Valve Thrombosis, Durability and Ongoing Antithrombotic Trials for TAVR

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The TCTAP 2018 Disclosure

Do-Yoon Kang, MD

I have no financial conflicts of interest to disclose concerning the presentation

TAVR Device Evolution

Devices for Transcatheter Aortic Valve Implantation

2007 → 2017

	Edwards Sapien THV	Edwards Sapien XT	Symentis Acurate TA	Abbott/St Jude Portico	Boston Scientific Lotus	Edwards Sapien 3	New Valve Technology Allegra	Medtronic Evolut R	Edwards Centera
									
Frame/[deployment]	Balloon-expandable stainless Steel	Balloon-expandable cobalt chromium	Self-expanding nitinol	Self-expanding nitinol	Mechanically-expandable Braided Nitinol	Balloon-espandable cobalt chromium	Self-expanding nitinol	Self-expanding nitinol	Self-expanding nitinol
Valve	Bovine pericardium	Bovine pericardium	Porcine pericardium	Bovine pericardium	Bovine pericardium	Bovine pericardium	Bovine pericardium	Porcine pericardium	Bovine pericardium
Seal/skirt/cuff	None	Polyethylene terephtalate (PET) fabric skirt	Polyethylene terephtalate	Porcine	Polycarbonate - based urethane material	Polyethylene terephtalate fabric cuff	None	None	Polyethylene terephtalate
Access	TF, TA	TF, TA	TA	TF, Tsc, TAo	TF	TF, TA, TAo	TF	TF	TF
Anti Calcification Treatment	None	Thermafix process™	None (glutaraldehyde Fixation)	Linx AC technology™	T-Guard™	Thermafix process™	None	Alpha-amino Oleic Acid	Thermafix process™

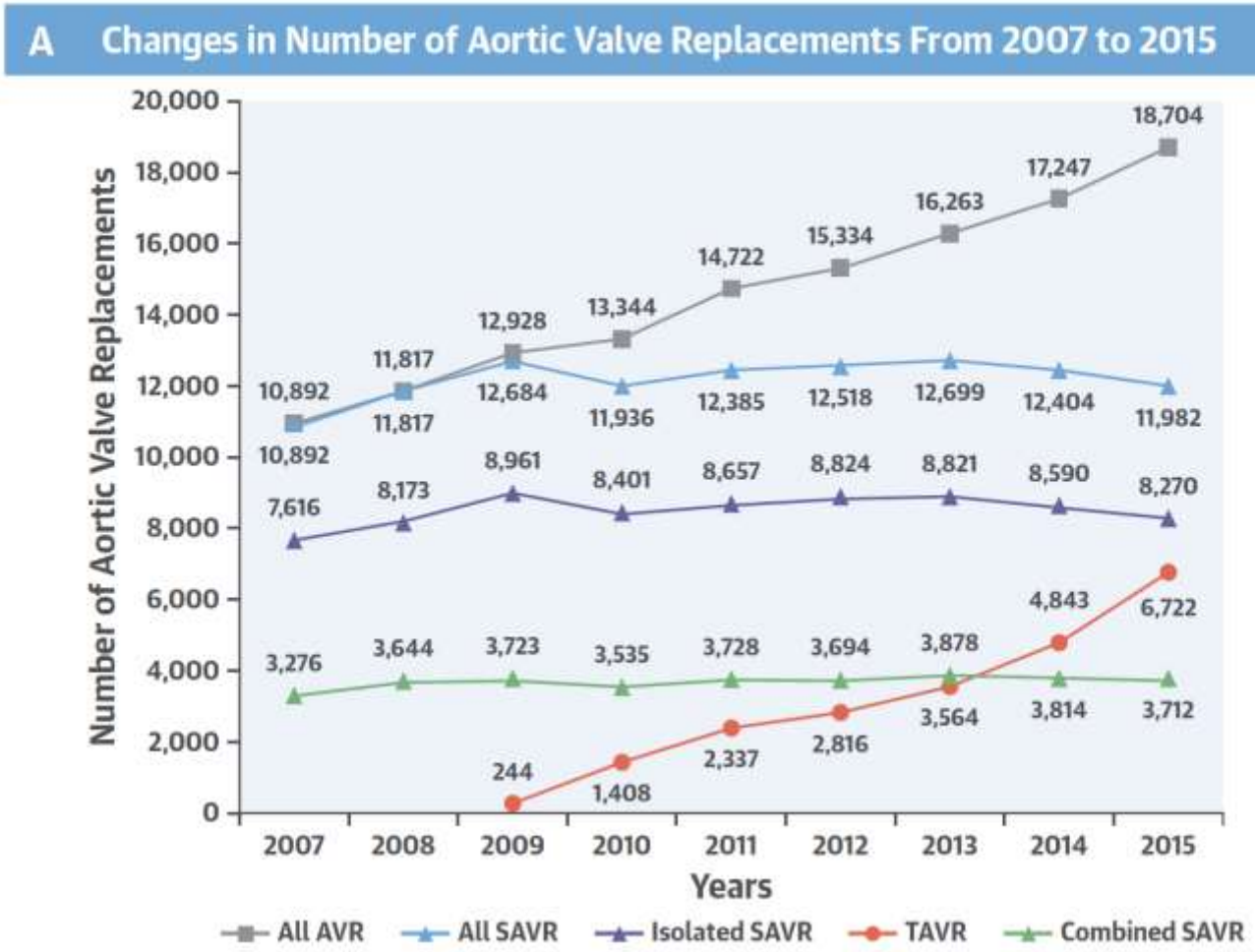
	Medtronic CoreValve	Jena Valve	Symentis Acurate Neo	Medtronic Evolut Pro	Boston Scientific Lotus Edge
					
Frame/[deployment]	Self-expanding nitinol	Self-expanding nitinol	Self-expanding nitinol	Self-expanding nitinol	Mechanically-expandable braided nitinol
Valve	Porcine pericardium	Porcine pericardium	Porcine pericardium	Porcine pericardium	Bovine pericardium
Seal/skirt/cuff	None	None	Polyethylene terephtalate	Porcine pericardium	Polycarbonate - based urethane material
Access	TF, TA, DA	TA	TF, TA	TF	TF
Anti Calcification Treatment	none (glutaraldehyde Fixation)	none (glutaraldehyde Fixation)	BioFix™	Alpha-amino Oleic Acid	T-Guard™

