What is Optimal Antithrombotic Regimen during and after TAVR?

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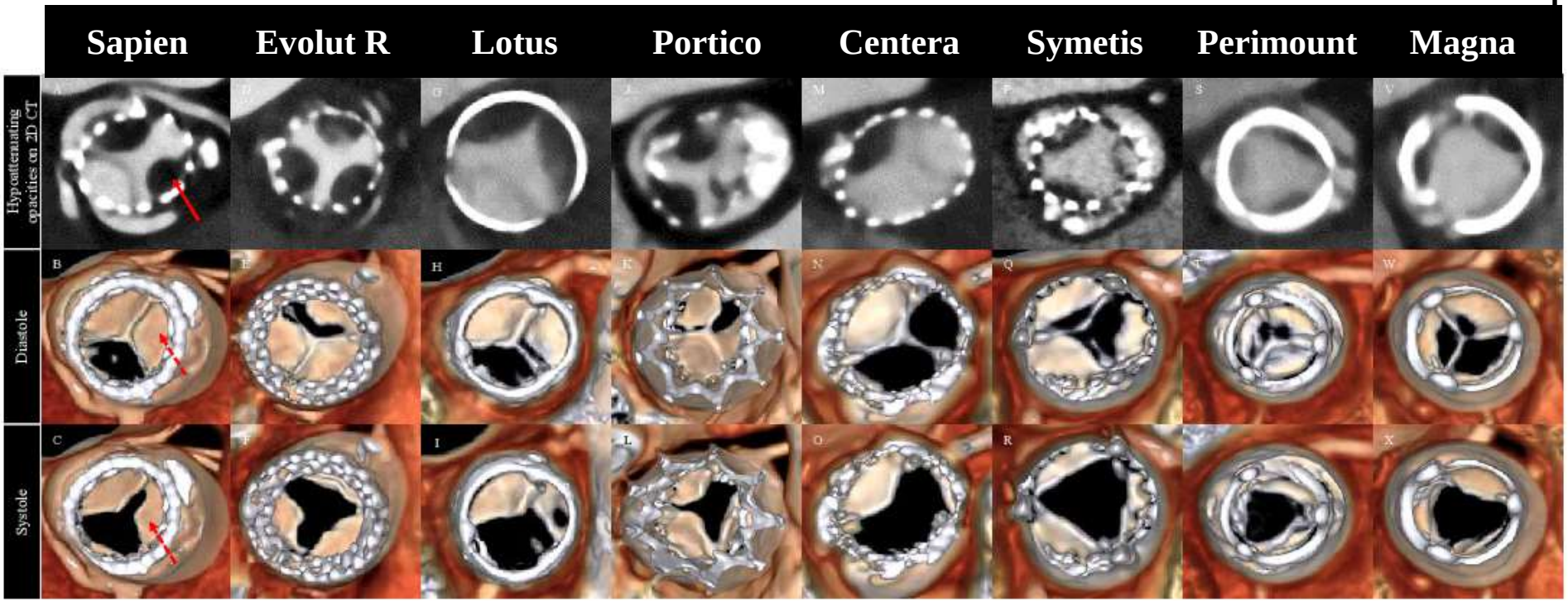
Key Questions

- What is more important in pathogenesis of valve thrombus thrombin or platelets?
- What regimen can be used most safely in this patient population which has high incidence of A Fib, thromboembolic disease and is also at greater risk of bleeding?
- What is available clinical data?
- What are key ongoing/planned trials?
- What are the society guidelines?

Subclinical Leaflet Thrombosis in multiple valve types is frequent



Makkar et NEJM 2015, Chakravarty et al Lancet 2017

Prevalence of reduced leaflet motion

Transcatheter vs. surgical bioprosthetic aortic valves: p=0.001

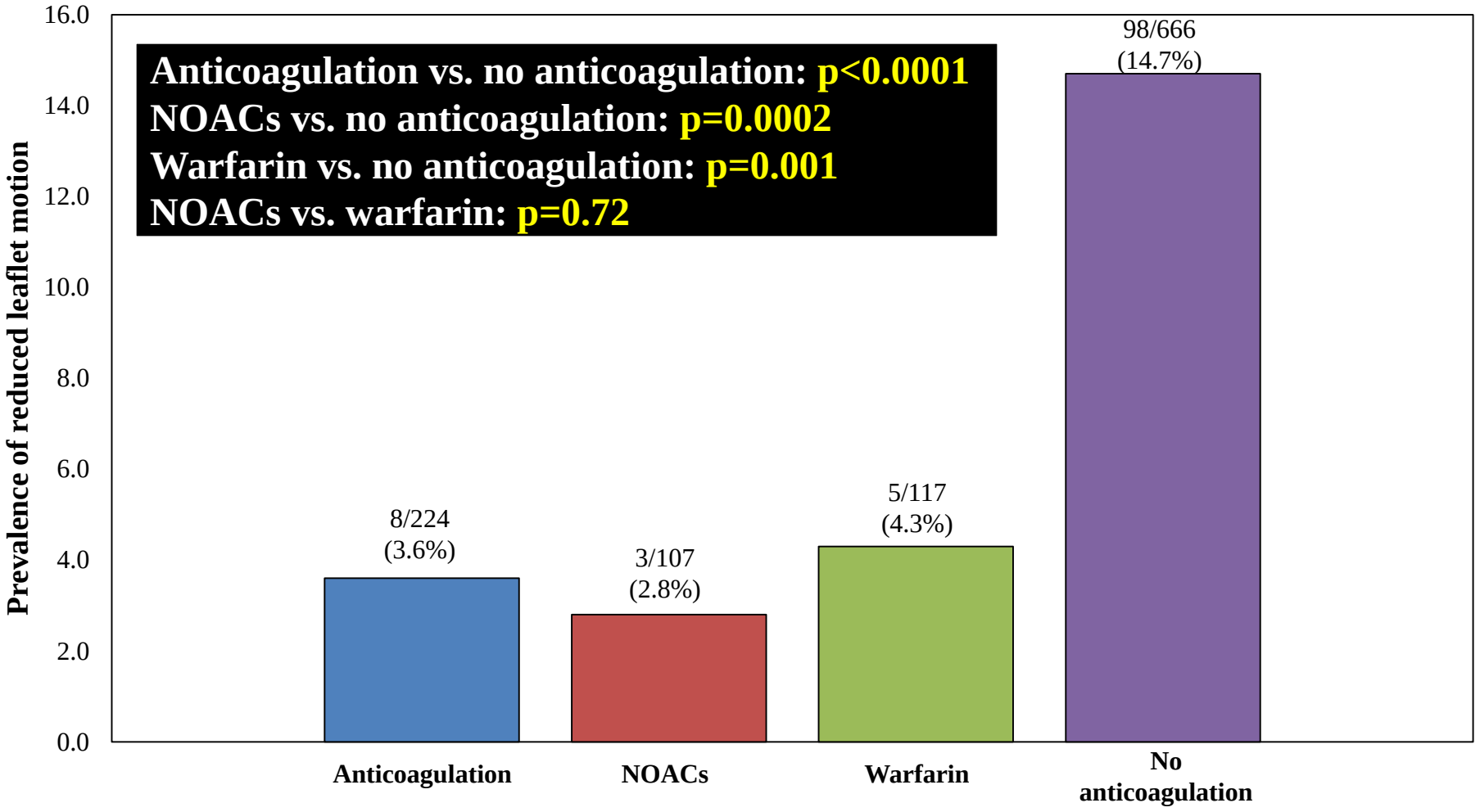
Reduced leaflet motion was present in 106 (11.9%) patients

Transcatheter valves
13.4% (101 out of 752)

Surgical valves
3.6% (5 out of 138)

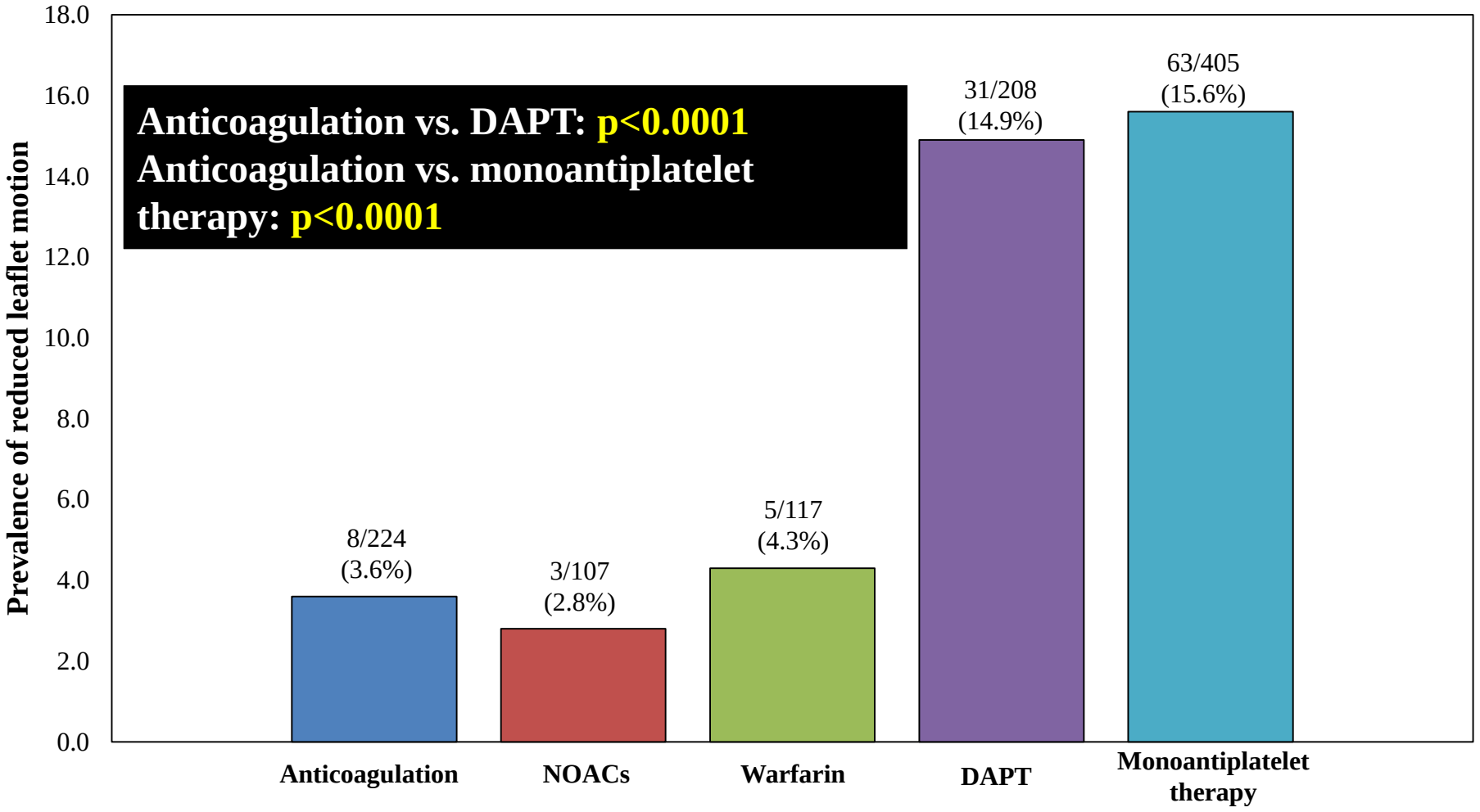
Anticoagulation and reduced leaflet motion

