Early Bioprosthetic Valve Leaflet Thickening: Imaging Observations, Clinical Implications, and Controversies

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ORIGINAL ARTICLE

Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

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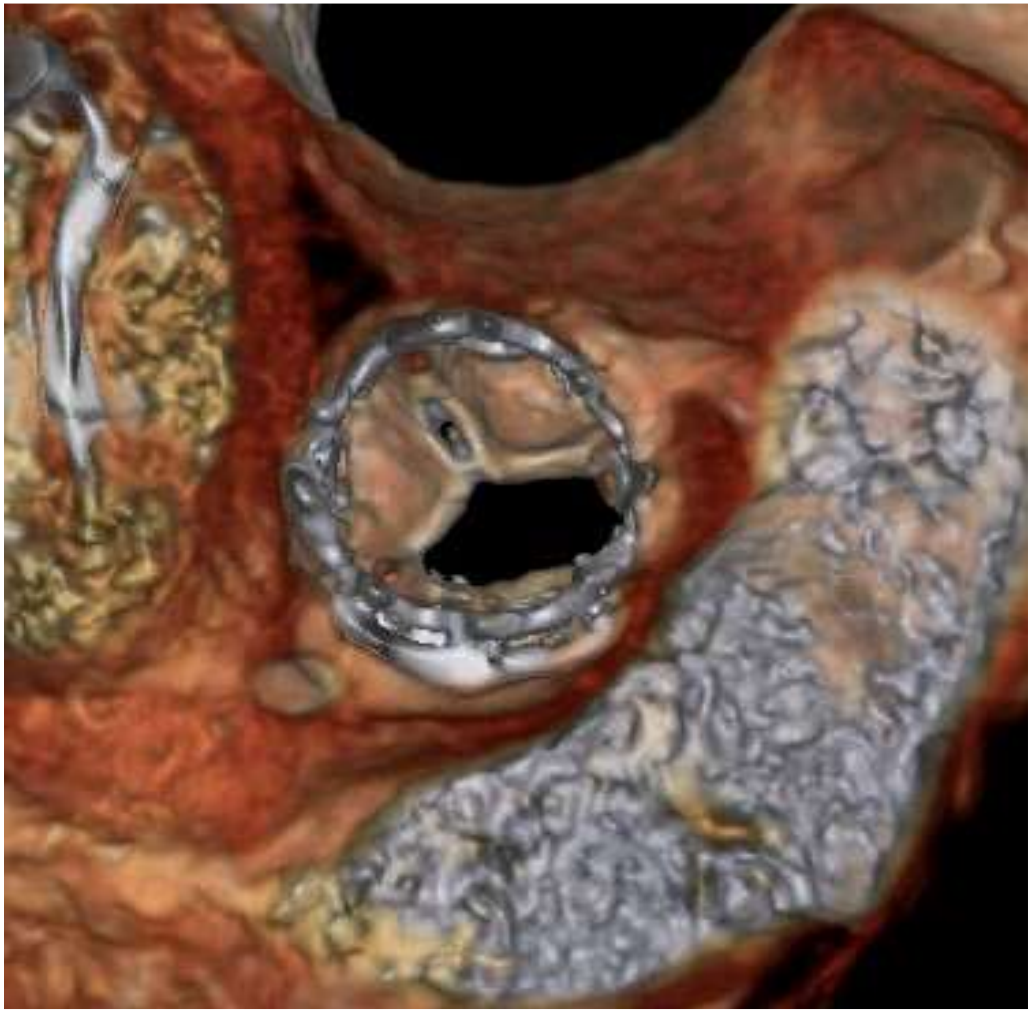
NEJM Oct 2015

Background

A finding of severely reduced leaflet motion noted in 2 patients in the early part of the Portico IDE study



Study population (n=187)

- *Portico IDE* study
  - 1:1 randomization of high risk patients between Portico and Commercial valve
  - 55 CT scans analyzed at 30 days prospectively (Sapien XT, Portico and CoreValve)

- *RESOLVE* registry (NCT02318342) at Cedars-Sinai Heart Institute
  - Real world registry
  - 70 CT scans at multiple time points after TAVR and SAVR

- *SAVORY* registry (NCT02426307) at Rigshospitalet, Copenhagen
  - Real world registry
  - 62 CT scans at multiple time points after TAVR and SAVR

- Core lab analysis of all CT scans. Echo core lab for Portico IDE.

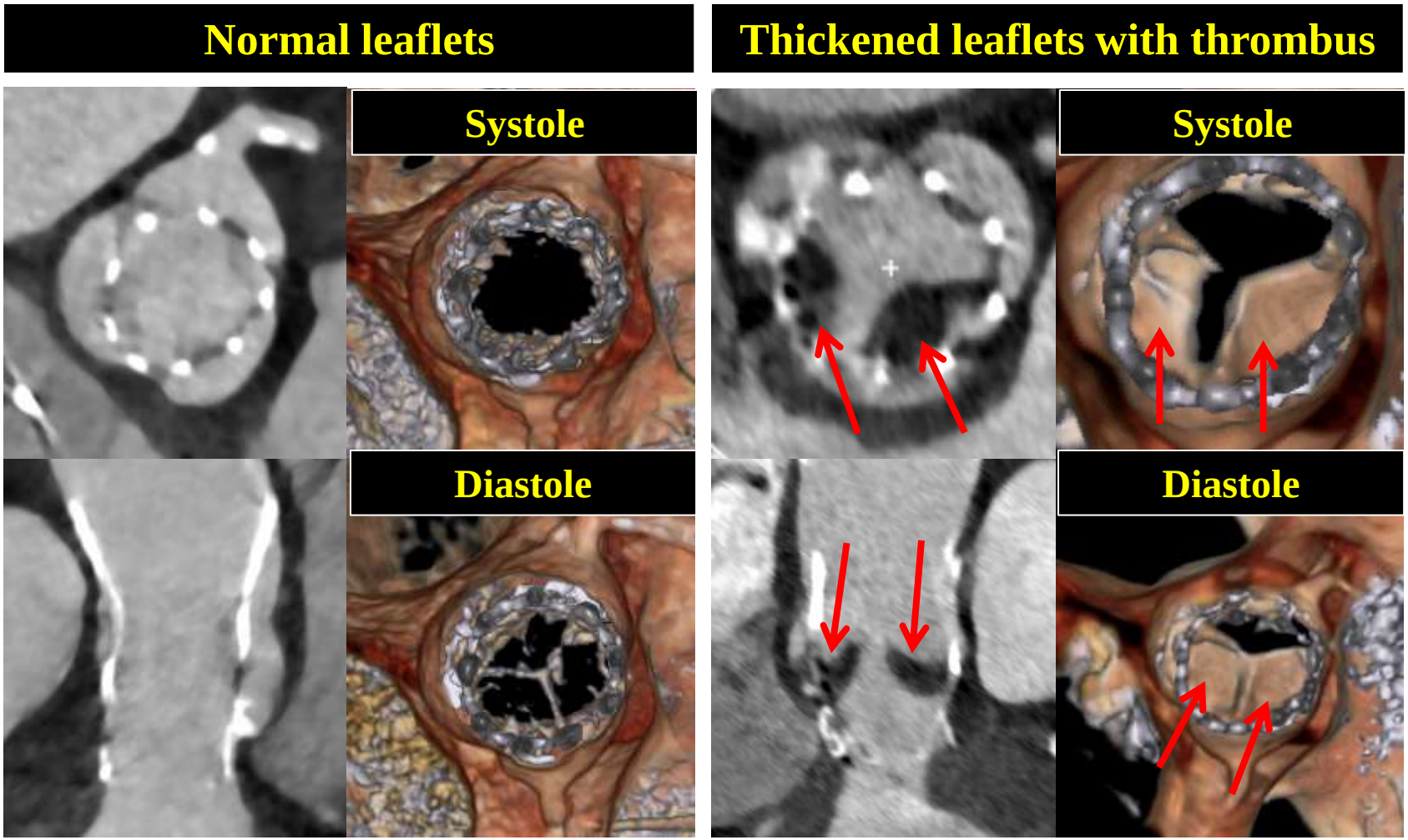
Results I

Prevalence of possible subclinical leaflet thrombosis

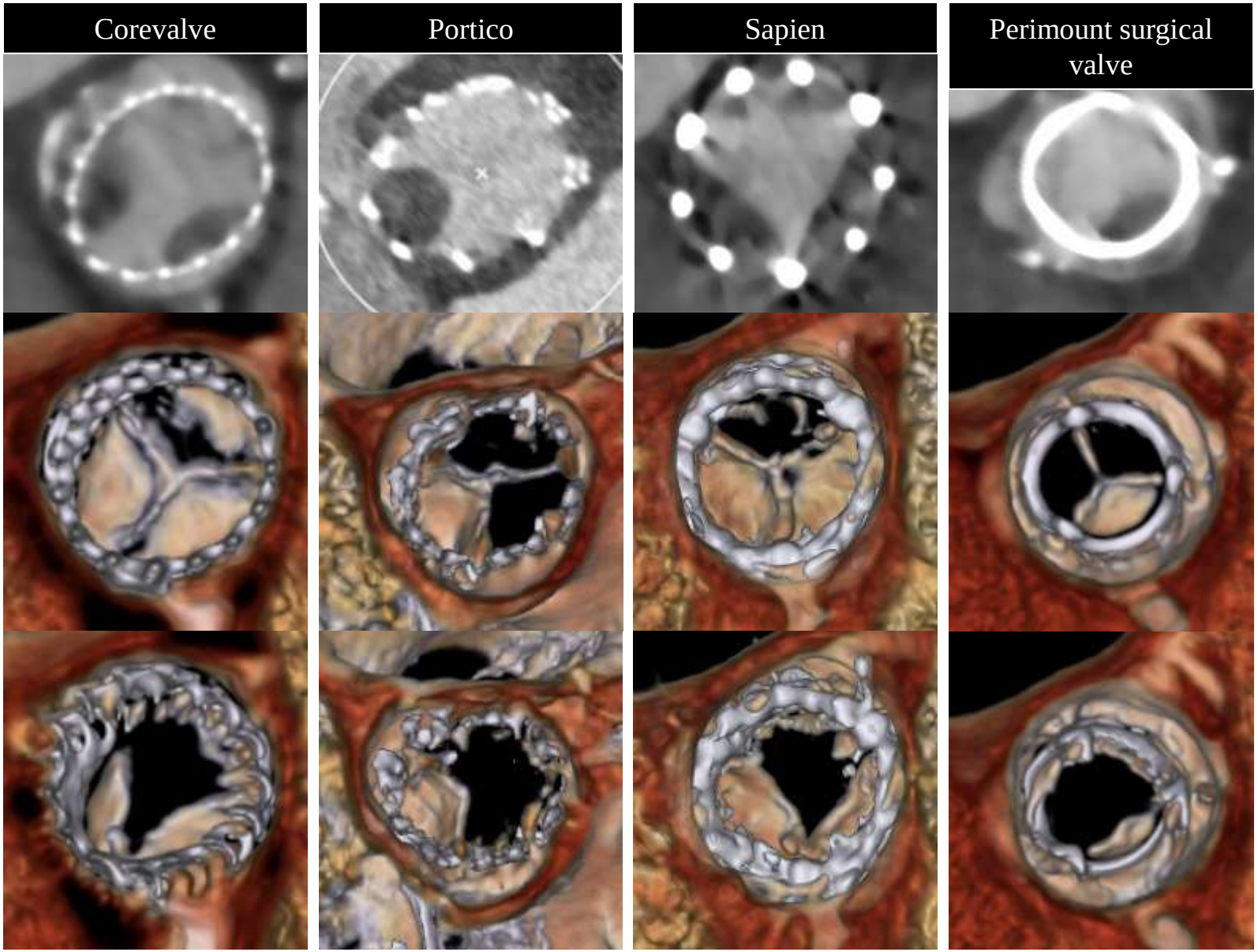
- The Portico IDE had reduced leaflet motion present in 22/52 (40·0%) of patients
  - 16/37 (43.2%) Portico, 6/14 (42.9%) Sapien XT and 0/4 (0%) CoreValve

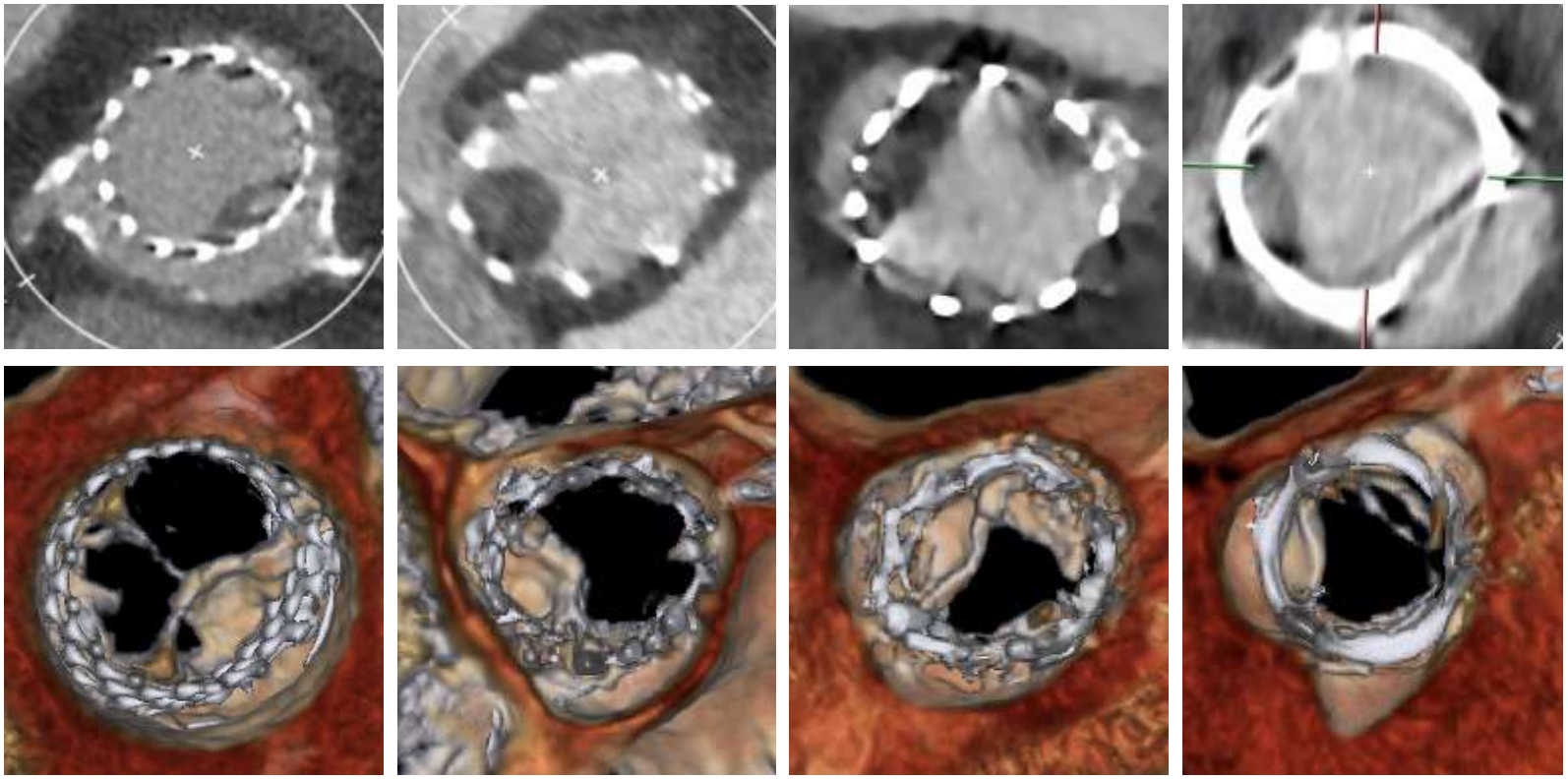
- The registries (RESOLVE and SAVORY) had reduced leaflet motion in 17 of 132 patients (13%).
  - 7/58 (12.1%) Sapien/XT/S3, 2/24 (8.3%) Corevalve, 1/8 Lotus (12.5%), 2/27 SAVR (7.4%)

