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Peri-procedural thrombocytopenia after aortic bioprosthesis implant: A systematic review and meta-analysis comparison among conventional, stentless, rapid-deployment, and transcatheter valves☆

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ABSTRACT

Background: Thrombocytopenia has been shown to occur soon after surgical biological aortic valve replacement (AVR), and recently reported also after transcatheter valve implantation (TAVI). The mechanism underlying this phenomenon is still unknown, and its clinical impact on the peri-operative outcome has been poorly investigated.
Methods: A systematic review and a meta-analysis of all available studies reporting data about peri-procedural thrombocytopenia on isolated bio-AVR, comparing rapid-deployment (RDV), stentless (stentless-AVR), and TAVI vs. stented (stented-AVR) valves, have been performed.
Results: Fifteen trials (2.163 patients) were included in the meta-analysis. Perioperative platelet reduction ranged from 35% to 55% in stented-AVR, from 60% to 77% in stentless-AVR, from 53% to 60% in RDV, and from to 21% to 72% in TAVI (apparently, balloon-expandable valves more frequently associated to thrombocytopenia). Stented-AVR required more red blood cells transfusion than stentless-AVR ($P < 0.0001$), whereas no difference has been found between RDV and stented-AVR. Platelet transfusion rate was very low in all surgical groups. No difference has been found in RDV and stentless-AVR vs. stented-AVR, in terms of reoperation for bleeding, and length-of-intensive care unit or hospital stay.
Conclusions: Thrombocytopenia-related major adverse events were mainly reported in TAVI patients, whereas clinically meaningless in surgical patients. Transient peri-procedural thrombocytopenia is common after bio-AVR, regardless of prosthesis's type or implant modality. It should receive appropriate monitoring and focused investigations.

1. Introduction

Cardiopulmonary bypass (CPB) has always been considered as the primary cause of perioperative thrombocytopenia (TCP) after cardiac surgery [1,2]. Recently, TCP has been specifically reported after biological aortic valve replacement (AVR) [3,4]. Changes in platelet metabolic biochemistry, shape, as well as receptor-mediated dysfunction and lysis, have been claimed to occur after blood contact with aortic bioprosthesis surfaces [5]. Notwithstanding, TCP has been associated especially with several types of aortic bioprostheses, namely stentless and rapid deployment (RDV) [3–7]. A wide range of perioperative TCP, ranging from small and clinically uneventful platelet count (PC) decrease to significant and clinically relevant TCP, has been shown after RDV implantation [3,4]. However, the phenomenon seems to not be confined only to surgically implanted valves. Indeed, recent studies reported transient perioperative TCP also in patients undergoing trans-catheter

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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aortic valve implantation (TAVI) [8–11]. Furthermore, peri-procedural TCP has been associated with in-hospital adverse events [8]. Acute kidney injury (AKI), major bleeding, vascular complications, need for blood transfusion, and longer intensive care unit (ICU) or in-hospital (IH) length-of-stay (LoS), were found to be associated with post-TAVI TCP [12–14]. However, controversial are the results concerning actual differences in TCP among the several bioprostheses, as well as in relation to peri-procedural, 30-day, and 1-year mortality, and conclusive explanation of this phenomenon has not yet been reported [9,14,15]. Therefore, a systematic review and meta-analysis have been performed to carefully analyze clinically available data and potential insights about this issue, as well as to clarify the potential clinical impact of peri-procedural TCP. The rate and extent of in-hospital TCP and its related outcomes, in relation to the implant of currently available tissue valve type as well as implant modalities, were investigated and will be presented.

2. Methods

Systematic review and meta-analysis were performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines. Complete details, including electronic search strategy, objectives, criteria for study selection, eligibility, data collection, and assessment of study quality, were registered and published online in PROSPERO International prospective register of systematic reviews (CRD42018106752) on August 31st, 2018 (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018106752).

2.1. Information sources and literature search

Eligible studies were identified by consulting the Cochrane Central Register of Controlled Trials (CENTRAL; Internet), MEDLINE, EMBASE, without date or language restriction. Keywords and MeSH terms pertinent to the exposure of interest were used in relevant combinations: “sutureless aortic prosthesis”, “thrombocytopenia”, “Perceval”, “Intuity”, “Enable”, “rapid deployment valve”, “TAVI”, “stentless aortic prosthesis”. The last search was run on August 15th, 2018. In addition to searching databases, we searched in trial registries and reference lists were carefully analyzed for pertinent studies.

2.2. Studies selection

Randomized controlled trials (RCTs), or prospective as well as retrospective observational cohort studies, were included in our analysis if they were comparing the peri-operative outcomes of patients undergoing isolated AVR with a stented bioprosthesis (*stented-AVR*) versus those of patients receiving a stentless (*stentless-AVR*), a rapid deployment (*RDV-AVR*), or a trans-catheter tissue valve (*TAVI*). The so-called “Sutureless” valves were included in the RDV-AVR group. All the available tissue valves mentioned in the literature were included in the analysis (see Supplemental data for details). Studies were not included in the analysis if they met one of the following exclusion criteria: (i) reviews, letters, case reports, animal experiments, and conference abstracts; (ii) incomplete information; (iii) studies in which outcomes were expressed as continuous variable. Inclusion and exclusion criteria for qualitative/quantitative analyses were summarized according to the PICOS (population, intervention, comparator, outcomes, and study design) approach (Supplemental data).

