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Edoxaban Monotherapy and Incidence of Transcatheter Heart Valve Leaflet Thrombosis — The Rotterdam Edoxaban (REDOX) Study

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ABSTRACT

Background: Trials comparing non-vitamin K oral anticoagulant (NOAC) versus antiplatelet-based strategies have shown a reduction of subclinical leaflet thrombosis at the cost of increased mortality and major-bleedings. NOACs were often combined with antiplatelet therapy.

Aims: The Rotterdam Edoxaban (REDOX) study aimed to evaluate the impact of edoxaban monotherapy on the incidence of hypo-attenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) and to evaluate safety in terms of mortality, thromboembolic events and major bleeding.

Methods: The REDOX study is a single-arm, open-label trial including patients after successful transcatheter aortic valve implantation (TAVI) with no formal indication for oral anticoagulation or dual antiplatelet therapy. Patients received edoxaban monotherapy for 3 months, followed by multislice computed tomography (MSCT). The primary endpoint was the occurrence of HALT. Clinical follow-up continued up to 1 year after TAVI.

Results: We included 58 patients, of which 50 reached study completion including MSCT scanning and eight withdrew consent before end of study. At 3-months follow-up, HALT of any grade was detected in 12.0% (95% confidence interval (CI): 5.0%–23.1%) of patients. HALT grade ≥ 3 occurred in 4.0% (95% CI: 0.8%–12.2%) of patients. At 1 year follow-up, all patients were alive and free of disabling strokes. Three patients had a non-disabling stroke and one patient had a major bleeding.

Conclusions: In the REDOX study, edoxaban monotherapy after TAVI was associated with a 12.0% incidence of any HALT and a 4.0% incidence of HALT grade ≥ 3. HALT was not associated with clinical events.

Abbreviations: CI, Confidence interval; HALT, Hypo-attenuated leaflet thickening; MSCT, Multislice computed tomography; NOAC, Non-vitamin K oral anticoagulant; RLM, Reduced leaflet motion; SLT, Subclinical leaflet thrombosis; TAVI, Transcatheter aortic valve implantation.

1 | Introduction

Bioprosthetic valve thrombosis is a rare but serious complication after transcatheter aortic valve implantation (TAVI). It is associated with increased incidence of stroke and may progress to bioprosthetic valve failure, causing progressive heart failure symptoms and increased mortality [1]. Subclinical leaflet thrombosis (SLT) is more common and can be identified by multislice-computed tomography (MSCT). SLT covers a spectrum of hypo-attenuated leaflet thickening (HALT) with or without reduced leaflet motion (RLM) [2]. Clinical significance of SLT remains unclear, but it has been linked to neurological events, increased transprosthetic gradients and increased rates of symptomatic hemodynamic valve deterioration [3, 4].

The incidence of SLT after TAVI varies between 2.9% and 40.0% [1]. MSCT substudies of the pivotal TAVI trials suggest a lower incidence in patients on oral anticoagulants [5, 6]. This preventive effect was confirmed by randomized trials in patients without formal indication for oral anticoagulation that compared non-vitamin K oral anticoagulants (NOACs) with or without single antiplatelet therapy versus antiplatelet-based strategies [7, 8]. However, these trials also demonstrated a signal of harm with NOAC through higher mortality and bleeding rates [9, 10].

In the randomized ADAPT TAVR trial [11], edoxaban monotherapy was associated with numerically lower SLT rate than dual antiplatelet therapy in a Korean TAVI population.

The Rotterdam Edoxaban (REDOX) study aims to evaluate the impact of edoxaban monotherapy on the incidence of HALT and RLM after TAVI in a western population and to evaluate safety in terms of mortality, ischemic events, and major bleedings.

2 | Methods

2.1 | Trial Design

The REDOX study is a prospective, single-arm, open-label trial investigating the incidence of HALT and RLM after TAVI in patients on edoxaban monotherapy without formal indication for oral anticoagulation. A detailed description of the study has been published previously [12].

In brief, eligible patients were prescribed full dose edoxaban (60 mg once daily) without concomitant antiplatelets for a duration of 3 months. Dose reduction to 30 mg per labeling was applied in patients with creatinine clearance 15–50 mL/min, body weight ≤ 60 kg or if patients used any of the P-glycoprotein inhibitors cyclosporine, erythromycin, or ketoconazole. Patients were started on edoxaban within 48 h after TAVI. Study drugs were dispensed by study investigators during index hospitalization. Any remaining study drugs were returned at the 3 months visit and remaining medication was counted.

At 3 months, edoxaban was switched to single antiplatelet therapy (aspirin 80–100 mg once daily, or clopidogrel 75 mg once daily in case of previous transient ischemic attack or stroke). Edoxaban was continued if new-onset atrial fibrillation occurred during the active study period. All patients underwent echocardiographic prosthetic valve assessment after TAVI before study enrollment. Clinical follow-up visits were planned 1 and 3 months after TAVI. ECG-gated contrast-enhanced MSCT scan was acquired at 3 months. Clinical and echocardiographic follow up were planned 1 year post TAVI per local practice.

2.2 | Patient Selection

Patients were eligible if they 1) underwent successful TAVI for severe aortic valve stenosis, 2) experienced no major periprocedural complications (i.e. overt stroke, uncontrolled bleeding, major vascular complication, or cardiac structural complication), and 3) had no formal indication for oral anticoagulants. TAVI success was defined as correct positioning of a single prosthetic heart valve into the proper anatomical location, and postprocedural mean aortic valve gradient < 20 mmHg, peak transvalvular velocity < 3.0 m/s and aortic valve regurgitation grade ≤ 2. Major vascular and cardiac structural complications were defined in concordance with the valve academic research consortium-3 consensus [13]. Key exclusion criteria were history of a life-threatening or major bleeding event (≥ BARC 3b) within the last year or high risk of bleeding, hypersensitivity or contraindications to edoxaban, percutaneous coronary intervention within 6 months requiring dual antiplatelet therapy and estimated glomerular filtration rate < 30 mL/min at the time of enrollment. A detailed description of in- and exclusion criteria is reported in Supporting Information S1: Table S1.

