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Dynamics of Thrombogenicity and Platelet Function and Correlation with Bleeding Risk in Patients Undergoing M-TEER Using the PASCAL System

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Abstract

Background Transcatheter mitral valve repair is performed in a patient population at risk for thrombotic and bleeding events. The effects on platelet function and reactivity and their association with bleeding events after mitral transcatheter edge-to-edge therapy (M-TEER) have not been systematically examined.

Objectives We sought to investigate the association of different parameters of platelet function and thrombogenicity with bleeding events post M-TEER.

Methods In this single-center study, 100 consecutive patients with mitral regurgitation receiving TEER were analyzed. Blood was taken directly from the guide-catheter in the left atrium before and after placing the device. Blood samples were analyzed using impedance aggregometry (Multiplate) and TEG6s. The results were compared pre- and postprocedural. The primary outcome was any bleeding complication according to the Bleeding Academic Research Consortium classification within 6 months.

Results A total of 41 patients experienced bleeding events. TEG analysis showed a significant decrease in ADP aggregation and increase in ADP inhibition. In ROC-analysis, TEG ADP aggregation and inhibition and Multiplate ADP aggregation showed moderate predictive values for bleeding events. The delta-ADP-Test (Multiplate) showed the strongest prediction of bleeding (area under the curve: 0.69). Adding platelet function and TEG markers to a model of clinical bleeding risk factors improved the prediction for bleeding events.

Keywords
- mitral regurgitation
- M-TEER
- bleeding
- thromboelastography
- platelet function

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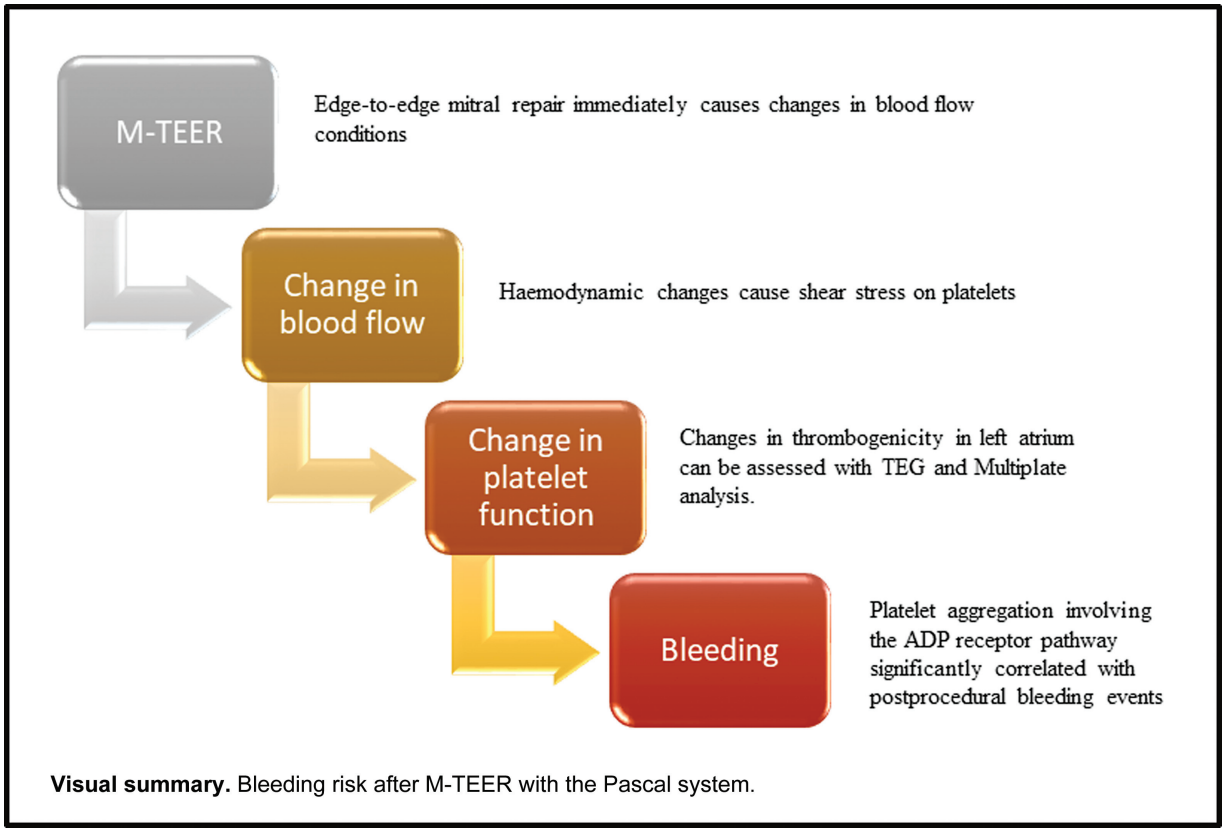

Visual summary. Bleeding risk after M-TEER with the Pascal system.

Conclusion This study indicates that thrombogenicity might be affected immediately after M-TEER probably due to changes in flow conditions. In particular, platelet aggregation involving the ADP receptor pathway significantly correlated with postprocedural bleeding events. Whether these results could guide peri-interventional antithrombotic therapy and improve peri- and postprocedural outcome requires further investigation.

Introduction

Transcatheter mitral valve repair is an established treatment for multimorbid patients suffering from symptomatic severe mitral valve regurgitation who are at high surgical risk. Previous studies have shown the safety and efficacy of this procedure.[1,2] Nevertheless, the transcatheter procedure is also associated with several complications. Bleeding complications are one of the most common adverse events occurring in up to 22% of patients[3,4] and lead to a prolonged hospital stay.[5] Extensive bleeding can also increase mortality.[4] On the other hand, preventing thromboembolic events is also important. Stroke rates after mitral transcatheter edge-to-edge repair (M-TEER) vary from 0.7 to 2.6% within 30 days of the intervention.[6] Up to 80% of patients suffer from atrial fibrillation or flutter (AF) and there is a high AF burden particularly in those patients with functional mitral regurgitation (MR).[7] Yet, there is no well-established standardized anticoagulation regimen for these patients.[8] Premedication with antithrombotic drugs due to other indications (e.g., AF, history of percutaneous coronary intervention [PCI]) is common in this patient cohort. M-TEER might lead to change in flow conditions in the left atrium and shear stress causing enhanced thrombogenicity and platelet activation. For transcatheter aortic valve implantation (TAVI), several studies have demonstrated the effect of this procedure on platelet function and coagulation.[9,10] These studies showed that coagulation capacity increased while platelet function decreased,[9] and that low strength of fibrin clot was associated with life-threatening bleeding complications.[10] The impact on hemostatic parameters after implantation of the PASCAL system has not been examined so far.