2.3. Data extraction

Two investigators (F.J., G.F.S.) independently screened titles and abstracts. A third investigator (R.L.) helped to solve any disagreement. After excluding non-relevant studies, full texts of potentially relevant articles were then screened for inclusion in the final analysis. Supplementary documents of published studies were also assessed, if available. A standardized form was used to extract data from included studies for assessment of study quality and evidence synthesis. Extracted information included: year of publication, study design, sample size, number of patients in each group, surgery details, baseline patient comorbidities and outcomes [post-operative PC, need of transfusions (red blood cells (RBCs), Platelet), re-explorations for bleeding, post-operative blood loos, ICULoS, IHLoS].

2.4. Endpoints and definitions

The primary endpoint was peri-procedural (up to hospital discharge) PC. TCP was defined as a PC $< 100 \times 10^3$/uL (severe TCP: PC $< 50 \times 10^3$/uL) [16]. Secondary end-points were RBCs and platelet transfusion, drainage blood loss 24 h after surgery, re-operation or revision for bleeding, and ICULoS as well as IHLoS.

2.5. Data analysis and risk of bias assessment

Meta-analysis was performed in accordance with recommendations of the Cochrane Handbook for Systematic Reviews of Intervention [17]. OpenMeta-Analyst software and Review Manager (RevMan), Version 5.2, for Macintosh were used to perform an intention-to-treat analysis where sufficient data were available. For dichotomous data presented only as percentages, we estimated frequencies using reported sample sizes for this outcome. For continuous outcomes, if mean and Standard Deviation (SD) were not available from the trial report, we calculated them from median (interquartile range) using the software available in RevMan [17]. Major sources of clinical heterogeneity would be associated with different patient groups. Heterogeneity within each meta-analysis using a X^2 test with significance set at a $P < 0.10$ was explored. We expressed the percentage of heterogeneity attributable to variation rather than to chance as I^2 [18]. We defined heterogeneity as follows: $I^2 = 0–40\%$, no or mild heterogeneity; $I^2 = 40–80\%$, moderate heterogeneity; and $I^2 > 80\%$, severe heterogeneity.

Quality was assessed using the Cochrane Collaboration's tool for assessing risk of bias for RCT. For not-RCT, quality was evaluated using the Newcastle-Ottawa Scale. Pooled effect estimates were expressed as risk ratios with 95% confidence interval (CI). For continuous outcomes, we pooled mean differences or standardized mean differences with 95% CI by using the inverse variance method. In order to be as conservative as possible, the random-effect method was used to take into account the variability among included studies.

Subgroup analyses were performed comparing different bio-prosthesis types and implant modality (RDV-AVR vs. stented-AVR; stentless-AVR vs. stented-AVR, TAVI vs. stented-AVR, and subgroup analysis) when there were no missing data. Review Manager was used to assess subgroup differences, with $P < 0.05$ considered statistically significant.

The main results of the review are synthetized in a ‘summary of findings' table (Supplemental Table 6). We included the following outcomes: peri-procedural PC (at 2nd post-operative day (POD)), RBCs and platelet transfusions, peri-procedural drainage blood loss for the surgical groups, re-exploration for bleeding, ICULoS, and IHLoS.

3. Results

3.1. Study selection

The PRISMA flow diagram, describing the study selection process along with the reasons for exclusion, is presented in the Supplemental material. After removal of reports not pertinent to the meta-analysis design, 15 studies were finally included in the data assessment [3,6,19–31]. Key characteristics of individual studies and enrolled patients are described in Supplemental data.

Twenty-seven trials that met our inclusion criteria were excluded after review of the full manuscript (Supplemental data).

3.2. Study characteristics

A total of 2.163 patients were available from 15 studies published until August 2018. A propensity matching was performed in six retrospective single-center studies and in one retrospective multicenter trial [6,21,22,24,27,28]. One prospective RCT was included in the analysis [24]. The most frequent implanted prostheses were stented tissue valves (1.142 patients), whereas 813 patients received RDV-AVR. A stentless prosthesis was implanted in 489 patients. A meta-analysis comparing stented-AVR vs. RDV-AVR and stented-AVR vs. stentless-AVR was performed. No paper comparing TAVI and stented-AVR fulfilled the inclusion/exclusion criteria (Supplemental data). A systematic review of all the studies addressing TAVI and related post-procedural TCP was carried out and used for this investigation (Supplemental Table 7) [8–15,33–38]. Quality assessment for observational studies identified no studies being of low quality defined as scoring maximal points in all 3 domains of the Newcastle-Ottawa score (Supplemental data). The RCTs were classified as at high risk of bias. The individual bias domains are presented in the risk of bias Supplemental material. There was a high risk of allocation bias.

3.3. Synthesis of results

The extent of TCP varied greatly in the different groups (Fig. 1).

3.3.1. Surgical group

Two trials comparing stented-AVR vs. RDV-AVR reported peri-procedural PC [3,20]. Although no meta-analysis could be performed because of missing and limited data, the incidence of post-operative TCP was significantly higher in the RDV-AVR group, compared to

