Effect on Mortality of Systemic Thromboinflammatory Response After Transcatheter Aortic Valve Implantation

Łukasz Kalińczuk, MD, PhD[a,*], Kamil Zieliński[b], Zbigniew Chmielak, MD, PhD[a], Gary S. Mintz, MD[c], Maciej Dąbrowski, MD[a], Jerzy Pręgowski, MD[a], Michał Proczka[b], Ilona Michałowska, MD, PhD[a], Katarzyna Czerwińska-Jelonkiewicz, MD[d], Hubert Łazarczyk, MCS[a], Marcin Demkow, MD, PhD[a], Tomasz Hryniewiecki, MD, PhD[a], and Adam Witkowski, MD, PhD[a]

After transcatheter aortic valve implantation (TAVI) there is consistently identified decrease in platelets accompanied by a leucocyte (white blood cell, WBC) increase. We aimed to analyze the prognostic value of early platelet and WBC count changes (thromboinflammatory response) after successful TAVI. Among 432 consecutive patients [median 83.0 years of age, 63.4% women], platelets and WBCs were measured before and for 7 days post-TAVI. Follow-up was 36.9 (21.4 to 48.0) months. Platelet decrease (Δ%Platelet-max) and parallel WBC increase (Δ%WBC-max) were seen at days 1 to 3. Both Δ%Platelet-max ≤ -37.6% and Δ%WBC-max > 72.5% predicted mortality (area under the curve = 0.569 and area under the curve = 0.626). The 30-day and 1-year mortality (13.1% and 26.2%) were highest among 28% patients with a greater decrease in platelets and a greater increase in WBCs; intermediate (0.9% and 12.3%) among 52.5% patients with either a greater decrease in platelets or a greater increase in WBCs, but not both; and lowest (0% and 6.6%) among 19.5% patients with a lesser decrease in platelets and a lesser increase in WBCs (p <0.001). Estimated 4-year mortality rates were 53.7% versus 36.2% versus 24.5%, respectively, p <0.001. Bleeding, surgical wounds, acute kidney, and brain injury predicted a more intense thromboinflammatory response, whereas use of the newer generations had the opposite effect. In conclusion, substantial thromboinflammatory response identified after successful TAVI predicts a higher long-term mortality. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:1741−1747)

Self-limited, acquired thrombocytopenia is associated with complications and mortality after surgical and transcatheter aortic valve implantation (TAVI).[1] The highest frequency, magnitude, and prolonged duration of postsurgical thrombocytopenia are reported for stentless or sutureless bioprostheses.[2] This is surprising as they have excellent hemodynamics and implantation is associated with shorter aortic cross-clamp. However, patients treated with them were older; had more cerebrovascular accidents, chronic obstructive pulmonary disease, atrial fibrillation; and higher EuroSCORE.[2] Similarly, increased inflammatory response is associated with worse early and long-term outcomes after TAVI.[3] This includes an increase in white blood cell (WBC) counts, which paralleled the decrease in platelets.[1,4] The present report analyzes the magnitude and clinical correlates of the platelet count decrease or WBC count increase after TAVI, separately and combined (thromboinflammatory response).

Methods

Out of 445 consecutive patients treated from August 2009 and October 2017 within a single-center after excluding patients with failed device implantation (n = 8) or death at day 0 (n = 5), there were 432 patients with device success. All patients were Heart Team qualified for TAVI, the study complied with the Declaration of Helsinki, all patients signed informed consent, and the study was approved by the local ethics committee.

From the hospital database, we retrieved serial measurements of platelets and WBCs before (within 3 days before and as close as possible to the procedure date) and within 7 days postprocedure. Laboratory evaluation was conducted at least once daily during an ICU stay and at the physician's discretion thereafter using autoanalyzer (Sysmex XS-1000i or XT-1800i, Sysmex Corporation, Kobe, Japan). In case of 2 measurements on the same day, the lower platelet and higher WBC count was used. Values were expressed as absolute values and percentages: (1) relative changes in platelets [Δ%platelets = (platelets postprocedure)/(baseline)]; (2) Δ%Platelet-max = (nadir platelets)/(baseline); (3) relative changes in leucocytes [Δ%WBC = (WBCs postprocedure)/(baseline)]; (4) Δ%WBC-max = (peak WBCs postprocedure)/(baseline).

Intense thromboinflammatory response was defined as platelet and WBC count changes both of which exceeded cutoffs predictive of long-term mortality. Also, we

identified patients with post-TAVI nadir platelets 50 to $99 \times 10^9/L$ (moderate thrombocytopenia) or $<50 \times 10^9/L$ (severe), as well as patients with peak WBCs $>12 \times 10^9/L$ or $<4 \times 10^9/L$ [WBC criterion of a systemic inflammatory response syndrome (SIRS)].[1,3] Identified were patients with an early ($\leq$3 days) versus a delayed ($\geq$4 days) platelet nadir counts.[1] Anemia was hemoglobin <13.0 g/dl (men) or <12.0 g/dl (women).