Volume rendered CT images of bioprosthetic valves



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

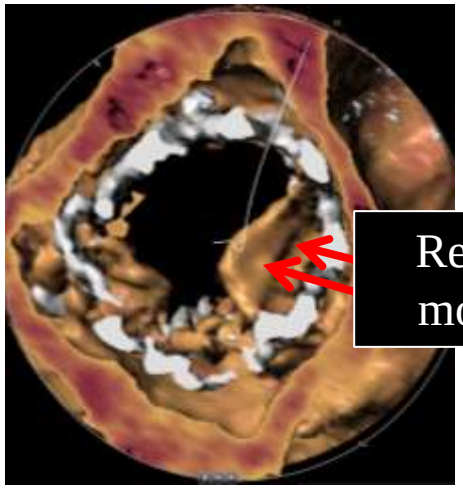




Corevalve Portico Sapien Magna Ease

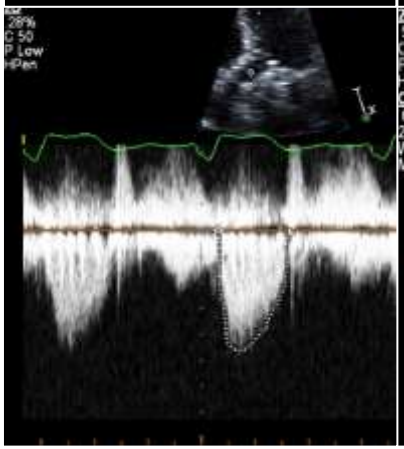
Results II: Role of TTE

This finding was invariably missed on TTE, which demonstrated normal transvalvular gradients

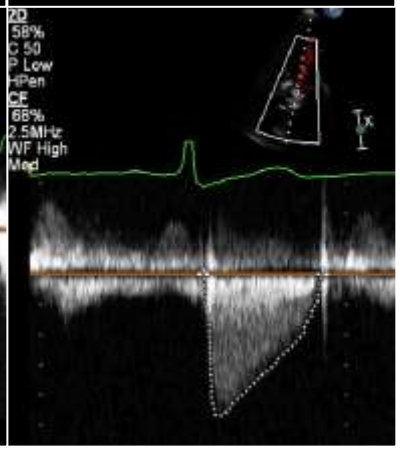


Reduced mobility

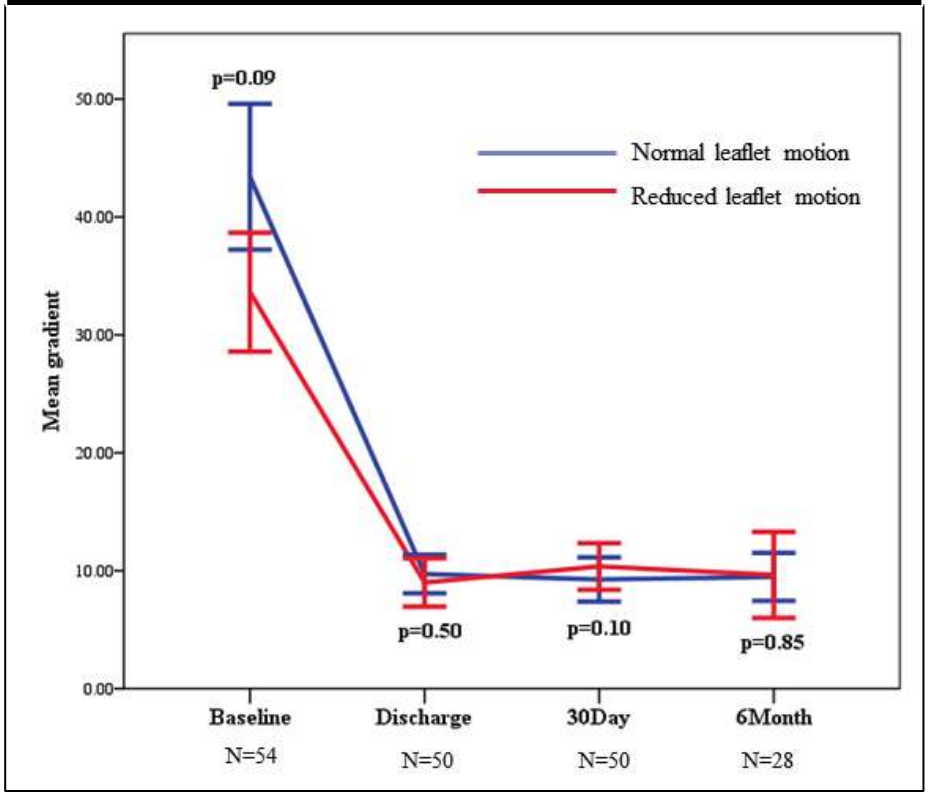
Day 1 mean gradient = 9 mmHg



Day 30 mean gradient = 9 mmHg

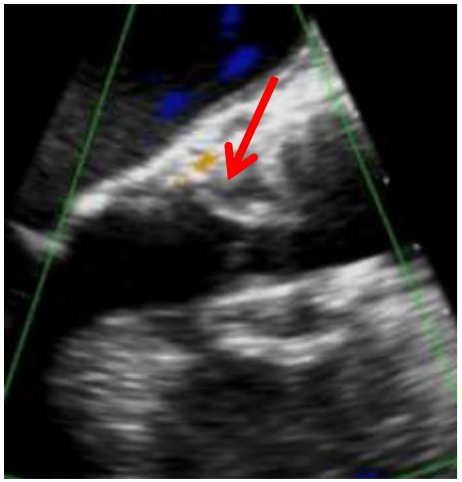


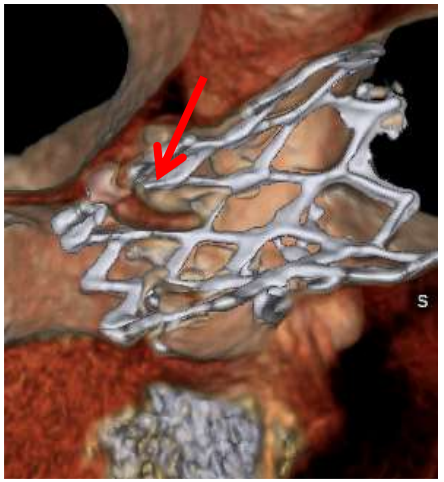
Portico IDE gradients in patients with and without reduced leaflet motion

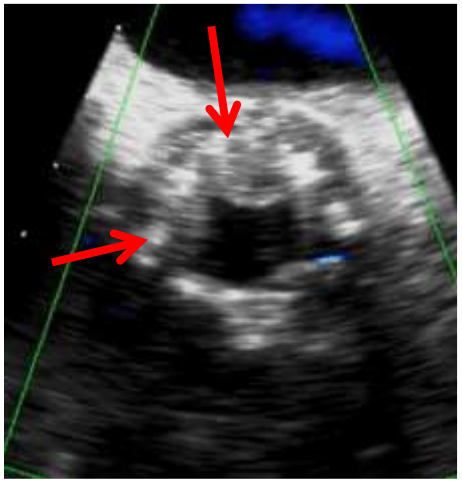


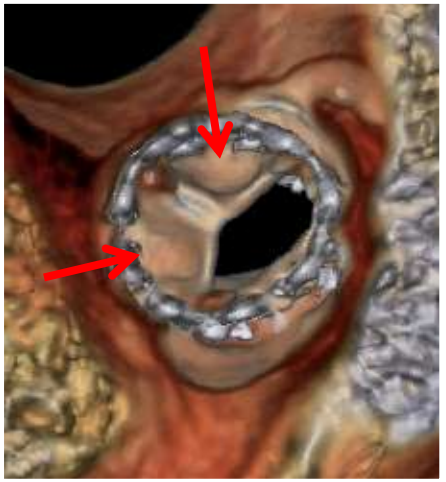
Results III: Role of TEE

There was 100% concordance in the assessment of leaflet motion between TEE and 4D VR-CT in 10 out 22 patients with reduced leaflet motion undergoing TEE



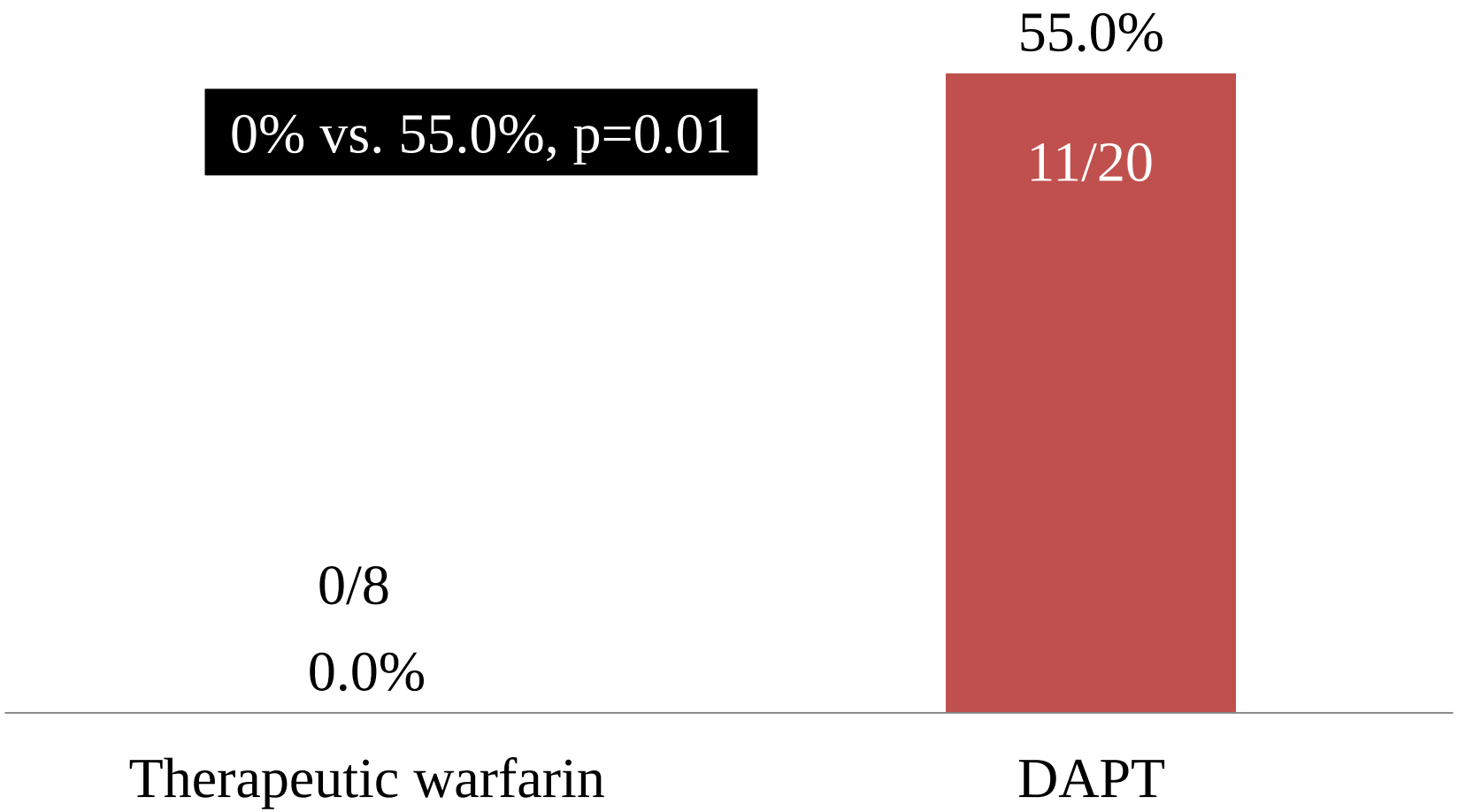






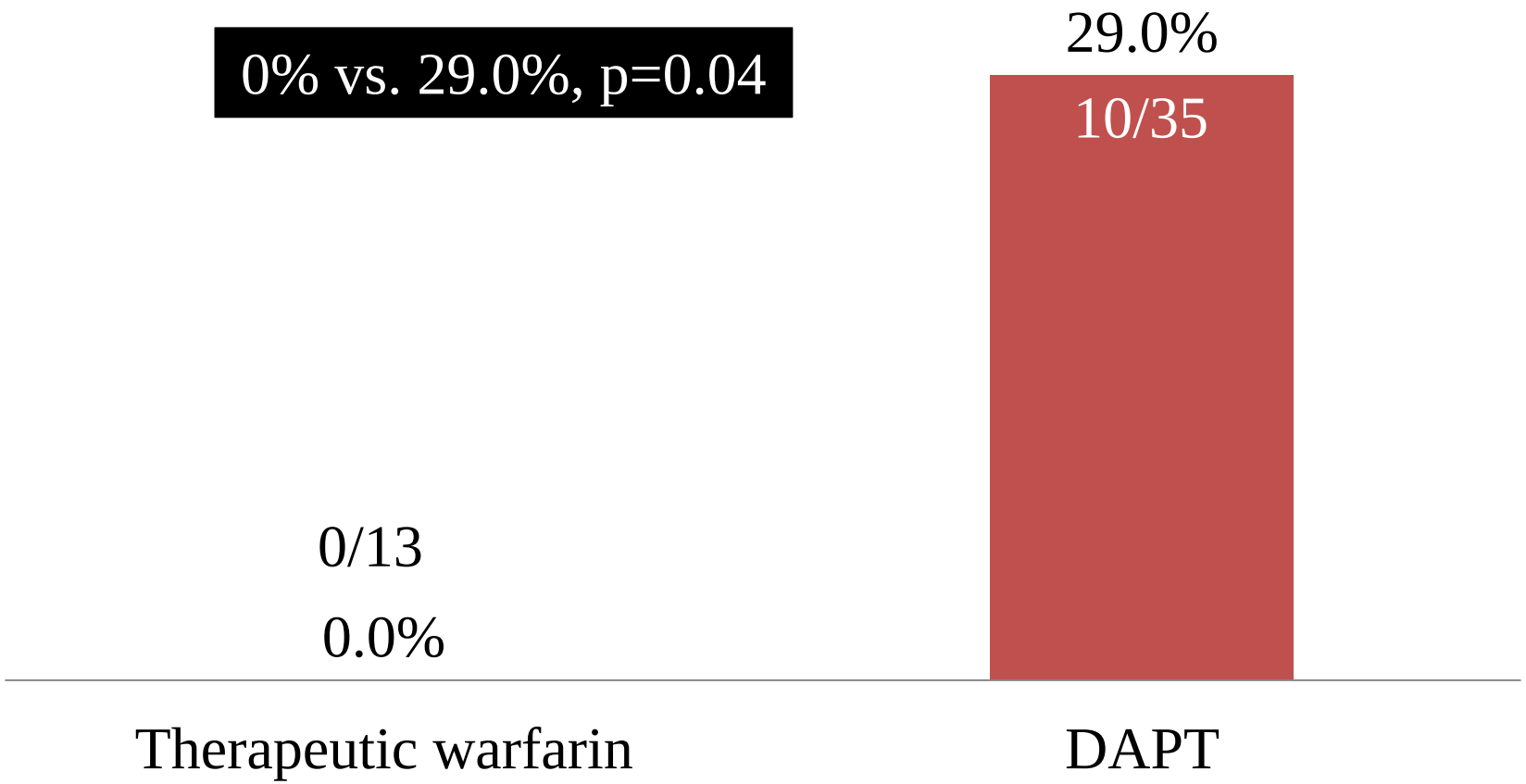
Results IV: Therapeutic warfarin vs. DAPT: Portico-IDE

