The Impact of Baseline Thrombocytopenia on Late Bleeding and Mortality After Transcatheter Aortic Valve Implantation (From the Japanese Multicenter OCEAN-TAVI Registry)

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Baseline thrombocytopenia was reported as a risk factor for bleeding or mortality in several medical areas, particularly in the cardiovascular field. This study aimed to assess the prognostic value of baseline thrombocytopenia in patients who had transcatheter aortic valve implantation. This study included 2,588 patients from the Optimized Catheter valvular intervention Japanese multicenter registry. Thrombocytopenia was defined as platelet count of $<150 \times 10^9$/L and was classified into moderate/severe ($<100 \times 10^9$/L) and mild ($\geqq 100$-$<150 \times 10^9$/L). At 3 years after index procedure, the moderate/severe thrombocytopenia group had a significantly higher cumulative composite late bleeding than the no thrombocytopenia group (log-rank test, $p < 0.0001$). Moreover, the moderate/severe thrombocytopenia group had a significantly higher cumulative all-cause, cardiovascular, and noncardiovascular mortality rates than the no thrombocytopenia group (log-rank test, $p < 0.0001$, $p = 0.0014$, $p < 0.0001$, respectively). After adjusting for confounders, the excess risk of moderate/severe and mild thrombocytopenia relative to no thrombocytopenia for the composite bleeding remained significant (hazard ratio 2.66: [95% confidence interval: 1.35 to 4.88], $p = 0.006$ and hazard ratio 2.10: [95% confidence interval: 1.36 to 3.21], $p = 0.001$, respectively). In conclusion, baseline thrombocytopenia was associated with an increased risk of late bleeding and poor prognosis. Baseline platelet level could be a prognostic marker for risk stratification. **(Am J Cardiol 2021;141:86−92)**

Transcatheter aortic valve implantation (TAVI) is a safer therapeutic option in symptomatic patients with severe aortic stenosis (AS) who cannot undergo surgery or who have high, intermediate, or even low surgical risk.[1−4] Thrombocytopenia is a common abnormality found in routine blood tests, particularly in elderly patients.[5] Baseline thrombocytopenia has been reported as a major risk factor in patients with ischemic heart disease.[6,7] The impact of preexisting thrombocytopenia on clinical outcomes in patients who underwent TAVI has not been fully investigated. Therefore, the impact of baseline thrombocytopenia on long-term clinical outcomes, including bleeding events and mortality after TAVI, was investigated using a large multicenter registry data.

Methods

The data of 2,588 patients with severe AS available from the OCEAN (Optimized transcatheter valvular intervention) registry were evaluated. The OCEAN registry is an ongoing, multicenter prospective registry of patients who underwent TAVI for severe AS in 14 Japanese institutions, [8,9] and the current data was reported from October 2013 to May 2017. This trial is registered with the University Hospital Medical Information Network (UMIN000020423). Patients' inclusion criteria have been previously reported.[10] This study protocol was approved by the ethics committee in each hospital. Before the procedure, a written informed consent was obtained from all patients included in this study. The study population was categorized into 3 groups based on the baseline platelet count according to the previous reports, including high bleeding risk definition by the Academic Research Consortium[7,11]: no thrombocytopenia (platelet count, $<150 \times 10^9$/L), mild thrombocytopenia (platelet count, 100 to 150×10^9/L), and moderate/severe

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thrombocytopenia (platelet count, $<100 \times 10^9$/L). The primary outcome measure of this study was late bleeding events (a composite of life-threatening or major bleeding) defined based on the Valve Academic Research Consortium-2 (VARC-2) criteria.[12] The bleeding events during the index procedure were excluded from the primary outcome measure. The secondary outcome measures were all-cause, cardiovascular, and non-cardiovascular deaths. The causes of death were classified according to the VARC-2 definitions. [12] Categorical variables were shown as number and percentage and were compared using the chi-square test. Continuous variables were expressed as mean and standard deviation or median and interquartile range and were compared using ANOVA or the Kruskal−Wallis test according to the distribution. Cumulative incidences were calculated using the Kaplan−Meier method and were compared using the log-rank test. The risks of mild thrombocytopenia and moderate/severe thrombocytopenia, respectively, relative to no thrombocytopenia (reference) for clinical outcome measures were estimated using the Cox proportional hazard models and were expressed as hazard ratios (HRs) and their 95% confidence intervals (CIs). A dummy code was used for mild thrombocytopenia and moderate/severe thrombocytopenia to estimate the HRs relative to no thrombocytopenia in the models. The 16 clinically relevant factors listed in Table 1 were included as the risk-adjusting variables in the multivariable Cox proportional hazard models. Parsimonious models were also constructed with the 10

