BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042587
Article Type:	Protocol
Date Submitted by the Author:	12-Jul-2020
Complete List of Authors:	Park, Hanbit; Asan Medical Center, Cardiology Kang, Do-Yoon; Asan Medical Center Ahn, Jung-Min; Asan Medical Center Kim, Kyung Won; Asan Medical Center WONG, Anthony; Queen Mary Hospital, Medicine LAM, Simon; Queen Mary Hospital, Medicine Yin, Wei-Hsian ; Cheng Hsin General Hospital Wei, Jeng; Cheng Hsin General Hospital Lee, Yung-Tsai; National Taiwan University Hospital Kao, Hsien-Li; National Taiwan University Hospital Lin, Mao-Shin; National Taiwan University Hospital Ko, Tsung-Yu; National Taiwan University Hospital Kim, Won-Jang; CHA Bundang Medical Center Kang, Se Hun; CHA Bundang Medical Center Ko, Euihong; Asan Medical Center Kim, Dae-Hee; Asan Medical Center Koo, Hyun Jung; Asan Medical Center Yang, Dong Hyun; Asan Medical Center Kang, Joon-Won; Asan Medical Center Jung, Seung Chai; Asan Medical Center Lee, Jae-Hong; Asan Medical Center Yun, Sung-Cheol; Asan Medical Center, Department of Biostatistics Park, Seung-Jung; Asan Medical Center Park, Duk-Woo; Asan Medical Center,
Keywords:	Valvular heart disease < CARDIOLOGY, Thromboembolism < CARDIOLOGY, Adult cardiology < CARDIOLOGY

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Rationale and design of the ADAPT-TAVR trial: a randomized comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement

Short title: Rationale and Design of ADAP-TAVR Trial

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

[1]Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Asan Image Metrics, Clinical Trial Center, Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea; [3]Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong; [4]Heart Center, Cheng Hsin General Hospital, Taipei, Taiwan; [5]Division of cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [6]Division of cardiology, Department of Internal Medicine, Hsin-Chu Branch, National Taiwan University Hospital, Hsin-Chu, Taiwan; [7]Department of Cardiology, CHA Bundang Medical Center, Seongnam, Korea; [8]Department of Radiology Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Asan Image Metrics, Asan Medical Center; [9]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [10]Division of Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Two first authors (Drs HB Park and DY Kang) contributed equally to this manuscript.

Total word count (main text): 4,291

Address for correspondence:

Dr. Duk-Woo Park

Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine,

388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea

Phone: +82-2-3010-3995; Fax: +82-2-487-5918; E-mail: dwpark@amc.seoul.kr

Abstract

Introduction: Optimal antithrombotic strategy following transcatheter aortic valve replacement (TAVR) is still unknown. We hypothesized that the direct factor Xa inhibitor edoxaban can potentially prevent subclinical leaflet thrombosis and cerebral embolization compared with conventional dual antiplatelet therapy (DAPT) in patients undergoing TAVR.

Methods and analysis: The ADAPT-TAVR trial is an international, multicenter, randomized, open-label, superiority trial comparing edoxaban-based strategy and DAPT strategy in patients without an indication for oral anticoagulation who underwent successful TAVR (ClinicalTrials.gov NCT03284827). A total of 220 patients are randomized (1:1 ratio), 1 to 7 days after successful TAVR, to receive either edoxaban (60 mg daily or 30 mg daily if patients had dose-reduction criteria) or DAPT using aspirin (100 mg daily) plus clopidogrel (75 mg daily) for 6 months. The primary study endpoint was an incidence of leaflet thrombosis on four-dimensional, volume-rendered cardiac computed tomography imaging at 6 months post-TAVR. The key secondary endpoints were the number of new lesions and new lesion volume on brain diffusion-weighted magnetic resonance imaging and the changes in neurological and neurocognitive function assessment between immediate post-TAVR and 6 months of study drug administration. Detailed clinical information on thromboembolic and bleeding events was also assessed.

Ethics and dissemination: The trial is being conducted in five major centers in three countries (South Korea, Hong Kong, and Taiwan), in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. The final study protocol and informed consent have been reviewed and approved by the ethics committee/institutional review boards and corresponding health authorities. The ADAPT-TAVR study will provide the evidence that

edoxaban-based strategy potentially reduces the risk of leaflet thrombosis and cerebral embolization compared with DAPT-based strategy in patients without an established indication for oral anticoagulation after successful TAVR.

Trial Registration numbers: ClinicalTrials.gov Identifier: NCT03284827

Keywords: anticoagulation; antiplatelet agents; cerebrovascular events; transcatheter aortic valve replacement; thrombosis

Strengths and limitations of this study

- The ADAPT-TAVR trial is a multinational, multicenter, prospective, randomized, open-label, superiority trial that compared the efficacy of a strategy of factor Xa inhibitor, edoxaban, and dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel in patients without an indication for chronic oral anticoagulants who underwent successful transcatheter aortic valve replacement (TAVR).
- The primary study endpoint is an incidence of leaflet thrombosis on four-dimensional, volume-rendered cardiac computed tomography at 6 months post-TAVR. The key secondary endpoints for assessment of cerebral embolization (documented with brain magnetic resonance imaging) and potentially associated neurological and neurocognitive function.
- The ADAPT-TAVR trial is planned to complete the 3-year enrollment period for the prespecified 220 subjects from the five participating centers.
- This trial will provide clinical evidence of the efficacy and safety of edoxaban-based anticoagulation strategy compared with DAPT strategy after successful TAVR with respect to leaflet thrombosis and associated cerebral embolization and neurocognitive function.
- This trial has adopted the surrogate imaging outcome as the primary and key secondary endpoints. Therefore, our trial was undertowed to detect any clinically relevant differences in efficacy and safety outcomes between two treatment strategies.

Introduction

Transcatheter aortic valve replacement (TAVR) has been positioned as a valuable treatment option for patients with symptomatic severe aortic stenosis (AS) who are at inoperable, high, or intermediate risk for conventional surgical aortic valve replacement (SAVR), on the basis of clinical evidence from multiple randomized clinical trials (RCTs).[1-7] Recently, TAVR has become a valid alternative to surgery in patients at low surgical risk.[8 9] Despite of such proven efficacy and safety of TAVR in patients with severe AS at diverse surgical risks, thromboembolic complications (stroke, systemic embolism, valve thrombosis, and venous thromboembolism) have been observed after TAVR. In addition, observational data reported that subclinical leaflet thrombosis and reduced leaflet motion of bioprosthetic aortic valves have been documented by four-dimensional computed tomography (CT),[10] and the presence of subclinical leaflet thrombosis may be associated with increased rates of transient ischemic attacks (TIAs) and composite of strokes or TIAs.[11] Despite excellent outcomes after TAVR with new-generation valves, prevention and treatment of subclinical leaflet thrombosis might offer a potential opportunity for further improvement in valve hemodynamics and long-term clinical outcomes.[12 13]

In routine clinical practice, optimal post-TAVR antithrombotic management is still controversial and a practice variation of antithrombotic regimens is substantially high without a strong evidence base for their recommendations.[14 15] Empirically, dual antiplatelet therapy (DAPT) of aspirin plus clopidogrel has been used for at least 6 months after TAVR,[1-9] and thus current practice guidelines recommend the use of DAPT early after TAVR,[16 17] although the recommendation is based mainly on expert consensus. After several studies reported that valve thrombosis developed in patients who received antiplatelet therapy alone but not in those who received anticoagulation therapy,[10 11] updated guidelines recommend that oral

anticoagulation (OAC) with vitamin K antagonist (VKA) may be a reasonable approach for at least 3 months after TAVR in patients at low risk of bleeding (Class IIb).[18] However, clinical evidence to support this recommendation are still lacking (level of evidence B-NR: data were derived from one or more non-randomized trials or meta-analysis of such studies).

Edoxaban once daily is a well-tolerated inhibitor of factor Xa that has demonstrated a superior safety with non-inferior efficacy compared with warfarin for prevention of stroke or systemic embolization or recurrent symptomatic venous thromboembolism in different clinical settings.[19 20] We hypothesize that edoxaban, a non-VKA oral anticoagulant (NOAC), potentially reduces the risk of subclinical leaflet thrombosis and cerebral embolization compared with conventional DAPT-based strategy in patients undergoing TAVR. The Anticoagulation versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization after Transcatheter Aortic Valve Replacement (ADAPT-TAVR) trial is a multicenter, randomized, open-label, active-treatment, controlled trial to compare the efficacy of NOAC with edoxaban and DAPT for prevention of leaflet thrombosis documented by high-resolution four-dimensional cardiac CT and cerebral embolization documented by brain magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), in patients who underwent successful TAVR procedure.

Methods

Trial Design and Objectives

The ADAPT-TAVR trial (ClinicalTrials.gov unique identifier: NCT03284827) is a multinational, multicenter, prospective, randomized, open-label, superiority trial that compared the efficacy of a strategy of anticoagulation with edoxaban and DAPT with aspirin

plus clopidogrel in patients without an indication for chronic OAC who underwent successful TAVR for symptomatic severe AS (**Figure1**). The trial is being conducted in five major centers in three countries (South Korea, Hong Kong, and Taiwan), in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. The final study protocol and informed consent have been reviewed and approved by the ethics committee/institutional review boards and corresponding health authorities of all participating sites.

The primary objective of ADAPT-TAVR is to demonstrate the superiority of a NOAC strategy with edoxaban (experimental arm) as compared to the current standard of care DAPT (control arm) in the prevention of leaflet thrombosis (documented by four-dimensional cardiac CT). The main secondary objective is to compare the two antithrombotic strategies with regard to the potential risk of cerebral embolization (documented with brain MRI) and the changes in neurological and neurocognitive function. Other objectives for clinical assessment are to investigate the time from randomization to the first occurrence of efficacy and safety clinical outcomes including death, myocardial infarction (MI), stroke or TIAs, or bleeding events.

Study Population

Patients aged ≥18 years with severe symptomatic AS who underwent successful TAVR (either native valve or valve-in-valve procedure with any approved/marketed device) were eligible for participation in the trial. A successful TAVR procedure was defined according the Valve Academic Research Consortium-2 (VARC-2) criteria as follows[21]: (1) correct position of a single prosthetic heart valve into the proper anatomical location; (2) intended performance of the prosthetic heart valve with presence of all 3 of the following conditions

post-TAVR (a. mean aortic valve gradient < 20 mmHg, b. peak transvalvular velocity <3.0 m/s, and c. no moderate or severe aortic valve regurgitation); and (3) absence of periprocedural major complications (any type of stroke, life-threatening bleeding, acute coronary artery obstruction requiring intervention, major vascular complication requiring intervention, unresolved acute valve thrombosis, or any requirement of a repeat procedure). The key exclusion criteria were any established indication for long-term anticoagulation (e.g., concomitant atrial fibrillation) and any absolute indication for DAPT (e.g., recent acute coronary syndromes or recent or concomitant percutaneous coronary intervention) at the time of screening. Detailed information on inclusion and exclusion criteria is listed in **Table 1**. The study protocol was approved by the internal review board at each participating center. Each patient received oral and written information and voluntarily signed a declaration of informed consent.

Randomization and Treatment Groups

Eligible patients who met the study inclusion criteria and met none of the exclusion criteria are randomly (1:1 ratio) assigned to receive either (1) NOAC with edoxaban (60 mg once daily or 30 mg once daily with dose-reduction criteria) or (2) DAPT with aspirin (100 mg once daily) plus clopidogrel (75 mg once daily) for 6 months after successful TAVR. Central randomization is performed with the use of an Interactive Web Response System and stratified by type of TAVR valve (balloon-expandable or self-expandable) and participating center with block sizes of 4 or 6. Randomization is performed after successful TAVR when the patient has stabilized (1 to 7 days after index TAVR procedure) and before hospital discharge. Duration of study drug treatment and subject follow-up will be six months.

