Heart, Lung and Circulation (2019) **28,** 1112–1120
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.05.200

ORIGINAL ARTICLE

Surgery for Active Infective Endocarditis of the Aortic Valve With Infection Extending Beyond the Leaflets

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Received 2 April 2018; accepted 28 May 2018; online published-ahead-of-print 20 June 2018

Background The optimal aortic substitute in extensive aortic valve active infective endocarditis (AIE) continues to be debated. To determine the surgical approach in aortic valve AIE with infection extension beyond the leaflets, we evaluated the outcome of reconstructive surgery with various valve substitutes in those patients.

Methods During 2000–2013, 168 patients had surgery for extensive aortic valve AIE. Patients were categorised based on aortic valve substitute: Group A: Stented aortic valve replacement (AVR), Group B: Stented AVR with patch support, Group C: Stentless valve, Group D: Aortic allograft, and Group E: Composite valve graft. Outcome parameters were mortality, postoperative cardiogenic or septic shock, stroke, or reinfection.

Results Stented valves with patch support were more frequently utilised in cases of native valve endocarditis ($p < 0.001$). Postoperative complications were comparable among groups. Concomitant preoperative extension of infection in the mitral valve predicted reinfection (OR 3.6; confidence interval 1.46–8.66; $p = 0.005$). Survival was not affected by operative group (log rank = 0.6). Univariable preoperative predictors of mortality were: septic shock (hazard ratio 8.3; 95% confidence interval 3.6–19.2; $p < 0.001$), ejection fraction (hazard ratio 0.96; 95% confidence interval 0.93–0.99; $p = 0.006$), preoperative cardiogenic shock (hazard ratio 1.9; 95%CI 1.1–3.6, $p = 0.02$) and concomitant mitral valve surgery (hazard ratio 1.8; 95% confidence interval 1.2–2.5; $p = 0.002$).

Conclusions Surgical treatment of extensive aortic valve infective endocarditis remains a challenge. Outcomes were not affected by the surgical complexity of aortic reconstruction procedure or valve substitute. Surgical approach should be tailored to individual patient's characteristics.

Keywords Infective endocarditis • Aorta • Valve surgery • Root abscess

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Introduction

Surgical treatment of aortic valve active infection endocarditis (AIE) with infection extending beyond valve leaflets carries high morbidity and mortality [1,2]. Early surgical intervention is recommended in surgically fit patients [1] and the guidelines consider the aortic allograft as the substitute of choice for left ventricular outflow tract (LVOT) reconstruction in those patients [3]. It was suggested that aortic allograft implantation would reduce the risk of recurrent infection [4]. However, due to the shortage of allografts, especially in emergency situations, stentless valves were used successfully as an alternative for LVOT reconstruction [5]. In other series, mechanical and bioprosthetic valves yielded comparable results to allografts regarding reinfection and survival when combined with complete debridement [6]. To determine the optimal surgical approach in patients with aortic valve AIE with infection extension beyond the leaflets, we evaluated the early and late outcomes of various surgical strategies and valve substitutes in our patients.

Material and Methods

Patients

Between October 2000 and 2013, 168 consecutive adult patients underwent surgery for extensive aortic valve AIE at Cardiac Surgery Department, Leuven University Hospitals, Leuven, Belgium.

We excluded patients with aortic valve AIE associated with permanently implanted pacemakers, and intravenous drug users because of the different pathology. Patients with concomitant surgical procedures not related to endocarditis were excluded.

Study Design

This is a retrospective cohort study. Based on the valve substitute used for LVOT reconstruction, we categorised our patients into five groups; Group A: Stented aortic valve replacement (AVR) (mechanical or bioprosthesis) (n = 49), Group B: Stented AVR with patch support (n = 36), Group C: Stentless valves (Medtronic Inc, Minneapolis, USA & Shelhigh Inc, Union, NJ, USA) (n = 50), Group D: Aortic allograft, Group (n = 24) E: Composite valve graft (n = 9).

Data

Data were retrieved from a cardiac surgery electronic database and data collection was approved by the Ethical Committee.

Surgery

Surgery was performed during the active phase of the disease with a median of 7 days from the diagnosis and before the end of antibiotic treatment. All patients were operated upon by median sternotomy with cardiopulmonary bypass.

