Antithrombotic therapy and bleeding events after aortic valve replacement with a novel bioprosthesis

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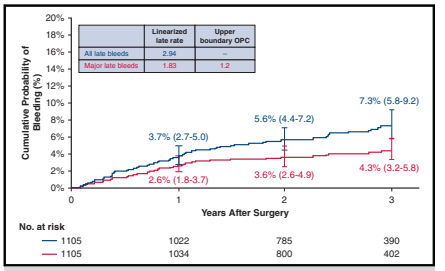
ABSTRACT

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 (Medtronic, Minneapolis, Minn) to examine whether this end point 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 postsurgery. Among the 51 late major bleeds, in 5 cases the patients were taking anticoagulant/antiplatelet medication for prophylaxis after surgical aortic valve replacement at the time of the event, whereas the remaining patients were taking medications for other reasons. Age (hazard ratio, 1.035; 95% confidence interval, 1.004-1.068), peripheral vascular disease (hazard ratio, 2.135; 95% confidence interval, 1.106-4.122), renal dysfunction (hazard ratio, 1.920; 95% confidence interval, 1.055-3.494), and antithrombotic medication use at the time of the event (hazard ratio, 1.417; 95% confidence interval, 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. (J Thorac Cardiovasc Surg 2021;161:66-75)



All late and major late bleeding to 3 years with linearized late major bleeding.

CENTRAL MESSAGE

The rate of bleeding events in the PERIGON trial reflects recent developments in nonvalve-related indications for antithrombotic therapies and scrutiny of investigational trials.

PERSPECTIVE

In the PERIGON trial, which provides safety and performance data on the novel Avalus valve (Medtronic, Minneapolis, Minn), bleeding events exceeded the percentage that reflects safety according to objective performance criteria. But with changing and broader indications for antithrombotic therapies and increased scrutiny around quality of trials, the objective performance criteria for bleeding may need adjustment because they no longer seem to reflect valve safety.

See Commentaries on pages 76 and 78.

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Abbreviations and Acronyms

DAPT = dual-antiplatelet therapy
ISO = International Organization for Standardization
OPC = objective performance criteria
PERIGON = Pericardial Surgical Aortic Valve Replacement Pivotal Trial for the Avalus valve
PVL = paravalvular leak
SVD = structural valve deterioration
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement

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The Pericardial Surgical Aortic Valve Replacement (PERIGON) Pivotal Trial is a nonrandomized, multicenter study of the Avalus bioprosthesis (Medtronic, Minneapolis, Minn), 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]

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 (St Paul, Minn) Trifecta and Edwards (Irvine, Calif) Inspiris valves.[1,2,4,5] Meanwhile, there have been no major revisions of the recommendations for anticoagulant prophylaxis after bioprosthetic valve implantation during the past 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 end points of the OPC and hemodynamic structural valve deterioration (SVD) to establish the safety profile of the Avalus valve at midterm follow-up.

MATERIALS AND METHODS

Study Design and Population

The design and primary results of the PERIGON 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 (SAVR) 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. Supraannular 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.

Bleeding Events

In PERIGON, 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 U blood transfusion or that caused >1 L 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 agent at the time of the bleeding event were adjudicated by the clinical events committee and used to calculate the valve-related bleeding safety end point (ie, OPC).[3] All other episodes of internal or external blood loss (eg, nosebleeds requiring nose packing as an outpatient or in an emergency department, 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 patients with any late bleeding event (major or minor) versus patients with no late bleeding event and patients with a late major bleeding event versus 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.

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 $\geq$20 mm Hg at any follow-up visit and an increase in gradient $\geq$10 mm Hg from discharge/3 to 6 months, and/or new moderate or severe transvalvular aortic regurgitation. Moderate hemodynamic SVD was defined as a mean gradient $\geq$20 mm Hg at any follow-up visit and an increase in gradient $\geq$10 mm Hg from discharge/3 to 6 months, and/or new moderate transvalvular aortic regurgitation; severe hemodynamic SVD was defined as mean gradient $\geq$40 mm Hg at any follow-up visit, an increase in mean gradient of $\geq$20 mm Hg from discharge/3 to 6 months, and/or new severe transvalvular aortic regurgitation.

Statistical Analysis

For categorical variables, the number and percentage of patients is presented. For continuous variables, the mean $\pm$ standard deviation is 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$\times$ 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 4 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. Table E1 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 whom 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 (Figure E1). Total follow-up was 2882.2 patient-years. A list of key baseline characteristics is provided in Table E1. Briefly, the mean age of all patients was 70.2 $\pm$ 9.0 years, and 75.1% were men. The mean Society of Thoracic Surgeons predicted risk of mortality score was 2.0% $\pm$ 1.4%, and 42.2% of patients were in New York Heart Association functional class III or IV. Almost 44% of 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 (Table E1).

