Failure of Hancock Pericardial Xenografts: Is Prophylactic Bioprosthetic Replacement Justified?

Uberto Bortolotti, MD, Aldo Milano, MD, Francisco Guerra, MD, Alessandro Mazzucco, MD, Eugenio Mossuto, MD, Gaetano Thiene, MD, and Vincenzo Gallucci, MD

Departments of Cardiovascular Surgery and Pathology, University of Padova Medical School, Padova, Italy

The incidence of major valve-related complications was evaluated in a series of patients in whom the Hancock pericardial xenograft was used for aortic (AVR; n = 84), mitral (MVR; n = 17) and mitral-aortic (MAVR; n = 13) valve replacement. At 7 years actuarial survival is 66% ± 8% after AVR, 64% ± 13% after MVR, and 41% ± 15% after MAVR, whereas actuarial freedom from valve-related death is 79% ± 7% after AVR, 78% ± 13% after MVR, and 81% ± 12% after MAVR. Actuarial freedom from thromboemboli and anticoagulant-related hemorrhage at 7 years is 93% ± 4% and 98% ± 2% after AVR and 83% ± 10% and 88% ± 11% after MVR; no such complications occurred after MAVR. Structural valve deterioration determined at reoperation, at autopsy, or by clinical investigation was observed in 34 patients with AVR (10.0 ± 0.2%/patient-year), in 10 with MVR (10.6 ± 3.3%/patient-year), and in 9 with MAVR (16.6 ± 5.5%/patient-year). After AVR, 19 patients underwent reoperation and 2 died before reoperation; 4 patients with MVR underwent reoperation, and 7 patients with MAVR underwent reoperation and 1 died before reoperation. Seventy-eight percent of the current survivors (13 patients with AVR, 7 with MVR, and 1 with MAVR) have clinical evidence of valve failure. At 7 years actuarial freedom from structural deterioration of the Hancock pericardial xenograft is 25% ± 7% after AVR, 29% ± 14% after MVR, and 0% after MAVR. The extremely poor durability of the Hancock pericardial xenograft, besides confirming the need for a closer noninvasive monitoring of Hancock pericardial xenograft recipients, justifies prophylactic replacement of this device in asymptomatic patients with clinical evidence of Hancock pericardial xenograft dysfunction.

(Ann Thorac Surg 1991;51:430–7)

Bioprostheses made of bovine pericardium, introduced as an alternative to porcine valves in 1970 [1], have shown an extremely high incidence of early mechanical failures, responsible for their limited durability [2–6].

For editorial comment, see page 357.

These results, together with the observation that dysfunction of pericardial xenografts can occur suddenly [7, 8], have suggested the need for a periodical follow-up of recipients of such devices and possibly elective reoperation in asymptomatic patients with clinical evidence of valve failure [4]. Patients receiving a Hancock pericardial xenograft (HPX) at our institution were therefore reevaluated mainly to assess the incidence of structural deterioration and to establish the most proper method of management of long-term survivors.

Material and Methods

A total of 97 HPXs were implanted in 84 patients during the interval from August 1981 to July 1984. There were 48 male and 36 female patients with a mean age of 55.7 ± 13 years (range, 13 to 75 years). Aortic valve replacement (AVR) was performed in 54 patients, mitral valve replacement (MVR) in 17, and combined mitral and aortic valve replacement (MAVR) in 13. The preoperative clinical characteristics of this patient population and the indications for valve replacement, as well as previous operations and associated surgical procedures, are summarized in Table 1.

Operative techniques and anticoagulant policy in HPX recipients have been previously reported [4, 6]. Particularly, patients with AVR were usually not anticoagulated or received oral anticoagulants only for the first 3 months. Patients with atrial fibrillation were indefinitely anticoagulated after MVR and MAVR in the presence of a large left atrium or left atrial thrombosis.