2.3 | Multislice Computed Tomography Scan Acquisition and Evaluation

The MSCT protocol was described in detail previously [12]. MSCT scan evaluation was performed by an experienced cardiac radiologist (RPJB) using dedicated software (IntelliSpace Portal, Philips, Eindhoven, The Netherlands). Multiplanar reconstructions were used to evaluate leaflet thickening and valve mobility. Cine images facilitated mobility evaluation. Grading of HALT and RLM was performed as described previously by Blanke et al. [2] HALT grade 0 was defined as no leaflet thickening, grade 1 as < 25% leaflet thickening, grade 2 as 25%–50% leaflet thickening, grade 3 as 50%–75% and grade 4 as > 75%. RLM severity was considered grade 0 if leaflet motion was normal, grade 1 if motion was minimally restricted and limited to the base, grade 2 if motion was mildly restricted and involving more than only the base, but < 50% of the leaflet, grade 3 if motion was moderately restricted and involving 50%–75% of leaflet and grade 4 if leaflets were largely immobile.

2.4 | Outcome Measures

The primary study endpoint was the occurrence of any HALT in ≥ 1 leaflet at 3 months after TAVI. Secondary endpoints were 1)

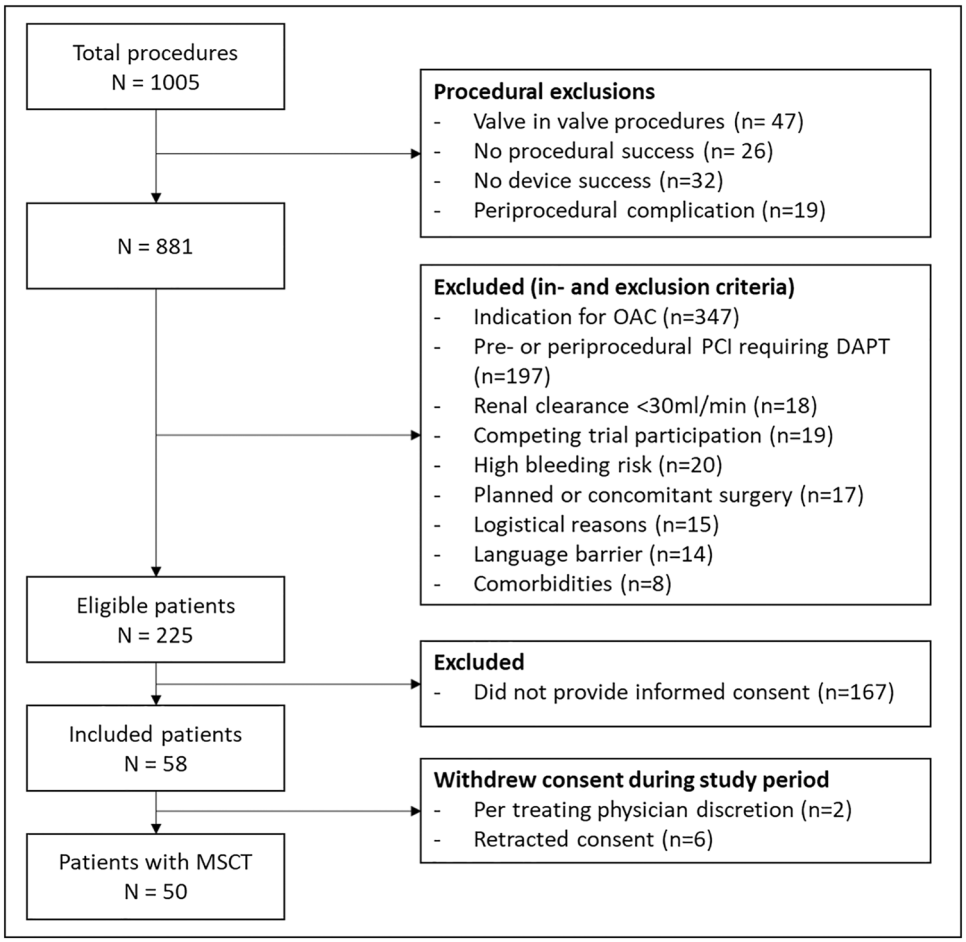

FIGURE 1 | Flowchart of the study inclusion process. DAPT, dual antiplatelet therapy; MSCT, multislice computed tomography; OAC, oral anticoagulation; PCI, percutaneous coronary intervention.

the incidence of RLM at 3 months; 2) the incidence of a composite endpoint of all-cause mortality, myocardial infarction, ischemic stroke or transient ischemic attack, systemic thromboembolism, clinical valve thrombosis and major bleeding at 1 year follow-up (in line with the net clinical benefit and the primary efficacy outcomes of the GALILEO trial [9] and the ATLANTIS trial [10], respectively); and 3) change in transprosthetic gradient by transthoracic echocardiography at 1 year follow-up as compared to the gradient post-TAVI on the predischarge echocardiogram.

