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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*

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Abstract

Background: It is unknown whether direct oral anticoagulant edoxaban can reduce leaflet thrombosis and the accompanying cerebral thromboembolic risk after transcatheter aortic-valve replacement (TAVR). Also, the causal relationship of subclinical leaflet thrombosis with cerebral thromboembolism and neurological or neurocognitive dysfunction remains unclear.

Methods: We conducted a multicenter, open-label randomized trial comparing edoxaban with dual antiplatelet therapy (DAPT; aspirin plus clopidogrel) in patients who had undergone successful TAVR and did not have an indication for anticoagulation. The primary end point was an incidence of leaflet thrombosis on four-dimensional computed tomography (CT) at 6-month. Key secondary end points were the number and volume of new cerebral lesions on brain magnetic resonance imaging (MRI) and the serial changes of neurological and neurocognitive function between 6-month and immediate post-TAVR.

Results: A total of 229 patients were included in the final intention-to-treat population. There was a trend toward a lower incidence of leaflet thrombosis in the edoxaban group than in the DAPT group (9.8% vs. 18.4%; absolute difference, −8.5%; 95% confidence interval [CI], −17.8% to 0.8%; P=0.076). The percentage of patients with new cerebral lesions on brain MRI (edoxaban vs. DAPT; 25.0% vs. 20.2%; difference, 4.8%; 95% CI, −6.4% to 16.0%) and median total new lesion number and volume were not different between two groups. Also, the percentages of patients with worsening of neurological and neurocognitive function were not different among the groups. The incidence of any or major bleeding events were not different between two groups. We found no significant association of the presence or extent of leaflet thrombosis with new cerebral lesions and a change of neurological or neurocognitive function.

Conclusions: In patients without an indication for long-term anticoagulation after successful TAVR, the incidence of leaflet thrombosis was numerically lower with edoxaban than with DAPT, but this was not statistically significant. The effect on new cerebral thromboembolism and neurological or neurocognitive function were also not different between two groups. Because the study was underpowered, the results should be considered hypothesis-generating, highlighting the need for further research.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT03284827

Keywords: aortic stenosis, anticoagulation, cerebral thromboembolism, leaflet thrombosis, transcatheter aortic-valve replacement

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Non-Standard Abbreviations and Acronyms

ADAPT-TAVR = Anticoagulation versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization after Transcatheter Aortic Valve Replacement
AS = aortic valve stenosis
CT = computed tomography
DAPT = dual antiplatelet therapy
ENVISAGE-TAVI AF = Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation
MRI = magnetic resonance imaging
NIHSS = National Institutes of Health Stroke Scale
NOAC = non-vitamin K direct anticoagulant
OAC = oral anticoagulation
RCTs = randomized clinical trials
TAVR = transcatheter aortic-valve replacement
VARC = Valve Academic Research Consortium

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Clinical Perspective

What is new?

- In this ADAPT-TAVR trial comparing the potential effect of edoxaban with dual antiplatelet therapy (DAPT) in patients without an indication for chronic anticoagulation after transcatheter aortic-valve replacement (TAVR), the incidence of leaflet thrombosis was numerically lower with edoxaban than with DAPT, but this was not statistically significant.
- The treatment effect on reduction of leaflet thrombosis was not associated with a reduction of new cerebral thromboembolism and a new development of neurological or neurocognitive dysfunction. Also, there was no significant relationship of subclinical leaflet thrombosis with an increased risk of cerebral thromboembolism and neurological dysfunction.
- The incidence of any or major bleeding events was not significantly different between the two groups.

What are the 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.
- 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.

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Introduction

Transcatheter aortic-valve replacement (TAVR) has become the established treatment for symptomatic severe aortic stenosis (AS) on the basis of clinical evidence from multiple large-scale randomized clinical trials (RCTs).[1-7] Most of these trials used dual antiplatelet therapy (DAPT; aspirin plus clopidogrel) as the default antithrombotic strategy after TAVR, which was empirically based on expert consensus. However, since possible subclinical leaflet thrombosis and reduced leaflet motion by four-dimensional computed tomography (CT) was reported and the potential risk of consequent embolic stroke was of concern,[8] several observational studies have suggested that these phenomena could be associated with an increased risk of ischemic cerebrovascular events and oral anticoagulation (OAC) was more effective than antiplatelet therapy in prevention or treatment of leaflet thrombosis.[9-13]

To resolve this unmet issue and to define the optimal antithrombotic strategy after TAVR, several RCTs have been conducted.[14-19] Most of these trials support a less potent antithrombotic strategy with a reduction of primary net clinical benefit, mainly driven by a lower risk of bleeding events. Based on these evidences, updated clinical guidelines recommend that aspirin or single antiplatelet therapy should be used in most patients with no indication for chronic OAC after TAVR.[20,21] However, it is still questioned whether a less potent antiplatelet therapy is sufficient to prevent leaflet thrombosis and reduce the risk of cerebral thromboembolic events.[22] Also, further and more systematic study of this imaging phenomenon to clarify the underlying mechanism of a thromboembolic risk and to assess its clinical consequences is eagerly demanded.

Recently, the Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation (ENVISAGE-TAVI AF) trial showed that non-vitamin K direct anticoagulant (NOAC) edoxaban was noninferior to vitamin K antagonists for the primary composite of

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adverse events, but was associated with a higher risk of major bleeding in patients who had an indication for oral anticoagulation for atrial fibrillation after TAVR.[19] In ADAPT-TAVR (Anticoagulation versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization after Transcatheter Aortic Valve Replacement), we investigated the effect of edoxaban as compared with DAPT for the prevention of leaflet thrombosis and the accompanying potential risks of cerebral thromboembolization and neurological or neurocognitive dysfunction in patients who did not have an indication for oral anticoagulation after successful TAVR.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Trial Design and Oversight

ADAPT-TAVR was a multinational, multicenter, prospective, randomized, open-label, adjudicator-masked trial.[23] The trial was conducted in compliance with the International Council for Harmonization and the Declaration of Helsinki. The trial protocol was approved by the ethics committees and corresponding health authorities for all participating sites. All the patients provided written informed consent to participate before trial enrollment.

This study 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. The sponsor covered all costs associated with the trial, including the cost of the anticoagulants and all imaging, neurological, and laboratory tests for trial purposes that were not otherwise clinically indicated. Data analyses were conducted by the Clinical Research Center of Cardiology in Asan Medical Center (Seoul,

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Korea) and were executed under the academic leadership of the investigators. An independent data and safety monitoring board provided oversight by periodically reviewing all reported serious adverse events. The principal investigator (the first author) had unrestricted access to the data after the database was locked. All the authors reviewed and critiqued subsequent drafts and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Detailed information on participating centers (Table S1) and trial organization (roles and responsibilities) (Table S2) is provided in the Data Supplement.

Patient Selection and Randomization

Patients 18 years of age or older without an indication for long-term anticoagulation who had undergone successful TAVR for severe aortic stenosis were eligible for enrollment. Successful TAVR was defined as correct positioning of any approved transcatheter bioprosthetic aortic valve into the proper anatomical location with the intended valve performance and without unresolved periprocedural complications.[24] Key exclusion criteria were any established indication for anticoagulation (e.g., atrial fibrillation), any absolute indication for dual antiplatelet therapy (e.g., acute coronary syndromes or recent or concomitant percutaneous coronary intervention), and severe renal insufficiency prohibiting CT imaging (estimated glomerular filtration rate, <30 ml per minute per 1.73 m^2 of body-surface area); the detailed inclusion and exclusion criteria are provided in the Data Supplement (Table S3). After written informed consent had been obtained, eligible patients were randomly assigned in a 1:1 ratio to receive edoxaban or dual antiplatelet therapy through an interactive Web-response system, stratified according to device type (balloon-expandable or self-expandable) and participating center. Randomization occurred 24 hours to 7 days after TAVR and before hospital discharge.