Anticoagulation vs. no anticoagulation

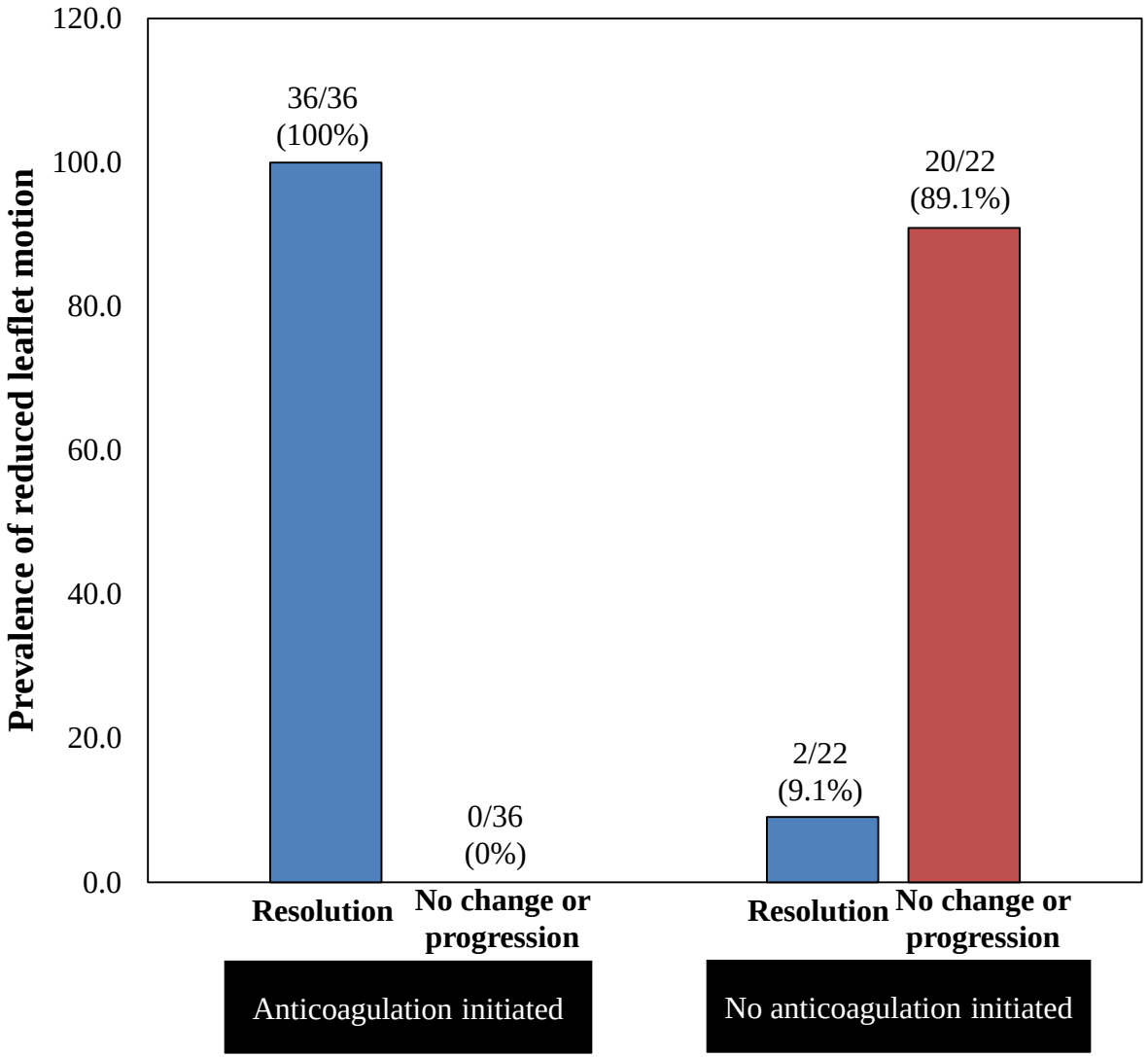


Anticoagulation and reduced leaflet motion

Anticoagulation vs. antiplatelet therapy



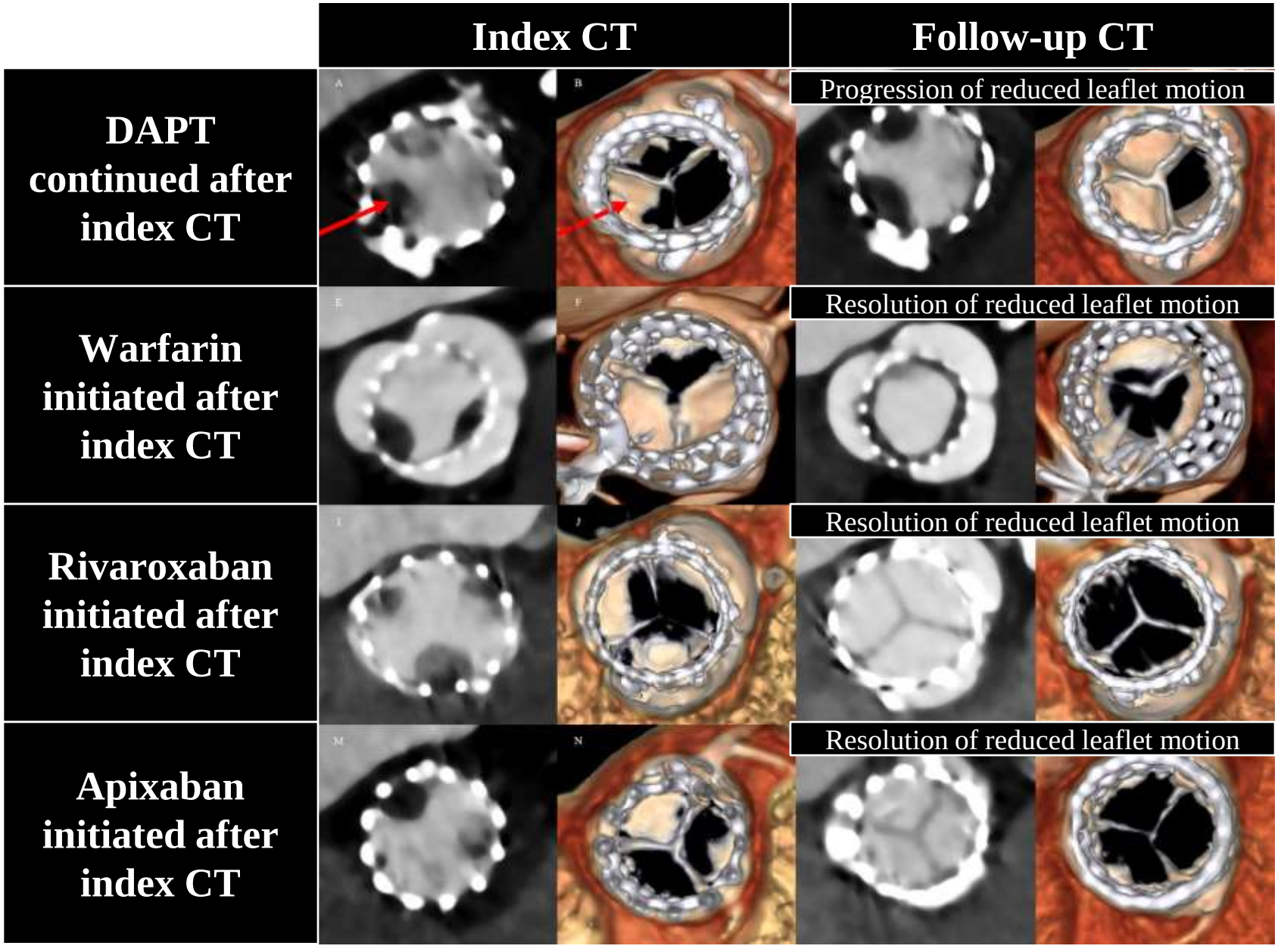
Impact of initiation of anticoagulation on reduced leaflet motion



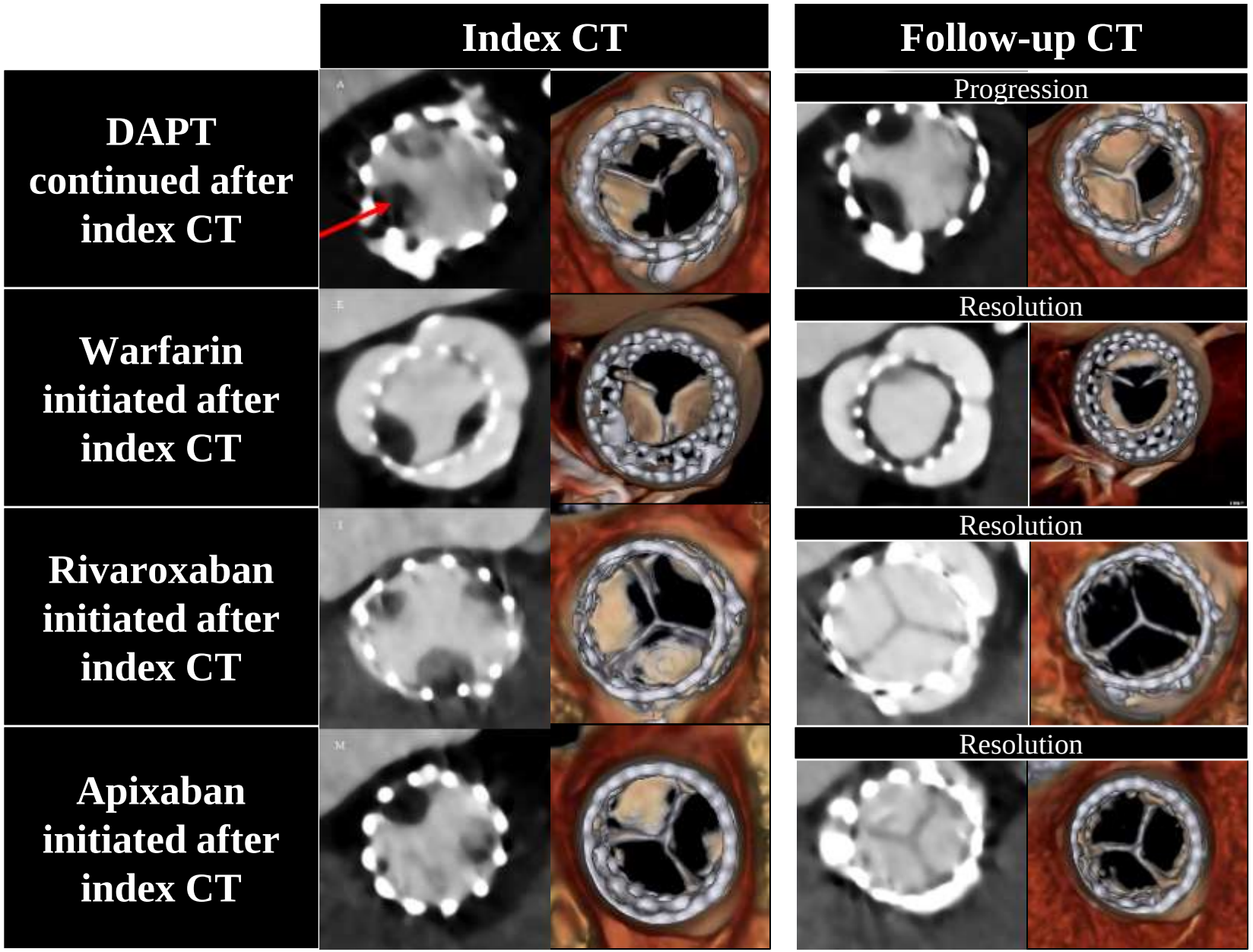
- **Resolution in 36 out of 36 patients** treated with anticoagulation (NOACs, n=12; warfarin, n=24)
- **Persistence/progression in 20 out of 22 patients** not treated with anticoagulation

P<0.0001

Anticoagulation vs. DAPT

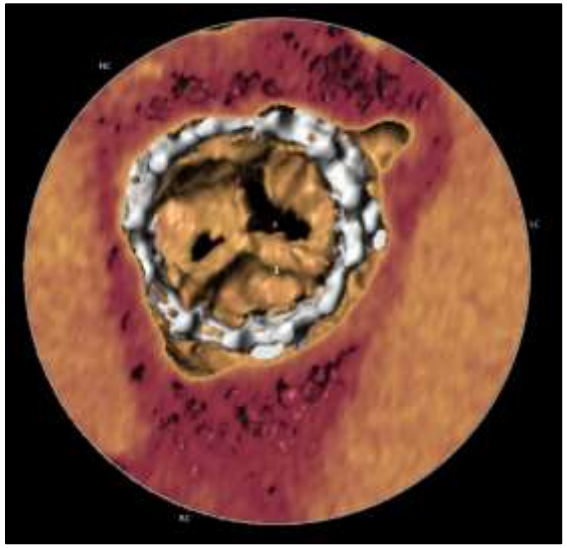


Anticoagulation vs. DAPT

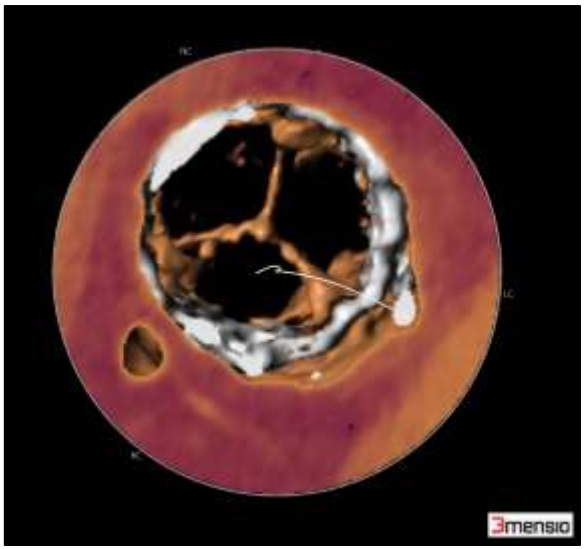


Recurrence of reduced leaflet motion following discontinuation of anticoagulation

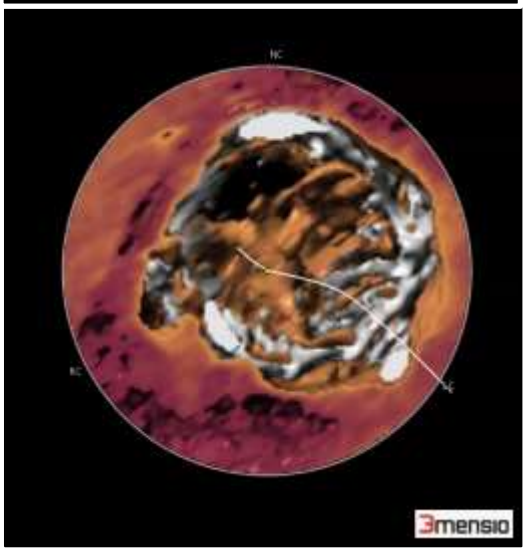
Baseline
Reduced leaflet motion



s/p Xarelto 10mg
Normal leaflet motion



Six months following discontinuation of xarelto
Reduced leaflet motion

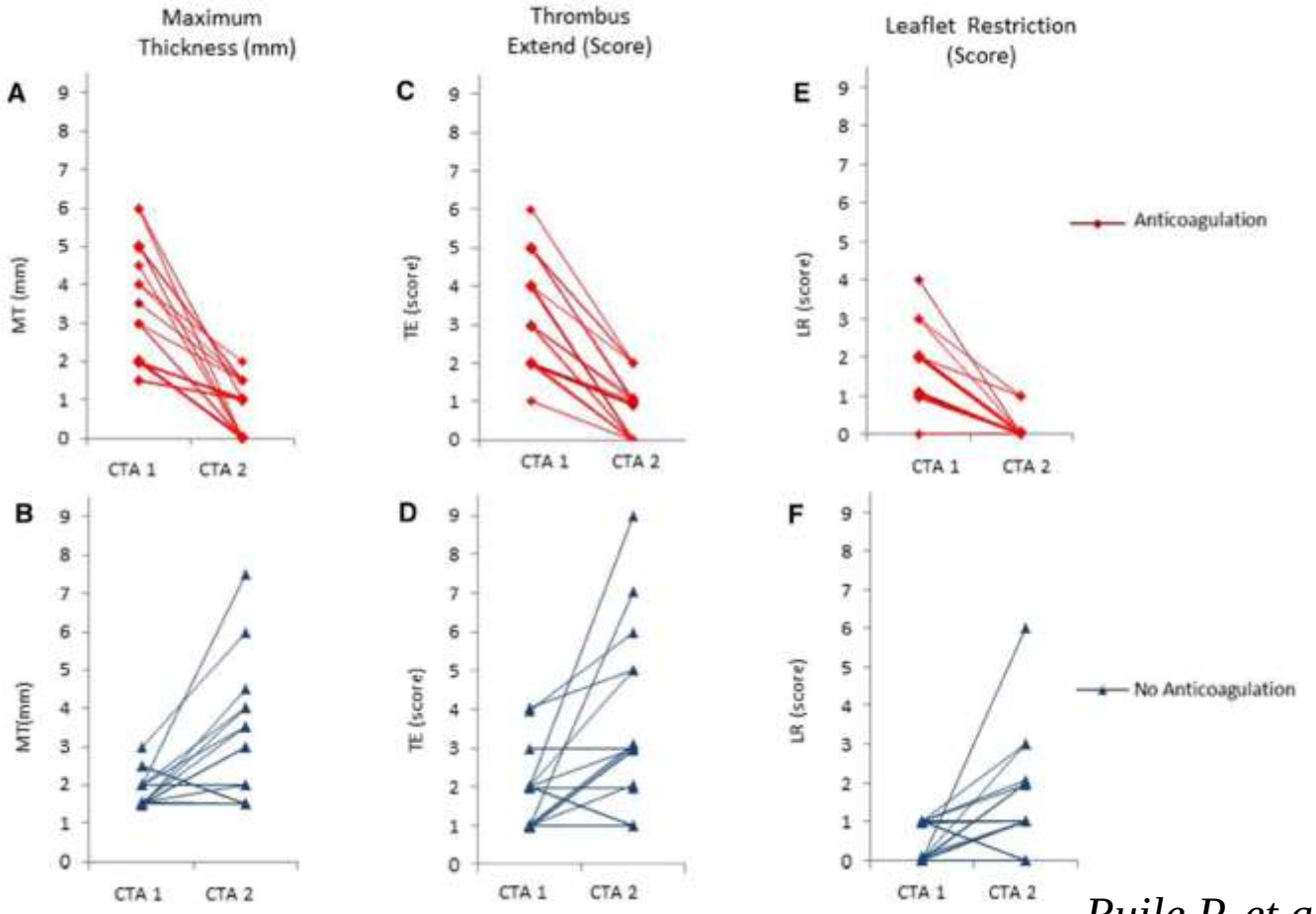


Reduced leaflet motion recurred in 4 out of 8 patients in whom anticoagulation was discontinued

