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Early and 1-year outcomes of aortic root surgery in patients with Marfan syndrome: A prospective, multicenter, comparative study

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Objective: To compare the 1-year results after aortic valve-sparing (AVS) or valve-replacing (AVR) aortic root replacement from a prospective, international registry of 316 patients with Marfan syndrome (MFS).

Methods: Patients underwent AVS (n = 239, 76%) or AVR (n = 77, 24%) aortic root replacement at 19 participating centers from 2005 to 2010. One-year follow-up data were complete for 312 patients (99%), with imaging findings available for 293 (94%). The time-to-events were compared between groups using Kaplan-Meier curves and Cox proportional hazards models.

Results: Two patients (0.6%)—1 in each group—died within 30 days. No significant differences were found in early major adverse valve-related events (MAVRE; $P = .6$). Two AVS patients required early reoperation for coronary artery complications. The 1-year survival rates were similar in the AVR (97%) and AVS (98%) groups; the procedure type was not significantly associated with any valve-related events. At 1 year and beyond, aortic regurgitation of at least moderate severity (≥2+) was present in 16 patients in the AVS group (7%) but in no patients in the AVR group ($P = .02$). One AVS patient required late AVR.

Conclusions: AVS aortic root replacement was not associated with greater 30-day mortality or morbidity rates than AVR root replacement. At 1 year, no differences were found in survival, valve-related morbidity, or MAVRE between the AVS and AVR groups. Of concern, 7% of AVS patients developed grade ≥2+ aortic regurgitation, emphasizing the importance of 5 to 10 years of follow-up to learn the long-term durability of AVS versus AVR root replacement in patients with MFS. (J Thorac Cardiovasc Surg 2014;147:1758-67)

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In patients with Marfan syndrome (MFS), cardiovascular complications have been the leading cause of mortality and morbidity, including dilatation and dissection of the aortic root and other segments of the thoracic aorta. If untreated, such complications can lead to life-threatening conditions, including aortic valve regurgitation, congestive heart failure, and aortic rupture.[1] The underlying cause of aortic disease involves impaired synthesis, secretion, and deposition of

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Abbreviations and Acronyms

AR = aortic regurgitation
AVR = aortic valve-replacing
AVS = aortic valve-sparing
MAVRE = major adverse valve-related event
MFS = Marfan syndrome
NSVD = nonstructural valve dysfunction
NYHA = New York Heart Association
SVD = structural valve deterioration

the fibrillin-1 protein, resulting from various *FBN1* gene mutations. The aortic root is especially prone to dilatation and dissection.[2] By some estimates, about 80% of adult patients with MFS will have dilated aortic roots.[3]

Before the introduction of aortic valve and ascending aorta replacement by Bentall and DeBono[4] in 1968, followed by the advent of aortic valve-sparing (AVS) aortic root replacement (remodeling technique of Yacoub and colleagues[5] in 1979 and the reimplantation procedure of David and Feindel[6] in 1988), the life expectancy of most patients with MFS did not exceed 40 years.[7] Numerous modifications were subsequently introduced, including a recently developed computer-modeled custom external aortic root support device.[8] The hope was that lifelong anticoagulation (mandatory after an aortic valve-replacing [AVR] procedure using a mechanical valve) could be avoided if the valve were preserved[6,9]; however, the potential for valve deterioration and the need for reoperation was unknown. Although many single-center analyses have reported mid-term success after AVS root replacement using the David and Feindel reimplantation technique, the native valve durability remains unclear because of limited follow-up durations, retrospective designs, single-center reporting, and insufficient sample sizes. A recent meta-analysis by Benedetto and colleagues[10] provided more insight; however, the results were concerning in that patients with MFS had a substantially greater risk of reoperation after an AVS procedure than after an AVR procedure.

This first prospective, multicenter, international registry study—Aortic Valve Operative Outcomes in Marfan Patients—was initiated to provide contemporary data regarding the clinical outcomes of AVS versus AVR aortic root replacement. We report the 1-year results for 316 patients with MFS who were enrolled in this registry.

METHODS

Study Design and Patient Recruitment

Patient enrollment continued from March 2005 until November 2010, when the enrollment target of 316 patients was reached. The Data Coordinating Center with 4 Study Cores coordinated the efforts of the 19 participating study centers (see the "Acknowledgment" section). After the preliminary analysis,[11] the target sample size was increased from 250 to 316 patients to allow detection of a 2.3-fold difference between the AVR and AVS groups in the risk of valve-related complications.[12]

The enrolled patients had confirmed MFS, had undergone AVS or AVR aortic root replacement, and were available for follow-up. No limitations regarding age, gender, previous cardiovascular intervention, or surgery acuity were included. The type of surgical repair was dependent on the patient's clinical situation and surgeon and patient preference. Using the 1996 Ghent nosology,[13] the Marfan Diagnostic Core (Johns Hopkins) confirmed the MFS diagnosis clinically for all patients.

Each participating institution's institutional review board or ethics committee approved the study protocol. Each patient gave written informed consent. The protected health information was coded. The funding agencies outside of Baylor College of Medicine had no role in data interpretation.

Data Collection and Definitions

The data collection and definitions had been previously described in detail.[11] The clinical data were collected preoperatively, at discharge, and 6, 12, 24, and 36 months postoperatively. Echocardiograms were obtained at the same times if possible or whenever available otherwise and were analyzed by the Imaging Core (Mayo Clinic). When digital images were not available, the echocardiographic reports were substituted. The 1-year follow-up period extended from 274 to 457 postoperative days (12 ± 3 months). The AVS and AVR groups were formed according to the initial operation performed; the AVS procedures were classified according to the definitions suggested by Miller.[14]

Valve-related morbidity and mortality were initially defined according to the 1996 American Association for Thoracic Surgery and Society of Thoracic Surgeons guidelines.[15] Valve-related complications included structural valvular deterioration (SVD), nonstructural valve dysfunction (NSVD), valve thrombosis, embolism, and bleeding. The consequences of morbid events were defined as reoperation on the aortic valve, valve-related mortality, sudden unexplained death, cardiac death, death from any cause, and permanent valve-related impairment. The 2008 revision of the American Association for Thoracic Surgery, Society of Thoracic Surgeons, and European Association for Cardio-Thoracic Surgery valve-reporting guidelines[16] introduced an updated composite indicator to capture all types of valve-related events—major adverse valve-related events (MAVRE)—which we used as a primary endpoint. The MAVRE variable was defined as all-inclusive valve-related morbidity and mortality and the need for permanent pacemaker or defibrillator implantation within 14 days of valve intervention.

