The Impact of Age in Prosthesis-patient Mismatch on Long-term Survival after Aortic Valve Replacement: *in-vitro* versus *in-vivo* Values

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Authors' contributions

This work was carried out in collaboration among all authors. Author AM designed the study, wrote the protocol and the first draft of the manuscript. Author AAC contributed to the study design and subsequent drafts. Author LC performed the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aim: We studied the effect of age on survival in the setting of prosthesis-patient mismatch (PPM).
Study Design: Retrospective single surgeon practice.
Place and Duration of Study: Cardiothoracic department, Mater Dei Hospital Malta, between January 1995 and December 2014.
Methodology: 572 consecutive patients undergoing aortic valve replacement (AVR) were divided into four age groups and followed up for a maximum of 20 years (mean 8.2). Date of death was derived from the National Statistics Office. PPM was classified according to defined criteria, and calculated according to manufacturers' tables (*in-vitro*) and from *in-vivo* values published by independent researchers. The impact of age and PPM on long-term survival was studied using the Cox proportional hazard model.

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Results: Mean *in-vitro* derived indexed effective orifice area (EOAi) was significantly higher than *in-vivo* EOAi (1.04±0.22 vs 0.93±0.16, *p*=0.000) and incidence of PPM was lower using *in-vitro* criteria (moderate 18.0% vs 24.1%, *p*=0.01, severe 1.9% vs 4.7%, *p*=0.008). For patients with mismatch the odds of dying (*in-vitro* vs *in-vivo*) was increased by 9.2% vs 38.1%, with moderate PPM 7.6% vs 30.9%, and with severe PPM 85.7% vs 69.7%. The odds of dying increased with age (by 7-8% for every year) and PPM severity. Age was a significant predictor of survival but PPM was not. For every 0.1unit increase in EOAi the risk of dying decreased by 8.0% (*in-vitro*) and 8.7% (*in-vivo*).
Conclusion: Age is a significant predictor of survival times, with the odds of dying increasing by about 7% for every additional year. Long-term survival hazard was increased by PPM but the effect was not significant. When EOAi is analysed as a continuous variable it significantly effects survival.

1. INTRODUCTION

Rahimtoola introduced the concept of prosthesis-patient mismatch (PPM), denoting an effective orifice area of the prosthetic valve too small for the patient's body size, in 1978 [1]. Valve manufacturers provide the surgeon with effective orifice area (EOA) tables based on *in-vitro* testing of prostheses [2,3]. However *in-vivo* testing by independent researchers has underlined the prevalent overestimation of EOA in these tables [4,5] and recommendations for EOA estimation have since been revised accordingly [6].

In turn manufacturers have developed valves designed for supra-annular implantation where the valve size label, based on the tissue annular diameter (TAD) is equal to the internal orifice diameter (IOD), in contrast to valves designed for intra-annular implantation where the IOD is smaller than the TAD [7]. Other design features such as a reduced sewing ring and external mounting of pericardial tissue are geared towards providing a larger EOA [8].

The mitigation of PPM is based on the premise that sub-optimal haemodynamics result in adverse clinical outcomes. Studies have demonstrated persistent left ventricular hypertrophy and dysfunction with consequent poorer functional class and quality of life [9], increased incidence of late cardiac events [10], and reduced durability of bioprosthetic valves [11]. The combined deleterious effects of these factors on long-term survival is, however, still controversial [12,13].

Advancing age impacts negatively on immediate, medium- and long-term survival after aortic valve replacement (AVR), but the direct effect of PPM remains unresolved [14-16]. In this paper we studied the effect of age and PPM on long-term survival applying both the manufacturers' in vitro EOA's as well as *in-vivo* values derived from independent researchers.

