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Outcomes 15 Years After Valve Replacement With a Mechanical Versus a Bioprosthetic Valve: Final Report of the Veterans Affairs Randomized Trial

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OBJECTIVES The goal of this study was to compare long-term survival and valve-related complications between bioprosthetic and mechanical heart valves.

BACKGROUND Different heart valves may have different patient outcomes.

METHODS Five hundred seventy-five patients undergoing single aortic valve replacement (AVR) or mitral valve replacement (MVR) at 13 VA medical centers were randomized to receive a bioprosthetic or mechanical valve.

RESULTS By survival analysis at 15 years, all-cause mortality after AVR was lower with the mechanical valve versus bioprosthesis (66% vs. 79%, $p = 0.02$) but not after MVR. Primary valve failure occurred mainly in patients <65 years of age (bioprosthesis vs. mechanical, 26% vs. 0%, $p < 0.001$ for AVR and 44% vs. 4%, $p = 0.0001$ for MVR), and in patients ≥65 years after AVR, primary valve failure in bioprosthesis versus mechanical valve was 9 ± 6% versus 0%, $p = 0.16$. Reoperation was significantly higher for bioprosthetic AVR ($p = 0.004$). Bleeding occurred more frequently in patients with mechanical valve. There were no statistically significant differences for other complications, including thromboembolism and all valve-related complications between the two randomized groups.

CONCLUSIONS At 15 years, patients undergoing AVR had a better survival with a mechanical valve than with a bioprosthetic valve, largely because primary valve failure was virtually absent with mechanical valve. Primary valve failure was greater with bioprosthesis, both for AVR and MVR, and occurred at a much higher rate in those aged <65 years; in those aged ≥65 years, primary valve failure after AVR was not significantly different between bioprosthesis and mechanical valve. Reoperation was more common for AVR with bioprosthesis. Thromboembolism rates were similar in the two valve prostheses, but bleeding was more common with a mechanical valve. (J Am Coll Cardiol 2000;36:1152–8) © 2000 by the American College of Cardiology

By the mid-1970s it was recognized that the major clinical problem with mechanical valves was thromboembolism, and the major problem with bioprosthesis was limited durability due to valve degeneration. Thus, it became necessary to compare outcomes between mechanical valves and bioprostheses; they were and still are the most common heart valve replacement devices. Of the "larger" trials comparing a mechanical valve with bioprosthesis, the Edinburgh trial (533 patients) demonstrated that (1) at 12 years there was a trend toward better survival with the mechanical valve ($p = 0.08$); the Department of Veterans Affairs (VA) trial reported similar outcomes for both mitral valve replacement (MVR) and aortic valve replacement (AVR) at five and 11 years (2,3).

This is the final report of the VA randomized trial, and it compares outcomes over an average of 15 years after randomization between mechanical and bioprosthetic heart valves.

METHODS

Between 1977 and 1982, 575 men undergoing single AVR ($n = 394$) or MVR ($n = 181$) were randomized in the operating room to receive either the Bjork-Shiley spherical disc mechanical prosthesis or a Hancock porcine bioprosthetic valve.

Details of the protocol and informed consent procedures, patient population, valve surgery, data collection, eligibility criteria, definition of valve-related complications and list of participating centers, investigators and committee members have been published (2–4). All patients provided written informed consent. A large number of baseline characteristics

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Abbreviations and Acronyms
AVR = aortic valve replacement
MVR = mitral valve replacement
VA = Veterans Affairs

and demographics were examined for differences between the two valve types for AVR and MVR. These included patient characteristics, hemodynamics, left ventricular function, functional class, valve lesion(s) and associated coronary artery disease (2,3). The only two statistically significant differences were in the patients undergoing MVR. There were fewer patients aged <50 years (17% vs. 24%) and more aged >70 years (11% vs. 0%) in the group who received the mechanical valve compared with those who received the porcine bioprosthesis, p = 0.013; additionally, there were more patients with systemic hypertension in the group receiving the mechanical valve (25% vs. 12%, p = 0.022). These differences are not unusual considering the large number of baseline characteristics that were examined. Some patient characteristics for the entire AVR and MVR group are shown in Table 1.

