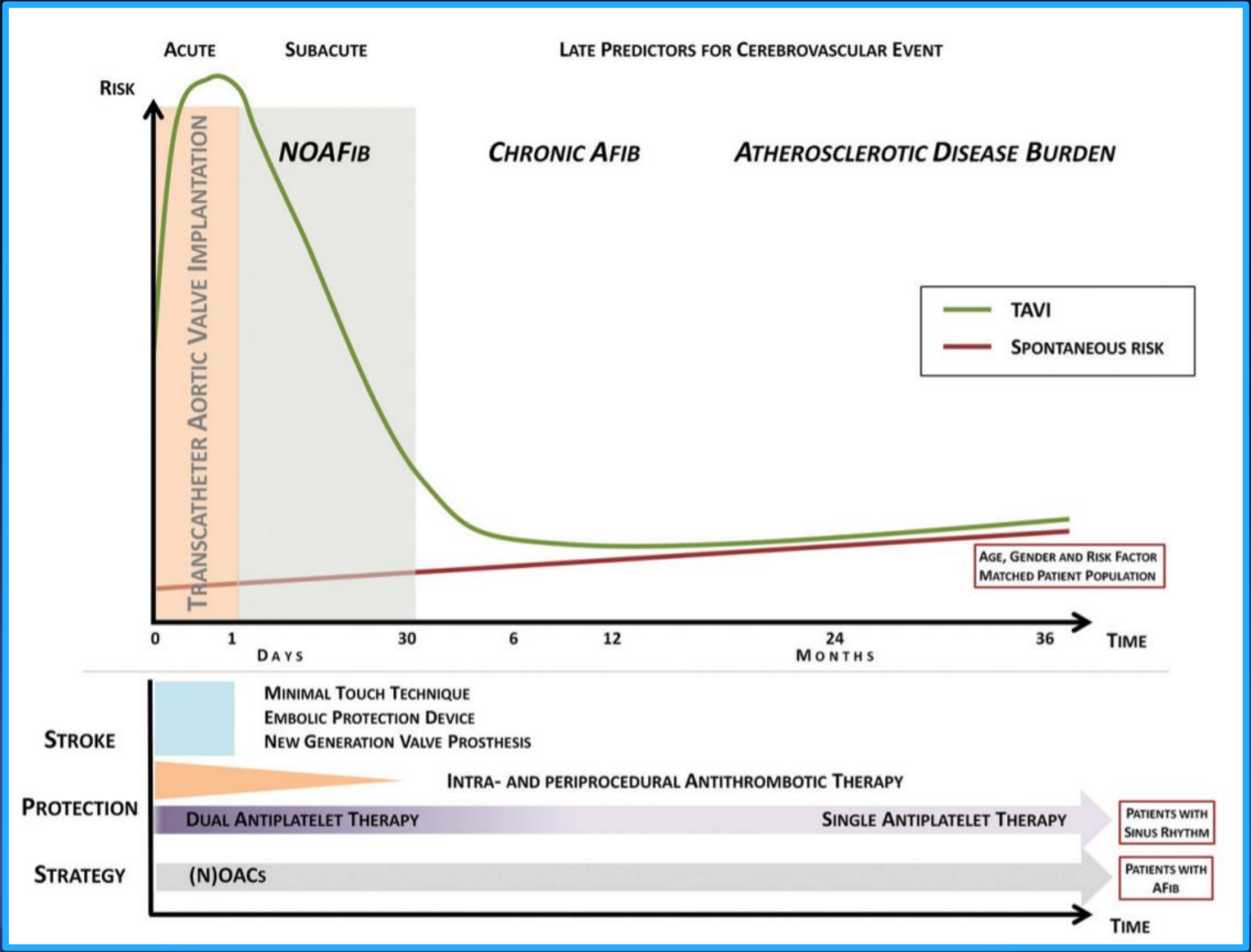
OAC in TAVR: Failed Galileo
NOAC Don't Work or Other Options?

Jung-Min Ahn, MD

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

Timing of CVA After TAVR



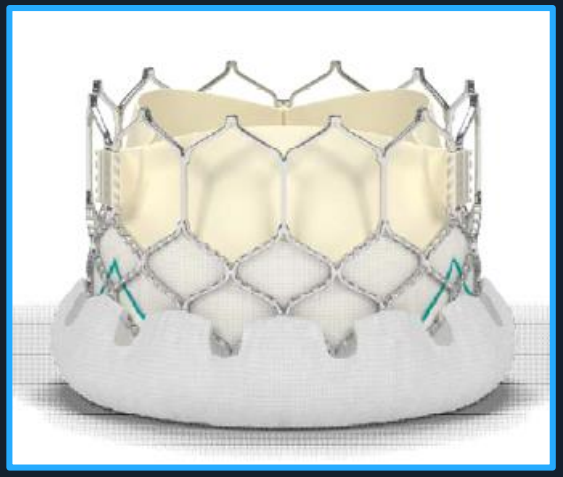
Stortecky et al. Circulation 2012;126:2921-4

Antithrombotic Guidelines After TAVR

Guidelines	Recommendations	Class-LOE
ACC/AHA 2017	***Patients without underlying indication for chronic OAC***	
	Anticoagulation with a VKA to achieve an international normalized ratio of 2.5 may be reasonable in patients at low risk of bleeding for at least 3 months.	IIb – B NR
	Clopidogrel 75 mg the first 6 months after TAVR may be reasonable in addition to lifelong aspirin 75-100 mg daily.	IIb – C
	Patients with underlying indication for chronic OAC	
	No specific recommendation.	
ESC/EACTS 2017	***Patients without underlying indication for chronic OAC***	
	DAPT should be considered for the first 3-6 months after TAVR, followed by lifelong SAPT in patients who do not need OAC for other reasons.	IIa – C
	SAPT may be considered after TAVR in the case of high bleeding risk.	IIb - C
	Patients with underlying indication for chronic OAC	
	Despite the lack of evidence, a combination of VKA and aspirin or thienopyridine is generally used but should be weighed against increased risk of bleeding.	Expert consensus

Why DAPT Post-TAVR?

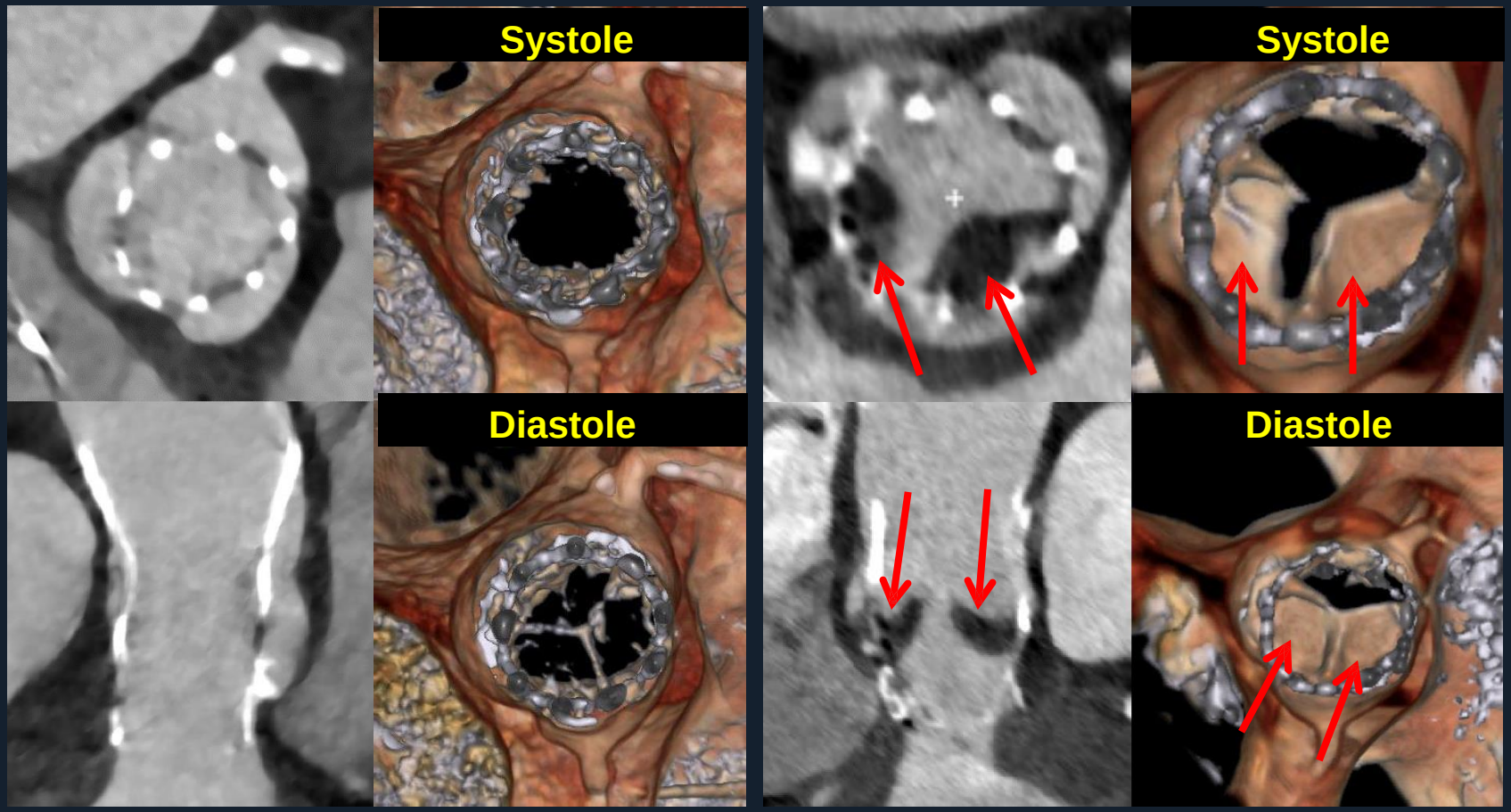
- Decision based on Consensus
  "It's like a stent" treat like
  Coronary or Peripheral stent



