Subclinical Leaflet Thrombosis in Surgical and Transcatheter Bioprosthetic Aortic Valves

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ORIGINAL ARTICLE

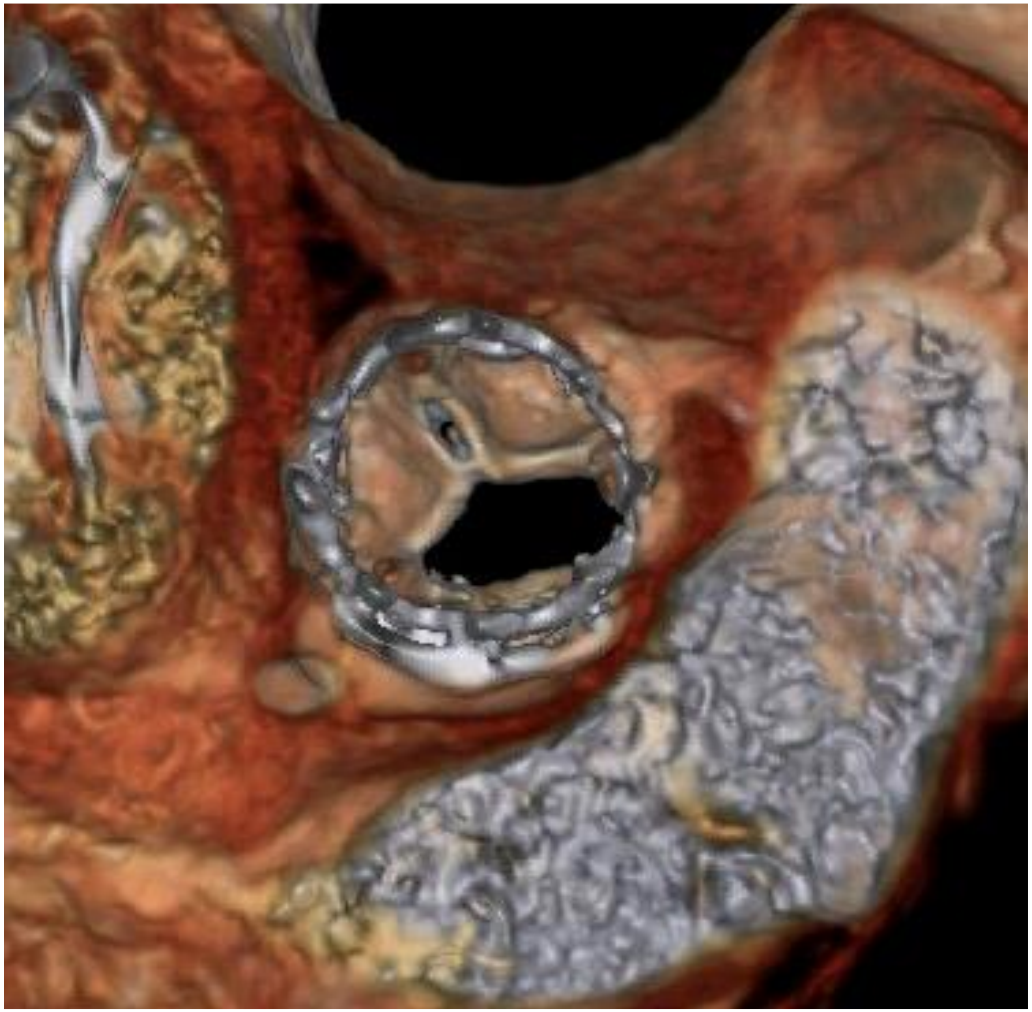
Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

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

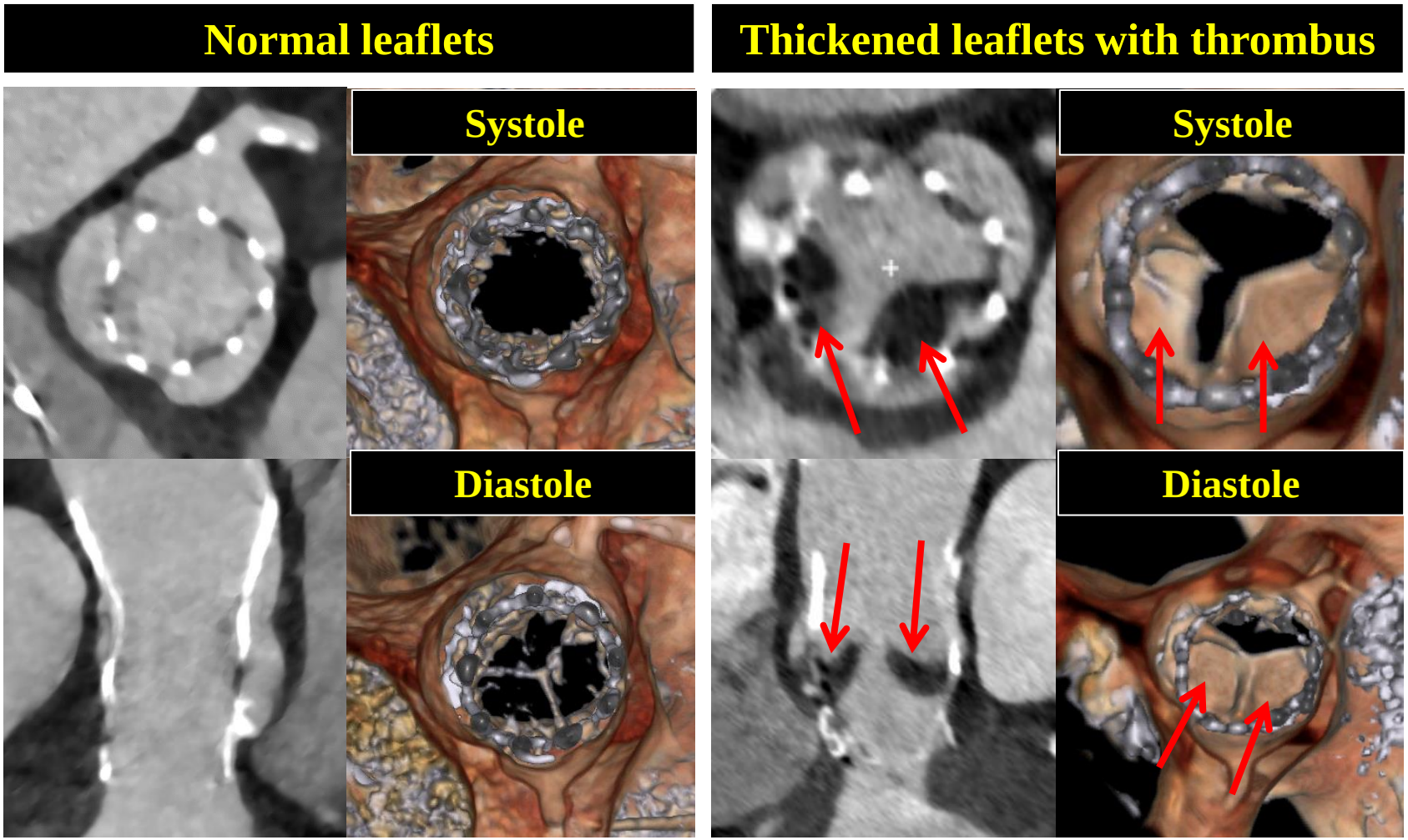
NEJM 2015

Background

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



Volume rendered CT images of bioprosthetic valves



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.

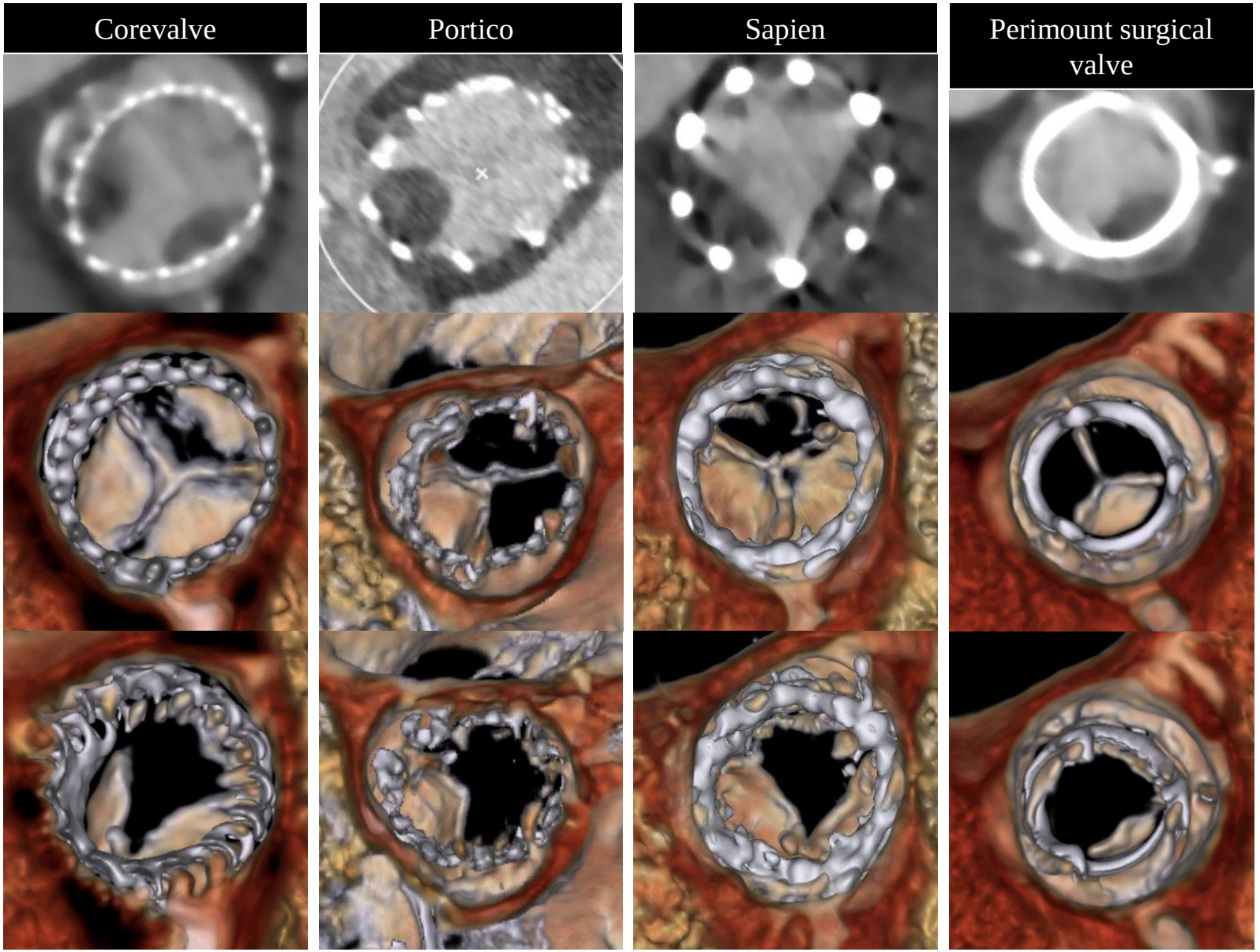
Results I

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

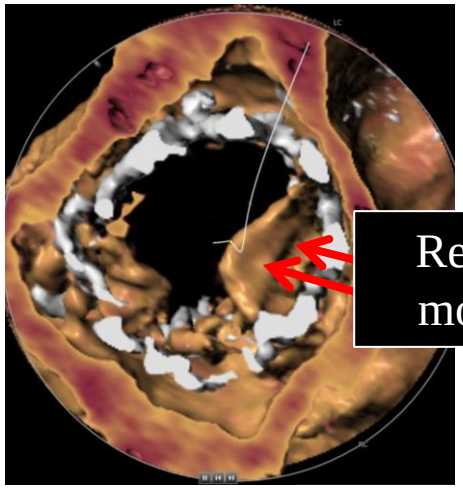
- The registries (RESOLVE and SAVORY) had reduced leaflet motion in 17 of 132 patients (13%).
  - 7/58 (12.1%) Sapien/XT/S3, 2/24 (8.3%) Corevalve, 1/8 Lotus (12.5%), 2/27 SAVR (7.4%)

