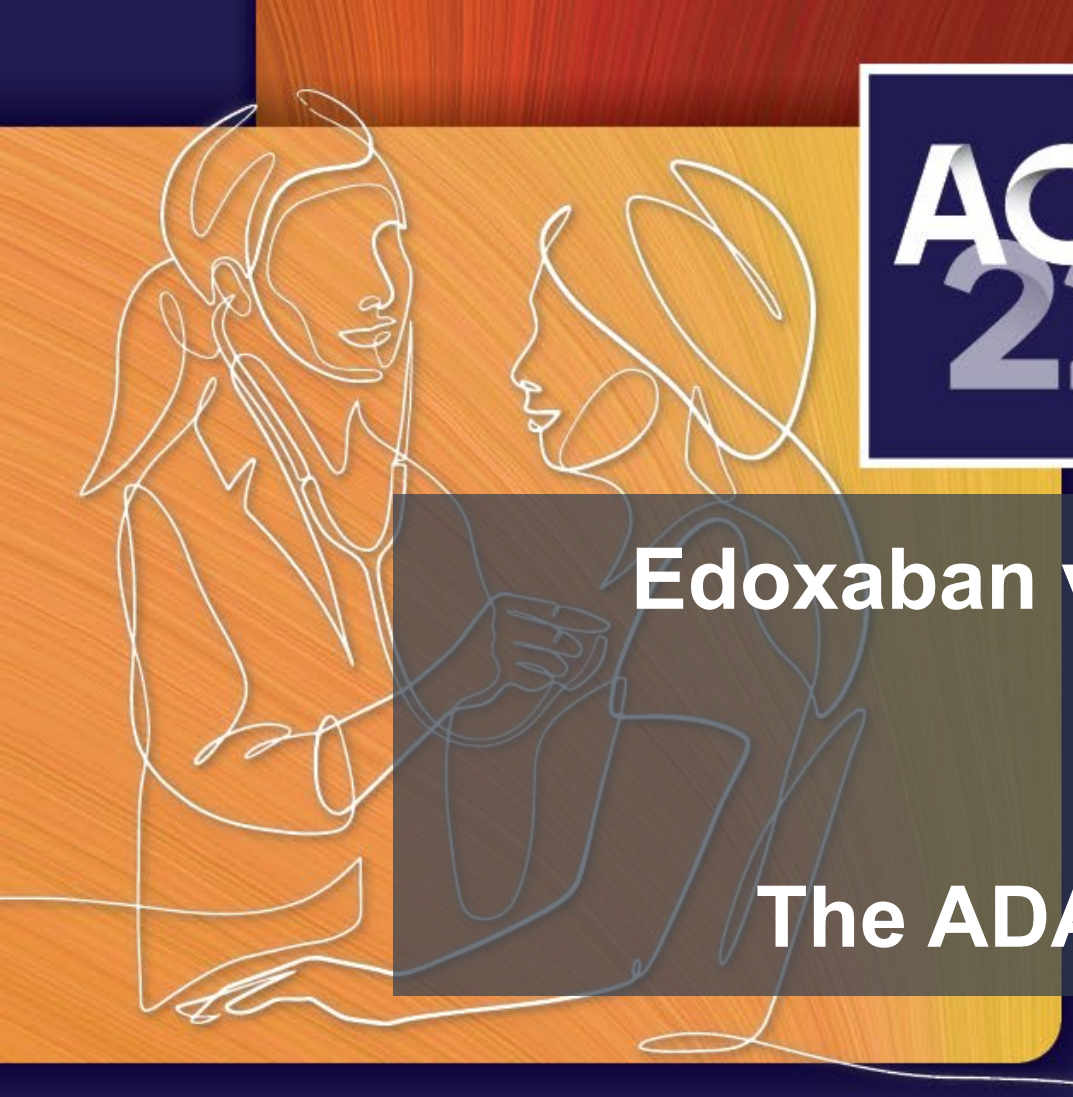

Edoxaban versus Dual Antiplatelet Therapy for Leaflet Thrombosis and Cerebral Thromboembolism after TAVR: The ADAPT-TAVR Randomized Clinical Trial

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

AMERICAN COLLEGE of CARDIOLOGY

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For the ADAPT-TAVR Investigators,

Asan Medical Center,

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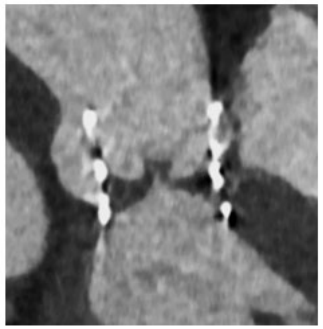
Disclosure

- The ADAPT-TAVR trial was an investigator-initiated trial and was funded by the CardioVascular Research Foundation (Seoul, Korea) and Daiichi Sankyo Korea Co., Ltd.
- The funders assisted in the design of the protocol but had no role in the conduct of the trial or in the analysis, interpretation, or reporting of the results.

