

# Valve Thrombosis, Durability and Ongoing Antithrombotic Trials for TAVR

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# TAVR Device Evolution

## Devices for Transcatheter Aortic Valve Implantation

2007

2017

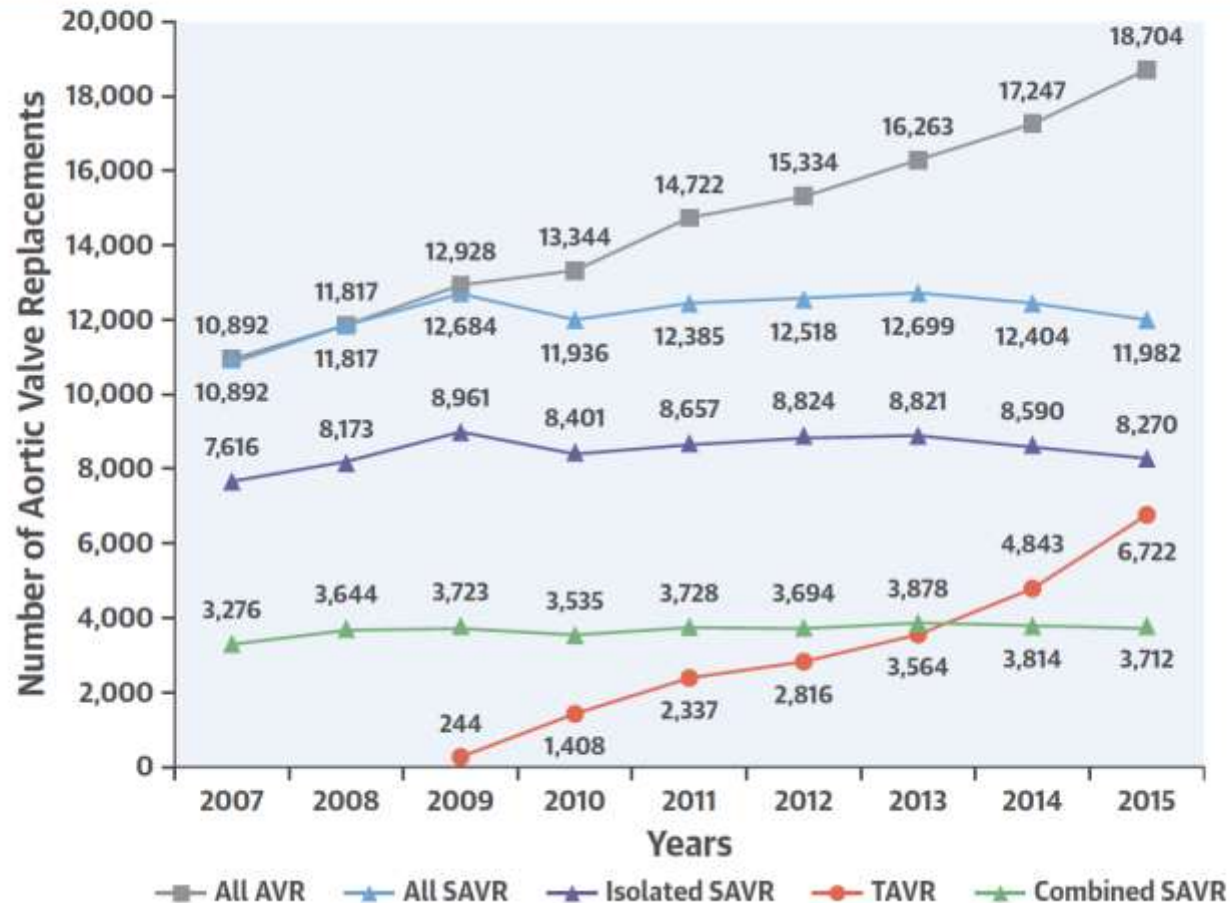
	EDWARDS SAPIEN THV	EDWARDS SAPIEN XT	SYMENTIS ACURATE TA	ABBOTT/ST JUDE PORTICO	BOSTON SCIENTIFIC LOTUS	EDWARDS SAPIEN 3	NEW VALVE TECHNOLOGY ALLEGRA	MEDTRONIC EVOLUT R	EDWARDS CENTERA
									
Frame/(deployment)	Balloon-expandable stainless Steel	Balloon-expandable cobalt chromium	Self-expanding nitinol	Self-expanding nitinol	Mechanically-expandable Braided Nitinol	Balloon-expandable 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 terephthalate (PET) fabric skirt	Polyethylene terephthalate	Porcine	Polycarbonate + based urethane material	Polyethylene terephthalate fabric cuff	None	None	Polyethylene terephthalate
Access	TF, TA	TF, TA	TA	TF, Tsc, TAO	TF	TF, TA, TAO	TF	TF	TF
Anti Calcification Treatment	None	Thermax process™	None (glutaraldehyde Fixation)	Link AC technology™	T-Guard™	Thermax process™	None	Alpha-amino Oleic Acid	Thermax 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	None	None	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™				

