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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

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Aims Numerous studies have linked prosthesis–patient mismatch (PPM) after aortic valve replacement (AVR) to adverse outcomes. Its correlation with long-term survival has been described but with contradicting results. This systematic review and meta-analysis of observational studies aims to determine the hazard of PPM after AVR.

Methods and results The Medline and EMBase databases were searched for English-language original publications. Two researchers independently screened studies and extracted data. Pooled estimates were obtained by random effects model. Subgroup analyses were performed to detect sources of heterogeneity. The search yielded 348 potentially relevant studies; 34 were included comprising 27 186 patients and 133 141 patient-years. Defined by the universally accredited indexed effective orifice area <0.85 cm^2/m^2, 44.2% of patients were categorized as having PPM. In 34.2 and 9.8% of patients moderate (0.65–0.85 cm^2/m^2) and severe (<0.65 cm^2/m^2) PPM was present, respectively. Prosthesis–patient mismatch was associated with a statistically significant increase in all-cause mortality (HR = 1.34, 95% CI: 1.18–1.51), but only a trend to an increase in cardiac-related mortality (HR = 1.51, 95% CI: 0.88–2.60) was recognized. Analysis by severity of PPM demonstrated that both moderate and severe PPM increased all-cause mortality (HR = 1.19, 95% CI: 1.07–1.33 and HR = 1.84, 95% CI: 1.38–2.45) and cardiac-related mortality (HR = 1.32, 95% CI: 1.02–1.71 and HR = 6.46, 95% CI: 2.79–14.97). Further analyses showed a consistent effect over separate time intervals during follow-up.

Conclusion Prosthesis–patient mismatch is associated with an increase in all-cause and cardiac-related mortality over long-term follow-up. We recommend that current efforts to prevent PPM should receive more emphasis and a widespread acceptance to improve long-term survival after AVR.

Keywords Prosthesis–patient mismatch • Meta-analysis • Aortic valve replacement • Survival

Introduction

The problem of prosthesis–patient mismatch (PPM) after valvular surgery has been a topic of discussion ever since it was first described in 1978.[1] Prosthesis–patient mismatch occurs when the effective orifice area (EOA) of the prosthesis is physiologically too small in relation to the patient's body size, thus resulting in abnormally high post-operative gradients. Hence, the parameter that

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has been used to characterize PPM is the indexed EOA (iEOA), i.e. the EOA of the prosthesis divided by the patient's body surface area.[2–4]

Results from clinical studies demonstrated the negative effect of PPM following aortic valve replacement (AVR) on left ventricular (LV) mass regression, recovery of LV systolic function, New York Heart Association functional class, quality of life, and bioprosthetic valve durability.[5,6] Furthermore, aortic PPM has been associated with increased incidence of operative mortality and late cardiac events.[7–11]

Although, patients with PPM have been shown to have worse haemodynamic and functional outcomes following AVR, survival analyses have not yet uniformly demonstrated that PPM is a predictor of increased mortality.[12,13] In an attempt to further explore the association of PPM and long-term survival after AVR in adults, a systematic review and meta-analysis was performed of both retro- and prospective cohort studies that stratify survival by the presence of PPM.

Methods

The reporting of this systematic review and meta-analysis is according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14]

Search strategy

In January 2011 the Medline and EMBase databases were systematically searched to identify published full-length English studies reporting the long-term survival of patients after AVR, stratified by the presence of PPM. No year of publication exclusion was implied. Studies were identified by a search using the following key words in all fields: 'mismatch OR PPM' AND 'AVR OR aortic valve replacement'. To ensure that no potentially valid studies were missed, the reference lists from reviews and included studies were checked.

Study inclusion

The title and abstract of studies identified by the search were independently screened by two investigators (S.J.H. and M.M.M) using the following criteria: (i) the publication was an original full-article contribution in a peer-reviewed journal; (ii) patients were adults; (iii) patients had undergone AVR with a bioprosthetic or mechanical valve; (iv) PPM was assessed; and (v) long-term survival a minimum of 5 years of follow-up was available and stratified for PPM. Studies reporting only a specific patient group (e.g. patients with renal failure) were excluded. For studies that met these criteria, or in case of uncertainty, the full-texts were further evaluated.

Finally, the study site(s), inclusion period, patient demographics (e.g. age), and diagnosis of potential studies 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.

Data extraction

From each study, we collected the design, number of patients, patient baseline characteristics, type of implanted valve, presence of PPM according to the corresponding iEOA cut-off threshold, follow-up, and patient-years of follow-up. If the number of patient-years was not mentioned, it was calculated by multiplying the number of patients with the mean follow-up. If data were unclear or unavailable, the authors were contacted by e-mail.

Studies that reported results of a PPM (iEOA <0.85, <0.80, or <0.75 cm^2/m^2) vs. no PPM group were included in the 'any PPM' analysis. Studies that reported results for moderate PPM (iEOA 0.65/0.60–0.90/0.85 cm^2/m^2) or severe PPM (iEOA <0.65 or <0.60 cm^2/m^2) separately were included in 'moderate PPM' and 'severe PPM' pooled analyses.

All-cause mortality and cardiac-related mortality were evaluated. Mortality was extracted as an HR. For studies that did not report an HR with corresponding variance, this was extracted per 6-month period from the Kaplan–Meier survival curve by two independent investigators (S.J.H. and R.L.J.O). Survival was obtained up to a representative number of patients at risk.[15,16] The method described by Williamson *et al.*[17] was used to estimate a logarithmic HR with corresponding variance when the number of patients at risk was given at each time frame. If these data were not provided, the method by Parmar *et al.*[18] was used. For each study, we used a spreadsheet programmed to estimate the overall HR with 95% confidence intervals (CI) using an inverse variance-weighted average.[19,20]

Statistical analysis

Statistical analyses were performed using Review Manager version 5.0 for Windows (The Cochrane Collaboration, 2008). A random-effects model was used to obtain pooled estimates. Weighting of studies was based on the standard error (SE) of the logarithmic HR, in which studies with a large SE are weighted less than studies with a small SE. Heterogeneity was examined with the I^2 statistic; whether this was statistically significant in subgroup analyses was explored with the Q test. Sources of heterogeneity were explored by subgroup analyses of study characteristics (study design, study location, year of publication, mean follow-up), patient characteristics (age, type of valve implanted), and the method used to define PPM. Sensitivity analyses were performed for the year of patient inclusion to study the effect of characteristics that may have changed over time.