- Protocol of RCT

  PARTNER I: *DAPT* for 6 months
  PARTNER II: *Aspirin* indefinitely
  Clopidogrel at least 1 month
  PARTNER III: *DAPT* at least 1 month
  Evolut R low risk trial: *DAPT* at least 1 months
  followed by *aspirin* through 1 year

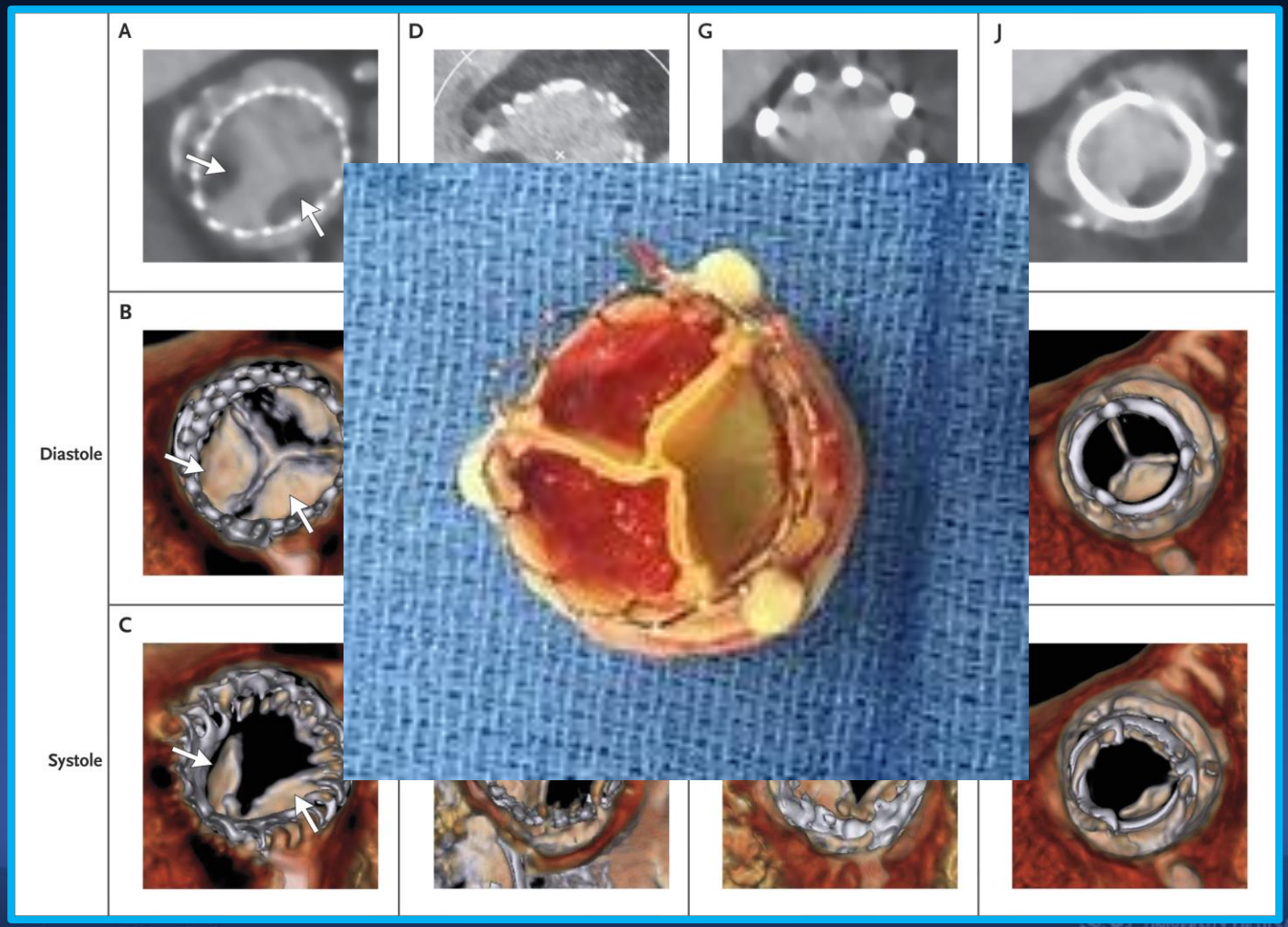
Valve Thrombosis



Makkar RR et al. N Engl J Med 2015;373:2015-2024

Subclinical Leaflet Thrombosis

Evidence of Reduced Leaflet Motion in Multiple Prosthesis Types



Makkar RR et al. N Engl J Med 2015;373:2015-2024

Subclinical leaflet thrombosis

Potential clinical consequences:

- Progression to clinical valve thrombosis
- Stroke
- Impaired hemodynamic performance
- Reduced durability of bioprosthetic aortic valves

…or Just an innocent bystander?

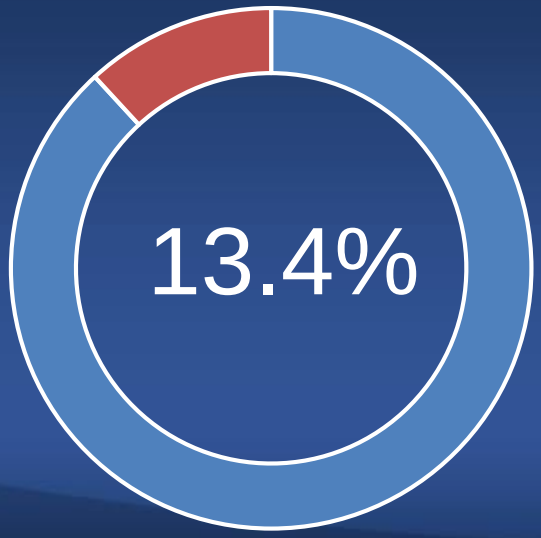
Prevalence of reduced leaflet motion

657 patients underwent CTs in the **RESOLVE registry** Cedars-Sinai Medical Center, LA

274 patients underwent CTs in the **SAVORY registry** Rigshospitalet, Copenhagen

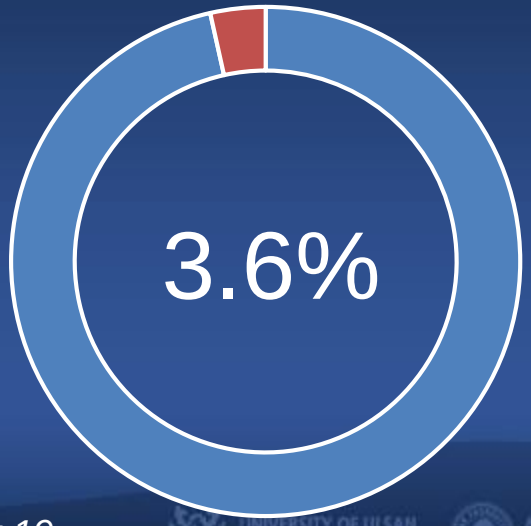
Reduced leaflet motion 106 (11.9%) patients

TAVR (N=752)



