Long-Term Durability Issue of TAVR
Uncertainty or Would Be OK

Duk-Woo Park, MD, PhD

Heart Institute, University of Ulsan College of Medicine,
Asan Medical, Seoul, Korea

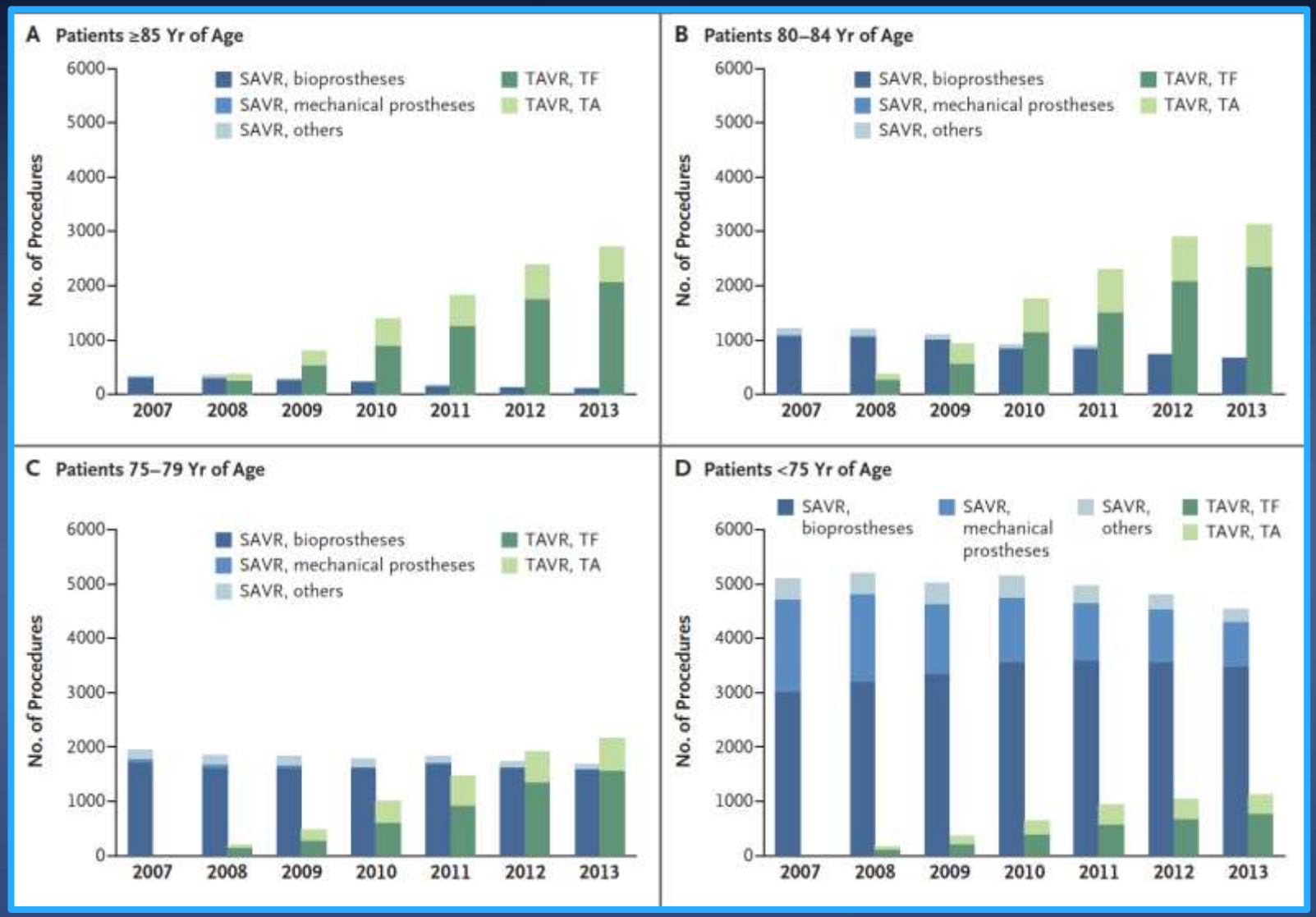
Conflict of Interest Statement

- I received lecture fees from
  - Edwards Lifesciences
  - Medtronic, and
  - Boston Scientific

RCT of TAVR:
Chain From High to Low-Risk

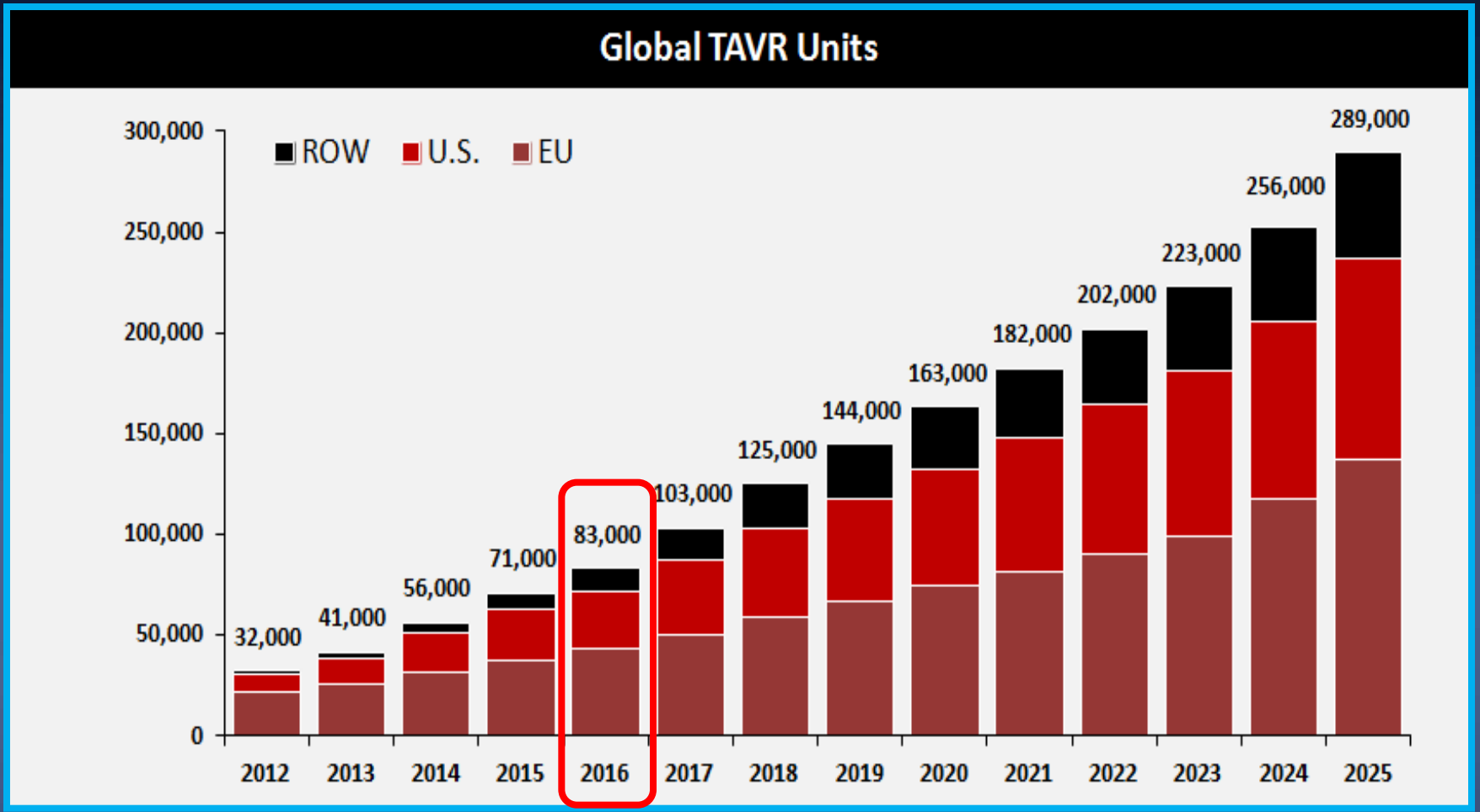
Trial Name	STS Score	Age
Inoperable Population		
PARTNER IB Trial	11.6	83
High Risk Population		
PARTNER IA Trial	11.8	84
CoreValve US Pivotal Trial	7.4	83
Intermediate Risk Population		
PARTNER IIA Trial	5.8	82
SURTAVI	4.4	80
Low Risk Population		
NOTION Trial	3.0	79

TAVR: "Rapid Applicability in Real World" in Germany from 2007 to 2013



N Engl J Med 2015;373:2438-47.

