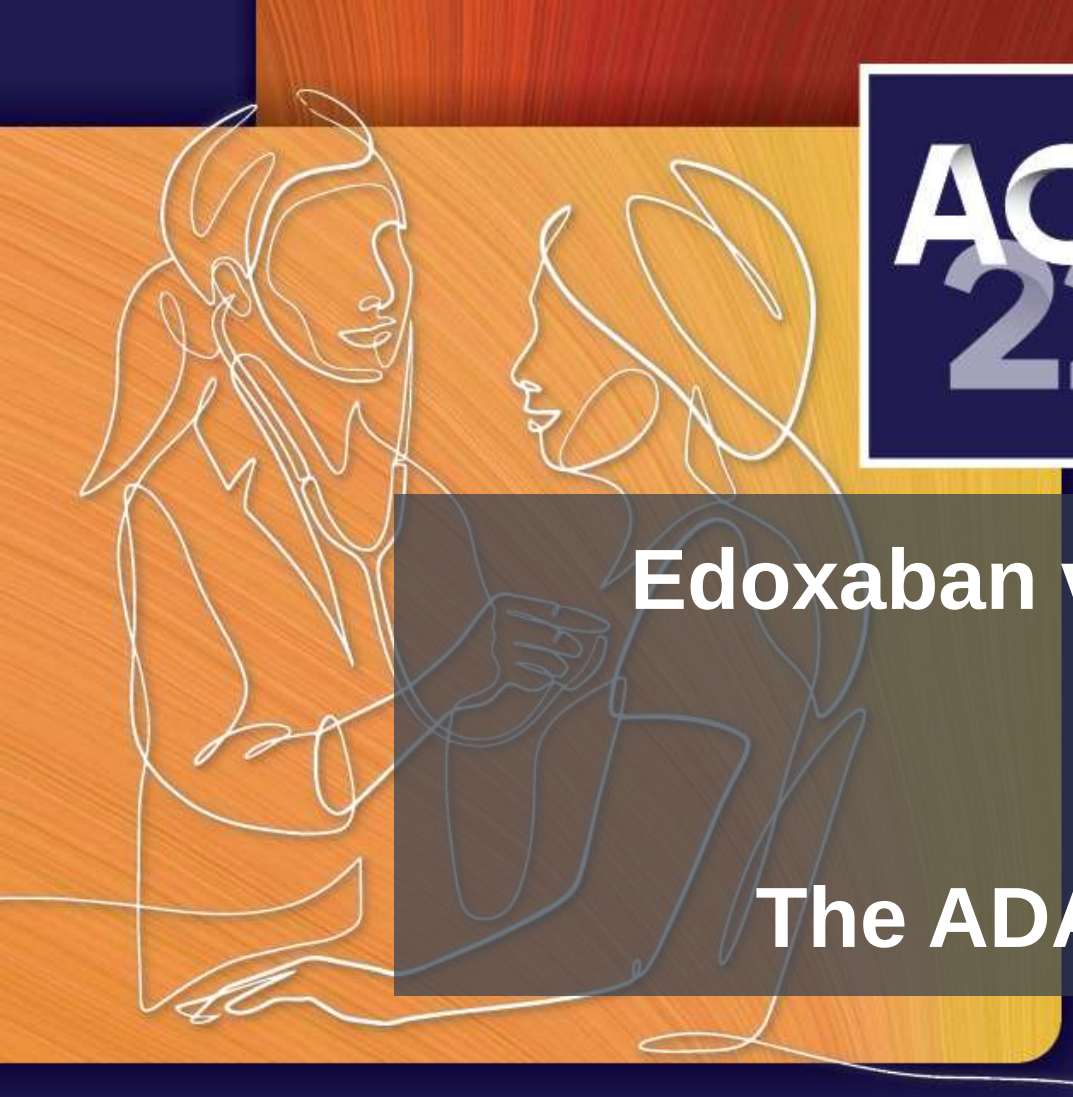
Key Message from the ADAPT-TAVR Trial:

What We Learned for Leaflet Thrombosis and Optimal Antithrombotic Strategy after TAVR?

Duk-Woo Park, MD, PhD

Asan Medical Center, Seoul, Korea



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,

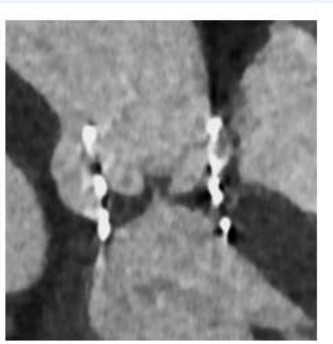
Asan Medical Center,

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.

Background

- The incidence of subclinical leaflet thrombosis by 4D-CT was not uncommon (approximately 10%~30%) and this phenomenon could be associated with increased risks of cerebral thromboembolism, stroke or TIA.[1-4]
- However, the causal relationship of leaflet thrombosis with cerebral embolic risk and neurological/neurocognitive dysfunction in patients undergoing TAVR is still unclear.
- Several RCTs have tested that NOAC-based strategy is more effective than conventional antithrombotic strategies for the prevention of leaflet thrombosis and thromboembolic risk in patients with or without OAC indication after TAVR.[5-8]

4D-CT, four-dimensional computed tomography; NOAC, non-vitamin K direct anticoagulant; OAC, oral anticoagulation; RCTs, randomized controlled trials; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

[1]Chakravarty T, et al. *Lancet* 2017;389:2383-2392. [2]Rashid HN, et al. *EuroIntervention* 2018;13:e1748-e1755. [3]Makkar RR, et al. *JACC* 2020;75:3003-3015. [4]Bogyi M, et al. *JACC: Cardiovascular Interventions* 2021;14:2643-2656. [5]Dangas GD et al. *NEJM* 2020;382:120-129. [6]Collet JP. et al. *ATLANTIS trial*. *ACC* 2021. [7]De Backer O et al. *NEJM* 2020;382:130-139. [8]Van Mieghem NM et al. *NEJM* 2021; 385:2150-2160.

Study Objectives

- **Primary objective →** to investigate the effect of edoxaban compared to DAPT for the prevention of leaflet thrombosis and the potential risks of cerebral thromboembolization and neurological or neurocognitive dysfunction in patients without an OAC indication after TAVR.