# TAVR Trends

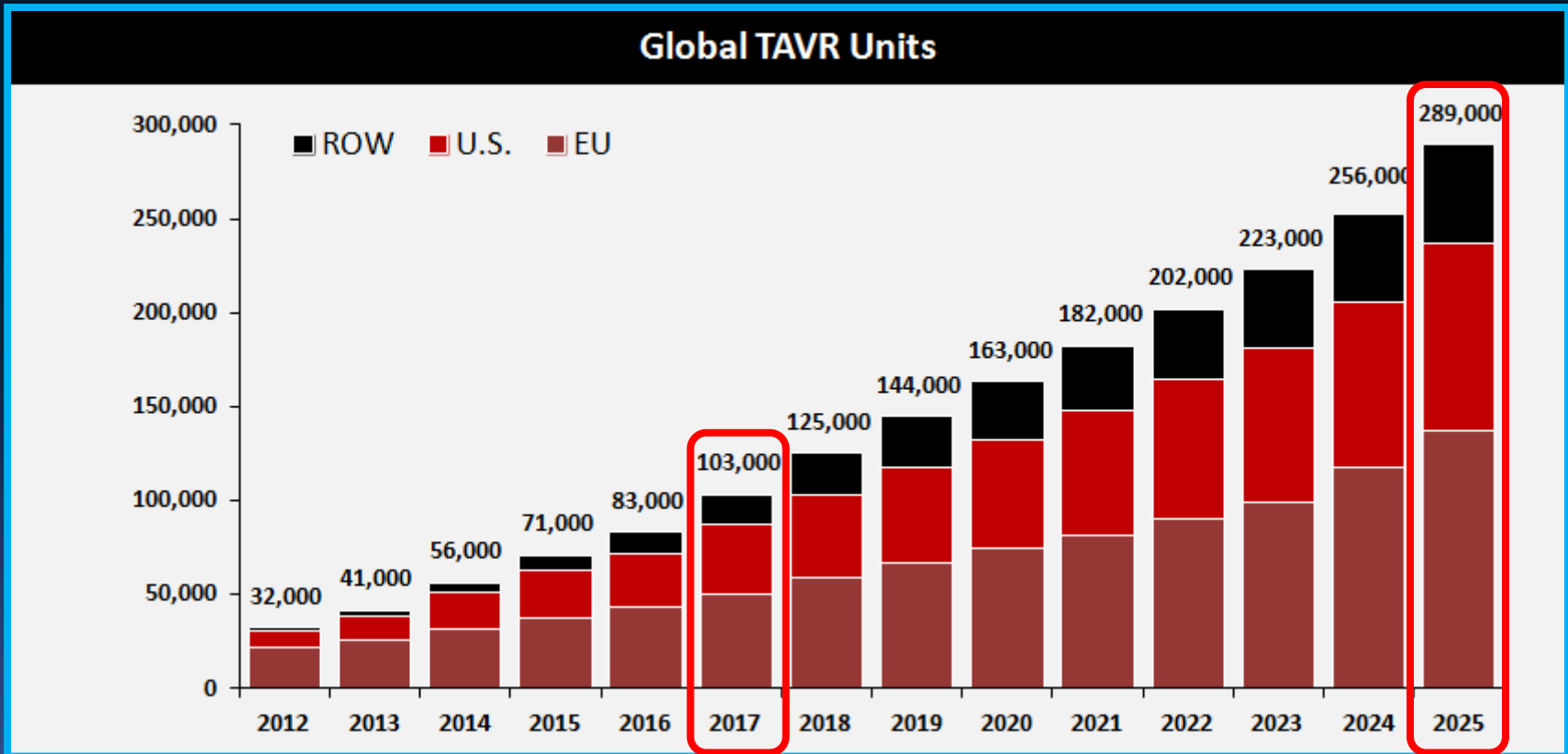
## National Trend in France, 2007~2015

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

**A** Changes in Number of Aortic Valve Replacements From 2007 to 2015



# 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

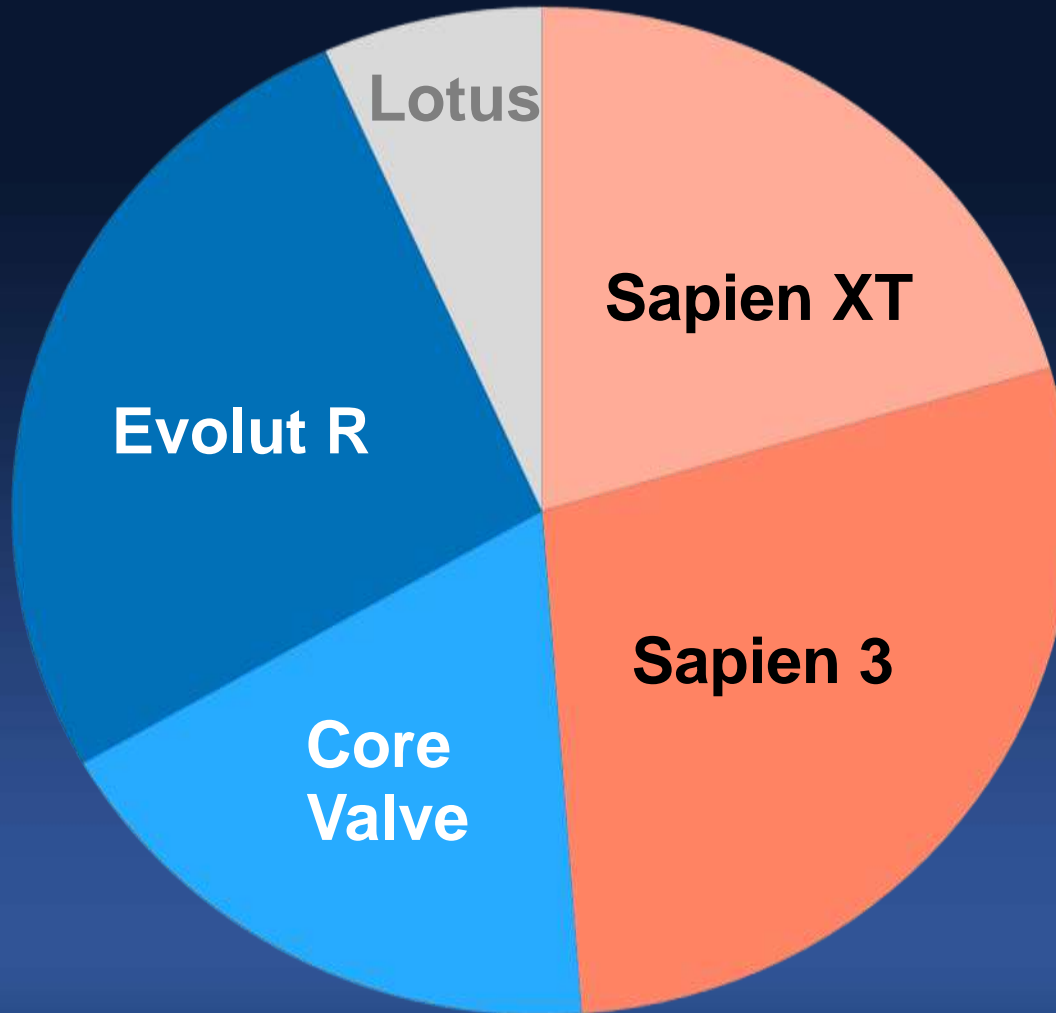
***This year > 100,000 and by 2025 almost 300,000!***

# TAVR in Korea

(2010~2017)

