**Original
Article**

Choice of Aortic Valve Prosthesis in a Rapidly Aging and Long-Living Society

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Purpose: The aim of this study was to evaluate the long-term results of aortic valve replacement (AVR) with mechanical (M) and bioprosthetic (B) valves as recommended by the Japanese guidelines.

Methods: From April 1995 to March 2014, 366 adult patients underwent AVR. Of these, 127 (35%) patients received M and 239 patients (65%) received B valves. A retrospective analysis of the entire and the selected 124 patients aged 60 to 70 years was carried out.

Results: In patients aged 60 to 70 years, the 15-year survival and freedom from reoperation were $88\% \pm 7\%$ and 100% for the M group and $34\% \pm 25\%$ ($p < 0.001$) and $73\% \pm 14\%$ ($p = 0.059$) for the B group, respectively. Among propensity score matching of the subgroup, there was no significant difference in survival and freedom from reoperation. The rate of thromboembolism was higher in the M (M: 0.58% vs B: 0.35% patient per year, $p < 0.001$) and the rate of hemorrhage was higher in the M group (M: 0.34% vs B: 0.12% patient per year, $p < 0.001$).

Conclusion: The current strategy of aortic valve choice based on the Japanese guidelines has provided excellent long-term results so far.

Keywords: valve choice, aortic valve replacement, heart valve prosthesis, long-term outcomes

Introduction

The current Japanese guidelines recommend a bioprosthetic (B) valve for aortic valve replacement (AVR) in patients aged more than 65 years. The staff surgeons in our facility have chosen the aortic prosthesis for each patient according to the current guidelines after discussing with the patients and their families and taking into account several factors such as age, comorbidities, and surgical/reoperation risk. However, the use of bioprosthetic valves in the aortic position has markedly increased in recent

years as the number of elderly patients in Japan has increased. The details of valve durability and anticoagulation therapy are sometimes beyond patient's ability to fully grasp, and many patients leave the choice of valve type to their surgeon's recommendation, based on his experience and preferences. Sometimes, clinicians find it hard to choose which type of valve to use for patients aged 60 to 70 years. This is because recent increases in Japanese longevity make it likely that the patient will outlive the useful life of a B valve and might require reoperation as an octogenarian, particularly if the patient is a female (females tend to outlive males in Japan, as elsewhere). In this study, we analyzed the clinical outcomes after AVR in Japan's rapidly aging society, focusing on the valve choice in the age group of 60 to 70 years through propensity score matching.

Patients and Methods

The university's research ethical committee approved this study and individual patient consent was waived.

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Table 1 Preoperative patient characteristics

Variables	M (n = 127)	B (n = 239)	<i>p</i> Value
Age (y)	55.5 ± 13.6	72.4 ± 6.8	<0.001
Male (%)	96 (75.6)	133 (55.6)	<0.001
Body surface area (m ²)	1.66 ± 0.19	1.54 ± 0.18	0.999
Mean follow-up (y)	7.3 ± 5.9 (1–19)	3.8 ± 3.7 (1–16)	<0.001
AS	19 (15%)	99 (41%)	<0.001
ASR	30 (24%)	81 (34%)	0.196
AR	73 (57%)	57 (24%)	<0.001
Bicuspid	17 (13%)	21 (9%)	0.219
NYHA functional class III or IV (%)	6 (4.7)	19 (7.9)	0.238
Diabetes (%)	11 (8.7)	32 (13.4)	0.181
Valve size (mm)	22.9 ± 3.3	20.9 ± 2.0	<0.0001
Endocarditis (%)	12 (9.4)	10 (4.2)	0.044
CKD (creatinine >2 mg/dL) (%)	9 (7.1)	32 (13.4)	0.069
Peripheral vascular disease (%)	9 (7.1)	24 (10.0)	0.348
Low preoperative EF (<40%) (%)	5 (3.9)	7 (2.9)	0.598
CABG (%)	13 (10.2)	57 (23.8)	0.001