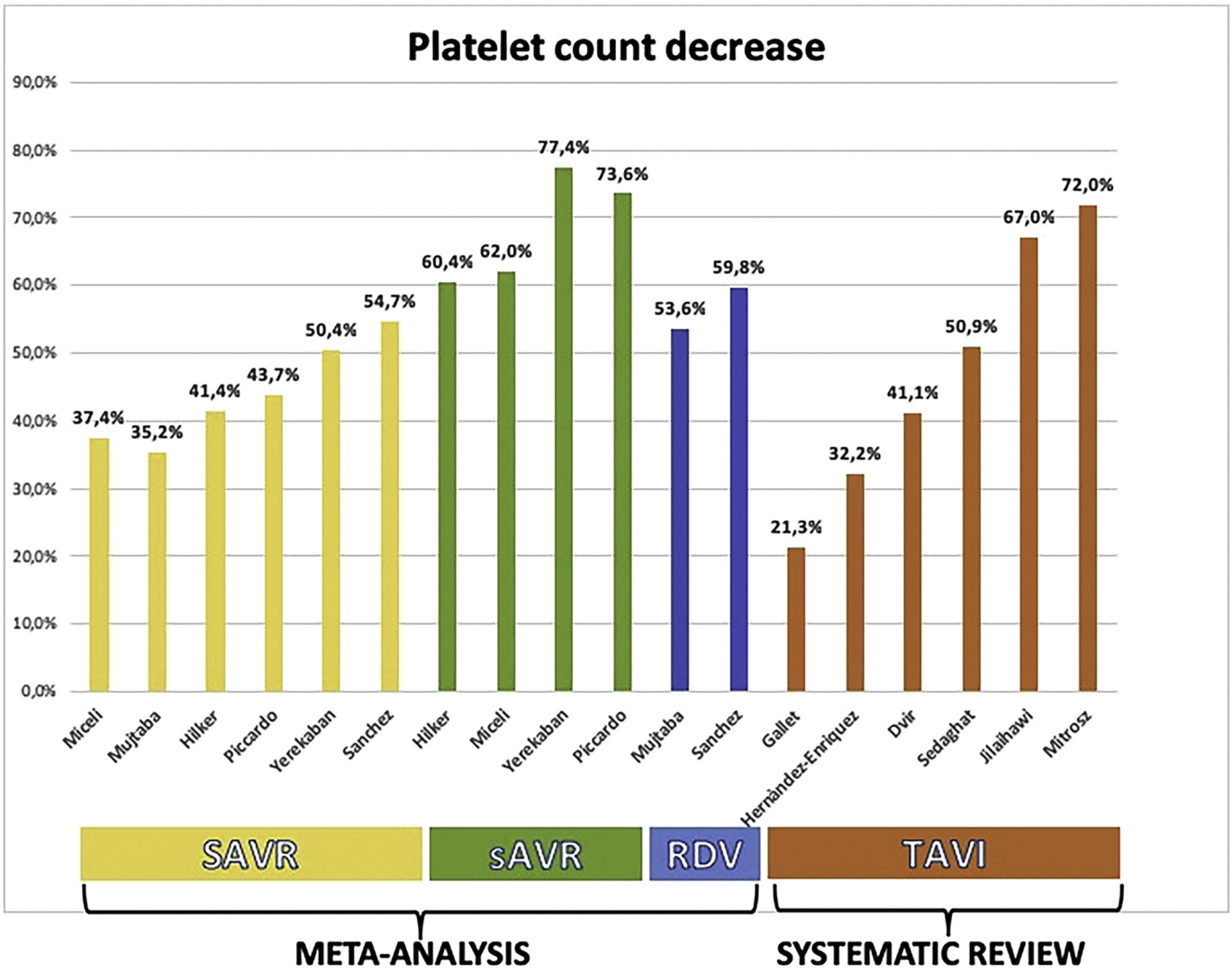


Fig. 1. Platelet count decrease in stented, stentless, rapid deployment and trans-catheter valve implantation.

stented-AVR group [3,20]. Four studies comparing stented vs. stentless tissue valves, moreover, evaluated the post-operative PC showing a higher rate of TCP in the stentless-AVR group ($p < 0.00001$, Fig. 2) [6,19,21,25]. A few studies addressed the TCP issue within the same valve-type group. For instance, a higher TCP rate has been shown in sutureless valves within the RDV group. No further investigation is available for the other valve types in stented-AVR. Based on the paucity of information in this respect, therefore, no conclusive evaluation nor comment could be reported whether any specific stented valve was at higher risk for perioperative TCP and related complications.

The need of platelet transfusion was reported only in two trials [20,26]. Konertz and colleagues reported no difference among groups (RDV-AVR, stented-AVR, or stentless-AVR) [26]. Conversely, Mujtaba and co-workers observed that the RDV-AVR group needed more platelet transfusions [20].

RBCs transfusion rates were reported in three studies comparing RDV and conventional stented bio-prostheses [3,26,28]. Stented-AVR patients showed a higher rate (30%) of RBCs transfusion than RDV-AVR subjects (20%); however, this was not statistically significant (Fig. 2). Three studies evaluated RBCs transfusion need and showed a higher rate in stented-AVR vs. stentless-AVR ($P < 0.0001$; Fig. 2) [6,26,27].

Only three trials, out the 15 evaluated, comparing RDV-AVR vs. stented-AVR, provided data concerning perioperative blood loss [3,20,31]. A significantly higher rate of peri-operative bleeding after stented-AVR was observed in two papers.

Seven trials assessing RDV-AVR vs. stented-AVR reported the number of patients who required reoperation for bleeding [3,20,22,24,26,29,31]. The analysis showed that this outcome was not associated with the type of tissue valve implanted (Fig. 2). Similarly, among four studies reporting a comparison between stentless and stented tissue valves, no difference was found between the groups in terms of need of surgical re-explorations for major bleeding (Fig. 2) [6,19,23,26].

The ICULoS has been reported in four trials assessing RDV-AVR vs. stented-AVR. Although not statistically significant, the outcome was favorable for subjects submitted to RDV-AVR (Fig. 3) [3,24,29,31]. The ICULoS was described in only two studies comparing stentless-AVR and stented-AVR [26,27]. Both trials showed a longer ICULoS for the patients with a stentless-AVR vs. stented-AVR [26,27].

