Effect of Transcatheter (via Femoral Artery) Aortic Valve Implantation on the Platelet Count and Its Consequences

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Decrease in blood platelet count has been described after percutaneous coronary intervention and surgical valve replacement, although no study has been performed in the setting of transcatheter aortic valve implantation (TAVI). The aim of this study was to address the incidence, mechanism, and impact of blood platelet count decrease after TAVI. One hundred forty-four consecutive patients (mean age 84 ± 7 years, 64 men) with severe symptomatic aortic stenosis who underwent TAVI from December 2007 to July 2011 were enrolled. Blood platelet count was recorded before and after aortic valve implantation. Decrease in blood platelet count was compared with in-hospital major adverse cardiovascular events (death, stroke, and major or life-threatening bleeding). Blood platelet count decreases occurred in all but 1 patient. The percentage of platelet count decrease averaged 34 ± 15% and was 24% greater than blood protein decrease. Decrease in platelet count was associated with a higher rate of prosthesis migration, longer x-ray and procedural times, and larger contrast amounts (230 ± 128 ml for the third tertile vs 170 ± 77 ml for the second and first tertiles, p = 0.0006), but no association was observed with regard to changes in bilirubin. In-hospital major adverse cardiovascular events (n = 50 [35%]) were observed more frequently in patients with severe platelet count decreases (21% for the first tertile, 35% for the second tertile, and 48% for the third tertile, p = 0.02). Finally, the percentage of blood platelet count decrease was the only predictor of in-hospital major adverse cardiovascular events (odds ratio 1.67, 95% confidence interval 1.05 to 2.67, p = 0.03). In conclusion, a decrease in platelet count is a common phenomenon after TAVI, and its severity is associated with poor outcomes. **(Am J Cardiol 2013;111:1619−1624)**

In recent years, transcatheter aortic valve implantation (TAVI) using stent-based prostheses has become an attractive alternative for high-risk elderly patients with symptomatic aortic stenosis.[1−4] This technique provides short- and long-term clinical and hemodynamic improvements. The most frequent complications associated with TAVI are bleeding and stroke.[5−12] Decreases in platelet counts have been observed after surgical aortic valve replacement[13−15] and also occur after TAVI in clinical practice. However, a decrease in platelet count and its clinical impact on outcome after TAVI have never been studied.

Methods

This study included 144 consecutive patients who underwent TAVI with self-expandable valves using the transfemoral approach from December 2007 to July 2011 at Henri Mondor University Hospital. The definition of severe aortic stenosis was determined by the echocardiographic findings of an aortic valve area <0.8 cm^2 or 0.6 cm^2/m^2, a peak aortic jet velocity >4.0 m/s, or a mean aortic valve gradient >40 mm Hg. All patients were screened before TAVI to determine whether they were considered unsuitable for surgical aortic valve replacement, according to a consensus between cardiac surgeons and cardiologists. Only patients with native aortic stenoses were included in the study. All patients provided written informed consent before enrollment in the registry.

The TAVI procedure was previously reported in detail.[2,16−19] Valve implantation was performed using the retrograde approach. The Medtronic CoreValve (Medtronic, Inc., Minneapolis, Minnesota) was used for all patients. Vascular access and closure were performed by means of a suture device (Prostar XL; Abbott Vascular, Redwood City, California). Dual-antiplatelet treatment with aspirin 75 mg and clopidogrel 75 mg was started the day before the procedure and followed thereafter, except for patients requiring oral anticoagulation by vitamin K antagonist. During the procedure, unfractionated heparin was injected to maintain an activated coagulation time of >250 seconds.

Blood platelet count was measured before valve implantation (baseline) and every day after the procedure until discharge. Blood samples were drawn by venipuncture every morning. Baseline and nadir platelet count after

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See page 1624 for disclosure information.

