Anticoagulation vs. Antiplatelet After TAVR: ADAPT-TAVR Trial

Duk-Woo Park, MD

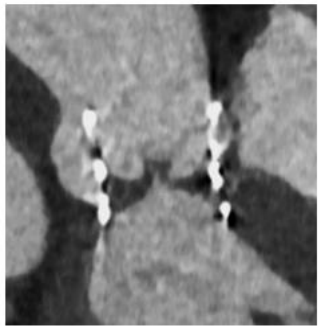
Asan Medical Center, Ulsan University College of Medicine,
Seoul, Korea

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.

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

What Is Known? What Is Unknown?

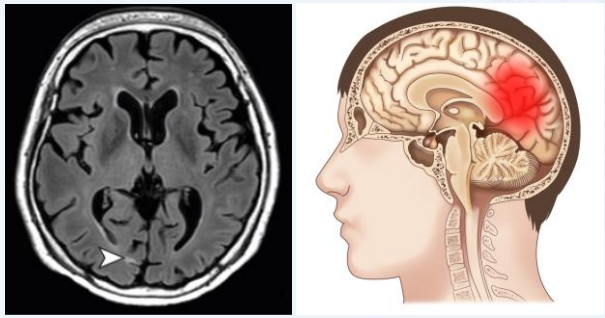


>75% of leaflet

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.

ACC 22

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

Duk-Woo Park, MD, PhD

For the ADAPT-TAVR Investigators,

Asan Medical Center,

University of Ulsan College of Medicine, Seoul, Korea

Twitter (@dukwoo_park)

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

AMERICAN COLLEGE of CARDIOLOGY

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

220 patients without OAC indication after successful TAVR

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

NOAC:
Edoxaban 60 mg or 30 mg once daily*
(N=110)

DAPT:
ASA plus Clopidogrel
(N=110)

Mandatory evaluations:

- 4D, Cardiac CT at 6-Mo after TAVR
- Serial brain MRI and neurological/neurocognitive function tests at baseline and 6-Mo