A separate analysis was performed with obtained HRs and corresponding SEs per 1-year period, calculated with the extraction spreadsheet. An overall pooled HR estimate per separate time period was obtained with a random effects model. Subsequently, the pooled year estimates were again combined to assess whether the HRs were different between intervals.

Funnel plots were produced for visualization of possible publication bias.[21]

Results

The database search yielded 348 potentially relevant studies (*Figure 1*). After the title and abstract were screened, 176 studies were excluded because they did not focus on AVR with bioprosthesis or mechanical valve and the association of PPM with survival. Another 73 studies were excluded because they were not original full-length contributions.

Ninety-nine full-text original articles were reviewed in more detail. Studies were further excluded for various reasons (*Figure 1*), and a remainder of 34 studies were included in the present systematic review (*Table 1*).[4,5,8,10,11,22–50] They comprised a total of 27 186 patients and 133 141 patient-years. In 27 studies with 21 802 patients, the iEOA threshold of 0.85 cm^2/m^2 was used, and 44.2% of patients were diagnosed with PPM. Seven studies

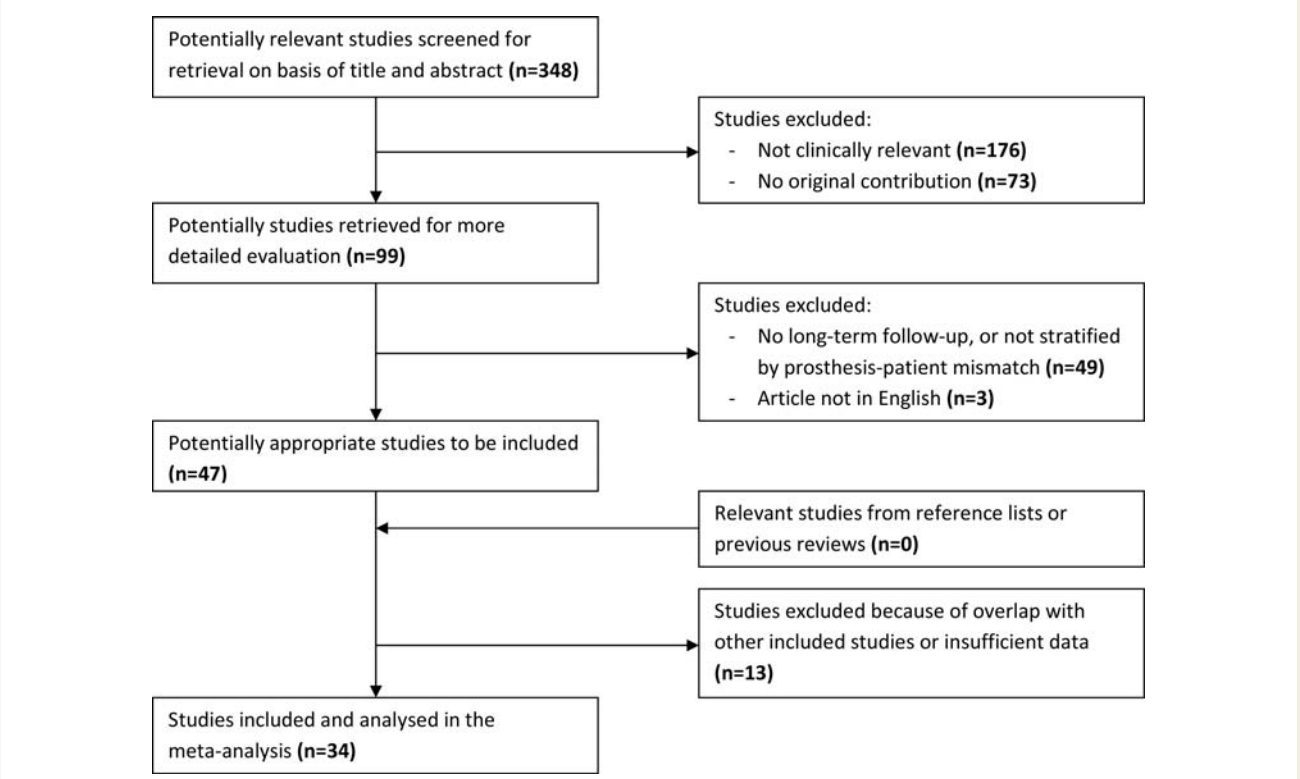

Figure 1 Flow diagram: systematic inclusion of studies for meta-analysis.

found that 34.2% of patients had moderate PPM (>0.65 to >0.85 cm^2/m^2), and 9.8% had severe PPM (<0.65 cm^2/m^2).

Long-term outcomes

Prosthesis–patient mismatch was associated with decreased long-term survival (HR = 1.34, 95% CI: 1.18–1.51) when compared with patients without PPM (*Figure 2*). In studies that stratified outcomes by the severity of PPM, both moderate (HR = 1.19, 95% CI: 1.07–1.33) and severe (HR = 1.84, 95% CI: 1.38–2.45) PPM showed a statistically significant increase in all-cause mortality.