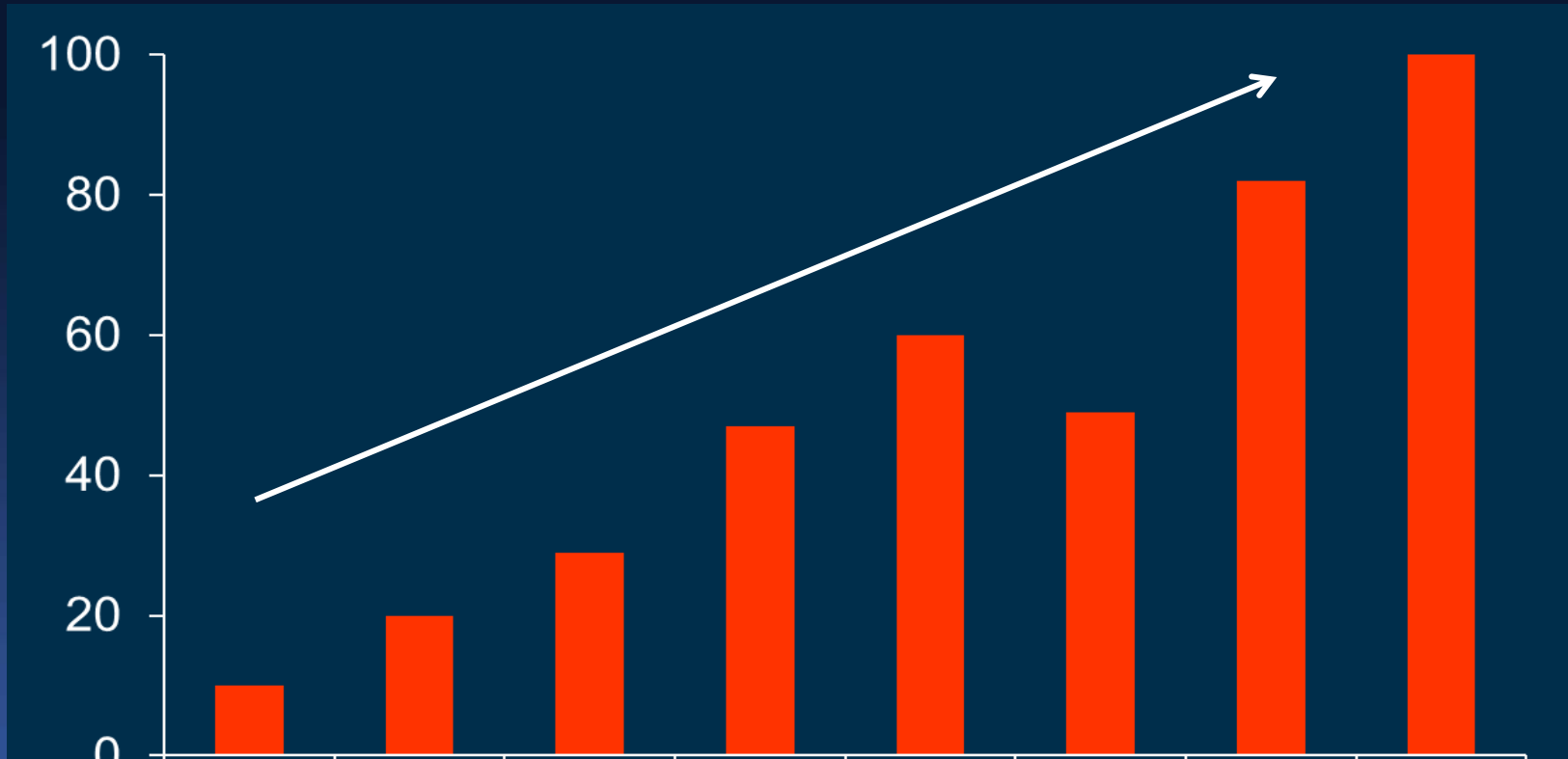


# Type of Valve



# ***TAVR in AMC***

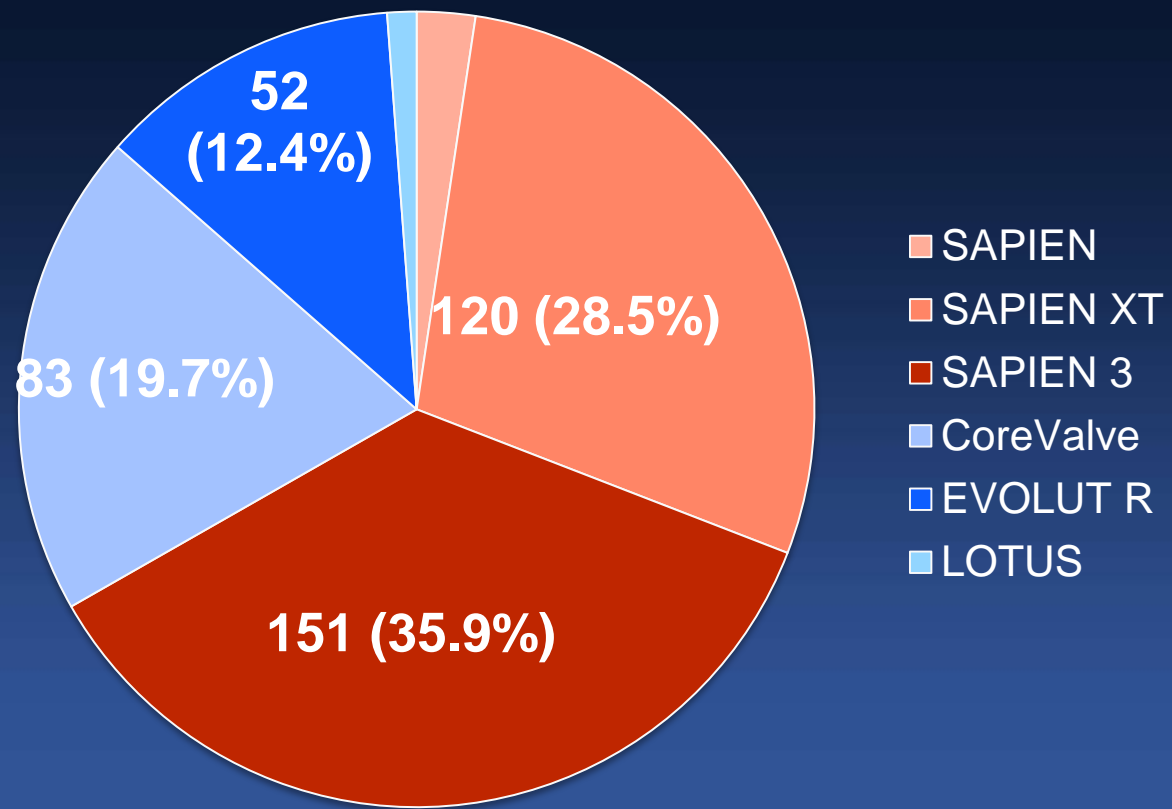
# TAVR in AMC (2010-2018.3, n=451)



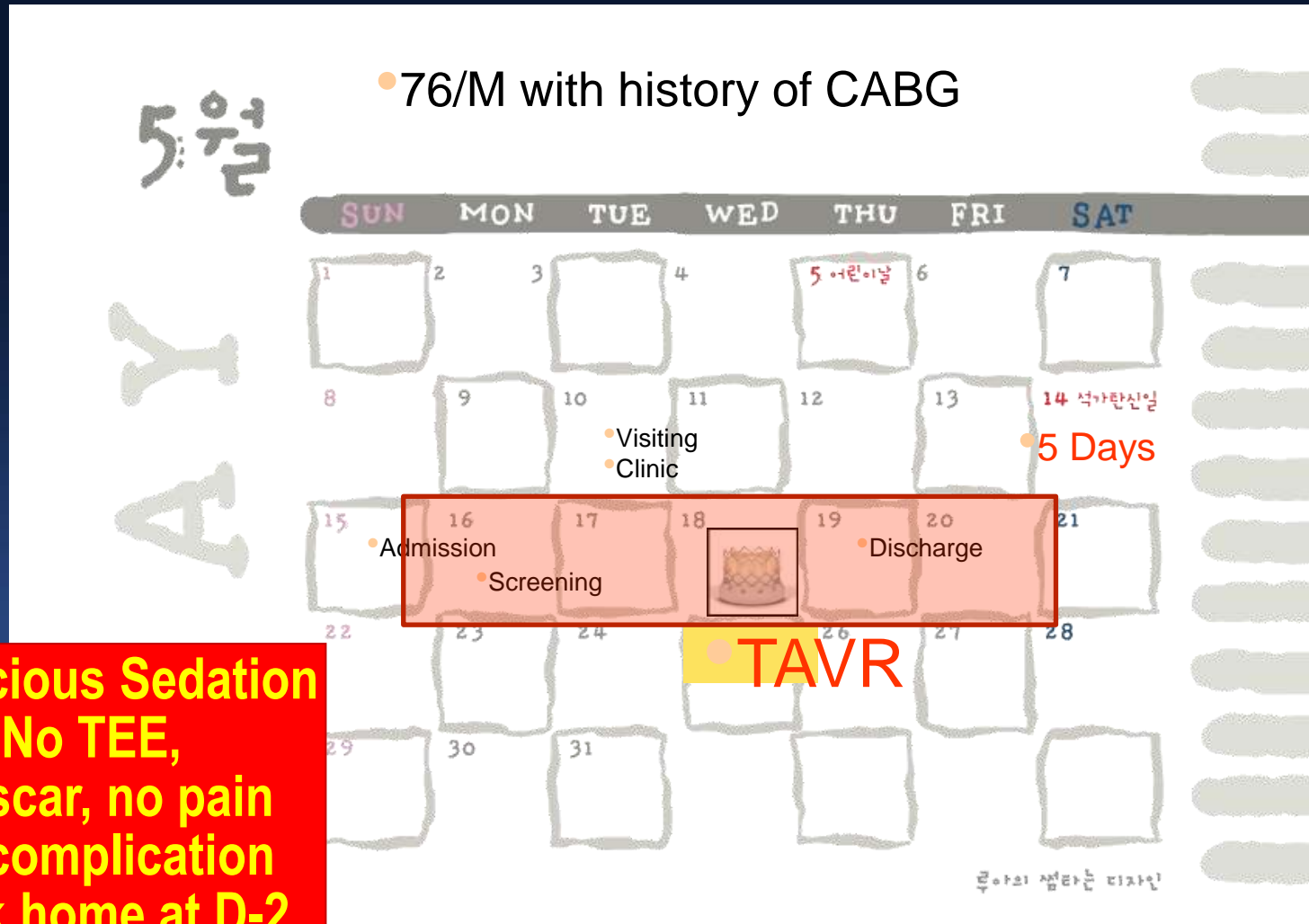
- Our targeted goal, this year ~ 150 per year.
- Our targeted goal, next year ~ 200 per year

