

Future Perspective for TAVR- What is Remained?

Eberhard Grube, MD, FACC, FSCAI

University Hospital, Dept of Medicine II, Bonn, Germany

Stanford University, Palo Alto, California, USA

Disclosure Eberhard Grube, MD

Physician Name

Company/Relationship

Speaker Bureau/Advisory Board:

Medtronic: C, SB, AB, OF
LivaNova: C, SB, AB
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Equity Interest:

InSeal Medical: E, AB,
MTEx: E, AB, SB
Cardiovalve: E, SB,
Claret: E, AB
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G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
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TAVR Journey - 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



Early Success was Driven by Several Factors Focusing on Making the TAVR Procedure Safe with Comparable Results to SAVR

Standardized and Consistent Patient Selection

Procedural 'Best Practices' Developed and Used Globally

Use of CT Sizing for Better Valve Selection

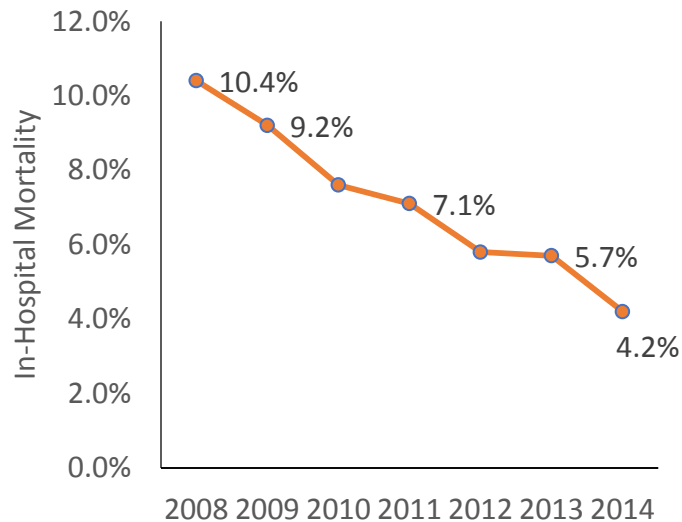
Early Mortality

Established TAVR Markets

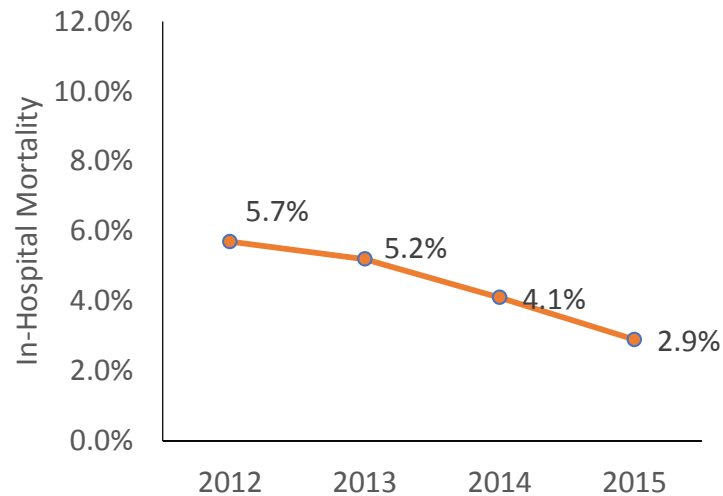
- *Within these established markets, rates of early mortality have steadily decreased with time. 30-day mortality is under 5% in contemporary practice.*
- *Each geography has also shown declining rates of complications which are known to impact mortality, such as aortic regurgitation, vascular injury, and severe acute complications such as annular rupture.*



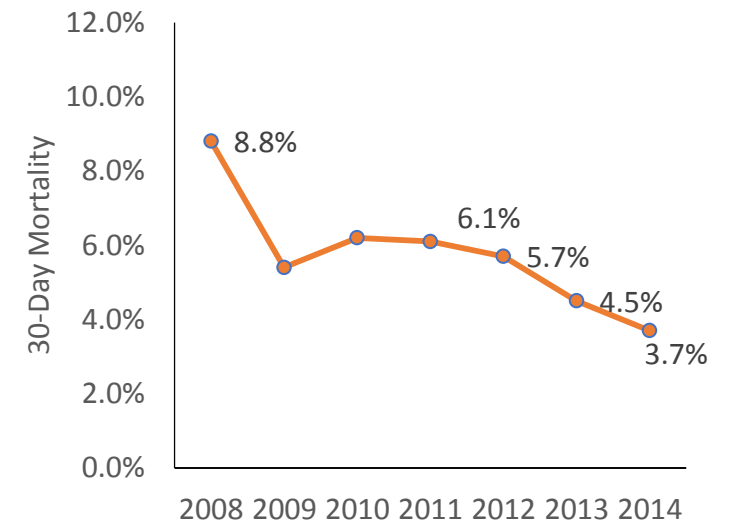
Germany



STS / ACC TVT Registry



UK TAVI Registry



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.

High Risk Patients

Mortality

Morbidity

Quality of Life

Focus

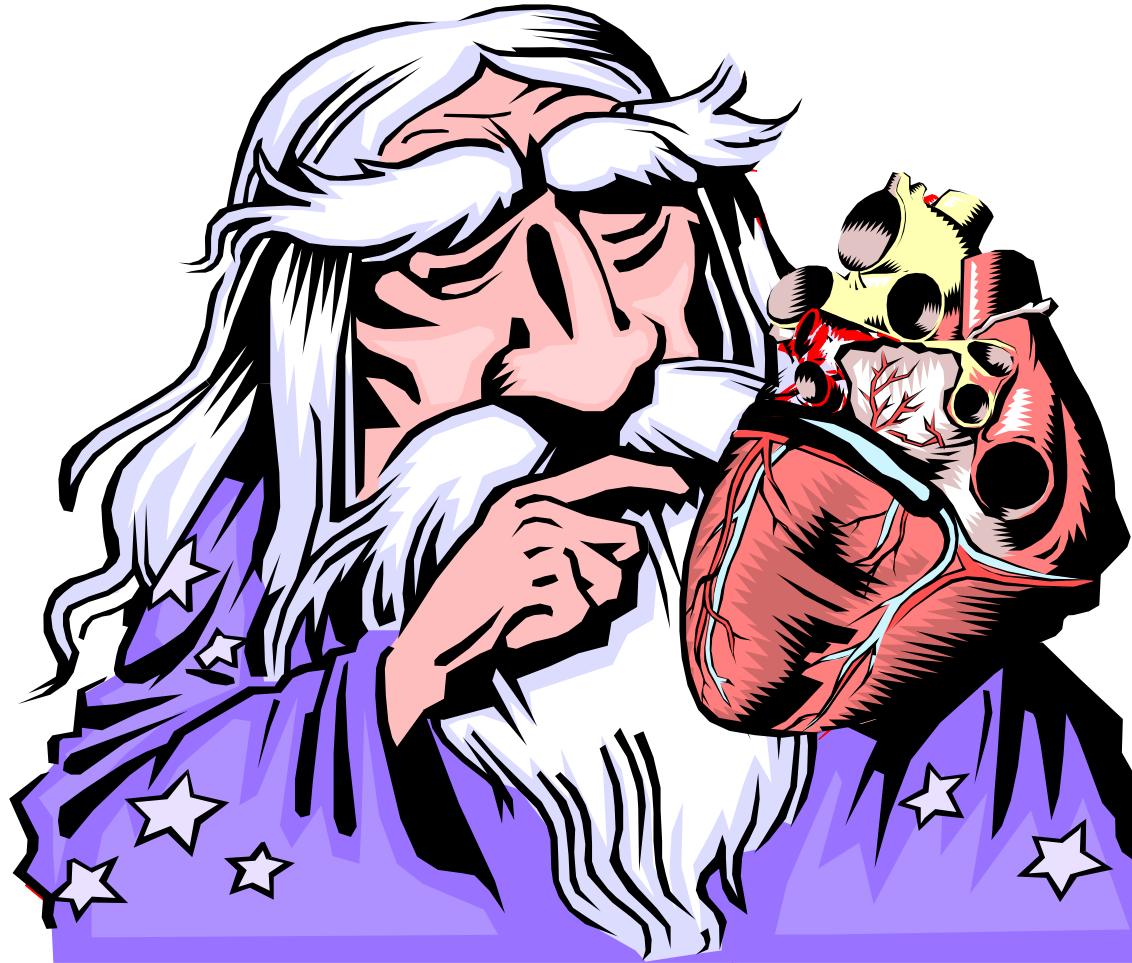
Low Risk Patients

**Valve Durability and
Performance**

Lifetime Management

Return to Daily Life

What lies ahead of us?



#1:

TAVR will be the treatment of choice for all isolated AS patients
and a reasonable treatment option for patients with
asymptomatic and moderate AS



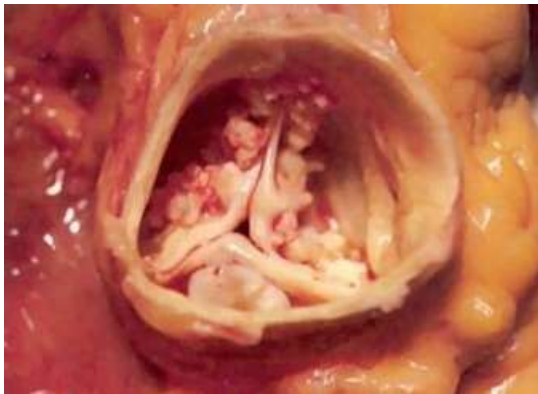
TAVR Next Steps

Although TAVR has become the gold standard for extreme- and high-risk patients, there are underserved patient populations that may benefit from TAVR.