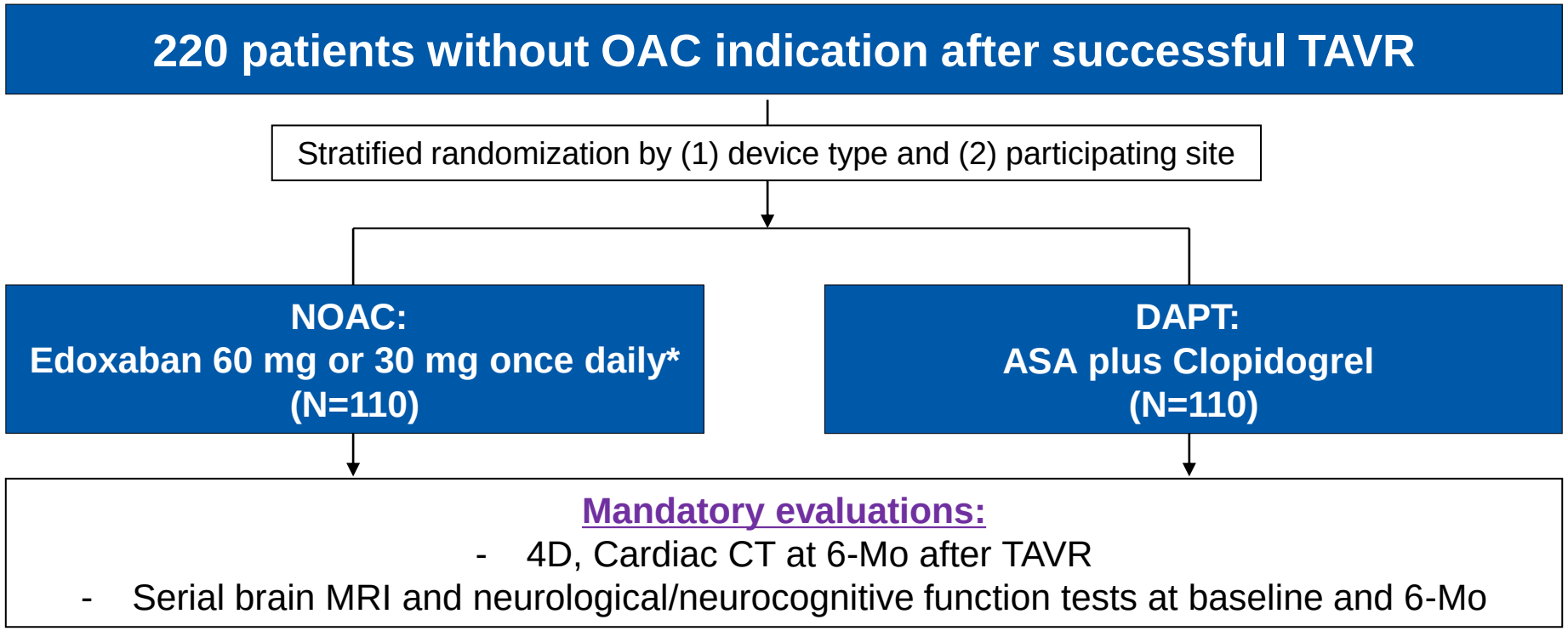
- **Secondary objective →** to determine the causal association of subclinical leaflet thrombosis with cerebral thromboembolism and neurological or neurocognitive dysfunction.

DAPT, dual antiplatelet therapy; OAC, oral anticoagulation; TAVR, transcatheter aortic valve replacement

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

Inclusion and Exclusion Criteria

INCLUSION

1. Man or woman (≥ 18 years) **with symptomatic AS**

2. Have a **successful TAVR** of an aortic valve stenosis (either native of valve-in-valve), defined as:
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location.[1]
   - Intended performance of the prosthetic heart valve - presence of all 3 conditions post-TAVR:
     - Mean aortic valve gradient < 20 mmHg
     - Peak transvalvular velocity (aortic valve maximum velocity) < 3.0 m/s
     - No severe or moderate aortic valve regurgitation
   - Without unresolved periprocedural complications

3. With **any approved/marketed TAVR device**

KEY EXCLUSION

1. Any established indication for anticoagulation (e.g., atrial fibrillation)
2. Any absolute indication for DAPT (e.g., ACS or recent PCI)
3. Severe renal insufficiency prohibiting CT imaging (eGFR<30)
4. Contraindication to aspirin, clopidogrel or edoxaban
5. Known bleeding diathesis
6. Clinically overt stroke within 3 months
7. Moderate and severe hepatic impairment or any hepatic disease associated with coagulopathy
8. Active malignancy

[1]Kappetein AP, et al. *J Am Coll Cardiol*. 2012;60:1438-1454.

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

Study Endpoints

Primary endpoint

- Incidence of leaflet thrombosis on 4D, volume-rendered CT at 6 months

Secondary endpoints

- Presence and number/volume of new cerebral lesions on brain MRI
- Serial change of neurological/neurocognitive assessment (NIHSS, mRS, and MoCA)
- Clinical safety and efficacy outcomes
- Serial echocardiographic parameters

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

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

Enrollment: 5 centers, 3 countries

Asan Medical Center
- DW Park, SJ Park
CHA Bundang Medical Center
- WJ Kim, SH Kang