The patients were categorized as having SVD or NSVD if they had echocardiographic aortic regurgitation (AR) grade $\geq$2+ or a decline by $\geq$1 New York Heart Association (NYHA) functional class caused by impairment of the operated valve, pursuant to the 2008 guidelines.[16] (This method of categorization violated the guidelines in that AR grade 1+ was not considered NSVD; see the justification in the "Discussion" section). Conversion from AVS to AVR surgery or from 1 type of AVR to another during the same operation was considered to indicate NSVD. Bleeding was classified as a valve-related event if it occurred after hospital discharge and caused death, hospitalization, or permanent injury or necessitated transfusion, regardless of whether the patient was taking anticoagulant or antiplatelet drugs. Early postoperative bleeding events, such as mediastinal hemorrhage requiring re-exploration, were recorded separately and were not categorized as valve-related complications. The definitions of non–valve-related cardiac, pulmonary, and renal complications have been described previously.[11]

Patients and Operations

Of the 375 consecutively screened patients who had a tentative MFS diagnosis, needed aortic root replacement, and agreed to participate in the present study, 316 (84%) met the inclusion criteria and were enrolled at 19 participating centers (Table E1). The 59 excluded patients included 54 who did not meet the Ghent criteria and 5 who had undergone isolated valve replacement instead of root replacement. The types of aortic root

TABLE 1. Operative details

Operative variable	Total (n = 316)	AVR (n = 77)	AVS (n = 239)	*P* value
Urgency of surgery				
Elective	288 (91)	59 (77)	229 (96)	<.01
Urgent	12 (4)	7 (9)	5 (2)	
Emergency	16 (5)	11 (14)	5 (2)	
Perfusion technique				
Cardiopulmonary bypass alone	246 (78)	55 (71)	191 (80)	.1
Circulatory arrest	70 (22)	22 (29)	48 (20)	.1
HCA without perfusion adjuncts	25 (36)	7 (32)	18 (38)	1.0
HCA with ACP	19 (27)	6 (27)	13 (27)	
HCA with RCP	23 (33)	8 (36)	15 (31)	
HCA with ACP + RCP	3 (4)	1 (5)	2 (4)	
Cardiopulmonary bypass time (min)	179 (141-256)	152 (115-197)	194 (148-270)	<.01*
Aortic crossclamp time (min)	145 (110-208)	115 (79-161)	156 (117-221)	<.01*
Operative time (min)	340 (266-429)	340 (245-405)	340 (275-441)	.1*
Concomitant procedures				
Hemiarch	52 (17)	15 (20)	37 (16)	.4
Full arch (without elephant trunk)	5 (2)	0	5 (2)	.2
Elephant trunk and arch	9 (3)	5 (6)	4 (2)	.03†
Mitral valve replacement	6 (2)	5 (6)	1 (0.4)	<.01†
Mitral valve repair	35 (11)	10 (13)	25 (10)	.5
Coronary artery bypass	13 (4)	4 (5)	9 (4)	.5*

Data presented as n (%) or median (interquartile range). *AVR*, Aortic valve-replacing; *AVS*, aortic valve-sparing; *HCA*, hypothermic circulatory arrest; *ACP*, antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion. *Independent samples Mann-Whitney *U* test. †Fisher's exact test.

replacement procedures and operative details are listed in Table E2 and Table 1, respectively. No female patients were pregnant at surgery. Of the 316 patients, 239 (76%) underwent an AVS procedure.

Follow-up Data

Complete 30-day and in-hospital outcome data were obtained for all 314 surviving patients. The Imaging Core had discharge echocardiographic images available for 240 patients (76%) and echocardiographic reports for 61 (19%), for a total of 301 (95%). Twenty-five (8%) of these patients had been treated at study sites that only assessed postprocedural AR echocardiographically during surgery and not at discharge; these patients' intraoperative postprocedural echocardiogram or report was used instead.

At ≥1 year, clinical follow-up data were available for 300 (97%) of the 310 surviving patients; 4 patients (1%) had been lost to follow-up, 4 (1%) had only echocardiographic follow-up data available, and 2 (1%) had follow-up data from a patient interview. The vital status for patients without clinical follow-up or interview data available was cross-checked with the Social Security Death Index. Clinical follow-up data within the 1-year point was available for 208 patients (69%); the remaining 92 (31%) had clinical follow-up data available for >1 year.

The results of the imaging studies obtained ≥1 year postoperatively were available for 293 (95%) of 310 surviving patients (271 echocardiograms read by the Imaging Core, 20 echocardiogram reports, and 2 electrocardiogram-gated magnetic resonance images). In 5 of the 271 echocardiograms read by the Imaging Core, technical obstacles precluded assessment of AR severity; therefore, local echocardiographic reports were used. For 122 patients (39%), the first follow-up echocardiogram or report was obtained beyond the 1-year follow-up window. For analysis purposes, the duration of clinical and echocardiographic follow-up was truncated at 457 days, except for 8 patients with later echocardiograms that showed AR grade ≥2+. In those 8 cases, the actual echocardiographic follow-up period was used in the analyses. No echocardiographic follow-up was available for 17 patients (5%; 4 patients were lost to follow-up, 10 had no follow-up echocardiograms, and 3 had echocardiograms or reports that could not be retrieved from an outside medical institution).

Statistical Analysis

Normally distributed continuous data are summarized as the mean ± standard deviation and compared between groups by using Student *t* tests. Non-normally distributed continuous data are summarized as the median and interquartile intervals, and the Mann-Whitney *U* test was used for between-group comparisons. Nominal data are presented as frequencies and percentages, and the chi-square or Fisher exact test was used for between-group comparisons, as appropriate. Differences associated with the operation type were assessed using Kaplan-Meier curves, and log-rank tests were used to analyze the time-to-event for each outcome variable, with statistical significance assessed by the log-rank statistic at the .05 level.

Cox proportional hazards models were used to compare the risks associated with patient characteristics (including demographic, preoperative, and operative variables) for each outcome while adjusting for procedure type. Each predictor variable (Appendix E1) was independently evaluated; only the predictors significant at the .05 level were subsequently entered in a multivariable model adjusting for type of operation.

RESULTS

Overall Outcomes

Early 30-day outcomes. One AVS patient died 1 day postoperatively because of bleeding, and 1 AVR patient died 7 days postoperatively of multiple organ failure, for an early overall mortality rate of 0.6%. The incidence of valve-related complications and MAVRE was 5% and 7%, respectively (Table 2). Valve-related morbid events included 8 cases of NSVD; 6 occurred intraoperatively and resulted in conversion from initial valve-sparing (n = 5) or homograft root replacement (n = 1) to placement of a mechanical composite valve graft.[17] One other patient required immediate reoperation to correct coronary artery

