Twenty Year Patient Survival and 17 Year Complications

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Abstract

Objective: Performance of the prostheses must be verified in the time domain. We report the 20-year survival of 230 patients operated of mitral replacement with Biocor Standard prosthesis in Padova and Verona and the 17 year prosthetic failure and complications of the series of Padova.

Methods: 230 patients, 150 females and 80 males, aged 71 ± 6.3 received 235 isolated mitral Prostheses in Verona (67) and Padova (168), between June 1989 and August 2004. Twenty-year survival including 1698 patient-years was complete. Prosthesis survival was evaluated in the patients of Padova with a 90% goodness of follow-up and included 905 patient-years.

Results: Twenty-seven operations were done in the eighties, 168 in the nineties, 52 in this century. Three operations were emergent, 20 urgent. The indication was prosthetic malfunction in 50 cases (21.7%), regurgitation in 114 (49.6%), stenosis in 22 (9.7%), mixed lesion in 44 (19.1%), concomitant CABG (Coronary Artery Bypass Graft) was performed in 23%. Overall survival was 6% (2-13%), Thirty day mortality was 8.9% (5.6-13.3%). The early hazard phase extended to 2.5 years with a linearized rate 1.4%/patient-years *vs.* a late rate of 7.2%/patient-years. Seventeen years freedom from reoperation was 80.5% (55.3-92.3%), actual 92% (86.4-94.5%), from SVD (Structural Valve Degeneration) 85.2% (52.6-96.1%) actual 94% (88.2-96.7%), from perivalvular leak 92.6% (86.5-96%), from embolism 83.1% (73-89.7%), from haemorrhage 83.8% (71.5-91.1%), from endocarditis 90.9% (82.4-95.4%), from pacemaker 77% (60.2-87.5%).

Conclusion: Mitral Biocor has optimal durability and average complications. Premature mortality (6% *vs.* 30% survival of US (United States) matched population) is unrelated to prosthesis performance and suggest failure of our surgical strategy of the past century.

Ultra mini abstract: 20 year Survival of patients is disappointing (6%) when compared to the matched US population (30%). The 17 year performance of the Biocor standard device compares with the best available prostheses. This therefore suggests an overall failure of our surgical strategy of the past century.

Introduction

The Biocor Standard prosthesis (Biocor Industrial, Belo Horizonte, Brazil) was a porcine valve fixed in glutaraldehyde at low pressure without anti-calcification treatment. The design aimed to improve tissue durability: leaflets of similar size were separately mounted on flexible stent to improve hemodynamic and the interaction between stent and suture of the leaflet tissue was covered with a pericardium sheet to improve durability. The Biocor model was chosen because of the unsatisfactory results of the first generation biologic valves and was used from June 89 to August 2004 in 230 patients of Verona & Padova Cardiac Surgery Centers, it was subsequently replaced from the Epic model with calcium mitigating treatment. Focus of the paper was 20 year survival of the patients which is affected from survival and complications of the prosthesis. We therefore update the postoperative events affecting 168 mitral prostheses, implanted in 163 patients operated on in Padova, with the aim to contribute data to our previously published [1] intermediate results.

Patients and Methods

Between June 1989 and August 2004, 88 Biocor standard mitral prostheses were implanted in Verona and 264 in Padova: 235 were single mitral prostheses implanted in a total of 230 patients (67 in Verona and 163 in Padova). Survival of the 230 patients (150 female and 80 male) and update of the prosthetic performance of the series of Padova were the focus of study.

Twenty-seven operations were done in the eighties, 168 in the nineties and 52 in the current century. Sex prevalence was female (150/80). Mean operative age was 70.8 ± 6.3, median 71, range 37-86 years. The median New York Heart Association (NYHA) functional class was III (mean value, 2.8 ± 0.8). Operative indications was prosthetic malfunction in 50 cases (21.7%), regurgitation in 114 (496%), stenosis in 22 (9.7%), mixed lesion in 44 (19.1%). Eighty-two (36%) patients had previous cardiac procedures: among these 50 mitral valve replacement, 12 open and 13 balloon commissurotomy, 7 coronary artery graft. Three emergent and 20 urgent operations were required. Prevalence of baseline risk factors are summarized (mean ± sd or %) in Table 1.

