Edoxaban vs. DAPT for Valve Thrombosis and Cerebral Thromboembolism After TAVR: Deep-Dive into ADAPT-TAVR Trial

Duk-Woo Park, MD

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

Disclosure

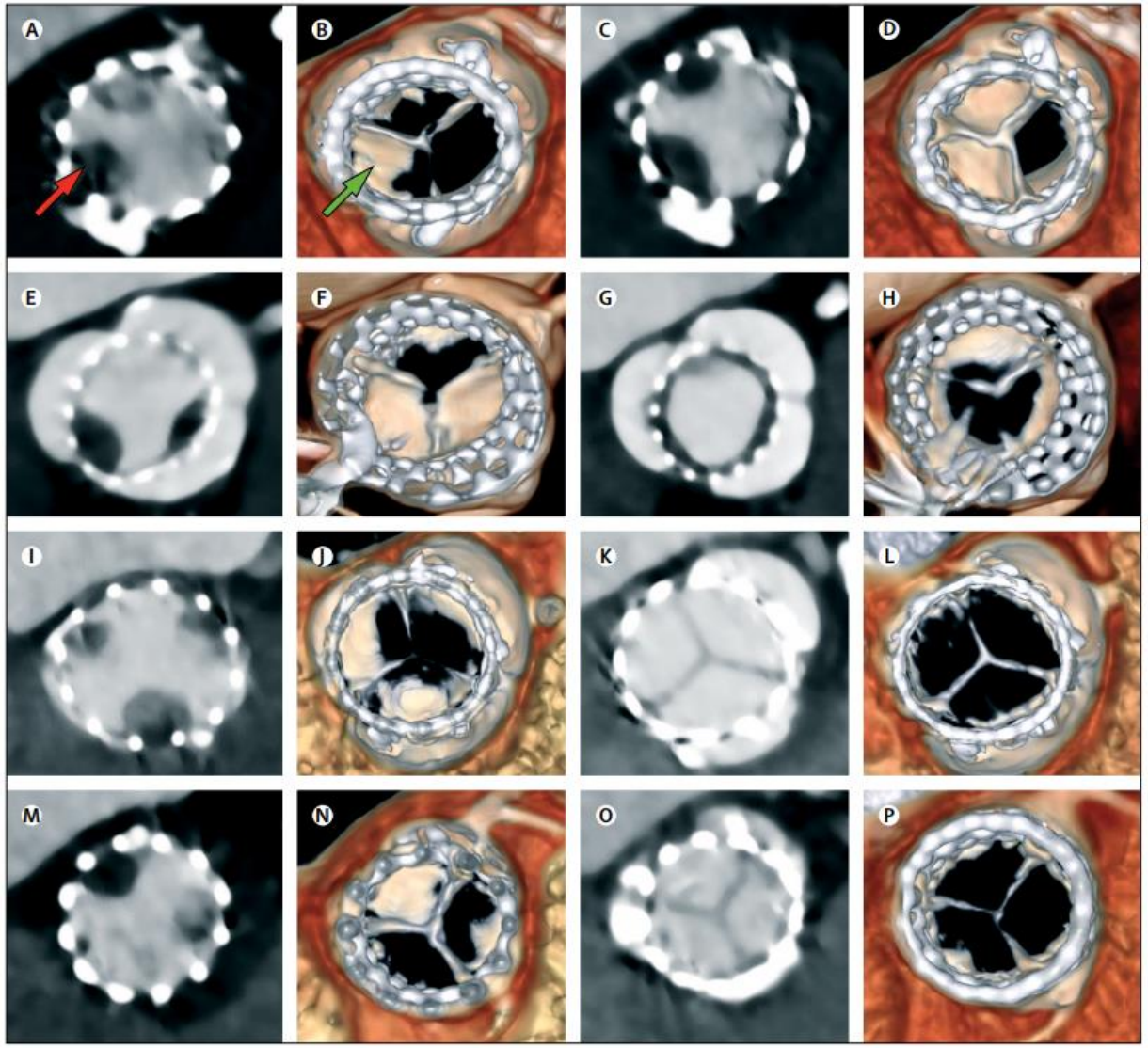
- Institutional grant/research funding to CardioVascular Research Foundation (CVRF, Korea) and/or Asan Medical Center from Abbott, Boston Scientific, Medtronics, Daiichi-Sankyo, Edwards Lifescience, HK InnoN, Daewoong Pharm, and ChongKunDang Pharm.

DAPT regimen in TAVR RCT Series

- Conventional 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

Subclinical leaflet thrombosis



DAPT

Warfarin

Rivaroxaban

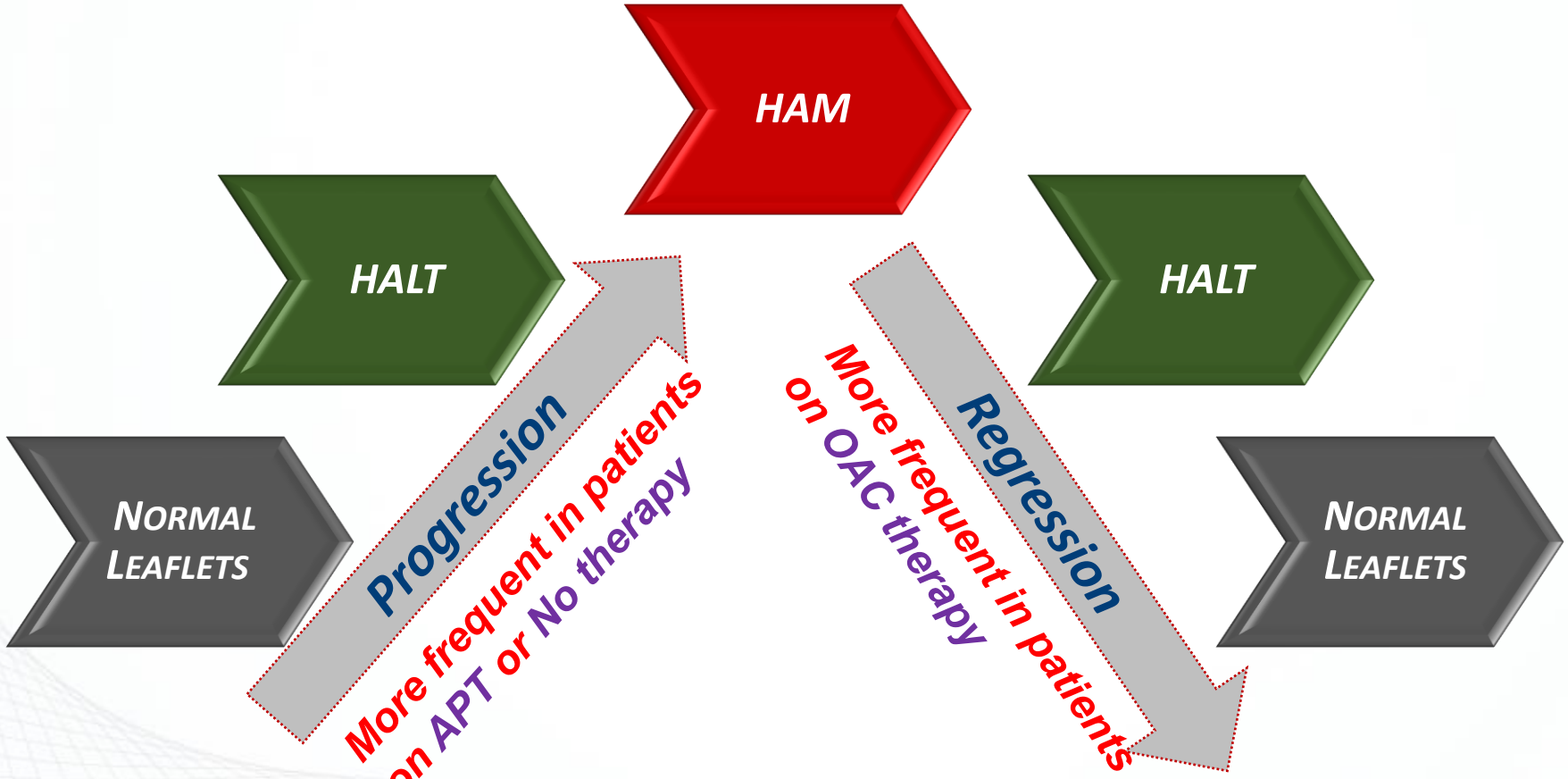
Apixaban

Lancet 2017;389:2383-92

Dynamic pattern of leaflet thrombosis with Anticoagulant Therapy

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%)



