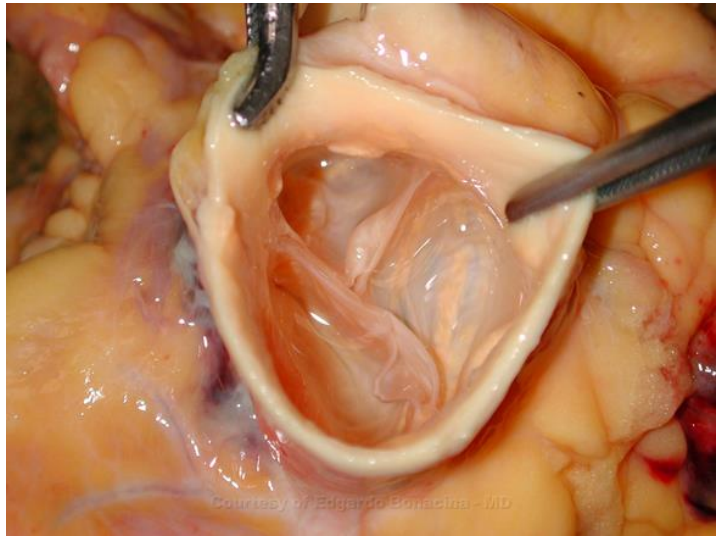
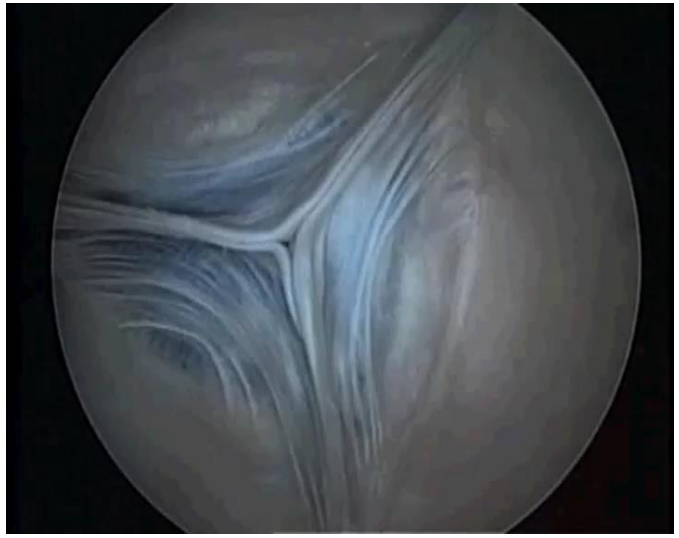
Are mechanical valves still useful in aortic position at the VIV era?

Pr Thierry Folliguet, MD, FACS, FESC
CHU Henri MONDOR ,
Assistance Publique, Hôpitaux de Paris
Créteil (94)
thierry.folliguet@aphp.fr

Ideal Prosthesis

Ideal valvular substitutes should have the same property than native valve





Bioprosthesis and Mechanical Valves

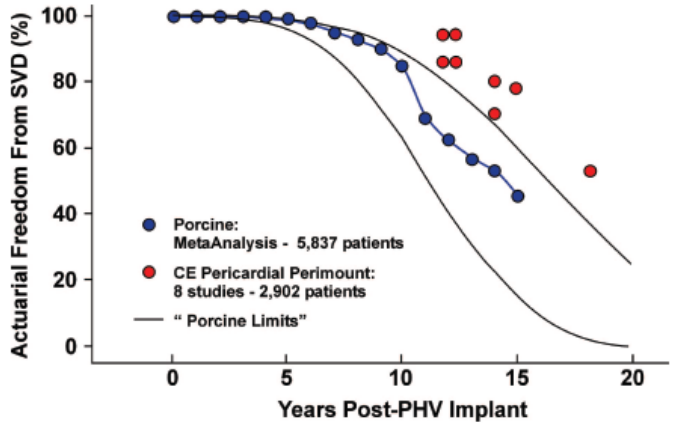


Figure 3. Porcine limits (black line) are the limits of SVD of earlier-model stented porcine bioprosthesis. Porcine (blue circles) is from a meta-analysis of later-model stented porcine bioprosthesis. Carpentier-Edwards is from studies of C-E pericardial Perimount valves (red circles). SVD indicates structural valve deterioration; CE, Carpentier-Edwards; and PHV, prosthetic heart valve. Reproduced from Rahimtoola et al[1] with permission of the publisher. Copyright © 2008, Elsevier.

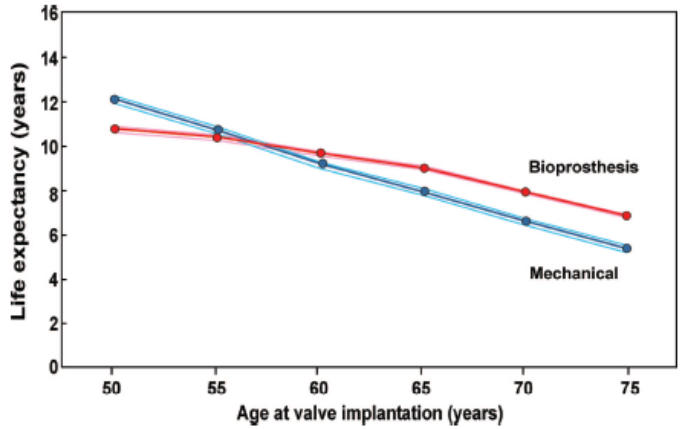
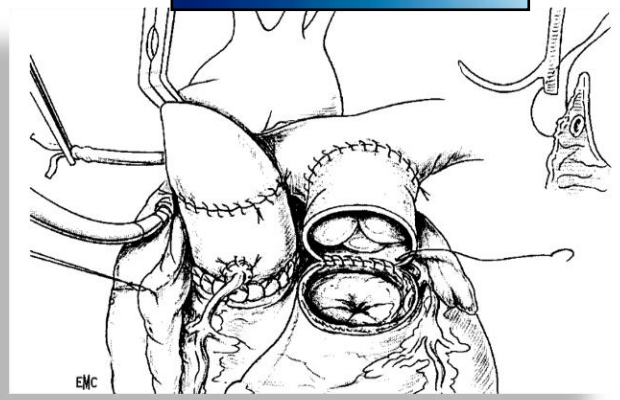


Figure 2. Event-free life expectancy after aortic valve replacement in the United States. Mean and 68% upper and lower confidence limits are shown. Adapted from van Geldorp et al[8] with permission of the publisher. Copyright © 2009, Elsevier.

Ross vs MV vs BP
(n=109 FU 8 years)

	VM	VB	AG
Thromboembolism	3.0	2.5	0
Thrombosed valve	0.8	0.2	0
Bleeding	3.5	1.4	0
Aortic insufficiency	1.2	1.2	0.7
Endocarditis	1.2	1.2	0.7



Does the Ross operation fulfill the objective performance criteria established for new prosthetic heart valves?

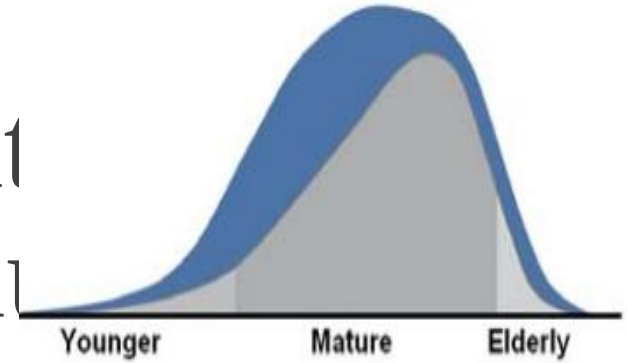
R Moidl. The Journal of Heart Valve Disease 2000;9:190-194

Expanding heart valve opportunity

Aging global populations in developed markets

Expanding tissue valve segment:

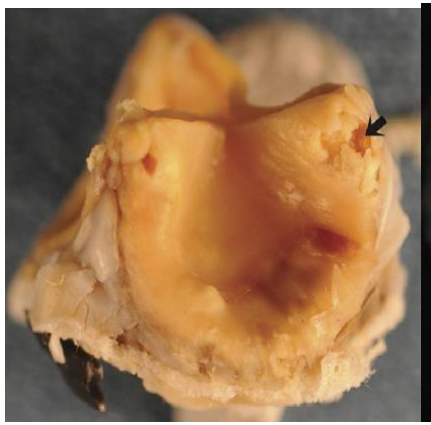
- Addressing younger patient innovative tissue valve solu
- Growing incomes drive adc tissue valves in emerging r

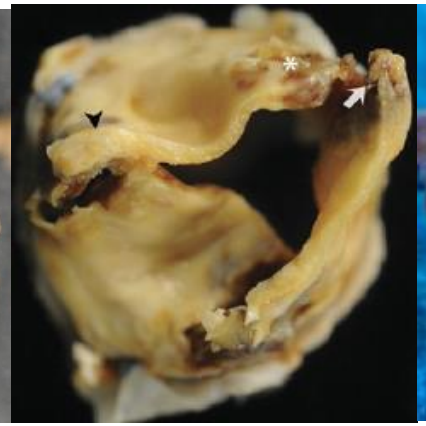


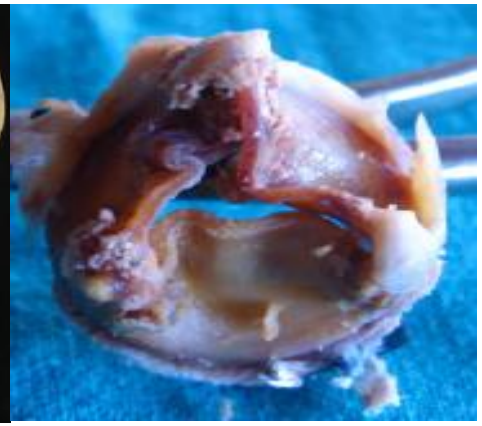
SJM Trifecta valve

Current bioprosthetic valves are not recommended for patients younger than 60 years of age who require aortic valve replacement.

