Cardiac valve operations after solid organ transplantation: A single-center experience

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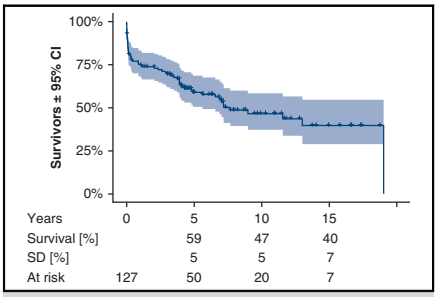
ABSTRACT

Objective: Cardiac valve operations in patients who have undergone solid organ transplantation (ie, kidney, liver, pancreas, heart, and lung) pose unique challenges due to patient comorbidities and to the need for immunosuppressive therapy. The aim of this retrospective study was to present our experience with patients with solid-organ transplant who had cardiac valve operation at the time or after transplantation.

Methods: Records of patients who had undergone cardiac valve operations after solid organ transplantation between January 1998 and January 2019 were retrospectively reviewed. Follow-up amounted to a median of 51 months (interquartile range, 5-88 months).

Results: Among the 14,465 patients who underwent treatment for a cardiac valvular pathology during the study period, 127 patients (0.9%) had undergone a solid organ transplantation (kidney: n = 9 [76%]; liver: n = 12 [9%]; pancreas: n = 4 [3%]; heart: n = 16 [13%]; lung: n = 9 [7%]). Postoperatively, 14 patients (11%) underwent rethoracotomy for bleeding and 24 patients (19%) required new dialysis treatment. Twenty-five patients (20%) died in-hospital. Postoperative course was worse in patients operated for endocarditis or undergoing concomitant transplantation and valve surgery. Overall survival was 59%, 47%, and 40%, but survival conditioned to hospital discharge was 73%, 58%, and 50% at 5-, 10-, and 15-year follow-up, respectively. Freedom from major valve-related events amounted to 77%, 56%, and 46%, respectively.

Conclusions: Although the high prevalence of postoperative complications, especially in patients with endocarditis or concomitant transplantation and valve surgery, survival conditioned to hospital discharge was satisfactory in patients undergoing valve surgery after solid organ transplantation. (J Thorac Cardiovasc Surg 2021;161:595-606)



Survival in patients receiving transplant after cardiac valve operation.

Central Message

Transplanted patients requiring cardiac valve operations showed a complicated postoperative course, but survival conditioned to hospital discharge was satisfactory. Young age was associated with SVD.

Perspective

Transplant patients undergoing cardiac valve operations represent a challenging surgical population. The studies published so far have focused on postoperative course and graft function, but not on valve morbidity and long-term survival. We aimed to fill this gap and provide appropriate information for planning surgery in this particular patient population.

See Commentary on page 607.

Continuous improvement in the long-term results after solid organ transplantation (ie, kidney, liver, heart, lung, and pancreas) has led to an increase in the population of patients who might require cardiac valve surgery after transplantation.

However, patients who have undergone transplant pose unique challenges to surgeons due to concomitant comorbidities; the lifelong need for immunosuppression therapy that may pose these patients at higher risk of infection;

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Abbreviations and Acronyms
CPB = cardiopulmonary bypass
SVD = structural valve deterioration

the choice of prosthesis type (biologic vs mechanical); and to the lack of data on long-term duration of bioprostheses in this particular patient population, which consists mostly of patients who are younger than age 65 years.

Recent reports on cardiac surgery after solid organ transplantation have shown satisfactory postoperative results and short-term survival, which was lower than the survival of patients who have not had a transplant undergoing cardiac surgery altogether. Moreover, most of the reports mixed results of coronary artery bypass grafting alone and of valve replacement or reconstruction, included only patients undergoing abdominal solid organ transplantation and did not report long-term data on prosthetic heart valve durability and morbidity.[1-16]

The aim of this retrospective study was to present our 20-year experience with transplanted patients who had undergone cardiac valve operation at the time of or after transplantation.

METHODS

Patients

Our hospital database was searched for patients who had undergone cardiac valve replacement or reconstruction at the time of or after solid organ (ie, kidney, liver, heart, lung, and pancreas) transplantation, between January 1998 and January 2019. These patients were included in the study.

Patients who had undergone kidney transplantation but later underwent graft nephrectomy due to chronic rejection before cardiac valve operation were not considered. Similarly, patients who had undergone cardiac valve operations before their transplant procedure were excluded.

Perioperative records of included patients were retrospectively reviewed. Follow-up was performed by retrospectively reviewing outpatient records and by contacting the patients, the referring physicians, and the involved cardiologists by telephone. Follow-up ended on January 31, 2019, was 100% complete, and amounted to a median of 51 months (interquartile range [IQR], 5-88 months; range, 0-228 months).

The hospital ethical review board waived the need for patient consent to the study because all patients and their parents had given consent for anonymized personal data to be handled for research purposes at the time of cardiac valve surgery. This study conformed to the Declaration of Helsinki.

Variable Definition

In-hospital mortality was defined as death occurring during the initial hospitalization for cardiac valve reconstruction or replacement.

Prosthetic heart valve morbidity and mortality were defined according to the American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery guidelines.[17] In particular, evidence of structural valve deterioration (SVD) was based both on echocardiograph reports[18] and on intraoperative evidence in those patients who underwent redo valve replacement for SVD.

The same definitions of mortality, major valve-related events, SVD, bleeding and cerebrovascular events, endocarditis, and cardiac valve redo were used for patients undergoing cardiac valve reconstruction only.[17]

Patient Management

Surgical techniques and cardiac valve prosthetic types, which were employed in transplanted patients during the study period, were the same as those used in contemporary patients not receiving a transplant.

At our institution, in transplanted patients undergoing an elective operation, maintenance immunosuppression therapy is usually stopped 24 hours before the operation, and substituted by an intravenous infusion of 200 mg hydrocortisone over 24 hours, which is then continued intraoperatively and early during the intensive care unit stay. The preoperative immunosuppression therapy was then restarted on the first postoperative day, either orally or intravenously in the case that the patient was still on mechanical ventilation. Blood levels of calcineurin and mechanistic target of rapamycin inhibitors were checked daily.

Intra- and postoperatively, particular attention was paid to preserve graft function, particularly in those patients undergoing combined transplantation and valve surgery. For example, in patients who received a kidney transplant, a pulsatile flow and a higher arterial blood pressure were maintained during crossclamp time. In patients who received a lung transplant, fluid infusion restriction was strictly pursued and ultrafiltration was usually used during cardiopulmonary bypass (CPB).

All patients received perioperative antibiotic prophylaxis or, in cases of operation for endocarditis, continued the preoperatively initiated antibiotic therapy.

Data Analysis

IBM SPSS version 25.0 (IBM-SPSS Inc, Armonk, NY) and R (R Foundation for Statistical Computing, Vienna, Austria) were used for the data analysis. Primary end points were all-cause mortality and the presence of a least 1 major valve-related event. Secondary end points were presence of SVD, bleeding and cerebrovascular events, endocarditis, non-SVD, and need for cardiac redo at follow-up.

Categorical and continuous variables were summarized as percentages and median and IQR, respectively. Preoperative, intraoperative, and postoperative categorical and continuous variables were compared among patients undergoing operation for endocarditis versus patients undergoing combined transplantation and valve surgery, versus the remaining patients, using the χ^2 test and the nonparametric Kruskal-Wallis test, respectively.

Survival estimates and freedom from end points were calculated by the product-limit method of Kaplan-Meier and reported as percent $\pm$ standard deviation. End points were compared between the aforementioned 3 groups, among patients with a biologic versus mechanical prosthesis, and among patients with valve repair only versus valve replacement using the log-rank test.

