Impact of Prosthesis-Patient Mismatch on the Regression of Secondary Mitral Regurgitation After Isolated Aortic Valve Replacement With a Bioprosthetic Valve in Patients With Severe Aortic Stenosis

Emiliano Angeloni, MD; Giovanni Melina, PhD; Philippe Pibarot, PhD; Umberto Benedetto, MD; Simone Refice, MD; Giuseppino M. Ciavarella, MD; Antonino Roscitano, MD; Riccardo Sinatra, MD; John R. Pepper, FRCS

Background—Secondary mitral regurgitation (SMR) is generally reduced after isolated aortic valve replacement (AVR), but there is important interindividual variability in the magnitude of this reduction. Prosthesis-patient mismatch (PPM) may hinder normalization of left ventricular geometry and pressure overload following AVR, therefore we aimed to investigate the relationship between PPM and regression of SMR following AVR for aortic valve stenosis.

Methods and Results—A total of 419 patients with AS who underwent isolated AVR at 2 institutions and presenting moderate SMR (mitral regurgitant volume 30 to 45 mL/beat) not considered for surgical correction were included in this study. Clinical and echocardiographic follow-up were completed at a median follow-up time of 37 months. PPM was defined as an indexed effective orifice area $<0.85$ cm$^2$/m$^2$ and was found in 170/419 patients (40.6%). There were no significant differences in baseline and operative characteristics between patients with or without PPM. Patients with PPM had less regression of SMR following AVR compared with those with no PPM (change in mitral regurgitant volume: $-11 \pm 4$ versus $-17 \pm 5$ mL, respectively; $P<0.0001$). Variables significantly associated with postoperative change in mitral regurgitant volume on univariable analysis were entered in a multivariable linear regression model, which showed indexed effective orifice area ($P<0.0001$) and left atrial diameter ($P=0.006$) to be independently associated with mitral regurgitant volume improvement. Patients with PPM also had less postoperative improvement in 6-minute walking test distance ($80\pm78$ versus $42\pm41$ m, $P<0.0001$).

Conclusions—PPM is associated with lesser regression of SMR following AVR. This unfavorable effect was associated with worse functional capacity. These findings emphasize the importance of operative strategies aiming to prevent PPM in patients with aortic valve stenosis and concomitant SMR. (Circ Cardiovasc Imaging. 2012;5:36-42.)

Key Words: valves ■ prosthetic valve ■ surgery ■ prosthesis-patient mismatch

Mitral regurgitation is present in about two thirds of patients with aortic stenosis (AS). It can be because of an intrinsic pathology of the mitral apparatus (organic) or secondary to AS (functional). In the latter, increased afterload and left ventricular (LV) remodeling may account for the development of secondary mitral regurgitation (SMR), and its severity is related to the transaortic pressure gradient.

Clinical Perspective on p 42

The surgical management of severe AS with concomitant SMR remains a source of debate. It has been previously shown that the degree of SMR decreases following aortic valve replacement (AVR). In light of these findings and of the incremental operative risk associated with concomitant mitral valve procedures, some surgeons choose to perform isolated AVR and avoid mitral valve repair or replacement in patients with severe AS and concomitant moderate SMR.

The mechanisms for SMR improvement after AVR for AS are related to several factors, including decrease in LV afterload, resulting in lower LV systolic pressures and MR driving forces. The relief of LV pressure overload achieved
by AVR is also associated with regression of LV remodeling and hypertrophy, which may improve coaptation of the mitral valve leaflets. Conditions preventing these processes may affect SMR regression following AVR and may contribute to the development of heart failure symptoms, thus having a negative impact on the early and long-term outcome.\textsuperscript{7,8}

Following AVR, prosthesis-patient mismatch (PPM) is a condition in which the effective orifice area (EOA) of the prosthetic valve implanted is too small in relation to the body size of the recipient,\textsuperscript{9} thus resulting in the persistence of high postoperative transaortic pressure gradients.\textsuperscript{10,11} The residual LV pressure overload imposed by PPM may hinder the normalization of LV geometry and mitral valve/annulus configuration. We hypothesized that PPM hinders the postoperative improvement in SMR following AVR, both directly by the presence of residual LV pressure overload and indirectly by the persistence of mitral annulus dilatation and mitral leaflet tethering associated with PPM-related persistence of adverse LV remodeling.