Radical debridement of all infected tissue and foreign material was used as mainstay to guide surgery. The aortic valve was carefully inspected and all infected or necrotic tissues around the valve were removed regardless of the importance of tissues involved or large defects created. Abscesses were debrided thoroughly not to leave any residual infected tissue in situ. Following debridement, the surgical instruments, gloves, and drapes were changed after excision of the valve to minimise contamination of the new prosthesis.

Fistulas were repaired with a pericardial patch. If aorto-ventricular (LV-Ao) dehiscence occurred after complete debridement, the aortic root was replaced. Pericardial patch was used to reconstruct the fibrous continuity of aorto-mitral curtain and valve prostheses were fixed to the patch and the rest of the annulus. The choice of the material and prosthesis for reconstruction was the surgeon's decision.

Endpoints

Study endpoints were in-hospital morbidities including major postoperative adverse events (n = 30; 19.6%), time-related mortality, and time-related reinfection. Survival for all patients at 1, 5 and 10 years was 78%, 73% and 66%. Freedom from reinfection was 89%, 87% and 78% at 1, 5 and 10 years. Postoperative echocardiographic follow-up data including the degree of aortic incompetence (AI) and ejection fraction (EF) were compared among groups.

Definitions

A multidisciplinary team of a cardiologist, infection disease specialist and cardiac surgeon decided on the therapeutic approach. Modified Duke criteria [7] was used to diagnose IE and all patients were managed according to the American Heart Association guidelines [8].

We defined extensive aortic valve AIE as perivalvular extension of infection in the form of annular or periannular abscess, intracardiac fistulas, or aorto-ventricular (LV-Ao) discontinuity (dehiscence), ventricular septal defects (VSD), or valvular extension of infection to the mitral or tricuspid valve or both or any combination of the above-mentioned pathologies.

Extension of infection beyond the aortic valve leaflets was diagnosed in all cases after in-hospital complete echocardiographic examination and confirmed in all cases intraoperatively by the operating surgeon.

Morbidities were defined as for the Society of Thoracic Surgeons national database [9]. Abscess (n = 124; 73.8%) on echocardiogram were defined as a supplementary echo-dense or echo-lucent area, with a diameter of more than 1 cm, visible in transthoracic echo (TTE) or transoesophageal echo (TEE) anatomically localised in the annulus and/or base of ascending aorta with or without the presence of flow (indicating a connection between the aorta and the abscess) [10]. Surgical diagnosis of abscess was based on the intraoperative presence of a paravalvular cavity with fluctuation or a cavity opened to the circulation or other destructive forms of

endocarditis [11]. LV-Ao dehiscence, defined as a separation between the aorta and left ventricle of more than half of its circumference, occurred in 12 patients (7.14%). A fistula was a communication between two adjacent cardiac chambers, found in 16 patients (9.5%).

Statistical Analysis

All analyses were performed using STATA 14 (Statacorp, College Station, TX, USA). Continuous variables are presented as a mean ± standard deviation and were compared with one-way ANOVA for variables with equal variance and Kruskal-Wallis test for variables with non-equal variance. Post-hoc Bonferroni test was used if ANOVA test was significant. Categorical variables are summarised as frequencies and percentages and compared by Chi-squared test or Fisher's exact test when frequency was <5. Logistic regression analysis was used to identify the predictors of postoperative binary outcomes and odds ratio were reported. Cox regression analysis was used to identify the predictors of time related mortality and reinfection and hazard ratio were reported.

Time related mortality and reinfection were assessed non-parametrically using Kaplan-Meier methods and Gehan-Wilcoxon and log-rank tests were used to test the equality of the curves at the start and at the end of the follow-up respectively. Mixed effect models were used to compare the change in EF among groups longitudinally.