Trial Treatment and Follow-Up

The edoxaban (experimental) group received 60 mg once daily or 30 mg once daily with

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dose-reduction criteria (a creatinine clearance [Cockcroft–Gault formula] of 30 to 50 ml per minute, a low body weight of 60 kg or less, or concomitant use of certain P-glycoprotein inhibitors) for 6 months. The DAPT (control) group received aspirin at 100 mg once daily plus clopidogrel at 75 mg once daily for 6 months, which was the standard of care after TAVR for patients who did not have an indication for oral anticoagulation at the time of trial enrollment.[25,26] Edoxaban was supplied by the sponsor to the participating sites, and antiplatelet drugs (aspirin and clopidogrel) were supplied according to local practice. In cases with new-onset atrial fibrillation after TAVR, the assigned treatment remained as the protocol in the edoxaban group, and an alternative use of NOAC or vitamin K antagonists was allowed in the DAPT group at the discretion of the treating physician.[23]

After enrollment, patients were followed at 1, 3, and 6 months. Data collected during follow-up visits include clinical symptoms, health status, and any related clinical events including rehospitalization or unintended hospital visits. For compliance check of study medications, the investigators have kept track of investigational drugs dispensed and/or administered to the subjects, which were used for compliance calculation. For all patients, a transthoracic echocardiogram was routinely performed at immediate post-TAVR, 1, and 6 months and hemodynamic structural valve deterioration was determined according to the standardized definitions.[27]

Imaging Studies, Neurological and Neurocognitive Assessment

Enrolled patients were routinely scheduled for a contrast-enhanced, electrocardiogram-gated cardiac CT scans with full cardiac-cycle coverage (four-dimensional CT) at the time of the 6-month follow-up visit after randomization. The cardiac CT images were analyzed for the presence of hypoattenuated leaflet thickening (possible leaflet thrombosis), leaflet motion based on opening limitation, stent eccentricity (%) and calcification burden.[23,28] The degree of hypoattenuated leaflet thickening and the severity of reduced leaflet motion were classified

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according to the standard definition.[29,30] Hypoattenuated thickening was also assessed at supravalvular, subvalvular, and sinus of Valsalva levels (Figure S1 in the Data Supplement). The results of the four-dimensional CT scan were concealed from the treating physician and patient until the end of the trial. Concomitantly, to detect possible cerebral thromboembolism, all patients were routinely scheduled for brain magnetic resonance imaging (MRI) scans at baseline (1–7 days after TAVR and before discharge) and at 6-month follow-up. All brain MRI scans were obtained including diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), and T2-star gradient (GRE) sequences, which are the important sequences for the imaging endpoint.[31] The brain MRI images were analyzed for the occurrence, number, and volume of new lesions on the 6-month DWI, FLAIR and GRE images compared with baseline MRI, respectively.[23]

The trial-specific standardized four-dimensional cardiac CT acquisition protocol (Table S4) and brain MRI protocol (Table S5) are provided in the Data Supplement. All participating sites were qualified for their CT and MRI imaging machines and capability to perform the standardized acquisition protocol by the imaging core laboratory. All CT and MRI images acquired from each site were anonymized and electronically transferred to a central server (AiCRO system; Asan Image Metrics, Seoul, Korea) for image archiving and blinded independent image review.[32] Imaging measurements were performed at a central imaging core laboratory (Asan Image Metrics; www. aimaicro.com) in a blinded manner, by independent cardiac radiologists and neuroradiologists who were not aware of the patients' identities and the random treatment assignment.[23]

Simultaneously, all study subjects were scheduled for detailed neurological and neurocognitive function assessments at baseline (1–7 days after TAVR and before discharge) and at 6-month follow-up. Neurological assessments included standard clinical scales of the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale, and

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neurocognitive function was assessed using the Montreal Cognitive Assessment, which was a primarily recommended screening measure of global cognition and cognitive impairment.[33] Worsening of neurological or neurocognitive end points were 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.[34,35] All neurological and cognitive assessments were performed by trained and certified staffs in each participating center, who were blinded to brain MRI findings and group assignment.

End Points

The primary end point was the incidence of valve leaflet thrombosis on cardiac CT scans at 6 months. Key secondary end points were the presence and number of new cerebral lesions and total new lesion volume on brain MRI and the results of serial neurological and neurocognitive assessments between immediate post-TAVR and 6 months. Other secondary end points included serial echocardiographic parameters, and efficacy and safety clinical end points, which included death, myocardial infarction, stroke, systematic thromboembolic event, bleeding events, and rehospitalization. All of the above outcomes and their components were adjudicated in a blinded manner by an independent clinical-events committee according to the Valve Academic Research Consortium (VARC)-2[24] and VARC-3 defintions[36] and the Neurologic Academic Research Consortium definitions.[33] A full list of trial end points (Table S6) and definitions (Table S7) are provided in the Data Supplement.

Statical Analysis

The sample size was estimated to simultaneously meet the primary end point of the incidence of leaflet thrombosis on cardiac CT and to meet the key secondary end point of the total new lesion number on brain MRI.[23] Based on the results from the RESOLVE and SAVORY registry,[9] we assumed an incidence of subclinical leaflet thrombosis of 15% in the DAPT group and 3% in the NOAC (edoxaban) group. It was estimated that 192 patients (96 patients

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in each arm) would need to be enrolled to provide a statistical power of 80% to detect this difference with a two-sided significance level of 0.05. Under an assumption that 10% of the patients would be lost to CT follow-up, a total sample of at least 220 patients was deemed to be sufficient to evaluate the primary end point. The final sample size was also met to demonstrate our hypothesis for key secondary end point of brain MRI findings; the edoxaban group would provide a 30% reduction of the number of new lesions compared to the DAPT group based on prior studies[34,37] (more details regarding the sample size estimation are provided in expanded methods in the Data Supplement).

The main analyses were performed according to the intention-to-treat principle. Secondary analyses of the primary and secondary end points were also performed in the per-protocol population; these populations are defined in Figure S2 in the Data Supplement. The percentages of patients with the primary and secondary CT end points (leaflet thrombosis and reduced leaflet motion) between the treatment group were compared using either the chi-square test or Fisher's exact test as appropriate. In sensitivity analysis to test for the effect of the loss of values due to missing CT data, missing value of the primary outcome data after randomization were imputed over a wide range of possible scenarios. The key secondary end points, consisting of total new lesion number and volume differences on MRI and the results of serial neurological and neurocognitive assessments (overall and its subcomponents) between the two randomized arms, were compared using the Wilcoxon rank sum test or Student's t-test as appropriate. Change scores were calculated by subtracting immediate post-TAVR scores from the 6-month scores. Differences between medians were estimated using the independent samples Hodges-Lehmann estimator. Cumulative event-free survival was estimated by means of Kaplan–Meier analyses. Cox proportional-hazards regression models were used to analyze the time from randomization to the first occurrence of efficacy and safety clinical end points. For primary and secondary end points, risk differences, risk ratios,

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and corresponding 95% confidence intervals were reported. The proportional-hazards assumption was confirmed using the Schoenfeld residuals test and graphical log-minus-log method; no relevant violations of the underlying assumption were found. Lastly, we evaluated whether there was a significant association of subclinical leaflet thrombosis or reduced leaflet motion with the risks of cerebral thromboembolism, a decline of neurological or neurocognitive function, and adverse events.

Since analyses were not corrected for multiple comparisons, the results of analyses other than that of the primary end point should be interpreted with caution and therefore inferences drawn from unadjusted confidence intervals may not be reproducible. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

Trial Population

From March 2018 through April 2021, 769 patients undergoing TAVR were assessed for eligibility and a total of 235 patients underwent randomization after successful TAVR in 5 centers in 3 countries (South Korea, Hong Kong, and Taiwan) (**Figure 1**); 115 patients were randomly assigned to the edoxaban group and 120 to the DAPT group. After randomization, 6 patients were excluded from analysis since these patients withdrew informed consent during the index hospitalization without ingestion of trial medications. Therefore, 111 patients receiving edoxaban and 118 patients receiving DAPT were included in the final intention-to-treat population.

The demographic and clinical characteristics of the patients at baseline were similar between the two trial groups (**Table 1**). The mean age of the patients was 80.1 years, and 41.9% of the patients were men. The mean Society of Thoracic Surgeons risk score was 3.3%. At trial entry, 61.3% of the randomized population of edoxaban group met any of the criteria

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for adjustment of the edoxaban dose and received reduced doses (30 mg once daily). The procedural and echocardiographic characteristics at baseline were described in **Table 2**, which were well balanced between the two randomized groups.

During the trial period, overall drug compliance and detailed information on stopping of study medications are summarized in Table S8 in the Data Supplement; thus, Figure S2 provides the same information for the per-protocol population. At 6 months, approximately 95% of eligible patients had cardiac CT and brain MRI scans as well as neurological and neurocognitive function tests (**Figure 1**). Completeness of CT scans, serial MRI scans, serial neurological or neurocognitive function tests, and clinical assessments between post-TAVR and 6-month is summarized in Table S9 in the Data Supplement.

