“Make It Simple”: TAVR Antithrombotics

Evidence-based Antiplatelet and Antithrombotic Therapy for TAVR

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Disclosure

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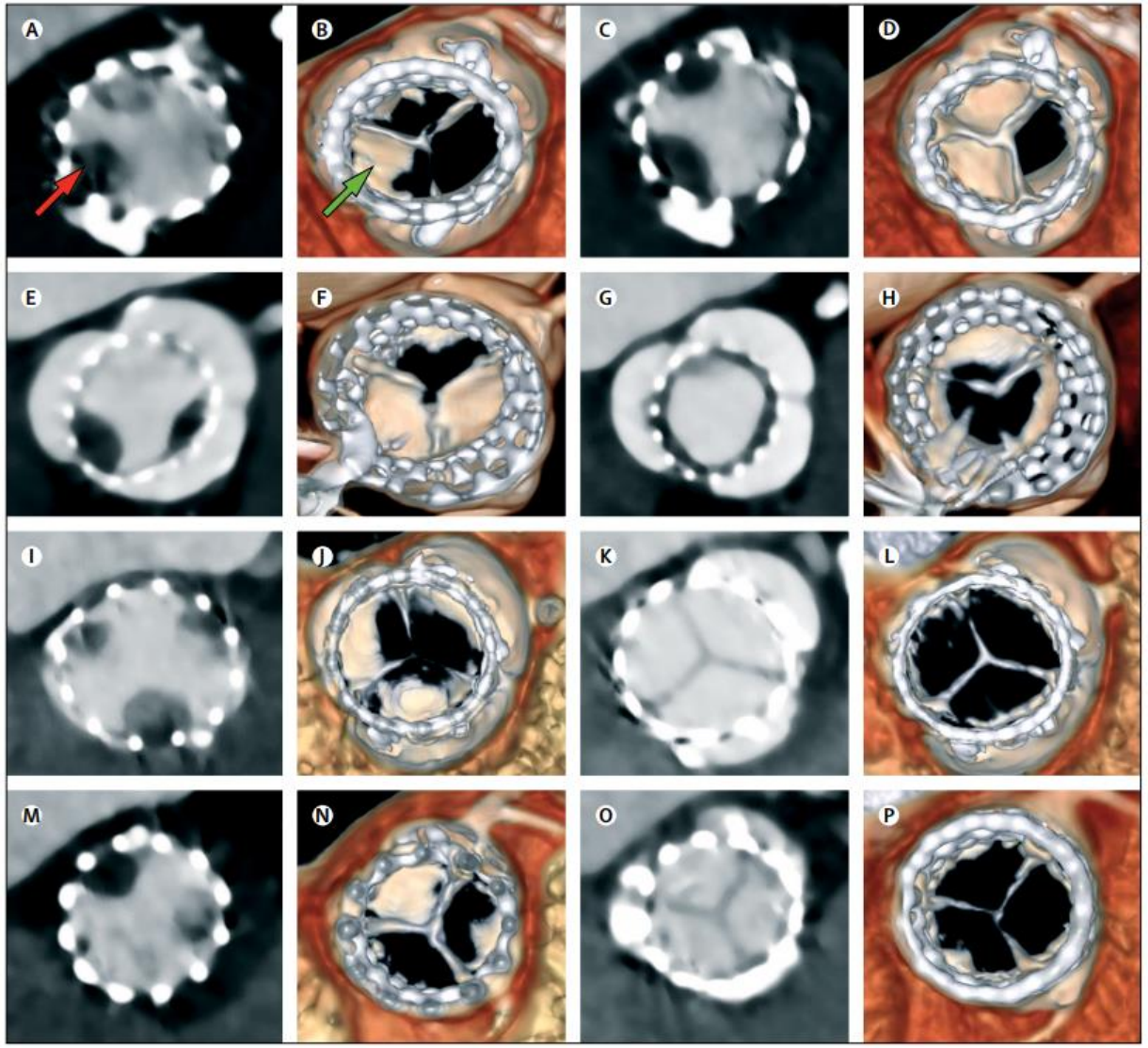
Dilemma between leaflet thrombosis and potent antithrombotics after TAVR



DAPT

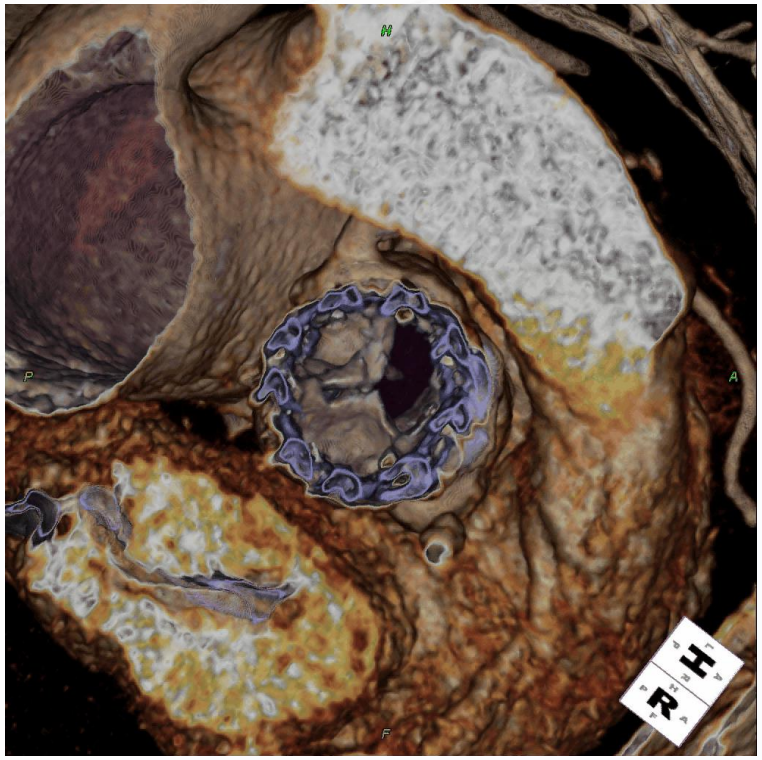
Warfarin

Rivaroxaban

Apixaban

Lancet 2017;389:2383-92

Subclinical leaflet thrombosis



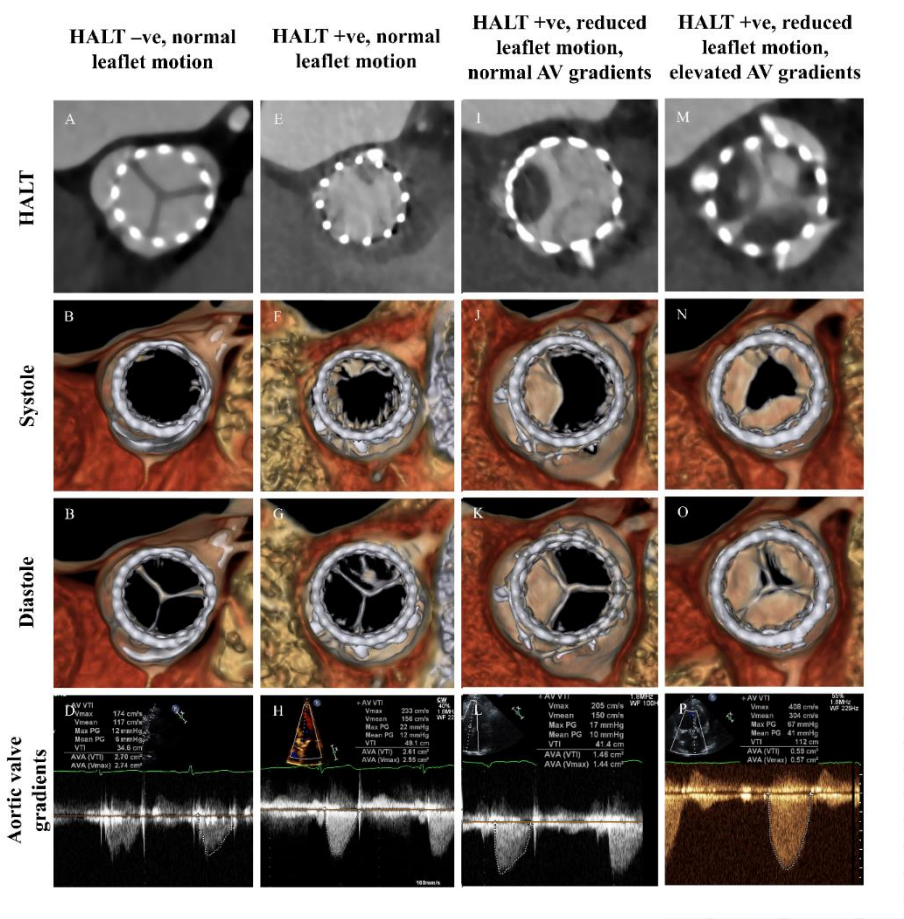
- Observed in all types of bio-prosthetic aortic valves
- Not associated with symptoms or high transvalvular gradient
- (N)OAC may prevent and resolve reduced leaflet thrombosis
- Uncertain association with increased risk of stroke/TIA and valve durability

