MEDICAL GRAND ROUNDS
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NATURAL HISTORY OF VALVULAR HEART DISEASE
and
THE PROGNOSES OF PATIENTS WITH PROSTHETIC VALVES

"I would not have such a heart in my bosum for the dignity of the whole body."

Macbeth

William Shakespeare

INTRODUCTION

In the evaluation of any operative procedure it is important to understand the natural history and complications of the disease process without surgical intervention. Therefore, an important analysis of the natural history of acquired valvular heart disease is a prerequisite to the assessment of valvular surgery.

A few generalities about natural history of valvular heart disease may be made to place in prospective the following data.

The prognosis for a patient with valvular disease treated medically or surgically is (a) dependent on the stage of the disease at which he is first seen (b) age dependent (c) type of valve disease dependent (d) number of valves involved and (e) associated disease dependent.

Stenotic valvular lesions tend to have a poorer prognosis than chronic regurgitant lesions and warrant earlier surgical intervention.

Acute valvular regurgitant lesions are poorly tolerated and may require immediate surgery.

Valvular lesions from acute myocardial infarction or endocarditis are poorly tolerated and may constitute an immediate surgical emergency, at a high mortality risk.

Valvular surgery in patients with concommitant coronary artery disease is at a higher risk.

The aortic and mitral valves are the valves most commonly in need of surgical correction and replacement in the adult, therefore, the natural history of isolated stenotic and regurgitant lesions of these valves will be considered in detail.

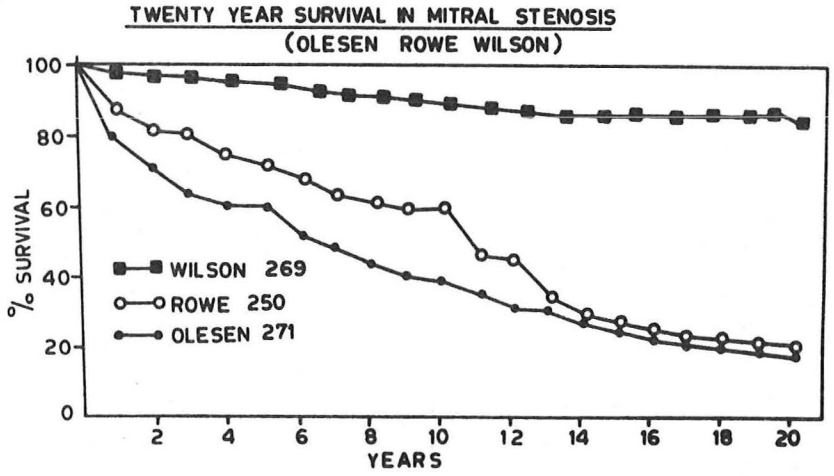
NATURAL HISTORY OF MITRAL STENOSIS

Clinical symptoms from rheumatic mitral stenosis may appear at almost any age from 6 through 80. However, the usual course of events is the development of the first attack of acute rheumatic fever at age 12 followed by a 20 year latent symptom free period. The murmur may be heard for 10 years before symptoms develop. The patient is usually in the third or fourth decade of life when he becomes symptomatic. The mitral orifice has decreased from 4-6 cm^2 to 1-1.5 cm^2.

In analysis of the course of mitral stenosis, one must consider the point in the history of the disease at which patients are entered into the study, i.e. shortly after the first attack of rheumatic fever with asymptomatic mitral stenosis or several years later when the patient becomes symptomatic.

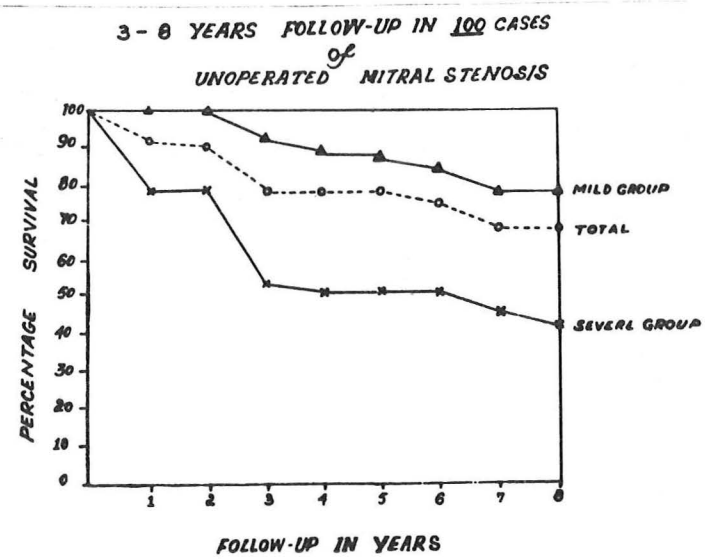
Roy and Gopinath recently summarized the natural history of surgically untreated mitral stenosis in three large series of patients: Olesen and Baden's series of 271 patients treated in the presurgical era between 1933 and 1949, Rowe and associates' group of 250 patients seen initially between 1925 and 1947, and Wilson and Lim's series of 269 patients with auscultatory evidence of mitral stenosis and insufficiency in which age 20 was considered the year of onset of mitral stenosis. The survival figures differ strikingly. Whereas 66% of Olesen and Baden's patients died within 10 years of diagnosis, only 7% of Wilson and Lim's patients died during the same number of years. It is clear from the published studies that when one examines a series of patients with mitral stenosis at different stages of the disease, the ultimate survival figures are highly dependent upon whether the patients are first seen in an asymptomatic or latent stage (as in most of Wilson and Lim's cases) or in the later symptomatic stage.

Olesen and Baden's study is particularly useful since the patients were classified according to various functional categories. Their patients in New York Heart Association functional class III had survival rates of 62% 5 years after diagnosis and approximately 38% 10 years after diagnosis, whereas class IV patients had only a 15% survival rate at 5 years and no survival after 8 years.



From Roy, et. al.

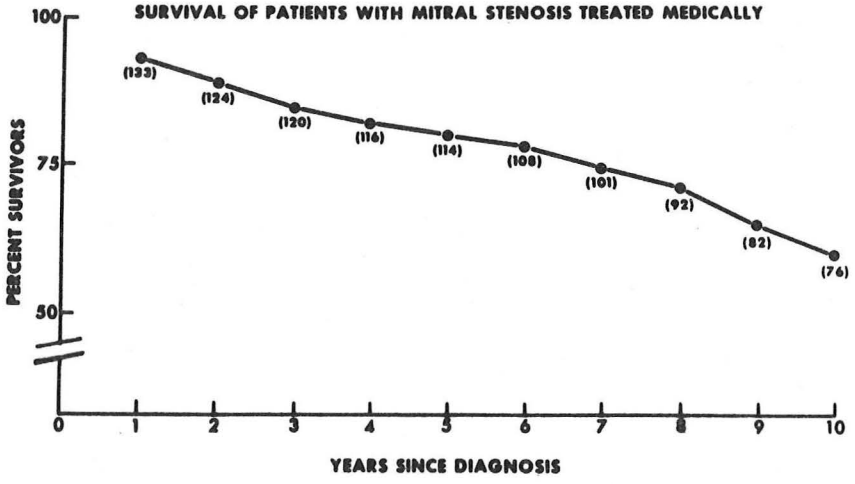
The composite survival in the 10 year follow-up of the 1,028 patients included in the above 3 series is 66%. The wide variability of survival at 20 years, 20-80%, is indicative of the time at which the patients were first detected and entered in the series.



From Roy, et.al.

The longevity of the patients is clearly related to the severity of the disease as illustrated by series reported by Roy and Gopinath above. Eighty percent of the mild patients and 47% of the severe patients were alive at 8 years.

An unselected mixed group of patients followed for 20 years at San Francisco General Hospital is reported below. It can be seen that a random series of patients with mitral stenosis diagnosed initially at different stages of the disease, 80% are alive after 5 years and 60% are alive after 10 years.



From Rapaport

It would thus appear that although the prognosis of medically treated patients with incapacitating symptoms of marked dyspnea or congestive heart failure is poor, the natural history of patients with asymptomatic or slightly symptomatic mitral stenosis is probably not so gloomy. Deaths in the medically treated groups have been due to congestive heart failure in 60-70%, to systemic or pulmonary embolism in 20-30%, and to bacterial endocarditis in 5-10% of the patients. It is reasonable to assume that with antistreptococcal penicillin prophylaxis and more energetic and efficient medical regimens, the natural history of medically managed mitral stenosis may now be somewhat better than in the past.

The average age of death from medically treated mitral stenosis is 48.

In consideration for surgery one must evaluate a patient with respect to the operative procedure. If a commissurotomy can be accomplished (a low risk procedure) early intervention would be justified (functional class II patients). However, if the mitral valve must be replaced then later intervention would be indicated (functional class III). The mitral valve usually must be replaced when the valve is heavily calcified or significant mitral regurgitation is present.

Certain indications of poor prognosis have been defined and may be indicators for operation. These are (1) atrial fibrillation (2) congestive heart failure (3) severe dyspnea on mild exertion and (4) signs of severe pulmonary hypertension.

1. Rapaport, E.: Natural history of aortic and mitral valve disease. Amer. J. Cardiol. 35:221-227, 1975.
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8. Wood, P.: An appreciation of mitral stenosis. Part I. Clinical features. Br. Med. J. 1051-1063, May 8, 1954.
9. Wood, P.: An appreciation of mitral stenosis. Part II. Investigations and results. Br. Med. J. 1113-1124, May 15, 1954.

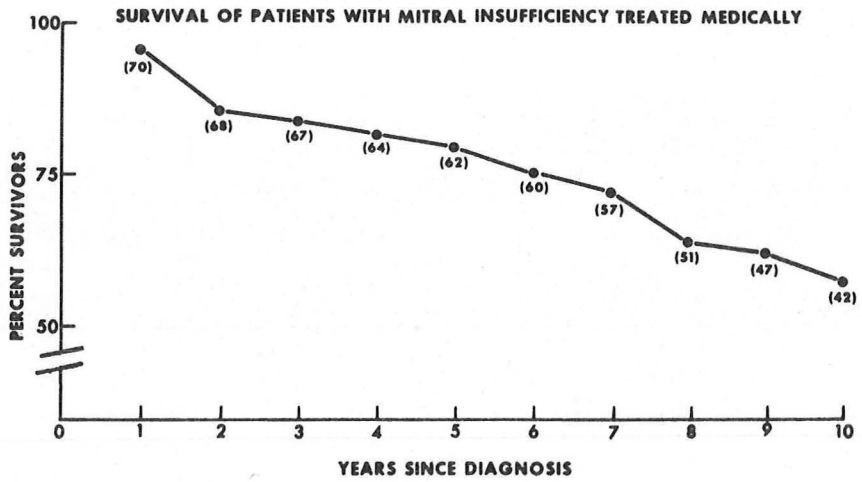
NATURAL HISTORY OF MITRAL INSUFFICIENCY

The etiology of mitral insufficiency represents a wide spectrum of disease and it is no surprise that the course of patients may be extremely variable depending upon the etiology of the mitral regurgitation, i.e. (1) acute chordae tendineae rupture may result in acute unrelenting pulmonary edema or (2) chronic rheumatic mitral regurgitation may not become symptomatic for 20 years.

Since the natural history of acute mitral insufficiency is usually dramatically different from that of the chronic form of the disease, distinction between the two is important. Causes of the acute condition include rupture of the chordae tendineae or of the papillary muscle and actual perforation or avulsion of the valve, which generally occurs as a result of acute myocardial infarction, bacterial endocarditis, trauma or as a postoperative complication of cardiac surgery. Although one tends to equate chronic mitral insufficiency with rheumatic heart disease, there are many other causes, including collagen disorders and congenital or hereditary disorders such as Marfan's syndrome, the floppy valve syndrome, endocardial cushion defects or a single papillary muscle with a parachute valve.

The natural history of patients with acute mitral regurgitation is extremely variable and often short - each patient must be individualized according to etiology and progression, therefore, only chronic mitral regurgitation can be analyzed in a meaningful composite.

Representative data has been published by Rapaport in San Francisco and illustrated below. These survival statistics are from patients who were treated medically with chronic mitral regurgitation. They tended to be diagnosed later in the course of their disease than patients with mitral stenosis yet the survival course is similar. Approximately 80% of the patients were alive 5 years from the time of diagnosis of mitral insufficiency and almost 60% were alive 10 years after the diagnosis. Any surgical procedure must improve on this survival time.



From Rapaport

10. Rapaport, E.: Natural history of aortic and mitral valve disease. Amer. J. Cardiol. 35:221-227, 1975.
11. Ellis, L.B. and Ramirez, A.: The clinical course of patients with severe "rheumatic" mitral insufficiency. Amer. Heart J. 78 (3):406-418, 1969.
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CLINICAL COURSE OF PATIENTS WITH RHEUMATIC MITRAL VALVE DISEASE

Paul Wood was the first to analyze the average course of patients with rheumatic mitral valve disease. It is of interest that both mitral insufficiency and mitral stenosis follow similar courses, in fact aortic insufficiency may closely parallel this same course. There is marked variability from patient to patient but a general reference has been developed.

LIFE HISTORY

	Latent Period			Duration of Symptoms in Years				From Onset
	Age Initial Attack	Latent Period years	Age Onset Symptoms	Class I	Class II	Class III	Class IV	to Total Disability
MS & MR	12	20	32	2.5	2.5	2.0	1.5	7

13. Wood, P.: An appreciation of mitral stenosis. Part I. Clinical features. Br. Med. J. 1051-1063, May 8, 1954.
14. Wood, P.: An appreciation of mitral stenosis. Part II. Investigations and results. Br. Med. J. 1113-1124, May 15, 1954.

NATURAL HISTORY OF AORTIC INSUFFICIENCY

Aortic insufficiency has a variety of etiological causes (rheumatic, leutic, dissection of aorta, trauma, endocarditis) and therefore a varied natural history resulting in differences of opinion regarding the natural course of the disease and accordingly the time for surgical intervention.

Acute severe aortic insufficiency from trauma, aortic dissection or endocarditis is poorly tolerated hemodynamically resulting in fulminant left ventricular failure. Medical therapy has almost no use and the treatment is immediate surgical intervention.

Chronic aortic insufficiency, usually from rheumatic etiology, is a striking contrast. The regurgitation develops slowly but progressively with a protracted course. The patient remains asymptomatic for years except perhaps for fatigue and exertional dyspnea. The volume load on the left ventricle results in little myocardial oxygen cost, the volume load progresses, the ejection fraction remains high and left ventricular compliance usually increases. The regurgitant volume may reach 80% of the total stroke volume. Peripheral vasodilatation develops reducing aortic impedence (resistance) and decreasing left ventricular work. With exercise the diastolic time shortens as heart rate increases resulting in less regurgitation with exercise and a remarkable exercise tolerance even in the setting of severe regurgitation.

Eventually cardiac decompensation occurs but usually quite late in the course of the disease associated with a large dilated left ventricle. Angina and congestive heart failure occur as a late manifestation of the disease. Sudden onset of pulmonary edema may occur in a previously asymptomatic patient. This may represent the hallmark of left ventricular myocardial deterioration.

The literature on the natural history of aortic regurgitation is difficult to analyze because of the varied time at which patients have entered studies in the course of their illness.

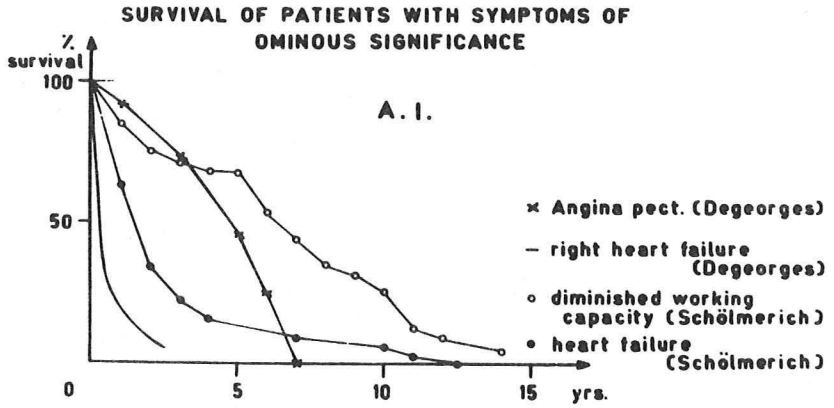
The ten-year mortality rate of patients with slight to moderate insufficiency from the time of diagnosis is 5 to 16%, a percentage which is only slightly higher than the average mortality of a normal population.

Most reports, deal with "free" aortic regurgitation, a term which is usually meant to imply aortic regurgitation with definite peripheral signs of disease, such as wide pulse pressure, enlarged left ventricle, rocking motion of the heart, or spontaneous arterial sounds. Even patients with well-defined severe disease have a relatively good prognosis. The statistics exhibiting the best prognosis for such patients are given by Degeorges and Delzant, who found that 12 of 16 patients were still alive more than 20 years after diagnosis and 4 of these patients were still free of symptoms. Most other authors report a death rate of approximately 45-55% after 10 years. However, most of these reports deal with severe regurgitation.