Patients discharged were reevaluated mostly by direct visit during a 6-month period ending in December 1989. All long-term survivors were scheduled for a two-dimensional transthoracic echocardiographic study on a biannual basis or whenever required by a change of clinical status. Criteria to define and evaluate valve-related complications are those recently recommended [9]. Linearized rates, expressed as percent per patient year (%/pt-y), are calculated for any of such complications, and

Accepted for publication Nov 2, 1990.

Address reprint requests to Dr Bortolotti, Istituto di Chirurgia Cardiovascolare, Università di Padova, Via Giustiniani, 2, 35128 Padova, Italy.

0003-4975/91/$3.50

Table 1. Summary of Preoperative Clinical Characteristics

Variable	AVR	MVR	MAVR
No. of patients	54	17	13
Male/female	33/21	5/12	10/3
Mean age (y)	55 ± 13	53 ± 12	58 ± 10
Age range (y)	13–73	22–70	38–75
Preoperative functional class			
NYHA II	1	. . .	. . .
NYHA III	40	15	7
NYHA IV	13	2	6
Cause of valvar disease			
Rheumatic	16	8	6
Calcific degeneration	18	. . .	. . .
Myxoid degeneration	7	3	4
Ischemic	. . .	1	. . .
Endocarditis	6	. . .	. . .
Congenital	1	. . .	. . .
Prosthesis failure	6	5	3
Cardiac rhythm			
Sinus	45	2	4
Chronic atrial fibrillation	9	15	9
Previous procedures			
AVR	6	2	3
MVR	. . .	5	2
Mitral valvoplasty	3	3	1
Coartectomy	1	. . .	. . .
Associated procedures			
MVR[a]	10	. . .	. . .
Mitral valvoplasty	2	. . .	. . .
Tricuspid valvoplasty	. . .	1	. . .
CABG	7	1	1

[a] *With other bioprostheses (Hancock porcine in 8 and Liotta in 2).*

AVR = aortic valve replacement; CABG = coronary artery bypass graft; MAVR = mitral-aortic valve replacement; MVR = mitral valve replacement; NYHA = New York Heart Association.

freedom from major postoperative events is expressed in actuarial fashion, including in all actuarial curves the operative mortality. Continuous data are presented as mean ± 1 standard error of the mean and categorical data as percent with the 70% confidence limits (CL).

Hancock pericardial xenografts explanted at reoperation or recovered at autopsy were studied with gross, microradiographic, histological, and ultrastructural investigations. Details of the results of a morphological study of HPX explants have been reported elsewhere [10].

Results

Early and Late Mortality

There were eight hospital deaths: 4 patients died after AVR (7.4%; 70% CL, 3.7% to 13.0%), 1 after MVR (5.8%; 70% CL, 0.7% to 18.6%), and 3 after MAVR (23%; 70% CL, 10.4% to 41.0%) (Table 2). The causes of death were the following: low output state in 4 patients after AVR, intraoperative cerebral damage in 1 patient after MVR, postoperative hemorrhage in 2 patients after MAVR, and low output syndrome in 1 patient after MAVR. None of the early deaths was valve-related.

In the entire series total follow-up is 452 pt-y; cumulative duration of follow-up is 304 pt-y after AVR (range, 0.4 to 8.3 years; mean, 5.9 ± 1.6 years); 94 pt-y after MVR (range, 0.6 to 8.3 years; mean, 5.8 ± 2.1 years), and 54 pt-y after MAVR (range, 0.9 to 8.0 years; mean, 5.4 ± 2.1 years). Follow-up is 100% complete in the entire series.

Of the 76 patients discharged 21 died in the late postoperative period. There were 12 late deaths after AVR (3.9 ± 1.1%/pt-y), 4 after MVR (4.2 ± 2.1%/pt-y), and 5 after MAVR (9.2 ± 4.1%/pt-y). The causes of late death are shown in Table 3. Actuarial survival at 7 years is 66% ± 8% after AVR, 64% ± 13% after MVR, and 41% ± 15% after MAVR (Fig 1).

Currently, 27 patients are alive with their original HPX in place: 18 with AVR, 8 with MVR, and 1 with MAVR; 13 are in functional class I, 9 in class II, and 5 in class III.