TABLE 2. Thirty-day outcomes after aortic root replacement

Adverse event	Total (n = 316)	AVR (n = 77)	AVS (n = 239)	*P* value
Mortality	2 (0.6)	1 (1)	1 (0.4)	.4*
Valve-related events				
NSVD	8 (3)	1 (1)	7 (3)	1.0*
Embolism	4 (1)	1 (1)	3 (1)	1.0*
Bleeding	5 (2)	2 (3)	3 (1)	.6*
Permanent pacemaker within 14 d	5 (2)	2 (3)	3 (1)	.6*
Valve-related morbidity	16 (5)	4 (5)	12 (5)	1.0*
MAVRE	21 (7)	6 (8)	15 (7)	.6*
Mediastinal re-exploration	19 (6)	7 (9)	12 (5)	.3*
Cardiac complications	64 (20)	27 (35)	37 (15)	<.01
Atrial or ventricular arrhythmia	44 (14)	15 (20)	29 (12)	.1
Pericardial effusion requiring drainage	10 (3)	4 (5)	6 (3)	.3*
Cardiac failure	8 (3)	4 (5)	4 (2)	.1*
MAVRE and cardiac complications	74 (24)	27 (36)	47 (20)	.1
Pulmonary complications	26 (8)	12 (16)	14 (6)	.01
Acute renal dysfunction	2 (1)	2 (3)	0	.1*
Total postoperative ventilation support time (h)	9 (5-17)	12 (8-24)	8 (5-15)	<.01†
Total ICU stay (h)	32 (22-53)	46 (24-72)	26 (22-49)	.02†
Length of hospital stay (d)	7 (5-9)	7 (6-10)	6 (5-9)	.01†

Data presented as n (%) or median (interquartile range). No 30-day cases of SVD, reintervention on the aortic valve, or operated valvular endocarditis occurred. *AVR*, Aortic valve-replacing; *AVS*, aortic valve-sparing; *NSVD*, nonstructural dysfunction; *MAVRE*, major adverse valve-related event; *ICU*, intensive care unit. *Fisher's exact test. †Independent samples Mann-Whitney *U* test.

kinking after an AVS operation (Florida sleeve procedure). Another patient required repair of a coronary artery pseudoaneurysm 6 days after an AVS procedure. The 4 cases of systemic embolism resulted in 2 reversible ischemic neurologic deficits, 1 transient ischemic attack, and 1 stroke. After discharge, 5 patients sustained valve-related bleeding complications, including 3 cases of cardiac tamponade requiring pericardial drainage, 1 of mediastinal bleeding requiring re-exploration, and 1 of gastrointestinal bleeding from an ulcer. Within 14 days postoperatively, 5 patients required a permanent pacemaker because of heart block. No early cases of SVD, valve thrombosis, or endocarditis occurred.

Twenty-seven bleeding events occurred before discharge and were not classified as valve-related complications. Eighteen necessitated mediastinal re-exploration, including 3 at the aortic root site (annular suture line or coronary anastomoses) and 3 at a left atriotomy site or distal aortic anastomosis. Of the 9 patients not requiring re-exploration, 4 had cardiac tamponade (drained in 3, treated conservatively in 1). Other bleeding sites included the left groin, sternum, chest tube tract, lower extremity, and an unidentifiable site.

Pericardial effusion requiring drainage occurred in 10 patients (bloody effusion in 8). One AVR patient experienced a myocardial infarction. Overall, both cardiac ($P < .01$) and pulmonary ($P = .01$) complications were more common in the AVR group (Table 2).

One-year outcomes. Six deaths occurred during the first year. The causes of death after 30 days included 1 drowning in the AVS group and 1 case of sepsis complicated by intracranial hemorrhage in the AVR group. In 2 AVS patients, the exact cause of death was unknown but was considered valve-related in accordance with the 2008 guidelines.[16] At 1 year, the overall survival and freedom from MAVRE was 98% and 86%, respectively (Table 3). Eight patients (3%) were in NYHA class III-IV, and 16 (6%) had AR grade ≥2+ (Table E3).

The complications after 30 days included NSVD or SVD (AR ≥2+) detected echocardiographically in 16 patients. Echocardiography could not easily distinguish between these modes of valve failure; thus, they were combined into a single NSVD/SVD outcome. The first echocardiographic examination available for 8 of these patients was performed beyond the 1-year threshold. The preoperative aortic valve morphology had been normal in all 16 patients. These patients were more likely than the other AVS patients to have had preoperative AR ≥2+ ($P = .03$), undergone AVS with the David I technique ($P = .054$), and had intraoperative, post-procedural, mild AR ($P < .01$). Bleeding events occurred in 3 patients, including bloody pleural effusion requiring thoracentesis (day 33), gastrointestinal bleeding requiring surgical intervention (day 199), and bloody pericardial effusion (day 128) treated with transfusion and a change in the anticoagulant regimen. Two patients experienced embolic events: 1 transient ischemic attack (day 41) and 1 stroke (day 248). One patient developed endocarditis (day 248). One AVS patient required surgical reintervention on the aortic valve and root for graft infection (day 219). No patient developed valve thrombosis beyond 30 days.

TABLE 3. One-year operative outcomes after aortic root replacement

Adverse event	Total (n = 316)	AVR (n = 77)	AVS (n = 239)	*P* value
Survival and freedom from valve-related events				
Overall survival	98 (96-99), 6/316	97 (91-100), 2/77	98 (96-100), 4/239	.6
Freedom from valve-related events				
Valve-related death	99 (97-100), 3/316	99 (93-100), 1/77	99 (97-100), 2/239	.7
NSVD/SVD	92 (89-95), 24/290	99 (92-100), 1/71	90 (85-93), 23/219	.04
Embolism	98 (96-99), 6/312	97 (91-100), 2/75	98 (96-100), 4/237	.6
Bleeding	97 (95-99), 8/312	93 (85-98), 5/75	98 (96-100), 3/237	.01
Endocarditis	100 (98-100), 1/316	99 (93-100), 1/75	100 (98-100), 0/237	.07
Reintervention	99 (98-100), 1/316	100 (95-100), 0/75	100 (98-100), 1/237	.6
Valve-related morbidity	89 (85-92), 35/312	91 (82-96), 7/77	88 (83-92), 28/235	.6
MAVRE	86 (81-90), 43/295	89 (80-95), 8/73	85 (79-89), 35/222	.5
MAVRE and cardiac complications	68 (63-74), 95/300	60 (48-71), 30/75	71 (65-77), 65/225	.04
Other complications				
Cardiac complications	72 (23)	29 (37)	43 (18)	<.01
Atrial or ventricular arrhythmia requiring treatment	51 (16)	17 (22)	34 (14)	.1
Pericardial effusion requiring drainage	10 (3)	4 (5)	6 (3)	.3
Cardiac failure	10 (3)	5 (6)	5 (2)	.07
Pulmonary complications	30 (9)	13 (17)	17 (7)	.01
Acute renal dysfunction	2 (1)	2 (3)	0	.1

Time-to-event estimates for survival and freedom from valve-related events were obtained using Kaplan-Mayer analysis and are presented as percentages (95% confidence intervals), and number of events/number of observations at the beginning of the interval; ''other complications'' are reported as n (%). In 8 of 24 patients, NSVD/SVD due to AR ≥2+ was detected by echocardiography beyond the 1-year threshold because earlier echocardiograms for these patients were not available. These time-to-event outcomes were compared using the log-rank statistic. No cases of valve thrombosis had developed by 1 year of follow-up. *AVR*, Aortic valve-replacing; *AVS*, aortic valve-sparing; *NSVD*, nonstructural dysfunction; *SVD*, structural valve deterioration; *MAVRE*, major adverse valve-related events.