Primary and Key Secondary End Points

In the intention-to-treat analysis, 10 of the 102 patients (9.8%) with CT scans that could be evaluated in the edoxaban group had at least one leaflet thrombosis, as compared with 20 of 109 (18.4%) in the DAPT group (difference, −8.5 percentage points; 95% confidence interval [CI], −17.8 to 0.8; P=0.076) (**Table 3** and **Figure 2**). Leaflet thrombosis with reduced motion of grade 3 or higher was observed in 3 of 102 patients (2.9%) in the edoxaban group and 8 of 109 (7.3%) in the DAPT group (difference, −4.4 percentage points; 95% CI, −10.3 to 1.5). Similar findings were noted in the analysis at the leaflet level. Results of sensitivity analyses of the primary end point in the intention-to-treat population and with a wide range of possible scenarios for missing CT data were also similar to those of the primary analysis (Figure S3 in the Data Supplement). Consistent results were obtained in the per-protocol analysis and detailed information on all available CT data analyses are reported in Table S10. The incidences of hypoattenuated thickening (possible thrombus) within sinus of Valsalva (12.8% vs. 22.0%, respectively) and at aortic valve complex dimension (37.3% vs. 48.6%, respectively) were also lower in the edoxaban group than in the DAPT group.

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In the intention-to-treat analysis, new cerebral lesions on serial MRI scans were found in 26 of 104 patients (25.0%) who were randomly assigned to the edoxaban group, as compared with 22 of 109 patients (20.2%) who were randomly assigned to the DAPT group (difference, 4.8 percentage points; 95% CI, −6.4 to 16.0) (**Table 3** and **Figure 2**). The median new lesion number was not different between the edoxaban group and the DAPT group (1, interquartile range [IQR], 1 to 2 vs. 1; IQR, 1 to 3, respectively). The median total new lesion volume was also not significantly different between the edoxaban vs. DAPT group (36.6; IQR, 13.7 to 145.0 mm^3 vs. 43.9; IQR, 23.5 to 83.5 mm^3, respectively). Consistent results were obtained in the per-protocol analysis and all available MRI data analyses are reported in Table S11 in the Data Supplement.

In the intention-to-treat population, the percentages of patients with worsening of serial neurological testing were similar between the edoxaban group and the DAPT group (the NIHSS: 5.0% [5/100] vs. 3.7% [4/108], respectively; difference, 1.3 percentage points; 95% CI, −4.3 to 6.9, and modified Rankin Scale: 2.0% [2/100] vs. 0.9% [1/108], respectively; difference, 1.1 percentage points; 95% CI, −4.1 to 19.7) (**Table 3** and **Figure 2**). The proportion of patients with worsening of neurocognitive function were also similar (the Montreal Cognitive Assessment: 30.0% [30/100] vs. 22.2% [24/108], respectively; difference, 7.8 percentage points; 95% CI, −4.2 to 19.7). Uniform findings were observed in the per-protocol analysis and all available information on neurological and neurocognitive function analyses are reported in Table S12 in the Data Supplement.

Clinical Events and Echocardiographic Findings

At 6 months, the incidences of efficacy outcomes (death, myocardial infarction, stroke, or systematic thromboembolic event) were each less than 3%, and were not different between the edoxaban group and the DAPT group (**Table 4**). Only 4 patients had a clinically overt

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ischemic stroke (2 patients in the edoxaban group and 2 patients in the DAPT group). The incidence of any or major bleeding events was also not different between the two groups.

There were no significant differences in various echocardiographic parameters between two randomized treatment groups at baseline, immediate post-TAVR, and 6-month follow-up (Table S13 in the Data Supplement). Also, there was no significant between-group difference in the rate of hemodynamic structural valve deterioration according to the randomized treatment group and the presence or absence of leaflet thrombosis (Table S14 in the Data Supplement).

Association of Leaflet Thrombosis with Cerebral Thromboembolism and Neurological and Neurocognitive Dysfunction

We assessed the association of subclinical leaflet thrombosis or reduced leaflet motion with the risks of cerebral thromboembolism, a decline of neurological or neurocognitive function, and relevant clinical outcomes (Table S15 in the Data Supplement). There were no significant differences in the rates of new cerebral lesions on MRI, a decline of neurological or neurocognitive function, and adverse clinical events between patients who did have leaflet thrombosis or reduced leaflet motion of grade 3 or higher and those without these phenomena. Also, there was no correlation between the number of leaflet thrombosis and the number of new cerebral lesions (**Figure 3**) or serial changes of neurological or neurocognitive function (**Figure 4**). There were also no significant differences in the rates of new cerebral lesions and a decline of neurological and neurocognitive function, according to the presence or absence of any hypoattenuated thickening at aortic valve complex, subvalvular, supravalvular, or sinus of Valsalva area (Figure S4 in the Data Supplement).

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Discussion

The ADAPT-TAVR trial compared the potential effect of edoxaban with DAPT for the prevention of leaflet thrombosis and the accompanying risks of cerebral thromboembolism and neurological or neurocognitive dysfunction by scientifically valid evaluations in patients without an indication for anticoagulation after TAVR. The main findings were as follows: (1) although the use of edoxaban reduced the incidence of primary end point of leaflet thrombosis at 6 months by 8.5 percentage points (risk ratio of 0.53), as compared with DAPT, the difference was not statistically significant, (2) the effect on reduction of leaflet thrombosis was not associated with a reduction of new cerebral lesions on MRI and a new development of neurological or neurocognitive dysfunction, and (3) we did not find any association of subclinical leaflet thrombosis with an increased risk of cerebral thromboembolism and neurological end points.

Previous observational studies suggested that the incidence of subclinical leaflet thrombosis was not uncommon (ranged from 7% to 38%) and this imaging phenomenon could be associated with an increased risk of stroke or transient ischemic attack.[8-10,12,13] These studies also suggested that OAC use could reduce leaflet thrombosis, which was associated with numerically lower rates of cerebrovascular events compared with single or dual antiplatelet therapy. However, most of prior studies might be hampered by inherent limitations of observational study, the different time points of CT evaluations, the lack of a causal relationship of leaflet thrombosis with cerebral thromboembolic events, and the heterogeneity of different antithrombotic agents, dosages, and combinations. In this clinical context, our ADAPT trial adds new clinical evidence on the effect of a specific NOAC of edoxaban for preventing leaflet thrombosis and the accompanying risks of cerebral thromboembolism and neurological/neurocognitive dysfunction as well as to provide

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scientific verification of the causal relationship between subclinical leaflet thrombosis and consequent cerebral adverse ischemic events.

Until recently, several RCTs have tested that NOAC-based strategy might be more effective than conventional antithrombotic strategies for the prevention of leaflet thrombosis and thromboembolic events in patients with or without OAC indication after TAVR.[15,18,19,30] Although most of trials showed that the incidence of leaflet thrombosis and reduced leaflet motion was significantly lower with NOAC, this effect did not translate into an improvement in clinical efficacy outcomes and it was significantly associated with an increased risk of major bleeding.[15,18,19] Our ADAPT-TAVR trial also showed discordant or dissociative findings between a reduction of leaflet thrombosis and the risks of cerebral thromboembolism and neurological endpoints. Therefore, it should be recognized that subclinical leaflet thrombosis has not been proven to affect the clinical outcomes among TAVR patients and this subclinical imaging phenomenon may not dictate the antithrombotic therapy (for prevention or treatment) after TAVR. Finally, on the basis of such cumulative evidence of recent trials including ADAPT-TAVR,[14-16,18] a decision-making for optimal antithrombotic therapy after TAVR should be considered in patient-centered outcomes while preserving a favorable overall clinical benefit-risk balance; thus, single antiplatelet therapy should be the standard of care for patients without an indication of chronic OAC.[20,21]

Since possible subclinical leaflet thrombosis by four-dimensional CT was reported in the investigational device exemption study and registry studies,[8] the Food and Drug Administration (FDA) has been closely monitoring this signal and its potential effect on the safety, effectiveness, and benefit–risk profile of bioprosthetic aortic valves.[38] Until recently, it has not yet been determined whether this phenomenon is clinically meaningful with a possible association of cerebral thromboembolism and valve dysfunction or just represents a subclinical advanced-imaging phenomenon. To confirm this causal association, ADAPT-

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TAVR trial conducted systematic serial evaluations of cardiac CT, brain MRI, and neurological or neurocognitive assessment, which provide insight into the temporal relationship and mechanisms underlying the potential detrimental effect of subclinical leaflet thrombosis on cerebral embolic events. Finally, our study did not show any association of the presence or extent of subclinical leaflet thrombosis with a risk of cerebral thromboembolism and neurological or neurocognitive dysfunction. From the clinical viewpoint, the absence of evidence of temporally related adverse clinical sequelae of imaging-detected leaflet thrombosis and reduced leaflet motion may not support the routine imaging screening tests for the detection of subclinical leaflet thrombosis as well as imaging-guided antithrombotic strategy in cases without hemodynamic or clinical significance.

