European Journal of Cardio-Thoracic Surgery 0 (2019) 1–11
doi:10.1093/ejcts/ezy466

ORIGINAL ARTICLE

Cite this article as: Sá MPBdO, de Carvalho MMB, Sobral Filho DC, Cavalcanti LRP, Rayol SdC, Diniz RGS *et al*. Surgical aortic valve replacement and patient–prosthesis mismatch: a meta-analysis of 108 182 patients. Eur J Cardiothorac Surg 2019; doi:10.1093/ejcts/ezy466.

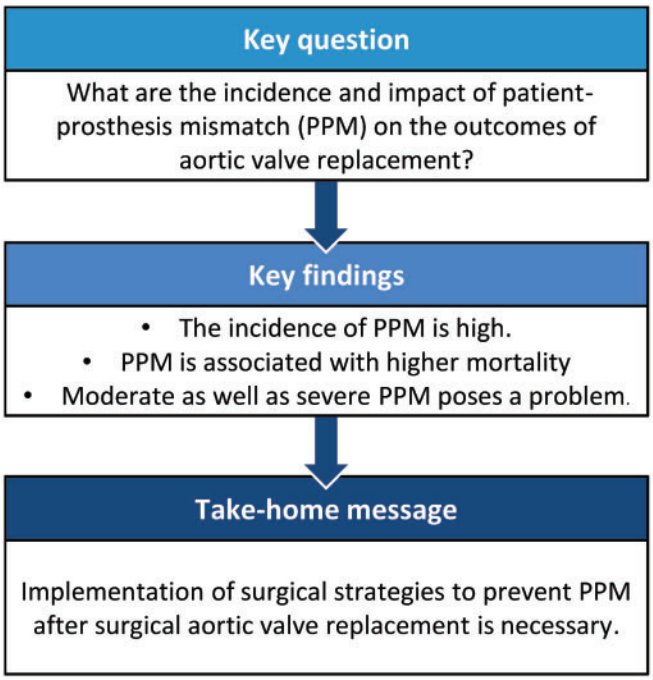
Surgical aortic valve replacement and patient–prosthesis mismatch: a meta-analysis of 108 182 patients

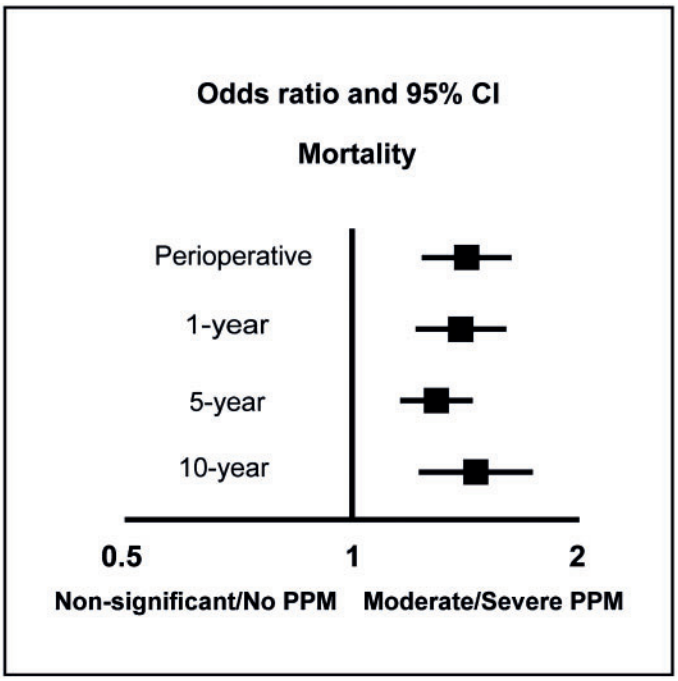
Michel Pompeu Barros de Oliveira Sá[a,b,c,*], Martinha Millianny Barros de Carvalho[b,c], Dário Celestino Sobral Filho[b,c], Luiz Rafael Pereira Cavalcanti[a,b], Sérgio da Costa Rayol[a,b], Roberto Gouvea Silva Diniz[a,b], Alexandre Motta Menezes[a,b], Marie-Annick Clavel[d], Philippe Pibarot[d] and Ricardo Carvalho Lima[a,b,c]

[a] Division of Cardiovascular Surgery of Pronto Socorro Cardiológico de Pernambuco—PROCAPE, Recife, Brazil
[b] University of Pernambuco—UPE, Recife, Brazil
[c] Nucleus of Postgraduate and Research in Health Sciences of Faculty of Medical Sciences and Biological Sciences Institute—FCM/ICB, Recife, Brazil
[d] Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Canada

* Corresponding author. Division of Cardiovascular Surgery of Pronto Socorro Cardiológico de Pernambuco—PROCAPE, Av. Eng. Domingos Ferreira no4172, Edf. Paquetá, apto 405, Recife, Pernambuco 51021-040, Brazil. Tel: +55-81-97733190; e-mail: michel_pompeu@yahoo.com.br (M.P.B.d.O. Sá).

Received 13 July 2018; received in revised form 10 December 2018; accepted 13 December 2018





Abstract

OBJECTIVES: This study sought to evaluate the impact of patient–prosthesis mismatch (PPM) on the risk of perioperative, early-, mid- and long-term mortality rates after surgical aortic valve replacement.

METHODS: Databases were searched for studies published until March 2018. The main outcomes of interest were perioperative mortality, 1-year mortality, 5-year mortality and 10-year mortality.

RESULTS: The search yielded 3761 studies for inclusion. Of these, 70 articles were analysed, and their data were extracted. The total number of patients included was 108 182 who underwent surgical aortic valve replacement. The incidence of PPM after surgical aortic valve replacement was 53.7% (58 116 with PPM and 50 066 without PPM). Perioperative mortality [odds ratio (OR) 1.491, 95% confidence interval (CI) 1.302–1.707; $P < 0.001$], 1-year mortality (OR 1.465, 95% CI 1.277–1.681; $P < 0.001$), 5-year mortality (OR 1.358, 95% CI 1.218–1.515; $P < 0.001$) and 10-year mortality (OR 1.534, 95% CI 1.290–1.825; $P < 0.001$) were increased in patients with PPM. Both severe PPM and moderate PPM were associated with increased risk of perioperative mortality, 1-year mortality, 5-year mortality and 10-year mortality when analysed together and separately, although we observed a higher risk in the group with severe PPM.

CONCLUSIONS: Moderate/severe PPM increases perioperative, early-, mid- and long-term mortality rates proportionally to its severity. The findings of this study support the implementation of surgical strategies to prevent PPM in order to decrease mortality rates.

Keywords: Aortic stenosis • Aortic valve replacement • Heart valve prosthesis • Meta-analysis • Prosthesis–patient mismatch

INTRODUCTION

Rationale

Previous meta-analyses have been published to evaluate whether patient–prosthesis mismatch (PPM) is a risk factor for short-term mortality and long-term mortality, showing an increase in all-cause mortality of 31%, 34%, 42% and 26%, respectively [1–4], in patients with any degree of PPM. Since the publication of these previous meta-analyses—the last one including articles published until 2014 [4]—new original data became available regarding the impact of PPM outcomes following surgical aortic valve replacement (SAVR).