NYHA: New York Heart Association; EF: ejection fraction; CKD: chronic kidney disease; CABG: coronary artery bypass grafting; AS: aortic stenosis; ASR: aortic stenosis and regurgitation; AR: aortic regurgitation

Patient population

Between April 1995 and March 2014, 366 adult patients underwent single AVR or combined AVR/coronary artery bypass grafting (CABG) (n = 61) at the Jikei University Hospital. In all, 127 (35%) patients received M valves, and 239 (65%) patients received B valves. The characteristics of the patients are summarized in **Table 1**. Follow-up was 94% complete, with a mean duration of 5.4 ± 4.5 years (range: 1–17.7).

Choice of prosthesis

The main criterion for choosing a B valve in the aortic position was age older than 65 years and the fundamental principle of valve selection was based on the current Japanese guidelines (http://www.j-circ.or.jp/guideline/pdf/JCS2012_ookita_h.pdf). The types and numbers of B valves used were Carpentier-Edwards Perimount (100); Magna (32) and Magna EASE (30; Edwards Lifesciences, Irvine, CA, USA); Medtronic Mosaic (28) and Ultra (22; Medtronic, Minneapolis, MN, USA); and St. Jude Medical (SJM) Trifecta (25) and SJM Epic (2; St. Jude Medical, St. Paul, Minnesota, MN, USA). The types of M valves inserted were SJM Standard (74) and SJM Regent (25; St. Jude Medical); ATS (27; ATS Medical, Minneapolis, MN, USA); and CarboMedics (1; Sorin SpA, Milan, Italy). These valves were chosen because they were commonly implanted during the study period at our institute.

Surgical procedure and management of anticoagulation

A midline sternotomy was performed in all the patients. After resection of the native aortic valve cusps, the valve size was measured with the sizer provided by the prosthesis manufacturer. The B valves were implanted in the supra-annular position with pledgeted 2-0 polyester sutures with a non-everting mattress suture technique. The M valves were implanted in the intra-annular position (with the exception of small valve sizes) using an everting mattress suture technique. In patients with a B valve, the target international normalized ratio (INR) was maintained between 1.5 and 2.5 for 3 months. Thereafter, patients received only aspirin, if not otherwise indicated. In patients with a mechanical prosthesis, INR has been maintained lifelong between 2.0 and 2.5.

Statistical analysis

Valve-related morbidity and mortality were reported according to definitions given in the Guidelines of the European Association for Cardio-thoracic Surgery.¹⁾ Data are expressed as the mean ± standard deviation (SD) and were compared using the paired Student's *t* test. A probability value of less than 0.05 was considered significant. Cumulative survival and freedom from reoperation were analyzed using the Kaplan–Meier method, and curves were compared with the log-rank test. In addition, propensity score analysis was performed through matching

Fig. 1 Recent changes of aortic valve choices in patients aged between 60 and 70 years.

between the two groups. The 14 known preoperative potential confounders were included in the logistic regression model, and the propensity scores were calculated for each patient. Using the propensity score, the patients with M valves were matched with the patients with B valves by a 5 to 1 digit matching algorithm using the nearest available one-to-one pair matching method. Statistical calculations were performed using a computerized statistical program (IBM SPSS Statistics 22).

Results

Recent changes in patient's age and valve choice

The mean age at surgery increased from 59 ± 13 years during the first half of the study period to 68 ± 12 ($p < 0.001$) years during the second half of the study period. Likewise, the use of the B valves increased from 55% to 71% during these periods. The valve size became smaller in both the M and B groups (M: 25.0 ± 1.5 to 21.6 ± 3.5 mm, B: 21.7 ± 2.3 to 20.6 ± 1.7 mm) during these periods. Although the total number of patients who received B valves increased from 55% to 71% during these periods, the proportion of patients aged 60 to 70 years who received B valves decreased from 70% to 64%. Moreover, the number of patients aged 60 to 65 years who received B valves decreased from 40% to 22% (Fig. 1).

