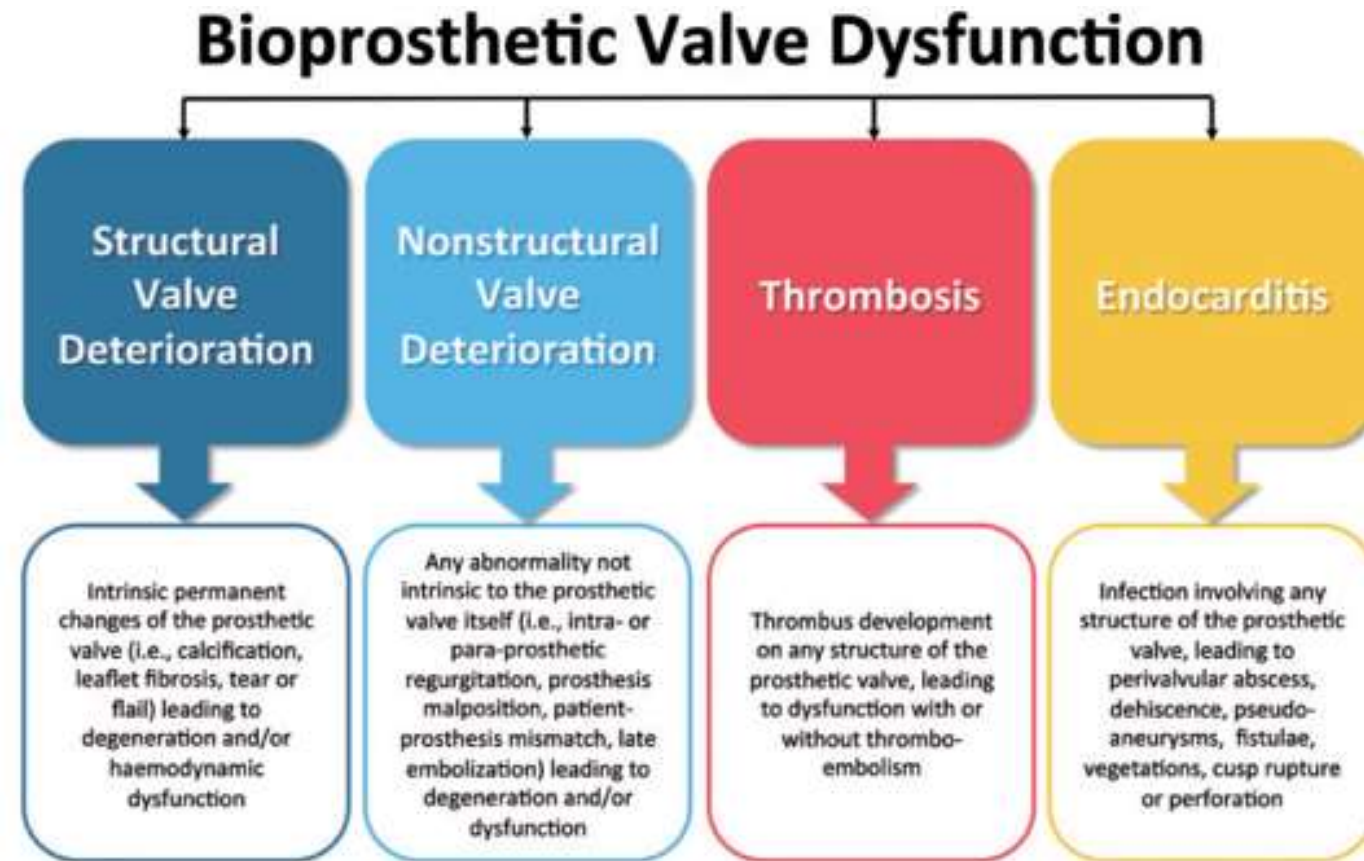
Input: PLAX and PSAX shown to the pre-trained network

Output: network integrates responses and makes diagnosis of valvular heart disease, rheumatic vs. non-rheumatic, and estimates the severity of AS (when present)

TAVI Device Selection

Durability Current State

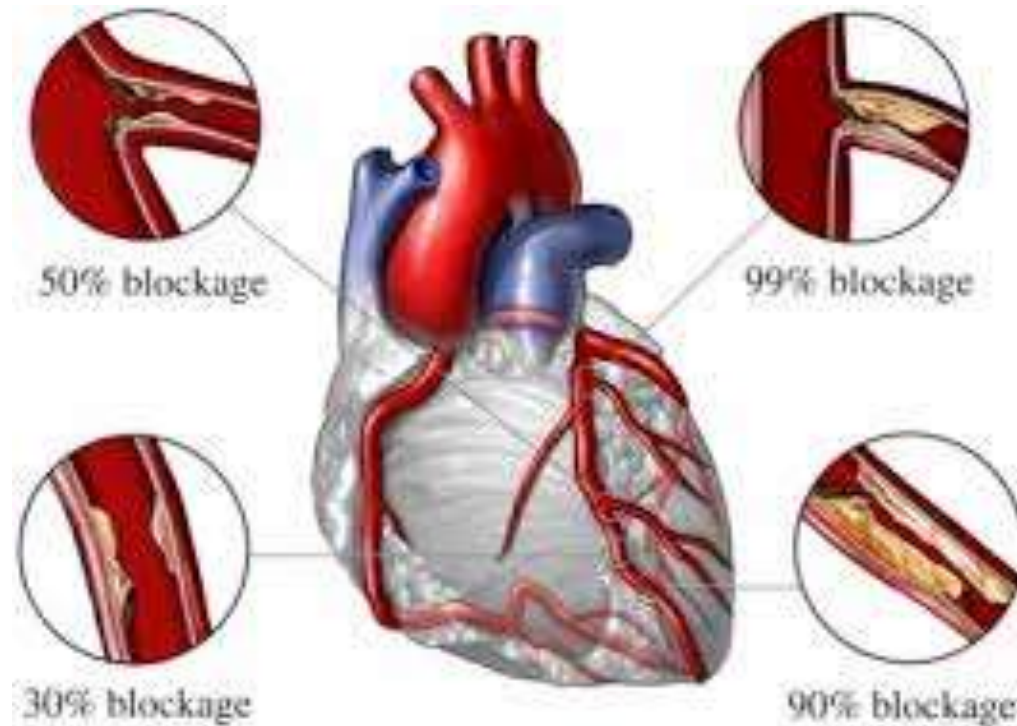
The consensus statement defined bioprosthetic valve dysfunction (BVD) as structural valve deterioration (SVD), non-structural valve deterioration (NSVD), thrombosis, and endocarditis



