JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 8, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.10.026

Predictors and Outcomes of Prosthesis-Patient Mismatch After Aortic Valve Replacement

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ABSTRACT

OBJECTIVES This study sought to evaluate predictors of prosthesis-patient mismatch (PPM) and its association with the risk of perioperative and overall mortality.

BACKGROUND PPM is associated with increased mid- and long-term mortality after surgical aortic valve replacement. Conflicting results have been reported with regard to its association with perioperative mortality.

METHODS Databases were searched for studies published between 1965 and 2014. Main outcomes of interest were perioperative mortality and overall mortality.

RESULTS The search yielded 382 studies for inclusion. Of these, 58 articles were analyzed and their data extracted. The total number of patients included was 40,381 (39,568 surgical aortic valve replacement and 813 transcatheter aortic valve replacement). Perioperative (odds ratio: 1.54; 95% confidence interval: 1.25 to 1.91) and overall (i.e., perioperative and post-operative) mortality (hazard ratio: 1.26; 95% confidence interval: 1.16 to 1.36) was increased in patients with PPM. The impact of PPM on mortality was higher in those studies in which the mean age of the patients was <70 years of age (and/or AVR with associated coronary artery bypass graft was included). Severe PPM was associated with increased risk of both perioperative and overall mortality, whereas moderate PPM was associated with increased risk of perioperative mortality but not of overall mortality. The impact of PPM was less pronounced in patients with larger body mass index (>28 kg/m^2) compared with those with lower index. Predictors of PPM were older age, female sex, hypertension, diabetes, renal failure, larger body surface area, larger body mass index, and the utilization of a bioprosthesis.

CONCLUSIONS PPM increases perioperative and overall mortality proportionally to its severity. The identification of predictors for PPM may be useful to identify patients who are at higher risk for PPM. The findings of this study support the implementation of strategies to prevent PPM especially in patients <70 years of age and/or with concomitant coronary artery bypass graft. (J Am Coll Cardiol Img 2016;9:924–33) © 2016 by the American College of Cardiology Foundation.

The concept of prosthesis-patient mismatch (PPM) has been first described by Rahimtoola in 1978 (1) as follows: “when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve.”

The severity of PPM following aortic valve replacement (AVR) is defined according to the indexed effective orifice area (iEOA) of the prosthetic valve and is classified as follows: none or mild when >0.85 cm^2/m^2; moderate when between 0.85 cm^2/m^2 and 0.65 cm^2/m^2; and severe when <0.65 cm^2/m^2 (2,3).

The prevalence of moderate PPM ranges between 20% and 70% and that of severe PPM between 2% and 20%, respectively (4). Some studies reported

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Dr. Pibarot has received a research grant for echo corelab analyses from Edwards Lifesciences; and has received speaker honoraria from St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 8, 2015; accepted October 15, 2015.

increased short- and long-term mortality (5-7), worse post-perioperative New York Heart Association functional class (7), and less regression of left ventricular (LV) hypertrophy (8-10). Nonetheless, other studies reported similar short-term mortality (11-14), survival (13,15-17), and regression in LV hypertrophy (18-20). Several explanations have been proposed to explain these discrepancies such as: 1) interstudy differences in the parameter used to define of PPM (i.e., indexed geometric orifice area versus iEOA) and in the method used to estimate the iEOA (iEOA predicted from in vitro data or from in vivo data, or iEOA measured by Doppler echocardiography in patients); 2) types and sizes of prosthesis used; and 3) population heterogeneity.

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To overcome the limitations of these retrospective studies, several meta-analyses have been published in order to evaluate whether PPM is a risk factor for short- and long-term mortality (21-23). Takagi et al. (23), Chen et al. (21), and Head et al. (22) report an increase of 31%, 34%, and 42%, respectively, in mid and late all-cause mortality in patients with any degree of PPM. Since the publication of these previous meta-analyses, new original data became available regarding the impact of PPM outcomes following transcatheter aortic valve replacement (TAVR). Several reports have shown that the incidence of PPM is lower following TAVR versus surgical aortic valve replacement (SAVR) (24-27).

The objective of this meta-analysis was to examine the predictors of PPM as well as its association with the risk of perioperative and overall mortality.

METHODS

A literature search was performed in PubMed, EMBASE, Ovid, and Google Scholar for studies published between 1965 and 2014 without language restriction according to the following criteria: "patient prosthesis mismatch" OR "prosthesis patient mismatch." The related articles function was used to broaden the search. The Cochrane library was also searched using the abovementioned terms. All the review articles whose subject was aortic patient-prosthesis mismatch, as well as their reference lists were also reviewed. Newcastle-Ottawa quality assessment scale was used to evaluate the quality of included papers (Online Table 1).

INCLUSION AND EXCLUSION CRITERIA. Articles were included if there was a direct comparison in outcomes between patients with any degree of PPM and no PPM. The following exclusion criteria were used to select the final articles for the meta-analysis: 1) <20 patients in any group; 2) use of parameter other than iEOA for defining PPM.