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

What is Known? and What is Unknown?



>75% of leaflet

SLT

Unknown

Causal association of SLT and 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 thromboembolism 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 accompanying potential risks of cerebral thromboembolization and neurological or neurocognitive dysfunction in patients without an OAC indication after TAVR.

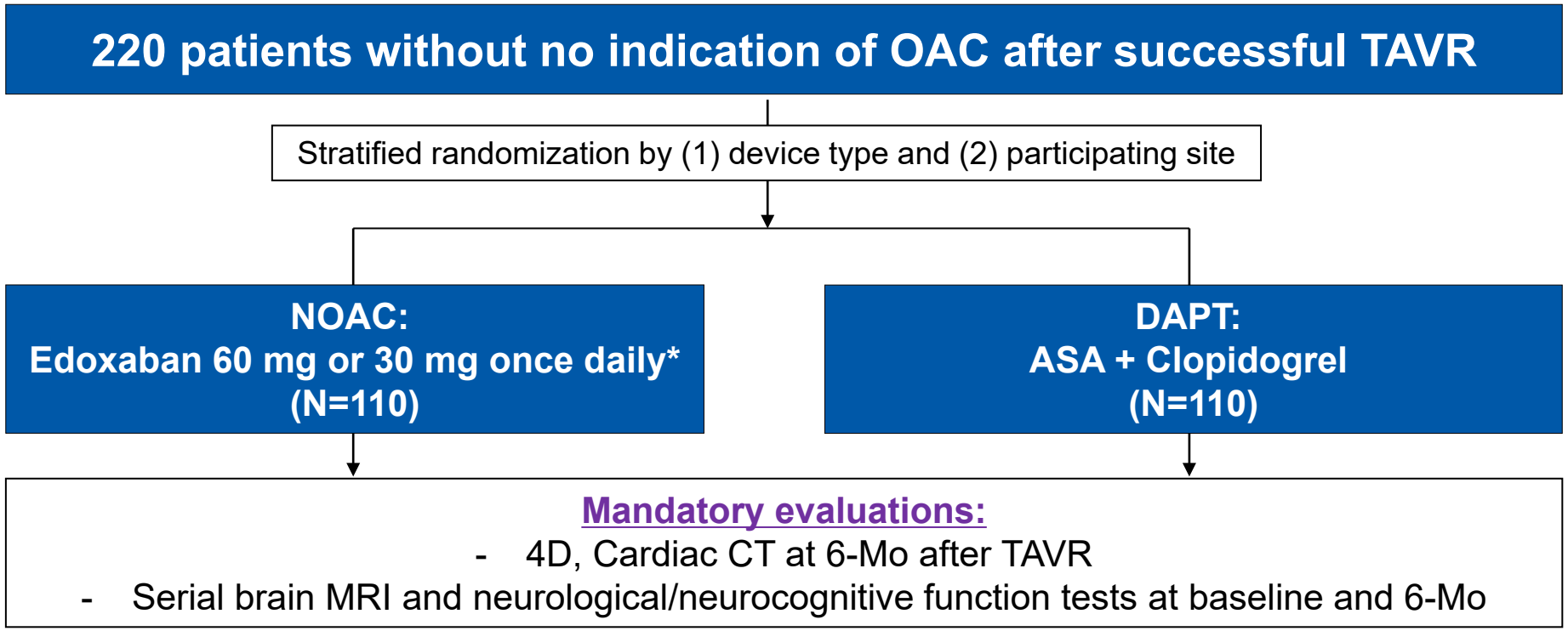
- Secondary objective → to determine the causal relationship of subclinical leaflet thrombosis with cerebral thromboembolism and neurological/neurocognitive dysfunction.

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.