Surgery: Standard operative procedures were used: paraseptal atrial incision, pledget supported interrupted sutures and posterior

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	Range	N	Mean ± sd	HR	Sd.	p-value
CONTINUOUS VARIABLES						
Age (years)	42-86	230	70.8 ± 6.34	1.04	0.013	0.005
Operative years	1989-2004	230	1996 ± 4.22	0.97	0.176	0.061
MPAP mmhg	Oct-65	138	32.3 ± 11.6	1.01	0.008	0.15
Ejection Fraction (%)	30-87	139	60.9 ± 11.8	0.97	0.009	0.004
CATEGORICAL VARIABLES	Cases	N	%	HR	Sd.	p-value
Male sex	80	230	34.8	1.6	0.157	0.003
Age >71 years	111	230	48.3	1.55	0.153	0.004
Verona	67	230	29.1	1.21	0.16	0.233
Operation date ≥ 2000	52	230	22.6	0.58	0.217	0.011
VALVE LESION						
Incompetence	114	230	49.6	1.17	0.178	0.305
stenosis	22	230	9.6	0.82	0.2	0.428
Steno-insufficiency	44	230	19.1	0.71	0.105	0.106
Prosthesis malfunction	50	230	21.7	1.19	0.176	0.325
PATHOLOGY						
Rheumatic	61	230	26.5	0.72	0.178	0.062
floppy valve	47	230	20.4	0.99	0.189	0.939
Ischemic pathology	22	230	9.6	1.48	0.257	0.127
endocarditis	12	230	5.2	0.74	0.386	0.432
OPERATIONS						
Previous Mitral prosthesis	50	230	21.7	1.19	0.176	0.325
Previous surgical commissurotomy	12	230	5.2	0.94	0.362	0.865
Previous balloon commissurotomy	13	230	5.6	0.81	0.343	0.543
Previous CABG	7	230	3.04	1.13	0.416	0.764
HEMODINAMIC						
Preoperative MPAP ≥ 35 mmHg	55	138	39.8	1.54	0.312	0.033
Ejection Fraction <40%	7	139	5	2.29	0.905	0.035
Preoperative IABP	3	230	1.3	3.72	0.585	0.025
Preoperative Pacemaker	9	230	3.9	1.1	0.362	0.789
CLINIC						
Preoperative atriomegaly	75	230	32.6	0.68	0.169	0.022
Preoperative left thrombus	23	230	10	1.03	0.263	0.913
Preoperative coronary pathology	61	230	26.5	1.55	0.169	0.009
Previous AMI	42	230	18.3	1.76	0.195	0.004
Previous BPOD	40	230	17.4	0.86	0.204	0.447
diabetes	23	230	10	0.99	0.263	0.99
hypertension	44	230	19.1	0.69	0.207	0.072
Previous stroke	5	230	2.2	1.65	0.583	0.389
NYHA class 4	50	230	20.6	1.83	0.186	0.001
Cardiogenic shock	4	230	1.7	3.55	0.63	0.0001
ASSOCIATED PROCEDURES.						
CABG	53	230	22.6	1.63	0.179	0.006
Left Atrial thrombectomy	14	230	6.1	1.01	0.326	0.969
Tricuspid valve repair	42	230	18.3	0.94	0.204	0.751
CEA	4	230	1.7	4.82	0.509	0.002
Ablation procedure	5	230	2.2	0.68	0.583	0.518

Prev: Previous; Preop: Preoperative; Mpap: Mean Pulmonary Arterial Pressure; Cabg: Coronary Artery Bypass Graft; Pathol: Pathology; Iabp: Intra Aortic Ballon Pulsation; AMI: Acute Myocardial Infarct; Nyha: New York Heart Class; BPOD: Bronchopulmonary Obstructive Disease; CEA: Carotid Endoarterectomy.

Table 1: Baseline risk factors prevalence and Hazard ratio for death.

chordae preservation. Prosthetic size ranged from 25 to 33, size 31 was the most used in 100 patients, next size was 29 used in 86 patients. In 53 cases (22.6%) coronary artery bypass graft procedure was associated. Oral anticoagulation (international normalized ratio, 2.0-3.0) was interrupted after 3 months, unless contraindicated.

Statistical Analysis

Analysis used the STATA package (Stata Corp LP Lakeway Drive, College Station, Texas 77845).

Patient follow-up

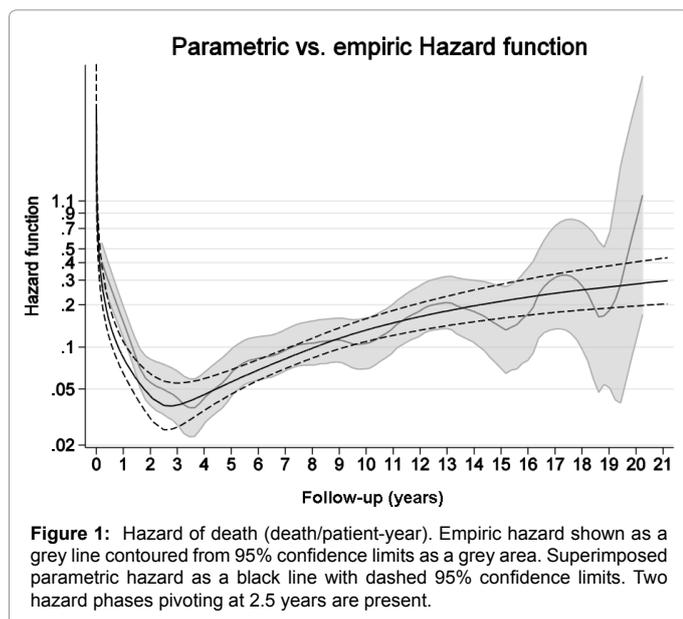Survival was calculated at a common closing date on January 1, 2012.

