Valve Prosthesis–Patient Mismatch (VP–PM)

A Long-Term Perspective

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The concept/phenomenon of valve prosthesis/patient mismatch (VP–PM), described in 1978, has stood the test of time. From that time to 2011, VP–PM has received a great deal of attention but studies have come to varying conclusions. This is largely because of the determination of prosthetic heart valve area [called effective orifice area index (EOAi)] by projection rather than by actual measurement, variable criteria to assess severity of EOAi and the timing of determination of EOAi. All prosthetic heart valves have some degree of VP–PM which must be placed in a proper clinical perspective. This can be done by determining its effects on function and outcomes. For mortality one needs to focus especially on severe/critical degree of VP–PM and determine the cause of death was due to VP–PM. For the period “beyond 2011” a road map is suggested that will have uniformity of assessment of VP–PM and a focusing on the important goals of VP–PM. (J Am Coll Cardiol 2012;60:1123–35)

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“Everything should be made as simple as possible, but not simpler.”

—Albert Einstein (1)

In 1978

The original paper that described valve prosthesis–patient mismatch (VP–PM) (2) stated that “Mismatch can be considered to be present when the effective prosthetic heart valve area, after insertion into the patient, is less than that of a normal human valve”; all prosthetic heart valves (PHVs) are smaller than normal and thus are inherently stenotic. Two issues were emphasized. 1) The PHV mismatch was stated to be “usually mild to moderate in severity and often of no immediate clinical significance.” However, it could be severe (as was illustrated in Table 1 of that paper) when, after mitral valve replacement, the effective orifice area (EOA) (also previously referred to as PHV area) was severely reduced from 1.8 cm² to 1.1 cm² (range, 0.89 to 0.54 cm²/m²); 14 months later, the patient had deteriorated symptomatically, and at rest, the mean left atrial pressure had increased from 16 to 37 mm Hg. 2) The EOA should be corrected for body size (EOA index [EOAi]), which, in the 1960s, was done for native aortic valve stenosis (AS) (3,4). This was illustrated in Figure 1 (of that publication and in this paper) where after aortic valve replacement (AVR) for severe isolated aortic regurgitation, the EOA averaged 1.7 cm² (range, 1.3 to 2.7 cm²) but, when corrected for body size, averaged 1.0 cm²/m² and ranged from 0.7 to 1.6 cm²/m².

Other issues that were discussed included the following:

1. The mismatch was related to 2 factors: a) the PHV that can be inserted in most patients has an effective EOAi that is less than that of the normal human valve and; b) the in vivo effective EOAi is further reduced because of endothelialization and tissue ingrowth.

2. The EOA is only 1 factor that has to be taken into account when selecting a valve replacement device for an individual patient.

3. The relationship between gradient and the EOA and PHV size is complex (Fig. 2).

4. In patients with moderate to severe VP mismatch severe to very severe VP–PM may develop with additional tissue ingrowth or thrombotic material, which could result in deterioration of cardiac function, which may be acute and could result in prosthetic thrombosis and sudden death.

5. When evaluating the poor late results of valve replacement on survival, functional class or left ventricular (LV) function it is important to evaluate PHV function and mismatch accurately.
After 1978

VP–PM: AVR. With the publication of VP–PM, surgeons were more careful and inserted the largest PHV that could be safely inserted. PHVs with improved hemodynamic profile have also been developed (5–7). As a result, severe VP–PM has become a much less common clinical problem (5,8).

The overwhelming majority of a large number of scientific publications have related to the aortic valve and not to mitral valve VP–PM; therefore, the rest of this paper is restricted to aortic VP–PM.

In conclusion, VP–PM has become an accepted part of the clinical aspect of PHV implantation.

How should VP–PM be measured? Different parameters have been evaluated to assess for the severity of VP–PM. The most commonly used measures of valve size are the EOA, the projected EOAi, and the geometric orifice area (GOA).

MEASURED EOAi. The EOA is a physiological parameter analogous to the native AVA. The EOA can be measured both invasively (2–4,9) and noninvasively using echocardiography/Doppler (10) or magnetic resonance imaging (11). The most readily and widely available method is echocardiography/Doppler. The accuracy of EOA echocardiographic measurement in the bioprosthetic valve is limited by the same pitfalls that are present in the measurement of the AVA; in particular, the LV outflow tract diameter may be more difficult to measure because of reverberation artifact caused by the prosthetic heart valve, but in these instances, the sewing ring diameter may be a sufficient surrogate (12). In the bileaflet mechanical valve, the central orifice may produce a high-velocity jet, causing an underestimation of the EOA. Pressure recovery occurs with both bioprosthetic and mechanical heart valves, although the implications of pressure recovery in PHVs have not yet been clarified. The EOAi has a complex relationship with the mean gradient across the aortic valve and PHV (2,13–15) (Figs. 2 and 3).

