Optimal Antithrombotic Strategy After TAVR

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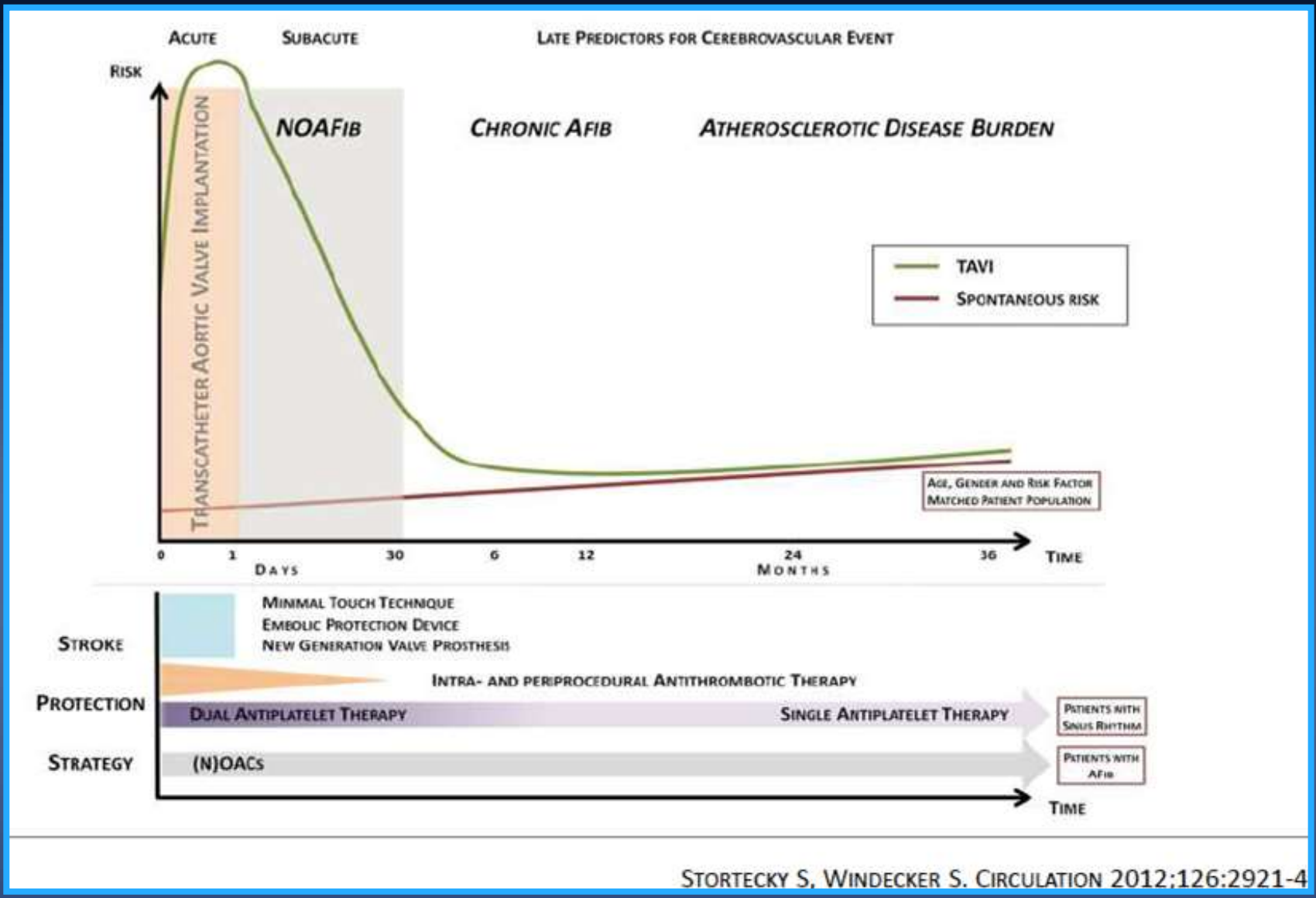
Disclosure Statement of Financial Interest

- Institutional grant/research funding to CardioVascular Research Foundation (CVRF, Korea) and/or Asan Medical Center from Daiichi-Sankyo, Abbott, Boston Scientific, Medtronics, Edwards, Biosensor, ChongKunDang Pharm and Daewoong Pharm,

Timing of Cerebrovascular Events after TAVR



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

Stortecky et al – Circulation 2012; 126:2921–4

8:00 AM - 8:15 AM

404-08 - Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients: Results of the PARTNER 3 Trial

Martin Leon, Michael Mack, The PARTNER 3 Trial Investigators, Columbia University Medical Center, New York, NY, USA, Baylor Scott & White Health, Plano, TX, USA

Add To My Itinerary

8:15 AM - 8:30 AM

404-09 - Self-Expanding Transcatheter or Surgical Aortic Valve Replacement in Patients at Low Risk of Surgical Mortality

Michael J. Reardon, Jeffrey Popma, Steven Yakubov, Hongyan Qiao, G. Michael Deeb, Houston Methodist DeBakey Heart & Vascular Center, Houston, TX, USA

Add To My Itinerary

Antithrombotics in Most Recent Trials

PARTNER-3

RANDOMIZATION AND PROCEDURES

Eligible patients were randomly assigned, in a 1:1 ratio, to undergo either TAVR with the SAPIEN 3 system or surgical aortic-valve replacement with a commercially available bioprosthetic valve. Randomization was conducted with the use of an electronic system, with block sizes of four, and was stratified according to site.

The SAPIEN 3 system and the procedures for TAVR and surgery have been described previously[18]; details are provided in Section D in the Supplementary Appendix. All TAVR procedures used the transfemoral access route. Balloon aortic valvuloplasty before and after TAVR was performed at the operator's discretion. Patients received aspirin (81 mg) and clopidogrel (≥300 mg) before TAVR and were advised to continue taking these medications for at least 1 month after the procedure.

Evolut Low Risk

Medtronic — Coronary and Structural Heart Clinical

3.3.10 Post-Implant Anti-thrombotic Therapy

Management of subject's anti-thrombotic regimen will be per the discretion of the investigator, in accordance with the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease.[13]

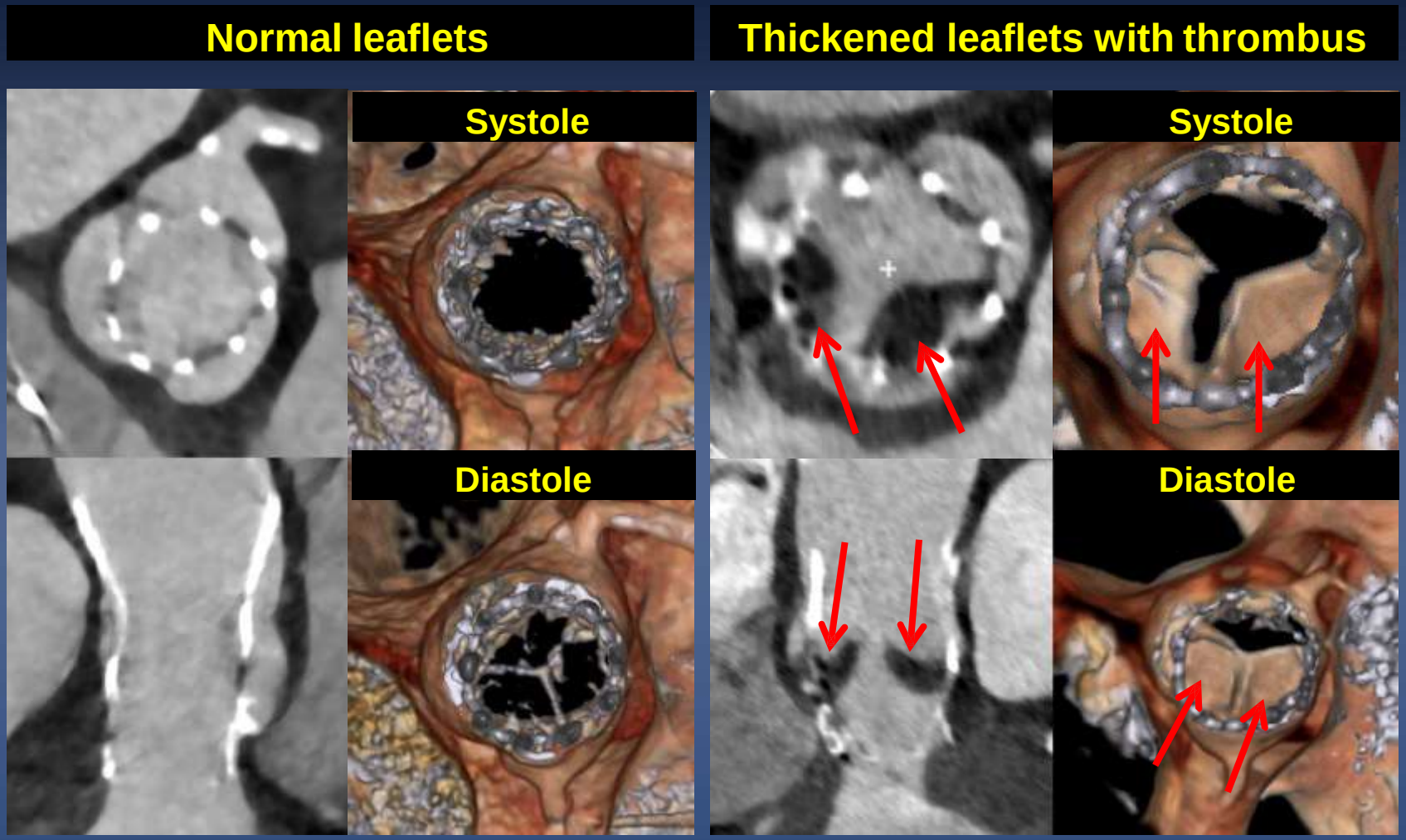
The recommended post implant anti-thrombotic regimen for TAVR subjects will be 30 days or more of Dual Anti-Platelet Therapy (DAPT) followed by aspirin through 12 months.

