TAVR:
Antithrombotic Strategy

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Disclosure Statement of Financial Interest

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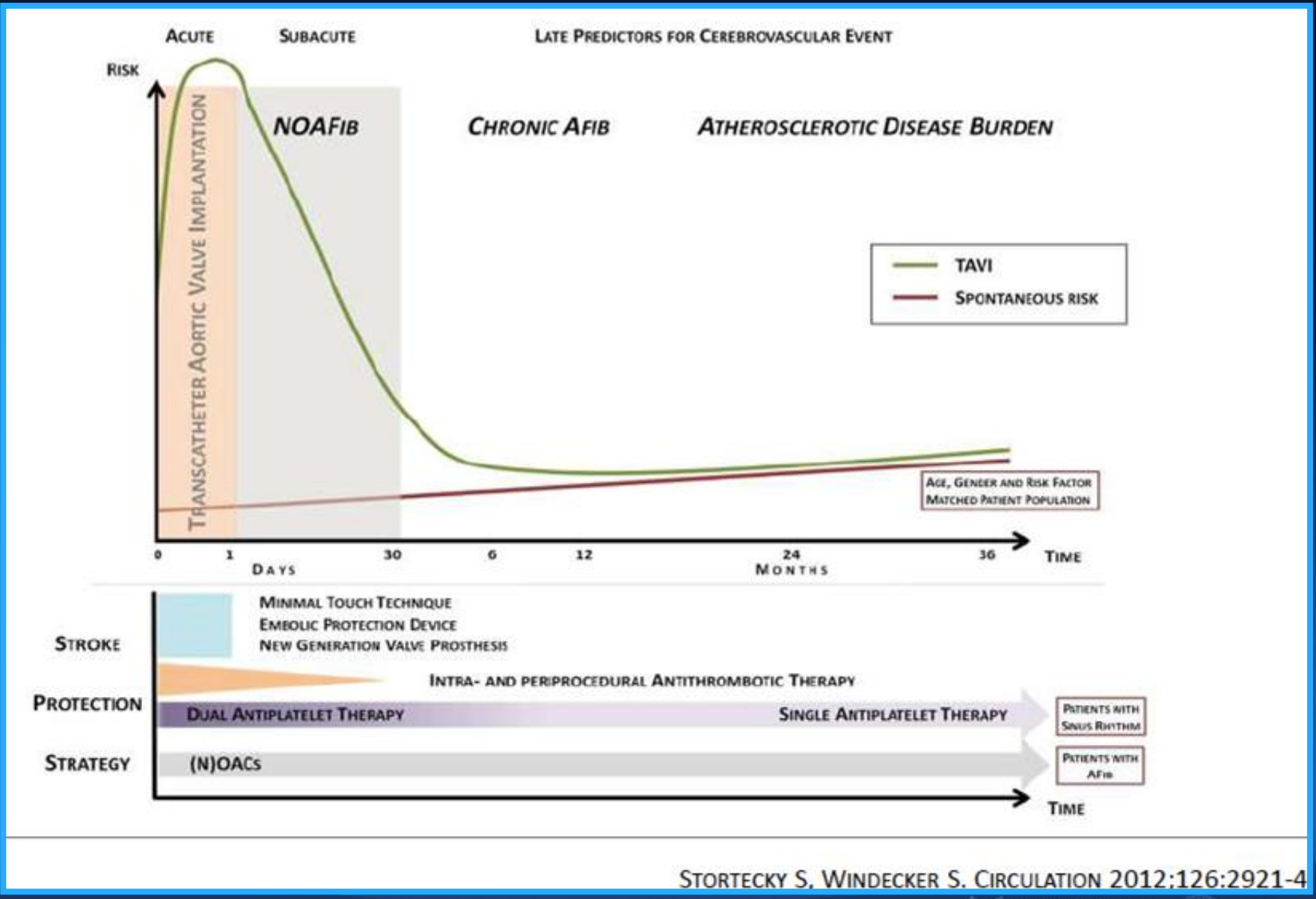
Medical Treatment After TAVR

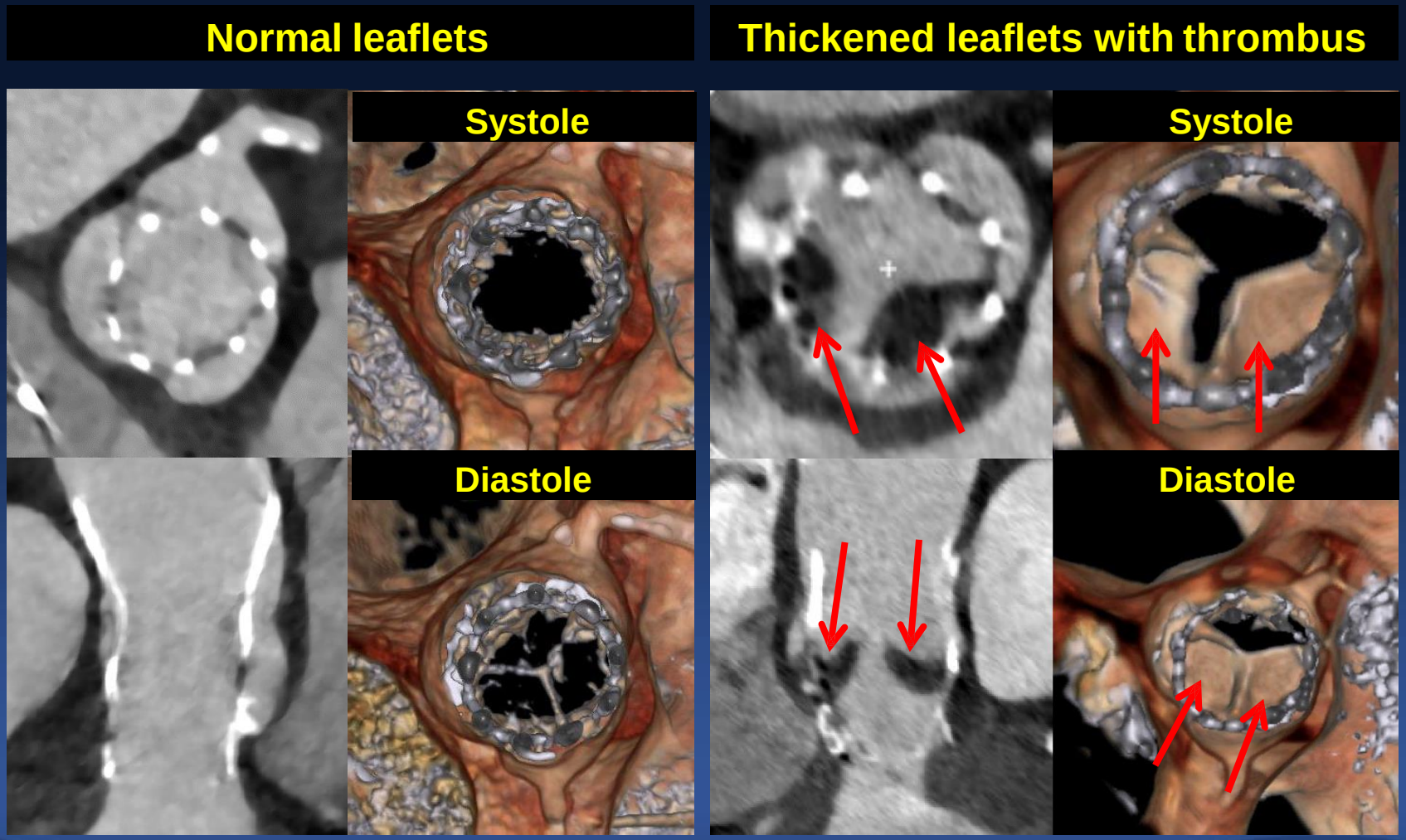
- Antithrombotic
- Low-Dose Diuretics
- HTN, DM, Lipid Drugs