Segal and associates and Scholmerich have tried to outline the natural history of this disease. Apparently, in all cases of aortic insufficiency of rheumatic origin a latent period between the rheumatic fever and the development of free aortic regurgitation occurs. Segal and associates give an average time interval of 7 years, and Scholmerich of 10 years. Then follows a period free of symptoms lasting on the average from 7 to 10.3 years. The time from the appearance of symptoms to the onset of right heart failure is given as 11 years by Scholmerich with another 2.5 years until death, whereas Segal, Harvey, and Hufnagel report an average of 6.4 years from the onset of symptoms until death. Even in these blatantly symptomatic cases the prognosis varies widely. The only exception to this

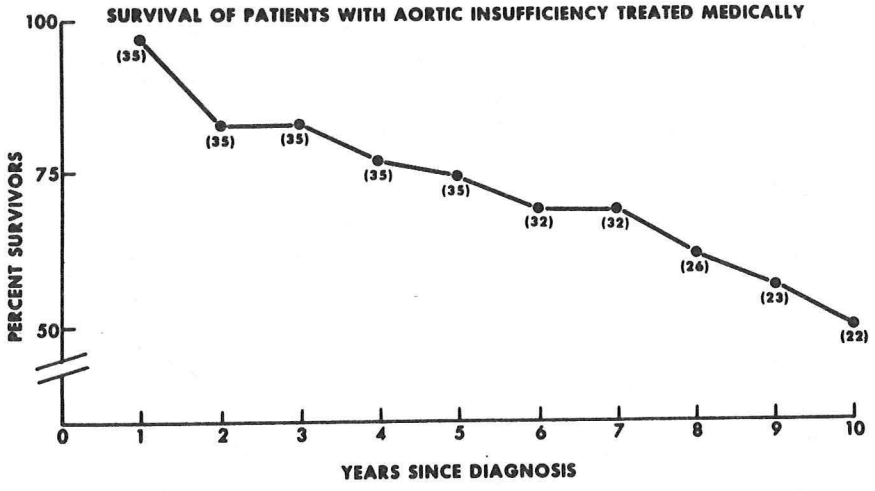
statistical variation occurs with right-sided heart failure and edema, in which death almost invariably occurs within 3 years.

The graph below shows this survival following onset of significant symptoms. This, of course, follows a prolonged asymptomatic period.



From Hegglin, et.al.

One of the better reports is by Rapaport illustrated below in a series of 35 random patients treated medically with chronic aortic insufficiency seen at various stages of their disease. In this series, 75% were alive at 5 years and 50% were alive at 10 years.



From Rapaport

A few clinical clues have been reported that are helpful in assessing the progression of regurgitation.

Spagnuolo, et.al. reported a 10-year follow-up of 174 young patients with chronic rheumatic aortic regurgitation and found 3 criteria of value in evaluating the patients' progression:

1) Significantly large left ventricles
2) Systolic blood pressure > 40 mm Hg
   Diastolic blood pressure < 40 mm Hg
3) Two ECG changes
   Left ventricular hypertrophy
   Left ventricular hypertrophy with strain

If only one or two of these three findings were present the patient fell in a low risk (0% - 10 year mortality) or intermediate risk (11% - 10 year mortality). If all three criteria were present the patients had a mortality of 33% at one year, 65% at three years and 87% at six years.

Importantly, all the series in the literature confirm that once congestive heart failure develops (usually on medical therapy) patients have a poor prognosis with a median survival of 2 years. Angina is relatively unusual (compared with aortic stenosis) and carries a median survival of 5 years.

Therapeutic Implications: Consideration of the patient with chronic aortic regurgitation for surgical intervention constitutes a serious therapeutic dilemma. Data now being accumulated from several surgical centers suggest that surgical mortality is higher in patients with chronic aortic regurgitation than in those with other valvular lesions. Equally important is the observation that myocardial failure may persist even after the volume load is alleviated. Thus, the available information suggests that an irreversible phase of left ventricular dysfunction occurs at some as yet unknown time in the course of aortic regurgitation.

In the asymptomatic patient irreversible myocardial dysfunction is developing insidiously and one could make a good theoretic case for eliminating the overload as soon as its severity is evident. However, it is necessary to consider the fate of a patient in his late teens or early 20's with fully developed aortic regurgitation who, managed medically, will probably remain asymptomatic and have a low morbidity and very low mortality until he approaches his fifth decade, as against recommendation for replacement of his aortic valve with a prosthesis having a 10 year attrition rate of 50% with an unknown course thereafter, as well as numerous nonfatal complications. Thus, both early operation and prolonged procrastination appear to be equally unsatisfactory approaches to patients with chronic aortic regurgitation. The dilemma can only be resolved with further progress in prosthetic valve design, further information about the natural history of the disease and, most importantly, information as to which of the hemodynamic abnormalities signify the onset of irreversible myocardial dysfunction.

The patient with aortic regurgitation should be followed with serial chest x-rays (watching for rapidly changing heart size), serial ECG's (watching for progressive changes of LVH) and most importantly, serial maximal exercise studies to determine the early onset of left ventricular deterioration as indicators for surgical intervention.

I feel most patients with significant aortic regurgitation should be prophylactically digitalized to prevent sudden onset of pulmonary congestion and perhaps prevent as rapid an increase in left ventricular size as regurgitation slowly increases.

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17. Hegglin, R., Scheu, H., and Rothlin, M.: Aortic insufficiency. Circulation 38 (Suppl V):V-77-V-92, 1968.
18. Massell, B.F., Amezcua, F.J., and Czoniczer, G.: Prognosis of patients with pure or predominant aortic regurgitation in the absence of surgery (abstr). Circulation 34 (Suppl. III):III-164, 1966.
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21. Morrow, A.G., Brawley, R.K., and Braunwald, E.: Effects of aortic regurgitation on left ventricular performance: Direct determinations of aortic blood flow before and after valve replacement. Circulation 31 and 32 (Suppl. I):I-80-I-93, 1965.
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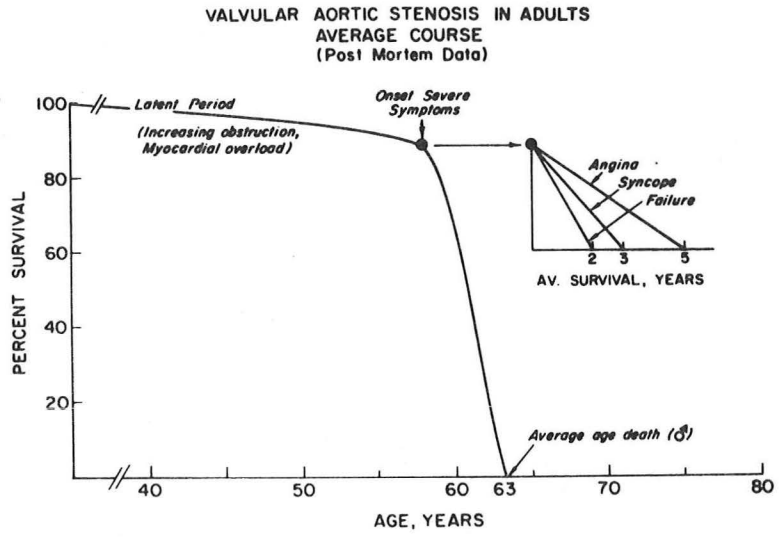
28. Bland, E.F. and Wheeler, E.O.: Severe aortic regurgitation in young people: A long-term perspective with reference to prognosis and prosthesis. New Eng. J. Med. 256:667, 1957.
29. Segal, J., Harvey, P.W. and Hufnagel, C.: Clinical study of one hundred cases of severe aortic insufficiency. Amer. J. Med. 21:200, 1956.

NATURAL HISTORY OF VALVULAR AORTIC STENOSIS

The most common cause of isolated valvular aortic stenosis in the adult is a bicuspid aortic valve that fibrosis and calcifies with age. Valvular aortic stenosis is characterized by a long asymptomatic latent period. Symptoms first appear when the orifice size diminishes from a normal 3 cm^2 to less than 1 cm^2. The hallmark symptoms are those of angina, syncope and/or congestive heart failure. A review of the literature of patients dying from isolated valvular aortic stenosis is best illustrated in the graph below taken from Morrow, et.al.

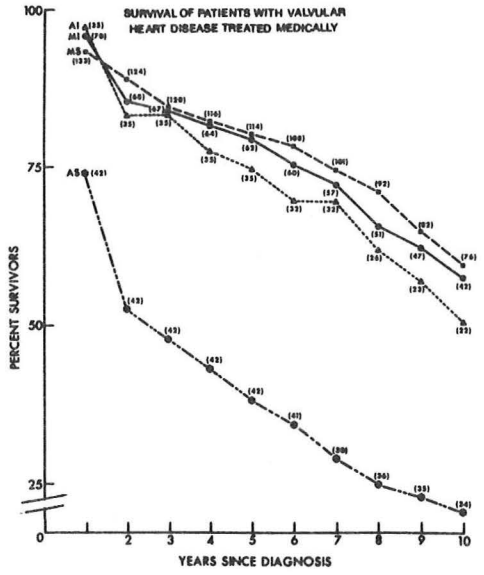


From Morrow, et.al.

It is clear that once aortic stenosis becomes symptomatic the natural history of the disease results in death in short order. The survival is also related to some degree to the presenting symptom, i.e. congestive heart failure has a worse prognosis than angina.

Similar results have been documented in other series (Frank; Bergeron; Braunwald).

The survival rate following symptoms with aortic stenosis is considerably worse than with other valvular lesions. Rapaport has shown graphically below the difference in survival in a series of patients from San Francisco General treated medically with aortic stenosis (A.S.), aortic insufficiency (A.I.), mitral insufficiency (M.I.), and mitral stenosis (M.S.).



Percent survival of patients with valvular heart disease treated medically. The poor prognosis of patients with aortic stenosis (AS) is readily contrasted with findings in patients with aortic insufficiency (AI), mitral insufficiency (MI) and mitral stenosis (MS).

From Rapaport

As we will see develop, the risk from aortic valve replacement and its complications are much better than the natural history of the disease, therefore, valvular aortic stenosis, with a few exceptions, is a surgical disease once symptoms become manifested.

30. Rapaport, E.: Natural history of aortic and mitral valve disease. Amer. J. Cardiol. 35:221-227, 1975.
31. Frank, S., Johnson, A., and Ross, J.,Jr.: Natural history of valvular aortic stenosis. Brit. Heart J. 35:41-46, 1973.
32. Morrow, A.G., et.al.: Obstruction to left ventricular outflow: Current concepts of management and operative treatment. Ann. Int. Med. 69 (6): 1255-1286, 1968.
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RESULTS OF MITRAL COMMISSUROTOMY

Mitral commissurotomy has proven its usefulness in alleviating symptoms for several years.

The literature is divided into two eras, the closed commissurotomy and the open commissurotomy and care must be used in extrapolating the data since a better operation is more likely to be done if the valve is visualized than if the procedure is blind. Thus, leaflet fracture, chordae tear and inadequate relief of stenosis is more likely to occur with the blind (no cardiopulmonary bypass) procedure. These difficulties often result in early failure (1-2 years) or early re-stenosis of the valve. If mitral valves re-stenose, they do so between 5-10 years (mean 7 years). The reported re-stenosis rate varies from 2-80% over 10 years. The higher "re-stenosis" rate represents "failure" rates and not simple re-stenosis alone resulting in confusion regarding reoccurrence of stenosis. The *failure* rate of mitral surgery can not be equated with re-stenosis since many other causes of failure are responsible for the high incidence of recurrence of symptoms, i.e. myocardial failure, progressive mitral regurgitation, associated valvular lesions, coronary embolization, etc.

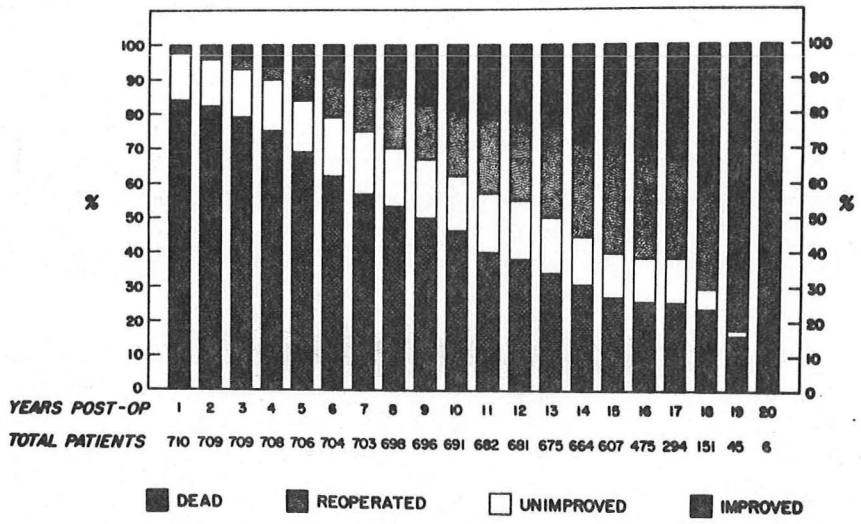
In the era of closed technique, the majority of patient improvement was maintained for a period of 6-7 years, after which rapid deterioration occurred. Significnat improvement (grade 1 and 2) was reported by McBoyle in more than 50% of his operated patients at the end of 5 years, but only 20% remained well after 8 years. Gialloreto and Tardif found that significant improvement was maintained in 82% of the patients for 5 years, after which they calculated that the rate of deterioration was 1.4% every year. They expected that by 20 years satisfactory improvement would be present in only about 54%.

Gialloreto and Tardif reported that the factors causing deterioration were inadequate surgery in 45%, atrial fibrillation in 38%, preoperative right ventricular failure in 36%, calcification in 52%, and other associated valve pathology in 56% of the patients. Belcher reported the rate of re-stenosis as 25% in 327 patients without calcification and 32% in 75 patients with heavy calcification. Late deaths in his series could be related to pre-existing mitral insufficiency ranging from 11% in 214 patients without any insufficiency to 75% in those with grade 2 insufficiency. If poor surgery is excluded, then late deterioration is due to atrial fibrillation, cardiac enlargement, myocardial failure, associated regurgitation, calcified valve, and re-stenosis.

The term "re-stenosis" needs some scrutiny. Re-stenosis, strictly speaking, should imply a recurrence of the stenosis of the mitral valve after it has been surgically corrected. However, for practical purposes it is used to describe the reappearance of symptoms and disability in a patient (after a period of well being) which originally led to surgery. Thus, it is likely that some patients with inadequate surgery may be wrongly labeled as having re-stenosis. At the Henry Ford Hospital symposium on cardiovascular surgery in 1955, Brock reported

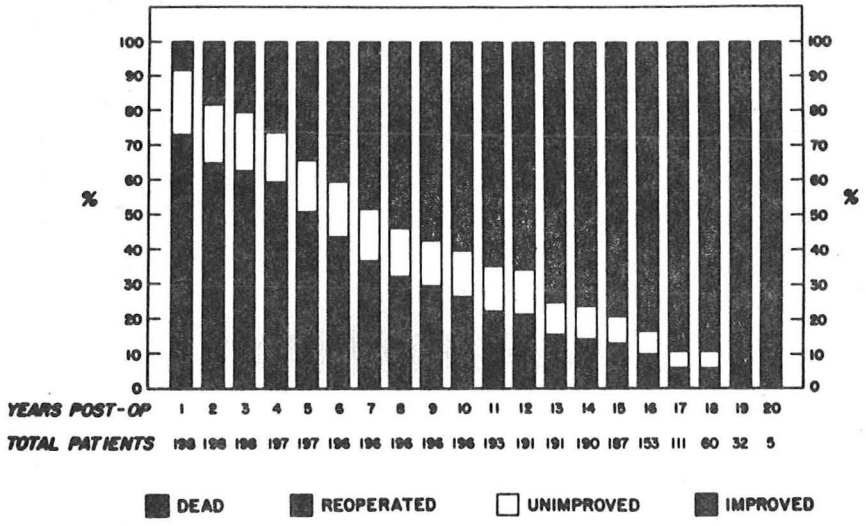
4 cases of re-stenosis in his series of 350, and Harken had 10 in 800 patients while Keys and Lam had a single case of re-stenosis in 180 mitral valvotomies. In 1957 Bailey and associates reported that of 1,000 patients with valvotomies, 22 had re-stenosis. Likoff and Uricchio estimated the rate of re-stenosis as 5% in 200 patients who were living for 5 years or more. Wood estimated that the rate of re-stenosis was 2% per annum at the Brompton Hospital in London. However, the rate of re-stenosis today seems to be related to the passage of time. Thus, Logan, Lowther, and Turner reported the rate of re-stenosis in 264 patients after mitral valvotomy as 30% in 5 years, 60% in 9 years, and 75% thereafter. McBoyle also related the occurrence of re-stenosis to the passage of time; less than 10% needed reoperation after 5 years, whereas almost 40% needed reoperation by the ninth year after the first operation. Similarly, in the series of Ellis and Harken, a second or third operation was necessary in only 6% after 5 years, but this increased to 20% after 9 years.

The results of closed commissurotomy by one surgical group (Harken, et.al., Harvard) in 1,000 patients followed for 20 years is diagramatically shown below separated into functional class III and IV patients preoperatively. The results from current techniques will probably improve on this postoperative course in future years.



Status of patients in Group III at each year of follow-up.

From Ellis and Harken

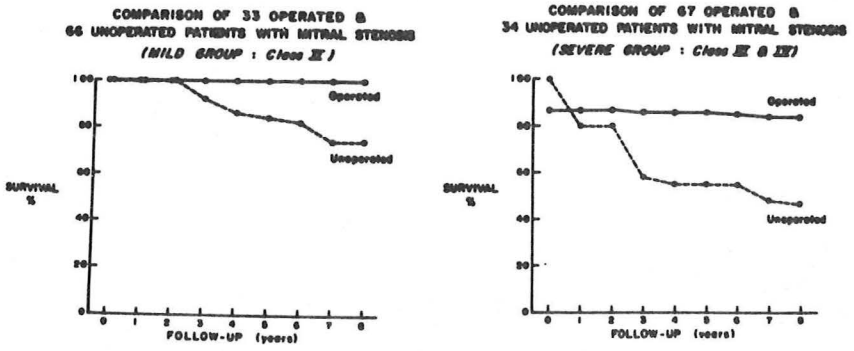


Status of patients in Group IV at each year of follow-up.