Lifetime Management

Coronary Artery Disease | PCI after TAVR

Preserving options for interventions beyond TAVR is critical for lifetime management of aortic stenosis patients especially as TAVR moves into younger patient populations.



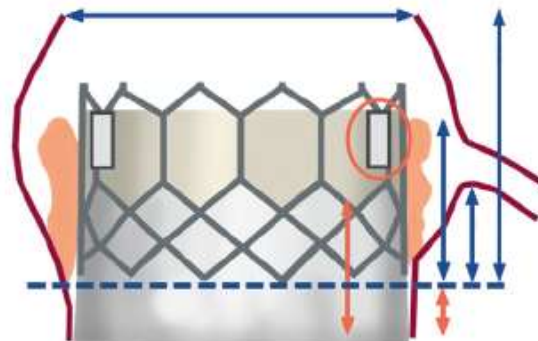
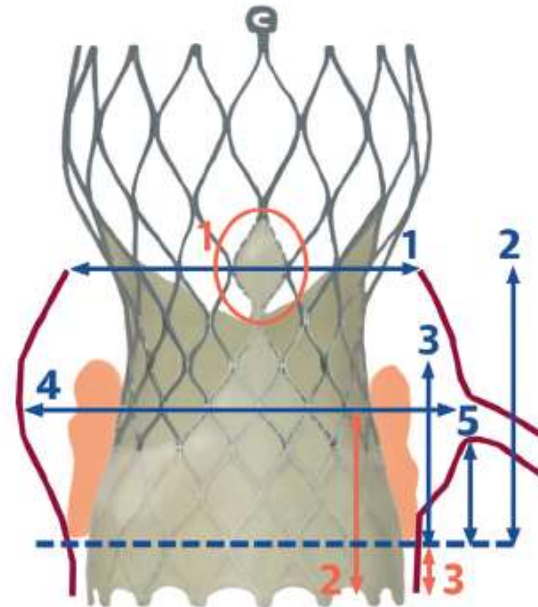
TAVI Device Selection

Post-TAVI PCI Current State

A recent review provided risk factors and guidelines for how to access the coronary arteries post-TAVI with self- and balloon-expandable valves

- The authors suggested that post-TAVI PCI is a TAVI problem, not a device problem
- Patients with narrow sinuses, low coronaries, and small sinotubular junctions are at increased risk with all TAVI devices

Factors Impacting Coronary Access



Anatomical

1. Sinotubular junction dimensions
2. Sinus height
3. Leaflet length and bulkiness
4. Sinus of Valsalva width
5. Coronary height

Device and Procedural

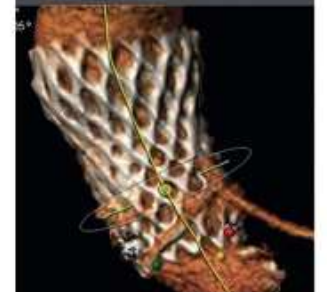
1. Commissural tab orientation
2. Sealing skirt height
3. Valve implant depth

Imaging Evaluation

Fluoroscopy



MDCT



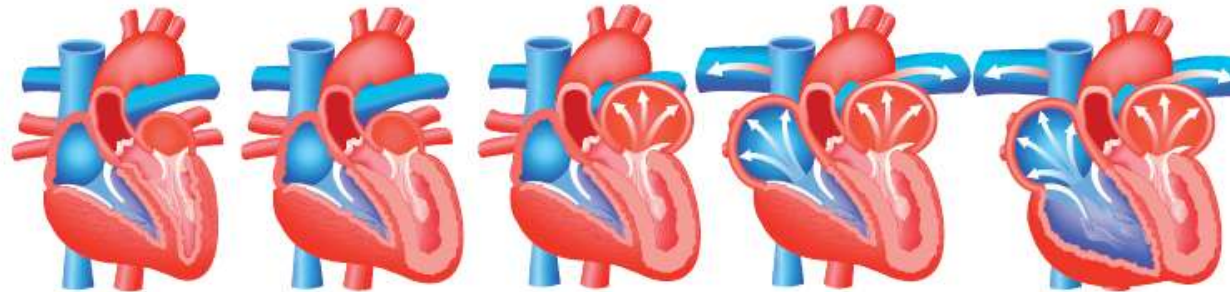
TAVR Revolution - 2019

The Future....

- The success of TAVR therapy has catalyzed a 'second wave' of clinical studies to explore the expansion of clinical indications (even beyond current surgery).
- There are many innovative TAVR-related technologies which are being actively explored!
- In the future, AS classification schemes and therapy trigger points will be redefined.