# TAVR in AMC

## Device



# In 2018, TAVR is a Routine Practice



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

# ***“Minimalist Approach”***

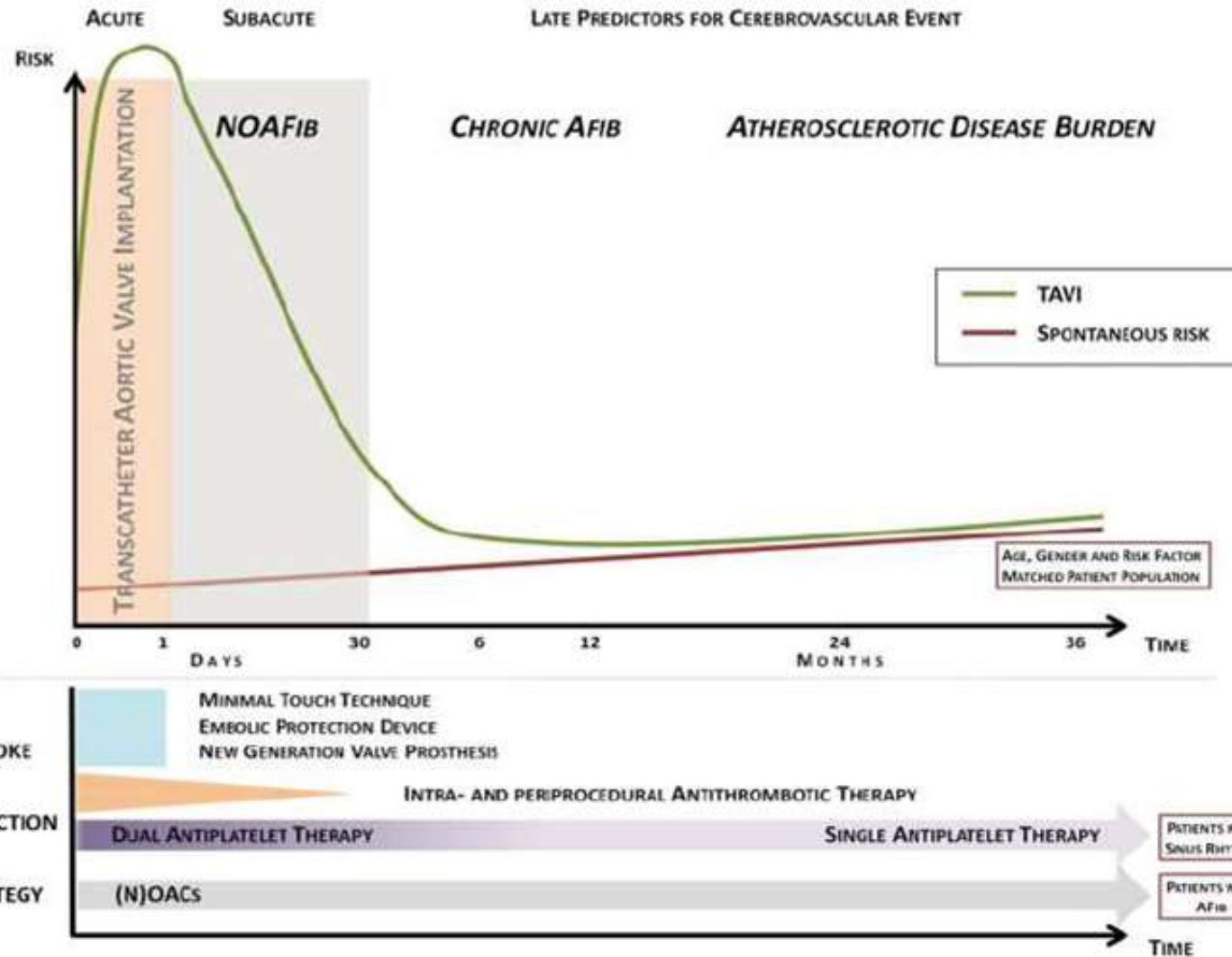
## **Post TAVR Care in AMC**

- 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**

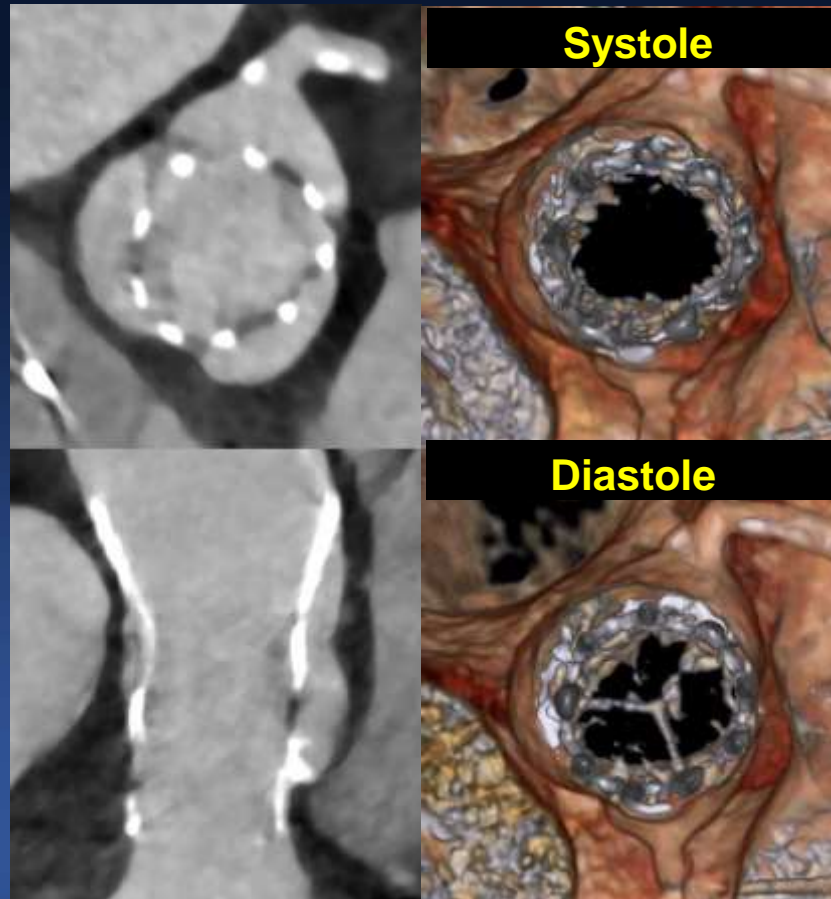
# Timing of CVA Events after TAVI



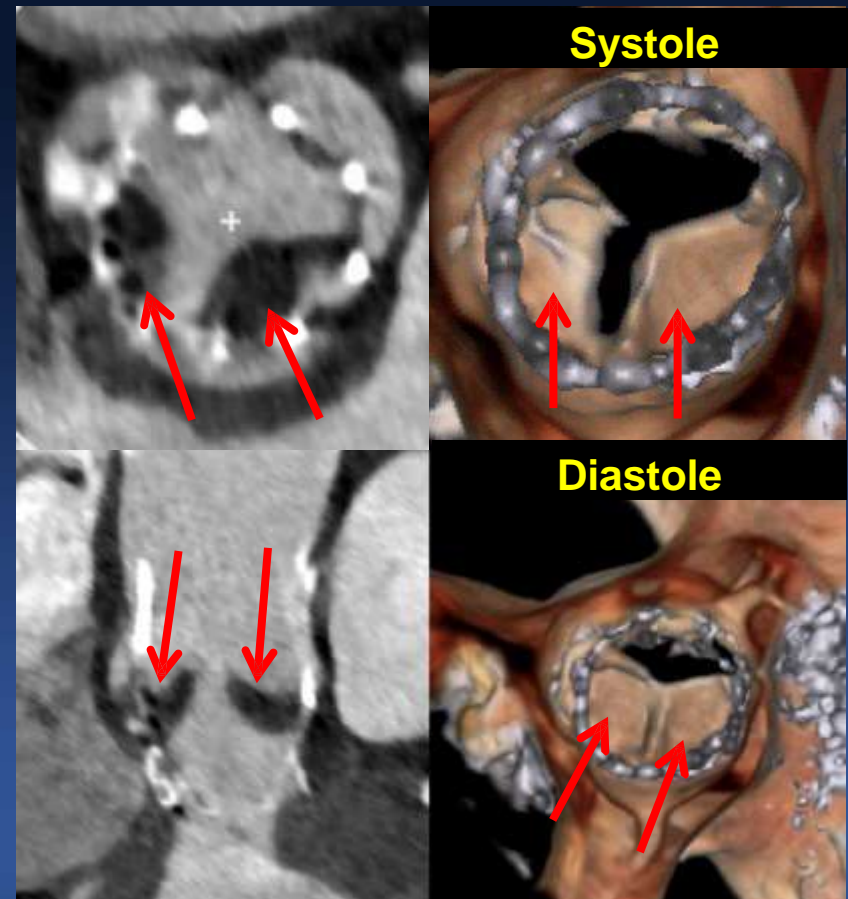
STORTECKY S, WINDECKER S. CIRCULATION 2012;126:2921-4

# 4D-CT after TAVR

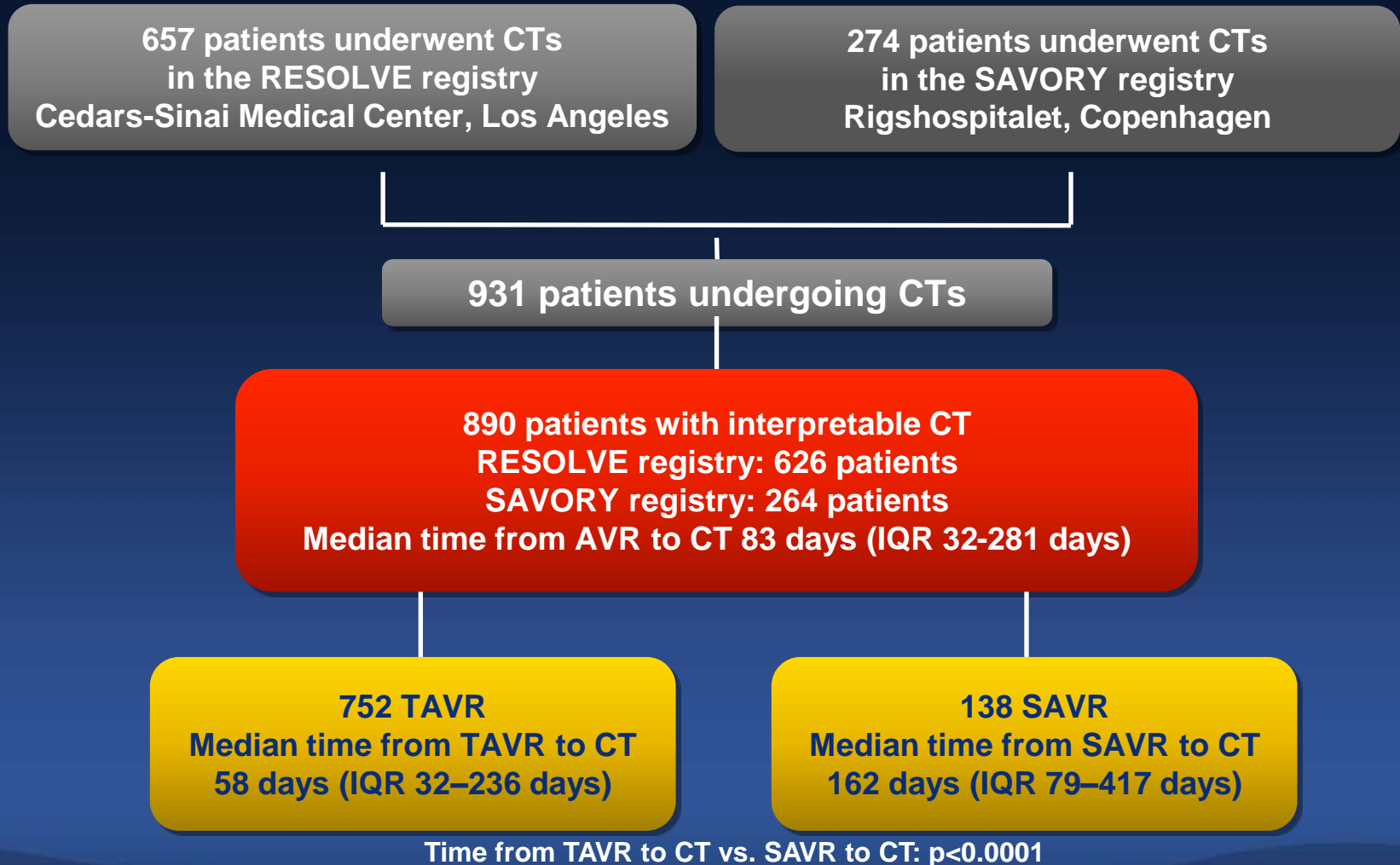
**Normal leaflets**



**Thickened leaflets with thrombus**



# Subclinical Leaflet Thrombosis in SVR and TAVR : 2 Observational Registry



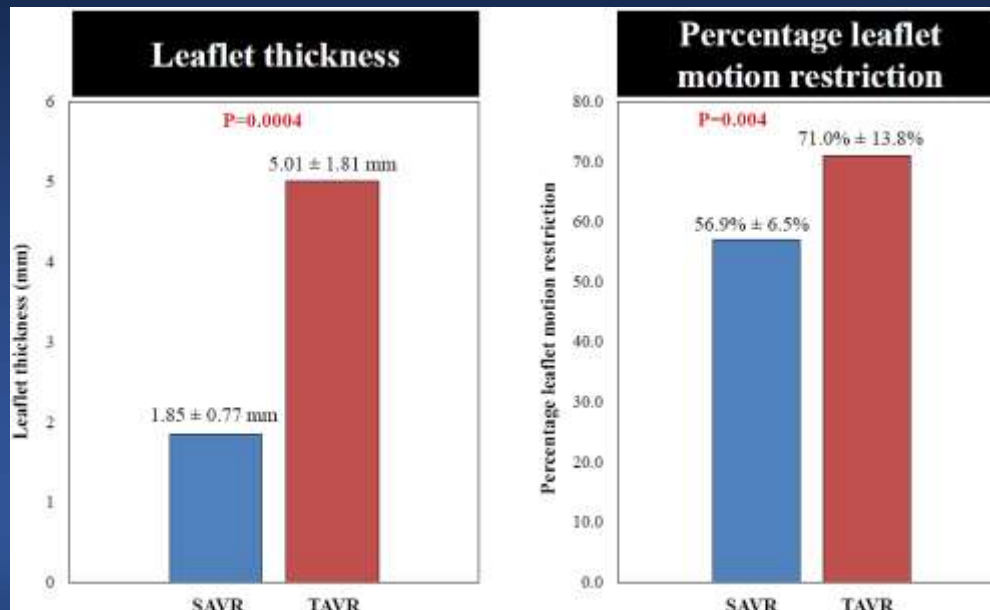
