

PATIENT PROSTHESIS MISMATCH IN STENTED BIOLOGIC AORTIC VALVE PROSTHESIS: 10 YEARS' RESULTS.

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Abstract

Objectives: The goal of this study is to establish the relation between aortic bio prosthesis, patient prosthesis mismatch (PPM) and short-term mortality and morbidity as well as and long-term mortality.

Methods: This is a single center retrospective study with 812 patients that underwent isolated stented biologic aortic valve replacement between 2007 and 2016. The projected indexed orifice area was calculated using the *in vivo* previously published values. Outcomes were evaluated with the indexed effective orifice area (iEOA) as a continuous variable and/or nominal variable. Multivariable models were developed including clinically relevant co-variables.

Results: In the study population 65.9% (n=535) had no PPM, 32.6% (n=265) had moderate PPM and 1.5% (n=12) severe PPM. PPM was related with diabetes (OR:1.738, CI95:1.333-2.266; $p<0.001$), heart failure (OR:0.387, CI95:0.155-0.969; $p=0.043$) and older age (OR:1.494, CI95:1.171-1.907; $p=0.001$). iEOA was not an independent predictor of in-hospital mortality (OR 1.169, CI 0.039-35.441) or MACCE (OR 2.753, CI 0.287-26.453).

Long term survival is significantly inferior with lower iEOA (HR 0.116, CI 0.041-0.332) and any degree of PPM decreases survival when compared with no PPM (Moderate: HR 1.542, CI 1.174-2.025; Severe HR 4.627, CI 2.083-10.276).

Conclusions: PPM appears to have no impact on short-term outcomes including mortality and morbidity. At ten years follow-up, moderate or severe PPM significantly reduces the long-term survival.

INTRODUCTION

Patient prosthesis mismatch (PPM) was initially described in 1978 by Rahimtoola as "the effective orifice valve area, after insertion into the patient, is less than a normal human valve".¹ Later it was defined by Pibarot et al. for the aortic valve as an indexed effective orifice area (iEOA) $\leq 0,85\text{cm}^2/\text{m}^2$, being moderate for values between 0.65-0.85 and severe when <0.65 .²

The definition used the iEOA that is measured after surgery, however it is clinically relevant to predict the EOA before surgery. Each prosthetic valve has a projected EOA derived from *in vivo* measurements and the internal geometric orifice area (GOA) that are published by the prosthesis manufactures.² The three values are significant predictors of PPM but the discriminative power for severe mismatch is lower with GOA and higher to EOA.³

A higher severity of PPM is associated with increased long-term and operative mortalities and neurologic complications.⁴ Conflicting results have been published as some studies showing no impact on long term mortality or only in subgroups.⁵ A recent STS database analysis demonstrated a longterm impact on survival [6]. Some

surgical strategies, such as aortic root enlargement and stentless bioprosthesis, can be used to avoid PPM. Transcatheter valve implantation (TAVI) was associated with less PPM than surgical aortic valve replacement in the initial trials.⁵

The goal of this study is to establish the relation between aortic bioprosthesis PPM and short-term mortality and morbidity as well as long-term mortality.

MATERIALS AND METHODS

Patients

Our internal database was retrospectively analyzed to identify all consecutive patients submitted to isolated aortic valve replacement (AVR). The initial population included 1496 patients. Patients were excluded if there was a mechanical prosthesis implanted (n=470), sutureless or stentless prosthesis (n=38), valve size larger or equal to 25 (n=68), reoperations (n=71), emergent procedures (n=6) or active endocarditis (n=31). These exclusion criteria were selected a priori because they could contribute to biased results. Therefore, the study population consisted

of 812 patients that underwent isolated stented biologic aortic valve replacement between 2007 and 2016.

Surgical technique

Surgery was done under standard cardiopulmonary bypass (CPB) and cardioplegic arrest using cold blood cardioplegia. Bioprosthesis were implanted in either a supra annular or annular position, using interrupted polyester sutures with or without pledgets according to the surgeon's choice. Postoperative single antiplatelet therapy was prescribed unless there was other indication for vitamin K antagonists or double antiplatelet therapy.

Outcomes and variable definition

Early post-operative outcomes were in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE). Late post-operative outcome was all-cause mortality.