Staging classification of aortic stenosis based on the extent of cardiac damage

Philippe G n reux^{1,2,3}, Philippe Pibarot⁴, Bj rn Redfors^{1,5}, Michael J. Mack⁶, Raj R. Makkar⁷, Wael A. Jaber⁸, Lars G. Svensson⁸, Samir Kapadia⁸, E. Murat Tuzcu⁸, Vinod H. Thourani⁹, Vasilis Babaliaros⁹, Howard C. Herrmann¹⁰, Wilson Y. Szeto¹⁰, David J. Cohen¹¹, Brian R. Lindman¹², Thomas McAndrew¹, Maria C. Alu¹³,



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m ² (Male) >95 g/m ² (Female)	Indexed left atrial volume >34mL/m ²	Systolic Pulmonary hypertension ≥60 mmHg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

TAVR Revolution - 2019

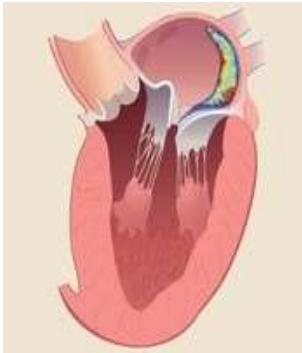
The Future....

- There are also many 'gaps' in TAVR knowledge which must be addressed (e.g. valve leaflet abnormalities, late TAVR SVD/durability, coronary access considerations, and optimal adjunctive pharmacotherapy).
- By all meaningful criteria however, TAVR has been a **BREAKTHROUGH** Technology in the management of patients with aortic stenosis!

Mitral Regurgitation

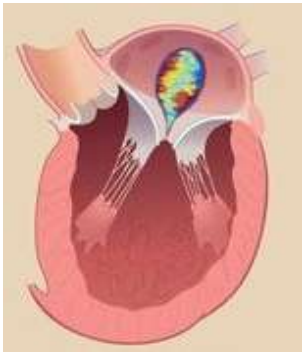
Current State

Mitral Regurgitation is the most prevalent form of mitral valve disease and affects >8% of people >65 years. Treatment options vary with etiology



- **Primary MR**

- Surgical treatment options are effective and not controversial
- Transcatheter edge-to-edge repair is recommended in those who are inoperable or at high surgical risk



- **Secondary MR**

- Management of secondary MR presents significant challenges since this type of MR is largely related to the disease process in the LV
- Therapy is primarily directed toward the underlying LV disorder and includes medical therapy, surgery, and transcatheter edge-to-edge repair

Mitral Regurgitation








Unmet Need

- Surgical treatment of MR yields acceptable results, especially for primary MR.
- However, patients with severe mitral regurgitation are often denied surgery. Reasons include:
 - ✓ Impaired LVEF
 - ✓ Older Age
 - ✓ Comorbidities / surgical risk status
- A toolbox of treatment options will be needed to treat this heterogeneous disease.
- There is a wide range of transcatheter devices are under development. It is difficult to predict which of these will be most effective and adopted into practice.

Mitral Regurgitation

Transcatheter Repair Devices

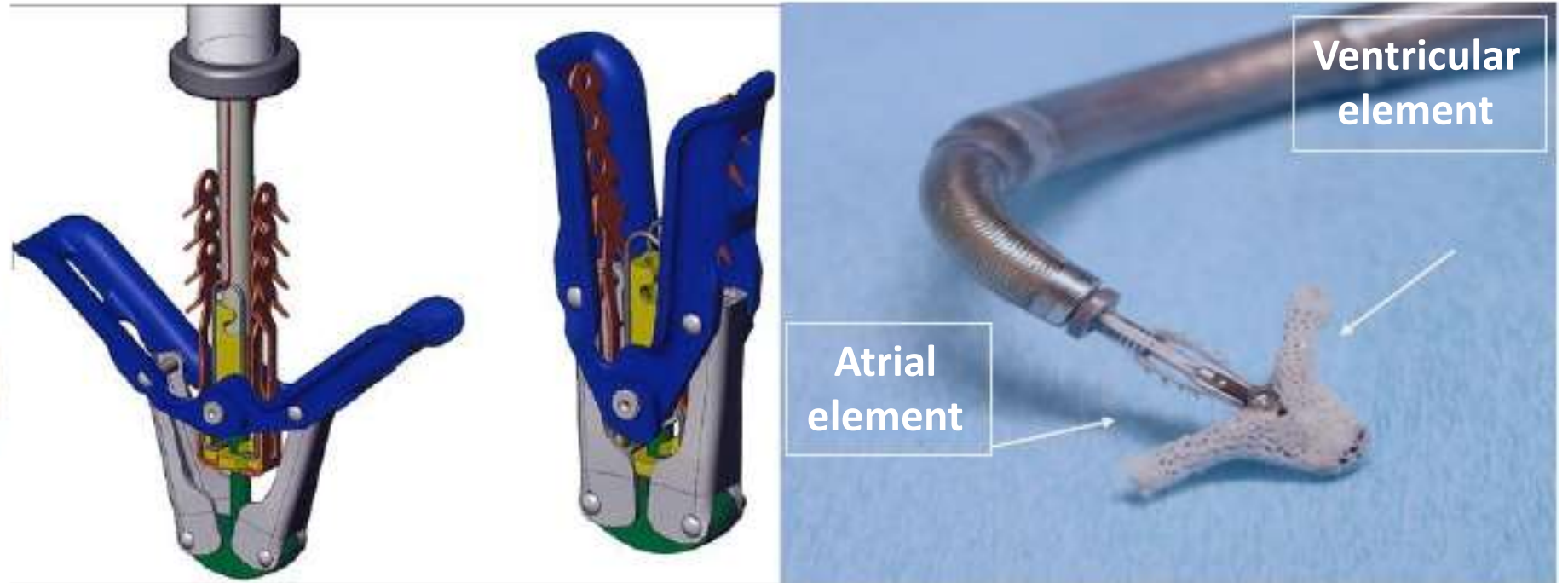
Current devices target the MV leaflets, chordal apparatus, and mitral annulus.

