Blood Coagulation Changes With or Without Direct Oral Anticoagulant Therapy Following Transcatheter Aortic Valve Implantation

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Thromboembolic events remain clinically unresolved after transcatheter aortic valve implantation (TAVI). The use of direct oral anticoagulant (DOAC) to reduce thrombosis associated with TAVI remains controversial. This study aimed at investigating the periprocedural change in blood coagulation and thrombolysis parameters in 199 patients undergoing transfemoral TAVI. Prothrombin activation fragment 1 + 2 (F1 + 2), thrombin−antithrombin complex (TAT), soluble fibrin monomer complex (SFMC), and fibrin/fibrinogen degradation product (FDP) levels were measured before and 1 hour after TAVI and 1, 2, and 7 days postoperatively. Of the 199 patients, 49 were treated with DOAC (apixaban in 32, edoxaban in 10, and rivaroxaban in 7). The F1 + 2 and TAT levels immediately increased 1 hour after TAVI and then gradually decreased in both groups. The SFMC level also significantly increased with a peak on day 1. The FDP level gradually increased, peaking on day 2. The values of F1 + 2, TAT, SFMC, and FDP in patients who used DOAC were significantly lower than those who did not use DOAC at 1 hour after TAVI in F1 + 2 (600 [452 to 765] vs 1055 [812 to 1340] pmol/L; $p < 0.001$), TAT (21.4 [16.2 to 37.0] vs 38.7 [26.4 to 58.7] μg/mL; $p < 0.001$) and on day 1 in SFMC (18.2 [9.4 to 57.9] vs 113.4 [70.9 to 157.3] μg/mL; $p < 0.001$) and day 2 in FDP (6.0 [4.7 to 10.0] vs 12.6 [8.2 to 17.4] μg/mL; $p < 0.001$). Ischemic stroke within 30 days after TAVI occurred in 3 patients (1.5%), who were not treated with DOAC.

Coagulation cascade activation was observed after TAVI. DOAC could reduce transient hypercoagulation following TAVI. **(Am J Cardiol 2021;147:88−93)**

Thromboembolic events remain clinically unresolved after transcatheter aortic valve implantation (TAVI).[1,2] The mechanism of thromboembolic events after TAVI is multifactorial. The activation of the coagulation pathway induced by valve implantation may stimulate thrombus formation.[1,3] However, blood coagulation change following TAVI was not fully investigated. The incidence of preexisting atrial fibrillation in patients with severe aortic valve stenosis is as high as 20% to 30%.[4] Although the use of direct oral anticoagulant (DOAC) for stroke prevention has increased, DOAC use to reduce thrombosis associated with TAVI remains controversial. This study aimed to investigate periprocedural change in blood coagulation and thrombolysis parameters in patients undergoing TAVR who used or did not use DOAC.

Methods

The study population consisted of 245 consecutive patients who underwent complete transfemoral TAVI for symptomatic severe aortic valve stenosis at Teikyo University Hospital from January 2017 to March 2019. Baseline demographics, procedural data, and clinical outcomes were prospectively collected. The exclusion criteria based on the TAVI procedure were as follows: (1) TAVI with a clinical trial valve (n = 6), (2) planned percutaneous coronary intervention, coronary artery bypass grafting, or thoracic endovascular aortic repair during TAVI (n = 2), (3) second valve implantation because of valve dislodgement (n = 2), and (4) transcatheter valve-in-valve implantation for degenerated aortic bioprosthetic valves (n = 2). Patients using vitamin K antagonist (n = 21) were also excluded from this study. Thus, 212 patients met the inclusion criteria. This study was approved by the institutional review board of the Teikyo University School of Medicine (Teikyo-14-045, 14-045-2). All patients provided informed consent before TAVI.