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

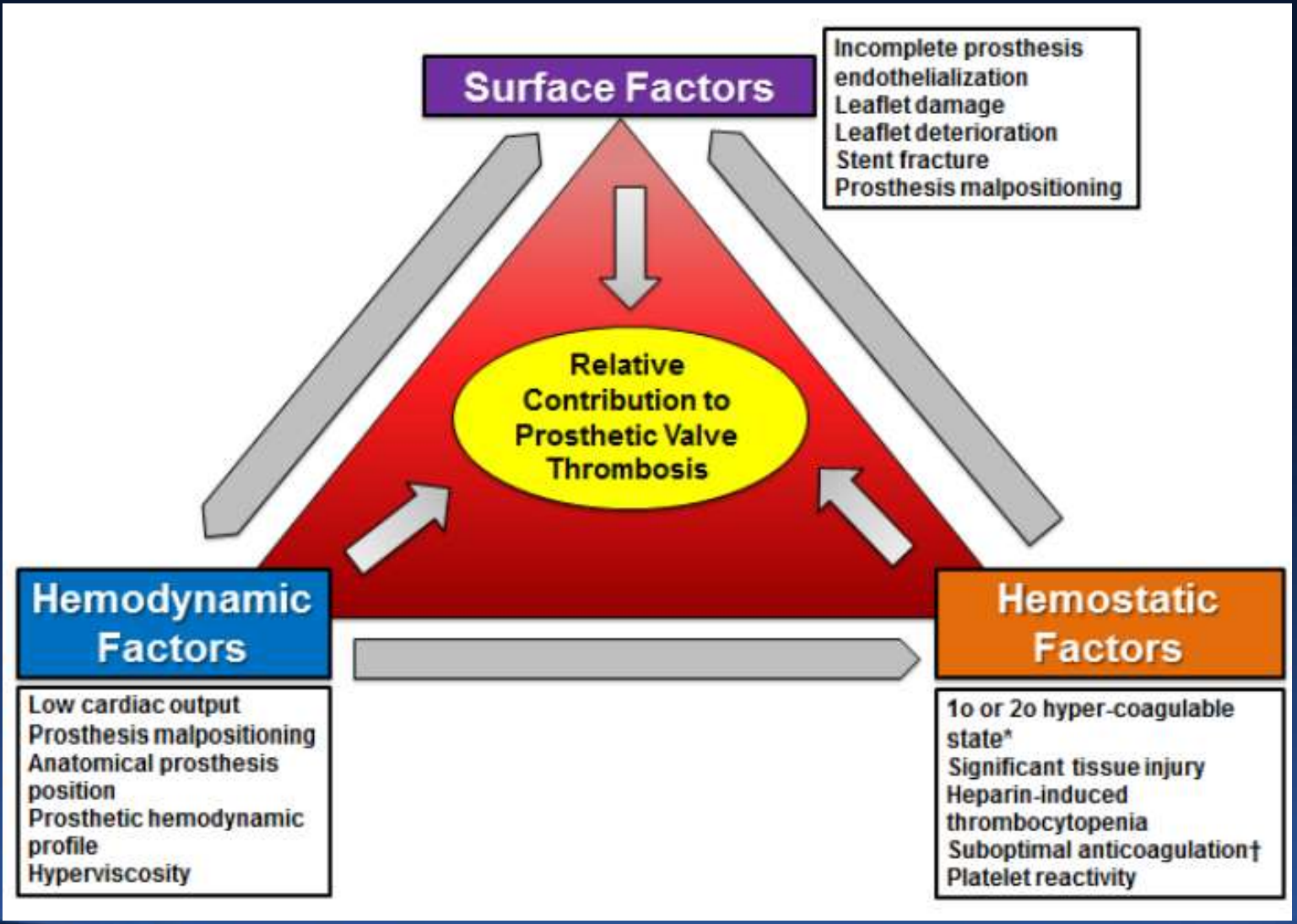


Leaflet thickening regressed in all 22 patients undergoing repeat CT

Leaflet thickening progressed in 11 of 16 patients

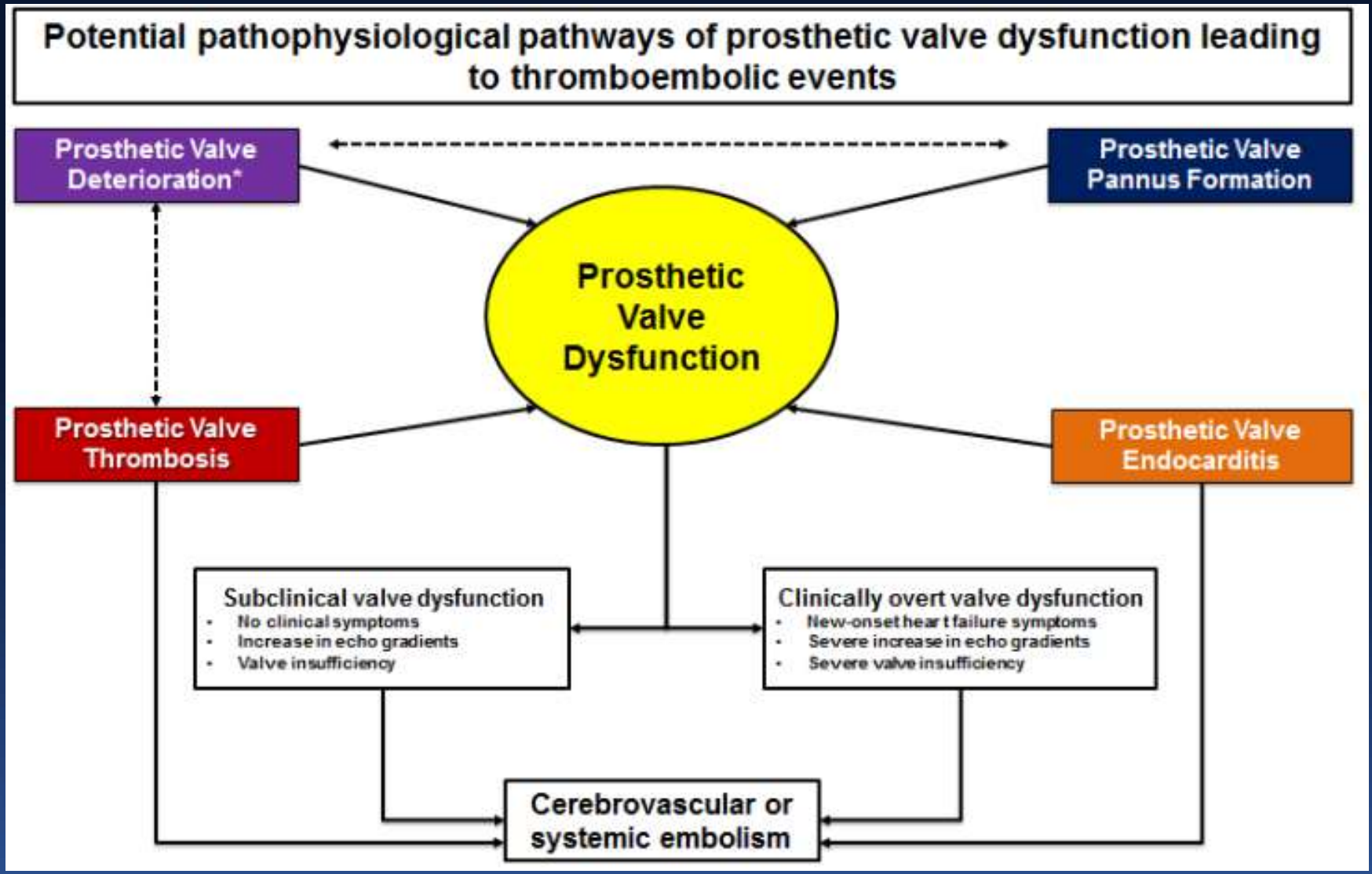
Ruile P. et al. Clin Res Cardiol 2017

Mechanisms of Prosthetic Valve Thrombosis



Mount Sinai Heart

Dangas G, Weitz J, Giustino G, Makkar R, Mehran R. JACC 2016; In press

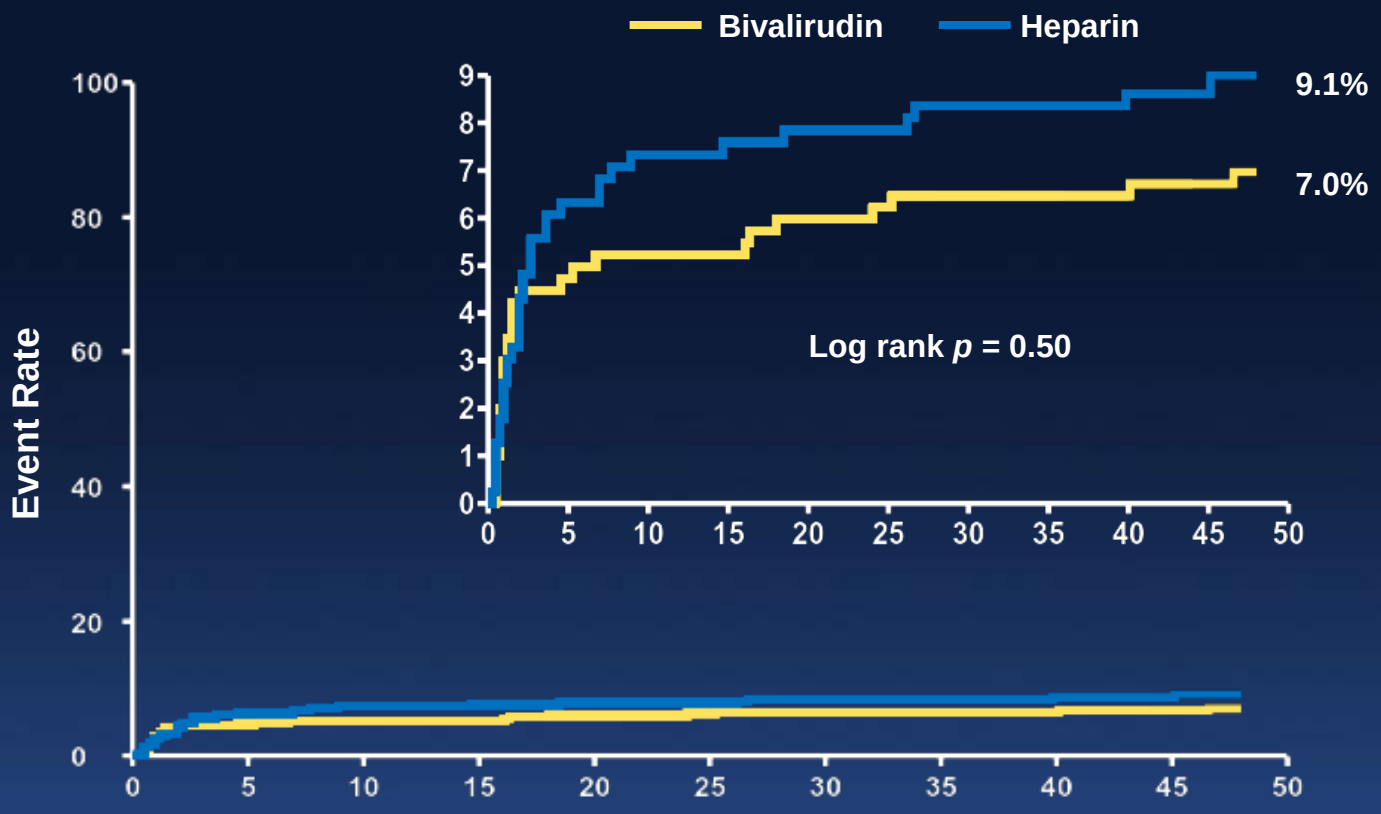


Mount Sinai Heart

Dangas G, Weitz J, Giustino G, Makkar R, Mehran R. JACC 2016; In press

BRAVO-3 Trial: Bivalirudin versus UH in patients undergoing TAVR

48-h Major bleeding (BARC ≥3b)



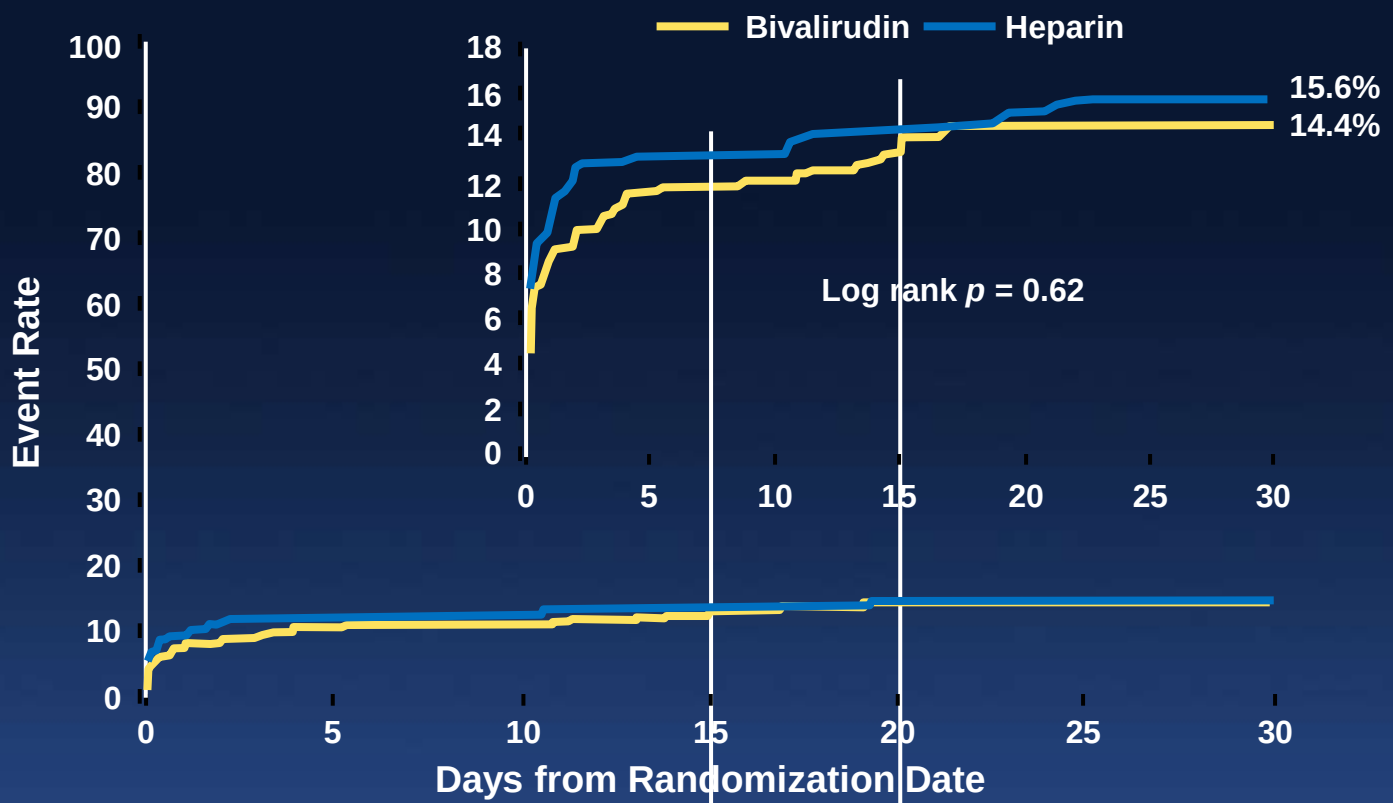
Patients at risk:

Bivalirudin	404	384	381	381	381	378	378	375	375	375	375	374	373
Heparin	398	371	367	366	365	364	364	361	361	361	360	360	358

Mount Sinai Heart

Dangas G et al, BRAVO-3 Investigators; *JACC* 2015;66(25):2860-8

BRAVO-3 trial: Net Adverse Clinical Events



Patients at risk:

Bivalirudin	404	354	349	342	337	329	270
Heparin	398	344	341	336	332	319	261

Dangas G et al, BRAVO-3 Investigators; *JACC* 2015;66(25):2860-8

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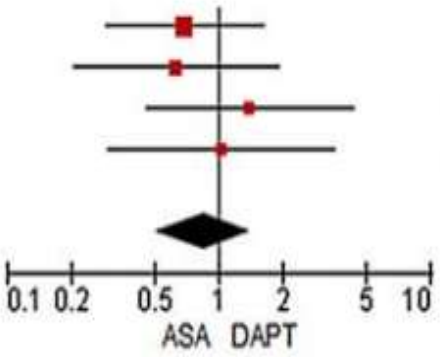
Is DAPT necessary?