Anatomic Target	Device	Description	Main Indications	Status	Reported # of Treated Patients
Mitral Leaflets	 MitraClip	Edge-to-Edge	Primary and Secondary MR	FDA Approved CE Mark	>80,000
	 Pascal	Edge-to-Edge	Primary and Secondary MR	CE Mark	>30
Mitral Annulus	 Carillon	Coronary Sinus cinching	Secondary MR	CE Mark	>500
	 Cardioband	Direct annuloplasty	Secondary MR	CE Mark	>100
	 Mitralign	Annular plication	Secondary MR	CE Mark	>100
Chordal Apparatus	 NeoChord	Artificial chordal implantation	Posterior leaflet flail/prolapse	CE Mark	>250
	 Harpoon	Artificial chordal implantation	Posterior leaflet flail/prolapse	-	<50

Imitate Prof Alfieri - MitraClip



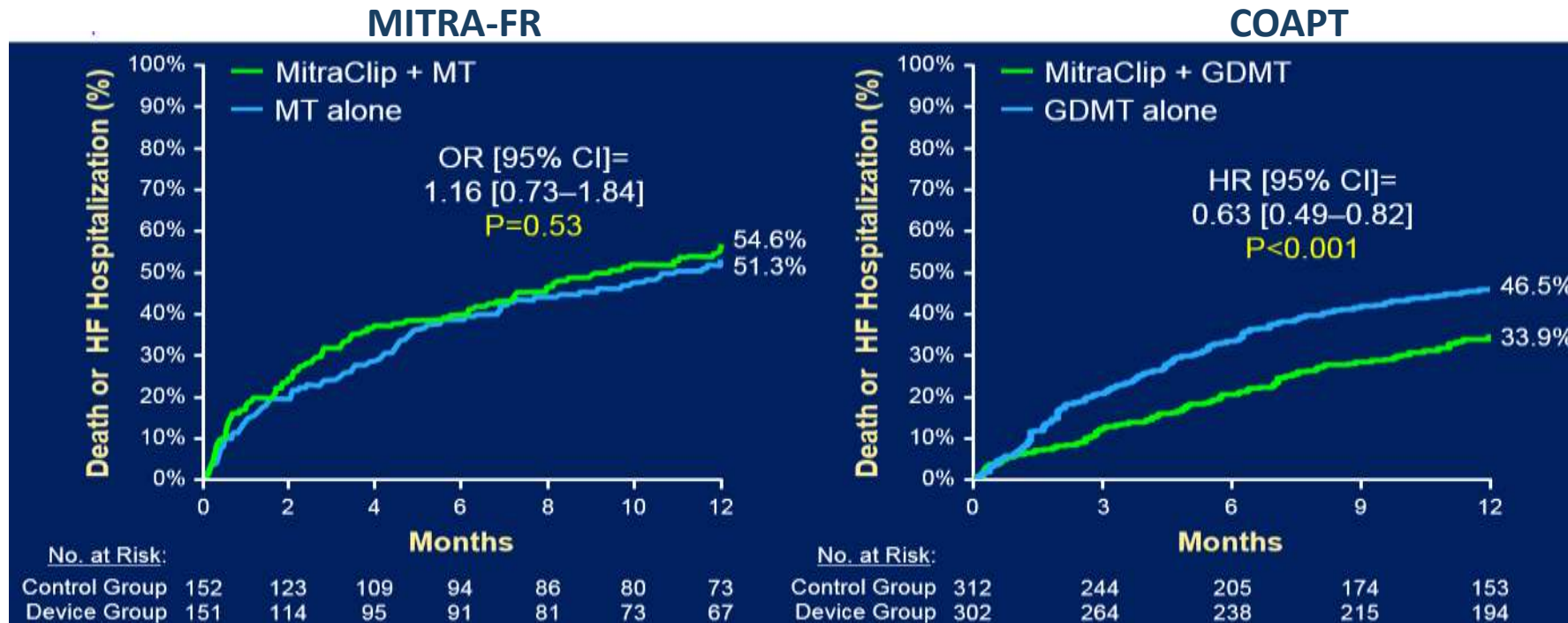
A



Mitral Regurgitation

Patient Selection

Together, MITRA-FR and COAPT have begun to provide information on secondary MR patients who may benefit from mitral valve interventions. Future TMV studies will continue to inform on patient selection.



¹Obadia, et. al. , *New Engl J Med* 2018; 379(24): 2297-2306; ¹Stone, et. al. , *New Engl J Med* 2018; 379(24): 2307-2318