P=0.001

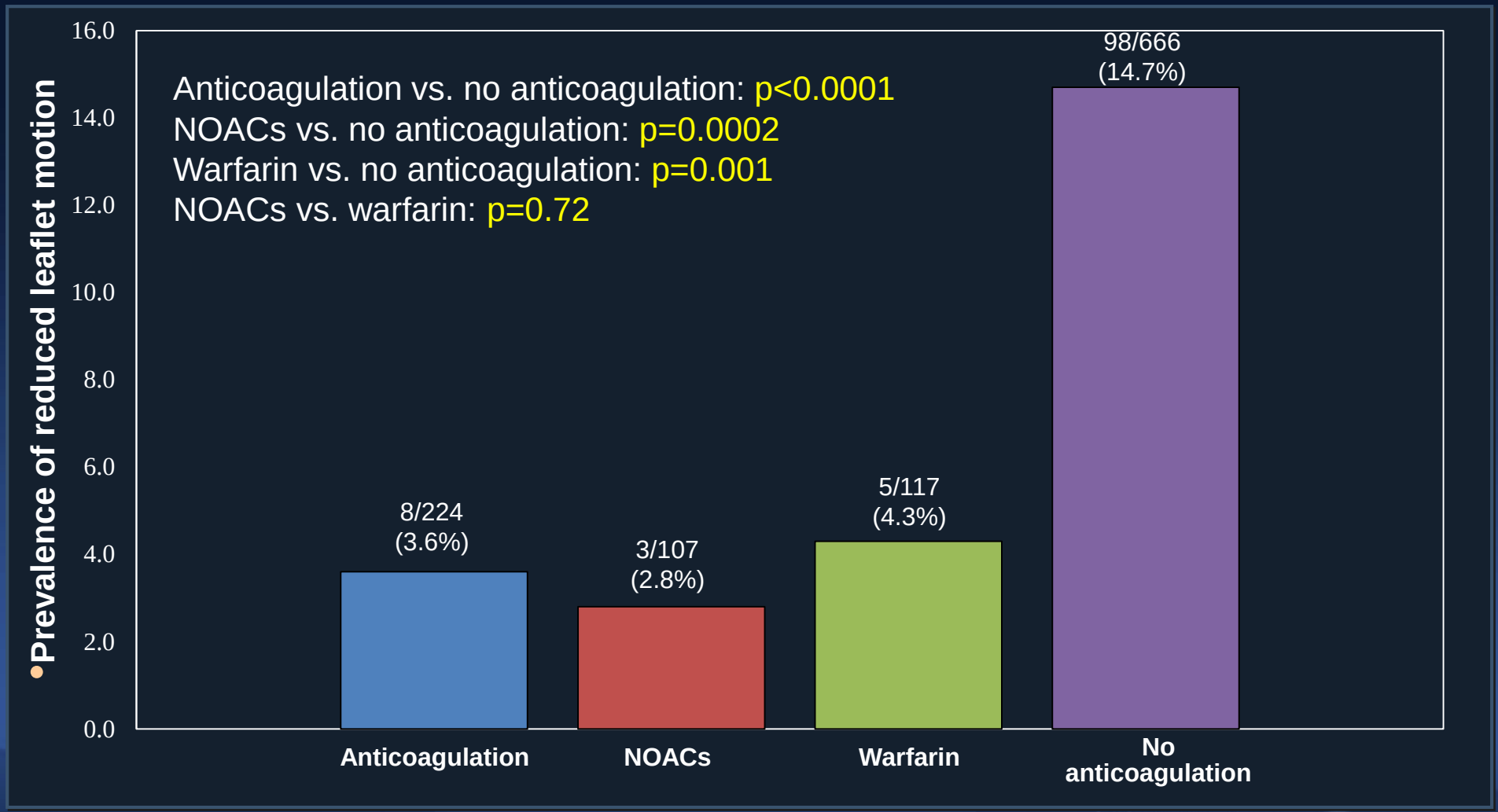
SAVR (N=138)



Chakravarty T, et al. Lancet. 2017 Mar 19.

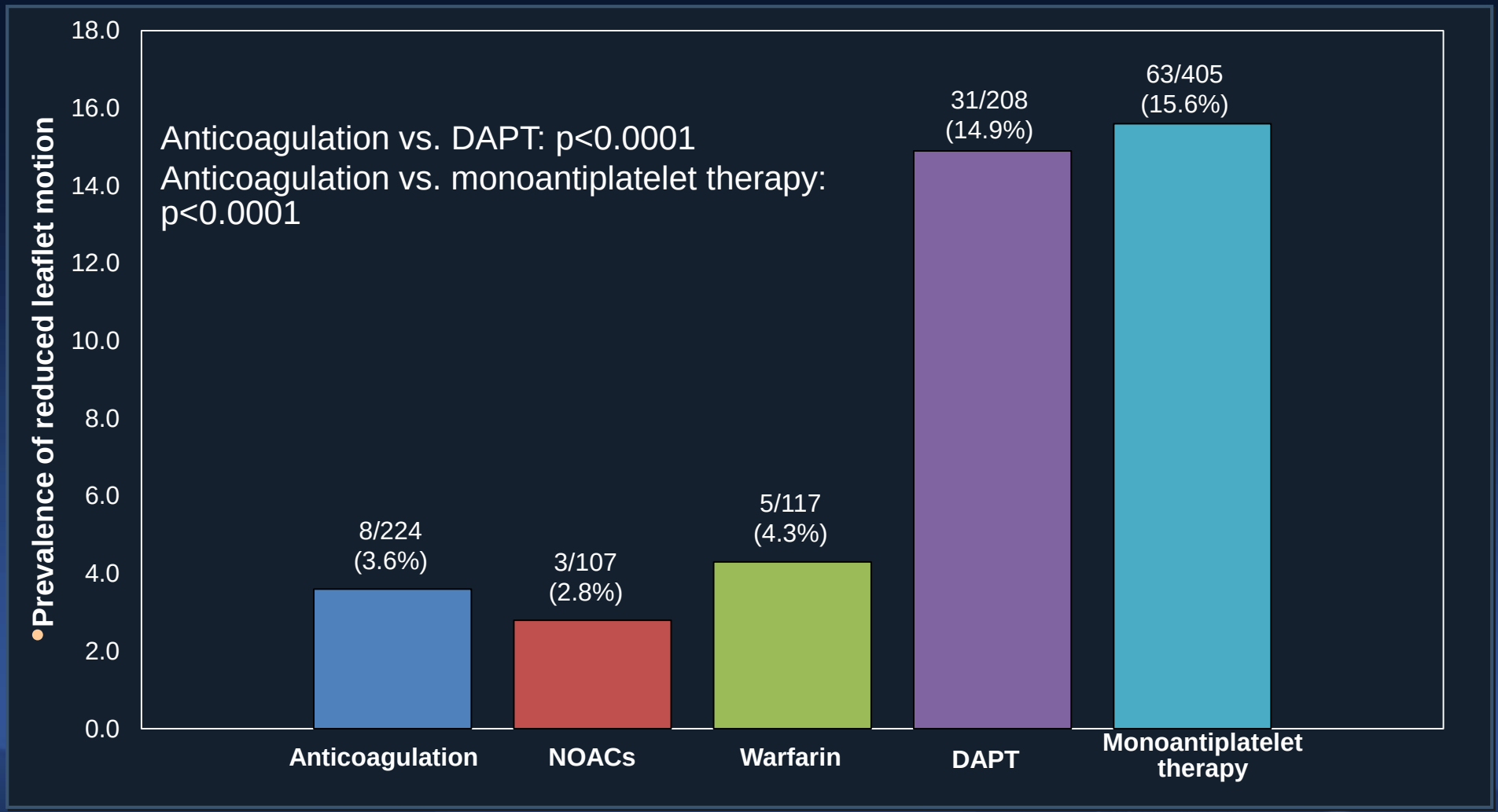
Anticoagulation and reduced leaflet motion

Anticoagulation vs. no anticoagulation



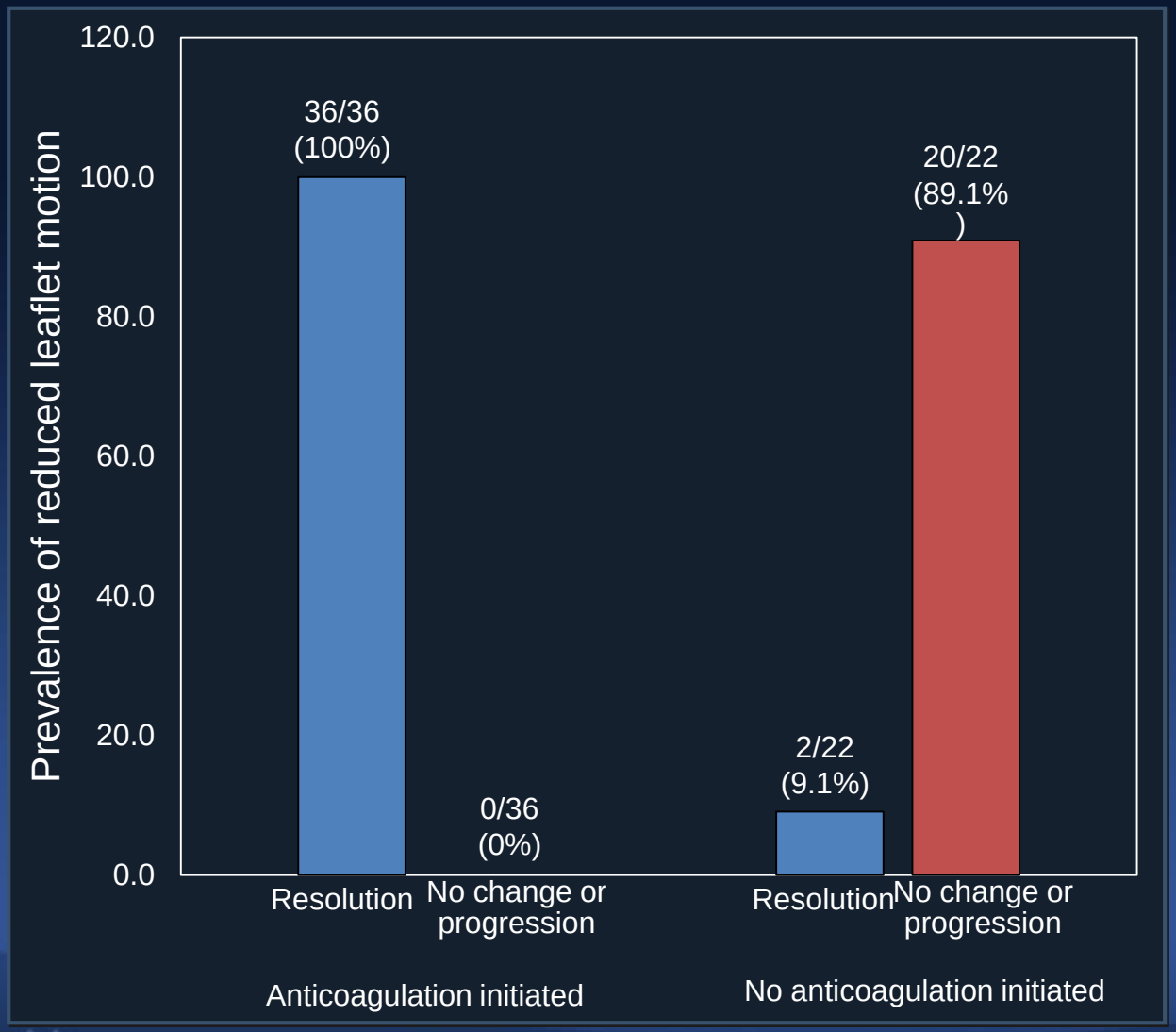
Chakravarty T, et al. Lancet. 2017 Mar 19.