The primary objective of this study was to evaluate the occurrence of bleeding complications after 6 months. Six months is the usual time frame for follow-up examinations after M-TEER to evaluate the long-term result with echocardiography. Additionally, we investigated whether any of the TEG or Multiplate parameters could be used as an independent predictor of bleeding complications.

Methods

Study Design and Population

In this single-center study, we analyzed 100 consecutive patients with MR (primary, secondary, and mixed etiology) receiving M-TEER with the PASCAL system after Heart Team decision at the Department of Cardiology of the Medical University Tübingen, Germany between July 2019 and December 2022. According to the instructions for use and our procedural protocol, the guide catheter (GC) was fully aspirated before positioning of the steering catheter in the left atrium and before removal of the GC to avoid air-/thromboembolism. Blood from the left atrium that would otherwise have been discarded was used for the analysis of thrombogenicity. After the implantation of the device, the second blood sample was taken from the left atrium also via aspiration. With these two blood samples, we performed thromboelastography (TEG) analysis and Multiplate impedance aggregometry. Other relevant information such as laboratory parameters (hemoglobin, glomerular filtration rate, etc.), periprocedural anticoagulation treatment, comorbidities, bleeding events, and follow-up examinations was collected in a specifically designed electronic database. The follow-up was set as scheduled hospital visit 6 months after M-TEER with a clinical examination of the patient and a transthoracic echocardiographic examination. We classified bleeding according to the Bleeding Academic Research Consortium (BARC) definition.[11] We categorized patients in two groups considering the outcome: no bleeding, which corresponds to BARC = 0, and bleeding event occurred (BARC $\geq$ 1). To describe the individual bleeding risk of the patient, we used the PRECISE-DAPT score that has been previously developed and validated in patients with coronary artery disease undergoing PCI.[12] This score has not been systemically validated in patients undergoing valvular interventions, but recent studies show an impact on bleeding risk prediction in valvular cohorts.[13] Although risk scores for mortality after M-TEER have been developed and validated,[14] there is currently no dedicated bleeding risk score for this patient cohort.

Ethical approval was already established as part of a biomaterial approval for a national research consortium (DFG, German Research Foundation)—Project number 374031971–TRR 240, 141/2018BO2. Written informed consent was previously obtained from all patients.

Multiplate and Thromboelastography

During the procedure, blood was taken directly from the left atrium before and after placing the device. These blood samples were analyzed using impedance aggregometry (Multiplate) and TEG6s. Both assays, Multiplate and TEG, were performed by a single operator who was trained in these methods and blinded regarding the clinical history and outcome of the patients. The results before and after successful procedure were compared. The results remained blinded to the interventional cardiologist. Quality checks of the Multiplate and TEG Analyzer were performed routinely.

The Multiplate Analyzer is used to determine platelet dysfunction and reactivity as well as the effects of antiplatelet therapy. Aggregation of platelets is measured in the blood by adding hirudin to prevent clotting. Platelet function was investigated after stimulation with adenosine diphosphate (ADP) test, arachidonic acid (ASPI test) or collagen (COL test), thrombin receptor activating peptide (TRAP test), and ristocetin (RISTO-test). The adherence of activated platelets to the surface of the sensor conductor leads to an increase in the electric resistance. The measured impedance correlates with the strength of aggregation. Details of this method and its association with outcome in other patient populations have been described previously.[15]

TEG is a standardized viscoelastic hemostatic assay. It includes measurement of clot formation time, velocity of clot formation, clot firmness, and fibrinolysis. The blood sample is rotated in a cup through 4° 4$\tilde{5}$ six times a minute, imitating venous flow to activate coagulation. Velocity and strength of clot formation are measured by a computer. The result is displayed as a thromboelastogram.[16] We used the standardized TEG6s with Platelet Mapping.

Procedural Technique

The PASCAL system is a CE-marketed device for edge-to-edge treatment of MR. In brief, the device is placed after transseptal puncture over a guide under transesophageal echocardiographic control. In most cases, the procedure was performed under deep sedation. All patients received central venous access for safe administration of drugs. The vascular access site was the right femoral vein, if suitable.

Antithrombotic Regimen

Oral anticoagulation was paused the day before the procedure. Oral antiplatelet drugs were continued throughout the hospitalization. Only two patients had no antithrombotic premedication. Patients on aspirin monotherapy ($n = 11$) were either loaded with clopidogrel after the procedure ($n = 4$) or were administered clopidogrel without loading. During procedure unfractionated heparin (UFH) was administered and coagulation was controlled by frequent measurements of activated clotting time (ACT). To prevent thromboembolic events, the target ACT was $\geq$300 seconds after transseptal puncture. After the procedure, all patients received low-dose heparinization for 8 to 12 hours during femoral compression. Thereafter, the antithrombotic regimen was heterogeneous and individual, dependent on comorbidities such as the need for permanent oral anticoagulation because of AF or the need for dual antiplatelet therapy (DAPT) due to recent PCI.

Statistical Methods

For statistical analysis, we used IBM SPSS Statistics (Version: 28.0.0.0 (190)). Continuous data are presented as mean with standard deviation, dependent on the normality of the distribution, as assessed by visual inspection of the histograms. Categorical variables are presented as counts and proportions. We used *t*-test for differences between the means and Fisher's exact test for differences between proportions. Differences in mean values with a two-tailed test result of $p < 0.05$ were considered statistically significant.

Receiver operating characteristic (ROC) curves were built using predictions from regression analysis and area under the curve (AUC) calculations were performed using the programming language Python (Python Software Foundation). The Youden index was calculated to identify an optimal cut point for the predictor of interest (i.e., delta ADP test). Cox regression and logistic regression analyses were performed using IBM SPSS Statistics.

Results

We included 100 patients in our study, of whom 41 developed bleeding events within 6 months. Baseline characteristics of the patient cohort, stratified according to patients with and without bleeding events, are shown in ►**Table 1**. Major bleeding (BARC ≥ 3) was observed in 14 patients (14%). The most frequent bleeding was bleeding at puncture site ($n = 23$, 56.1%), and only three patients experienced a gastrointestinal bleeding. Preinterventional oral anticoagulation or oral antiplatelet medication showed no differences at baseline between patients with and without bleeding events. Importantly, pre- and periprocedural activated coagulation time (ACT) test showed similar results between those patients who had a bleeding event and those who did not. Patients who developed bleeding had a significantly higher PRECISE-DAPT score and more frequently a history of bleeding than those who did not.

