Prosthesis-Patient Mismatch in Bovine Pericardial Aortic Valves
Evaluation Using 3 Different Modalities and Associated Medium-Term Outcomes

Satish Jacob Chacko, MD; Asimul H. Ansari, MD; Patrick M. McCarthy, MD; S. Chris Malaisrie, MD; Adin-Cristian Andrei, PhD; Zhi Li, MS; Richard Lee, MD, MBA; Edwin McGee, MD; Robert O. Bonow, MD, MS; Jyothy J. Puthumana, MD

Background—The prevalence of prosthesis-patient mismatch (PPM) and its impact on survival after aortic valve replacement have not been clearly defined. Historically, the presence of PPM was identified from postoperative echocardiograms or preoperative manufacturer-provided charts, resulting in wide discrepancies. The 2009 American Society of Echocardiography (ASE) guidelines proposed an algorithmic approach to calculate PPM. This study compared PPM prevalence and its impact on survival using 3 modalities: (1) the ASE guidelines–suggested algorithm (ASE PPM); (2) the manufacturer-provided charts (M PPM); and (3) the echocardiographically measured, body surface area–indexed, effective orifice area (EOAi PPM) measurement.

Methods and Results—A total of 614 patients underwent aortic valve replacement with bovine pericardial valves from 2004 to 2009 and had normal preoperative systolic function. EOAi PPM was severe if EOAi was ≤0.60 cm²/m², moderate if EOAi was 0.60 to 0.85 cm²/m², and absent (none) if EOAi was ≥0.85 cm²/m². ASE PPM was severe in 22 (3.6%), moderate in 22 (3.6%), and absent (none) in 586 (95.4%). ASE PPM was similar to manufacturer-provided PPM (P=1.00). ASE PPM differed significantly from EOAi PPM (P<0.001), which identified severe mismatch in 170 (29.7%), moderate in 191 (33.4%), and absent (none) in 211 patients (36.9%). Irrespective of the PPM classification method, PPM did not adversely affect midterm survival (average follow-up, 4.1±1.8 years; median, 3.9 years; range, 0.01–8 years). There were no reoperations for PPM.

Conclusions—In patients with normal systolic function undergoing bovine pericardial aortic valve replacement, the prevalence of PPM using the algorithmic-ASE approach was low and correlated well with manufacturer-provided PPM. Independent of the method of PPM assessment, PPM was not associated with medium-term mortality. (Circ Cardiovasc Imaging. 2013;6:776-783.)

Key Words: ASE ■ aortic valve replacement ■ prosthesis-patient mismatch
much lower than the prevalence obtained from postoperative echocardiographic measurements.\textsuperscript{1,5,15}

The 2009 American Society of Echocardiography (ASE) guidelines suggested an alternative algorithmic approach for evaluating prosthetic aortic valves and identifying PPM.\textsuperscript{16} In this model, PPM was only considered if certain other criteria besides EOA were met. It was suggested that if true PPM existed, it would be corroborated by abnormal echocardiographic measurements of aortic jet velocity, acceleration time, and dimensionless velocity index.

The relative prevalence of PPM using these 3 methods has not been studied in patients with normal left ventricular (LV) function undergoing AVR. In this investigation, we determined the prevalence of PPM after AVR using the 3 methods (EOAi, manufacturer based, and ASE guidelines based) and assessed PPM association, as identified by any of the above approaches, with medium-term survival.

\section*{Methods}

Data for this project were obtained from the Cardiovascular Research Database (CARD) in the Clinical Trials Unit of the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital. This database was approved by the Institutional Review Board at Northwestern University (project #STU00012288). Any subjects refusing participation in the project were not included in the analysis. CARD was queried for all patients who underwent a bioprosthetic AVR from April 2004 to December 2009. Survival was determined by CARD surveys, medical record review, and the Social Security Death Index.