Estimated Global TAVI Procedure Growth



SOURCE: Credit Suisse TAVI Comment –January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

In the near future, young age is not an exclusion criteria for TAVR anymore…

Longevity of Artificial Aortic Valve!!!

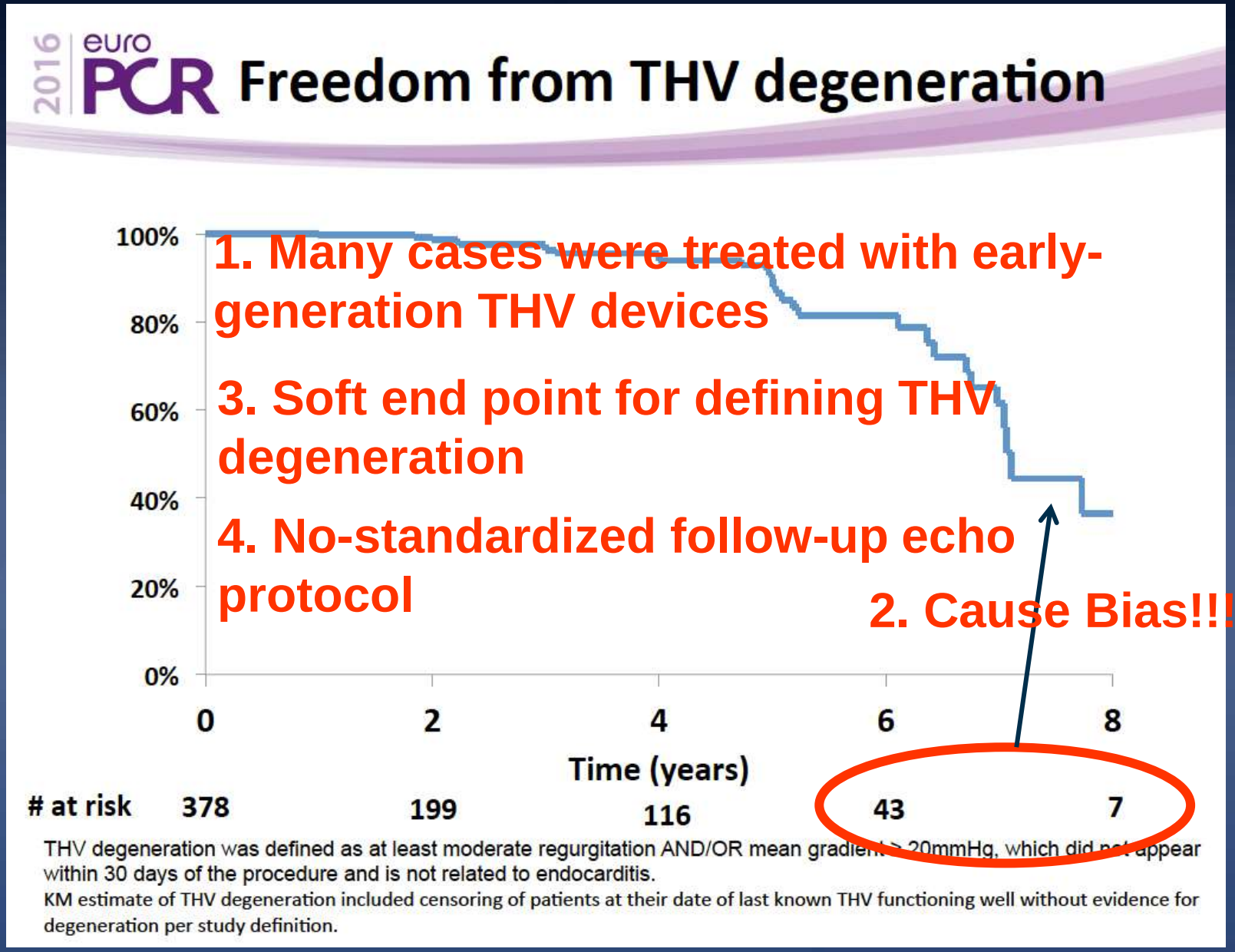
Mechanical Surgical Valves	Bioprosthetic Surgical Valves	Bioprosthetic TAVR Valves
Lifelong	*>10 Years*	*>10 Years???*

Why Durability Issue is So Important?

- Durability has been and remains the major concern before wide-spread adoption of TAVR procedure.
  - In a patient with a life expectancy of 5 to 7 years, TAVR is absolutely fine.
  - We should be cautious before widespread adoption in patients with a life expectancy of more than 10 years.

- TAVR trials in lower-risk patients will include at least 10-year follow-up.

‘Signal’ of Poor Durability



Current available data about THV durability…..

PARTNER 5-year FU in Lancet (March, 2015)

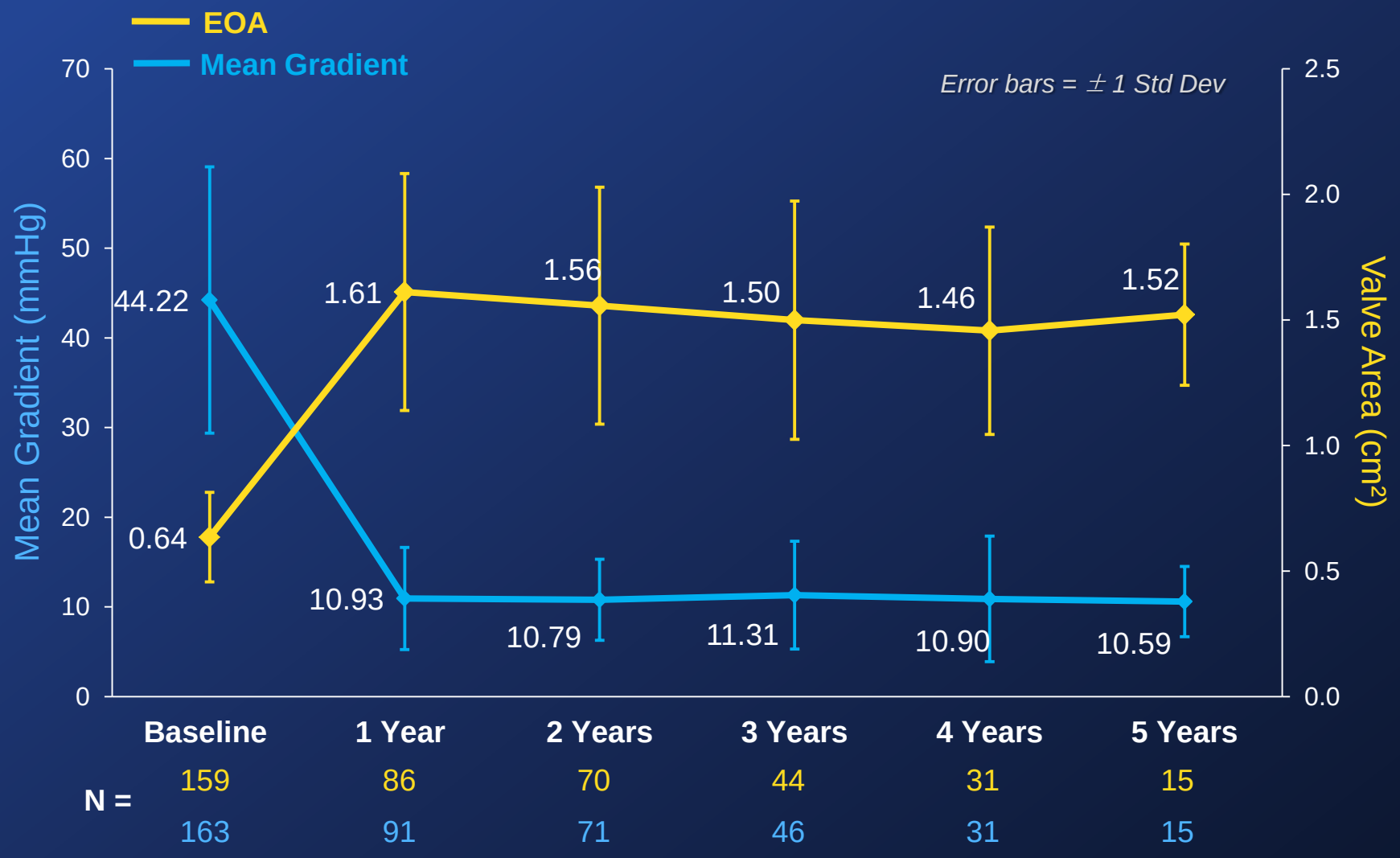
5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial

