# Optimal Antithrombotic Therapy After TAVR and Ongoing Clinical Trials

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# Conflict of Interest Statement

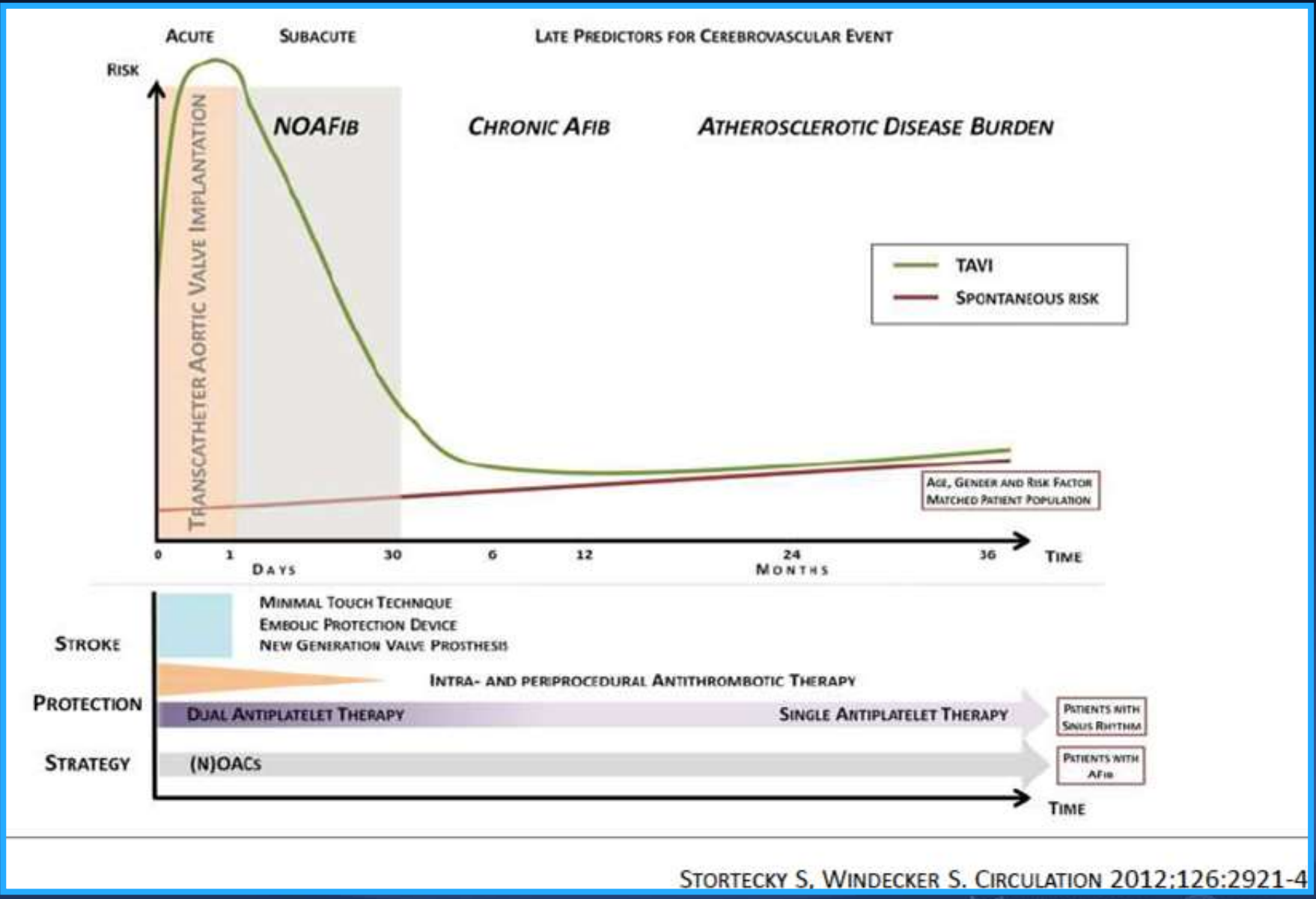
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

| Affiliation/Financial Relationship | Company |
| --- | --- |
| Consulting Fees/Honoraria | Edwards LifeSciences |
| Consulting Fees/Honoraria | Medtronic Inc |
| Consulting Fees/Honoraria | Boston Scientific |

# Medical Treatment After TAVR

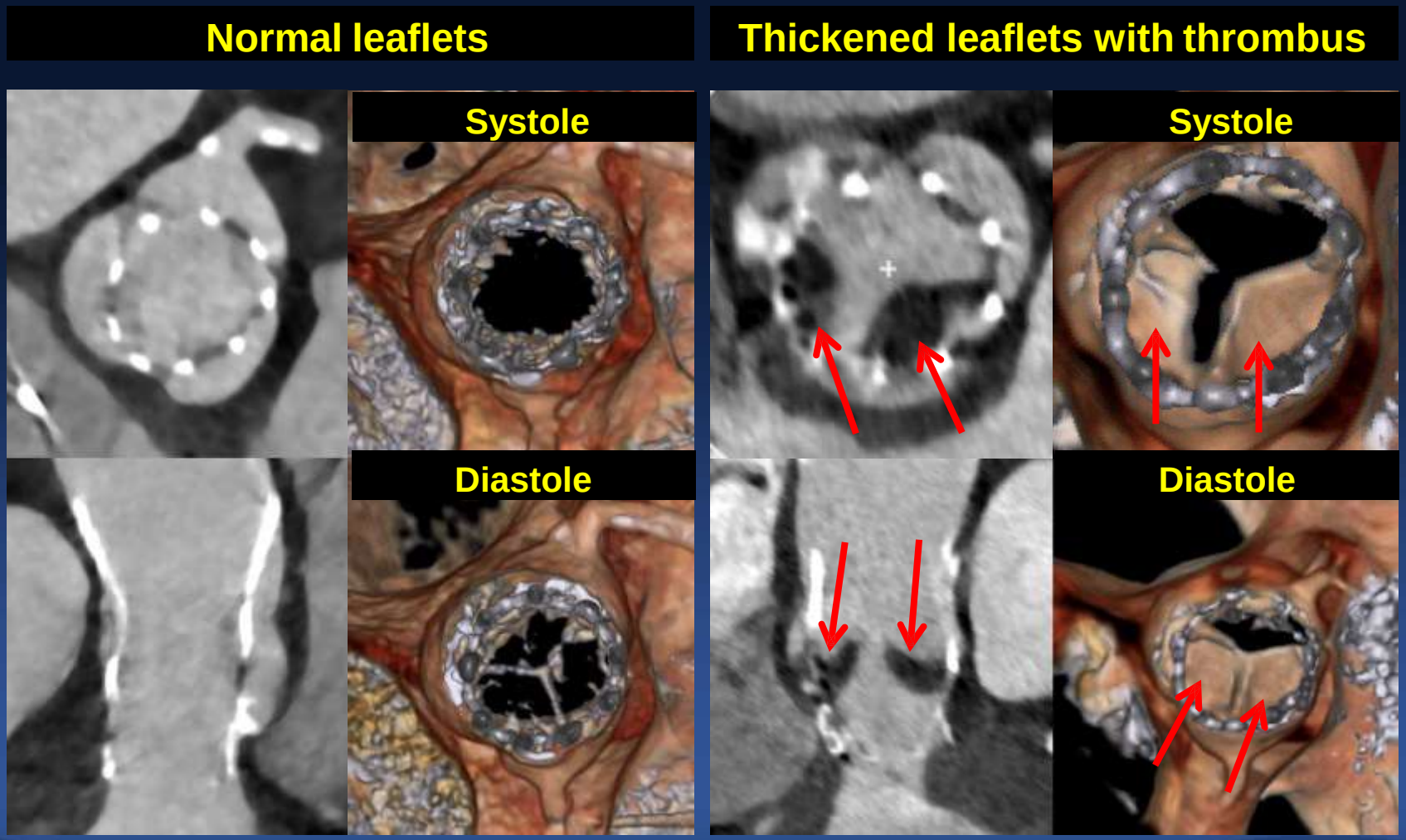
- Antithrombotic
- Low-Dose Diuretics
- HTN, DM, Lipid Drugs