The recommended post implant regimen for SAVR subjects will be a Vitamin K Antagonist (VKA) or aspirin in accordance with current guidelines.

Why DAPT Post-TAVR?

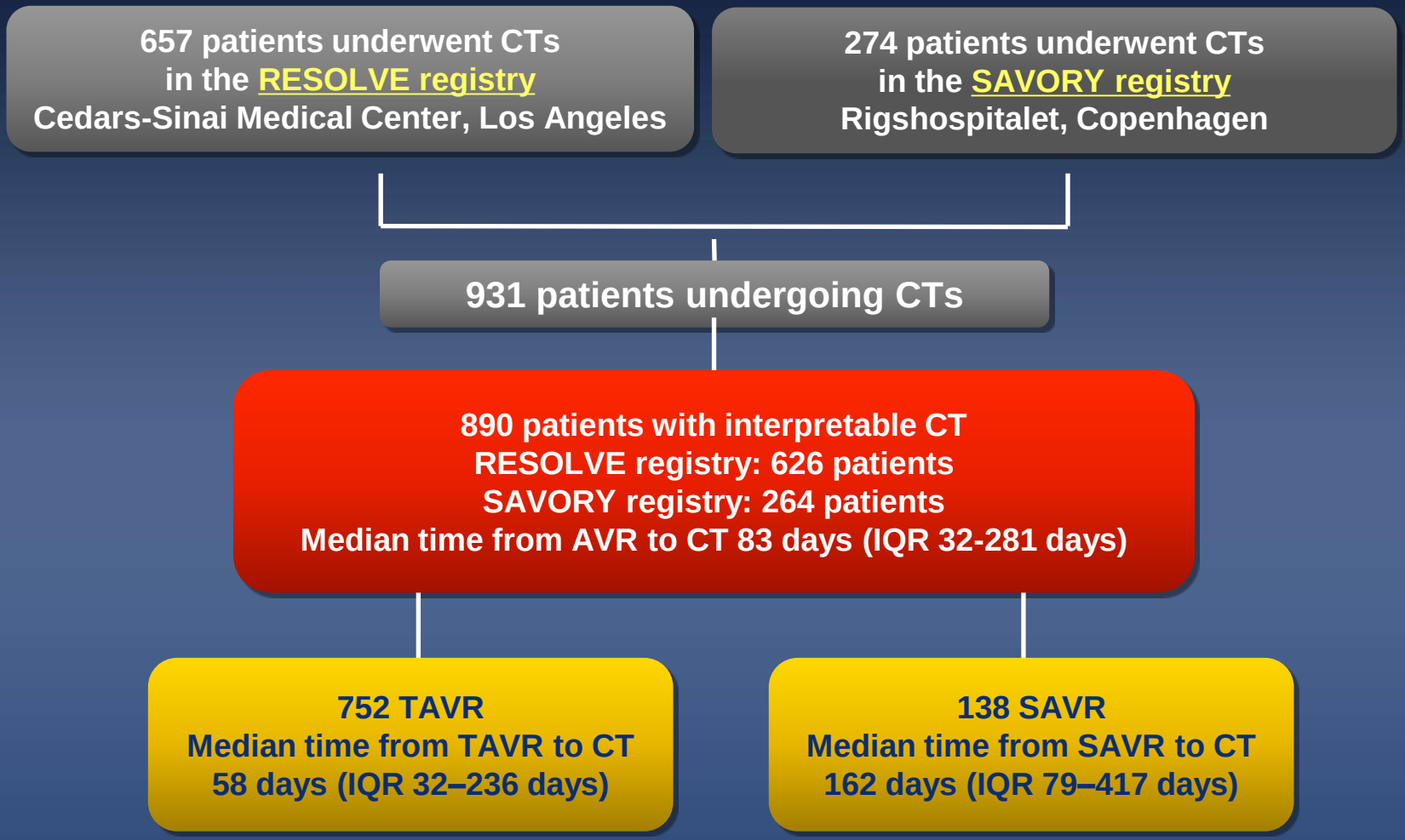
- Regimen
  - 6 months Clopidogrel
  - Aspirin indefinitely
- Decision based on expert consensus
  - **“It’s like a stent”-** treat like coronary or peripheral
  - Rationale for treatment: Decrease stroke risk, Decrease risk for MI

4D-CT after TAVR



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.

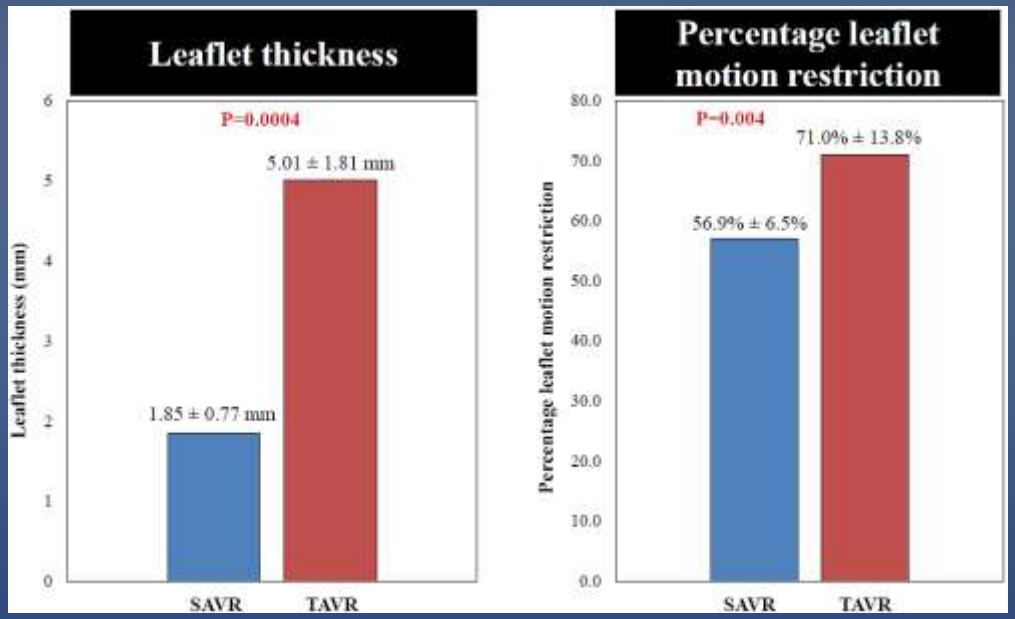
Prevalence of reduced leaflet motion

Reduced leaflet motion 106 (11.9%) patients

TAVR: 13.4% (101 out of 752)

SAVR: 3.6% (5 out of 138)

