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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_{HKH}), clot strength without platelet function (MA_{ActF}), time to initiation of clots formation by coagulation factors (R_{HKH}) and platelet function (G_p). G_p is activated by thrombin, and not affected by antiplatelet agents. It is calculated as $[(5000\times MA_{HKH})/(100 - MA_{HKH})] - [(5000\times MA_{ActF})/(100 - MA_{ActF})]$. Finally, $MA_{ADP/AA}$ and $G_{ADP/AA}$, which reflect clot strength and platelet aggregation mediated by ADP/thromboxane A_2 receptors, respectively, were also examined using the same method as for G_p.

Results MA_{HKH} continued to decrease until POD 3, indicating antithrombotic change after TAVI. G_p continuously decreased for 3 days after TAVI, while MA_{ActF} increased significantly on POD 3. Furthermore, R_{HKH} shortened on POD 1 and POD 3, suggesting increased coagulation capacity after TAVI. Finally, G_{ADP} in clopidogrel-naive patients was reduced for 3 days after TAVI, while G_{AA} in aspirin-naive 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 implicated in the decreased platelet function. These results may be useful for considering optimal perioperative antithrombotic therapy in TAVI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although previous studies using thromboelastography (TEG 6s) have reported a mild thrombophilic tendency after valve implantation through transcatheter aortic valve implantation (TAVI), 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 conventional platelet aggregometry study reported that platelet reactivity declines immediately after TAVI, reaching its lowest level on the third day, followed by a gradual recovery.

WHAT THIS STUDY ADDS

⇒ In this study using TEG platelet mapping, the coagulation capacity increased over the three POD after TAVI; however, platelet function decreased over time, resulting in antithrombotic change postoperatively. The ADP receptor system may be more involved in the decreased platelet function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In the post-TAVI period, there was a decreased platelet function and an increased coagulation capacity, resulting in antithrombotic change. This suggests that protocols for the use of postoperative antiplatelet agents need to be reconsidered. In addition, there was a great deal of individual variability in the efficacy of antiplatelet therapy, particularly in some patients taking clopidogrel, who were at high risk for bleeding as determined by TEG 6s platelet mapping, suggesting the need for individualised monitoring of platelet function.

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%.[1] In addition, leaflet thrombosis after TAVI generally occurs in 7% of patients, and 1.2% are symptomatic.[2] 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]

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 perioperative antithrombotic strategy for TAVI, it is necessary to ascertain the perioperative 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 intraprocedural 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 perioperative 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) MA_{HKH}: 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) MA_{ActF}: Represents fibrin-only blood clot strength without platelet function. (3)/(4) $MA_{ADP/AA}$: Represents the clot strength when thrombin generation is inhibited, ADP/TXA_2 receptors are stimulated, and platelets are activated specifically for each receptor, respectively.

Furthermore, for MA_{ADP}, high on-treatment platelet reactivity (HTPR) and low on-treatment platelet reactivity (LTPR) were defined from previous studies[10] as follows: HTPR=MA_{ADP} >47 mm, LTPR=MA_{ADP} <31 mm. In addition to MA, R_{HKH}, 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 R_{HKH} because the effect of OAC cannot be denied even if it is withdrawn on the day of surgery.

The blood clot elasticity (G, dyne/cm^2) was calculated as another clot strength measure from MA as follows: G = (5000 × 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_T (converted from MA_{HKH}) and the fibrin-only clot strength without platelet function, G_{SC} (converted from MA_{ActF}).[11] G_P (dyne/cm^2) = G_T G_{SC} = [(5000 × MA_{HKH} / (100 – MA_{HKH})] - [(5000 × MA_{ActF}) / (100 – MA_{ActF})]. G_P represents platelet aggregation capacity maximally activated by thrombin and is not affected by the use of antiplatelet medications. $G_{ADP/AA}$ (dyne/cm^2) represents platelet aggregation capacity activated by ADP/TXA_2 receptors, respectively, and is calculated similarly to G_P above. $G_{ADP/AA}$ = [(5000 × $MA_{ADP/AA}$ / (100 – $MA_{ADP/AA}$)] – [(5000 × MA_{ActF}) / (100 – MA_{ActF})]

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).[12] Continuous variables are expressed as means±SD/medians±IQR according to normal/non-normal distribution.