# Timing of CerebroCVA Events after TAVI



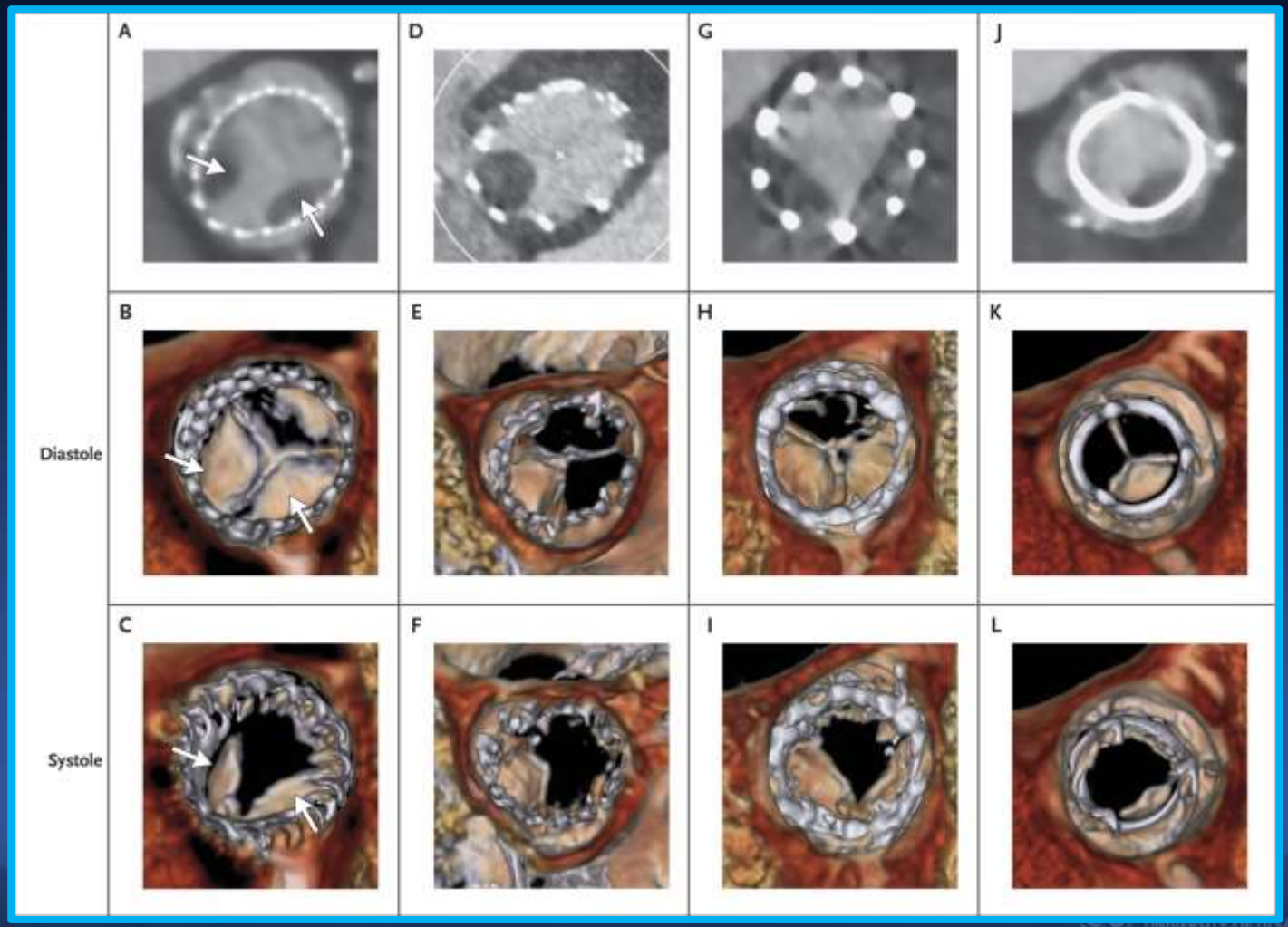

Stortecky S, Windecker S. Circulation 2012;126:2921-4

# 4D-CT after TAVR



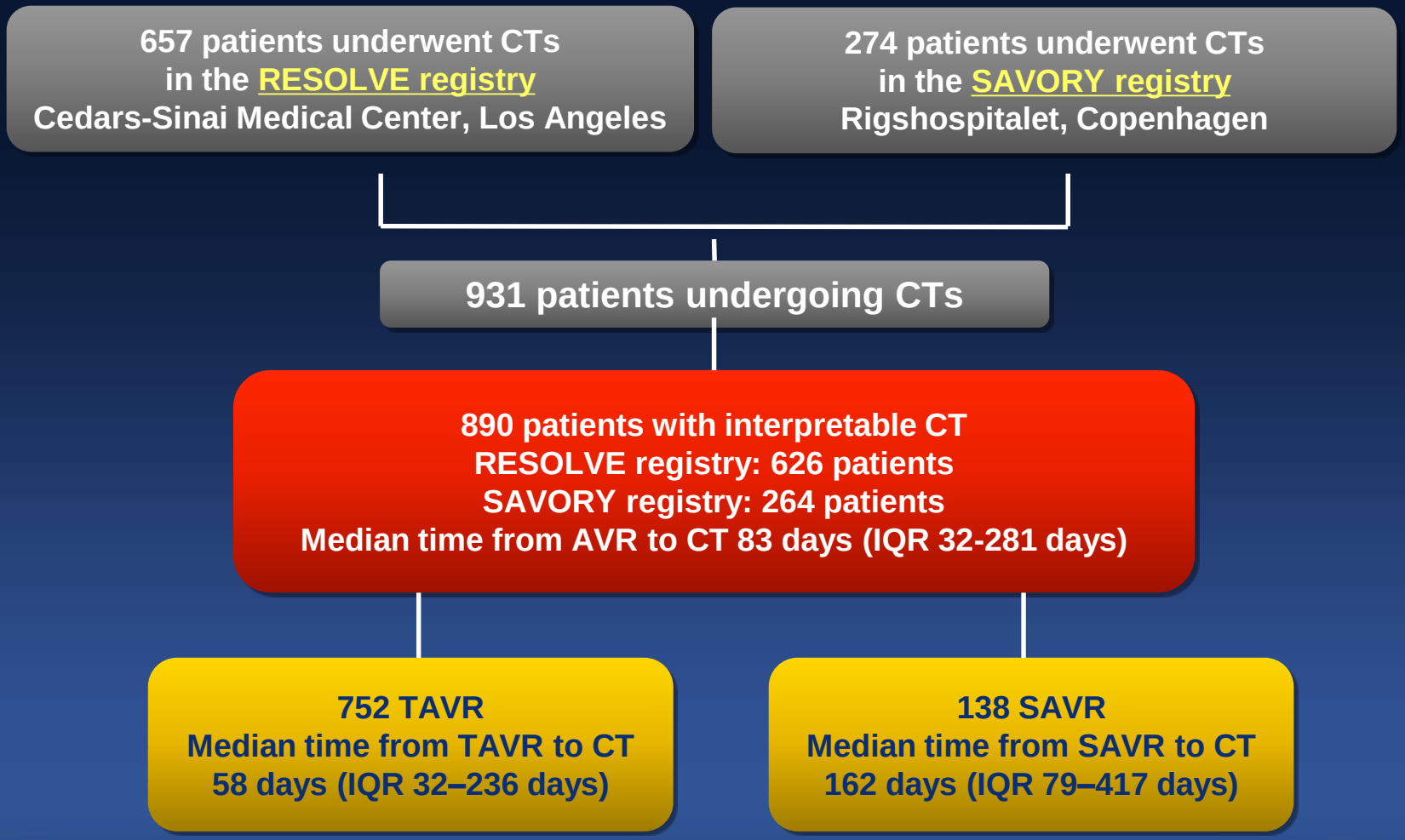
# Subclinical Leaflet Thrombosis after TAVR