# Prevalence of reduced leaflet motion

Reduced leaflet motion 106  
(11.9%) patients

**TAVR:**  
13.4% (101 out of 752)

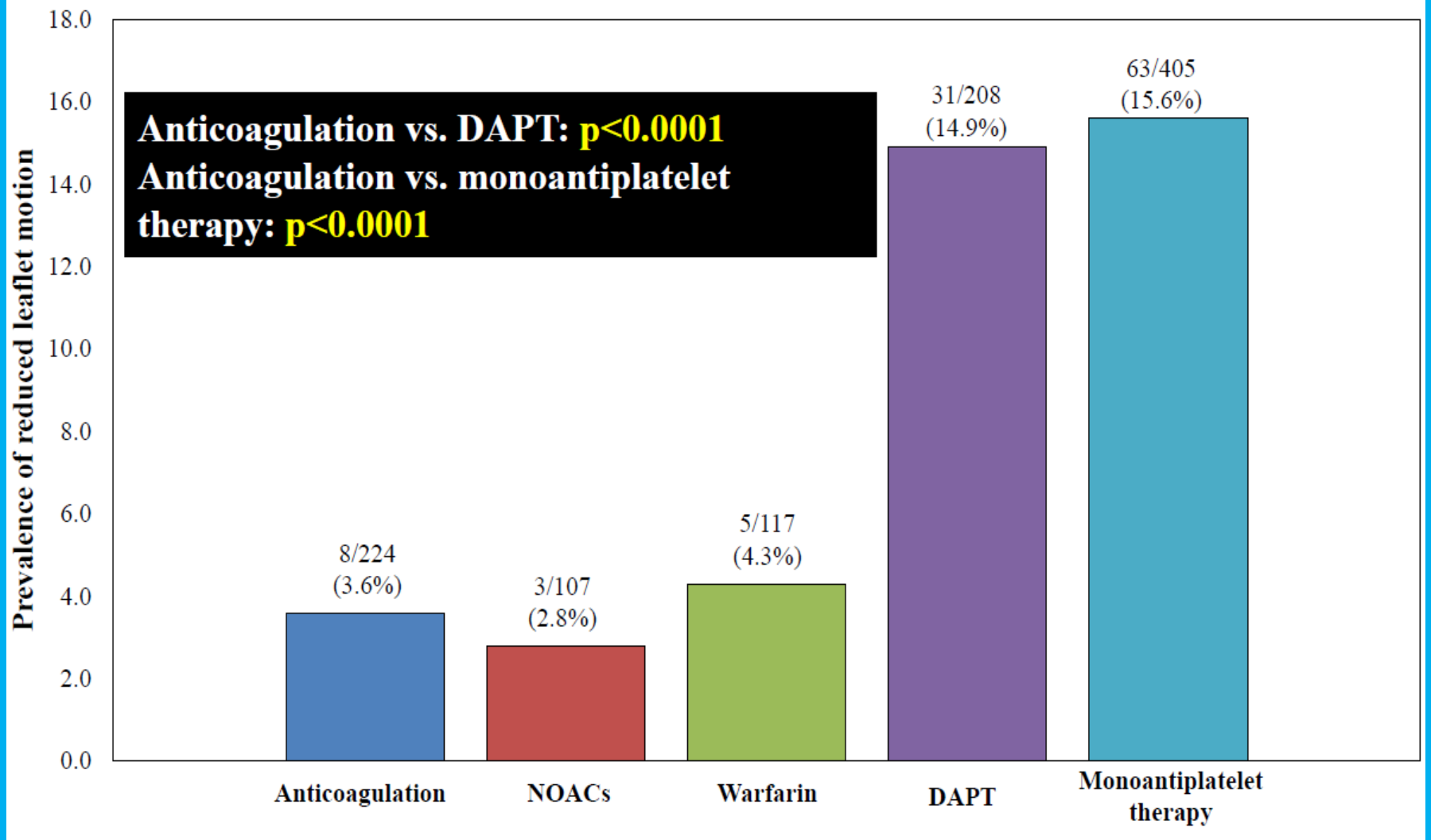
**SAVR:**  
3.6% (5 out of 138)

**TAVR vs. SAVR:  $p=0.001$**

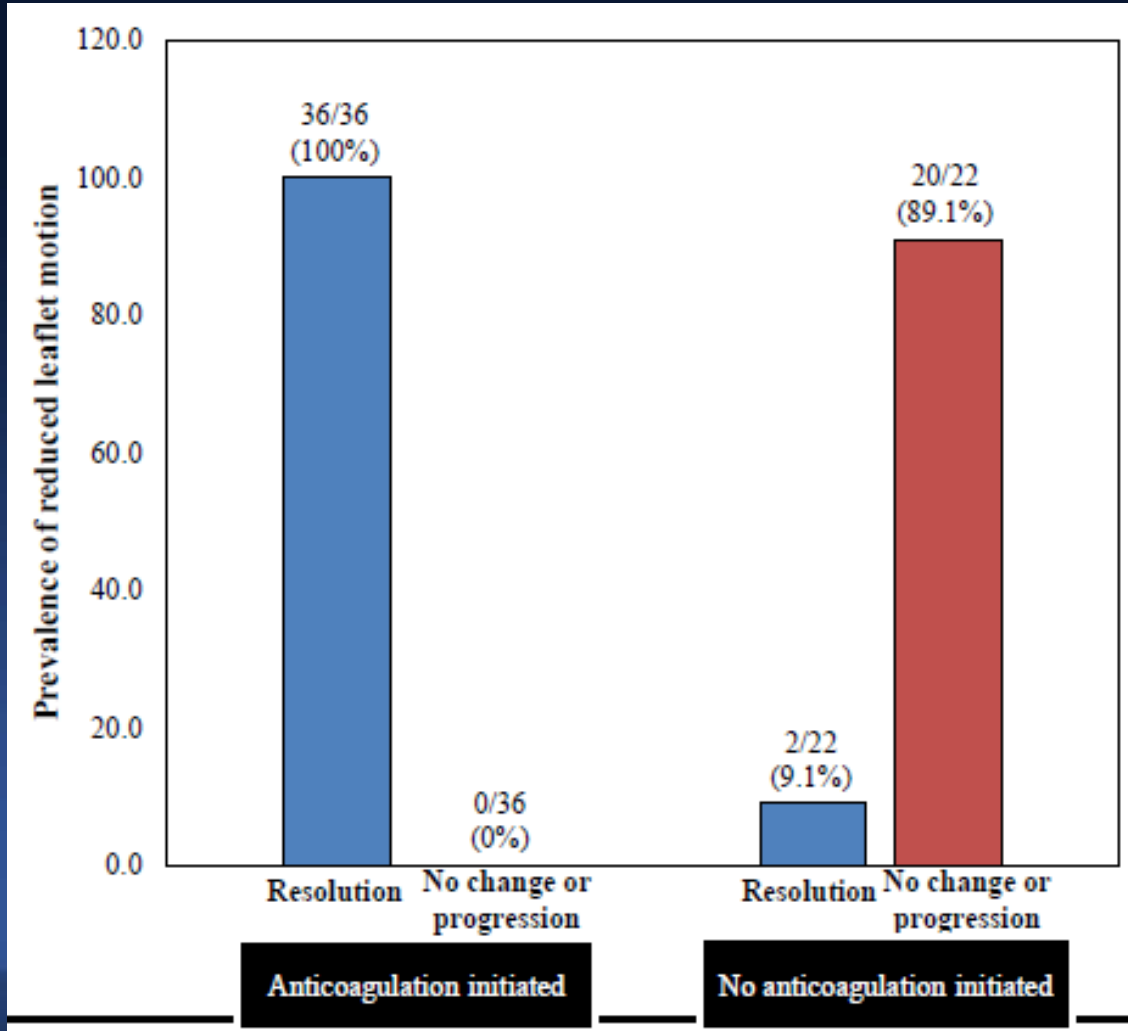


# Analysis of Antithrombotic Regimen

## 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 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

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)		HR (95% CI)	p-value
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years		
<b>Non-procedural events</b>						
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
<b>Strokes/TIAs</b>	<b>20/784 (2.6%)</b>	<b>1.75</b>	<b>8/106 (7.6%)</b>	<b>5.71</b>	<b>3.30 (1.45-7.50)</b>	<b>0.004</b>
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
<b>TIAs</b>	<b>7/784 (0.9%)</b>	<b>0.60</b>	<b>5/106 (4.7%)</b>	<b>3.48</b>	<b>5.89 (1.87-18.60)</b>	<b>0.002</b>

# Current 2017 ACC/AHA Guideline : TAVR

<b>IIb</b>	<b>C</b>	<b>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.</b>	2014 recommendation remains current.
<b>III: Harm</b>	<b>B</b>	<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).</b>	2014 recommendation remains current.

