Keynote Lecture Series

Prosthesis-patient mismatch in transcatheter and surgical aortic valve replacement

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Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of a normally functioning prosthetic valve is too small in relation to the patient's body size. The effect of PPM on outcomes and valve durability have gained credibility, making this an important possibly preventable risk factor. Transcatheter aortic valve replacement (TAVR) generally has a lower incidence of PPM than surgical aortic valve replacement (SAVR). Current surgical literature and randomized trials show an association between severe PPM and mortality in patients with SAVR but there is less evidence for an association with TAVR. Differences in the incidence of PPM may be related to the methods and cutoffs for measuring mismatch. This review will discuss the current state of field and propose standardization of measurement methods which may more accurately risk stratify patients.

Keywords: Transcatheter aortic valve replacement (TAVR); surgical aortic valve replacement (SAVR); prosthesis-patient mismatch (PPM)

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Introduction

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of a normally functioning prosthetic valve is too small in relation to the patient's body size (1,2). PPM results in increased left ventricular afterload and higher transvalvular pressure gradients (TPGs) (3), and may adversely impact prognosis, particularly when PPM is severe (4,5). Transcatheter aortic valve replacement (TAVR) has been shown to have less PPM than surgical aortic valve replacement (SAVR) (6). Although meta-analysis of SAVR studies show an association of PPM with mortality (4,7,8), data is controversial regarding the impact following TAVR (3,6,9,10). Controversies in literature have raised several issues, including: (I) what is the correct method for determining the incidence of PPM? (II) What are the adverse outcomes associated with PPM? (III) Are there real differences in outcomes associated with TAVR PPM compared to SAVR PPM? (IV) Are differences in valve design related to the incidence of PPM?

Definition and methods for assessing prevalence of PPM

PPM and high transvalvular gradients occur when the prosthetic valve EOA is too small for the patient's body size. The relationship between the TPG, EOA, and transvalvular flow (Q) can be simplified according to the Gorlin equation as follows (11): $TPG = Q^2/(k \times EOA^2)$, where k is constant. Q depends on the cardiac output, which is positively correlated with the body surface area (BSA) (12). The TPG is directly related to the square of Q and inversely related to the square of the EOA. Thus, PPM and high TPG occurs when the prosthetic valve EOA is too small for the patient's body size (1). Importantly, a high transprosthetic gradient may also be related to a high flow state, aortic regurgitation,

Table 1 Grading scheme for PPM

Severity of PPM	Indexed EOA (cm^2/m^2)
BMI <30 kg/m^2	
Insignificant	>0.85
Moderate	0.85–0.66
Severe	≤0.65
BMI ≥30 kg/m^2	
Insignificant	>0.70
Moderate	0.70–0.56
Severe	≤0.55

The suggested cutoffs for insignificant, moderate and severe PPM are listed by normal BMI (<30 kg/m^2) and increased BMI (≥30 kg/m^2). PPM, prosthesis-patient mismatch; EOA, effective orifice area; BMI, body mass index.

or acquired prosthetic valve stenosis caused by non-structural valve dysfunction (i.e., thrombosis, endocarditis) or structural valve deterioration (SVD). Conversely, because the transvalvular gradient is flow dependent, a low gradient does not necessarily exclude the presence of PPM, and the gradient may be low even in the presence of PPM.

PPM is categorized based on the indexing EOA to BSA (*Table 1*). Importantly, the measurement of EOA quantifies stroke volume for surgical or transcatheter valves proximal to the sewing ring or stent frame. The indexed EOA (EOAi) cutoffs define PPM are ≤0.85 cm^2/m^2 for moderate and ≤0.65 cm^2/m^2 for severe PPM (13-15). However, in obese patients (body mass index ≥30 kg/m^2), the use of these EOAi cut-points may result in an overestimation of the incidence and severity of PPM because of over-indexation phenomenon. It is thus recommended to apply lower cutoff values in these patients: ≤0.70 cm^2/m^2 for moderate and ≤0.55 cm^2/m^2 for severe PPM (13). The prevalence and impact of PPM may be overestimated following AVR because of low flow state (i.e., pseudo-PPM), pressure recovery and obesity (16). As noted, PPM occurs when the EOA of a normally functioning prosthetic valve is too small in relation to the patient's body size however the flow requirements for muscle are not the same as for fat. Thus, using different indexed cutoffs for grading PPM severity has been advocated by the VARC-3 consensus document (14). Many studies have failed to use different cut-offs for PPM severity and thus not only overestimate the prevalence of the PPM, but may underestimate the impact of PPM in patients with normal body weight.

