

# Drug & Innovation Updates

## Patient – Prosthesis Mismatch

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Patient-prosthesis mismatch (PPM) refers to placement of a small prosthetic aortic valve, relative to the patient's size, resulting in less regression of left ventricular mass, poor valvular hemodynamics, reduced exercise capacity, recurrent congestive heart failure, and increased mortality.<sup>1,2</sup> Indexing the prosthetic valve effective orifice area (EOA) to the patient's body surface area (BSA) [EOA/BSA=EOAi] further defines severity, with an EOAi < 0.6 cm<sup>2</sup>/m<sup>2</sup> being considered severe. Should the selection of a prosthetic aortic valve be determined by the projected EOAi? <sup>3-11</sup> What EOAi is considered clinically significant PPM? For patients with projected PPM, should the surgeon place a stentless valve, homograft, or perform a root enlargement procedure, all of which prolong cardiopulmonary bypass and aortic cross clamp time and increase the potential for bleeding, morbidity, and mortality (2.5% to 7.1%)? <sup>5,6</sup> Investigations including more than 26,000 patients have not consistently shown a correlation between a study's defined PPM and outcome. <sup>4-11</sup> In addition, there is no defined EOAi which would be considered inadequate (i.e. PPM). Depending on the definition of PPM, which varies from < 0.6 to < 1.2 cm<sup>2</sup>/m<sup>2</sup>, the incidence ranges from less than 10% to as high as 35%. <sup>4-11</sup>

Hanayama reported a 3.8% (17/1129) incidence of clinically significant PPM, defined as an elevated transvalvular gradient (mean > 21 mmHg; peak > 38 mmHg) and an EOAi ≤ 0.6 cm<sup>2</sup>/m<sup>2</sup>.<sup>4</sup> These cutoffs represented the lowest deciles of the study group and are also consistent with severe aortic stenosis and the belief that ventricular changes are secondary to increased ventricular afterload.<sup>3,4</sup> Of these 17 patients, six had evidence of prosthetic valve dysfunction and one had an erroneous reading. Of the remaining 10 patients with true PPM, only three (0.27%) had an inadequate reduction in left ventricular mass index. Overall, there was no correlation between long-term mortality and PPM.<sup>4</sup> The authors conclude that clinically significant PPM was uncommon and not associated with worse long-term outcome.<sup>4</sup>

Several authors have reported increased operative or 30-day mortality (1 vs. 2%; 0.14 vs. 2.63%; 5 vs. 8%) for patients with PPM (4,5,7,10). In one investigation, the authors defined PPM as non-existent (> 0.85 cm<sup>2</sup>/m<sup>2</sup>), moderate (> 0.65 to ≤ 0.85 cm<sup>2</sup>/m<sup>2</sup>), or severe (< 0.65 cm<sup>2</sup>/m<sup>2</sup>), the latter two representing 38% of the study population, with only 2% being defined as severe PPM.<sup>5</sup> The short-term mortality was 3%, 6%, and 25.9%, respectively, with a relative risk of 11.4 for the severe group.<sup>5</sup> When combined with an ejection fraction < 40%, the mortality of PPM increased by a factor of seven (when compared to no PPM with normal systolic function) in the moderate and severe groups (mod PPM 1.8 vs. 7.1%; severe PPM 11.3 vs. 77.1%).<sup>5</sup> Although suggestive that PPM is associated with greater short-term mortality, patients with PPM were demographically different and were more likely to have had emergency surgery, concomitant CABG, hypertension, and diabetes.<sup>5</sup> Also in this study, patients with PPM underwent root enlargement more frequently (11.8 vs. 4.2%; p = 0.0004), perhaps contributing to early mortality.<sup>6</sup> Other independent predictors of short term mortality after aortic valve replacement include increased age, chronic lung disease, reduced ejection fraction, NYHA class III/IV, endocarditis, emergency surgery, concomitant CABG, mitral valve surgery, reoperations, and prolonged CPB time (>120 minutes).<sup>5,9</sup>

Measures of long-term outcome, such as exercise capacity, recurrent congestive heart failure, valvular hemodynamics, left ventricular mass regression, and mortality are not consistently associated with PPM or are often only one of several independent predictors of outcome.<sup>8,11-13</sup> Koch did not report an association between PPM (EOAi < 0.85 cm<sup>2</sup>/m<sup>2</sup>) with long term functional capacity based on the Duke Activity Scale Index.<sup>12</sup> Instead, poor function was seen in patients with renal dysfunction, elevated central

venous pressure, and worse preoperative function.<sup>12</sup> Although Pibarot reported that patients with PPM (EOAi < 0.85 cm<sup>2</sup>/m<sup>2</sup>) displayed a worse hemodynamic (greater increase in transvalvular gradient and a lesser increase in EOA) response during stress, there were no differences in cardiac output, exercise capacity, peak oxygen consumption, and anaerobic threshold.<sup>11</sup> Other investigators reported associations between PPM (< 0.8 to < 0.9 cm<sup>2</sup>/m<sup>2</sup>) and recurrent congestive heart failure,<sup>13</sup> and less left ventricular mass regression,<sup>9</sup> however other independent predictors of outcomes included age, preoperative NYHA classification, left ventricular dysfunction, atrial fibrillation, coronary artery disease, tobacco use, greater preoperative left ventricular mass and reoperation status.<sup>13</sup>