There were 1057 patients who met the above criteria, of whom 728 (69\%) underwent AVR with Edwards Lifesciences (Irvine, CA) bovine pericardial valves and had normal preoperative LV systolic function (ejection fraction $\geq$50\%). For 114 of them (16\% of 728), we could not determine PPM status as follows: 32 had transesophageal echocardiography (26 on surgery day and 6 later during hospital stay) that were not appropriate for assessing PPM, whereas 82 patients had transthoracic echocardiography that were of poor quality and could not be interpreted to infer PPM. The remaining 614 patients had a postoperative echocardiogram within 1 month of surgery and represent the basis for this analysis. The analysis cohort and the 114 patients excluded were vastly similar in baseline characteristics and comorbid conditions. We included patients undergoing concomitant surgical procedures, such as mitral valve repair or replacement, tricuspid valve surgery, and coronary artery bypass graft surgery. Of the 614 patients, 340 (55\%) had pure aortic stenosis, 91 (15\%) had pure aortic regurgitation, 121 (20\%) had both aortic stenosis and aortic regurgitation, 33 (5\%) had no aortic regurgitation and no aortic stenosis, and 29 (5\%) could not be classified. Summary of valves implanted is shown in Table 1. Patients with LV systolic dysfunction (ejection fraction $<50\%$) were not included in this analysis because of the possibility that a lower velocity across the valve may inappropriately classify normal valve function, even in the setting of PPM.

PPM per ASE guidelines was defined as peak aortic jet velocity $>3$ m/s, dimensionless velocity index $>0.25$, and acceleration time $<100$ ms. On the basis of algorithmic approach suggested by the ASE,\textsuperscript{16} manufacturer’s guidelines, or EO Ai from postoperative echocardiograms, PPM was categorized as none (absent), moderate, or severe if EO Ai $\geq0.85$, $>0.6$, and $<0.85$ cm$^2$/m$^2$, or $<0.6$ cm$^2$/m$^2$, respectively.\textsuperscript{16} Medium-term all-cause mortality was assessed by PPM degree for each of the 3 classification methods.

In 203 patients (33\% of initial 614), a follow-up echocardiogram was obtained 26 months after AVR (average time, 2.5±1.5 years postoperatively). Early and late postoperative PPM prevalence were compared using the ASE and the EO Ai criteria.

\begin{table}[h]
\centering
\caption{Summary of Valves Implanted}
\begin{tabular}{l|c|c}
\hline
Valve Generation & Frequency & Percent \\
\hline
Carpentier-Edwards Magna & 483 & 78.7 \\
Carpentier-Edwards Perimount Theon & 131 & 21.3 \\
Total & 614 & 100 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Baseline Patient Characteristics by ASE and EO Ai PPM Degree}
\begin{tabular}{l|c|c|c|c|c|c}
\hline
& \multicolumn{3}{c|}{ASE PPM (n=614)} & \multicolumn{3}{c}{EO Ai PPM (n=572)} \\
Variable & None & Moderate & Severe & $P$ Value & None & Moderate & Severe & $P$ Value \\
\hline
Female sex, no. (\%) & 212 (36) & 4 (67) & 10 (45) & 0.21 & 73 (35) & 65 (34) & 77 (45) & 0.047 \\
Age, mean±SD & 67.4±13.8 & 71.8±12.8 & 61.0±15.0 & 0.07 & 66.6±13.5 & 68.1±13.6 & 67.4±14.5 & 0.57 \\
Aortic stenosis, no. (\%) & 446/567 (79) & 6 (100) & 18 (82) & 0.42 & 162/204 (79) & 144/184 (78) & 132/166 (80) & 0.95 \\
Aortic regurgitation, no. (\%) & 216/573 (38) & 2 (33) & 5 (23) & 0.36 & 76/203 (37) & 68/190 (36) & 57/166 (34) & 0.82 \\
Body mass index, kg/m$^2$; mean±SD & 28.0±5.6 & 27.8±6.5 & 30.3±5.6 & 0.19 & 27.6±4.8 & 28.7±6.1 & 28.3±6.0 & 0.17 \\
Diabetes mellitus, no. (\%) & 91 (16) & 1 (17) & 2 (9) & 0.71 & 18 (9) & 39 (20) & 33 (19) & 0.001* \\
Hypertension, no. (\%) & 393 (67) & 4 (67) & 18 (82) & 0.35 & 134 (64) & 134 (70) & 123 (72) & 0.15 \\
Chronic lung disease, no. (\%) & 77 (13) & 0 (0) & 4 (18) & 0.50 & 23 (11) & 22 (12) & 30 (18) & 0.11 \\
Peripheral vascular disease, no. (\%) & 43 (7) & 1 (17) & 4 (18) & 0.13 & 14 (7) & 14 (7) & 14 (8) & 0.84 \\
Cerebrovascular disease, no. (\%) & 84 (14) & 0 (0) & 4 (18) & 0.53 & 29 (14) & 22 (12) & 33 (19) & 0.10 \\
NYHA class III/IV, no. (\%) & 194 (33) & 2 (33) & 4 (18) & 0.34 & 69 (33) & 57 (30) & 58 (34) & 0.67 \\
Prior MI, no. (\%) & 36 (6) & 0 (0) & 0 (0) & 0.40 & 9 (4) & 17 (9) & 8 (5) & 0.11 \\
Coronary artery disease, no. (\%) & 267/577 (46) & 3 (50) & 8/167 (36) & 0.64 & 92/207 (44) & 95/189 (50) & 73/167 (44) & 0.38 \\
Ejection fraction, mean±SD & 61±7 (N=577) & 60.8±7.4 & 62.0±5.1 & 0.82 & 62±7 (n=209) & 61±7 (N=186) & 61±6 (N=167) & 0.13 \\
Ambler score, median (Q1, Q3) & 3.0 (1.0, 7.3) & 6.7 (4.1, 11.7) & 2.1 (0.6, 4.1) & 0.14 & 3.0 (1.0, 5.5) & 4.1 (1.4, 7.3) & 4.1 (1.4, 9.3) & 0.003* \\
\hline
\end{tabular}
\begin{flushleft}
\textsuperscript{*}Statistically significant at 2-sided 5\% alpha level.
ASE indicates American Society of Echocardiography; EO Ai, indexed effective orifice area; MI, myocardial infarction; NYHA, New York Heart Association; and PPM, prosthesis-patient mismatch.
\end{flushleft}
\end{table}

