The appreciation of prosthetic heart valves

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Chapter 7

Antithrombotic Therapy and Bleeding Events After Aortic Valve Replacement With a Novel Bioprosthesis

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J Thorac Cardiovasc Surg 2021

Abstract

Objective:
Several recent-generation surgical tissue valves have been found to have bleeding rates exceeding rates recommended by regulatory bodies. We explored bleeding events using data from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve to examine if this endpoint remains relevant for the evaluation of bioprostheses.

Methods:
Patients (n=1115) underwent aortic valve replacement. Bleeding and thromboembolic event episodes in patients within 3 years postimplant were analyzed for frequency, timing, and severity, focusing on patients taking antiplatelet/anticoagulant medications at the time of the event. Clinical and hemodynamic outcomes are also reported.

Results:
At 3 years, the Kaplan-Meier cumulative probability estimate of all-cause death was 7.2% (cardiac, 3.6%; valve-related, 1.1%). The Kaplan-Meier cumulative probability estimates of all and major hemorrhage were 8.7% and 5.2%, respectively. Ninety-nine bleeding events occurred in 86 patients: most occurred >30 days post-surgery. Among the 51 late major bleeds, in 5 cases the patients were taking anticoagulant/antiplatelet medication for post-SAVR prophylaxis at the time of the event, while the remaining patients were on medications for other reasons. Age (HR: 1.035, 95% CI: 1.004-1.068), peripheral vascular disease (2.135, 1.106-4.122), renal dysfunction (1.920, 1.055-3.494), and antithrombotic medication use at the time of the event (1.417, 1.048-1.915) were associated with late bleeds (major and minor).

Conclusions:
Overall clinical outcomes demonstrated low mortality and few complications except for major bleeding. Most bleeding events occurred >30 days after surgery and in patients taking antiplatelet and/or anticoagulation for indications other than postimplant prophylaxis.

Introduction

The PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial is a nonrandomized, multicenter study of the Avalus bioprosthesis (Medtronic, Minneapolis, MN), a low-profile, stented bovine pericardial valve. The primary analyses of the trial demonstrated low overall mortality and valve-related adverse events at 1 year of follow-up and hemodynamic performance comparable to that of other surgical aortic valves(1, 2).

Of interest, the Avalus valve exceeded the threshold for bleeding events in the objective performance criteria (OPC) established by the International Standards Organization (ISO)(3) for safety evaluation(1, 2). Although it is uncertain whether this is related to the new valve, our findings are in accordance with high bleeding rates in other recent premarket approval trials of the St. Jude Medical Trifecta and Edwards Inspiris valves(1, 2, 4, 5). Meanwhile, there have been no major revisions of the recommendations for anticoagulant prophylaxis after bioprosthetic valve implantation over the last decades(6, 7).

This study was designed to evaluate the incidence of bleeding and thromboembolic complications after bioprosthetic aortic valve replacement with the Avalus valve. Besides identifying predictors of bleeding events, the study focused on the indication and type of anticoagulant therapy at the time of the bleeding or thromboembolic event. To answer whether the bleedings were related to the prosthesis, we hypothesized that the majority of bleedings were due to anticoagulant prophylaxis for indications other than the prosthesis itself. The secondary objective of this study was to evaluate the other endpoints of the OPC and hemodynamic structural valve deterioration (SVD) to establish the safety profile of the Avalus valve at mid-term follow-up.

Materials And Methods

Study Design and Population

The design and primary results of the PERIGON Pivotal Trial were previously reported(1, 2). In brief, patients with symptomatic moderate or severe aortic stenosis, or chronic severe aortic regurgitation, and a clinical indication for surgical aortic valve replacement were eligible for enrollment. Inclusion and exclusion criteria were previously described in detail(1, 2). Concomitant procedures were allowed but were limited to left atrial appendage ligation, coronary artery bypass grafting, patent foramen ovale closure, ascending aortic aneurysm/dissection repair not requiring circulatory arrest, and subaortic membrane resection not requiring myectomy. Surgeons were allowed to choose the approach for valve implantation and the strategies for cardioplegia

and cardiopulmonary bypass. Supra-annular positioning was recommended by the manufacturer. The trial was conducted at 38 sites in Europe, Canada, and the United States(1, 2) .

After the first year of follow-up, clinical and echocardiographic evaluations were performed annually with additional telephone contacts at 18 and 30 months. Annual clinical and echocardiographic follow-up will continue through 5 years for all centers and for up to 12 years for a subset of centers. This manuscript describes bleeding events and reports outcomes through 3 years of follow-up.

Clinical Outcomes

Clinical outcomes included mortality and valve-related adverse events, ie, thromboembolism, valve thrombosis, all and major bleeding, all and major paravalvular leak (PVL), endocarditis, hemolysis, nonstructural valve dysfunction, reintervention, and explant. Late linearized rates of thromboembolism, valve thrombosis, major bleeding, major PVL, and endocarditis were assessed for comparison with the 2015 OPC.(3) Adverse events were adjudicated by an independent clinical events committee.

Table 1. Kaplan-Meier cumulative probability estimates of mortality and valve-related adverse events in patients with up to 3 years of follow-up

