

# Combined surgery for valve and coronary artery disease

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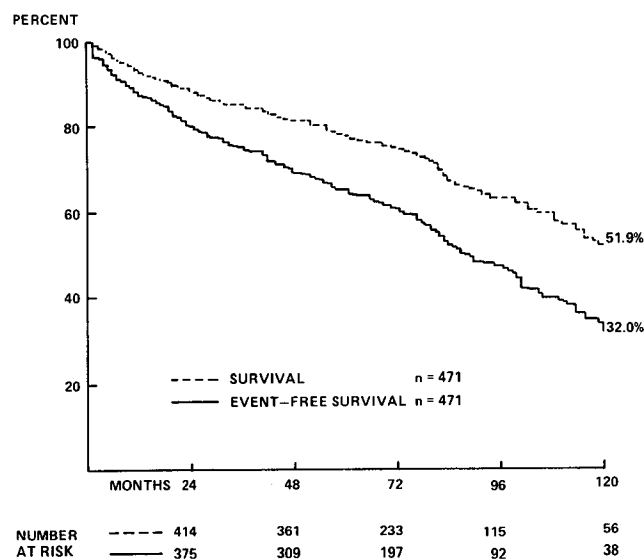
**Patients with valvular heart disease often have coexisting coronary artery disease. Studies of the first 500 patients undergoing aortic valve replacement (AVR) combined with coronary bypass grafting (1967–1981) and the first 300 patients undergoing mitral valve replacement (MVR) combined with coronary bypass grafting (1970–1983) at the Cleveland Clinic documented overall in-hospital mortality at 5.9% and 7.3%, respectively. Late survival of patients after AVR and bypass grafting exceeded that for patients after MVR and bypass grafting. In both groups, patients who received bioprostheses and who did not take warfarin had superior survival.**

**Index terms:** Coronary disease • Heart surgery • Heart valve diseases • Review articles

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Patients who need valvular heart surgery often have coronary artery disease in addition to valvular dysfunction.<sup>1–3</sup> The American population is aging, more elderly patients are undergoing valve surgery, and the older the patients the more common coronary artery disease is. After the start of the coronary bypass era in 1967, surgeons began to combine bypass grafting and valve surgery for patients with both types of pathology. Early reports of combined operations reported substantial levels of perioperative mortality,<sup>4–6</sup> and some authors questioned the wisdom of combining valve replacement and bypass grafting.<sup>7</sup> However, recent analyses of the Cleveland Clinic experience with operations combining valve and coronary surgery have demonstrated that perioperative mortality has

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**Fig. 1.** Survival and event-free survival (Kaplan-Meier) for patients who survived operative hospitalization for aortic valve replacement combined with bypass grafting. Numbers of patients at risk at selected intervals are shown below the figure. Survival was 88%, 77%, and 52% at two, five, and 10 postoperative years, respectively. Event-free survival was 80%, 65%, and 32% at two, five, and 10 postoperative years, respectively. (From Lytle et al<sup>8</sup> by permission).

not been unduly high,<sup>1,2</sup> and the late results have been favorable, particularly for patients with a combination of aortic valve disease and coronary atherosclerosis.<sup>3</sup> This review will focus on the early and late results of operations combining valve and coronary surgery and the factors influencing those results.

### Aortic valve replacement combined with coronary bypass grafting.

It has been our policy to perform coronary arteriography for all patients over the age of 35 years who need aortic valve replacement, regardless of whether or not they have had angina. It has also been policy to treat significant coronary lesions (stenoses of >50%) in patients undergoing aortic valve replacement with bypass grafting. To assess the results of these strategies, the first 500 consecutive patients who have undergone primary operation for coronary bypass grafting combined with aortic valve replacement at the Cleveland Clinic were evaluated.<sup>1,3</sup> This series extended from 1967 to 1981.