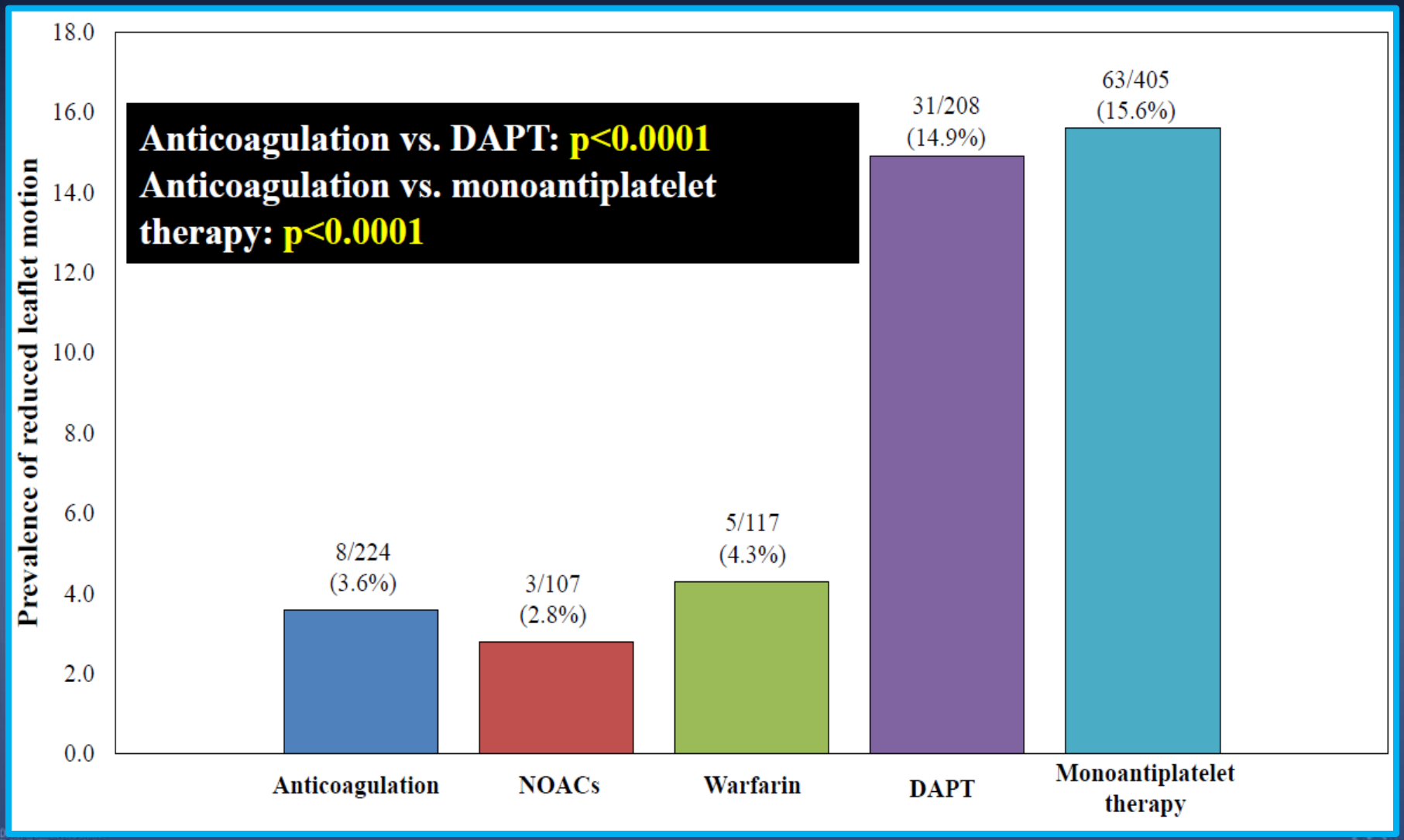
TAVR vs. SAVR: p=0.001



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

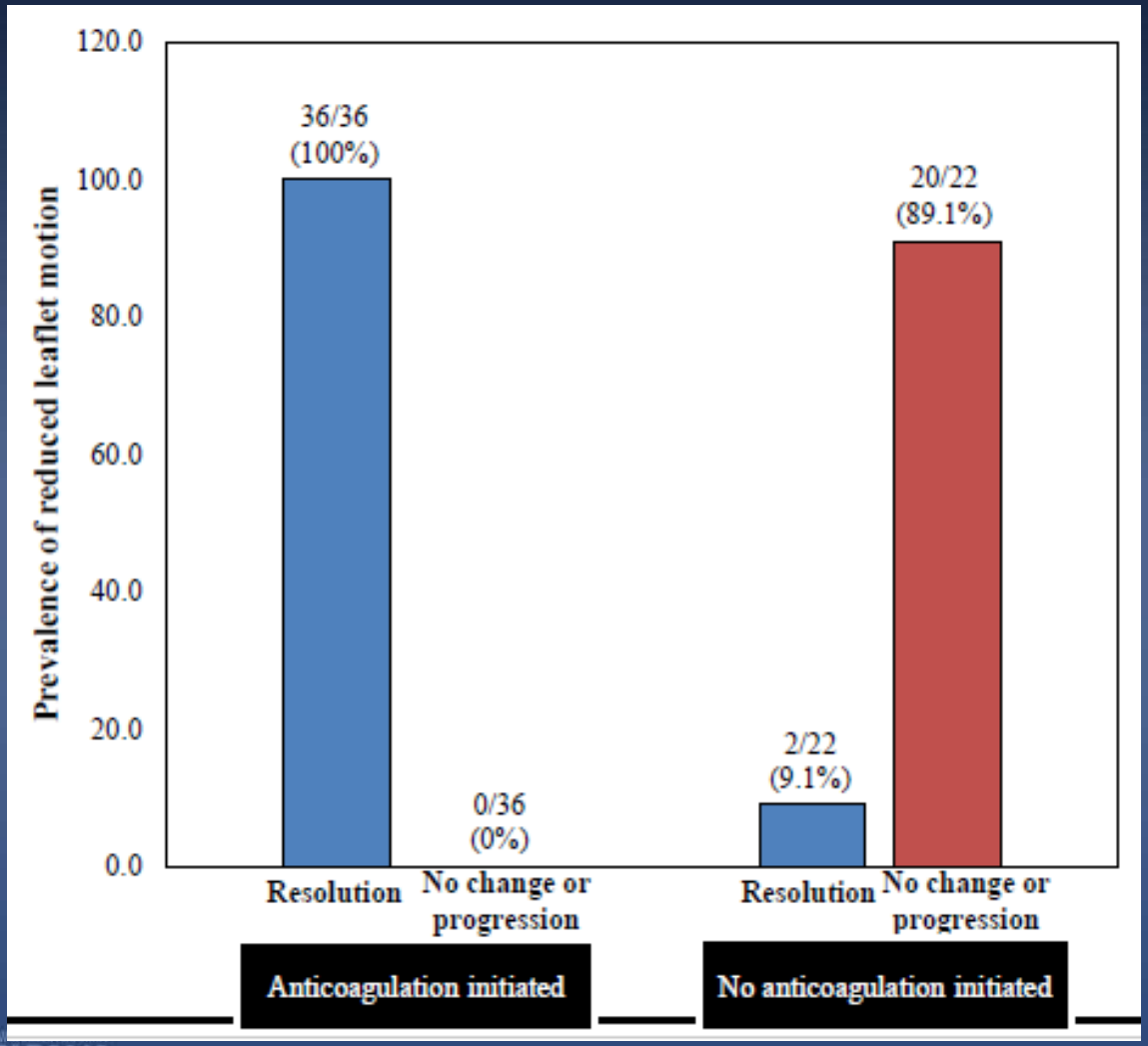
Analysis of Antithrombotic Regimen

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

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-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

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

Current 2017 ESC Guideline

Bioprosthesis	Class	Level
Anticoagulation		
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

Bioprosthesis	Class	Level
Anticoagulation		
SAPT may be considered after TAVR in the case of high bleeding risk.	IIb	C
OAC may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.	IIb	C