Objectives

We aimed to investigate whether PPM increases the risk for death after SAVR. This analysis was planned in accordance with the current guidelines for performing comprehensive systematic reviews and meta-analysis, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [5] guidelines. We prespecified our analytical plan and registered the study protocol with PROSPERO, the international prospective register of systematic reviews (CRD42018089883).

METHODS

Eligibility criteria

With the Population, Intervention, Comparison, Outcome and Study design (PICOS) strategy, studies were considered if (i) the population comprised patients who underwent SAVR; (ii) there was a group of patients who developed moderate PPM (with indexed effective orifice area (iEOA) between 0.85 cm^2/m^2 and 0.65 cm^2/m^2) or severe PPM (iEOA $\leq$ 0.65 cm^2/m^2) after SAVR; (iii) there was a control group of patients with non-significant/no PPM (iEOA > 0.85 cm^2/m^2); (iv) outcomes studied included any of the following: perioperative, 1-year, 5-year and 10-year mortality rates; and (v) studies were retrospective, prospective, randomized or non-randomized.

Information sources

The following databases were used (until April 2018): MEDLINE; EMBASE; CENTRAL/CCTR (Cochrane Controlled Trials Register); ClinicalTrials.gov; SciELO (Scientific Electronic Library Online); LILACS (Literatura Latino Americana em Ciências da Saúde); Google Scholar and reference lists of relevant articles.

Search

We conducted the search with the following terms: 'mismatch OR PPM OR patient-prosthesis mismatch OR prosthesis-patient mismatch' AND 'AVR OR aortic valve replacement.'

Study selection

The following steps were taken as done in previous studies of ours [6–10]: (1) identification of titles of records through searching databases; (2) the removal of duplicates; (3) screening and selection of abstracts; (4) assessment for eligibility through full-text articles and (5) the final inclusion in study. One reviewer followed steps 1–3. Two independent reviewers followed step 4 and selected studies. Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer made the final decision.

Data items

The crude end points were perioperative, 1-year, 5-year and 10-year mortality rates.

Data collection process

Two independent reviewers extracted the data as done in previous studies of ours [6–10]. When there was disagreement about the data, a third reviewer checked them and made the final decision. From each study, we extracted patient characteristics, study design and outcomes. When the data were not clearly available in the articles, we contacted the authors of the original articles by email.

Risk of bias in individual studies

Included studies were assessed for the following characteristics: retrospective or prospective; randomized or non-randomized; multicentric or not; selection bias, detection bias, attrition bias and adequacy of multivariable adjustment for possible confounders. Taking these characteristics into account, the papers were classified into A (low risk of bias), B (moderate risk of bias) or C (high risk of bias). Two independent reviewers assessed the risk

of bias. Agreement between the 2 reviewers was assessed with kappa statistics for full-text screening and rating of relevance and risk of bias. When there was disagreement about risk of bias, a third reviewer checked the data and made the final decision as done in previous studies of ours [6–10].

Summary measures

The principal summary measures were odds ratio (OR) with 95% confidence interval (CI) and *P* values (considered statistically significant when $P < 0.05$) for death. The meta-analysis was completed with the software Comprehensive Meta-Analysis (version 2, Biostat, Inc., Englewood, NJ, USA) as done in previous studies of ours [6–10].

Synthesis of the results

Adopting the same statistical approach outlined in previous studies of ours [6–10], forest plots were generated for graphical presentations of clinical outcomes, and we performed the I^2 test and χ^2 test for the assessment of heterogeneity across the studies [11]. Interstudy heterogeneity was explored using the χ^2 statistic, but the I^2-value was calculated to quantify the degree of heterogeneity across the studies that could not be attributable to chance alone. When I^2 was more than 50%, significant statistical heterogeneity was considered to be present. Each study was summarized by the OR, whose values were combined across studies using a weighted DerSimonian–Laird random effects model [12].

Risk of bias across studies

To assess the publication bias, a funnel plot was generated for each outcome, statistically assessed by Begg and Mazumdar's test [13] and Egger's test [14], as done in previous studies of ours [6–10].

Sensitivity analysis

We analysed the pool data regarding the outcomes according to PPM severity (moderate or severe). We also investigated the influence of each study on the overall effect—by sequentially removing one study—to test the robustness of the main results, so that we could verify whether any study had an excessive influence on the overall results. Furthermore, we analysed the data as to the period when patients were operated on (over the past 10 years, to study more contemporary patients), the type of valve in the studies (only biological or only mechanical) and the way the iEOA was measured (predicted from EOA measured *in vitro* by the manufacturer, predicted from published normal reference values of EOA measured *in vivo* or measured directly in each patient by Doppler echocardiography following SAVR).

RESULTS

Study selection

At first, we identified 3761 articles, of which 76 studies were considered relevant and read as full text. Seventy publications (Supplementary Material, References) satisfied the pre-established eligibility criteria. The level of concordance between the reviewers regarding the study relevance and study validity was excellent (Kappa = 0.86) and good (Kappa = 0.84), respectively. Figure 1 displays the search strategy.

Study characteristics

A total of 108 182 patients (moderate/severe PPM: 58 116 patients; non-significant/no PPM: 50 066 patients) were included from studies published from 1998 to 2018. The incidence of moderate/severe PPM after SAVR was 53.7%, varying from 6.1% to 93.8%. The studies consisted of patients whose mean or median age varied from 46.5 years to 81.0 years. There were studies mostly from North America, Europe and Asia and only 1 from Latin America. All the studies were observational, 32.8% were prospective, 17.1% were multicentric and 77.1% had some multivariate adjustment for possible confounders. Other characteristics are described elsewhere (Supplementary Material, Table S1). The overall internal validity was considered moderate risk of bias (Supplementary Material, Table S2).

Synthesis of the results

The OR for perioperative mortality in the 'PPM' group compared with the 'non-significant/no PPM' group in each study is reported in Fig. 2. There was evidence of moderate statistical heterogeneity of treatment effect among the studies for perioperative mortality. The overall OR (95% CI) of perioperative mortality showed a statistically significant difference between the groups, with higher risk in the 'PPM' group (random effects model: OR 1.491, 95% CI 1.302–1.707; $P < 0.001$).

The OR for 1-year mortality in the 'PPM' group compared with the 'non-significant/no PPM' group in each study is reported in Fig. 3. There was evidence of moderate statistical heterogeneity of treatment effect among the studies for perioperative mortality. The overall OR (95% CI) of 1-year mortality showed a statistically significant difference between the groups, with higher risk in the 'PPM' group (random effect model: OR 1.465, 95% CI 1.277–1.681; $P < 0.001$).

The OR for 5-year mortality in the 'PPM' group compared with the 'non-significant/no PPM' group in each study is reported in Fig. 4. There was evidence of high statistical heterogeneity of treatment effect among the studies for perioperative mortality. The overall OR (95% CI) of 5-year mortality showed a statistically significant difference between the groups, with higher risk in the 'PPM' group (random effect model: OR 1.358, 95% CI 1.218–1.515; $P < 0.001$).