Results

Patients' Characteristics

The surgical groups have comparable patients' characteristics (Table 1). Stented valve with a patch support (Group B) was implanted more frequently in patients with native valve endocarditis (NVE) ($p < 0.001$). Stented valves with or

Table 1 **Comparison of the preoperative and operative patients' characteristics among groups.**

	Group A Stented graft (n = 49)	Group B Stented valve with patch support (n = 36)	Group C Stentless valve (n = 50)	Group D Allograft (n = 24)	Group E Composite graft (n = 9)	P
Demographics						
Age	71.4 ± 13.5	72.3 ± 15.6	69.7 ± 16.3	61.3 ± 18.6	68.3 ± 10.9	0.08
Male	16 (32.7%)	9 (25%)	18 (36%)	7 (29.2%)	5 (44.6%)	0.5
Comorbidities						
Prior cardiac surgery	19 (38.8%)	9 (25%)	35 (70%)	14 (58.3%)	6 (66.7%)	<0.001
COPD	2 (4.1%)	1 (2.8%)	3 (6%)	0	0	0.8
Renal failure	5 (10.2%)	3 (8.3%)	5 (10%)	1 (4.2%)	1 (11.1%)	0.9
Cardiogenic shock	14 (28.6%)	12 (33.3%)	10 (20%)	4 (16.7%)	3 (33.3%)	0.5
Septic shock	2 (4.1%)	3 (8.3%)	3 (6%)	0	0	0.7
Stroke	6 (12.2%)	4 (11.1%)	8 (16%)	2 (8.3%)	0	0.8
LVESd	32.3 ± 5.6	31.1 ± 8.8	36.8 ± 4.97	45.5 ± 8.6	32 ± 1.2	0.004
LVEDd	51.3 ± 6.6	49.2 ± 6.98	48.3 ± 5.9	56.4 ± 9.9	48.5 ± 13.4	0.09
EF	55.7 ± 13.6	54.3 ± 9.3	52.7 ± 8.6	53 ± 12.1	62.2 ± 12.6	0.01
Native aortic valve endocarditis	32 (65.3%)	28 (77.7%)	16 (32%)	14 (58.3%)	3 (33.3%)	<0.001
Prosthetic aortic valve endocarditis	17(34.7%)	8 (22.2%)	34 (68%)	10 (41.7%)	6 (66.7%)	
Extension of infection in MV	34 (69.4%)	21 (58.3%)	8 (16%)	5(20.8%)	3 (33.3%)	<0.001
Extension of infection in TV	5 (10.2%)	4 (11.1%)	6 (12%)	2 (8.3%)	1 (11.1%)	0.9
Abscess	18 (36.7%)	30 (83.3%)	49 (98%)	21 (87.5%)	6 (66.7%)	<0.001
Fistula	1 (2.04%)	5 (13.89%)	8 (16%)	2 (8.3%)	0	0.1
LV-Ao Dehiscence	0	0	11 (22%)	1 (4.1%)	0	<0.001
VSD	0	1 (2.8%)	0	1 (4.1%)	1 (11.1%)	0.04
Mitral valve replacement	32 (65.3%)	9 (25%)	5 (10%)	0	3 (33.3%)	<0.001
Mitral valve repair	3 (6.12%)	10 (27.78%)	11 (22%)	1 (4.1%)	0	0.047
Tricuspid valve replacement	3 (6.12%)	1 (2.8%)	1 (2%)	0	1 (11.1%)	0.5
Tricuspid valve repair	3 (6.12%)	3 (8.3%)	6 (12%)	2 (8.3%)	0	0.9

Abbreviations: COPD, chronic obstructive pulmonary disease; LVESd, left ventricular end systolic diameter; LVEDd, left ventricular end diastolic diameter; VSD, ventricular septal defects; MV, mitral valve; TV, triscupid valve; EF, ejection fraction.

without patch support (Group A and B) were commonly implanted in patients with concomitant extension of infection in the mitral valve ($p < 0.001$). Allografts, stentless valves and composite grafts (Group C, D and E) were commonly used in patients with abscess ($p < 0.001$), LV-Ao dehiscence ($p < 0.001$), VSD ($p = 0.04$) and prosthetic valve endocarditis (PVE) ($p < 0.001$).

Microbiology of AIE

The most common organisms were *Streptococcus* species (Table 2). *Staphylococcus aureus* infection was associated with aortic root abscess ($p = 0.03$). Three patients had *Candida albicans* infection (1.79%) and were included in the ''others'' group.

Postoperative Adverse Events

Thirty-three (33) patients (19.6%) had major adverse events postoperatively. This included new stroke, cardiogenic shock and/or septic shock. Postoperative septic shock occurred in 8.33% (n = 14) patients with a median of 5 (IQR; 1–12) days from the operation. Postoperative cardiogenic shock (n = 16; 9.25%) was diagnosed with a median of 1.5 (IQR; 1–9) days from the operation. Stroke (n = 15; 8.93%) occurred within 5 (IQR; 2–21) days after the operation.