Table 1
Baseline characteristics

Variables	Overall (n = 2,588)	Thrombocytopenia			p value
		None (n = 1,805)	Mild (n = 620)	Moderate/severe (n = 163)	
Baseline platelet count (10^9/L)*	177 (142−215)	199 (174−233)	131 (120−140)	84 (70−92)	<0.0001
Age (years)	84.4 ± 5.2	84.3 ± 5.2	84.9 ± 5.0	82.7 ± 5.9	<0.0001
>=85*,†	1,337 (51.7%)	916 (50.8%)	353 (56.9%)	68 (41.7%)	0.0009
Woman*,†	1,793 (69.3%)	1,287 (71.3%)	397 (64.0%)	109 (66.9%)	0.0028
Body mass index (kg/m^2)	22.2 ± 3.6	22.2 ± 3.7	22.3 ± 3.6	21.7 ± 3.3	0.24
<25*,†	2,067 (79.9%)	1,442 (79.9%)	487 (78.6%)	138 (84.7%)	0.22
Body surface area (m^2)	1.43 ± 0.17	1.43 ± 0.17	1.44 ± 0.18	1.43 ± 0.16	0.45
NYHA class 3/4*,†	1,321 (51.0%)	904 (50.1%)	323 (52.1%)	94 (57.7%)	0.15
Peripheral artery disease*,†	377 (14.6%)	258 (14.3%)	95 (15.3%)	24 (14.7%)	0.82
Prior myocardial infarction†	168 (6.5%)	109 (6.0%)	45 (7.3%)	14 (8.6%)	0.3
Coronary artery disease	954 (36.9%)	652 (36.1%)	252 (40.7%)	50 (30.7%)	0.03
Proximal LAD or LMT lesion†	141 (5.4%)	99 (5.5%)	37 (6.0%)	5 (3.1%)	0.35
Prior cerebrovascular event†	301 (11.6%)	203 (11.3%)	78 (12.6%)	20 (12.3%)	0.65
Prior coronary artery bypass grafting	169 (6.5%)	98 (9.2%)	56 (9.0%)	98 (5.4%)	0.003
Diabetes mellitus	555 (21.5%)	362 (20.1%)	150 (24.2%)	43 (26.4%)	0.03
Insulin therapy*,†	75 (2.9%)	49 (2.7%)	20 (3.2%)	6 (3.7%)	0.67
Hypertension†	1,990 (76.9%)	1,390 (77.0%)	480 (77.4%)	120 (73.6%)	0.58
Chronic atrial fibrillation*,†	248 (9.6%)	160 (8.9%)	73 (11.8%)	15 (9.2%)	0.1
Chronic obstructive pulmonary disease†	385 (14.9%)	268 (14.9%)	91 (14.7%)	26 (16.0%)	0.92
Chronic kidney disease*,†	1,809 (70.0%)	1,239 (68.6%)	443 (71.5%)	127 (77.9%)	0.03
Liver disease*,†	76 (2.9%)	23 (1.3%)	19 (3.1%)	34 (20.9%)	<0.0001
Active cancer*,†	124 (4.8%)	75 (4.2%)	29 (4.7%)	20 (12.3%)	<0.0001
Logistic Euro SCORE (%)	12.8 (8.4−20.9)	12.8 (8.3−20.5)	13.0 (8.5−21.5)	14.4 (8.7−25.2)	0.08
EuroSCORE II (%)	3.7 (2.3−6.0)	3.6 (2.3−5.8)	4.0 (2.5−6.1)	4.4 (2.3−8.4)	0.008
Society of Thoracic Surgeons score (%)	6.6 (4.5−9.5)	6.5 (4.4−9.2)	6.6 (4.6−10.6)	7.3 (4.9−11.9)	0.005
Laboratory data					
Creatinine (mg/dl)	0.91 (0.73−1.18)	0.89 (0.72−1.15)	0.94 (0.74−1.26)	0.98 (0.82−1.35)	<0.0001
Estimated glomerular filtration rate (ml/min)	51.4 ± 19.4	52.3 ± 19.4	50.0 ± 19.1	45.8 ± 19.4	<0.0001
Hemoglobin (g/dl)	11.3 ± 1.7	11.3 ± 1.6	11.3 ± 1.7	10.4 ± 1.6	<0.0001
Anemia (Hemoglobin <11g/dl)†	1,140 (56.0%)	761 (42.2%)	270 (43.6%)	109 (66.9%)	<0.0001
white blood cell count (μL)	5,645 ± 1,941	5,904 ± 1,902	5,190 ± 1,717	4,431 ± 2,375	<0.0001
Echocardiographic data					
Left ventricular ejection fraction (%)	59.2 ± 12.7	59.4 ± 12.6	59.2 ± 12.6	57.6 ± 13.9	0.36
Aortic valve area (cm^2)	0.63 ± 0.17	0.64 ± 0.17	0.62 ± 0.18	0.62 ± 0.17	0.006
Indexed aortic valve area (cm^2/m^2)	0.44 ± 0.12	0.45 ± 0.12	0.43 ± 0.12	0.44 ± 0.12	0.0002
Peak aortic velocity (m/sec)	4.6 ± 0.79	4.5 ± 0.78	4.7 ± 0.79	4.6 ± 0.82	<0.0001
Mean gradient (mmHg)	50.6 ± 18.2	49.7 ± 17.8	53.1 ± 19.0	50.9 ± 19.0	0.0003
Aortic regurgitation ≧ moderate	274 (10.5%)	187 (10.4%)	70 (11.3%)	17 (10.4%)	0.81