Samir R Kapadia, Martin B Leon, Raj R Makkar, E Murat Tuzcu, Lars G Svensson, Susheel Kodali, John G Webb, Michael J Mack, Pamela S Douglas, Vinod H Thourani, Vasilis C Babaliaros, Howard C Herrmann, Wilson Y Szeto, Augusto D Pichard, Mathew R Williams, Gregory P Fontana, D Craig Miller, William N Anderson, Jodi J Akin, Michael J Davidson†, Craig R Smith, for the PARTNER trial investigators*

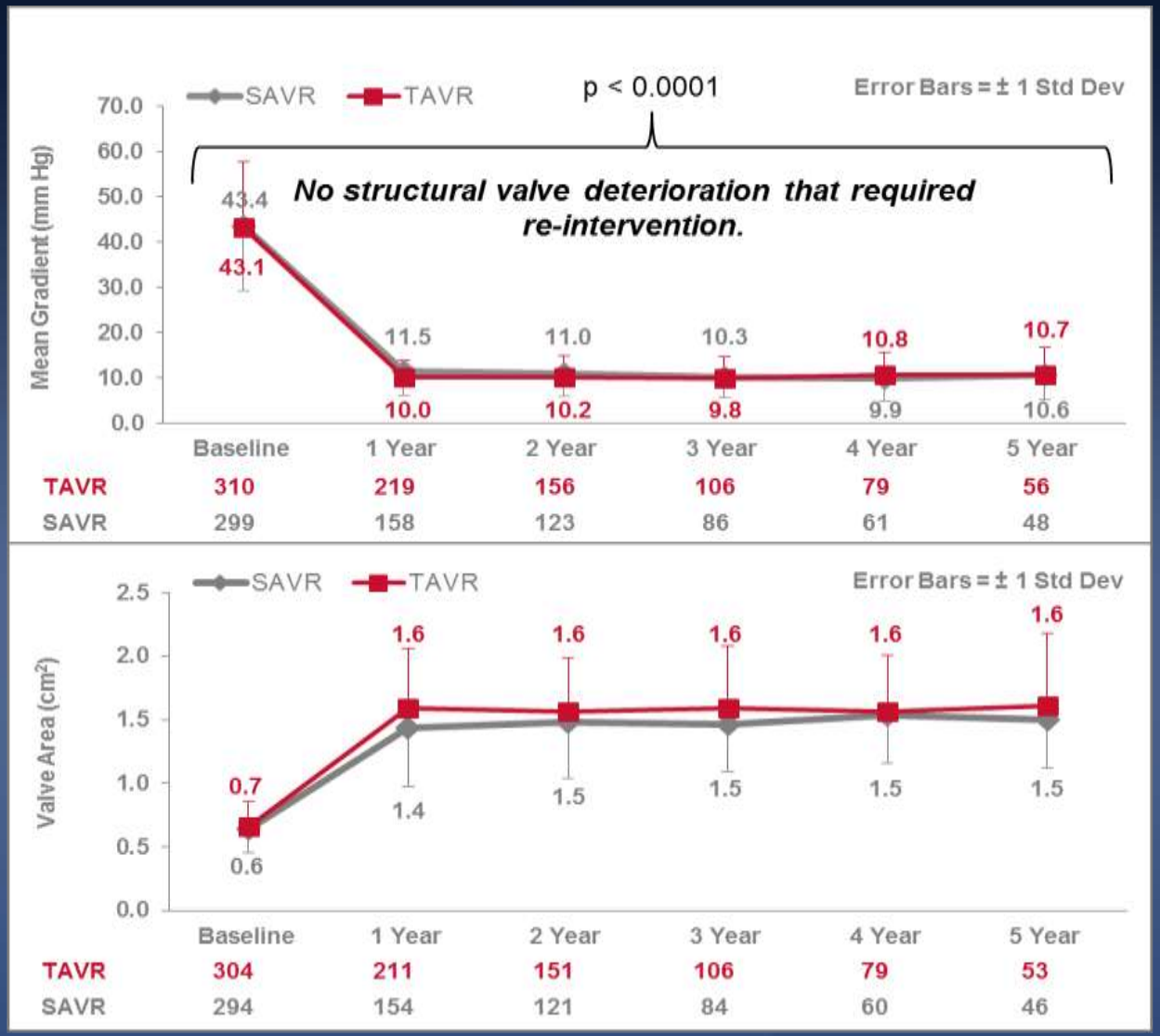
5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

Michael J Mack, Martin B Leon, Craig R Smith, D Craig Miller, Jeffrey W Moses, E Murat Tuzcu, John G Webb, Pamela S Douglas, William N Anderson, Eugene H Blackstone, Susheel K Kodali, Raj R Makkar, Gregory P Fontana, Samir Kapadia, Joseph Bavaria, Rebecca T Hahn, Vinod H Thourani, Vasilis Babaliaros, Augusto Pichard, Howard C Herrmann, David L Brown, Mathew Williams, Jodi Akin, Michael J Davidson†, Lars G Svensson, for the PARTNER 1 trial investigators*

Mean Gradient & Valve Area (AT)
Cohort B - All Patients



The PARTNER Trial (Cohort A): 5-Year Data



Mack M et al. Lancet 2015;6736(15)60308-7

Mid-Term Hemodynamic Trends and Between Echo Changes in Transcatheter Aortic Valves in the PARTNER 1 Trial