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

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

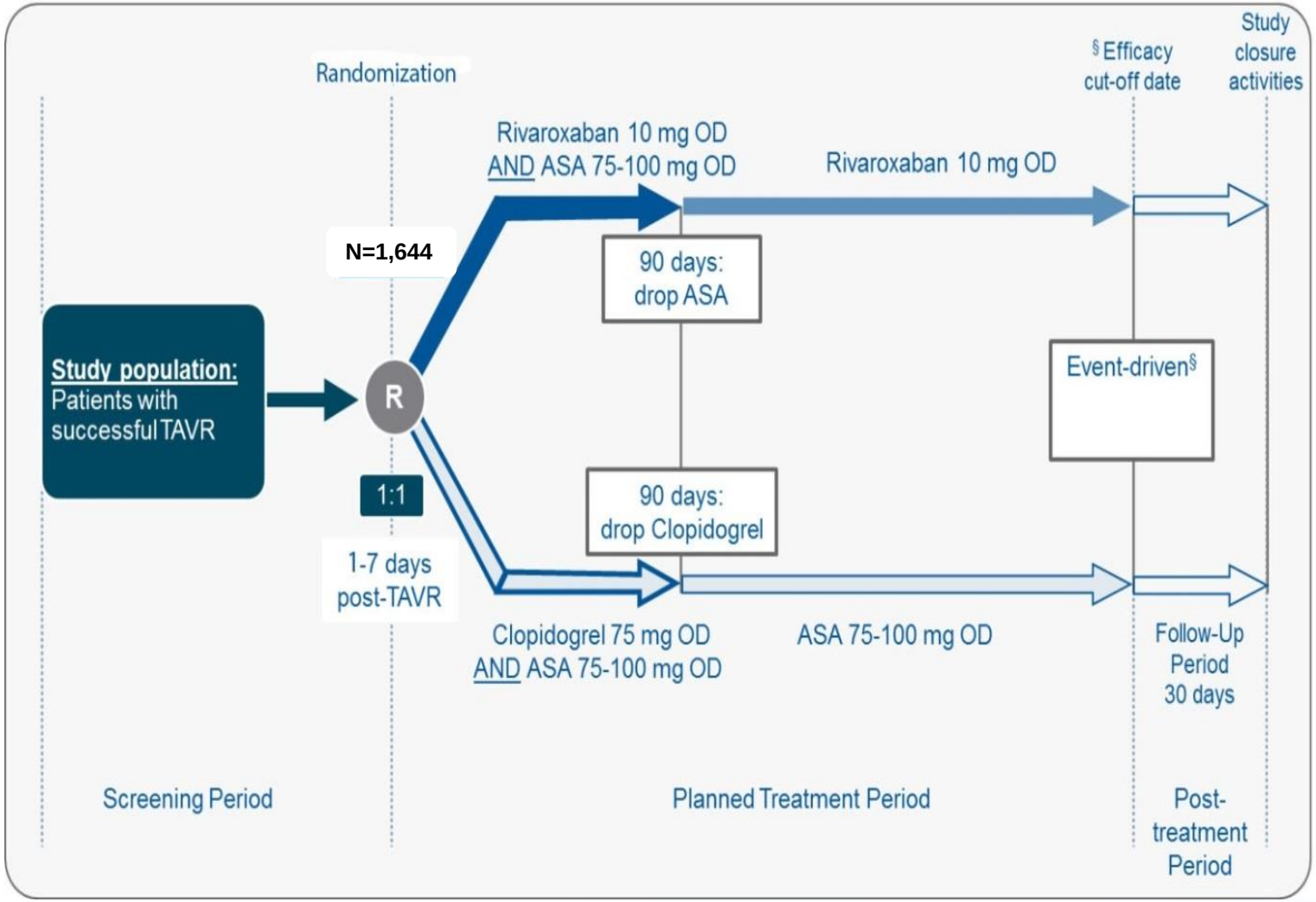
Trials	Target Population	Estimated Enrollment	Antithrombotic Regiment Evaluated	Primary End Points	Timeline	Anticipated Completion Date
POPULAR-TAVI[106]; NCT02247128	All-comers undergoing TAVR.; cohort A: no need for long-term OAC; cohort B: need for long-term OAC	1000	Cohort A: SAPT vs 3-mo DAPT; cohort 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

GALILEO Trial

- Open label, international, multicenter, event-driven, randomized, controlled trial comparing a rivaroxaban-based antithrombotic strategy vs. an antiplatelet-based strategy post-successful TAVR

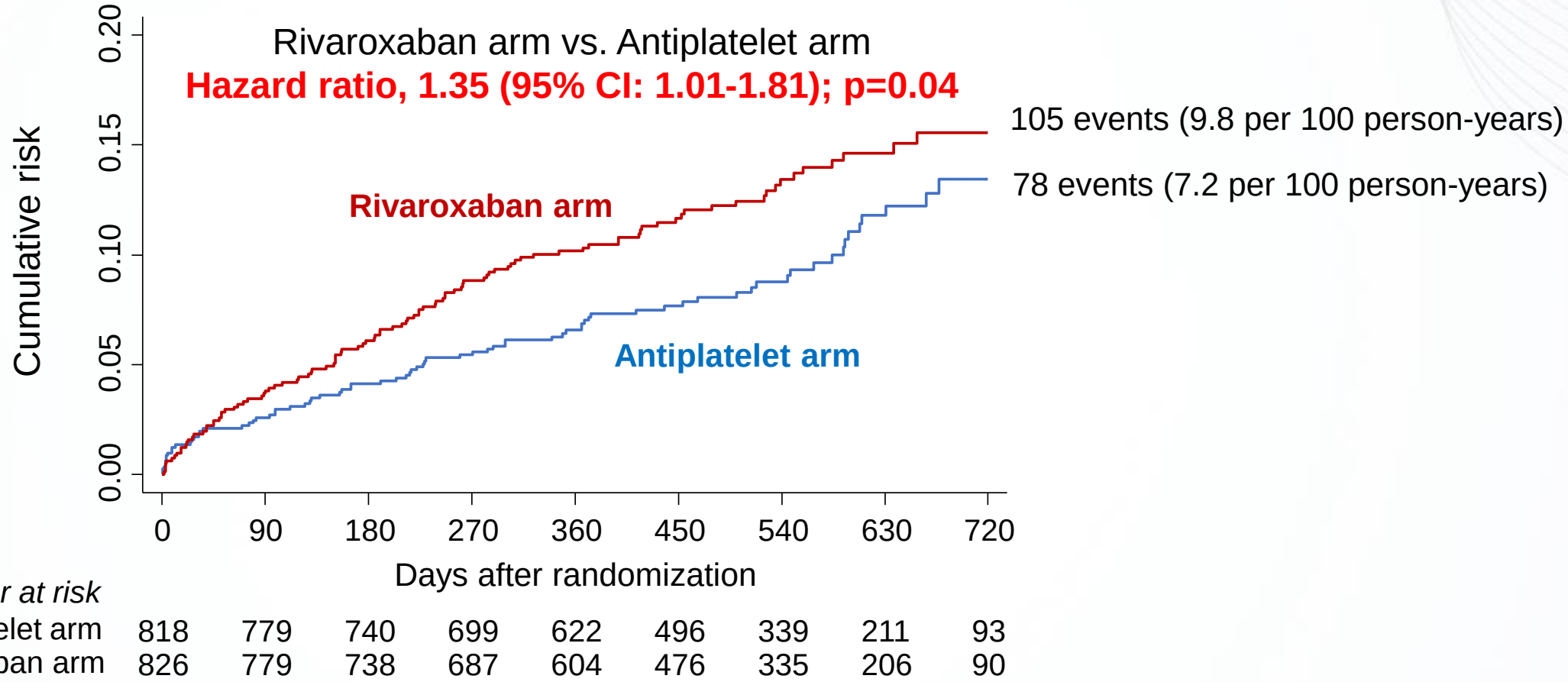
- **Primary efficacy endpoint**: death, stroke, MI, systemic thromboembolism, symptomatic valve thrombosis, or deep venous thrombosis or pulmonary embolism

