Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults

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Objectives: The aim of this study was to determine long-term survival and clinical outcomes after elective isolated mechanical aortic valve replacement in young adults.

Methods: A clinical observational study was conducted in a cohort of 450 consecutive adults less than 65 years of age who had undergone elective isolated mechanical aortic valve replacement (AVR) between 1997 and 2006. Patients who had undergone previous cardiac surgery, and those undergoing concomitant procedures or urgent surgery were excluded. Follow-up was 93.3% complete with a mean follow-up of 9.1 ± 3.5 years. The primary end point was survival. Life table analyses were used to determine age- and gender-matched general population survival. Secondary end points were reoperation and valve-related complications.

Results: Overall actuarial survival at 1, 5, and 10 years was $98\% \pm 1\%$, $95\% \pm 1\%$, and $87\% \pm 1\%$, respectively, which was lower than expected in the age- and gender-matched general population in Quebec. Actuarial freedom from prosthetic valve dysfunction was $99\% \pm 0.4\%$, $95\% \pm 1\%$, and $91\% \pm 1\%$ at 1, 5, and 10 years, respectively. Actuarial freedom from valve reintervention was $98\% \pm 1\%$, $96\% \pm 1\%$, and $94\% \pm 1\%$ at 1, 5 and 10 years, respectively. Actuarial survival free from reoperation at 10 years was $82\% \pm 2\%$. Actuarial freedom from major hemorrhage was $98\% \pm 1\%$, $96\% \pm 1\%$, and $90\% \pm 2\%$ at 1, 5, and 10 years, respectively.

Conclusions: In young adults undergoing elective isolated mechanical AVR, survival remains suboptimal compared with an age- and gender-matched general population. Furthermore, there is a low but constant hazard of prosthetic valve reintervention after mechanical AVR. (J Thorac Cardiovasc Surg 2014;148:1341-6)

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Aortic valve disease is one of the most common indications for surgery in patients less than 65 years of age. However, the ideal aortic valve substitute remains unknown. This is partly due to the lack of data on long-term outcomes in this specific patient population. More importantly, most long-term studies of aortic valve replacement (AVR) include patients at higher risk (urgent operations, concomitant coronary revascularization, reoperations), which makes it more challenging to assess outcomes related to the actual procedure.¹⁻³ Nevertheless, recent evidence has shown excess long-term mortality in patients undergoing AVR compared with an age- and sex-matched general

population, and this discrepancy was most pronounced in the youngest age group.⁴

A longer life expectancy exposes young adults to a higher lifelong risk of prosthesis-related complications after AVR, most notably in the form of thromboembolic events, hemorrhage, and reoperation. Bioprosthetic valves have limited long-term durability and therefore carry an inherent risk of reoperation in young adults. Nevertheless, they have a low thrombogenic risk and have the advantage of avoiding anticoagulation. In contrast, mechanical prostheses provide better long-term durability with low risk of prosthesis reintervention, and are thus often considered the option of choice in young adults with aortic valve disease.⁵ Nevertheless, mechanical prostheses carry a thrombogenic risk and therefore mandate long-term anticoagulation with an associated risk of major bleeding. Although some studies have examined long-term results after AVR, few have focused on contemporary results of isolated mechanical AVR in young adults.

The aim of this study was to assess long-term survival in a contemporary series of consecutive young adults undergoing elective isolated mechanical AVR compared with the age- and gender-matched general population in Quebec. The secondary objective was to describe the occurrence of long-term valve-related complications after AVR in this patient population.

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Abbreviations and Acronyms

AVR	= aortic valve replacement
INR	= international normalized ratio
MAPE	= major adverse prosthetic events
MHI	= Montreal Heart Institute

MATERIALS AND METHODS**Patients**

All patients less than 65 years old undergoing AVR at the Montreal Heart Institute (MHI) between January 1997 and October 2006 were screened. Mechanical AVR was the procedure of choice in this patient population unless there was a specific contraindication for anticoagulation or because of patient preference. In total, 1158 patients were identified. Of those, 208 underwent bioprosthetic valve replacement (18%; mean age, 55 ± 10 years) and 950 underwent mechanical valve replacement (82%; mean age, 53 ± 9 years). All patients were followed on a yearly basis by mail questionnaires and phone interviews at our institution's dedicated Valve Clinic. Patients undergoing emergency surgery, concomitant procedures (including coronary bypass, other valve repair, ascending aorta replacement, Bentall procedure, annular enlargement procedures, Maze radiofrequency ablation, and atrial or ventricular septal defect closure) and those who had undergone previous cardiac surgery were excluded ($n = 500$ patients). The study population consisted of 450 consecutive patients undergoing elective isolated mechanical AVR. Preoperative baseline characteristics are presented in Table 1. Mean age at surgery was 53 ± 9 years (68% male). Aortic stenosis was the indication in 337 patients (75%), aortic regurgitation in 68 patients (15%), and mixed aortic disease in 45 patients (10%). The mean EuroSCORE II⁶ was $1.1\% \pm 0.6\%$.