In-hospital mortality is defined as mortality of any cause before discharge. MACCE is defined as a composite endpoint including at least one of the following in-hospital variables: all-causes mortality, stroke, myocardial infarction, multiple organ failure or cardiac arrest.

Follow-up data was obtained from a national database and represents the all-cause mortality. It was 99.8% complete (2 patients lost to follow-up) with a mean time of $4,5 \pm 2.77$ years (median 4.19 years, interquartile range 2.17-6.6).

PPM was classified according to the published criteria by Pibarot et al as an iEOA $\leq 0.85 \text{cm}^2/\text{m}^2$, values between 0.65-0.85 as moderate and < 0.65 as severe.² The calculations were done using projected indexed EOA, obtained by previous published in vivo measurements for different valve types and sizes (Table 1). The PPM group in this study was defined as $\text{iEOA} \leq 0.85 \text{cm}^2/\text{m}^2$. iEOA was analysed as a continuous variable for all outcomes. Categorized PPM (none, moderate or severe) was studied only for long-term mortality.

Statistical analysis

Categorical variables are presented as number and valid percentage (excluding missing values). Continuous variables are presented as mean \pm standard deviation or median (interquartile range) depending on the

distribution. Kolmogorov-Smirnov test was used to assess the normal distribution. Categorical variables were compared using χ^2 test or Fisher exact test (when at least one cell < 5). Normal distributed continuous variables were compared with Student's T-test and Levene's test for variance equality assessment. Mann-Whitney U-test was used for independent samples not normally distributed.

Logistic regression analysis was performed to evaluate predictors of in-hospital mortality and MACCE. All covariates included on the model were selected a priori based on clinical relevance and it was not a stepwise method.

Survival was analysed with Kaplan-Meier and log rank test. Cox regression was used to evaluate predictors of long-term mortality. All covariates included in the model were selected a priori based on clinical relevance and it was not a stepwise method. Covariates include: age, gender, diabetes, smoking, NYHA, heart failure, history of stroke, other neurologic disability, extra-cardiac arteriopathy, haemodialysis, pulmonary disease, hepatic disease, gastrointestinal disease, sinus rhythm, urgent procedure and aortic regurgitation.

A p value < 0.05 was considered significant. Statistical analysis was done with IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.

RESULTS

PPM incidence and predictors

In the study population 65.9% (n=535) of patients had no PPM, 32.6% (n=265) had moderate PPM and 1.5% (n=12) severe PPM. Due to the small number of cases of severe PPM, and small number of events except for the long-term survival, no further separated evaluations were made, so the PPM group consisted of 277 (34.1%) patients and the control group of 535 (65.9%) patients.

The most relevant pre-operative and operative data are reported in table 2. Both groups were similar, except that female gender, diabetes, older age and higher body surface area (BSA) were more prevalent in the PPM group.

The most frequent prosthesis size implanted was 21 mm (47.4%), then 23 mm (31.2%) and finally 19 mm

Table 1 Projected effective area by brand and prosthesis size

Valve prosthesis	19	21	23	Reference
Mitroflow and Crown (Sorin Group, Milan, Italy)	1.2	1.5	1.8	[22]
Perimount Magna (Edwards Lifesciences, Irvine, CA)	1.58	1.9	2.07	[23]
Epic (St. Jude Medical, Minnesota, USA)	1.44	1.57	1.69	[24]
Trifecta (St. Jude Medical, Minnesota, USA)	1.4	1.6	1.8	[25]
Mosaic (Medtronic, Minneapolis, MN)	1.2	1.3	1.5	[26]
Hancock II (Medtronic, Minneapolis, MN)		1.48	1.83	[27]

