Thrombocytopenia after implantation of the Perceval S aortic bioprosthesis

Philipp Stegmeier, MD,[a] Markus Schlömicher, MD,[a] Hugo Stiegler, MD,[b,c] Justus T. Strauch, MD,[a] and J. F. Matthias Bechtel, MD[a]

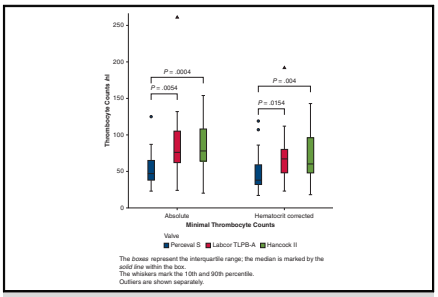
ABSTRACT

Objective: The Perceval S bioprosthesis (LivaNova PLC, London, United Kingdom) is based on the Freedom Solo aortic bioprosthesis (LivaNova PLC), which has been reported to be associated with perioperative thrombocytopenia. We compared platelet counts after aortic valve replacement with the Perceval S with those with other aortic valve bioprostheses.

Methods: A total of 87 patients receiving aortic valve replacement were included in this retrospective study; 25 patients received the Perceval S, 23 patients received the Labcor TLPB-A (Labcor, Belo Horizonte, Brazil), and 39 patients received the Hancock II bioprosthesis (Medtronic, Minneapolis, Minn). Thrombocyte count was corrected for hematocrit. Multivariable analyses were performed to assess the potential effect of other variables.

Results: Preoperatively, there were no differences in platelet counts comparing the Perceval S group (median 200/nl, interquartile range, 157-252) and the control group (Labcor: median 213/nl, interquartile range, 160-246, Hancock: median 227/nl, interquartile range, 183-280, $P = .23$). Postoperatively, there was significant evidence that the minimum platelet count (median, Perceval: 47, interquartile range, 38-66; Labcor: 76, interquartile range, 61-110; Hancock: 78, interquartile range, 61-111/nl; $P = .001$), both absolute and corrected, was lower for the Perceval S, even after allowing for other variables. The significant difference in absolute platelet counts persisted until discharge or death. However, there were no significant differences regarding blood loss, transfusion requirements, or rates of reoperation for bleeding.

Conclusions: After aortic valve replacement, platelet counts in patients with the Perceval S decrease more severely compared with other bioprostheses, but in our small study we found no evidence of a detrimental clinical effect of this phenomenon. Future studies have to confirm our findings and investigate a cause for this phenomenon. (J Thorac Cardiovasc Surg 2020;160:61-8)



The Perceval S (LivaNova PLC, London, United Kingdom) bioprosthesis has significantly lower minimum postoperative thrombocyte counts.

CENTRAL MESSAGE

Platelet counts after aortic valve replacement with the Perceval S (LivaNova PLC, London, United Kingdom) bioprosthesis decrease significantly more compared with other biological valves, but without apparent clinical consequences.

PERSPECTIVE

Reports link the implantation of a Freedom Solo (Sorin Group, Milan, Italy) aortic bioprosthesis with transient thrombocytopenia. We report that the Perceval S (LivaNova PLC, London, United Kingdom) aortic bioprosthesis, which is based on the Freedom Solo (Sorin Group), is also associated with lower thrombocyte counts postoperatively than other valves. We did not identify any variable that influenced this association and found no significant evidence of a detrimental effect.

See Commentaries on pages 69 and 70.

The bovine Perceval S sutureless aortic bioprosthesis (Sorin Group, Milan, Italy; LivaNova PLC, London, United Kingdom) was developed to be implanted without the need for sutures.[1-3] The Perceval S reduces crossclamp time, has favorable hemodynamics, and has a low risk of patient–prosthesis mismatch.[1-7]

From the Department for [a]Cardiothoracic Surgery and [b]Clinical Chemistry, Transfusion Medicine and Laboratory Medicine, University Hospital Bergmannsheil, Ruhr Universität Bochum, Bochum, Germany; and [c]Medizinisches Versorgungszentrum für Labormedizin und Mikrobiologie Ruhr GmbH, Essen, Germany.

Received for publication Sept 23, 2018; revisions received June 25, 2019; accepted for publication July 10, 2019; available ahead of print Sept 26, 2019.

Address for reprints: J. F. Matthias Bechtel, MD, Klinik für Herz- und Thoraxchirurgie, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany (E-mail: matthias.bechtel@bergmannsheil.de).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.07.046

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
IQR = interquartile range

Scanning this QR code will take you to the article title page to access supplementary information.

The Perceval S aortic bioprosthesis is based on a stentless aortic valve bioprosthesis of the same manufacturer—the Freedom Solo valve. Multiple publications described thrombocytopenia associated with implantations of the Freedom Solo,[8-11] but the reason for the phenomenon remained unclear. Despite similarities between the Freedom Solo and the Perceval valves, the thrombocyte count after implantation of the Perceval was not systematically studied until recently. We initiated a retrospective study on the course of thrombocyte counts after implantation of the Perceval in our own patients.

PATIENTS AND METHODS

Patients

For the purpose of this study, all patients who received a Perceval S aortic bioprosthesis (LivaNova PLC, London, United Kingdom; formerly Sorin Group, Saluggia, Italy) at the Department of Cardiothoracic Surgery, University Hospital Bergmannsheil in Bochum, Germany, were retrospectively analyzed. All implantations were performed between August 2009 and October 2010, and these patients were part of the pivotal or the CAVALIER trials exploring the safety and performance of the Perceval bioprosthesis.[2,12] No implantations of the Perceval bioprosthesis were performed after that period.

All elective patients who received a biological aortic valve replacement during the same time period served as controls. These patients received, at the discretion of the surgeon, a Labcor TLPB-A (Labcor, Belo Horizonte, Brazil) or a Hancock II (Medtronic, Minneapolis, Minn) aortic bioprosthesis. No other biological aortic bioprostheses were used during the study period at our department. Because of a different availability in valve sizes for the 3 bioprostheses, only patients with valve sizes between 21 and 25 mm were included in the study. Three patients with active endocarditis (Perceval: 0, Labcor TLPB-A: 2, Hancock II: 1) were excluded.

Finally, 87 patients were included: 25 patients with the Perceval, 23 patients with the Labcor TLPB-A, and 39 patients with the Hancock II. The preoperative demographics of the patients are shown in Table 1. Preoperative intake of phenprocoumon, heparin, or aspirin was defined as within 5 days preoperatively. The local ethics commission approved the study and waived the need of informed consent (Institutional Review Board No. 16-5666).