Follow-up was done by telephone interview of patients or their relatives. In 43 untraced patients survival was certified by municipal population registries. Total follow-up time was 1698-year (mean 7.2 ± 5.49, median 7.8 years, Inter Quartile Range (IQR) 1.7-11.4, maximal follow-up 21-year) and it was complete. Analysis of survival used the Kaplan-Meier method and was fitted with flexible parametric survival model [2]. Risk factors selection used the bootstrap-bagging methodology [3]. All p-values of the paper are two-tails, unless differently specified. Survival was compared to survival of the United States (US) population matched for age and sex, using the Hakulinen's cohort estimate method [4].

Prosthesis follow-up

The events according to ACC/AHA 2006 guidelines (9) were collected from 163 Padova patients (109 female and 54 male, aged 72.9 ± 5.3 years, range 51-86 years), five patients, who received a second isolated Biocor standard prosthesis in a redo operation, were entered twice in the statistical analysis (n=168). In 25 untraced patients we used for analysis purposes the last recorded available contact. The collected total follow-up time was 905 years (mean 5 ± 4.6 maximum 17.6) and the goodness of follow-up was 90% of the maximal. To account for repeated events in the same patient the clock was reset at each episode. This required time splitting in 189 records. Time related hazard was shaped according to reference [5]. The 17-year freedom from event was calculated by Kaplan-Meier method and linearized event rate was calculated. Incidence rate ratio was used to compare linearized rates. Reoperation probability and Structural Valve Degeneration (SVD) probability was also reported in the setting of the precluding event death, usually referred to as "actual" estimate, 95% confidence limits and 2 tails p-values were used.
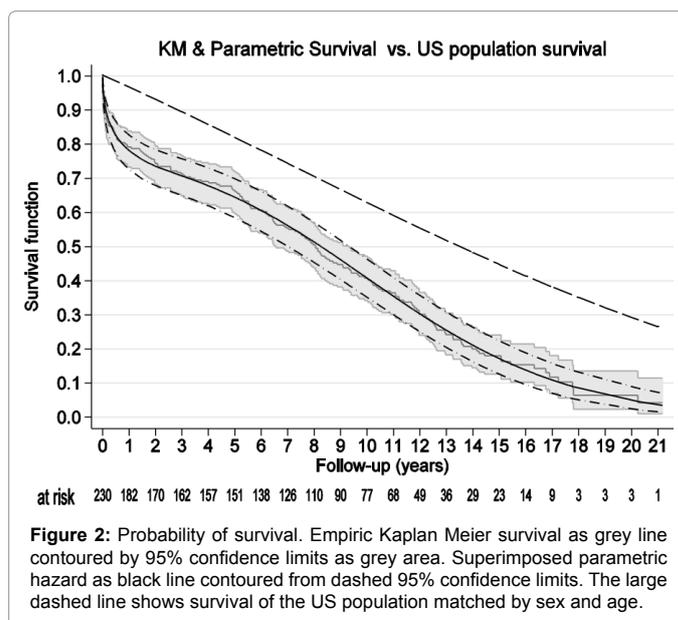
Results

Perioperative mortality (30 day) was 8.9% (5.6-13.3%). Sixteen died in Padova and five in Verona (p=0.80). There were two hazard phases pivoting at 2.5 year (Figure 1). The early hazard includes 66 deaths and the late hazard 115 deaths. The causes are reported in Table 2. Most of the known causes (49%) were cardiac related, 14% were prostheses related, 23% were unknown.

Figure 1: Hazard of death (death/patient-year). Empiric hazard shown as a grey line contoured from 95% confidence limits as a grey area. Superimposed parametric hazard as a black line with dashed 95% confidence limits. Two hazard phases pivoting at 2.5 years are present.

EARLY DEATHS	N°	LATE DEATHS	N°
Cardiac	25	Cardiac	31
Acute Myocardial Infarction	9	Acute Myocardial Infarction	3
Multiple Organ Failure	2	Multiple Organ Failure	1
Sudden Death	4	Sudden Death	4
Sepsis	1	Sepsis	2
Respiratory Failure	2	Respiratory Failure	2
Pulmonary Embolism	1	*Alzheimer-Perusini Disease*	2
Hepatic Failure	1	Peritoneal Infection	2
Acute Renal Failure	1	Chronic Renal Failure	7
Prosthesis Dehiscence	2	Structural Valve Degeneration	1
Acute Endocarditis	2	Acute Endocarditis	3
Cerebral Embolism	3	Ictus/Cerebral Embolism	3
Cerebral Hemorrhage	1	Cerebral Hemorrhage	2
Visceral Hemorrhage	2	Visceral Hemorrhage	2
Cancer	3	Cancer	15
Unknown	7	Unknown	35
TOTAL	**66**		**115**

Table 2: Causes/modes of death.