The change in G_P (dyne/cm^2) during the TAVI perioperative period was set as the primary outcome; the change in various MA (mm), G (dyne/cm^2) 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 1 Baseline characteristics of the enrolled patients

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

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_{ActF}, 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_{ActF} 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:

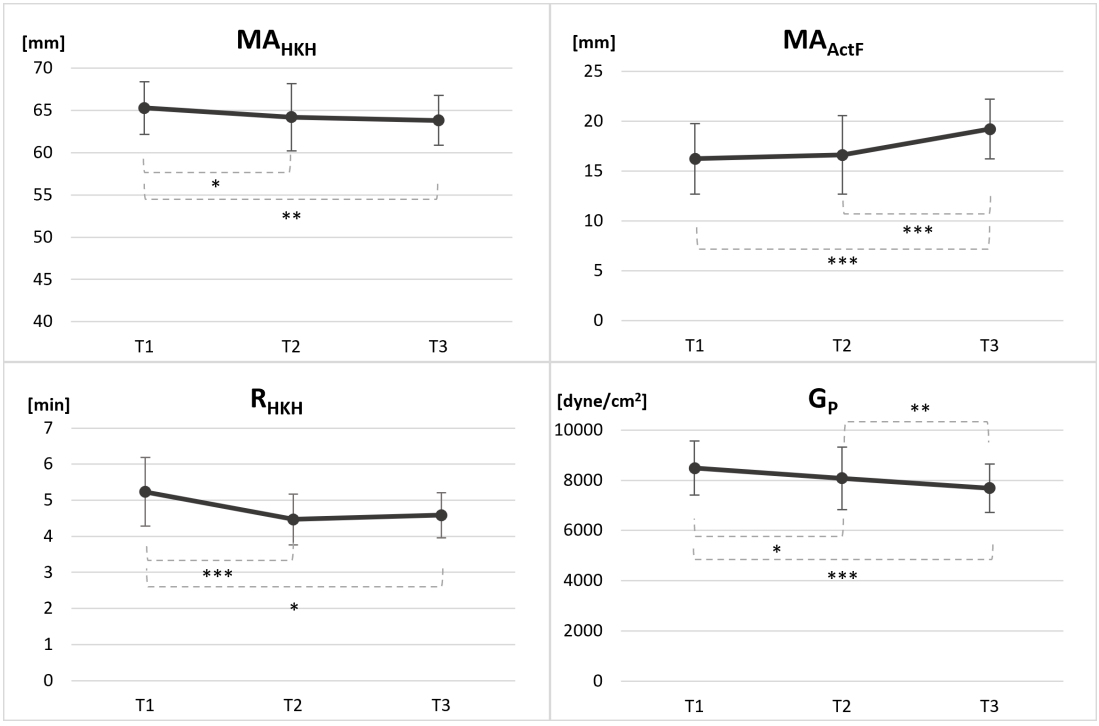

Figure 1 Changes in MA_{HKH}, MA_{ActF}, R_{HKH} and G_p at each time point. T1: just before operation (before heparin administration), T2: first postoperative day, T3: third postoperative day. *p<0.05, **p<0.01, ***p<0.001. P values show the significance of change between each point. MA_{HKH} significantly decreased on the first and third postoperative days compared with the preoperative value. MA_{ActF} did not change between the preoperative period and day 1; however, it increased significantly on day 3. R_{HKH} significantly decreased on the first and third postoperative days compared with the preoperative value. G_p showed a significant postoperative decrease over time.

p=0.021, 0.0001, 0.0087), showing that maximum platelet function continued to decrease for 3 days after TAVI.

Effects of antiplatelet drugs

The distributions of $MA_{ADP/AA}$ 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/TXA_2 receptors

The $G_{ADP/AA}$ transition is shown in figure 3 and table 2. G_{ADP}, 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, G_{ADP} in clopidogrel-treated patients did not change significantly during the perioperative period.

On the other hand, G_{AA}, which reflects TXA_2 receptor-mediated platelet aggregation, did not change significantly in patients not taking aspirin during the perioperative period (figure 3, lower column), suggesting that TXA_2 receptor-mediated platelet aggregation is unaffected by TAVI. Conversely, G_{AA} 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 MA_{ADP} 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.