Other clinical trials using NOACs for preventing leaflet thrombosis and thromboembolic events have noted higher bleeding rates compared with antiplatelet therapy or conventional OAC.[15,19] Recently, ENVISAGE-TAVI AF trial showed that edoxaban was associated with a higher risk of major bleeding (due mainly to more major gastrointestinal bleeding) than vitamin K antagonists, in which 46.4% of the trial population met any of the criteria for adjustment of the edoxaban dose and received reduced doses.[19] By contrast, given substantial inter-racial difference in demographic and clinical characteristics in TAVR patients,[39] approximately 61% of the randomized cohort in our trial received reduced dose of edoxaban and this may result in underestimation of bleeding risk if a similar strategy is applied in Western patients.

Several limitations of the trial should be considered. First, ADAPT-TAVR was an open-label trial, which was potentially subject to reporting and ascertainment bias. However, all CT and MRI images were independently measured in a blinded fashion at an imaging core laboratory, and the neurological and clinical outcomes were prespecified with the use of standardized definitions and adjudicated by an independent blinded clinical-events committee.

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Second, the ADAPT-TAVR trial has adopted surrogate imaging outcomes as the primary and key secondary end points. Therefore, its limited sample size was too small to allow for a sufficient correlation of imaging findings with adverse clinical events. Also, our trial was underpowered to detect any meaningful differences in clinical efficacy and safety outcomes. Third, hypoattenuated leaflet thickening that we observed could be associated with subclinical leaflet thrombosis. However, our study is limited by the absence of pathological confirmation. Fourth, since appearance or resolution of leaflet thrombosis have been reported to be dynamic processes[11,12] and follow-up period of our trial is relatively short, the long-term effect of leaflet thrombosis or different antithrombotic strategies on bioprosthetic valve durability is still unknown. Finally, we excluded patients with an established indication for OAC, which might be at least one-third of the TAVR population. Thus, our findings cannot be directly extrapolated to this population.

In conclusion, in patients without an established indication for long-term anticoagulation after successful TAVR, there was a trend in favor of the edoxaban group than the DAPT group in the incidence of subclinical leaflet thrombosis on CT scans, which was not statistically significant. The effect on reduction of leaflet thrombosis was not associated with a reduction of new cerebral lesions and a new development of neurological or neurocognitive dysfunction. Also, there was no association between subclinical leaflet thrombosis and temporally related changes of new cerebral thromboembolic lesions and neurological end points. However, the study had insufficient statistical power to allow for a conclusive interpretation, hence further research is needed in this area.

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Authors Contributions

conception and design — DW Park, SJ Park; *analysis and interpretation of data* — DW Park, SC Yun, SJ Park; *drafting of the manuscript* — DW Park, JM Ahn, DY Kang, SC Yun, SJ Park; *critical revision of the manuscript for important intellectual content* — DW Par, JM Ahn, DY Kang, KW Kim, HJ Koo, DH Yang, SC Jung, BJ Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, SC Yun, SA Lee, EH Ko, HB Han, DH Kim, JW Kang, JH Lee, SJ Park; *final approval of the manuscript* — DW Par, JM Ahn, DY Kang, KW Kim, HJ Koo, DH Yang, SC Jung, BJ Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, SC Yun, SA Lee, EH Ko, HB Han, DH Kim, JW Kang, JH Lee, SJ Park; *statistical expertise* — SC Yun; *obtaining of* research f*unding* — DW Park, SJ Park; *administrative, technical, or logistic support* — DW Par, JM Ahn, DY Kang, KW Kim, HJ Koo, DH Yang, SC Jung, BJ Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, SC Yun, SA Lee, EH Ko, HB Han, DH Kim, JW Kang, JH Lee, SJ Park; *acquisition of data* — DW Par, JM Ahn, DY Kang, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, EH Ko, SJ Park.

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Disclosures

DWP reports grants from Daiichi-Sankyo, grants from ChongKunDang Pharm, grants from Daewoong Pharm, personal fees from Edwards, grants and personal fees from Abott Vascular, personal fees from Medtronic, outside the submitted work. SJP reports grants and personal fees from Abott Vascular, grants from Daiichi-Sankyo, grants from ChongKunDang Pharm, grants from Daewoong Pharm, grants and personal fees from Edwards, outside the submitted work. All other authors declare no competing interests.

Supplemental Materials

Expanded Methods

Data Supplement Tables S1–S15

Data Supplement Figures S1–S4

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Table 1. Baseline Clinical Characteristics of the Patents in the Intention-to-Treat Population*

Characteristic	Edoxaban Group (N = 111)	DAPT Group (N = 118)	P Value
Age — yr	80.2±5.2	80±5.3	0.78
Male sex — no. (%)	49 (44.1)	47 (39.8)	0.51
Body weight ≤60kg — no. (%)	55 (49.6)	63 (53.4)	0.56
Body-mass index†	24.8±3.8	24.8±4.3	0.99
Body-surface area — kg/m^2	1.60±0.17	1.59±0.16	0.51
STS risk score‡			
Mean	3.1±2.1	3.5±2.7	0.74
Category — no. (%)			0.20
Low (<4)	86 (77.5)	86 (72.9)	
Intermediate (4 to 8)	23 (21.6)	26 (22.0)	
High (>8)	1 (0.9)	6 (5.1)	
EuroSCORE II value§	2.3±3.5	2.4±2.1	0.32
NYHA class III or IV — no. (%)	30 (27.0)	31 (26.3)	0.90
Diabetes mellitus — no. (%)	35 (31.5)	36 (30.5)	0.87
Hypertension — no. (%)	81 (73.0)	84 (71.2)	0.76
Hyperlipidemia — no. (%)	81 (73.0)	92 (78.0)	0.38
Current smoker — no. (%)	7 (6.3)	7 (5.9)	0.91
Congestive heart failure — no. (%)	17 (15.3)	12 (10.2)	0.24
Coronary artery disease — no. (%)¶	32 (28.8)	34 (28.8)	0.99
Prior myocardial infarction — no. (%)	1 (0.9)	2 (1.7)	>0.99
Prior PCI — no. (%)	18 (16.2)	14 (11.9)	0.34
Prior CABG — no. (%)	2 (1.8)	3 (2.5)	>0.99
Prior cerebrovascular disease — no. (%)	6 (5.4)	11 (9.3)	0.26
Carotid disease — no. (%)	6 (5.4)	5 (4.2)	0.68
Peripheral arterial disease — no. (%)	7 (6.3)	11 (9.3)	0.40
Chronic lung disease — no. (%)	25 (22.5)	31 (26.3)	0.51
Serum Creatinine — mg/dl	0.94±0.29	0.94±0.29	0.86
Creatinine clearance by Cockcroft–Gault formula — ml/min	61.0±21.5	59.2±18.7	0.50
Creatinine clearance ≤50 ml/min — no. (%)	38 (34.2)	47 (39.8)	0.38

* Plus–minus values are means ± SD. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, DAPT dual antiplatelet therapy, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage. A score of greater than 8% indicates high risk, 4 to 8% intermediate risk, and less than 4% low risk.

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§ Scores on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II range from 0 to 100, with higher scores indicating a greater risk of death within 30 days after the procedure.
¶ Coronary artery disease is defined as previous myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.