No difference was found in both comparisons (RDV-AVR vs. stented-AVR, stentless-AVR vs. stented-AVR) concerning the IHLoS (Fig. 3) [4,23,24,26–30].

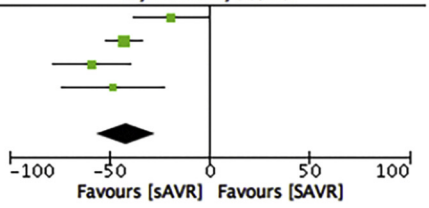
3.3.2. *Trans-catheter valve implantation (TAVI) group*

Fourteen trials reported TCP or a trend of reduced peri-procedural PC after TAVI, ranging from 25% to 100% (Fig. 1, Supplemental Table 7) [8–15,33–38]. The I^2 test result showed severe heterogeneity. Using

A. Post-operative platelet count

Study or Subgroup	sAVR Mean	sAVR SD	sAVR Total	SAVR Mean	SAVR SD	SAVR Total	Weight	Mean Difference IV, Random, 95% CI
Hilker 2008	105	46	41	124	40.7	37	23.6%	-19.00 [-38.24, 0.24]
Miceli 2011	79.7	36.3	116	122.5	43.3	206	34.7%	-42.80 [-51.67, -33.93]
Piccardo 2010	64	34	36	123	48	36	23.6%	-59.00 [-78.21, -39.79]
Yerekaban 2008	74.6	40.6	20	122.9	41.4	20	18.1%	-48.30 [-73.71, -22.89]
Total (95% CI)			**213**			**299**	**100.0%**	**-42.01 [-56.69, -27.32]**

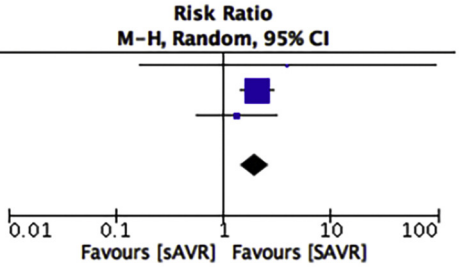
Heterogeneity: Tau² = 141.58; Chi² = 8.76, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 5.61 (P < 0.00001)



B. RBCs transfusion

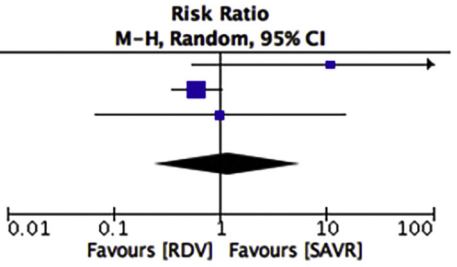
Study or Subgroup	sAVR Events	sAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Konertz 2017	1	27	0	36	1.0%	3.96 [0.17, 93.70]
Schaefer 2018	54	77	26	77	85.2%	2.08 [1.47, 2.93]
Yerekaban 2008	8	20	6	20	13.8%	1.33 [0.57, 3.14]
Total (95% CI)		**124**		**133**	**100.0%**	**1.97 [1.43, 2.70]**
Total events	63		32			

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 4.16 (P < 0.0001)



Study or Subgroup	RDV Events	RDV Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Konertz 2017	2	16	0	36	19.3%	10.88 [0.55, 214.58]
Sanchez 2015	10	27	31	50	58.8%	0.60 [0.35, 1.02]
Shalabi 2016	1	22	1	22	21.9%	1.00 [0.07, 15.00]
Total (95% CI)		**65**		**108**	**100.0%**	**1.17 [0.24, 5.63]**
Total events	13		32			

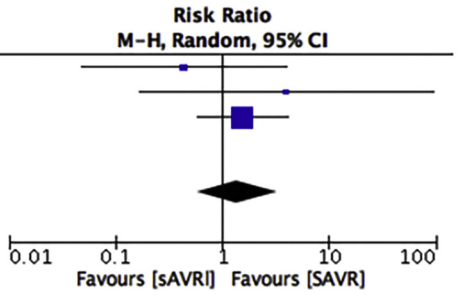
Heterogeneity: Tau² = 1.02; Chi² = 3.85, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 0.20 (P = 0.84)



C. Reoperation for bleeding

Study or Subgroup	sAVR Events	sAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Fouquet 2017	1	27	3	35	15.5%	0.43 [0.05, 3.93]
Konertz 2017	1	27	0	36	7.5%	3.96 [0.17, 93.70]
Miceli 2011	7	116	8	206	77.0%	1.55 [0.58, 4.18]
Yerekaban 2008	0	20	0	20		Not estimable
Total (95% CI)		**190**		**297**	**100.0%**	**1.37 [0.57, 3.26]**
Total events	9		11			

Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)



Study or Subgroup	RDV Events	RDV Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Dalèn 2015	7	171	11	171	39.0%	0.64 [0.25, 1.60]
Gilmanov 2014	9	133	5	133	29.2%	1.80 [0.62, 5.23]
Konertz 2017	1	16	0	36	3.4%	6.53 [0.28, 152.17]
Mujtaba 2018	2	72	2	100	8.9%	1.39 [0.20, 9.63]
Sanchez 2015	0	27	3	50	3.9%	0.26 [0.01, 4.86]
Shrestha 2013	2	50	2	70	9.0%	1.40 [0.20, 9.61]
Vola 2015	1	41	3	42	6.7%	0.34 [0.04, 3.15]
Total (95% CI)		**510**		**602**	**100.0%**	**0.99 [0.56, 1.77]**
Total events	22		26			