PROJECTED EOAi. The projected EOAi is obtained by using reference data to find the EOA for the labeled size and model of the PHV that was implanted. This is indexed to the patient’s body surface area to obtain the projected EOAi. Reference data are derived primarily from in vivo measurements of the EOA in patients but also have been obtained using in vitro measurements under pulsatile flow conditions (16). Dumesnil et al. (15) demonstrated a strong correlation between the projected EOA and the in vivo EOA (r = 0.86, SEE ±0.16 cm², p < 0.005). Pibarot et al. (17) also demonstrated strong correlation between the projected EOAi and the in vivo EOA (r = 0.84, SEE ±0.15 cm²; EOA in vivo, r = 0.95; EOA in vitro, r = −0.03; p < 0.0001). In a later study, Pibarot et al. (18) demonstrated that the projected EOA had a 73% sensitivity and 80% specificity for the prediction of combined moderate and severe (frequently referred to as moderate-severe) VP–PM. Bleiziffer et al. (19) also investigated the correlation between the projected EOAi and the measured EOAi. They demonstrated a more modest correlation between the projected EOAi and the measured EOAi when using their own institutional data (r = 0.62, p < 0.001) as well as published reference data (r = 0.53). Importantly, their institutional data came from echocardiography/Doppler studies performed 6 months post-operatively. The projected EOAi had a sensitivity of 54% and specificity of 83% for predicting severe VP–PM.

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(20), the correlation between the projected EOAi and the EOAi measured within 10 days post-operatively was \( r = 0.49 \) (p value not specified). The projected EOAi had a discriminative power of 0.72 for predicting severe VP–PM and sensitivity of 75% and specificity of 52% for predicting moderate-severe VP–PM.

In conclusion, using the projected EOAi in predicting severe VP–PM has a low accuracy; therefore, the projected EOAi to determine prediction and outcomes of VP–PM is of limited value. Other limitations of the projected EOAi are discussed in the section on prediction of VP–PM.

**Geometric orifice area.** The GOA is an ex vivo measurement of the valve area. It is obtained by measuring the diameter of the inner surface of the PHV and calculating the area, assuming the valve has a circular orifice. The GOA also does not take into account factors related to leaflet or disk resistance or to morphological changes in the valve after implantation. Furthermore, the valve may change shape as it is manipulated during implantation. GOA does not predict VP–PM (19).

**Assessment of severity of VP–PM.** With aortic VP–PM, the obstruction to the LV outflow tract is similar to that seen with native AS. Thus, the severity of aortic VP–PM should be assessed by the same criteria as for severe AS. In the 1960s, severe AS was defined: 1) by Braunwald as the mean aortic valve gradient, measured after energy recovery (also called pressure recovery), of \( \geq 50 \) mm Hg (3), which was corroborated in a large series of patients in 1988 (21); and 2) as an AVA index of \( \leq 0.6 \) cm\(^2\)/m\(^2\) determined after energy recovery (4). In 1989, a review of the natural history of unoperated AS in the previous 2 decades provided criteria for assessment of severity of AS (22). Measured stroke volume in stable patients undergoing diagnostic cardiac catheterization on 2 consecutive days showed a mean change of 9%, and, thus, it was thought that the confidence interval of calculated AVA was \( \sim 10\% \) (23). A prospective natural history of AS showed poor outcomes in those with severe AS using the criteria of \( \leq 0.7 \) cm\(^2\)/m\(^2\) (24); however, the valve area of all patients in that study was \( <0.63 \) cm\(^2\)/m\(^2\), as measured at cardiac catheterization. Other studies also assessed severe VP–PM as an EOAi of \( \leq 0.6 \) cm\(^2\)/m\(^2\) (20,25–32). Braunwald (33) has recommended critical AS is an AVA index of \( \leq 0.4 \) cm\(^2\)/m\(^2\) after energy recovery. In 2000, on the basis of the EOAi previously referred to as PHV index, by echocardiography/Doppler the diagnosis of severe and moderate VP–PM was stated to be \( \leq 0.65 \) cm\(^2\)/m\(^2\) and \( >0.65 \) to 0.85 cm\(^2\)/m\(^2\), respectively (14). These values were picked by computer on the basis of the average of increase of mean gradient in relation to the reduction in valve area (Fig. 3). There was a spread of gradient at these levels of the EOAi, but the confidence intervals of the gradients and the EOAi were not presented. Moreover, none of the techniques used to measure the EOA allow for calculating the mean EOA to hundredth of a centimeter; the precision, reproducibility, and variability of values of an EOAi of 0.65 and 0.85 have not been presented.