There are several studies on PPM\textsuperscript{10–14} and several others on the prevalence of SMR in AS and its outcome following AVR,\textsuperscript{2,3,5–8} but only one examined the impact of PPM on the postoperative evolution of concomitant mitral regurgitation SMR,\textsuperscript{3} and this study included a relatively small number (42) of patients. The main objective of this study was thus to examine the relationship between PPM and regression of SMR following AVR for AS.

Methods

Patients’ Selection and Characteristics

We retrospectively analyzed the data of all patients with severe AS who underwent isolated AVR with a bioprosthetic valve between May 2003 and May 2009 at 2 tertiary centers (Royal Brompton Hospital, London, United Kingdom, and Azienda Ospedaliera Policlinico Sant’Andrea, Rome, Italy). Indications for surgery were: presence of symptoms, aortic valve area less than 0.8 cm\textsuperscript{2}, and mean transaortic pressure gradient >50 mm Hg. Only patients presenting with preoperative SMR not addressed by surgery were eligible for this study. We included patients with moderate SMR, quantified as a mitral regurgitant volume (MRV) >29 but <46 mL/beat, in the absence of any recognizable intrinsic leaflet, annular, chordal, or papillary muscle abnormality.\textsuperscript{15} Patients with concomitant coronary artery bypass graft or concomitant mitral valve procedure were excluded.

The prostheses used in this series were the Medtronic Mosaic (Medtronic Inc, Minneapolis, MN) and PERIMOUNT Magna ( Edwards Lifesciences LLC, Irvine, CA), and they were all inserted in a supra-annular fashion.

Doppler-Echocardiographic Assessment

Clinical and echocardiographic assessment were performed prior to AVR and at 12-months after operation and once a year afterward. At each visit, all patients underwent a complete M-mode, bidimensional and Doppler transthoracic echocardiographic assessment by means of a Sonos 7500 system (Phillips Medical Ultrasound). All echocardiographic studies were reviewed in a core laboratory and independently reviewed by 2 echocardiologists. LV ejection fraction was calculated by using the Simpson biplane method. Mitral regurgitation was quantified using MRV calculated with the use of the Doppler volumetric method according to the European Association of Echocardiography and American Society of Echocardiography guidelines.\textsuperscript{15,16} The MRV was calculated as the difference between the mitral and aortic stroke volumes. The aortic stroke volume was calculated by multiplying the LV outflow tract cross-sectional area by the LV outflow tract velocity time integral, measured by pulsed wave Doppler 5 to 10 mm below the aortic annulus. Mitral annular diameter was measured in the apical 4- and 2-chamber views, and mitral annular area was calculated with ellipsoidal formulae. Mitral annular velocity time integral was measured in apical 4-chamber view with pulsed wave Doppler at the level of the annulus. The intraobserver and interobserver variability for the measurement of MRV in the echo core lab were 8±9\% and 10±11\%, respectively.

LV mass was calculated according to the European Association of Echocardiography and American Society of Echocardiography guidelines\textsuperscript{16} and indexed to height\textsuperscript{2,7} (indexed LV mass [LVMi]). The LV outflow tract diameter was measured immediately underneath the prosthetic sewing ring. The in vivo prosthetic valve EOA was calculated with the use of the continuity equation. Calculated values of EOA were then compared with the normal reference values of EOA provided for each type and size of prosthetic valve in the guidelines of the American Society of Echocardiography.\textsuperscript{17} The indexed EOA (EOAi) was calculated by dividing the measured EOA by the patient’s body surface area at the time of follow-up. PPM was defined\textsuperscript{18} absent as EOAi >0.85 cm\textsuperscript{2}/m\textsuperscript{2}, moderate as an EOAi between 0.85 and 0.65 cm\textsuperscript{2}/m\textsuperscript{2} and severe as an EOAi ≤0.65 cm\textsuperscript{2}/m\textsuperscript{2}. The transaortic gradient was measured by means of continuous-wave Doppler echocardiography and the simplified Bernoulli equation. All Doppler measurements were obtained as the average of at least 3 cycles in patients with sinus rhythm or more than 5 cycles in those with atrial fibrillation. A subset of patients (n=86) from the Italian Centre also underwent a 6-minute walk test (6MWLT) according to a standardized procedure before and after AVR.\textsuperscript{19}