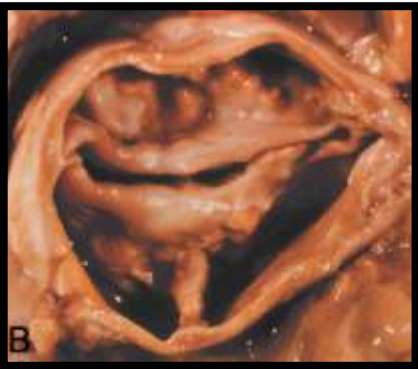
Low Risk



Asymptomatic AS



Bicuspid AS

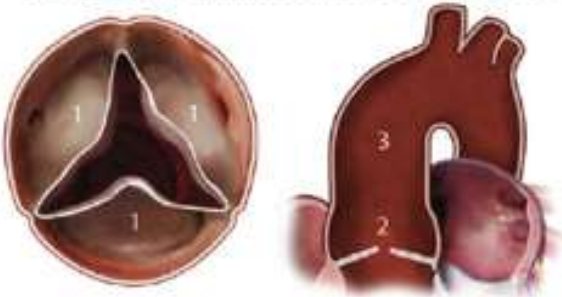


Moderate AS

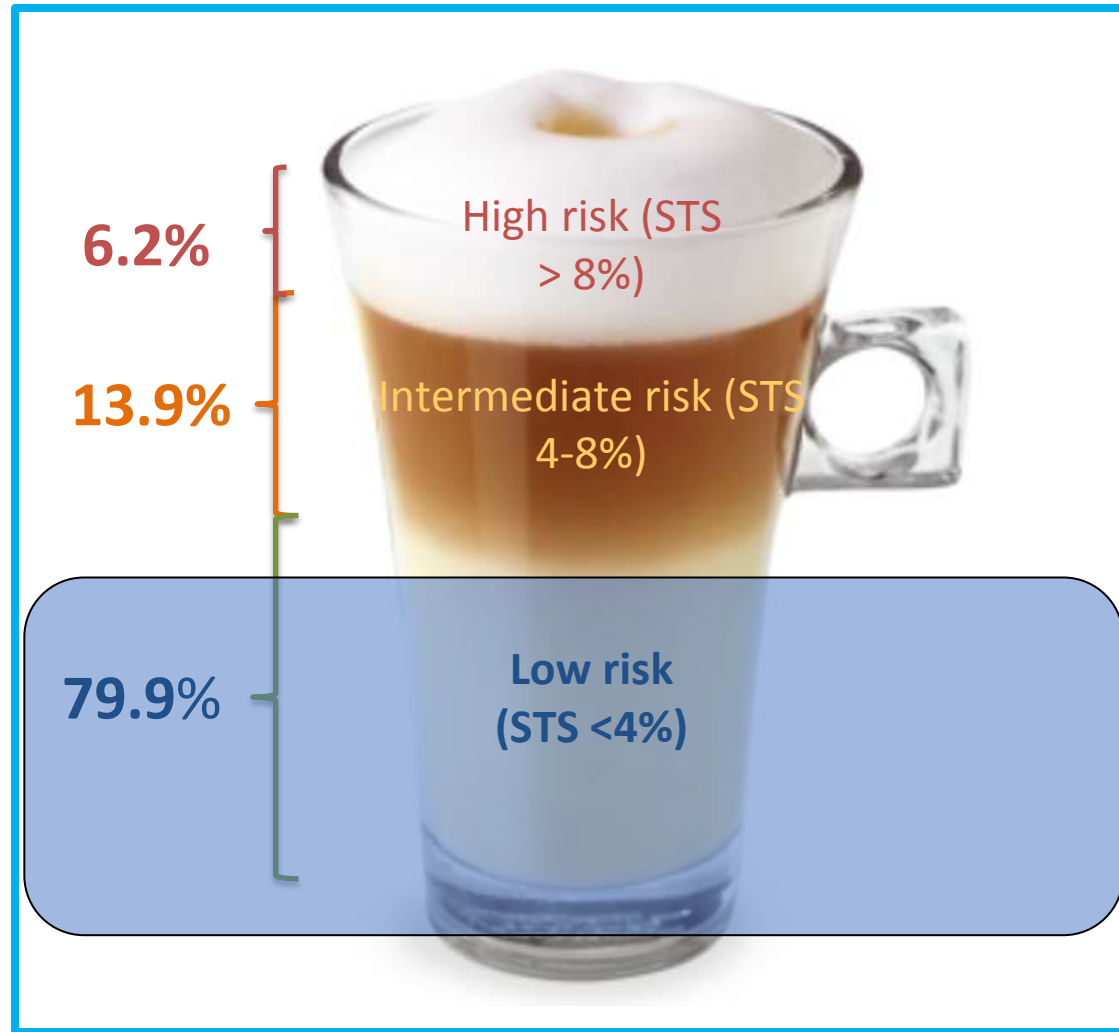
	Valve Area (cm2)	Maximum Aortic Velocity (mmHg)	Mean Pressure Gradient (mmHg)
Mild	1.5-2	2.5-3.0	< 25
Moderate	1.0-1.5	3.0-4.0	25-40
Severe	0.6-1.0	>4.0	>40
Critical	< 0.6		

Aortic Regurgitation

- 1- Minimal or absent cusp calcification
- 2- Dilated aortic root
- 3- Frequent coexistence of dilated ascending aorta



STS database 2002-2010 (141,905 pts)



***The 'holy grail'
80% low-risk
AS patients!***

Courtesy of N. Piazza, V. Thourani

Low Risk

Current Status | LRT Trial - **Conclusions**



The **1 year Results** from the multicenter, investigator sponsored, **Low-Risk TVR (LRT) Trial were recently reported**. The study propensity matched low-risk TAVR patients to isolated SAVR patients from the STS database.

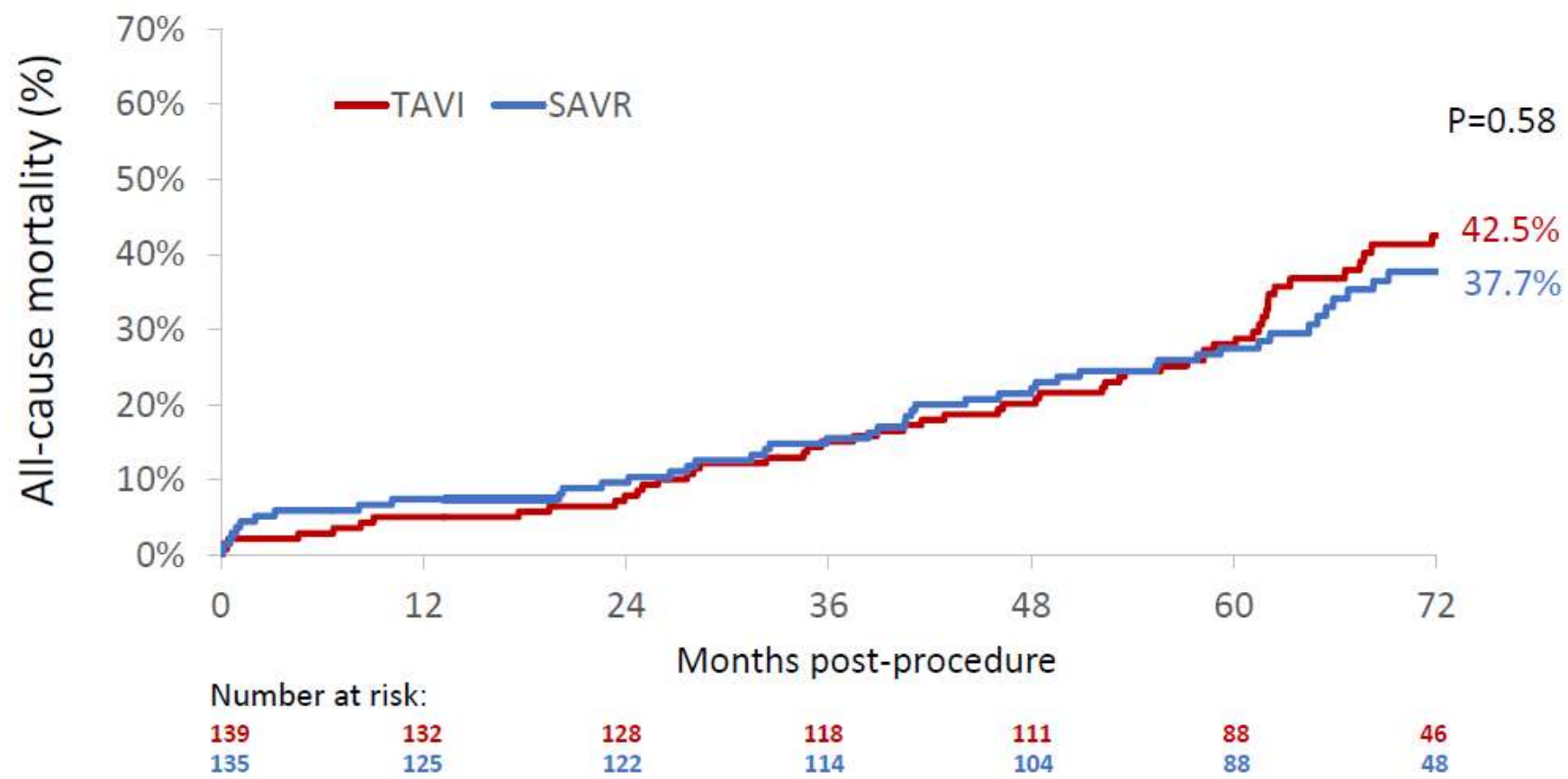
Early and 1 year outcomes were excellent with no/low mortality or disabling stroke out to 1 year.

- **TAVR outcomes were similar or better than SAVR, including a near-significant ($p=0.079$) benefit in mortality**

Low Risk

Current Status | NOTION

The NOTION clinical outcomes demonstrated *outstanding results with TAVR in lower risk patients*. Both death from any cause and cardiovascular death were similar to SAVR *out to 6 years*.



¹Sondergaard, presented at EuroPCR 2018

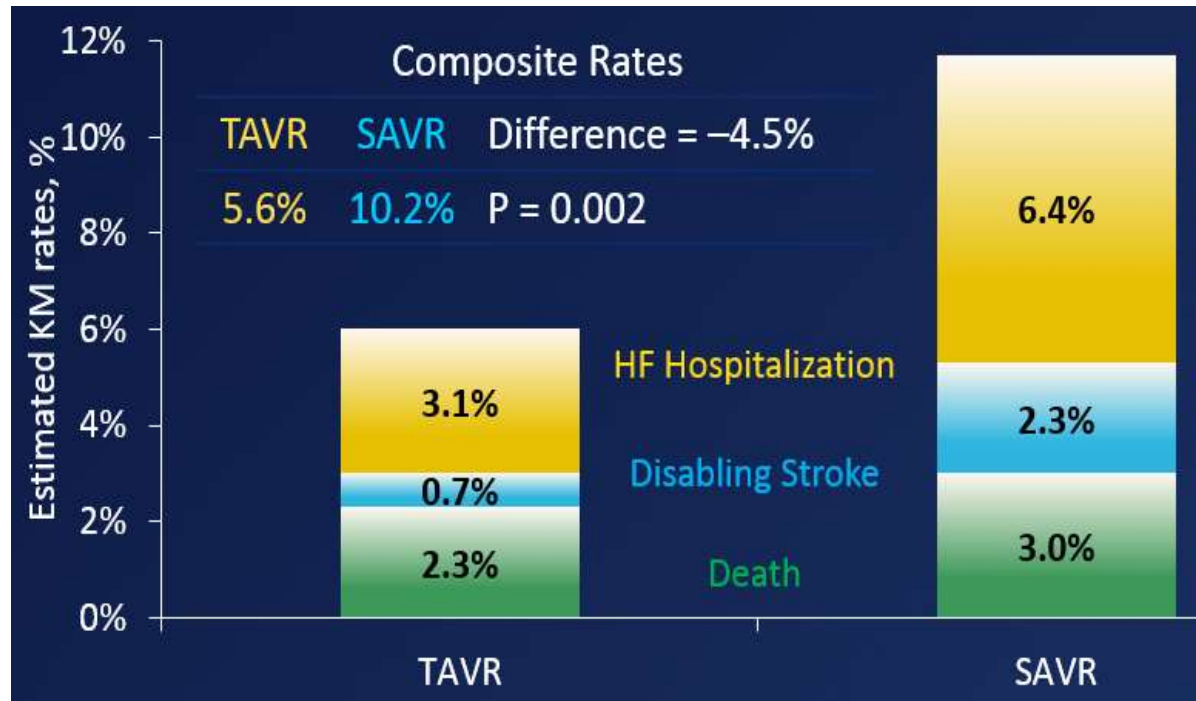
TAVR

Low Risk

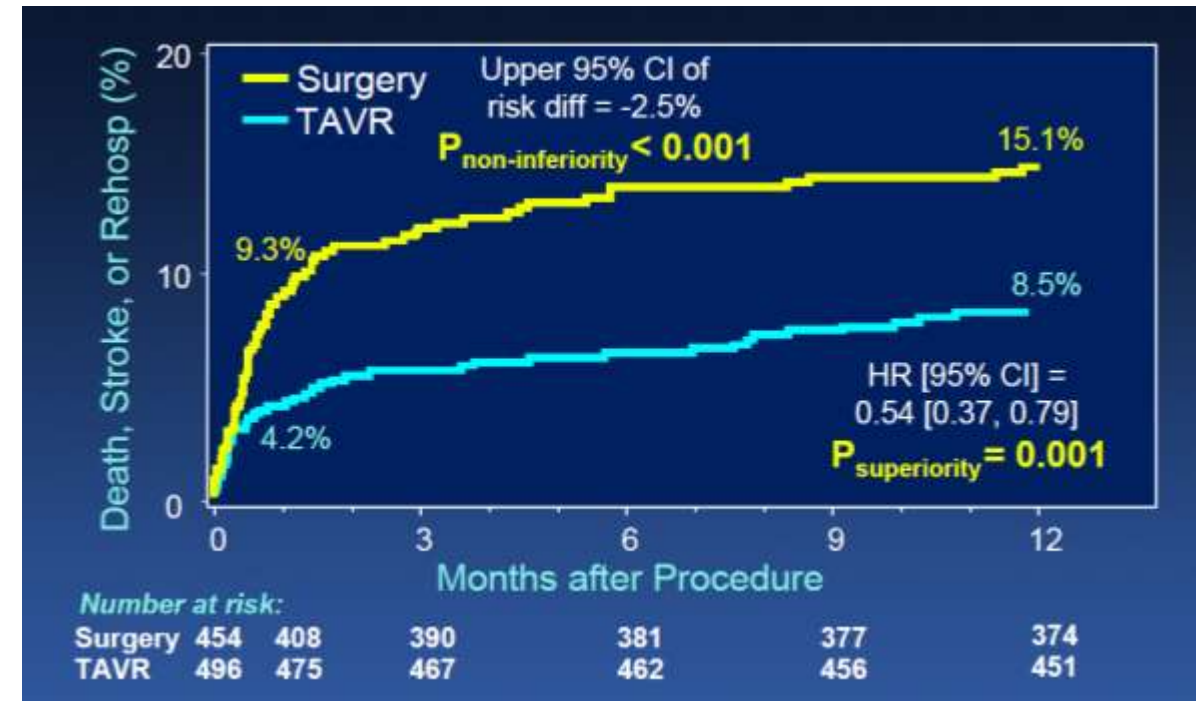
Results from the randomized Evolut Low-Risk and PARTNER 3 Trials demonstrated **success of the Evolut platform and SAPIEN 3 device in low surgical risk patients.**

