How to Manage Failed Transcatheter Heart Valve

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Disclosure Statement of Financial Interest

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

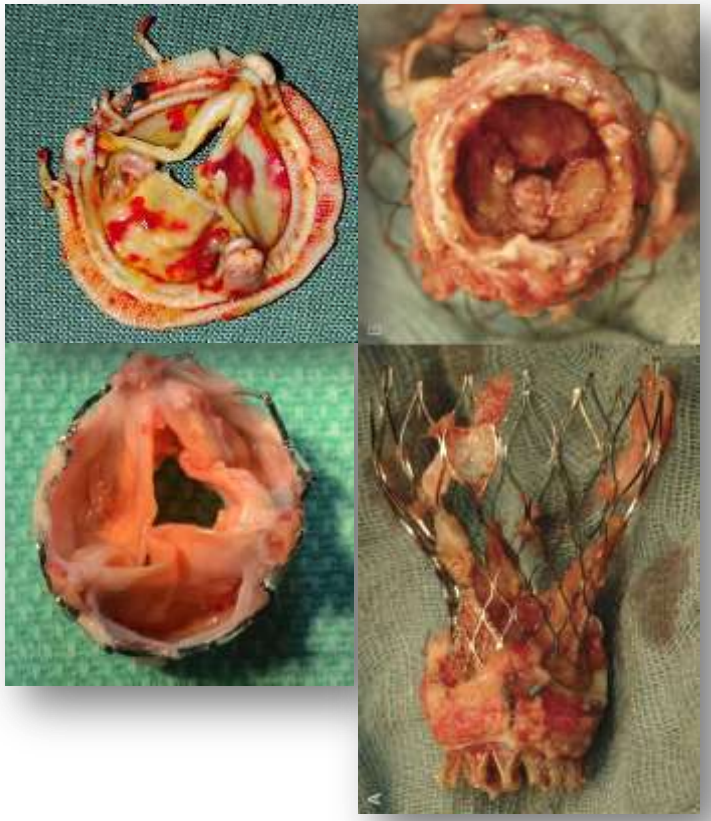
Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences
• Grant/Scientific Advisory Board	• Medtronic
• Executive Physician Council	• Boston Scientific Corp

Failure Mode

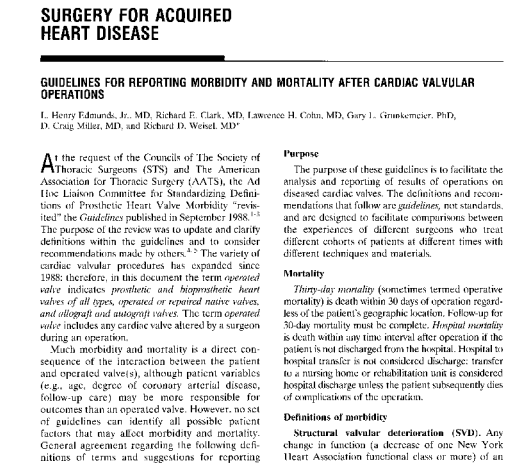
- Structural valve deterioration
- Thrombosis
- Endocarditis

Structural Valve Deterioration

- What is it ?
- How is it assessed ?
- What is the incidence in bioprosthetic valves ?
- How is it treated ?
- What are the differences between SAVR and TAVR ?



What is Structural Valve Deterioration (SVD) ? Definition published in 1996



SURGERY FOR ACQUIRED HEART DISEASE

GUIDELINES FOR REPORTING MORBIDITY AND MORTALITY AFTER CARDIAC VALVULAR OPERATIONS

L. Henry Edmunds, Jr., MD, Richard E. Clark, MD, Lawrence H. Cohn, MD, Gary L. Grunkemeier, PhD, D. Craig Miller, MD, and Richard D. Weisel, MD*

At the request of the Councils of The Society of Thoracic Surgeons (STS) and The American Association for Thoracic Surgery (AATS), the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity "revisited" the *Guidelines* published in September 1988.[1-3] The purpose of the review was to update and clarify definitions within the guidelines and to consider recommendations made by others.[4-7] The variety of cardiac valvular procedures has expanded since 1988; therefore, in this document the term *operated valve* indicates *prosthetic and bioprosthetic heart valves of all types, operated or repaired native valves, and allograft and autograft valves.* The term *operated valve* includes any cardiac valve altered by a surgeon during an operation.

Much morbidity and mortality is a direct consequence of the interaction between the patient and operated valve(s), although patient variables (e.g., age, degree of coronary arterial disease, follow-up care) may be more responsible for outcomes than an operated valve. However, no set of guidelines can identify all possible patient factors that may affect morbidity and mortality. General agreement regarding the following definitions of terms and suggestions for reporting

Purpose

The purpose of these guidelines is to facilitate the analysis and reporting of results of operations on diseased cardiac valves. The definitions and recommendations that follow are *guidelines*, not standards, and are designed to facilitate comparisons between the experiences of different surgeons who treat different cohorts of patients at different times with different techniques and materials.

Mortality

Thirty-day mortality (sometimes termed operative mortality) is death within 30 days of operation regardless of the patient's geographic location. Follow-up for 30-day mortality must be complete. *Hospital mortality* is death within any time interval after operation if the patient is not discharged from the hospital. Hospital to hospital transfer is not considered discharge; transfer to a nursing home or rehabilitation unit is considered hospital discharge unless the patient subsequently dies of complications of the operation.

Definitions of morbidity

Structural valvular deterioration (SVD). Any change in function (a decrease of one New York Heart Association functional class or more) of an

Structural deterioration definition

- Any change in valve function resulting from an *intrinsic* abnormality causing stenosis or regurgitation.
- This category includes valve deterioration exclusive of infected or thrombosed valves as determined by reoperation, autopsy, or clinical investigation.
- The term *structural deterioration* refers to changes *intrinsic* to the valve such as wear, stress fracture, poppet escape, calcification, leaflet tear, stent creep, and disruption or stenosis of a reconstructed valve.

L. Henry Edmunds, Jr., M.D., et al. | Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations, J Thorac Cardiovasc Surg 112:708-11, 1996

How is SVD assessed in surgical valves?

- Assessment of SVD using only clinical evaluation (echo, auscultation, NYHA class) was deemed to be rather subjective, reported rates varied widely from center to center.
- Thus, most centers/studies used the more definitive diagnosis of SVD upon explant of the valve
  - Advantage: removes any subjective evaluation of valve failure
  - Disadvantage: only re-operated valves/patients go into the equation…..

Freedom from Re-Operation for SVD

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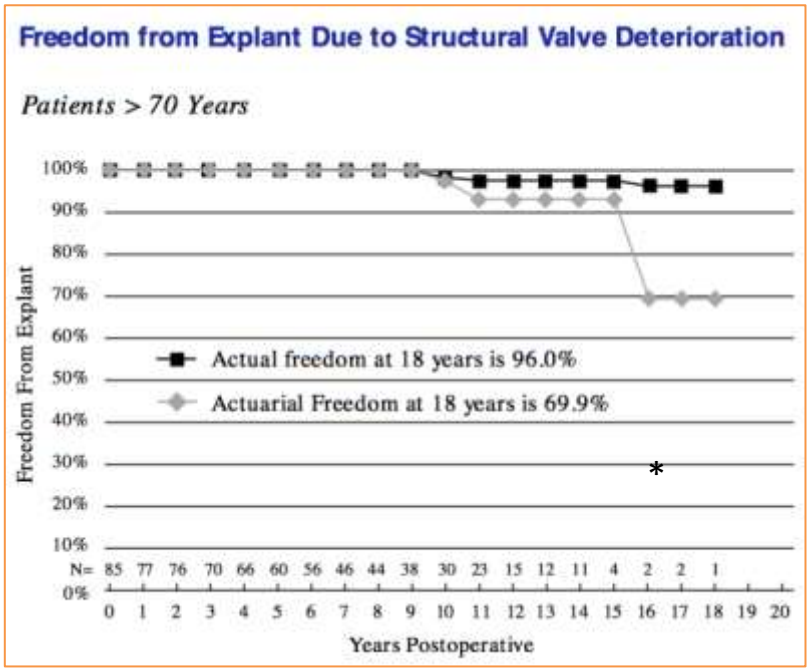
Freedom from SVD

How do we assess surgical valve durability?
20-year results: Freedom from re-operation for SVD



Structural valve deterioration (SVD)(1)

- Explant due to structural valve deterioration (SVD) was required in 36 patients.
- The primary mode of failure was calcification in 35 patients and leaflet tear in one.
- The mean duration of implantation of prostheses with SVD was 17.3 ± 4.0 years.

*** Actuarial freedom from means the percentage of patients whose valve will actually fail before they die. This risk is less than the risk which the usual actuarial curve describes.**(2)

(1) Frater RW *et al.* | Long-term durability and patient functional status of the Carpentier-Edwards Perimount pericardial bioprosthesis in the aortic position. | J Heart Valve Dis. 1998 Jan;7(1):48-53.

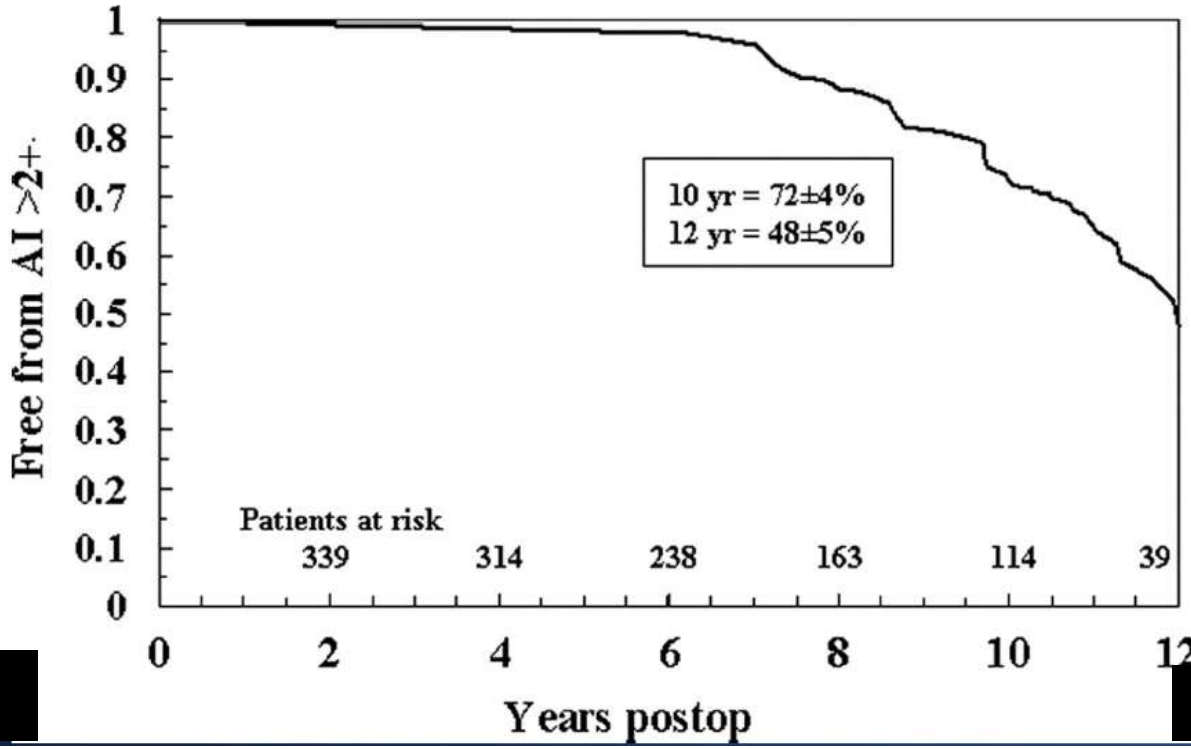
(2) Grunkemeier GL *et al.* | Actuarial versus actual risk of porcine structural valve deterioration. | J Thorac Cardiovasc Surg. 1994 Oct;108(4):709-18.