**In conclusion,** the severity of aortic VP–PM should be assessed by the same criteria that are used for native AS (Table 1) (22,33–37). There is an increasing consensus that severe AS should be assessed by the criterion of an AVAi of \( \leq 0.6 \) cm\(^2\)/m\(^2\) (36); it would be reasonable that this criterion should also be applied to severe VP–PM.

**When should the severity of VP–PM be determined?**Virmani (38) has described that there are 4 phases of physiological healing of mechanical and bioprosthetic PHVs; they are: “platelet and fibrin deposition, inflammation, granulation tissue, and finally encapsulation. Long-term device fibrous encapsulation with extension to adjacent tissues add to structural stability.” Bioprosthetic valves undergo morphological changes of both the tissue material as well as the supporting structures, which may contribute to VP–PM. Valve leaflets become covered by fibrin, platelets, and other cellular material. The matrix of the leaflets undergoes microcalcification as well insulation with plasma materials, causing changes in the matrix structure. These changes may change the resistive properties of leaflet materials. In both mechanical and bioprosthetic valves, a fibrous sheath may also encapsulate the supporting structure of the valve, encroaching on the PHV orifice and also possibly causing valve leaflet or disk immobilization (39–41).

In 1988, the Veterans Administration Randomized Trial of PHV presented the findings of repeat research cardiac catheterization that was performed approximately 6 months after PHV implantation. For PHVs of the same size, there
was a wide range of EOAs (Fig. 4) (42). Two more recent echocardiographic/Doppler studies from the Mayo Clinic of patients studied within 1 week of mitral porcine mitral bioprosthesis (43) (Fig. 5) and of tricuspid mechanical prostheses (44) showed a wide range of gradients and EOAs with the same size of PHV, even in the same brand of PHV.

There are at least several explanations for these findings. 1) PHVs of the same labeled size are not necessarily of precisely the same size. Bioprostheses and other biological valves may also have differences in tissue materials. 2) There are variations from patient to patient with regard to healing changes, hemodynamic conditions, and pressure recovery.

In conclusion, it is best to measure VP–PM early (at 1 week after PHV implantation or at time of hospital discharge) to determine the variations in actual size of the PHV that was implanted in an individual patient. Importantly, VP–PM should also be assessed at 6 to 12 months when the physiological and other morphological changes in the PHV are mostly complete. The severity of VP–PM determined at this time can be expected to determine the long-term impact of VP–PM on patients’ outcomes.

Outcomes. Studies investigating the importance of moderate and severe VP–PM have focused on hospital and long-term mortality, LV mass regression, and measures of patients’ functional status and quality of life. These studies have had mixed results, likely due to methodological differences in the studies and the patient population being studied. Studies varied in the parameter used to assess VP–PM, the EOAi values at which moderate and severe VP–PM were defined, and whether moderate and severe VP–PM were evaluated separately or grouped together, that is, as moderate-severe VP–PM. Furthermore, studies also have differed in patient’s age, LV systolic function, LV mass index, and the presence of associated coronary artery disease. There is likely a complex interplay between different patient-related factors and VP–PM on outcomes (45).

Given these considerations, studies that used a measured EOAi, where measurement was done 6 to 2 months after
PHV implantation and separated the data of moderate from severe VP–PM, provide the most reliable assessment of VP–PM in assessing patient outcomes. Furthermore, given the large number of comorbid cardiac and noncardiac conditions in patients undergoing AVR, multivariate analysis should be performed for any conclusions regarding the influence of VP–PM on outcomes. For assessing the role of VP–PM on survival, deaths due to cardiac causes should be evaluated separately, and, again, multivariate analysis should be performed.

LITERATURE SEARCH. In January 2012, a PubMed search was performed using the terms “patient prosthesis mismatch,” “valve prosthesis patient mismatch,” and a general search for patient prosthesis mismatch for all English-language articles published from 1998 to the current time. The search returned 402 articles, of which 159 were excluded (18 related to mitral valve replacement, 1 related to the Ross principle, 83 related to prosthesis other than heart valves, and 12 related to children, and 10 studies were not available at our institution). To ensure that no studies were missed, the references of the studies obtained were reviewed for any further studies that provided outcomes in relation to VP–PM. Of the remaining articles, 37 provided data regarding outcomes in relation to VP–PM.

A. Studies using a measured EOAi. Given the considerations outlined previously, studies using direct measurement of the EOAi in individual patients after surgery will have the most sensitivity and specificity for VP–PM.