Decreased incidence of subclinical leaflet thrombosis



Results IV: Therapeutic warfarin vs. DAPT: Registries

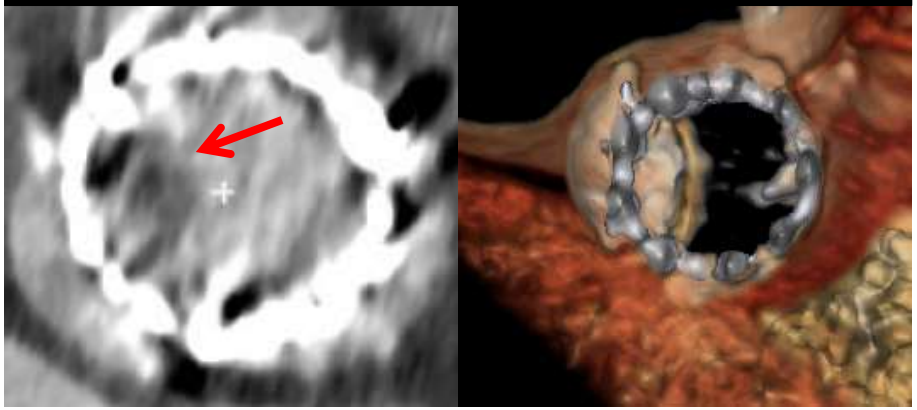
Decreased incidence of subclinical leaflet thrombosis



Results V: Natural history of this phenomenon

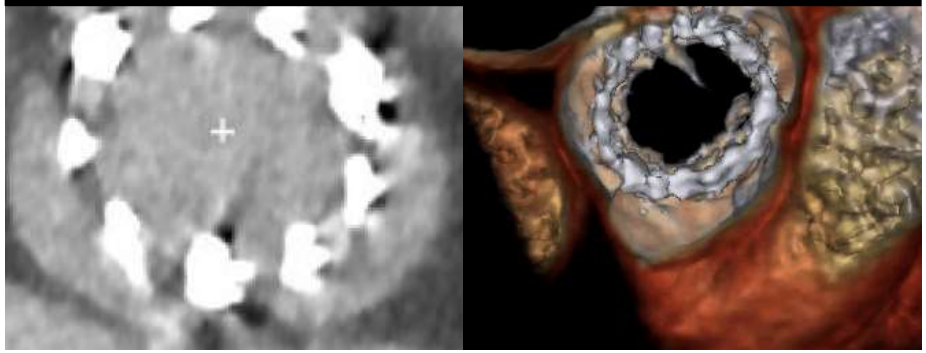
Anticoagulation was associated with resolution of thrombus and restoration of leaflet motion in 11 out of 11 patients

Reduced leaflet motion on 30-day CT



Patient was started on Warfarin

Resolution of thrombus and restoration of leaflet motion on 7 month follow-up CT

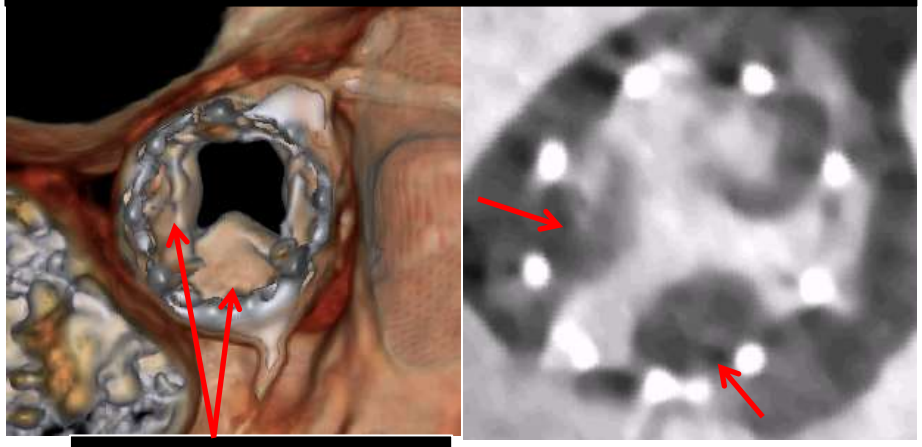


Results V: Natural history of this phenomenon

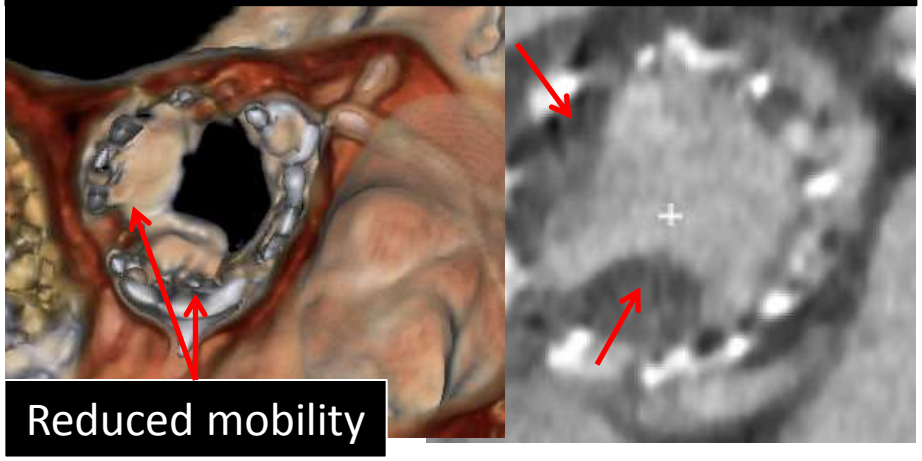
Persistence of thrombus and reduced leaflet motion in 9 out of 10 patients without therapeutic anticoagulation

Persistent reduced leaflet motion on subtherapeutic warfarin (INR 1.1)

30-day post-TAVR CT
Reduced leaflet motion



Follow-up CT 7 months later
Reduced leaflet motion



Results VI: Clinical outcomes – Portico IDE

	Normal Leaflet Motion	Reduced Leaflet Motion	P value
	Number of patients		
PORTICO IDE			
Patients in study	33	22	
Death†	1	2	0.56
Myocardial infarction‡	1	1	>0.99
Stroke/TIA§	0	2	0.16
Stroke	0	2	0.16
TIA	0	0	>0.99

† One patient with normal leaflet motion died 111 days after valve implantation from congestive heart failure. Of the two deaths among patients with reduced leaflet motion, one was the result of a myocardial infarction 147 days after valve implantation and the other was the result of pneumonia 249 days after valve implantation.

‡ The myocardial infarction occurred 1 day after valve implantation and 27 days before computed tomography (CT) in the group with normal leaflet motion and 147 days after valve implantation and 114 days after CT in the group with reduced leaflet motion.

§ In the two patients with stroke, the event occurred 6 hours after TAVR (with CT performed 1 day after TAVR) in one patient and 1 day after TAVR (with CT performed 28 days after TAVR) in the second patient. The first patient had multiple risk factors for stroke, including atrial fibrillation and substantial spontaneous echo contrast in the left atrium on echocardiography during TAVR.

Results VI: Clinical outcomes – Registries

	Normal Leaflet Motion	**Reduced Leaflet Motion**	P value
	Number of patients		
Registries			
Patients in study	115	17	
Death	0	0	>0.99
Myocardial infarction	0	0	>0.99
Stroke/TIA¶	1	3	0.007
Stroke	1	0	>0.99
TIA	0	3	0.002

¶ In the group with normal leaflet motion, one patient had a stroke 1 day after TAVR (with CT performed 35 days after TAVR). In the group with reduced leaflet motion, three patients had transient ischemic attacks: one that occurred 15 days after TAVR (with CT performed 39 days after TAVR), a second that occurred 239 days after TAVR (with CT performed 24 days after TAVR), and a third that occurred 147 days after TAVR (with CT performed 32 days after TAVR).

Conclusion of NEJM manuscript

In conclusion, reduced aortic-valve leaflet motion occurred in patients with bioprosthetic aortic valves and was easily detected noninvasively by four-dimensional, volume-rendered CT. Therapeutic anticoagulation with warfarin, but not therapy with antiplatelet drugs, prevented and effectively treated this phenomenon. Better characterization of this observation is needed to determine its frequency and evaluate its clinical effect.

Uncertainty and Possible Subclinical Valve Leaflet Thrombosis

David R. Holmes, M.D., and Michael J. Mack, M.D.

Table 1. Questions Raised by the Study by Makkar et al.

What is the true incidence of reduced aortic-valve leaflet motion? Is it device-specific, is it specific to transcatheter aortic-valve replacement (TAVR), or does it occur as frequently with surgical aortic-valve replacement?
Is reduced leaflet motion caused by thrombus formation on the leaflets? If so, is subclinical leaflet thrombosis related to the stent structure or to deployment strategies (e.g., undersizing or oversizing or other patient-specific factors)?
What does this abnormality mean clinically? How frequent are strokes or transient ischemic attacks in patients with this finding? Should the list of clinical events of potential concern be broadened to include valve durability, central aortic regurgitation, sudden death, or recurrent or unrelenting heart failure?
What is the natural history of the abnormality? When (and at what intervals) should it be evaluated, and does it play a role in premature structural valve deterioration?
What treatment strategy should be studied? If anticoagulation is presumed to be the most effective strategy, will adverse outcomes associated with bleeding result in more complications than this abnormality?
What is the most effect imaging approach for monitoring this abnormality? Is monitoring needed in all patients, and if so, when?
Does this issue need to be fully resolved before the expansion of Food and Drug Administration approval of TAVR for lower-risk patients?

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.

The FDA is mindful of the perceived and real complications associated with routine and possibly unnecessary applications of advanced or invasive imaging and with prolonged anticoagulation, especially in high-risk populations. However, the potential for increased risks of late adverse clinical events related to reduced leaflet motion or thrombosis warrants careful systematic investigation. The absence of evidence of temporally related adverse clinical sequelae of imaging-detected reduced leaflet motion suggests that additional bench and clinical testing can be carried out while normal clinical care continues under the currently approved indications for transcatheter or surgical placement of bioprosthetic aortic valves.

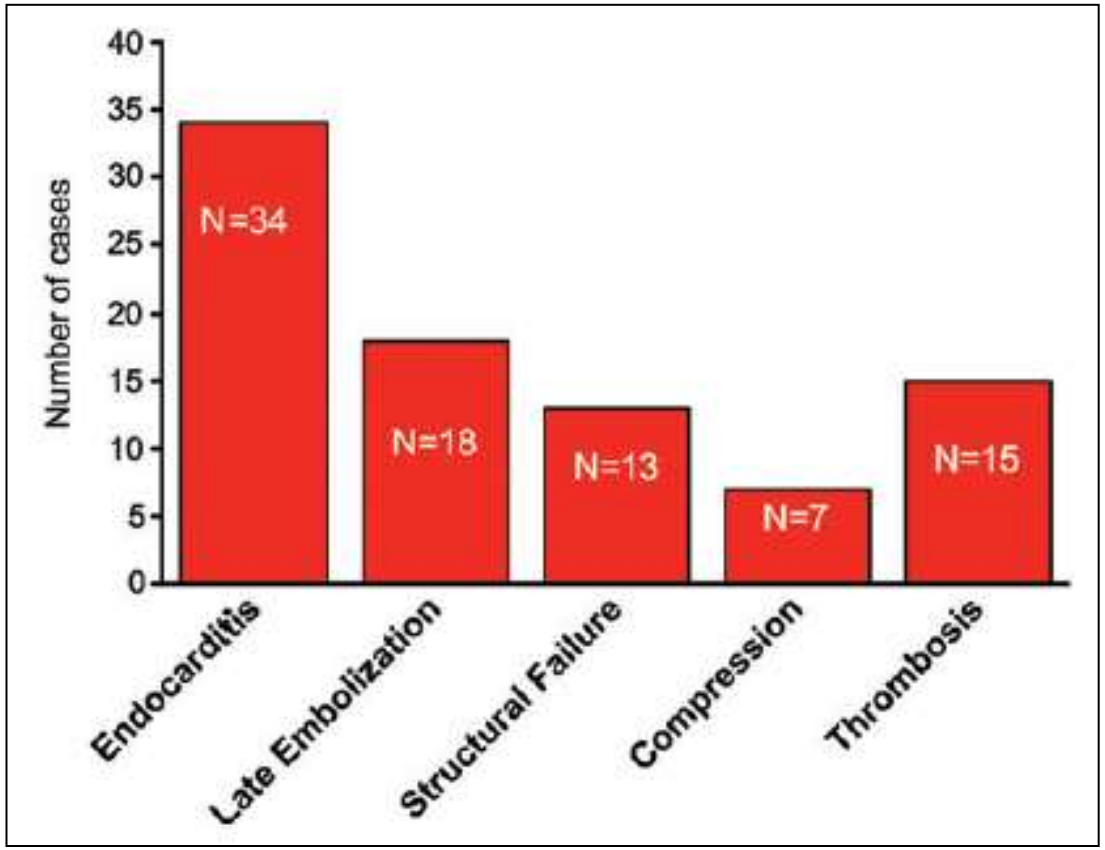
We at the FDA believe that the available clinical evidence supports the conclusion that these valves remain safe and effective and that findings to date concerning reduced leaflet motion have not changed the overall favorable benefit–risk balance for these valves when they are used for their approved indications. These devices reduce symptoms, improve quality of life, and save and prolong the lives of appropriately selected patients. This view is supported by the favorable observed benefit–risk profile and the durability data obtained over the past 30 years for the currently approved surgically implanted bioprosthetic aortic valves.

