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PROTOCOL

Rationale and Design of the CREATE Trial: A Multicenter, Randomized Comparison of Continuation or Cessation of Single Antithrombotic Therapy at 1 Year After Transcatheter Aortic Valve Replacement

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BACKGROUND: Current guidelines and expert consensus recommend lifelong single antiplatelet therapy for patients undergoing transcatheter aortic valve replacement who have no indication for anticoagulation or dual antiplatelet therapy. However, there is no direct evidence from randomized controlled trials supporting this practice. Furthermore, the optimal duration of antiplatelet therapy in this population has not been adequately investigated.

METHODS AND RESULTS: CREATE (A Multicenter Randomized Controlled Study to Evaluate Cessation of Antithrombotic Therapy at 1 Year in TAVR Patients–The CREATE Study) is a prospective, multicenter, open-label, randomized controlled trial for patients who have undergone successful transcatheter aortic valve replacement and have no indication for long-term oral anticoagulation or antiplatelet therapy. Eligible patients are free from major bleeding and ischemic events for 1 year post-procedure before being randomized 1:1 to single antiplatelet therapy (control group) or no antiplatelet therapy (experimental group). The primary efficacy end point is the incidence of bleeding events, defined by the VARC-3 (Valve Academic Research Consortium-3) criteria, at 1-year postrandomization. The primary safety end point is a composite of cardiac death, myocardial infarction, and ischemic stroke at 1 year. The trial is powered for both superiority in efficiency and noninferiority in safety. Accordingly, a total of 3380 patients will be enrolled.

CONCLUSIONS: The CREATE trial aims to assess if stopping antiplatelet therapy at 1-year after transcatheter aortic valve replacement reduces bleeding risk without increasing ischemic events in patients not requiring chronic antithrombotic therapy.

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Key Words: antiplatelet therapy ■ aortic stenosis ■ transcatheter aortic valve replacement ■ treatment withdrawal

Transcatheter aortic valve replacement (TAVR) is a well-established treatment for symptomatic severe aortic stenosis across the entire surgical risk spectrum.[1–4] Previous guidelines and expert consensus have recommended dual-antiplatelet therapy (DAPT) for the first 1 to 6 months, followed by lifelong

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Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
CREATE	A Multicenter Randomized Controlled Study to Evaluate Cessation of Antithrombotic Therapy at 1 Year in TAVR Patients–The CREATE Study
DAPT	dual antiplatelet therapy
NAPT	no antiplatelet therapy
OCEAN-TAVI	Optimized Transcatheter Valvular Intervention–Transcatheter Aortic Valve Implantation
SAPT	single antiplatelet therapy
SLT	subclinical leaflets thrombosis
TAVR	transcatheter aortic valve replacement
VARC-3	Valve Academic Research Consortium-3

single antiplatelet therapy (SAPT) for patients with no indication for anticoagulation, to prevent stroke and other thromboembolic events for several months post-procedure.[3,5,6] However, there is insufficient evidence to support the necessity of lifelong antiplatelet therapy in this setting.[7–9]

The OCEAN-TAVI (Optimized Transcatheter Valvular Intervention–Transcatheter Aortic Valve Implantation) observational registry study[10] demonstrated that the risk of both all bleeding and major bleeding after TAVR is higher than the incidence of stroke, and that late bleeding events significantly increase long-term mortality.[11] Furthermore, a post hoc analysis of patients at high bleeding risk[12] without indications for antithrombotic therapy showed that no antithrombotic therapy (NAPT) at discharge did not differ from SAPT or DAPT in terms of the incidence of net adverse clinical events, which include cardiovascular death, stroke, myocardial infarction, and life-threatening or major bleeding over a 3-year follow-up period. Importantly, NAPT was associated with a lower incidence of life-threatening or major bleeding.[13] However, the conclusion on antithrombotic option from OCEAN-TAVI cannot be considered as powerful evidence to confirm that NAPT at discharge is better than long-term SAPT or DAPT for patients without chronic antithrombotic indications compared with a randomized controlled trial. In addition, considering perioperative ischemic events and subclinical leaflets thrombosis (SLT), we do not advocate premature discontinuation of antithrombotic agents.