The OR for 10-year mortality in the 'PPM' group compared with the 'non-significant/no PPM' group in each study is reported in Fig. 5. There was evidence of high statistical heterogeneity of treatment effect among the studies for perioperative mortality. The overall OR (95% CI) of 10-year mortality showed a statistically significant difference between the groups, with higher risk in the 'PPM' group (random effect model: OR 1.534, 95% CI 1.290–1.825; $P < 0.001$).

Risk of bias across studies

Figure 6 displays statistically significant asymmetries around the axis for 1-year mortality and 5-year mortality but no asymmetry

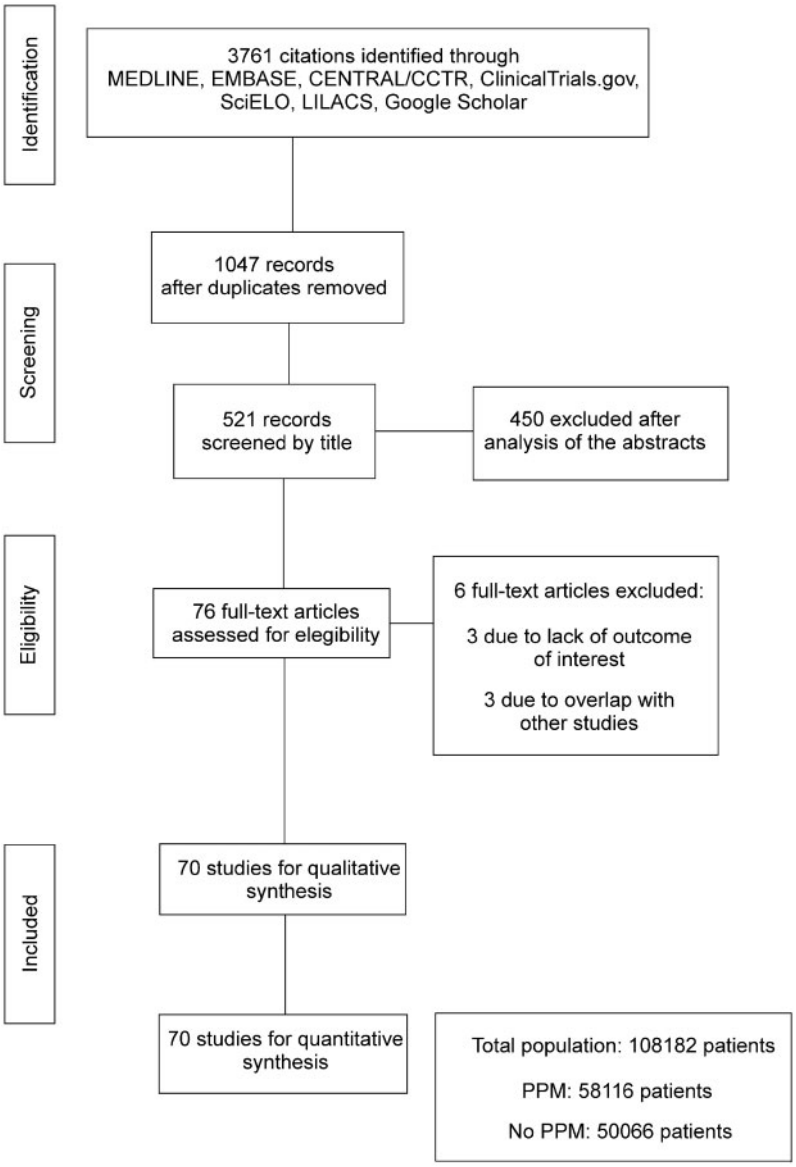


Figure 1: Flow diagram of studies included in data search. CCTR: Cochrane Controlled Trials Register; LILACS: Literatura Latino Americana em Ciências da Saúde; PPM: patient–prosthesis mismatch; SciELO: Scientific Electronic Library Online.

around the axis for perioperative mortality and 10-year mortality. This means that we observed a high risk of publication bias related to the former 2 outcomes and low risk of publication bias to the latter 2 outcomes.

Sensitivity analysis

We observed in the sensitivity analyses (see Table 1) that the risk for mortality was higher in the groups with PPM regardless of the severity (moderate or severe) when we compared them with the non-significant/no PPM group. However, when we compared severe versus moderate PPM, we observed that the former had a higher risk than the latter. Statistical heterogeneity of the effects was massively present.

When we removed the studies one-by-one from the analysis to establish whether any of the individual studies had any special impact on the pooled results, no particular effect was observed.

When we analysed studies including patients who underwent SAVR only within the last 10 years to assess more contemporary patients, we found that the overall OR (95% CI) for perioperative mortality showed a statistically significant difference between the groups, with higher risk in the 'PPM' group (random effect model: OR 1.750, 95% CI 1.167–2.623; $P = 0.007$—see Table 2).

When we analysed studies according to the type of valves, we found that the overall OR (95% CI) for perioperative mortality showed a statistically significant difference between the groups, with higher risk in the 'PPM' group for mechanical valves (random effect model: OR 1.750, 95% CI 1.167–2.623; $P = 0.007$—see Table 2) but not for biological valves. We highlight that most of the studies included both types of prostheses, and we were not able to analyse separately their data regarding the type of prostheses.

When we analysed the data according to how the iEOA was measured to define the presence of PPM (whether *in vivo*, *in vitro*

