Three-year hemodynamic performance, left ventricular mass regression, and prosthetic-patient mismatch after rapid deployment aortic valve replacement in 287 patients

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Objective: Superior aortic valve hemodynamic performance can accelerate left ventricular mass regression and enhance survival and functional status after surgical aortic valve replacement. This can be achieved by rapid deployment aortic valve replacement using a subannular balloon-expandable stent frame, which functionally widens and reshapes the left ventricular outflow tract, to ensure a larger effective orifice area compared with conventional surgical valves. We report the intermediate-term follow-up data from a large series of patients enrolled in the Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON) trial.

Methods: In a prospective, multicenter (6 European hospitals), single-arm study, 287 patients with aortic stenosis underwent rapid deployment aortic valve replacement using a stented trileaflet bovine pericardial bioprosthesis. Core laboratory echocardiography was performed at baseline, discharge, and 3 months, 1 year, and 3 years after rapid deployment aortic valve replacement.

Results: The mean patient age was 75.7 ± 6.7 years (range, 45-93; 49.1% women). The mean aortic valve gradient significantly decreased from discharge to 3 years of follow-up. The mean effective orifice area remained stable from discharge to 3 years. At 1 year, the left ventricular mass index had decreased by 14% ($P < .0001$) and at 3 years by 16% ($P < .0001$) compared with at discharge. The prevalence of severe patient-prosthesis mismatch was 3% at discharge and remained stable during the follow-up period.

Conclusions: In a large series of elderly patients with symptomatic severe aortic stenosis, rapid deployment aortic valve replacement using a subannular balloon-expandable stent frame demonstrated excellent hemodynamic performance and significant left ventricular mass regression. With continued follow-up, future studies will establish whether these favorable structural changes correlate with improvement in long-term survival and functional status. (J Thorac Cardiovasc Surg 2014;148:2854-61)

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Elevated transvalvular gradients can contribute to persistent left ventricular (LV) hypertrophy and diastolic dysfunction after aortic valve replacement (AVR), which can contribute to patient-prosthesis mismatch (PPM) and decreased survival.¹ Superior aortic valve hemodynamic performance can accelerate LV mass regression and enhance long-term survival and functional status after surgical AVR.²⁻⁶ Sutureless and rapid deployment aortic valve prostheses have recently been introduced into clinical practice in Europe and Asia, and several studies have demonstrated early safety and efficacy.⁷⁻⁹

A rapid deployment AVR (RDAVR) system with a subannular balloon-expandable stent frame, which could lead to widening of the LV outflow tract (valve inflow) and a larger effective orifice area (EOA) compared with conventional surgical valves, has been investigated in an ongoing multicenter trial.¹⁰ We report the intermediate-term follow-up data from a large series of patients enrolled in a clinical trial of RDAVR, with a particular focus on the hemodynamic outcomes.

Abbreviations and Acronyms

AVR	= aortic valve replacement
CABG	= coronary artery bypass grafting
EOA	= effective orifice area
LV	= left ventricular
NYHA	= New York Heart Association
PARTNER	= Placement of Aortic Transcatheter Valves
PPM	= patient-prosthesis mismatch
PVL	= paravalvular leak
RDAVR	= rapid deployment aortic valve replacement
TRITON	= Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve

METHODS**Study Population**

The Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON) trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01445171) no. NCT01445171) was a prospective, nonrandomized, single-arm, multicenter trial conducted in 6 European hospitals. The study design and methods have been previously described by Kocher and associates.¹⁰ A total of 295 consecutive patients with aortic stenosis or aortic stenosis insufficiency requiring elective AVR with or without concomitant coronary artery bypass grafting (CABG) were enrolled; 287 of these were treated with the Edwards Intuity Valve System (model 8300A; Edwards Lifesciences Corp, Irvine, Calif), a stented trileaflet bovine pericardial bioprosthesis with a balloon-expandable, cloth-covered skirt frame at the inflow aspect (Figure 1). The ethics committee of each participating center reviewed and approved the study protocol, and all patients provided written informed consent.

RDAVR System

RDAVR with the Edwards Intuity Valve System was performed through either a minimally invasive technique or full sternotomy, as previously described by Kocher and associates.¹⁰ After standard aortotomy, the native aortic valve leaflets were removed and annular calcium was debrided using conventional techniques. Three equidistant guiding sutures were placed through the nadir of the aortic annulus and then through the corresponding positions on the valve sewing ring. Using the delivery system, the valve was lowered onto the annulus using the guiding sutures. Once the valve was seated, the balloon catheter was expanded to rapidly deploy the valve. After deployment, the delivery system was removed, the guiding sutures were tied down, and the aortotomy was closed.

