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Aortic Valve Replacement

A Prospective Randomized Evaluation of Mechanical Versus Biological Valves in Patients Ages 55 to 70 Years

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Objectives The aim of this study was to determine long-term results between bioprosthetic (BP) and mechanical (MP) aortic valves in middle-aged patients.

Background It has not been established which is the best aortic valve substitute in patients ages 55 to 70 years. We conducted a randomized study to compare long-term outcomes between BP and MP aortic valves.

Methods Between January 1995 and June 2003, 310 patients were randomized to receive a BP or an MP aortic valve. Primary end points of the study were survival, valve failure, and reoperation.

Results One hundred fifty-five patients received a BP valve, and 155 patients received an MP valve. Four patients died, perioperatively, in the MP group (2.6%), and 6 patients died in the BP group (3.9%, $p = 0.4$). At late follow-up (mean 106 ± 28 months) 41 patients died in the MP group and 45 patients died in the BP group ($p = 0.6$). There was no difference in the survival rate at 13 years between the MP and BP groups. Valve failures and reoperations were more frequent in the BP group compared with the MP group ($p = 0.0001$ and $p = 0.0003$, respectively). There were no differences in the linearized rate of thromboembolism, bleeding, endocarditis, and major adverse prosthesis-related events (MAPE) between the MP and BP valve groups.

Conclusions At 13 years, patients undergoing aortic valve replacement either with MP or BP valves had a similar survival rate as well the same rate of occurrence of thromboembolism, bleeding, endocarditis, and MAPE, but patients who had undergone aortic valve replacement with BP valves faced a significantly higher risk of valve failure and reoperation. (J Am Coll Cardiol 2009;54:1862–8) © 2009 by the American College of Cardiology Foundation

According to the Adult Cardiac Surgery Database, in the U.S. 17,592 aortic valve replacements (AVRs) and 14,957 AVRs with concomitant coronary artery bypass graft (CABG) were performed in 2007 (personal communication, STS Adult Cardiac Surgery National Database, The Society of Thoracic Surgeons, Chicago, Illinois, May, 2008). Usually these patients arrive at surgery already knowing the type of valve best suited to them, because they have had a thorough conversation with the cardiac surgeon. Nevertheless, in clinical practice we encounter patients who, even after a detailed explanation concerning the pros and cons of the mechanical (MP) and biological (BP) valves, are baffled about the decision and leave the responsibility of their valve choice entirely to the surgeon's experience.

But, although there is wide consensus on the type of valve to be put in younger and in older patients, aortic valve choice in the ages between 55 and 70 years is very difficult, because in this age span patients are no longer truly young and not yet truly old. This is the "threshold age" where it is difficult to balance the risk of the anticoagulation therapy with the need for a reoperation (1); furthermore, this age span comprises a consistent number of patients in need of AVR, and as of 2006, the American College of Cardiology/American Heart Association Practice Guidelines do not shed clear light on the best valve choice (2).

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Therefore, we thought that in this particular age group and only with patients who left the choice of their valve to the surgeon, a randomization would be possible and meaningful.

In this study we investigated clinical outcomes after a randomized insertion of a BP or MP aortic valve in 55- to 70-year-old patients who dictated to us the choice of their aortic prosthesis.

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Methods

From January 1995 to June 2003, 1,120 patients ages 55 to 70 years underwent AVR at 2 centers. Seven hundred twenty-eight patients (65%), after an exhaustive conversation with the surgeon, had a clear idea of which valve type they wanted, whereas 392 patients (35%) were still hesitant about the valve choice. To these patients we explained in detail the aim of our study. After adequate (transthoracic and/or transesophageal) echocardiographic examination, 31 patients with an aortic annulus <21 mm were excluded. Thirty-four patients, although wavering, did not give their consent to participate in the study, whereas 327 patients accepted. After written consent was obtained, a closed envelope (containing a letter "M" for mechanical or a letter "B" for biological) was opened, and the type of prosthesis was told to the patient at least 24 h before surgery; therefore the patient was fully aware of the type of valve chosen. Seventeen patients were further excluded either because they subsequently changed their mind (n = 10) or because of annulus mismatch at surgery (n = 7). Thus, 310 patients formed the basis of our study.