In patients assigned to the edoxaban group (experimental arm), the investigational

product is open-labeled edoxaban 60 mg or 30 mg tablet taken orally once daily for 6 months. Edoxaban is started at the time of randomization and irrespective of the pre-existing antithrombotic regimen. Edoxaban 30 mg tablet orally once daily is given for randomized patients with the following dose-reduction criteria: (1) body weight ≤60 kg, (2) moderate to severe renal impairment (defined as a calculated creatinine clearance [Cockroft-Gault formula] between 15 and 50 mL/min), or (3) concomitant P-glycoprotein inhibitors (cyclosporine, dronedarone, erythromycin, or ketoconazole). Patients assigned to the DAPT group (control arm) will receive aspirin 100 mg and clopidogrel 75 mg once daily. Naïve patients will initially be loaded with aspirin (200 mg) and clopidogrel (300 mg) according to local practice. After 6 months of study medications in both groups, patients will continue to use low-dose aspirin (100 mg) alone indefinitely.

In case new-onset atrial fibrillation (NOAF) occurs after randomization, given that the potential thromboembolic risk of NOAF after TAVR could be substantial,[22] full oral anticoagulation will be implemented with maintenance of the original treatment assignment. In the edoxaban group, the assigned treatment remains as the protocol. In the DAPT group, use of VKA or NOAC was allowed at the treating physician's discretion. Because this protocol adaptation is an integral part of the study protocol regimens, endpoints occurring under post-NOAF study treatments are retained in the primary study analysis (intention-to-treat principle).

Study Endpoints and Follow-Up

The primary and secondary endpoints of the ADAP-TAVR trial are listed in **Table 2**. The primary study endpoint is an incidence of leaflet thrombosis on four-dimensional, volume-rendered cardiac CT at 6 months post-TAVR. The key secondary endpoints for assessment of

cerebral embolization and potentially associated neurologic function are the number of new lesions and new lesion volume on brain MRI scans at 6 months relative to immediate post-TAVR and the changes of neurological and neurocognitive function assessment between post-TAVR and 6 months of study drug administration. Other secondary endpoints for assessment of ischemic and bleeding complications includes death (all-cause, cardiovascular or non-cardiovascular), MI, stroke (disabling or non-disabling) or TIAs, or bleeding events (life-threatening or disabling, major bleeding, or minor). Serial echocardiographic parameters (the mean transaortic valve pressure gradient and velocity time integral ratio) are also assessed at baseline, post-procedure, and 6-month follow-up. All clinical endpoints are adjudicated according to VARC-2 criteria[23] and the NeuroARC definitions.[24] Detailed definitions of clinical endpoints are summarized in **Appendix Table 1**. The investigators in each center should complete case report forms for all events and provide sufficient information for central review. All components of the primary and secondary endpoints are blindly adjudicated by an independent Clinical Event Committee (CEC).

After completion of the TAVR procedure, all study patients are monitored per institutional standard of care. The study subjects are followed at 1 month (±2 weeks), 3 months (±2 weeks) and 6 months (±1 month). Data collected during all follow-up visits also include clinical symptoms, such as dyspnea (New York Heart Association [NYHA] class), angina status (Canadian Cardiovascular Society [CCS] class), and any related clinical events including rehospitalization or unintended hospital visits. For compliance check, the investigator will keep track of investigational drug dispensed and/or administered to the subjects and it is for compliance calculation.

To confirm the occurrence of leaflet thrombosis of bioprosthetic valves, all subjects undergo four-dimensional, volume-rendered cardiac CT at 6 months (± 1 month) after the

TAVR. To evaluate the clinical effect of antithrombotic strategy and cerebral embolization by leaflet thrombosis, we perform brain MRI at 1–7 days after TAVR and 6 months after initiating study drug administration. Transthoracic echocardiography is performed at baseline, 1–7 days after immediate post-TAVR, 1 month and 6 months after initiating study drug administration.

Acquisition and Archive of Cardiac CT and Brain MRI

A central imaging core lab (Asan Image Metrics; www.aim-aicro.com) is in charge of image acquisition and archive. The image core lab establishes the standardized acquisition protocols of cardiac CT and brain MRI imaging through gathering all CT/MRI machines and acquisition protocols of cardiac CT and brain MRI in each participating site. All sites should be qualified for their imaging machines and capability to perform the standardized acquisition protocol by the imaging core lab. All CT/MRI images acquired from each site are anonymized and electronically transferred to a central server (AiCRO system; Asan Image Metrics, Seoul, Korea) for image archiving images and blinded independent image review.[25]

All cardiac CT scans are performed with a dedicated four-dimensional, volume-rendered CT acquisition protocol with intravenous contrast administration as mandated at each participating site. The archived CT images are reconstructed to generate the sagittal and coronal images (two- and three-chamber views) of the aortic root and volume-rendered En-face view images of the device. Detailed information on acquisition and reconstruction methodology of cardiac CT is summarized in **Appendix Table 2**. The standardized cardiac CT protocols comply with international expert consensus reports.[26-28]

All brain MRI scans are obtained including DWI, fluid attenuated inversion recovery

(FLAIR), and T2-star gradient (GRE) sequences which are the important sequences for image endpoint. Other sequences such as localizer, T1-weighted image, T2-weighted image, or MR angiography, can be allowed to use institutional protocols. The MRI sequences are in compliance with the 2018 American Heart Association/American Stroke Association guidelines and several prior large-scale clinical trials.[29 30] Detailed information on acquisition protocols of brain MRI is summarized in **Appendix Table 3**.

Core Laboratory Image Analyses

An independent image review committee (IIRC) is organized by the central imaging core lab (Asan Image Metrics) for the analysis of CT and MRI data from the ADAPT-TAVR trial in a blinded fashion. Two cardiac radiologists analyze cardiac CT images, and two neuroradiologists evaluate brain MRI images in an independent and blinded manner. In cases of discrepancy, the adjudication was made by open discussion and consensus between radiologists and investigators. The adjudication variables are presence of valvular thrombosis and occurrence of new DWI-positive lesions, FLAIR-positive lesions, or GRE-positive lesions. The adjudication rates between readers and the rationale of adjudication should be recorded. The detailed items on the image analysis of cardiac CT and brain MR images are summarized in **Appendix Table 4 and 5**, respectively.

The cardiac CT images are analyzed for presence of valve thrombosis, presence of leaflet thickening, leaflet motion based on opening limitation, stent eccentricity (%), and calcification volume.[31] Presence of valve thrombosis is checked when there are hypoattenuated abnormal lesion(s) attached at the 1 or more THV leaflet, subvalvular area, supravalvular area, or left ventricular outflow tract (LVOT). The location of valve thrombosis should be determined from one or more of the followings: leaflet, subvalcular area,

supravalvular area, and LVOT. Leaflet motion is assessed based on grade of opening limitation on a volume-rendered En-face image of the aortic-valve prosthesis at maximal leaflet opening. Leaflet motion is categorized as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion) in at least one valve leaflet. We classified patients with mild or no restriction of leaflet motion as having normal leaflet motion. The stent eccentricity is defined as 1-(minimum stent diameter / maximum stent diameter) at the level of inflow, valvular area and outflow tract. If there is calcification, readers should measure the volume of calcification at the annulus or sinus or Valsalva level. Calcification can be measured using the threshold of CT numbers greater than 850 Hounsfield unit.

The brain MRI images are analyzed for occurrence, number, and volume of new lesions on the 6-month DWI/FLAIR and GRE images compared to baseline MRI (immediate post-TAVR), respectively. The new lesions on DWI or FLAIR may reflect ischemic lesions due to thromboembolic events but also might be attributed to other nonspecific lesions. The new lesions on GRE are regarded as new hemorrhagic lesions. The occurrence of new lesion is defined when a lesion is seen only on 6-month MRI and not on baseline MRI. The number of new lesions is counted based on new separate lesions on 6-month MRI. The volume is calculated as the sum of volumes of all separate new lesions on 6-month brain MRI.

Neurological and Neurocognitive Function Assessment

All study subjects will undergo detailed neurologic and neurocognitive function assessment at post-TAVR(1–7 days after TAVR and before discharge) and 6 months of study drug administration. Neurologic assessments include standard clinical scales (the National Institutes of Health Stroke Scale [NIHSS] and the modified Rankin Scale [mRS]), and

cognitive assessments include the Montreal Cognitive Assessment (MoCA). Dedicated attending staff will be identified at each center to perform the neurological and cognitive assessments; these subjects are NIHSS certified, trained in administration of the mRS and cognitive tests, and are blinded to brain MRI findings and treatment groups.

Sample Size Estimation and Statistical Analyses

Sample size was estimated to simultaneously meet the primary endpoint of the incidence of leaflet thrombosis on cardiac CT and meet the key secondary endpoint of the total new lesion number on brain MRI. Based on the results from RESOLVE and SAVORY registry,[11] we assumed an incidence of subclinical leaflet thrombosis of 15% in the DAPT group and of 3% in the NOAC (edoxaban) group. Enrollment of 192 patients (96 patients in each arm) would provide the study with a statistical power of 80% to detect this difference with a two-sided significance level of 0.05. Assuming 10% attrition rate of CT follow-up loss at 6 months, a total of 220 patients (110 patients per each arm) are finally planned. In similar setting of post-TAVR status, there are no benchmark MRI data at immediate post-TAVR and follow-up on which to base control arm assumption. Among the two landmark trials (CLEAN-TAVI[32] and SENTINEL[33]) involving brain MRI at post-TAVR, the median number of new lesions in the entire brain (with reference of the control arm) at immediate post-TAVR was 16 (interquartile range [IQR], 10–24) in the CLEAN-TAVI trial and 5 (IQR, 2–10) in the SENTINEL trial. It is expected that the absolute new lesion number between 6 months and immediate post-TAVR would be lower than the lesions number between immediate post-TAVR and baseline (pre-TAVR). Thus, we assumed that the mean number of new lesions in the entire brain between 6 months and immediate post-TAVR would be approximately 10. Our hypothesis for key secondary endpoint of brain DW-MRI is that the use of edoxaban

would provide a 30% reduction in the number of positive DW MRI–perfused brain lesions following TAVR at 6 months relative to post-TAVR in the entire brain compared with the use of DAPT. Given a standard deviation (SD) of 7, which was based on the value of the CLEAN-TAVI trial, for the measure and assuming a dropout rate of 20%, a total of 218 patients (109 patients per each group) was estimated for the study to have a power of 80% at a two-sided α-level of 0.05. To meet the predefined estimation of this key secondary endpoint, the final sample size was estimated as a total of 220 patients (110 patients per each arm).

The primary and secondary endpoint analyses are conducted on the full analysis set of all randomized patients according to the intention-to-treat principle. The Fisher exact test is used to compare categorical variables. Continuous variables, presented as mean±SD or medians with IQRs as appropriate, are compared with the use of the Student's t-test or the Mann-Whitney U test. The key secondary endpoint, consisting of new median lesion number differences between the two randomized arms, was compared using the Wilcoxon rank sum test. A z-score for each neurocognitive function domain is calculated on the basis of normative mean ± SD for each neurocognitive test. Change scores are calculated by subtracting immediate-post-TAVR scores from the 6-month post-TAVR scores. Cumulative event curves are generated by means of the Kaplan-Meier method. The 95% confidence interval of the hazard ratio will be presented using a Cox model for survival analysis. Trial data are held by the trial coordination center at the Asan Medical Center. Analyses will be performed by independent statistical analysts who was unaware of randomized drug. All P-values are two-sided, and values <0.05 are considered statistically significant.

Study Committees

The executive committee (EC) is composed of principal investigators of clinical sites and persons who will organize this study. The EC will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. National lead investigators and academic experts are part of the steering committee and responsible for the protocol implementation and study recruitment. An independent data safety monitoring board (DSMB) has the responsibility of monitoring safety during the trial: the members of the DSMB will not be among those who directly control the sponsor of this study and periodically review the safety data according to a dedicated charter and make recommendations based on safety analyses, protocol deviation, imaging failures, and 6-month follow-up reports. The CEC consists of interventional and non-interventional cardiologists who are also independent and blinded. The CEC is charged of the development of specific criteria used for the categorization of clinical events in the study, which are based on the protocol and will adjudicate all suspected study endpoints as detailed in the specific charter.