Because we have to face the competing risks of nonfatal events (eg, SVD, non-SVD, endocarditis, reintervention for any cause, and bleeding and cerebrovascular events) and death in the described analyses, we performed further analyses with R to find out the rates of patients having died without a previous nonfatal event and of those having experienced a nonfatal event. This analysis was stratified according to the presence of a valve reconstruction only or a bioprosthesis versus the presence of a mechanical prosthesis. The previously described Kaplan-Meier statistics were calculated to permit comparisons with performance descriptions from the literature.

For the multivariable analysis, all-cause mortality, presence of at least 1 major valve-related event, and SVD were considered as time-to-event outcomes.

The variables tested for association with the end points were those reported in Tables 1-4 (84 variables total). Patients with missing data were censored. Each variable was first tested for univariable association with the single time-dependent end point. Then, the models for each outcome were constructed, including risk factors with univariable P values $\leq .1$. Results were reported as hazard ratios, with 95% confidence interval and corresponding P value. The proportional hazards assumption was tested using the complementary log–log Kaplan-Meier plots and including the time-dependent coefficients into the regression models. The variables that did not satisfy this assumption were not included in the multivariable models. Results were controlled by performing a forward and backward regression

TABLE 1. Preoperative patient characteristics

Variable	Overall (N = 127)	Endocarditis only (n = 15)*	Concomitant Tx and VS (n = 12)	Remaining patients (n = 100)	*P* value†
Age (y)	59 (49-67)	46 (35-559)	51 (43-58)	62 (54-69)	<.001
<60	64 (51)	12 (80)	11 (92)	41 (41)	<.001
60-70	46 (36)	3 (20)	1 (8)	42 (42)	.027
>70	17 (13)	0	0	17 (17)	.071
EuroSCORE II (%)	2.3 (1.5-4.1)	3.3 (2.3-6.6)	1.7 (1.2-4.1)	2.2 (1.3-3.6)	.093
BSA (m^2)	1.9 (1.7-2.0)	1.8 (1.7-1.9)	2.0 (1.9-2.1)	1.8 (1.7-2.0)	.095
Female	40 (32)	2 (13)	2 (17)	36 (36)	.11
Chronic renal failure	63 (50)	8 (53)	2 (17)	53 (53)	.056
Arterial hypertension	75 (59)	6 (40)	3 (25)	66 (66)	.007
Peripheral artery disease	21 (17)	3 (20)	1 (8)	17 (17)	.69
Cerebrovascular disease‡	4 (3)	1 (7)	0	3 (3)	.60
Diabetes mellitus	16 (13)	2 (13)	0	14 (14)	.38
Insulin	9 (7)	2 (13)	0	7 (7)	.40
Hyperlipidemia	21 (17)	3 (20)	1 (8)	17 (17)	.69
Chronic lung disease	21 (17)	1 (7)	8 (67)	12 (12)	<.001
LVEF <40%	30 (24)	2 (13)	3 (25)	25 (25)	.61
NYHA functional class					
I	10 (8)	2 (13)	2 (17)	6 (6)	.30
II	15 (12)	1 (7)	0	14 (14)	.29
III	35 (28)	3 (20)	2 (17)	30 (30)	.48
IV	9 (7)	3 (20)	4 (33)	2 (2)	<.001
Syncope	17 (13)	5 (33)	0	12 (12)	.029
Angina	22 (17)	1 (7)	0	21 (21)	.11
Atrial fibrillation	30 (24)	1 (7)	3 (25)	26 (26)	.26
Cardiac redo	29 (23)	5 (33)	2 (17)	22 (22)	.54
Coronary artery disease	50 (39)	5 (33)	2 (17)	43 (43)	.18
Aortic dissection	5 (4)	1 (7)	0	4 (4)	.18
Endocarditis	17 (13)	15 (100)	2 (17)	0	<.001

Values are presented as median (interquartile range) or n (%). *Tx*, Transplantation; *VS*, valve surgery; *EuroSCORE II*, European System for Cardiac Operative Risk Evaluation II; *BSA*, body surface area; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association. *Two additional patients showed evidence of endocarditis but also underwent a concomitant Tx and therefore were counted in the combined Tx and VS group. †*P* values refer to the comparison between the 3 groups (ie, endocarditis, combined Tx and VS, and remaining patients). ‡Includes transient ischemic attack, reversible ischemic neurological deficit, and stroke.

analysis. Any era effect was controlled after stratification of multivariable analysis according to early (1998-2008) versus late (2009-2019) eras. Only the results after stratification were reported.

RESULTS

Preoperative Patient Characteristics

Between January 1998 and January 2019, among the 14,465 patients undergoing operation for a cardiac valvular pathology at our institution, 127 patients (0.9%) who underwent a solid organ transplant with functioning allografts underwent valve surgery.

Preoperative patient characteristics are reported in Tables 1 and 2. Fifty-three patients (42%) underwent operation between 1998 and 2008, and the remaining 74 patients (58%) underwent operation between 2009 and 2019.

Twelve patients (9%) had a cardiac valve pathology that required treatment at the time of transplantation (kidney, n = 1; liver, n = 1; heart, n = 2; lung, n = 7; and combined liver and lung, n = 1). Seventeen patients (14%) underwent operation for endocarditis (transplantation: kidney, n = 8; liver, n = 3; heart, n = 2; lung, n = 2; and combined kidney and liver transplantations, n = 2), 2 of them requiring concomitant transplantation and valve surgery.

Patients with endocarditis or needing a concomitant transplantation were younger and showed a higher New York Heart Association functional class than the remaining patients. Patients with endocarditis presented more often with a valvular regurgitation, whereas patients with a concomitant transplantation underwent more often a lung transplant procedure (n = 8).

TABLE 2. Transplanted organs and cardiac valve pathology

Variable	Overall (N = 127)	Endocarditis only (n = 15)*	Concomitant Tx and VS (n = 12)	Remaining patients (n = 100)	*P* value†
Transplant					
Lung	9 (7)	1 (7)	8 (67)	0	<.001
Heart	16 (13)	2 (13)	2 (17)	12 (12)	.89
Kidney	97 (76)	10 (67)	1 (8)	86 (86)	<.001
Liver	12 (9)	4 (27)	2 (17)	6 (6)	.026
Pancreas	4 (3)	0	0	4 (4)	.57
>1 Transplanted organ	10 (8)	2 (13)	1 (8)	7 (7)	.69
Immunosuppression therapy					
Cyclosporine	61 (48)	7 (47)	8 (67)	46 (46)	.39
Tacrolimus	44 (35)	5 (33)	4 (33)	35 (35)	.98
Azathioprine	9 (7)	0	0	9 (9)	.27
Mycophenolate mofetil	75 (59)	9 (60)	11 (92)	55 (55)	.051
Everolimus	4 (3)	1 (7)	1 (8)	2 (2)	.35
Sirolimus	5 (4)	0	0	5 (5)	.48
Prednisolone	110 (87)	13 (87)	12 (100)	85 (85)	.35
Single-drug therapy	12 (9)	2 (13)	0	10 (10)	.46
Double-drug therapy	52 (41)	6 (40)	2 (17)	44 (44)	.19
Triple-drug therapy	63 (50)	7 (47)	10 (83)	46 (46)	.049
Valve pathology					
Aortic					
Stenosis	39 (31)	0	1 (8)	38 (38)	.003
Regurgitation	25 (20)	9 (60)	1 (8)	15 (15)	<.001
Combined	25 (20)	3 (20)	3 (25)	19 (19)	.88
Mitral					
Stenosis	6 (5)	0	1 (8)	5 (5)	.57
Regurgitation	30 (24)	9 (60)	1 (8)	20 (20)	.001
Combined	6 (5)	0	0	6 (6)	.43
Tricuspid					
Stenosis	0	0	0	0	
Regurgitation	23 (18)	1 (7)	5 (42)	17 (17)	.052
Pulmonary					
Stenosis	0	0	0	0	
Regurgitation	3 (2)	0	0	3 (3)	.66

Values are presented as n (%). *Tx*, Transplantation; *VS*, valve surgery. *Two additional patients showed evidence of endocarditis but also underwent a concomitant Tx and therefore were counted in the combined Tx and VS group. †*P* values refer to the comparison between the 3 groups (ie, endocarditis, combined Tx and VS, and remaining patients).

