Comparison of the Frequency of Thrombocytopenia After Transfemoral Transcatheter Aortic Valve Implantation Between Balloon-Expandable and Self-Expanding Valves

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Thrombocytopenia after transcatheter aortic valve implantation (TAVI) is common and has been related to worse clinical outcomes. Comparison of platelet kinetics among different types of valves is limited. Our objectives were to analyze the differences in drop platelet count (DPC) between balloon-expandable valves (BEVs) and self-expanding valves and their prognostic implications after TAVI. Patients who underwent transfemoral TAVI from 2008 to 2016 were included. Exclusion criteria were severe baseline thrombocytopenia and periprocedural death. Postprocedural platelet counts were collected. Two groups were created: DPC ≤30 and DPC >30%. Valve Academic Research Consortium-2 criteria were used to define outcomes. Study population included 609 patients (age 84.7 ± 6.0, 46.6% males). The mean DPC was 32.5 ± 13.9%. The DPC was higher in the BEV arm (33.9 ± 14.2 vs 30.7 ± 13.4%, p = 0.006), and the nadir was reached later in comparison to the self-expanding valve arm (3.0 ± 1.3 vs 2.5 ± 1.1 days, p <0.001). After multivariable analysis, the use of BEV, known coronary artery disease, and left ventricle ejection fraction were the factors associated with a higher rate of DPC >30%. At 30 days, the DPC >30% was related with a higher rate of life-threatening and/or major bleeding (6.8 vs 2.1%, p = 0.009) and death (3.5 vs 0.8%, p = 0.036). At 1 year, the difference in mortality disappeared. In conclusion, in this cohort of patients, the use of BEV seems to be associated with a higher risk of DPC after TAVI. A DPC ≥30% was related with increased risk of life-threatening and/or major bleeding and death at 30 days. Larger and prospective studies are needed to understand this phenomenon. **(Am J Cardiol 2019;123:1120−1126)**

Transcatheter aortic valve implantation (TAVI) has become the standard of care of inoperable, high, and selected intermediate-risk patients with symptomatic aortic stenosis.[1−4] However, there are still challenges to be addressed to be able to offer this treatment to low-risk or younger population. Minimizing periprocedural complications remains essential because they are related to higher mortality and prolonged in-hospital stay.[5] TAVI-related thrombocytopenia is a common phenomenon and has been associated with worse clinical outcomes.[6−12] The etiology remains unknown and seems to be multifactorial.[13] The objectives of the present study were to analyze the differences in drop platelet counts (DPC) between balloon-expandable valves (BEVs) or self-expanding valves (SEVs) in patients who underwent transfemoral TAVI and the implications of a significant DPC in clinical outcomes.

Methods

We prospectively included patients with severe aortic stenosis who underwent transfemoral TAVI in our center between January 2008 and December 2016. The patients were considered noncandidates for surgery by the local Heart Team. We excluded patients with baseline platelet count $<100 \times 10^9$/L, those with periprocedural death (until 72 hours after TAVI) and those in whom post-TAVI platelet counts were not available.

The choices of vascular access, type, and size of the valves were at discretion of the local Heart Team. Patients were treated either with balloon-expandable Sapien, Sapien XT, or Sapien 3 valves (Edwards Lifesciences, Irvine,

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Marco Hernández-Enríquez received a research grant for this specific project from "Fundació Privada Daniel Bravo Andreu," Barcelona, Spain.

See page 1125 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2018.12.036

California) or self-expanding CoreValve or Evolut R (Medtronic, Inc., Minneapolis, Minnesota). Because the sample of subjects treated with other valves was small, they were also excluded from the analysis.

Transfemoral vascular access and closure were performed in standard fashion.[14,15] Surgical cutdown and closure was used when the program started, but since 2012 our technique evolved to completely percutaneous approach using 2 Proglide vascular closure devices (Abbott Vascular, Chicago, Illinois). Since then, we also use local anesthesia with conscious sedation as a first-line approach. All patients received unfractioned heparin to maintain a minimum active clotting time >250 seconds after the insertion of the femoral sheet. Protamine (1 mg for each 100 U of heparin, maximal dose 50 mg) was administrated routinely at the time of vascular closure. Aspirin was recommended before TAVI. Dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day was systematic for patients with recent percutaneous coronary intervention and was left at the discretion of the treating physician in the other cases. Patients requiring oral anticoagulation received vitamin K antagonist or novel oral anticoagulants.