The in-hospital (perioperative) mortality for

these patients was 5.9% (29 deaths). Most of the deaths were cardiac in nature (only five were noncardiac), and there was a strong association between the occurrence of perioperative myocardial injury and in-hospital death. The use of cold potassium cardioplegia for myocardial protection decreased the rate of perioperative myocardial infarction and lowered perioperative mortality. Of 260 patients undergoing surgery with the use of anoxic arrest, 20 (7.7%) died, while of the 237 patients receiving cold potassium cardioplegia intraoperatively, nine (3.8%) died ( $p = 0.06$ ). Multivariate testing confirmed the independent influence of cardioplegia in decreasing mortality. Other investigators have also found that the use of cardioplegia has been associated with a decreased mortality for these complex operations.<sup>8</sup>

Preoperative and operative variables were tested with univariate and multivariate analyses to identify factors influencing operative risk. Gender (women had a higher risk), aortic insufficiency, and advanced age were patient-related factors associated with an increased in-hospital mortality. Gender had by far the strongest influence, and even improved myocardial protection has not overcome the influence of gender. When cardioplegia was used, seven of 39 women (18%) and two of 198 men (1%) died in-hospital. Study of patients undergoing isolated coronary revascularization has also shown that women have had a higher perioperative risk than men, but the difference has not been as dramatic.<sup>9</sup> The use of cardioplegia for myocardial protection has eliminated aortic insufficiency as a risk factor. We did not find that indexes of left ventricular function or the severity of coronary artery disease such as left main stenosis, number of stenotic vessels, or the number of bypass grafts performed had any effect on in-hospital mortality.

As the risk of combining bypass grafting and aortic valve replacement has been lowered, an increasing number and a wider spectrum of patients have been considered for surgery. Our first 500 patients underwent operation between 1967 and 1981. During the five-year period from 1980 through 1985, 490 patients underwent aortic valve replacement combined with bypass grafting with an in-hospital mortality of 26 patients (5.3%). The more recent group has not been studied in detail as the first 500 patients have been, but it is noteworthy that 31% (152 patients) of the 1980–1985 group were 70 years of age or older compared with 15% (75 patients) in the

initial 500-patient subset. For the 1980–1985 group, in-hospital mortality was 4.4% (15 deaths of 338 cases) for patients <70 years and 7.2% for patients 70 years or older. In other words, one reason for the slight increase in perioperative mortality in recent years is that more older patients are having surgery.

The in-hospital mortality of approximately 4% for operations combining aortic valve replacement and coronary bypass grafting in the current surgical period is approximately twice that for isolated aortic valve replacement, an observation also made by Cohn et al.<sup>8</sup> However, multivariate analysis of the perioperative mortality of aortic valve operations by Scott et al.<sup>10</sup> did not implicate coronary bypass grafting as a factor independently increasing risk. Rather, patient-related variables covariant with the occurrence of coronary artery disease, particularly advanced age, were the factors increasing mortality.

When aortic valve replacement combined with coronary bypass grafting is undertaken as a reoperation, the risk of perioperative mortality is increased relative to the risk for primary operations. In a study of cardiac reoperations, the in-hospital mortality of a first reoperation for aortic valve replacement and revascularization was 17% (seven deaths of 41 cases).<sup>11</sup> The risk of a first reoperation for isolated aortic valve replacement was 10%. Although univariate comparison of the risk of combined reoperation with the risk for reoperative isolated aortic valve replacement did not show a statistically significant increase in mortality, a trend is apparent. Multivariate analyses to identify variables with independent influence increasing risk showed advanced age had a strong adverse impact and the presence of coronary artery disease had a slight adverse impact.