There was no difference among groups regarding postoperative cardiogenic shock ($p = 0.1$), septic shock ($p = 0.37$) and stroke ($p = 0.29$) (Table 3). Preoperative univariable predictors of postoperative adverse events are shown in Table 4.

Reinfection

Median follow-up was 4.5 years and ranged from 1 day to 13.25 years. Reinfection occurred in 23 patients. Reinfection ratio was highest with a composite graft (33.3%) and lowest with stentless valves (0%) (log rank test overall $p = 0.01$) (Figure 1). Post-hoc analysis demonstrated a significantly higher reinfection rate of patients in group A ($p = 0.003$).

Reinfection free survival at 1, 3 and 5 years were 82%, 77% and 64% for group A and 90%, 87% and 87% for group B. In group D, reinfection free survival at 1 year was 86% and 78% at 10 years and in group E was 78% and 66% at 1 and 10 years respectively. By univariable analysis, concomitant preoperative extension of infection in the mitral valve (OR 3.6; CI 1.46–8.66; $p = 0.005$) and aortic root abscess (OR 0.23; CI 0.1–0.54; $p = 0.001$) predicted reinfection (Table 5).

No significant difference in reoperation for reinfection was present between the operative groups (log rank $p = 0.09$). Freedom from reoperation in all patients at 1, 5 and 10 years were 92%, 90% and 85%.

Mortality

A total of 47 deaths occurred during the follow-up and 18 patients had operative mortality (within 30 days of the operations). No difference in mortality among groups (Gehan-Wilcoxon $p = 0.7$, log rank test $p = 0.6$) (Figure 2). Univariable preoperative predictors of mortality are shown in Table 5.

Survival at 1, 5 and 10 years were 77%, 72% and 67% in group A, 75%, 69% and 55% in group B, 77%, 75% and 75% for group C, 83%, 70% and 65% for group D; and 88% (unchanged from 1–10 years) in Group E.

Echocardiographic Follow-Up

Group E (composite valve graft) had higher preoperative EF. No significantly different changes in EF were found among groups in comparison to group A as the reference group (p-value 0.8, 0.4, 0.96 and 0.057 respectively).

Progression of AI at 1, 3 and 6 months postoperatively was statistically significant in group D (Allograft) ($p = 0.08$, 0.02 and 0.002 respectively). At the sixth month postoperatively, one patient progressed to AI grade III and two patients to AI grade II compared to one patient in group A with a bioprosthetic valve.

Discussion

Aortic valve AIE with infection extension beyond the valve leaflets still presents a surgical challenge. Definition on which valve substitute should be utilised for reconstruction of the LVOT and which one is associated with better survival, function and lower reinfection rate is the subject of ongoing debate. Surgical options available for reconstruction of the

Table 2 **Microbiology of the infective endocarditis.**

	Group A Stented graft (n = 49)	Group B Stented valve with patch support (n = 36)	Group C Stentless valve (n = 50)	Group D Allograft (n = 24)	Group E Composite graft (n = 9)	P
Staphylococcus aureus	3 (6.1%)	7 (19.4%)	7 (14%)	6 (25%)	5 (55.6%)	0.051
Coagulase-negative staphylococcus	7 (14.3%)	8 (22.2%)	10 (20%)	5 (20.8%)	0	0.6
Streptococcus species	21 (42.9%)	13 (36.1%)	16 (32%)	5 (20.8%)	2 (22.2%)	0.7
Entercoccus faecalis	10 (20.4%)	2 (5.6%)	10 (20%)	2 (8.3%)	1 (11.1%)	0.2
Others	2 (4.1%)	3 (8.33%)	2 (4%)	4 (16.67%)	0	0.3
Gram Negative	6 (12.2%)	3 (8.3%)	5 (10%)	2 (8.3%)	1 (11.1%)	0.98

Table 3 Postoperative adverse events.