Intraoperative Patient Characteristics

Intraoperative characteristics are reported in Tables 3 and 4. Median time between first transplantation and cardiac valve operation was 87 months (IQR, 35-204 months). One hundred ten patients (87%) underwent valve replacement with (n = 8) or without (n = 102) associated valve repair, and the remaining 17 patients (13%) underwent valve reconstruction only. Sixty-one patients (48%) required combined major cardiac surgical procedures (2 procedures, n = 45; 3 procedures, n = 13; 4 procedures, n = 3) (Table E1).

Among the 110 patients who underwent valve replacement, 66 patients (60%) received bioprostheses and 44 patients (40%) received mechanical prostheses, with a preference for a bioprosthesis after 2008 (44% vs 71% before and after 2008; $P = .006$). Commercially available prostheses were implanted (Table E2). Two patients underwent transcatheter aortic valve implantation through a transaortic approach.

Transplanted patients undergoing operation for endocarditis underwent an urgent or emergency operation more often than patients in the other 2 groups. CPB time was longer in patients undergoing operation for endocarditis or undergoing concomitant transplantation (Table 3).

Postoperative Patient Characteristics

Postoperative course is reported in Table 4. Twenty-five patients (20%) required new hemodialysis treatment (transplantation: liver, n = 3; heart, n = 4; lung, n = 5; kidney, n = 11; and combined, n = 2). Thirteen of these patients (54%) recovered renal function before hospital discharge. Twenty-three patients (18%) showed postoperative infectious episodes (urinary tract infection, n = 4; sepsis as a consequence of preoperative endocarditis, n = 2; secondary wound healing disorders, n = 4; peritonitis due to colon perforation, n = 3; acute cholangitis, n = 1; mediastinitis, n = 2; or respiratory tract infections, n = 7).

TABLE 3. Intraoperative patient characteristics

Variable	Overall (N = 127)	Endocarditis only (n = 15)*	Concomitant Tx and VS (n = 12)	Remaining patients (n = 100)	*P* value†
Combined transplantation and valve surgery	12 (9)	0	12 (100)	0	
Elective operation	98 (77)	2 (13)	9 (75)	87 (87)	<.001
Urgent operation	19 (15)	8 (53)	2 (17)	9 (9)	<.001
Emergency operation	10 (8)	6 (40)	0	4 (4)	<.001
Aortic valve replacement	88 (69)	13 (87)	5 (42)	70 (70)	.040
Biologic	52 (41)	5 (33)	4 (33)	43 (43)	.66
Mechanical	36 (28)	8 (53)	1 (8)	27 (27)	.029
Aortic valve reconstruction	2 (2)	0	0	2 (2)	.76
Ascending aorta replacement	14 (11)	2 (13)	0	12 (12)	.43
Aortic arch replacement	7 (6)	1 (7)	0	6 (6)	.68
Mitral valve replacement	26 (20)	5 (33)	2 (17)	19 (19)	.41
Biologic	9 (7)	1 (7)	1 (8)	7 (7)	.98
Mechanical	17 (13)	4 (27)	1 (8)	12 (12)	.26
Mitral valve reconstruction	13 (10)	2 (13)	0	11 (11)	.45
Tricuspid valve replacement	8 (6)	1 (7)	0	7 (7)	.64
Biologic	7 (6)	1 (7)	0	6 (6)	.68
Mechanical	1 (1)	0	0	1 (1)	.87
Tricuspid valve reconstruction	14 (11)	1 (7)	5 (42)	8 (8)	.002
Pulmonary valve replacement	4 (3)	0	0	4 (4)	.57
Coronary artery bypass grafting	38 (30)	2 (13)	0	36 (36)	.012
>1 Major cardiac surgical procedure	61 (48)	8 (53)	0	53 (53)	.002
Cardiopulmonary bypass time (min)	120 (86-171)	149 (107-207)	181 (134-190)	107 (82-152)	<.001
Crossclamp time (min)	72 (55-96)	97 (72-122)	63 (53-109)	71 (53-89)	.14

Values are presented as n (%) or median (interquartile range). *Tx*, Transplantation; *VS*, valve surgery. *Two additional patients showed evidence of endocarditis but also underwent a concomitant Tx and therefore were counted in the combined Tx and VS group. †*P* values refer to the comparison between the 3 groups (ie, endocarditis, combined Tx and VS, and remaining patients).

Patients undergoing operation for endocarditis and patients undergoing concomitant transplantation and valve surgery showed a more complicated postoperative course, with greater need for new hemodialysis, and longer intensive care unit and hospital stay times (Table 4).

Mortality

Survival and risk factors for all-cause mortality are reported in Tables 4, 5, and 6; Tables E3 and E4; and in Figure 1.

Twenty-five patients (20%) (transplantation: kidney, n = 15; heart: n = 1; lung: n = 5; combined, n = 4) died before hospital discharge, 18 patients (14%) within 30 days after the valve operation. In-hospital mortality was higher in patients who underwent operation for endocarditis (53%) and in patients with concomitant transplant and valve surgery (50%) than in the remaining patients (11%; $P < .001$) (Table 4).

In-hospital mortality was cardiac-related in 10 patients, infection-related in 13 patients, and due to hemorrhagic shock following gastrointestinal bleeding in a patient with colon diverticulitis and preoperative thrombocytopenia, and to failure of the concomitant transplanted liver in another patient. Among the 10 patients who died for cardiac-related reasons, death was valve-related in 5 patients (intraoperative death due to atrioventricular dehiscence after mitral valve replacement, n = 1; sudden, unexplained death after unsuccessful cardiopulmonary resuscitation, n = 3; and stroke, n = 1).

Thirty-five patients had died at follow-up, due to cardiac- (n = 15) and infection-related (n = 6) events, to malignancy (n = 8), and to chronic graft dysfunction (chronic lung allograft dysfunction [n = 1] and chronic kidney allograft dysfunction [n = 5]). Among the 15 patients who died for cardiac-related reasons, death was valve-related in 6 patients (death related to reintervention on the operated valves [n = 3]; sudden, unexplained death [n = 2]; and death related to operated valve endocarditis [n = 1]). Survival conditioned to hospital discharge was 73% ± 5%, 58% ± 6%, and 50% ± 8% at 5-year, 10-year, and 15-year follow-up and did not differ between the 3 aforementioned groups ($P = .26$).