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 11.0 (SPSS, Chicago, IL). Variables were checked for normality by means of the Kolmogorov-Smirnov test for normal distribution, and normality was accepted when P≥0.05. Continuous variables are shown as mean with standard deviation. All categorical data were displayed as percentages. Differences in baseline characteristics were compared using the \( \chi^2 \) test for categorical variables and \( t \) test for continuous variables. A paired \( t \) test was used to compare the walked distance before and after AVR. Reduction of SMR was quantified as MRV decrease (preoperative MRV-MRV at last follow-up). Univariable linear regression analysis was performed to identify factors correlated with MRV decrease following AVR. A multivariable regression analysis was performed to identify factors independently associated with MRV decrease after AVR. Age, sex, and clinically relevant variables with a probability value <0.2 on univariable analysis were incorporated into the multivariable model. In the univariable and multivariable regression analyses, data were expressed as regression coefficient \( \beta \) and probability value, statistical significance was defined as \( P \leq 0.05 \). For these analyses, PPM was expressed with the use of the continuous variable (ie, EOAi rather than with the use of the dichotomous variable [PPM versus no PPM]). Cumulative survival was estimated with the stratified Kaplan-Meier method and compared between groups using a log-rank test.

Results

Study Sample

We retrospectively analyzed the data of 931 consecutive patients undergoing isolated AVR at the 2 participating institutions; of those, 233 (25\%) patients were excluded because they did not have severe AS. Among 698 remaining patients, 427 (61.2\%) had concomitant SMR with a MRV comprised between 30 and 45 mL/beat. Eight/427 (1.9\%) of
these patients died early after AVR and were not included in the study. The flow chart of the enrolling process is depicted in Figure 1.

The study population thus consisted of 419 hospital survivors (295 males, mean age 66.9±14.2 years) who underwent AVR with a stented bioprosthetic valve. After AVR, the measured EOA was within normal range in all patients, and none of the patients had >mild aortic regurgitation. Hence, none of the patients included in this series had significant acquired prosthetic valve dysfunction. Of these patients, 170/419 (40.6%) had PPM, and 41/419 patients (9.8%) had severe PPM. All patients had complete clinical and echocardiographic follow-up with a median follow-up time of 37 (maximum 84) months. There were no statistically significant differences in age, sex distribution, body surface area, preoperative LV ejection fraction, LVMi, degree of MR (MRV and severity) replacement; AS, aortic stenosis; SMR, secondary mitral regurgitation.

**Factors Associated With Less Postoperative Regression of SMR**

After a median follow-up of 37 months (range: 12 to 60 months), mean MRV absolute decrease was 14.4±4.9 mL/beat in the whole series. The decrease in MRV was significantly \( P<0.0001 \) (Figure 2) smaller in the PPM group (11.2±3.9 mL/beat) compared with the no-PPM group (16.5±4.5 mL/beat). The increase in mitral valve leaflet coaptation length was also smaller in patients with PPM (+0.8±2.3 versus +2.1±2.2 mm; \( P<0.0001 \)). At postoperative follow-up, peak transprosthetic gradient was, as expected, significantly higher (33±12 versus 26±10 mm Hg, \( P<0.0001 \)), and LVMi was higher (120±46 and 111±32 g/m\(^2.7\); \( P=0.03 \)) in the PPM group compared with the no-PPM group. Of note, the magnitude of LVMi regression (defined as preoperative LVMi-LVMi at last follow-up) was, on average, 2-fold smaller (10±10 versus 20±20 g/m\(^2.7\); \( P<0.0001 \)) in the PPM group. Furthermore, although baseline values of systolic pulmonary arterial pressure (PAPs) were similar in both groups (PPM: 36.2±12.5 mm Hg versus no PPM: 35.8±11.4; \( P=0.54 \)); the postoperative values were significantly higher in the PPM group (33.5±10.1 mm Hg versus 27.8±9.6 mm Hg; \( P=0.008 \)).