	Group A Stented graft (n = 49)	Group B Stented valve with patch support (n = 36)	Group C Stentless valve (n = 50)	Group D Allograft (n = 24)	Group E Composite graft (n = 9)	P
Operative mortality	5 (10.2%)	5 (13.9%)	5 (10%)	3 (12.5%)	0	0.9
Postoperative cardiogenic shock	3 (6.12%)	6 (16.7%)	7 (14%)	0	0	0.1
Postoperative septic shock	4 (8.2%)	5 (13.9%)	5 (10%)	0	0	0.37
Postoperative stroke	7 (14.3%)	4 (11.1%)	4 (8%)	0	0	0.29
Reinfection	12 (24.5%)	4 (11.1%)	0	4 (16.7%)	3 (33.3%)	0.001
Reoperation for infection	7/12 (53.3%)	3/4 (75%)	0	4/4 (100%)	2 (66.7%)	0.5

LVOT in those patients are AVR with bioprosthetic or mechanical valves with or without patch support, stentless valve, aortic allograft or composite valve graft. In discussing various surgical options for extensive aortic valve AIE, we should realise that very sick patients with systemic infection and valve destruction are usually presented for surgery. In cases of paravalvular abscess, radical resection of all infected tissues is a critical step before choosing a valve substitute [12]. If there is LV-Ao dehiscence after extensive debridement, aortic root replacement becomes mandatory. That explains the results of our study in which stentless valves and conduits, allografts and composite valve grafts were used more frequently in PVE because periannular abscess formation and LV-Ao dehiscence were commonly observed in these patients. Stented valves with patch support were more frequently implanted in patients with NVE in which fibrous continuity between aortic and mitral valves was reestablished by a pericardial patch [13].

Aortic valve AIE with infection extension is a heterogenous disease with variable clinical outcomes. We reported in our study the postoperative adverse events, time related mortality and reinfection and lastly, postoperative echocardiographic data.

Postoperative Adverse Events

Most of our patients were treated initially in referring hospitals; patients were referred to our centre for surgery after medical management failed, and they were often in cardiac failure with multiorgan dysfunction. Previous studies have demonstrated better surgical outcomes if the procedure was performed early in complicated AIE [1,3]. Despite the clinical high surgical risk profile of our population, the overall early results were excellent.

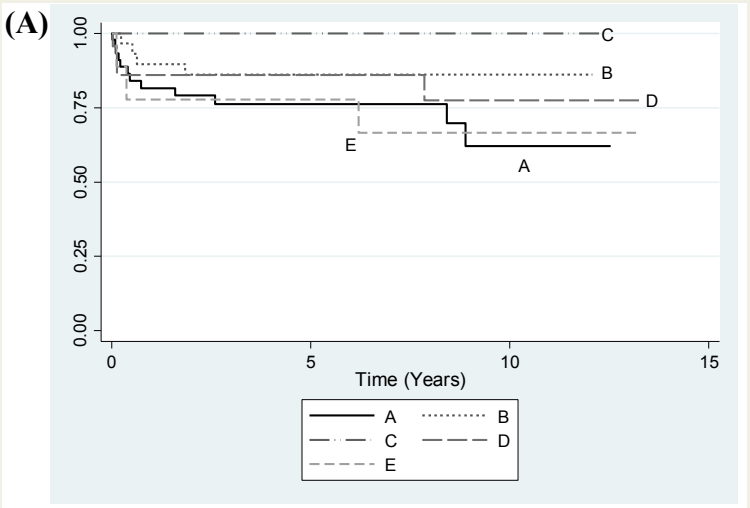
Choice of the valve substitute didn't affect the occurrence of postoperative adverse events. Univariable analysis showed that preoperative haemodynamics were the main determinants of the postoperative complications which emphasises the importance of early surgery before the development of shock.

Reinfection

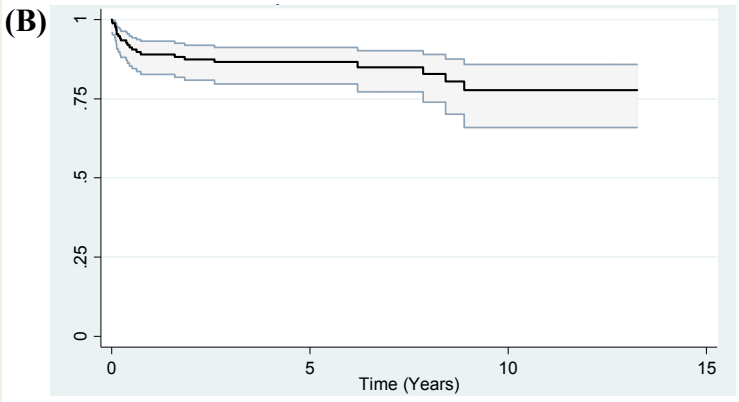
Reinfection after surgery for IE is a major concern because of its association with higher morbidity and mortality. Concomitant infection extension towards the mitral valve predicted reinfection. Consistent with other studies, risk of reinfection was the highest in the first 12 months postoperatively [14]. Previous reports showed valve reinfection with a bio- or mechanical prosthesis was the highest early after surgery and decreased afterwards [15]. In contrast, the allograft and freestyle didn't have a phase of increased risk but a low constant hazard [14]. In our patients, allografts showed low constant risk of infection compared to other groups which had increased early risk but these observations didn't reach a statistically significant level, which could be attributed to the low occurrence of reinfection.

