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Impact of Prosthesis-Patient Mismatch on Long-Term Survival After Aortic Valve Replacement

Influence of Age, Obesity, and Left Ventricular Dysfunction

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Objectives This study was designed to evaluate the effect of valve prosthesis-patient mismatch (PPM) on late survival after aortic valve replacement (AVR) and to determine if this effect is modulated by patient age, body mass index (BMI), and pre-operative left ventricular (LV) function.

Background We recently reported that PPM is an independent predictor of operative mortality after AVR, particularly when associated with LV dysfunction.

Methods The indexed valve effective orifice area (EOA) was estimated in 2,576 patients having survived AVR and was used to define PPM as not clinically significant if it was >0.85 cm^2/m^2, as moderate if >0.65 and ≤ 0.85 cm^2/m^2, and severe if ≤ 0.65 cm^2/m^2.

Results After adjustment for other risk factors, severe PPM was associated with increased late overall mortality (hazard ratio [HR]: 1.38; $p = 0.03$) and cardiovascular mortality (HR: 1.63; $p = 0.0006$) in the whole cohort. Severe PPM was also associated with increased overall mortality in patients <70 years old (HR: 1.77; $p = 0.002$) and in patients with a BMI <30 kg/m^2 (HR: 2.1; $p = 0.006$), but had no impact in older patients or in obese patients. Moderate PPM was a predictor of mortality in patients with LV ejection fraction $<50\%$ (HR: 1.21; $p = 0.01$), but not in patients with preserved LV function.

Conclusions Moderate PPM is associated with increased late mortality in patients with LV dysfunction, but with normal prognosis in those with preserved LV function. Notwithstanding the previously demonstrated deleterious effect of severe PPM on early mortality, this factor appears to increase late mortality only in patients <70 years old and/or with a BMI <30 kg/m^2 or an LV ejection fraction $<50\%$. (J Am Coll Cardiol 2009;53:39–47) © 2009 by the American College of Cardiology Foundation

Valve prosthesis-patient mismatch (PPM) is present when the effective orifice area (EOA) of the inserted prosthetic valve is too small in relation to body size (1,2). Its main hemodynamic consequence is to generate higher than expected gradients through normally functioning prosthetic valves. There have been some discrepancies in the published reports about the impact of PPM on post-operative outcomes. Several studies reported that PPM is an independent predictor of cardiac events and mortality after aortic valve replacement (AVR) (3–7); others failed to demonstrate a significant effect of PPM on post-operative outcomes (8–12). These discrepancies may be explained, at least in part, by the fact that the investigators used different parameters and criteria to identify PPM and quantify its severity (13,14). Also, these discrepancies may be related to differences in the baseline characteristics of the patient populations included in these studies. Several factors including age, body mass index (BMI), and pre-operative status of left ventricular (LV) function may potentially influence the effect of PPM on post-operative outcomes.

We previously reported that PPM is associated with increased operative mortality after AVR, particularly when associated with LV dysfunction (5). The objective of this study was to evaluate the effect of PPM on late survival after AVR in a large series of patients and to determine if this

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Abbreviations and Acronyms

AVR = aortic valve replacement
BMI = body mass index
BSA = body surface area
CABG = coronary artery bypass graft
CI = confidence interval
EOA = effective orifice area
HR = hazard ratio
LV = left ventricular
LVEF = left ventricular ejection fraction
PPM = valve prosthesis-patient mismatch

effect is modulated by patient age, BMI, and pre-operative LV function.

Methods

Eligibility criteria. All patients who underwent a first AVR with or without coronary artery bypass grafting surgery (CABG) at Laval Hospital between January 1992 and December 2005 were eligible for this study. Of the 2,820 eligible patients, those (n = 167; 6%) who died during or within 30 days of surgery were excluded. Moreover, PPM could not be assessed in 77 (3%) patients because data on normal reference EOA were not available. The study population was thus composed of 2,576 patients (mean age 68.5 ± 10 years; 61% male). Fifty-six percent of these patients received a stented bioprosthesis, 22% received a stentless bioprosthesis, 22% received a mechanical prosthesis, and 44% underwent concomitant CABG. Table 1 shows the distribution of the prosthesis models implanted in this series. Contemporary models were used in 95% of these patients.

Data collection. Clinical, operative, and outcomes data were prospectively collected and validated. Database was queried retrospectively. Survival data were obtained from the death certificates of the Registry Office of the Quebec Government. Follow-up information was available in 98% of the patients. LV ejection fraction was available in 2,361 (92%) of the patients.

PPM definition. The projected indexed EOA was derived from the published normal in vivo EOA values for each model and size of prosthesis implanted in this cohort (Table 1) (15–21), as previously described and validated (13,22). PPM was defined as not clinically significant if the projected indexed EOA was >0.85 cm^2/m^2, as moderate if it was >0.65 and ≤0.85 cm^2/m^2, and as severe if it was ≤0.65 cm^2/m^2.

