# Impact of Patient–Prosthesis Mismatch Following Aortic Valve Replacement on Short-Term Survival: A Retrospective Single Center Analysis of 632 Consecutive Patients with Isolated Stented Biological Aortic Valve Replacement

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## Abstract

**Objectives**  The impact of patient–prosthesis mismatch (PPM) after aortic valve replacement (AVR) on short-term and long-term mortality remains controversial. The objective of this study was to evaluate the incidence and severity of PPM and its impact on short-term survival in a large cohort of patients treated with isolated stented biological AVR in a single institution.

**Methods**   We analyzed retrospectively data of 632 consecutive patients with aortic stenosis undergoing isolated stented biological AVR between January 2007 and February 2012 at our institution. PPM was defined as an indexed effective orifice area $\leq 0.85$ cm$^2$/m$^2$. Statistical analyses were performed to identify influencing variables on valve size implanted.

**Results**   Of the 632 patients investigated, 46% were females and mean age was $71.9 \pm 10.4$ years. PPM was observed in 93.8% (593 of 632 patients). In 71% of the patients, moderate (0.65–0.85 cm$^2$/m$^2$) PPM was present and in 22.8% severe ($< 0.65$ cm$^2$/m$^2$) PPM was present. The 30-day mortality was 1.4% (9 of 632 patients) with all being females. PPM was not associated with increased 30-day mortality. Multiple regression analyses demonstrated the usefulness of sex, height, body mass index, and body surface area as simultaneous predictors of the valve size implanted ($R^2 = 0.39$).

**Conclusion**   PPM had no discernable impact on short-term survival, although it was present in 93.8% of our patients following isolated stented biological AVR.

**Keywords**
► aortic valve and root
► heart valve surgery
► outcomes (mortality morbidity)

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## Introduction

The concept of patient–prosthesis mismatch (PPM) was first described by Rahimtoola in 1978.[1] PPM is described as the effective orifice area of an implanted bioprosthesis which is too small for creating a sufficient stroke volume in relation to the patient's body surface area (BSA). To characterize PPM, the indexed effective orifice area (iEOA) is used by dividing the EOA of the chosen valve prosthesis by the patient's BSA.[2] There are different options for the calculation of iEOA, by using either the manufacturer-generated charts (in vitro–derived data) or the echocardiographic parameters (in vivo–obtained measurements) for the EOA of the biological valve prosthesis indexed with BSA. In general, the manufacturer-generated charts reveal a higher EOA compared with the real-life in vivo echocardiographic measurements. We used only the in vivo parameters for the calculation of iEOA.

Many authors demonstrated that PPM leads to reduced left ventricular mass regression, impaired hemodynamics, or increased rate of cardiac events after aortic valve replacement (AVR).[3–5] Current data suggest that PPM may influence outcome in patients undergoing transcatheter aortic valve implantation.[6] To overcome PPM-related issues, valve prostheses were optimized for larger orifice areas to meet the challenge of small annulus, avoiding annulus reconstruction techniques associated with risk especially in the presence of calcified or lacerable annulus tissue. Although numerous studies about PPM have been published, the impact of PPM after AVR on short-term and long-term mortality still remains controversial.[7–11] Even the prevalence of PPM is described with a wide range between 19% and more than 70%.[3,12]

The objective of this study was to evaluate the incidence and severity of PPM and its impact on short-term survival in a large cohort of patients treated with isolated stented biological AVR. Statistical analyses were conducted to identify influencing variables for valve size implanted.

## Methods

Data of 632 consecutive patients with aortic stenosis undergoing isolated stented biological AVR were retrospectively analyzed between January 2007 and February 2012 at our Department of Cardiovascular Surgery. For aortic valve prosthesis, PPM was stratified to be severe if the iEOA is $< 0.65$ cm$^2$/m$^2$ and to be moderate if the value is between 0.65 and 0.85 cm$^2$/m$^2$. PPM is classified as not clinically significant for an iEOA $> 0.85$ cm$^2$/m$^2$. To calculate the iEOA for our patients, we divided the data published for the in vivo EOA by the individual patient's BSA.[13,14]

Prostheses sizes and types were recorded for all patients. Hancock II (Medtronic, Minneapolis, Minnesota, United States) tissue heart valves were mainly used for annulus sizes $\geq 21$ mm, while Carpentier Edwards S.A.V. (Edwards, Irvine, California, United States) and Trifecta (St. Jude Medical, St. Paul, Minnesota, United States) bioprostheses were mainly used for annulus sizes $< 21$ mm.