Data regarding baseline clinical characteristics, procedural variables, and in-hospital outcomes were prospectively collected in accordance with VARC-2. Database also included fever ($\geq$38°C) and infection (established diagnosis with antibiotic treatment).

Survival status and date of death were obtained from the National Registry of Population (PESEL database). The primary end points were all-cause 1-year and 4-year mortality. Four-year all-cause mortality was analyzed, including noncardiac deaths unrelated to the TAVI procedure, as manifestations of baseline co-morbidities and frailty.

All patients underwent pre- and postprocedural echocardiography for maximal and mean aortic valve (AV) gradients, AV area, and left ventricle ejection fraction (LVEF). The ECG-gated computed tomography was used for access site selection and valve sizing (SOMATOM, Siemens Healthineers, Erlangen, Germany). All had coronary artery examination.

The procedure was performed by either transfemoral or alternative accesses.[5] An early generation CoreValve (CoreValve ReValving Technology, Medtronic, Inc., Minneapolis, Minnesota); Edwards SAPIEN; SAPIEN XT (Edwards Lifesciences, Irvine, California) or newer generation Evolut-R/-Pro (Medtronic, Inc.); SAPIEN 3 (Edwards Lifesciences); Acurate neo (Boston Scientific Corporation, Maple Grove, Minnesota)]; Engager (Medtronic, Inc.); or Lotus Edge (Boston Scientific Corporation) were implanted.[6]

Categorical data were compared with chi-square or Fisher's exact tests. Normally distributed variables were compared using Student's *t* test and Fisher's analysis of variance. The Mann-Whitney and Kruskal-Wallis analysis of variance were used for comparisons of variables with non-normal distributions; these are presented as the median and interquartile range (interquartile range). Using receiver operating characteristic curve (ROC) analysis, we examined the performance of early changes in platelets and WBCs to predict 4-year mortality; the maximum value of the Youden Index was used as a criterion for cut-off point selection with the highest predictive performance, and respective areas under the ROC curve (AUC) were presented.

Multinomial logistic and linear regressions were used as appropriate to search for independent correlates of (1) greater decrease in platelets, (2) greater increase in WBCs, and (3) combination. Survival rates were assessed using Kaplan-Meier analysis and compared with the Log-rank test with land-mark analysis of patients who survived at 1-year. Long-term all cause-mortality predictors were identified using Cox regression. p <0.05 was considered significant. Statistical analysis was performed using the SPSS 16.0 Statistical (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics are seen in Table 1. VARC-2 safety end point was recognized in 117 (27.1%) patients, with 30-day and 1-year mortality rates of 3.0% (n = 13) and 13.4% (n = 58), respectively. Median follow-up was 36.9 (interquartile range: 21.4 to 48.0) months, with 100% follow-up at 12 months, 92.8% at 24 months, 57.6% at 36 months, and 53.7% at 48 months. Estimated 4-year mortality was 36.3%.

Platelet decrease was seen on day 1 [Δ%Platelets = -27.5% (-35.2% -19.4%)], reaching a nadir on day 2 to 3 [Δ%Platelet-max = -41.4% (-51.6% to -32.3%)]. WBC increase was seen on day 1 [Δ%WBC = 37.7% (14.5% to 68.1%)], with its peak at day 1 to 3 [Δ%WBC-max = 46.9% (21.1% to 76.3%)]. Δ%Platelet-max and Δ%WBC-max correlated weakly (r = -0.206; p <0.001).

The Δ%Platelet-max $\leq-37.6\%$ (74.0% sensitivity and 41.4% specificity; AUC = 0.569; p = 0.023, recognized in

Table 1

Baseline clinical, echocardiographic, and procedural characteristics (n = 432)

Clinical characteristic		Echocardiography	
Age (years)	82 (77.0-85.0)	Mean AVG (mm Hg)	50.2 (41.0-63.0)
Women	284 (63.4%)	AVA (cm^2)	0.70 (0.52-0.80)
Surgical high-risk*	292 (67.6%)	LVEF <50%	98 (22.7%)
Diabetes mellitus	163 (37.0%)	LVEF <35%	32 (7.4%)
Chronic renal disease	175 (39.1%)	*Procedural characteristics*	
Previous stroke/TIA	61 (14.1%)	Transfemoral access	346 (80.1%)
Previous MI	95 (22.0%)	Transapical/aortic access	57 (14.2%)
Atrial fibrillation	124 (28.7%)	Supra-annular valve	223 (51.6%)
Implanted pacemaker	66 (15.3%)	Newer generation valve	170 (39.4%)
Previous PCI	130 (30.1%)	Predilatation	256 (59.3%)
Prior cardiac surgery	85 (19.7%)	Postdilatation	97 (22.5%)
COPD	56 (13.0%)	Maximal AVG post-TAVI (mm Hg)	16.0 (12.0-22.0)
		Moderate PVL	123 (28.5)

AVG = aortic valve gradient; AVA = aortic valve area; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVL = paravalvular leak; TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack.