Timing of CerebroCVA Events after TAVI



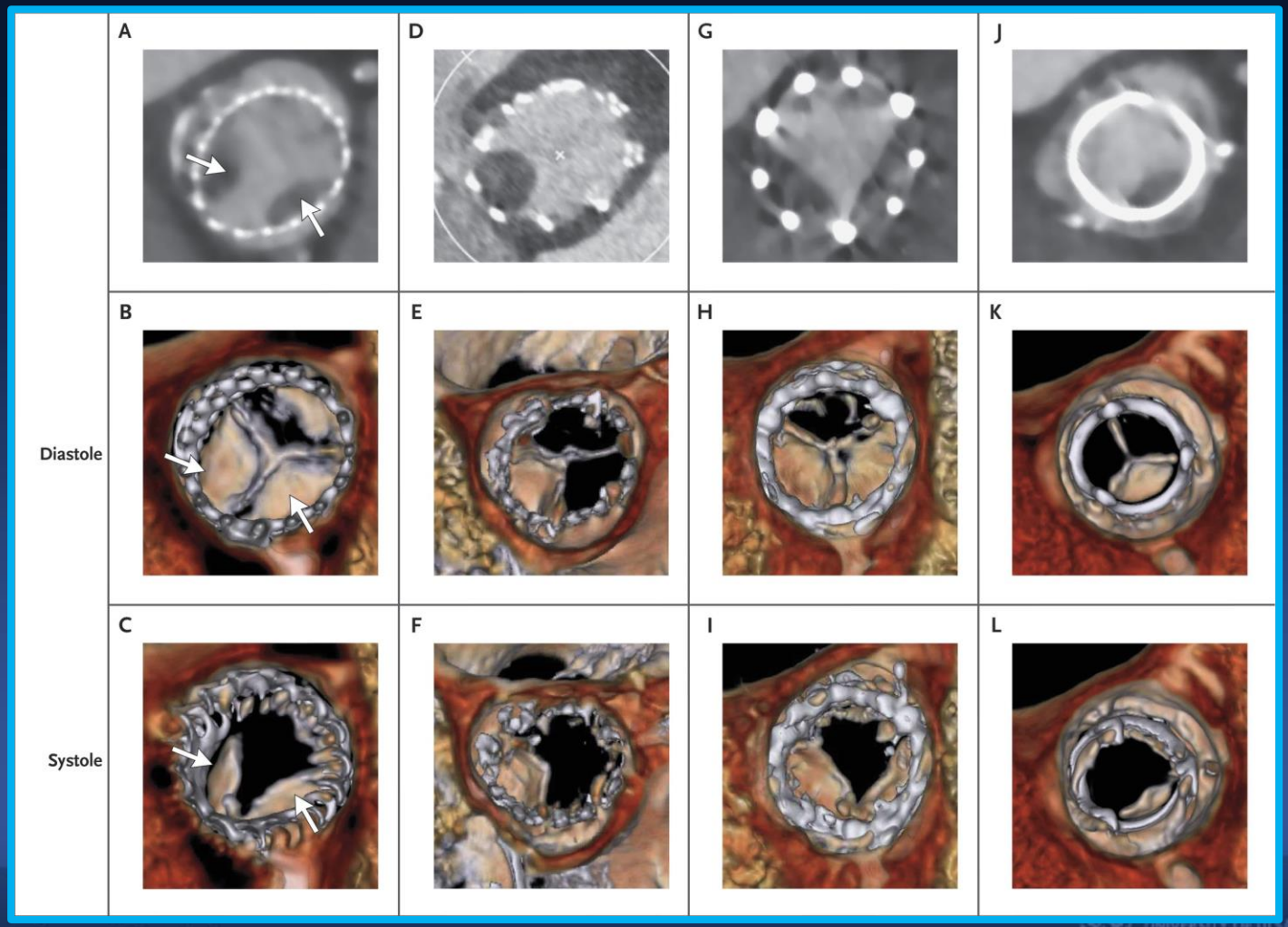
Stortecky S, Windecker S. Circulation 2012;126:2921-4

4D-CT after TAVR



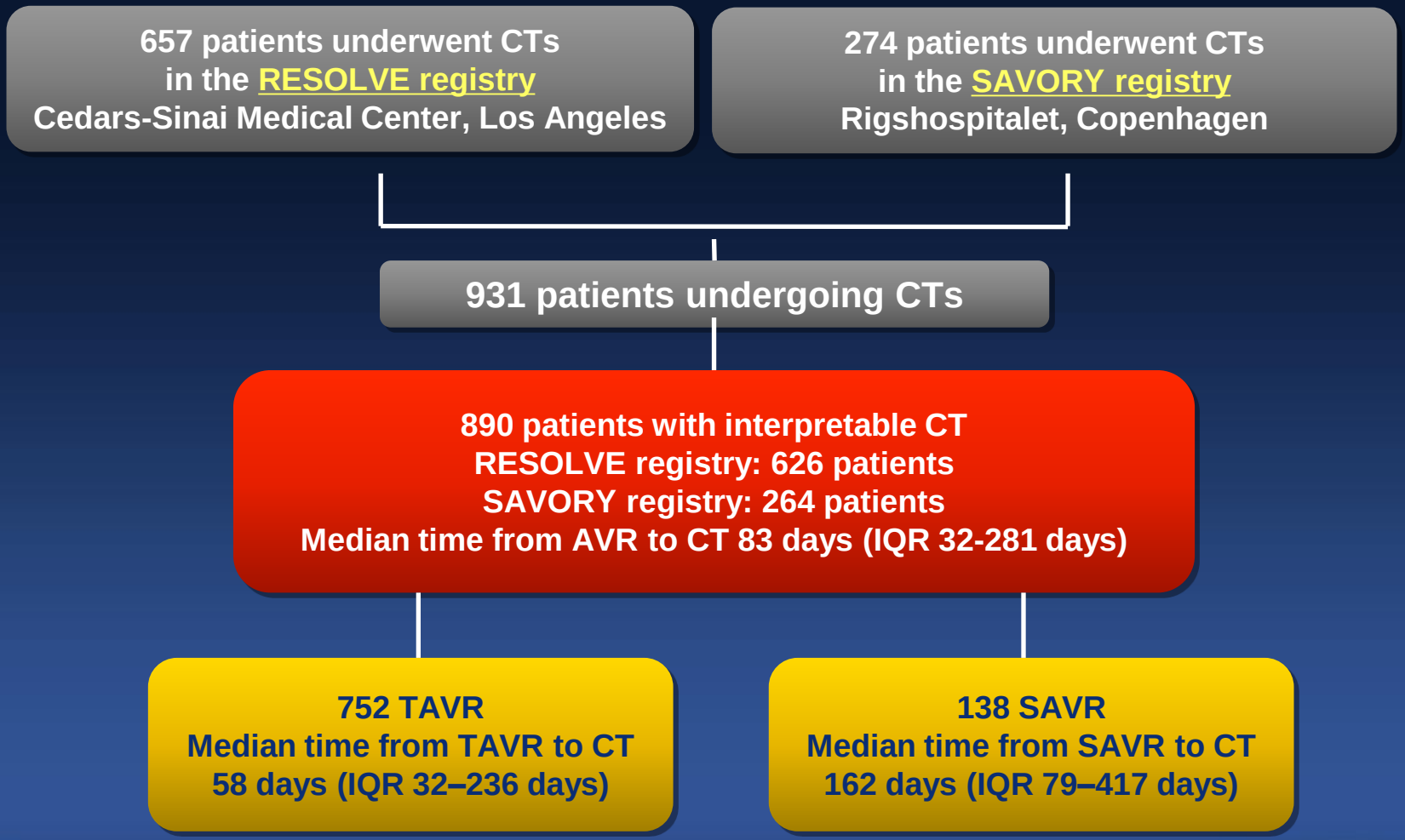
Subclinical Leaflet Thrombosis after TAVR

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.