Study End Points

Primary end points were the minima of platelet counts during the hospital stay, the time until that minimum was reached, and the platelet count at discharge. For absolute platelet counts, a hematocrit-corrected thrombocyte count was generated to reduce the effects of transfusions/hemodilution and to compare platelet counts of different patients:

$$PLATELET\ corrected(t) = PLATELET(t) x \frac{HEMATOCRIT(t)}{HEMATOCRIT(preoperatively)}$$

Secondary end points were in-hospital death; the need for transfusions of packed red blood cells, platelets, or fresh-frozen plasma; events of bleeding and re-thoracotomy; blood loss via drainages after 24 and 48 hours; and thrombotic or cardiovascular events.

Valves

The Perceval is a trileaflet bovine pericardial valve fixed in a nitinol metal frame that allows to compress and deploy the Perceval with a delivery system without the need for sutures.[1-3] The Perceval is fixed in glutaraldehyde, detoxified with homocysteic acid,[12] and stored in an aldehyde-free solution[13]; therefore, rinsing is not required. The Perceval is now available in 4 different sizes. At the beginning of this study's observation period, only 3 valve sizes were available.

The Labcor TLPB-A bioprosthesis is a porcine valve fixed in a glutaraldehyde solution, mounted on a Celcon ring (Celanese, Irving, Tex)[14] and available in 5 sizes. The Hancock II is also a porcine valve fixed in a glutaraldehyde solution, available in 5 sizes, mounted on a Delrin stent (DuPont, Wilmington, Del).[15,16]

Surgical Technique

Standard median sternotomy was used except for 5 patients who received a Perceval and 3 patients who received a Labcor TLPB-A who underwent a partial upper sternotomy. After application of an initial dose of 300 U/kg heparin, cardiopulmonary bypass (CPB) was initiated. Additional heparin was given to achieve or maintain an activated clotting time of more than 400 seconds. After aortic crossclamping, a transverse aortotomy (for Perceval) or an S-shaped aortotomy (for Labcor TLPB-A and Hancock II) was performed. After inspection of the valve, it was resected and the aortic annulus was decalcified. Sizing was performed as recommended by the manufacturer of the bioprosthesis used. The Labcor TLPB-A and the Hancock II bioprostheses were implanted using multiple U-stitches with pledgets. The Perceval was implanted sutureless using position sutures for guiding implantation. Concomitant procedures are shown in Table E1 and did not differ significantly between the groups.

Blood Samples

Blood samples were taken on the day before surgery, at arrival to the intensive care unit, and approximately at 12-hour intervals for the next 3 days in all patients. Thereafter, blood sampling was directed by the clinical course with at least 1 additional control on the day before discharge.

Statistical Analysis

For statistical analysis, SPSS 23.0 (IBM, Armonk, NY) and R version 3.51 were used. Frequencies are given as absolute numbers and percentages. Continuous variables are given as median with interquartile range (IQR). The Kruskal–Wallis test was used to check for differences among the 3 groups. Direct between-group comparisons were performed using the chi-square test or Mann–Whitney U test. Multivariable analyses to

TABLE 1. Patient demographics

	Perceval S (LivaNova PLC, London, United Kingdom) (n = 25)	Labcor TLPB-A (Labcor, Belo Horizonte, Brazil) (n = 23)	Hancock II (Medtronic, Minneapolis, Minn) (n = 39)	*P* value
Male	11 (44%)	16 (70%)	29 (59%)	.195
Age				
Median	79	75	74	.015*
IQR	74.5-82.0	72.0-78.0	70.0-79.0	
Hypertension	22 (88%)	21 (91%)	35 (90%)	.932
Diabetes mellitus	7 (28%)	5 (22%)	16 (41%)	.253
Renal insufficiency	5 (20%)	6 (26%)	12 (31%)	.634
Anticoagulation				
LMWH	13 (52%)	12 (52%)	17 (44%)	.733
Phenprocoumon	0 (0%)	2 (9%)	2 (5%)	.348
Antiplatelet therapy				
ASA 100 mg	7 (28%)	7 (30%)	14 (36%)	.682
Dual antiplatelet therapy	2 (8%)	0 (0%)	2 (5%)	
Cardiac comorbidities				
Coronary heart disease	15 (60%)	11 (48%)	30 (77%)	.060
Additional valvular defect	9 (36%)	7 (30%)	10 (26%)	.610
ICD or pacemaker	1 (4%)	1 (4%)	1 (3%)	.918
Ectasia of aorta	0 (0%)	0 (0%)	1 (2%)	
Surgery				
Partial upper sternotomy	5 (20%)	3 (13%)	0 (0%)	.060
Concomitant procedures†	9 (36%)	11 (48%)	19 (49%)	.574
Total intrasurgical heparin dose (IU)				
Median	26,400	34,600	32,000	.001*
IQR	23,050-29,700	26,100-40,500	27,200-37,000	
Duration of surgery (min)				
Median	151	202	229	.106*
IQR	132.5-228.0	151.0-256.0	162.0-261.0	
CPB time (min)				
Median	75	124	121	<.001*
IQR	63.0-96.0	86.0-161.0	101.0-155.0	
Crossclamp time (min)				
Median	50	77	81	<.001*
IQR	35.0-61.0	59.0-102.0	71.0-102.0	

IQR, Interquartile range; *LMWH*, low-molecular-weight heparin; *ASA*, acetylsalicylic acid; *ICD*, implantable cardioverter defibrillator; *CPB*, cardiopulmonary bypass. *Kruskal-Wallis test. †Excluding Morrow myectomy.

check the effects of other variables on platelet count time to minimum platelet count were carried out using nonparametric multiple regression models. Two different approaches were used. First, models were constructed with valve types and 1 other variable as regressor variables; then a final multivariable model was computed including all variables with a *P* value of .10 or less in these models using backward elimination. Second, a multivariable model was constructed with simultaneous consideration of all potential covariables. Variables included were age, sex, preoperative platelet count, valve size, surgeon, approach, intraoperative heparin dose, execution of subvalvular myectomy (Morrow), execution of other concomitant procedures, crossclamp time, and CPB duration. These covariables were chosen because of their potential to interfere with the postoperative thrombocyte count directly (age, sex, preoperative platelet count, valve size, heparin dose, operation times) or indirectly via blood loss/operation time (surgeon, approach, concomitant procedures). The Bonferroni correction was applied.

RESULTS

Patient Demographics

Preoperative variables (Table 1) did not differ significantly among the groups except for age. Patients in the Perceval group tended to be older than patients in the Labcor TLPB-A group ($P = .036$) and were significantly older than patients in the Hancock II group ($P = .006$) (Table 1).