Despite the low in-hospital mortality for aortic valve replacement combined with bypass grafting, the most important issues are long-term survival and the quality of life for the late survivors. The 471 hospital survivors from our 500-patient series have been followed up and the data analyzed as part of two studies. For the first study, late survivors had been followed at a mean postoperative interval of 41 postoperative months<sup>1</sup> and, for the second study, at a mean interval of 85 months after operation.<sup>3</sup> Overall survival was 88%, 81%, 74%, 63%, and 52% at two, four, six, eight, and 10 postoperative years, respectively (Fig. 1). Univariate analyses followed by multivariate testing with Cox proportional hazard

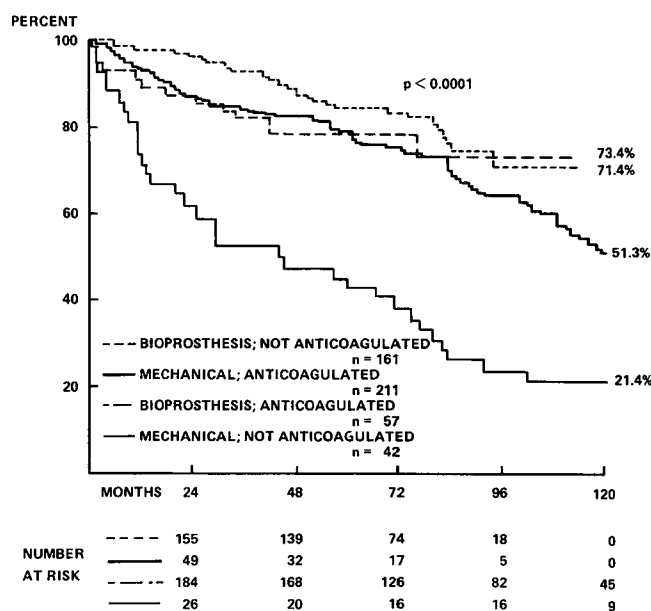
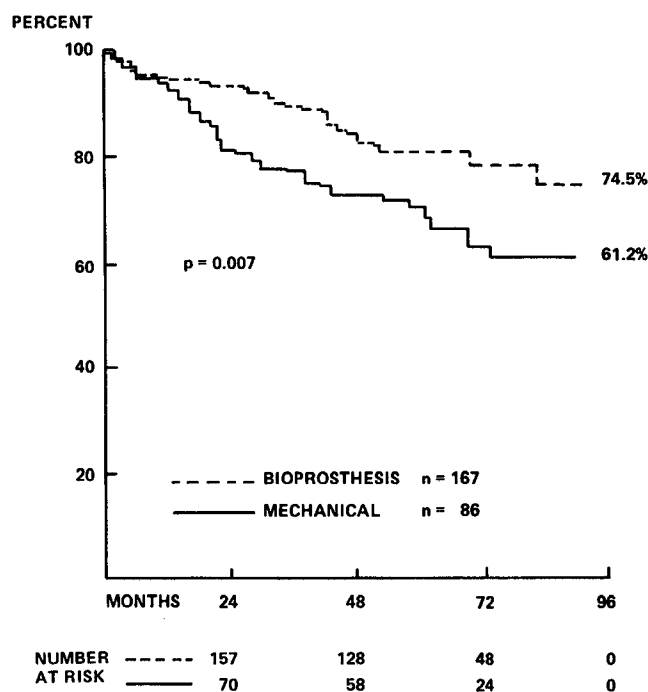


Fig. 2. Late survival following aortic valve replacement combined with coronary bypass grafting according to the type of valve implanted (mechanical v. bioprosthesis) and whether or not the patient took warfarin postoperatively. Patients with bioprostheses who did not take warfarin had the best survival. (From Lytle et al<sup>3</sup> by permission.)

models showed that the patient-related variables that had independent influence decreasing late survival were age >60 years ( $p < 0.001$ ), a radiographic cardiothoracic ratio of >50% ( $p = 0.03$ ), age >70 years ( $p = 0.049$ ), and NYHA function class III or IV ( $p = 0.001$ ). In addition, use of a mechanical prosthesis was a factor independently associated with decreased late survival ( $p = 0.001$ ). A second statistical model was examined in which patients were grouped not only according to the type of prosthesis that was used, but also on the basis of whether or not they took warfarin postoperatively. Patients who had a mechanical prosthesis and who were not taking warfarin had the worst late survival ( $p < 0.001$ ), and those who had bioprostheses (porcine heterografts) and who were not taking warfarin had the best late survival ( $p = 0.03$ ). Figure 2 shows univariate comparisons of survival curves for patients subdivided according to the type of prosthesis and whether or not they took warfarin postoperatively.