Follow-up procedure. From 1977 to 1985, follow-up procedure for death, valve-related complications, functional status and adequacy of anticoagulation was obtained at semiannual clinic visits. Since then data on death and valve-related complications have been obtained by mailed questionnaires supplemented by telephone calls. Follow-up was terminated September 30, 1995. The completeness of the mortality data has been checked against two national databases on deaths: the VA Beneficiary Identification and Records Locator Subsystem and the National Death Index. Of patients not identified as having died by any of the follow-up mechanisms, all except 16 had one or more mailed questionnaire or telephone contacts for valve-related complications in the final year of the study. The last contact for these 16 patients occurred in 1991 for three patients, 1992 for three patients, 1993 for six patients and January to September 1994 for four patients. Thus, follow-up for valve-related complications through the final year of the study, the 18th year since the initial randomization, was 97% complete (559 of 575).

Table 1. Selected Patient Demographics and Characteristics at Baseline

	AVR		MVR	
No. of patients	394		181	
Age:				
≤50 years	47	(11.9%)	37	(20.4%)
51–60 years	161	(40.9%)	82	(45.3%)
61–70 years	156	(39.6%)	53	(29.3%)
≥71 years	30	(7.6%)	9	(5.0%)
Smoking	162	(41.1%)	73	(40.3%)
Atrial fibrillation	24	(6.1%)	99	(55.0%)
Paroxysmal nocturnal dyspnea	151	(38.3%)	98	(54.1%)
Dyspnea at rest	88	(22.3%)	59	(32.6%)
NYHA functional class				
Class IV	70	(17.9%)	40	(22.2%)
Class III	206	(52.6%)	118	(65.6%)
Class II and I	116	(29.6%)	22	(12.2%)
Peripheral edema	117	(29.7%)	71	(39.2%)
Pleural effusion	37	(9.7%)	33	(19.0%)
Systemic hypertension	134	(34.0%)	33	(18.2%)
Diabetes	13	(3.6%)	7	(4.3%)
Renal failure (creatinine >2 mg/dL)	27	(6.9%)	8	(4.4%)
LV ejection fraction				
<0.30	4	(1.0%)	0	(0.0%)
0.30–0.50	0	(0.0%)	0	(0.0%)
≥0.51	390	(99.0%)	181	(100.0%)
Associated coronary artery disease (≥50% stenosis)				
Present	104	(26.3%)	53	(29.2%)
CBS: 1-vessel disease	27	(6.8%)	16	(8.8%)
2-vessel disease	36	(9.1%)	20	(11.0%)
3-vessel disease	41	(10.4%)	17	(9.4%)
Other concomitant surgery	152	(38.6%)	65	(35.9%)

AVR = aortic valve replacement; CBS = coronary bypass surgery; LV = left ventricular; MVR = mitral valve replacement; NYHA = New York Heart Association.

Study end points. The two primary study end points were time to death from any cause (including operative death) and time to first occurrence of any of the following valve-related complications (2,3): systemic embolism, clinically important bleeding, prosthetic valve endocarditis, valve thrombosis, nonthrombotic valve obstruction, prosthetic valvular regurgitation (subclassified into perivalvular and central valvular regurgitation) and reoperation on the randomly assigned valve. Definitions of these complications have been published previously (3,4). Primary valve failure was defined as nonthrombotic valve obstruction or central valvular regurgitation.

When a suspected valve-related complication or death was identified, records of the hospitalization were obtained. A subcommittee of three physicians blinded as to the type of randomized valve made the final determination of whether the death or nonfatal event was a complication of the randomized valve; if it was not a valve-related complication, the subcommittee would determine whether the events were due to a cardiac cause, noncardiac cause or that the cause could not be determined. Sudden death without an autopsy or obvious cause was classified as valve-related.

Statistical analyses. Differences in baseline characteristics between the two randomization groups were compared using the *t* test for continuous variables and the chi-square (or Fisher exact test when appropriate) for categorical variables; no adjustment for multiple comparisons was made. Time to death and first valve-related complication were compared between the two randomization groups using the Kaplan-Meier estimator (5) and the log-rank statistic (6). All p values were two-tailed. Results were considered to be statistically significant if the p value was ≤0.05.