2. METHODOLOGY

572 consecutive patients in a single-surgeon practice (61% male, mean age 65.1±11.4) requiring surgical AVR /+coronary artery bypass grafting (CABG) between January 1995 and Dec 2015 were enrolled in the study. Patients requiring other additional surgery or trans-catheter aortic valve implantation were excluded. Data was collected prospectively and date of death was derived from the National Statistics Office. The population was divided into four age groups of comparable size: age15-59 (n=148), 60-67 (n=145), 68-74 (n=149), >74 (n=130). The maximum follow-up period was 20 years, with a mean of 8.2 and a median of 7.6 years.

All patients underwent surgery under normothermic cardiopulmonary bypass and myocardial protection was with antegrade cold cardioplegia. CABG was performed in the standard fashion and the graft of first choice was the internal thoracic artery.

The cut-off point for xenografts implantation was set at age 70 and this was adhered to in 93% of patients below 70 and 95% of patients above 70. The choice of valves evolved with time in line with newer models with the promise of superior haemodynamics (Table 1). No root-enlargement procedures were undertaken.

Moderate PPM was defined as an indexed effective orifice area (EOAi, effective orifice area per m^2 body surface area) of 0.65-0.85 cm^2/m^2 and severe as <0.65 cm^2/m^2, and was calculated according to tables (*in-vitro*) supplied by the valve manufacturers and also from *in-vivo* values published by independent researchers (Table 2).

Table 1. Valves implanted during the study period

	1995-2002*	2002-2015**
Mechanical 19, 21	CarboMedics reduced	CarboMedics TopHat
23	CarboMedics standard	CarboMedics TopHat
25	CarboMedics standard	CarboMedics standard
Xenograft 19, 21, 23	Carpentier edwards perimount	Sorin mitroflow
25	Carpentier edwards perimount	Carpentier edwards perimount

11 St Jude Medical (SJM) Toronto SPV valves inserted during this period
**7 Perceval valves inserted during this period*

Table 2. EOA values

Model	Size19	Size 21	Size 23	size 25	Source	Reference
CarboMedics	1.0	1.54	1.63	1.98	*In-vivo*	17,18
	1.0	1.44	1.95	1.98	*In-vitro*	3
Carpentier edwards	1.1	1.5	1.8	1.8	*In-vivo*	12,19,20
	1.3	1.5	1.8	2.0	*In-vitro*	21
Sorin MitroFlow	1.2	1.5	1.8	2.3	*In-vivo*	12,22,23,24
	1.7	2.1	2.8	2.8	*In-vitro*	3,25
SJM Toronto SPV			1.5	1.7	*In-vivo*	26
		1.3	1.5	1.7	*In-vitro*	2

Size refers to valve size implanted.
Source (in-vivo) is derived from independent researchers' data in postoperative patients.
Source (in-vitro) is derived from manufacturers' data from laboratory tests.
Reference column refers to publications from which the EOA values are derived

2.1 Statistical Analysis

The impact of age and vitro/vivo PPM classification on long-term survival was studied using the Cox proportional hazard model. This model combines a baseline hazard function of time with an exponentiated term including a linear combination of the predictors (age and vitro/vivo PPM classification). Parameters are estimated by maximizing the partial likelihood function with respect to the parameters and the hazard ratios are the exponential values of these parameter estimates.

3. RESULTS

185 patients died and the remaining 387 were right censored. Fig. 1 shows the Kaplan-Meier survival curves for the four age groups.

48 patients received a size 19, 190 patients a size 21, 198 patients a size 23 and 136 patients a size 25 valve. Mean *in-vitro* derived EOAi was significantly higher than *in-vivo* EOAi (1.04±0.22 vs 0.93±0.16, *p*=0.000) and incidence of PPM was lower using *in-vitro* criteria (moderate 18.0% vs 24.1%, *p*=0.01, severe 1.9% vs 4.7%, *p*=0.008).