	Kaplan-Meier Estimate, % (95% CI)					
Event	**30 Days**	**1 Year**	**2 Years**	**3 Years**	**Linearized Late Event Rate[1]**	**2× OPC[1]**
No. of patients completing visit	1110	1042	865	572		
All death	0.9 (0.5,1.6)	3.0 (2.1, 4.1)	5.5 (4.2, 7.0)	7.2 (5.6, 9.0)	2.44	
Cardiac death	0.5 (0.2,1.1)	1.5 (0.9,2.4)	2.7 (1.9, 3.9)	3.6 (2.5, 4.9)	NA	
Valve-related death	0.0 (NA)	0.3 (0.1, 0.8)	1.0 (0.5, 1.8)	1.1 (0.6, 1.9)	0.43	
Thromboembolism	1.4 (0.8,2.2)	2.7 (1.9, 3.8)	4.2 (3.1, 5.5)	4.9 (3.6, 6.3)	1.58	3.0
Valve thrombosis	0.0 (NA)	0.0 (NA)	0.1 (0.0, 0.5)	0.2 (0.0, 0.8)	0.11	0.08
All bleeding	1.5 (0.9,2.4)	5.1 (3.9, 6.5)	7.0 (5.6, 8.7)	8.7 (7.0, 10.6)	2.94	
Major bleeding	1.0 (0.5,1.7)	3.5 (2.5, 4.7)	4.5 (3.4, 5.8)	5.2 (4.0, 6.8)	1.83	1.2
All paravalvular leak	0.2 (0.0,0.6)	0.5 (0.2, 1.0)	0.7 (0.3, 1.3)	0.7 (0.3, 1.3)	0.18	
Major paravalvular leak	0.1 (0.0,0.5)	0.2 (0.0, 0.6)	0.2 (0.0, 0.6)	0.2 (0.0, 0.6)	0.04	0.6
Endocarditis	0.2 (0.0,0.6)	1.1 (0.6, 1.9)	2.0 (1.3, 3.0)	2.6 (1.7, 3.8)	0.90	1.0
Hemolysis	0.0 (NA)	0.0 (NA)	0.0 (NA)	0.0 (NA)	0.00	
Non-structural valve dysfunction	0.2 (0.0,0.6)	0.5 (0.2, 1.0)	0.7 (0.3, 1.3)	0.7 (0.3, 1.3)	0.18	
Reintervention	0.3 (0.1,0.8)	0.8 (0.4, 1.5)	1.4 (0.8, 2.2)	2.0 (1.3, 3.1)	0.64	
Explant	0.3 (0.1,0.8)	0.8 (0.4, 1.5)	1.2 (0.7, 2.1)	1.9 (1.2, 3.0)	0.61	

[1]Percentage per patient-year. OPC late event rates are based on ISO 5840:2015 (3).
CI, confidence interval; OPC, objective performance criteria.

Bleeding Events

In the PERIGON Pivotal Trial, a bleeding event was broadly defined as any episode of internal or external bleeding. A major bleeding event was any bleeding episode that resulted in death, hospitalization, reoperation, centesis, or a decrease in hemoglobin to <7 g/dL; that required >3 units of blood transfusion; or that caused >1 L of blood loss. Per ISO 5480:2015(3), bleeding events associated with major trauma or a major operation unrelated to the prosthesis were excluded. In addition, all valve-related bleeding events that occurred in patients taking an antiplatelet and/or anticoagulant at the time of the bleeding event were adjudicated by the clinical events committee and used to calculate the valve-related bleeding safety endpoint (OPC)(3). All other episodes of internal or external blood loss (eg, nosebleeds requiring nose packing as an outpatient or in the ER, hematomas due to trauma or surgery not requiring transfusion, or minor ocular hemorrhage) were considered minor bleeding events. Early bleeding events were defined as those occurring ≤30 days postimplant, whereas late bleeding events were those that occurred >30 days postimplant.

The timing (days postimplant) of both major and minor bleeding events out to 3 years was reviewed. Baseline and procedural characteristics were examined to determine differences between (1) patients with any late bleeding event (major or minor) vs patients with no late bleeding event and (2) patients with a late major bleeding event vs patients with no late major bleeding event (ie, no bleeding or minor bleeding event).

Medication use was categorized as follows: no medication, aspirin or other antiplatelet only, aspirin and other antiplatelet (dual-antiplatelet therapy, DAPT), anticoagulant only, and any antiplatelet (ie, aspirin or other antiplatelet) and anticoagulant. In addition, source documents were reviewed to determine medication use at the time of the bleeding event and the indication for the medication.

Table 2. Indications for antiplatelet and/or anticoagulant use at the time of late major bleeding events (N=51)

	Aspirin or Other Antiplatelet (n=18)	DAPT (n=2)	Anticoagulant Alone (n=11)	Aspirin and/or Other Antiplatelet + Anticoagulant (n=17)	Other (n=3)
Post-SAVR prophylaxis	4			1	
CAD and/or prior stent placement	9	1		5	1
Congestive heart failure	1				1
Prior myocardial infarction or other thromboembolic event	3			1	1
Pre-existing atrial fibrillation			8	7	
New-onset atrial fibrillation			3	2	
Miscellaneous[1]	1	1		1	

CAD, coronary artery disease; DAPT, dual-antiplatelet therapy; SAVR, surgical aortic valve replacement. [1]Miscellaneous indications include ocular migraine (n=1), acute limb injury (n=1), and infectious endocarditis (n=1).

Thromboembolic Events

Thromboembolic events were broadly defined as a clot or other particulate matter not associated with infection that originated on or near the bioprosthetic valve and was transported to another part of the body. Diagnosis could be indicated by a new, permanent or transient, focal or global neurologic deficit (exclusive of hemorrhage), any peripheral arterial embolus (unless proved to have resulted from another cause), or acute myocardial infarction that occurred in patients with known normal coronary arteries. We examined the timing of thromboembolic events as well as the use of antithrombotic medication, and indications, at the time of the event.

Hemodynamic Outcomes

Echocardiographic outcomes were adjudicated by a central core laboratory (MedStar, Washington, DC). Effective orifice area, mean gradient, and aortic regurgitation (transvalvular and paravalvular) were assessed at each visit. In a separate analysis, the incidence of hemodynamic SVD at 3 years was calculated. Hemodynamic SVD was defined through modification of the European consensus definition, as has been published elsewhere.(8),(9) Total hemodynamic SVD was defined as a mean gradient ≥20 mm Hg at any follow-up visit and an increase in gradient ≥10 mm Hg from discharge/3-6 months, and/or new moderate or severe transvalvular aortic regurgitation. Moderate hemodynamic SVD was defined as a mean gradient ≥20 mm Hg at any follow-up visit and an increase in gradient ≥10 mm Hg from discharge/3-6 months, and/or new moderate transvalvular aortic regurgitation; severe hemodynamic SVD was defined as mean gradient ≥40 mm Hg at any follow-up visit, an increase in mean gradient of ≥20 mm Hg from discharge/6-6 months, and/or new severe transvalvular aortic regurgitation.