Patient and public involvement

For development of this study protocol, there was no direct patient or public involvement. However, we planned to disseminate the overall results of the study to the participants and the public, such as presenting primary results in the international scientific meeting and publicizing our research in medical news and various academic lectures.

Results and Trial Status

The ADAPT-TAVR trial is planned to complete the 3-year enrollment period for the

prespecified 220 subjects from the five participating centers. The first patient was enrolled on March 2018, and 180 patients have been enrolled until May 2020. Enrollment may be completed approximately at the late term of 2020, and primary results of the ADAPT-TAVR trial will be available by the middle or late term of 2021.

Discussion

The ADAPT-TAVR trial is a randomized controlled trial to define optimal antithrombotic strategy using direct acting factor Xa inhibitor after TAVR with regards to prevention of leaflet thrombosis and cerebral embolization. This trial will provide randomized evidences of the efficacy and safety of edoxaban-based anticoagulation strategy compared with DAPT strategy after successful TAVR without indication of chronic OAC.

Initially, safety concern has been raised after the initial report of cardiac CT findings in patients who had stroke after TAVR during an ongoing clinical trial.[10] Consecutively, observational registries also showed that subclinical leaflet thrombosis more frequently developed in bioprosthetic aortic valves, more commonly in TAVR (13%) than in SAVR (4%).[11] In this study, OAC (both VKA and NOACs) was more effective than DAPT in prevention or treatment of subclinical leaflet thrombosis (4% vs. 15%), and clinically subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes. Although there was limited evidence supporting the association of leaflet thrombosis and cerebral embolic events,[34] the Food and Drug Administration (FDA) has raised the safety concerns of TAVR and has been closely monitoring this signal.[35] The FDA also recommended that whether reduced leaflet motion was clinically meaningful for patients with TAVR, the loss of mobility of one or more leaflets detected by CT rendered the valve

structurally dysfunctional and demands additional investigation. After such safety concern has been raised in several studies,[10 11 36-39] updated guidelines suggest that OAC within at least 3 months is reasonable considering the possibility of leaflet thrombosis.[18] However, there still has been inadequate evidence to support these OAC recommendations in patients undergoing TAVR.

Until recently, the underlying mechanism of bioprosthetic valve thrombosis has not been clearly elucidated. The implanted TAVR valve adds a prothrombotic environment, which might be related to perturbations in blood flow (i.e., stagnant blood) and activation of various hemostatic factors within the neosinus,[12] and this condition may favor subclinical thrombosis and valve hemodynamic deterioration. Although it is still unknown whether post-TAVR produced-thrombi have a predominant platelet- or thrombin-related origin, thrombin plays a key role in the formation of thromboembolic events; the mechanisms of platelet activation and coagulation are highly interdependent, with thrombin playing a central role in both pathways.[40] Given that direct factor Xa inhibitors target specifically factor Xa and decrease the conversion of prothrombin to active thrombin, thereby diminishing fibrin formation, and reducing coagulation and platelet activation, and NOAC have shown superiority or non-inferiority versus VKA in preventing cardio-embolic events with a consistent reduction in bleeding events, it might be reasonable to consider a systemic anticoagulation strategy with NOAC regimen to prevent subclinical leaflet thrombosis and reduce the long-term thromboembolic risk after TAVR.

However, a systematic anticoagulation strategy after TAVR should be tested in RCTs. Recently, the primary results from the Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) showed that NOAC strategy with

rivaroxaban at a dose of 10 mg (with low-dose aspirin for the first 3 months) was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than antiplatelet-based strategy (low-dose aspirin with clopidogrel at a dose of 75 mg for the first 3 months) in patients without an established indication for anticoagulation after successful TAVR.[41] In an imaging substudy of GALILEO, a rivaroxaban-based antithrombotic strategy was more effective than an antiplatelet-based strategy in preventing subclinical leaflet motion abnormalities (2.1% vs. 10.9%).[42] However, these findings cannot recommend routine imaging for the detection of reduced leaflet motion or routine use of anticoagulation after TAVR with the aim of preventing leaflet motion abnormalities, given the unfavorable clinical outcomes with rivaroxaban in the main GALILEO trial. Regarding this important issue, an OAC strategy alone or NOAC strategy instead of VKA is actively being tested in several ongoing RCTs (ATLANTIS trial NCT02664649[43]; POPular-TAVI[44] NCT02247128, ENVISAGE-TAVI AF[45] NCT02943785 and AVATAR NCT02735902). The release of the primary results of such consecutive trial may provide compelling evidence to resolve the clinical unmet need for optimal antithrombotic strategy in the routine clinical practice of TAVR, which is rapidly expanding into low-risk patients. Additionally, the potential preventive role of anticoagulation with NOAC for preventing leaflet thrombosis and cerebral embolization after TAVR can be only objectively documented by cardiac CT and brain MRI, which was not yet confirmed by RCTs, and this evidence will be supported by the primary results of the ADAPT-TAVR trial.

Some limitations of this trial should be considered. First, bias in event ascertainment cannot be ruled out given the open-label trial design. Second, the ADAPT-TAVR trial has adopted the surrogate imaging outcome as the primary and key secondary endpoints. Therefore, our key findings based on imaging modalities may not fully support the clinical

rationale with regard to any effect or change in the treatment strategy (antithrombotic treatment switch). Third, our trial was undertowed to detect any clinically relevant differences in efficacy and safety outcomes between two treatment strategies. 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 such population.

Conclusion

The ADAPT-TAVR trial is an investigator-initiated, multinational, multicenter, open-label, randomized trial that compare the effectiveness of NOAC with edoxaban and DAPT with aspirin and clopidogrel in the prevention of subclinical leaflet thrombosis and potentially associated cerebral embolization. The ADAPT-TAVR trial will provide randomized evidence of the efficacy and safety of an edoxaban-based strategy compared with an antiplatelet-based regimen after successful TAVR in the absence of an established indication for OAC.

Acknowledgements We thank the staff of the ADAPT-TAVR trial, the other members of the cardiac catheterization laboratories and the heart-team at the participating centers, and the study coordinators for their efforts in collecting clinical data and ensuring the accuracy and completeness of the data.

Contributors *Study conception and design* — DW Park, H Park, DY Kang, JM Ahn, SJ Park; *drafting of the study protocol* — H Park, KW Kim, DW Park; *critical revision of the study protocol for important intellectual content* — H Park, DY Kang, JM Ahn, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, E Ko, DH Kim, HJ Koo, DH Yang, JW Kang, SC Jung, JH Lee, SC Yun, SJ Park, DW Park; *statistical expertise* — SC Yun; *obtaining of* research f*unding* — DW Park; *administrative, technical, or logistic support* — H Park, DY Kang, JM Ahn, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, E Ko, DH Kim, HJ Koo, DH Yang, JW Kang, SC Jung, JH Lee, SC Yun, SJ Park, DW Park; *acquisition of data* — H Park, DY Kang, JM Ahn, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, E Ko, DH Kim, HJ Koo, DH Yang, JW Kang, SC Jung, JH Lee, SC Yun, SJ Park, DW Park; All authors approved the final manuscript.

Funding The ADAPT-TAVR trial is partly funded by Daiichi Sankyo Inc. and CardioVascular Research Foundation (CVRF, Seoul, Korea). None of the study leadership accepted any compensation for their roles in this study, other than expenses. The principal investigators accept responsible for the design and conduct of this study, all study analyses, and the drafting and editing of all manuscripts.

Competing interests None declare.

Patient and public involvement For development of this study protocol, there was no direct

patient or public involvement. However, we planned to disseminate the overall results of the study to the participants and the public, such as presenting primary results in the international scientific meeting and publicizing our research in medical news and various academic lectures.

Patient consent for publication Not required

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Figure Legends

Figure 1. Study Flow Diagram

Successful TAVR as defined in the "study population and methods" section.

Abbreviations: ASA, aspirin; CT, computed tomography; DAPT, dual antiplatelet therapy; NOAC, non-vitamin K antagonist oral anticoagulant; TAVR, transcatheter aortic valve replacement

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
1. Patients aged ≥18 with symptomatic AS who underwent successful TAVR procedure* (either native valve or valve-in-valve with any approved/marketed device) * A successful TAVR is defined as device success according to the VARC-2 criteria[21]: (1) Correct positioning of a single prosthetic heart valve into the proper anatomical location (2) Intended performance of the prosthetic heart valve (no prosthesis- patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation (3) Absence of periprocedural complications (any type of stroke, life-threatening bleeding, acute coronary artery obstruction requiring intervention, major vascular complication requiring intervention, unresolved acute valve thrombosis, or any requirement of a repeat procedure) 2. The patient or guardian agrees to the study protocol and the schedule of clinical follow-up, and provides informed, written consent, as approved by the appropriate institutional review board/ethical Committee of the respective clinical site
Exclusion criteria
1. Any atrial fibrillation with an indication for chronic oral anticoagulation (OAC) 2. An ongoing indication for OAC or any other indication for continued treatment with any OAC 3. Any ongoing indication for DAPT (recent acute coronary syndrome or PCI within 12 months) 4. Planned coronary or vascular intervention or major surgery 5. The risk of bleeding increased due to the following reasons at the time of TAVR procedure: a. History of gastrointestinal ulcers within 1 month b. Malignant tumor with high risk of bleeding

c. Brain or spinal cord injury within 1 month

d. History of intracranial or intracerebral hemorrhage within 12 months

e. Esophageal varices

f. Arteriovenous malformations

g. Vascular aneurysms

h. Spinal or intracerebral vascular abnormalities

i. Active bleeding

j. Hemoglobin level <7.0% or platelet count ≤50,000 / mm^3

k. History of major surgery within 1 month

6. Clinically overt stroke within the last 3 months
7. Moderate and severe hepatic impairment, and any hepatic disease associated with coagulopathy
8. Severe renal impairment (creatinine clearance by Cockcroft-Gault equation<30 mL/min per 1.73 m^2), chronic dialysis, or post-TAVR unresolved acute kidney injury
9. Terminal illness with life expectancy <6 months
10. History of hypersensitivity to edoxaban, aspirin or clopidogrel
11. Severe hypertension
12. Prosthetic heart valve replacement for which anticoagulant therapy is essential
13. Moderate to severe mitral stenosis
14. Pulmonary embolism requiring thrombolysis or pulmonary embolectomy
15. Active participation in another drug or device investigational study, which was not completed in the primary endpoint follow-up period
16. Pregnancy test results are positive (all pregnant women should undergo urinary human chorionic gonadotropin (hCG) testing within 7 days prior to screening and / or randomization)