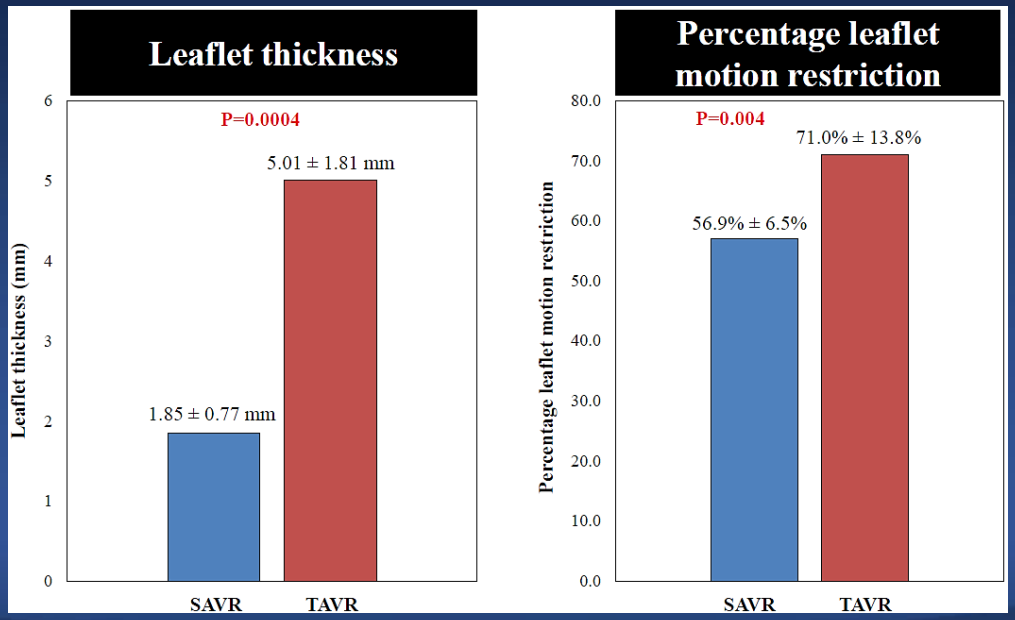
Prevalence of reduced leaflet motion

Reduced leaflet motion 106 (11.9%) patients

TAVR: 13.4% (101 out of 752)

SAVR: 3.6% (5 out of 138)