2.5 | Statistical Analysis

Continuous variables were presented as means and standard deviations or medians and 25th–75th percentile depending on distribution. Normality was evaluated using the Shapiro-Wilk test and visual inspection of Q-Q plots. Categorical variables were presented as counts and percentages. Kaplan-Meier estimates were calculated to determine the incidence of the composite endpoint and clinical outcomes. For MSCT results at patient level, 95% confidence intervals (CI) of percentages were calculated based on assumed binomial distributions. For results at leaflet level, to take into account the clustering of the data, the Wilson score interval for clustered binary data was used, as introduced by Saha et al. [14] as an adaptation of the Wilson score interval for independent binary data. Additionally, in an exploratory analysis, the incidence of HALT (any grade and grade ≥ 3) was compared using a Chi-square test of proportions with the treatment and control arms of the MSCT-substudy of the GALILEO trial [7], the MSCT substudy of the ATLANTIS trial [8] and the ADAPT TAVR trial [11]. A two-sided p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics version 28.0 (IBM, Chicago, IL, United States) and R version 4.3.2, packages: survival, ggplot2, bpcp (R Core Team (2023), R foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Patient Population

A total of 881 patients underwent successful TAVI between August 2019 and August 2023 (i.e. device success and no major procedural complications) for severe aortic stenosis. Of these, 225 patients did not have a formal indication for oral anticoagulation or dual antiplatelet therapy, and did not meet any of the other exclusion criteria (and thus were eligible for study inclusion). Ultimately, 167 patients did not provide

TABLE 1 | Patient characteristics of patients included the REDOX study.

	Complete cohort $n = 58$	Patients that underwent MSCT $n = 50$	Patients that did not undergo MSCT $n = 8$
Baseline Characteristics			
Age, mean ± SD	77.8 ± 5.1 years	77.5 ± 5.1	79.6 ± 5.1 years
Male sex, *n* (%)	33 (56.9%)	31 (62.0%)	2 (25.0%)
GFR < 50 mL/min, *n* (%)	7 (12.1%)		
GFR, mean ± SD	66.8 ± 14.3 mL/min	67.1 ± 14.8 mL/min	64.8 ± 11.4 mL/min
Body weight < 60 kg, *n* (%)	3 (5.2%)	2 (4.0%)	1 (12.5%)
BMI, mean ± SD	28.9 ± 5.2 kg/m^2	28.8 ± 5.3 kg/m^2	29.5 ± 5.0 kg.m^2
Hypertension, *n* (%)	35 (60.3%)	29 (58.0%)	6 (75.0%)
Hypercholesterolaemia, *n* (%)	9 (15.5%)	8 (16.0%)	1 (12.5%)
Prior stroke or TIA	13 (22.4%)	12 (24.0%)	1 (12.5%)
Diabetes Mellitus	16 (27.6%)	14 (28.0%)	2 (25.0%)
Peripheral artery disease	6 (10.3%)	5 (10.0%)	1 (12.5%)
Prior PCI	4 (6.9%)	3 (6.0%)	1 (12.5%)
Prior CABG	9 (15.5%)	8 (16.0%)	1 (12.5%)
Prior valve intervention	0 (0%)	0 (0%)	0 (0%)
Dose reduction criteria met, *n* (%)	10 (17.2%)	8 (16.0%)	2 (25.0%)
STS, median (25th–75th percentile)	1.7% (1.3–2.8)	1.7% (1.3–2.8)	2.3% (1.7–3.5)
Euroscore 2, median (25th–75th percentile)	1.8% (1.4–2.6)	1.8 (1.3–2.7)	2.3% (1.5–2.4)
CHADS-VASc score, median (25th–75 th percentile)	4 (3–5)	4 (3–5)	3.5 (3–4.75)
HASBLED score, median (25th–75th percentile)	2 (1–4)	2 (1–3)	1 (1–2)
Procedural Characteristics			
Local anesthesia, *n* (%)	58 (100%)	50 (100%)	8 (100%)
Cerebral protection, *n* (%)	32 (55.2%)	29 (58.0%)	3 (37.5%)
Predilatation, *n* (%)	27 (46.6%)	24 (48.0%)	3 (37.5%)
Postdilatation, *n* (%)	14 (24.1%)	12 (24.0%)	2 (25.0%)
Balloon-expandable valve, *n* (%)	19 (32.8%)	17 (34.0%)	2 (25.0%)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; PCI, percutaneous coronary intervention; SD, standard deviation; STS, society of thoracic surgeon predicted risk of mortality; TIA, transient ischemic attack.

informed consent and the REDOX study included 58 patients. A flowchart of study inclusion is shown in Figure 1.

Patient characteristics are shown in Table 1. Mean age was 77.8 ± 5.1 years, 33/58 (56.9%) were male, mean estimated glomerular filtration rate was 66.8 ± 14.3 mL/min and mean BMI was 28.9 ± 5.2 kg/m^2. Median STS score was 1.7% (1.3%–2.8%) and median EuroScore II was 1.8% (1.4%–2.6%). Edoxaban dose reduction criteria were met in 10/58 (17.2%) patients, 7 had an estimated glomerular filtration rate below 50 mL/min and 3 had body weight equal or less than 60 kg.

Six patients withdrew consent during the active study period and two patients discontinued study participation per discretion of the treating physician because of an alleged allergic reaction to the study drug. The final study population comprised 50 patients who completed the 3-months follow-up and underwent MSCT scanning. Forty-seven patients used edoxaban until the day of the MSCT scan. One patient discontinued edoxaban at 77 days after TAVI because of diarrhea, two patients discontinued edoxaban after 3 and 22 days respectively because of dizziness. Forty-four patients completed the 1 year follow-up.

3.2 | Primary and Key-Secondary Enpoints

MSCT scanning was performed in 50 patients (Table 2). Median time to MSCT from study drug initiation was 91 days (90–94 days). Any HALT was detected in 6/50 patients

TABLE 2 | Three months MSCT results at patient and leaflet level.

	n	Percentage	95% CI
Patient Level			
HALT			
Any HALT	6/50	12.0%	5.2%–23.1%
At least one leaflet with HALT grade ≥ 2	4/50	8.0%	2.8%–17.9%
At least one leaflet with HALT grade ≥ 3	2/50	4.0%	0.8%–12.2%
At least one leaflet with HALT grade 4	1/50	2.0%	0.2%–9.0%
RLM	0/50	0.0%	0.0%–4.9%
Leaflet Level			
HALT			
Any HALT	14/150	9.3%	4.3%–19.2%
≥ Grade 2	9/150	6.0%	2.2%–15.1%
≥ Grade 3	4/150	2.7%	0.6%–10.4%
Grade 4	3/150	2.0%	0.4%–10.5%
RLM	0/150	0.0%	0.0%–7.1%

Note: For results at patient level, 95% confidence intervals (CI) of percentages were calculated based on assumed binomial distributions. For results at leaflet level, the Wilson score interval for clustered binary data was used.
Abbreviations: CI, confidence interval; HALT, hypo-attenuated leaflet thickening; MSCT, Multisclice computed tomography; RLM, reduced leaflet motion.