Prosthesis–patient mismatch was associated with a 1.51-fold (95% CI: 0.88–2.60) non-significant increase in cardiac-related mortality (*Figure 3*). Differentiation by moderate and severe PPM demonstrated HRs of 1.32 (95% CI: 1.02–1.71) and 6.46 (95% CI: 2.79–14.97), respectively.

There was a constant hazard over time for all-cause mortality ($P = 0.93$) (*Figure 4*). The cardiac-related analysis showed more variation in HRs over time.

Sensitivity analysis with studies that included patients operated after 1990 and after 1995 demonstrated that the effect was slightly higher with later inclusion, but this difference was not statistically significant (*Table 2*). No analyses were performed for the moderate and severe PPM group for cardiac-related mortality, due to the low number of studies included ($n = 3$).

Sources of heterogeneity

The subgroup analyses detected statistical heterogeneity between bioprosthetic and mechanical valves (*Figure 5*). There was also a statistically significant heterogeneity in the all-cause mortality analysis by determining the EOA, but this is likely due to the low number of studies that used echocardiographic measurement because this heterogeneity was not significant in other analyses. Again, no analyses were performed for the moderate and severe PPM group for cardiac-related mortality.

Publication bias

There was no evidence of publication bias in funnel plots of all-cause and cardiac-related mortality survival assessments (Supplementary material online, *Figure 1*).

Discussion

Prosthesis–patient mismatch has been associated with reduced LV mass regression, impaired physical recovery, and higher incidence of adverse cardiac events after AVR; however, no consistent association between PPM and long-term survival has been established.[13] The current unprecedented meta-analysis shows a significant reduction in overall and cardiac-related long-term survival for patients with PPM after AVR. Moreover, this association increases with PPM severity and appears constant over time.

Table 1 Study characteristics

First author	Year of publication	Study location	Inclusion	Study design	No. of patients	Male gender (%)	Mean age (Years)	Type of valve	iEOA cut-off (cm^2/m^2)	PPM (%)	Mean follow-up (years)	Mortality analysis
Sakamoto	2010	Japan	1996–2008	Retrospective	342	61.7	69.7	Bioprosthetic	<0.85	28	3.2	Overall
Jamieson	2010	Canada	1982–2003	Retrospective	3343	65.7	68.1	Mix	≤0.85	54	6.2	Overall
Flameng	2010	Belgium	1991–2003	Retrospective	564	51	73.6	Bioprosthetic	<0.85	51	6.1[a]	Overall
Bleiziffer	2010	Germany	2000–2007	Retrospective	645	56.4	72.3	Bioprosthetic	<0.85	40	2.7	Cardiac
Urso	2009	Spain	2000–2007	Retrospective	163	49.7	78.0	Mix	≤0.85	43	3.1	Overall
Mrowczynksi	2009	Germany	1995–2004	Retrospective	309	63.6	71.6	Mix	<0.85	66	2.8[a]	Overall
Moon	2009	USA	1992–2007	Retrospective	1399	58.5	71.1	Bioprosthetic	<0.85	62	3.8	Overall
Mohty	2009	Canada	1992–2005	Retrospective	2576	61	68.5	Mix	≤0.85	32	4.8	Both
Mannacio	2009	Italy	1997–2002	Retrospective	157	67.4	66.7	Mix	≤0.75	61	7.0	Overall
Vicchio	2008	Italy	1988–2006	Retrospective	345	33.0	74.5	Mechanical	<0.85	60	4.2	Overall
Tsutsumi	2008	Japan	1990–2009	Retrospective	124	50.8	59.3	Mechanical	<0.85	20	9.1	Cardiac
Ryomoto	2008	Japan	1990–2007	Retrospective	101	45.5	72.4	Mix	≤0.85	34	3.1	Overall
Mascherbauer	2008	Austria	1998–2005	Prospective	361	47.4	69.5	Mix	≤0.80	54	4.2	Overall
Kohsaka	2008	USA	1993–1998	Prospective	469	66.7	56.1	Mechanical	≤0.85	43	7.9[a]	Overall
Kato	2008	Japan	1986–2006	Retrospective	84	50	68.5	Mix	≤0.85	25	4.5	Both
Florath	2008	Germany	1996–2005	Retrospective	533	54.2	71.1	Mix	≤0.85	80	4.7	Overall
Tao	2007	Japan	2000–2005	Retrospective	150	45.3	68.7	Mechanical	≤0.85	23	2.5	Both
Nozohoor	2007	Sweden	1996–2006	Retrospective	1797	—	—	Mix	≤0.85	53	4.3	Overall
Monin	2007	France	1994–2005	Prospective	139	74.1	72	Mix	≤0.85	57	3.7[a]	Overall
Kato	2007	Japan	1990–2005	Retrospective	146	56.8	68.2	Mix	≤0.85	45	4.5	Both
Garcia Fuster	2007	Spain	1994–2005	Retrospective	339	55.8	66.5	Mix	≤0.85	38	6.9	Cardiac
Walther	2006	Germany	1996–2004	Prospective	4131	62.8	58.9	Mix	<0.85	29	5.2	Overall
Tasca	2006	Italy	1997–2003	Prospective	315	49.8	70.8	Mix	≤0.80	47	3.7	Overall
Moon	2006	USA	1992–2004	Retrospective	1400	57.2	66.8	Mix	<0.75	38	3.8	Overall
Mohty	2006	USA	1985–2000	Retrospective	388	31.4	62.3	Mechanical	≤0.85	43	5.3	Overall
Howell	2006	UK	1997–2005	Prospective	1418	61.6	65.5	Mix	<0.85	56	3[a]	Overall
Flameng	2006	Belgium	1985–2003	Retrospective	506	50	73.3	Bioprosthetic	<0.85	20	6.1	Overall
Penta de Peppo	2005	Italy	1991–2002	Prospective	83	71.1	46.5	Mechanical	<0.85	28	6.7	Cardiac
Ruel	2004	Canada	1976–2001	Prospective	1226	58.6	63.8	Mix	≤0.85	77	4.3	Cardiac
Milano	2002	Italy	1981–1995	Retrospective	229	20.1	63.7	Mechanical	≤0.90	73	10	Both
Hanayama	2002	Canada	1990–2000	Prospective	768	66.0	64.7	Mix	<0.60	10	3.5	Overall
Frapier	2000	France	1986–1990	Retrospective	90	62.2	72.6	Bioprosthetic	≤0.85	71	7.3[a]	Both
Rao	2000	Canada	1976–1996	Prospective	2154	60.1	66.1	Bioprosthetic	≤0.75	11	6.2	Both
Pibarot	1998	Canada	1986–1995	Prospective	392	71.7	68.4	Bioprosthetic	≤0.85	45	—	Overall