The observation that patients who had bioprostheses experienced a more favorable survival than patients who received a mechanical valve is



**Fig. 3.** Survival for patients undergoing aortic valve replacement combined with coronary bypass grafting from 1978 through 1981, according to whether they received bioprostheses or a mechanical prosthesis. Patients with bioprostheses had superior survival. (From Lytle et al<sup>3</sup> by permission.)

important. Physicians cannot alter patient-related variables, but the type of valve prosthesis that is implanted is controllable. The initial study suggested that patients with bioprostheses had better survival, but because of a limited follow-up interval, that observation could only be applied to the four-postoperative-year time frame. The second study, with a mean follow-up interval of seven years and minimum follow-up of 43 months, confirmed the observations that patients with a porcine valve had better long-term survival, and the subgroup that was not given warfarin had the best survival of all. Other studies of aortic valve replacement are inconsistent on the issue of whether the type of prosthesis that is used influences long-term survival. Cohn et al<sup>8</sup> compared long-term results after aortic valve replacement with either disk or porcine valves for a heterogeneous group of patients undergoing aortic valve replacement with or without associated procedures and found that the patients with porcine valves had better survival, although only univariate statistical methods were used.<sup>8</sup> Mitchell et

al<sup>12</sup> used multivariate techniques to identify a porcine valve as a factor enhancing survival after aortic valve replacement with or without associated procedures. However, in their study, mechanical and porcine valves were used in sequential rather than concurrent time frames. Data compiled by Johnson et al<sup>13</sup> showed a slightly increased survival (though not statistically significant, perhaps because of the small number of patients in each group) for patients with porcine valves undergoing combined operations.

The time period during which patients undergo surgery is a factor that must be considered in the evaluation of the long- or short-term results of valve replacement. To compare patients with different valve prostheses who had undergone surgery in the same surgical period and to examine a group with patient-related characteristics most akin to our current surgical candidates, the patients undergoing surgery from 1978 to 1981 were studied as a separate subset. Survival for the group was 81% and 75% at four and six postoperative years, respectively. Univariate and multivariate testing showed that patients in this subgroup with bioprostheses had better survival than the patients with mechanical valves (Fig. 3).

In our studies of the long-term results of valve surgery, late cardiac events were defined as death, reoperation, stroke (permanent neurologic deficit), thromboembolic event, endocarditis, hospitalization for bleeding or transfusion, myocardial infarction, hospitalization for congestive heart failure, and presence of class III or IV symptoms. Survival without the occurrence of any of these complications was defined as event-free survival. Late event-free survival for the in-hospital survivors of aortic valve replacement combined with bypass grafting (Fig. 1) was 80%, 65%, 47%, and 32% at two, five, eight, and 10 postoperative years, respectively.

Determinants of late event-free survival after aortic valve replacement and bypass grafting were identified with univariate and multivariate testing. Advanced age and moderate or severe impairment of left ventricular function were the patient-related variables that decreased event-free survival. In the statistical model where valve type alone was examined, the presence of a bioprosthesis had a positive effect on event-free survival. When valve type was examined along with anticoagulant status, patients with mechanical valves who were not taking warfarin had the

worst event-free survival and patients with porcine valves who were not taking warfarin had the best event-free survival.