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

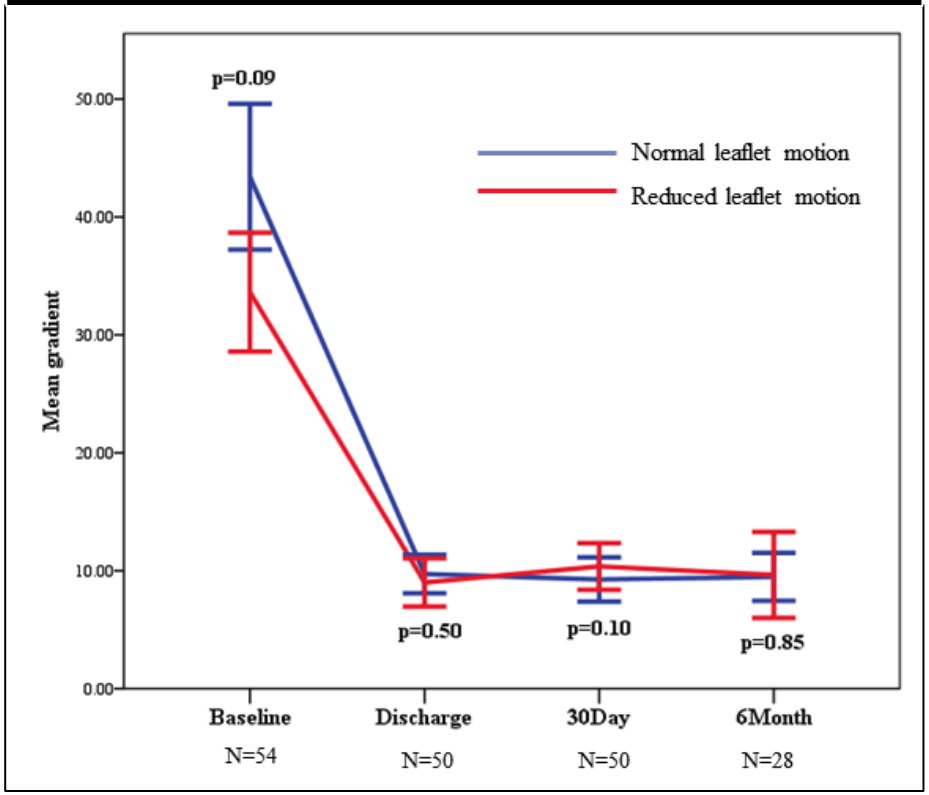


Results II: Role of TTE

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

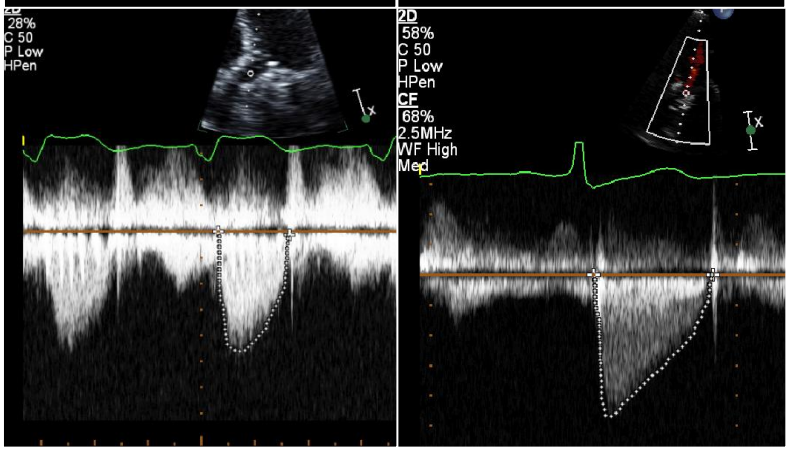


Portico IDE gradients in patients with and without reduced leaflet motion



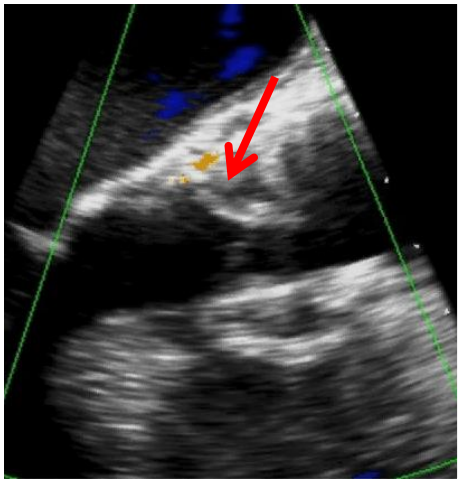
Day 1 mean gradient = 9 mmHg

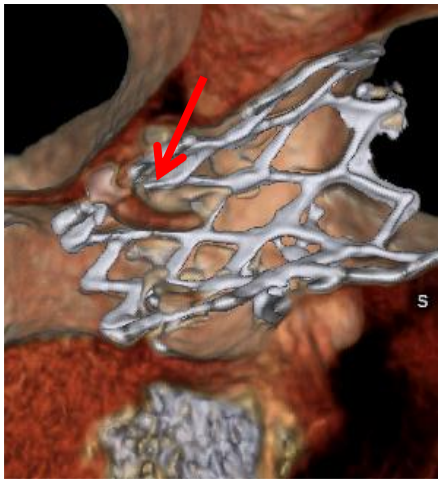
Day 30 mean gradient = 9 mmHg

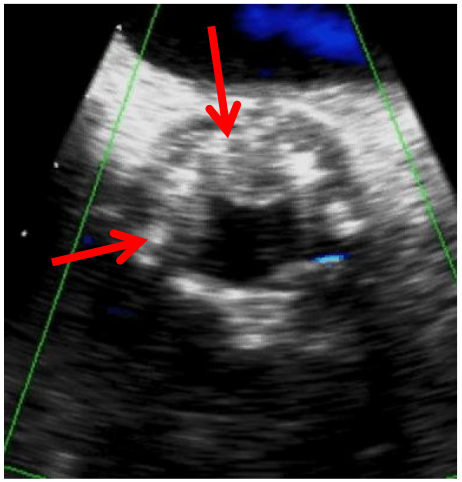


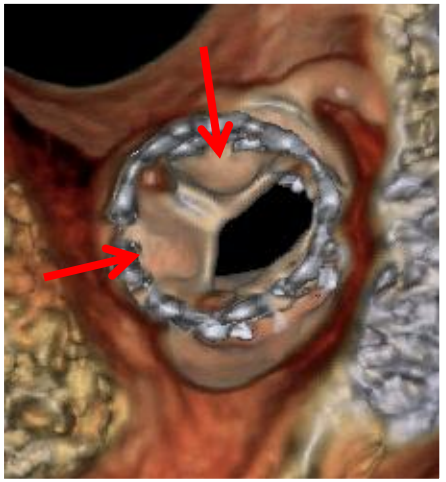
Results III: Role of TEE

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



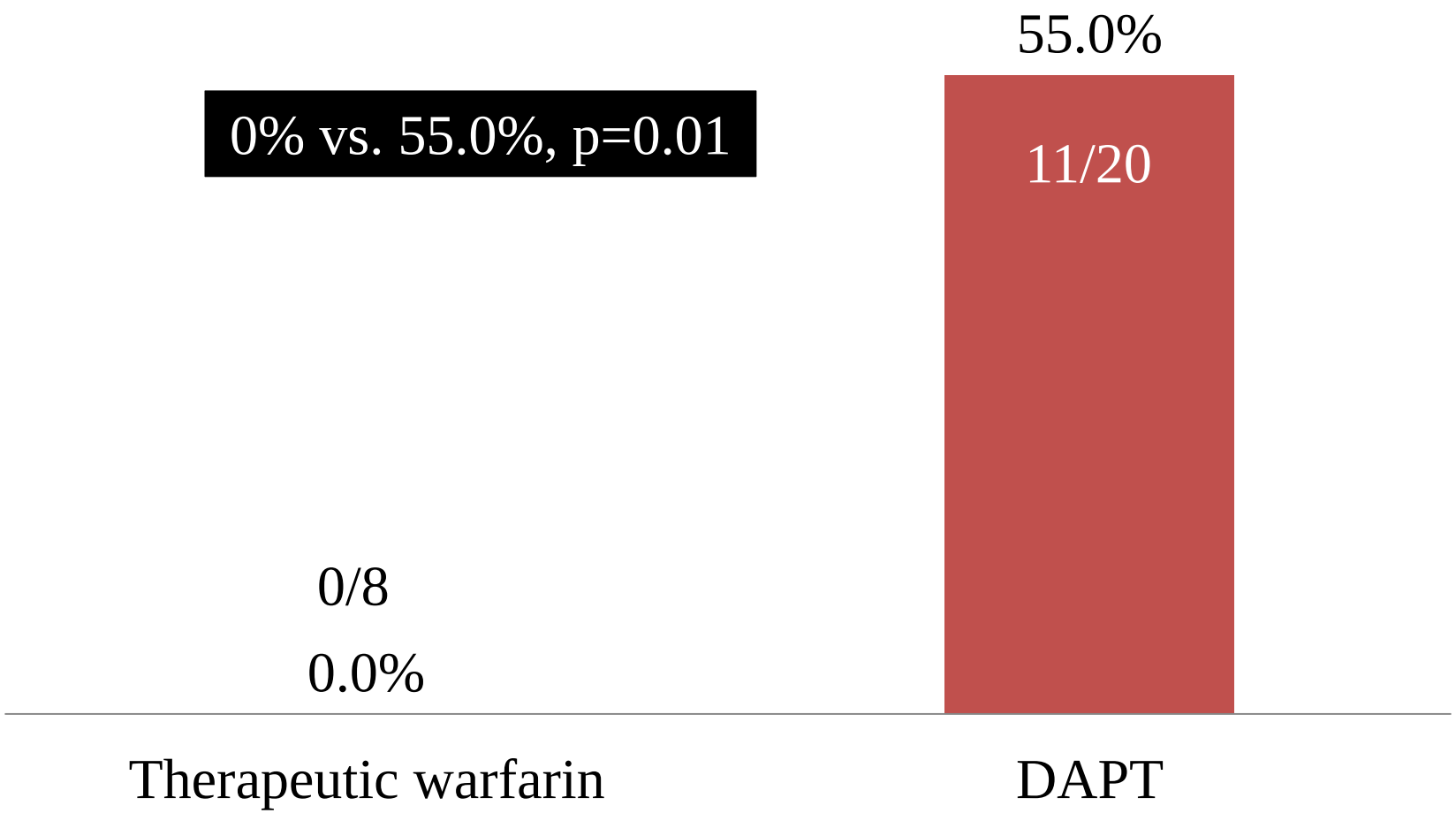






Results IV: Therapeutic warfarin vs. DAPT: Portico-IDE

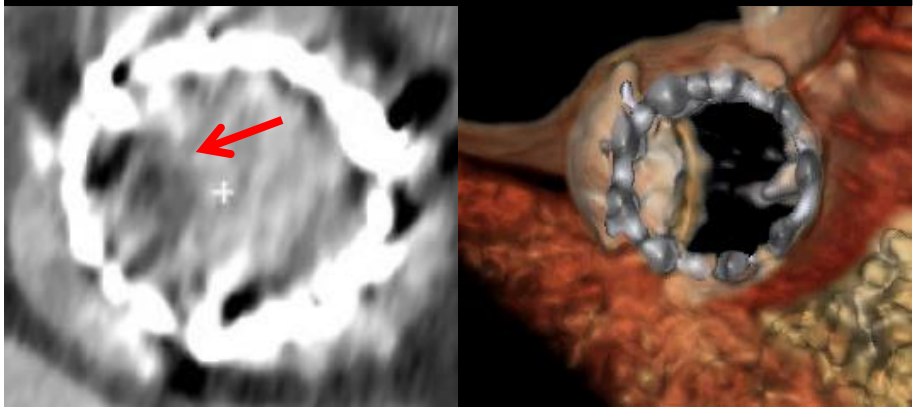
Decreased incidence of subclinical leaflet thrombosis



Results V: Natural history of this phenomenon

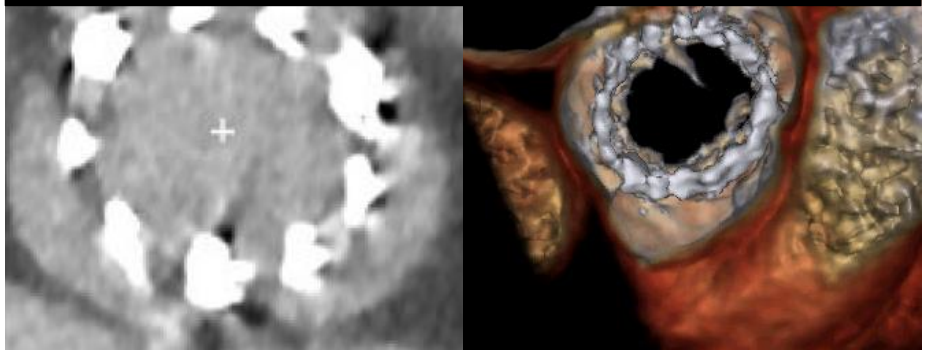
Anticoagulation was associated with resolution of thrombus and restoration of leaflet motion in 11 out of 11 patients

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

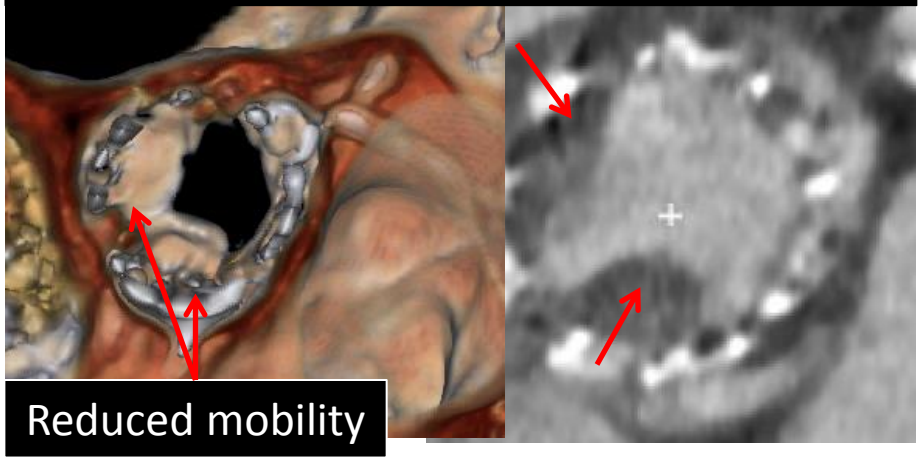
Persistence of thrombus and reduced leaflet motion in 9 out of 10 patients without therapeutic anticoagulation

Persistent reduced leaflet motion on subtherapeutic warfarin (INR 1.1)

30-day post-TAVR CT
Reduced leaflet motion

Reduced mobility

Follow-up CT 7 months later
Reduced leaflet motion



Reduced mobility

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?

Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

*Tarun Chakravarty, Lars Søndergaard, John Friedman, Ole De Backer, Daniel Berman, Klaus F Kofoed, Hasan Jilaihawi, Takahiro Shiota, Yigal Abramowitz, Troels H Jørgensen, Tanya Rami, Sharjeel Israr, Gregory Fontana, Martina de Knegt, Andreas Fuchs, Patrick Lyden, Alfredo Trento, Deepak L Bhatt, Martin B Leon, Raj R Makkar, on behalf of the RESOLVE and SAVORY Investigators**

Lancet online March 19, 2017

Research in context

Evidence before this study

We searched MEDLINE on Feb 1, 2017, for articles published in English, with the search terms "bioprosthetic valve thrombosis", "transcatheter aortic valve thrombosis", "subclinical leaflet thrombosis", "hypoattenuating leaflet thickening", and "TAVR thrombosis". Although symptomatic thrombosis represents the extreme end of the spectrum of bioprosthetic aortic valve thrombosis and is probably under-reported (prevalence of 1–2%), been attributed to subclinical leaflet thrombosis in previously reported series. The published series have several limitations, including absence of complete clinical follow-up, no core laboratory assessment of transthoracic echocardiograms, no information about differences in the prevalence and severity of subclinical leaflet thrombosis between transcatheter and surgical valves, no adjudication of neurological events, and no information about the efficacy of novel oral anticoagulants (NOACs).

Added value of this study

We report, to our knowledge, the largest study to date of 931 patients who had CT scans done after surgical or transcatheter aortic valve replacement (TAVR) to assess reduced leaflet motion and its effect on clinical outcomes. This study is the first, to our knowledge, to report differences in subclinical leaflet thrombosis between surgical and transcatheter aortic valves. Findings from this study are also the first, to our knowledge, to show the potential efficacy of NOACs in the prevention and treatment of subclinical leaflet thrombosis in bioprosthetic aortic valves. The frequency and severity of subclinical leaflet thrombosis was lower in surgical than in transcatheter aortic valves. Patients with reduced leaflet motion had a small, but significant, increase in valve gradients. Anticoagulation was better than dual antiplatelet therapy (DAPT; transient ischaemic attacks and strokes or transient ischaemic attacks associated with reduced leaflet motion, although the rates of strokes were not significantly different.

Implications of all the available evidence

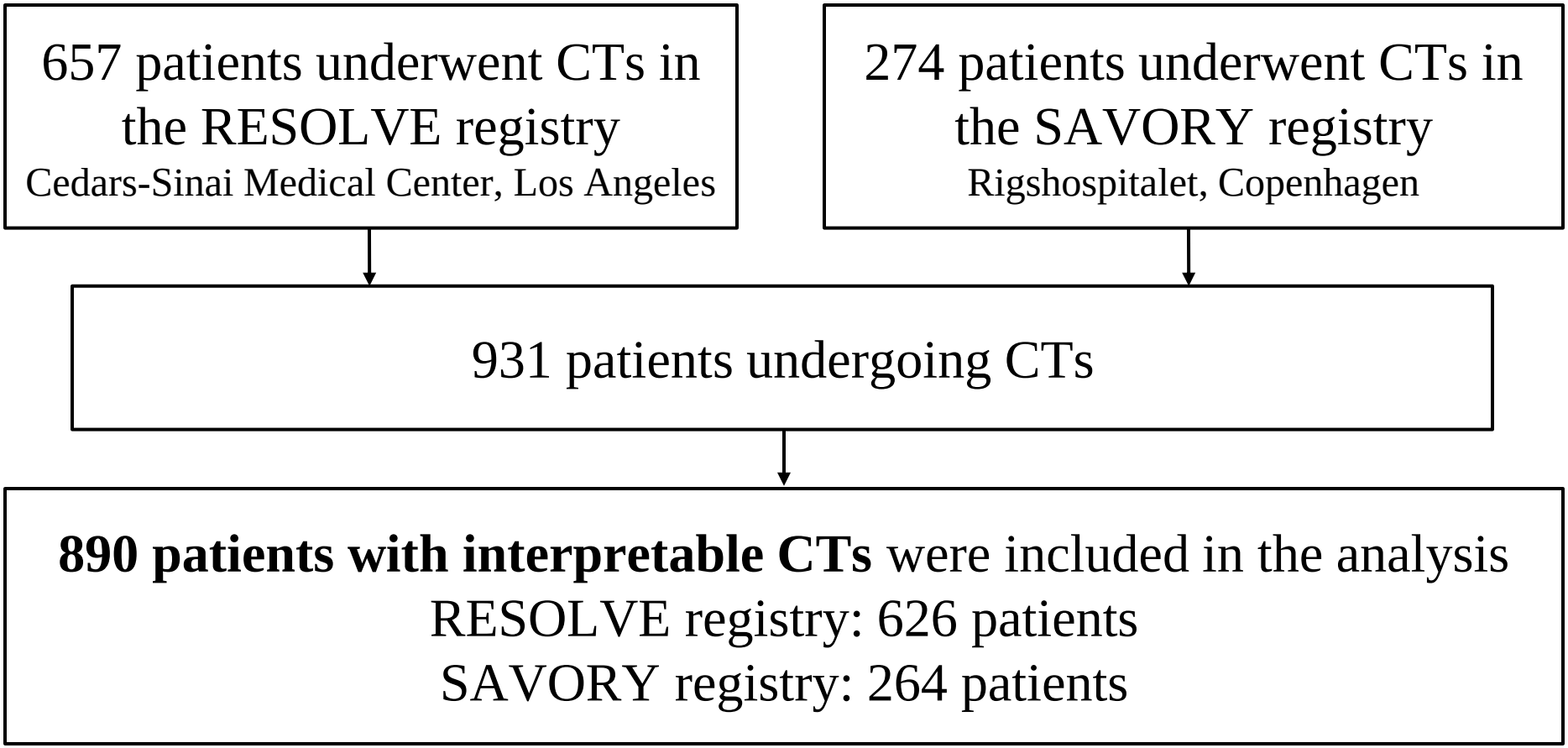
Our findings question the guidelines recommending DAPT after TAVR and raise the issue of whether or not warfarin or NOACs are more appropriate in certain patients than is DAPT.
The risk-benefit profile of anticoagulation will be established in future clinical trials. Despite excellent outcomes after TAVR with the new-generation valves, room might exist for further improvement in outcomes through an understanding of the predictors of reduced leaflet motion and consideration of a short course of anticoagulation if findings from ongoing randomised trials substantiate these existing findings.

Study Objectives

To study subclinical leaflet thrombosis of bioprosthetic aortic valves in terms of

- Prevalence in a large heterogenous cohort of patients
- Differences in TAVR and SAVR
- Impact of novel-oral anticoagulants (NOACs)
- Impact on valve hemodynamics
- Impact on clinical outcomes

Study design



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)

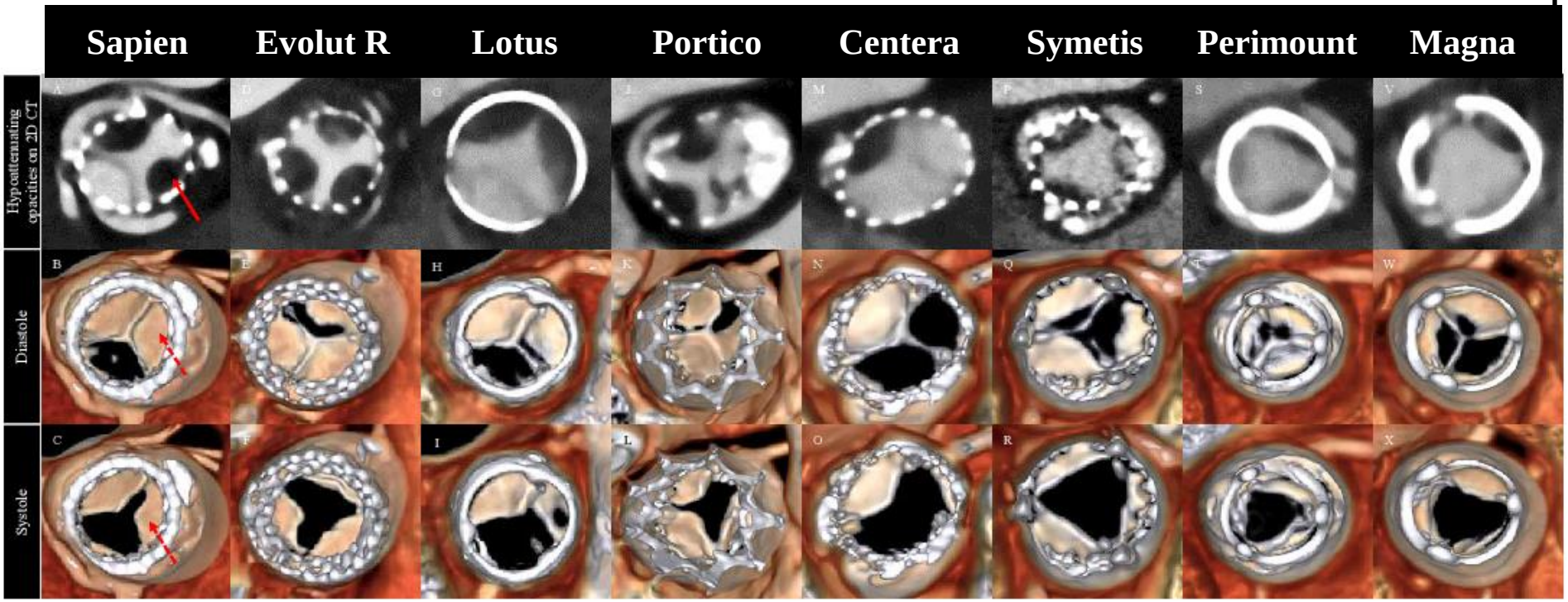
752 transcatheter valves
Median time from TAVR to CT
58 days (IQR 32–236 days)

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

Study methodology

- All echocardiograms were analyzed in a blinded manner.
- Data on the antiplatelet and antithrombotic therapy were collected on all clinic visits.
- Clinical follow-up was obtained in all patients for death, myocardial infarction (MI), stroke and transient ischemic attack (TIA).
- All neurologic events, including strokes and TIAs, were adjudicated in a blinded manner by a stroke neurologist.