PPM for TAVR valves is often defined with the use of the EOAi directly measured by transthoracic echocardiography at the pre-discharge or 30-day echocardiogram. However, measured EOAi has several limitations: (I) EOAi quantification is subject to echocardiographic technical pitfalls and measurement errors of that particular study; and (II) EOAi is flow-dependent and may thus overestimate the severity of PPM in patients with a low-flow state (3,17). To overcome this limitation, the use of the predicted EOAi has been proposed to define PPM; this parameter is calculated by dividing the normal reference value of EOA for the implanted model and size of prosthesis by the patient's BSA (13,18). The normal reference values of EOA for surgical valves are derived from various sources, such as mean echo data from various patient cohorts or the reported size of manufacturers. This measurement cannot account for changes in implantation technique (i.e., everting *vs.* non-everting native leaflets, using pledgets or no pledgets). For the TAVR normative data, hundreds of echocardiograms were analyzed by Echocardiographic Core Laboratories which likely reduces variability of measurements although for these valves as well, implantation technique may influence the accuracy of the measurements. *Table 2* is an example of reference values for surgical valves (19), and *Tables 3,4* includes the known reference values for commercially-available transcatheter heart valves (THVs) (20).

The vast majority of SAVR studies have used the predicted EOAi to examine the incidence and impact of PPM, whereas most TAVR studies have only used the measured EOAi. The difficulty in acquiring high quality echocardiograms immediately following a median sternotomy likely has driven use of predicted EOAi following SAVR. The pitfall of using the predicted EOA for SAVR has been the high variability of normative data published by investigators and industry (21). Amorim *et al.* reported a high variability of reported "normative" data where, for instance, the normal expected EOA for a 25 mm Mosaic valve ranged from 1.7 to 2.39 cm^2 with a poor correlation between reported EOA and mean transvalvular gradients. Although measured EOA and gradients performed in 11 SAVR studies showed a strong, positive correlation supporting the use of measured and not predicted EOA for the assessment of PPM in SAVR (21), Sá and colleagues performed a meta-analysis of 70 studies

Table 2 Normal reference values of effective orifice areas for the surgical bioprosthetic aortic valves

Prosthetic valve type	Prosthetic valve size (mm)					
	19	21	23	25	27	29
Stented bioprosthetic valves (cm^2)						
Biocor (Epic)	1.0±0.3	1.3±0.5	1.4±0.5	1.9±0.7	–	–
Carpentier-Edwards Perimount	1.1±0.3	1.3±0.4	1.5±0.4	1.8±0.4	2.1±0.4	2.2±0.4
Carpentier-Edwards Magna	1.3±0.3	1.5±0.3	1.8±0.4	2.1±0.5	–	–
Hancock II	–	1.2±0.2	1.3±0.2	1.5±0.2	1.6±0.2	1.6±0.2
Mosaic	1.1±0.2	1.2±0.3	1.4±0.3	1.7±0.4	1.8±0.4	2.0±0.4
Mitroflow	1.1±0.2	1.2±0.3	1.4±0.3	1.6±0.3	1.8±0.3	–
Trifecta	1.4	1.6	1.8	2.0	2.2	2.4
Stentless bioprosthetic valves (cm^2)						
Medtronic Freestyle	1.2±0.2	1.4±0.2	1.5±0.3	2.0±0.4	2.3±0.5	–
Pirma Edwards	–	1.3±0.3	1.6±0.3	1.9±0.4	–	–
St. Jude Medical Toronto SPV	–	1.3±0.3	1.5±0.5	1.7±0.8	2.1±0.7	2.7±1.0
Mechanical valves (cm^2)						
ATS Medical[†]	1.1±0.3	1.6±0.4	1.8±0.5	1.9±0.3	2.3±0.8	–
Carbomedics Standard and Top Hat	1.0±0.4	1.5±0.3	1.7±0.3	2.0±0.4	2.5±0.4	2.6±0.4
Medtronic-Hall	1.2±0.2	1.3±0.2	–	–	–	–
On-X	1.5±0.2	1.7±0.4	2.0±0.6	2.4±0.8	3.2±0.6	3.2±0.6
St. Jude Medical Standard	1.0±0.2	1.4±0.2	1.5±0.5	2.1±0.4	2.7±0.6	3.2±0.3
St. Jude Medical Regent	1.6±0.4	2.0±0.7	2.2±0.9	2.5±0.9	3.6±1.3	4.4±0.6

Modified from Lancellotti *et al.* (13). Data are presented as mean ± standard deviation. [†], for the ATS Medical supra-annular valve, the label valve sizes are 18, 20, 22, 24, and 26 mm.