In the subset of 86 patients who underwent 6MWT distance, preoperative walked distance was 272±103 and 276.4±98 m in the PPM (n=35/86, 40.7%) and no-PPM (n=51/86, 59.3%) group, respectively (\( P=0.83 \)). These patients showed similar baseline characteristics (age, sex, comorbidities, and echo measurements) and similar rate of PPM (35/86, 40.7%) when compared with the general population of the study.

At follow-up, patients with PPM walked 314±86 m (\( P=0.07 \); with respect to preoperative), while those with no PPM walked 356±103 m (\( P=0.0001 \); with respect to preoperative). The increase in 6MWT distance (last postoperative follow-up–preoperative) was larger in the PPM group (80±78 m versus 42±41 m, \( P<0.0001 \)).

A linear regression analysis was performed with postoperative MRV decrease as dependent variable and preoperative confounding factors, operative data, and EOAi as independent variables. At univariable analysis (Table 2), variables significantly associated with postoperative MRV decrease were: preoperative left atrial diameter (\( P=0.001 \)), preoperative LV ejection fraction (\( P=0.01 \)), and prosthetic valve EOAi (\( P=0.0001 \)). Baseline MRV, LV end-diastolic diameter, and LV ejection fraction were not significantly correlated to MRV decrease but were nonetheless included in the multivariate model because they were considered to be clinically relevant and had a probability value <0.2 on univariable analysis. On multivariable regression analysis (Table 2), only EOAi (\( P<0.0001 \)) and preoperative left atrial diameter (\( P=0.006 \)) were found to be independently associated with the decrease in MRV after AVR. The multivariable model significantly predicted MRV decrease at follow-up (model \( R^2=61; P<0.0001 \)). Goodness-of-fit of the model was evaluated by means of the coefficient of determination \( R^2 \) adjusted for the number of independent variables entered in the model (\( \hat{R}^2 \) adjusted=0.76).

### Impact of Impaired Regression of SMR on Clinical Outcomes

Patients having a postoperative decrease in MRV <15 mL (111/419, 26.5%) had similar survival compared with those with a MRV decrease >15 mL (3-year survival rate: 81±2.6 versus 82±1.8%); however, they had significantly less regression of LVMi during follow-up (+3±8 versus −49±16 g/m\(^2.7\) for patients with and without MRV decrease ≤15 mL, respectively). In the subset of 86 patients who underwent 6MWT, the walked distance at follow-up was shorter in the patients with an MRV decrease ≤15 mL (268±99 versus 299±104 meters; \( P=0.005 \)).

### Discussion

The main finding of this study was that PPM is associated with lesser regression of SMR following isolated AVR in
patients with severe AS and concomitant SMR. This association was independent of other preoperative and operative variables. Furthermore, patients with PPM also had less regression of LV hypertrophy and less improvement in 6MWT distance, thus further emphasizing the clinical relevance of these results.

The surgical management of patients with severe AS and concomitant moderate SMR remains controversial. On the one hand, a significant proportion (almost 30%) of these patients have persistent SMR after isolated AVR, and this may negatively impact their clinical outcome.5–8,20–22 On the other hand, a more aggressive approach involving both AVR and mitral valve procedure is associated with an increased operative risk.4–6 In light of this important dilemma, it is crucial to identify and, whenever it is possible, to modify the risk factors associated with the postoperative persistence of SMR.

Impact of Prosthesis-Patient Mismatch
In patients with ischemic heart disease, the persistence or recurrence of SMR after coronary artery bypass graft surgery is associated with worse outcome.23 In the context of patients with severe AS and concomitant moderate SMR undergoing

Table 1. Preoperative and Postoperative Follow-Up Data Stratified for Presence of Prosthesis-Patient Mismatch