*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

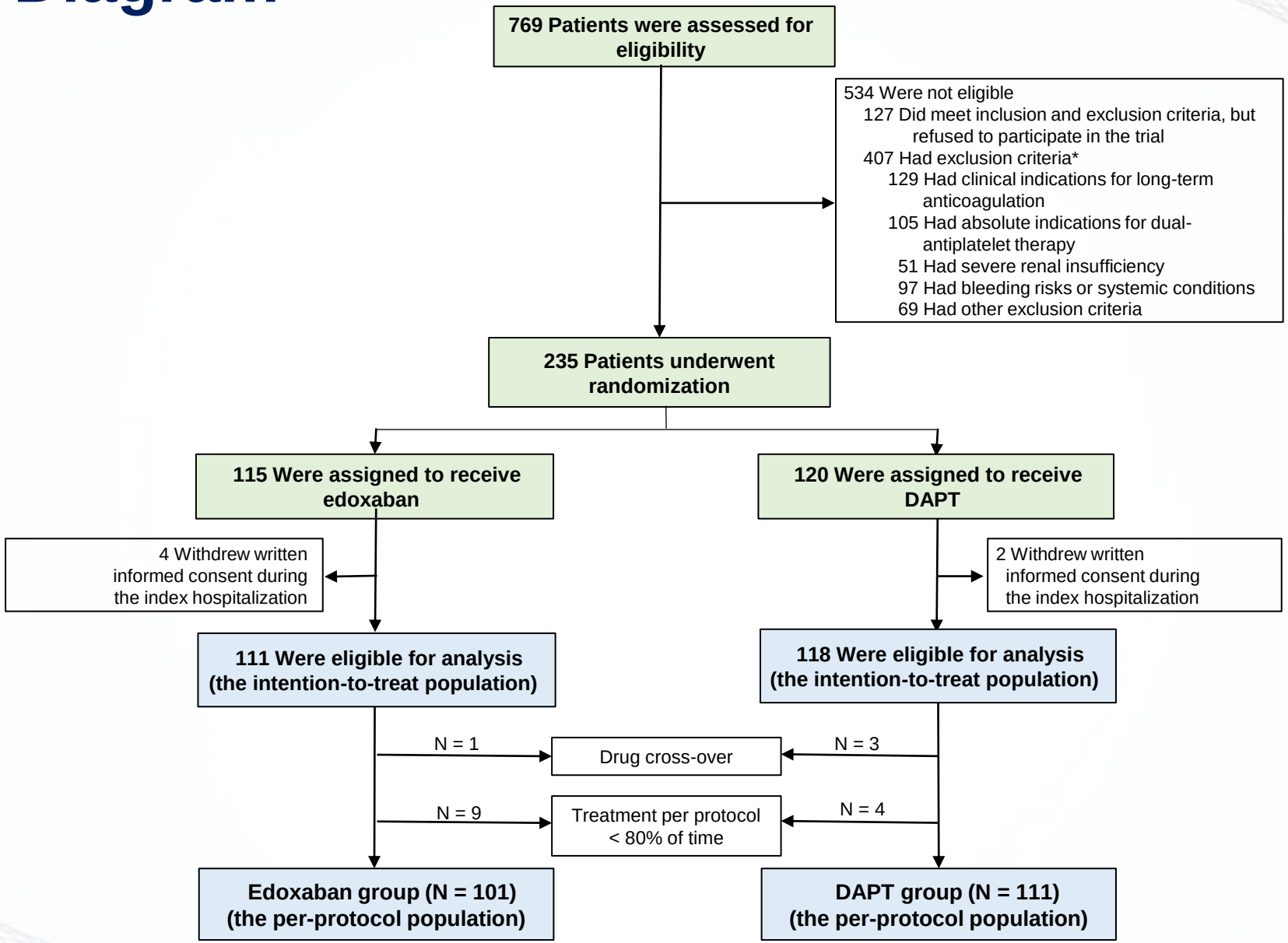
Cheng Hsin General Hospital
- WH Yin, J Wei, YT Lee
National Taiwan University Hospital
- HL Kao, MS Lin, TY Ko

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.