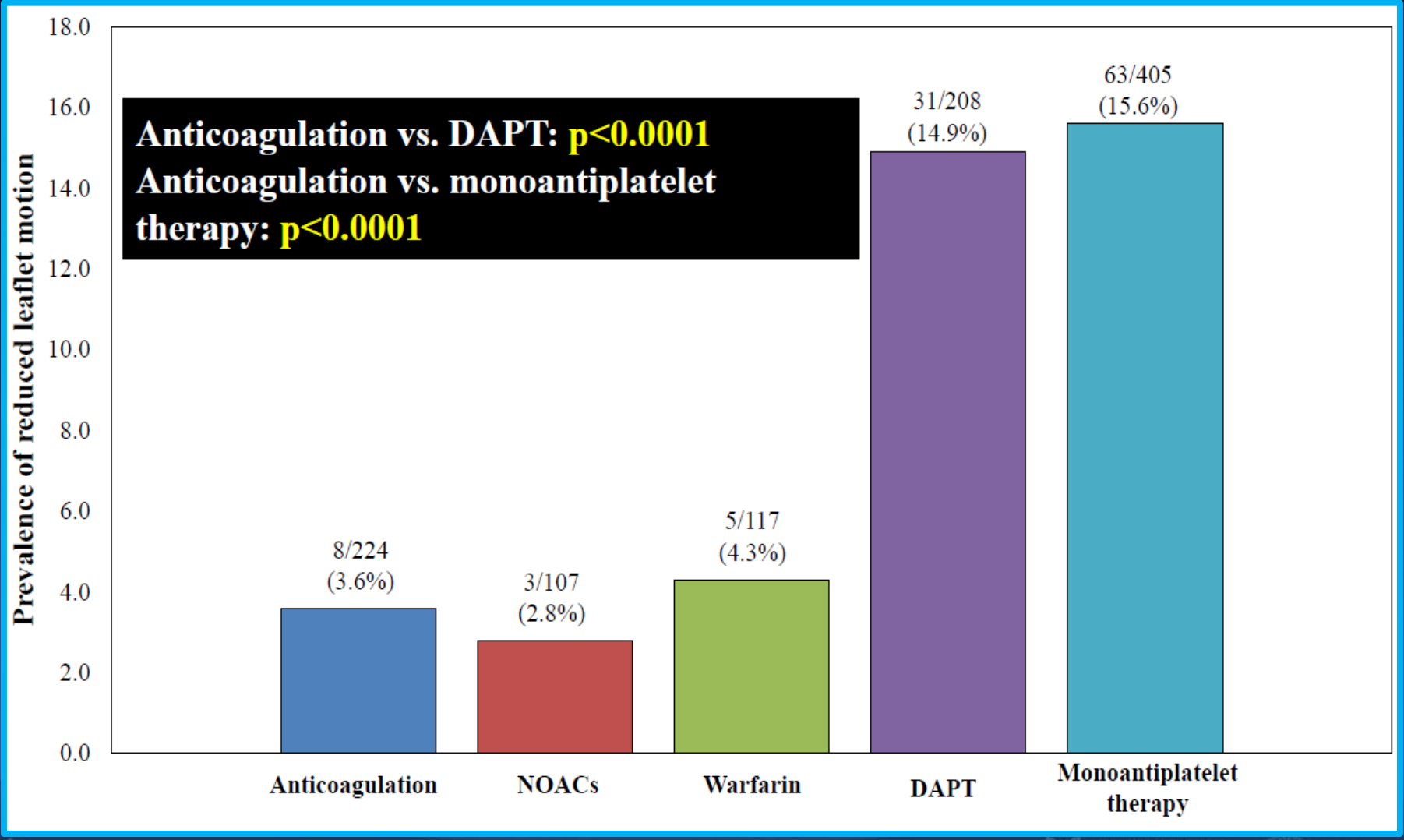
TAVR vs. SAVR: p=0.001



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

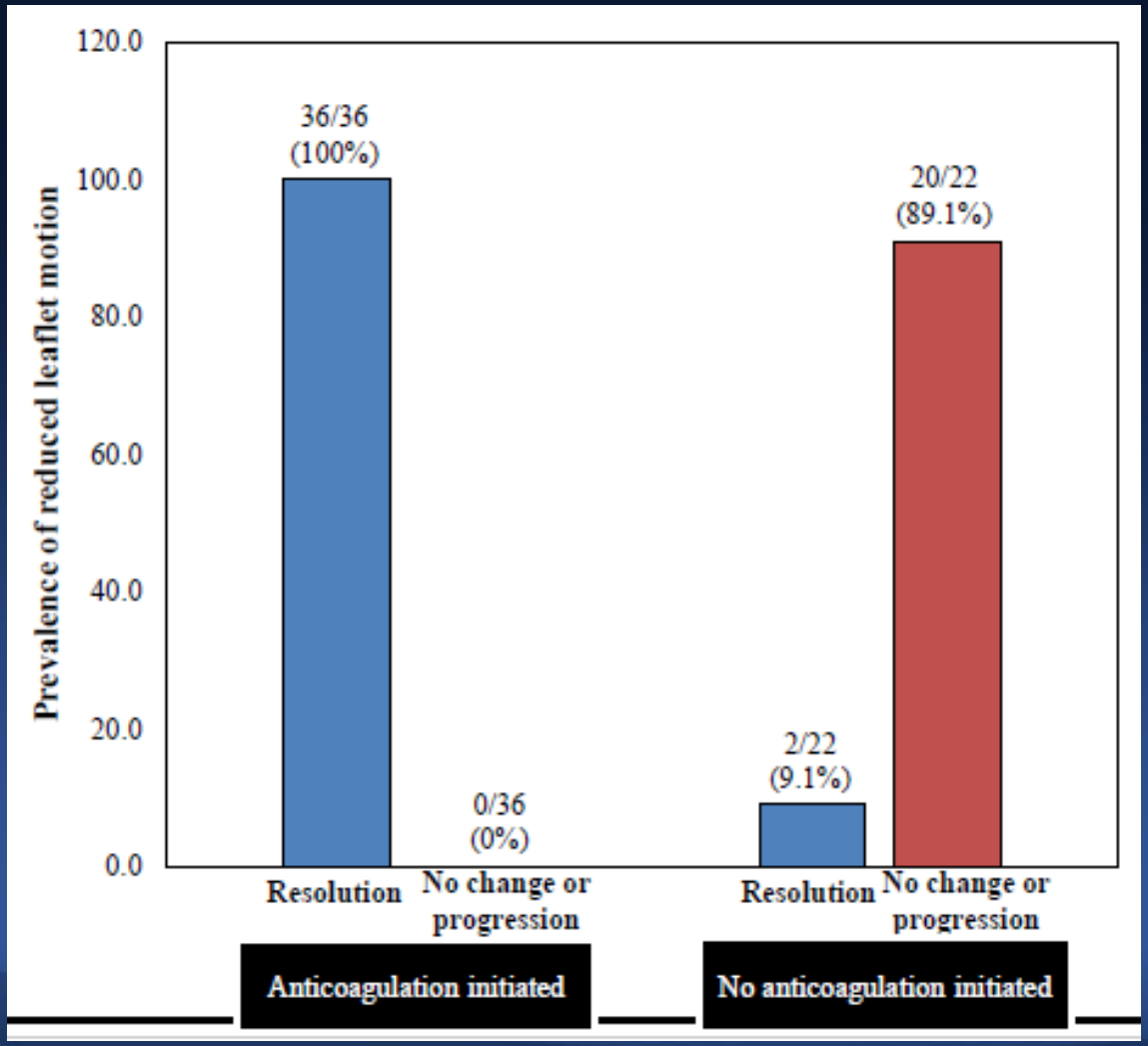
Analysis of Antithrombotic Regimen

Anticoagulation vs. antiplatelet therapy



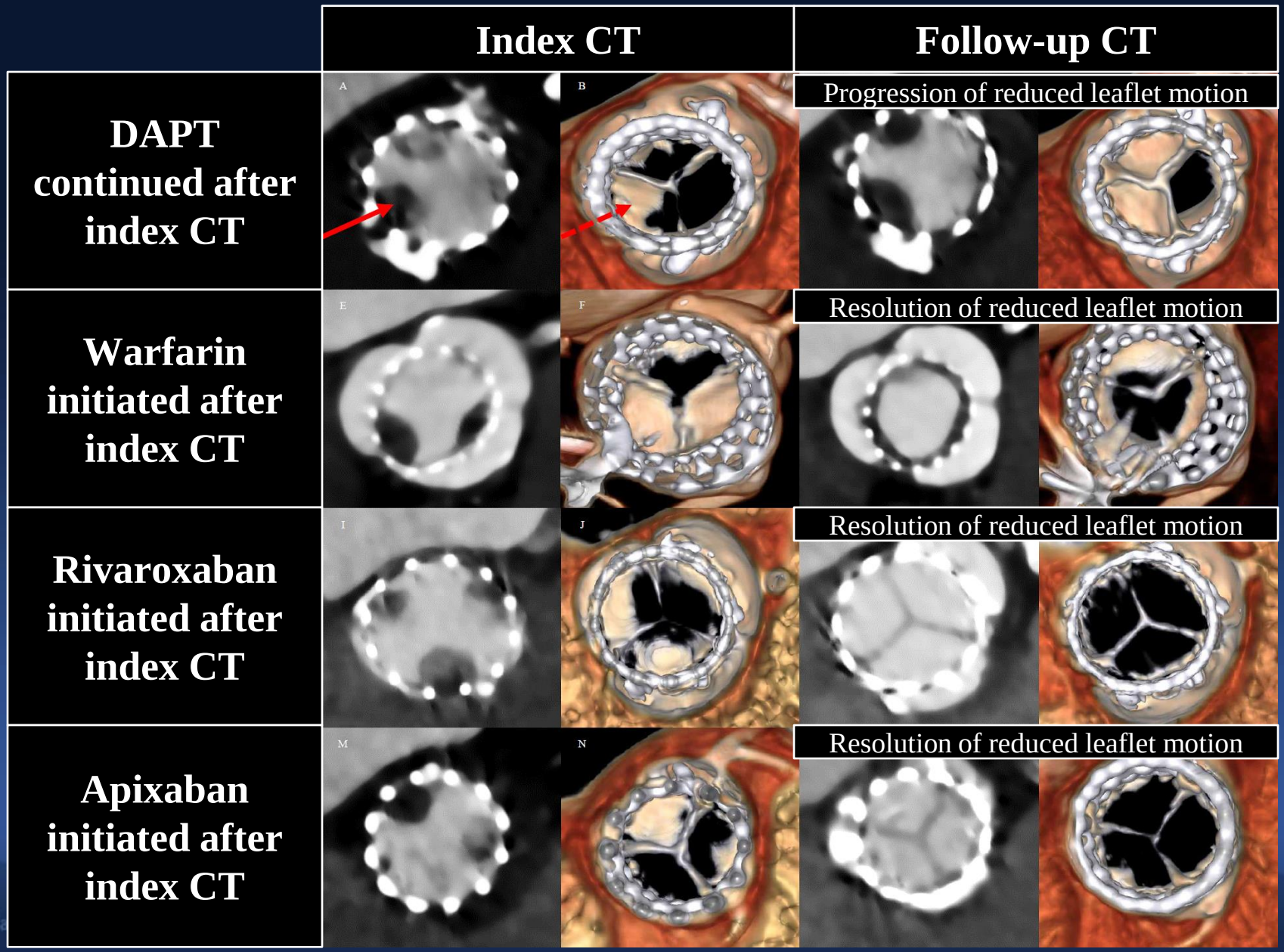
Chakravarty T, et al. Lancet. 2017 Mar 19.