We evaluated the incidence and severity of PPM and its impact on 30-day mortality. Patient's characteristics (age, sex,

height, weight, body mass index, and BSA) were analyzed to identify influencing variables for valve size implanted.

### Surgical Technique

All patients were operated through a full median sternotomy with cardiopulmonary bypass in cardioplegic arrest. Cold blood cardioplegia (Buckberg Solution, Köhler Chemie, Germany) was applied in an antegrade and retrograde fashion after cross clamping the ascending aorta. Venting of the left ventricle was implemented through the right upper pulmonary vein. In all cases, continuous $CO_2$ insufflation was performed. Through a transverse aortotomy, the calcified aortic valve was excised. Meticulous care in decalcifying the aortic annulus was performed to prevent paravalvular leaks. After sizing of the aortic annulus, the largest suitable prosthesis was implanted in supra-annular position with interrupted sutures reinforced by pledgets.

### Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation. Categorical variables were summarized as absolute number (percentage). Statistical analysis was performed using the Mann–Whitney test when comparing two groups and the Kruskal–Wallis test when comparing three or more groups. The chi-square test or Fisher exact test was used for comparison of categorical variables as appropriate. A multiple linear regression analysis was performed to identify independent variables for valve size implanted. Starting with the full model including valve size as the dependent variable and sex, age, weight, height, BMI, BSA, time on cardiopulmonary bypass, and hospitalization time as independent variables, a backward–forward model selection procedure according to the Akaike Information Criterion was employed. $P > 0.05$ was defined as not significant.

## Results

Of the 632 patients investigated, 46% were females and mean age was $71.9 \pm 10.4$ years. All patient characteristics are given in ►Table 1. Sizes of the different biological valve prostheses are summarized in ►Fig. 1. Medtronic Hancock II biological aortic valves were mainly used for annulus sizes $\geq 21$ mm (588 patients; 93.0%), while Carpentier Edwards and St. Jude Medical Trifecta biological valves were used for annulus sizes $< 21$ mm (15 patients; 2.4%) and for 29 patients (4.6%) with annulus sizes $\geq 21$ mm.

Overall, PPM was observed in 93.8% (593 of 632 patients). In 71% of the patients, moderate PPM (0.65–0.85 cm$^2$/m$^2$) was present and in 22.8% severe PPM ($< 0.65$ cm$^2$/m$^2$) was present. Only in 39 patients (6.2%), AVR was not associated with PPM.

The 30-day mortality was 1.4% (9 of 632 patients) with all of these early deaths occurring in females. Of these nine patients, one patient exhibited severe PPM, in six patients moderate PPM, and in two patients no PPM was present (►Table 2). While cardiac-related deaths occurred in three patients, six patients died of noncardiac reasons (pneumonia, septic multiorgan failure).

**Table 1** Characteristics of 632 patients

| Sex | |
|---|---|
| Female | 291 (46%) |
| Male | 341 (54%) |
| Age (y) (mean ± SD) | 71.9 ± 10.4 |
| BMI (kg/m²) (mean ± SD) | 27.7 ± 5.5 |
| BSA (m²) (mean ± SD) | 1.9 ± 0.2 |
| Time on cardiopulmonary bypass (min) (mean ± SD) | 114 ± 10.4 |
| Length of hospital stay (d) (mean ± SD) | 13.7 ± 10.9 |
| EuroScore (additive) (mean ± SD; median; range) | 7.1 ± 2.6; 7; 2–18 |

Abbreviations: BMI, body mass index; BSA, body surface area; EuroScore, European System for Cardiac Operative Risk Evaluation; SD, standard deviation.

### Analysis of "Patients' Characteristics and Aortic Valve Size"

We analyzed patients' baseline characteristics (age, sex, height, weight, body mass index, and BSA) to identify variables that influenced the chosen valve size.