Reduced leaflet motion in multiple valve types



Prevalence of reduced leaflet motion

Transcatheter vs. surgical bioprosthetic aortic valves: p=0.001

Reduced leaflet motion was present in 106 (11.9%) patients

Transcatheter valves
13.4% (101 out of 752)

Surgical valves
3.6% (5 out of 138)

Baseline characteristics

Patients with surgical and transcatheter aortic valves

Characteristic	SAVR (N=138)	TAVR (N=752)	p-value
Age-year	71·9±8·6	80·7±8·4	<0·0001
Male sex-no. (%)	88 (63·8%)	413 (54·9%)	0·05
Medical condition - no. (%)			
Chronic kidney disease	6 (4·8%)	82 (11·7%)	0·02
Hemodialysis	0 (0%)	9 (1·3%)	0·23
Hypercoagulable disorder	0 (0%)	9 (1·4%)	0·61
Hypertension	101 (73·2%)	666 (88·7%)	<0·0001
Prior stroke	9 (6·6%)	63 (8·4%)	0·47
Prior transient ischemic attack	3 (2·2%)	39 (5·2%)	0·19
Hyperlipidemia	93 (67·9%)	584 (77·8%)	0·01
Diabetes	28 (20·3%)	187 (24·9%)	0·25
PCI within 3 months prior to AVR	7 (5·2%)	90 (12·0%)	0·02
Congestive heart failure	68 (49·3%)	604 (80·6%)	<0·0001
Syncope	2 (1·5%)	48 (6·4%)	0·02
Atrial fibrillation	31 (22·6%)	219 (29·2%)	0·11
Baseline echocardiogram			
Ejection fraction - %	57·2±11·5	57·7±12·9	0·30
Mean aortic valve gradient - mmHg	43·6±14·4	44·4±14·1	0·91
Peak aortic valve gradient - mmHg	72·5±22·3	74·4±22·7	0·82
VTI ratio	0·26±0·12	0·23±0·08	0·04
Anticoagulation at the time of discharge	31 (22·5%)	187 (24·9%)	0·54
Anticoagulation at the time of CT	38 (27·5%)	186 (24·7%)	0·49
Timing from AVR to CT	162·5 days (80 – 417 days)	58 days (32 – 235 days)	<0·0001
0-6 months	74 (53·6%)	520 (69·2%)	
6-12 months	26 (18·8%)	84 (11·2%)	
>12 months	38 (27·5%)	148 (19·7%)	

AVR=Aortic valve replacement; CT=computed tomogram

Data are mean ± standard deviation or median (interquartile range) for continuous variables; N (%) for categorical variables

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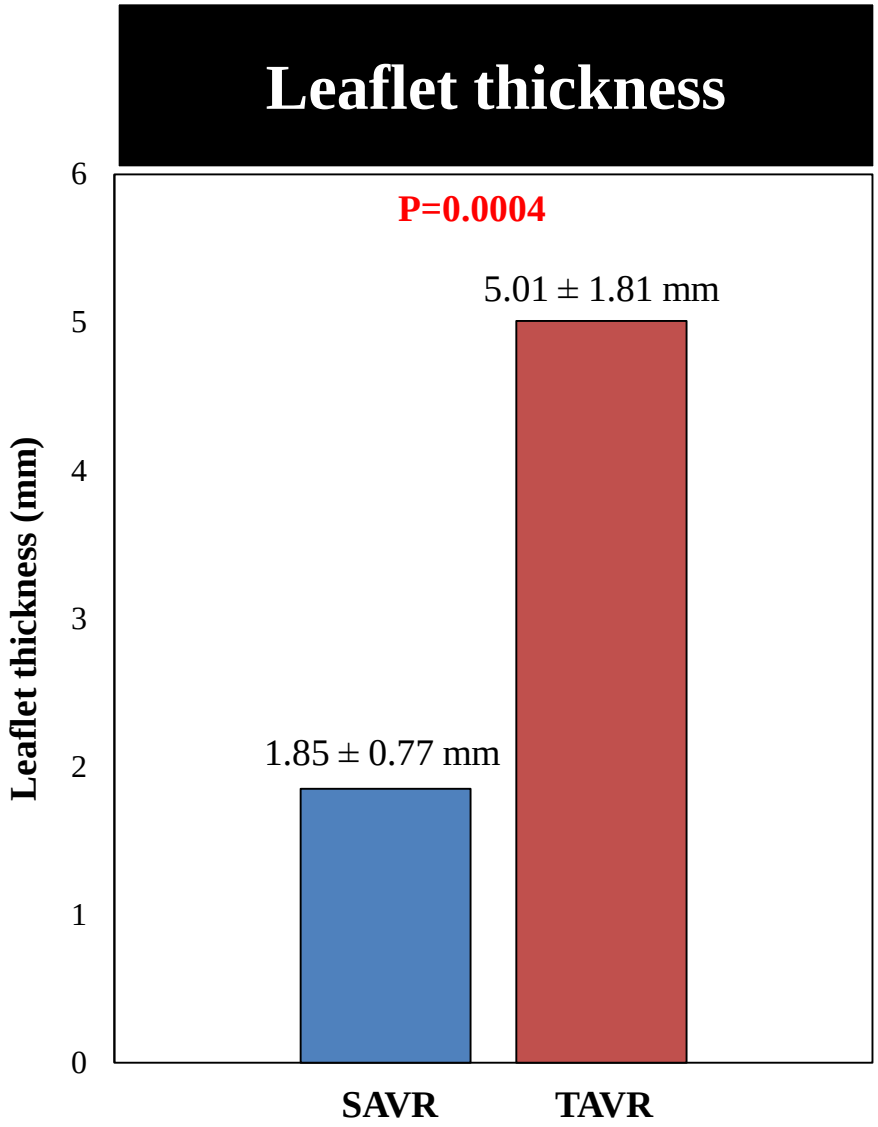
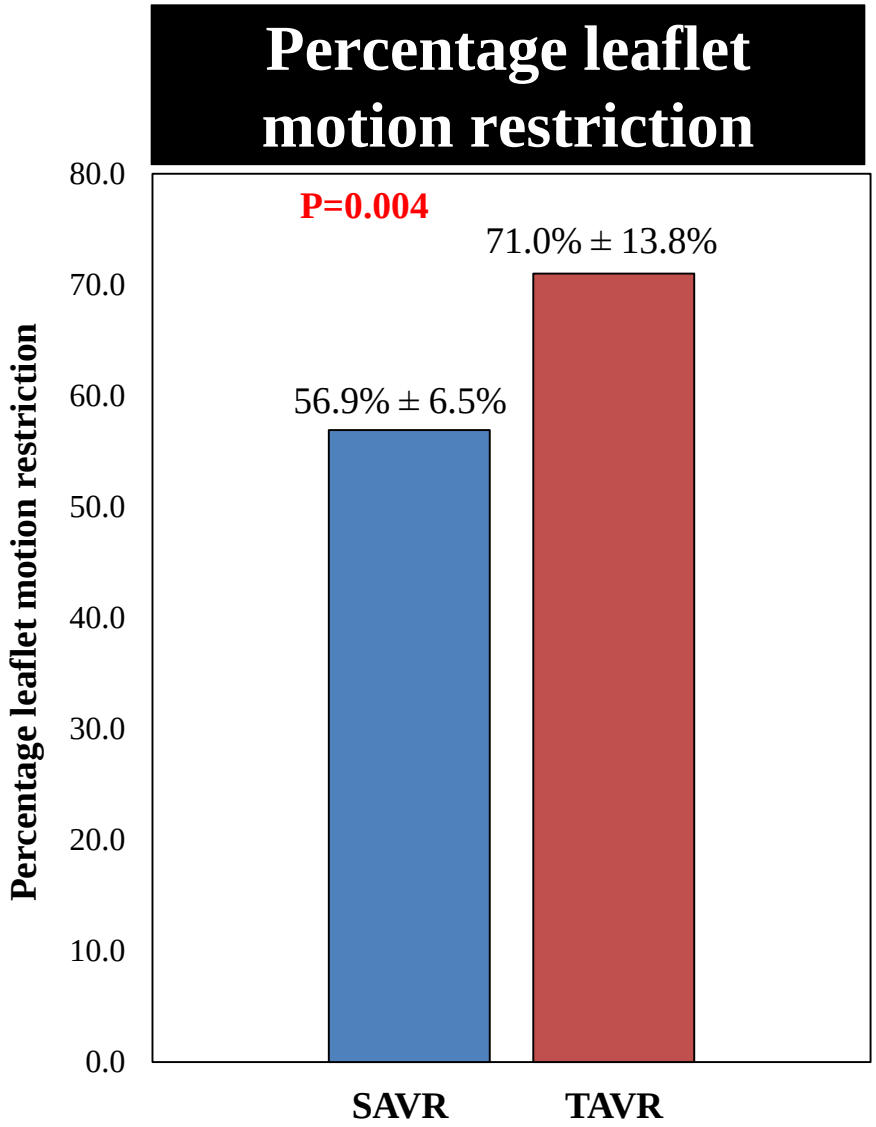
Severity of reduced leaflet motion

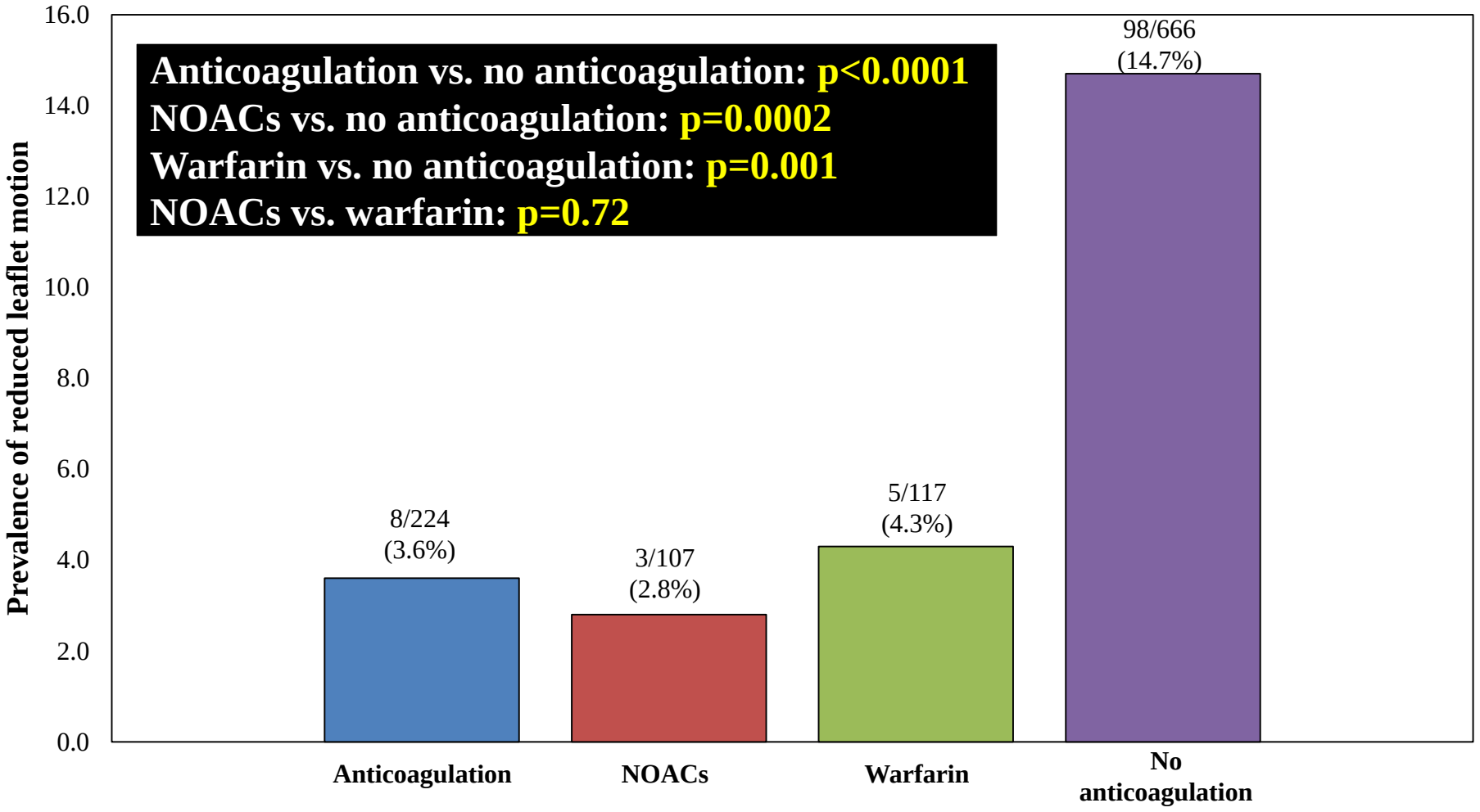
Surgical vs. transcatheter valves





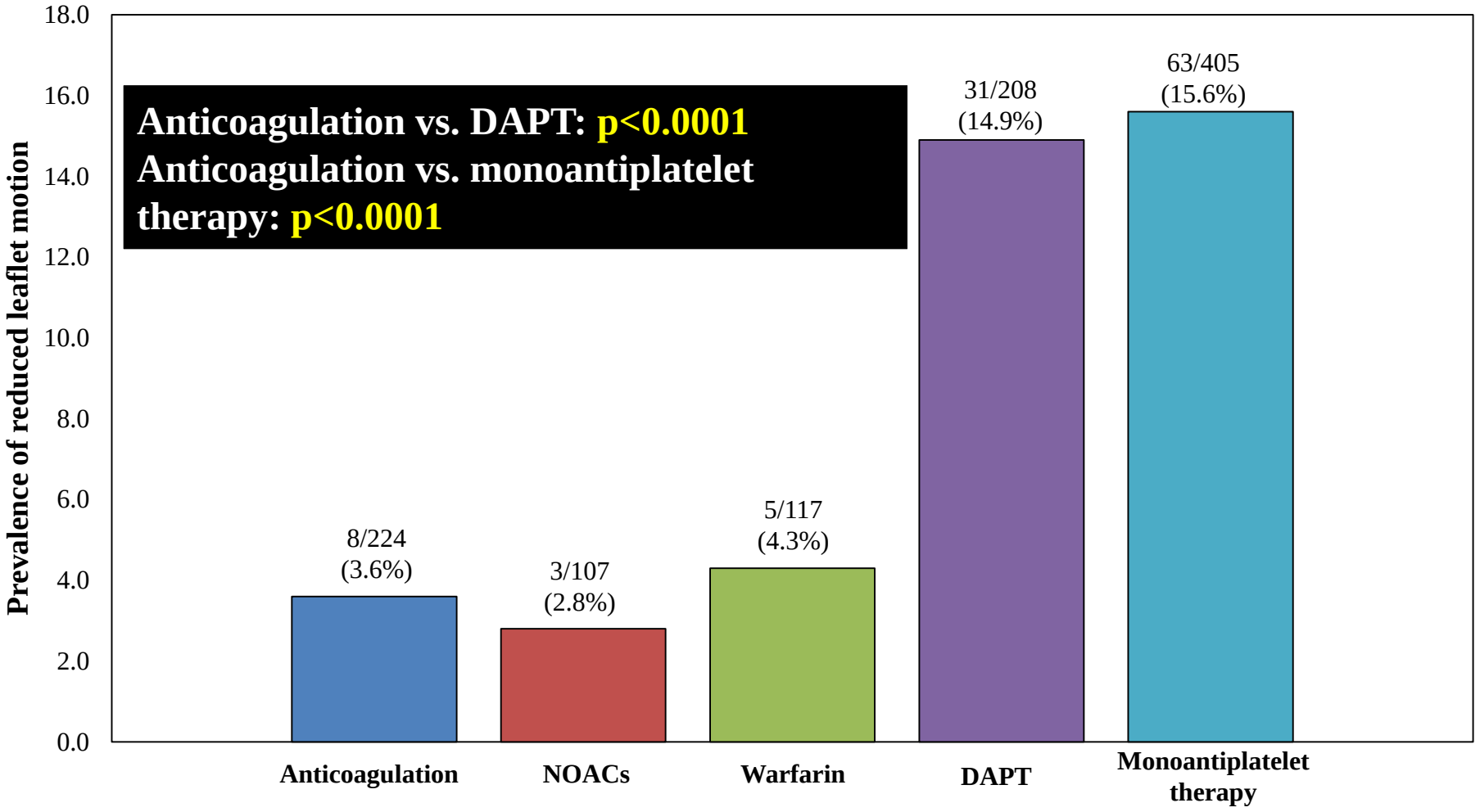
Anticoagulation and reduced leaflet motion

Anticoagulation vs. no anticoagulation



Anticoagulation and reduced leaflet motion

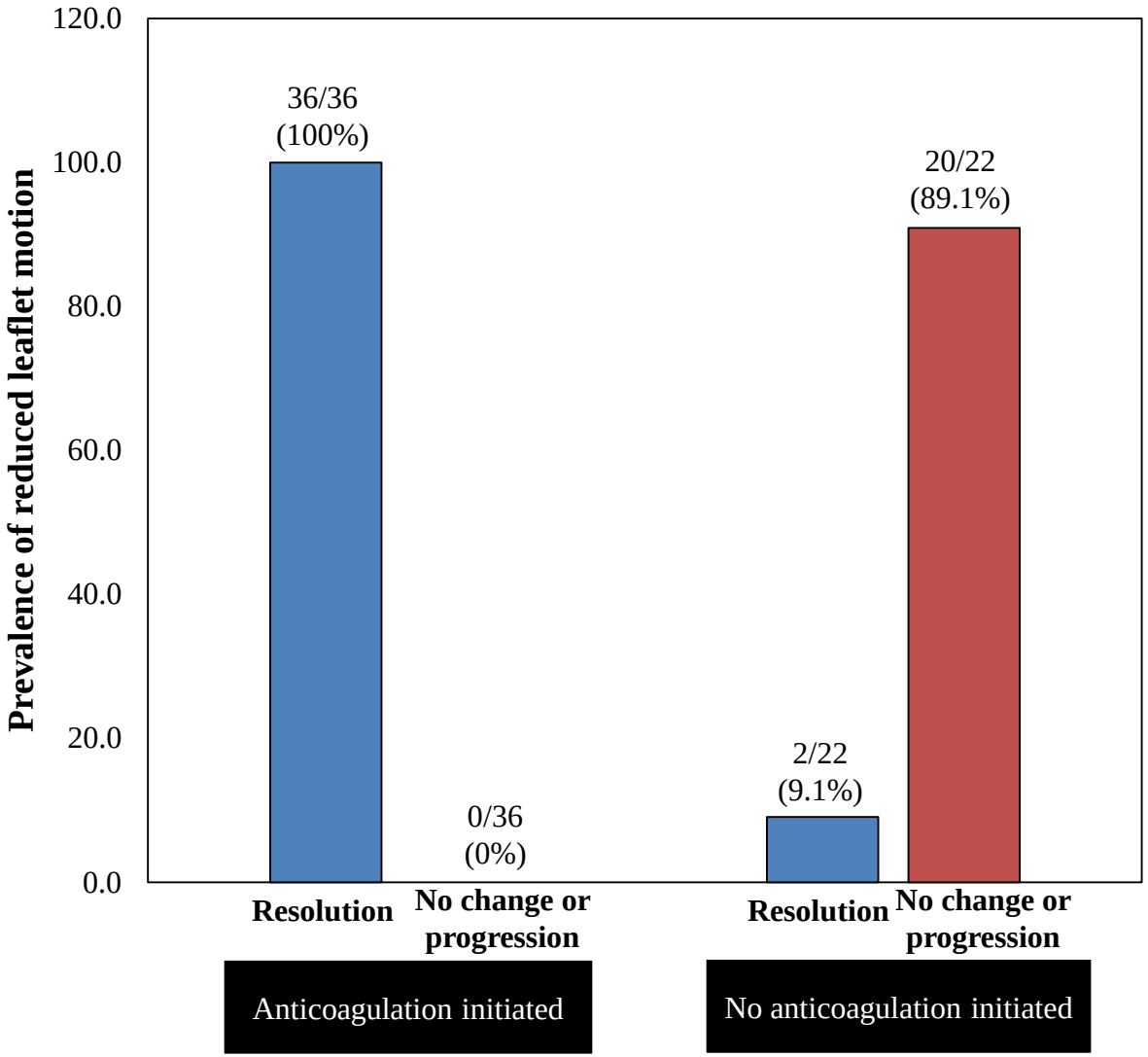
Anticoagulation vs. antiplatelet therapy



Multivariate predictors of reduced leaflet motion

	Odds ratio (95% CI)	p-value
Age	1·04 (1·01-1·07)	0·01
Ejection fraction	0·98 (0·97-1·00)	0·02
Surgical vs transcatheter valve	0·33 (0·11-0·96)	0·04
Anticoagulation	0·24 (0·10-0·58)	0·002
Time to CT	1.00 (0.98-1.02)	0.67
Atrial fibrillation	0.62 (0.31-1.23)	0.17
BMI	0.97 (0.93-1.02)	0.17