iEOA, indexed effective orifice area; PPM, prosthesis–patient mismatch.
[a]Median follow-up.

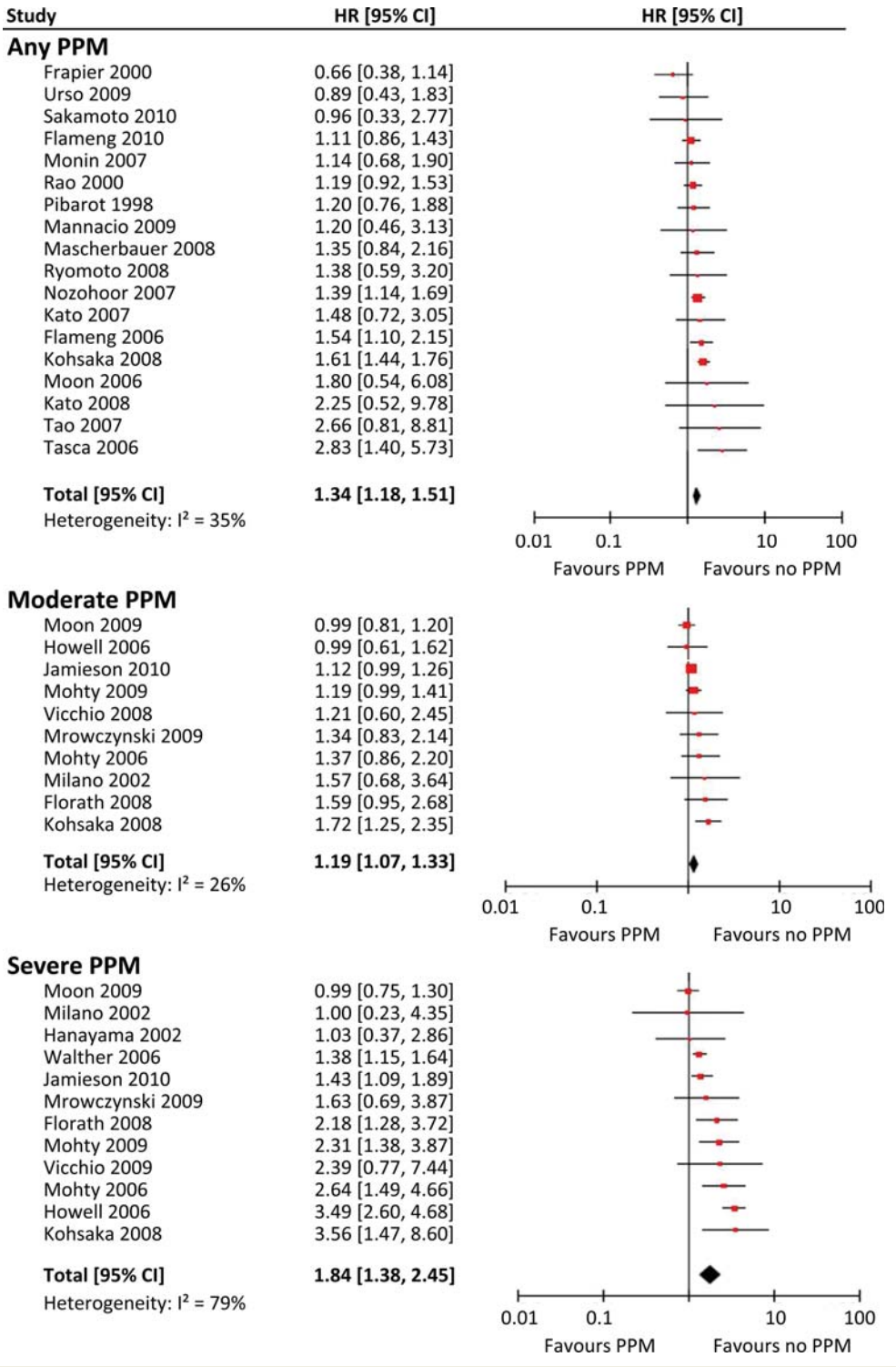

Figure 2 Pooled estimate for all-cause mortality: ratios demonstrate the additional hazard with prosthesis–patient mismatch in relation to a no prosthesis–patient mismatch reference group. Studies that stratified results according to the severity of prosthesis–patient mismatch are analysed individually. HR, hazard ratio; CI, confidence interval; PPM, prosthesis–patient mismatch.

These results have important clinical implications given that PPM is a potentially modifiable risk factor.

