

Long-Term Outcome of the Mitroflow Pericardial Bioprosthesis in the Elderly after Aortic Valve Replacement

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Background and aim of the study: The current trend in Europe and the USA demonstrates an increased number of tissue valves being implanted. However, studies presenting long-term follow up of the Mitroflow pericardial bioprosthesis are relatively scarce. In the present study, the long-term outcome of the Mitroflow in the aortic position was analyzed in a geriatric population using actuarial statistics; risk factors for early and late mortality were also evaluated.

Methods: Between 1990 and 1993, 152 elderly (mean age 79.5 ± 3.1 years; range: 75-91 years) patients each received a Mitroflow bioprosthesis implanted in the aortic position. A follow up was conducted in January 2003 and was 100% complete. Concomitant coronary artery bypass grafting was performed in 74 patients (49%). Valve-related outcomes were evaluated using actuarial statistics. Overall survival was

Biological heart valve prostheses have been used in cardiac surgery for over 30 years. The bioprostheses have a definite advantage compared to mechanical valve prostheses, as they do not require life-long anti-coagulant therapy. The main disadvantages with tissue valves are their limited durability, including the risk of late structural valve deterioration (SVD). The current trend in Europe and the USA demonstrates an increased number of tissue valves being implanted. This is probably related to an ageing population, in combination with expectations of improved durability due to new anti-calcification methods and designs in

compared to that in an age- and gender-matched population. A multivariate analysis of risk factors for mortality was also performed.

Results: Actuarial freedom from structural valve deterioration was 99% and 82% at five and 10 years, respectively. Actuarial freedom from stroke, bleeding, prosthetic valve endocarditis and valve explant at 10 years were $80 \pm 5\%$, $94 \pm 3\%$, $93 \pm 3\%$ and $89 \pm 4\%$, respectively. Risk factors for mortality during follow up were male gender, small valves (≤ 21 mm), preoperative NYHA class III/IV, greater age, and long intraoperative perfusion time.

Conclusion: The Mitroflow pericardial bioprosthesis demonstrated a good long-term performance after aortic valve replacement, suggesting it to be a feasible option in elderly patients.

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tissue valve prostheses. There are currently two main types of biological valve prosthesis in use for aortic valve replacement (AVR): bioprostheses made from bovine pericardium, and porcine bioprostheses. The pericardial bioprostheses have demonstrated excellent hemodynamics, but in the past certain questions have been raised regarding their long-term durability (1-4). Recently, Gao et al. demonstrated excellent long-term results with Carpentier-Edwards pericardial prostheses when compared to Carpentier-Edwards porcine valves (5).

The traditional statistical method for evaluating valve-related events in prosthetic heart valves is actuarial statistics (6). However, long-term studies evaluating the Mitroflow valve in a geriatric population, including risk factors for poor outcome, are relatively scarce (7,8). The study aim was to evaluate the long-term outcomes of the Mitroflow bioprosthesis in the aortic position in elderly patients. Overall survival was also compared to that in an age- and gender-matched Swedish population, and a multivariate analysis of risk factors for mortality was also performed.

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Clinical material and methods

Patients

Between January 1990 and December 1993, a total of 152 consecutive patients aged ≥ 75 years (mean age 79.5 ± 3.1 years; range: 75 to 91 years) each received a Mitroflow pericardial bioprosthesis implanted in the aortic position at the authors' department. Patient characteristics are summarized in Table I. Patients with a pre-existing or concomitant valve replacement in another position were excluded from the present study.

Surgical procedure

The surgical procedures were performed in standard manner, using crystalloid cardioplegia. The operative details are listed in Table II. Patients were treated with warfarin anticoagulation (International Normalized Ratio 2.0-3.0) for three months postoperatively.

Table I: Patient ($n = 152$) preoperative characteristics.

Parameter	No. of patients
Age (years)*	79.5 ± 3.1
Age >80 years	55 (36)
Gender	
Male	60 (39)
Female	92 (61)
Valve lesion	
Aortic stenosis	126 (83)
Aortic insufficiency	4 (3)
Mixed lesion	21 (14)
Peak aortic gradient (mmHg)	93
NYHA functional class	
I	1 (1)
II	33 (22)
III	102 (67)
IV	16 (11)
Syncope	34 (22)
Hypertension	33 (22)
Previous myocardial infarction	26 (17)
Renal insufficiency [†]	17 (11)
Previous CVA	16 (11)
Obesity (BMI ≥ 30 kg/m ²)	12 (8)
Peripheral vascular disease	8 (5)
Emergent/urgent procedure	6 (4)
Carotid artery disease	4 (3)
LVEF <30%	12 (8)
COPD (FEV ₁ ≤ 1.0)	10 (7)

*Mean \pm SD.