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

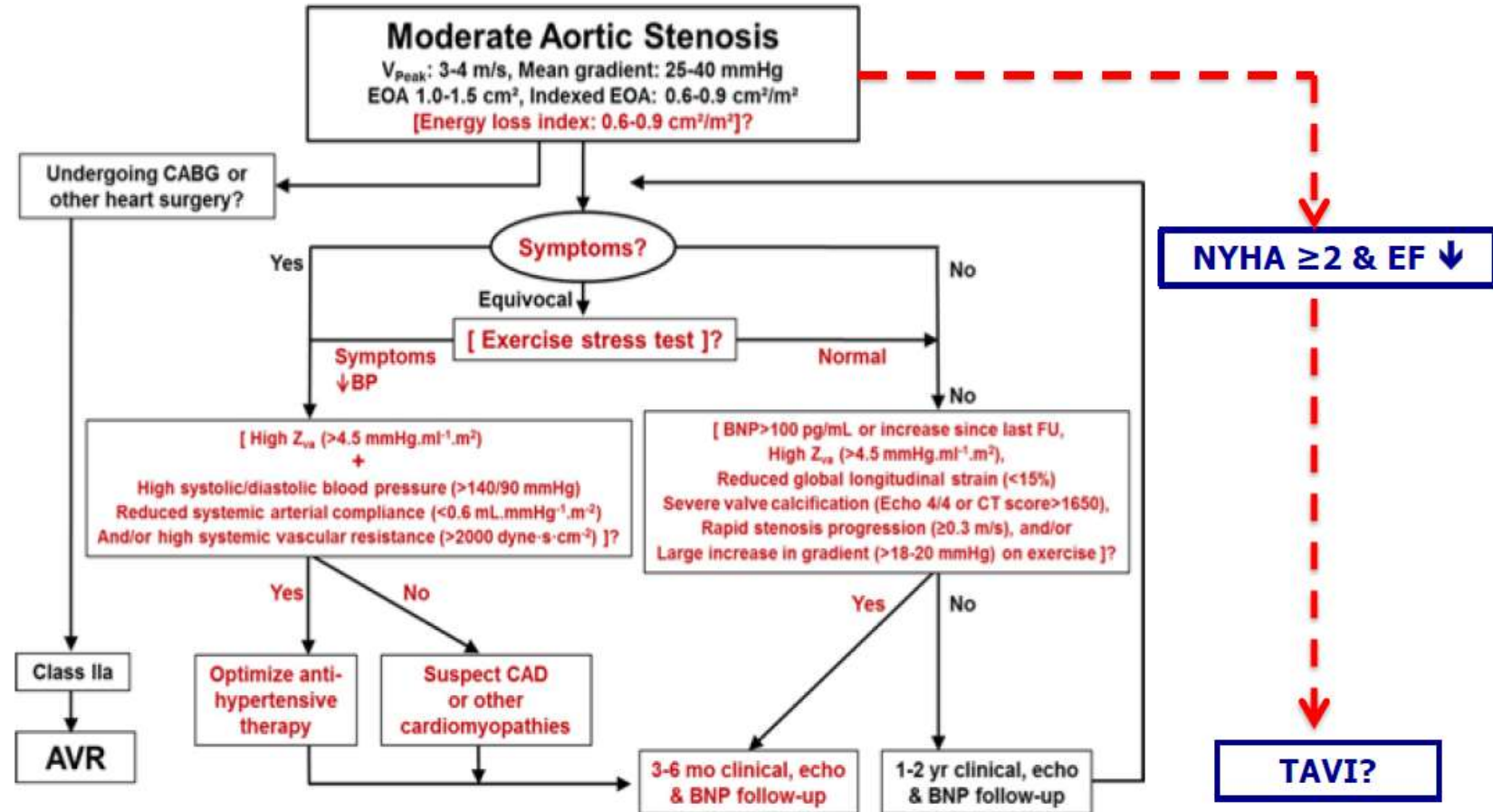


Moderate and Asymptomatic Aortic Stenosis

Current State

Guidelines, including recent updates from ESC/EACTS and ACC/AHA, are lacking evidence.

Randomized trial results are needed as outcomes of TAVR in moderate AS patients is mostly limited to case studies.



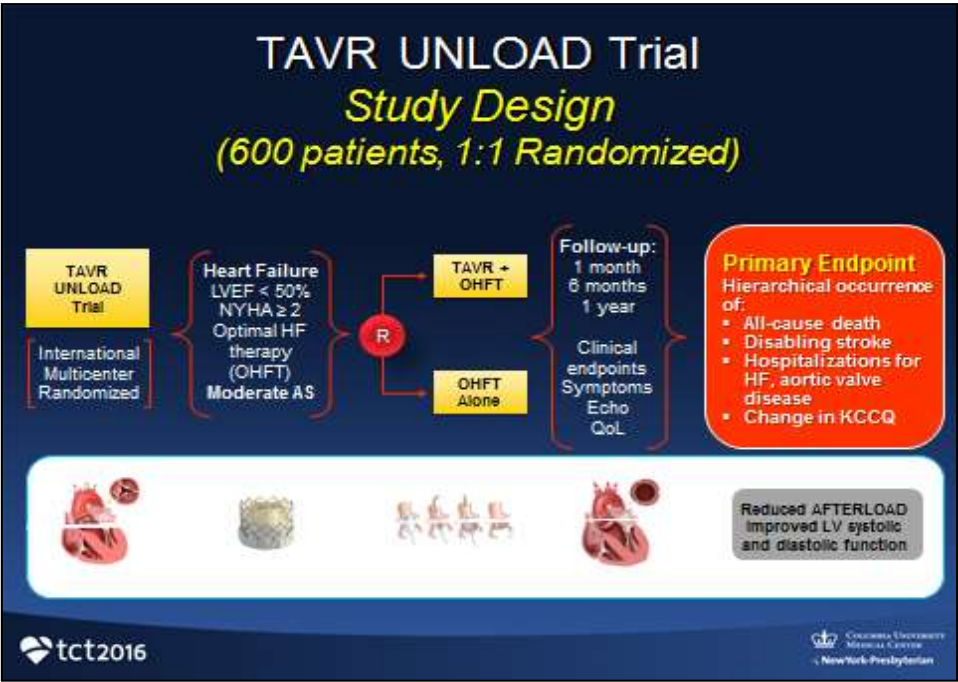
Moderate and Asymptomatic Aortic Stenosis

Current State

Clinical Trials are currently underway and earlier intervention in these patients will be performed and will prevent myocardial damage and functional decline.

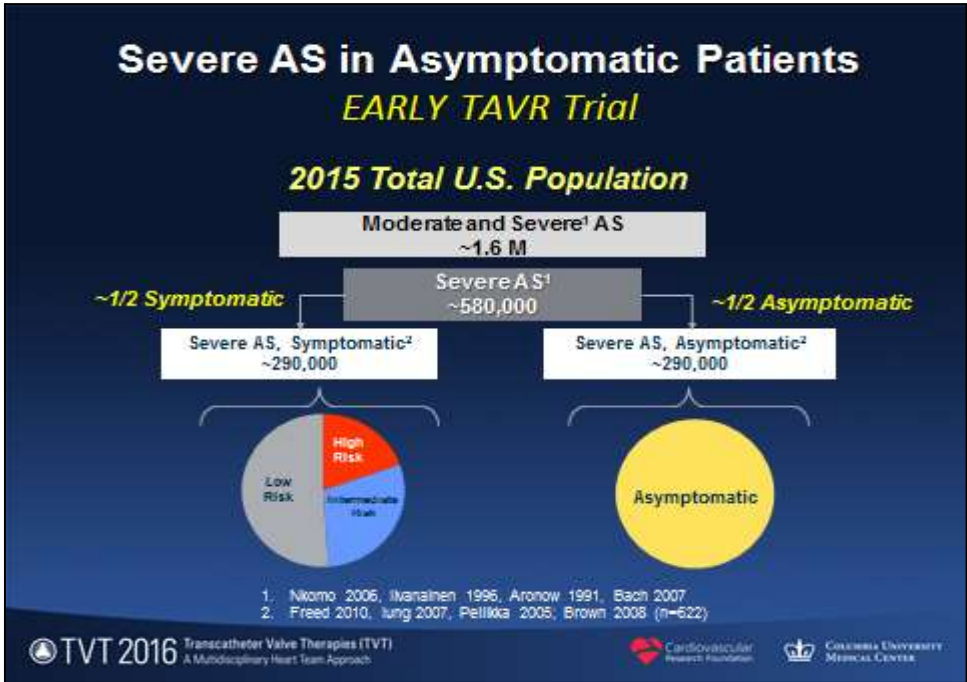
TAVR UNLOAD

TAVI will be compared to medical therapy in patients with moderate AS, symptoms of heart failure, and reduced EF



EARLY TAVR

TAVI will be applied to asymptomatic patients with severe AS

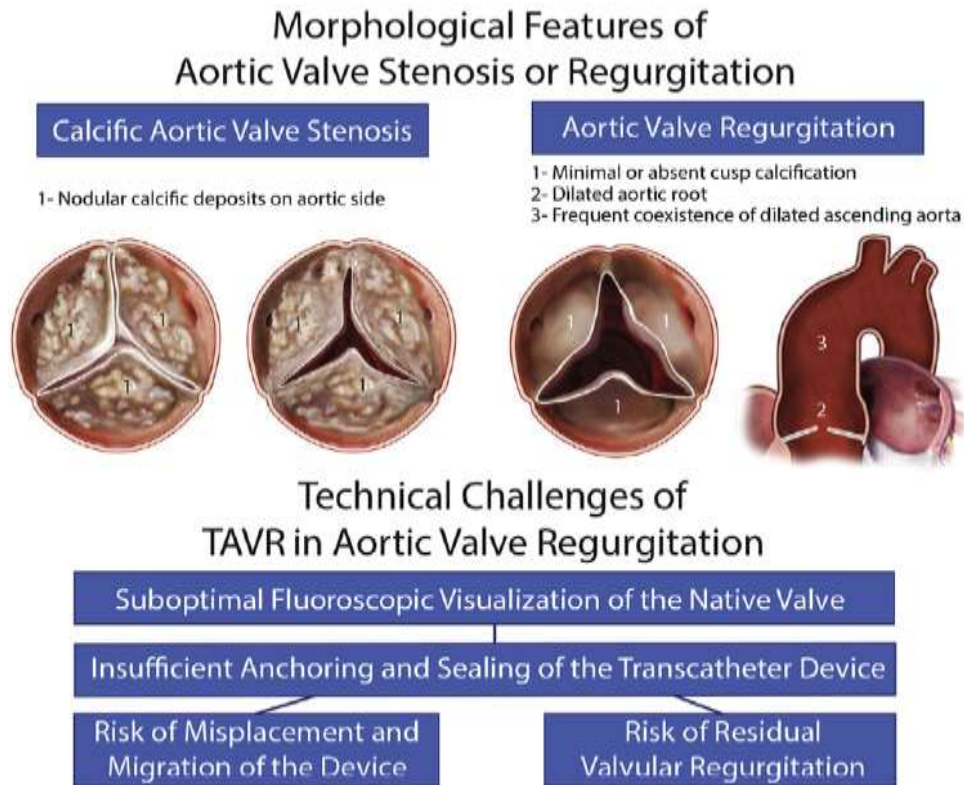


TAVR

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

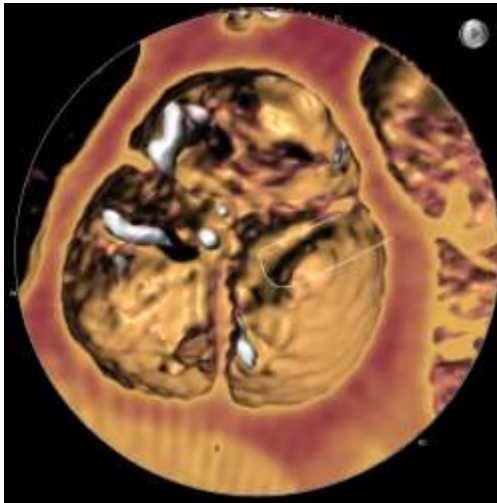
POTENTIAL ANATOMIC FEATURE	PROCEDURAL CONCERNS
Elliptical annulus	Impairs positioning and sealing
Large annulus	May be out of TAV size range
Assymetric leaflets and / or assymetric leaflet calcification	Impedes expansion, leads to gradients or PVL
Fused commissures (raphe)	Risk of rupture (during BAV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