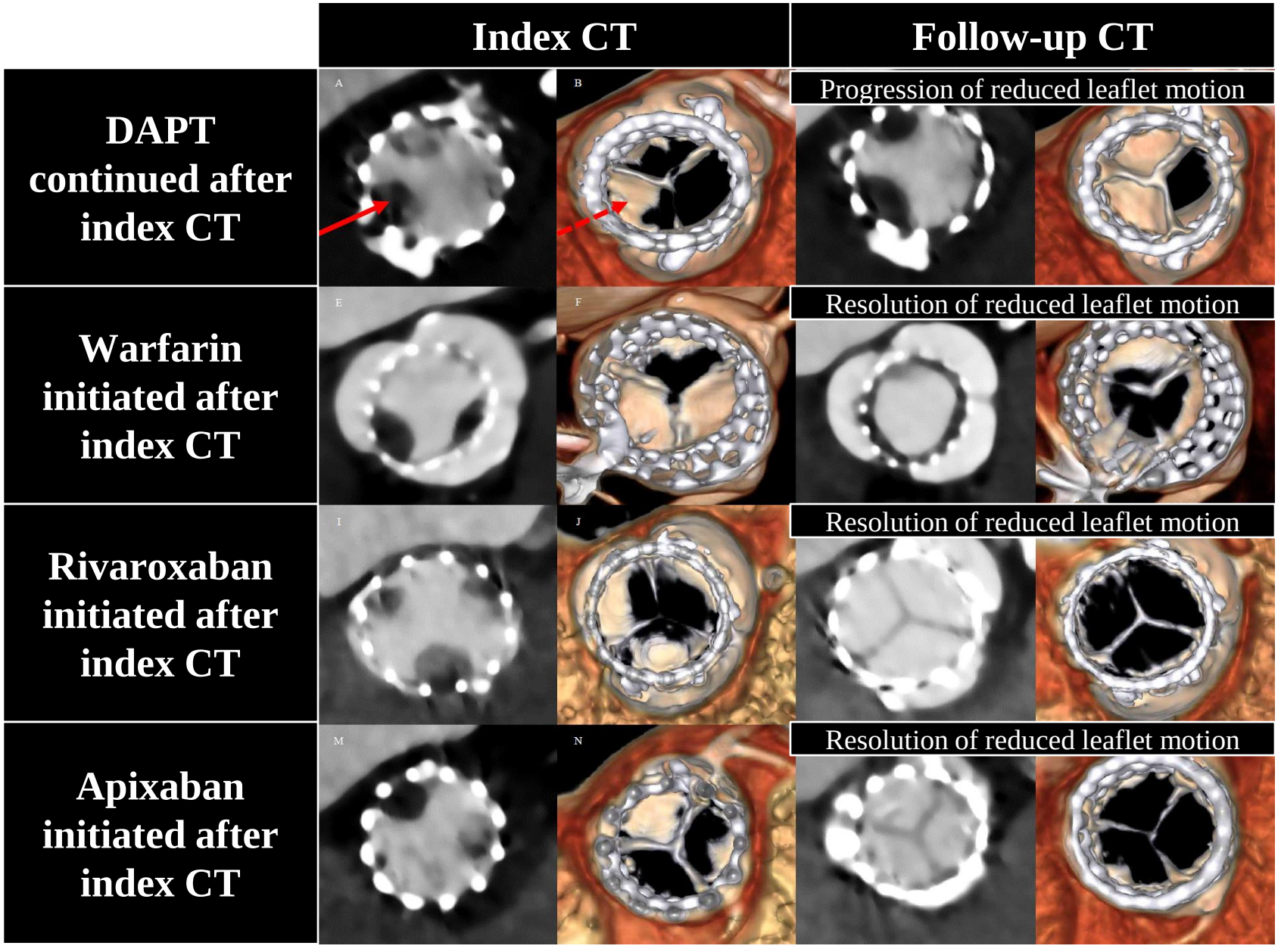
Impact of initiation of anticoagulation on reduced leaflet motion



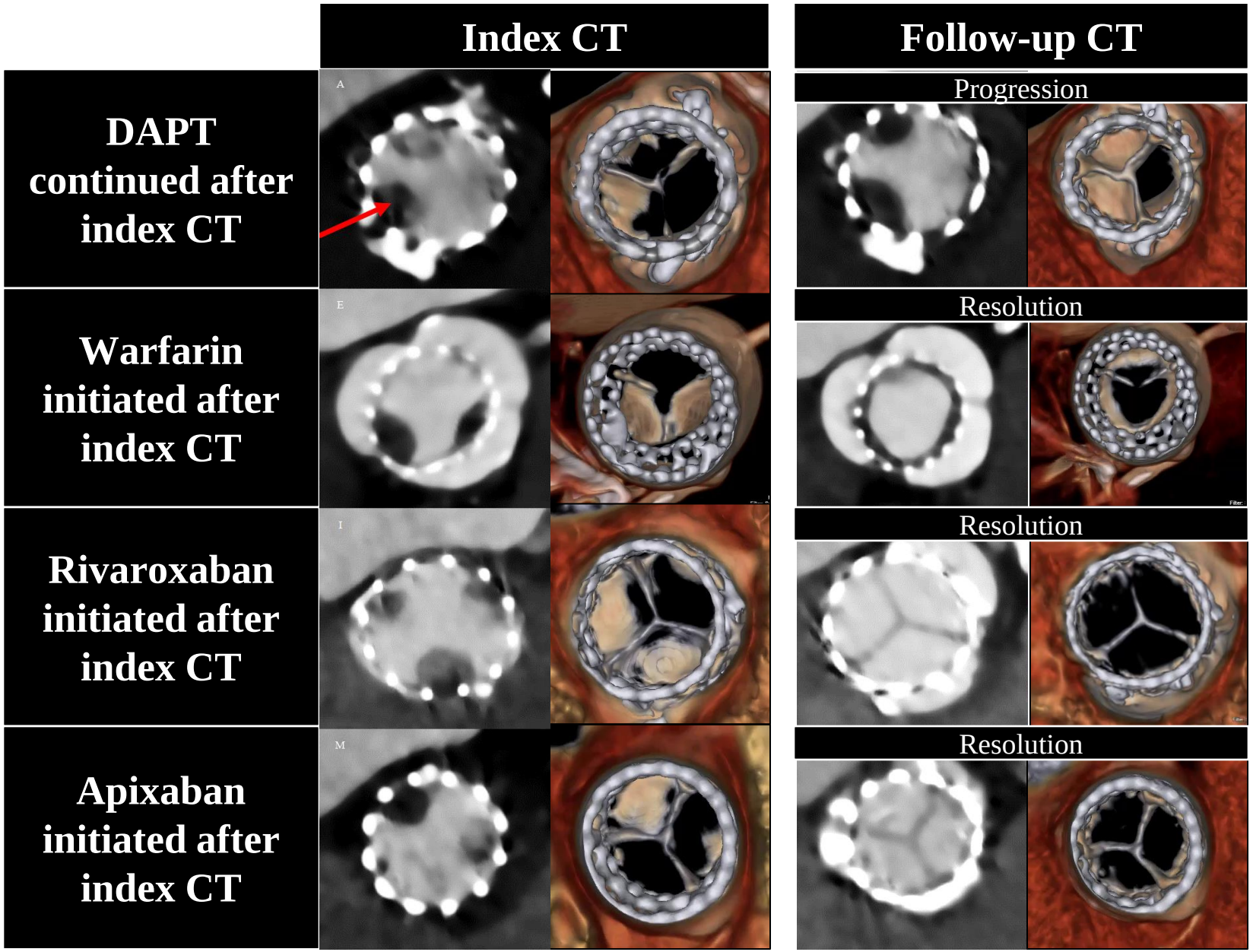
- **Resolution in 36 out of 36 patients** treated with anticoagulation (NOACs, n=12; warfarin, n=24)
- **Persistence/progression in 20 out of 22 patients** not treated with anticoagulation

P<0.0001

Anticoagulation vs. DAPT

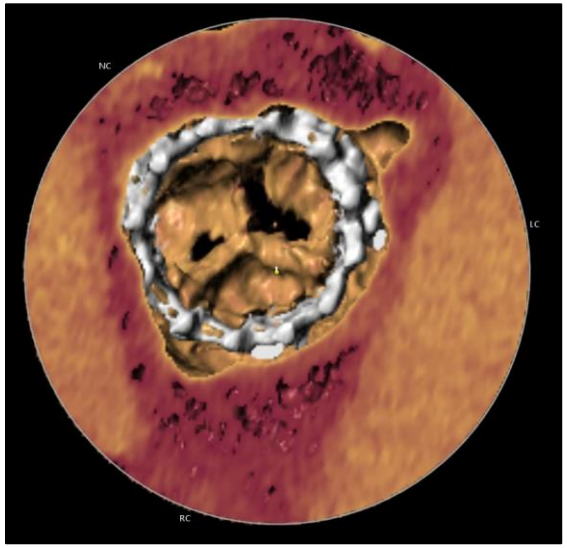


Anticoagulation vs. DAPT

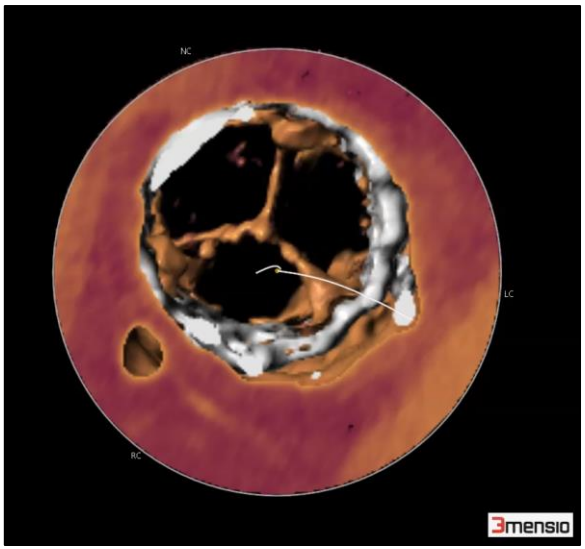


Recurrence of reduced leaflet motion following discontinuation of anticoagulation

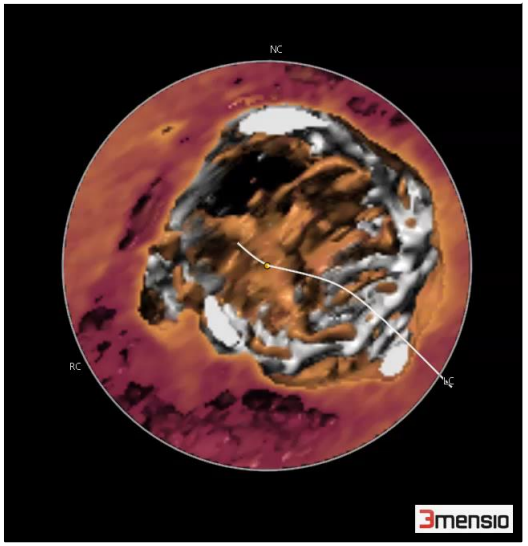
Baseline
Reduced leaflet motion



s/p Xarelto 10mg
Normal leaflet motion

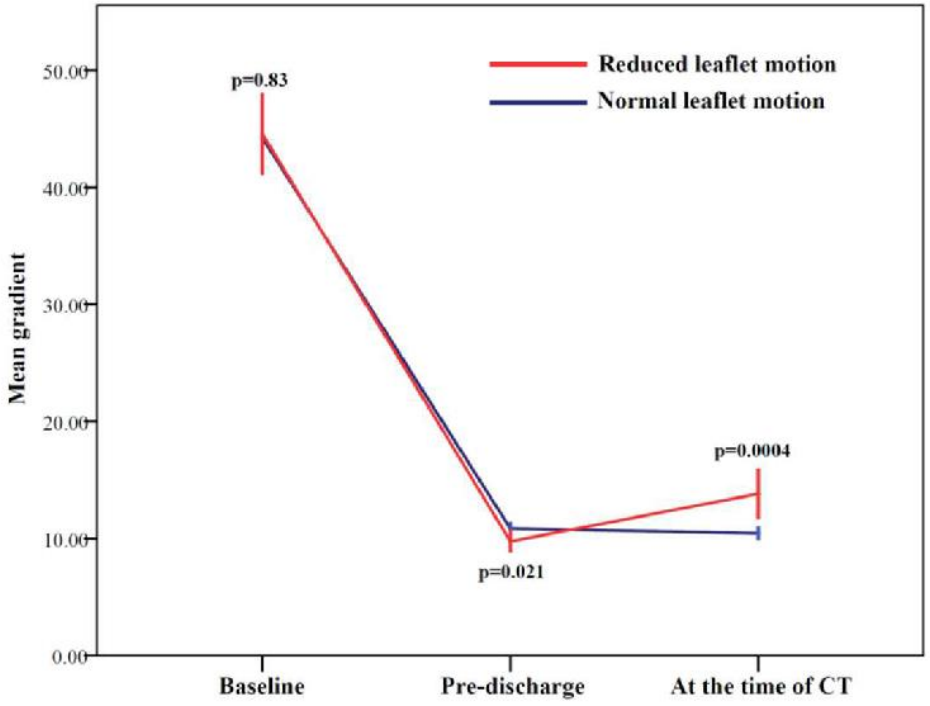


Six months following discontinuation of xarelto
Reduced leaflet motion



Reduced leaflet motion recurred in 4 out of 8 patients in whom anticoagulation was discontinued

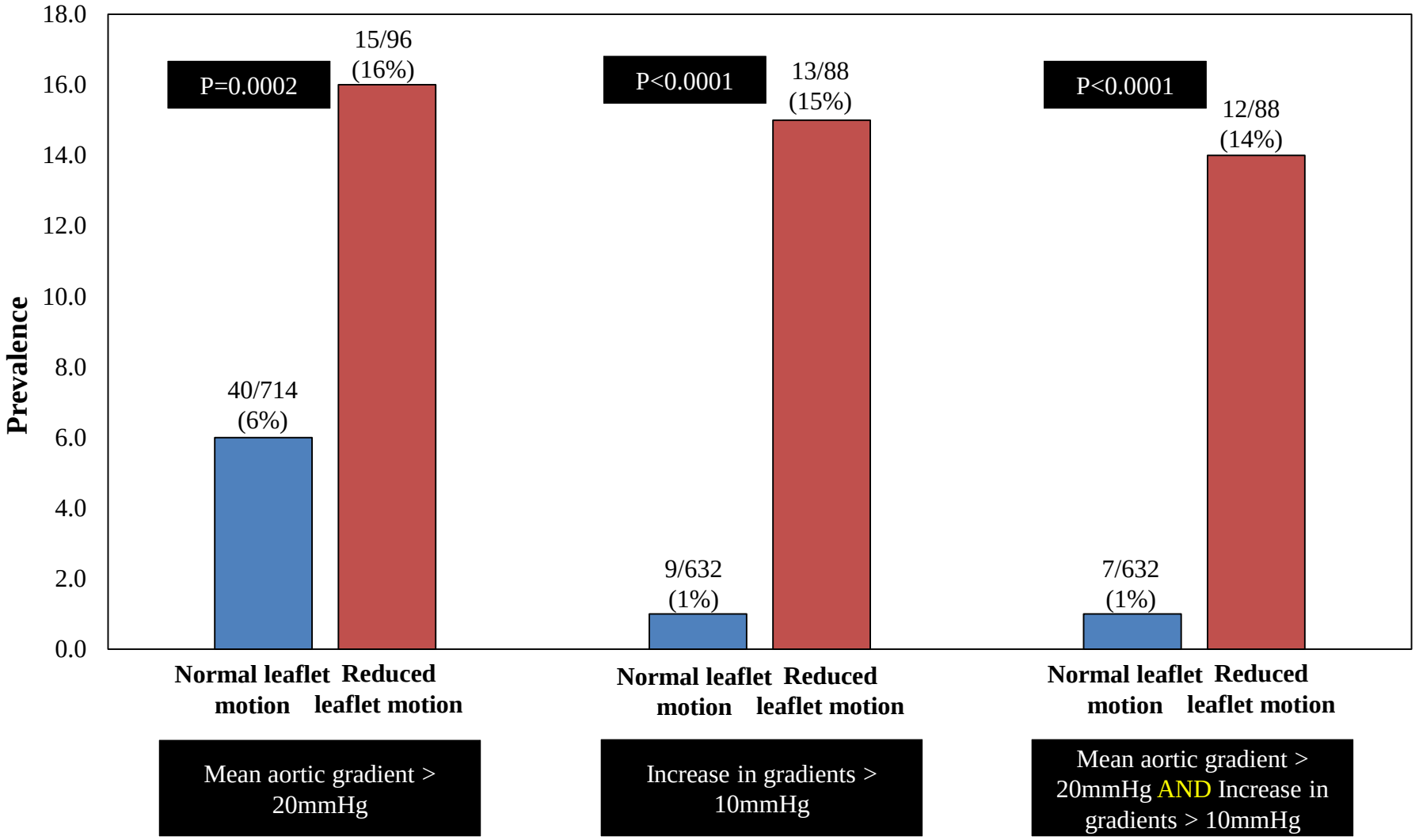
Impact of reduced leaflet motion on valve hemodynamics



Increased mean gradients at the time of CT in patients with reduced leaflet motion

13·8±10·0 mmHg vs. 10·4±6·3 mmHg, p=0.0004

Increased gradients in patients with reduced leaflet motion



Impact of reduced leaflet motion on clinical outcomes

All clinical events post-TAVR/SAVR included

No significant difference in strokes; but increased risk of TIAs and strokes/TIAs

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)			
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Hazard ratio (95% CI)	p-value
All events						
Death	34/784 (4·3%)	2·91	4/106 (3·8%)	2·66	0·96 (0·34-2·72)	0·94
Myocardial infarction	4/784 (0·5%)	0·34	1/106 (0·9%)	0·67	1·91 (0·21-17·08)	0·56
Strokes/TIAs	27/784 (3·4%)	2·36	11/106 (10·4%)	7·85	3·27 (1·62-6·59)	0·001
All strokes*	22/784 (2·8%)	1·92	6/106 (5·7%)	4·12	2·13 (0·86-5·25)	0·10
Ischemic strokes	21/784 (2·7%)	1·83	6/106 (5·7%)	4·12	2·23 (0·90-5·53)	0·08
TIAs	7/784 (0·9%)	0·60	6/106 (5·7%)	4·18	7·02 (2·35-20·91)	0·0005

TIA=Transient ischemic attack

* All strokes include hemorrhagic and ischemic strokes

Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves

Gregor Pache[1]*, Simon Schoechlin[2], Philipp Blanke[3], Stephan Dorfs[2], Nikolaus Jander[2], Chesnal D. Arepalli[3], Michael Gick[2], Heinz-Joachim Buettner[2], Jonathon Leipsic[3], Mathias Langer[1], Franz-Josef Neumann[2], and Philipp Ruile[2]

Prevalence of hypoattenuating lesions
10% (16/156 patients)

EHJ 2015

Transcatheter Aortic Heart Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications

Nicolaj C. Hansson, MD, Erik L. Grove, MD, PhD, Henning R. Andersen, MD, DMSc, Jonathon Leipsic, MD, Ole N. Mathiassen, MD, PhD, Jesper M. Jensen, MD, PhD, Kaare T. Jensen, MD, PhD, Philipp Blanke, MD, Tina Leetmaa, MD, Mariann Tang, MD, Lars R. Krusell, MD, Kaj E. Klaaborg, MD, Evald H. Christiansen, MD, PhD, Kim Terp, MD, Christian J. Terkelsen, MD, DMSc, Steen H. Poulsen, MD, DMSc, John Webb, MD, Hans Erik Bøtker, MD, DMSc, Bjarne L. Nørgaard, MD, PhD

JACC

- 405 patients with Sapien-XT or Sapien 3 valve undergoing MDCT
- Prospective gated CT scan using 2nd generation CT scanner
- Echocardiograms performed 1-3 months and 12 months post-TAVR

- **THV thrombosis noted in 28/405 (7%) patients**
- **Subclinical leaflet thrombosis 23/405 (5.7%)**
- **Clinical leaflet thrombosis 5/28 (1.2%)**