Vranckx P et al. Eur Heart J. 2017;38:3341-3350

TAVR Trends

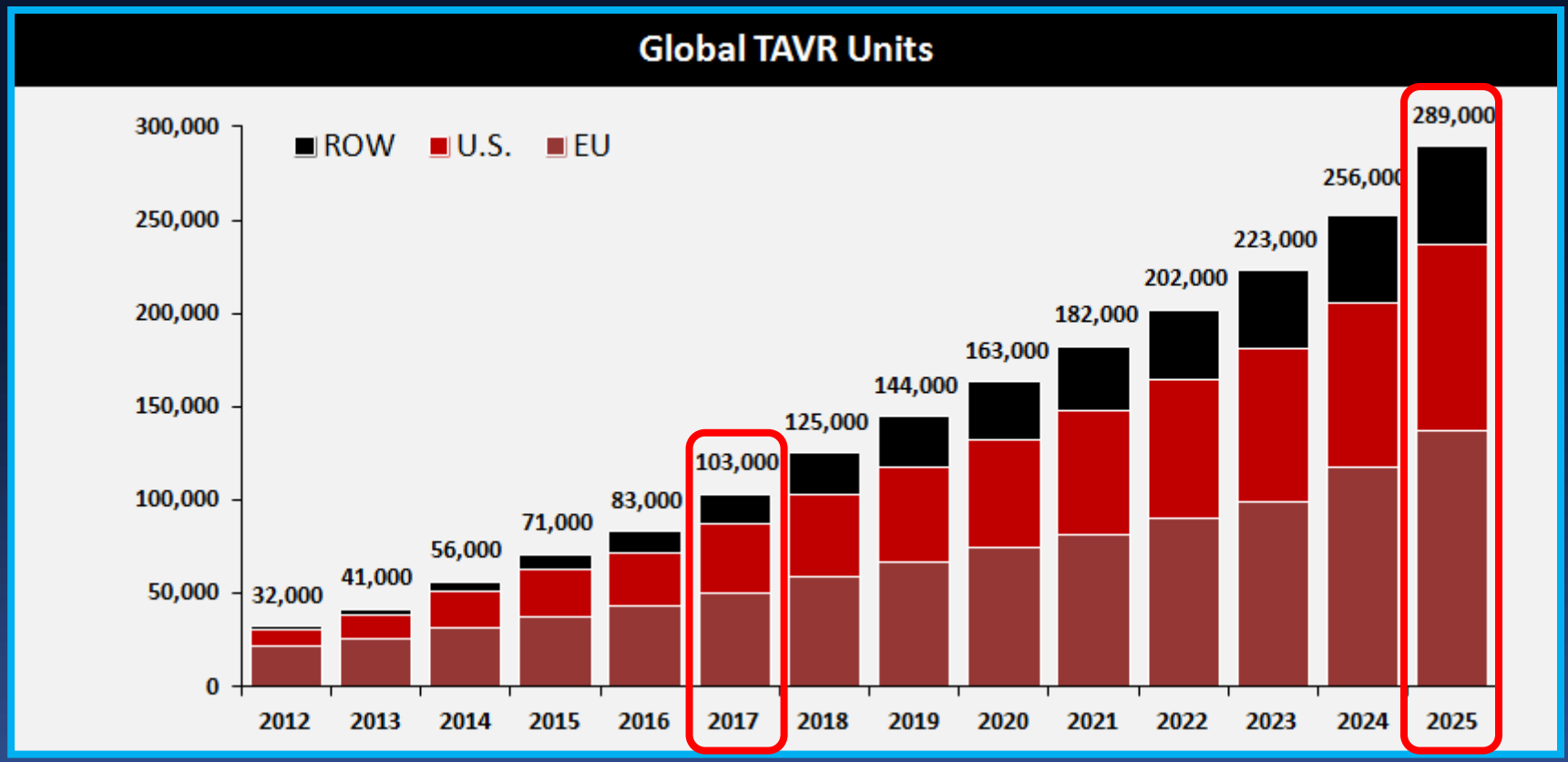
National Trend in France, 2007~2015

CENTRAL ILLUSTRATION Changes in Number, Type, and Mortality Rates of AVRs in France From 2007 to 2015



Nguyen V et al. JAm Coll Cardiol 2018;71:1614–27.

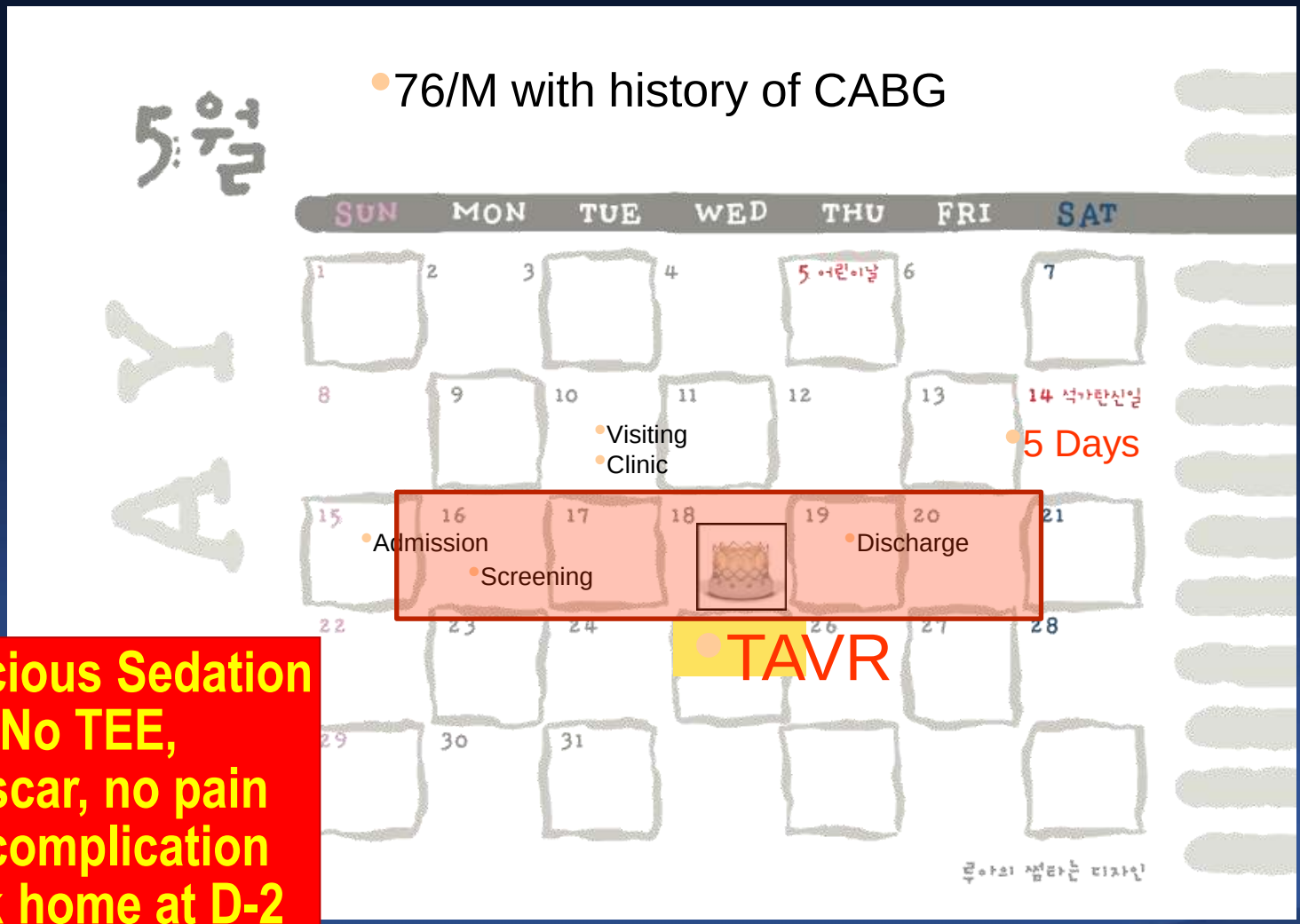
Estimated Global TAVR Growth



SOURCE: Credit Suisse TAVI Comment –January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

This year > 100,000 and by 2025 almost 300,000!

In 2018, TAVR is a Routine Practice



- Conscious Sedation
- No TEE,
- No scar, no pain
- No complication
- Back home at D-2

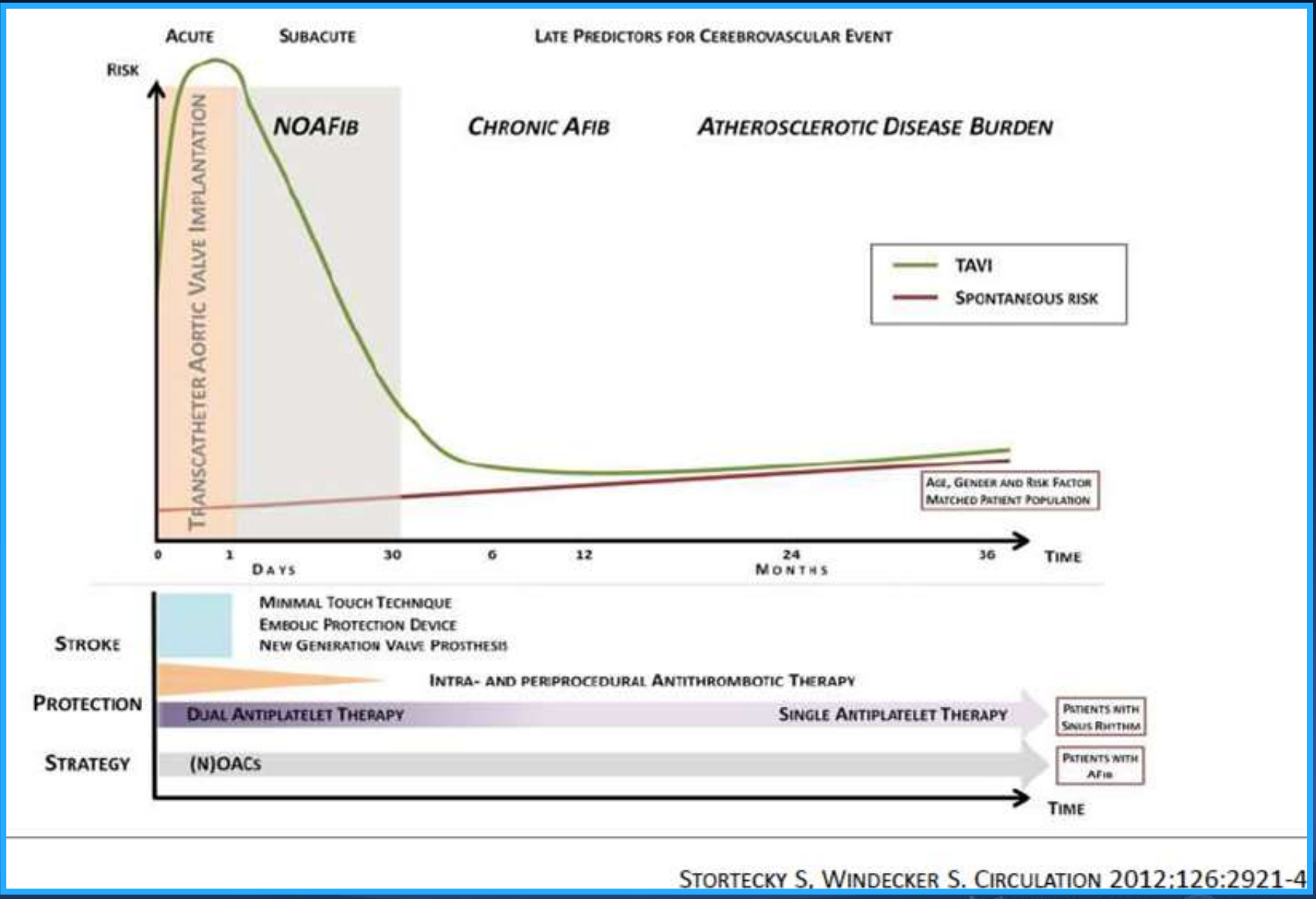
"Minimalist Approach"
Post TAVR Care in AMC