A power calculation estimated that approximately 155 patients/group were required to have a minimum of 80% power to detect a 10% difference in mortality between the 2 groups with a 2-sided alpha of 0.05. This power calculation assumed a probability of death at 10 years after AVR to be approximately 60% (3).

Patients considered for this study had not undergone previous cardiac surgery procedures, did not have active endocarditis, did not have aortic root disease, and did not have contraindications to warfarin anticoagulation. Only single AVR patients with or without CABG were enrolled on the grounds that concomitant procedures (mitral and/or tricuspid, ascending aorta) might significantly increase the operative risk and make the results more difficult to interpret. Patients with concomitant CAGB were included, because they constitute a large fraction of those undergoing AVR in our center as well as in others (4–6). Because we could randomize only patients who dictated their valve choice to us, to reach a meaningful number of patients, these were enrolled in 2 centers whose surgeons had received the same surgical training and shared the same surgical indications. The protocol was approved by the institutional review board, and each patient provided written informed consent before enrollment.

During the 8-year period of this study, the following aortic bioprostheses were used: 93 Carpentier-Edwards SAV (Edwards Lifesciences, Irvine, California) and 62 Carpentier-Edwards Pericardial. The aortic MPs used were: 107 St. Jude Medical (St. Jude Medical, Inc., St. Paul, Minnesota) and 48 CarboMedics (Sorin SpA, Milan, Italy). These valves were chosen because they were the most commonly used at our centers.

The AVR was undertaken through a median sternotomy, with standard cardiopulmonary bypass under mild hypothermia (32°C), with cold blood cardioplegia. All valves (either BP or MP) were implanted with interrupted horizontal mattress sutures with pledgeted 2-0 nonabsorbable braided polyester.

Patients with aortic MPs postoperatively received lifelong warfarin anticoagulation, with a target of the international normalized ratio (INR) of 2.0 to 2.5. Patients with aortic bioprostheses received warfarin as an anticoagulant for 8 to 12 weeks only with the same target of INR.

Abbreviations and Acronyms

AVR = aortic valve replacement
BP = biological prosthesis
CABG = coronary artery bypass graft
INR = international normalized ratio
MAPE = major adverse prosthesis-related events
MP = mechanical prosthesis
NYHA = New York Heart Association
VA = Veterans Administration

Patients were seen annually by a cardiac surgeon of our teams. Missing information was completed with the patient's physician and/or his or her family. The follow-up was closed on June 2008 and was 98.6% complete.

Study end points. Primary study end points were survival, structural valve deterioration (defined as valve failure), and reoperation. We reported overall, cardiac-related, and valve-related mortality. Sudden, unexplained deaths were included in valve-related mortality.

Secondary end points were the occurrence of major adverse prosthesis-related events (MAPE): thromboembolism, bleeding, endocarditis, structural valve deterioration, and nonstructural dysfunction (pannus and paravalvular leak).

These complications were defined according to the guidelines for reporting mortality and morbidity after cardiac valve intervention (7).

Statistical analysis. Continuous data are presented as mean ± SD. The Fisher exact test (for sparse data) or chi-square test was used to compare categorical variables, whereas *t* tests (Mann-Whitney *U* test) were used to compare continuous variables between valve groups. Two-tailed tests of significance are reported, and p values <0.05 are considered statistically significant. The rate of valve-related events, such as thromboembolism, bleeding, and valve failure, was calculated with linearized rates expressed as events/100 patient-years of follow-up and reported with a 95% confidence interval. The likelihood ratio test was used to compare the linearized rates between the valve groups. A Cox proportional hazard regression model was used to analyze a set of time-dependent covariates associated with late cardiac-related mortality. Kaplan-Meier analysis was used to study patient survival and event-free status, with the log-rank test (Cox-Mantel) to ascertain differences between the groups. Data were analyzed by SPSS version 14.0 for Windows (SPSS, Inc., Chicago, Illinois).