Safety and efficacy of ASA vs. DAPT after TAVR: patient-level pooled analysis of 672 patients

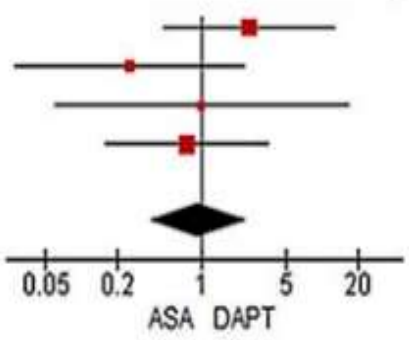
NACE

Study	Odds Ratio (95% CI)
Durand et al (2014)	0.69 (0.30-1.62)
Poliacikova et al (2013)	0.63 (0.20-1.91)
Stabile et al (2014)	1.39 (0.45-4.27)
Ussia (2011)	1.03 (0.30-3.52)
	0.83 (0.48-1.43)



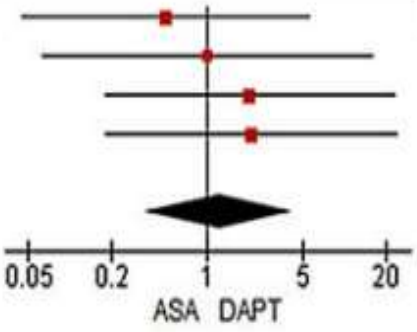
All-cause mortality

Study	Odds Ratio (95% CI)
Durand et al (2014)	2.50 (0.49-12.89)
Poliacikova et al (2013)	0.25 (0.03-2.24)
Stabile et al (2014)	1.00 (0.06-16.37)
Ussia (2011)	0.75 (0.16-3.59)
	0.91 (0.36-2.27)



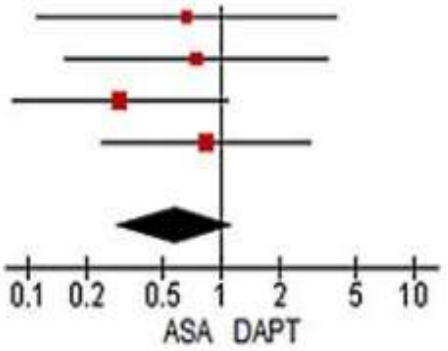
Stroke

Study	Odds Ratio (95% CI)
Durand et al (2014)	0.50 (0.05-5.51)
Poliacikova et al (2013)	1.0 (0.06-15.99)
Stabile et al (2014)	2.03 (0.18-23.06)
Ussia (2011)	2.11 (0.18-24.24)
	1.21 (0.36-4.03)



LTB and major bleeding

Study	Odds Ratio (95% CI)
Stabile et al (2014)	0.83 (0.24-2.90)
Durand et al (2014)	0.30 (0.08-1.09)
Poliacikova et al (2013)	0.67 (0.11-3.99)
Ussia (2011)	0.75 (0.16-3.59)
	0.56 (0.28-1.11)



Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve
The ARTE Randomized Clinical Trial

Josep Rodés-Cabau, MD,
on behalf of the ARTE investigators

ARTE Trial - Study Design

Prospective, randomized, open label, multicenter study

Patients randomized
(the day prior to the TAVR procedure)

Aspirin 80-100mg/d

-Start at least 24hrs before TAVR

-Continued for at least 6 months

Aspirin 80-100mg/d + Clopidogrel 75mg/d

Clopidogrel treatment

-Initial dose of 300 mg followed by 75 mg/d

Transfemoral approach

-Start within 24hrs before TAVR

-Continued for 3 months

Transapical/Transaortic/Transcarotid approach

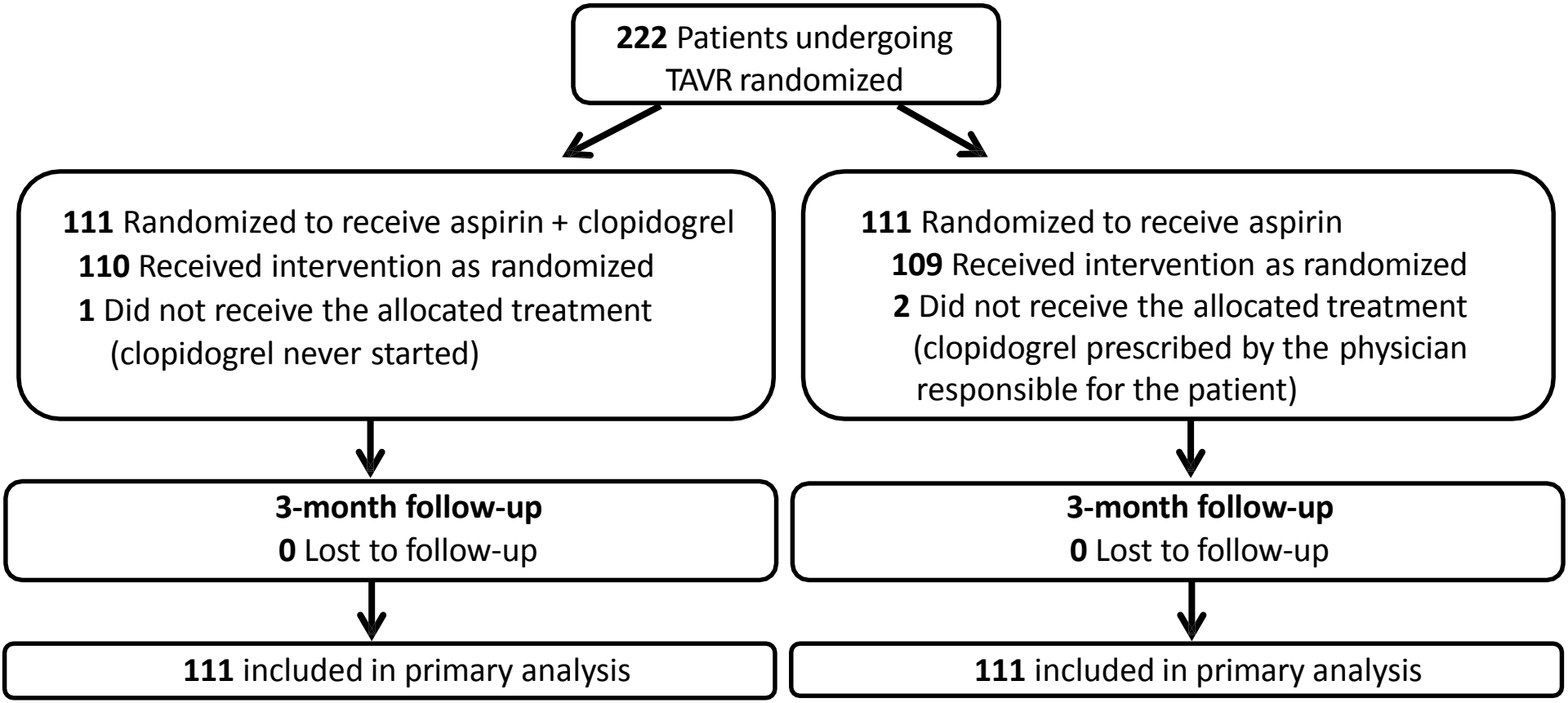
-Start within 24hrs after TAVR

-Continued for 3 months

Clinical visit/phone contact at 1- 3- and 12-month follow-up

ARTE Trial - Results

Flowchart of the Study Population

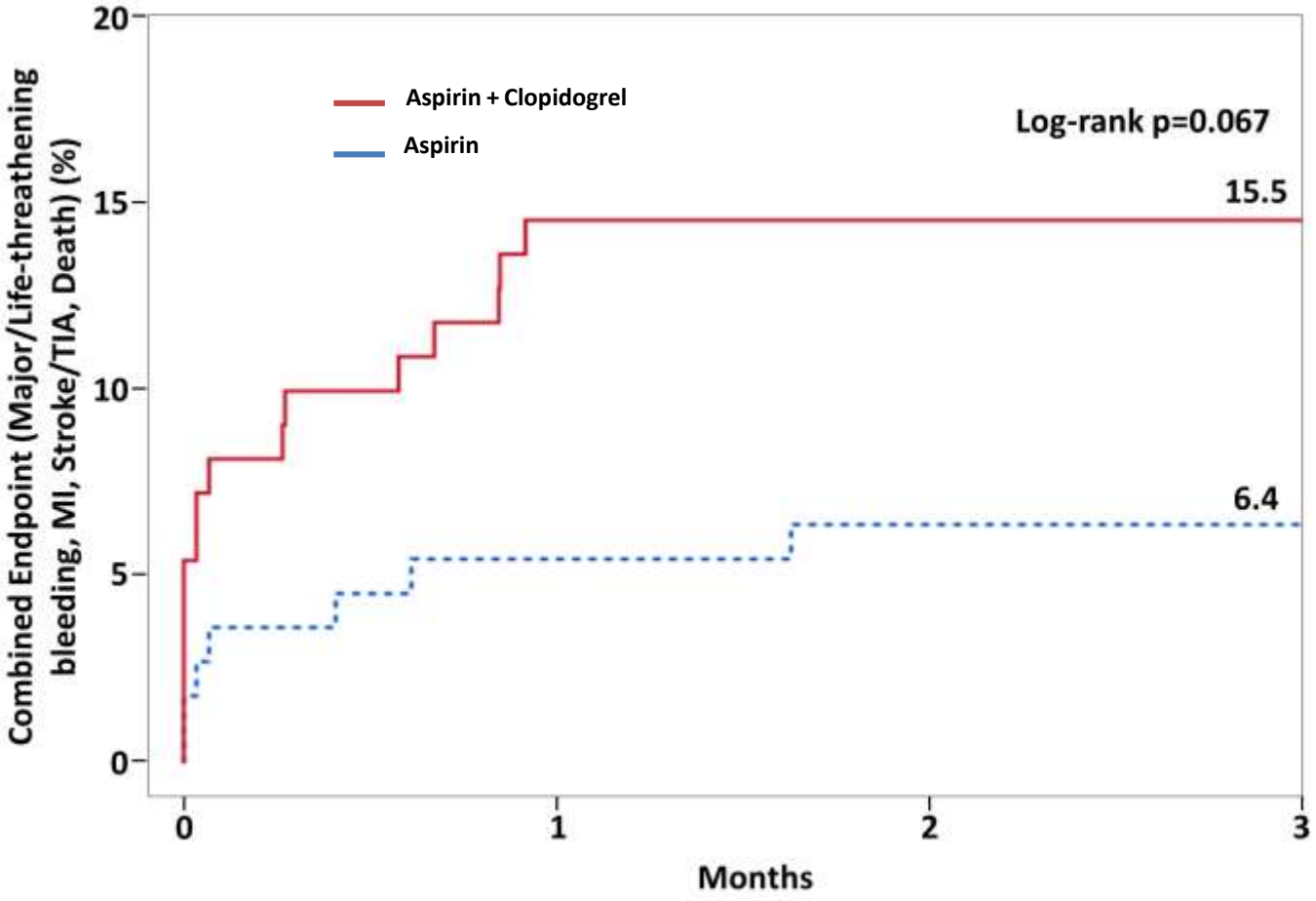


Study Outcomes (90 days)

	Aspirin + Clopidogrel n=111	Aspirin n=111	OR (95% CI)	P value
Combined endpoint* (primary endpoint)	17 (15.3)	8 (7.2)	2.31 (0.95–5.62)	0.065
Major/life-threatening bleeding	12 (10.8)	4 (3.6)	3.22 (1.01–10.34)	0.038
Major bleeding	5 (4.5)	3 (2.7)	1.68 (0.39–7.21)	0.484
Life-threatening bleeding	7 (6.3)	1 (0.9)	7.34 (0.89–60.71)	0.065
Myocardial infarction	4 (3.6)	1 (0.9)	4.13 (0.45–37.60)	0.175
Stroke/TIA	3 (2.7)	1 (0.9)	3.11 (0.32–30.43)	0.313
Disabling stroke	1 (0.9)	1 (0.9)	0.97 (0.06–15.81)	0.983
Nondisabling stroke	2 (1.8)	0	—	—
TIA	0	0		
Death	7 (6.3)	4 (3.6)	1.78 (0.51–6.27)	0.370

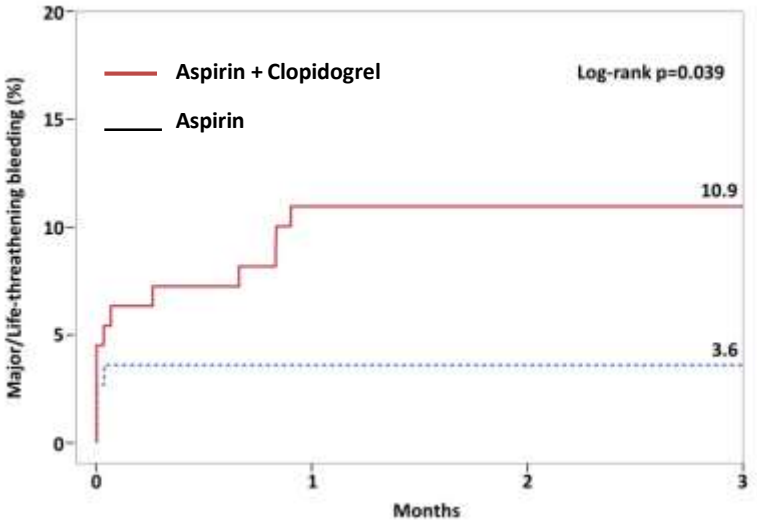
*Death, myocardial infarction, stroke or TIA, or major or life-threatening bleeding.