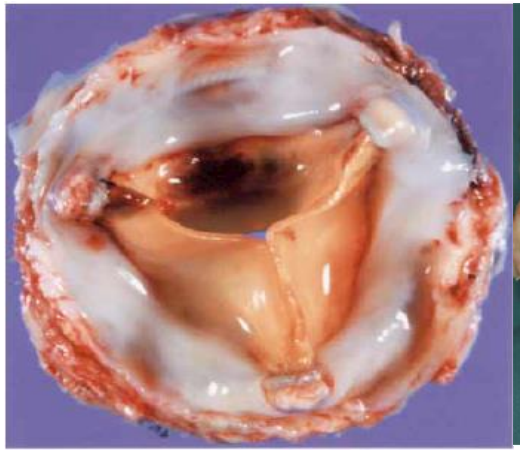
Sorin Mitroflow valves

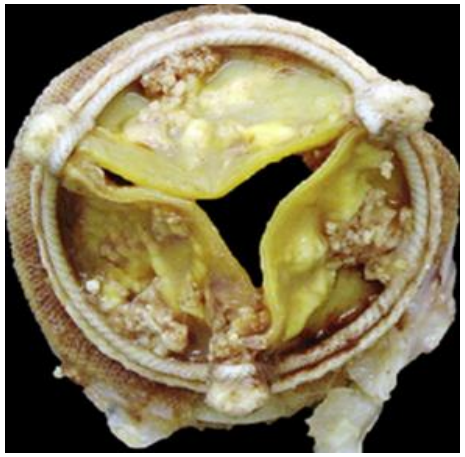






Carpentier-Edwards valves





2017 AHA/ACC Guidelines

- Options for aortic heart valves for tissue and mechanical.

Tissue Valves

- Perception versus reality, tissue valves

3) Transcatheter Valve in Valve (VIV)

- Perception versus reality of VIV as a long-term durable option

4) Mechanical Valves

- Perception versus reality for mechanical heart valves in younger patients

Recommendations for prosthetic valve selection		
Mechanical prostheses		
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications to long-term anticoagulation.	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated SVD.	I	C
Biological prostheses		
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good-quality anticoagulation is unlikely (adherence problems, not readily available), contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, adherence problems, lifestyle, occupation), and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis.	I	C
A bioprosthesis is recommended in case of reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I	C

Section 5. Recommended mode of intervention In patients with aortic stenosis				
Revised	The choice for intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality. In addition, the local expertise and outcomes data for the given intervention must be taken into account.	I	The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.	I
Revised	SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II <4% or logistic EuroSCORE I <10%, and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation).	I	SAVR is recommended in younger patients who are low risk for surgery (<75 years and STS-PROM/ EuroSCORE II <4%) or in patients who are operable and unsuitable for transfemoral TAVI.	I
Revised	TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team.	I	TAVI is recommended in older patients (≥75 years), or in those who are high-risk (STS-PROM/ EuroSCORE II >8%) or unsuitable for surgery.	I
Revised	In patients who are at increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10%, or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI being favoured in elderly patients suitable for transfemoral access.	I	SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical and procedural characteristics.	I
New			Non-transfemoral TAVI may be considered in patients who are inoperable for SAVR and unsuitable for transfemoral TAVI.	IIb

2017 AHA/ACC Guidelines (most recent update)

All Other Aortic Mechanical Valve Anticoagulation

Patients with bileaflet aortic valves:

INR of 2.5 (between 2.0 and 3.0) in patients with no risk of TE

"…Provides a reasonable balance [of risks]"

Patients with higher thromboembolic risk:

INR of 3.0 (between 2.5 and 3.5)

AF, previous thromboembolism, hypercoagulable state, severe LV dysfunction

All patients with mechanical valves:

75-100 mg Aspirin daily is recommended

unless contraindicated

2017 AHA/ACC Guidelines (most recent update)

Bioprosthetic Valve Anticoagulation

Patients with bioprosthetic aortic valves:

May eventually require life-long anticoagulation and there is an increased risk of ischemic stroke early after operation, particularly in the first 90 to 180 days after operation with bioprosthetic AVR.[1]

Patients with low risk of bleeding:

To avoid higher-than-recognized incidence of leaflet thrombosis, an INR target of 2.5 (range 2.0 – 3.0) may be reasonable for at least 3 and as long as 6 months after bioprosthetic AVR.[1]

All patients with bioprosthetic valves:

75-100 mg Aspirin daily is recommended unless contraindicated[1]

The Dilemma

Valve Selection: Open Surgical

Mechanical Valves

- **Pros:**
  Likely lifetime durability
- **Cons:**
  Anticoagulation,
  elevated bleeding risk

Tissue Valves

- **Pros:**
  No anticoagulation for most patients
- **Cons:**
  Structural valve deterioration, increasing risk for reintervention over time, accelerated in young pts.

2017 AHA/ACC Guidelines

Valve selection: Patient age considerations

Mechanical

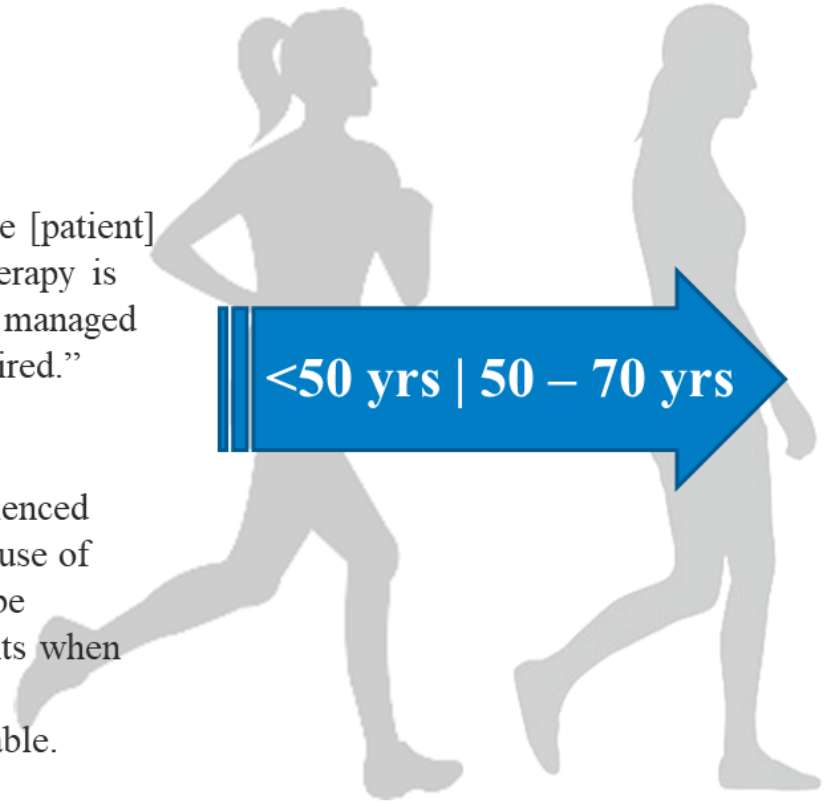
- Favored Choice

Bioprosthetic

- Recommended for "any age [patient] for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired."

Ross Procedure

- When performed by experienced surgeon, the less common use of pulmonary autograft may be considered in young patients when VKA anticoagulation is contraindicated or undesirable.



Mechanical or Bioprosthetic

- "…it is reasonable to individualize the choice of either a mechanical or bioprosthetic valve prosthesis on the basis of individual patient factors and preferences, after full discussion of the trade-offs involved."[1]

Nishimura R et al., 2017 AHA/ACC Guidelines. Circulation. 2017;135:e1159–e1195.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement

Andrew B. Goldstone, M.D., Ph.D., Peter Chiu, M.D., Michael Baiocchi, Ph.D., Bharathi Lingala, Ph.D., William L. Patrick, M.D., Michael P. Fischbein, M.D., Ph.D., and Y. Joseph Woo, M.D.

N Engl J Med 377;19 nejm.org November 9, 2017

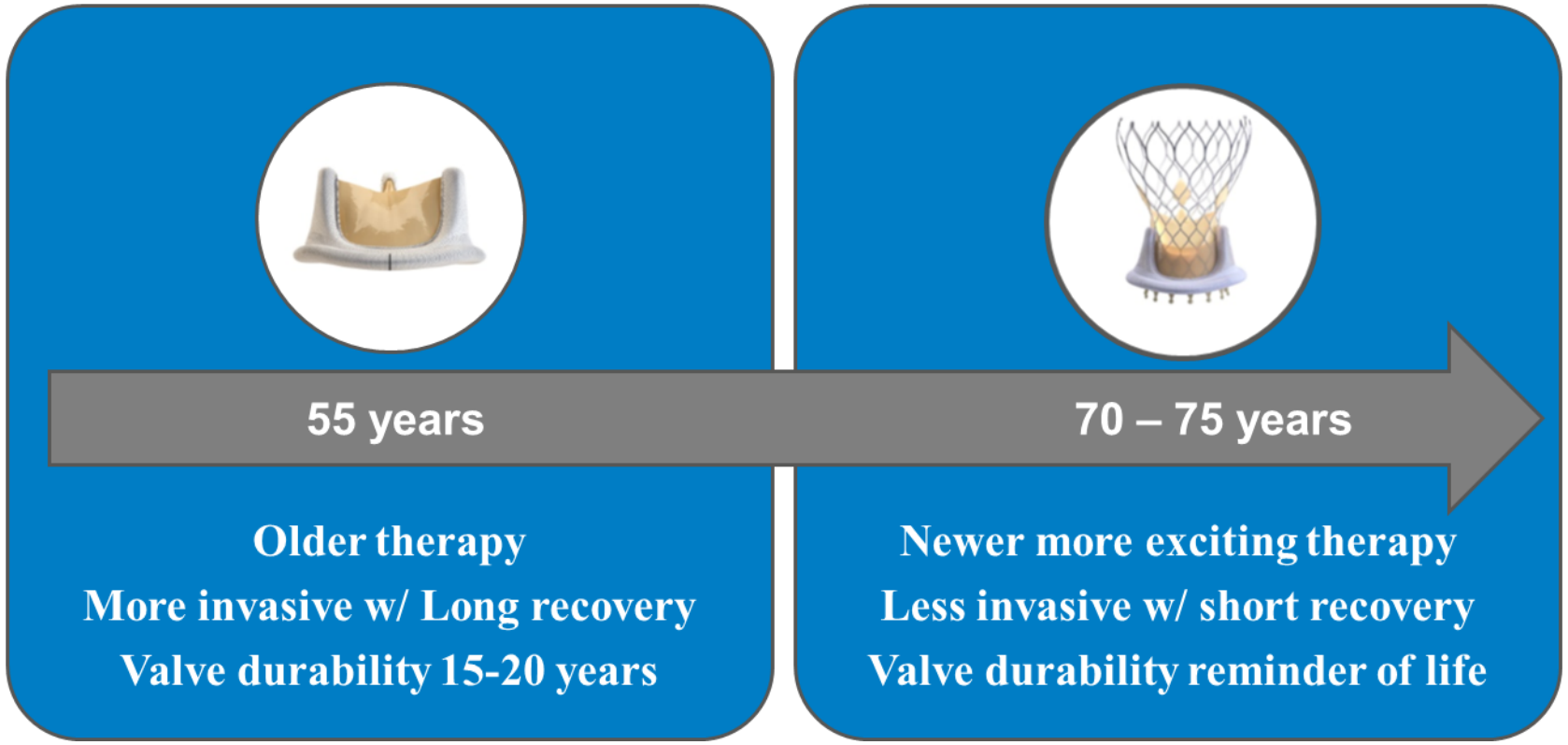
Survival advantage after Mechanical Valve Replacement