Transcatheter valve thrombosis

- *Trepels et al. Circulation 2009*
  - First report of Edwards-SAPIEN thrombosis
- *Lancellotti et al. Circulation: Cardiovascular Interventions 2013*
  - First report of CoreValve thrombosis
- *Pache et al. European Heart Journal 2013*
  - First report of subclinical TAVR thrombosis

Transcatheter heart valve failure: a systematic review

Darren Mylotte[1,2], Ali Andalib[1], Pascal Thériault-Lauzier[1], Magdalena Dorfmeister[3], Mina Girgis[1], Waleed Alharbi[1], Michael Chetrit[1], Christos Galatas[1], Samuel Mamane[1], Igal Sebag[4], Jean Buithieu[1], Luc Bilodeau[1], Benoit de Varennes[5], Kevin Lachapelle[5], Ruediger Lange[3], Giuseppe Martucci[1], Renu Virmani[6], and Nicolo Piazza[1,3]*



15 cases of TAVR valve thrombosis reported from 12/02-03/14

14 symptomatic
1 subclinical

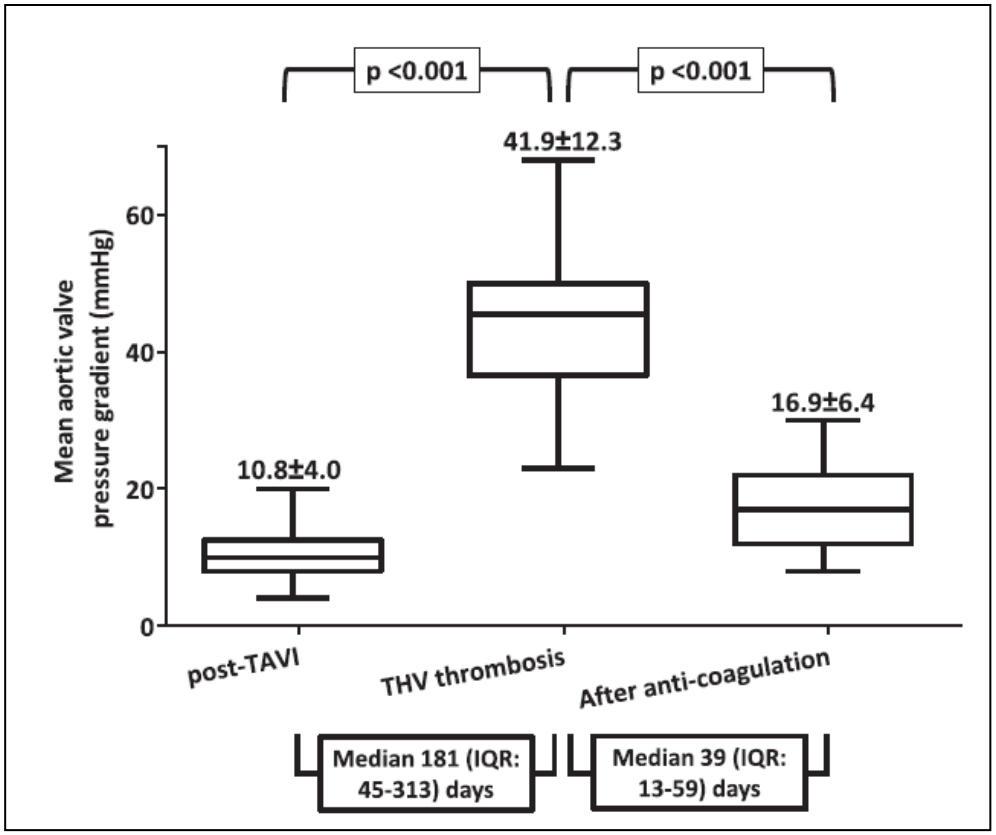
Mylotte D. et al. European Heart Journal 2015

Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis

Circulation: Cardiovascular Interventions

Multicenter, multinational registry of patients with TAVR thrombosis

26 out of 4266 patients undergoing TAVR (0.61%)



- **Median time to THV thrombosis: 181 days**
- **Median time to resolution of thrombus with anticoagulation: 39 days**

Latib A. et al. Circulation: Cardiovascular Interventions 2015

Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis

Circulation: Cardiovascular Interventions

Multicenter, multinational registry of patients with TAVR thrombosis

26 out of 4266 patients undergoing TAVR (0.61%)

	n=26
Median time to THV thrombosis, d	181 (IQR, 45–313; range, 3–735)
Incidence of THV thrombosis	26/4266 (0.61)
Edwards Sapien or Sapien XT	20/2813 (0.71)
Medtronic CoreValve	6/1453 (0.41)
Clinical presentation	
Dyspnea	17 (65.4)
No worsened symptoms	8 (30.8)
NSTEMI, acute heart failure	1 (3.8)
Echo findings at THV thrombosis	
LVEF, %	58.0±10.6
Mean aortic valve gradient, mm Hg	40.5±14.0
Mean aortic valve gradient <20 mm Hg*	2 (7.7)
Maximal aortic valve gradient, mm Hg	65.1±19.0
Worsened AR (to more than moderate) as compared with post procedure	2 (7.7)
Thrombus morphology	
Thickened leaflets or thrombotic apposition of leaflets	20 (76.9)
Thrombotic mass on leaflets	6 (23.1)

All cases had clinical evidence of valve thrombus

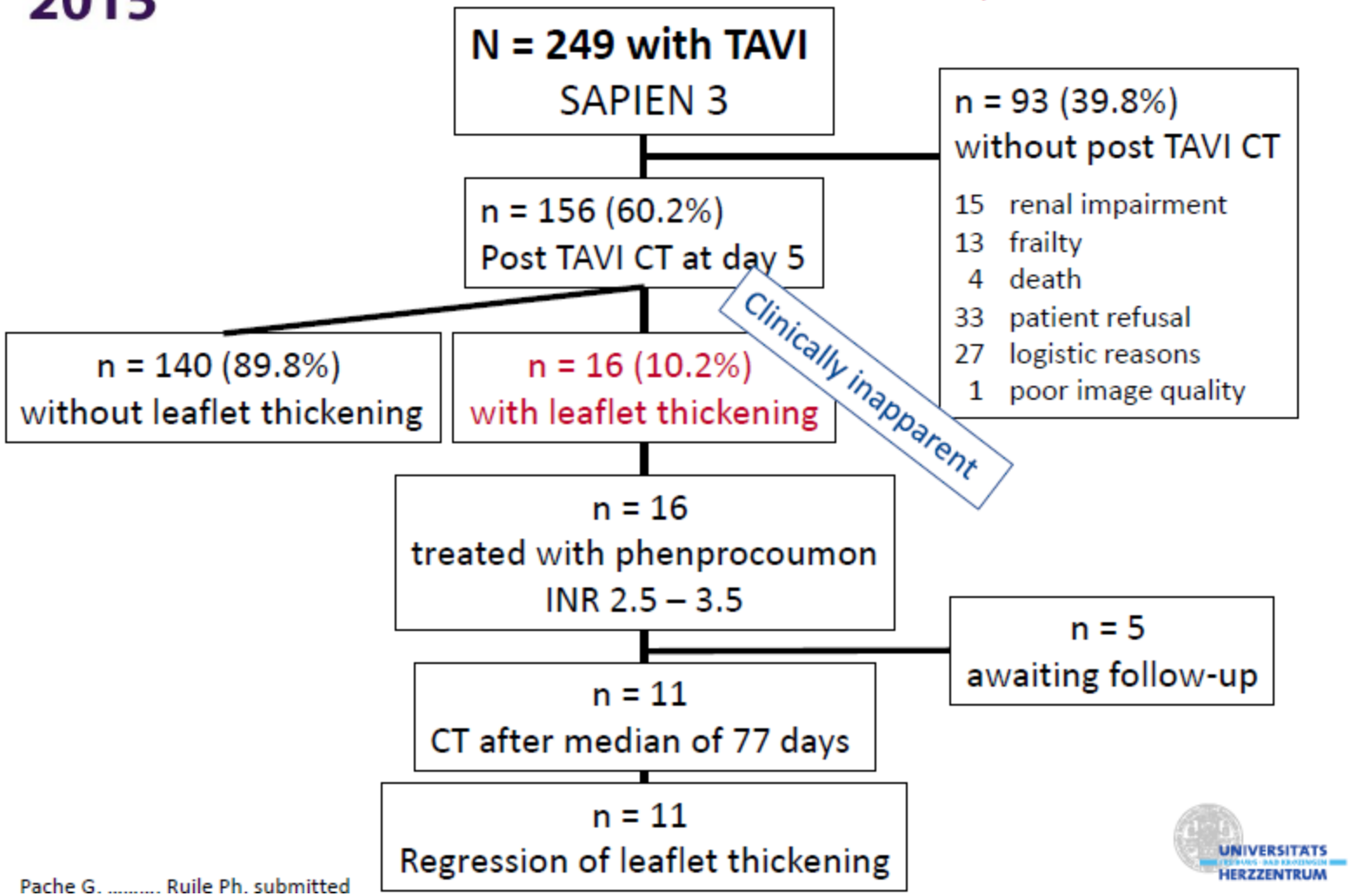
- 17/26 (65.4%) had worsening dysnea on exertion
- 1/26 (3.8%) presented with NSTEMI
- 24/26 (92%) patients had elevated gradients

Latib A. et al. Circulation: Cardiovascular Interventions 2015

euro PCR 2015

Systematic assessment

February 2014 – March 2015



Pache G. ..... Ruile Ph. submitted

UNIVERSITÄTS HERZZENTRUM

Pache et. Al. European Heart Journal Oct 2015

euro PCR 2015

Antithrombotic regimens

		All patients (n=156)	No leaflet thickening (n=140)	Leaflet thickening (n=16)	P-Value
Antithrombotic regime at Implantation	Mono-antiplatelet therapy	45 (28.8)	39 (27.8)	6 (37.5)	0.420
	Dual-antiplatelet therapy	111 (71.2)	101 (72.2)	10 (62.5)	
Antithrombotic regime at CTA	Mono-antiplatelet therapy	17 (10.9)	14 (10.0)	3 (18.8)	0.468
	Dual-antiplatelet therapy	76 (48.7)	70 (50.0)	6 (37.5)	
	Mono-antiplatelet therapy + Anticoagulation	63(40.4)	56 (40.0)	7 (43.7)	