RESULTS

Operative mortality. Operative mortality has been described in detail previously; it was 7.7% (44/575) (2). There

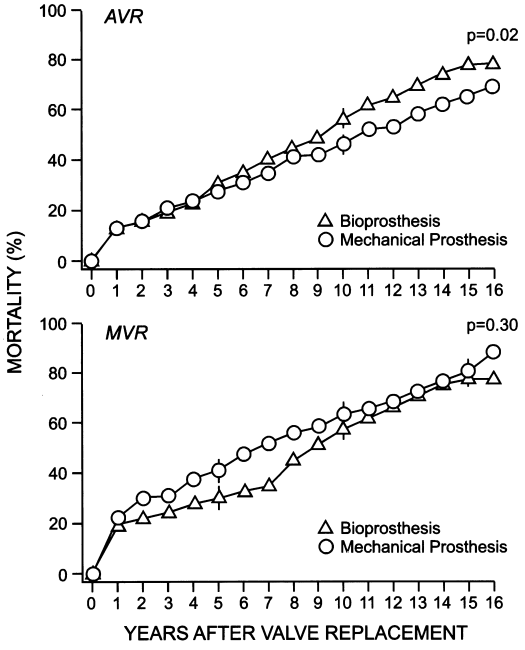

Figure 1. Death from any cause (including operative mortality). AVR = aortic valve replacement; MVR = mitral valve replacement.

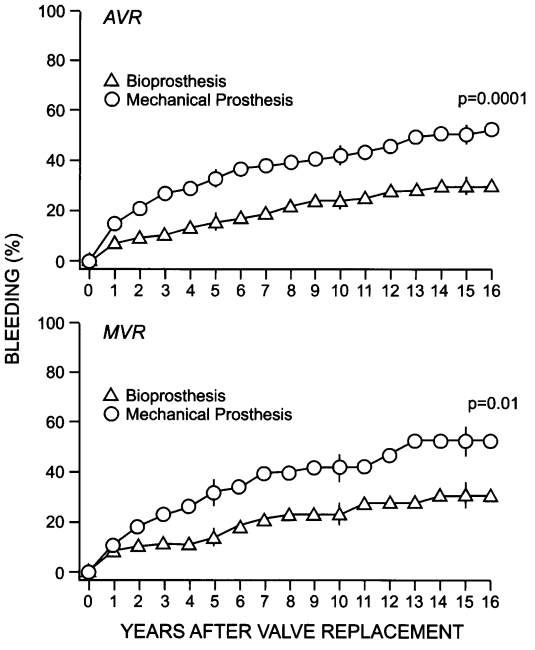

Figure 3. One or more clinically significant bleed(s). AVR = aortic valve replacement; MVR = mitral valve replacement.

were no significant differences between the two randomization groups.

Primary end points of the study. Primary end points are illustrated in Figures 1 through 5 and summarized in Table 2.

Mortality. *All-cause mortality.* Patients undergoing AVR with a mechanical valve had a significantly lower 15-year mortality than those with a bioprosthetic valve (66 ± 3% [mean ± SE] vs. 79 ± 3%, p = 0.02). For MVR, there was no statistically significant difference between the two randomization groups.

Causes of death. The causes of death are summarized in Table 3. For AVR, valve-related deaths accounted for 37%

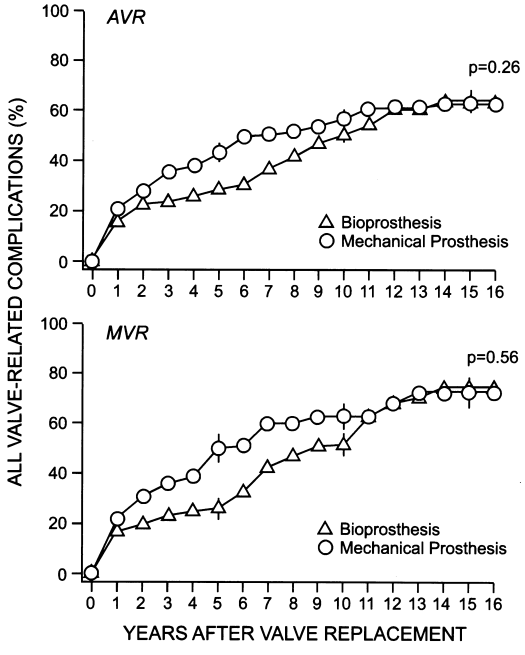

Figure 2. Occurrence of one or more valve-related complications (bleeding, endocarditis, systemic embolism, nonthrombotic valve obstruction, valvular regurgitation or valve thrombosis). AVR = aortic valve replacement; MVR = mitral valve replacement.