The study site(s) and inclusion were compared to ensure minimal patient overlap in different publications. If extensive overlap existed, only the publication with the largest or diagnostically most complete cohort (e.g., all patients instead of only patients with aortic stenosis) was included.

Studies were included in either of the following pooled analyses: no clinically significant PPM versus PPM (iEOA <0.85 cm^2/m^2); no clinically significant PPM versus moderate PPM (iEOA <0.85 cm^2/m^2 and ≥ 0.65 cm^2/m^2); no clinically significant PPM versus severe PPM (iEOA <0.65 cm^2/m^2); and moderate PPM versus severe PPM.

OUTCOMES. The primary outcomes were perioperative mortality and overall mortality. Perioperative mortality was defined as death at any time interval if the patient was not discharged or death within 30 days after operation if the patient was discharged (28). Overall mortality corresponds to all-cause mortality occurring during the entire follow-up period of each study and it thus includes both perioperative and post-operative mortality. Secondary outcomes were change in left ventricular ejection fraction (LVEF), change in left ventricular mass index (LVMi), and post-perioperative neurologic complications (PNC). Post-operative LVEF and LVMi were included only if they were measured after a minimum of 3 months after surgery. The following variables were obtained in order to determine their predictive value for the occurrence of PPM, perioperative mortality, and overall mortality following AVR: sex; age; hypertension; diabetes; renal failure; body surface area (BSA); body mass index (BMI); pre-operative mean gradient; aortic valve area; LVEF; and prosthesis type.

STATISTICAL ANALYSES. For each individual study, hazard ratios reflecting long-term mortality along with their corresponding variances were calculated. When only the survival curves were available, these were inspected and the overall mortality rates were estimated for 6-month intervals using the method of Parmar et al. (29). Overall log hazard ratios (HR) using inverse variances as weights were then calculated for each study. Mantel-Haenszel odds ratio (OR) was used as the summary statistic for categorical variables. For continuous variables, the summary statistic chosen was the mean difference.

ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

BMI = body mass index

BSA = body surface area

CABG = coronary artery bypass graft

CI = confidence interval(s)

HR = hazard ratio(s)

iEOA = indexed effective orifice area

LV = left ventricular

LVEF = left ventricular ejection fraction

LVMi = left ventricular mass index

OR = odds ratio(s)

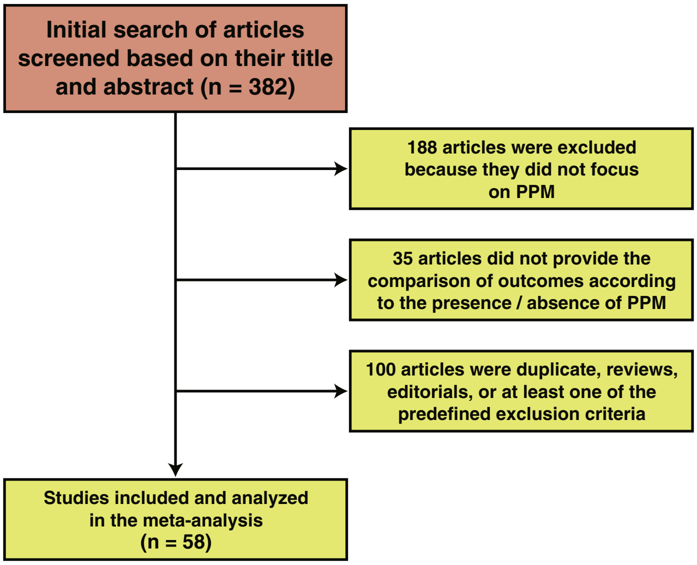
PNC = post-perioperative neurological complications

PPM = prosthesis-patient mismatch

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

FIGURE 1 **Flow Chart for the Inclusion of Studies in the Meta-Analysis**



Initial number of retrieved studies from database search was 382. After applying the exclusion criteria described elsewhere, the total number of studies included for analysis was 58. PPM = prosthesis-patient mismatch.

Heterogeneity was examined using Cochran's Q as well as the I^2 statistic. The degree of heterogeneity was graded as low (<25%), moderate (25% to 75%), and high (>75%) (30). Due to patient and treatment procedure heterogeneity in the included studies, a random effects model was used to calculate the summary statistics and their 95% confidence intervals (CI). Subgroup analysis and meta-regression were performed to assess covariates using the enter method for perioperative mortality and overall mortality. Q-test for heterogeneity was performed to compare perioperative and overall mortality between subgroups (p heterogeneity). Meta-regression analysis was performed to examine the association between the following covariates and mortality in the PPM group: age (as continuous and categorical variable); BMI; BSA; sex; hypertension; diabetes; prosthesis type; pre-perioperative New York Heart Association functional class III; TAVR. The methods used to estimate the iEOA and define PPM included: the iEOA predicted from in vitro EOA (EOA derived from in vitro measurements by the manufacturer and divided by patient's BSA) and the iEOA predicted from in vivo iEOA (EOA derived from published in vivo reference values for each valve and divided by BSA) and the measured iEOA (EOA measured in each patient by Doppler echocardiography). In order to obtain the most precise parameter estimates possible, weighted least squares with weights that are inversely proportional to the variance were used for meta-regression. Funnel plots were inspected to assess the potential of publication bias. Meta-analyses results are displayed in forest plots. Analysis was conducted using Review Manager version 5.2 (The Cochrane Collaboration, Update Software, Oxford, United Kingdom).