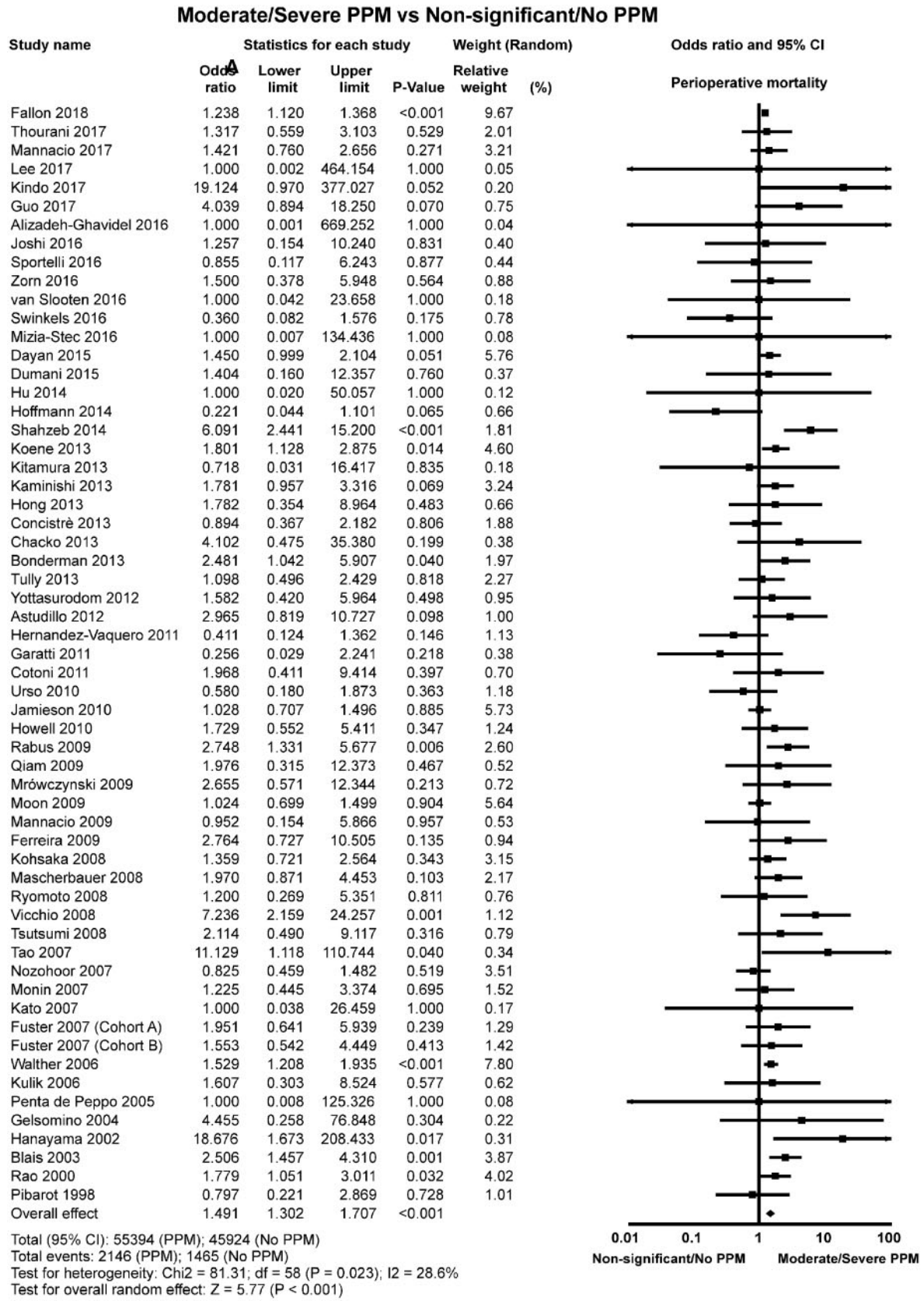


Figure 2: Odds ratio and conclusions plot of perioperative mortality. The summary effect of moderate/severe PPM on perioperative mortality is shown. CI: confidence interval; PPM: patient–prosthesis mismatch.

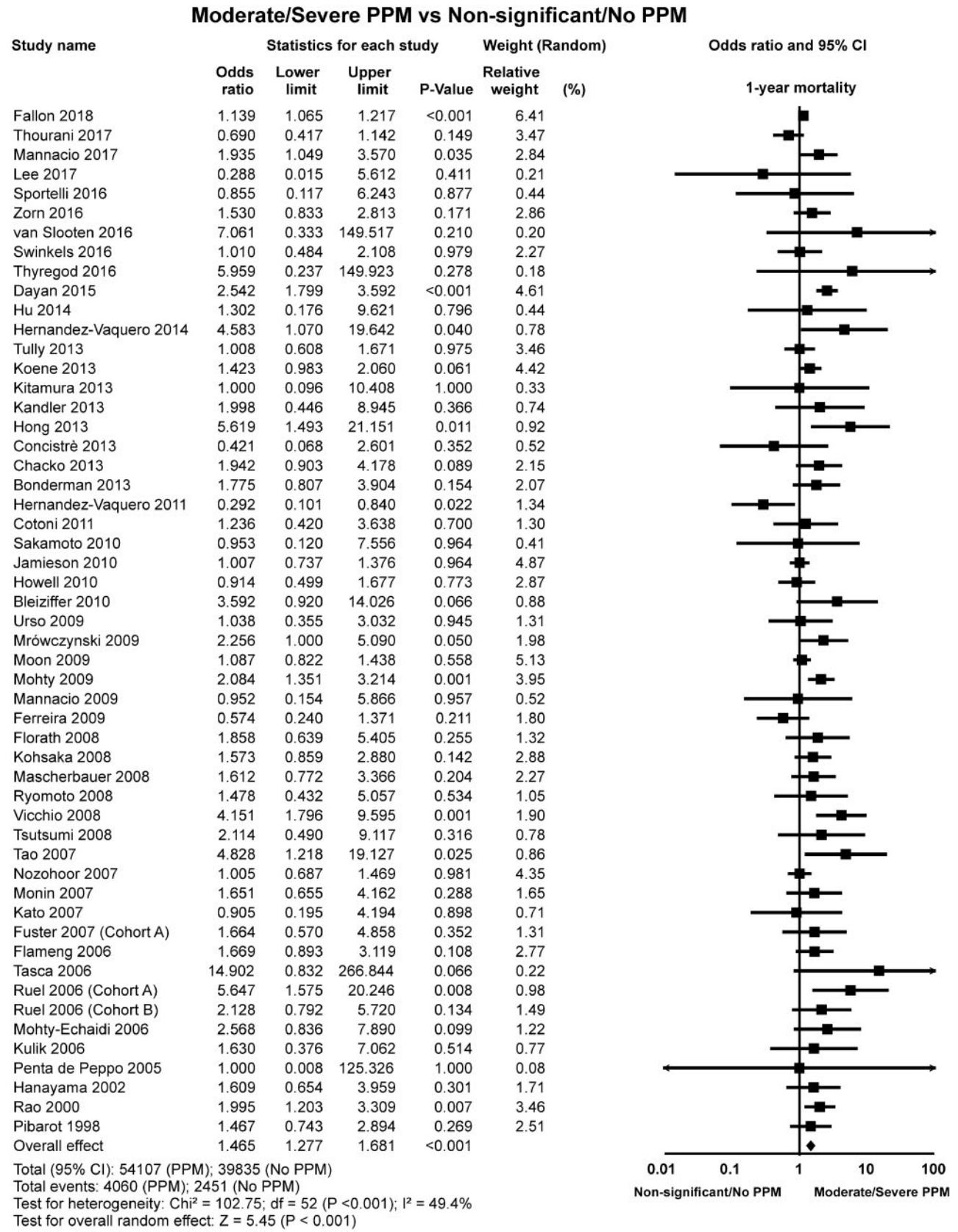


Figure 3: Odds ratio and conclusions plot of 1-year mortality. The summary effect of moderate/severe PPM on 1-year mortality is shown. CI: confidence interval; PPM: patient–prosthesis mismatch.