The need for reoperation is a concern that is often cited in regard to the use of bioprostheses. Of the 471 in-hospital survivors of aortic valve replacement and bypass graft, 22 patients have undergone 25 reoperations. However, these reoperations were caused by a multiplicity of problems including the progression of coronary artery disease in the native circulation, graft failure, endocarditis, periprosthetic leak, mitral valve dysfunction, and intrinsic failure of either mechanical or porcine valves. In fact, only seven reoperations were caused by intrinsic failure of a bioprosthesis. It is probable that as the follow-up of these patients exceeds 10 years, the frequency of reoperation for bioprosthesis failure will increase, but in the first seven years after operation, valve failure had not been a major problem. Finally, valve failure should not be evaluated as a phenomenon isolated from other complications. When survival and other cardiac events are considered along with reoperation, the patients with bioprostheses had superior survival and event-free survival despite the problem of degeneration of porcine valves.

The overall outlook for patients undergoing aortic valve replacement and coronary revascularization is quite good regardless of their advanced age and complex pathology. The perioperative risk is low, and for patients managed using our ideal management strategy (placement of a porcine valve and avoidance of warfarin anticoagulation), late survival was 96%, 85%, and 71% at two, five, and eight postoperative years, respectively (Fig. 2).

### Mitral valve replacement combined with coronary bypass grafting

Patients with a combination of mitral valve and coronary artery disease present physicians with a more complex set of problems than patients with aortic valve and coronary disease do and study of these patients is more difficult. Aortic valve and coronary artery disease occur concurrently, but aortic valve disease is not caused by ischemia. Mitral valve dysfunction can be a result of ischemia, as well as on the basis of rheumatic or degenerative pathology. Furthermore, mitral dysfunction can sometimes be treated with valve-conserving operations. Thus, patients undergoing mitral valve replacement are only a subset of

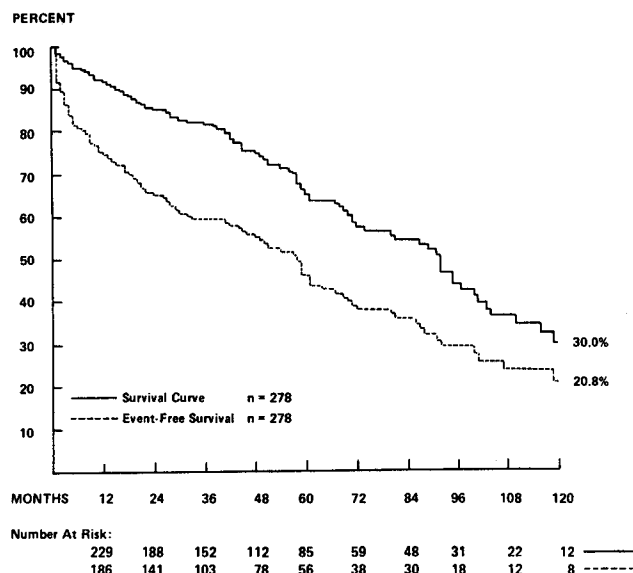
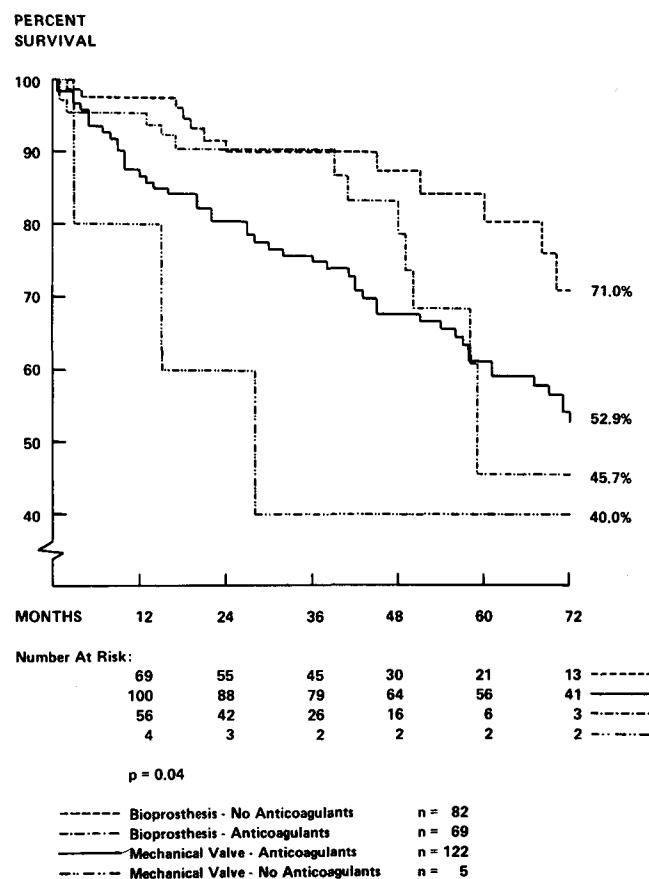