Statistical methods. Results are expressed as mean ± SD or percentages unless otherwise specified. The cohort was divided into 3 groups according to PPM severity: nonsignificant, moderate, and severe. Baseline data were compared for statistical significance using a 1-way analysis of variance, chi-square, and Fisher exact test when the number of patients in 1 category was ≤5.

Cumulative probability of survival was estimated with the Kaplan-Meier method and compared between groups by using a log-rank test. Cox proportional-hazards regression models were used to determine whether moderate and severe PPM were associated with survival after adjusting for potential confounding variables. Clinically relevant variables and those with a value of $p < 0.1$ on univariate analysis were incorporated into the multivariate models. Additional analysis was performed to control for selection bias potentially related to PPM. A propensity score representing the likelihood of having severe PPM was calculated for each patient by using a logistic regression analysis that identified variables independently associated with severe PPM. Variables included in the logistic regression analysis were: sex, BMI, diabetes, predominant aortic stenosis, prosthesis size <21 mm, prosthesis type (bioprosthesis vs. mechanical valve), and cardiopulmonary bypass time. The propensity score was then incorporated into subsequent proportional-hazards models. All statistical analyses were performed with a

Table 1 Normal Reference Values of Effective Orifice Areas for Prostheses Implanted in This Series

Prostheses	Patients, n (%)	Prosthetic Valve Size, mm						Ref. #
		19	21	23	25	27	29	
Aortic stented bioprostheses								
Medtronic Intact	133 (5)	0.9	1.0	1.3	1.4	1.7	2.0	—
Medtronic Mosaic	712 (28)	1.1	1.2	1.4	1.7	1.8	2.0	(15)
Medtronic Hancock II	49 (2)	1.1	1.2	1.3	1.5	1.6	1.6	(15)
Carpentier-Edwards Perimount	183 (7)	1.1	1.3	1.5	1.8	2.1	2.2	(15)
Carpentier-Edwards Magna	293 (11)	1.3	1.7	2.1	2.3	—	—	(17,18)
Mitroflow	108 (4)	1.1	1.3	1.5	1.8	—	—	(19)
Aortic stentless bioprostheses								
Medtronic Freestyle	520 (20)	1.2	1.4	1.5	2.0	2.3	—	(15)
St. Jude Medical Toronto SPV	59 (2)	—	1.3	1.5	1.7	2.1	2.7	(15)
Cryolife O'Brien	6 (0.2)	—	1.2	1.6	1.9	2.0	2.2	(20)
Aortic mechanical prostheses								(15)
St. Jude Medical Standard	321 (12)	1.0	1.4	1.5	2.1	2.7	3.2	(15)
St. Jude Medical Regent	129 (5)	1.6	2.0	2.2	2.5	3.6	4.4	(16)
MCRI On-X	85 (3)	1.5	1.7	2.0	2.4	3.2	3.2	(16)
Medtronic Advantage	50 (2)	—	1.7	2.2	2.8	3.3	3.9	(21)
Carbomedics Standard	5 (0.2)	1.0	1.5	1.7	2.0	2.5	2.6	(15)

commercially available software package JMP IN 5.1 (SAS Institute Inc., Cary, North Carolina).

Results

Moderate PPM was present in 31% of patients and severe PPM in 2%. Pre-operative and operative data are shown in Table 2. Compared with patients with nonsignificant PPM, those with moderate or severe PPM had a larger BMI and a higher prevalence of female sex, hypertension, diabetes mellitus, and coronary artery disease, as well as a history of renal failure, predominant aortic stenosis, and small prosthesis size (≤21 mm). Patients with moderate PPM, but not those with severe PPM, were significantly older compared with patients with nonsignificant PPM. Mechanical prosthesis implantation was more frequent in the severe PPM group than in the moderate or nonsignificant PPM groups. In a subset of 496 patients in whom a Doppler-echocardiographic examination was performed 1 month after operation in our institution, the measured indexed EOAs were very similar to the projected indexed EOAs in the same groups, and the peak and mean transprosthetic gradients were significantly higher in patients with PPM, and especially those with severe PPM, compared with those with nonsignificant PPM (Table 2).

Impact of PPM on mortality. Mean follow-up was 4.8 ± 3.4 years (median, 4.3 years; maximum, 14 years). There were 559 deaths during follow-up. Late survivals were 79 ± 1% at 5 years and 59 ± 2% at 10 years. For patients with severe PPM, 5-year (74 ± 8%) and 10-year survival (40 ± 10%) were significantly lower than for patients with nonsignificant PPM (5-year survival: 84 ± 1%; 10-year survival: 61 ± 2%; p = 0.01) (Fig. 1A). There was also a trend (p = 0.06) toward lower survival in the severe PPM group when compared with the moderate PPM group (5-year survival: 81 ± 2%; 10-year survival: 57 ± 3%) and in the moderate PPM group when compared with the nonsignificant PPM group (p = 0.055).