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 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. Figure E2 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

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

Event	Kaplan-Meier estimate				Linearized late event rate*	Upper boundary OPC performance criteria†
	30 d	1 y	2 y	3 y		
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)	1.22	
Valve-related death	–	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	–	–	0.1 (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	–	–	–	–	–	
Nonstructural 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	

Values are presented as % (95% confidence interval) unless otherwise noted. *OPC*, Objective performance criteria. *Percentage per patient-year. †Objective performance criteria late event rates are based on ISO 5840:2015.[3]

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).

Seven patients died within 30 days of the last bleeding event (range, 0-15 days). One patient had a total of 4 bleeding events before death, 1 patient had 2 bleeding events before death, and 5 had 1 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 more than half of patients were taking aspirin or another antiplatelet agent only, and nearly one third of patients were taking no

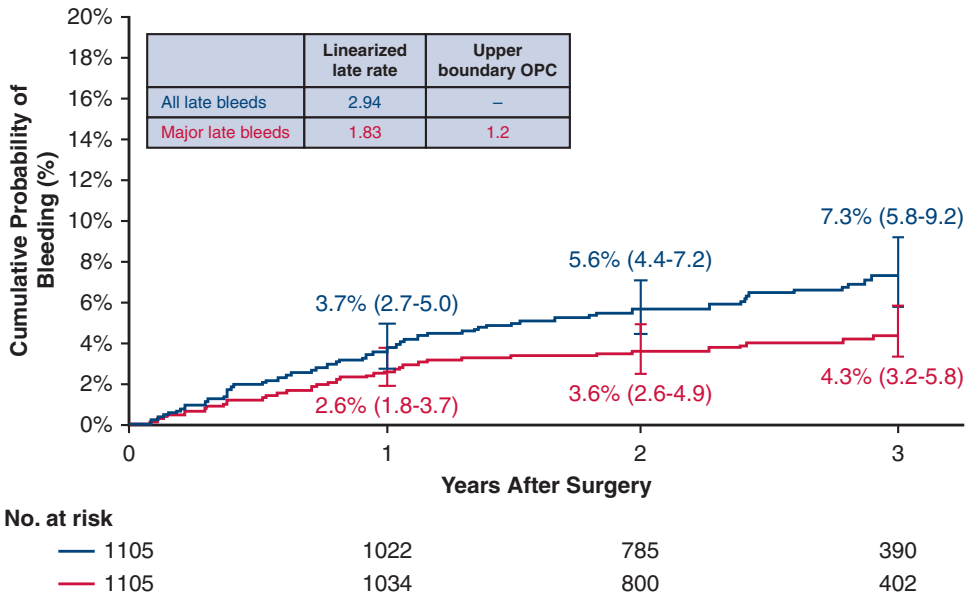

FIGURE 1. All late and late major bleeding to 3 years with linearized late major bleeding. *OPC*, Objective performance criteria.

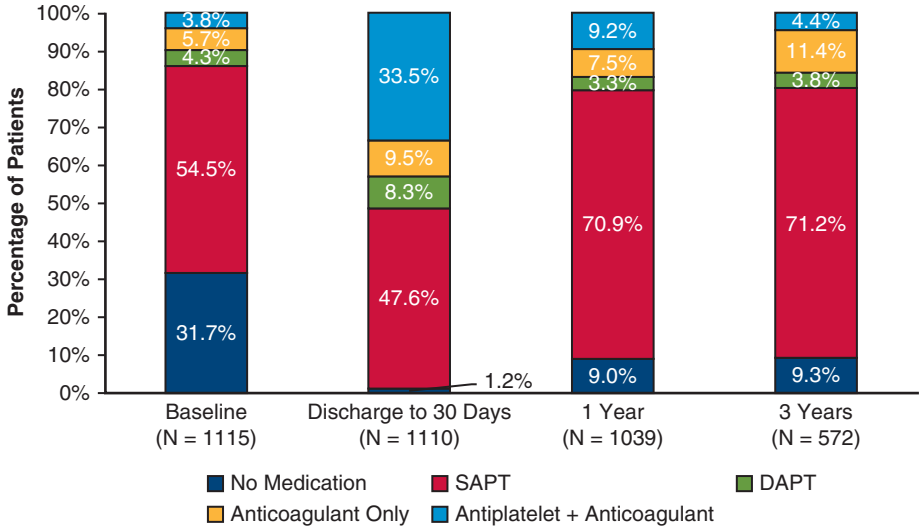

FIGURE 2. Distribution of medication use over time. The single antiplatelet therapy (*SAPT*) category comprises aspirin or another antiplatelet alone and includes patients with only *other antiplatelet* selected on the case report form, whereas the dual antiplatelet therapy (*DAPT*) category includes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

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-SAVR prophylaxis.

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, those with 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 Table E1.