Chacko et al. PPM in Bovine Pericardial Aortic Valves 777
Statistical Analyses
Continuous variables were compared by PPM degree using t tests, Wilcoxon rank-sum test, 1-way ANOVA, or the Kruskal–Wallis test. Categorical variables were compared by PPM degree using the \( \chi^2 \) or Fisher exact test. Medium-term survival for each PPM classification rule was estimated using the Kaplan–Meier method, with group comparisons based on the log-rank test. Late adverse events by PPM severity and classification rule were summarized using rates per 10 person-years of follow-up and compared using binomial distribution–based exact tests. Association among PPM classification methods was assessed using Kendall \( \tau_b \) correlation coefficient. Agreement between PPM classification rules was quantified using Cohen \( \kappa \) statistic. Changes in PPM severity from early to late follow-up were compared using Kendall \( \tau_b \) correlation coefficient for association and Cohen \( \kappa \) statistic for agreement. Mean gradient value comparisons were based on paired t tests. Statistical significance was declared at 5% 2-sided \( \alpha \) level, and no adjustments for multiplicity were made. All statistical analyses were performed using SAS version 9.3 statistical software (SAS Inc, Cary, NC).

Results
Clinical Findings and Outcomes
Patient characteristics, including demographics, pre- and intraoperative information, echocardiography data, and all-cause mortality, are summarized by ASE and EOAi PPM degree in Tables 2 and 3. A detailed description of PPM prevalence by valve size is presented in Figure 1. Of the 614 patients, only 5 (<1%) required an aortic root enlargement (Table 3). The 30-day mortality was 1% (\( n=6 \); predicted mortality by Ambler score 5.6±6.6% on average and a 3% median) in the entire