Makkar et al. NEJM. 2015;373:2015-24

Valve Thrombus presents as a spectrum..

Thrombus on bioprosthetic valves can present as a spectrum

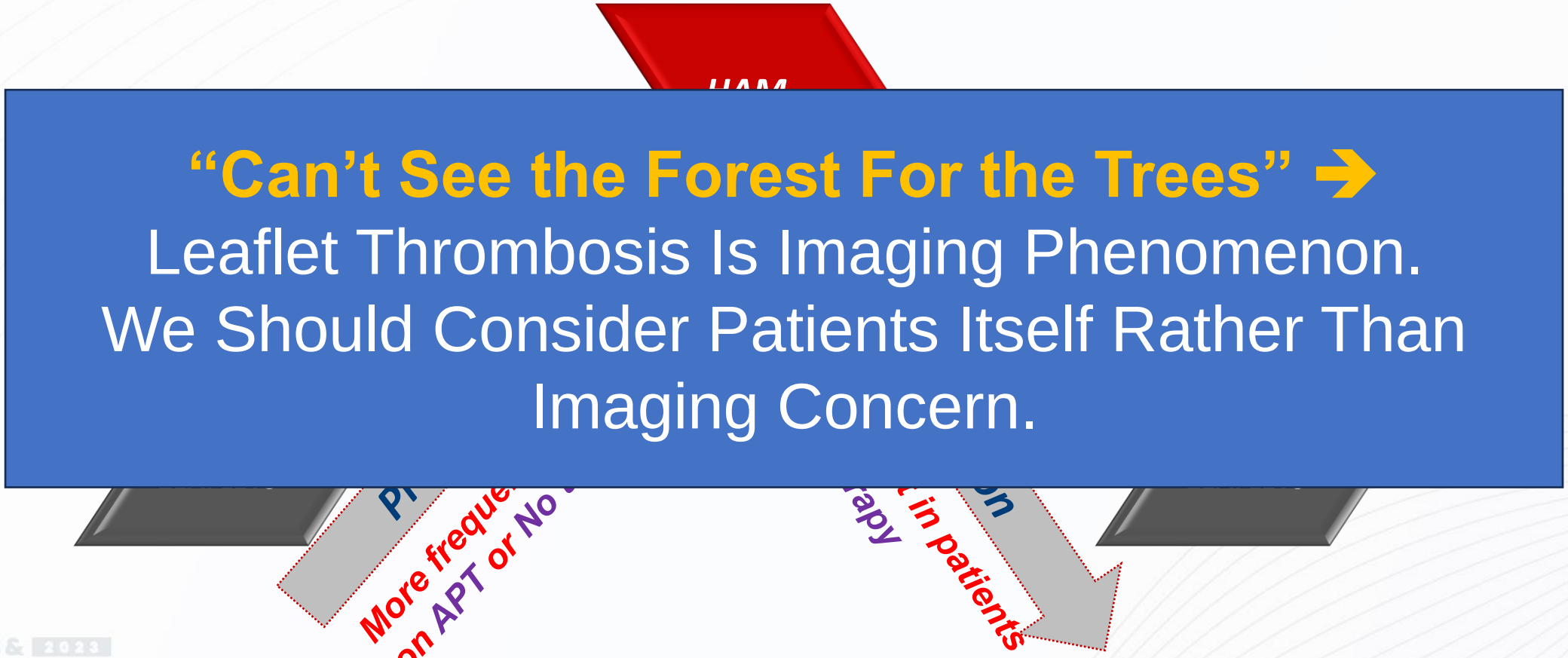
1. HALT with relatively normal leaflet motion
2. HALT with reduced leaflet motion, but normal gradients
3. Clinical valve thrombosis with elevated gradients



DYNAMIC PATTERN OF LEAFLET THROMBOSIS

84 patients from the SAVORY registry (61 TAVI and 23 SAVR), in whom first and second CT scans were performed at 140 ± 152 days and 298 ± 141 days after valve implantation, respectively

Hypo-attenuating leaflet thickening was noted in 32 patients (38.1%), with HAM in 17 (20.2%)

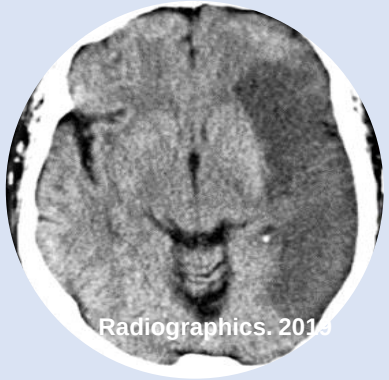


"Can't See the Forest For the Trees" ➔
Leaflet Thrombosis Is Imaging Phenomenon.
We Should Consider Patients Itself Rather Than Imaging Concern.