## 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.*

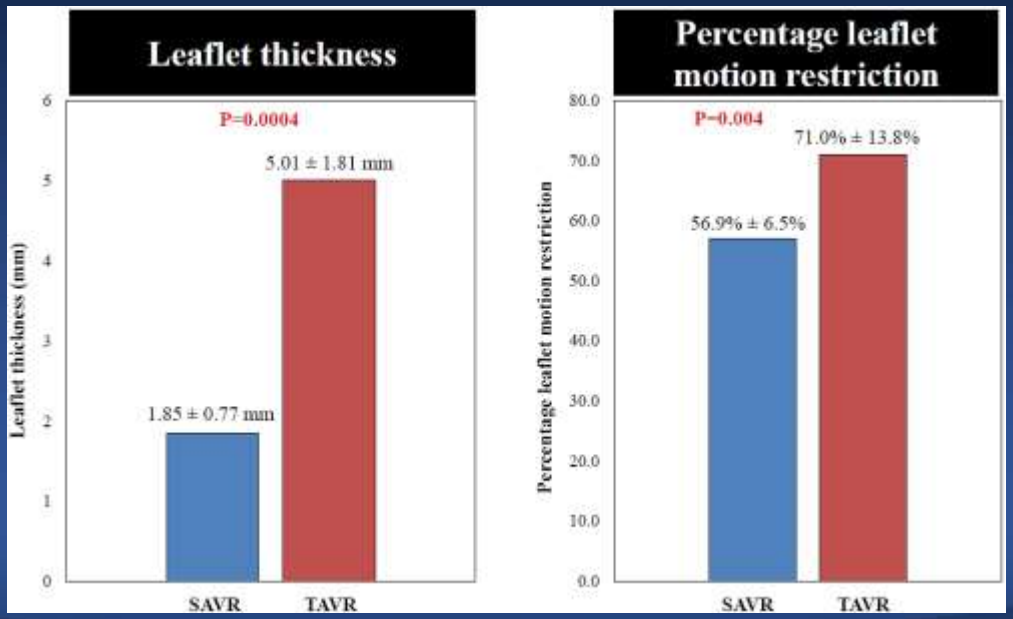
# Prevalence of reduced leaflet motion

**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**

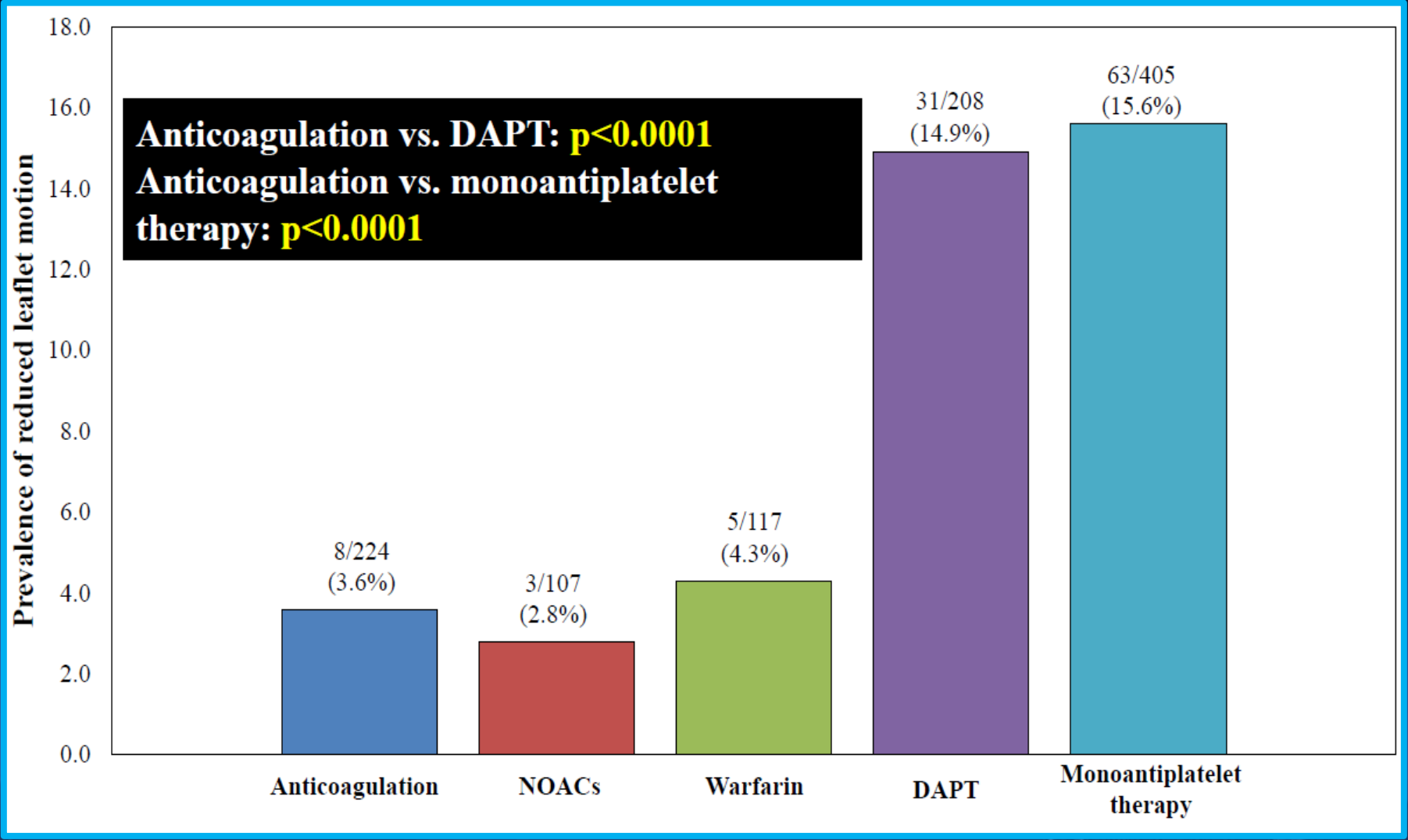





*Chakravarty T, et al. Lancet. 2017 Mar 19.*

# Analysis of Antithrombotic Regimen

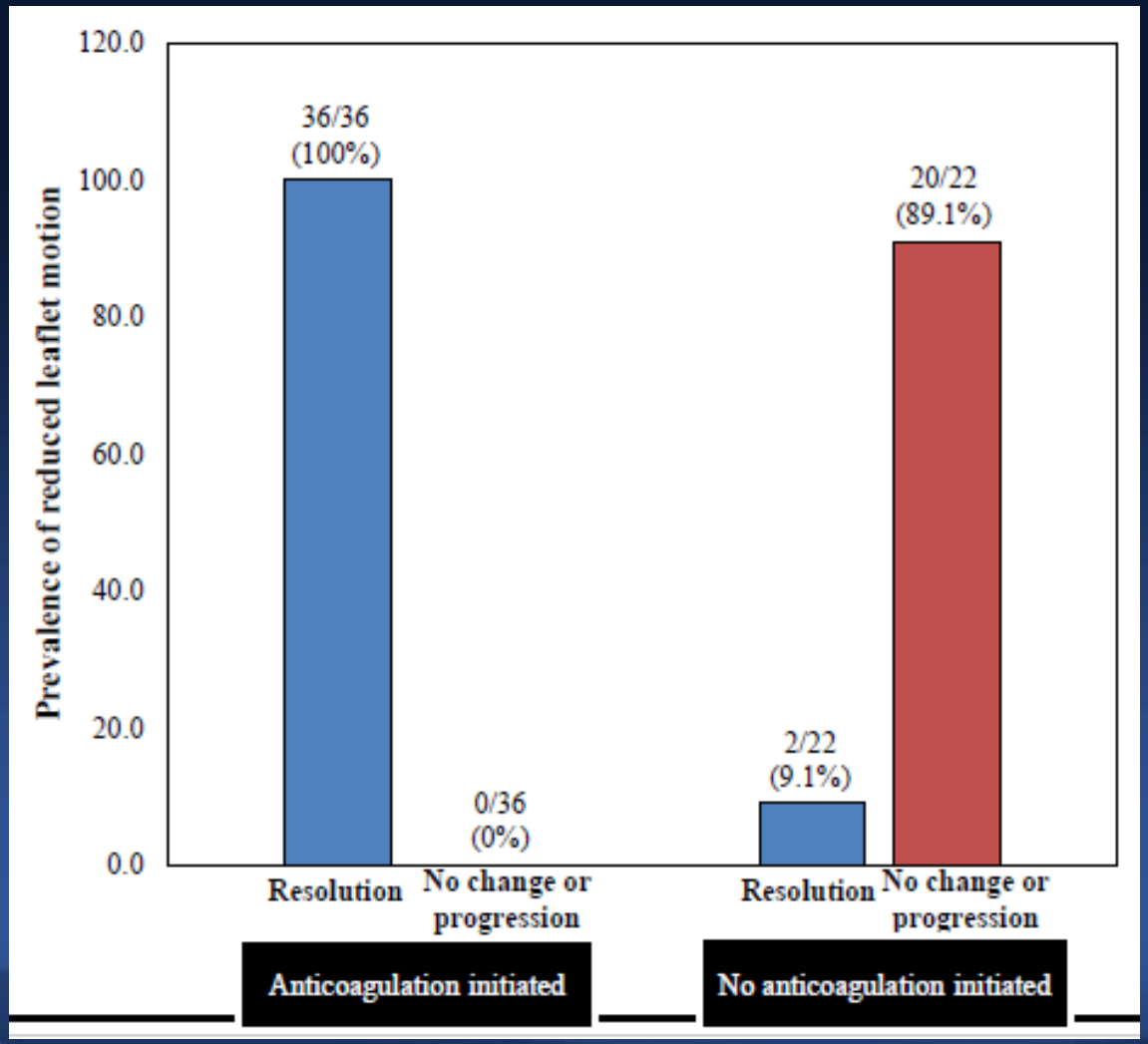
## Anticoagulation vs. antiplatelet therapy