Statistical Analysis

For categorical variables, the number and percentage of patients are presented. For continuous variables, the means and standard deviations are presented. The cumulative probability of mortality and valve-related adverse events at 3 years was estimated using the Kaplan-Meier method. Linearized rates of late thromboembolism, valve thrombosis, major bleeding, major PVL, and endocarditis were calculated as the number of events per total patient-years of follow-up, expressed as a percentage. Per ISO 5840:2015(3), the rates of these adverse events should be below 2× the published rate. A univariable Fine-Gray regression model(10) was fitted to identify baseline and procedural characteristics for a late bleeding event out to 3 years, with late defined as >30 days postimplant.

A multivariable Fine-Gray regression model(10) was fit to explore the effects of baseline characteristics and antithrombotic medication on the hazard of late bleeding events, adjusting for the competing risk of death. Antithrombotic medication use was included as a time-dependent variable in the model to compare the hazard of bleeding between different antithrombotic medication therapies, considering medication use at the beginning of each follow-up visit window. Based on results of preliminary analysis, antithrombic medication use was considered as a continuous variable with four levels. No antithrombotic medication was used as the baseline comparator, with aspirin or antiplatelet use only considered as the next level, followed by either anticoagulant only or DAPT. Aspirin and/or antiplatelet with an anticoagulant was considered as the highest antithrombotic medication level. Appendix Table 1 lists the baseline patient and procedural characteristics evaluated in the Fine-Gray univariable model. Age, atrial fibrillation, carotid artery disease, coronary artery disease, diabetes, peripheral vascular disease, renal dysfunction/insufficiency, and stroke were considered for inclusion in the multivariable model based on the results of the univariable Fine-Gray model.

In the Kaplan-Meier and Fine-Gray analyses, we considered time to first event due to the low number of recurrent bleeding events. Analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Patient Follow-up

The study enrolled 1278 patients, of which 1115 received the study valve and were thus included in the analysis. At the time of analysis, median follow-up duration was 2.9 years and 572 patients had completed the 3-year follow-up visit (Appendix Figure 1). Total follow-up was 2882.2 patient-years. A list of key baseline characteristics is provided in Appendix Table 1. Briefly, the mean age of all patients was 70.2±9.0 years, and 75.1%

were male. The mean Society of Thoracic Surgeons predicted risk of mortality score was 2.0±1.4%, and 42.2% of patients were in New York Heart Association class III/IV. Almost 44% of the patients had coronary artery disease. Aortic stenosis was the primary indication for valve replacement in 84.3% of patients. Concomitant procedures were performed in approximately half of all patients, including coronary artery bypass grafting in 32.5% of patients (Appendix Table 1).

Clinical Outcomes

A summary of clinical safety events through 3 year is provided in Table 1. At 3 years, the Kaplan-Meier cumulative probability estimate of all-cause death was 7.2% (cardiac death, 3.6%; valve-related death, 1.1%). The rate of bleeding was 8.7% at 3 years, and major bleeding was 5.2%. The rate of thromboembolism was 4.9% at 3 years. Other events were less common, including endocarditis (2.6%), reintervention (2.0%), and explant (1.9%). Table 1 also shows the linearized rates of late thromboembolism, valve thrombosis, major bleeding, major PVL, and endocarditis, along with the OPC standards (twice the published rate) for those events.

Bleeding Events

During 3-year follow-up, 99 bleeding events occurred in 86 patients. There were 19 early (ie, within 30 days) events -and in 17 patients: 12 were classified as major and 7 as minor. There were 80 late (>30 days) bleeding events in 70 patients: 51 were major and 29 minor. Appendix Figure 2 illustrates the timing of the bleeding events. Seventy-six patients each had 1 bleeding event (45 major and 31 minor). Eight patients each had 2 bleeding events (both bleeding events were major in 5 patients and minor in 2 patients, and in 1 patient the first bleed was major and the second minor). One patient had 3 bleeding events during follow-up; all were major and occurred >1 year postimplant (days 416, 666, and 942). One patient had 4 bleeding events during follow-up; again, all were major bleeds occurring >1 year after the procedure (days 428, 955, 963, and 966). The Kaplan-Meier cumulative probability estimate of all late bleeding events and late major bleeding events were 7.3% and 4.3% at 3 years of follow-up, respectively (Figure 1).

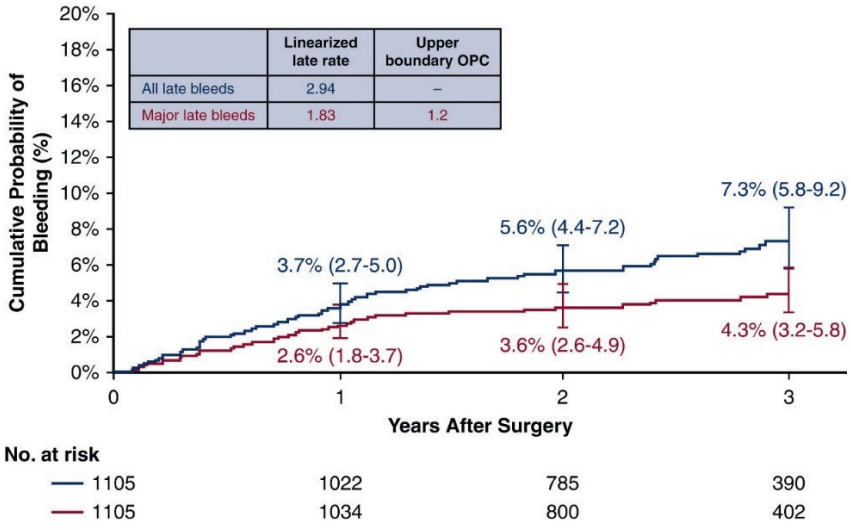

Figure 1. All late and late major bleeding to 3 years (KM) with linearized late major bleeding.

Seven patients died within 30 days of the last bleeding event (range, 0 to 15 days). One patient had a total of four bleeding events before death, one patient had two bleeding events before death, and five had only one bleeding event before death. All bleeding events experienced by these patients were classified as major.

Figure 2 shows the distribution of medication use from baseline through 3 years. At baseline just over half of patients were taking aspirin or another antiplatelet agent only, and nearly one third of patients were taking no antithrombotic medication. Early after operation nearly half of the patients were taking aspirin or another antiplatelet only, and slightly more than one third were taking aspirin or another antiplatelet with an anticoagulant. Primary indications for medication use at the time of late bleeding events are reported in Table 2 and Figure 3. As shown, most patients were taking an antiplatelet and/or anticoagulant for conditions other than post-surgical aortic valve replacement (SAVR) prophylaxis.