Queen Mary Hospital
- SCC Lam, AYT Wong

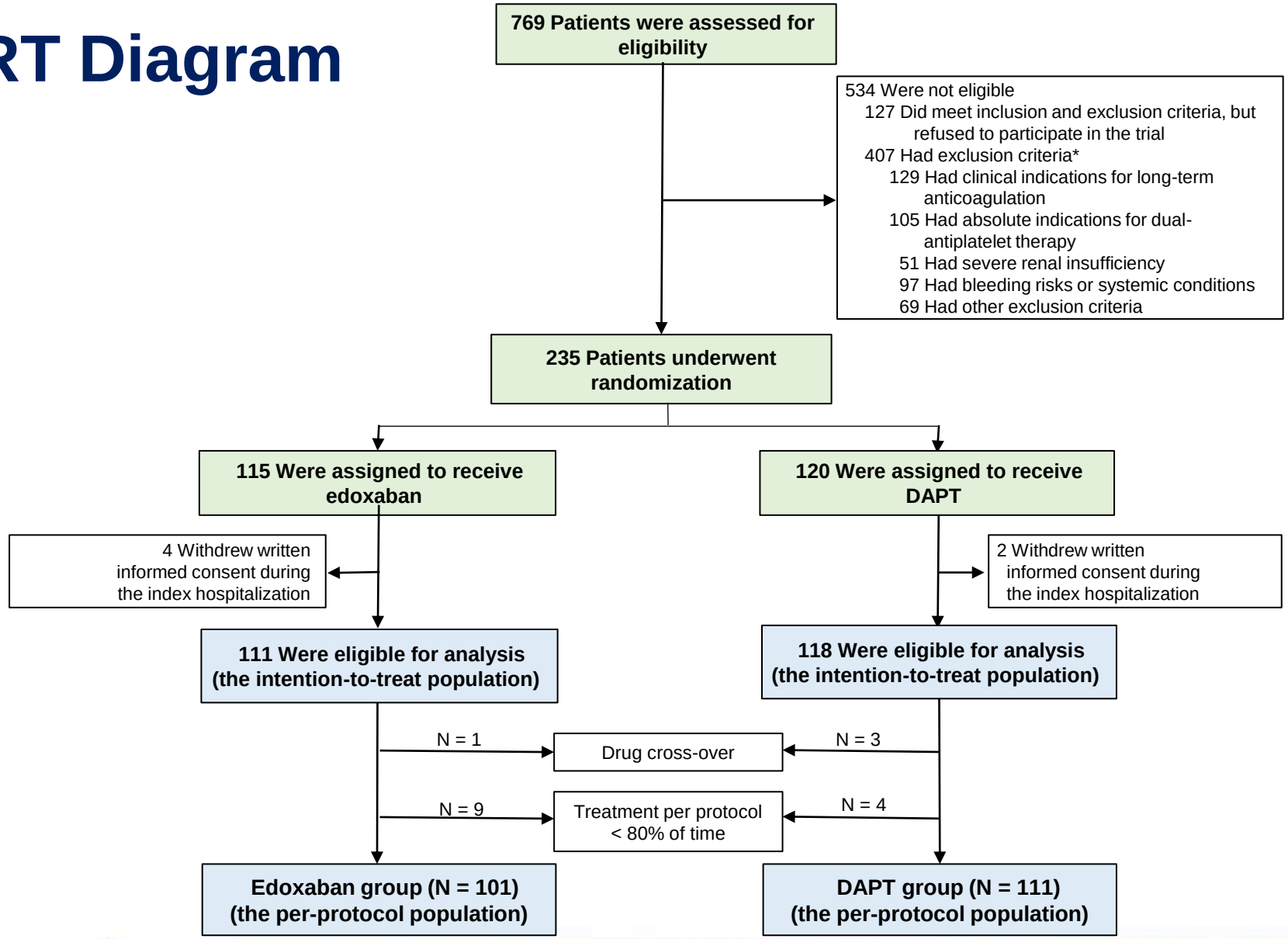
Cheng Hsin General Hospital
- WH Yin, J Wei, YT Lee
National Taiwan University Hospital
- HL Kao, MS Lin, TY Ko

Executive Committee: DW Park (Trial PI), SJ Park, SCC Lam, WH Yin, HL Kao, WJ Kim
Data Monitoring Committee: MS Lee (Chairperson), BK Koo, YG Ko, YH Jeong, JH Kim
Clinical Events Committee: CH Lee (Chairperson), JH Lee, JH Kim

Imaging (CT and MRI) Core Lab: Asan Image Metrics (Imaging Corelab), KW Kim (Chairperson), DH Yang (CT corelab), SC Jung (MRI corelab)

Neurocognitive function and echo Core Lab: JH Lee (Chair, Neurology Corelab), SA Lee (Chair, Echo. Corelab)

CONSORT Diagram



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.

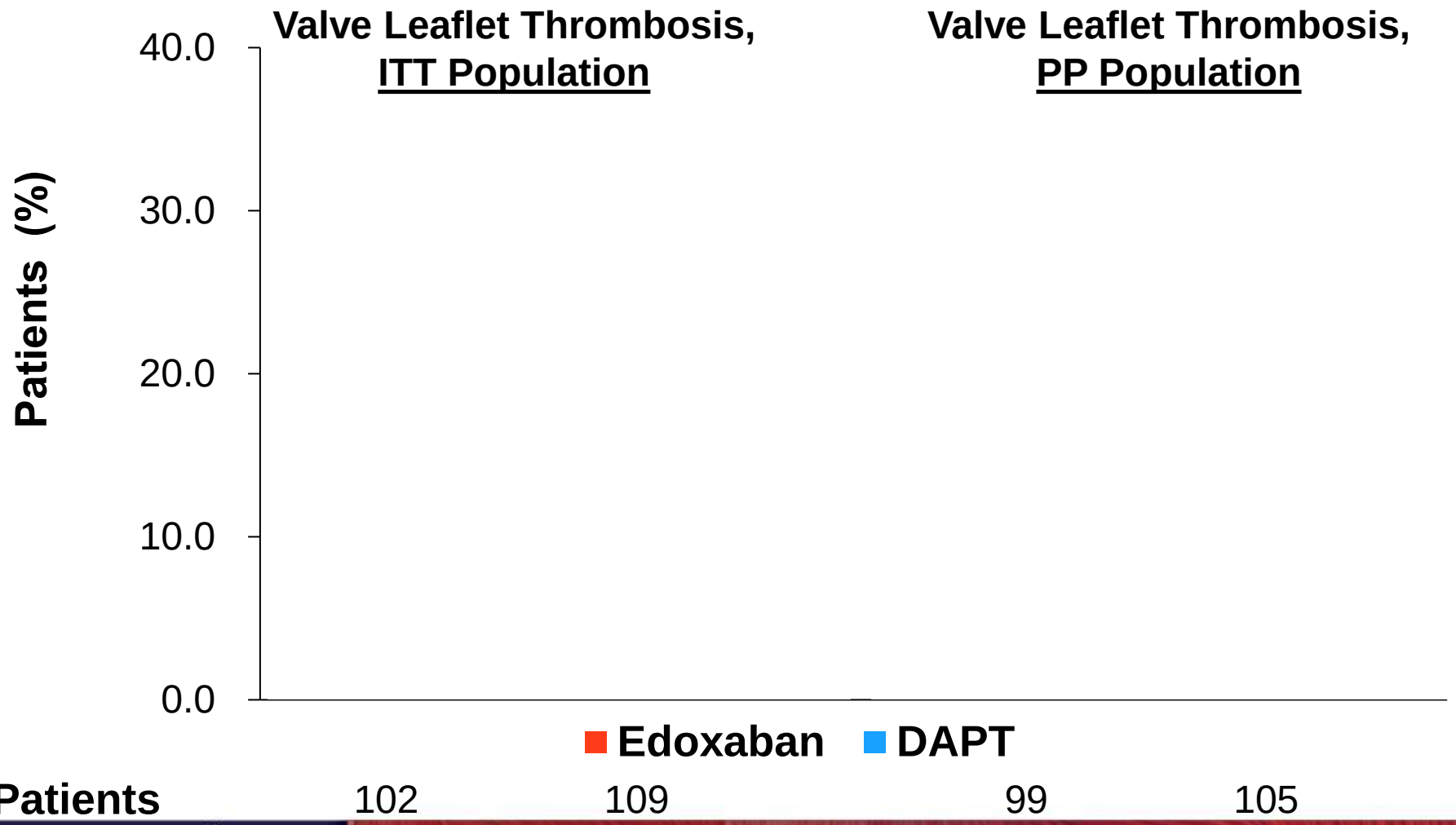
Completeness of Imaging & Neurocognitive Assessment