Severe aortic valve stenosis was diagnosed based on the results of physical examination and transthoracic echocardiography using Philips IE33 or EPIC E7. For aortic valve stenosis quantification, we measured the transaortic peak velocity, maximum and mean transaortic pressure gradient,

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and aortic valve area using the continuity equation based on the guidelines of the American Society of Echocardiography.[5] Severe aortic valve stenosis was defined as transaortic peak velocity of ≥4 m/s and/or mean aortic valve gradient of ≥40 mm Hg. Additionally, the left ventricular stroke volume index was evaluated using the following formula: left ventricular outflow tract velocity time integral × left ventricular outflow tract area/body surface area. Low flow was defined as stroke volume index of <35 mL/m^2. Patients with low-flow severe aortic valve stenosis (aortic valve area of ≤1.0 cm^2) were included in this study.

All study patients were treated with transfemoral TAVI using balloon-expandable valves as the SAPIEN 3 valve (Edwards Lifesciences, Irvine, CA) or self-expanding valves as the Evolut R or Evolut Pro (Medtronic, Minneapolis, MN). Transfemoral TAVI was performed with complete percutaneous access with vascular closure devices. The use of each valve device (balloon-expandable or self-expanding valve) was based on the decision of the operator depending on anatomical and clinical suitability of the study patient. Post-TAVI balloon dilatation was performed in patients with residual moderate or severe paravalvular regurgitation. The severity of paravalvular regurgitation was determined using either transthoracic echocardiography or transesophageal echocardiography immediately after TAVI.

Dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day was administered in the entire periprocedural phase until February 2018. From March 2018, patients received single antiplatelet therapy (aspirin or clopidogrel) before TAVI and dual antiplatelet therapy in the morning of the next day after TAVI. All patients received unfractioned heparin to maintain a minimum active clotting time of >250 seconds after the insertion of the femoral sheath. Protamine (1 mg for each 1000 U of heparin) was routinely administered at the time of puncture site closure.

Some patients were on DOACs prior to TAVI for clinical indications, and the DOAC was discontinued on the day of the procedure, but resumed the day after the procedure. DOAC and single antiplatelet therapy combination was generally used after TAVI in patients needing anticoagulant therapy.

Prothrombin activation fragment 1 + 2 (F1 + 2) as a molecular marker of thrombin generation, thrombin−antithrombin complex (TAT) as a marker of thrombin neutralization, soluble fibrin monomer complex (SFMC) as a marker of thrombophilia, and fibrin/fibrinogen degradation product (FDP) as a marker of fibrinolysis were assessed before and 1 hour (POD 0) after TAVI and 1 (POD 1) and 2 (POD 2) days postoperatively. If possible, coagulation parameters were also measured 7 days (POD 7) after TAVI. F1 + 2 was assessed using enzyme-linked immunosorbent assay. TAT level was measured using chemiluminescent enzyme immunoassay, SFMC using latex immunoturbidimetric assay, and FDP using latex agglutination method. The reference value for each molecular marker was determined by the manufacturer: F1 + 2, 69 to 229 pmol/L; TAT, ≤2.9 ng/mL; SFMC, ≤6.1 μg/mL; and FDP, ≤4.9 μg/mL.

We investigated the clinical endpoints as 30-day mortality, ischemic stroke, myocardial infarction, and vascular and bleeding complications according to VARC-2 criteria.[6]

Categorical data were expressed as frequency counts and percentages. Continuous data were expressed as median and interquartile range. Categorical data were compared using the chi-squared or Fisher's exact test. Continuous data were compared between groups using the Mann−Whitney *U* test or Wilcoxon signed-rank test, as appropriate. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics software (version 25.0, SPSS, Inc., Chicago, Illinois).