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

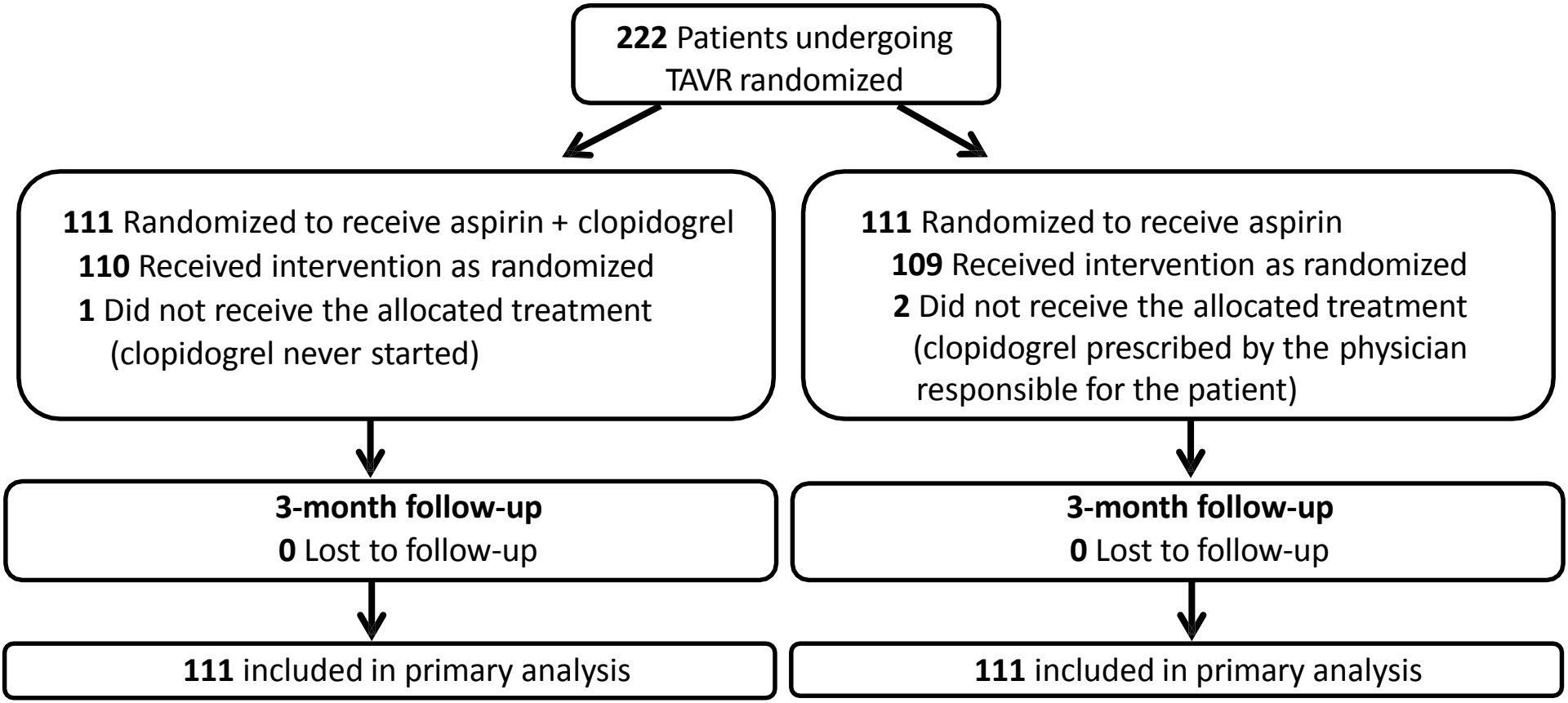
-Start within 24hrs after TAVR

-Continued for 3 months

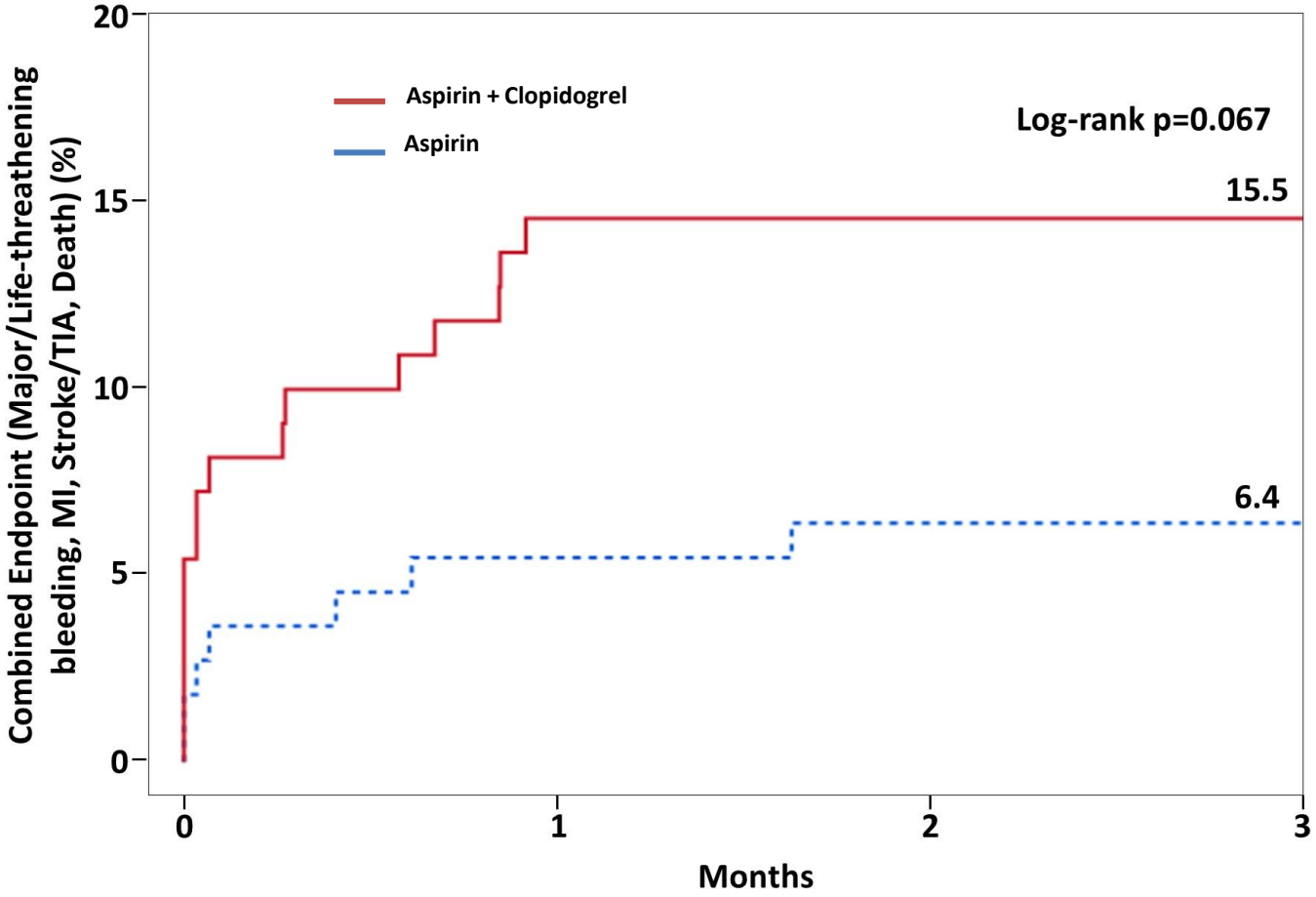
Clinical visit/phone contact at 1- 3- and 12-month follow-up

ARTE Trial - Results

Flowchart of the Study Population

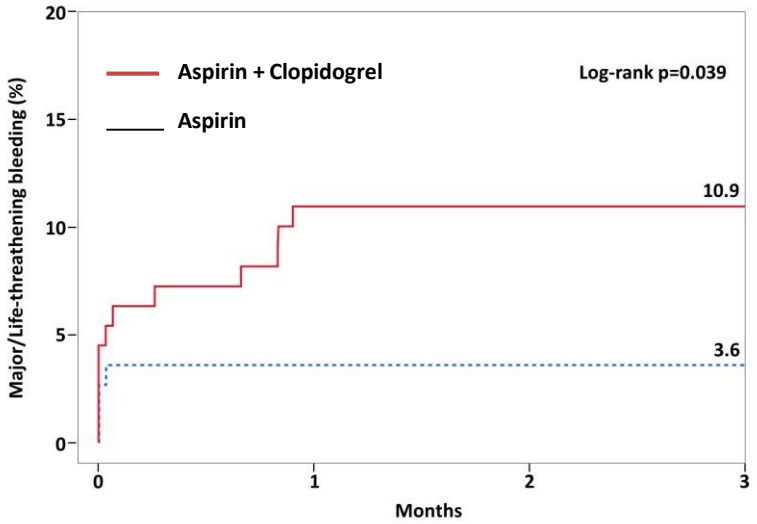


Kaplan-Meier Curves (Combined Endpoint)

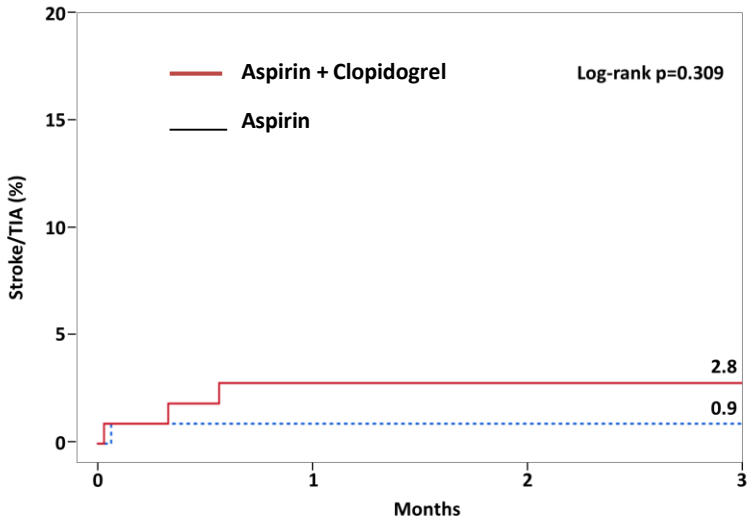


Kaplan-Meier Curves (Ischemic, Bleeding Events)