Freedom from SVD Toronto Valve

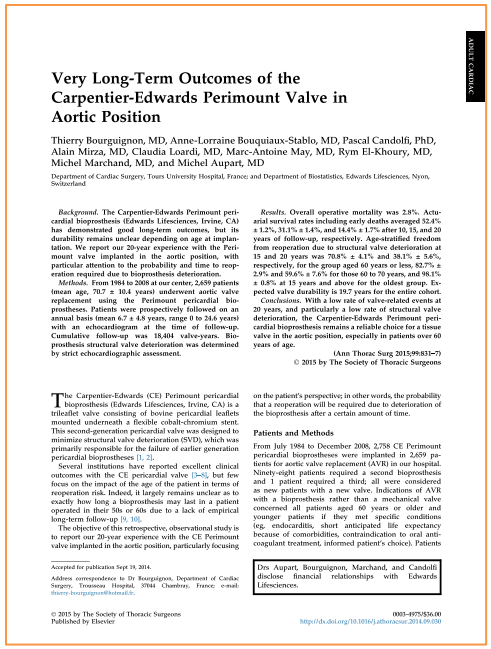
Not all surgical valves show the same good durability

The Toronto Stentless Valve - Freedom from structural valve degeneration

David T. E. et al.; J Thorac Cardiovasc Surg 2008;135:19-24



Long-term follow-up of surgical bioprothesis: Newer Definition of SVD



ADULT CARDIAC

Very Long-Term Outcomes of the Carpentier-Edwards Perimount Valve in Aortic Position

Thierry Bourguignon, MD, Anne-Lorraine Bouquiaux-Stablo, MD, Pascal Candolfi, PhD, Alain Mirza, MD, Claudia Loardi, MD, Marc-Antoine May, MD, Rym El-Khoury, MD, Michel Marchand, MD, and Michel Aupart, MD

Department of Cardiac Surgery, Tours University Hospital, France; and Department of Biostatistics, Edwards Lifesciences, Nyon, Switzerland

Background. The Carpentier-Edwards Perimount pericardial bioprosthesis (Edwards Lifesciences, Irvine, CA) has demonstrated good long-term outcomes, but its durability remains unclear depending on age at implantation. We report our 20-year experience with the Perimount valve implanted in the aortic position, with particular attention to the probability and time to reoperation required due to bioprosthesis deterioration.

Methods. From 1984 to 2008 at our center, 2,659 patients (mean age, 70.7 ± 10.4 years) underwent aortic valve replacement using the Perimount pericardial bioprostheses. Patients were prospectively followed on an annual basis (mean 6.7 ± 4.8 years, range 0 to 24.6 years) with an echocardiogram at the time of follow-up. Cumulative follow-up was 18,404 valve-years. Bioprosthesis structural valve deterioration was determined by strict echocardiographic assessment.

Results. Overall operative mortality was 2.8%. Actuarial survival rates including early deaths averaged 52.4% ± 1.2%, 31.1% ± 1.4%, and 14.4% ± 1.7% after 10, 15, and 20 years of follow-up, respectively. Age-stratified freedom from reoperation due to structural valve deterioration at 15 and 20 years was 70.8% ± 4.1% and 38.1% ± 5.6%, respectively, for the group aged 60 years or less, 82.7% ± 2.9% and 59.6% ± 7.6% for those 60 to 70 years, and 98.1% ± 0.8% at 15 years and above for the oldest group. Expected valve durability is 19.7 years for the entire cohort.

Conclusions. With a low rate of valve-related events at 20 years, and particularly a low rate of structural valve deterioration, the Carpentier-Edwards Perimount pericardial bioprosthesis remains a reliable choice for a tissue valve in the aortic position, especially in patients over 60 years of age.

(Ann Thorac Surg 2015;99:831–7)

The Carpentier-Edwards (CE) Perimount pericardial bioprosthesis (Edwards Lifesciences, Irvine, CA) is a trileaflet valve consisting of bovine pericardial leaflets mounted underneath a flexible cobalt-chromium stent. This second-generation pericardial valve was designed to minimize structural valve deterioration (SVD), which was primarily responsible for the failure of earlier generation pericardial bioprostheses [1, 2].

Several institutions have reported excellent clinical outcomes with the CE pericardial valve [3–8], but few focus on the impact of the age of the patient in terms of reoperation risk. Indeed, it largely remains unclear as to exactly how long a bioprosthesis may last in a patient operated in their 50s or 60s due to a lack of empirical long-term follow-up [9, 10].

The objective of this retrospective, observational study is to report our 20-year experience with the CE Perimount valve implanted in the aortic position, particularly focusing on the patient's perspective; in other words, the probability that a reoperation will be required due to deterioration of the bioprosthesis after a certain amount of time.

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0003–4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2014.09.030

Patients and Methods

From July 1984 to December 2008, 2,758 CE Perimount pericardial bioprostheses were implanted in 2,659 patients for aortic valve replacement (AVR) in our hospital. Ninety-eight patients required a second bioprosthesis and 1 patient required a third; all were considered as new patients with a new valve. Indications of AVR with a bioprosthesis rather than a mechanical valve concerned all patients aged 60 years or older and younger patients if they met specific conditions (eg, endocarditis, short anticipated life expectancy because of comorbidities, contraindication to oral anticoagulant treatment, informed patient's choice). Patients

Drs Aupart, Bourguignon, Marchand, and Candolfi disclose financial relationships with Edwards Lifesciences.

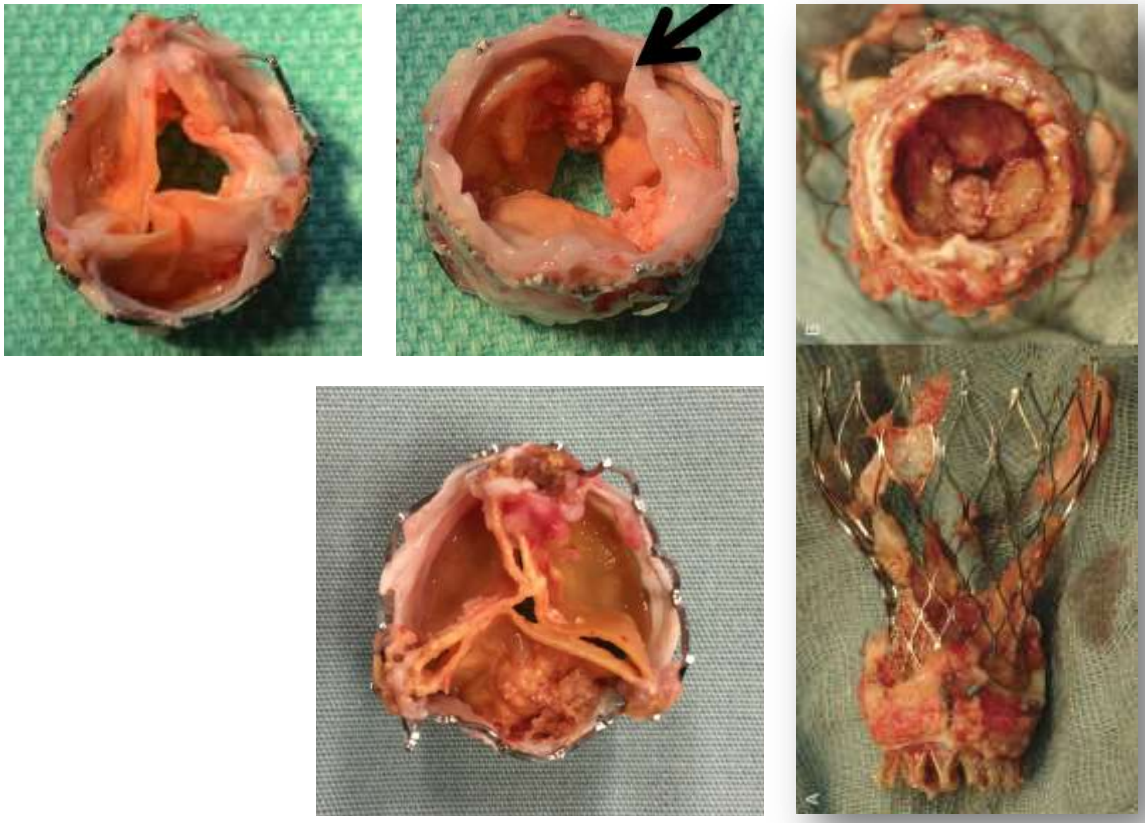
Structural Valve Deterioration (SVD) and Reoperation for SVD

- The bioprosthesis was considered to have deteriorated on strict echocardiographic assessment whenever severe aortic stenosis (mean transvalvular gradient > 40 mm Hg) or severe aortic regurgitation (effective regurgitant orifice area > 0.30 cm2, vena contracta > 0.6 cm) was observed, even if the patient was asymptomatic.

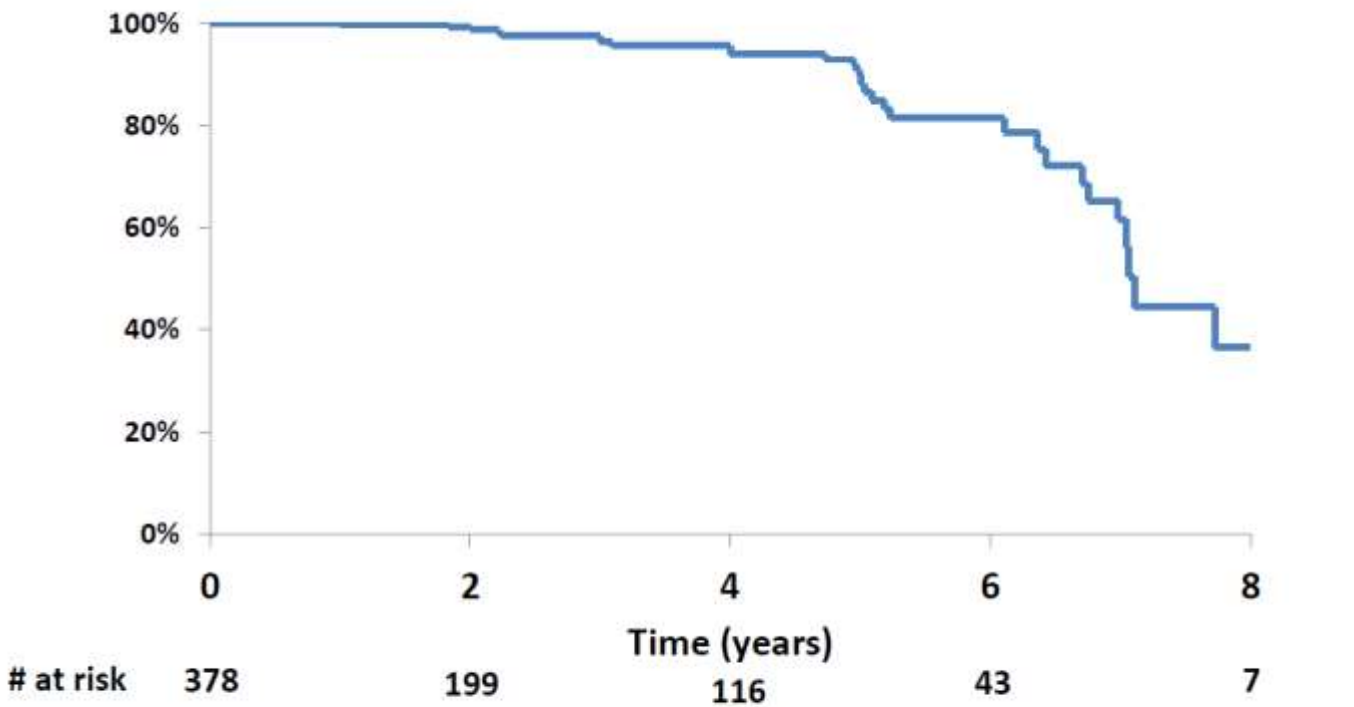
Bourguignon T. *et al* | Very Long-Term Outcomes of the Carpentier-Edwards Perimount Valve in Aortic Position | Ann Thorac Surg 2015;99:831–7

What is the durability of TAVR?