or during pregnancy or lactation

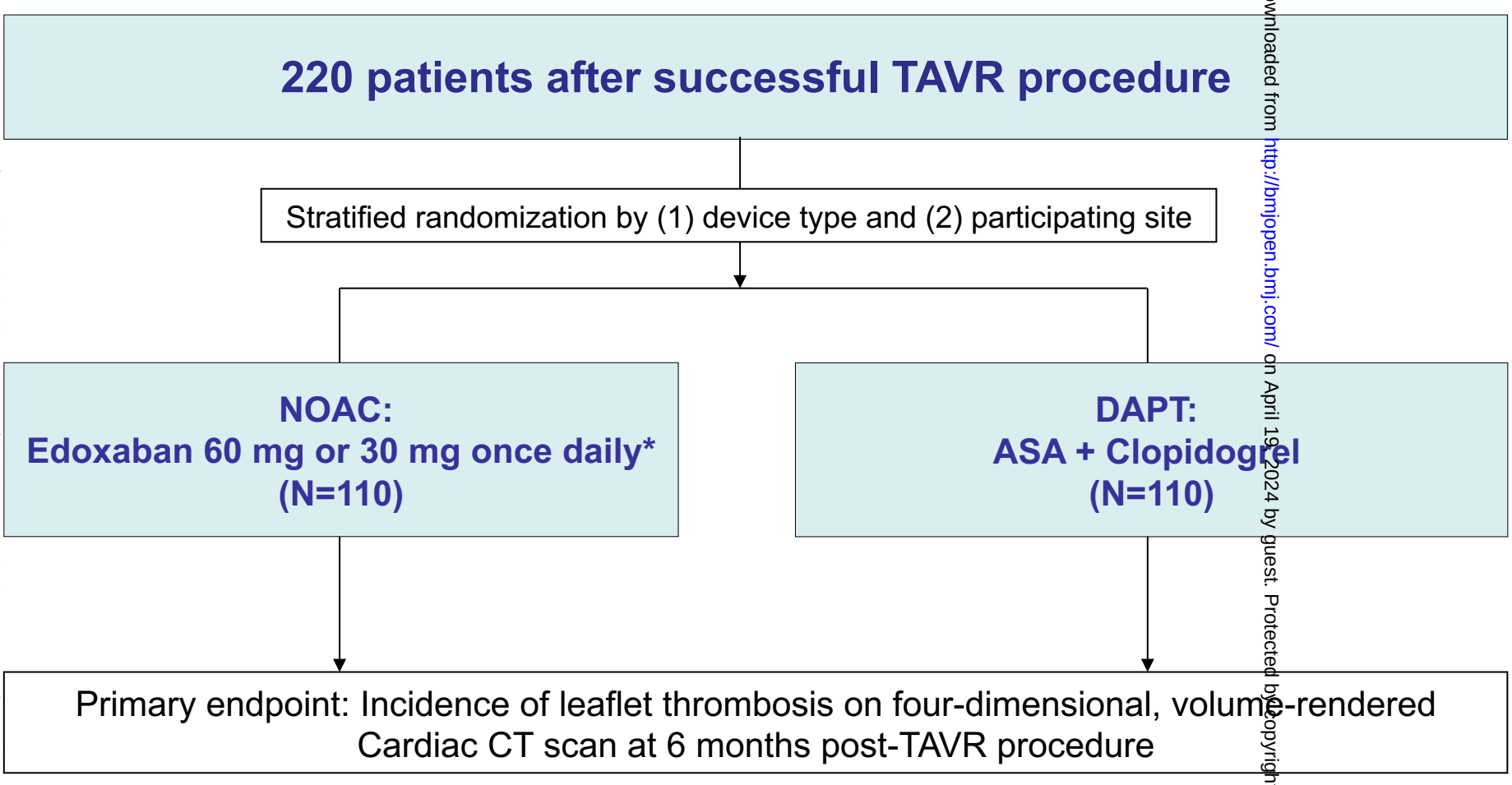
17. Genetic problem with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
18. Current or history of aspirin- or NSAIDs-induced asthma
19. Hemophilia
20. Use of methotrexate at doses of ≥15 mg per week
21. Unsuitable condition to undergo brain MRI and/or cardiac CT (e.g., tremor from Parkinson's disease). This is at the discretion of the investigators

Table 2. Primary and Secondary Endpoints

Primary Endpoint
Incidence of leaflet thrombosis on four-dimensional, volume-rendered cardiac CT imaging at 6 months post-TAVR procedure
Secondary Endpoints*
1. Number of new lesions on brain MRI scans at 6 months relative to immediate post-TAVR 2. New lesion volume on brain MRI 3. Neurological and neurocognitive function 4. Echocardiographic parameters (mean transaortic valve pressure gradient and velocity time integral ratio at baseline and 6-month follow-up) 5. Death (all-cause, cardiovascular, or non-cardiovascular mortality) 6. Myocardial infarction 7. Stroke (disabling or non-disabling) or transient ischemic attack 8. Bleeding event (life-threatening or disabling, major bleeding, or minor) *All clinical endpoints are adjudicated according to the VARC-2[21] and the NeuroARC[24] definitions

Anticoagulant versus ***D***ual ***A***ntiplatelet Therapy for ***P***reventing Leaflet ***T***hrombosis After ***T***ranscatheter ***A***ortic ***V***alve ***R***eplacement

ADAPT-TAVR Trial



*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).

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: H Park, DY Kang, JM Ahn, et al. "Rationale and design of the ADAPT-TAVR trial: a randomized comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement"

Appendix Table 1. Definitions of Clinical Endpoints.

All clinical endpoints are adjudicated according to current VARC-2[1] and the NeuroARC[2] definitions. Each of clinical endpoints is defined as follows:

Endpoint	Definition
Death	All-cause mortality was used rather than cardiac mortality to eliminate the need for possibly difficult adjudication of causes of death, especially given the relatively low mortality expected. In addition, the cause of death will be adjudicated as being due to cardiovascular causes or non-cardiovascular causes. Cardiovascular death includes any of the following criteria: • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause Non-cardiovascular death is defined as any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, or suicide)
MI	MI (non-procedural) is defined as any one of the following criteria: (1) detection of rise and/or fall of cardiac biomarkers (preferably troponin) with a least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following: a) symptoms of ischemia, b) ECG changes indicative of new

	ischemia (new ST-T changes or new LBBB), c) new pathological Q-waves in at least two contiguous leads, or d) imaging evidence of a new loss of viable myocardium or new wall motion abnormality, (2) sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation or new LBBB, and/ or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood (3) pathological findings of an acute myocardial infarction
Stroke and TIA	**Diagnostic criteria** • Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke: duration of a focal or global neurological deficit >24 h or <24 h if available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death • TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct Confirmation of the diagnosis by at least one of the following: • Neurologist or neurosurgical specialist • Neuroimaging procedure (CT or brain MRI), but stroke may be diagnosed on clinical grounds alone **Stroke classification** • Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue • Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

	• A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke definitions** • Disabling stroke: a modified Rankin Scale (mRS) score of ≥2 at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline • Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline
Bleeding events	Life-threatening or disabling bleeding is defined as any one of the following criteria: • Fatal bleeding (BARC type 5) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units* (BARC type 3b) Major bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery and does not meet criteria of life-threatening or disabling bleeding Minor bleeding (BARC type 2 or 3a, depending on the severity) • Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major

Appendix Table 2. Trial-Specific Standardized Cardiac CT Protocol

Items	Minimum requirements of acquisition protocols
CT scanners	GE Healthcare: 64 channel or above (e.g., Optima 660, Revolution HD/GSI, Revolution CT) Philips Healthcare: 64 channel or above (e.g., Ingenuity, iCT Elite, IQon Spectral CT) Siemens Healthineers: dual source or above (e.g., Somatom Definition AS, AS+, or Flash) Toshiba 320 or above (e.g., Aquilion ONE, Aquilion ONE Vision)
Minimum gantry rotation time (ms)	350 ms or below
Kernal	Manufacturer's recommendation
kVp, mAs, AEC	Manufacture's setting (site can utilize institutional protocols for kVp, mAs, and automatic exposure control).
ECG-gating	Imaging of the aortic root must use ECG-synchronization, using either two separate acquisitions (ECG-synchronized for the aortic root and non-gated for the aorta) or single ECG-synchronized acquisition of the entire volume
Scan coverage	Scan to include at least the aortic arch and whole heart (from the upper wall of aortic arch to lower cardiac border) in cranio-caudal direction
Patient position	The preferred subject position is supine with arms raised above the head and the heart centered within the gantry. Special attention should be paid to ensure proper positioning and firm contact of ECG leads to ensure a high R-peak amplitude and low baseline noise.
Image Reconstruction & Slice thickness	Iterative image reconstruction methods/algorithms are recommended according to manufacturers' setting and should meet the following minimum requirements: - Slice thickness should be ≤ 1.0 mm. - Recommendation for single source CT scanners (GE, Toshiba, Philips): 0.6 mm slices with 0.3 mm overlap and iterative reconstruction for evaluation at 5% intervals within the 0%-95% RR range - Recommendation of dual-source CT scanners (Siemens): 0.5 mm slices with 0.25 mm overlap with iterative reconstruction for evaluation at 10% intervals within the 0%-90% RR range

	- Recommended optimal timing: at lower heart rates (<65 bpm), the optimal timing is during late-diastole, while at higher heart rates (>65 to 70 bpm) the optimal timing is more frequently (but not always) during end-systole.
Spatial Resolution	≤0.5 × 0.5 mm in x–y plane and ≤1 mm in z-axis
Display FOV	Adjusted according to the heart size
Matrix	512 × 512
Contrast agent	Non-ionic CT contrast agents should be used.
Contrast Injection (Volume, Rate)	Injection volume: 50-120 cc per institutional protocols. Injection rate: 4-7 cc/s per institutional protocols. Scan timing determination: Bolus tracking (preferred) and test bolus methods should be used.
Others	Heart rate (HR) reduction with β-blockade is not performed.
* Note: The site can modify the abovementioned in the inevitable situation such as emergent patients' care or technical issues in the machines or scanning rooms. In these cases, the images can be used for clinical trials after quality check from Asan Image Metrics staffs.	

Appendix Table 3. Standardized Brain Protocols of DWI, GRE, and FLAIR

Items	Requirements		
	Axial DWI	**Axial GRE**	**Axial 2D FLAIR**
Tesla	1.5–3.0 Tesla		
Coil	Head coil or Neurovascular (NV) coil. The number of channels is 8 or above.		
Sequence	EPI[a]	T2* weighted GRE	TSE[b] and equivalent
FOV	190–250 mm	190–250 mm	190–250 mm
Matrix	128×128 or above	128×128 or above	256×256 or above
Resolution	2.0×2.0mm²	2.0×2.0mm²	2.0×2.0mm²
TR	2000 ms or above	400-1000 ms	6000 ms or above
TE	110 ms or below	15-32ms	100-140 ms
TI	Not available (NA)	NA	2200-2500 ms
Slice thickness	3.0–5.0 mm	3.0–5.0 mm	3.0–5.0 mm
Gap thickness	0–2.5 mm	0–2.5 mm	0–2.5 mm
Diffusion Option (B-value)	At least two b-values of 0 s/㎟ and 1000 s/㎟ should be included. The other b-values such as above 1000s/㎟ are optional).	NA	NA
Parallel Imaging	Recommend (up to 2X)	Recommend (up to 2X)	Recommend (up to 2X)

[a]In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.