Anticoagulation and reduced leaflet motion
Anticoagulation vs. antiplatelet therapy



Chakravarty T, et al. Lancet. 2017 Mar 19.

Impact of initiation of anticoagulation on reduced leaflet motion

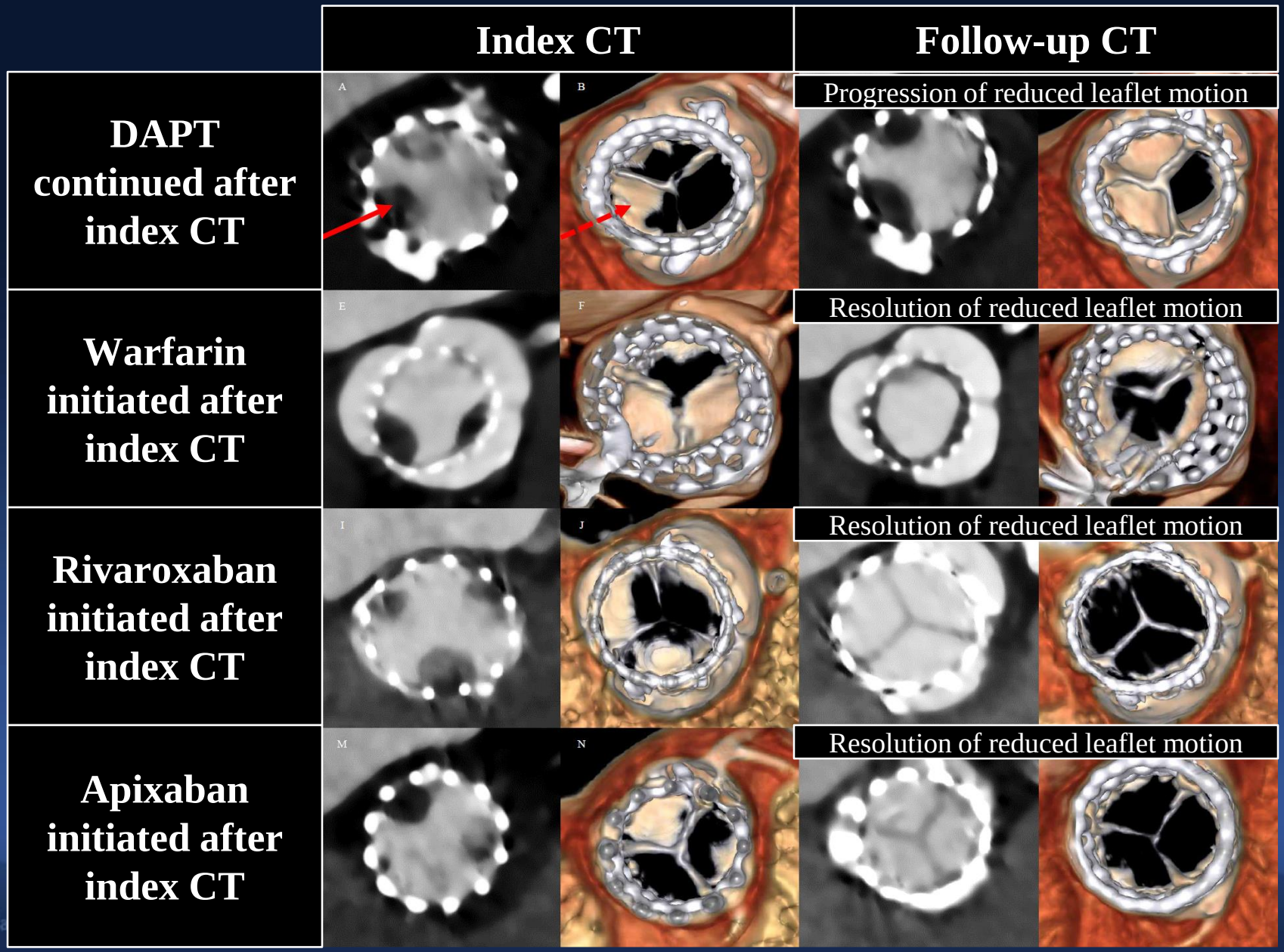


- Resolution in 36 out of 36 patients treated with anticoagulation (NOACs, n=12; warfarin, n=24)
- Persistence/progression in 20 out of 22 patients not treated with anticoagulation

P<0.0001

Chakravarty T, et al. Lancet. 2017 Mar 19.

Anticoagulation vs. DAPT



Clinical Impact of Leaflet Thrombosis

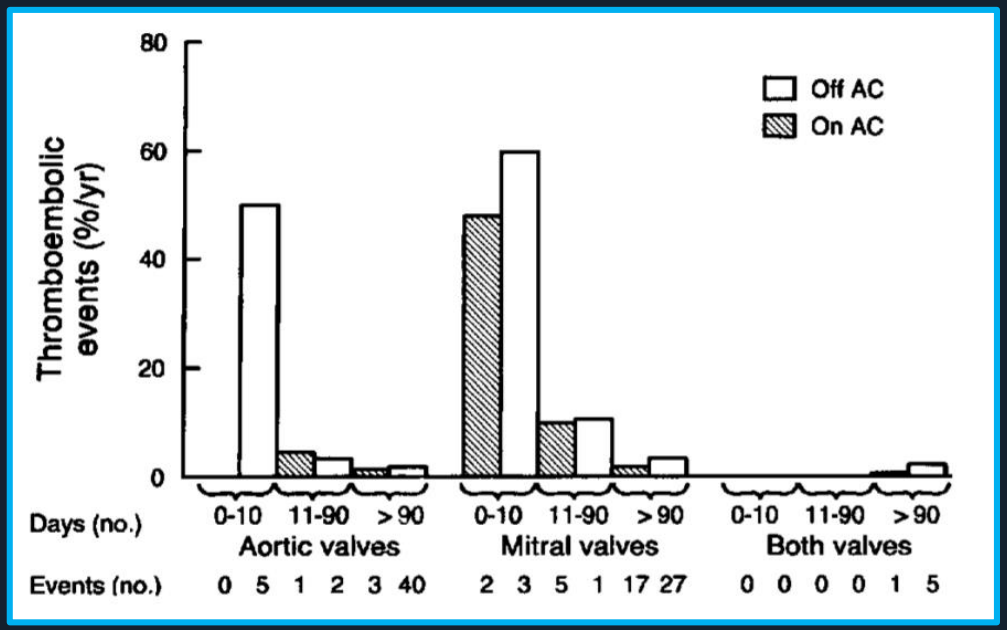
Only non-procedural events (>72 hours post-TAVR/SAVR) included

Non-procedural events	Normal leaflet motion (N=784) n/N (%)	Normal leaflet motion (N=784) Rate per 100 person-years	Reduced leaflet motion (N=106) n/N (%)	Reduced leaflet motion (N=106) Rate per 100 person-years	HR (95% CI)	P
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	20/784 (2·6%)	1·75	8/106 (7·6%)	5·71	3·30 (1·45-7·50)	0·004
All strokes*	15/784 (1·9%)	1·31	4/106 (3·8%)	2·75	2·14 (0·71-6·44)	0·18
Ischemic strokes	14/784 (1·8%)	1·22	4/106 (3·8%)	2·75	2·29 (0·75-6·97)	0·14
TIAs	7/784 (0·9%)	0·60	5/106 (4·7%)	3·48	5·89 (1·87-18·60)	0·002

Chakravarty T, et al. Lancet. 2017 Mar 19.