►**Table 2** demonstrates the changes in thrombogenicity before and after placing the device. *p*-Values were calculated with *t*-test for paired samples. ►**Figs. 1** to **3** also illustrate

Table 1 Baseline characteristics

	Total cohort, $n = 100$	No bleeding, $n = 59$	Bleeding, $n = 41$	*p*-Value
Age (y), mean	78.7 ± 7.2	78.6 ± 7.3	78.8 ± 7.1	0.908
Gender (f/m)	45/55	29/30	16/25	0.317
Chronic kidney disease, *n*	44 (44%)	25	19	0.694
Prehistory of bleeding, *n*	12	3	9	0.011
PRECISE-DAPT score, mean	28 ± 13.4	24.8 ± 10.8	32.6 ± 15.4	0.004
Preinterventional echocardiography				
MR severe (≥III°), *n*	70	43	27	0.431
Type MR (primary/secondary/mixed), *n*	66/20/13	35/15/8	31/5/5	0.211
Cardiomyopathy (ischemic/dilated/other), *n*	17/10/12	13/7/7	4/3/5	0.293
EF (%), mean	47.1 ± 13.2	45.1 ± 14.1	50.1 ± 11.2	0.057
PA pressure mean (mmHg)	25.7 ± 9.5	25.9 ± 9.4	25.4 ± 9.7	0.816
Preinterventional antithrombotics				
SAPT	12	9	3	0.230
DAPT	12	7	5	0.960
(N)OAC	51	31	20	0.711
(N)OAC + APT	23	11	12	0.214
Preinterventional laboratory variables				
Hemoglobin (g/dL), mean	12 ± 2	12.2 ± 1.8	11.7 ± 2.2	0.294
WBC	7,455.2 ± 2,182.9	7,611.9 ± 2,411.2	7,229.8 ± 1,809.9	0.368
Platelet count	215.6 ± 73.6	218.8 ± 69.8	211 ± 79.4	0.613
Creatinine (mg/dL), mean	1.4 ± 1	1.3 ± 0.6	1.6 ± 1.4	0.230
GFR	54.2 ± 19.4	55.4 ± 18.4	52.5 ± 21	0.477
INR, mean	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.968
aPTT (s), mean	28.8 ± 11.2	27.4 ± 8.7	30.7 ± 13.8	0.190
Procedural characteristics				
Highest ACT (s), mean	339.3 ± 45	335.9 ± 40.6	344 ± 51	0.452
Number of implanted devices, *n*	1.3 ± 0.6	1.2 ± 0.5	1.4 ± 0.8	0.155
P_{mean} (mmHg), mean	2.9 ± 1.3	2.8 ± 1.5	3 ± 0.9	0.454

Abbreviations: DAPT, dual antiplatelet therapy; EF, ejection fraction; GFR, glomerular filtration rate; MR, mitral regurgitation; (N)OAC, (new) oral anticoagulation; PA, pulmonary artery; PRECISE DAPT, clinical bleeding risk score (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy); SAPT, single antiplatelet therapy; WBC, white blood cells.
Note: *p*-Values were calculated using *t*-test for differences between the means and Fisher's exact test for differences between proportions.

Table 2 Differences pre- and post-TEER in Multiplate and TEG parameters

	Mean value pre-	Mean value post-	Mean value delta	*p*-Value
Multiplate				
ADP test (units)	35.38 ± 20.07	37.59 ± 21.86	2.60 ± 11.48	0.042
ASPI test (units)	39.03 ± 21.12	44.70 ± 28.68	5.29 ± 12.99	<0.001
TRAP test (units)	72.94 ± 27.31	76.18 ± 26.05	3.70 ± 13.77	0.012
COL test (units)	59.12 ± 37.03	65.42 ± 42.98	6.44 ± 26.52	0.023
RISTO test (units)	81.99 ± 48.10	87.17 ± 52.14	5.66 ± 25.98	0.043
TEG				
R (Min.)	7.33 ± 2.06	7.08 ± 1.88	−0.37 ± 1.12	0.002
K (Min.)	1.35 ± 0.40	1.38 ± 0.44	0.02 ± 0.35	0.504
Angle (degree)	72.27 ± 4.05	71.89 ± 4.5	−0.34 ± 3.19	0.310
MA_{HKH} (mm)	67.15 ± 2.99	66.49 ± 3.33	−0.62 ± 1.97	0.004
MA_{ADP} (mm)	59.49 ± 8.83	57.08 ± 10.7	−1.93 ± 3.78	< 0.001
MA_{ActF} (mm)	16.17 ± 7.53	16.21 ± 5.54	−0.08 ± 4.59	0.873
LY30 (%)	0.091 ± 0.71	0.045 ± 0.21	−0.035 ± 0.77	0.672
ADP aggregation (%)	84.53 ± 17.36	81.27 ± 19.7	−2.39 ± 10.75	0.038
ADP inhibition (%)	14.78 ± 15.55	18.73 ± 19.7	3.15 ± 7.15	<0.001

Abbreviations: ADP, adenosine diphosphate; COL, collagen; TEER, transcatheter edge-to-edge repair; TRAP, thrombin receptor activating peptide.
Note: *p*-Values were calculated using *t*-test for differences between the means.

these changes. ►**Fig. 1** shows the differences pre- and post-M-TEER considering all Multiplate parameters. For better illustration, ►**Figs. 2** and **3** only demonstrate statistically significant changes in TEG parameters.

►**Table 3** shows the differences in Multiplate and TEG assays between bleeding and nonbleeding groups. We selected exclusively those parameters for further analyses which showed statistical significance in the *t*-test ($p < 0.05$). In the bleeding cohort, ADP aggregation was reduced before and after the implantation. Furthermore, M-TEER led to a further decrease in ADP-induced platelet activation. This test shows efficacy of ADP-receptor