[b]TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

Appendix Table 4. Cardiac CT Analysis Form

Valvular thrombosis □ Presence □ Absence			
	Location of thrombosis	**Presence**	**Size of thrombosis (mm), if present.**
1	**THV leaflet**	□ Presence □ Absence	
2	**Subvalvular area**	□ Presence □ Absence	
3	**Supravalvular area**	□ Presence □ Absence	
4	**Left ventricle outflow tract (LVOT)**	□ Presence □ Absence	
Leaflet motion based on grade of opening limitation * Opening limitation = a / b * 100 % (a= radius of stent frame, b = orthogonal line through the affected leaflet to the center of the frame)			
1	**leaflet 1 (right)**	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile	
	leaflet 2 (left)	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile	
	leaflet 3 (non)	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile	

Stent eccentricity (%)				
		Long diameter (mm)	**Short diameter (mm)**	**Eccentricity (%)**
1	**At the level of inflow**			
2	**At the level of valvular**			
3	**At the level of outflow**			

Calcification volume			
		Yes or No?	**Volume(mm^2)**
1	**At the level of annulus**	□ Yes □ No	
2	**At the level of sinus**	□ Yes □ No	
3	**At the level of Valsalva level**	□ Yes □ No	
Comments			

Appendix Table 5. Brain MRI Analysis Form

1. DWI-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe DWI findings):		
2. FLAIR-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe FLAIR findings):		
3. GRE-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe GRE findings):		

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BMJ Open

Rationale and design of the ADAPT-TAVR trial: a randomized comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042587.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Nov-2020
Complete List of Authors:	Park, Hanbit; Asan Medical Center, Cardiology Kang, Do-Yoon; Asan Medical Center Ahn, Jung-Min; Asan Medical Center, Cardiology Kim, Kyung Won; Asan Medical Center WONG, Anthony; Queen Mary Hospital, Medicine LAM, Simon; Queen Mary Hospital, Medicine Yin, Wei-Hsian ; Cheng Hsin General Hospital Wei, Jen; Cheng Hsin General Hospital Lee, Yung-Tsai; National Taiwan University Hospital Kao, Hsien-Li; National Taiwan University Hospital Lin, Mao-Shin; National Taiwan University Hospital Ko, Tsung-Yu; National Taiwan University Hospital Kim, Won-Jang; CHA Bundang Medical Center Kang, Se Hun; CHA Bundang Medical Center Ko, Euihong; Asan Medical Center Kim, Dae-Hee; Asan Medical Center Koo, Hyun Jung; Asan Medical Center Yang, Dong Hyun; Asan Medical Center Kang, Joon-Won; Asan Medical Center Jung, Seung Cahi; Asan Medical Center Lee, Jae-Hong; Asan Medical Center Yun, Sung-Cheol; Asan Medical Center, Department of Biostatistics Park, Seung-Jung; Asan Medical Center Park, Duk-Woo; Asan Medical Center,
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice, Radiology and imaging
Keywords:	Valvular heart disease < CARDIOLOGY, Thromboembolism < CARDIOLOGY, Adult cardiology < CARDIOLOGY

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Rationale and design of the ADAPT-TAVR trial: a randomized comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement

Short title: Rationale and Design of ADAPT-TAVR Trial

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

[1]Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Asan Image Metrics, Clinical Trial Center, Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea; [3]Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong; [4]Heart Center, Cheng Hsin General Hospital, Taipei, Taiwan; [5]Division of cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [6]Division of cardiology, Department of Internal Medicine, Hsin-Chu Branch, National Taiwan University Hospital, Hsin-Chu, Taiwan; [7]Department of Cardiology, CHA Bundang Medical Center, Seongnam, Korea; [8]Department of Radiology Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Asan Image Metrics, Asan Medical Center; [9]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [10]Division of Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Two first authors (Drs HB Park and DY Kang) contributed equally to this manuscript.

Total word count (main text): 4,281

Funders: The ADAPT-TAVR trial is partly funded by Daiichi Sankyo Inc. and CardioVascular Research Foundation (CVRF, Seoul, Korea) (grant number: AMCCV 2017-08).

Address for correspondence:

Dr. Duk-Woo Park

Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine,

388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea

Phone: +82-2-3010-3995; Fax: +82-2-487-5918; E-mail: dwpark@amc.seoul.kr

Abstract

Introduction: Optimal antithrombotic strategy following transcatheter aortic valve replacement (TAVR) is still unknown. We hypothesized that the direct factor Xa inhibitor edoxaban can potentially prevent subclinical leaflet thrombosis and cerebral embolization compared with conventional dual antiplatelet therapy (DAPT) in patients undergoing TAVR.

Methods and analysis: The ADAPT-TAVR trial is an international, multicenter, randomized, open-label, superiority trial comparing edoxaban-based strategy and DAPT strategy in patients without an indication for oral anticoagulation who underwent successful TAVR (ClinicalTrials.gov NCT03284827). A total of 220 patients are randomized (1:1 ratio), 1 to 7 days after successful TAVR, to receive either edoxaban (60 mg daily or 30 mg daily if patients had dose-reduction criteria) or DAPT using aspirin (100 mg daily) plus clopidogrel (75 mg daily) for 6 months. The primary endpoint was an incidence of leaflet thrombosis on four-dimensional, volume-rendered cardiac computed tomography imaging at 6 months post-TAVR. The key secondary endpoints were the number of new lesions and new lesion volume on brain diffusion-weighted magnetic resonance imaging and the changes in neurological and neurocognitive function assessment between immediate post-TAVR and 6 months of study drug administration. Detailed clinical information on thromboembolic and bleeding events were also assessed.

Ethics and dissemination: Ethic approval has been obtained from the Ethics Committee /Institutional Review Board of Asan Medical Center (approval number: 2017-1317) and this trial is also approved by National Institute of Food and Drug Safety Evaluation of Republic of Korea (approval number: 31511). Results of this study will be disseminated in scientific publication in reputed journals.

Trial registration number: ClinicalTrials.gov Identifier: NCT03284827

Keywords: anticoagulation; antiplatelet agents; cerebrovascular events; transcatheter aortic valve replacement; thrombosis

Strengths and limitations of this study

- The ADAPT-TAVR trial is a multinational, multicenter, prospective, randomized, open-label, superiority trial comparing efficacy and safety of edoxaban vs. dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel in patients undergoing transcatheter aortic valve replacement (TAVR).
- The primary endpoint is an incidence of leaflet thrombosis on 4-D, volume-rendered cardiac computed tomography at 6 months post-TAVR and the key secondary endpoints are cerebral embolization (documented with brain magnetic resonance imaging) and neurological and neurocognitive function.
- This trial is planned to complete the 3-year enrollment period for the prespecified 220 subjects from the five participating centers.
- This trial will provide important clinical insights on edoxaban-based anticoagulation strategy compared with DAPT strategy post-TAVR with respect to leaflet thrombosis and associated cerebral embolization and neurocognitive function.
- This trial may be underpowered to detect any clinically relevant differences in clinical outcomes between two treatment strategies.

Introduction

Transcatheter aortic valve replacement (TAVR) has been positioned as a valuable treatment option for patients with symptomatic severe aortic stenosis (AS) who are at inoperable, high, or intermediate risk for conventional surgical aortic valve replacement (SAVR), on the basis of clinical evidence from multiple randomized clinical trials (RCTs).[1-7] Recently, TAVR has become a valid alternative to SAVR even in patients at low surgical risk.[8 9] Despite of such proven efficacy and safety of TAVR in patients with severe AS at diverse surgical risks, thromboembolic complications (stroke, systemic embolism, valve thrombosis, and venous thromboembolism) have been observed post-TAVR. In addition, observational data reported that subclinical leaflet thrombosis and reduced leaflet motion of bioprosthetic aortic valves have been documented by four-dimensional computed tomography (CT),[10] and the presence of subclinical leaflet thrombosis might be associated with increased rates of stroke or transient ischemic attacks (TIAs).[11-13] Despite excellent outcomes after TAVR with newer-generation valves, prevention and optimal management of subclinical leaflet thrombosis can offer a potential opportunity for further improvement in valve hemodynamics and durability.[14]

In routine clinical practice, optimal post-TAVR antithrombotic therapy is still controversial and a practice variation of antithrombotic regimens is substantially high without strong evidences for their recommendations.[15] Empirically, dual antiplatelet therapy (DAPT) of aspirin plus clopidogrel has been used for at least 6 months after TAVR,[1-9] although such recommendation was based mainly on expert consensus. After several studies reported that valve thrombosis developed in patients receiving antiplatelet therapy alone but not in those receiving oral anticoagulation (OAC) therapy,[10 11] updated guidelines recommend that OAC with vitamin K antagonist (VKA) may be a reasonable approach for at least 3 months after TAVR in patients at low risk of bleeding (Class IIb).[16] However, clinical evidence to support

this recommendation are still lacking (level of evidence B-NR: data were derived from one or more non-randomized trials or meta-analysis of such studies).

Edoxaban once daily is a well-tolerated inhibitor of factor Xa that has demonstrated a superior safety with non-inferior efficacy compared with VKA for prevention of stroke or systemic embolization or recurrent symptomatic venous thromboembolism in diverse clinical settings.[17] [18] We hypothesize that edoxaban, a non-VKA oral anticoagulant (NOAC), potentially reduces the risk of subclinical leaflet thrombosis and cerebral embolization compared with conventional DAPT-based strategy in patients undergoing TAVR. The Anticoagulation versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization after Transcatheter Aortic Valve Replacement (ADAPT-TAVR) trial is a multicenter, randomized, open-label, active-treatment, controlled trial to compare the efficacy of edoxaban and DAPT for prevention of leaflet thrombosis documented by high-resolution four-dimensional (4-D) cardiac CT and cerebral embolization documented by brain magnetic resonance imaging (MRI) and associated neurological and neurocognitive function in patients who underwent successful TAVR procedure.

Methods and Analysis

Trial Design and Objectives

The ADAPT-TAVR trial (ClinicalTrials.gov unique identifier: NCT03284827) is a multinational, multicenter, prospective, randomized, open-label, superiority trial that compared the efficacy of a strategy of OAC with edoxaban and DAPT with aspirin plus clopidogrel in patients without an indication for chronic anticoagulation who underwent successful TAVR for symptomatic severe AS (**Figure1**). The trial is being conducted in five major centers in

three countries (South Korea, Hong Kong, and Taiwan).

The primary objective of ADAPT-TAVR is to demonstrate the superiority of a NOAC strategy with edoxaban (experimental arm) as compared to the current standard of care DAPT (control arm) in the prevention of leaflet thrombosis (documented by 4-D cardiac CT). The main secondary objective is to compare the two antithrombotic strategies with regard to the potential risk of cerebral embolization (documented with brain MRI) and the changes in neurological and neurocognitive function. Other objectives for clinical assessment are to investigate the time from randomization to the first occurrence of efficacy and safety clinical outcomes including death, myocardial infarction (MI), stroke or TIAs, or bleeding events.

Study Population

Patients aged ≥ 18 years with severe symptomatic AS who underwent successful TAVR procedure (either native valve or valve-in-valve) with any approved/marketed device (i.e., SAPIEN 3, Evolut R, or Evolut PRO) were eligible for participation in the trial. A successful TAVR procedure was defined according the Valve Academic Research Consortium-2 (VARC-2) criteria as follows[19]: (1) correct position of a single prosthetic heart valve into the proper anatomical location; (2) intended performance of the prosthetic heart valve with presence of all 3 of the following conditions post-TAVR (a. mean aortic valve gradient < 20 mmHg, b. peak transvalvular velocity <3.0 m/s, and c. no moderate or severe aortic valve regurgitation); and (3) absence of periprocedural major complications (any type of stroke, life-threatening bleeding, acute coronary artery obstruction requiring intervention, major vascular complication requiring intervention, unresolved acute valve thrombosis, or any requirement of a repeat procedure). The key exclusion criteria were any established indication for long-term

anticoagulation (e.g., concomitant atrial fibrillation) and any absolute indication for DAPT (e.g., recent acute coronary syndromes or recent or concomitant percutaneous coronary intervention) at the time of screening. Detailed information on inclusion and exclusion criteria is listed in **Table 1**.

Randomization and Treatment Groups

Eligible patients who met the study inclusion criteria and met none of the exclusion criteria are randomly (1:1 ratio) assigned to receive either (1) NOAC with edoxaban (60 mg once daily or 30 mg once daily with dose-reduction criteria) or (2) DAPT with aspirin (100 mg once daily) plus clopidogrel (75 mg once daily) for 6 months after successful TAVR. Central randomization is performed with the use of an Interactive Web Response System and stratified by type of TAVR valve (balloon-expandable or self-expandable) and participating center with block sizes of 4 or 6. Randomization is performed after successful TAVR when the patient has stabilized (1 to 7 days after index TAVR procedure) and before hospital discharge. Duration of study drug treatment and subject follow-up will be at least six months.

In patients assigned to the edoxaban group (experimental arm), the investigational product is open-labeled edoxaban 60 mg or 30 mg tablet taken orally once daily for 6 months. Edoxaban is started at the time of randomization and irrespective of the pre-existing antithrombotic regimen. Edoxaban 30 mg tablet orally once daily is given for randomized patients with the following dose-reduction criteria: (1) body weight ≤60 kg, (2) moderate to severe renal impairment (defined as a calculated creatinine clearance [Cockroft-Gault formula] between 15 and 50 mL/min), or (3) concomitant P-glycoprotein inhibitors (cyclosporine, dronedarone, erythromycin, or ketoconazole). Patients assigned to the DAPT group (control

arm) will receive aspirin 100 mg and clopidogrel 75 mg once daily. Naïve patients will initially be loaded with aspirin (200 mg) and clopidogrel (300 mg) according to local practice. After 6 months of study medications in both groups, patients will continue to use low-dose aspirin (100 mg) alone indefinitely.