Among the 559 deaths, 259 (46%) were classified as being of cardiovascular cause. Freedom from cardiovascular-related death was 92 ± 1% at 5 years and 79 ± 2% at 10 years in the whole series, and it was significantly lower in patients with severe PPM (5-year: 78 ± 7%; 10-year: 50 ± 11%) than in those with moderate PPM (5-year: 90 ± 1%; 10-year: 77 ± 3%; p = 0.0004) and in those with nonsig-

Table 2 Baseline Pre-Operative and Operative Data as a Function of the Severity of Prosthesis-Patient Mismatch

Variables	Nonsignifcant PPM (n = 1,739)	Moderate PPM (n = 797)	Severe PPM (n = 40)	p Value
Pre-operative data				
Age, yrs	68 ± 10	71 ± 9*	69 ± 11	<0.0001
Female, %	33	50*	67*†	<0.0001
BSA, m^2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.3*†	<0.0001
BMI, kg/m^2	26 ± 5	29 ± 5*	32 ± 7*†	<0.0001
CAD, %	57	63*	75*	0.0003
NYHA functional class III to IV, %	61	68*	67*	<0.0001
Hypertension, %	54	59*	68*†	<0.0001
Diabetes, %	18	28*	35*†	<0.0001
Renal failure, %	10	13*	18*†	<0.0001
Chronic lung disease, %	19	19	15	NS
TIA/stroke, %	8	6	10	NS
Predominant AS, %	54	63*	72*†	<0.0001
LVEF, %	59 ± 15	60 ± 14	62 ± 13	NS
LVEF <50%, %	19	17	18	NS
Operative data				
Mechanical prosthesis, %	24	14	43*†	<0.0001
Prosthesis size ≤21 mm, %	16	38*	80*†	<0.0001
Concomitant CABG, %	43	46	58	NS
CPB time, min	116 ± 40	117 ± 51	132 ± 56*†	0.05
Projected EOAI, cm^2/m^2	1.1 ± 0.2	0.8 ± 0.05*	0.6 ± 0.04*†	<0.0001
Post-operative (1-month) data				
EOAI, cm^2/m^2‡	1.1 ± 0.2	0.8 ± 0.06*	0.6 ± 0.08*†	<0.0001
ΔP_{Peak}, mm Hg‡	22 ± 8	27 ± 9*	37 ± 16*†	<0.0001
ΔP_{Mean}, mm Hg‡	11 ± 4	15 ± 5*	21 ± 9*†	<0.0001

Data are mean ± SD or percentage of patients. *Significant difference with nonsignificant PPM group; †significant difference with moderate PPM group. ‡These data were available in a subset of 496 patients.

AS = aortic stenosis; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CPB = cardiopulmonary bypass; ΔP_{Peak} and ΔP_{Mean} = peak and mean transprosthetic gradients; EOAI = indexed effective orifice area; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association; PPM = prosthesis-patient mismatch; TIA = transient ischemic accident.

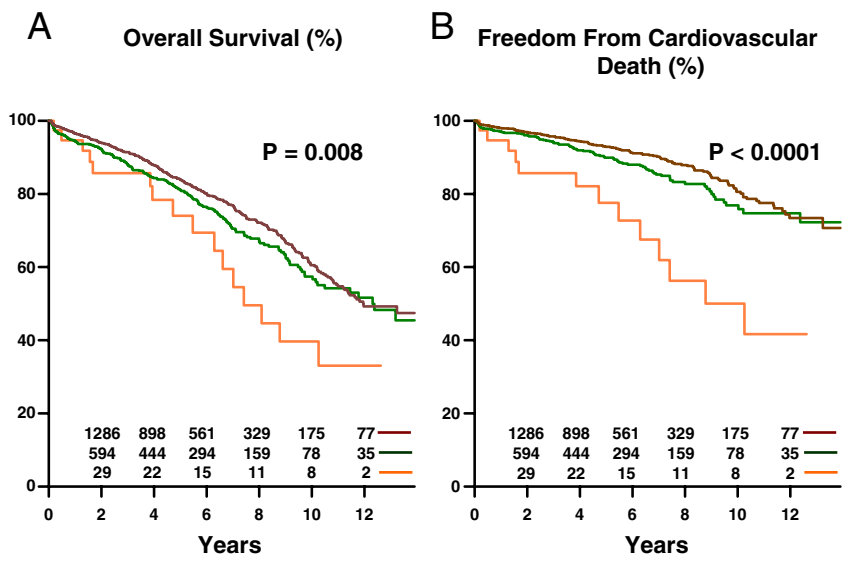

Figure 1 **Late Overall Survival and Freedom From Cardiovascular Death**

Brown line indicates nonsignificant prosthesis-patient mismatch (PPM); **green line** indicates moderate PPM; **orange line** shows severe PPM.

nificant PPM (5-year: 93 ± 1%; 10-year: 81 ± 2%; p < 0.0001) (Fig. 1B).