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

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)

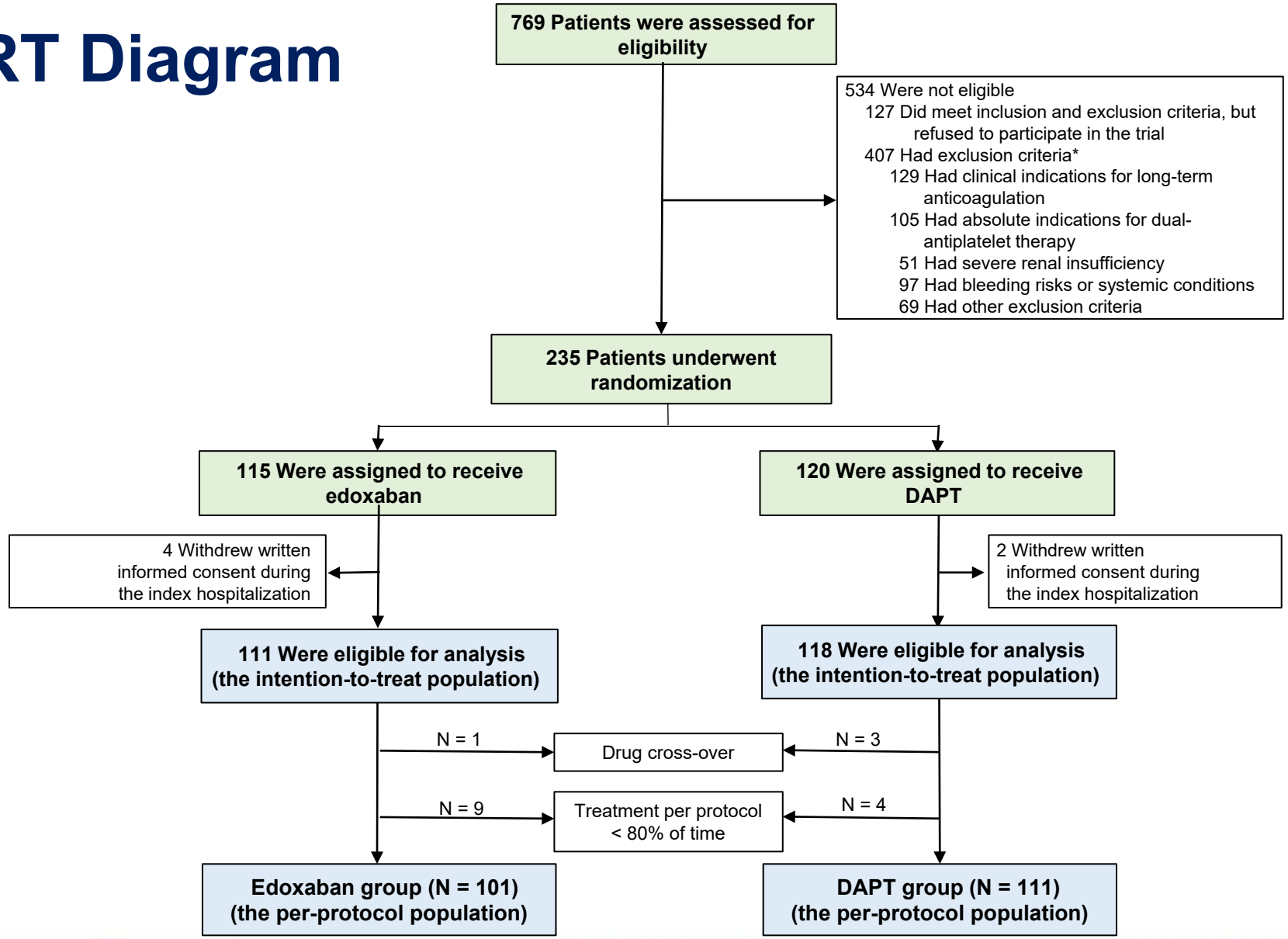
Sample Size & Statistical Analysis

- Under an assumption that an incidence of leaflet thrombosis of 15% in the DAPT group and 3% in the NOAC (edoxaban) group based on prior data,[1] a total sample of 220 patients was deemed to be sufficient to evaluate the primary endpoint with a statistical power of 80%, a 2-sided significance level of 0.05 and attrition rate of 10% (CT follow-up loss).
- The final sample size was also met to demonstrate that the edoxaban group would provide a 30% reduction of the number of new cerebral lesions on MRI compared to the DAPT group based on prior available data[2-3]
- The main analyses were performed according to the ITT principle and secondary analyses were also performed in the PP population

ITT, intention-to-treat; PP, per-protocol.

[1]Chakravarty T, et al. *Lancet* 2017;389:2383-2392. [2]Haussig S, et al. *JAMA* 2016;316:592-601. [3]Kapadia SR, et al. *JACC* 2017;69:367-377 .

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.