(12.0%, 95% CI: 5.2%–23.1%) and HALT ≥ grade 3 was found in 2/50 patients (4%, 95% CI: 0.8%–12.2%). There were no cases of RLM. At leaflet level, 14/150 leaflets (9.3%, 95% CI: 5.5%–14.8%) were affected by any grade of HALT. HALT grade ≥ 3 occurred in 4/150 leaflets (2.7%, 95% CI: 0.9%–6.2%). Of eight patients receiving low dose edoxaban that underwent MSCT scanning, one had mild HALT (grade 1 leaflet thickening of one leaflet).

In the MSCT substudy of the GALILEO trial, incidence of any HALT in the control arm (receiving dual antiplatelet therapy with aspirin and clopidogrel) was 33/102 (32.4%) patients. Using a Chi-square test for proportions, we found that this was significantly higher than the incidence of HALT in our cohort ($p = 0.002$). In the rivaroxaban arm, incidence of any HALT was 12/97 (12.4%), which was not statistically different from our reported rates ($p = 0.936$).

The MSCT substudy of the ATLANTIS trial found an incidence of any thrombus (as surrogate for HALT) in 82/283 (29.0%) of patients in the control arm of the stratum 2 cohort (i.e. without indication for oral anticoagulation and receiving single or dual antiplatelet therapy using aspirin and/or clopidogrel), which was significantly higher than the incidence in our cohort ($p = 0.008$). HALT ≥ grade 3 in the ATLANTIS 4D-MSCT substudy occurred in 39/283 (13.8%) of patients in the stratum 2 antiplatelet group, which was significantly higher than in our study patients on edoxaban monotherapy ($p = 0.045$). In the apixaban arm of the stratum 2 cohort, incidence of any thrombus/HALT was 47/275 (17.1%) and incidence of HALT ≥ grade 3 was 22/275 (8.0%), which were numerically (but not significantly) higher than the incidences in REDOX ($p = 0.339$ and $p = 0.124$, respectively).

In the ADAPT TAVR trial, incidence of any HALT in the control arm (receiving dual antiplatelet therapy with aspirin and clopidogrel) was 20/109 (18.4%) patients, which was not statistically significantly different from the incidence in our cohort ($p = 0.363$). The incidence of any HALT in the Edoxaban arm of ADAPT TAVR was 10/102 (9.8%) and was not statistically different from the incidence in REDOX ($p = 0.602$).

Key population characteristics of the REDOX study are tabulated next to those of GALILEO, ATLANTIS and ADAPT TAVR in Supporting Information S1: Table S2.

3.3 | Clinical Outcomes

Clinical outcomes are summarized in Table 3. No deaths, myocardial infarctions, or systemic venous thromboembolisms occurred during the study period. At 3 months, one patient experienced a non-disabling pontine stroke that fully recovered and two patients had a transient ischemic attack. One major bleeding was reported 2 days after initiating edoxaban in a patient with an external iliac artery pseudoaneurysm, which was treated with thrombin injection. Five patients developed new-onset atrial fibrillation.

Between 3 months and 1 year follow-up, two more patients experienced a non-disabling stroke. One patient without HALT at 3 months had an increased gradient by echocardiography at 1 year (mean gradient 29 mmHg vs. 16 mmHg predischarge). Repeat MSCT-scanning confirmed valve thrombosis with HALT of all 3 leaflets and RLM of 1 leaflet. Treatment with a vitamin K antagonist normalized the gradient.

TABLE 3 | Overview of clinical outcomes at 3 months and 1 year after start of edoxaban therapy.

	Events	Percentage	95% CI
3 MONTHS			
Composite endpoint[a]	4	7.1%	0.001%–13.4%
Mortality	0	0.0%	0%–7.0%
Myocardial infarction	0	0.0%	0%–7.0%
Systemic venous thromboembolism	0	0.0%	0%–7.0%
Stroke or TIA	3	5.5%	0%–11.3%
Disabling stroke	0	0.0%	0%–7.0%
Non-disabling stroke	1	1.9%	0%–5.6%
TIA	2	3.6%	0%–8.3%
Major bleeding	1	1.8%	0%–5.1%
Clinical valve thrombosis	0	0.0%	0%–7.0%
1 YEAR			
Composite endpoint[a]	7	13.9%	3.7%–23.1%
Mortality	0	0.0%	0%–8.2%
Myocardial infarction	0	0.0%	0%–8.2%
Systemic venous thromboembolism	0	0.0%	0%–8.2%
Stroke or TIA	5	10.1%	1.2%–18.2%
Disabling stroke	0	0.0%	0%–8.2%
Non-disabling stroke	3	6.6%	0.0%–13.6%
TIA	2	3.4%	0.0%–8.3%
Major bleeding	1	1.8%	0.0%–5.1%
Clinical valve thrombosis	1	2.3%	0.0%–6.7%

[a]Composite of mortality, myocardial infarction, sytemic venous thromboembolism, ischemic stroke or TIA, major bleeding and valve thrombosis.
Abbreviations: CI, confidence interval; TIA, transient ischemic attack.

