Changes in platelet function and coagulation after transcatheter aortic valve implantation evaluated with thromboelastography

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ABSTRACT
Introduction The possibility of hypercoagulability during the perioperative period of transcatheter aortic valve implantation (TAVI) has been noted; however, there is still a controversy regarding the appropriate perioperative antithrombotic therapy. The study investigated coagulation and platelet functions during the TAVI perioperative period using thromboelastography (TEG 6s platelet mapping).

Methods A prospective observational study was conducted on 25 patients undergoing TAVI. TEG platelet mapping was performed at three time points: on admission to the operating room (before heparinisation), on postoperative day (POD) 1 and on POD 3. Perioperative changes observed included: maximum clot strength (MA_HK), clot strength without platelet function (MA_Ac), time to initiation of clots formation by coagulation factors (R_6s) and platelet function (G_p). G_p is activated by thrombin, and not affected by antiplatelet agents. It is calculated as [(5000×MA_HK)/(100 – MA_Ac)] − [(5000×MA_Ac)/(100 – MA_Ac)]. Finally, MA_ADPPP2A and G_ADP, which reflect clot strength and platelet aggregation mediated by ADP/thromboxane A2 receptors, respectively, were also examined using the same method as for G_p.

Results MA_HK continued to decrease until POD 3, indicating antithrombotic change after TAVI. G_p continuously decreased for 3 days after TAVI, while MA_AcF increased significantly on POD 3. Furthermore, R_6s shortened on POD 1 and POD 3, suggesting increased coagulation capacity after TAVI. Finally, G_MA in clopidogrel-naïve patients was reduced for 3 days after TAVI, while G_AM in aspirin-naïve patients showed no significant change perioperatively.

Conclusions In this study involving TEG platelet mapping, coagulation capacity increased while platelet function decreased, resulting in antithrombotic change for 3 days after TAVI. The ADP receptor system may be more involved in the decreased platelet function. This may be useful for considering optimal perioperative antithrombotic therapy in TAVI.

INTRODUCTION
Prophylaxis of thromboembolic complications after transcatheter aortic valve implantation (TAVI) is an important issue. The stroke rate after TAVI varies from 3% to 4%. In addition, leaflet thrombosis after TAVI generally occurs in 7% of patients, and 1.2% are asymptomatic. Conversely, perioperative bleeding complications are a problem in patients receiving antithrombotic therapy. Bleeding complications were reported in 24.1% of patients after TAVI. The most frequently reported was bleeding at the
puncture site. Approximately 3.7% of patients develop life-threatening bleeding, such as cardiac tamponade or compartment syndrome due to puncture site bleeding.3–5  

There is still a controversy regarding the appropriate periprocedural antithrombotic regimen. Conventionally, dual antiplatelet therapy (DAPT) had been recommended for 6 months after TAVI; however, in recent years, some reports have recommended single antiplatelet therapy.4–6 In the 2020 American College of Cardiology/American Heart Association guideline, low-dose single-agent aspirin was renamed class IIa, and DAPT was renamed class IIb.7 Furthermore, to determine the appropriate periprocedural antithrombotic strategy for TAVI, it is necessary to ascertain the periprocedural changes in coagulation capacity and platelet function.

Thromboelastography (TEG) differs from conventional coagulation and platelet function tests in that it measures the strength of clots as an interaction between platelets and fibrinogen, which may more accurately reflect the risk of bleeding and thromboembolism. Only a few studies have examined changes in coagulation and platelet function using TEG after TAVI. Although previous studies using TEG 6s have reported periprocedural thrombophilic tendency after valve implantation in TAVI,8 there have been no studies after postoperative day (POD) 1. In addition, the trend of platelet function has not yet been adequately studied, particularly with TEG 6s. A study using conventional multiple electrode impedance aggregometry reported that platelet reactivity declines immediately after TAVI, reaching its lowest level on the third day, followed by a gradual recovery.9

In this study we used TEG 6s to investigate changes in following items during the TAVI perioperative period: (1) coagulation and platelet function, (2) receptor-specific changes in platelet aggregation capacity and (3) the effects of antiplatelet agents.

METHODS

Study population

This was a prospective, observational, single-centre study. Patients undergoing TAVI in the centre between February and April 2021 were recruited prospectively. All participants were screened for inclusion.