CONCLUSIONS

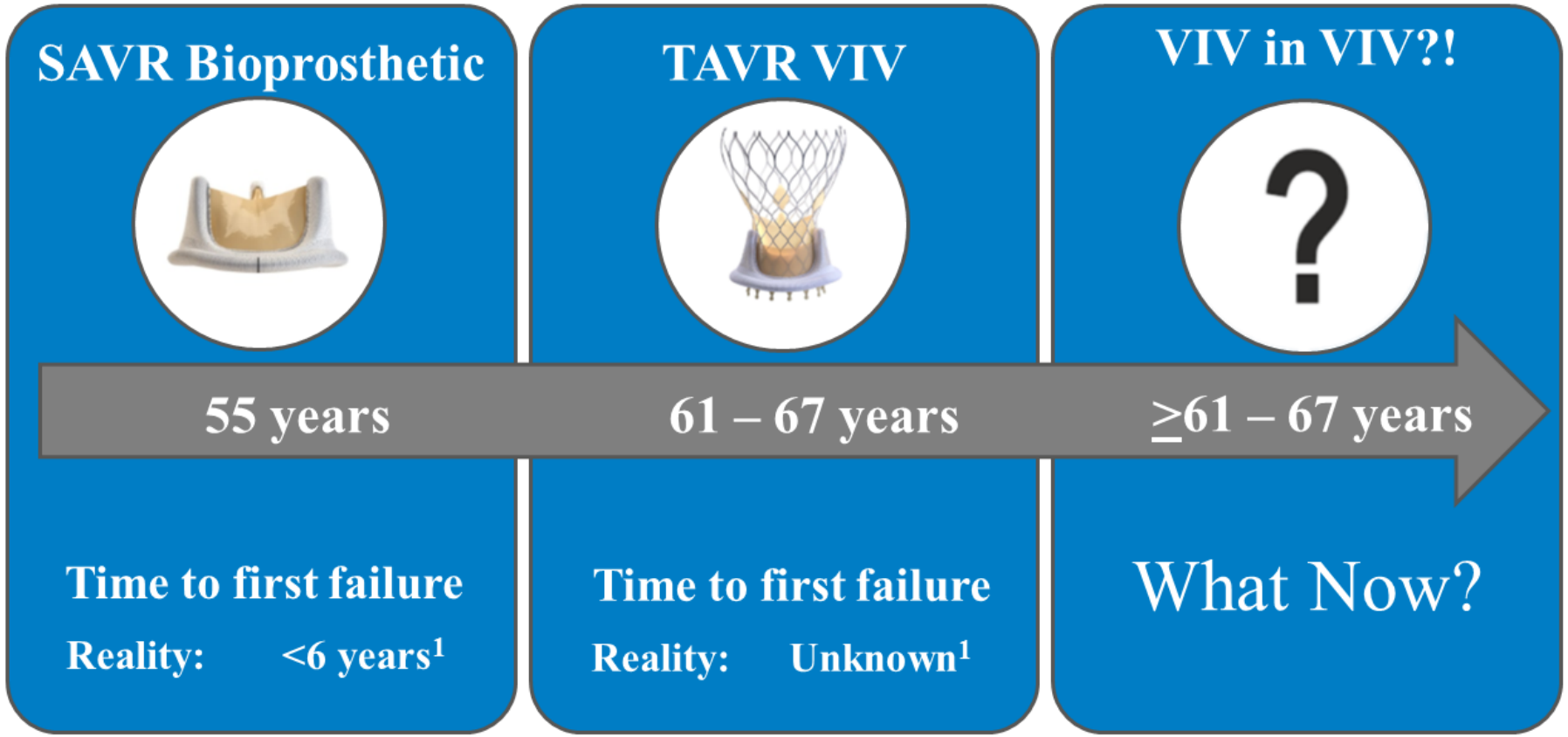
The long-term mortality benefit that was associated with a mechanical prosthesis, as compared with a biologic prosthesis, persisted until 70 years of age among patients undergoing mitral-valve replacement and until 55 years of age among those undergoing aortic-valve replacement. (Funded by the National Institutes of Health and the Agency for Healthcare Research and Quality.)

California statewide data base- 9,900 AVR, 15,000 MVR

What does the 55 year old patient hear??



What the 55 year old patient <u>should</u> know:

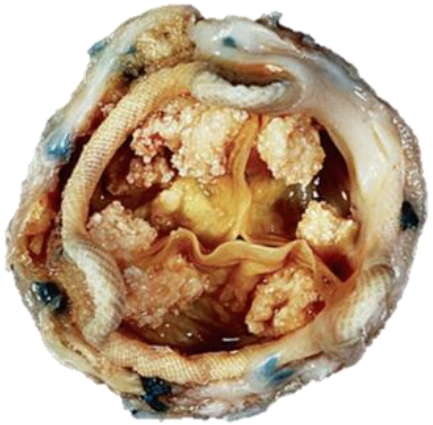


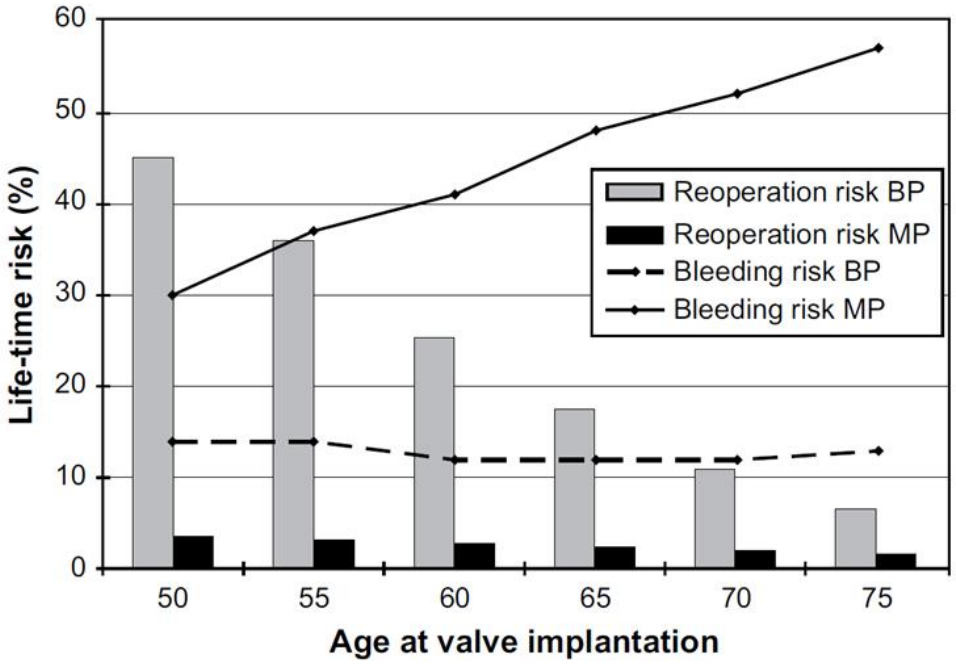
Time since last SAVR for VIV, median (IQR), yrs.: 9 (6-12)

Risk of Reoperation

Bioprosthetic vs. Mechanical Aortic Valves

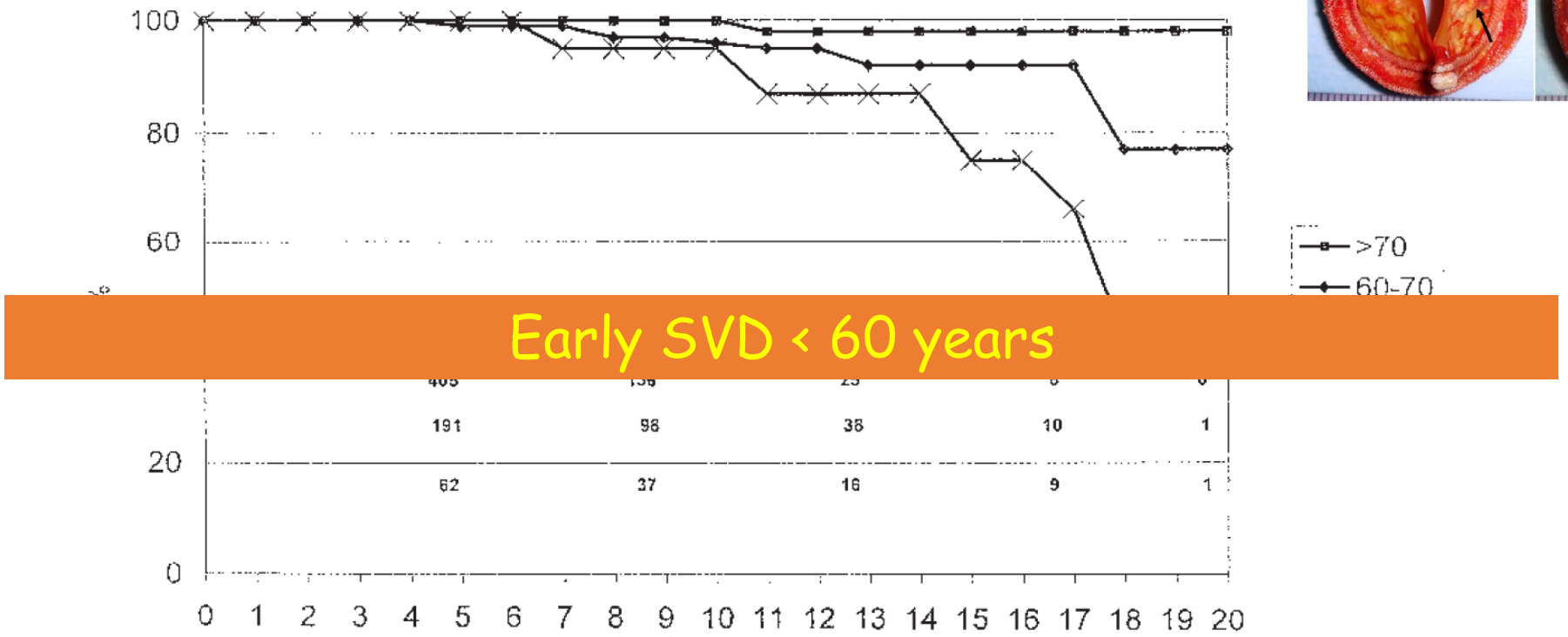
For 55 year old patients, risk of needing reoperation is ~10x higher than mechanical valves.





van Geldorp M et al., J Thorac Cardiovasc Surg. 2009;137:881-6.

