An investigator-sponsored pragmatic randomized controlled trial of AntiCoagulation vs AcetylSalicylic Acid after Transcatheter Aortic Valve Implantation: Rationale and design of ACASA-TAVI

Christopher S. Dodgson, MD [a,e], Jan Otto Beitnes, MD, PhD [a], Sophie F. Kløve, RN [a], Jon Herstad, MD [b], Anders Opdahl, MD, PhD [c], Ragnhild Undseth, MD, PhD [d], Christian H. Eek, MD, PhD [a], Kaspar Broch, MD, PhD [a,e,f], Lars Gullestad, MD, PhD [a,e,f], Lars Aaberge, MD, PhD [a], Ketil Lunde, MD, PhD [a], Bjørn Bendz, MD, PhD [a,e], and Øyvind H. Lie, MD, PhD [a] *Oslo, Norway; Bergen, Norway*

Background The optimal antithrombotic therapy after transcatheter aortic valve implantation (TAVI) is unknown. Bioprosthetic valve dysfunction (BVD) is associated with adverse outcomes and may be prevented by anticoagulation therapy. A dedicated randomized trial comparing monotherapy NOAC to single antiplatelet therapy has not been performed previously. We hypothesize that therapy with any anti-factor Xa NOAC will reduce BVD compared to antiplatelet therapy, without compromising safety.

Methods ACASA-TAVI is a multicenter, prospective, randomized, open-label, blinded endpoint, all-comers trial comparing a monotherapy anti-factor Xa NOAC strategy (*intervention arm*) with a single antiplatelet therapy strategy (*control arm*) after successful TAVI. Three-hundred and sixty patients without indication for oral anticoagulation will be randomized in a 1:1 ratio to either apixaban 5 mg twice per day, edoxaban 60 mg daily, or rivaroxaban 20 mg daily for 12 months followed by acetylsalicylic acid 75 mg daily indefinitely, or to acetylsalicylic acid 75 mg daily indefinitely. The 2 co-primary outcomes are (1) incidence of Hypo-Attenuated Leaflet Thickening (*HALT*) on 4-dimensional cardiac CT at 12 months, and (2) a *Safety Composite* of VARC-3 bleeding events, thromboembolic events (myocardial infarction and stroke), and death from any cause, at 12 months.

Results The first 100 patients had a mean age of 74 ± 3.6 years, 33% were female, the average body-mass index was 27.9 ± 4.4 kg/m^2, and 15% were smokers. A balloon-expanded valve was used in 82% and a self-expandable valve in 18%.

Conclusions The trial is planned, initiated, funded, and conducted without industry involvement.

Trial Registration ClinicalTrials.gov Identifier NCT05035277. (Am Heart J 2023;265:225–232.)

Background and rationale

The use of transcatheter aortic valve implantation (TAVI) for patients with symptomatic severe aortic valve stenosis has increased exponentially since the first successful intervention 2 decades ago.[1] The indication for TAVI has expanded from compassionate use in very old high-risk individuals to include low-risk patients down to 65 years of age.[2] In many centers the number of TAVI procedures has exceeded that of surgical aortic valve re-

From the [a]Department of Cardiology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [b]Department of Cardiology, Haukeland University Hospital, Bergen, Norway, [c]Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway, [d]The Intervention Centre, Oslo University Hospital, Oslo, Norway, [e]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [f]K. G. Jebsen Cardiac Research Centre, University of Oslo, Oslo, Norway

Abbreviations: ASA, acetylsalicylic acid; BVD, bioprosthetic valve dysfunction; HALT, hypo-attenuated leaflet thickening; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACE, major adverse cardiac events; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium; 4D cardiac CT, 4-dimensional cardiac computed tomography.

Submitted June 1, 2023; accepted August 21, 2023

Reprint requests: *Øyvind H. Lie, MD, PhD, FESC, Department of Cardiology, Oslo University Hospital, Rikshospitalet, PO Box 4950, Nydalen, Oslo, Norway 0424.*

E-mail address: oyvlie@gmail.com.

0002-8703

https://doi.org/10.1016/j.ahj.2023.08.010

placement (SAVR).[3] Therefore, efforts to preserve valve durability and longevity are increasingly important.