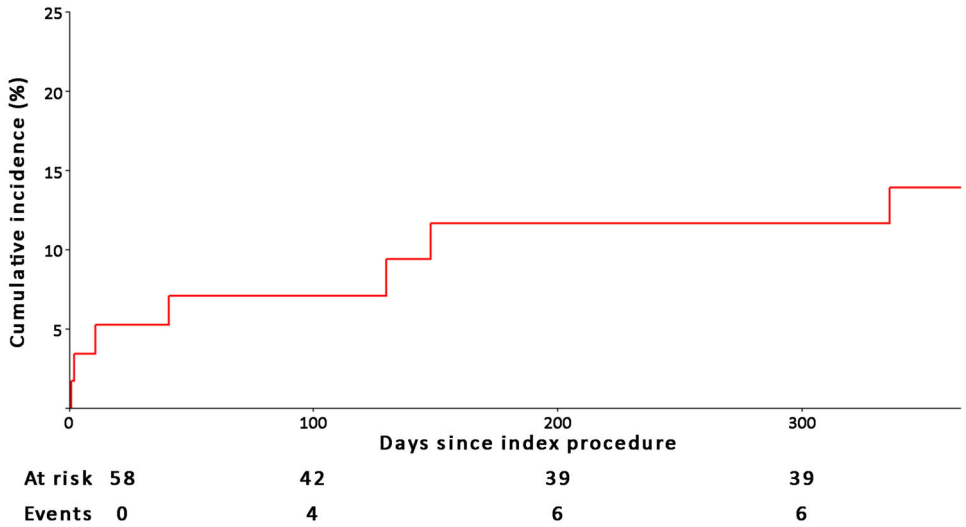

FIGURE 2 | Cumulative incidence of the composite endpoint consisting of mortality, myocardial infarction, systemic venous thromboembolism, stroke or transient ischemic attack, major bleeding and clinical valve thrombosis. [Color figure can be viewed at wileyonlinelibrary.com]

At 1 year, the composite endpoint of mortality, myocardial infarction, systemic venous thromboembolism, ischemic stroke or transient ischemic attack, clinical valve thrombosis, major bleeding and clinical valve thrombosis occurred in 13.9% (95% CI: 3.7%–23.1%) of patients (Figure 2).

Patients with HALT at 3-months had an otherwise uneventful follow-up up to 1 year. Notably, one patient had ≥ grade 3 HALT in all three leaflets at the 3-month MSCT without RLM, but was asymptomatic and transprosthetic gradient by transthoracic echocardiography was only slightly elevated (peak

TABLE 4 | Echocardiographic changes between in-hospital post-TAVI and 1-year post-TAVI echocardiograms compared to pre-TAVI measurements.

	Pre-TAVI ***n*** **= 58**	**Δ**	**In-hospital** ***n*** **= 58**
LVEF, mean ± SD	55.3% ± 8.3%	*+2.6% ± 8.0%*	57.9% ± 10.7%
Mean pressure gradient, mean ± SD	44.9 ± 12.4 mmHg	*−33.5 ± 12.3 mmHg*	11.4 ± 4.2 mmHg
Peak velocity, mean ± SD	4.3 ± 0.5 m/s	*−2.1 ± 0.6 m/s*	2.2 ± 0.4 m/s
AVA, mean ± SD	0.8 ± 0.2 cm^2	*+1.1 ± 0.6 cm^2*	1.9 ± 0.6 cm^2
	Pre-TAVI ***n*** **= 40**	**Δ**	**1-year** ***n*** **= 40**
LVEF, mean ± SD	55.7% ± 7.7%	*−2.1% ± 8.8%*	53.5% ± 11.0%
Mean pressure gradient, mean ± SD	45.3 ± 11.5 mmHg	*-33.9 ± 11.6 mmHg*	11.4 ± 4.8 mmHg
Peak velocity, mean ± SD	4.3 ± 0.5 m/s	*-2.1 ± 0.6 m/s*	2.2 ± 0.4 m/s
AVA, mean ± SD	0.8 ± 0.2 cm^2	*+1.0 ± 0.4 cm^2*	1.8 ± 0.4 cm^2

Abbreviations: AVA, aortic valve area; LVEF, Left ventricular ejection fraction; SD, standard deviation; TAVI, transcatheter aortic valve implantation.