Results

Because of the clinical course after TAVI, 13 patients were excluded as follows: (1) patients who did not receive antiplatelet drug (n = 5), (2) patients who newly started oral anticoagulant (OAC) until 24 hours postoperatively (n = 4), and (3) lack of blood coagulation parameters until POD 2 (n = 4). Therefore, 199 patients were included in this study. Baseline characteristics of study patients are shown in Table 1. Of all study patients, 49 were treated with DOAC because of a preexisting atrial fibrillation. Regarding DOAC therapy, 32 patients (65.3%) received apixaban (2.5 mg twice daily), 10 (20.4%) received edoxaban (30 mg daily), and 7 (14.3%) received rivaroxaban (10 mg daily). Echo parameters (ejection fraction, transaortic peak velocity, and aortic valve mean gradient) were significantly different in patients who used and did not use DOAC.

Coagulation and fibrinolysis parameters could be measured until POD 2 after TAVI in 199 patients, but until POD 7 in 180 (90.5%) patients. Changes over time of coagulation and fibrinolysis status in patients who used and did not use DOAC following TAVI are shown in Figure 1 and Table 2. The F1 + 2 and TAT levels immediately increased, and the median F1 + 2 and TAT levels after TAVI were extremely high and then gradually decreased in both groups. The SFMC level also significantly increased with a peak on POD 1 and gradually decreased. The FDP level gradually increased after TAVI, peaking on POD 2 and decreasing on POD 7. The F1 + 2, TAT, SFMC, and FDP levels on POD 7 were statistically significantly higher compared with those at baseline (Table 2). Moreover, in patients who did not use DOAC, the values of these parameters were significantly greater than those with DOAC at all measurement points (POD 0 to 7; Figure 1). The difference in the coagulation status between 3 DOACs (F1 + 2, TAT, and SFMC) is shown in Table 3. The maximum values of the 3 coagulation parameters after TAVI were the most suppressed with apixaban compared with the 2 other DOACs.

Ischemic stroke occurred in 3 patients (1.5%) within 30 days after TAVI. All 3 patients with ischemic stroke were not treated with DOAC. Of the 3 patients, one had stroke during TAVI and the remaining 2 had stroke within 24 hours after TAVI. The coagulation parameter value in these 2 cases was high (case 1: F1 + 2, 826 pmol/L; TAT, 21.6 ng/mL; SFMC, 142.9 μg/mL; case 2: F1 + 2, 594 pmol/L; TAT, 8.1 ng/mL; SFMC, 49.3 μg/mL), which corresponded to hypercoagulable state. Myocardial infarction occurred in one patient due to delayed coronary occlusion following the procedure. Major bleeding occurred in 7

Table 1.
Patients demographics

Variable	DOAC		p value
	NO (n = 150)	YES (n = 49)	
Age (years)	84 (82-88)	84 (81-89)	0.893
Men	38 (25%)	15 (31%)	0.468
Hypertension	129 (86%)	44 (90%)	0.494
Dyslipidemia*	103 (69%)	33 (67%)	0.863
Diabetes Mellites	57 (38%)	17 (35%)	0.678
Chronic kidney disease	73 (49%)	26 (53%)	0.593
Smoker	25 (17%)	8 (16%)	0.956
Active cancer	8 (5%)	3 (6%)	0.537
Echo parameters			
Ejection Fraction, %	61.0 (55.0-64.0)	57.0 (46.0-62.0)	0.002
Baseline trans-aortic peak velocity, m/sec	451.5 (408.0-513.0)	405.0 (349.5-448.0)	< 0.001
Baseline aortic valve mean gradient, mmHg	46.0 (36.0-58.3)	39.0 (24.3-48.3)	< 0.001
Baseline aortic valve area, cm^2	0.69 (0.51-0.81)	0.65 (0.55-0.82)	0.834
Procedural characteristics			
Post-dilatation	4 (3%)	1 (2%)	0.641
Balloon expandable valve	91 (61%)	33 (67%)	0.402
Prosthesis regurgitation (grade ≥2)	7 (5%)	2 (4%)	0.611

Unless indicated otherwise, data are presented as median [interquartile range] or as n (%).
DOAC = Direct oral anticoagulant.
* Dyslipidemia was defined as abnormal level of lipids in the blood.

patients (3.5%), and vascular complications occurred in 7 (3.5%). In the 30-day follow-up, 4 patients (2.0%) died. The occurrence of these clinical endpoints did not statistically significantly differ in patients who used and did not use DOAC (Table 4).