TAVR bioprotheses long-term follow-up:
Based on freedom SVD



TAVR bioprotheses long-term follow-up: Based on THV Degeneration



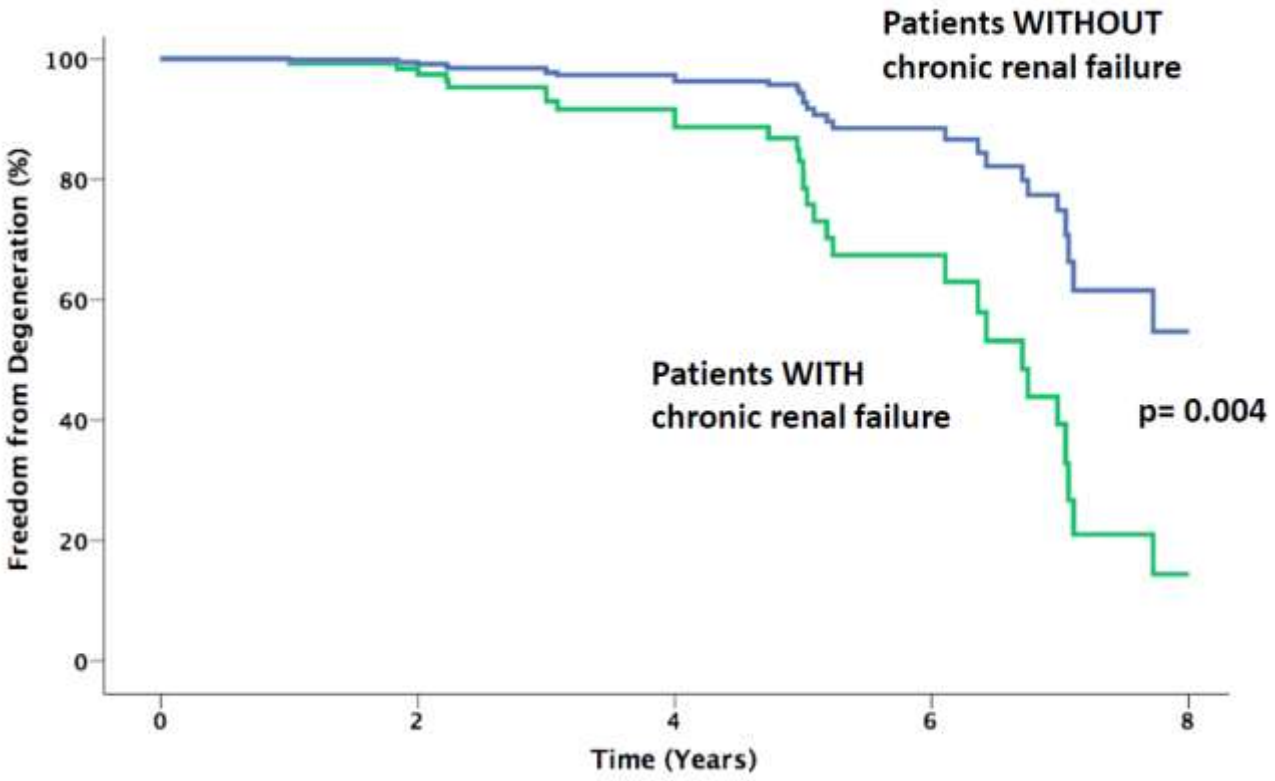
THV degeneration was defined as at least moderate regurgitation AND/OR mean gradient ≥ 20mmHg, which did not appear within 30 days of the procedure and is not related to endocarditis.
KM estimate of THV degeneration included censoring of patients at their date of last known THV functioning well without evidence for degeneration per study definition.

<u>Definition of THV Degeneration:</u>

- Moderate aortic regurgitation
  And/or
- Mean Gradient ≥ 20mmHg
- Not related to endocarditis

D. Dvir, EuroPCR 2016

TAVR bioprotheses long-term follow-up: Based on THV Degeneration



Baseline renal failure (GFR<60cc/min) was the strongest correlate for THV degeneration HR=3.22, CI 1.45-7.15, p=0.004

Treatment for SVD

- Observation
- TAVR V in V

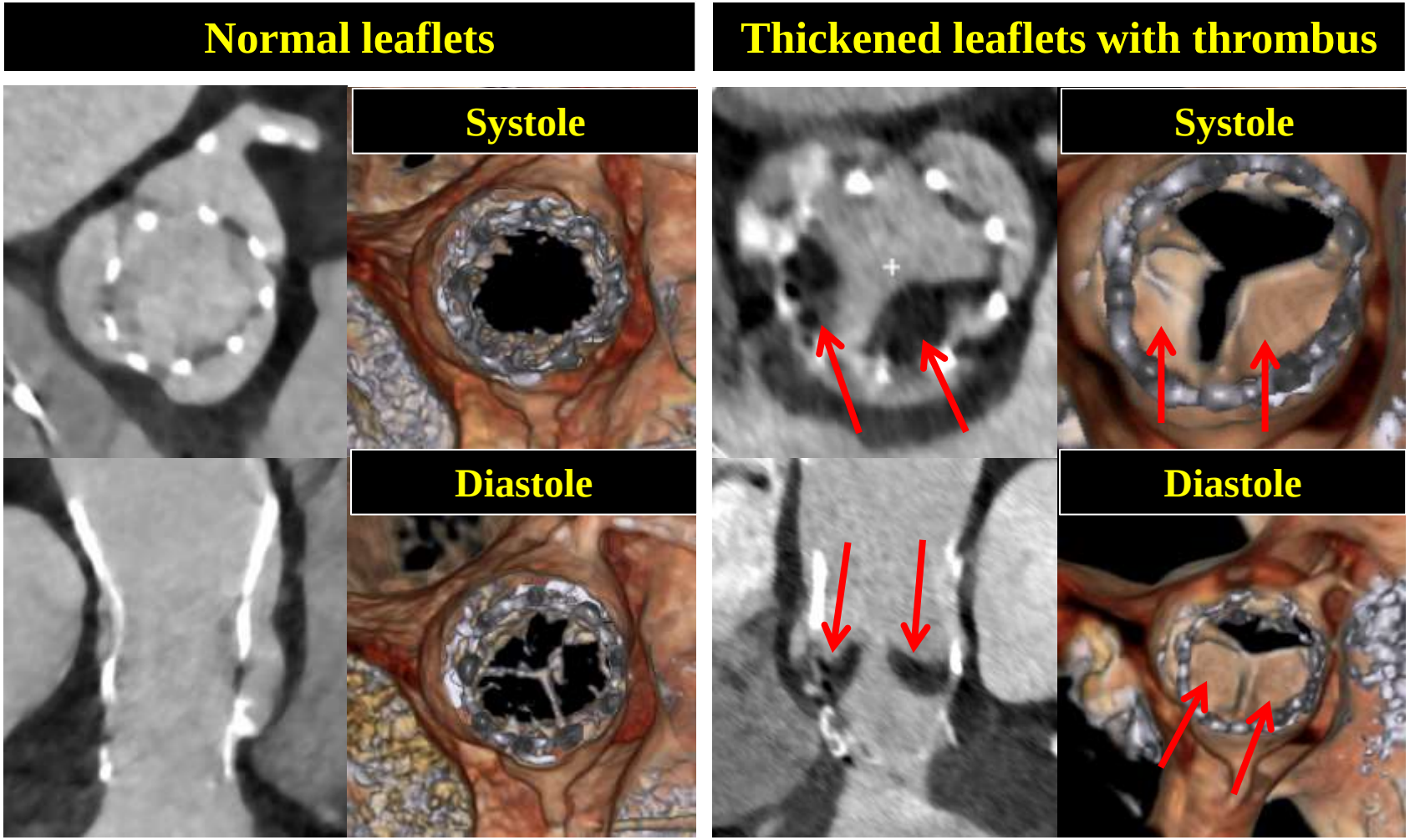
Prevalence of subclinical leaflet thrombosis is more common than clinical thrombosis

ORIGINAL ARTICLE

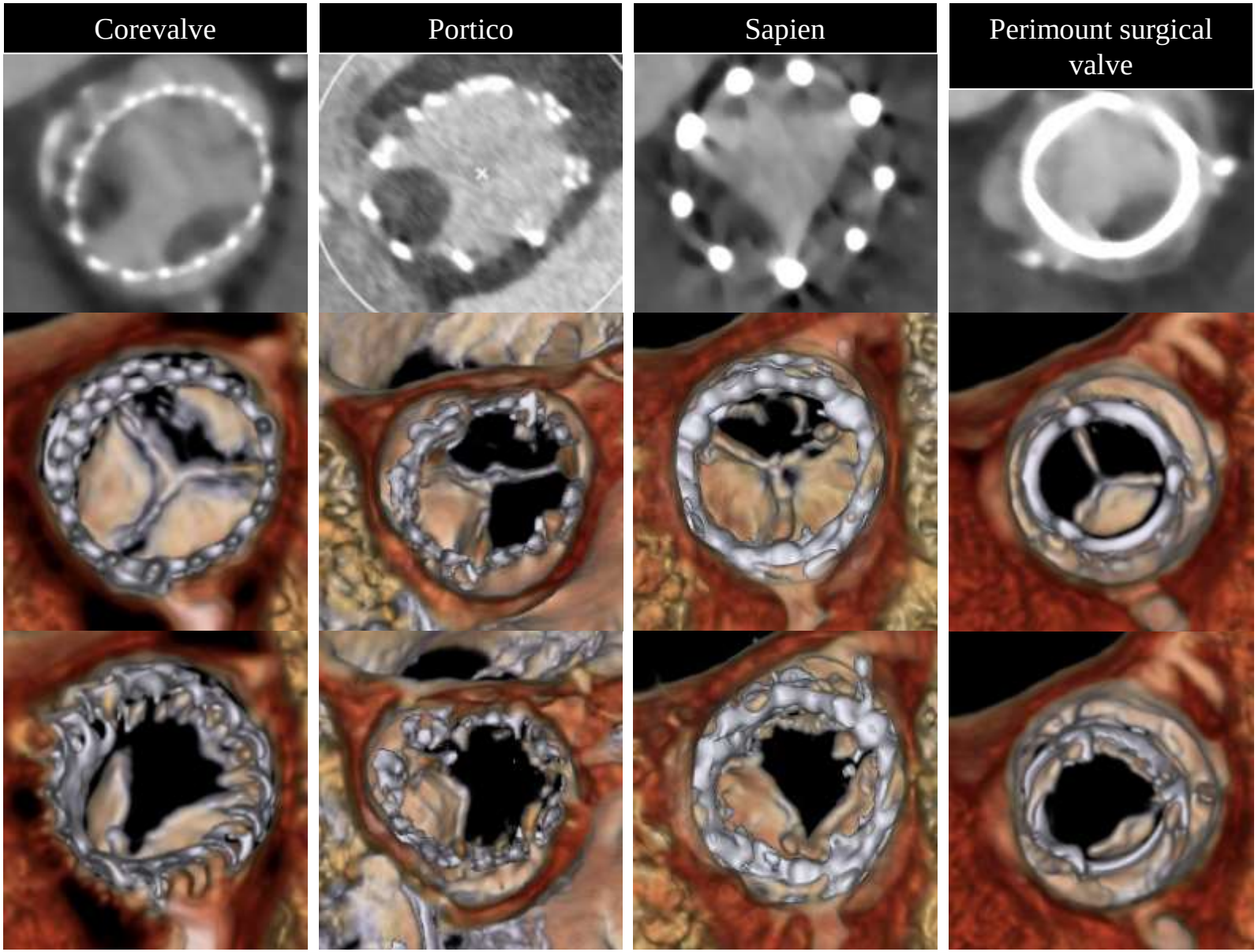
Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