### Table 3. Intraoperative and Postoperative Characteristics by ASE and EOAi PPM Degree

<table>
<thead>
<tr>
<th>Variable</th>
<th>None (n=564)</th>
<th>Moderate (n=6)</th>
<th>Severe (n=22)</th>
<th>P Value</th>
<th>None (n=211)</th>
<th>Moderate (n=191)</th>
<th>Severe (n=170)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve size, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>44 (8)</td>
<td>2 (33)</td>
<td>4 (18)</td>
<td>0.025</td>
<td>10 (5)</td>
<td>15 (8)</td>
<td>23 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>21</td>
<td>125 (21)</td>
<td>3 (50)</td>
<td>9 (41)</td>
<td></td>
<td>33 (16)</td>
<td>40 (21)</td>
<td>55 (32)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>183 (31)</td>
<td>0 (0)</td>
<td>5 (23)</td>
<td></td>
<td>65 (31)</td>
<td>61 (32)</td>
<td>48 (28)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>149 (25)</td>
<td>1 (17)</td>
<td>4 (18)</td>
<td></td>
<td>62 (29)</td>
<td>45 (24)</td>
<td>33 (19)</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>80 (14)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td>38 (18)</td>
<td>29 (15)</td>
<td>10 (6)</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.89</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Annular enlargement, no. (%)</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Concomitant CABG procedure, no. (%)</td>
<td>201 (34)</td>
<td>3 (50)</td>
<td>9 (41)</td>
<td>0.60</td>
<td>61 (29)</td>
<td>76 (40)</td>
<td>60 (35)</td>
<td>0.07</td>
</tr>
<tr>
<td>Concomitant MV surgery, no. (%)</td>
<td>82 (14)</td>
<td>2 (33)</td>
<td>1 (5)</td>
<td>0.17</td>
<td>19 (9)</td>
<td>24 (13)</td>
<td>35 (21)</td>
<td>0.004</td>
</tr>
<tr>
<td>Concomitant TV surgery, no. (%)</td>
<td>39 (7)</td>
<td>2 (33)</td>
<td>2 (9)</td>
<td>0.036</td>
<td>11 (5)</td>
<td>13 (7)</td>
<td>18 (11)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cross clamp time, min; median (Q1, Q3)</td>
<td>89 (67, 118)</td>
<td>97 (80, 125)</td>
<td>73.0 (60.0, 110.0)</td>
<td>0.36</td>
<td>88 (70, 120)</td>
<td>89 (64, 118)</td>
<td>89 (63, 115)</td>
<td>0.75</td>
</tr>
<tr>
<td>Predischarge complications, no. (%)</td>
<td>220 (38)</td>
<td>5 (83)</td>
<td>8 (36)</td>
<td>0.07</td>
<td>78 (37)</td>
<td>69 (36)</td>
<td>71 (42)</td>
<td>0.50</td>
</tr>
<tr>
<td>Reoperation for bleeding, no. (%)</td>
<td>31 (5)</td>
<td>3 (50)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
<td>12 (6)</td>
<td>7 (4)</td>
<td>9 (5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Prolonged ventilation, no. (%)</td>
<td>41 (7)</td>
<td>1 (17)</td>
<td>2 (9)</td>
<td>0.62</td>
<td>12 (6)</td>
<td>11 (6)</td>
<td>17 (10)</td>
<td>0.19</td>
</tr>
<tr>
<td>Renal failure, no. (%)</td>
<td>17 (3)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.83</td>
<td>6 (3)</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Permanent stroke, no. (%)</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.22</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Transient ischemic attack, no. (%)</td>
<td>4 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.91</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Heart block, no. (%)</td>
<td>25 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.54</td>
<td>7 (3)</td>
<td>10 (5)</td>
<td>8 (5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiac arrest, no. (%)</td>
<td>12 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.75</td>
<td>5 (2)</td>
<td>2 (1)</td>
<td>5 (3)</td>
<td>0.43</td>
</tr>
<tr>
<td>Atrial fibrillation, no. (%)</td>
<td>129 (22)</td>
<td>3 (50)</td>
<td>5 (23)</td>
<td>0.26</td>
<td>46 (22)</td>
<td>44 (23)</td>
<td>39 (23)</td>
<td>0.95</td>
</tr>
<tr>
<td>Readmitted to the ICU, no. (%)</td>
<td>32 (5)</td>
<td>0 (0)</td>
<td>2 (9)</td>
<td>0.64</td>
<td>10 (5)</td>
<td>10 (5)</td>
<td>10 (6)</td>
<td>0.88</td>
</tr>
<tr>
<td>Total hours in ICU, median (Q1, Q3)</td>
<td>32 (24, 55)</td>
<td>25.4 (25.0, 53.2)</td>
<td>30.1 (23.9, 51.0)</td>
<td>0.77</td>
<td>36 (24, 53)</td>
<td>29 (24, 53)</td>
<td>33 (24, 67)</td>
<td>0.42</td>
</tr>
<tr>
<td>Length of stay, median (Q1, Q3)</td>
<td>6.0 (5.0, 8.0)</td>
<td>8.0 (6.0, 14.0)</td>
<td>6.5 (5.0, 7.0)</td>
<td>0.42</td>
<td>6.0 (5.0, 8.0)</td>
<td>6.0 (5.0, 8.0)</td>
<td>6.0 (5.0, 8.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Discharged to home, no. (%)</td>
<td>442/580 (76)</td>
<td>4 (80)</td>
<td>19 (86)</td>
<td>0.53</td>
<td>169/209 (81)</td>
<td>140/189 (74)</td>
<td>126/167 (75)</td>
<td>0.23</td>
</tr>
<tr>
<td>Readmission within 30 days, no.</td>
<td>84/580 (15)</td>
<td>3/5 (60)</td>
<td>4 (18)</td>
<td>0.016</td>
<td>27/209 (13)</td>
<td>35/189 (19)</td>
<td>24/167 (14)</td>
<td>0.28</td>
</tr>
<tr>
<td>30-Day mortality, no. (%)</td>
<td>6 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.87</td>
<td>1 (0.5)</td>
<td>1 (1)</td>
<td>4 (2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Peak velocity, mean±SD</td>
<td>2.3±0.4</td>
<td>3.5±0.3</td>
<td>3.4±0.3</td>
<td>&lt;0.001</td>
<td>2.2±0.5</td>
<td>2.4±0.5</td>
<td>2.6±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient, mean±SD</td>
<td>11.6±4.7 (N=582)</td>
<td>22.8±3.5</td>
<td>25.6±6.4</td>
<td>&lt;0.001</td>
<td>10.1±4.4</td>
<td>12.3±5.0</td>
<td>15.0±6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVI, median (Q1, Q3)</td>
<td>0.5 (0.4, 0.6)</td>
<td>0.4 (0.4, 0.5)</td>
<td>0.4 (0.3, 0.4)</td>
<td>&lt;0.001</td>
<td>0.6 (0.5, 0.7)</td>
<td>0.5 (0.4, 0.6)</td>
<td>0.4 (0.3, 0.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ASE indicates American Society of Echocardiography; CABG, coronary artery bypass graft; DVI, dimensionless velocity index; EOAi, indexed effective orifice area; ICU, intensive care unit; MV, mitral valve; PPM, prosthesis-patient mismatch; and TV, tricuspid valve.
patient cohort, 0.5% (n=1) in the isolated AVR group, and 0% in the AVR/coronary artery bypass graft group. Follow-up duration in the entire cohort was 4.1±1.8 years on average, with a median of 3.9 years and a range of 0.01 to 8 years.