The marked statistical significant heterogeneity in the explorative subgroup analyses is mainly related to the type of prosthesis, whether this was a bioprosthetic or mechanical valve. The type of prosthesis could be a confounding factor, as mechanical valves are implanted more often in younger patients. These patients generally have a more active life style and higher metabolic rate,

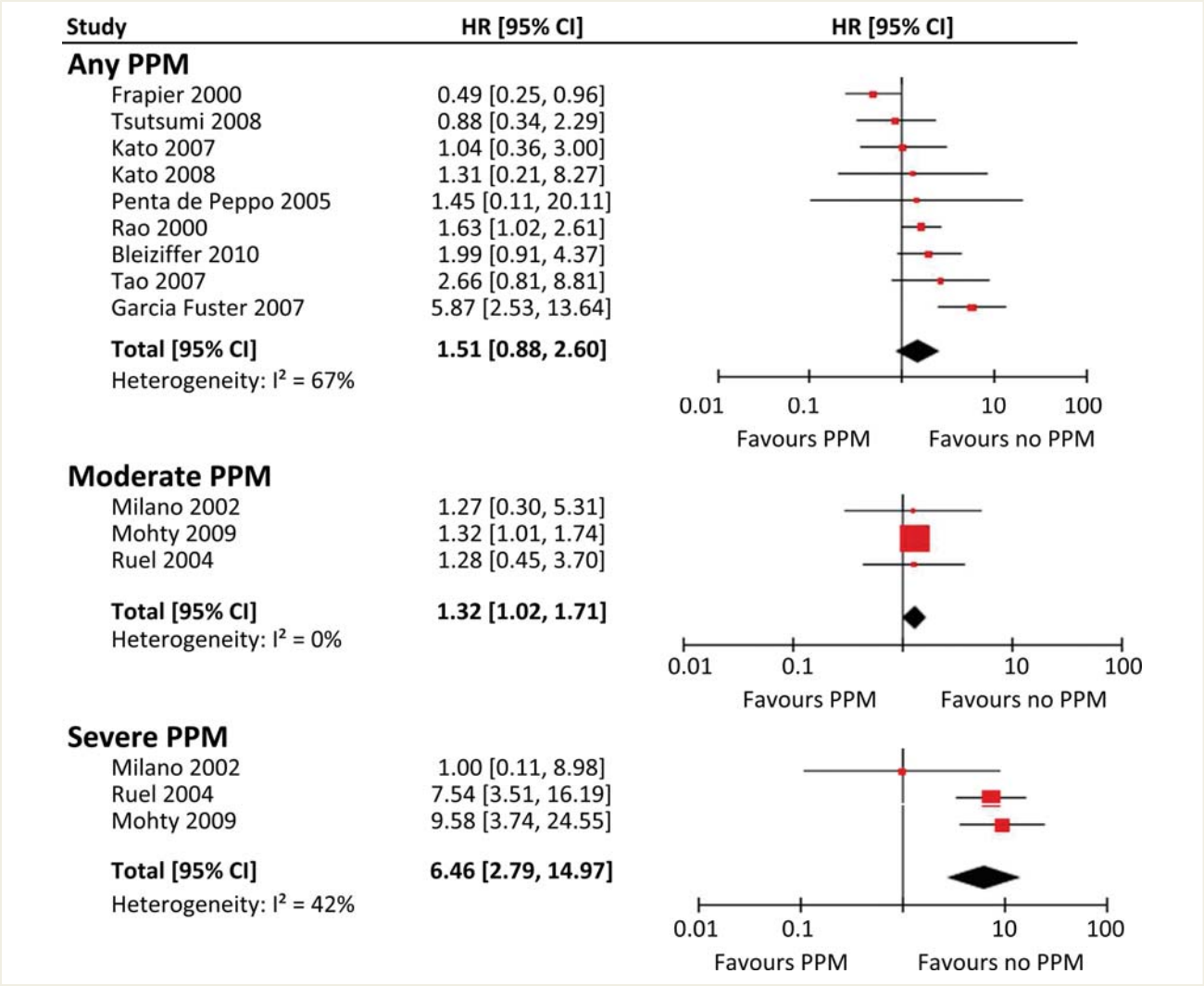

Figure 3 Pooled estimate for cardiac-related mortality: ratios demonstrate the additional hazard with prosthesis–patient mismatch in relation to a no prosthesis–patient mismatch reference group. Studies that stratified results according to the severity of prosthesis–patient mismatch are analysed individually. HR, hazard ratio; CI, confidence interval; PPM, prosthesis–patient mismatch.

thereby increasing the flow and thus the gradient across the valve in case of PPM.[13] In this regard, some studies have suggested that the impact of PPM on post-operative survival is more pronounced in younger patients than in older ones.[31,45] In this study, individual patient data were unavailable and the results from subgroup analyses should be regarded as hypothesis-generating. Future PPM studies should report the incidence and outcomes of patients with a mechanical and bioprosthetic valve separately, so that evidence is more substantiated.

Several factors may explain the association between PPM and reduced survival after AVR. The persistent LV afterload imposed by PPM may impair the post-operative recovery of the coronary flow reserve[51] and hinder the regression of LV hypertrophy and dysfunction.[8,27,52] Other negative outcomes previously reported in association with aortic PPM may have contributed to increase post-operative mortality, including: abnormalities of the Von Willebrand factor and associated bleeding complications,[53,54] higher occurrence of exercise-induced arrhythmias,[44] and higher incidence of late congestive heart failure.[8] Unger *et al.*[55] also observed that, in patients with severe aortic stenosis and concomitant mild mitral regurgitation, PPM is associated with more important residual regurgitation after operation. A recent study showed that PPM is an important risk factor for early structural valve deterioration of aortic bioprostheses.[5] Finally, PPM may also be a surrogate marker for other co-morbidities (e.g. small calcified aortic root).