From Ellis and Harken

Medical versus Surgical Treatment

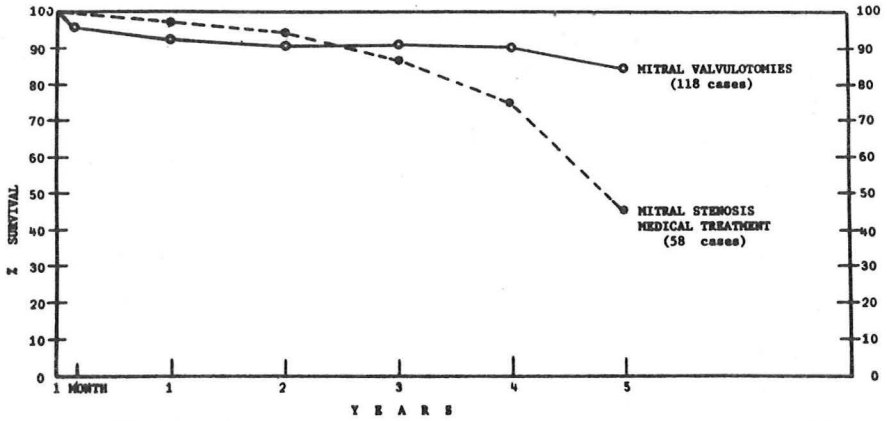
Roy and Gopinath reported a comparison of operated patients (closed commissurotomy) with a control series separated into functional class. See below.



From Roy, et.al.

These results show significant improvement in mortality with surgery.

Munoz, et.al. from Caracas reports the best series of randomized patients comparing the natural history of the disease with the results following valvulotomies shown below.



Actuarial survival curves in 58 cases of rheumatic mitral stenosis treated medically and 118 cases submitted to mitral valvulotomy.

From Munoz

To summarize, mitral valvulotomy is of proven benefit in alleviating symptoms with a low mortality rate (3-10% depending upon functional class) a significant number of patients will deteriorate with time and require reoperation, but with newer techniques these numbers should be small. The systemic embolic rate with and after surgery is probably not different than in the natural history of the disease and of course the incidence of endocarditis is no different pre- or post-operative.

39. Ellis, L.B., Singh, J.B., Morales, D.D. and Harken, D.E.: Fifteen to twenty year study of one thousand patients undergoing closed mitral valvuloplasty. Circulation 48:357-364, 1973.
40. Roy, S.B. and Gopinath, N.: Mitral stenosis. Circulation 37 and 38 (Suppl. V): V-68-V-76, 1968.
41. Ellis, L.B. and Harken, D.E.: Closed valvuloplasty for mitral stenosis. New Eng. J. Med. 270:643, 1964.
42. McBoyle, D.: Comparison of medical and surgical treatment of mitral stenosis. Brit. Heart J. 23:377, 1961.
43. Gialloreto, O. and Tardif, B.: Observations of the value of mitral commissurotomy. Canad Med. Ass. J. 89:589, 1963.
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47. Likoff, W. and Uricchio, J.F.: Results of mitral commissurotomy. JAMA 166: 738, 1958.
48. Logan, A., Lowther, C.P. and Turner, R.W.D.: Reoperation for mitral stenosis. Lancet 1:443, 1962.

EMBOLI BEFORE AND AFTER MITRAL COMMISSUROTOMY

Systemic embolization in patients with mitral stenosis has been proposed as an indication for surgical intervention. A series of 149 patients well studied by Kellogg, et.al. before and after mitral commissurotomy revealed little difference in the rate of emboli before; and with or after mitral commissurotomy and reported the following:

In a series of 149 patients subjected to mitral commissurotomy, 28% had preoperative systemic embolization. Nine patients, or 6%, had systemic emboli associated with surgery. Of the 136 patients surviving surgery, 12.5% had subsequent systemic emboli with an incidence of 4.8% per patient-year, comparable to the reported natural incidence of systemic emboli of 4.0% per patient-year.

This suggests that mitral commissurotomy does not prevent systemic emboli and does not decrease the natural incidence of such emboli. Unless there are other indications for mitral commissurotomy, systemic embolization may best be prevented with prolonged anticoagulant therapy.

Atrial fibrillation appears to predispose to systemic emboli before commissurotomy. Following surgery the incidence of emboli was less in functional class I and II than in III and IV, but prior to surgery the incidence was essentially the same in the two groups.

Contrary to a published report, the presence of atrial thrombosis or calcified mitral valve was not accompanied by an increased incidence of preoperative systemic emboli.

The observations concerning pulmonary infarction suggest that mitral commissurotomy has little effect on the incidence of pulmonary emboli, which probably occur as late manifestations in the course of rheumatic heart disease.

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50. Logan, A. and Turner, R.: Mitral stenosis: Diagnosis and treatment. Lancet 1: 1057, 1953.
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CAUSES OF MORBIDITY AND MORTALITY WITH PROSTHETIC VALVE SURGERY

Causes of Morbidity and Mortality in the Early Post-operative Period (< 2 months) after Cardiac Valve Replacement

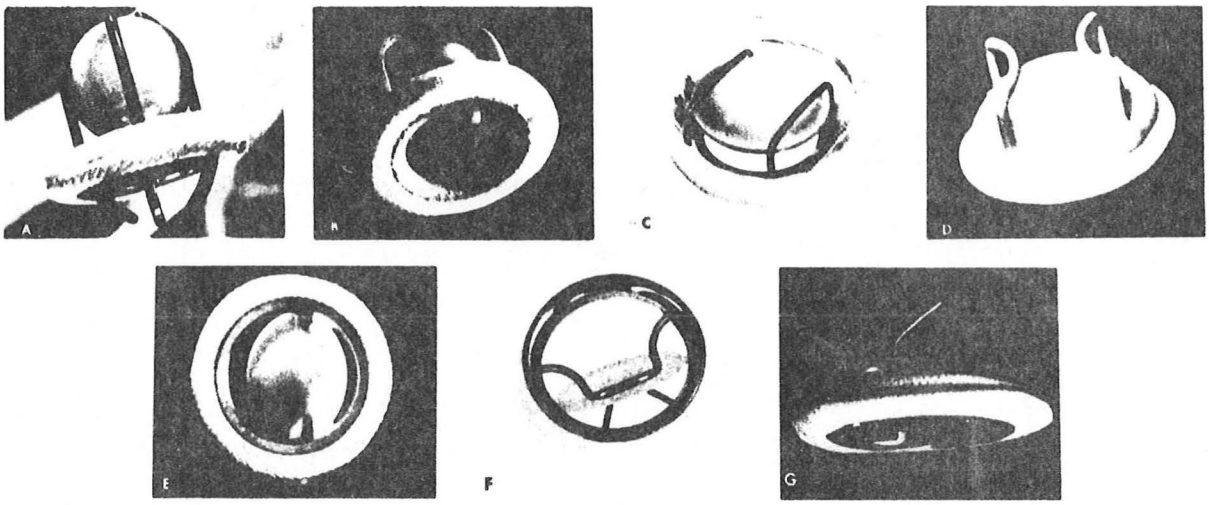
Technical mishap
Hemorrhage
Thromboemboli - air, calcium, silicone or other foreign material, blood components (large, small; systemic, pulmonary)
Undiagnosed or uncorrected cardiac disease - valvular, coronary atherosclerosis, other
Cerebrovascular accident
Respiratory insufficiency
Hepatic or renal disease
Prosthetic dysfunction - stenosis, incompetence, thrombosis, peribasilar leak
Infection - prosthesis, other sites
Primary cardiac failure
  Pump failure or arrest in operating room
  Sudden death (arrhythmia)
  Low cardiac output syndrome
  Hemolysis

Causes of Morbidity and Mortality in the Late Post-operative Period (> 2 months) after Cardiac Valve Replacement

Prosthetic dysfunction - stenosis; incompetence; thrombosis; peribasilar leak; infection; degeneration of ball, disc or tissue
Thromboembolism - pulmonary, systemic
Hepatitis
Cerebrovascular accident
Underlying cardiac disease - valvular, coronary atherosclerosis, chronic CHF, other
Sudden (arrhythmia)
Noncardiac
Hemolysis

55. Joassin. A. and Edwards, J.E.: Cardiovascular Clinics 5 (1):169, 1973.
56. Roberts, W.C., Bulkley, B.H. and Morrow, A.G.: Prog. Cardiovasc. Dis. 15:539, 1973.

*Outline compliments Dr. Maximillian Buja - Cardiac Pathology Division



2. Some of the currently used prostheses for mitral valve replacement. The Smeloff-Cutter valve (A) employs a titanium double cage with a silastic ball. The ball does not seat in the valve ring but passes through it, being restrained by the cage underneath. This design permits a smaller ball to be used than in a comparable Starr-Edwards valve. The Braunwald-Cutter valve (B) employs a silastic ball. The metallic inflow ring is entirely covered with polypropylene mesh and the cage struts with knit dacron, both ultra-thin to limit excessive tissue ingrowth into the orifice. Cage is open-ended to eliminate the area of heaviest fibrin deposit, found experimentally to be at the cage apex. The Kay-Shiley valve (C) is representative of the caged disc prosthesis. The cage is Stellite, and the disc is silastic. The sewing ring is fabricated from Teflon or Dacron cloth. The model illustrated incorporates a "muscle guard," designed to prevent interference with disc movement by the ventricular muscle. The Beall valve (D) is a caged Teflon disc valve. Sewing ring and base are covered with Dacron velour, and the titanium cage legs are coated with Teflon. In the Wada valve (E), the ring is made from titanium, the sewing ring of knit Teflon and the occluder of "Halon." The disc pivots 60° about the hinges to the open position, providing unobstructed flow through the major orifice. The hinge mechanism holds the disc in place, since there is no cage. In the Bjork-Shiley valve (F), the ring and cage are of Stellite, the suture ring of Teflon and the disc of Delrin (acetyl resin), a plastic chosen because of its fatigue endurance. The free-floating disc tilts open to 50°, providing unobstructed flow through the major orifice. The disc of the Lillehei-Kaster valve (G) is made from pyrolite-carbon and is retained by a titanium housing that permits the disc to open to a maximum angle of 80°. The soft sewing ring is of porous Dacron cloth. The metal valve housing can be rotated within the sewing ring to permit optimal alignment of the disc after fixation. A controlled, small amount of back-flow is permitted around the closed valve, thought to be beneficial in inhibiting clot formation.

AORTIC VALVES

Model 2310-20

This is the current totally cloth-covered prosthesis, which was introduced in 1968. It has cloth-covered struts, a stellite poppet and a composite seat of metal studs which project through the cloth lining of the valve seat.

Model 1200-60

This is the current non cloth-covered prosthesis which was introduced in 1966. It has bare metal struts, a silastic poppet and an extended cloth covering of the inflow orifice.

Model 1000

This was the early caged-ball prosthesis. It was introduced in 1961 and was implanted in patients through 1965. It has bare metal struts, a silastic poppet and a metal inflow face with three feet projecting into the orifice.

MITRAL VALVES

Model 6310-20

This is the current totally cloth-covered prosthesis, introduced in 1968. It has cloth-covered struts, a stellite poppet and a composite seat of metal studs projecting through the cloth lining of the seat.

Model 6120

This is the current non cloth-covered prosthesis, introduced in 1965. It has bare metal struts, a silastic poppet and an extended cloth covering of the inflow orifice.

Model 6000

This was the first generally available mitral caged-ball prosthesis. It was introduced in 1961, and was implanted in patients through 1965. It has bare metal struts, a silastic poppet and a metal inflow face.

PROSTHETIC DYSFUNCTION

Prosthetic dysfunction may occur immediately in the postoperative period or may be a delayed phenomenon occurring several years after valve replacement usually due to thrombosis or degeneration of the mechanical system of the valve.

The causes of abnormal function of the prosthetic valve are stenosis, incompetence, thrombosis, perivalvular leaks, infection, degeneration of the poppet, disc, or tissues, or technical errors in insertion.

Malfunction can be a result of clott or tissue ingrowth into the valve apparatus resulting in an abnormally functioning poppet or disc with resultant stenosis or regurgitation or emboli. Fabric coverings have become worn and ragged resulting in fabric emboli. Dehiscence of the sewing ring due to suture breakage or disruption from the sewing bed because of friable, calcific or necrotic tissue is a major cause of dysfunction. The valve struts or cage may interfer with ventricular contraction resulting in abnormal ventricular function. The cage may be inserted in a small aorta resulting in the aortic wall impeding the motion of the poppet causing stenosis or insufficiency. Hemolysis or embolization may be signs of these problems. The sudden onset of chest pain or dyspnea may also be a hallmark of valve failure and require immediate evaluation of the patient for possible valve replacement.

Physical findings may be those of anemia, peripheral embolic signs similar to endocarditis or abnormal valve sounds and/or murmurs of regurgitation, stenosis or perivalvular leaks.

Each prosthetic valve, under normal conditions, produces sounds which are not only peculiar to that valve but also in some way common to other valves. Aortic and mitral caged ball (e.g., Starr-Edwards, Magovern) and caged disc (e.g., Beall, Kay-Shiley) valves have opening and closing clicks. The so-called hinged valves (e.g., Wada-Cutter, Bjork-Shiley), however, have muffled or absent opening sounds with only a prominent closing click. Before adequate diagnosis may be made, the exact style and nature of the valve must therefore be known. It is also possible for virtually any aortic prosthesis to exhibit a moderate systolic murmur in one patient but not in another. A changing condition, however, within the same patient, signifies the possibility of obstruction or beginning abnormality, such as the ingrowth of pannus or fibrous tissue onto the cage struts or surrounding tissue. Prosthetic mitral valves seldom exhibit prominent diastolic murmurs, while a characteristic opening click is usually found occurring at about the time of the opening snap of mitral stenosis (0.07-0.15 sec. after S_2). A prominent diastolic murmur may signify the beginning of valvular obstruction from either a supravalvular or infravalvular disease process. In general, the Starr-Edwards caged ball valves do not permit valvular regurgitation during full seating of the ball. The Magovern ball valve, the Wada-Cutter and Bjork-Shiley disc valves, however, have inherent regurgitation of small degree, which is ordinarily faintly audible. In these latter valves, it is usually impossible to differentiate a periprosthetic leak from normal valvular function by physical examination alone if the closing click remains intact.

Abnormal Auscultatory Findings

The most common abnormalities found during auscultation are loss of either opening or closing clicks, muffled metallic sounds, variability in sound from beat to beat, a change in the sound from one examination to the other, or the total loss of both clicks. Ordinarily, the decrease or loss of a closing click represents poor seating of the poppet due to restriction of excursion, reduced poppet velocity, a poor approximation of the poppet to the valve seat due to extrinsic interference. A decreased opening click in the case of caged poppet prostheses suggests poppet variance, restriction of motion, or possibly suture dehiscence with partial cocking and reduced excursion. Variability in the opening click, particularly increased sounds, suggests partial restriction of the poppet requiring an increased pressure to provide full opening. Examination of the peripheral blood pressure may confirm a higher pressure with a louder click, suggesting interference with the poppet motion and partial valvular obstruction.

An extensive review of each type of valve and its specific problems is beyond the scope of this protocol. The major complications and methods of detection will follow in this review.

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59. Rosky, L.P. and Rodman, T.: Medical aspects of open-heart surgery. New Eng. J. Med. 274 (15):833-840, 1966.
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61. Kloster, F.E., Herr, R.H., Starr, A. and Griswold, H.E.: Hemodynamic evaluation of a cloth-covered Starr-Edwards valve prosthesis. Circulation 39 and 40 (Suppl. I):I-119-I-125, 1969.
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64. Roberts, W.C. and Morrow, A.G.: Late postoperative pathological findings after cardiac valve replacement. Circulation 35 and 36 (Suppl. I):I-48-I-62, 1967.
65. Roberts, W.C. and Morrow, A.G.: Mechanisms of acute left atrial thrombosis after mitral valve replacement: Pathologic findings indicating obstruction to left atrial emptying. Amer. J. Cardiol. 18:497-503, 1966.
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70. Roberts, W.C., Lambird, P.A., Gott, V.L. and Morrow, A.G.: Fatal aortic regurgitation following replacement of the mitral and aortic valves: A mechanical complication of double valve replacement. J. Thorac. Cardiovasc. Surg. 52 (2):189-192, 1966.
71. Roberts, W.C. and Morrow, A.G.: Cardiac valves and the surgical pathologist. Arch. Path. 82:309-313, 1966.
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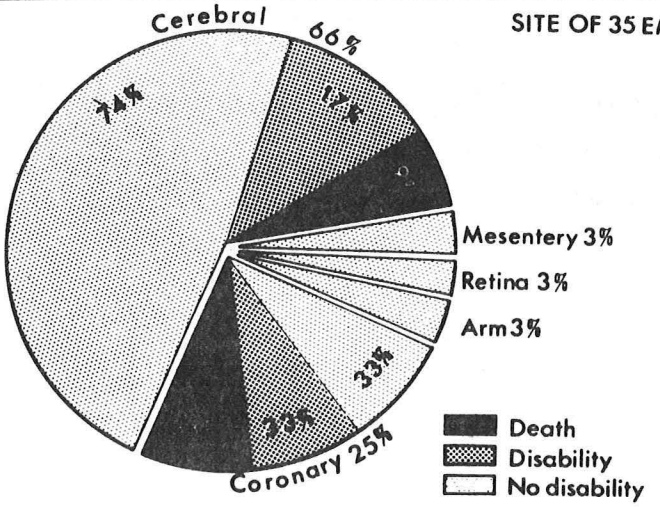
THROMBOEMBOLIC COMPLICATIONS

Systemic emboli have been a major threat following replacement of cardiac valves. Attempts to reduce the risk include anticoagulant drugs, pharmalogic agents reducing platelet adhesiveness, and partial or total covering of metal parts by Dacron and Teflon. Continued improvement in the incidence of emboli has resulted from these developments and now the homograft and heterograft valves are almost free of embolic complications.

An appraisal of embolic phenomenon associated with prosthetic valves is important since over 50,000 patients have these valves in place.

Friedli, et.al. have extensively analyzed a series of 170 patients with a mean follow-up time of 26 months following mitral and aortic valve replacement primarily with the Starr-Edwards prostheses to evaluate the use of anticoagulant therapy.