Comparison of the 3 PPM Classification Rules
When assessing association, the prevalence of PPM using the ASE algorithm compared favorably with that based on the manufacturer’s chart estimates (Kendall τ-b=-0.015; SE=0.005; P=1.00; Figure 1). PPM using the EOAI-based algorithm was significantly different from ASE guidelines–based PPM (Kendall τ-b=0.226; SE=0.028; P<0.001). We found no statistically significant difference between EOAI PPM and manufacturer-provided PPM (M PPM; Kendall τ-b=0.039; ASE=0.027; P=0.42), likely because of the reduced statistical power. Agreement between SE algorithm-based PPM and M PPM was low (Cohen κ K=-0.006; SE=0.003; P=1.00). However, although weak, agreement between ASE- and EOAI-based PPM classifications was statistically significant (K=0.08; SE=0.02; P<0.001). Agreement between M PPM and EOAI-based PPM could not be computed because there were no severe M PPM cases among the 572 patients with an EOAI PPM assessment.

PPM by ASE Algorithm
Using the ASE algorithm (Tables 3 and 4), PPM was absent (none) in 586 (95.4%) patients, moderate in 6 (1%), and severe in 22 (3.6%). ASE PPM was associated with smaller prosthesis size (P=0.025; Table 3) and concomitant tricuspid valve surgery (P=0.036; Table 3). There were no statistically significant associations between PPM and age, body mass index, New York Heart Association (NYHA) functional class III/IV, or Ambler score. There was no significant association between ASE PPM and 30-day mortality (P=0.87; Table 3). Medium-term all-cause mortality was not significantly different by PPM degree (P=0.44; Figure 2). Two-year survival rates in the none, moderate, and severe PPM groups were 91%, 67% (only 4 of 6 patients at-risk), and 91%, respectively, whereas 3-year survival rates were 88%, 67%, and 86%, respectively (Figure 2).