Transcatheter Aortic Heart Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications

Nicolaj C. Hansson, MD, Erik L. Grove, MD, PhD, Henning R. Andersen, MD, DMSc, Jonathon Leipsic, MD, Ole N. Mathiassen, MD, PhD, Jesper M. Jensen, MD, PhD, Kaare T. Jensen, MD, PhD, Philipp Blanke, MD, Tina Leetmaa, MD, Mariann Tang, MD, Lars R. Krusell, MD, Kaj E. Klaaborg, MD, Evald H. Christiansen, MD, PhD, Kim Terp, MD, Christian J. Terkelsen, MD, DMSc, Steen H. Poulsen, MD, DMSc, John Webb, MD, Hans Erik Bøtker, MD, DMSc, Bjarne L. Nørgaard, MD, PhD

JACC

- 405 patients with Sapien-XT or Sapien 3 valve undergoing MDCT
- Echocardiograms performed 1-3 months and 12 months post-TAVR
- **THV thrombosis noted in 28/405 (7%) of patients**

Risk of THV thrombosis was lower in patients on warfarin, compared to those not on warfarin

1.8% vs. 10.7%

RR 6.09, 95% CI 1.86-19.84

Transcatheter Aortic Heart Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications

Nicolaj C. Hansson, MD, Erik L. Grove, MD, PhD, Henning R. Andersen, MD, DMSc, Jonathon Leipsic, MD, Ole N. Mathiassen, MD, PhD, Jesper M. Jensen, MD, PhD, Kaare T. Jensen, MD, PhD, Philipp Blanke, MD, Tina Leetmaa, MD, Mariann Tang, MD, Lars R. Krusell, MD, Kaj E. Klaaborg, MD, Evald H. Christiansen, MD, PhD, Kim Terp, MD, Christian J. Terkelsen, MD, DMSc, Steen H. Poulsen, MD, DMSc, John Webb, MD, Hans Erik Bøtker, MD, DMSc, Bjarne L. Nørgaard, MD, PhD

JACC

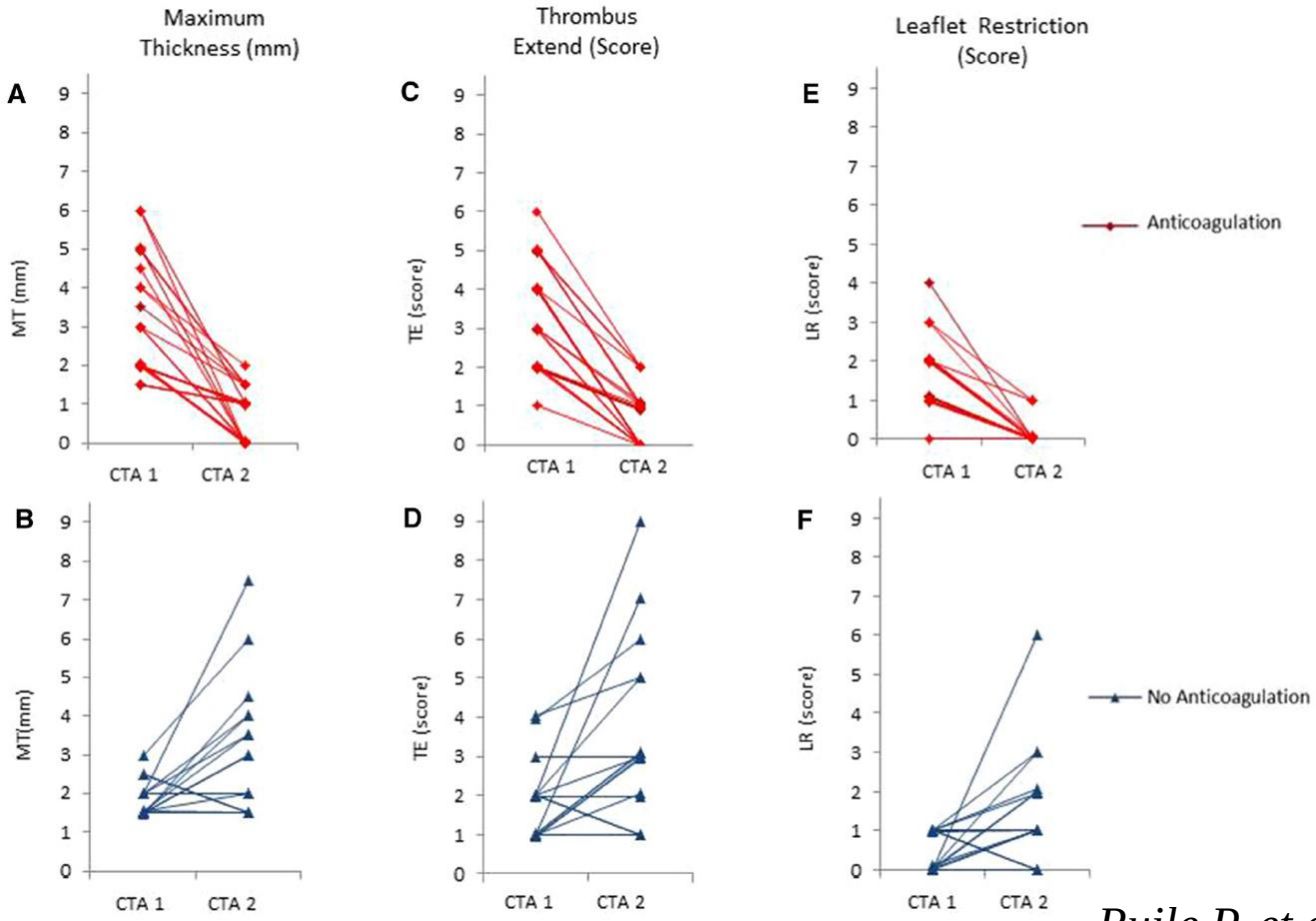
- 405 patients with Sapien-XT or Sapien 3 valve undergoing MDCT
- Echocardiograms performed 1-3 months and 12 months post-TAVR
- **THV thrombosis noted in 28/405 (7%) of patients**

Treatment with warfarin resulted in resolution of THV thrombosis and normalized THV function in 85% of patients

Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation

51 patients with leaflet thickening (29 patients treated with anticoagulation and 22 patients treated with DAPT)

Repeat CT obtained in 22 patients on AC and 16 patients on DAPT



Leaflet thickening regressed in all 22 patients undergoing repeat CT

Leaflet thickening progressed in 11 of 16 patients

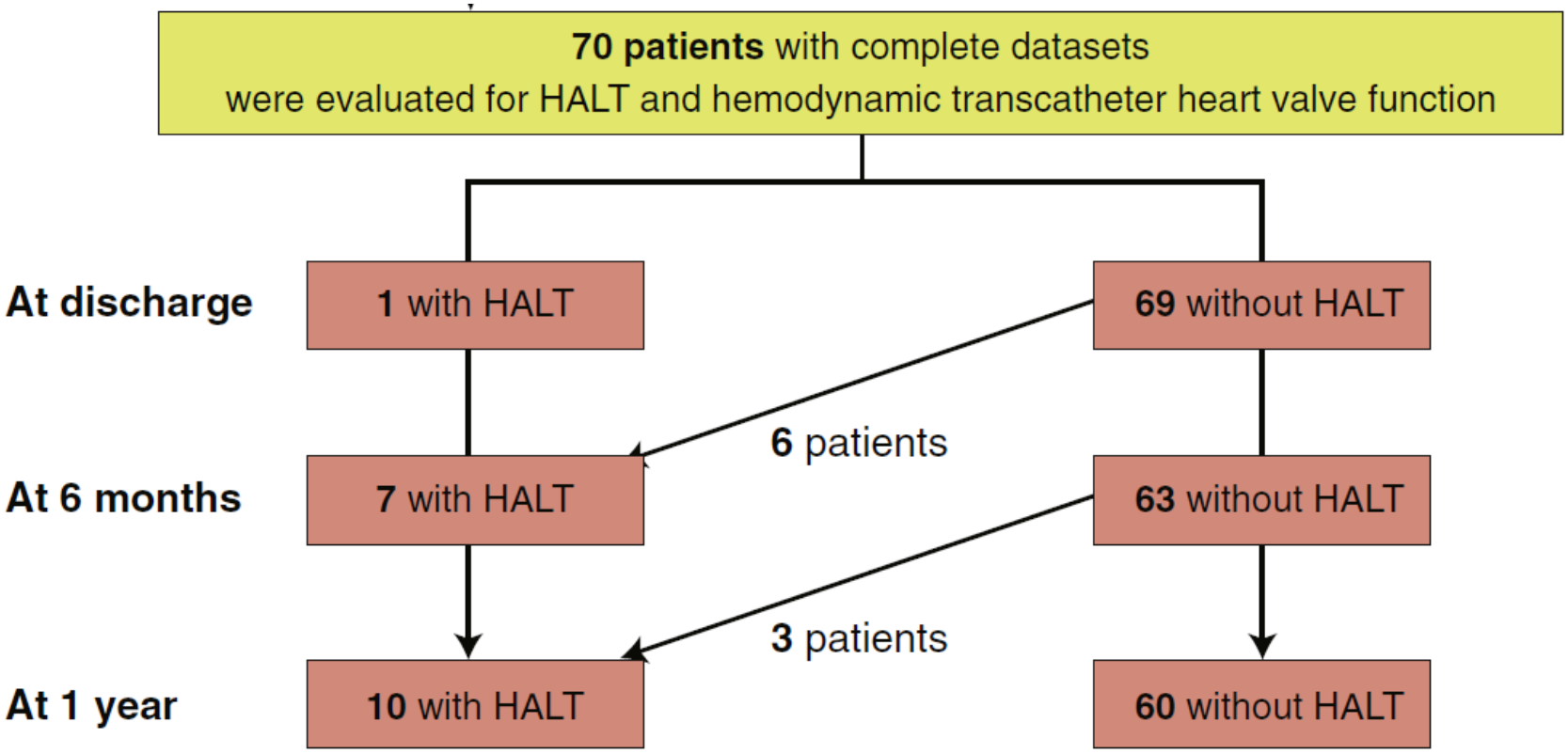
Ruile P. et al. Clin Res Cardiol 2017

Incidence, Predictors, and Mid-Term Outcomes of Possible Leaflet Thrombosis After TAVR

- 70 patients with Sapien-XT valve
- CTs performed at discharge, 6 months and 1 year post-TAVR

Prevalence of hypoattenuation associated leaflet thickening

1.4% at discharge, 10% at 6 months, 14.3% at 1 year



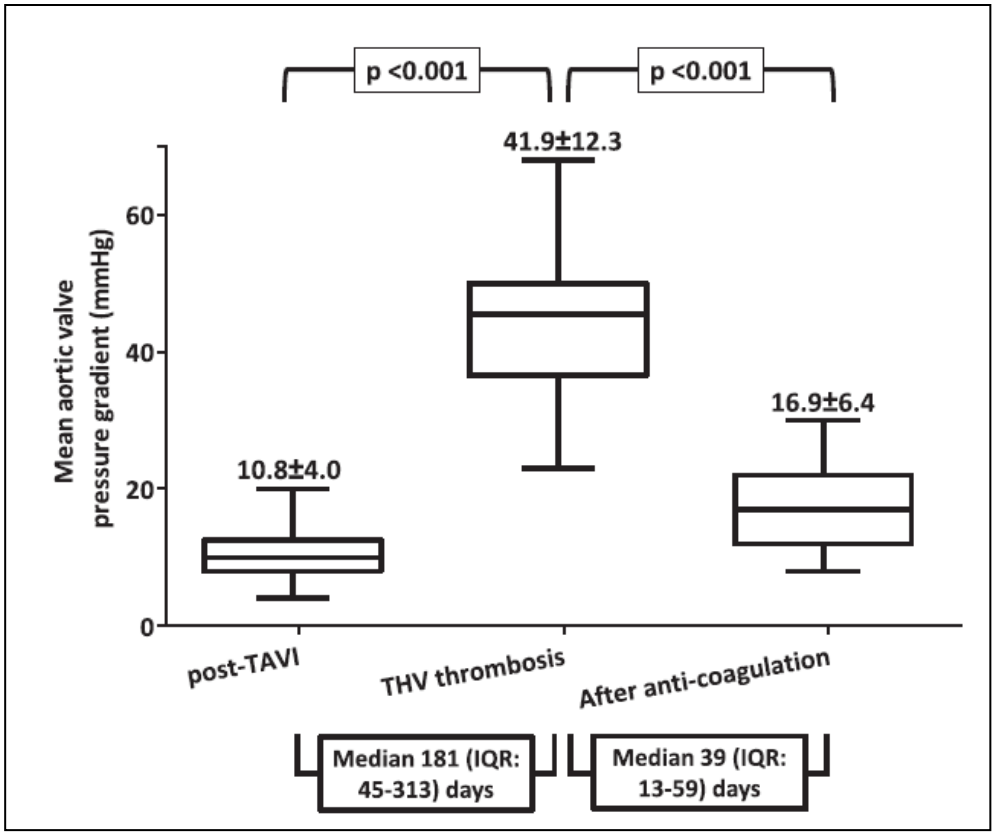
Yanagisawa. R. et al. JACC: Cardiovascular Imaging 2017

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

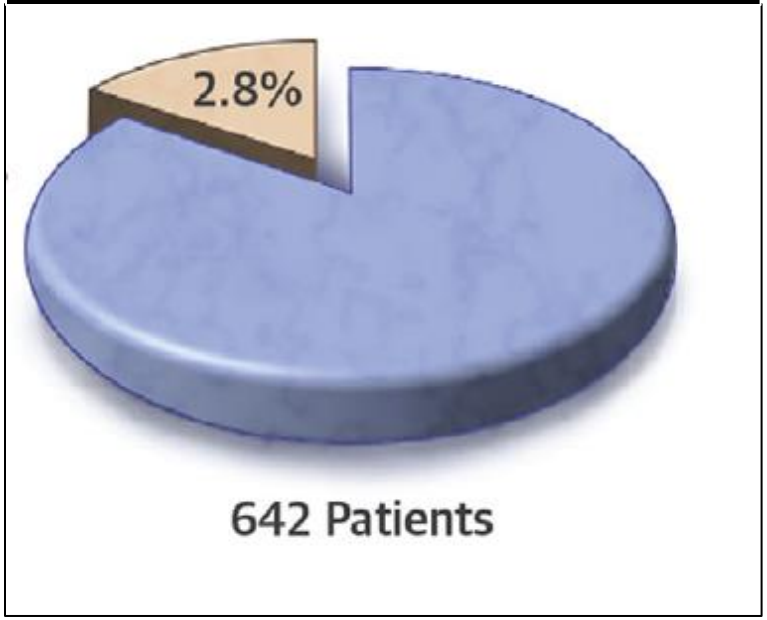
Clinical Bioprosthetic Heart Valve Thrombosis After Transcatheter Aortic Valve Replacement

Incidence, Characteristics, and Treatment Outcomes

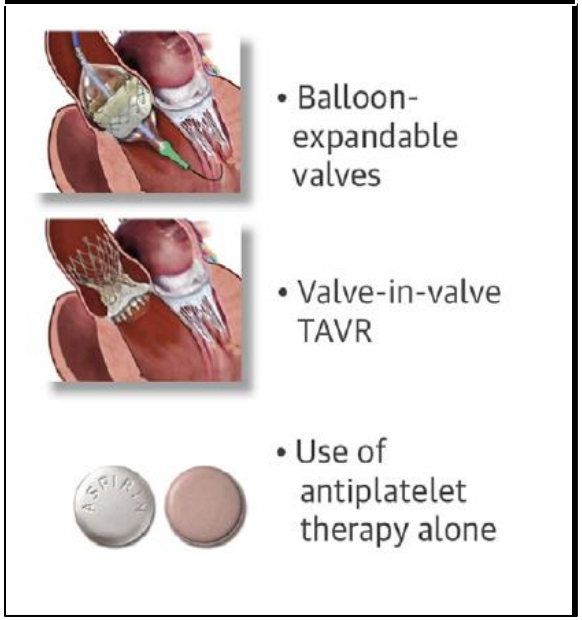
Single center registry of 642 patients undergoing TAVR

- 305 CoreValve, 281 Sapien and 56 Lotus
- Oral anticoagulation in 261 patients, DAPT in 377 patients
- No case of valve thrombosis in patients on anticoagulation