LAD=left anterior descending coronary artery, NYHA=New York Heart Association.
Data were shown as n (%), mean±SD, or median (IQR).
Baseline platelet count is measured just before index TAVR procedure.
* 10 variables incorporated into the multivariable analysis as the parsimonious model for major bleeding events.
† 16 variables incorporated into the multivariable analysis as the full-adjusting model.

clinically most relevant risk-adjusting variables listed in Table 1, because of the small number of patients with outcome. All statistical analyses were performed using JMP ver 10.0 software (SAS Institute Inc., Cary, North Carolina). All reported p values were 2 tailed, and p values <0.05 were considered statistically significant.

Results

Baseline characteristics are shown in Table 1. In 2,588 patients in the entire cohort, patients with moderate/severe thrombocytopenia, mild thrombocytopenia, and no thrombocytopenia were 163 (6.3%), 620 (24.0%), and 1,805 (69.7%), respectively (Figure 1). The baseline characteristics significantly differed in the 3 groups. Patients with moderate/severe thrombocytopenia were younger and more often had a history of liver disease or active cancer (Table 1). As regards laboratory data, patients with moderate/severe thrombocytopenia had higher creatinine level and anemia. Regarding procedural characteristics, patients with moderate/severe thrombocytopenia had higher incidences of acute kidney injury and red blood cell transfusion than those with no or mild thrombocytopenia (Supplemental Table 1).

The cumulative 3-year incidence of the primary outcome measure (a composite of life-threatening, disabling bleeding, or major bleeding) increased with the increasing severity of thrombocytopenia (3.6%, 7.3%, and 14.1% in the no, mild, moderate/severe thrombocytopenia groups, respectively; $p < 0.0001$) (Figure 2 and Table 2). After adjusting for confounders, the excess risk of moderate/severe and mild thrombocytopenia relative to no thrombocytopenia for the primary outcome measure remained significant (HR 2.66: [95% CI: 1.35 to 4.88], $p = 0.006$ and HR 2.10: [95% CI: 1.36 to 3.21], $p = 0.001$, respectively, Table 2). No significant differences were found in the cumulative 30-day incidences of the primary outcome measure in the 3 groups (1.8%, 1.5%, and 0.8%, respectively; log-rank $p = 0.25$, Figure 3). Based on the landmark analysis at 30 days, the patients with moderate/severe and mild thrombocytopenia had significantly higher cumulative incidence of the primary outcome measure than those with no thrombocytopenia beyond 30 days ($p < 0.0001$, Figure 3).