Perioperative histories and late outcomes

During the perioperative period, four patients died in the M group and eight patients died in the B group (3.1% vs 3.3%, $p = 0.92$) (Table 2). The 5-, 10-, and 15-year overall actuarial survival was $88\% \pm 3\%$, $85\% \pm 4\%$, and

Table 2 Hospital and Late death

Hospital death	M (3.9%)	B (3.3%)
Cause		
LOS	1	3
Pneumonia	1	1
Cerebrovascular accident	1	1
PVE	1	1
DIC	1	0
Lung abscess	0	1
GI bleeding	0	1
Late death	M (6.2%)	B (4.2%)
Cause		
Cancer	2	4
Sudden death	1	1
PVE	1	1
Cerebrovascular accident	0	3
AMI	2	0
Rupture of TAA	1	1
Pneumonia	1	0

LOS: low output syndrome; PVE: prosthetic valve endocarditis; DIC: disseminated intravascular coagulation; GI: gastrointestinal; AMI: acute myocardial infarction; TAA: thoracic aortic aneurysm

$85\% \pm 4\%$ for the M group and $86\% \pm 3\%$, $55\% \pm 6\%$, and $43\% \pm 7\%$ for the B group, respectively ($p = 0.220$). The 15-year overall freedom from reoperation was $98\% \pm 2\%$ for the M group and $89\% \pm 5\%$ for the B group ($p = 0.015$). Only one patient (0.8%) underwent reoperation in the M group because of prosthetic valve endocarditis. In the B group, eight patients (3.3%) underwent reoperation. Of these, four patients were diagnosed as structural valve deterioration (SVD) and the others were prosthetic valve endocarditis.

Outcomes in patients aged 60 to 70 years after propensity score matching

There were 124 (34%) patients aged 60 to 70 years. In total, 41 patients (33%) received M valves and 83 patients (67%) received B valves. We selected 14 variables to eliminate the differences between the M and the B groups, and propensity score matching was performed. After constituting the propensity-matched M and B groups, our final study population generated 28 matched pairs (Table 3). Using one-to-one matching, there was no significant difference in actuarial survival and freedom from reoperation between the matched M and B groups (Figs. 2A and 2B).

Thromboembolism and hemorrhage

There were significant differences in the linearized rate (% patient per year) of thromboembolism and

Table 3 Preoperative patient characteristics aged 60 to 70 years before and after propensity matching

	Unadjusted			Adjusted		
	M (n = 41)	B (n = 83)	p Value	M (n = 28)	B (n = 28)	p Value
Age (y)	63.7 ± 2.9	67.3 ± 2.5	<0.001	64.3 ± 2.8	65.3 ± 2.6	0.112
Male (%)	26 (63.4)	44 (53.0)	0.275	16 (57.1)	12 (42.9)	0.285
Body surface area (m ²)	1.65 ± 0.21	1.57 ± 0.18	0.021	1.58 ± 0.16	1.49 ± 0.21	0.032
Mean follow-up (y)	5.9 ± 4.8	5.2 ± 4.3	0.572	7.0 ± 5.6	7.8 ± 5.7	0.596
NYHA functional class	1.7 ± 0.5	1.5 ± 0.7	0.024	1.7 ± 0.5	1.3 ± 0.6	0.003
NYHA functional class III or IV (%)	1 (2.4)	10 (12.0)	0.078	0	1 (3.6)	0.313
Diabetes (%)	5 (12.1)	7 (8.4)	<0.001	2 (7.1)	3 (10.7)	0.639
Valve size (mm)	22.5 ± 2.8	21.4 ± 2.3	0.049	22.5 ± 2.8	21.4 ± 2.3	0.049
Endocarditis (%)	1 (2.4)	5 (6.0)	0.386	0	2 (7.1)	0.15
CKD (creatinine >2 mg/dL) (%)	5 (13.1)	3 (3.6)	0.068	2 (7.1)	4 (12.1)	0.388
Peripheral vascular disease (%)	4 (9.8)	10 (12.0)	0.707	2 (7.1)	2 (7.1)	1
Low preoperative EF (<40%) (%)	2 (4.9)	10 (12.0)	0.207	2 (7.1)	1 (3.6)	0.553
CABG (%)	7 (17.0)	9 (10.8)	0.334	3 (10.7)	3 (10.7)	1
Previous cardiac surgery (%)	3 (7.3)	5 (6.0)	0.785	3 (10.7)	1 (3.6)	0.299