Endpoints

The safety endpoints included valve-related mortality, thromboembolic events, study valve thrombosis, major bleeding events, paravalvular leakage, and prosthetic valve endocarditis. The performance endpoints included technical success, procedural success, change in logistic EuroSCORE I, improvement in New York Heart Association (NYHA) functional classification, and valve hemodynamic performance. Embolism was defined as a free-flowing blood clot or lesion material located in the systemic or pulmonary circulation and occurring in the absence of infection after the immediate perioperative period. Valve thrombosis was defined as a blood clot not associated with infection, causing dysfunction of the heart valve substitute. A bleeding event was defined as any episode of major internal or external bleeding that caused death, hospitalization, or permanent injury (eg, vision loss) or necessitated transfusion. Major paravalvular leak (PVL) was defined as paravalvular

regurgitation graded as +3 moderate or +4 severe according to the core laboratory evaluation of the echocardiogram. Endocarditis is an inflammation or infection of the endocardium (ie, the inner lining of the heart muscle) and, most commonly, the heart valves. It is typically caused by a bacterial infection but can be caused by fungus. Technical success was defined as delivery and deployment of the study valve within 2 attempts. Procedural success was defined as technical success and the absence of complications requiring device reoperation, permanent pacemaker implantation (with baseline sinus rhythm and no conduction issues), or death. Additional details on these definitions have been previously reported by Kocher and associates.¹⁰

Follow-up

The clinical and echocardiographic follow-up data were collected per protocol at baseline, discharge, 3 and 12 months postoperatively, and yearly thereafter for 5 years. All hemodynamic data were reviewed by an independent echocardiographic core laboratory (Columbia University Medical Center, New York, NY). Complications were adjudicated by an independent clinical events committee. Aggregate follow-up data were reviewed by an independent data safety monitoring board.

Data Management

As the study sponsor, Edwards Lifesciences managed the collection and monitoring of the data; however, it did not have a role in the interpretation of the data.

Statistical Analysis

Continuous variables are summarized as the mean $\pm$ standard deviation and categorical variables as percentages. Complications were summarized for the early (≤ 30 days after the index procedure) and late (> 30 days after the index procedure) periods. Early rates were calculated as the number of events divided by the number of patients receiving the study valve. Linearized rates for complications were calculated for the late period as the number of late events divided by the number of late patient-years (482.3 late patient-years). Inference statistics comparing continuous variables among the measurement points were made using a linear mixed effect model. Two-sided tests were used, and a type I error significance level of 0.05 was considered. All data were from a data extract date of February 14, 2014.

RESULTS**Baseline Patient and Echocardiographic Characteristics**

The baseline patient and echocardiographic characteristics are presented in Table 1. In total, 287 patients (mean age, 75.7 ± 6.7 years; 49.1% women) received the Edwards Intuity valve (Edwards Lifesciences) with a total accumulated follow-up of 482.3 late patient-years. The mean follow-up for all enrolled subjects was 1.8 ± 0.9 years. The mean logistic EuroSCORE I was 8.4 ± 6.7 , with 53.2% of the patients (150 of 282) in NYHA class III and IV. The mean body mass index was 28.0 ± 4.3 kg/m², with a mean preoperative aortic annulus diameter of 23.0 ± 2.2 mm. The mean prosthesis size was 23.1 ± 1.9 mm; the median prosthesis size was 23 mm. The prosthesis size distribution is listed in Table 1. After 23 mm, the frequency of using the 21- and 25-mm devices was similar.

Early and Late Morbidity, Mortality, and Functional Status

Early (≤ 30 -day) all-cause mortality was 1.7% (heart failure in 1, cardiogenic shock in 2, thromboembolic event

FIGURE 1. A, Rapid deployment aortic valve: Edwards Intuity Valve System (model 8300A). B, Echocardiographic image of implanted Edwards Intuity Valve System (model 8300A).

in 1, and multiorgan failure due to sepsis in 1; Table 2). Early complications included thromboembolic events in 13 patients (4.5%), including stroke in 8 (2.8%), major bleeding events in 7 (2.4%), major PVL (>2+) in 2 (0.7%), and valve explantation in 4 (1.4%). The causes of early explantation were reported as bleeding during and after the procedure. No early cases of valve-related thrombosis or endocarditis developed (Table 2). The early event rate for renal dysfunction, reoperation for bleeding, deep sternal wound infection, and respiratory dysfunction was 5.2% (n = 15), 7.7% (n = 22), 3.1% (n = 9), and 2.8% (n = 8), respectively.