Predictors of mortality. On univariate analysis (Table 3), the predictors of late post-operative overall mortality were older age, coronary artery disease, hypertension, diabetes, history of renal failure, history of chronic obstructive pulmonary disease, reduced LV ejection fraction (LVEF), the use of a mechanical prosthesis, and severe PPM (age-adjusted hazard ratio [HR]: 1.44; 95% confidence interval [CI]: 1.19 to 1.97; p = 0.01). Moderate PPM also tended to be associated with higher mortality on univariate analysis (age-adjusted HR: 1.07; 95% CI: 0.99 to 1.17; p = 0.06).

Table 3 **Univariate and Multivariate Predictors of Late Overall Mortality**

	Univariate Analysis		Multivariate Analysis			
			Model #1		Model #2	
Variables	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)
Pre-operative variables						
Age, yrs	<0.0001	1.06 (1.05–1.08)	**<0.0001**	**1.06 (1.05–1.08)**	**<0.0001**	**1.06 (1.05–1.08)**
Sex	0.41	0.96 (0.89–1.04)	0.60	0.97 (0.87–1.09)	0.77	0.98 (0.87–1.10)
BMI, kg/m^2	0.009	0.97 (0.95–0.99)	0.11	0.98 (0.96–1.0)	0.26	0.97 (0.92–1.02)
NYHA functional class III to IV	0.04	1.22 (1.01–1.49)	0.43	1.08 (0.88–1.35)	0.43	1.08 (0.88–1.36)
LVEF, %	0.0001	0.99 (0.98–0.99)	**0.004**	**0.99 (0.98–0.99)**	**0.003**	**0.99 (0.98–0.99)**
CAD	<0.0001	1.22 (1.11–1.33)	**0.01**	**1.12 (1.01–1.24)**	**0.02**	**1.12 (1.01–1.24)**
Hypertension	0.0006	1.15 (1.05–1.26)	0.54	1.03 (0.93 to 1.13)	0.53	1.03 (0.93–1.13)
Diabetes	<0.0001	1.25 (1.14–1.38)	**0.0001**	**1.24 (1.11–1.39)**	**0.0001**	**1.24 (1.12–1.38)**
Renal failure	<0.0001	1.51 (1.38–1.67)	**0.0001**	**1.26 (1.13–1.41)**	**0.0001**	**1.26 (1.12–1.41)**
Chronic lung disease	<0.0001	1.43 (1.31–1.57)	**<0.0001**	**1.34 (1.21–1.48)**	**<0.0001**	**1.37 (1.24–1.50)**
Predominant AS	0.09	0.93 (0.085–1.02)	0.65	1.02 (0.92–1.12)	0.89	1.00 (0.90–1.12)
Operative variables						
Prosthesis (≤21 mm)	0.28	1.06 (0.96–1.17)	0.97	0.99 (0.87–1.14)	0.68	1.05 (0.82–1.33)
Concomitant CABG	0.04	1.19 (1.00–1.40)	0.07	0.79 (0.62–1.01)	0.06	0.78 (0.61–1.0)
Mechanical prosthesis	0.0008	1.16 (1.06–1.27)	0.87	1.01 (0.88–1.15)	0.8	1.01 (0.88–1.17)
Moderate PPM	0.09	1.07 (0.99–1.17)	0.65	0.97 (0.88–1.08)	0.64	0.99 (0.89–1.09)
Severe PPM	0.01	1.44 (1.01–1.97)	**0.03**	**1.38 (1.03–1.7)**	**0.04**	**1.34 (1.01–1.70)**
Propensity score	0.01	2.33 (1.16–4.76)	—	—	0.59	1.45 (0.66–3.23)

Bold indicates statistical significance on multivariate analysis. Model #1: without adjustment for propensity score. Model #2: with adjustment for propensity score.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

On multivariate analysis (Table 3), after adjusting for the variables with a p value <0.1 on univariate analysis as well as for sex and BMI, severe PPM was independently associated with increased late mortality (HR: 1.38; 95% CI: 1.03 to 1.77; p = 0.03); moderate PPM did not come out as an independent predictor. After further adjustment for the propensity score, severe PPM remained significantly associated with increased mortality (HR: 1.34; 95% CI: 1.01 to 1.70; p = 0.04) (Table 3).