* Surgical high-risk (logistic EuroSCORE I $\geq$10% or EuroSCORE II $\geq$4%).
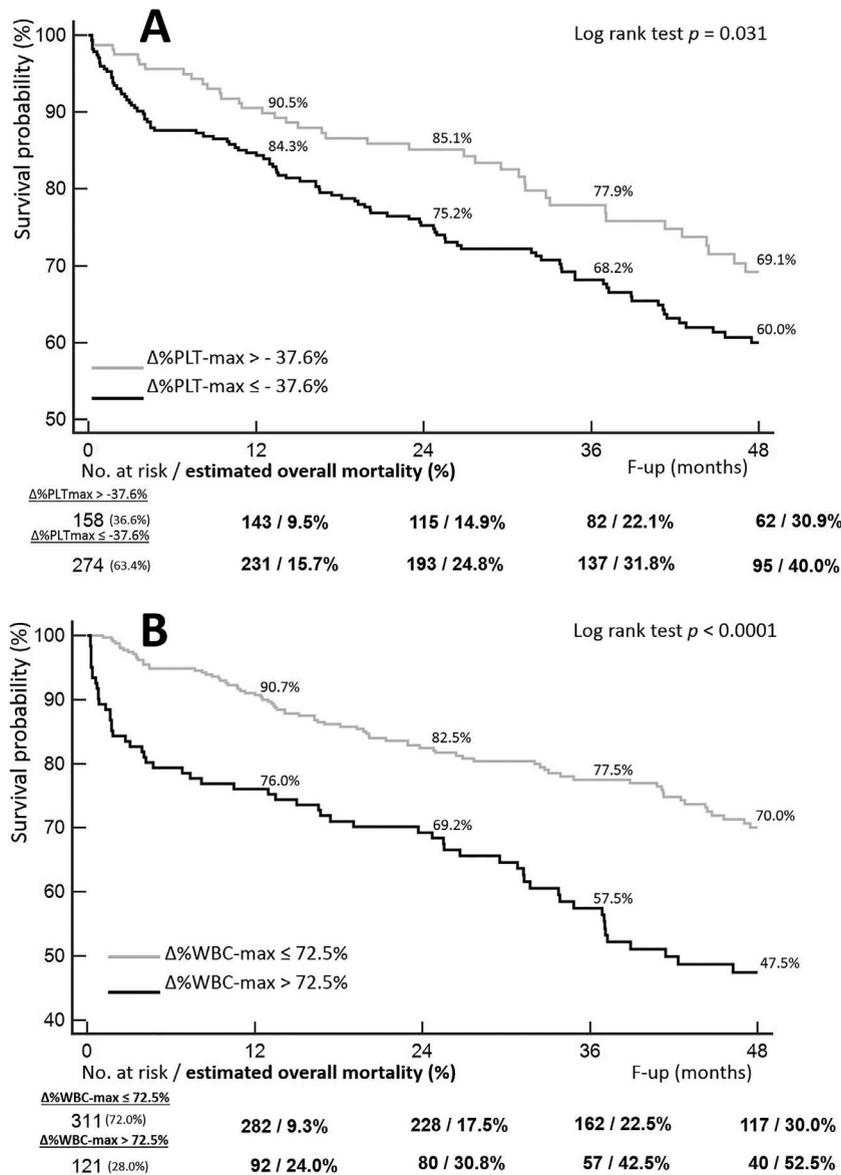
Number (%) or median (IQR).

Figure 1. Long-term all-cause mortality differed significantly according to the magnitude of an early maximal platelet decrease (Δ%Platelet-max, *A*) and early maximum WBCs rise (Δ%WBC-max, *B*).

274 [63.4%] patients) and Δ%WBC-max >72.5% (45.7% sensitivity and 79.9% specificity; AUC = 0.612, p = 0.0003, recognized in 121 [28.0%] patients) were cutoffs predicting subsequent 4-year mortality (Figure 1, respectively).

Patients with delayed time-to-platelet nadir count (9.7%), versus those with its early occurrence (53.7%), had higher rates of 1-year (33.3% vs 12.5%, p = 0.002, respectively) and later mortality, but also significantly larger absolute values of Δ%Platelet-max and median Δ%WBC-max (Supplement).

As per the ROC, there were 121 patients (28.0%) with a lesser decrease in platelets and a lesser increase in WBCs (Group 1); 227 patients (52.5%) with either a greater decrease in platelets or a greater increase in WBCs, but not both (Group 2); and 84 patients (19.4%) with both a greater decrease in platelets and a greater increase in WBCs (Group 3). There was a significant increase in all VARC-2 in-hospital

clinical outcomes across Groups 1 versus 2 versus 3, except for new permanent pacemaker implantation, minor bleeding, and minor vascular complications (Table 2). Indices of 30-day and 1-year mortality were highest in Group 3 (13.1% and 26.2%), intermediate in Group 2 (0.9% and 12.3%), and lowest in Group 1 (0% and 6.6%), both p <0.001. Estimated 4-year mortality rates were highest in Group 3, intermediate in Group 2, and lowest in Group 1 (53.7% vs 36.2% vs 24.5%, p <0.001, AUC = 0.665, Figure 2). Subsequent mortality differed among the studied Groups for the first 12 months and during the following 36 months for patients alive at 1-year (Supplement).