Sondergaard L et al. European Heart Journal (2017) 38, 2201–2207

Thrombotic and Bleeding Risk in TAVI Patients

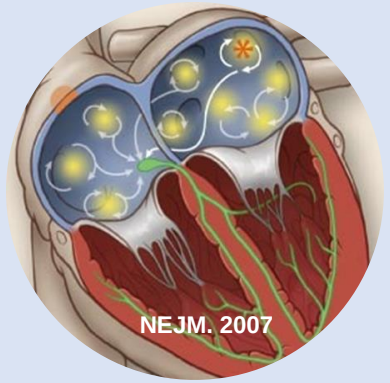
Thrombotic Risk



Stroke

Prosthetic Valve Thrombosis

Myocardial Infarction



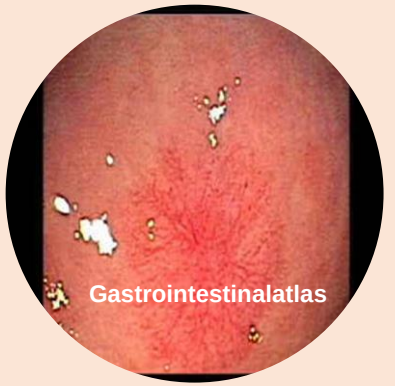
New-onset Atrial fibrillation

Bleeding Risk

Patient

- ✓ Age
- ✓ Antithrombotic therapy
- ✓ Anemia
- ✓ Bleeding history
- ✓ diathesis

Heyde syndrome

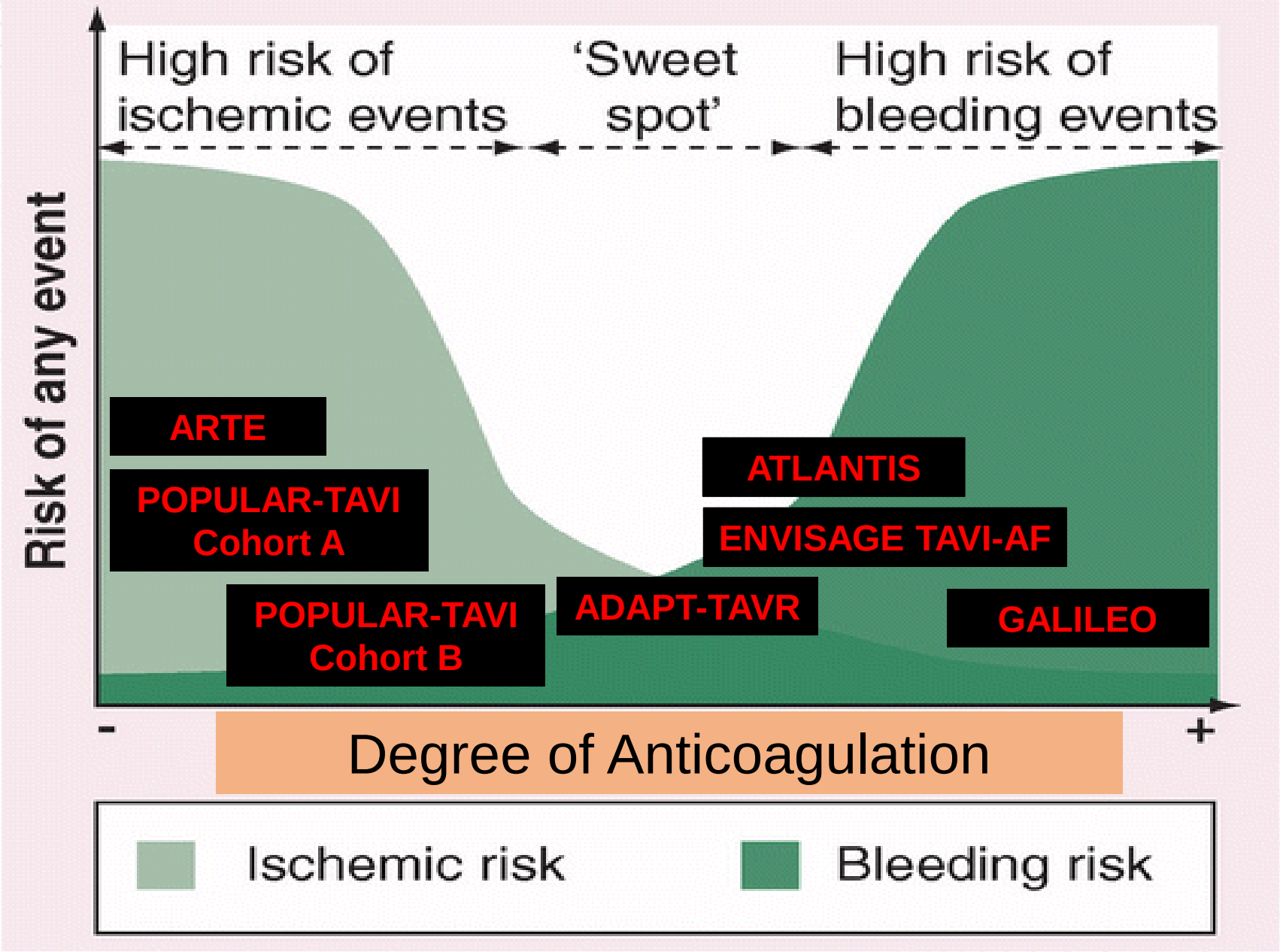


Angiodysplasia

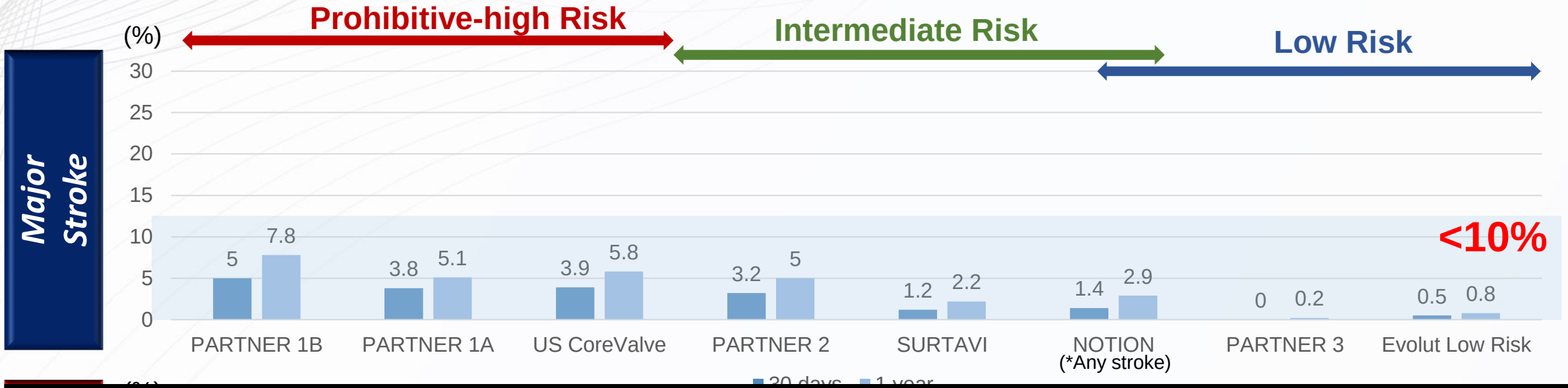
Table 3. Main Ongoing Randomized Trials Evaluating Antithrombotic Regimen After TAVR

Trials	Target Population	Estimated Enrollment	Antithrombotic Regiment Evaluated	Primary End Points	Timeline	Anticipated Completion Date
POPULAR-TAVI[106]; NCT02247128	All-comers undergoing TAVR.; cohort A: no need for long-term OAC; cohort B: need for long-term OAC	1000	Cohort A: SAPT vs 3-mo DAPT; cohort B: VKA vs VKA+clopidogrel (3-mo duration)	Freedom from all BARC-defined bleeding complication at 1 y after TAVR	12 mo	Early 2020
GALILEO[107]; NCT02556203	Successful TAVR without indication for long-term OAC	1644	Rivaroxaban 10 mg (qd)+3-mo ASA (75–100 mg qd) vs ASA (75–100 mg qd)+3-mo Clopidogrel (75 mg qd)	Death, any stroke, MI, symptomatic valve thrombosis, DVT/PE, noncentral nervous system systemic embolism, life-threatening, disabling or major VARC-2 bleeding	Cutoff date was event-driven but expected duration of treatment is 720 d	Ended; results to be presented in 2019
ATLANTIS[108]; NCT02664649	Successful TAVR	1509	Apixaban (5 mg bd*) vs standard of care	Efficacy: Death, MI, stroke, systemic emboli, bioprosthesis thrombus, DVT/PE; safety: life-threatening, disabling or major VARC-2 bleeding	12±1 mo	2020
ENVISAGE-TAVI AF[109]; NCT02943785	Successful TAVR with AF or NOAF	1400	Edoxaban (60 mg qd)±antiplatelet therapy vs VKA±antiplatelet therapy	Efficacy: Death, MI, stroke, systemic embolism, valve thrombosis, ISTH major VARC-2 bleeding; safety: ISTH major bleeding	Cutoff date will be event-driven with an anticipated median follow-up of 2 y	November 2020
AUREA; NCT01642134	High-risk patient to SAVR with no need for long-term OAC	124	3-mo DAPT vs VKA	New areas of cerebral infarction at MRI	3 mo	April 2019
AVATAR; NCT02735902	Need for long-term OAC	170	VKA monotherapy vs VKA+ASA	Death, MI, stroke, valve thrombosis, ISTH major VARC-2 bleeding	12 mo	April 2020
TICTAVI; NCT02817789	All-comers undergoing TAVR	308	Ticagrelor vs ASA+clopidogrel	VARC-2 safety end point: death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney injury, major vascular complications, coronary artery obstruction or valve-related dysfunction requiring intervention	30 d	2018
REAC TAVI;	All-comer undergoing	65	3-mo ticagrelor vs 3-mo	Platelet reactivity	3 mo	August 2018

What Are Optimal Solutions? Potential NOAC Role?