- Short stay (1 day) in ICU
- Optional temporary pacemaker
- Early mobilization
- Avoid polypharmacy
- Cardiac Rehabilitation Clinic

Medical Treatment After TAVR

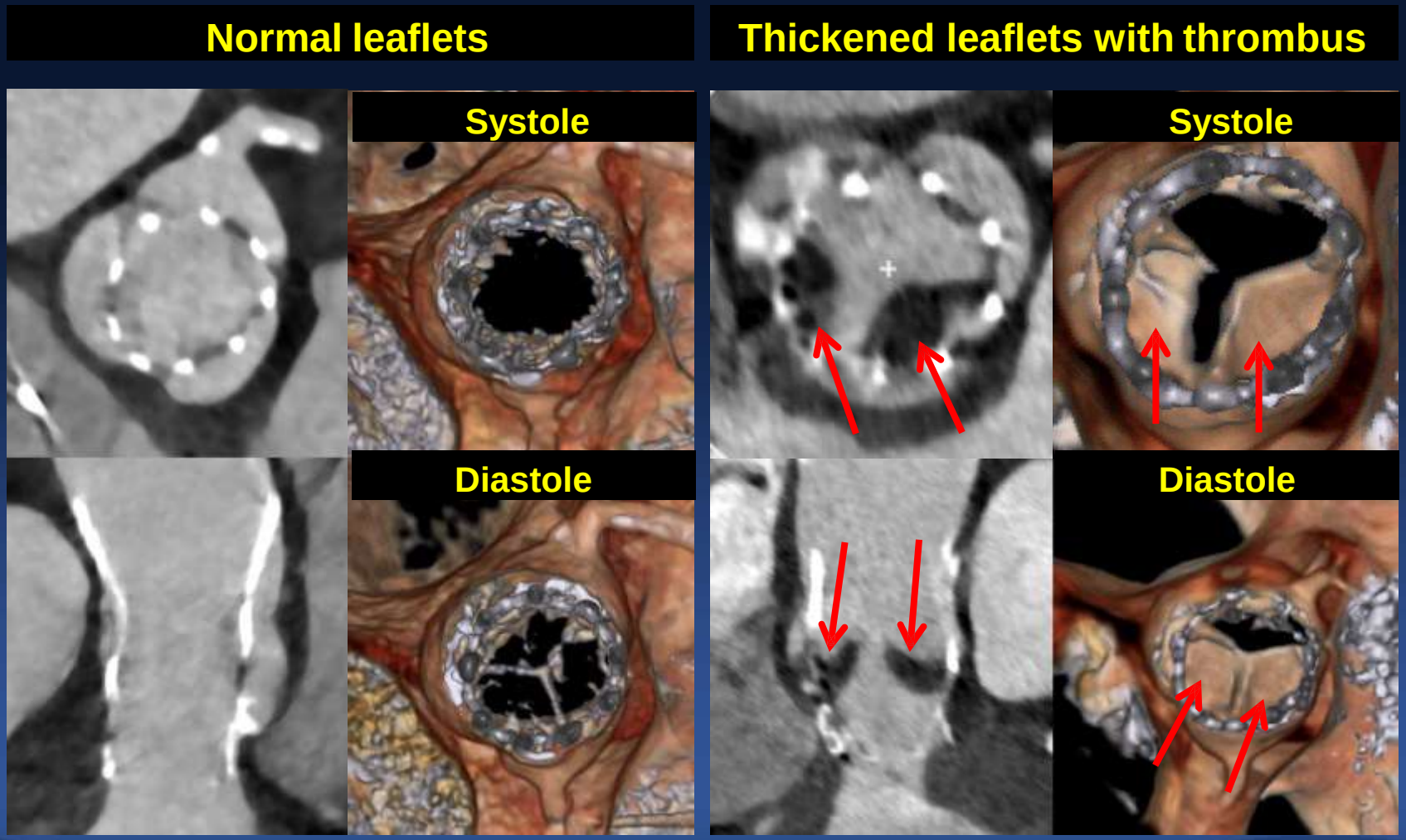
- Antithrombotic
- Low-Dose Diuretics
- HTN, DM, Lipid Drugs