Late (>30-day) all-cause mortality was 3.7% (n = 18) per late-patient year for all patients (Table 2), with 2 deaths adjudicated as valve-related. The causes of late mortality were respiratory failure in 2, infection in 2, ruptured aortic aneurysm in 1, cancer in 3, myocardial infarction in 2, stroke in 1, multisystem organ failure in 2, cardiac arrest in 1, endocarditis in 1, cerebral hemorrhage due to head trauma in 1, sepsis in 1, and natural death in 1. Late thromboembolic events were reported as 1.7% (n = 8) per late-patient year (4 events led to a stroke), and late major PVL events were reported as 1.2% (n = 6) per late-patient year. Late endocarditis events were reported in 0.2% (n = 1) of the patients. Valve explants occurred in 3 patients (0.6% per late patient-year) due to major PVL, endocarditis, and aortic root aneurysm in 1 patient each. No cases of

TABLE 1. Clinical and echocardiographic variables at baseline

Variable	Value
Age (y)	287; 75.7 ± 6.7*
Sex	
Female	49.3 (141/286)
Male	50.7 (145/286)
Logistic EuroSCORE (%)	282; 8.4 ± 6.7
NYHA classification	
I	5.0 (14/282)
II	41.8 (118/282)
III	50.0 (141/282)
IV	3.2 (9/282)
Echocardiographic variables	
Body surface area (m ²)	286; 1.9 ± 0.2
Body mass index (kg/m ²)	286; 28.0 ± 4.3
Aortic annulus diameter (mm)	238; 23.0 ± 2.2
Indexed annulus diameter (mm/m ²)	237; 12.2 ± 1.4
LVEF (%)	188; 61.2 ± 11.1
Valve size distribution (mm)	
19	2.1 (6/287)
21	29.6 (85/287)
23	34.5 (99/287)
25	27.2 (78/287)
27	6.6 (19/287)
Valve size	
Patients (n)	287
Mean ± SD (mm)	23.1 ± 1.9
Median (mm)	23

Data presented as number of patients; mean ± SD or % (n/N), unless otherwise noted. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SD, standard deviation; EuroSCORE, European System for Cardiac Operative Risk Evaluation. *Baseline data missing for 1 subject.

valve-related thrombosis, hemolysis, or structural valve deterioration were reported.

At the 3-month and 1-year follow-up points, NYHA functional class improvement was observed in 72.6% and 75.1% of the population, respectively, and 24.7% and 22.9% of the patients reported the same NYHA class as at baseline (Table 3). Among the patients in NYHA class III or IV, 90% (118 of 131) had improved ≥1 functional class at 1 year postoperatively.

Hemodynamic Outcomes

Core laboratory echocardiographic data were obtained at discharge and the 3-month, 1-year, and 3-year follow-up intervals. The mean gradient at 3 months, 1 year, and 3 years was 9.0 ± 3.4, 9.0 ± 3.6, and 8.7 ± 4.1 mm Hg, respectively, significantly lower than at discharge (P < .0001 for discharge vs 3 months and 1 year, P = .0031 for discharge vs 3 years). The LV mass at 3 years was 178.5 ± 42.8 g, lower than that at 3 months and 1 year postoperatively (196.6 ± 49.8 and 184.3 ± 47.7 g, respectively). In contrast, the LV mass index at 3 years was significantly lower than at discharge (P < .0001). The mean EOA and indexed EOA remained unchanged throughout the follow-up period at

TABLE 2. Early and late safety events

Event	Early	Late events
	(≤30 d; n = 287)	(>30 d; n = 482.32)
Mortality	1.7 (5)	3.7 (18)
Thromboembolism	4.5 (13)	1.7 (8)
Valve thrombosis	0.0 (0)	0.0 (0)
Major bleeding	2.4 (7)	0.8 (4)
Endocarditis	0.0 (0)	0.2 (1)
Major paravalvular leak (>2+)	0.7 (2)	1.2 (6)
Explantation	1.4 (4)	0.6 (3)
Renal failure or dysfunction	5.2 (15)	1.7 (8)
Reoperation for bleeding	7.7 (22)	0.0 (0)
Deep sternal wound infection	3.1 (9)	0.6 (3)
Respiratory dysfunction	2.8 (8)	0.4 (2)

Data presented as % (n) for early events and %/late patient-year (n) for late events.