RESULTS

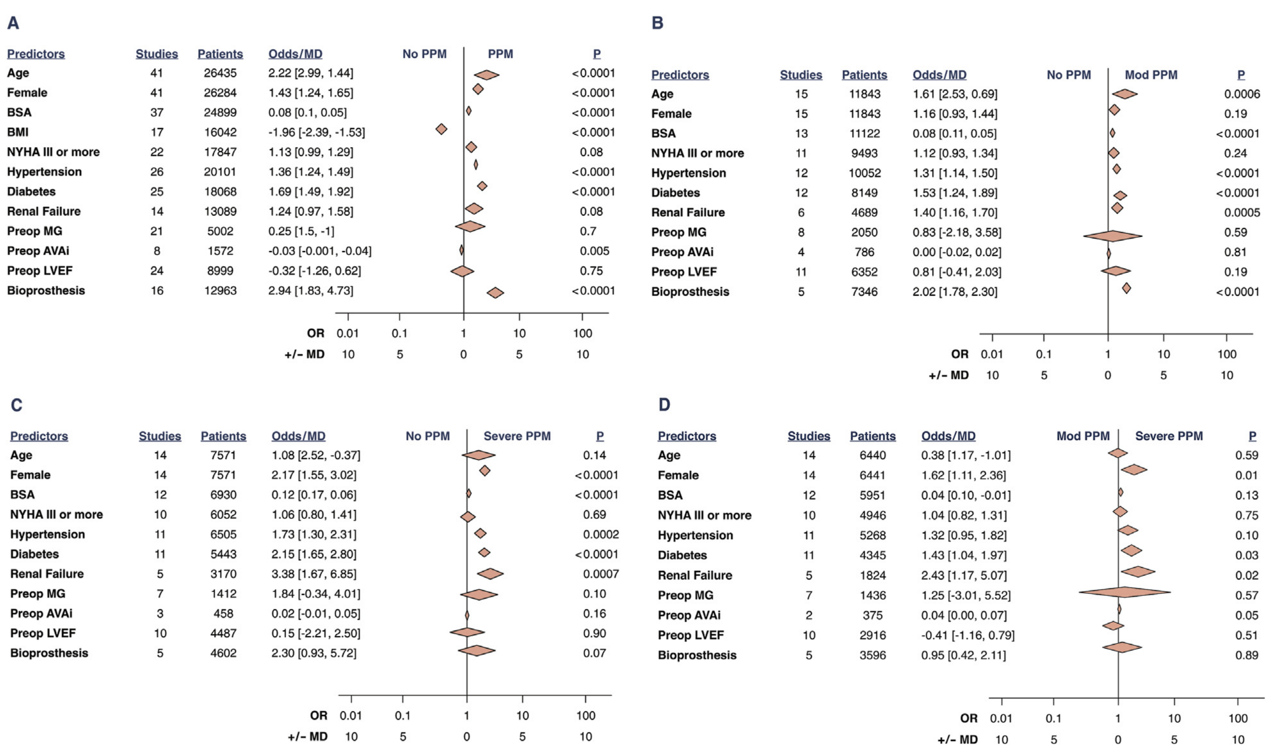
The database search yielded 382 potential studies for inclusion (**Figure 1**). Of these, 58 articles were analyzed and their data extracted by 2 independent observers. The total number of patients included was 40,381. The incidence of female sex was 45.8%; the mean age of the whole population was 68.8 ± 0.1; and PPM was present in 43.8%. SAVR was performed in 54 of the included studies and TAVR in 4. iEOA was measured in 17 studies, predicted from in vivo values in 34 and predicted from in vitro values in 7. A detailed description of the patient characteristics of each study is shown in Online Tables 2 and 3.

PREDICTORS FOR PPM. Older age, female sex, larger BSA and BMI, diabetes, hypertension, renal failure, and implantation of a bioprosthesis rather than a mechanical valve were associated with increased risk for PPM (**Figure 2**).