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, 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

TABLE 2. Indications for antiplatelet and/or anticoagulant use at the time of late major bleeding events

Indication	Aspirin or other antiplatelet (n = 20 events)	Dual-antiplatelet therapy (n = 3 events)	Anticoagulant alone (n = 10 events)	Aspirin and/or other antiplatelet + anticoagulant (n = 18 events)
Post-SAVR prophylaxis	4			1
Pre-existing condition*				
CAD/CVD/PVD	10	2		5
Prior stent placement	1	2		
Congestive heart failure	2			
Prior myocardial infarction or other thromboembolic event	4		1	1
Pre-existing atrial fibrillation			8	7
New-onset atrial fibrillation/flutter			3	3
Miscellaneous†	1	1		1

SAVR, Surgical aortic valve replacement; *CAD*, coronary artery disease; *CVD*, cardiovascular disease; *PVD*, peripheral vascular disease. *Fifty-one late major bleeding events occurred in 43 patients. Patients may have had >1 indication for medication. †Miscellaneous indications include ocular migraine (n = 1), acute limb injury (n = 1), and infectious endocarditis (n = 1).

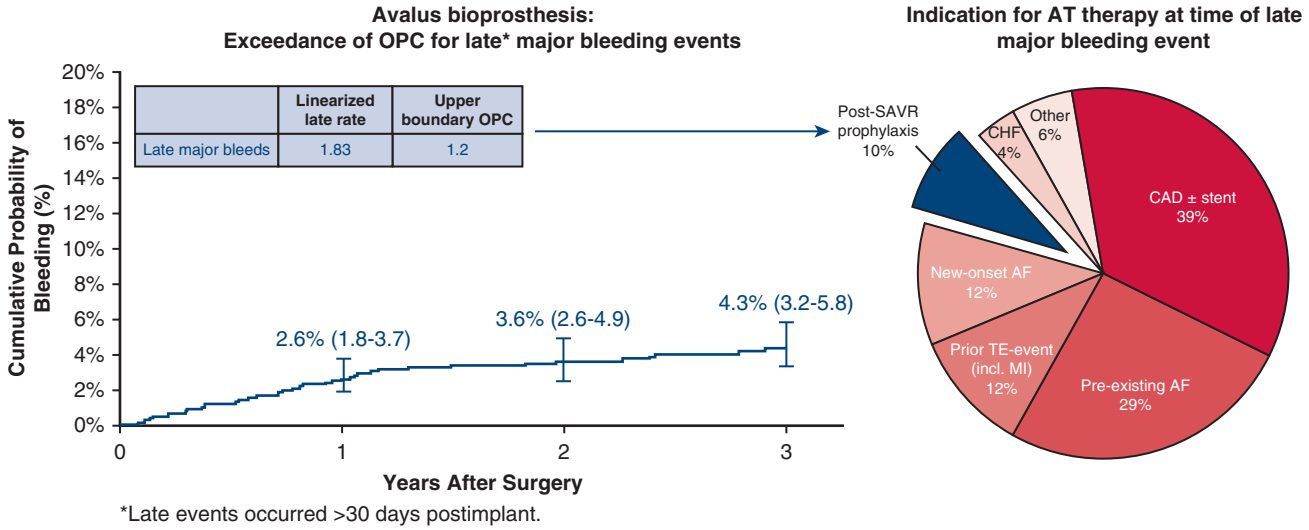

FIGURE 3. Antithrombotic (*AT*) therapy and late major bleeding events after aortic valve replacement with a novel bioprosthesis. The results suggest the objective performance criteria (*OPC*) for bleeding events require revision due to broader indications for AT therapy and improved quality of clinical trials. Percentages of patients with each indication total more than 100% because some patients had more than 1 indication for AT medication. *SAVR*, Surgical aortic valve replacement; *CHF*, congestive heart failure; *CAD*, coronary artery disease; *AF*, atrial fibrillation; *TE*, thromboembolic; *MI*, myocardial infarction.

shown, most patients were taking an antiplatelet and/or anticoagulant medication for conditions other than post-SAVR prophylaxis.

Hemodynamic Performance

At 3 years, effective orifice area and mean aortic gradient appeared stable (Figure E3). Transvalvular regurgitation rates were low, with only 0.6% and 0.2% of patients experiencing moderate or severe regurgitation, respectively (Figure E4). No patients had moderate or severe paravalvular regurgitation at 3 years (Figure E5). Hemodynamic SVD occurred in 3.2% of all patients; severe hemodynamic SVD was present in 4 patients (0.4%) (Table E2).

DISCUSSION

We found that the linearized late major bleeding event rate in 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 linearized rate of late thromboembolic events did not exceed the OPC.