[†]Serum creatinine >130 μ mol/l.

Values in parentheses are percentages.

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular accident; FEV₁: Forced expiratory volume in 1 s; LVEF: Left ventricular ejection fraction.

Patients undergoing concomitant coronary artery bypass grafting received life-long treatment with aspirin postoperatively.

Data acquisition

Patient information was collected primarily from medical records, death certificates and autopsy reports. This was supplemented with telephone contacts made to the patient or to their relatives or the responsible family doctor when needed. The study population formed part of a larger population and has been followed up at regular intervals. No patient was lost to follow up. The mean follow up was 6.2 ± 3.2 years; total follow up was 946.1 patient-years (pt-yr). An age-, gender- and procedure-time-matched population for comparison of overall survival was provided from the Swedish general population database of the Swedish National Board of Health. All valve-related complications were identified according to guidelines for reporting morbidity and mortality after cardiac valve operations (9). The number of echocardiographic investigations performed during follow up depended on the local routines in the referring hospitals; a total of 76 patients (50%) underwent postoperative echocardiography. If a patient underwent several investigations during follow up, the result of the most recent investigation was reported. The causes of late death were made available from the Swedish National Board of Health. The NYHA class was estimated in all 23 patients alive at follow up in January 2003 (mean follow up from initial cardiac surgery was 10.1 years; range: 9.1 to 11.4 years).

Statistical analysis

A univariate analysis was carried out to detect risk

Table II: Patient operative characteristics.

Parameter	No. of patients
Surgical procedure	
AVR	76 (50)
AVR + CABG	74 (49)
AVR + Other	2 (1)
Valve size (mm)	
21	85 (56)
23	52 (34)
25	13 (9)
27	2 (1)
Aortic root enlargement	3 (2)
Perfusion time (min)*	117 ± 34
Aortic cross-clamp time (min)*	83 ± 21

*Values are mean \pm SD.

Values in parentheses are percentages.

AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting.

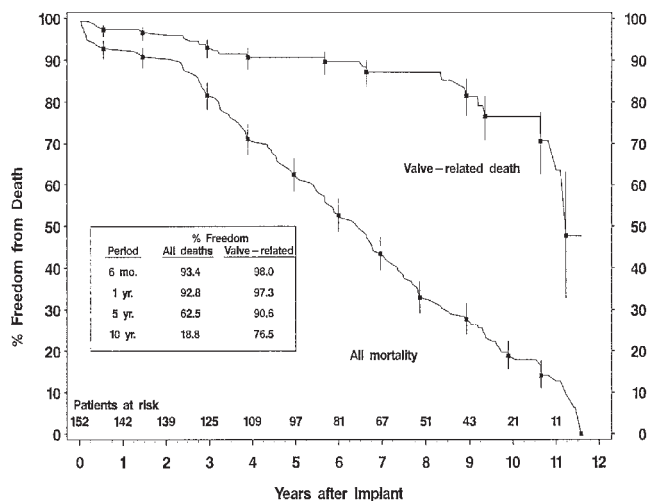


Figure 1: Overall actuarial survival versus actuarial freedom from valve-related mortality.

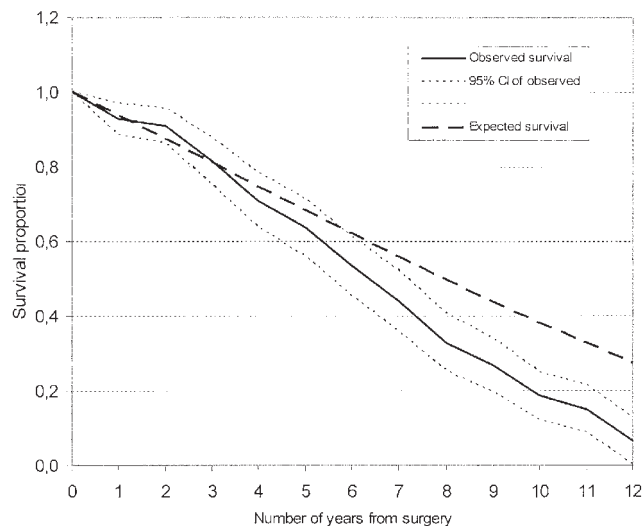


Figure 2: Overall survival following aortic valve replacement compared to an age- and gender-matched Swedish general population.