TABLE 4. Intraoperative blood products and postoperative course

Variable	Overall (N = 127)	Endocarditis only (n = 15)*	Concomitant Tx and VS (n = 12)	Remaining patients (n = 100)	*P* value†
Blood products, intraoperative					
PRBCs (U)	3 (2-5)	4 (0-7)	4 (2-6)	3 (2-5)	.54
FFPs (U)	2 (0-4)	1 (0-5)	5 (0-14)	2 (0-4)	.55
PCs (U)	1 (0-2)	2 (0-2)	2 (2-2)	0 (0-2)	.014
ICU stay (d)	3 (1-5)	9 (3-21)	12 (3-47)	2 (1-4)	.001
In-hospital stay (d)	18 (13-28)	23 (13-47)	32 (18-55)	17 (13-24)	.048
Complications					
Rethoracotomy for bleeding	14 (11)	3 (20)	0	11 (11)	.26
Dialysis	47 (37)	8 (53)	9 (75)	30 (30)	.004
New postoperative dialysis	25 (20)	4 (27)	8 (67)	13 (13)	<.001
New temporary postoperative dialysis	13 (10)	3 (20)	2 (17)	8 (8)	.27
Venoarterial ECMO	3 (2)	0	1 (8)	2 (2)	.32
Stroke	6 (5)	3 (20)	1 (8)	2 (2)	.008
Postoperative infection	23 (18)	7 (47)	4 (33)	12 (12)	.002
Tracheostomy	15 (12)	5 (33)	5 (42)	5 (5)	<.001
Atrial fibrillation	35 (28)	1 (7)	4 (33)	30 (30)	.15
Pacemaker implant	5 (4)	0	0	5 (5)	.49
In-hospital mortality (d)	25 (20)	8 (53)	6 (50)	11 (11)	<.001
30	18 (14)	4 (27)	4 (33)	10 (10)	
60	24 (19)	7 (47)	6 (50)	11 (11)	
90	25 (20)	8 (53)	6 (50)	11 (11)	

Values are presented as n (%) or median (interquartile range). *Tx*, Transplantation; *VS*, valve surgery; *PRBC*, packed red blood cells; *FFP*, fresh frozen plasma; *PC*, platelet concentrate; *ICU*, intensive care unit; *ECMO*, extracorporeal membrane oxygenation. *Two additional patients showed evidence of endocarditis but also underwent a concomitant Tx and therefore were counted in the combined Tx and VS group. †*P* values refer to the comparison between the 3 groups (ie, endocarditis, combined Tx and VS, and remaining patients).

Overall survival was better, although not significantly better, in patients undergoing valve repair or valve replacement with a biologic prosthesis (n = 83) versus patients undergoing valve replacement with a mechanical prosthesis (n = 44), and in patients undergoing valve repair only (n = 17) versus patients undergoing valve replacement (n = 110) (Tables E3 and E4).

Major Valve-Related Events

Thirty-three patients (26%) experienced at least 1 major valve-related event (need for pacemaker within 14 days after valve operation [n = 5], valve-related mortality [n = 11], and valve-related morbidity [n = 23]), with 5 patients experiencing more than 1 event. Freedom from major valve-related events and the Cox analysis showing risk factors for having at least 1 major valve-related event are reported in Tables 5 and 6, and in Tables E3 and E4.

SVD and its risk factors are reported in Table 5, in Tables E3, E4, and E5, and in Figure E1. At follow-up, 11 (11%) of the 102 patients who survived to hospital discharge, developed SVD. Nine patients had received a bioprosthesis (aortic valve prosthesis [n = 4], tricuspid valve prosthesis [n = 3], or pulmonary valve homograft or prosthesis [n = 3]), and showed prosthesis stenosis (n = 7) or regurgitation (n = 3) at the last available transthoracic echocardiograph report. Among these patients, 1 showed stenosis of both the previously implanted aortic valve prosthesis and pulmonary homograft. One patient developed severe regurgitation of the reconstructed mitral valve after combined aortic valve replacement and mitral valve repair. Another patient with a mechanical aortic prosthesis showed regurgitation due to hypomobility of a prosthesis disk, potentially from a thrombus, which was not detected by transthoracic echocardiograph. Increasing age at the time of cardiac valve operation was a protective factor against SVD (hazard ratio, 0.94; 95% confidence interval, 0.89-0.98; $P = .013$) (Table E5). The area under the curve for age versus SVD was 0.81 (95% confidence interval, 0.66-0.96; $P = .001$) at receiver operating characteristic analysis.

Eleven out of 102 patients (11%) underwent cardiac redo operation. In 9 patients, reintervention was valve-related: endocarditis (n = 4) of a previously repaired mitral valve (n = 2) and of a previously implanted mitral and aortic valve prosthesis (n = 2); SVD (n = 3) of a previously implanted tricuspid valve bioprosthesis and of a previously repaired mitral valve, non-SVD due to paravalvular leakage of a mechanical mitral valve prosthesis (n = 1), and patient–prosthesis size mismatch of an intraoperatively normal appearing tricuspid bioprosthesis (n = 1). Three of these patients died while hospitalized after cardiac redo operation. Of the remaining 2 patients, 1 patient underwent cardiac retransplantation combined with kidney

TABLE 5. End points

Variable	Overall (N = 127)	Endocarditis only (n = 15)*	Concomitant Tx and VS (n = 12)	Remaining patients (n = 100)
Overall survival (%)				
5 y	59 ± 5	47 ± 13	25 ± 13	65 ± 5
10 y	47 ± 5	16 ± 13	17 ± 11	55 ± 6
15 y	40 ± 7		17 ± 11	45 ± 8
P value†				<.001
Freedom from major valve-related events (%)				
5 y	77 ± 4	66 ± 17	83 ± 15	77 ± 5
10 y	56 ± 7	33 ± 25	83 ± 15	59 ± 8
15 y	46 ± 9		83 ± 15	45 ± 11
P value†				.18
Freedom from SVD (%)				
5 y	92 ± 3	86 ± 13	100	92 ± 3
10 y	77 ± 8	86 ± 13	100	79 ± 8
15 y	69 ± 10		100	69 ± 12
P value†				.083
Freedom from non-SVD (%)				
5 y	96 ± 2	100	100	96 ± 2
10 y	96 ± 2	100	100	96 ± 2
15 y	96 ± 2		100	96 ± 2
P value†				.83
Freedom from cardiac redo for any reason (%)				
5 y	90 ± 3	71 ± 17	83 ± 15	92 ± 3
10 y	84 ± 5	71 ± 17	83 ± 15	85 ± 6
15 y	84 ± 5		83 ± 15	85 ± 6
P value†				.29
Freedom from bleeding, thrombosis, and embolism (%)				
5 y	95 ± 2	100	100	94 ± 3
10 y	93 ± 3	100	100	92 ± 4
15 y	93 ± 3		100	92 ± 4
P value†				.72
Freedom from endocarditis (%)				
5 y	96 ± 2	86 ± 13	83 ± 15	98 ± 2
10 y	92 ± 4	86 ± 13	83 ± 15	93 ± 4
15 y	92 ± 4		83 ± 15	93 ± 4
P value†				.29

Values are presented as mean ± standard deviation. *Tx*, Transplantation; *VS*, valve surgery; *SVD*, structural valve deterioration; *non-SVD*, non-structural valve dysfunction. *Two additional patients showed endocarditis but also underwent a concomitant transplantation and therefore were counted in the combined Tx and VS group. †*P* values refer to the comparison between the 3 groups (ie, endocarditis, combined Tx and VS, and remaining patients).

transplantation 24 months after initial cardiac valve operation and the other underwent aortic arch replacement.

Six out of 102 patients (6%) developed endocarditis of a previously repaired or replaced valve. Four patients underwent cardiac redo, 1 patient died before cardiac redo could be performed, and 1 patient was treated conservatively.

Five patients (5%) experienced severe bleeding (gastrointestinal [n = 3] and other [n = 1]) or cerebrovascular (transient ischemic attack [n = 1]) events that were not related to endocarditis. Another 3 patients (3%) showed non-SVD (paravalvular leakage [n = 1] and patient–prosthesis mismatch [n = 2]).