Discussion

The main findings of this study can be summarized as follows: (1) the blood coagulation pathway was immediately activated after TAVI, (2) coagulation and fibrinolysis

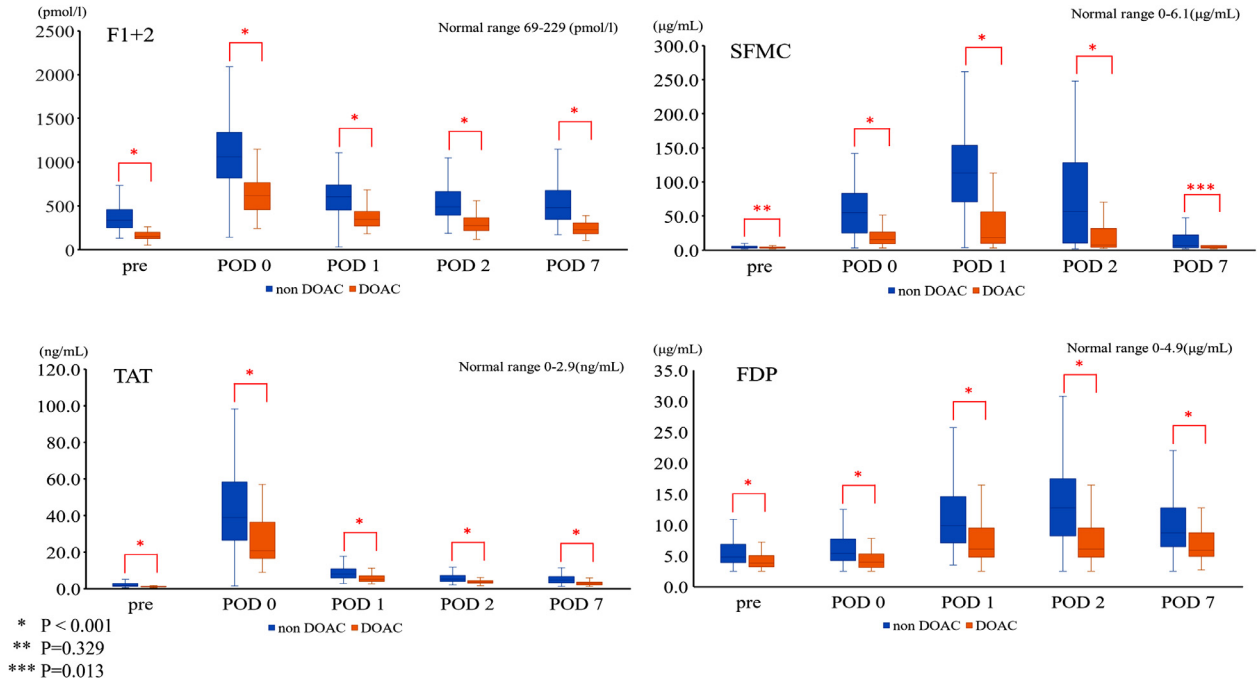

Figure 1. Change in blood coagulation and fibrinolysis parameters following TAVI. The coagulation and fibrinolysis parameters (F1+2, TAT, SFMC, and FDP) were assessed before and immediately after transcatheter aortic valve implantation (TAVI) (POD 0) and 1 (POD 1), 2 (POD 2), and 7 (POD 7) days postoperatively. The boxes show the interquartile range, with the median value indicated by the horizontal line. TAVI = transcatheter aortic valve implantation; F1+2 = prothrombin activation fragment 1+2; TAT = thrombin-anti-thrombin complex; SFMC = soluble fibrin monomer complex; FDP = fibrin/fibrinogen degradation product.