- **Primary safety endpoint**: VARC-2 major, disabling or life-threatening bleeding



Primary Efficacy Endpoint (Intention-to-treat)

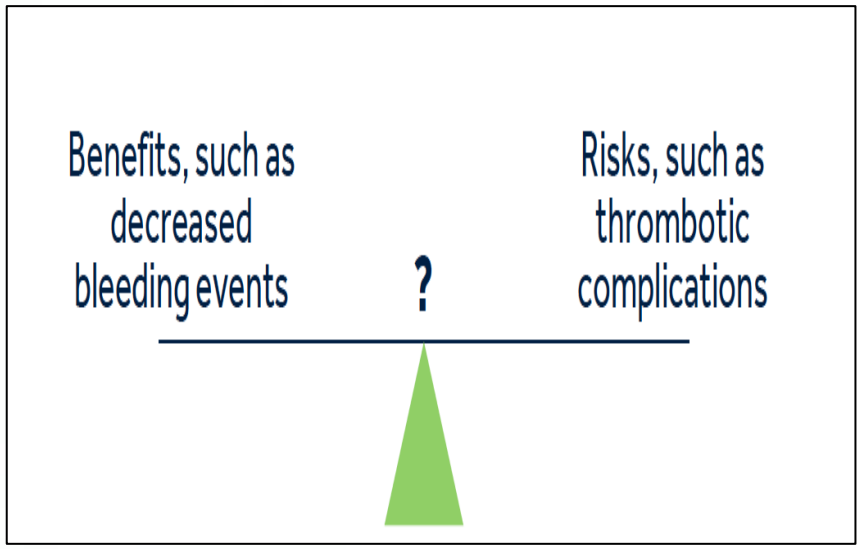
Time to death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis or systemic embolism



Why RCTs for TAVR Patients Failed?

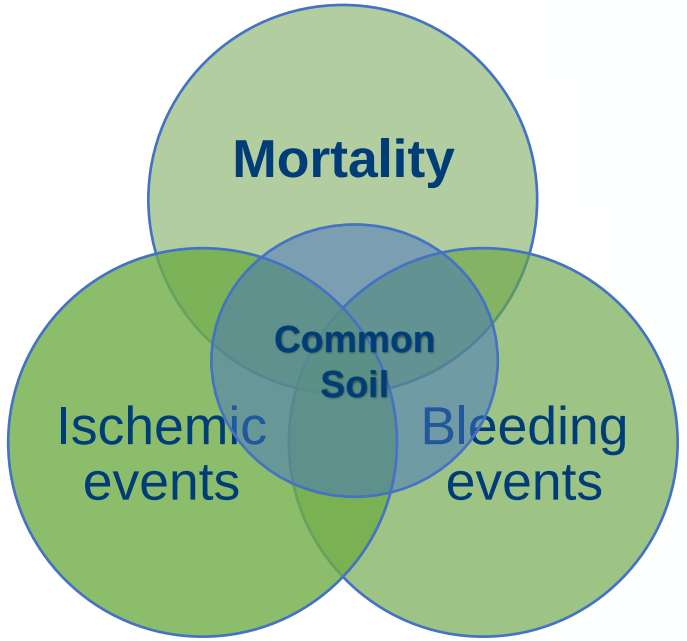
Ischemic & Bleeding Leverage Is More Complex in Elderly TAVR Patients

