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Perioperative thrombocytopenia predicts poor outcome in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Purpose: To determine the time point at which thrombocytopenia after TAVI procedure is an indicator of the worst prognosis, with special consideration of perioperative platelet and coagulation activation as its potential causes.

Methods: Thirty two patients (mean age 78.5 ± 7.9 years, 62% females) qualified for TAVI procedure were prospectively evaluated. Platelet counts were assessed at baseline and for the next three postoperative (POD) days. Platelet activation was evaluated by P-selectin (PS, serum, ELISA) and platelet factor 4 (PF-4, CTAD plasma), and blood coagulation activation by prothrombin fragments 1 + 2 (F1 + 2, plasma, ELISA). Composite end point (CEP) including death and the need of cardiovascular rehospitalization was assessed after a mean of 14.1 ± 6.7 months.

Results: During the follow up period half of the patients reached CEP. Thrombocytopenia was more profound and frequent in patients with CEP as compared to those without ($p < 0.05$). No differences regarding either the biomarkers of platelet (PS, PF-4) or coagulation (F1 + F2) activation between the groups with and without CEP were found. Patients with moderate-to-severe thrombocytopenia at baseline had worse prognosis (log-rank test, $p = 0.0003$). Based on the receiver operating characteristic curve analysis, the differences between platelet count on each postoperative day and the baseline count did not have any predictive value in CEP occurrence.

Conclusions: Patients with thrombocytopenia following TAVI procedure have poor prognosis, however, the changes on the particular days are not more important than initial platelet count. Further studies are needed to evaluate platelet and blood coagulation activation as potential causes of thrombocytopenia and impaired prognosis related to it.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is an alternative procedure for patients with severe symptomatic aortic valve stenosis who are not qualified for open heart surgery [1]. It has been proved that TAVI improves quality of life and reduces symptoms [2]. However, patients undergoing this intervention might develop several periprocedural complications, such as bleeding, vascular complications, acute kidney injury, extended hospitalization, or low platelet blood count [3,4,5]. Platelet loss and thrombocytopenia have been described in both surgical as well as transcatheter aortic valve replacement, however the exact etiology of TAVI-related thrombocytopenia has remained unknown [5,6]. A decrease in platelet count can result from heamodilution, the use of contrast agent or an imbalance between enhanced platelet consumption and reduced platelet production. This might be related to the increase in platelet and coagulation activity [7].

Platelet loss following TAVI procedures impairs future prognosis. This risk, however, is closely related to the degree of

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thrombocytopenia [5,8]. The most common is mild thrombocytopenia (platelet count $\geq 100 \times 10^3/\mu L$), which occurs in about 35% of patients after TAVI procedure, and is usually benign and transient [9]. Moderate-to-severe thrombocytopenia (platelet count $< 100 \times 10^3/\mu L$) is observed in a similar percent of patients, however, it is related to the impaired outcome [9].

In our study, we sought to evaluate the exact prognostic time point of thrombocytopenia following TAVI procedure in the special aspect of enhanced perioperative platelet and coagulation activation as its potential causes.

2. Material and methods

Thirty two patients (mean age 78.5 ± 7.9 years, 62% females) with severe symptomatic aortic valve stenosis qualified for TAVI procedure (Edwards Sapien XT) and operated between March 2013 and April 2015 were prospectively analyzed. The detailed patients' characteristics has already been published elsewhere [10].

Patients who needed dual antiplatelet therapy were excluded. All patients after the procedure received aspirin. Low molecular weight heparin was given according to the clinical indications (mean dose 45.0 ± 16.8 mg, median therapy duration 3.5 [3–5.5.] days). The choice of operational access (transapical vs. transfemoral) as well as perioperative management have been described elsewhere [10].