Prevention of prosthesis–patient mismatch

The observed increased mortality hazard should encourage surgeons to prevent PPM. As opposed to most other risk factors for post-operative mortality, PPM may be avoided or its severity may be reduced by the application of a preventive strategy at the time of operation.[6,56,57] The first step in this strategy is to

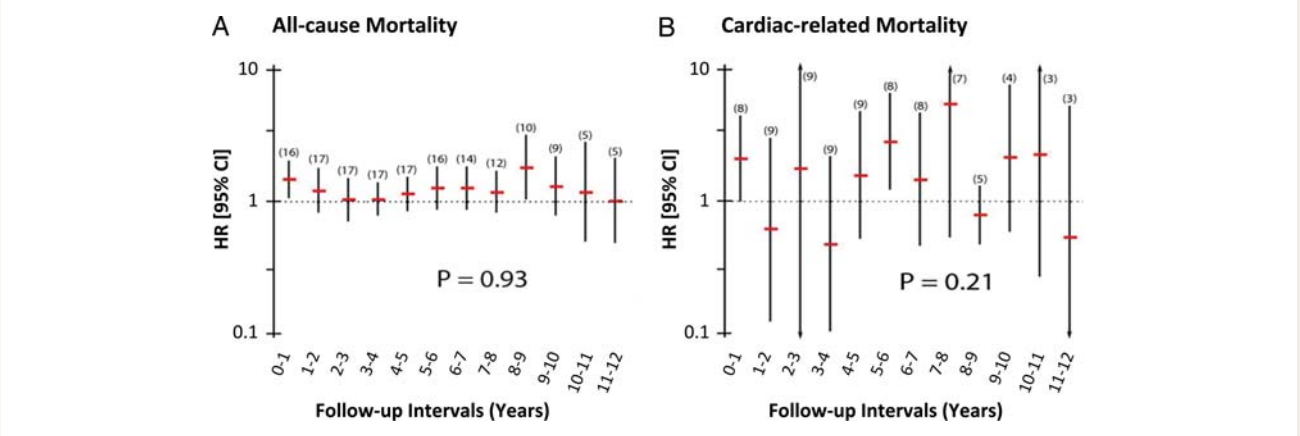

Figure 4 Hazard of mortality in separate time intervals: pooled estimates of studies to detect variance in all-cause (*A*) and cardiac-related (*B*) hazard over separate intervals during follow-up. Within the first year of follow-up, studies were excluded if analyses were performed without hospital mortality. The number of studies with corresponding lengths of follow-up is indicated between brackets. HR, hazard ratio; CI, confidence interval.

Table 2 Sensitivity analysis with patient inclusion after 1990 and 1995

	HR (95% CI)	*P* for heterogeneity
All-cause mortality		
Any PPM		0.71
All studies ($n = 18$)	1.34 (1.18–1.51)	
Patient inclusion >1990 ($n = 13$)	1.43 (1.27–1.61)	
Patient inclusion >1995 ($n = 7$)	1.42 (1.13–1.77)	
Moderate PPM		0.87
All studies ($n = 10$)	1.19 (1.07–1.33)	
Patient inclusion >1990 ($n = 6$)	1.24 (1.03–1.49)	
Patient inclusion >1995 ($n = 3$)	1.27 (0.96–1.69)	
Severe PPM		0.94
All studies ($n = 12$)	1.84 (1.38–2.45)	
Patient inclusion >1990 ($n = 8$)	1.86 (1.26–2.73)	
Patient inclusion >1995 ($n = 4$)	2.06 (1.33–2.39)	
Cardiac-related mortality		
Any PPM		0.67
All studies ($n = 9$)	1.51 (0.88–2.60)	
Patient inclusion >1990 ($n = 6$)	1.97 (1.04–3.74)	
Patient inclusion >1995 ($n = 2$)	2.18 (1.13–4.19)	
Moderate PPM	—[a]	
Severe PPM	—[a]	

[a]Not assessed due to low number of studies. PPM, prosthesis–patient mismatch.

calculate the minimal prosthetic valve EOA required to avoid PPM by multiplying patient's body surface area by 0.85.[6] The second step is to select a prosthetic valve model and size that fits into the patient's aortic annulus/root and that meets the minimum EOA calculated in the first step. It is important to emphasize that the currently available prosthetic valve models are not equivalent in terms of sizing and haemodynamic performance.[6,58] For example, the implantation of a 21-mm valve can produce an EOA ranging between 1.2 ± 0.1 and 2.0 ± 0.7 cm^2, depending on the type of prosthesis.[13,58] Given the significant improvements in prostheses design, contemporary prevention of PPM can largely be accomplished by the implantation of prosthetic valve models