Kaplan-Meier Curves (Combined Endpoint)

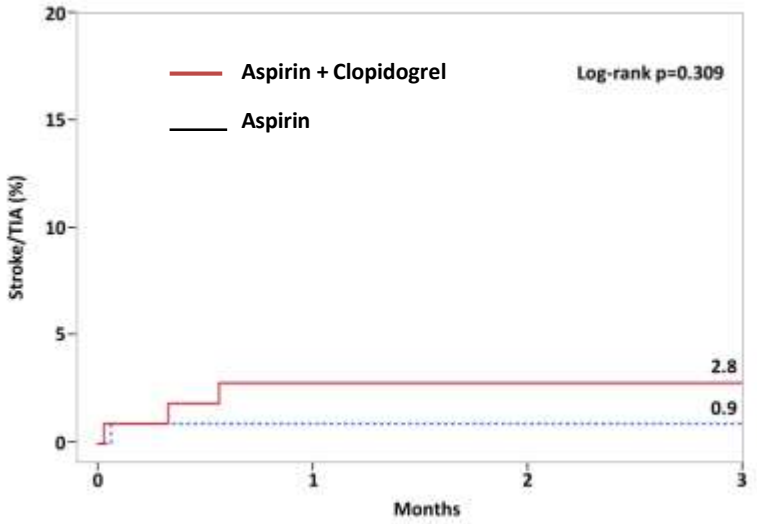


Kaplan-Meier Curves (Ischemic, Bleeding Events)

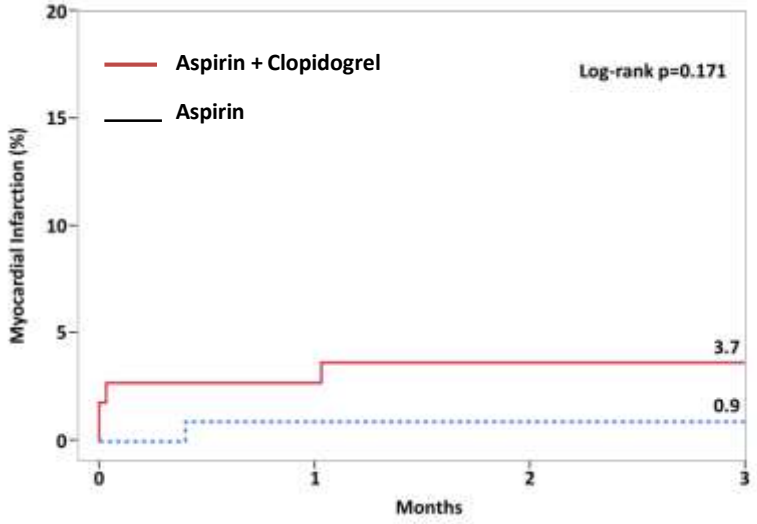
Major or life-threatening bleeding



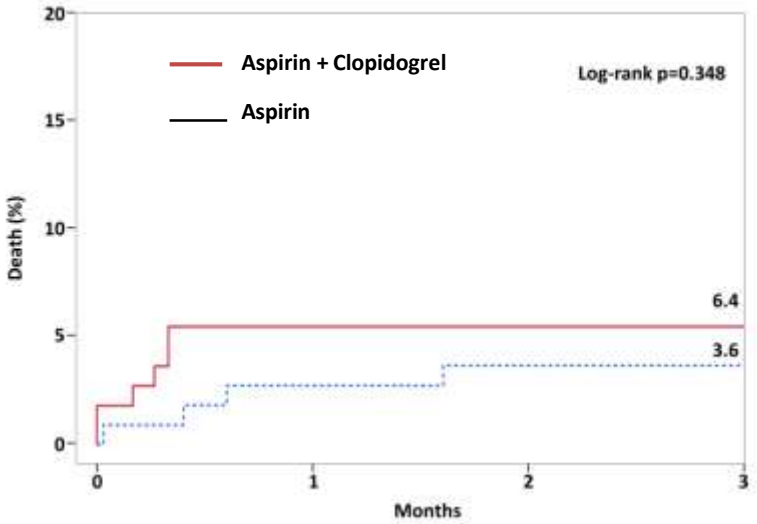
Stroke or TIA



Myocardial infarction (MI)



Death

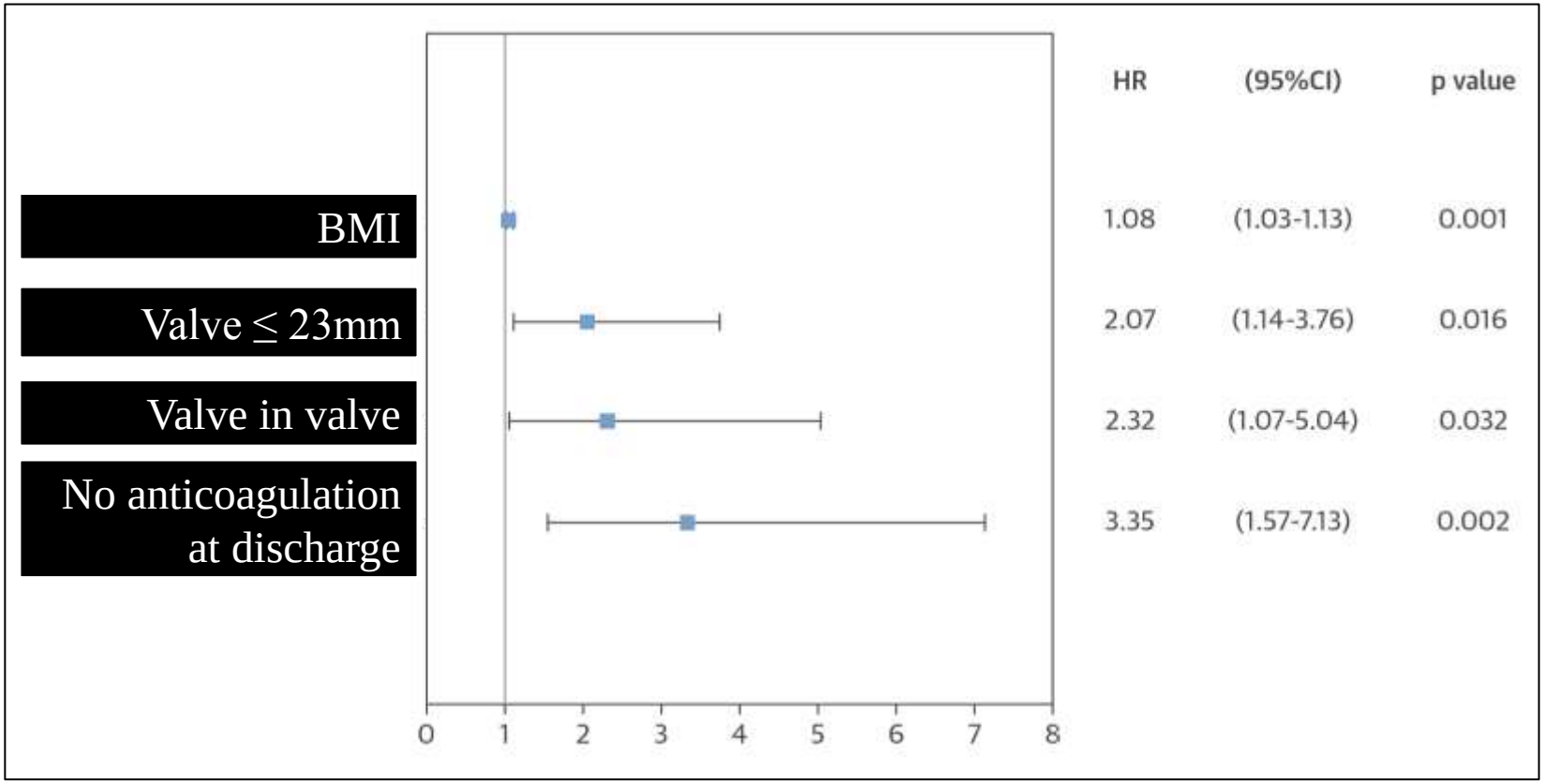


Does anticoagulation help after TAVR?

Predictors of valve hemodynamic degeneration after TAVR

1521 patients undergoing TAVR

Valve hemodynamic degeneration = 10mmHg rise in transvalvular gradients

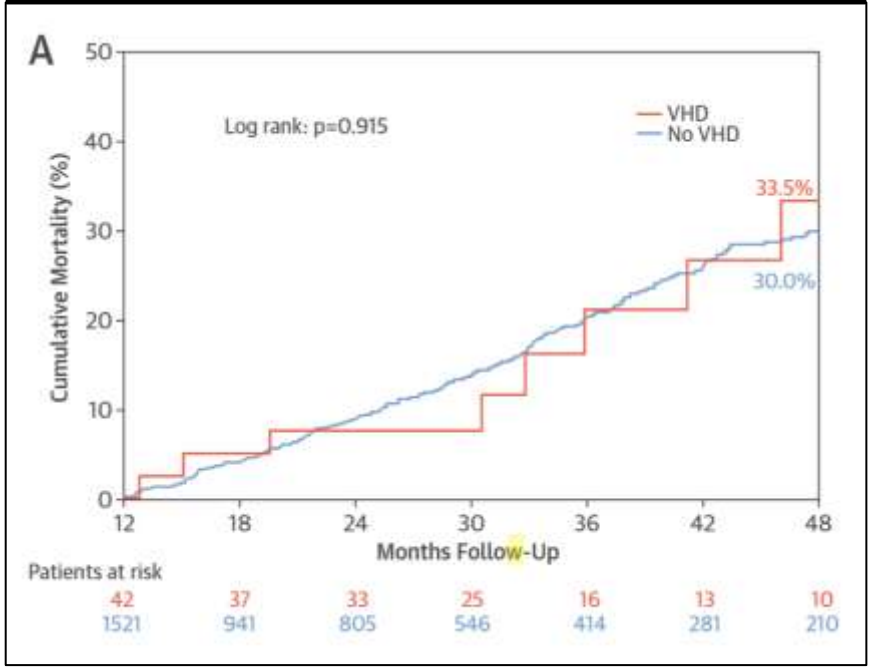


Del Trigo M. et al. JACC 2016

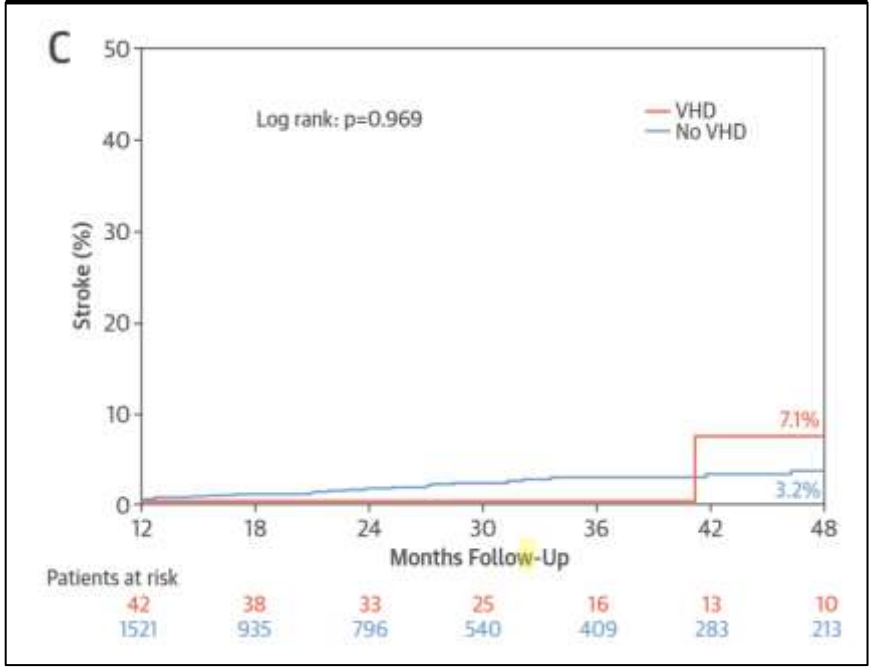
Valve hemodynamic degeneration and clinical outcomes

No significant increase in mortality or stroke

Mortality



Stroke

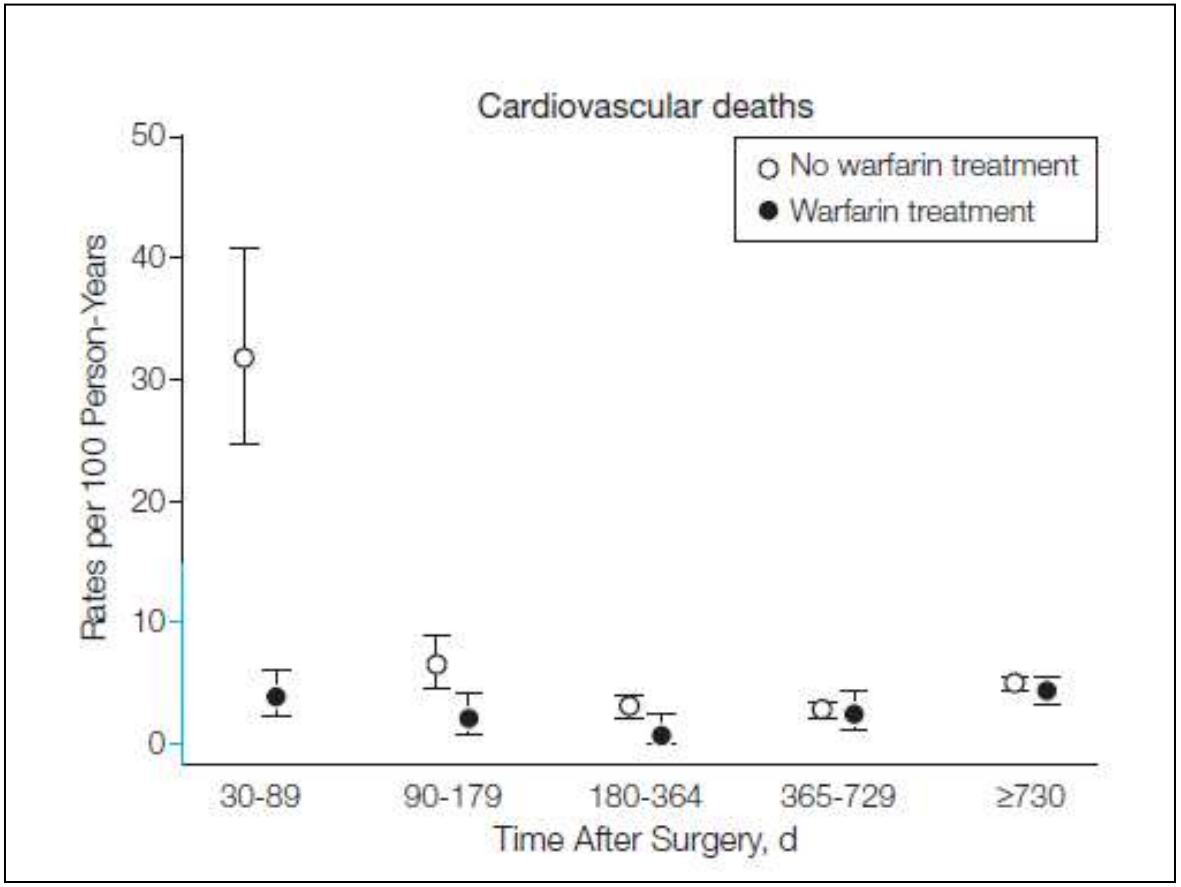


Del Trigo M. et al. JACC 2016

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

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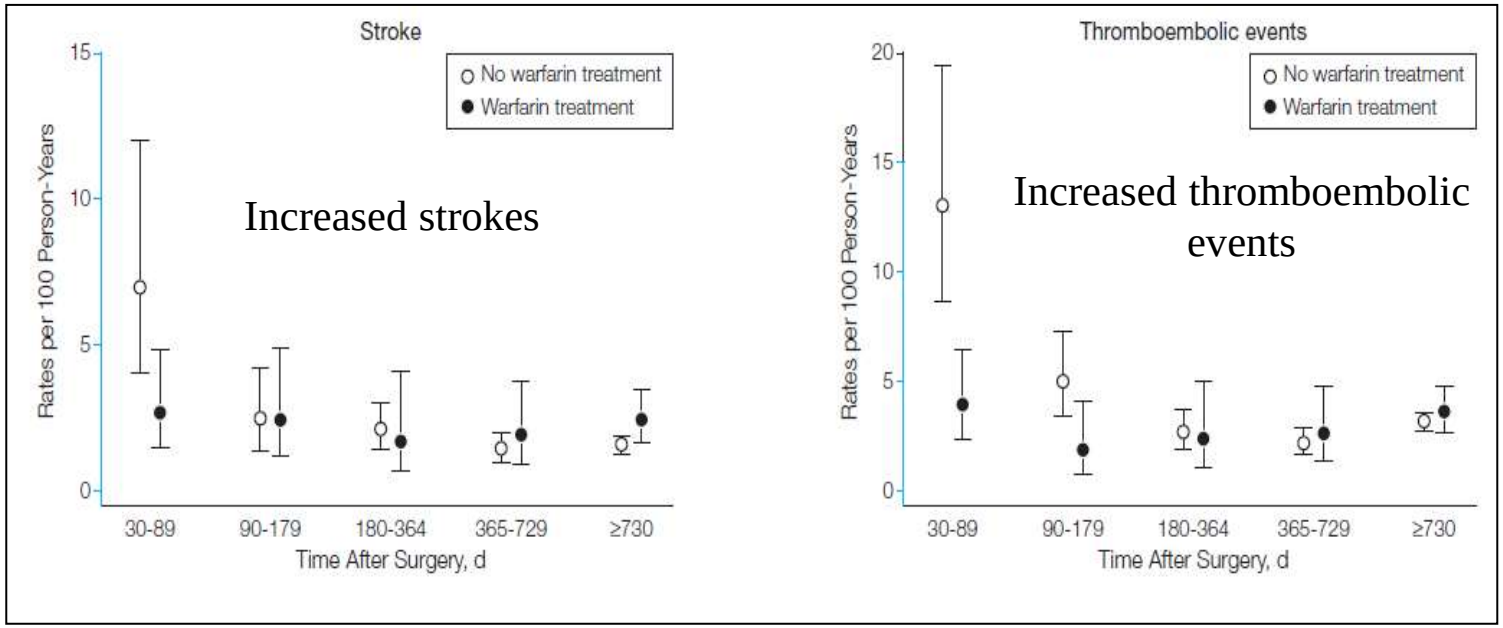