Five Year Results

Pamela S. Douglas, MD

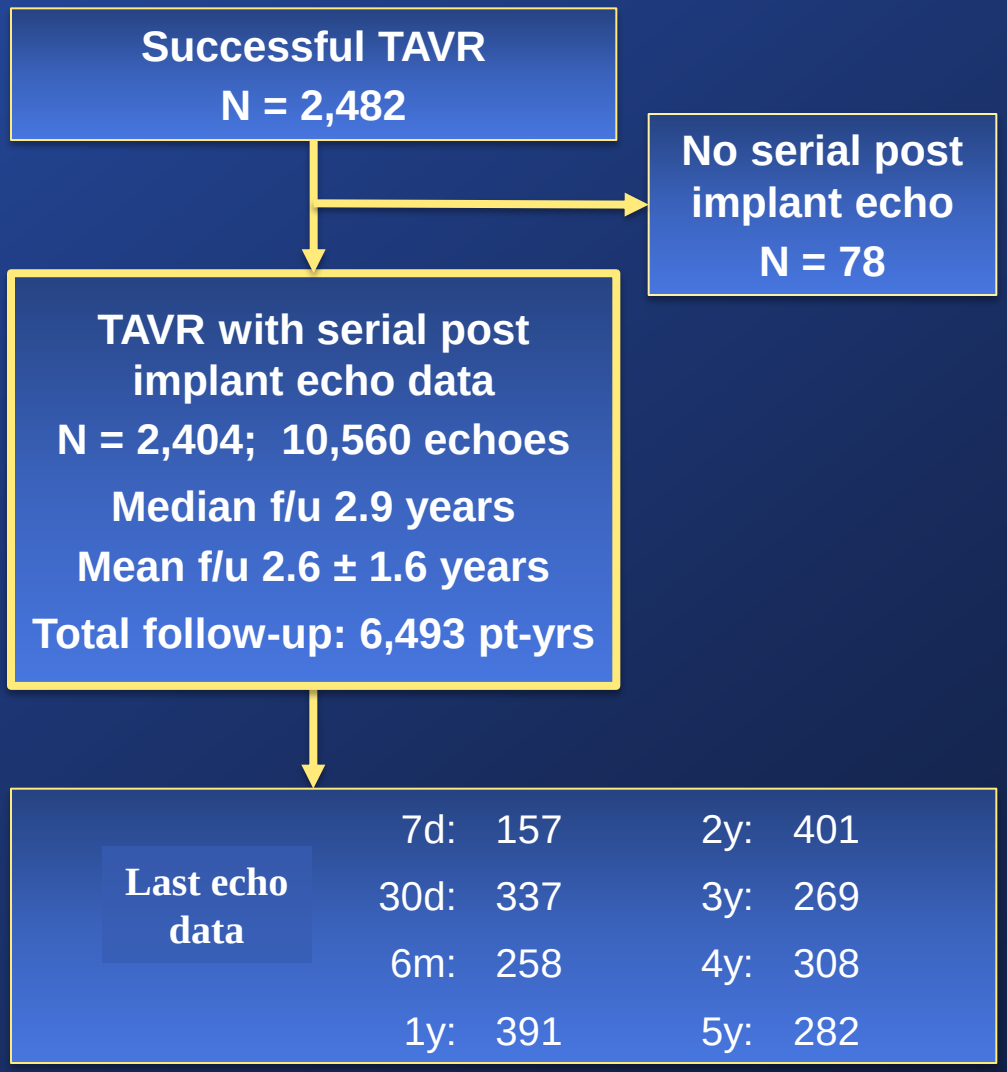
on behalf of The PARTNER Trial Investigators
and The PARTNER Publications Office

TCT 2016 | Washington DC | November 1, 2016

Methods

- Population: All successful TAVRs in PARTNER 1A, 1B and continued access trials using 1st gen SAPIEN THV device
- Post implant echoes per protocol at approx. 7d, 30d, 6m, and 1, 2, 3, 4, 5 yrs; Analyzed by a single core laboratory
- Echocardiographic parameters
  - **AV mean gradient**
  - **Doppler velocity index (DVI)**
  - **[Effective orifice area (EOA)]**
- Clinical endpoints (adjudicated)
  - Death
  - AV reintervention

Cohort Derivation and Characteristics



Population characteristics

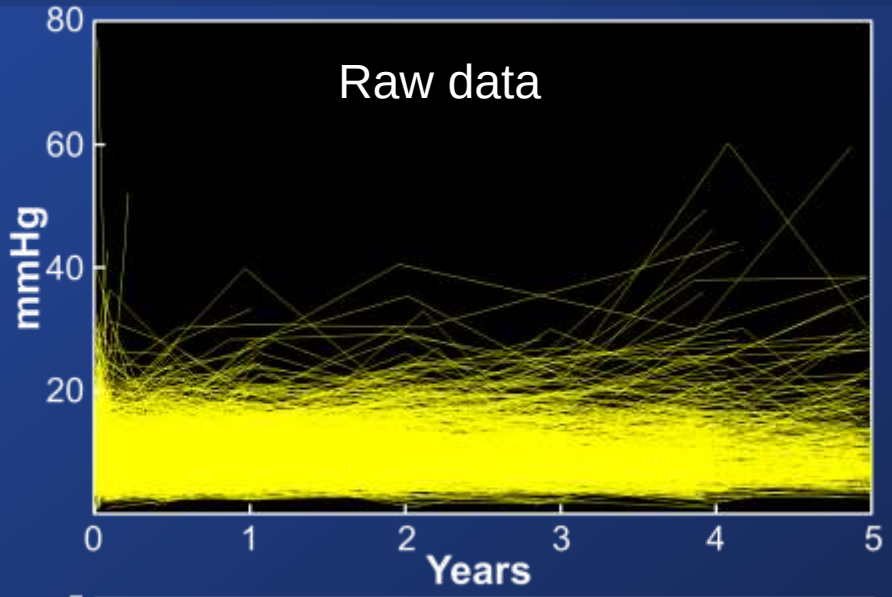
- Mean age 84.5 yrs
- 48% female
- 95% NYHA class 3-4
- 92% obstructive CAD
- Severe AS: AVA 0.65 cm^2

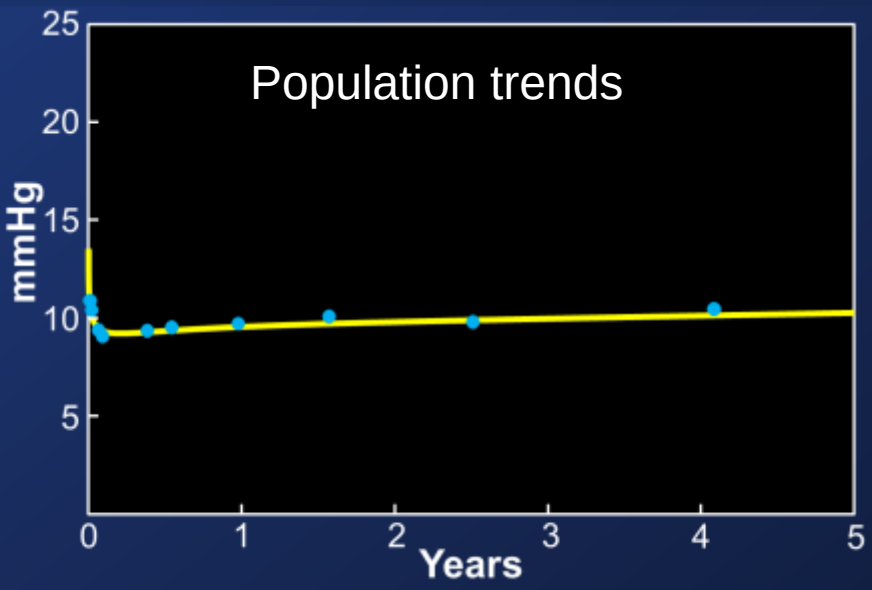
- THV size: 52% 23; 48% 26
- Access: 43% TA ; 57% TF