The cumulative 3-year incidence of all-cause death also increased with the increasing severity of thrombocytopenia (23.2%, 27.0%, and 49.4% in the no, mild, moderate/severe thrombocytopenia groups, respectively; $p < 0.0001$) (Figure 4A). After adjusting for confounders, the excess mortality risk of moderate/severe thrombocytopenia relative to no thrombocytopenia remained significant (HR 1.79: [95% CI: 1.31 to 2.40], $p = 0.0003$, Table 2), while the mortality risk of mild thrombocytopenia relative to no thrombocytopenia was attenuated (HR 1.24: [95% CI: 1.00 to 1.53], $p = 0.051$, Table 2). After adjusting for confounders, the excess noncardiovascular mortality risk of moderate/severe thrombocytopenia relative to no thrombocytopenia remained significant (HR 1.92: [95% CI: 1.31 to 2.76], $p = 0.001$, Table 2).

Discussion

The key findings of this study were the following: (1) moderate/severe and mild thrombocytopenia at baseline had significantly higher risks for composite late bleeding events (life-threatening, disabling bleeding, or major bleeding) throughout the 3 years after index procedure (TAVI) than no thrombocytopenia. Based on the landmark analysis, no significant difference was found as regards bleeding events within 30 days, although a significant difference was found beyond 30 days. (2) Moderate/severe thrombocytopenia had significantly higher risk for all-cause and noncardiovascular deaths, which tend to be significant especially in noncardiovascular death.

Although thrombocytopenia is a well-known risk factor for bleeding, several bleeding risk criteria did not include thrombocytopenia as a component. [13] However, the definition of high bleeding risk for patients who underwent percutaneous coronary intervention that was recently proposed by the Academic Research Consortium for High Bleeding Risk included moderate or severe thrombocytopenia as a major criteria.[7]

In this study, in-hospital death and procedural bleeding events (a composite of life-threatening, disabling bleeding, or major bleeding) tended to be higher in the thrombocytopenia group (moderate/severe or mild), although no significant difference was found in the 3 groups. Baseline thrombocytopenia could affect in-hospital outcomes, such as post procedural hemorrhage.[14] The difference in the findings between the previous study and our study was likely owing to the smaller patient cohort in this study. Sannino et al. reported that patients with baseline thrombocytopenia (<100,000 cell/ml) who underwent TAVI was associated

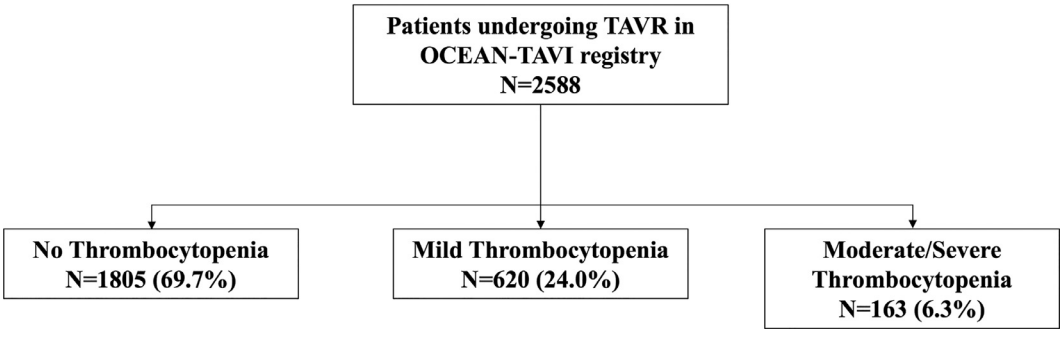


Figure 1. Study flowchart. TAVI = transcatheter aortic valve implantation

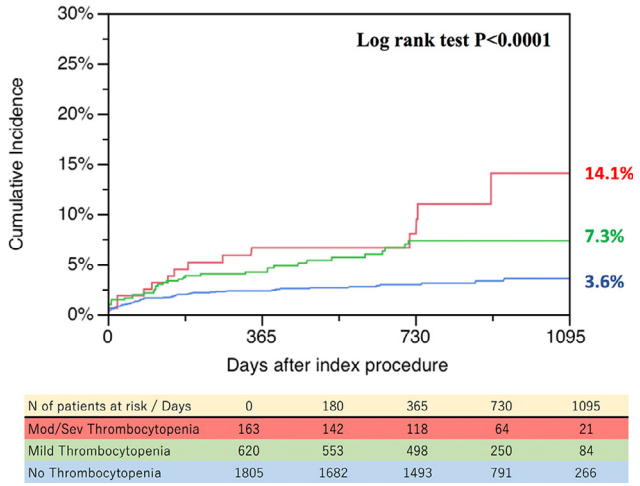


Figure 2. The cumulative incidence of the primary outcome measure (a composite of life-threatening, disabling bleeding, or major bleeding).Mod/Sev = moderate/severe

