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Leaflet Thickening and Motion After Transcatheter Aortic Valve Replacement: Design and Rationale of the Rotterdam Edoxaban Trial

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ABSTRACT

Background: Multislice computed tomography (MSCT) may reveal hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion (RELM) in approximately 15 % of patients after transcatheter aortic valve replacement (TAVR). These supposedly thrombogenic phenomena may be associated with neurological events and increased transprosthetic gradients. It is unclear whether oral anticoagulant therapy -specifically a factor Xa inhibitor- could affect the incidence of HALT/RELM.

Study design: The Rotterdam EDOXaban (REDOX) trial is an investigator-initiated, single-center, prospective registry in which 100 patients with no formal indication for oral anticoagulant drugs or dual antiplatelet therapy, will receive a 3-month treatment with edoxaban, followed by a MSCT to detect HALT/RELM. The primary endpoint is the incidence of HALT at 3-months follow-up. Secondary endpoints include the incidence of RELM at 3 months; change in transprosthetic gradients at 1 year and the clinical composite endpoint of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism, valve thrombosis and major bleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) at 1 year follow up.

The study is powered to demonstrate with 90 % statistical power and a 0.025 alpha a 4 % incidence of HALT with edoxaban as compared to the expected 15 % rate with an antiplatelet regimen and will enroll 100 patients to account for loss of follow-up or CT-drop out.

Conclusion: The REDOX trial will investigate the short-term effect of an Xa-inhibitor on the incidence of HALT after TAVR. (ClinicalTrials.gov Identifier: NCT04171726).

1. Background

Transcatheter aortic valve replacement (TAVR) is a well-established treatment for elderly with symptomatic severe aortic stenosis (AS) [1–4]. In approximately 15 % of TAVR patients, post-implant multislice computed tomography (MSCT) reveals hypo-attenuated leaflet thickening (HALT), believed to be a thrombotic phenomenon given its lower incidence in patients on oral anticoagulants (OAC) [5–7]. HALT may be associated with thromboembolic events, reduced leaflet motion (RELM), increased transprosthetic gradients and impaired bioprosthetic valve durability [6,8–10] (Fig. 1).

After surgical aortic valve replacement (SAVR) with a bioprosthesis -based on two large registries- guidelines recommend 3 months of either aspirin alone or aspirin with warfarin depending on the patient's bleeding risk [11,12]. These results cannot be extrapolated to TAVR given the fact that the native aortic valve is left in situ and could represent a thrombogenic milieu due to local blood flow turbulences and stasis, incomplete prosthesis apposition and incomplete endotheliazation [1,13]. The optimal anti-thrombotic regimen after TAVR is unclear and empirically based. Current guidelines recommend dual antiplatelet therapy (DAPT) for 3 to 6 months after TAVR. The Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial undermined this recommendation and demonstrated more bleeding or thromboembolic events with aspirin and clopidogrel versus aspirin alone [14]. 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 reported a higher risk of death or thromboembolic complications and a higher risk of bleeding with aspirin plus a 10 mg rivaroxaban dose as compared to DAPT. [15] Mono therapy with non-

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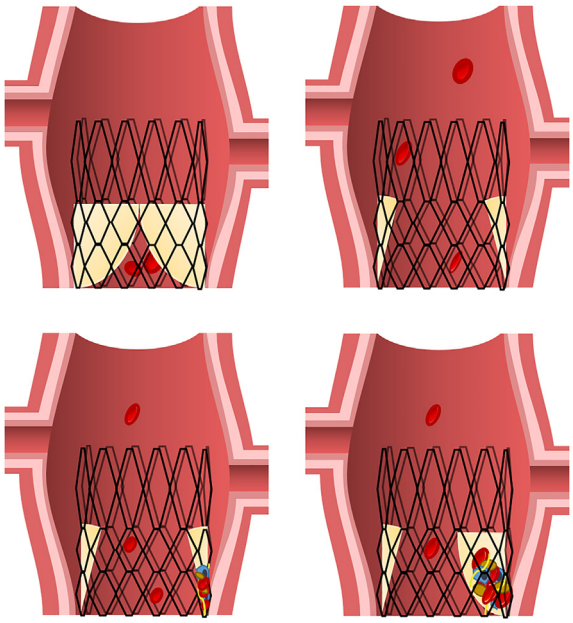