Table 2
The changes over time of coagulation and fibrinolysis status in patients who used and did not use DOAC following TAVI

	DOAC	Pre-TAVI	POD 0	p	POD 1	p	POD 2	p	POD 7	p
F1+2 (pmol/L)	NO	331 (248-460)	1055 (812-1340)	<0.001	600 (452-740)	<0.001	490 (393-671)	<0.001	481 (343-680)	<0.001
	YES	148 (124-195)	600 (452-765)	<0.001	343 (268-465)	<0.001	274 (220-376)	<0.001	232 (178-310)	<0.001
TAT (ng/mL)	NO	1.7 (1.1-2.8)	38.7 (26.4-58.7)	<0.001	7.9 (5.8-10.9)	<0.001	5.2 (4.0-7.1)	<0.001	4.6 (3.1-6.6)	<0.001
	YES	1.0 (0.8-1.3)	21.4 (16.5-37.0)	<0.001	5.0 (3.8-7.0)	<0.001	3.5 (2.9-4.5)	<0.001	2.9 (2.1-3.7)	<0.001
SFMC (μg/mL)	NO	3.5 (2.8-5.7)	55.1 (25.3-83.1)	<0.001	113.4 (70.9-157.3)	<0.001	57.5 (11.5-128.7)	<0.001	6.8 (3.5-22.8)	<0.001
	YES	3.1 (2.9-4.6)	15.4 (8.8-25.6)	<0.001	18.2 (9.4-57.9)	<0.001	7.4 (4.1-33.2)	<0.001	4,4 (3.0-10.0)	<0.001
FDP (μg/mL)	NO	4.8 (3.9-6.8)	5.4 (4.2-7.7)	<0.001	10.0 (7.1-14.7)	<0.001	12.6 (8.2-17.4)	<0.001	8.7 (6.4-13.1)	<0.001
	YES	3.8 (3.2-4.9)	3.9 (3.1-5.3)	0.327	6.2 (4.8-8.4)	<0.001	6.0 (4.7-10.0)	<0.001	5.9 (4.9-9.0)	<0.001

P※ vs. pre-TAVI. Data are presented as median [interquartile range].

DOAC = Direct oral anticoagulant; F1+2 = Prothrombin activation fragment 1+2; TAVI = transcatheter aortic valve implantation; TAT = thrombin-anti-thrombin complex; SFMC = soluble fibrin monomer complex; FDP = thrombophilia and fibrin/fibrinogen degradation product.

Table 3
Clinical outcomes

Variable	DOAC		P value
	NO (n=150)	YES (n=49)	
Myocardial infarction	1 (0.7%)	0	0.754
Ischemic stroke	3 (2%)	0	0.426
30 days-mortality	3 (2%)	1 (2%)	0.680
Vascular complications	6 (4%)	1 (2%)	0.451
Major bleeding	5 (3%)	2 (4%)	0.549

Data are presented as n (%).

DOAC = Direct oral anticoagulant.

parameter values in patients who used DOAC were significantly lower than those in patients who did not use DOAC, and (3) the incidence of ischemic stroke within 30 days after TAVI was 1.5% and all were not treated with DOAC.

Previous studies demonstrated that hypercoagulable state has been known to develop during cardiovascular surgery[7–9] and after endovascular therapy, including stent-graft implantation for aortic aneurysm.[10,11] In this study, it was confirmed that the same phenomenon occurred after TAVI. Data in the literature on coagulation status after TAVI were limited. Sedaghat et al. investigated coagulation and fibrinolysis parameters, such as TAT, F1 + 2, and D-dimer, before and after TAVI.[12] Although the study population was only 35 patients, the time course of TAT in the perioperative period was consistent with our study. Regarding F1 + 2, comparing the results of our study with those in the literature was impossible, because the reference standard values and units were different.