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Table 1 Pre-Operative and Perioperative Patient Characteristics

Variables	MP (n = 155)	BP (n = 155)	p Value
Age, yrs	64.0 ± 7.6	63.5 ± 3.9	0.4
Male	66 (42.5)	78 (50.3)	0.2
NYHA functional class	3.0 ± 1.3	3.0 ± 0.7	0.9
NYHA functional class III or IV	119 (76.8)	117 (75.5)	0.9
Diabetes	23 (14.8)	19 (12.3)	0.6
COPD	43 (27.7)	39 (25.2)	0.7
Renal failure	10 (6.5)	8 (5.2)	0.8
Peripheral vascular disease	21 (13.5)	18 (11.6)	0.7
EF pre-operative (%)	47.8 ± 12.0	48.7 ± 9.8	0.3
EF <30%	12 (7.7)	11 (7.1)	0.8
Urgent or emergency status	11 (7.1)	12 (7.7)	0.9
Coronary artery disease	41 (26.4)	52 (33.5)	0.5
Previous myocardial infarction	8 (5.2)	11 (7.1)	0.6
Median valve size, mm	23	23	1
CABG	36 (23.2)	43 (27.7)	0.4
Cardiopulmonary bypass time, min	74.2 ± 9.2	73.5 ± 9.9	0.5
Aortic cross-clamp time, min	53.5 ± 10.8	52.9 ± 9.3	0.6

Values are presented as mean ± SD or n (%).
BP = biological prosthesis; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; MP = mechanical prosthesis; NYHA = New York Heart Association.

Results

Patient variables, including clinical characteristics, are depicted in Table 1. There were no clinical or periprocedural differences between the MP and BP groups. In both groups, median valve size implanted was 23 mm. Four patients died, perioperatively (30 days), in the MP group (2.6%), and 6 patients died in the BP group (3.9%, p = 0.4). Causes of hospital mortality and early complications are depicted in Table 2.

At late follow-up (range 43 to 161 months, mean 106 ± 28 months), 41 patients died in the MP group and 45 patients died in the BP group (p = 0.6). Overall mortality, causes of mortality, and the occurrence of MAPE are given in Table 3. Linearized rates of valve-related events are shown in Table 4. There were no differences in linearized rate of thromboembolism, bleeding, endocarditis, valve thrombosis, and occurrence of MAPE between the MP and BP valve groups, although a statistical trend (p = 0.08) for increased bleeding in the MP group was noted.

Table 2 Hospital Results

Variables	MP (n = 155)	BP (n = 155)	p Value
Hospital mortality	4 (2.6)	6 (3.9)	0.4
Causes			
Perioperative myocardial infarction	1 (6.4)	2 (1.3)	0.5
Low cardiac output syndrome	2 (1.3)	3 (1.9)	0.5
Cerebrovascular accident	1 (6.4)		0.5
Pulmonary complications		1 (6.4)	0.5
Complications			
Inotropic support	54 (34.9)	61 (39.3)	0.5
Intra-aortic balloon pump	2 (1.3)	4 (2.6)	0.5
Myocardial infarction	6 (3.9)	8 (5.2)	0.8
Neurological complications	6 (3.9)	5 (3.2)	0.9
Respiratory complications	11 (7.1)	13 (8.4)	0.8
Prolonged intubation (>48 h)	13 (8.4)	9 (5.8)	0.5
Renal failure	2 (1.3)	1 (6.4)	0.5
Blood losses (ml)	690 ± 340	730 ± 290	0.3
Reoperation for bleeding	3 (1.9)	4 (2.6)	0.5
ICU stay, days	2.2 ± 0.6	2.3 ± 0.7	0.2
Prolonged ICU stay (>10 days)	3 (1.9)	4 (2.6)	0.5
LOS, days	6.8 ± 1.1	6.9 ± 1.2	0.1

Values are presented as n (%) or mean ± SD.
ICU = intensive care unit; LOS = length of stay; other abbreviations as in Table 1.