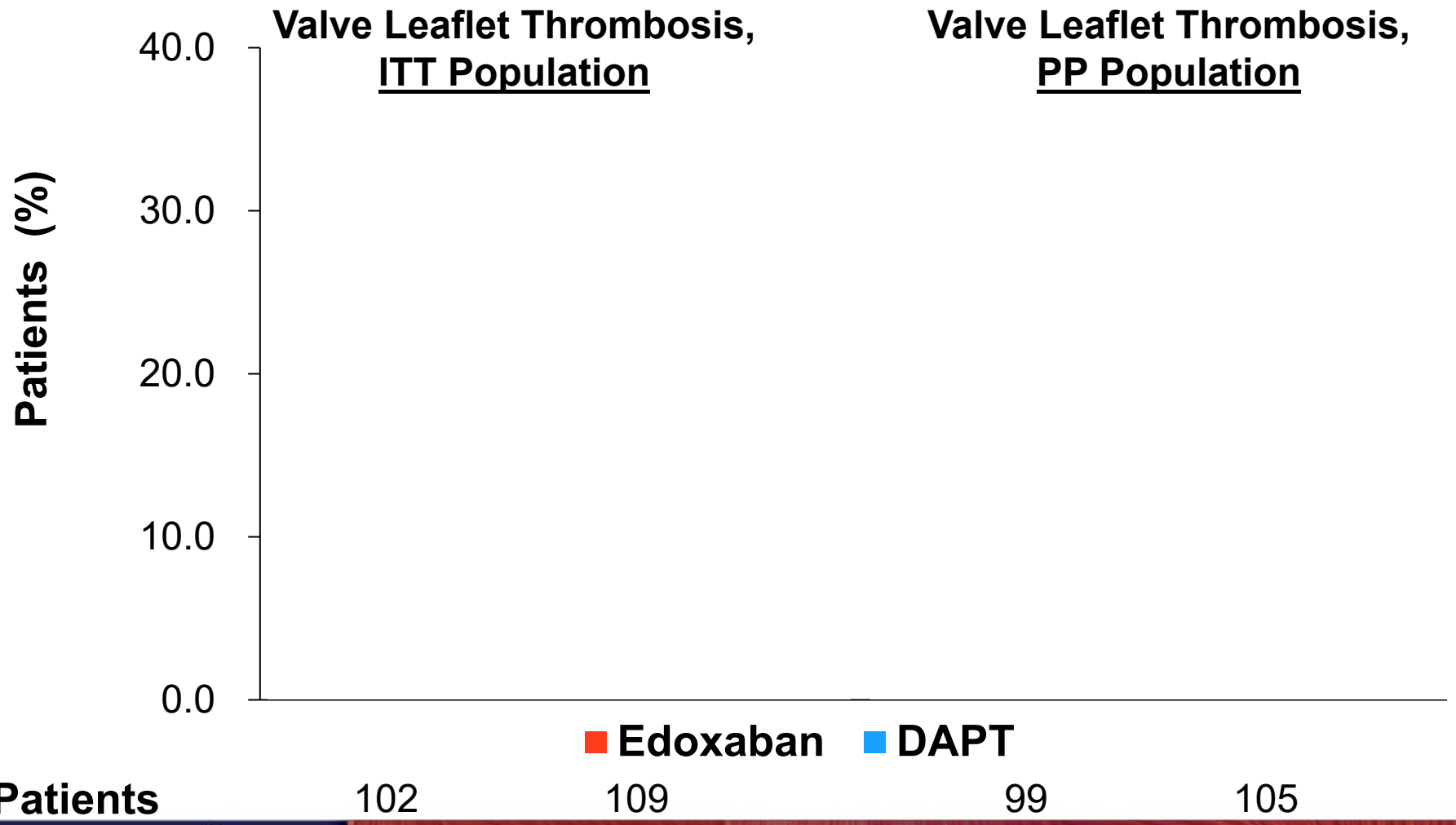
Completeness of Imaging & Neurocognitive Assessment

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 matching*		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

