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Perioperative D-dimer levels after transcatheter aortic valve replacement: Comparison of patients with and without anticoagulant therapy

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Transcatheter aortic valve replacement (TAVR) has become an established treatment option for severe aortic valve stenosis. Given this situation, leaflet thrombosis of prosthesis after TAVR has been raised as a persisting concern, as it might cause systemic embolism or valve failure [1]. A prior report showed the relationship between leaflet thrombosis on enhanced computed tomography and elevated D-dimer level [2], which is a product of fibrinolysis and is used as a sensitive marker of intravascular thrombus [3]. An antiplatelet agent is used in the current standard antithrombotic regimen after TAVR; however, some recent reports suggest that patients treated with anticoagulant therapy after TAVR were at lower risk of leaflet thrombosis than those treated without anticoagulant therapy [4, 5]. The purpose of this study was to compare the D-dimer levels during the perioperative period of TAVR between patients with and without anticoagulant therapy.

From among 114 consecutive patients who received TAVR between April 2016 and June 2019 at Nagoya University Hospital, subjects were identified with available perioperative D-dimer levels (more than once within 7 days after TAVR). Patients were excluded if their postoperative D-dimer levels were not available (n = 19), anticoagulant therapy was changed to antiplatelet therapy or vice versa within 7 days (n = 2), antithrombotic therapy was not started within 5 days of TAVR (n = 5), or the baseline D-dimer level before TAVR was extremely high (D-dimer level > 10 IU/mL; n = 1). Finally, 87 patients were analyzed in this study. The highest D-dimer levels were defined within 7 days after TAVR as "peak D-dimer" and the D-dimer level before TAVR as "baseline D-dimer". ΔD-dimer was also calculated with peak and baseline D-dimer levels.

Categorical variables are presented as numbers and percentages, and continuous variables are presented as mean ± standard deviation or median (interquartile range). To compare the categorical variables, χ^2 or the Fisher exact test was used. Continuous variables were compared using a t test or the Mann-Whitney test. P values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 26.0 (SPSS, Chicago, Illinois).

Patient characteristics are shown in Table 1. Of the 87 patients, 21 received anticoagulants (2 received warfarin; 12, direct oral anticoagulants [DOAC]; and 7, both DOAC and single antiplatelet agents). Seventeen patients received anticoagulants for atrial fibrillation at baseline, and the other 4 patients started taking anticoagulants after TAVR. Sixty-six patients received only antiplatelet agents without anticoagulants (11 received dual and 55 received single antiplatelet therapy). The patients treated with anticoagulant therapy had atrial fibrillation more frequently.

The perioperative D-dimer levels are shown in Table 1. The peak D-dimer level was significantly lower in the patients treated with anticoagulants than in those treated without anticoagulants (2.38

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Table 1. Baseline characteristics and perioperative D-dimer levels.

	Anticoagulant (n = 21)	Non-anticoagulant (n = 66)	P
Baseline characteristics			
Age [years]	84 ± 4	84 ± 5	0.51
Male	7 (33%)	22 (33%)	1.00
Height [cm]	148 (146–160)	147 (143–153)	0.20
Body weight [kg]	48 (42–54)	48 (41–61)	0.68
Body mass index	21.8 (19.2–26.6)	22.5 (18.9–26.7)	0.17
Hypertension	16 (76%)	50 (76%)	0.97
Dyslipidemia	14 (67%)	38 (58%)	0.46
Diabetes mellitus	7 (33%)	23 (35%)	0.90
eGFR < 60 mL/min/1.73 m^2	12 (57%)	48 (73%)	0.18
Atrial fibrillation	17 (81%)	2 (3%)	< 0.001
Extracardiac arteriopathy	4 (19%)	9 (14%)	0.38
Active cancer	2 (10%)	0 (0%)	0.06
Previous cardiac surgery	3 (15%)	4 (6%)	0.22
STS score	5.9 (5.0–8.9)	5.6 (4.4–7.6)	0.41
Echocardiography			
Left ventricular ejection fraction [%]	66.5 (62.0–75.0)	64.5 (59.0–71.9)	0.34
Mean pressure gradient [mmHg]	43.3 (38.7–51.2)	43.5 (36.0–62.1)	0.78
Aortic valve area [cm^2]	0.57 ± 0.15	0.60 ± 0.18	0.38
Computed tomography			
Annulus area [cm^2]	420.9 ± 63.9	410.7 ± 76.8	0.59
Annulus perimeter [mm]	73.9 ± 5.6	73.0 ± 6.2	0.62
Mean sinus of Valsalva diameter [mm]	29.6 ± 3.1	29.5 ± 3.1	0.95
Procedural characteristics			
Approach site:			0.55
Transfemoral	20 (95%)	61 (92%)	
Non-transfemoral	1 (5%)	5 (8%)	
Prosthesis type:			0.79
SAPIEN XT/3	14 (67%)	46 (70%)	
Evolut R/Pro	7 (33%)	20 (30%)	
Antithrombotic therapy:			
Warfarin only	2	0	
DOAC only	12	0	
DOAC + SAPT	7	0	
DAPT	0	11	
SAPT	0	55	
Perioperative D-dimer levels			
Baseline D-dimer level [IU/mL]	0.50 (0.50–0.65)*	1.10 (0.64–1.95)*	0.003
Peak D-dimer level [IU/mL]	2.38 (1.74–4.29)	5.15 (2.64–8.51)	0.001
ΔD-dimer	1.56 (0.83–2.48)*	5.05 (2.10–7.76)*	< 0.001

eGFR — estimated glomerular filtration rate; STS — Society of Thoracic Surgeons; DOAC — direct oral anticoagulant; DAPT — dual antiplatelet therapy; SAPT — single antiplatelet therapy; ΔD-dimer — peak minus baseline D-dimer levels; *Baseline D-dimer levels were available in 16 patients with anticoagulant and 46 patients without anticoagulant, therefore, ΔD-dimer was calculated in those patients

IU/mL [1.74–4.29 IU/mL] vs. 5.15 IU/mL [2.64––8.51 IU/mL]; p = 0.001). The baseline D-dimer (0.50 IU/mL [0.50–0.65 IU/mL] vs. 1.10 IU/mL [0.64–1.95 IU/mL]; p = 0.003) and Δ-dimer levels (1.56 IU/mL [0.83–2.48 IU/mL] vs. 5.05 IU/mL [2.10–7.76 IU/mL]; p < 0.001) were significantly

lower in the patients with, than in those without anticoagulant therapy.

Preliminary data showed that the baseline, peak, and D-dimer levels were significantly lower in patients with anticoagulant therapy. Recent reports suggest the effectiveness of anticoagulant therapy for prevention and treatment of leaflet thrombosis after TAVR [4, 5], and the present data may support these results. D-dimer levels could be affected by various factors, and suppression of the increase in D-dimer level might not directly demonstrate the effectiveness of anticoagulant therapy. Prior reports have shown that D-dimer levels decreased in patients with atrial fibrillation after initiation of DOAC therapy [6], and anticoagulant therapy might suppress the coagulation reaction and formation of leaflet thrombosis of prosthesis after TAVR. However, the effectiveness of a prevention for leaflet thrombosis does not mean it is the optimal therapy for patients undergoing TAVR [7, 8] because the balance between safety and efficacy for the various issues should be considered in clinical practice. Further investigations are required to address the optimal antithrombotic regimen in patients undergoing TAVR.

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