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Table 1
Baseline patient characteristics (n = 144)

Variable	Value
Age (yrs)	84 ± 7
Men	64 (44%)
European System for Cardiac Operative Risk Evaluation score (%)	24 ± 12
Society of Thoracic Surgeons score (%)	12 ± 8
Aortic maximal velocity (m/s)	4.3 ± 0.8
Aortic valve area (cm^2)	0.7 ± 0.2
Left ventricular ejection fraction (%)	49 ± 14
Diabetes mellitus	35 (24%)
Hypertension*	109 (76%)
Dyslipidemia†	78 (54%)
Previous myocardial infarction	29 (13%)
Previous vascular disease	29 (20%)
Previous cerebrovascular event	17 (12%)
Previous cardiac surgery	20 (14%)
Chronic obstructive pulmonary disease	37 (26%)
New York Heart Association class	2.8 ± 0.6
Creatinine (μmol/L)	111 ± 38
Estimated glomerular filtration rate (ml/min)	55 ± 23
Hemoglobin (g/dl)	11.9 ± 1.7
Platelet count (10^9/L)	216 ± 67

Data are expressed as mean ± SD or as number (percentage).

* Blood pressure >140/90 mm Hg, previous diagnosis of hypertension, or use of antihypertensive medication.

† Low-density lipoprotein >100 mg/dl or use of lipid-lowering medication.

TAVI was used to determine the maximum percentage of platelet count decrease. Blood was collected into ethylenediaminetetraacetic acid Vacuette tube (Greiner Bio-One, Kremsmünster, Austria) and processed for automatic platelet numeration (Beckman Coulter, Brea, California). The normal range of platelet count values for the automatic numeration is 150 × 10^9/L to 500 × 10^9/L, and the coefficient variation is <5%. The nadir of platelet count was defined as the minimum platelet count before any blood transfusion during the hospitalization period.

Clinical follow-up was carried out through clinical visits or phone calls during the hospital stay and after 30 days. Major adverse cardiovascular events (MACEs) were prospectively collected during this period. The primary outcome was in-hospital MACEs, defined as all-cause death, life-threatening and major bleeding, and stroke during the hospitalization period as defined by the Valve Academic Research Consortium classification.[20] Device success and 30-day combined safety data were evaluated according to the Valve Academic Research Consortium criteria. The combined safety end point was defined as follows: all-cause mortality, major stroke, life-threatening bleeding, stage 3 acute kidney injury, periprocedural myocardial infarction, major vascular complications, and a repeat procedure for valve-related dysfunction.

Continuous variables with normal distributions are expressed as mean ± SD and nominal variables as percentages. To compare numerical data between groups, paired and unpaired Student's *t* tests were used as appropriate. Nominal variables were compared using chi-square tests. Kendall's correlation was used for trend testing. Multivariate analyses were performed using linear regression. Survival

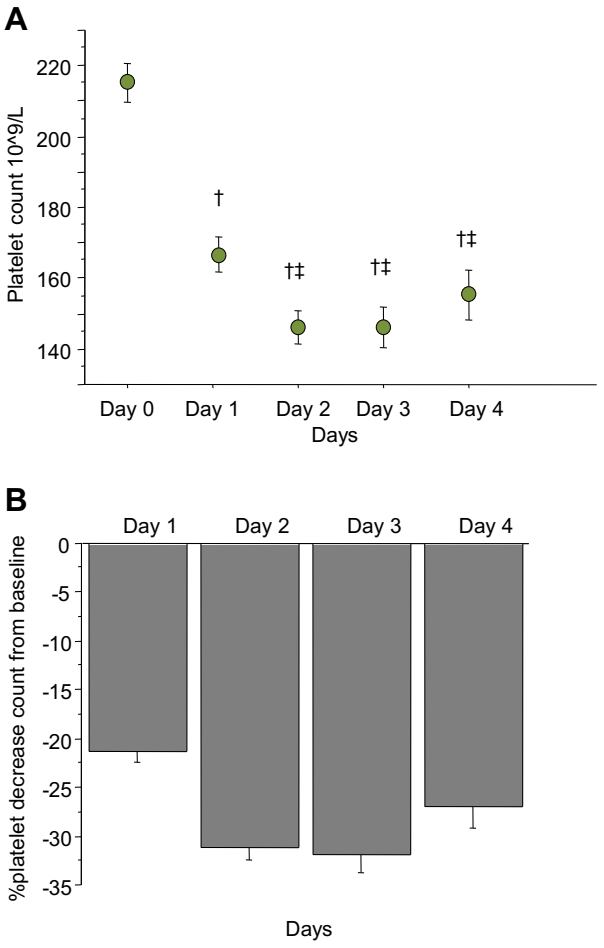

Figure 1. Platelet count course after TAVI *(A)* and percentage decrease from baseline *(B)* (mean ± SE). †p <0.0001 versus day 0; ‡p <0.005 versus day 1.