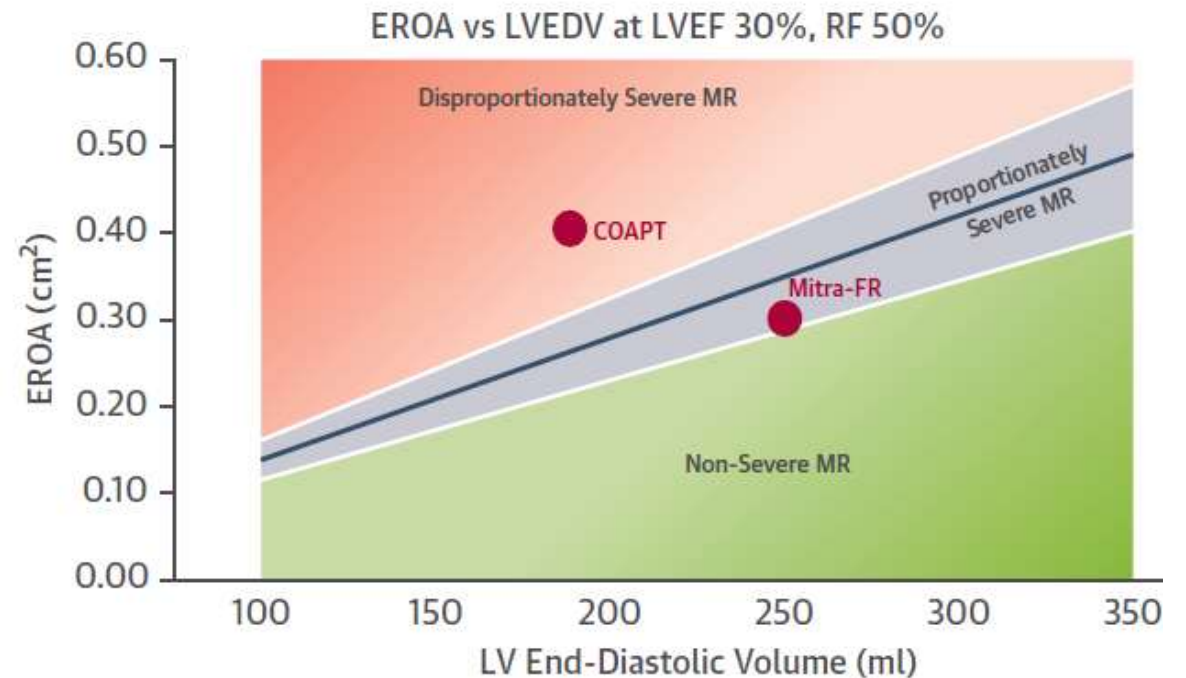
Secondary Mitral Regurgitation

Transcatheter Repair Patient Selection

As new therapies become available, it becomes increasingly important to identify those patients who benefit from a particular therapy vs. those who will not.

A recent framework based on EROA and LVEDV was proposed to identify patients who may benefit from transcatheter edge-to-edge therapy. The authors proposed the following sub-categories of secondary MR

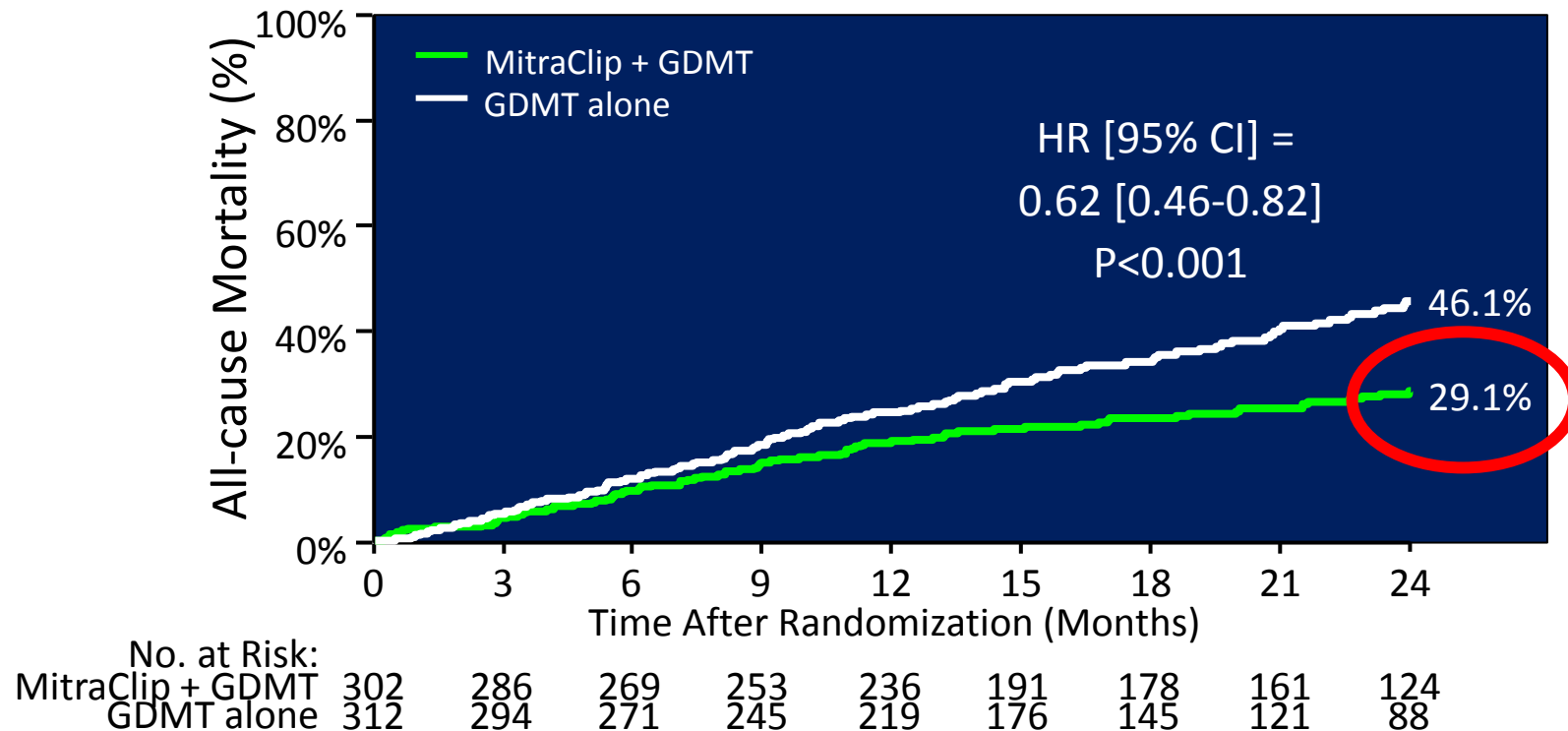
- **Proportionate MR**
 - MR is expected due to the degree of LV dilatation
 - No TMVr benefit (MITRA-FR patients)
- **Disproportionate MR**
 - MR is unexpected relative to degree of LV dilatation
 - Likely TMVr benefit (COAPT patients)
- **Non-severe MR**
 - No TMVr benefit



Secondary Mitral Regurgitation Unmet Need

Outcomes of the COAPT trial will be difficult to replicate in a “real-world” setting as demonstrated by the MITRA-FR trial. Even in those COAPT patients successfully treated with the MitraClip device, nearly 30% of patients had died at 2 years.

Despite the incredible success of COAPT, there remains a significant unmet need in secondary MR patients.