Intraoperative Variables

As expected, implantation of a Perceval S bioprosthesis was associated with significantly shorter aortic crossclamp time ($P < .001$) and CPB duration ($P < .001$) compared with the other 2 bioprostheses (Table 1). Consequently, the total

amount of heparin administered during CPB was significantly lower in the Perceval group ($P = .001$) (Table 1). The frequency and distribution of concomitant procedures did not differ significantly between the groups (Tables 1 and E1). Valve sizes are shown in Table 2. A significantly higher proportion of larger valve sizes was used in the Perceval group.

Thrombocyte Count

Preoperatively, there were no statistically significant differences among the groups ($P = .228$) (Table 3). Postoperatively, there was significant evidence that the minimum platelet count was lower for the Perceval (median: 47/nl) than for the Labcor TLPB-A (median: 76/nl) or Hancock II (median: 78/nl), $P = .001$. Using the hematocrit-corrected thrombocyte count did not change this finding ($P = .004$) (Table 3 and Figure 1).

Multivariable analyses were carried out to check the effects of other factors on the minimum platelet count. Considering these co-variables did not affect the main conclusion that the minimum platelet count was lower in the Perceval group (Table E2 shows the models). As might be expected, preoperative thrombocyte count was positively associated with postoperative minimum platelet count. Using the minimum corrected platelet counts did not significantly alter the findings (Table E3).

There was significant evidence that time from the end of surgery to the minimum platelet count was different between the 3 bioprostheses. Patients in the Perceval group tended to have the longest time to minimum platelet count (median: 67 hours); this was significantly longer than in the Hancock II group (median: 40 hours, $P = .003$), but the evidence was not significant in comparison with the Labcor TLPB-A group (median: 44 hours, $P = .28$) (Table 3). By using multivariable analyses, none of the variables examined were significantly associated with time to platelet minimum (Tables E4 and E5).

There was significant evidence that the platelet count at discharge or death was lower for the Perceval group (median: 166/nl) than for the Labcor TLPB-A (median: 255/nl) or Hancock II (median: 315/nl) group ($P < .001$). Using the hematocrit-corrected thrombocyte count did weaken the evidence for a difference between the Perceval and Labcor TLPB-A groups ($P = .067$ after Bonferroni correction), but not for the difference between the Perceval and Hancock II groups ($P = .0006$) (Table 3).

Using multivariable analyses (with the same co-variables as described earlier) did not affect the effect of the valve type on the thrombocyte count at death/discharge, neither absolute nor hematocrit corrected (Tables E6 and E7).

Effect of Surgeon

Because only 2 of 8 surgeons implanted the Perceval S, the effect of surgeon on the thrombocyte count and time to minimum thrombocyte count could only be evaluated in a subgroup of 46 patients. With the use of multivariable modeling, no effect of surgeon on these outcomes could be found (Table E8).

Clinical Study End Points

There was no statistically significant difference regarding perioperative mortality ($P = .281$): Perceval: n = 2 (8%); Labcor TLPB-A: n = 3 (13%); Hancock II: n = 1 (3%). No patient was diagnosed with heparin-induced thrombocytopenia.

There were no significant differences regarding perioperative transfusion requirements (Table 4) or blood loss into the drainage at 24 and 48 hours postoperatively. Rates of reoperation for bleeding did not differ significantly ($P = .157$): Perceval: n = 5 (20%), Labcor TLPB-A: n = 1 (4%), and Hancock II: n = 3 (8%), nor did any other postoperative clinical variable assessed (data not shown).

Patients in all groups stayed in the hospital for comparable periods of time until discharge/death: Perceval (median: 12 days) versus Labcor TLPB-A (median: 13 days) ($P = .780$); Perceval versus Hancock II (median: 12 days) ($P = .482$).

Comment

Our study shows that the platelet counts of patients with the Perceval decreased significantly more and tended to reach the minimum later compared with patients with the other valve implants examined. We also found evidence that this difference persisted at least until discharge or death.

TABLE 2. Valve sizes (labeled diameter)

	Perceval S	Labcor TLPB-A	Hancock II	Overall *P* value*
21 mm	4 (16%)	8 (35%)	15 (39%)	
23 mm	7 (28%)	13 (57%)	15 (39%)	
25 mm	14 (56%)	2 (9%)	9 (23%)	
				.005

Percentages may not add to 100 because of rounding. *Kruskal–Wallis test.

TABLE 3. Thrombocyte counts and time to nadir

Thrombocyte count (n)	Valve	Median	IQR	Overall *P* value*	Paired *P* value†
Preoperatively	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	200 213 227	157-252 160-246 183-280	.228	
Minimum Absolute	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	47 76 78	38-66 61-110 61-111	.001	1 vs 2: .005 1 vs 3: .0004
Minimum Hematocrit-corrected	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	38 67 60	31-64 47-84 48-97	.004	1 vs 2: .015 1 vs 3: .004
At discharge/death Absolute	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	166 255 315	112-232 180-384 216-401	<.001	1 vs 2: .028 1 vs 3: <.0001
At discharge/death Hematocrit-corrected	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	146 241 249	87-240 145-363 191-381	.002	1 vs 2: .067 1 vs 3: .0006
Time to nadir (h) Absolute	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	66.8 43.7 40.0	34.8-76.5 24.1-65.0 18.0-47.8	.006	1 vs 2: .28 1 vs 3: .003
Time to nadir (h) Hematocrit-corrected	1. Perceval S 2. Labcor TLPB-A 3. Hancock II	64.8 43.3 24.3	40.8-76.0 7.3-65.0 10.8-53.5	.001	1 vs 2: .086 1 vs 3: .0002

IQR, Interquartile range. *Kruskal–Wallis test. †Mann–Whitney *U* test with Bonferroni correction.

Since we initiated our study, Albacker[13] described the same phenomenon for the Perceval in a smaller cohort of patients. Sánchez and colleagues,[17] Jiritano and colleagues,[18] and Casha and colleagues[19] made similar observations in small groups of patients receiving the Perceval. In addition, Mujtaba and colleagues[20] also reported a significant postoperative decrease in platelet count with slow recovery, and Stanger and colleagues[21] observed it not only for the Perceval but also for the 2 other bioprostheses of the same manufacturer.

A dramatic platelet count decrease and delayed recovery after aortic valve replacement have been described in multiple publications for the previous valve model of the Sorin Group/LivaNova PLC, the Freedom Solo.[8-11] Most studies denied a clinical impact of the platelet decrease on patients,[8-11] but Hirnle and colleagues[22] described higher transfusion requirements and even 1 death after thrombocytopenia. In our study, there were no statistically significant differences in mortality, blood loss, or other bleeding events and duration of hospitalization between the Perceval and control groups. Noticeable but without statistical significance was that 20% of the Perceval group required reoperation because of bleeding, compared with 4% in the Labcor TLPB-A and to 8% in the Hancock II group. Although not statistically significant, this raises some skepticism whether the thrombocytopenia was truly without clinical consequences; however, another possible explanation for this unusual high frequency of reoperation for bleeding is that we had no experience with transverse aortotomies (as needed for implantation of the Perceval) before. We saw no statistically significant differences for the use of blood products, in contrast to Albacker[13] and Mujtaba and colleagues,[20] who described a higher use of packed red blood cells and platelet transfusions for the Perceval.