Theory



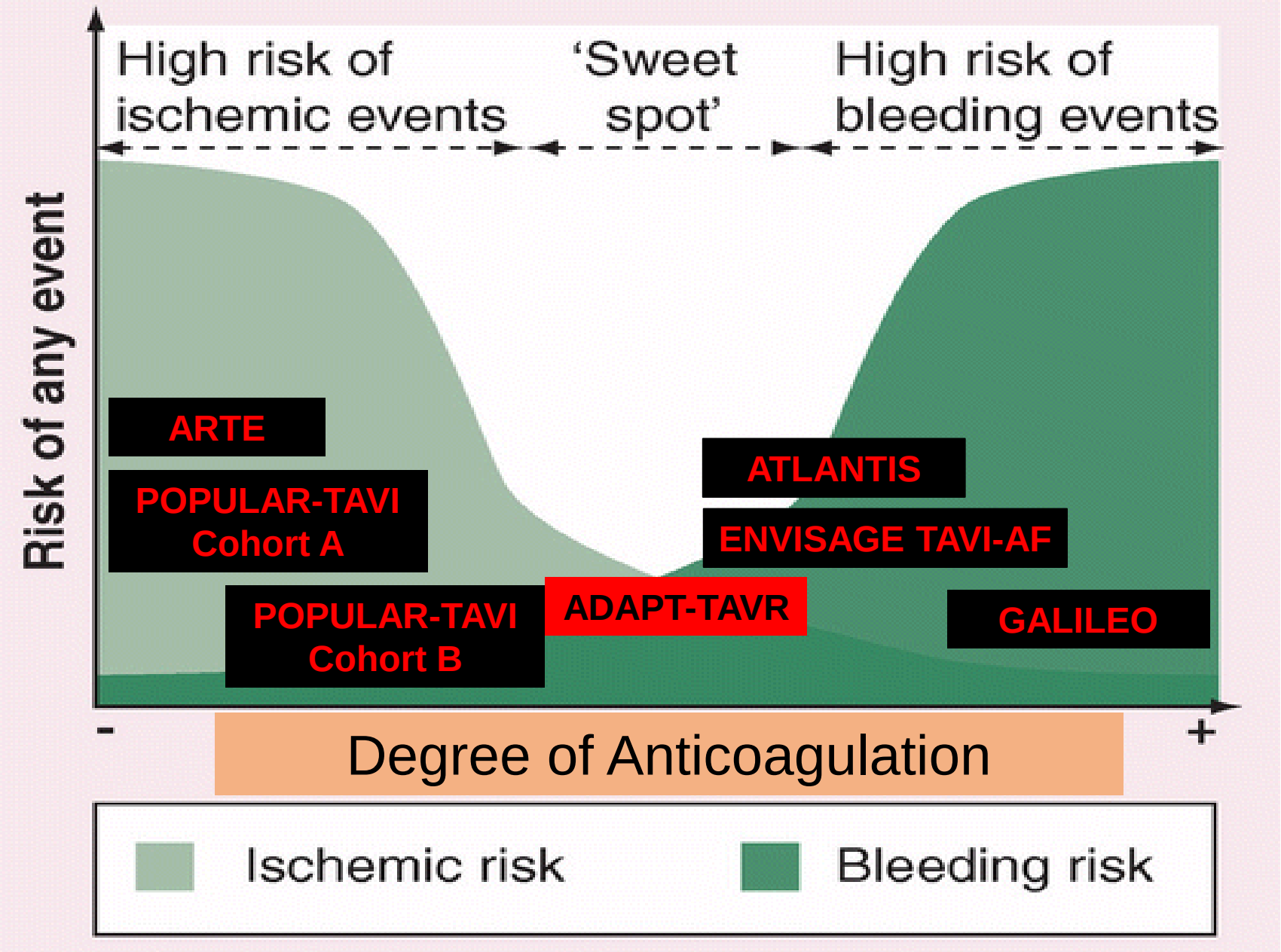
Applicable to
Younger population

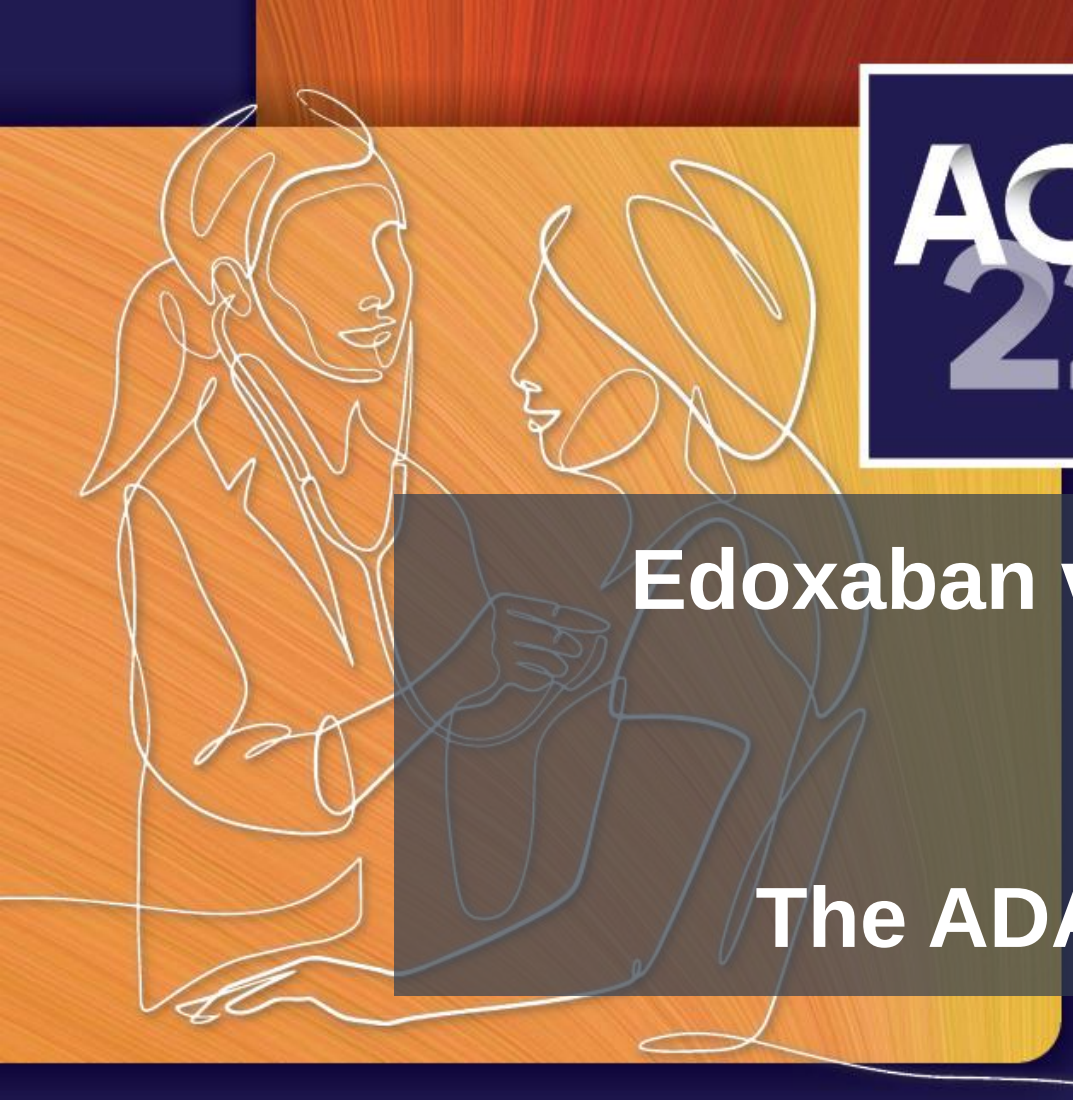
Reality



Clustering effect in
Fragile, Old Age

What Are Next Solutions? Potential NOAC Role?





ACC 22

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

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

Duk-Woo Park, MD, PhD

For the ADAPT-TAVR Investigators,

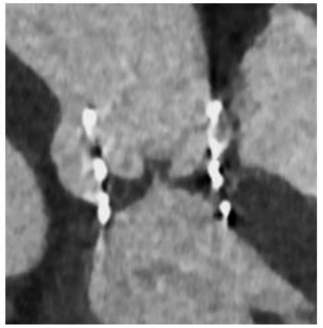
Asan Medical Center,

University of Ulsan College of Medicine, Seoul, Korea

Twitter (@dukwoo_park)

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

What Is Known? What Is Unknown?

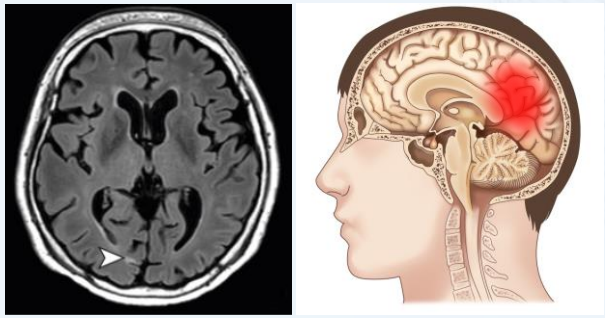


>75% of leaflet

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

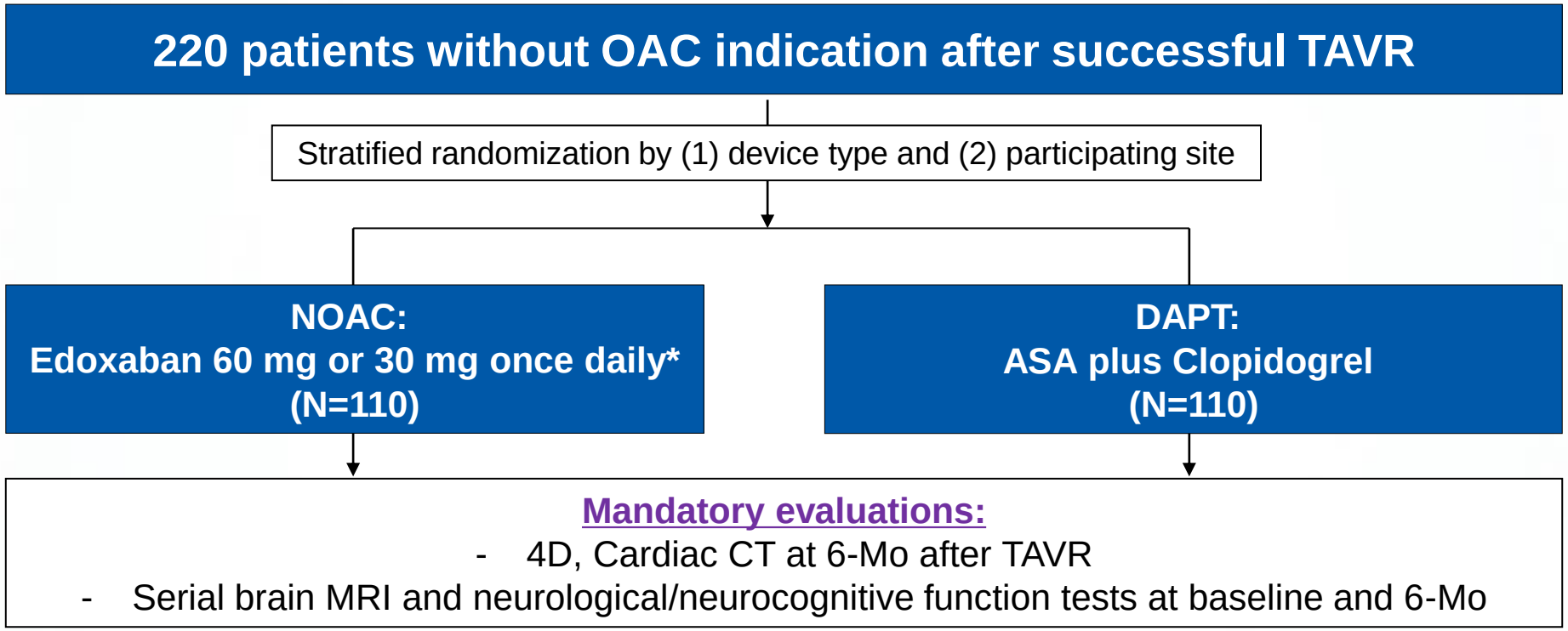
SLT, subclinical leaflet thrombosis; OAC, oral anticoagulation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

[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.