Platelet counts were assessed at baseline (B−baseline), and for the next three postoperative (POD) days. According to the latest data, platelet count $< 100 \times 10^3/\mu L$ has been considered as moderate-to-severe thrombocytopenia [9]. Platelet activation was assessed by P-selectin (PS, sP-Selectin/CD62P, ELISA Kit 96, Catalog Number BBE6, R&D) and platelet factor 4 (PF-4, Asserochrom PF-4, 00951, plasma sample collected on CTAD anticoagulant, Diagnostica Stago, S.A.S.) and blood coagulation activation was evaluated by prothrombin fragments 1 + 2 (F1 + 2, plasma, Homo sapiens, SEA710Hu 96 Test, USCN) before the procedure, on POD-1 and POD-3 (ELISA). Composite end point (CEP) including death and the need of cardiovascular rehospitalization was assessed after a mean of 14.1 ± 6.7 months.

The study design was compliant with the Helsinki Declaration of 1975 as revised in 1996 and it was approved by the local institutional committee on human research (Institutional Review Board − Local Bioethics Committee of Bialystok Medical University). Informed consent from all participants studied for the report was obtained.

2.1. Statistical analysis

The distribution of all variables was verified with Kolmogorov-Smirnov test. Data are expressed as mean ± standard deviation (SD) or median [interquartile range], depending on distribution. Statistical analysis was performed using t-student test or Mann-Whitney test for continuous data and χ^2 test for categorical variables. Pearson's correlation coefficient was used to examine the relationship between 2 continuous variables. Receiver operator characteristic curves (ROC) were plotted to determine the prognostic value of platelet count changes. $P < 0.05$ was deemed statistically significant. A statistical software package Statistica 10 (USA) was used for the analysis.

3. Results

The detailed baseline patients' clinical, echocardiographic and perioperative characteristics has already been published [10]. During the follow up period sixteen patients (50%) had combined clinical endpoint (12 patients died during the follow up period, 4 patients were rehospitalized due to cardiovascular causes). The comparison of the assessed variables in the group of patients with and without CEP is shown in Table 1. Baseline platelet count in patients with CEP was $152.24 \pm 48.22 \times 10^3/\mu L$, while in patients without CEP was $191.65 \pm 51.59 \times 10^3/\mu L$, respectively, $p < 0.02$, Table 1, Fig. 1. In patients with CEP significantly lower platelet counts (compared to the patients without CEP) until POD-3 were found ($p < 0.05$, Table 1, Fig. 1). During the postoperative period the most prominent platelet count drop was on POD-0 in both groups, however, patients with CEP had significantly greater platelet count drop (difference between POD-0−after the procedure and baseline values) as compared to patients without CEP ($64.5 \pm 48.5 \times 10^3/\mu L$ *vs.* $40.1 \pm 28.3 \times 10^3/\mu L$, $p = 0.04$). In patients with CEP higher baseline aortic valve peak and mean gradients were found ($p < 0.05$), Table 1. Patients who had CEP needed more packed red blood cells (PRBCs) transfusion ($p < 0.05$), but no platelet concentrate transfusion (p = ns) during the index of hospitalization was needed. No statistically significant differences regarding either the biomarkers of platelet (PS, PF-4) or coagulation (F1 + F2) activation between the group with and without CEP were found (p = ns), Table 1.

Moderate-to-severe thrombocytopenia was significantly more frequent at baseline and on all three postoperative days in the group of patients with CEP as compared to the patients without CEP, Fig. 2. Furthermore, survival analysis revealed that patients with moderate-to-severe thrombocytopenia at baseline statistically significantly more often had CEP as compared to the patients without baseline moderate-to-severe thrombocytopenia (log-rank test, $p = 0.0003$, Kaplan-Meier curves, Fig. 3).

Table 1
The differences between analyzed variables in patients with and without composite clinical end point.