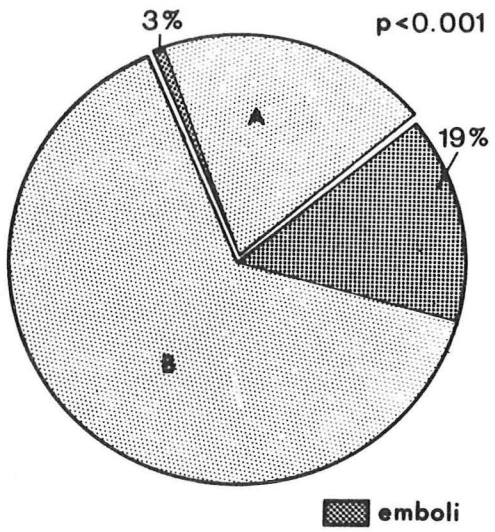
Thirty-five embolic episodes occurred as seen below.



Location of 35 emboli, with percentage of fatal outcome and permanent disability.

From Friedli, et.al.

The necessity of good anticoagulant control is shown in the diagram below.

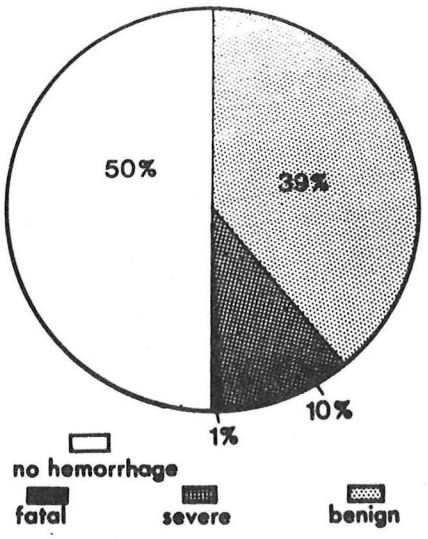


Incidence in a group (A) with good anticoagulant control (15% or less inadequate values as compared to a group (B) with less satisfactory control (more than 15% inadequate values), (A) comprises 33 patients, 1 with embolism; (B) 137 patients, 16 with embolism.

From Friedli, et.al.

The group (A) patients had prothrombin times less than 30%.

Hemorrhagic complications were frequent as seen below.

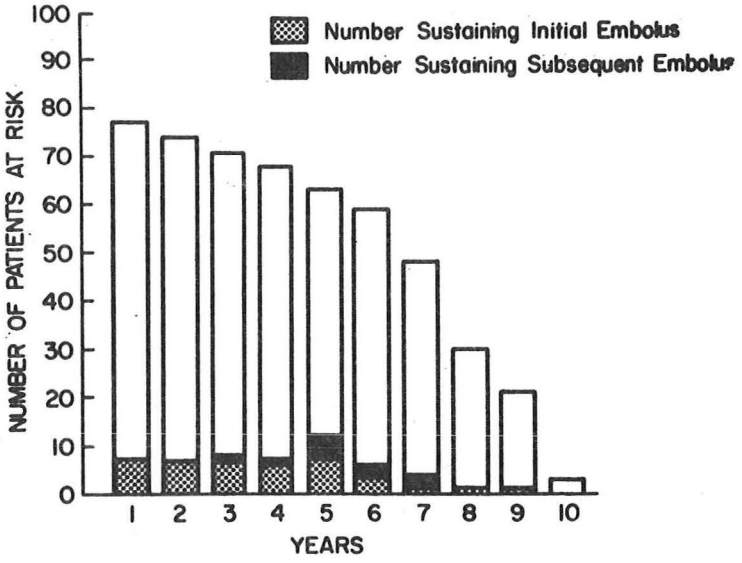


Hemorrhagic complications in 170 patients receiving anticoagulants.

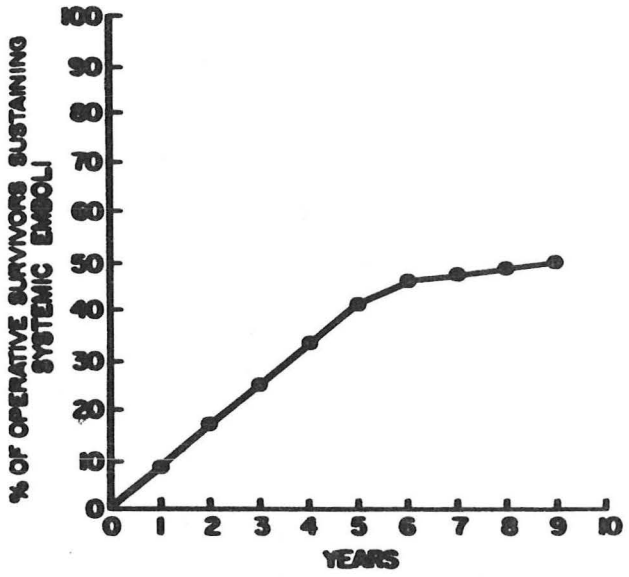
From Friedli, et.al.

Hemorrhagic phenomena were reported in half of the patients. Thirty-nine percent had benign episodes like bruises, epistaxis, and minor hematomas. Ten percent had serious hemorrhage necessitating hospital care, and transfusions in most instances. Two patients died (1.2%), one of severe retroperitoneal hemorrhage, and the other one of diffuse gastrointestinal tract bleeding. Thus, we see anticoagulant therapy is necessary but not without serious risks involved.

Morrow, et.al. reported the embolic rate of 100 patients on anticoagulants followed for 10 years with cloth-covered Starr-Edwards mitral prostheses. The results are seen below.



Number of patients surviving operation who have sustained an initial systemic embolus, and the number who have sustained subsequent systemic emboli, in each postoperative year.

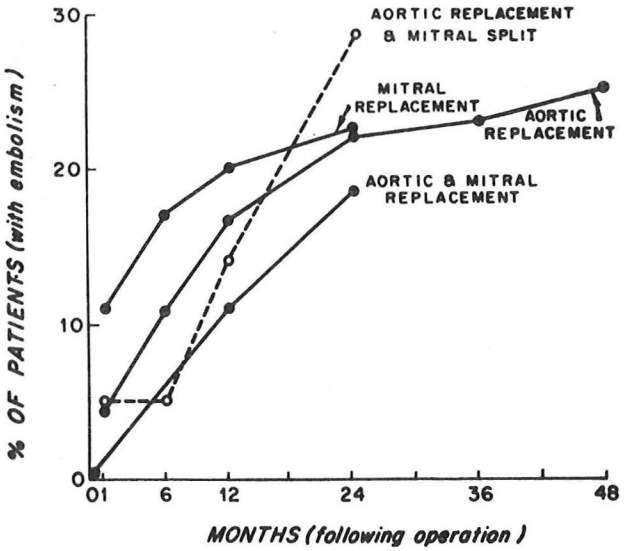


Cumulative percentage of patients surviving operation who have sustained at least one systemic embolus.

From Morrow, et.al.

Systemic arterial emboli occurred throughout the postoperative period. Thirty-three of the 83 operative survivors (40%) had emboli in the first 5 years, and 12 of the 62 patients (19%) at risk greater than 5 years have had at least one embolic episode later than 5 years after operation; in 7 of these 12 patients this was their first embolic episode. Seven of the 8 deaths caused by emboli have occurred 4 or more years postoperatively.

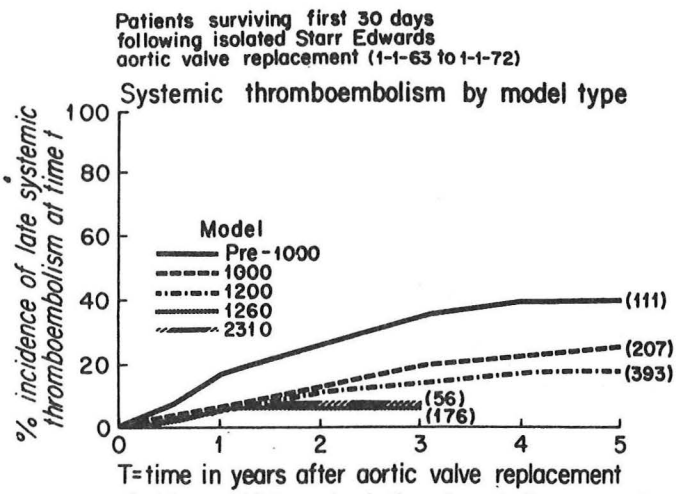
The incidence of emboli are different with different or multiple valves replaced as seen in this series of 283 patients reported by Akbarian from Massachusetts General Hospital.



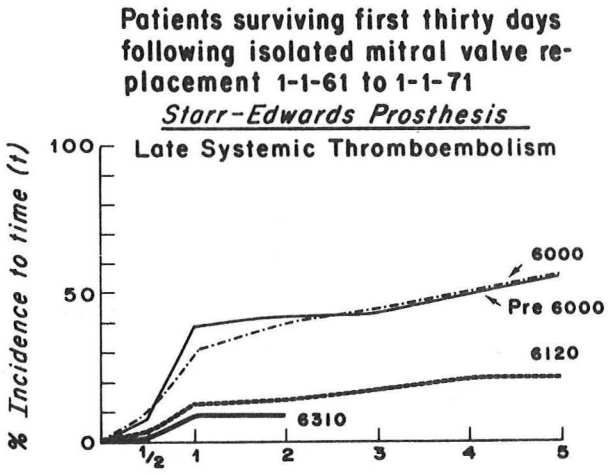
Incidence of postoperative thromboembolism among various groups of patients.

From Akbarian, et.al.

The rate of embolization has declined with the improvement in valve design, i.e. cloth covering, metal poppet, etc. This is illustrated in the following series.

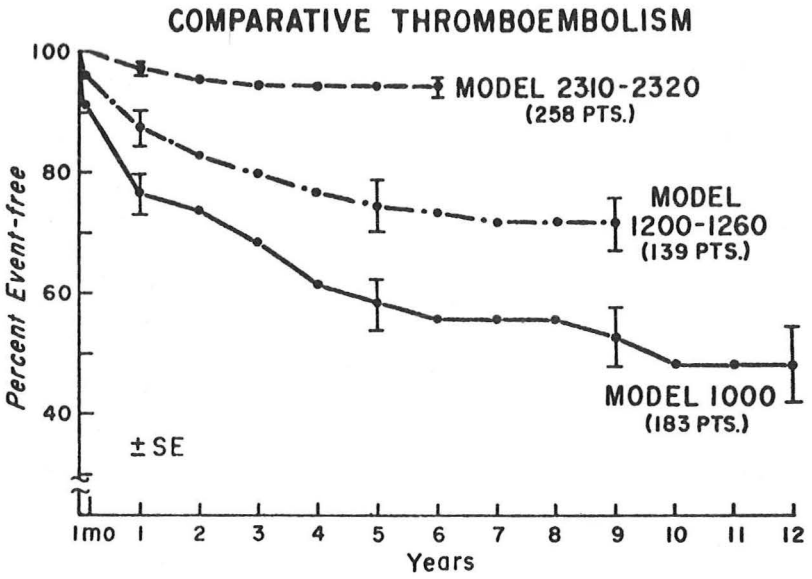


Incidence of late systemic thromboembolism, according to model of prosthesis, in operative survivors of isolated Starr-Edwards aortic valve replacement.

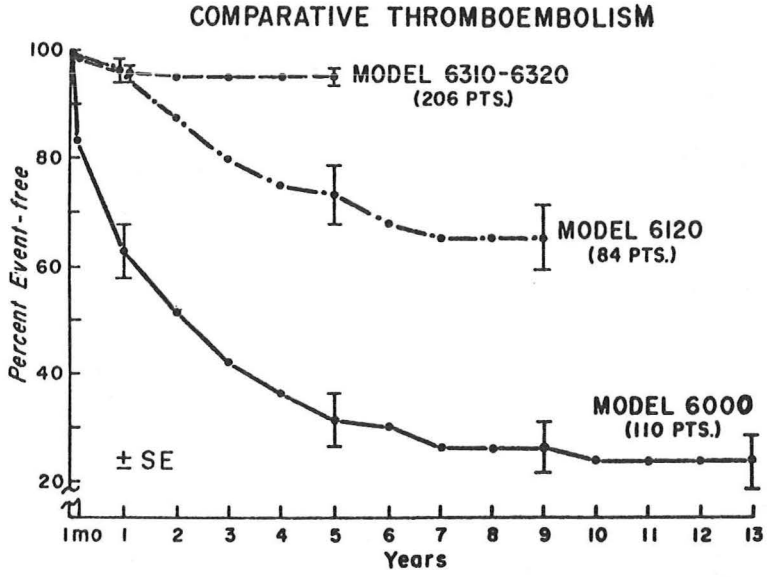


Incidence of late systemic thromboembolism, according to model of prosthesis used, in operative survivors of isolated Starr-Edwards mitral valve replacement.

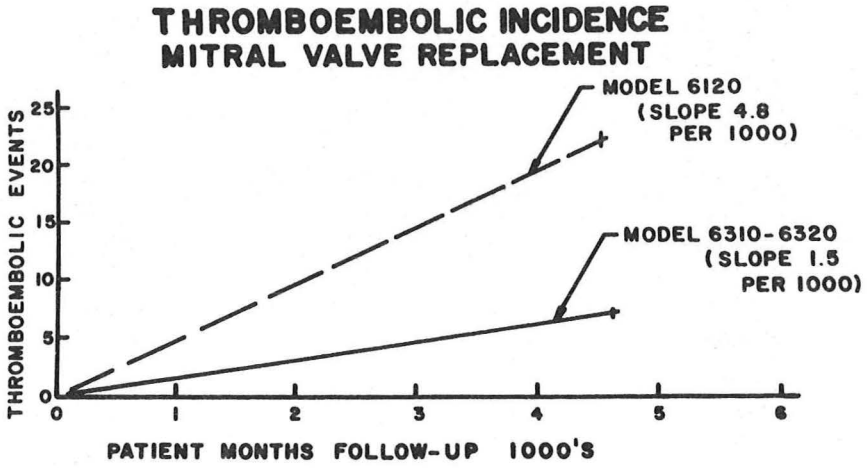
From Barnhorst and McGoon



From Albert Starr - Aortic Prosthesis



From Albert Starr - Mitral Prosthesis



From Albert Starr - Mitral Prosthesis

All of the above patients reported were on Coumadin anticoagulation although often not adequate. Isom and Spencer have reviewed the incidence of emboli and hemorrhage in their patients with prosthetic valves in the table below.

EMBOLIC AND BLEEDING COMPLICATIONS IN STUDY GROUP

	On Warfarin Sodium Emboli/Patient-months	Hemorrhagic bleeding	Off Warfarin Sodium Emboli/Patient-months
Aortic	0/2,052	10	1/786
Mitral	3/2,081	5	3/402
Mitral and aortic	1/670	0	2/130
Mitral and tricuspid	0/186	1	3/32

To summarize the data:

THROMBOEMBOLISM

Incidence = 2-10%/year; < often 5 years
Majority cerebral and coronary
↓ With adequate and stable anticoagulation
↑ Mitral valves
↑ Atrial fibrillation
↓ Cloth-covered valves

ANTITHROMBOGENIC THERAPY

Warfarin Sodium (Coumadin)
Prothrombin time = < 30%
(1½ times normal)
↓ Emboli by > 50%

HEMORRHAGE/YEAR ON COUMADIN

25% Total
5% Severe
0.5 - 1% Fatal

74. Isom, O.W., Williams, C.D., Falk, E.A., Spencer, F.C. and Glassman, E.: Evaluation of anticoagulant therapy in cloth-covered prosthetic valves. Circulation 47 and 48 (Suppl. III):III-48-III-50, 1973.
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ANTICOAGULATION AND ANTIPLATELET THERAPY

As a general rule, anticoagulants (Coumadin or its derivatives) are recommended for all patients with prosthetic valves.

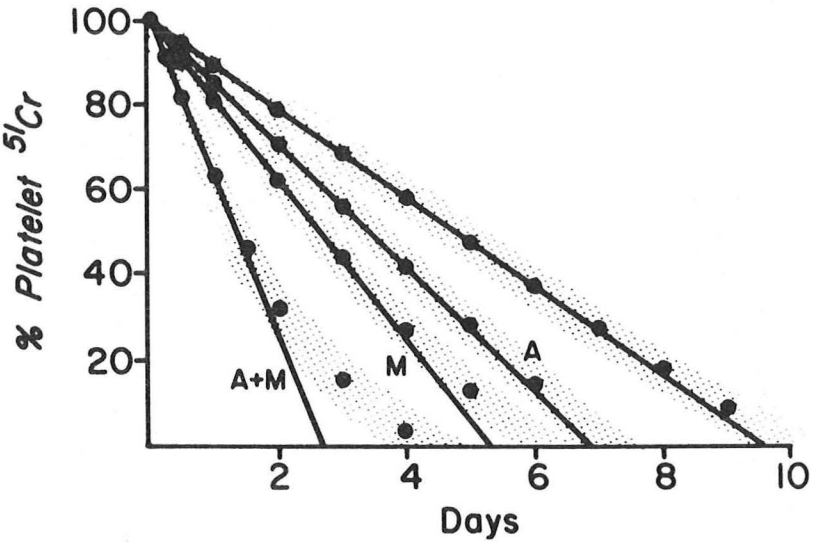
Homograft and heterograft valves appear to be relatively free of embolic complications and need not be anticoagulated.

The search for agents that do not give bleeding problems and yet reduce embolic complications has lead to the evaluation of dipyridamole (Persantin) and aspirin in patients with prosthetic valves since both these agents have an antiplatelet aggregation effect. Sullivan, Harken and Gorlin have reported a double blind study using dipyridamole (Persantin) 400 mg daily along with adequate anticoagulation using Coumadin (in all patients). The embolic rate decreased from 14.3% to 1.3% with the addition of Persantin over a one year period. This suggests that Persantin may be useful, although this study does have an inordinately high embolic rate in the control group and remains open to question.

Surgical groups are using a combination of Coumadin, and/or Persantin or Persantin and aspirin post valve replacement but matched published series are yet unavailable. Persantin is expensive and apparently is just as effective if used in 1/4 the dose (100 mg daily) if combined with 10 grains of aspirin daily.

The following platelet survival studies are of importance in patients with prosthetic valves.