Exclusion criteria were as follows: (1) patients without consent; (2) patients with conversion to open heart surgery; (3) patients with blood volume loss >500 cc during the procedure; (4) patients with perioperative fresh frozen plasma or platelet transfusion; (5) patients needing urgent surgery; (6) patients with suspected bleeding or clotting disorder; (7) cases of complication with other moderate or severe valve diseases; (8) patients on multidrug antithrombotic therapy and (9) cases of perioperative modification of antithrombotic therapy.

Clinical management

Patients with severe symptomatic aortic stenosis (AS) and indication for TAVI, as diagnosed by the heart team, were included. All procedures were performed transfemorally using the SAPIEN-3 (Edwards Life Sciences, California, USA), EvolutR or PRO (Medtronic, Dublin, Ireland) prosthesis.

All patients received single antithrombotic therapy with aspirin, clopidogrel, or an oral anticoagulant (OAC (FXa inhibitor: Edoxaban 30–60 mg/day or Apixaban 10 mg/day)), which was started at least 48 hours before the procedure and continued daily. In addition, intravenous heparin (100 IU/kg) was administered before valve deployment, which was reversed with protamine. Regarding clopidogrel and aspirin, there was no perioperative withdrawal, and OAC was withdrawn on only the day of surgery. Furthermore, the choice of antithrombotic agent was based on the patient’s preoperative medications; otherwise, a single antiplatelet agent was started depending on the cardiologist’s choice. A periprocedural evaluation was performed by medical specialists on all cases, including fundamental data, preoperative risk factors and clinical events related to bleeding and thrombosis.

Thromboelastography

Three whole blood samples were obtained from each patient and collected in a 2 mL tube (Venoject; Terumo; Tokyo, Japan) containing sodium heparin. The first was taken preanaesthesia (preheparin) (T1). The second and the third were taken in the morning of the first (T2) and third (T3) POD, respectively. At each point, blood was analysed with TEG 6s platelet mapping (Haemonetics, Braintree, MA, USA). TEG 6s platelet mapping included four types of tests: kaolin/heparinase (HKH), reptilase/factorXIIIa/abciximab (ActF), ADP, Arachidonic acid (AA). The manufacturer’s recommendations regarding the use of TEG 6s were followed.

TEG 6s shows blood clot strength as maximum amplitude (MA, mm); the significance of MA in each reagent is explained as follows: (1) MAHKH: Maximum clot strength, formed by platelets and fibrin after producing thrombin for maximum platelet activation, indicates comprehensive coagulation and platelet function and is unaffected by antiplatelet medication. (2) MAADP: Represents fibrin-only blood clot strength without platelet function. (3)/(4) MAADP/AA: Represents the clot strength when thrombin generation is inhibited, ADP/TXA2 receptors are stimulated, and platelets are activated specifically for each receptor, respectively.

Furthermore, for MAADP, high on-treatment platelet reactivity (HTPR) and low on-treatment platelet reactivity (LTPR) were defined from previous studies10 as follows: HTPR=MAADP >47 mm, LTPR=MAADP <31 mm. In addition to MA, RHKHF, a parameter that reflects the time to initiation of clot formation by coagulation factors, was also examined. Twenty-one patients who were not taking OAC were examined for RHKHF because the effect of OAC cannot be denied even if it is withdrawn on the day of surgery.
The blood clot elasticity (G, dyne/cm²) was calculated as another clot strength measure from MA as follows: \[ G = \frac{(5000 \times MA)}{(100 - MA)} \]. The platelet component of the blood clot elasticity, \( G_p \), was then expressed as the difference between the maximum clot strength, \( G_p \) (converted from \( MA_{HKH} \) and the fibrin-only clot strength without platelet function, \( G_{SC} \) (converted from \( MA_{ADP} \)). \[ G_p = \left[ \frac{(5000 \times MA_{HKH})}{(100 - MA_{HKH})} \right] - \left[ \frac{(5000 \times MA_{SC})}{(100 - MA_{SC})} \right], \]

\[ G_p \] represents platelet aggregation capacity maximally activated by thrombin and is not affected by the use of antiplatelet medications. \( G_{ADP/AA} \) (dyne/cm²) represents platelet aggregation capacity activated by ADP/TXA2 receptors, respectively, and is calculated similarly to \( G_p \) above. \[ G_{ADP/AA} = \left[ \frac{(5000 \times MA_{ADP/AA})}{(100 - MA_{ADP/AA})} \right] - \left[ \frac{(5000 \times MA_{SC})}{(100 - MA_{SC})} \right] \]

Data regarding the following items of the general blood collection tests were also collected from the medical records: Complete blood count, Prothrombin time (PT)/international normalised ratio (INR), activated partial thromboplastin time (APTT) and fibrinogen level.