1. Survival
   a. Operative or 30-day mortality. As discussed previously, the measured EOAi immediately post-operatively does not necessarily reflect the EOAi in the long term. Hanayama et al. (27) showed increased early mortality in patients with severe VP–PM; however, this study did not correct for confounding variables. Subsequent studies have shown that VP–PM using a measured EOAi does not have a significant impact on operative or 30-day mortality (28,46).

b. Long-term mortality
   i. Moderate VP–PM. Five studies measured the EOAi and examined the impact of moderate VP–PM on mortality (Table 2) (20,25,28,32,46). None of them showed an increased mortality with moderate VP–PM.
   ii. Severe VP–PM. Seven studies measured the EOAi and examined the impact of severe VP–PM on mortality (Table 3) (20,25,27,28,32,46,47). The incidence of severe VP–PM ranged from 6.9% to 39.8%. Two studies showed an increased mortality with severe VP–PM (20,25) and 5 other studies did not document an increase in mortality (27,28,32,46,47). Of the studies that did not show an increase in mortality, 1 study had a mean follow-up of 1.19 ± 0.76 years, and in another study, only 4 of 58 patients had severe VP–PM.
   iii. Moderate–severe VP–PM. Studies that measured the EOAi and combined moderate and severe VP–PM showed no statistically significant increase in mortality in this group (Table 3) (45,48–51). The incidence of moderate–severe VP–PM ranged from 3.3% to 65.7%. Given that severe VP–PM has a significant impact on mortality, whereas the influence of mod-
### Table 2: Summary of Studies That Used Measured EOAi to Assess VP-PM: Data of Moderate and Severe VP-PM Analyzed Separately

<table>
<thead>
<tr>
<th>Study population</th>
<th>Milano et al. (28)</th>
<th>Hanayama et al. (27)</th>
<th>Mohty-Echahidi et al. (25)</th>
<th>Florath et al. (20)</th>
<th>Nozohoor et al. (46)</th>
<th>Vicchio et al. (32)</th>
<th>Okamura et al. (47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of EOA assessment</td>
<td>Measured before hospital discharge</td>
<td>Measured EOAI on serial post-operative echocardiograms</td>
<td>Measured EOAI: 91% were measured within 30 days post-operatively</td>
<td>Measured within 10 days of AVR</td>
<td>Measured by echocardiography</td>
<td>Measured at 1 yr follow-up</td>
<td>Measured by echocardiography at discharge</td>
</tr>
<tr>
<td>Definition of VP-PM</td>
<td>Moderate: EOAi &gt; 0.60 and ≤ 0.90 cm²/m²; severe: ≤ 0.60 cm²/m²</td>
<td>Moderate: &gt; 0.85 cm²/m²; severe: ≤ 0.85 cm²/m²</td>
<td>Mild: &lt; 0.85 cm²/m²; moderate: ≤ 0.85 cm²/m²; severe: ≤ 0.60 cm²/m²</td>
<td>Moderate-severe: ≤ 0.85 cm²/m²; severe: ≤ 0.65 cm²/m²</td>
<td>Severe: &lt; 0.60 cm²/m²; moderate: 0.61–0.84 cm²/m²; severe: &lt; 0.65 cm²/m²</td>
<td>Moderate-severe: &lt; 0.85 cm²/m²; severe: &lt; 0.65 cm²/m²</td>
<td></td>
</tr>
<tr>
<td>% with VP-PM</td>
<td>Moderate: 149/205 (72.7%); severe: 24/205 (11.7%)</td>
<td>Moderate: 168/388 (43.3%); severe: 66/388 (17.0%)</td>
<td>Moderate: 277/533 (52%); severe: 150/533 (28%)</td>
<td>Overall: severe: 39.8%. Sorin Soprano: moderate-severe: 84%; severe: 36%; Medtronic Mosaic: moderate-severe: 74%; severe: 46%</td>
<td>Moderate: 175/345 (50.7%); severe: 33/345 (9.6%)</td>
<td>Moderate-severe: 18/58 (31%); severe: 4/58 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Type of prosthetic valve</td>
<td>19- or 21-mm St. Jude Mechanical valve</td>
<td>Homograft: 7/1129 (0.6%); bioprosthesis: 500/1129 (44.3%); stentless: 211/1129 (18.7%); mechanical 411/1129 (36.4%) (data for all patients with AVR during study period)</td>
<td>Bioprosthetic: 85/533 (15.9%); stentless: 284/633 (53.3%); mechanical: 164/533 (30.8%)</td>
<td>Sorin Soprano: 235/372 (63.1%); Medtronic Mosaic: 137/372 (26.9%)</td>
<td>Bileaflet mechanical valves</td>
<td>17-mm St. Jude valve</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>8 ± 5 yrs</td>
<td>Not given for total population</td>
<td>Echocardiography performed at median 6 days. 331/388 (91%) occurred within 30 days. Clinical follow-up: 5.3 ± 3.3 yrs</td>
<td>Clinical follow-up: 4.2 ± 3.1 yrs</td>
<td>4.2 ± 3.1 yrs</td>
<td>32.6 ± 19.6 months (in entire cohort)</td>
<td></td>
</tr>
<tr>
<td>Short-term outcome</td>
<td>Moderate: no impact on hospital mortality; severe: no impact on hospital mortality</td>
<td>Severe: early mortality was higher in patients (2.63% vs. 0.14%, p &lt; 0.001). No multivariate analysis done.</td>
<td>Moderate: no impact on hospital mortality; severe: no impact on hospital mortality</td>
<td></td>
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</tbody>
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Continued on next page
erate VP–PM is not likely to be significant, grouping patients with moderate and severe VP–PM together, will likely only have an impact on mortality if there is a sufficient proportion of patients with severe VP–PM.