Fig. 4. Survival and event-free survival for the 278 in-hospital survivors with mitral valve replacement combined with bypass grafting. Survival was 85%, 66%, and 31%, and event-free survival, 65%, 46%, and 21%, at two, five, and 10 postoperative years, respectively. (From Lytle et al<sup>2</sup> by permission of the publisher and the American Heart Association.)

the total group of patients with mitral valve pathology severe enough to warrant surgery. Since the indications for mitral valve repair *v.* mitral valve replacement vary tremendously among different institutions, comparison of studies is difficult.

The results of mitral valve replacement combined with bypass grafting for the first 300 consecutive patients undergoing that operation, a series extending from 1970 to 1983, were studied.<sup>2</sup> Preoperatively, 68% of these patients had angina, a figure lower than the 83% of the patients in our aortic valve and revascularization series who had angina. Isolated mitral valve dysfunction rarely causes angina, and in this population, angina must be attributed to the presence of coronary artery disease. The prevalence of angina was associated with both the type of mitral valve pathology and the number of stenotic coronary vessels. Of 47 patients with ischemic mitral valve disease, five (10.6%) had no angina, compared with 42 of 102 (41%) with rheumatic and 45 of 147 (31%) with degenerative valve disease ( $p = 0.002$ ). Of patients with one-, two-, and three-vessel disease, 53%, 75%, and 78%, respectively, had angina ( $p < 0.001$ ).





**Fig. 5.** Survival of patients who survived operative hospitalization for mitral valve replacement combined with bypass grafting according to the prosthesis-anticoagulation group. Patients with bioprostheses who did not take warfarin had the best survival—81% at five postoperative years. (From Lytle et al<sup>2</sup> by permission of the publisher and the American Heart Association.)

Previous studies of patients undergoing mitral valve replacement combined with bypass grafting have cited figures for in-hospital mortality ranging from 14% to 24%<sup>6,14-17</sup>. Of the 300 patients in our series, 22 (7.3%) died in-hospital. Half of the patients died from cardiac and half from noncardiac causes, an observation different from that regarding our patients undergoing aortic valve replacement and grafting where almost all perioperative deaths were cardiac in nature and the relationship of perioperative mortality with the occurrence of new myocardial injury was very strong. Furthermore, the use of cardioplegia has not significantly decreased the incidence of either perioperative death or perioperative myocardial infarction for the mitral valve and revascularization group.<sup>2</sup>

Determinants of in-hospital mortality as identified by univariate and multivariate analyses were radiographic cardiac enlargement (cardiothoracic ratio) (>50%), cardiac rhythm (patients without sinus rhythm were at increased risk), left main stenosis (>50%), and serum bilirubin (>2 mg%). Univariate testing indicated that left ventricular end-diastolic pressure of >30 mmHg and pulmonary capillary wedge pressure of >40 mmHg were associated with increased risk, but their independent influence could not be confirmed with multivariate testing since data were not available for all patients.