Sex, age, weight, height, and BSA were each associated with the valve size (►**Fig. 2**; Kruskal–Wallis $p < 0.001$ for each of these tests). To determine the best combination of predictors, a multiple linear regression analysis with model selection as described above was performed. The final model included sex, height, body mass index, and BSA as simultaneously useful predictors of the valve size implanted ($R^2 = 0.39$). In male patients, valve sizes of 24.7 ± 1.8 mm (range, 19–31 mm) and in female patients 22.3 ± 1.5 mm (range, 19–27 mm) were implanted. In summary, in female patients, smaller prostheses were used than in male patients. Moreover, in taller and more obese patients, larger bioprostheses were implanted.

### Analysis of "Patients' Characteristics and PPM"

Additionally, sex ($p = 0.014$), weight ($p < 0.001$), height ($p < 0.001$), BMI ($p < 0.001$), and BSA ($p < 0.001$) were each significantly associated with PPM. Female patients
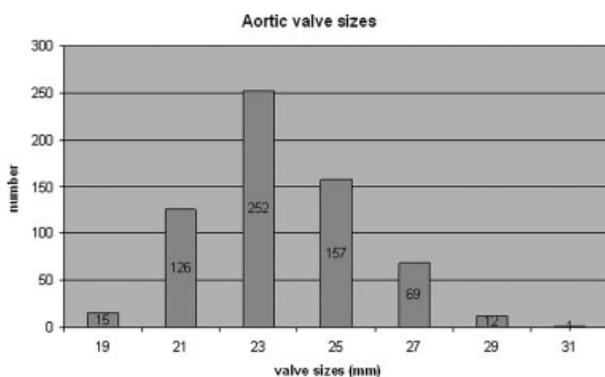


**Fig. 1** Distribution of implanted aortic bioprostheses.

with increased weight, increased height, higher BMI, or higher BSA had a more severe PPM.

A comparison of two groups (valve size group ≤ 21 mm [141 patients] and valve size group > 21 mm [491 patients]) in relation to PPM demonstrated a significantly higher incidence of severe PPM in patients with implanted valve sizes ≤ 21 mm ($p < 0.001$).

PPM of any degree was not found to be associated with an increased 30-day mortality.

## Discussion

The impact of PPM after AVR on short-term and long-term survival remains controversial.[3–5,7–11] PPM is defined as an iEOA ≤ 0.85 cm²/m² and the severity of PPM is associated with less symptomatic improvement caused by less left ventricular mass regression, impaired hemodynamics at rest and during exercise, and more cardiac events after AVR.[3–5] In contrast, no impact of PPM on short-term or long-term mortality has been published by Howell et al[15] and Blackstone et al.[16] It seems to be important to characterize the severity of PPM in a standardized manner. It was proposed by Dumesnil et al to determine the EOA in vivo rather by echocardiography than by manufacturers' charts.[2] The manufacturer-generated charts (in vitro) often reveal a higher EOA and should be interpreted with caution because there is no standardization for creating these charts. The in vitro measurements often overestimate the real EOA and can thereby result in PPM of various extend, consequently.

In different studies, the prevalence of PPM is described with a wide range between 19 and 70%.[3,12] In our study, PPM was present in 93.8% of all patients using the real-life in vivo echocardiographic parameters for EOA. Nevertheless, excellent results were obtained in regard to a very low 30-day mortality of 1.4%. Interestingly, all of these early deaths occurred in women with various degrees of PPM (►**Table 2**). Even more, only one patient of these nine early deaths (11.1%) had a severe PPM, while eight of nine patients (88.9%) presented with moderate or none PPM. Therefore, we conclude that PPM has in general no impact on short-term survival for patients treated with isolated stented biological AVR. Nevertheless, Hong et al described a detrimental effect of PPM on long-term outcome in a large single center experience in more than 300 patients undergoing AVR.[17] Therefore, our short-term results need to be reevaluated after a longer postoperative period, so we started a follow-up analysis of these 632 patients following AVR concerning long-term survival and quality of life.

Admittedly, the overall incidence of PPM of 93.8% was very high, which was also surprising for the authors themselves. Nevertheless, the majority of PPM patients (71%) showed just moderate PPM, while 22.8% of patients were presented with severe PPM. The latter may correlate more with the common incidences of PPM in literature. As the design of our study was strictly retrospective, an all-comers collective (632 *consecutive* patients) was presented without any inclusion or exclusion criteria. Additionally, we used only the in vivo–obtained measurements for EOA which will result in a higher incidence for PPM.