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

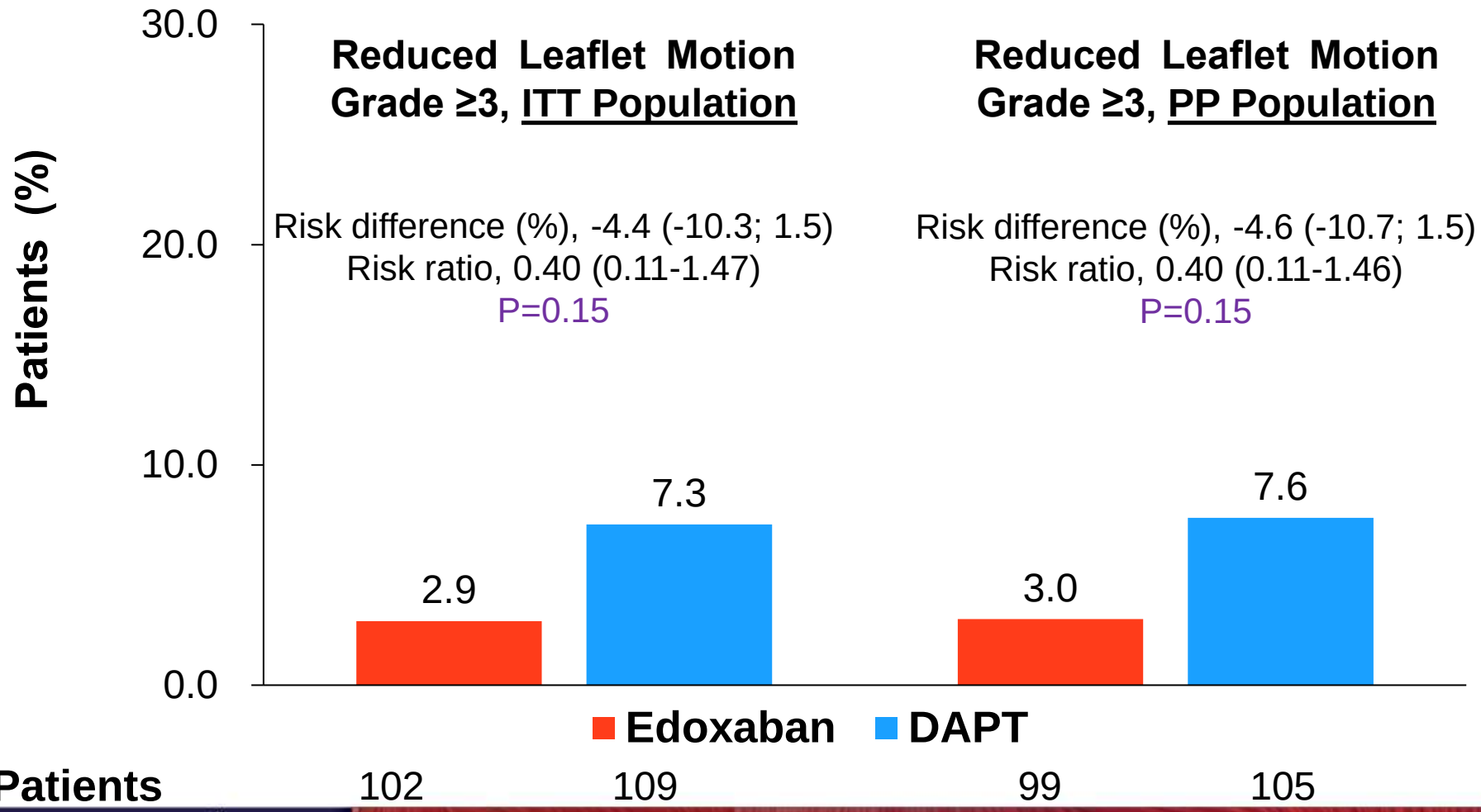
4D-CT Primary End Points



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)

*P values are derived from the chi-square test or Fisher's exact test as appropriate.