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

Volume rendered CT images of bioprosthetic valves



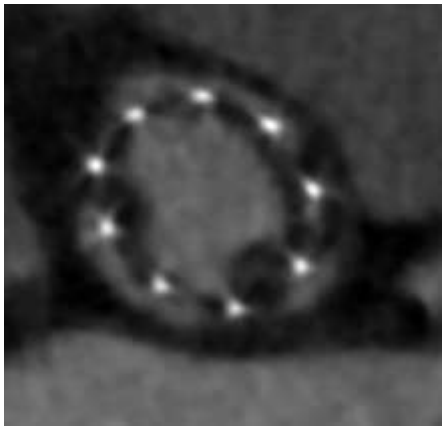
Reduced leaflet motion was observed in all valve types including surgical bioprostheses



HALT & HAM definitions

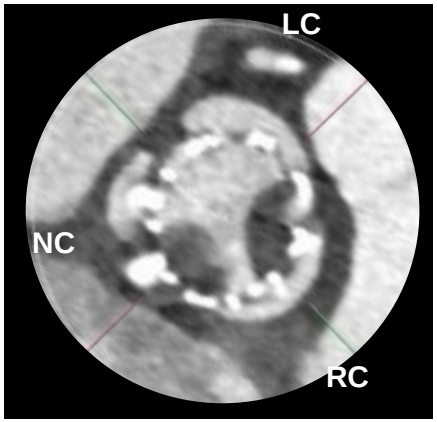
HALT: Hypo-Attenuating Leaflet Thickening

- Involving the periphery and base of the leaflet and extend to varying degrees to the edges of the leaflet



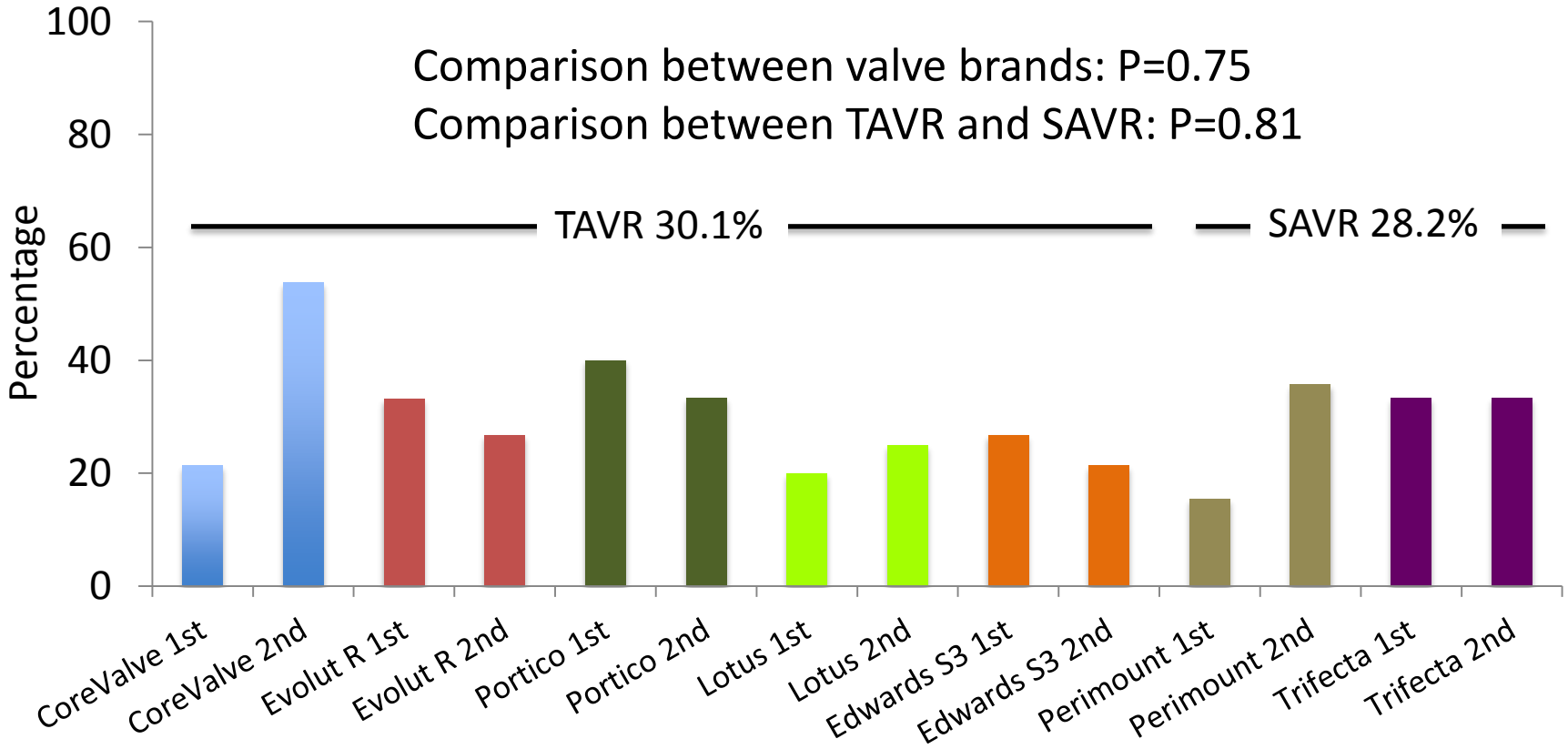
HAM: Hypo-Attenuation affecting Motion

- Reduction in leaflet motion *in the presence of HALT*
- A reduction in leaflet excursion of more than 50% was considered significant