Antithrombotic Trials After TAVR

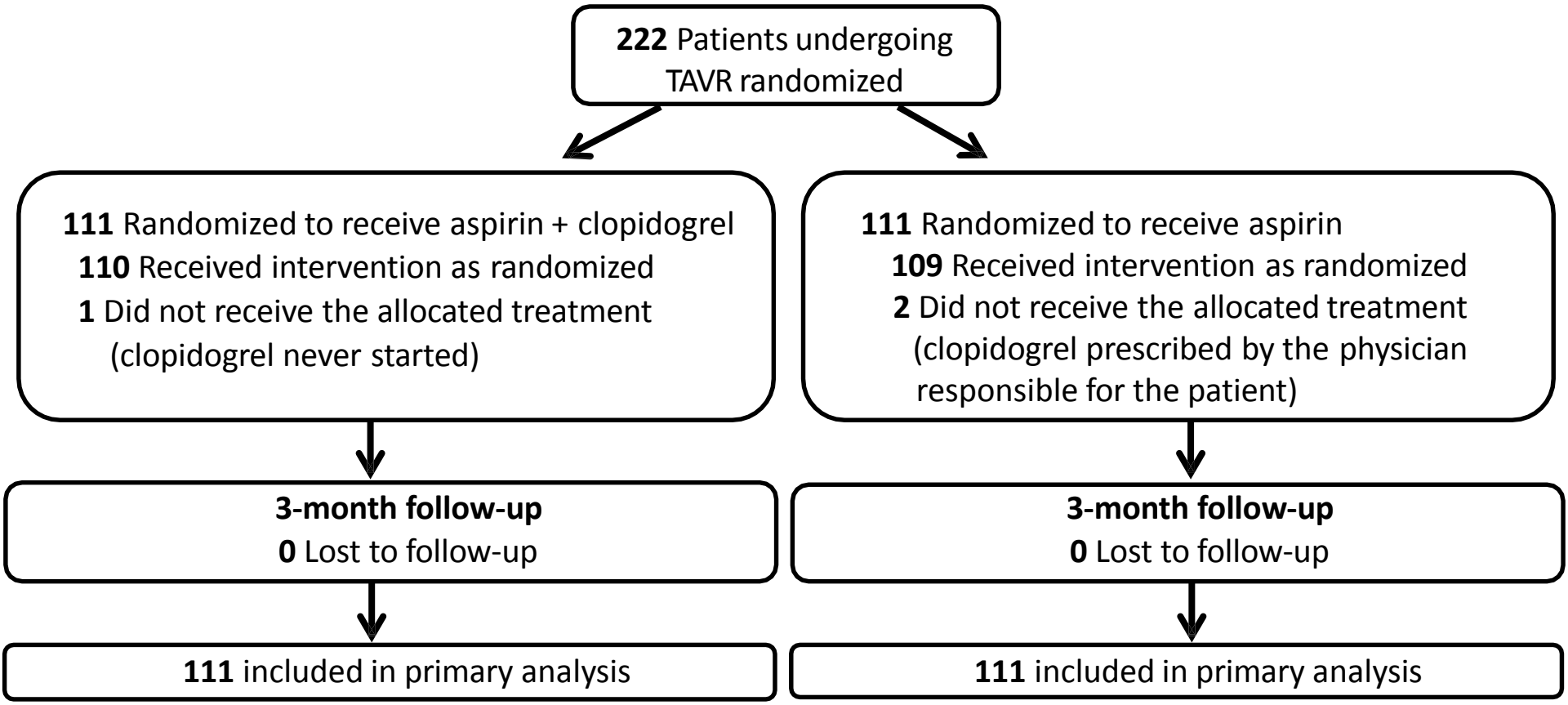
Omission of Clopidogrel

- ARTE Trial
- POPular TAVI Trial
- CLOE Trial

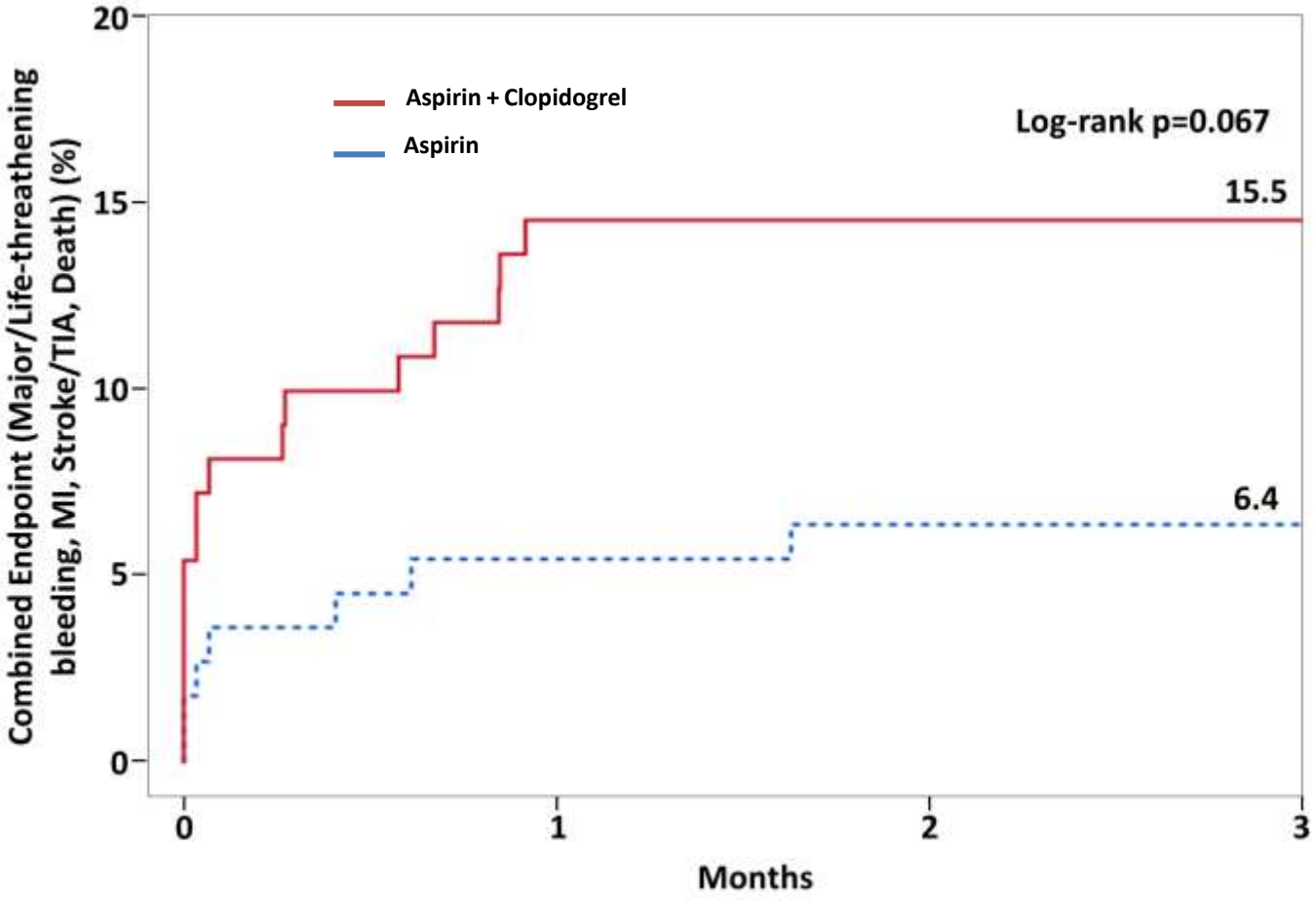
NOAC Trial

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

ARTE Trial

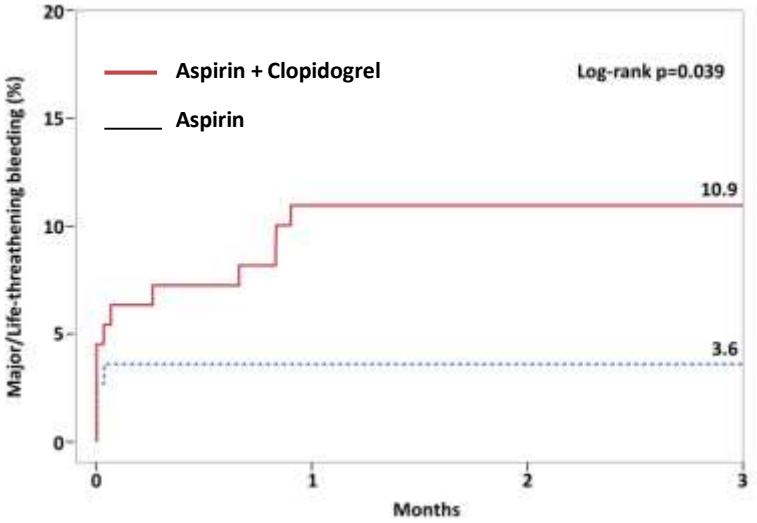

222 Patients undergoing TAVR randomized
111 Randomized to receive aspirin + clopidogrel
110 Received intervention as randomized
1 Did not receive the allocated treatment (clopidogrel never started)
111 Randomized to receive aspirin
109 Received intervention as randomized
2 Did not receive the allocated treatment (clopidogrel prescribed by the physician responsible for the patient)
3-month follow-up
0 Lost to follow-up
3-month follow-up
0 Lost to follow-up
111 included in primary analysis
111 included in primary analysis

Kaplan-Meier Curves (Combined Endpoint)

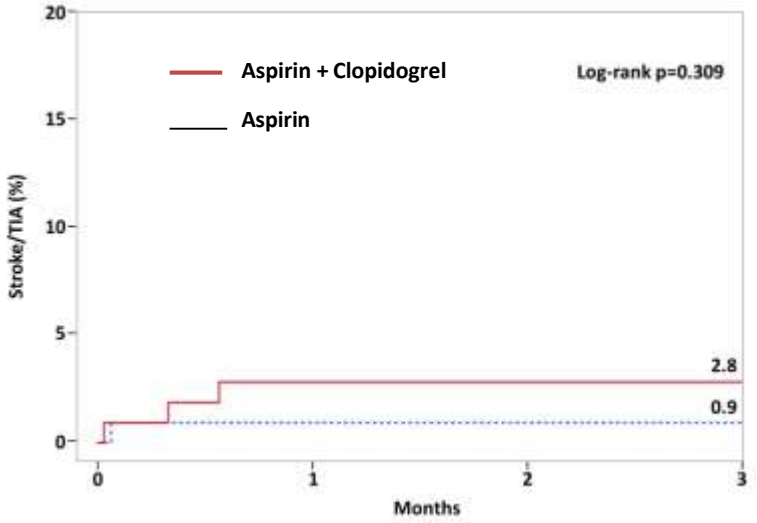


Kaplan-Meier Curves (Ischemic, Bleeding Events)

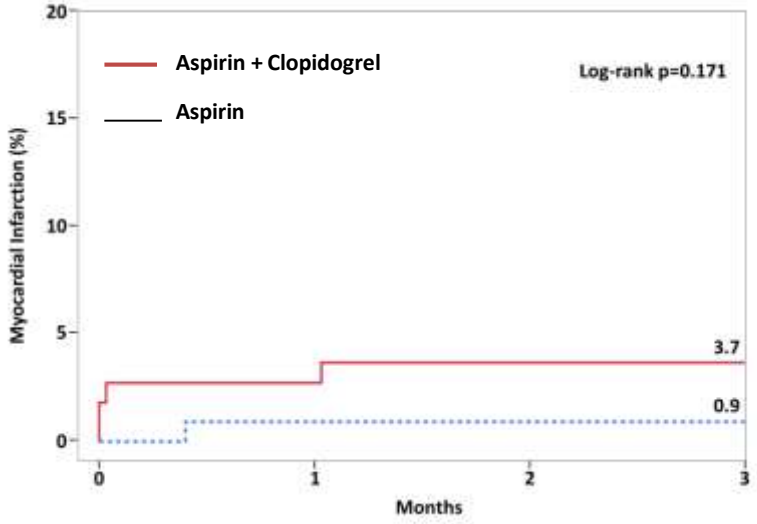
Major or life-threatening bleeding



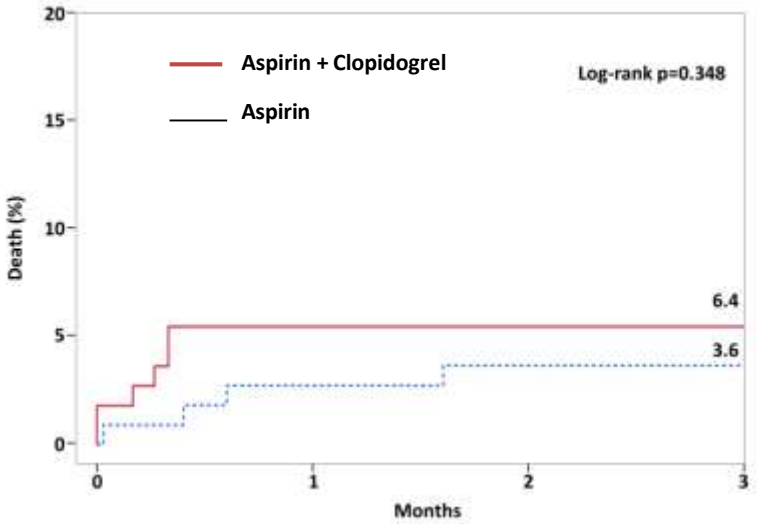
Stroke or TIA



Myocardial infarction (MI)