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

Baseline Characteristics, ITT Population

	Edoxaban group (N=111)	DAPT group (N=118)
Clinical characteristics		
Age, years	80.2±5.2	80.0±5.3
Male sex	49 (44.1%)	47 (39.8%)
Body weight ≤60kg	55 (49.6%)	63 (53.4%)
STS risk score	3.1±2.1	3.5±2.7
EuroSCORE II value	2.3±3.5	2.4±2.1
NYHA class III or IV	30 (27.0%)	31 (26.3%)
Diabetes mellitus	35 (31.5%)	36 (30.5%)
Coronary artery disease	32 (28.8%)	34 (28.8%)
Prior PCI	18 (16.2%)	14 (11.9%)
Prior cerebrovascular dis.	6 (5.4%)	11 (9.3%)
Peripheral artery disease	7 (6.3%)	11 (9.3%)
Chronic lung disease	25 (22.5%)	31 (26.3%)
Creatine clearance (ml/min)	61.0±21.5	59.2±18.7
Creatine clearance ≤50	38 (34.2)	47 (39.8)
Use of low-dose edoxaban	68 (61.3%)	-

	Edoxaban group (N=111)	DAPT group (N=118)
Procedural characteristics		
Pre-TAVR balloon angioplasty	40 (36.0%)	41 (34.8%)
Valve type		
Balloon-expandable	101 (91.0%)	105 (89.0%)
Self-expandable	10 (9.0%)	13 (11.0%)
Valve-in-valve	0 (0.0)	4 (3.4%)
Transfemoral approach	110 (99.1%)	117 (99.2%)
MAC anesthesia	84 (75.7%)	92 (78.0%)
New permanent pacemaker	13 (11.7%)	13 (11.0%)
Post-TAVR echo characteristics		
AV area, cm^2	1.7±0.4	1.6±0.4
Mean AV gradient, mmHg	13.4±5.1	14.3±5.4
LVEF, %	64.4±10.0	64.2±9.5
Paravalvular aortic regurgitation		
Mild	105 (97.2%)	112 (97.3%)
Moderate or severe	3 (2.8%)	3 (2.7%)

AV, aortic valve; LVEF, left ventricular ejection fraction; MAC, Monitored anesthetic care; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

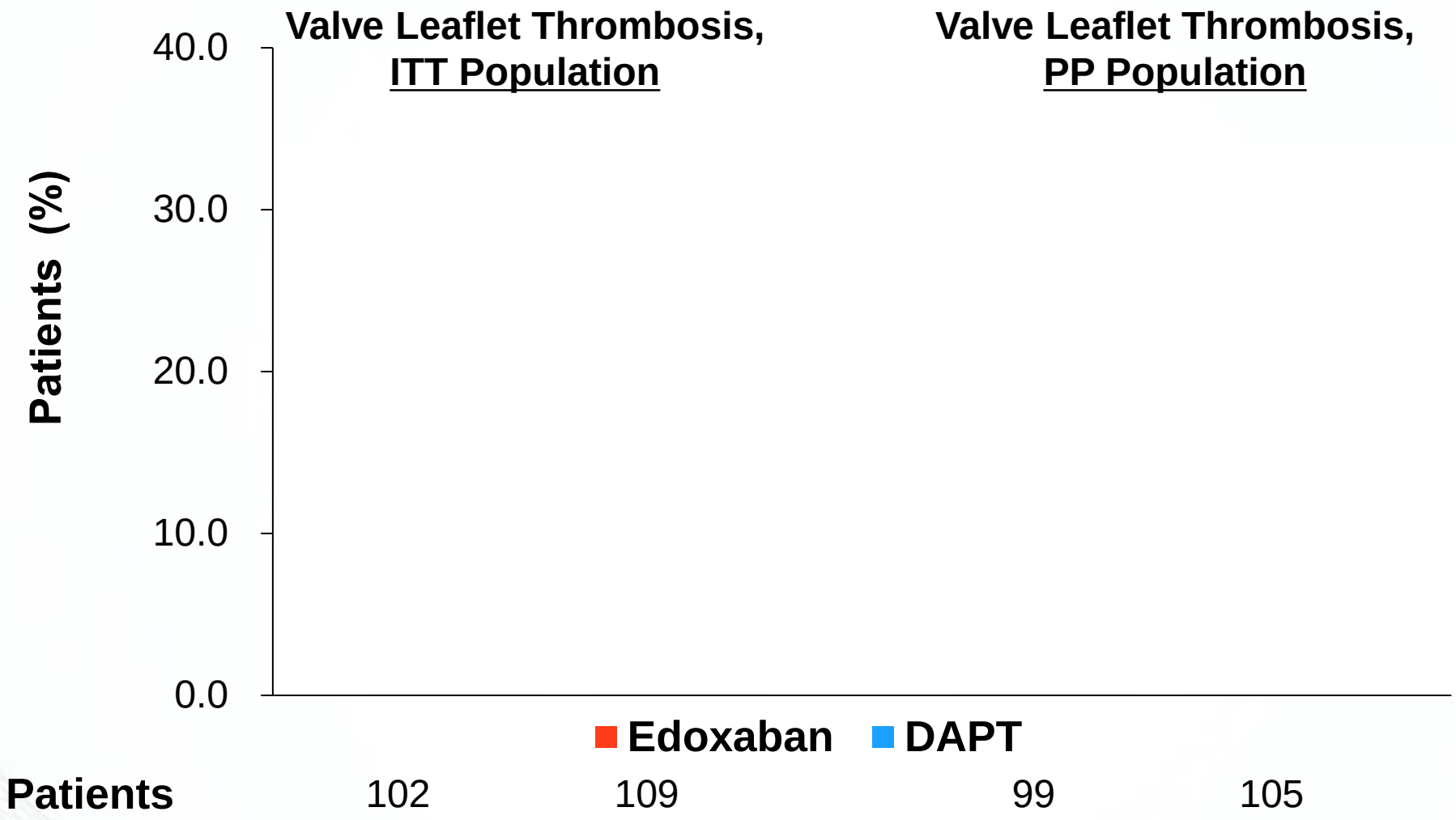
Completeness of Imaging & Neurocognitive Assessment

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

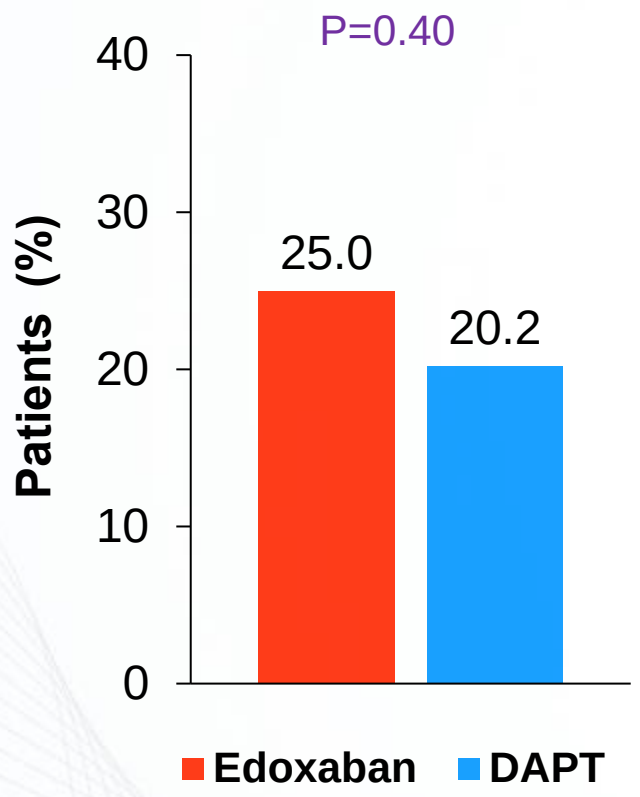
4D-CT Primary End Points



The degree of hypoattenuated leaflet thickening and the severity of reduced leaflet motion were classified according to the standard definition (Blanke P, et al. JACC Cardiovasc Imaging. 2019;12:1-24)