PPM by Manufacturer Estimates
Using the manufacturer’s estimates (Table 4), PPM was absent (none) in 611 (99.5%), moderate in 2 (0.3%), and severe in 1 (0.2%). As the vast majority of patients did not have PPM, it was not feasible to determine factors associated with M PPM. There was no significant association between M PPM and 30-day mortality (P=1.00). Medium-term all-cause mortality was not significantly different by PPM degree (P=0.44; Figure 2). Two-year survival rates in the none, moderate, and severe PPM groups were 91%, 100%, and 100%, respectively, whereas 3-year survival rates were 88%, 50% (only 1 of 2 patients at-risk), and 100%, respectively (Figure 2).

PPM by EOAI
Using the EOAI estimates (Table 4), PPM was absent (none) in 211 (36.9%), moderate in 191 (33.4%), and severe in 170 (29.7%). EOAI PPM was associated with smaller prosthesis size (Table 3; P<0.001), female sex (Table 2; P=0.047), diabetes mellitus (P=0.001), and an increased Ambler score (P=0.003). There was no significant association between EOAI PPM and age, body mass index, or NYHA functional class III/IV. There was no significant association between EOAI PPM and 30-day mortality (P=0.22). Medium-term all-cause mortality was not significantly different by PPM degree (Figure 2; P=0.81). Three-year survival rates in the none, moderate, or severe PPM groups were 88%, 87%, and 88%, respectively (Figure 2).

Early Versus Late Follow-Up PPM
Early versus late postoperative echocardiography information is summarized in Figure 3 and Table 5 using both the ASE and the EOAI PPM classification rules. In terms of

Table 4. Prevalence of PPM Degree by Classification Rule

<table>
<thead>
<tr>
<th>PPM Classification Rule</th>
<th>None</th>
<th>Moderate</th>
<th>Severe</th>
<th>PPM Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASE guidelines (n=614)</td>
<td>536</td>
<td>6 (1.0%)</td>
<td>22 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Manufacturer chart (n=614)</td>
<td>611</td>
<td>2 (0.3%)</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>EOAI (N=572)</td>
<td>211</td>
<td>191 (33.4%)</td>
<td>170 (29.7%)</td>
<td></td>
</tr>
</tbody>
</table>

ASE indicates American Society of Echocardiography; EOAI, indexed effective orifice area; and PPM, prosthesis-patient mismatch.
association, early and late ASE PPM was not significantly different (Kendall $\tau$-b=$-0.12; SE=0.20; $P=0.14$). Early and late EOAI PPM was also not significantly different (Kendall $\tau$-b=$-0.07; SE=0.07; $P=0.26$). There was low-to-moderate significant agreement between early and late ASE PPM (Cohen $\kappa$ K=0.21; SE=0.11; $P=0.009$). No significant agreement was found between early and late EOAI-based PPM ($K=0.08; SE=0.05; P=0.14$).

**Postdischarge Adverse Events**

Of the 608 patients alive 30 days postoperatively, we had follow-up information for 538 (88.5%), obtained by clinical follow-up or CARD survey data. Follow-up for vital status was available for all study participants (100%). The rate of PPM-related reoperation was 0%.

The NYHA functional class III/IV incidence and Congestive Heart Failure -related hospital admission were available in 460 and 494 patients, respectively. There were no significant differences in NYHA functional class III/IV incidence among none, moderate, and severe PPM: 3.9%, 0.0%, and 5.9% by the ASE guidelines; 3.1%, 0%, and 5.9% by the ASE guidelines; 3.1%, 6.4%, and 1.6% by EOAI; and 3.9%, 0.0%, and 0.0% by the manufacturer chart, respectively. CHF-hospital admission rates per 10 person-years were also not significantly different for none, moderate, and severe patients with PPM: 0.13, 0, and 0 by the ASE guidelines; 0.06, 0.15, and 0.19 by EOAI; and 0.13, 0, and 0 by the manufacturer chart, respectively.

**Discussion**

Our data indicate that the ASE guidelines–based algorithmic approach for evaluation of PPM compares favorably with the manufacturer-provided estimates of PPM among patients with normal systolic function who undergo AVR with a bovine pericardial aortic valve. Medium-term survival and late adverse events were unrelated to PPM severity as estimated by any of the 3 PPM assessment methods.