Operative Data and Anticoagulation Management

Implanted mechanical prostheses were distributed as follows: Carbomedics (Sorin Group, Milan, Italy) in 402 (89%) patients, St Jude Medical (St Jude Medical Inc, St Paul, Minn) in 35 (8%) patients, and Medtronic Advantage (Medtronic, Minneapolis, Minn) in 13 (3%) patients. The mean clamping time was 62 ± 15 minutes and the mean cardiopulmonary bypass time was 83 ± 20 minutes. Anticoagulation therapy with warfarin was started in all patients on the second postoperative day. Close anticoagulation follow-up in specialized clinics was performed and the target internationalized normalized ratio (INR) ranged between 2 and 3.

Follow-up and Data Collection

Approval was obtained from our local ethics committee. All data were prospectively collected through the MHI Valve Clinic. Additional data were gathered from medical records. The follow-up period for this study ended in September 2012. Mean follow-up time was 9.1 ± 3.5 years (total follow-up was 4099 patient-years). Follow-up was 93% complete.

Reference population survival estimates were generated from publicly available Province of Quebec survival tables for each patient according to age and sex.

Outcomes

Outcomes were recorded according to the Society of Thoracic Surgery Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions.⁷ The primary outcome of this study was death from any cause and was divided into early mortality (30 days after surgery) and late mortality. Secondary outcomes reported were prosthesis dysfunction including structural and nonstructural valve dysfunction, thromboembolic events (stroke, transient ischemic attack, and non-cerebral embolic events), endocarditis, valve thrombosis, and significant

hemorrhage, which was defined as major bleeding requiring hospitalization or transfusion. Major adverse prosthetic events (MAPE) included a composite of all the aforementioned outcomes. Causes of death were reported as valve-related, cardiac, and noncardiac.

Statistical Analysis

Continuous variables are presented as the mean $\pm$ standard deviation and categorical variables are reported as frequency (percentage). All outcomes were analyzed using actuarial methods. Patients were censored at the time of death or at the time of their last follow-up if the outcome of interest had not occurred. Expected survival of a sex- and age-matched population was obtained using the Hakulinen method.⁸

Predictors of mortality were assessed using a multivariable logistic regression model. Variables screened as potential confounders were the preoperative baseline characteristics. All variables with a P value $< .20$ on univariate analysis were considered as having a potential confounding effect. A nonautomated variable selection was performed. Variables with a P value $< .05$ were retained in the multivariate Cox regression. Data were analyzed using SAS 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS**Early Complications**

Thirty-day mortality was 1.1% ($n = 5$). Causes of early death were myocardial infarction ($n = 2$), endocarditis ($n = 1$), malignant arrhythmia ($n = 1$), and massive bleeding ($n = 1$). New onset of atrial fibrillation or flutter was reported in 141 patients (31%). Postoperative bleeding (< 48 hours) requiring reintervention occurred in 23 patients (5%). Late pericardial effusion necessitating surgical drainage after the start of anticoagulation (48 hours to 30 days after surgery) was observed in a further 43 patients (10%). Although anticoagulation was started progressively on the second postoperative day, INR rates were > 3 in 47% of patients at the time of drainage. A pacemaker was implanted for atrioventricular block in 17 patients (4%). Stroke occurred in 7 patients (2%). Details on postoperative complications are summarized in Table 1.

Long-Term Survival

Late mortality occurred in 58 patients (13%) during the follow-up period. The cause of death was valve related in 31 patients (53%), cardiac related in 10 patients (17%), and noncardiac related in 17 patients (30%). Details on causes of late deaths are presented in Table 2. Actuarial survival at 1, 5, and 10 years was $98\% \pm 1\%$, $95\% \pm 1\%$, and $87\% \pm 1\%$, respectively. At each time point, survival was lower than in the age- and gender-matched general population of Quebec (Figure 1). Expected survival in the age- and gender-matched general population was 99.6%, 97.6%, and 94.2% at 1, 5, and 10 years, respectively.