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Table 2. Baseline Procedural and Echocardiographic Characteristics of the Patents in the Intention-to-Treat Population*

Characteristic	Edoxaban Group (N = 111)	DAPT Group (N = 118)	P Value
Procedural characteristics			
Pre-TAVR balloon valvuloplasty — no. (%)	40 (36.0)	41 (34.8)	0.84
Valve type — no. (%)			0.61
Balloon-expandable	101 (91.0)	105 (89.0)	
Self-expandable	10 (9.0)	13 (11.0)	
Specific valve type			0.68
Sapien 3	100 (90.1)	104 (88.1)	
Evolut R	5 (4.5)	7 (5.0)	
CoreValve	0 (0.0)	1 (0.8)	
Evolut PRO	3 (2.7)	5 (4)	
Acurate Neo	3 (2.7)	1 (0.8)	
Valve size			0.59
20 mm	4 (3.6)	6 (5.1)	
23 mm	42 (37.8)	39 (33.1)	
25 mm	1 (0.9)	0 (0.0)	
26 mm	46 (41.4)	57 (48.3)	
29 mm	18 (16.2)	14 (11.9)	
31 mm	0 (0.0)	1 (0.8)	
34 mm	0 (0.0)	1 (0.8)	
Valve-in-valve — no. (%)	0 (0.0)	4 (3.4)	0.12
Transfemoral approach — no. (%)	110 (99.1)	117 (99.2)	>0.99
Type of anesthesia — no. (%)			0.68
General	27 (24.3)	26 (22.0)	
Monitored care	84 (75.7)	92 (78.0)	
Post-TAVR permanent pacemaker — no. (%)	13 (11.7)	13 (11.0)	0.87
Post-TAVR echocardiographic characteristics			
Aortic valve area — cm^2	1.7±0.4	1.6±0.4	0.13
Mean aortic valve gradient — mm Hg	13.4±5.1	14.3±5.4	0.17
Left ventricular ejection fraction (%)	64.4±10.0	64.2±9.5	0.86
Paravalvular aortic regurgitation — no. (%)			>0.99
None or mild	105 / 108 (97.2)	112 / 115 (97.3)	
Moderate or severe	3 / 108 (2.8)	3 / 115 (2.7)	

* Plus–minus values are means ± SD. Percentages may not total 100 because of rounding. DAPT dual antiplatelet therapy, and TAVR transcatheter aortic-valve replacement.

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Table 3. CT and MRI Imaging Endpoints and Neurological Endpoints in the Intention-to-Treat Population*

Outcomes	Edoxaban Group	DAPT Group	Risk Difference (95% CI)	Risk Ratio (95% CI)	P Value
	No. / total no. (%)		Percentage Points		
Four-dimensional CT end points					
Hypoattenuated leaflet thickening†					
Patient level					
At least one thickened leaflet	10/102 (9.8)	20/109 (18.4)	-8.54 (-17.82 to 0.73)	0.53 (0.26 to 1.09)	0.08
At least two thickened leaflets	4/102 (3.9)	6/109 (5.5)	-1.58 (-7.29 to 4.12)	0.71 (0.21 to 2.45)	0.75
At least three thickened leaflets	0/102 (0.0)	2/109 (1.8)	-1.83 (-4.49 to 0.82)	NA	0.50
Leaflet level					
Leaflets with any degree of leaflet thickening	14/306 (4.6)	28/327 (8.6)	-3.99 (-8.77 to -0.8)	0.53 (0.25 to 1.15)	0.11
Leaflets with leaflet thickening >50% involvement	6/306 (2.0)	8/327 (2.5)	-0.49 (-3.06 to 2.09)	0.80 (0.24 to 2.70)	0.72
Reduced leaflet motion‡					
Patient level					
At least one thickened leaflet with grade ≥1 reduced motion	10/102 (9.8)	20/109 (18.4)	-8.54 (-17.82 to 0.73)	0.53 (0.26 to 1.09)	0.08
At least one thickened leaflet with grade ≥2 reduced motion	6/102 (5.9)	14/109 (12.8)	-6.96 (-14.73 to 0.80)	0.46 (0.18 to 1.15)	0.08
At least one thickened leaflet with grade ≥3 reduced motion	3/102 (2.9)	8/109 (7.3)	-4.40 (-10.29 to 1.49)	0.40 (0.11 to 1.47)	0.15
Leaflet level					
Leaflets with grade ≥1 reduced motion	14/306 (4.6)	28/327 (8.6)	-3.99 (-8.77 to 0.8)	0.53 (0.25 to 1.15)	0.11
Leaflets with grade ≥2 reduced motion	9/306 (2.9)	16/327 (4.9)	-1.95 (-5.44 to 1.54)	0.60 (0.23 to 1.58)	0.30
Leaflets with grade ≥3 reduced motion	5/306 (1.6)	8/327 (2.5)	-0.81 (-3.31 to 1.69)	0.67 (0.18 to 2.55)	0.55
Brain MRI end points§					
Presence of new lesions — no./total.no (%)	26/104 (25.0)	22/109 (20.2)	4.82 (-6.41 to 16.04)	1.24 (0.75 to 2.04)	0.40
Presence of a single new lesion — no./total.no (%)	19/104 (18.3)	15/109 (13.8)	4.51 (-5.34 to 14.36)	1.33 (0.71 to 2.47)	0.37

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Presence of multiple new lesions — no./total.no (%)	7/104 (6.7)	7/109 (6.4)	0.31 (-6.35 to 6.97)	1.05 (0.38 to 2.89)	0.93
Number of total new lesions, median (IQR)	1 (1 to 2)	1 (1 to 3)	0 (0 to 0)¶	NA	0.85
Total new lesion volume (mm^3), median (IQR)	36.6 (13.7 to 145.0)	43.9 (23.5 to 83.5)	1.9 (-42.6 to 21.9)¶	NA	0.88
Neurological and neurocognitive function‖					
Neurologic assessment					
Paired NIHSS assessment — no./total.no (%)	100/111 (90.0)	108/118 (91.5)	-1.44 (-8.93 to 6.06)	0.98 (0.91 to 1.07)	0.71
Worsening, any — no./total.no (%)	5/100 (5.0)	4/108 (3.7)	1.30 (-4.27 to 6.86)	1.35 (0.37 to 0.49)	0.74
Worsening with new cerebral lesions — no./total.no (%)	2/100 (2.0)	1/108 (0.9)	1.07 (-2.21 to 4.36)	2.16 (0.20 to 23.46)	0.61
Paired modified Rankin Scale — no./total.no (%)	100/111 (90.0)	108/118 (91.5)	-1.44 (-8.93 to 6.06)	0.98 (0.91 to 1.07)	0.71
Worsening, any — no./total.no (%)	2/100 (2.0)	1/108 (0.93)	1.07 (-4.14 to 19.70)	2.16 (0.20 to 23.46)	0.69
Worsening with new cerebral lesions — no./total.no (%)	1/100 (1.0)	0/108 (0.0)	-1.0 (-1.12 to 3.12)	NA	0.48
Cognitive assessment					
Paired Montreal Cognitive Assessment — no./total.no (%)	100/111 (90.0)	108/118 (91.5)	-1.44 (-8.93 to 6.06)	0.98 (0.91 to 1.07)	0.71
Worsening, any — no./total.no (%)	30/100 (30.0)	24/108 (22.2)	7.78 (-4.15 to 19.70)	1.35 (0.85 to 2.14)	0.20
Worsening with new cerebral lesions — no./total.no (%)	7/100 (7.0)	4/108 (3.7)	3.30 (-2.84 to 9.44)	1.89 (0.57 to 6.26)	0.29

* Analyses were not corrected for multiple comparisons. The relative risk was described by the risk ratio (for edoxaban compared to DAPT) and corresponding 95% confidence interval (CIs), which was calculated by the logistic regression analysis. BARC denotes Bleeding Academic Research Consortium, DAPT dual antiplatelet therapy, NA not applicable, NIHSS the National Institute of Health Stroke Scale, and VARC Valve Academic Research Consortium

† Hypoattenuated leaflet thickening was defined as visually identifiable increased leaflet thickness on contrast-enhanced multiplanar reformats, carefully aligned with the long and short axes of the valve prosthesis.[29] The extent of leaflet thickening can be graded on a subjective 4-tier grading scale along the curvilinear orientation of the leaflet: no thickening, <25% involvement of leaflet, 25% to 50% involvement of leaflet, 51% to 75% involvement of leaflet, and >75% involvement of leaflet.[29,30] For leaflet-level analyses, the logistic regression with generalized estimating equations was used to account for the natural correlation with measurements and the clustering effect on the same patient.

‡ Leaflet motion was assigned a grade from 0 to 4: grade 0 denotes unrestricted, grade 1 minimally restricted (with restriction limited to the base), grade 2 mildly restricted (involving more than the base but <50% of the leaflet), grade 3 moderately restricted (involving >50% but <75% of the leaflet), and grade 4 largely immobile.[29,30] For leaflet-level analyses, the logistic regression with generalized estimating equations was used to account for the natural correlation with measurements and the clustering effect on the same patient.

§ The presence and amount of new cerebral thromboembolic lesions was determined on the basis of FLAIR (fluid attenuated inversion recovery) images on brain MRI.