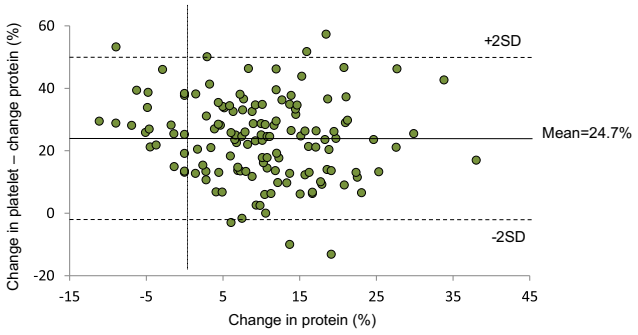

Figure 2. Difference between changes in protein and platelet (y axis) according to changes in protein (x axis).

time-to-event analysis was performed using Kaplan-Meier curves. Two-tailed p values <0.05 were considered as statistically significant.

Results

Patients' baseline characteristics are listed in Table 1. All patients had severe symptomatic aortic stenosis, with a mean peak aortic jet velocity of 4.3 ± 0.8 m/s, a mean aortic

Table 2
Population characteristics and outcomes according to platelet decrease by tertile

Variable	Percentage of Platelet Count Decrease by Tertile			p Value
	First	Second	Third	
Age (yrs)	84 ± 8	85 ± 7	83 ± 8	0.50
Creatinine (μmol/L)	113 ± 44	107 ± 33	112 ± 35	0.70
Hemoglobin (g/L)	11.4 ± 1.5	12.2 ± 1.5	12.1 ± 1.8	0.02
Antithrombotic treatment				
Aspirin	34 (70%)	29 (60%)	26 (54%)	0.20
Clopidogrel	35 (71%)	32 (66%)	29 (60%)	0.60
Vitamin K antagonist	14 (31%)	18 (37%)	10 (21%)	0.20
Procedural characteristics				
Postdilatation	6 (13%)	5 (10%)	6 (13%)	0.80
X-ray time (minutes)	17 ± 7	18 ± 7	24 ± 13	0.002
Procedural time (minutes)	70 ± 20	72 ± 22	92 ± 33	<0.0001
Contrast amount (ml)	172 ± 77	169 ± 77	227 ± 128	0.006
>1 prosthesis	0	0	3	0.04
Prosthesis migration	0	0	5	0.005
Aortic regurgitation ≥2	5 (10%)	10 (21%)	11 (23%)	0.30
Biologic characteristics				
Platelet count at baseline (10^9/L)	209 ± 66	219 ± 63	221 ± 72	0.60
Platelet count nadir (10^9/L)	172 ± 55	146 ± 42	108 ± 38	<0.0001
Platelet count decrease (%)	18 ± 7	33 ± 4	50 ± 10	<0.0001
Protein decrease (%)	7 ± 15	10 ± 8	14 ± 9	0.01
Hematocrit decrease (%)	9 ± 19	17 ± 19	17 ± 10	0.02
Bilirubin increase (%)	21 ± 48	44 ± 75	31 ± 74	0.30
Valve Academic Research Consortium				
Procedural success	48 (100%)	47 (98%)	42 (88%)	0.009
30-day combined safety end point	4 (8%)	4 (8%)	14 (29%)	0.004
Stroke	1 (2%)	4 (8%)	5 (10%)	0.20
Major and life-threatening bleeding	9 (19%)	14 (29%)	19 (40%)	0.08
Major vascular complications	4 (8%)	5 (10%)	10 (21%)	0.20
Myocardial infarction	0 (0%)	2 (4%)	1 (2%)	0.40
Other complications				
In-hospital mortality	1 (2%)	3 (6%)	7 (15%)	0.06
30-day mortality	1 (2%)	4 (8%)	7 (15%)	0.08
MACEs	10 (21%)	17 (35%)	23 (48%)	0.02
Hemoglobin loss (g/dl)	1.6 ± 1.1	1.9 ± 1.2	2.8 ± 1.6	<0.0001
Red blood cell transfusion	5 (10%)	5 (10%)	17 (35%)	0.001