Incidence of valve thrombosis



Predictors of valve thrombosis

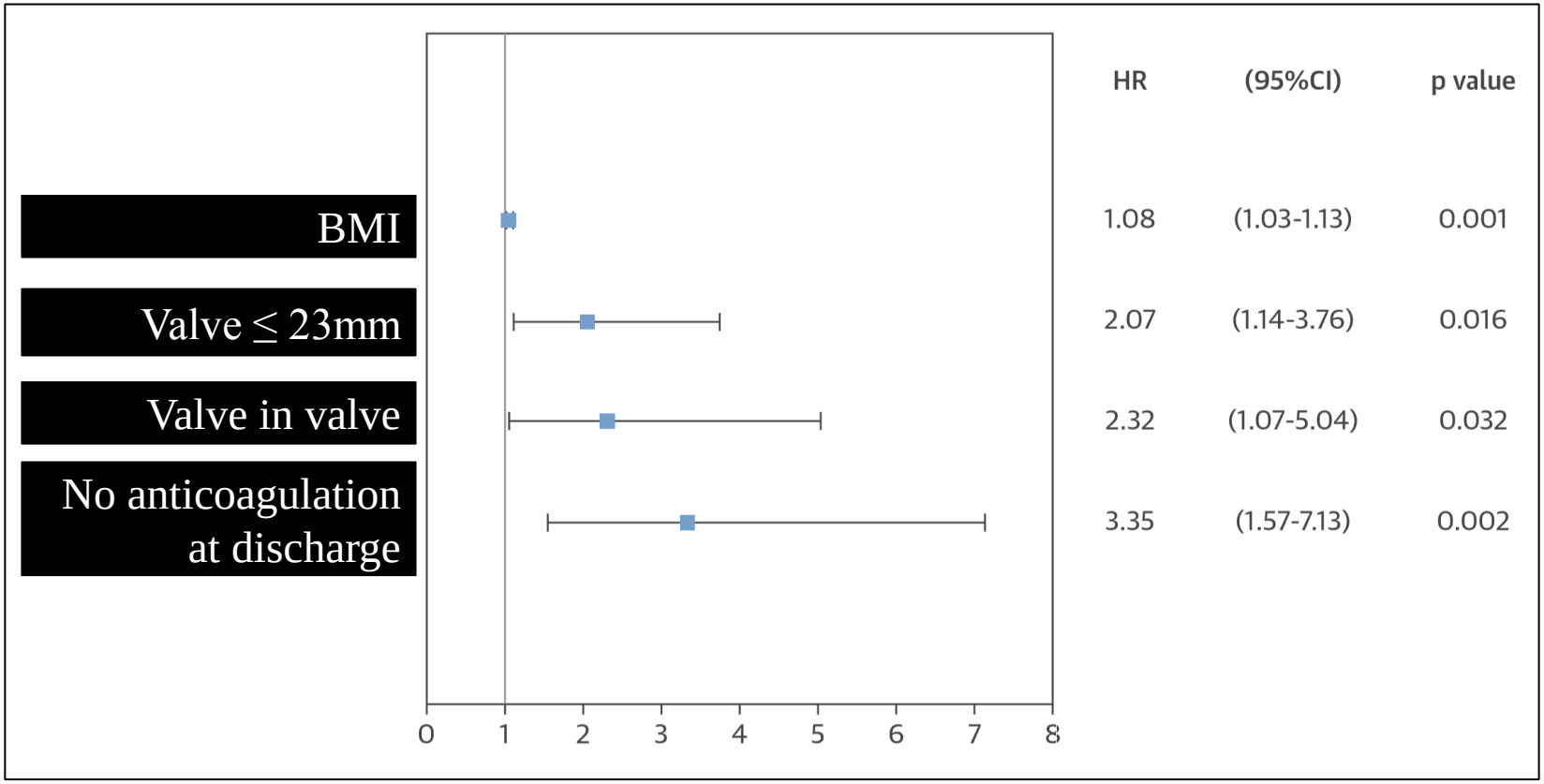


Jose et al. JACC: Cardiovascular Interventions 2017

Predictors of valve hemodynamic degeneration after TAVR

1521 patients undergoing TAVR

Valve hemodynamic degeneration = 10mmHg rise in transvalvular gradients

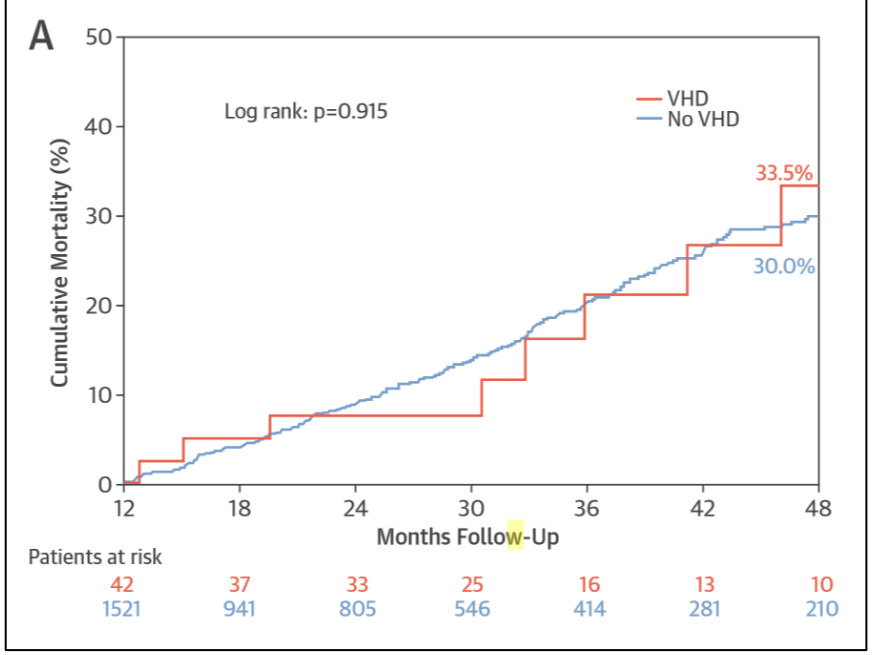


Del Trigo M. et al. JACC 2016

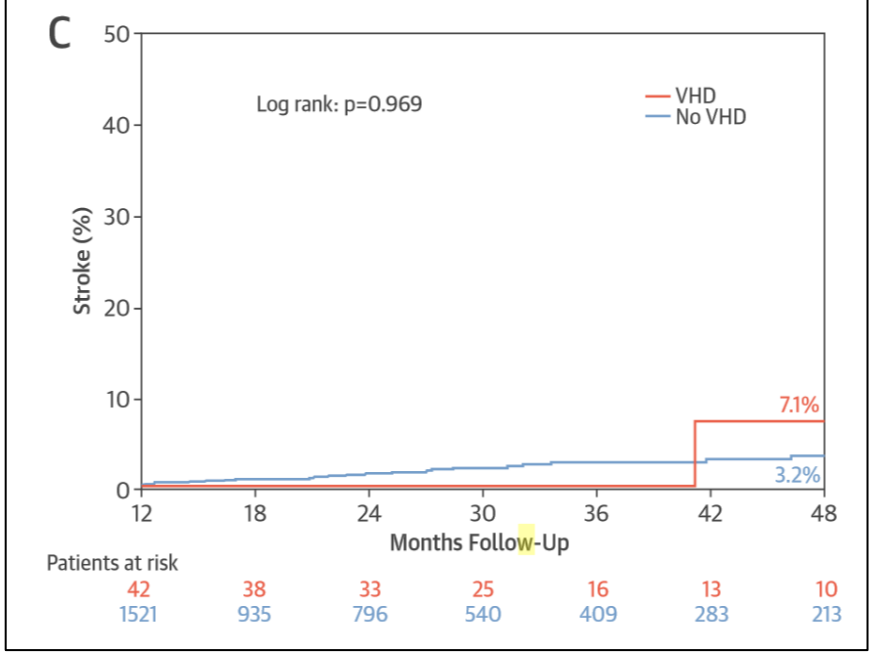
Valve hemodynamic degeneration and clinical outcomes

No significant increase in mortality or stroke

Mortality



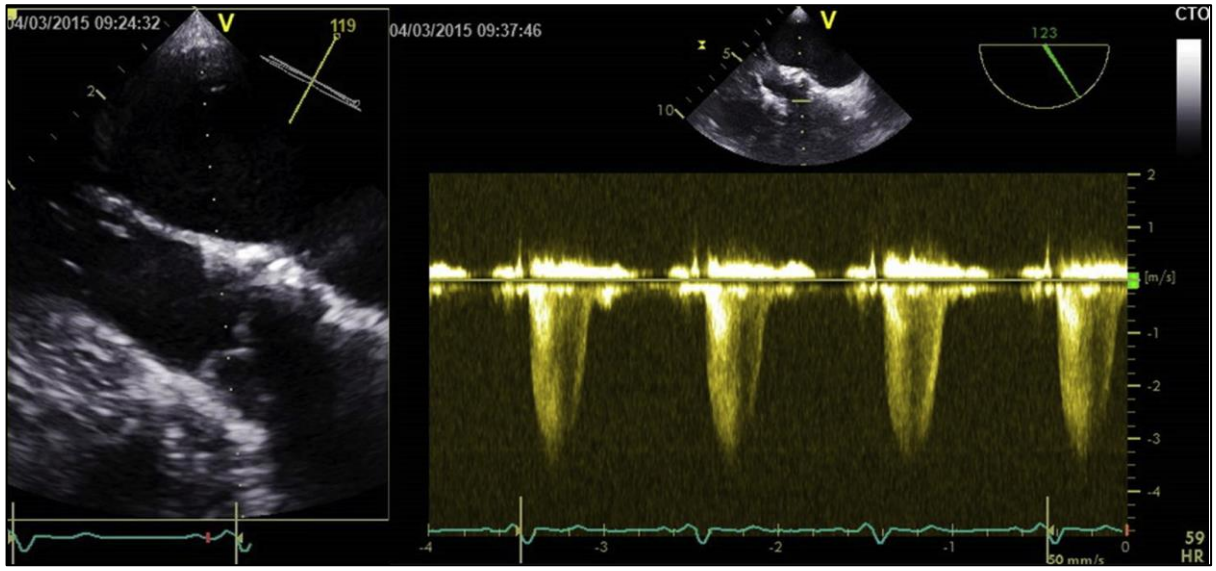
Stroke



Del Trigo M. et al. JACC 2016

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

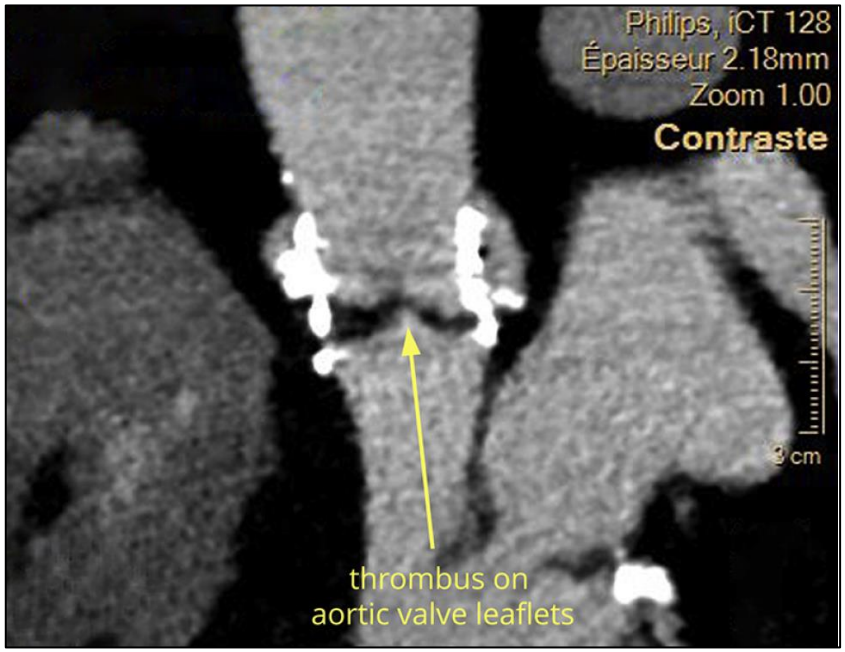
Valve thrombosis 4 years post-TAVR



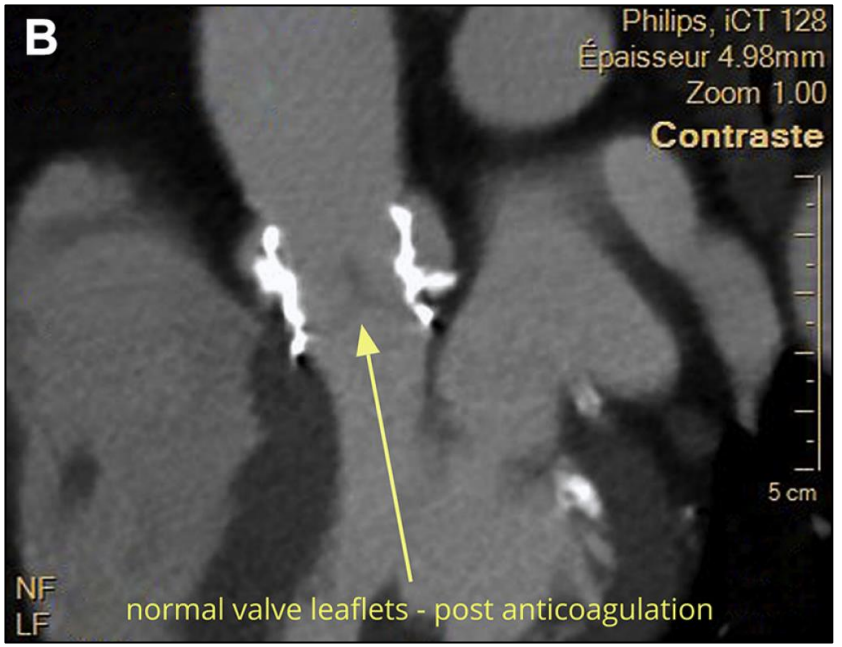
Very Early Thrombosis of Sapien 3 Valve

Sapien3 valve thrombosis 3 days post-TAVR

Valve thrombosis



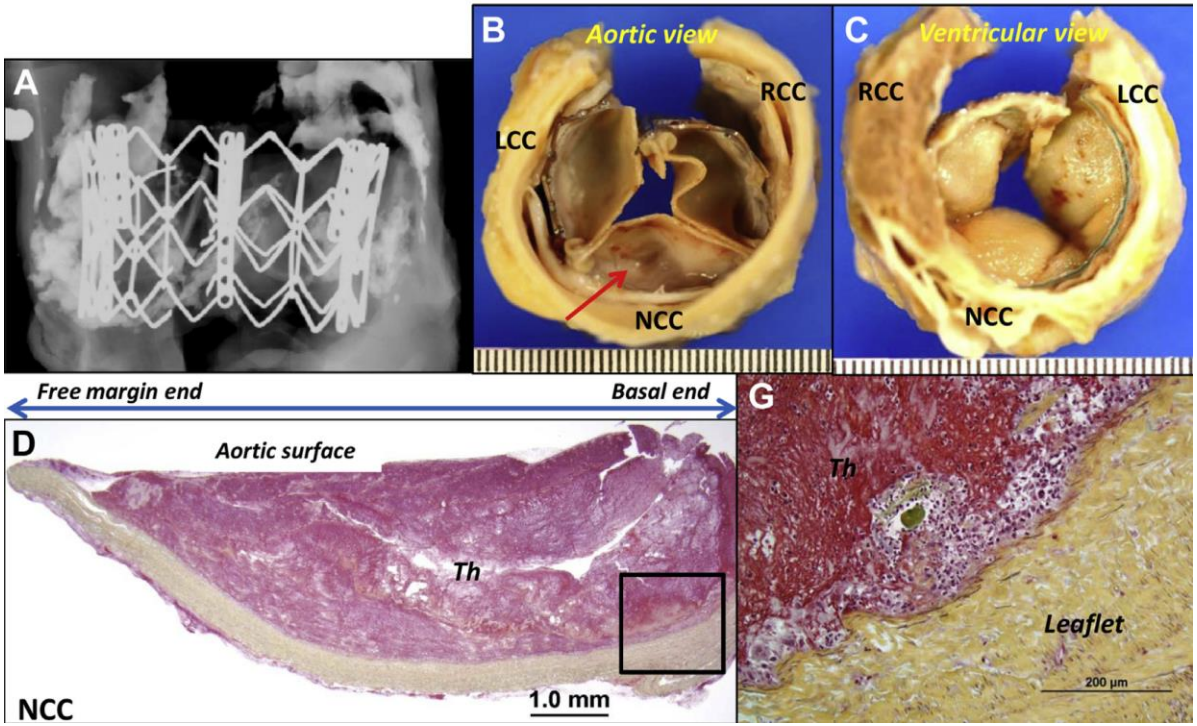
Resolution with anticoagulation



Neylon A. et al. JACC: Cardiovascular Interventions 2016

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

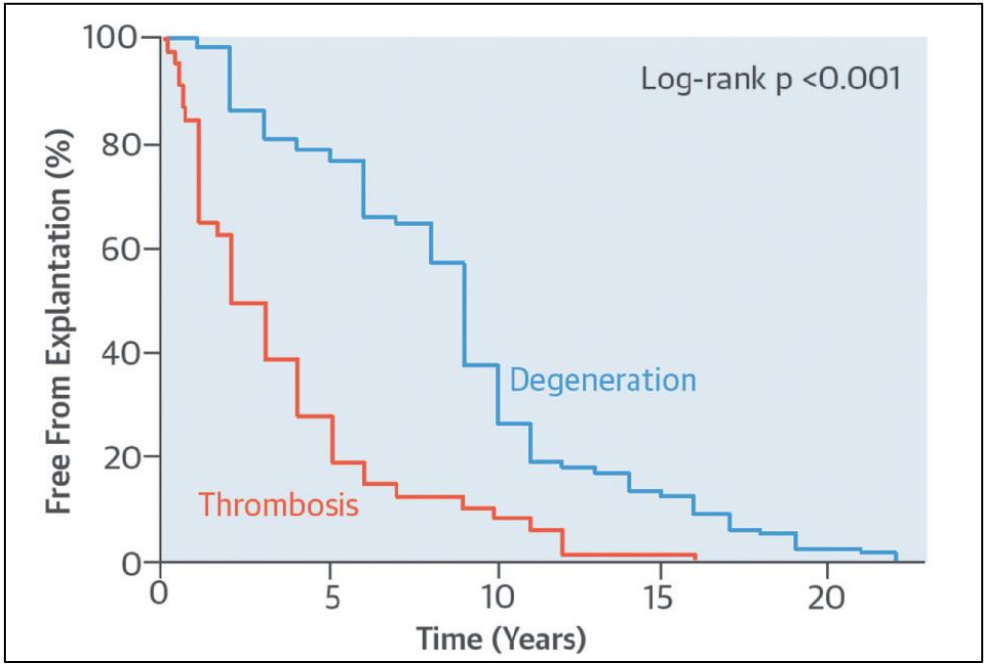
Bioprosthetic Valve Thrombosis Versus Structural Failure

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)



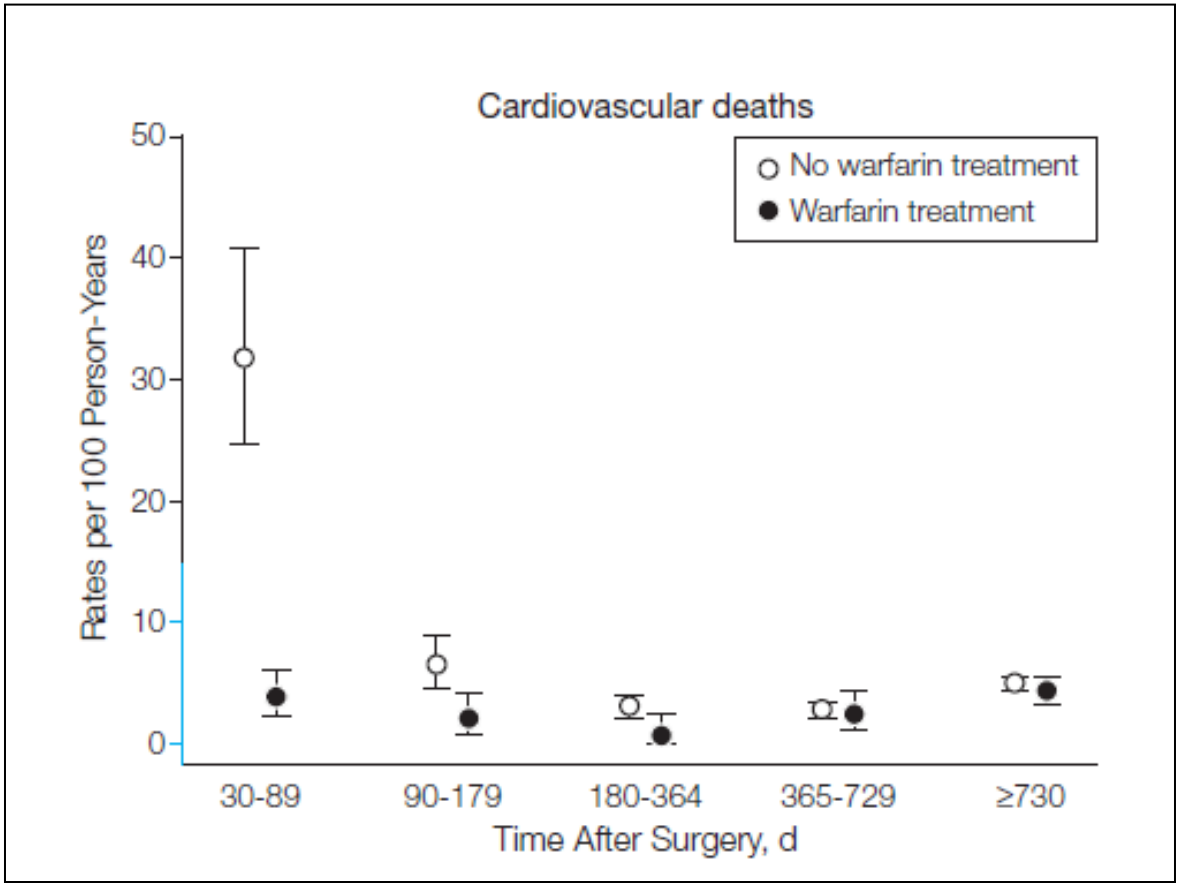
BPVT referred for surgical intervention occurs significantly earlier than BPV degeneration