For approval of surgical aortic valves, the Food and Drug Administration relies on 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

TABLE 3. Univariable Fine-Gray proportional hazard analysis of patient and procedure-related 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% confidence interval)	*P* value
Age (y)	69.9 ± 9.0	73.3 ± 7.9	1.048 (1.017-1.080)	<.01
Atrial fibrillation	97 (9.4)	12 (17.1)	1.939 (1.046-3.594)	.04
Carotid artery disease	90 (8.7)	12 (17.1)	2.085 (1.116-3.895)	.02
Coronary artery disease	445 (43.0)	37 (52.9)	1.474 (0.923-2.355)	.11
Diabetes	271 (26.2)	24 (34.3)	1.487 (0.906-2.440)	.12
Peripheral vascular disease	66 (6.4)	12 (17.1)	2.847 (1.505-5.387)	<.01
Renal dysfunction/insufficiency	100 (9.7)	14 (20.0)	2.304 (1.270-4.181)	<.01
Stroke	37 (3.6)	5 (7.1)	2.000 (0.815-4.908)	.13

Values are presented as mean ± standard deviation or n (%).

TABLE 4. Multivariable Fine-Gray analysis of all late bleeding events

Parameter	Late bleeding Hazard ratio (95% confidence interval)	*P* value
Age	1.035 (1.004-1.068)	.03
Carotid artery disease	1.598 (0.855-2.989)	.14
Peripheral vascular disease	2.135 (1.106-4.122)	.02
Renal dysfunction/insufficiency	1.920 (1.055-3.494)	.03
Antithrombotic medication	1.417 (1.048-1.915)	.02

and colleagues[11] and incorporated into the Food and Drug Administration heart valve guidance and later into the 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 medications 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 Trifecta, Inspiris, and 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 PERIGON participants was 91.3% and 94.8%, respectively. The vast majority of patients who experienced a bleeding event were using antithrombotic therapies for indications other than the newly replaced aortic valve, including preexisting atrial fibrillation, coronary artery disease, prior stent, or congestive heart failure (Table 2 and Figure 3). Of the antithrombotic medication categories considered, the combined use of antiplatelet and anticoagulant therapies had the greatest influence on the hazard of late bleeding events. Whether this combination is necessary is debatable, as recent transcatheter aortic valve replacement (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] Because 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. Because 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.

Our findings are comparable to those of other contemporary trials; the freedom from all bleeding events was 95.0% for the Inspiris valve at 2 years, and freedom from major bleeding events at 3 years was 89.3% for the Trifecta valve.[5,14] The rate of thromboembolic events in the present study, 1.5% per late patient-year, was slightly lower compared to the Inspiris and Trifecta valves, with respective event rates of 2.1% and 1.9%. Although the rate of bleeding events in PERIGON 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 TAVR versus SAVR trials reported a 24.5%

TABLE 5. Indications for antiplatelet and/or anticoagulant use at the time of thromboembolic events

Indication	Aspirin or other antiplatelet (n = 26 events)	Dual-antiplatelet therapy (n = 5 events)	Anticoagulant alone (n = 6 events)	Aspirin and/or other antiplatelet + anticoagulant (n = 7 events)	Unknown/none (n = 11 events)
Post-SAVR prophylaxis	7	1	2	1	
Pre-existing condition*					
CAD/CVD/PVD	11	4	1	3	2
Prior stent placement			1		
Pre-existing atrial fibrillation	6		4	5	3
Carotid endarterectomy	1				
History of TIA/stroke	6	1	3	5	4
Compartment syndrome		1			
Unknown	1				5

SAVR, Surgical aortic valve implantation; *CAD*, coronary artery disease; *CVD*, cardiovascular disease; *PVD*, peripheral vascular disease; *TIA*, transient ischemic attack. *Fifty-five thromboembolic events occurred in 43 patients. Patients may have had >1 indication for medication.

(low-risk Placement of Aortic Transcatheter Valves trial [PARTNER 3]) and an 8.9% (Evolut low-risk trial) incidence of major bleeding in the surgical arms at 1 year.[15,16] In comparison, 1 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 and colleagues[18] used the same guidelines as PERIGON.[19] However, the definition of bleeding events in the PERIGON 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 U blood transfusion or that caused >1 L 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. Because the definition and monitoring of adverse events have become more rigorous for recent investigational trials, exceeding 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.

The results reported here represent the longest follow-up available on the Avalus valve. Overall hemodynamic performance in this trial demonstrates stable gradients and effective orifice area through 3 years after surgical valve replacement, in addition to low Kaplan-Meier probabilities of reintervention (2.0%) and requirement for explantation (1.9%). Because hypoattenuated leaflet thickening may be related to early SVD,[20] the comparison of SVD rates after surgical or TAVR is relevant. Although all patients receive DAPT therapy after TAVR, nearly half of 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 patients undergoing TAVR and 26.6% total SVD and 1.7% severe SVD in patients undergoing SAVR.[21]

Limitations

The 3-year follow-up visit was not completed for all participating patients at the time of analyses (Figure E1). 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 >1 other antiplatelet agent. Although 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 because 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.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Sunday_May5/1.%20PLENARY/1.%20PLENARY/16h%20-%2018h/P3_6.mp4.