Moderate/Severe PPM vs Non-significant/No PPM

Study name	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight (%)
Fallon 2018	1.131	1.088	1.177	<0.001	5.21
Mannacio 2017	2.157	1.618	2.876	<0.001	3.84
Lee 2017	0.808	0.307	2.126	0.666	1.02
Sportelli 2016	0.503	0.259	0.977	0.042	1.78
Swinkels 2016	0.963	0.630	1.471	0.861	2.92
Dayan 2015	1.521	1.229	1.882	<0.001	4.37
Hu 2014	0.479	0.155	1.477	0.200	0.79
Hernandez-Vaquero 2014	2.460	1.085	5.575	0.031	1.33
Tully 2013	0.845	0.636	1.123	0.245	3.86
Koene 2013	1.078	0.793	1.467	0.631	3.70
Kitamura 2013	0.138	0.026	0.746	0.021	0.39
Kandler 2013	0.728	0.309	1.718	0.469	1.23
Hong 2013	2.817	1.120	7.089	0.028	1.10
Concistrè 2013	0.894	0.367	2.182	0.806	1.16
Bonderman 2013	1.417	0.858	2.338	0.173	2.49
Hernandez-Vaquero 2011	0.830	0.399	1.730	0.620	1.55
Cotoni 2011	1.220	0.575	2.591	0.604	1.50
Sakamoto 2010	1.505	0.420	5.390	0.530	0.64
Jamieson 2010	1.140	0.958	1.357	0.139	4.63
Howell 2010	0.786	0.528	1.169	0.234	3.09
Bleiziffer 2010	1.752	1.085	2.829	0.022	2.60
Urso 2009	0.764	0.376	1.550	0.455	1.63
Mrówczynski 2009	2.170	1.286	3.663	0.004	2.37
Moon 2009	0.901	0.722	1.125	0.358	4.31
Mohty 2009	1.252	1.010	1.551	0.040	4.36
Mannacio 2009	0.615	0.171	2.221	0.458	0.63
Florath 2008	1.696	0.977	2.945	0.060	2.24
Kohsaka 2008	1.755	1.121	2.747	0.014	2.78
Mascherbauer 2008	1.612	0.772	3.366	0.204	1.55
Ryomoto 2008	1.658	0.661	4.160	0.281	1.11
Vicchio 2008	2.521	1.372	4.633	0.003	1.99
Tsutsumi 2008	2.114	0.490	9.117	0.316	0.50
Tao 2007	2.271	0.760	6.786	0.142	0.83
Nozohoor 2007	1.713	1.380	2.127	<0.001	4.34
Monin 2007	1.021	0.515	2.025	0.952	1.71
Kato 2007	1.500	0.694	3.241	0.302	1.45
Fuster 2007 (Cohort A)	2.947	1.419	6.117	0.004	1.56
Flameng 2006	1.377	0.853	2.224	0.191	2.60
Tasca 2006	3.078	1.468	6.454	0.003	1.53
Ruel 2006 (Cohort A)	2.843	1.487	5.436	0.002	1.84
Ruel 2006 (Cohort B)	3.287	1.641	6.583	0.001	1.68
Mohty-Echaidi 2006	1.627	0.949	2.792	0.077	2.29
Kulik 2006	2.063	0.726	5.868	0.174	0.90
Penta de Peppo 2005	1.810	0.282	11.599	0.532	0.32
Hanayama 2002	1.609	0.654	3.959	0.301	1.14
Rao 2000	1.776	1.110	2.844	0.017	2.65
Pibarot 1998	1.215	0.734	2.012	0.448	2.47
Overall effect	1.358	1.218	1.515	<0.001	

Total (95% CI): 52990 (PPM); 38751 (No PPM)
Total events: 13020 (PPM); 7591 (No PPM)
Test for heterogeneity: Chi² = 139.06; df = 46 (P < 0.001); I² = 66.9%
Test for overall random effect: Z = 5.51 (P < 0.001)

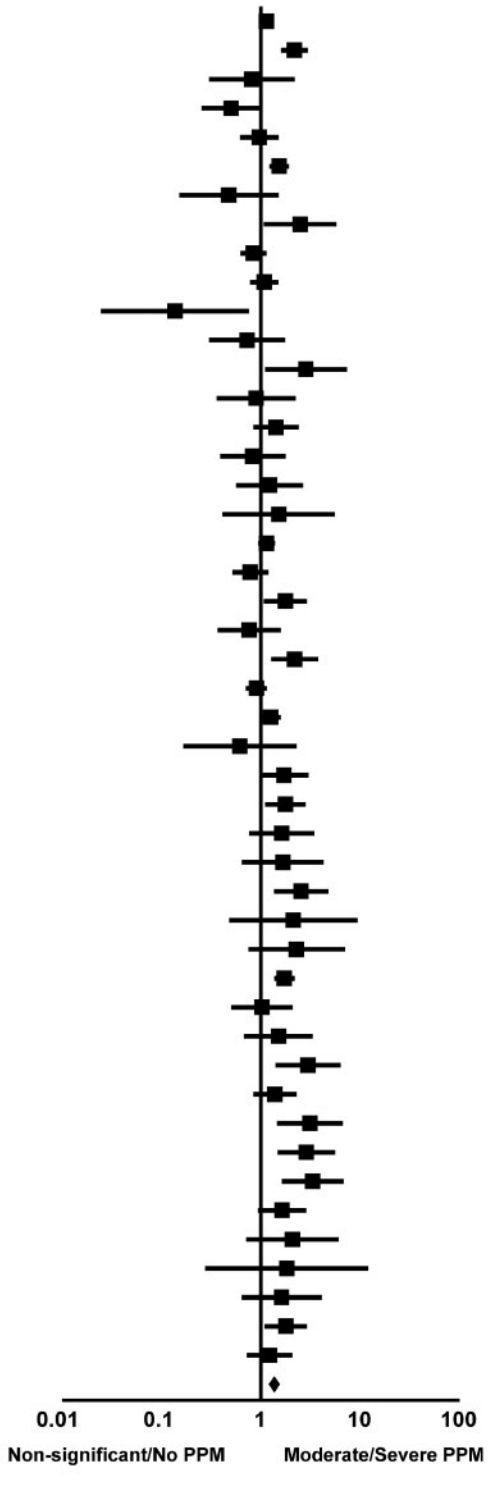


Figure 4: Odds ratio and conclusions plot of 5-year mortality. The summary effect of moderate/severe PPM on 5-year mortality is shown. CI: confidence interval; PPM: patient–prosthesis mismatch.