Heterogeneity: Tau² = 0.00; Chi² = 5.40, df = 6 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

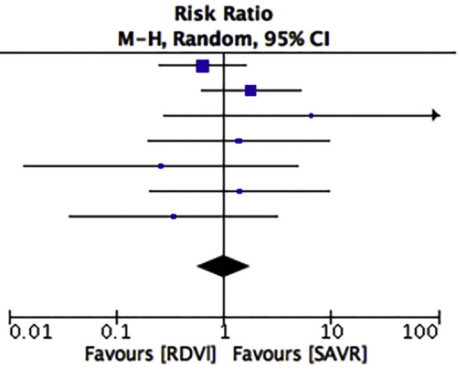


Fig. 2. Forrest plots showing pooled effect estimated from random-effects models comparing stentless vs. stented aortic tissue valves and rapid deployment vs. stented tissue valves for post-operative platelet count (A), red blood cell transfusion (B), and reoperation for bleeding (C).

the random effect analysis, the pooled prevalence of TCP in patients with TAVI was 55.1% (95% CI = 28.1–82.1), Fig. 4.A. Six studied reported TCP after a self-expandable tissue valves (SEV) implantation [10,12,15,36–38]. Three studied reported TCP after a balloon-expandable (BEV) implantation [8,33,34]. TCP was reported in five papers including patients receiving SEV and BEV [9,11,13,14,35].

TAVI patients enrolled in the reviewed studies received RBCs and platelet transfusions ranging from 18.7% to 42%, and from 6.2% to 12%, respectively. Although TCP after TAVI (37%) was not significantly related to major bleeding or stroke, it was independently associated with in-hospital mortality ($p = 0.002$) [15]. The higher rate of major bleeding was 16.4% (72.2% of the patients with TCP needed transfusions [13].

A sub-group analysis of the studies included in the present systematic review revealed that BEV patients experienced a higher rate of post-procedural TCP (Fig. 4.B). Furthermore, TCP after TAVI was associated with a high rate of major and life-threatening bleeding, major vascular complications, in-hospital sepsis, AKI, prolonged ICULoS, and 30-day as well as 1-year mortality [8,9,12–15,35–37].

4. Discussion

The current meta-analysis and systematic review showed that transient peri-procedural TCP is common after bio-prosthetic implant at aortic position, regardless of the type or the implant modality. Stentless-AVR is apparently associated with a higher rate of post-operative TCP. However, it seems not associated with more complicated post-operative outcomes, except for RBCs transfusions, when compared to stented-AVR. TCP-related major clinical events, like blood transfusion, major bleeding, vascular complications, and long ICULoS, have been instead reported mostly after TAVI.

Platelets play a major role in hemostasis and are involved in inflammatory and thromboembolic mechanisms [39]. They can be activated in various circumstances, such as blood exposure to foreign/altered surfaces or by shear stress [39]. Declines in PC, diagnosed as TCP, are a common and usually transient event after cardiac surgery with CPB [1]. Currently, the underlying mechanisms for TCP's occurrence are controversial, even if the most likely cause is an increased platelet turnover and destruction secondary to aberrant activation [1,39,40]. Although several studies impute post-operative TCP to a heparin-induced mechanism (HIT), its occurrence is rare after cardiac surgery (1% to 3%) [2,41].

Unusual extent of post-operative TCP has recently been reported after AVR [40]. Platelet activation, aggregation, and generation of procoagulant microparticles, and shear stress-induced von Willebrand factor (vWF) secondary to blood flow through the artificial valve have been claimed as causative factors for peri-procedural TCP [42–44]. Blood can become hypercoagulable by shear-induced platelet activation and generation of microparticles [44]. However, non-physiological shear stress could induce shedding of platelet receptor and loss of high-molecular-weight-multimers of vWF, which may result, paradoxically, in contribution to bleeding complications [44]. The effect of this phenomenon, however, could vary according to the type, the profile, and the hemodynamic performance of the implanted prosthesis [43]. Moreover, Repossini and colleagues, indeed, reported that patients with no preoperative TCP and larger implanted bio-prosthesis sizes have a decreased risk for postoperative TCP [45]. In 2006, Le Guyader and colleagues analyzed platelet activation after AVR with two kinds of mechanical valves and three types of bioprostheses [43]. At the 8th POD,