In recent years the relationship between subclinical thrombosis of the bioprosthetic leaflets and adverse outcomes has come to light. Subclinical leaflet thrombosis is a common finding after TAVI. The reported prevalence is between 15% and 40%, dependent on prosthesis factors, patient factors, and type of antithrombotic medication used.[4-6] Subclinical leaflet thrombosis, and its recommended imaging correlate hypo-attenuated leaflet thickening (*HALT*), has been associated with early bioprosthetic valve dysfunction (BVD), bioprosthetic valve failure, and worse clinical outcomes. Subclinical leaflet thrombosis has been associated with increased risk of transient ischemic attack and stroke.[7-9] An observational study reported an important association between *HALT* and mortality.[10]

During the advent of TAVI, postprocedure antithrombotic strategies were empirically extrapolated from the PCI field. Treatment was based on expert consensus and there was large heterogeneity in approaches between centres.[11-13] Strategies have since been refined with insights gained from randomized studies like ARTE, ENVISAGE-TAVI AF, and POPular TAVI.[14-17] As the potential negative clinical implications of subclinical leaflet thrombosis and *HALT* become more apparent, so does the imperative to prevent their occurrence.

The current recommendation for antithrombotic therapy after TAVI is a single antiplatelet agent for patients without traditional indication for oral anticoagulation, and oral anticoagulation without antiplatelet therapy for patients with clinical indications (such as atrial fibrillation or venous thromboembolism).[18] Oral anticoagulation, either with a vitamin K antagonist or a Non-vitamin K antagonist oral anticoagulant (NOAC), is reported to be more effective than antiplatelet therapy (either single or dual) in both the prevention and treatment of BVD related to subclinical thrombosis.[7,8,19-21] Whether the prevention of subclinical leaflet thrombosis translates to a net clinical benefit for patients is unknown.

AntiCoagulation vs AcetylSalicylic Acid after Transcatheter Aortic Valve Implantation (ACASA-TAVI) will address two clinical questions: First, whether systematic treatment with NOAC for 12 months will reduce the prevalence of HALT, and subsequently prevent early BVD. Second, whether there are safety concerns associated with a monotherapy NOAC strategy.

Methods and analyses

Trial design and objectives

ACASA-TAVI (ClinicalTrials.gov unique identifier: NCT05035277) is an investigator-sponsored, multicenter, prospective, randomized (1:1), open-label, blinded endpoint (PROBE) all-comers trial comparing the efficacy and safety of oral anticoagulation vs single antiplatelet therapy after successful TAVI. The trial is planned, initiated, funded, and conducted without industry involvement. Patients are enrolled at 3 high-volume centers in Norway (Oslo University Hospital Rikshospitalet, Oslo University Hospital Ullevål, and Haukeland University Hospital) where a total of approximately 1,000 TAVI procedures are performed each year.

The primary objective of ACASA-TAVI is to assess the possible superiority of a NOAC monotherapy strategy (intervention arm) as compared with the current standard of care single antiplatelet therapy (control arm) in the prevention of bioprosthetic valve dysfunction, whilst assessing noninferiority for safety (Figure 1). The secondary objectives of ACASA-TAVI are to assess whether an initial NOAC-based regimen improves clinical outcomes in the intermediate and long term. This translates to composite outcomes of major adverse cardiac events (MACE) at 5 and 10 years after TAVI.

Study population and eligibility criteria

All patients aged between 65 and 80 years with severe aortic stenosis and no indication for anticoagulation who undergo successful TAVI at any of the study sites are screened for eligibility for participation in the trial. Successful TAVI is defined according to the latest Valve Academic Research Consortium criteria (VARC-3).[22] Patients with bicuspid aortic valve or previous aortic valve replacement are eligible for participation. An upper age limit of 80 years was chosen to limit loss to follow-up and competing mortality risk, as well as to facilitate intermediate and long-term (5 and 10 year) follow-up of the significance of early HALT prevention.

ACASA-TAVI is a pragmatic trial that aims to enrol a real-world population to generate generalizable data. Therefore, there are relatively few and relevant exclusion criteria (Table 1). The exclusion criteria are contraindication to either NOAC or antiplatelet therapy, conventional indication for NOAC (eg, atrial fibrillation), or antiplatelet therapy (eg, recent percutaneous coronary in-