4D-CT Outcomes



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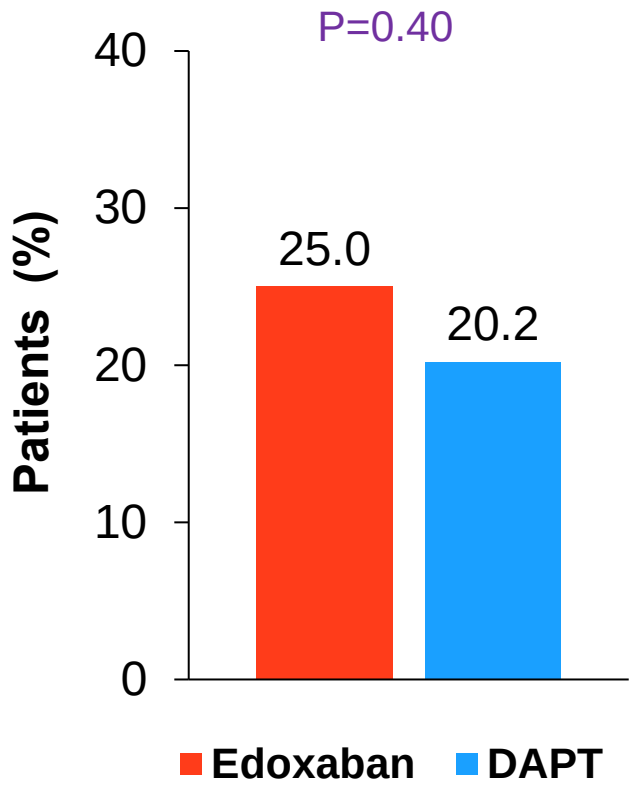
*P values are derived from the chi-square test or Fisher's exact test as appropriate.

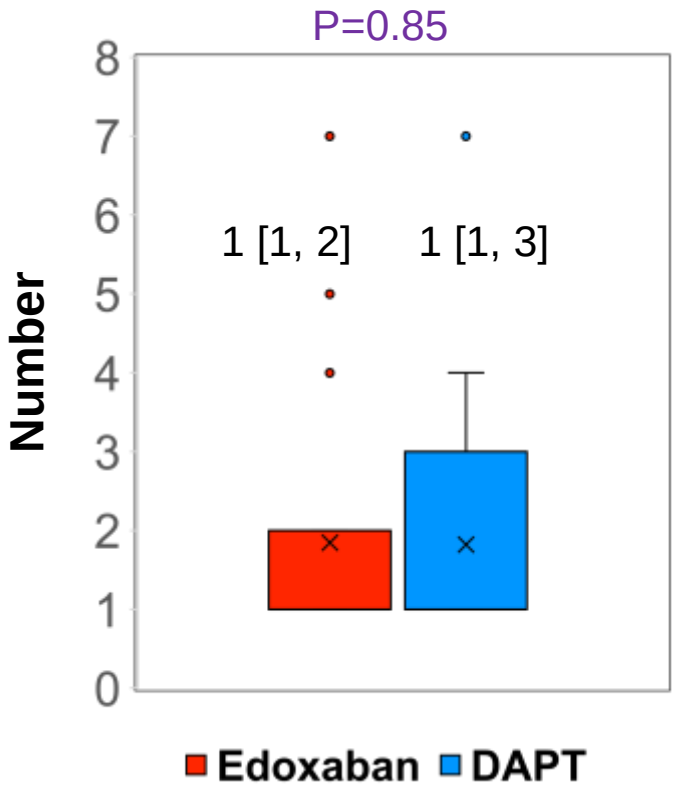
MRI End Points, ITT Analysis

Presence of New Cerebral Lesions



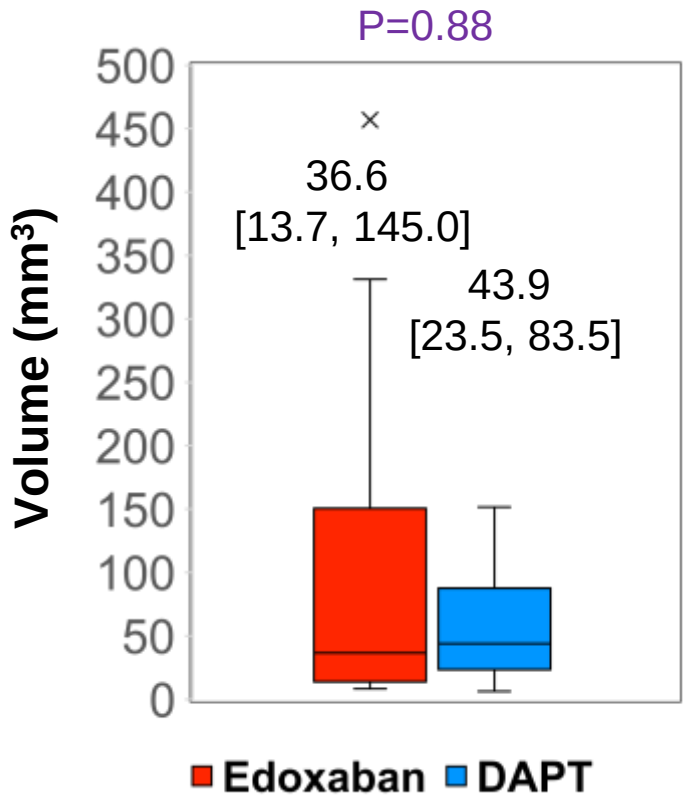
No. of Patients	104	109

Median Number of Total New Lesions



104	109

Median Volume of Total New Lesions (mm^3)