Cardiac and pulmonary complications were both less common after the initial 30 days (Table 3). Ten patients had cardiac complications (days 32 to 419): 5 had atrial or ventricular arrhythmias, 2 had heart block, 2 had congestive heart failure, and 1 had myocarditis. Five pulmonary complications (which developed from days 33 to 189) included 3 pleural effusions requiring drainage and 2 cases of pneumonia.

Comparison of AVR and AVS Groups

The AVR patients were generally older and sicker than the AVS patients. The AVR group had more patients in NYHA class III-IV and with more severe AR, larger aortic sizes, and a greater prevalence of ascending aortic dissection, cardiomyopathy, and renal failure. Previous cardiovascular operations (Table E1) and urgent or emergency operations (Table 1) were more frequent in the AVR group. The AVR group needed more concomitant elephant trunk arch grafting or mitral valve replacement than the AVS group (Table 1). In contrast, as expected, the aortic crossclamp, cardiopulmonary bypass, and total operative times were longer in the AVS group.

Early mortality did not significantly differ between the 2 groups ($P = .4$). The rates of early valve-related and cardiac complications, MAVRE, and combined MAVRE and cardiac complications were similar; however, pulmonary problems were more prevalent in the AVR group, which also had a longer mean ventilator support time. The intensive care unit stay and overall hospital stay were both longer for the AVR patients (Table 2).

The Kaplan-Meier analysis of the 1-year outcomes reflected the between-group differences (Table 3, Figures 1 and 2). Although the major endpoints—including overall survival ($P = .6$), freedom from MAVRE ($P = .6$), and valve-related morbidity ($P = .7$)—were similar between the groups, freedom from combined NSVD/SVD was greater in the AVR group (99%) than in the AVS group (90%; $P = .04$). AR of at least moderate severity (≥2+) was present in all 16 cases of combined NSVD/SVD that developed after 30 days in the AVS group. In contrast, only 1 patient had AR ≥2+ in the AVR group. The freedom from bleeding rate was 93% in the AVR group versus 99% in the AVS group ($P = .01$). The AVR patients had more combined MAVRE and cardiac complications (57% vs 70%, $P = .006$) than the AVS patients. The AVR group also had more cardiac and pulmonary complications. Overall, 7 patients were in NYHA class III and 1 was in class IV. No significant difference was present between the 2 groups ($P = .5$; Table E3).

Cox regression analysis did not identify procedure type as a risk factor for any of the 1-year adverse endpoints. Of the covariates tested for inclusion in the Cox regression model (Appendices E1 and E2), preoperative AR ≥2+ was significantly associated with valve-related complications ($P = .04$), and intraoperative postprocedural AR was significantly associated with MAVRE ($P = .03$), valve-related complications ($P = .02$), and combined NSVD/SVD ($P < .01$). Preoperative mitral regurgitation ≥2+ was significantly associated with combined MAVRE

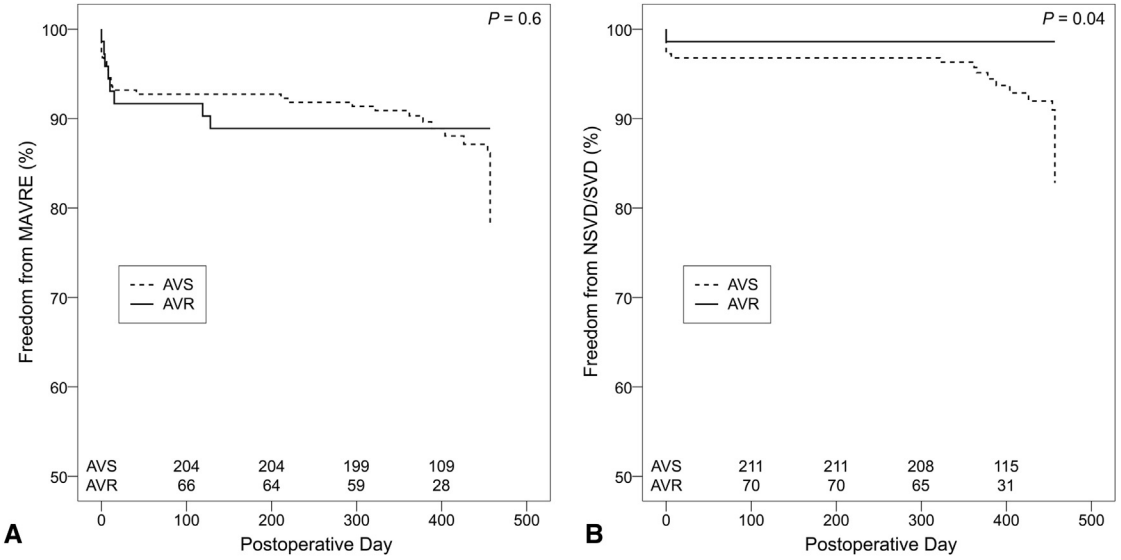

FIGURE 1. Kaplan-Meier analysis of 1-year valve-related events comparing patients who underwent aortic valve-sparing (*AVS*) and aortic valve-replacing (*AVR*) root replacement. The *P* value was obtained by computing the log-rank statistic. A, Freedom from major adverse valve-related events (*MAVRE*). B, Freedom from nonstructural valve dysfunction/structural valve deterioration (*NSVD/SVD*).

and cardiac complications ($P = .0049$). Preoperative mitral regurgitation $\geq 2+$ was also associated with a greater risk of MAVRE ($P = .01$), and preoperative tricuspid valve regurgitation $\geq 2+$ was associated with a greater risk of bleeding ($P = .04$). However, the 95% confidence intervals for the last 2 associations were wide because of the low number of events during the first postoperative year.

DISCUSSION

The present study is the first prospective investigation to compare the outcomes in patients with MFS concurrently undergoing aortic root replacement using either the AVR or AVS technique. The multicenter design enabled us to determine whether the results would be "generalizable" around the world; it also allowed enough patients to be enrolled within 5 years to potentially avoid the confounding effects of changes in surgical technique. Although the idea was appealing, it would have been unrealistic to attempt to conduct this trial in a randomized fashion; we decided it was in the patients' interest to allow the surgeons to perform whichever procedure they believed was best for each patient in light of that patient's particular clinical circumstances.

Since this study began in 2005, newer techniques for preserving the aortic valve have been developed. Transcatheter aortic valve replacement has been gaining popularity for elderly, very sick patients with aortic stenosis[18] and has been proposed as a potential "salvage" procedure if the preserved native aortic valve fails. Treasure, Pepper, and Golesworthy and their colleagues from London[19] have developed a customized, computer-designed external support mesh prosthesis that can be implanted without cardiopulmonary bypass; they have argued that this device can be used to prevent future aortic root expansion when the patient has not yet reached the conventional thresholds for surgical root replacement. It cannot be used, however, if the patient has AR or if the annulus is markedly dilated.