Figure 2: Probability of survival. Empiric Kaplan Meier survival as grey line contoured by 95% confidence limits as grey area. Superimposed parametric hazard as black line contoured from dashed 95% confidence limits. The large dashed line shows survival of the US population matched by sex and age.

Overall survival

was 79% (73-84%) at 1 year, 66% (60-72%) at 5, 41% (34-47%) at 10, 18% (13-24%) at 15 and 6% (2-13%) at 20 years. This result was compared to survival of the age and sex matched US population, which was 30% (p<0.0001) at 20 years (Figure 2).

Risk Factors: Overall Series

Univariate relative hazard

Univariate relative hazard of the risk factors is summarized in Table 1, columns 5 to 7. Concomitant Carotid Endoarterectomy (CEA), preoperative Intra-Aortic Balloon Pump (IABP) or emergent operations were the most powerful, but rare incremental risk factors.

Multivariate parametric analysis

Multivariate parametric analysis selected as significant and independent incremental risk factors male sex (HR (Hazard Ratio)

1.7 p=0.002), NYHA (New York Heart Association) Class IV (HR 1.5, p=0.03), Older Age (AGE ≥ 71 years, HR 1.9, p<0.001) and High mean pulmonary artery pressure (MPAP>35 mmHg, HR 1.6, p=0.03). Actuarial survival according to these incremental risk factors show up in Figure 3. A recent operative year (≥ 2000) (HR 0.65, p=0.015) was the single risk neutralization factor, therefore 10 year survival in the recent operative decade was 47% (30-61%) vs. 38% (31-46%) (p<0.0001), with a linearized event rate of 7 vs. 12%/ patient-years.

The predicted survival results of the most favourable operative scenario (last decade operation, female sex, younger operative age ≤ 71 years, NYHA class ≤ 3 and, MPAP ≤ 35 mmHg) are similar to survival of the matched US population (female 31%, male 28% at 20 years). Survival of the worst scenario (male sex, older operative age >71 and NYHA class 4, MPAP >35 mmHg) is prohibitive (Figure 4).

Multivariate parametric analysis of the early hazard phase (<2.5 year)

The independent significant risk factors were NYHA Class IV (HR 3.2, p=0.002), high MPAP >35 mmhg, HR 2.3, p=0.03), previous Acute Myocardial Infarction (AMI) (HR 2.3, p=0.017), concomitant Carotid Endoarterectomy (CEA) +CABG (HR 3.8, p=0.01).
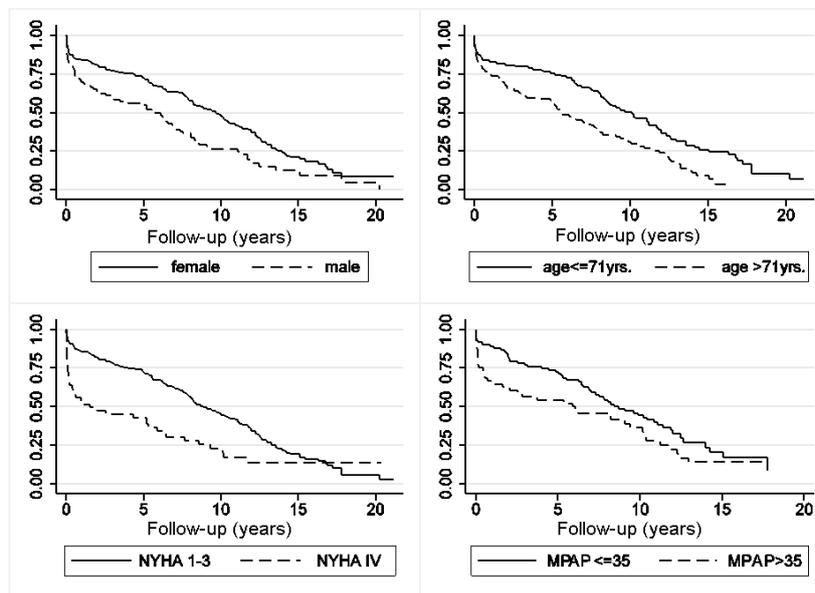

Figure 3: Probability of survival. Empiric Kaplan Meier survival according to significant incremental risk factors: sex, operative age, NYHA class, and Mean arterial pulmonary pressure (MPAP) in mmHg.
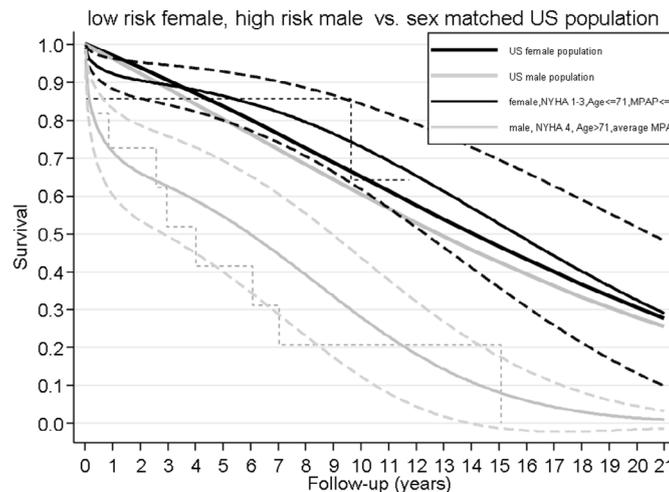