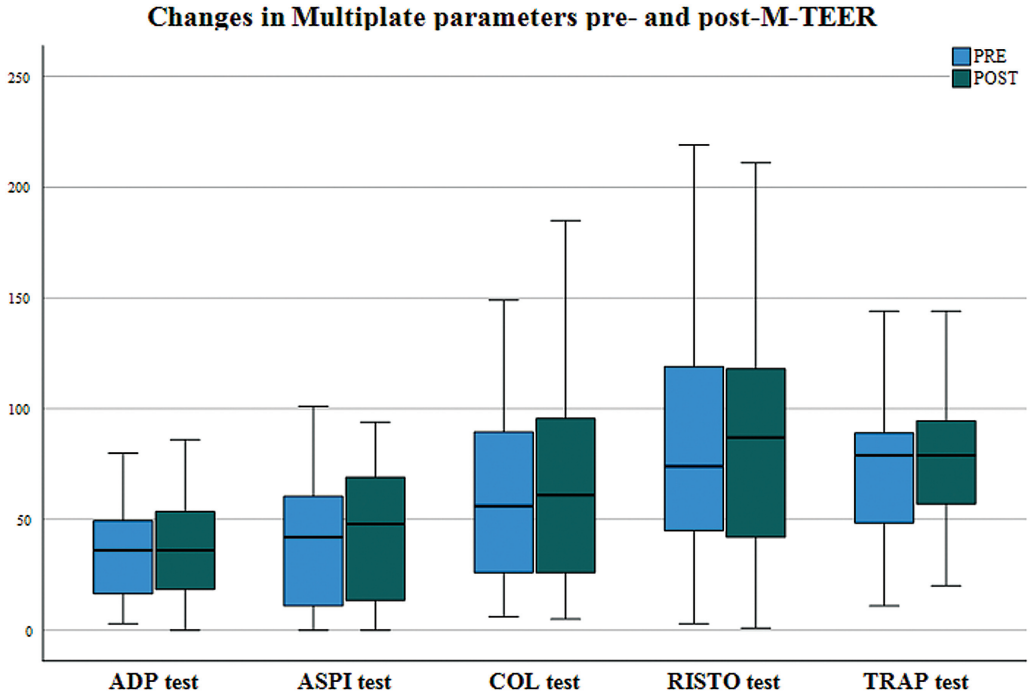

Fig. 1 Changes in Multiplate parameters pre- and post-M-TEER. Boxplots were created using SPSS, showing median, minimum, and maximum.

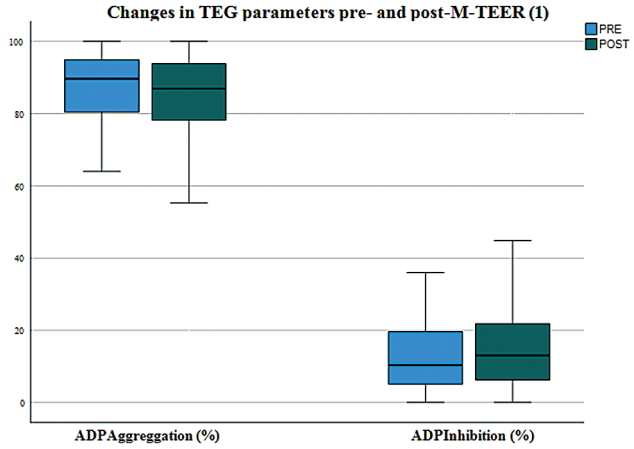

Fig. 2 Changes in TEG parameters pre- and post-M-TEER (1). Boxplots were created using SPSS, showing median, minimum, and maximum. M-TEER, mitral transcatheter edge-to-edge repair; TEG, thromboelastography.

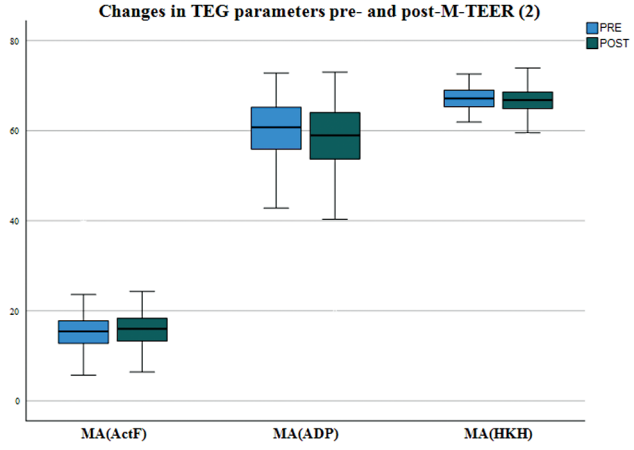

Fig. 3 Changes in TEG parameters pre- and post-M-TEER (2). Boxplots were created using SPSS, showing median, minimum, and maximum. M-TEER, mitral transcatheter edge-to-edge repair; TEG, thromboelastography.

antagonists such as clopidogrel and prasugrel. Consistent with this, TEG analysis demonstrated similar significant decrease in ADP aggregation and increase in ADP inhibition.

We also found a significantly reduced platelet activation by collagen in the bleeding group after M-TEER as shown in ►**Table 3**. In addition, differences in platelet function between pre- and post-PASCAL implantation were observed as shown in ►**Table 3** and COL-dependent platelet aggregation was significantly reduced in the bleeding group.

For further investigation of possible predictors of bleeding, we conducted ROC curve analysis for those values which proved to be statistically significant in the univariate analysis. Results are shown in ►**Figs. 4** to **6**.

For TEG analysis, ADP aggregation and inhibition showed significant differences between the bleeding and no bleeding groups at baseline pre-M-TEER. Nevertheless, with ROC analysis, ADP aggregation and inhibition were not found to be accurate predictors of bleeding, with AUC values between 0.57 and 0.63. Similarly, the COL test was not a useful independent predictor of bleeding (AUC: 0.57–0.60). The best predictor of bleeding was the delta-ADP test (AUC: 0.69).

►**Fig. 6B** shows the prediction of bleeding using the established clinical score, the PRECISE-DAPT score, with an AUC of 0.65, which is inferior to the delta-ADP test. For the delta-ADP test, we performed the Kaplan–Meier analysis for bleeding events during the follow-up of 180 days, using the Youden index of our delta-ADP ROC curve as cut-off, and showed this to be highly significant ($p = 0.004$; ►**Fig. 7**). ►**Fig. 8** shows that a delta-ADP above the Youden index of 2.5 is associated with a reduced rate of bleeding events. ►**Fig. 9** illustrates a classification of bleeding risk according to delta-ADP and PRECISE-DAPT score, showing all patients with bleeding events and the percentage of patients with bleeding in each risk category.

COX regression analysis confirmed the statistically significant influence of delta-ADP ($p = 0.002$) on bleeding events over time, and its ability to predict bleeding compared with the established PRECISE-DAPT score ($p = 0.018$), while gender and age alone were not predictive of bleeding (►**Table 4**). To prove these results, logistic progression analysis was performed (►**Table 5**). A delta-ADP value ≤ 2.5 is correlated with a 4.712 times chance of bleeding event ($p < 0.001$).

Discussion

To the best of our knowledge, this is the first study to assess changes in thrombogenicity in relation to TEER, as detected by TEG and aggregometry. Both assays—Multiplate and TEG6s—are established methods to assess platelet function, efficacy of antithrombotic therapy, and parameters of clot formation. If these parameters are deemed to be predictive for bleeding risk, antithrombotic management could be personalized in a more restrictive anticoagulation or antiplatelet regime in high-risk patients, for example, single antiplatelet therapy instead of DAPT or a single loading dose of clopidogrel instead of continuous dose.