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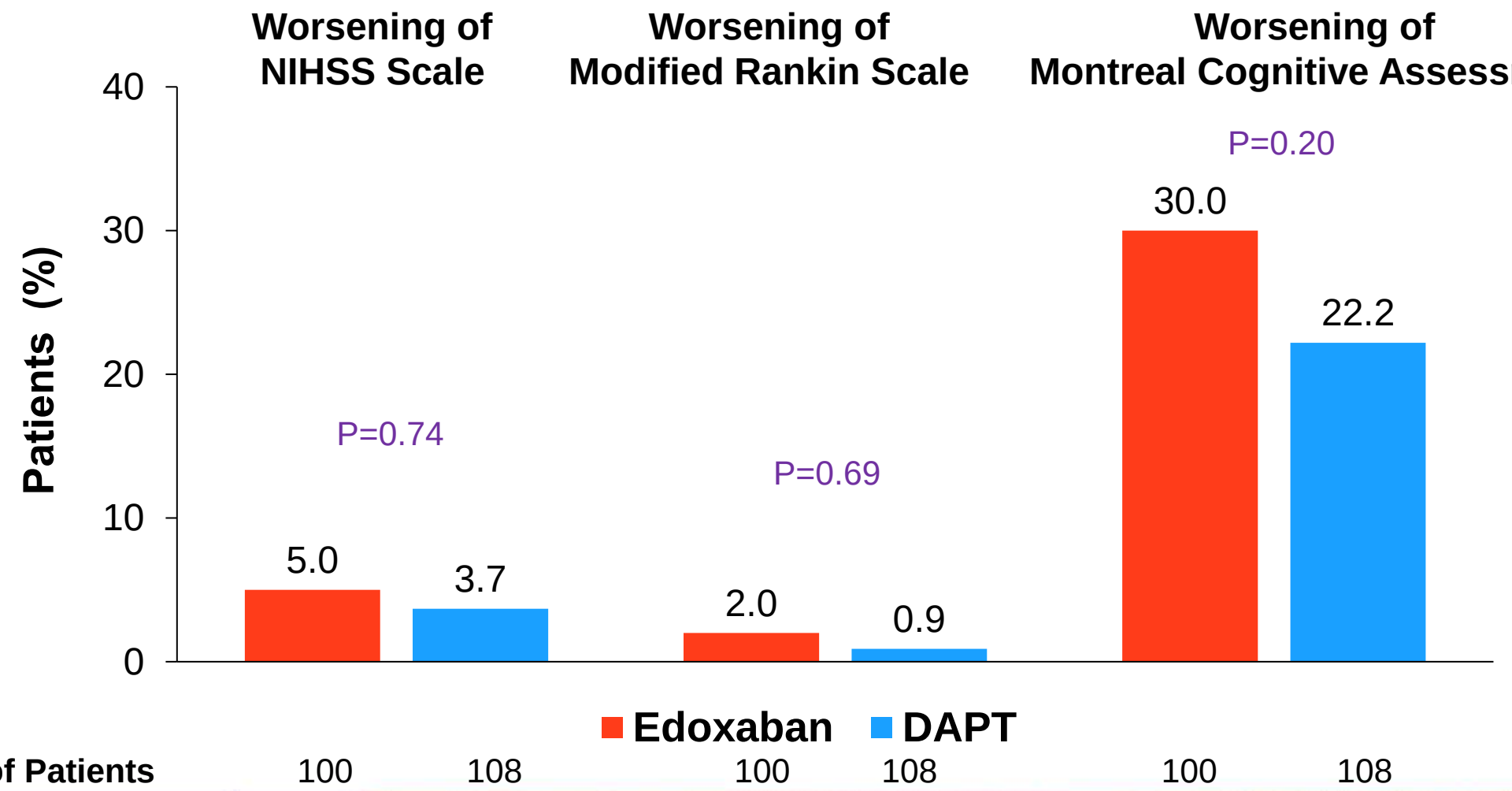
P values are derived from the chi-square test or Fisher's exact test as appropriate.
Median differences calculated as independent samples Hodges-Lehmann median difference estimates.

Neurological & Neurocognitive End Points, ITT Analysis

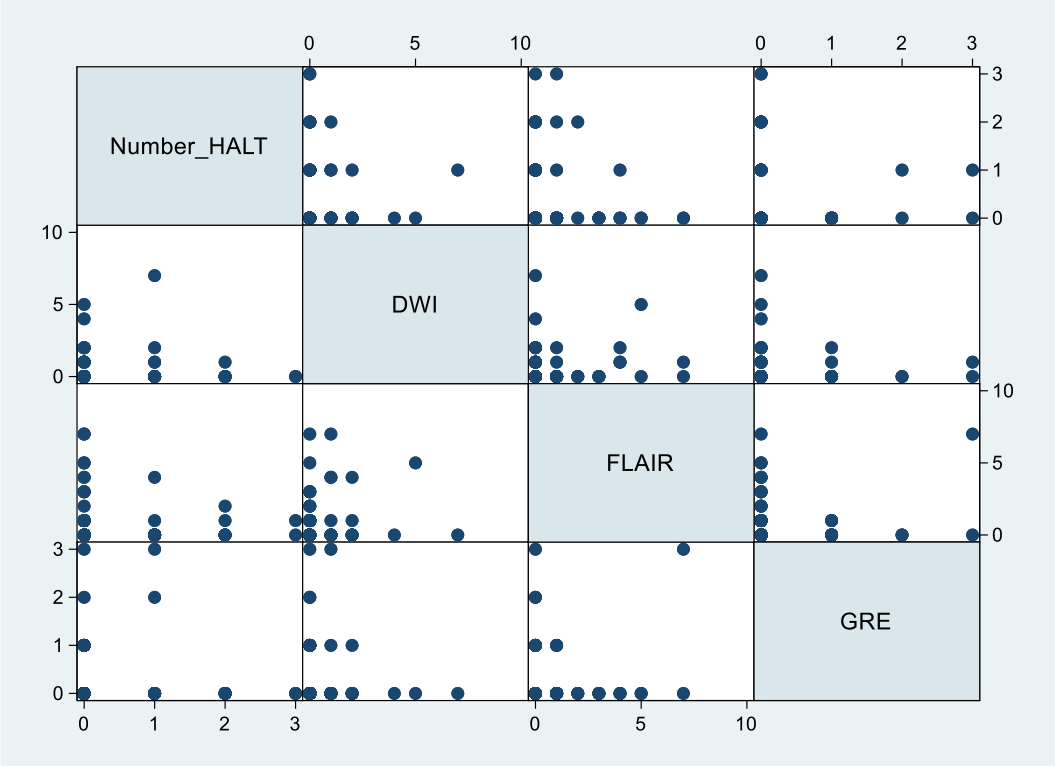


NIHSS, National Institutes of Health Stroke Scale

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.