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

	T1	T2	T3
Platelet mapping			
MA_{HKH} (mm)	66 (63.2, 67.6)	65.5 (61.4, 67.6)*	64.7 (61.2, 65.7)**
MA_{ActF} (mm)	16.2 (14.0, 20.1)	16.7 (13.8, 20.8)	19.6 (17.2, 21.8)**
R_{HKH} (min)	5.1 (4.7, 5.75)	4.4 (4.0, 4.9)***	4.6 (4.1, 4.9)*
G_P (dyne/cm^2)	8571 (7806, 9121)	8125 (7038, 9095)*	7795 (6958, 8236)***
G_{ADP} (dyne/cm^2)			
Clopidogrel	3778 (1364, 6258)	2344 (1475, 4841)	3199 (2807, 5575)
Non-Clopidogrel	7402 (6377, 7930)	5592 (4740, 6429)***	5534 (3095, 6350)***
G_{AA} (dyne/cm^2)			
Aspirin	2873 (1928, 5103)	1410 (404, 2300)**	840 (239, 1897)**
Non-Aspirin	8088 (364, 8814)	7216 (1851, 8515)	7177 (5946, 7845)
Laboratory tests			
Haemoglobin (g/L)	111 (101, 128)	105 (92, 115)	107 (99, 116)
Platelet count (10^3/mm^3)	17.4 (14.7, 28.1)	13.7 (11.2, 20.6)***	12.8 (9.9.18.6)***
PT-INR	0.96 (0.89, 1.06)	0.98 (0.93, 1.03)	0.97 (0.93, 1.06)
APTT(s)	30.8 (28.2, 35.6)	32.5 (30.4, 35.4)	31.3 (29.2, 33.8)
Fibrinogen (mg/dL)	360 (314, 435)	321 (281, 392)*	374 (339, 412)

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

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.

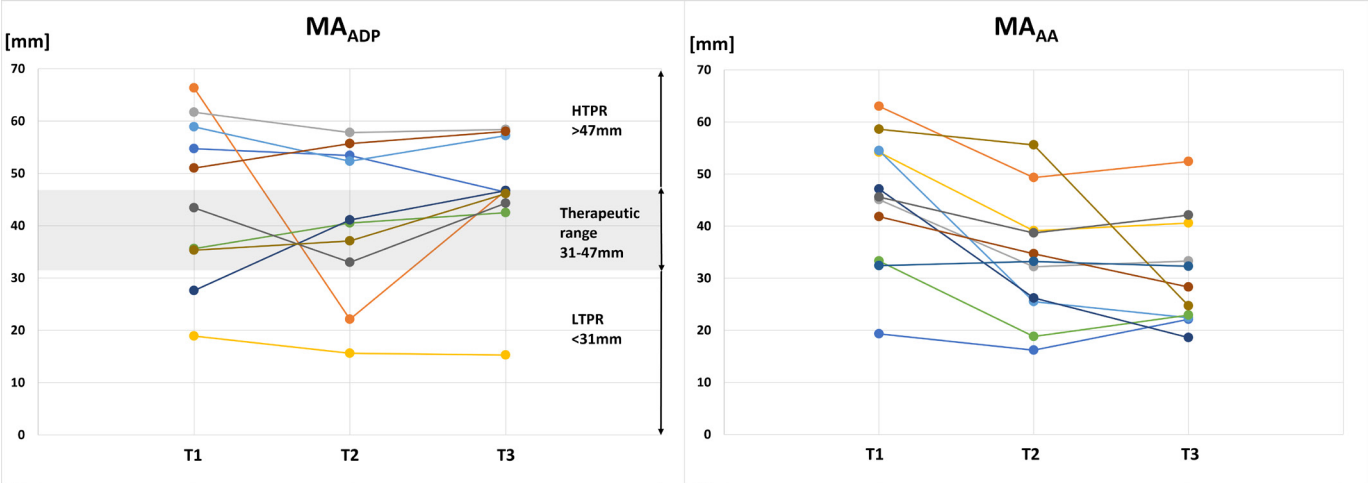

Figure 2 The distribution of $MA_{ADP/AA}$ values in patients taking clopidogrel/aspirin. HTPR: high on-treatment platelet reactivity, LTPR: low on-treatment platelet reactivity. T1: just before operation (before heparin administration), T2: first postoperative day, T3: third postoperative day. Patients taking clopidogrel are classified as HTPR, therapeutic range, or LTPR, based on MA_{ADP} value. HTPR cases were prominent. LTPR 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; LTPR, low on-treatment platelet reactivity.