Fig. 1. Hypo-attenuating leaflet thickening (HALT) and reduced leaflet motion (RELM).
A and B: normal prosthetic heart valve function during diastole (A) and systole (B).
C: Hypo-attenuating leaflet thicking (HALT) with normal leaflet motion.
D: Reduced leaflet motion (RELM) where the opening of at least one leaflet is affected.

vitamin K anticoagulants (NOAC) after TAVR in patients with no formal indication for anticoagulant therapy has never been studied. Edoxaban is an oral, reversible, direct factor Xa inhibitor that was non-inferior to warfarin in the prevention of stroke or systemic embolic events, but with significantly lower rates of bleeding and death from cardiovascular causes in patients with atrial fibrillation in the Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) trial. [16]

The Rotterdam EDOXaban (REDOX) was designed to investigate whether mono therapy with Edoxaban after TAVR in patients with no formal indication for OAC or DAPT was safe and could reduce the incidence of HALT.

2. Methods

2.1. Study aims

The primary objective of the REDOX trial is to investigate the impact of Edoxaban on the incidence of HALT after TAVR as determined by MSCT at 3 months.

Secondary endpoints are (1) the occurrence of RELM, (2) the change in transprosthetic gradients (pre-discharge and at one year follow-up) and (3) clinical composite endpoint of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism, valve thrombosis, and major bleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) at 1 year follow up.

2.2. Planned sample size and statistical analysis

Observational studies reported incidences of HALT ranging from 2.9 to 40.0 % [6,8,9,17–22]. A recent meta-analysis calculated a crude incidence of HALT of 15.1 % in a general TAVR population, of note: in GALILEO 4D a more liberal definition of HALT was applied that resulted in a higher incidence of 32 % in patients on antiplatelet therapy [5,17]. Patients on OAC, seemed to have a lower expected HALT rate of approximately 4 % [8]. A total of 87 subjects would be required to demonstrate a significant reduction of HALT incidence from 15 % to 4 % with a one-sided alpha of 0.025 and 90 % power. To accommodate for the patients lost to follow-up and MSCT-drop outs the overall sample size was set a 100 subjects.

All data will be evaluated in both the intention-to-treat and the as-treated population. The as-treated population is defined as at least 90 days of edoxaban treatment. For continuous variables, statistical summaries will include n (number of subjects), mean and standard deviation or median and interquartile range depending on normality. For categorical variables, statistical summaries will include counts and percentages. Percentages will be reported with one decimal place. The primary endpoint is the occurrence of thickening of at least one prosthetic leaflet, which will be presented as a count and percentage. In an exploratory analysis this rate will be compared with the rate of leaflet thickening in the control arm of the Galileo trial using a Chi-Square test for proportions. A one-sided p-value <0.025 will be considered statistically significant. Secondary study parameters will be presented in a descriptive manner and no statistical analyses will be performed.

2.3. Study eligibility and screening

Patients will be screened within 48 h after successful transfemoral TAVR for native degenerative and calcified severe aortic stenosis. Indication for TAVR is determined by the multidisciplinary heart team, patients are eligible for inclusion regardless of surgical risk. Successful TAVR is defined as the correct positioning of a single transcatheter heart valve into the proper anatomical location with a residual mean aortic valve gradient <20 mmHg, peak transvalvular velocity lower <3 m/s and no more than moderate aortic regurgitation. Patients with major periprocedural complications such as overt stroke, uncontrolled bleeding and major vascular complications will be excluded (Table 1).

Patients may not have a formal indication for dual antiplatelet drug therapy (e.g. recent or concomitant percutaneous coronary intervention) or oral anticoagulant drugs (e.g. mechanical valve prosthesis or atrial fibrillation Other exclusion criteria include a history of life-threatening or major bleeding, malignancies with a high risk of bleeding or recent unresolved brain or spinal injury. Because patients require contrast administration for the follow-up MSCT, patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min will be excluded. All subjects will provide written informed consent prior to enrollment.

2.4. Investigational product

Edoxaban is an oral, non-vitamin K antagonist (VKA) anticoagulant that selectively inhibits factor Xa. Factor Xa defines the upstream conjuncture for the intrinsic and extrinsic coagulation pathway. It achieves maximum concentrations within 1 to 2 h, and 50 % is excreted by the kidney [16]. Edoxaban is available in two doses; either 30 (eGFR <50 mL/min) or 60 mg dosed once-daily. The investigational product is provided by the sponsor, patients will receive two bottles containing 60 tablets (i.e. 120 in total). After three months the patients will return the 2 bottles and the remaining tablets will be counted.