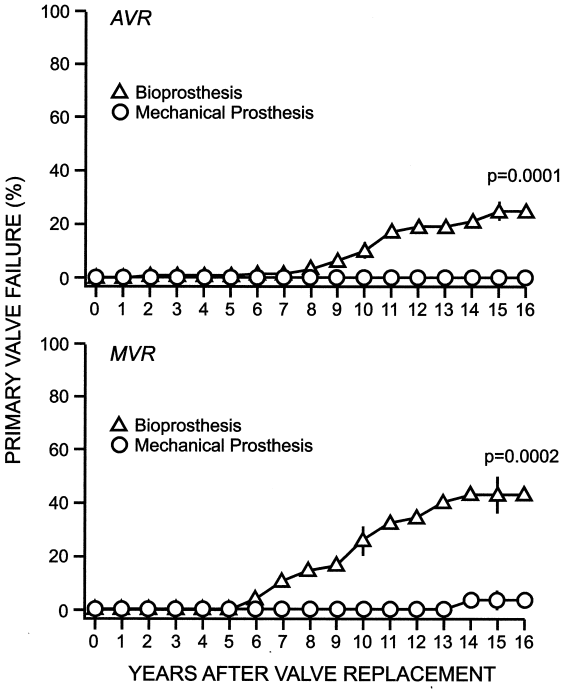

Figure 4. Primary valve failure (nonthrombotic valve obstruction or central valvular regurgitation). AVR = aortic valve replacement; MVR = mitral valve replacement.

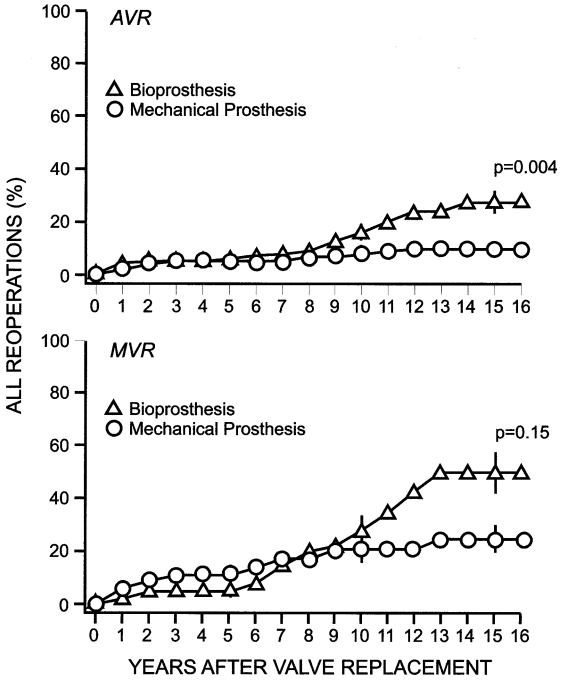

Figure 5. Reoperation for any reason on randomized valve. AVR = aortic valve replacement; MVR = mitral valve replacement.

of all deaths with a mechanical valve and 41% with a bioprosthetic valve. Primary valve failure accounted for 8 of 63 valve-related deaths in the bioprosthetic AVR group and none in the mechanical valve group. For MVR, valve-related deaths accounted for 44% of all deaths in the mechanical valve group and 57% in the bioprosthesis group. Primary valve failure accounted for 9 of 42 valve-related deaths in the bioprosthesis MVR group.

Of valve-related deaths, for AVR with mechanical valve and bioprosthesis, bleeding was the cause in 24% and 11%, respectively, and sudden death was the cause in 35% and 38%, respectively. Of valve-related deaths, for MVR with mechanical valve and bioprosthesis, bleeding was the cause in 25% and 14%, respectively, and sudden death was the cause in 31% and 26%, respectively.

Complications. *All valve-related complications.* There were no statistically significant differences between the two groups for both AVR and MVR.

Systemic embolism, infective endocarditis, valve thrombosis. There were no statistically significant differences between the two groups for both AVR and MVR.