<b>IIb</b>	<b>B-NR</b>	<b>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).</b>	<b>NEW:</b> 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

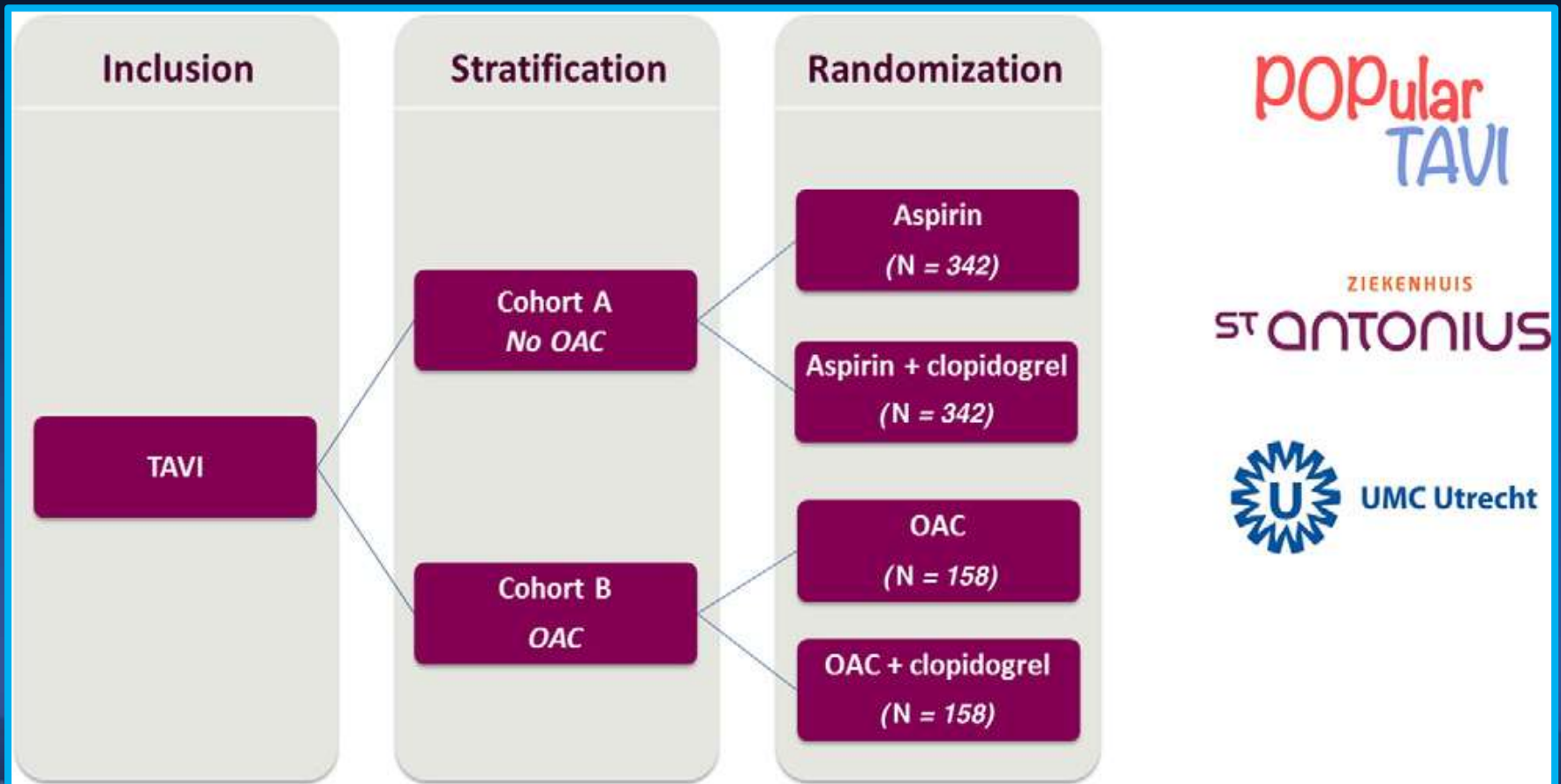
- POPular TAVI Trial
  - CLOE Trial

## 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

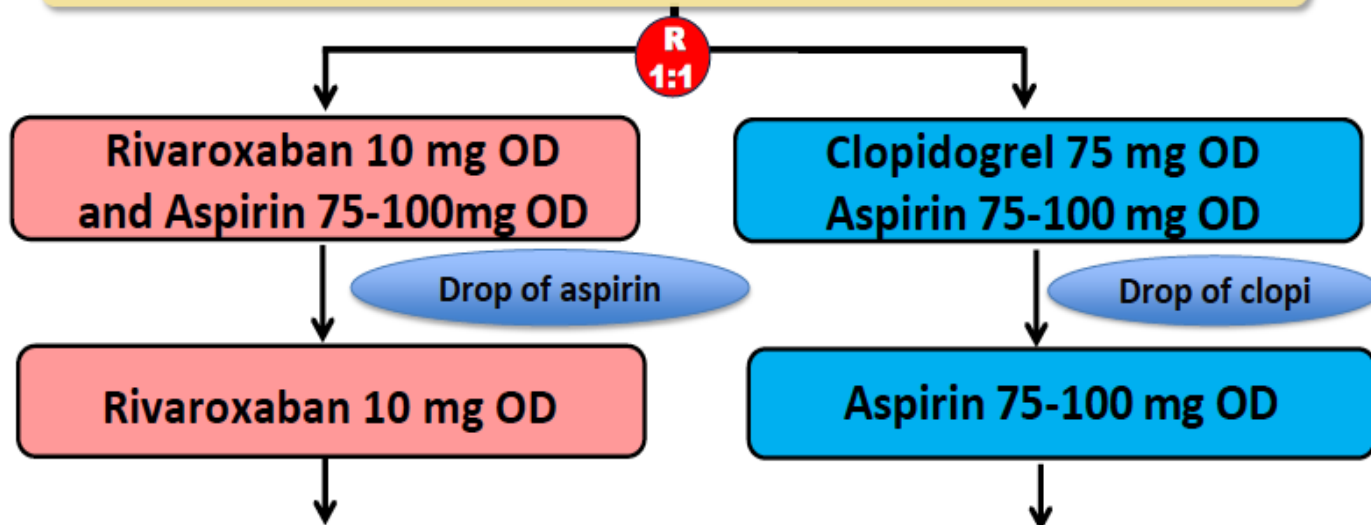
- Cost-Effectiveness
- QoL
- Frailty
- CTA Leaflet Substudy
- MRI Brain Substudy