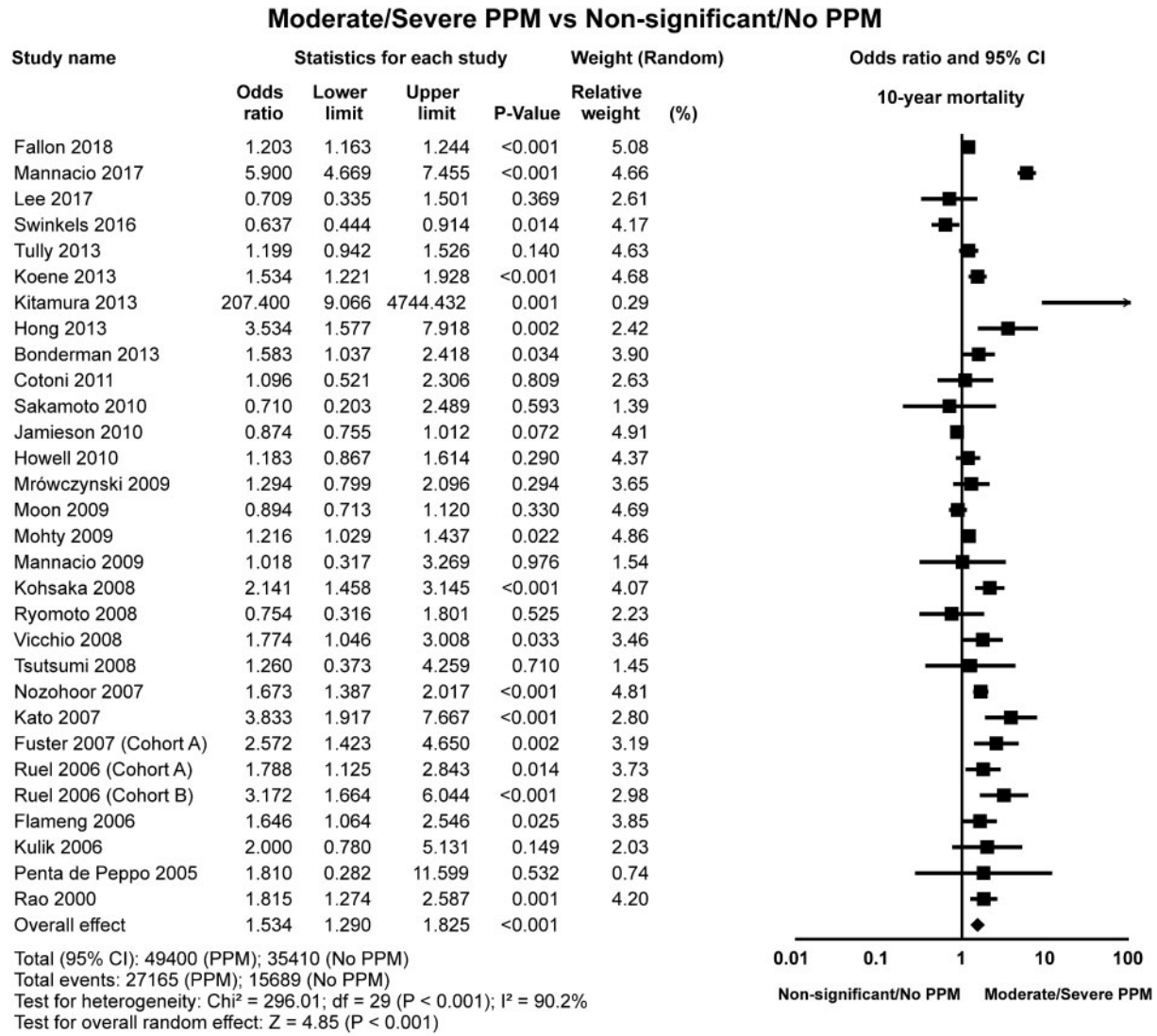


Figure 5: Odds ratio and conclusions plot of 10-year mortality. The summary effect of moderate/severe PPM on 10-year mortality is shown. CI: confidence interval; PPM: patient–prosthesis mismatch.

or measured by echocardiography), we found that the overall OR (95% CI) for perioperative mortality showed a statistically significant difference with higher risk in the 'PPM' group regardless of the way by which iEOA was measured (see Table 2).

DISCUSSION

Summary of evidence

To our knowledge, this is the largest meta-analysis of studies performed to date that provides incremental value by demonstrating that patients with moderate/severe PPM have higher risk for perioperative, early-, mid- and long-term mortality rates in comparison to those with non-significant/no PPM. We also observed that more than half of the patients leave the operation room with significant PPM, which already has a negative impact on the perioperative period. Moreover, mortality rates increase not only with severe PPM but also with moderate PPM, with the former having a worse effect on mortality than the latter.

Some considerations

These results have important clinical implications, given that PPM is a potentially modifiable risk factor. Until now, 4 meta-analyses dealt with patients with PPM after SAVR [1–4], and a plethora of studies has emerged since the last one [4]. Dayan *et al.* [4] published a meta-analytical study including 58 studies with 40 381 patients (39 568 SAVR and 813 transcatheter aortic valve replacement) and observed that severe PPM is associated with poorer long-term survival, but, when it comes to the effect of moderate PPM, the studies were not unanimous. Although Dayan *et al.* [4] found that moderate PPM increases the risk of perioperative death, they did not observe the same for the overall mortality, which was explained by a possible vulnerability of the heart to some remaining afterload in the perioperative period, albeit just moderate. Contrasting with these results, we found that moderate PPM was significantly associated with increased mortality, not only in the perioperative period but also in the early-, mid- and long-term follow-up. Furthermore, we observed that severe PPM has an even greater negative impact on mortality than moderate PPM.