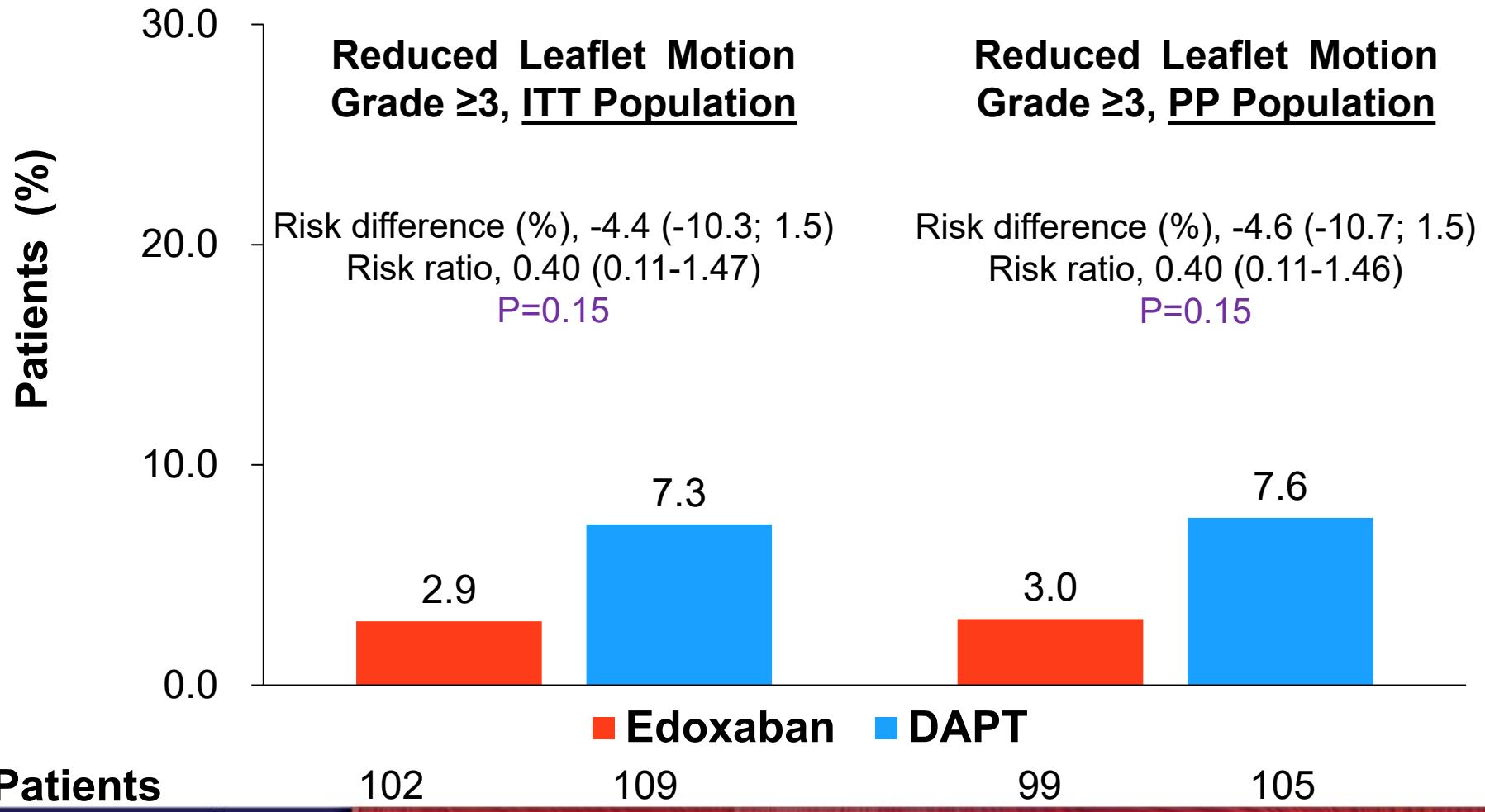
4D-CT Primary End Points



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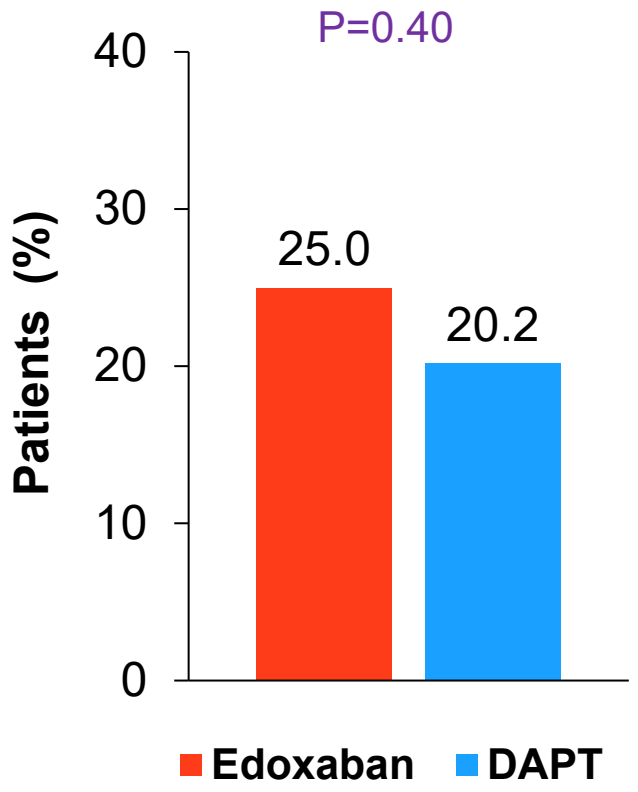
*P values are derived from the chi-square test or Fisher's exact test as appropriate.