Except for SVD ($P = .053$), outcomes did not differ between patients who received a valve repair only or a bioprosthesis versus patients who received a mechanical prosthesis (Table E3 and Figure E1). Competing risk analysis for nonfatal morbidity events in patients receiving a valve repair only or a bioprosthesis versus patients receiving a mechanical prosthesis is reported in Figure 2.

Conversely, those few patients undergoing valve repair only (n = 17) showed a nonsignificant trend toward better outcome-free survival than patients who underwent valve replacement (Table E4).

DISCUSSION

This retrospective single-center study showed that transplanted patients undergoing cardiac valve surgery at or after solid organ transplantation had a complicated postoperative

TABLE 6. Univariable and multivariable risk factors for having at least 1 major valve-related events and overall mortality

Variable	Univariable *P* value	Multivariable Hazard ratio* (95% Confidence interval)	*P* value
Major valve-related event (n = 33)			
Categorical variables			
NYHA functional class III	.032	2.50 (1.16-5.37)	.019
Mitral valve stenosis	.009	6.93 (1.81-26.48)	.001
Pulmonary valve regurgitation	.027	3.52 (0.99-12.54)	.052
Elective operation	.056		
Urgent operation	.001	4.35 (1.74-10.84)	.002
Mechanical mitral valve replacement	.088		
Postoperative venoarterial ECMO	.069		
Postoperative stroke	.10	4.79 (1.31-17.44)	.018
Continuous variables			
Age (y)	.002		
BSA (m^2)	.006	0.13 (0.03-0.51)	.003
Crossclamp time (min)	.037		
Overall mortality (n = 60)			
Categorical variables			
NYHA functional class IV	.05		
Syncope	.024		
Chronic lung disease	.004	2.01 (1.07-3.76)	.029
Endocarditis	.004		
Lung transplantation	.001		
Combined transplantation and valve surgery	.002		
Elective operation	<.001		
Urgent operation	<.001	3.60 (1.89-6.87)	<.001
Mechanical mitral valve replacement	.013	2.20 (1.11-4.36)	.023
Rethoracotomy for bleeding	.005		
Dialysis	<.001		
Postoperative infection	<.001	5.08 (2.68-9.62)	<.001
Continuous variables			
BSA (m^2)	.022		
Cardiopulmonary bypass time (min)	<.001	1.005 (1.001-1.009)	.018
Crossclamp time (min)	<.001		
ICU stay (d)	.003		
Hospital stay time (d)	.094		

NYHA, New York Heart Association; *ECMO*, extracorporeal membrane oxygenation; *BSA*, body surface area; *ICU*, intensive care unit. *Cox proportional hazards regression model.

course, especially those patients who were operated for endocarditis and those who underwent combined transplantation and valvular surgery, almost half of them dying while in the hospital (Table 4). Indeed, in patients without concomitant transplantation and without endocarditis, in-hospital mortality dropped to 11%. Moreover, survival conditioned to hospital discharge did not differ among the 3 groups.

In comparison to the previously published reports,[1-16] the worse postoperative results in our study population were thus due to the inclusion of patients requiring valvular surgery at the time of transplantation (9%), to the higher number of patients with endocarditis (17%), to the higher number of combined valvular procedures (61%), and the exclusion of patients who underwent coronary artery bypass grafting alone.

The need for combined valvular procedures prolongs CPB times, which emerged as a risk factor for overall mortality (Table 6). Previous studies showed that the increase of percent combined cardiac surgical procedures paralleled the increase in mortality in transplanted patients undergoing cardiac surgery.[3,6,13,16] Moreover, Sarma and colleagues[8] showed that combined aortic and mitral valve replacement was among the strongest predictors of all-cause mortality in a population of 1335 kidney-transplanted patients after cardiac valve replacement.

Concomitant cardiac valvular operation and transplantation also prolongs operative and CPB times and may impair postoperative graft function. Particularly, in our study, 4 patients died in-hospital after concomitant lung transplantation and aortic valve replacement. Another patient required redo aortic valve replacement for endocarditis 4 months after combined aortic valve replacement and lung transplantation, and died in-hospital of sepsis after colon perforation. All these patients required median

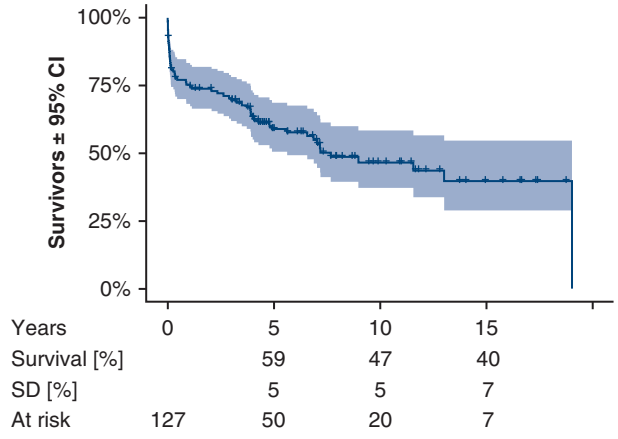


FIGURE 1. Survival in transplanted patients undergoing cardiac valve surgery along the study period. Survival (%) and patients at risk are reported under the *x*-axis. *CI*, Confidence interval; *SD*, standard deviation.

sternotomy or a clamshell incision, and CPB. In comparison to sternum-sparing bilateral thoracotomies, median sternotomy was performed, potentially conferring a higher risk of respiratory tract infections. Moreover, we have recently demonstrated that patients who underwent lung transplantation with CPB support fared worse than patients who required intraoperative extracorporeal membrane oxygenation.[19] Therefore, since 2010, we have abandoned the strategy of performing any combined valvular surgery and lung transplantation. Whenever possible, we perform valve surgery before lung transplantation. Transcatheter procedures, such as transcatheter aortic valve implantation, have recently become another option in solid organ transplantation.[20-22]

The results of this study confirm the deleterious role of preoperative endocarditis.[23] Patients with endocarditis usually undergo urgent and complex operations that prolong CPB times, all factors that emerged as risk factors for mortality in our study. However, incidence of endocarditis at follow-up was low and comparable to the incidence reported by a previous study performed at our institution with 832 patients undergoing biologic aortic valve replacement.[24]

Moreover, our findings underline the importance of postoperative antibiotic prophylaxis, careful aseptic procedures during operation, and meticulous wound management in preventing postoperative infection. Therefore, at our institution, all patients undergo antibiotic therapy early after operation, at least until inflammatory markers such as C-reactive protein and leukocyte levels are clearly falling.