Table 3 Mean gradient, effective orifice area and DI for Evolut R by valve size in native aortic stenosis, measured at 30 days following implant

Valve type	Valve size (mm)			
	23	26	29	34
Evolut R—30 days				
EOA (cm^2)	1.09±0.26 [3]	1.69±0.40 [71]	1.97±0.54 [129]	2.60±0.75 [52]
MGrad (mmHg)	14.97±7.15 [3]	7.53±2.65 [77]	7.85±3.08 [141]	6.30±3.23 [57]
DI	0.42±0.04 [3]	0.61±0.13 [75]	0.59±0.14 [135]	0.58±0.15 [55]

Modified from Hahn (20). Values expressed as mean ± standard deviation [n]. Note the differences in "n" for each valve type and size. DI, Doppler index; EOA, effective orifice area; MGrad, mean transaortic gradient.

Table 4 Mean gradient, effective orifice area and DI for SAPIEN 3 by valve size in native aortic stenosis, measured at 30 days following implant

Valve type	Valve size (mm)			
	20	23	26	29
SAPIEN 3—30 days				
EOA (cm^2)	1.22±0.22 [47]	1.45±0.26 [471]	1.74±0.35 [626]	1.89±0.37 [326]
MGrad (mmHg)	16.23±5.01 [47]	12.79±4.65 [471]	10.59±3.88 [626]	9.28±3.16 [326]
DI	0.42±0.07 [47]	0.43±0.08 [471]	0.43±0.09 [626]	0.40±0.09 [326]

Modified from Hahn (20). Values expressed as mean ± standard deviation [n]. Note the differences in "n" for each valve type and size. DI, Doppler index; EOA, effective orifice area; MGrad, mean transaortic gradient.

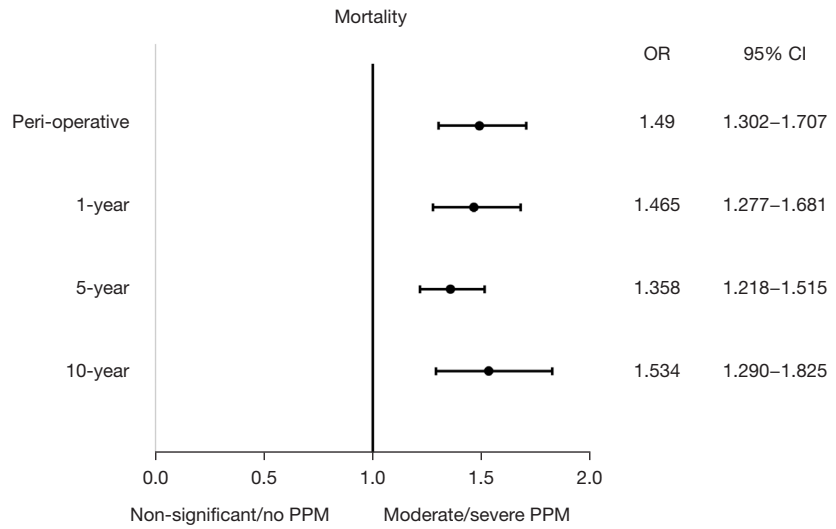

Figure 1 Outcomes of moderate/severe PPM. Meta-analysis of 70 articles including 108,182 patients who underwent surgical aortic valve replacement, showed moderate/severe PPM increases perioperative, early-, mid- and long-term mortality rates proportionally to its severity. Modified from Sá *et al.* (7). PPM, prosthesis-patient mismatch; OR, odds ratio; CI, confidence interval.

reporting moderate/severe PPM using predicted EOAi and found an association with perioperative mortality, 1-year mortality, 5-year mortality and 10-year mortality (*Figure 1*) (7).