Table 3 Late Results

Variables	MP (n = 149)	BP (n = 147)	p Value
Overall mortality	41 (27.5%)	45 (30.6%)	0.6
Cardiac-related mortality	25 (16.7%)	32 (21.7%)	0.3
Valve related mortality	10 (6.7%)	12 (8.1%)	0.8
MAPE	35 (23.4%)	42 (28.6%)	0.4

MAPE = major adverse prosthesis-related events (valve-related mortality not included); other abbreviations as in Table 1.

At follow-up, we also observed that, although all patients in the MP group were receiving lifelong anticoagulation with warfarin sodium, in the BP group a substantial number of patients, 31 (21.1%), were receiving warfarin sodium, and 38 (25.8%) were receiving antiaggregation with ticlopidine or aspirin at discretion of the treating physician. In this BP group, 5 patients with warfarin (16.1%), 3 patients with antiaggregation (7.9%), and 1 patient without anticoagulation/antiaggregation (1.3%) suffered from bleeding episodes. There was no difference in bleeding between patients taking warfarin and patients taking antiaggregation ($p = 0.2$), whereas there was difference in bleeding between patients taking warfarin versus other patients of the same group ($p = 0.02$). The bleeding rate in patients with BP who were not receiving warfarin, 4 of 116 patients (3.4%), was less than in patients with MP with warfarin, 19 of 149 (12.7%) ($p = 0.001$).

Valve failures and reoperations were more frequent in the BP group compared with the MP group: $p = 0.0001$ and $p = 0.0003$, respectively (Table 4).

Cox hazard regression showed that worse New York Heart Association functional class ($p = 0.01$), adjunct of myocardial revascularization procedures ($p = 0.001$), and low ejection fraction ($p = 0.05$) were independent predictors of late mortality (Table 5).

At 160 months there were no differences in overall ($p = 0.2$) and cardiac-related mortality ($p = 0.3$) between MP and BP (Figs. 1 and 2).

Occurrence of all MAPE, although never reaching a significant difference between MP and BP (0.1), started to diverge beginning at 10 years (Fig. 3), when valve failures and reoperations became significantly more frequent in BP valve recipients compared with MP valve recipients.

Table 4 Linearized Rate of Valve-Related Events

Variables	MP (n = 149) %/pt-yr (95% CI)	BP (n = 147) %/pt-yr (95% CI)	p Value
Thromboembolism	0.54 (0.14–0.94)	0.24 (0.03–0.51)	0.3
Bleeding	1.47 (0.81–2.13)	0.72 (0.25–0.19)	0.08
Endocarditis	0.38 (0.04–0.72)	0.24 (0.03–0.51)	0.7
Valve failure	0	2.17 (1.35–2.98)	0.0001
Valve thrombosis	0.23 (0.03–0.49)	0	0.2
Nonstructural dysfunction	0.23 (0.03–0.49)	0.24 (0.03–0.51)	0.6
Reoperation	0.62 (0.19–1.05)	2.32 (1.48–3.18)	0.0003

CI = confidence interval; other abbreviations as in Table 1.

Table 5 Cox Hazards Regression: Independent Predictors of Late Mortality

Covariates	p Value	Hazard Ratio	95% CI
Age	0.7	1.010	0.947–1.077
Sex	0.8	0.960	0.580–1.587
Mechanical valve	0.2	0.730	0.446–1.196
NYHA functional class	0.01	1.063	1.018–1.060
Urgent or emergency operation	0.7	1.172	0.506–2.713
Low EF	0.05	1.476	1.034–2.107
CABG	0.001	3.472	2.063–5.844
Diabetes mellitus	0.5	0.784	0.382–1.608
COPD	0.1	1.915	0.828–4.432
Chronic renal failure	0.9	1.050	0.388–2.843

Abbreviations as in Table 1.