Baseline characteristics, procedural data, and clinical outcomes were collected. Laboratory analyses were performed before the procedure, daily during postprocedural intensive care unit stay, and at the physician discretion in the cardiology ward and were retrospectively collected. Standard follow-up included 30-day and 1-year visits after the hospital discharge. This follow-up was performed either on site or by telephone contact. All patients gave written informed consent before the procedure and for the anonymous use of their data. The study protocol was approved with the local ethics committee and was in accordance with the 1975 Declaration of Helsinki. Also, our center is an active participant in the FRANCE TAVI Registry, an initiative from the French Society of Cardiology and subject to regular data quality checks.[16,17]

Postprocedural events were defined according to the Valve Academic Research Consortium-2 criteria.[18] Nadir platelet count was defined as the lowest record platelet count during hospitalization. DPC was calculated with this formula: [%DPC= 100 × (baseline platelet count − nadir platelet count)/baseline platelet count.[8]

Continuous variables are presented as mean ± standard deviation, categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's *t* test for continuous variables and chi-square or Fisher's exact test for categorical variables, when appropriate. Main effect estimates are presented with their 95% confidence interval. To estimate the association between valve type and DPC, a multivariable logistic regression analysis was performed. The DPC was categorized into 2 groups. The groups were determined based on the median DPC (DPC ≤30% and DPC >30%). Variables exhibiting a p value <0.15 in the univariable analysis were included in the multivariable model. Kaplan-Meier method was used for cumulative survival analysis after 1 year. To compare the survival between patients with DPC <30% and patients with DPC ≥30%, the log-rank test was used as appropriate. All statistical analyses were performed with Stata Statistical Software 10 (StataCorp, LLC, College Station, Texas).

Results

Baseline and procedural characteristics of the study population are summarized in Table 1. The flow chart of the study is shown in Figure 1. During the 8-year period of the study, 999 patients underwent TAVI. After exclusion of 390 subjects, the final population analyzed included 609 patients. The mean age of the population was 84.7 ± 6 years old and 46.6% were males. The patients treated with SEVs had significant lower rate of peripheral vascular disease and higher amount of contrast was used in their procedures. There were no significant differences among the other baseline characteristics.

Table 2 summarizes the changes in platelet count values according to the type of valve. Figure 2 depicts the kinetics of platelet count values according to the type of valve. All patients, except for 6 (0.98%) had a decrease in platelet count after the procedure. The mean DPC post-TAVI was 32.5 ± 13.9%. The DPC percentage was significantly higher in the BEV group in comparison with the SEV group. Also, subjects treated with BEVs reached the nadir later than the treated with SEVs.

The univariable and multivariable analyses of factors related with a high DPC after TAVI are presented in Tables 3 and 4, respectively. In the univariable analysis, the female gender, lower rate of known coronary artery disease, lower Logistic EuroSCORE, higher left ventricle ejection fraction, and the use of BEVs were related to a ≥30% of DPC. After multivariable analysis, the factors associated with a higher DPC were the use of BEV, known coronary artery disease, and left ventricle ejection fraction. Fewer patients were treated with DAPT in the DPC ≥30% group in comparison with the DPC <30% group (90 [24.4%] vs 86 [35.8%], p = 0.002).

Thirty-day clinical outcomes are summarized in Table 5. A high DPC was associated with higher rate of life-threatening or major bleeding and mortality at 30 days. In a subgroup of 10 patients with periprocedural death in whom the platelet count was available, there was also a higher DPC in comparison with the patients included in the study (19.5 ± 14.5 vs 34.8% ± 25.7, p <0.002). There were no significant differences in the mortality rate between groups (10% vs 13.3%, p = 0.198) at 1-year follow-up. Kaplan-Meier survival curve at 1 year is shown in Figure 3.

Discussion

Major results are summarized as follows: (1) a decrease in platelet count values after TAVI is a frequent finding, (2) the implantation of a BEV was associated with a higher DPC compared with the use of SEV, and (3) a DPC >30% was associated with higher rates of major and life-threatening bleeding and death at 30 days after TAVI compared with a DPC ≤30%.