Table 1. Eligibility criteria

Inclusion criteria

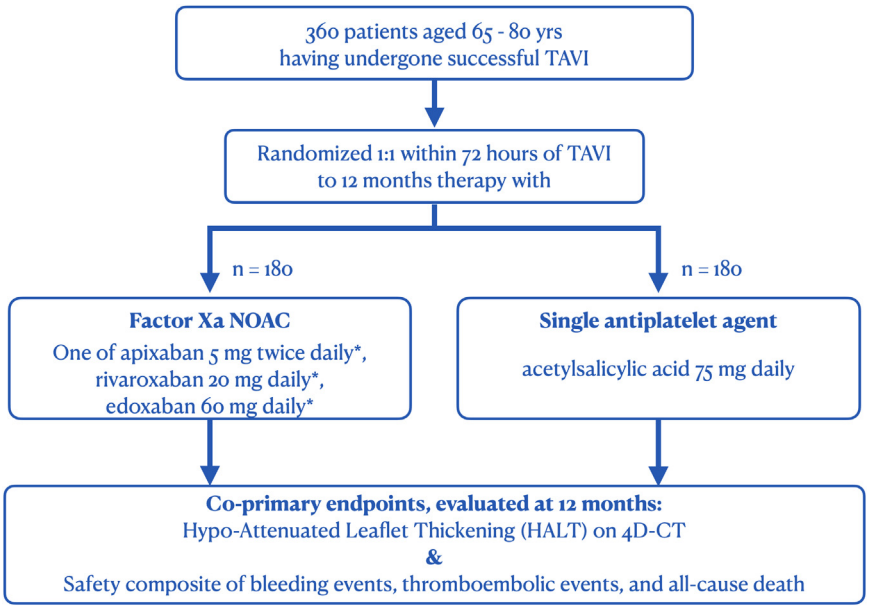
- Patients aged 65-80 years after successful TAVI
- Signed informed consent and expected compliance with protocol

Exclusion criteria

- Contraindication to anticoagulation or antiplatelet therapy
- Conventional indication for anticoagulation or antiplatelet therapy
- Inability to start study medication within 72 hours of TAVI
- Concomitant use of inducers or inhibitors of CYP3A4 or P-glycoprotein

TAVI, transcatheter aortic valve implantation.

Figure 1



Study design. *Dose reduction according to the drug label. Apixaban 2.5 mg twice daily if 2 of the following: (1) age ≥80 years (not relevant at inclusion but may occur during follow-up), (2) body weight ≤60 kg, serum creatinine ≥1.5 mg/dL [133 μmol/L]. Rivaroxaban 15 mg daily if creatinine clearance 15 to 49 mL/min. Edoxaban 30 mg daily if one of the following: (1) Creatinine clearance 15 to 50 mL/min, (2) body weight ≤60 kg, (3) concomitant use of the following P-glycoprotein inhibitors (cyclosporine, dronedarone, erythromycin, or ketoconazole). NOAC, non-vitamin K antagonist oral anticoagulant; TAVI, transcatheter aortic valve implantation.

tervention), inability to initiate trial medication within 72 hours of TAVI, or concomitant use of inhibitors of CYP3A4 or P-glycoprotein (which potentially interact with the study medication). Patients with indication for antithrombotic therapy where both strategies are reasonable are eligible for randomization. Inclusion began in December 2021. Baseline characteristics of the first 100 trial participants are presented for context (Table 2).

Randomization

All eligible patients must provide written, informed consent before randomization to antithrombotic treatment with either an anti-factor Xa NOAC for 12 months followed by acetylsalicylic acid (ASA) indefinitely (intervention), or to ASA indefinitely (control). Central randomization is performed in a 1:1 ratio using an interactive web response system (VieDoc) using balanced, permuted blocks.

Treatment groups

We hypothesize that there is a class effect of anti-factor Xa NOAC medication. In patients randomized to treatment with a NOAC (intervention arm), the investigational product is therefore an open-label anti-Xa type NOAC, either apixaban, rivaroxaban, or edoxaban. The

Table 2. Baseline characteristics of the first 100 trial participants

Age (years)	74.4 (± 3.6)
Sex	33% female
Body-mass index (kg/m^2)	27.9 (± 4.4)
Coronary artery disease	17%
Hypertension	74%
Diabetes mellitus	27%
Heart failure	4%
Previous stroke	11%
Chronic obstructive pulmonary disease	11%
Permanent pacemaker	3%
Troponin T (ng/L)	15.5 (IQR 11-23.5)
NT-proBNP (ng/L)	366 (IQR 175-628)
Glomerular filtration rate (ml/min / 1.73 m^2)	75.9 (±17)
Pre-TAVI echocardiography parameters	
Left ventricular ejection fraction (%)	54 (±7)
Stroke volume (mL)	85 (±20)
Aortic valve mean gradient (mmHg)	49 (±9.7)
Aortic valvular area (cm^2)	0.8 (±0.2)
Procedural characteristics	
Balloon-expanded valve	82%
Self-expanding valve	18%

All values are presented as means with standard deviation (±) or medians with interquartile ranges (IQR) unless otherwise stated. Coronary artery disease was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.

choice of NOAC is a shared decision between the patient and the treating clinician. NOAC of direct thrombin inhibition type (dabigatran) will be avoided to minimize heterogeneity of mechanism of effect and effect size. The treatment is initiated within 72 hours after randomization, accommodating clinical judgement and any subsequent invasive procedures (such as pacemaker implantation), and continues for 12 months. Thereafter, treatment will be converted to ASA 75 mg daily indefinitely.