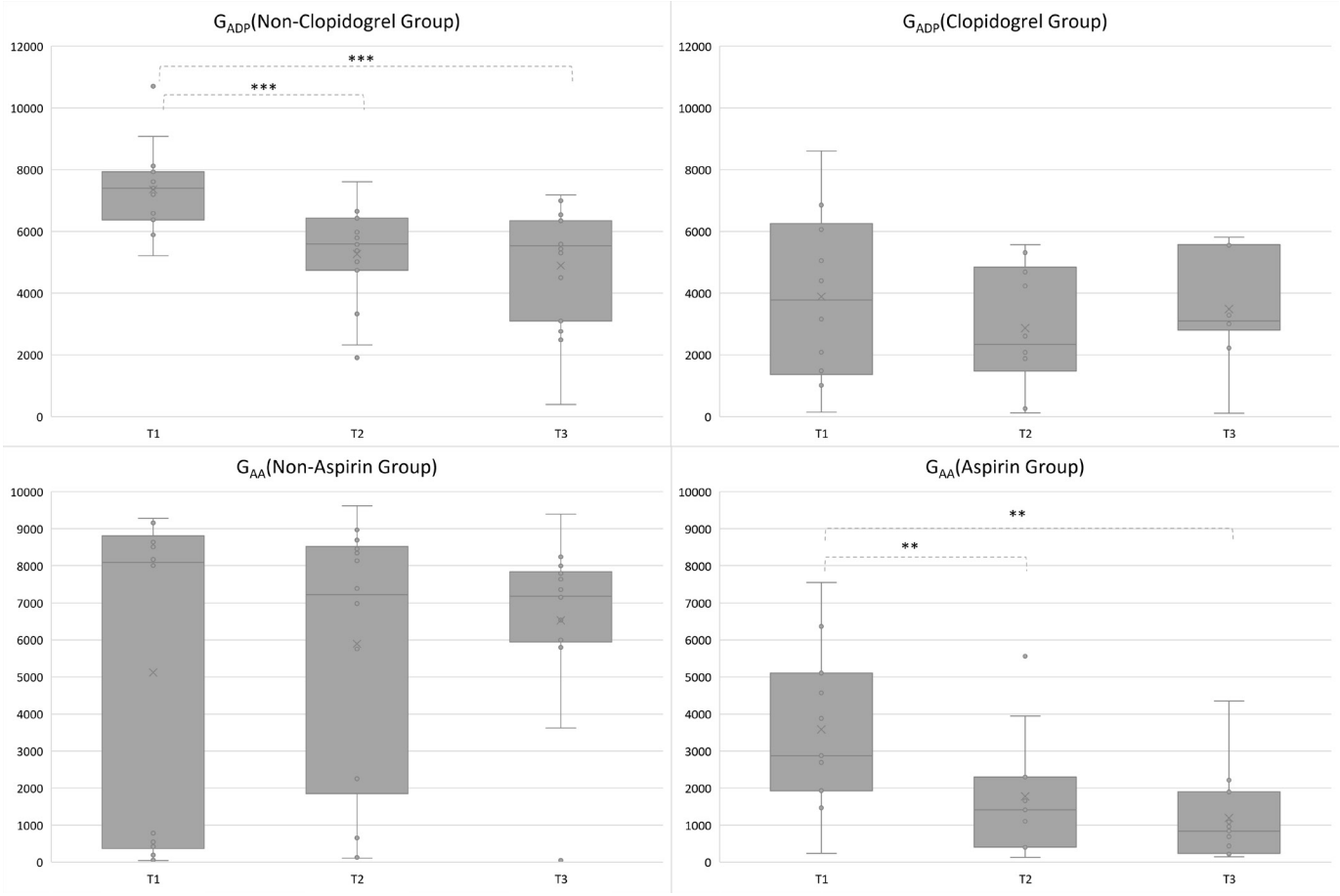

Figure 3 (Upper column) Changes in G_{ADP} (clopidogrel group/non-clopidogrel group) at each time point. (Lower column) Changes in G_{AA} (aspirin group/non-aspirin group) at each time point. T1: just before operation (before heparin administration), T2: first postoperative day, T3: third postoperative day. **p<0.01, ***p<0.001. P values show the significance of the change between each point. (Upper column) In the non-clopidogrel group, G_{ADP} was significantly decreased on the first and third postoperative days compared with the preoperative value. In the clopidogrel group, G_{ADP} showed no significant change throughout the period. (Lower column) In the aspirin group, G_{AA} was significantly decreased on the first and third postoperative days compared with the preoperative value. In the non-aspirin group, G_{AA} showed no significant change throughout the period.

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 = (5000 × 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_p, decreased for 3 days after TAVI. Platelet counts also decreased similarly. These results are generally consistent with a report based on conventional platelet aggregation assays[9] 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_{ActF}, 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,[14 15] this study gives the impression of a higher proportion of patients with HTPR of MA_{ADP}. Possible reasons for this include the fact that 18%–23% of the Japanese population is clopidogrel resistance due to genetic polymorphisms in CYP2C19,[16] 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 MA_{ADP}. 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.[17] Detecting these patients may be important. Similarly, there were large individual differences in MA_{AA}, 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 MA_{ADP} associated with bleeding complications was often 31 mm[14]; however, in the perioperative TAVI period, 47 mm or less was associated with bleeding.[3] 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/TXA_2 receptors

In patients not taking clopidogrel, G_{ADP} represents ADP receptor-stimulated platelet aggregation, which is reduced for 3 days after TAVI. In patients not taking aspirin, G_{AA} represents TXA_2 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 TXA_2 system is less affected. The postoperative decrease in G_{AA} in aspirin-treated patients might also reflect reduced platelet activation by the ADP system.