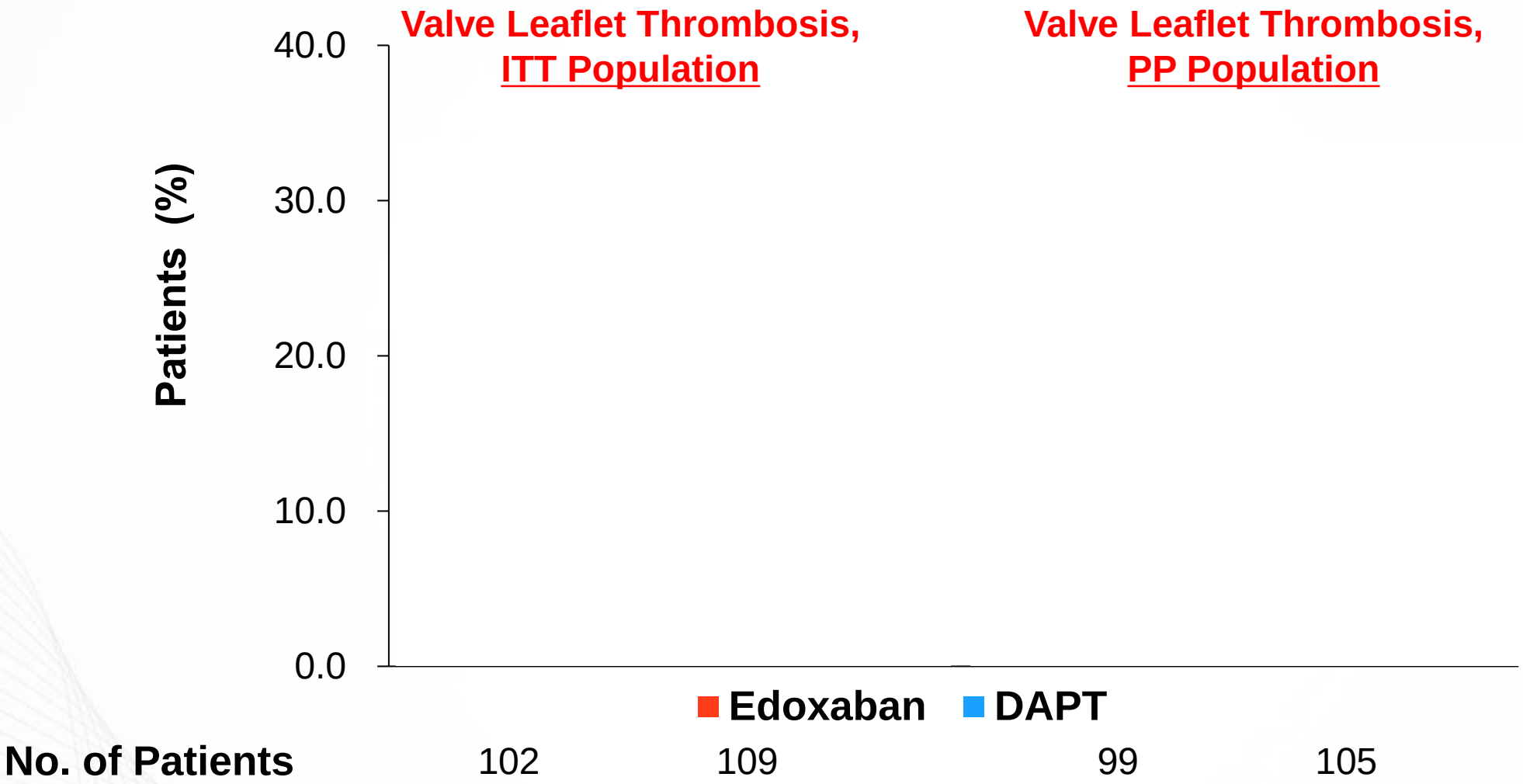
Completeness of Imaging & Neurocognitive Assessment