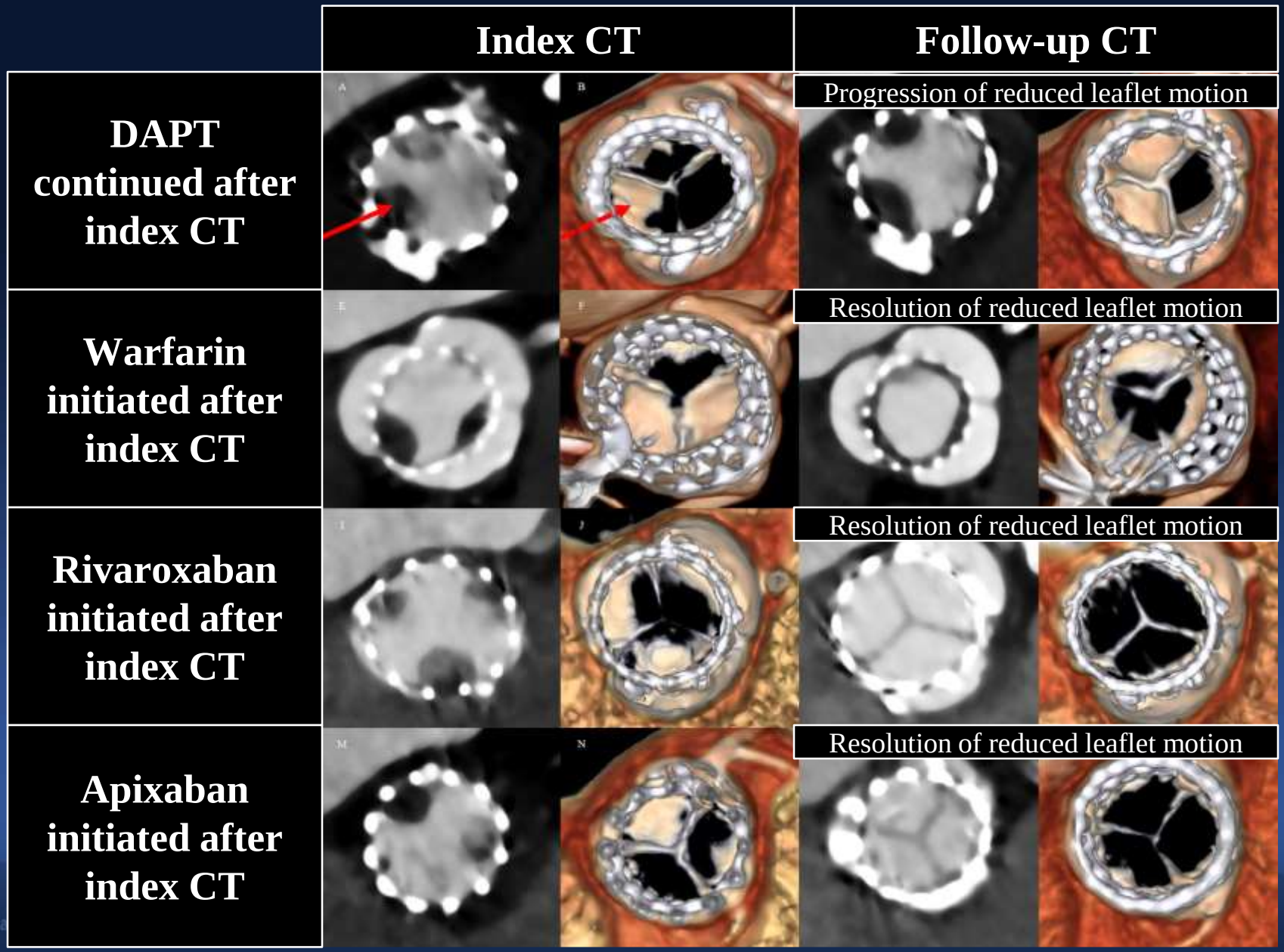

*Chakravarty T, et al. Lancet. 2017 Mar 19.*

# 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**

# 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) | | Reduced leaflet motion (N=106) | | | |
|---|---|---|---|---|---|---|
| | n/N (%) | Rate per 100 person-years | n/N (%) | Rate per 100 person-years | HR (95% CI) | p-value |
| **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** |