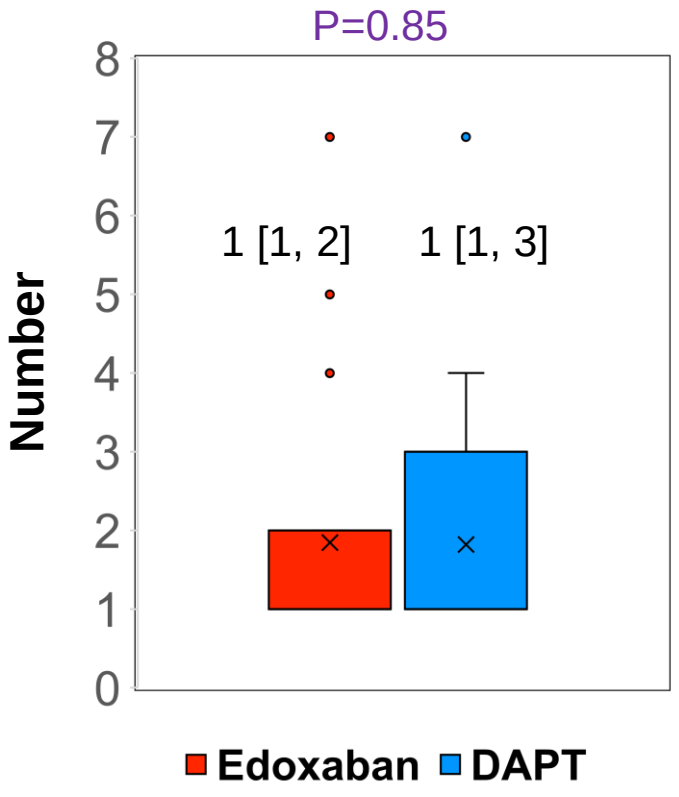
MRI End Points, ITT Analysis

Presence of New Cerebral Lesions



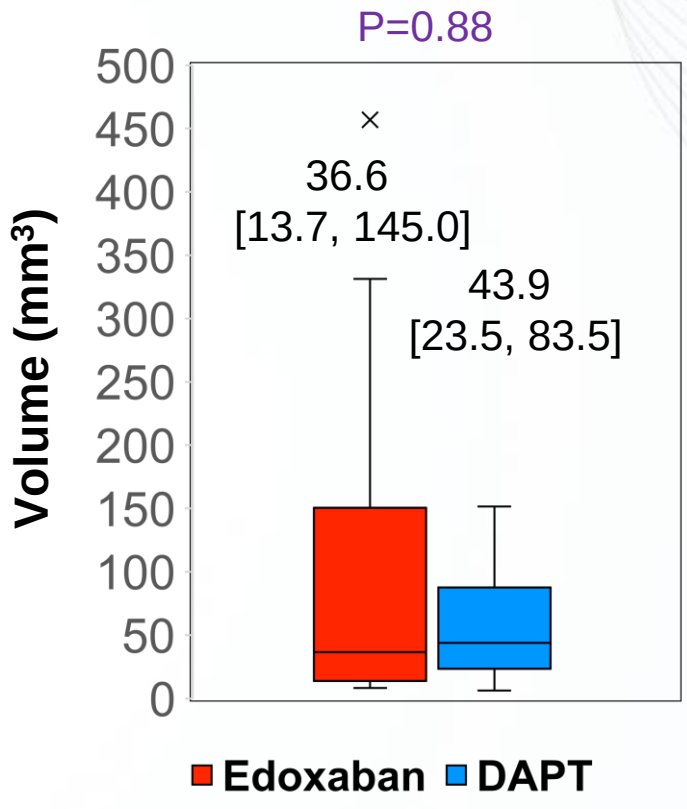
No. of Patients	Edoxaban	DAPT
	104	109

Median Number of Total New Lesions



Edoxaban	DAPT
104	109

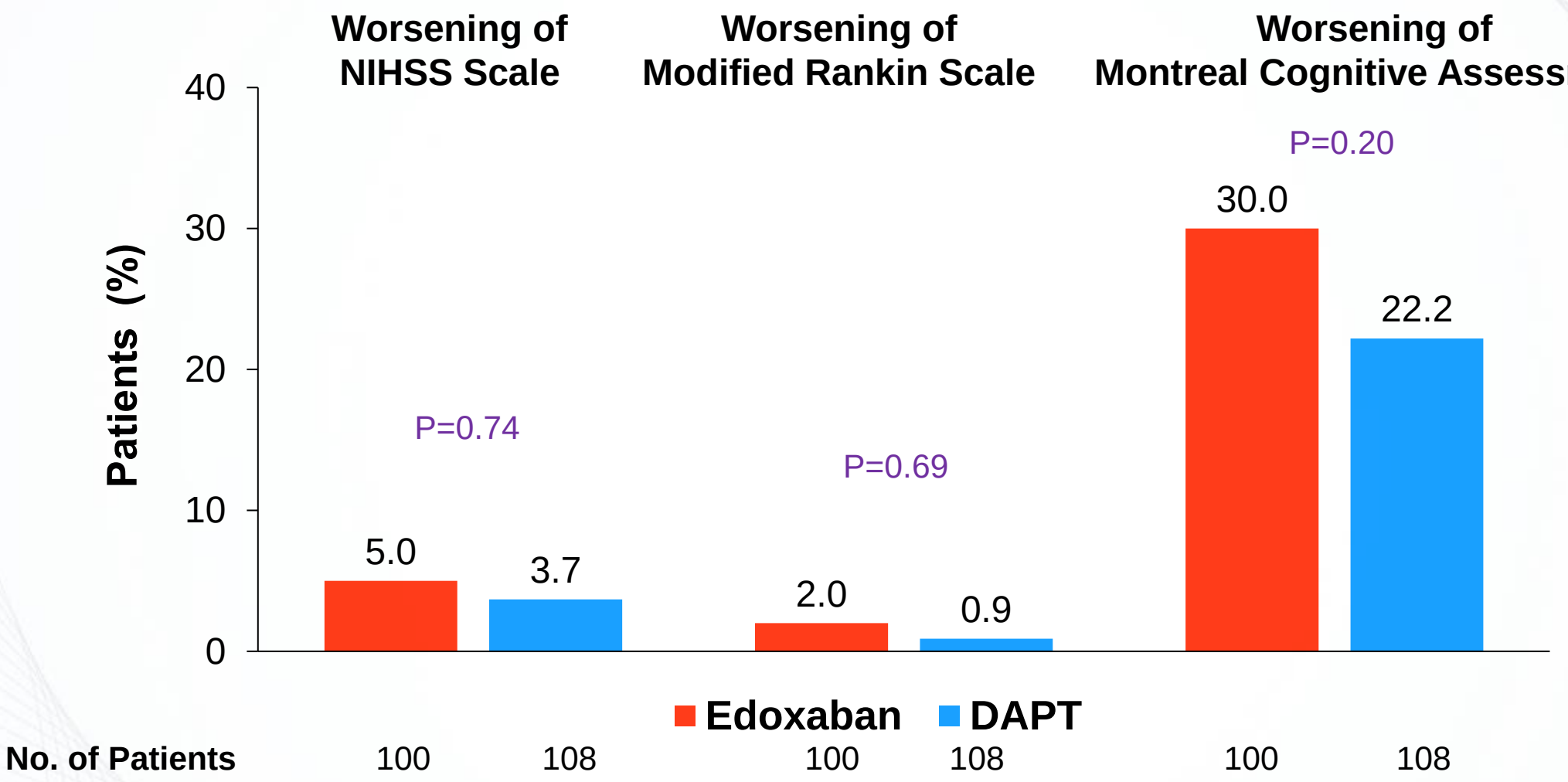
Median Volume of Total New Lesions (mm^3)