Timing of CVA Events after TAVI



Stortecky S, Windecker S. Circulation 2012;126:2921-4

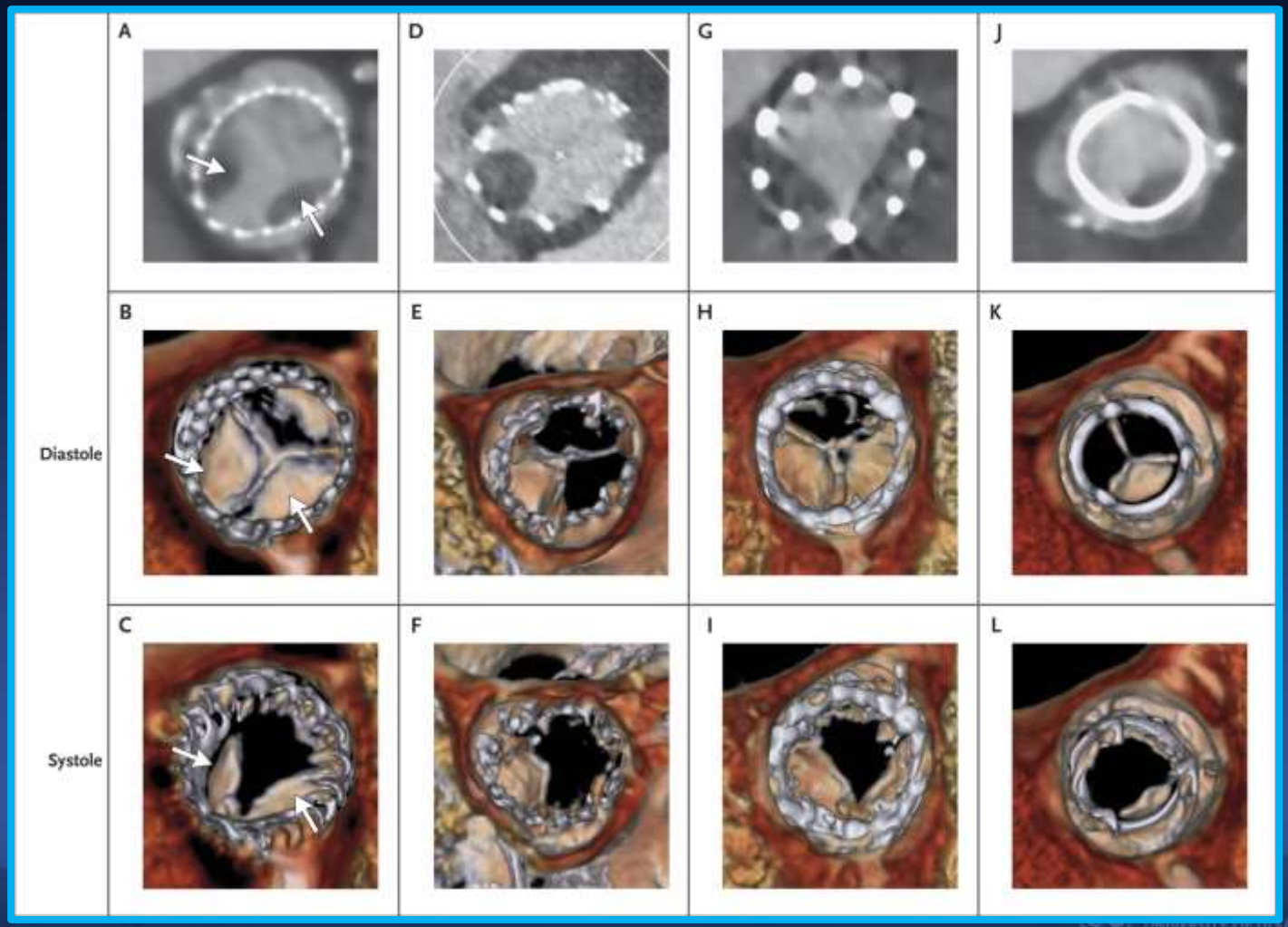
4D-CT after TAVR



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

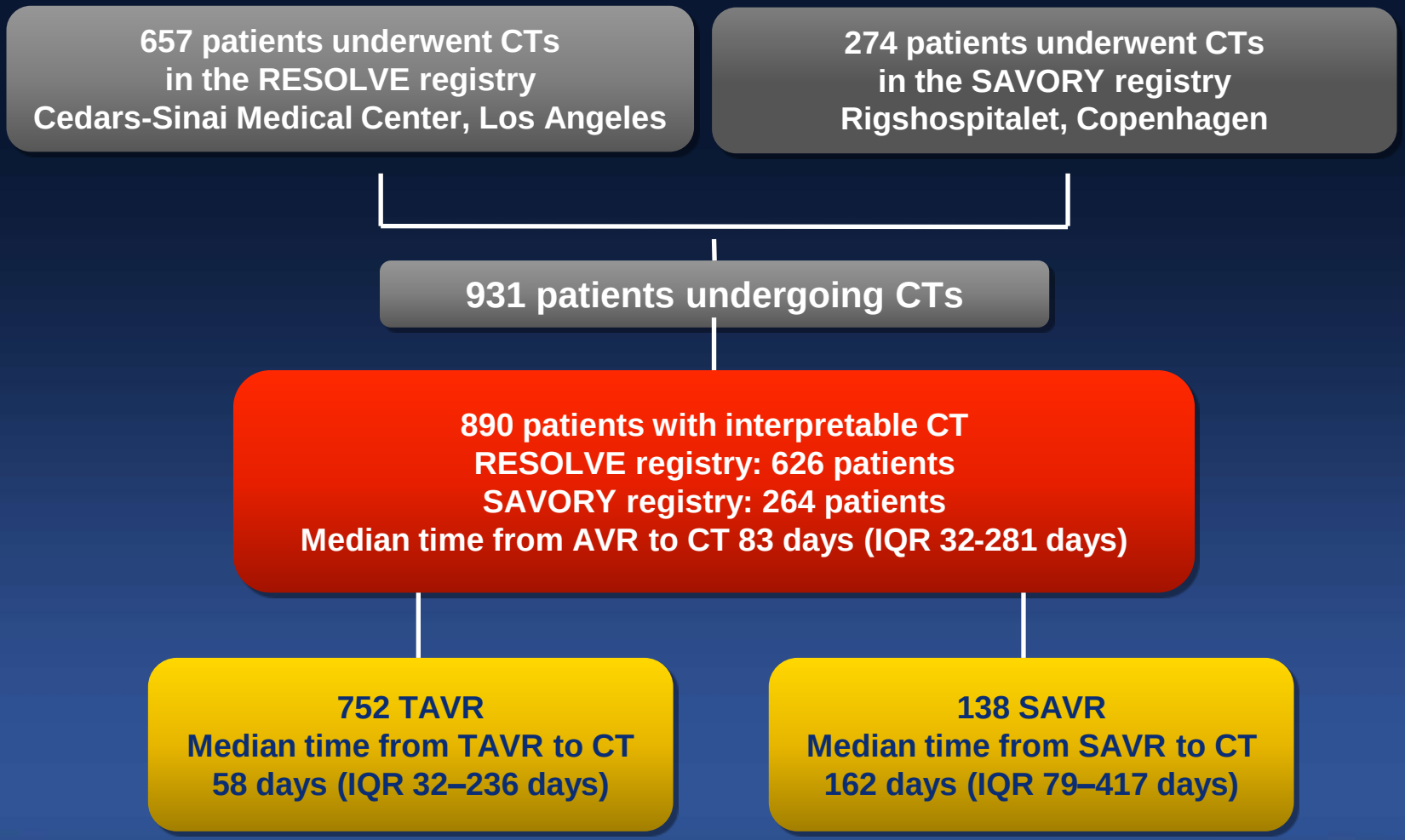
Subclinical Leaflet Thrombosis after TAVR

Evidence of Reduced Leaflet Motion in Multiple Prosthesis Types



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

Subclinical Leaflet Thrombosis in SVR and TAVR : 2 Observational Registry



Time from TAVR to CT vs. SAVR to CT: p<0.0001

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

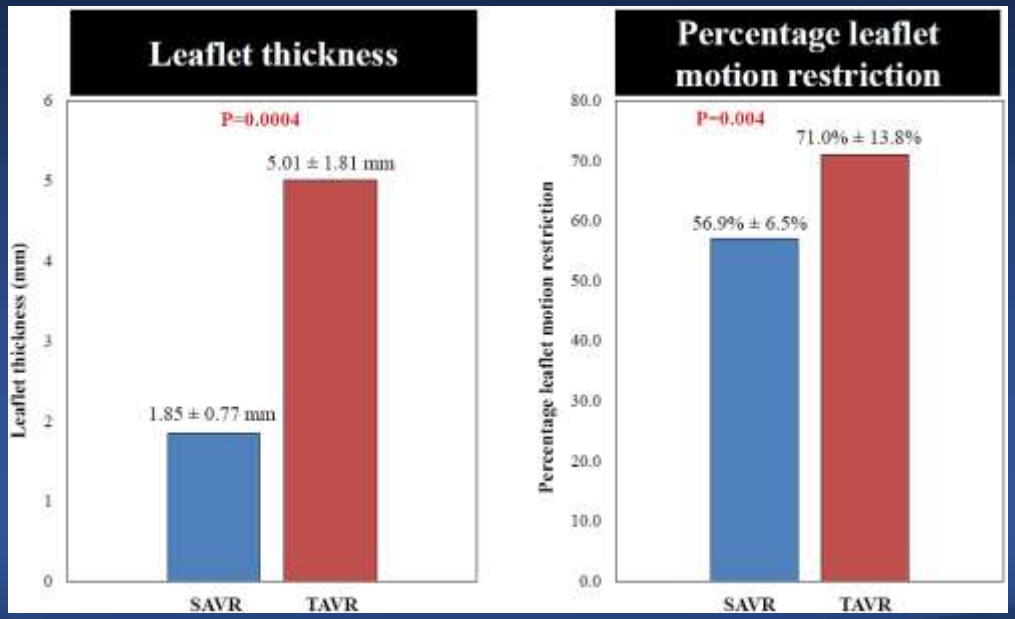
Prevalence of reduced leaflet motion

Reduced leaflet motion 106 (11.9%) patients

TAVR: 13.4% (101 out of 752)

SAVR: 3.6% (5 out of 138)