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

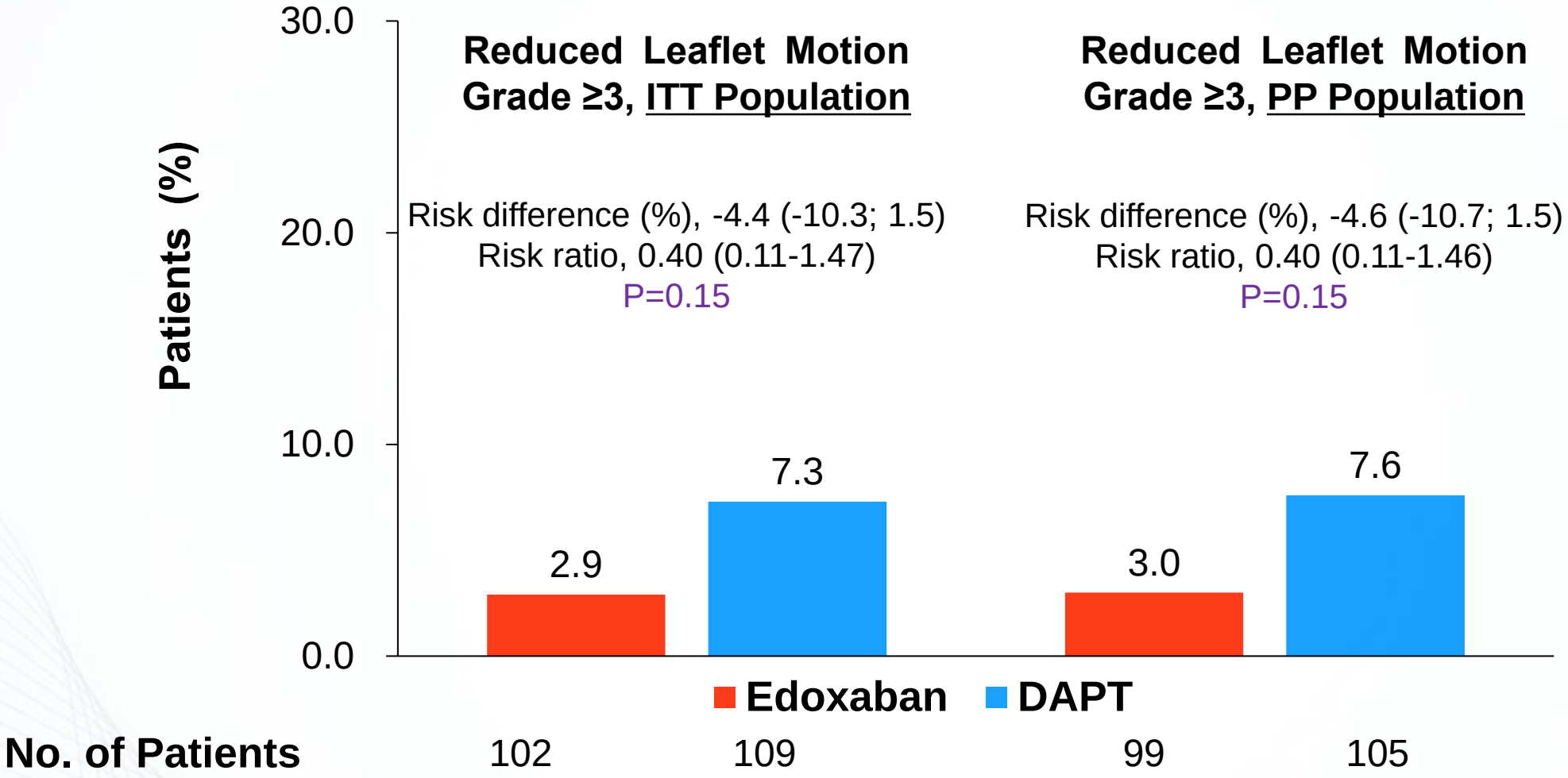
4D-CT Primary End Points



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.