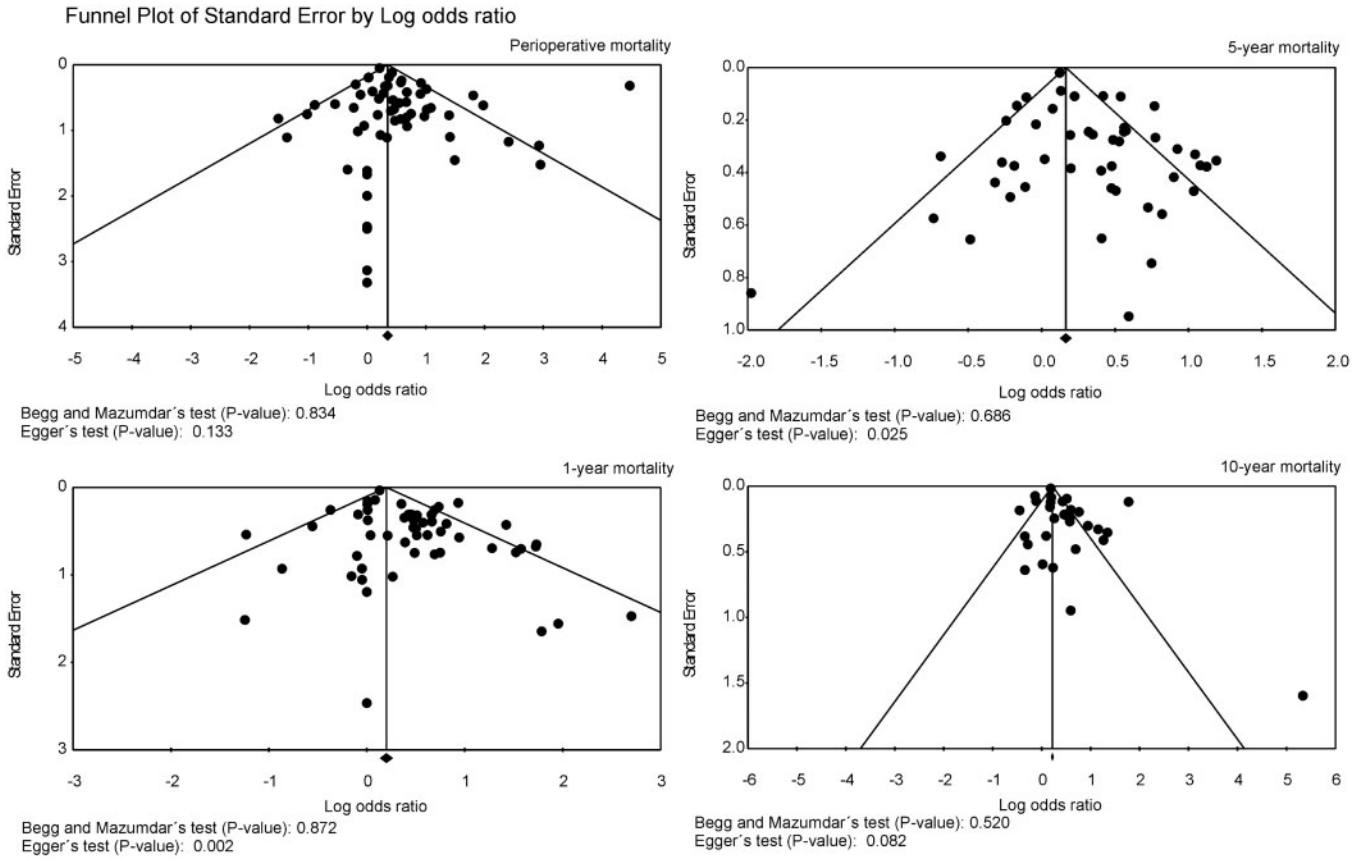


Figure 6: Publication bias. Funnel plot analysis of the outcomes on perioperative mortality, 1-year mortality, 5-year mortality and 10-year mortality.

Table 1: Sensitivity analysis

Perioperative mortality	Studies (*N*)	Patients (*N*)	Summary measures			Heterogeneity	
			OR	95% CI	*P*-value	I^2 (%)	χ^2 *P*-value
Moderate PPM[a]							
Perioperative	32	76 540	1.283	1.095–1.503	<0.001	25.9	0.002
1 year	30	76 494	1.232	1.020–1.489	0.031	66.3	<0.001
5 years	27	75 446	1.231	1.091–1.388	0.001	65.4	<0.001
10 years	18	67 842	1.310	1.028–1.668	0.029	92.6	<0.001
Severe PPM[a]							
Perioperative	26	40 723	2.284	1.566–3.329	<0.001	61.4	<0.001
1 year	24	38 480	2.136	1.575–2.897	<0.001	65.0	<0.001
5 years	18	36 659	1.841	1.401–2.418	<0.001	78.1	<0.001
10 years	13	35 152	1.963	1.173–3.285	<0.001	94.3	<0.001
Severe PPM versus moderate PPM							
Perioperative	23	50 924	1.736	1.252–2.406	0.001	51.2	0.003
1 year	20	48 532	1.532	1.169–2.006	0.002	53.5	0.003
5 years	17	47 536	1.412	1.165–1.710	<0.001	56.7	0.002
10 years	13	46 555	1.476	1.103–1.952	0.009	79.3	<0.001

[a]Compared with non-significant/no PPM.

CI: confidence interval; OR: odds ratio; PPM: patient–prosthesis mismatch.

Considering that we observed an incidence of PPM after SAVR higher than 50% that implies higher rates of mortality, it would be no exaggeration to say that this problem has reached epidemic proportions, and surgeons would have to take measures to counter the risk of PPM after SAVR in order to decrease mortality.

Patient–prosthesis mismatch as a global health issue: different realities in developed and developing countries

Fallon *et al.* [15] observed recently, in the USA, that the incidence of PPM has been decreasing over the years. In 2004, the

Table 2: Sensitivity analysis

Perioperative mortality	Studies (*N*)	Patients (*N*)	Summary measures			Heterogeneity	
			OR	95% CI	*P*-value	I^2 (%)	χ^2 *P*-value
Patients included only within the last 10 years[a]	10	7245	1.750	1.167–2.623	0.007	0.0	0.886
Type of valve[a]							
Only mechanical	14	3431	1.678	1.145–2.457	0.008	40.8	0.088
Only bioprosthesis	9	6251	1.330	0.858–2.060	0.203	0.0	0.491
iEOA measurement[a]							
In vitro	10	15 241	1.787	1.450–2.203	<0.001	9.9	0.350
In vivo	32	77 286	1.272	1.071–1.512	0.006	27.6	0.077
Doppler echocardiography	17	8791	1.799	1.309–2.472	<0.001	0.0	0.565

[a]Comparing moderate/severe PPM with non-significant/no PPM.

CI: confidence interval; iEOA: indexed effective orifice area; OR: odds ratio; PPM: patient–prosthesis mismatch.

incidence of moderate and severe PPM was 60.1% and 13.8% respectively, whereas in 2014, these rates decreased to 46.8% for moderate PPM and 6.2% for severe PPM. Although this represents a 22% reduction in moderate PPM and 55% reduction in severe PPM, their data mean that, even in the USA, more than 50% of the patients still leave the operation room with a considerable degree of PPM. In addition, we must not leave unmentioned that Fallon *et al.* [15] showed that, among the valve models implanted by year, 2 increasingly common implant models were the Magna and Trifecta, which made up 47% and 19%, respectively. However, we must highlight that not all the countries of the world can afford the so-called 'new-generation' prostheses with a better profile. In the largest country of Latin America (Brazil), for example, a non-negligible fraction of the patients are operated on at centres of the public health system, where the patients cannot receive these new generation prostheses simply because they are not available in the system due to the price. It is a very different reality. When it comes to these new models of prostheses (including stentless, sutureless and transcatheter valves), they may well be the reality in Europe and in the USA but not within the public health systems in Latin America (including Brazil), Africa and most part of Asia, where surgeons have to work with other types of prostheses with 'older' technology.

In Europe and in the USA, PPM is often diagnosed in small elderly women experiencing calcific aortic stenosis who are very obese, so that the implantation of a 21-mm biological valve would result in PPM. Surgeons from developed countries might think that these patients would rarely be so active to the point of resulting in a real clinical problem, and thus, they should not worry about this issue. On the other hand, in developing countries, surgeons mostly come across younger patients who are part of the working age population who experience rheumatic heart disease, which means that surgeons throughout the world have to deal with very different patients.

What might be the solution to this problem?

There is no easy answer to this question, but we find that surgical aortic root enlargement (SARE) would allow for larger prosthesis implantation and might be a useful adjunct to SAVR. Some surgeons (maybe most of them) are reluctant to perform such surgical procedure because they think that it implies higher operative mortality rates, although the medical literature has given fresh evidence to the contrary.

Rocha *et al.* [16] showed that SARE does not increase the operative mortality of SAVR among 7039 patients (SAVR, $n = 5185$; SAVR + SARE, $n = 1854$). In-hospital mortality was actually higher in the latter group (3.0% vs 4.3%, $P = 0.008$), but when the cohort was restricted to isolated SAVR with or without SARE, mortality was not statistically significant different (1.1% vs 1.7%, $P = 0.290$). Following adjustment baseline characteristics, SAVR + SARE was not associated with an increased risk of in-hospital mortality when compared with SAVR (OR 1.030, $P = 0.850$). The results were also similar when propensity matching was used for baseline characteristics. Correia *et al.* [17], Penaranda *et al.* [18] and Dhareshwar *et al.* [19] also found that SARE does not increase mortality in the context of SAVR.