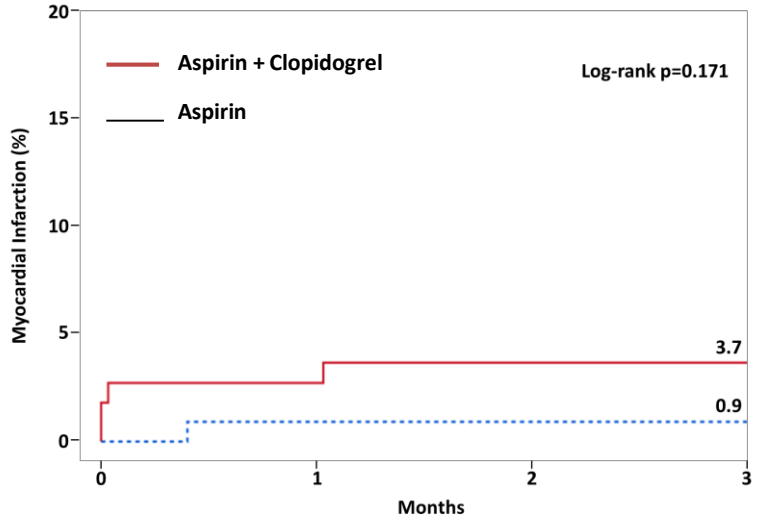
Major or life-threatening bleeding



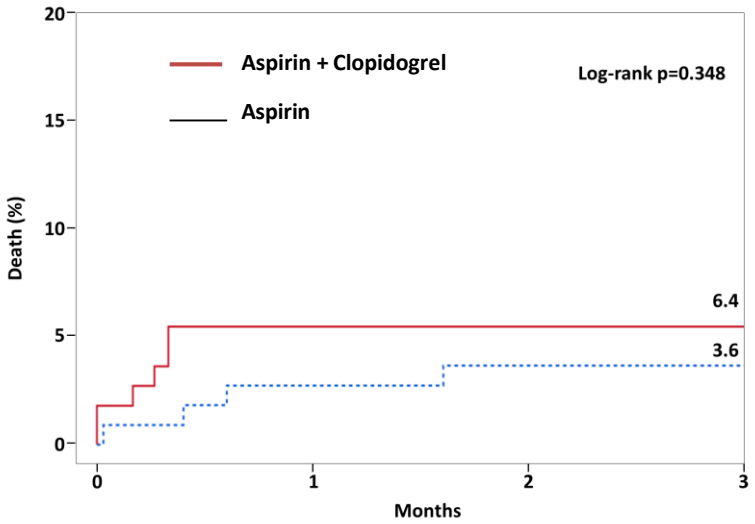
Stroke or TIA



Myocardial infarction (MI)

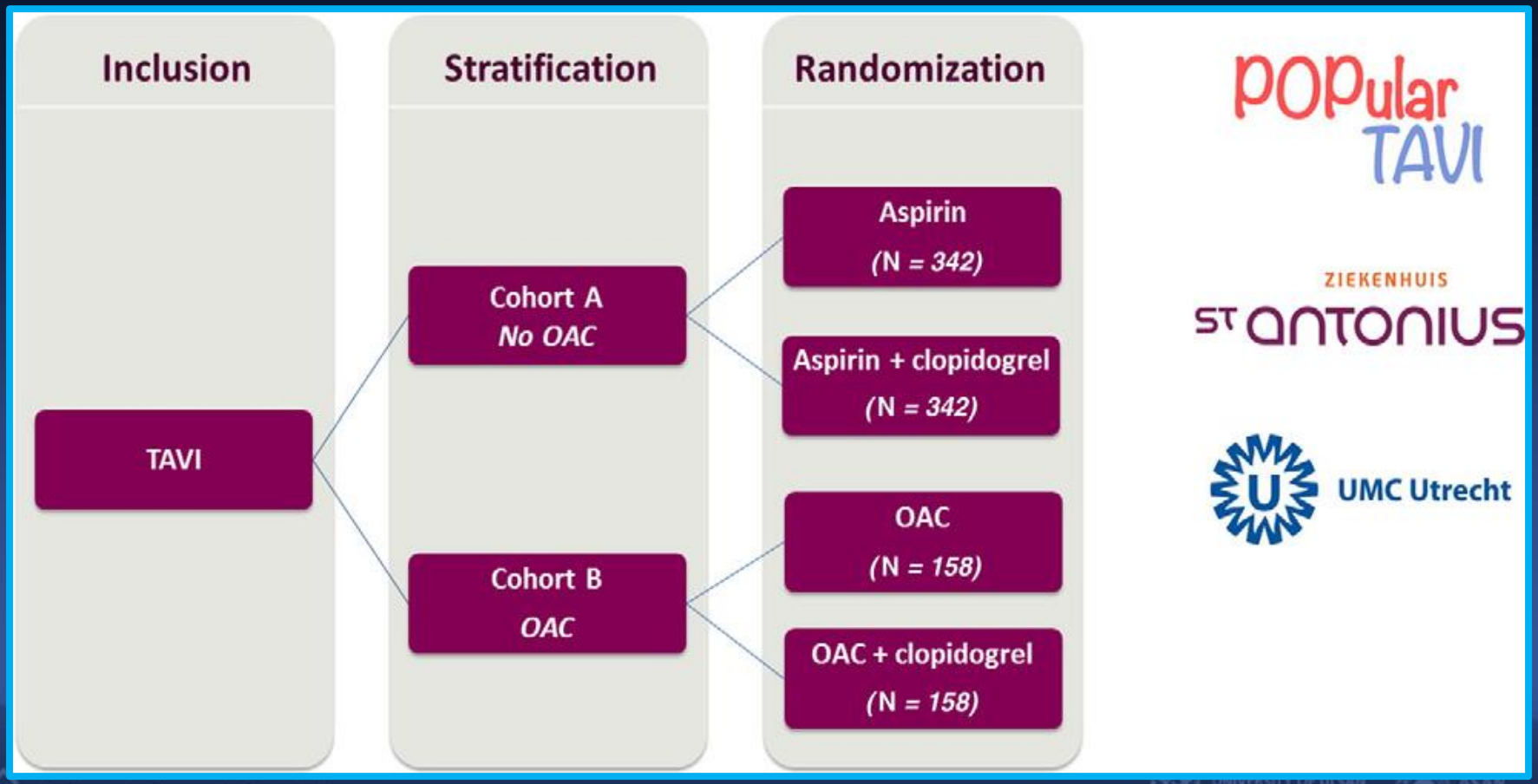


Death



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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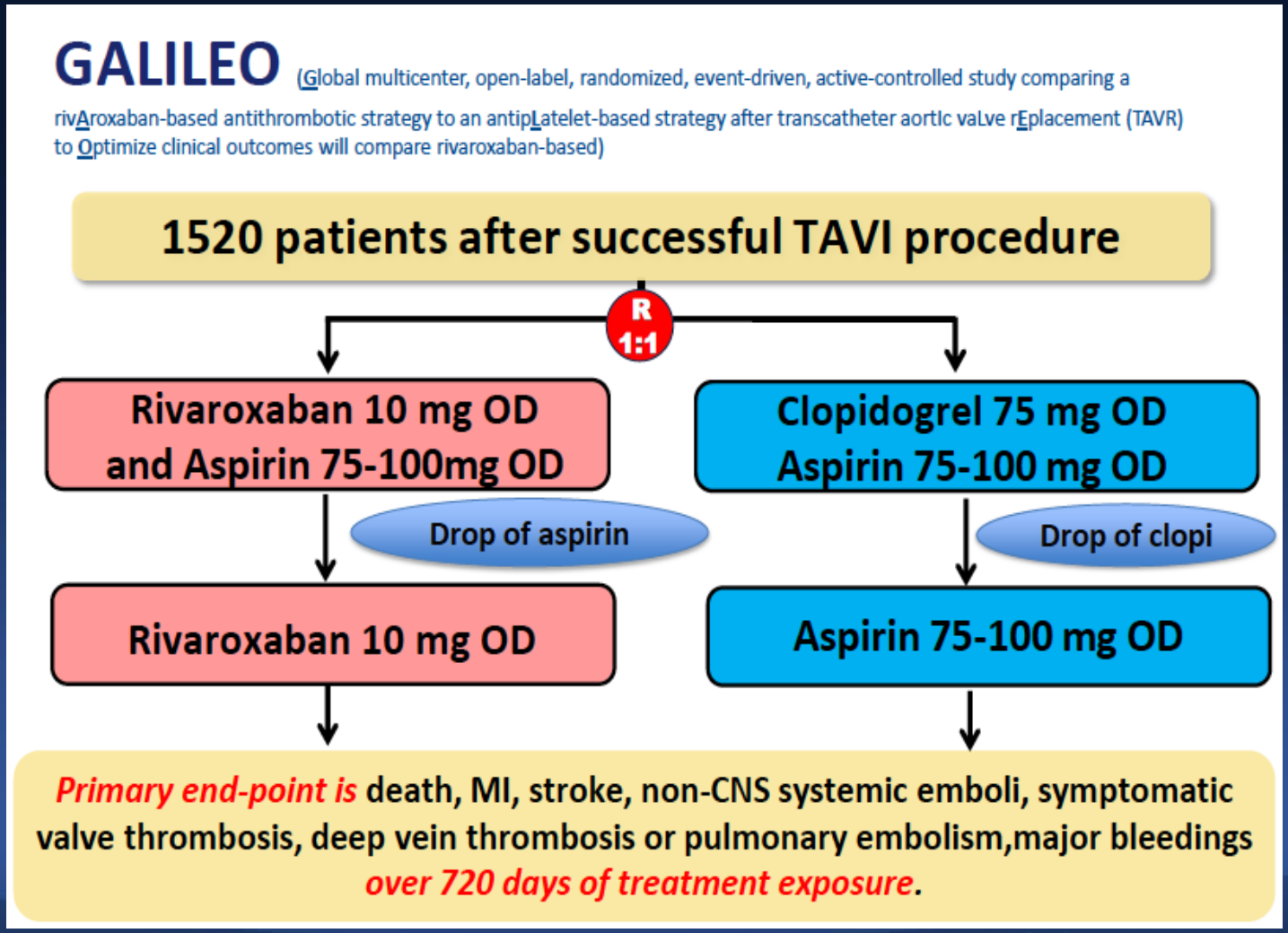
- ENVISAGE TAVI-AF Trial
- ADAPT-TAVR Trial