# 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

# Antithrombotic Trials After TAVR

## Omission of Clopidogrel

- ARTE Trial
- POPular TAVI Trial
- CLOE Trial

## NOAC Trial

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

# 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**

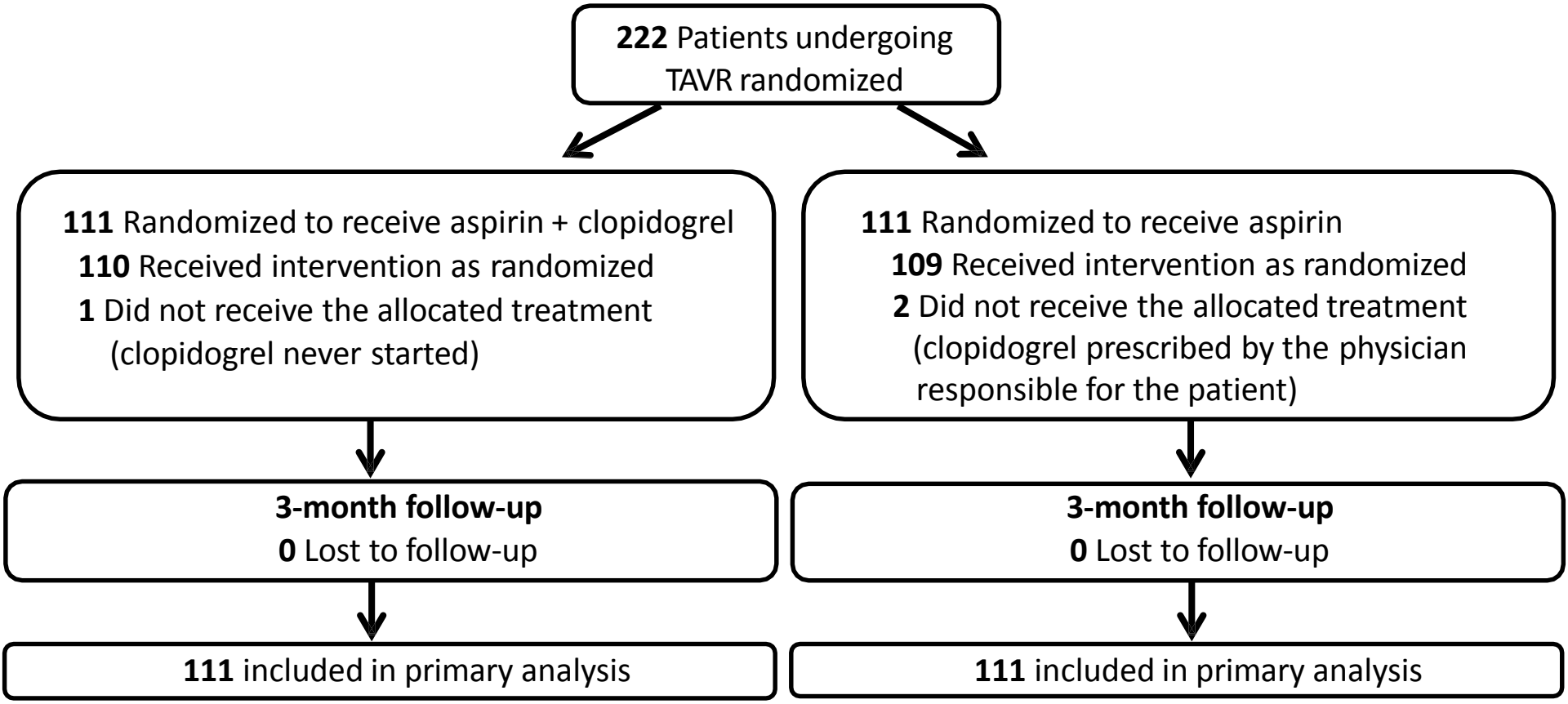
-Start within 24hrs after TAVR

-Continued for 3 months

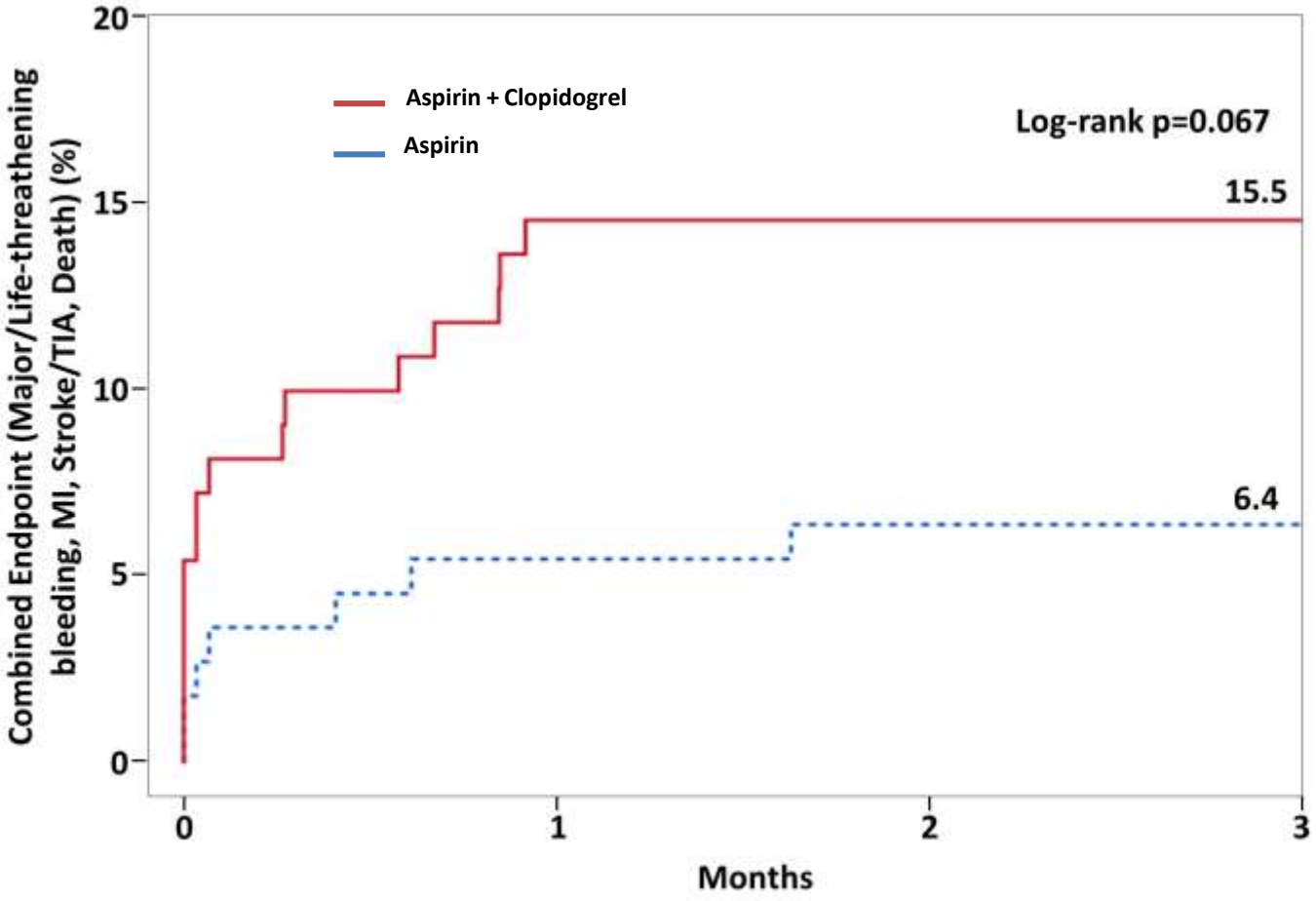
Clinical visit/phone contact at 1- 3- and 12-month follow-up