**Table 2** The 30-day mortality

| | Aortic valve sizes (mm) | EuroScore (additive) | Age (y) | BMI (kg/m²) |
|---|---|---|---|---|
| Nine patients (1.4%)—all being females (range) | 19–23 | 8–13 | 76–91 | 18–45 |
| No PPM: two patients (22.2%) | | | | |
|     Patient 1 | 21 | 9 | 87 | 20 |
|     Patient 2 | 21 | 13 | 84 | 45 |
| Moderate PPM: six patients (66.7%) | | | | |
|     Patient 1 | 19 | 13 | 76 | 28 |
|     Patient 2 | 21 | 9 | 80 | 24 |
|     Patient 3 | 21 | 12 | 81 | 18 |
|     Patient 4 | 21 | 9 | 81 | 21 |
|     Patient 5 | 23 | 10 | 91 | 27 |
|     Patient 6 | 23 | 10 | 80 | 23 |
| Severe PPM: one patient (11.1%) | | | | |
|     Patient 1 | 23 | 8 | 78 | 27 |

Abbreviations: BMI, body mass index; EuroScore, European System for Cardiac Operative Risk Evaluation; PPM, patient–prosthesis mismatch.
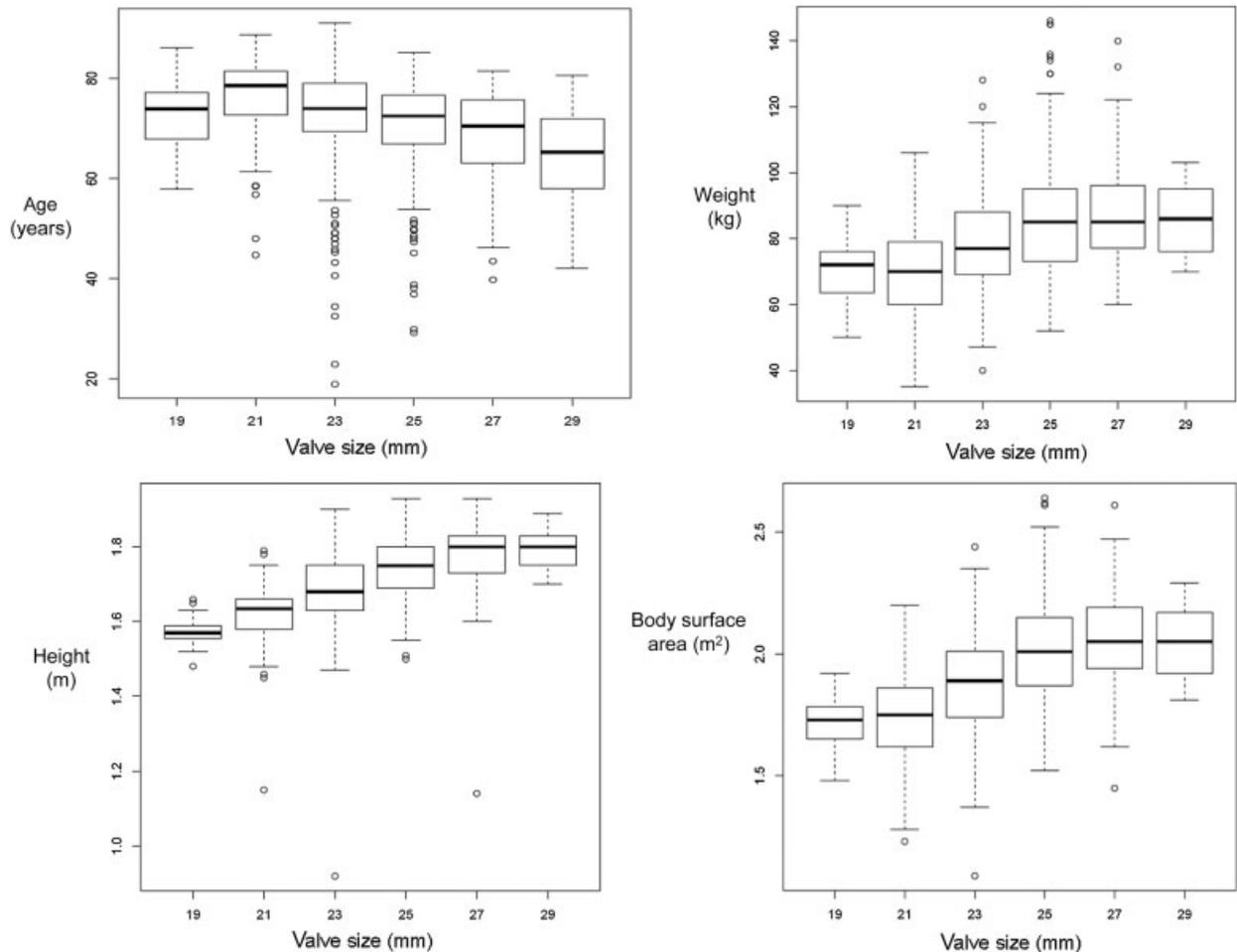