Perivalvular regurgitation. This was more common after MVR with the mechanical valve (17 ± 5% vs. 7 ± 4%, p = 0.05).

Bleeding. There was greater bleeding in the mechanical valve group than there was in the bioprosthetic valve group for both AVR (51 ± 4% vs. 30 ± 4%, p = 0.0001) and for MVR (53 ± 7% vs. 31 ± 6%, p = 0.01).

Primary valve failure. Primary valve failure was significantly greater in those with a bioprosthesis than it was with a mechanical valve, both for AVR (23 ± 5% vs. 0 ± 0%, p = 0.0001) and for MVR (44 ± 8% vs. 5 ± 4%, p = 0.0002). The primary valve failure after MVR with mechanical valve was not due to structural valve deterioration; it was due to incorrect valve placement at the index operation, necessitating removal and replacement at the same procedure.

Virtually all of the primary valve failures occurred in patients <65 years of age (18 of 20 in the AVR group and 20 of 21 in the MVR group).

In a post hoc analysis in those aged <65 years, primary valve failure was greater with bioprosthesis than it was with mechanical valve for AVR (26 ± 6% vs. 0%, p < 0.0001) and also after MVR (44 ± 8% vs. 4 ± 4%, p = 0.0001). In those ≥65 years of age, primary valve failure was not significantly different between a bioprosthesis and the mechanical valve for AVR (9 ± 6% vs. 0%, p = 0.16). The number of patients ≥65 years with MVR is very small (n = 17 for mechanical valve, n = 9 for bioprosthesis); at 15 years primary valve failure rates after MVR were 6 ± 6% for mechanical valve and 20 ± 18% for bioprosthetic valve, p = 0.97.

Reoperations on randomized valve. Reoperation rate was higher after AVR with the bioprosthetic valve than with the mechanical valve (29 ± 5% vs. 10 ± 3%, p = 0.004). After

Table 2. Probability of an Outcome Event at 15 Years After Valve Replacement

	Aortic Valve Replacement			Mitral Valve Replacement		
	Mechanical	Bioprosthetic	p Value	Mechanical	Bioprosthesis	p Value
	n = 198	n = 196		n = 88	n = 93	
Death from any cause	66 ± 3%	79 ± 3%	0.02	81 ± 4%	79 ± 4%	0.30
Any valve-related complication	65 ± 4%	66 ± 5%	0.26	73 ± 6%	81 ± 5%	0.56
Systemic embolism	18 ± 4%	18 ± 4%	0.66	18 ± 5%	22 ± 5%	0.96
Bleeding	51 ± 4%	30 ± 4%	0.0001	53 ± 7%	31 ± 6%	0.01
Endocarditis	7 ± 2%	15 ± 5%	0.45	11 ± 4%	17 ± 5%	0.37
Valve thrombosis	2 ± 1%	1 ± 1%	0.33	1 ± 1%	1 ± 1%	0.95
Perivalvular regurgitation	8 ± 2%	2 ± 1%	0.09	17 ± 5%	7 ± 4%	0.05
Reoperation	10 ± 3%	29 ± 5%	0.004	25 ± 6%	50 ± 8%	0.15
Primary valve failure	0 ± 0%	23 ± 5%	0.0001	5 ± 4%	44 ± 8%	0.0002

n = number of patients randomized; p = significance of difference between mechanical and bioprosthetic valve groups.

Table 3. Causes of Death (% of All Deaths)

	Aortic Valve Replacement		Mitral Valve Replacement	
	Mechanical	Bioprosthetic	Mechanical	Bioprosthetic
Prosthesis related	37%	41%	44%	57%
Cardiac—not prosthesis related	17%	21%	31%	19%
Noncardiac	36%	26%	18%	9%
Undetermined	10%	12%	7%	15%

MVR reoperation was not statistically significantly different between the two randomization groups.

DISCUSSION

The principal long-term findings of this randomized trial are:

1. Use of a mechanical valve resulted in a lower mortality and a lower reoperation rate after AVR.
2. The mortality after MVR was similar with the use of the two prosthetic valve types.
3. There were virtually no primary valve failures with the use of a mechanical valve.
4. Primary valve failure after AVR and MVR occurred more frequently in patients with a bioprosthetic valve, especially in patients aged <65 years.
5. The primary valve failure rate between bioprosthesis and mechanical valve was not significantly different in those aged ≥65 years.
6. Use of a bioprosthetic valve resulted in a lower bleeding rate.
7. There were no significant differences between the two valve types with regard to other valve-related complications, including thromboembolism and all complications.