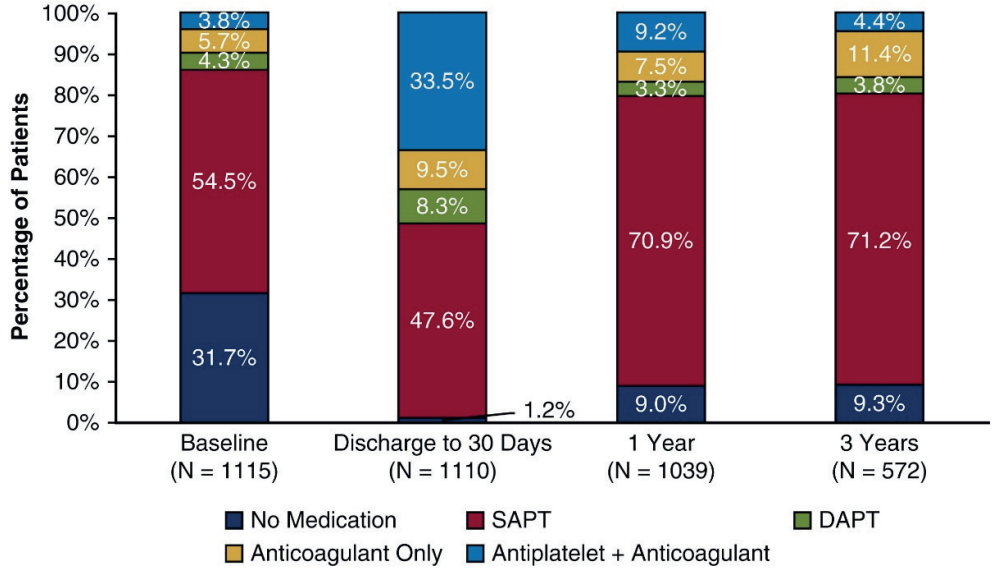

Figure 2. Distribution of medication use over time. SAPT = single antiplatelet and comprises aspirin or another antiplatelet alone. DAPT = dual antiplatelet. The SAPT category includes patients with only "other antiplatelet" selected on the case report form, whereas the DAPT category includes patients with both "aspirin" and "other antiplatelet" selected. It is possible that some patients in either group were taking >1 antiplatelet at the follow-up visit.

The results of the univariable analysis are shown in Table 3. Table 4 presents the results of the multivariable analysis, and indicates that the risk of any late bleeding event was greater in older patients, those with preoperative peripheral vascular disease, preoperative renal dysfunction, and those taking antithrombotic medication at the time of the event. The baseline and procedural characteristics of patients in these subgroup analyses are listed in Appendix Table 1.

Thromboembolic Events

There were 55 thromboembolic events in 49 patients out to 3 years of follow-up. Forty-three patients had a single thromboembolic event: 25 embolic strokes (6 early, 19 late), 17 transient ischemic attacks (5 early, 12 late), and 1 peripheral embolus (early). Six patients each had 2 thromboembolic events: 3 patients each had 2 embolic strokes (all late), and 3 patients each had 1 stroke and 1 transient ischemic attack (in 1 patient both events were early, in 2 patients had an early stroke and a late transient ischemic attack). Primary indications for medication use at the time of thromboembolic events are reported in Table 5. As shown, most patients were taking an antiplatelet and/or anticoagulant for conditions other than post-SAVR prophylaxis.

Table 3. Univariable Fine-Gray proportional hazard analysis of patient and procedural characteristics associated with any late bleeding event within 3 years of follow-up. Late events were those occurring >30 days postimplant. Analysis of late events includes subjects with more than 30 days of follow up.

Variable	No Late Bleeding Events (N=1035)	Late Bleeding Events (N=70)	Hazard Ratio (95% CI)	P-value
Age (years)	69.9 ± 9.0	73.3 ± 7.9	1.048 (1.017-1.080)	0.002
Atrial fibrillation	97 (9.4%)	12 (17.1%)	1.939 (1.046-3.594)	0.036
Carotid artery disease	8.7% (90)	17.1% (12/70)	2.085 (1.116-3.895)	0.021
Coronary artery disease	43.0% (445/1035)	52.9% (37/70)	1.474 (0.923-2.355)	0.105
Diabetes	26.2% (271/1035)	34.3% (24/70)	1.487 (0.906-2.440)	0.116
Peripheral vascular disease	66 (6.4%)	12 (17.1%)	2.847 (1.505-5.387)	0.001
Renal dysfunction/ insufficiency	100 (9.7%)	14 (20.0%)	2.304 (1.270-4.181)	0.006
Stroke	3.6% (37)	7.1% (5)	2.000 (0.815-4.908)	0.130

CI, confidence interval.

Hemodynamic Performance

At 3 years, effective orifice area and mean aortic gradient appeared stable (Appendix Figure 3). Transvalvular regurgitation rates were low, with only 0.6% and 0.2% of patients experiencing moderate or severe regurgitation, respectively (Appendix Figure 4). No patients had moderate or severe paravalvular regurgitation at 3 years (Appendix Figure 5). Hemodynamic SVD occurred in 3.2% of all patients; severe hemodynamic SVD was present in 4 patients (0.4%) (Appendix Table 2).

Discussion

We found that the late linearized major bleeding event rate of the PERIGON exceeded the OPC for new prosthetic valves. However, in the vast majority of the patients with late major bleeding events, the indication for antithrombotic therapy was not related to post-SAVR prophylaxis but to comorbid conditions. The late linearized rate of thromboembolic events did not exceed the OPC.

For approval of surgical aortic valves, the Food and Drug Administration relies on objective performance criteria (OPC) established on linearized rates of late valve-related adverse events. Historically, for surgical valves, the OPCs, including bleeding, were developed in the early 1990s, based on the work of Grunkemeier et al(11) and incorporated into the Food and Drug Administration heart valve guidance and later into the International Organization for Standardization (ISO) 5840 standard for heart valves. At that time, mechanical valve implantation was much more prevalent, and hemorrhage events were incorporated as a means to identify possible signals of elevated anticoagulation in patients taking anticoagulation for prevention of thrombus formation after valve implantation. The bleeding definitions employed were broad and included bleeding events in subjects taking anticoagulation or antiplatelet therapy. In

recent generations of bioprosthetic valves, it has been observed that many of these valves have not met the historical bleeding OPC. This includes the St. Jude Medical Trifecta, Edwards Inspiris, and Medtronic Avalus valves(1, 2, 4, 5).