PRIMARY OUTCOMES. Perioperative mortality. Any degree of PPM (OR: 1.54; 95% CI: 1.25 to 1.91; $p < 0.0001$) and moderate PPM (OR: 1.57; 95% CI: 1.17 to 2.11; $p = 0.003$) were associated with a ~1.5-fold increase risk of perioperative mortality, whereas severe PPM (OR: 2.57; 95% CI: 1.12 to 5.88; $p = 0.03$) was associated with a ~2.5-fold increase in mortality. When compared with moderate PPM, severe PPM showed a trend toward an increase in mortality (OR: 1.68; 95% CI: 0.89 to 3.14; $p = 0.11$) (**Figure 3**, Online Figure 1).

Subgroup analysis revealed that the impact of PPM on mortality was higher in those studies in which the mean age of the patients was <70 years of age (OR: 1.62; 95% CI: 1.67 to 1.92; $p < 0.0001$) and/or AVR ± coronary artery bypass graft (CABG) was included (as opposed to isolated AVR only) (OR: 1.60; 95% CI: 1.25 to 2.04; $p = 0.0003$). When only studies with isolated AVR were included, no effect of PPM on mortality was evidenced (OR: 1.45; 95% CI: 0.93 to 2.26; $p = 0.1$). When we included only studies in which valve replacement was done through TAVR (OR: 1.13; 95% CI: 0.51 to 2.52; $p = 0.76$), no difference in mortality was found between patients with PPM versus no PPM.

FIGURE 2 Summary Effect for Predictors of PPM



Summary effect for predictors of the following: **(A)** any degree of PPM (overall PPM) versus no PPM; **(B)** moderate PPM versus no PPM; **(C)** severe PPM versus no PPM; and **(D)** moderate versus severe PPM. AVAi = indexed aortic valve area (cm^2/m^2); BMI = body mass index (kg/m^2); BSA = body surface area (m^2); LVEF = left ventricular ejection fraction (%); MD = mean difference; MG = mean gradient (mm Hg); OR = odds ratio; PPM = prosthesis-patient mismatch; Preop = preoperative.

Studies in which the mean BMI was >28 kg/m^2 (OR: 1.29; 95% CI: 0.81 to 2.04; p = 0.28) did not show increased perioperative mortality as opposed to those in which mean BMI was <28 kg/m^2 (OR: 1.78; 95% CI: 1.05 to 3.01; p = 0.03) (**Figure 4**).

Multiple meta-regression analysis failed to identify significant association between covariates and perioperative mortality in the group of patients with PPM (Online Table 4).

Overall mortality. Any degree of PPM was associated with increased overall mortality (HR: 1.26; 95% CI: 1.16 to 1.36; $p < 0.0001$) when compared with no PPM. Mortality was also increased in patients with severe PPM (HR: 1.43; 95% CI: 1.14 to 1.80; p = 0.002) but not in those with moderate PPM (HR: 1.01; 95% CI: 0.95 to 1.08; p = 0.68) when compared with no PPM. Patients with severe PPM had increased risk of overall mortality versus patients with moderate PPM (HR: 1.33; 95% CI: 1.18 to 1.51; $p < 0.0001$) (**Figure 3**, Online Figure 2).

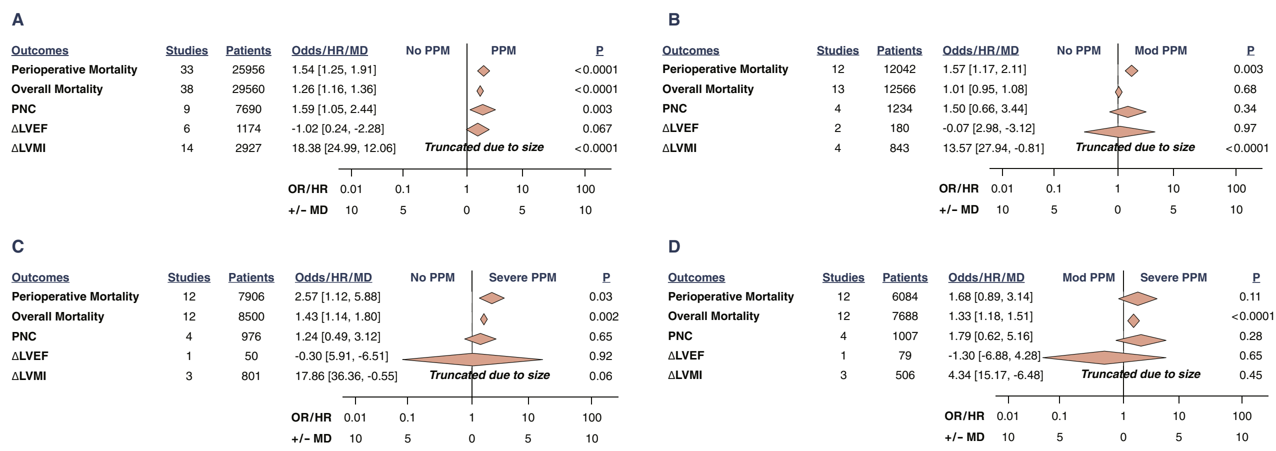
Subgroup analysis revealed increased overall mortality for each of the evaluated subgroups except when only studies in which isolated AVR was performed were included (HR: 1.32; 95% CI: 0.95 to 1.8; p = 0.1). The impact of PPM on mortality was significantly more important (p = 0.015) in the studies where the mean BMI was <28 kg/m^2 (HR: 2.37; 95% CI: 1.42 to 3.95; p = 0.003) compared with those where the BMI was >28 kg/m^2 (HR: 1.14; 95% CI: 1.07 to 1.22; p = 0.0001) (**Figure 5**). Meta-regression analysis identified larger values of BMI associated with decreased overall mortality within the group of patients with PPM (Beta = -0.109; p = 0.05) (Online Table 5, Online Figure 3).