BAV Classification (modified)

CTA Imaging

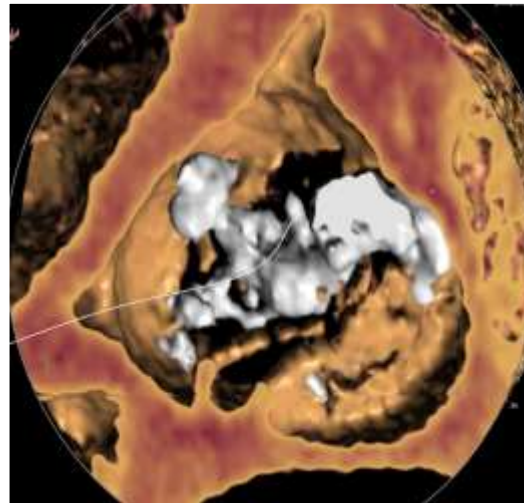
(from 14 centers in North America, Europe and Asia)

Tricommissural



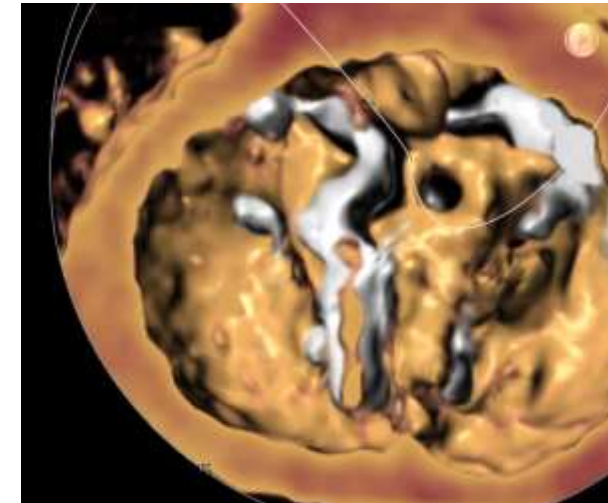
3 commissures
V-like orifice
“functional or acquired”

*Bicommissural
Raphe-type*



2 commissures, 1 raphe
Slit-like orifice

*Bicommissural
Non Raphe-type*



2 commissures, no raphe
Slit-like orifice

#2:

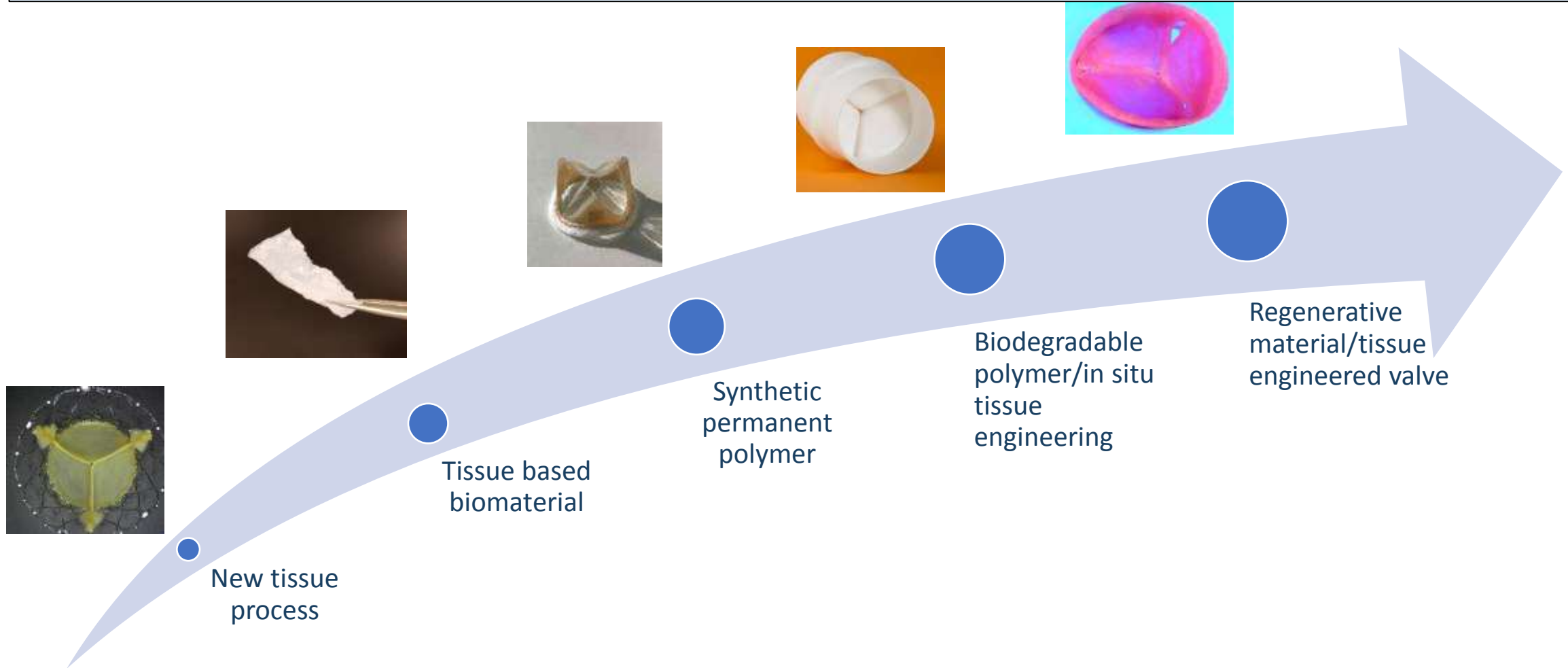
New technologies will make TAVR safer and easier



Device Technology

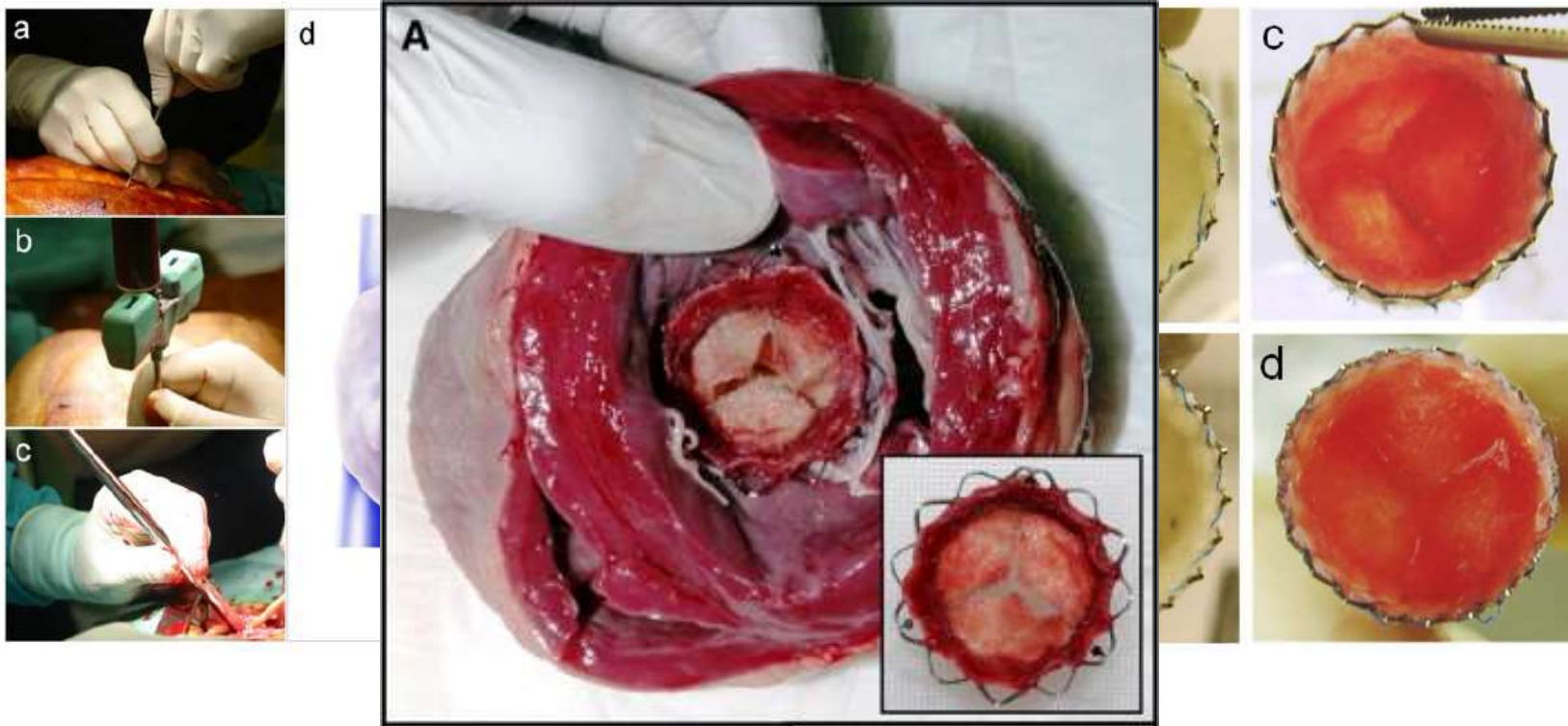
Alternative Materials

New tissue processes and novel materials are actively being researched, and this research may address shortcomings of current bioprosthetic valves.