The dosing of NOAC follows standard clinical practice for anticoagulation. The standard dose of apixaban is 5 mg twice daily. The dose should be reduced to 2.5 mg twice daily if 2 or more of the following criteria are present: (1) age $\geq$ 80 years (not relevant at inclusion but may occur during follow-up), (2) body weight $\leq$ 60 kg, (3) serum creatinine $\geq$1.5 mg/dL (133 μmol/L). The standard dose of rivaroxaban is 20 mg daily. The dose should be reduced to 15 mg daily in patients with moderate to severe renal impairment (creatinine clearance 15-49 mL/min). The standard dose of edoxaban is 60 mg daily. The dose should be reduced to 30 mg daily if one of the following criteria are present: (1) moderate to severe renal impairment (creatinine clearance 15-50 mL/min), (2) body weight $\leq$60 kg, (3) concomitant use of the following P-glycoprotein inhibitors (cyclosporine, dronedarone, erythromycin or ketoconazole). The rationale for dosing of NOAC is based on observational data on the prevention and treatment of HALT.[7,8,19-21]

Patients assigned to the antiplatelet group (control arm) will receive ASA, the current standard of care, indefinitely. The standard dosing is 75 mg daily and there are no dose adjustments. In ASA-naïve patients a single loading dose of 300 mg is administered prior to TAVI. In patients who are intolerant to ASA, conversion to clopidogrel is recommended as per current clinical practice.

Medication compliance is self-reported by trial participants, resembling clinical practice.

Management of treatment cross-over

Patients randomized to the control arm (ASA) who develop a clinical indication for anticoagulation (eg, atrial fibrillation) during follow-up will cross over to the NOAC group. Conversely, patients in the NOAC group who develop an indication for antiplatelet therapy (eg, percutaneous coronary intervention) will cross over to the ASA group. All patients will remain in their originally allocated arm for analysis (intention-to-treat analysis of initial strategy). Per-protocol analyses will be performed for safety as predefined.

Follow-up and study outcomes

Primary outcome measures

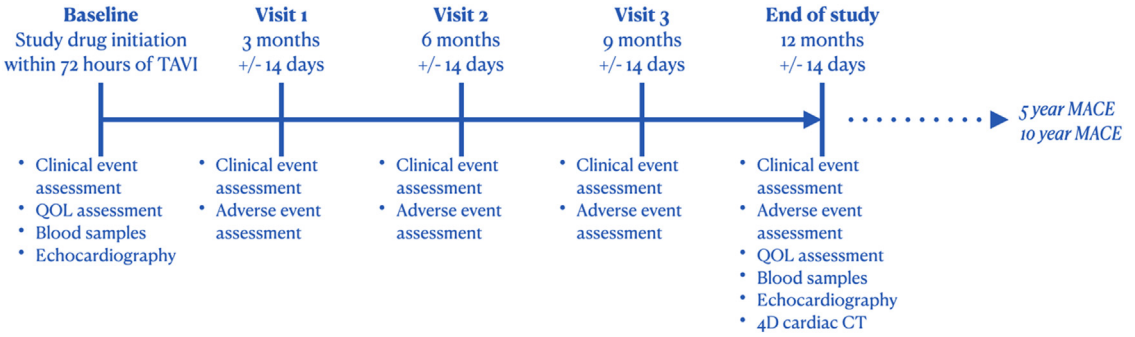
After TAVI and inclusion into the trial the patients´baseline characteristics are noted, including physical examination, medical history, and concomitant medication. We collect blood samples and record self-reported quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), and data from echocardiograms obtained before and after the procedure. We contact patients by telephone at 3, 6, and 9 months. Twelve months after randomization, the patients are invited to an on-site visit. At the 12-month visit, we perform 4-dimensional cardiac computed tomography (4D cardiac CT), echocardiography, collect blood samples, and record self-reported quality of life. Clinical parameters, protocol adherence, and adverse events are assessed at all visits (Figure 2).