Is Age a limitant factor for Bioprosthesis implantation? Yes



Early SVD < 60 years

Aupart M et al.
Perimount Pericardial Bioprosthesis for Aortic Calcified Stenosis: 18-Year Experience with 1,133 Patients - *The Journal of Heart Valve Disease 2006;15:768-776*

Longevity of Bioprosthetic Valves

Patients 50-65 years

Perception: 20 year valve durability

Reality:

- Mean time to SVD was 13±5 years
- Risk of Reoperation due to SVD
  - ~10% at 10 years
  - ~25% at 15 years
  - ~50% by 20 years
- Only 3% of population reach 20 years

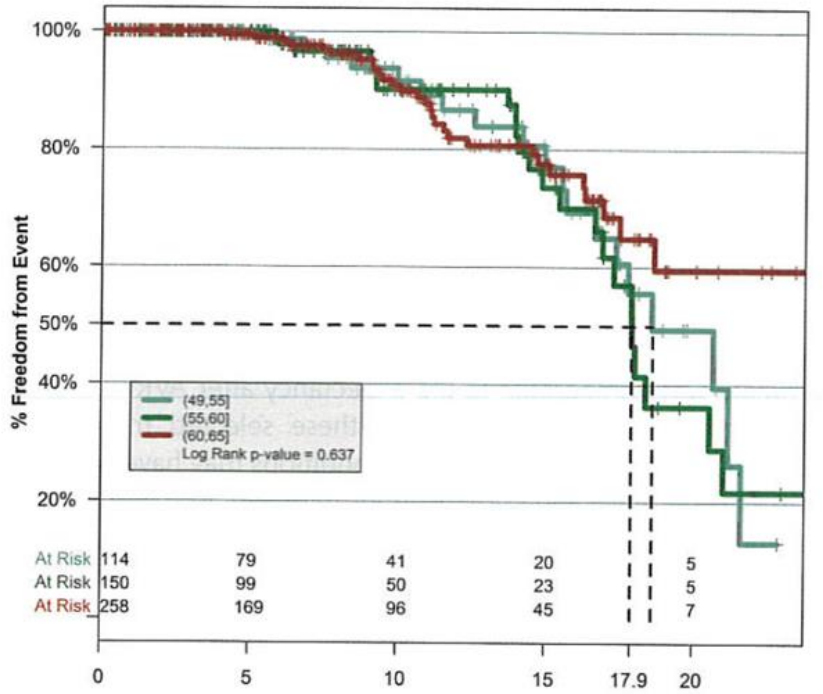


Figure 4: Kaplan–Meier estimates of freedom from reoperation due to structural valve deterioration (SVD) by age group. Age was not a significant risk factor among this age subgroup. SVD: structural valve deterioration.

Bourguignon T et al., Eur J Cardiothorac Surg. 2016;1462-8.

Longevity of Bioprosthetic Valves

Patients <65 years

Perception:
"Excellent long-term durability has previously been reported when using the CE pericardial valve at select institutions, and our experience reaffirms these findings."

Reality:

- Patients <65 years start to receive explants at 7 years
- Limited long-term data on <65 years patients (6 patients at 12.5 years)
- Freedom from reoperation for SVD at 12.5 years was:
  - 34.7% for patients <65 years
  - 89.4% for patients 65 to 75 years
  - 99.5% for patients >75 years

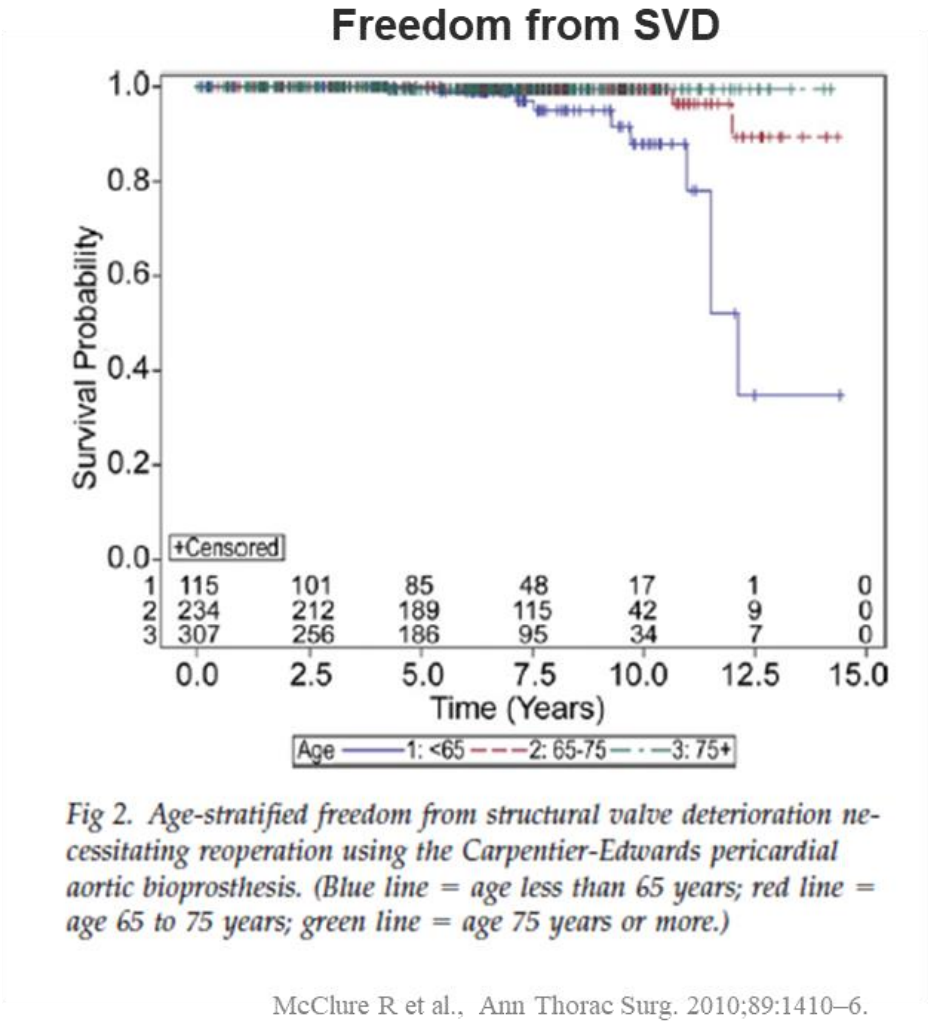


Fig 2. Age-stratified freedom from structural valve deterioration necessitating reoperation using the Carpentier-Edwards pericardial aortic bioprosthesis. (Blue line = age less than 65 years; red line = age 65 to 75 years; green line = age 75 years or more.)

McClure R et al., Ann Thorac Surg. 2010;89:1410–6.

Full Disclosure

Young Patients Who Choose a Tissue Valve

"Some otherwise healthy young patients may choose a bioprosthesis to avoid anticoagulation with warfarin, but this decision should be made with the full understanding that:

- the choice may increase late mortality,
- oral anticoagulation may be necessary in the future,
- subsequent management of prosthesis failure with transcatheter valve-in-valve insertion is an attractive but unproven long-term strategy."

Anticoagulation

VIV Unproven

Suri R and Schaff H. Circulation. 2013;128:1372-80.

Life Expectancy & Heart Valve Choice

Age Dependent

Perception: For heart valve patients <60yrs, bioprosthetic aortic valve durability exceeds life expectancy.

Reality: Life expectancy for heart valve patients <60yrs is 15 – 19 years, however the mean time to reoperation due to SVD for a bioprosthetic aortic valve is 13±5 years with explants occurring as early as 6 years.

Heart Valve Patients by Age

Bourguignon T et al., Eur J Cardiothorac Surg. 2016;1462-8. van Geldorp M et al., J Thorac Cardiovasc Surg. 2009;137:881-6.

Bioprosthetic Valves in Patients ≤60 years

Perception:

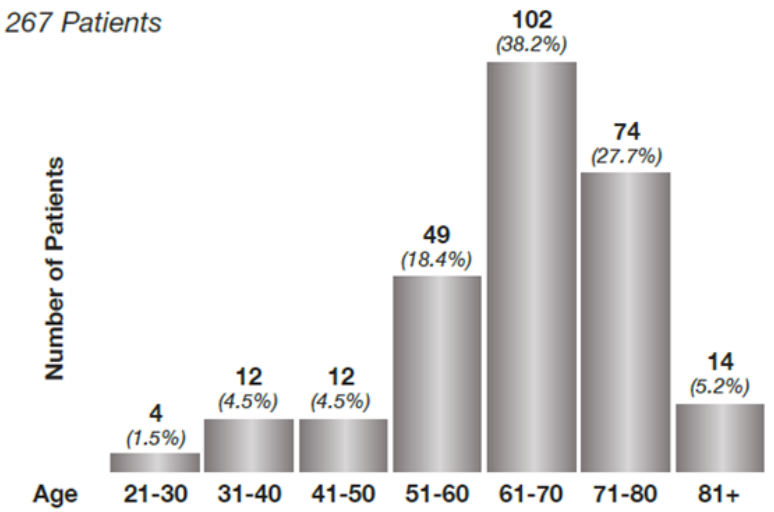
- 20 year valve durability for all ages

Reality:

- Durability data for patients ≤60 years is omitted

- All explanted valves due to SVD were adjudicated prior to being included/excluded from data

Figure 1: Age Distribution at Implant



Durability data omitted for these patients <60 years (28%)

Carpentier-Edwards PERIMOUNT Pericardial Aortic Bioprosthesis: 20 Year Results. http://www.edwards.com/devices/heart-valves/aortic-pericardial, downloaded on 09/27/2016.