<table>
<thead>
<tr>
<th>Variables</th>
<th>PPM (n=170)</th>
<th>No-PPM (n=249)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67.2±15.2</td>
<td>66.9±12.7</td>
<td>0.83</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>121 (71)</td>
<td>169 (68)</td>
<td>0.59</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.82±0.26</td>
<td>1.81±0.34</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>102 (60)</td>
<td>151 (61)</td>
<td>0.92</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>26 (15)</td>
<td>43 (17)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>90 (53)</td>
<td>129 (52)</td>
<td>0.92</td>
</tr>
<tr>
<td>Chronic renal disease, n (%)</td>
<td>6 (3.5)</td>
<td>11 (4.1)</td>
<td>0.84</td>
</tr>
<tr>
<td>Chronic pulmonary disease, n (%)</td>
<td>18 (10)</td>
<td>29 (12)</td>
<td>0.63</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>8 (5)</td>
<td>15 (6)</td>
<td>0.83</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.3±12.4</td>
<td>63.6±11.6</td>
<td>0.27</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>48.2±7.6</td>
<td>48.8±7.1</td>
<td>0.38</td>
</tr>
<tr>
<td>LVMi, g/m²²</td>
<td>131.6±35.2</td>
<td>129.2±39.8</td>
<td>0.53</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.58±0.18</td>
<td>0.64±0.21</td>
<td>0.04</td>
</tr>
<tr>
<td>Trans-aortic peak gradient, mm Hg</td>
<td>79.1±21.2</td>
<td>77.4±22.3</td>
<td>0.44</td>
</tr>
<tr>
<td>Trans-aortic mean gradient, mm Hg</td>
<td>59.8±8.6</td>
<td>58.3±7.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Mitral RV, ml/beat</td>
<td>36.9±2.8</td>
<td>36.3±3.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Mitral leaflet coaptation length, mm</td>
<td>5.6±1.9</td>
<td>5.8±2.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure, mm Hg</td>
<td>36.2±12.5</td>
<td>35.8±11.4</td>
<td>0.54</td>
</tr>
<tr>
<td>Prosthetic valve size, mm</td>
<td>21.2±1.5</td>
<td>23.1±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative follow-up data</td>
<td></td>
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</tr>
<tr>
<td>EOAi, cm²/m²²</td>
<td>0.77±0.06</td>
<td>0.97±0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trans-aortic peak gradient, mm Hg</td>
<td>33.2±11.7</td>
<td>25.6±10.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trans-aortic mean gradient, mm Hg</td>
<td>21.8±6.4</td>
<td>17.1±4.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitral RV, mean (ml/beat)</td>
<td>25.1±3.3</td>
<td>20.4±5.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitral RV decrease, mean (ml/beat)</td>
<td>11.2±3.9</td>
<td>16.5±4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitral leaflet coaptation length, mm</td>
<td>6.4±2.6</td>
<td>7.9±2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitral coaptation length increase, mm</td>
<td>+0.8±2.3</td>
<td>+2.1±2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.5±11.7</td>
<td>63.1±14.6</td>
<td>0.65</td>
</tr>
<tr>
<td>LVMi, g/m²²</td>
<td>119.7±46.4</td>
<td>111.4±32.3</td>
<td>0.03</td>
</tr>
<tr>
<td>LVMi regression, g/m²²</td>
<td>9.5±10.1</td>
<td>20.2±19.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure, mm Hg</td>
<td>33.5±10.1</td>
<td>27.8±9.6</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as the mean±standard deviation, categorical variables as frequency and (percentage). PPM indicates prosthesis-patient mismatch; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic volume; LVMi, Left ventricular mass index; RV, Regurgitant volume; EOAi, effective orifice area index.
isolated AVR, several studies\textsuperscript{5,8,21,22} have reported that the postoperative persistence of SMR is associated with increased risk of heart failure symptoms and cardiac-related death. The degree of SMR generally improves after isolated AVR but to a variable extent depending on the patient.\textsuperscript{3} The fall in LV cavity pressure achieved by AVR translates into an immediate decrease in the transmirtal systolic pressure gradient and thereby into a reduction in SMR. Of note, this is also corroborated by the drop in pulmonary artery systolic pressures found among patients without PPM. Moreover, the regression of LV hypertrophy and positive remodeling of LV cavity and mitral annulus that occurs after AVR further contribute to the reduction of SMR; however, owing to various preoperative and operative factors (including PPM), the reduction of transaortic gradient, and thus of LV pressure overload, as well as the regression of LV hypertrophy and dilatation varies extensively from one patient to the other and is often incomplete, thereby explaining the persistence of SMR in a substantial proportion of the patients. In the present study, 28\% (117/419) of the patients had no or minimal reduction in MRV (ie, <15 mL) after isolated AVR, and PPM was found to be the main independent determinant of the postoperative persistence of SMR. These findings corroborate and extend those of Unger and colleagues,\textsuperscript{3} obtained in a smaller series of patients with mitral regurgitation of diverse aetiologies (ie, primary and secondary). In the latter study, the negative association between PPM and regression of mitral regurgitation following AVR was observed only in the subset of patients with organic mitral regurgitation but not in that with SMR. This may be because of, at least in part, the small number (21) of patients with SMR included in this previous study. In contrast, in the present study that included 419 patients with SMR, we found a strong independent association between PPM and lesser regression of SMR following AVR. The results of the 6MWT obtained in a subset of patients further confirm the clinical impact of both SMR persistence and PPM. The residual LV pressure overload related to PPM can hinder the postoperative normalization of LV mass and geometry, as illustrated by the results of the present study. Indeed, patients with PPM had less regression of LV hypertrophy and less improvement in mitral leaflet coaptation length after MVR compared with those with no PPM, despite similar baseline preoperative values in both groups.