Statistical analysis
All statistical analyses were performed by using EZR V.1.41 (Jichi Medical University, Saitama, Japan). Continuous variables are expressed as means±SD/medians±IQR according to normal/non-normal distribution.
The change in \( G_p \) (dyne/cm²) during the TAVI perioperative period was set as the primary outcome; the change in various MA (mm), G (dyne/cm²) and R (min) during the perioperative period were examined and set as the secondary outcomes.
The analysis methods used were the univariate type III repeated-measures/Friedman test and the Student's t-test/Mann-Whitney U test, following the normal/non-normal distribution pattern. Furthermore, the Bonferroni method was used to correct for multiplicity. A two-tailed test result of p<0.05 was considered a statistically significant difference.
The frequencies were expressed as percentages for categorical variables, including high platelet reactivity, therapeutic range and low platelet reactivity.

RESULTS
Thirty-eight consecutive patients undergoing TAVI were considered. Finally, 13 patients met the exclusion criteria, and 25 were enrolled in this study.

Baseline characteristics
Baseline characteristics are shown in table 1.
Approximately 76% of the patients were female; the mean age was 82.8±7.3. Perioperative antithrombotic medications were aspirin in 44% of patients (n=11), clopidogrel in 40% of patients (n=10) and OAC in 16% of patients (n=4).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N=25)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>82.8±7.3</td>
</tr>
<tr>
<td>Female</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7±5.0</td>
</tr>
<tr>
<td>EuroSCORE II</td>
<td>4.1±3.4</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Post-PCI</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Perioperative antithrombotic treatment</td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Cardiac ultrasound</td>
<td></td>
</tr>
<tr>
<td>PG max (mm Hg)</td>
<td>84.8±25.4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.9±10.2</td>
</tr>
<tr>
<td>Vmax (m/s)</td>
<td>4.6±0.67</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.69±0.25</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
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<tr>
<td>Self-expandable valve</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>BAV</td>
<td>15 (60%)</td>
</tr>
</tbody>
</table>

Data are presented as median±SD or n (%).
AVA, aortic valve area; BAV, balloon aortic valvuloplasty; BMI, body mass index; CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PG, pressure gradient; TIA, transient ischaemic attack.

Perioperative changes in blood clots strength
Changes in platelet and coagulation function \( MA_{HKH} \), \( MA_{ADP} \), \( G_p \) and \( R_{HKH} \) trends are shown in figure 1 and table 2.
The \( MA_{HKH} \) value was significantly lower on POD 1 and POD 3 compared with the preoperative value. (T1 vs T2, T1 vs T3, T2 vs T3: \( p=0.046, 0.0076, 0.70 \)). The decreased maximum clot strength means antithrombotic change for 3 days after TAVI \( MA_{SC} \) value, which represents the strength of fibrin-only clots without platelet, was significantly increased on POD 3 compared with the preoperative value. (T1 vs T2, T1 vs T3, T2 vs T3: \( p=1.0, 0.0067, 0.0002 \)). The value of \( R_{HKH} \) was significantly shorter on POD 1 and POD 3 than the preoperative value (T1 vs T2, T1 vs T3, T2 vs T3: \( p=0.00027, 0.01, 1.0 \)). These results suggest an increased coagulation capacity after TAVI.
The \( G_p \) value decreased significantly over time until 3 days postoperatively (T1 vs T2, T1 vs T3, T2 vs T3: \( p<0.05 \)).
Effects of antiplatelet drugs
The distributions of MAADP/AA value in clopidogrel/aspirin-treated patients are shown in figure 2.

In clopidogrel-treated patients, there were many cases of deviation from the therapeutic range, and HTPR cases were prominent. LTPR cases were seen in 10%–20% of the patients throughout the perioperative period.

The MA AA value of patients taking aspirin was widely distributed from 10 to 60 mm, and the individual differences were conspicuous.

Changes in platelet function mediated by ADP/TXA2 receptors
The GADP/AA transition is shown in figure 3 and table 2. GADP, which reflects ADP receptor-mediated platelet aggregation, was significantly lower on POD 1 and POD 3 in clopidogrel-naive patients compared with preoperative values (figure 3. T1 vs T2, T1 vs T3, T2 vs T3: p=0.00018, 0.00018, 0.76). ADP receptor-mediated platelet aggregation decreased for 3 days after TAVI. In contrast, GADP in clopidogrel-treated patients did not change significantly during the perioperative period.