A larger proportion of patients with severe PPM (by *in-vivo* and *in-vitro* values) had a 19 mm valve (47.9% and 29.9%), a larger proportion with moderate PPM had a 21 mm valve (29.0% and 39.5%), and a larger proportion of patients without PPM had a 23 mm (70.7% and 95.0%) or 25 mm valve (96.3% and 95.6%). This association was significant with both the *in-vitro* and *in-vivo* classifications.

The incidence of PPM was higher in younger patients (age group 60-67, *in-vitro* and *in-vivo*: 29.0% and 37.2%, 68-74 15.4% and 20.8%, >74 10.8% and 22.3%). The independent samples t-test was used to compare mean age between patients with PPM and those without. The mean age of patients with PPM (n=165) was 2.3 years lower than those without (n=407) (63.22±10.61 vs 65.52±11.6, *p*=0.029).

Table 3 shows that age is a significant predictor of survival times and that for every incremental year the odds of dying increase by around 7%. Moreover, for patients with mismatch the odds of dying (*in-vitro* and *in-vivo*) were respectively 9.2% and 38.1% higher compared to patients with no PPM, but the increase was not statistically significant.

3

For patients with moderate and severe PPM, the odds of dying were respectively 7.6% and 85.7% higher compared to patients with no PPM, using *in-vitro* values, and 30.9% and 69.7% higher using *in-vivo* values. These increases were not statistically significant (Table 4).

Age was significant predictor of survival times, however PPM was not significant. This is attributed mainly to the low incidence of mismatch, particularly for severe PPM.
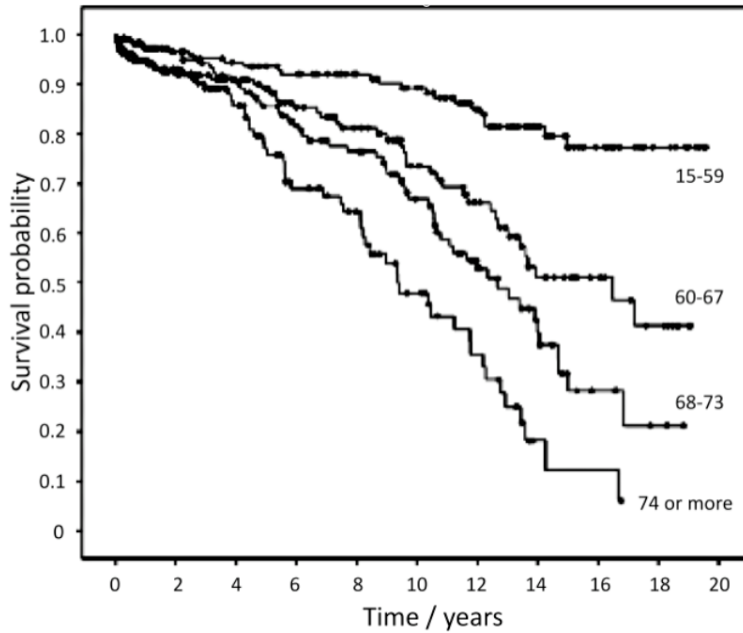

Fig. 1. Kaplan-Meier survival curves for the four age groups

Table 3. Cox regression relating survival time to age and PPM (*in-vitro* vs *in-vivo*)

Predictor	Parameter estimate	SE	*p* value	Hazard Ratio	95% lower	CI higher
Age	0.069	0.009	0.000	1.071	1.053	1.090
In-vitro PPM	0.088	0.185	0.634	1.092	0.760	1.568
In-vivo PPM	0.323	0.192	0.094	1.381	0.947	2.013
No PPM	0			1		

SE: standard error, CI: confidence interval

Table 4. Cox regression relating survival time to age and severity of *in-vitro* and *in-vivo* PPM