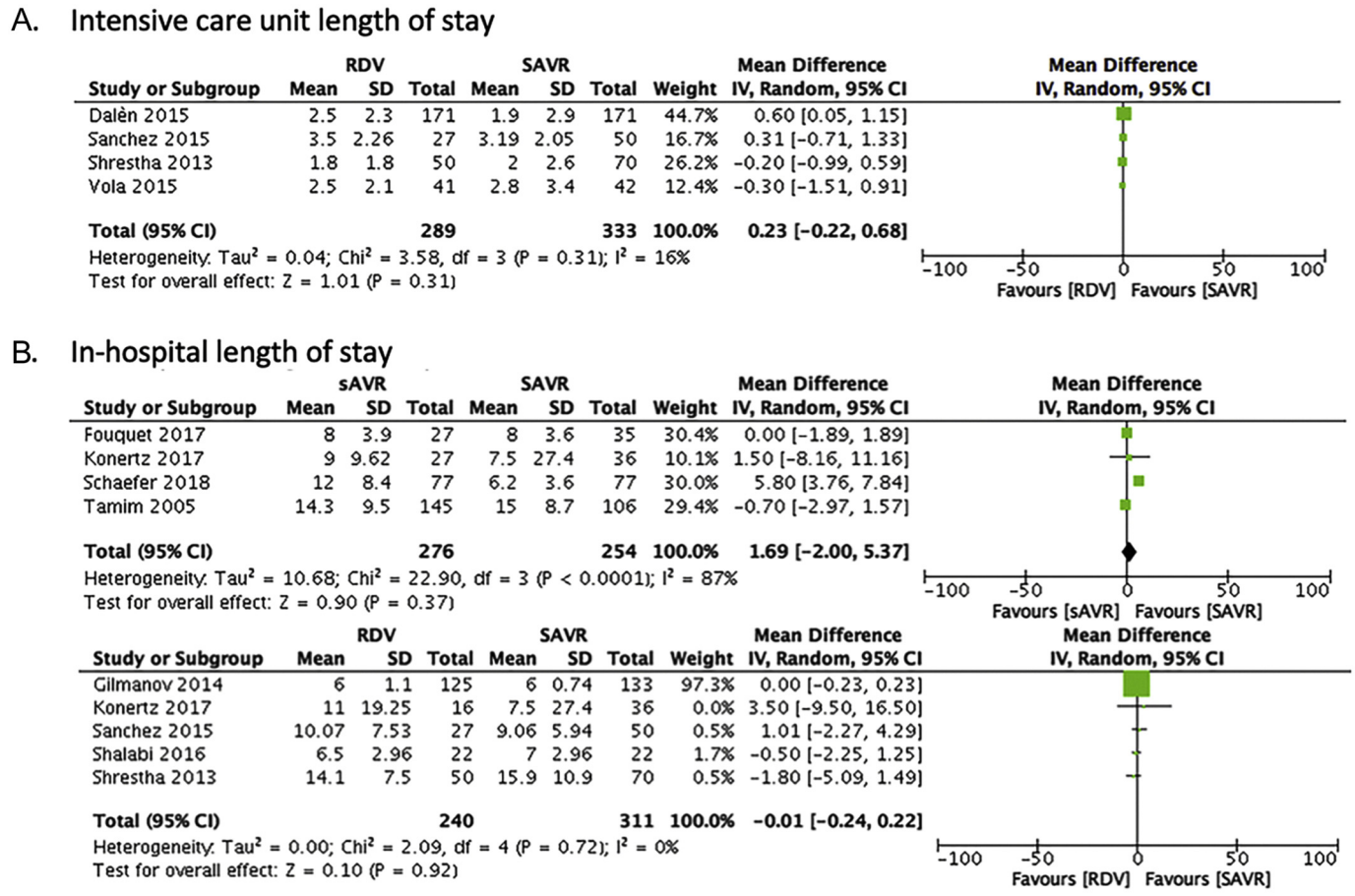
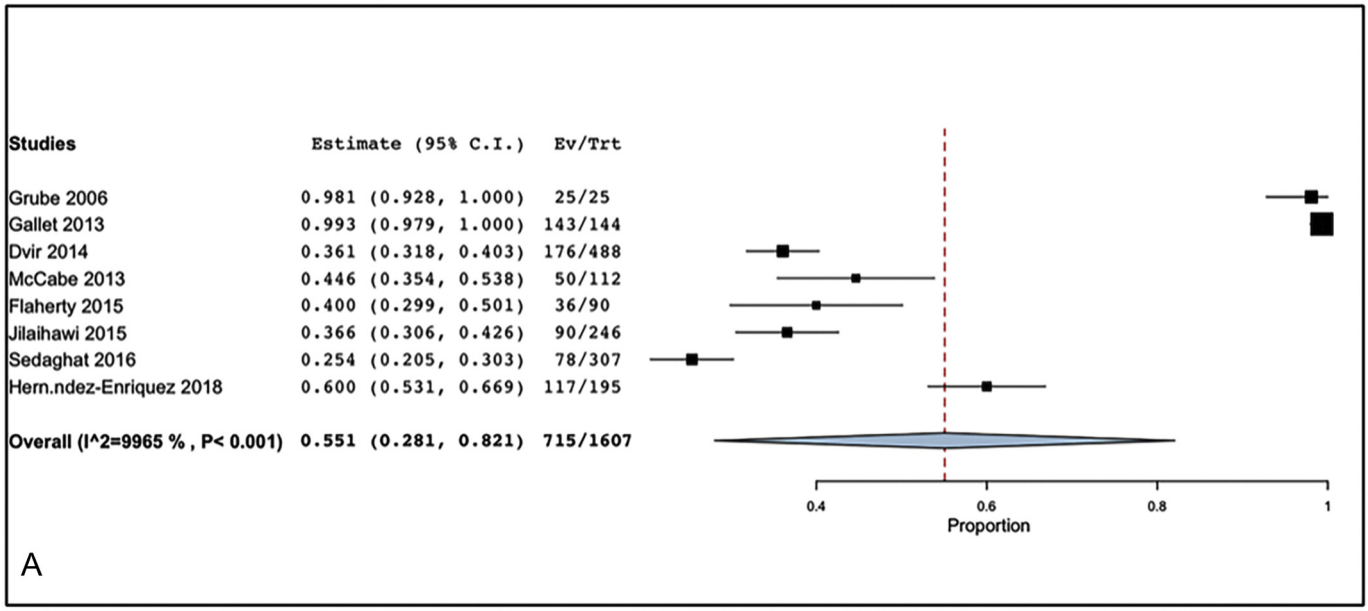


Fig. 3. Forrest plots showing pooled effect estimated from random-effects models comparing stentless vs. stented aortic tissue valves and rapid deployment vs. stented tissue valves for, Intensive Care Unit (A) and in-hospital (B) length-of-stay.