2. LV mass regression

Studies have also assessed the impact of VP–PM on LV mass regression. Traditionally, the state of the myocardium has been referred to as LV hypertrophy when evaluated by electrocardiography and imaging techniques such as angiography, echocardiography, and magnetic resonance imaging. However, in reality, these are measures of increased LV mass because they are measuring cardiac myocytes, blood vessels, connective tissue, and fibrosis; in the normal heart, only about one half of the cells are cardiomyocytes, and fibroblasts are the predominant cell types in the remainder (52–54). This is important because increased LV mass may be due to changes in factors other than myocyte hypertrophy. Indeed, LV mass regression is complicated by multiple factors including female sex (29), the degree of pre-operative LV hypertrophy (55), the presence of systemic hypertension (56), renal dysfunction (57), and pre-operative LV fibrosis (58). These should be kept in mind when considering the effect of VP–PM on LV mass regression because LV mass regression is multifactorial.

Several studies using a measured EOAi have attempted to elucidate the role of VP–PM in LV mass regression. Tasca et al. (29,59) demonstrated that a larger increase from the pre-operative AVA to the post-operative EOAi was associated with increased LV mass regression at a mean follow-up of 1.5 years. Dalmau et al. (60) demonstrated that at 5-year follow-up, moderate-severe VP–PM was associated with a higher incidence of increased LV mass (odds ratio: 12.6; 95% confidence interval: 2.6 to 44.1; \( p < 0.001 \)). On the other hand, several studies showed that there is no association between moderate-severe VP–PM and long-term LV mass regression (49,50,61). Gelsomino et al. (51) demonstrated that up to 1 year post-operatively, patients with moderate-severe VP–PM had a higher LV mass index compared with those patients without VP–PM; however, at 3-year follow-up, patients with VP–PM had a similar LV mass as those patients without VP–PM.

3. Functional status and quality of life

Bleiziffer et al. (62) demonstrated that moderate-severe VP–PM and the presence of coronary artery disease are predictors of decreased exercise capacity 6 months post-operatively. However, moderate-severe VP–PM does not significantly affect long-term functional class (28,50) or quality of life based on the Short Form-36 questionnaire (49). The greater the amount
Table 3  Summary of Studies That Use Measured EOAi to Assess VP-PM: Data of Moderate and Severe VP-PM Are Combined