Sources of heterogeneity

The statistical heterogeneity in the analyses might be related to various sources, for example, to the type of prosthesis (bioprosthetic or mechanical valve). The type of valve could be a confounding factor, as mechanical valves are implanted more often in younger patients, who generally have a more active lifestyle and faster metabolism, thereby increasing the cardiac workload, the transvalvular flow and, consequently, the gradient across the valve in case of PPM [20]. This rationale is valid to such an extent that there are some studies suggesting that the impact of PPM on postoperative survival is more pronounced in younger patients than in elderly [21, 22]. Curiously, we also observed in our sensitivity analysis a higher risk in the 'PPM' group for mechanical valves but not for biological valves. Just a word of caution: most of the studies were composed of a mixed pool of patients (receiving biological or mechanical valves), and we were not able to break down the data in those studies, otherwise, we could have gone deeper in the analysis.

Another important source of heterogeneity might be the definition of PPM applied in the studies. Indeed, when we carried out subgroup analyses according to the method used to define PPM, we observed that the use of predicted (measured *in vitro* by the manufacturers or *in vivo* from published normal reference values) or measured iEOA had similar impact on the risk of perioperative mortality. On the one hand, our results show that PPM is associated with higher rates of mortality regardless of the definition applied. On the other hand, it is noteworthy that the

analyses according to the methods showed different statistical values of heterogeneity, with Doppler echocardiography demonstrating virtually no heterogeneity.

Furthermore, as the publications included a span of 20 years with patients who underwent surgical procedures over the past 42 years, one might think that PPM was a 'problem of the old days' due to 'antiquated prostheses,' which might well be another source of heterogeneity. As such rationale would seem to be plausible, we decided to carry out a subgroup analysis including patients who underwent SAVR over the past 10 years, which would include virtually only contemporary prostheses. Our analysis showed that PPM seems to remain a 'problem of our days.'

Risk of bias and limitations of the present study

As we described in our previous meta-analytical studies [6–10], 'there are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups. This meta-analysis included data from studies that reflect the "real world" but, on the other hand, are less limited by publication bias, treatment bias, confounders and a certain tendency to overestimate treatment effects observed in the observational studies, since patient selection alters outcome and, thus, makes non-randomized studies less robust'.

Moreover, considerable statistical heterogeneity was observed in all the analyses, but we used the random effects model to counterbalance this aspect. We also observed some publication bias in the outcomes. We must remind the readers of the fact that research with statistically significant results is more likely to be submitted to medical journals and published than work with null or non-significant results, and that the former is also more likely to appear more prominently in English, in higher impact journals. All the aforementioned aspects lead to the appearance of publication biases, but, in this case, we cannot state that the impact of PPM on mortality rates observed in our study is due to bias.

CONCLUSIONS

This meta-analysis found that moderate/severe PPM is associated with a significant increase in perioperative, early-, medium- and long-term mortality rates after SAVR.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Chen J, Lin Y, Kang B, Wang Z. Indexed effective orifice area is a significant predictor of higher mid- and long-term mortality rates following aortic valve replacement in patients with prosthesis-patient mismatch. Eur J Cardiothorac Surg 2014;45:234–40.

[2] Head SJ, Mokhles MM, Osnabrugge RLJ, Pibarot P, Mack MJ, Takkenberg JJM. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J 2012;33:1518–29.

[3] Takagi H, Yamamoto H, Iwata K, Goto SN, Umemoto T. A meta-analysis of effects of prosthesis-patient mismatch after aortic valve replacement on late mortality. Int J Cardiol 2012;159:150–4.

[4] Dayan V, Vignolo G, Soca G, Paganini JJ, Brusisch D, Pibarot P. Predictors and outcomes of prosthesis-patient mismatch after aortic valve replacement. JACC Cardiovasc Imaging 2016;9:924–33.

[5] Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.

[6] Sá MPBO, Oliveira Neto LAP, Nascimento GCS, Vieira EES, Martins GL, Rodrigues KC *et al.* Closure of patent foramen ovale versus medical therapy after cryptogenic stroke: meta-analysis of five randomized controlled trials with 3440 patients. Braz J Cardiovasc Surg 2018;33:89–98.

[7] Sá MP, Cavalcanti PE, Santos HJ, Soares AF, Miranda RG, Araújo ML *et al.* Flow capacity of skeletonized versus pedicled internal thoracic artery in coronary artery bypass graft surgery: systematic review, meta-analysis and meta-regression. Eur J Cardiothorac Surg 2015;48:25–31.

[8] Sá MPBO, Soares AF, Miranda RGA, Araújo ML, Menezes AM, Silva FPV *et al.* Stopping versus continuing acetylsalicylic acid before coronary artery bypass surgery: a systematic review and meta-analysis of 14 randomized controlled trials with 4499 patients. Eur J Cardiothorac Surg 2017;52:838–47.

[9] Sá MPBO, Soares AF, Miranda RGA, Araújo ML, Menezes AM, Silva FPV *et al.* CABG surgery remains the best option for patients with left main coronary disease in comparison with PCI-DES: meta-analysis of randomized controlled trials. Braz J Cardiovasc Surg 2017;32:408–16.

[10] Ferraz Cavalcanti PE, Sá MP, Santos CA, Esmeraldo IM, de Escobar RR, de Menezes AM *et al.* Pulmonary valve replacement after operative repair of tetralogy of Fallot: meta-analysis and meta-regression of 3,118 patients from 48 studies. J Am Coll Cardiol 2013;62:2227–43.

[11] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[12] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105–14.

[13] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[14] Egger M, Davey Smith G, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[15] Fallon JM, DeSimone JP, Brennan JM, O'Brien S, Thibault DP, DiScipio AW *et al.* The incidence and consequence of prosthesis-patient mismatch after surgical aortic valve replacement. Ann Thorac Surg 2018; 106:14–22.

[16] Rocha RV, Manlhiot C, Feindel CM, Yau TM, Mueller B, David TE *et al.* Surgical enlargement of the aortic root does not increase the operative risk of aortic valve replacement. Circulation 2018;137:1585–94.

[17] Correia PM, Coutinho GF, Branco C, Antunes MJ. Long-term follow-up of patients undergoing aortic root enlargement for insertion of a larger prosthesis. Eur J Cardiothorac Surg 2016;50:82–8.

[18] Penaranda JG, Greason KL, Pislaru SV, Schaff HV, Daly RC, Park SJ *et al.* Aortic root enlargement in octogenarian patients results in less patient prosthesis mismatch. Ann Thorac Surg 2014;97:1533–8.

[19] Dhareshwar J, Sundt TM, Dearani JA, Schaff HV, Cook DJ, Orszulak TA. Aortic root enlargement: what are the operative risks? J Thorac Cardiovasc Surg 2007;134:916–24.

[20] Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol 2000;36:1131–41.

[21] Moon MR, Pasque MK, Munfakh NA, Melby SJ, Lawton JS, Moazami N *et al.* Prosthesis-patient mismatch after aortic valve replacement: impact of age and body size on late survival. Ann Thorac Surg 2006;81:481–8.

[22] Mohty D, Dumesnil JG, Echahidi N, Mathieu P, Dagenais F, Voisine P *et al.* Impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: influence of age, obesity, and left ventricular dysfunction. J Am Coll Cardiol 2009;53:39–47.