Daily changes in platelet and WBC counts are displayed separately for Groups 1 to 3 (Supplement). Detailed comparisons of clinical, echocardiographic, and procedural parameters among Groups 1 to 3 presented are in Supplement.

Table 2
In-hospital events according to the magnitude of the platelet and WBC response, analyzed among Groups 1, 2, and 3

VARC-2 safety end points	Group 1 (n = 121)	Group 2 (n = 227)	Group 3 (n = 84)	p value
LT/D bleeding	**3 (2.5%)**	**14 (6.2%)**	**14 (16.7%)**	**<0.001**
Major bleeding	**12 (9.9%)**	**41 (18.1%)**	**23 (27.4%)**	**0.005**
Minor bleeding	48 (39.7%)	74 (32.6%)	30 (35.7%)	0.418
Red blood cell transfusion	**27 (22.3%)**	**74 (32.6%)**	**46 (54.8%)**	**<0.001**
Major vascular complications	**12 (9.9%)**	**44 (19.4%)**	**23 (27.4%)**	**0.005**
Minor vascular complications	48 (39.7%)	72 (31.7%)	31 (36.9%)	0.306
Acute kidney injury	**1 (0.8%)**	**7 (3.1%)**	**12 (14.3%)**	**<0.001**
Stroke	1 (0.8%)	3 (1.3%)	4 (4.8)	0.084
New permanent pacemaker	17 (15.0%)	42 (18.3%)	18 (20.0%)	0.629
Fever (≥38˚C)	**7 (5.8%)**	**23 (10.1%)**	**17 (20.2%)**	**0.004**
- day 1 post procedure	5.0 (3.0-7.0)	4.0 (3.0-8.0)	3.0 (2.5-8.5)	0.838
Infection	5 (4.1%)	16 (7.0%)	8 (9.5%)	0.303
- day 1 post procedure	4.0 (0.0-6.0)	4.5 (3.25-7.5)	4.0 (0.5-12.0)	0.547
Composite VARC-2 end point	**16 (13.2%)**	**59 (26.0%)**	**42 (50.0%)**	**<0.001**

Bold values indicate those with corresponding p value of <0.05.

LT/D = life threatening or disabling; VARC = Valve Academic Research Consortium.

Group 1 were patients with a lesser decrease in platelets and a lesser increase in WBCs (Δ%Platelet-max >−37.6% and Δ%WBC-max ≤72.5%).

Group 2 were patients with either a greater decrease in platelets or a greater increase in WBCs, but not both (Δ%Platelet-max ≤−37.6% or Δ%WBC-max >72.5%).

Group 3 were patients with both a greater decrease in platelets and a greater increase in WBCs (Δ%Platelet-max ≤−37.6% and Δ%WBC-max >72.5%).

History of stroke/TIA, atrial fibrillation, and LVEF <50%, were preprocedural predictors of 4-year all-cause mortality (Table 3). Of VARC-2 in-hospital clinical outcomes, life-threatening or disabling bleeding and acute kidney injury were independent correlates of outcome. The risk of 4-year mortality was almost 2 times higher among Group 2 patients and 3 times higher among Group 3 patients (both compared to Group 1, Table 3). The above relations were true in the subgroup of patients treated only via a peripheral vessel and in the subgroup of patients without life-threatening bleeding or major vascular complications (Supplement). The 1-year prognosis among patients with implanted newer generation differed significantly and in the same manner as the entire cohort (Supplement).