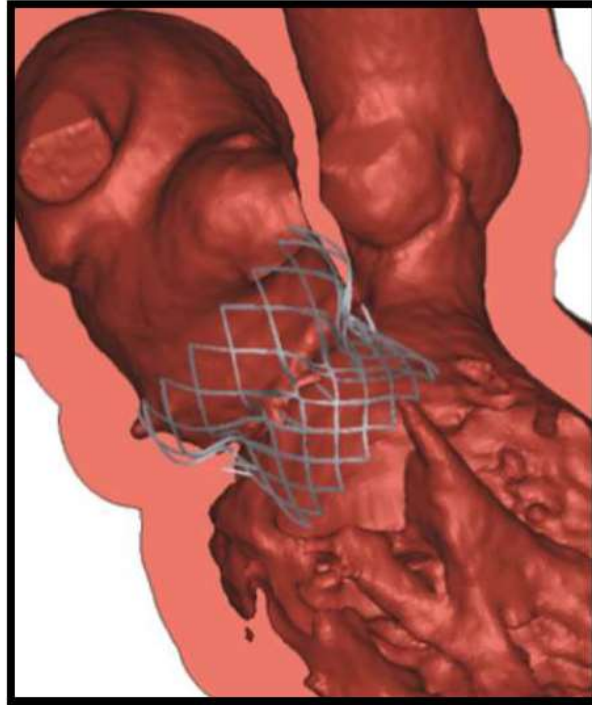
Mitral Regurgitation

Transcatheter Replacement Devices | Design Targets

Anchor

Seal

Avoid interference



Adaptable

Recapture

Durable

User friendly

Challenges for Transcatheter Mitral Valve Intervention



Challenges for TMVR Development

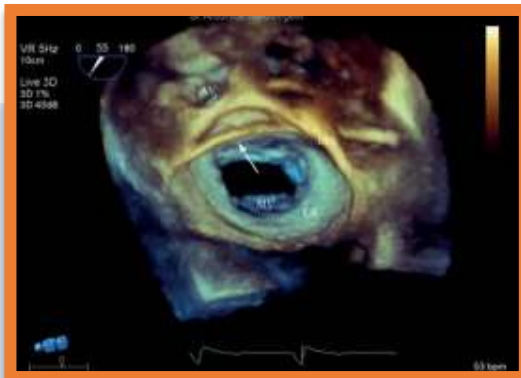


- Mitral Valve Pathology
- Absence of Calcium
- Variable Calcification (MAC)
- Sub-valvular apparatus
- Large Effective Orifice Area
- Large Annular Range

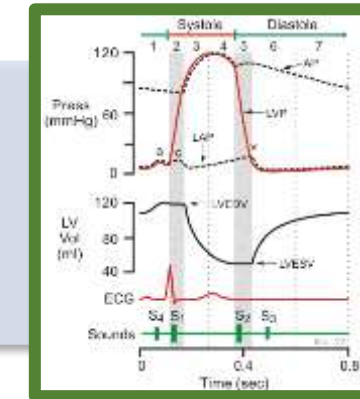
Anatomy & Pathology

Dynamic Environment

- Ventricular & Annular Motion
- High Transvalvular Gradients
- High Dislodgement Forces



- Poor Ventricular Function
- Thin Ventricular Walls
- Steering
- Delivery System Profile










Access & Positioning

Mitral Regurgitation

Transcatheter Replacement Devices in Human Use

There are a number of transcatheter MV replacement (TMVR) devices under development that show excellent MR reduction and ease of use, but poor safety outcomes compared to transcatheter repair devices.

Technologies		Reported Human Experience
Tendyne		230+
Intrepid		185+
Fortis		40+
Tiara		37+
Evoque		23+
Caisson		12+
HighLife		11+
TOTAL		538+

Mitral Valve Therapies

Future Therapies

There is a vast number of devices under development that vary drastically in treatment mechanism.

The success of future TMV devices will require:

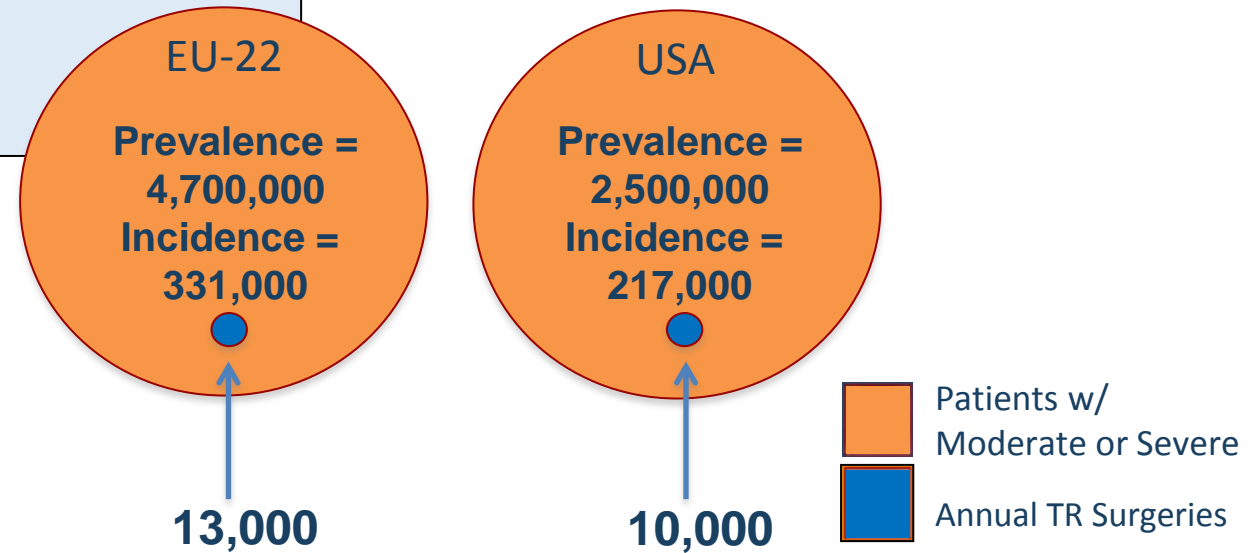
- High safety profile
- MR reduction similar to surgery
- Minimal anatomical exclusions
- Transseptal/transfemoral delivery
- Predictive deployment and ease of use