Also, severe PPM was independently associated with increased cardiovascular mortality on univariate (age-adjusted HR: 1.80; 95% CI: 1.32 to 2.32; p = 0.0005) and multivariate (HR: 1.63; 95% CI: 1.15 to 2.20; p = 0.0006 and HR: 1.55; 95% CI: 1.16 to 2.25; p = 0.005 after adjustment for propensity score) analyses; moderate PPM was not (Table 4).

Interaction between PPM and age, BMI, and LV ejection fraction. There was a significant interaction between PPM and age (Figs. 2A and 2B). Indeed, severe PPM was associated with increased overall mortality in the subset of patients <70 years old (HR: 1.77; 95% CI: 1.1 to 2.58; p = 0.02), but had no significant effect on survival in older patients. After adjustment for other risk factors and for propensity score, severe PPM was associated with a 1.77-fold increase in mortality (95% CI: 1.24 to 2.39; p = 0.002) in the patients <70 years old.

Furthermore, there was also an interaction between PPM and BMI (Figs. 2C and 2D). Severe PPM had a highly significant impact on survival (age-adjusted HR: 1.59; 95% CI: 1.13 to 2.09; p = 0.008) in the subset of patients (n = 1,986; 75%) with a BMI <30 kg/m^2. However, this effect was no longer significant in the obese patients (BMI ≥30 kg/m^2). After adjustment for other risk factors and for propensity score, severe PPM was associated with a 2.1-fold (95% CI: 1.26 to 3.19; p = 0.006) increase in mortality in patients with a BMI <30 kg/m^2.

Moderate-to-severe PPM (indexed EOA ≤0.85 cm^2/m^2) was an independent predictor of late mortality in patients with a pre-operative LVEF <50% (age-adjusted HR: 1.22; 95% CI: 1.05 to 1.41, p = 0.007; HR adjusted for other risk factors and for propensity score: 1.21; 95% CI: 1.03 to 1.41, p = 0.01), but not in patients with preserved LV systolic function (p = NS) (Figs. 2E and 2F). The number of patients with LV dysfunction and severe PPM was too small to allow for separate analysis in these patients. This can likely be attributed to the fact that a large proportion of the patients having concomitant pre-operative LV dysfunction and severe PPM died in the early post-operative period (5) and were therefore excluded from this study. When excluding the patients with severe PPM from the analysis, moderate PPM remained significantly associated with increased mortality (age-adjusted HR: 1.17; 95% CI: 1.01 to 1.37, p = 0.04; HR adjusted for other risk factors and for propensity score: 1.18; 95% CI: 1.01 to 1.37, p = 0.03).

Discussion

One important finding of this study is that severe PPM is an independent predictor of late mortality in patients undergoing AVR. The results of this study also confirm previous data (5,23,24) showing that even a moderate PPM has a detrimental impact on post-operative survival in the context of a depressed LV function. Moreover, the results of this study show that the impact of PPM on late survival differs

Table 4 Univariate and Multivariate Predictors of Late Cardiovascular Mortality

	Univariate Analysis		Multivariate Analysis Model #1		Multivariate Analysis Model #2	
Variables	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)
Pre-operative variables						
Age, yrs	<0.0001	1.08 (1.06–1.09)	**<0.0001**	**1.07 (1.05–1.09)**	**<0.0001**	**1.07 (1.05–1.09)**
Sex	0.07	0.89 (0.79–1.01)	0.53	0.95 (0.80–1.12)	0.72	0.97 (0.82–1.15)
BMI, kg/m^2	NS	1.006 (0.98–1.03)	0.63	1.01 (0.97–1.03)	0.35	0.96 (0.89–1.04)
NYHA functional III to IV	0.03	1.36 (1.02–1.85)	0.11	1.30 (0.94–1.86)	0.11	1.31 (0.93–1.87)
LVEF, %	<0.0001	0.98 (0.97–0.99)	**0.0002**	**0.98 (0.97–0.99)**	**0.0002**	**0.98 (0.97–0.99)**
CAD	<0.0001	1.39 (1.22–1.59)	**0.002**	**1.27 (1.09–1.49)**	**0.02**	**1.26 (1.08–1.48)**
Hypertension	0.0002	1.27 (1.11–1.44)	0.53	1.05 (0.90–1.21)	NS	1.05 (0.90–1.21)
Diabetes	0.0001	1.32 (1.15–1.51)	**0.01**	**1.22 (1.04–1.43)**	**0.007**	**1.26 (1.06–1.48)**
Renal failure	<0.0001	1.57 (1.36–1.80)	**0.004**	**1.28 (1.07–1.50)**	**0.007**	**1.26 (1.06–1.49)**
Chronic lung disease	<0.0001	1.34 (1.17–1.53)	**0.001**	**1.28 (1.10–1.49)**	**0.001**	**1.28 (1.10–1.49)**
Operative variables						
Prosthesis (≤21 mm)	0.03	1.17 (1.01–1.35)	0.64	1.04 (0.85–1.28)	0.21	1.25 (0.88–1.75)
Concomitant CABG	0.001	1.51 (1.18–1.94)	0.63	0.91 (0.64–1.33)	0.56	0.89 (0.62–1.31)
Mechanical prosthesis	0.09	0.88 (0.75–1.01)	0.07	**1.20 (0.98–1.46)**	**0.05**	**1.22 (0.99–1.48)**
Moderate PPM	0.11	1.10 (0.97–1.25)	0.67	0.96 (0.82–1.13)	0.63	0.96 (0.82–1.15)
Severe PPM	0.0005	1.80 (1.32–2.32)	**0.0006**	**1.63 (1.15–2.20)**	**0.005**	**1.55 (1.17–2.25)**
Propensity score	0.49	1.43 (0.53–4.17)	—	—	0.22	1.04 (0.33–3.33)