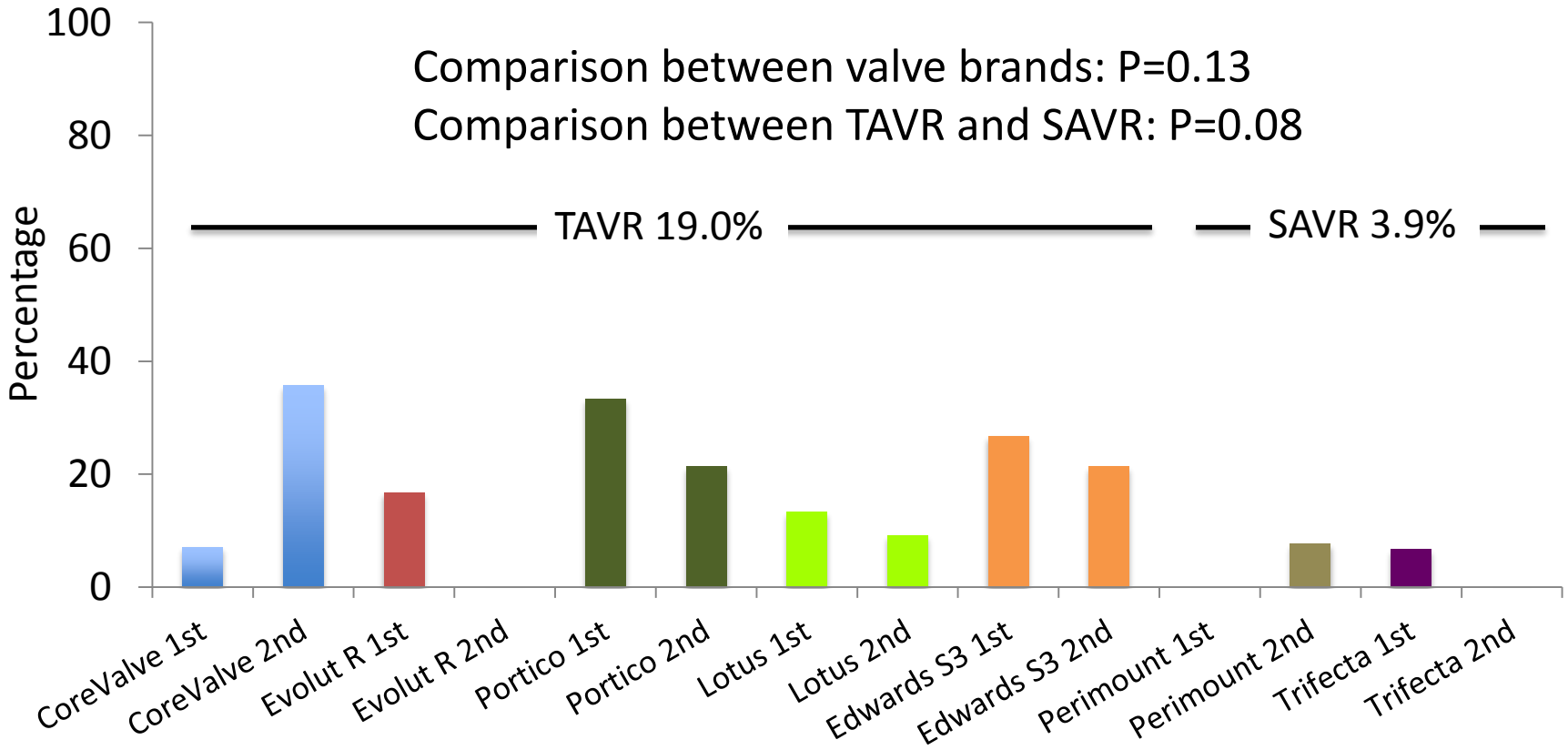
Prevalence of HALT

baseline and follow-up scan

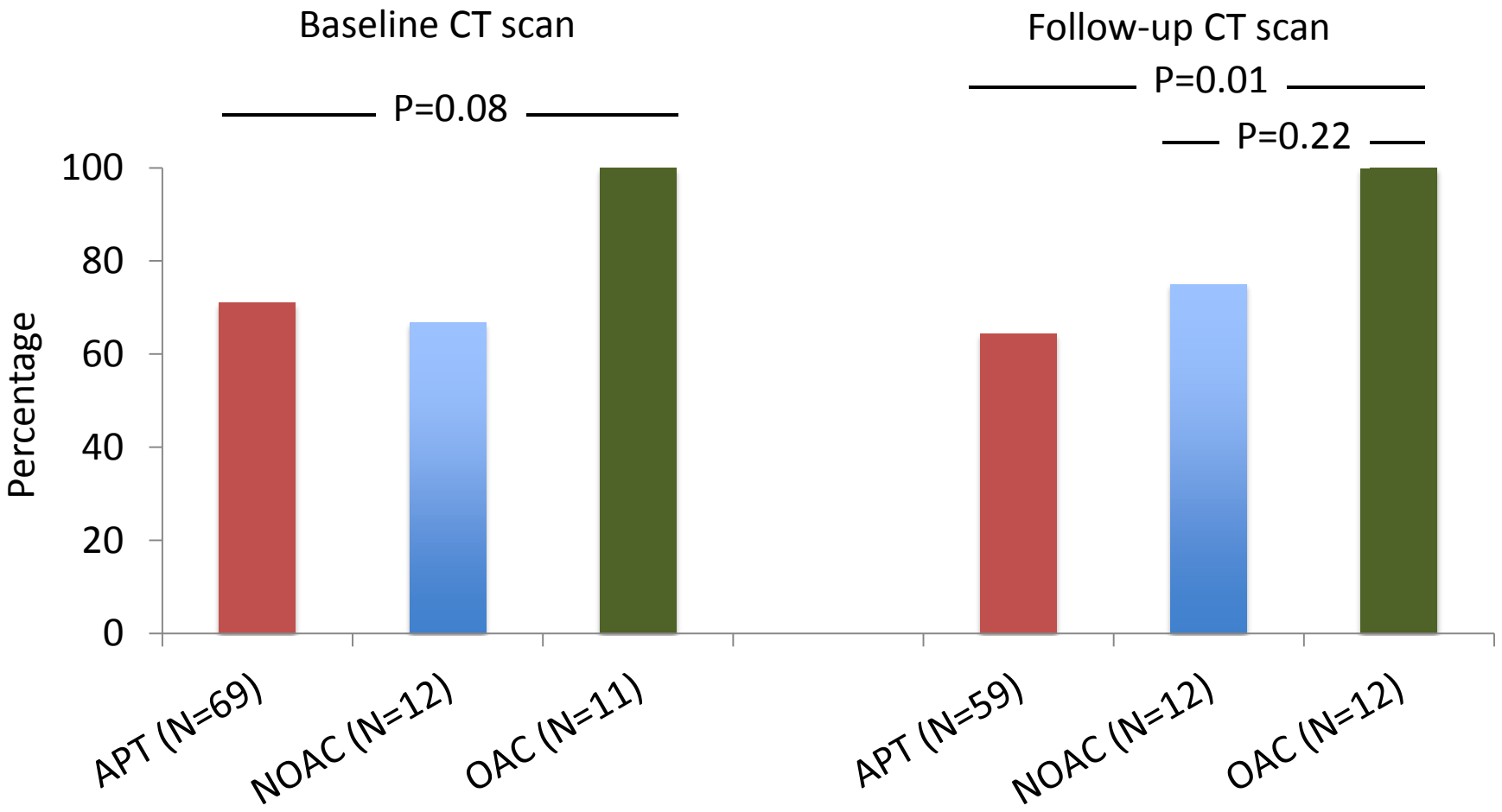


Prevalence of HAM

baseline and follow-up scan



Medication & freedom from HALT



Incidence of valve thrombosis – Bad Segeberg Experience

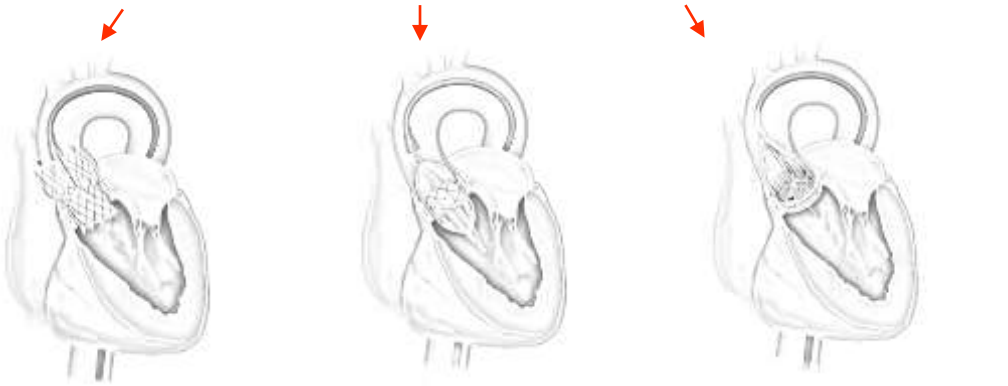
TAVR, *N=649*

642 patients

Self expanding, n= 309
Balloon expandable, n=284
Differential deployment, n=56

Valve thrombosis, *N=18*

Overall Incidence: 2.8%



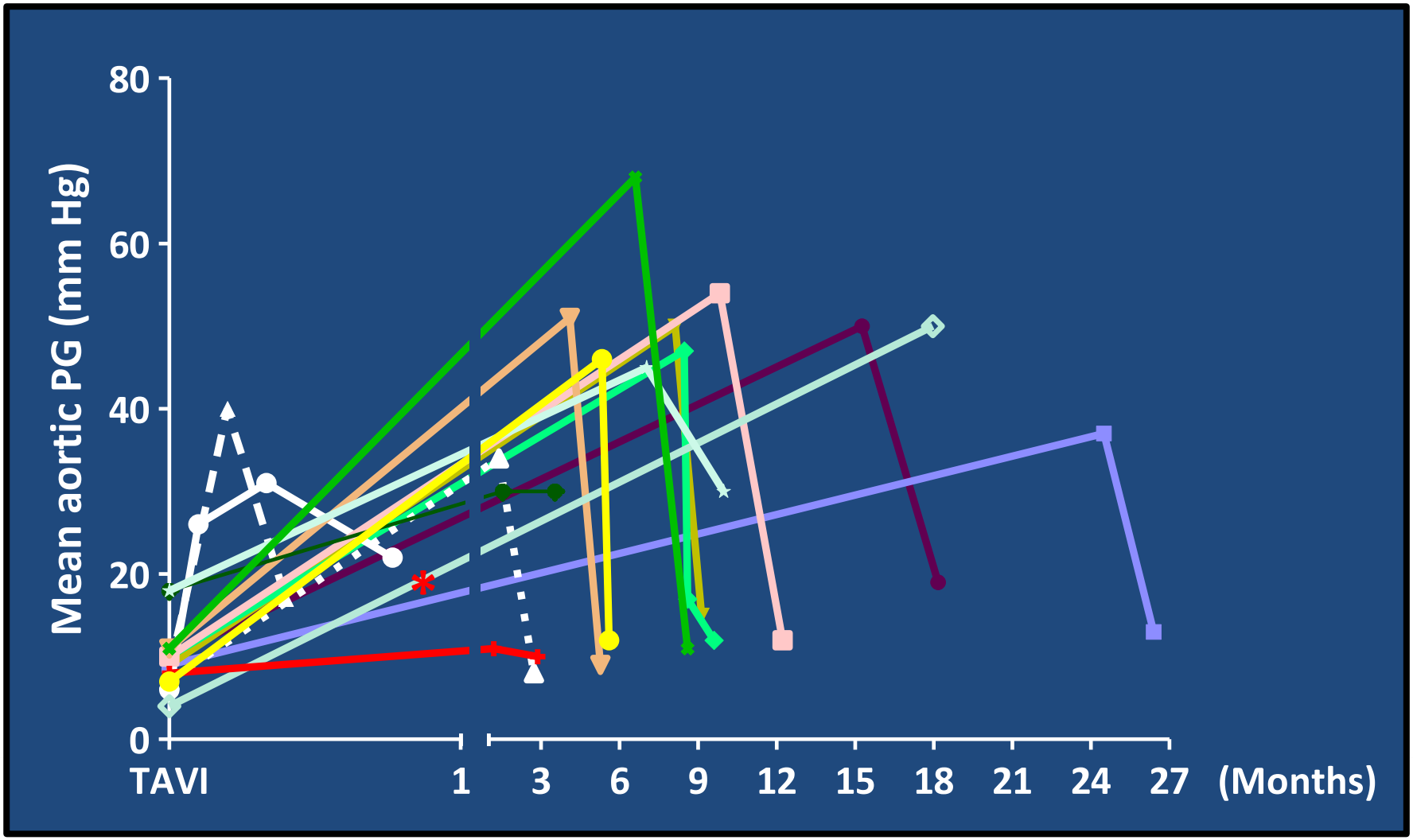
CoreValve, *n=3*

SAPIEN, *n=13*

Lotus, *n=2*

Slide courtesy of Dr Abdel-Wahab

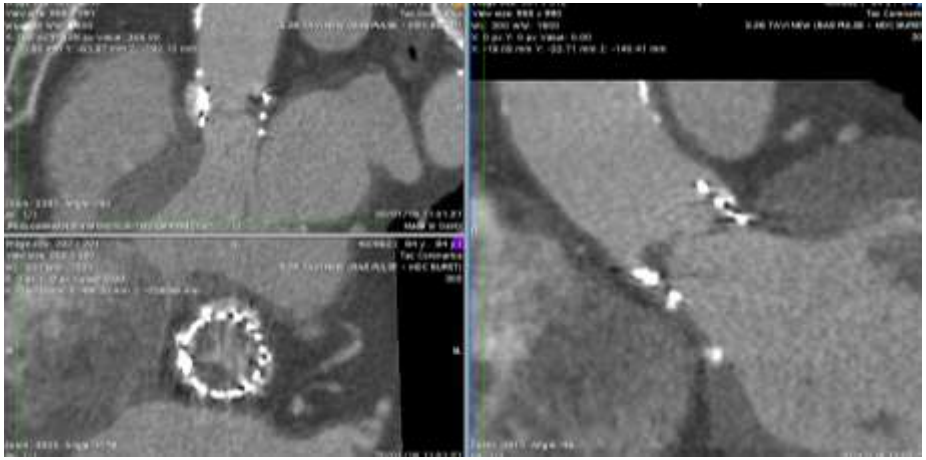
Onset is Variable but may occur as early as 3 days to as late as 3 years after TAVR



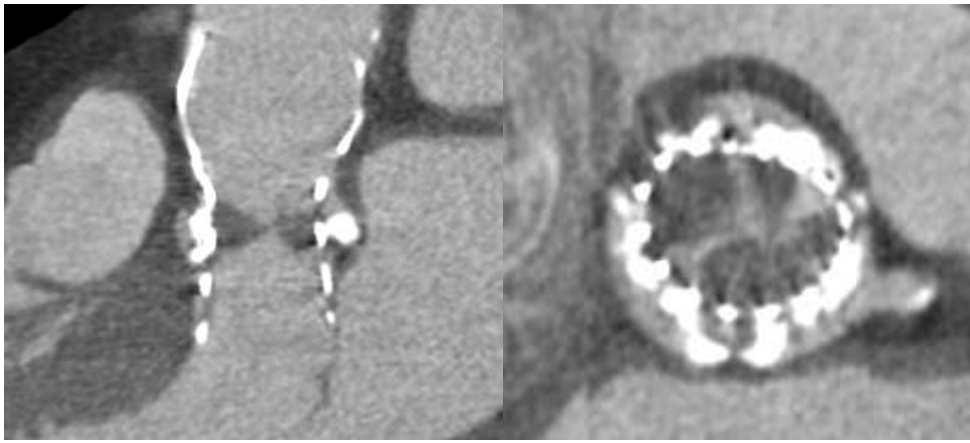
Clinical presentation

- Presentation of Clinical Thrombosis
  - Dyspnea in 2/3
  - High or increasing gradient in over 90%
  - Embolic phenomenon appear to be uncommon
- No clearly identified predictors
  - Thombophilias
  - Valve-in-valve (Abdel Wahab et al.)