<table>
<thead>
<tr>
<th>Study population</th>
<th>Gelsomino et al. (51)</th>
<th>Sakamoto et al. (48)</th>
<th>Vicchio et al. (49)</th>
<th>Bleiziffer et al. (45)</th>
<th>Garatti et al. (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR with Cryolife O'Brien bioprosthesis; hospital survivors</td>
<td>62</td>
<td>51</td>
<td>134 survivors of AVR</td>
<td>645</td>
<td>78</td>
</tr>
<tr>
<td>Time of EOAi assessment</td>
<td>Measured at time of discharge</td>
<td>Mean echocardiographic follow-up: 2.2 ± 1.5 yrs</td>
<td>Not provided</td>
<td>Measured at 6.5 ± 1.5 months</td>
<td>Not provided</td>
</tr>
<tr>
<td>Definition of VP-PM</td>
<td>EOAi: ≤0.85 cm²/m²</td>
<td>Moderate: &lt;0.85 cm²/m²; severe: ≤0.60 cm²/m²</td>
<td>EOAi: &lt;0.85 cm²/m²</td>
<td>EOAi: &lt;0.85 cm²/m²</td>
<td>EOAI &lt;0.85 cm²/m²</td>
</tr>
<tr>
<td>% with VP-PM</td>
<td>12/62 (19.4%) at discharge; at 6 months, 2/61 (3.3%)</td>
<td>9/51 (17.6%) with moderate VP-PM; no patients with severe VP-PM</td>
<td>88/134 (65.7%)</td>
<td>248/622 (39.9%)</td>
<td>29/78 (37%)</td>
</tr>
<tr>
<td>Type of prosthetic valve</td>
<td>21- or 23-mm Cryolife O'Brien valve</td>
<td>19-mm Carpentier- Edwards Perimount</td>
<td>19-mm mechanical valves</td>
<td>Bioprosthetic 583/645 (90.4%); stentless: 62/645 (9.6%)</td>
<td>St. Jude bileaflet, Sorin Bicarbon Slim</td>
</tr>
<tr>
<td>Follow-up</td>
<td>37 ± 12 months</td>
<td>2.4 ± 1.8 yrs</td>
<td>3.9 ± 2.7 yrs</td>
<td>Clinical: mean 2.66 (range, 0.45 to 7.19) yrs; echocardiography at 6.5 ± 1.5 mo</td>
<td>Discharge, annual: 83 ± 45 months</td>
</tr>
<tr>
<td>Short-term outcome</td>
<td>No statistically significant difference in long-term mortality</td>
<td>No overall or valve-related mortality with moderate VP-PM; no difference in risk of thromboembolism with moderate VP-PM</td>
<td>No difference in overall survival, valve-related complications</td>
<td>1. Increased cardiac mortality if logarithmic EOAi used as a continuous variable, but not if VP-PM taken as a category. 2. Increased cardiac mortality with residual left ventricular hypertrophy with VP-PM compared with residual LV hypertrophy without VP-PM</td>
<td>No difference in gradients or mortality for patients with VP-PM</td>
</tr>
</tbody>
</table>

Data for moderate and severe are combined.
LV = left ventricular; other abbreviations as in Table 2.

of myocardial fibrosis before AVR results in a worse New York Heart Association functional class postoperatively (58) (Fig. 6).

B. Studies using a predicted EOAi. A large number of studies used the projected EOAi to assess the severity of VP-PM (Online Appendix). Given the limitations of a projected EOAi discussed previously, this presents a serious methodological limitation, and results should be interpreted very cautiously. It is of little surprise that these studies present conflicting results regarding the impact of VP-PM on long-term mortality. Several of these studies have shown an interaction between patient characteristics and VP-PM.

C. Studies using the GOA index. The problems related to using GOA as a measure of VP-PM were discussed previously. Several large studies have also demonstrated that the GOA index and the z-score of the valve internal diameter do not predict long-term mortality (63,64) and quality of life (65). Therefore, studies that used the GOA to evaluate outcomes are not discussed further.

D. Using the EOAi as a continuous variable. The influence of VP-PM on mortality may be more carefully assessed by using the EOAi as a continuous variable. In doing so, studies avoid creating categorical variables that may have additional confounding factors that are difficult to assess. Studies using the EOAi as a continuous variable have shown that a lower EOAi is associated with increased mortality (25,45). This is compatible with the knowledge that the more the narrowing of the LV outflow tract, the worse the outcome; this is similar to valvular AS. Interestingly, the study by Bleiziffer et al. (62), which demonstrated that the EOAi as a continuous variable was associated with increased mortality, was unable
to demonstrate increased mortality using a cutoff of 0.85 cm$^2$/m$^2$ to define VP–PM. This makes evident the difficulty in documenting the increased mortality of VP–PM when combining the data of moderate and severe VP–PM, that is, in moderate-severe VP–PM. However, Bleiziffer et al. did not demonstrate a specific value of an EOAi that increases mortality, for example, at critical VP–PM ($<0.40$ cm$^2$/m$^2$) versus severe VP–PM ($<0.60$ cm$^2$/m$^2$) (Fig. 7).

**Prediction and prevention of severe VP–PM.** The importance of the “need for a technique which will permit accurate pre-operative prediction of the valve size the surgeon will realistically be able to insert in an individual patient” was emphasized in the original description of VP–PM (2). Important in this statement is that valve size refers to the EOAi rather than the labeled valve size. This was elaborated by Pibarot and Dumesnil (14) using a 3-step protocol: 1) calculate the BSA using the Dubois method; 2) determine the minimum EOA required to ensure an EOAi of $0.85$, $0.8$, or $0.75$ cm$^2$/m$^2$ based on the minimum required EOAi for a given patient; and 3) select the type and size of the valve greater or equal to the minimal EOA value obtained in step 2.