Data are expressed as mean ± SD or as number (percentage).

gradient of 47 ± 17 mm Hg, and a mean aortic valve area of 0.7 ± 0.2 cm^2. After aortic valve implantation, the mean peak aortic jet velocity and mean aortic gradient decreased to 2.3 ± 2.3 and 9 ± 4 mm Hg, respectively, and the mean aortic valve area increased to 2.0 ± 0.4 cm^2. Significant postprocedural aortic regurgitation (mild to severe, grade ≥2/4) was observed in 26 patients (18%).

Blood platelet count at baseline before TAVI averaged 216 × 10^9/L ± 67 × 10^9/L (range 77 × 10^9/L to 441 × 10^9/L). Decrease in platelet count after TAVI occurred in all but 1 patient. The minimum platelet count averaged 170 × 10^9/L ± 54 × 10^9/L (range 41 × 10^9/L to 336 × 10^9/L) and was observed 2.5 ± 1.1 days after TAVI (Figure 1). The decrease in platelet count averaged 34 ± 15% (18 ± 7% for the first tertile, 33 ± 4% for the second tertile, and 55 ± 10% for the third tertile). Overall, 90 patients had moderate thrombopenia (platelet count 50 × 10^9/L to 150 × 10^9/L), and only 3 had severe thrombopenia (platelet count <50 × 10^9/L). No patients received platelet transfusions, and dual-antiplatelet treatment was withdrawn in patients with severe thrombopenia, except for aspirin when recent stent implantation had been performed. Blood protein decrease was poorly correlated with the severity of platelet count decrease (r^2 = 0.039, p = 0.02). In addition, decreases in hematocrit and blood proteins count averaged 11% and 15%, respectively, while the decrease in platelet count was systematically 24% greater than the plasmatic protein decrease (Figure 2). In addition, platelet change failed to correlate with change in hematocrit (r^2 = 0.007, p = 0.30) and bilirubin (r^2 = 0.004, p = 0.40). Patients with the most severe platelet count decreases (third tertile) had more complex procedures: 5 patients in the third tertile compared with none in the second and first tertiles had prosthesis displacement that required new prosthesis valve implantations in 3 patients (p = 0.04), resulting in lower procedural success in the third tertile. Moreover, patients in the third tertile had more prolonged procedural and x-ray times and larger contrast amounts (Table 2). The differences in procedural duration persisted even after excluding patients with prosthesis displacement (23 ± 13 min in the third tertile vs 17 ± 7 min in the second and first tertiles, p = 0.0008, for x-ray time, and 89 ± 32 vs 71 ± 21 min, respectively, p = 0.0001, for procedure time). Multivariate analysis demonstrated that procedural time (β = 0.23, p = 0.02) and prosthesis migration (β = 0.17, p = 0.03) were the 2 independent predictors of platelet count decrease.

Kaplan-Meier curves for survival and MACE-free survival are shown in Figure 3. In-hospital and 30-day mortality were 7% (n = 11) and 8% (n = 12), respectively. Overall, MACEs occurred in 50 patients (35%) during the hospitalization period (11 deaths, 10 strokes and 42 episodes of major bleeding; Table 2, Figure 4). Blood transfusions were delivered in 27 patients, and 8 patients required surgical hemostatic intervention. Bleeding complications, stroke, and in-hospital death were correlated with the severity of platelet count decrease (Figure 4). MACEs were greater in patients with severe platelet count decreases (20% in the first tertile, 38% in the second tertile, and 46% in the third tertile, p = 0.02; Figure 4). MACEs were observed in 0 (0%), 35 (39%), and 14 (27%) patients with severe, moderate, and no thrombopenia, respectively. MACEs remained associated with the importance of platelet count decrease even after the exclusion of patients with procedural failure (p = 0.03; Figure 5). In addition, the relation between platelet count decrease and MACEs was more significant (p = 0.008) after exclusion of the 30 "learning curve" patients (Figure 4). Finally, blood platelet count decrease was the only predictor of in-hospital MACEs (odds ratio 1.67,