Thus, the primary objective of this analysis was to further understand the bleeding events that occurred. At 3 years, freedom from all and major bleeding events in the PERIGON Pivotal Trial was 91.3% and 94.8%, respectively. The vast majority of patients who suffered a bleeding event were using antithrombotic therapies for indications other than the newly replaced aortic valve, eg, pre-existing atrial fibrillation, coronary artery disease, prior stent, or congestive heart failure (Table 2 and Figure 3).

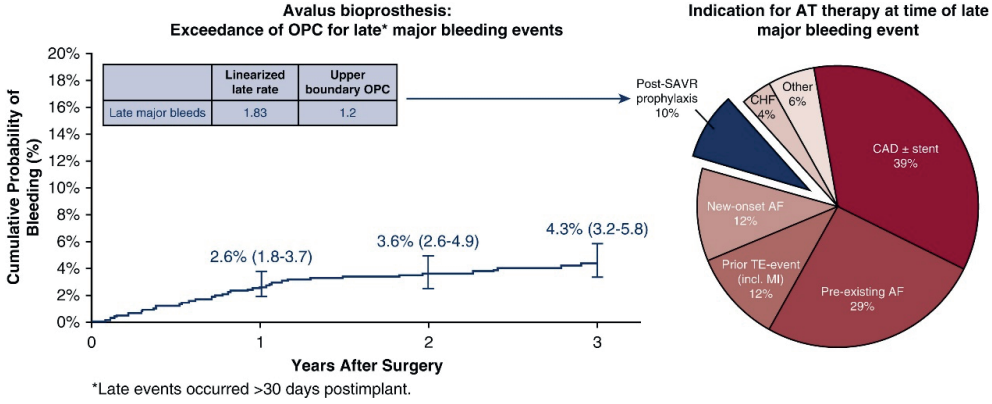

Figure 3. Antithrombotic (AT) therapy and late major bleeding events after aortic valve replacement with a novel bioprosthesis. The objective performance criteria (OPC) for bleeding events require revision due to broader indications for AT therapy and improved quality of clinical trials. AF indicates atrial fibrillation; CAD, coronary artery disease, CHF, congestive heart failure; MI, myocardial infarction; SAVR, surgical aortic valve replacement; TE, thromboembolic.

Of the antithrombotic medication categories considered, the combined use of antiplatelet and anticoagulant therapies had the greatest impact on the hazard of late bleeding events. Whether this combination is necessary is debatable, as recent TAVR studies have demonstrated that the addition of antiplatelet therapy to anticoagulant therapy does not decrease the risk of stroke(12) or thromboembolic events(13), but does increase the risk of bleeding in patients with atrial fibrillation. In accordance with these findings, our results demonstrate linearized late event rates that surpassed the OPC for bleeding events and remained within the OPC for thromboembolic events(3). As antithrombotic therapy is aimed at preventing thromboembolic complications while avoiding bleeding complications, this may suggest that the use of antithrombotic therapy was too aggressive and current protocols require revision. However, it is important to note that the majority of patients with late bleeding events required antithrombotic

therapy for comorbidities unrelated to the prosthesis. As determining the optimal antithrombotic treatment strategy after SAVR was outside the scope of the original study, it remains unclear whether these patients would benefit from less antithrombotic therapy. Our study does highlight the importance of routine examination to determine whether patients have a valid indication for therapy during follow-up.

Table 4. Multivariable Fine-Gray Analysis of All Late Bleeding Events

		Late Bleeding	
Parameter	**Hazard Ratio**	**95% CI**	**P value**
Age	1.035	1.004-1.068	0.03
Carotid artery disease	1.598	0.855-2.989	0.14
Peripheral vascular disease	2.135	1.106-4.122	0.02
Renal dysfunction/insufficiency	1.920	1.055-3.494	0.03
Antithrombotic medication	1.417	1.048-1.915	0.02

Our findings are comparable to those of other contemporary trials; the freedom from all bleeding events was 95.0% for the Edwards Inspiris at 2 years, and freedom from major bleeding events at 3 years was 89.3% for the Abbott Trifecta(5, 14). The rate of thromboembolic events in the present study, 1.5% per late patient-year, was slightly lower compared to the Edwards Inspiris and Abbott Trifecta, with respective event rates of 2.1% and 1.9%. While the exceedance of the OPC for bleeding events in the PERIGON trial is rightfully questioned, it is important to highlight that the reporting of bleeding events may be susceptible to subjectivity. For example, the latest low-risk transcatheter aortic valve replacement (TAVR) vs SAVR trials reported a 24.5% (low-risk PARTNER 3) and 8.9% (low-risk Evolut R) incidence of major bleeding in the surgical arms at 1 year(15, 16). In comparison, one of the studies on which the current OPC criteria are based had a freedom from bleeding estimate of 99% after 5 years(17). For the reporting of adverse events, Celiento et al. used the same guidelines as the PERIGON Pivotal Trial(18). However, the definition of bleeding events in the PERIGON Pivotal Trial was substantially more broad. Besides any bleeding episode that resulted in death, hospitalization, reoperation, or centesis, the definition of major bleeding included a decrease in hemoglobin to <7 g/dL that required >3 units of blood transfusion or that caused >1 L of blood loss. In addition, the extensive monitoring in the PERIGON Pivotal Trial, with routine follow-up visits and telephone contacts, increases the detection rate of minor adverse events such as nosebleeds and hematomas. As the definition and monitoring of adverse events have become more rigorous for recent investigational trials, the exceedance of the OPC for bleeding may reflect a change in study design rigor rather than an actual increase in bleeding rates. This would furthermore explain why other contemporaneous trials have also exceeded the OPC for bleeding.[7]

Table 5. Primary indications antiplatelet and/or anticoagulant use at the time of thromboembolic events.