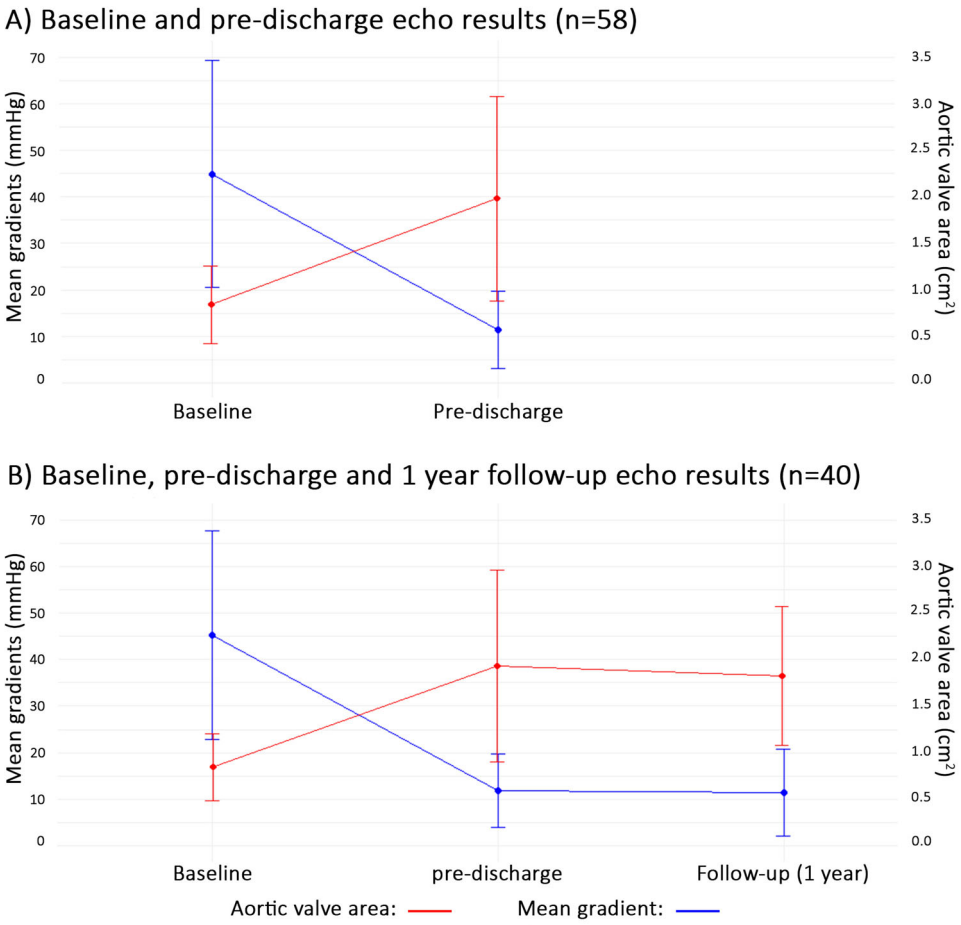

FIGURE 3 | Changes in echocardiographic measurements at baseline and predischarge for all patients (A, $n = 58$) and at baseline, predischarge and at 1 year for patients with 1-year follow-up (B, $n = 40$). Vertical whiskers present 95% confidence intervals. [Color figure can be viewed at wileyonlinelibrary.com]

velocity of 2.4 m/s vs. 1.9 m/s predischarge and mean pressure gradient of 12 mmHg vs. 9 mmHg predischarge). This patient was treated per standard therapy with aspirin 80 mg once daily and at 1 year follow up remained asymptomatic with normalization of the transthoracic gradient (peak velocity 2.0 m/s, mean pressure gradient 11 mmhg).

3.4 | Echocardiographic Results

Echocardiographic outcomes are presented in Table 4 and Figure 3. Forty-four patients completed 1-year follow-up and echocardiographic follow-up was available for 40/44 patients at 1 year. Mean left ventricular ejection fraction was 55.3% ± 8.3%

TABLE 5 | Echocardiographic measurements pre-TAVI, in-hospital post-TAVI and at 1-year post-TAVI for patients with HALT.

	Pre-TAVI $n = 6$	In-hospital $n = 6$	1-year $n = 6$
LVEF, mean ± SD	60.2% ± 3.5%	66.3% ± 7.8%	54.5% ± 4.1%
Mean pressure gradient, mean ± SD	41.7 ± 4.5 mmHg	9.2 ± 3.5 mmHg	8.0 ± 2.0 mmHg
Peak velocity, mean ± SD	4.2 ± 0.3 m/s	2.0 ± 0.3 m/s	1.9 ± 0.2 m/s
AVA, mean ± SD	0.8 ± 0.2 cm^2	1.8 ± 0.4 cm^2	1.9 ± 0.3 cm^2

Abbreviations: AVA, aortic valve area; LVEF, Left ventricular ejection fraction; SD, standard deviation; TAVI, transcatheter aortic valve implantation.

at baseline and remained stable after TAVI and up to 1 year. Mean transvalvular pressure gradient predischarge was 11.4 ± 4.2 mmHg with an aortic valve area of 1.9 ± 0.6 cm^2. There was no evidence for a change in peak transvalvular velocity (mean difference 0.1 m/s, 95% CI: −0.1−0.2, $p = 0.435$), mean pressure gradient (mean difference 0.5 mmHg, 95% CI: −1.0−1.9, $p = 0.505$) and aortic valve area (mean difference 0.13 cm^2, 95% CI: −0.06−0.32, $p = 0.186$) between predischarge echocardiography and echocardiography at 1 year. These findings were similar when focusing only on patients with HALT, although numbers were too small to perform statistical testing (Table 5).

4 | Discussion

The REDOX study evaluated the effects of edoxaban monotherapy on the incidence of HALT and RLM at 3 months following TAVI in patients without formal indication for oral anticoagulation. Any HALT occurred in 12.0% and HALT grade ≥ 3 in 4.0%. There were no cases of RLM. Treatment with edoxaban was safe, with only one major bleeding event in the context of a pseudo-aneurysm.

The 12.0% incidence of any HALT in the REDOX study is comparable to the incidence in the rivaroxaban group of the GALILEO trial (12.4%) and the edoxaban arm of ADAPT TAVR trial (9.8%), and is slightly (albeit not significantly) lower than the incidence in the apixaban group of stratum 2 of the ATLANTIS trial (17.1%). Of note, all patients in GALILEO and 46.2% of patients receiving apixaban in ATLANTIS received concomitant antiplatelet therapy [7, 8]. Importantly, REDOX was not powered to demonstrate a difference between NOACs in the prevention of HALT. In an exploratory analysis we found a statistically significant reduction in the incidence of HALT with edoxaban monotherapy when compared to the control arms receiving single or dual antiplatelet therapy in GALILEO and ATLANTIS. Interestingly, there was no evidence for a statistically significant difference with the dual-antiplatelet group of the ADAPT TAVR trial. However, more balloon-expandable valves were used in these randomized trials than in REDOX (GALILEO: 48.2% and 43.9%, ATLANTIS: 47.2% and 48.5%, and ADAPT TAVR: 91% and 90%; vs. 32.8%). A recent meta-analysis found a 59% higher incidence of SLT including HALT with balloon expandable valves than with self-expanding valves [3]. Furthermore, the ADAPT TAVR trial was a Korean study and people with a Southeast Asian descent seem to have enhanced pharmacokinetic and pharmacodynamic responses to most antithrombotic agents, but reduced responsiveness to clopidogrel and edoxaban [15, 16]. This may have affected safety and efficacy outcomes of the ADAPT TAVR.

Respecting the limited sample size of the present study, we found no RLM in REDOX, which contrasts with the 10% RLM rates in GALILEO and ADAPT TAVR [7, 11]. Nevertheless, incidences of significant RLM (i.e. ≥ grade 3) were reportedly low in all three trials (GALILEO 1.0%, ATLANTIS 0.5% and ADAPT TAVR 1.6% at leaflet level).