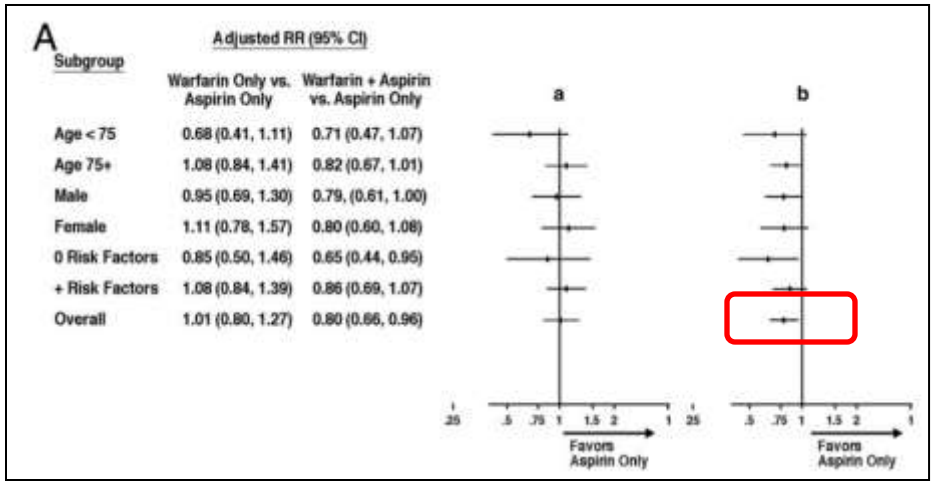
Merie C. et al. JAMA 2012

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

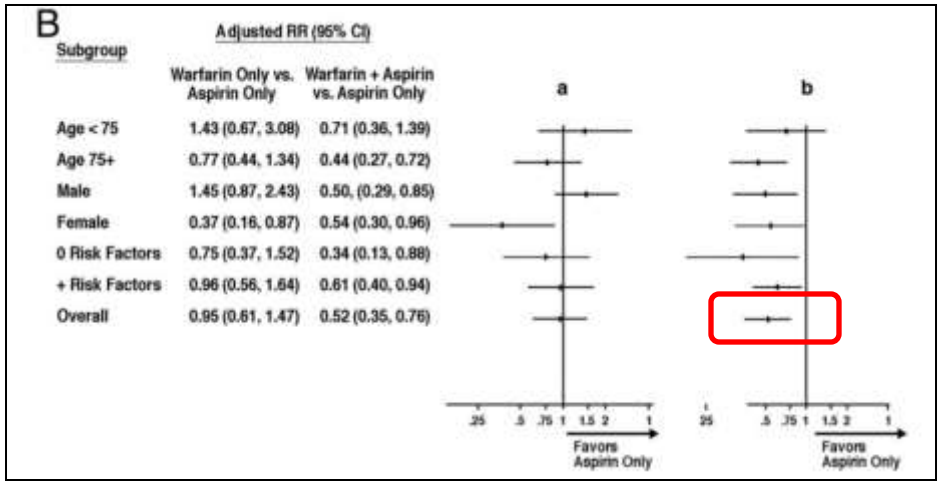
25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

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

The CLOE Trial – Study Scheme (NHLBI, NIH submission)

Dangas, Mack, Gelijns, Moskowitz, Parides, Mehran, Marx et al

Successful TAVR in the STS/SCC TVT Registry n=4,000

Control Arm [No-Clopidogrel]
Stratum 1: Aspirin (81 mg qD)
Stratum 2: Warfarin (INR 2–3) or a NoAC

1:1 Randomization

Treatment Arm [+Clopidogrel]
Stratum 1: Clopidogrel (75 mg qD) + Aspirin (81 mg qD)
Stratum 2: Clopidogrel (75 mg qD) + Warfarin (INR 2–3) or a NoAC

Minimum duration of randomized therapy 6 months

CLINIC FOLLOW-UP: 1, 6, 12 Months

Secondary Endpoints

- Single Component of the Primary Efficacy and Safety Endpoints at 6 and 12 months
- Net Adverse Clinical Events: the composite of the primary efficacy or safety endpoint.
- Bleeding endpoint as per the TIMI and ISTH definitions

Primary Efficacy Endpoint (6 Months)

Composite of Death, Stroke, MI, Valve Thrombosis or Systemic Thromboembolism

Primary Safety Endpoint

Major / Life-Threatening VARC-2 Bleeding

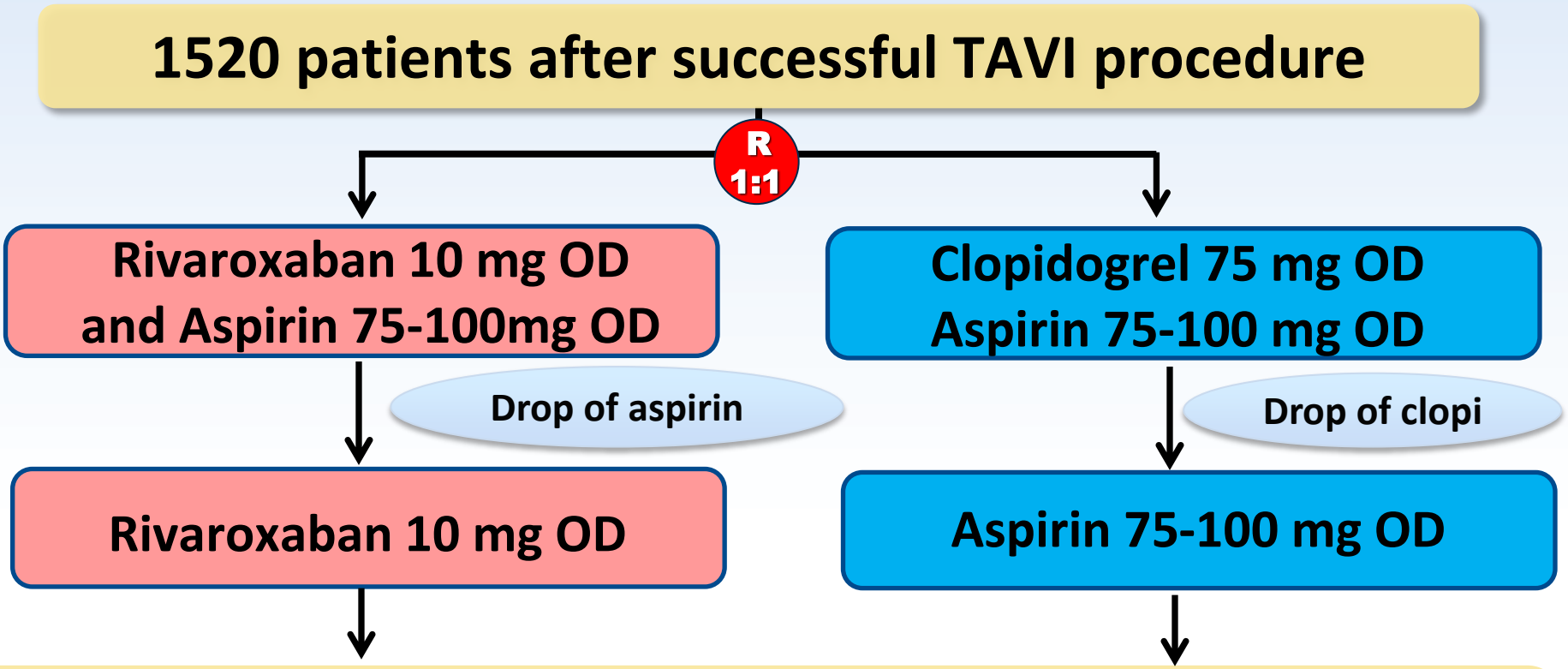
Ancillary Studies

- Cost-Effectiveness
- QoL
- Frailty
- CTA Leaflet Substudy
- MRI Brain Substudy

Sinai Heart

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*****.**

The GALILEO Trial
CTA and MRI Substudies

GALILEO 4D

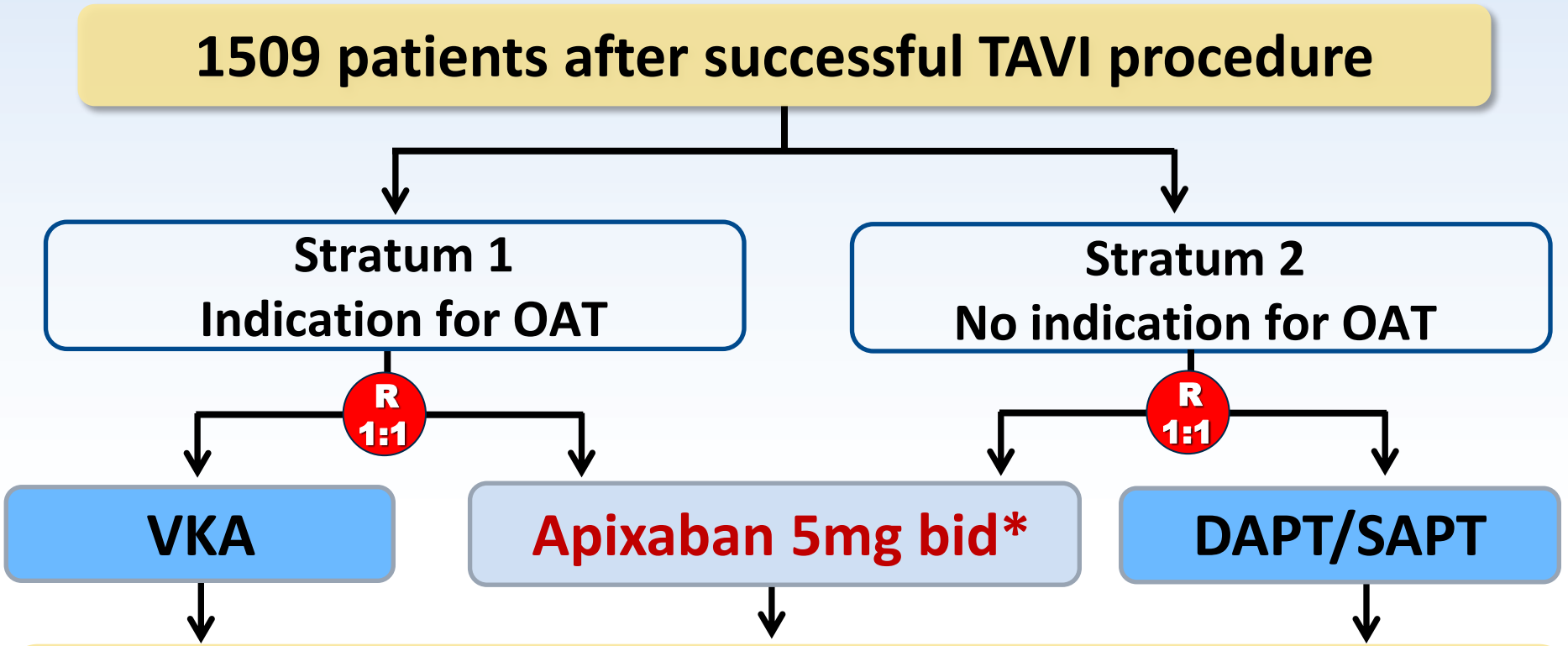
- N = 300 patients; 1 CTA done at 3 months
- Primary endpoint: rate of patients with at least one prosthetic leaflet with > 50% motion reduction as assessed by cardiac 4DCT-scan at 3 months after TAVR
- Will test superiority of rivaroxaban-based versus clopidogrel-based strategy
- Secondary endpoints include leaflet thickening, echocardiographic mean gradient & EOA and NYHA class

GALILEO MRI Substudy
EARTH

- N = 180 patients
- Primary endpoint: TLV (mm3) assessed with DW-MRI at 3 months
- Will test superiority of rivaroxaban-based versus clopidogrel-based strategy
- DW-MRI also performed pre-TAVR and post-TAVR (both inhospital) for the 2ary endpooint of periprocedure embolization

NCT02556203

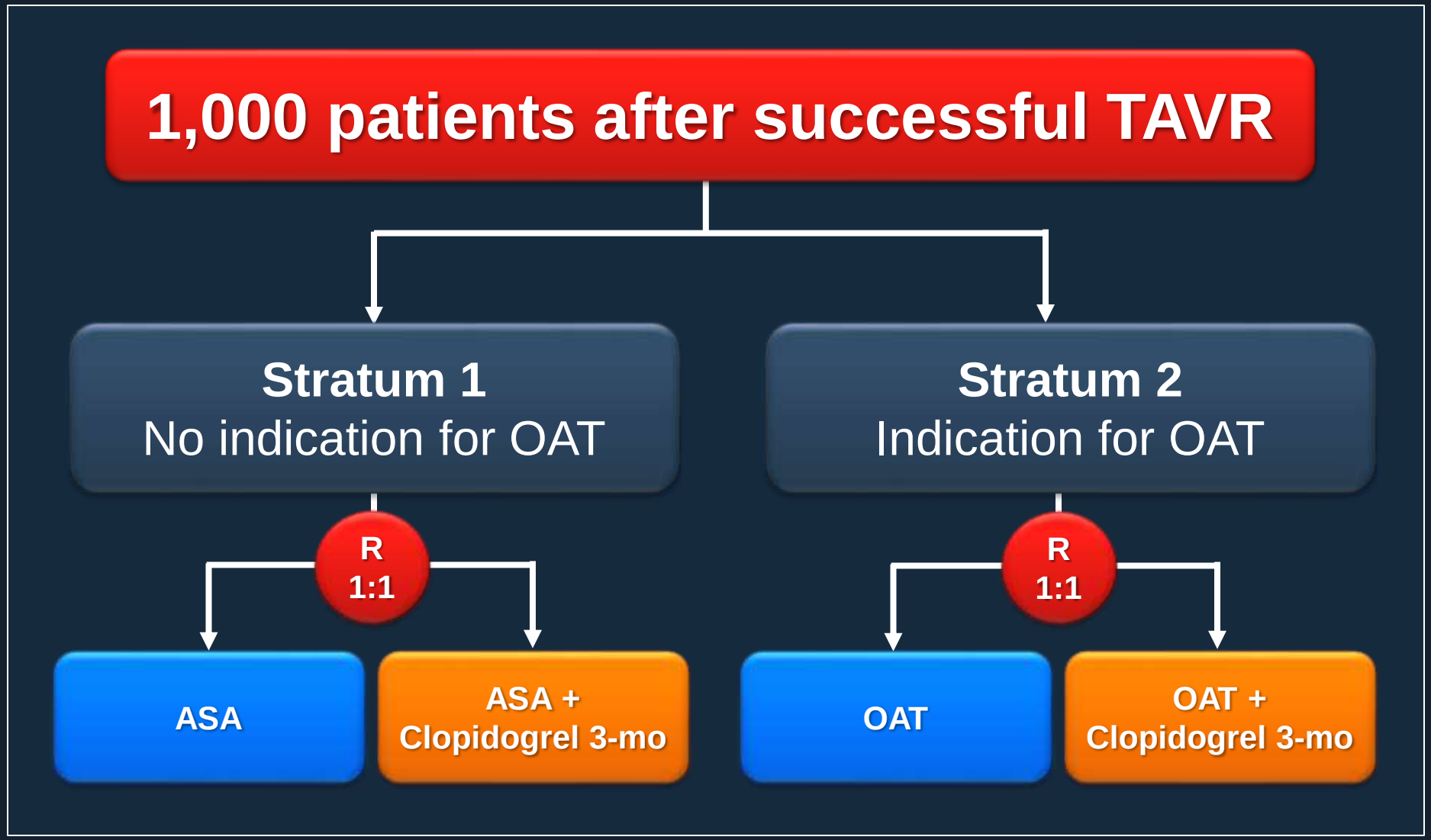
ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)



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).