For THV bioprostheses, early studies used measured EOA to predict the incidence of PPM, however following the report of expected normal hemodynamics following TAVR (20), predicted PPM could be determined. As expected, the predicted PPM rates were significantly lower than measured PPM (3,22). A study from the PARTNER 2, SAPIEN 3 registry compared predicted and measured EOA and showed a lower incidence of PPM when using the predicted EOAi method compared to the 30-day measured EOAi, with a lower incidence of PPM in TAVR compared to SAVR (*Figure 2*) (23). Only the severe PPM by the predicted EOAi method was independently associated with events in SAVR after adjustment for sex and Society of Thoracic Surgeons (STS) score [hazard ratio (HR) =3.18; 95% confidence interval (CI): 1.69–5.96; P<0.001], whereas in TAVR, there was no association between outcomes and PPM by any method, likely in part related to the very low incidence of moderate or severe predicted PPM. In another study of 1,088 TAVR patients by Ternacle *et al.* (55% male, age 79.1±8.4 years, and STS score 6.6±4.7; balloon-expandable device in 83%), the incidence of PPM was also markedly lower when defined by predicted *vs.* measured EOAi (P<0.001) (3). Balloon-expandable device implantation [odds ratio (OR) =1.90; P=0.029] and valve-in-

Incidence of prosthesis-patient mismatch

1. Incidence of severe PPM is markedly lower with predicted *vs.* measured EOAi.
2. TAVR has lower incidence of severe PPM compared to SAVR, regardless of the EOAi method used to identify PPM.

Impact of prosthesis-patient mismatch on outcomes

1. In SAVR, severe PPM by the predicted EOAi method is rare but independently associated with worse outcomes.
2. In TAVR, severe PPM by the predicted EOAi method is absent.
3. In both SAVR and TAVR, moderate PPM is not associated with worse outcomes.

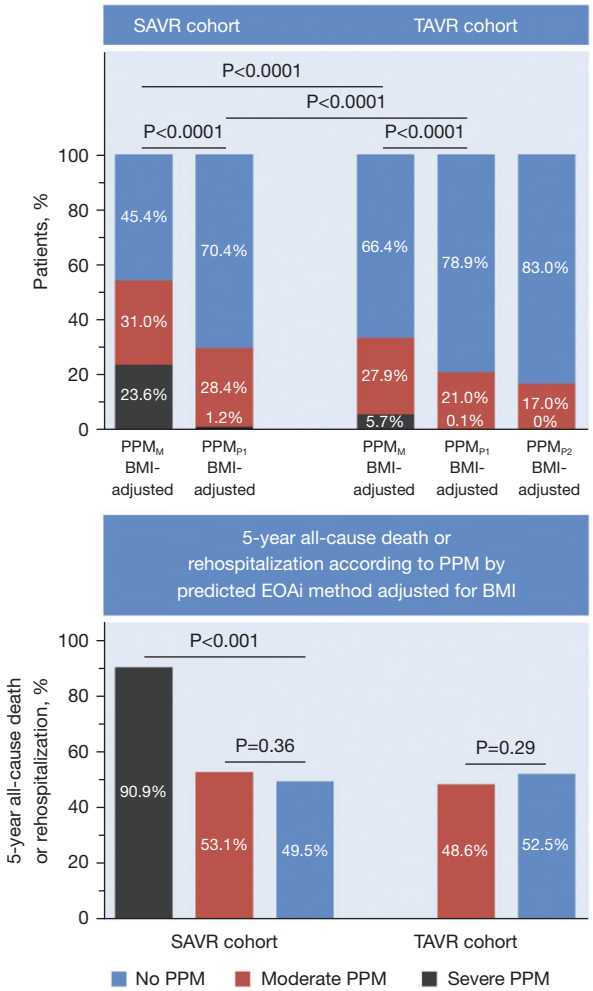

Figure 2 Incidence of PPM by measured or predicted methods. (A) Incidence of PPM following SAVR by EOAi measured by echocardiography (PPM_M) or predicted by method 1 from published expected EOA according to valve model and size (PPM_{P1}), with and without adjustment for obesity. (B) Incidence of PPM following TAVR by measured EOAi method (PPM_M), by predicted EOAi method 1 (PPM_{P1}), or predicted by method 2 from published expected EOA according to CTA aortic annulus area (PPM_{P2}), with and without adjustment for obesity. Reproduced with permission from Ternacle *et al.* (3). PPM, prosthesis-patient mismatch; EOAi, indexed effective orifice area; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; BMI, body mass index.

valve procedure (n=118; OR =3.21; P<0.001) were the main factors associated with PPM occurrence. Compared with measured PPM, predicted PPM showed stronger association with high residual gradient (≥20 mmHg) but notably, severe measured or predicted PPM was not associated with clinical outcomes. This association of predicted PPM (and not measured PPM) with gradient ≥20 mmHg, was recently confirmed in a small single-site study, which also found an association with failure to improve symptoms following TAVR (24).