SECONDARY OUTCOMES. PNC was increased in patients with PPM and there was less LV mass regression in patients with PPM versus those with no PPM (**Figure 3**, Online Figure 4). The presence of PPM did not influence the change in LVEF after surgery.

DISCUSSION

The main findings of this study are as follows: 1) moderate and severe PPM are associated with a 1.5- and 2.5-fold increase in the risk of 30-day mortality following AVR; 2) severe PPM is associated

FIGURE 3 Summary Effect for Impact of PPM on Outcomes



This figure shows the summary effect of PPM on outcomes including perioperative mortality, overall mortality, PNC, and post-operative change in LVEF and LVMi. The panels show the risk of these outcomes with the following: **(A)** any degree of PPM versus no PPM; **(B)** moderate PPM versus no PPM; **(C)** severe PPM versus no PPM; and **(D)** moderate PPM versus severe PPM. HR = hazard ratio; LVMi = left ventricular mass index (g/m^2); PNC = post-operative neurologic complications; other abbreviations as in Figures 1 and 2.

with a 1.4-fold increase in overall mortality, whereas moderate PPM is not significantly associated with increased risk of overall mortality; 3) the impact of PPM on mortality appears to be more important in patients <70 years of age, and/or undergoing concomitant coronary artery bypass graft surgery; 4) moderate and severe PPM are associated with lesser regression of LV hypertrophy; and 5) the impact of PPM on mortality was less pronounced in patients with higher BMI.

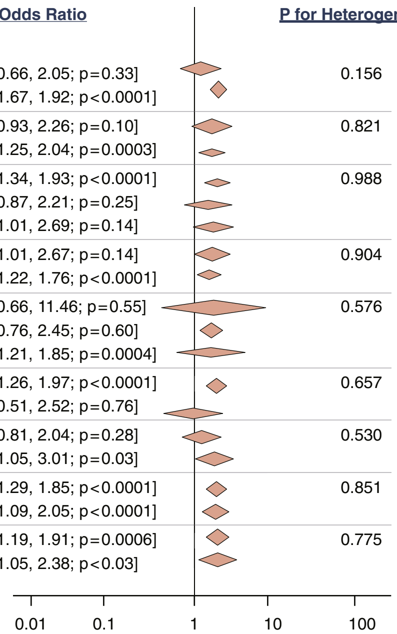
PPM has been associated with increased perioperative mortality, reduced long-term survival, less improvement in symptoms, and regression of LV mass (2). Until now, 3 meta-analyses have been published addressing mainly the long-term survival in patients with PPM (21-23). All of them agree that overall PPM and severe PPM are associated with reduced long-term survival. There are however discrepancies among these studies with regard to the impact of moderate PPM. The largest published meta-analysis by Head et al. (22) included a total of 34 studies comprising 27,186 patients. Several studies have been published since the inclusion period of the latest published meta-analysis. In particular, several studies reporting the incidences and impact of PPM in series of patients undergoing TAVR have been published recently (27). Our current meta-analysis is the largest meta-analysis to date (58 studies comprising 40,381 patients) including for the first-time cohort of patients undergoing TAVR. Furthermore, this is the first meta-analysis to examine the impact of PPM on both perioperative and overall mortality and to assess the predictors for PPM.

PERIOPERATIVE MORTALITY. Based on the results of this meta-analysis, PPM has a significant impact on perioperative mortality and this impact is much more important with severe versus moderate PPM. In contrast to previous meta-analyses, we found that even a moderate PPM is associated with a significant increase in the risk of perioperative mortality. This may be explained by the fact that, in the perioperative period, the LV function is highly vulnerable to residual afterload, even if it is moderate.

The subgroup analysis revealed that perioperative mortality was higher in patients with PPM when including the studies in which patients underwent AVR with or without CABG. However, the impact of PPM on perioperative mortality was no longer significant when including only studies in which their patients underwent only isolated AVR. This latter finding should be interpreted with caution given that there were few studies and a small number of patients with only isolated AVR. Patients with severe aortic stenosis have markedly reduced coronary flow reserve and previous studies have shown that PPM hinders the recovery of coronary reserve following AVR (31). This negative effect may be more important in patients with coronary artery disease and may explain the higher impact of PPM on mortality in patients who underwent CABG at the time of AVR.