Edoxaban	DAPT
104	109

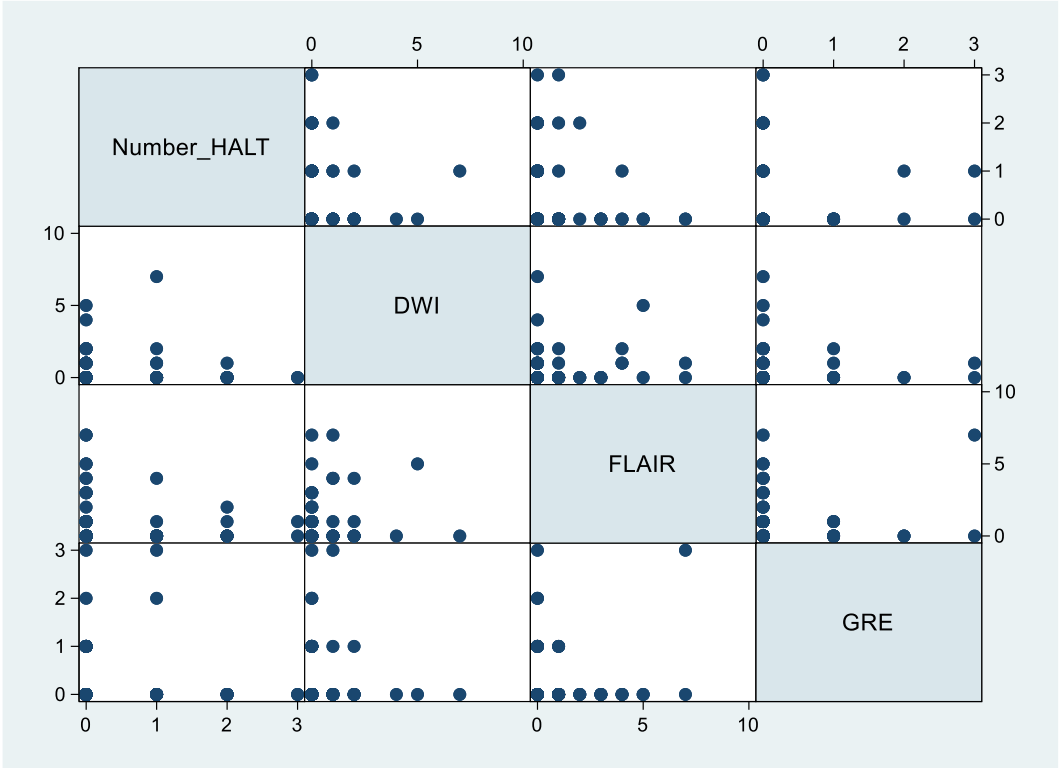
P values are derived from the chi-square test or Fisher's exact test as appropriate.
Median differences calculated as independent samples Hodges-Lehmann median difference estimates.

Neurological & Neurocognitive End Points, ITT Analysis



P values are derived from the chi-square test or Fisher's exact test as appropriate.
Worsening is defined as ≥1 point increase in NIHSS, ≥1 point increase in modified Rankin scale, or ≥1 point decrease in Montreal Cognitive Assessment scores as compared to baseline.

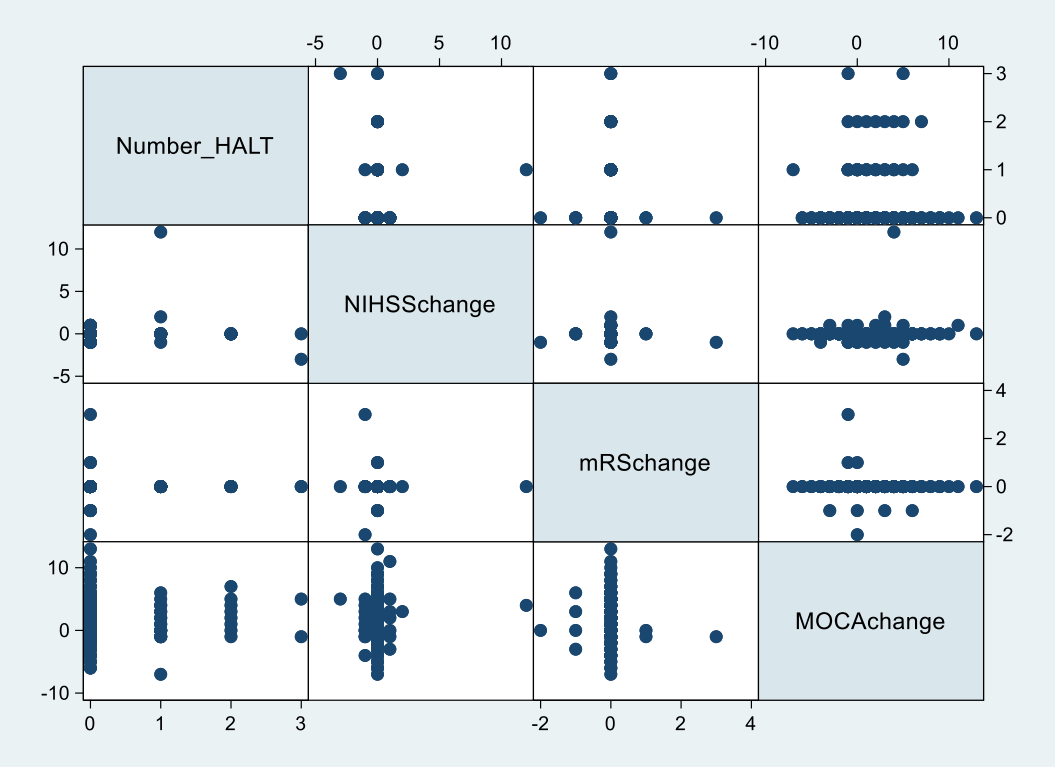
Association of Severity of HALT with Extent of New Lesions on Brain MRI



		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

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

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

Circulation. 2022;146:466–479.

Misconception on Leaflet Thrombosis after TAVR
: NEJM Editorial for the GALILEO Trial

Treatment after TAVR –

Rick A. Nishimu

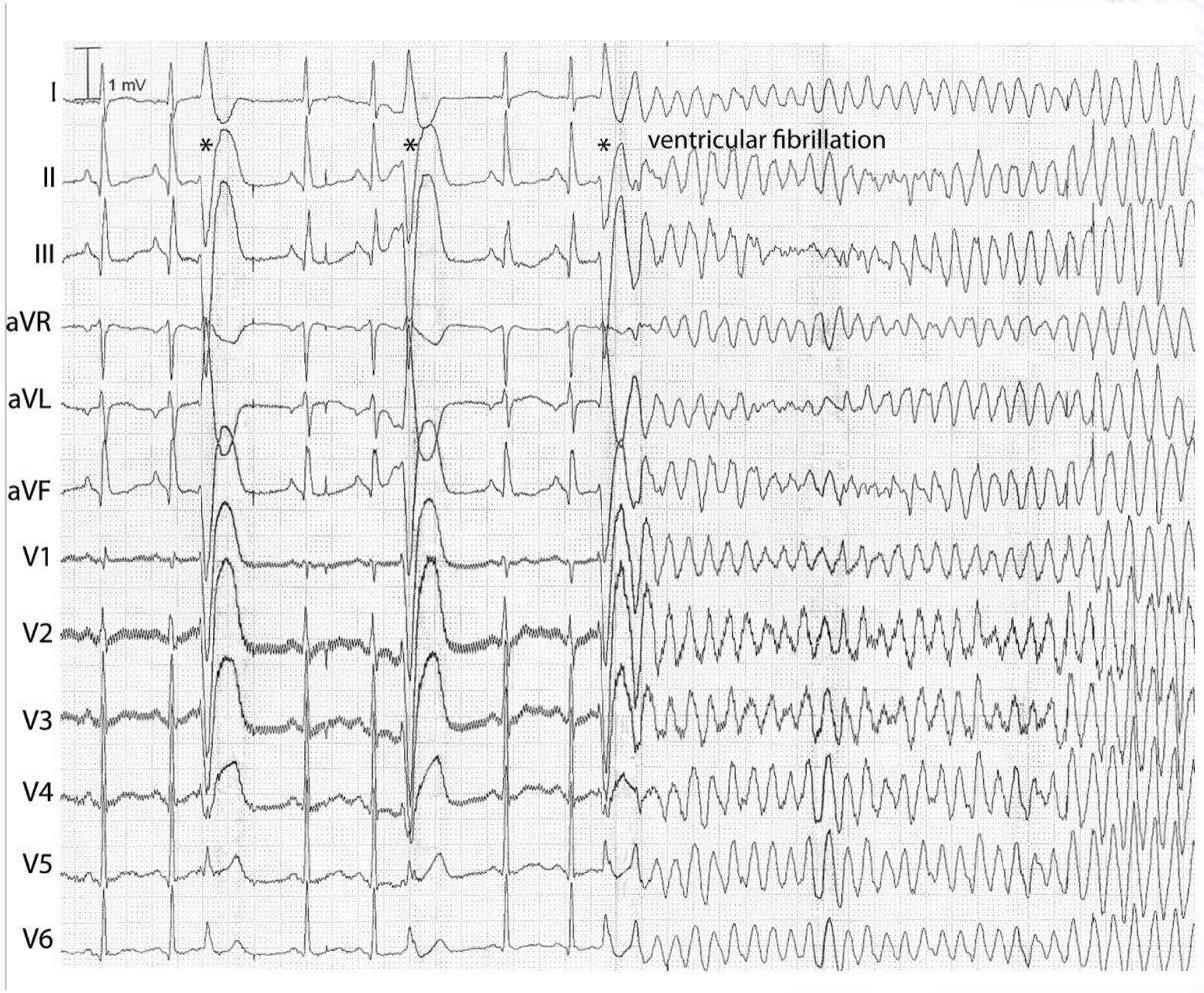
Transcatheter aortic-valve replacement transformed the treatment of severe a sis. However, questions remain re long-term outcomes of this procedur the risk of thromboembolic compli valve deterioration. It has been recc leaflet thrombosis of surgically implar thetic valves may result in stenosis a reversed by oral anticoagulants.[1] early leaflet thrombosis has been i hypoattenuated leaflet thickening a leaflet motion on four-dimensiona tomographic (CT) imaging in more t patients and could be a potential contributor to future adverse events. the long-term effects of hypoattenu thickening and reduced leaflet mot unknown, observational studies hav ed resolution of these imaging findin anticoagulants and fewer cases of val tion if oral anticoagulants were give implantation.[2-4]