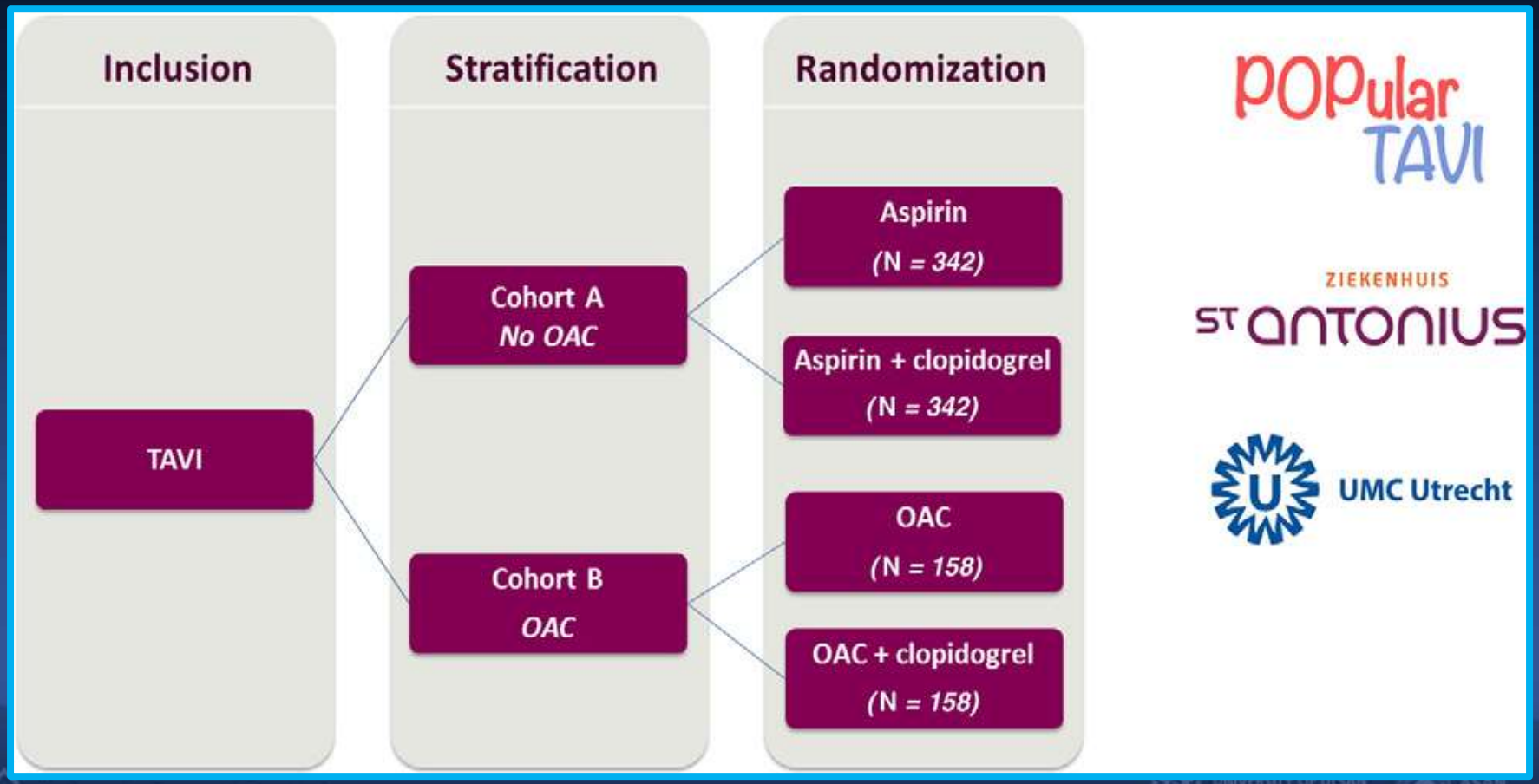


Death



Ongoing Trials
: Popular-TAVI (N=1,000)

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

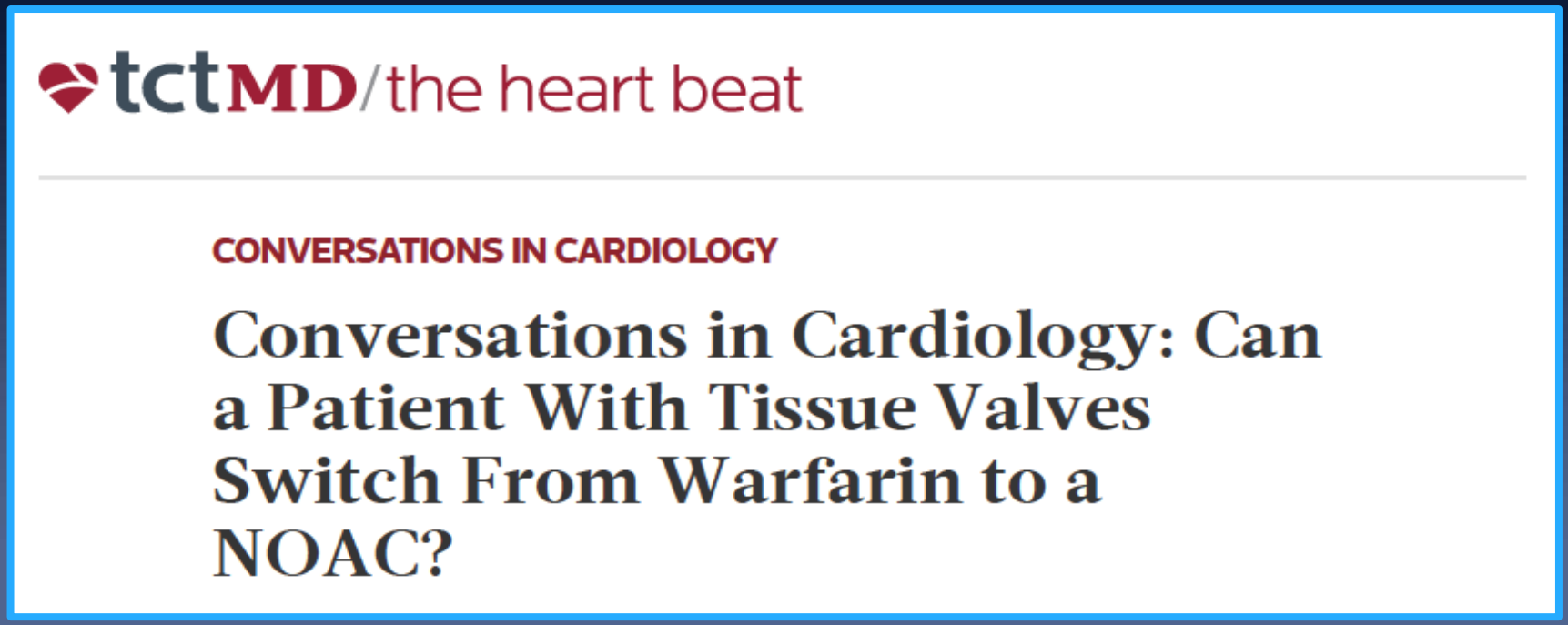
Primary Safety Endpoint

Major / Life-Threatening VARC-2 Bleeding

Ancillary Studies

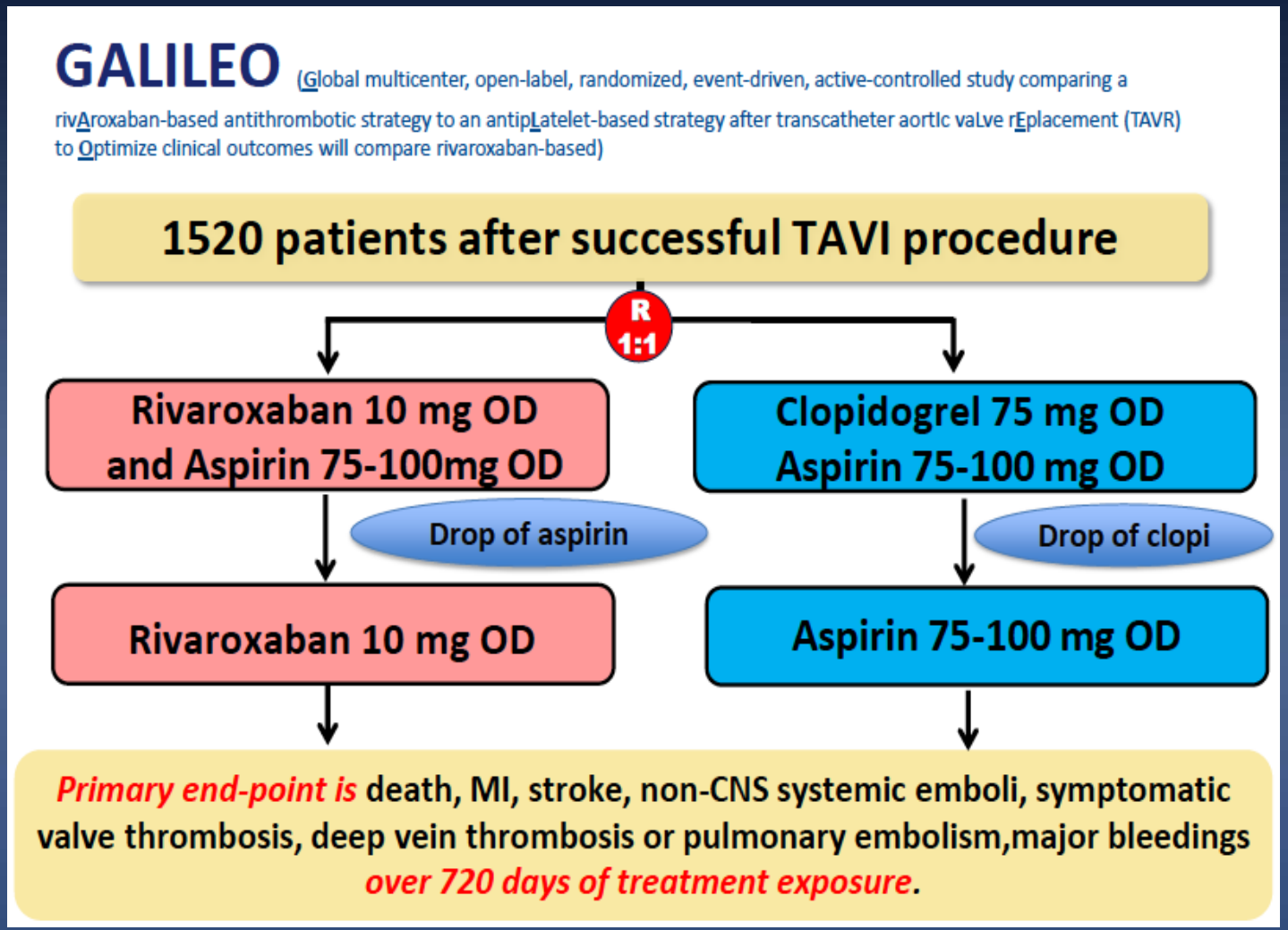
- Cost-Effectiveness
- QoL
- Frailty
- CTA Leaflet Substudy
- MRI Brain Substudy

Oral Anticoagulants for TAVR



However, no oral anticoagulants in the factor Xa or IIa inhibitor class are approved for use following TAVR.