The present 1-year analysis has confirmed our previous findings[11] in a larger number of patients. The AVR group was older, had more comorbidities, and more often required emergency or urgent operations. The unadjusted log-rank comparisons of valve-related complications showed a greater prevalence of combined NSVD/SVD in the AVS group. However, bleeding events, non–valve-related cardiac adverse events, and pulmonary complications were more common in the AVR group. The composite MAVRE endpoint did not differ between the AVS and AVR groups, apparently because the differences in individual valve-related complications offset each other in the composite MAVRE variable. Although the Cox regression analysis showed that procedure type had no important influence on any endpoint, the greater prevalence of NSVD/SVD in the AVS group 1 year postoperatively should serve as an alert—much longer follow-up is necessary to reveal the true durability of the AVS approach in patients with MFS. This observation reinforces the conclusion of the recent meta-analysis by Benedetto and colleagues,[10] who examined 11 retrospective studies that compared valve-related composite outcomes (ie, combined reintervention, thromboembolic event, and endocarditis) and individual complications after either AVS or AVR root replacement in patients with MFS. They found no difference in the composite outcome; however, the AVS

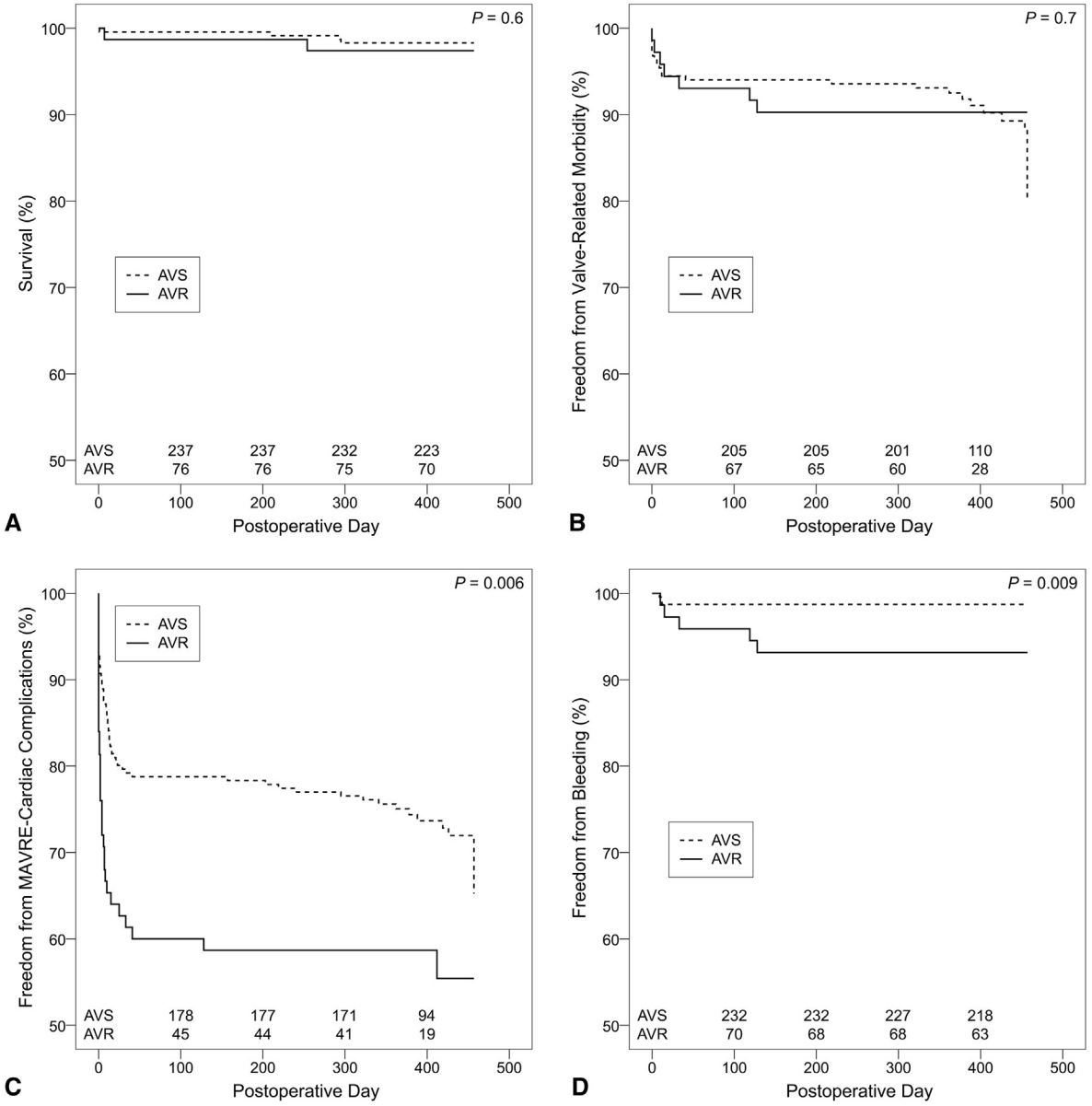

FIGURE 2. Kaplan-Meier analysis of 1-year overall survival and freedom from valve-related events comparing patients who underwent aortic valve-sparing (*AVS*) and aortic valve-replacing (*AVR*) root replacement. The *P* value was obtained by computing the log-rank statistic. A, Overall survival. B, Freedom from valve-related complications. C, Freedom from combined major adverse valve-related events (*MAVRE*) and cardiac complications. D, Freedom from bleeding.

patients more frequently required surgical reintervention, and the AVR patients had a greater incidence of thromboembolic complications (these 2 individual complications cancelled each other's effects when combined in the composite outcome variable).[10] The greater 1-year prevalence of NSVD/SVD in our study and the greater reintervention rate reported by Benedetto and colleagues[10] question the durability of the preserved native aortic valve in patients with MFS. Future investigations that include more patients followed up for long periods are clearly necessary; such studies will also determine the mortality risk associated with reoperation after AVS procedures if the valve fails.

Finally, the 2008 American Association for Thoracic Surgery, Society of Thoracic Surgeons, and European Association for Cardio-Thoracic Surgery valve-reporting guidelines[16] have stipulated that residual or recurrent mitral or tricuspid regurgitation must be more than mild to qualify as NSVD; however, no similar $\geq$2+ threshold has been stated for AR after aortic valve repair or AVS aortic root replacement. Because mild (1+) AR is common after AVS (occurring in 25% of AVS patients in the present

study), classifying it as NSVD would have caused us to overestimate the incidence of NSVD, and it would not represent a clinically important complication. We suggest that the next iteration of the valve-reporting guidelines be modified according to these findings. The Stanford group recently reported that mild (1+) residual AR was present in fully 43% of their patients 1 year after David reimplantation AVS. However, it remained stable in 85% to a median of 57 months, had progressed to 2+ in only 12% at a median of 28 months and remained stable thereafter, and had degenerated to 4+ in only 1 patient.[20] Hence, our present finding of a greater incidence of NSVD/SVD in the AVS group probably did not portend premature valve failure or the need for reoperation in the medium term, and it certainly did not represent failure of the fundamental valve-sparing concept in patients with MFS.