NYHA: New York Heart Association; CKD: chronic kidney disease; EF: ejection fraction; CABG: coronary artery bypass grafting

Fig. 2 Kaplan–Meier curves of survival and reoperation in patients aged 60 to 70 years before and after propensity score matching.

hemorrhage between M and B groups. The rate of thromboembolism was higher in the M group (M: 0.58% vs B: 0.35% patient per year, $p < 0.001$) and the rate of hemorrhage was higher in the M group (M: 0.34% vs B: 0.12% patient per year, $p < 0.001$).

Discussion

There have been only two large randomized studies comparing the outcomes of M and B valves, and both were performed in the late 1970s: the Edinburgh Heart Valve Trial²⁾ and the Veterans Affairs (VA) Trial.³⁾ Both randomized studies had roughly similar findings, namely, higher bleeding and lower mortality/reoperation with the use of M valves. These data are quite consistent with the current reports in summary. In 2009, a randomized study conducted by Stassano et al. in patients aged

55 to 70 years (which they regarded as the threshold age range) yielded almost the same results as the previous two randomized studies.⁴⁾ The term “threshold age” is the age at which an implanted bioprostheses will likely outlive the patient.⁵⁾

In this study, the use of B valves markedly increased from 55% between 1995 and 2004 to 71% between 2005 and 2013. This was primarily due to the rapid increase in the number of elderly patients. In particular, the number of patients over 70 years of age increased from 30% between 1995 and 2004 to 60% between 2005 and 2013. In 2013, in Japan, bioprostheses accounted for 78% of all valves implanted in the aortic position, whereas in 2003 they accounted for only 38%; in the mitral position in 2013, bioprostheses accounted for 42% of all valves implanted, whereas only 23% in 2003.⁶⁾ Japan has the world's fastest aging population. Japan is predicted to

change from an aging society (the proportion of the population of those 65 years of age or older at 7% or higher) to an aged society (the proportion of the population of those 65 years of age or older at 14% or higher) in 24 years, whereas in France, Sweden, and the UK, this change is predicted to occur in 115, 85, and 47 years, respectively ("World Population Prospects: The 2008 Revision Population Database," United Nations). Bioprostheses are widely believed to be inferior to mechanical valves in terms of durability and they are associated with a significantly higher rate of reoperation than mechanical prostheses. Recently, however, there have been several papers that recommended B valves for patients younger than 65 years because of its improved durability.⁷⁻¹³⁾ In addition, the revised American Heart Association and American College of Cardiology guidelines released in 2014 recommend either a B or a M valve in patients between 60 and 70 years of age (Level of Evidence: B), a B valve in patients aged more than 70 years, and an M valve in patients aged less than 60 years (Level of Evidence: B).¹⁴⁾ On the other hand, there have been some reports that did not support lowering the cutoff age for B valves to less than 65 years because of insufficient evidence.¹⁵⁻¹⁷⁾ Forcillo et al. found that the rate of freedom from reoperation for SVD of the Carpentier-Edwards pericardial valve averaged 60% and 30% at 15 and 20 years after surgery, respectively, in patients younger than 60 years of age compared with 90% at 15 years after surgery in patients 60 to 70 years of age and 99% at 10 years after surgery in patients older than 70 years of age.¹⁸⁾ Aupart et al. reported that actuarial freedom from SVD at 18 years varied from 99% in patients aged 70 years to 77% in those aged 60 to 70 years, and 45% in patients younger than 60 years and patient age was the only factor to influence durability.¹⁹⁾ Hanania suggested that M valves should be recommended to all the patients aged less than 70 years because of their greater life expectancy and risks associated with reoperation.²⁰⁾ Concerning the risk of reoperation, Potter et al. demonstrated that the risk of the reoperation is similar to that in primary AVR patients with a mean age of 64 years.²¹⁾ van Geldorp et al. reported that lifetime risk of reoperation was 25% with a B valve versus 3% with a M valve for patients aged 60 years.¹²⁾