Independent correlates of Δ%Platelet-max ≤−37.6%, Δ%WBC-max >72.5%, or the combination (Group 3) are presented in Table 4. Linear regression revealed that only 33% of the variability of the dependent variable (Group 3) was predictable from its independent correlates ($R^2 = 0.329$; p <0.0001).
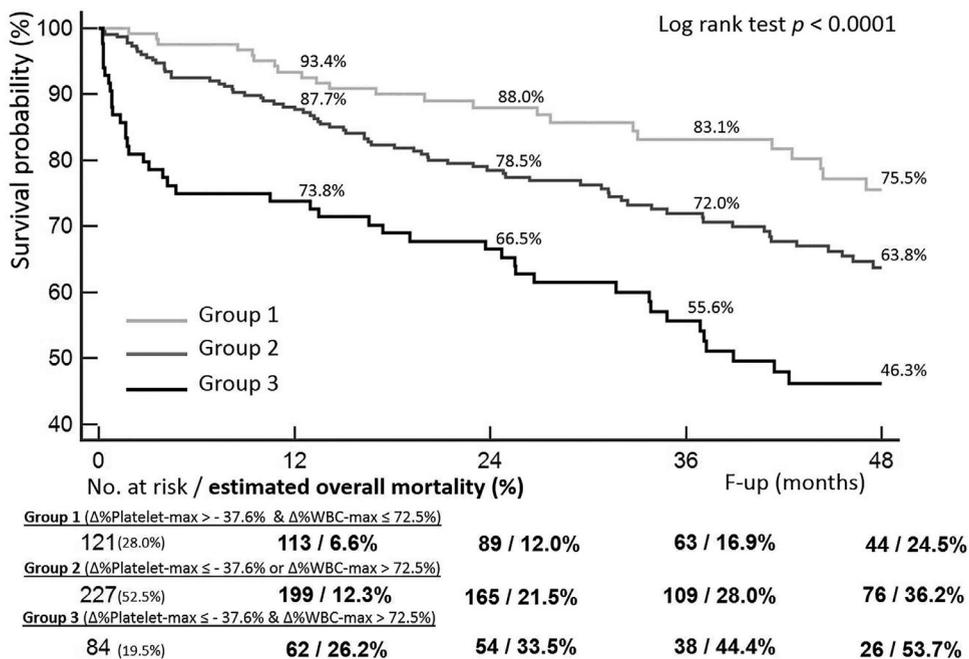

Figure 2. Estimated mortality rates were highest in Group 3 (a greater decrease in platelets and a greater increase in WBCs), intermediate in Group 2 (either a greater decrease in platelets or a greater increase in WBCs, but not both) and lowest in Group 1 (a lesser decrease in platelets and a lesser increase in WBCs).

Table 3
Predictors of all-cause 4-year mortality

| | All-cause 4-year mortality | | | | | |
| | Univariate | | | Multivariable | | |
	Exp(b)	95% CI	p value	Exp(b)	95% CI	p value
Men	**1.615**	**1.131-2.305**	**0.008**	1.389	0.790-2.441	0.246
Chronic renal disease	**1.965**	**1.379-2.801**	**<0.001**	1.459	0.975-2.184	0.066
Stroke/TIA history	**1.626**	**1.033-2.559**	**0.036**	**1.656**	**1.004-2.731**	**0.048**
COPD	**1.606**	**1.035-2.492**	**0.035**	1.511	0.897-2.544	0.121
Atrial fibrillation	**1.605**	**1.112-2.316**	**0.012**	**1.531**	**1.006-2.330**	**0.047**
LVEF <50%	**1.745**	**1.190-2.558**	**0.004**	**1.708**	**1.056-2.762**	**0.029**
Anemia	**1.475**	**1.035-2.101**	**0.031**	1.492	0.955-2.331	0.079
Surgical high-risk*	**1.564**	**1.031-2.371**	**0.035**	1.209	0.721-2.028	0.472
LT/D bleeding	**2.732**	**1.637-4.560**	**<0.001**	**1.905**	**1.026-3.540**	**0.041**
RBC transfusion	**1.604**	**1.124-2.291**	**0.009**	1.131	0.740-1.727	0.569
Acute kidney injury	**5.554**	**3.223-9.572**	**<0.001**	**3.276**	**1.726-6.219**	**<0.001**
SIRS (WBC criteria)	**2.249**	**1.549-3.266**	**<0.001**	1.548	0.948-2.528	0.081
Group 2 vs Group 1	**2.124**	**1.247-3.620**	**0.006**	**1.935**	**1.099-3.408**	**0.022**
Group 3 vs Group 1	**3.903**	**2.213-6.886**	**<0.001**	**3.174**	**1.593-6.325**	**0.001**

Bold values indicate those with corresponding p value of <0.05.

COPD = chronic obstructive pulmonary disease; LT/D = life-threatening/disabling; LVEF = left ventricular ejection fraction; RBC = red blood cell; SIRS = systemic inflammatory response syndrome; TIA = transient ischemic attack; WBC = white blood cell count.

* Surgical high-risk (logistic EuroSCORE I ≥10% or EuroSCORE II ≥4%).

Group 1 were patients with a lesser decrease in platelets and a lesser increase in WBCs (Δ%Platelet-max >−37.6% and Δ%WBC-max ≤72.5%). Group 2 were patients with either a greater decrease in platelets or a greater increase in WBCs, but not both (Δ%Platelet-max ≤−37.6% or Δ%WBC-max >72.5%). Group 3 were patients with both a greater decrease in platelets and a greater increase in WBCs (Δ%Platelet-max ≤−37.6% and Δ%WBC-max >72.5%).