This method of Pibarot and Dumesnil has been demonstrated to reduce the incidence of moderate-severe VP–PM when using reference data obtained by in vivo measurement performed 6 to 12 months after PHV implantation (19).

However, there are several difficulties to recognize when using methods to prevent VP–PM:

A. Projected EOAi

1. The projected EOAi has limited value in predicting the presence or absence of VP–PM (18–20,66) (also see above). The EOA of a given model and size of valve has a range of values and may vary between patients (Table 4) (19,42). Thus, even with the best values of VP–PM, there is an EOAi range that may occur in any 1 patient (Fig. 8).

2. Reference data for EOA of different valves is available in the literature and also provided by PHV manufacturers in the form of tables. Manufacturer-provided tables have several flaws. The data provided in these tables comes from a multitude of sources and includes in vitro data, the GOA, and in vivo data obtained at different time intervals after PHV implantation (67,68). Manufacturer-provided tables may use “favorable EOA data” (67,68). Furthermore,
they provide only the mean EOA without range or confidence intervals. Ideally, given these considerations, EOA values should be based on in vivo measurements made 6 to 12 months after implantation (Table 5). Values provided should include the mean ± SD and range, as well as median and interquartile range.

3. There is no standard for the labeling of valve sizes, and valves with the same labeled valve size differ in external diameter and consequently may not fit into the same aortic root (69). Tables generally refer to the labeled valve size. This makes comparison between different models and sizes difficult.

Table 4 EOA Determined at 6 Months After AVR for PHV Labeled Size 23

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>n</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards Perimount</td>
<td>113</td>
<td>1.82</td>
<td>1.7–1.9</td>
</tr>
<tr>
<td>Edwards Perimount Magna</td>
<td>38</td>
<td>1.82</td>
<td>1.7–2.0</td>
</tr>
<tr>
<td>Medtronic Mosaic</td>
<td>23</td>
<td>1.53</td>
<td>1.3–1.8</td>
</tr>
<tr>
<td>Sorin Mitroflow</td>
<td>19</td>
<td>1.53</td>
<td>1.4–1.7</td>
</tr>
<tr>
<td>Sorin Freedom Solo</td>
<td>7</td>
<td>2.00</td>
<td>1.6–2.3</td>
</tr>
<tr>
<td>St. Jude Epic Supra</td>
<td>35</td>
<td>1.81</td>
<td>1.6–2.0</td>
</tr>
<tr>
<td>St. Jude Toronto Root</td>
<td>6</td>
<td>1.60</td>
<td>1.4–1.8</td>
</tr>
</tbody>
</table>

For several valves, there are <10 patients. Reprinted, with permission, from Bleiziffer et al. (45). PHV = prosthetic heart valve; other abbreviations as in Table 2.

Table 5 PHV Areas From Randomized In Vivo Trials

<table>
<thead>
<tr>
<th>PHV Size, mm</th>
<th>PHV Area Index, cm²/m²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 23</td>
<td>0.74 ± 0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C-E 23</td>
<td>0.79 ± 0.08</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>B C-E 25</td>
<td>0.80 ± 0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C-E 25</td>
<td>0.85 ± 0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>B C-E 22.9</td>
<td>1.17 ± 0.27</td>
<td>0.01</td>
</tr>
<tr>
<td>B C-E 22.4</td>
<td>0.94 ± 0.36</td>
<td>0.01</td>
</tr>
<tr>
<td>C-E 24.8</td>
<td>0.83 ± 0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Soprano valve</td>
<td>0.87 ± 0.20</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>C C-E 22.9</td>
<td>1.9 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>C-E 24.8</td>
<td>1.74 ± 0.66</td>
<td>NS</td>
</tr>
<tr>
<td>D C-E 24.8</td>
<td>0.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>C-E 24.8</td>
<td>0.88 ± 0.22</td>
<td>NS</td>
</tr>
<tr>
<td>E C-E 24.3</td>
<td>1.07 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>C-E 24.2</td>
<td>0.80 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>C-E 24.3</td>
<td>0.87 ± 0.3</td>
<td>0.028</td>
</tr>
<tr>
<td>F C-E 24.3</td>
<td>1.12 ± 0.28</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>Medtronic</td>
<td>0.79 ± 0.20</td>
<td></td>
</tr>
</tbody>
</table>

Data for A through E are from Rahimtoola (35) with permission. Data for F from Dalmau et al. (60). C-E = Carpentier-Edwards.

B. Severity of VP–PM

1. A projected EOAi that falsely predicts the presence of VP–PM may cause the patient to undergo a series of unnecessary steps intended to prevent VP–PM. The surgical techniques available to prevent VP–PM are less than ideal. Data are needed to determine whether the increased risk of techniques used to prevent VP–PM outweigh the risk of VP–PM and improve patient outcomes (70).