Table 2 Population baseline characteristics

Variables	Overall n=812, n (%)	No PPM n=535, n (%)	PPM n=277, n (%)	p-value*
Female gender	477 (58.7)	300 (56.1)	177 (63.9)	0.032
Age, (IQR)	76 (72-80)	76 (71-80)	77 (73-80)	0.02
Active smokers	118 (14,6)	85 (16)	33 (12)	0.12
BSA kg/m ² , mean±SD	1.79±0.19	1.75±0.19	1.85±0.17	<0.001
NYHA class III-IV	173 (21.5)	107 (20.2)	66 (23.9)	0.222
LVEF less than 50%	101 (13.8)	68 (14,1)	33 (13)	0.683
Heart failure	26 (3.3)	20 (3,9)	6 (2.2)	0.22
Non-Sinus rhythm	96 (11.9)	71 (13.4)	25 (9.1)	0.071
Urgent procedure	43 (5.4)	29 (5.5)	14 (5.2)	0.865
Extracardiac arteriopathy	59 (7.7)	35 (6.5)	24 (8.7)	0.269
History of stroke	62 (7.6)	40 (7.5)	22 (8)	0.83
Pulmonary disease	85 (10.5)	54 (10.2)	31 (11.2)	0.647
Gastrointestinal disease	60 (7.4)	44 (8.3)	16 (5.8)	0.119
Hepatic disease	2 (0.2)	1 (0.2)	1 (0.4)	0.647
Hemodialysis	19 (2.4)	15 (2.8)	4 (1.5)	0.224
Aortic regurgitation moderate or severe	87 (10.9)	56 (10.7)	31 (11.3)	0.78
EuroSCORE II, median (IQR)	1.41 (0.98-2.52)	1.4 (0.97-2.52)	1.42 (0.997-2.52)	0.683
CPB time (min), median (IQR)	81 (72-95)	80 (72-95)	84 (72-96)	0.147
Aortic cross-clamping time (min), median (IQR)	60 (51-71)	60 (51-72)	60 (50.5-71)	0.473

BSA – body surface area; CPB – Cardiopulmonary bypass; IQR - interquartile range; LVEF – Left ventricle ejection fraction

*Comparison between No PPM and PPM groups.

(21.4%). PPM is significantly more prevalent in smaller valvular sizes ($p<0.001$), 66.7% ($n=116$) in 19 mm) than in larger sizes (15.4% ($n=39$) in 23 mm).

On our multivariable model PPM was related with diabetes (OR:1.738, CI95:1.333-2.266; $p<0.001$), non-heart failure (OR:0.387, CI95:0.155-0.969; $p=0.043$) and older age (OR:1.494, CI95:1.171-1.907; $p=0.001$).

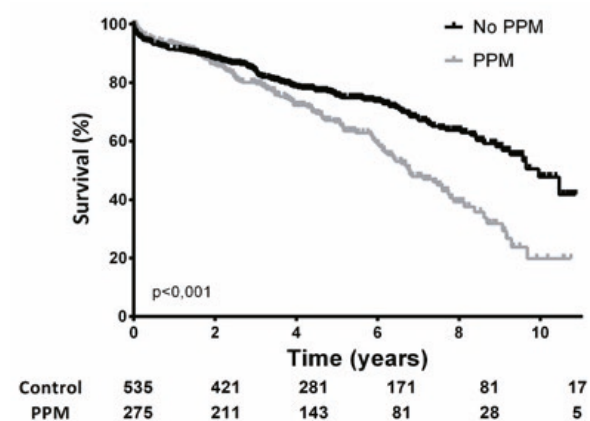
Early post-operative Outcomes

Overall in-hospital mortality was 3.1% ($n=25$), 1.4% in the PPM group and 3.9% in the non PPM group, statistically non-significant ($p=0,055$) on univariable analysis. On multivariable analysis, extra cardiac arteriopathy was an independent predictor of in-hospital mortality (OR 3.49 CI 1.02-11.91) and iEOA was not (Table 3).

Overall MACCE was 7.2% ($n=54$), 5.7% in the PPM group and 8% in the non PPM group with non-significant difference ($p=0.247$) on univariable analysis. On multivariable analysis pulmonary disease (OR 2.533 CI 1.104-5.811) and haemodialysis (OR 4.324 CI 1.008-18.555) were MACCE's independent predictors. iEOA was not a MACCE independent predictor (Table 4).

Late outcome

Survival decreases with the severity of the operative PPM over a ten year follow-up period ($p<0.001$). The curves separated at two years and thereafter the difference increases (Figure 1). When PPM is classified under three categories,

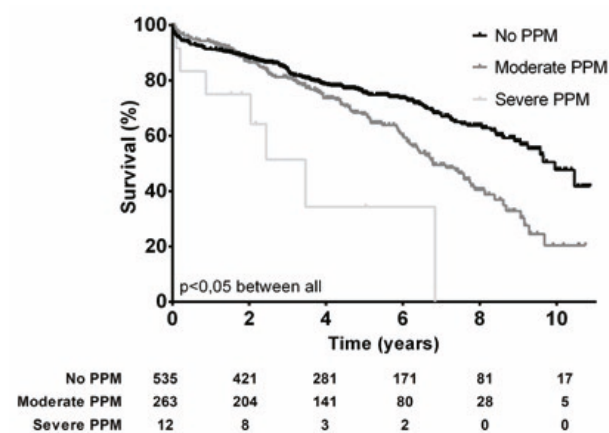

Figure 1

Prevalence of patient prosthesis mismatch by prosthesis number.