Conflict of Interest Statement

This study was funded by Medtronic. Dr Klautz receives research support from Medtronic, consultation and proctoring fees from Medtronic and LivaNova, and participates in speakers bureaus for Medtronic, LivaNova, and Edwards Lifesciences. Dr Vriesendorp receives research support from Medtronic. Dr Dagenais is a consultant, speaker, and trainer for Medtronic. Dr Bapat is a consultant for Medtronic and Boston Scientific and has received speaker fees from Medtronic, Edwards Lifesciences, Boston Scientific, and LivaNova. Dr Moront is a consultant, speaker, and trainer for Medtronic, a consultant for Edwards Lifesciences, and a consultant for LSI. Ms Gearhart and Dr Kappetein are employees of Medtronic. Dr Sabik receives research support from Edwards Lifesciences (local principal investigator for Intuity Trial) and Abbott (North American principal investigator for EXCEL Trial); is an advisory board member for Medtronic and LivaNova;

teaches educational courses for Medtronic; and is a consultant to Medtronic, Edwards, and Sorin. All other authors have nothing to disclose with regard to commercial support.

Ryan Palmer contributed to study design and management. Jessica Halverson provided study management. Julie Linick provided editorial support under the direction of the lead author and reviewed the manuscript for data accuracy. All are employees of Medtronic.

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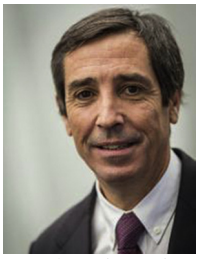
Key Words: surgical aortic valve replacement, aortic tissue valves, antiplatelet/anticoagulant-related bleeding

Discussion



Dr Miguel Sousa Uva *(Lisbon, Portugal)*. Thank you, Dr Sabik, for this very clear and well-organized presentation, and thanks for sending me the manuscript in advance.

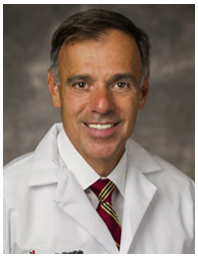
Two years ago at this meeting in Boston, you presented the 1-year results of the Avalus bioprosthetic valve (Medtronic, Minneapolis, Minn). You hypothesized at that moment that the reason for higher bleeding was related to patient medication due to associated conditions, and this is the subject of today's presentation. The reported linearized late event rate for major bleeding in the Pericardial Surgical Aortic Valve Replacement Pivotal Trial was above, as you said, the objective performance criteria, in line with other modern bioprosthetic pericardial valves. You have shown us that, at discharge, 43% of patients were taking anticoagulants or anticoagulants plus antiplatelet therapies, whereas at 3 years this was the case only in 16% of patients. So most of these patients were on anticoagulation and antiplatelet therapies for other conditions than the prophylaxis after surgical aortic valve replacement. You performed multivariable Cox proportional hazard regression showing that frail patients, older patients, peripheral vascular disease, renal insufficiency, and diabetes were independent predictors for bleeding.

We now have 572 patients available for follow-up at 3 years, and there was, fortunately, only a very low rate of valve explants, 1.9%, and so we are reassured that this valve is safe in terms of major adverse events, and durability, of course, at 3 years is still too short.

You have not mentioned, but the hemodynamic performance of the valve was evaluated by echocardiography at

6 months and as late as follow-up, and we have observed that mean gradients were stable. But the results presented and published in the *Journal of Thoracic and Cardiovascular Surgery* showed one third of patients had a significant prosthesis–patient mismatch (PPM).

So my first question. Did you look into reasons for this low indexed effective orifice area reaching almost one third of patients with this bioprosthetic valve?



Dr Joseph F. Sabik *(Cleveland, Ohio).* Thank you. I think that's a very good question. And I suppose the way I think about it is the same way I think about this objective performance criteria for bleeding. Our patients have changed over time. We are seeing bleeding in patients with biological valves, something we wouldn't expect, and it is because of all of their comorbid conditions that is leading to anticoagulant therapy and their bleeding. I think when I think about PPM, I joke around with my residents, I said, you know, when I first came on I was a staff surgeon. It was very rare for me to operate on somebody weighing >80 kg. Today it is very rare for me to operate on somebody weighing <100 kg, it seems. And so I think our patient population is changing, and sometimes we have large patients in small bodies.

And so I think we probably need to think a little bit different about PPM and that maybe we are seeing these artificially low or higher rates of PPM really because of the size of our patients. I think you bring up a very good point. We are following these patients very closely, and we are not seeing the deterioration you talked about because of these findings.

So I think as probably a subject of another paper is, do we really need to look at PPM as well just because our patient population is changing over time.

Dr Sousa Uva. Thank you. My second question concerns the protocol. Did the trial protocol recommend a specific antithrombotic protocol at discharge and did it specify any type of self-monitoring or self-management international normalized ratio?