	CEP (+)	CEP (−)	p
Number of patients, % (n)	50 (16)	50 (16)	
RBC (B), $\times 10^6/\mu L$	3.92 ± 0.11	4.53 ± 0.22	0.02
Hb (B), g/dL	11.5 ± 0.30	13.2 ± 0.41	0.002
Fibrinogen, mg/dL	401.23 ± 121.34	440.89 ± 56.23	0.01
PLT (B), $\times 10^3/\mu L$	152.24 ± 48.22	191.65 ± 51.59	0.02
PLT (POD-0), $\times 10^3/\mu L$	112.67 ± 36.72	157.82 ± 61.94	0.02
PLT (POD-1), $\times 10^3/\mu L$	101.23 ± 33.92	134.30 ± 40.12	0.02
PLT (POD-2), $\times 10^3/\mu L$	72.54 ± 33.37	105.92 ± 24.84	0.004
PLT (POD-3), $\times 10^3/\mu L$	91.54 ± 63.52	106.91 ± 30.76	0.04
MPV (B), fL	12.56 ± 1.26	10.27 ± 1.22	0.37
MPV (POD-0), fL	9.67 ± 1.88	9.14 ± 1.45	0.47
MPV (POD-1), fL	11.06 ± 1.02	10.67 ± 0.58	0.20
Radiation time, min.	14 [13–19]	16 [14–23]	0.31
Radiation dose, mGy	382 [225–889]	638 [428–1146]	0.15
Contrast, mL	227.64 ± 87.41	230.53 ± 58.98	0.79
Creatinine, mg/mL	1.15 ± 0.33	0.99 ± 0.29	0.05
Euroscore II, points	4.8 [3.6–5.6]	6 [3.6–7.9]	0.5
Aortic peak gradient, mmHg	97.43 ± 27.67	74.23 ± 21.05	0.004
Aortic mean gradient, mmHg	61.25 ± 17.02	42.34 ± 13.56	0.01
PRBCs, units	2 [1–5]	0 [0–2]	0.03
Platelet concentrate, units	1 [0–1]	0	0.56
PS (B), ng/mL	68.97 ± 16.54	62.31 ± 21.89	0.63
PS (POD-1), ng/mL	74.03 ± 15.05	75.88 ± 23.99	1.00
PS (POD-3), ng/mL	67.21 ± 14.89	73.00 ± 19.81	0.51
F1 + 2 (B), pg/mL	60.83 ± 15.85	38.08 ± 15.84	0.71
F1 + 2 (POD-1), pg/mL	34.38 ± 11.10	40.85 ± 17.75	0.66
F1 + 2 (POD-3), pg/mL	31.08 ± 18.28	45.42 ± 16.80	0.44
PF-4 (B), IU/mL	1471.89 ± 455.42	1212.74 ± 616.56	0.35
PF-4 (POD-1), IU/mL	991.76 ± 559.96	1077.17 ± 476.74	0.65
PF-4 (POD-3), IU/mL	1490.97 ± 557.08	1466.04 ± 613.83	1.00

Data are presented as mean ± standard deviation or median [interquartile range]. B – baseline; CEP – composite end-point; F1 + 2–prothrombin fragments 1 + 2; Hb – hemoglobin; MPV – mean platelet volume; PF-4 – platelet factor 4; PLT – platelet count; POD – postoperative day; PRBCs – packed red blood cells; PS – P-selectin; RBC−red blood cells; SD – standard deviation.