Because valve area is dependent on flow, the expected normal values for prosthetic valves may be larger in the setting of normal flow, and lower in the setting of low flow. In the PARTNER 2 SAPIEN 3 registry, up to 30% of patients had low flow. Lower flow may occur immediately following TAVR implant, creating pseudo-severe PPM. It is thus recommended to perform EOA measurements at 30 days post-AVR when the highly prevalent low-flow state during and early after the procedure has resolved or to use the predicted EOAi instead. In addition, normal reference valve areas for the balloon-expandable valve that takes into account flow have recently been published (17). Reassessing

Table 5 Summary of PPM prevalence and mortality risk

Study/trial	Method of quantifying PPM	Incidence of severe PPM	Impact on mortality
Meta-analysis—SAVR (4)	Predicted	10%	HR: 1.84*
STS registry—SAVR (25)	Predicted	11%	HR: 1.19*
PARTNER 1—SAVR *vs.* TAVR (6)	Measured	28 *vs.* 20%*	HR: 1.78* *vs.* 0.52
CORE VALVE HR—SAVR *vs.* TAVR (10)	Measured	21 *vs.* 7%*	HR: 1.60* (SAVR + TAVR)
PARTNER 2A-S3i—SAVR *vs.* TAVR (3)	Predicted/measured	24 *vs.* 6%*	HR: 1.34* *vs.* 1.27
PARTNER 3—SAVR *vs.* TAVR (26)	Measured	6 *vs.* 5%	HR: 1.31* (SAVR + TAVR)
TVT registry—TAVR (BE and SE) (9)	Measured	12%	HR: 1.19*
TVT registry—TAVR (SE only) (27)	Measured	5.3%	HR: 1.00
TAVI—SMALL registry (28)	Measured	9.4%	HR: 4.27*

This table summarizes the prevalence and outcomes of PPM from both randomized and non-randomized studies. *, P<0.05 for difference between groups. PPM, prosthesis-patient mismatch; SAVR, surgical aortic valve replacement; HR, hazard ratio; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TVT, Transcatheter Valve Therapy; BE, balloon-expandable; SE, self-expanding.

Table 6 Predictors of PPM

SAVR predictors of PPM
Dayan *et al.* (8): older age, female sex, diabetes, hypertension, renal failure, large BSA and BMI, bioprosthesis (*vs.* mechanical) valves
Kim *et al.* (29): intra-annular prostheses (*vs.* supra-annular) bioprosthesis
Tavakoli *et al.* (30): stented (*vs.* stentless) bioprosthesis
TAVR predictors of PPM
Herrmann *et al.* (9): younger age, female sex, atrial fibrillation, severe MR or TR, small THV (≤23-mm diameter), valve-in-valve procedure, larger BSA, non-white/Hispanic race, lower EF
Miyasaka *et al.* (31): younger age, larger BSA, smaller aortic valve area, smaller annulus area, no balloon post-dilatation, and use of balloon-expandable valve
Stamou *et al.* (32): age <70 years, BMI >30 kg/m^2, history of atrial fibrillation, black race, and small THV (≤23-mm diameter)
Leone *et al.* (28): intra-annular valves (note: post-dilation and valve oversizing protects against PPM)

Some of the predictors of PPM reported in the literature are listed below by implantation technique: SAVR and TAVR. PPM, prosthesis-patient mismatch; SAVR, surgical aortic valve replacement; BSA, body surface area; BMI, body mass index; TAVR, transcatheter aortic valve replacement; MR, mitral regurgitation; TR, tricuspid regurgitation; THV, transcatheter heart valve; EF, ejection fraction.

predicted PPM using the flow-adjusted values may uncover pseudo-severe PPM which occurs in the low flow state.

Accurate assessment of the patient's annular size and indexing the expected EOA of the prosthesis to the patient's BSA at the time of prosthesis implantation are essential to preventing PPM. To that end, a downloadable application "Valve PPM" is now available which allows the calculation of the EOA to avoid any PPM and severe PPM, also listing appropriate valve types/sizes to avoid PPM.

Predictors and outcomes associated with PPM in SAVR and TAVR

Depending on the method of assessment, severe PPM occurs in 2–20% of SAVRs (*Table 5*) (3,4,6,9,10,25-28). Predictors of SAVR PPM in one meta-analysis were: older age, female sex, hypertension, diabetes, renal failure, larger BSA, larger body mass index, and the utilization of a bioprosthetic (*vs.* mechanical) valve (*Table 6*) (8,9,28-32). The rate of severe PPM differs according to type of surgical

valve: stented bioprosthetic valves > stentless > sutureless > Ross. Long-term clinical outcome of PPM is associated with adverse cardiovascular events especially in the presence of pre-existing left ventricle dysfunction or with concomitant procedure such as coronary artery bypass graft surgery. Multiple meta-analyses (4,7,8) as well as registry analyses (25), show a significant association between PPM and mortality, as well as other clinical outcomes such as lower left ventricular mass regression, less mitral regurgitation reduction, less improvement in functional class and lower exercise capacity, increased incidence of heart failure hospitalization (1,4,33-35). PPM may also predispose patients to SVD (36). Finally, there appears to be a greater clinical impact of severe and even moderate PPM in specific groups of patients such as those with preexisting LV dysfunction or hypertrophy, those with concomitant mitral regurgitation, and in those <65–70 years of age (37).