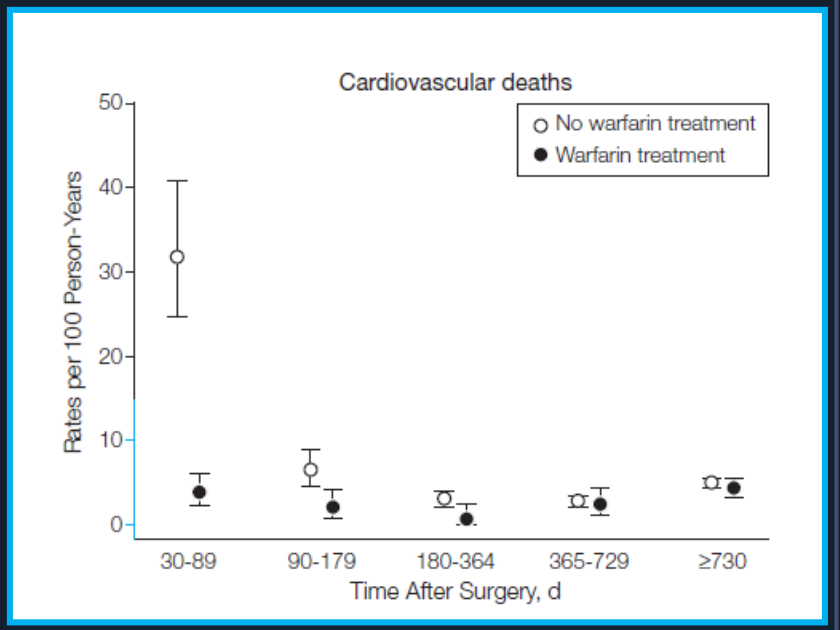
Experience of Bioprosthetic Surgical Valve

Incidence of Thrombotic Events



J Am Coll Cardio11995;25:1111-9

Effect of Warfarin



Merie C. et al. JAMA 2012

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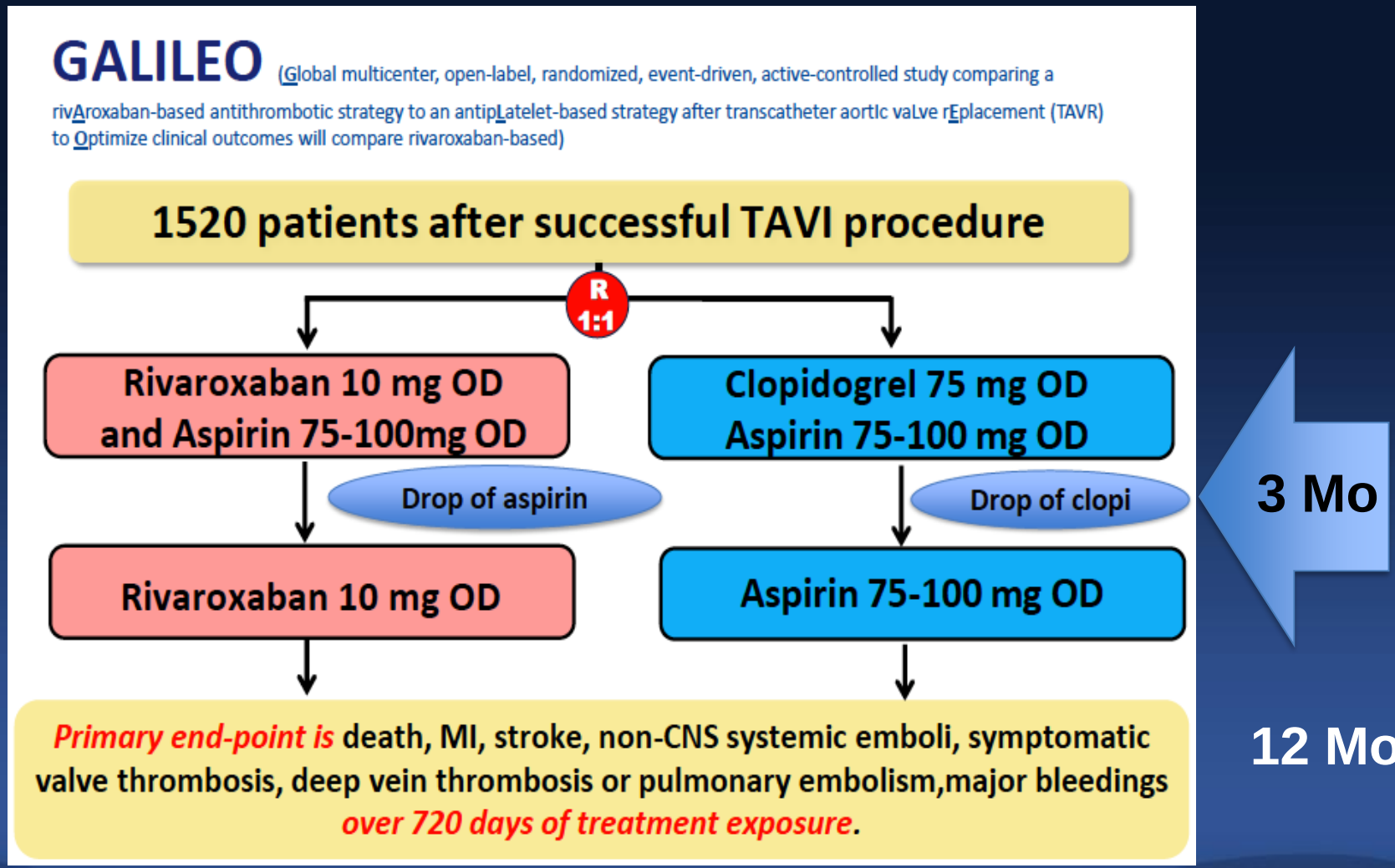
Current Landscape of Adjunctive Pharmacotherapy Clinical Trials for TAVR

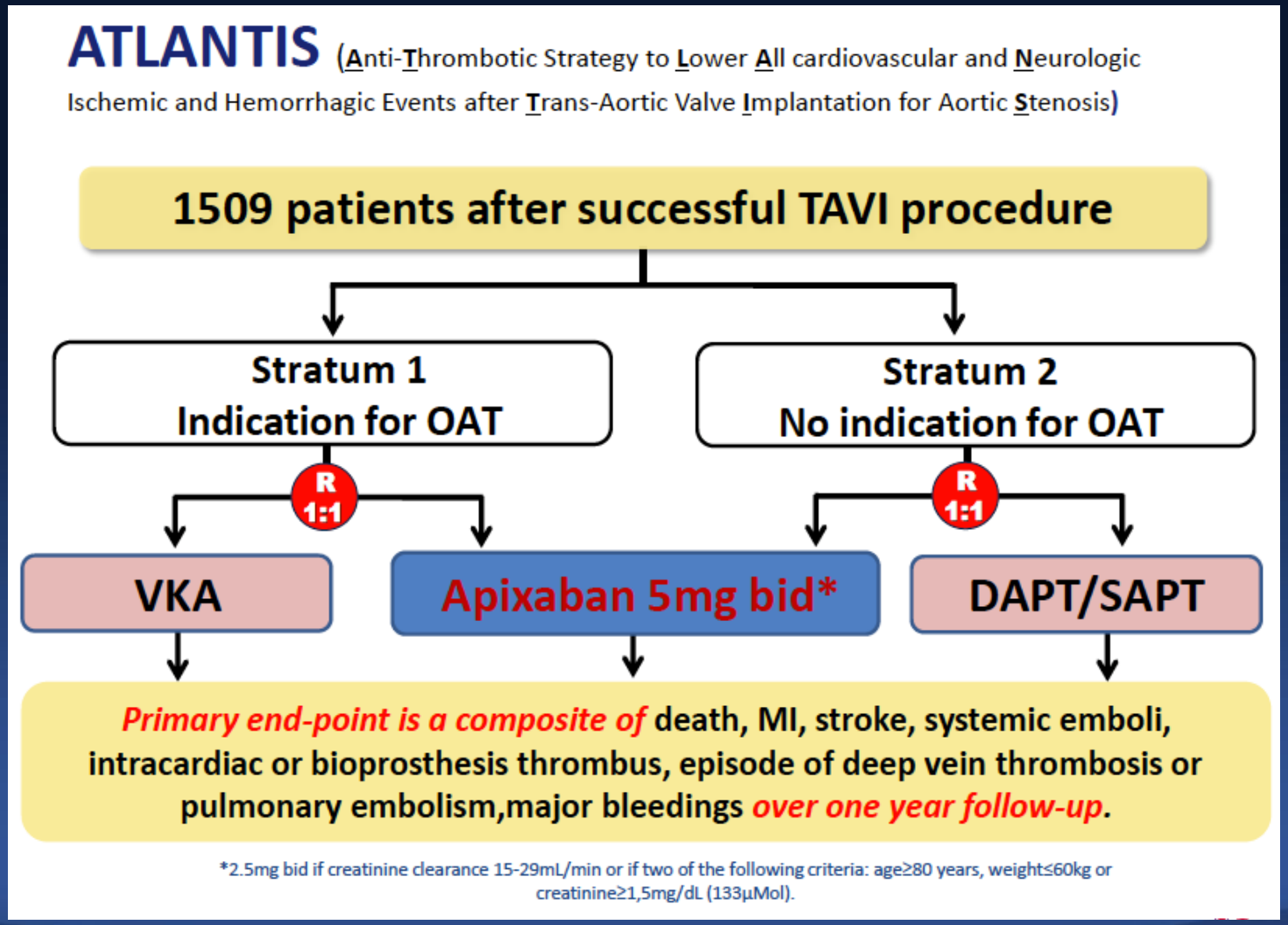
	Patients with no indication for OAT	Patients with indication for OAT
Studies of antiplatelet strategies	ARTE	AVATAR
	POPular TAVI	POPular TAVI
	CLOE	CLOE
Studies comparing antiplatelet and anticoagulant strategies	AUREA	
	GALILEO (Rivaroxaban)	
	ATLANTIS (Apixaban)	
	ADAPT-TAVR (Endoxaban)	
Studies comparing anticoagulant strategies		ATLANTIS (Apixaban)
		ENVISAGE-TAVI AF (Endoxaban)