# Ongoing Trials : GALILEO

## 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)

1520 patients after successful TAVI procedure



3 Mo

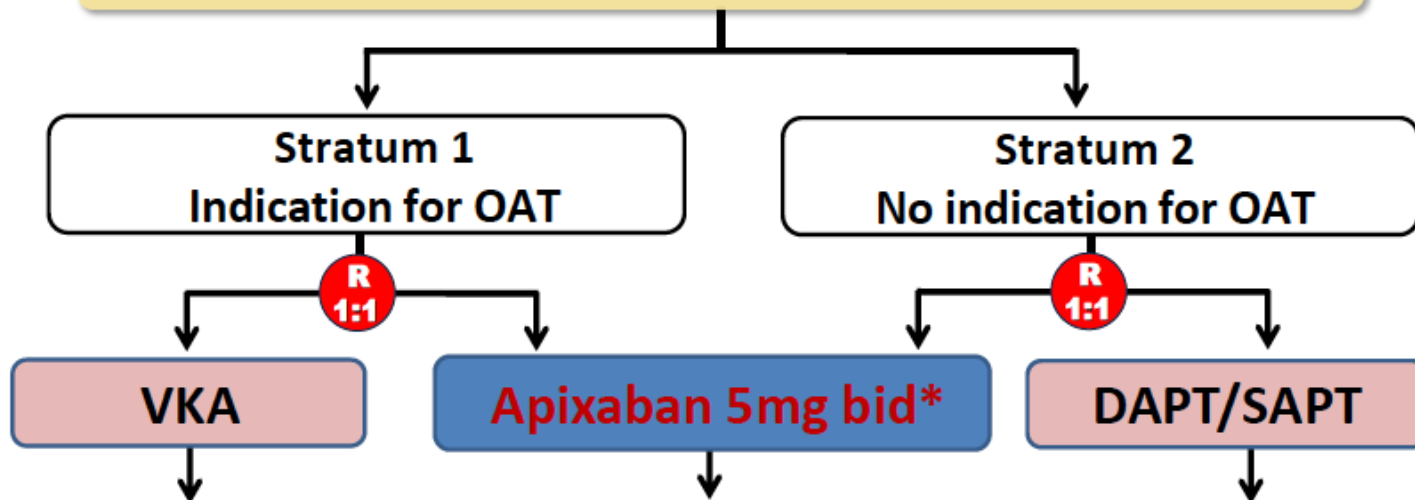
12 Mo

**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.**

# Ongoing Trials : ATLANTIS

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

1509 patients after successful TAVI procedure



**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).

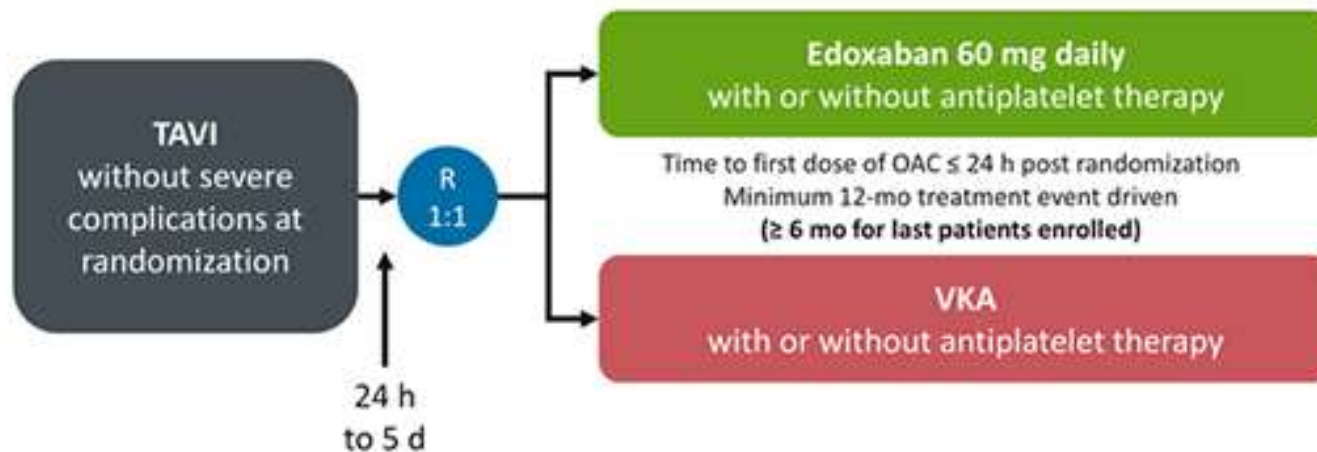


# Ongoing Trials

## : 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

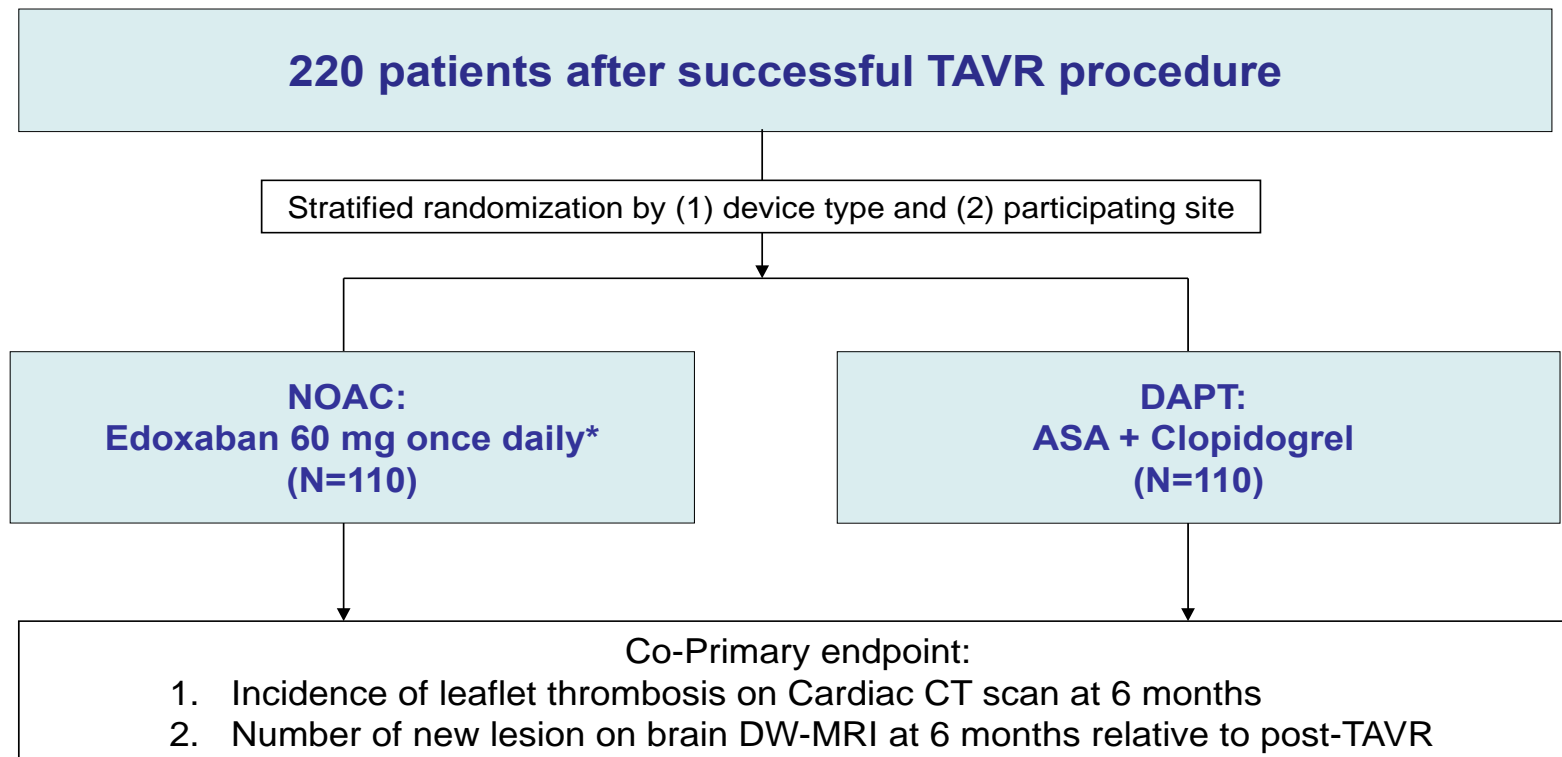
**Seung-Jung Park (Trial Chair) / Duk-Woo Park (Trial Co-chair)**

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

# Trial Scheme: ADAPT-TAVR Trial

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

## 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-D, 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  $\geq 19$  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 ( $\pm$  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

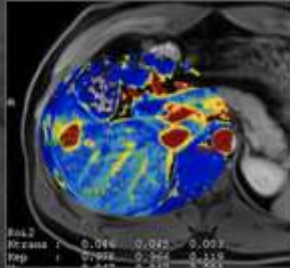
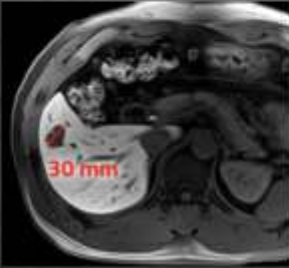
**Asan Image Metrics**  
마산병원시험영상의학지원팀

기관소개   조직구성   서비스   연구지원의뢰   IT 시스템   Datasharing   Study


로그인

## Imaging endpoints in clinical trials


Asan Image Metrics - AIM




ROI2	0.046	0.045	0.003
ROI3	0.046	0.045	0.003
ROI4	0.046	0.045	0.003




의료영상 전문인력에 의한  
신뢰할 수 있는 결과



웹 기반 프로세스에 의한  
신속한 결과



최신영상기법에 대한  
전문 지식으로 높은 품질



국제 기준(FDA)에 맞는  
표준화된 프로세스 구축

**"임상시험에서 영상 프로토콜 설계부터 촬영 및 분석까지  
통합적인 자문 및 영상지원 서비스를 통해  
효율적이고 신속 정확한 임상시험이 진행되도록 지원합니다."**

# 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 for their recommendations.
  - Practice variation in the real world is substantially high.
  - Clinical trials on antithrombotic regimens are ongoing & expanding.

The background of the slide is a photograph of a mountainous landscape, rendered in a monochromatic blue color scheme. The image shows several layers of rolling hills and mountains, with the foreground hills being darker and more detailed, and the background hills fading into a lighter blue. The sky is a pale, clear blue. The overall effect is serene and professional.

# **Thank You !!**

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