Given that TAVR indications have expanded to entire spectrum of surgical risk patients, along with advancements in technology and operator experience,[14–16] the duration of antiplatelet therapy for patients without chronic antithrombotic indications is an issue that needs to be addressed for both preventing ischemic risk and not increasing late bleeding risk.[17] Therefore, we designed the CREATE (A Multicenter Randomized Controlled Study to Evaluate Cessation of Antithrombotic Therapy at 1 Year in TAVR Patients–The CREATE Study) trial, a randomized comparison of continuation versus cessation of antiplatelet strategy in patients without chronic anticoagulant and antiplatelet indications at 1 year after TAVR to achieve a balance between preventing ischemic and bleeding risk.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The CREATE trial (ChiCTR2400087454) is an investigator-initiated, nationwide, multicenter, open-label, randomized comparison of NAPT (experimental group) versus SAPT (control group) in patients 1 year post-TAVR. The intention is to recruit 3380 patients from 20 valvular interventional cardiology centers across China (Figure 1; trial design, Table S1). The trial is designed by Drs Song and Wu in collaboration with the statistical director Dr Pocock. The steering committees will oversee the medical, scientific, and operational aspects of the trial, ensure the integrity of data analysis, and be responsible for presenting the results at the end of study. The study will be conducted in full compliance with the ethical principles of the Declaration of Helsinki, including obtaining informed consent from each participant before initiation of any study procedures. This study was approved by ethics committee of Beijing Anzhen Hospital Capital Medical University.

Study Objectives

The primary aim of the CREATE trial is to evaluate the efficacy of NAPT versus SAPT in reducing clinically relevant bleeding, without increasing ischemic risk, at 1 year after TAVR. This will be assessed in patients who have no indications for long-term anticoagulant or antiplatelet therapy.

The secondary objective is to compare the safety of NAPT versus SAPT 1 year post-TAVR in terms of valve function, SLT, and transvalvular hemodynamics during follow-up.

Study Population

The study intends to enroll 3380 patients who have no indications for long-term anticoagulation or antiplatelet therapy and who have successfully undergone TAVR

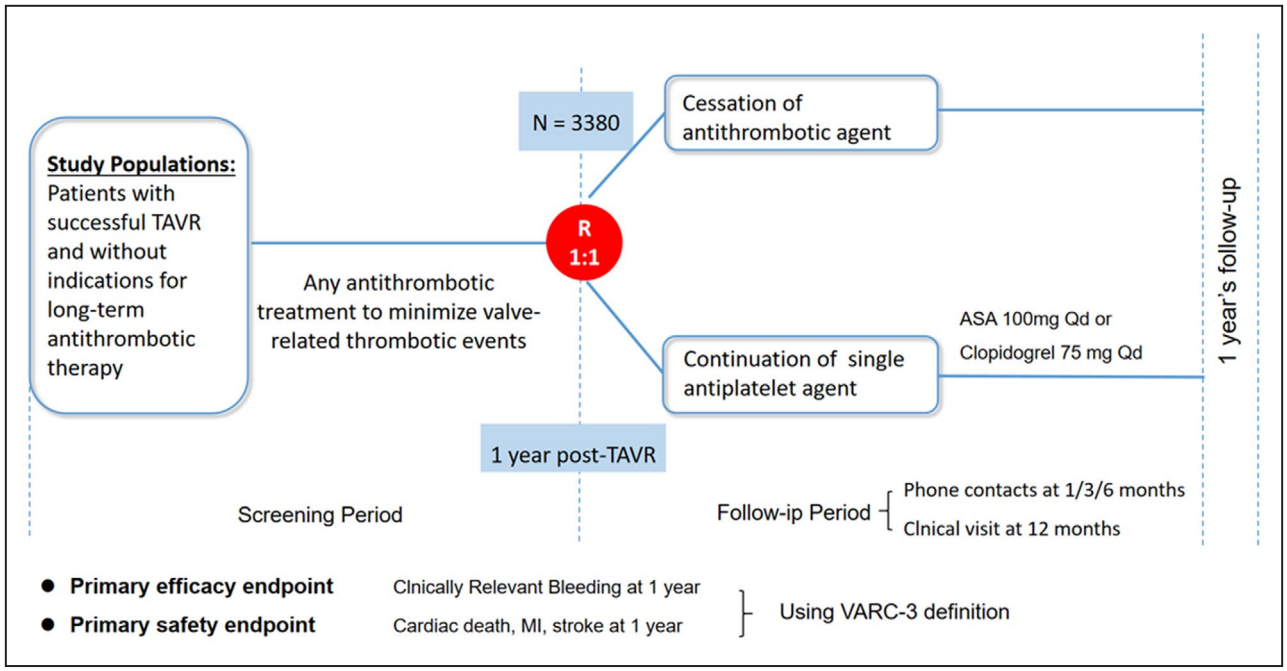

Figure 1. Trial design.
ASA indicates aspirin; MI, myocardial infarction; N, patient number; R, ratio; TAVR, transcatheter aortic valve replacement; and VARC-3, Valve Academic Research Consortium-3.