Many possible explanations for the observed thrombocytopenia associated with the Freedom Solo and Perceval valves have been suggested, but none have been proven. It is not clear whether the 2 phenomena are linked. However, this seems highly likely, considering the many similarities the valves have. There is some indirect evidence from a recent study by Stanger

and colleagues[21] that detoxification of the Freedom Solo and Perceval valves with homocysteic acid may play a role. Stanger and colleagues[21] compared 3 types of aortic bioprostheses from the Sorin/LivaNova group with a mechanical, an equine sutureless, and a stented bovine valve from other manufacturers: The valves from the Sorin/LivaNova group were associated with a significantly greater decrease in postoperative platelets, but increased bleeding problems were not found.

Homocysteine and homocysteic acid, used for detoxification of the Freedom Solo[10,23] and Perceval,[12] are able to activate NMDA receptors, thereby inducing apoptosis in cells,[24] in this case maybe in thrombocytes.[13,25]

On the contrary, Repossini and colleagues[26] argued that homocysteic acid is present in healthy humans: For toxic effects, concentrations between 300 and 500 mol/L are required.[24] Such concentrations seem implausible because the valves are washed twice in a homocysteine acid–free solution before storage, and the storage solution is also free of homocysteine acid.[26] In addition, a toxic effect of the storage solution itself seems unlikely after Pozzoli and colleagues[9] described that changing the valve preparation process immediately before implantation from nonrinsing to rinsing the Freedom Solo with a saline solution did not prevent thrombocytopenia. However, Stanger and colleagues[21] claim to have detected concentrations of homocysteine acid for the Freedom Solo and its storage solution comparable to those of patients with untreated homocystinuria. Unfortunately, the corresponding data were not published until today, so the validity and relevance of this claim cannot be appraised.

Repossini and colleagues[27] discussed a possible influence of the implantation technique, but this is contradicted by the different implantation techniques used for the Perceval and Freedom Solo.

Yerebakan and colleagues[8] and Altintas and colleagues[28] argued that possibly mechanical stress on platelets led to thrombocytopenia, but Stanger and colleagues[21] argued that in this case the effect would not be expected to be transient.

Repossini and colleagues[27,29] questioned whether the observed phenomenon for the Freedom Solo was actually "real" and not in fact a pseudothrombocytopenia. Stanger and colleagues[30] showed for Freedom Solo that this was not the case. However, because of our study's retrospective design, we could not investigate the occurrence of pseudothrombocytopenia with the Perceval.

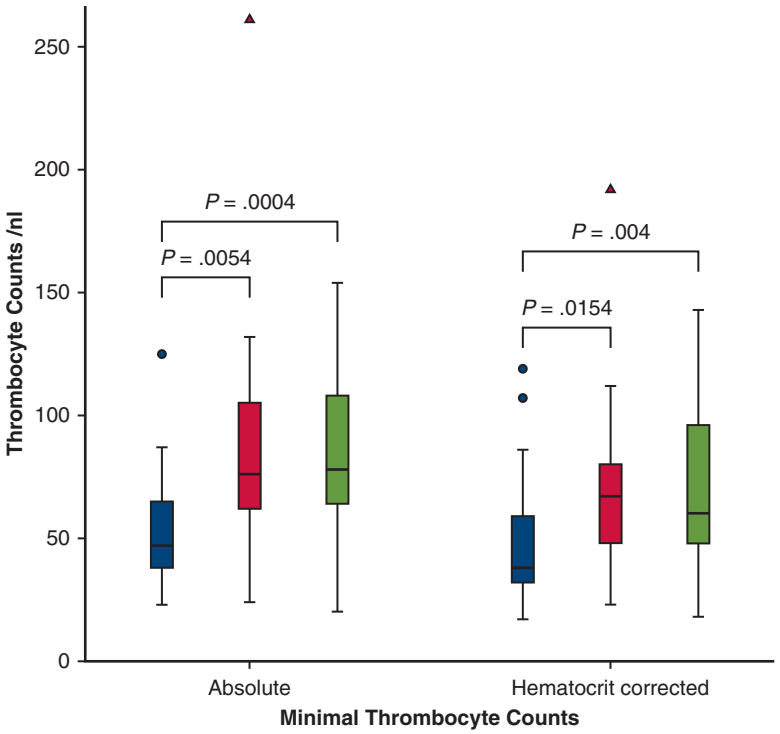


FIGURE 1. Box and whisker plot of the minimum thrombocyte count after Perceval S (LivaNova PLC, London, United Kingdom) implantation. Implantation of the Perceval S bioprosthesis (*blue boxes*) was associated with significant lower absolute minimum postoperative thrombocyte counts compared with the Labcor TLPB-A (Labcor, Belo Horizonte, Brazil) aortic bioprosthesis (*red boxes*) and the Hancock II (Medtronic, Minneapolis, Minn) (*green boxes*). This remained valid after correction of the thrombocyte count for the hematocrit using the formula $PLATELET\ corrected(t) = PLATELET(t) x \frac{HEMATOCRIT(t)}{HEMATOCRIT(preoperatively)}$ where (t) is the value of platelets and hematocrit at the moment of the lowest measured thrombocyte count. The *boxes* represent the IQR; the median is marked by the *solid line* within the box. The whiskers mark the 10th and 90th percentiles. Outliers are shown separately.

TABLE 4. Perioperative results and transfusion requirements

	Perceval S	Labcor TLPB-A	Hancock II	*P* value
Reoperation for bleeding	5 (20%)	1 (4%)	3 (8%)	.157
Death	2 (8%)	3 (13%)	1 (3%)	.281
PRBC (n)				
Median	6	6	6	.956
IQR	4.0-12.5	2.0-10.0	5.0-9.0	
Platelet concentrates (n)				
Median	0	0	0	.122
IQR	0-0	0-0	0-0	
FFP (n)				
Median	0	0	0	.328
IQR	0-4.0	0-4.0	0-0	
Prothrombin complex concentrates (mL)				
Median	0	0	0	.031
IQR	0-1750	0-0	0-0	
Fibrinogen concentrate (g)				
Median	0	0	0	.286
IQR	0-1	0-0	0-0	
Fibrin glue (mL)				
Median	0	0	0	.414
IQR	0-0	0-0	0-0	
Coagulation factor XIII (mL)				
Median	0	0	0	.423
IQR	0-0	0-0	0-0	

PRBC, Packed red blood cells; *IQR*, interquartile range; *FFP*, fresh-frozen plasma.