**Fig. 2** Boxplots showing distribution of age, weight, height, and body surface area, respectively, according to aortic valve size implanted (each $p < 0.001$, Kruskal–Wallis test).

Sex, height, body mass index, and BSA were each significantly correlated with implanted valve size. Female patients received smaller biological aortic valves than male patients, and patients with more height, higher BMI, or increased BSA received larger aortic bioprostheses. A significantly higher number of patients with 19 or 21 mm prostheses implanted suffered from severe PPM compared with patients with implanted valve sizes > 21 mm. The results of our multiple linear regression analysis underline the surgeon's preoperative assessment concerning the presumably valve size.

The vast majority of our patients received a Medtronic Hancock II bioprosthesis (93%), while 7% of patients were treated with a Carpentier Edwards valve or a St. Jude Medical Trifecta valve. As the Medtronic Hancock II bioprosthesis is not manufactured for 19 mm size, we were forced to use alternative products. In 15 patients (2.4%), annulus sizes < 21 mm were present and we had to implant other valve types than Medtronic Hancock II. Some surgeons used in exceptional cases, for instance short distance form, a coronary ostium to the aortic annulus, one of the two alternative valves even in aortic annulus sizes ≥ 21 mm (in 4.6% of all AVR). But our standard aortic valve is still the Medtronic Hancock II bioprosthesis. The reason for using alternative bioprosthesis than the Medtronic Hancock II was not based on the expected PPM.

There are different surgical procedures in adults for aortic root enlargements to implant at least one-size larger aortic valve prosthesis, like the Manouguian or Nicks technique.[18,19] All these operative techniques can be performed with good results but are associated with longer bypass and aortic cross-clamping times. The implantation of a larger aortic valve prosthesis results in an increase in EOA of 0.1 to 0.2 cm$^2$. The extension of the operative procedure to implant biological valve with larger sizes is always patient adjusted but seems to be not necessary concerning 30-day mortality.

We absolutely support the point of view that the postoperative gradient is lowered in patients following AVR for aortic valve stenosis even in terms of moderate-to-severe PPM. But otherwise there are numerous of studies analyzing PPM as a strong and an independent predictor of short-term mortality.[7]

Some surgeons calculate PPM during valve implantation to avoid at least severe PPM. However, iEOAs are often overestimated by using the manufactured-generated charts (in vitro data). Our policy to implant the largest suitable valve prosthesis is independent from the resulting PPM. At our department, no PPM charts are used perioperatively in our operating rooms and no techniques for aortic root enlargements are used routinely to lower the incidence of PPM. Nevertheless, we see a very low 30-day mortality rate of 1.4%, which confirms our operative strategy until now.

To our mind, there is still a need for further studies concerning impact of PPM on short-term and especially long-term survival. Long-term survival and quality of life of our collective will be presented from our research group after finishing the ongoing follow-up.

With our study, we were able to demonstrate that a high incidence of PPM has not to be associated with an elevated 30-day mortality nowadays using modern surgical techniques and well-established biological aortic valves.

## Limitation of the Study

The main limitation of the presented study is its retrospective design. We analyzed only patients following isolated stented biological AVR between January 2007 and February 2012. Unfortunately, we can present only the additive EuroScore and not the logistic EuroScore. Another limitation is the focus on 30-day mortality after AVR. Long-term survival and quality of life of these patients will be presented from our group soon, after finishing the ongoing study.

## Conclusion

Although present in 93.8% of our patients following isolated stented biological AVR, PPM showed no impact on short-term survival.

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