2.5. Study procedures

All subjects will be treated according to standard of care, including a multidisciplinary heart team discussion for treatment allocation to TAVR and an MSCT to guide access-site strategy and bioprosthesis selection. All procedures will be done under local anesthesia. Sentinel embolic protection (Boston Scientific, Marlborough MA, USA) will be used if anatomically feasible. Heparin and protamin use is at the operators discretion and will target an activated clotting time of 250 s during valve deployment. After the procedure patients start with the investigational drug one day (and no later than two days) after TAVR without concomitant antiplatelet therapy. All subjects undergo a pre-discharge transthoracic echocardiogram prior to study enrollment. Clinical follow-up is planned at 1, 3 and 12 months post-TAVR. At the 3-

Table 1
In- and exclusion criteria.

Inclusion criteria
- Patients that completed successful elective TAVI for severe native aortic valve stenosis with any commercially-available transcatheter heart valve
o Correct positioning of a single prosthetic valve into the proper anatomical location
o Device success, defined by
▪ Mean aortic valve gradient <20 mmHg
▪ Peak transvalvular velocity <3.0 m/s
- No more than moderate aortic valve regurgitation
- No periprocedural complications
o No overt stroke
o No uncontrolled bleeding
o No major vascular complication
- No formal indication for oral anticoagulation
Exclusion criteria
- History of life-threatening or major bleeding event ≥ BARC 3b definitions within the last year
- Other conditions with a high risk of bleeding
o An active peptic ulcer or upper gastrointestinal bleeding within last 3 months prior to enrolment
o Malignancy with high risk of bleeding
o Recent unresolved brain of spinal injury
o Spinal or ophthalmic surgery within last 3 months prior to enrolment
o Intracranial haemorrhage
o Esophagal varices
o Atriovenous malformations with high risk of bleeding
o Vascular aneurysms
o Major intraspinal or intracerebral vascular abnormalities
- No percutaneous coronary intervention within 6 months prior to randomization requiring (dual) antiplatelet therapy after the TAVI procedure.
- Renal impairment defined as by dialysis-dependency or eGFR <30 mL/min at time of enrolment
- Active bleeding or bleeding diasthesis including thrombocytopenia (platelet count <50.000 cells/UL), thrombobasthenia, haemophilia or von Willebrand disease
- Patients unable to adhere to or complete the investigational protocol for any reason including but not limited to geographical residence, psychiatric condition or life-threatening disease
- Pregnant or breast-feeding subjects
- Current participation in clinical trials that potentially interfere with the current study

months follow-up visit patients undergo and MSCT and are switched to single antiplatelet therapy unless new onset atrial fibrillation has arisen and the patient will continue on label edoxaban therapy. Additional transthoracic echocardiography is planned to evaluate transprosthetic gradient in patients with RELM ≥3 (Fig. 2).

2.6. CT-scan protocol

Patients will undergo a contrast-enhanced cardiac CT scan 3 months after TAVI. No beta-blockers are administered. Imaging is performed on a dual source CT scanner (SOMATOM Force, Siemens Healthcare, Forchheim, Germany) with iodinated contrast agent with a concentration of 320 mg/ml (Visipaque, GE Healthcare, Cork, Ireland) at a flow rate of 5 mL per second. A first 65 mL 100 % contrast agent bolus is followed by a second 40 mL bolus with diluted contrast agent (with 70 % contrast and 30 % saline). Bolus tracking is done in the ascending aorta. Images are acquired using retrospective ECG-gating with dose modulation. The full tube current will be used for the first 45 % of the R-R interval, followed by a reduced current (20 % of the initial level) for the rest of the interval. Dose-modulation is used to optimize the balance between diagnostic accuracy and radiation dose. Automatic kilovoltage selection is used and the reference tube current set at 150 mAs at a reference kV of 120. The images are reconstructed with a Bv36 kernel, a slice thickness of 0.75 mm and an increment of 0.40 mm at every 5 % of the R-R interval.