factors for early and late mortality. A multivariate analysis of independent risk factors for early and late mortality was performed using the Cox proportional hazard regression model (10). Hazard ratios with 95% confidence intervals were estimated. In the multivariate models, age and gender were initially included together with the variables, one at a time, that univariately had p-values <0.20. In the next step, the variables

with the lowest p-value were included, together with age and gender. The procedure was then continued in a corresponding manner. In the final model, all variables included showed significant associations (p <0.05). Actuarial survival was plotted using the Kaplan-Meier method, and the log-rank test was used to compare differences in survival between the two groups. Data were analyzed using SAS version 6.12 software (SAS Institute, Cary, NC, USA).

Table III: Causes of late mortality.

Cause of death	No. of patients (n = 125)
Cardiac	68 (54)
Heart failure	49
MI/arrhythmia	19
Valve-related and bleedings	23 (18)
CVA/thromboembolism	7
Bleedings	6
SVD	6
PVE	4
Non-cardiac	34 (27)
Carcinoma	11
Infection	11
Renal insufficiency	3
Trauma	2
PVD	2
Other*	5

*Causes of death: suicide (n = 1); age weakness (n = 1); chronic obstructive pulmonary disease (n = 1); dementia (n = 2).

Values in parentheses are percentages.

CVA: Cerebrovascular accident; MI: Myocardial infarction; PVD: Peripheral vascular disease; PVE: Prosthetic valve endocarditis; SVD: Structural valve deterioration.

Results

Early and late mortality

The hospital mortality was 2.6% (n = 4). There were 125 late deaths (13.2%/pt-yr). The causes of late death are listed in Table III. The actuarial overall survival rate was $92.8 \pm 2.1\%$ (n = 142) at one year, $62.5 \pm 3.9\%$ (n = 97) at five years, and $18.8 \pm 3.3\%$ (n = 21) after 10 years (Fig. 1). The comparison to a gender-, age- and time-matched Swedish general population indicated a progressive excess mortality among the valve patients after the first three years (Fig. 2). Patients who preoperatively were in NYHA class I/II showed a significantly higher freedom from cardiac death when compared to patients in preoperative NYHA classes III or IV (p = 0.01). The results of the univariate and multivariate analysis of risk factors for mortality are presented in Table IV.

Structural valve deterioration

Eleven patients with SVD were identified with clinical findings in combination with echocardiographic signs. Actuarial freedom from SVD was 100% at one year, $98.5 \pm 1.0\%$ at five years, and $81.9 \pm 5.4\%$ at 10 years (Fig. 3). One patient underwent re-do surgery

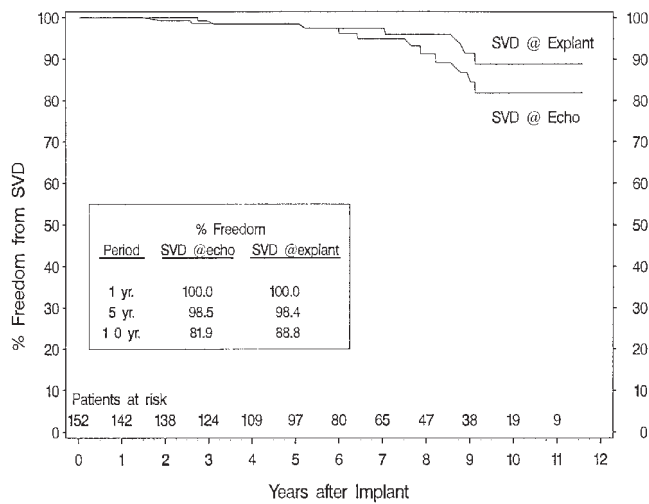


Figure 3: Actuarial freedom from structural valve deterioration (SVD) at echocardiography versus SVD at explantation (data include three patients who did not undergo explant due to comorbidity).