In case new-onset atrial fibrillation (NOAF) occurs after randomization, given that the potential thromboembolic risk of NOAF after TAVR is substantial,[20] full OAC will be implemented with maintenance of the original treatment assignment. In the edoxaban group, the assigned treatment remains as the protocol. In the DAPT group, use of VKA or NOAC was allowed at the treating physician's discretion. Because this protocol adaptation is an integral part of the study protocol regimens, endpoints occurring under post-NOAF study treatments are retained in the primary study analysis (intention-to-treat principle).

Study Endpoints and Follow-Up

The primary and secondary endpoints of the ADAPT-TAVR trial are listed in **Table 2**. The primary study endpoint is an incidence of leaflet thrombosis on 4-D, volume-rendered cardiac CT at 6 months post-TAVR. The key secondary endpoints for assessment of cerebral embolization, which was assessed by the number of new lesions and new lesion volume on brain MRI scans at 6 months relative to immediate post-TAVR, and the new changes of neurological and neurocognitive function assessment between post-TAVR and 6 months of study drug administration. Other secondary endpoints for assessment of ischemic and bleeding complications includes death (all-cause, cardiovascular or non-cardiovascular), MI, stroke (disabling or non-disabling) or TIAs, or bleeding events (life-threatening or disabling, major bleeding, or minor). Serial echocardiographic parameters (the mean transaortic valve pressure gradient and velocity time integral ratio) are also assessed at baseline, post-procedure, and 6-

month follow-up. All clinical endpoints are adjudicated according to VARC-2 criteria[21] and the NeuroARC definitions.[22] Detailed definitions of clinical endpoints are summarized in **Appendix Table 1**. The investigators in each center should complete case report forms for all events and provide sufficient information for central review. All components of the primary and secondary endpoints are blindly adjudicated by an independent Clinical Event Committee (CEC).

After completion of the TAVR procedure, all study patients are monitored per institutional standard of care. The study subjects are followed at 1 month (±2 weeks), 3 months (±2 weeks) and 6 months (±1 month). Data collected during all follow-up visits also include clinical symptoms, such as dyspnea (New York Heart Association [NYHA] class), angina status (Canadian Cardiovascular Society [CCS] class), and any related clinical events including rehospitalization or unintended hospital visits. For compliance check, the investigator will keep track of investigational drug dispensed and/or administered to the subjects and it is for compliance calculation.

To confirm the occurrence of leaflet thrombosis of bioprosthetic valves, all subjects undergo 4-D, volume-rendered cardiac CT at 6 months (± 1 month) after the TAVR. To evaluate the clinical effect of antithrombotic strategy and cerebral embolization by leaflet thrombosis, we perform brain MRI at 1–7 days after TAVR and 6 months after initiating study drug administration. Transthoracic echocardiography is routinely performed at baseline, 1–7 days after immediate post-TAVR, 1 month and 6 months after initiating study drug administration. Standardized definitions of structural deterioration and valve failure are used for the echocardiographic imaging assessment of bioprosthetic valve dysfunction.[23]

Acquisition and Archive of Cardiac CT and Brain MRI

A central imaging core lab (Asan Image Metrics; www.aim-aicro.com) is in charge of image acquisition and archive. The image core lab establishes the standardized acquisition protocols of cardiac CT and brain MRI imaging through gathering all CT/MRI machines and acquisition protocols of cardiac CT and brain MRI in each participating site. All sites should be qualified for their imaging machines and capability to perform the standardized acquisition protocol by the imaging core lab. All CT/MRI images acquired from each site are anonymized and electronically transferred to a central server (AiCRO system; Asan Image Metrics, Seoul, Korea) for image archiving images and blinded independent image review.[24]

All cardiac CT scans are performed with a dedicated 4-D, volume-rendered CT acquisition protocol with intravenous contrast administration as mandated at each participating site. The archived CT images are reconstructed to generate the sagittal and coronal images (two- and three-chamber views) of the aortic root and volume-rendered En-face view images of the device. Detailed information on acquisition and reconstruction methodology of cardiac CT is summarized in **Appendix Table 2**. The standardized cardiac CT protocols comply with international expert consensus reports.[25 26]

All brain MRI scans are obtained including diffusion-weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR), and T2-star gradient (GRE) sequences which are the important sequences for image endpoint. Other sequences such as localizer, T1-weighted image, T2-weighted image, or MR angiography, can be allowed to use institutional protocols. The MRI sequences are in compliance with the 2018 American Heart Association/American Stroke Association guidelines.[27] Detailed information on acquisition protocols of brain MRI is summarized in **Appendix Table 3**.

Core Laboratory Image Analyses

An independent image review committee (IIRC) is organized by the central imaging core lab (Asan Image Metrics) for the analysis of CT and MRI data from the ADAPT-TAVR trial in a blinded fashion. Two cardiac radiologists analyze cardiac CT images, and two neuroradiologists evaluate brain MRI images in an independent and blinded manner. In cases of discrepancy, the adjudication was made by open discussion and consensus between radiologists and investigators. The adjudication variables are presence of valvular thrombosis and occurrence of new DWI-positive lesions, FLAIR-positive lesions, or GRE-positive lesions. The adjudication rates between readers and the rationale of adjudication should be recorded. The detailed items on the image analysis of cardiac CT and brain MR images are summarized in **Appendix Table 4 and 5**, respectively.

The cardiac CT images are analyzed for presence of valve thrombosis, presence of leaflet thickening, leaflet motion based on opening limitation, stent eccentricity (%), and calcification volume.[28] Presence of valve thrombosis is checked when there are hypoattenuated abnormal lesion(s) attached at the 1 or more THV leaflet, subvalvular area, supravalvular area, or left ventricular outflow tract (LVOT). The location of valve thrombosis should be determined from one or more of the followings: leaflet, subvalcular area, supravalvular area, and LVOT. Leaflet motion is assessed based on grade of opening limitation on a volume-rendered En-face image of the aortic-valve prosthesis at maximal leaflet opening. Leaflet motion is categorized as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion) in at least one valve leaflet. We classified patients with mild or no restriction of leaflet motion as having normal leaflet motion. The stent eccentricity is defined as 1- (minimum stent diameter / maximum stent diameter) at the level of inflow, valvular area and outflow tract. If there is calcification, readers should measure the volume of calcification at the annulus or sinus or

Valsalva level. Calcification can be measured using the threshold of CT numbers greater than 850 Hounsfield unit.

The brain MRI images are analyzed for occurrence, number, and volume of new lesions on the 6-month DWI/FLAIR and GRE images compared to baseline MRI (immediate post-TAVR), respectively. The new lesions on DWI or FLAIR may reflect ischemic lesions due to thromboembolic events but also might be attributed to other nonspecific lesions. The new lesions on GRE are regarded as new hemorrhagic lesions. The occurrence of new lesion is defined when a lesion is seen only on 6-month MRI and not on baseline MRI. The number of new lesions is counted based on new separate lesions on 6-month MRI. The volume is calculated as the sum of volumes of all separate new lesions on 6-month brain MRI.

Neurological and Neurocognitive Function Assessment

All study subjects will undergo detailed neurologic and neurocognitive function assessment at post-TAVR(1–7 days after TAVR and before discharge) and 6 months of study drug administration. Neurologic assessments include standard clinical scales (the National Institutes of Health Stroke Scale [NIHSS] and the modified Rankin Scale [mRS]), and cognitive assessments include the Montreal Cognitive Assessment (MoCA). Dedicated attending staff will be identified at each center to perform the neurological and cognitive assessments; these subjects are NIHSS certified, trained in administration of the mRS and cognitive tests, and are blinded to brain MRI findings and treatment groups.

Sample Size Estimation and Statistical Analyses

Sample size was estimated to simultaneously meet the primary endpoint of the incidence of

leaflet thrombosis on cardiac CT and meet the key secondary endpoint of the total new lesion number on brain MRI. Based on the results from RESOLVE and SAVORY registry,[11] we assumed an incidence of subclinical leaflet thrombosis of 15% in the DAPT group and of 3% in the NOAC (edoxaban) group. Enrollment of 192 patients (96 patients in each arm) would provide the study with a statistical power of 80% to detect this difference with a two-sided significance level of 0.05. Assuming 10% attrition rate of CT follow-up loss at 6 months, a total of 220 patients (110 patients per each arm) are finally planned. In similar setting of post-TAVR status, there are no benchmark MRI data at immediate post-TAVR and follow-up on which to base control arm assumption. Among the two landmark trials (CLEAN-TAVI[29] and SENTINEL[30]) involving brain MRI at post-TAVR, the median number of new lesions in the entire brain (with reference of the control arm) at immediate post-TAVR was 16 (interquartile range [IQR], 10–24) in the CLEAN-TAVI trial and 5 (IQR, 2–10) in the SENTINEL trial. It is expected that the absolute new lesion number between 6 months and immediate post-TAVR would be lower than the lesions number between immediate post-TAVR and baseline (pre-TAVR). Thus, we assumed that the mean number of new lesions in the entire brain between 6 months and immediate post-TAVR would be approximately 10. Our hypothesis for key secondary endpoint of brain DW-MRI is that the use of edoxaban would provide a 30% reduction in the number of positive DW MRI–perfused brain lesions following TAVR at 6 months relative to post-TAVR in the entire brain compared with the use of DAPT. This relative risk reduction was based on the clinical observation of prior registry[11] and the assumption of trial with similar concept.[31] Given a standard deviation (SD) of 7, which was based on the value of the CLEAN-TAVI trial, for the measure and assuming a dropout rate of 20%, a total of 218 patients (109 patients per each group) was estimated for the study to have a power of 80% at a two-sided α-level of 0.05. To meet the predefined estimation of this key secondary endpoint, the final sample size was estimated as a total of 220 patients (110 patients per each arm).

The primary and secondary endpoint analyses are conducted on the full analysis set of all randomized patients according to the intention-to-treat principle. The Fisher exact test is used to compare categorical variables. Continuous variables, presented as mean±SD or medians with IQRs as appropriate, are compared with the use of the Student's t-test or the Mann-Whitney U test. The key secondary endpoint, consisting of new median lesion number differences between the two randomized arms, was compared using the Wilcoxon rank sum test. A z-score for each neurocognitive function domain is calculated on the basis of normative mean ± SD for each neurocognitive test. Change scores are calculated by subtracting immediate-post-TAVR scores from the 6-month post-TAVR scores. Cumulative event curves are generated by means of the Kaplan-Meier method. The 95% confidence interval of the hazard ratio will be presented using a Cox model for survival analysis. Trial data are held by the trial coordination center at the Asan Medical Center. Analyses will be performed by independent statistical analysts who was unaware of randomized drug. All P-values are two-sided, and values <0.05 are considered statistically significant.

Study Committees

The executive committee (EC) is composed of principal investigators of clinical sites and persons who will organize this study. The EC will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. National lead investigators and academic experts are part of the steering committee and responsible for the protocol implementation and study recruitment. An independent data safety monitoring board (DSMB) has the responsibility of monitoring safety during the trial: the members of the DSMB will not be among those who directly control the sponsor of this study and periodically review the safety data according to a dedicated charter

and make recommendations based on safety analyses, protocol deviation, imaging failures, and 6-month follow-up reports. The CEC consists of interventional and non-interventional cardiologists who are also independent and blinded. The CEC is charged of the development of specific criteria used for the categorization of clinical events in the study, which are based on the protocol and will adjudicate all suspected study endpoints as detailed in the specific charter.