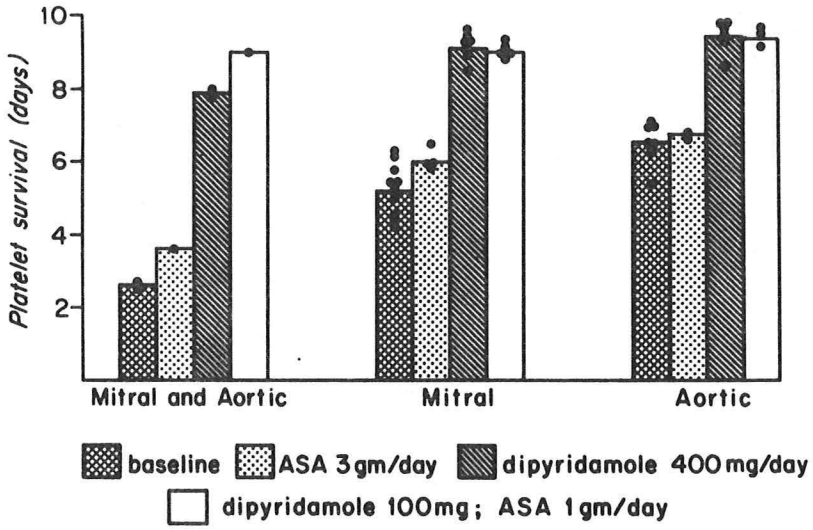
Harker and Slichter first measured platelet survival time in a series of normals and 18 patients with aortic, mitral and combined Starr valve prostheses. The results are illustrated on page 32.



Composite disappearance curves of ^{51}Cr-labeled platelets in normal subjects compared with patients who have received cardiac prostheses of the aortic valve (A), the mitral valve (M) and both aortic and mitral valves (A+M). The average platelet life-span is obtained by extrapolation of the initial slope of the disappearance curve to "zero" activity[6,8,9] as indicated by the solid line. The shaded area represents $\pm$ 1 S.E.

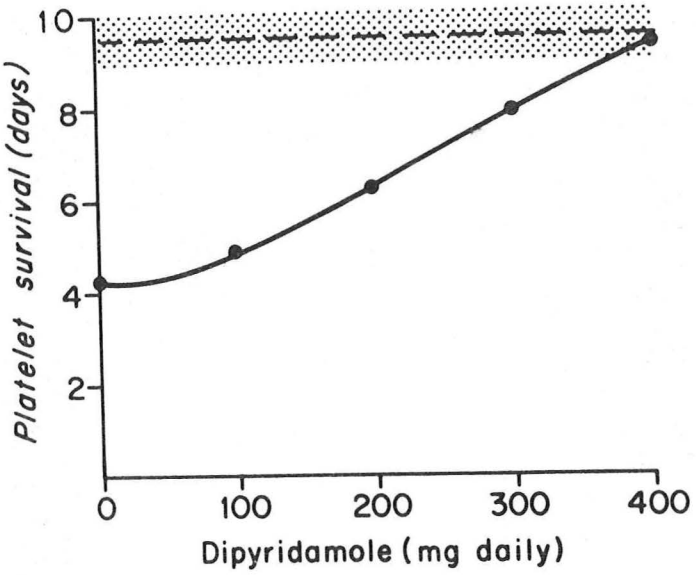
From Harker and Slichter

They also demonstrated the improvement in platelet survival with dipyridamole and with aspirin illustrated below.



Effect on platelet survival of dipyridamole and acetylsalicylic acid (ASA) in patients with prostheses of the mitral and aortic valves. Little or no effect was produced by ASA in correcting platelet consumption by the artificial valve, whereas dipyridamole, 100 mg four times daily, or dipyridamole-ASA combination in a single daily dose prevented valve-related platelet consumption.

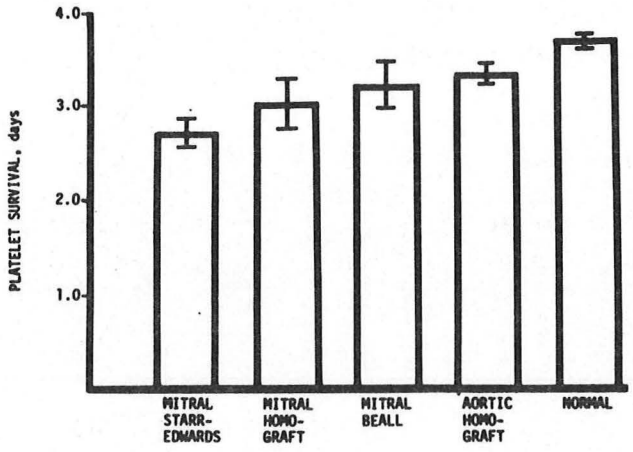
From Harker and Slichter



Dipyridamole dosage was directly related to the correction in platelet survival toward normal (shown as broken line ± 1 S.E.). Dipyridamole was given in four equally divided doses daily. Platelet survival became normal when 100 mg of dipyridamole was given four times a day.

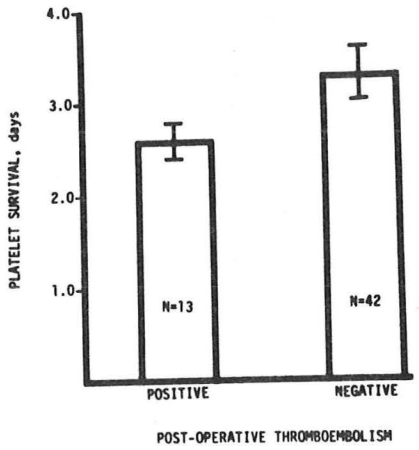
From Harker and Slichter

The results suggest the usefulness of these drugs in prevention of emboli however embolic complications were not evaluated. Weily, et.al. evaluated embolic complications pre- and post-op, correlating them with platelet survival illustrated below suggesting the usefulness of platelet survival times (and indirectly Persantin and aspirin) in the evaluation and prevention of emboli.

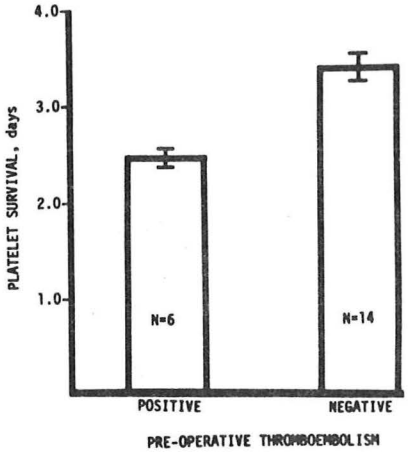


Platelet Survival Half-Time (± S.E.M.) in Patients with Substitute Mitral and Aortic Valves.

From Weily, et.al.



. Relation between Platelet Survival Half-Time and Thromboembolism (after Valve Replacement) in Patients with Substitute Valves.



Relation between Postoperative Platelet Survival Half-Time and Preoperative Thromboembolism in Patients with Mitral-Valve Replacement with Newer Prostheses (Beall, Series 6300 Starr-Edwards) and Stented Aortic Homografts.

From Weily, et.al.

General recommendations for anticoagulant therapy are outlined below.

ANTITHROMBOGENIC THERAPY

1. Dipyridamole (Persantin) and Warfarin Sodium
   400 mg daily
   ↓ Emboli by 70-99%
2. Dipyridamole (Persantin)
   400 mg daily
   ? Incidence of emboli
3. Dipyridamole (Persantin) and ASA
   100 mg dipyridamole daily
   1 gm ASA daily
   ? Incidence of emboli

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HEMOLYSIS

While clinically significant hemolytic anemia has been reported in only 5-10% of patients with aortic ball-valve prostheses, compensated hemolysis is much more frequent and is thought by some to be an almost constant finding. This variability in the reported incidence and severity of hemolysis may be related to the methods used to detect hemolysis as well as to the type of prosthesis inserted.

The red cell has a critical tolerance to shearing stress. High shearing stresses cause stretching of the membrane with tearing and cell fragmentation. Fragmented calls or schistocytes are not specific for heart valve hemolysis since fragmentation is an important final common pathway for red cell destruction in a variety of hemolytic states. However, the number of fragmented cells in the peripheral blood of patients with artificial heart valves appears to bear a direct relationship to the severity of the hemolysis. Thus schistocyte counts are useful in the evaluation of the extent of hemolysis.

The red cell is rich in LDH fractions 1 and 2. Hemolysis results in elevated serum levels, and increased concentrations of both total LDH and the isoenzyme LDH 1 have been reported in patients with aortic prostheses. LDH levels in moderate to severe hemolysis exceed 500 mU/ml.

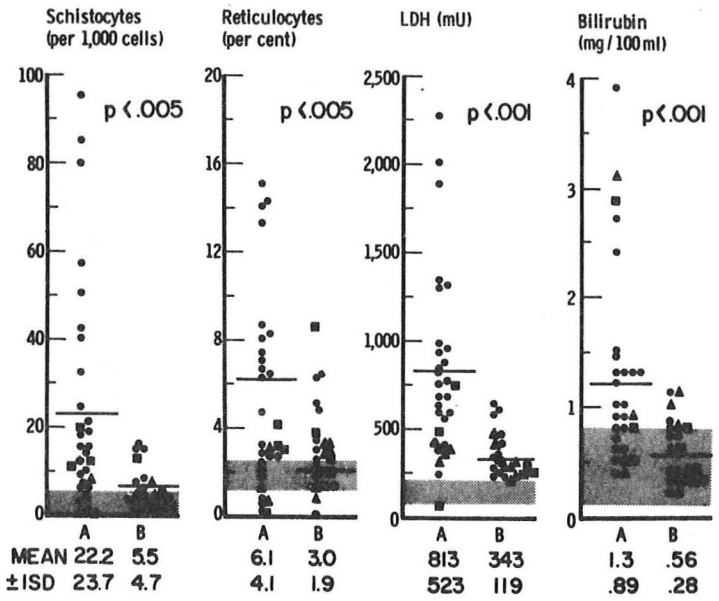
Red cell fragmentation results in loss of a piece of membrane which may or may not contain hemoglobin. Free hemoglobin dissociates into half molecules which are rapidly bound to plasma haptoglobin. The hemoglobin-haptoglobin complex is too large to pass through the glomerulus and is cleared from the circulation by the reticuloendothelial system. After plasma haptoglobin has been depleted, the half molecules (molecular weight, 34,000) pass through the glomerular filter into the proximal tubule, and the free hemoglobin remaining in the circulation is oxidized to methemoglobin. When large quantities of hemoglobin are presented to the tubule,

the transport mechanism is exceeded and hemoglobinuria occurs. When smaller quantities are filtered, hemoglobin is absorbed by the cells of the proximal tubule where it is converted to ferritin and hemosiderin. Later when the tubule cells desquamate, hemosiderin granules may be seen by light microscopy in the sediment stained for iron. Thus hemoglobinuria occurs acutely with massive hemolysis while hemosiderinuria is found in chronic intravascular hemolysis.

With hemolysis, hemoglobinuria is observed only in those patients with the most severe hemolysis. Hemosiderinuria is frequently seen 3 months or more postoperatively but was rarely observed less than 4 weeks postoperatively. This lag in excretion is presumably due to the time required for the iron to be metabolized by the proximal tubule cells and for the tubule cells to desquamate.

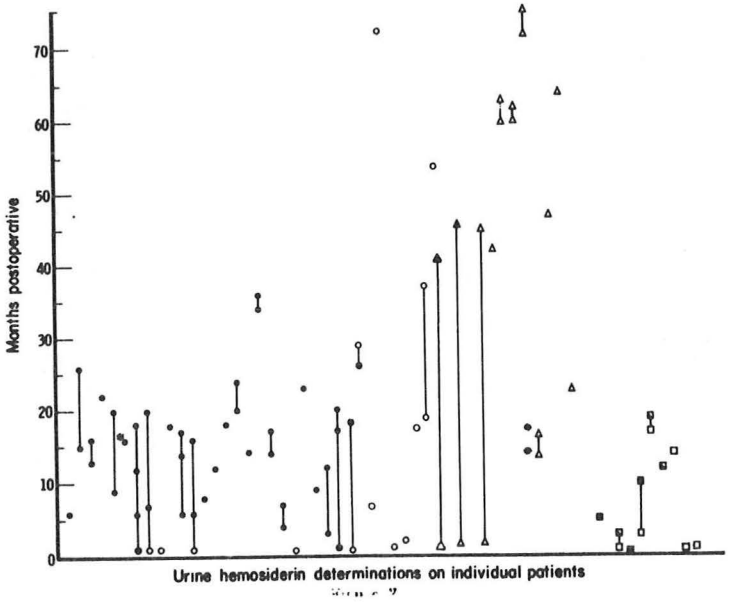
In studies reported by Eyster, hemosiderinuria was observed in 81% of patients without haptoglobin and in 47% of patients with haptoglobin studied 3 or more months postoperatively. Since haptoglobin can be regenerated within several days following cessation of hemolysis while iron appears in the urine at a very slow rate, the simultaneous presence of haptoglobin and hemosiderin is probably indicative of intermittent rather than continuous hemolysis. Thus, a previous hemolytis episode could explain why hemosiderinuria was detected at a time when haptoglobin was present.

Eyster also studied 54 patients with 3 different prostheses; Starr-Edwards, Magovern, Cutter. They found more hemolysis in the patients with Starr-Edwards valves. The results of their studies are seen in the following two graphs.



Comparison of schistocyte counts, reticulocyte counts, serum LDH and bilirubin determinations (A) in the patients without haptoglobin and (B) in patients with haptoglobin. The most recent representative set of values is plotted for patients studied more than once. Normal ranges are shown by shaded areas. Key: ● = Starr-Edwards valve; ▲ = Magovern valve; ■ = Cutter valve.

From Eyster



Urine hemosiderin determinations after operation. Serial determinations on individual patients are connected by a vertical line. Key: o = Starr-Edwards valve; Δ = Magovern valve; □ = Cutter valve; ● = positive; o = negative; ⊖ = faintly positive; * = months following reoperation for ball variance.

From Eyster

Based on these observations, the following approach to the hematologic evaluation and management of patients with aortic ball-valve prostheses has been formulated. It is proposed that *cardiac hemolysis* be defined as mild, moderate or severe according to the following criteria:

Mild:	Hemosiderinuria or absence of haptoglobins but S < 10/1,000 cells, R < 5%, LDH < 500 mU/ml.
Moderate:	Hemosiderinuria or absence of haptoglobins but S > 10/1,000 cells, R > 5%, LDH > 500 mU/ml.
Severe:	All of above plus hemoglobinuria.

It is suggested that haptoglobin levels be obtained during the first 3-6 months following surgery. Virtually all patients have decreased haptoglobins, but patients with significant degrees of hemolysis almost always have no haptoglobins. Schistocyte counts, reticulocyte counts, and LDH and bilirubin determinations are helpful in estimating the severity of hemolysis in patients without haptoglobins.

Urines should be routinely evaluated for the presence of hemosiderin at 6-month intervals following surgery. As soon as hemosiderin is detected, the patient should be given iron by mouth. Iron therapy should be continued indefinitely since hemosiderinuria is usually persistent and may lead eventually to iron deficiency. One cannot rely on the absence of anemia to exclude hemolysis since many patients with significant hemolysis manage to maintain normal hematocrits by increasing red cell production as much as eightfold. This increased rate of production can be sustained only as long as an adequate supply of iron is available.

Propranolol has been reported to be useful in decreasing the degree of hemolysis, especially with aortic valve prosthesis. The decrease in dp/dt or rate of ejection of stroke volume around the prosthesis results in a decrease in red cell destruction. Most patients can be managed with the above medical treatment. However, an occasional patient will require surgery and replacement of the prosthesis with a homograft or heterograft valve (which are usually free of hemolytic complications) or repair of a paravalvular leak.

An additional complication of chronic hemolysis is the development of pigment gallstones. Gallstones occur in 5-10 times the frequency in patients with prosthetic valves as compared with normals; thus patients with prosthetic valves are prone to attacks of cholecystitis.

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ENDOCARDITIS AND PROSTHETIC VALVES

Endocarditis is not an uncommon complication of valve replacement. The incidence varies in the literature from 20% to less than 1%. With current precautions at time of surgery and perhaps to prophylactic antibiotic usage, the incidence in most centers is less than 1%. However, the outcome is still grim when it does occur resulting in mortalities of 60-80% with early and 40-50% with late infections.

The bacteriology, predisposing factors and prognosis are different in early and late (> 60 days) infections of prosthetic valves.

A review of the bacteriology in early and late cases is listed below.

Bacteriology of Combined Series of Prosthetic Valve Endocarditis

	Early endocarditis*						Late endocarditis					
Reference	Total cases	Staph aureus	Staph epidermidis	Streptococci	Gram Neg Rods	Other	Total cases	Staph aureus	Staph epidermidis	Streptococci	Gram Neg Rods	Other
Amoury et al.[2]	9		7		1	1	3	1	2			
Stein et al.[3]	15	8	1	1	3	2	2		1			1
Okies et al.[4]	11	1	6	1	2	1	7		5	2		
Fraser et al.[5]	5	1	4				5		1	1	1	2
Shafer et al.[6]	8		2	2	2	2	1		1			
Yeh et al.[7]	11	2	1		5	3	3		1		2	
Killen et al.[11]	6	2	3			1	5		2			3
Total	65	14	24	4	13	10	26	1	13	3	3	6

*Defined as endocarditis occurring less than 30–60 days after valve replacement.

From Dismukes

The mortality in the early infections ranges between 60-80%. The higher mortality in the early group may be due to at least 3 factors: immediate post-operative valvular dysfunction, the debilitated state of the postoperative patient and the more virulent and resistant organisms causing infection. *Candida* infection has been almost universally fatal when occurring on prosthetic valves. The bacteriology of the late cases contrasts with that of the early cases and more nearly resembles that of classical subacute bacterial endocarditis. In the combined series of 26 cases of late prosthetic valve endocarditis compiled from the literature only 3 cases were due to *streptococci* and 14 others to *staphylococci*. Regardless of which group of late cases is considered, the organisms are generally less virulent than those causing early endocarditis. Furthermore, the bacteriology is somewhat predictable if one considers the factors which predispose to late endocarditis in patients with prosthetic valves. In contrast to the early cases, the recognized sources of infection in the late group are not related to operation but to such factors as dental and genitourinary manipulation.