Figure 4: Survival of low risk female and high risk male vs. age and sex matched US population. Empiric Kaplan Meier survival (scaled lines) fitted by continuous survival lines and dashed 95% confidence limits predicted from multivariable analysis. Gray lines: survival of males with NYHA class 4 and age older than 71 years and average mean pulmonary pressure (MPAP). Black lines: survival of females NYHA class 1-3 and age ≤ 71 years and mean pulmonary pressure (MPAP) ≤ 35 mmHg. Thick Lines: survival of matched US population (black=females, grey=males).

Multivariate parametric analysis of the late hazard phase (>2.5 years)

The independent risk factors were older age >71 year (HR 1.59, p=0.018) with a linearized event rate of 8 *vs.* 6%/patient-years and history of coronary artery disease (HR 1.8, p=0.006) with a linearized rate of 9.5 *vs.* 6.4 %/patient-years.

Prosthesis follow-up at 17 years

168 prostheses presented 76 events. Actuarial freedom and linearized incidence are summarized in Table 3. With the exception of reoperations and SVD the hazard incidence of other unfavourable events (Figure 5) is maximum in the first postoperative year (≥ 10%/patient-years) (7.5%/patient-years for endocarditis) and rapidly decreases at 1%/patient-years or less thereafter. There is no late phase, therefore the shorter follow-up the higher the event rate.

| Actuarial freedom from complication					Padova (905 patient-years)		Mykén (1195 patient-years)			
	% Freedom	SD	95% LCL	95% UCL	Event n°	Rate %y	Event n°	Rate %y	Rate ratio	p-value
Reoperations	80.5	8.94	55.31	92.33	13	1.44	11	0.9	1.56	0.28
Dehiscence	92.6	2.32	86.44	96.03	10	1.1	----	----	----	----
Hemorrhage	83.8	4.85	71.49	91.12	14	1.55	13	1	1.42	0.37
Embolism	83.1	4.16	73.04	89.71	18	1.99	26	2.2	0.91	0.77
Endocarditis	90.9	3.12	82.42	95.39	9	0.99	9	0.7	1.32	0.56
SVD	85.2.	9.67	52.59	96.09	3	0.33	11	0.9	0.36	0.11
Pacemaker	77	6.82	60.21	87.45	16	1.77	----	----	----	----
SVD: Structural Valve Degeneration; LCL: Lower Confidence Limit; UCL: Upper Confidence Limit; Rate %y: %/patient-years.										