On multivariate analysis, decreased preoperative left ventricular ejection fraction ($P = .001$), decreased preoperative glomerular filtration rate ($P = .002$), diabetes ($P < .0001$), obesity ($P = .008$), hypothyroidism ($P = .007$), and asthma ($P = .014$) were independent predictors of long-term mortality. Patient age at the time of surgery was not associated with late mortality.

TABLE 1. Demographic characteristics and early complications of 450 young adults who underwent isolated mechanical aortic replacement

Demographic data	N (%)
Age	
18-35 y	17 (4)
35-50 y	111 (25)
50-65 y	322 (71)
Gender	
Men	304 (68)
Cardiovascular risk factors	
Hypertension	169 (38)
Diabetes	57 (13)
Smoker	129 (29)
Dyslipidemia	144 (32)
New York Heart Association class	
III	182 (40)
IV	13 (3)
Cause	
Congenital	257 (57)
Degenerative calcification	117 (26)
Rheumatic	30 (7)
Subacute or resolved endocarditis	11 (2)
Others	35 (8)
Left ventricular ejection fraction	
<40%	35 (8)
40%-55%	55 (12)
>55%	360 (80)
Indication	
Aortic stenosis	337 (75)
Aortic regurgitation	68 (15)
Mixed aortic disease	45 (10)
Prosthesis	
Carbomedic	402 (89)
St Jude Medical	35 (8)
Medtronic Advantage	13 (3)
Early complications	
Atrial fibrillation/flutter	141 (31)
Bleeding necessitating reoperation (<48 h)	23 (5)
Late (<30 d) pericardial effusion requiring drainage	43 (10)
Arteriovenous block necessitating pacemaker implantation	17 (4)
Acute renal failure	17 (4)
Deep wound infection	13 (3)
Stroke	7 (2)
Transient ischemic attack	5 (1)
Myocardial infarction	4 (1)

Actuarial survival for patients less than 50 years of age was 88% ± 3% at 10 years, which did not differ significantly from the rest of the cohort.

Prosthesis Dysfunction and Valve Reintervention

Prosthesis dysfunction was reported in 37 patients. All involved nonstructural valve dysfunction: 32 paravalvular leaks (86%) and 5 patient-prosthesis mismatches as determined by echo gradients (14%) (Table 2). There was no correlation between valve dysfunction and any specific

TABLE 2. Late causes of death and valve-related complications

Cause of death	N (%)
Valve-related death	31 (53)
Reintervention	4
Thrombembolism	2
Massive hemorrhage	1
Valve thrombosis	1
Sudden unexplained death	20
Mediastinal infection	1
Endocarditis	2
Other cardiac death	10 (17)
Myocardial infarction	3
Heart failure	7
Noncardiac	17 (30)
Valve-related complications	
Major bleeding event	38 (8)
Gastrointestinal	15
Cerebral	7
Thoracic	5
Musculoskeletal	3
Urologic	3
Other	5
Prosthesis dysfunction	37 (8)
Paravalvular leak	32
Prosthesis-patient mismatch	5
Prosthesis thrombosis	3 (0.1)
Endocarditis	10 (2)
Thromboembolism	41 (9)
Stroke	21
Transient ischemic attack	19
Systemic embolism	1
Valve reintervention	26 (6)
Replacement	17
Repair	9

valve type. Actuarial freedom from prosthetic valve dysfunction was 99% ± 0.4%, 95% ± 1%, and 91% ± 1% at 1, 5, and 10 years, respectively (Figure E1, A). Survival free from prosthesis dysfunction was 95% ± 1%, 88% ± 2%, and 79% ± 3% at 1, 5, and 10 years, respectively (Figure E1, B).

Reintervention was necessary in 26 patients. The main indication for reoperation was paravalvular leak (n = 17; 65%). Other causes were endocarditis (n = 4; 15%), prosthesis thrombosis (n = 2; 8%), aortic root dilatation (n = 2; 8%), and patient-prosthesis mismatch (n = 1; 4%). Median interval between the first and second intervention was 4.6 ± 3.8 years (range, 40 days to 11.9 years). Actuarial freedom from aortic valve reintervention was 98% ± 1%, 96% ± 1%, and 94% ± 1% at 1, 5, and 10 years, respectively (Figure 2, A). Survival free from valve reintervention was 95% ± 1%, 89% ± 1%, and 82% ± 2% at 1, 5, and 10 years, respectively (Figure 2, B). This was uniformly observed for patients younger and older than 50 years of age. Operative mortality associated with redo AVR was 15% (n = 4).