Dr Sabik. You know, I apologize, I don't remember. It has been a while since I have looked at that, but my guess would be is that that was left up to the individual sites. But I would have to recheck the protocol.

Dr Sousa Uva. Thank you. Finally, as you know, subclinical valve thrombosis has been detected by 4-dimensional computerized tomography and occurs with a rate of around 7% for surgical bioprostheses and around 14% after transcatheter aortic valve replacement. Although this is subclinical, this phenomenon may be a mechanism involved in late valve degeneration, although this is a hypothesis. The rate of hemodynamic structural valve deterioration occurred only in 3% of all patients, which is reassuring.

So my last question: Could this low rate of even moderate valve degeneration be related to the fact that patients were under anticoagulation and do you plan to perform any 4-dimensional computed tomography scans in a subset of these patients?

Dr Sabik. That's an excellent question. Obviously we are always trying to balance the risk versus the benefit, and to me it's very interesting to just look at the correlation between the period of time when patients were bleeding and the amount of anticoagulants they were on and then clearly the anticoagulants were pulled back by their doctors and the bleeding went away, but are we going to switch 1 problem for another? I think that's an excellent question.

To my knowledge, we are following these patients and a group of these patients are going to be followed to well beyond 10 years, but with echocardiography and not with 4-dimensional computed tomography.

Dr Sousa Uva. Thank you.

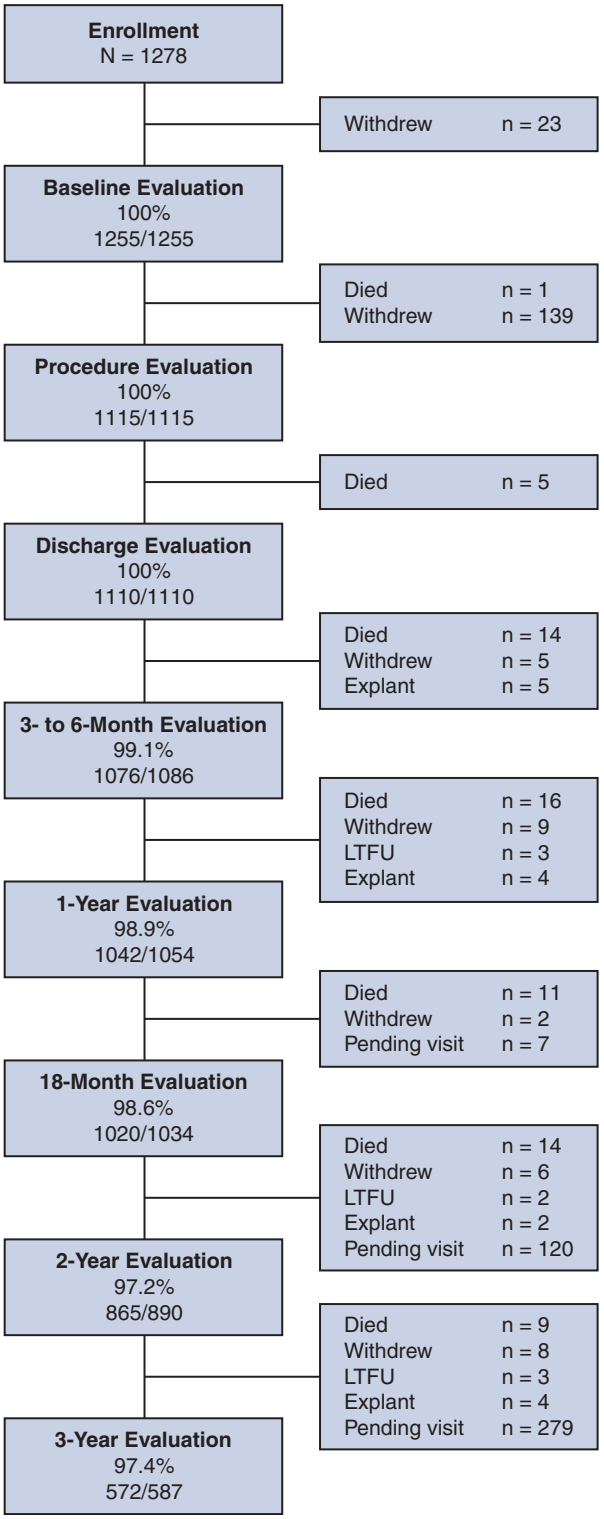


FIGURE E1. Consolidated Standards of Reporting Trials diagram of compliance and patient flow through the study. Percentages indicate the compliance rate for follow-up (number of visits completed/number of visits expected). *LTFU*, Lost to follow-up.