THROMBOTIC AND BLEEDING RISKS IN RCTS



If you define primary trial endpoint as the net clinical composite including major bleeding events, you can always achieve positive trial with ***less potent antithrombotic strategy***.

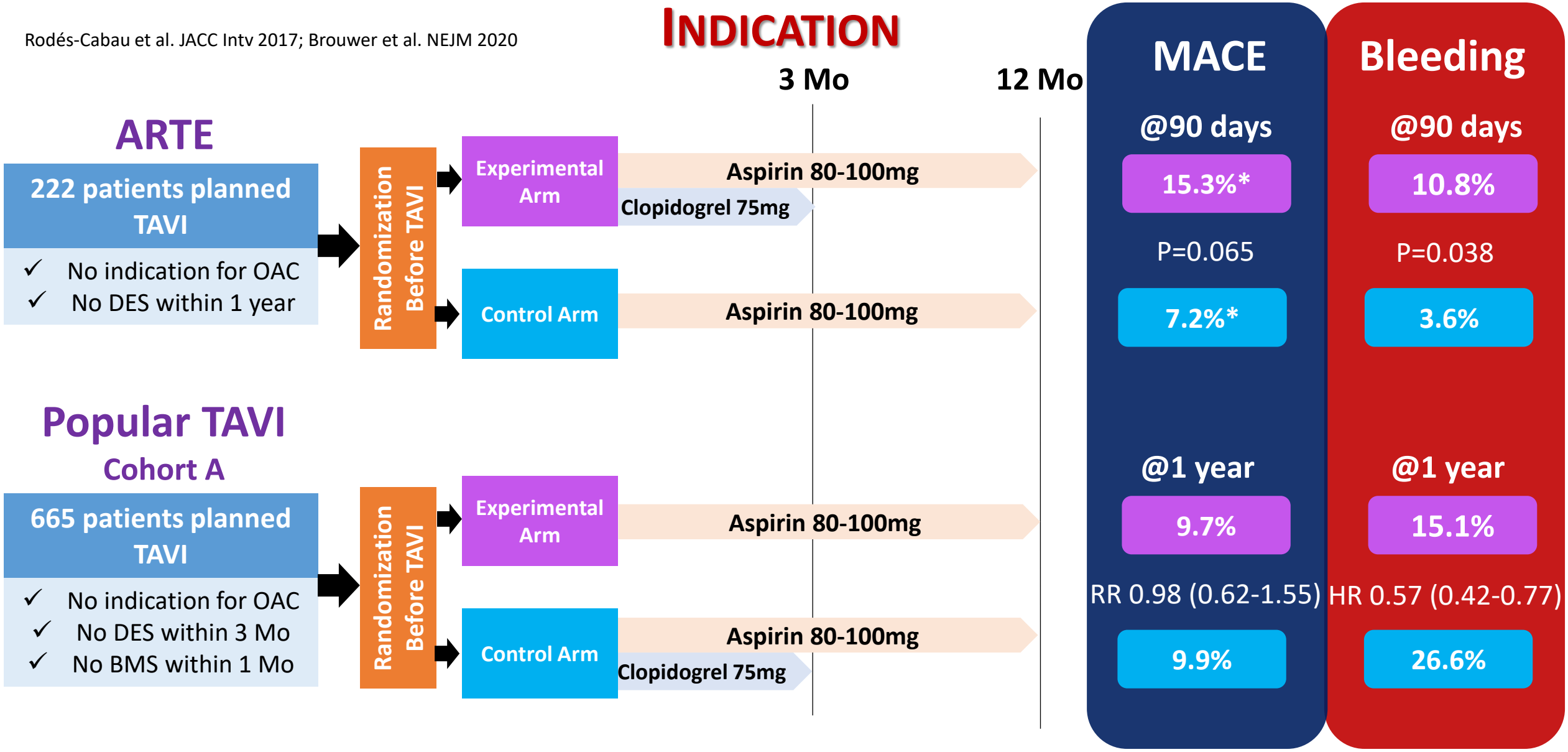
⇒ This seems to be attractive for trial investigators

⇒ Is it sufficient to guide your decision-making?

CLINICAL TRIALS: DAPT VS. SAPT IN PATIENTS WITHOUT OAC

Rodés-Cabau et al. JACC Intv 2017; Brouwer et al. NEJM 2020

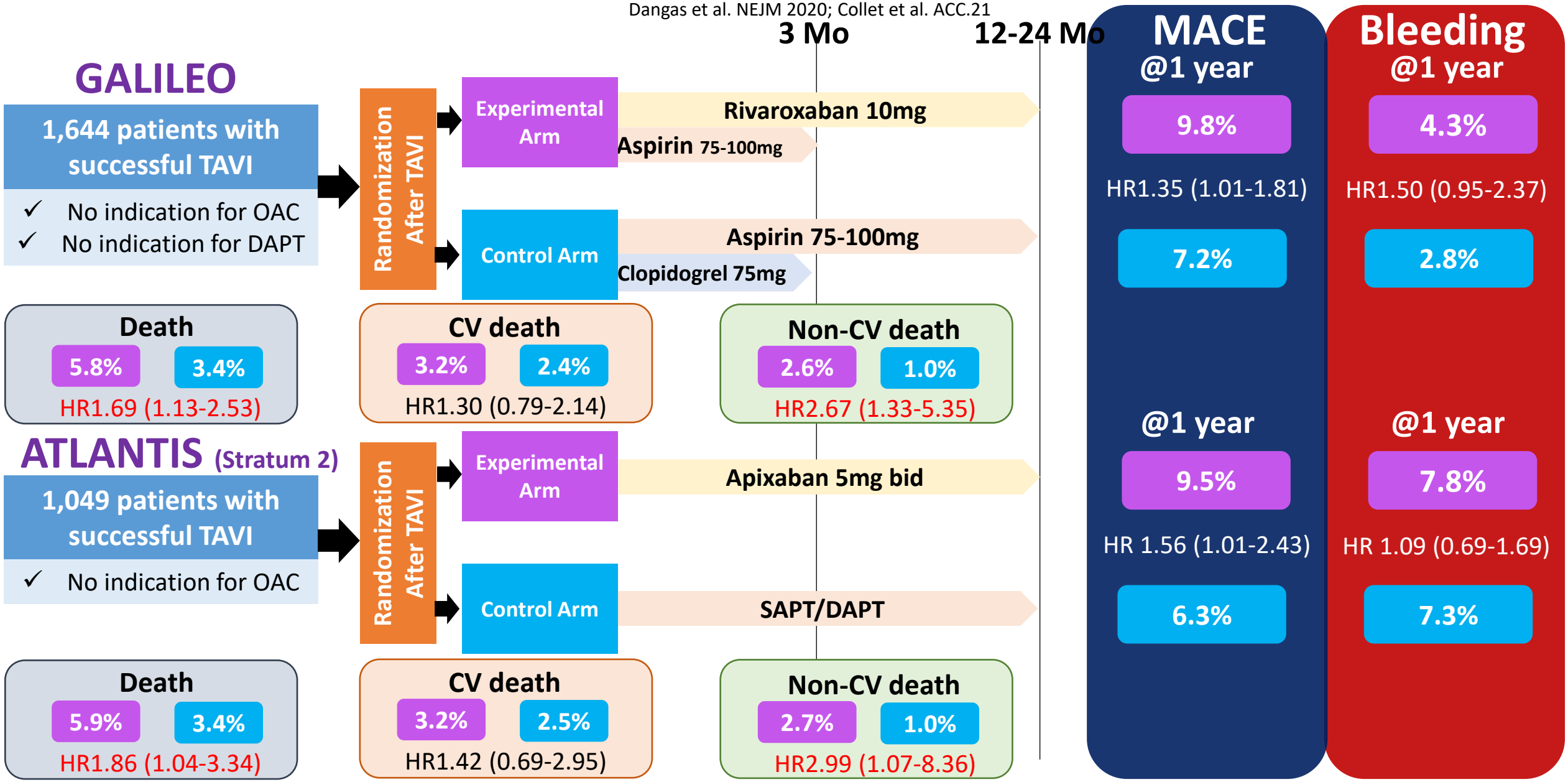
INDICATION



MACE: Composite of CV death, stroke, MI, (major or life-threatening bleeding)*ARTE