FIGURE 4 Subgroup Analysis for Effect of PPM on Perioperative Mortality

	Studies	Sample Size PPM	Sample Size No PPM	Odds Ratio	P for Heterogeneity
Older than 70	15	4015	5055	1.16 [0.66, 2.05; p=0.33]	0.156
Younger than 70	18	5420	11466	1.62 [1.67, 1.92; p<0.0001]	
No CABG	13	2249	5251	1.45 [0.93, 2.26; p=0.10]	0.821
With CABG	20	7186	11270	1.60 [1.25, 2.04; p=0.0003]	
IEOA in vitro	7	2560	9973	1.61 [1.34, 1.93; p<0.0001]	0.988
IEOA in vivo	14	5517	4961	1.39 [0.87, 2.21; p=0.25]	
IEOA measured	12	1551	1890	1.65 [1.01, 2.69; p=0.14]	
Only AS	16	2613	2179	1.64 [1.01, 2.67; p=0.14]	0.904
AS and AR	17	6822	14342	1.47 [1.22, 1.76; p<0.0001]	
Mechanical	3	88	264	2.76 [0.66, 11.46; p=0.55]	0.576
Bioprosthesis	12	1527	966	1.36 [0.76, 2.45; p=0.60]	
Mixed	18	7233	11665	1.50 [1.21, 1.85; p=0.0004]	
SAVR	30	9222	16148	1.58 [1.26, 1.97; p<0.0001]	0.657
TAVR	3	213	373	1.13 [0.51, 2.52; p=0.76]	
BMI>28	6	2867	4737	1.29 [0.81, 2.04; p=0.28]	0.530
BMI<28	4	565	3642	1.78 [1.05, 3.01; p=0.03]	
Before 2007	8	2598	5373	1.55 [1.29, 1.85; p<0.0001]	0.851
After 2007	25	6837	11148	1.50 [1.09, 2.05; p<0.0001]	
Non-US studies	29	8260	15272	1.51 [1.19, 1.91; p=0.0006]	0.775
US studies	4	1175	1249	1.58 [1.05, 2.38; p<0.03]	



This figure shows the summary effect of any degree of PPM versus no PPM in several subgroups. iEOA in vitro, refers to iEOA predicted from EOA measured in vitro by the manufacturer; iEOA in vivo, refers to iEOA predicted from published normal reference values of EOA measured in vivo; iEOA measured refers to iEOA measured directly in each patient by Doppler echocardiography following AVR. Before and after 2007 refers to the publication year of the study. AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bypass graft; iEOA = indexed effective orifice area; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; other abbreviations as in **Figures 1 and 2**.

It is interesting to note that the impact of PPM on perioperative mortality was much more important in studies whose population had a mean age ≤70 years. Consistently, Moon et al. (32) and Mohty et al. (33) have shown that the impact of PPM on long-term mortality is more pronounced in younger patients. Potential explanations for these findings are that: 1) younger patients have increased metabolic demand and thus higher cardiac output requirements; 2) younger patients have a longer life expectancy and are therefore exposed to the risk of PPM and LV overload for a longer period of time; and 3) elderly patients often have other cardiovascular and non-cardiovascular morbidities that may mask the negative impact of PPM.

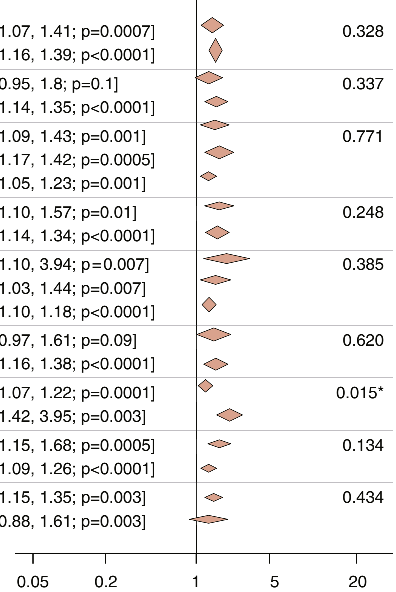
According to our subgroup analysis, PPM identified with the use of predicted (from in vitro or in vivo EOA) or measured iEOA had similar impact on the risk of perioperative or overall mortality. Although the incidence of PPM varies depending on the method used for estimation of iEOA, our results show that all 3 of these methods have similar accuracy for predicting the risk of mortality associated with PPM. The predicted iEOA, however, has the advantage of being easily obtainable in each patient and of being available for preventive strategies.