The clinical features in the early and late groups are very similar. Fever was present in all of the late group patients and clinical evidences of endocarditis (for example, splenomegaly and petechiae) in approximately one half, just as with the early cases.

The most compelling reason for calling attention to patients with late prosthetic valve endocarditis is to reemphasize the importance of prophylactic antibiotics in this group of patients during those periods when they are in special danger of acquiring bacteremia. Of the 10 episodes of late endocarditis caused by *streptococci*, bacteremia in 6 appeared to originate from the oral cavity or genitourinary tract and was probably preventable in each case.

SOURCE OF INFECTION AND/OR PREDISPOSING FACTOR(S)*

Source of predisposing factor	Early	Late
Contaminated I.V. catheter	1	0
Cystoscopy and caruncle excision	0	1
Dilation and curettage	0	1
Dental		
caries, abscess	1	1
manipulation	1	4
Paravalvular leak - immediate postop	4	0
Pneumonia	4	0
Preexisting endocarditis (same organism)	2	1
Primary skin lesion	0	1
Reoperation within 48 hours	2	0
Upper respiratory infection with epistaxis	0	1
Urinary tract infection	1	1
Wound infection		
abdominal	1	1
sternal	6	1
Unknown	3	7

* Two or more sources of factors occurred in eight episodes (seven early and one late).

From Dismukes

In patients with prosthetic valves who undergo any manipulation likely to produce a transient bacteremia, adequate prophylaxis during and after the procedure is imperative. Such manipulations might include dental procedures, minor skin surgery, genitourinary procedures, or any operation through a contaminated field. Furthermore, patients with prosthetic valves with localized infection of the skin or urinary tract should receive immediate medical attention and should be given appropriate antibiotics.

Starr's group has published recommendations for antibiotic prophylaxis and treatment of infection if it occurs. The type and mode of therapy will differ depending upon the organism and the infectious disease group!

Recommendations for Prophylactic Antimicrobial Therapy

Procedure	Suspected bacterium	Antimicrobics
Dental	Streptococcus sp., viridans group	Procaine penicillin G 600,000 u i.m. 1 hr before the procedure and daily for 2 more days. Alternatives include penicillin V 400,000 u q 6 hrs orally, erythromycin 250 mg or clindamycin 150 mg q 6 hrs orally for 3 days.
Genitourinary	Streptococcus fecalis	Procaine penicillin G 1.2 million u q 8 hrs i.m. and streptomycin, 0.5 g q 12 hrs i.m. Begin therapy 1 hr before the procedure and continue for 72 hrs.
Cardiac catheterization	Staphylococcus aureus or epidermidis	Cephalexin 250 mg orally 1 hr before and q 6 hrs for 72 hrs.

Recommendations for Antimicrobial Therapy of Bacterial Prosthetic Endocarditis

Organism	Antibiotic therapy*	Alternate antibiotic therapy*
Streptococcus sp., viridans group (susceptible to 0.3 mcg/ml of penicillin G)	Crystalline penicillin G one million u q 4 hrs i.v. or procaine penicillin G 1.2 million u q 6 hrs i.m. for 4 weeks	Cephalothin 1 g q 4 hrs i.v. or vancomycin 0.5 g q 6 hrs i.v. for 4 weeks
Streptococcus sp. enterococcal or viridans group (susceptible to more than 0.3 mcg/ml of penicillin G)	Crystalline penicillin G 20 million u i.v. daily and streptomycin 0.5 g q 12 hrs i.m. for 6 weeks	Ampicillin 2 g q 4 hrs i.v. and gentamicin 5 mg per kg body weight daily or vancomycin 0.5 g q 6 hrs i.v. for 6 weeks
Staphylococcus aureus or epidermidis (susceptible to 0.6 mcg/ml)	Crystalline penicillin G 20 million u i.v. daily for 6 weeks†	Cephalothin 2 g q 3 or 4 hrs or vancomycin 1 g q 6 hrs i.v. for 6 weeks†
Staphlococcus aureus or epidermidis (susceptible to more than 0.6 mcg/ml of penicillin G)	Nafcillin or oxacillin 2–3 g q 3 or 4 hrs i.v. for 6 weeks†	None
Gram-negative bacilli	Therapy is guided by antibiotic susceptibility tests. Bactericidal antibiotics such as kanamycin, ampicillin, carbenicillin, gentamicin, cephalothin or streptomycin are preferable	None
Negative blood cultures	Cephalothin 2 g q 6 hrs i.v., crystalline penicillin 20 million u daily i.v., and streptomycin 0.5 g q 12 hrs for 6 weeks	None

*If normal renal function.
†See Discussion section for suppressive therapy.

From Starr

My personal recommendation for antibiotic prophylaxis in patients with prosthetic valves undergoing surgical procedures, i.e. dental extractions, G.U. surgery, is full treatment for endocarditis (20 M.U. penicillin I.V. daily and 1 gm streptomycin I.M.) until the surgical wounds are reasonably healed.

Reoperation may be necessary in patients with infected prosthetic valves. Patients who have signs and symptoms of hemodynamic instability as manifested by development of paravalvular leak or progressive heart failure, systemic embolization, or persistent infection should be strongly considered for early reoperation, even at the risk of higher morbidity and mortality than at initial operation and at the risk of suturing the new prosthesis into an infected area. Okies, et.al., Stason, et.al., and Griffin, et.al. have reported good results with valve replacement in patients with active endocarditis. Results in these patients, lend support to the concept of an aggressive surgical approach to certain patients with infected valve prostheses.

Dismukes has compared his series of infected valves treated with antibiotics alone or with reoperation. The results are listed below and are somewhat discouraging.

OUTCOME OF PATIENTS WITH PROSTHETIC VALVE ENDOCARDITIS

	Survival		Survival	
	Early	Late	Early	Late
Antibiotics alone	4	7	10	6
Antibiotics plus surgery	2	4	3	2
Total	6	11	13	8

From Dismukes

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AORTIC-BALL VARIANCE

The original 1000 series Starr-Edwards valve had a silastic (Silicone) poppet (ball). The silastic reacts with blood lipids causing early lipid "lakes", cracks, splitting and deterioration of the ball when placed in the aortic position. The poppet may split or shrink and dislodge from its cage resulting in systemic embolization and wide open aortic regurgitation and sudden death. The poppet may become asymmetrical and stick in the open or closed position also causing death. Emboli may form on or about the poppet and cage resulting in poppet dysfunction or embolization.

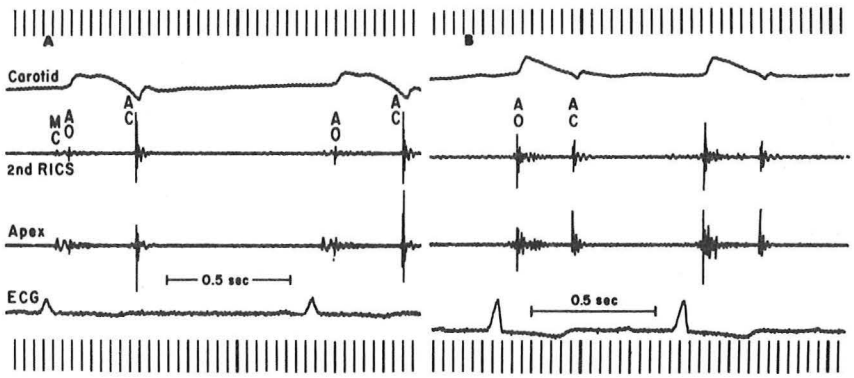
Fortunately, these silastic poppets have been replaced by metal poppets that do not show deterioration with time. However, patients are still living who have the original 1000 series valves, therefore a brief summary of methods used in detecting ball variance is important.

DIAGNOSIS OF AORTIC BALL VARIANCE

Absent opening sound by auscultation
Consistently abnormal phonocardiogram
Radiographic evidence of cracking, lipid lakes, or impingement
Recurrent embolic phenomena, especially for 3 years
Onset of aortic regurgitation after the first year

Above is a list of methods used in diagnosing ball variance. The phonocardiographic sounds generated by the aortic prosthesis usually shows an opening sound louder than the closing sound or an AO/AC ratio of greater than 0.7, a decrease of the AO/AC sound to less than 0.5 indicates that ball variance is most likely present and the patient should be reoperated and the poppet or valve replaced.

A phonocardiogram pre- and post-op with ball variance is shown below.



A. Phonocardiogram before operation, showing a decrease in the intensity of the aortic opening sound (AO) as compared with the aortic closure sound (AC).
B. Postoperative phonocardiogram after replacement of an abnormal poppet with a new silastic ball. The AO and AC are of normal character and intensity. MC=Mitral closure sound; carotid=carotid pulse tracing; 2nd RICS= phonocardiogram at the second right intercostal space at the sternal edge; apex=phonocardiogram at the cardiac apex.

From Hylen

Symptoms and signs of ball variance are fatigue, dyspnea on exertion, palpitations, dizzy spells, angina, systemic emboli, hemolytic anemia and recent aortic regurgitation.

115. Hylen, J.C., Kloster, F.E., Herr, R.H., Hull, P.Q., Ames, A.W., Starr, A. and Griswold, H.E.: Phonocardiographic diagnosis of aortic ball variance. Circulation 38:90-102, 1968.
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STENOSIS OF PROSTHESES

The Starr-Edwards prostheses 2300 and 6300 series were stenotic because of a small orifice size. This has been corrected in the 2310 and 6310 and later series. Hemodynamic findings in the different models of Starr-Edwards valves are seen in the table below.

AORTIC VALVE PROSTHESIS

MODEL	MEAN AORTIC GRADIENT			AORTIC VALVE AREA		
	Aver. mm Hg	Range	n	Aver. cm^2	Range	n
1000	21	0-35	32	1.5	1.0-2.8	16
2300	41	17-68	12	0.9	0.7-1.2	12
2310	15	7-28	15	1.5	1.2-1.7	15

MITRAL VALVE PROSTHESIS

MODEL	MITRAL MEAN GRADIENT			MITRAL VALVE AREA		
	Aver. mm Hg	Range	n	Aver. cm^2	Range	n
6000	4.4	1.0-9.0	20	2.4	1.3-4.0	18
6120	7.4	0-13.0	12	1.9	1.0-2.5	8
6300	9.4	5.6-12.5	12	1.6	1.2-2.2	12
6310	4.9	3.1-8.5	10	2.6	1.9-3.5	10

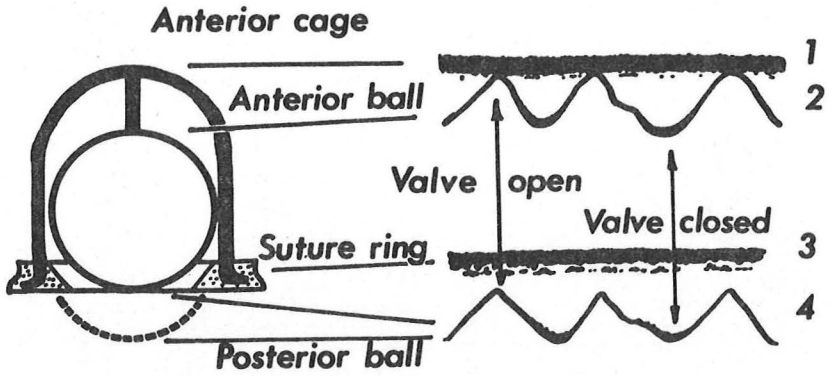
One should also be aware that inertial factors begin to play a major role in the movement of the poppet in the Starr-Edwards prosthesis as heart rate increases. The valve begins to lose its function above heart rates of 140 and the patient may develop syncope from low cardiac output. This is especially important when doing exercise testing. One should not exceed heart rates of 140 during exercise testing.

ECHOCARDIOGRAPHIC EVALUATION OF PROSTHETIC VALVES

Studies utilizing the echocardiogram in the diagnosis of prosthetic valve function are now becoming more frequent. Correlation of the echocardiogram with phonocardiography, apexcardiography, and cinefluorography have defined the movement patterns for normally functioning prosthetic valves. Other reports have shown that valve function may be characterized by velocity of poppet motion, poppet excursion, and relation of poppet and cage motion to other cardiac events. Obvious defects of prosthetic function have been documented by the echocardiogram. Thus far, however, all information derived from this method has also been easily available from other equally safe noninvasive diagnostic procedures, such as the phonocardiogram and cinefluorogram. Further experience with echocardiography may be expected to extend its diagnostic capabilities in dealing with prosthetic values. It is conceivable that it will become uniquely valuable in the early recognition of motion disorders of the poppet and cage.

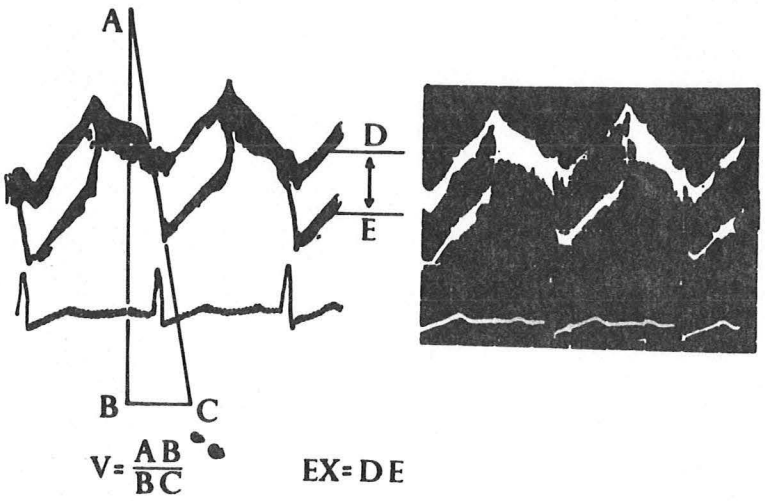
Johnson, et.al. has described an echocardiographic method of evaluating prosthetic valve motion and velocity of motion. This method can be used to detect abnormal poppet motion.

ANTERIOR BODY SURFACE



In vitro movement of ball when cage is held stationary. Traces 2 and 4 move toward the anterior surface as the valve opens and recede when the valve closes. The posterior surface of the ball appears to be beyond the suture ring.

From Johnson



Traces 1 and 2 from a 2M Starr-Edwards valve implanted in a patient. The closing velocity (V) can be measured from the slope of the closing trace (AC). Excursion (EX) is measured from the most anterior part of each trace while the valve is closed.

From Johnson

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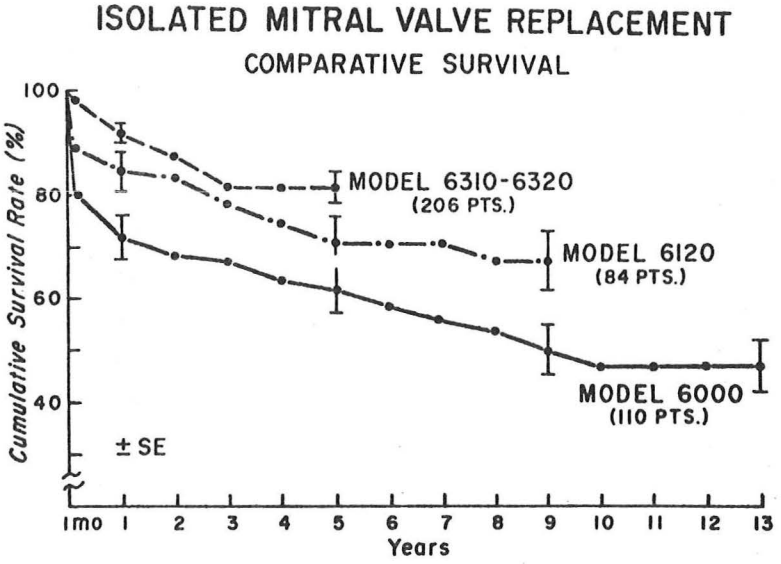
ACTUARIAL SURVIVAL WITH PROSTHETIC VALVES

The true test of a surgical procedure is the early and late mortality associated with or as a result of the procedure. Several large cardiac surgical centers have published their long-term follow-up of patients with prosthetic valves. One must remember that the vast majority of patients have a dramatic symptomatic improvement following their valve replacement, usually returning from functional class III patients pre-op to class I or II post-op.

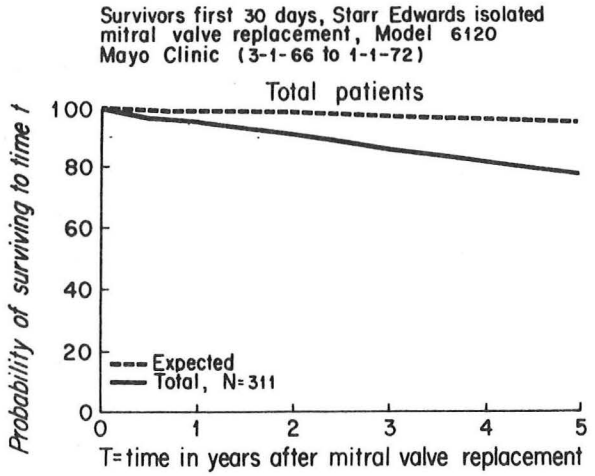
A picture is worth a thousand words, therefore the following published actuarial curves should be adequate information. These survival curves should be compared with those curves derived from the medically (or natural history) treated patients.

MITRAL VALVE PROSTHESIS



From Starr

The most striking difference between the survival curves is the initial mortality. The surgical techniques obviously improved and are more important than the valve model. If one subtracts the initial in-hospital mortality, the curves are not significantly different! However one would hope that the curve with Model 6310-6320 will become fairly flat for several years.

