Cardiac Bioprostheses in the 1990s

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The first successful heart valve replacements were carried out in 1960 with the use of mechanical prostheses.1-3 Because of the risk of thromboembolism that is inherent to all mechanical prostheses and the hazards of continuous anticoagulation, fewer thrombogenic tissue valves were developed.4-9 In the early 1960s, homograft replacement of the aortic valve was reported,6,7 and shortly thereafter, valve replacements with porcine bioprostheses were used.8,9 The adequate hemodynamic properties, low thrombogenicity, and freedom from substantial structural degeneration during the first years after implantation made the bioprostheses a very attractive alternative to mechanical valves.10-12 The absence of need for anticoagulation appeared to be of particular advantage for valve replacement in patients engaged in competitive sports, women wishing to become pregnant, and elderly patients, in whom bleeding complications are most likely to occur. A true consensus about the indications for bioprosthetic valve replacement was, however, never reached in the debate between enthusiastic supporters of tissue valves and skeptical surgeons who were concerned about the long-term durability of the bioprostheses. Nevertheless, bioprostheses were implanted with increasing frequency from the 1970s until the early 1980s, and they were the standard valve substitutes for aortic, mitral, and tricuspid valves in many institutions. After the mid 1980s, the use of bioprostheses decreased due to growing concern about long-term durability of these valves. In the United Kingdom, 1984 was the peak year for use of tissue valve implants; almost 50% of all cardiac valve replacements were with bioprostheses. Over the next 5 years, use of bioprostheses decreased to less than one third of the total.13

Types of Bioprostheses

During the past two decades, the largest experience with prosthetic valve replacement has been with the glutaraldehyd-fixed, frame-mounted Hancock and Carpentier-Edwards porcine valves. Over time, modifications of valve design have been accomplished in both prostheses. In 1976, the Hancock modified orifice bioprosthesis was developed to improve hemodynamic performance in the small aortic root.14 This prosthesis features a composite design that removes one coronary cusp and its flow-impeding muscle shelf and replaces it with a cusp from a second larger valve. The probability of freedom from structural valve dysfunction and reoperation at 10 years is similar to that of the Hancock standard valve.14 Similarly, in the early 1980s, the Carpentier-Edwards supra-annular prosthesis was developed to improve hemodynamic properties and durability of the valve. However, the long-term performance of the supra-annular type was not better than that of the standard Carpentier-Edwards valve.15 New valve developments include the Medtronic Intact porcine valve16 and the stentless porcine aortic bioprosthesis.17 In the former, a special fixation process was used that is claimed to enable the leaflets to remain pliable and hence increase longevity. The stentless bioprosthesis has superior hemodynamics compared with mounted bioprostheses, but its durability is unknown. Whether improved longevity can be achieved remains to be shown, and only longer clinical observations can substantiate present claims.

In the 1970s, in addition to porcine bioprostheses, pericardial bovine bioprostheses were widely used.18-20 Although initial reports were optimistic, especially due to the excellent hemodynamic properties of the small models,21,22 the long-term experience with pericardial valves was not as good as that with porcine bioprostheses.20,23,24 The rate of structural valve failure was higher and tissue degeneration occurred earlier than in porcine valves. Moreover, pericardial degenerated valves tend to break acutely in an unpredictable way, putting the patient in great jeopardy. Thus, pericardial bioprostheses can no longer be recommended.24 Tissue valves from other animals have not gained more widespread clinical use.25 Fascia lata and dura mater valves are no longer used.