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

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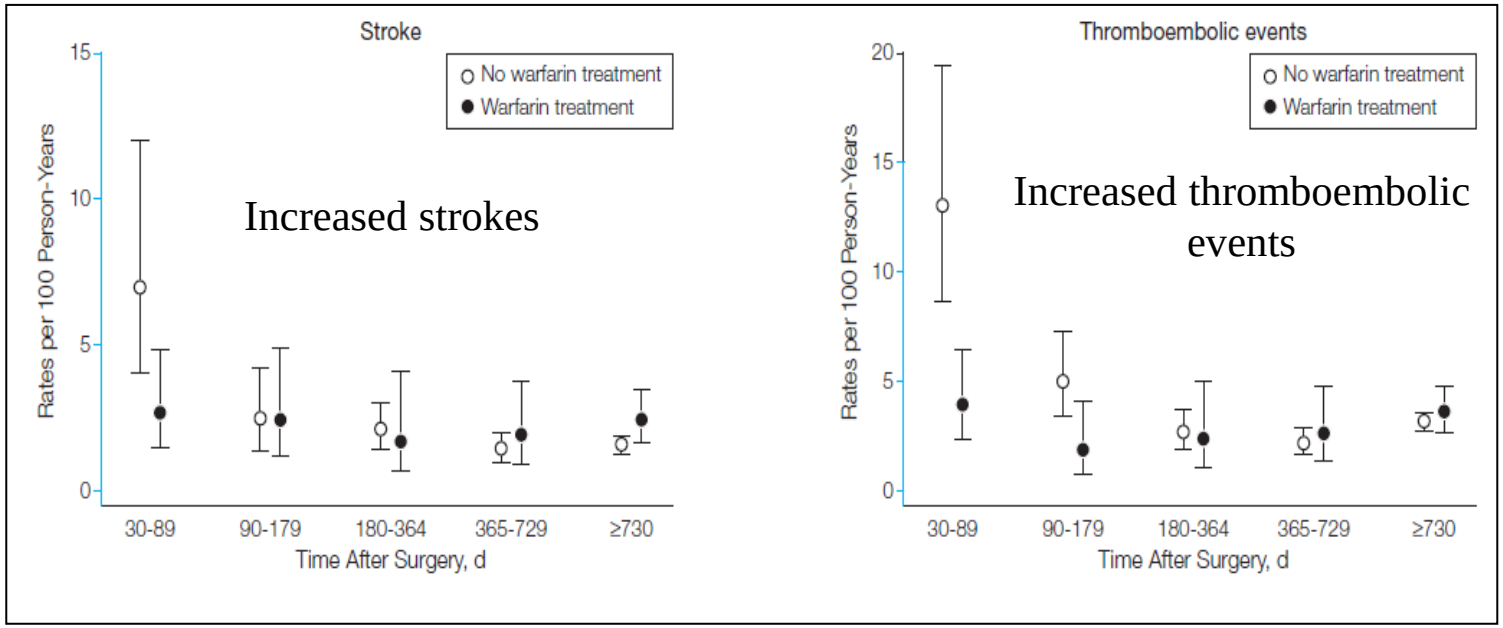


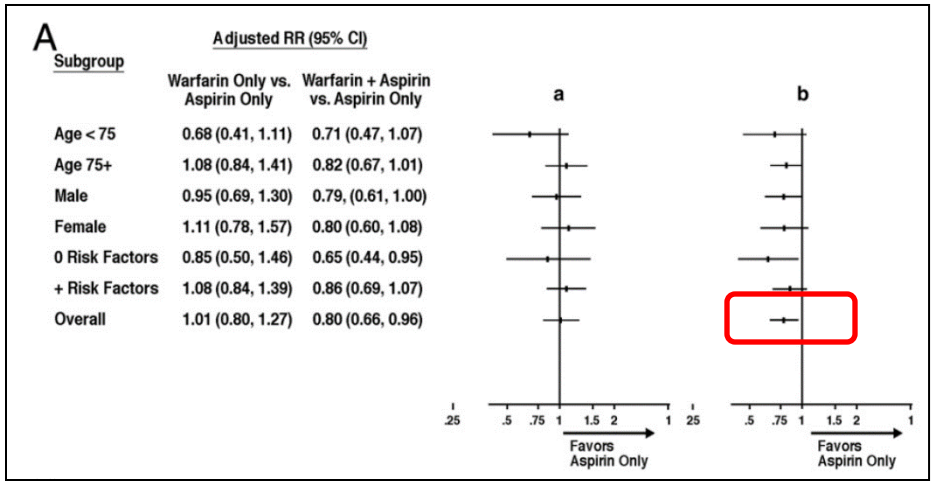
Merie C. et al. JAMA 2012

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

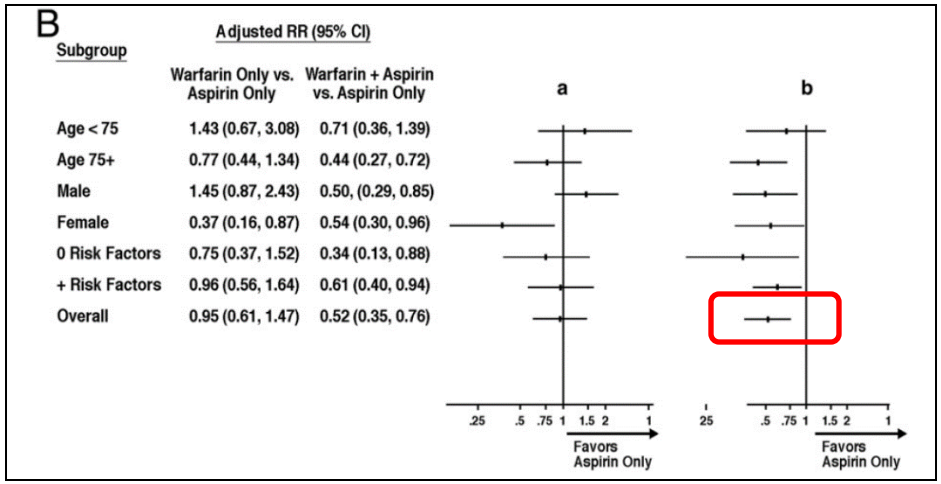
25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

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

Conclusions

- In a heterogeneous cohort of aortic bioprosthetic valves, the reduced leaflet motion occurred 12 % of the time on 4D CT.

- Patients undergoing SAVR, compared with TAVR, had lower incidence of reduced leaflet motion (3.6% vs. 12%; $p<0.04$). However, patients undergoing SAVR were different than TAVR reflecting contemporary practice with lower age and fewer comorbidities.

- Anticoagulation with both warfarin and NOACs ***and not DAPT which is the standard of care*** were effective in prevention and treatment of reduced leaflet motion.

- Majority of cases of subclinical leaflet thrombosis diagnosed by 4D CT are hemodynamically silent and hence missed by TTE

Conclusions, *contd.*

- Patients with subclinical leaflet thrombosis had a small but significant increase in transvalvular gradients compared to patients without subclinical leaflet thrombosis

- A greater proportion of patients with subclinical leaflet thrombosis (15% vs. 1%) had hemodynamically significant increase in gradients (aortic valve gradients>20mmHg and increase in aortic valve gradients>10mmHg).

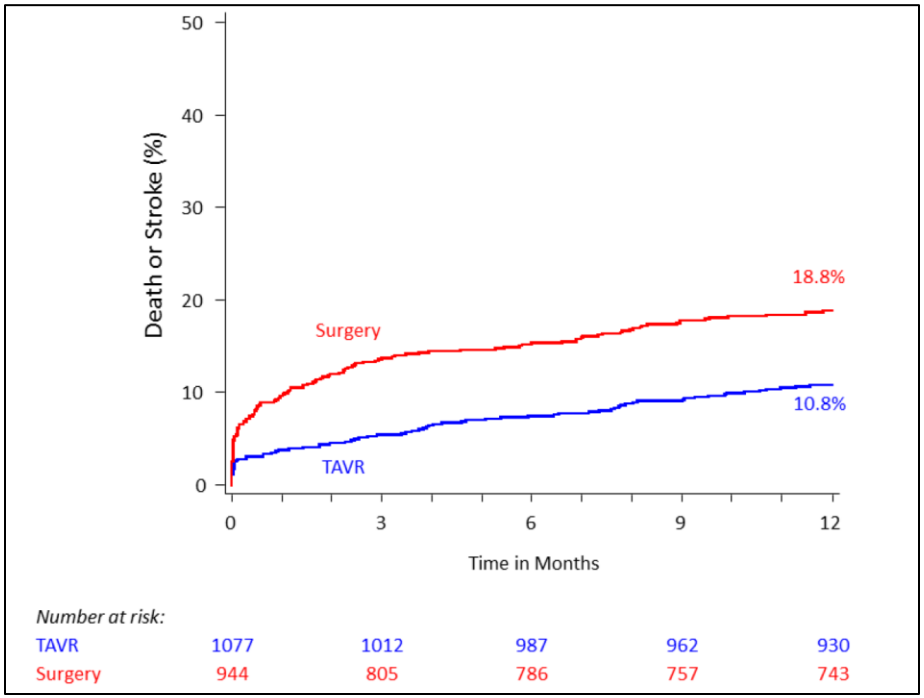
- While the death, MI and stroke rates were not significantly different between the 2 groups, subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes/TIAs.

Clinical implications

- The imaging findings in our analysis question the current standard of care (dual antiplatelet therapy post-TAVR); thus DAPT can be considered dispensable in the appropriate clinical setting. Our findings raise the issue if anticoagulation is more appropriate in certain patients.
- Our data call for clinical trials of routine CT imaging and anticoagulation as TAVR moves into lower risk patients and for the first time provide evidence on the efficacy of NOACs on bioprosthetic valve thrombosis
- In the appropriate clinical setting such as TIAs, stroke, new onset heart failure; or even small increase in gradients post-procedure should lead to vigilance and CT imaging.
- The reduced leaflet motion observed on CT secondary to leaflet thrombosis and increase in gradients may provide insights into a preventable mechanism of structural valve deteriorartion in some patients

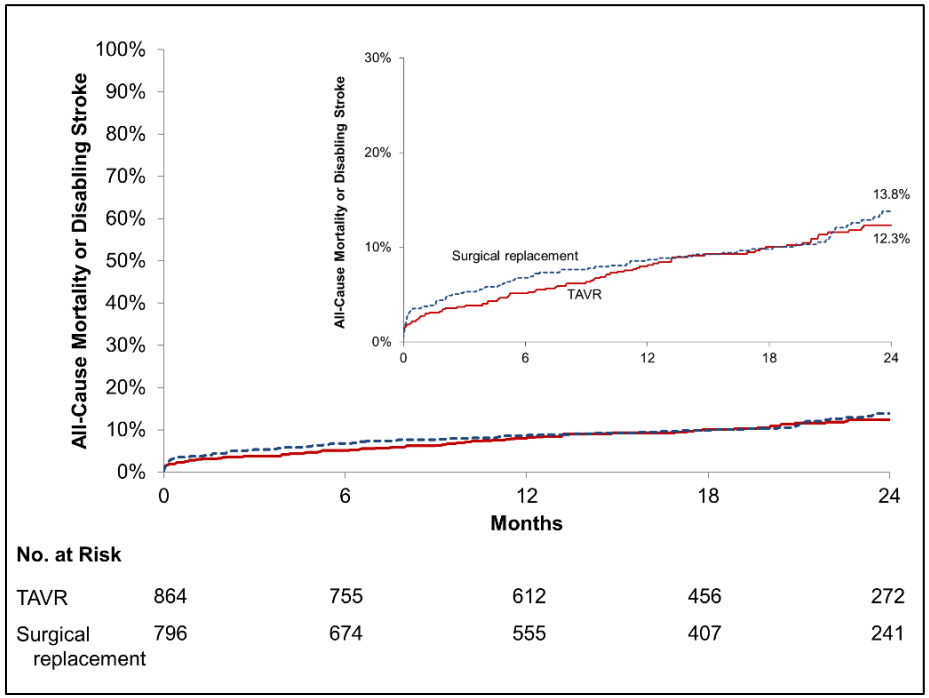
The choice of therapy (SAVR or TAVR) and device is best guided by clinical outcomes data in clinical trials rather than a single imaging finding such as subclinical leaflet thrombosis

Lower 1-year death/stroke rates with Sapien 3, compared with surgery



Thourani V. et al. Lancet 2015

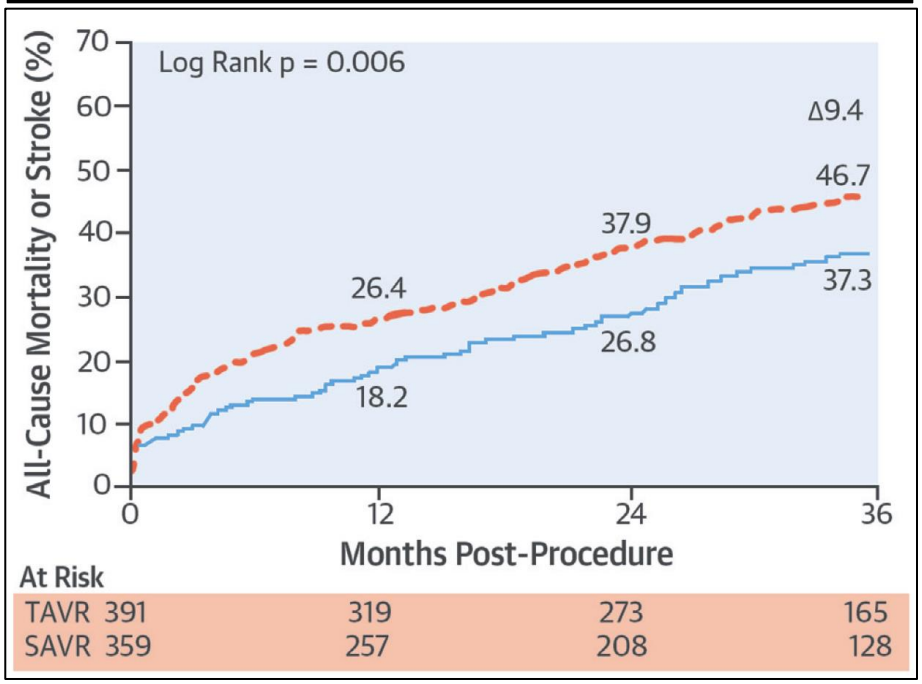
Similar 2-year death/stroke rates with CoreValve, compared with surgery



Reardon M. et al. NEJM 2017

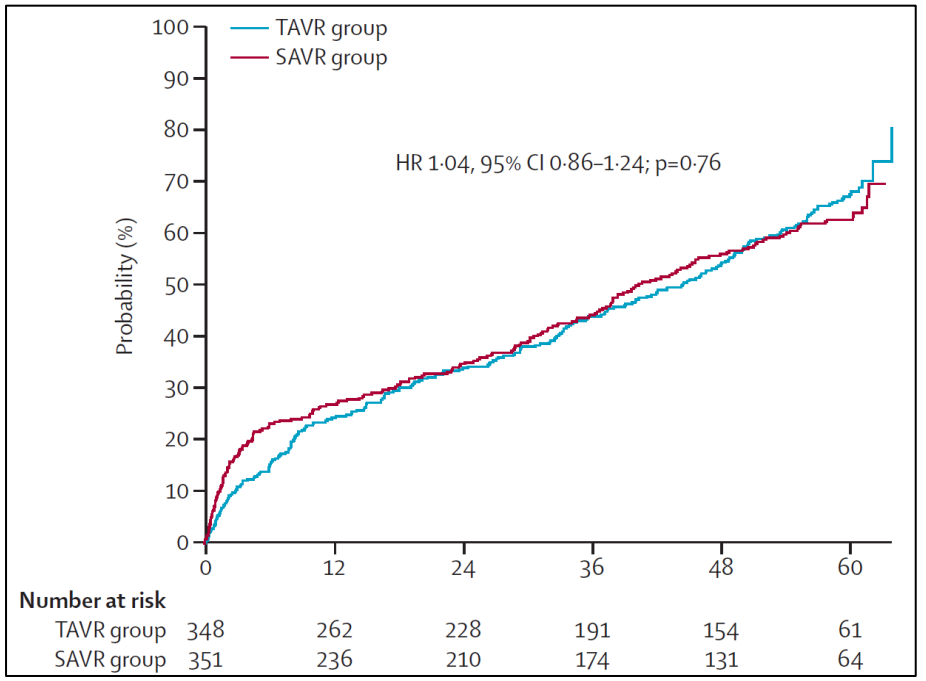
Despite excellent clinical outcomes of newer generation valves our study findings can help further optimize adjunctive pharmacotherapy which may result in further improvements.

Lower 3-year death/stroke rates with CoreValve, compared with surgery



Deeb M. et al. JACC 2016

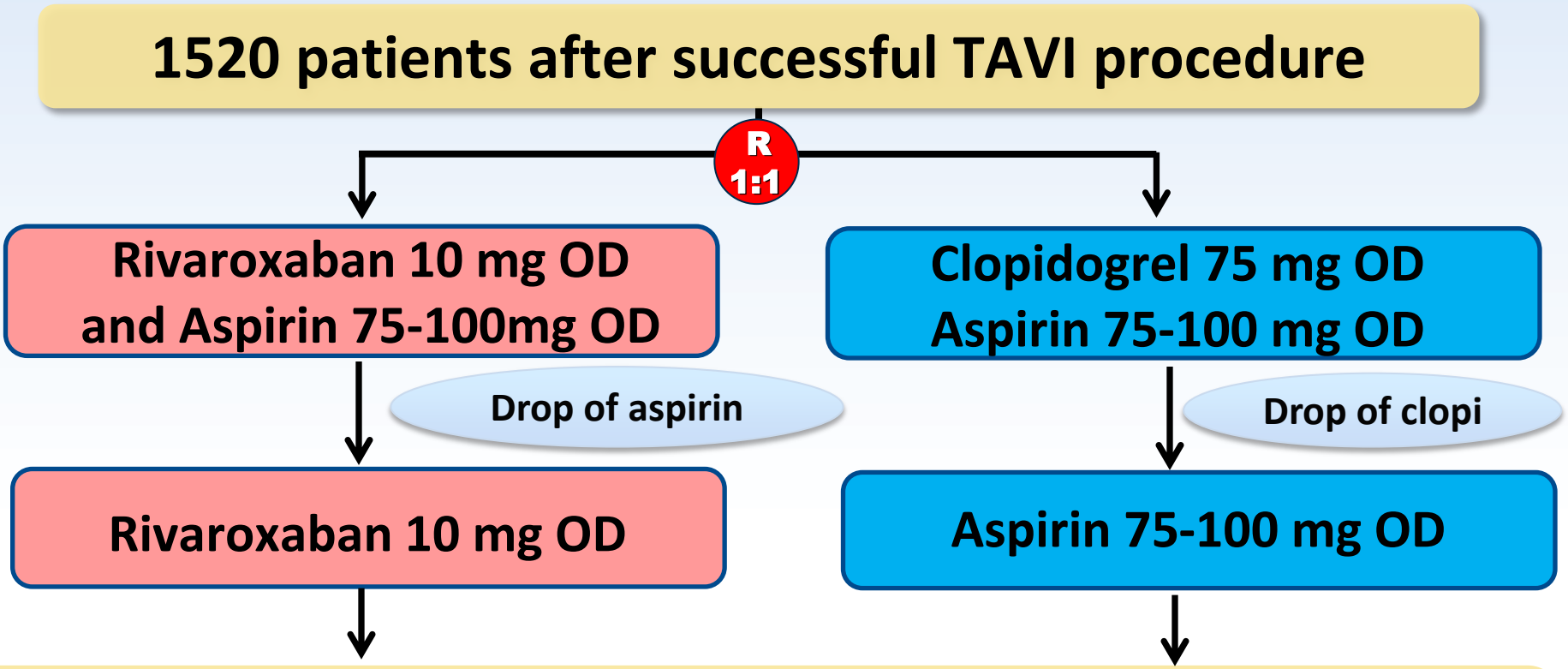
Similar 5-year death rates with Edwards-SAPIEN, compared with surgery