Pache G, ..., Ruile Ph, submitted

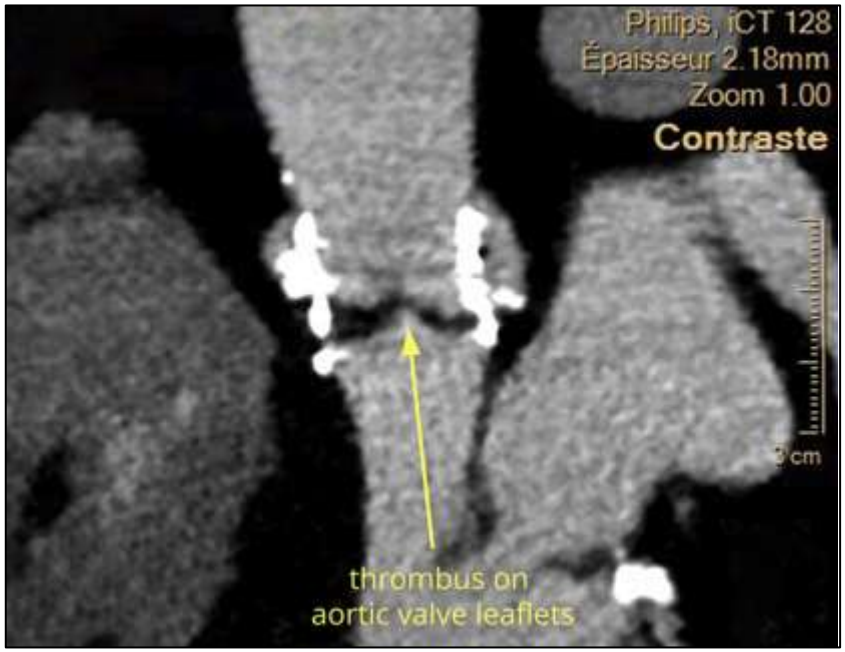
UNIVERSITÄTS HERZZENTRUM

Pache et. Al. European Heart Journal Oct 2015

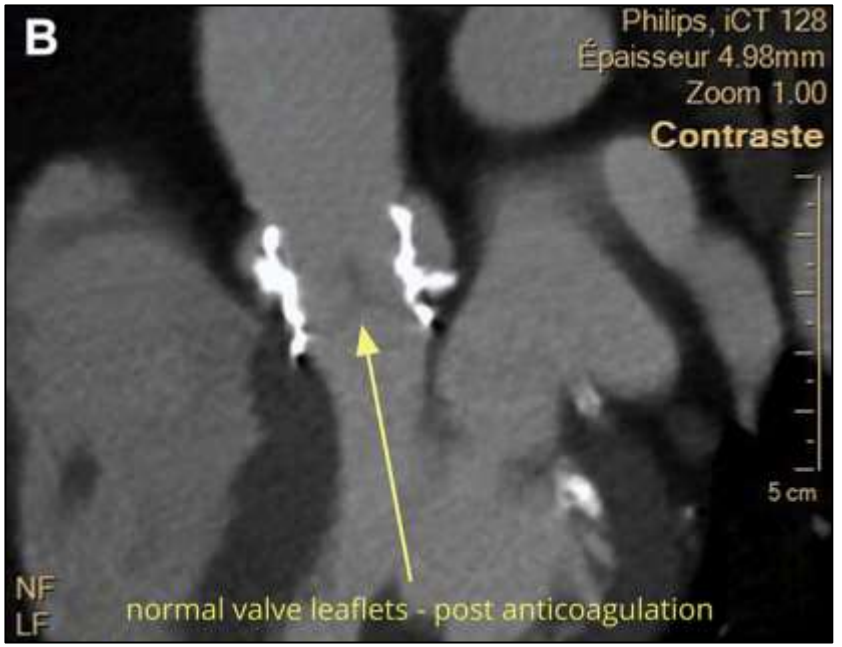
Very Early Thrombosis of Sapien 3 Valve

Sapien3 valve thrombosis 3 days post-TAVR

Valve thrombosis



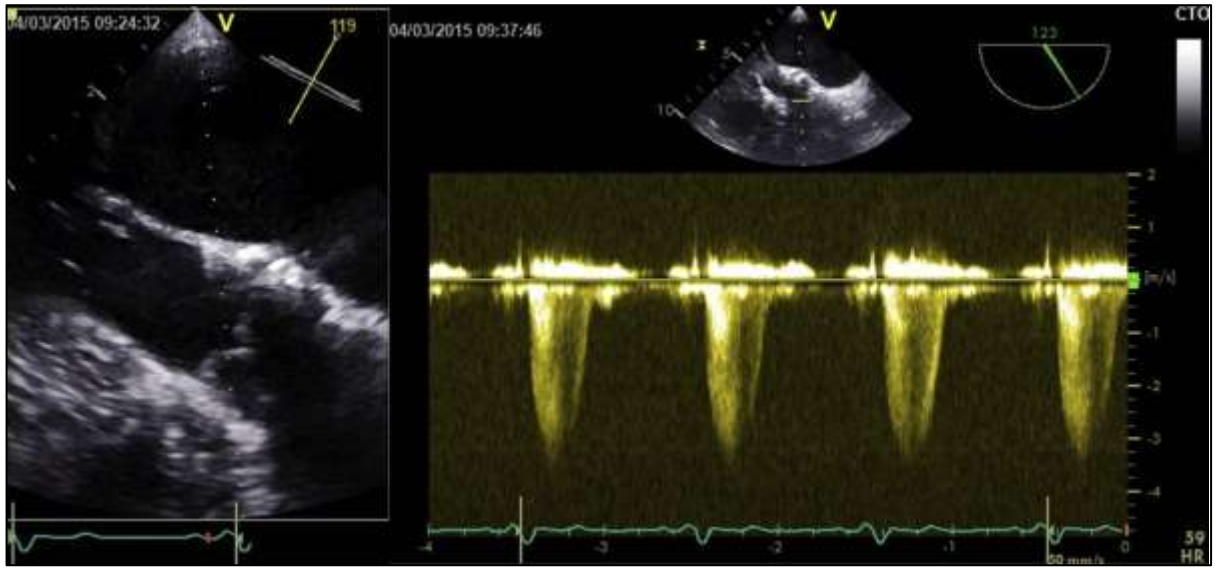
Resolution with anticoagulation

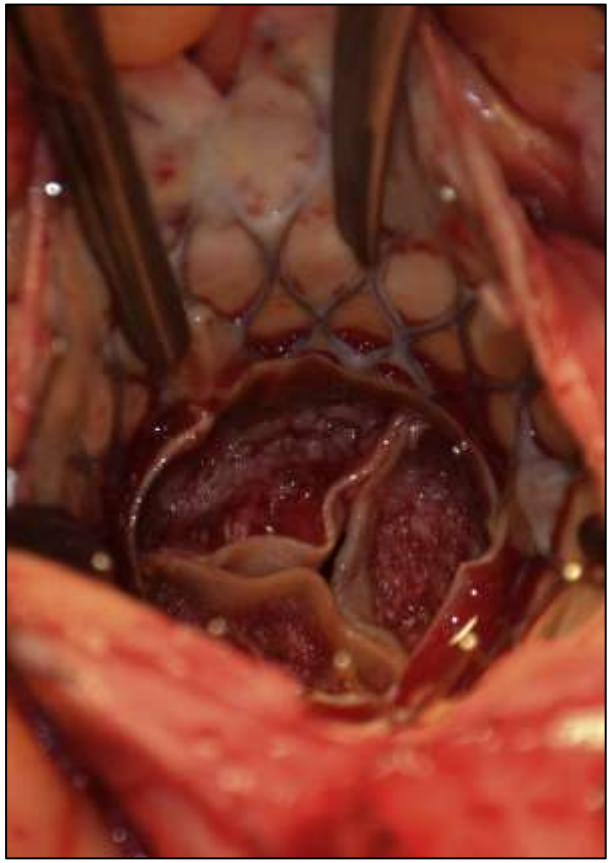


Neylon A. et al. JACC: Cardiovascular Interventions 2016

Very Late Thrombosis of a Transcatheter Aortic Valve-in-Valve

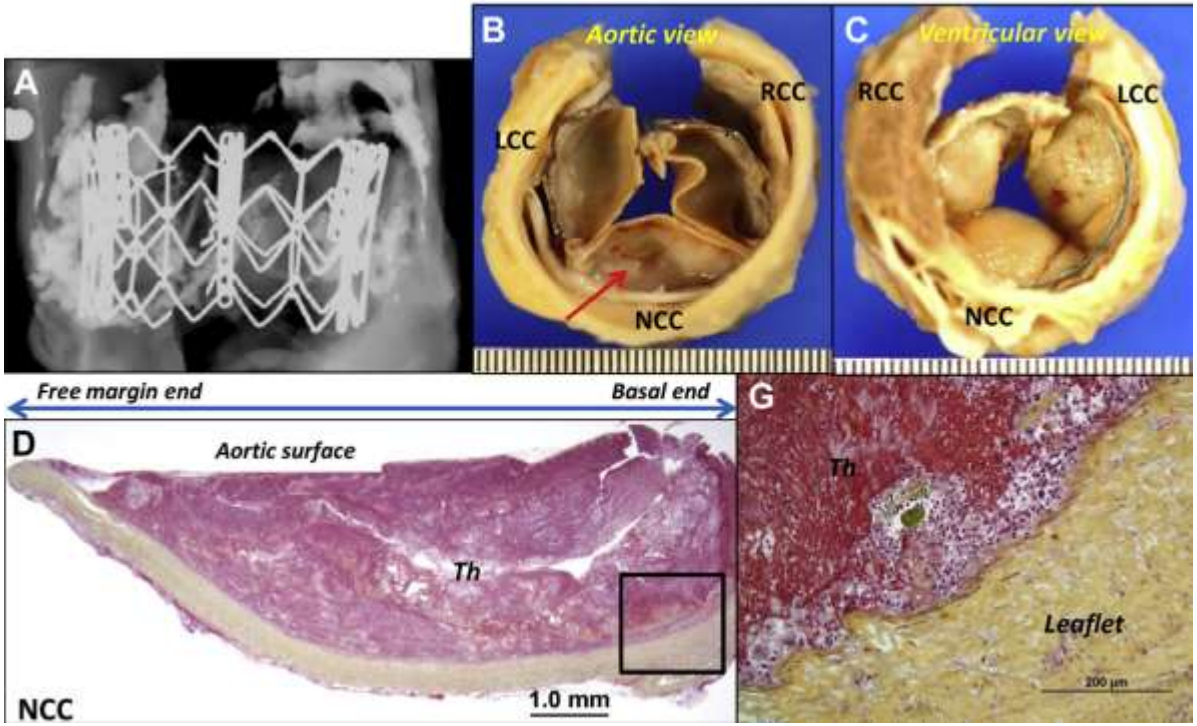
Valve thrombosis 4 years post-TAVR





Thrombus Formation Following Transcatheter Aortic Valve Replacement

Histopathology fndings in 3 cases of TAVR valve thrombosis



Thrombus develops primarily on the aortic side of the valve leaflets

De Marchena E. et al. JACC: Cardiovascular Interventions 2015

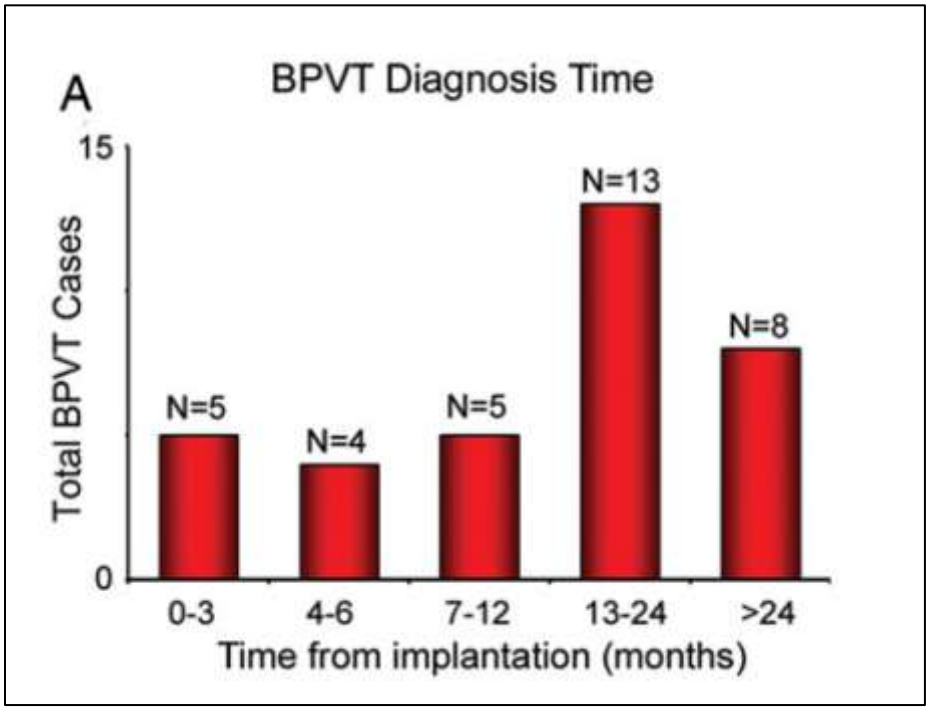
Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series

Sorin V. Pislaru[a,*], Imad Hussain[a], Patricia A. Pellikka[a], Joseph J. Maleszewski[b], Richard D. Hanna[a], Hartzell V. Schaff[c] and Heidi M. Connolly[a]

Mayo Clinic experience

Peak incidence at 12-24 months after AVR

32 cases of bioprosthetic valve thrombosis



- 9 out of 10 patients on anticoagulation at the time of diagnosis were *sub-therapeutic*
- 1 patient with tricuspid valve thrombus, on therapeutic anticoagulation, but with severe RV dysfunction

Pislaru S. et al. European Journal of Cardio-Thoracic Surgery 2015

Bioprosthetic Valve Thrombosis Versus Structural Failure

Clinical and Echocardiographic Predictors

Mayo Clinic experience

46 cases (12%) of bioprosthetic valve thrombosis out of 397 consecutive explanted bioprosthetic valves

Predictors of bioprosthetic valve thrombosis

Echocardiographic variables

Clinical variables

	Total Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Variables					
A. 50% mean gradient increase	1	45	89	68	77
B. Increase cusp thickness	1	74	69	55	84
C. Abnormal cusp mobility	1	63	70	51	81
D. Paroxysmal AF	1	63	73	54	80
E. Subtherapeutic INR	1	30	92	67	73
Combination of variables					
A and B	2	86	57	50	89
A, B, and C	3	72	90	78	87
A, B, C, and D	4	70	94	87	86
A, B, C, D, and E	5	66	93	85	89

Egbe A. et al. JACC 2015

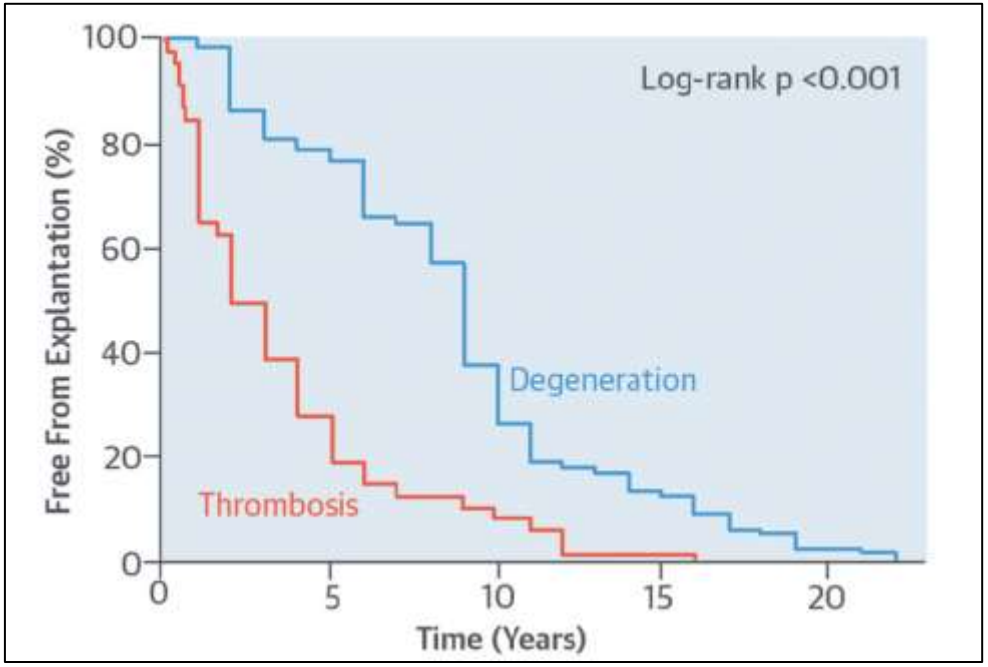
Bioprosthetic Valve Thrombosis Versus Structural Failure

Clinical and Echocardiographic Predictors

Mayo Clinic experience

46 cases (12%) of bioprosthetic valve thrombosis out of 397 consecutive explanted bioprosthetic valves

- Valve thrombosis (n=46)
- Matched cases of valve degeneration (n=92)



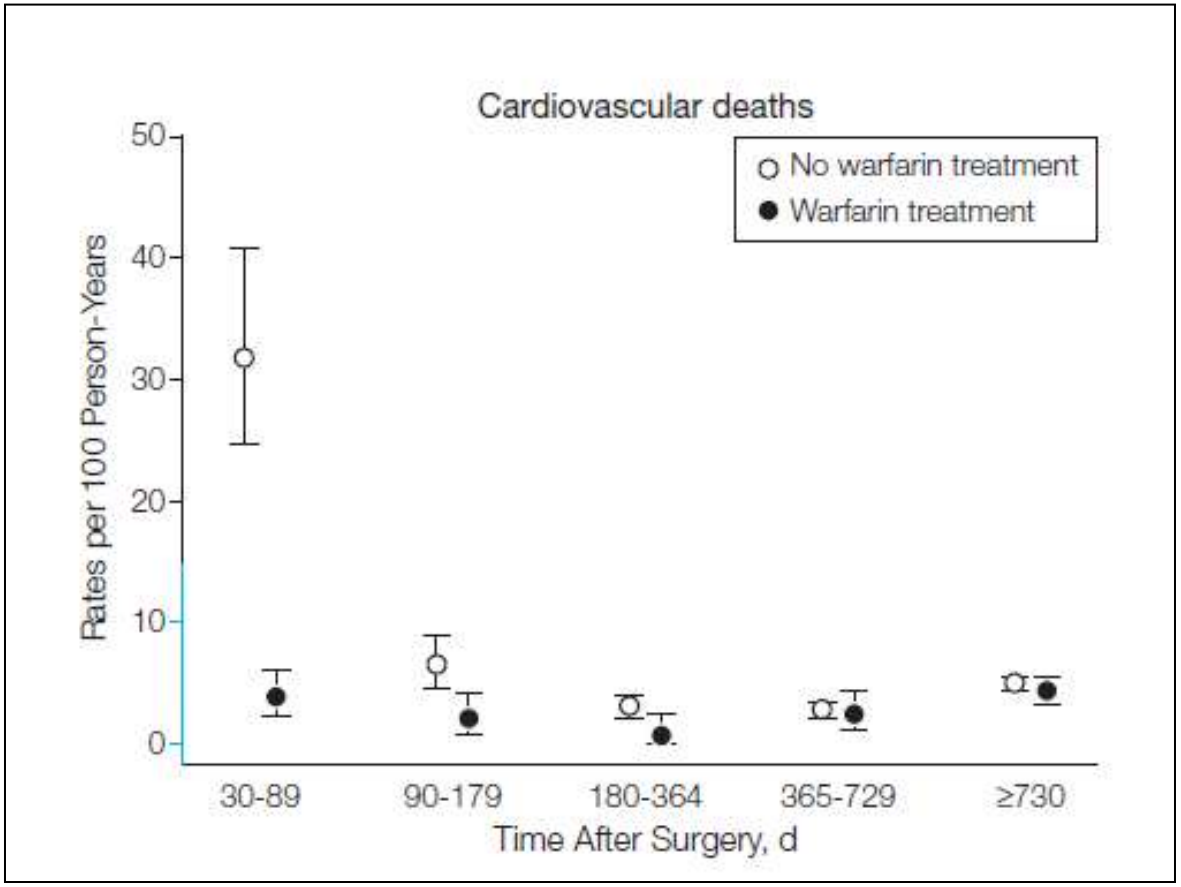
BPVT referred for surgical intervention occurs significantly earlier than BPV degeneration

Egbe A. et al. JACC 2015

Association of warfarin therapy with clinical events after bioprosthetic AVR: Danish Registry

4075 patients undergoing bioprosthetic AVR in the Danish Registry

Discontinuation of warfarin treatment within 6 months after bioprosthetic AVR associated with worse outcomes