Zurich Tissue Engineered Heart Valve

A “Living” Aortic Valve



Courtesy of Simon P. Hoerstrup, MD, PhD

Xeltis

Endogenous Tissue Restoration (ETR)

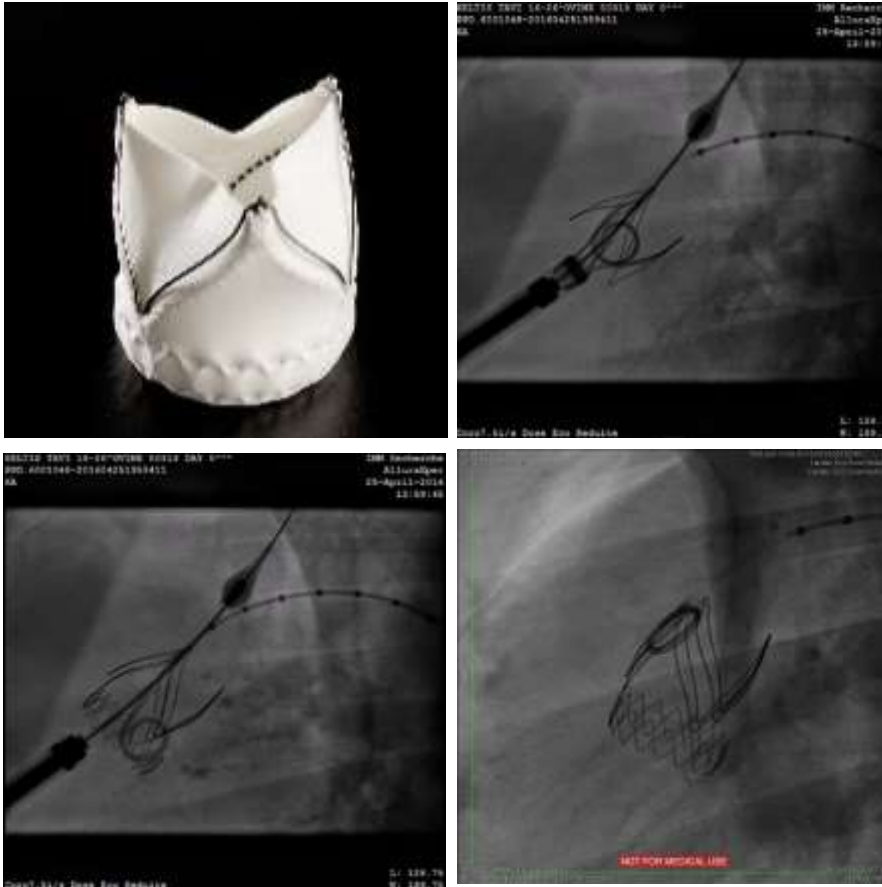


*Valve after
bioabsorption*

- Synthetic matrix made of novel bioabsorbable supramolecular polymers using electrospinning techniques
- Polymer leaflets mounted on nitinol self-expanding frame
- Regrowth of endogenous tissue coincident with bioabsorption of polymer implant
- Natural self-healing anti-inflammatory leaflets

Xeltis

Endogenous Tissue Restoration (ETR)



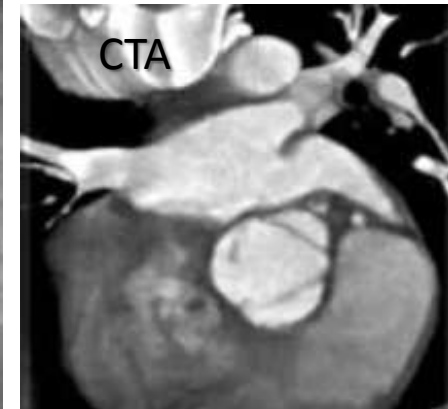
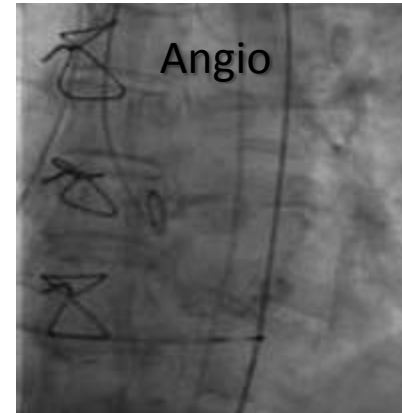
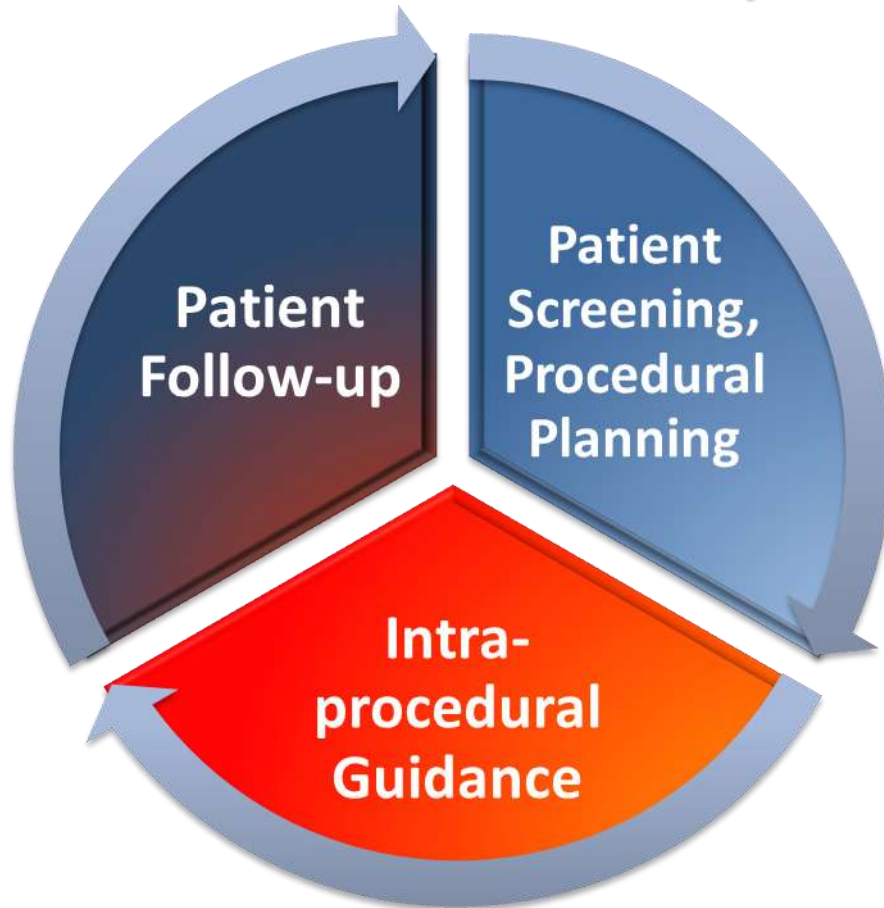
Aortic Valve

- Safety demonstrated in >50 sheep
- 96% device success
- 3 and 6 months FU complete
- Preliminary 12 months data available and encouraging
- Hemodynamic performance stable over time

TAVR

Accessory Devices/**Imaging Technologies**

Multi-modality Imaging is the RULE!

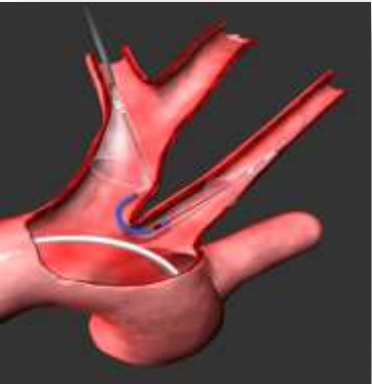


TAVR

Accessory Devices

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

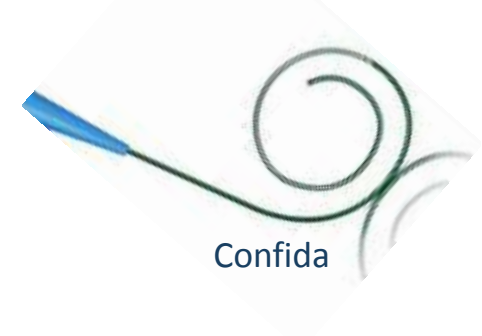
Neuroprotection devices



Expandable in-line sheath



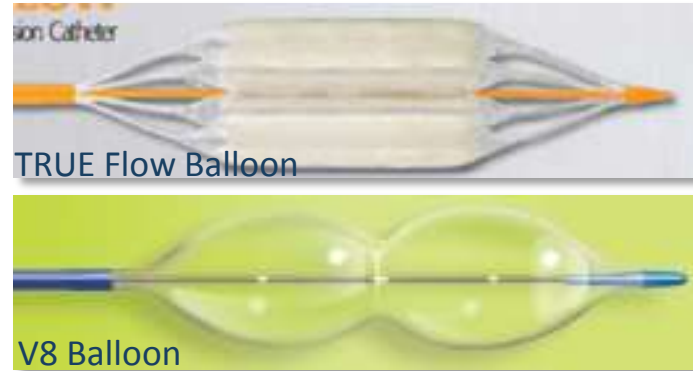
Dedicated wires and pacing leads



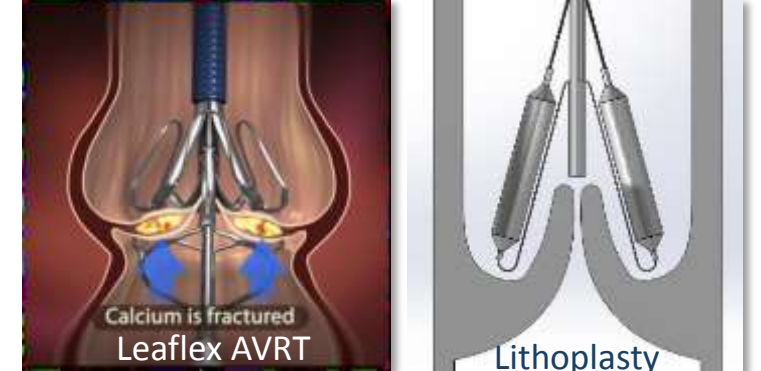
Large-hole closure devices



Balloon Aortic Valvuloplasty



Calcium Management Tools



#3:

TAVR device performance will drive device selection and strategies for the lifetime management of TAVR and SAVR patients will be optimized



TAVR Device Selection

Current Devices

Valve designs vary drastically and the selection process can be complicated. Valve selection might be essential in optimizing device performance and patient outcomes.

Self Expanding



Evolut R/Pro



Portico

Balloon/Mechanically Expandable



SAPIEN 3



Lotus



MyVal

Self Expanding



CENTERA



ACURATE neo

Supra-Annular



Evolut R



Evolut PRO



SAPIEN 3



Lotus



MyVal



Portico



ACURATE neo

Intra-Annular

Supra-Annular

TAVR Newcomers

Global Landscape (#25)

- Sapien 3
- Evolut R
- Lotus

***Current
Leaders!***

- Jena Valve
- Centera
- Venus A Valve

- J – Valve Ausper
- VitaFlow (Microport)
- Taurus One
- Tri
- C

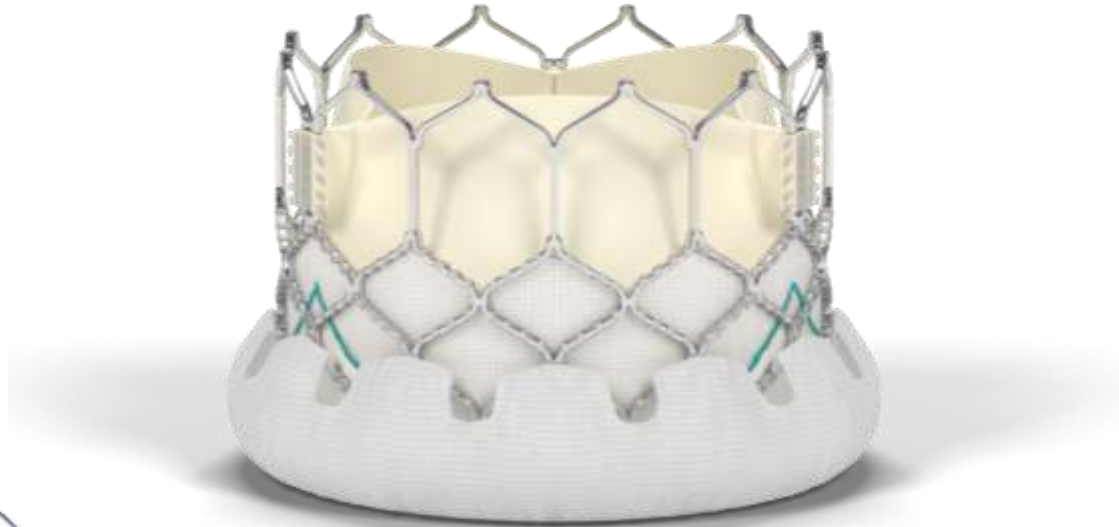
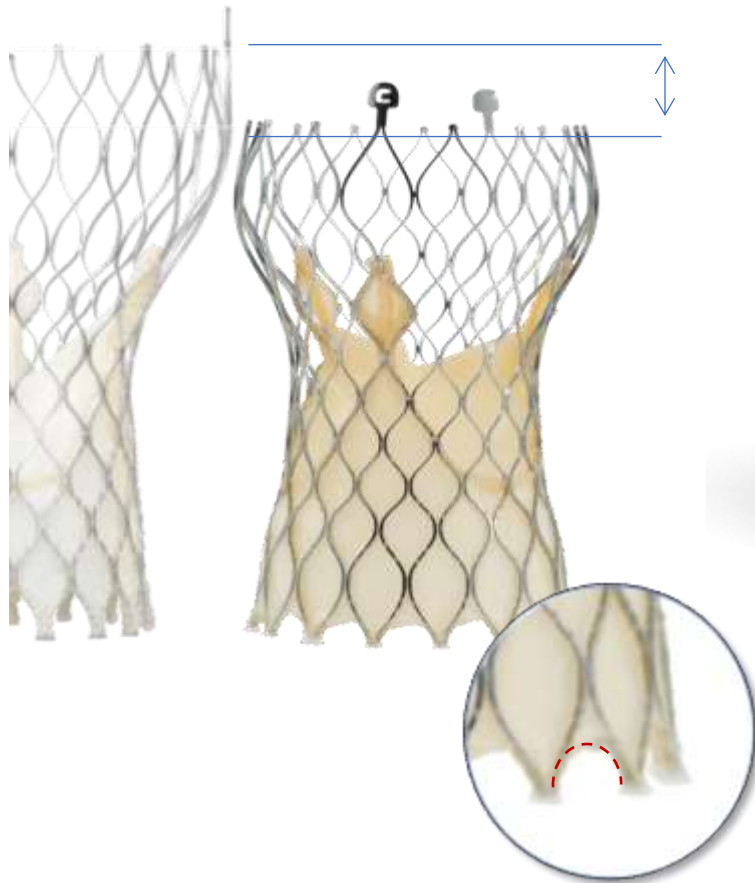
***Future
Contenders?***