Advancement of Anticalcification Treatment

Bioprosthetic Valves

Perception: New additions of various chemical treatments for bioprosthetic valves have significantly improve their longevity.

Reality: 'No long-term clinical data is available'

Edwards® RESILIA, PERIMOUNT

"No long-term clinical data are available that evaluate the impact of RESILIA or PERIMOUNT tissue valves in patients."[1,2]

Medtronic® Mosaic®

"*No clinical data* are available which evaluate the long-term impact of AOA® tissue treatment and the Physiologic Fixation process in patients."[3]

St. Jude Medical® Trifecta™

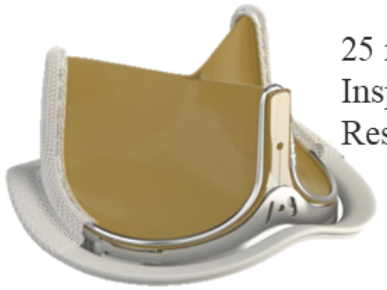
"There is *no clinical data* currently available that evaluates the long-term impact of anticalcification tissue treatment in humans."[4]

1. Edwards Lifesciences, Resilia Tissue. http://www.edwards.com/_layouts/Edwards.moss.web.webapp/resilia-eu/, downloaded on 12/08/2017.
2. Edwards Lifesciences website. http://www.edwards.com/devices/heart-valves/aortic, downloaded on 07/19/2016.
3. Medtronic website. http://www.medtronic.com/us-en/healthcare-professionals/products/cardiovascular/heart-valves-surgical/mosaic-mosaic-ultra-bioprostheses.html, downloaded on 07/26/16.
4. St. Jude Medical website. https://www.sjm.com/en/professionals/featured-products/structural-heart/tissue-heart-valves/aortic-and-mitral-valves/trifecta-valve, downloaded on 07/26/16.

Edwards' INSPIRIS RESILIA – VFit Technology

Perception:

- The need for future surgical reoperations due to SVD of bioprosthesis can be avoided with TAVR Valve-In-Valve (VIV).
- The INSPIRIS RESILIA VFit* SAVR allows the valve to be enlarged due to an expandable frame.



25 mm
Inspiris
Resilia

23 mm
Sapien XT

Reality: Safety, effectiveness, and long-term durability of expanding the frame of the INSPIRIS RESILIA for valve-in-valve procedures have not been established.

From Edward's website: *"These features have not been observed in clinical studies to establish the safety and effectiveness … for use in valve-in-valve."

Edwards Lifesciences, Resilia Tissue. http://www.edwards.com/_layouts/Edwards.moss.web.webapp/resilia-eu/, downloaded on 12/08/2017.

Bioprosthetic Valve: Restricted Leaflet Motion

Perception: Tissue valve leaflet thrombosis is rare.

Reality: 3D and 4D CT scans and TEE showed reduced tissue leaflet motion in 8-12% of SAVR & 10-40% TAVR tissue valves which may be related to thrombosis.[2]

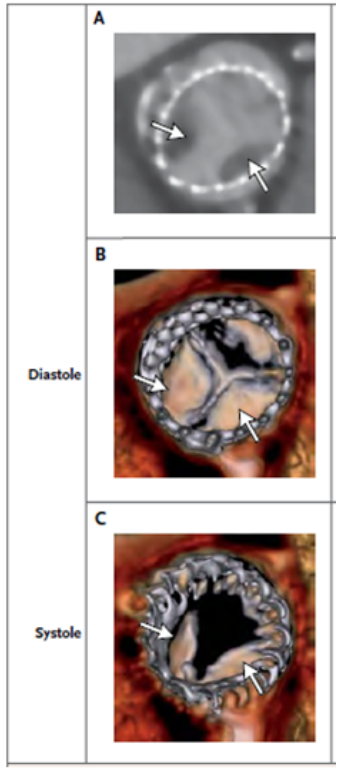
New FDA mandate: Two IDE trials for TAVR vs. SAVR in patients with low surgical risk include sub studies with 4D CT for thrombosis[3]

Considerations:

The potential for increased risks of:

- late neurologic events and myocardial infarction,
- unexplained heart failure or death,
- and early structural-valve deterioration."[1]

The Incidence of bioprosthetic valve thrombosis is likely underestimated given the higher detection rate with 4DCT [5]



"Evidence of Reduced Leaflet Motion in Multiple Prosthesis Types. Shown are hypoattenuating opacities on two-dimensional computed tomography (CT) (maximum intensity projection of gray-scale image) and volume-rendered CT (color images) for multiple prosthesis types, including the CoreValve (Panels A through C, arrows) [...]."[4]

1. Laschinger J et al., N Engl J Med. 2015; 373:1996-8. 2. FDA Notification about Bioprosthetic Aortic Valve Reduced Leaflet Motion, http://www.fda.gov/MedicalDevices/Safety/CDRHPostmarketSurveillance/ucm465417.htm, downloaded on 08/04/2016. 3. Mack M and Holmes D. J Thorac Cardiovasc Surg. 2016;152:952-3. 4. Makkar R et al., N Engl J Med. 2015; 373:2015-24. 5. Basra S. et al., Clinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Aortic Valves by 4DCT. Annals of Thoracic Surgery, August 2018, in press.

Tissue Valve Thrombosis and Valvular Dysfunction[1,2]

Perception: It has been estimated that bioprosthetic valve thrombosis (BPVT) incidence is 1%.

Reality: The true incidence is unknown, as is the time of its occurrence.

Expert Opinion and Recommendations:

- "The presence of thrombus on bioprosthetic valves, and not degeneration, [is what] causes valve dysfunction."
- Recommendation: "Prolonged anticoagulation after bioprosthetic valve implantation"
- More research is needed to diagnose, prevent, and treat patients with tissue valves to improve long-term outcomes and avoid redo surgery.

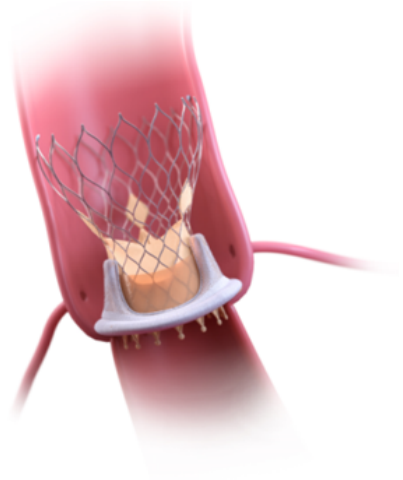
1. Egbe et al., J Thorac Cardiovasc Surg 2016;152:978-80.
2. Kirkner. Thor Surg News. Nov 2016;12:11:12-13.

2017 AHA/ACC Guidelines

TAVR Valve in Valve (VIV)

VIV is reasonable for the following patients:

- severely symptomatic, tissue AVR stenosis, high or prohibitive risk of reoperation, and whom improvement in hemodynamics is anticipated
  - which is "only in patients with larger-sized prosthesis."



Nishimura et al., 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159–e1195.

2017 AHA/ACC Guidelines – continued

Valve in Valve (VIV)

- **No Long Term Data** or extensive long-term follow-up of transcatheter valves [placed in a valve in valve procedure] is available.
- **Not all bioprostheses** are suitable for a future valve-in-valve procedure
- **VIV Requires** a smaller valve to be placed making PPM a potential problem
- **Root Enlargement** should be considered in patients with a small annulus to ensure that there is not an initial prosthesis patient mismatch
  - How often is a root enlargement performed by surgeons?

Nishimura et al., 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159–e1195.

Strategy for TAVR VIV

Reoperative SAVR Bioprosthetic

Perception: As *younger* patients' tissue valve wears out, a transcatheter VIV is a good option.

Reality: Transcatheter valve-in-valve (VIV) insertion is an attractive but unproven long-term strategy[1]

- **Primarily for high risk AVR patients, but targeting low/intermediate risk now**
- **Procedure includes several efficacy and safety concerns, such as:**
  - Elevated post-procedural **gradients** in the setting of small bioprostheses,
  - A high **malposition** rate in inexperienced hands […],
  - The potential for **coronary obstruction**."[2]
- **Additional considerations:**
  - Structural Valve Deterioration[4]
  - Paravalvular leaks[5]
  - Restricted Leaflet Motion[4]
  - Pacemaker implantation[5]

Asymmetric Degeneration 5 yrs after TAVI[3]

1. Suri R and Schaff H. Circulation. 2013;128:1372-80. 2. Dvir D and Webb J. Circ J. 2015;79:695–703. 3. Dvir D. First look at long-term durability of transcatheter heart valves: Assessment of valve function up to 10-years after implantation. EuroPCR 2016 presentation 4. Laschinger J et al., N Engl J Med. 2015; 373:1996-8. 5. Dvir D et al., JAMA. 2014;312:162-70.

Strategy for TAVR VIV

How many SAVR bioprosthetic valves are "large"?

Perception: The majority of SAVR (surgical aortic valve replacement) tissue valves implanted prior to a VIV are "large" valves.

Reality: In the largest VIV registry to date, 69% of patients had "intermediate" or "small" valves.[1]

= Not Reasonable for TAVR VIV[3]

SAVR Valve Sizes Defined for VIV:[1]

- Large = ≥25mm (31%)
- Intermediate = >21 to <25mm (39%)
- Small = ≤21mm (30%)

Do patients considering a SAVR tissue valve know that they do not reasonably qualify for VIV when they receive a tissue valve <25mm?

PERIMOUNT® Tissue Valves Sold in US:[2]

67% are Small and Intermediate Sizes (≤21 to <25mm)

1. Dvir. JAMA. 2014;312:162-70.
2. IMS US Sales Report, Q4, 2010 to Q3, 2016. Perimount models 2700, 2800, and 3300. Report run by CryoLife Marketing, 04/10/2017. Data on file.
3. Nishimura et al., Circulation. 2017;135:e1159–e1195.