In patients undergoing TAVI, several studies have evaluated the usefulness of TEG to predict major cardiovascular and bleeding events.[9,10,17] One of these, which also used TEG platelet mapping, revealed a decrease in ADP-dependent platelet aggregation and clot strength measured 3 days after TAVI implantation.[9] Another study showed an increase in platelet aggregation measured by Multiplate.[18] This study revealed similar results: an increase in platelet aggregation in Multiplate test, and a decrease in platelet function in TEG analysis. The discrepancies between both tests indicate a complex dysfunction of platelets. One explanation might be that the tests focus on different aspects of platelet function. Multiplate measures the platelet aggregation capacity under the influence of different agonists, while TEG measures the mechanic stability of clot strength and the interactions between platelets, fibrin, and other coagulation factors. Therefore, the discrepancy might indicate that platelets are enhanced in aggregation when stimulated with different agonists but might be impaired in

Table 3 Differences pre- and post-TEER between patients with versus without bleeding events

	No bleeding	Bleeding	*p*-Value
TEG pre-TEER			
R (Min.)	7.1 ± 1.6	7.6 ± 2.6	0.230
K (Min.)	1.3 ± 0.3	1.4 ± 0.5	0.440
Angle (degree)	72.4 ± 3.2	72 ± 5.2	0.311
MA_{HKH} (mm)	67.1 ± 3.3	67.2 ± 2.5	0.882
MA_{ADP} (mm)	60.8 ± 7.1	57.6 ± 10.6	0.053
MA_{ActF} (mm)	15.4 ± 5.4	17.3 ± 9.8	0.213
LY30 (%)	0.1 ± 0.9	0.05 ± 0.2	0.625
ADP aggregation (%)	87.8 ± 11.7	79.8 ± 22.5	0.041
ADP inhibition (%)	12.2 ± 11.7	18.8 ± 19.3	0.066
Multiplate pre-TEER			
ADP	38.4 ± 17.6	31.1 ± 22.7	0.086
ASPI	38.8 ± 26.8	37.9 ± 27.9	0.736
TRAP	76.7 ± 24.2	67.5 ± 30.8	0.115
COL	61.4 ± 35.8	55.9 ± 38.9	0.464
RISTO	86 ± 42.8	76.3 ± 54.9	0.356
TEG post-TEER			
R (Min.)	6.8 ± 1.7	7.4 ± 2.0	0.162
K (Min.)	1.4 ± 0.4	1.4 ± 0.4	0.806
Angle (degree)	72.1 ± 4.3	1.62 ± 4.8	0.633
MA_{HKH} (mm)	66.3 ± 3.8	66.7 ± 2.5	0.579
MA_{ADP} (mm)	59 ± 7.9	54.4 ± 13.4	0.069
MA_{ActF} (mm)	15.5 ± 5.1	17.2 ± 6.1	0.132
LY30 (%)	0.1 ± 0.3	0.01 ± 0.04	0.099
ADP aggregation (%)	85.6 ± 13.1	75 ± 25.4	0.024
ADP inhibition (%)	14.4 ± 13.1	25 ± 25.4	0.024
Multiplate post-TEER			
ADP	43.1 ± 20.1	29.9 ± 22.1	0.004
ASPI	49.3 ± 28.8	38.3 ± 27.6	0.073
TRAP	80.3 ± 23.4	70.4 ± 28.7	0.073
COL	73.3 ± 46.5	54.5 ± 35.3	0.039
RISTO	94.9 ± 53.5	76.3 ± 48.9	0.096
TEG delta			
R (Min.)	−0.4 ± 1	−0.4 ± 1.2	1
K (Min.)	0.05 ± 0.4	−0.01 ± 0.3	0.418
Angle (degree)	−0.4 ± 3.5	−0.3 ± 2.8	0.977
MA_{HKH} (mm)	−0.8 ± 1.9	−0.4 ± 2.1	0.430
MA_{ADP} (mm)	−1.5 ± 3.1	−2.6 ± 4.5	0.164
MA_{ActF} (mm)	0.1 ± 2	−0.3 ± 6.7	0.731
LY30 (%)	−0.1 ± 1	0.01 ± 0.04	0.667
ADP aggregation (%)	−1.6 ± 4.9	−3.5 ± 15.8	0.423
ADP inhibition /%)	1.6 ± 4.9	5.3 ± 9.2	0.014

(*Continued*)

Table 3 (*Continued*)

	No bleeding	Bleeding	*p*-Value
Multiplate delta			
ADP	5.5 ± 11.7	−1.5 ± 11.4	0.006
ASPI	7.9 ± 15.2	1.7 ± 8.1	0.014
TRAP	4.5 ± 14	2.6 ± 13.6	0.522
COL	10.1 ± 27.7	0.1 ± 23.6	0.053
RISTO	7.9 ± 28.1	2.6 ± 22.7	0.350

Abbreviations: ADP, adenosine diphosphate; COL, collagen; TEER, transcatheter edge-to-edge repair; TRAP, thrombin receptor activating peptide.
Note: *p*-Values were calculated using *t*-test for differences between the means and Fisher's exact test for differences between proportions.

their capacity to contribute to mechanical clot strength when interacting with fibrin and other coagulation factors in overall hemostasis. This could be due to qualitative platelet dysfunction, impaired fibrin interaction, or other systemic factors. Nevertheless, clinical implications include potential impact on bleeding risk.

Although M-TEER procedures represent a great advance in the treatment of valvular heart disease,[19] there are no

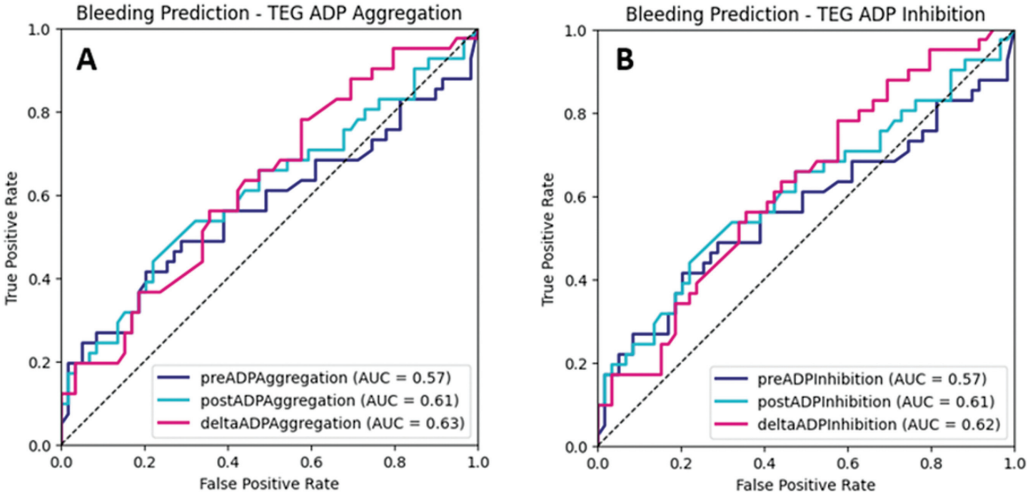

Fig. 4 ROC curve for predicting bleeding with pre- and post-implantation-TEER TEG parameters. (**A**) ROC curve for ADP aggregation and (**B**) ROC curve for ADP Inhibition. ROC curves were generated with Python. ROC, receiver operating characteristic; TEER, transcatheter edge-to-edge repair; TEG, thromboelastography.