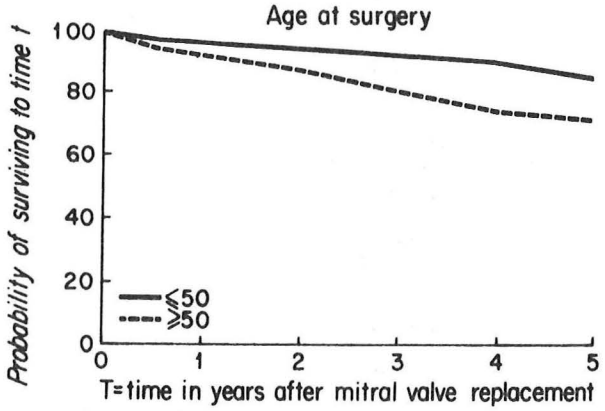


Late survival statistics in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120 (March 1966 to January 1972).

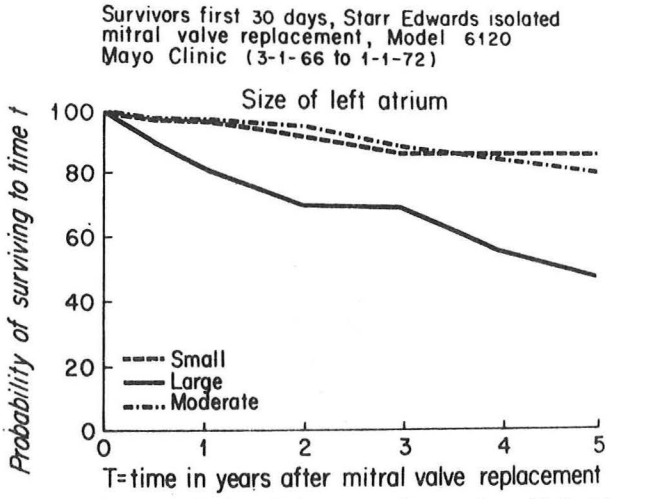
From Barnhorst and McGoon-342 patients

Note: The in-hospital mortality is not included- thus the survival curve appears significantly better, but if one projects a 10-15% initial mortality the curves are similar to those from Starr.

Age and left atrial size were significantly related to survival and are accumulative risks.

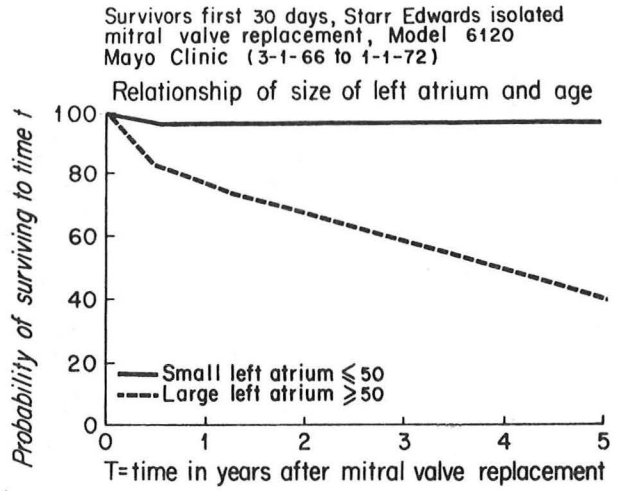


Late survival statistics, according to age at operation, in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.



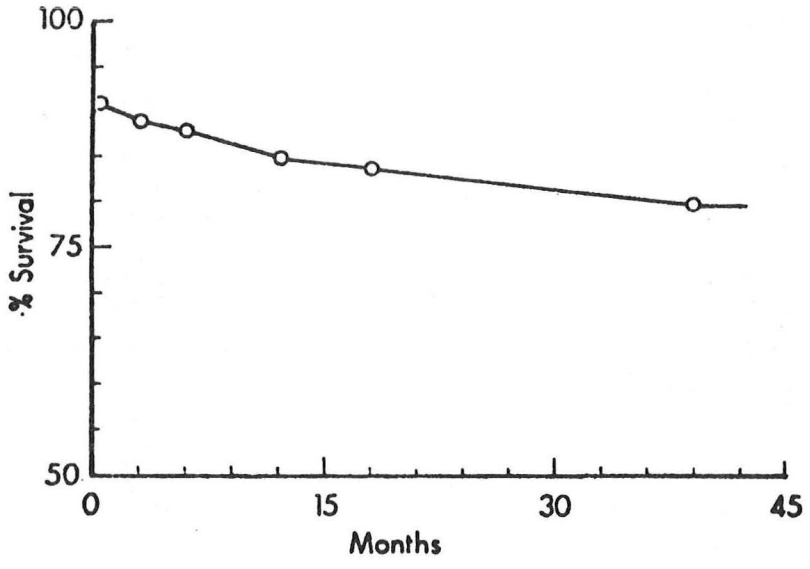
Late survival statistics, according to size of left atrium, in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.

From Barnhorst and McGoon-342 patients



Late survival statistics according to relation of size of left atrium and age in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.

From Barnhorst and McGoon-342 patients



Actuarial curve depicting survival in 92 patients undergoing isolated mitral valve replacement. A survival rate approaching the normal population can be seen at 24 months postoperatively.

From Isom, et.al.

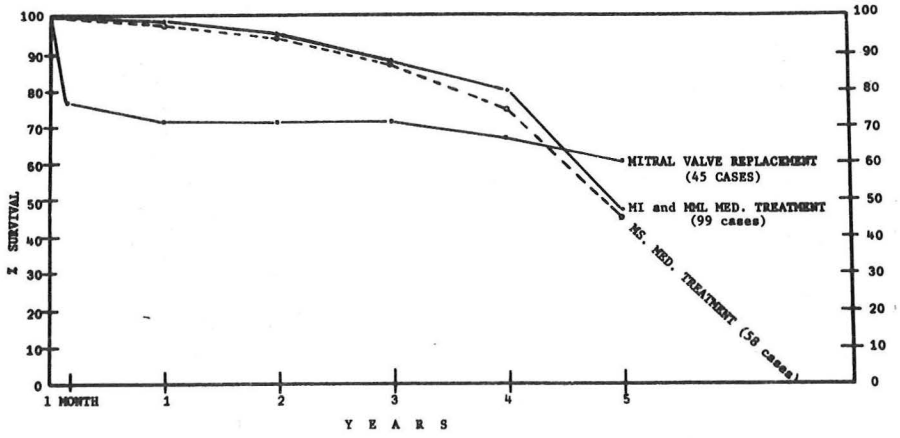
Typical causes of late death from mitral prostheses are shown below from Isom, et.al.

ISOLATED MITRAL VALVE REPLACEMENT
(92 patients)

	No. of deaths
Causes of early death	8 (8.7%)
Arrhythmias	3
Bleeding	2
Neurological injury (air)	2
Low output	1
Causes of late death	10 (10.9%)
Arrhythmias	3
Neurologic (on anticoagulants)	2
Congestive heart failure	2
CNS embolus	1
Hepatitis	1
Unknown	1

Legend: CNS, central nervous system

Perhaps the most important report is the randomized study of Munoz from Caracas, Venezuela showing the survival following valve replacement compared with the natural history of the disease under medical therapy. Unfortunately, their initial mortality was inordinantly high at 24% resulting in no improvement in longevity until 5 years had lapsed - ? Survival of the Fittest ?

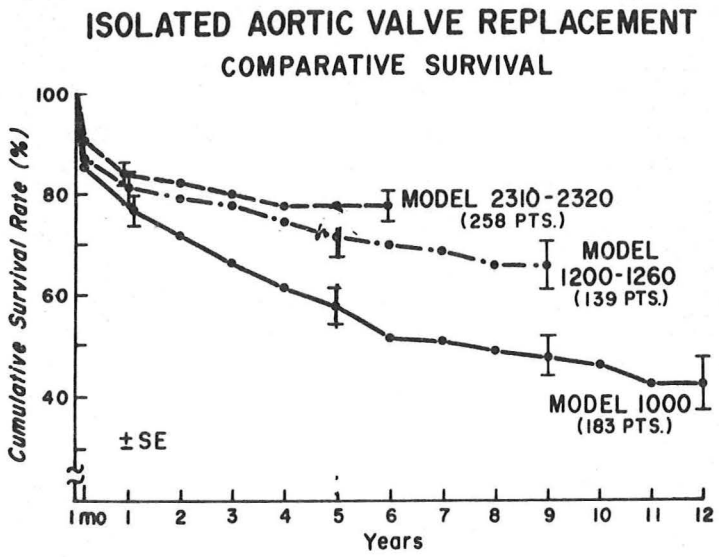


MI = Mitral Insufficiency; MML = Mixed Mitral Lesion; MS = Mitral Stenosis

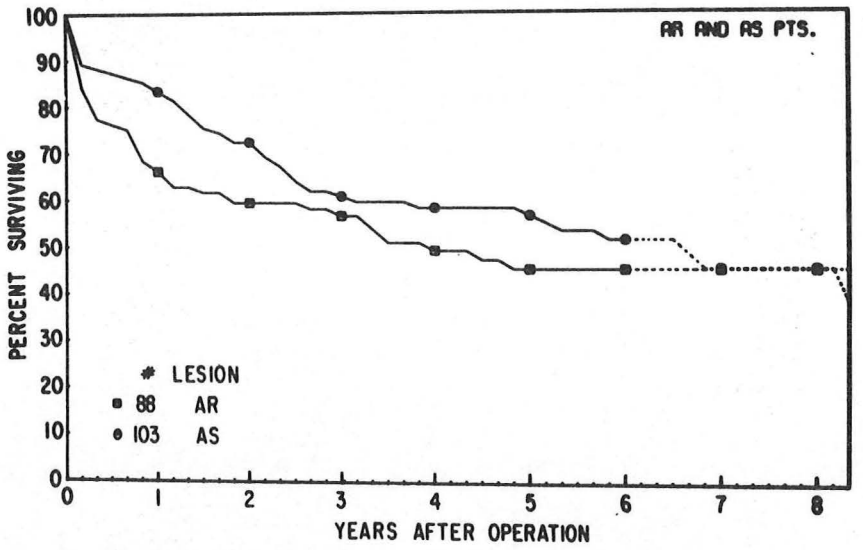
Actuarial survival curves in 58 cases of rheumatic mitral stenosis treated medically, 99 cases of mitral insufficiency and mixed mitral lesions treated medically and 45 cases of rheumatic mitral valve disease submitted to mitral valve replacement.

Almost All Starr-Edwards Prostheses From Munoz

AORTIC VALVE PROSTHESIS

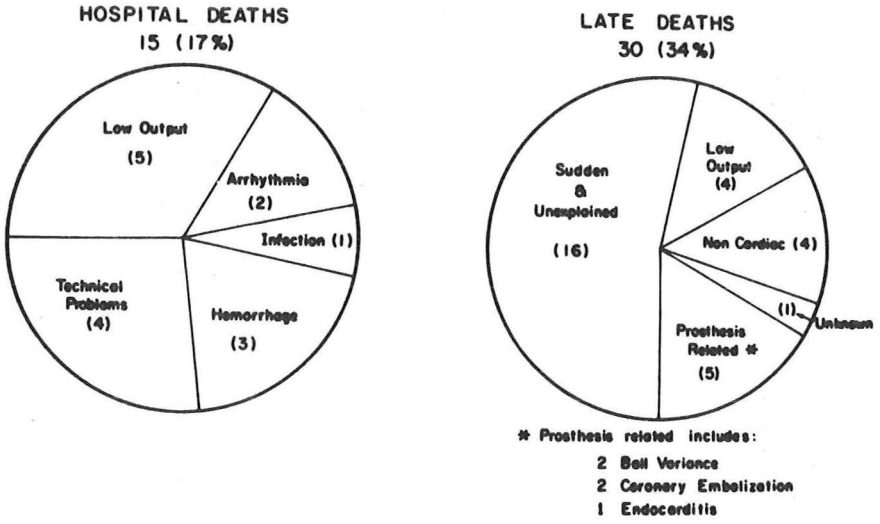


From Starr



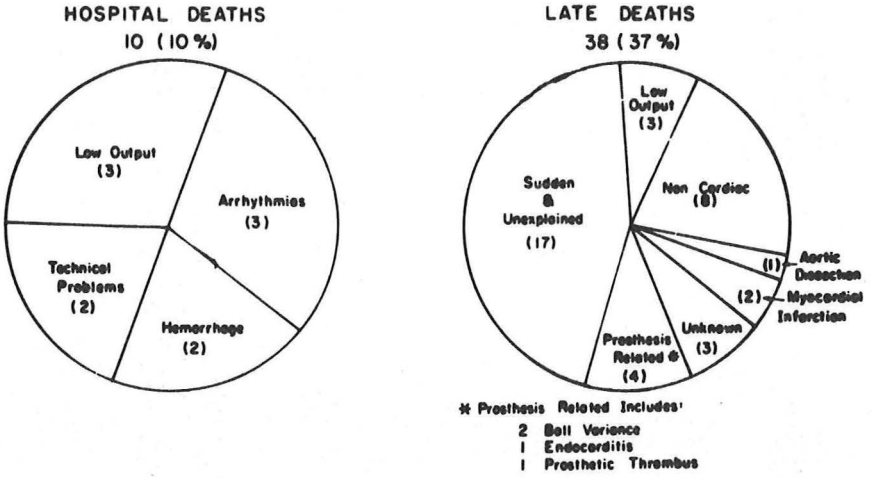
Percent survival of the 88 patients with aortic regurgitation and the 103 patients with aortic stenosis is plotted as a function of the time after operation. The legend in the lower left hand corner of the graph denotes the symbols used to describe the curve for each group and the number of patients in each group. The same general format is used in all plots of survival. The dashed lines denote that after the sixth postoperative year the number of patients under observation is too small for meaningful analysis. From Hirshfeld and Morrow

They also analyzed the cause of death with aortic valve replacement as related to pre-operative diagnosis. (191 patients)



Causes of hospital and late deaths in patients with aortic regurgitation.

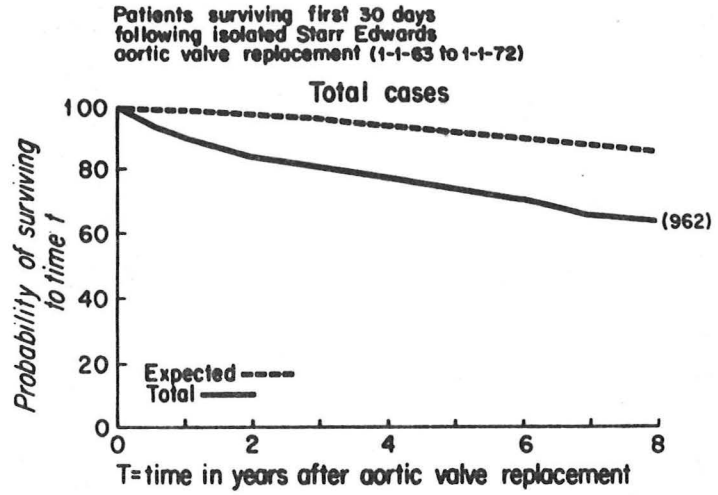
From Hirshfeld, et.al.



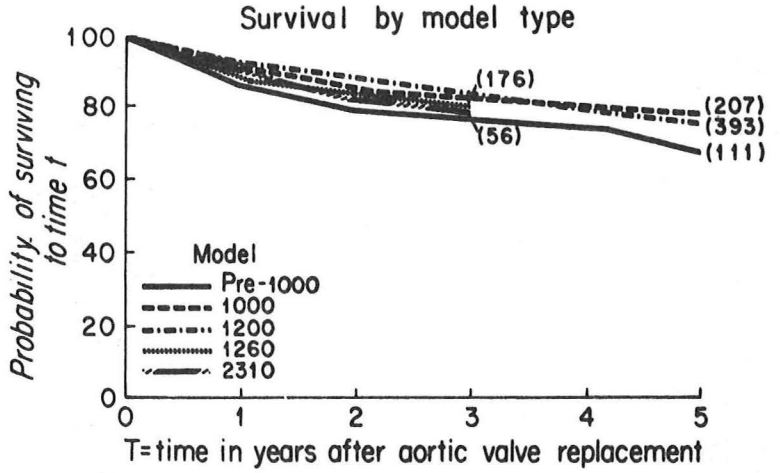
Causes of hospital and late deaths in patients with aortic stenosis.

From Hirshfeld, et.al.

From Barnhorst and McGoon (below) the inhospital mortality has been excluded.

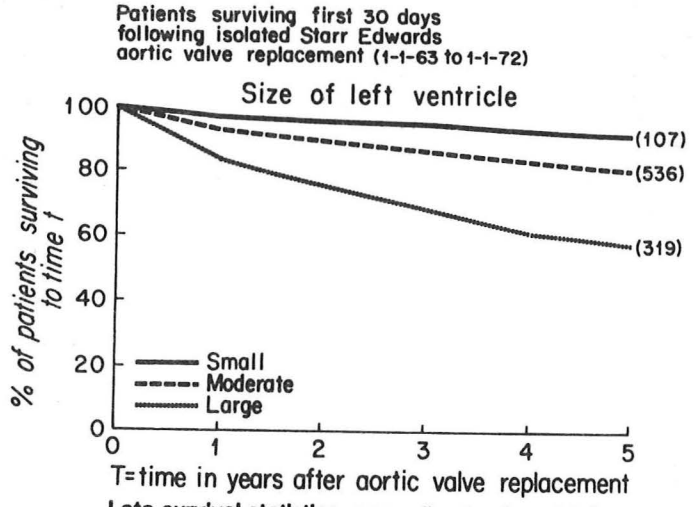


Late survival statistics in operative survivors of isolated Starr-Edwards aortic valve replacement.