FIGURE 1. Survival in young adults undergoing isolated mechanical aortic valve replacement (AVR) compared with a sex- and age-matched population in Quebec.

Three deaths occurred after emergency redo procedures for endocarditis ($n = 2$) and prosthesis thrombosis ($n = 1$). One death was reported after elective redo surgery for paravalvular leak.

Thromboembolic and Major Bleeding Events

Forty-one thromboembolic events occurred in 39 patients. Of those, 21 were strokes (51%), 19 were transient ischemic events (46%), and 1 was a noncerebral embolic event (2%) (Table 2). Median interval to thromboembolic events was 2.2 years. Overall actuarial freedom from thromboembolism was $97\% \pm 1\%$, $93\% \pm 1\%$, and $91\% \pm 2\%$ at 1, 5, and 10 years respectively (Figure E2).

Thirty-eight patients experienced at least 1 significant hemorrhagic event. Actuarial freedom from major hemorrhage was $98\% \pm 1\%$, $96\% \pm 1\%$, and $90\% \pm 2\%$ at 1, 5, and 10 years, respectively (Figure E3).

Valve Thrombosis, Endocarditis, and MAPEs

Three patients experienced prosthesis thrombosis and 2 underwent reoperation. One patient died before reaching the hospital. Prosthetic valve endocarditis was reported in 10 patients (2%). Actuarial freedom from endocarditis was $98.6\% \pm 0.5\%$, $98.1\% \pm 0.6\%$, and $98.1\% \pm 0.6\%$ at 1, 5, and 10 years, respectively.

Overall, actuarial survival free from MAPEs was $92\% \pm 1\%$, $82\% \pm 2\%$, and $73\% \pm 2\%$ at 1, 5, and 10 years, respectively (Figure 3).

DISCUSSION

The present study represents a contemporary series of consecutive young adults undergoing elective isolated mechanical AVR. In the current era with good long-term follow-up, the choice of an aortic valve substitute in young adults undergoing surgery for isolated aortic valve disease is a difficult decision. The ideal AVR that combines durability, low risk of long-term complications, and good long-term survival remains elusive. Because of their longer durability in young adults, mechanical prostheses were the option of choice for these patients in our center.

Survival

The major finding from this study is that survival in this young adult population undergoing elective isolated mechanical AVR fails to match that of the matched general population. Despite surgical correction of aortic valve disease (stenosis in most patients), there is a continuing long-term relative death hazard in these young patients, which exceeds what would be expected in the general population. This is in accordance with data from Kvidal and colleagues,⁴ who reported excess mortality in a study of more than 2300 adults undergoing biological and mechanical AVR. This was particularly more pronounced in younger patients, with an observed/expected death ratio

FIGURE 2. A, Actuarial freedom from valve reintervention after mechanical isolated aortic valve replacement in young adults. B, Survival free from valve reintervention after mechanical isolated aortic valve replacement in young adults.

FIGURE 3. Survival free from major adverse prosthetic events (MAPE) after mechanical isolated aortic valve replacement in young adults.

of 4.5 in young adults less than 50 years of age.⁴ The current study highlights that AVR for isolated aortic valve disease remains a palliative solution. This is also in concordance with several studies examining long-term outcomes after different aortic valve substitutes in young adults. Using the Hancock II bioprosthesis (Medtronic Inc, Minneapolis, Minn), David and colleagues⁹ reported 55% survival at 20 years in patients less than 60 years of age (and 30% freedom from reoperation). Similarly, using the On-X mechanical prosthesis (On-X Life Technologies, Austin, Tex), Chambers and colleagues¹⁰ reported a linearized rate of mortality of 2.2% per patient-year in a population of 214 isolated AVRs. These findings are in contrast with a series of recently published studies showing restoration of survival after the Ross procedure in young adults.¹¹⁻¹⁵ Although this may be due in part to patient selection, it could be related to the suboptimal profile of mechanical prostheses, both at rest and with exercise. In young adults who are physically active, this exposes the left ventricle to persistent strain, potential fibrosis, and decreased coronary flow reserve.^{16,17} Although this remains speculative, trying to understand the excess mortality observed in this patient population is important to improve long-term clinically relevant outcomes. An important issue that warrants further investigation pertains to the role of earlier surgical intervention in asymptomatic patients on long-term outcomes, including survival. Some recent studies suggest a potential benefit for earlier intervention in these patients.¹⁸ Although this may have had an impact on our study population, it is difficult to assess in a retrospective analysis.