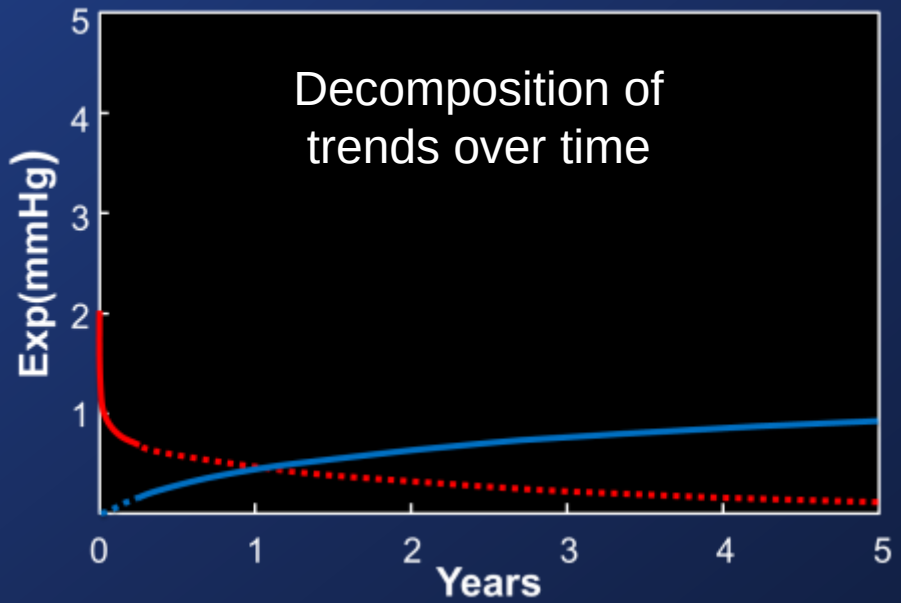
Survival w/o reintervention

- 39% at 5 years by non-adjusted parametric estimate

AV Mean Gradient Population Trends: Early Post Implant and Midterm to 5 Yrs



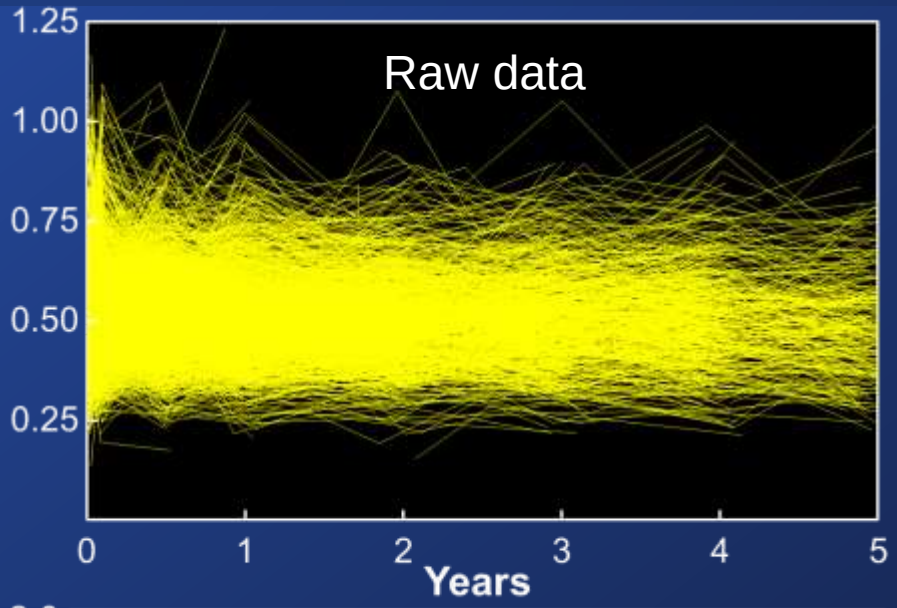


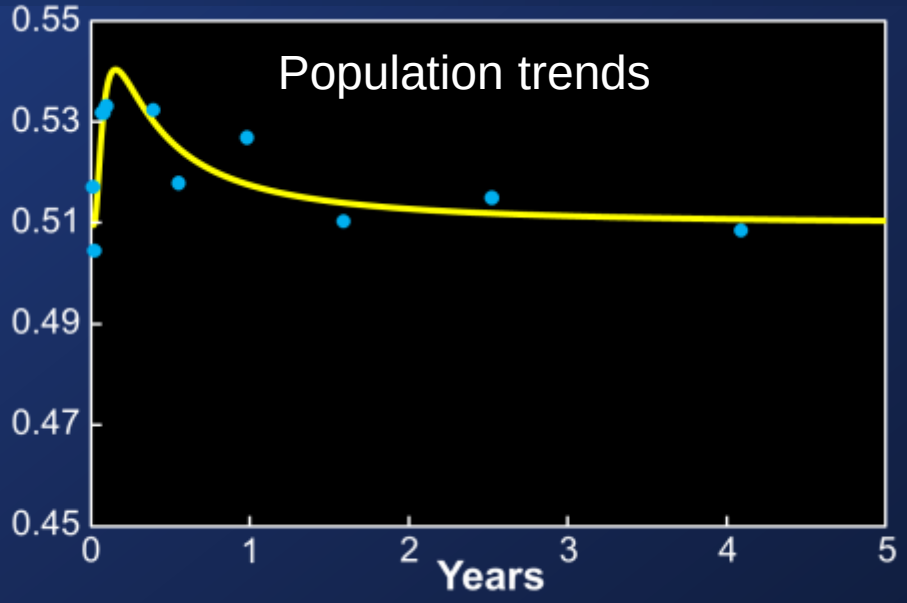


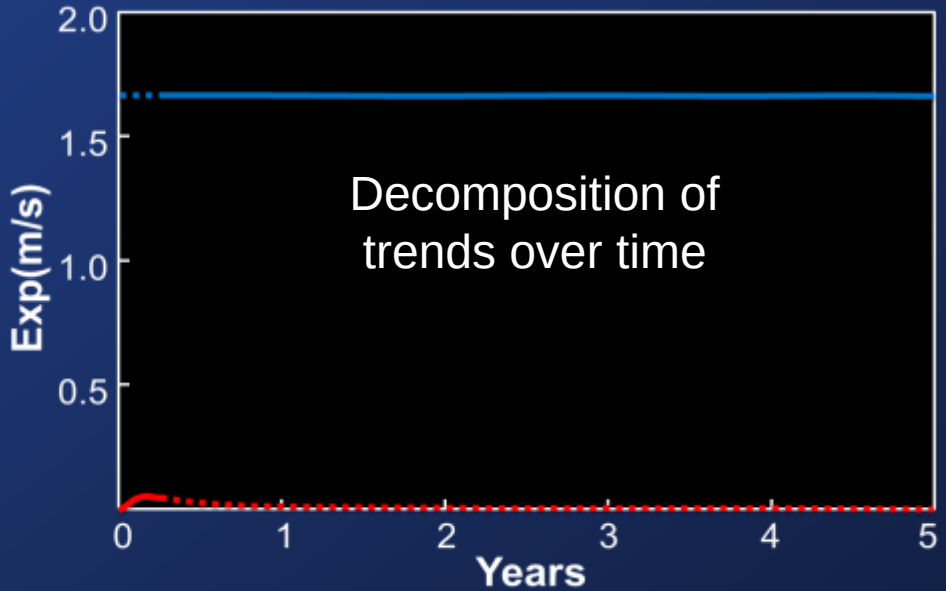
Early change:
12.1 to 9.2 mmHg

Late change:
9.2 to 10.3 mmHg
Slope: 0.0018± 0.0039

AV DVI Population Trends: Early Post Implant and Midterm to 5 Yrs





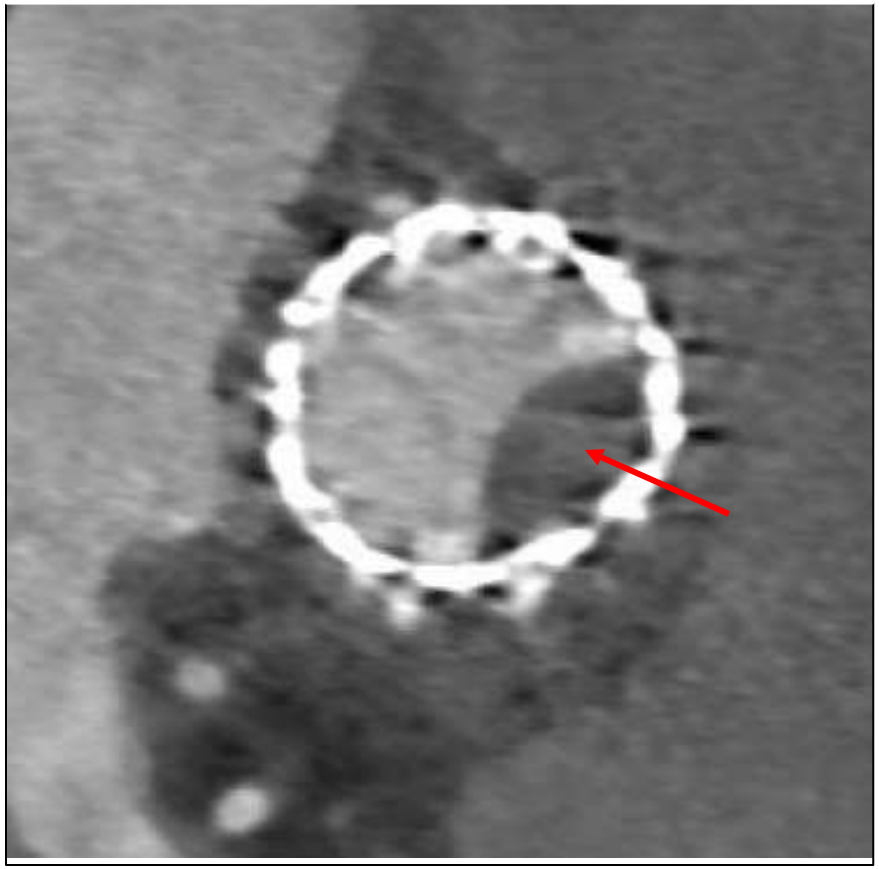


Early change:
0.51 v 0.54

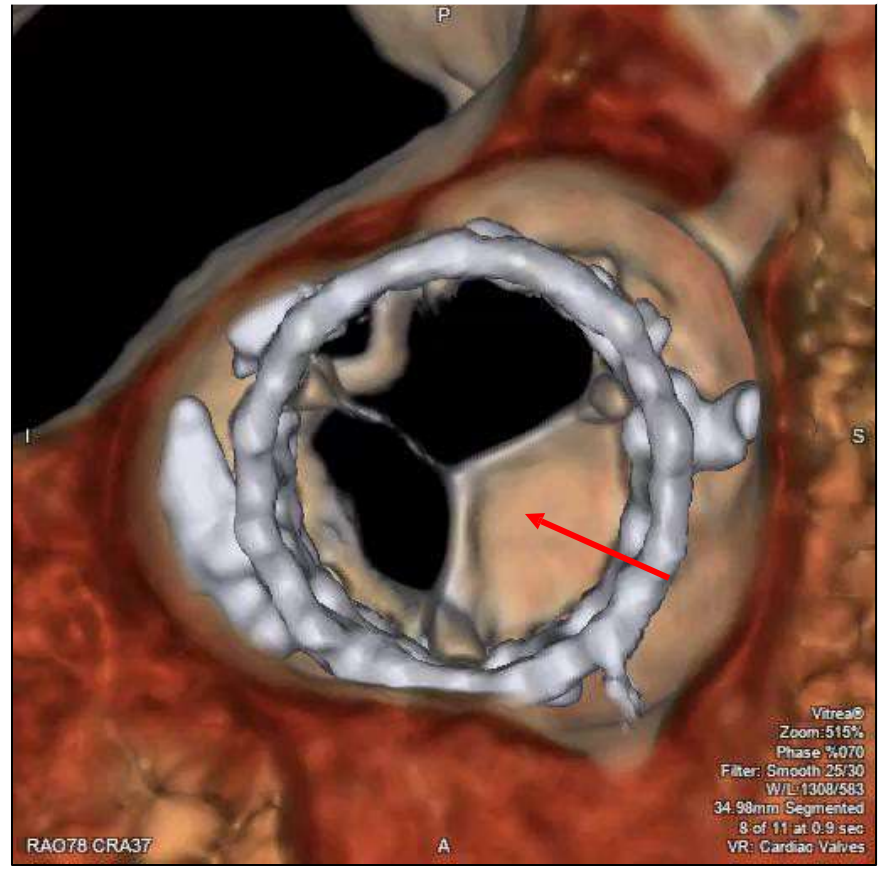
Late change:
0.54 v 0.51
Slope: -0.0052 ± 0.0011

4D-CT Angiogram of Bioprosthetic Aortic Valve

Hypoattenuating opacity



Reduced leaflet motion



Long-Term Durability; Ongoing Issues

The NEW ENGLAND JOURNAL of MEDICINE

PERSPECTIVE

Reduced Leaflet Motion in Bioprosthetic Aortic Valves — The FDA Perspective

John C. Laschinger, M.D., Changfu Wu, Ph.D., Nicole G. Ibrahim, Ph.D., and Jeffrey E. Shuren, M.D., J.D.

Related article, p. 2015

Whether reduced leaflet motion is clinically meaningful or represents a subclinical advanced-imaging phenomenon, the loss of leaflet mobility renders the valve dysfunctional and demands additional investigation.

Makkar, R.R., et al. N Engl J Med 2015;373:2015-24.

Study design

657 patients underwent CTs in the RESOLVE registry
Cedars-Sinai Medical Center, Los Angeles

274 patients underwent CTs in the SAVORY registry
Rigshospitalet, Copenhagen

931 patients undergoing CTs

890 patients with interpretable CTs were included in the analysis
RESOLVE registry: 626 patients
SAVORY registry: 264 patients