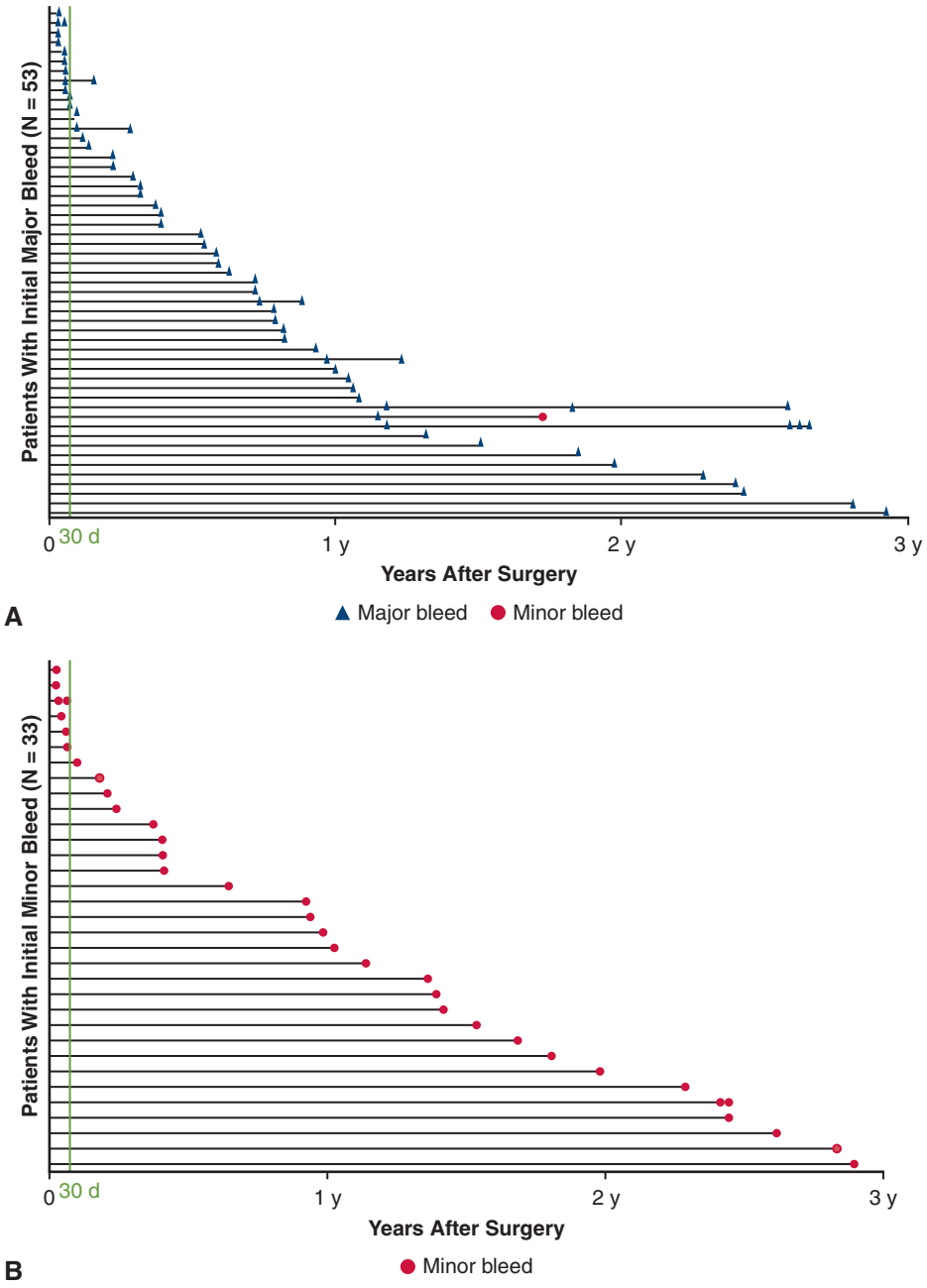


FIGURE E2. Time to bleeding events. A, In patients with an initial major bleed. B, In patients with an initial minor bleed.

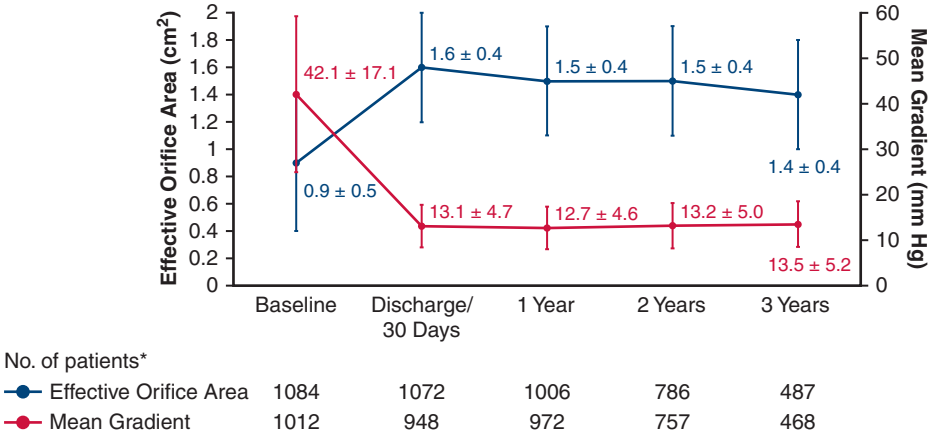


FIGURE E3. Mean aortic gradient and effective orifice area from baseline to 3 years. *Number of patients with evaluable echocardiograms.