Study Limitations

Although this is one of the largest studies describing the phenomenon of thrombocytopenia in the Perceval, the number of patients is relatively small. Another limitation is the absence of another bovine pericardial valve among the control groups. At that time, however, no such valves were implanted in patients in our department. The time interval was chosen in which Perceval valves were implanted. We chose not to mix it with data from another time interval to keep variations in treatment as small as possible.

Another major limitation of our study is its retrospective design: Prospective randomized trials should eliminate hidden factors and include follow-up examinations especially after Flameng and colleagues[1] described a platelet decrease after 6 and 12 months. Future studies should also clarify whether the phenomenon is caused by pseudothrombocytopenia.

CONCLUSIONS

Absolute and hematocrit-corrected minimal platelet counts were significantly lower in the Perceval group than in the control groups, and this association was not affected by any other variable examined. At discharge or death, a difference in platelet counts was still detectable. In our study, this phenomenon was not associated significantly with adverse clinical outcomes. However, in light of reports of other groups,[13,20] this thrombocytopenia should be taken seriously, and other surgeons are encouraged to look at their data on whether they can confirm our observation of a thrombocytopenia after Perceval S implantation and if there are clinical consequences associated with it.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

The authors thank Dr Derek Robinson, Mathematics Department, University of Sussex, Great Britain, for this expert statistical analysis.

References

1. Flameng W, Herregods M-C, Hermans H, Van der Mieren G, Vercalsteren M, Poortmans G, et al. Effect of sutureless implantation of the Perceval S aortic

valve bioprosthesis on intraoperative and early postoperative outcomes. *J Thorac Cardiovasc Surg*. 2011;142:1453-7.
2. Shrestha M, Folliguet TA, Pfeiffer S, Meuris B, Carrel T, Bechtel M, et al. Aortic valve replacement and concomitant procedures with the Perceval valve: results of European trials. *Ann Thorac Surg*. 2014;98:1294-300.
3. Folliguet TA, Laborde F, Zannis K, Ghorayeb G, Haverich A, Shrestha M. Sutureless Perceval aortic valve replacement: results of two European centers. *Ann Thorac Surg*. 2012;93:1483-8.
4. Mazine A, Teoh K, Bouhout I, Bhatnagar G, Pelletier M, Voisine P, et al. Sutureless aortic valve replacement: a Canadian multicentre study. *Can J Cardiol*. 2015;31:63-8.
5. Santarpino G, Pfeiffer S, Concistré G, Grossmann I, Hinzmann M, Fischlein T. The Perceval S aortic valve has the potential of shortening surgical time: does it also result in improved outcome? *Ann Thorac Surg*. 2013;96:77-82.
6. Ranucci M, Frigiola A, Menicanti L, Castelvecchio S, de Vincentiis C, Pistuddi V. Aortic cross-clamp time, new prostheses, and outcome in aortic valve replacement. *J Heart Valve Dis*. 2012;21:732-9.
7. Di Eusanio M, Phan K. Sutureless aortic valve replacement. *Ann Cardiothorac Surg*. 2015;4:123-30.
8. Yerebakan C, Kaminski A, Westphal B, Kundt G, Ugurlucan M, Steinhoff M, et al. Thrombocytopenia after aortic valve replacement with the Freedom Solo stentless bioprosthesis. *Interact Cardiovasc Thorac Surg*. 2008;7:616-20.
9. Pozzoli A, De Maat GE, Hillege HL, Boogaard JJA, Natour E, Mariani MA. Severe thrombocytopenia and its clinical impact after implant of the stentless Freedom Solo bioprosthesis. *Ann Thorac Surg*. 2013;96:1581-6.
10. Miceli A, Gilmanov D, Murzi M, Parri M, Cerillo AG, Bevilacqua S, et al. Evaluation of platelet count after isolated biological aortic valve replacement with Freedom Solo bioprosthesis. *Eur J Cardiothorac Surg*. 2012;41:69-73.
11. Piccardo A, Rusinaru D, Petitprez B, Marticho P, Vaida I, Tribouilloy C, et al. Thrombocytopenia after aortic valve replacement with Freedom Solo bioprosthesis: a propensity study. *Ann Thorac Surg*. 2010;89:1425-30.
12. Laborde F, Fischlein T, Hakim-Meibodi K, Misfeld M, Carrel T, Zembala M, et al. Clinical and haemodynamic outcomes in 658 patients receiving the Perceval sutureless aortic valve: early results from a prospective European multicentre study (the Cavalier trial). *Eur J Cardiothorac Surg*. 2016;49:978-86.
13. Albacker TB. Thrombocytopenia associated with Perceval sutureless aortic valve replacement in elderly patients: a word of caution. *Heart Surg Forum*. 2015;18:E093-7.
14. Pavie AJ, Nzomvuama AN, Bonnet N, Bors VH, Gandjbakhch I. Aortic valve replacement with the composite Labcor porcine bioprosthesis in the elderly. *J Cardiovasc Surg (Torino)*. 2001;42:317-22.
15. Wright J, Eberhardt C, Gibbs M, Saul T, Gilpin C. Hancock II—an improved bioprosthesis. In: Cohn LV, Gallucci V, eds. *Cardiac Bioprostheses*. New York: NY: Medical Books; 1982:425-44.
16. Rizzoli G, Bottio T, Thiene G, Toscano G, Casarotto D. Long-term durability of the Hancock II porcine bioprosthesis. *J Thorac Cardiovasc Surg*. 2003;126:66-74.
17. Sánchez E, Corrales J-A, Fantidis P, Tarhini IS, Khan I, Pineda T, et al. Thrombocytopenia after aortic valve replacement with Perceval S sutureless bioprosthesis. *J Heart Valve Dis*. 2016;25:75-81.
18. Casha AR, Manché A, Camilleri L, Yamagata K, Santucci S, Gauci M, et al. Sutureless Perceval aortic valve implantation compared with conventional Mitroflow valve replacement. *Indian J Thorac Cardiovasc Surg*. 2018;34:109-15.
19. Jiritano F, Cristodoro L, Malta E, Mastroroberto P. Thrombocytopenia after sutureless aortic valve implantation: comparison between Intuity and Perceval bioprostheses. *J Thorac Cardiovasc Surg*. 2016;152:1631-3.
20. Mujtaba SS, Ledingham S, Shah AR, Schueler S, Clark S, Pillay T. Thrombocytopenia after aortic valve replacement: comparison between sutureless Perceval S valve and Perimount Magna Ease bioprosthesis. *Braz J Cardiovasc Surg*. 2018;33:169-75.
21. Stanger O, Grabherr M, Gahl B, Longnus S, Meinitzer A, Fiedler M, et al. Thrombocytopaenia after aortic valve replacement with stented, stentless and sutureless bioprostheses. *Eur J Cardiothorac Surg*. 2017;51:340-6.
22. Hirnle T, Juszczyk G, Tycińska A, Stankiewicz A, Żak G, Lewczuk A, et al. Thrombocytopenia and perioperative complications after stentless Freedom Solo valve implantation. *Kardiol Pol*. 2013;71:334-40.
23. Hilker L, Wodny M, Ginesta M, Wollert H-G, Eckel L. Differences in the recovery of platelet counts after biological aortic valve replacement. *Interact Cardiovasc Thorac Surg*. 2009;8:70-3.
24. Boldyrev AA. Molecular mechanisms of homocysteine toxicity. *Biochemistry (Mosc)*. 2009;74:589-98.
25. Albacker TB. Invited commentary. *Ann Thorac Surg*. 2010;89:1430-1.
26. Repossini A, Muneretto C, Martini G. Thrombocytopenia after Sorin Freedom Solo valve implant. *Ann Thorac Surg*. 2011;91:1307.
27. Repossini A, Bloch D, Muneretto C, Piccoli P, Bisleri G, Beholz S. Platelet reduction after stentless pericardial aortic valve replacement. *Interact Cardiovasc Thorac Surg*. 2012;14:434-8.
28. Altintas G, Diken AI, Hanedan O, Yurdakok O, Ozyalcin S, Kucuker S, et al. The Sorin Freedom SOLO stentless tissue valve. *Tex Heart Inst J*. 2013;40:50-5.
29. Repossini A, Tononi L, Martinil G, Di Bacco L, Girolettiz L, Rosati F, et al. Platelet activation after Sorin Freedom Solo valve implantation: a comparative study with Carpentier-Edwards Perimount Magna. *J Heart Valve Dis*. 2014;23:777-82.
30. Stanger O, Gahl B, Grabherr M, Krausler R, Longnus S, Meinitzer A, et al. Freedom SOLO-associated thrombocytopaenia is valve-dependent and not due to in vitro pseudothrombocytopaenia. *Heart Lung Circ*. 2017;26:268-75.