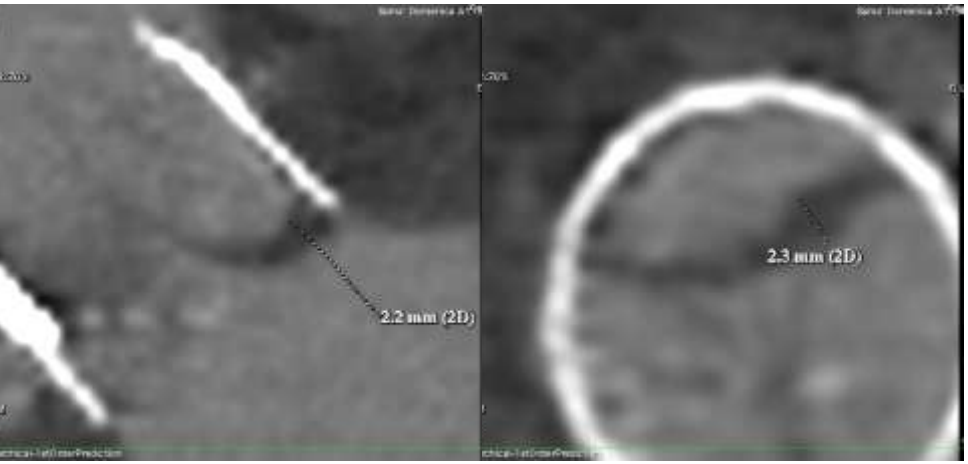
Thrombosis can occur with any of the currently available devices



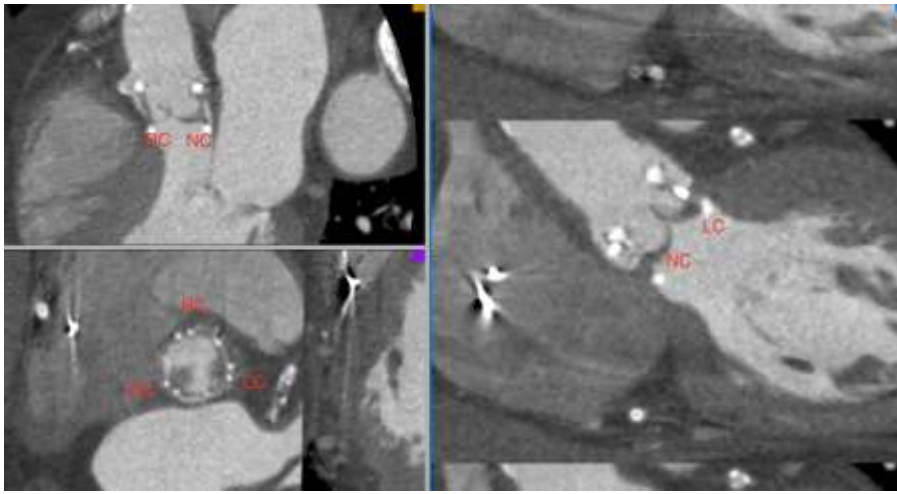
Edwards



CoreValve

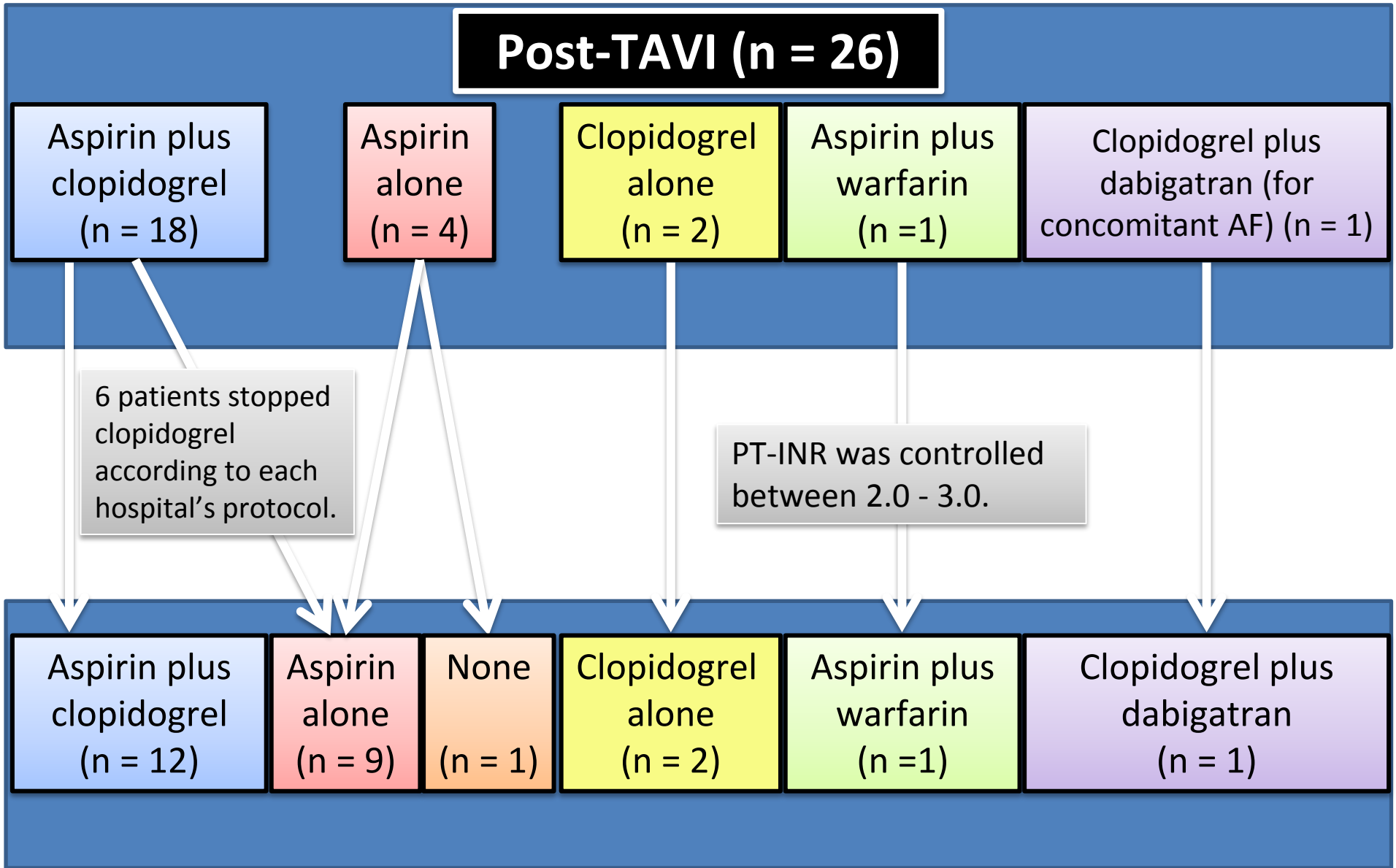


Lotus

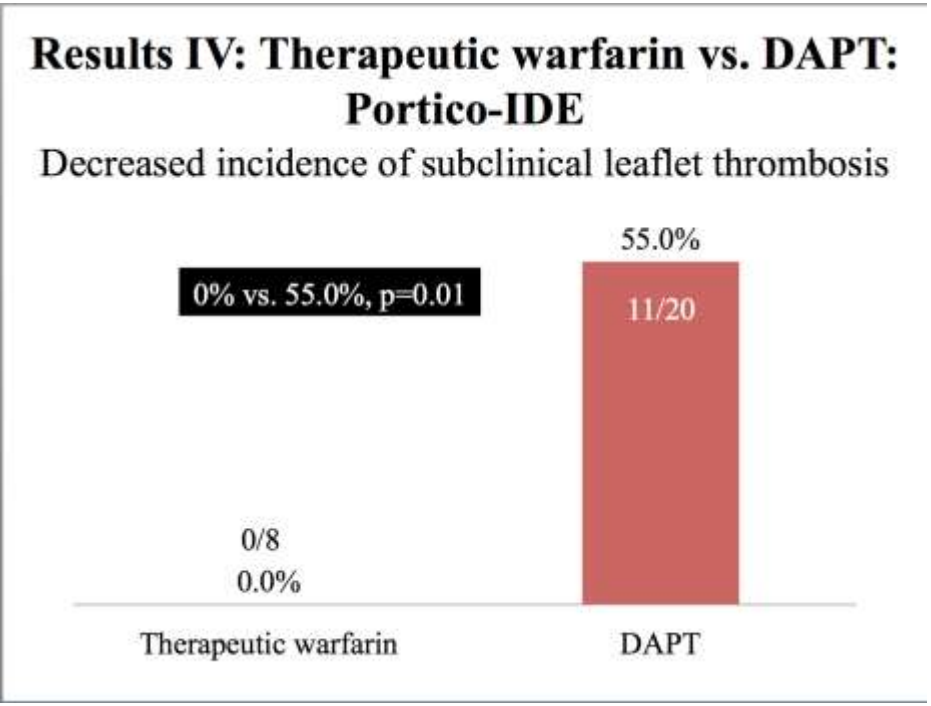


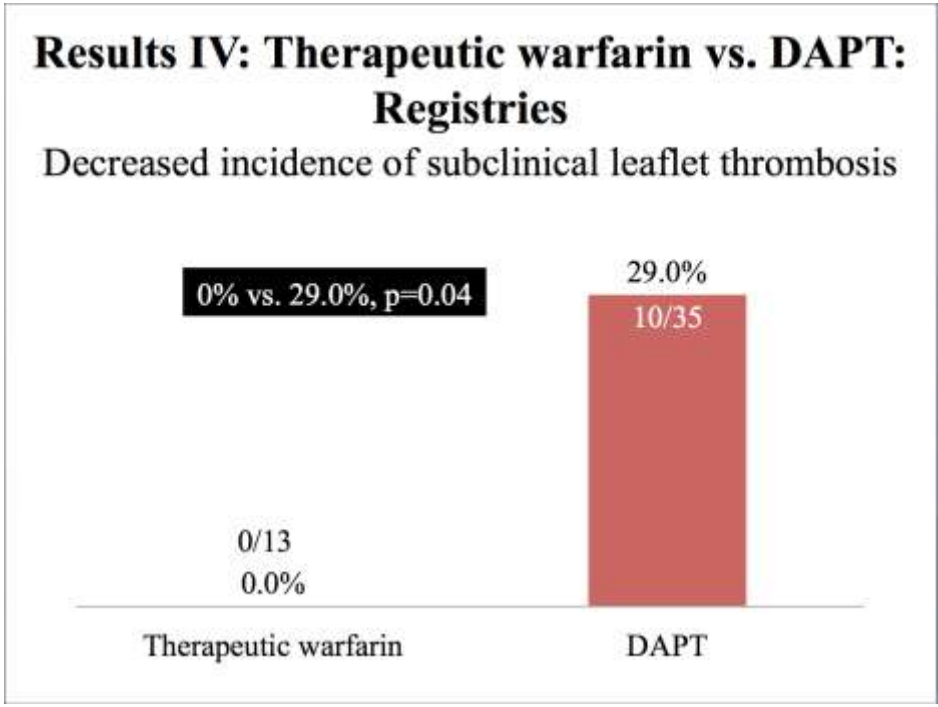
Direct Flow

Relationship to DAPT is unclear



Relationship to DAPT is unclear but Warfarin appears to be protective!