Studies of mitral valve replacement and revascularization are not consistent regarding the determinants of perioperative mortality. Patient-related variables, which have been cited by other authors as being significant but which we did not find to be important, include age >60 years, class IV symptoms, left ventricular ejection fraction, and ischemic mitral valve pathology.<sup>14-16</sup>

The perioperative mortality of mitral valve replacement combined with bypass grafting is higher than that for isolated mitral valve replacement. However, two groups have noted that although patients undergoing revascularization were at higher risk, the group that was at the highest risk was composed of patients who had coronary artery disease but who did not undergo bypass grafting in association with mitral valve replacement.<sup>15,18</sup> This observation indicates that it is the coronary pathology that causes the increased risk, not the bypass grafting that is done to treat that pathology. First reoperations for mitral valve replacement and bypass grafting have been relatively safe; 38 such operations have been performed with four perioperative deaths (11%) through 1984.<sup>11</sup>

Again, the critical issues revolve around the late results, and in general, the late results of mitral valve replacement and bypass grafting have not been as good as the results following aortic valve replacement and revascularization. For the 278 late survivors of our 300-patient series, survival was 85%, 66%, and 31% at two, five, and 10 postoperative years, respectively (Fig. 4). Survival at two postoperative years was approximately the same as that observed after aortic valve replacement revascularization, but between two and five postoperative years, there was more attrition in the mitral group. Relative to the aortic valve patients, congestive heart failure was a more common mode of late death and

sudden death a less common mode of late death for the mitral valve group.

Multivariate testing to identify determinants of late mortality implicated preoperative ventricular arrhythmias, moderate or severe impairment of left ventricular function, and rheumatic valve pathology as patient-related factors having a significant ( $p < 0.05$ ) negative effect on late survival. However, the management-related variables of valve type and anticoagulation policy had the strongest influence on late survival. Patients with bioprostheses who were not taking warfarin had better survival than other subgroups (Fig. 5).

The heterogeneity of patients undergoing mitral valve replacement and bypass grafting makes analysis difficult. For example, the type of mitral valve pathology is associated with long-term survival as patients with degenerative valve disease have better long-term survival than those with rheumatic or ischemic mitral valve pathology. However, even within the subgroup of patients with ischemic valve disease, there are further subgroups that have different survival outcomes. The late survival of patients surviving surgery for acute papillary muscle rupture is excellent while the late survival for patients surviving operation for papillary muscle infarction (but not ruptured) or mitral insufficiency on the basis of previous infarction without documented papillary muscle pathology was poor (Fig. 6).

There was a high rate of occurrence of late cardiac events for the in-hospital survivors of mitral valve replacement and bypass grafting as event-free survival for the entire group was 65%, 46%, and 21%, at two, five, and 10 postoperative years, respectively (Fig. 4). In other words, fewer than half of the hospital survivors lived five years without the occurrence of a late cardiac event. The most common late event was the occurrence of congestive heart failure, which was experienced by 77 patients of whom 55 eventually died.

Multivariate analysis of the determinants of event-free survival demonstrated that valve type and anticoagulant status had the strongest impact. Again, patients with bioprostheses who were not taking anticoagulants had the best results.

Some other studies of the late results of valve surgery, one from Scotland,<sup>19</sup> the other from Yale University,<sup>20</sup> have not detected differences in survival or event-free survival based on prosthesis type. However, those studies have involved quite heterogeneous groups of patients and de-