Study Limitations

The limitations inherent in the present prospective registry design included the impossibility of standardizing surgical techniques and the possibility of important baseline differences between patient groups. Additional limitations of the study included its nonrandomized design, short follow-up period (1 year), and the lack of imaging information for 7% of the patients at ≥1 year. Another challenge was accurately interpreting the echocardiograms: various echocardiographic techniques were used, and the quality of the images varied. Also, it was impossible to discern in the AVS group whether the AR should represent SVD or NSVD; thus, they were grouped together. Finally, we had to rely on a 1-year echocardiographic report for 20 patients whose digital images were not obtainable or interpretable. The original study was powered to detect a 2.3-fold increased risk of valve-related complications, assuming 3 years of follow-up. Therefore, the 1-year data analysis provided less power to detect significant differences than the upcoming 3-year analysis because fewer events had occurred at 1 year. Because of the insufficient power and multiple hypothesis testing, the 1-year findings should be interpreted with caution. Nonetheless, the data we have presented provide the best comparison to date of the AVS and AVR approaches for aortic root repair.

CONCLUSIONS

Despite the added complexity of AVS root replacement, this approach was not associated with greater 30-day mortality or a greater MAVRE rate than AVR root replacement. At 1 year, no differences were found in survival, valve-related morbidity, or MAVRE; however, more bleeding events occurred after AVR and more valve dysfunction (NSVD/SVD) after AVS. Of concern, 7% of AVS patients developed ≥2+ AR during the follow-up period. This finding, combined with the increasing popularity of AVS root replacement, mandates continued follow-up of this well-defined cohort for 5 to 10 years to evaluate the mid- and long-term durability of AVS versus AVR root replacement in patients with MFS.

The Marfan Foundation and the Data Coordinating Center at Baylor College of Medicine express their gratitude to the domestic and international study institutions whose contributions are described below. The study could not have been conducted without their tireless efforts in patient enrollment and data collection.

Stephen N. Palmer, PhD, ELS, contributed to the editing of the manuscript. Scott A. Weldon, MA, CMI, contributed to figure preparation.

Study institutions

Study Cores: Institution (Core Director)

Data Coordination Center and Surgical Core: Baylor College of Medicine (J. S. Coselli, Study Principal Investigator)

Marfan Diagnostic Core: Johns Hopkins Hospital (H. C. Dietz)

Imaging Core: Mayo Clinic, Rochester (H. M. Connolly)

Genetic Repository: University of Texas Medical School at Houston (D. M. Milewicz)

Participating Study Sites: Institution (Site Principal Investigator, Number of Patients Enrolled)

Argentina: Institute of Cardiology and Cardiovascular Surgery—Favaloro Foundation (R. R. Favaloro, 19 patients)

Canada: University of Ottawa Heart Institute (K-L. Chan, 3 patients)

Germany: Hannover Medical School (A. Haverich, 11 patients); Medical University of Luebeck (H. H. Sievers, 13 patients); University of Leipzig (F. W. Mohr, 21 patients)

The Netherlands: Leiden University Medical Center (M. I. M. Versteegh, 3 patients)

United States: Baylor College of Medicine (J. S. Coselli, 15 patients); Central Maine Heart and Vascular Institute (R. P. Cochran, C. Frumiento, 1 patient); Johns Hopkins Hospital (V. L. Gott, L. A. Vricella, 32 patients); Loyola University Medical Center (J. P. Schwartz, 3 patients); Mayo Clinic, Rochester (T. M. Sundt III, H. V. Schaff, 55 patients); Missouri Baptist Medical Center (N. T. Kouchoukos, 8 patients); Montefiore Medical Center (A. DeAnda, 2 patients); New York Presbyterian–Cornell Hospital (L. N. Girardi, 29 patients); Northwestern University Feinberg School of Medicine (T. G. Gleason, C. Malaisrie, 8 patients); Stanford University (D. C. Miller, 49 patients); University of Pennsylvania (J. E. Bavaria, 28 patients); University of Pittsburgh (T. G. Gleason, 2 patients); Washington University (M. R. Moon, 14 patients).

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Discussion

Dr Gosta Pettersson *(Cleveland, Ohio).* I represent myself and Dr Stewart, who was the original discussant on this report. I congratulate you for a nice presentation. I congratulate the group for having put together this registry.

The inclusiveness is really the strength of the study, it represents a real world experience. I am, however, in doubt about the ability of this study to distinguish between the AVR and AVS procedures. Nevertheless, this is a remarkable effort to provide better data on how we should treat these patients, because there are still many open questions.

There are 19 centers involved in this registry, but a few centers have provided a larger number of patients. Is there anything to learn about the learning curve of the AVS procedure from this?

Dr Coselli. Yes, 2 things. One, if you consider the 30-day data, there were basically no deaths, no strokes, et cetera. The data from 30 days were excellent for the groups from this collection of institutions. So, consequently, there really was not much in the way of an impact from a learning curve.

When we considered mortality and valve-related events and the influence of the institution, we did not find that it was statistically significant. However, the problem is that with 19 institutions and so many events, it defies a legitimate statistical evaluation.

Dr Pettersson. The age range was from 4 to 70 years, and most recently, the percentage of valve-sparing operations approached 100%. Have you identified any limitations, any contraindications to valve-sparing? Also, what about age? The 4-year-old did not make it, and you said it was nonvalve-related, but still that is an interesting question.

Dr Coselli. I do not recall the exact numbers in the very low end of the pediatric age group, but clearly the 4-year-old patient was a bit of an outlier. However, when we considered age as a variable for valve outcome and survival, it was not a statistically significant factor.

Dr Pettersson. AVS was performed using a number of different techniques. Did that have any effect on residual AR?

Dr Coselli. No, that did not arise. Again, it had to do with the total number of events and the wide number of small variations in technique. So, no, this particular evaluation could not specifically answer that question.

Dr Pettersson. There were a larger number of bleeding events, and you separated them into valve-related and nonvalve-related. A valve-sparing procedure is a significantly longer operation than just replacing the aortic valve—did that not affect bleeding?

Dr Coselli. That is very interesting. There was increased complexity with AVS compared with a standard Bentall operation, removing the patients who had undergone concomitant arch operations, mitral valve repair, et cetera. Thus, although the cardiopulmonary bypass times and crossclamp times were longer, that did not influence the early results or, ultimately, the long-term results.

Dr Pettersson. My final question relates to the conversions. At which stage during the operation did the surgeons decide to abandon trying to save the valve? Conversion after 2.5 hours of crossclamp time is of great concern.

Dr Coselli. We described this group of 6 patients in our 2011 publication. Surgeons abandoned saving the valve if post-procedural excessive aortic regurgitation could not be corrected. While the crossclamp duration before conversion could not be obtained, the total crossclamp time exceeded 3 hours for 5 of the 6 patients. Except for one patient who developed early cardiac tamponade and severe mitral valve regurgitation, there were no short-term or follow-up complications in this group.

Dr Pettersson. Thank you, and I also thank the Association for the privilege to discuss this report.

Dr Marc R. Moon *(St Louis, Mo).* It is remarkable that operative mortality only occurred in 2 patients with this very complex procedure and complex disease. One of the problems with developing a new innovative technique is that sometimes it is not reproducible. However, Drs David and Yacoub hit the nail on the head. They were able to develop an incredibly complex procedure that is reproducible and safe.