Tricuspid Valve Therapies

Unmet Need

Historically, the tricuspid valve has largely been ignored giving it the nickname the “forgotten valve.” Current guideline recommendations favor *early surgical repair in patients* undergoing left-sided surgery, yet few patients receive surgical treatment for TR due to:

- Lack of strong guideline recommendations
- Misconceptions on TR improvement after aortic or MV surgery
- Concerns over operative mortality
- Limited long-term outcomes data



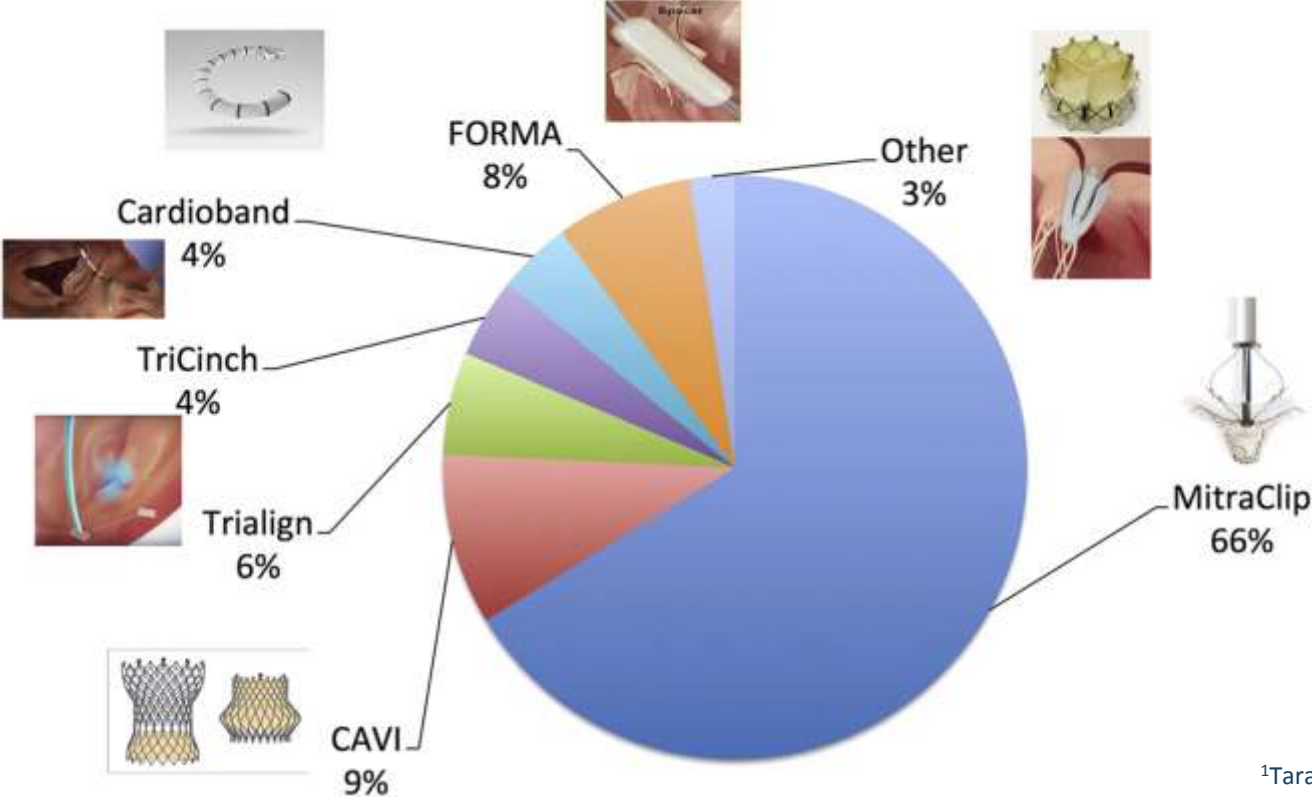
* Copyright 2017, Dymedex Consulting, Minneapolis, MN (over 200 papers reviewed)

¹Leon, presented at London Valves 2017

Tricuspid Regurgitation

Current State of Transcatheter Therapies

A recent report on 312 high-risk patients included in the international TriValve Registry showed 92% of patients undergoing transcatheter therapies had functional/secondary TR. Patients were mainly treated with therapies designed for the mitral space and saw a 73% procedural success rate with excellent safety outcomes.