Valvular homografts have been used mainly as valved conduits on the right side of the heart. For a long time, the experience with homografts for aortic valve replacement has been limited to a few centers.6,7,26 After the mid 1980s, the procurement of human valves has greatly improved, mainly in connection with expanding heart transplantation programs. Homografts are available semicommercially and used increasingly for aortic valve replacement.26

Structural Changes of Implanted Bioprosthetic Valves

After implantation in the human heart, bioprosthetic tissue undergoes a complex, time-dependent process of structural changes, finally resulting in dysfunction of the valve. Thus, the replacement of the great majority of bioprostheses is required for tissue degeneration.27-29 The failure of porcine and other bioprosthetic tissues is

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mainly due to increasing cuspal calcification.\textsuperscript{30} Noncalcific mechanical failure and design-related tears are of lesser clinical importance. Calcific deposits developed first at the cuspal commissures and basal attachments because these parts of the valve receive the greatest hemodynamic stress.\textsuperscript{30} The calcification process extends to the center of the leaflet, occasionally producing thick, spongolike formations that ulcerate through the cuspal surface. Calcific deposits increase tissue stiffness, reduce the pliability of the cusps, and lead consecutively to stenosis of prosthetic valves. Tears and rupture of the cusp, the causes of severe valvular incompetence, essentially are secondary to calcification. In contrast to pericardial valves, tears and rupture of noncalcified porcine valves are rare.\textsuperscript{30} Ultrastructurally, the deposition of calcium is related to cuspal connective tissue cells and collagen.\textsuperscript{30,31} It is hypothesized that calcification of bioprosthetic tissue occurs because of the inability of devitalized cells to maintain a low intracellular content of free calcium in the presence of high extracellular calcium.\textsuperscript{30} Calcification varies in individual patients, but there are important host and implant-related factors. The host factors are mainly metabolic (eg, age, renal function, pregnancy, calcium intake) and are not immunological or inflammatory in nature.\textsuperscript{30,31} The main implant factors involve tissue pretreatment and preparation. Intensive experimental research has been done to inhibit the mineralization of the bioprosthetic tissue through the use of different chemical anticalcification agents.\textsuperscript{30,31} Unfortunately, no breakthrough has been achieved.

\textbf{Bioprostheses Versus Mechanical Valves}

\textit{Information From Observational Studies}

The weakness of bioprostheses is their limited durability, and the weaknesses of mechanical valves are their enhanced thrombogenicity and the hazards of chronic anticoagulation.\textsuperscript{32-37} Durability of bioprostheses is crucially dependent on the site and duration of implantation as well as on the age of the patient.\textsuperscript{24,27,29,37-40} In observational studies with follow-up of 10 or more years,\textsuperscript{27,29,37-40} freedom from primary tissue failure in the same age group is approximately 5% to 10% higher for aortic than for mitral valve replacement at 10 years and is even 10% to 20% higher at 12 to 13 years.\textsuperscript{38} Thus, longevity of mitral bioprostheses appears to be less than that of aortic ones, probably due to exposure to more pressure and stress when the valve is closed.\textsuperscript{41,42} Nonperpendicular flow over a mitral prosthesis during systole may be an additional factor contributing to the increased rate of tissue degeneration. Because tear and tear on the atrioventricular valve resulting from systolic pressure rise are lower in the right than in the left ventricle, the longevity of tricuspid bioprostheses is better than that of mitral bioprosthetic implants.\textsuperscript{43,44}

Bioprosthetic valve failure not only is a function of the site and time after implantation but also is crucially dependent on the age of the patient.\textsuperscript{24,28,38,39} Whereas in a 30-year-old patient freedom from valve reoperation is about 40% at 10 years, the incidence of valve failure in those more than 70 years old is low with freedom from reoperation of about 90% for aortic and 80% for mitral position. Other determinants of reduced longevity of bioprostheses are diabetes, renal disease, and hypercalcemia.

Increased thrombogenicity and bleeding complications from anticoagulant treatment are the main drawbacks of implantation of mechanical valves. However, in patients with bioprostheses, thromboembolic events also occur, as do hemorrhages, because long-term anticoagulation is used in 8% to 16% of patients with bioprostheses in the aortic position and in 31% to 79% of those with a bioprosthesis in the mitral position.\textsuperscript{45} A history of embolization, atrial fibrillation, massive left atrial enlargement, and heart failure consequent to impaired left ventricular function are the main reasons for the use of long-term anticoagulation in patients with bioprostheses.