with worse clinical outcomes, such as 30-day mortality (HR 13.18; 95% CI 4.49 to 38.64; $p < 0.001$) and 1-year mortality (HR 5.90; 95% CI 2.68 to 13.02; $p < 0.001$).[15] Our findings were consistent with these results as regards long-term outcome; however, our findings were not consistent as regards the 30-day mortality.

In this study, patients with thrombocytopenia (moderate/severe and mild) received more red blood cell transfusion. Red blood cell transfusion was reported to be significantly associated with a higher 30-day mortality in patients with acute coronary syndrome.[16] Transfusion increases interleukin-10 (an anti-inflammatory cytokine) concentration and decreases tumor necrosis factor-α (an pro-inflammatory cytokine) concentration. [17] This immunosuppressive effect may predispose to infection.[17] The immunomodulation effect of blood transfusion might be linked to an adverse outcome for the long-term period.

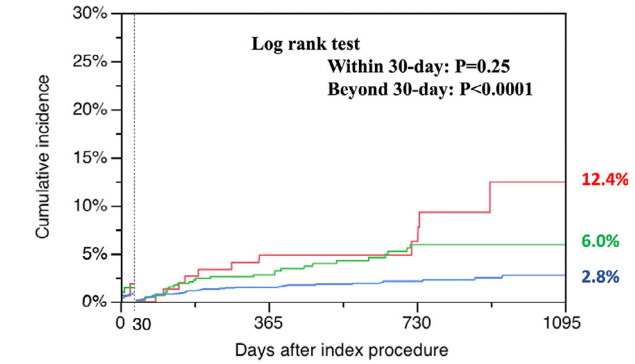
Another study revealed the association of thrombocytopenia with poor outcomes in patients with other cardiovascular diseases.[18,19] This study showed that patients with thrombocytopenia died much more frequently from noncardiovascular diseases. TAVI could be safely performed even in patients with thrombocytopenia; however, the noncardiovascular causes of TAVI were responsible for the majority of later deaths in these patients. Thrombocytopenia itself is not a marker of frailty,[20] but from a broad perspective, it may be an expression of frailty with respect to bone marrow aging.[13] The baseline thrombocytopenia could be a simple surrogate marker of predicting poor outcomes after TAVI.

Atrial fibrillation is generally regarded as a risk factor for mortality, especially cardiovascular mortality.[21] Thrombocytopenia in patients with atrial fibrillation is associated with an increased mortality as well as in patients with other cardiovascular diseases.[22] Thrombocytopenia in patients with atrial fibrillation had a significantly higher bleeding risk even if the severity of thrombocytopenia was mild (platelet count, 100 to 150 $\times$ 10^9/L) and did not have higher ischemic risk.[23] In the current study, the excess risk of atrial fibrillation for composite bleeding was not observed (Supplemental Table 2); however, atrial fibrillation had a

Table 2
Crude and adjusted effects of thrombocytopenia for clinical outcomes

	No thrombocytopenia (n = 1,805)	Mild thrombocytopenia versus no thrombocytopenia (n = 620)				Moderate/severe thrombocytopenia versus no thrombocytopenia (n = 163)			
	Number of patients with event (cumulative 3-year incidence, %)	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Number of patients with event (cumulative 3-year incidence, %)	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Composite bleeding (life-threatening and major)	51 (3.6%)	36 (7.3%)	2.13 (1.39–3.26)	0.0007	2.10 (1.36–3.21)	0.001	14 (14.1%)	3.21 (1.71–5.63)	0.0006	2.66 (1.35–4.88)	0.006
All-cause death	281 (23.2%)	122 (27.0%)	1.32 (1.06–1.62)	0.013	1.24 (1.00–1.53)	0.051	62 (49.4%)	2.63 (1.98–3.44)	<0.0001	1.79 (1.31–2.40)	0.0003
Cardiovascular death	113 (9.4%)	47 (11.5%)	1.26 (0.89–1.75)	0.2	1.20 (0.85–1.68)	0.3	19 (18.7%)	1.99 (1.19–3.16)	0.011	1.58 (0.92–2.57)	0.1
Non-cardiovascular death	168 (15.2%)	75 (17.6%)	1.36 (1.03–1.77)	0.03	1.27 (0.96–1.67)	0.09	43 (37.9%)	3.07 (2.17–4.25)	<0.0001	1.92 (1.30–2.76)	0.001