1.7 ± 0.2 cm² and 0.9 ± 0.1 cm²/m², respectively (Table 4). The mean gradient and EOA stratified according to valve size are presented in Table 5.

Freedom from major PVL (>+2) was ≥98% at each of the follow-up intervals (Table 6). The incidence of severe PPM (indexed EOA ≤ 0.65 cm²/m²) among all subjects was ≤3% at each of the follow-up intervals (Table 7). As previously described by Clavel and colleagues,¹¹ a small aortic annulus was defined as an annular diameter of ≤20 mm. In the subgroup of patients with a small aortic annulus, a greater prevalence of severe PPM was seen at discharge (20%; 2 of 10) and 1 year (15%; 2 of 13; Table 7). At 3 months and 3 years, the incidence of severe PPM in this small aortic annulus subgroup was 8% (1 of 12) and 0% (0 of 5), respectively. No difference was seen in the incidence of severe PPM in the subset of patients with an aortic annulus diameter of >20 mm (*P* = .84) across all follow-up intervals.

DISCUSSION

The Edwards Intuity Valve System was uniquely designed to facilitate RDAVR in patients with aortic

stenosis. To properly evaluate its safety and efficacy, a prospective, multicenter, single-arm study was undertaken—the TRITON Trial. The Intuity valve was implanted in 287 patients in 6 European centers. At 3 years, the data demonstrated a low mean transvalvular gradient (mean, 8.7 mm Hg in all patients) and significant LV mass regression (Δ LV mass index compared with discharge, −16%). Compared with the standard surgical bioprostheses,¹² the Intuity could be associated with larger EOAs in smaller valve sizes, a lower risk of PPM, and a low rate of moderate or severe postoperative PVL. The notable hemodynamic results were also accompanied by a significant improvement in functional status, in particular, in highly symptomatic patients. At baseline, 53% of patients were in NYHA class III or IV, and improvement in functional class was observed in 90% of these patients during the follow-up period.

RDAVR using the Edwards Intuity Valve System has been demonstrated to be safe. We previously reported the 1-year outcomes of the initial 152 patients treated using the first-generation Intuity Valve System (model 8300A; Edwards Lifesciences) and found a mortality rate of 2.1%, despite a mean patient age of 75.5 years.¹⁰ Nearly 60% of the cases were AVR only and 25% were AVR plus CABG. The operative approach involved a minimally invasive incision (ie, upper hemisternotomy or right anterior thoracotomy) in nearly one half of the patients who underwent isolated AVR. Technical device success was achieved in 96% (146 of 152) of the patients. For isolated AVR, the crossclamp and cardiopulmonary time was 41 and 66 minutes and for AVR plus CABG, 60 and 96 minutes, respectively. Early (≤30-day) mortality and complications were uncommon and included valve-related mortality in 1.4% of the patients, thromboembolism in 2.7%, valve explantation in 1.4%, and reoperation for bleeding in 0.7%.

The present report has extended these observations to 287 patients, of whom 138 were treated using the second-generation Intuity Valve System (model 8300AB; Edwards Lifesciences). In the second-generation device, 3 minor design modifications were made to enhance seating during implantation. First, the number of cloth layers on the frame was reduced and the cloth was shifted down closer to the inflow edge of the annulus frame. With the cloth on the annulus frame moved down, the resulting tissue annulus diameter was reduced by 1 mm. Second, the single, crimped cloth-covered, expandable stainless steel frame was double crimped to further reduce the implant profile. Third, the valve holder is now cusp-mounted instead of commissural-mounted to increase the visibility for the nadir suture markers.

In the extended cohort of 287 patients, 55% underwent AVR only and 27% AVR plus CABG. Minimally invasive incisions were used in 55% of the 158 patients undergoing isolated AVR. In contrast, analysis of the national cardiac

TABLE 3. Summary of NYHA improvement from 3 months to 1 year

Follow-up	NYHA class				Total (n = 287)
	I	II	III	IV	
3 mo					
Patients (n)	12	111	128	8	259
Improved	0 (0.0)	74 (66.7)	106 (82.8)	8 (100.0)	188 (72.6)
Same	8 (66.7)	34 (30.6)	22 (17.2)	0 (0.0)	64 (24.7)
Worse	4 (33.3)	3 (2.7)	0 (0.0)	0 (0.0)	7 (2.7)
1 y					
Patients (n)	12	106	125	6	249
Improved	0 (0.0)	69 (65.1)	112 (89.6)	6 (100.0)	187 (75.1)
Same	9 (75.0)	35 (33.0)	13 (10.4)	0 (0.0)	57 (22.9)
Worse	3 (25.0)	2 (1.9)	0 (0.0)	0 (0.0)	5 (2.0)

Data presented as n (%). The number of patients changed over time because subjects exited the study owing to death, explantation, or other reasons and represents the number of subjects with both baseline and follow-up NYHA data. NYHA, New York Heart Association.