CLINICAL TRIALS: OAC IN PATIENTS WITHOUT OAC INDICATION

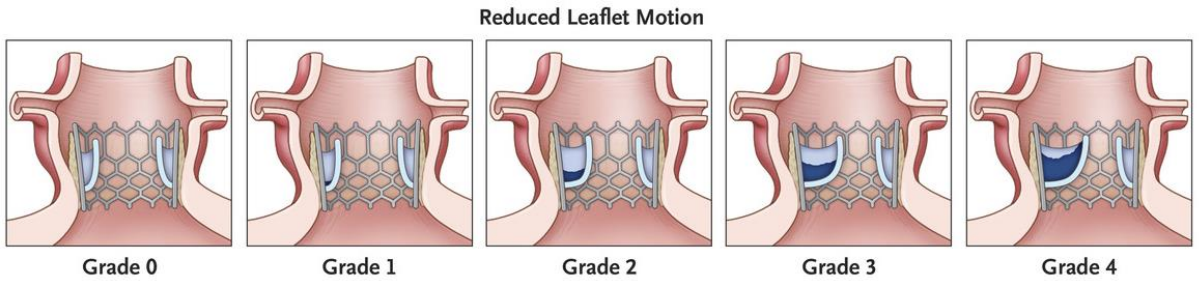
Dangas et al. NEJM 2020; Collet et al. ACC.21

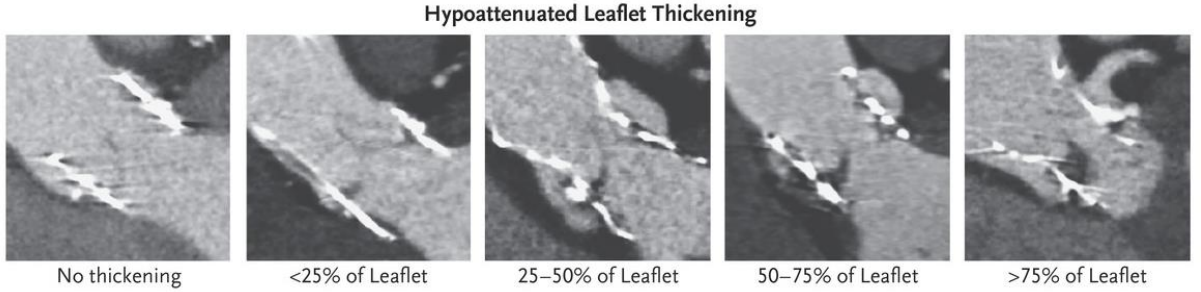


MACE: Composite of death, stroke, systemic embolism, (MI, symptomatic valve thrombosis, DVT/PE)* GALILEO

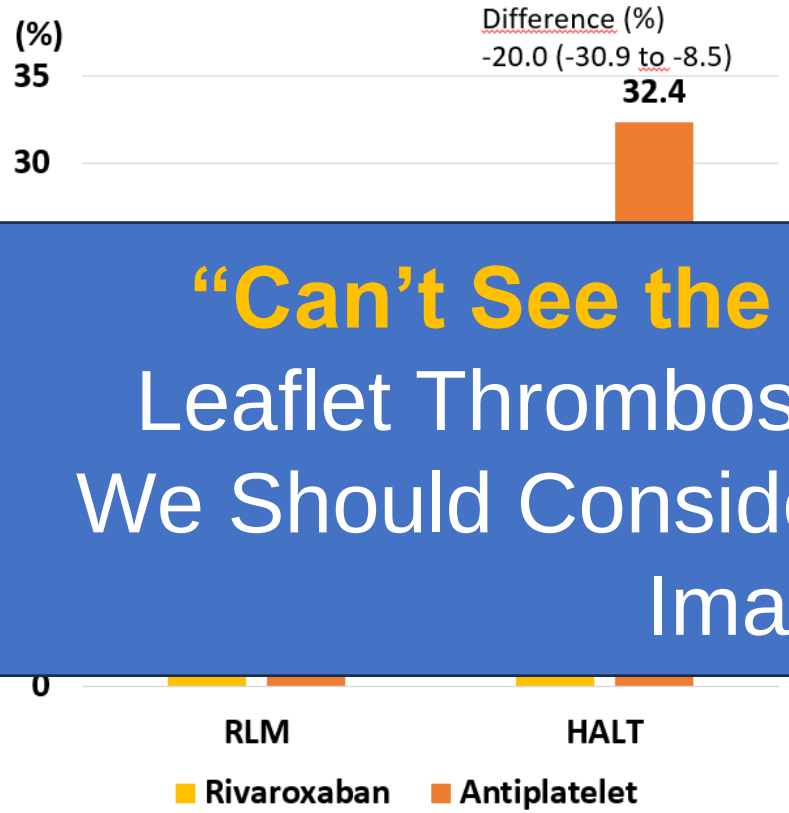
CLINICAL TRIALS: OAC IN PATIENTS WITHOUT OAC INDICATION

Dangas et al. NEJM 2020; Collet et al. ACC.21

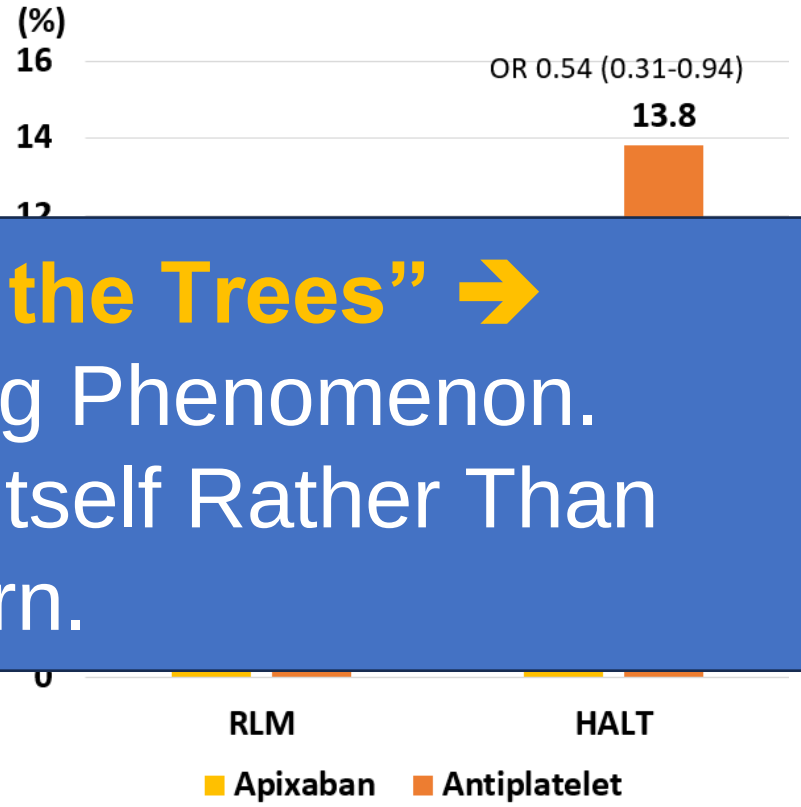




GALILEO 4D



ATLANTIS 4D-CT (Stratum 2)



"Can't See the Forest For the Trees" ➔

Leaflet Thrombosis Is Imaging Phenomenon.
We Should Consider Patients Itself Rather Than Imaging Concern.