Table 3: Postoperative events.
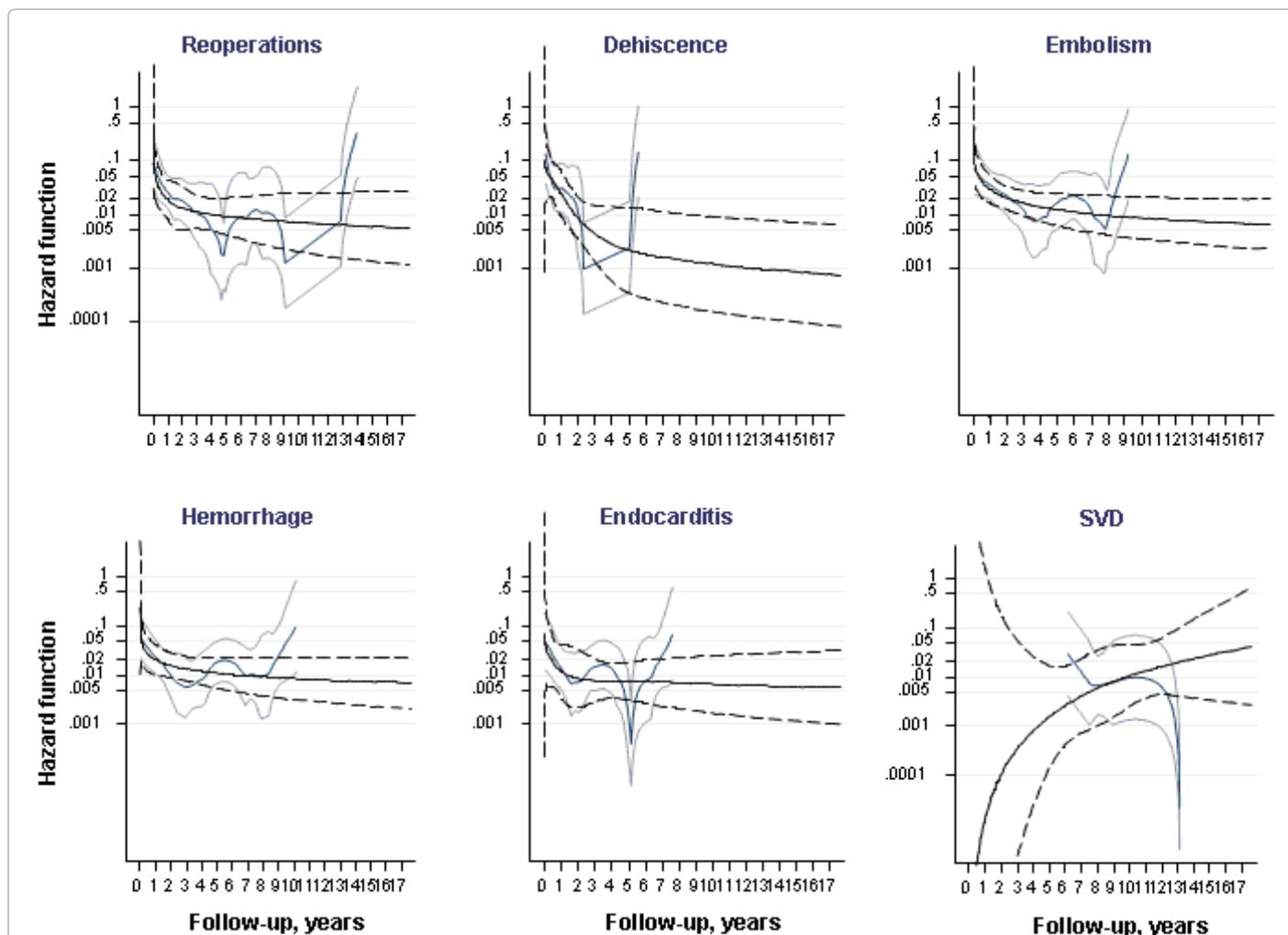
Figure 5: Hazard of postoperative events (event/patient-year). Grey lines: empiric hazard with 95% confidence limits. Black lines: superimposed parametric hazard estimate with dashed 95% confidence limits.

Freedom from reoperation

There were 13 reoperations on 12 patients, the prosthesis was replaced with a new Biocor standard in 5 cases. In 2 cases it was replaced by mechanical prostheses (Saint Jude and CarboMedics). Progression of aortic stenosis in 3 patients required new implant of a pericardial Carpentier-Edwards, Biocor Standard and Biocor Epic respectively, a forth patients received an aortic pericardial Carpentier-Edwards and a new mitral Biocor Standard. Cause of replacement was dehiscence in 6 cases, SVD in 2, SVD after endocarditis in 1, prosthetic thrombosis in 1. There was a single perioperative death in an emergency operation due to cardiogenic shock from overlooked critical aortic stenosis. Actuarial reoperation freedom was 80.5% (55.3-92.3%) at 17 years, actual was 92% (86.4-95.5%), reoperation rate was 1.44 %/patient-years, (Table 3). Reoperations were required as early as 10 days after operation and as late as 14 years. Hazard shape shows an early high hazard phase, due to 6 prosthesis dehiscence, 1 acute endocarditis and 1 overlooked aortic stenosis.

Late episodes were related to progression of disease in the aortic valve (2) and SVD. The mean interval from reoperation to death was 7 ± 5.1 years. Two patients reoperated on for dehiscence were still alive after 14 and 17 years. Four died after a mean survival of 5.8 years. There was no relation with sex or operative age.

Prosthetic perivalvular leak

Beside the 6 operated patients it occurred in 4 more medically treated cases. It occurred within 2 years, with a single later case, diagnosed at 5.6 years from operation. One patient died of preoperative unrecoverable shock. Three refused reoperation and were all dead within a mean of 1.7 years and a maximum 4.8 years. The actuarial freedom from leak was therefore 92.6% (86.4-96%) the event rate 1.10 %/patient-years. There was a significantly higher hazard (HR 4.2, p=0.02) in patients operated on because of a previous mitral prosthesis malfunction and in patients operated on for steno-insufficiency (HR 3.8, p=0.04)

Embolic events

There were 18 brain embolisms, they were fatal in 4 cases, 7 patients recovered, and 6 had permanent cerebral damages. A single patient had severe peripheral embolism. Forty-five percent of the patients were anticoagulated and 33% was in sinus rhythm. The hazard of embolism was higher in early postoperative years with a median interval of 1.6 years, mean 2.6, maximum of 9.2 years. The actuarial freedom was 83.1% (73.0–89.7%), the linearized rate 1.99 %/patient-years. The incidence rate ratio between patients younger/older than 70 years was 0.0127/0.021=0.60 (p<0.44).