Bold indicates statistical significance on multivariate analysis. Model #1: without adjustment for propensity score. Model #2: with adjustment for propensity score. Abbreviations as in Tables 2 and 3.

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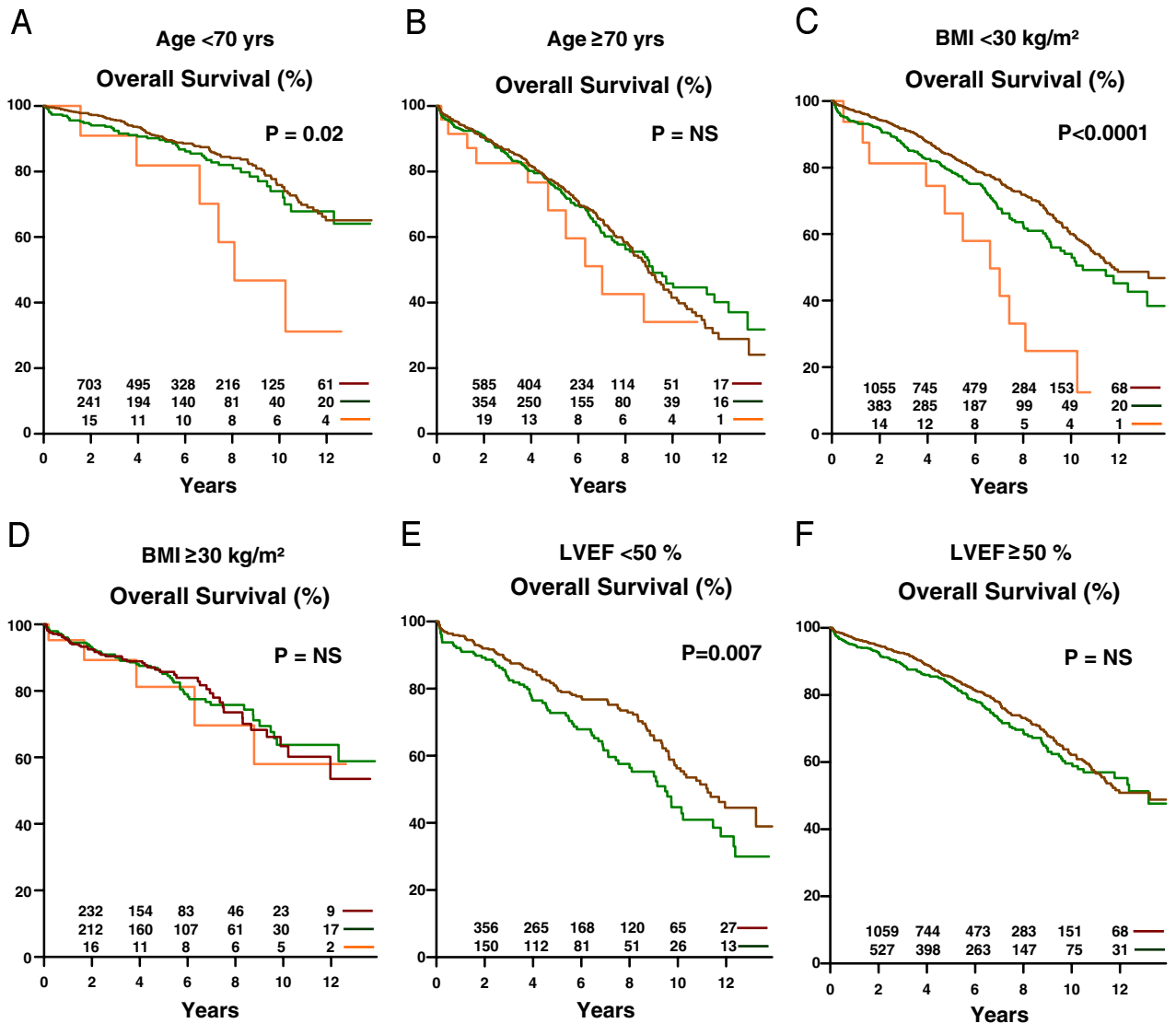