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

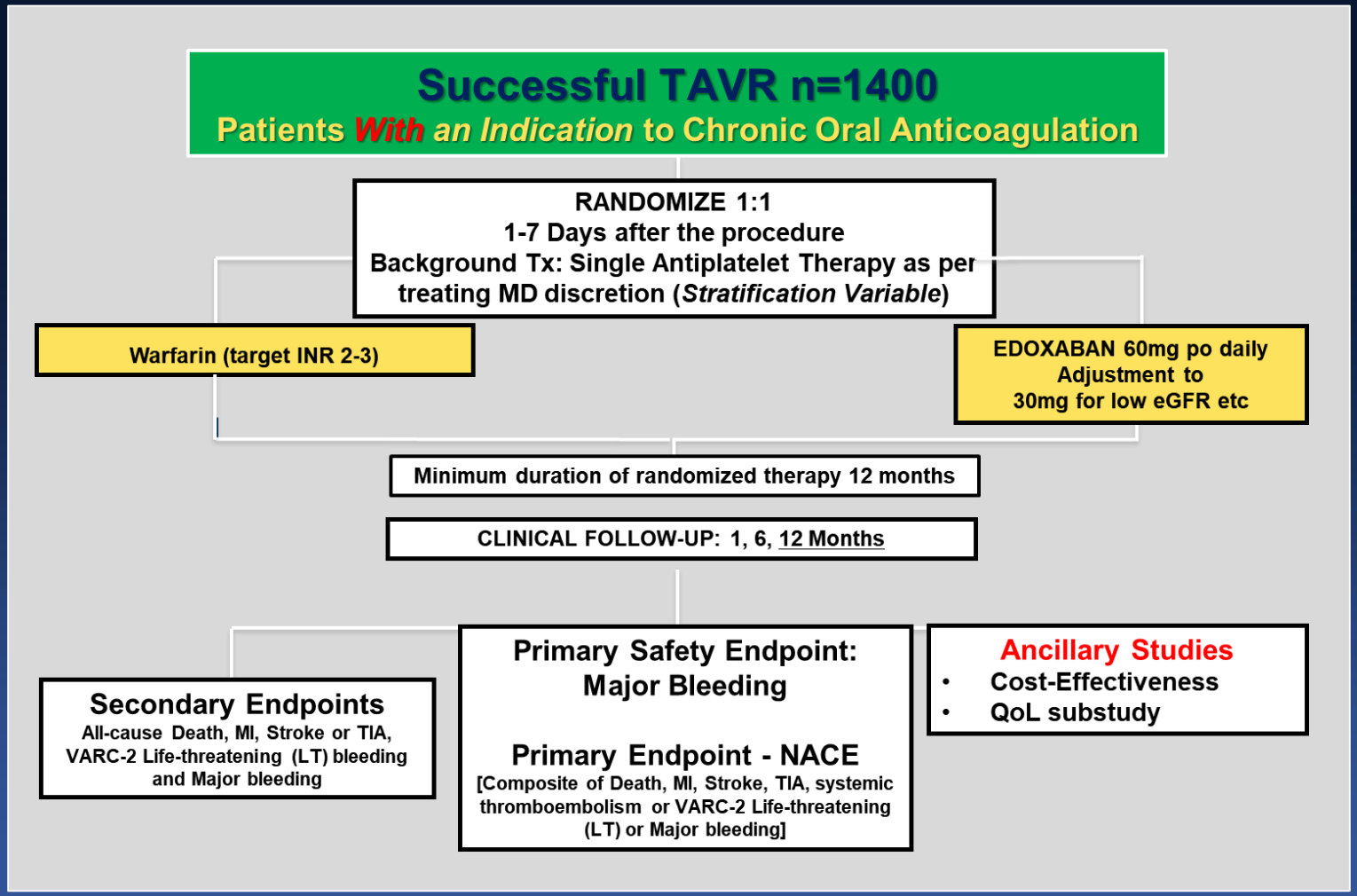
GALILEO Trial



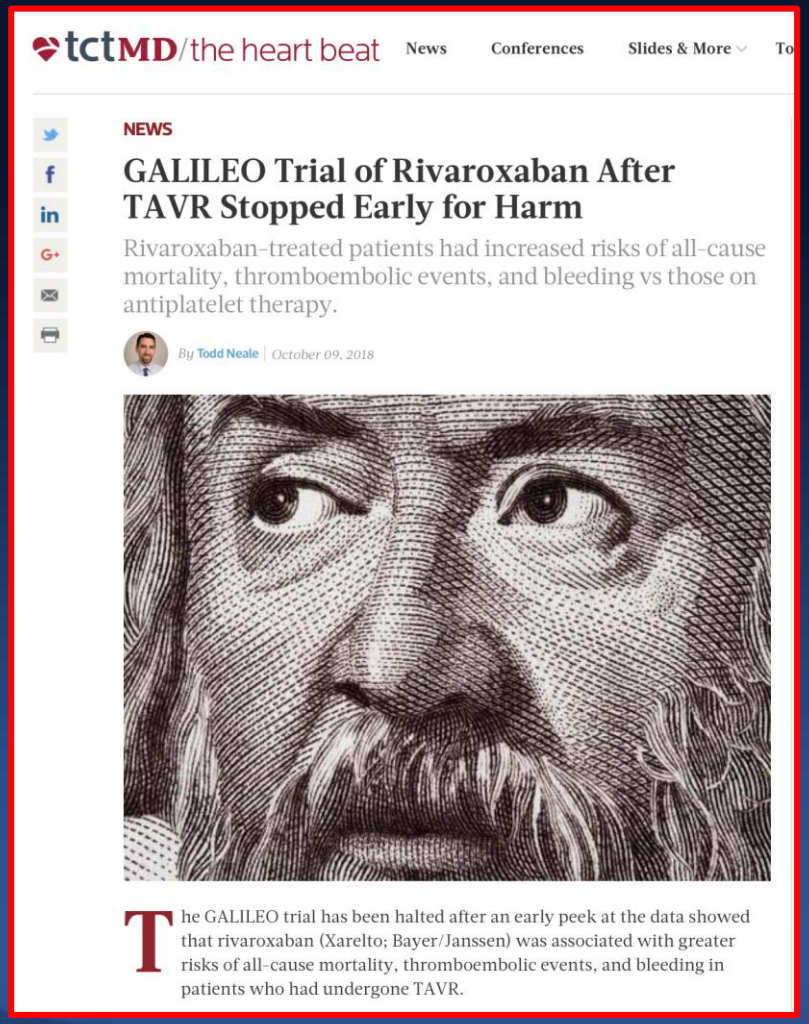
ATLANTIS


ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)
1509 patients after successful TAVI procedure
Stratum 1
Indication for OAT
Stratum 2
No indication for OAT
R 1:1
R 1:1
VKA
Apixaban 5mg bid*
DAPT/SAPT
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).

ENVISAGE


Successful TAVR n=1400
Patients With an Indication to Chronic Oral Anticoagulation
RANDOMIZE 1:1
1-7 Days after the procedure
Background Tx: Single Antiplatelet Therapy as per treating MD discretion (Stratification Variable)
Warfarin (target INR 2-3)
EDOXABAN 60mg po daily
Adjustment to
30mg for low eGFR etc
Minimum duration of randomized therapy 12 months
CLINICAL FOLLOW-UP: 1, 6, 12 Months
Secondary Endpoints
All-cause Death, MI, Stroke or TIA, VARC-2 Life-threatening (LT) bleeding and Major bleeding
Primary Safety Endpoint:
Major Bleeding
Primary Endpoint - NACE
[Composite of Death, MI, Stroke, TIA, systemic thromboembolism or VARC-2 Life-threatening (LT) or Major bleeding]
Ancillary Studies
• Cost-Effectiveness
• QoL substudy

GALILEO Failed, Oct 2018



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NEWS

GALILEO Trial of Rivaroxaban After TAVR Stopped Early for Harm

Rivaroxaban-treated patients had increased risks of all-cause mortality, thromboembolic events, and bleeding vs those on antiplatelet therapy.

By Todd Neale | October 09, 2018

The GALILEO trial has been halted after an early peek at the data showed that rivaroxaban (Xarelto; Bayer/Janssen) was associated with greater risks of all-cause mortality, thromboembolic events, and bleeding in patients who had undergone TAVR.

	Rivaroxaban	Antiplatelet
First thromboembolic events	11.4%	8.8%
Death	6.8%	3.3%
Primary bleeding	4.2%	2.4%

Final results of the study are expected in the first quarter of 2019 (?) – tctMD

Why Failed, NOAC Don't Work ?