Dr Coselli. Agreed.

Dr Hitoshi Ogino *(Tokyo, Japan).* Thank you very much for an interesting study and presentation.

My questions are very simple. Unfortunately, some of the patients developed a stroke during the operation or at the long-term period. What was the cause of the embolism or stroke? What do you think about that?

Dr Coselli. That I do not know in detail. There were 4 cases of early and 2 cases of late embolism that will be described in the upcoming publication.

Dr Ogino. Another question. Some patients developed AR at the long-term period. What is the cause of the AR? Have you analyzed it or did you study it?

Dr Coselli. We are still analyzing that. Again, the imaging core is with Heidi Connolly at Mayo Clinic, and the numbers were still small enough for analysis. However, it was basically leaflet deterioration over time. We know that annular dilatation was not an issue; thus, it was almost always leaflet deterioration.

But what we are going to have to eventually go back and study and determine, and I think this is probably more the core of your question, is whether any of those valve leaflets were prolapsing below the annulus when the patient left the operating room. We are still in the process of evaluating those sorts of factors, but do not have the information for this particular presentation.

Dr Ogino. Thank you very much.

Dr Marc R. Moon *(St Louis, Mo).* What is the planned long-term follow-up for these patients, and is the study closed now to accrual?

Dr Coselli. Yes. Accrual of the study has been completed. We believe it is reasonably powered. It was initially set up as, in effect, a short-term 3-year follow-up study.

If we can acquire the funding to continue to monitor these patients and pull the data together at the core sites, we will try to continue it for at least 10 years, although it would be ideal to continue for even longer.

This was a unique group of patients because they were all fully vetted for Marfan syndrome through a single, highly qualified genetic program, and all the analysis of the imaging was performed by a single renowned individual.

Thus, the follow-up has been very, very good and the quality of the data excellent. We will just have to see how this holds up over time.

Dr Leonard N. Girardi *(New York, NY).* You saw over time that a move away from AVR occurred, and almost everybody was undergoing AVS. Did you see a similar move away from remodeling toward reimplantation?

Dr Coselli. Yes. Only 1 remodeling was performed in the whole series, and this patient underwent intraoperative conversion. Almost all these institutions had adopted the inclusion technique and had moved away from the Yacoub technique very, very early on, for all the reasons that we accept.

APPENDIX E1. VARIABLES TESTED FOR INCLUSION IN REGRESSION MODEL

1. Type of surgery (AVR vs AVS)
2. Study site
3. Age at surgery
4. Gender
5. Race
6. Smoking status
7. Preoperative New York Heart Association class
8. Preoperative composite aortic regurgitation severity
9. Preoperative composite mitral regurgitation severity
10. Preoperative composite tricuspid regurgitation severity
11. Preoperative dissection
12. Preoperative dissection acuity
13. Preoperative aortic valve disease
14. History of mechanical composite valve graft surgery
15. History of aortic valve resuspension
16. History of homograft aortic root replacement
17. History of mitral valve replacement
18. History of mitral valve repair
19. Hypertension
20. Coronary artery disease
21. Heart failure
22. Cardiac arrest
23. Cardiac arrhythmia
24. Myocardial infarction
25. Endocarditis
26. Dialysis
27. Diabetes
28. Blood urea nitrogen/creatinine ratio
29. Operating surgeon
30. Crossclamp time
31. Cardiopulmonary bypass time
32. Concomitant surgical procedure

APPENDIX E2. KAPLAN-MEIER AND COX REGRESSION ANALYSES

Kaplan-Meier Analysis

Kaplan-Meier curve analysis suggested that the AVR patients were at greater risk of combined MAVRE and cardiac complications ($P = .006$) and bleeding ($P = .01$) than were the AVS patients. The AVS patients appeared to have a greater risk of NSVD/SVD ($P = .04$). The type of surgery was not significantly associated with MAVRE ($P = .6$), overall mortality ($P = .6$), valve-related mortality ($P = .7$), valve-related complications ($P = .7$), embolism ($P = .3$), reintervention ($P = .6$), or endocarditis ($P = .1$).

Cox Regression Analysis

- MAVRE

  The risk of MAVRE among patients with mitral regurgitation (MR) grade $\geq 2+$ was about 2.6 times greater than among patients with none/trivial/grade 1+ MR after adjustment for surgery type and postprocedural intraoperative aortic regurgitation (AR; $P = .01$). The risk of MAVRE among patients with postprocedural intraoperative AR grade $\geq 1+$ was 2.2 times greater than among patients with no postprocedural AR after adjustment for surgery type and MR grade ($P = .03$). The surgery type itself was not significantly associated with MAVRE (hazard ratio, 0.72; 95% confidence interval [CI], 0.3-1.8).

- Combined MAVRE and cardiac morbidity

  After adjustment for composite MR severity ($P = .005$), the surgery type was no longer significantly associated with combined MAVRE and cardiac morbidity ($P = .75$). The risk of experiencing this combined event was about 2.2 times greater for patients with MR grade $\geq 2+$ than for patients with a lower MR grade (none, trivial, or grade 1+).

- Death from all causes

  Patients with preoperative MR grade $\geq 2+$ were more likely to die of any cause than were those with a lower MR grade (hazard ratio, 19.7; 95% CI, 1.6-247.9; $P = .02$) after adjustment for surgery type. We considered this hazard ratio to be only an indication of a possible relationship, not a reliable estimate, because the 95% CI was extremely wide. The surgery type was not associated with all-cause mortality ($P = .52$).

- Valve-related complications

  The risk of valve-related complications among patients with preoperative AR grade $\geq 2+$ was 2.2 times (95% CI, 1.05-4.4; $P = .04$) greater than it was among patients with lower preoperative AR, after adjustment for postprocedural intraoperative AR and surgery type. Postprocedural intraoperative AR grade $\geq 1+$ was associated with a 2.4-fold (95% CI, 1.2-4.8) increased risk of valve-related complications after adjustment for surgery type and preoperative AR. The surgery type was not a significant predictor of valve-related complications after adjustment for preoperative AR grade 2+ and postprocedural intraoperative AR ($P = .57$).

- Bleeding

  The surgery type ($P = .26$) was no longer significantly associated with bleeding after adjustment for tricuspid regurgitation severity ($P = .004$). The risk of bleeding among patients with tricuspid regurgitation severity grades 2+ or 3+ was about 12.6 times (95% CI, 2.3-70.3) greater than that of patients with none, trivial, or grade 1+ tricuspid regurgitation severity.

We considered this hazard ratio to be only an indication of a possible relationship, not a reliable estimate, because the 95% CI was very wide.

- NSVD/SVD

  Patients with postprocedural intraoperative AR were 4.0 times more likely (95% CI, 1.7-9.1) to have NSVD/SVD than were patients who did not have AR. The analysis was adjusted for surgery type, which itself was not significantly associated with NSVD/SVD ($P = .14$).