Although the previously published studies reported only patient survival,[1-7,9,12,13,15,16] we also report major valve-related events (Table 5) and stratified them between patients who had received a biologic versus mechanical prosthesis, and a valve repair only versus replacement (Tables E3 and E4). Although the number of events for each outcome might be small, we showed that the 10-year freedom from SVD of only 70% in patients with a bioprosthesis was lower than the 10-year freedom from SVD of 81% recently reported by our group.[25] The worse 10-year freedom from SVD in the present study was due to the inclusion of patients who underwent tricuspid valve replacement and pulmonary valve replacement, which made up two thirds of patients who developed SVD. At our institution, tricuspid valve replacement with biologic prosthesis for severe tricuspid valve regurgitation after heart transplantation has been preferred over replacement with a mechanical prosthesis, because among other reasons, it allows for future endomyocardial biopsies to be performed.[4,5,26] Transcatheter valve-in-valve tricuspid valve replacement may play a role in the future for replacing degenerated biologic tricuspid valve prostheses.[27]

Younger age at the time of cardiac valve operation showed a good specificity and sensibility for SVD. We have previously demonstrated the association of young age and SVD in patients who have not experienced solid organ transplant undergoing AVR using the Mitroflow prosthesis (LivaNova, London, United Kingdom).[24] A stronger immunologic reaction against the prosthetic tissue has been considered among the possible mechanisms leading to a higher SVD incidence in younger versus older patients.[28,29] However, our study shows that immunosuppression drugs have no protective influence against SVD. This finding might be due in part to the side effects caused by the long-term therapy with immunosuppression drugs, such as diabetes mellitus, hyperlipidemia, and arterial hypertension, which generally contribute to the increased risk of adverse cardiovascular events in patients who have experienced an organ transplant, and might explain in part the lack of benefit of immunosuppression drugs against SVD. The Ross operation using the pulmonary valve autograft for aortic valve replacement excludes this immunologic reaction against the bioprosthetic tissue. However, the Ross operation implies a 2-valve operation, the homograft for pulmonary valve replacement is prone to SVD (Table 6 and Table E5), and the technical complexity of the Ross operation may prolong CPB and crossclamp times, which may further impair graft function. Decellularized aortic homografts as well as decellularized mitral valves may represent an alternative solution in younger patients having undergone transplant requiring elective aortic valve replacement and mitral valve replacement.[30,31] Furthermore, the better freedom from major valve-related events in patients undergoing valve repair only (Table E4) underlines the importance of valve reconstruction whenever possible.

Finally, the great need for new hemodialysis remains a concern in our study. However, among the 86 patients who had a kidney transplant without endocarditis or concomitant transplantation and valve surgery, need for

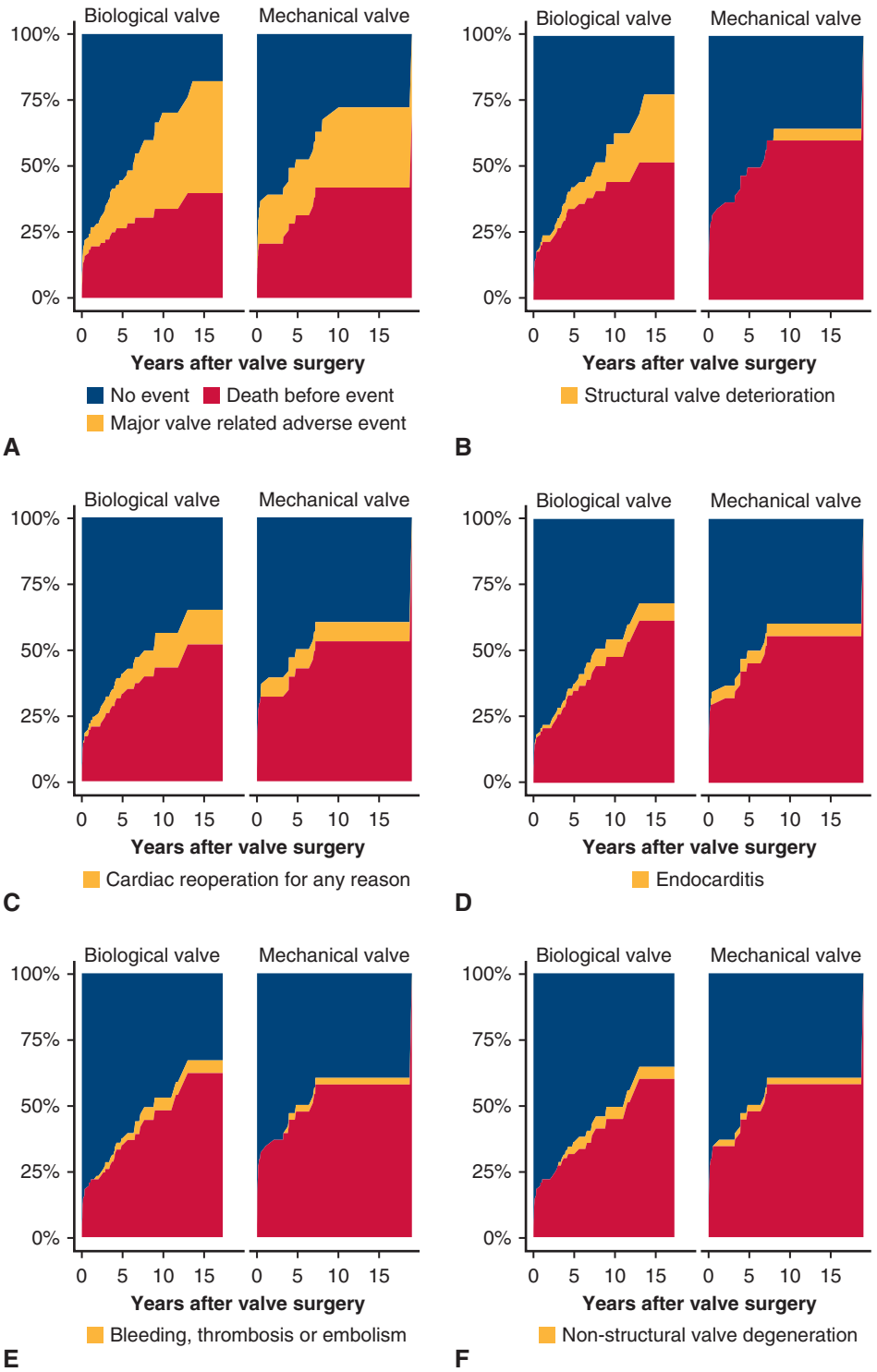


FIGURE 2. Competing risk factor analysis stratified according to the presence of a valve repair only or a bioprosthesis versus the presence of a mechanical prosthesis. A, Any postoperative major valve-related events before death. B, Structural valve deterioration. C, Cardiac reoperation for any reason. D, Endocarditis. E, Bleeding, thrombosis, and embolism event. F, Nonstructural valve deterioration. The figure elements represent the patient fraction that died without having experienced the event (*red area*), the fraction of patients that have experienced the named event (*yellow stripe*), and the percentage of patients without the event at the time indicated at the *x*-axis (*blue space*).