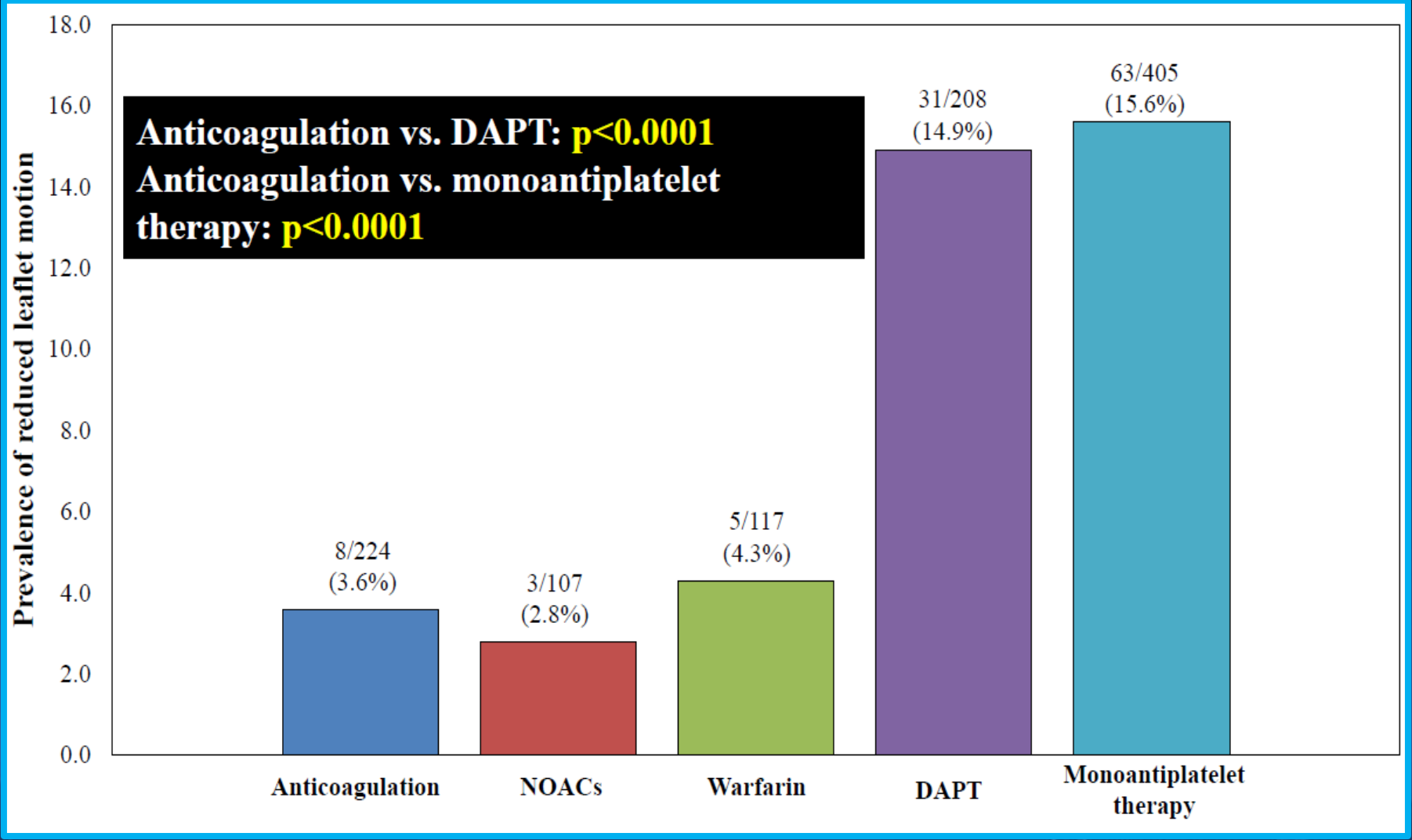
TAVR vs. SAVR: p=0.001



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

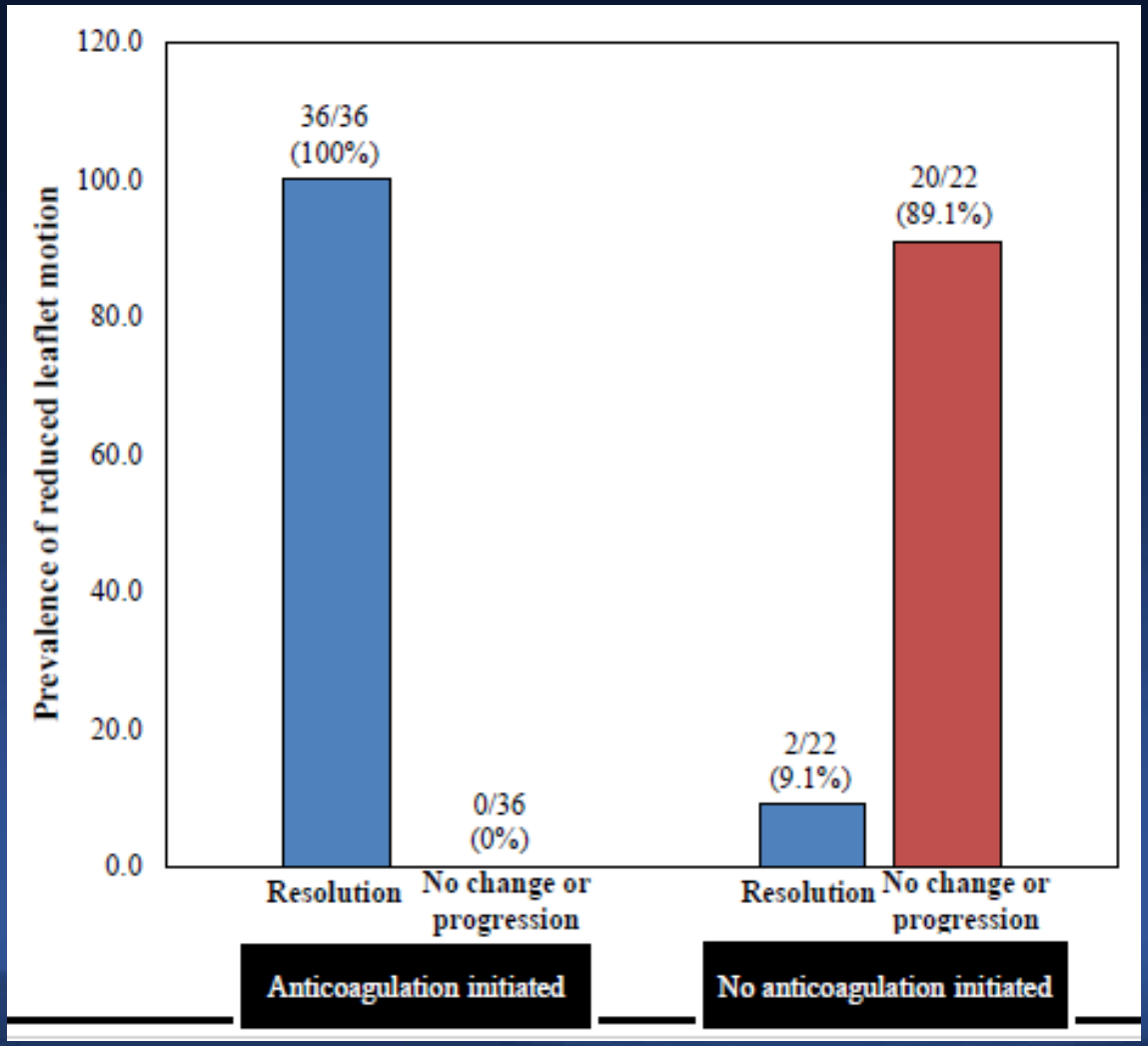
Analysis of Antithrombotic Regimen

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 in 20 out of 22 patients** not treated with anticoagulation
  - **P<0.0001**

Clinical Impact of Leaflet Thrombosis

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

All 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-value
Death	34 (4%)	2.91	4 (4%)	2.66	0.96 (0.34-2.72)	0.94
Myocardial infarction	4 (1%)	0.34	1 (1%)	0.67	1.91 (0.21-17.08)	0.56
Stroke / TIAs	27 (3%)	2.36	11(10%)	7.85	3.27 (1. 62-6.59)	0.001
All stroke	22 (3%)	1.92	6 (6%)	4.12	2.13 (0.86-5.25)	0.10
Ischemic stroke	21 (3%)	1.83	6 (6%)	4.12	2.23 (0.90-5.53)	0.08
TIA	7 (1%)	0.60	6 (6%)	4.18	7.02 (2.35-20.91)	0.0005

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

Current 2017 ACC/AHA Guideline : TAVR

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.	2014 recommendation remains current.
III: Harm	B	Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses (200,212,213).	2014 recommendation remains current.

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).**	**NEW:** Studies have shown that valve thrombosis may develop in patients after TAVR, as assessed by multidetector computerized tomographic scanning. This valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA.
See Online Data Supplement 6.			