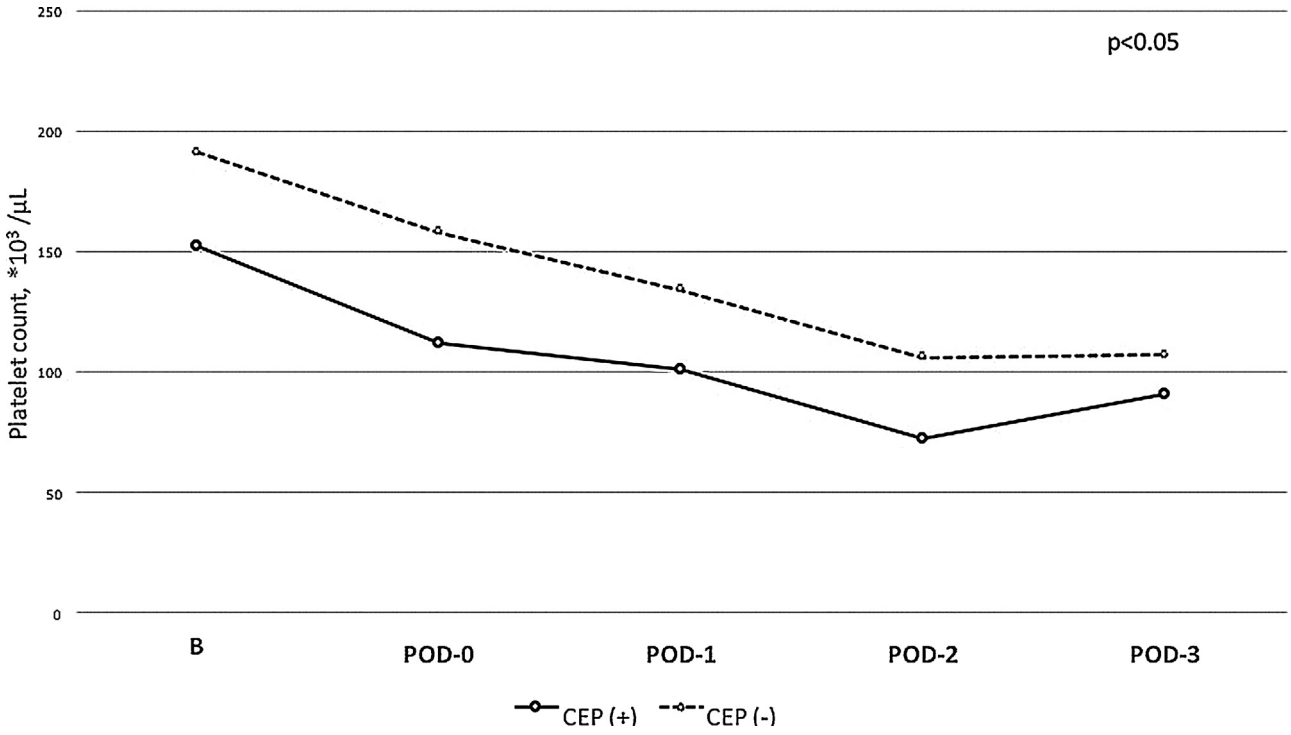

Fig 1. The changes in platelet counts on the following postoperative days in patients with and without composite end point.
B – baseline; CEP – composite end point; POD – postoperative day.