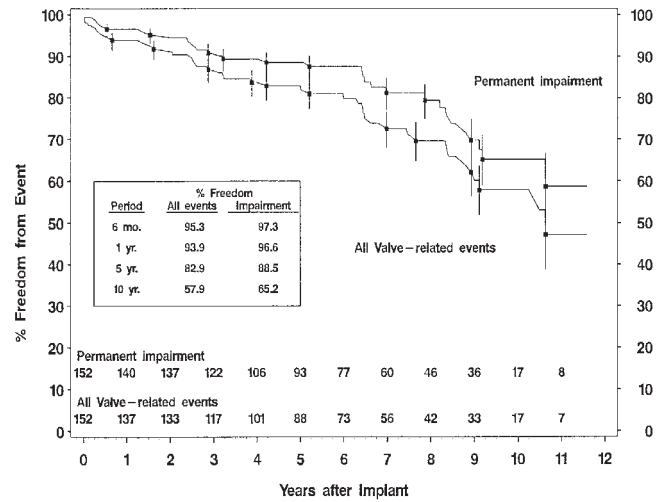


Figure 4: Actuarial freedom from valve-related morbidity versus actuarial freedom from permanent valve-related impairment.

due to prosthetic calcification with cuspal tear during follow up, and three patients had severe aortic insufficiency that required reoperation, but they were not referred for reoperation due to severe comorbidities. The remaining seven patients declined the offer of redo surgery, or were not symptomatic. Actuarial freedom from SVD resulting in valve explant or death was 100% at one year, $98.4 \pm 1.1\%$ at five years, and $88.8 \pm 4.4\%$ at 10 years (Fig. 3).

Thromboembolism

Twenty-four patients experienced a total of 34 neurological events (eight transient ischemic attacks and 26 strokes). The linearized rate was 3.7% per pt-yr. Actuarial freedom from thromboembolism (TE) was $95.9 \pm 1.7\%$ at one year, $88.4 \pm 2.7\%$ at five years, and $74.8 \pm 5.2\%$ at 10 years. Actuarial freedom from stroke was $97.2 \pm 1.4\%$ at one year, $91.9 \pm 2.4\%$ at five years, and $79.9 \pm 5.2\%$ at 10 years.

Bleeding events

Six patients suffered from major bleeding events during follow up (linearized rate 0.7%/pt-yr). Actuarial freedom from bleeding events was $98.6 \pm 1.0\%$ at one year, $96.2 \pm 1.7\%$ at five years, and $94.2 \pm 2.6\%$ at 10 years.

Prosthetic valve endocarditis

Seven patients suffered from seven cases of prosthetic valve endocarditis (PVE) during follow up (one patient underwent prosthetic explant due to PVE but died perioperatively). The linearized rate of PVE was 0.7% per pt-yr. Actuarial freedom from PVE was $99.3 \pm 0.7\%$ at one year, $97.8 \pm 1.3\%$ at five years, and $92.7 \pm 2.7\%$ at 10 years.

Non-structural valve dysfunction

No patient experienced non-structural valve dysfunction during the follow up period.

Table IV: Univariate and multivariate analysis of risk factors.

Covariate	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Valve size (≤ 21 mm)	1.42	1.00-2.04	2.07	1.27-3.37
Greater age	1.13	1.06-1.19	1.11	1.05-1.18
Male gender	1.38	0.97-1.96	2.53	1.58-4.06
Perfusion time	1.008	1.002-1.013	1.007	1.001-1.012
NYHA class III/IV	1.78	1.13-2.80	1.73	1.09-2.74

CI: Confidence interval; HR: Hazard ratio.

Valve-related mortality and morbidity

Twenty-three patients died from valve-related causes during follow up: seven with thromboembolism, six with SVD, four with PVE, three major gastrointestinal bleedings (one patient with antiplatelet therapy and two patients without any anticoagulation or antiplatelet therapy), two intracranial bleedings, and one patient with a subdural hematoma. Actuarial freedom from valve-related mortality was $97.3 \pm 1.3\%$ at one year, $90.6 \pm 2.5\%$ at five years, and $76.5 \pm 5.3\%$ at 10 years (Fig. 1). Forty-three patients were documented with a valve-related complications during follow up. Actuarial freedom from valve-related complications was $93.9 \pm 2.0\%$ at one year, $82.9 \pm 3.2\%$ at five years, and $57.9 \pm 5.8\%$ at 10 years (Fig. 4). Thirty-one patients developed a permanent valve-related impairment, the majority related to cerebrovascular accidents, SVD and bleedings. Actuarial freedom from permanent valve-related impairment was $96.6 \pm 1.5\%$ at one year, $88.5 \pm 2.7\%$ at five years, and $65.2 \pm 6.0\%$ at 10 years (Fig. 4).

Long-term NYHA functional class

Among the 23 long-term survivors were 17 patients in NYHA class I and six in class II. All patients but two (both in preoperative NYHA class II) had an improved postoperative NYHA class compared to their preoperative status.