Figure 2 **Impact of Prosthesis-Patient Mismatch on Late Overall Survival**

(A) Patients <70 years old. **(B)** Patients ≥70 years old. **(C)** Body mass index (BMI) <30 kg/m^2. **(D)** BMI ≥30 kg/m^2. **(E)** Pre-operative left ventricular ejection fraction (LVEF) <50%. **(F)** LVEF ≥50%. **Brown line** indicates nonsignificant prosthesis-patient mismatch (PPM); **green line** shows moderate PPM in **A, B, C, and D**, and moderate-severe PPM in **E and F**; **orange line** indicates severe PPM.

markedly depending on age and BMI of the patients. These new findings emphasize the importance of tailoring the PPM preventive strategy to the baseline characteristics of the patient.

Comparison with previous studies. The results of the present study are consistent with those from several previous studies showing that PPM, and especially severe PPM, significantly affects late survival (3,4,6,25,26). On the other hand, other studies reported no significant association between PPM and survival (8–12). The discrepancies among the previous studies may be, at least in part, due to the fact that some of these studies (8–10) have identified PPM with the use of the geometric orifice area or the in vitro EOA provided by the manufacturers, instead of the in vivo EOA (27). In this regard, previous studies demonstrated that the indexed geometric orifice area or the indexed EOA derived from manufacturers' in vitro data have little or no sensitivity to detect PPM (13,22). Differences in age distribution, prevalence of obesity, and prevalence of moderate versus severe PPM in the patient populations may also help explain the discrepancies observed among previous studies. To this effect, studies conducted in younger patient populations (3,25) generally found that PPM has a significant impact on late survival; studies in elderly populations (11,12) often failed to demonstrate any significant association.

Interaction between PPM and age. The results of this study reveal that severe PPM has a significant negative effect on late survival in patients <70 years old, but not in the elderly population. These results are consistent with those of Moon et al. (7), suggesting that the impact of PPM on post-operative outcomes is more pronounced in young patients than in older ones. This finding might be related to the fact that younger patients have higher cardiac output requirements. They indeed have higher basal metabolic rates and are generally more physically active. Also, because they have a longer life expectancy, younger patients are exposed to the risk of PPM for a longer period of time.

A possible explanation for the late effect of PPM on survival could be that patients with PPM undergoing long-term bioprosthetic valve degeneration or development of pannus have less EOA "reserve" and will therefore develop severe stenosis of their valves more rapidly than patients without PPM undergoing the same processes. This additive effect of PPM and acquired prosthesis dysfunction may likely be more important in younger patients given that they are at higher risk for rapid calcific degeneration of their bioprosthetic valve. Also, older patients might be more likely to die from other causes before this process has any impact. These hypothetical mechanisms, however, remain to be confirmed by further studies.

Interaction between PPM and obesity. An important finding of this study is that the PPM has an important negative impact on survival in patients with a BMI <30 kg/m^2, but no significant impact in obese patients. This finding is most likely related to the fact that the use of the body surface area for normalization of EOA may overestimate the prevalence and severity of PPM in obese patients. Future studies will be necessary to determine if the indexation of EOA can be improved or refined in the case of obese patients. In this regard, the investigators of the Strong Heart Study reported that fat-free mass, which represents the metabolically active tissues, accounts for 20% to 40% of the weight difference between lean and obese individuals of the same height (28). They also demonstrated that stroke volume and cardiac output are more strongly related to fat-free mass than to adipose mass or other anthropometric measures. Hence, a potentially interesting avenue would be to index the EOA for the fat-free mass since this parameter appears to be the main determinant of cardiac output in normal-weight, overweight, and obese people.

Interaction between PPM and LV function. From the standpoint of pathophysiology, it is logical to consider that patients with reduced ventricular reserve are more vulnerable to the residual afterload excess imposed by PPM on the LV. Previous studies from this laboratory (5) have shown increased early mortality in patients with a combination of moderate PPM and LV dysfunction as well as in all patients with severe PPM, irrespective of LV function. Mortality also tended to be increased in patients with moderate PPM without LV dysfunction, but this result was not statistically significant (5). Studies from other laboratories (23,24) also demonstrated that the impact of moderate PPM on mid-term mortality is more important in patients with pre-existing LV dysfunction than in those with preserved LV function. The question that we aimed to answer in the context of the present study was as follows: could there be a natural selection process in the sense that patients with severe PPM having survived operation could have a relatively good long-term prognosis? Or on the other hand, do they continue to have a worse prognosis? The results of this study, in fact, reveal that patients with moderate PPM and preserved pre-operative LV systolic function continue to have a good prognosis, similar to that in patients without PPM; those with moderate or severe PPM and LV dysfunction continue to have worse prognoses in the long term. Moreover, the present study shows that severe PPM is also associated with increased late mortality independently of LV function, but only in patients <70 years old and/or with a BMI <30 kg/m^2. The latter result may suggest that PPM has less impact in older patients and/or obese patients because of lesser cardiac output requirements in relation to body size. On the other hand, it should not be interpreted that the same is necessarily true with regard to early mortality since it may well be that older and/or obese patients are at a higher risk of early mortality, but having survived, would indeed have a relatively good prognosis because of lesser cardiac output requirements. Further studies will be necessary to elucidate this point.