Entry criteria in the multivariable model were p <0.05 in the univariable analysis. Other variables analyzed were age, weight, height, diabetes, previous myocardial infarction, previous percutaneous coronary intervention, pacemaker implanted, previous cardiac surgery, AVA, preprocedural AV maximal gradient, bicuspid AV, LVEF <50%, aspirin or dual antiplatelet preloading, access site, valve type (supra vs intra-annular, self vs balloon deployed, early vs newer valve generations), valve diameter, surgically exposed access site, surgical closure of access site, predilatation, postdilatation, postprocedural AV maximal gradient, moderate paravalvular leak, postprocedural fever or infection, major vascular complications, major bleeding, new permanent pacemaker, baseline platelets and WBC counts, occurrence of post-TAVR moderate or severe thrombocytopenia.

Table 4
Multivariable predictors of the magnitude of thromboinflammatory response

Predictors of greater platelets decrease (Δ%Platelet-max ≤ −37.6%)	Exp(b)	95% CI	p value
Baseline platelets count	1.004	1.000-1.007	0.034
Surgical closure of vascular access	1.801	1.033-3.142	0.038
LT/D bleeding	3.656	1.093-12.226	0.035
Red blood cell transfusion	2.411	1.315-4.421	0.004
Predictors of greater leucocytes increase (Δ%WBC-max >72.5%)			
COPD	2.738	1.349-5.559	0.005
LVEF <35%	2.941	1.128-7.667	0.027
Baseline leucocyte count	0.720	0.616-0.843	<0.001
Transapical or direct aortic access	2.944	1.456-5.950	<0.001
Newer generation valve	0.308	0.168-0.565	<0.001
Acute kidney injury	13.282	3.291-53.609	<0.001
Stroke	12.415	2.176-70.850	0.005
Predictors of greater platelets drop and leucocytes increase (Group 3)			
Transapical or direct aortic access	4.834	1.594-14.658	0.005
Newer generation valve	0.212	0.092-0.487	<0.001
Surgical access closure	3.494	1.512-8.072	0.003
Acute kidney injury	31.285	3.278-298.552	0.003
Red blood cell transfusion	3.243	1.573-6.685	0.001

COPD = chronic obstructive pulmonary disease; LT/D = life-threatening or disabling; LVEF = left ventricular ejection fraction; WBC = white blood cells.

Entry criteria in the multivariable model were p <0.05 in the univariable analysis. Other factors did not affect the magnitude of the thromboinflammatory response including age, sex, weight, height, myocardial infarction history, diabetes mellitus, chronic renal disease, previous cardiac surgery or percutaneous coronary intervention, implanted pacemaker, anemia, surgical high-risk, aspirin or dual antiplatelet preloading, baseline AVA and AV maximal gradient, bicuspid AV, percutaneous coronary intervention pre-TAVR, valve size and type (supra vs intra-annular; self vs balloon deployed), pre- and postdilatation, radiation and fluoroscopy time, postprocedural AV maximal gradient, moderate paravalvular leak, major vascular complication.

Discussion

This is the first study combining early relative changes in platelet and WBC counts post-TAVI into a single prognostic index aimed at predicting long-term outcomes after successful TAVI. Both parameters are routinely evaluated, easy to use and inexpensive.

The main findings of this study are as follows. (1) After TAVI, there is a consistent fall in platelets accompanied by WBCs increase; both are transient and independently predict higher long-term (4-year) mortality. (2) Combined assessment of these markers increases their single predictive performance. (3) Independent predictors of intense thromboinflammatory response post-TAVI were (a) transapical or direct aortic access, (b) early generation bioprosthesis implantation using dedicated delivery systems, (c) vascular access site surgical closure, (d) acute kidney injury, and (e) red blood cell transfusion. (4) Groups with an increased thromboinflammatory response had a significant and stepwise increase in in-hospital safety end points (VARC-2) and subsequent 4-year mortality.

Timing of the postprocedural platelet decrease was uniform across the 3 Groups, with the lowest platelets at the end of the week in Group 3, but values similar to baseline at discharge.[1,7−9] Platelet decrease measured previously in absolute and relative values was associated with in-hospital events and both 30-day and 1-year mortality.[1−11] Patients with delayed post-TAVI thrombocytopenia currently had greater platelet decrease and this may be a more accurate explanation of their worse outcome than its timing.[1]

The timing of the WBC increase in our analysis was also uniform, with its count exceeding $>10 \times 10^9/L$ only in Group 3 and values at the end of the week and at discharge were both similar to the preprocedural.[1,3] An early and evolving inflammatory response post-TAVR was observed in 40% of patients fulfilling ≥ 2 SIRS criteria, and 83.6% of these fulfilling WBC criteria.[3] Corresponding frequency of WBC increase reported after transfemoral was 77% and 92% after transapical TAVI, similar for CoreValve and Edwards SAPIEN XT.[12−14] Frequency of WBC increase and its timing was observed equally among patients fulfilling or not WBC criteria of SIRS. WBC increase was greater with SIRS, with its peak was equal to twice baseline (versus $1.3\times$ in non-SIRS patients), what is similar to the current magnitude of WBC increase in Group 3.[3] Fulfilling WBC criteria alone was an independent predictor of mortality, consistent with the current results.[12] SIRS was associated with higher 1-year mortality also after exclusion of patients suffering from peri-TAVR major complications, alike to our results.[3]

In the current study 63.4% of patients with % platelet decrease $\leq -37.6\%$ had higher 4-year mortality (Figure 1) with 31.6% and 9.9% having moderate or severe thrombocytopenia, respectively. Similarly, 28.0% of patients with a %WBC increase $>72.5\%$ had a higher 4-year mortality with 45.5% fulfilling WBC criteria of SIRS. By applying relative measures of platelet decrease or WBC increase, we were able to uncover subjects who, using absolute measures, were not considered to have thrombocytopenia or an inflammatory response.