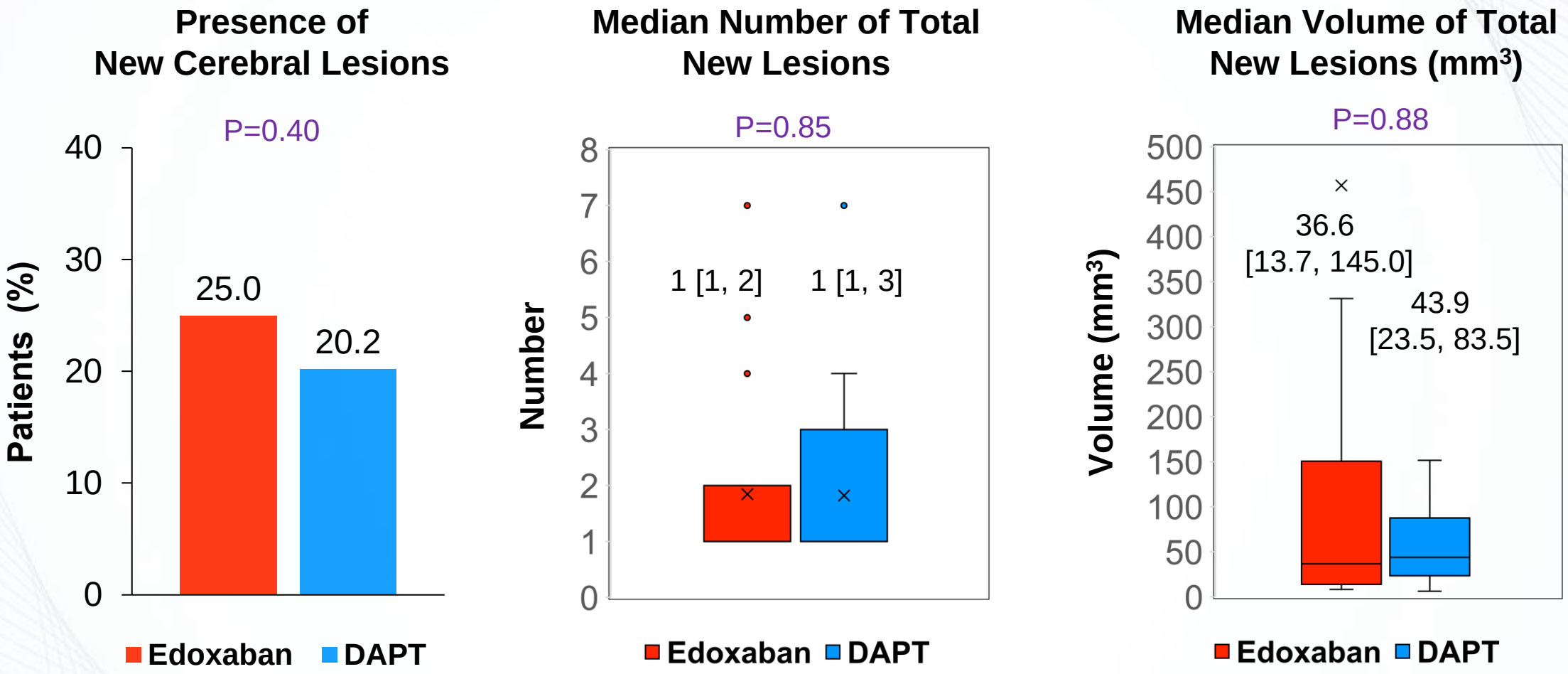
4D-CT Outcomes



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.