TABLE 4. Echocardiographic data at follow-up

Variable	Follow-up				P value			
	Discharge	3 mo	1 y	3 y	Overall	Discharge vs 3 mo	Discharge vs 1 y	Discharge vs 3 y
EOA (cm ²)	1.7 ± 0.2 (178)	1.7 ± 0.2 (204)	1.7 ± 0.2 (211)	1.7 ± 0.2 (58)	.1579	.5696	.2367	.0286
EOA index (cm ² /m ²)	0.9 ± 0.1 (164)	0.9 ± 0.1 (195)	0.9 ± 0.1 (186)	0.9 ± 0.1 (47)	.0730	.0158	.2940	.8804
Mean gradient (mm Hg)	10.7 ± 4.2 (226)	9.0 ± 3.4 (224)	9.0 ± 3.6 (230)	8.7 ± 4.1 (59)	<.0001	<.0001	<.0001	.0031
Cardiac output (L/min)	5.1 ± 1.1 (189)	4.8 ± 1.1 (211)	4.8 ± 1.1 (215)	4.6 ± 1.0 (60)	.0002	<.0001	.0007	.0052
Septal thickness (mm)	13.0 ± 1.8 (148)	11.8 ± 1.6 (197)	11.5 ± 1.5 (216)	11.2 ± 1.2 (57)	<.0001	<.0001	<.0001	<.0001
Posterior thickness (mm)	12.5 ± 1.6 (141)	11.5 ± 1.5 (194)	11.0 ± 1.3 (210)	10.6 ± 1.0 (55)	<.0001	<.0001	<.0001	<.0001
LV mass (g)	217.9 ± 62.3 (100)	196.6 ± 49.8 (161)	184.3 ± 47.7 (178)	178.5 ± 42.8 (44)	<.0001	<.0001	<.0001	<.0001
LV mass index (g/m ²)	116.0 ± 31.9 (92)	105.0 ± 23.4 (155)	99.2 ± 23.3 (162)	97.5 ± 18.9 (38)	<.0001	<.0001	<.0001	<.0001

Data presented as mean ± standard deviation. *P* values and pairwise comparisons versus discharge were from longitudinal analyses. EOA, Effective orifice area; LV, left ventricular.

surgery database of the German Society for Thoracic and Cardiovascular Surgery reported that partial sternotomy constituted <20% (2168 of 11,906) of all isolated surgical AVR procedures in 2012.¹³ The technical success rate improved to >97% in the present study with increased experience and improved training. Early and late (>30-day) mortality and complications remained relatively constant, including an all-cause mortality rate of 1.7% and 3.7% per patient-year and valve-related mortality rate of 1.0% and 0.4% per patient-year, respectively. These excellent outcomes support the clinical safety of the Edwards Intuity Valve System and could promote its use for minimally invasive surgery.

When deciding which bioprosthetic valve to select for an individual patient, an important consideration is the long-term durability. Technological advances in bovine pericardial tissue treatment have been associated with improved valve durability. In 1985, the XenoLogiX

(Edwards Lifesciences) tissue treatment process was introduced, which used ethanol and surfactant to extract >90% of phospholipids from pericardial tissue after glutaraldehyde fixation. The reported clinical experience with XenoLogiX has been very good. McClure and associates¹⁴ reported on 1000 patients who had undergone AVR with the XenoLogiX-treated Carpentier-Edwards Perimount and been followed up for 17 years. The actuarial freedom from structural valve deterioration at 15 years was 89% for patients aged 65 to 75 years and 99.5% for patients >75 years. In another study, Forcillo and associates¹⁵ followed up 2405 patients who had undergone AVR using the Carpentier-Edwards Perimount during a 25-year period. The actuarial freedom from reoperation for structural valve deterioration was 95% at 10 years and 90% at 15 years for patients aged 60 to 70 years and 99% at 10 years in patients >70 years. Given that the Carpentier-Edwards Perimount bioprosthesis is a core component of the Edwards Intuity