Table 2. Summary of Major Postoperative Complications

	AVR		MVR		MAVR	
Complication	No.	%/pt-y	No.	%/pt-y	No.	%/pt-y
Late death	12	3.9 ± 1.1	4	4.2 ± 2.1	5	9.2 ± 4.1
Valve-related death	8	2.6 ± 0.1	2	2.1 ± 1.5	2	3.7 ± 2.6
Thromboembolism	3	0.1 ± 0.1	3	3.2 ± 1.8	. . .	. . .
Fatal	1	0.03 ± 0.03	1	1.0 ± 1.0	. . .	. . .
Anticoagulant-related hemorrhage	2	0.6 ± 0.4	1	1.0 ± 1.0	. . .	. . .
Fatal	1	0.03 ± 0.03	. . .	. . .	. . .	. . .
Endocarditis	6	2.0 ± 0.7	1	1.0 ± 1.0	. . .	. . .
Paraprosthetic leak	1	0.03 ± 0.03	. . .	. . .	. . .	. . .
Reoperation	23	7.5 ± 1.6	4	4.2 ± 2.1	7	13.0 ± 5.0
Structural deterioration[a]	34	10.0 ± 0.2	10	10.6 ± 3.3	9	16.6 ± 5.5

[a] Determined at reoperation, autopsy, or clinical investigation.

AVR = aortic valve replacement; MAVR = mitral-aortic valve replacement; MVR = mitral valve replacement.

Table 3. Causes of Late Death

Cause	AVR	MVR	MAVR
Cardiac	2	1	2
Valve-related			
Endocarditis	2	. . .	. . .
Structural deterioration	2	. . .	1
Reoperation	2	. . .	1
Thromboembolism	1	1	. . .
Anticoagulant-related hemorrhages	1	. . .	. . .
Sudden, unexplained	. . .	1	. . .
Malignancy	1	1	1
Unknown	1	. . .	. . .
Total	12	4	5

AVR = aortic valve replacement; MAVR = mitral-aortic valve replacement; MVR = mitral valve replacement.

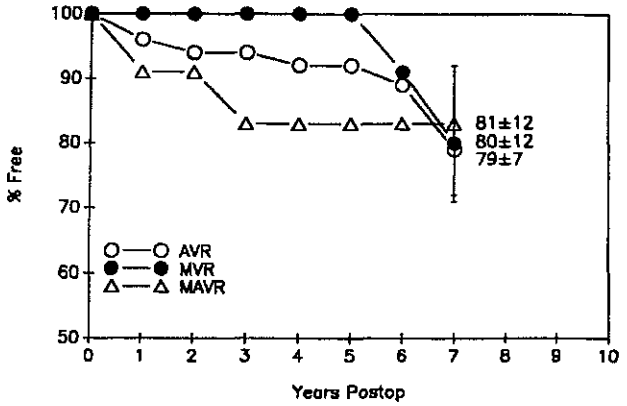

Fig 2. Actuarial freedom from valve-related death. (Abbreviations as in Fig 1.)

There were eight valve-related deaths in the AVR group (2.6 ± 0.1%/pt-y), because of endocarditis in 2 patients, at reoperation for HPX structural deterioration in 2, because of HPX structural deterioration without reoperation in 2, because of cerebral embolism in 1, and because of gastric hemorrhage in 1. There were two valve-related deaths after MVR (2.1 ± 1.5%/pt-y), due to cerebral embolism in 1 and sudden, unexplained death in the other. Finally, there were two valve-related deaths among patients with MAVR (3.7 ± 2.6%/pt-y): 1 patient died of low output syndrome at reoperation because of structural failure of both HPXs and 1 died at home because of failure of both HPXs proved at autopsy. Actuarial freedom from valve-related deaths at 7 years is 79% ± 7% after AVR, 80% ± 12% after MVR, and 81% ± 12% after MAVR (Fig 2).