---

**Figure 2.** Kaplan–Meier survival curves by prosthesis-patient mismatch (PPM) classification rule and degree. Kaplan–Meier curves depict survivorship using different PPM modalities: (1) American Society of Echocardiography (ASE) guidelines, (2) the manufacturer-provided charts, and (3) the echocardiographically measured, body surface area–indexed, effective orifice area (EOAI PPM), and (4) PPM by any of the 3 modalities. None, moderate, and severe PPM are shown in blue, red and green, respectively. Survivorship at 1, 2, and 3 years after surgery using each PPM modality is included. Irrespective of assessment method, PPM was not a determinant of medium-term mortality.
The risk of PPM is determined by the surgeon’s choice of prosthesis size in the operating room. Because the surgeon cannot predict the postoperative gradient for a specific patient, projected EOA values provided by the manufacturer in the form of a chart have been commonly used during valve implantation to avoid PPM. If the smallest acceptable size valve by the chart does not fit the annulus, the surgeon has to determine whether to perform root enlargement (<1% of our cohort) or whether the risk of a root enlargement is higher than that of PPM (0.5% M PPM in our study). Our findings suggest that the manufacturer-provided projected EOA correlates well with the prevalence of mismatch as assessed by the ASE algorithmic approach.

In a series of 1265 patients undergoing AVR, Blais et al reported a significant increase in early mortality among patients with moderate and severe PPM as judged by EOAi, particularly in those with impaired LV function. Among 805 patients who underwent AVR, Ruel et al17 reported an adjusted hazard ratio of 2.8 for death (confidence interval, 1.1–8.0; P=0.03) in patients with impaired LV function and PPM (defined as EOAi≤0.85 cm²/m²) compared with patients with impaired LV function and no PPM. In addition, there was also a decline in freedom from heart failure symptoms and diminished LV mass regression compared with patients with LV dysfunction but no PPM. However, there were no differences in 10-year survival or clinical symptoms in those with normal LV function. Their series included patients undergoing mechanical (54%), bioprosthetic (39%), and homograft (7%) AVR. Similarly, Mohty et al18 reported that moderate PPM was detrimental only in patients with impaired LV function and severe PPM only in patients <70 years of age, and body mass index <30 kg/m².18

We selected patients with normal LV systolic function who underwent AVR. There were no significant differences in mortality or late morbidity by PPM degree, whether PPM was estimated by the ASE guidelines–based algorithmic approach, the manufacturer-provided estimates, or the EOAi obtained from the postoperative echocardiogram. Given that we excluded patients with impaired LV function, we excluded the higher risk cohort known to have severe adverse consequences from PPM as suggested by prior investigators. Given that only 33% of our patients had follow-up echos, we were not able to adequately assess other possible consequences of PPM, including quality of life or LV mass regression or progression.

### Table 5. Summary of ASE and EOAi PPM Degree for Patients With Late Follow-Up Echos

<table>
<thead>
<tr>
<th>Early PPM degree</th>
<th>Late PPM Degree</th>
<th>Association: Kendall τ-b Correlation Coefficient (SE)</th>
<th>Agreement: Cohen κ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASE guidelines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>189</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total (n)</td>
<td>196</td>
<td>4</td>
</tr>
<tr>
<td><strong>EOAi classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total (n)</td>
<td>66</td>
<td>52</td>
</tr>
</tbody>
</table>

ASE indicates American Society of Echocardiography; EOAi, indexed effective orifice area; and PPM, prosthesis-patient mismatch.
Patient groups with differing valve types have also made it challenging to draw conclusions about PPM. Koch et al.\textsuperscript{20} showed that bioprosthetic valves have a significantly higher indexed EOA than mechanical valves. As such, in studies that enroll patients with different proportions of mechanical and bioprosthetic valves, results are difficult to interpret. Doenst et al.\textsuperscript{21} investigated the EOA of different valve types and showed that size 21 valves from different manufacturers varied significantly in published EOA values. Proper hemodynamic comparison between these different valve types can thus be misleading.

Our experience is heavily weighted toward bovine pericardial supra-annular prosthesis. The Edwards Lifesciences (Irvine, CA) Perimount Magna valve has demonstrated good long-term durability.\textsuperscript{22} As opposed to early generation bioprostheses, these designs include a lower profile and cusp height, as well as a scalloped and compliant sewing ring. These changes may facilitate implantation, particularly in patients with a small aortic annulus and with a narrow sinotubular junction. Our study, which predominantly included patients undergoing AVR using the Perimount Magna valve (78.5%), confirms these findings, with rare use of root enlargement.