Key Words: thrombocytopenia, aortic valve replacement, sutureless prosthesis

TABLE E1. Concomitant procedures

	Perceval S (LivaNova PLC, London, United Kingdom)	Labcor TLPB-A (Labcor, Belo Horizonte, Brazil)	Hancock III (Medtronic, Minneapolis, Minn)	*P* value
Concomitant procedures (excluding Morrow myectomy)	9 (36%)	11 (48%)	19 (49%)	.574
Coronary artery bypass	7 (28%)	9 (39%)	18 (46%)	
Tricuspid valvuloplasty	1 (4%)	2 (9%)	1 (3%)	
Mitral valvuloplasty	0 (0%)	1 (4%)	0 (0%)	
Mitral valve replacement	0 (0%)	0 (0%)	1 (3%)	
Aortic replacement	0 (0%)	1 (4%)	0 (0%)	
Ligature or resection of atrial appendage	2 (8%)	1 (4%)	1 (3%)	
Maze procedure	0 (0%)	0 (0%)	1 (3%)	
Morrow myectomy	5 (20%)	0 (0%)	1 (3%)	.009

TABLE E2. Results of the multivariable model with minimum uncorrected platelet count as dependent variable

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Age, y	Male sex*	Preoperative thrombocyte count (/nl)	Valve size† (23 mm)	Valve size† (25 mm)	Approach‡	Total heparin dosage (IU)	Subvalvular myectomy*	Concomitant procedure§	Crossclamp (min)	CPB (min)
Estimated coefficients	−82.085	0	28.081	26.833	0.793	9.656	0.313	8.291	4.581	−2.303	0.001	−7.460	5.932	0.057	−0.408
Standard errors	70.747	NA	8.766	8.714	0.783	6.404	0.0551	6.832	10.145	11.675	0.0004	8.879	7.268	0.030	0.021
P values	.249	NA	.002	.003	.314	.135	<.001	.228	.653	.844	<.001	.403	.417	.849	.052

A nonparametric multiple regression mode with simultaneous consideration of all variables potentially influencing the thrombocyte count and minimum uncorrected platelet count as the response variable was fitted. The model shows that the Labcor TLPB-A and Hancock II bioprostheses were consistently associated with a higher minimum uncorrected postoperative platelet count than the Perceval S bioprosthesis. The minimum uncorrected platelet count was also significantly higher in patients with a higher preoperative platelet count and higher total intraoperative heparin application. *CPB*, Cardiopulmonary bypass; *NA*, not applicable. *Coded as No = 0 and Yes = 1. †Valves were available in 3 sizes for analysis. Size 21 mm served as reference. ‡Coded as 1 = full sternotomy and 2 = partial sternotomy. §Concomitant procedures except subvalvular myectomy; coded as No = 0 and Yes = 1.

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Preoperative thrombocyte count (/nl)	Total heparin dosage (IU)	Crossclamp (min)
Estimated coefficients	−3.099	0	20.273	22.764	0.172	0.002	−0.313
Standard errors	15.188	NA	9.226	9.305	0.057	0.0004	0.140
P values	.839	NA	.031	.017	.003	<.001	.028

A nonparametric multiple regression model with backward elimination of all variables with a $P \leq .10$ were included (valve types, male sex, preoperative platelet count, total intraoperative heparin application, crossclamp time and CPB duration) and minimum uncorrected platelet count as the response variable was fitted. In a step before, multivariable models including the 3 valve types plus 1 extra variable as regressor variables had been constructed, details not shown. The *P* values of these models served as entry criterion as described. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher minimum uncorrected postoperative platelet count than the Perceval S bioprosthesis. The minimum uncorrected platelet count was also significantly higher in patients with higher preoperative platelet count and higher total intraoperative heparin application; and significantly lower with increasing crossclamp time. *NA*, Not applicable.