TABLE 5. Effective orifice area and mean gradient stratified by valve size

Valve size (mm)	Follow-up point			
	Discharge (n = 265)	3 mo (n = 253)	1 y (n = 249)	3 y (n = 62)
EOA (cm ²)				
Overall	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2
Valve size (mm)				
19	1.3 ± 0.2 (2)	1.4 ± 0.2 (5)	1.3 ± 0.1 (2)	1.5 ± — (1)
21	1.6 ± 0.2 (50)	1.6 ± 0.2 (62)	1.6 ± 0.2 (68)	1.6 ± 0.3 (22)
23	1.8 ± 0.2 (63)	1.7 ± 0.2 (73)	1.7 ± 0.2 (72)	1.7 ± 0.1 (19)
25	1.8 ± 0.2 (53)	1.8 ± 0.2 (52)	1.8 ± 0.2 (52)	1.8 ± 0.2 (14)
27	1.8 ± 0.2 (10)	1.9 ± 0.2 (12)	1.9 ± 0.2 (17)	1.7 ± 0.0 (2)
Mean gradient (mm Hg)				
Overall	10.7 ± 4.2	9.0 ± 3.4	9.0 ± 3.6	8.7 ± 4.1
Valve size (mm)				
19	25.0 ± 2.4 (5)	18.6 ± 5.4 (6)	17.0 ± 4.2 (5)	12.6 ± — (1)
21	10.7 ± 3.3 (66)	9.2 ± 2.9 (67)	9.9 ± 3.2 (69)	10.0 ± 4.1 (22)
23	10.6 ± 3.5 (80)	8.9 ± 2.9 (78)	9.0 ± 3.6 (79)	7.2 ± 3.2 (20)
25	9.9 ± 4.1 (60)	8.5 ± 3.2 (57)	8.2 ± 3.1 (60)	9.1 ± 4.7 (14)
27	9.0 ± 3.8 (15)	6.8 ± 1.5 (16)	6.2 ± 1.5 (17)	5.8 ± 1.4 (2)

Data presented as mean ± standard deviation; data in parentheses represent the number of subjects who completed an echocardiographic examination at the indicated visit; not all variables were evaluable. EOA, Effective orifice area.

TABLE 6. Paravalvular aortic regurgitation data at follow-up

Severity	Follow-up point			
	Discharge	3 mo	1 y	3 y
0 (None)	69.6 (179)	64.9 (163)	62.9 (156)	54.8 (34)
+1 (Trivial/trace)	25.3 (65)	28.7 (72)	30.2 (75)	37.1 (23)
+2 (Mild)	3.9 (10)	4.4 (11)	5.6 (14)	6.5 (4)
+3 (Moderate)	0.8 (2)	1.6 (4)	1.2 (3)	1.6 (1)
+4 (Severe)	0.4 (1)	0.4 (1)	0.0 (0)	0.0 (0)

Data presented as % (n).

Valve System, it would be reasonable to expect similar long-term durability for our RDAVR cohort.

In addition to long-term durability, another important factor influencing valve choice is hemodynamic performance, with the primary goal being to avoid PPM. First described by Rahimtoola⁴ in 1978, PPM occurs when the EOA of the implanted prosthetic valve is less than that of a normal human valve. The adverse effects of severe PPM include less improvement in heart failure symptoms and functional class,⁵ impaired exercise capacity,² reduced LV mass regression,^{5,6} and greater early (30-day) and intermediate (>5-year) mortality rates.^{3,5} In a study of 2576 patients who survived AVR, Mohty and associates³ found that severe PPM (defined as an indexed EOA of ≤ 0.65 cm²/m²) was associated with decreased 5- and 10-year survival (74% and 40%, respectively), significantly worse than those for patients with mild or no PPM (5- and 10-year survival rate, 84% and 61%, respectively).

The limitations inherent in calculating the EOA using the continuity equation, in particular, the operator-dependent echocardiographic measurement of the LV outflow tract diameter, have made comparisons of different valve studies difficult.¹⁶ This issue can be reconciled, however, using an echocardiographic core laboratory, which will reduce the variability and enhance the interpretation of the echocardiographic results. In the present study, the indexed EOA and rate of severe PPM were calculated by the echocardiographic core laboratory as 0.9 cm²/m² and 3% (6 of 186) at 1 year. For perspective, Hahn and associates¹⁷ reported the echocardiographic core laboratory substudy of the Placement of Aortic Transcatheter Valves (PARTNER) trial cohort A, which included a surgical AVR control group. The rate of severe PPM among the 142 AVR patients from their study was nearly 30% (42 of 142) at 1 year. Although both groups had severe aortic stenosis, the baseline characteristics and echocardiographic findings of the patients in the PARTNER trial depicted a higher risk population with features predictive of postoperative PPM, such as advanced age, coronary artery disease, diabetes, and renal failure.⁶ Nevertheless, it is unlikely that these differences alone sufficiently explain the 10-fold increase in severe PPM.