- None of the predictor variables were significantly associated with valve-related death, embolism, reintervention, or endocarditis using Cox proportional hazards modeling.

TABLE E1. Patient characteristics

Variable	Total (n = 316)	AVR (n = 77)	AVS (n = 239)	*P* value
Age (y)	35 ± 13 (4-70)	39 ± 14 (8-70)	33 ± 13 (4-65)	<.01
Male gender	203 (64)	55 (71)	148 (62)	.1
Hypertension	68 (22)	21 (27)	47 (20)	.2
Hypercholesterolemia	8 (3)	2 (3)	6 (3)	1.0*
Diabetes	2 (1)	0	2 (1)	1.0*
Smoking† (no. of observations)	315	77	238	.7
Current smoker	24 (8)	6 (8)	18 (8)	
Former smoker	59 (19)	12 (16)	47 (20)	
Recent cerebrovascular accident	0	0	0	NA
COPD	11 (4)	2 (3)	9 (4)	1.0*
Pneumonia				.1
Current	1 (0.3)	1 (1)	0	
Previous	12 (4)	5 (7)	7 (3)	
Coronary artery disease	3 (1)	2 (3)	1 (0.4)	.1*
MI within 24 h	1 (0.3)	0	1 (0.4)	1.0*
Cardiomyopathy				.01
Current	7 (2)	5 (7)	2 (1)	
Previous	3 (1)	1 (1)	2 (1)	
MV disease				.7
Current	192 (61)	50 (65)	142 (59)	
MV prolapse	150 (47)	34 (44)	116 (49)	
MV regurgitation ≥2+	9 (3)	6 (8)	3 (1)	
Combined	33 (10)	10 (13)	23 (10)	
Previous	8 (3)	2 (3)	6 (3)	
History of endocarditis	2 (1)	1 (1)	1 (0.4)	.4*
Coagulopathy	6 (2)	3 (4)	3 (1)	.2*
NYHA class				.05
I	216 (68)	45 (58)	171 (72)	
II	79 (25)	23 (30)	56 (23)	
III	12 (4)	4 (5)	8 (3)	
IV	9 (3)	5 (7)	4 (2)	
NYHA class III-IV	21 (7)	9 (12)	12 (5)	.06
Bicuspid aortic valve	8 (3)	3 (4)	5 (2)	.4*
LVEF (%)	60 (55-65; 271)	60 (55-65; 66)	60 (55-65; 205)	.2‡
Sinus rhythm	309 (98)	75 (97)	234 (98)	.7*
AR (no. of observations)	307	76	231	<.01
None/trivial (0)	123 (40)	17 (22)	106 (46)	
Mild (1+)	107 (35)	21 (28)	86 (37)	
Moderate (2+)	40 (13)	13 (17)	27 (12)	
Moderate to severe (3+)	14 (5)	10 (13)	4 (2)	
Severe (4+)	23 (8)	15 (20)	8 (4)	
AR ≥ 2+	77 (25)	38 (50)	39 (17)	<.01
Aortic dimensions (mm)				
Annulus	26 (23-28; 275)	26 (24-29; 67)	25 (23-27; 208)	.01‡
Sinuses of Valsalva	50 (47-53; 306)	53 (49-58; 74)	49 (46-52; 232)	<.01‡
Sinotubular junction	37 (33-43; 197)	39 (34-46; 50)	36 (32-41; 147)	.05
Ascending aortic dissection	30 (10)	18 (23)	12 (5)	<.01
Dissection type				<.01
Acute	13 (4)	7 (9)	6 (3)	
Chronic	17 (5)	11 (14)	6 (3)	
Aortic rupture	1 (0.3)	0	1 (0.4)	1.0*
Previous CV surgery	29 (9)	17 (21)	12 (5)	<.01

(Continued)

TABLE E1. Continued

Variable	Total (n = 316)	AVR (n = 77)	AVS (n = 239)	*P* value
Previous CV operations (n)				<.01
1	21 (7)	11 (14)	10 (4)	
2	6 (2)	4 (5)	2 (1)	
≥3	2 (1)	2 (3)	0	
Previous CV surgery type				
AV resuspension	1 (0.3)	1 (1)	0	.2*
AV replacement, CVG	2 (1)	2 (3)	0	.6*
Homograft root	1 (0.3)	1 (1)	0	.2*
MV repair/replacement	9 (3)	3 (4)	6 (3)	.5*
Aortic aneurysm repair				
Ascending aorta	4 (1)	3 (4)	1 (0.4)	.05*
Descending thoracic aorta	5 (2)	3 (4)	2 (1)	.1*
Abdominal aorta	4 (1)	2 (3)	2 (1)	.3*
Aortic dissection repair				
Stanford A	8 (3)	7 (9)	1 (0.4)	<.01*
Stanford B	6 (2)	3 (4)	3 (1)	.2*
Other	6 (2)	4 (5)	2 (1)	.03*
Creatinine (mg/dL)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	<.01‡
Renal failure				<.01
Current	3 (1)	3 (4)	0	
Previous	1 (0.3)	1 (1)	0	

Data presented as mean ± standard deviation (range), n (%), median (interquartile range), or median (interquartile range; number of observations). *AVR*, Aortic valve-replacing; *AVS*, aortic valve-sparing; *COPD*, chronic obstructive pulmonary disease; *MI*, myocardial infarction; *MV*, mitral valve; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *AR*, aortic regurgitation; *CV*, cardiovascular; *AV*, aortic valve; *CVG*, composite valve graft. *Fisher exact test. †Patients were considered nonsmokers if they had stopped smoking ≥5 years before aortic root surgery. ‡Independent samples Mann-Whitney *U* test.

TABLE E2. Types of aortic root replacement (n = 316)

Root replacement type	n (%)
Valve-replacing	77 (24)
Mechanical composite valve graft	63
Stented bioprosthetic composite valve graft	8
Stentless porcine root	4
Homograft root	2
Valve-sparing	239 (76)
Reimplantation	238
David V	144
Stanford modification	20
Other modifications	4
David I	79
David IV	14
Florida sleeve	1
Yacoub remodeling	1

TABLE E3. New York Heart Association class and aortic regurgitation 1 year after aortic root replacement

Adverse event	Total	AVR	AVS	*P* value
NYHA class	294	71	223	.5
I	246 (78)	60 (78)	186 (78)	
II	40 (13)	8 (10)	32 (13)	
III	7 (2)	2 (3)	5 (2)	
IV	1 (0.3)	1 (1)	0	
Aortic regurgitation	288	71	217	.05
None/trivial (0)	206 (71)	60 (85)	146 (67)	
Mild (1+)	66 (23)	11 (15)	55 (25)	
Moderate (2+)	12 (4)	0	12 (6)	
Moderate to severe (3+)	3 (1)	0	3 (1)	
Severe (4+)	1 (0.3)	0	1 (0.5)	
Aortic regurgitation ≥2	16 (6)	0	16 (7)	.02

Data presented as n (%). *AVR*, Aortic valve-replacing; *AVS*, aortic valve-sparing; *NYHA*, New York Heart Association.