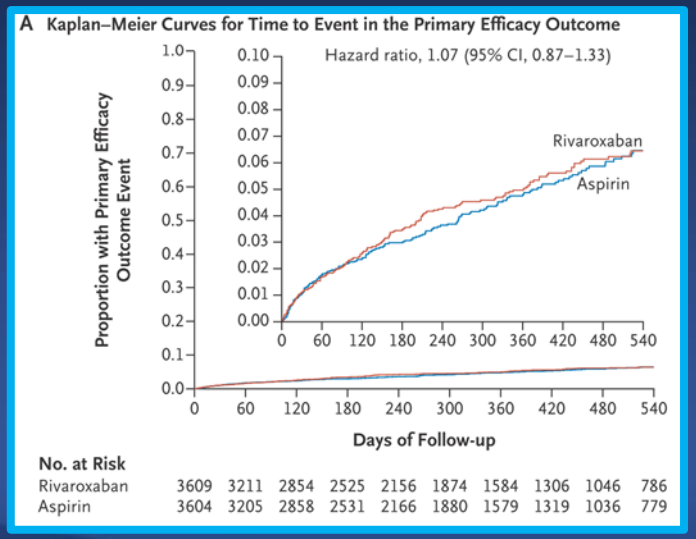
- Study Drug:
  Rivaroxaban
- Study Design
  The combination of aspirin in early period
- The Complex Ischemic & Bleeding Leverage In Elderly TAVR Patients with Considerable Surgical Risk

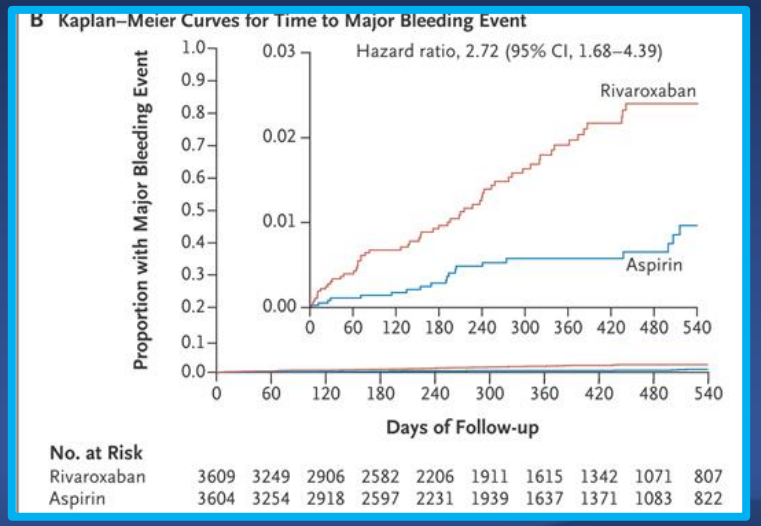
Rivaroxaban ?

NAVIGATE ESUS trial

- Stroke prevention after embolic stroke of undetermined cause
- Rivaroxaban 15mg vs aspirin

Bleeding





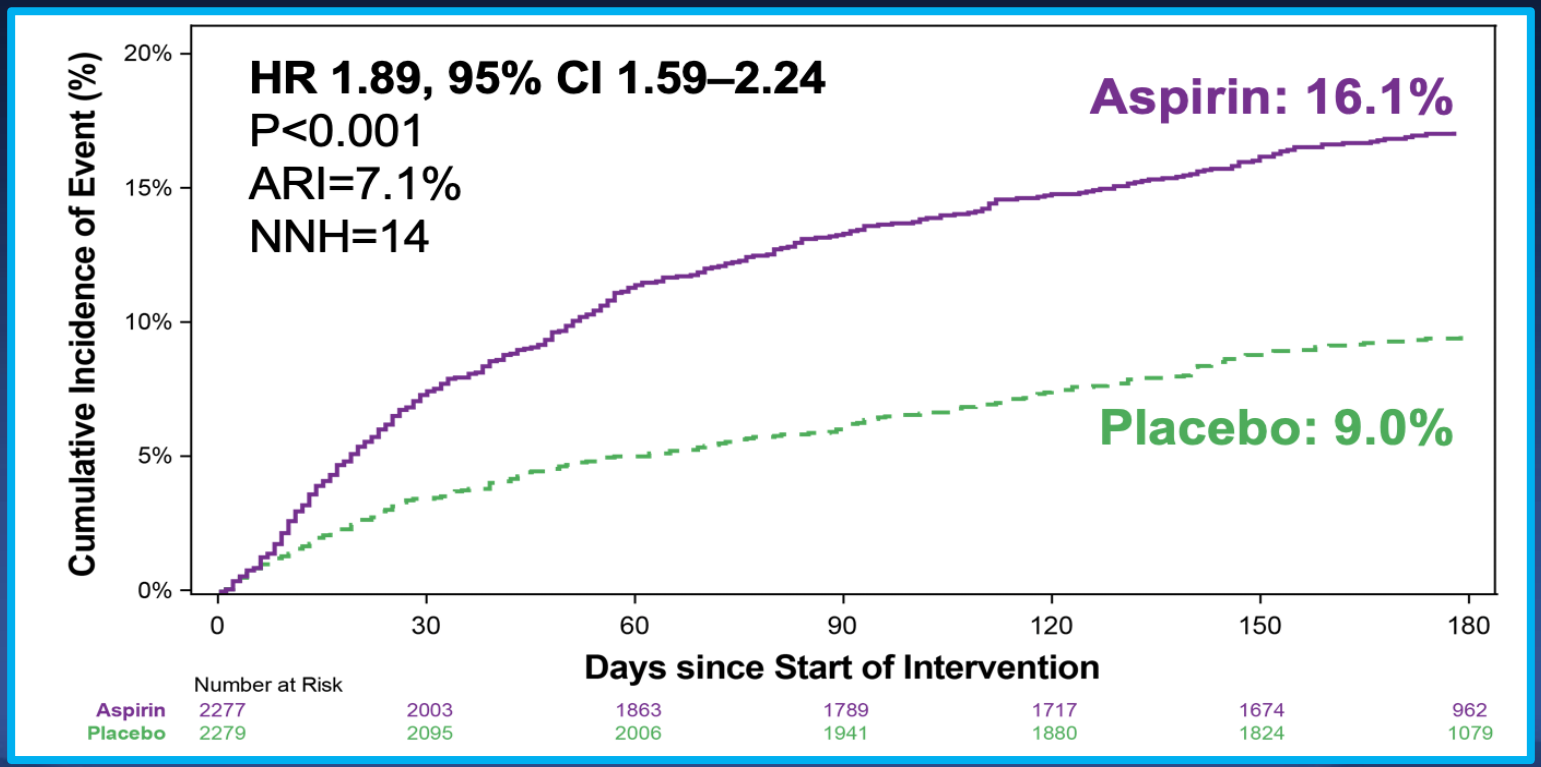
N Engl J Med 2018; 378:2191-2201

The Combination with Aspirin ?

AUGUSTUS Trial:

Antithrombotic therapy in PCI with A.fib

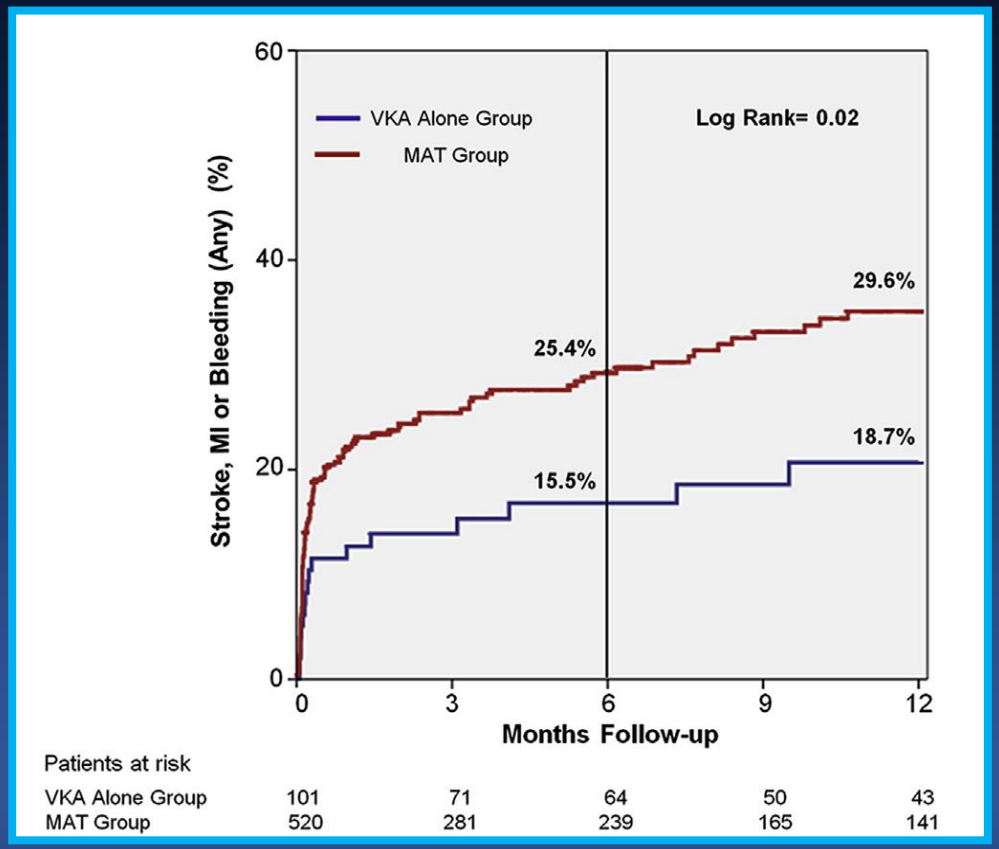
Bleeding



N Engl J Med 2019, March 7.