Thromboembolic Complications

Thromboembolic complications occurred in 3 patients with AVR (0.1 ± 0.1%/pt-y). Of these 2, who were not anticoagulated, had a cerebral embolism after 20 and 28 months, respectively, both of which resolved without sequelae; the third patient, who had also a porcine valve in the mitral position and was anticoagulated, sustained a fatal cerebral embolism after 22 months. Two patients had embolic complications after MVR (3.2 ± 1.8%/pt-y): 1 of them, who was not anticoagulated, had a cerebral embolism after 4 years with permanent hemiparesis and the other, while still on anticoagulants, had two episodes of peripheral embolism 14 months and 5 years after MVR; the last one, causing acute occlusion of the aortic bifurcation, required emergency embolectomy with subsequent death due to acute renal failure. No thromboembolic complications were observed in patients with MAVR. Actuarial freedom from thromboemboli at 7 years is 93% ± 4% after AVR, 83% ± 10% after MVR, and 100% after MAVR (Fig 3).

Anticoagulant-Related Hemorrhage

Major hemorrhagic complications were observed in 3 patients, 2 with AVR (0.6 ± 0.4%/pt-y) and 1 with MVR (1.0 ± 1.0%/pt-y). Two patients had gastric bleeding 1 and 2 months after AVR, and 1 of these patients died; both

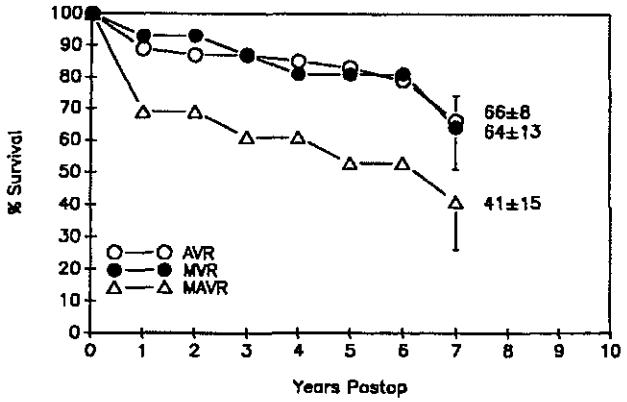

Fig 1. Actuarial survival after isolated aortic (AVR), mitral (MVR), and mitral-aortic (MAVR) valve replacement with the Hancock pericardial xenograft.

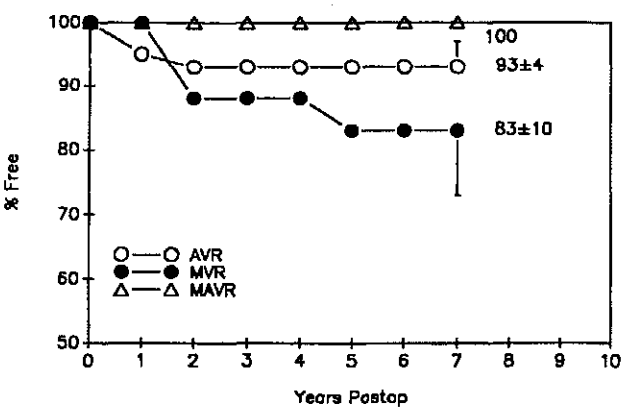

Fig 3. Actuarial freedom from thromboembolic complications. (Abbreviations as in Fig 1.)

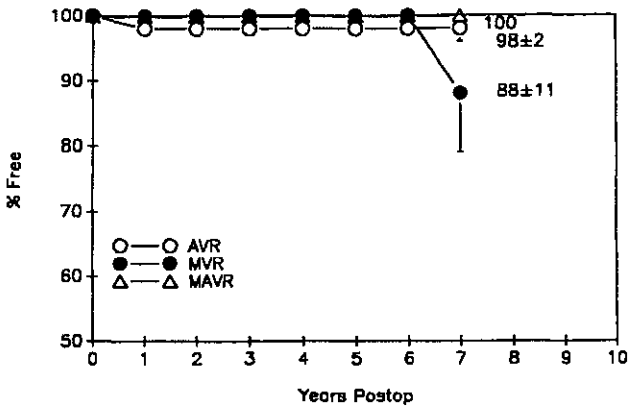

Fig 4. Actuarial freedom from hemorrhage related to chronic anticoagulation. (Abbreviations as in Fig 1.)