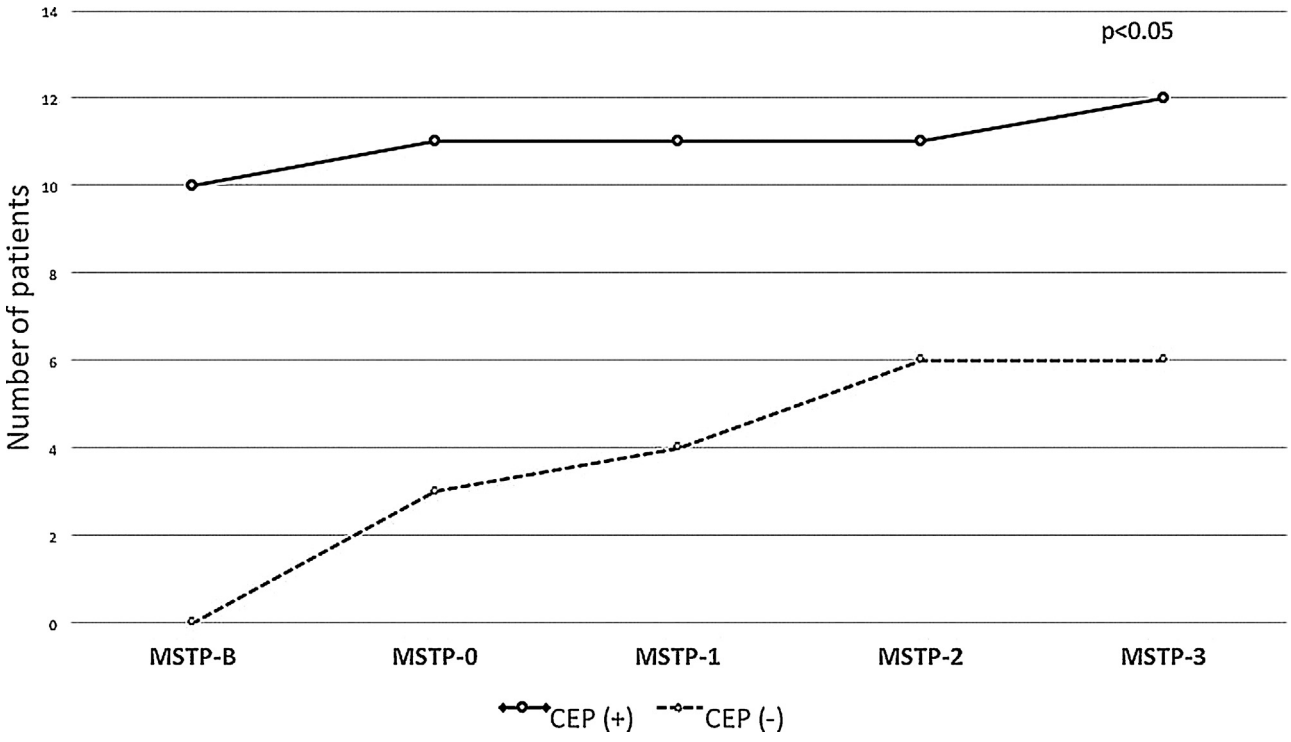

Fig. 2. The frequency of patients with moderate-to-severe thrombocytopenia on the particular days depending on the occurrence of composite end point.
B – baseline; CEP – composite end point; MSTP – moderate-to-severe thrombocytopenia.