POPular TAVI – Design Overview



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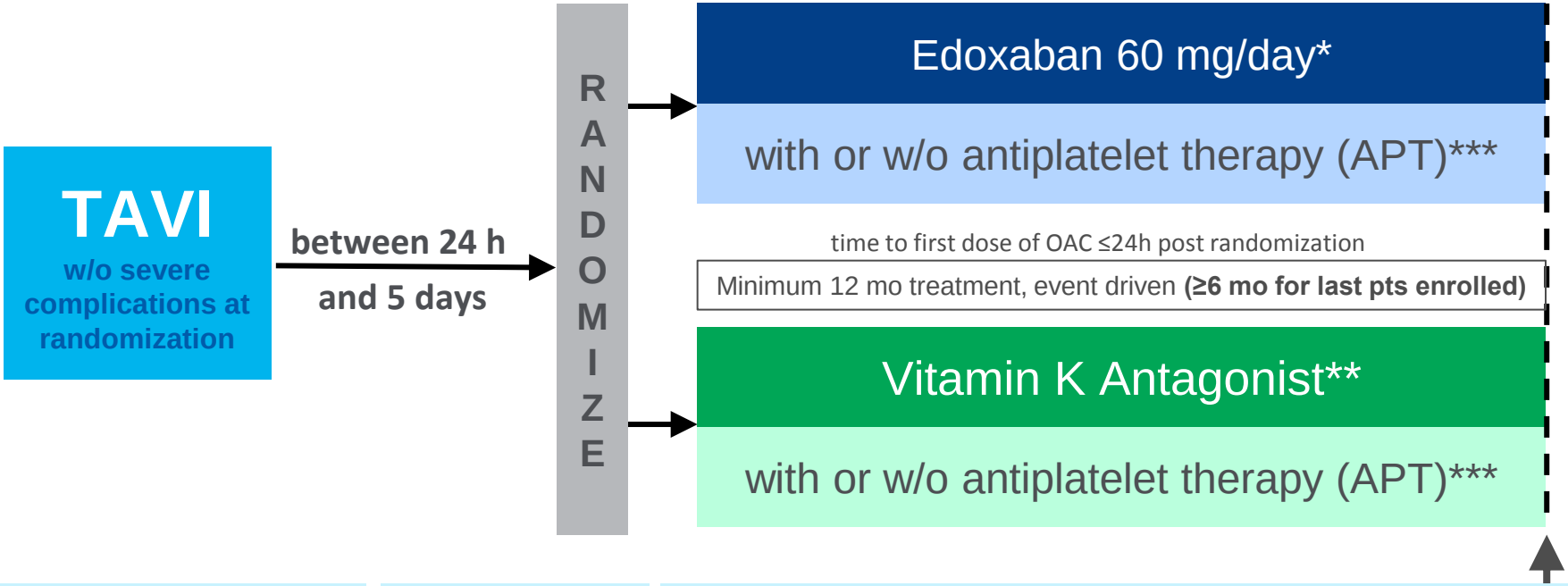
Catania, Italy

NCT02247128; Nijenhuis VJ, et al. Am Heart J. 2016;173:77-85

ENVISAGE-TAVI AF

Global PIs: G. Dangas, N. vanMieghem

PROBE design: prospective, randomized, open label, blinded evaluation Edoxaban based regimen vs VKA based regimen in N ≈1400 AF patients (≈ 2500 patient-years)



Edoxaban dose reduction to 30mg if

- **CrCL 15- ≤50 ml/min**
- **BW ≤60 kg***
- **P-gp inhibitors per local label***

***no dose reduction in US for AF**

** **VKA as approved in countries, target INR 2-3**

*** **Without other indication for APT: Either no APT or SAPT up to 3 months, i.e., ASA or a P2Y12 inhibitor (preferably clopidogrel).**

In PCI: SAPT, i.e., any P2Y12 inhibitor (preferably Clopidogrel) or ASA. DAPT is only allowed post stenting for 1 month after PCI.

With other potential indication for APT: Either no APT or SAPT, i.e., any P2Y12 inhibitor (preferably clopidogrel) or ASA indefinitely.

All APT needs predclaration by type, dose, & duration (projected last dose)

AF = atrial fibrillation; AP = antiplatelet, APT = antiplatelet therapy; ASA = aspirin; DAPT= dual antiplatelet therapy; Edo = edoxaban; h = hour; INR = international normalized ratio; mo = months, OAC=oral anticoagulant OD=once-daily; P-gp=P-glycoprotein; pts=patients; R=randomization, SAPT=single antiplatelet therapy; TAVI=transcatheter aortic valve implantation; VKA=vitamin K antagonist.

Current Landscape of Adjunctive Pharmacotherapy Clinical Trials for TAVR

	Patients with no indication for OAT	Patients with indication for OAT
Studies of antiplatelet strategies	ARTE	AVATAR
	POPular TAVI	POPular TAVI
	CLOE	CLOE
Studies comparing antiplatelet and anticoagulant strategies	AUREA	
	GALILEO	
	ATLANTIS	
Studies comparing anticoagulant strategies		ATLANTIS
		ENVISAGE-TAVI AF

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Capodanno D, Leon MB. EuroIntervention 2016;12:Y1-Y5

ARTE and AVATAR: Design and Status

	ARTE	AVATAR
Patients	200 pts with no indication for OAT	170 pts with indication for OAT
Experimental	ASA 80 mg/day (at least 6-mo) + Clopidogrel 75 mg/day (3-mo)	VKA (INR 2-3)
Control	ASA 80 mg/day (at least 6-mo)	VKA plus ASA 75-100 mg/day
Masking	Open label	Open label
Primary endpoint	Composite of death, MI, ischemic stroke/TIA or life threatening/major bleeding at 12 months	Composite of death from any cause, MI, stroke, valve thrombosis and hemorrhage ≥ 2 as defined by VARC 2
Status	**As of October 7, close to 200 patients have been randomized. Enrollment completed in Q4 2016**	**Enrollment begins in November 2016**

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NCT01559298; NCT02735902

2017 ACC/AHA guidelines for TAVR

IIb	B-NR	Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding (203,210,211).
IIb	C	Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.

Bonow R. et al. Circulation 2017

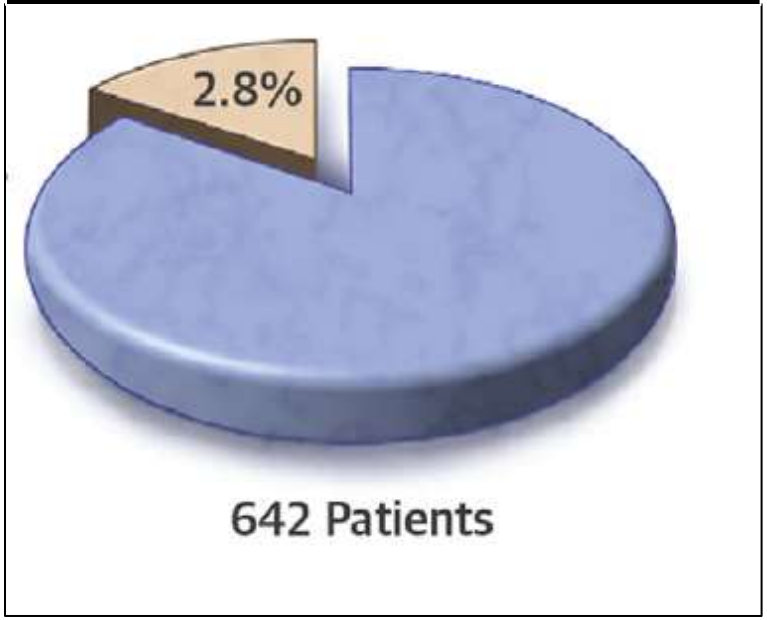
Clinical Bioprosthetic Heart Valve Thrombosis After Transcatheter Aortic Valve Replacement

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

- Balloon-expandable valves

- Valve-in-valve TAVR

- Use of antiplatelet therapy alone

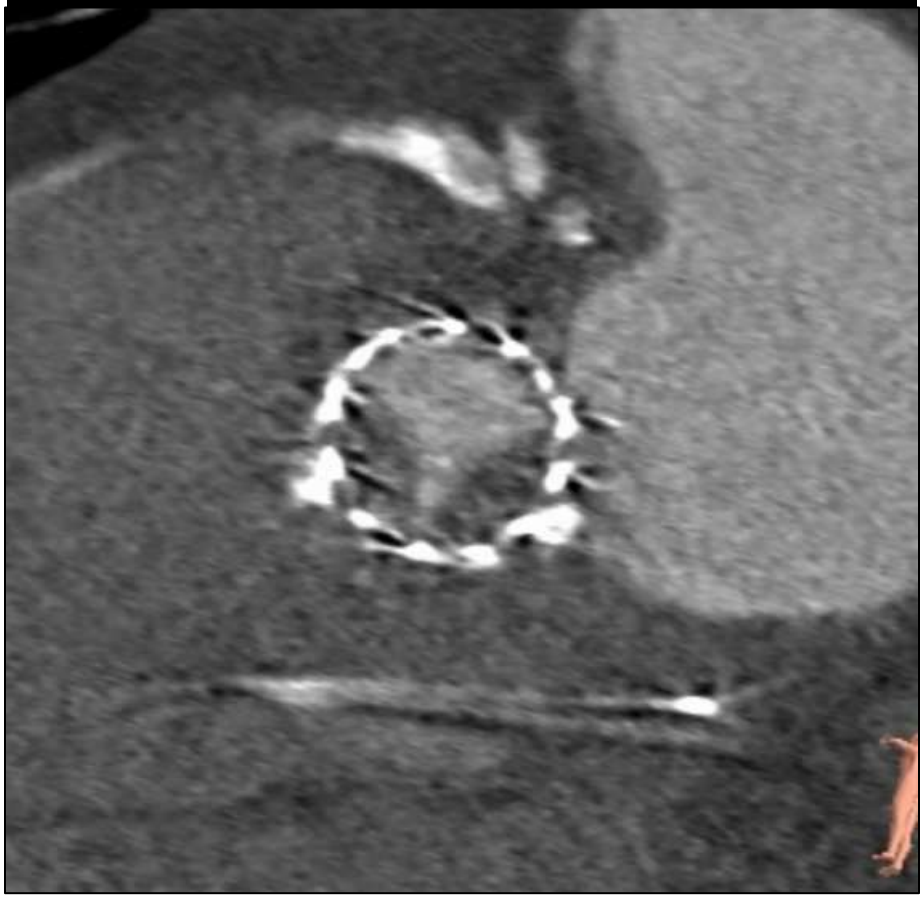
Jose et al. JACC: Cardiovascular Interventions 2017

94 y/o male s/p 29mm Sapien 3 valve

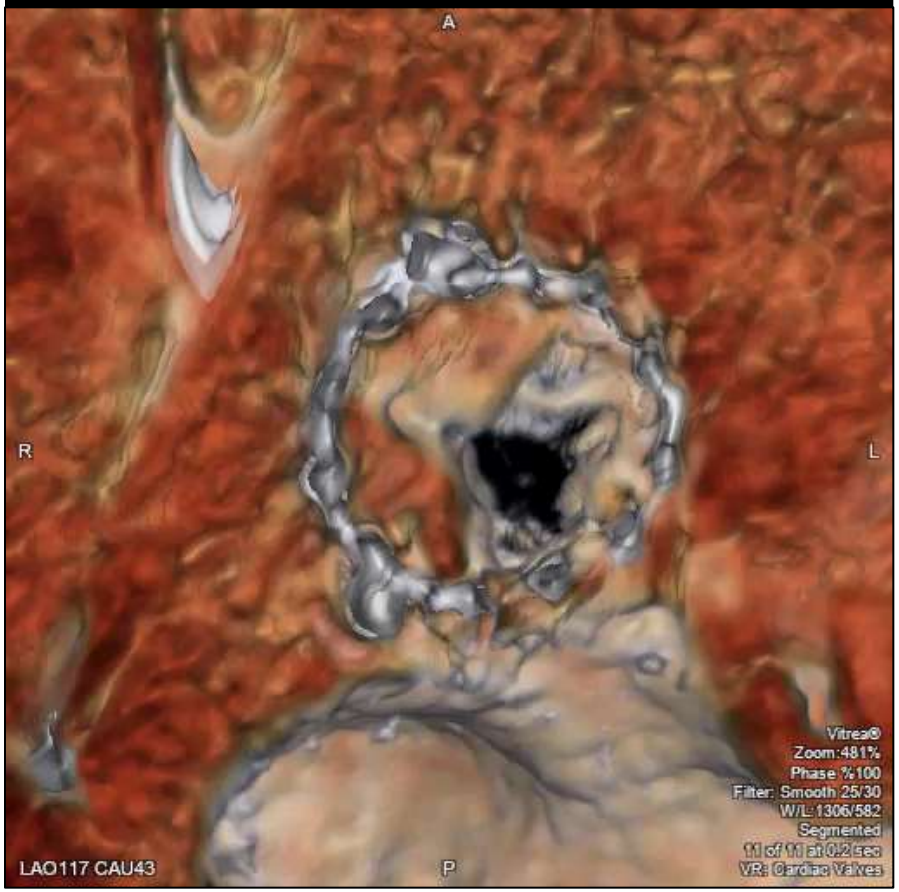
Experiencing recurrent strokes and thromboemboli