Discussion

This prospective study of 310 patients between 55 and 70 years of age who underwent AVR with MPs and BPs indicates that: 1) overall mortality is similar between MP and BP groups; 2) the incidences of valve failures and reoperations are greater in the BP group; and 3) the incidence of MAPE is similar in MP and BP groups.

Randomized clinical trials represent the best evidence regarding the relative risks and benefits of tissue and MP valves, because they avoid bias and confounding incidental to nonrandomized studies. But randomized studies are difficult to carry out, because patients in need of valve replacement arrive at surgery already knowing the type of valve chosen. Therefore, these patients cannot be forced into a randomized study. At the same time, even in the case in which the choice is left to the surgeon's experience, usually surgeons prefer MP valves in young patients and BP valves in older patients, although there might be important comorbidities or other patient preferences that favor one type or another prosthetic valve. Therefore, we could randomize only middle-aged patients in whom it is really difficult to balance the risk of anticoagulation therapy with the need for a reoperation. This age span comprises a large number of patients in need of AVR (4–6).

There have been only 2 randomized studies that have compared survival and valve-related complications associated with the use of MP or BP valves, and these studies have helped physicians in the choice of the type of valve best suited to their patients (2,3,8–10). However, these studies did not focus on a specific age group, had a considerable number of redo-sternotomy patients at initial valve operation, had a perioperative mortality not acceptable for the current times, and dealt with valve types no longer in use, thus potentially biasing the choice of one valve type versus the other.

Mortality. In our study there were no differences in mortality at 5, 10, and 13 years. In the Veterans Administration (VA) Study, patients who underwent AVR with MPs had a significantly lower 15-year mortality rate than those with a BP valve (8). In the Edinburgh Heart Valve Trial, at 12

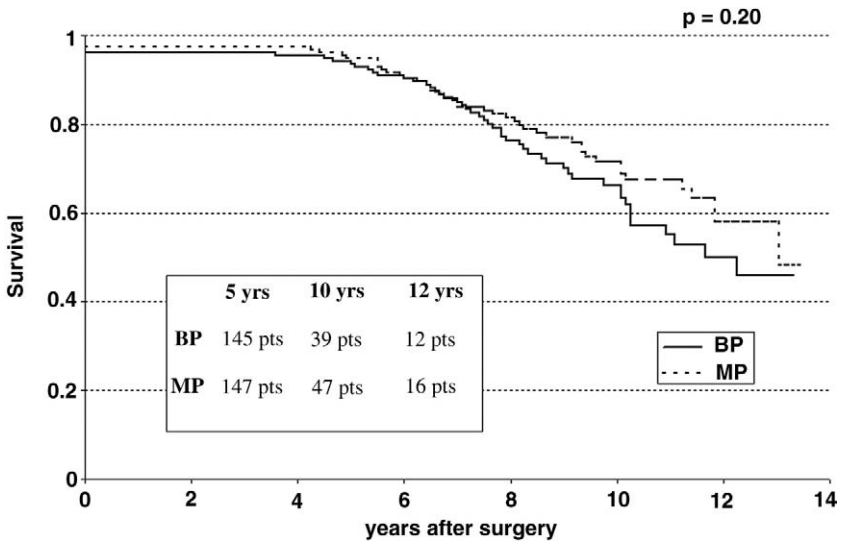

Figure 1 Overall Survival of Patients Who Received Either MP or BP Valves

BP = biological prosthesis; MP = mechanical prosthesis.

years there was a survival advantage of the MP valve group compared with the BP valve group, but this advantage disappeared at 20 years (10). Brown et al. (5), in a 1-to-1 study, matched patients age 50 to 70 years who had undergone AVR and found a 10-year survival of 68% in the MP group and 50% in the BP group ($p < 0.1$). Also, Lund and Bland (4) in a meta-analysis with regression analyses did not find significant differences in the death rate between MP and BP valves when corrected for age.