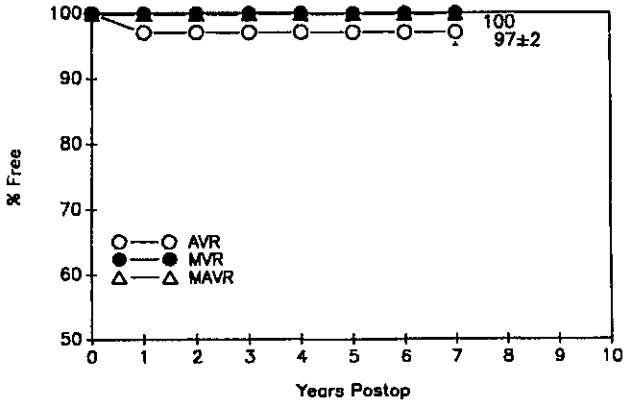

Fig 6. Actuarial freedom from paraprosthetic leak. (Abbreviations as in Fig 1.)

patients were still on anticoagulants. One patient with MVR had a nonfatal gastrointestinal hemorrhage after 6 years. Actuarial freedom from anticoagulant-related hemorrhages at 7 years is 98% ± 2% after AVR, 88% ± 11% after MVR, and 100% after MAVR (Fig 4).

Endocarditis

Endocarditis involved 6 patients with AVR (2.0 ± 0.7%/pt-y) and 1 with MVR (1.0 ± 1.0%/pt-y). Of the AVR patients 3 underwent successful reoperation after 7, 29, and 47 months, respectively; 2 died without reoperation and 1 was apparently cured with medical treatment. One patient with MVR underwent reoperation successfully after 24 months. Actuarial freedom from endocarditis at 7 years is 85% ± 7% after AVR, 93% ± 6% after MVR, and 100% after MAVR (Fig 5).

Paraprosthetic Leak

Paraprosthetic leak was observed only in 1 patient with AVR (0.03 ± 0.03%/pt-y), who underwent successful HPX replacement after 16 months. Actuarial freedom from this complication at 7 years is 97% ± 2% after AVR and 100% after MVR and MAVR (Fig 6).

Reoperation

A total of 34 patients required reoperation during the follow-up period. Reoperation was performed in 23 after AVR (7.5 ± 1.6%/pt-y), because of paraprosthetic leak in 1 and endocarditis in 3 without deaths, and because of structural deterioration in 19 with 2 deaths (10.5%; 70% CL, 3.5% to 23.2%); of the latter, 1 had emergency reoperation because of acute onset of HPX regurgitation and 1 died at his second reoperation. Four patients underwent reoperation after MVR, 1 because of endocarditis and 3 because of structural deterioration without deaths. Finally, 7 patients with MAVR underwent reoperation because of structural deterioration of the aortic (4 patients), mitral (1 patient), or both HPXs (2 patients) with one death (14.3%; 70% CL, 1.8% to 40.6%). However, in all patients but 1 both HPXs were explanted, replacing simultaneously also the one that appeared grossly normal. Actuarial freedom from reoperation for all

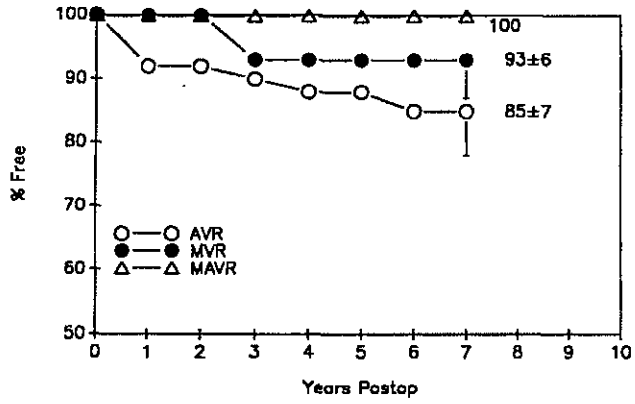

Fig 5. Actuarial freedom from prosthetic valve endocarditis. (Abbreviations as in Fig 1.)