Hemorrhagic events

There were 14 events, they were fatal in 3 cerebral cases and in 4 visceral cases. Seven patients with visceral bleeding recovered. The hazard was higher in early postoperative years occurring at a mean of 2.6 years and a maximum of 9.2 years. The actuarial freedom was 83.8% (71.5.-91.1%). It was related to Coumadin intake in 12 cases (86%), unrelated in two visceral bleeding. The hazard was higher early after operation with a median interval of 2.1 years (mean 3.3, maximum 10.2) the linearized rate was 1.48 %/patient-years.

Endocarditis

There were 9 episodes. A single patient was successfully reoperated in the acute phase. All others underwent medical therapy that was unsuccessful in 5 cases. Two patients survived the infection but one of them required reoperation for SVD of the damaged valve after 2.6 years. Freedom from endocarditis was 91% (82.4-95.4%). The hazard was higher early after operation with a mean and median interval of 3.3 years and a maximum of 10.2 years. The linearized rate was 0.99%/patient-years. The hazard of postoperative endocarditis was significantly related to preoperative endocarditis in 33.3% of the cases.

SVD

SVD occurred in 3 cases 6, 10 and 14 years since operation. Their operative age was respectively 71, 69, and 66 years. Two patients were successfully reoperated on. The third patient, who was by then 79 year old, refused operation. There was a forth patient reoperated on 3.5 years after valve implant. This early SVD was related to valve damage due to a postoperative acute endocarditis, therefore true SVD freedom was 85.2 ± 9.67 (52.6-96.1%), actual 94% (88.2-96.7%), linearized rate was 0.33 %/patient-years and the hazard function showed a rising hazard (Figure 5).

Insertion

Pacemaker insertion was required in 16 patients, actuarial freedom was 77.0 (60.2-87.5%), the hazard function showed a slight increase with time, the linearized rate was 1.77 %/patient-years.

Clinic

At 17 years of follow-up 45 of 163 patients were still alive: mean NYHA class was 1.95 ± 0.82 vs. 2.72 ± 0.79 preoperatively. NYHA had improved 1 class or more in 54% of the patients and worsened in 10%. Twenty-four % of the patients recovered sinus rhythm, 5% progressed to atrial fibrillation, 18% to pacemakers. Seventy-four % used warfarin.

Discussion

This study updates our previous data [1] including the survival of patients operated on at the University of Verona. In the evolving bioprosthetic era the Brasilian Biocor Standard project neutralized the risks due to high pressure leaflet fixation, porcine muscular leaflet, rigid stents and Dacron exposure to circulation [6-8]. The offered solutions represented an intermediate step between the first generation bioprosthetic valves and the Biocor Epic model. This has been object of an early evaluation (mean follow-up=2.2 patient-year) by Jamieson [9], with a lower late mortality rate than our (6.6% vs. 7.2%/patient-years) but with higher embolism rate (2.6 %/patient-years vs. 1.9%).

We must judge success of new technology, despite safeguards imposed from the regulators, on real–life results. In this respect our 6% (2-13%) 20 year survival is identical to the one reported from Borger in 559 Hancock II mitral valve recipients aged 67 ± 11 years at operation [10] but it is disappointing when compared to the 16.4 ± 4.7 reported from Mykén [11] in 194 Finnish patients. Only three of our patients, operated on at 56, 60 and 65 years of age survived more than 20 years.

The comparison of results between surgical series is debated [12]. There are endogenous differences among series in baseline patient's risk factors and many exogenous differences: health systems, facilities, patient's selection over decades of surgery and analytical methodologies. In this respect the obvious most relevant difference with Mykén experience [11] is the significantly (p<0.001) older mean age of our patients (72.9 ± 5.3), 8 year older of the Finnish patients (64.9 ± 12.3): 18% of our patients were younger than 65 years vs. 79/194 (41%) in Myken series, no wonder if older patient have a shorter survival.

A neutral survival benchmark is required! In our opinion this

benchmark is locally the survival of the age and sex matched national population and internationally that of the US population:

Twenty year survival of the age matched US female population is 31% and it is 28% for the males. There is a 25% proportion of premature deaths in our series when compared to the US population. Nonetheless survival is strongly dependent from patient's frailty. In Figure 4 we have therefore compared the US population estimates with actuarial and parametric predictions of our most favourable operative scenario (last decade operation, female sex, Younger operative age ≤ 71 years, NYHA class ≤ 3 and, MPAP ≤ 35 mmHg). This shows that actuarial survival (limited to 12 years) and the parametrically predicted survival are better than the female and male US population who are included within the 95% confidence limits of our predictions. On the contrary observed actuarial and parametric survival of our worst operative scenario (male sex, older operative age >71 and NYHA class 4) are definitely worst and their confidence limits do not include the US population estimates (Figure 4).