The incidence of the composite endpoint of mortality, myocardial infarction, systemic venous thromboembolism, ischemic stroke or transient ischemic attack, major bleeding and valve thrombosis was 16.3%. This is in line with the NOAC arms of GALILEO (16.6%) and ATLANTIS (18.4%) [9, 10]. Of note, both GALILEO and ATLANTIS reported higher mortality rates with the respective NOAC based regimen, but there were no deaths in REDOX. Patients in REDOX were slightly younger (77.8 years vs. GALILEO: 80.4 and 80.8 years, ATLANTIS: 81.6 and 82.3 years and ADAPT TAVR: 80.2 and 80.0 years for the respective treatment and control arms of the trials), and had lower Society of Thoracic Surgery predicted risk of mortality scores (1.7% vs. GALILEO: 4.0% and 4.3%, ATLANTIS: 5.14% and 5.14% and ADAPT TAVR: 3.1% and 3.5%) [9–11].

The lower age and surgical risk may also reflect a lower bleeding risk-profile. Indeed, the median HASBLED score in our population was 2 and only one major bleeding occurred (2.4%), which is lower than in GALILEO (mean HASBLED of 2.8 with 5.6% major bleedings), ATLANTIS (5.8% major bleedings) and ADAPT TAVR (5.4% major bleedings). Furthermore, only 17.2% of REDOX patients had dose reduction criteria and received low-dose edoxaban, whereas in ATLANTIS, a third of patients in the apixaban group were prescribed low-dose regimens, and in ADAPT TAVR 61.3% of patients in the edoxaban group received low-dose edoxaban.

The occurrence of HALT at 3 months was not associated with adverse events during our study period, although patient numbers were relatively small and follow-up duration was only 1 year. Meta-analyses linked SLT to increased incidences of cerebrovascular ischemic events and heart failure symptoms [1, 3]. However, spontaneous SLT resolution has also been described in 50% of cases [17].

In REDOX, we found a single case of clinical valve thrombosis after discontinuation of edoxaban, which manifested as an increased transvalvular gradient at 1 year follow-up in the absence of thromboembolic events or heart failure symptoms.

Vitamin K antagonist initiation resulted in normalization of the transvalvular gradient.

Previous work demonstrated an association between SLT and increased incidence of hemodynamic valve dysfunction [4]. This study followed 116 patients with early HALT incidence for a median of 3 years. Although mortality or ischemic event rates were not increased, incidence of symptomatic hemodynamic valve deterioration (defined as an increase in mean peak gradient of ≥ 10 mmHg or a mean peak gradient ≥ 20 mmHg with new symptoms) was increased sixfold to an incidence of almost 10%.

At present, systematic NOAC use in patients after TAVI with no formal indication for oral anticoagulation is not indicated due to the aforementioned signal of harm in the randomized controlled trials. Therefore, SAPT remains the antithrombotic therapy of first choice [9, 10]. However, the signal of harm within these trials was primarily linked to a predominantly elderly population with higher operative and bleeding risks. Further research should focus on NOAC monotherapy in younger, lower-risk patients who may benefit from freedom of SLT and potentially a lower risk of structural valve degeneration and longer durability.

4.1 | Limitations

REDOX has several limitations. The study was prematurely ended because of slow enrollment and has a limited sample size. Yet, we enrolled 50 patients with MSCT scans at 90 days after TAVI for comprehensive assessment of HALT/RLM. Its open study design may also have introduced selection bias. The small sample size precluded additional analyses on impact of edoxaban dosing or transcatheter valve platform. This was a single arm trial that evaluated the effects of edoxaban monotherapy and any comparisons with other strategies (e.g. other NOAC or SAPT/DAPT) are therefore hypothesis generating. Nevertheless, we believe the consistent findings in our exploratory analysis comparing edoxaban monotherapy with control arms of existing RCTs merit further study.

5 | Conclusions

In patients with no formal indication for oral anticoagulation, edoxaban monotherapy after TAVI is safe and associated with low SLT incidence.

Author Contributions

Rik Adrichem: conceptualization and design of the study, data acquisition, interpretation and analysis, drafting of the original manuscript, approval of the submitted manuscript. **Maarten P. van Wiechen:** conceptualization and design of the study, data acquisition and interpretation, critical revision of the manuscript, approval of the submitted manuscript. Wiebe G. Knol data acquisition and interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Thijmen W. Hokken:** data acquisition and interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Joris F. Ooms:** data acquisition and interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Mark M. P. van den Dorpel:** data acquisition and interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Sarah Verhemel:** data acquisition and interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Isabella Kardys:** data interpretation and analysis, critical revision of the manuscript, approval of the submitted manuscript. **Rutger-Jan Nuis:** data interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Joost Daemen:** data interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Alexander Hirsch:** data interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Ricardo P. J. Budde:** data interpretation, critical revision of the manuscript, approval of the submitted manuscript. **Nicolas M. Van Mieghem:** conceptualization and design of the study, data interpretation and analysis, drafting of the original manuscript, approval of the submitted manuscript.

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Ethics Statement

All study procedures were in accordance with the declaration of Helsinki. The conduct of the study was approved by the institutional review board (MEC-2019-0249) and the trial was preregistered at clinicaltrials.gov (NCT04171726). All patients provided written informed consent.