Relationship to DAPT is unclear but Warfarin appears to be protective!

TAVR, *N=649*

Antiplatelets
n = 378

Oral Anticoagulants
n =267

P <0.001

Valve thrombosis, N=18 (4.8%)

Valve thrombosis, N=0

CoreValve, *n=3*

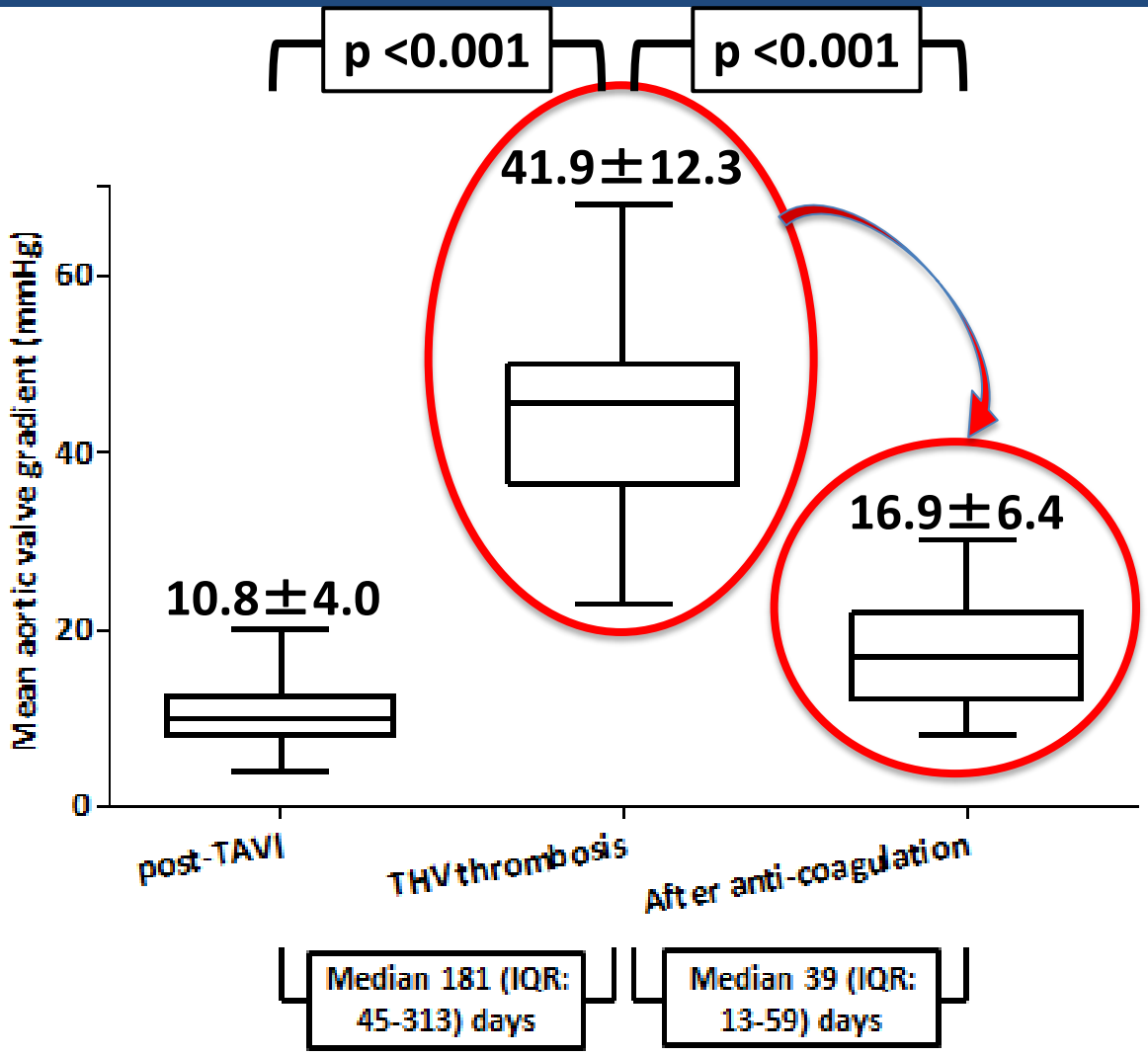
SAPIEN, *n=13*

Lotus, *n=2*

Incidence of valve thrombosis on antiplatelets = 4.8%

Slide courtesy of Dr Abdel-Wahab

Response to anticoagulation is usually rapid

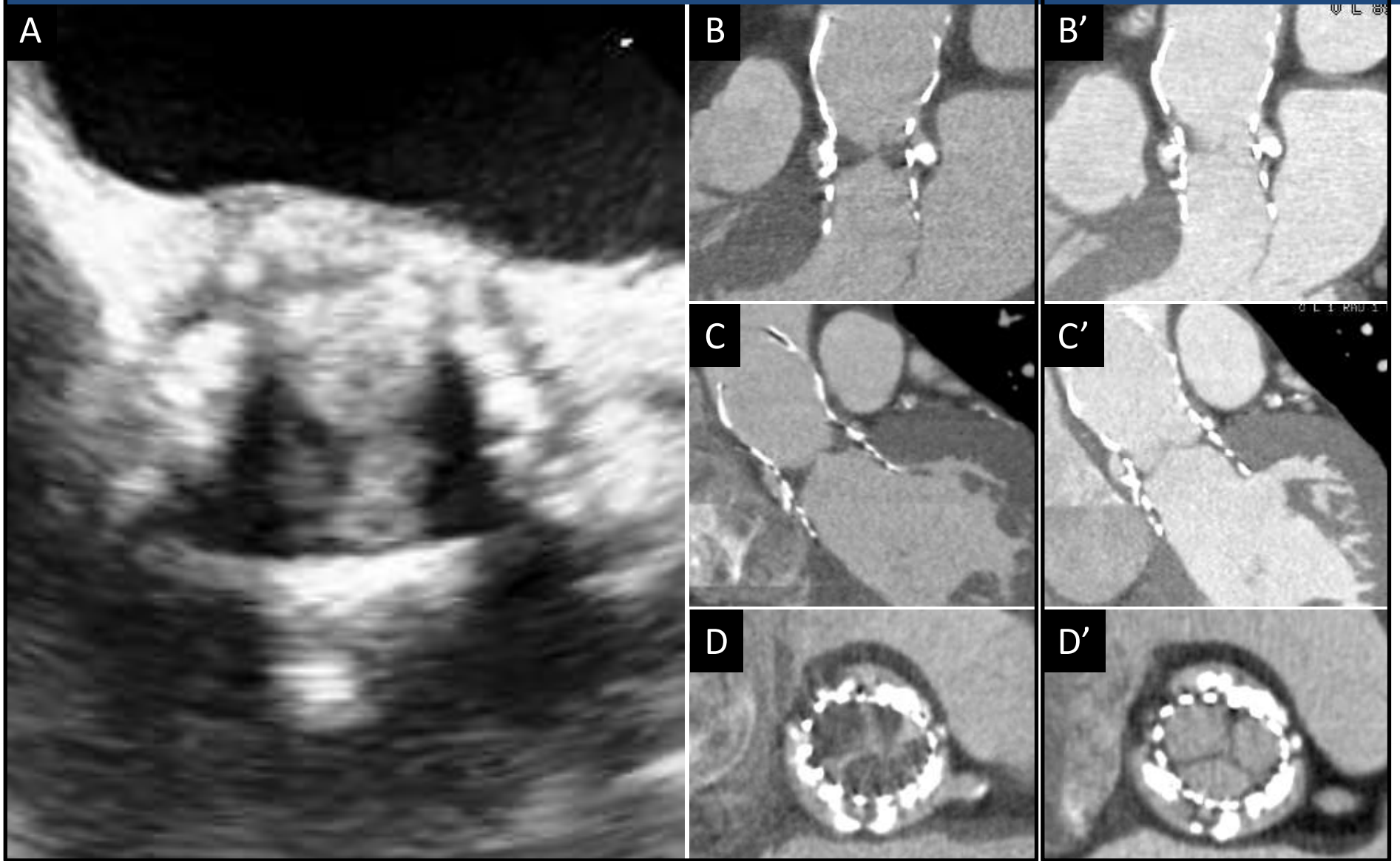


23/26 (88.4%) patients were successfully treated with anticoagulation.

Never too late for a trial of Anticoagulation

Increase in gradient found (10→50) **at 17-months after TAVI. Patient treated only DAPT until 32 months after TAVI with minimal change in gradient (32mmHg).** Switched to AC 15-mo after 1st signs of THV thrombosis

Complete resolution (8mmHg) after **8-mo of AC**



Treatment for HALT, HAM and Thrombosis

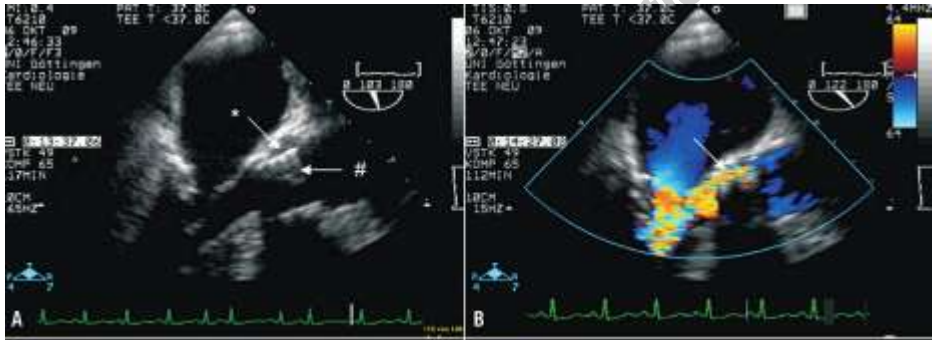
- Warfarin
- ? And DAPT

Koh YS et al. Eur J Cardiothorac Surg 2013.