Mack M. et al. Lancet 2015

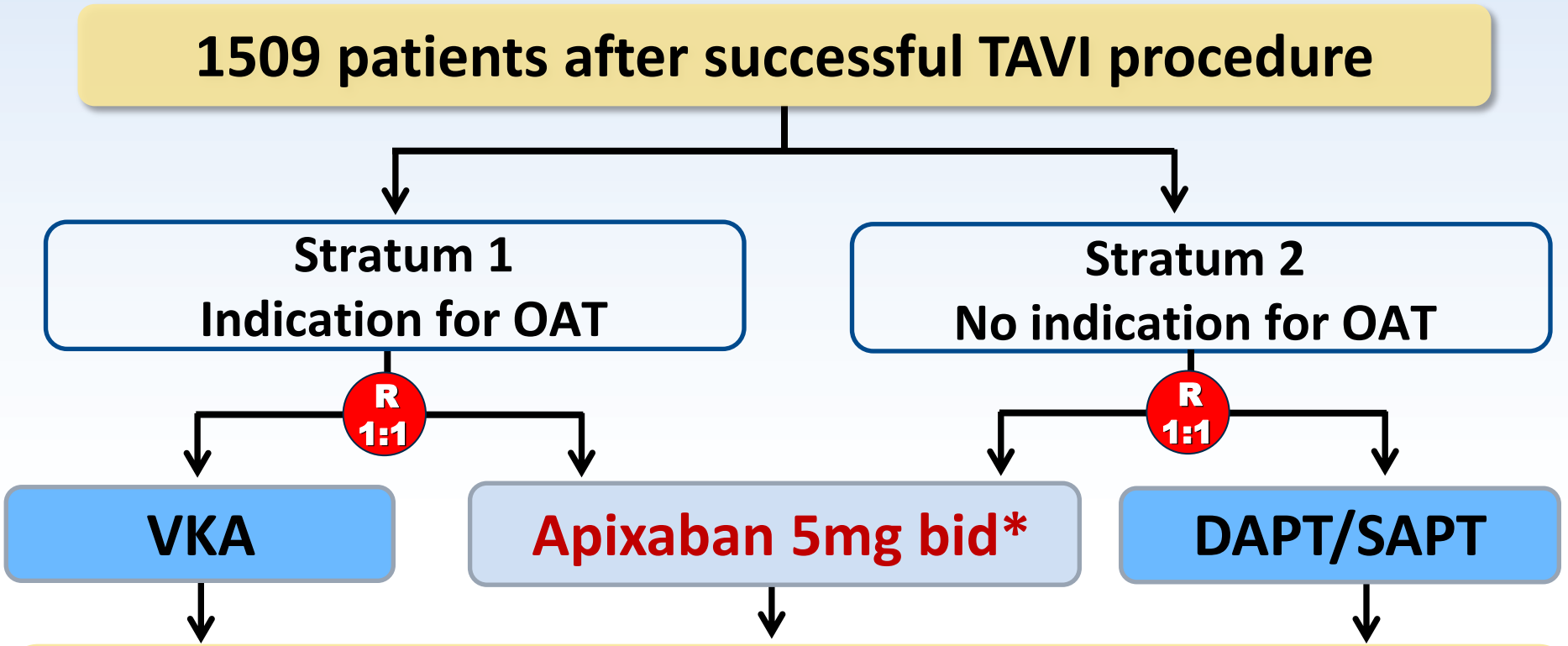
GALILEO

(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)



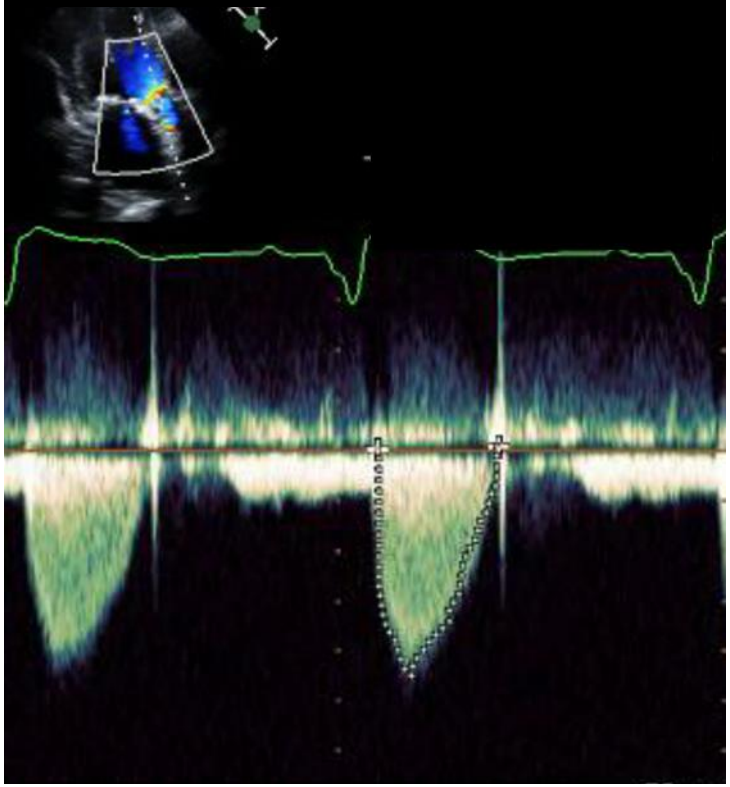
Primary end-point is a composite of **death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism,major bleedings** ***over one year follow-up*****.**

*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).

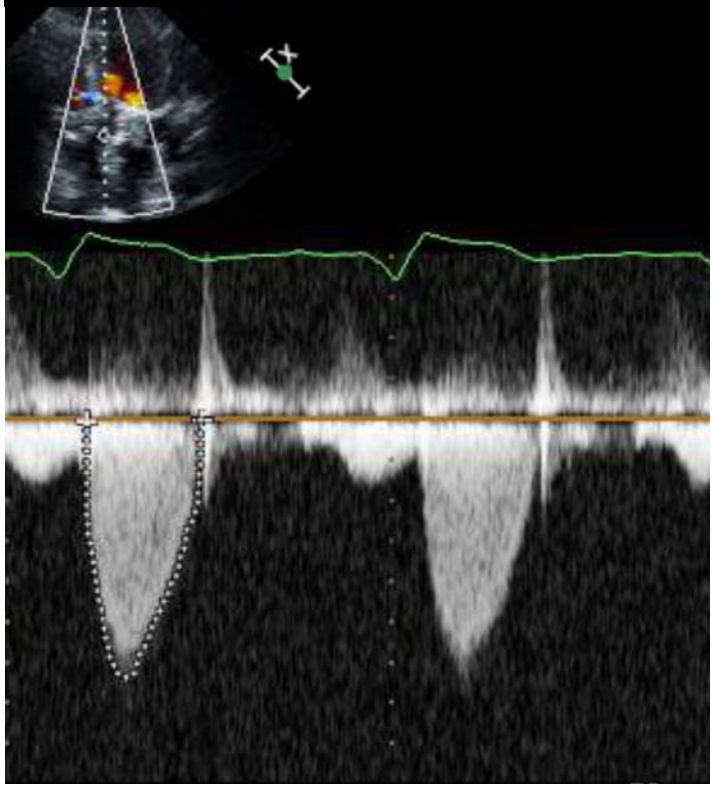
67 y/o male physician s/p TAVR with 29mm Sapien3 valve

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

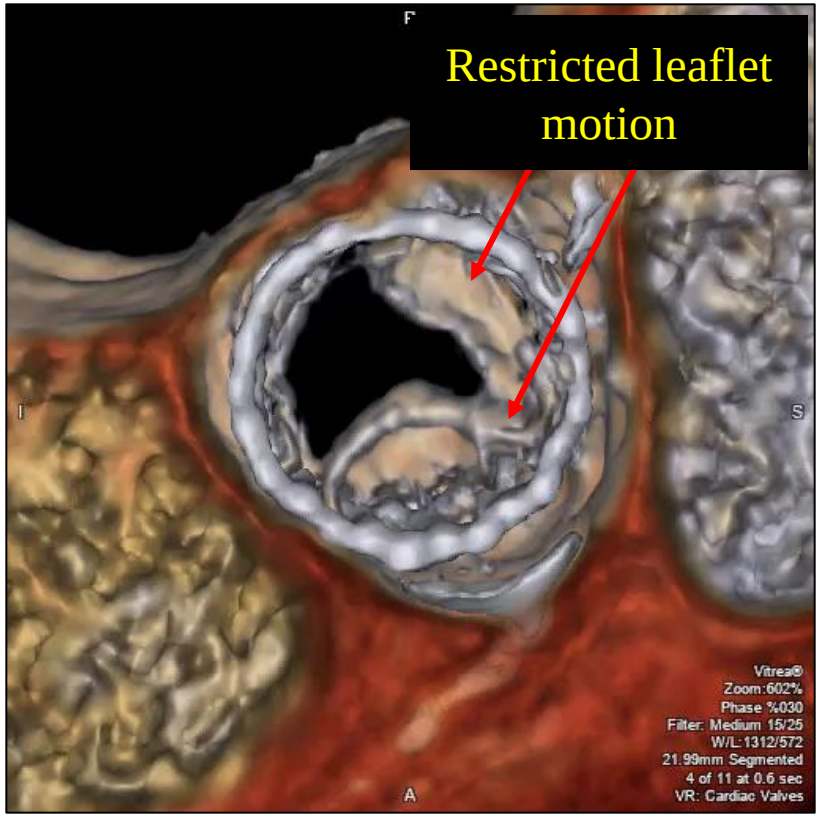
Day 1 TTE
Gradient 10mmHg

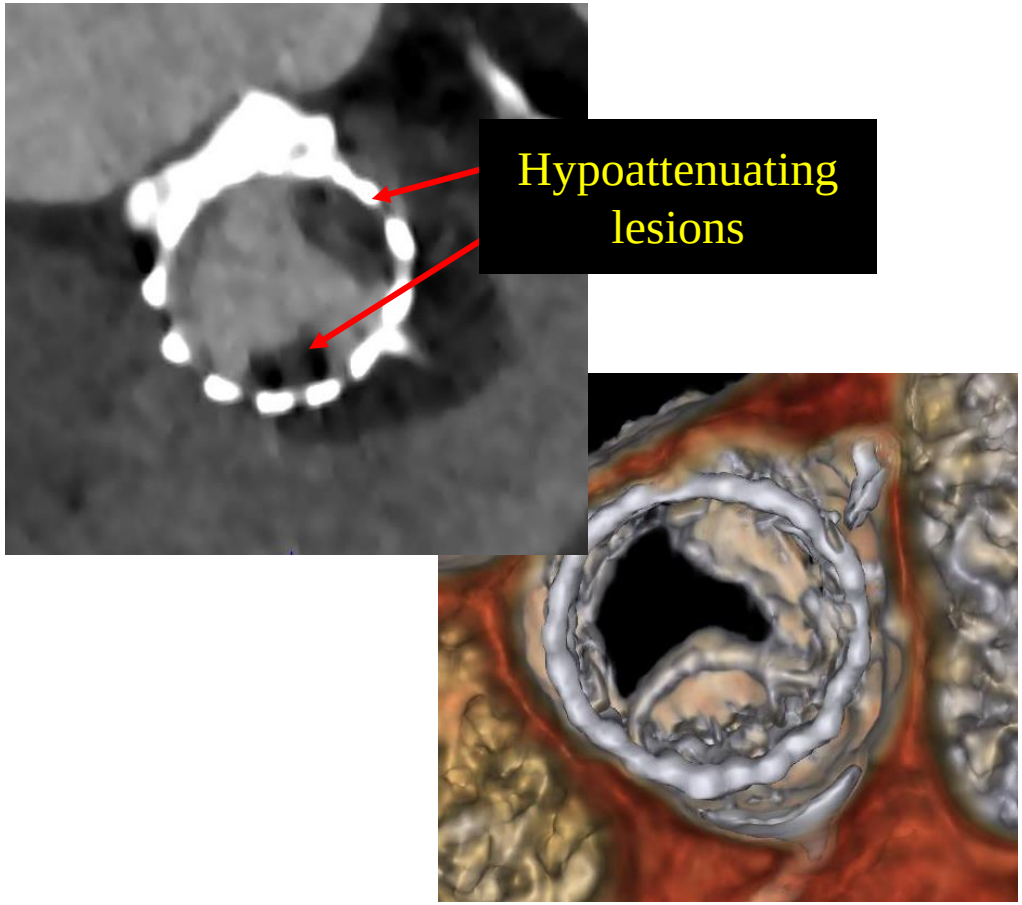


4 months post-TAVR
Gradient 23mmHg



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

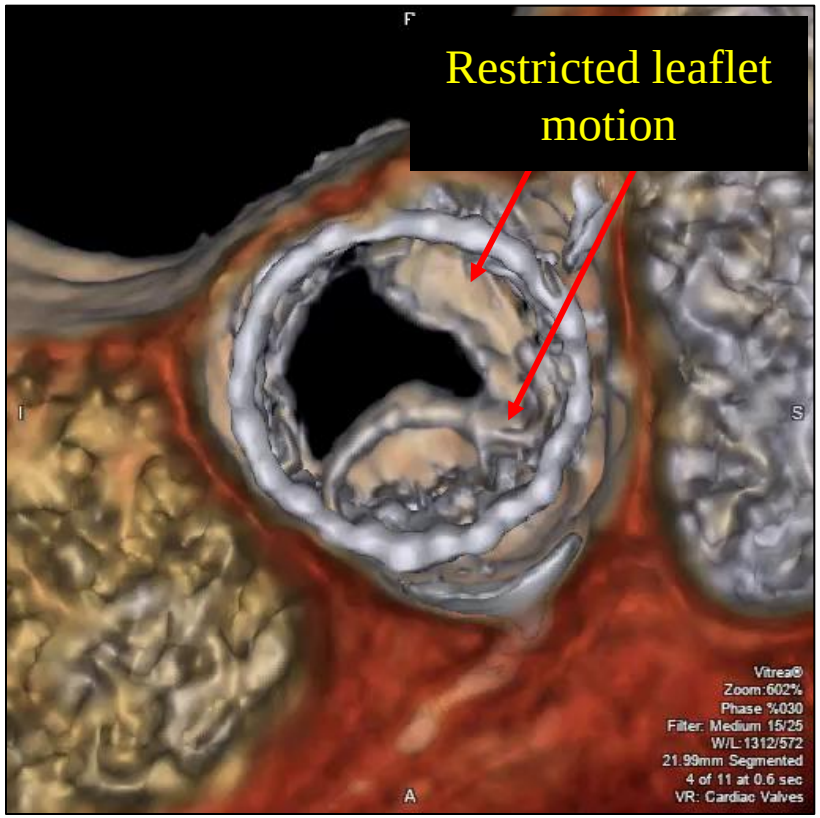


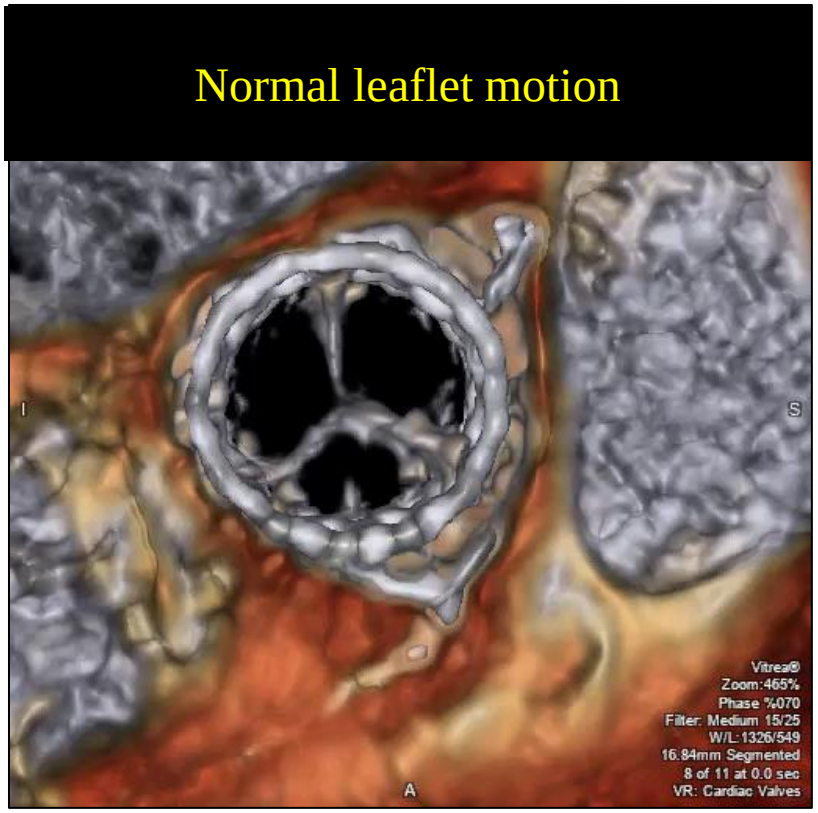


Leaflet motion restored following anticoagulation with warfarin (INR 2-3)

Repeat CT performed after 3 months

Resolution of symptoms with anticoagulation





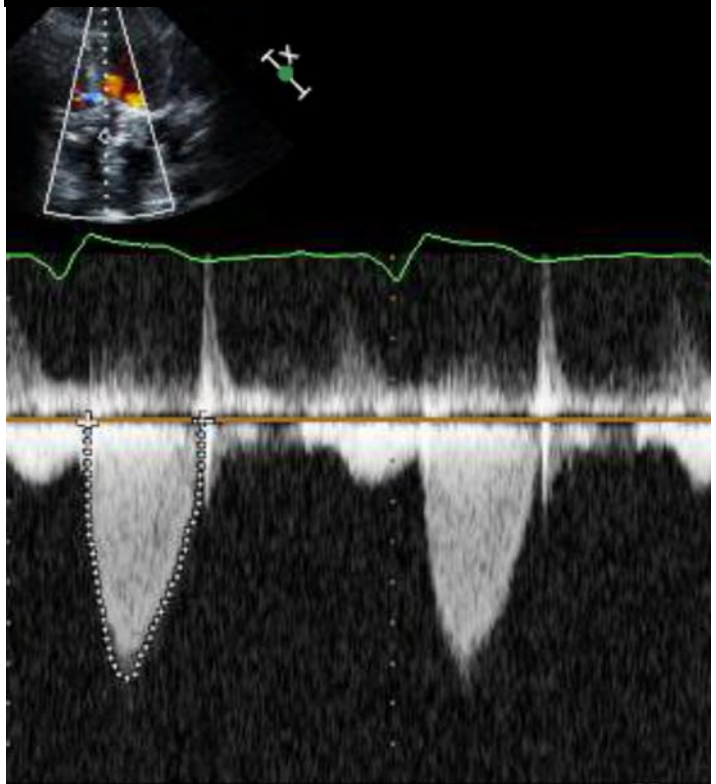
Normalized transvavular gradients with anticoagulation (warfarin, INR 2-3)

Repeat TTE performed after 3 months

Resolution of symptoms with anticoagulation

Pre-anticoagulation

Gradient 23mmHg



Post-anticoagulation

Gradient 11mmHg