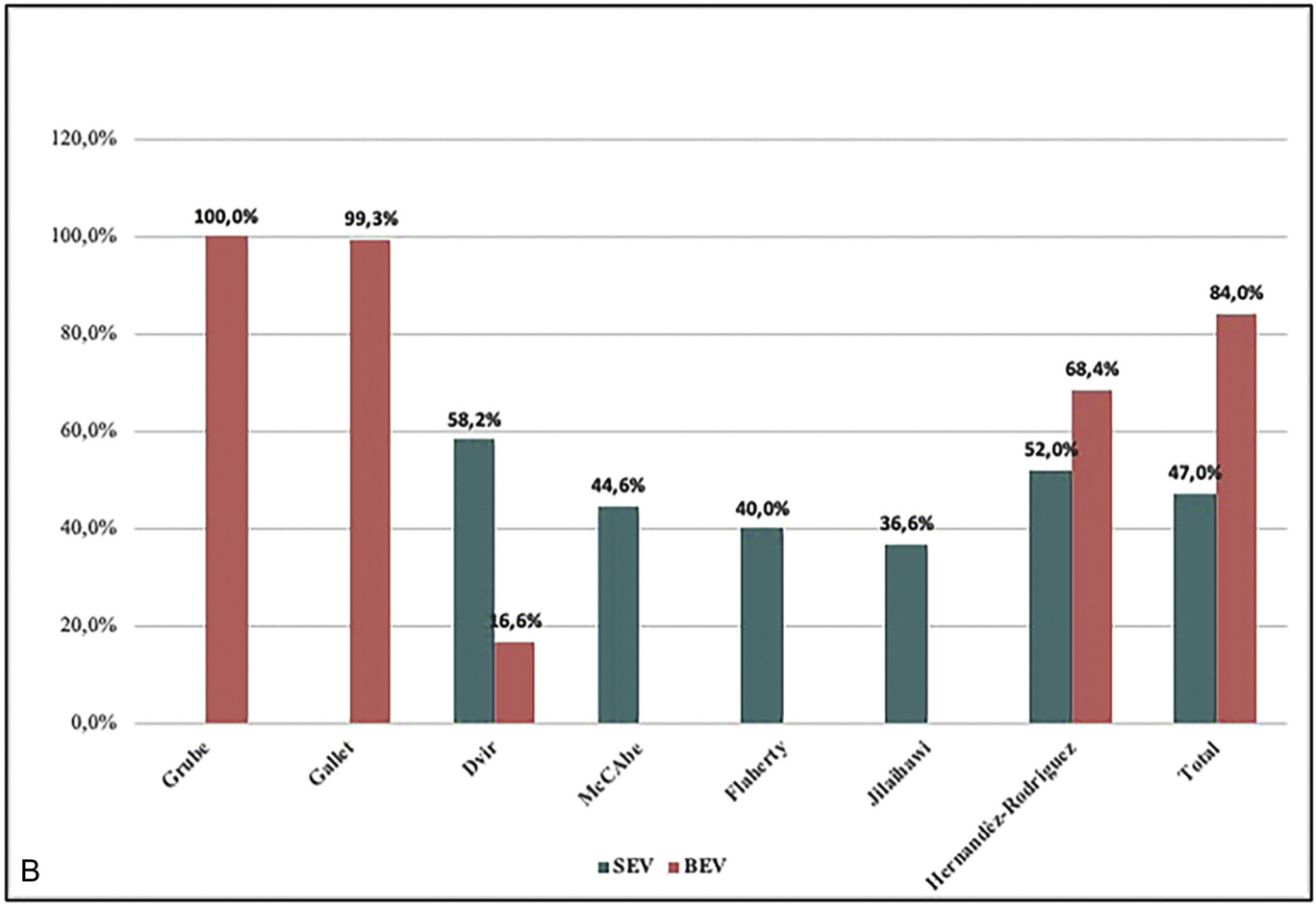


Fig. 4. A) Pooled prevalence of thrombocytopenia in TAVI patients. B) Patients that experienced thrombocytopenia after balloon-expandable and self-expandable trans-catheter aortic valves implantation.

platelet activation occurred in both groups, but it was still present at 2-month follow-up only in bioprostheses [43]. Similarly, van Straten and associates observed that patients receiving an aortic bio-prosthesis had a lower platelet nadir within the 5th POD, compared to mechanical prosthesis group [7]. Bio-prostheses, therefore, appear more prone to be associated with or to elicit perioperative TCP than mechanical prostheses [7]. Moreover, prosthesis size might play a role. Too small bio-prostheses, indeed, were associated with TCP [19]. A greater trans-prosthetic gradient due to a small bio-prosthesis size, in fact, might create high shear stress with consequently platelet disruption.

Significant peri-operative TCP was recently observed in several reports after biological stentless valves implantation, mostly Freedom

Solo bio-prosthesis [6,19,21,25,26]. Likewise, we observed the same finding including in the analysis also other stentless tissue valves. Hilker and coauthors described a higher occurrence of PC < 100×10^3/uL between 2nd and 5th POD in patients receiving a stentless valve (71.9%), compared to the stented group (36.6%) [25]. Piccardo and colleagues reported that severe TCP occurred in 25% and 3% of patients with the stentless and the stented valve, respectively ($P < 0.0001$) [21]. Similarly, Miceli and associated observed a higher incidence of TCP in stentless-AVR compared to control group (24.1% vs. 4.4%, $p < 0.0001$) [19]. Stentless-related TCP's origin has been investigated and be potentially related to other factors, besides the use of CPB and heparin. Indeed, Yerebakan and colleagues speculated that the homocysteic acid in the prosthesis storage fluid may induce TCP because of an otherwise uncharacterized toxic effect on platelets [6]. However, this explanation remains not confirmed as the transferred amount of acid is probably too low to injure platelets [19].