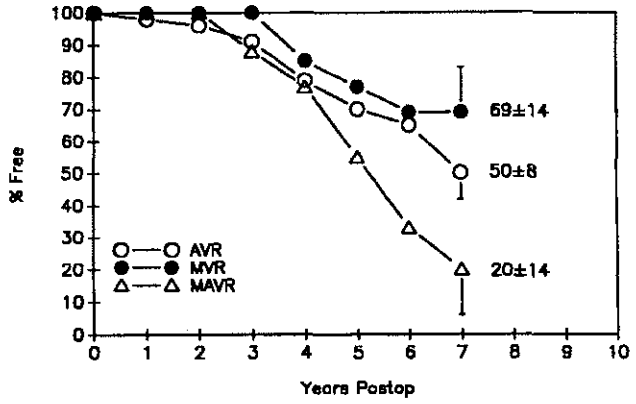

Fig 7. Actuarial freedom from reoperation due to all causes. (Abbreviations as in Fig 1.)

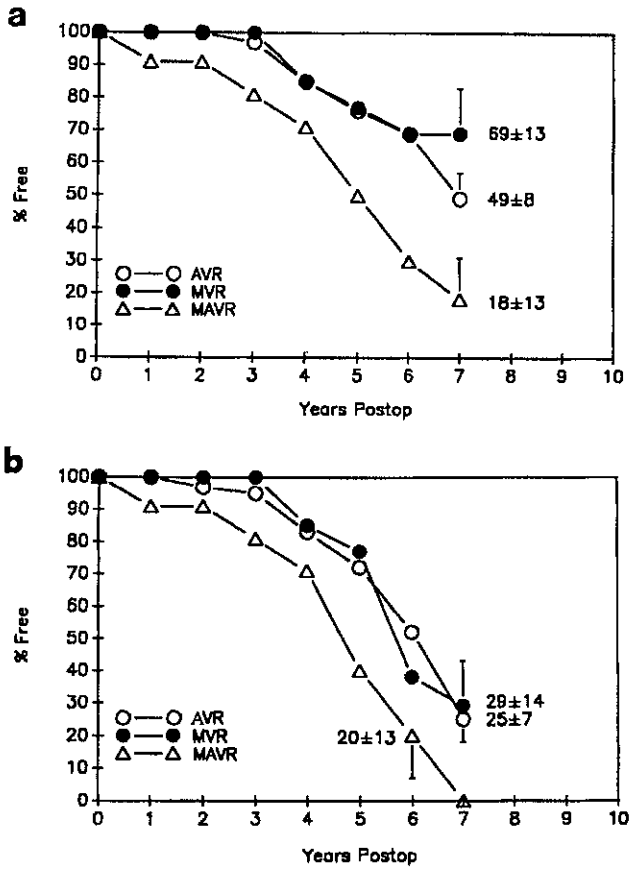

Fig 8. (a) Actuarial freedom from prosthesis structural deterioration requiring reoperation or causing death. (b) Actuarial freedom from structural deterioration determined at reoperation, autopsy, or clinical investigation. (Abbreviations as in Fig 1.)

causes at 7 years is 50% ± 8% after AVR, 69% ± 14% after MVR, and 20% ± 14% after MAVR (Fig 7).

Structural Deterioration

A total of 32 patients underwent reoperation or died because of HPX structural deterioration, 21 after AVR (7.0 ± 1.5%/pt-y), 3 after MVR (3.1 ± 1.8%/pt-y), and 8 after MAVR (14.8 ± 5.2%/pt-y). After AVR 19 patients underwent reoperation and 2 died without reoperation after a mean interval of 5.0 ± 1.4 years (range, 2.9 to 7.7 years). All patients with MVR underwent reoperation after a mean interval of 4.2 ± 0.9 years (range, 3.2 to 5.1 years). After MAVR 7 patients underwent reoperation and 1 died without reoperation after a mean interval of 4.6 ± 1.3 years (range, 2.8 to 6.5 years).