CLINICAL TRIALS: OAC VS. OAC + SAPT IN PATIENTS WITH OAC INDICATION

Nijenhuis et al. NEJM 2020

Popular TAVI

Cohort B

326 patients planned TAVI

- ✓ Indication for OAC
- ✓ No DES within 3 Mo
- ✓ No BMS within 1 Mo

Randomization Before TAVI

Experimental Arm: OAC (VKA or DOAC)

Control Arm: OAC (VKA or DOAC) + Clopidogrel 75mg

3 Mo

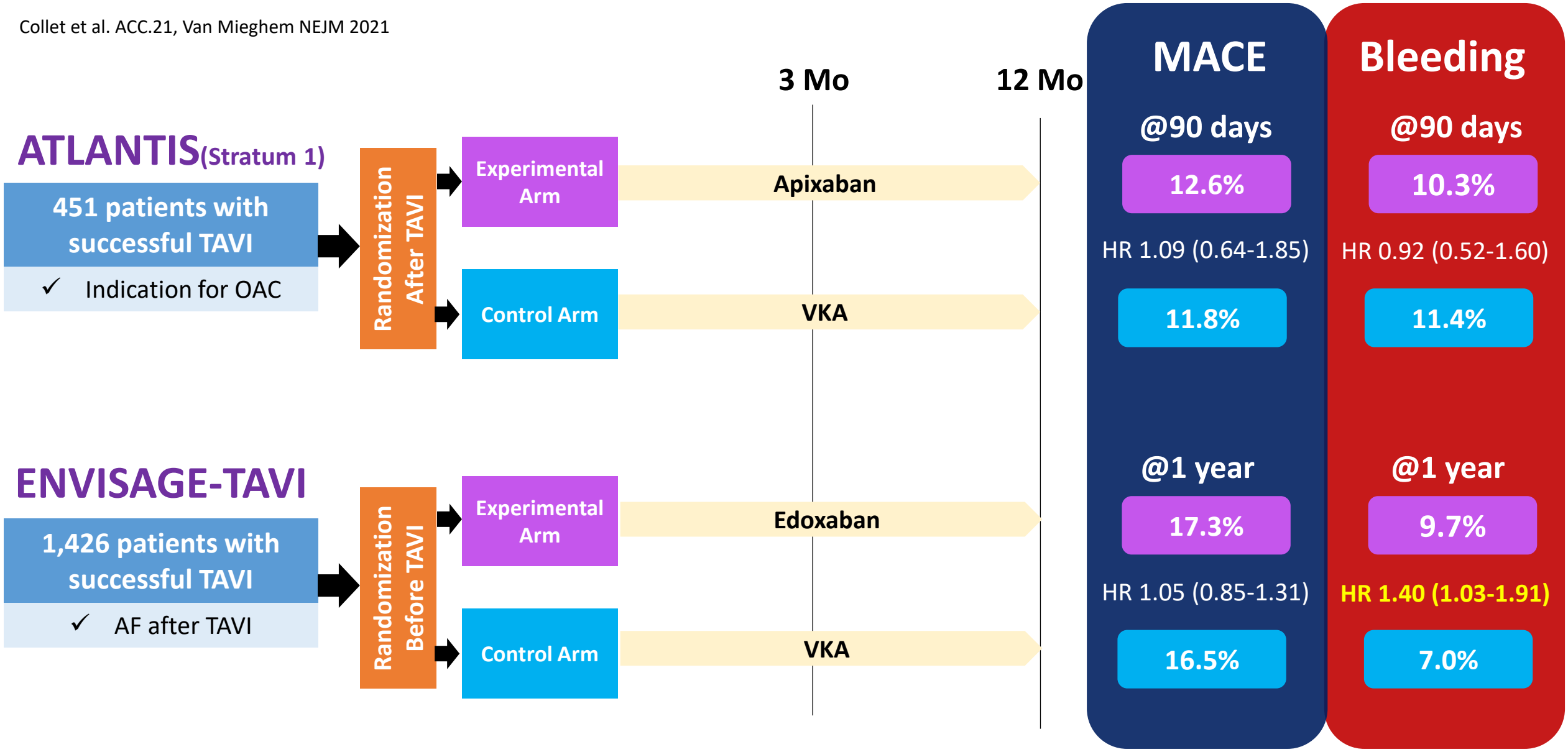
12 Mo

	MACE	Bleeding
	@1 year	@1 year
Experimental Arm	13.4%	21.7%
	HR 0.77 (0.46-1.31)	RR 0.63 (0.43-0.90)
Control Arm	17.3%	34.6%

MACE: Composite of CV death, ischemic stroke, or MI

CLINICAL TRIALS: VKA VS. NOAC IN PATIENTS WITH OAC INDICATION

Collet et al. ACC.21, Van Mieghem NEJM 2021

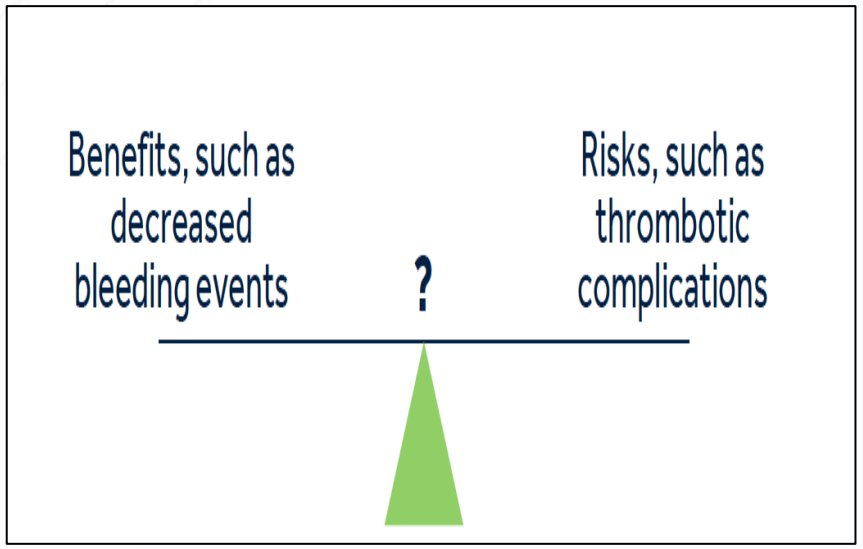


MACE: Composite of death, stroke, systemic embolism, (MI, symptomatic valve thrombosis, major bleeding)* *ENVISAGE-TAVI

Why Several RCTs for TAVR Patients Failed?