Historically, preventive surgical strategies to decrease the risk of PPM have not been shown to improve outcomes. Kulik et al.\textsuperscript{23} prospectively studied 712 patients with small aortic roots after AVR. Aortic root enlargement was performed in 172 of these patients. Root enlargement enabled the insertion of 23-mm prosthesis in 51% of patients and resulted in significantly lower postoperative gradients and larger EOAi (both $P<0.01$) compared with the control group. However, despite a lower incidence of PPM in the root enlargement group, there was no difference in 10-year survival ($85\pm10\%$ versus $86\pm6\%$; $P=0.85$).

**Limitations**

We selected only patients with preserved LV systolic function because of the possibility that a lower velocity across the valve may inappropriately classify normal valve function in the setting of PPM. We thus potentially did not include patients with PPM and concomitant LV dysfunction, which as noted previously represents a higher risk cohort. Hence, our findings are applicable only to patients with preserved systolic function.

As we selected patients who underwent AVR with a bovine pericardial valve to maintain group homogeneity, our findings are applicable only to assessment of PPM in these valves. The contemporary practice across North America is to use bioprosthetic valves for AVR in patients >60 years of age. At our institution, in the past 5 years, 94% of AVR have used bioprosthetic valves, of which 93% were pericardial tissue valves. These valves have shown good long-term durability, as demonstrated by 77% freedom from structural valve dysfunction at 15 years of follow-up.\textsuperscript{24}

Our average duration of follow-up in the entire cohort was 4.1±1.8 years, with a median of 3.9 years and a range of 0.01 to 8 years. Similar studies in the literature that have found worse outcomes in patients with PPM have followed patients for an average of ≥5 years after surgery.\textsuperscript{15} Continued follow-up for adverse outcomes is warranted in our patient population.

As was mentioned above, follow-up information was available for 538/608 patients alive at 30 days (88.5%) through clinical follow-up or CARD survey data. Follow-up for vital status was available for 100% of all study participants. We think that we have adequately captured significant adverse events because NYHA class III/IV incidence and CHF-related hospital admission were available in 460 and 494 patients, respectively. It is possible, however, that some cases may not be captured in our analysis.

Because our patient population is primarily referral based, only a subgroup of 203 (33%) of the total 614 patients had follow-up echocardiograms in our hospital, hence limiting the medium-term echocardiographic data.

In conclusion, our study findings suggest that the prevalence of PPM in patients with normal systolic function undergoing bovine pericardial AVR is rare. PPM prevalence using the ASE algorithm is not significantly different from that based on the manufacturer-provided estimates and hence these charts can be used in routine clinical practice. We have shown that the immediate postoperative echocardiogram provides a reliable method to assess PPM because there is significant early to late agreement in PPM prevalence using the ASE algorithm. Irrespective of the PPM assessment method, PPM was not a determinant of medium-term mortality.

**Disclosures**

Dr McCarthy is consultant for Edwards Lifesciences. The other authors report no conflicts.

**References**


**CLINICAL PERSPECTIVE**

Our data suggest that the prevalence of patient-prosthesis mismatch (PPM) in patients undergoing bioprosthetic aortic valve replacement with preserved systolic function is reduced, and that estimates of PPM using manufacturers’ charts correlate well with postoperative PPM assessment using the algorithm by the American Society of Echocardiography guidelines for evaluation of prosthetic valves. More importantly, American Society of Echocardiography PPM assessment has good medium-term prognosis. We have shown that these patients do not have an increased risk of CHF-related hospital admissions, reoperations, and most importantly, no increase in all-cause medium-term mortality during an average follow-up of 4.1±1.8 years. These data will potentially assist with optimal valve selection in the operating room for patients with normal ejection fraction, knowing that the clinical impact of PPM in these patients over the medium-term is small.
Prosthesis-Patient Mismatch in Bovine Pericardial Aortic Valves: Evaluation Using 3 Different Modalities and Associated Medium-Term Outcomes


Circ Cardiovasc Imaging. 2013;6:776-783; originally published online August 7, 2013; doi: 10.1161/CIRCIMAGING.112.000319

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/6/5/776

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org/subscriptions/