Despite the finding that changes in platelets and WBCs were only transient, they were associated with a higher and

increasing mortality along the follow-up period. This pattern was similar to observations in only 1-year follow-up.[1,3,12,14] We speculated that transient changes could be associated with procedural as well as intrinsic patient characteristic (i.e., frailty).

Correlates of an early platelet count decrease suggest that the probable mechanisms are patient or procedure-related—such as consumption attributable to acute blood loss and hemostasis—and not to the prosthesis itself.[10] A nadir platelet count $<100 \times 10^9/L$ occurred in 15% of patients treated with valvuloplasty alone.[8] Peripheral smears pre- versus post-TAVI did not indicate platelet injury. Finally, acquired thrombocytopenia was recognized with similar frequency between patients treated with bivalirudin versus unfractionated heparin.[15]

We found that the use of newer generation valves was associated with a less intense inflammatory response, perhaps due to the smaller size of the delivery systems, triggering less injury. We extended previous observation to the group of self-deployed devices (76% of the currently analyzed newer generation valves) and documented for the first time significantly lower platelets decrease (Supplement).[16] Patients with acute kidney injury have greater atheroma burden in the proximal aorta that could be dislodged during TAVI with embolization to the renal arteries.[17] The current association of an intense thromboinflammatory and acute kidney injury and less intense when using newer valves with less bulky delivery systems suggest that the primary mechanism of these phenomena is acute injury of aortic wall.[18]

WBC increase post-TAVI appeared to be associated with a higher proinflammatory status (chronic obstructive pulmonary disease or lower LVEF) and periprocedural injury (surgical access, acute kidney injury, or acute brain damage). There was only a weak correlation between platelet decrease and WBC increase, and it was predicted in only 33% of Group 3. Therefore, it was likely that the magnitude of the thromboinflammatory responses after TAVI was primarily dependent on intrinsic patient characteristic (i.e., frailty) with frequent, albeit clinically silent injury to the vasculature.[18]

This was a single-center study based on a retrospective analysis of laboratory results obtained on routine clinical basis. We lacked data on other long-term clinical outcomes. Analysis of other markers could have allowed broader insight into the inflammatory response. It is unknown if any patient had suspected heparin-induced thrombocytopenia, but none had established diagnosis.

Our data document a consistent, early, transient fall in platelets accompanied by WBC increase after TAVI. Combined assessment of these markers can be used as a single, simple prognostic index predictive of long-term (4-year) mortality. Described predictors of intense thromboinflammatory response could help to identify patients of worse prognosis early.

Disclosures

Scientific and Edwards Lifesciences. All other authors have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.036.