# ARTE Trial - Results

## Flowchart of the Study Population

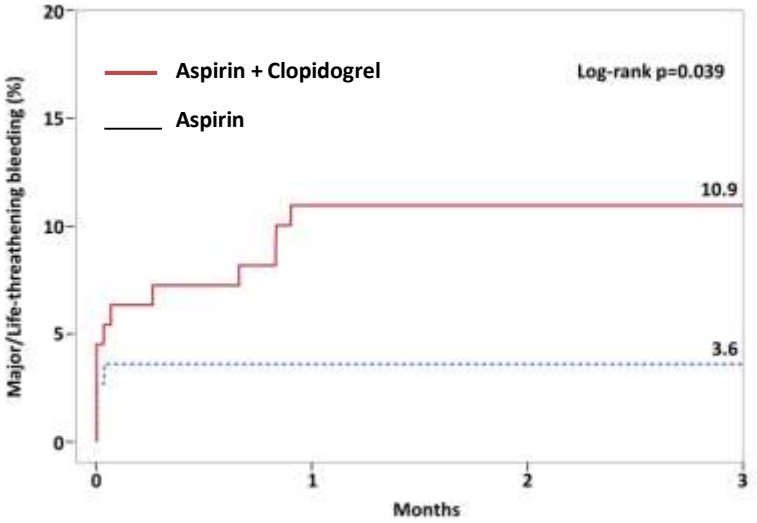


# Kaplan-Meier Curves (Combined Endpoint)

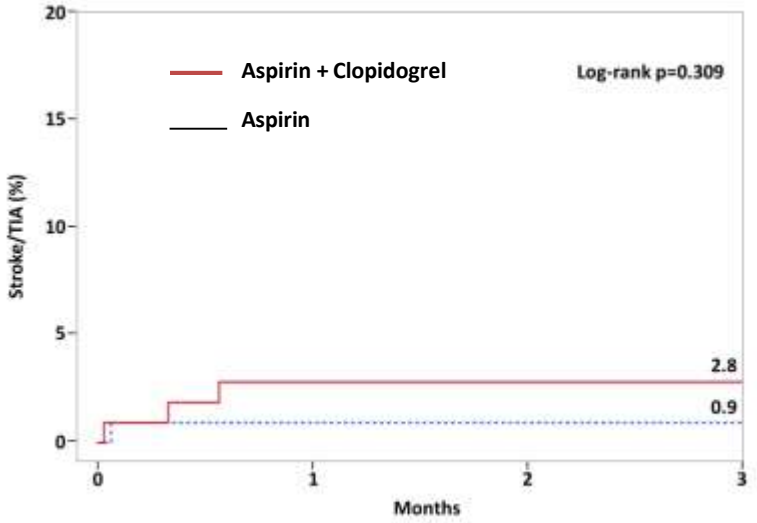


# Kaplan-Meier Curves (Ischemic, Bleeding Events)

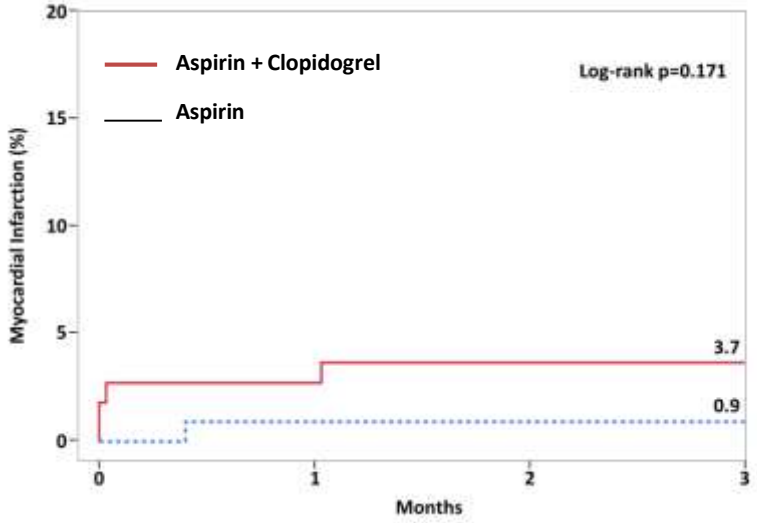
## Major or life-threatening bleeding



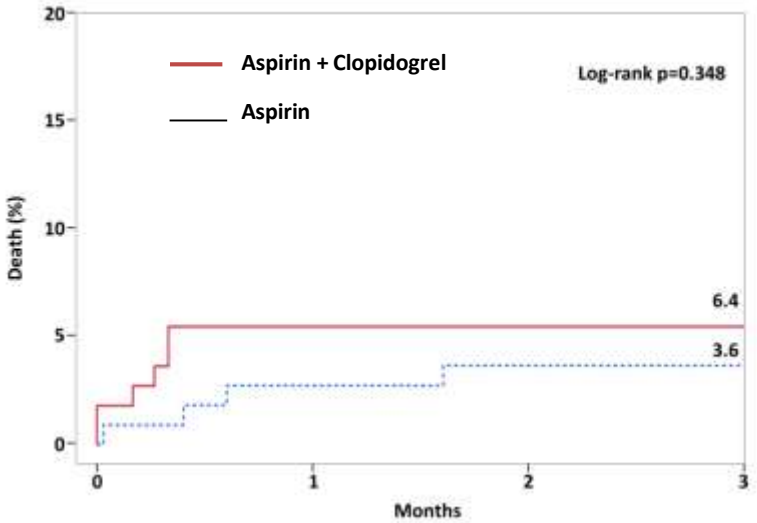