This negative impact on LV remodeling and mitral valve geometry, combined with the persistence of elevated LV systolic pressure and thus of high systolic transmitral gradient, may explain the smaller reduction in SMR in the patients with PPM. These results have important clinical implications, given that, as opposed to other risk factors identified in the present study or in previous studies with regard to the post-AVR persistence of SMR, PPM is the only one that can be prevented at the time of operation.

Enlarged left atrial diameter was also found to be independently associated with less improvement in SMR after AVR in the present study, which is consistent with the findings of previous studies.\textsuperscript{7,8} Enlarged left atrial size is most likely a surrogate marker for more advanced/longstanding LV remodeling, fibrosis, and/or dysfunction, with potentially irreversible alteration in mitral annulus/valve geometry.

**Clinical Implications**

The results of this study underline the importance of avoiding PPM in patients with severe AS and concomitant SMR undergoing AVR. PPM can be prevented, or its severity can

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**Table 2. Univariable and Multivariable Analysis of Variables Associated With Mitral Regurgitant Volume Decrease After Aortic Valve Replacement**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable Analysis</th>
<th></th>
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<th></th>
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<th>Multivariable Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>( \beta ) Coefficient</td>
<td>95% CI</td>
<td>( P ) Value</td>
<td>( \beta ) Coefficient</td>
<td>95% CI</td>
<td>( P ) Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.17</td>
<td>-0.37 to 0.04</td>
<td>0.11</td>
<td>-0.10</td>
<td>-0.21 to 0.09</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>-0.14</td>
<td>-0.29 to 0.02</td>
<td>0.13</td>
<td>-0.04</td>
<td>-0.15 to 0.19</td>
<td>0.22</td>
<td></td>
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<tr>
<td>Preoperative LVEDD</td>
<td>0.04</td>
<td>-0.09 to 0.12</td>
<td>0.18</td>
<td>0.06</td>
<td>-0.21 to 0.18</td>
<td>0.17</td>
<td></td>
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<tr>
<td>Preoperative LVEF</td>
<td>0.31</td>
<td>0.06 to 0.52</td>
<td>0.01</td>
<td>0.17</td>
<td>-0.01 to 0.25</td>
<td>0.09</td>
<td></td>
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<tr>
<td>Preoperative LA diameter</td>
<td>-0.42</td>
<td>-0.58 to -0.23</td>
<td>0.0001</td>
<td>-0.32</td>
<td>-0.24 to -0.46</td>
<td>0.006</td>
<td></td>
<td></td>
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<tr>
<td>Preoperative MRV</td>
<td>0.07</td>
<td>0.01 to 0.24</td>
<td>0.15</td>
<td>0.11</td>
<td>-0.01 to 0.16</td>
<td>0.09</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Prosthetic valve EOAi</td>
<td>0.41</td>
<td>0.22 to 0.57</td>
<td>0.0001</td>
<td>0.28</td>
<td>0.17 to 0.49</td>
<td>&lt;0.0001</td>
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CI indicates confidence interval; LA, left atrial; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MRV, mitral regurgitant volume; EOAi, indexed effective orifice area index.
be reduced, by implanting a prosthesis with a better hemo-
dynamic performance (eg, a newer generation of stented
bioprosthesis or bileaflet mechanical valve implanted in
a complete supra-annular position or a stentless bioprosthesis)
or by performing a root enlargement procedure; however,
the latter procedure should be considered only when PPM
cannot be avoided with the use of currently available pro-
theses and when the risk-benefit ratio is considered favorable.
In patients with moderate SMR and severely enlarged left
atrium, a procedure targeting the mitral valve apparatus/
annulus (restrictive annuloplasty, etc) should be envisioned
besides the performance of AVR and prevention of PPM.