	Aspirin or Other Antiplatelet (n=27)	DAPT (n=5)	Anticoagulant Alone (n=8)	Aspirin and/or Other Antiplatelet + Anticoagulant (n=4)
Post-SAVR prophylaxis	7	1	1	
CAD and/or stent placement	10	2	1	1
Pre-existing atrial fibrillation	3		5	2
Carotid endarterectomy	1			
History of TIA/stroke	5	1	1	1
Compartment syndrome		1		
Unknown	1			

The results reported here represent the longest follow-up available on the Avalus valve. Overall hemodynamic performance in this trial demonstrates stable gradients and EOA through 3 years after surgical valve replacement, in addition to low Kaplan-Meier probabilities of reintervention (2.0%) and requirement for explantation (1.9%). As hypoattenuated leaflet thickening may be related to early SVD(3), the comparison of SVD rates after surgical or transcatheter aortic valve replacement is relevant. While all patients receive DAPT therapy after TAVR, nearly half of the patients in the PERIGON Pivotal Trial received either no antithrombotic therapy or only single-antiplatelet therapy at discharge. At 3 years, only 3.2% of patients demonstrated signs of hemodynamic SVD, and only 0.4% were classified as severe. The definition used in this present analysis is a modification of the European consensus definition, which defines SVD only in patients with an actual worsening of the mean gradient in subsequent echocardiographic evaluations(8). In comparison, a recent randomized TAVR study that utilized a similar modified SVD definition reported 1.4% and 12.4% total SVD at 6 years for, respectively, the TAVR and SAVR arms(9). Additionally, a separate 5-year randomized TAVR study that strictly followed the Capodanno definition of SVD reported 9.2% total SVD and 0.8% severe SVD in TAVR patients and 26.6% total SVD and 1.7% severe SVD in SAVR patients(19).

Limitations

The 3-year follow-up visit was not completed for all participating patients at the time of analyses (Appendix Figure 1). The DAPT category for the medication use analyses included subjects with both "aspirin" and "other antiplatelet" checked on the case report form. It is possible some of these patients were taking more than one "other" antiplatelet. While medication use was monitored at routine visits, the exact moment of changes in medication use is unknown, which could potentially influence the results of our multivariable model. In addition, our conclusions are limited by the definition of bleeding safety events per ISO 5480, as only anticoagulant-related bleeding events were adjudicated by the clinical events committee. However, this limitation is consistent with other premarket approval trials.

Conclusions

Overall clinical outcomes have demonstrated low mortality and few complications at 3-year follow-up, except for a bleeding rate that exceeds the OPC. Most bleeding events occurred >30 days after the procedure and occurred mainly in patients who were taking antiplatelet and/or anticoagulation for indications other than postimplant prophylaxis. Few patients have exhibited signs of hemodynamic SVD at 3 years.