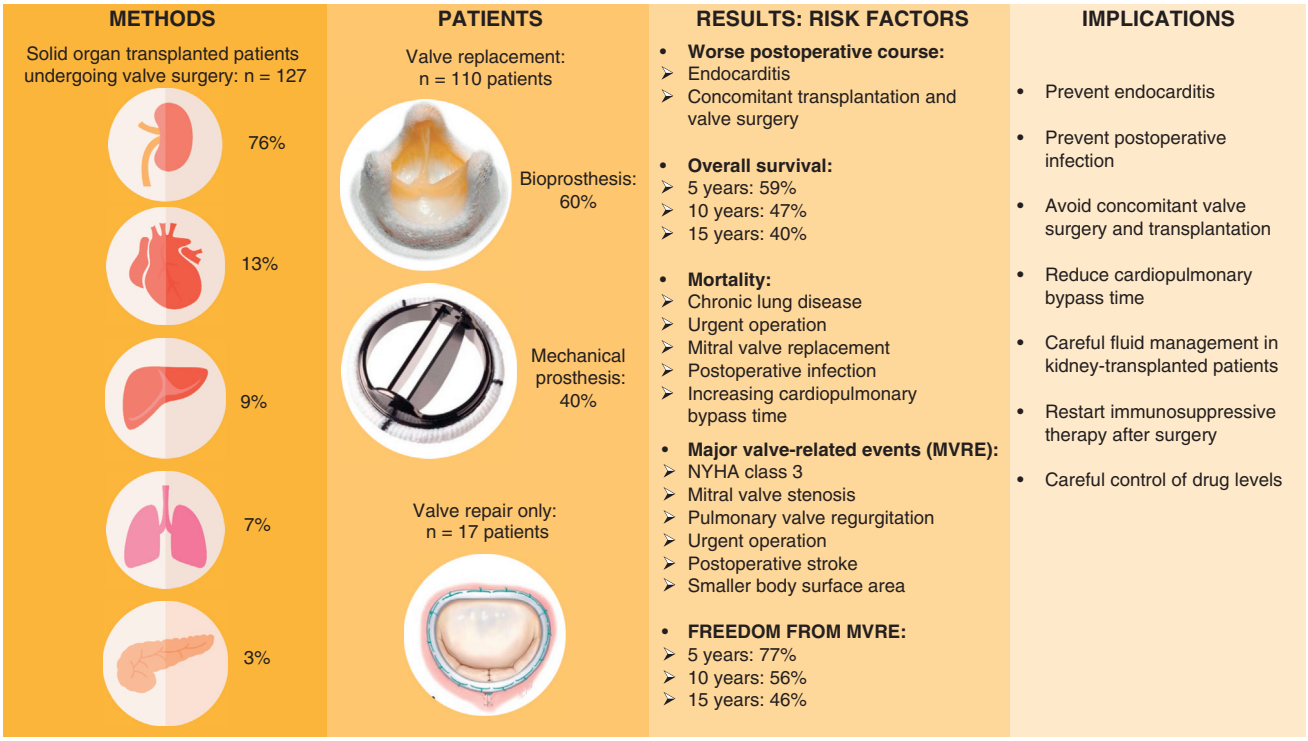


FIGURE 3. The main results of the study. Between January 1998 and January 2019, 127 solid organ transplant patients (kidney, 76%; heart, 13%; liver, 9%; lung, 7%; pancreas, 3%) underwent cardiac valve surgery. One hundred ten patients underwent valve replacement, and 17 patients underwent cardiac valve repair only. Postoperative course was worse in patients operated for endocarditis and in patients who underwent concomitant transplantation and valve surgery. Survival and the risk factors for all-cause mortality as well as freedom from major valve-related events (*mVRE*) and risk factors for mVRE are reported. The key factors for improving patient survival are prevention of endocarditis and of postoperative infections, avoidance of combined transplantation and valve surgery, reduction of cardiopulmonary bypass time, prompt postoperative restart of preoperative immunosuppressive therapy with careful control of drug levels, and careful fluid management in kidney transplant patients. *NYHA*, New York Heart Association.

new-onset hemodialysis dropped to 13%, being temporary in 6 patients. As aforementioned, reduction of CPB time, maintenance of a pulsatile flow during CPB, careful perioperative fluid management and prompt postoperative initiation of preoperative immunosuppressive therapy are of paramount importance to protect the renal grafts.

Study Limitations

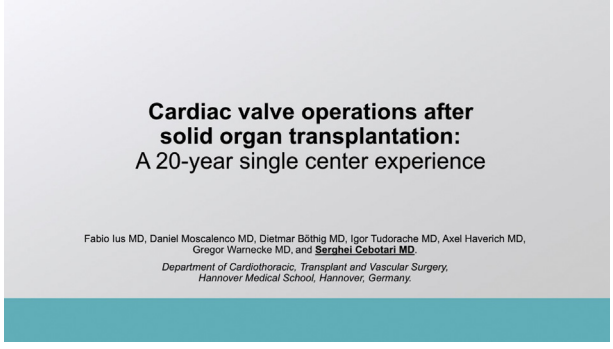
The single-center nature of this study may impede the extension of the results to other centers.

Although many variables were considered in the Cox analysis, it may be possible that other variables had not been considered and thus had confounded the results of the study.

We did not include a matched population of patients who had never experienced an organ transplant undergoing valve surgery. In our opinion, including a control population matched by predefined variables such as sex or age would have introduced more confounding factors to our analysis.

CONCLUSIONS

Although we observed high in-hospital mortality and prevalence of postoperative complications, survival conditioned to hospital discharge and freedom from endocarditis were satisfactory in patients undergoing valve surgery after solid organ transplantation. Young patients who had received a bioprosthesis were at increased risk of SVD. Prosthesis choice and operative strategy should be based on patient and graft survival expectancy. Prevention of



VIDEO 1. We believe that prevention of endocarditis, avoidance of combined transplantation and valve surgery and of postoperative infections, and prompt postoperative restart of preoperative immunosuppressive therapy with careful control of drug levels are of paramount importance to reduce overall mortality and morbidity in patients undergoing solid organ transplantation after cardiac valve surgery. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32243-3/fulltext.

endocarditis, avoidance of combined transplantation and valve surgery, and fewer postoperative infections should reduce overall mortality (Figure 3 and Video 1).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Monday_May6/206BD/206BD/S69%20-%20Rapid%20Fire%20abstracts%20IV%20-%20Valve/S69_12_webcast_083049599.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: solid organ transplantation, cardiac valve surgery, long-term outcomes

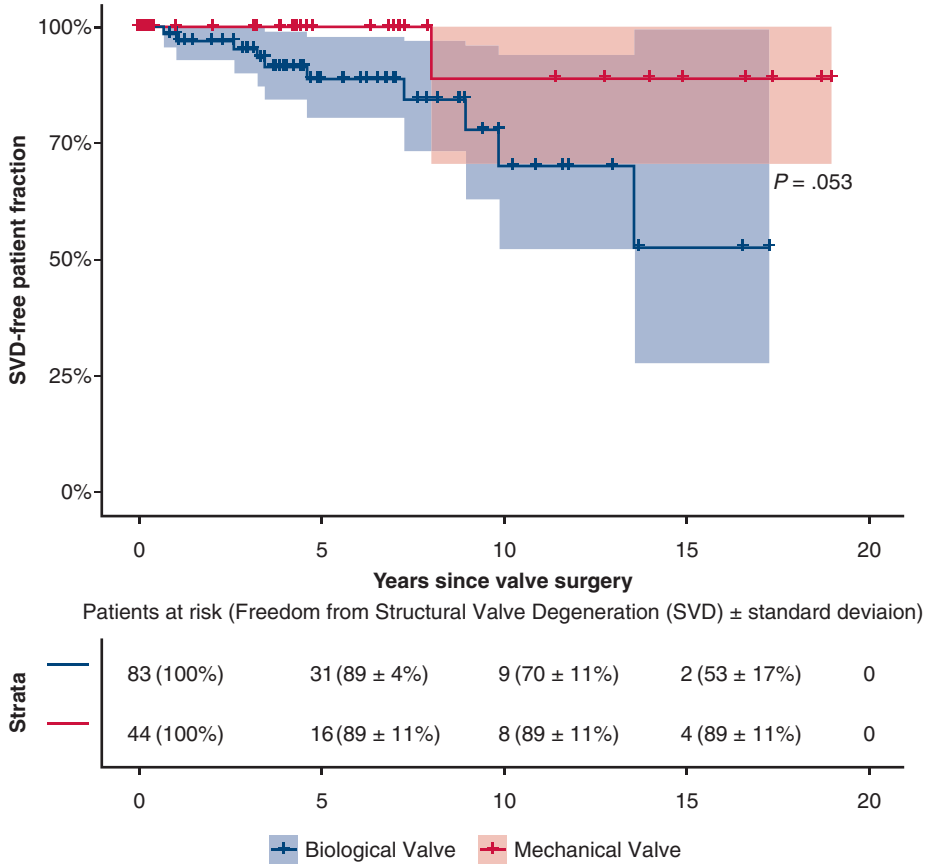

FIGURE E1. Freedom from structural valve deterioration (*SVD*) reported as percent ± standard deviation and stratified according to the presence of a bioprosthesis or valve repair only (n = 83) versus a mechanical prosthesis (n = 44). Freedom from SVD was worse in patients with a bioprosthesis or valve repair only ($P = .053$). Patients at risk are reported below the *x*-axis.