Discussion

The results of the present study demonstrated good long-term durability of the Mitroflow bioprosthesis, and a low rate of prosthesis explant, analyzed up to 11 years postoperatively, in a geriatric population. The present data compared well with those of a recently published report (8).

Due to a growing population of the elderly in the Western world, the numbers of tissue valve implantations are increasing (11). Moreover, there is renewed interest in the use of pericardial tissue valves, with recent studies having demonstrated superior results for bovine bioprostheses with regard to both valve-related long-term outcome and hemodynamics (5,12). Recently, Jennings et al. demonstrated excellent hemodynamic performance in vitro, and ease of implantation with the Mitroflow valve (2). The opinion of these authors that the Mitroflow pericardial is especially suitable for elderly patients with a small annulus, due mainly to its excellent hemodynamics, has been supported in clinical studies (1,4).

The present results for SVD at 10 years (Fig. 3) compared well with previous reports of the Mitroflow bioprosthesis in the aortic position (1,13-15). Loisanse et al. demonstrated a relatively high rate of SVD with the Mitroflow pericardial valve in a younger population

(3) whereas, by contrast, Pomar et al. showed an excellent freedom from SVD at 10 years (14). The present data showed SVD to be a relatively frequent occurrence, though the clinical consequences were limited and very few valve explants were required due to SVD. This might also reflect difficulties in comparing different studies, even when following current guidelines. Houel et al. suggested equivalent durability between the Mitroflow pericardial valve and the Carpentier-Edwards porcine valve in patients aged ≥ 75 years, with freedom from SVD of 100% in 10 years (4). The in-hospital mortality was also higher in the Mitroflow group (9.3% versus 2.1%), though patients with a small aortic annulus were selected to receive the Mitroflow bioprosthesis (4). Yankah et al. presented their long-term experience with the Mitroflow valve prosthesis after AVR in a recent study including 696 patients in a subgroup aged ≥ 70 years (7). These authors reported a relatively high early mortality, most likely due to a high percentage of emergent procedures, although long-term data showed excellent durability and a low rate of valve-related reoperations during follow up (7). As patients receiving tissue valves are generally old and have a high rate of late mortality (Fig. 1), many die before any valve-related deterioration occurs.

In the present study, a relatively high incidence of TE was reported, this most likely being related to the high incidence of comorbidities in this aged population. A high incidence of cardiac-related events in the elderly following cardiac surgery, and its impact on the patients' quality of life, has been reported previously by the present authors' group (16). The majority of patients suffering from TE did not undergo computed tomography in order to confirm any causal diagnosis; rather, all potential valve-related events were included. The difficulty of separating valve-related events from 'background' comorbidity is a limitation in prosthetic valve evaluations, especially in the elderly where there is a high incidence of comorbidity. Thus, any comparison of results between different studies should be made with caution. The present patients were compared to an age-, gender- and procedure-time-matched general Swedish population, and this indicated an increased mortality rate in patients undergoing AVR (Fig. 2). Whilst this contradicts previous findings from the present authors' group, the finding is most likely related to selection bias as several elderly patients with long life expectancy received mechanical valves during the study period (17). Several independent predictors of mortality following AVR were identified using multivariate analysis. Some of these risk factors, including greater age and high preoperative NYHA class, are intuitive and confirm the previous findings of Minami et al. (1).

Study limitations

The main limitation of the present study was its retrospective design, although the study cohort formed part of a larger patient population that had been followed up at regular intervals. While a prospective study might add further information, the ideal design is not always feasible in a surgical setting, for practical or ethical reasons. In an effort to compensate for the lack of a randomized control group a comparison was made with an age-, gender- and time-matched general Swedish population. Moreover, both the numbers of patients aged ≥ 75 years and the mean follow up period were substantial compared to previous studies with the Mitroflow valve. During the study period the Mitroflow was the only tissue valve available at the authors' department, and this may have reduced selection bias. Finally, during the study period the authors' department was the only cardiothoracic surgery center available in the region, and all patients who underwent AVR were admitted to this clinic. A further limitation was the rather small number of echocardiographic examinations performed during the follow up; hence, the observed incidence of SVD might be considered as an underestimate. It should be noted that in the present study the data were presented as 'freedom from SVD' and not only 'freedom from explant due to SVD', which is commonly used in biological valve reports.

In conclusion, the results of the present study with the Mitroflow valve in elderly patients after AVR demonstrated excellent short-term and good long-term performance that compared well with that obtained with other established tissue valves.

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