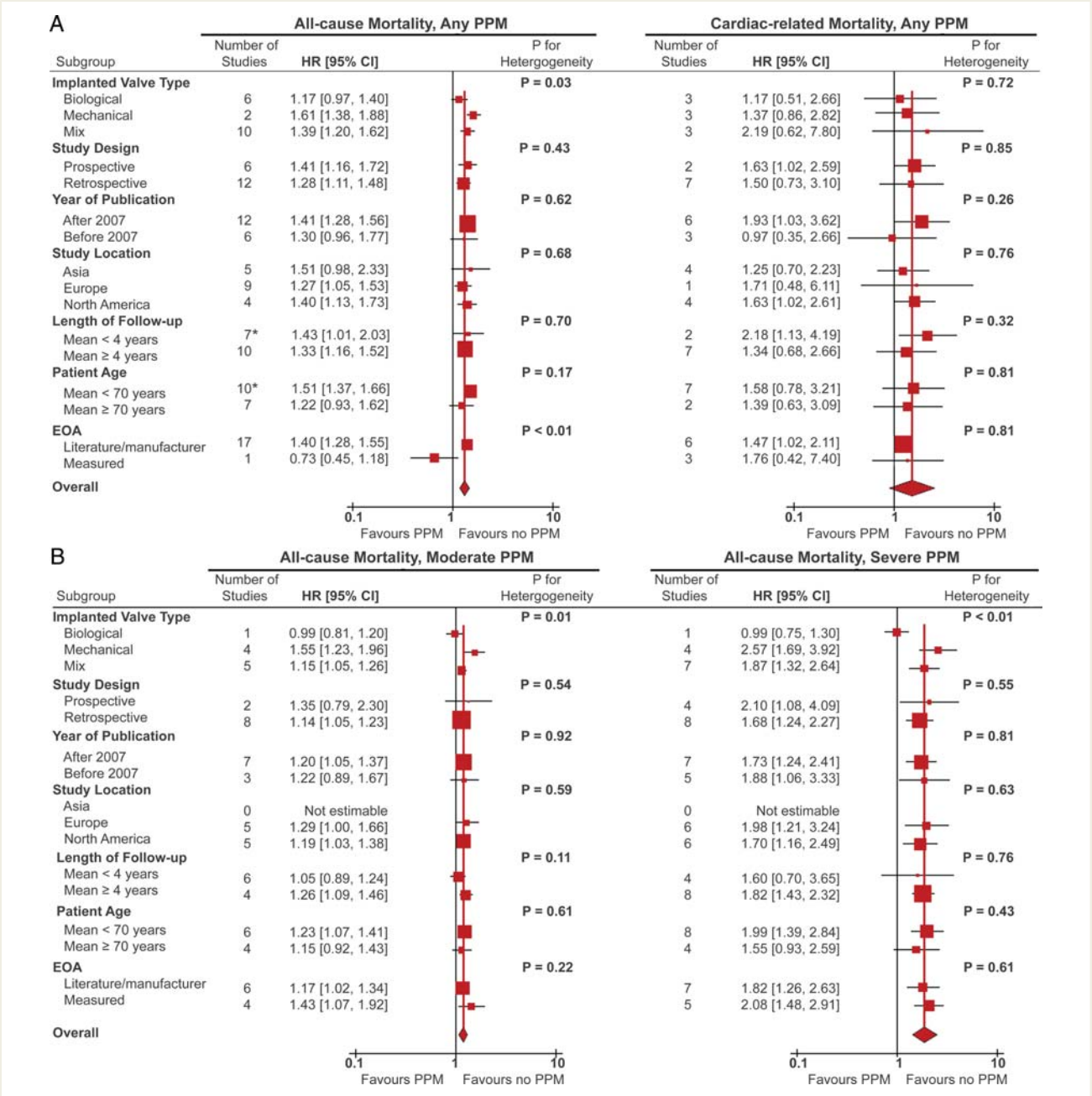

Figure 5 Subgroup analyses to explore the source of heterogeneity: all-cause and cardiac-related results were analysed according to baseline- and study-related factors (*A*). Moderate and severe analyses (*B*) were also performed for all-cause mortality, but not for cardiac-related mortality due to the low number of studies included ($n = 3$). HR, hazard ratio; CI, confidence interval; PPM, prosthesis–patient mismatch. *Analysis excluded one study because of missing data.

providing better haemodynamic performance. In cases where severe PPM cannot be avoided with the use of currently available prosthetic valves, aortic root enlargement may be contemplated if the risk–benefit ratio is considered acceptable. Root enlargement is a surgical technique to accommodate a valve with a larger EOA and thereby avoiding PPM. This procedure has shown to be effective in reducing rates of PPM, although none of these studies have shown that annulus enlargement results in improved long-term survival.[59,60]

Two recent studies have reported that valve haemodynamics are superior with transcatheter aortic valve implantation (TAVI) than with surgical AVR, especially in the subset of patients with small aortic root.[61,62] In these studies, PPM was less frequently present in TAVI patients (11 and 17.8%) than those who underwent AVR (27 and 30.5%, respectively).[61,63] Transcatheter aortic valve implantation may thus provide another potential alternative to avoid PPM in high-risk patients and yet provide a less invasive procedure. Although initial results with TAVI are promising,

Table 3 Literature-derived effective orifice areas of popular valves

	Valve size (mm)					
	19	21	23	25	27	29
Stented bioprostheses						
Mosaic	1.1 ± 0.2	1.2 ± 0.3	1.4 ± 0.3	1.7 ± 0.4	1.8 ± 0.4	2.0 ± 0.4
Hancock II	—	1.2 ± 0.1	1.3 ± 0.2	1.5 ± 0.3	1.6 ± 0.2	1.6 ± 0.2
CE Perimount	1.1 ± 0.3	1.3 ± 0.4	1.5 ± 0.4	1.8 ± 0.4	2.1 ± 0.4	2.2 ± 0.4
CR Magna[a]	1.3 ± 0.3	1.7 ± 0.3	2.1 ± 0.4	2.3 ± 0.5	—	—
Biocor (Epic)[a]	—	1.3 ± 0.3	1.6 ± 0.3	1.8 ± 0.4	—	—
Mitroflow[a]	1.1 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	—	—
Stentless bioprostheses						
Medtronic Freestyle	1.2 ± 0.2	1.4 ± 0.2	1.5 ± 0.3	2.0 ± 0.4	2.3 ± 0.5	—
SJM Toronto SPV	—	1.3 ± 0.3	1.5 ± 0.5	1.7 ± 0.8	2.1 ± 0.7	2.7 ± 1.0
Mechanical prostheses						
Medtronic Hall	1.2 ± 0.2	1.3 ± 0.2	—	—	—	—
Medtronic Advantage[a]	—	1.7 ± 0.2	2.2 ± 0.3	2.8 ± 0.6	3.3 ± 0.7	3.9 ± 0.7
SJM Standard	1.0 ± 0.2	1.4 ± 0.2	1.5 ± 0.5	2.1 ± 0.4	2.7 ± 0.6	3.2 ± 0.3
SJM Regent	1.6 ± 0.4	2.0 ± 0.7	2.2 ± 0.9	2.5 ± 0.9	3.6 ± 0.13	4.4 ± 0.6
On-X	1.5 ± 0.2	1.7 ± 0.4	2.0 ± 0.6	2.4 ± 0.8	3.2 ± 0.6	3.2 ± 0.6
CarboMedics	1.0 ± 0.4	1.5 ± 0.3	1.7 ± 0.3	2.0 ± 0.4	2.5 ± 0.4	2.6 ± 0.4

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CE, Carpentier-Edwards; SJM, St Jude Medical
[a]Results are based on a limited number of patients.

studies to date have only included a small number of patients. These results should thus be interpreted with caution and further studies in larger series of patients are needed to corroborate the usefulness of this procedure for the prevention of PPM.