2. Prevention of all instances of VP–PM is, at present, not possible. There is a need for a change of emphasis in the prevention of VP–PM. Many studies have discussed prevention of moderate-severe, which includes both moderate and severe VP–PM. There is need to focus on prevention of severe VP–PM. This occurs with an EOAi ≤0.6 cm²/m², and, allowing for a 10% variability in determining the severity of VP–PM, the goal should be an EOAi ≤0.7 cm²/m².

C. Patient-related factors

1. It is unclear what an acceptable EOAi is for an individual patient. This likely depends on several patient-related factors such as age, left ventricular systolic function, severity of LV hypertrophy, and patient expectation of the level of activity after valve replacement.

2. Although avoidance of VP–PM is preferable, several factors must be taken into account when deciding the choice of PHV (Table 6) (71). Choice of a prosthetic heart valve with an EOA that avoids mismatch must be considered in light of other competing factors such as structural valve deterioration and other complications.

In conclusion, at the present time, one cannot accurately and reliably predict severe, or even critical, VP–PM. Obvi-
Factors to Consider When Choosing a PHV

<table>
<thead>
<tr>
<th>Age of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid conditions: cardiac and noncardiac</td>
</tr>
<tr>
<td>Expected life span of patient</td>
</tr>
<tr>
<td>Choose a PHV</td>
</tr>
<tr>
<td>That does not require root replacement for isolated aortic valve disease</td>
</tr>
<tr>
<td>With long-term follow-up outcomes that are at least as good as the best of the available PHV</td>
</tr>
<tr>
<td>With which individual physicians and medical centers have the necessary skill and experience</td>
</tr>
<tr>
<td>Probability of adherence and compliance with warfarin therapy</td>
</tr>
<tr>
<td>Patient’s wishes and expectations</td>
</tr>
<tr>
<td>Other extenuating circumstances</td>
</tr>
</tbody>
</table>

Reprinted, with permission, from Rahimtoola (35).

VP–PM in transcatheter valve therapy. VP–PM has been described in percutaneously implanted aortic valves. The incidence of severe VP–PM in the Edwards Sapien valve has been reported to be 11% to 18.2% when measured 6 to 12 months after implantation (72,73). In the Medtronic Corevalve, the incidence of severe VP–PM has been reported to be 2% to 16% when measured at the time of hospital discharge (74–76). The study of the Corevalve by Giannini et al. (76) also evaluated VP–PM 6 months after transcatheter valve therapy and found 12% incidence of severe VP–PM. Propensity–matched data suggest that the incidence of VP–PM is less than in surgical PHV implantation (72). In a study using the Cribier–Edwards and Edwards SAPIEN valves to perform transcatheter valve therapy, patients who had surgical AVR had smaller EOAi despite starting with a larger aortic valve annulus (77). However, more data are needed before conclusions can be reached.

Beyond 2011

The concept/phenomenon of VP–PM has stood the test of time. Several of the expectation and predictions that have not been fulfilled are reviewed here. Thus, it is reasonable to review changes that need to be made in the assessment of VP–PM.

1. EOAi should be measured at 1 to 4 weeks or at hospital discharge to evaluate the actual valve size that was implanted. This should also be done at 6 to 12 months to evaluate the severity of VP–PM that will affect long-term outcomes.

2. The grading of severity of VP–PM should be similar to another common LV outflow tract obstruction, namely, valvular AS. VP–PM can be mild (EOAi >0.9 cm²/m²), moderate (EOAi ≥0.6 to 0.9 cm²/m²), or severe (EOAi ≤0.6 cm²/m²).

3. Mild VP–PM, like mild AS, is unlikely to have clinically significant untoward effects. Outcomes with moderate and severe VP–PM should be evaluated separately. Moderate VP–PM is unlikely to reduce survival unless there is progression of valve obstruction, for example, with pannus formation. Severe VP–PM has negative effects on outcomes, but its effect on mortality is still unproven, and more focused study is needed. To assess the effects of VP–PM on mortality, the goal should be to determine by multivariate analysis the role of VP–PM on mortality due to cardiac causes (78).

4. Prediction of severity of VP–PM is problematic. The primary goal should be not to prevent VP–PM but rather to prevent severe VP–PM.

5. Use of the EOAi as a continuous variable may help to define the level of severe VP–PM that results in increased mortality, and this may occur at a critical level of obstruction (≤0.4 cm²/m²) (Fig. 7).

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REFERENCES


Key Words: patient prosthesis valvular.

APPENDIX

For supplemental tables, please see the online version of this article.