The incidence of severe PPM in TAVR similarly depends on the method of assessment (predicted *vs.* measured) but ranges from 5–20% in studies using measured PPM method (*Table 5*). A small annulus has minimal impact on the risk of PPM, likely related to the mechanics of TAVR (i.e., valve expansion to the native annulus without a sewing ring) and the nearly linear relationship between annular size and body size (38). Predictors of TAVR PPM (*Table 6*) include younger age and smaller valve size, larger body mass index, intra-annular (*vs.* supra-annular) THV, and valve-in-valve (*vs.* native TAVR), atrial fibrillation and non-White/Hispanic race. Less PPM may be seen with oversizing the valve (28) and balloon post-dilation (31). Multiple studies show a significantly higher incidence of severe PPM with the balloon-expandable valve compared to the self-expandable valve (39,40). The TAVI-SMALL 2 registry enrolled 628 patients in an international retrospective registry, which included patients with severe AS and small annuli (annular perimeter <72 mm or area <400 mm^2); of note, the mean age—83 years and 89% were women (40). This study confirmed that balloon-expandable and intra-annular valves predicted the presence of severe PPM in small annuli.

The impact of TAVR PPM on mortality has been inconsistent (*Table 5*). The TAVR trials, using either measured or predicted PPM, has not shown a significant association with mortality for either balloon-expandable or self-expanding valves (3,6,10,27). Randomized trial analyses have shown an increased risk of mortality with significant PPM when TAVR and SAVR cohorts are combined (6,10). When PPM occurs in patients with a small TAVR however, there is a more than four-fold increase in mortality risk which may be more important in patients <70 years of age, and/or undergoing concomitant coronary artery bypass grafting and less pronounced in patients with larger body mass index (>28 kg/m^2) compared with those with lower index. Recent data from the STS-Transcatheter Valve Therapy (TVT) registry which combined at all THV types, showed that severe TAVR PPM occurred in 12.1% of patients and was associated with increased mortality (HR =1.19; 95% CI: 1.09–1.310; P<0.001) (9). In a separate analysis of the STS-TVT registry, severe PPM occurred in 5.3% of TAVRs with the self-expanding valve but was not associated with mortality (27). This incidence is much higher than what has been reported in the randomized TAVR trials and conflicts with the individual THV trial studies (6,10). Differences in between-study outcomes would depend on the methods of calculating EOA for PPM classification. The STS/TVT database uses site-measured EOA which likely introduced significant measurement variability. The use of echo core labs in the randomized trials likely reduces the measurement variability. PPM in valve-in-valve procedures may be related to pre-existing PPM of the surgical valve (41) but the 5-year result of the PARTNER 2 Valve-in-Valve Registry failed to show any adverse outcomes associated with PPM (42).

Differences in outcomes: TAVR *vs.* SAVR and TAVR "real-world" *vs.* "randomized"

Prior studies have suggested that SAVR has a higher prevalence of PPM than TAVR (*Table 5*). This makes anatomic sense when one considers that the stented THV will expand to the size of the native annulus and has a thinner stent frame than a surgical sewing ring. Conversely, the TAVR implant retains the native calcified leaflets which may not allow full expansion of the THV. In the most recent PARTNER 3 trial (43), larger SAVR valves were used and more aortic root enlargements were performed compared to earlier trials, which likely resulted in smaller TAVR EOAs compared to SAVR EOAs (1.7±0.02 *vs.* 1.8±0.02 cm^2). Despite higher ejection fraction (84.2%±0.71% *vs.* 76.6%±0.81%) and stroke volume index (41.9±0.35 *vs.* 38.0±0.40 mL/m^2) in TAVR *vs.* SAVR cohorts, there was still more severe PPM for SAVR compared to TAVR (6.3% *vs.* 4.3%). This counterintuitive finding suggests that SAVR may be associated with low-flow pseudo-PPM however the clinical impact of this entity is unknown. The supra-annular position of the self-expanding valve may help explain the even lower rates of severe PPM in the low risk Evolut trial

where severe PPM occurred at 12 months in 1.8% of the patients in the TAVR group and in 8.2% in the surgery group (44).