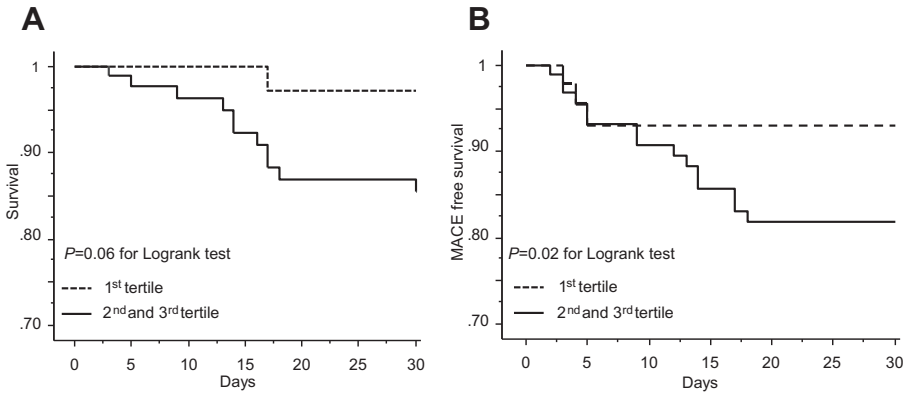

Figure 3. Kaplan-Meier curves for survival and MACE-free survival according to platelet tertiles.

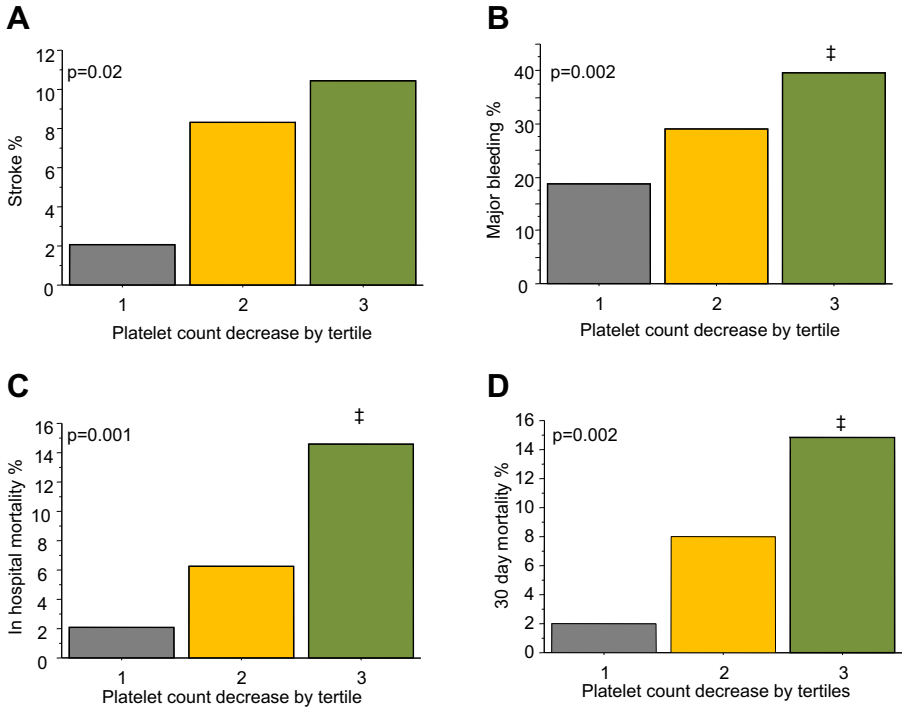

Figure 4. Stroke *(A)*, major bleeding *(B)*, in-hospital mortality *(C)*, and 30-day mortality *(D)* according to the severity of platelet count decrease; p values are indicated for trend test. ‡p <0.05 versus first tertile.