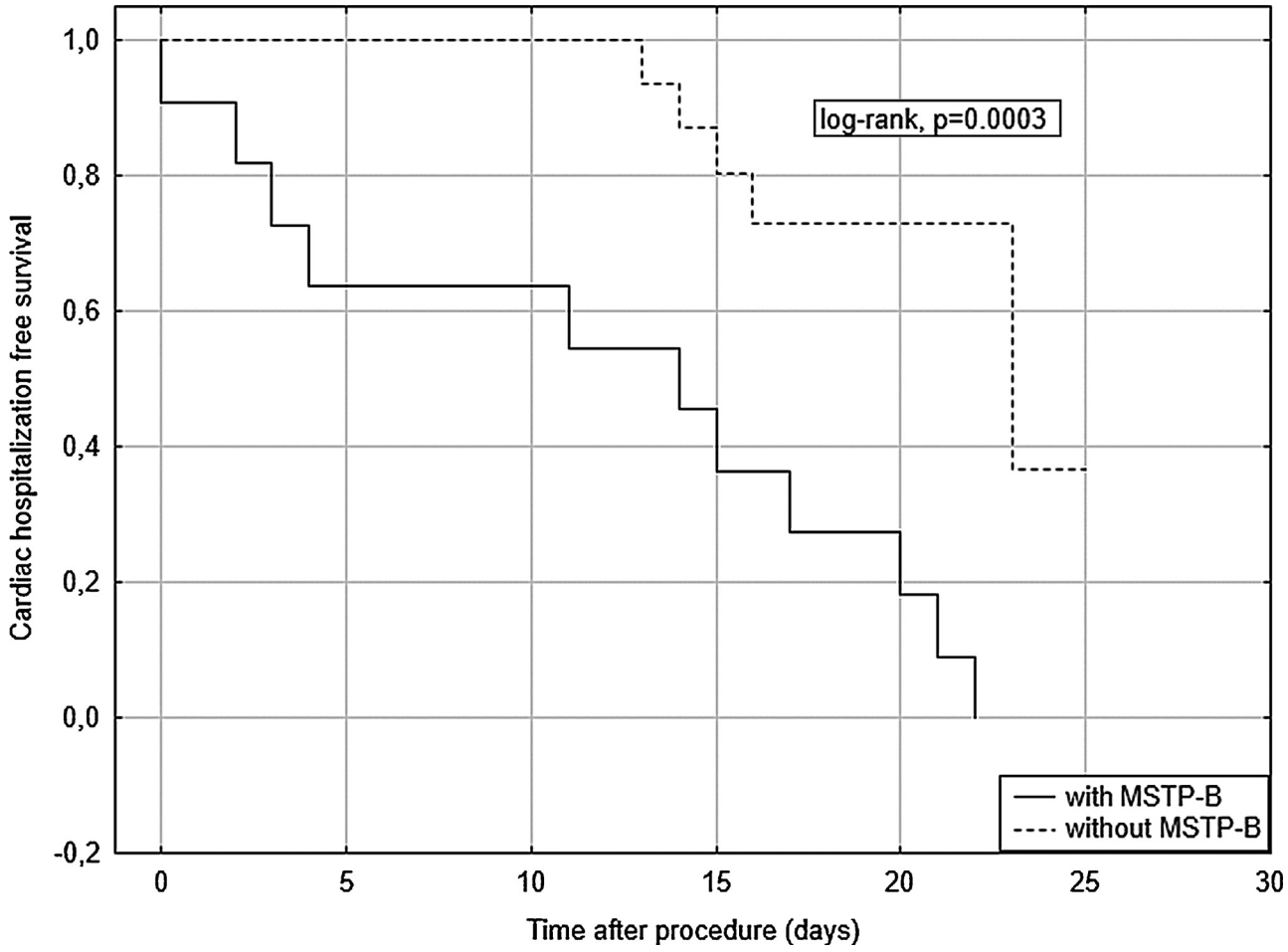

Fig. 3. Kaplan-Meier curves of the cardiac hospitalization free survival in patients with and without moderate-to-severe thrombocytopenia at baseline. MSTP-B – moderate-to-severe thrombocytopenia at baseline.

Table 2
Univariate analysis of the variables affecting clinical end-point occurrence.

	R^2	b	p
Creatinine-B	0.386	0.183	0.04
POD-B	0.334	−0.137	0.04
MPV-B	0.130	−0.130	0.50
POD-0	0.368	−0.102	0.05
MPV-0	0.261	−0.034	0.05
POD-1	0.353	−0.091	0.06
MPV-1	0.025	−0.037	0.8
POD-2	0.479	−0.199	0.009
MPV-2	0.187	−0.002	0.33
POD-3	0.491	−0.212	0.07
MPV-3	0.137	−0.018	0.48
AVA-B	0.123	0.070	0.09
Max gradient- B	0.494	0.215	0.007
Mean gradient-B	0.486	0.207	0.008
Time of procedure	0.121	0.023	0.53
Contrast	0.154	0.013	0.43
GFR	0.012	0.038	0.94
RBC-B	0.298	−0.092	0.04
Hb-B	0.421	−0.151	0.09

AVA – aortic valve area; B – baseline; b – regression coefficient; GFR – glomerular filtration rate; Hb – hemoglobin; MPV – mean platelet volume; POD – postoperative day; R^2 – significance of the regression coefficient; RBC – red blood cells.

In univariate analysis the following variables indicated the occurrence of CEP: higher baseline creatinine level, more severe aortic stenosis, lower baseline red blood cells (RBCs) count, hemoglobin (Hb) value and platelet count as well as lower platelet level on POD-2 and POD-3 and the need for PRBCs transfusion, Table 2. Platelet count assessed on POD-0 reached the border value ($b = -0.102$, $p = 0.05$), Table 2.

Based on the ROC analysis, platelet count changes (differences between platelet count on each postoperative day and the baseline count) did not have any predictive value in CEP prognosis.