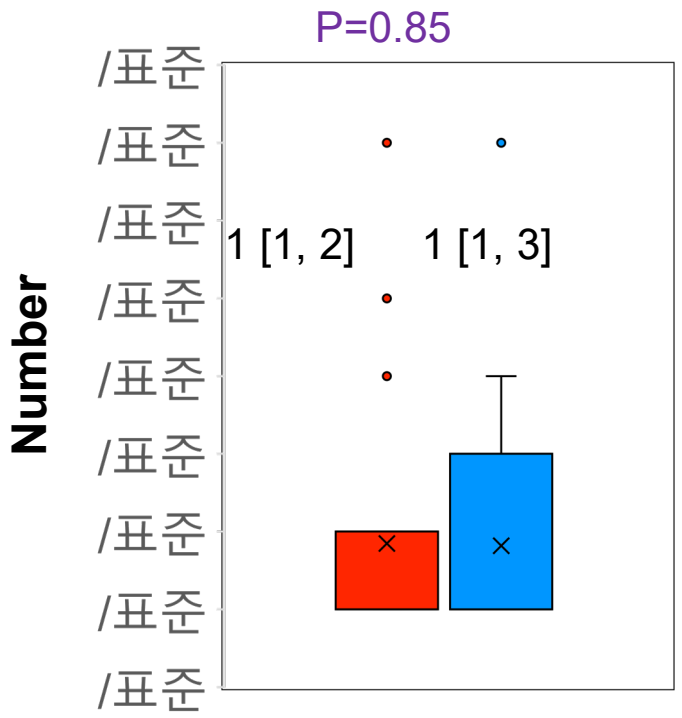
MRI End Points, ITT Analysis

Presence of New Cerebral Lesions



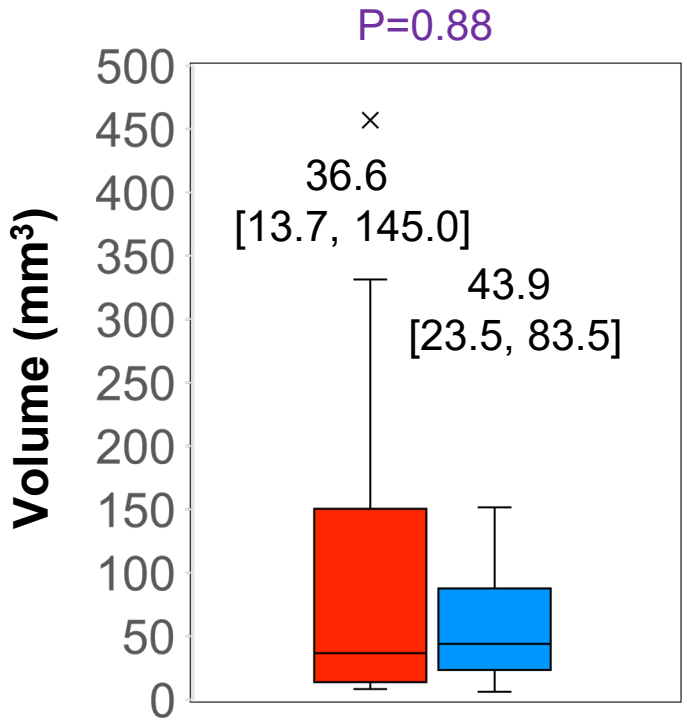