Long-Term Valve-Related Complications

In this cohort, survival free from MAPEs was 73% at 10 years. Thromboembolic events and anticoagulation-related major bleeding were the most frequent valve-related

complications observed in this study. Risk of thromboembolism, mainly in the form of cerebral embolic events, was similar to what has been reported in other studies with third-generation mechanical AVR (0.9%/patient-year in the present study).¹⁹⁻²¹ In addition, there was a significant long-term risk of major bleeding. Previous studies have reported similar hazards of anticoagulation-associated major hemorrhage after mechanical AVR (1%/patient-year at 10 years in the present study).^{19,20} The high occurrence of these complications despite a close follow-up of INR might be explained, at least in part, by poor compliance with anticoagulation therapy in this young population. Data from Mokhles and colleagues²² suggest that survival of young adults undergoing mechanical AVR with self-managed anticoagulation closely resembles that of the general population at a mean follow-up of 6.3 years. No valve-related deaths were reported in that series. Conversely, in the present study, more than half of the reported causes of late mortality were cardiac or valve related. This highlights the potential benefit of self-managed anticoagulation in reducing valve-related events by optimizing INR control and thus minimizing the risks of anticoagulation inherent in the implantation of a mechanical prosthesis. Although most of our patients are closely followed in a dedicated anticoagulation clinic, few are under self-management programs, which may contribute to the higher rate of valve-related complications observed. Furthermore, recent data suggest that lower INR targets may result in lower rates of valve-related events. Interim data from PROACT (Prospective Randomized On-X Valve Reduced Anticoagulation Clinical Trial) examining different anticoagulation regimens with the On-X prosthesis in a carefully selected and prospectively followed population (mean age 55 years) show that the rates of valve-related complications were significantly reduced in the lower (1.5-2.0) versus standard (2.0-3.0) anticoagulation cohorts. Nevertheless, the rate of major bleeding in the low anticoagulation group was 1.48%/patient-year and the rate of neurologic events was 1.98%/patient-year. These outcomes do not differ significantly from those observed in our patient population. Thus, the impact of reduced anticoagulation targets remains to be fully determined.

The low but constant risk of prosthetic dysfunction and reintervention after isolated mechanical AVRs was another important observation of the present study. Paravalvular leak was the most common cause of valve dysfunction and reintervention. This form of nonstructural valve deterioration is encountered in 1% to 5% of patients undergoing AVR,²³ and may have important long-term implications in young adults with mechanical prostheses, causing left ventricular dysfunction and exposing patients to potential reoperation. The Veteran Affairs randomized study²⁴ had previously reported a

hazard of reoperation similar to that reported in the present study. Other studies^{19,25} have reported lower risks of reintervention. Notwithstanding these discrepancies, the risk of reintervention remains low in this population, especially compared with young adults undergoing AVR with bioprostheses.²⁴ Nevertheless, the present study challenges the commonly held belief that mechanical prostheses are lifelong substitutes. It follows that the risk of valve reoperation should be taken into account alongside the anticoagulation-related risks in the decision-making process leading to the choice of a mechanical aortic valve substitute in young adults.

Limitations

Completeness of follow-up was 93%, which may have influenced the results or caused underreporting of some valve-related events. This was mainly due to the long follow-up period in this young and mobile population, which introduced some loss to follow-up. In addition, the cause of death remained unknown in 24% of deceased patients, making definitive conclusions with regard to the causes of mortality in this young patient population more difficult. Although most patients were closely followed in dedicated anticoagulation clinics, few were on self-management programs, thus preventing any analysis of the impact of the anticoagulation management strategy on observed outcomes.

CONCLUSIONS

Late survival in young low-risk adults (<65 years) undergoing elective isolated mechanical AVR is lower than expected in an age- and gender-matched general population. In most cases, the excess mortality is cardiac or valve related, confirming that the choice of prosthesis in these patients can have major clinical implications. Furthermore, there is a low but constant hazard of prosthetic valve dysfunction requiring reintervention after mechanical AVR. Findings from this contemporary study should serve as a blueprint for informing young adults undergoing isolated AVR about potential long-term outcomes. In light of these findings, continued efforts are warranted to improve long-term results in this patient population.

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FIGURE E1. A, Actuarial freedom from prosthesis dysfunction after mechanical isolated aortic valve replacement in young adults. B, Survival free from prosthesis dysfunction after mechanical isolated aortic valve replacement in young adults.

FIGURE E2. Actuarial freedom from valve thromboembolic events after mechanical isolated aortic valve replacement in young adults.

FIGURE E3. Actuarial freedom from valve-related significant hemorrhagic events after mechanical isolated aortic valve replacement in young adults.

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