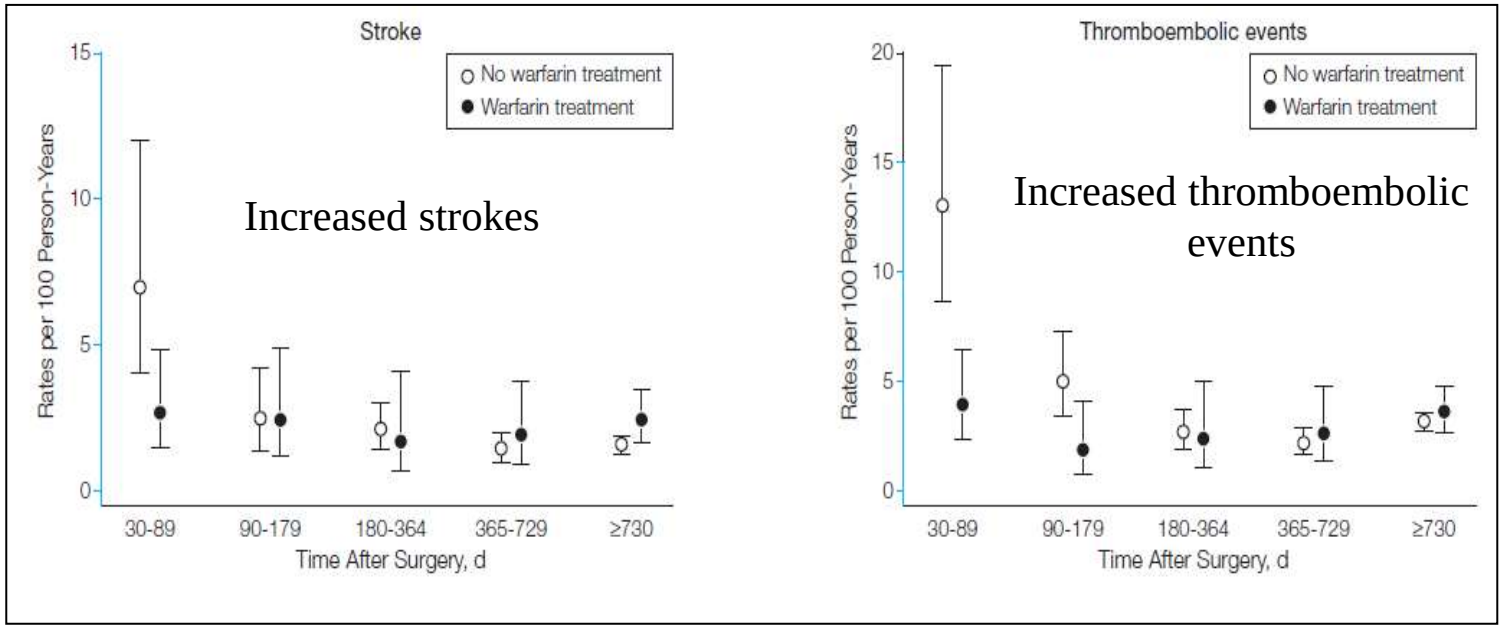


Merie C. et al. JAMA 2012

Association of warfarin therapy with clinical events after bioprosthetic AVR: Danish Registry

4075 patients undergoing bioprosthetic AVR in the Danish Registry

Discontinuation of warfarin treatment within 6 months after bioprosthetic AVR associated with worse outcomes



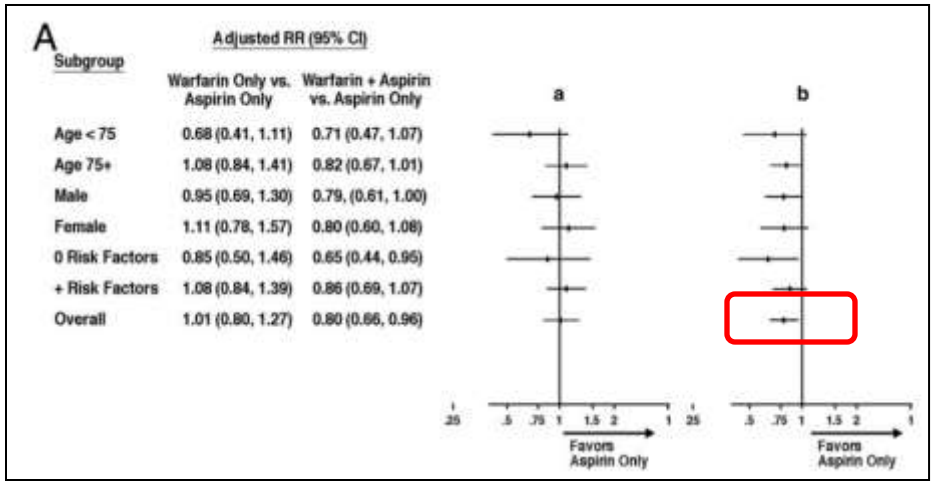
Merie C. et al. JAMA 2012

Association of warfarin therapy with clinical events after bioprosthetic AVR: STS database

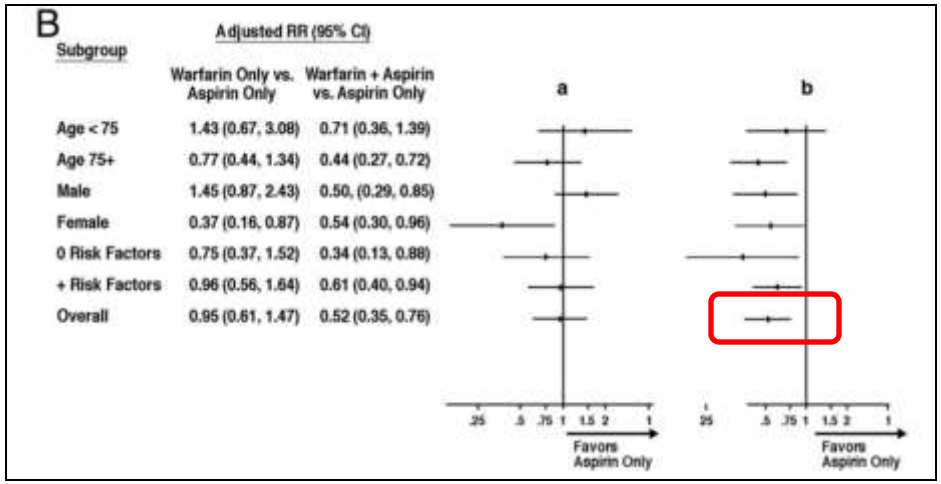
25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

Warfarin plus aspirin associated with a reduced risk of death and embolic events, compared to aspirin alone

Death



Thromboembolism



Brennan M. et al. JACC 2012

Association of warfarin therapy with clinical events after bioprosthetic AVR: STS database

25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

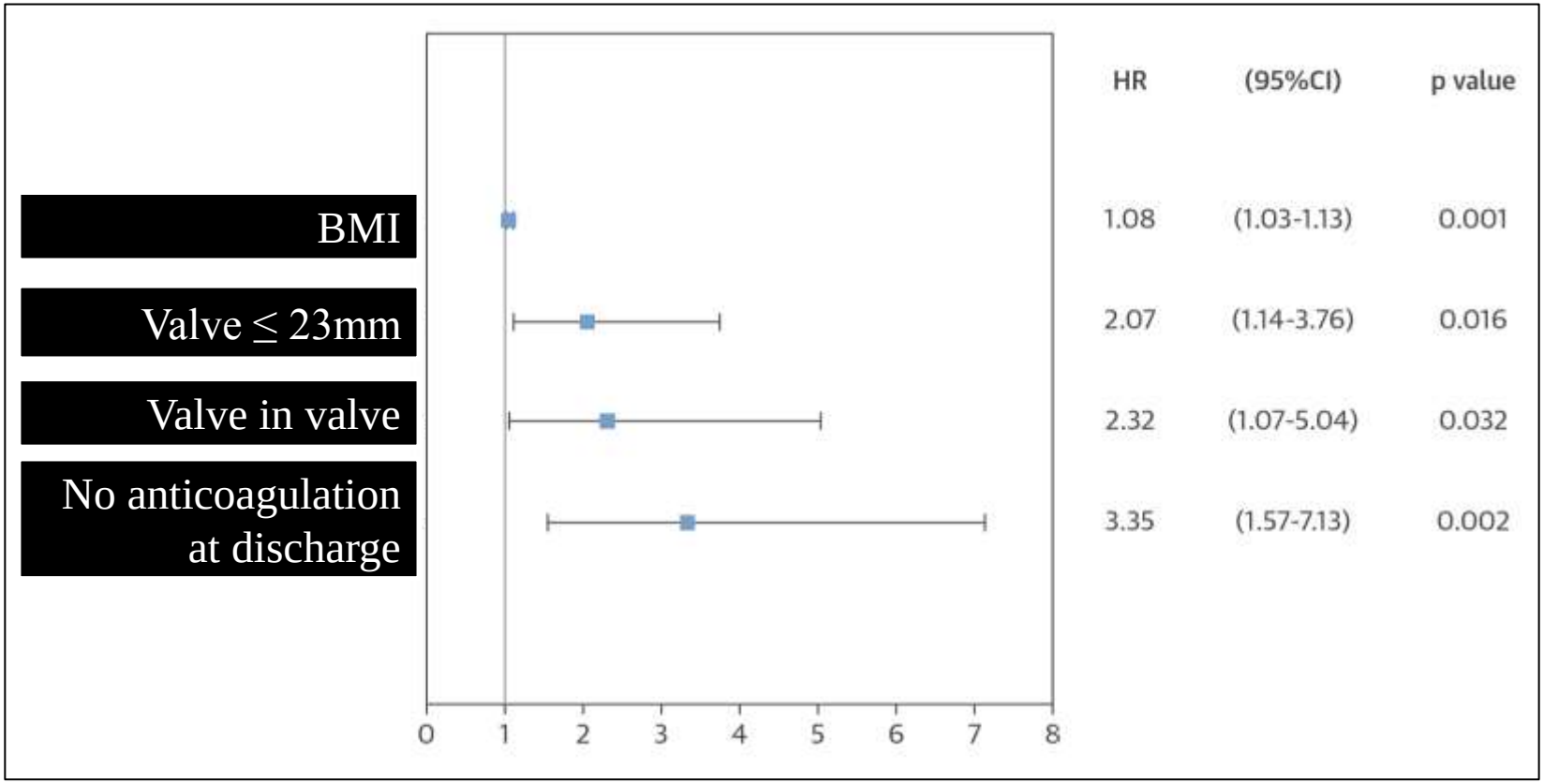
"The **addition of warfarin to aspirin** at hospital discharge would be a reasonable treatment option, on the basis of these results, with an expected number needed to **avert 1 death of 153 patients and 1 embolic event of 212 patients.**The therapeutic benefit observed with the addition of warfarin to aspirin was not without risk in this elderly cohort, **and 1 additional bleeding event was observed at 3 months for every 55** patients treated with warfarin".

Brennan M. et al. JACC 2012

Predictors of valve hemodynamic degeneration after TAVR

1521 patients undergoing TAVR

Valve hemodynamic degeneration = 10mmHg rise in transvalvular gradients

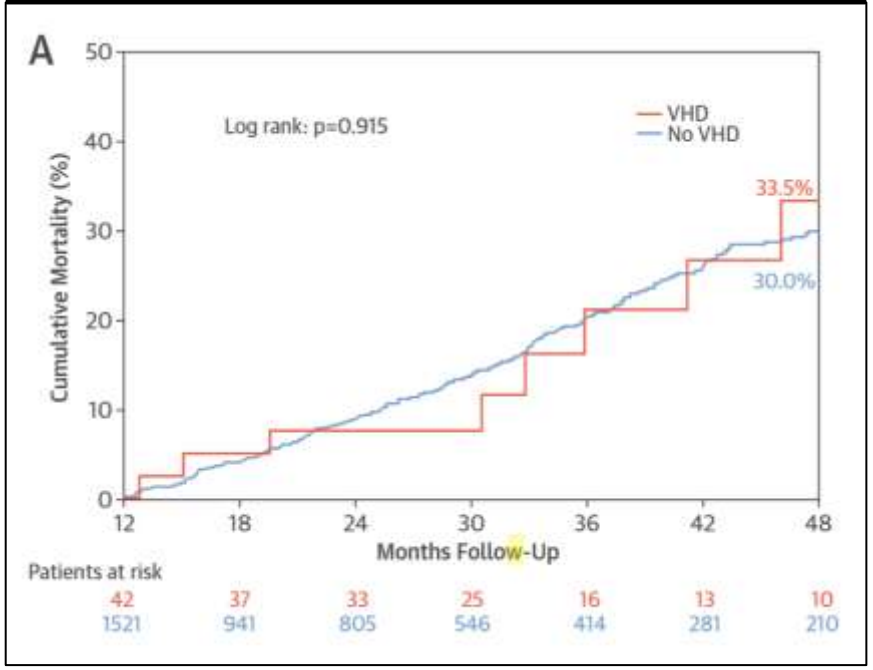


Del Trigo M. et al. JACC 2016

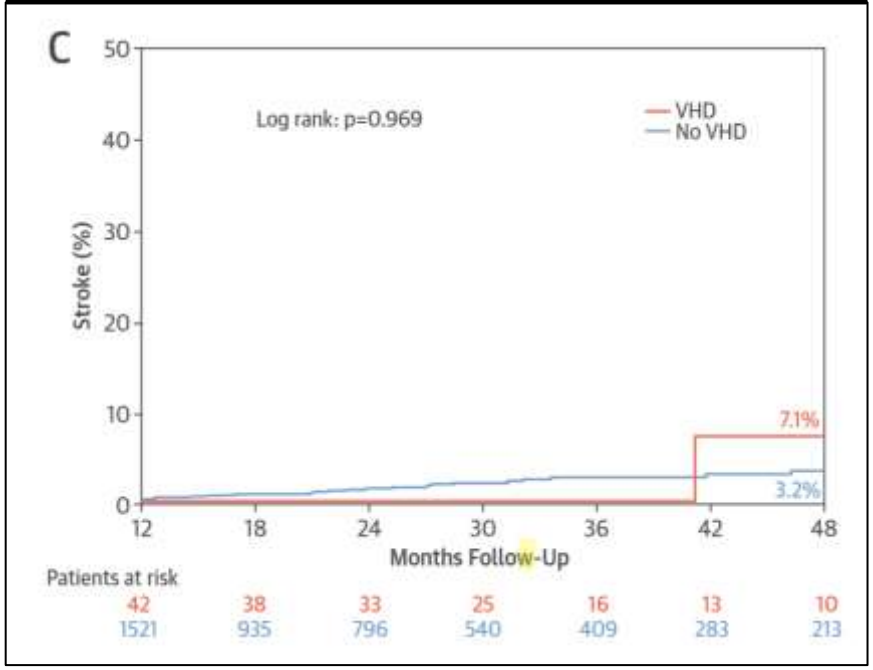
Valve hemodynamic degeneration and clinical outcomes

No significant increase in mortality or stroke

Mortality



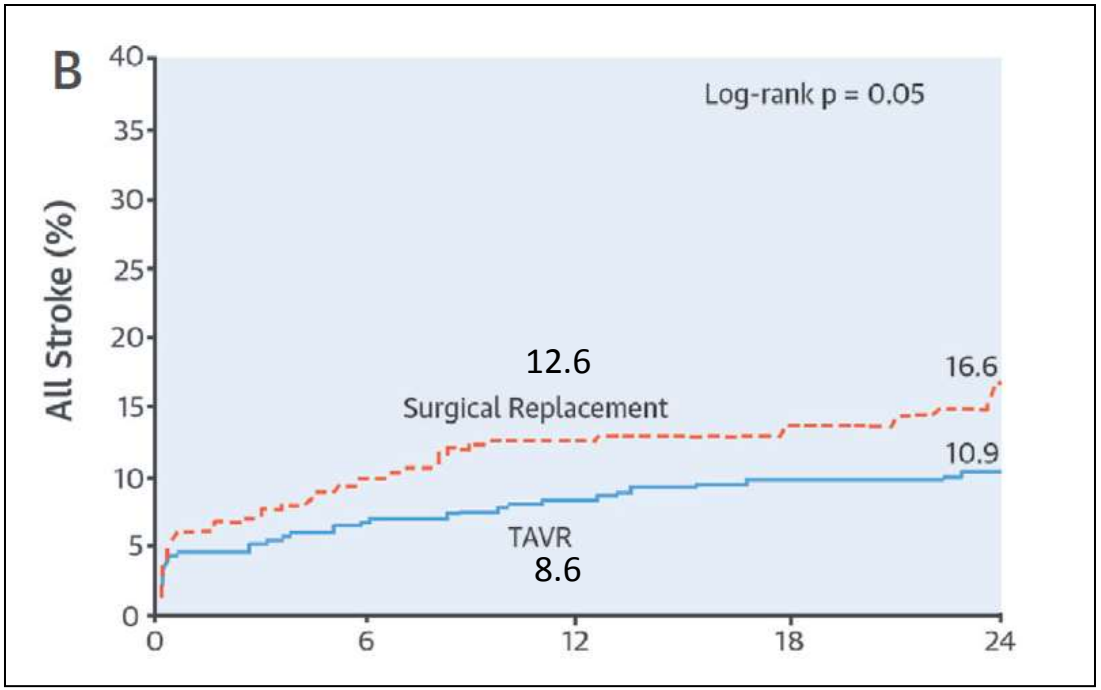
Stroke



Del Trigo M. et al. JACC 2016

Risk of stroke incremental with time in the CoreValve pivotal study

@4-5% per year for both TAVR and SAVR



Reardon M. et al. JACC 2015

Should we treat Leaflet Thrombosis?