Thrombocytopenia after TAVI is frequent. The average DPC after TAVI described ranges between 34% and 38%.[8–10] A decrease in platelet counts was documented since the first CoreValve in-humans study.[19] However, it was not until 7 years later when Gallet et al reported a systematically decrease in platelet counts related to TAVI and associated its severity with worse clinical outcomes.[9] Again, only patients treated with CoreValve prostheses

Table 1
Baseline and procedural characteristics of the study population according to the type of the implanted valve

Variable	Total (n = 609)	BEV (n = 349)	SEV (n = 260)	p Value
Age (years)	84.7 ± 6.0	84.7 ± 6.0	84.6 ± 6.1	0.929
Men	284 (46.6%)	162 (46.4%)	122 (46.9%)	0.902
Body mass index (kg/m^2)	26.0 ± 5.2	26.0 + 5.1	26.1 ± 5.3	0.823
Hypertension	414 (68.0%)	244 (69.9%)	170 (65.4%)	0.236
Diabetes mellitus	168 (27.6%)	98 (28.1%)	70 (26.9%)	0.752
Atrial fibrillation on admission ECG	199 (33.1%)	111 (32.5%)	88 (34.0%)	0.695
Peripheral vascular disease	46 (7.6%)	33 (9.5%)	13 (5.0%)	0.040
Previous stroke or TIA	65 (10.7%)	33 (9.5%)	32 (12.3%)	0.260
Previous percutaneous coronary intervention	193 (31.7%)	116 (33.2%)	77 (29.6%)	0.342
Previous coronary artery bypass grafting	60 (9.9%)	29 (8.3%)	31 (11.9%)	0.139
Known coronary artery disease	273 (44.8%)	161 (46.1%)	112 (43.1%)	0.453
Baseline Creatinine (mg/dl)	1.11 (0.88 - 1.38)	1.11 (0.86 - 1.38)	1.09 (0.89 - 1.39)	0.943
STS-PROM score (%)	7.1 ± 3.8	7.4 ± 4.0	6.7 ± 3.5	0.051
Logistic EuroSCORE 1 (%)	19.1 ± 10.0	19.1 ± 9.7	19.1 ± 10.5	0.984
Left ventricular ejection fraction (%)	51.5 ± 14.75	50.7 ± 14.8	52.5 ± 14.5	0.150
Mean transaortic gradient (mm Hg)	44.0 ± 15.8	43.1 ± 15.6	45.2 ± 16.1	0.128
AVA (cm^2)	0.74 ± 0.24	0.74 ± 0.23	0.74 ± 0.26	0.979
Procedural characteristics				
Procedural success	603 (99.0%)	346 (99.1%)	257 (98.9%)	0.716
Valve size (mm)				<0.001
<26	161 (26.4%)	146 (41.8%)	15 (5.8%)	
26	261 (42.9%)	157 (45.0%)	104 (40.0%)	
29	154(25.3%)	46 (13.2%)	108 (41.5%)	
31	33 (5.4%)	0 (0.0%)	33 (12.7%)	
General anesthesia	209 (34.4%)	134 (38.5%)	75 (29%)	0.014
Contrast volume (ml)	166 ± 58	153 ± 51	185 ± 61	<0.001

AVA = aortic valve area; BEV = balloon-expandable valves; SEV = self-expanding valves; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Values are mean ± standard deviation (or median [interquartile range for baseline creatinine] or absolute numbers and percentages).

were included. In contrast, descriptions of DPC in Sapien valves are also available.[7,11,20] In fact, the largest publication so far in this topic included patients treated mostly with BEV (>96%).[8] Our study includes a comparable proportion of each type of valve and suggests that patients treated with BEV develop higher DPC.

The etiology of DPC after TAVI is complex and multifactorial. TAVI patients develop a higher DPC than patients who are treated with isolated aortic valvuloplasty.[20] In this regard, BEV valves were related to higher DPC could raise the question about a prosthesis factor, as previously suggested in another study.[12] Perhaps, the differences in the design of the prothesis, the smaller diameter of valves used in the BEV group or a more stressful implantation technique leading to endothelial damage and shear stress modification, could be hypothesized as possible explanations.[21] Recently, malpositioning of the valve has been suggested as a strong predictor of DPC after TAVI, supporting the study of shear stress in its pathophysiology.[10]