The principal objective of ACASA-TAVI is to assess whether NOAC therapy can reduce the prevalence of HALT after TAVI without compromising safety. This study question translates to 2 co-primary outcomes, where both null hypotheses must be rejected for the intervention to be considered successful: The first co-primary outcome is hypo-attenuated leaflet thickening (*HALT*) as documented by 4D cardiac CT at 12 months post randomization. The definition of *HALT* will be the visual assessment of increased thickness of at least 1 bioprosthetic leaflet on a semiquantitative grading scale, as defined by the VARC-3 criteria (Figure 3).[22] This outcome will be assessed for *superiority* of NOAC vs ASA. All 4D cardiac CT examinations will be blindly adjudicated at a core lab. The second co-primary outcome will assess whether routine treatment with NOAC will lead to more bleeding events, and whether withholding platelet inhibitors will lead to more thromboembolic events. This translates to a *Safety Composite* of (1) all types of VARC-3 bleeding events, (2) thromboembolic events (myocardial infarction and stroke from any cause), and (3) death from any cause, at 12 months. This outcome will be assessed for noninferiority of NOAC vs ASA.

Secondary outcome measures

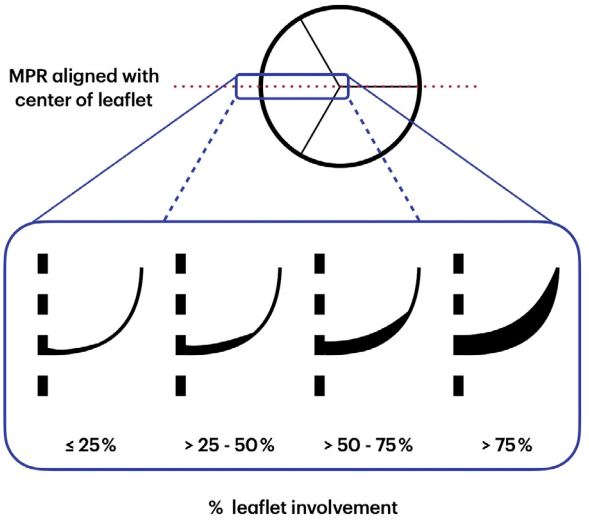
The key secondary outcomes include a clinical efficacy composite of freedom from all-cause mortality, freedom from stroke, freedom from hospitalization for procedure- or valve-related causes, and freedom from a KCCQ overall summary score <45 or decline from baseline > 10 points. Further key secondary outcomes are testing of the second co-primary outcome (*Safety Composite*) for superiority, thromboembolic events, all types of VARC-3 bleeding events, and all-cause mortality. These key secondary outcomes will be tested in hierarchical order, meaning that hypothesis testing stops at the first non-significant endpoint. A user panel was consulted in the establishment of hierarchy and emphasized the importance of quality of life assessment. Secondary safety outcomes include the number of adverse events and serious adverse events, and individual evaluation of type 1 to 4 VARC-3 bleeds. Prespecified subgroup analyses include the use of balloon-expanded vs self-expandable valve, and the use of postdilatation. Further prespecified subgroup analyses, and exploratory secondary outcomes, are described in full in the study protocol.[23]

Figure 2



Trial timeline. MACE, major adverse cardiac events; QOL, quality of life; TAVI, transcatheter aortic valve implantation.

Figure 3



Assessment of hypo-attenuated leaflet thickening *(HALT)* by computed tomography imaging using multiplanar reconstruction alignment. The dashed red line indicates the orientation of the long-axis views in the lower row, aligned with the center of the cusps. The extent of leaflet thickening can be graded on a subjective 4-tier grading scale along the curvilinear orientation of the leaflet. Typically, hypo-attenuated leaflet thickening appears meniscal-shaped on long-axis reformats, with greater thickness at the base than towards the center of the leaflet. Adapted from VARC-3.[22] MPR, multiplanar reconstruction.

Echocardiography is a widely accessible and validated method of assessing bioprosthetic valve function. Repeated echocardiograms at baseline and at 12 months will determine the degree of hemodynamic valve deterioration. Stages 1 to 3 of valve deterioration will be defined as suggested in VARC-3.[22] All echocardiograms will be blindly adjudicated at a core lab.

Blinded outcome adjudication

The trial employs a PROBE design, wherein treatment allocation is open-label during the course of the study, but all outcomes (*HALT* on 4D cardiac CT and clinical events) are adjudicated in a blinded fashion to preserve impartiality. Echocardiographers are blinded to study group allocation at the time of image acquisition, and the echocardiograms are assessed off-line in a blinded manner. Even though the adjudication of clinical events in the *Safety Composite* is blinded, we cannot exclude that bias may be introduced by the trial staff when filling the case report files. Data monitoring will be performed to minimize this.