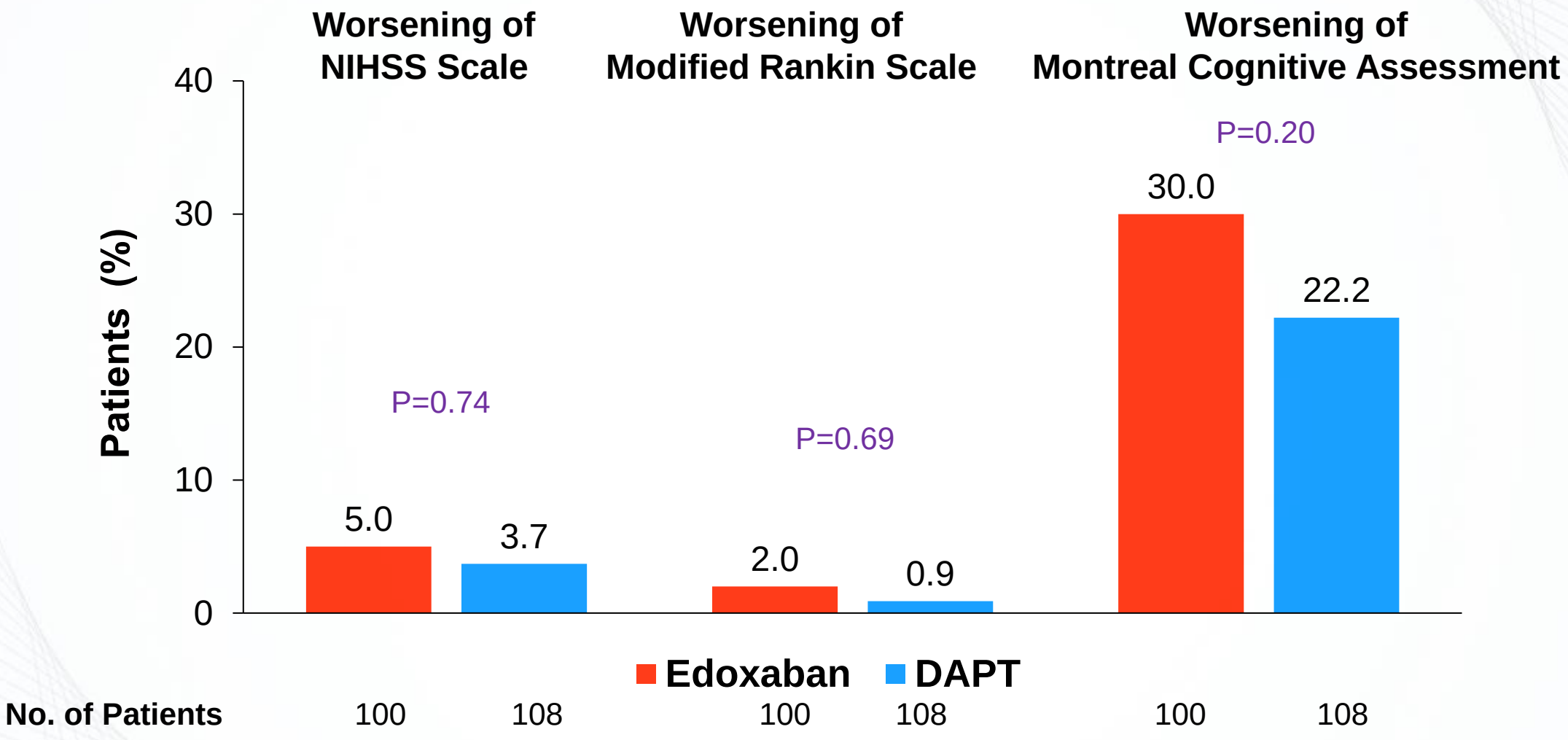
MRI End Points, ITT Analysis



No. of Patients	Edoxaban	DAPT
Presence of New Cerebral Lesions	104	109
Median Number of Total New Lesions	104	109
Median Volume of Total New Lesions (mm³)	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.

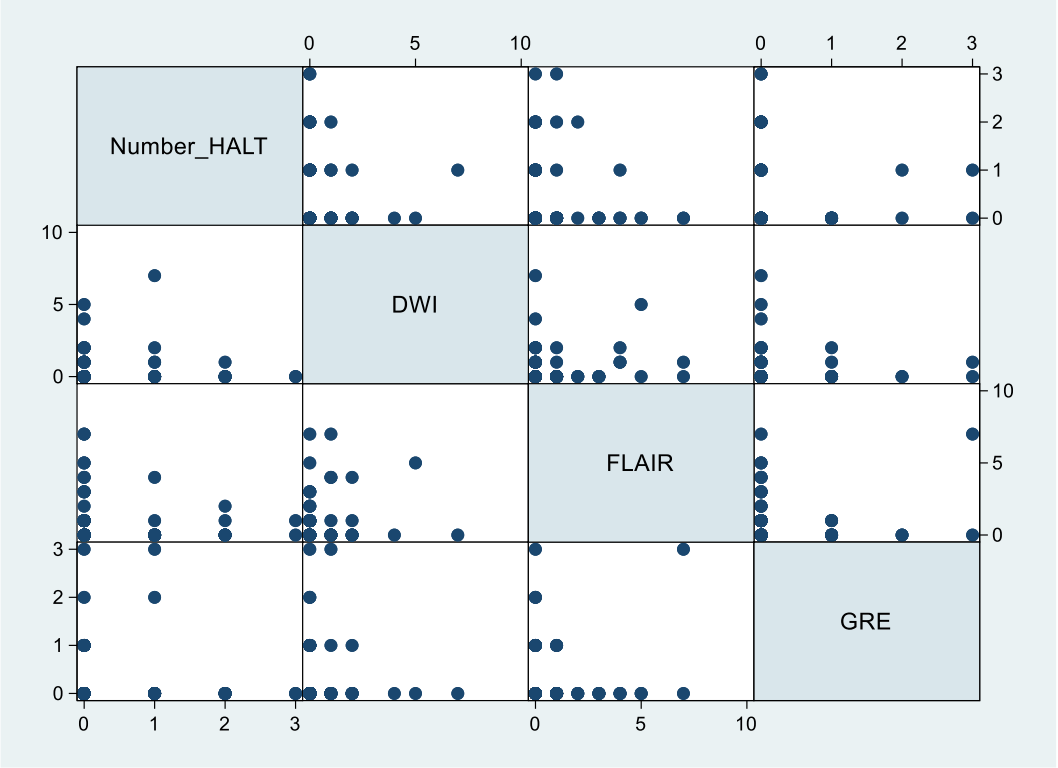
Neurological & Neurocognitive End Points, ITT Analysis