PPM and valve durability

Recent studies have not shown a significant difference in valve durability between SAVR and TAVR however long-term follow-up is still lacking. In the life-time management decision-making process, valve durability becomes a focus and the effect of PPM on SVD of SAVR valves has been reported. Mahjoub *et al.* prospectively studied 194 patients with bioprosthetic SAVR, mean time interval since SAVR was 7.9±3 years; 24% developed calcification on multi-detector computed tomography (CT) (45). PPM was the strongest predictor of valve calcification (OR =3.67; 95% CI: 1.25–10.6; P=0.01). Flameng *et al.* followed 664 SAVR patients for a median of 6.1 years and showed that PPM was independently associated with a 2.3-fold increase in the risk of SVD (35). This association may be related to higher mechanical leaflet stress in the setting of high flow rates and higher mechanical leaflet stress related to under-expansion of the valve (46-48).

Valve design and incidence of PPM

Surgical valve designs may significantly influence the incidence of PPM (49), particularly evident when comparing the expected normal hemodynamics of a stented, stentless and homograft bioprostheses (*Table 2*). Supra-annular implanted valves show lower rates of PPM compared to other types of porcine bioprosthetic valves. Stentless porcine valves have been shown to have low rates of PPM when compared to stented bioprosthetic valves, likely due to the lack of stents which allows for more space within the valves and likely creates a higher EOA.

Few direct comparisons of THV designs evaluate possible differences in the incidence of PPM with different valve types. When looking at the reported incidences of PPM by valve type, PPM is more common with balloon-expandable *vs.* self-expanding TAVR (16). Outcomes associated with PPM, however, appear less significant with balloon-expandable compared to self-expanding TAVR (HR =1.1–1.3 *vs.* HR =1.6–1.8, respectively). Some of these differences could relate to differences in valve design and pressure recovery.

Pressure recovery downstream of the aortic valve constitutes an important factor affecting the calculation of PG across the valve and therefore the aortic valve area (50). The pressure gradient measured at the vena contracta (i.e., the pressure gradient measured by echo Doppler) represents the greatest pressure difference across a stenotic orifice. However, downstream from the vena contracta the kinetic energy of the blood is converted back to potential energy (pressure) with pressure recovery in the ascending aorta. Although both the vena contracta gradient and pressure recovered gradients exist *in vivo*, the recovered pressure represents the net pressure seen by the left ventricle and may be the most relevant hemodynamic measurement (13). The amount of pressure recovery is dictated by several factors such as turbulence (51), velocity of blood at the orifice and the geometry of the aorta (52).

In a recent *in vitro* study of the two commercially-available THVs, Hatoum *et al.* showed that while gradients at the vena contracta are higher with the balloon-expandable, in part because of a slight increase in gradient within the stent frame, the net gradient after pressure recovery was significantly lower compared to self-expanding THV (53). Thus, efficiency of pressure recovery significantly depends on valve type likely due to stent interference with the recovering blood flow (54), and the calculated EOA using the vena contracta gradients underestimates the downstream valve area, and overestimate the severity of PPM for the balloon-expandable valve.

The CHOICE trial randomized 240 high-risk patients to receiving either balloon-expandable valve or self-expanding valve and followed through 30 days. EOAi was slightly larger in the self-expanding valve *vs.* the balloon-expandable valve cohort (1.1 *vs.* 1.0 cm^2, P=0.04), and mean gradient lower (6.6 *vs.* 8.9 mmHg, P<0.001) (55). This is consistent with supra-annular design of the self-expanding valve prosthetic valve and the intra-annular position of the balloon-expandable valve. The hemodynamic benefits of the larger self-expanding valve orifice may be offset by a significantly higher moderate/severe perivalvular regurgitation rate, 18.3% *vs.* 4.1%, P<0.001, when compared with balloon-expandable valve at 1-year follow-up (56). At 5-year follow-up the incidence of paravalvular leak between the valve types had equalized but the mean gradient widened (12.2 mmHg for the balloon-expandable valve *vs.* 6.9 mmHg for the self-expanding valve, P=0.001) (57). There was still no difference in clinical outcome between the valve types suggesting that gradients alone do not drive outcomes. The generalizability of even

Table 7 Summary of reasons for discrepancy in the effects of severe PPM on outcomes