Limitations
This is not a randomized study, and, despite the use of a priori
definitions of end points and covariates, selection bias or
unidentified confounders may have influenced the results. As
our findings are based on an observational cohort, they may
not necessarily be generalizable to all patients with concom-
itant moderate SMR undergoing isolated AVR. These find-
ings are also not generalizable to patients with concomitant
organic mitral regurgitation. Further studies are needed to
confirm and extend these findings.

Conclusion
The results of this study suggest that PPM may hinder the
regression of SMR in patients with severe AS undergoing
isolated AVR. This negative effect was also associated with
worse functional capacity. These findings provide a strong
impetus for the application of preventive strategies at the
time of operation to avoid PPM or reduce it severer.

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References
1. Come PC, Riley MF, Ferguson JF, Morgan JP, McKay RG. Prediction of
severity of aortic stenosis: accuracy of multiple non-invasive parameters.
2. Brener SJ, Duffy CI, Thomas JD, Stewart WJ. Progression of aortic
stenosis in 394 patients: relation to changes in myocardial and mitral
Cosyns B, Dedodbeecker C, Lancellotti P. Impact of prosthesis-patient
mismatch on mitral regurgitation after aortic valve replacement. *Heart.*
EM, Sisto D, Lisosky DS, Cochran RP, Clough RA, Boss RA Jr, Kramer
RS, O’Connor GT; Northern New England Cardiovascular Disease Study
Group. Outcomes of patients undergoing concomitant aortic and mitral
S155–S162.
5. Brasch AV, Khan SS, DeRobertis MA, Kong JH, Chiu J, Siegel
RJ. Change in mitral regurgitation severity after aortic valve replace-
Doyle D. Moderate degree mitral regurgitation impact early mid-term
clinical outcome in patients undergoing isolated aortic valve replacement
7. Waissbren EC, Stevens LM, Avery EG, Picard MH, Vlahakes GJ,
Aguiarot AK. Changes in mitral regurgitation after replacement of the
history and predictors of outcome in patients with concomitant functional
mitral regurgitation at the time of aortic valve replacement. *Circulation*.
2006;114:1541–1546.
10. Pibarot P, Dumensil JG. The relevance of prosthesis-patient mismatch
764–765.
11. Vicchio M, Della Corte A, De Santo LS, De Feo M, Caianellio G,
Scardone M, Cotrufo M. Prosthesis-patient mismatch in the elderly:
2008;86:1791–1797.
Germann E, Chan F, Lichtenstein SV. Effect of prosthesis-patient
mismatch on long-term survival with aortic valve replacement: assessment
FW, Gunnert M. Patient-prosthesis mismatch affects short- and
Pibarot P. Impact of prosthesis-patient mismatch on long-term survival after
aortic valve replacement: influence of age, obesity, and left ventric-
15. Lancellotti P, Moura L, Piera LA, Aguirre-Popescu BA, Tribouilloy
C, Hagendorff A, Monshou JL, Badano L, Zamborini JL. European Asso-
ciation of Echocardiography. European Association of Echocardiography
recommendations for the assessment of valvular regurgitation. Part 2:
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pelikka
PA, Picard MH, Roman MJ, Seward J, Shaniwes J, Solomon S, Spencer
KT, St John Sutton M, Stewart W; American Society of Echocardiogra-
phy’s Nomenclature and Standards Committee; Task Force on Chamber
Quantification; American College of Cardiology Echocardiography Commit-
tee; American Heart Association; European Association of Echocar-
diography; European Society of Cardiology. Recommendations for
Dumensil JG, Foster E, Gottlieben JS, Grayburn PA, Khandheria BK,
Levine RA, Marx GR, Miller FA Jr., Nakatani S, Quiñones MA,
Rakowski H, Rodriguez LL, Swaminathan M, Waggener AD, Weissman