Is this finding related to an inadequate or failing prosthesis? A large series has been recently published from Myken in Finland. Finland and Italy are both founded on a public health service and committed to high quality data, nonetheless we must complain that Italian citizens and Statistical data repositories oppose resistance to share individual data with researchers because of "privacy" issues and legislation [13]. Our survey of prosthetic survival and prosthesis related events is therefore limited to an "acceptable" 90% goodness of fit [14] and to a maximum follow-up of 17 years. With this loss of follow-up our comparison with the Mykén results rely on linearized rates more than on probabilities and the reported differences (Table 3) are statistically nonsignificant. Linearized rates assume that the risk is constant with time and are clearly inappropriate if hazard is increasing, as in tissue failure (SVD), an event where comparison of actuarial and actual probabilities is preferable: concerning SVD, Mykén reports a 79.3% ± 6.0% actuarial freedom and 91% actual freedom at 20 years [11]. In the 17 years of prosthetic follow-up we operated on 3 SVD cases, all of them aged > 65 years at operation. Our SVD freedom was 85.2 ± 9.67 (52.6-96.1%), actual 94% (88.2-96.7), in the same range of time Myken reported 9 SVD reoperations in patients with an operative age of 64 ± 12 years, the calculated freedom was 81.3% ± 6% [15]. The Incidence Rate Ratio was 0.36 (.064-1.36), stating that our rate was significantly (one-way p-value=0.05) lower than the rate observed in the Finnish series. This is partly due to confounding from operative age, shorter mean follow-up of our patients (5 ± 4.6 *vs.* 6.2 ± 5.6 years) [16], medical selection and absence of commissure dehiscence [7,8], never observed in our series. The mean age of our patients was (72.9 ± 5.3 years) years *vs.* 64.9 of the Finnish, only 8.6% of our patients had an operative age ≤ 65 years *vs.* 41% in Mykén series and 48% was older than 71 years (Table 1). David and colleagues [17] report the 15 year actual freedom from SVD in recipients of the Hancock II prosthesis aged more than 65 years and it is 89% ± 4%, within the 95% CL of our estimate (88.2-96.7). Pomerantzeff [18] has reported a 15 year SVD freedom of 84.0 ± 9.8% in Brazilian patients aged 61 to 80 years at operation and of 51.8 % in patients aged 51-60. Kiraly, who operated on an exceptionally young population (mean age 48 ± 14 years), reported a 76.7% SVD freedom at 14 years [19]. We therefore think that adequacy of the prosthesis can be better estimated from the overall freedom from reoperation: Our freedom was 80.5% (actual 92%), the reoperation rate was 1.44 %/patient-years as compared to 0.9% in Mykén series, The incidence rate ratio was 1.56 (0.64-3.84), p=0.28. The main cause of reoperation was paravalvular leak in 6 patients, 4 more patients with this diagnosis were not operated on and deteriorated rapidly. In 80% of our patients the complication occurred after reoperation for leaking or degenerated prostheses and

appears therefore patient-intrinsic or due to technical factors, not to Biocor design and materials. Mykén and coll. report 27 paravalvular leaks, but a rate comparison is not possible because the number of events affecting the mitral position is lacking in their paper [11]. For all other unfavourable events the Food and Drug Administration has formulated objective performance criteria for new heart valve approvals based on linearized rates [12] that are reported in Table 3. Hemorrhagic episodes were more frequent in our than in Mykén series: our freedom was 79.5% (63.5-89%) with linearized rates of 1.55 *vs.* 1.0 % patient-year (hazard rate ratio 1.42, p=0.37) and was strongly related to warfarin use. Our embolism rate (1.99 %/patient-years) is somewhat higher than the 1.82 %/patient-years reported by Mykén at 17 years [15]. The hazard rate ratio was 0.91 (p=0.77) and it was higher in older patients, as in Mykén. Freedom from Endocarditis was 91% as in Mykén (92%) [11] but the linearized rate a little higher 1.32 %/patient-years (0.46-3.75 %/patient-years, p=0.56). Preoperative endocarditis was a risk factor for postoperative endocarditis recurrence [16-23].

Conclusion

The study confirms the validity of the Biocor prosthesis in the difficult mitral position with a low rate of SVD, absence of leaflet tears and a low embolic rate, in patients significantly (p<0.001) older than in Mykén series. Anticoagulation complications, which may be serious in an aging population, occurred with rates similar to those generally observed. The premature mortality of many patients, as compared to the general population, stresses the failure of the surgical strategy available in the past century: 22% of the patients in this series were operated on because of malfunction of an earlier prosthesis and the older age compared to age of Finnish patients suggest some delay of treatment. Mitral stenosis is on retreat and the approach to mitral regurgitation, which was the most common pathology in this series (114/230, 50%) is today mostly treated with conservative procedures. Analysis of risk factors shows the importance of early aggressive treatment, either non-invasive or surgical, to anticipate the penalty imposed on late survival from atrioventricular remodelling, atrial fibrillation pulmonary hypertension and cardiac failure. A number of new advancement in surgical strategy has been already implemented in the second decade of this century with a marked improvement of patient survival.

Study Limits

23% unknown causes of deaths, analysis of failure and complications of the prosthesis is limited to the 168 prostheses implanted in Padova, with 90% goodness of follow-up.

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