We were able to confirm that opposed to what was observed in series of patients undergoing SAVR, PPM had no significant impact on perioperative mortality in patients who underwent TAVR. This may be related to the fact that TAVR is generally performed in elderly patients, in whom the impact of PPM is less important, as illustrated by the results of our subgroup analysis. Furthermore, a recent post-hoc analysis of the PARTNER (Placement of Aortic Transcatheter Valve Trial) (27), revealed that: 1) PPM was less frequent and less severe following TAVR than following SAVR; and 2) patients who have PPM following TAVR have less paravalvular regurgitation, which may confound the association between PPM and mortality in these patients.

OVERALL MORTALITY. Our findings are similar to those of Chen et al. (21) and Tagaki et al. (23): that is,

FIGURE 5 Subgroup Analysis for Effect of PPM on Overall Mortality

	Studies	Sample Size PPM	Sample Size No PPM	Hazard Ratio	P for Heterogeneity
Older than 70	16	3250	2691	1.22 [1.07, 1.41; p=0.0007]	0.328
Younger than 70	21	8168	15088	1.26 [1.16, 1.39; p<0.0001]	
No CABG	9	1176	1662	1.32 [0.95, 1.8; p=0.1]	0.337
With CABG	28	10242	16117	1.24 [1.14, 1.35; p<0.0001]	
IEOA in vitro	5	2043	7933	1.25 [1.09, 1.43; p=0.001]	0.771
IEOA in vivo	23	7530	8136	1.29 [1.17, 1.42; p=0.0005]	
IEOA measured	9	1845	1710	1.13 [1.05, 1.23; p=0.001]	
Only AS	16	2250	2662	1.32 [1.10, 1.57; p=0.01]	0.248
AS and AR	21	9168	15117	1.24 [1.14, 1.34; p<0.0001]	
Mechanical	5	1416	2376	2.08 [1.10, 3.94; p=0.007]	0.385
Bioprosthesis	10	1653	3685	1.22 [1.03, 1.44; p=0.007]	
Mixed	22	8349	11718	1.19 [1.10, 1.18; p<0.0001]	
Propensity	4	1097	2322	1.25 [0.97, 1.61; p=0.09]	0.620
Not propensity	33	10321	15457	1.26 [1.16, 1.38; p<0.0001]	
BMI>28	8	3675	6885	1.14 [1.07, 1.22; p=0.0001]	0.015*
BMI<28	5	852	806	2.37 [1.42, 3.95; p=0.003]	
Before 2007	11	4212	8412	1.39 [1.15, 1.68; p=0.0005]	0.134
After 2007	26	7206	9367	1.18 [1.09, 1.26; p<0.0001]	
Non-US studies	33	10295	16361	1.25 [1.15, 1.35; p=0.003]	0.434
US studies	4	1123	1418	1.19 [0.88, 1.61; p=0.003]	



This figure shows the summary effect of any degree of PPM versus no PPM in several subgroups. iEOA in vitro, refers to iEOA predicted from EOA measured in vitro by the manufacturer; iEOA in vivo, refers to iEOA predicted from published normal reference values of EOA measured in vivo; iEOA measured refers to iEOA measured directly in each patient by Doppler echocardiography following AVR. Propensity refers to studies that have used propensity score matched cohorts. Before and after 2007 refers to publication year. Abbreviations as in Figures 1, 2, and 4.

overall mortality is increased in patients with any degree of PPM and in those with severe PPM but not in those with moderate PPM when compared with patients without PPM. Furthermore, we found that patients with severe PPM also have a higher risk of overall mortality compared with those with moderate PPM. This may be explained by the fact that once LV function and hemodynamics have stabilized following the early post-AVR period, the impact of a moderate PPM on subsequent outcome is less important.

The increased risk of late mortality associated with severe PPM may be related to: 1) the persistence of LV hypertrophy and impaired coronary flow reserve and/or the persistence/recurrence of heart failure due to the residual LV afterload related to PPM (34,35); 2) the persistence of concomitant untreated mitral and tricuspid regurgitation (36,37); and 3) the accelerated structural degeneration of bioprosthetic valves (38,39).

In contrast to what was observed for perioperative mortality, the impact of PPM on overall mortality was similar in younger versus older patients. As for perioperative mortality, the impact of PPM was not significant in the studies that included only isolated AVR without CABG.

The results of this study also show that the impact of PPM on perioperative and overall mortality, although significant, is less pronounced in patients with larger BMI than in those with lower BMI. Consistent with these findings, Mohty et al. (33) have previously shown that PPM is a powerful predictor of overall mortality in patients with a BMI <30 kg/m^2 but is not significantly associated with increased mortality in patients with a BMI >30 kg/m^2. This finding is most likely related to the fact that, in overweight and obese patients, the cardiac output requirement does not increase in proportion to the increase in BSA that results from the larger body weight. Hence, the EOA indexed to BSA may overestimate the degree of PPM in patients with larger BMI. Further studies will need to refine the indexation of EOA for these patients. To overcome this limitation of the iEOA, the Valve Academic Research Consortium 2 recommendations suggested to use lower cutpoint values of iEOA to identify PPM in obese patients: that is, <0.70 cm^2/m^2 for moderate PPM and <0.60 cm^2/m^2 for severe PPM (40).