No. of Patients	104	109

Median Number of Total New Lesions



104	109

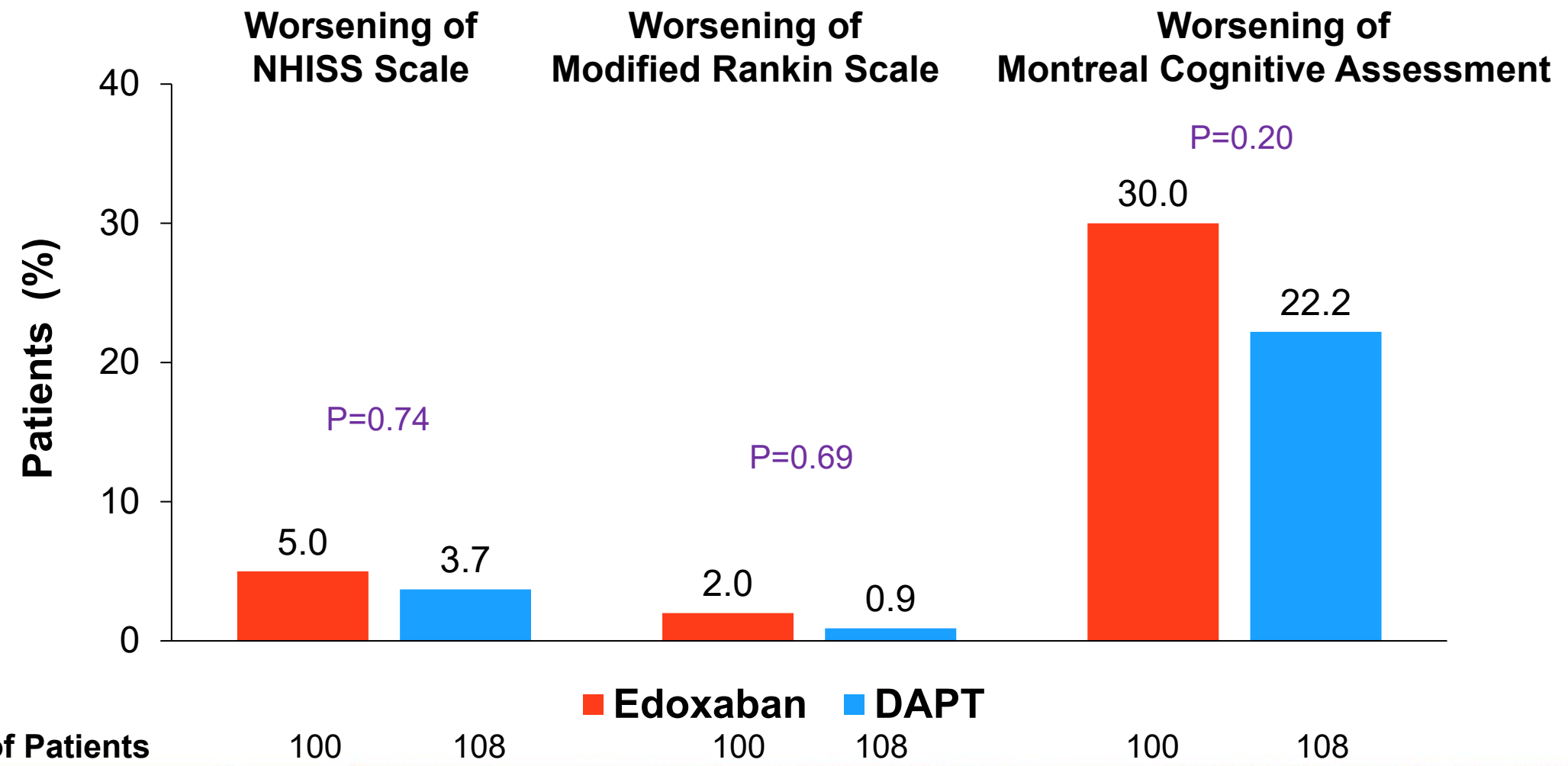
Median Volume of Total New Lesions (mm^3)