- (D. onik)
- (Var, Meril Lifescience)
- HLT Meridian
- NVT (Nautilus)
- Xeltis
- Zurich TEHV

Current “Standards” for TAVR

MDT Evolut R (PRO)

Edwards Sapien 3/Ultra



“Next in Line” for TAVR

LOTUS (Edge)



ACURATE neo



PORTICO



“Rebooting” or Increasing Momentum

JENA Valve



CENTERA



VENUS A Valve



Lifetime Management

TAV-in-SAV and TAV-in-TAV

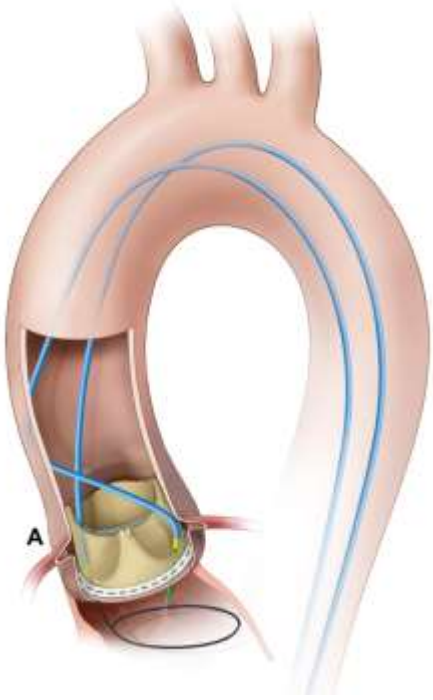
With both SAVR and TAVR bioprosthetic valves being implanted in younger patients, the need for transcatheter therapies to treat failing valves is well recognized.

New techniques and technologies are currently being developed to facilitate TAV-in-SAV and TAV-in-TAV procedures.

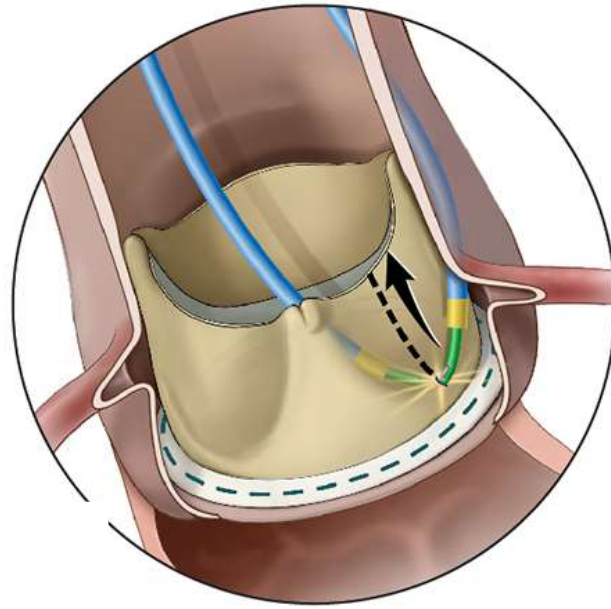
Lifetime Management

New Technique for Valve-in-Valve | **BASILICA**

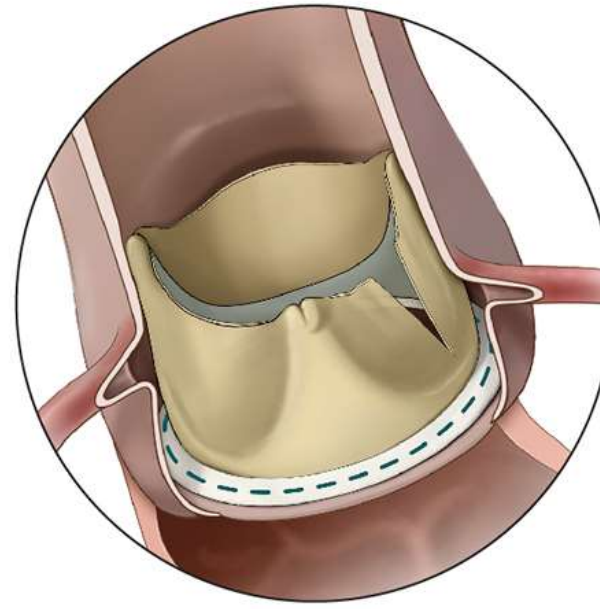
The BASILICA technique may help reduce coronary obstruction post valve-in-valve



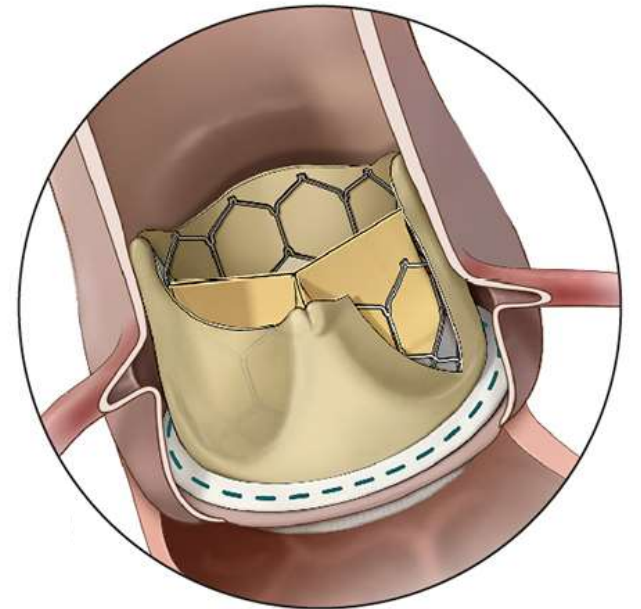
Leaflet wire traversal
and snaring



Leaflet slicing



Sliced leaflet

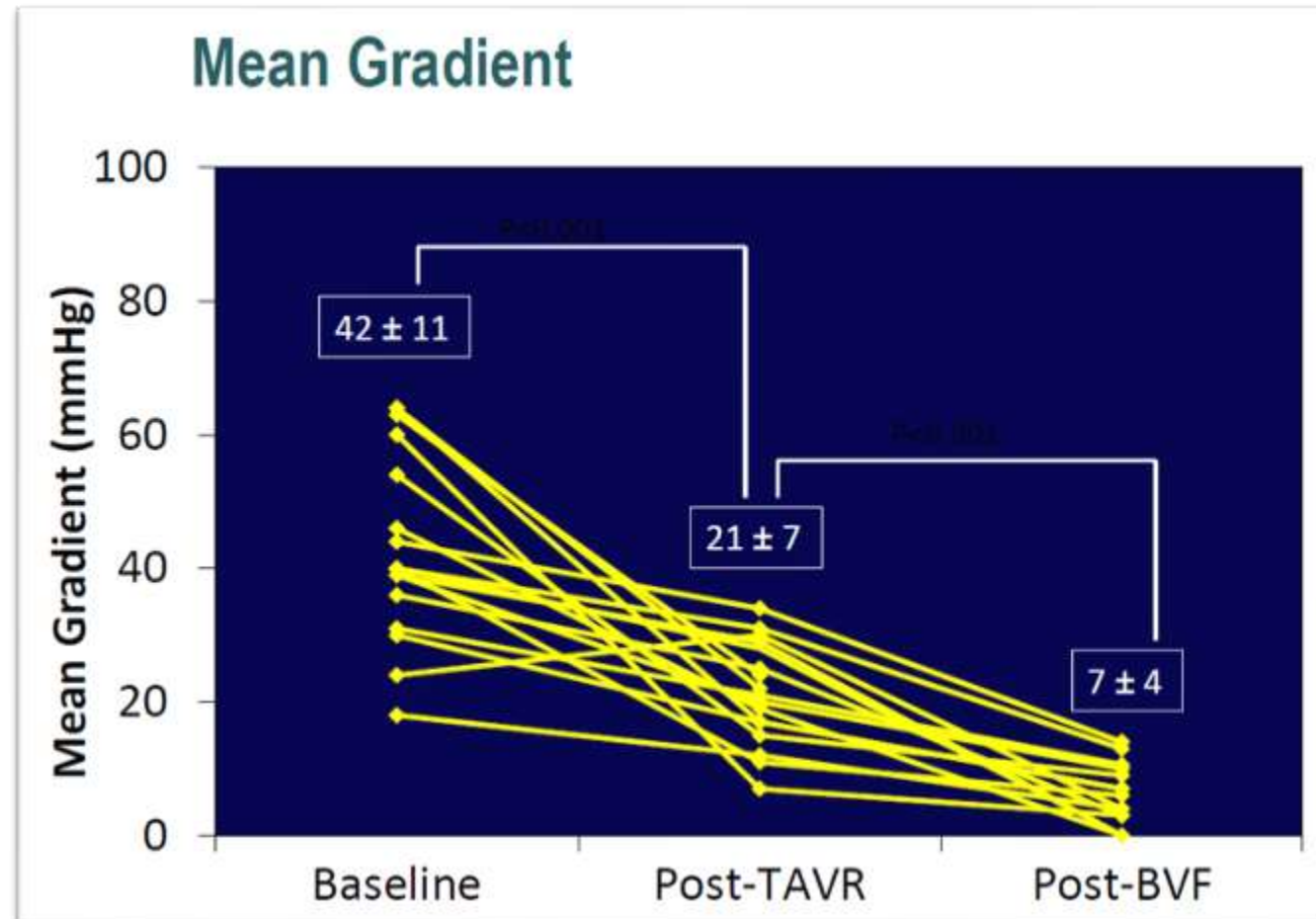
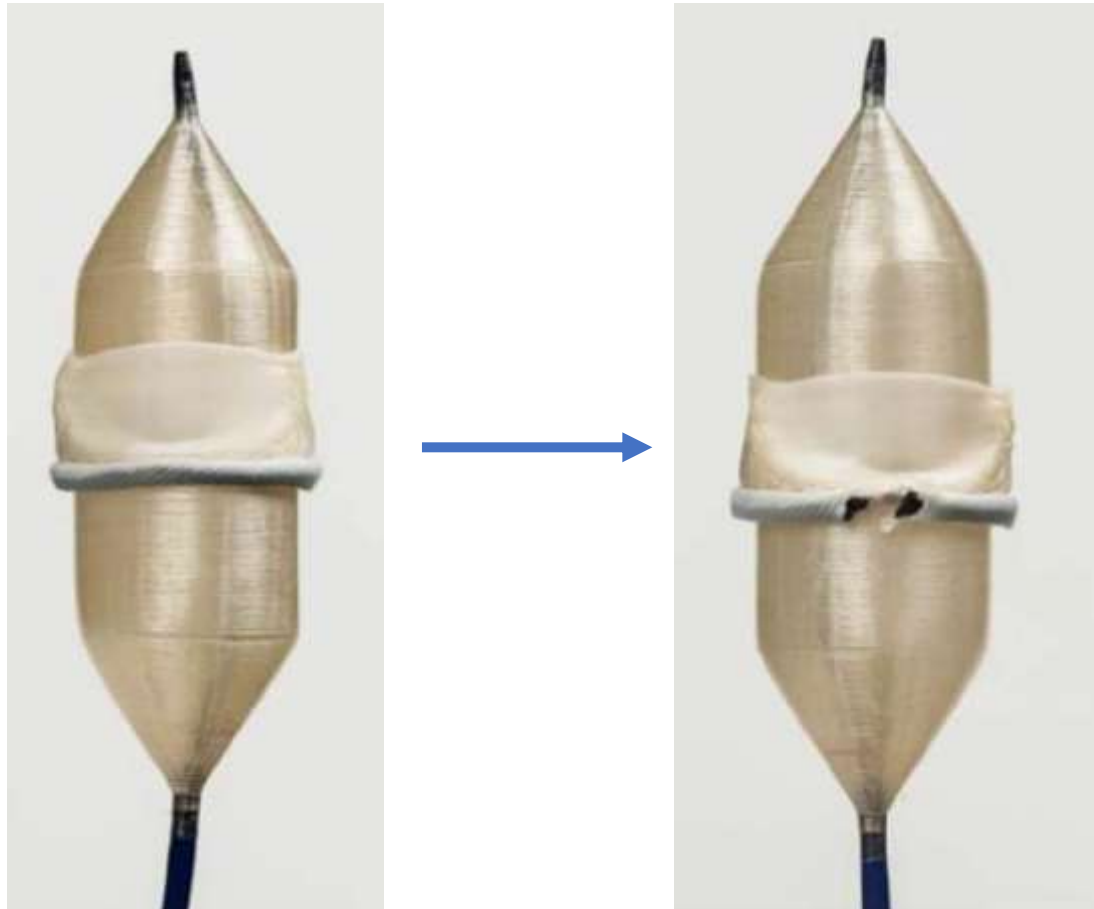