## Stroke or TIA




## Myocardial infarction (MI)

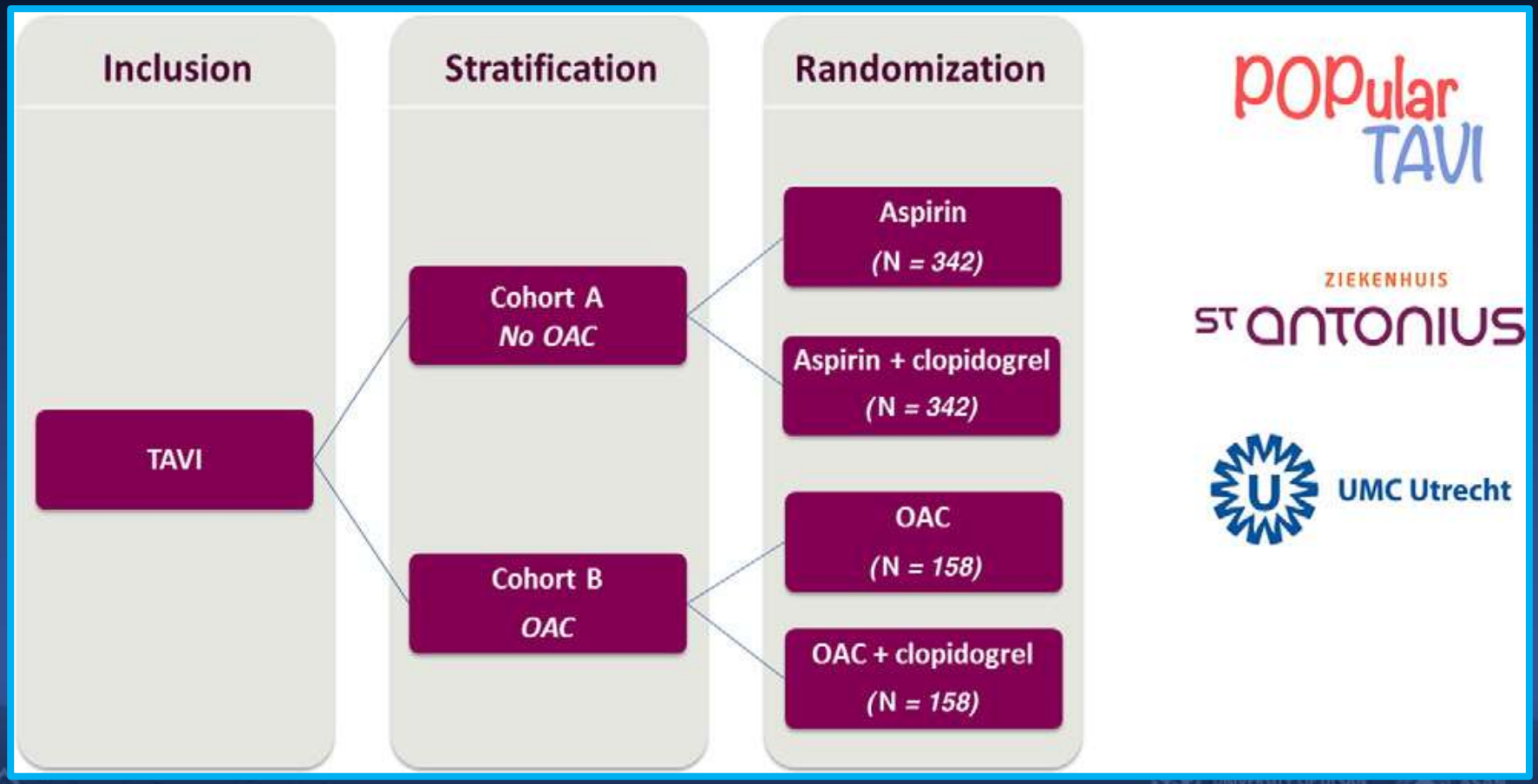



## Death



# 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

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**NOAC Trial**

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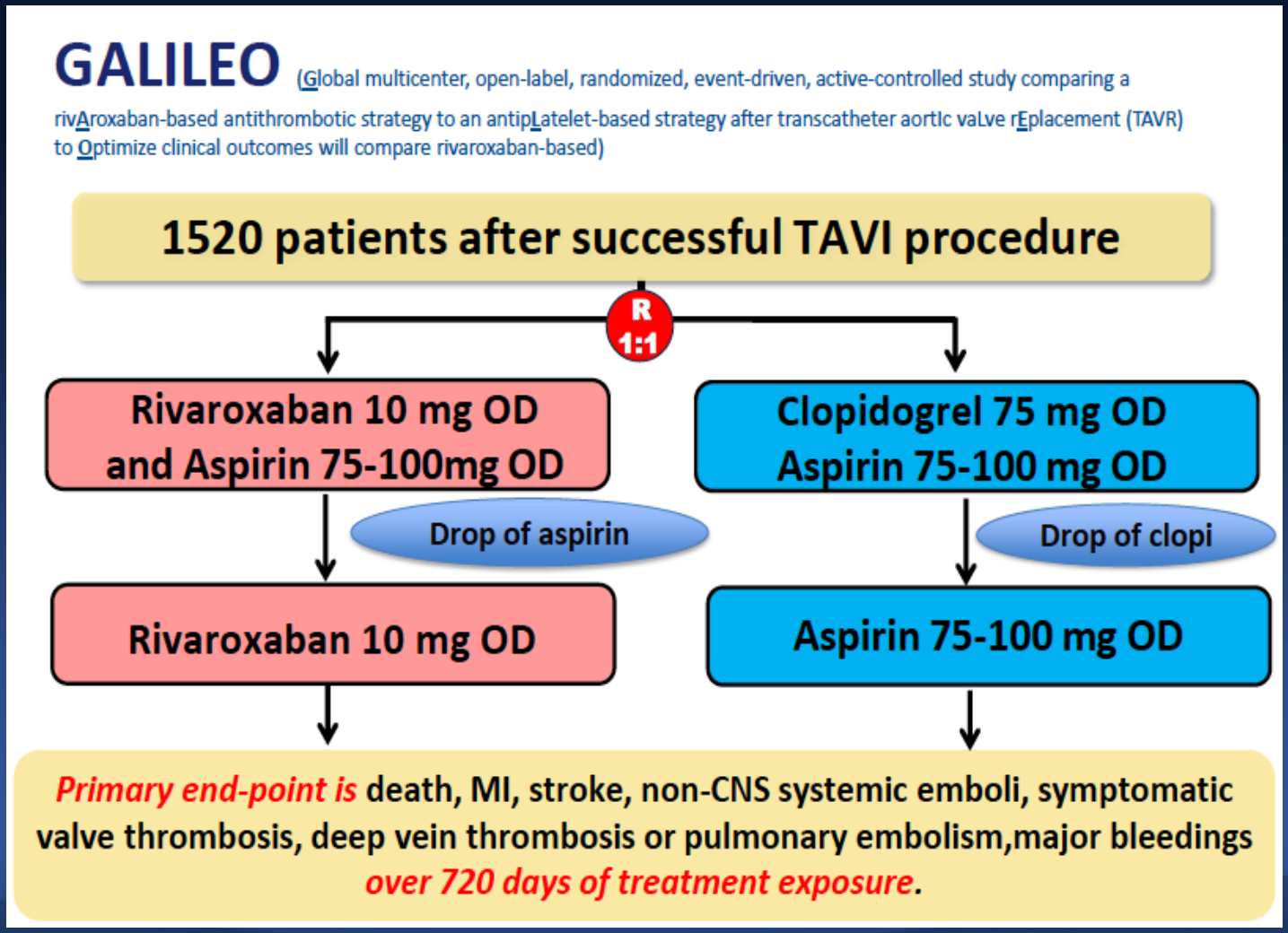
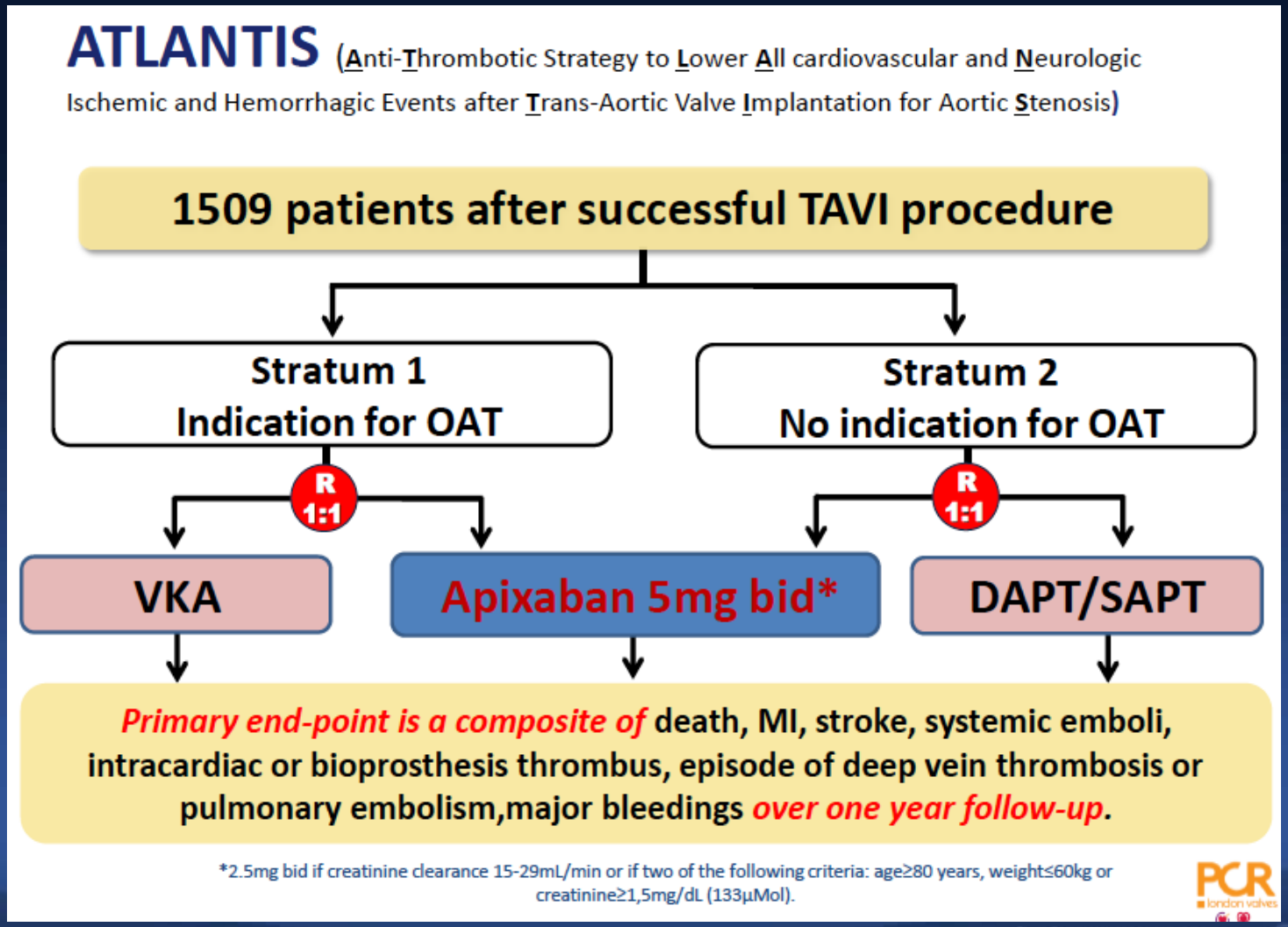
- ATLANTIS Trial
- ENVISAGE TAVI-AF Trial
- ADAPT-TAVR Trial