and are taking SAPT or DAPT before randomization. Patients must also be free from major adverse events such as death, myocardial infarction, stroke, systemic thromboembolic events, or bleeding during the first year postprocedure. Successful TAVR[18] is defined by the following criteria:

1. Correct positioning of a single prosthetic heart valve at the appropriate anatomical location.
2. Satisfactory valve performance, indicated by following criteria post-TAVR: No severe or moderate aortic valve regurgitation, a peak transvalvular velocity <3.0 m/s, and a mean aortic valve gradient <20 mm Hg.
3. Absence of periprocedural complications, including: any type of stroke; life-threatening bleeding (graded by VARC [Valve Academic Research Consortium]-2 criteria), acute coronary artery obstruction requiring intervention, major vascular complication requiring intervention (including access-site vascular complications, any new ipsilateral peripheral ischemia, distal embolization from a vascular source, aortic dissection, aortic rupture, ventricular perforation, cardiac tamponade, and annulus rupture), unresolved acute valve thrombosis, or the need for a repeat procedure.

The key exclusion criteria are shown in Table 1.

Enrollment will require a patient's written informed consent before randomization. Consent will also be obtained for the collection of life status and clinical events at the end of the extended follow-up period.

Randomization, Treatment, and Follow-Up

Randomization is open-label and conducted from the first year after TAVR with data collection on medication use, blood tests, imaging, and adverse events at each follow-up time point. Patients in the control group will receive either aspirin (100 mg daily) or clopidogrel (75 mg daily), at the discretion of the treating physician. Patients in the experimental group will not receive any antiplatelet medication. All other treatments will be left to the discretion of the treating physician and are not dictated by the study protocol.

Before randomization, patients will visit the valvular center to assess their eligibility and current medication status. Eligible patients who are event-free and remain on an antiplatelet agent will be randomized 1:1 to either continuation of SAPT (aspirin 100 mg or clopidogrel 75 mg) or the NAPT group using a centralized, stratified block randomization method. Stratification will be based on the study center to ensure equal distribution of participants across sites, minimizing center-specific biases. A fixed block size of 4 will be used to maintain balance within each center. Randomization will be conducted through a secure, web-based interactive web response system, ensuring allocation concealment. After enrollment and baseline data collection, the interactive web response system will generate a randomization code, which will be sent to a designated

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
1. Patients ≥18 y of age. 2. Patients diagnosed with severe aortic stenosis who underwent successful TAVR for >12 mo. 3. Patients who did not experience myocardial infarction, stroke, or rehospitalization due to bioprosthetic valve dysfunction within 12 mo after TAVR. 4. Patients agree to follow the study plan and to complete the follow-up. 5. Patients understand the purpose of the study, voluntarily participated in the study, and signed informed consent forms that were reviewed and approved by the ethics committee.
Exclusion criteria
1. Patients with indications for long-term anticoagulation (eg, pulmonary embolism, deep vein thrombosis, history or new onset of atrial fibrillation, mechanical valve replacement). 2. Patients with indications for long-term antiplatelet therapy (eg, ischemic stroke, coronary and/or carotid and/or peripheral arterial lumen stenosis >50%, prior PCI or CABG). 3. Patients with valvular heart disease who need to receive an anticoagulant, such as severe mitral valve stenosis. 4. Imaging findings of arterial lumen stenosis >50%. 5. Patients with inherited or acquired defects such as anticoagulant protein, coagulation factor, fibrinolysin, or high thromboembolic tendency due to acquired risk factors. 6. Patients diagnosed with bioprosthetic valve failure. 7. Patient diagnosed with lower extremity intermuscular venous thrombosis. 8. Patients who have active bleeding. 9. Patients who have active malignancies. 10. Patients with life expectancy <1 y. 11. Researchers believe the patient is not suitable to participate in the clinical trial.

CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; and TAVR, transcatheter aortic valve replacement.

researcher not involved in clinical end point evaluation. Investigators will then assign the allocated treatment and inform participants accordingly. The entire randomization process will be managed by the project coordination center to ensure oversight and blinding of data managers and statisticians.

Patients diagnosed with SLT evaluated by multidetector computed tomography before enrollment are not excluded, although antiplatelet medications may be switched to anticoagulant. If there are concerns that continued participation may expose the patient to undue risks related to valve dysfunction or thrombotic events, the patient will be withdrawn from the study until the thrombosis is resolved. Whether to re-enroll these patients after thrombosis resolution is at the discretion of the study principal investigator. The details surrounding the time points and follow-up throughout the trial are outlined in Figure 2. An independent data safety monitoring board (DSMB) will conduct periodic data reviews every 6 months. When the clinical event is a medical emergency, the treating physician may choose to initiate or discontinue therapy as necessary for appropriate patient management.

Study End Points

The primary efficacy end point is the occurrence of clinically relevant bleeding, defined as VARC-3[19] types 1, 2, 3, or 4 bleeding occurring during the 12 months after randomization.

The primary safety end point is the occurrence of composite of cardiac death, myocardial infarction,[20] and ischemic stroke/transient ischemic attack according to VARC-3 definition during the 12 months after randomization.

Secondary end points are the occurrence of: (1) all-cause mortality within 12 months; (2) composite of cardiovascular death, myocardial infarction, and stroke within 12 months; (3) net clinical benefit, defined as the composite of all-cause death, stroke, myocardial infarction, and clinically relevant bleeding; (4) bleeding complications defined as BARC (Bleeding Academic Research Consortium) types 1, 2, 3, or 5; (5) Hypoattenuated leaflet thickening grade 3 or higher, evaluated by multidetector computed tomography assessment 1 year postintervention, categorized as <25%, 25% to 50%, 50% to 75%, >75%; and (6) reduced leaflet motion grade 3 or higher, evaluated by multidetector computed tomography assessment 1 year postintervention, categorized as no motion restriction, <50% motion restriction, ≥50% motion restriction, complete motion restriction[19] (Table 2). All clinical events will be evaluated by an independent clinical event committee.

Power, Sample Size, and Statistical Considerations

Primary Efficacy End Point

The sample size estimation for this study is based on the primary efficacy end point, which is clinically relevant bleeding during the 12 months after randomization, based on a superiority hypothesis. The corresponding statistical hypothesis test is:

$$H0: \pi_T - \pi_C \geq 0,$$

$$H1: \pi_T - \pi_C < 0.$$

In the formula, π_T represents the expected 1-year incidence rate of the primary efficacy end point events in the experimental group, whereas π_C represents the 1-year incidence rate of the primary efficacy end point events in the control group. By reviewing the literature related to the antithrombotic therapy after TAVR[11,21–23] integrating retrospective data from the Interventional Center of Valvular Heart Diseases of Beijing Anzhen Hospital, and considering clinical experts' opinions, the expected incidence rate of the primary efficacy end point for the NAPT group has been set at 2.0% and for the SAPT group at 3.7%. The type I error α is set at (1-sided) 0.025, and the test power 100 (1–β) is set at

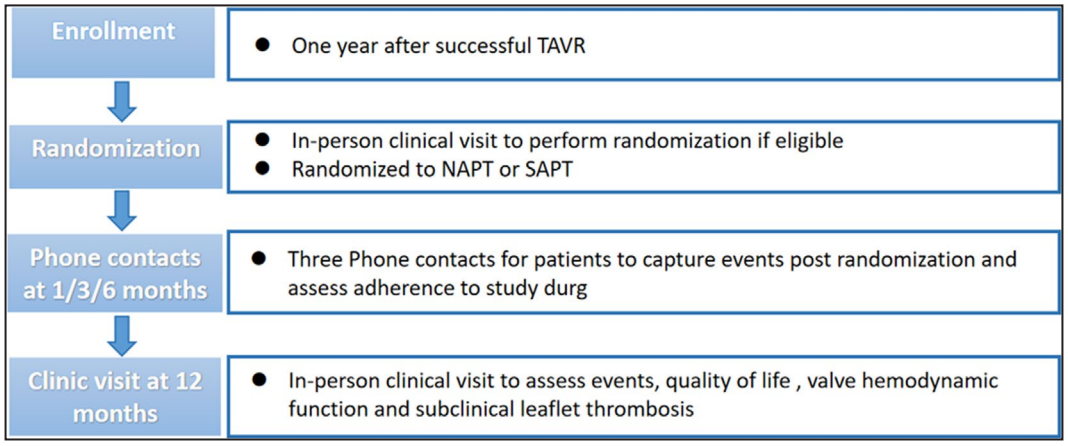

Figure 2. Follow-up time point.
NAPT indicates no antithrombotic therapy; SAPT, single antiplatelet therapy; and TAVR, transcatheter aortic valve replacement.