CI=confidence interval; HR=hazard ratio.

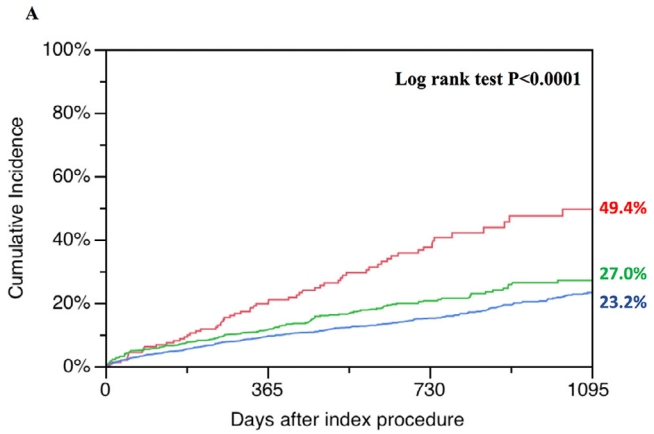


N of patients at risk / Days	0	30	180	365	730	1095
Mod/Sev Thrombocytopenia	163	158	142	118	64	21
Mild Thrombocytopenia	620	595	553	498	250	84
No Thrombocytopenia	1805	1766	1682	1493	791	266

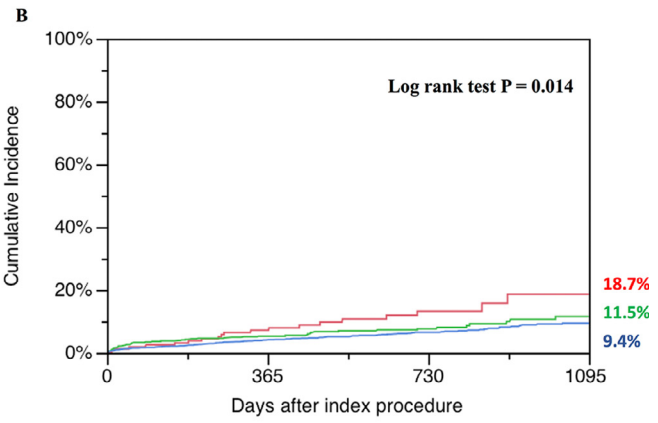
Figure 3. The cumulative incidence of the primary outcome measure within and beyond 30 days. Mod/Sev=moderate/severe

significantly higher risk for all-cause death regardless of the type of atrial fibrillation. The reason for the result of association between atrial fibrillation and composite bleeding in this study was unclear. Bleeding risk factors, such as low creatinine clearance, bleeding history, and low body weight, should be taken into account when considering antithrombotic therapy after TAVI in patients with thrombocytopenia and atrial fibrillation.

The optimal antithrombotic therapy after TAVI is still under debate.[24] Current guidelines recommend the use of oral anticoagulation only for patients with transcatheter implanted bioprosthesis who have other indications for anticoagulation.[25,26] The result of the POPular TAVI trial (Cohort B) support the recommendation. In patients who underwent TAVI who were receiving oral anticoagulation, oral anticoagulation alone was better than oral anticoagulation plus clopidogrel in terms of serious bleeding. [27] According to the result of the POPular TAVI trial (Cohort A), the recommendation of antithrombotic therapy after TAVI for patients without an established indication for anticoagulation therapy should receive aspirin alone.[28] In this study, patients with baseline thrombocytopenia (particularly moderate/severe thrombocytopenia) had a higher risk for late bleeding events. In patients with thrombocytopenia, selecting the



N of patients at risk / Days	0	180	365	730	1095
Mod/Sev Thrombocytopenia	163	148	124	66	21
Mild Thrombocytopenia	620	570	514	261	90
No Thrombocytopenia	1805	1706	1513	805	270