According to Pibarot and Dumesnil,¹⁸ 2 major factors contribute to PPM: (1) pathologic changes that characterize aortic stenosis (ie, annular calcification and fibrosis, which

TABLE 7. Effective orifice area index and incidence of severe patient-prosthesis mismatch by stratified by aortic annular size

Variable	Follow-up point			
	Discharge	3 mo	1 y	3 y
All subjects				
EOAi (cm ² /m ²)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Severe PPM	3 (5/164)	2 (4/195)	3 (6/186)	2 (1/47)
Mean gradient (mm Hg)	10.7 ± 4.2	9.0 ± 3.4	9.0 ± 3.6	8.7 ± 4.1
Annular size ≤20 mm				
EOAi (cm ² /m ²)	0.8 ± 0.1	0.9 ± 0.2	0.8 ± 0.1	0.9 ± 0.2
Severe PPM	20 (2/10)	8 (1/12)	15 (2/13)	0 (0/5)
Mean gradient (mm Hg)	11.2 ± 3.7	8.6 ± 3.0	9.8 ± 3.3	6.4 ± 3.5
Annular size >20 mm				
EOAi (cm ² /m ²)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Severe PPM	2 (3/131)	1 (2/151)	2 (3/144)	3 (1/32)
Mean gradient (mm Hg)	10.8 ± 4.4	9.0 ± 3.4	8.9 ± 3.7	8.5 ± 4.1

Data presented as mean ± standard deviation or % (n/N). EOAi, Effective orifice area index; PPM, patient-prosthesis mismatch.

restrict the diameter of the bioprosthetic implant); and (2) the structural support of the stented bioprosthesis, which occupies space within the aortic root and reduces the EOA available for blood flow. Because the Edwards Intuity valve is built around a Carpentier-Edwards Perimount bioprosthesis, one could expect a similar PPM rate to that observed from conventional AVR series. However, the very low rate of severe PPM observed in the present study suggests another factor might be contributing to the hemodynamic performance of the Intuity valve. The balloon-expandable, cloth-covered stent frame sits in a subannular position, where it might, hypothetically, optimize the flow characteristics through the valve inlet by widening and reshaping the LV outflow tract. Additional studies, including magnetic resonance imaging flow assessment, are required to more fully investigate this hypothesis.

Significant PVL is associated with an increased risk of late mortality after AVR. Kodali and associates¹⁹ reported on 348 patients at high risk for surgery and subsequently randomized to transcatheter aortic valve replacement in the PARTNER Trial. The rate of moderate or severe PVL after transcatheter aortic valve replacement in these patients was 7.0% at 1 year and 6.9% at 2 years. Moreover, the presence of moderate or severe PVL was associated with significantly greater late mortality than in patients without PVL. In contrast, surgical AVR has usually been associated with an extremely low rate of postoperative PVL. Of the 351 high-risk patients randomized to surgical AVR in the PARTNER trial, the rate of moderate or severe PVL was 1.9% at 1 year and 0.9% at 2 years.¹⁹ The present study with Edwards Intuity observed a rate of moderate or severe PVL of 1.2% at 1 year. This rate appears comparable to that after surgical AVR.

Study Limitations

The TRITON trial was a single-arm study without an active comparator group. Hence, it might be vulnerable to

selection and channeling biases. Because “roll-in” cases were not excluded, the outcomes reflect the effect of a learning curve. During the enrollment phase of the study, considerable emphasis was placed on procedural training and the sharing of best practices. Nonetheless, the possibility of performance bias could not be excluded. The clinical endpoints were objectively defined a priori, and the outcomes were independently determined by a clinical events committee and an echocardiographic core laboratory. Hence, the detection and measurement biases were mitigated but not eliminated. However compelling the data appear to be at this interim analysis, the number of patients followed up out to 3 years was small; hence, our findings should be considered preliminary.

CONCLUSIONS

The results of the TRITON trial have confirmed the safety and efficacy of RDAVR using the Edwards Intuity Valve System. At 3 years, the Intuity valve was associated with a low mean transvalvular gradient and significant LV mass regression. Moreover, compared with standard surgical bioprostheses, the Edwards Intuity might be associated with larger EOAs in smaller valve sizes, a lower risk of PPM owing to the structural valve design, and a low rate of significant postoperative PVL. These hemodynamic benefits were accompanied by significant improvements in patient functional status.