80%. Hence, at least 1521 patients per group are required. Considering potential attrition (10%) and other factors during the study, the final anticipated sample size is set at 1690 patients per group, totaling 3380 patients.

The formula for sample-size calculation is:

$$n = \frac{\left(Z_{1-\alpha}+Z_{1-\beta}\right)^2 \times \left(\pi_T\left(1-\pi_T\right)+\pi_C\left(1-\pi_C\right)\right)}{\left(\pi_T-\pi_C\right)^2}$$

In the formula, n is the required sample size for each group, π_T represents the event rate for the experimental group (NAPT), π_C represents the total rate for the control group (SAPT), $Z_{1-\alpha}$ represents the 1-α quantile of the standard normal distribution, and $Z_{1-\beta}$ represents the 1-β quantile of the standard normal distribution. For α=0.025, $Z_{1-\alpha}$=1.96. For β=0.2, $Z_{1-\beta}$=0.84.

Primary Safety End Point

This study also calculated the sample size based on the primary safety end point, which is the composite of cardiac death, ischemic stroke/transient ischemic attack, and myocardial infarction during the 12 months after randomization based on a noninferiority hypothesis. The corresponding statistical hypothesis test is:

$$H0: \pi_T - \pi_C \geq \Delta,$$

$$H1: \pi_T - \pi_C < \Delta.$$

In the formula, π_T represents the expected 1-year incidence rate of the primary safety end point events in the experimental group, whereas π_C represents the 1-year incidence rate of the primary safety end point events in the control group. By reviewing the literature reporting the long-term outcomes after TAVR,[24–27] integrating retrospective data from the Interventional Center of Valvular Heart Diseases of Beijing Anzhen Hospital, and considering clinical experts' opinions, the expected incidence rate of the primary safety end point for both the NAPT and SAPT groups has been set at 4.1% (π_T=π_C=4.1%). The noninferiority margin is set at 2.05%, the type I error α of the statistical test is set at (1-sided) 0.025, and the test power 100 (1-β) is set at 80%. Hence, at least 1470 patients per group are required. Considering potential attrition (10%) and other factors during the study, this sample size is increased to 1690 patients per group, totaling 3380

Table 2. Efficacy and Safety End Points

Primary efficacy end point The occurrence of clinically relevant bleeding, defined as VARC-3 types 1, 2, 3, or 4 bleeding occurring from randomization to 12 mo.
Primary safety end point Composite of cardiac death, myocardial infarction, ischemic stroke/transient ischemic attack according to VARC-3 definitions occurring from randomization to 12 mo.
Secondary end points Secondary end points are the occurrence of: 1. All-cause mortality within 12 mo: All causes of death should be recorded, both noncardiac and cardiac, including assessment of device relatedness. 2. Composite end point at 12 mo, including cardiovascular death, MI, and stroke. 3. Net clinical benefit, defined as the composite of all-cause death, stroke, MI, and bleeding. 4. Bleeding complications, defined as BARC types 1, 2, 3, or 5. 5. HALT grade 3 or higher: Evaluated by MDCT assessment 1 y postintervention, categorized as <25%, 25%–50%, 50%–75%, >75%. 6. RLM grade 3 or higher: Evaluated by MDCT assessment 1 y postintervention, categorized as no motion restriction, <50% motion restriction, ≥50% motion restriction, complete motion restriction.

BARC indicates Bleeding Academic Research Consortium; HALT, hypoattenuated leaflet thickening; MDCT, multidetector computed tomography; MI, myocardial infarction; RLM, reduced leaflet motion; and VARC-3, Valve Academic Research Consortium-3.

patients, to be consistent with the efficacy hypothesis power calculation.