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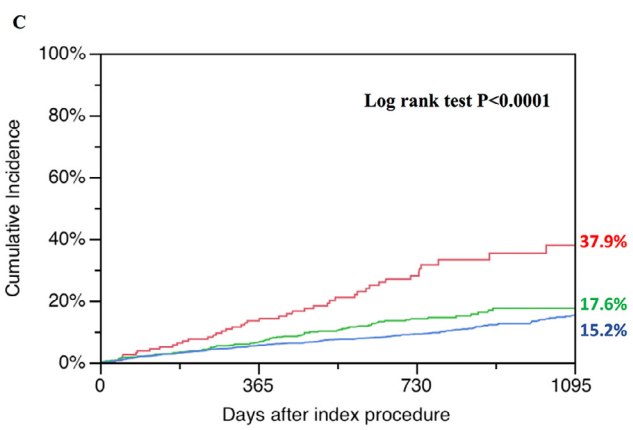

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Figure 4. The cumulative incidence of all-cause death (A), cardiovascular death (B), and non-cardiovascular death (C). Mod/Sev = moderate/severe

antithrombotic therapy and its intensity should be appropriately adjusted. In other words, patients who have other indications for anticoagulation should receive anticoagulation only, and patients without an established indication for anticoagulation therapy should receive aspirin only in terms of optimizing the risk for late bleeding.

This study has several limitations. First, the OCEAN registry is not a randomized study; thus, the baseline clinical characteristics have several differences. Second, the serial change of platelet count is also significant; in other words, the acquired thrombocytopenia after TAVI is a typical phenomenon, although this study only focused on the baseline platelet count. Third, the causes of thrombocytopenia were not evaluated. Fourth, parsimonious and full-adjusting models were constructed for multivariable adjustment. However, the number of late bleeding events in this study was small; therefore, the baseline oral medication was not included as a covariate. Fifth, in this study, the red blood cell transfusion was recorded, whereasplatelet transfusion was not recorded. In conclusion, patients with both moderate/severe thrombocytopenia at baseline had higher risks for bleeding events and mortality.

Authors contribution

Shinya Ito: Conceptualization, Writing - Original Draft.
Tomohiko Taniguchi: Writing – Review & Editing.
Shinichi Shirai: Supervision.
Kenji Ando: Supervision.
Yusuke Watanabe: Investigation.
Masanori Yamamoto: Writing-Review & Editing, Investigation, Project administration.
Toru Naganuma: Investigation.
Kensuke Takagi: Investigation.
Masahiro Yamawaki: Investigation.
Norio Tada: Investigation.
Futoshi Yamanaka: Investigation.
Minoru Tabata: Investigation.
Hiroshi Ueno: Investigation.
Fumiaki Yashima: Investigation.
Kentaro Hayashida: Investigation, Project administration.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.017.

1. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrman HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown D, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–1620.
2. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubow SJ, Grube E, Makkar R, Conte LJ, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PWJC, Kappetein AP. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321–1331.
3. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–1705.
4. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zone GL 3rd, Forrest JK, Tcheche D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706–1715.
5. Biino G, Santimone I, Minelli C, Sorice R, Frongia B, Traglia M, Ulivi S, Castelnuovo AD, Gögele M, Nutile T, Francavilla M, Sala C, Pirastu N, Cerletti C, Iacoviello L, Gasparini P, Toniolo D, Ciullo M, Pramstaller P, Pirastu M, Gaetano G, Balduini CL. Age- and sex-related variations in platelet count in Italy: a proposal of reference ranges based on 40987 subjects' data. *PLoS One* 2013;8:e54289.
6. Ayoub K, Marji M, Ogunbayo G, Masri A, Abdel-Latif A, Ziada K, Vallurupalli S. Impact of chronic thrombocytopenia on in-hospital outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2018;11:1862–1868.
7. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson M, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee A, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation* 2019;140:240–261.
8. Yamamoto M, Shimura T, Kano S, Kagase A, Kodama A, Koyama Y, Watanabe Y, Tada N, Takagi K, Araki M, Shirai S, Hayashida K. Impact of preparatory coronary protection in patients at high anatomical risk of acute coronary obstruction during transcatheter aortic valve implantation. *Int J Cardiol* 2016;217:58–63.
9. Watanabe Y, Kozuma K, Hioki H, Kawashima H, Nara Y, Kataoka A, Shirai S, Tada N, Araki M, Takagi K, Ymanaka F, Yamamoto M, Hayashida K. Comparison of results of transcatheter aortic valve implantation in patients with versus without active cancer. *Am J Cardiol* 2016;118:572–577.
10. Watanabe Y, Kozuma K, Hioki H, Kawashima H, Nara Y, Kataoka A, Shirai S, Tada N, Araki M, Takagi K, Yamanaka F, Yamamoto M, Hayashida K. Comparison of results of transcatheter aortic valve implantation in patients with versus without cctive cancer. *Am J Cardiol* 2016;118:572–577.
11. McCarthy CP, Steg G, Bhatt DL. The management of antiplatelet therapy in acute coronary syndrome patients with thrombocytopenia: a clinical conundrum. *Eur Heart J* 2017;38:3488–3492.
12. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane Aj, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. *J Thorac Cardiovasc Surg* 2013;145:6–23.