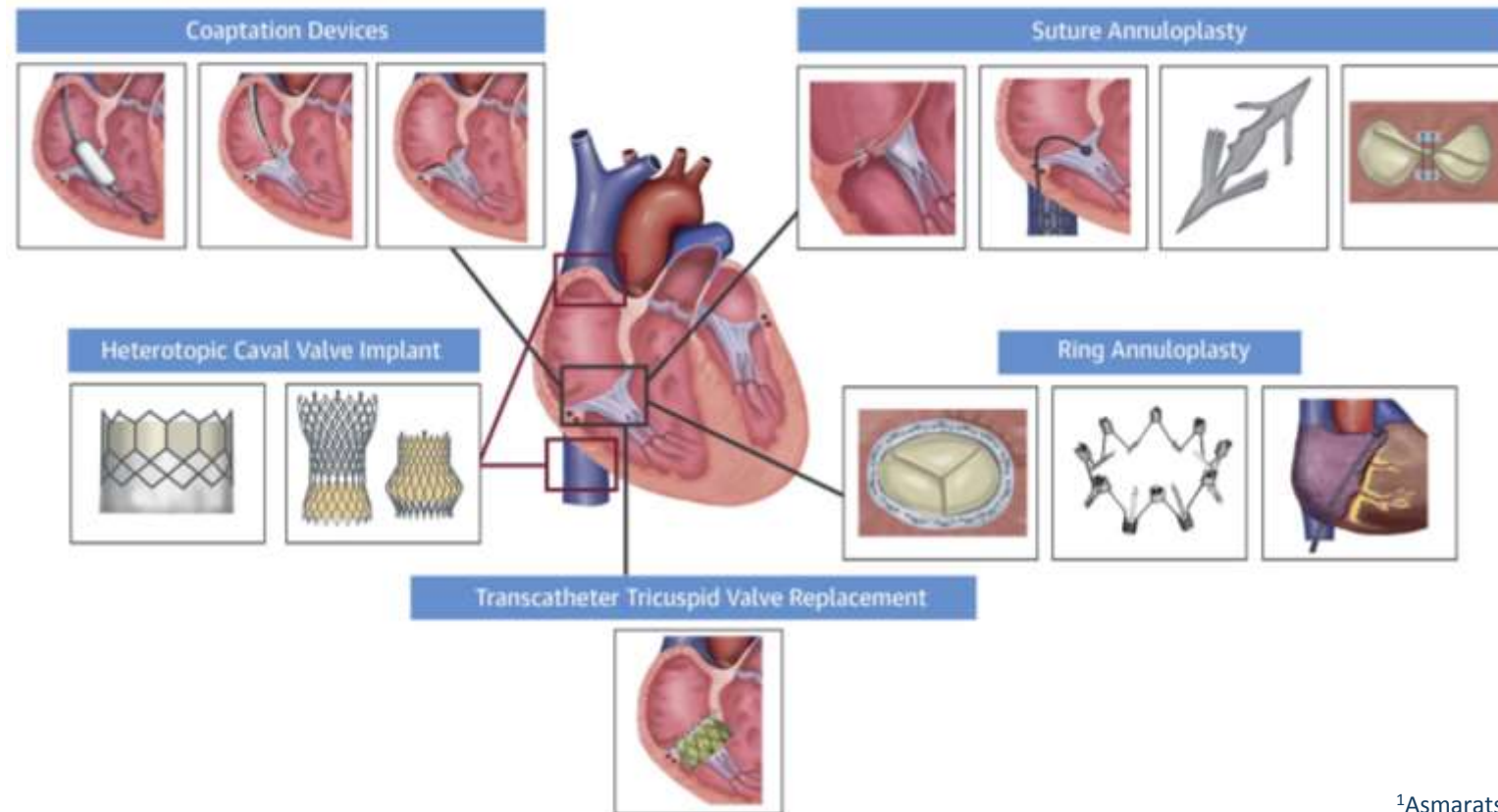


¹Taramasso et. al. , *J Am Coll Cardiol Interv* 2019; 12(2): 151-154

Tricuspid Regurgitation

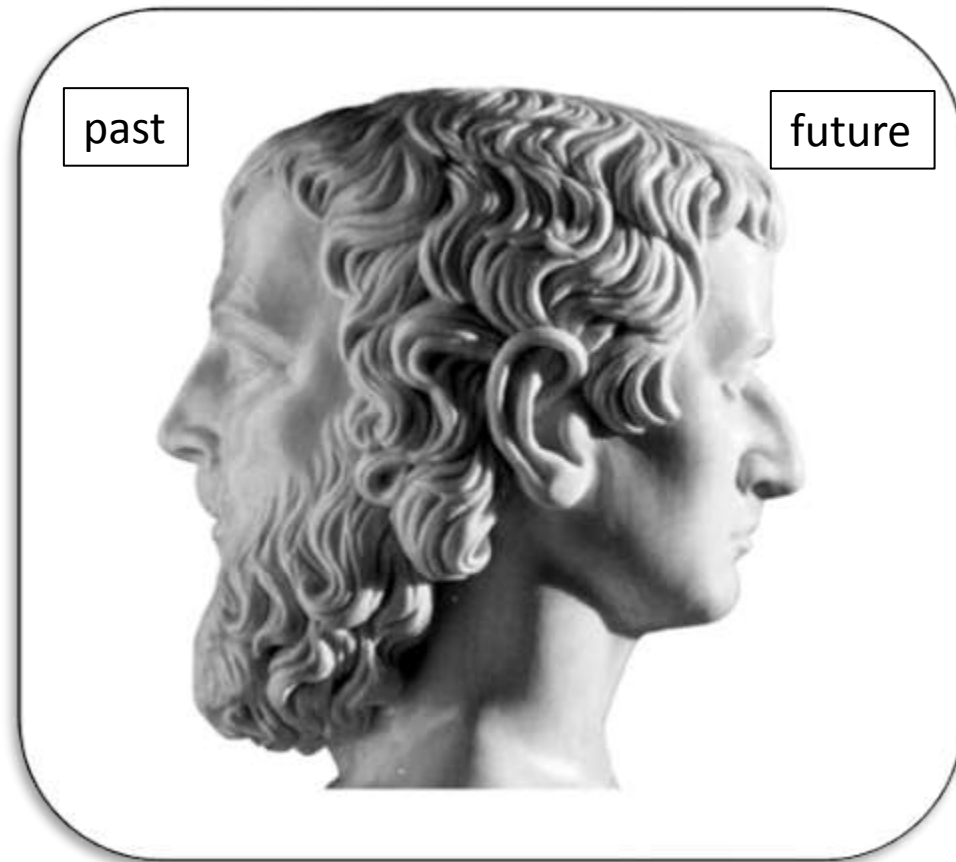
Novel Therapies

Novel transcatheter devices are in the early stages of development and may provide additional options for patients in the future.



JANUS

*the Roman God of beginnings and transitions
(looking to the past and the future)*



Interventional Cardiology

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