Recently, Grunkemeier and Rahimtoola\textsuperscript{45} analyzed data regarding thromboembolism, valve thrombosis, and bleeding complications from a number of well-done observational studies with reasonably complete statistics for patients with Starr, Björk-Shiley, St Jude, and Medtronic-Hall mechanical prostheses or with Hancock and Carpentier-Edwards bioprostheses. In both the aortic and the mitral series, the average weighted risk for thromboembolism did not differ for the mechanical valves and the bioprostheses, although the absolute risk was higher in the mitral (2% to 3.5% thromboembolic events per year) than in the aortic position (1% to 2% thromboembolic events per year) (Fig 1). There was more variation within the series using a particular valve than among mean values for different valves. Thus, it appears that factors other than valve type have an important impact on the risk of thromboembolism. With respect to valve thrombosis, however, there were distinct differences between mechanical valves and bioprostheses (Fig 2). In the aortic position, valve thrombotic events ranged from 0.05% (Medtronic-Hall) to 0.25% per year (Björk-Shiley) for mechanical prostheses, whereas it was less than 0.03% per year for bioprostheses. Similarly, in the mitral position, valve thrombosis rates for mechanical valves (except for Medtronic-Hall) clearly exceeded those of Hancock and Carpentier-Edwards bioprostheses. Bleeding complications occurred at the known rate of 1% to 2% per year for continuous anticoagulation in the patients with mechanical valves, whereas they ranged between 0.1% and 0.3% per year for the patients with bioprostheses in the aortic position and between 0.6% and 0.7% per year for patients with bioprostheses in the mitral position.

In summary, it is evident from the numerous observational studies that bioprostheses increasingly result in valve failure due to structural degeneration 7 years after implantation and that valve thrombosis and bleeding complications, but not thromboembolisms, are less frequent in patients with bioprostheses than in those with mechanical valves.

\textit{Information From Randomized Studies}

Of paramount importance for more clearly defining the role of valve replacement by bioprostheses and mechanical valves with respect to long-term outcome are two randomized trials independently conducted in the United States (Veterans Administration Cooperative Study on Valvular Heart Disease)\textsuperscript{36} and the United Kingdom (Edinburgh Heart Valve Trial).\textsuperscript{35,37} Björk-Shiley spherical disc valves were compared with Han-
cock bioprostheses in the Veterans Administration trial and with Hancock and Carpentier-Edwards bioprostheses in the Edinburgh trial. Patients entered into the Veterans Administration trial were older, were exclusively men, were more symptomatic, had a higher incidence of angiographically documented coronary disease, and were less likely to have had a prior mitral valvotomy. The mean follow-up in the Veterans Administration trial was 5 years; results of the Edinburgh trial have been reported after a mean follow-up of 5.6\textsuperscript{35} and 12 years.\textsuperscript{37} At the 5-year follow-up, the Edinburgh study showed no differences in the rates of overall survival, valve failure, or valve-related complications.\textsuperscript{35} Similarly, the Veterans Administration study found no difference in survival; there was, however, a significantly lower incidence of valve-related complications (eg, bleeding, systemic embolism, endocarditis, valvular regurgitation, valve thrombosis, nonthrombotic valve obstruction, and reoperation on the randomized valve for any other reason) in the patients who had received a porcine bioprosthesis. The increased rate of valve-related complications in the patients with mechanical valves was almost entirely due to the increased risk of bleeding with long-term anticoagulation. The incidence of clinically significant bleeding was higher in the Veterans Administration trial than in the Edinburgh trial. This is likely to be related to the higher intensity of anticoagulation in the Veterans Administration trial (prothrombin time, 2- to 2.5-fold that of control) than in the Edinburgh study (1.3- to 1.8-fold that of control).\textsuperscript{36,37}