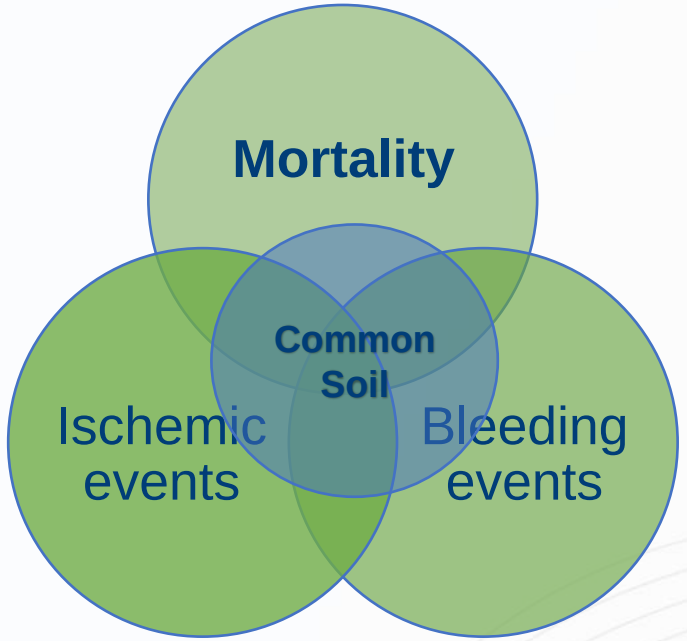
Ischemic & Bleeding Leverage Is More Complex in Elderly TAVR Patients

Theory: balanced



Applicable to Younger ACS or PCI population

Reality: imbalanced



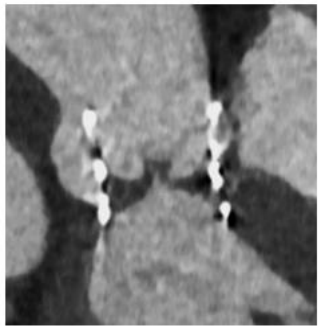
Clustering effect in Fragile, Elderly TAVR Patients

Key Questions regarding HALT/RLM

- Does HALT/RLM lead to clinical events?
- Does HALT/RLM cause structural valve degeneration?

Subclinical Leaflet Thrombosis (SLT) after TAVR[1-4]

What Is Known? What Is Unknown?

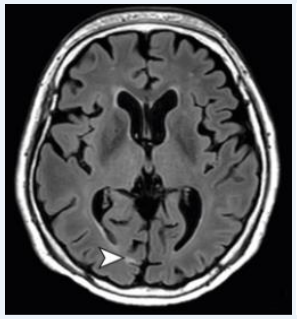


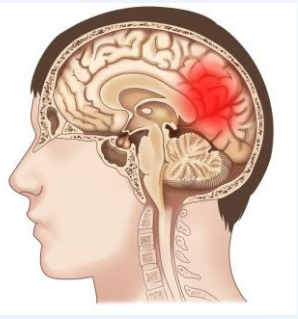
>75% of leaflet

SLT

Unknown

Causal relationship of SLT with cerebral embolism





Cerebral thromboembolism
Stroke or TIA

Known

OAC can reduce SLT

OAC therapy

Unknown

OAC can reduce SLT-related cerebral embolism

SLT, subclinical leaflet thrombosis; OAC, oral anticoagulation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

[1]Makkar RR, et al. *NEJM*. 2015;373:2015-2024. [2]Chakravarty T, et al. *Lancet* 2017;389:2383-2392. [3]Makkar RR, et al. *JACC* 2020;75:3003-3015. [4]Bogyi M, et al. *JACC: Cardiovascular Interventions* 2021;14:2643-2656.

Circulation

ORIGINAL RESEARCH ARTICLE

Edoxaban Versus Dual Antiplatelet Therapy for Leaflet Thrombosis and Cerebral Thromboembolism After TAVR: The ADAPT-TAVR Randomized Clinical Trial

Duk-Woo Park, MD; Jung-Min Ahn, MD; Do-Yoon Kang, MD; Kyung Won Kim, MD; Hyun Jung Koo, MD; Dong Hyun Yang, MD; Seung Chai Jung, MD; Byungjun Kim, MD; Yiu Tung Anthony Wong, MD; Cheung Chi Simon Lam, MD; Wei-Hsian Yin, MD; Jeng Wei, MD; Yung-Tsai Lee, MD; Hsien-Li Kao, MD; Mao-Shin Lin, MD; Tsung-Yu Ko, MD; Won-Jang Kim, MD; Se Hun Kang, MD; Sung-Cheol Yun, PhD; Seung-Ah Lee, MD; Euihong Ko, MD; Hanbit Park, MD; Dae-Hee Kim, MD; Joon-Won Kang, MD; Jae-Hong Lee, MD; Seung-Jung Park, MD; for the ADAPT-TAVR Investigators

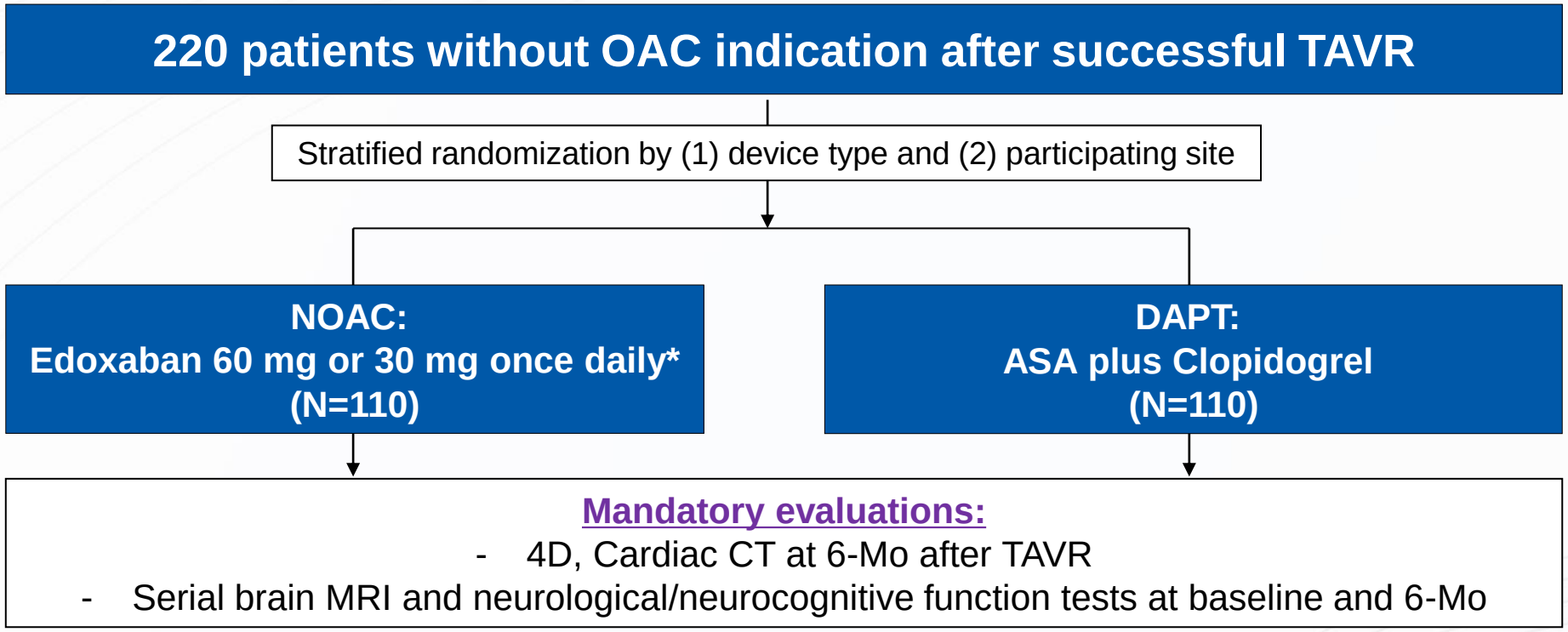
Park DW, et al. Circulation. 2022;April;[E-pub ahead of print].

Circulation. 2022;146:466–479.

Study 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).