TABLE E3. Results of the multivariable model with minimum corrected platelet count as dependent variable

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Age, y	Male sex*	Preoperative thrombocyte count (/nl)	Valve size† (23 mm)	Valve size† (25 mm)	Approach‡	Total heparin dosage (IU)	Subvalvular myectomy*	Concomitant procedure§	Crossclamp (min)	CPB (min)
Estimated coefficients	−52.466	0	21.264	21.016	0.477	6.254	0.270	2.507	0.958	7.364	0.001	−3.061	11.423	0.117	−0.398
Standard errors	54.469	NA	7.177	7.107	0.628	5.637	0.040	6.626	9.266	11.256	0.0004	12.923	6.895	0.2849	0.198
P values	.338	NA	.004	.004	.450	.270	<.001	.706	.918	.515	.002	.813	.101	.682	.048

A nonparametric multiple regression model with simultaneous consideration of all variables potentially influencing the thrombocyte count and minimum corrected platelet count as the response variable was fitted. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher minimum corrected postoperative platelet count than the Perceval S bioprosthesis. The minimum corrected platelet count was also significantly higher in patients with higher preoperative platelet count and higher total intraoperative heparin application, and it was significantly lower with increasing duration of CPB. *CPB*, Cardiopulmonary bypass; *NA*, not applicable. *Coded as No = 0 and Yes = 1. †Valves were available in 3 sizes for analysis. Size 21 mm served as reference. ‡Coded as 1 = full sternotomy and 2 = partial sternotomy. §Concomitant procedures except subvalvular myectomy; coded as No = 0 and Yes = 1.

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Preoperative thrombocyte count (/nl)	Total heparin dosage (IU)	CPB (min)
Estimated coefficients	−13.249	0	19.656	17.625	0.251	0.001	−0.260
Standard errors	9.497	NA	6.136	6.149	0.035	0.0003	0.056
P values	.167	NA	.002	.005	<.001	<.001	<.001

A nonparametric multiple regression model with backward elimination of all variables with a $P \leq .10$ were included (valve types, preoperative platelet count, total intraoperative heparin application, crossclamp time, and CPB duration) and minimum corrected platelet count as the response variable was fitted. In a step before, multivariable models including the 3 valve types plus 1 extra variable as regressor variables had been constructed; details not shown. The *P* values of these models served as entry criterion as described. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher minimum corrected postoperative platelet count than the Perceval S bioprosthesis. The minimum corrected platelet count was also significantly higher in patients with higher preoperative platelet count and higher total intraoperative heparin application, and significantly lower with increasing CPB duration. *CPB*, Cardiopulmonary bypass; *NA*, not applicable.

TABLE E4. Results of the multivariable model with time to minimum uncorrected platelet count as dependent variable

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Age, y	Male sex*	Preoperative thrombocyte count (/nl)	Valve size† (23 mm)	Valve size† (25 mm)	Approach‡	Total heparin dosage (IU)	Subvalvular myectomy*	Concomitant procedure§	Crossclamp (min)	CPB (min)
Estimated coefficients	−130.608	0	−7.789	−35.637	2.002	7.016	0.027	−33.666	−11.969	−11.022	0.0004	−7.682	−10.576	−1.222	1.197
Standard errors	157.415	NA	17.118	18.234	1.597	14.034	0.091	23.749	15.243	22.300	0.001	27.573	18.085	1.087	1.044
P values	.409	NA	.650	.054	.213	.618	.765	.160	.435	.622	.706	.781	.560	.264	.255

A nonparametric multiple regression modes with simultaneous consideration of all variables potentially influencing the thrombocyte count and time to minimum uncorrected platelet count as the response variable was fitted. In this model, no variable is significantly associated with the response variable. *CPB*, Cardiopulmonary bypass; *NA*, not applicable. *Coded as No = 0 and Yes = 1. †Valves were available in 3 sizes for analysis. Size 21 mm served as reference. ‡Coded as 1 = full sternotomy and 2 = partial sternotomy. §Concomitant procedures except subvalvular myectomy; coded as No = 0 and Yes = 1.

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II
Estimated coefficients	58.966	0	3.159	−24.704
Standard errors	6.562	NA	19.952	7.246
P values	<.001	NA	.895	.001

When multivariable models including the 3 valve types plus 1 extra variable as regressor variables are constructed, only valve type = Hancock II was significantly associated with time to minimum uncorrected platelet count. *NA*, Not applicable.

TABLE E5. Results of the multivariable model with time to minimum corrected platelet count as dependent variable

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Age, y	Male sex*	Preoperative thrombocyte count (/nl)	Valve size† (23 mm)	Valve size† (25 mm)	Approach‡	Total heparin dosage (IU)	Subvalvular myectomy*	Concomitant procedure§	Crossclamp (min)	CPB (min)
Estimated coefficients	−345.103	0	−58.552	−79.311	5.139	35.470	−0.020	−31.187	−34.844	−10.035	0.000009	−43.333	−6.269	−1.568	1.687
Standard errors	235.608	NA	47.111	42.782	2.905	23.271	0.135	25.542	27.940	25.878	0.001	37.587	24.013	1.339	1.189
P values	.147	NA	.217	.067	.081	.131	.884	.226	.216	.699	.995	.252	.795	.245	.160

A nonparametric multiple regression model with simultaneous consideration of all variables potentially influencing the thrombocyte count and time to minimum corrected platelet count as the response variable was fitted. In this model, no variable is significantly associated with the response variable. *CPB*, Cardiopulmonary bypass; *NA*, not applicable. *Coded as No = 0 and Yes = 1. †Valves were available in 3 sizes for analysis. Size 21 mm served as reference. ‡Coded as 1 = full sternotomy and 2 = partial sternotomy. §Concomitant procedures except subvalvular myectomy; coded as No = 0 and Yes = 1.

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II
Estimated coefficients	87.663	0	−24.126	−56.823
Standard errors	28.672	NA	35.506	29.002
P values	.003	NA	.500	.053

A nonparametric multiple regression model with backward elimination of all variables with a $P \leq .10$ were included (age) and time to minimum corrected platelet count as the response variable was fitted. In a step before, multivariable models including the 3 valve types plus 1 extra variable as regressor variables had been constructed, details not shown. The *P* values of these models served as entry criterion as described. In this model, no variable is significantly associated with the response variable. *NA*, not applicable.

TABLE E6. Results of the multivariable model with uncorrected platelet count at discharge/death as dependent variable

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Age, y	Male sex*	Preoperative thrombocyte count (/nl)	Valve size† (23 mm)	Valve size† (25 mm)	Approach‡	Total heparin dosage (IU)	Subvalvular myectomy*	Concomitant procedure§	Crossclamp (min)	CPB (min)
Estimated coefficients	−180.761	0	156.292	198.341	3.349	−21.957	0.645	60.445	64.978	26.992	−0.002	67.324	−12.010	−0.031	−0.272
Standard errors	259.251	NA	39.204	41.604	3.081	26.990	0.232	40.305	41.246	50.794	0.002	55.692	36.095	1.354	0.9951
P values	.488	NA	<.001	<.001	.280	.418	.007	.137	.119	.597	.251	.230	.740	.982	.776

A nonparametric multiple regression model with simultaneous consideration of all variables potentially influencing the thrombocyte count and uncorrected platelet count at discharge/death as the response variable was fitted. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher uncorrected platelet count at discharge/death than the Perceval S bioprosthesis. The uncorrected platelet count at discharge/death was also significantly higher in patients with higher preoperative platelet count. *CPB*, Cardiopulmonary bypass; *NA*, not applicable. *Coded as No = 0 and Yes = 1. †Valves were available in 3 sizes for analysis. Size 21 mm served as reference. ‡Coded as 1 = full sternotomy and 2 = partial sternotomy. §Concomitant procedures except subvalvular myectomy; coded as No = 0 and Yes = 1.