Valve failure and reoperation. In our study the only difference between MP and BP valves was related to valve failures and reoperations, both events penalizing the bioprostheses.

In the VA randomized study the incidences of primary valve failure and reoperation after AVR were significantly greater in the BP valve group ($p = 0.0001$ and $p = 0.0003$, respectively) (8). In the 20-year Edinburgh trial, reoperation was more common in BP aortic valve patients compared

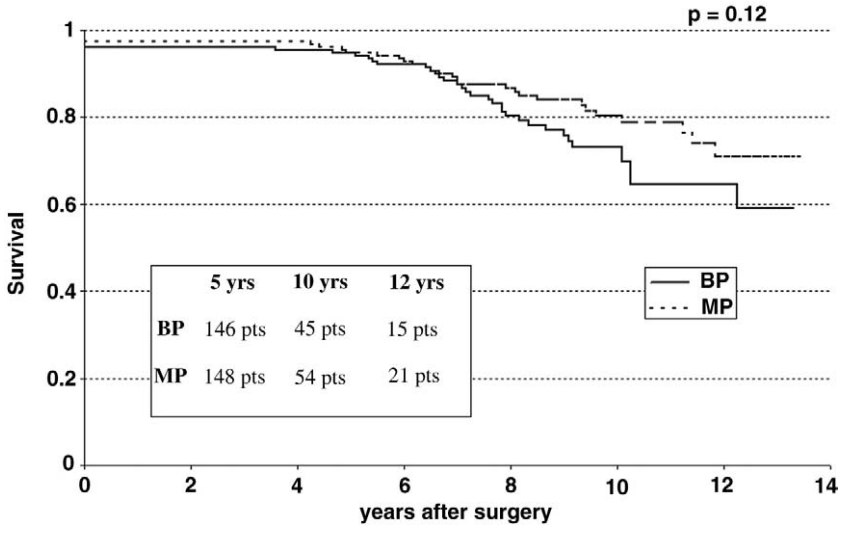

Figure 2 Cardiac-Related Survival of Patients Who Received Either MP or BP Valves

Abbreviations as in Figure 1.

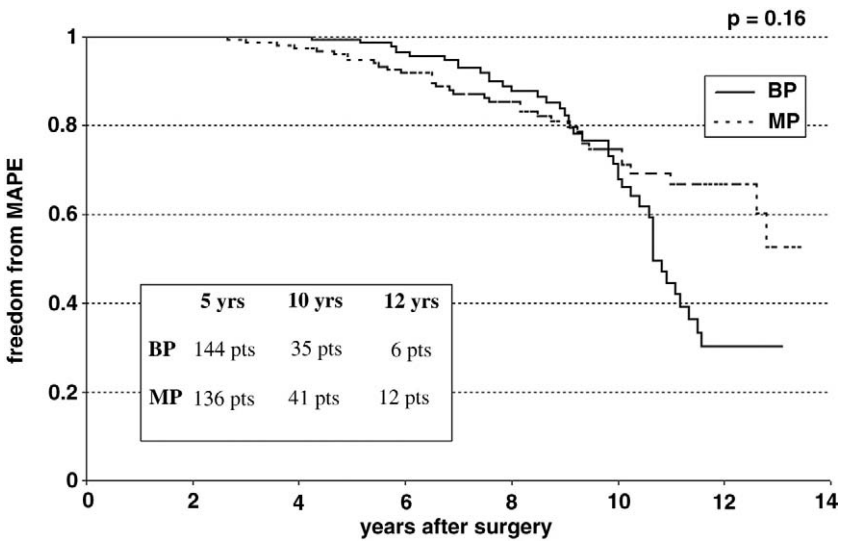

Figure 3 **Freedom From MAPE for Patients Who Received Either MP or BP Valves**

MAPE = major adverse prosthetic-related events; other abbreviations as in Figure 1.