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

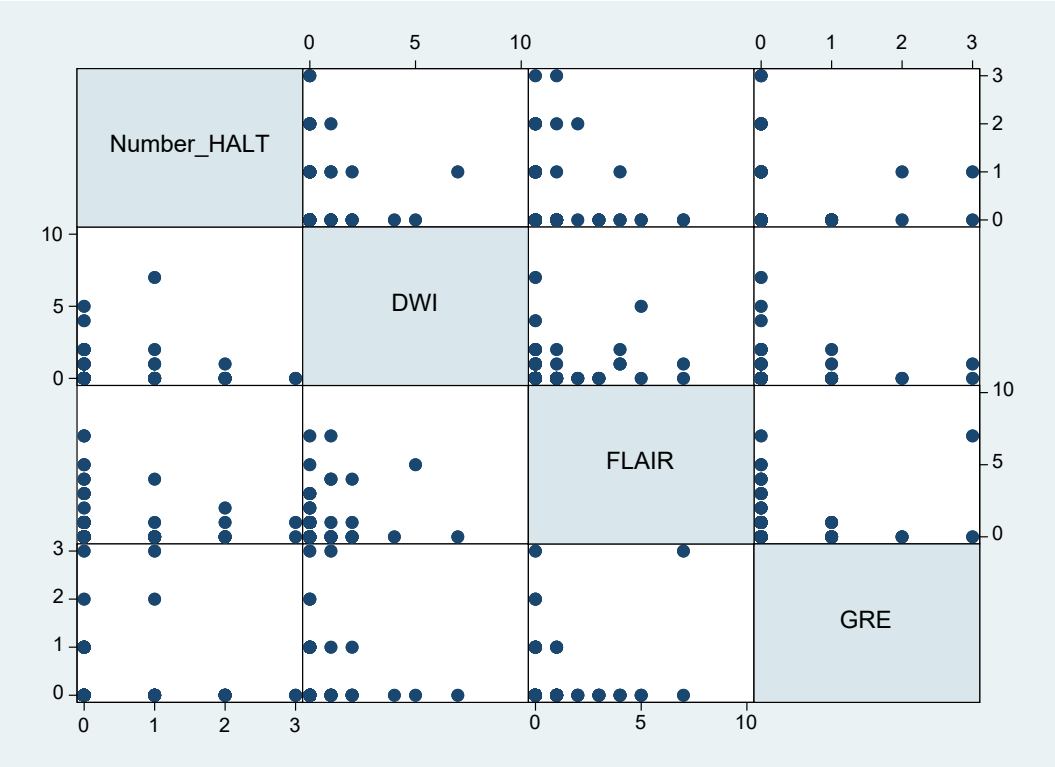


NIHSS, National Institutes of Health Stroke Scale

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.

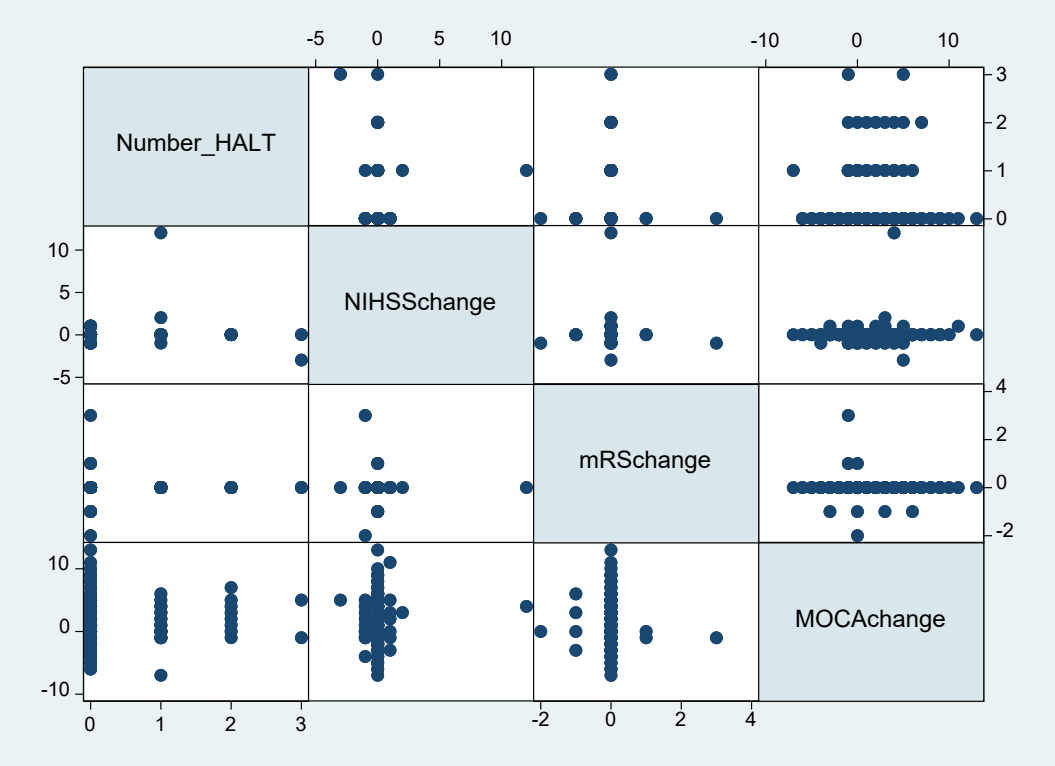
Association of Severity of HALT with Extent of New Lesions on Brain MRI



		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.

Limitations

- This trial was an open-label trial, which was potentially subject to reporting and ascertainment bias.
- This trial adopted surrogate imaging outcomes as the primary and key secondary end points; thus, our study was underpowered to detect any meaningful differences in clinical efficacy and safety outcomes.
- Follow-up period was relatively short; the long-term effect of leaflet thrombosis or different antithrombotic strategies on bioprosthetic valve durability is still unknown.
- Our findings cannot be directly extrapolated to patients with an established indication for OAC (approximately, one third of TAVR patients).

Conclusions

- 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 association between subclinical leaflet thrombosis and temporally related changes of new cerebral thromboembolic lesions and neurological end points.

Circulation

Supplementary

Clinical Implications

- 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 the routine imaging screening tests for the detection of this phenomenon and imaging-guided antithrombotic strategies in cases without hemodynamic or clinical significance.