- Should we treat *symptomatic* leaflet thrombosis? Definitely YES

- Should we treat *asymptomatic* leaflet thrombosis?

Yes-we treat thrombus in other location why not here, may be too late to find out if it affects valve durability, there is a signal for TIAs

No-there is no definite impact on outcomes yet, risk of bleeding may not be trivial. We need to elucidate this phenomenon better.

Should we routinely do CTs on all patients post TAVR?

- Best done systematically in research protocols with the involvement of imaging experts
- Radiation and contrast use may be an issue
- What would we do with the information in patients who are not candidates for anticoagulation?
- There should be low threshold to image in patients with suspected valve dysfunction, thrombo-embolic events

My perspective

- We started with a finding that we thought was an imaging artifact. We have established that this is a real finding. We have also established with a reasonable, but not unquestionable certainty, that this may be related to leaflet thrombosis.
- There is no conclusive evidence regarding the clinical significance of this finding. This requires longer and larger adequately powered studies.
- In appropriate clinical situations (elevated gradients, worsening heart failure, stroke/TIA, MI and other clinical situations concerning for embolic phenomenon), CT imaging should be performed to rule out leaflet thrombus.

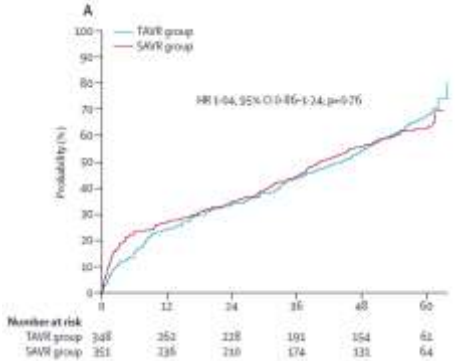
My perspective

- While a case for routine CT scanning in clinical practice cannot be made at this time. This is best studied in registries/ research protocols, with the involvement of imaging experts.
- Similarly, routine anticoagulation in all patients post-TAVR cannot be recommended, given the high risk of bleeding in the current TAVR population and the uncertain clinical significance of this finding.
- These findings provide a sound rationale for some of the planned studies with different antithrombotic regimens post-TAVR and question current guidelines of dual antiplatelet therapy. Imaging should be incorporated in some of the planned pharmacologic studies.

My perspective

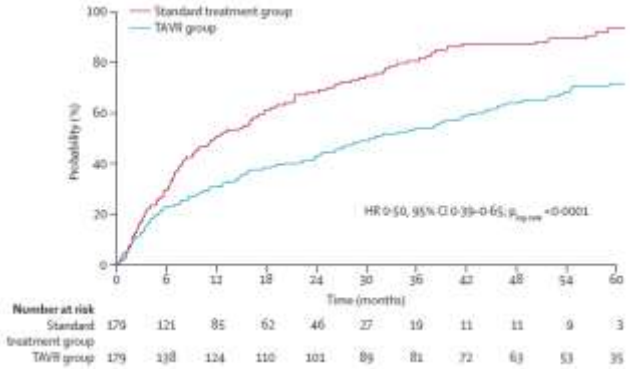
Adoption/expansion of TAVR should primarily be guided by large randomized trials/registries focused on clinical outcomes.

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

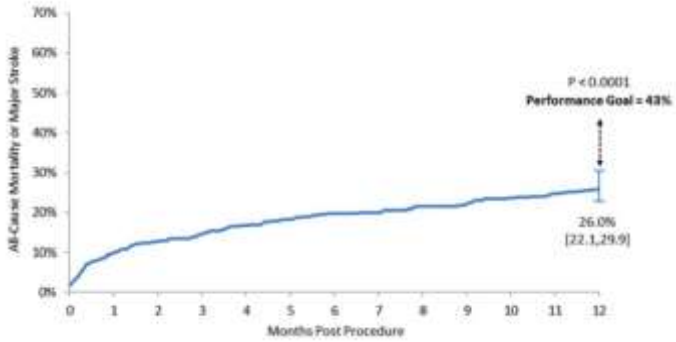


Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis

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



Transcatheter Aortic Valve Replacement Using A Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery



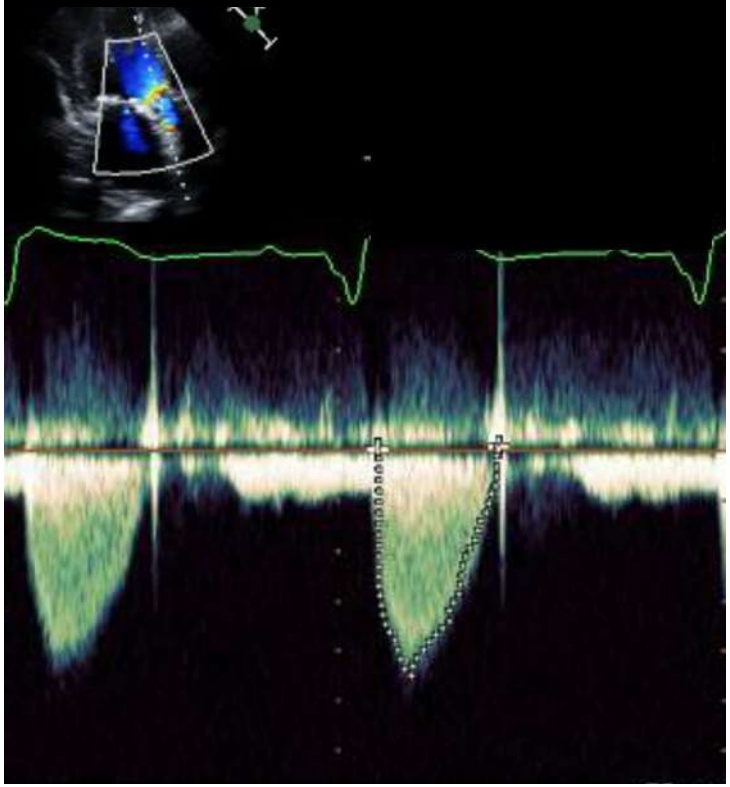
RESOLVE Study (NCT02318342)

- Ongoing, multicenter registry being expanded to 1000 patients post-TAVR/Surgical AVR
- Corelab analysis of contrast CT scans
- Corelab analysis of echocardiograms
- Contact:
  - makkarr@cshs.org
  - Hasan.Jilaihawi@cshs.org
  - Tarun.Chakravarty@cshs.org

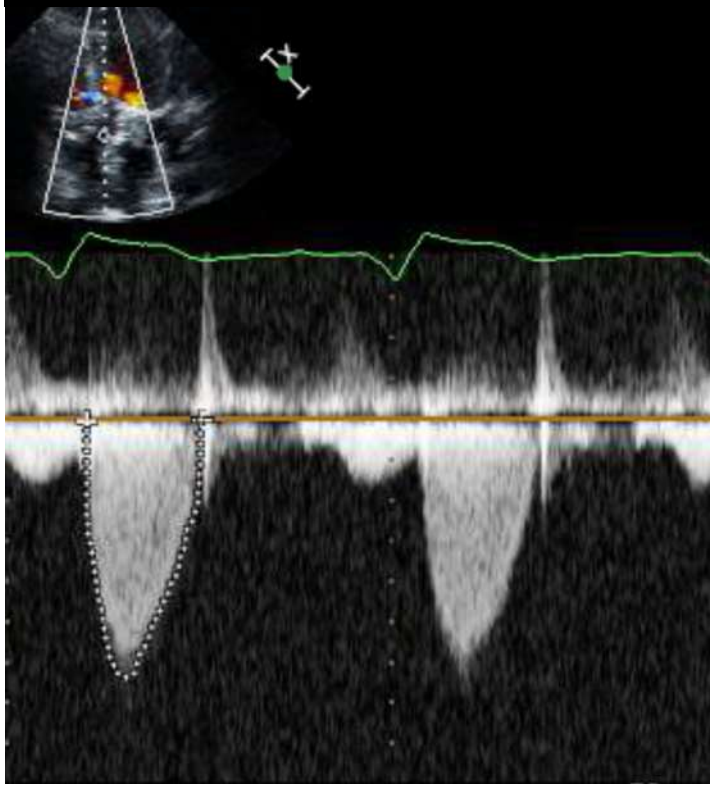
67 y/o male physician s/p TAVR with 29mm Sapien3 valve

Worsening shortness of breath 4 months post-TAVR
Transvalvular gradients elevated from 10 mmHg to 23 mmHg