4. Discussion

In the current study we searched for the exact time point of the worst predicting thrombocytopenia following TAVI procedure in the aspect of the various periprocedural causes which may lead to its occurrence. We investigated the selected group of patients without dual antiplatelet therapy for special assessment of perioperative platelet and blood coagulation activation as the potential causes of thrombocytopenia leading to the adverse outcome. Based on our results, we suggest possible platelet and coagulation activation following TAVI procedure, but independent of the CEP occurrence. Platelet and coagulation hyperactivity as a result of the exposure to the stents struts of the valve implanted during the procedure have been described among other causes of thrombocytopenia [11]. Thus, it could be interesting to assess these processes in the aspect of periprocedural thrombocytopenia, which worsens prognosis. However, in our study among all clinical and periprocedural variables, only platelet counts, baseline

creatinine concentration together with RBCs count, Hb level and the severity of the valve disease as well as the need for PRBCs transfusion influenced the incidence of CEP.

Severe thrombocytopenia after TAVI procedure has been reported as a marker of unfavorable early and late outcome associated with certain pre-existing, periprocedural as well as postoperative predictors [7]. As it was shown in our previous publication, the greatest platelet drop was found right after the procedure, with platelet count reaching its nadir level on POD-2 and since then slowly began to recover [10]. Additionally pre-existing thrombocytopenia itself was associated with higher long-term non-cardiac mortality and bleeding in patients undergoing percutaneous coronary interventions [12]. In the current study, pre-existing thrombocytopenia together with perioperative further platelet drop were more profound in patients with CEP. This course of platelet count has also been confirmed by other authors [5,13]. Moderate-to-severe thrombocytopenia was found in over 53% of all patients [10], which was in contrast to the previous reports, where it occurred in about 37% of patients [5]. Moreover, in the current study, moderate-to-severe thrombocytopenia was more frequent at baseline as well as on the following postoperative days in the group of patients with CEP as compared to those with good prognosis. Kaplan-Meier curves suggested that low platelet count before the procedure could be linked with worse prognosis after TAVI. To prove this more accurately, we used a modern statistical analysis. ROC curves analysis revealed that the changes on the particular days are not linked with worse prognosis, suggesting that more important are initial platelet values. This could be, at least to our knowledge, one of the first studies highlighting the importance of the pre-existing thrombocytopenia in TAVI patients.

The influence of thrombocytopenia on survival is related to the bleeding complications, but it has primarily been described as a marker of bad global clinical patient's condition [7]. This, at least partially, is confirmed by our results. Patients with CEP had more severe aortic valve stenosis. Moreover, these patients had pre-existing anemia, renal dysfunction and needed more frequently PRBCs transfusion after the procedure. However, no significant perioperative bleeding complications in this group of patients were found.

Transfusion of PRBCs after TAVI procedure is associated with higher mortality, longer hospitalization and impaired clinical outcome [14]. Gastrointestinal bleeding together with vascular complications are the most common cause of the need of PRBCs transfusion [14]. In our study, only red blood cells transfusion, but not platelet transfusions influenced the outcome, which might be related to a small sample of the study patients. Moreover, in spite of the significantly lower platelet count following the procedure, no differences regarding platelet concentrate transfusion during the index of hospitalization between the groups were found.

Renal failure is a well-known risk factor of many cardiovascular diseases. Fried et al. [15] performed a population-based study – the group of 5808 patients have been prospectively evaluated. In 11.2% of them renal insufficiency was found and elevated creatinine was a relevant predictor of increased mortality, cardiovascular disease, heart failure as well as leg claudication. Moreover, a linear correlation between increasing creatinine and the rate of cardiovascular events was found [15]. Interestingly, impaired baseline renal function influences not only future prognosis, but also further platelet drop [13].

4.1. Summary

The precise explanation of impaired prognosis following TAVI procedures which is related to thrombocytopenia is unclear and needs further studies on a greater number of patients. Among potential causes of thrombocytopenia platelet and blood coagulation activation seems to be an underestimated, poorly examined but promising factor. However, based on our results, baseline patients' condition together with initial thrombocytopenia have the most important influence on worse prognosis.