In 21 (78%) of the current survivors, 13 with AVR, 7 with MVR, and 1 with MAVR, clinical and echocardiographic signs of HPX dysfunction have been documented at a mean of 5.8 ± 1.5 years after operation (range, 1.8 to 7.9 years), with predominant incompetence in 87% and stenosis in 13%. Including these patients the overall linearized incidence of HPX structural deterioration is 10.0 ± 0.2%/pt-y after AVR, 10.6 ± 3.3%/pt-y after MVR, and

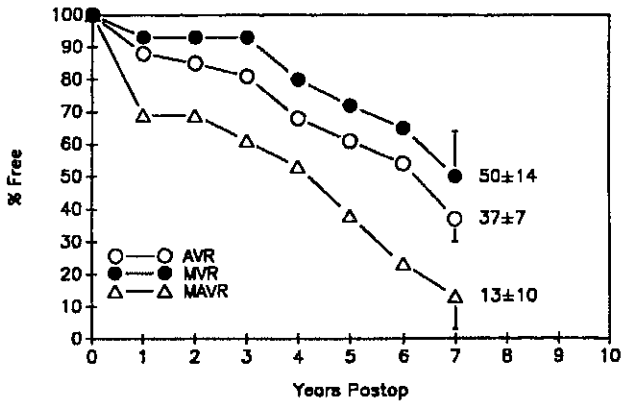

Fig 9. Actuarial freedom from valve-related death and reoperation. (Abbreviations as in Fig 1.)

16.6 ± 5.5%/pt-y after MAVR. At 7 years, actuarial freedom from structural deterioration causing reoperation or death is 49% ± 8% after AVR, 69% ± 13% after MVR, and 18% ± 13% after MAVR (Fig 8a); actuarial freedom from structural deterioration, determined by reoperation, autopsy, or clinical investigation, is 25% ± 7% after AVR, 29% ± 14% after MVR, and 0% after MAVR (Fig 8b).

Overall Valve Performance

Actuarial freedom from valve-related death and reoperation at 7 years is 37% ± 7% after AVR, 50% ± 14% after MVR, and 13% ± 10% after MAVR (Fig 9). Actuarial freedom from valve-related death and permanent disability at 7 years is 73% ± 7% after AVR, 74% ± 13% after MVR, and 61% ± 13% after MAVR (Fig 10). Actuarial freedom from valve-related death and morbidity at 7 years is 14% ± 6% after AVR, 7% ± 7% after MVR, and 0% after MAVR (Fig 11).

Morphology of Hancock Pericardial Xenograft Explants

The typical morphological substrates of HPX failure have been described in detail previously [10]. Briefly, most of the explants removed because of structural deterioration

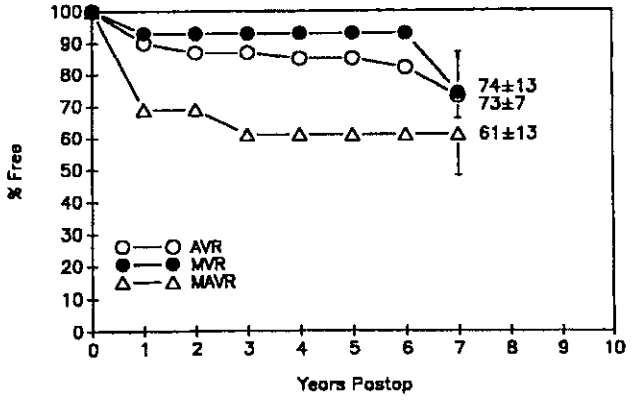

Fig 10. Actuarial freedom from valve-related death and permanent disability. (Abbreviations as in Fig 1.)

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.