Valve types and timing of CT

Time from TAVR to CT vs. SAVR to CT: p<0.0001

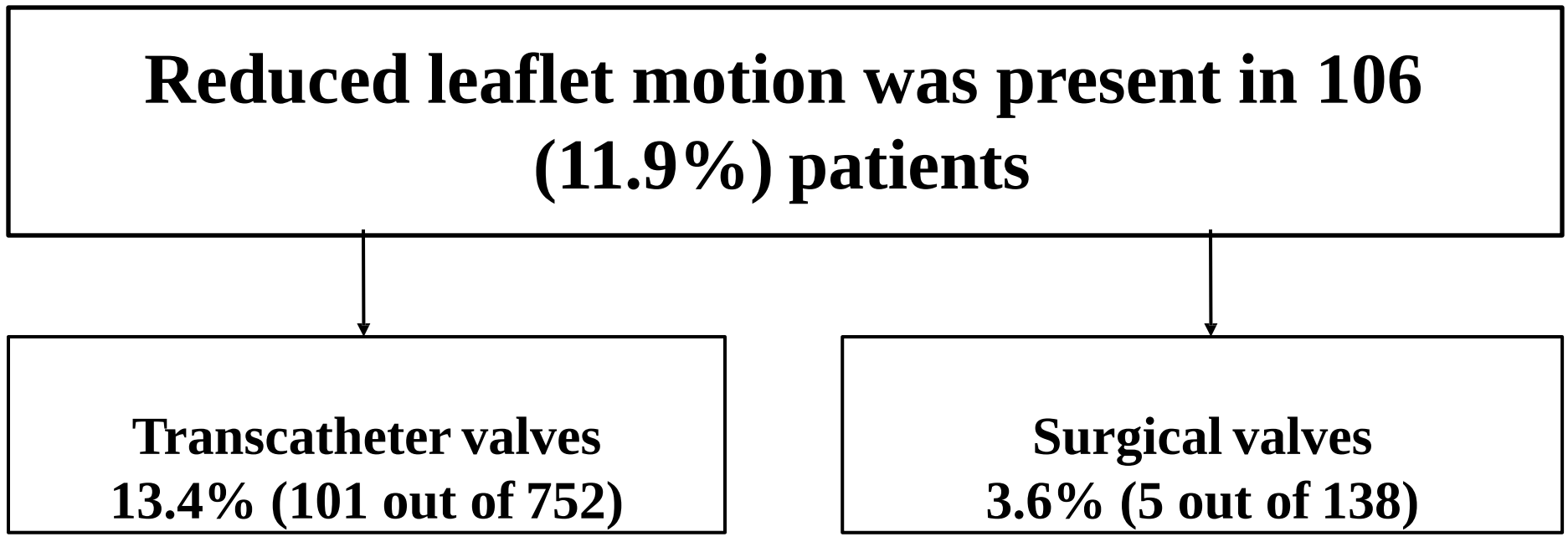
890 patients with interpretable CTs
Median time from AVR to CT 83 days (IQR 32-281 days)

752 transcatheter valves Median time from TAVR to CT 58 days (IQR 32–236 days)

138 surgical valves Median time from SAVR to CT 162 days (IQR 79–417 days)