Table 3 In-hospital mortality predictors

Variable	Odds ratio (95% CI)	p-value
Age (years/10)	2.387 (0.981-5.808)	0.055
Females	0.792 (0.313-2.006)	0.623
Diabetes	0.322 (0.084-1.235)	0.099
NYHA III/IV	0.851 (0.261-2.78)	0.79
History of Stroke	3.011 (0.753-12.04)	0.119
Extracardiac arteriopathy	3.490 (1.023-11.905)	0.046
Haemodialysis	3.385 (0.345-33.238)	0.296
Pulmonary disease	1.657 (0.434-6.316)	0.46
Gastrointestinal disease	0.469 (0.056-3.890)	0.483
Non-sinus rhythm	0.983 (0.278-3.469)	0.979
Urgent	2.037 (0.399-10.413)	0.393
Aortic regurgitation (mod-sev)	0.471 (0.06-3.71)	0.475
iEOA (cm ² /m ²)	1.169 (0.039-35.441)	0.929

iEOA – Indexed effective orifice area


Figure 2 Survival by the presence of patient prosthesis mismatch.

survival is significantly different between the three degrees, being inferior in severe PPM (Figure 2). On univariable analysis, survival is significantly lower on patients with 19 mm prosthesis compared with 23mm ($p=0.015$).

On multivariable analysis, the risk of death increases with the reduction of the iEOA (HR 0.116, CI 0.041-0.332) as a continuous variable. The independent predictors of death were: older age, diabetes, pulmonary disease, hepatic disease and non-sinus rhythm (Table 5).

Moderate or severe PPM raises the risk of death by 60% (HR 1.608, CI 1.230-2.102). Dividing in the three classes, moderate PPM against no PPM raises the risk of death by 54.2% (HR 1.542, CI 1,174-2.025; $p=0.002$) and severe PPM leads to a 4.627 fold increase of risk (HR 4.627, CI 2.083-10.276; $p<0.001$). The other long-term

mortality independent predictor remains the same in all models.

DISCUSSION

This single center study reached two main findings. Firstly, PPM moderate or severe has no correlation with in-hospital mortality or MACCE after biological AVR. Secondly, survival decreases with lower iEOA for any degree of PPM.

One meta-analysis reported female gender, older age, hypertension, NYHA class III or more and diabetes as the main predictors of moderate or severe PPM.⁴ Our study reached similar results, as diabetes, non-heart failure and older age are predictors of moderate or severe PPM.

Literature has contradictory conclusions regarding the relation between in-hospital mortality and PPM on aortic biological AVR. Several studies only on aortic bio-prosthesis showed no association between PPM and in-hospital mortality⁷⁻¹⁰ or only such a relation in patients less than 70 years.¹¹ Other studies, with biological and mechanical prosthesis, have found an increase in-hospital mortality¹²⁻¹⁴ One meta-analysis has shown a 50% increase in 30 days mortality for any degree of PPM.⁴ Our study found no relation between PPM and in-hospital mortality or the composite endpoint of mortality and morbidity.

Long-term survival is reported in literature with conflicting results. Some studies have found an increased long-term mortality related to PPM^{14,15}, other failed to find impact on long-term mortality.^{8,10,13} Bleiziffer *et al.* analysed iEOA as a continuous variable and found a significant impact on cardiac mortality that was not significant when