Recent reports demonstrated a significant drop in PC after implant of a RDV, whose biological structure is very similar to stentless tissue valve [9,20,46,47]. In 2015, Albacker and colleagues first described a significant decline in PC after RDV-AVR [32,46]. This phenomenon is usually transient and subclinical [3,4,20,49]. Indeed, PC recovers slowly within 7–10 days from AVR [3,4,20,46]. Few studies, however, reported a higher rate of blood transfusion after RDV-AVR [3,20,22,23].

Similar to stentless-AVR, the mechanism underlying TCP after RDV is still unknown. Several studies reported the same hypotheses [3,29,46,47]. An increased shear-stress due to transvalvular blood flow appears an unlikely explanation, due to RDV better design and hemodynamic performance than stented-AVR [47].

TCP after AVR is not an event strictly confined to surgically implanted bio-prostheses. Indeed, recent studies have reported a temporary decrease in PC after TAVI [8–15,32–38]. Although large RCTs comparing TAVI versus stented-AVR have been performed in the last years, none of them have specifically addressed peri-procedural TCP [48,49]. The results of the present systematic review demonstrate that post-TAVI TCP may occur, and may be associated with relevant adverse effects, as major bleeding (>2RBCs transfusion), and 30-day as well as 1-year mortality. The major influence of TCP on survival seems to be related to the bleeding complications. Wang and coworkers observed that post-TAVI bleeding was associated with a 323% increase in 30-day postoperative mortality [50]. Moreover, TCP-related hemorrhagic complications, and consequently RBCs transfusions, might increase exponentially in TAVI patients needing anticoagulation for permanent or new onset atrial fibrillation. Therefore, an increased 1-year mortality rate in TAVI patients with TCP is most likely due to bleeding, transfusions, and prolonged hospitalization [51].

PC systematically decreases after TAVI, with a reduction ranging from 21% to 72% as compared to pre-operative value [8,9,13,15,37,38]. As for stentless-AVR and RDV-AVR, TCP is a temporary event [37]. Different hypotheses have been advanced to explain this phenomenon, some of them replicating the factors considered for surgical AVR. As specific determinants of TCP, platelet activation triggered by endothelial damage caused by prosthesis implantation, fibrinogen binding on metallic armatures, and shear stress modifications due to prosthesis implantation, are proposed potential mechanisms [38]. Reduced production or increased platelet consumption should be also considered [9]. Furthermore, it has been hypothesized that TCP might be a consequence of low-osmolar contrast agents used during the implantation [8,37]. In this respect, there are divergent data regarding contrast-dependent platelet aggregation as a reason for TCP [38]. A larger volume of contrast used during the interventional procedure might indicate more difficult procedures resulting in greater mechanical platelet destruction [38]. Notwithstanding, post-TAVI TCP occurred more frequently in BEV valves (Fig. 4.B). The use of larger sheaths, predilatation, surgical cut-down for the femoral access, and a higher rate of general anesthesia among BEV patients could play a pivotal role [37]. This issue, moreover, could complicate also the decision-making process about perioperative use of antiplatelet agents or oral anticoagulants which, on the other hand, may also influence PC [52]. The therapy with unfractioned heparin, aspirin, and clopidogrel or other antiplatelet drugs could be one of the reasons for TCP [13]. This issue, nonetheless, seems to be more complex. Because platelet activation elicits TCP, antiplatelet agents might have some protective effect [52]. Thus, it is not evident if antiplatelets should be withdrawn when TCP occurs.

A definitive explanation for post-TAVI TCP, as for the surgery-related event, remains, however, still mostly undefined.

4.1. Limitations of research and risk of bias

Limitations of this meta-analysis merit careful consideration. The analysis suffers from the quality of the included articles, mainly retrospective, and with unclear risks of bias. There were not enough samples in our analysis for some data items. Our meta-analysis did not include all of the 15 studies for every outcome parameter investigated. Consequently, the number of patients analyzed for the meta-analysis varied greatly for each outcome, generally comprising only a fraction of the whole study population. Moreover, many of the studies did not indicate pre-operative PC, the use of drugs associated with thrombocytopenia, or the prior exposure to heparin, and heparin management post-operatively. Most studies, moreover, did not report the administration of antiplatelets, making difficult to explore the eventual correlations. Furthermore, the studies lack data regarding the aortic valve morphology and prosthesis size. Accordingly, we were not able to make further analyses, or a meta-regression for the evaluation of the potential risk factors for TCP. Moreover, the present meta-analysis included in each group several types of bioprostheses, with different hemodynamic performances and most likely different effect on platelets.

5. Conclusions

The present systematic review and meta-analysis showed that early peri-operative TCP is a common event after biological prosthesis implant at aortic position. This event, moreover, occurs mostly after trans-catheter, stentless, and RDV valves as compared to conventional stented prostheses.

The origin of this phenomenon is still unclear. It has been shown to be potentially more clinically relevant in TAVI patients, whereas this issue remains controversial in surgical patients. A better understanding and awareness of the underlying mechanism or predisposing factors of such a peri-procedural event require further investigations. TCP certainly remains an event to be monitored during the hospital stay whenever a biological prosthesis in implanted at aortic position.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.056.

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