Mortality. The 15-year mortality was high. This is not surprising because of many adverse patient characteristics at baseline (Table 1), and most of the deaths (>40% to 60%) were not related to the prosthesis (Table 3). Previously, it was emphasized that results of valve surgery with regard to survival, complications, valve function, cardiac function and functional class are dependent on patient-related factors, type of surgery, type of prosthesis and health care delivery factors (7). This is also the case in more recent studies: Of 843 patients undergoing AVR with the Hancock modified orifice valve, 15-year late mortality (i.e., excluding 5% operative mortality) was 72% (8), and, of 841 patients undergoing AVR, the mortality at 10 years was 46% and 50% with the St. Jude mechanical valve and Carpentier Edwards porcine valve, respectively (9). However, one must be very cautious about comparing findings from different studies (10).

In this trial, the Bjork-Shiley tilting-disk mechanical valve was utilized because, at the time of the start of this study, it was very popular, and approximately 360,000 standard valves have been implanted (11,12). It is estimated that there are 38,000 of the Bjork-Shiley CC valves still present in patients (13). There is no good documentation of the superiority for outcomes with "newer" valves as compared with "older" valves (that are still in use) when baseline patient characteristics are identical or at least similar. For example, a recent randomized trial from the U.K. compared the Starr-Edwards valve to the St. Jude valve. Preliminary results showed that at the end of five years, there was no statististically significant difference in outcomes between the two valves (14). A recent study showed no difference in survival or event-free survival at 10 years between the St. Jude valve and bioprosthesis (9). These studies provide data that support the findings in this trial that survival after valve replacement is dependent, to a major degree, on patient-related factors (7).

In this trial, a 15-year follow-up was needed to document a better survival with the mechanical valve. This is not surprising because primary valve failure after AVR with a porcine bioprosthesis begins at about 7 to 8 years and accelerates after 9 to 10 years (Fig. 4). The increased mortality with bioprosthetic versus mechanical valve after AVR was probably due to more deaths from primary valve failure (8 vs. 0). Almost all of the excess deaths with bioprosthesis after AVR occurred in the 10 to 15 year time period, which is a 13% difference over a five-year time period (years 11 through 15).

Valve-related complications. The initial concept that bioprostheses are associated with a lower embolic rate is disproven in patients who have similar baseline characteristics. This is also not surprising because there is a wide range of the incidence of these and other complications with the use of identical valve types (15,16) indicating complication rates are most likely due to patient related factors in the different studies and to differences in criteria of diagnosis and ascertainment of complications (7,10). The patients in this trial had one or more risk factors for thromboembolism, which would be expected to be equally distributed between the mechanical and bioprosthetic groups in a randomized trial such as the present one. Furthermore, the follow-up in this trial was 97% complete, and the determination of valve-related complications and causes of death were made by consensus of a committee of three who were blinded to valve type.

With the use of a mechanical valve, there were no primary valve failures with AVR and only one with MVR; the latter was not due to structural valve deterioration. The incidence of primary valve failure, reoperation and mortality was lower after AVR with use of the mechanical valve. With a

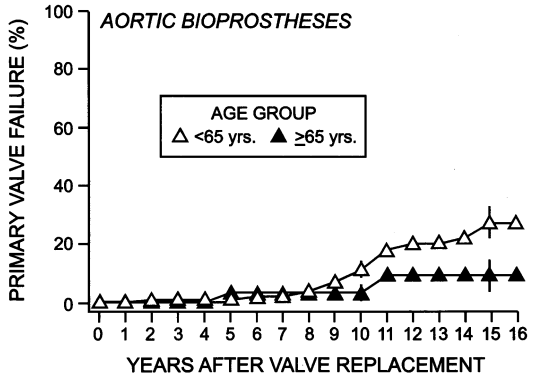

Figure 6. Primary valve failure among aortic valve replacement patients <65 and ≥65 years of age. AVR = aortic valve replacement; MVR = mitral valve replacement.

lower rate of primary valve failure in those aged ≥65 years (Fig. 6), the beneficial effects of the use of mechanical valve for AVR are not likely to occur in those aged ≥65 years. A word of caution with regard to MVR—the numbers of patients with bioprosthetic valve at risk in those aged ≥65 years are too small (n = 17 for mechanical valve, n = 9 for bioprosthetic valve) to be confident about the lower rate of bioprosthetic valve failure. Other studies have documented lower bioprosthetic failure in those in the ranges of ages ≥60 up to ≥70 years (12).