Predictor	Parameter estimate	SE	*p* value	Hazard ratio	95% lower	CI higher
In-vitro						
Age	0.068	0.009	0.000	1.070	1.052	1.088
Moderate PPM	0.073	0.186	0.695	1.076	0.747	1.549
Severe PPM	0.619	0.406	0.127	1.857	0.838	4.155
In-vivo						
Age	0.069	0.009	0.000	1.071	1.053	1.090
Moderate PPM	0.270	0.206	0.190	1.309	0.875	1.960
Severe PPM	0.529	0.455	0.246	1.697	0.695	4.143
No PPM	0			1		

Table 5 shows that for patients with mismatch the odds of dying were respectively (*in-vitro* and *in-vivo*) 100.7% and 91.3% for 19 mm valves; 23.3% and 68.8% for 21 mm valves; 12.6% and 13.5% for 23 mm valves and 8.0% and 7.4% for 25 mm valves. Despite certain high hazard ratios for PPM, statistical significance was not reached, mainly because the incidence of mismatch was rather small, particularly for the 23 mm and 25 mm valves.

When we consider EOAi as a continuous parameter rather than classifying it into three categories, namely: no PPM, moderate PPM and severe PPM, we find that a higher EOAi was associated with a significantly decreased hazard ratio of dying, both when using the *in-vitro* data and well as with the *in-vivo* data (Table 6).

For every 0.1-unit increase in EOAi the hazard of dying, rather than surviving, decreases by 8.0% (*in-vitro* criteria) and by 8.7% (*in-vivo* criteria) given that other effects are kept fixed. Age remains a significant predictor of long-term survival in that for every year increase in the patient's age the hazard ratio of dying rather than surviving increases by 2% to 3%.

The change in use of valve models from the beginning of 2002 resulted in a significant decrease in PPM by *in-vitro* criteria (Table 7). This was due largely in part to the difference in manufacturers' values for EOA from the Carpentier Edwards Perimount to the Sorin Mitroflow (size 21:1.5 cm^2 to 2.1 cm^2, size 23:1.8 cm^2 to 2.8 cm^2).

From our analysis we conclude that age was a significant predictor of survival, whereas PPM failed to reach a statistically significant effect on long-term survival. This situation applied for moderate and severe mismatch, for all valve sizes used, and for calculations based on the manufacturers' EOA's as well as those provided by independent researchers. In contrast, when analyzing EOAi as a continuous variable we find that it exerts a significant incremental effect on long-term survival.

Table 5. Cox regression relating survival time to age and valve size: *in-vitro* and *in-vivo* PPM calculation

Predictor	Parameter estimate	SE	*p* value	Hazard ratio	95% lower	CI higher
In-vitro						
Age	0.072	0.010	0.000	1.075	1.055	1.095
Size 19 PPM	0.697	0.421	0.098	2.007	0.880	4.582
Size 21 PPM	0.209	0.223	0.349	1.233	0.796	1.910
Size 23 PPM	0.119	0.364	0.744	1.126	0.552	2.299
Size 25 PPM	0.077	0.517	0.882	1.080	0.392	2.975
In-vivo						
Age	0.070	0.009	0.000	1.073	1.054	1.093
Size 19 PPM	0.649	0.364	0.074	1.913	0.938	3.902
Size 21 PPM	0.524	0.315	0.096	1.688	0.911	3.130
Size 23 PPM	0.127	0.293	0.665	1.135	0.639	2.016
Size 25 PPM	0.071	0.204	0.728	1.074	0.720	1.601
no PPM	0			1		

Table 6. Cox regression relating survival time to age and EOAi: *in-vitro* and *in-vivo* calculation

	Parameter estimate	SE	Wald	df	*p* value	Hazard Ratio	95% lower	CI higher
Age	0.022	0.005	20.099	1	0.000	1.023	1.013	1.033
EOAi *in-vitro*	-0.083	0.024	11.569	1	0.001	0.920	0.877	0.965
Age	0.027	0.005	29.067	1	0.000	1.028	1.017	1.038
EOAi *in-vivo*	-0.091	0.030	9.171	1	0.002	0.913	0.861	0.968

df: degrees of freedom associated with each parameter estimate.
Wald test: used to test the true value of the parameter, based on the sample estimate