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.

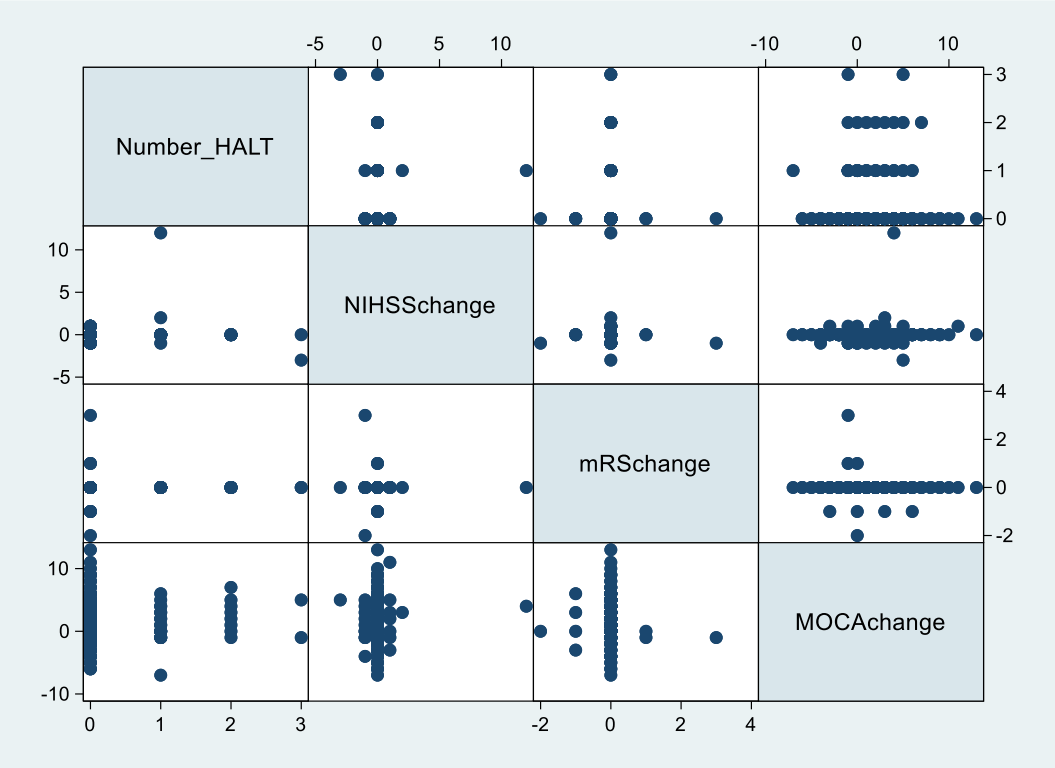
Association of Severity of HALT with Extent of New Lesions on Brain MRI



		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.

Conclusion

- 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

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.

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.