13. Valgimigli M, Costa F. Chronic thrombocytopenia and percutaneous coronary intervention: the virtue of prudence. *JACC Cardiovasc Interv* 2018;11:1869–1871.
14. Fugar S, Behnamfar O, Okoh AK, Alabre AF, Salia S, Kosinski M, Mahmood A, Jolly N, Doukky R, Kavinsky CJ. Impact of chronic thrombocytopenia on in-hospital outcomes and healthcare resource utilization after transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2019;96:1–9.
15. Anna S, Robert CS, Hebeler RF Jr, Szerlip M, Mack MJ, Grayburn PA. Clinical relevance of baseline TCP in transcatheter aortic valve replacement. *J Invasive Cardiol* 2017;29:353–358.
16. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;292:1555–1562.
17. Twomley KM, Rao SV, Becker RC. Proinflammatory, immunomodulating, and prothrombotic properties of anemia and red blood cell transfusions. *J Thromb Thrombolysis* 2006;21:167–174.
18. Ito S, Watanabe H, Morimoto T, Yoshikawa Y, Shiomi H, Shizuta S, Ono K, Yamaji K, Soga Y, Hyodo M, Shirai S, Ando K, Horiuchi H, Kimura T. Impact of baseline thrombocytopenia on bleeding and mortality after percutaneous coronary intervention. *Am J Cardiol* 2018;121:1304–1314.
19. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, Oi M, Akao M, Kobayashi Y, Toyofuku M, Izumi T, Tada T, Chen PM, Murata K, Tsuyuki Y, Saga S, Sasa T, Sakamoto J, Kinoshita M, Togi K, Mabuchi H, Takabayashi K, Watanabe H, Shiomi H, Kato T, Makiyama T, Ono K, Kimura T. Influence of baseline platelet count on outcomes in patients with venous thromboembolism (from the COMMAND VTE Registry). *Am J Cardiol* 2018;122:2131–2141.
20. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;63:747–762.
21. Gomez-Outes A, Lagunar-Ruiz J, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2016;68:2508–2521.
22. Pastori D, Antonucci E, Violi F, Palareti G, Pignatelli P. Thrombocytopenia and mortality risk in patients with atrial fibrillation: an analysis from the START registry. *J Am Heart Assoc* 2019;8:e012596.
23. Park J, Cha MJ, Choi YJ, Lee E, Moon I, Kwak S, Kwon S, Yang S, Lee S, Choi E, Oh S. Prognostic efficacy of platelet count in patients with nonvalvular atrial fibrillation. *Heart Rhythm* 2019;16:197–203.
24. Dangas GD, Tijssen JGP, Wöhrle J, Sondergaard L, Gilard M, Möllmann H, Makker RR, herrmann HC, Giustino G, Baldus S, De Backer O, Guimaraes AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schäfer U, Seeger J, Tchetche D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;382:120–129.
25. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e1159–e1e95.
26. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, lung B, Lancellotti P, Lansac E, Munoz DR, Rosenhek R, Sjögren J, Mas PT, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.
27. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Tousek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, ten Berg JM. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;382:1696–1707.
28. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Tousek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, ten Berg JM. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *New Engl J Med* 2020;383:1447–1457.