Valve-in-Valve

Lifetime Management

New Technique for Valve-in-Valve | *Valve Cracking*

Using balloon dilation to fracture the ring of surgical valves may be a useful technique in patients with small valves to improve gradients post valve-in-valve procedure.



TAVR Device Selection

Durability Current State

In 2018, there were much needed advances in providing standard definitions of valve failure and valve surveillance.

The ESC/EATCS/EAPCI provided a consensus statement aiming to level the playing field between TAVR studies as well as with SAVR trials which will allow a better understanding of TAVR durability (as well as SAVR durability).

Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Davide Capodanno^{1*†}, Anna S. Petronio^{2†}, Bernard Prendergast³, Helene Eltchaninoff⁴, Alec Vahanian⁵, Thomas Modine⁶, Patrizio Lancellotti⁷, Lars Sondergaard⁸, Peter F. Ludman⁹, Corrado Tamburino¹, Nicolò Piazza¹⁰, Jane Hancock³, Julinda Mehilli¹¹, Robert A. Byrne¹², Andreas Baumbach¹³, Arie Pieter Kappetein¹⁴, Stephan Windecker¹⁵, Jeroen Bax¹⁶, and Michael Haude¹⁷

TAVR Device Selection

Durability Current State

The consensus statement made important distinctions of bioprosthetic valve dysfunction (BVD) between structural valve deterioration (SVD), non-structural valve deterioration (NSVD), thrombosis, and endocarditis

These definitions will be included into the upcoming VARC 3 Update

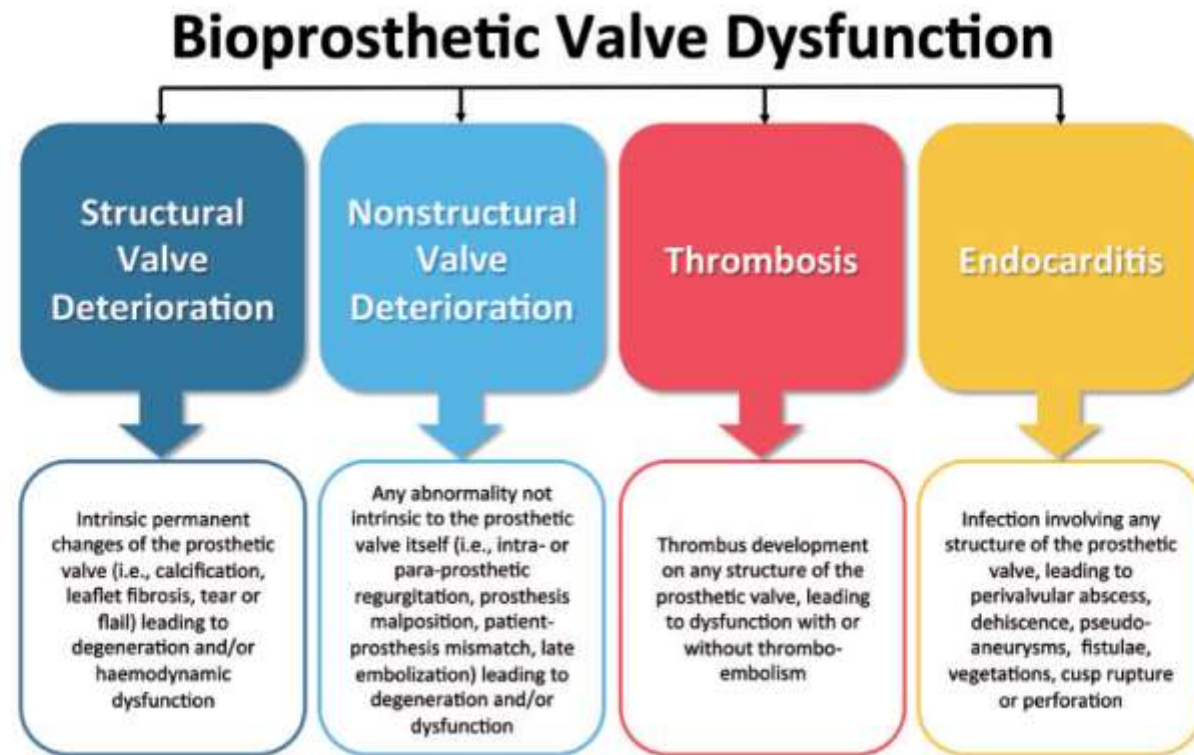


Figure 1: Causes of bioprosthetic valve dysfunction.

TAVR Device Selection

Durability Evidence

Durability definitions from the new consensus statement have been applied to six studies analyzing long-term data in a real-world setting, with more studies coming in 2019

TAVR durability in studies with the new definitions has been promising with low rates of both SVD and BVF

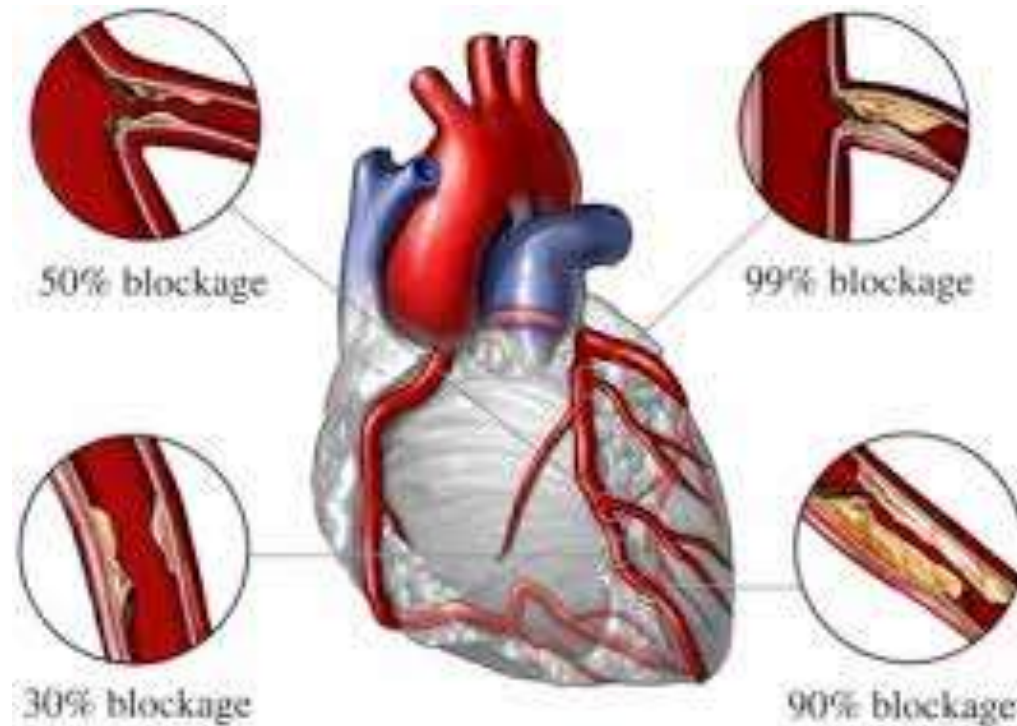
Study	N	Valve	Follow-up	Survival*	Severe SVD	BVF
Sondergaard et al.	280	CoreValve	6 years	57.5%	0.7%	7.5%***
Deutsch et al.	300	Various	7 years	23.2%	- **	3.7%
Eltchaninoff et al.	378	Various BE	8 years	9.6%	3.2%	0.6%***
Barbanti et al.	288	Various	8 years	29.8%	5.9%	4.5%***
Holy et al.	152	CoreValve	8 years	27.0%	0%	4.5%***
Sokoloff et al.	589	Various	10 years	8%	8.0%	3.4%***
*Actuarial analysis ** 14.3% moderate or severe SVD (cumulative incidence function) ***Actual analysis (cumulative incidence function)					~0-8%	~1-8%

Abbreviations: BE, balloon-expandable

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.