Intermediate (1-5 years) and long-term (> 5 years) all-cause mortality is variably associated with PPM<sup>4,7,10,12,13</sup> as well as a host of additional variables (Table 1). Although overall mortality has not been found to be related to PPM,<sup>4,10,12</sup> investigations have demonstrated that valve-related mortality beyond seven years<sup>7</sup> and congestive heart failure-related mortality<sup>13</sup> were significantly greater for patients with PPM. Although there is no randomized prospective study to confirm or refute the association between PPM and outcome, clinicians would agree that there is a subset of patients for which aggressive efforts at preventing PPM is of benefit. Moon evaluated the 10-year mortality of 1,400 patients after aortic valve replacement. In this study, PPM was defined as < 0.75 cm<sup>2</sup>/m<sup>2</sup>.<sup>9</sup> Predictors of operative mortality included age, renal dysfunction, NYHA IV, congestive heart failure, mitral valve surgery, reoperations, and emergent surgery.<sup>9</sup> Long-term predictors of survival were similar, and also included left ventricular systolic dysfunction. When grouped by BSA (< 1.7 m<sup>2</sup>; 1.7 to 2.1 m<sup>2</sup>; and > 2.1 m<sup>2</sup>) and age (< > 60 years old), the authors found that for smaller or older patients, PPM did not impact on survival. However, for younger and medium, or large sized patients, PPM impacted on survival.

Because of varying definitions of PPM, and a host of confounding variables, the data does not demonstrate a consistent association between PPM and clinical outcomes. However, there is probably a subset of patients for which aggressive efforts to ensure a larger EOAi are worthy. This subset may include younger and larger patients who are physically very active, and are expected to have greater longevity (> 7 years). Preventing PPM may also be important in the presence of left ventricular systolic dysfunction. Surgical decisions should consider these variable as well as the daily activities of the patient and the difficulty in performing more aggressive surgery.

Table 1: Confounding variables predicting short- and/or long-term outcome after aortic valve replacement.

Variable	References
NYHA Class III/IV	4,6,7,9,13
Congestive Heart Failure	9
Diabetes Mellitus	9
Chronic Lung Disease	5,9,13
Older Age	6,7,9,12,13
Female	12
Central venous pressure > 12	12
Preoperative Functional Capacity	12
Preoperative Creatinine > 1.3 mg/dl	9,12
Atrial Arrhythmias; Atrial fibrillation	13
LVEF < 40-50%	5,9,13
Endocarditis	5,9
Reoperation	9,12
Coronary Artery Disease/Concomitant CABG	5,6,13
Mitral Procedure; Mitral Disease	6,9
CPB time > 120 minutes	5
Emergency Surgery	5,9

NYHA- New York Heart Association; CABG- coronary artery bypass grafting; CPB- cardiopulmonary bypass

References are online at [www.scahq.org](http://www.scahq.org)

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#### References:

1. Rahimtoola SH: The problem of valve prosthesis-patient mismatch. *Circulation* 1978;58:20-24.
2. David TE: Is prosthesis-patient mismatch a clinically relevant entity? *Circulation* 2005;111:3186-3187.
3. Otto CM, Burwash IG, Legget ME et al: A prospective study of asymptomatic valvular aortic stenosis: Clinical, echocardiographic and exercise predictors of outcome. *Circulation* 1997;95:2262-2270.
4. Hanayama N, Christakis GT, Mallidi HR, Joyner CD, Fremes SE, Morgan CD, Mitoff PRR, Goldman BS: Patient prosthesis mismatch is rare after aortic valve replacement: Valve size may be irrelevant. *Ann Thorac Surg* 2002;73:1822-1829.
5. Blais C, Dumesnil JG, Baillet R, Simard S, Doyle D, Pibarot P: Impact of valve prosthesis-patient mismatch on short-term mortality after aortic valve replacement. *Circulation* 2003;108:983-988.
6. Sommer KE, David TE: Aortic valve replacement with patch enlargement of the aortic annulus. *Ann Thorac Surg* 1997;63:1608-1612.
7. Rao V, Jamieson E, Ivanov J, Armstrong S, David TE: Prosthesis-patient mismatch affects survival after aortic valve replacement. *Circulation* 2000;102:III-5 to III-9.
8. Tasca G, Brunelli F, Cirillo M, DallaTomba M, Mhagna Z, Troise G, Quaini E: Impact of valve prosthesis-patient mismatch on left ventricular mass regression following aortic valve replacement. *Ann Thorac Surg* 2005;79:505-510.
9. Moon MR, Pasque MK, Munfakh NA, Melby SJ, Lawton JS, Moazami N, Codd JE, Crabtree TD, Barner HB, Damiano Jr RJ: Prosthesis-patient mismatch after aortic valve replacement: Impact of age and body size on late survival. *Ann Thorac Surg* 2006;81:481-489.
10. Blackstone EH, Cosgrove DM, Jamieson WRE, Birkmeyer NJ, Lemmer JH Jr, Miller DC, Butchart EG, Rizzoli G, Yacoub M, Chai A: Prosthesis size and long-term survival after aortic valve replacement. *J Thor Cardiovasc Surg* 2003;126:783-796.
11. Pibarot P, Dumesnil JG, Jobin J, Lemieux M, Honos G, Durand L-G: Usefulness of the indexed effective orifice area at rest in predicting an increase in gradient during maximum exercise in patients with bioprosthesis in the aortic valve position. *Am J Cardiol* 1999;83:542-546.
12. Koch CG, Khandwala F, Estafanous FG, Loop FD, Blackstone EH: Impact of prosthesis-patient size on functional recovery after aortic valve replacement. *Circulation* 2005;111:3221-3229.
13. Ruel M, Rubens FD, Masters RG, Pipe AL, Bedard P, Hendry PJ, Lam BK, Burwash IG, Goldstein WG, Brais MP, Keon WJ, Mesana TG: Late incidence and predictors of persistent or recurrent heart failure in patients with aortic prosthetic valves. *J Thorac Cardiovasc Surg* 2004;127:149-159.