The formula for sample size calculation is:

$$n = \frac{\left(Z_{1-\alpha} + Z_{1-\beta}\right)^2 \times \left[\pi_T \times \left(100 - \pi_T\right) + \pi_C \times \left(100 - \pi_C\right)\right]}{\left(\pi_T - \pi_C - \Delta\right)^2}$$

In the formula, n represents the required sample size for each group, π_T represents the total % rate for the experimental group, π_C represents the total % rate for the control group, Δ represents the clinically meaningful noninferiority margin, $Z_{1-\alpha}$ represents the 1-α quantile of the standard normal distribution, and $Z_{1-\beta}$ represents the 1-β quantile of the standard normal distribution.

Therefore, a sample size of 3380 subjects will provide sufficient statistical power for both the superiority test of the primary efficacy end point and the noninferiority test of the primary safety end point.

Analysis Populations

In this study, the study population will comprise the following 2 analysis data sets.

Full Analysis Set

Determined by the intention-to-treat principle, this set includes all randomized participants analyzed according to the treatment to which they were assigned, regardless of whether they fully adhered to the trial protocol or completed the entire study.

Per-Protocol Set

The per-protocol set includes participants follow-up while they fully complied with the trial protocol, excluding any follow-up time when they did not fully adhere to the protocol or withdrew from the trial midway. This is a subset of the full analysis set. For example, if a patient discontinues the assigned SAPT after 3 months, the first 3 months of treatment should still be included in the per-protocol set.

Statistical Analysis

Descriptive Analysis

Categorical data are described using frequencies and proportions, whereas quantitative data are described as mean±SD (x±SD) or median (interquartile range), depending on whether they follow a normal distribution.

Primary End Point Analysis

For both primary safety and efficacy end points, the principle of intention-to-treat analysis using the full analysis set is followed. All participants who are randomized will be included in the statistical analysis according to the intervention assigned at randomization, regardless of treatment adherence.

Even so, we anticipate that a few patients will be censored before 12 months follow-up; that is, they will be lost to follow-up at some point between the date of randomization and 12 months later. Accordingly, in each treatment group, the percentage of patients experiencing a primary end point at 12 months will be estimated using the Kaplan-Meier method. The standard error of each percentage will be calculated using the Greenwood method as the main approach. Additionally, a sensitivity analysis using the complementary log–log scale will be performed to evaluate the robustness of confidence intervals around the estimated survival curves. To compare the Kaplan-Meier estimated percentages of primary end points between the experimental and control groups, a Z test will be used. The test statistic is calculated as follows:

$$Z = \frac{P_T - P_C}{\sqrt{SE_{P_T}^2 + SE_{P_C}^2}}$$

where P_T and P_C are the Kaplan-Meier estimated percentage of having the primary end point in experimental and control groups. SE_{PT} and SE_{PC} are the corresponding standard errors. Z is a standardized normal deviate from which the *P* value is obtained. For the observed treatment difference P_T–P_C, a 95% CI will also be calculated.

For the primary safety end point, which involves a noninferiority hypothesis, the Z test is modified as follows: $Z = \frac{(P_T - P_C) - \Delta}{\sqrt{SE_{P_T}^2 + SE_{P_C}^2}}$,

where Δ is the predefined no-inferiority margin of 2.05%. Again, from the standardized normal deviate, the *P* value for noninferiority is obtained. Also, for the primary safety end point, the 95% CI for the treatment difference P_T–P_C will be calculated.

Secondary End Points Analysis

The number and incidence rate of secondary end points and adverse events will be described separately for the experimental and control groups, again using the Kaplan-Meier method to correct for any loss to follow-up in the analysis of event outcomes. For categorical data, group comparisons are performed using the χ^2 test or using the Fisher exact test when ≥1 cell has expected frequencies <5; for quantitative data with a nonskew distribution, group comparisons are made using the t test; otherwise, group comparisons are conducted using the Wilcoxon rank sum test. Additionally, all adverse events observed in each group will be described in terms of their specific manifestations, severity, and potential relationship to the investigational product.

Subgroup Analyses

The 1-year event rates for the primary bleeding and ischemic end points will be assessed across various subgroups based on patient characteristics and valve function. These subgroups will include those ≥75 versus <75 years of age, female sex, diabetes, chronic kidney disease (estimated glomerular filtation rate <60 mL/min per 1.73 m^2),[28,29] Society of Thoracic Surgeons (STS)-predicted risk of mortality (PROM) score[30] <4% versus ≥4%, high risk bleeding (The Valve Academic Research Consortium for High Bleeding Risk, VARC-HBR),[31] cardiac function, presence or absence of arterial lumen stenosis, valve type and valve size (Table 3).