Management of HALT at 12-month follow-up

There is currently no consensus on treatment of isolated HALT without clinical symptoms. If HALT is established on 4D-CT and the patient experiences symptoms judged to be related to valve degeneration, or is found to have stage 2 or 3 hemodynamic valve deterioration on echocardiogram, treatment will be considered. Trial-specific investigations will be made available to independent clinicians who will evaluate whether pharmacological or structural intervention is indicated according to clinical practice.

Extended follow-up for clinical outcome

HALT has been detected from as early as 5 days to 1 year after TAVI and beyond.[5,6,24] The relationship between timing of leaflet thrombosis and clinical outcomes is not fully understood. Likewise, it is unclear whether prevention of early BVD could lead to improved long-term outcome. Therefore, we plan to assess major adverse cardiac events (MACE) 5 and 10 years after randomization. MACE will be defined as a composite of cardiac death, heart failure hospitalization, re-intervention with valve-in-valve TAVI, stroke, myocardial infarction, and VARC-3 type 2 to 4 bleeding.

Sample size estimation and planned statistical analyses

Based on previous studies, the first co-primary outcome (*HALT*) can be expected to occur in approximately 20% of patients treated with ASA.[19,25] *HALT* is a surrogate outcome, and a possible effect must be considerable to argue clinical relevance. Based on previous reports suggesting a 60% to 70% reduction in HALT with anticoagulation therapy, a premise of 50% reduction of HALT seems both reasonable and relevant. The trial requires the randomization of 310 patients in a 1:1 fashion to obtain 80% power with a 2-sided 0.05 alpha for a 50% reduction in the primary efficacy outcome in the NOAC group. A 50% reduction is clinically relevant and is a realistic effect size based on previous indirect data.[19,25] The estimated sample size for the second co-primary outcome *(Safety Composite)* is more complex and relies on additional assumptions. Previous expected estimates of 1-year rate of the *Safety Composite* outcome have been presented at 34% in the ASA-group[16] and 31% in the NOAC group.[17] We considered a noninferiority margin of 35% relative to the active comparator to be clinically meaningful and adopted the previous estimates of event rates. The 35 % relative margin is similar to the noninferiority margins used in previous trials involving NOACs.[26,27] A 1-sided 0.025 alpha requires 310 patients to be randomized 1:1 to obtain 80% power to show noninferiority. To account for loss to follow-up and withdrawal of consent in 10% to 15% of participants, we aim to randomize 360 patients to ensure power for both co-primary outcomes (*HALT, superiority*, and *Safety Composite, noninferiority*). Because ACASA-TAVI is a strategy trial, no adjustments for crossover were made. A sensitivity analysis for the per-protocol population will be performed and reported. The *Safety Composite* will be analyzed in the per-protocol population.

There is no convincing evidence suggesting that 1 anti Xa-type NOAC is superior to another, and we believe that there is a substantial class effect of these drugs. This is reflected in clinical practice. Because ACASA-TAVI is a clinician initiated and industry independent trial, we find it reasonable to test the strategy of prescribing a NOAC rather than comparing individual drugs. Any sign of heterogeneity between NOAC drugs will only be interpreted as hypothesis generating.

Process monitoring and mitigation strategies

To assess whether our estimations are reasonable we will count the total number of the co-primary outcomes when 50% of the 12-month visits have been performed. This number should be somewhere around 10% to 20% for *HALT* and 25% to 40% for the *Safety Composite* outcome. Testing between groups will not be performed to preserve trial blinding. The steering committee will assess whether the number of events deviates substantially from the anticipated, and whether mitigation strategies need to be implemented. Potential mitigation strategies include sample size revision, enriching the study population with older age groups (up to 85 years of age), including transient ischemic attack to the *Safety Composite*, and reordering of the clinical outcomes.

Statistical analyses

The co-primary outcomes at 12 months will be tested using chi-square tests of proportions. The first co-primary outcome will be tested for superiority using a 2-sided chi-square test at the 0.05 significance level in the intention-to-treat population. The second co-primary outcome *(Safety Composite)* will be tested for noninferiority using the computed 1-sided noninferiority limit corresponding to an upper end of the 95% confidence interval of the NOAC group 11.9% above the proportion in the ASA group in the per-protocol population.

Organization

The steering committee is composed of senior members of the Department of Cardiology at Oslo University Hospital, Rikshospitalet. A user panel, consisting of 2 patients and a coordinator, was consulted during the planning and execution of the trial. An independent data safety monitoring board, consisting of an experienced clinical cardiologist and independent trial statistician, is responsible for monitoring safety during the trial. An independent trial statistician will perform the statistical analyses. No formal stopping criteria are defined; the data safety monitoring board will give recommendations of stopping the trial if they consider interim data to be convincing.