PREDICTORS FOR PPM. Female sex, older age, hypertension, diabetes, and renal failure were the main predictors for PPM in our analysis. Women often have a smaller annulus, which may increase the risk of PPM. The other predictive factors are associated with increased risk of calcification of aortic annulus and aorta, which may also limit the ability of the surgeon to implant a larger valve. Older patients also more frequently receive bioprosthetic rather than mechanical valves.

PPM shares several common risk factors (older age, female sex, hypertension, diabetes) with heart failure with preserved ejection fraction. Heart failure with preserved ejection fraction is generally associated with paradoxical low-flow, that is, reduced stroke volume index despite preserved LVEF, which has been shown to be a risk factor for mortality following AVR (41,42). It is thus difficult to determine what exactly is the respective contribution of PPM versus heart failure with preserved ejection fraction/paradoxical low-flow versus associated comorbidities (e.g., coronary artery disease, diabetes, hypertension, renal failure) to the increased risk of adverse events. Nonetheless, a previous study reported that PPM and paradoxical low-flow aortic stenosis have additive effects on mortality risk following AVR and the coexistence of these 2 conditions was associated with the poorest outcome (42).

According to our meta-analysis, the use of a bioprosthetic valve increases almost 3 times the risk for PPM. Due to their design, mechanical valves have better hemodynamic performance with larger iEOA and lower gradients compared with bioprosthetic valves of the same generation (43). Nonetheless, newer generations of bioprosthetic valves have improved hemodynamics and are associated with lower rates of PPM (44,45).

CLINICAL IMPLICATIONS. The risk of PPM can be estimated by calculating the predicted iEOA (using in vivo reference values) at the time of AVR (46,47). The PPM preventive strategy should be individualized according to the anticipated severity of PPM and the patient's baseline risk profile. In light of the results of the present meta-analysis, severe PPM should be avoided in every patient undergoing AVR, whereas preventive measure should be considered in patients with anticipated moderate PPM presenting vulnerability factors to PPM including: age $<$70 years, BMI $<$28 kg/m^2, and concomitant CABG. Although this was not confirmed in the present study, several previous studies also emphasized the important of avoiding any degree of PPM in patients with depressed LVEF (6). Nowadays, several options are available to prevent PPM, including the implantation of newer generation of surgical prosthetic valves including sutureless valves (44), aortic root enlargement in selected patients (48), and TAVR (27).

STUDY LIMITATIONS. We did not use individual data, therefore, results and conclusions drawn from meta-regression analysis regarding independent predictors should be interpreted cautiously. In the context of a meta-analysis, it is not possible to perform a standard multivariable analysis with comprehensive adjustment for the potential confounding variables.

The subgroup analyses with respect to age (younger vs. older than 70 years) and BMI were not performed with the individual data, but with the mean values of age and BMI reported in the included studies.

The same issue also applies to the isolated AVR versus AVR ± CABG subgroup analysis. Although the isolated AVR subgroup is homogenous (i.e., 100% of the patients in the included studies underwent isolated AVR), the AVR ± CABG subgroup is composed of studies including both isolated AVR and AVR combined with CABG. Due to the inherent limitations of meta-analysis and the heterogeneity of patients in each subgroup, no comparisons can be made between them regarding mortality (e.g., younger vs. older than 70 years old; isolated AVR vs. AVR ± CABG). Therefore, the results of the subgroup analyses and meta-regression should not be considered as definitive but rather as hypothesis generating.

CONCLUSIONS

PPM is associated with increased perioperative and overall mortality and post-operative neurologic complications. Its impact on mortality increases with increasing severity of PPM. In the present meta-analysis, severe PPM had a significant impact on both perioperative and overall mortality, whereas moderate PPM had an impact only on perioperative mortality. No difference in mortality between patients with or without PPM was found after TAVR. Patients with larger BMI appear to be protected from the increased mortality associated with PPM. Patient-related predictors of PPM include older age, female sex, hypertension, diabetes, and renal failure.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Severe and moderate PPM after AVR are associated with worse operative mortality. Overall mortality is only affected by severe PPM.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Female sex, age, diabetes, hypertension and renal failure are the main predictors for PPM.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TAVR is associated with reduced mortality in patients with PPM. This option should be considered especially in patients <70 years of age and/or with concomitant CABG with high risk of post-operative PPM.

TRANSLATIONAL OUTLOOK: Additional studies are needed to define precisely which patients with PPM are at increased risk of operative and overall mortality in order to evaluate the possible beneficial effect of TAVR instead of SAVR in these cases.

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KEY WORDS aortic stenosis, aortic valve replacement, heart valve prosthesis, meta-analysis, prosthesis-patient mismatch

APPENDIX For supplemental tables, figures, and references, please see the online version of this article.