Mount Sinai Heart

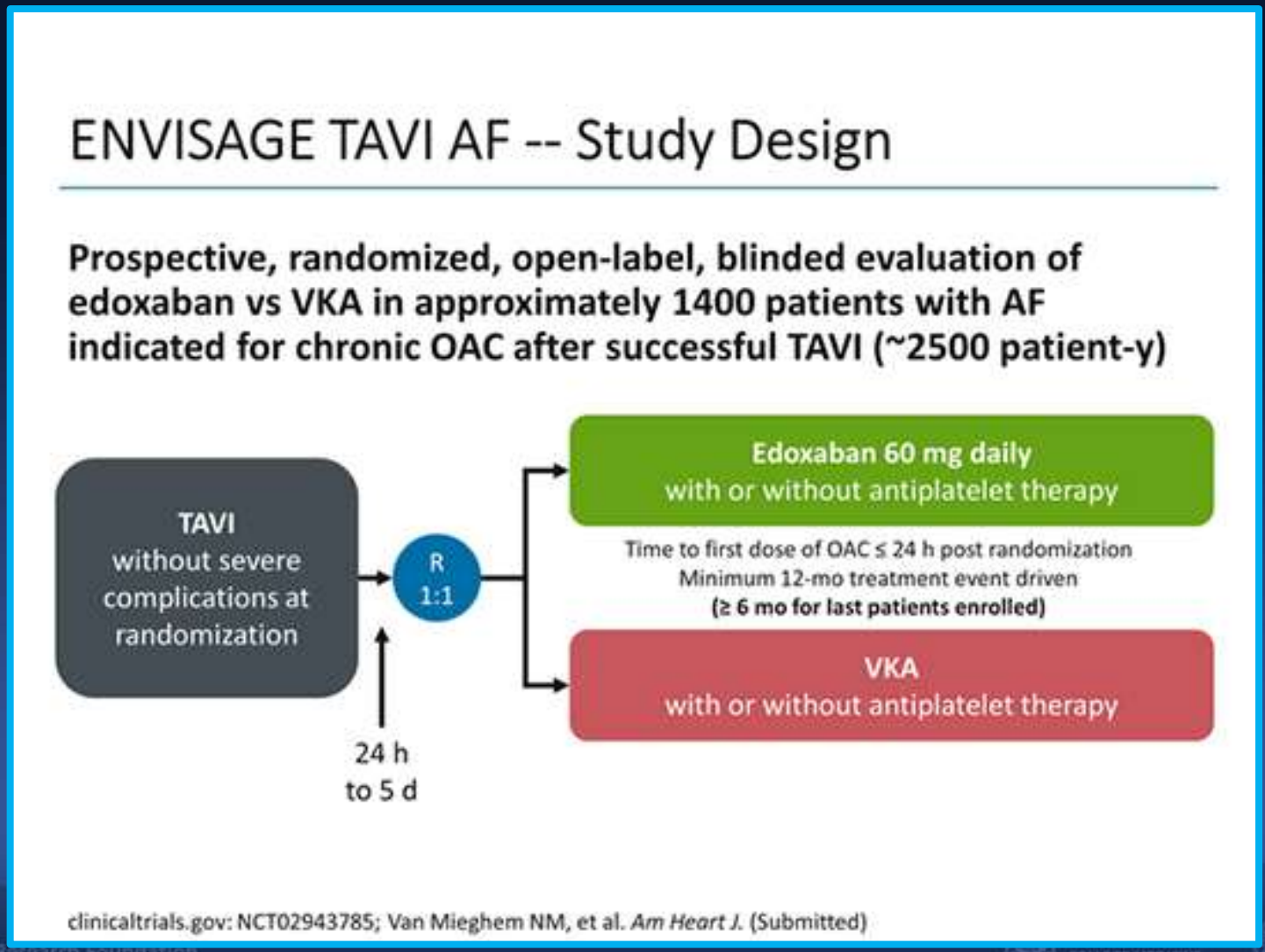
# Ongoing Trials
# : GALILEO



# Ongoing Trials : ATLANTIS



# Ongoing Trials
# : ENVISAGE TAVI-AF



# 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

# What is ADAPT-TAVR trial?

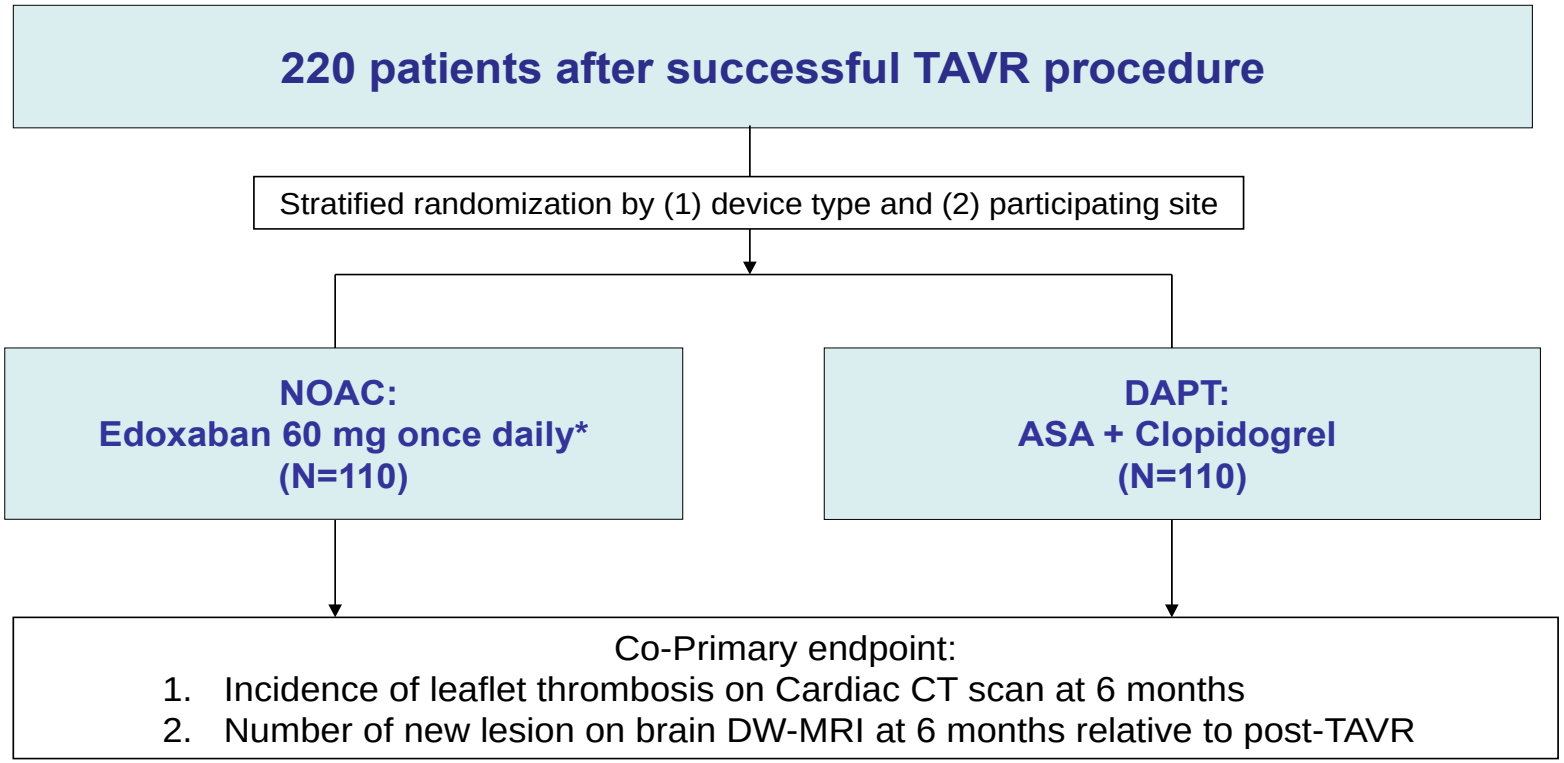
- A multi-center, multi-national randomized, open-label, active-treatment, controlled trial.

- To compare the efficacy of NOAC (edoxaban) vs. DAPT (aspirin and clopidogrel) for prevention of leaflet thrombosis (4-D volume-rendered cardiac CT) and cerebral embolization (brain DW-MRI imaging) in patients without an absolute indication for chronic OAC after successful TAVR.

# Trial Scheme: ADAPT-TAVR Trial

***A***nticoagulant 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

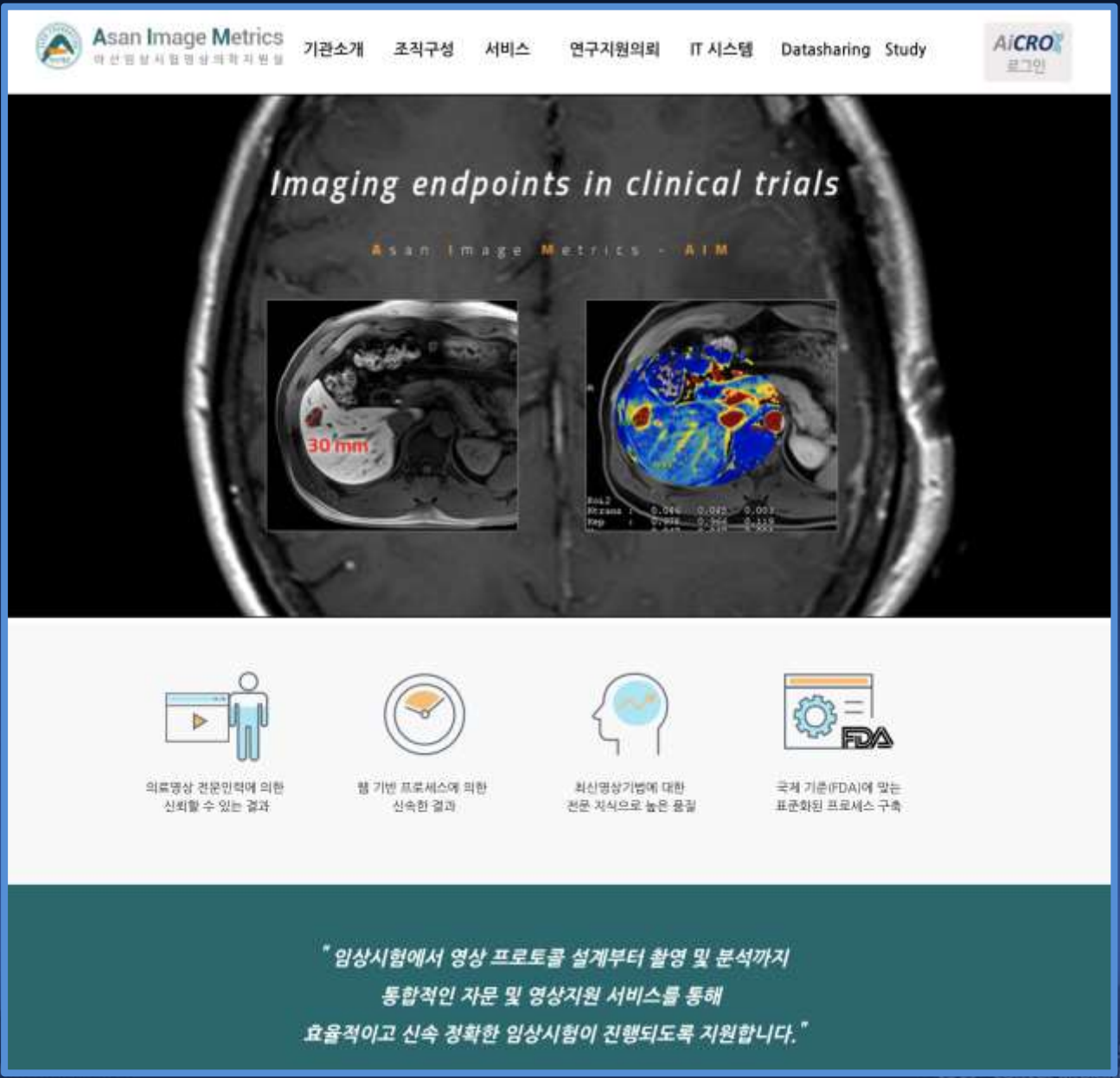
- Leaflet motion; defined as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet) in at least one valve leaflet

# 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



## Site core lab service: 원내에서 수행되는 임상시험 영상관리

연구지원의뢰 바로가기

Asan Image Metrics
아산임상시험영상의학지원실

- 영상, 조직검사 및 시술 코디네이션
- 영상관련 서류작업 (장비성적서, Site survey, Data transfer form)
- 임상시험 영상분석: RECIST, WHO, irRC, volumetry 등
- 디지털 영상 익명화/돌출

Protocol → Coordination of Imaging studies → Acquisition using Standardized protocol → Quality Assessment → Imaging Analysis

## Central core lab service: 다기관 임상시험 영상관리 및 독립적 영상평가

연구지원의뢰 바로가기

영상 프로토콜 설계
Image charter/SOP 작성

참여기관 교육 및 모니터링

표준프로토콜에 의한 영상촬영

영상 품질 관리
영상 데이터 관리

영상 프로세싱 및 분석
독립적 영상평가

*High Quality*
*Academic Imaging CRO*

데이터 신뢰도 | 업무 효율성 | 시험비용

# 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 – 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.

# Thank You !!

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