Strategy for TAVR VIV

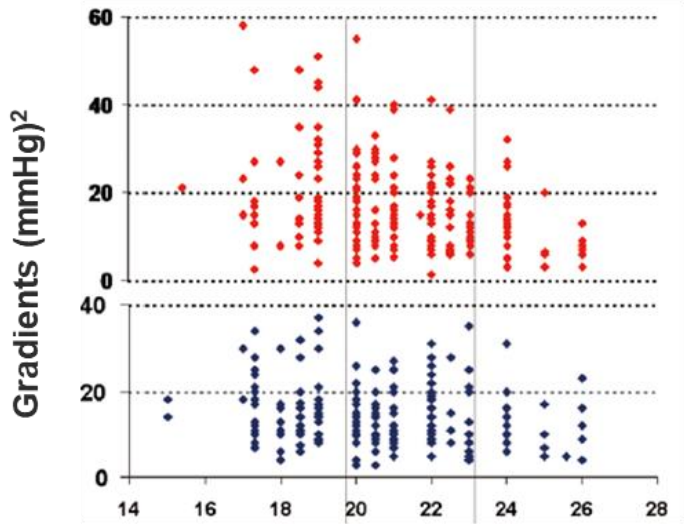
Prosthesis Patient Mismatch (PPM), Gradients, and Mortality

Perception: The outcomes of VIV are equivalent to a de novo TAVR procedure

Reality: VIV hemodynamics are poor and mortality is excessive in ≤21 mm SAVR valves.

PPM and Gradients from VIV Registry Data:[1]

- 62% PPM*
- 31.8% Severe PPM
- Gradients in many patients: ≥20 mmHg to ≥40 mmHg
- Excess Mortality at ≤1 year was correlated with small surgical bioprosthesis (≤21 mm; hazard ratio, 2.04; 95%CI, 1.14-3.67; $P = .02$)



1. Dvir D et al., JAMA. 2014;312:162-70.
*Calculation from descriptive statistics with PPM as iEOA <0.85m²/m²
2. Chart from Dvir D and Webb J. Circ J. 2015;79:695–703.

Valve Aortique

Valve in Valve

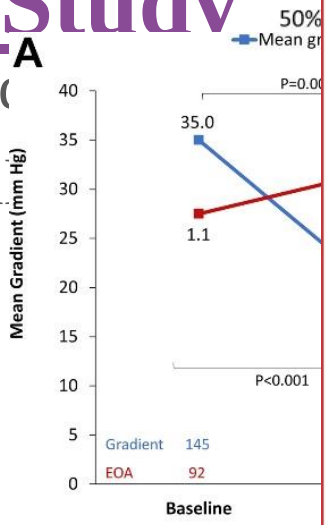
VIVA Study

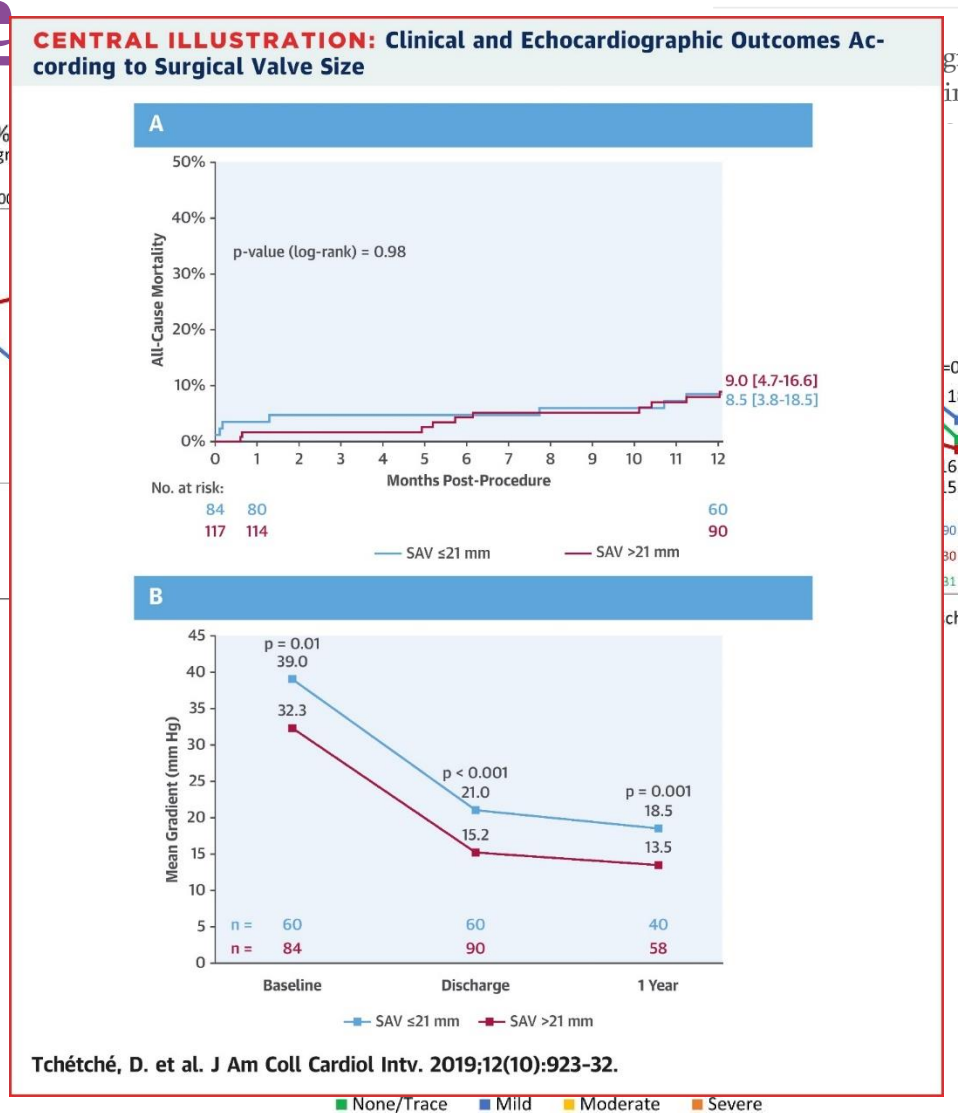
VIVA Stu

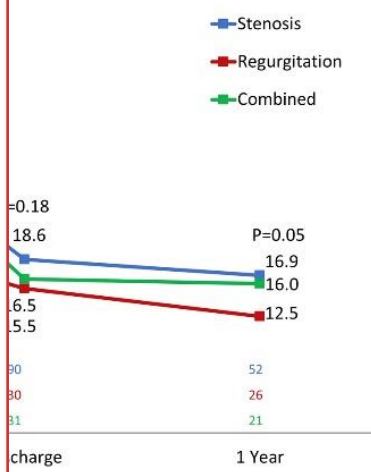
entre tai

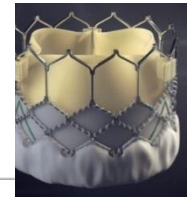
JACC: Cardiovascular Interventions
Volume 12, Issue 10, 27 May 2019, Pages 923-932