Table 4 MACCE predictors

Variable	Odds ratio (95% CI)	p-value
Age (years/10)	1.43 (0.849-2.409)	0.178
Females	0.791 (0.415-1.507)	0.476
Diabetes	0.712 (0.353-1.438)	0.343
Smoker	0.687 (0.257-1.84)	0.455
NYHA III/IV	0.677 (0.295-1.557)	0.359
Heart failure	1.184 (0.233-6.021)	0.839
History of Stroke	1.714 (0.653-4.502)	0.274
Extracardiac arteriopathy	2.095 (0.841-5.217)	0.112
Haemodialysis	4.324 (1.008-18.555)	0.049
Pulmonary disease	2.533 (1.104-5.811)	0.028
Gastrointestinal disease	0.368 (0.083-1.632)	0.189
Non-Sinus rhythm	0.992 (0.424-2.323)	0.986
Urgent	1.061 (0.287-3.929)	0.929
Aortic regurgitation (mod-sev)	0.276 (0.064-1.198)	0.086
iEOA (cm ² /m ²)	2.753 (0.287-26.453)	0.38

iEOA – Indexed effective orifice area

Table 5 Long term mortality predictors

Variable	Hazard ratio (95% CI)	p-value
Age (years/10)	1.99 (1.53-2.588)	<0.001
Females	0.955 (0.718-1.268)	0.748
Diabetes	1.428 (1.082-1.885)	0.012
Smoker	1.218 (0.808-1.837)	0.347
NYHA III/IV	1.048 (0.76-1.446)	0.775
Heart failure	1.441 (0.809-2.566)	0.214
History of Stroke	0.865 (0.513-1.457)	0.585
Extracardiac arteriopathy	1.253 (0.832-1.888)	0.28
Haemodialysis	1.667 (0.655-4.24)	0.284
Pulmonary disease	1.746 (1.208-2.522)	0.003
Hepatic disease	14.742 (3.493-62.216)	<0.001
Gastrointestinal disease	0.936 (0.588-1.492)	0.782
Non-Sinus rhythm	1.567 (1.114-2.204)	0.01
Urgent	1.441 (0.858-2.418)	0.167
Aortic regurgitation (mod-sev)	0.988 (0.673-1.449)	0.949
iEOA (cm ² /m ²)	0.116 (0.041-0.332)	<0.001

iEOA – Indexed effective orifice area

iEOA was dichotomized.¹⁶ A recently published STS database based study reported an 8% higher risk of late death in moderate PPM and 32% in severe PPM.⁶ Three meta-analyses reported an increased risk with any degree of PPM but not when moderate PPM is compared with no PPM.^{4,17,18} One meta-analysis demonstrated a decreased survival in moderate and severe PPM.¹⁹

In our study, we chose to include only isolated AVR with biological prosthesis to eliminate the possible bias related to concomitant procedures, especially coronary surgery. Mechanical prosthesis implantation is reducing year by year, and as percutaneous biological options are increasing, so we decided to study specifically biological valves. Our main result, namely, the increased risk of late mortality with any degree of PPM is different from some of the previous published meta-analysis and is in concordance with the STS database study.⁶

These findings can have direct clinical implications, as the risk of PPM can be predicted using iEOA. The surgeon can evaluate several options to reduce that risk, which may include: new generation prosthesis, careful consideration of aortic root enlargement²⁰ and TAVI.²¹

Limitations

Due to the retrospective nature of the study, there are several confounders that can bias the results. An effort to minimize this was made by using several clinical relevant variables in the multivariable analysis. However, we are aware that some confounders are very difficult to measure and were not recorded, such as frailty and other subjective characteristics that can influence surgeon decisions, short and long-term outcomes.

Due to the small number of events regarding in-hospital mortality and MACCE, we decided not to do group analysis and iEOA was only evaluated as a continuous variable. These results need to be interpreted with caution.

We used the projected iEOA that is derived from previous published in vivo measurements. These values have a greater discriminative power than the geometrical orifice area, but the best value is the iEOA measured by echocardiogram after surgery.³ However, these measurements are useless at the time of surgery when choices need to be made and the surgeon needs a way to predict the result. Therefore, we decided to use projected iEOA because it is the most important value for the surgeons.

Another limitation is the lack of echocardiographic follow up studies with late iEOA and left ventricle mass regression assessment that could provide potential mechanisms for the observed correlation between PPM and decreased long-term survival.

CONCLUSIONS

In conclusion, we found that PPM appears to have no impact on short-term outcomes including mortality

and morbidity. In a ten-year follow-up, however moderate or severe PPM significantly reduces the long-term survival. Therefore, every effort should be made to reduce the incidence of any degree of PPM.

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