Handling of Missing Data

For missing primary end point data, no imputation method will be used, and we will rely on observed data for analyses. Patients who withdraw or are lost to follow-up will remain in the analysis per the intention-to-treat principle. Reasons for all withdrawals or dropouts will be documented and summarized in the statistical report. Details of the imputation methods will be specified in the statistical analysis plan.

Safety Monitoring

An independent DSMB will conduct regular evaluations of the accumulating study data to assess interim outcomes, with prespecified statistical stopping guidelines, as outlined in the DSMB charter. The DSMB will comprise individuals with no direct affiliation with the study sponsor or the principal investigator, ensuring impartial oversight. The data under review will include both adjudicated and nonadjudicated ischemic events, bleeding events, and other serious adverse events, to proactively identify any potential safety concerns. Based on these safety assessments, the DSMB may propose protocol adjustments, temporary suspension, or early termination of the trial, and will provide recommendations to the executive committee. All final decisions on any trial modifications will reside with the executive committee.

Sensitivity Analyses

Two sensitivity analyses will be conducted: (1) a sensitivity analysis using Cox regression stratified by site to account for potential between-center heterogeneity and (2) a sensitivity analysis on the estimation of survival curves using the complementary log–log scale, to assess the robustness of confidence intervals generated by the Greenwood method.

DISCUSSION

The hypothesis of the CREATE trial is that 1 year of antiplatelet therapy after the TAVR procedure is sufficient to prevent ischemic events while reducing the risk of late bleeding in patients without chronic indications for anticoagulant or antiplatelet therapy. This distinguishes CREATE from other TAVR trials, where antithrombotic agents are added to conventional treatment to reduce risk of thrombosis, but this increases bleeding risk. CREATE's intervention involves active withdrawal of antiplatelet therapy 1 year post-TAVR, and the trial's efficacy will be measured primarily by reductions in bleeding. It is the first randomized controlled trial to explore the potential value of shortening the duration of antithrombotic therapy in patients undergoing TAVR. This randomized design to continue or withdraw medication has been advocated by leading academic and regulatory authorities, to achieve a better benefit–risk ratio for patients undergoing TAVR.

The recent POPULAR-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial focused on simplifying antithrombotic strategies in patients undergoing TAVR without an indication for anticoagulation.[23] In this trial, patients were assigned to aspirin alone or aspirin plus clopidogrel for 3 months, and it demonstrated that the incidence of bleeding and the composite of bleeding or thromboembolic events were significantly less on aspirin alone during 1-year follow-up. However, lifelong aspirin may not provide the best trade-off between efficacy and safety in this population. Kobari et al were the first to report outcomes following elective withdrawal of antiplatelet therapy at discharge in 3575 patients undergoing TAVR, who had no indication for oral anticoagulation and experienced no procedural complications, as part of the OCEAN-TAVI registry. Among the study population, 293 patients were discharged

Table 3. Predefined Subgroup Analysis

Major subgroups of interest	
1.	Women
2.	Older population (>75 y of age)
3.	Diabetes
4.	Prior cancer
5.	Weight <60 kg
6.	Creatinine clearance <30 mL/min
7.	Prior CAD
8.	Anticoagulation therapy within 1 y after TAVR
9.	Type of valve
10.	Size of valve
11.	Mean gradient at randomization (≥20 mm Hg, ≥30 mm Hg)
12.	HALT and RLM
13.	Aortic regurgitation
14.	Patient–prosthesis mismatch
Other subgroups of interest	
1.	Patients on aspirin
2.	Patients on clopidogrel
3.	Left ventricle ejection fraction <50% at randomization
4.	Surgical risk score
5.	Anemia at admission

CAD indicates coronary artery disease; HALT, hypoattenuated leaflet thickening; RLM, reduced leaflet motion; and TAVR, transcatheter aortic valve replacement.

without antiplatelet therapy (NAPT) and compared with the SAPT and the DAPT patients, respectively.[13] After 3 years of follow-up, the incidence of all bleeding events was lower in the NAPT group compared with DAPT (adjusted hazard ratio [HR], 0.51 [95% CI, 0.27–0.95]) and to SAPT (adjusted HR, 0.63 [95% CI, 0.33–1.19]). No significant differences were observed in rates of all-cause death, cardiovascular death, stroke, or myocardial infarction among the groups. This observational study, although at risk of potential bias, opens up a novel perspective, which provides the scope to evaluate alternative antithrombotic strategy in the TAVR population in a randomized trial.