5. Conclusions

Patients with thrombocytopenia following TAVI procedure have poor prognosis in the postoperative period, however the changes on the particular days are not more important than the initial platelet count. Further studies on a greater number of patients are needed to evaluate platelet and blood coagulation activation as well as other potential causes influencing the occurrence of thrombocytopenia and impaired prognosis related to it.

5.1. Study limitations

The main study limitation was a small group of analyzed patients, thus obtained results should be taken with caution. However, we selected patients without dual antiplatelet therapy and examined them precisely. The study of various causes leading to thrombocytopenia which is worsening prognosis is interesting and crucial, especially in the presence of a potential imbalance between enhanced platelet consumption and reduced platelet production after TAVI procedure.

Disclosure of interest

The authors have not transmitted any conflicts of interest.

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References

[1] Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. PARTNER trial investigators: two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366(18):1686–95.
[2] Kleczyński P, Bagieński M, Sorysz D, Rzeszutko L, Trębacz J, Tomala M, et al. Short- and intermediate-term improvement of patient quality of life after transcatheter aortic valve implantation: a single-centre study. Kardiol Pol 2014;72(7):612–6.
[3] Möllmann H, Kim WK, Kempfert J, Walther T, Hamm C. Complications of transcatheter aortic valve implantation (TAVI): how to avoid and treat them. Heart 2015;101(11):900–8.
[4] Kaier K, Reinecke H, Naci H, Frankenstein L, Bode M, Vach W, et al. The impact of post-procedural complications on reimbursement, length of stay and mechanical ventilation among patients undergoing transcatheter aortic valve implantation in Germany. Eur J Health Econ 2017(February), doi:http://dx.doi.org/10.1007/s10198-017-0877-7.
[5] Jilaihawi H, Doctor N, Chakravarty T, Kashif M, Mirocha J, Cheng W, et al. Major thrombocytopenia after balloon-expandable transcatheter aortic valve replacement: prognostic implication to surgical aortic valve replacement. Catheter Cardiovasc Interv 2015;85(1):130–7.
[6] Mitrosz M, Chlabicz M, Hapaniuk K, Kaminski KA, Sobkowicz B, Piszcz J, et al. Thrombocytopenia associated with TAVI–the summary of possible causes. Adv Med Sci 2017;62(2):378–82.
[7] Dvir D, Généreux P, Barbash IM, Kodali S, Ben-Dor I, Williams M, et al. Acquired thrombocytopenia after transcatheter aortic valve replacement: clinical correlates and association with outcomes. Eur Heart J 2014;35(38):2663–71.
[8] Gallet R, Seemann A, Yamamoto M, Hayat D, Mouillet G, Monin JL, et al. Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences. Am J Cardiol 2013;111(11):1619–24.
[9] McCabe JM, Huang PH, Riedl LA, Devireddy SR, Grondell J, Connors AC, et al. 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(4):633–41.
[10] Mitrosz M, Kazimierczyk R, Sobkowicz B, Waszkiewicz E, Kralisz P, Frank M, et al. The causes of thrombocytopenia after transcatheter aortic valve implantation. Thromb Res 2017;156:39–44.

[11] Rodés-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. J Am Coll Cardiol 2013;62(25):2349–59.
[12] Raphael CE, Spoon DB, Bell MR, Psaltis PJ, Kidd S, Loh SX, et al. Effect of preprocedural thrombocytopenia on prognosis after percutaneous coronary intervention. Mayo Clin Proc 2016;91(8):1035–44.
[13] Flaherty MP, Mohsen A, Moore 4th JB, Bartoli CR, Schneibel E, Rawasia W, et al. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. Catheter Cardiovasc Interv 2015;85(1):118–29.
[14] Kleczynski P, Dziewierz A, Bagienski M, Rzeszutko L, Sorysz D, Trebacz J, et al. Association between blood transfusions and 12-month mortality after transcatheter aortic valve implantation. Int Heart J 2017;58(1):50–5.
[15] Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. J Am Coll Cardiol 2003;41(8):1364–72.