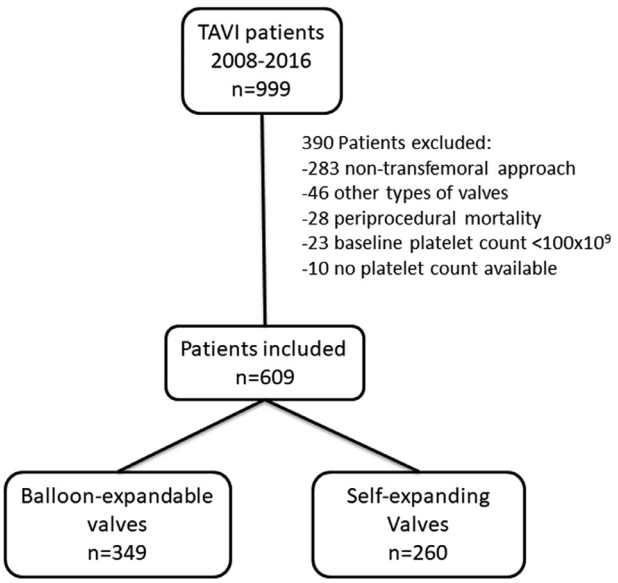

Figure 1. Study flowchart. From 2008 to 2016, 999 patients were treated with TAVI. After exclusion of 390 patients, a total of 601 patients were finally included in the analysis.

Table 2
Periprocedural platelet count values according to the type of the implanted valve

Variable	BEV (n = 349)	SEV (n = 260)	p Value
Platelet count at baseline (10^9/L)	224 ± 62	222 ± 69	0.677
Platelet count nadir (10^9/L)	146 ± 47	153 ± 51	0.102
Days to nadir	3 (2-4)	2 (2-3)	<0.001
Drop platelet count (%)	33.9 ± 14.2	30.7 ± 13.4	0.006

BEV = balloon-expandable valves; SEV = self-expanding valves.

Values are mean ± standard deviation and median (interquartile range).

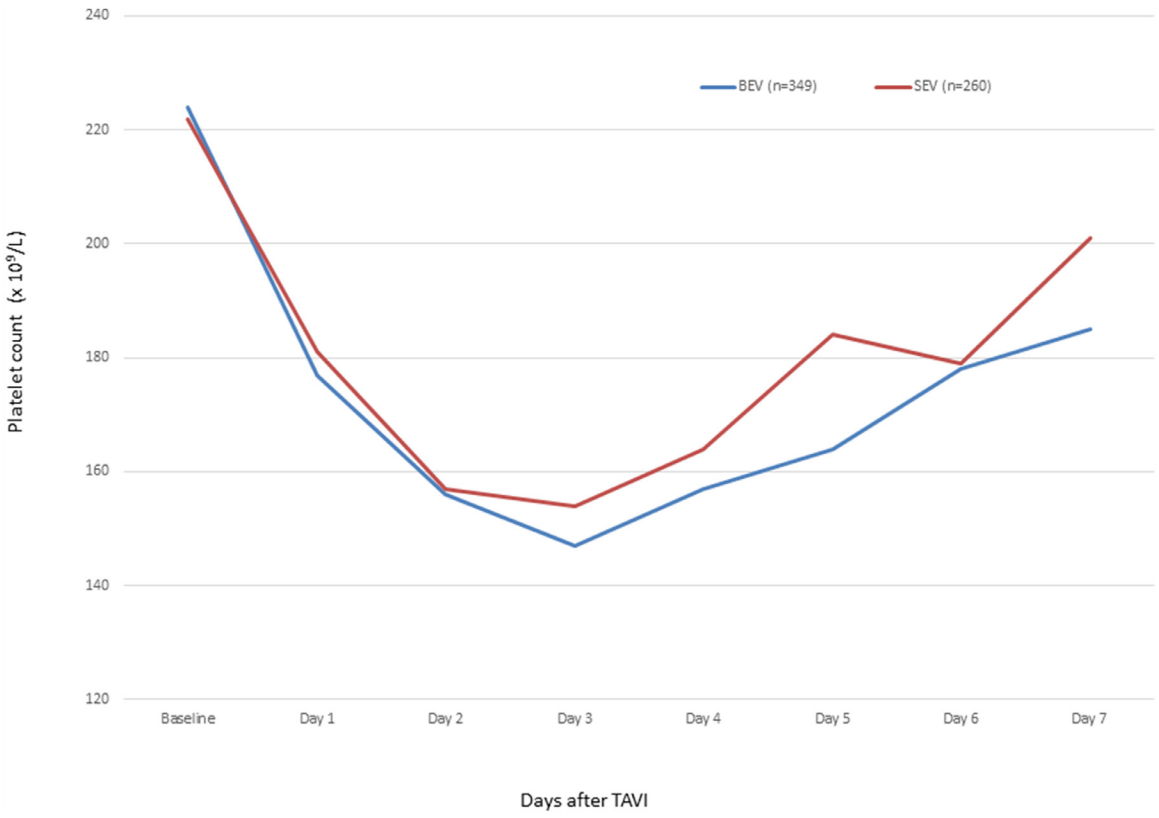

Figure 2. Differences of the kinetics of drop platelet count (DPC) between the balloon-expandable valve (BEV) and self-expanding valve (SEV) groups.