1. Dvir D, Généreux P, Barbash IM, Kodali S, Ben-Dor I, Williams M, Torguson R, Kirtane AJ, Minha S, Badr S, Pendyala LK, Loh JP, Okubagzi PG, Fields JN, Xu K, Chen F, Hahn RT, Satler LF, Smith C, Pichard AD, Leon MB, Waksman R. Acquired thrombocytopenia after transcatheter aortic valve replacement: clinical correlates and association with outcomes. *Eur Heart J* 2014;35:2663–2671.
2. Shrestha M, Folliguet T, Meuris B, Dibie A, Bara C, Herregods MC, Khaladj N, Hagl C, Flameng W, Laborde F, Haverich A. Sutureless Perceval S aortic valve replacement: a multicenter, prospective pilot trial. *J Heart Valve Dis* 2009;18:698–702.
3. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Müller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. *Eur Heart J* 2012;33:1459–1468.
4. Sexton TR, Wallace EL, Chen A, Charnigo RJ, Reda HK, Ziada KM, Gurley JC, Smyth SS. Thromboinflammatory response and predictors of outcomes in patients undergoing transcatheter aortic valve replacement. *J Thromb Thrombolysis* 2016;41:384–393.
5. Chmielak Z, Witkowski A, Dąbrowski M, Demkow M, Kuśmierski K, Sitkowska E, Jastrzębski J, Szymański P, Hryniewiecki T, Czerwińska K, Stępińska J. Comparison of mid-term results of transcatheter aortic valve implantation in high-risk patients with logistic EuroSCORE ≥ 20% or < 20. *Kardiol Pol* 2016;74:224–230.
6. Pilgrim T, Lee JKT, O'Sullivan CJ, Stortecky S, Ariotti S, Franzone A, Lanz J, Heg D, Asami M, Praz F, Siontis GCM, Vollenbroich R, Räber L, Valgimigli M, Roost E, Windecker S. Early versus newer generation devices for transcatheter aortic valve implantation in routine clinical practice: a propensity score matched analysis. *Open Heart* 2018;5:e000695.
7. Grube E, Laborde JC, Gerckens U, Felderhoff T, Sauren B, Buellesfeld L, Mueller R, Menichelli M, Schmidt T, Zickmann B, Iversen S, Stone GW. Percutaneous implantation of the corevalve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. *Circulation* 2006;114:1616–1624.
8. McCabe JM, Huang PH, Riedl LA, Devireddy SR, Grondell J, Connors AC, Davidson MJ, Eisenhauer AC, Welt FG. Incidence and implications of idiopathic thrombocytopenia following transcatheter aortic valve replacement with the Edwards Sapien(©) valves: a single center experience. *Catheter Cardiovasc Interv* 2014;83:633–641.
9. Gallet R, Seemann A, Yamamoto M, Hayat D, Mouillet G, Monin JL, Gueret P, Couetil JP, Dubois-Randé JL, Teiger E, Lim P. Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences. *Am J Cardiol* 2013;111:1619–1624.
10. Jilaihawi H, Doctor N, Chakravarty T, Kashif M, Mirocha J, Cheng W, Lill M, Nakamura M, Gheorghiu M, Makkar RR. Major thrombocytopenia after balloon-expandable transcatheter aortic valve replacement: prognostic implications and comparison to surgical aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:130–137.
11. Sedaghat A, Falkenberg N, Sinning JM, Kulka H, Hammerstingl C, Nickenig G, Oldenburg J, Pötzsch B, Werner N. TAVI induces an elevation of hemostasis-related biomarkers, which is not causative for post-TAVI thrombocytopenia. *Int J Cardiol* 2016;221:719–725.
12. Lindman BR, Goldstein JS, Nassif ME, Zajarias A, Novak E, Tibrewala A, Vatterott AM, Lawler C, Damiano RJ, Moon MR, Lawton JS, Lasala JM, Maniar HS. Systemic inflammatory response syndrome after transcatheter or surgical aortic valve replacement. *Heart* 2015;101:537–545.
13. Rettig TC, Rigter S, Nijenhuis VJ, van Kuijk JP, ten Berg JM, Heijmen RH, van de Garde EM, Noordzij PG. The systemic inflammatory response syndrome predicts short-term outcome after transapical transcatheter aortic valve implantation. *J Cardiothorac Vasc Anesth* 2015;29:283–287.
14. Schwietz T, Behjati S, Gafoor S, Seeger F, Doss M, Sievert H, Zeiher AM, Fichtlscherer S, Lehmann R. Occurrence and prognostic impact of systemic inflammatory response syndrome in transfemoral and transapical aortic valve implantation with balloon- and self-expandable valves. *EuroIntervention* 2015;10:1468–1473.
15. Dangas GD, Lefèvre T, Kupatt C, Tchetche D, Schäfer U, Dumonteil N, Webb JG, Colombo A, Windecker S, JM0 Ten Berg, Hildick-Smith D, Mehran R, Boekstegers P, Linke A, Tron C, Van Belle E, Asgar AW, Fach A, Jeger R, G0 Sardella, Hink HU, Husser O, Grube E, Deliargyris EN, Lechthaler I, Bernstein D, Wijngaard P, Anthopoulos P, Hengstenberg C, BRAVO- Investigators. Bivalirudin versus heparin anticoagulation in transcatheter aortic valve replacement: the randomized BRAVO-3 trial. *J Am Coll Cardiol* 2015;66:2860–2868.
16. Sexton T, Alkhasova M, de Beer M, Lynch D, Smyth S. Changes in thromboinflammatory profiles across the generations of transcatheter aortic heart valves. *J Thromb Thrombolysis* 2019;47:174–178.
17. Shishikura D, Kataoka Y, Pisaniello AD, Delacroix S, Montarello JK, Nicholls SJ, Worthley SG. The extent of aortic atherosclerosis predicts the occurrence, severity, and recovery of acute kidney injury after transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2018;11:e006367.
18. Kakefuda Y, Hayashida K, Yamada Y, Yashima F, Inohara T, Yanagisawa R, Tanaka M, Arai T, Kawakami T, Maekawa Y, Tsuruta H, Itabashi Y, Murata M, Sano M, Okamoto K, Yoshitake A, Shimizu H, Jinzaki M, Fukuda K. Impact of subclinical vascular complications detected by systematic postprocedural multidetector computed tomography after transcatheter aortic valve implantation using balloon-expandable Edwards SAPIEN XT heart valve. *Am J Cardiol* 2017;119:1100–1105.