Cardiac CT performed to rule out valve thrombus

Hypoattenuating lesions



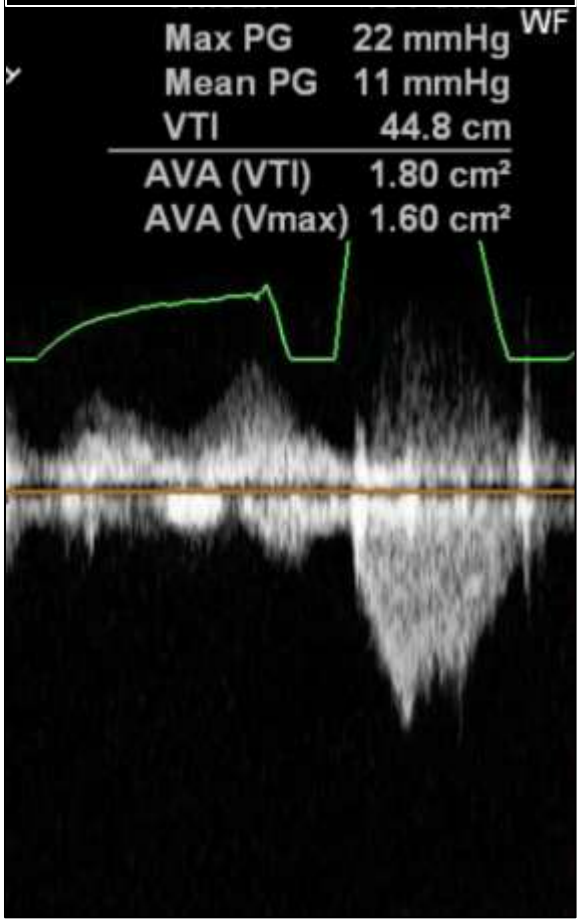
Severely restricted leaflet motion



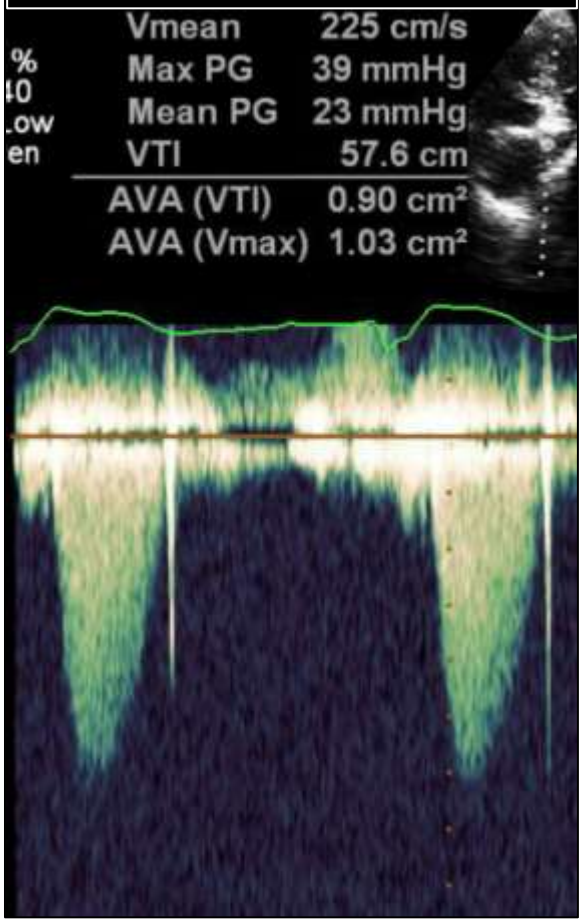
TTE revealed rise in gradients

Patient started on rivaroxaban 10mg daily, repeat CT pending

Day 1 post-TAVR
Mean gradient 11mmHg



30-day post-TAVR
Mean gradient 23mmHg



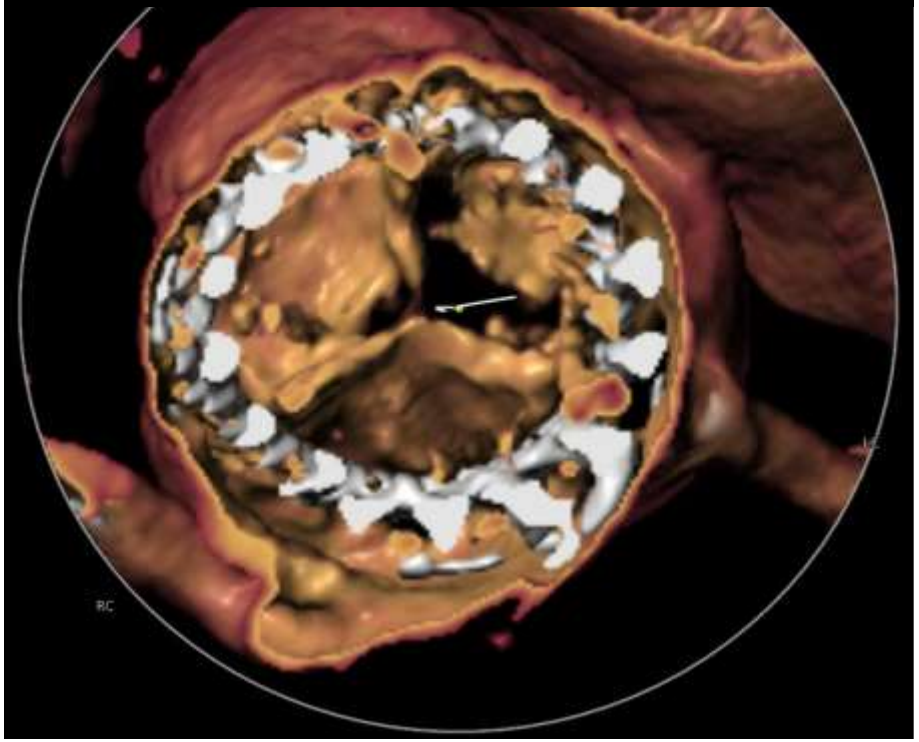
83 y/o female s/p TAVR with 26mm Evolut valve

Patient enrolled in RESOLVE registry

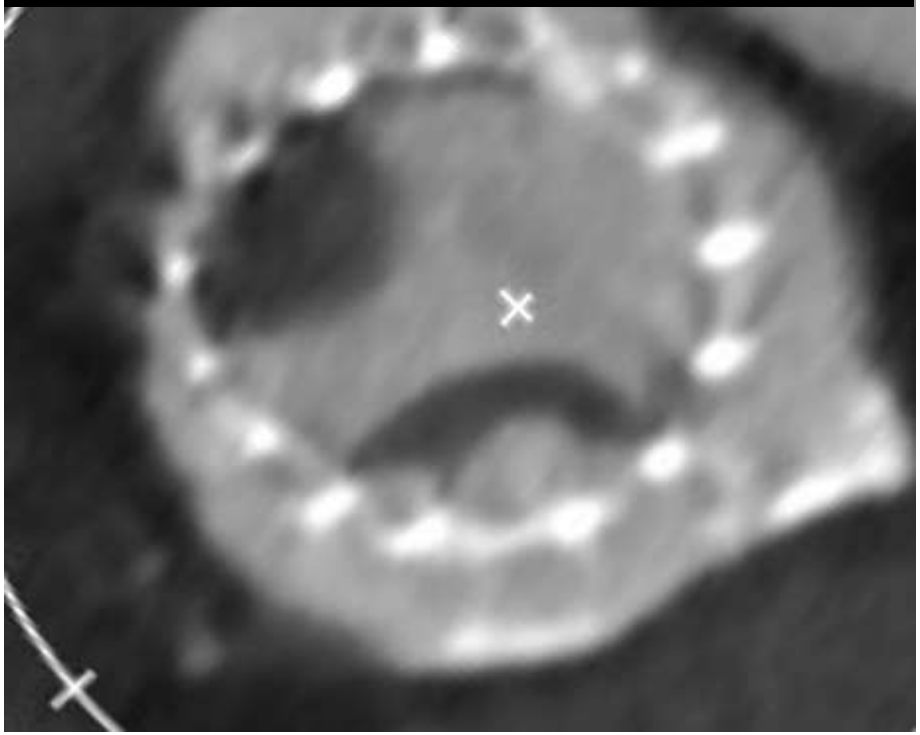
Cardiac CT performed at 1 month post-TAVR

Patient already on warfarin, INR 2.5

Severely reduced leaflet motion

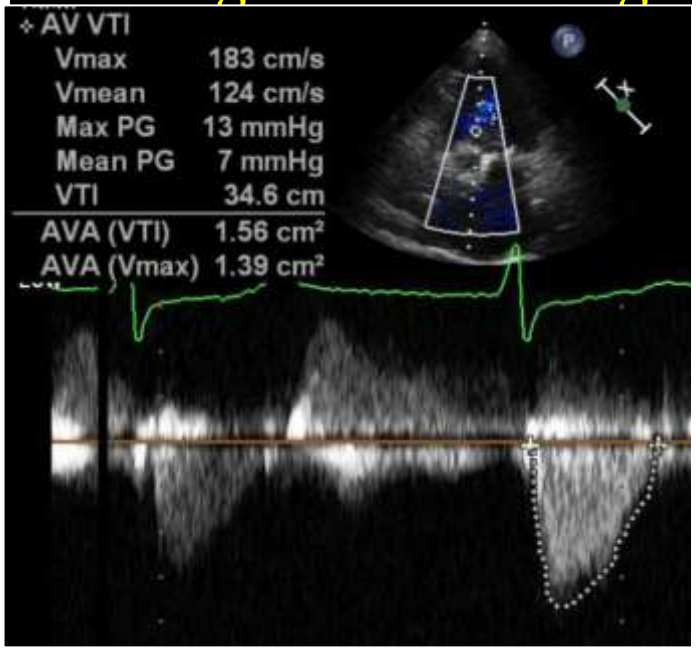


Hypoattenuating lesions

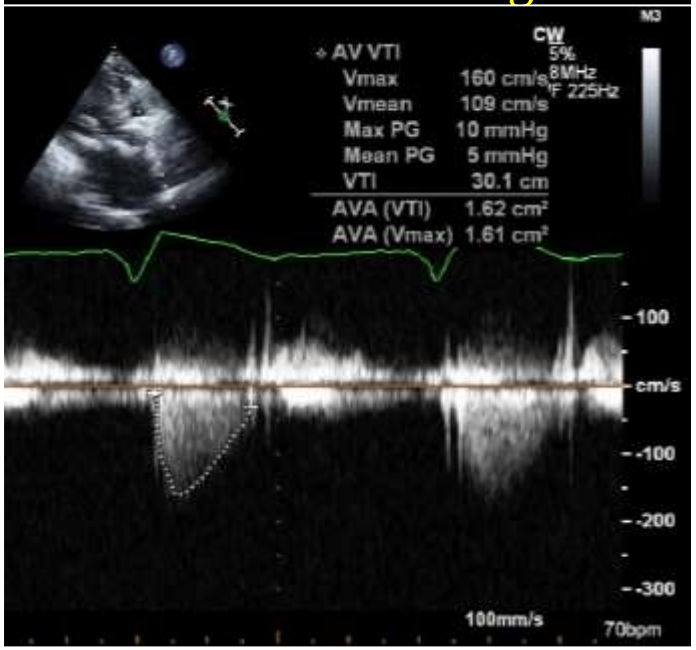


Normal valve gradients despite reduced leaflet motion

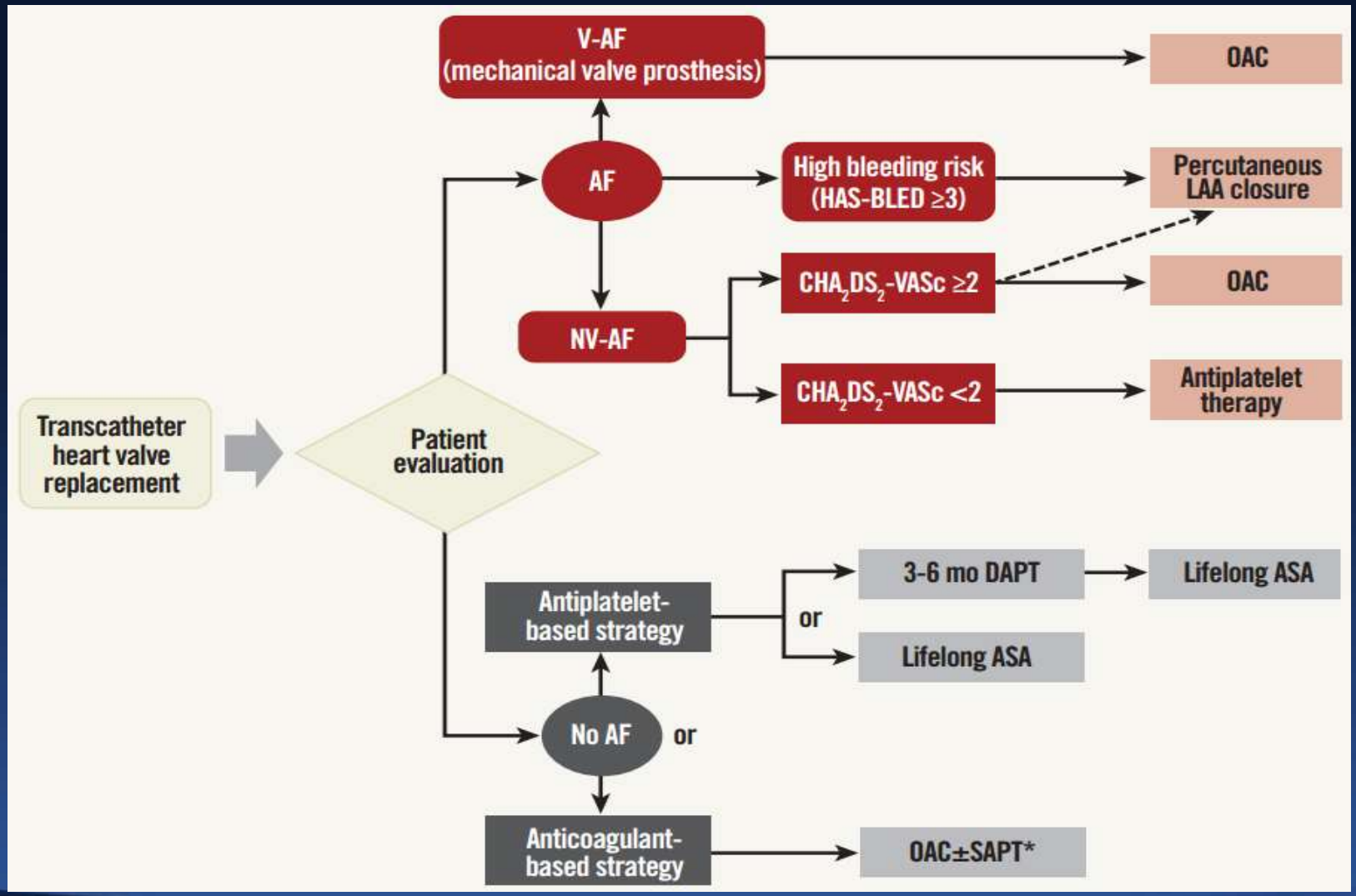
Day 1 TTE
Mean gradient 7mmHg



1 month TTE
Gradient 5mmHg



Strategies to prevent thrombo-embolic complications <u>after</u> TAVR



Mount Sinai Heart

Giustino & Dangas. Eurointervention 2015; 11 Suppl W:W26-31

Final Thoughts..

- There are no definite guidelines for antithrombotic treatment after TAVR.. There are significant variations in practice
- Anticoagulation is more effective than antiplatelet agents in preventing and treating valve thrombosis-imaging studies suggest NOACs may be as effective as VKA.
- Limited data suggest that mono antiplatelet therapy may be as effective as DAPT with less risk of bleeding
- Use of bivalirudin compared to heparin during TAVR offers no clinical advantage. Heparin is the standard of care..offers convenience of reversal at the end of the procedure
- Large studies are ongoing and will guide the most optimal therapy in the near future
- In the interim use of 3-6 month anticoagulation with VKA or NOACs in patients who are at low risk of bleeding may be reasonable
- For patients who have subclinical or clinical thrombosis 3 month therapy may not be adequate…