The above noted benefits with use of a mechanical valve were offset by a higher bleeding rate when compared with the bioprosthetic valve. This was the result of at least two factors: 1) as expected, many patients with a bioprosthesis were not anticoagulated; and 2) the level of anticoagulation was excessive because the protocol called for prothrombin time to be maintained at 2.0 to 2.5 times control. This was standard practice in many (but not all) centers in the U.S. and resulted in variable levels of anticoagulation due to variations in the thromboplastin activity used in the assay. In two randomized trials with prosthetic heart valves of low-intensity versus high-intensity anticoagulation, low-intensity anticoagulation resulted in similar thromboembolism rates but a lower bleeding rate (17,18). In the Edinburgh trial the incidence of bleeding was 1% to 1.5% per year (1). In 928 patients with atrial fibrillation, 25% of whom had valve disease, protimes greater than 2.0 did not result in further reduction of emboli but produced greater bleeding with a relative risk of 3.0 (19). In the recent Stroke Prevention in Atrial Fibrillation III randomized trial of atrial fibrillation, with an INR of 2.0 to 3.0, the bleeding rate was 1.5% per year (20). These data show that with a lower level of anticoagulation, bleeding on long-term follow-up is much less of a problem and attests to the problem of excessive anticoagulation (21).

In this trial patients with a bioprosthesis also had a "high" bleeding rate (Fig. 3) because, in all patients with bioprosthesis (many of whom were not anticoagulated but are included in the bioprosthetic group), the incidence of bleeding was 30% and 31% at 15 years for AVR and MVR, respectively. This is the result of at least three factors:

1. some patients received anticoagulation for reasons unrelated to prosthesis type,
2. excessive anticoagulation, and
3. nonanticoagulated patients may have bleeding episodes from peptic ulcer disease, etc. This "baseline" bleeding cannot be reliably separated from anticoagulation-related bleeding in anticoagulated patients, and risks of bleeding in nonanticoagulated patients have to be considered in complications of patients with prosthetic heart valves; therefore, we counted all episodes that met the definition of clinically significant bleeding for both anticoagulated and nonanticoagulated patients. At present, in patients who are at-risk for thromboembolism (12,22) and would require anticoagulation therapy because of these risks, the benefit of a lower bleeding rate with a bioprosthetic valve compared with a mechanical valve should be less. Based on data from the recent SPAF III trial (21) (vide supra) maintaining an INR of 2.0 to 3.0, the bleeding rate at the present time at 15 years with a mechanical aortic valve would be expected to be about ≤23%.

Clinical implications. When a patient needs valve surgery, the choice is between valve repair and valve replacement, either with a mechanical valve or a biological valve. Our study has addressed the outcomes of patients randomized between a mechanical valve versus porcine bioprosthesis (heterograft/xenograft).

In this trial for all valve-related complications, there was no significant difference between the two valve types. The advantages of the use of the mechanical valve for AVR (lower mortality, primary valve failure and reoperation) were offset by a higher bleeding rate. From a clinical point of view, one has to balance the severity and clinical implications of complications (23), in this trial bleeding versus valve failure, reoperation and death. With current recommendations of a lower level of anticoagulation and, thus, an expected lower bleeding rate, the mechanical valve would be advantageous for AVR in those aged <65 years, and the bioprosthesis would be advantageous for AVR in those aged ≥65 years, especially if such patients did not need anticoagulation for other risk factors. Extreme caution should be exercised regarding conclusions drawn from this trial regarding primary valve failure in patients aged ≥65 years for MVR with bioprosthesis because of the small number of those patients in this study.

Patients should be informed of their choices for valve replacement, as well as the known risks and benefits of each prosthesis documented by randomized trials (Edinburgh, VA and others) and by many other studies. Patient preferences and individual patient circumstances play an important role in the decision of the final choice of the prosthetic heart valve.

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