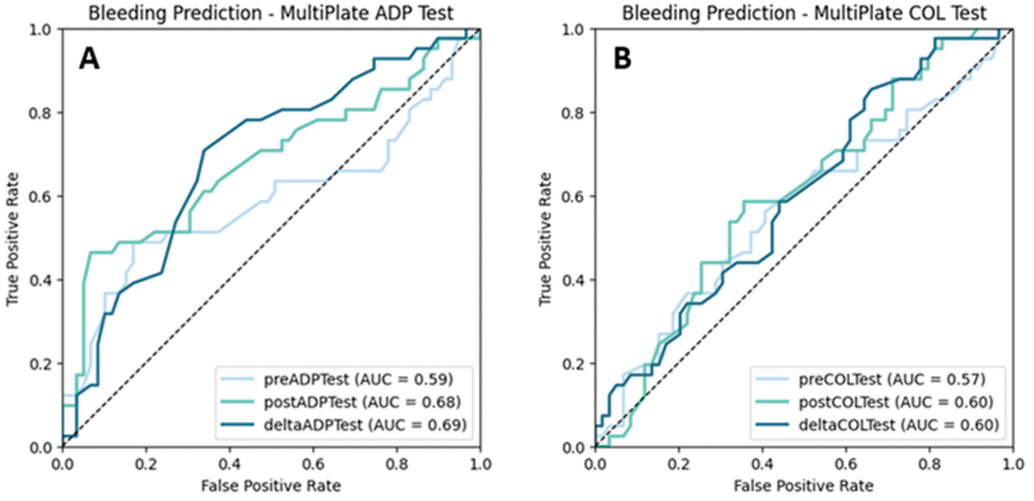

Fig. 5 ROC curve for predicting bleeding with pre- and post-implantation-TEER Multiplate parameters. (**A**) ROC curve for ADP test and (**B**) ROC curve for COL test. ROC curves were generated with Python. ADP, adenosine diphosphate; COL, collagen; ROC, receiver operating characteristic; TEER, transcatheter edge-to-edge repair.

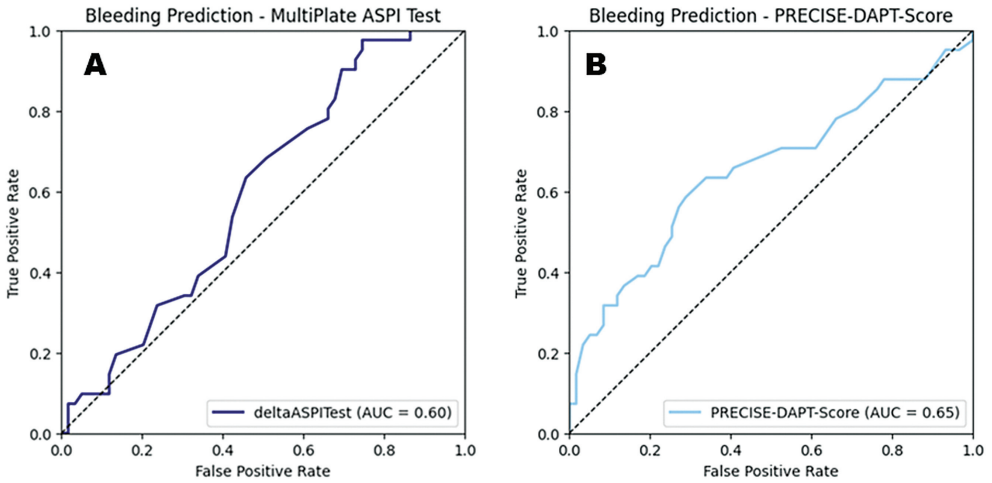

Fig. 6 (A) ROC curve for predicting bleeding with delta ASPI test; (B) ROC curve for predicting bleeding with PRECISE-DAPT score. ROC curves were generated with Python. ROC, receiver operating characteristic.

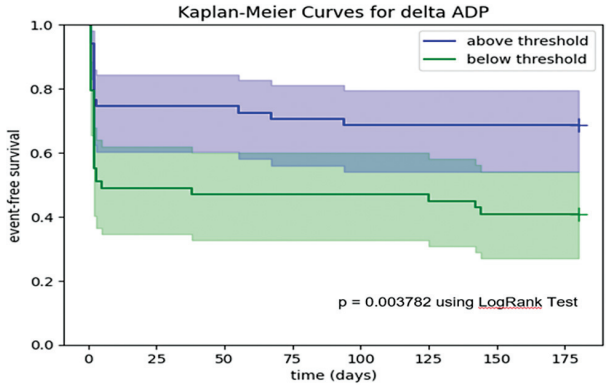

Fig. 7 Kaplan–Meier curve showing bleeding-free time considering Youden index for delta-ADP. Delta ADP, postADP – preADP (Multiplate parameters post- and pre-M-TEER). Kaplan–Meier curve was generated with SPSS. ADP, adenosine diphosphate; M-TEER, mitral transcatheter edge-to-edge repair.

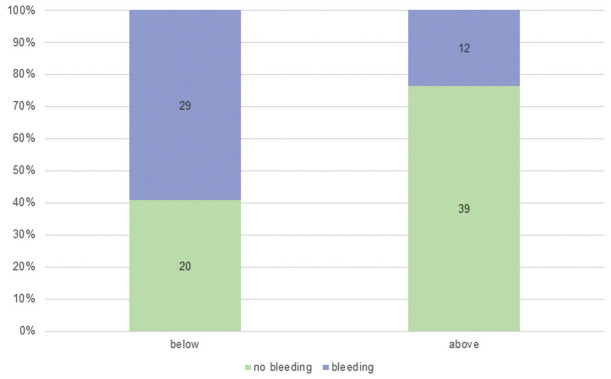

Fig. 8 Bleeding events categorized by delta-ADP values below or above Youden index 2.5. Delta ADP, postADP – preADP (Multiplate parameters post- and pre-M-TEER). ADP, adenosine diphosphate; M-TEER, mitral transcatheter edge-to-edge repair.