The Combination with Aspirin ?

A multicenter evaluation comprising 621 patients with AF undergoing TAVR

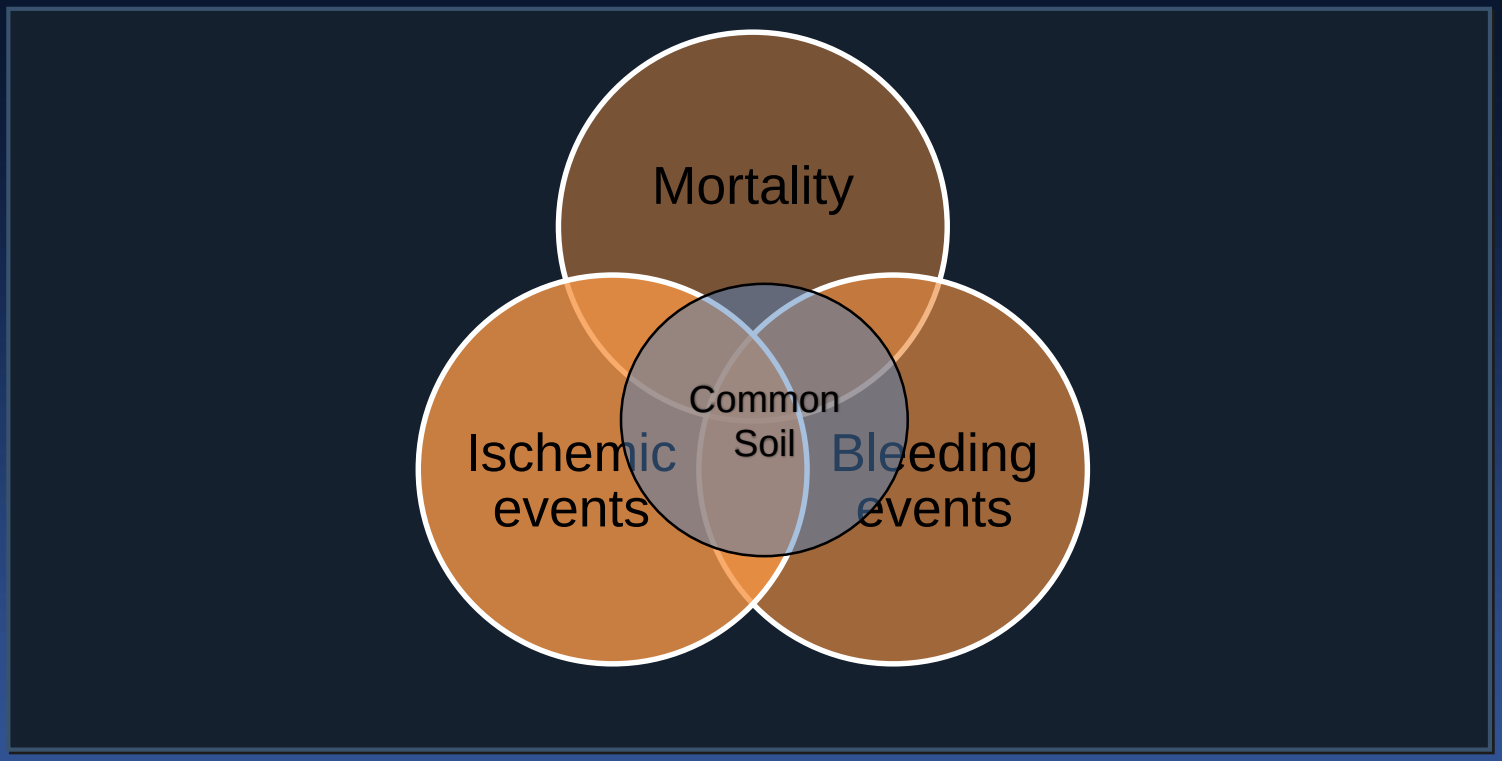


VKA + Antiplatelet

VKA alone

Abdul-Jawad Altisent O et al JACC Cardiovasc Interv. 2016 Aug 22;9(16):1706-17

The Complex Ischemic & Bleeding Leverage In Elderly TAVR Patients with Considerable Surgical Risk



Applicable to
Fragile, Older TAVR population

ADAPT-TAVR Trial

Anticoagulant versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement

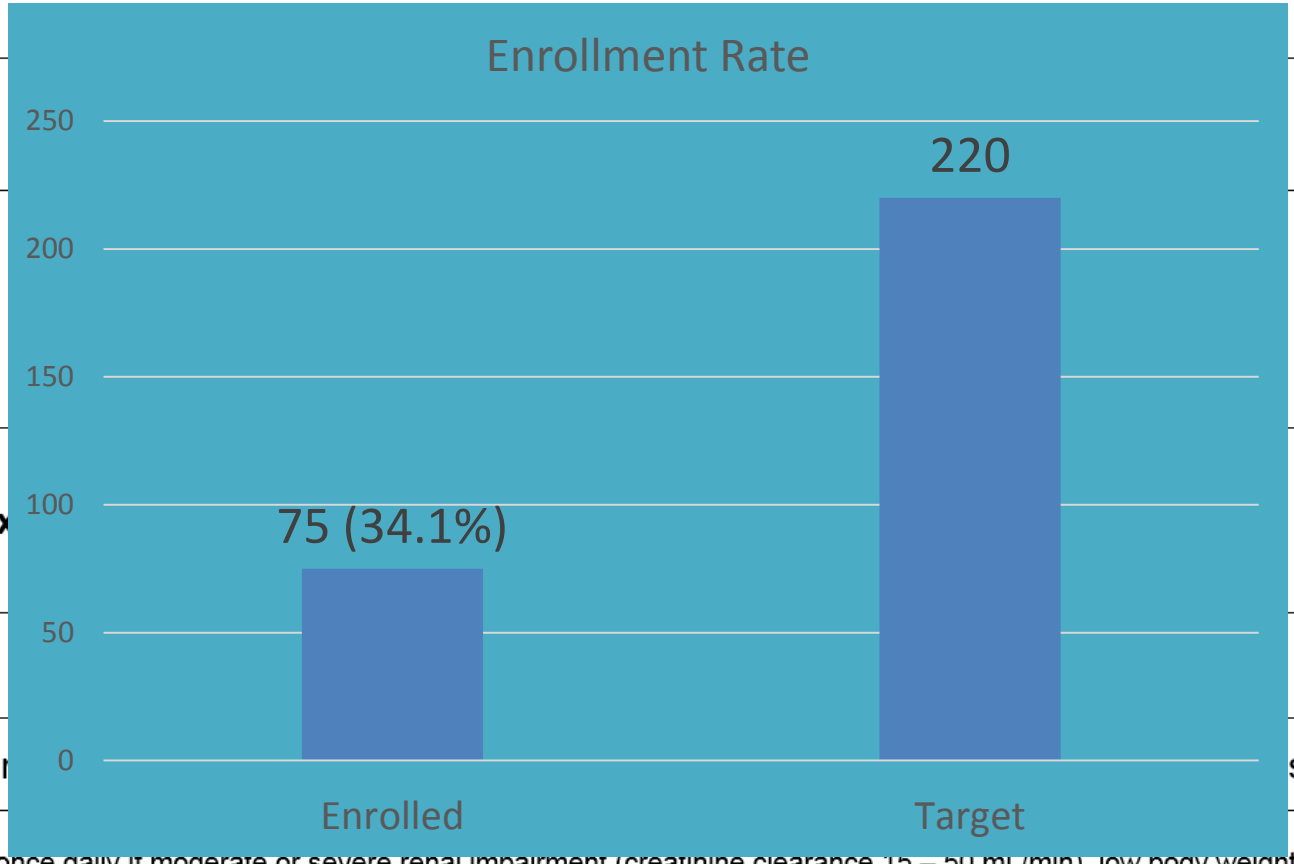
Seung-Jung Park (Trial Chair)
Duk-Woo Park (Trial Co-chair)

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

Trial Design: ADAPT-TAVR Trial

Anticoagulant versus ***D***ual ***A***ntiplatelet Therapy for ***P***reventing Leaflet ***T***hrombosis After ***T***ranscatheter ***A***ortic ***V***alve ***R***eplacement

ADAPT-TAVR Trial



*30 mg once daily if moderate or severe renal impairment (creatinine clearance 15 – 50 mL/min), low body weight ≤60kg, or concomitant use of P-glycoprotein inhibitors (cyclosporin, dronedarone, erythromycin, ketoconazole).

Antithrombotic Strategy after TAVR

- TAVR patients have multiple thrombotic- and bleeding-related comorbidities. Thus, it make optimal antiplatelet and anticoagulant management to be complex.
- Currently, optimal antithrombotic strategy following TAVR is still debating.
- Guidelines differ on anticoagulation strategies in TAVR,
  - Without a strong evidence base for their recommendations.
  - Practice variation in the real world is substantially high.
  - Clinical trials on different antithrombotic regimens are ongoing & expanding.