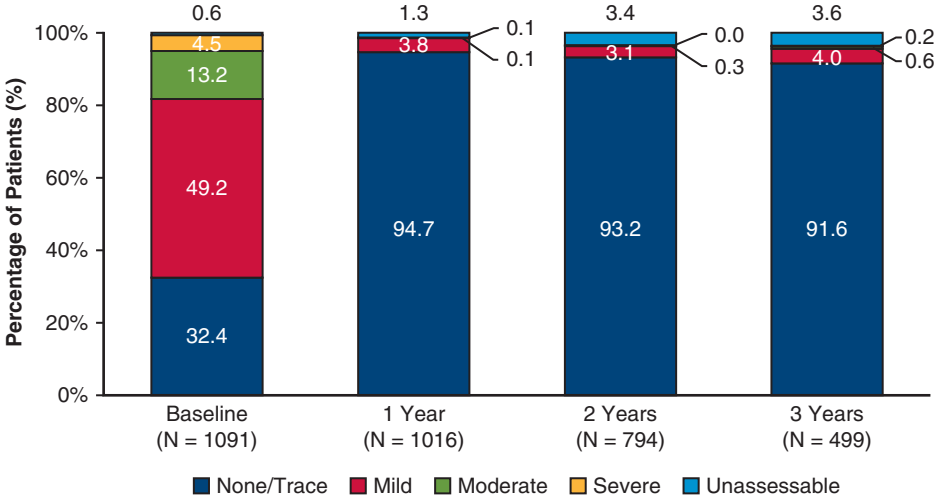


FIGURE E4. Transvalvular regurgitation from baseline to 3 years.

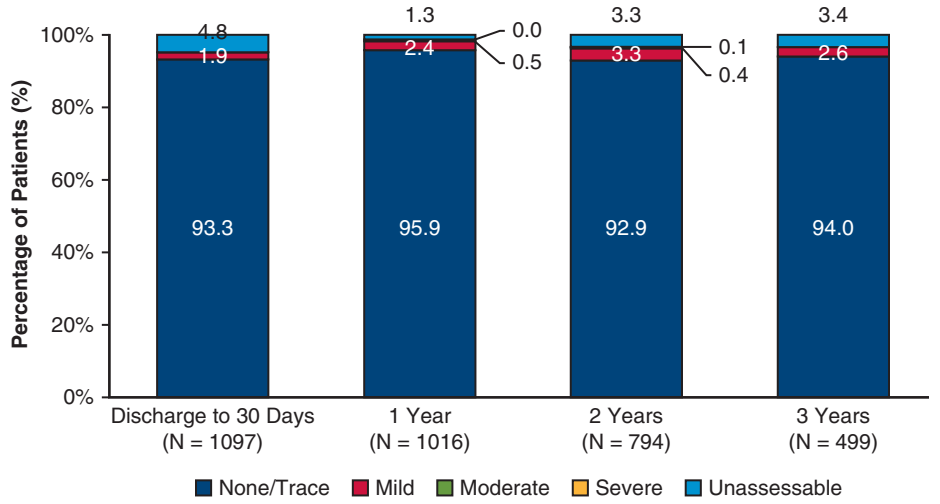


FIGURE E5. Paravalvular regurgitation from discharge/30 days to 3 years.

TABLE E1. Patient baseline and procedure-related characteristics

Characteristic	All patients (N = 1115)	Late bleeding events*		Late major bleeding events*	
		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)

Values are presented as mean ± standard deviation or n (%). *Late was defined as >30 days postimplant.

TABLE E2. Hemodynamic structural valve deterioration through 3 years

Criterion	Prevalence* (N = 1104)
Total SVD	35 (3.2)
Mean gradient at any time ≥20 mm Hg AND an increase ≥10 mm Hg from discharge/3-6 mo	33 (3.0)
Moderate or severe transvalvular aortic regurgitation, new from discharge	2 (0.2)
Moderate hemodynamic SVD	31 (2.8)
Mean gradient at any time ≥20 mm Hg AND an increase ≥10 mm Hg from discharge/3-6 mo	29 (2.6)
Moderate transvalvular aortic regurgitation, 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 ≥20 mm Hg from discharge/3-6 mo	3 (0.3)
Severe transvalvular aortic regurgitation, new from discharge	0 (0.0)

Values are presented as n (%). *SVD*, Structural valve deterioration. *Echocardiograms were unavailable or unevaluable for 11 patients. Definition modified from Capadanno and colleagues.[8]