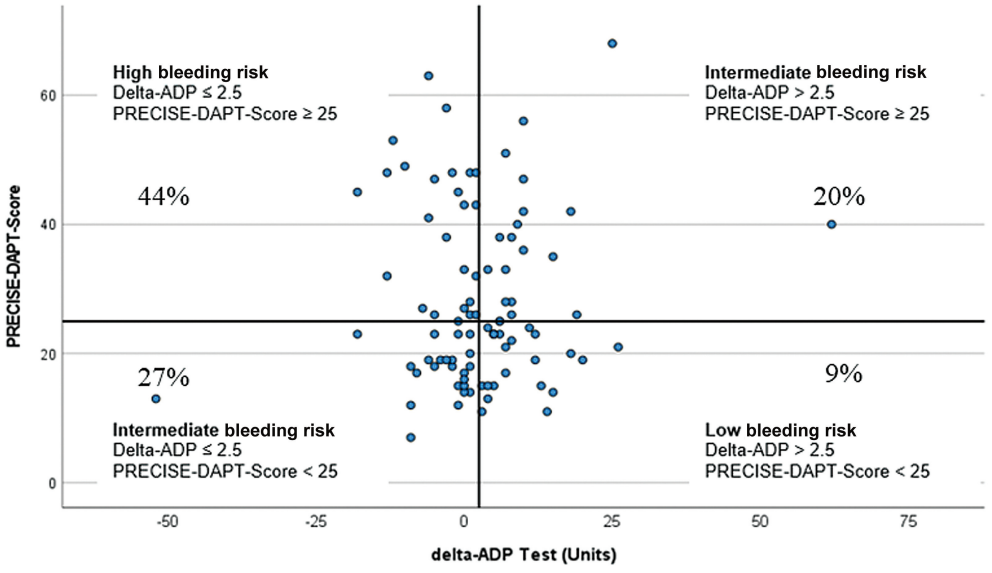

Fig. 9 Classification of bleeding risk by delta-ADP and PRECISE-DAPT score. Delta ADP, postADP – preADP (Multiplate parameters post- and pre-M-TEER); PRECISE DAPT, clinical bleeding risk score (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy). ADP, adenosine diphosphate; M-TEER, mitral transcatheter edge-to-edge repair.

Table 4 COX regression analysis with hazard ratios

	Significance	Hazard ratio	Confidence interval	
Age (per year increase)	0.744	1.008	0.961	1.057
Gender (if female)	0.231	0.678	0.359	1.28
PRECISE DAPT (per unit increase)	0.016	1.025	1.005	1.047
Delta ADP (per unit increase)	0.002	0.955	0.928	0.983

Abbreviations: Delta ADP, postADP – preADP (Multiplate parameters post- and pre-M-TEER); PRECISE DAPT, clinical bleeding risk score (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy).
Note: COX regression analysis was performed using SPSS.

Table 5 Logistic regression analysis with odds ratios

	Significance	Odds ratio	Confidence interval	
Age (per year increase)	0.907	1.003	0.949	1.061
Gender (if female)	0.318	0.662	0.295	1.487
SAPT (if true)	0.239	0.439	0.111	1.731
DAPT (if true)	0.960	1.032	0.303	3.508
NOAK (if true)	0.711	0.860	0.387	1.910
PRECISE DAPT (per unit increase)	0.006	1.047	1.013	1.081
Delta ADP $\leq$ 2.5 (if true)	$<$0.001	4.712	1.990	11.159

Abbreviations: Delta ADP, postADP – preADP (Multiplate parameters post- and pre-M-TEER); PRECISE DAPT, clinical bleeding risk score (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy).
Note: Logistic regression analysis was performed using SPSS.

standardized guidelines for the antithrombotic regimen and the assessment of bleeding risk. There is a great heterogeneity in anticoagulation and antiplatelet therapy pre- and postintervention among patients undergoing TEER, whereas the peri-interventional regimen is usually standardized.[20,21] Stroke and thrombus formation after TEER are known complications which should impact the anticoagulatory regimen.[21–24] A high proportion (80%) of patients undergoing M-TEER have AF due to concomitant atriopathy, and the optimal antithrombotic regimen and risk for thrombotic and bleeding risk after TEER is unknown. To date, there are no standardized recommendations regarding the addition of antiplatelet therapy after TEER in these patients. The risk of bleeding increases with comorbidities such as kidney failure, age, and frailty.[4,25,26] In our cohort of patients, we found that periprocedural testing may provide prognostic value for the prediction of bleeding. The most useful test in our study was the delta-ADP test. Other parameters, which are usually considered to increase bleeding risk, such as chronic kidney disease or diabetes mellitus, were not significantly associated with bleeding events in our cohort. Furthermore, we demonstrate that the PRECISE-DAPT score was less accurate in the prediction of bleeding events than the delta-ADP test as demonstrated in ►**Fig. 5B**. Accordingly, the delta-ADP test might improve bleeding prediction. However, in this study AUC was moderately high, which does not permit for individual prognosis estimation.

This study has a few limitations. We are aware that the present findings are hypothesis-generating and warrant validation in larger cohorts. The sample size is small and there was a relatively low number of major bleeding events, limiting the statistical power of the analysis for more severe bleeding events. However, minor (BARC-2) bleeding events are also clinically relevant, as shown previously in other cardiovascular disease conditions.[5,27,28] Nevertheless, the rate of major bleeding is relatively high in comparison to previous registries investigating bleeding events after M-TEER. A possible explanation is that most of these studies used the Mitral Valve Academic Research Consortium (MVARC) definition, which is more restrictive to the classifications of major bleeding events.[5] Thus, transfusion of $\geq$3 units of whole blood or packed red blood cells qualifies for major bleeding in the MVARC classification, whereas in the BARC classification, any transfusion with overt bleeding is sufficient for major bleeding definition.[11,29] We could not analyze the relationship between the hematological tests and thrombotic events, as these were too few events during follow-up in the present cohort. Thus, we believe that the bleeding risk is potentially more clinically relevant in the early phase (i.e., 6 months) after M-TEER and identification of bleeding risk predictors is more important. Whether the trade-off between bleeding and thrombotic risk changes over time is uncertain. The etiology of MR was heterogenous, representing an all-comer scenario. We did not systematically analyze whether there are differences in the results with regard to the etiology of MR and the stage of heart failure. The results of the tests are prone to processing errors and the individual results have not been reproduced by intra-

individual sequential testing. The timing and sampling of the blood was standardized according to the procedural protocol, minimizing the potential bias of the effect of periprocedural anticoagulation. Nevertheless, the periprocedural use of UFH might suggest dynamic chances in coagulation activity. Thus, the effect of UFH does not explain the differences in thrombogenicity before and after placing the device since ACT measurements were comparable among all patients. Furthermore, we did not observe a significant difference in ACT levels between patients with and without bleeding events. Further studies should test the hypothesis that use of platelet function and TEG markers to guide antithrombotic therapy may modify postprocedural bleeding events in patients undergoing M-TEER. Another limitation are the differences in pre- and post-TEER platelet measurements between the Multiplate and TEG systems as discussed before. Although these differences could be explained, large-scale clinical evidence based on this topic still needs to be updated.