Conflicts of Interest

Rutger-Jan Nuis received research grant support from Vifor Pharma and Merill, and consulting fees from Edwards Lifesciences, Abbott, Boston Scientific. Joost Daemen received institutional grant/research support from Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic, Microport, Pie Medical, and ReCor medical, and consultancy and speaker fees from Abbott, Abiomed, ACIST medical, Boston Scientific, Cardialysis BV, CardiacBooster, Kaminari Medical, ReCor Medical, PulseCath, Pie Medical, Siemens Health Care and Medtronic. Alexander Hirsch received a research grant from GE Healthcare and consultancy/speaker fees from GE Healthcare and Bayer. He is advisory board member of Medis and was MRI corelab supervisor of Cardialysis BV. Ricardo PJ Budde received speakers fees from Bayer and Institutional support to Erasmus MC by Bayer, Heartflow and Siemens. Nicolas M. Van Mieghem has received grant support/research contracts from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, Daiichi Sankyo, Astra Zeneca and PulseCath BV and has received consulting/speaker fees from Abbot Vascular, Boston Scientific Corporation, Medtronic, Daiichi Sankyo, PulseCath BV, JenaValve, and Amgen. The other authors declare no conflicts of interest.

Data Availability Statement

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

References

1. T. Rheude, C. Pellegrini, S. Stortecky, et al., "Meta-Analysis of Bioprosthetic Valve Thrombosis After Transcatheter Aortic Valve Implantation," *The American Journal of Cardiology* 138 (2021): 92–99, https://doi.org/10.1016/j.amjcard.2020.10.018.

2. P. Blanke, J. R. Weir-McCall, S. Achenbach, et al., "Computed Tomography Imaging in the Context of Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR): An Expert Consensus Document of the Society of Cardiovascular Computed Tomography," *JACC. Cardiovascular imaging* 12 (2019): 1–24, https://doi.org/10.1016/j.jcmg.2018.12.003.

3. M. Bogyi, R. E. Schernthaner, C. Loewe, et al., "Subclinical Leaflet Thrombosis After Transcatheter Aortic Valve Replacement: A Meta-Analysis," *JACC. Cardiovascular interventions* 14 (2021): 2643–2656.

4. M. Hein, S. Schoechlin, U. Schulz, et al., "Long-Term Follow-Up of Hypoattenuated Leaflet Thickening After Transcatheter Aortic Valve Replacement," *JACC. Cardiovascular interventions* 15 (2022): 1113–1122, https://doi.org/10.1016/j.jcin.2022.04.018.

5. R. R. Makkar, P. Blanke, J. Leipsic, et al., "Subclinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Valves," *Journal of the American College of Cardiology* 75 (2020): 3003–3015, https://doi.org/10.1016/j.jacc.2020.04.043.

6. P. Blanke, J. A. Leipsic, J. J. Popma, et al., "Bioprosthetic Aortic Valve Leaflet Thickening in the Evolut Low Risk Sub-Study," *Journal of the American College of Cardiology* 75 (2020): 2430–2442, https://doi.org/10.1016/j.jacc.2020.03.022.

7. O. De Backer, G. D. Dangas, H. Jilaihawi, et al., "Reduced Leaflet Motion After Transcatheter Aortic-Valve Replacement," *New England Journal of Medicine* 382 (2020): 130–139, https://doi.org/10.1056/NEJMoa1911426.

8. G. Montalescot, A. Redheuil, F. Vincent, et al., "Apixaban and Valve Thrombosis After Transcatheter Aortic Valve Replacement: The ATLANTIS-4D-CT Randomized Clinical Trial Substudy," *JACC. Cardiovascular interventions* 15 (2022): 1794–1804, https://doi.org/10.1016/j.jcin.2022.07.014.

9. G. D. Dangas, J. G. P. Tijssen, J. Wöhrle, et al., "A Controlled Trial of Rivaroxaban After Transcatheter Aortic-Valve Replacement," *New England Journal of Medicine* 382 (2020): 120–129, https://doi.org/10.1056/NEJMoa1911425.

10. J. P. Collet, E. Van Belle, H. Thiele, et al., "Apixaban vs. Standard of Care After Transcatheter Aortic Valve Implantation: The ATLANTIS Trial," *European Heart Journal* 43 (2022): 2783–2797, https://doi.org/10.1093/eurheartj/ehac242.

11. D. W. Park, J. M. Ahn, D. Y. Kang, et al., "Edoxaban Versus Dual Antiplatelet Therapy for Leaflet Thrombosis and Cerebral Thromboembolism After TAVR: The ADAPT-TAVR Randomized Clinical Trial," *Circulation* 146 (2022): 466–479, https://doi.org/10.1161/CIRCULATIONAHA.122.059512.

12. M. P. van Wiechen, I. El Azzouzi, W. G. Knol, et al., "Leaflet Thickening and Motion After Transcatheter Aortic Valve Replacement: Design and Rationale of the Rotterdam Edoxaban Trial," *Cardiovascular Revascularization Medicine* 44 (2022): 67–70.

13. P. Généreux, N. Piazza, M. C. Alu, et al., "Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research," *Journal of the American College of Cardiology* 77 (2021): 2717–2746, https://doi.org/10.1016/j.jacc.2021.02.038.

14. K. K. Saha, D. Miller, and S. Wang, "A Comparison of Some Approximate Confidence Intervals for a Single Proportion for Clustered Binary Outcome Data," *The International Journal of Biostatistics* 12 (2016).

15. H. K. Kim, U. S. Tantry, H. W. Park, et al., "Ethnic Difference of Thrombogenicity in Patients with Cardiovascular Disease: A Pandora Box to Explain Prognostic Differences," *Korean Circulation Journal* 51 (2021): 202–221.

16. H. K. Kim, U. S. Tantry, S. C. Smith, Jr., et al., "The East Asian Paradox: An Updated Position Statement on the Challenges to the Current Antithrombotic Strategy in Patients With Cardiovascular Disease," *Thrombosis and Haemostasis* 121 (2021): 422–432.

17. L. Sondergaard, O. De Backer, K. F. Kofoed, et al., "Natural History of Subclinical Leaflet Thrombosis Affecting Motion in Bioprosthetic Aortic Valves," *European Heart Journal* 38 (2017): 2201–2207, https://doi.org/10.1093/eurheartj/ehx369.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.