Table 3
Univariable analysis of factors related to high DPC

Variable	Total (n = 609)	DPC <30% (n = 240)	DPC ≥30% (n = 369)	p Value
Age (years)	84.7 ± 6.0	83.9 ± 6.5	85.1 ± 5.7	0.016
Men	284 (46.6%)	128 (53.3%)	156 (42.3%)	0.008
Body mass index (kg/m^2)	26.0 ± 5.2	26.1 ± 5.1	26.0 ± 5.2	0.900
Hypertension	414 (68.0%)	158 (65.8%)	256 (69.4%)	0.360
Diabetes mellitus	168 (27.6%)	71 (29.6%)	97 (26.3%)	0.374
Atrial fibrillation	199 (33.1%)	77 (32.8%)	122 (33.3%)	0.885
Baseline creatinine (mg/dl)	1.11 (0.88 - 1.38)	1.09 (0.88 - 1.38)	1.11 (0.87 - 1.39)	0.885
Previous stroke	65 (10.7%)	29 (12.1%)	36 (9.8%)	0.363
Known coronary artery disease	273 (44.8%)	124 (51.7%)	149 (40.4%)	0.006
STS-PROM score (%)	7.1 ± 3.8	7.0 ± 3.7	7.2 ± 3.9	0.666
Logistic EuroSCORE 1 (%)	19.1 ± 10.0	20.1 ± 10.3	18.4 ± 9.8	0.041
Left ventricular ejection fraction (%)	51.5 ± 14.7	48.5 ± 15.1	53.4 ± 14.1	<0.001
Mean transaortic gradient (mm Hg)	44.0 ± 15.8	43.5 ± 16.6	44.4 ± 15.3	0.523
AVA (cm^2)	0.74 ± 0.24	0.74 ± 0.21	0.75 ± 0.26	0.707
Procedural characteristics				
Balloon-expandable prosthesis	349 (57.3%)	122 (50.8%)	227 (61.5%)	0.009
Procedural success	603 (99.0%)	238 (99.2%)	365 (98.9%)	0.760
General anesthesia	209 (34.4%)	92 (38.3%)	117 (31.9%)	0.102
Contrast volume (ml)	166 ± 58	164 ± 59	168 ± 58	0.423

AVA = aortic valve area; BEV = balloon-expandable valves; SEV = self-expanding valves; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Values are mean ± standard deviation (or median [Interquartile range for baseline creatinine] or absolute numbers and percentages).

The possible causes could remain on the procedure itself rather than on the valve properties. The use of larger sheaths for vascular access in the BEVs could play an important factor related to higher DPC. Also, general anesthesia has been related to a more severe platelet count decrease after TAVI.[10] However, we did not find significant differences in DPC in patients treated with general anesthesia. This could be explained due to a higher use of local

Table 4
Multivariable analysis of factors associated with DPC

Variable	Odds ratio (95% conf. interval)	p Value
Balloon-expandable valve	1.72 (1.23-2.42)	0.002
Known coronary artery disease	0.69 (0.49-0.97)	0.031
Left ventricular ejection fraction (%)	1.02 (1.01-1.04)	<0.001

anesthesia in our population. The use of conscious sedation and local anesthesia seems to be equally safe and has been related to lower procedural times and shorter in-hospital stay.[22,23]

The use of iodinated contrast agents has been proposed as another possible etiologic factor.[9] Their chemical properties, an immunoallergic reaction or genetic predisposition, are some of the probable explanations to understand this relation. In our study, we used higher amount of contrast in the SEVs group. This might be due to a higher need of aortographies to obtain a good position of a repositionable valve, especially if no echocardiographic guidance is performed. However, when we compared the groups according to the DPC we did not find differences according to the amount of contrast administrated. Also, we cannot exclude that patients treated with dual antiplatelet treatment and coronary disease were also older and had more endothelial dysfunction that could play a role in thrombocytopenia.