Table 7. Incidence of PPM before and after the change in valve models in 2002

			PPM no	(*in-vitro* yes)	Total
Phase	Pre-2002	Count	160	54	214
		Percentage	74.8	25.2	100
	Post-2002	Count	298	60	358
		Percentage	83.2	16.8	100
Total		Count	458	114	572
		Percentage	80.1	19.9	100

$X^2(1) = 6.027, p = 0.014$

4. DISCUSSION

In a large meta-analysis of the impact of PPM on long-term survival, Head et al concluded that all-cause mortality was significantly increased and cardiac-related mortality non-significantly increased [27]. The authors stressed the importance of PPM prevention especially in younger patients who often receive a mechanical prosthesis, causing a higher negative impact on survival. A number of studies included in this analysis failed to demonstrate a significant effect of PPM. Only one of the 34 studies had a longer mean follow-up of 9.1 years vs 8.2 in our study [28] and a second was comparable, with a median of 7.3 years vs 7.6 in our study [29]. Both studies showed no effect (Frapier 2000 HR 0.49 [95% CI 0.25, 0.96], Tsutsumi 2008 HR 0.88 [95% CI 0.34, 2.29]), suggesting that the duration of follow-up may be an important factor.

Our study demonstrated PPM to be more prevalent in younger patients and we therefore analyzed the interaction of age and PPM on long-term survival. While age was an independent significant predictor of curtailed survival, PPM was not. Particularly with older patients, the duration of follow-up is largely determined by the age at operation. The interaction of age and follow-up duration may play an important role in determining long-term outcomes, a longer follow-up favoring age as the significant predictor. Although PPM is known to result in persistent left ventricular hypertrophy and accelerated xenograft dysfunction, the combined effect of these factors with advancing age renders the effect on long-term survival more complex. Our study suggests that age, and indirectly, follow-up duration, are more important than PPM in determining long-term survival.

When we analyze EOA as a continuous variable, rather than categorizing it into no PPM, moderate PPM and severe PPM, we find that it significantly affects long-term survival. A contributing factor to this finding is the low incidence of PPM, particularly of the severe category, limiting its statistical significance. Surgeons should be cognizant of this phenomenon when implanting an aortic prosthesis.

Although the manufacturers' declared EOA's resulted in a lower incidence of mismatch when compared to calculations using independent researchers' values, both incidences and degrees of mismatch failed to significantly affect long-term survival. In spite of criticisms in the literature leveled at the manufacturers' tables, our study showed them to be clinically valid [5]. We did not include our own EOAi's measured after valve implantation, only calculating this value from published data, as this represents the situation encountered during valve replacement. We recommend that both the manufacturers' as well as independent researchers' data is available in the operating theatre to help the surgeon in deciding on valve model and size.

In line with current recommendations important consideration should be given to the prevention of PPM whenever possible, by implanting valves of an adequate size and with superior haemodynamic performance. When this is not possible root enlargement may be contemplated, although this procedure increases operative complexity and has not been shown to benefit long-term survival [30]. We effected a change to newer generation prostheses in 2002 with a resultant decrease in the incidence of PPM. However other studies have shown that this strategy does not affect mortality [27].

5. CONCLUSION

Age is a significant predictor of long-term survival, with the odds of dying increasing by about 7% for every additional year. EOAi exerts a significant incremental effect on survival with every 0.1 unit increase decreasing the risk of dying by 8%. Long-term survival hazard was increased by PPM but the effect was not significant, irrespective of the severity of the

PPM, the valve size implanted, and the source of the EOA values, whether provided by the valve manufacturers or independent researchers.

CONSENT

The Hospital Scientific Ethical Committee waived the necessity for consent as the study was retrospective and patient data was anonymised.

ETHICAL APPROVAL

The authors obtained the necessary ethical approval from the Hospital Scientific Ethical Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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