A somewhat different picture of the relative merits of bioprostheses and mechanical valves is obtained when results after 12 years in the Edinburgh trial are considered.\textsuperscript{37} There was a trend to improved actuarial survival with the Björk-Shiley prosthesis ($P=.08$) (Fig 3). No difference in survival existed between patients who had received a Hancock bioprosthesis and those with a Carpentier-Edwards bioprosthesis. Reoperation for prosthetic valve replacement occurred more often in patients with a porcine prosthesis (37.1%) than in those with a Björk-Shiley prosthesis (8.5%, $P<.001$). Of note is the 21% (14 of 68 cases) in-hospital death rate for reoperation in patients with bioprostheses. Bleeding requiring hospitalization or blood transfusion was more frequent in the patients with mechanical valves (18.6%) than in those with bioprostheses (7.1%, $P<.01$). There was no significant difference in actuarial occurrence of embolism or endocarditis in the two treatment groups.

![Events/100 valve-years](image1.png)

**FIG 1.** Thromboembolism rates with various aortic (left) and mitral (right) valve prostheses. Each circle represents a series, with area proportional to valve-years of experience in the series. Weighted averages for each valve model are given by horizontal bars. (From Grunkemeier and Rahimtoola,\textsuperscript{45} reprinted with permission of Annu Rev Med.)

![Events/100 valve-years](image2.png)

**FIG 2.** Bar graphs of thrombotic stenosis rates with various aortic (left) and mitral (right) valve prostheses for the series depicted in Fig 1. Vertical bars represent average linearized rates (left vertical axis), and plus symbols indicate total valve-years of follow-up. (From Grunkemeier and Rahimtoola,\textsuperscript{45} reprinted with permission of Annu Rev Med.)
When all adverse events were considered (death, reoperation, major bleeding, major embolism, and endocarditis), freedom of these events was higher in those with a Björk-Shiley valve (38.6%) than in those with a bioprosthesis (27.4%, \( P<.01 \)), essentially due to the significantly more favorable outcome in the subgroup of patients with mitral valve replacement. Thus, it appears that the increased incidence of reoperation in the bioprosthesis group had more than offset the increased incidence of major bleeding in patients with a Björk-Shiley prosthesis.

Some conclusions can be drawn from the numerous observational studies and the two randomized studies of valve replacement with bioprostheses and mechanical valves. Bioprostheses have their golden period during the first 6 to 7 years after implantation, with excellent hemodynamics and reduced valve-related complications. Thereafter, there is increasing frequency of structural valve degeneration, leading to an increasing rate of reoperation. Therefore, long-term outcome beyond 7 years after implantation of a bioprosthesis appears clearly compromised, and the randomized Edinburgh trial has documented a superiority of outcome with the spherical Björk-Shiley prosthesis in comparison to Hancock and Carpentier-Edwards bioprostheses. However, the extrapolation of the Edinburgh trial results to other mechanical or bioprosthetic valves is scientifically questionable, particularly in light of the recent problems with a specific “improved” model of a much used mechanical prosthesis.\(^46\) Finally, perioperative mortality for valvular replacement is still much higher than for the primary operation.\(^{27,47-49}\) There is a wide variation in the reported perioperative mortality rates for reoperation of bioprostheses in articles published recently (Table). Surgical mortality is low in a patient with primary tissue failure and stable hemodynamics but increases exponentially for emergency operations.\(^{29,48,50}\) Mortality increases with each consecutive operation.\(^{48}\)

Complications from long-term anticoagulation in patients with mechanical prostheses have decreased recently. It has been shown that less rigorous anticoagulation regimens in valvular patients are associated with less clinically significant bleeding without an increase in thromboembolic complications.\(^{51,52}\) Thus, the danger of hemorrhage is less of an argument against the use of mechanical prostheses today.