Whether routine anticoagulation vent leaflet thrombosis and ultimat clinical outcomes after TAVR was t

these results and never use a direct oral anticoagulant after TAVR, we might be ignoring a potential strategy to improve long-term outcomes. Second, we could ignore the trial results and adamantly hold to the initial belief that formed the trial hypothesis. However, we should be reminded of CAST (Cardiac Arrhythmia Suppression Trial), in which treatment of premature ventricular complexes after infarction (assumed to be triggers for sudden death) by antiarrhythmic drugs, the prevailing standard of care at the time, was actually associated with excess deaths.[7] Third, we might question whether the major adverse outcomes were actually related to the direct oral anticoagulant. Most of the deaths in the rivaroxaban group were sudden or were due to noncardiovascular causes, and a minority of the patients who died had had a bleeding event. In addition, 37% of the patients discontinued rivaroxaban during the trial, and most deaths occurred long after drug discontinuation; the "on-treatment" analysis did not document a significant hazard from the drug. Fourth, we might consider the results of the primary trial as being a failure of the specific components of the trial

30 Years Ago, Misconception on VPBs after MI : Deja-vu on leaflet thrombosis after TAVR

Ventricular premature repolarization are a risk factor for sudden and nonsudden cardiac death after MI



Misconception Refuted by RCT

The New England
Journal of Medicine

Volume 324 MARCH 21, 1991 Number 12

MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO

The Cardiac Arrhythmia Suppression Trial

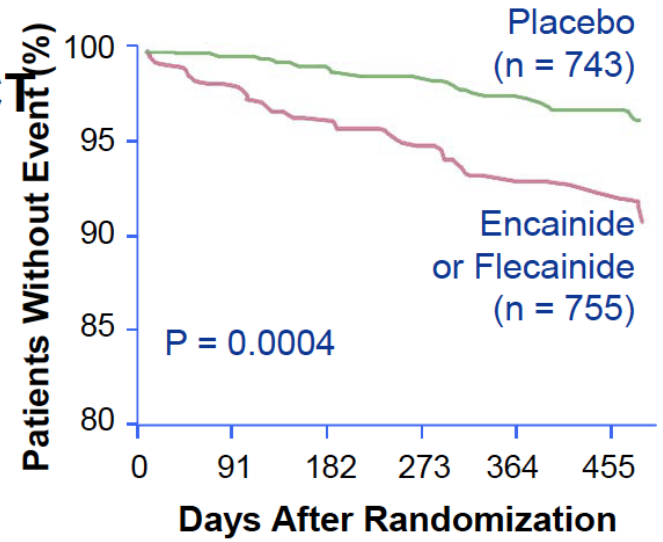
Debra S. Echt, M.D., Philip R. Liebson, M.D., L. Brent Mitchell, M.D., Robert W. Peters, M.D., Dulce Obias-Manno, R.N., Allan H. Barker, M.D., Daniel Arensberg, M.D., Andrea Baker, R.N., Lawrence Friedman, M.D., H. Leon Greene, M.D., Melissa L. Huther, David W. Richardson, M.D., and the CAST Investigators*

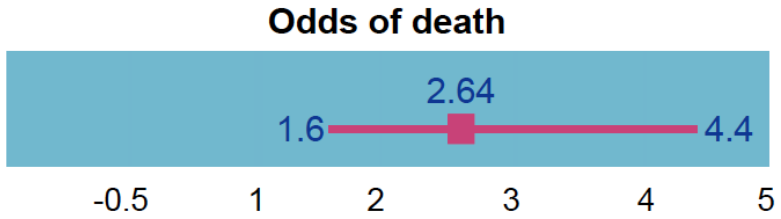
Abstract *Background and Methods.* In the Cardiac Arrhythmia Suppression Trial, designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death, patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. The use of encainide and flecainide was discontinued because of excess mortality. We examined the mortality and morbidity after randomization to encainide or flecainide or their respective placebo.

Results. Of 1498 patients, 857 were assigned to receive encainide or its placebo (432 to active drug and 425 to placebo) and 641 were assigned to receive flecainide or its placebo (323 to active drug and 318 to placebo). After a mean follow-up of 10 months, 89 patients had died: 59 of arrhythmia (43 receiving drug vs. 16 receiving placebo; P = 0.0004), 22 of nonarrhythmic cardiac causes (17 receiving drug vs. 5 receiving placebo; P = 0.01), and 8 of noncardiac causes (3 receiving drug vs. 5 receiving placebo). Almost all cardiac deaths not due to arrhythmia were attributed to acute myocardial infarction with shock (11 patients receiving drug and 3 receiving placebo) or to chronic congestive heart failure (4 receiving drug and 2 receiving placebo). There were no differences between the patients receiving active drug and those receiving placebo in the incidence of nonlethal disqualifying ventricular tachycardia, proarrhythmia, syncope, need for a permanent pacemaker, congestive heart failure, recurrent myocardial infarction, angina, or need for coronary-artery bypass grafting or angioplasty.

Conclusions. There was an excess of deaths due to arrhythmia and deaths due to shock after acute recurrent myocardial infarction in patients treated with encainide or flecainide. Nonlethal events, however, were equally distributed between the active-drug and placebo groups. The mechanisms underlying the excess mortality during treatment with encainide or flecainide remain unknown. (N Engl J Med 1991; 324:781-8.)

Treating VPBs Post MI: CAST RCT





Echt, New Engl J Med, 1991

Current VHD Guidelines

2021 ESC/EACTS Guidelines

Transcatheter aortic valve implantation		
OAC is recommended lifelong for TAVI patients who have other indications for OAC.[501 f]	I	B
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.[495,496,521]	I	A
Routine use OAC is not recommended after TAVI in patients with no baseline indication for OAC.[497]	III	B

2020 ACC/AHA Guidelines

2a	B-R	5. For patients with a bioprosthetic TAVI, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (12-14).
2b	B-NR	10. 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 (12,13,29).
2b	B-NR	11. 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 (23,31-33).
3: Harm	B-R	12. For patients with bioprosthetic TAVI, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75-100 mg) is contraindicated in the absence of other indications for oral anticoagulants (30).

Our ADAP-TAVR trial results strongly support "current VHD guidelines in TAVR patients without OAC indication"

"Simpler is Best"

VHD, Valvular Heart Disease

Clinical Key Messages from the ADAPT-TAVR

- Subclinical leaflet thrombosis has not been proven to affect the clinical outcomes for patients who underwent TAVR.

- The absence of adverse clinical sequelae of imaging-detected subclinical leaflet thrombosis does not support (1) routine imaging screening tests for the detection of this phenomenon and (2) imaging-guided antithrombotic strategies in cases without hemodynamic or clinical significance.

- If subclinical leaflet thrombosis is not clinically relevant phenomenon, **“less-is-more” concept of antithrombotic strategy** would be optimal management for TAVR patients - this was adopted in current guidelines