Prosthetic valve endocarditis after transcatheter aortic valve implantation: the incidence in a single-centre cohort and reflections on clinical, echocardiographic and prognostic features

- First 180 patients, median 319 days FU
- 5 cases of IE (4 early onset, 1 late onset)
  - 2 fatal
- Overall incidence 3.4%
- Comments
  - Difficult to diagnose
  - TAVI patients particularly vulnerable
  - Limited experience with image interpretation
- Mechanisms
  - Paravalvular leak common - possible nidus for infection
  - Role of stiff wire – endothelial damage
  - Lack of complete endothelialisation
  - Role of leaflet thickening
  - Lots of metal
  - Residual valve disease

	Case 1	Case 2	Case 3	Case 4	Case 5
Patient	male, 80 y	female, 81 y	female, 80 y	male, 85 y	female, 91 y
log. EuroSCORE	30%	48%	41%	23%	25%
Type of prosthesis	CoreValve 29 mm	Edwards SAPIEN 23 mm	Edwards SAPIEN 23 mm	Edwards SAPIEN 23 mm	Edwards SAPIEN 23 mm
Approach	transfemoral	transapical	transapical	transfemoral	transapical
Time between TAVI and hosp. for PVE	207 days	146 days	379 days	187 days	696 days
Delay of diagnosis	none	none	64 days	none	none
Type of PVE	early-onset	early-onset	early-onset	early-onset	late-onset
Level of diagnosis (modified Duke criteria[14])	Definite diagnosis (criteria IA, IIA, a, b, c)	Definite diagnosis (criteria IA, IIA, a, b)	Definite diagnosis (criteria IA, IIA, a, b, c)	Definite diagnosis (criteria IB, a, b, d)	Possible diagnosis (criteria IA, a, b)
Predisposing conditions (apart from prosthetic aortic valve)	Diabetes, MRSA-colonisation, Prosthetic mitral valve	Diabetes, reactivation tuberculosis	none	complicated in-hospital course after TAVI (renal replacement therapy, new pacemaker)	very advanced age
Device function directly after TAVI	mild paravalvular AR	moderate paravalvular AR	mild paravalvular AR	moderate paravalvular AR	no relevant AR
Pathogen (blood cultures)	MRSA	Enterococcus faecalis	Enterococcus faecalis	Escherichia coli	Viridans streptococci
Outcome	died	alive	alive	died	alive



Puls M *et al*

EuroIntervention 2013;8:**1407-1418** published online ahead of print September 2012

TAVR-Associated Prosthetic Valve Infective Endocarditis

Results of a Large, Multicenter Registry

- Multicentre study: 2572 patients in 14 centres - elderly high risk cohort (mean age 80, STS 13)
- 55% procedures in catheter lab - 1191 BE, 1343 SE
- Overall incidence of IE 1.1% (n=29) - TF 1.1%, TA 2.0% (BE 1.9%, SE 0.5%)
- Early/intermediate onset in 80% - majority managed medically - one year survival 38%

TABLE 1 Microbiological Etiology in Patients With TAVR-PIE Diagnosis

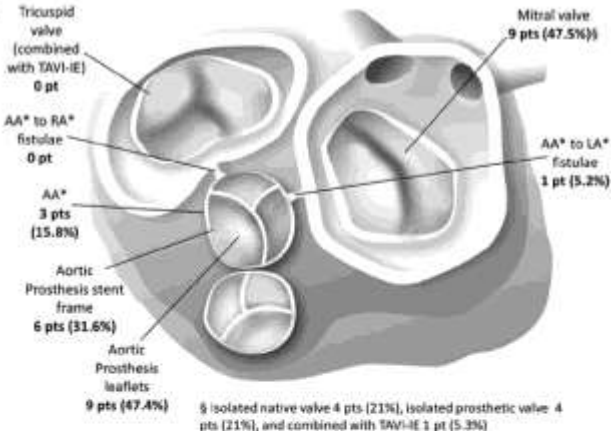
	All TAVR-PIE (n = 29)	Early-Onset (n = 8)	Intermediate-Onset (n = 15)	Late-Onset (n = 6)
Staphylococcus	9 (31)	4 (50)	3 (20)	2 (33)
S aureus	4 (14)	2 (25)	2 (13)	–
Coagulase-negative staphylococci	5 (17)	2 (25)	1 (6.5)	2 (33)
Enterococci	6 (21)	1 (13)	3 (20)	2 (33)
Streptococcus	4 (14)	–	4 (27)	–
Viridans group streptococci	1 (3.4)	–	1 (7)	–
Other streptococci	3 (10)	–	3 (20)	
HACEK	1 (3.4)	–	1 (7)	–
Non-HACEK gram negative bacteria*	1 (3.4)	–	1 (7)	–
Granulicatella adiacens	1 (3.4)	–	1 (7)	–
Polymicrobial†	1†	1†		–
Typical micro-organisms	13 (45)	2 (25)	9 (60)	2 (33)
Negative cultures	5 (17)	4 (50)	1 (7)	–
N/A	3 (10)	–	1 (7)	2 (33)

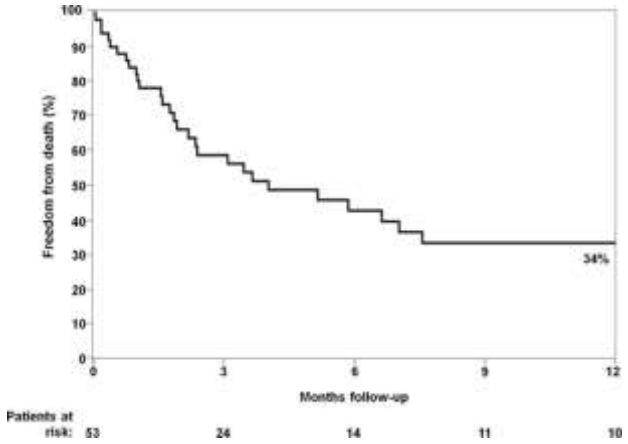
Latib A *et al*. J Am Coll Cardiol 2014;64:2176-2178.

Infective Endocarditis After Transcatheter Aortic Valve Implantation

Results From a Large Multicenter Registry

- Multicentre registry
  - 7944 TAVI recipients (mean 70 yrs, 57% male)
  - Mean FU 1.1+/- 1.2 yrs
- Incidence of IE 0.67% (n=53)
  - ET intubation (HR 3.9)
  - Corevalve (HR 3.1)
- Microbiology
  - *Staphylococcus aureus* 21%,
  - Coagulase negative *Staphylococcus aureus* 24%
  - Enterococci 21%
- Management
  - Complications common (CHF 68%)
  - Medical therapy predominant
  - Reintervention 11%
- Mortality
  - In-hospital 47%
  - One year 66%





Amot-Santos IJ *et al*. Circulation 2015;131:1566-1574.

Incidence, Predictors, and Outcome of Patients Developing Infective Endocarditis Following Transfemoral Transcatheter Aortic Valve Replacement

Norman Mangner, MD; Felix Woitek, MD; Stephan Haussig, MD; Florian Schlotter, MD; Georg Stachel, MD; Robert Höllriegel, MD; Johannes Wilde, MD; Anna Lindner, MD; David Holzhey, MD; Sergey Leontyev, MD; Friedrich W. Mohr, MD; Gerhard Schuler, MD; Axel Linke, MD

- **Single centre cohort** of 55 patients (Leipzig, Germany): TAVR-IE 2006 - 2014
- **Cumulative incidence 3.02%**; incidence rate 1.82% per patient year. Definite IE 64%, possible IE 36% (modified Duke)
- **Early IE (<12 months) 75%** - median 35 days post-procedure, late IE 25% - median 628 days
- Risk factors: on multivariate analysis, **chronic hemodialysis (HR 8.37; 95% CI 2.54- 27.63; p < 0.001)** & peripheral artery disease (HR: 3.77; 95% CI 1.88-7.58; p < 0.001)
- Microbiology: **S. aureus (38%), *Enterococci* (31%)**, CNS 9.1%, *Streptococci* 3.6%
- **35 patients (65%) had indication for surgery**: heart failure 37%, sepsis/septic shock 41%, large vegetation 19%, structural complications 19%, MRSA 5.5%, systemic embolism 22%
- Management: 46 (84%) antibiotics alone, **9 (16%) surgery**
- **Outcome: In-hospital mortality 64% with a median survival of 28 days; 1 year mortality rate 75%**

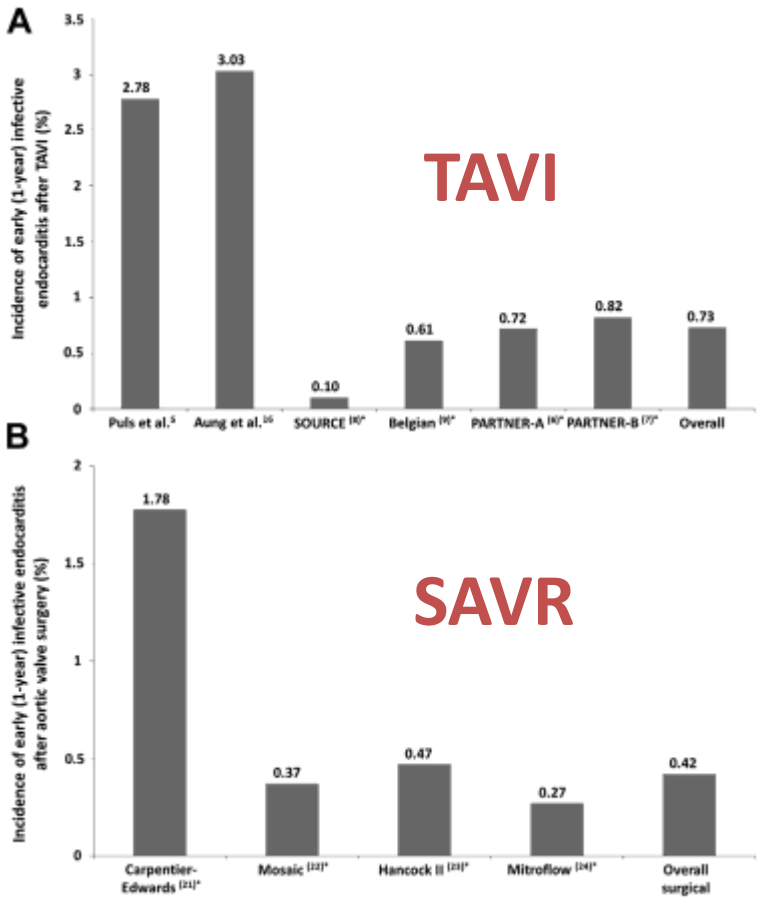
J Am Coll Cardiol. 2016;67(24):2907-2908. doi:10.1016/j.jacc.2016.03.588

Prosthetic Valve Endocarditis After Transcatheter Valve Replacement

A Systematic Review

28 publications
60 patients

- All studies 2000 - 2013
- 32 TAVI, 28 TPVR
  - TAVI – high risk elderly (c. 80 yrs)
  - TPVR – significantly younger (c. 19 yrs)
- Incubation 5 months (IQR 2-9 months)
- Microbiology
  - TAVI enterococci (34%)
  - TPVR *Staphylococcus aureus*
- Severe complications >>> surgery
  - 70% of TAVI-IE cohort
  - Re-intervention in only 41%
- In-hospital mortality
  - TAVI 34%
  - TPVR 7%



Amat Santos IP *et al*. J Am Coll Cardiol Intv 2015;8:334-346.

Treatment for TAVI IE

- The incidence of IE after TAVI seems to be at least as high as after SAVR
  - Patients – elderly, comorbidities, frequent healthcare exposure, residual cardiac lesions
  - Procedure - cath lab environment
  - Valve – multiple hypotheses and conflicting literature
- Diagnosis is challenging and outcomes are poor
  - Late presentation and low rates of surgical intervention
- More aggressive treatment algorithms are appropriate (particularly in lower risk cohorts)
- Specific risk factors for IE after TAVI are poorly defined
- Large real-world cohorts are required to better define risk factors for TAVI-IE and establish optimal treatment