On the other hand, GA, which reflects TXA2 receptor-mediated platelet aggregation, did not change significantly in patients not taking aspirin during the perioperative period (figure 3, lower column), suggesting that TXA2 receptor-mediated platelet aggregation is unaffected by TAVI. Conversely, GA in patients taking aspirin was significantly lower on POD 1 and 3 than preoperative values (T1 vs T2, T1 vs T3, T2 vs T3: p=0.0029, 0.0029, 0.72).

Results of general blood collection are shown in table 2.

Platelet counts were significantly lower on POD 1 and POD 3 than those observed preoperatively (T1 vs T2, T1 vs T3, T2 vs T3: p=0.0000025, 0.00041, 0.05364). The fibrinogen level was significantly lower on POD 1 than on POD 3 and preoperatively (T1 vs T2, T1 vs T3, T2 vs T3: p=0.01362, 0.76170, 0.00032). In addition, haemoglobin, PT-INR and APTT levels did not change significantly perioperatively.

Clinical outcomes
There were no death or symptomatic embolic complications postoperatively before discharge from the hospital. Regarding bleeding complications, 1 case out of 25 patients had difficulty in postoperative management due to intraoperative epistaxis from the nasal airway insertion site. This patient was on clopidogrel and had a preoperative MAADP value of 35.6 mm, near the lower end of the therapeutic range.

Three of the 25 patients received red blood cell transfusions in the perioperative period, but all of these transfusions were of 2 units. No patients received fresh frozen plasma or platelet transfusions.
DISCUSSION
The novelty of this study
Blood viscoelasticity testing was performed using TEG 6s platelet mapping over 3 days after TAVI. In addition, by calculating the elasticity of the blood clots, the coagulation and platelet functions were separated, and their changes were examined. TEG 6s platelet mapping measures the strength of blood clots formed by whole blood components, such as coagulation factors (except von Willebrand factor), platelets, fibrinolytic system and inflammatory cells. It is believed to reflect clinical events better, including bleeding and thromboembolic events.

Table 2  Result of TEG 6s platelet mapping and laboratory tests

<table>
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<tr>
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<th>T1</th>
<th>T2</th>
<th>T3</th>
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<tbody>
<tr>
<td><strong>Platelet mapping</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MA_{ADP} (mm)</td>
<td>66 (63.2, 67.6)</td>
<td>65.5 (61.4, 67.6)*</td>
<td>64.7 (61.2, 65.7)**</td>
</tr>
<tr>
<td>MA_{ACTF} (mm)</td>
<td>16.2 (14.0, 20.1)</td>
<td>16.7 (13.8, 20.8)</td>
<td>19.6 (17.2, 21.8)**</td>
</tr>
<tr>
<td>R_{KOH} (min)</td>
<td>5.1 (4.7, 5.75)</td>
<td>4.4 (4.0, 4.9)**</td>
<td>4.6 (4.1, 4.9)*</td>
</tr>
<tr>
<td>G_p (dyne/cm²)</td>
<td>8571 (7806, 9121)</td>
<td>8125 (7038, 9095)*</td>
<td>7795 (6958, 8236)***</td>
</tr>
<tr>
<td>G_{AA} (dyne/cm²)</td>
<td></td>
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<tr>
<td>Clopidogrel</td>
<td>3778 (1364, 6258)</td>
<td>2344 (1475, 4841)</td>
<td>3199 (2807, 5575)</td>
</tr>
<tr>
<td>Non-Clopidogrel</td>
<td>7402 (6377, 7930)</td>
<td>5592 (4740, 6429)***</td>
<td>5534 (3095, 6350)***</td>
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<tr>
<td><strong>Laboratory tests</strong></td>
<td></td>
<td></td>
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<tr>
<td>Haemoglobin (g/L)</td>
<td>111 (101, 128)</td>
<td>105 (92, 115)</td>
<td>107 (99, 116)</td>
</tr>
<tr>
<td>Platelet count (10^3/mm³)</td>
<td>17.4 (14.7, 28.1)</td>
<td>13.7 (11.2, 20.6)***</td>
<td>12.8 (9.9,18.6)***</td>
</tr>
<tr>
<td>PT-INR</td>
<td>0.96 (0.89, 1.06)</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.97 (0.93, 1.06)</td>
</tr>
<tr>
<td>APTT(s)</td>
<td>30.8 (28.2, 35.6)</td>
<td>32.5 (30.4, 35.4)</td>
<td>31.3 (29.2, 33.8)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>380 (314, 435)</td>
<td>321 (281, 392)*</td>
<td>374 (339, 412)</td>
</tr>
</tbody>
</table>

Data are presented as median (25th, 75th percentile). *p<0.05, **p<0.01, ***p<0.001.