95% confidence interval 1.05 to 2.67, p = 0.03, on multivariate analysis; Table 3).

Discussion

Platelet count decrease has been reported after percutaneous coronary intervention[21] and surgical aortic valve replacement.[13,14] In the setting of TAVI, platelet count decrease was described in a first-in-humans study[22] that enrolled very few patients, and to our knowledge, no other study has focused on platelet count decrease since that initial experience. Our study had 2 important results: (1) platelet count systematically decreased after TAVI, with an average decrease of 34 ± 15%, and (2) a decrease in platelet count strongly influenced patient outcome.

A decrease in platelet count had been previously studied in percutaneous coronary intervention and had been shown to be associated with the use of low-osmolar contrast agents.[21] In agreement with these studies, we also observed that patients with severe platelet count decreases after TAVI received more contrast agent. Hemolysis and hemodilution probably contribute little to platelet count decrease, as a poor correlation was observed between platelet count decrease and protein decrease, and no correlation was found with bilirubin. All patients received unfractionated heparin, so heparin probably does not take part in differences observed in platelet count decreases. Similarly, most patients were receiving antiplatelet treatment, and no association was observed between these treatments and decrease in platelet count.

In percutaneous coronary intervention, no clear mechanism explains the association between low-osmolar contrast agents and the decrease in platelet count except a potential effect on platelet activation.[23] In the setting of TAVI

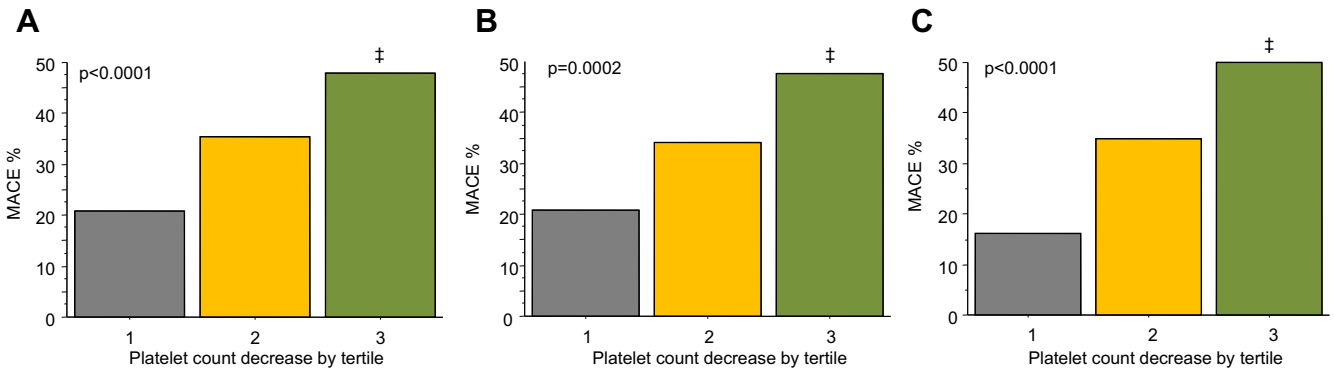

Figure 5. In-hospital MACEs according to platelet tertiles in all patients *(A)*, patients with procedural success only *(B)*, and after exclusion of the 30 "learning curve" patients *(C)*; p values are indicated for trend test. ‡p <0.05 versus first tertile.