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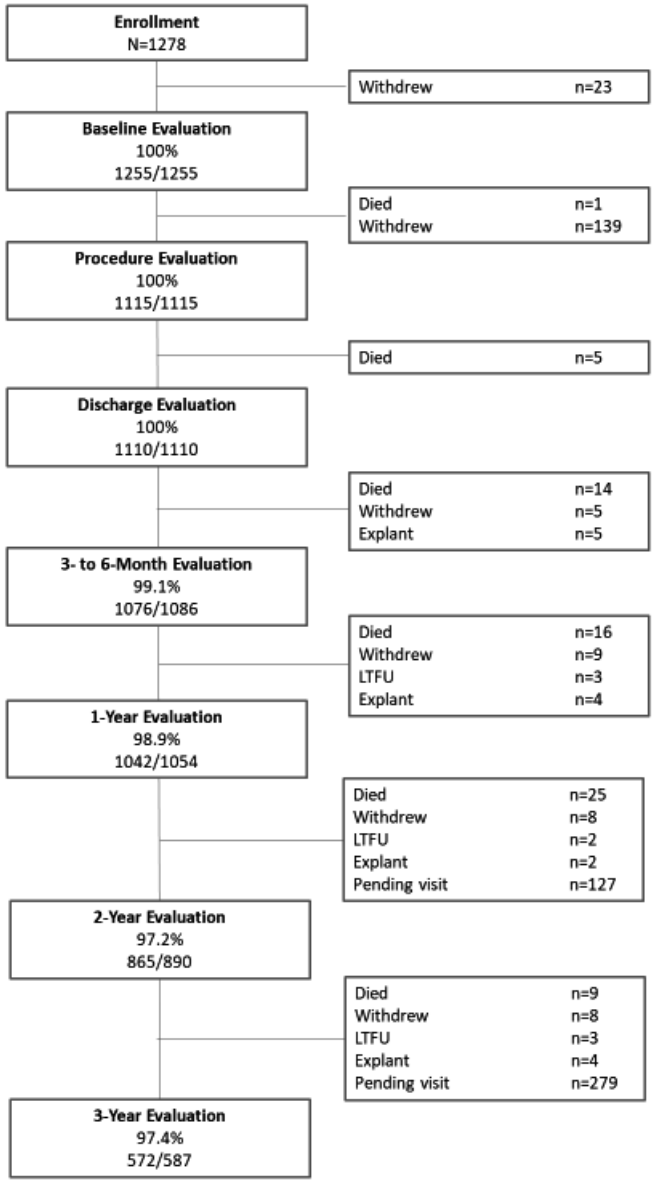
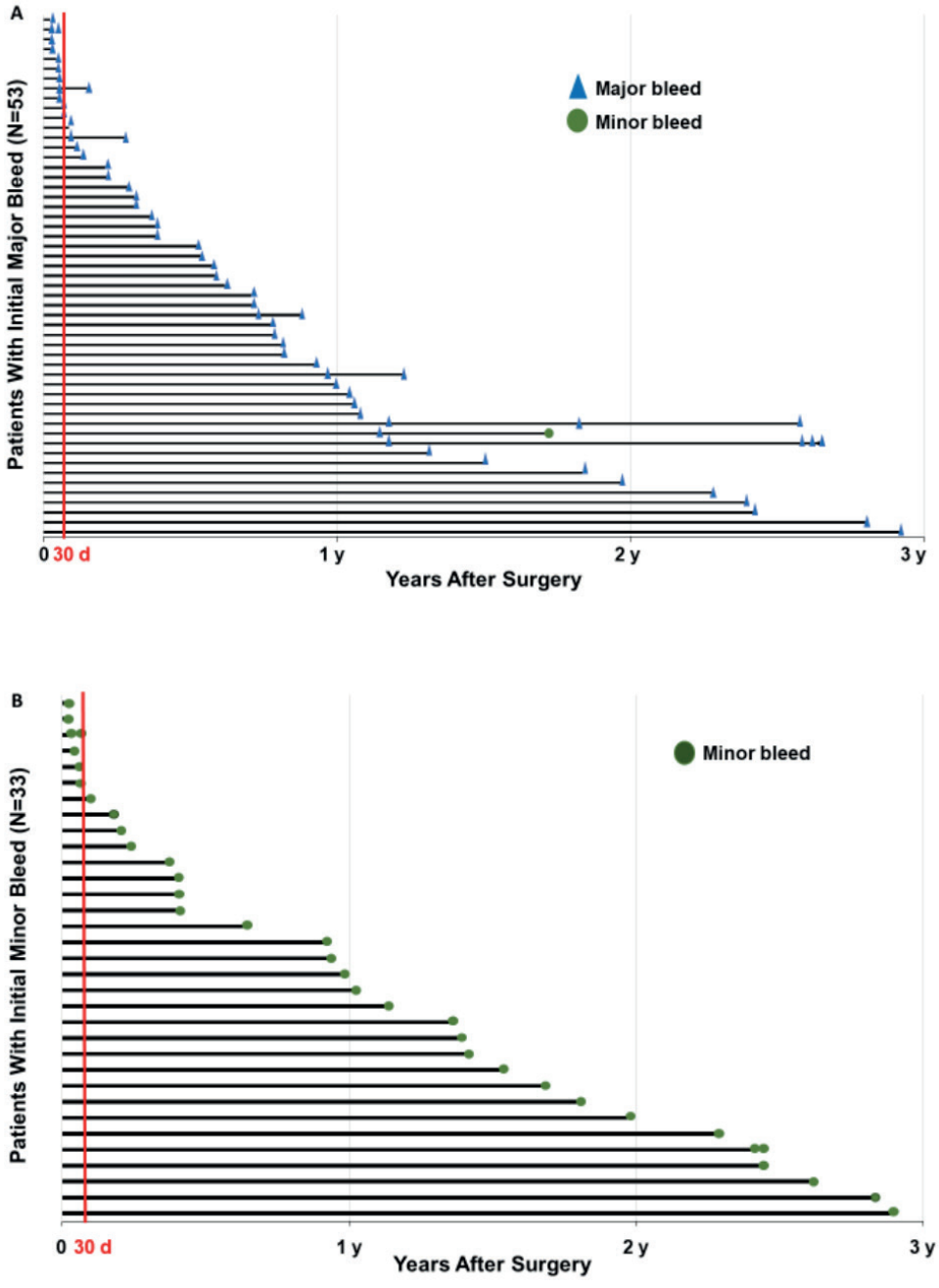
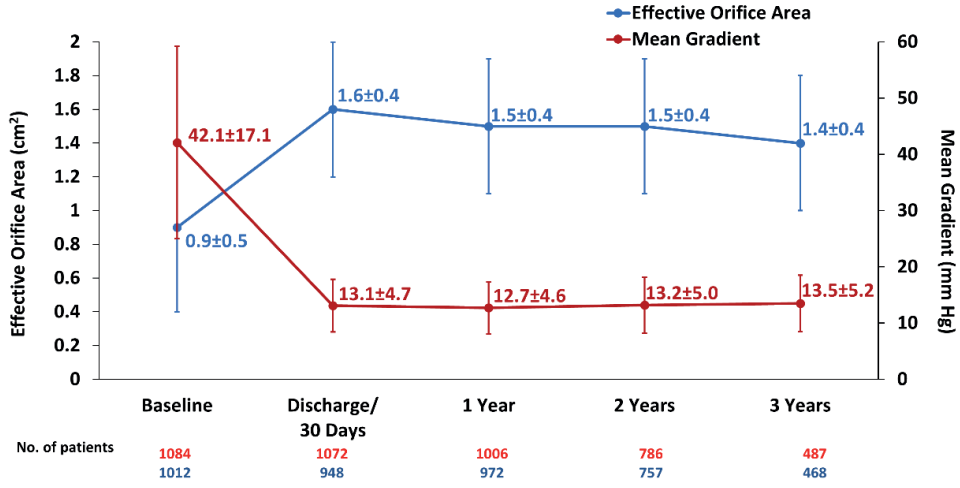
Appendix



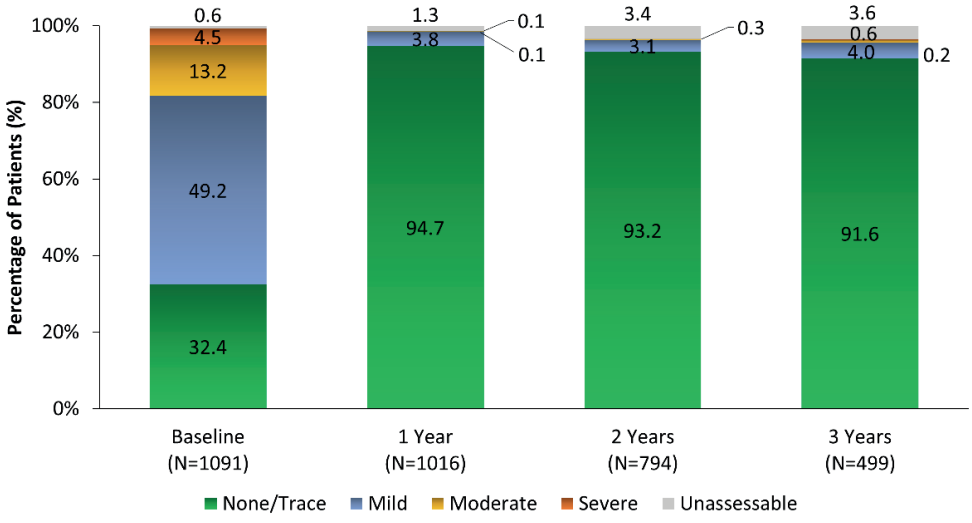
Appendix Figure 1. CONSORT diagram of compliance and patient flow through the study. Percentages indicate the compliance rate for follow-up (number of visits completed/number of visits expected.