Conclusion

This study using TEG6s platelet mapping and Multiplate showed that thrombogenicity is immediately affected after the PASCAL implantation, possibly caused by shear stress on platelets and altered flow conditions. These effects were significantly correlated with bleeding events. Whether these results could guide periprocedural and long-term antithrombotic therapy, and thus improve clinical outcome, requires further investigation.

What is known about this topic?

- Transcatheter mitral valve repair is an established treatment: previous studies have shown the safety and efficacy of this procedure.
- Bleeding complications are common adverse events: bleeding is associated with prolonged hospital stay and also increased mortality but until now there is no well-established standardized anticoagulation regimen for these patients

What does this paper add?

- Thrombogenicity in left atrium is immediately affected after the PASCAL implantation.
- Intraprocedural assessment of TEG and Multiplate parameters may help to predict bleeding complications and personalize antithrombotic therapy.

Conflict of Interest
D.J.A. reports receiving consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Faraday, Haemonetics, Janssen, Merck, Novartis, Novo Nordisk, PhaseBio, PLx Pharma, Pfizer, Sanofi, and Vectura, outside the submitted work; D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Faraday, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. T.G. reports receiving speaker honoraria/research grants from Astra Zeneca, Bayer, Bristol Myers Squibb/Pfizer, Ferrer/Chiesi, Medtronic, and Edwards Lifesciences. None of them was related to this study.

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References

1 Feldman T, Kar S, Rinaldi M, et al; EVEREST Investigators. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol 2009;54 (08):686–694
2 Feldman T, Foster E, Glower DD, et al; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364(15):1395–1406
3 Schnitzler K, Hell M, Geyer M, Kreidel F, Münzel T, von Bardeleben RS. Complications following MitraClip implantation. Curr Cardiol Rep 2021;23(09):131
4 Körber MI, Silwedel J, Friedrichs K, et al. Bleeding complications after percutaneous mitral valve repair with the MitraClip. Am J Cardiol 2018;121(01):94–99
5 Paukovitsch M, Schepperle N, Pott A, et al. Impact of bleeding complications after transcatheter mitral valve repair. Int J Cardiol Heart Vasc 2021;32:100707
6 Geis N, Raake P, Kiriakou C, et al. Temporary oral anticoagulation after MitraClip - a strategy to lower the incidence of post-procedural stroke? Acta Cardiol 2020;75(01):61–67
7 Doldi P, Stolz L, Orban M, et al. Transcatheter mitral valve repair in patients with atrial functional mitral regurgitation. JACC Cardiovasc Imaging 2022;15(11):1843–1851
8 Calabrò P, Gragnano F, Niccoli G, et al. Antithrombotic therapy in patients undergoing transcatheter interventions for structural heart disease. Circulation 2021;144(16):1323–1343
9 Harada M, Sajima T, Onimaru T, et al. Changes in platelet function and coagulation after transcatheter aortic valve implantation evaluated with thromboelastography. Open Heart 2022;9(02): e002132
10 Rymuza B, Zbroński K, Scisło P, et al. Thromboelastography for predicting bleeding in patients with aortic stenosis treated with transcatheter aortic valve implantation. Kardiol Pol 2018;76(02): 418–425
11 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123(23):2736–2747
12 Costa F, van Klaveren D, James S, et al; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389(10073):1025–1034
13 Seoudy H, Thomann M, Frank J, et al. Procedural outcomes in patients with dual versus single antiplatelet therapy prior to transcatheter aortic valve replacement. Sci Rep 2021;11(01):15415

14 Estévez-Loureiro R, Shah N, Raposeiras-Roubin S, et al. Cross-validation of risk scores for patients undergoing transcatheter edge-to-edge repair for mitral regurgitation. J Soc Cardiovasc Angiogr Interv 2023;3(02):101227

15 Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 2019;12(16):1521–1537

16 Shaydakov ME, Sigmon DF, Blebea J. Thromboelastography. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2024. Accessed March 14, 2024 at: http://www.ncbi.nlm.nih.gov/books/NBK537061/

17 Fanning J, Roberts S, Merza M, et al. Evaluation of latest viscoelastic coagulation assays in the transcatheter aortic valve implantation setting. Open Heart 2021;8(01):e001565

18 Jimenez-Quevedo P, Espejo-Paeres C, Mcinerney A, et al. Impact of platelet reactivity on subclinical valve thrombosis in patients treated with TAVR. Eur Heart J 2023;44(Supplement_2):ehad 655.2242

19 Stone GW, Lindenfeld J, Abraham WT, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379(24):2307–2318

20 Hohmann C, Ludwig M, Walker J, et al. Real-world anticoagulatory treatment after percutaneous mitral valve repair using MitraClip: a retrospective, observational study on 1300 patients. Clin Res Cardiol 2022;111(08):889–899

21 Whitlow PL, Feldman T, Pedersen WR, et al; EVEREST II Investigators. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) high risk study. J Am Coll Cardiol 2012;59(02): 130–139

22 Hamm K, Barth S, Diegeler A, Kerber S. Stroke and thrombus formation appending to the MitraClip: what is the appropriate anticoagulation regimen? J Heart Valve Dis 2013;22(05): 713–715

23 Bekeredjian R, Mereles D, Pleger S, Krumsdorf U, Katus HA, Rottbauer W. Large atrial thrombus formation after MitraClip implantation: is anticoagulation mandatory? J Heart Valve Dis 2011;20(02):146–148

24 Shah MA, Dalak FA, Alsamadi F, Shah SH, Qattea MB. Complications following percutaneous mitral valve edge-to-edge repair using MitraClip. JACC Case Rep 2021;3(03):370–376

25 Ohta M, Hayashi K, Mori Y, et al. Impact of frailty on bleeding events related to anticoagulation therapy in patients with atrial fibrillation. Circ J 2021;85(03):235–242

26 Eggebrecht H, Schelle S, Puls M, et al. Risk and outcomes of complications during and after MitraClip implantation: Experience in 828 patients from the German TRAnscatheter mitral valve interventions (TRAMI) registry. Catheter Cardiovasc Interv 2015; 86(04):728–735

27 Ndrepepa G, Schuster T, Hadamitzky M, et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012;125(11): 1424–1431

28 Yoon YH, Kim YH, Park KM, et al. Impact of in-hospital bleeding on major adverse cardiac events and stroke using Bleeding Academic Research Consortium Classification in patients who undergoing percutaneous coronary intervention. Am J Cardiol 2013;111(07): 91B

29 Stone GW, Adams DH, Abraham WT, et al; Mitral Valve Academic Research Consortium (MVARC) Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the mitral valve Academic Research Consortium. J Am Coll Cardiol 2015;66(03):308–321