An important argument against the use of bioprostheses is the unpredictability of the primary tissue failure: in some patients, the valve will fail early, during the first 5 to 10 years, with accompanying major disappointment and loss of trust on the part of the patient. Finally, tissue failure in a patient with a bioprosthesis is not always insidious but can assume proportions of a true clinical emergency, with all of the inherent risks of urgent operation, pulmonary edema, prolonged intubation, and sepsis. In some of these patients, the urgency of the clinical situation does not even allow a proper preoperative evaluation (eg, coronary angiography) because the patient has to be taken to the operating room as soon as possible.\(^{53}\)

### Indications for Bioprosthetic Valve Replacement

At the present time, there are only a few generally accepted indications for bioprosthesis implantation. These are patients with contraindications to continuous anticoagulation (eg, bleeding disorders, Osler’s disease, intestinal polyposis, angiodysplasia) and those in whom the prothrombin time cannot be adequately regulated (eg, compliance problems due to alcoholism, impaired mental function, or drug abuse; health service problems such as that in some Third World countries). A possible indication for bioprosthesis is the patient more than 70 years old who needs aortic valve replacement. In this age group, the occurrence of structural valve degeneration is in general slower and survival is more dependent on non–valve-related complications.\(^{54}\) Thus, the elderly aortic valve patient whose survival is limited can expect to enjoy the remaining years without reoperation and complications arising from long-term anticoagulation. About 40% to 50% of these patients survive operation for 10 and more years. The number of patients with severe primary tissue failure will not be negligible after 10 years, even in this age group. Reoperation in a patient who is 80 years old or older is risky.

An increasing number of cardiac surgeons prefer homografts to bioprostheses in the aortic position.\(^{10}\) The long-term results of homografts in the aortic position are comparable to those of bioprostheses. The experience, however, is limited to a few centers that have

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**Figure 3. Plot of actuarial survival of patients randomly assigned to receive either a mechanical Björk-Shiley 60° spherical tilting-disc valve or a porcine bioprosthesis. (From Bloomfield et al,\(^37\)** reprinted with permission of N Engl J Med.)

**Table:** Surgical Mortality for Bioprosthetic Valve Reoperation According to Recent Reports

<table>
<thead>
<tr>
<th>Reference</th>
<th>Date</th>
<th>No. of patients</th>
<th>Surgical mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield et al</td>
<td>1991</td>
<td>85</td>
<td>19</td>
</tr>
<tr>
<td>Akins et al</td>
<td>1990</td>
<td>60</td>
<td>10</td>
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<tr>
<td>Pansini et al</td>
<td>1990</td>
<td>183</td>
<td>9</td>
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<tr>
<td>Jamieson et al</td>
<td>1990</td>
<td>147</td>
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<tr>
<td>Jones et al</td>
<td>1990</td>
<td>194</td>
<td>5</td>
</tr>
<tr>
<td>Magilligan et al</td>
<td>1989</td>
<td>176</td>
<td>12.5</td>
</tr>
<tr>
<td>Cohn et al</td>
<td>1989</td>
<td>194</td>
<td>7</td>
</tr>
<tr>
<td>Gallo et al</td>
<td>1988</td>
<td>97</td>
<td>7 AVR</td>
</tr>
<tr>
<td>Antunes et al</td>
<td>1986</td>
<td>98</td>
<td>10</td>
</tr>
<tr>
<td>Bortolotti et al</td>
<td>1985</td>
<td>64</td>
<td>12.5</td>
</tr>
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AVR, aortic valve replacement; MVR, mitral valve replacement.
performed homograft implantations for 20 years or longer.\textsuperscript{24,45,55,56} Homografts also deteriorate with time, and after 20 years, less than 10\% are still in function.\textsuperscript{26} It is questionable whether new sterilization and pre-treatment procedures will improve the long-term performance of homografts.\textsuperscript{26} Therefore, the decision to perform homograft implantation should be made with the same reservations as for bioprostheses. Homograft implantation is the preferred treatment of patients with infective aortic endocarditis and, especially, destroyed aortic root, as frequently is found with prosthetic endocarditis. For these patients, homograft composite grafts offer the only viable and recurrence-free solution.\textsuperscript{57}