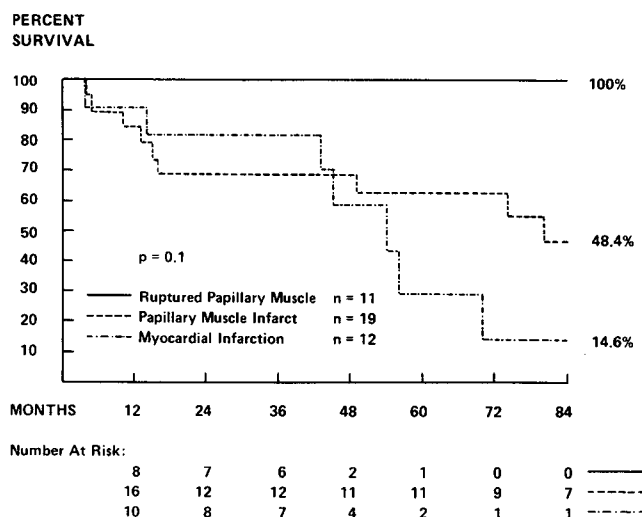


Fig. 6. Late survival of patients with ischemic mitral valve pathology who survived operative hospitalization for mitral valve replacement combined with bypass grafting. There have been no late deaths for patients who underwent surgery for a ruptured papillary muscle. Survival for patients undergoing surgery for an infarcted (but not ruptured) papillary muscle and those with mitral insufficiency caused by myocardial infarction without papillary muscle rupture or infarction have been less favorable.

spite the overall size of the study groups, the subsets with coronary artery disease were relatively small. Furthermore, the mean age of the patients reviewed was younger than those involved in our studies of combined surgery. Our data indicating that bioprostheses produce superior late results apply specifically to patients undergoing combined valve and coronary surgery. It is our opinion that it is reasonable to extend the same conclusion that bioprostheses enhance late results to older patients without coronary artery disease who are undergoing isolated valve replacement, but as yet we do not have data documenting the superiority of that approach in patients without coronary artery disease.

Abnormal postoperative left ventricular function generates a high level of postoperative morbidity and mortality following mitral valve replacement and bypass grafting. Two variations in surgical approach have been used in the last few years in attempts to combat this problem. There are some experimental and clinical data to indicate that removal of the mitral valve subvalvular mechanism, the chordae tendinae, and papillary

muscles at the time of mitral valve replacement may have a detrimental effect on postoperative left ventricular function.<sup>21</sup> Recently, it has been our approach to leave the subvalvular mechanism intact when performing mitral replacement. More promising, however, has been a concerted effort in the direction of conserving the entire mitral valve.

Valve-conserving operations to treat both mitral stenosis and mitral insufficiency have always been available, but the arrival of valve prostheses that were reasonably effective generated a surgical period where valve replacement was usually used unless simple reconstructive operations could be performed. Despite that trend, some surgeons, most notably Carpentier et al<sup>22</sup> have gained experience with complex valve reconstructions for mitral insufficiency caused by degenerative or ischemic disease and have reported favorable long-term results. The bulk of their extensive experience has involved younger patients without coronary artery disease and it cannot yet be concluded that patients who, in the past, may have undergone mitral replacement and bypass grafting will have a similar late experience after mitral valve reconstruction and revascularization. However, valve reconstruction has seemed a possible way to avoid the late prosthesis-related complications of valve replacement and to diminish the impact of postoperative congestive heart failure on late morbidity and mortality. Experience at the Cleveland Clinic with mitral valve repair combined with revascularization has been quite favorable both in terms of a low perioperative mortality and the avoidance of postoperative congestive heart failure, and constitutes our preferred approach to combined mitral valve and coronary pathology whenever possible. As experience has increased, it has been possible to reconstruct most dysfunctional mitral valves in patients who also have coronary artery disease. The impact of this approach on the long-term outcome has not yet been documented, but the early results are encouraging.<sup>23</sup>

### Conclusion

Our studies of combined surgery for patients with valve and coronary disease have enhanced our understanding of this problem. Despite the advanced stage and complex pathology of these patients, the operative risk is, in general, low and the long-term results are favorable, indicating that combined operation is not an exercise in

futility. When valve replacement must be done, bioprostheses are the valves of choice.

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