Table 4 Predictors of postoperative adverse events.

	Odds ratio	P	95% Confidence Interval
Stroke	5.4	0.001	2.0–14.5
Ejection fraction	0.91	<0.001	0.87–0.96
Cardiogenic shock	5.28	<0.001	2.3–11.9
Primary surgery	0.26	0.002	0.11– 0.61
Native valve endocarditis	0.32	0.011	0.14–0.77



	3 month	1 year	5 years	10 years
A	38	33	18	7
B	29	26	13	3
C	43	37	12	2
D	18	17	13	8
E	8	7	7	2



	3 months	1 year	5 year	10 years
Number at risk	136	120	63	22

Figure 1 (A) Reinfection free survival curve in the 5 operative groups (B) Overall reinfection free survival curve with a 95% confidence interval.

Table 5 Predictors of mortality and reinfection.

	Hazard ratio	P	95% Confidence Interval
Mortality			
Cardiogenic shock	1.9	0.02	1.1–3.6
Septic shock	8.3	<0.001	3.6–19.2
Ejection fraction	0.96	0.006	0.93–0.99
Concomitant mitral valve surgery	1.8	0.002	1.2–2.5
Reinfection			
Mitral infective endocarditis	3.6	0.005	1.46–8.66
Aortic Root Abscess	0.23	0.001	0.1–0.54

Aortic allografts were associated with lower risk of reinfection, ranging from 3.8 to 6.8% and were considered the graft of choice in aortic IE patients complicated by root abscess [16]. Our finding showed that stentless valves were an effective substitute for allografts, confirming the results of recent reports [1,17].

Aortic root abscess, fistula and LV-Ao dehiscence weren't associated with reinfection in our series. This confirms that radical debridement of the infected material is the main clue to preventing reinfection and, even in cases without aortic root abscess, microscopic extension of infection could be present. Comparable results can be achieved with mechanical prosthesis if radical debridement of the infected tissue is performed [13].

Mortality

Mortality in IE remains relatively high [1,18] and higher mortality is expected in cases complicated with local extension of infection or sepsis. Even with the current technological advancement, mortality of extensive aortic IE remains high [2,19].

In our series, survival did not differ among operative groups. We identified predictors of mortality (preoperative cardiogenic shock and septic shock, EF and concomitant mitral surgery) confirming the results of other series [20].

Other prognostic factors associated with higher mortality were identified in other series, such as high number of comorbidities, advanced age, renal insufficiency, type-I diabetes mellitus and heart failure [21,22].

The treatment of patients with concomitant extension of infection in the mitral valve was challenging and confirmed by previous reports [23]. Like our study, a previous study showed that the choice of MV repair the type of mitral valve surgery (repair or replacement) did not influence mortality [2]. These results confirm the importance of early surgery before spreading of infection to the mitral valve.

In our study, root abscess and LV-Ao dehiscence didn't affect mortality which was suggested in other studies [2,24]. A radical debridement of all infected tissue with proper surgical techniques is mandatory to control of the infection.

Timing of surgery in patients with preoperative stroke is controversial [25]. We performed surgery within a median of 4.5 days after stroke and we couldn't find any association with postoperative mortality.

In other studies *Staphylococcus aureus* IE was associated with a poor prognosis and 30–40% in-hospital mortality [26,27]. Our results didn't show any association between mortality and the causative organism. Explanations for these results could be attributed to early surgical intervention during active Staphylococcal IE together with aggressive debridement of the infected tissue.