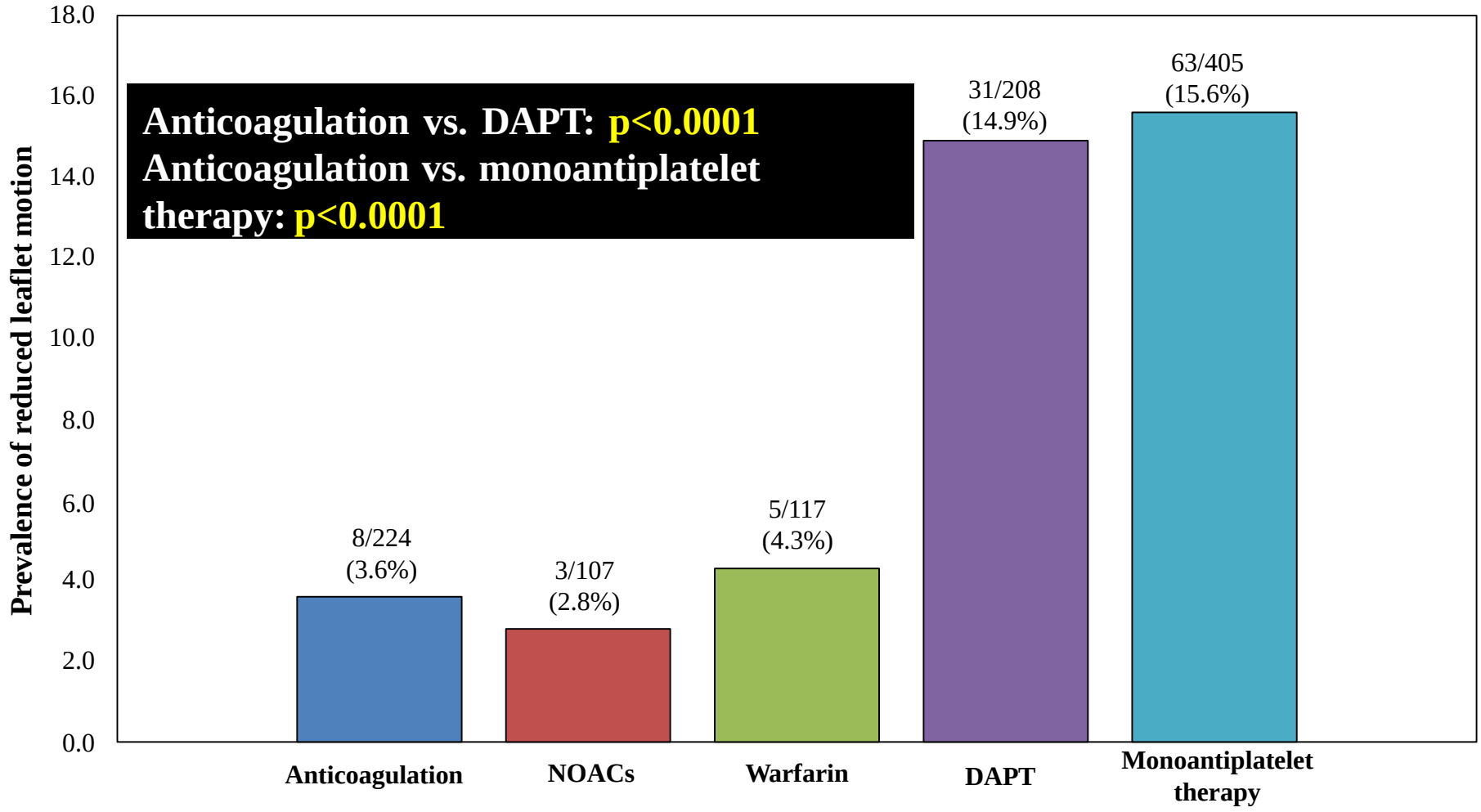
Prevalence of reduced leaflet motion

Transcatheter vs. surgical bioprosthetic aortic valves: p=0.001

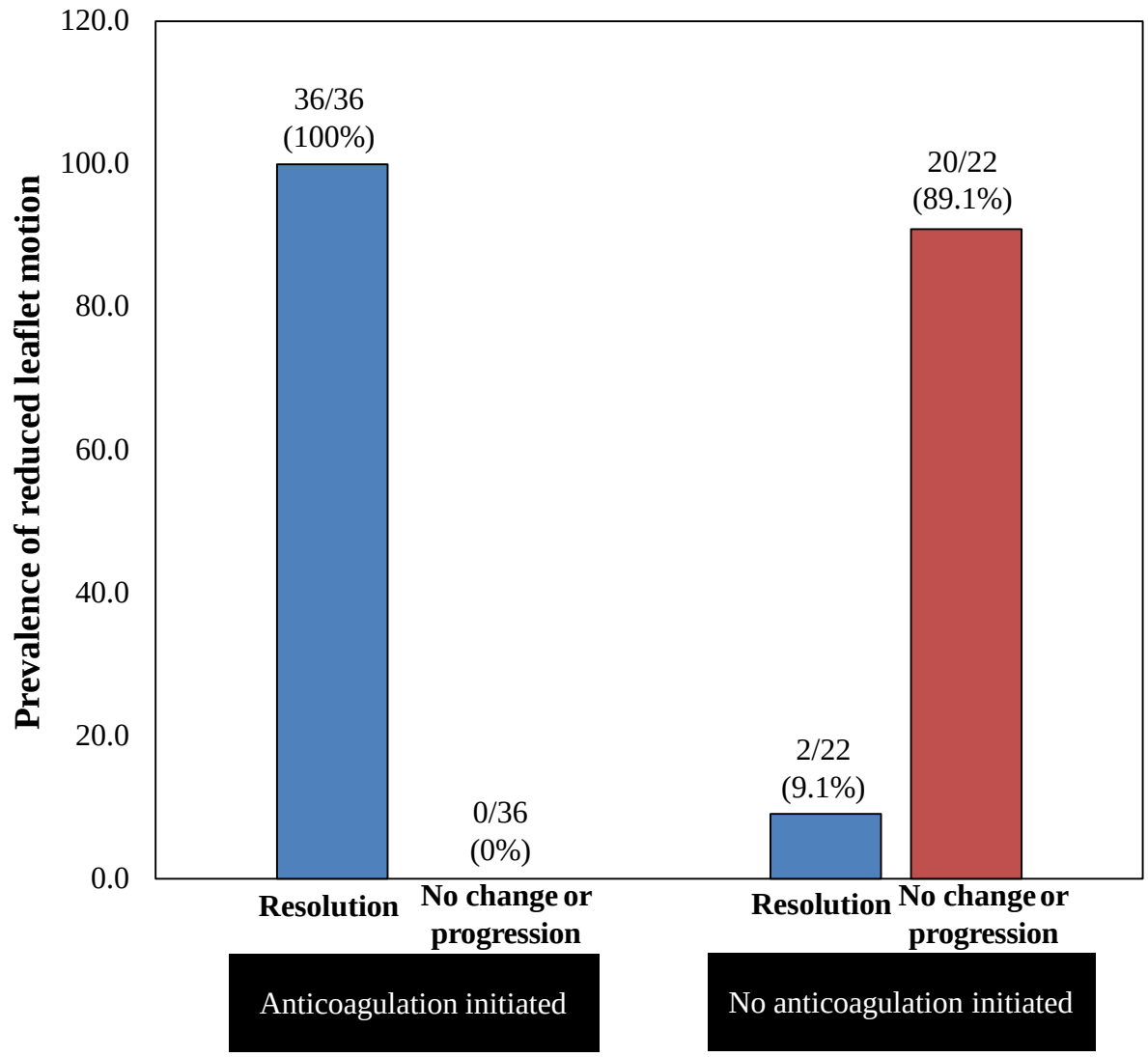


Anticoagulation and reduced leaflet motion

Anticoagulation vs. antiplatelet therapy



Impact of initiation of anticoagulation on reduced leaflet motion



- **Resolution in 36 out of 36 patients** treated with anti coagulation (NO ACs, n=12; warf arin, n=24)
- **Persistence/progres sion in 20 out of 22 patients** not treated with anticoagulati on

P<0.0001

GALILEO

(Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes will compare rivaroxaban-based)

1520 patients after successful TAVI procedure

R 1:1

Rivaroxaban 10 mg OD and Aspirin 75-100mg OD

Drop of aspirin

Rivaroxaban 10 mg OD

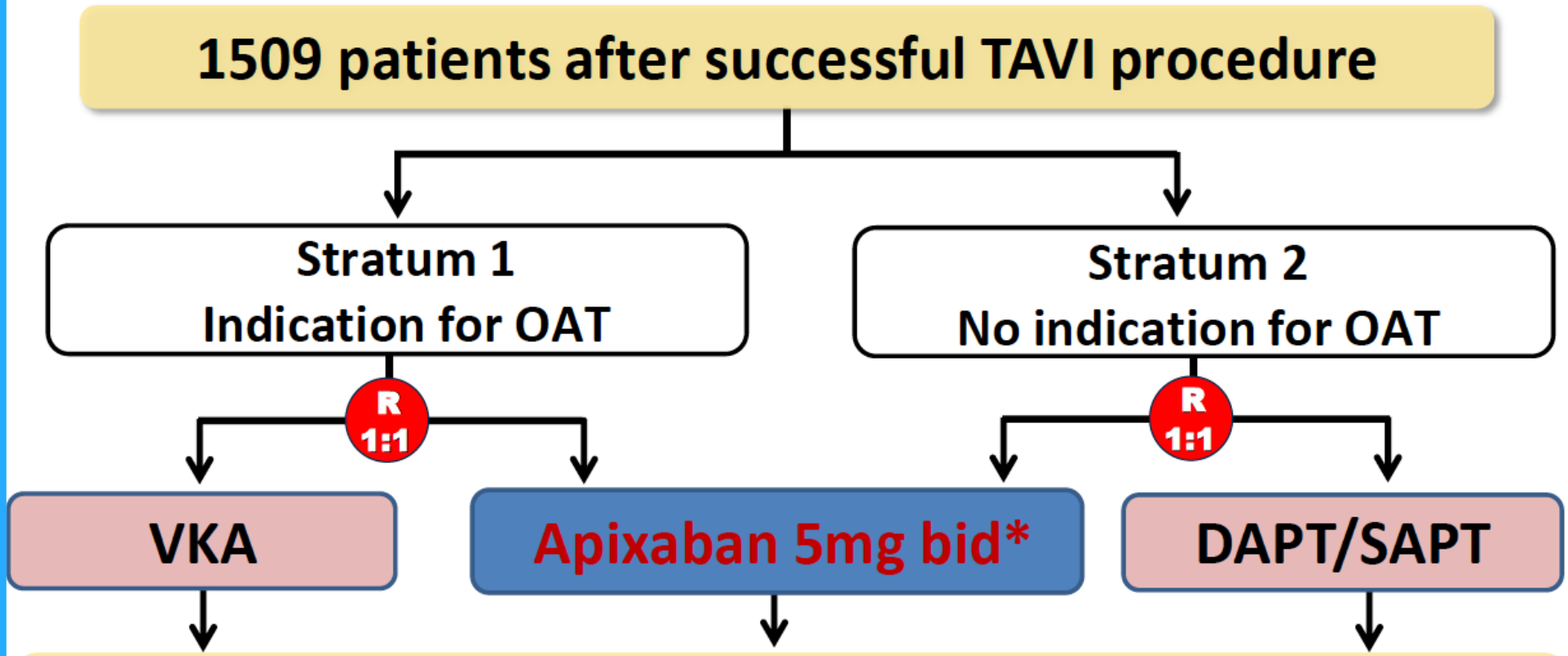
Clopidogrel 75 mg OD Aspirin 75-100 mg OD

Drop of clopi

Aspirin 75-100 mg OD

Primary end-point is **death, MI, stroke, non-CNS systemic emboli, symptomatic valve thrombosis, deep vein thrombosis or pulmonary embolism,major bleedings** ***over 720 days of treatment exposure*****.**

ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)



Primary end-point is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism,major bleedings *over one year follow-up*.

In Summary…

- Current data demonstrated that population hemodynamic trends show excellent durability of the SAPIEN THV without structural deterioration to 5 years.
- Subclinical leaflet thrombosis occurred frequently in bioprosthetic aortic valves, more commonly in TAVR than in SAVR.
- Anticoagulation (both NOACs and warfarin), but not dual antiplatelet therapy, was effective in prevention or treatment of subclinical leaflet thrombosis.

In Summary…

- We are current doing and waiting longer-term follow-up of hemodynamic and clinical data in additional RCTs and several registries.

- The question of whether or not anticoagulation should be recommended is best answered by the two-RCTs (GALILEO and ATLANTIS study) assessing the safety and efficacy of routine anticoagulation in patients after TAVR.

In Clinical Viewpoint…

- Most implanted tissue valves (SAVR and TAVR) can be safely treated by a less invasive approach (TAVR Valve-in-Valve).
- High risk/older patients should be safely/effectively treated by TAVR.
- Low risk/young patients should be carefully evaluated in trials (PARTNER 3 and EVLOLUTE Low-Risk) and in the meantime for them SAVR should remain the treatment of choice.