Lifetime Management

Coronary Artery Disease | PCI after TAVR

Today, studies have shown coronary access post-TAVR is possible in the majority of cases

	Kerckhoff-Klinik	Segeberg Registry	UK Registry	TAVR-LM Registry
Incidence	35 / 1,000 (3.5%)	17 / 296 (5.7%)	18 / 2,588 (0.7%)	9 / 6,405 (0.1%)
ACS Indication	11.4%	37.5%	65%	78%
Time to Intervention Post-TAVI	233 ± 158 days	17.7 months (range: 1-72)	136 days (range: 1-1092)	368 days (IQR: 204-534)
Type of TAV Implanted			Not Reported	
CoreValve	29%	100%		44%
SAPIEN XT	54%			55%
JenaValve	3%			
Symetis	11%			
Portico	3%			
Procedural Success	74%	95.8%	Not Reported	100%

¹Blumenstein, et al., *Clin Res Cardiol* 2015; 104:632-39; ²Allali, et al., *Cardiovasc Revasc Med* 2016; epub ahead of print; ³Snow, et al., *Int J Cardiol* 2015; 199:253-60;

⁴Chakravarty, et al., *J Am Coll Cardiol* 2016; 67:951-60

#4: TAVR pharmacology will be optimized



Lifetime Management

Anticoagulation | Valve Thrombosis

Valve thrombosis has come to the forefront with studies reporting

- Reduced leaflet motion in 22 of 55 (40%) patients analyzed from the PORTICO IDE Cohort (16 of 37 (40%) Portico patients, 6 of 14 (43%) Sapien XT patients, and 0 of 4 (0%) CoreValve patients).
- In the pooled RESOLVE and SAVORY registry patients, ***reduced leaflet motion in 14% of TAVR patients and 7% of SAVR patients***

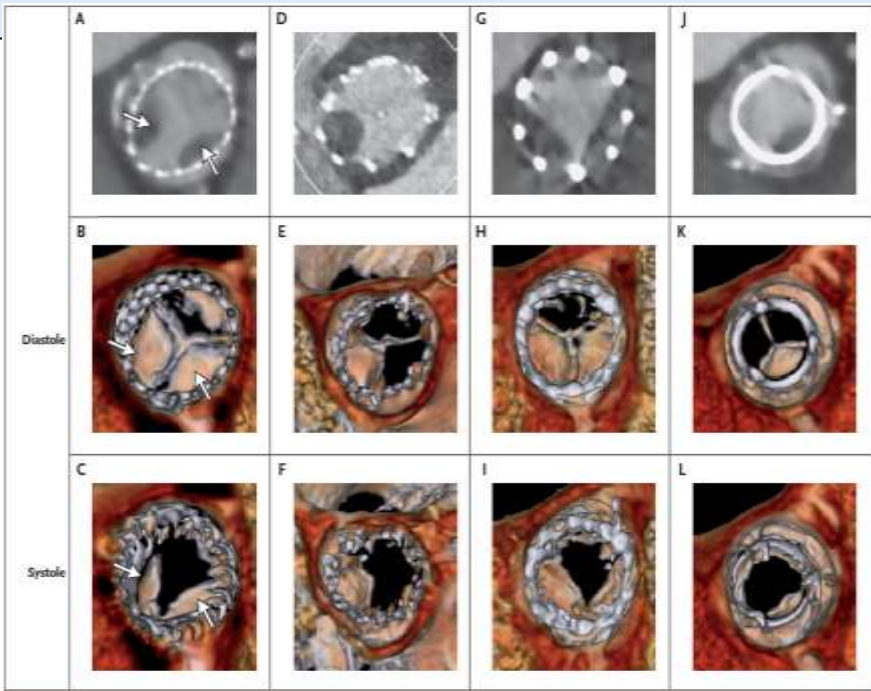
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Possible Subclinical Leaflet Thrombosis
in Bioprosthetic Aortic Valves

R.R. Makkar, G. Fontana, H. Jilaihawi, T. Chakravarty, K.F. Kofoed, O. De Backer, F.M. Asch, C.E. Ruiz, N.T. Olsen, A. Trento, J. Friedman, D. Berman, W. Cheng, M. Kashif, V. Jelnin, C.A. Kliger, H. Guo, A.D. Pichard, N.J. Weissman, S. Kapadia, E. Manasse, D.L. Bhatt, M.B. Leon, and L. Søndergaard

ABSTRACT



¹Makkar, et al., *N Engl J Med*. 2015 Nov 19;373(21):2015-24

Lifetime Management

Anticoagulation

Current clinical antithrombotic therapy post-TAVR is mostly empirical and practice variation is quite high. Clinical trials are currently underway and will bring clarity and guidance on this important topic.

Post TAVR Implant strategy will change and Anticoagulation will probably be recommended

	No indication to OAT	Indication to OAT
1. Studies of antiplatelet strategies	<div>ARTE (NCT01559298) ASA vs. DAPT</div> <div>POPular TAVI (NCT02247128) ASA vs. DAPT</div> <div>CLOE (Announced) ASA vs. DAPT</div>	<div>AVATAR (NCT02735902) ASA+VKA vs. no VKA</div> <div>POPular TAVI (NCT02247128) Clopidogrel+VKA vs. VKA</div> <div>CLOE (Announced) Clopidogrel+VKA vs. VKA</div>
2. Studies of antiplatelet vs. anticoagulant strategies	<div>AUREA (NCT01642134) DAPT vs. VKA</div> <div>GALILEO (NCT02556203) Rivaroxaban + ASA vs. DAPT</div> <div>ATLANTIS (NCT02664649) Apixaban vs. Aspirin or DAPT</div>	
3. Studies of anticoagulant strategies		<div>ATLANTIS (NCT02664649) Apixaban vs. VKA</div> <div>ENVISAGE TAVI (NCT02943785) Edoxaban* vs. VKA*</div>

¹Capodanno, et al., presented at London Valves 2017

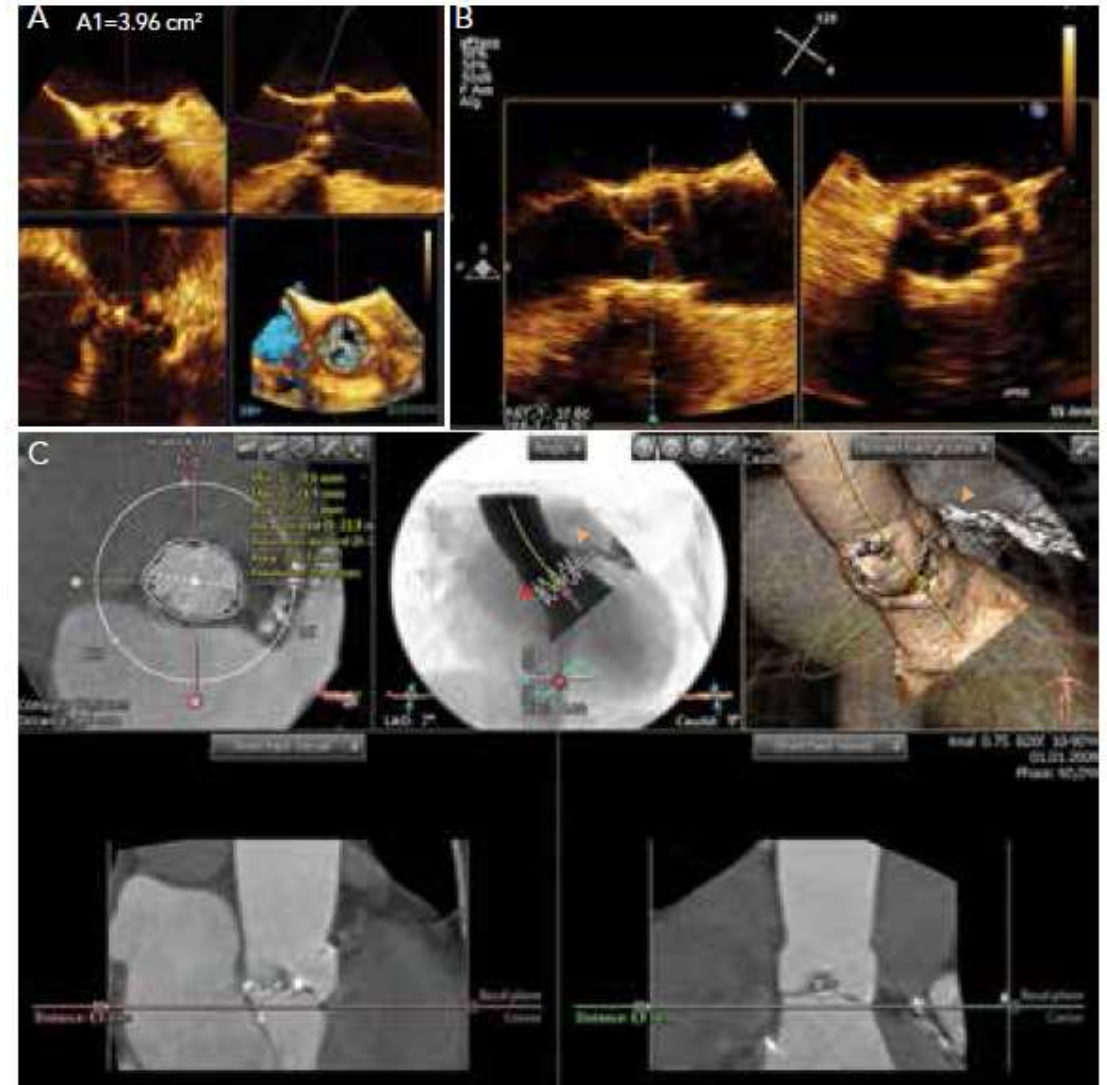
#5:

A disease state continuum of care will emerge



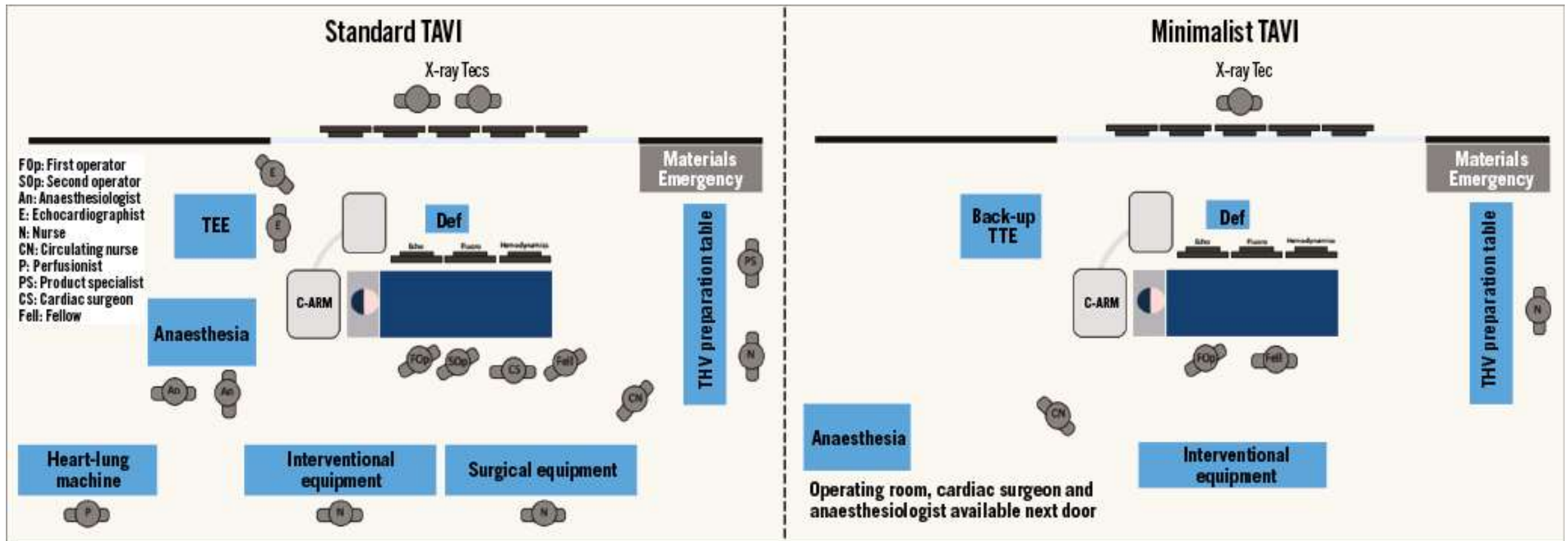
Diagnosis

In the next decade, TAVR will see an improvement in diagnostic capabilities and an enhanced ability to identify pre-existing conditions. This will allow for earlier diagnosis with a positive impact on prognosis.



Procedure

The next decade will see optimization of the TAVR procedure and lower resource utilization making the procedure more efficient and economical.



Post-acute

Innovations in monitoring of arrhythmic disorders and heart failure will lead to faster diagnoses and better post-care management

Reveal LINQ Implantable Monitor



CardioMEMS Heart Failure System



SEEQ Mobile Telemetry



LifeWatch Mobile Telemetry

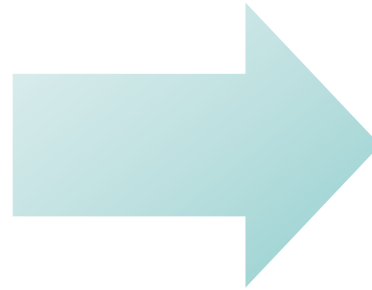


Grey Heart Failure Monitoring Device



Post-discharge

Longer-term management of TAVR patients will improve with the ability to monitor patients from home with minimal disruption to their daily lives. This technology, along with improved home care pathways, will allow a greater number of patients to discharge to home.



TAVR Journey - 2019



Final Thoughts

TAVR Revolution - 2019

The Future....

- There are still '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!