2.7. Scan evaluation

Experienced imagers will evaluate all scans on a workstation with dedicated software (IntelliSpace Portal, Philips, Eindhoven, The Netherlands). Multiplanar reformatting is used to evaluate the aspect and mobility of the valve leaflets. Cine imaging is used to aid the mobility assessment. HALT is evaluated in a longitudinal plane perpendicular to the aortic annulus. As previously proposed, the severity of leaflet thickening is scored on a five point scale: grade 0 for no leaflet thickening, grade 1 for <25 %, grade 2 for 25–50 %, grade 3 for 50–75 % and grade 4 when >75 % of the leaflet is affected. [23] In the presence of leaflet thickening, a similar scale is used to score reduced leaflet motion: grade 0 for no restriction, grade 1 for minimal restriction, grade 2 for mild restriction, grade 3 for moderate restriction and grade 4 for largely immobile leaflets [17].

2.8. Data management and monitoring

All baseline and follow-up data will be collected and stored in OpenClinica (OpenClinica LLC, Waltham MA, USA), an electronic Case Report Form (eCRF) application. All data will be anonymized and subjects will be linked to a study ID number. Data will only be shared with the investigators involved. Monitoring will take place according to the Dutch Federation of University Medical Centres (NFU).

2.9. Study status and timeline

The REDOX trial is actively enrolling patients since August 2019 and has reached the 40 % inclusion in April 2022. There was a lag in inclusion

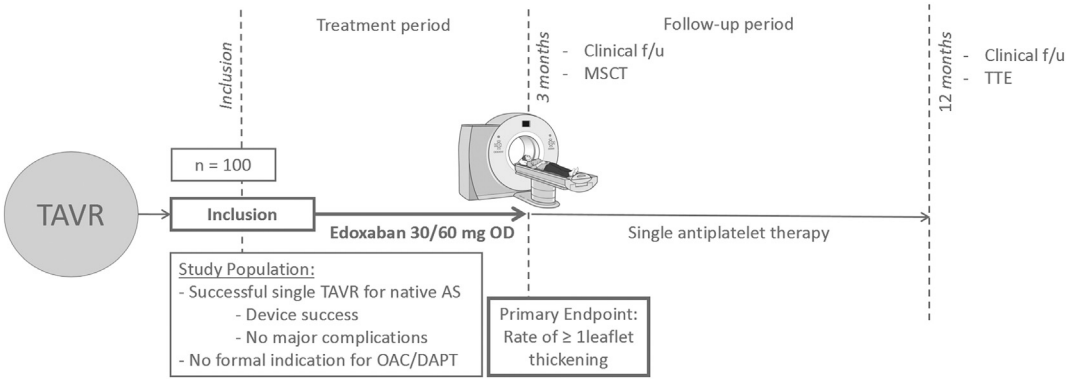

Fig. 2. Rotterdam EDOXaban study design. TAVR: transcatheter aortic valve replacement. AS: aortic stenosis. OAC: Oral Anticoagulans. DAPT: Dual antiplatelet therapy. MSCT: multislice computed tomography. TTE: transthoracic echocardiography.

due to the COVID-19 pandemic, but at current pace the study is expected to complete enrolment in Q4 of 2022.

3. Conclusion

The REDOX trial is an investigator-initiated, single-center, prospective registry that will assess the effect of a Xa-inhibitor on the incidence of leaflet thickening in TAVR patients without an indication for OAC.

CRediT authorship contribution statement

Maarten P. van Wiechen: Methodology, Writing – original draft, Data curation. **Ikram el Azzouzi:** Methodology, Writing – review & editing. **Wiebe G. Knol:** Writing – review & editing, Software. **Rik Adrichem:** Methodology, Writing – review & editing, Data curation. **Thijmen W. Hokken:** Writing – review & editing, Data curation. **Joris F. Ooms:** Writing – review & editing, Data curation. **Marjo J. de Ronde-Tillmans:** Writing – review & editing, Data curation. **Joost Daemen:** Supervision. **Peter P. de Jaegere:** Supervision. **Alexander Hirsch:** Supervision. **Ricardo P.J. Budde:** Conceptualization, Supervision. **Nicolas M. Van Mieghem:** Conceptualization, Supervision, Funding acquisition.

Declaration of competing interest

Joost Daemen received institutional research support from Abbott Vascular, Boston Scientific, Medtronic, Pie Medical and PulseCath BV, and consultancy and speaker fees from Boston Scientific, ReCor, Pie Medical, Medtronic and PulseCath BV.

Nicolas Van Mieghem received research grants from Abbott, Boston Scientific, Edwards Lifesciences, Teleflex, Medtronic, Daiichi Sankyo, PulseCath BV.

All other authors declared no conflict of interest.

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