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Preoperative thrombocyte count (/nl)
Estimated coefficients	58.863	0	80.277	120.010	0.605
Standard errors	45.157	NA	29.775	25.868	0.215
P values	.196	NA	.009	<.001	.006

A nonparametric multiple regression model with backward elimination of all variables with a $P \leq .10$ were included (valve types, male sex, preoperative platelet count, subvalvular myectomy) and uncorrected platelet count at discharge/death as the response variable was fitted. In a step before, multivariable models including the 3 valve types plus 1 extra variable as regressor variables had been constructed, details not shown. The *P* values of these models served as entry criterion as described. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher uncorrected platelet count at discharge/death than the Perceval S bioprosthesis. The uncorrected platelet count at discharge/death was also significantly higher in patients with higher preoperative platelet count. *NA*, Not applicable.

TABLE E7. Results of the multivariable model with corrected platelet count at discharge/death as dependent variable

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Age, y	Male sex*	Preoperative thrombocyte count (/nl)	Valve size† (23 mm)	Valve size† (25 mm)	Approach‡	Total heparin dosage (IU)	Subvalvular myectomy*	Concomitant procedure§	Crossclamp (min)	CPB (min)
Estimated coefficients	−166.015	0	148.401	188.323	3.162	−46.201	0.651	57.606	70.870	23.819	−0.003	88.322	6.671	0.301	−0.569
Standard errors	271.749	NA	41.653	42.349	3.304	28.052	0.235	40.841	41.008	50.580	0.002	56.300	36.349	1.401	0.916
P values	.543	NA	<.001	<.001	.341	.103	.007	.162	.088	.639	.221	.121	.855	.831	.536

A nonparametric multiple regression model with simultaneous consideration of all variables potentially influencing the thrombocyte count and corrected platelet count at discharge/death as the response variable was fitted. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher corrected platelet count at discharge/death than the Perceval S bioprosthesis. The corrected platelet count at discharge/death was also significantly higher in patients with higher preoperative platelet count. *CPB*, Cardiopulmonary bypass; *NA*, not applicable. *Coded as No = 0 and Yes = 1. †Valves were available in 3 sizes for analysis. Size 21 mm served as reference. ‡Coded as 1 = full sternotomy and 2 = partial sternotomy. §Concomitant procedures except subvalvular myectomy; coded as No = 0 and Yes = 1.

	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Preoperative thrombocyte count (/nl)
Estimated coefficients	46.164	0	56.998	100.673	0.621
Standard errors	46.020	NA	29.033	27.755	0.218
P values	.319	NA	.053	<.001	.006

A nonparametric multiple regression model with backward elimination of all variables with a $P \leq .10$ were included (valve types, preoperative platelet count, subvalvular myectomy, concomitant procedure and crossclamp time) and corrected platelet count at discharge/death as the response variable was fitted. In a step before, multivariable models including the 3 valve types plus 1 extra variable as regressor variables had been constructed, details not shown. The *P* values of these models served as entry criterion as described. The model shows that the Labcor TLPB-A and the Hancock II bioprostheses were consistently associated with higher corrected platelet count at discharge/death than the Perceval S bioprosthesis. The corrected platelet count at discharge/death was also significantly higher in patients with higher preoperative platelet count. *NA*, Not applicable.

TABLE E8. Analysis of the subgroup of 46 patients who underwent operation by the 2 surgeons who used all 3 valve types

Effect of surgeon, results of the nonparametric multivariable models with minimum uncorrected platelet count as dependent variable					
	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Surgeon 2*
Estimated coefficients	54.421	0	23.089	25.957	1.575
Standard errors	5.961	NA	10.1756	11.605	8.068
P values	<.001	NA	.026	.028	.846
Effect of surgeon, results of the nonparametric multivariable models with minimum corrected platelet count as dependent variable					
	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Surgeon 2*
Estimated coefficients	46.381	0	18.136	17.433	3.960
Standard errors	6.573	NA	8.984	11.735	6.846
P values	<.001	NA	.047	.141	.565
Effect of surgeon, results of the nonparametric multivariable models with time to minimum uncorrected platelet count as dependent variable					
	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Surgeon 2*
Estimated coefficients	50.796	0	−9.467	−47.165	15.711
Standard errors	8.894	NA	11.654	9.034	10.736
P values	<.001	NA	.419	<.001	.147
Effect of surgeon, results of the nonparametric multivariable models with time to minimum corrected platelet count as dependent variable					
	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Surgeon 2*
Estimated coefficients	97.922	0	−42.806	−61.073	−19.730
Standard errors	39.230	NA	26.499	14.201	32.757
P values	.015	NA	.110	<.001	.549
Effect of surgeon, results of the nonparametric multivariable models with uncorrected platelet count at discharge/death as dependent variable					
	Intercept	Perceval S (Reference)	Labcor TLPB-A	Hancock II	Surgeon 2*
Estimated coefficients	183.918	0	75.452	213.472	−4.689
Standard errors	26.051	NA	40.893	59.128	31.826
P values	<.001	NA	.069	<.001	.883
Effect of surgeon, results of the nonparametric multivariable models with corrected platelet count at discharge/death as dependent variable					
	Intercept	Perceval S (reference)	Labcor TLPB-A	Hancock II	Surgeon 2*
Estimated coefficients	168.616	0	48.621	185.334	6.431
Standard errors	22.0054	NA	34.478	67.294	31.619
P values	<.001	NA	.198	.007	.839

Nonparametric multiple regression models with the 6 different variables given as the response variables and valve type and surgeon as regressor variables were fitted. In none of these models, surgeon was found to be a statistically significant variable; the results regarding valve type are largely consistent with the findings from the complete group of patients. *NA*, Not applicable. *Eight different surgeons implanted the Labcor TLPB-A and the Hancock II during the study period, but only 2 of them implanted the Perceval S. Therefore, the analysis of surgeon was limited to the 46 patients whom these 2 surgeons operated upon, and surgeon 1 served as reference.