TABLE E1. Combined major cardiac surgical procedures (N = 61)

Procedure	Result
AVR + CABG	18 (30)
AVR + replacement of the ascending aorta	9 (15)
AVR + replacement of the ascending aorta + CABG	2 (3)
AVR + TV repair	1 (2)
AVR + PVR	1 (2)
AVR + MVR	4 (7)
AVR + MVR + CABG	4 (7)
AVR + MVR + replacement of the ascending aorta	1 (2)
AVR + MVR + TVR	1 (2)
AVR + MVR + TV repair	2 (3)
AVR + MVR + TV repair + CABG	2 (3)
AVR + MV repair	2 (3)
AV repair + replacement of the ascending aorta + CABG	1 (2)
AV repair + MV repair + replacement of the ascending aorta + CABG	1 (2)
MVR + CABG	4 (7)
MVR + TV repair	1 (2)
MV repair + CABG	4 (7)
MV repair + TV repair	1 (2)
MV repair + TV repair + CABG	2 (3)

Values are presented as n (%). *AVR*, Aortic valve replacement; *CABG*, coronary artery bypass grafting; *TV*, tricuspid valve; *PVR*, pulmonary valve replacement; *MVR*, mitral valve replacement; *TVR*, tricuspid valve replacement; *MV*, mitral valve.

TABLE E2. Types of prostheses used for cardiac valve replacement (N = 110)

Valve type	Result
Aortic valve replacement	88
Biologic	
Carpentier Edwards* any type	33 (38)
Livanova† Mitroflow	7 (8)
Livanova† Perceval	2 (2)
Medtronic‡ Mosaic	1 (1)
Vascutek§ Aspire	1 (1)
St Jude|| Medical Epic	1 (1)
St Jude|| Medical Trifecta	1 (1)
Vascutek§ Elan	3 (3)
SyGan¶ all-biologic xeno-pericardial conduit	1 (1)
Carpentier Edwards* Sapien 3	2 (2)
Mechanical	
St Jude Medical|| any type	33 (38)
Livanova† ATS	2 (2)
CryoLife# OnX	1 (1)
Mitral valve replacement	26
Biologic	
Carpentier Edwards* any type	3 (12)
Vascutek§ Aspire	4 (15)
Medtronic‡ Mosaic	2 (8)
Mechanical	
St Jude Medical|| any type	13 (50)
CryoLife# OnX	4 (15)
Tricuspid valve replacement	8
Biologic	
Carpentier Edwards* any type	5 (64)
Vascutek§ Aspire	1 (12)
Medtronic‡ Mosaic	1 (12)
Mechanical	
St Jude Medical||	1 (12)
Pulmonary valve replacement	4
Homograft	3 (75)
Medtronic‡ Contegra pulmonary valved conduit	1 (25)

Values are presented as n (%). *Carpentier Edwards, Irvine, Calif. †LivaNova PLC, London, United Kingdom. ‡Medtronic, Minneapolis, Minn. §Vascutek, Inchinnan, United Kingdom. ||St Jude Medical, St Paul, Minn. ¶SyGan Medical GMBH, Berlin, Germany. #CryoLife Inc, Kennesaw, Ga.

TABLE E3. End points in patients undergoing valve repair or valve replacement with a biologic prosthesis (n = 83) versus patients undergoing valve replacement with a mechanical prosthesis (n = 44)

Variable	Biologic (n = 83)	Mechanical (n = 44)	*P* value
Overall survival (%)			
5 y	64 ± 6	49 ± 8	
10 y	51 ± 7	40 ± 8	
15 y	35 ± 10	40 ± 8	.21
Freedom from major valve-related events (%)			
5 y	78 ± 5	74 ± 8	
10 y	50 ± 10	65 ± 11	
15 y	37 ± 13	56 ± 13	.87
Freedom from SVD (%)			
5 y	89 ± 4	100	
10 y	70 ± 11	89 ± 11	
15 y	53 ± 17	89 ± 11	.053
Freedom from non-SVD (%)			
5 y	96 ± 3	96 ± 4	
10 y	96 ± 3	96 ± 4	
15 y	96 ± 3	96 ± 4	.94
Freedom from cardiac redo for any reason (%)			
5 y	90 ± 4	89 ± 6	
10 y	81 ± 8	89 ± 6	
15 y	81 ± 8	89 ± 6	.78
Freedom from bleeding, thrombosis, and embolism (%)			
5 y	95 ± 3	96 ± 4	
10 y	91 ± 5	96 ± 4	
15 y	91 ± 5	96 ± 4	.54
Freedom from endocarditis (%)			
5 y	97 ± 2	93 ± 5	
10 y	91 ± 5	93 ± 5	
15 y	91 ± 5	93 ± 5	.93

Values are presented as mean ± standard deviation. *SVD*, Structural valve deterioration; *non-SVD*, nonstructural valve deterioration.

TABLE E4. End points in patients undergoing valve repair only (n = 17) versus patients undergoing valve replacement (n = 110)

Variable	Valve repair only (n = 17)	Valve replacement (n = 110)	*P* value
Overall survival (%)			
5 y	62 ± 13	58 ± 5	
10 y	52 ± 14	46 ± 6	
15 y	52 ± 14	37 ± 7	.66
Freedom from major valve-related events (%)			
5 y	87 ± 9	75 ± 5	
10 y	69 ± 17	53 ± 8	
15 y	69 ± 17	39 ± 11	.31
Freedom from SVD (%)			
5 y	100	91 ± 4	
10 y	100	74 ± 9	
15 y	100	63 ± 12	.15
Freedom from non-SVD (%)			
5 y	100	96 ± 3	
10 y	100	96 ± 3	
15 y	100	96 ± 3	.48
Freedom from cardiac redo for any reason (%)			
5 y	92 ± 7	90 ± 4	
10 y	74 ± 18	85 ± 6	
15 y	74 ± 18	85 ± 6	.72
Freedom from bleeding, thrombosis and embolism (%)			
5 y	100	94 ± 3	
10 y	100	92 ± 4	
15 y	100	92 ± 4	.37
Freedom from endocarditis (%)			
5 y	92 ± 7	97 ± 2	
10 y	92 ± 7	94 ± 3	
15 y	74 ± 18	94 ± 3	.17

Values are presented as mean ± standard deviation. *SVD*, Structural valve deterioration; *non-SVD*, nonstructural valve deterioration.

ADULT

TABLE E5. Univariable and multivariable risk factors for structural valve deterioration (SVD) (n = 11)

Variable	Univariable	Multivariable	
	P value	Hazard ratio (95% Confidence interval)	*P* value
Categorical variable			
Arterial hypertension	.090		
Cardiac redo	.017		
Coronary artery disease	.037	0.079 (0.007-0.931)	.044
Endocarditis	.065		
Aortic valve stenosis	.082		
Pulmonary valve regurgitation	<.001		
Tricuspid valve prosthesis, biologic	.025	12.86 (2.26-72.99)	.004
Pulmonary valve prosthesis, biologic	<.001	7.51 (1.12-50.09)	.037
Biologic vs mechanical prosthesis	.088		
Immunosuppression therapy with prednisolone	.028		
Postoperative infection	.095		
Continuous variable			
Age (y)	<.001	0.94 (0.89-0.98)	.013
Body surface area (m^2)	.002		

ADULT