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Discussion

Dr Y. Joseph Woo (Stanford, Calif). My disclosure is that last year at Penn, I was the principal investigator for the Intuity valve trial and had the opportunity to implant both first- and second-generation devices.

Dr Wahlers, I congratulate you and your co-investigators on your excellent presentation, outstanding results, and pioneering leadership in conveying innovative technologies into clinical practice.

With this presentation and the report by Kocher and Borger,¹⁰ the TRITON team has demonstrated high procedural success, shortened crossclamp and bypass times, enhanced minimally invasive approaches, low paravalvular regurgitation rates, excellent midterm clinical outcomes, LV mass regression, and persistent single-digit mean gradients, with particular benefit in the smaller annulus. I have 4 questions.

First, your hypothesis for the mechanism of generating a larger EOA in the smaller annulus is that the balloon expandable stent mechanically widens the LV outflow tract. Did you observe an elevated incidence of transient conduction abnormalities or mechanical interference with mitral valve anterior leaflet mobility or function?

Dr Wahlers. Dr Woo, thank you very much for the question.

I think the balloon expansion widens the outflow tract a little bit but not permanently. We have not seen any dysfunctions leading to pacemaker implantation, reflected by the pacemaker implant rate, which was low or comparable to that with other prostheses.

Also, no interference with the mitral valve anterior leaflet has been reported to date. That might be also related to the, let us say, acceptable height of the prosthesis. The valve is not so deep sitting in the LV outflow tract; thus, we have concluded that it does not interfere.

Dr Woo. Thank you. Second, the size 19 Intuity valve compared well with the reference echocardiographic data of the EOAs of various other bioprostheses. However, when you study the rest of the tabular data and you compare the Intuity valve against the Magna, on which the Intuity was based, the data you presented revealed that the size 23 and 25 Intuity EOAs, even with the expanded LV outflow tract, were actually smaller than the corresponding Magna EOAs. How would you reconcile this?

Dr Wahlers. Well, this is difficult to explain. What I can tell you from the raw data is that we did not have all the values assessed in every individual patient at all follow-up points. That might have influenced the small sizes of the numbers, and we will have to wait for larger patient numbers to correct for that.

Dr Woo. Thank you. Third, based on either perception or direct experience, would you be kind enough to offer any comparisons between this device and another sutureless aortic bioprosthesis widely available in Europe?

Dr Wahlers. That is a good point. I think the advantage of this valve is that one has a conventional valve mounted on a stent, and all other valves have new designs. That is the first point.

So, the new designs have to prove they will have the same durability as that of the Magna design, which has already been proved. That addresses the first point.

The second point is that with the balloon dilatation of the LV outflow tract, I think the fitting will be better in general compared with that of the other valves available and, therefore, more reproducible.

Dr Woo. Thank you. Finally, given relative differences in the magnitude of the procedure and device costs among transcatheter aortic valve replacement, RDAVR, and standard bioprostheses, where do you envision the ultimate niche for rapid deployment or sutureless AVR?

Dr Wahlers. Well, this is a difficult question to answer. If one can purchase this type of prosthesis for the same price as that of a stented prosthesis, I would totally switch in the small sizes. So, it is a question of the policy of the company regarding where to place the costs.

It is really an advantage to use this valve in patients in whom one wants to have a short clamp time. So, for redo procedures, combined procedures in which one has impaired LV function, and, perhaps, also in the small sizes, such as I mentioned, 19 or 21 mm, the valve might provide advantages with regard to the parameters I showed.

Dr Woo. Thank you again for your leadership in advancing the field.

Dr Wahlers. Thank you very much for your kindness.

Dr Hans-Joachim Schäfers (*Homburg/Saar, Germany*). One quick question—you said in your presentation that the pacemaker rate was 6%, which is somewhat greater than that after conventional AVR, and valve related was 3%. How did you differentiate between the 2?

Dr Wahlers. Let me explain the data. If the patient had pre-existent disturbances, such bundle branch block, this led more easily to a pacemaker being needed postoperatively. All other pacemaker implantations were counted as directly related to the valve implantation in patients who had not had these problems preoperatively.

We wanted to be very exact in our analysis, and if you compare the percentage 6.9% for early pacemaker implantation, this compares fairly well with the published data for pacemaker rates in patients with a stented bioprosthesis. So, it is not higher, which perhaps was suspected due to the stent design before.