Ethics and dissemination

This trial was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. Ethic approval and informed consent form have been obtained from the Ethics Committee /Institutional Review Board of Asan Medical Center (approval number: 2017-1317) and the trial was also approved by National Institute of Food and Drug Safety Evaluation of Republic of Korea (approval number: 31511). The study background and main objective as well as potential benefits and risks will be fully explained to the participants and their families. All participants voluntarily signed a declaration of informed consent. We planned to disseminate the overall results of the study to the participants and the public, such as presenting primary results in the international scientific meeting and publicizing our research in medical news and various academic lectures.

Discussion

The ADAPT-TAVR trial is a randomized controlled trial to define optimal antithrombotic strategy using direct acting factor Xa inhibitor, edoxaban after TAVR with regards to

prevention of leaflet thrombosis and cerebral embolization. This trial will provide randomized evidences of the efficacy and safety of edoxaban-based anticoagulation strategy compared with DAPT strategy after successful TAVR without indication of chronic OAC.

Initially, safety concern has been raised after report of cardiac CT findings in patients who had stroke after TAVR from an ongoing clinical trial.[10] Large-sized observational registry showed that subclinical leaflet thrombosis more frequently developed in TAVR (13%) than in SAVR (4%),[11] but recent reports from CT substudies of low-risk RCTs showed comparable incidences of leaflet thrombosis after TAVR and SAVR.[13 32] In prior observation, OAC (both VKA and NOACs) was more effective than DAPT in prevention or treatment of subclinical leaflet thrombosis (4% vs. 15%), and clinically subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes.[11] Although there was limited evidence supporting the association of leaflet thrombosis and cerebral embolic events, the Food and Drug Administration (FDA) has raised the safety concerns of TAVR and has been closely monitoring this signal.[33] The FDA also recommended that whether reduced leaflet motion was clinically meaningful for patients with TAVR, the loss of mobility of one or more leaflets detected by CT rendered the valve structurally dysfunctional and demands additional investigation. After such safety concern has been raised in several studies,[10 11 34 35] updated guidelines suggest that OAC within at least 3 months is reasonable considering the possibility of leaflet thrombosis.[16] However, there still has been inadequate evidence to support these OAC recommendations in patients undergoing TAVR.

Until recently, the underlying mechanism of bioprosthetic valve thrombosis were not clearly determined. The implanted TAVR valve adds a prothrombotic environment, which might be related to perturbations in blood flow (i.e., stagnant blood) and activation of various hemostatic factors within the neosinus,[14] and this condition may favor subclinical thrombosis

and valve hemodynamic deterioration. Moreover, some studies suggested that the intra-annular valves was more prone to higher risk of leaflet thrombosis than the supra-annular valve,[11 36] which would be the rationale of stratified randomization by type of TAVR valve (balloon-expandable or self-expandable) in this trial. Although it is still unknown whether post-TAVR produced-thrombi have a predominant platelet- or thrombin-related origin, thrombin plays a key role in the formation of thromboembolic events; the mechanisms of platelet activation and coagulation are highly interdependent, with thrombin playing a central role in both pathways.[37] Given that direct factor Xa inhibitors target specifically factor Xa and decrease the conversion of prothrombin to active thrombin, thereby diminishing fibrin formation, and reducing coagulation and platelet activation, it might be reasonable to consider a systemic anticoagulation strategy with NOAC regimen to prevent subclinical leaflet thrombosis and reduce the long-term thromboembolic risk after TAVR.

In this context, a systematic anticoagulation strategy after TAVR should be tested in RCTs. Recently, the primary results from the Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) showed that NOAC strategy with rivaroxaban at a dose of 10 mg (with low-dose aspirin for the first 3 months) was associated with higher risks of thromboembolic complications, bleeding events, and mortality than DAPT strategy (low-dose aspirin with clopidogrel at a dose of 75 mg for the first 3 months) in patients without an OAC indication after successful TAVR.[38] In an imaging substudy of GALILEO, a rivaroxaban-based antithrombotic strategy was more effective than DAPT strategy in preventing subclinical leaflet motion abnormalities (2.1% vs. 10.9%).[39] Unfortunately, these findings cannot recommend routine imaging for the detection of reduced leaflet motion or routine use of anticoagulation after TAVR for preventing leaflet motion abnormalities, given

the unfavorable clinical outcomes with rivaroxaban. Subsequent reports from the POPular TAVI trial Cohort A and B showed that aspirin or oral anticoagulation alone was associated with a lower incidence of bleeding and similar risk of thromboembolic events as compared with dual therapy with clopidogrel.[40 41] Regarding this important issue, an OAC strategy alone or NOAC strategy instead of VKA is actively being tested in another ongoing RCTs including the ADAPT-TAVR trial (ATLANTIS trial: NCT02664649, ENVISAGE-TAVI AF: NCT02943785, and AVATAR: NCT02735902). The release of the key results of such consecutive trial may provide compelling evidence to resolve the clinical unmet need for optimal antithrombotic strategy in the routine clinical practice of TAVR. In addition, the potential preventive role of anticoagulation with NOAC for preventing leaflet thrombosis and cerebral embolization after TAVR, which was not yet confirmed by RCTs, will be supported by the primary results of the ADAPT-TAVR trial.

It should be acknowledged that this study has several limitations. First, bias in event ascertainment cannot be ruled out given the open-label trial design. Second, the ADAPT-TAVR trial has adopted the surrogate imaging outcome as the primary and key secondary endpoints. Therefore, our key findings based on imaging modalities may not fully support the compelling clinical rationale with regard to efficacy and safety of NOAC strategy. Third, our trial was underpowered to detect any clinically relevant differences in clinical outcomes between two treatment strategies. 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 such population.

Trial Status

The ADAPT-TAVR trial is planned to complete the 3-year enrollment period for the prespecified 220 subjects from the five participating centers. The first patient was enrolled on March 2018, and 200 patients have been enrolled until October 2020. Enrollment may be completed approximately by the end of 2020. Primary results of the ADAPT-TAVR trial will be available by late-term of 2021.

Acknowledgements We thank the staff of the ADAPT-TAVR trial, the other members of the cardiac catheterization laboratories and the heart-team at the participating centers, and the study coordinators for their efforts in collecting clinical data and ensuring the accuracy and completeness of the data.

Contributors *Study conception and design* — DW Park, H Park, DY Kang, JM Ahn, SJ Park; *drafting of the study protocol* — H Park, KW Kim, DW Park; *critical revision of the study protocol for important intellectual content* — H Park, DY Kang, JM Ahn, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, E Ko, DH Kim, HJ Koo, DH Yang, JW Kang, SC Jung, JH Lee, SC Yun, SJ Park, DW Park; *statistical expertise* — SC Yun; *obtaining of* research f*unding* — DW Park; *administrative, technical, or logistic support* — H Park, DY Kang, JM Ahn, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, E Ko, DH Kim, HJ Koo, DH Yang, JW Kang, SC Jung, JH Lee, SC Yun, SJ Park, DW Park; *acquisition of data* — H Park, DY Kang, JM Ahn, KW Kim, YTA Wong, CCS Lam, WH Yin, J Wei, YT Lee, HL Kao, MS Lin, TY Ko, WJ Kim, SH Kang, E Ko, DH Kim, HJ Koo, DH Yang, JW Kang, SC Jung, JH Lee, SC Yun, SJ Park, DW Park; All authors approved the final manuscript.

Funding The ADAPT-TAVR trial is partly funded by Daiichi Sankyo Inc. and CardioVascular Research Foundation (CVRF, Seoul, Korea) (grant number: AMCCV 2017-08). None of the study leadership accepted any compensation for their roles in this study, other than expenses. The principal investigators accept responsible for the design and conduct of this study, all study analyses, and the drafting and editing of all manuscripts.

Competing interests None declared.

Patient and public involvement For development of this study protocol, there was no direct patient or public involvement. However, we planned to disseminate the overall results of the

study to the participants and the public, such as presenting primary results in the international scientific meeting and publicizing our research in medical news and various academic lectures.

Patient consent for publication Not required

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Figure Legends

Figure 1. Study Flow Diagram

Successful TAVR as defined in the "study population and methods" section.

Abbreviations: ASA, aspirin; CT, computed tomography; DAPT, dual antiplatelet therapy; NOAC, non-vitamin K antagonist oral anticoagulant; TAVR, transcatheter aortic valve replacement

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
1. Patients aged ≥18 with symptomatic AS who underwent successful TAVR procedure* (either native valve or valve-in-valve with any approved/marketed device) * A successful TAVR is defined as device success according to the VARC-2 criteria[19]: (1) Correct positioning of a single prosthetic heart valve into the proper anatomical location (2) Intended performance of the prosthetic heart valve (no prosthesis- patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation (3) Absence of periprocedural complications (any type of stroke, life-threatening bleeding, acute coronary artery obstruction requiring intervention, major vascular complication requiring intervention, unresolved acute valve thrombosis, or any requirement of a repeat procedure) 2. The patient or guardian agrees to the study protocol and the schedule of clinical follow-up, and provides informed, written consent, as approved by the appropriate institutional review board/ethical Committee of the respective clinical site
Exclusion criteria
1. Any atrial fibrillation with an indication for chronic oral anticoagulation (OAC) 2. An ongoing indication for OAC or any other indication for continued treatment with any OAC 3. Any ongoing indication for DAPT (recent acute coronary syndrome or PCI within 12 months) 4. Planned coronary or vascular intervention or major surgery 5. The risk of bleeding increased due to the following reasons at the time of TAVR procedure: a. History of gastrointestinal ulcers within 1 month b. Malignant tumor with high risk of bleeding

c. Brain or spinal cord injury within 1 month

d. History of intracranial or intracerebral hemorrhage within 12 months

e. Esophageal varices

f. Arteriovenous malformations

g. Vascular aneurysms

h. Spinal or intracerebral vascular abnormalities

i. Active bleeding

j. Hemoglobin level <7.0% or platelet count ≤50,000 / mm^3

k. History of major surgery within 1 month

6. Clinically overt stroke within the last 3 months
7. Moderate and severe hepatic impairment, and any hepatic disease associated with coagulopathy
8. Severe renal impairment (creatinine clearance by Cockcroft-Gault equation<30 mL/min per 1.73 m^2), chronic dialysis, or post-TAVR unresolved acute kidney injury
9. Terminal illness with life expectancy <6 months
10. History of hypersensitivity to edoxaban, aspirin or clopidogrel
11. Severe hypertension
12. Prosthetic heart valve replacement for which anticoagulant therapy is essential
13. Moderate to severe mitral stenosis
14. Pulmonary embolism requiring thrombolysis or pulmonary embolectomy
15. Active participation in another drug or device investigational study, which was not completed in the primary endpoint follow-up period
16. Pregnancy test results are positive (all pregnant women should undergo urinary human chorionic gonadotropin (hCG) testing within 7 days prior to screening and / or randomization) or during pregnancy or lactation