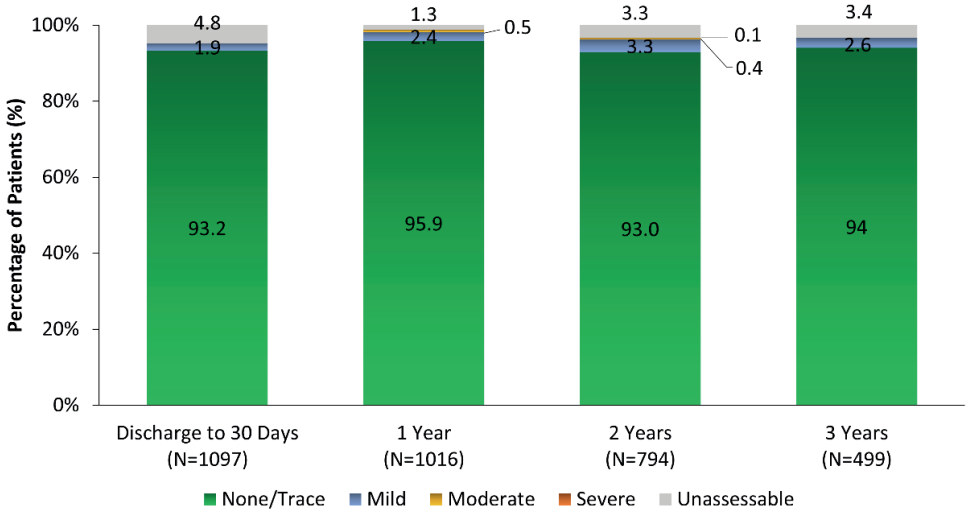
Appendix Figure 2. Time to bleeding events in patients with (A) an initial major bleed or (B) an initial minor bleed.



Appendix Figure 3. Mean aortic gradient and effective orifice area from baseline to 3 years.



Appendix Figure 4. Transvalvular regurgitation from baseline to 3 years.



Appendix Figure 5. Paravalvular regurgitation from baseline to 3 years.

Appendix Table 1. Patient baseline and procedural characteristics examined in the univariable Fine-Gray model.

		Late Bleeding Events*		Late Major Bleeding Events*	
Characteristics	**All Patients (N=1115)**	**None (N=1035)**	**Late Bleeding (N=70)**	**None (N=1062)**	**Late Major Bleeding (N=43)**
Age, y	70.2±9.0	69.9±9.0	73.3±7.9	69.9±9.0	74.4±8.0
Male gender	837 (75.1%)	778 (75.2%)	52 (74.3%)	795 (74.9%)	35 (81.4%)
Body mass index, kg/m^2	29.4±5.4	29.4±5.4	29.4±5.5	29.4±5.4	29.7±5.6
Atrial fibrillation	112 (10.0%)	97 (9.4%)	12 (17.1%)	101 (9.5%)	8 (18.6%)
Bleeding	24 (2.2%)	23 (2.2%)	1 (1.4%)	23 (2.2%)	1 (2.3%)
Cancer	160 (14.3%)	145 (14.0%)	13 (18.6%)	151 (14.2%)	7 (16.3%)
Carotid artery disease	103 (9.2%)	90 (8.7%)	12 (17.1%)	96 (9.0%)	6 (14.0%)
Chronic obstructive lung disease	130 (11.7%)	118 (11.4%)	11 (15.7%)	119 (11.2%)	10 (23.3%)
Congestive heart failure	221 (19.8%)	200 (19.3%)	17 (24.3%)	204 (19.2%)	13 (30.2%)
Coronary artery disease	486 (43.6%)	445 (43.0%)	37 (52.9%)	461 (43.4%)	21 (48.8%)
Diabetes	298 (26.7%)	271 (26.2%)	24 (34.3%)	278 (26.2%)	17 (39.5%)
Hypertension	849 (76.1%)	782 (75.6%)	57 (81.4%)	804 (75.7%)	35 (81.4%)
Liver disease	24 (2.2%)	21 (2.0%)	1 (1.4%)	21 (2.0%)	1 (2.3%)
Myocardial infarction	99 (8.9%)	90 (8.7%)	9 (12.9%)	92 (8.7%)	7 (16.3%)
Peripheral vascular disease	81 (7.3%)	66 (6.4%)	12 (17.1%)	71 (6.7%)	7 (16.3%)
Renal dysfunction/insufficiency	119 (10.7%)	100 (9.7%)	14 (20.0%)	103 (9.7%)	11 (25.6%)
Stroke/cerebrovascular accident	44 (3.9%)	37 (3.6%)	5 (7.1%)	40 (3.8%)	2 (4.7%)
Percutaneous coronary intervention	158 (14.2%)	145 (14.0%)	11 (15.7%)	148 (13.9%)	8 (18.6%)
Concomitant coronary artery bypass graft	362 (32.5%)	337 (32.6%)	23 (32.9%)	344 (32.4%)	16 (37.2%)

*Late was defined as >30 days postimplant. †Dual-antiplatelet therapy includes subjects with both aspirin and other antiplatelet checked. Patients may have been taking >1 other antiplatelet.

Appendix Table 2. Hemodynamic structural valve deterioration (SVD) through 3 years

	N=1104*
Total SVD	35 (3.2%)
Mean gradient at any time of ≥20 mm Hg AND an increase of ≥10 mm Hg from discharge/3-6 months	33 (3.0%)
Moderate or severe transvalvular AR (new from discharge)	2 (0.2%)
Moderate hemodynamic SVD	31 (2.8%)
Mean gradient at any time of ≥20 mm Hg AND an increase of ≥10 mm Hg from discharge/3-6 months	29 (2.6%)
Moderate transvalvular AR (new from discharge)	2 (0.2%)
Severe hemodynamic SVD	4 (0.4%)
Mean gradient at any time ≥40 mm Hg	3 (0.3%)
An increase of mean gradient of ≥20 mm Hg from discharge/3-6 months	3 (0.3%)
Severe transvalvular AR (new from discharge)	0 (0.0%)

Definition modified from Capadanno et al.[8] *Echocardiograms were unavailable or unevaluable for 11 patients.