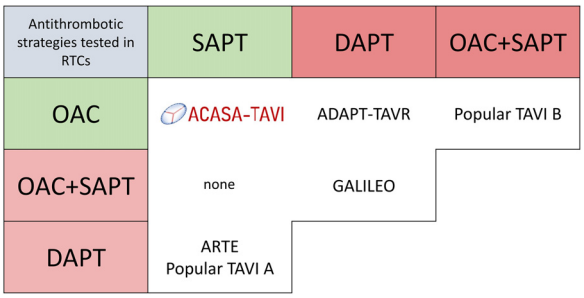
Ethics and dissemination

This trial is conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable regulatory requirements. The trial protocol[23] was approved by the Regional Ethics Committee of South-Eastern Norway (ref. 247400) and by the Norwegian Medicines Agency (ref. 21/13399-9).

The study background and main objective as well as potential benefits and risks will be fully explained to the participants. All participants voluntarily sign a declaration of informed consent. It is emphasized that study participation is voluntary, and that withdrawal is allowed at any time without prejudice to subsequent clinical care. The overall results will be submitted for publication in peer-reviewed academic journals and disseminated at international scientific meetings.

The funding sources have had no role in the conception of the study and will not participate in the implementation of the trial, in the analyses of the results, or in the decision to publish. Funding was obtained through a public research grant from South-Eastern Norway Health Authorities (Grant no.2022084).

Figure 4



Randomized controlled trials comparing different antithrombotic strategies after transcatheter aortic valve implantation. Green fields indicate the recommended strategy for patients with and without independent indications for oral anticoagulation. The ongoing NOTION-4 trial will assess the value of short-term NOAC after TAVI. DAPT, dual antiplatelet therapy, OAC, oral anticoagulation, RCT, randomized controlled trial, SAPT, single antiplatelet therapy.

Discussion

The field of antithrombotic therapy after TAVI is changing rapidly. Several trials evaluating anticoagulation in the setting of TAVI have used more potent combinations of antithrombotic medication than is current clinical practice.[28-30] Many of these trials have tested dual antiplatelet therapy as the comparator, or a combination of antiplatelet agent and anticoagulation as the intervention (Figure 4).

Anticoagulant vs dual antiplatelet therapy for preventing leaflet thrombosis after transcatheter aortic valve replacement (ADAPT-TAVR) $n = 235$, tested dual antiplatelet therapy vs edoxaban 60 mg daily for the primary outcome of *HALT* on 4D-CT.[30] There was a signal in favor of edoxaban being associated with fewer instances of *HALT* (9.8% vs 18.4%; absolute difference, −8.5% [95% CI,−17.8% to 0.8%]; $P = .076$) but the trial was powered for a formidable effect size and was likely underpowered for a clinically meaningful benefit or for clinical outcomes.

The global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes (GALILEO) trial ($n = 1,644$) evaluated rivaroxaban 10 mg alongside 3 months of ASA (75 to 100 mg) vs ASA (75 to 100 mg) alongside 3 months of clopidogrel 75 mg in patients without established indication for oral anticoagulation.[29] This study was terminated early due to safety concerns in the oral anticoagulation + ASA group. There was an increase in rates of death or first thromboembolic event in the rivaroxaban group, but no difference in the rates of major, disabling, or life-threatening bleeding. This trial was conducted with more potent antithrombotic regimens in both arms than ACASA-TAVI. A substudy of GALILEO showed a significantly lower incidence of *HALT* in the NOAC arm, with an absolute risk reduction of 20% (from 32.4% to 12.4%).[19]

The antithrombotic strategy to lower all cardiovascular and neurologic ischemic and hemorrhagic events after trans-aortic valve implantation for aortic stenosis (ATLANTIS) trial ($n = 1,500$) found that apixaban 5 mg twice daily was not superior to the standard-of-care arm, but did meet noninferiority for net clinical benefit.[28] The trial included 3 arms, with a broad range of antithrombotic regimens. Only 20.8% of patients without indication for oral anticoagulation in the standard of care arm received single antiplatelet therapy (either ASA or clopidogrel), which is the current standard of care. In the apixaban arm 26.3% received either single antiplatelet therapy or DAPT alongside apixaban, potentially contributing negatively to outcomes. Importantly, there was no increased risk of ischemic events or bleeding events in the apixaban arm. A substudy of the ATLANTIS trial showed a reduction in valve thrombosis in the NOAC arm vs antiplatelet arm.[20]

ACASA-TAVI is, to the best of our knowledge, the first head-to-head randomized clinical trial comparing the 2 recommended antithrombotic strategies; a single antiplatelet agent vs monotherapy NOAC after TAVI. Enrolment is on-schedule, and the milestone 100th patient was included in January 2023.