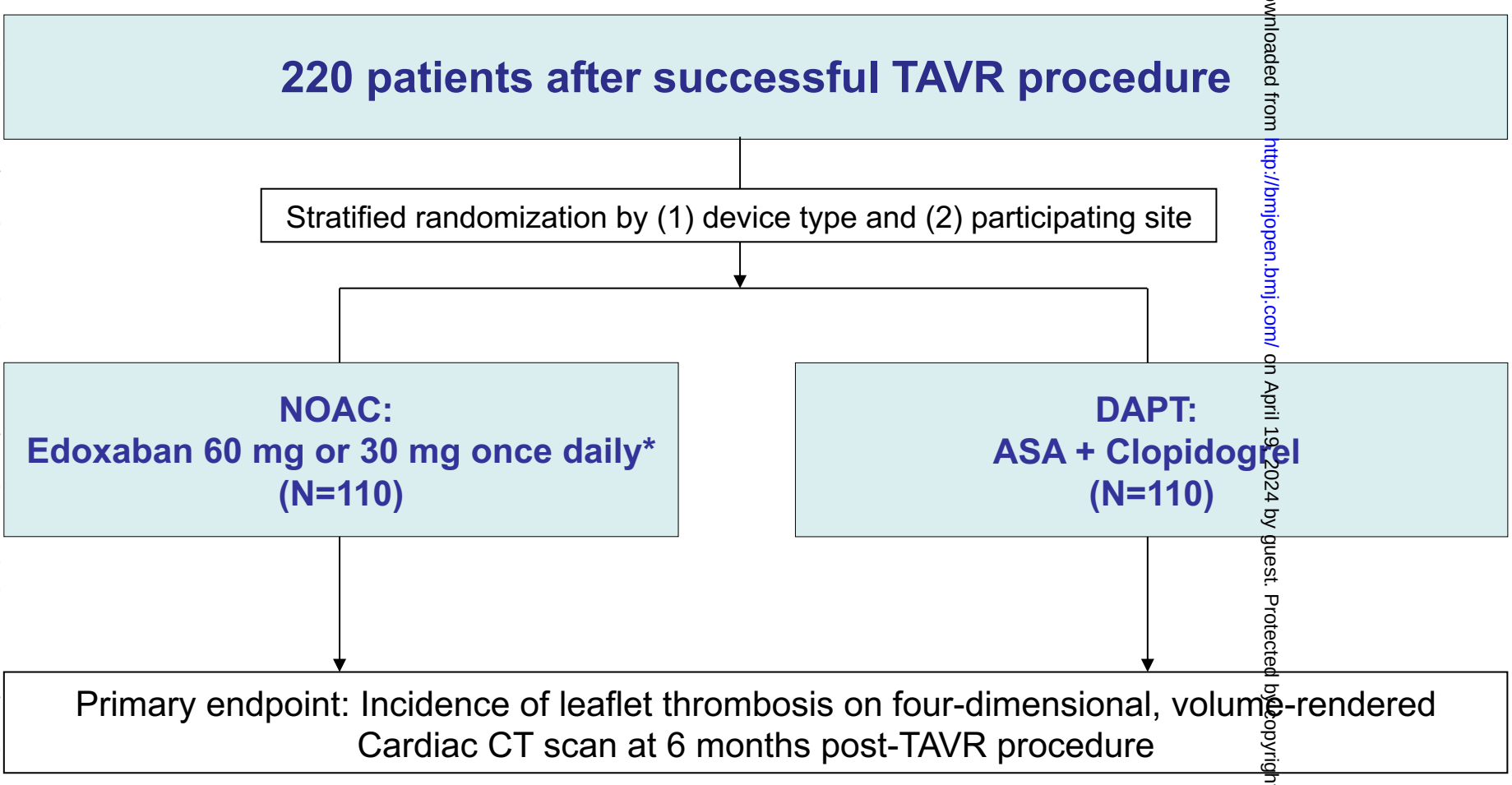
17. Genetic problem with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
18. Current or history of aspirin- or NSAIDs-induced asthma
19. Hemophilia
20. Use of methotrexate at doses of ≥15 mg per week
21. Unsuitable condition to undergo brain MRI and/or cardiac CT (e.g., tremor from Parkinson's disease). This is at the discretion of the investigators

Table 2. Primary and Secondary Endpoints

Primary Endpoint
Incidence of leaflet thrombosis on four-dimensional, volume-rendered cardiac CT imaging at 6 months post-TAVR procedure
Secondary Endpoints*
1. Number of new lesions on brain MRI scans at 6 months relative to immediate post-TAVR 2. New lesion volume on brain MRI 3. Neurological and neurocognitive function 4. Echocardiographic parameters (mean transaortic valve pressure gradient and velocity time integral ratio at baseline and 6-month follow-up) 5. Death (all-cause, cardiovascular, or non-cardiovascular mortality) 6. Myocardial infarction 7. Stroke (disabling or non-disabling) or transient ischemic attack 8. Bleeding event (life-threatening or disabling, major bleeding, or minor) *All clinical endpoints are adjudicated according to the VARC-2[19] and the NeuroARC[22] definitions

Anticoagulant versus ***D***ual ***A***ntiplatelet Therapy for ***P***reventing Leaflet ***T***hrombosis After ***T***ranscatheter ***A***ortic ***V***alve ***R***eplacement

ADAPT-TAVR Trial



*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).

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: H Park, DY Kang, JM Ahn, et al. "Rationale and design of the ADAPT-TAVR trial: a randomized comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement"

Appendix Table 1. Definitions of Clinical Endpoints.

All clinical endpoints are adjudicated according to current VARC-2[1] and the NeuroARC[2] definitions. Each of clinical endpoints is defined as follows:

Endpoint	Definition
Death	All-cause mortality was used rather than cardiac mortality to eliminate the need for possibly difficult adjudication of causes of death, especially given the relatively low mortality expected. In addition, the cause of death will be adjudicated as being due to cardiovascular causes or non-cardiovascular causes. Cardiovascular death includes any of the following criteria: • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause Non-cardiovascular death is defined as any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, or suicide)
MI	MI (non-procedural) is defined as any one of the following criteria: (1) detection of rise and/or fall of cardiac biomarkers (preferably troponin) with a least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following: a) symptoms of ischemia, b) ECG changes indicative of new

	ischemia (new ST-T changes or new LBBB), c) new pathological Q-waves in at least two contiguous leads, or d) imaging evidence of a new loss of viable myocardium or new wall motion abnormality, (2) sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation or new LBBB, and/ or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood (3) pathological findings of an acute myocardial infarction
Stroke and TIA	**Diagnostic criteria** • Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke: duration of a focal or global neurological deficit >24 h or <24 h if available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death • TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct Confirmation of the diagnosis by at least one of the following: • Neurologist or neurosurgical specialist • Neuroimaging procedure (CT or brain MRI), but stroke may be diagnosed on clinical grounds alone **Stroke classification** • Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue • Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

	• A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke definitions** • Disabling stroke: a modified Rankin Scale (mRS) score of ≥2 at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline • Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline
Bleeding events	Life-threatening or disabling bleeding is defined as any one of the following criteria: • Fatal bleeding (BARC type 5) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units* (BARC type 3b) Major bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery and does not meet criteria of life-threatening or disabling bleeding Minor bleeding (BARC type 2 or 3a, depending on the severity) • Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major

Appendix Table 2. Trial-Specific Standardized Cardiac CT Protocol

Items	Minimum requirements of acquisition protocols
CT scanners	GE Healthcare: 64 channel or above (e.g., Optima 660, Revolution HD/GSI, Revolution CT) Philips Healthcare: 64 channel or above (e.g., Ingenuity, iCT Elite, IQon Spectral CT) Siemens Healthineers: dual source or above (e.g., Somatom Definition AS, AS+, or Flash) Toshiba 320 or above (e.g., Aquilion ONE, Aquilion ONE Vision)
Minimum gantry rotation time (ms)	350 ms or below
Kernal	Manufacturer's recommendation
kVp, mAs, AEC	Manufacture's setting (site can utilize institutional protocols for kVp, mAs, and automatic exposure control).
ECG-gating	Imaging of the aortic root must use ECG-synchronization, using either two separate acquisitions (ECG-synchronized for the aortic root and non-gated for the aorta) or single ECG-synchronized acquisition of the entire volume
Scan coverage	Scan to include at least the aortic arch and whole heart (from the upper wall of aortic arch to lower cardiac border) in cranio-caudal direction
Patient position	The preferred subject position is supine with arms raised above the head and the heart centered within the gantry. Special attention should be paid to ensure proper positioning and firm contact of ECG leads to ensure a high R-peak amplitude and low baseline noise.
Image Reconstruction & Slice thickness	Iterative image reconstruction methods/algorithms are recommended according to manufacturers' setting and should meet the following minimum requirements: - Slice thickness should be ≤ 1.0 mm. - Recommendation for single source CT scanners (GE, Toshiba, Philips): 0.6 mm slices with 0.3 mm overlap and iterative reconstruction for evaluation at 5% intervals within the 0%-95% RR range - Recommendation of dual-source CT scanners (Siemens): 0.5 mm slices with 0.25 mm overlap with iterative reconstruction for evaluation at 10% intervals within the 0%-90% RR range

	- Recommended optimal timing: at lower heart rates (<65 bpm), the optimal timing is during late-diastole, while at higher heart rates (>65 to 70 bpm) the optimal timing is more frequently (but not always) during end-systole.
Spatial Resolution	≤0.5 × 0.5 mm in x–y plane and ≤1 mm in z-axis
Display FOV	Adjusted according to the heart size
Matrix	512 × 512
Contrast agent	Non-ionic CT contrast agents should be used.
Contrast Injection (Volume, Rate)	Injection volume: 50-120 cc per institutional protocols. Injection rate: 4-7 cc/s per institutional protocols. Scan timing determination: Bolus tracking (preferred) and test bolus methods should be used.
Others	Heart rate (HR) reduction with β-blockade is not performed.
* Note: The site can modify the abovementioned in the inevitable situation such as emergent patients' care or technical issues in the machines or scanning rooms. In these cases, the images can be used for clinical trials after quality check from Asan Image Metrics staffs.	

Appendix Table 3. Standardized Brain Protocols of DWI, GRE, and FLAIR

Items	Requirements		
	Axial DWI	**Axial GRE**	**Axial 2D FLAIR**
Tesla	1.5–3.0 Tesla		
Coil	Head coil or Neurovascular (NV) coil. The number of channels is 8 or above.		
Sequence	EPI[a]	T2* weighted GRE	TSE[b] and equivalent
FOV	190–250 mm	190–250 mm	190–250 mm
Matrix	128×128 or above	128×128 or above	256×256 or above
Resolution	2.0×2.0mm²	2.0×2.0mm²	2.0×2.0mm²
TR	2000 ms or above	400-1000 ms	6000 ms or above
TE	110 ms or below	15-32ms	100-140 ms
TI	Not available (NA)	NA	2200-2500 ms
Slice thickness	3.0–5.0 mm	3.0–5.0 mm	3.0–5.0 mm
Gap thickness	0–2.5 mm	0–2.5 mm	0–2.5 mm
Diffusion Option (B-value)	At least two b-values of 0 s/㎟ and 1000 s/㎟ should be included. The other b-values such as above 1000s/㎟ are optional).	NA	NA
Parallel Imaging	Recommend (up to 2X)	Recommend (up to 2X)	Recommend (up to 2X)

[a]In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.

[b]TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

Appendix Table 4. Cardiac CT Analysis Form

Valvular thrombosis □ Presence □ Absence			
	Location of thrombosis	**Presence**	**Size of thrombosis (mm), if present.**
1	**THV leaflet**	□ Presence □ Absence	
2	**Subvalvular area**	□ Presence □ Absence	
3	**Supravalvular area**	□ Presence □ Absence	
4	**Left ventricle outflow tract (LVOT)**	□ Presence □ Absence	

Leaflet motion based on grade of opening limitation

* Opening limitation = a / b * 100 %

(a= radius of stent frame, b = orthogonal line through the affected leaflet to the center of the frame)

1	**leaflet 1 (right)**	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile	
	leaflet 2 (left)	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile	
	leaflet 3 (non)	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile	

Stent eccentricity (%)

		Long diameter (mm)	**Short diameter (mm)**	**Eccentricity (%)**
1	**At the level of inflow**			
2	**At the level of valvular**			
3	**At the level of outflow**			

Calcification volume

		Yes or No?	**Volume(mm^2)**
1	**At the level of annulus**	□ Yes □ No	
2	**At the level of sinus**	□ Yes □ No	
3	**At the level of Valsalva level**	□ Yes □ No	

Comments

Appendix Table 5. Brain MRI Analysis Form

1. DWI-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe DWI findings):		
2. FLAIR-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe FLAIR findings):		
3. GRE-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe GRE findings):		

References

1. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 2012;42:S45-60.
2. Lansky AJ, Messé SR, Brickman AM, et al. Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials. *An Academic Research Consortium Initiative* 2017;69:679-91.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7-8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	33-35
	4b	Settings and locations where the data were collected	16
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	15-16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9-10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9-10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9-10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9-10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	16
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20-21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	7
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.