GALILEO Trial



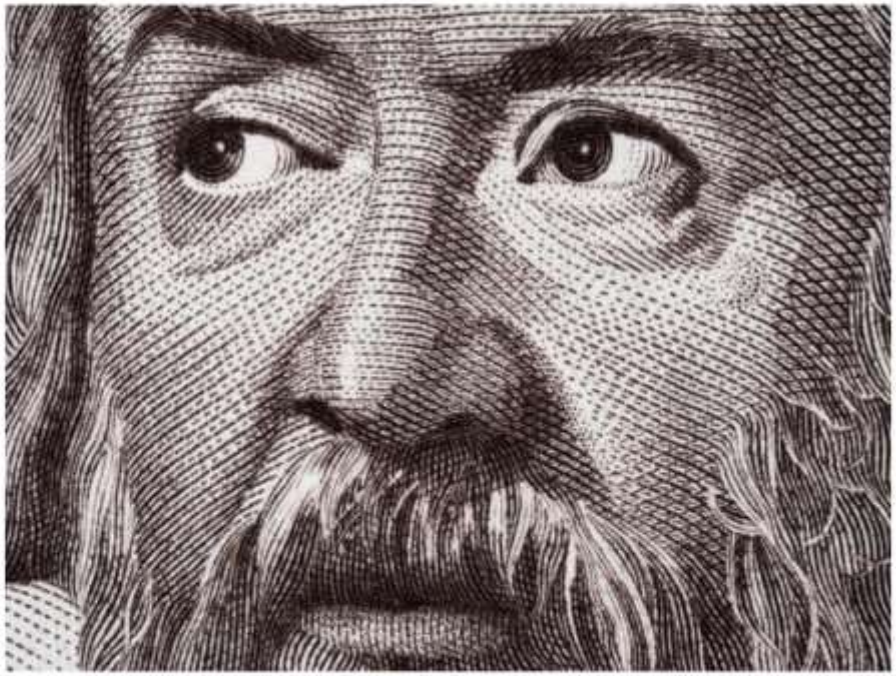
3 Mo

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.

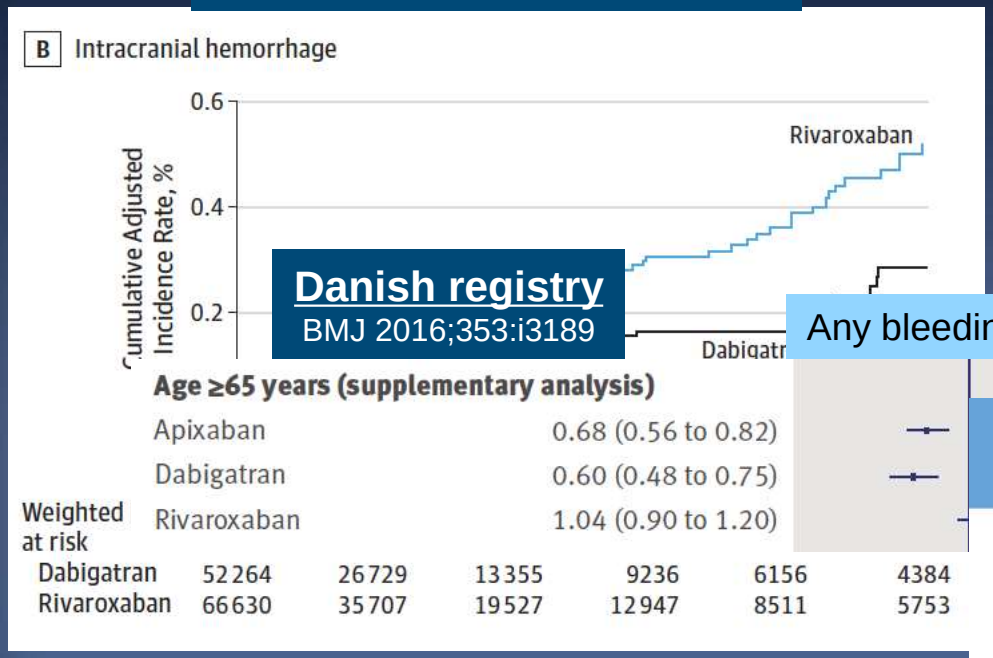
GALILEO Trial,
Preliminary Results After An Early Peak

	Rivaroxaban	Antiplatelet
A 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.

Why Failed GALILEO?
Rivaroxaban Effect?

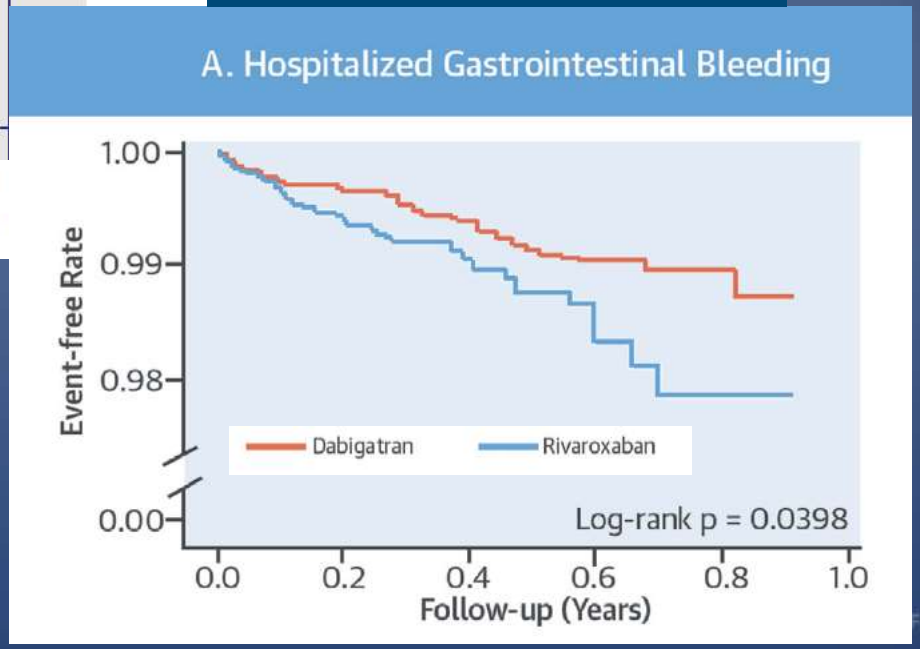
Medicare data
JAMA Intern Med. 2016;176:1662-1671.



Danish registry
BMJ 2016;353:i3189

Any bleeding

Taiwan registry
J Am Coll Cardiol 2016;68:1389–401.

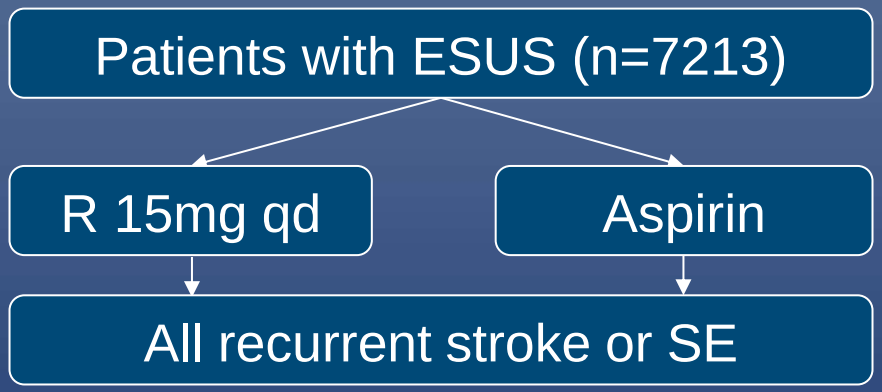


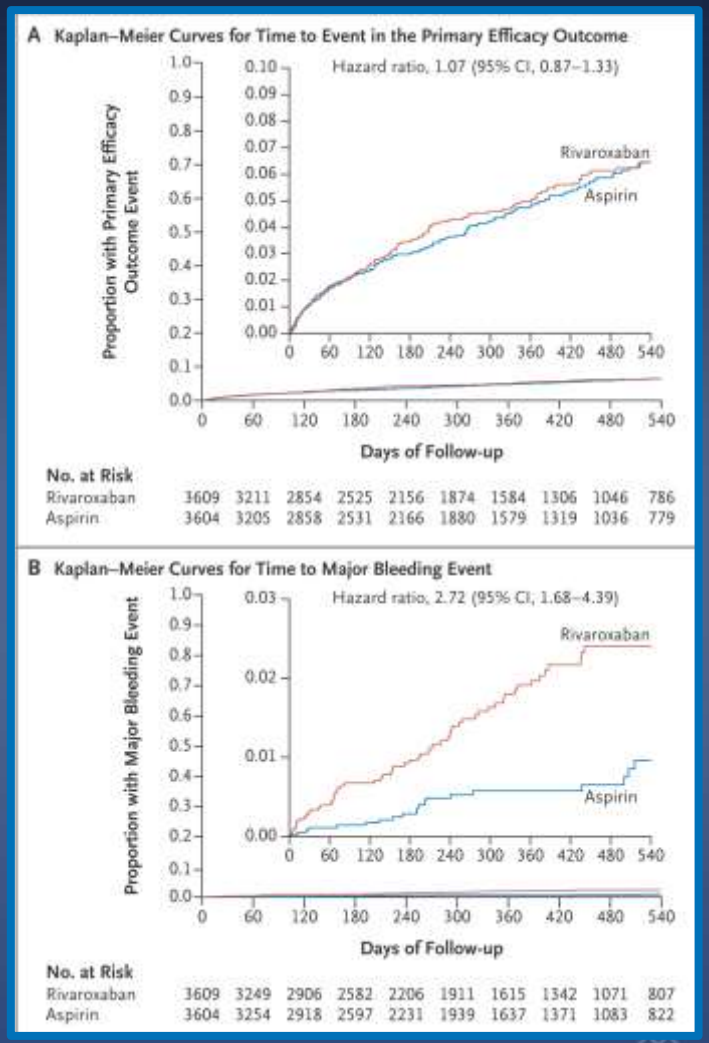
Why Failed GALILEO?
Rivaroxaban Effect in Non-AF Patients?