with MP aortic valve patients (p = 0.0001) (10). Freedom from reoperation on the aortic valve was not significantly different between MP and BP valve patients at 10 years in the 1-to-1 matched patients study of Brown et al. (5). We observed that the risk of valve failure with consequent reoperation begins to rise by 10 years and increases progressively with time, without observing a leveling off or reduction in risk of tissue valve failure. Khan et al. (11) in a 20-year comparison of tissue and MP valve found similar results.

Other valve-related complications. The linearized incidence of the other prosthesis-related events (i.e., thromboembolism, bleeding, endocarditis, and valve thrombosis) failed to show differences between the 2 types of valve.

Interestingly, we did not find differences in the rate of bleeding between MPs and BPs, although we observed a trend (p = 0.08) toward increased bleeding in the MP group. Hammermeister et al. (8) in the VA trial observed a greater bleeding rate in the MP aortic group than in the BP aortic group (p = 0.0001). Also, in the Edinburgh trial, the incidence of all episodes (major and minor) of bleeding was significantly higher in the MP aortic valve group compared with the BP aortic valve group (10). Brown et al. (5) observed hemorrhagic complications in 15% of patients with MP valves and in 7% with BP valves (p = 0.01). The lack of difference in bleeding episodes between MP and BP valves might be ascribed either to our low-intensity anticoagulation in MP valve patients or to the fact that in the BP valve patients group a significant number of patients were receiving warfarin sodium or antiaggregation at late follow-up. Our anticoagulation protocol with a target of the INR of 2.0 to 2.5 is somewhat less than that usually recommended, and this lower INR target might have implications regarding the ability to extrapolate these data to other sites. In 2 randomized trials with prosthetic heart valves, low-intensity anticoagulation resulted in a lower bleeding rate than in patients with the standard dose of anticoagulation (12,13). With increasing time from operation, a greater number of our BP valve replacement patients were placed on anticoagulation/antiaggregation therapy by their cardiologist and/or physician due to many causes: atrial fibrillation, transient ischemic attack, chamber enlargement, and so on. Therefore, implantation of a BP valve does not ensure that in the future the patient will avoid anticoagulation/antiaggregation and does not protect the patient from the "normal" occurrence of gastrointestinal, urogenital, and cerebral bleeding (4).

The incidence of thromboembolism did not differ between the 2 groups, underscoring the efficacy of the anticoagulation regimen and maybe disproving the concept that bioprostheses are associated with a lower embolic rate. A possible explanation is that, as tissue valves deteriorate, they might become a source for thromboembolism (14); other causes might be the insurgence of atrial fibrillation, enlargement of heart chambers associated with low ejection fraction, and so on.

There is uncertainty as to whether the adjunct of coronary revascularization in patients undergoing AVR leads to long-term survival similar to that of patients without coronary revascularization requiring AVR. In the present report, the adjunct of a myocardial revascularization procedure influenced late mortality. Kvidal et al. (15) observed that patients with concomitant AVR and CABG showed decreased long-term survival. However, these patients were older at the time of operation. Consequently, age adjust-

ment reduced the effect on observed survival, and there was no significant difference in relative survival (15).

Study limitations. Due to our randomization protocol, the population sizes were small. Thus, the power to comment on clinical events might be somewhat limited.

All post-operative medications were at the discretion of the treating physician and, therefore, might have impacted the clinical outcomes differently in the 2 groups.

Patient quality of life was not measured, and this might be an important limitation of this study.

Conclusions

AVR with MP valves in middle-aged patients seems to be an advantageous solution. Further investigation and data collection will allow the assessment of valve performance and the quality of life that they offer over a more extended period of time.

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Key Words: aortic valve replacement ■ biological valve ■ mechanical valve ■ valve outcomes.