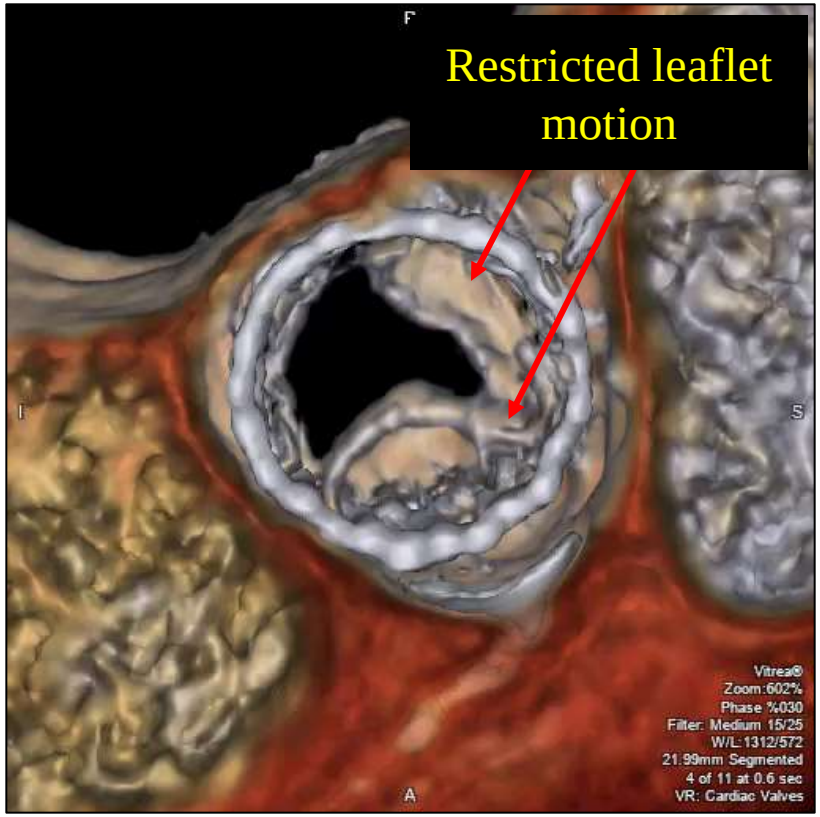
Day 1 TTE
Gradient 10mmHg

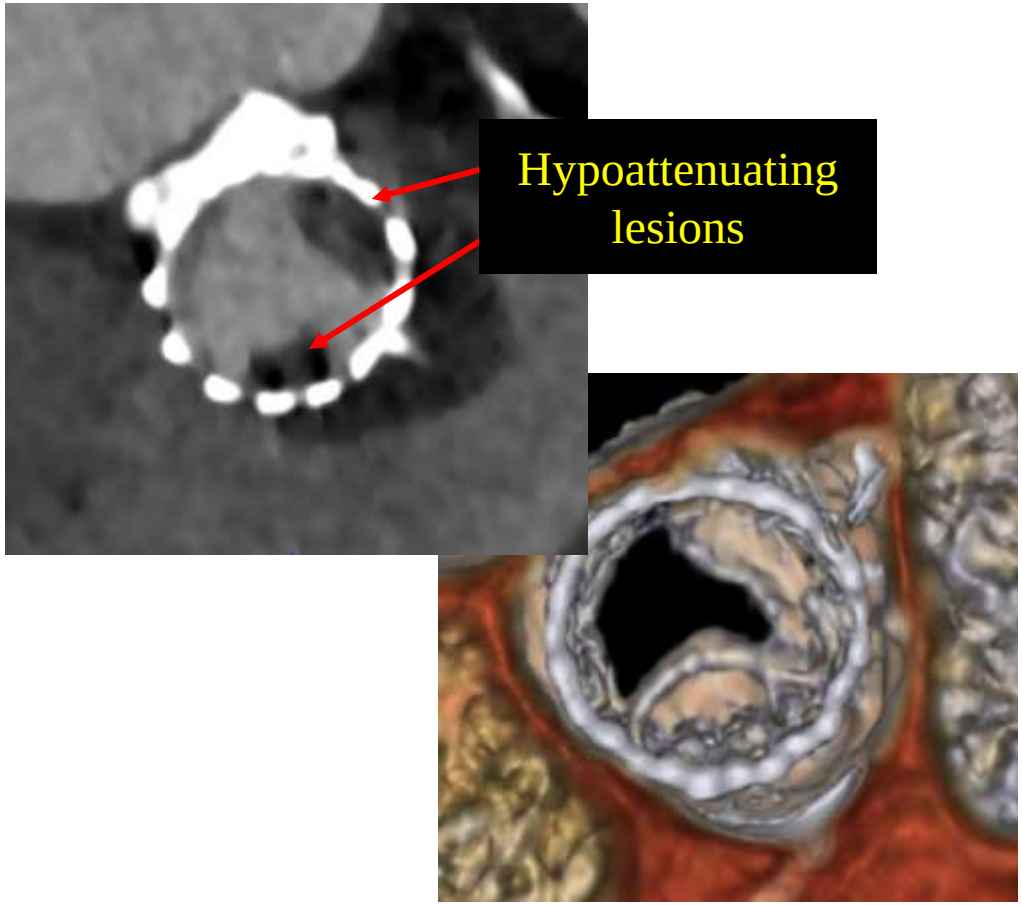


4 months post-TAVR
Gradient 23mmHg



Leaflet thickening and restricted leaflet motion noted on 4D VR-CT

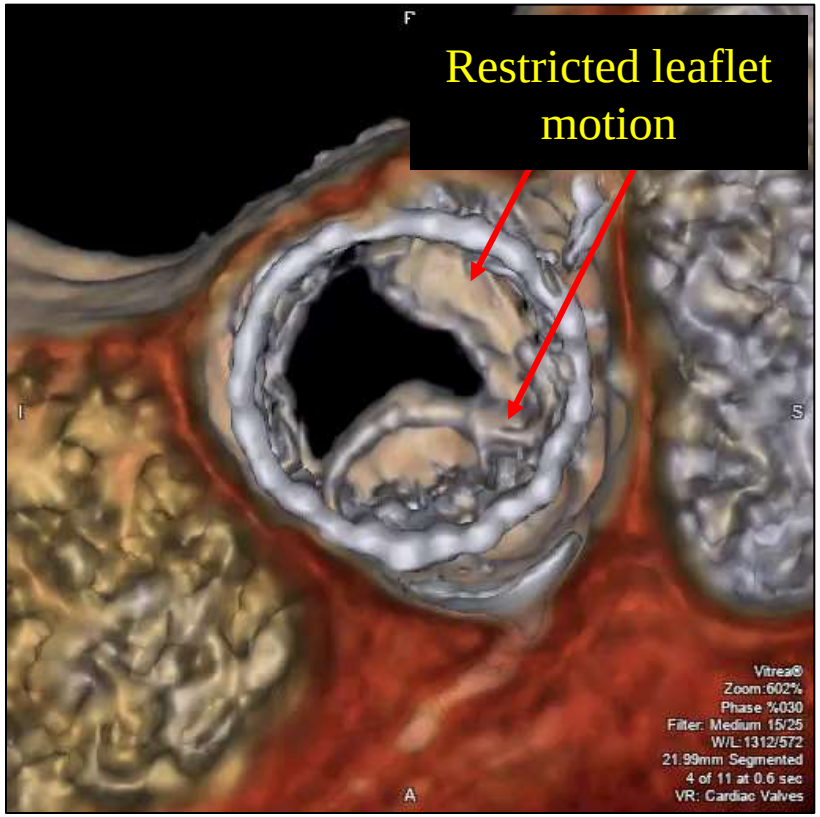


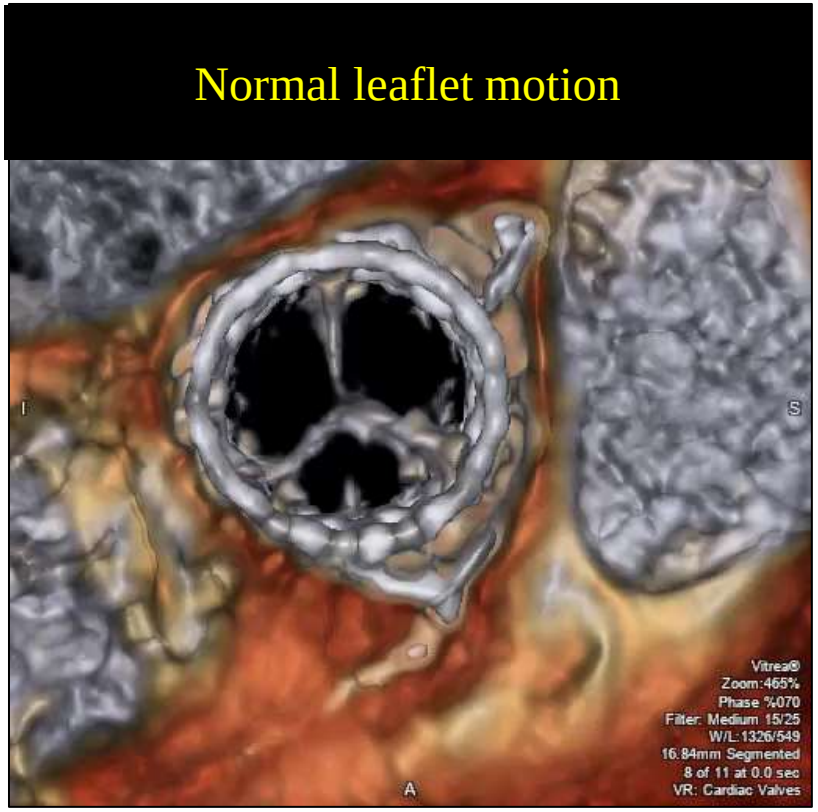


Leaflet motion restored following anticoagulation with warfarin (INR 2-3)

Repeat CT performed after 3 months

Resolution of symptoms with anticoagulation





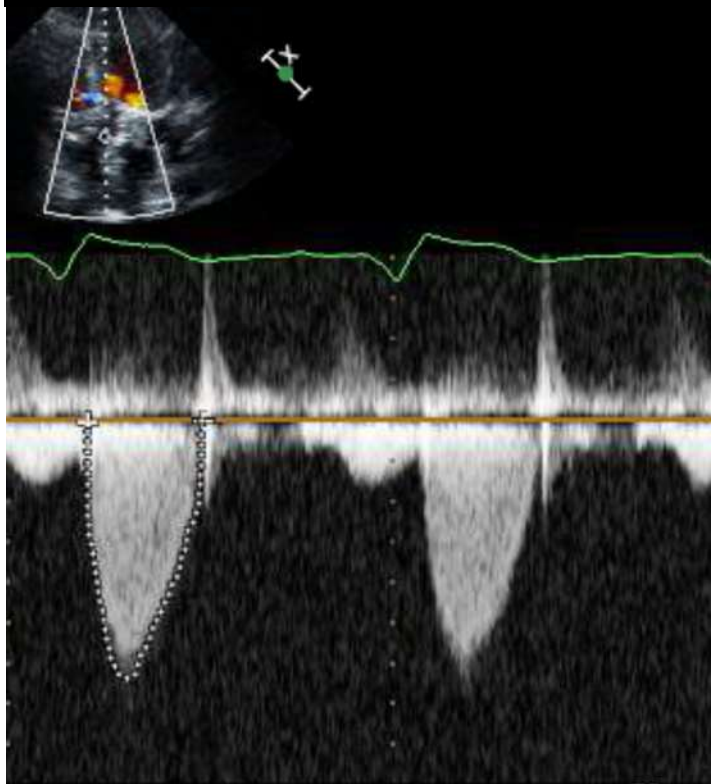
Normalized transvavular gradients with anticoagulation (warfarin, INR 2-3)

Repeat TTE performed after 3 months

Resolution of symptoms with anticoagulation

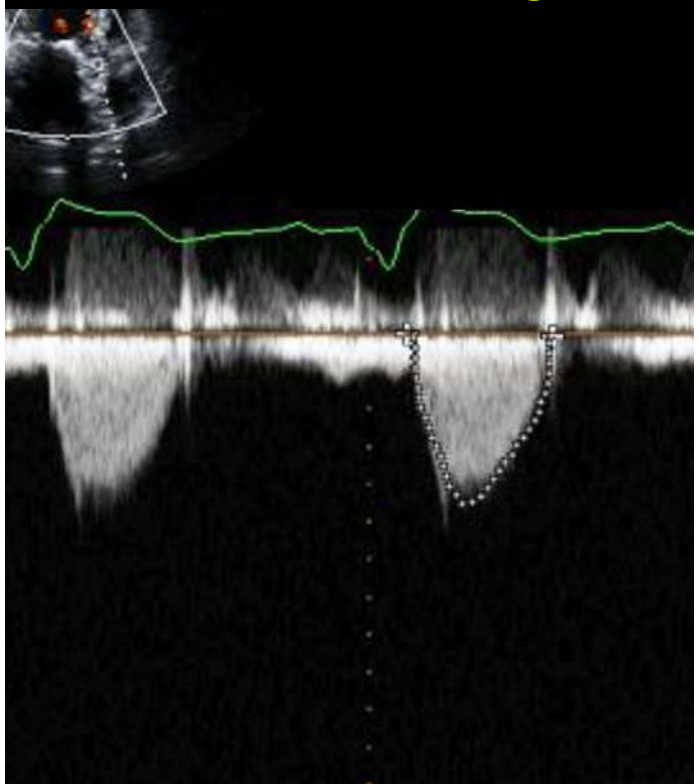
Pre-anticoagulation

Gradient 23mmHg



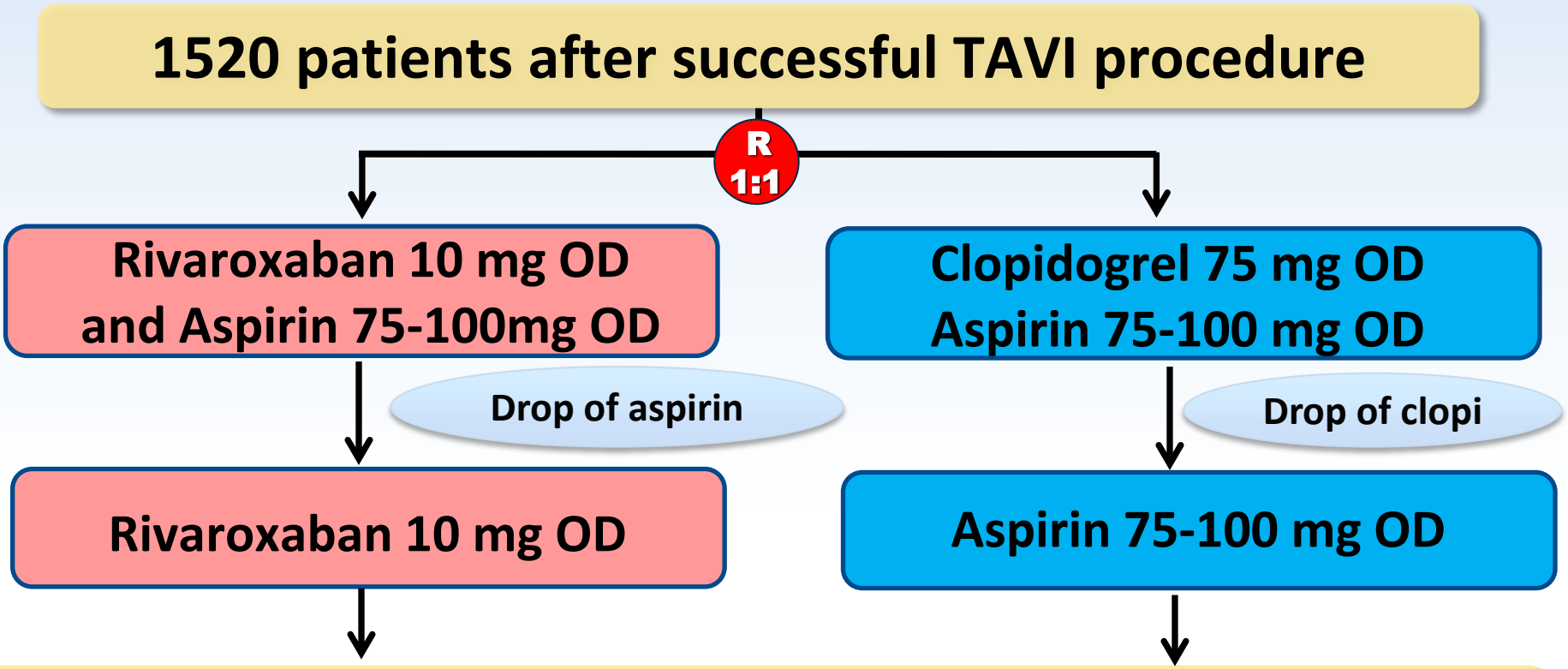
Post-anticoagulation

Gradient 11mmHg



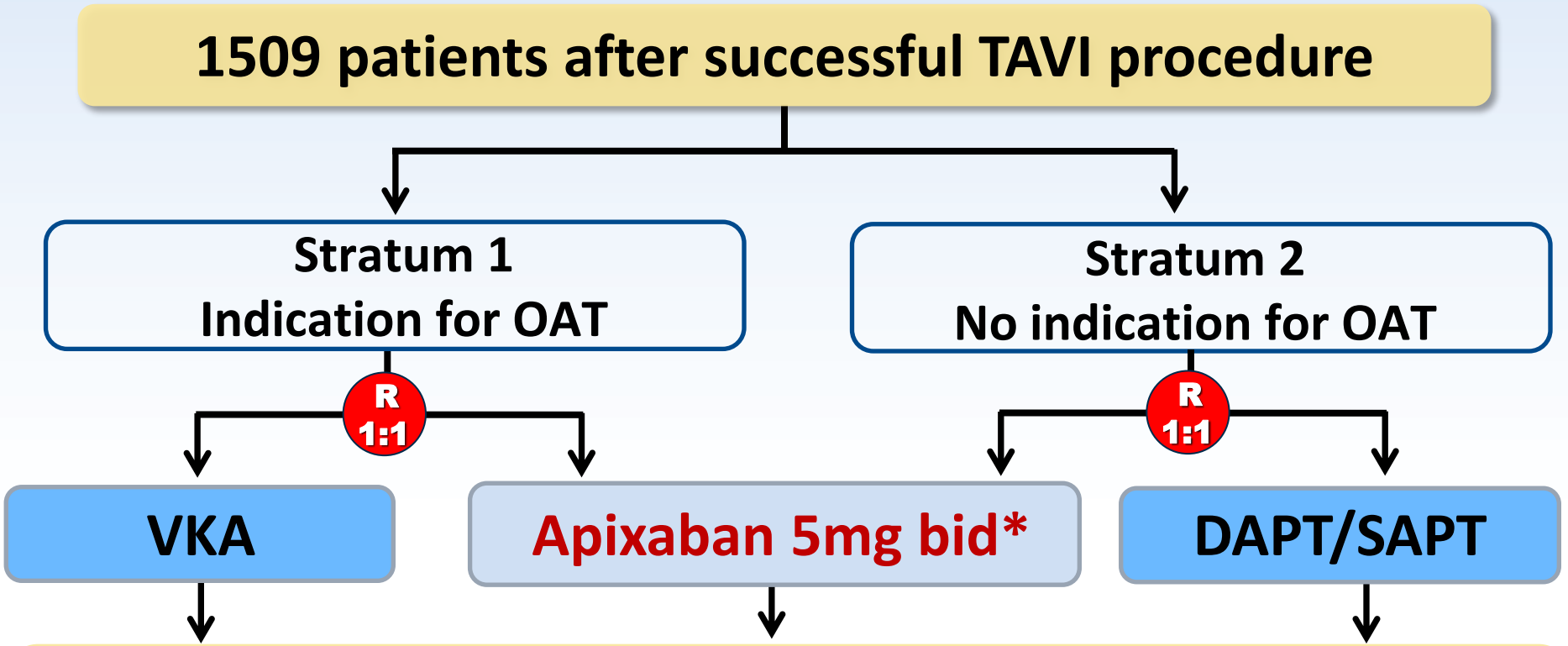
GALILEO

(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)



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*****.**

*2.5mg bid if creatinine clearance 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133µMol).