There is no guideline on the timing of DOAC interruption before TAVI. In this study, DOAC was skipped on the day of TAVI and then readministered from POD 1 after TAVI. Thus, anticoagulation by DOAC was inadequate within 24 hours after TAVI. Although the effect of DOAC was insufficient, the peak values of each coagulation and fibrinolysis parameter in patients who used DOAC were significantly lower than those who did not use DOAC following TAVI. The residual effects by DOAC may affect these outcomes. In fact, it has been demonstrated that trough level of rivaroxaban inhibits thrombin generation.[13,14] Furthermore, in a study investigating the pharmacokinetic and pharmacodynamic profiles of plasma concentrations and anti-factor Xa activity in both apixaban (2.5 mg twice daily) and rivaroxaban (10 mg once daily), they could be measured up to 24 hour after DOAC interruption.[15]

Thromboembolic events after TAVI were a serious problem.[1,16] Particularly, the occurrence of ischemic cerebrovascular events affects mortality and quality of life after TAVI. Previous studies revealed that the incidence of cerebral infarction after TAVI within 30 days was approximately 2%.[17] Particularly, more than half of cerebral infarction cases occurred in the acute phase within 24 hours after TAVI.[18,19] Cerebral infarction in the acute phase after TAVI was thought to be largely caused by procedural factors.[20] Damage to the endothelium following valve implantation may cause coagulation cascade and platelet activation, resulting in thrombus generation. Several studies examined the histopathology of embolic materials captured during TAVI.[21–24] These studies revealed that materials were captured in 90% of patients, of whom 50% had at least one particle of debris of >1 mm. Approximately 70% to 90% of materials captured during TAVI were thrombus, consisting of platelets, fibrin, and erythrocytes. Clinically silent brain infarctions newly diagnosed by cerebral

Table 4
The change of blood coagulation on the peak level among 3 DOACs

Variable	Apixaban (n = 32)	Edoxaban (n = 10)	Rivaroxaban (n = 7)	P value
F1+2 (pmol/L)	537 (419-676)	757 (568-923)	790 (642-1150)	0.003
TAT (ng/mL)	19.5 (16.5-26.5)	40.7 (24.3-51.6)	37.5 (18.4-49.5)	0.014
SFMC (μg/mL)	21.4 (12.5-58.6)	60.4 (47.8-125.5)	22.1 (16.2-70.8)	0.027
FDP (μg/mL)	6.2 (5.1-9.4)	9.1 (6.2-16.7)	6.1 (4.2-16.9)	0.219

Data are presented as median [interquartile range].

DOAC = Direct oral anticoagulant; F1+2 = Prothrombin activation fragment 1+2; TAT = thrombin-anti-thrombin complex; SFMC = soluble fibrin monomer complex; FDP = thrombophilia and fibrin/fibrinogen degradation product.

magnetic resonance imaging were also detected in up to two-thirds of patients following TAVI.[25,26] Thrombus caused by transient hypercoagulation after TAVI may contribute to ischemic cerebral infarction, which has been shown to increase the risk of future stroke.

This was a single-center observational study with a limited sample size. TAVI complications were only few. However, the incidence rate of ischemic stroke in this study was not different from that in a recent large registry study.[16] Coagulation and fibrinolysis parameters were measured only up to 7 days after TAVI. Thus, the long-term effects of hypercoagulation status after TAVI have not been investigated.

In conclusion, this study showed that the coagulation cascade was significantly activated after TAVI. The values of coagulation and fibrinolysis parameters in patients who used DOAC were significantly lower than those who did not use DOAC following TAVI.

Author contributions

Taiga Katayama: Data Curation, Formal analysis, Writing - Original Draft. Naoyuki Yokoyama: Conceptualization, Methodology, Project administration, Writing - Review & Editing. Yusuke Watanabe: Writing - Review & Editing. Shinji Takahashi: Data Curation. Hirofumi Hioki: Data Curation. Kazuo Kawasugi: Writing - Review & Editing. Ken Kozuma: Supervision.

Disclosures

Yusuke Watanabe is proctor for Edwards Japan and Medtronic Japan. The other authors report no conflicts of interest.

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