Conflict of interest

None reported.

References

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.
2. Writing Committee M, Otto CM, Nishimura RA, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021;77:e25–e197.
3. Carroll JD, Mack MJ, Vemulapalli S, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. J Am Coll Cardiol 2020;76:2492–516.
4. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015–24.
5. Makkar RR, Blanke P, Leipsic J, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. J Am Coll Cardiol 2020;75:3003–15.
6. Blanke P, Leipsic JA, Popma JJ, et al. Bioprosthetic aortic valve leaflet thickening in the evolut low risk sub-study. J Am Coll Cardiol 2020;75:2430–42.

7. Bogyi M, Schernthaner RE, Loewe C, et al. Subclinical leaflet thrombosis after transcatheter aortic valve replacement: a meta-analysis. JACC Cardiovasc Interv 2021;14:2643–56.
8. Chakravarty T, Sondergaard L, Friedman J, et al. Makkar RR, resolve, investigators S. subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383–92.
9. Rashid HN, Gooley RP, Nerlekar N, et al. Bioprosthetic aortic valve leaflet thrombosis detected by multidetector computed tomography is associated with adverse cerebrovascular events: a meta-analysis of observational studies. EuroIntervention 2018;13:e1748–e1e55.
10. Garcia S, Fukui M, Dworak MW, et al. Clinical impact of hypoattenuating leaflet thickening after transcatheter aortic valve replacement. Circ Cardiovasc Interv 2022;15:e011480.
11. Cerrato E, Nombela-Franco L, Nazif TM, et al. Evaluation of current practices in transcatheter aortic valve implantation: the WRITTEN (WoRldwIde TAVI ExperieNce) survey. Int J Cardiol 2017;228:640–7.
12. Petronio AS, Capranzano P, Barbato E, et al. Current status of transcatheter valve therapy in Europe: results from an EAPCI survey. EuroIntervention 2016;12:890–5.
13. Sherwood MW, Vemulapalli S, Harrison JK, et al. Variation in post-TAVR antiplatelet therapy utilization and associated outcomes: insights from the STS/ACC TVT registry. Am Heart J 2018;204:9–16.
14. Rodes-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (aspirin versus aspirin + clopidogrel following transcatheter aortic valve implantation) randomized clinical trial. JACC Cardiovasc Interv 2017;10:1357–65.
15. Van Mieghem NM, Unverdorben M, Hengstenberg C, et al. Edoxaban versus vitamin K antagonist for atrial fibrillation after TAVR. N Engl J Med 2021;385:2150–60.
16. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med 2020;383:1447–57.
17. Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med 2020;382:1696–707.
18. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561–632.
19. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. N Engl J Med 2020;382:130–9.
20. Montalescot G, Redheuil A, Vincent F, et al. Apixaban and valve thrombosis after transcatheter aortic valve replacement: the ATLANTIS-4D-CT randomized clinical trial substudy. JACC Cardiovasc Interv 2022;15:1794–804.
21. Sondergaard L, De Backer O, Kofoed KF, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. Eur Heart J 2017;38:2201–7.
22. Varc-3 Writing C, Genereux P, Piazza N, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. Eur Heart J 2021;42:1825–57.
23. Lie ØH. Anticoagulation versus acetylsalicylic acid after transcatheter aortic valve implantation (ACASA-TAVI) study protocol. Clinical Trials https://clinicaltrials.gov/ProvidedDocs/77/NCT05035277/Prot_002.pdf. (accessed January 19, 2023 2023).
24. Hein M, Schoechlin S, Schulz U, et al. Long-term follow-up of hypoattenuated leaflet thickening after transcatheter aortic valve replacement. JACC Cardiovasc Interv 2022;15:1113–22.
25. Rogers T, Shults C, Torguson R, et al. Randomized trial of aspirin versus warfarin after transcatheter aortic valve replacement in low-risk patients. Circ Cardiovasc Interv 2021;14:e009983.
26. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
27. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
28. Collet JP, Van Belle E, Thiele H, et al. Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial. Eur Heart J 2022;43:2783–97.
29. Dangas GD, Tijssen JGP, Wohrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. N Engl J Med 2020;382:120–9.
30 Park DW, Ahn JM, Kang DY, et al. Edoxaban versus dual antiplatelet therapy for leaflet thrombosis and cerebral thromboembolism after TAVR: the ADAPT-TAVR randomized clinical trial. Circulation 2022;146:466–79.