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

- **NAVIGATE ESUS trial**
  - Embolic stroke of undetermined stroke (ESUS): non-lacunar brain infarcts without substantial proximal arterial stenosis or major cardioembolic sources
  - Represents 80-90% of cryptogenic stroke





N Engl J Med 2018; 378:2191-2201

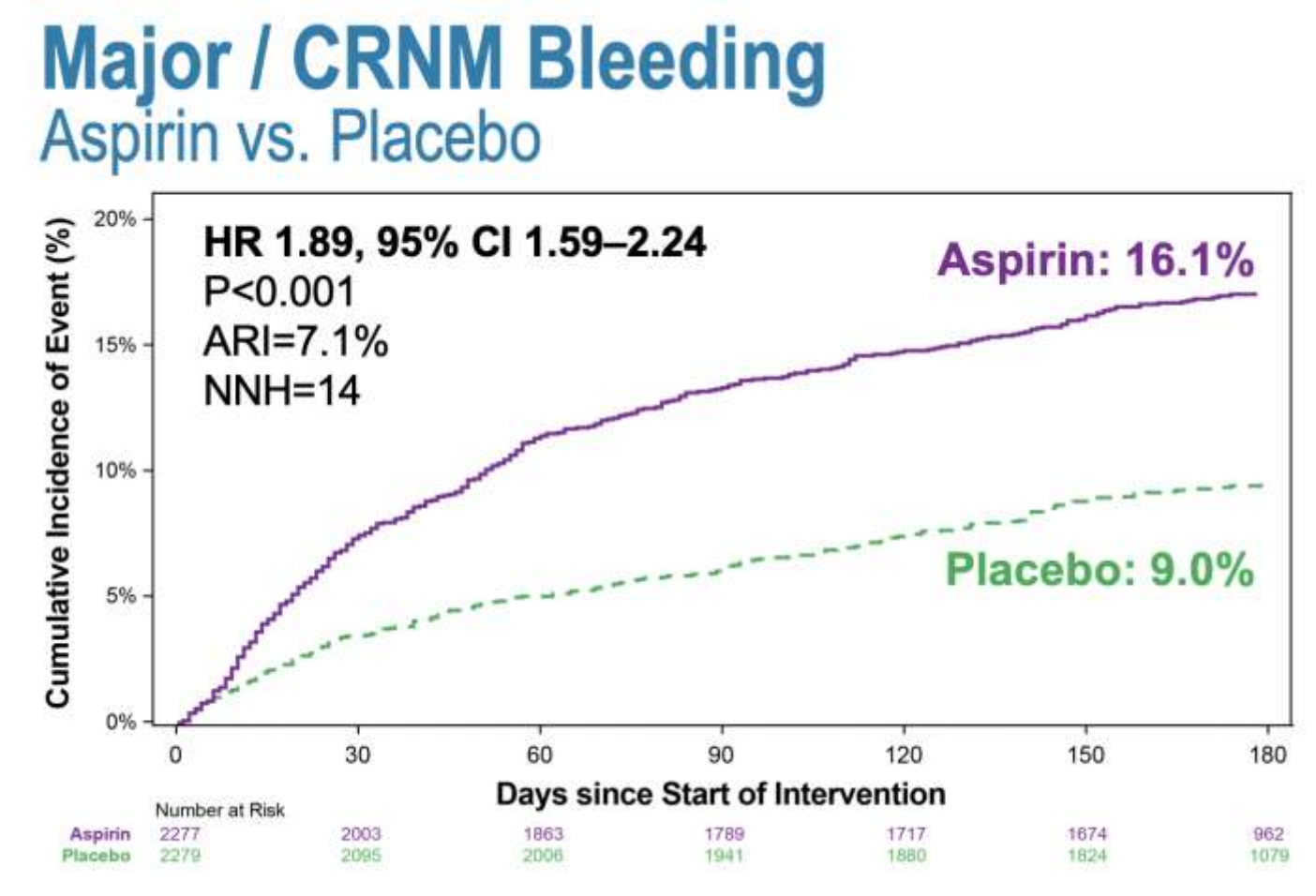
NOAC in NON-AF Patients

- Expanded Rivaroxaban Indication
  - Stable CAD or peripheral vascular disease (O?): COMPASS
  - ~~CAD + HF (X): COMMANDER HF~~
  - ~~ESUS (X): NAVIGATE-ESUS~~
  - ~~Extended Thromboprophylaxis (X): MARINER~~

- **NOAC** is **not** beneficial, but associated with excessive risk of bleeding **in patients without AF** other than COMPASS indication

Why Failed GALILEO?
Aspirin Effect (added to NOAC) ?

Key Lesson from the AUGUSTUS Trial

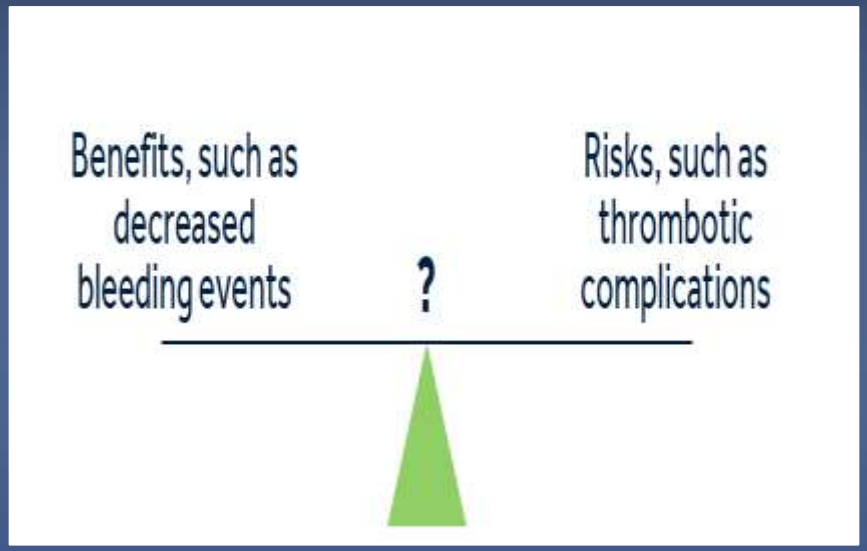


N Engl J Med 2019, March 7.

Why Failed GALILEO?

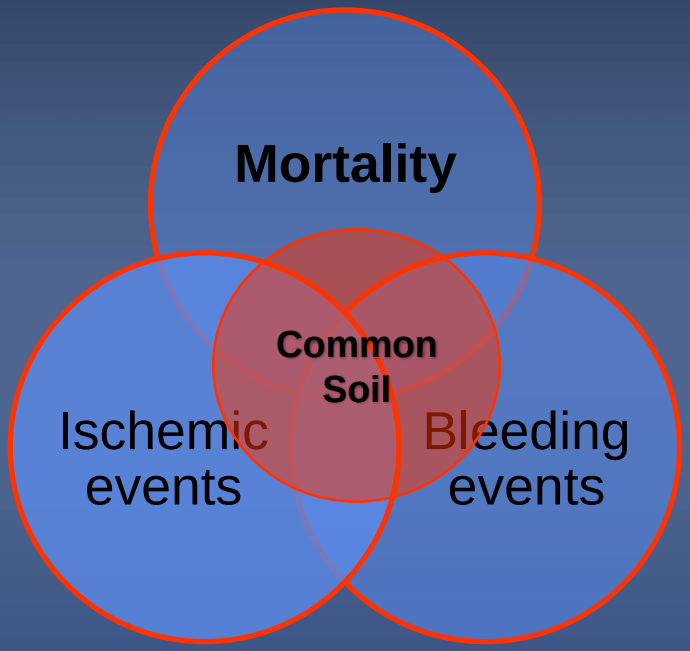
Ischemic & Bleeding Leverage Is More Complex in Elderly TAVR Patients