Echocardiographic Follow-Up Data

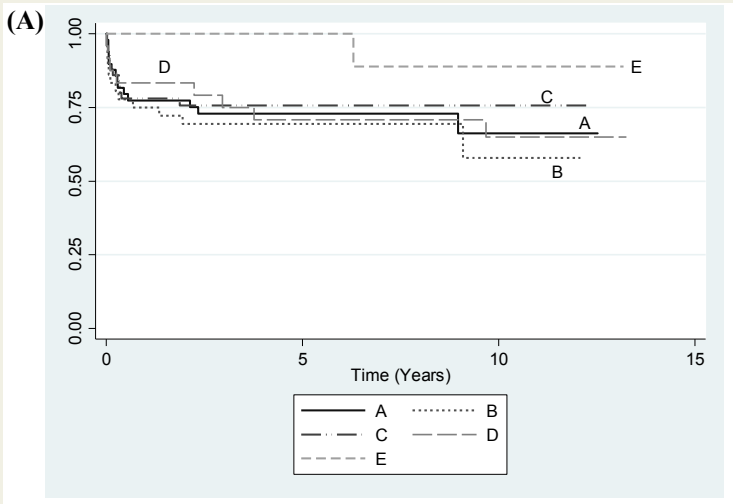
Echocardiographic data show that operative group D (Aortic allografts) had a significant increase in the degree of aortic incompetence during follow-up which is consistent with other published reports [27]. Despite the statistically significant progression of AI, this happened only in three patients compared to other surgical groups.

Ejection fraction increased postoperatively with all valve substitutes except with composite grafts. The changes in EF were non-significant among groups.

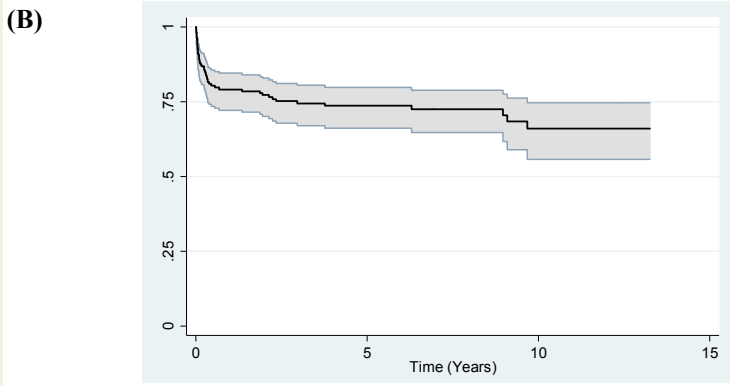
These echocardiographic findings are comparable among groups and don't support the preference for one conduit over the other.

Strengths and Limitations

Although this is a single-centre study of 168 surgically treated extensive aortic valve AIE patients with follow-up data up to 13 years, it may be one of the largest series comparing five operative strategies in this high-risk population. It is an observational study in which referral and selection bias may affect results, but we think this is a reasonable approach to assess the outcome in this non-common disease. We had a low number of complications even if combined, this underpowers the multivariable analysis. Univariable analysis was used and consequently, adjustment for possible confounders can't be tested which may have biased the findings. Moreover, generalisation of the results is an issue because this is a single-centre experience.



	1 Month	1 Year	3 Years	5 Years	10 Years
A	44	36	29	20	9
B	31	27	21	14	3
C	46	37	24	12	2
D	22	20	18	16	11
E	9	9	9	9	3



	1 Month	1 Year	3 Years	5 Years	10 Years
Number at risk	152	129	101	71	28

Figure 2 (A) Kaplan Meier survival curve in the 5 operative groups (B) Overall survival curve with a 95% confidence interval.

Conclusion

The surgical treatment of extensive aortic valve AIE remains challenging. Early surgery is recommended before the disease compromises the preoperative haemodynamics. Beside the preoperative haemodynamics, extension of infection to the mitral endocarditis and mitral surgery negatively affected the outcome. Complexity of aortic reconstruction procedure or valve substitute didn't affect mortality. Radical debridement of all infected tissue is essential to control the

infection and stentless valves seem a good alternative to allografts. Optimal surgical approach should be tailored to individual patient characteristics.

Acknowledgment

Abdelmotagaly Elgalad received a grant from the Ministry of Higher Education in Egypt.

Author Disclosures

No conflict of interest.

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