NJ, Zabaloigtia M. American Society of Echocardiography’s Guidelines
and Standards Committee; Task Force on Prosthetic Valves; American
College of Cardiology Cardiovascular Imaging Committee; Cardiac
Imaging Committee of the American Heart Association; European Asso-
ciation of Echocardiography; Japanese Society of Cardiology; Japanese
Society of Echocardiography; Canadian Society of Echocardiography;
American College of Cardiology Foundation; American Heart Asso-
ciation; European Association of Echocardiography; European Society of
Cardiology; Japanese Society of Echocardiography; Canadian Society
of Echocardiography. Recommendations for evaluation of prosthetic valves
with echocardiography and doppler ultrasound: a report from the
American Society of Echocardiography’s Guidelines and Standards Com-
18. Pibarot P, Dumensil JG. Prosthesis-patient mismatch: definition, clinical
SI, Kronenberg MW, Boss RB, Kohn RM, Guillette M, Greenberg B,
Woods PA, Bournass MG; the SOLVD Investigators. Prediction of mor-
tality and morbidity with a 6-minute walk test in patients with left
20. Wan CK, Suri RM, Li Z, Orszulak TA, Daly RC, Schaff HV, Sundt
TM III. Management of moderate functional mitral regurgitation at the
time of aortic valve replacement: Is concomitant mitral valve repair necessary?
21. Barreiro CJ, Patel ND, Fitton TP, Williams JA, Bonde PN, Chan V,
Alejo DE, Gott VL, Baumgartner WA. Aortic valve replacement and
concomitant mitral valve regurgitation in the elderly: impact on survival and
22. Caballero-Borrego J, Gómez-Doblas J, Caballero-Canellio G,
Francisco-Jiménez JM, Melero JM, Porras C, Olalla E, De Teresa Galván
E. Incidence, associated factors and evolution of non-severe functional mitral regurgi-

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Patients with severe aortic stenosis undergoing aortic valve replacement often show a degree of functional mitral regurgitation. Surgery on the aortic valve is expected to reduce the pressure overload of the left ventricle, thus resulting in some improvement of mitral regurgitation. In the settings of aortic prosthesis-patient mismatch, that reduction of left ventricular systolic pressures is lower because of the smaller aortic effective orifice area of such patients, and this large study demonstrates that aortic prosthesis-patient mismatch has a negative impact on the regression of concomitant functional mitral regurgitation. The clinical impact of the less effective postoperative regression of mitral regurgitation was demonstrated by the worse performance at the 6-minute walk test, although 3-year survival was similar. Left atrial diameter was the only preoperative factor associated with postoperative regression of mitral regurgitation, suggesting that one should take this into consideration in planning whether concomitant mitral valve surgery is indicated in the presence of an enlarged left atrium and at least moderate mitral regurgitation; however, given that double valve surgery carries increased morbidity and mortality risk, prosthesis-patient mismatch is a potentially modifiable risk factor that should be considered when performing aortic valve replacement and techniques employed to optimize valve size and profile.
Impact of Prosthesis-Patient Mismatch on the Regression of Secondary Mitral Regurgitation After Isolated Aortic Valve Replacement With a Bioprosthetic Valve in Patients With Severe Aortic Stenosis

Emiliano Angeloni, Giovanni Melina, Philippe Pibarot, Umberto Benedetto, Simone Refice, Giuseppino M. Ciavarella, Antonino Roscitano, Riccardo Sinatra and John R. Pepper

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