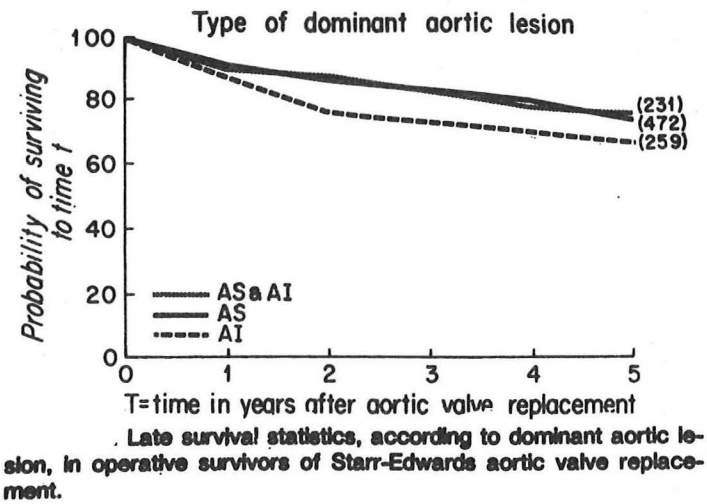


.. Late survival statistics, according to model of prosthesis, in operative survivors of isolated Starr-Edwards aortic valve replacement.

From Barnhorst and Mc Goon (continued)

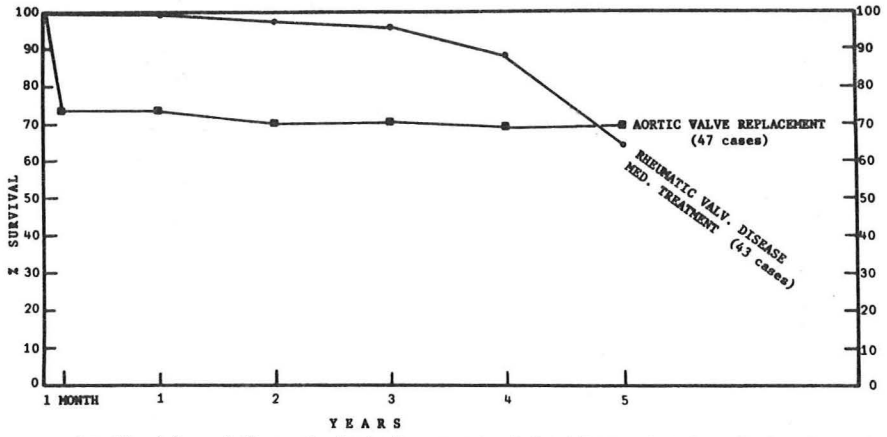


. Late survival statistics, according to size of left ventricle, in operative survivors of isolated Starr-Edwards aortic valve replacement.



. Late survival statistics, according to dominant aortic lesion, in operative survivors of Starr-Edwards aortic valve replacement.

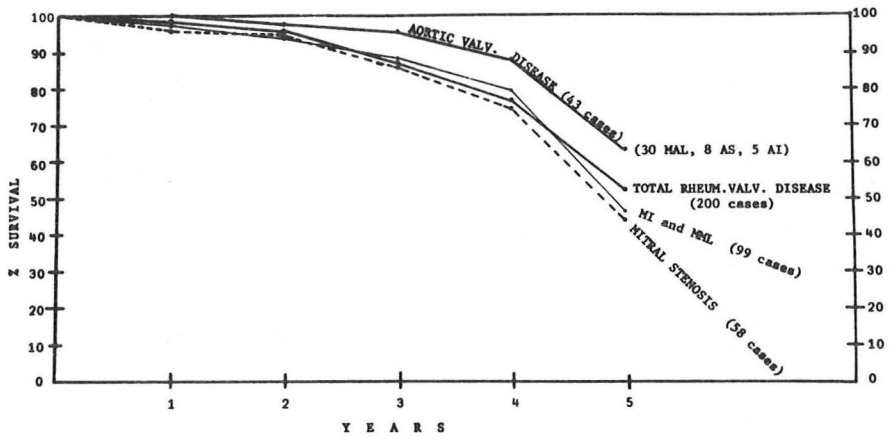
The randomized study from Caracus, Venezuela by Munoz compares the surgical survival with the medically treated (natural history) aortic valve disease. The initial mortality of 26% is inordinately high and therefore the curves do not cross until the fifth year - ? Survival of the Fittest ?



Actuarial survival curves in 43 cases of aortic valve disease treated medically and 47 cases submitted to aortic valve replacement.

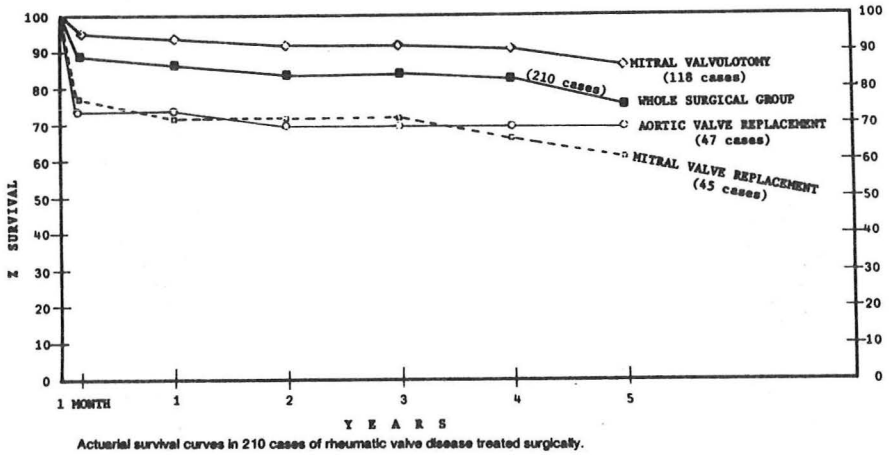
From Munoz

The composite of the natural history and the surgical survival is illustrated in the following two graphs from Munoz.



MAL = Mixed Aortic Lesion. AS = Aortic Stenosis. AI = Aortic Insufficiency.
MI = Mitral Insufficiency. MML = Mixed Mitral Lesion.

*. Actuarial survival curves in 200 cases of rheumatic valve disease treated medically.

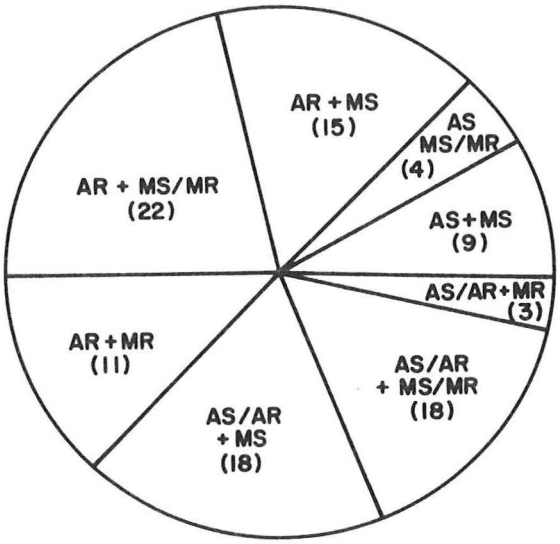


Actuarial survival curves in 210 cases of rheumatic valve disease treated surgically.

MULTIPLE VALVE REPLACEMENT

Multiple valve replacement is associated with an increase in operative risk and a shortened survival when compared with single valve replacement. This is no surprise knowing the complications of prosthetic valves but more importantly is the increased severity of the underlying heart disease necessitating more than one valve replacement. It also is apparent that multiple valve replacement for stenotic lesions carries a higher risk than with regurgitant lesions.

The following data from the NIH group is one of the better analysis. Below is illustrated the types of valvular lesions the patients had prior to surgery.



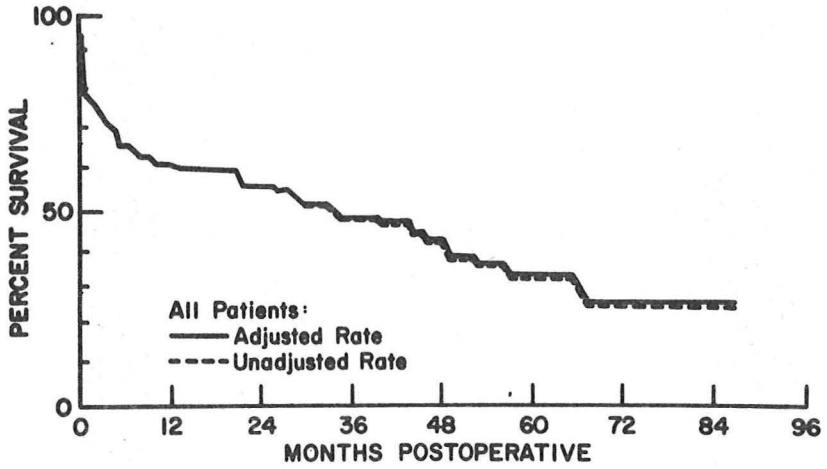
Predominant lesions of patients. AS= aortic stenosis; AR = aortic regurgitation; MS = mitral stenosis; MR = mitral regurgitation.

From Morrow

Operation

Aortic prosthesis used		Mitral prosthesis used		Tricuspid operation	
Starr-Edwards	96	Starr-Edwards	92	None	89
Model 1000	19	Model 6000	21	Valvuloplasty or valvulotomy	2
Model 1200	27	Model 6120	26	Valve replacement	9
Model 2300	14	Model 6130	3	Starr-Edwards (6300)	1
Model 2310	24	Model 6300	11	Kay-Shiley	6
Model 2320	12	Model 6310	21	Porcine heterograft	1
Magovern	3	Model 6320	8	Björk-Shiley	1
Porcine heterograft	1	Model 6520 (disc)	2		
		Kay-Shiley	5		
		Porcine heterograft	3		

From Morrow



Actuarial curve or life table for the first 95 patients. The solid line depicts relative rate of survival, adjusted for deaths in a matched group. Twenty-two percent initial mortality and 50% mortality by 24 months.

From Levine and Morrow

Kittle, et.al. in a combined study of 1,860 patients undergoing valve replacement in six institutions found the following results.

VALVE PROSTHESIS - MORTALITY

	Total	Hospital Mortality	Post-Discharge Mortality
Aortic	283	57 (20%)	25
Mitral	216	50 (23%)	10
Tricuspid	3	2	0
A and M	49	13 (27%)	7
M and T	21	10 (48%)	2
A and M and T	16	8 (50%)	0
Total	588	140 (24%)	44

Cooley's group reported 124 patients undergoing combined mitral and aortic valve disease. The operative mortality was *28%*. When both valves were stenotic the mortality was 53% and when both were insufficient the mortality was 9%.

These data suggest an inordinately high combined early and late mortality for multiple valve replacement which must be considered in recommending the operation.

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PROGNOSIS OF VALVE REPLACEMENT OVER AGE 60

The mortality in heart valve surgery has declined during the last decade due to refinements in operative technique and prosthetic valves. This has lead to a less stringent criteria for patient selection. Elderly patients were selected for surgery and two reports of valve replacement in patients over 60 have appeared. Finegan, et.al. and Oh, et.al. both report successful surgery and recommend the procedure as having only a slight increased risk over younger patients. However, close analysis of both reports show a combined operative and late mortality rate (2 years) in excess of 30%. This mortality equals or exceeds the expected mortality from the natural history of the valvular disease and therefore further evidence must be forthcoming before most patients in this age group with severe valvular disease are operated.

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PREGNANCY AND PROSTHETIC VALVES

Pregnancy is ill advised in any patient with a prosthetic valve primarily because of increased risk of complications and shortened maternal life expectancy. However, several reports of patients successfully completing term pregnancies on anticoagulants have been reported. Coumadin has been used as the anticoagulant during pregnancy then discontinued 48 hours prior to delivery. Coumadin or heparin were then used in the early post-partum period. This regimen has not resulted in hemorrhagic complications. Deliveries have even been carried out during the time the patient was anticoagulated with Coumadin without a significant increase in hemorrhage.

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TISSUE VALVES - HOMOGRAFTS AND HETEROGRAFTS

The current trend in valve replacement is toward the use of homograft and heterograft valves. The most extensive experience has been with the free aortic homograft valve. This valve is taken as fresh as possible, sterilized, usually frozen and inserted in the aortic area. A few have been inverted and placed in the mitral area, however, this is technically very difficult. The stinted homograft has also been used extensively. An aortic homograft is prepared in advance under sterile techniques by suturing the aortic valve leaflet and some of the valve ring to a sewing ring, then sterilized. This may be used in either the aortic or inverted in the mitral position.

A variety of other tissues have been used to make valve leaflets and mounted on sewing rings; pericardium, dura mater and fascia lata. Variable success has been reported with these valves.

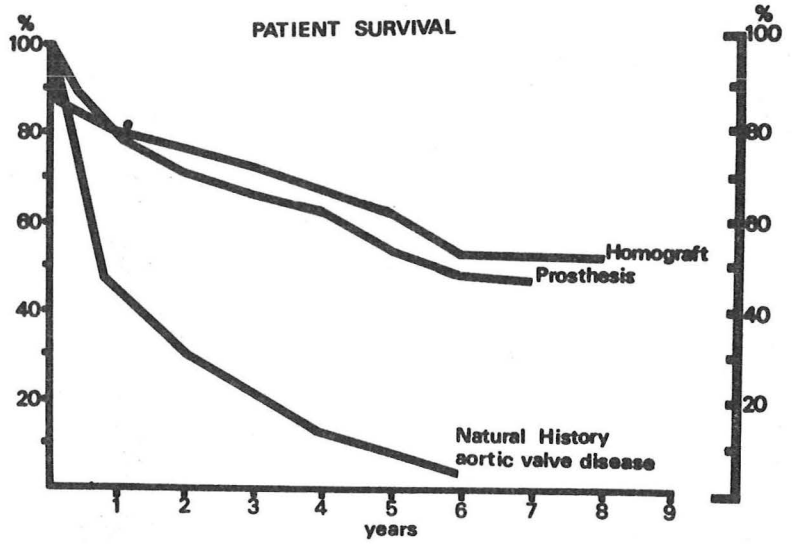
The most current trend is to use porcine heterograft valves which are pre-prepared, mounted on sewing rings, sterilized and commercially available. These valves tend to be slightly stenotic.

The advantages of tissue valves are several: (1) unimpeded central blood flow (2) absence of thromboembolism (3) no anticoagulants with their hemorrhagic complication (4) no hemolysis and (5) possible increased longevity.

Their disadvantages are (1) difficulty in sterilization without producing degeneration of the leaflets and early failure (2) availability (homografts) (3) minor regurgitation is frequently present and (4) late degeneration may occur at 5-8 years (unproved).

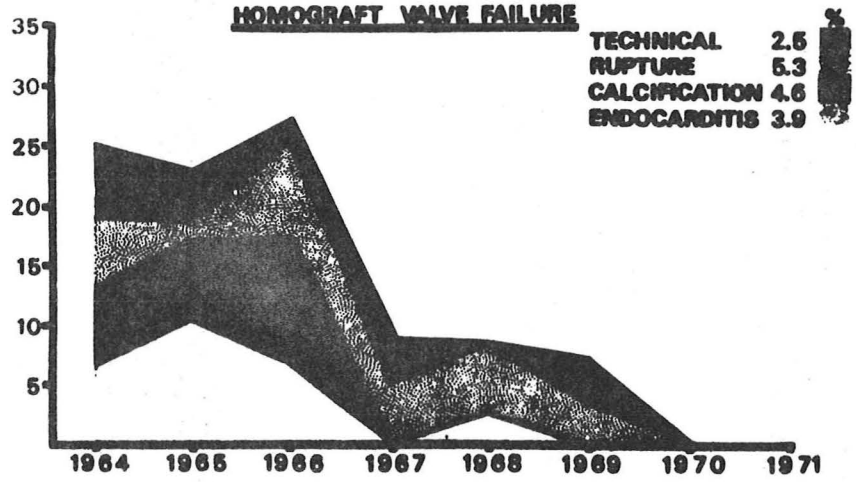
Very little literature is currently available on the recently developed porcine heterograft valves with current commercial processing and only time will allow us to evaluate this new valve substitute.

The homograft valve has been used for several years and typical published data regarding survival and failure and thromboemboli are shown in the graphs below from Ross.

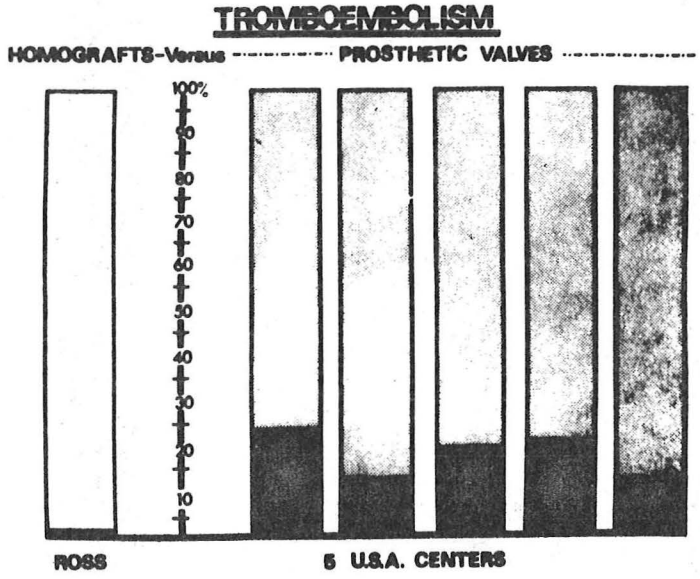


Survivor curve for homograft series from Guy's Hospital and the National Heart Hospital compared with a mean survivor curve for five prosthetic valve series. The survivor curve for untreated aortic stenosis is also included.

Ross (continued)



The dramatic reduction in valve failures since 1967 may be related to a change from freeze-dried valves.



Comparison of incidence of thromboembolism after aortic valve replacement in homografts and mechanical valves over similar periods of time.

The expected advantage from tissue valve is the low rate of thromboembolism and the relatively slow rate of failure when the valve does fail, i.e. slowly developing regurgitation.

Whereas failure with mechanical prostheses is usually a sudden and catastrophic event, a bright future awaits the successful processing and use of tissue valves.

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"My heart is turn'd to stone;
I strike it,
and it hurts my hand."

- Shakespeare, Othello, Act IV