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¶ Differences calculated as independent samples Hodges-Lehmann median difference estimates.
‖ Neurological and neurocognitive function data are reported as number (%) of patients with a worsening of NIHSS, modified Rankin scale, Montreal Cognitive Assessment scores at 6-month follow-up compared to baseline. 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.[34,35]

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Table 4. Clinical Outcomes in the Intention-to-Treat Population*

Outcomes	Edoxaban Group	DAPT Group	Risk Difference (95% CI)	Risk Ratio (95% CI)	P Value
	No. / total no. (%)		Percentage Points		
Clinical end points at 6 months†					
Death	3/111 (2.7)	2/118 (1.7)	1.01 (-2.80 to 4.82)	1.48 (0.25 to 8.75)	0.68
From cardiovascular causes	3	0			
From noncardiovascular causes	0	2			
From valve-related mortality	1	0			
Myocardial infarction	1/111 (0.9)	3/118 (2.5)	-1.64 (-4.98 to 1.70)	0.45 (0.05 to 3.83)	0.62
Stroke	2/111 (1.8)	2/118 (1.7)	0.11 (-3.29 to 3.51)	1.05 (0.15 to 7.45)	>0.99
Ischemic	2	2			
Hemorrhagic	0	0			
Disabling stroke	1	0			
Nondisabling stroke	1	2			
Systemic thromboembolic event	2/111 (1.8)	0/118 (0.0)	1.80 (-0.79 to 4.39)	NA	0.23
Bleeding events					
VARC-2 criteria	13/111 (11.7)	15/118 (12.7)	-1.00 (-9.48 to 7.48)	0.93 (0.44 to 1.96)	0.82
Minor bleeding	7	11			
Major bleeding	6	3			
Life-threatening or disabling bleeding/BARC type 5	0	1			
VARC-3 criteria	13/111 (11.7)	15/118 (12.7)	-1.00 (-9.48 to 7.48)	0.93 (0.44 to 1.96)	0.82
Type 1	10	13			
Type 2	3	1			

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Type 3	0	0			
Type 4	0	1			
Rehospitalization according to VARC-3 criteria	17/111 (15.3)	14/118 (11.9)	3.45 (-5.43 to 12.34)	1.29 (0.67 to 2.49)	0.45
Procedure-related or valve-related hospitalization	3	2			
Other cardiovascular hospitalization	4	3			
Non-cardiovascular hospitalization	10	9			

* Analyses were not corrected for multiple comparisons. BARC denotes Bleeding Academic Research Consortium, DAPT dual antiplatelet therapy, NA not applicable, and VARC Valve Academic Research Consortium

† Clinical end points were adjudicated according to the VARC-2[24] and VARC-3[36] definitions. Event rates (%) were estimated with the use of a Kaplan–Meier survival analysis of data from the intention-to-treat population and the relative risk was described by the hazard ratio (for edoxaban compared to DAPT) and corresponding 95% confidence interval (CIs), which was calculated by the Cox proportional hazards models.

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Figure Legends

Figure 1. Screening, Randomization, Treatment, and Follow-up

CT denotes computed tomography, and MRI, magnetic resonance imaging.

* Because some patients had multiple exclusion criteria, the sum of number in each exclusion category may exceed the total number of patients with exclusion criteria.

Figure 2. CT Imaging End Points, MRI Imaging End points, and Neurological or Neurocognitive Function End Points in the Intention-To-Treat Population

Panel A shows the percentages of patients who had leaflet thrombosis and at least one prosthetic valve leaflet with reduced motion of grade 3 or higher in the edoxaban group and the dual antiplatelet group. The degree of hypoattenuated leaflet thickening and the severity of reduced leaflet motion were classified according to the standard definition.[29,30] Panel B shows the percentages of patients who had new cerebral lesions, the median new lesion number, and the median total new lesion volume on serial MRI scans in the edoxaban group and the dual antiplatelet group. The presence and amount of new cerebral thromboembolic lesions was determined on the basis of FLAIR images on the brain MRI. Panel C shows the percentages of patients with worsening of serial neurological testing (the NIHSS and the modified Rankin Scale) and those with worsening of neurocognitive function (the Montreal cognitive assessment). 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.[34,35]

DAPT denotes dual antiplatelet therapy, FLAIR fluid attenuated inversion recovery, and NIHSS the National Institute of Health Stroke Scale.

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Figure 3. Correlation of Severity of HALT with Extent of New Lesions on Brain MRI

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

Figure 4. Correlation of Severity of HALT with Decline of Neurological and Neurocognitive Function

HALT indicates hypoattenuated leaflet thickening, MOCA Montreal Cognitive Assessment, mRS modified Rankin Scale, and NIHSS the National Institute of Health Stroke Scale.

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769 Patients were assessed for eligibility

534 Were not eligible
- 127 Did meet inclusion and exclusion criteria, but refused to participate in the trial
- 407 Had exclusion criteria*
  - 129 Had clinical indications for long-term anticoagulation
  - 105 Had absolute indications for dual-antiplatelet therapy
  - 51 Had severe renal insufficiency
  - 97 Had bleeding risks or systemic conditions
  - 69 Had other exclusion criteria

235 Patients underwent randomization

115 Were assigned to receive edoxaban group

120 Were assigned to receive dual-antiplatelet therapy group

4 Withdrew written informed consent during the index hospitalization

2 Withdrew written informed consent during the index hospitalization

111 Were eligible for analysis (the intention-to-treat population)

118 Were eligible for analysis (the intention-to-treat population)

3 Died at <180 days
1 Were withdrawn by Physician
0 Were lost to follow-up

2 Died at <180 days
1 Were withdrawn by Physician
0 Were lost to follow-up

107 Completed 6-mo follow-up
- 104 (97.2%) Had cardiac CT scan
- 104 (97.2%) Had brain MRI
- 102 (95.3%) Had neurological and neurocognitive test

115 Completed 6-mo follow-up
- 109 (94.8%) Had cardiac CT scan
- 110 (95.7%) Had brain MRI
- 110 (95.7%) Had neurological and neurocognitive test