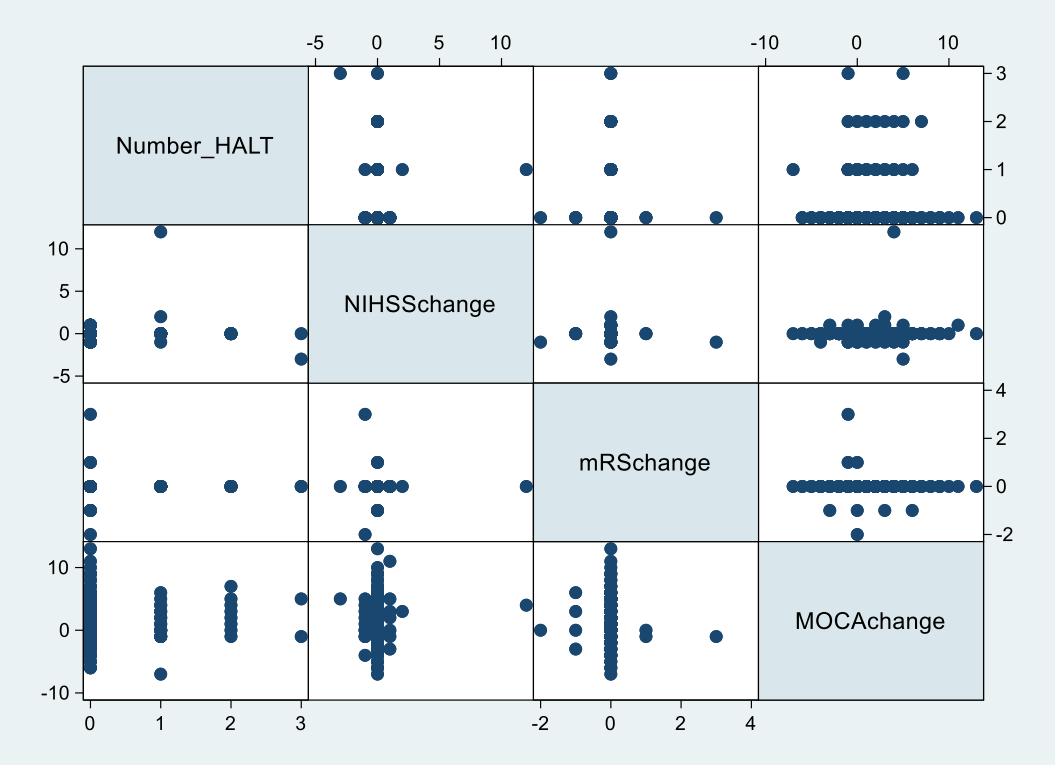
Association of Severity of HALT with Extent of New Lesions on Brain MRI



		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

Clinical Outcomes at 6 Month, ITT Population

Outcomes*	Edoxaban group (N=111) n (%)	DAPT group (N=118) n (%)	Risk Difference (95% CI)	Hazard Ratio (95% CI)†
Efficacy Outcomes				
Death	3 (2.7%)	2 (1.7%)	1.0 (-2.8; 4.8)	1.48 (0.25-8.75)
Cardiovascular death	3	0		
Non-cardiovascular death	0	2		
Stroke	2 (1.8%)	2 (1.7%)	0.1 (-3.3; 3.5)	1.05 (0.15-7.45)
Ischemic	2	2		
Hemorrhagic	0	0		
Myocardial infarction	1 (0.9%)	3 (2.5%)	-1.6 (-4.9; 1.7)	0.45 (0.05-3.83)
Systemic thromboembolic event	2 (1.8%)	0 (0)	1.8 (-0.8; 4.4)	not applicable
Safety Outcomes				
Bleeding events	13 (11.7%)	15 (12.7%)	-1.0 (-9.5; 7.5)	0.93 (0.44-1.96)
Minor bleeding	7	11		
Major bleeding	6	3		
Life-threatening or disabling bleeding	0	1		
Rehospitalization	17 (15.3%)	14 (11.9%)	3.5 (-5.4; 12.3)	1.29 (0.67-2.49)

* Clinical end points were adjudicated according to the VARC-2 and VARC-3 definitions.
† Hazard ratio (for edoxaban compared to DAPT) and corresponding 95% CI was calculated by the Cox proportional hazards models.

Key Summary

- The overall incidence of leaflet thrombosis on CT scans was less frequent (8.5% difference; risk ratio of 0.53) with the edoxaban therapy than with the DAPT therapy, although it did not reach statistical significance.

- The incidence of new cerebral thromboembolism on brain MRI and new development of neurological or neurocognitive dysfunction were not different between two groups.

- There was no causal association of leaflet thrombosis with temporal-related changes of new cerebral thromboembolism and neurological end points.

Circulation

10.1161/CIRCULATIONAHA.122.059512

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

Running title: *Park et al.; Edoxaban vs. DAPT after TAVR*

Duk-Woo Park, MD[1]; Jung-Min Ahn, MD[1]; Do-Yoon Kang, MD[1]; Kyung Won Kim, MD[2]; Hyun Jung Koo, MD[3]; Dong Hyun Yang, MD[3]; Seung Chai Jung, MD[3]; Byungjun Kim, MD[4], Yiu Tung Anthony Wong, MD[5]: Cheung Chi Simon Lam, MD[5]; Wei-Hsian Yin, MD[6]; Jeng Wei, MD[6]; Yung-Tsai Lee, MD[6]; Hsien-Li Kao, MD[7]; Mao-Shin Lin, MD[7]; Tsung-Yu Ko, MD[8]; Won-Jang Kim, MD[9]; Se Hun Kang, MD[9]; Sung-Cheol Yun, PhD[10]; Seung-Ah Lee, MD[1]; Euihong Ko, MD[1]; Hanbit Park, MD[11]; Dae-Hee Kim, MD[1]; Joon-Won Kang, MD[3]; Jae-Hong Lee, MD[12]; and Seung-Jung Park, MD[1], for the ADAPT-TAVR Investigators