Mount Sinai Heart

GALILEO Trial

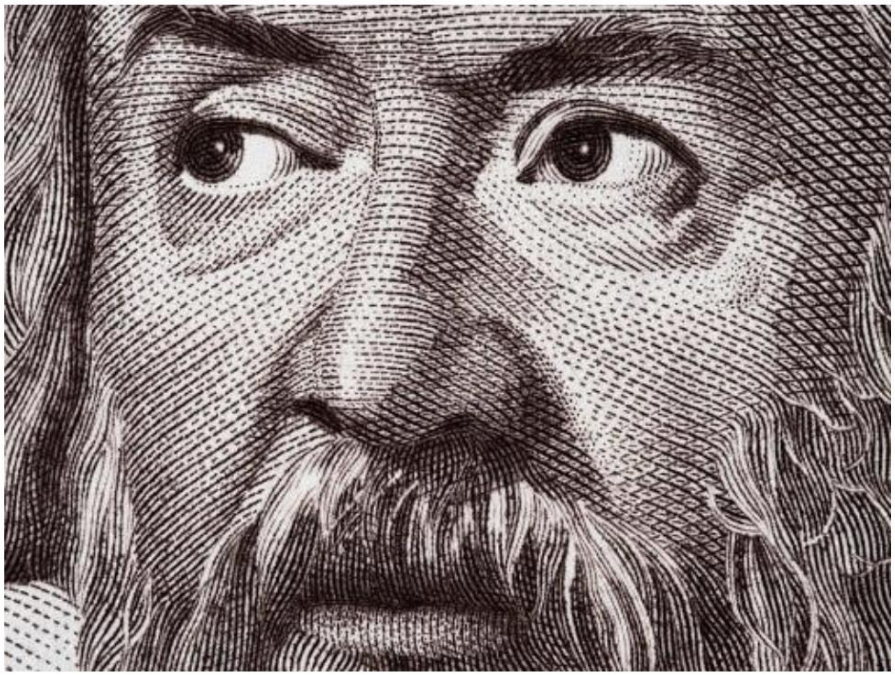


NEWS

GALILEO Trial of Rivaroxaban After TAVR Stopped Early for Harm

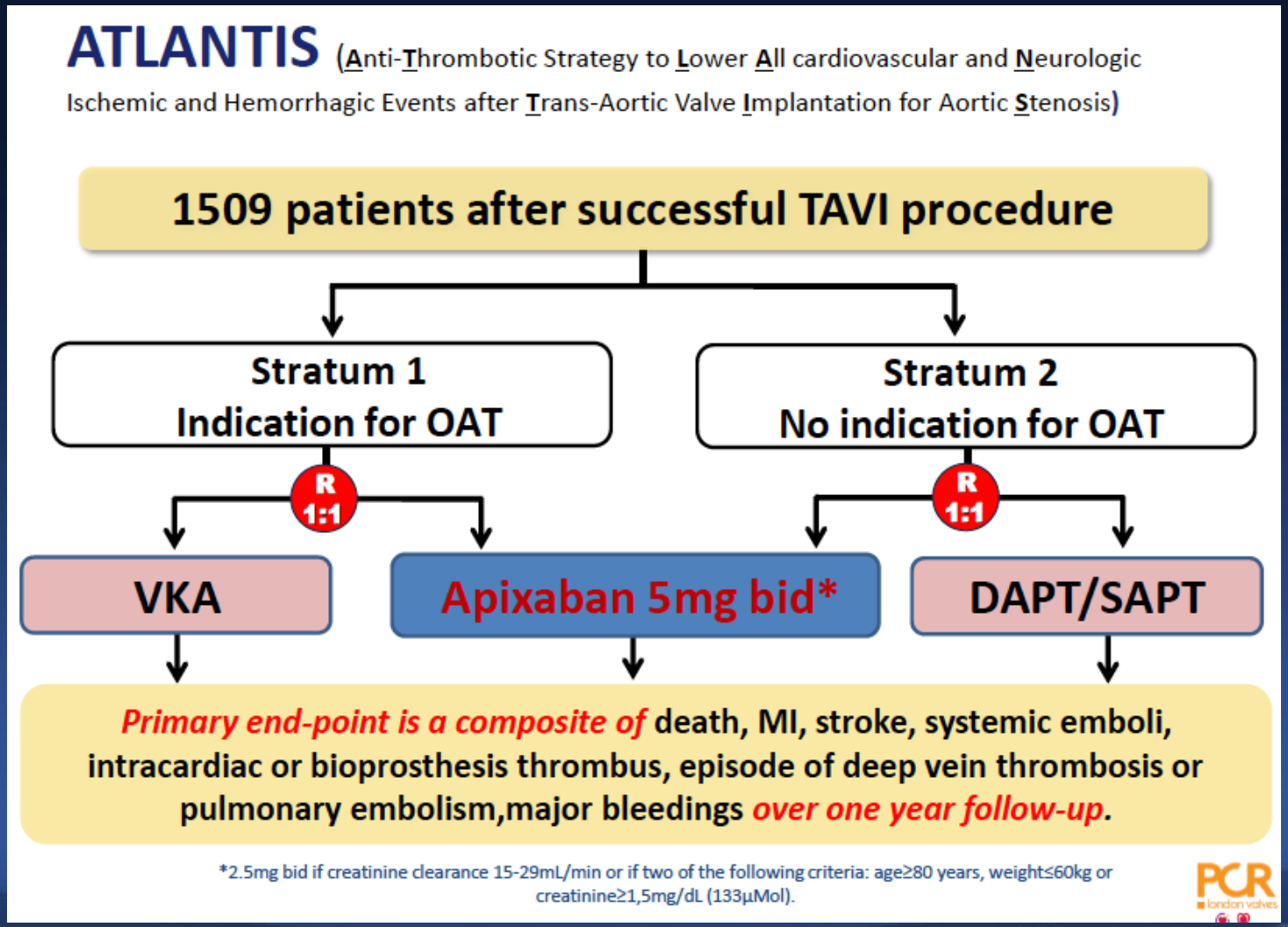
Rivaroxaban-treated patients had increased risks of all-cause mortality, thromboembolic events, and bleeding vs those on antiplatelet therapy.

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.