Furthermore, the different effects of TAVI on the ADP and TXA_2 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.[18 19] In TAVI, blood turbulence occurs after valve implantation.[20] 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 TXA_2 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

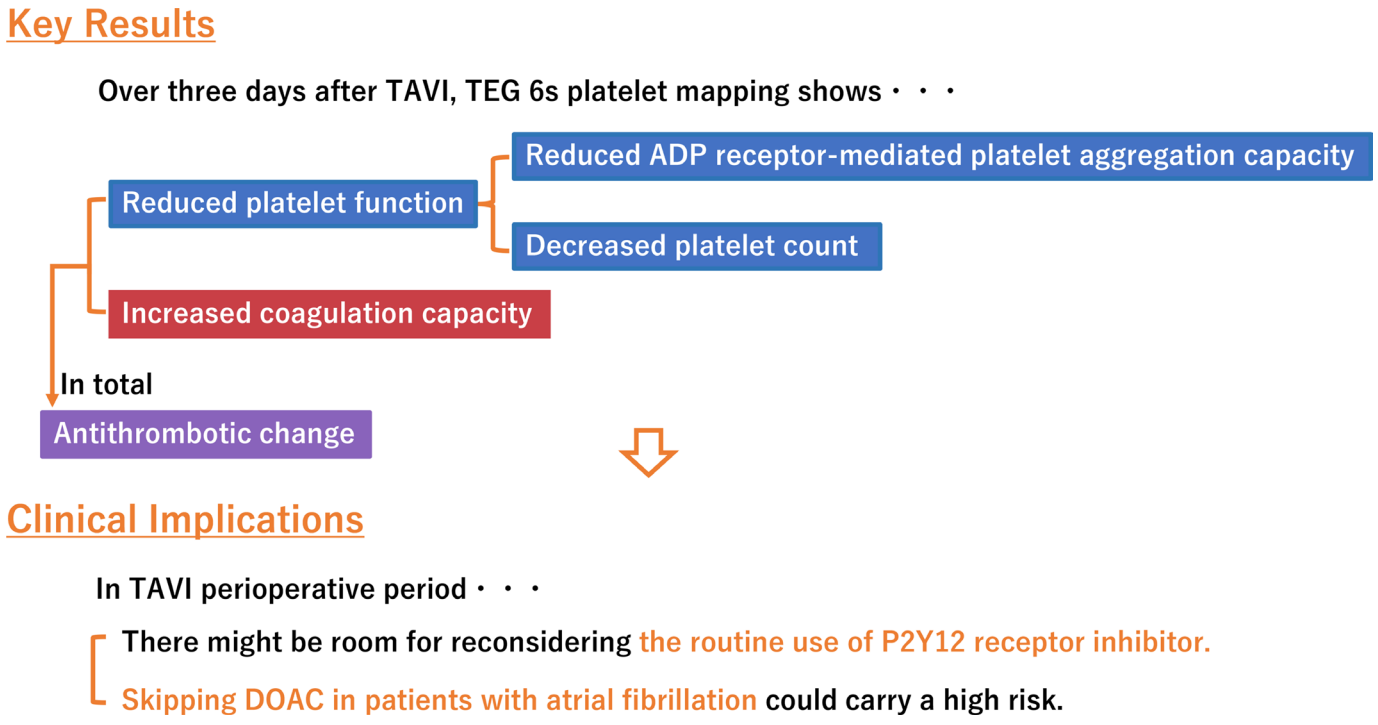

Figure 4 Key results and clinical implications.

cascade, resulting in thrombosis,[20 21] 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.[22 23] Since conventional platelet aggregation tests are expensive, time-consuming, and do not necessarily reflect clots 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 G_p, which represents maximum platelet aggregation capacity, is reportedly unaffected by antiplatelet medication. Moreover, $G_{ADP/AA}$ was mainly studied in patients not using the corresponding antiplatelet agent.

Finally, although the methodology of measuring ADP/TXA_2 receptor-mediated platelet aggregation capacity from $G_{ADP/AA}$ 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.

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