Reasons for discrepant incidence of PPM following AVR
Method of EOA calculation (measured *vs.* predicted)
Failure to correct cutoffs for obesity
Timing of measurement (immediate *vs.* later)
Effect of underlying flow state
Method of gradient determination (invasive *vs.* non-invasive)
Reasons for discrepant outcomes of PPM following AVR
Method of EOA calculation (measured *vs.* predicted)
Incomplete correction for confounding and competing outcomes variables (i.e., paravalvular aortic regurgitation, low flow state, other survival limitations)
Underpowered analysis (i.e., in setting of low disease incidence)
Limited follow-up (i.e., ≤1 year)

Modified from Herrmann *et al.* (37). PPM, prosthesis-patient mismatch; AVR, aortic valve replacement; EOA, effective orifice area.

these recent studies are uncertain given the continuous technical improvements in subsequent generations of TAVR.

Reducing discrepancies in PPM reporting

Clearly standardizing the methods for measuring EOA following both surgical and transcatheter valve replacement, should be adopted. The ideal measurement protocol uses the outer-to-outer border of the stented valve at its ventricular tip as the measure of left ventricular outflow tract (LVOT) consistent with the methodology used for prosthetic surgical valves. Pulse wave Doppler is then performed by placing the sample volume just apical to THV stent and the stroke volume across the valve calculated (58). There are nonetheless, multiple pitfalls to this measurement: (I) obtaining on-axis sagittal plane images of a circular or elliptical stent frame (i.e., bisecting the largest dimension in systole); (II) ill-defined LVOT diameter in the setting of a THV positioned below the annulus (i.e., with stent frame protruding into the left ventricular outflow space) which might cause overestimation of stroke volume if the native anatomy is used to calculate valve area; (III) inaccurate positioning of the pulsed wave Doppler sample volume (either too apical or within the stent frame). Because of these numerous limitations, the use of predicted EOA could reduce the variability introduced by site-measured EOA.

Nonetheless, there are limitations to using predicted EOA: (I) the accuracy of the reported normal reference values particularly when based on small numbers of patients; (II) the variability of actual deployment size for TAVR, given the wide native annular range that a given valve size can address; and (III) the generalizability of normative data must take into account patient-specific factors such as small annuli in females, valve-in-valve procedures, low flow, non-White and Hispanic patients, and atrial fibrillation (37). Valve-in-valve (42) and flow-dependent normative hemodynamics (17) have been reported for the balloon-expandable valve and may improve the accurate assessment of PPM incidence and outcomes. In addition, there are other possible reasons for the discrepant reported outcomes of PPM in the literature (*Table* 7) (37). For instance, STS-TVT analysis reporting a ~20% increased risk of mortality with significant PPM in TAVR patients, did not adjust for paravalvular regurgitation or other confounding and competing risks.

Clinical context

Although using the predicted EOAi for a given THV can be performed using the normative data published, the discussion above raises significant issues with the clinical value of such an exercise for all TAVR valves. For TAVR, the rates of PPM are very low and contribute to the tenuous association with mortality. Randomized trials suggest no significant mortality, and non-randomized data

show a low risk for increased mortality, which may be related to a variety of confounders. Nonetheless, given the evidence of the negative impact of PPM on SVD for SAVR, avoiding PPM has clinical importance. In addition, the hemodynamic differences between the self-expanding and balloon-expandable valve which may support a lower PPM rate in the supra-annular valves, must be balanced by the higher risk of paravalvular regurgitation, new permanent pacemakers, as well as issues of coronary re-access and higher stroke rates associated with the self-expanding valve. It thus seems more rational to make valve choice based on factors other than PPM.

Conclusions

The measurement of PPM is nuanced with multiple hemodynamic variables affecting quantitation of prosthetic EOA. The identification and grading of PPM should preferably use the predicted EOAi and apply different cutoffs depending on body size. Other confounders such as pseudo-PPM due to low flow, and pressure recovery, require further study. However, when using the predicted EOAi to assess PPM, it is critical to use reliable sources for the normal reference values of EOAs for the different models and sizes of TAVR or SAVR valves.

TAVR is associated with less PPM than SAVR and severe PPM in SAVR is associated with increased mortality. Thus, an individualized approach to valve choice should always be made, considering these differences in outcomes related to PPM, as well as differences in incidence and outcomes associated with other complications.

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Footnote

Conflicts of Interest: R.T.H. is Echo Core Lab Director for multiple transcatheter aortic valve replacement trials for which she receives no direct compensation. P.P. is Echo Core Lab Director for multiple transcatheter aortic valve replacement trials for which he receives no direct compensation.

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