The indication for bioprosthetic mitral valve replacement is seldom given, except perhaps for very old patients in the absence of atrial fibrillation. Many older patients with mitral valve replacement can be managed by reconstructive procedures, and those requiring valve replacement usually qualify for a mechanical valve because anticoagulation is necessary for a variety of non-valve-related reasons. Finally, bioprosthetic valve replacement may be considered in women of childbearing age who wish to have children so they can avoid embroyopathy and high fetal wastage associated with warfarin treatment; however, they must be informed about the accelerated rate of valve degeneration and the risks associated with bioprosthesis reoperation. According to a recent report,\textsuperscript{58} the risk for mother and child in women with mechanical prostheses has been overestimated, and the accelerated tissue degeneration is a considerable problem of bioprostheses during pregnancy.\textsuperscript{58,59}

There also are firm contraindications for the use of bioprostheses; they should be avoided at all costs in children and adolescents, having failed miserably in some Third World countries.\textsuperscript{50,61} In these patients, aortic homografts and mitral valve reconstruction are attractive alternatives. Furthermore, bioprostheses should not be used in patients needing combined aortic and mitral valve replacement because asynchronous deterioration of mitral and aortic prostheses can lead to the necessity of removing an absolutely normal prosthesis to spare the patient a third, undoubtedly riskier, procedure later. The use of bioprostheses is questionable in patients receiving aortocoronary bypass grafts; the reoperation is technically more demanding with a risk of damage to the functioning coronary conduits. Finally, there is little indication for the use of bioprostheses in composite grafts, in which a large part of the ascending aorta has to be replaced by a tube graft with reimplantation of the coronary arteries. Failure of the bioprosthesis necessitates the complex, risky removal of the composite graft, with a possibility of disastrous complications.

Surveillance of the Patient With a Bioprosthesis

Structural valve degenerations leading to regurgitant lesions are in most instances adequately detected by auscultation. The clinical assessment of a stenotic mitral bioprosthesis is difficult because the typical physical signs of mitral stenosis often are absent. The diagnosis of structural valve degeneration relies therefore predominantly on Doppler echocardiography, which can identify degeneration 2 to 3 years before the patient becomes symptomatic and needs reoperation.\textsuperscript{62} In the mitral position, leaflets of bioprostheses are better visualized by transesophageal echocardiography than by transthoracic echocardiography. Transthoracic echocardiography was reported to have failed to detect moderate or severe regurgitation detected by transesophageal echocardiography in approximately 20\% of patients with bioprosthesis mitral valves.\textsuperscript{62}

Thus, in patients with bioprostheses, regardless of whether symptoms are present or absent, regular Doppler echocardiographic follow-up examinations should be carried out starting no later than 6 to 7 years after implantation. It is by this regular echocardiographic surveillance that tissue degeneration can be detected early enough to proceed to elective valve rereplacement.\textsuperscript{62} Reoperation in severely symptomatic (New York Heart Association functional class IV) patients or carried out as an emergency procedure is associated with considerable perioperative mortality.\textsuperscript{29,50} As a general rule, one should proceed to reoperation in the presence of documented bioprosthesis degeneration when the patient becomes symptomatic or when the hemodynamic load reaches such a degree that would qualify for surgery in a patient with native valvular disease.

Antibiotic prophylaxis for bacterial endocarditis in patients with bioprosthetic valves is identical to that in those with mechanical valves and is performed according to established guidelines. If bacterial endocarditis should occur on a bioprosthetic valve, there is a chance of cure by medical therapy if major valve destruction or valve-ring abscess formation is absent.\textsuperscript{63,64} The tissue degeneration is accelerated after conservatively cured bacterial endocarditis, and such patients need very close surveillance.\textsuperscript{64}

In summary, the enthusiasm for bioprosthetic valve replacement prevailing among many but not all surgeons in the 1980s has given way, in the 1990s, to fewer and more specific indications. Whether more durable tissue valves will become available is uncertain. Before new devices can be introduced for a new round of worldwide bioprosthetic valve replacement, rigorous prospective testing will be mandatory.\textsuperscript{65}

References

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