gical Aortic Bioprostheses
ing Device: 1-Year Results
VIVA Postmarket Study







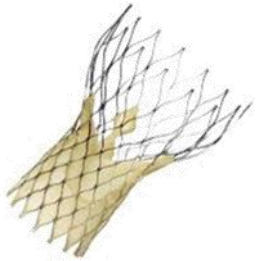


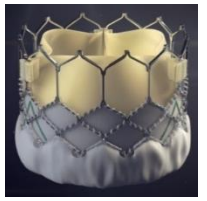
Valve Aortique

Valve in Valve

1006 pts

entre tai





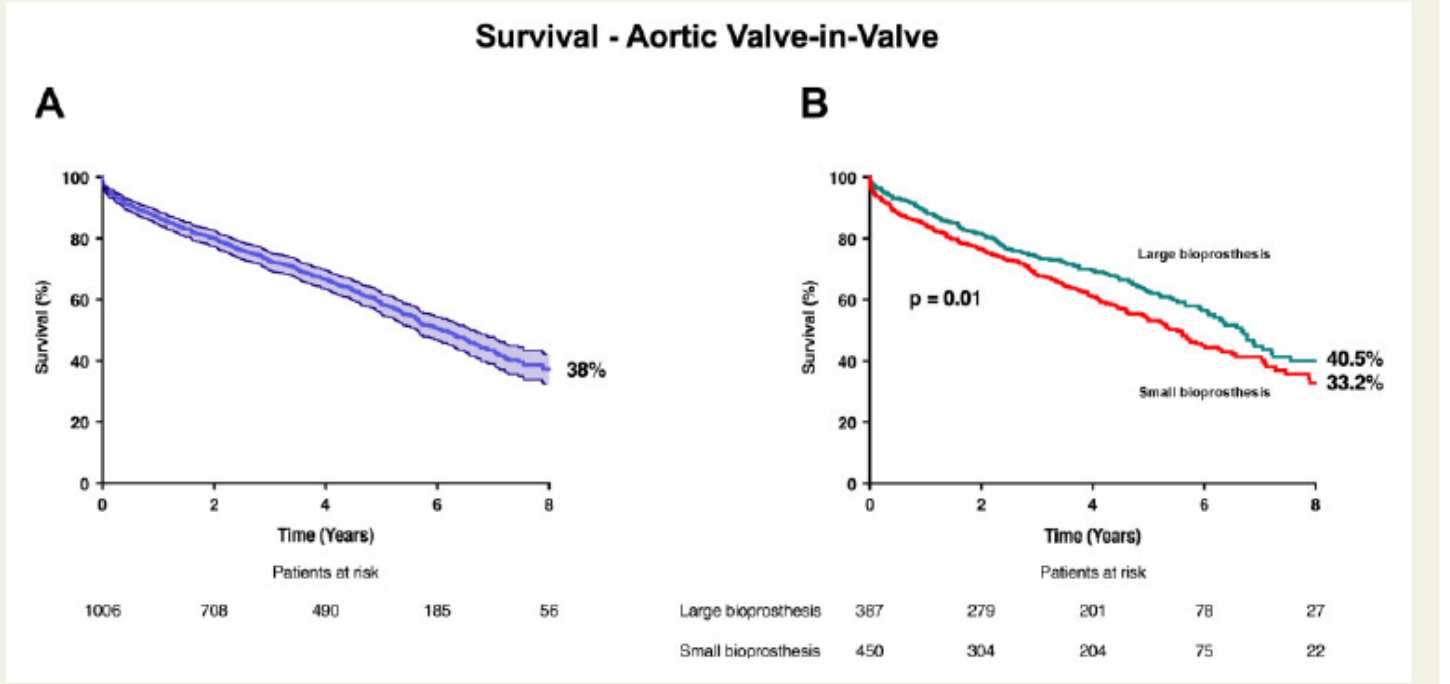


Figure 1 Kaplan–Meier model of survival after aortic valve-in-valve. (*A*) All patients included in the analysis. (*B*) Patients with small bioprostheses (i.e. true internal diameter ≤20 mm) had worse survival at 8 years. Note that bioprosthetic valves without a known standard for internal diameter size, such as homografts, were not included (from Bleiziffer S, Simonato M, Webb JG, Rodés-Cabau J, Pibarot P, Kornowski R, Kornowski S, Erlebach M, Duncan A, Seiffert M, Unbehaun A, Frerker C, Conzelmann L, Wijeysundera H, Kim W-K, Montorfano M, Latib A, Tchetche D, Allali A, Abdel-Wahab M, Orvin K, Stortecky S, Nissen H, Holzamer A, Urena M, Testa L, Agrifoglio M, Whisenant B, Sathananthan J, Napodano M, Landi A, Fiorina C, Zittermann A, Veulemans V, Sinning J-M, Saia F, Brecker S, Presbitero P, De Backer O, Søndergaard L, Bruschi G, Franco LN, Petronio AS, Barbanti M, Cerillo A, Spargias K, Schofer J, Cohen M, Muñoz-Garcia A, Finkelstein A, Adam M, Serra V, Teles RC, Champagnac D, Iadanza A, Chodor P, Eggebrecht H, Welsh R, Caixeta A, Salizzoni S, Dager A, Auffret V, Cheema A, Ubben T, Ancona M, Rudolph T, Gummert J, Tseng E, Noble S, Bunc M, Roberts D, Kass M, Gupta A, Leon LB, Dvir D. Long-term outcomes after transcatheter aortic valve implantation in failed bioprosthetic valves. See pages 2731–2742).

Impact of Prosthesis Patient Mismatch

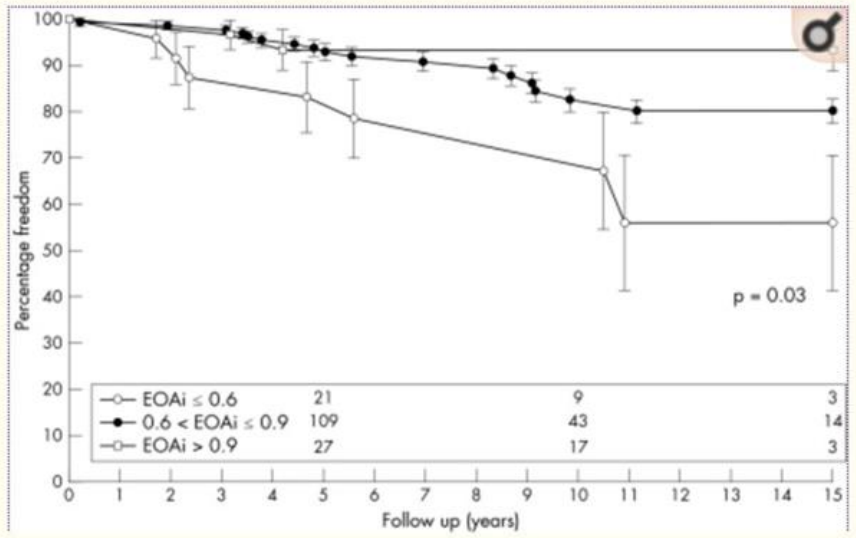


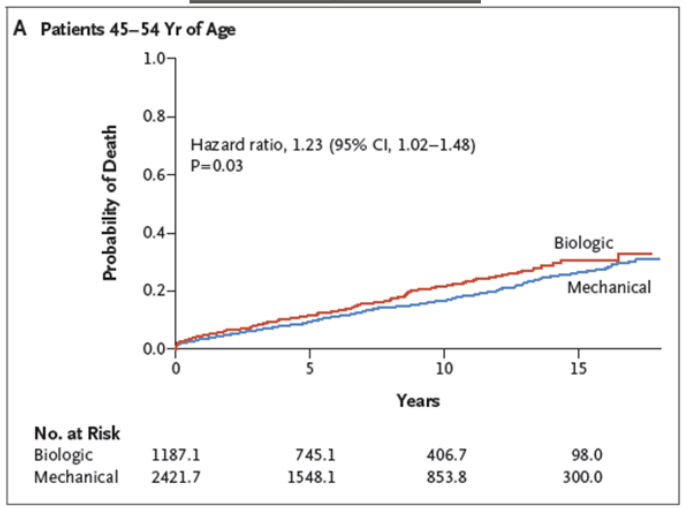
Figure 4 Freedom from late cardiac events in patients with non-significant (indexed EOA (EOAi) >0.9 cm^2/m^2; squares), moderate (EOAi >0.6 cm^2/m^2 and ⩽0.9 cm^2/m^2; solid circles), or severe (EOAi ⩽0.6 cm^2/m^2; open circles) mismatch. Reproduced from Milano *et al*[11] with permission of the Society of Thoracic Surgeons.

Pibarot P and Dumesnil J: Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart 2006 Aug; 92(8) 1022-1029

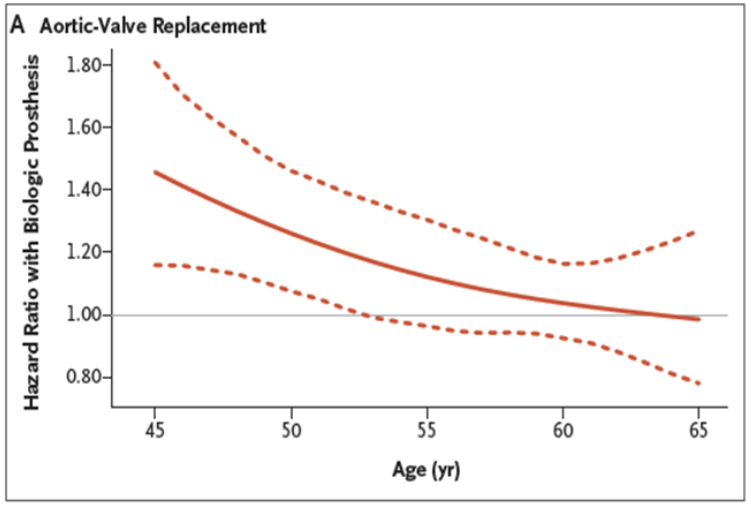
Mortality after Aortic-Valve Replacement Biologic or Mechanical Prosthesis

Mechanical aortic valves have a survival benefit at 15 years for patients up to 55 years, however bioprosthetic valves do not show a benefit until after 65 years.

Probability of Death



Age Dependent Hazard of Death



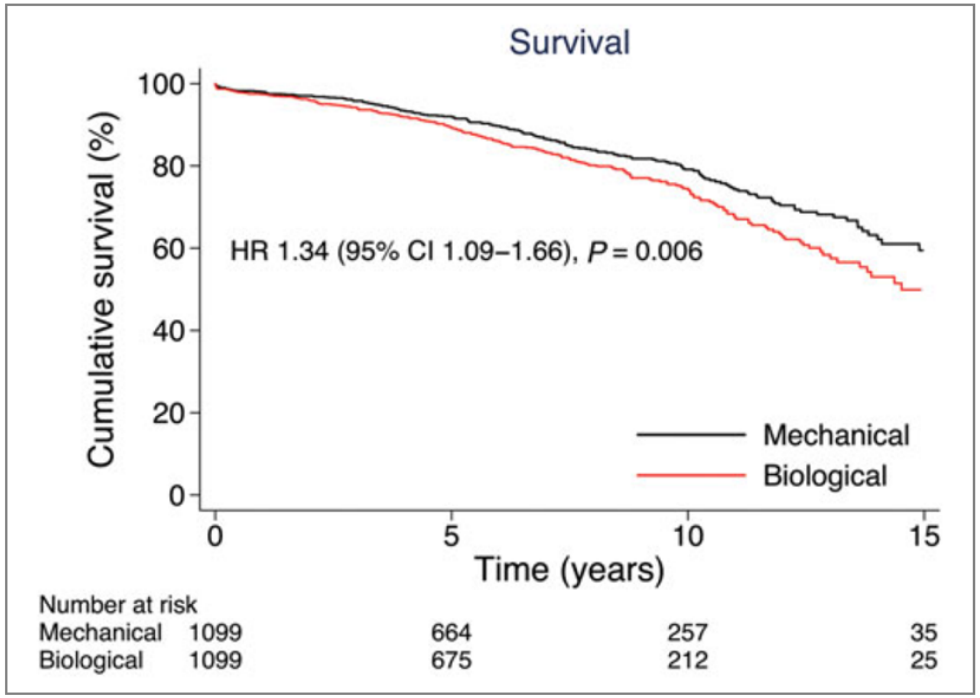
Goldstone AB et al. N Engl J Med 2017;377:1847-1857.

Mortality after Aortic-Valve Replacement

Biologic or Mechanical Prosthesis

European Heart Journal

Mechanical aortic valves have a **survival benefit at 15 years** for patients 50 to 69 years.



Glaser N et al., Euro Heart J. 2016;37:2658-67.

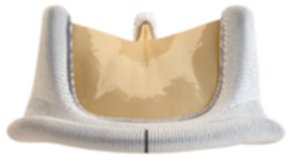
The Dilemma Revisited

The On-X Aortic Valve: New Generation Mechanical Valve

Other Mechanical Valves

On-X Mechanical Valve

Tissue Valve



On-X Advantages Vs. Other Bileaflet Valves

Reduced Anticoagulation
Easier to Manage
Prevention of Pannus

On-X Advantages Vs. Tissue Valves

Lifetime Durability

Reduced Risk of Reoperation

On-X Prosthetic Heart Valve Instructions for Use.