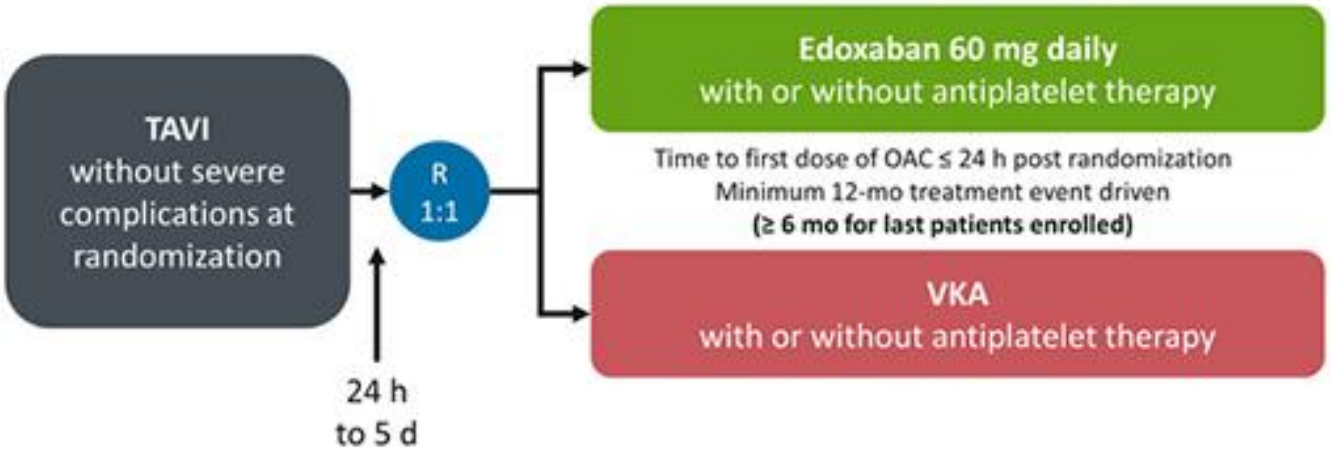
Ongoing Trials
: ATLANTIS



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

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

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

220 patients after successful TAVR procedure

Stratified randomization by (1) device type and (2) participating site

NOAC: **Edoxaban 60 mg once daily*** **(N=110)**	**DAPT:** **ASA + Clopidogrel** **(N=110)**

Co-Primary endpoint:

1. Incidence of leaflet thrombosis on Cardiac CT scan at 6 months
2. Number of new lesion on brain DW-MRI at 6 months relative to post-TAVR

*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

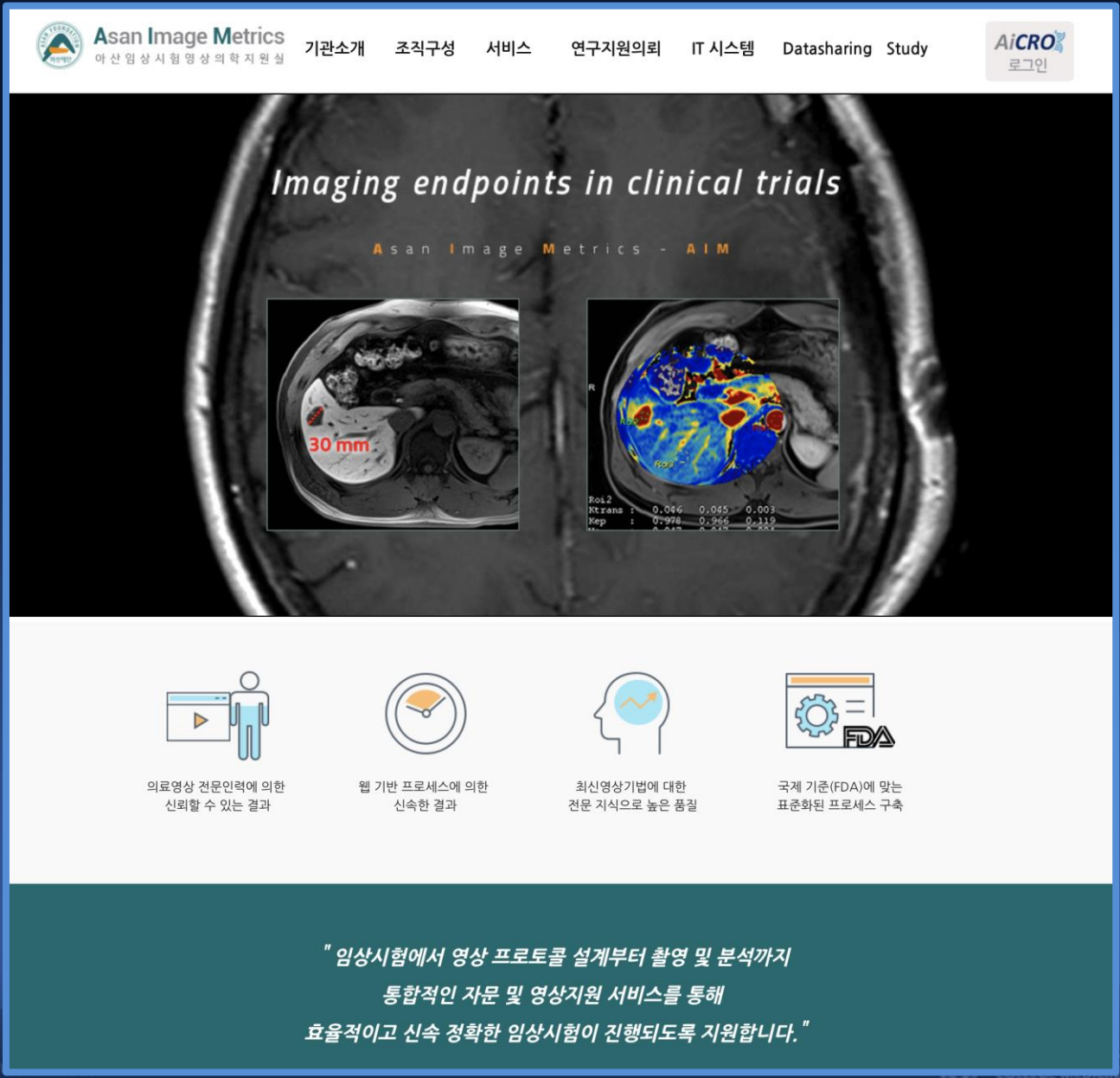
- Leaflet motion; defined as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet) in at least one valve leaflet

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/불출

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

Quantitative Imaging Biomarkers Alliance RSNA

국제 기준에 맞는 시스템
Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

참여기관 교육 및 모니터링

SAMSUNG 삼성의료원

서울아산병원 Asan Medical Center

SNUH 서울대학교병원

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).

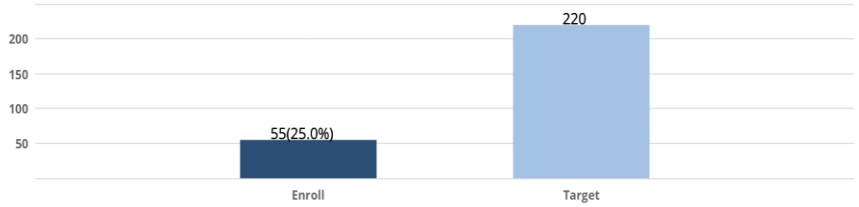
- Neurologic assessments included standard clinical scales (the National Institutes of Health Stroke Scale [NIHSS] and the modified Rankin Scale [mRS]), and cognitive assessments included the Montreal Cognitive Assessment (MoCA).

ADAPT-TAVR Trial: Current Status

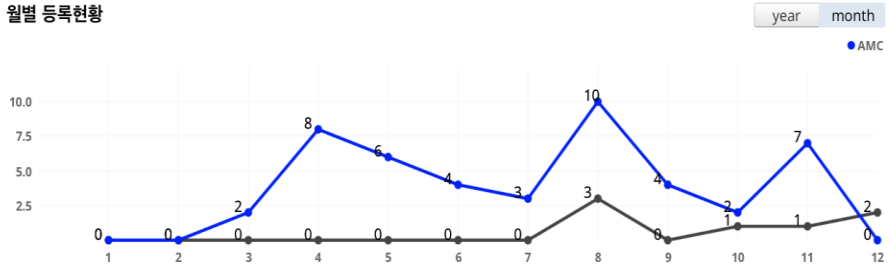
Communication TAVR > ADAPT-TAVR Trial

overview | current status | paper

목표대비 등록현황



월별 등록현황



edit

ISSUE

1. AMC 등록 시작
2. DAPT group: Aspirin & Prasugrel 처방

★ Complete AV block과 PPM: SAE 보고대상에서 제외로 계획변경 (MFDS 2018/07/02 승인)

add

Search:

no.	nation	site	PI	status	enrolled	last enroll date
				Total	**53**	
1	KR	서울아산병원	박덕우	Enrollment	46	2018-11-28
2	KR	차의과학대학교 분당차병원	김원장	Enrollment	2	2018-10-04
3	HK	Queen Mary Hospital	Simon C.C. Lam	Enrollment	5	2018-12-03
4	TW	National Taiwan University hospital	Paul Hsien Li Kao	Contract	0	
5	TW	Cheng Hsin General Hospital	Jeng Wei	IRB	0	

Showing 1 to 6 of 6 entries

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.