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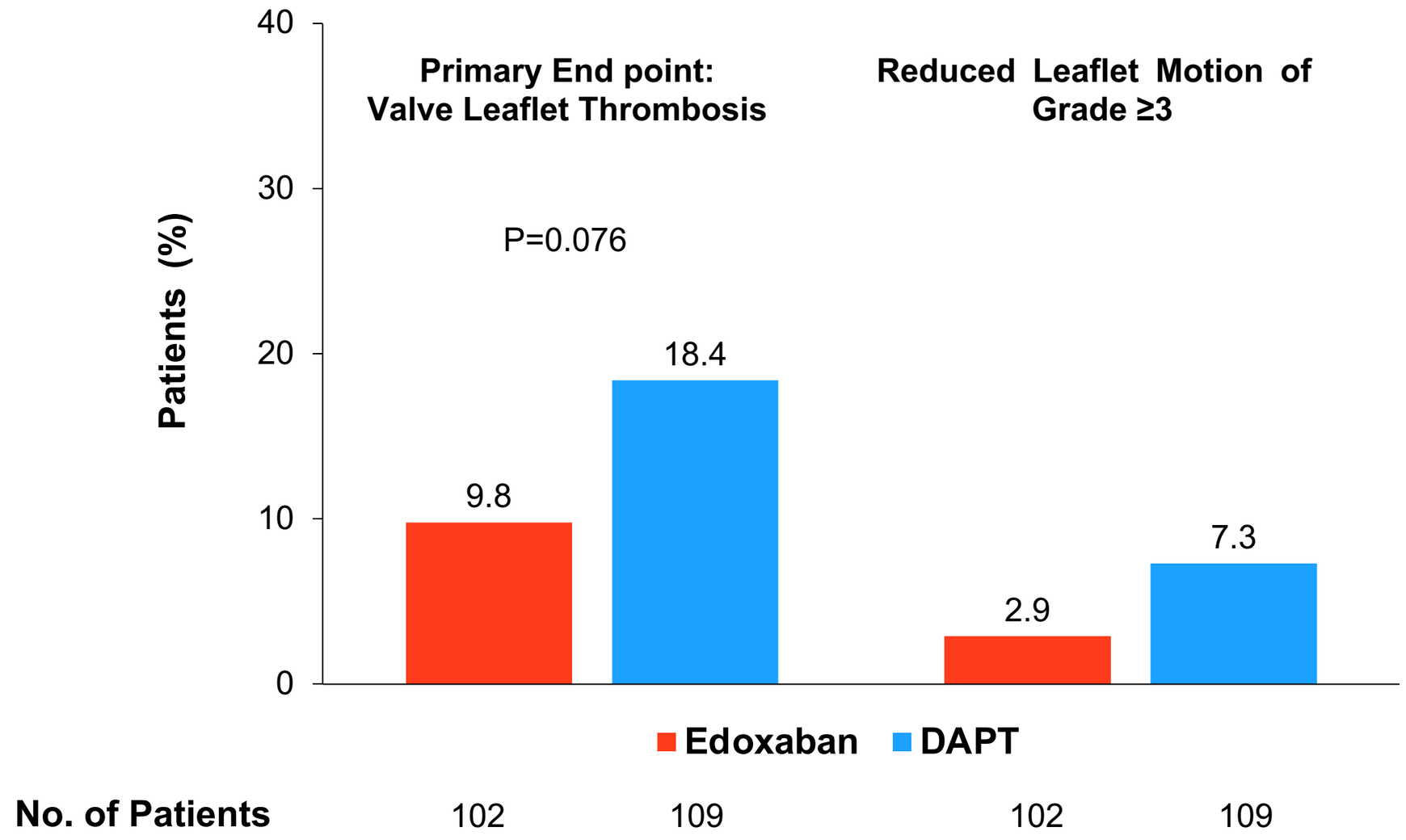
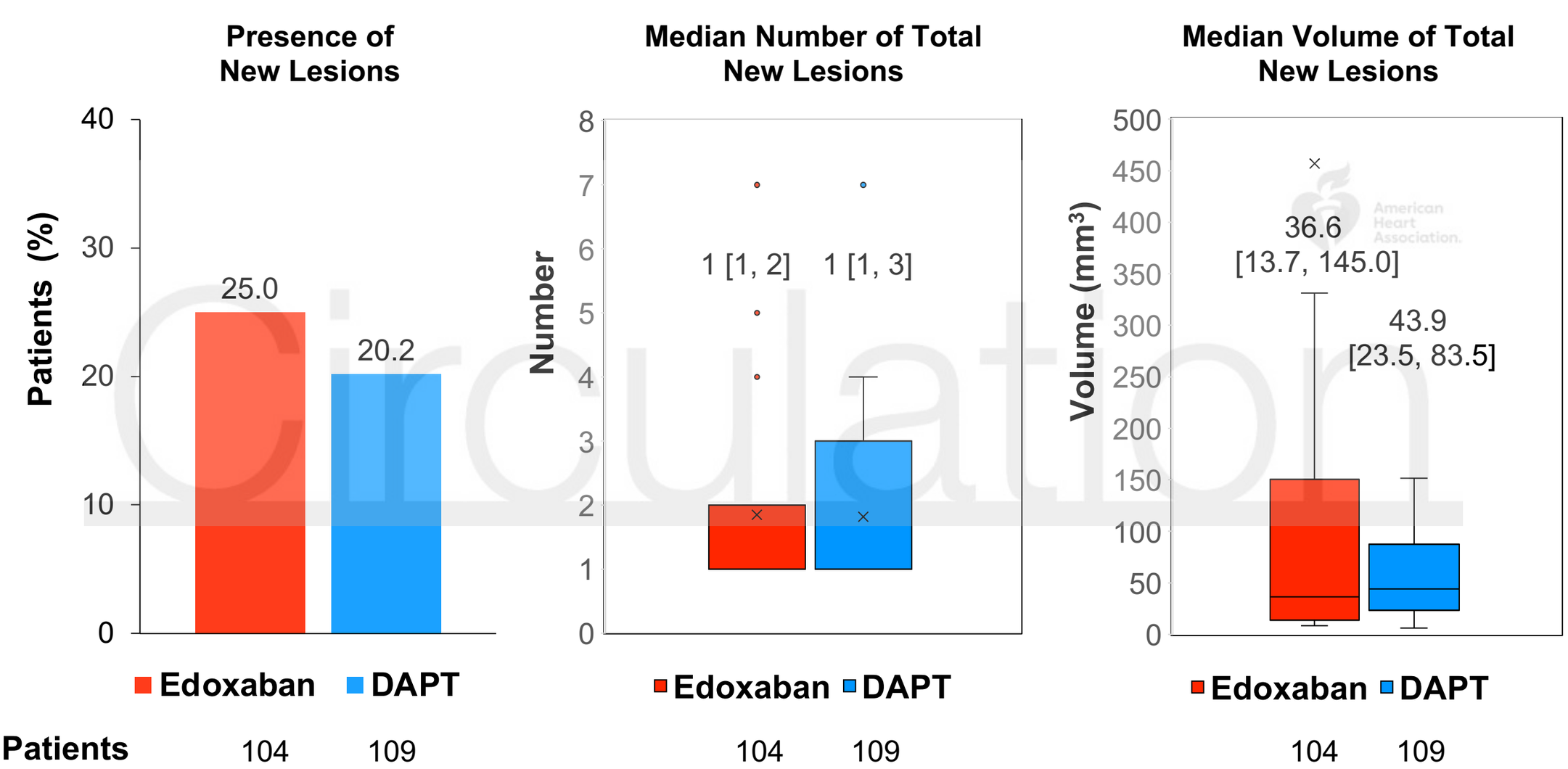
A CT End Points, Intention-to-Treat Analysis