PROACT (Reduced INR) High Risk Arm

Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement

John D. Puskas, MD, MSc,[a] Marc Gerdisch, MD,[b] Dennis Nichols, MD,[c] Lilibeth Fermin, MD,[d] Birger Rhenman, MD,[d] Divya Kapoor, MD,[d] Jack Copeland, MD,[e] Reed Quinn, MD,[f] G. Chad Hughes, MD,[g] Hormoz Azar, MD,[h] Michael McGrath, MD,[h] Michael Wait, MD,[i] Bobby Kong, MD,[j] Tomas Martin, MD,[k] E. Charles Douville, MD,[l] Steven Meyer, MD, PhD,[m] Jian Ye, MD MSc,[n] W.R. Eric Jamieson, MD,[o] Lance Landvater, MD,[p] Robert Hagberg, MD,[q] Timothy Trotter, MD,[r] John Armitage, MD,[s] Jeffrey Askew, MD,[s] Kevin Accola, MD,[t] Paul Levy, MD,[u] David Duncan, MD,[v] Bobby Yanagawa, MD, PhD,[w] John Ely, MS,[x] Allen Graeve, MD,[c] for the PROACT Investigators*

Position	PROACT Study Design	Standard (Control)	Low Dose (Test)	Status
Aortic	Multicenter(n=41), randomized, controlled, non-inferior trial design, 1 or more TE risk factors, home INR monitoring	**Enrollment:** n=190 **First 90 days:** 2.0 – 3.0 INR **Long-term:** 2.0 – 3.0 INR **Aspirin:** 81 mg/day	**Enrollment:** n=185 **First 90 days:** 2.0 – 3.0 INR **Long-term:** 1.5 – 2.0 INR Aspirin: 81 mg/day	**Study completed** (>5 year FU, n=375) - >60% lower bleeding, non-inferior TE rate - Low INR labeling approved by FDA/CE - JACC Publication 2018 - Low INR added to AHA/ACC Guidelines
Mitral	Multicenter(n=41), randomized, controlled, non-inferior trial design, 1 or more TE risk factors, home INR monitoring	**First 90 days:** 2.5 – 3.5 INR **Long-term:** 2.5 – 3.5 INR **Aspirin:** 81 mg/day	**First 90 days:** 2.5 – 3.5 INR **Long-term:** 2.0 – 2.5 INR **Aspirin:** 81 mg/day	**Actively enrolling** (n=310) - ~500 pt-yrs FU - Trending to non-inferiority - ~3 years to FDA approval

1. On-X Prosthetic Heart Valve Instructions for Use
2. Puskas J et al,. J Thorac Cardiovasc Surg. 2014; 147:1202-11.

PROACT (Reduced INR) High Risk Arm

TABLE 4 Outcomes in the High-Risk Arm

	Standard Warfarin (INR 2.0-3.0) (1,090.0 pt-yrs)		Low-Dose Warfarin (INR 1.5-2.0) (945.2 pt-yrs)		Rate Ratio (Standard/Low-Dose Warfarin)	95% CI	p Value
	n	Rate (%/pt-yr)	n	Rate (%/pt-yr)			
Primary endpoint	102	9.35	52	5.50	0.59	0.42-0.82	0.002
Components of co-primary endpoint							
Major bleeding	43	3.94	15	1.59	0.40	0.22-0.72	0.002
Minor bleeding	38	3.49	12	1.27	0.36	0.19-0.70	0.002
Cerebral bleeding	4	0.37	1	0.11	0.29	0.03-2.58	0.30
Total bleeding	81	7.43	27	2.86	0.38	0.25-0.59	<0.001
Stroke	7	0.64	7	0.74	1.15	0.40-3.29	0.80
TIA	11	1.01	12	1.27	1.26	0.56-2.85	0.60
Any neurological event	18	1.65	19	2.01	1.22	0.64-2.32	0.50
Peripheral TE event	1	0.09	4	0.42	4.61	0.52-41.28	0.20
Valve thrombosis	2	0.18	2	0.21	1.15	0.16-8.19	0.90
Major bleed, TE event or thrombosis	64	5.87	40	4.23	0.72	0.49-1.07	0.10
Sudden death	3	0.28	3	0.32	1.15	0.23-5.72	0.90
Valve-related mortality	4	0.37	2	0.21	0.58	0.11-3.15	0.50
Total mortality	17	1.56	13	1.38	0.88	0.43-1.82	0.70

The primary composite endpoint includes death, any bleeding (major or minor), and any TE and valve thrombosis.
Abbreviations as in Table 2.

Bleeding – 67% Reduction

Stroke – No Difference

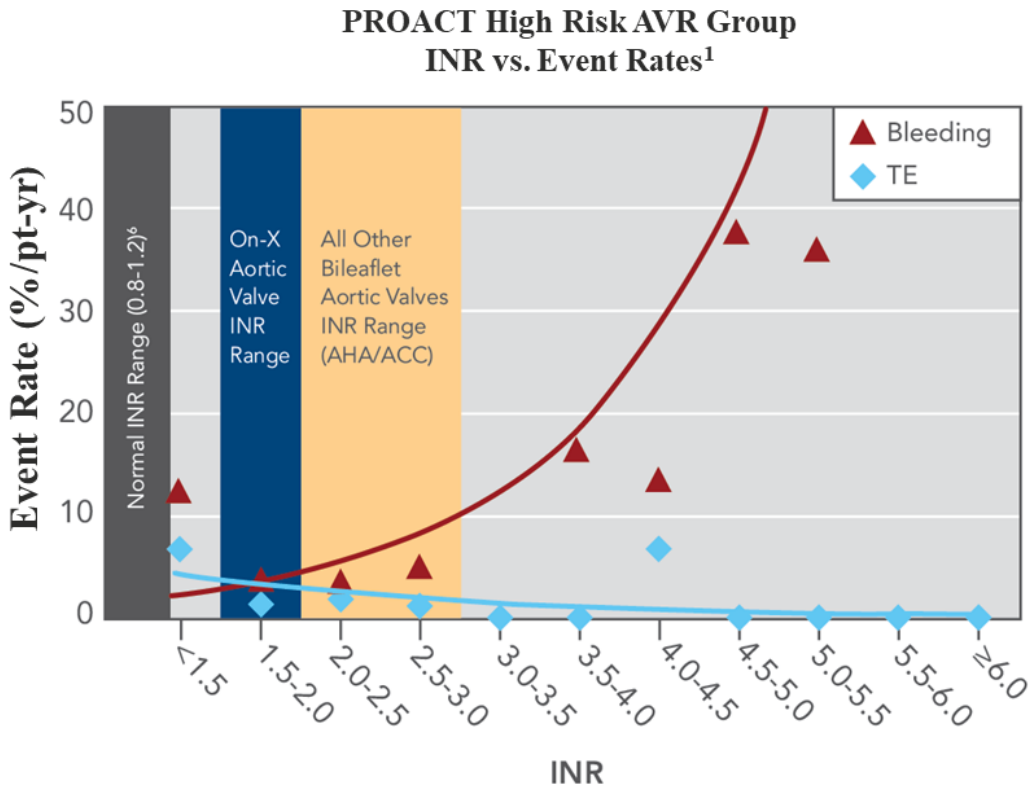
Mortality – 24% Reduction

1. On-X Prosthetic Heart Valve Instructions for Use
2. Puskas J et al. J Thorac Cardiovasc Surg. 2014; 147:1202-11.

PROACT Results: AVR High Risk Group

Test group had
>60% reduction in total bleeding events

No difference in TE rates between groups



1. Data on File. 6. Levine M et al., Can Fam Physician. 2012;58:e465-71.

Part 2: 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease

A mechanical prosthesis should be considered in patients aged <60 years for prostheses in the aortic position and aged <65 years for prostheses in the mitral position [462, 464]. [e]	IIa	B

2021 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by 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: Alec Vahanian * (ESC Chairperson) (France), Friedhelm Beyersdorf*[1] (EACTS Chairperson) (Germany), Fabien Praz (ESC Task Force Coordinator) (Switzerland), Milan Milojevic[1] (EACTS Task Force Coordinator) (Serbia), Stephan Baldus (Germany), Johann Bauersachs (Germany), Davide Capodanno (Italy), Lenard Conradi[1] (Germany), Michele De Bonis[1] (Italy), Ruggero De Paulis[1] (Italy), Victoria Delgado (Netherlands), Nick Freemantle[1] (United Kingdom), Martine Gilard (France), Kristina H. Haugaa (Norway), Anders Jeppsson[1] (Sweden), Peter Jüni (Canada), Luc Pierard (Belgium), Bernard D. Prendergast (United Kingdom), J. Rafael Sádaba[1] (Spain), Christophe Tribouilloy (France), Wojtek Wojakowski (Poland), ESC/EACTS

Conclusions

1) 2017 AHA/ACC Guidelines – Mechanical and Tissue Aortic Valves[1]

<50 yrs: Mechanical – favored choice; Tissue - for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.

50-70 yrs: Mechanical or Tissue is a reasonable choice

2) Tissue Valves[2,3]

Perception: Tissue valves last >15 yrs in younger patients

Reality: Time to first failure of tissue valves can be 5 to 7 yrs in younger patients

1. Nishimura et al., 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159–e1195. 2. McClure R et al., Ann Thorac Surg. 2010;89:1410–6. 3. Bourguignon T et al., Eur J Cardiothorac Surg. 2016;1462-8.

Conclusions (continued)

3) VIV

- **Perception:** The majority of patients have large SAVR tissue valves and qualify for VIV
- **Reality:** The majority of patients do not qualify for VIV due to smaller size SAVR valves
  - 67% of Edwards PERIMOUNT® tissue valves sold are not large sizes
  - 62% of VIV patients have PPM (32% severe)[1,2]

4) Mechanical Valves

- **Perception:** Mechanical valve patients can't stay active
- **Reality:** On-X Aortic Heart Valve has excellent hemodynamics, potential reduced bleeding risk, and no reoperation for structural valve deterioration (SVD).[3]

1. IMS US Sales Report, Q4, 2010 to Q3, 2016. PERIMOUNT models 2700, 2800, and 3300. Report run by CryoLife Marketing, 04/10/2017. Data on file. 2. Dvir D et al., JAMA. 2014;312:162-70. 3. On-X Prosthetic Heart Valve Instructions for Use.

Conclusions (continued)

5) Survival

Perception: There is no significant difference in survival for patients receiving a mechanical or tissue aortic valve replacement.

Reality: Recent studies show a survival benefit for mechanical over tissue for AVR patients at 15 years with one study showing a significant survival benefit in patients 50-69 years.[1,2]

1. Glaser N et al., Euro Heart J. 2016;37:2658-67.
2. Goldstone AB et al. N Engl J Med 2017;377:1847-1857.

Merci