CREATE aims to challenge the prevailing guideline recommendations for lifelong aspirin use following TAVR, which raises concerns about a higher incidence of bleeding or gastric mucosal injury for approximately one-third of patients undergoing TAVR who do not have existing indications for chronic anticoagulation or antiplatelet therapy. Meantime, several placebo-controlled trials have investigated the paradoxical role of aspirin in balancing ischemic and bleeding risks in primary prevention settings.[32–34]

In addition, the primary objective of the CREATE trial is to examine the effects of antiplatelet withdrawal 1 year post-TAVR, which has circumvented the high incidence time phase of ischemic events. Due to the risk factors for both bleeding and ischemia always overlapping on individuals, withdrawing the antiplatelet at an appropriate time could avoid the risk of late bleeding-related mortality. We anticipate that patients enrolled in CREATE who are at high risk for bleeding and low risk for ischemia will mirror a real-world preference for discontinuing antiplatelet therapy.

To validate this hypothesis, the CREATE trial incorporates 2 primary hypotheses: (1) a superiority hypothesis positing that discontinuation of antiplatelet therapy 1 year after TAVR reduces the incidence of bleeding events compared with the control group receiving SAPT and (2) a noninferiority hypothesis asserting that discontinuation does not increase the incidence of ischemic composite end point events. Sample-size parameters were determined based on prior literature, retrospective data from our center, and expert consensus, culminating in the final estimation. The study hypothesizes that at 1-year postintervention, the incidence of bleeding events will be 2.0% in the intervention group versus 3.7% in the control group. Given that the study population is not restricted to high bleeding-risk patients and the follow-up period is only 1 year, the expected intergroup difference is modest at 1.7%. Nevertheless, bleeding risks associated with antithrombotic therapy accumulate over time,[33,35] and bleeding events can severely impact patient outcomes once they occur.[36] For the noninferiority hypothesis on ischemic composite end points, the noninferiority margin was set at 2.05%, aligning with the commonly accepted practice of defining a margin of 1.5 on a ratio scale as clinically acceptable in similar studies. Additionally, clinical experts confirmed that a 2.05% margin is also acceptable from a clinical standpoint.

Compared with patients undergoing bioprosthetic surgical aortic valve replacement, early anticoagulant therapy is to prevent thromboembolic events during the process of endothelialization of the cloth sewing ring. Therefore, clinical guidelines-recommended duration of warfarin therapy is for it to be prescribed at first 3 to 6 months, but the risks of anticoagulant-related hemorrhage are highest during this period, which becomes a significant risk of complications.[37,38] Based on the mechanical anchoring by radial force of the TAVR prosthesis,[39] a neo-sinus is created between the bioprosthetic leaflet and the stent frame, which fosters a condition conducive to thrombosis,[40,41] leading to reduced leaflet blood washout, prolonged blood stasis and regional low-velocity flow, and ultimately, platelet activation and aggregation that precipitates leaflet thrombosis.[42] Thus, we do not advocate immediate withdrawal of antithrombotic medicine at discharge, which is the main difference with the OCEAN-TAVI study. The CREATE trial is based on the premise that a 1-year course of antithrombotic therapy is sufficient to address early and predominantly valve-related thrombotic events, including acute thrombosis and SLT,[43,44] thereby providing a rationale to stop aspirin at the 1 year mark. We did not specify antithrombotic strategy within 1 year post-TAVR but will exclude patients with SLT identified by multidetector computed tomography who require anticoagulant therapy before randomization. After this period, whether patients undergoing TAVR still require antiplatelet therapy remains unknown, and this forms the primary objective of the CREATE trial.

In conclusion, we will explore whether the process of antithrombotic strategy after TAVR initially behaves similarly to after percutaneous coronary intervention. Although most previous randomized controlled trials adopted routine antithrombotic agents according to guidelines to prevent ischemic events, the lifelong course of antiplatelets recommended by expert consensus is not universally standard. CREATE is poised to offer valuable and novel insights into antithrombotic strategies for up to 30% of patients undergoing TAVR in the real world who have no indications for long-term antithrombotic treatment.

Current Status

The first patient was enrolled in the CREATE trial on August 27, 2024, with the study anticipated to continue through August 2026. To date, 20 sites have been activated, and patient recruitment is currently in progress (Table S2).

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
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