Theory



Applicable to Younger population

Reality

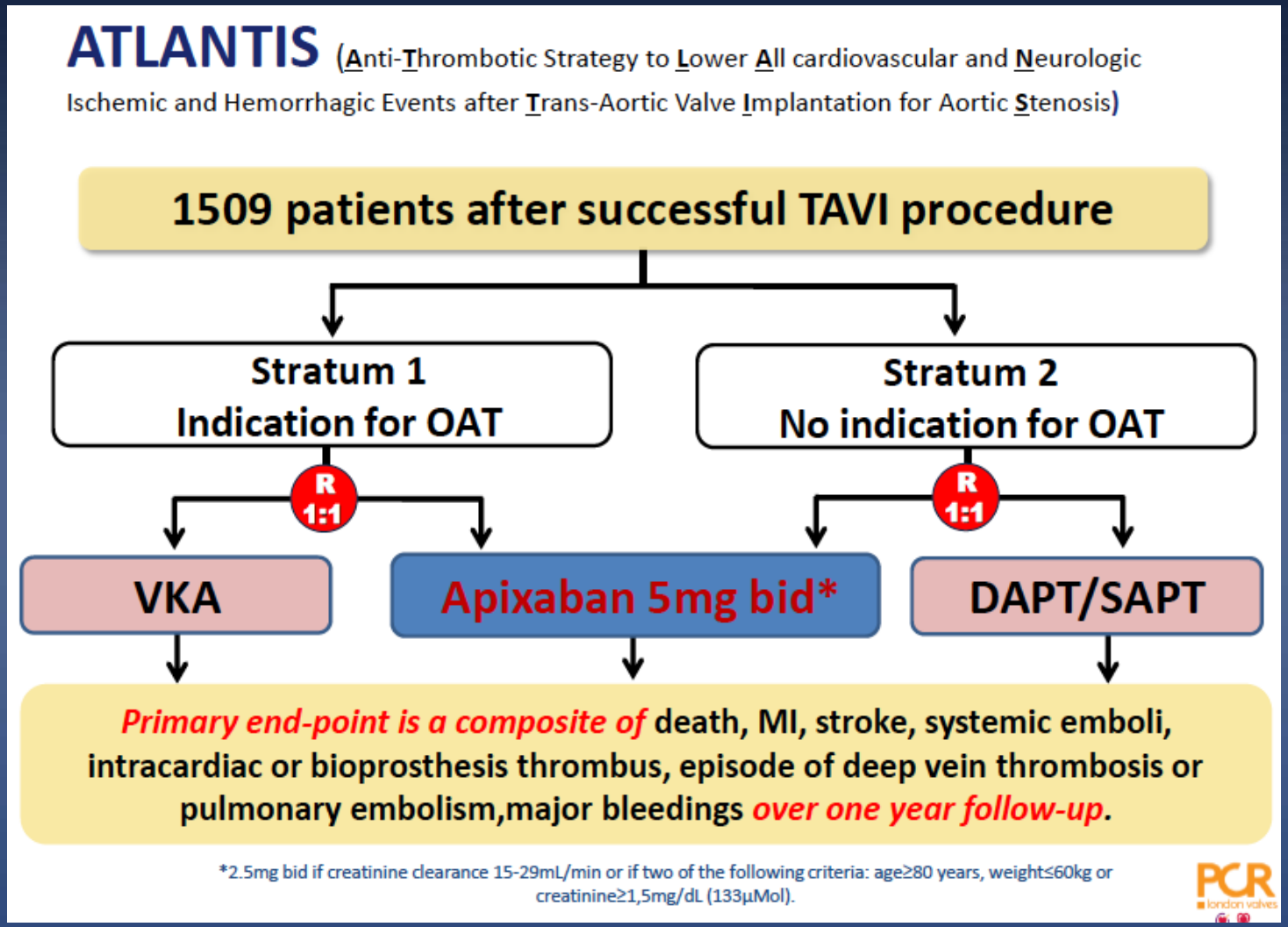


Clustering Effect in Fragile, Old Age

Common sense approach in 2019 (till we have guidance from clinical trials)

- No reason to rush to anticoagulate

Ongoing Trials
: ATLANTIS



- ENVISAGE Trial – Current Status ~700 pts

PIs: G. Dangas, N. vanMieghem

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

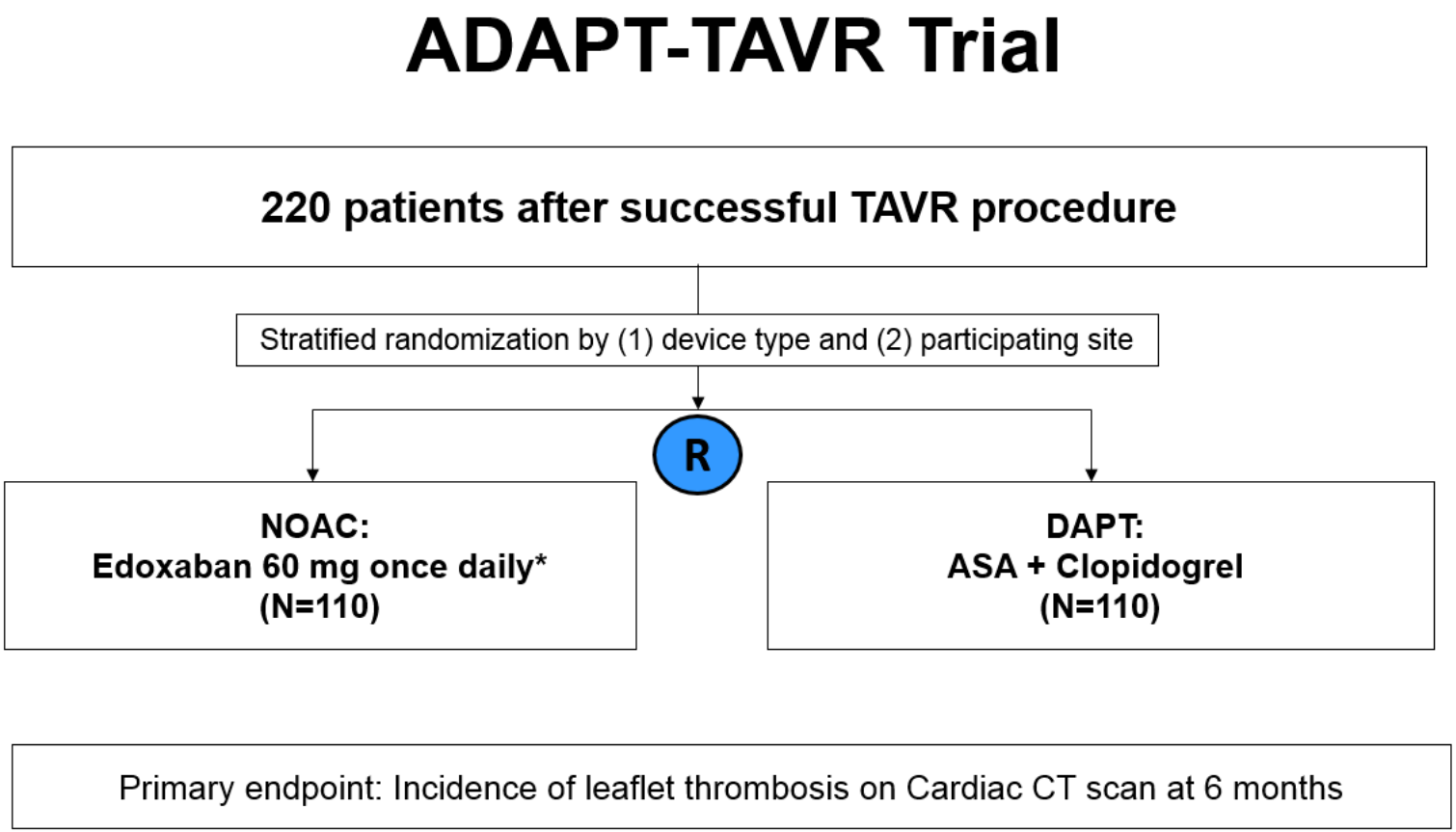
[Composite of Death, MI, Stroke, TIA, systemic thromboembolism or VARC-2 Life-threatening (LT) or Major bleeding]

Ancillary Studies

- Cost-Effectiveness
- QoL substudy

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



*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).

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

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

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).

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

Quantitative Imaging Biomarkers Alliance

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

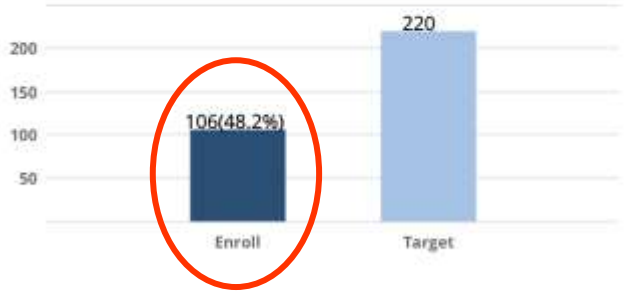
SAMSUNG 삼성의료원 | 서울아산병원 Asan Medical Center

SNUH 서울대학교병원

High Quality
Academic Imaging CRO

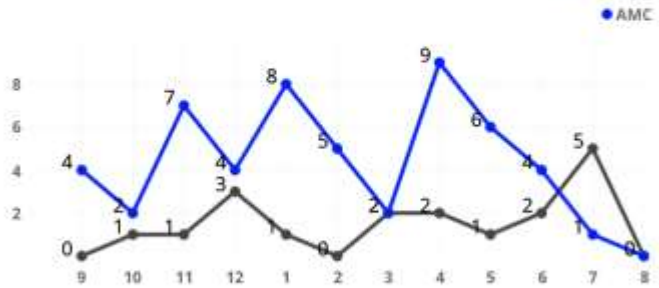
데이터 신뢰도 | 업무 효율성 | 시험비용

목표대비 등록현황



월별 등록현황

year | month



edit

ISSUE

1. AMC 등록 시작
2. DAPT group: Aspirin & Pregrel 처방
3. 중간 분석 at 50% 등록 완료: safety & Imaging outcome based on EMR description

★ 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	**106**	
1	KR	서울아산병원	박덕우	Enrollment	85	2019-07-03
2	KR	차의과학대학교 분당차병원	김원장	Enrollment	2	2018-10-04
3	HK	Queen Mary Hospital	Simon C.C. Lam	Enrollment	12	2019-06-26
4	TW	National Taiwan University hospital	Paul Hsien Li Kao	Enrollment	4	2019-07-30
5	TW	Cheng Hsin General Hospital	Jeng Wei	Enrollment	3	2019-07-3

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Summary
: Antithrombotic Strategy After TAVR

- TAVR patients have multiple thrombotic- and bleeding-related comorbidities.
- The choice and duration of antithrombotic treatment after TAVR still remains a matter of hot debate.
- The optimal anticoagulation after all bioprosthetic valves (especially transcatheter) is under active investigation with the findings of frequent HALT with or without HAM after TAVR.
- **GALILEO** was failed, yet the role of NOAC after TAVR and any difference between available NOACs will be supported by ongoing consecutive RCTs such as **ATLANTIS**, **ENVISAGE TAVI-AF**, and **ADAPT-TAVR** Trial.