Table 3
Variables associated with major adverse cardiovascular events

Variable	All	MACEs		p Value
		Yes (n = 50)	No (n = 94)	
Age (yrs)	84 ± 7	85 ± 6	84 ± 7	0.40
European System for Cardiac Operative Risk Evaluation score (%)	24 ± 12	24 ± 10	24 ± 13	0.90
New York Heart Association class	2.8 ± 0.6	2.8 ± 0.6	2.7 ± 0.7	0.80
Creatinine (μmol/L)	111 ± 38	112 ± 32	111 ± 41	0.80
Hemoglobin (g/dl)	11.9 ± 1.7	12.1 ± 1.7	11.8 ± 1.6	0.40
Left ventricular ejection fraction (%)	49 ± 14	50 ± 14	48 ± 14	0.50
Maximal aortic velocity (m/s)	4.3 ± 0.8	4.3 ± 0.8	4.3 ± 0.8	0.90
Aortic valve area (cm^2)	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.10
Systolic pulmonary pressure (mm Hg)	49 ± 15	46 ± 13	51 ± 16	0.10
X-ray time (minutes)	19 ± 10	19 ± 9	19 ± 10	0.90
Procedural time (minutes)	78 ± 27	84 ± 31	75 ± 24	0.07
Contrast amount (ml)	189 ± 100	197 ± 97	186 ± 101	0.50
Prosthesis migration	5	1	4	0.50
Procedural success	95	92	97	0.20
Aortic regurgitation ≥2	26 (18)	17 (18)	9 (18)	0.90
Platelet count at baseline (10^9/L)	216 ± 67	220 ± 65	214 ± 68	0.60
Platelet count nadir (10^9/L)	140 ± 52	137 ± 55	144 ± 51	0.40
Percentage decrease in platelet count	34 ± 15	38 ± 14	32 ± 16	0.02
Patients in tertile 3	33%	44%	27%	0.03
Patients in tertile 2 or 3	67%	80%	60%	0.01

Data are expressed as mean ± SD or as number (percentage).

procedures, comparison with surgical aortic valve replacement suggests that platelet activation may be involved in the mechanism of platelet count decrease. Indeed, except for extracorporeal circulation, several steps of surgical valve replacement that promote platelet activation[15,24–27] are present in the TAVI procedure: endothelial damage caused by prosthesis implantation, fibrinogen binding on metallic armatures, and shear stress modifications due to prosthesis implantation.[28] As suggested by the correlation between TAVI procedure complications (rate of prosthesis migration, contrast amount, and procedural time) and platelet count decrease, tissue injury during aortic valve implantation may play an important part in platelet activation. Platelet activation after surgical valve replacement has been shown to be predictive of worse outcomes.[15,26] It is tempting to suggest that the association between patient outcomes and the severity of platelet count decreases is caused by severe platelet activation. Indeed, platelet activation may promote thrombosis and take part in the higher rate of stroke observed with higher platelet count decreases. In the first report of platelet count decrease after TAVI, by Grube et al,[22] platelet count decrease was related to platelet activation. However, in that first-in-humans study, extracorporeal circulatory support, which is known to promote platelet activation and destruction, was routinely used.

In our study, TAVI procedural complications were not predictive of outcomes, and platelet count decrease was the only predictor of MACEs. This may be explained by the small sample size of the population, which limits statistical power, or by the fact that platelet count decrease is a more sensitive marker of outcome because of its potential impact on bleeding and thrombotic complications. In addition, it supports the hypothesis that platelet count decrease severity reflects the intensity of platelet activation and inflammatory response induced by tissue injury related to prosthesis valve implantation. The deleterious impact of inflammation after TAVI procedure was recently reported by Sinning et al.[29] In that study, the investigators reported a rate of systemic inflammation response in 40% of patients (61 of 151) after TAVI. They showed that systemic inflammation was associated with the amount of contrast used and postprocedural TAVI complications. However, they did not investigate platelet count in their study. Finally, our results underline the need to carefully monitor platelet count after TAVI, and future prospective studies are needed to better clarify the underlying mechanism and specific treatment to prevent platelet activation.

The study design (retrospective and observational) carries all the limitations inherent to such an investigation, especially the lack of data that formally demonstrate the mechanism of platelet count decrease, as platelet activation parameters were not routinely recorded. Further prospective studies including platelet activity measurement are needed to confirm our hypotheses and to verify whether outcomes are related to platelet activation.

Disclosures

The authors have no conflicts of interest to disclose.

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