Several studies have demonstrated the occurrence of prosthetic valve thrombosis after TAVR, as assessed by multidetector computerized tomography, which shows reduced leaflet motion and hypo-attenuating opacities. The incidence of this finding has varied from 7% to 40%, depending on whether the patients are from a clinical trial or registry and whether some patients received anticoagulation with VKA (203,210,211). Up to 18% of patients with a thrombus formation developed clinically overt obstructive

Ongoing Antithrombotic Trials after TAVR

Omission of Clopidogrel

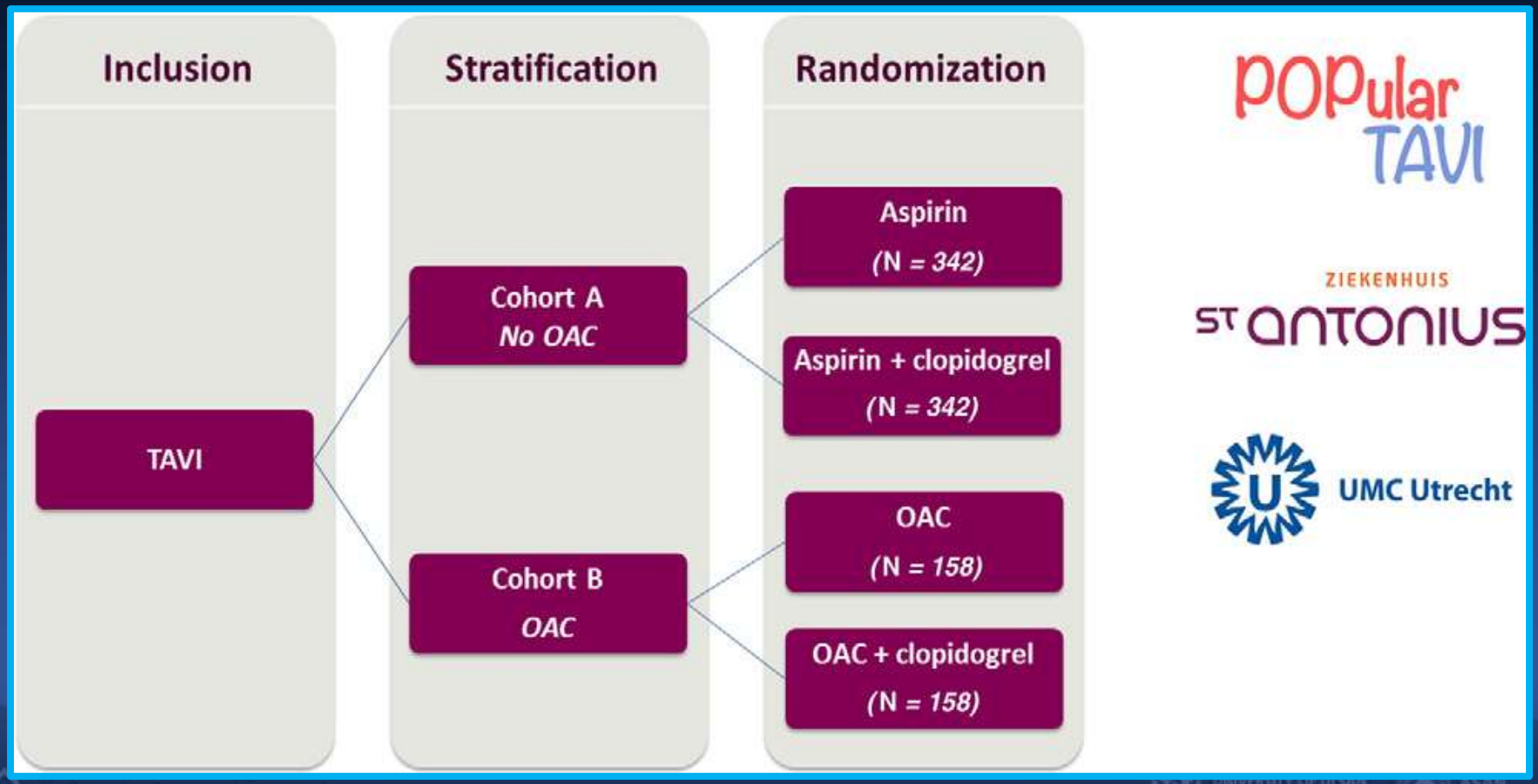
- POPular TAVI Trial
- CLOE Trial

NOAC Trial

- GALILEO Trial
- ATLANTIS Trial
- ENVISAGE TAVI-AF Trial
- ADAPT-TAVR Trial

Ongoing Trials
: Popular-TAVI

To test if monotherapy with aspirin or OAC vs additional clopidogrel after TAVI reduces bleeding with a favorable net-clinical benefit.