MA_{ADP}, MA_{ACTF}, APTT, activated partial thromboplastin time; HKH, kaolin with heparinase; PT-INR, prothrombin time-international normalised ratio; T1, just before operation (before heparin administration); T2, first postoperative day; T3, third postoperative day; TEG, thromboelastography.

Figure 2  The distribution of MA_{ADP/AA} values in patients taking clopidogrel/aspirin. HTPR: high on-treatment platelet reactivity, LTTPR: low on-treatment platelet reactivity. T1: just before operation (before heparin administration), T2: first postoperative day, T3: third postoperative day. Patients taking clopidogrel are classified as HTPR, therapeutic range, or LTTPR, based on MA_{ADP} value. HTPR cases were prominent. LTTPR cases were seen in 10%–20% of the patients throughout the perioperative period. MA_{AA} values were widely distributed from 10 to 60 mm, and individual differences were conspicuous. HTPR, high on-treatment platelet reactivity; LTTPR, low on-treatment platelet reactivity.
As a conventionally used parameter, MA does not necessarily have a linear relationship with actual blood clot strength. However, the blood clot elasticity (G) used in this study was calculated from MA using the formula: \( G = \frac{5000 \times MA}{100 - MA} \), which more accurately reflects actual blood clot strength. Therefore, it is reasonable to calculate platelet function from the difference in G with and without platelet activation.11

Changes in platelet and coagulation function

First, maximal platelet aggregation capacity, expressed as \( G_A \), decreased for 3 days after TAVI. Platelet counts also decreased similarly. These results are generally consistent with a report based on conventional platelet aggregation assays9 and a report about the time course of platelet counts.13 It is unclear in this study whether the decreased platelet count brought about the decreased platelet function; this should be clarified in prospective studies.11

Next, \( MA_{HKH} \), which represents coagulation capacity excluding platelet function, was significantly elevated on POD 3. In addition, the \( R_{HKH} \) value, which reflects the time until the initiation of clot formation by coagulation factors, was significantly shorter on POD 1 and POD 3 than preoperatively. These results suggest that coagulation capacity is enhanced after TAVI. This was not reflected by conventional coagulation test results, including PT-INR, APTT and fibrinogen levels.

Finally, concerning maximum clot strength \( MA_{HKH} \), previous studies have shown that the \( MA_{HKH} \) value transiently increases immediately after TAVI and normalises 6 hours postoperatively.8 The present results show that \( MA_{HKH} \) decreases from POD 1 to POD 3, indicating an antithrombotic change that may have resulted from a stronger effect of decreased platelet function than increased coagulation capacity after TAVI. These results may suggest that patients are more at risk for bleeding than for thromboembolism in the immediate post-TAVI period. In light of the above, there may be room for reconsidering antiplatelet therapy in the search for appropriate antithrombotic therapy after TAVI. Large-scale clinical studies that compare the occurrence of
thromboembolic events, and bleeding events, among others, may be needed.

**Effects of antiplatelet drugs**

Compared with other reports using TEG 6s, this study gives the impression of a higher proportion of patients with HTPR of MAADP. Possible reasons for this include the fact that 18%–23% of the Japanese population is clopidogrel resistance due to genetic polymorphisms in CYP2C19, as well as the influence of the protocol of administration. Loading dose was not administered at the start of clopidogrel administration.

On the other hand, some patients were classified into LTPR of MAADP. Another study using VerifyNow has also reported a hyper-response to clopidogrel was observed in one-third of patients undergoing TAVI and was related to bleeding. Detecting these patients may be important. Similarly, there were large individual differences in MAADP even among patients taking aspirin, suggest the need for personalised tailor-made therapy regarding antiplatelet therapy after TAVI.

It should also be noted that the thromboelastography (TEG) cut-off values used in this study are currently based on perioperative studies for percutaneous coronary intervention (PCI) patients. In the perioperative PCI period, the target lower limit of MAADP associated with bleeding complications was often 31 mm; however, in the perioperative TAVI period, 47 mm or less was associated with bleeding. Considering these reports, the cut-off values that predict clinical events in the perioperative period for TAVI and PCI may differ. Furthermore, embolisms, such as in stent thrombosis, may be of greater concern after PCI; in contrast, bleeding complications from the surgical procedure may be of more concern after TAVI. Extensive studies are awaited regarding appropriate cut-off values for bleeding/embolic complications in the perioperative TAVI period.