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

Treatment after TAVR –

Rick A. Nishimu

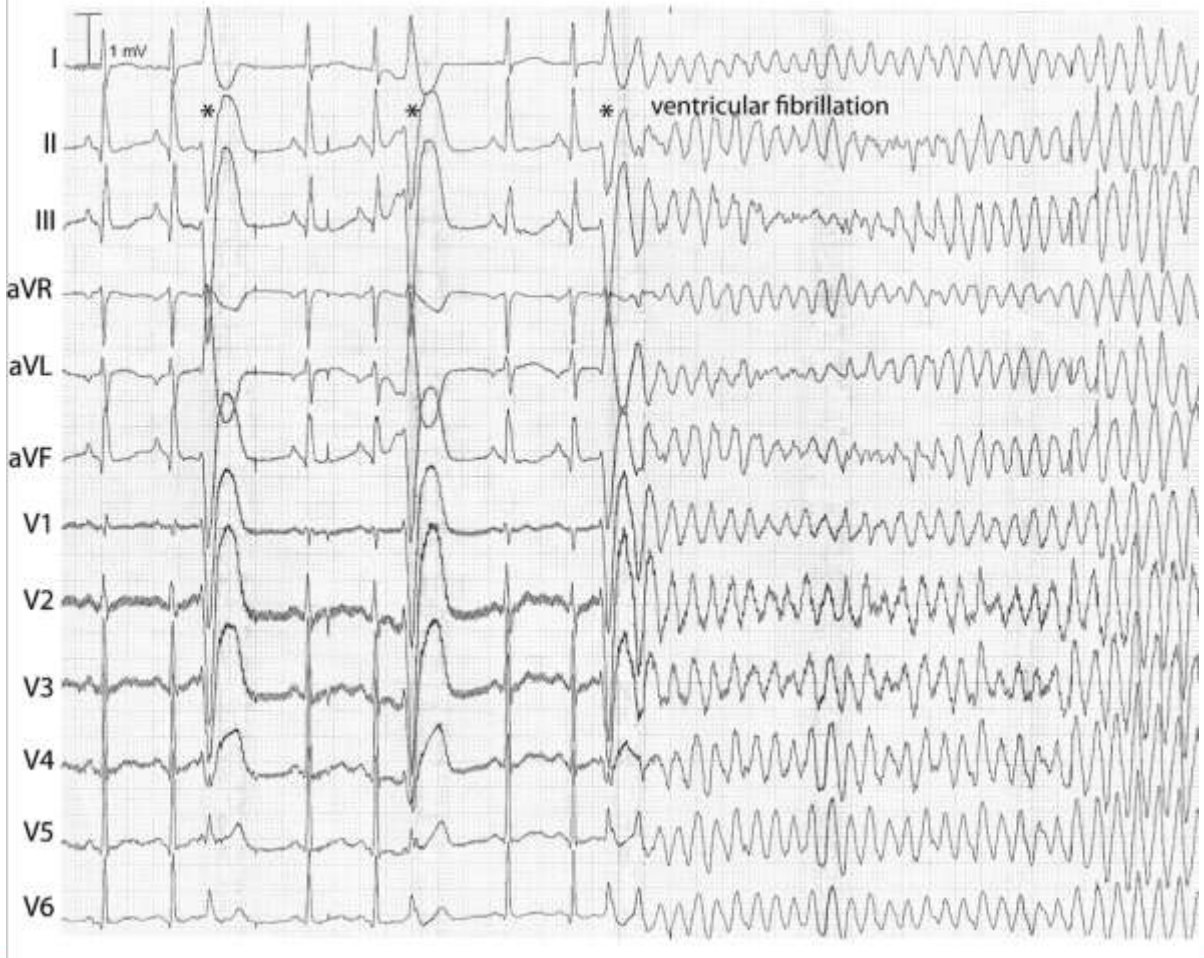
Transcatheter aortic-valve replacement transformed the treatment of severe sis. However, questions remain re long-term outcomes of this procedur the risk of thromboembolic compli valve deterioration. It has been reco leaflet thrombosis of surgically implar thetic valves may result in stenosis a reversed by oral anticoagulants.[1] early leaflet thrombosis has been i hypoattenuated leaflet thickening a leaflet motion on four-dimensiona tomographic (CT) imaging in more 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

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

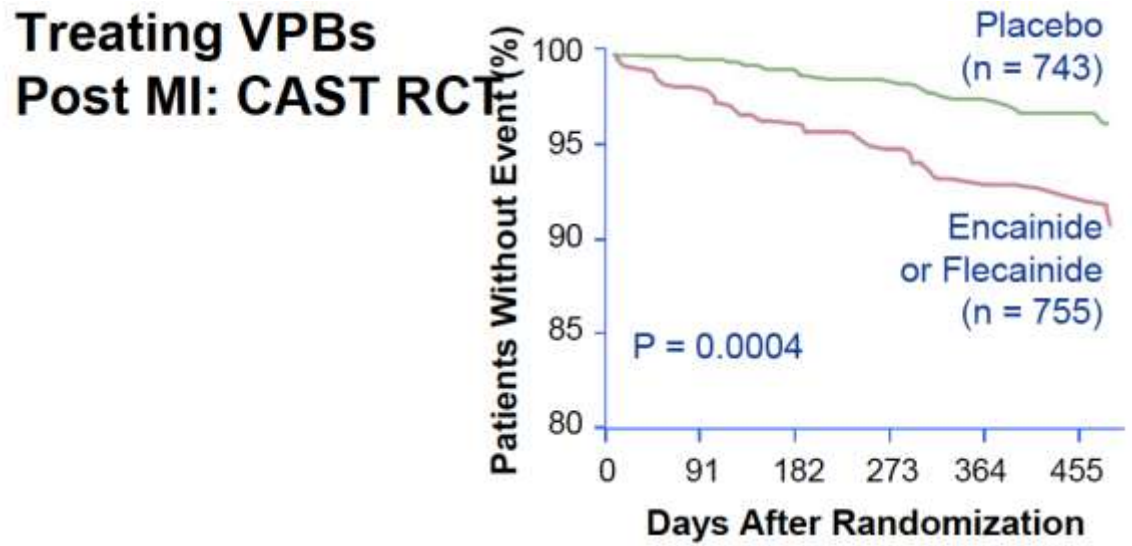
The Cardiac Arrhythmia Suppression Trial

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.)



Echt, New Engl J Med, 1991

Clinical Key Messages

- Subclinical leaflet thrombosis has not been proven to affect the clinical outcomes for patients who underwent TAVR, and thus this imaging phenomenon should not dictate the antithrombotic therapy for its prevention after TAVR.

- The absence of evidence of temporally related 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.