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

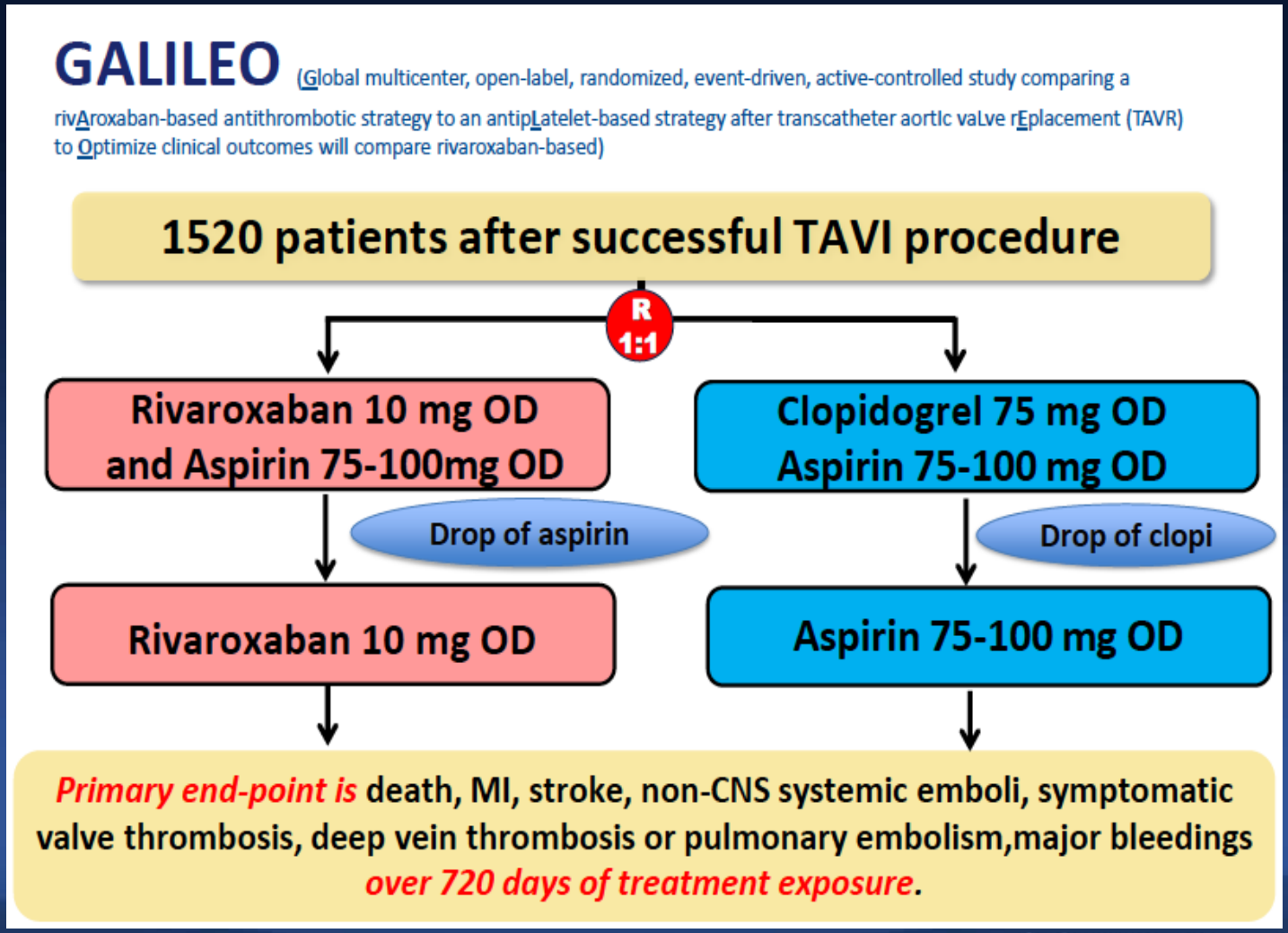
Primary Safety Endpoint

Major / Life-Threatening VARC-2 Bleeding

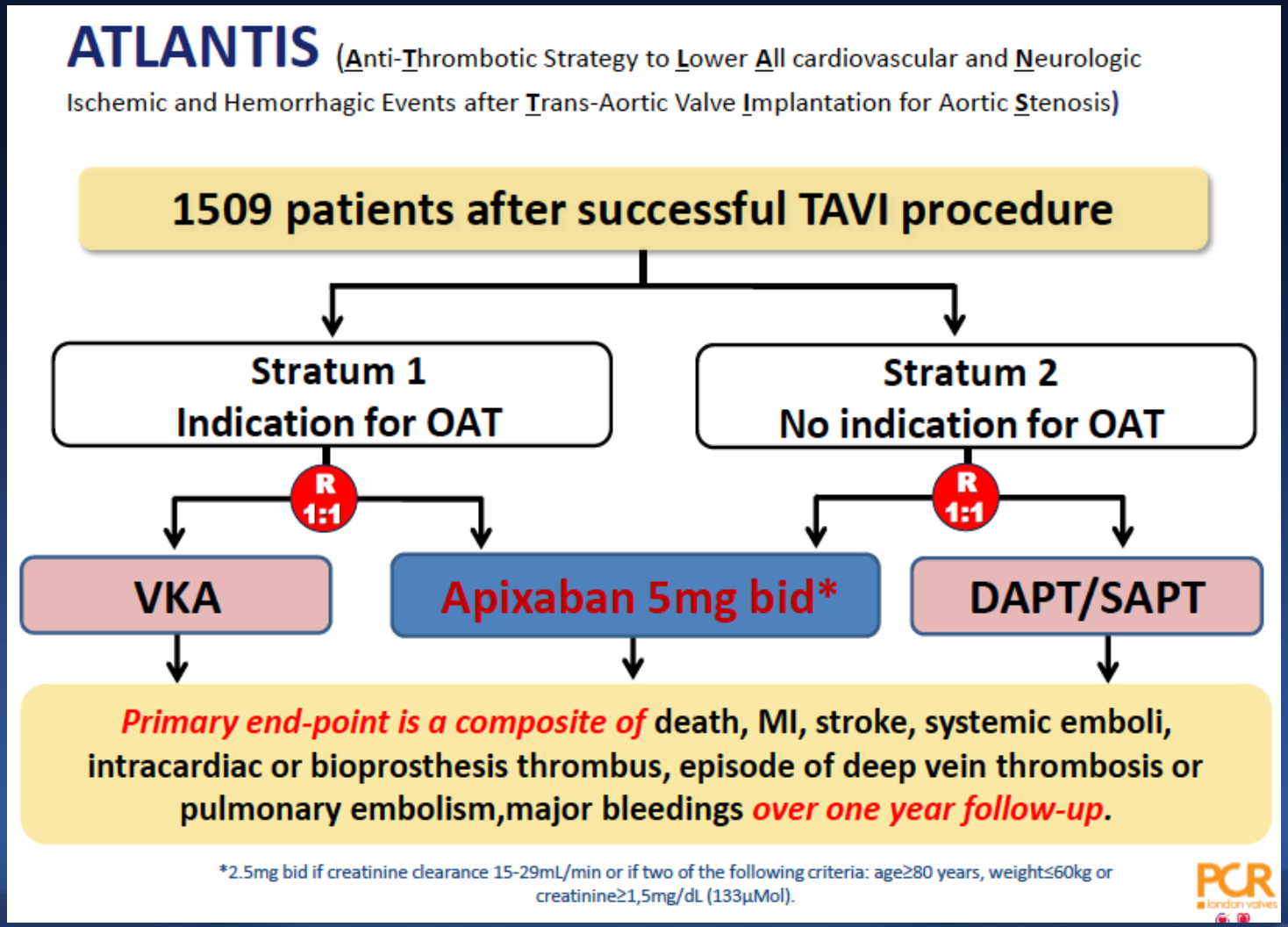
Ancillary Studies

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

Ongoing Trials
: GALILEO



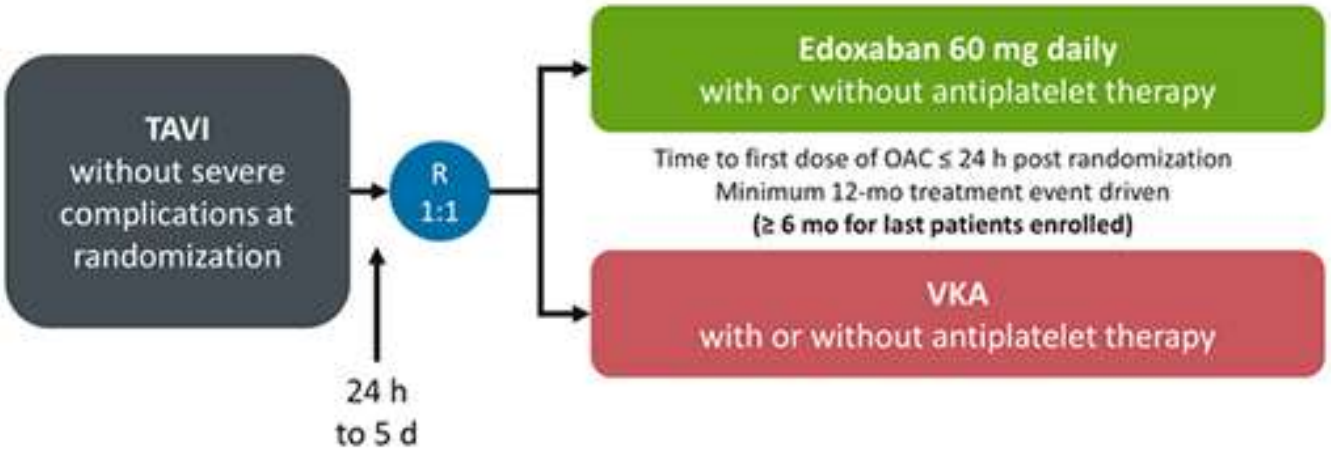
Ongoing Trials : ATLANTIS



Ongoing Trials
: ENVISAGE TAVI-AF

ENVISAGE TAVI AF -- Study Design

Prospective, randomized, open-label, blinded evaluation of edoxaban vs VKA in approximately 1400 patients with AF indicated for chronic OAC after successful TAVI (~2500 patient-y)



clinicaltrials.gov: NCT02943785; Van Mieghem NM, et al. *Am Heart J.* (Submitted)

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)