**Changes in platelet aggregation capacity mediated by ADP/TXA2 receptors**

In patients not taking clopidogrel, GADP represents ADP receptor-stimulated platelet aggregation, which is reduced for 3 days after TAVI. In patients not taking aspirin, GA represents TXA2 receptor-mediated platelet aggregation, which did not change significantly during the TAVI perioperative period. These results suggest that platelet activation by the ADP system is suppressed for 3 days postoperatively, whereas activation by the TXA2 system is less affected. The postoperative decrease in GA in aspirin-treated patients might also reflect reduced platelet activation by the ADP system.

Furthermore, the different effects of TAVI on the ADP and TXA2 systems suggest that platelet function suppression mechanisms other than reduced platelet counts may be at work. Previous studies have shown that platelet reactivity to ADP is reduced by increased expression of CD39 (an ADPase and ATPase), when shear stress occurs. In TAVI, blood turbulence occurs after valve implantation. This may be responsible for the suppression of the ADP system. Further case series may be needed to investigate the effect of TAVI on the TXA2 system.

**Clinical implications**

The key results and clinical implications of this study are shown in figure 4. Previous studies have shown that blood turbulence after TAVI activates the coagulation pathways.
cascade, resulting in thrombosis, which is a potential cause of thromboembolism after TAVI. Traditionally, this thrombotic tendency has been noted in the perioperative TAVI period, and antiplatelet therapy has been primarily administered similarly to the post-PCI period. However, the present study results show that platelet function is decreased, especially, ADP receptor-mediated platelet aggregation capacity was reduced, and coagulation capacity is increased after TAVI, resulting in decreased maximum clot strength, representing a postoperative antithrombotic effect. This suggests the need to reconsider protocols using antiplatelet agents in the postoperative period. Specifically, ADP receptor antagonist loading pre-TAVI could be redundant or even should be avoided. Also, pausing direct OAC in patients with atrial fibrillation could possibly carry a higher risk of thromboembolism due to the increased coagulation capacity.

In addition, there was a great deal of individual variability in the antiplatelet therapy effects, particularly in some patients taking clopidogrel, who were at high risk of bleeding as determined by TEG 6s platelet mapping. Finally, since the study results show that ADP receptor-mediated platelet aggregation is suppressed after TAVI, individual platelet function monitoring, particularly in patients taking clopidogrel, might be preferable.

**Limitations**
First, this study’s sample size was small. Therefore, we could not investigate the association between TEG 6s data and clinical outcomes. Second, TEG 6s platelet mapping was the only platelet function assay used in this study and was not investigated in combination with other assays. However, there was some evidence that TEG 6s platelet mapping provides a more accurate estimate of in vivo platelet aggregation capacity than conventional platelet aggregation tests. Since conventional platelet aggregation tests are expensive, time-consuming, and do not necessarily reflect clot strength, it might be worthwhile to consider whether platelet function testing by TEG could be an alternative. In addition, the minimum preoperative antiplatelet medication in this study was relatively short (3-day preoperative period). However, most participants in this study (86%) had taken antiplatelet agents for at least 5 days before surgery, and GpIIb/IIIa, which represents maximum platelet aggregation capacity, is reportedly unaffected by antiplatelet medication. Moreover, GADP/AA was mainly studied in patients not using the corresponding antiplatelet agent.

Finally, although the methodology of measuring ADP/TXA2 receptor-mediated platelet aggregation capacity from GADP/AA seems reasonable, it has not been reported so far, and its validity needs to be examined in the future.

**CONCLUSION**
This study using TEG 6s platelet mapping showed that coagulation capacity increased over the three days after TAVI surgery. In contrast, platelet function decreased over time, resulting in decreased maximum clot strength, representing antithrombotic change for 3 days postoperatively. The ADP receptor system may be more involved in decreased platelet function. These results may be useful for consideration in perioperative antithrombotic therapy. Furthermore, there are large individual differences in the efficacy of antiplatelet agents in the perioperative TAVI period, suggesting the need for individual monitoring using TEG.

**REFERENCES**
7. Writing Committee Members, 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 College of Cardiology Committee on Practice Guidelines.”

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**Patient consent for publication** Not applicable.

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**Data availability statement** Data are available on reasonable request.

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