Park H et al. BMJ Open. 2021;11:e042587

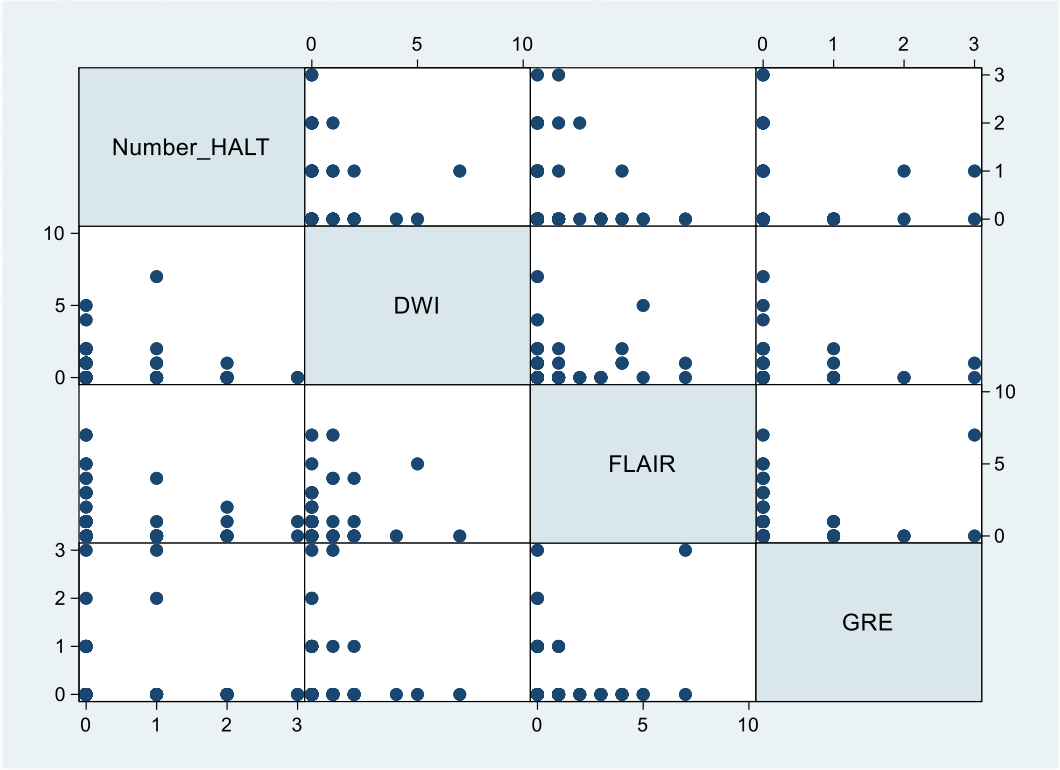
Completeness of Imaging & Neurocognitive Assessment

Measurement	Cardiac CT	Brain MRI	NIHSS	mRS	MoCA
Post-TAVR (~ before Discharge)		★ (98.3%)	★ (98.3%)	★ (98.3%)	★ (98.3%)
6-Mo follow-up	★ (95.9%)	★ (96.4%)	★ (95.5%)	★ (95.5%)	★ (95.5%)
Completeness of serial evaluations*		95.9%	93.7%	93.7%	93.7%

* Completeness of imaging or neurological assessments at 6 months was estimated among eligible patients who were alive at 6 months and did not withdraw during follow-up.

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment

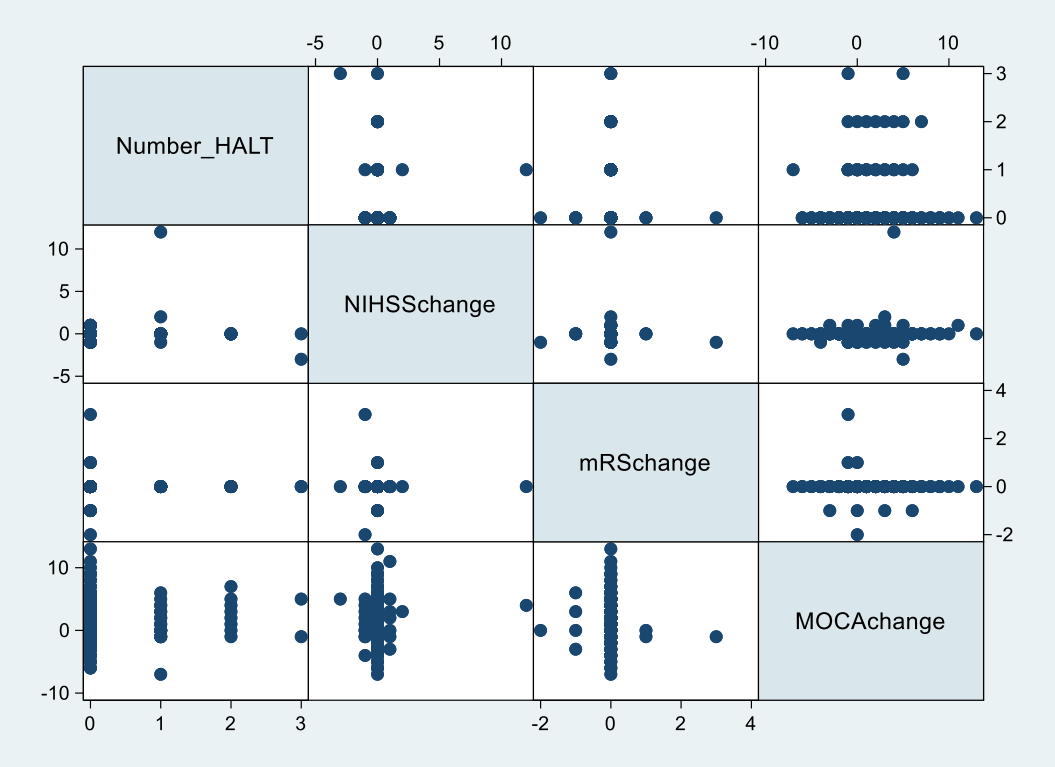
“No Association” of Severity of HALT with Extent of New Lesions on Brain MRI



		Number of New Lesions on DWI-MRI	Number of New Lesions on FLAIR-MRI	Number of New Lesions on GRE-MRI
Number of HALT Per-Patient	N	209	209	209
	Spearman Rho	**0.09**	**-0.04**	**-0.02**
	P-Value	**0.19**	**0.60**	**0.81**

HALT, hypoattenuated leaflet thickening; DWI, diffusion weighted image; FLAIR, fluid attenuated inversion recovery; GRE, gradient echo; MRI, magnetic resonance imaging

“No Association” of Severity of HALT with Decline of Neurological Assessments



		Serial Change of NIHSS Score	Serial Change of mRS Score	Serial Change of MOCA Score
Number of HALT Per-Patient	N	204	204	204
	Spearman Rho	**0.01**	**0.02**	**0.03**
	P-Value	**0.94**	**0.77**	**0.68**

HALT, hypoattenuated leaflet thickening; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment

Guideline Recommendations For Management of Antithrombotic Therapy After TAVI

EUROPEAN SOCIETY OF CARDIOLOGY

Antithrombotic therapy after TAVI	Class	Level
OAC is recommended lifelong for TAVI patients who have other indications for OAC.	I	B
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	I	A
Routine use of OAC is not recommended after TAVI in patients with no baseline indication for OAC.	III	B

Given no association of HALT and cerebral thromboembolic risk,
Our ADAP-TAVR trial results strongly support "current VHD guidelines in TAVR patients without OAC indication"
"Simpler is Best"

American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY

anticoagulants.		
For patients with a bioprosthetic TAVI who are at low risk of bleeding, dual antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months after valve implantation.	IIb	B
For patients with a bioprosthetic TAVI who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation	IIb	B
For patients with a bioprosthetic TAVI, treatment with low-dose rivaroxaban (10mg daily) plus aspirin (75-100 mg) is contraindicated in the absence of other indications for oral anticoagulants.	III	B

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

Summary
Antithrombotics after TAVR: "Make It Simple"

- Current available RCTs showed "no benefit" of DOAC with "considerable hazards" in patients without OAC indications and "neutral effect" in patients with OAC indications.
- Subclinical leaflet thrombosis has not been proven to directly affect thromboembolic events after TAVR; this evidence does not support imaging-guided antithrombotic strategies in cases without

One Singe Message:

Antithrombotic therapy after TAVR

"Treat the patient, not the valve" approach!