Clinical implications. As opposed to the other risk factors for operative mortality after AVR, PPM can be avoided or its severity can be reduced, with the use of a preventive strategy at the time of operation (13,18,29–31). Alternate surgical procedures that may be considered to prevent PPM include: insertion of a prosthesis with a better hemodynamic performance, such as a stentless bioprosthesis or a new generation of stented bioprosthesis or bileaflet mechanical valve implanted in the supra-annular position; and aortic root enlargement to accommodate a larger size of the same prosthesis model. This latter procedure should logically be considered only in patients in whom occurrence of PPM, and particularly severe PPM, cannot be avoided with the use of a better performing prosthesis and in whom the risk-benefit ratio of doing such a procedure is considered acceptable.

The present results corroborate previous recommendations with regard to the prevention of PPM (16), that is, that it should ideally be avoided in all patients with LV dysfunction and that severe PPM should be considered as carrying a poor prognosis regardless of LV function. On the other hand, it provides additional evidence that moderate PPM is well tolerated in patients without LV dysfunction.

As for the influence of age and/or BMI in patients with anticipated severe PPM, the results should be considered, at this time, as providing additional information and might become useful in the clinical decision-making process in the individual patient. Indeed, it has become apparent that when considering AVR, the projected indexed EOA of the

prosthesis to be implanted should be routinely calculated, and if PPM is projected, the information should be interpreted in light of the patient's clinical status including age, lifestyle, BMI, LV function, presence of severe LV hypertrophy, and others, as well as the risk-benefit ratio of doing an alternate surgical procedure. In this sense, the present results provide additional information, but given the deleterious effect of severe PPM on early mortality, even in patients with preserved LV function, it remains to be determined if projected severe PPM could possibly become acceptable in an elderly patient with a combination of normal LV function, limited physical activity, and other factors significantly increasing the risk of performing an alternate surgical procedure. Likewise, it remains to be determined if BMI has a similar impact on early mortality.

Study limitations. The study is retrospective in design, so patient characteristics in the 3 PPM groups were intrinsically different. Propensity score adjustment was used to reduce selection bias. Nonetheless, it is always possible that a selection bias or unidentified confounders might have influenced the results. On the other hand, one could argue that PPM is, among all the other pre-operative or operative factors, the only one that can be easily modified at the time of operation.

In the present study, PPM was identified with the use of the projected indexed EOA. Previous studies demonstrated that this parameter correlates well with the post-operative indexed EOA measured by Doppler-echocardiography and that it provides good sensitivity and specificity for the prediction of PPM (13,22). However, owing to various post-operative factors including low or high flow state conditions, development of prosthesis dysfunction after implantation, and measurement errors, the post-operative EOA may be substantially different from the projected EOA in some patients. Nonetheless, in the subset of 496 patients in whom Doppler-echocardiographic exam was performed 1 month after operation, the measured indexed EOAs were very similar to the projected indexed EOAs in the same groups, so it is very unlikely that this limitation would have significantly influenced the overall results.

Beyond the prolongation of life, the improvement of a patient's quality of life is also an important objective of AVR. This aspect was not addressed in the present study. Nonetheless, previous studies have reported that moderate/severe PPM is a powerful independent predictor of post-operative functional class (32) and maximum exercise capacity (33). Hence, the results of this study on the impact of PPM on late survival cannot be generalized to other post-operative outcomes such as functional outcome and early mortality.

Conclusions

The present study analyzed the potential effects of moderate and severe PPM on late mortality in patients having survived AVR. Results suggest that moderate PPM is associated with increased late mortality in the patients with LV dysfunction, but with normal prognosis in those with preserved LV function. Notwithstanding the previously demonstrated strong deleterious influence of severe PPM on operative mortality even if LV function is preserved, this factor appears to increase late mortality only in patients <70 years old and/or with a BMI <30 kg/m^2 or an LVEF $<50\%$. Further studies are necessary to confirm the relevance of this observation with regard to the clinical decision-making process.

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