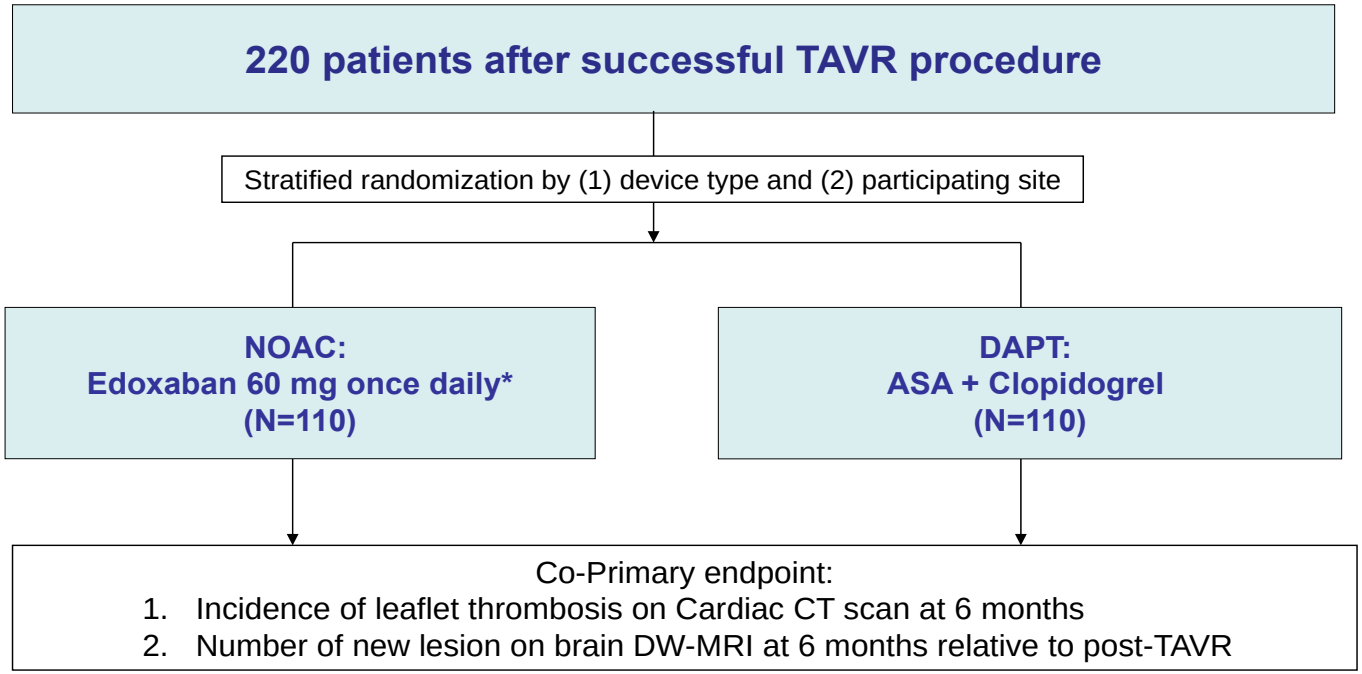
Heart Institute, Asan Medical Center,

University of Ulsan College of Medicine, Seoul, Korea

Trial Scheme: 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).

Study endpoints

Primary

The primary study end points were pre-defined;

Incidence of leaflet thrombosis on 4-dimensional, volume-rendered cardiac CT imaging at 6 months

Study endpoints

Secondary

- Number of new lesions on brain DW-MRI scans at 6 months relative to immediate post-TAVR
- Death (all-cause, cardiovascular, or non-cardiovascular mortality)
- MI
- Stroke or TIA (disabling or non-disabling)
- Bleeding event (life-threatening or disabling, major bleeding, or minor bleeding)
- Echocardiographic parameter (the mean transaortic valve PG and velocity time integral ratio at baseline and 6-month follow-up).
- New lesion volume on MRI scans
- Neurological and neurocognitive function

*All clinical endpoints are adjudicated according to the VARC-2 definition and the NeuroARC definition

Inclusion criteria

1. Aged ≥19 years with successful TAVR procedure
2. Either native valve or valve-in-valve with any approved/marketed device

* A successful TAVR is defined as device success according to the VARC-2 criteria:

Exclusion criteria

1. Any AF with an indication for chronic OAC.
2. An ongoing indication for OAC or any other indication for continued treatment with any OAC
3. Any ongoing indication for DAPT (recent ACS or PCI within 12 months)
4. Planned coronary or vascular intervention or major surgery
5. Clinically significant bleeding patients or patients with increased bleeding risk due to underlying conditions
6. Clinically overt stroke within the last 3 months

Cardiac CT imaging

- For all patients enrolled in this trial, CT (four-dimensional, volume-rendered) will be performed at 6 months (± 1 month) after TAVR to confirm the

1. presence of the leaflet thrombosis of THV
2. quantitative assessment of leaflet motion

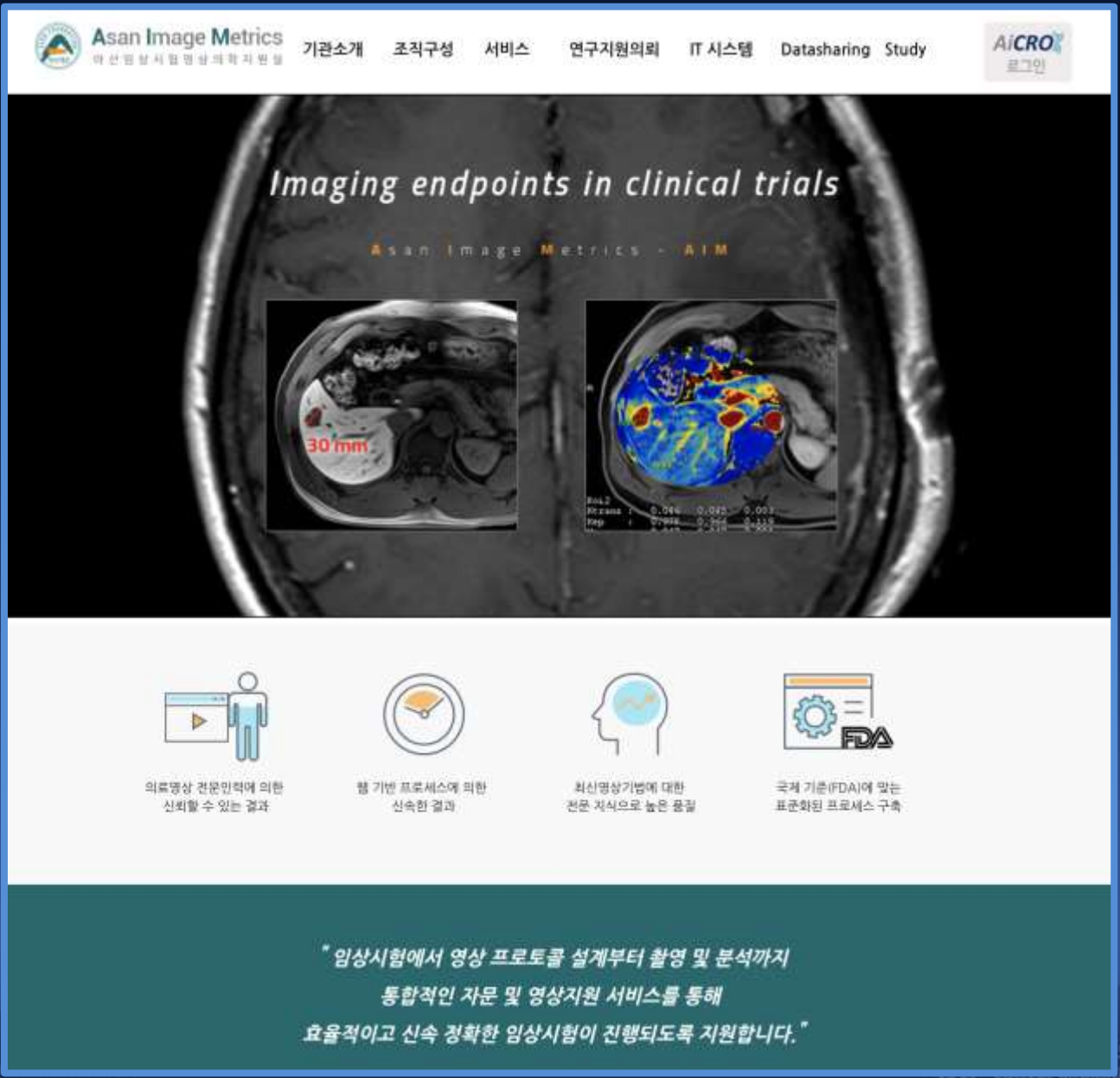
- Leaflet motion; defined as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet) in at least one valve leaflet

Brain MRI imaging

- For all patients enrolled in this trial, diffusion-weighted (DW) brain MRI using a 3-T scanner will be performed at 1-7 days (baseline) and 6 months (follow-up).

- Follow-up MRI imaging will be matched with immediate post-TAVR scans, and subtraction analyses are performed to identify new lesions in the entire brain. MRI outcomes included calculation of number and volume of new DWIs (postprocedure – 6 months) by subtraction of the existing baseline lesions in the whole brain.

Dedicated Imaging Core Laboratory



Neurological and Neurocognitive function assessment

- All study subjects will undergo detailed neurologic and cognitive assessment at 1-7 days (baseline) and 6 months (follow-up).

- Neurologic assessments included standard clinical scales (the National Institutes of Health Stroke Scale [NIHSS] and the modified Rankin Scale [mRS]), and cognitive assessments included the Montreal Cognitive Assessment (MoCA).

Summary – Medical Tx after TAVR
Antithrombotic Strategy

- TAVR patients have multiple thrombotic- and bleeding-related comorbidities. Thus, it make optimal antiplatelet and anticoagulant management to be complex.
- Currently, the optimal antithrombotic strategy following TAVR is not entirely clear.
- 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 antithrombotic regimens are ongoing & expanding.

Thank You !!

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