In terms of outcomes, previous reports found a higher 30-day mortality rate, prolonged ICU stay, and higher rates of major vascular complications, life-threatening bleeding, sepsis, acute kidney injury and multiple blood transfusions in patients developing severe thrombocytopenia.[7–11] Our results agree with them and show an association between significant DPC after TAVI and major and/or life-threatening bleeding and mortality at 30 days. Although thrombocytopenia can directly increase bleeding events, the effect of a high DPC can be a consequence of a rapid platelet consumption during several adverse events including vascular complications and bleeding, and can be viewed as a marker of systemic inflammatory response after TAVI.[8,24] In fact, an elevation of inflammatory markers such as C-reactive protein, interleukin-6, S100A8/A9 and leucocytes has been previously described.[25,26]

Finally, the routine follow-up of platelet counts after TAVI seems to be an easy and cheap marker of risk and should continue to be part of the postprocedural care. Also, a relation between low platelet counts at discharge and possible

Table 5
Thirty-day outcomes of patients with high DPC after TAVI

Variable	Total (n = 609)	DPC <30% (n = 240)	DPC ≥30% (n = 369)	p Value
Myocardial infarction	3 (0.5%)	1 (0.4%)	2 (0.5%)	1.000
Life-threatening/major bleeding	30 (4.9%)	5 (2.1%)	25 (6.8%)	0.009
Major vascular complication	33 (5.4%)	11 (4.6%)	22 (6.0%)	0.463
Acute Kidney injury (AKIN 2/3)	28 (4.9%)	8 (3.6%)	20 (5.6%)	0.276
Stroke	21 (3.5%)	6 (2.5%)	15 (4.1%)	0.301
Mortality	15 (2.5%)	2 (0.8%)	13 (3.5%)	0.036

AKIN = acute kidney injury; DPC = drop platelet count; TIA = transient ischemic attack.
Values are absolute numbers and percentages.

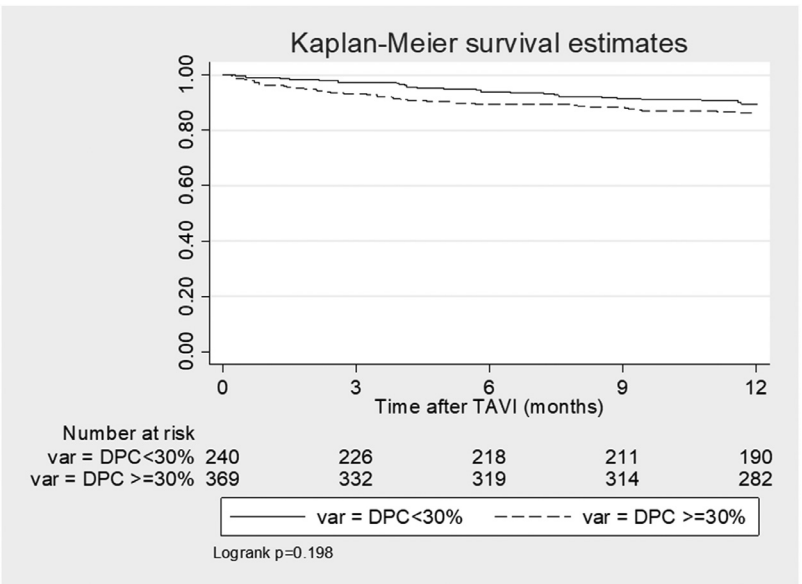

Figure 3. Kaplan-Meier 1-year survival curves after TAVI according to the percentage of drop platelet count (DPC).

leaflet thrombosis has been recently described.[27] Larger and prospective studies including imaging, inflammatory, and hemostasis biomarkers are needed to fully understand the etiology and consequences of this phenomenon.

All the inherent limitations of an observational and retrospective study apply for this study. No platelet activation, inflammation, or hemolysis parameters were systematically measured. The rate of heparin-induced thrombocytopenia is not reported. Nevertheless, the reported incidence of this complication is <0.5%.[28] Specific data of malpositioning or leaflet thrombosis were not collected.

In conclusion, the use of BEV seems to be associated with a higher risk of DPC after TAVI. A DPC ≥30% was related with increased risk of life-threatening and/or major bleeding and death at 30 days.

Disclosures

The authors have no conflicts of interest to disclose.

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