In 2013, Japanese women and men aged 60 years can expect to live another 28.5 and 22.8 years; at 65 years, they can expect to live another 19.1 and 24.0 years; and at 70 years, they can expect to live another 19.6 and 15.3 years, respectively. Thus, patients aged between 65

and 70 years who undergo AVR can expect to outlive their bioprostheses, especially female patients, and there is a high probability that they will have to undergo reoperation as octogenarians. In this study, most staff surgeons in our facility followed the current Japanese guidelines and implanted M valves in patients 60 to 65 years of age during the study period despite the low risk of reoperation.²¹⁾ Survival and freedom from reoperation were comparable between the two groups after propensity score matching preoperative characteristics. The most important concern when choosing valves in patients 60 to 70 years of age is not the risk of reoperation but the possibility of reoperation, which the patient will receive in his or her 80s. With this in mind, most patients in our facility tended to avoid B valves despite the fact that B valves eliminate the risks of lifelong anticoagulation. Elderly high-risk patients with a degenerative bioprosthesis may be suitable for valve-in-valve implantation,²²⁻²⁴⁾ but most of the elderly Japanese patients with the implanted small valves (19 mm: 40%, 21 mm: 34%) may be poor candidates for valve-in-valve procedure with the current available technology.^{22,23)}

Arom et al. reported a hemorrhage rate of only 0.48% per year and a thromboembolic rate of 0.8% per year with a target INR of 1.8 to 2.5.²⁵⁾ Torella et al. reported that a low INR range of 1.5 to 2.5 resulted in a similar rate of thromboembolic events and a significant reduction in bleeding complications compared with the standard range INR of 2.0 to 3.0.²⁶⁾ Stassano et al. did not find any difference in the rate of bleeding between M and B valves with a target INR of 2.0 to 2.5.⁴⁾ In the VA trial, Hammermeister et al. suggested that a lower level of anticoagulation expected lower bleeding rate and M valves would be beneficial in patients aged less than 65 years.³⁾ In Japan, the target INR is lower than that of most Western countries.^{24,25)} The INR was maintained between 1.5 and 2.6 in this study and the rate of bleeding or thromboembolism showed less frequency.²⁷⁾ The results underscored the efficacy of the anticoagulation regimen and call into question the belief that bioprostheses are associated with a lower embolic rate.

The main limitation of this study is that it was not a randomized but retrospective comparison between B and the M valves. The relatively small size of the cohort and the use of multiple types of prosthetic valves in a single institution also potentially confounded the results. It remains unclear whether the durability and function differ among the different types of B and M valves used in this study. To answer these questions, prospective randomized

trials are needed. Nevertheless, the present valve choices under the current Japanese guidelines reflected the physician's real thinking for small Japanese patients living in a rapidly aging and long-living society.

In summary, the current strategy of aortic valve choice based on the Japanese guidelines that recommend a B valve for patients more than 65 years of age has provided excellent long-term results so far. But both physicians and patients must understand that implanting B valves in patients around the criteria age increases the chance of that patient having to undergo reoperation in their 80s, and that this risk might outweigh the risks of chronic anticoagulation (especially when these risks have been shown to be lower in Japan than elsewhere). Moreover, over 70% of B valves were small valves (label size ≤ 21 mm) and those valves may not be amenable to the transcatheter valve-in-valve procedure with the current available technology. We believe that the criteria age of 65 years is suitable and should not be lowered to take into account the increasing longevity of the Japanese population.

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