Prevention of PPM needs to be stressed especially in younger patients. These patients often receive a mechanical valve, and PPM may have a higher impact on survival. Other studies have also emphasized the importance of avoiding PPM in patients with depressed LV systolic function given that they are most vulnerable to the residual LV afterload associated with PPM.[7,64,65]

Haemodynamics and effective orifice area

There is a strong inverse relationship between pressure gradients and iEOA, which has led to a widely accepted iEOA cut-off for defining PPM at 0.85 cm^2/m^2 for moderate and 0.65 cm^2/m^2 for severe PPM. Significant valve gradients at rest or during exercise can be avoided with an iEOA >0.85 cm^2/m^2.[13] It has been shown that patients without PPM have stable haemodynamics, while an increase in gradient has been demonstrated in patients with an iEOA ≤ 0.85 cm^2/m^2, which is even worse in patients with severe PPM (≤ 0.65 cm^2/m^2).[4] Hence, the difference in gradient that is observed at rest between patients with PPM vs. those with no PPM increases dramatically with exercise and is associated with an increase in the flow rate. It should, however, be emphasized that some patients may exhibit a relatively low gradient despite the presence of a small iEOA. This 'pseudo-normalization' of gradient is related to the presence of a low-flow state, similar to what occurs in patients with low-flow, low-gradient aortic stenosis. Patients with PPM and a low gradient are likely at higher risk for adverse events.

Over time valve companies have developed prosthetic valves with better haemodynamic performance and thus with larger EOAs. The older generation of prostheses tends to have smaller EOAs for a given prosthesis size (*Table 3*). This meta-analysis includes studies with a long-time period of patient inclusion. Many centres, however, are still using certain popular valves (e.g. St Jude Medical Standard mechanical valve, CarboMedics mechanical valve, Perimount bioprosthesis, etc). The use of a newer generation of valve prostheses may influence the prevalence of PPM, but, as shown in this analysis, the effect of PPM on mortality will not change.

Company-provided iEAO charts should be interpreted with caution. There are no standards for creating these charts and it has been shown that the most optimistic EOA values are often chosen to be reported.[56,66,67] A more reliable and manufacturer-independent source of reference EOA data has been published by Pibarot *et al.*[58] and is displayed in *Table 3*. This table can be used to predict the average post-operative EOA for each given model and size of prosthesis. This information is particularly useful to anticipate the risk of PPM at the time of operation. If, after calculating the predicted iEOA from *Table 3* (with information of valve model and sizing) and patient's body surface area, the surgeon concludes that there is risk of PPM, and especially of severe PPM, an alternative prosthesis model and/or surgical

technique could be used to avoid PPM or, at least, reduce its severity. A comparison of the different models of prostheses based on the label size in *Table 3* may be misleading given that the dimensions of the sizers and the correspondence with the label prosthesis size may vary from one manufacturer to the other. The establishment of universal sizers and a sizing process that would be the same for all prosthetic valves of all manufacturers would certainly help to implement operative strategies for the prevention of PPM.

Study limitations

To reduce the limitations inherent to meta-analysis, we included multiple databases in the literature search, and used minimal exclusion criteria. As a result, a wide time horizon of patient inclusion is present, which some consider problematic due to changes in cardiac surgery and echocardiography. However, sensitivity analysis by years of patient inclusion could not demonstrate a difference in HRs when only studies with inclusion of patients operated after 1990 and 1995 were used.

First of all, many of the studies were retrospective by design and, therefore, follow-up was incomplete. The method by Williamson *et al.*[17] to estimate HRs from Kaplan–Meier is a widely accepted method recommended in the PRISMA guidelines,[19] but the corresponding HR is not as accurate as to when reported in the original paper. Nonetheless, a subgroup analysis by study design was unable to detect a difference in effect between retro-and prospective studies. The quality of studies was generally high because completion of follow-up was often >95%.

Secondly, only 8 of the 34 studies used EOAs determined by echocardiographic measurement. Although direct measurement is considered a more appropriate method, the other studies used previously reported reference values of the EOA to calculate the iEOA, due to a lack of post-operative echocardiographic data.[5,13] It is possible that some patients may thus have been misclassified with the use of this 'projected' iEOA. However, the utilization of the iEOA measured by Doppler echocardiography early after operation also has limitations. Its accuracy may be altered by LV outflow or chronotropic conditions and by technical pitfalls or measurement errors. Furthermore, data are not available on patients who died in the operative or early post-operative periods. Nevertheless, the subgroup analysis demonstrated no difference in outcomes in studies using measured or reference values, and long-term survival is significantly impaired in both categories of studies (*Figure 5*).

Thirdly, despite significant efforts to instruct authors to report results according to guidelines,[68] outcome reporting in the included studies differed considerably. In some studies hospital or procedure-related mortality was in-or excluded. In several instances, the in-or exclusion was not even specified. Both authors and editors of journals should be encouraged to use uniform definitions and reporting of outcomes. Meta-analysis is an important method in clinical research. With standardized methods and reporting, a larger number of studies can be included in meta-analyses and evidence can be more accurately and less spuriously defined.[69]

Conclusions

Although the adverse effect of PPM on long-term survival has been denied in some studies, this meta-analysis of 34 studies with 27 186 patients demonstrates a significant increase in all-cause and cardiac-related mortality over long-term follow-up after AVR. Current efforts to prevent PPM should therefore receive more emphasis and widespread acceptance to improve long-term survival.

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