B MRI End Points, Intention-to-Treat Analysis



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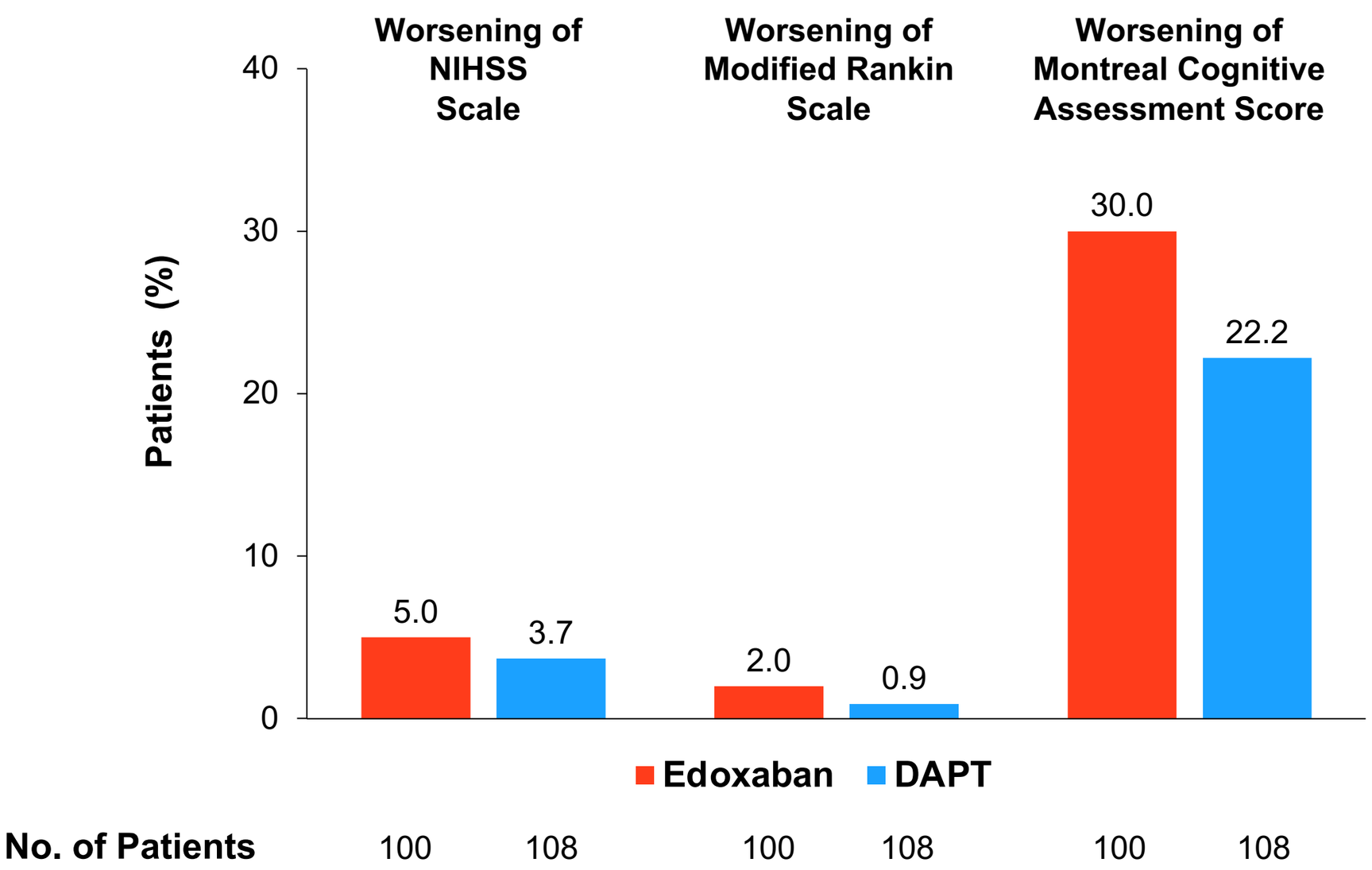
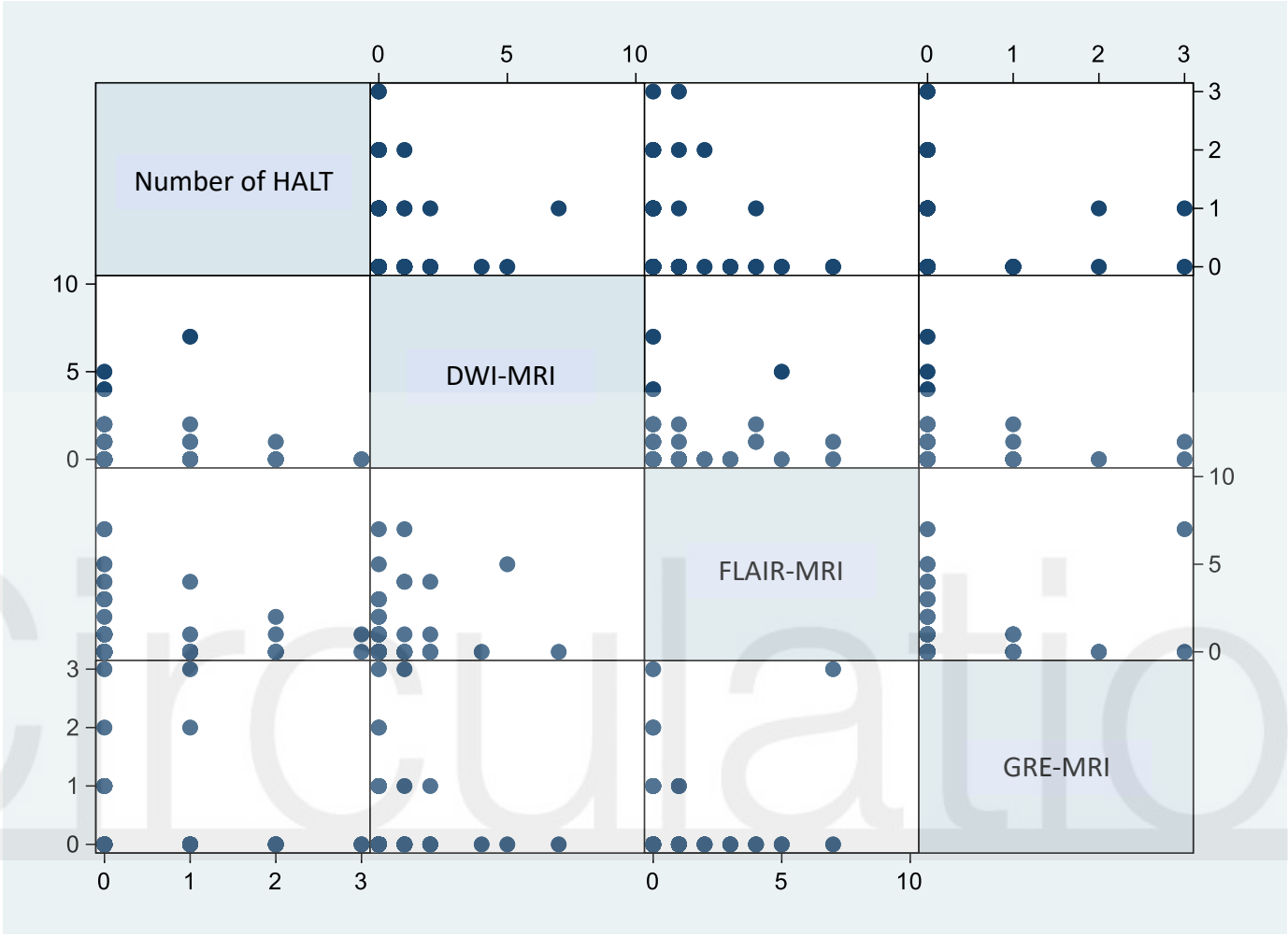
C Neurological or Neurocognitive Function End Points, Intention-to-Treat Analysis





		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

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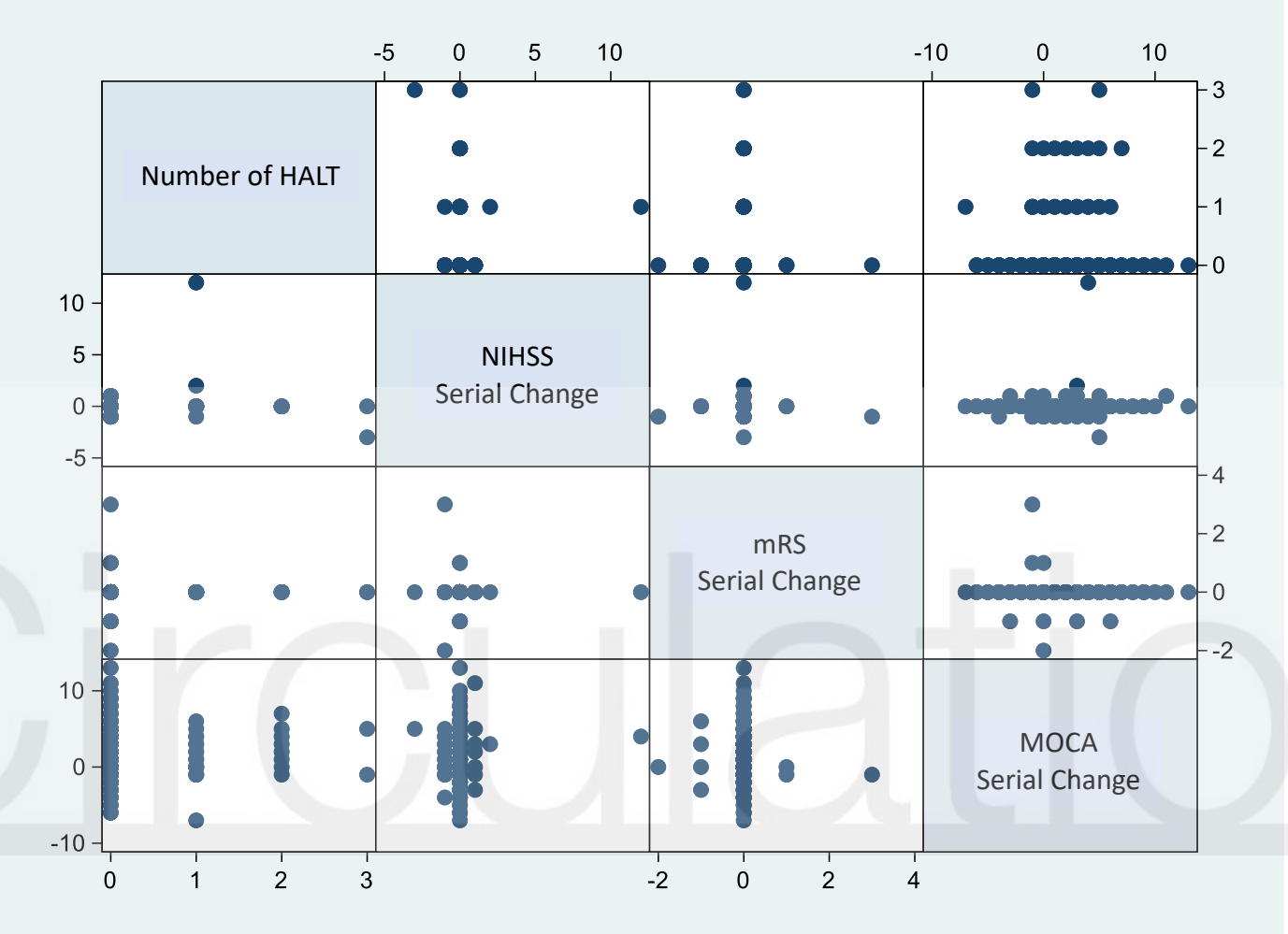

		Serial Change of NIHSS Score	Serial Change of mRS Score	Serial Change of MOCA Score
Number of HALT Per-Patient	N	204	204	204
	Spearman Rho	0.01	0.02	0.03
	P-Value	0.94	0.77	0.68

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