# Aortic valve disease : novel imaging insights from diagnosis to therapy

Ewe, See Hooi

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# Hemodynamic and Clinical Impact of Prosthesis–Patient Mismatch After Transcatheter Aortic Valve Implantation

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**Objectives** This study examined the mid-term hemodynamic and clinical impact of prosthesis–patient mismatch (PPM) in patients undergoing transcatheter aortic valve implantation (TAVI) with balloon-expandable valves.

**Background** PPM can be observed after aortic valve surgery. However, little is known about the incidence of PPM in patients undergoing TAVI.

**Methods** Echocardiography and clinical assessment were performed in 165 patients at baseline, before hospital discharge, and at 6 months after TAVI. PPM was defined as an indexed effective orifice area $\leq 0.85$ cm$^2$/m$^2$.

**Results** Thirty patients (18.2%) showed PPM before hospital discharge. At baseline, patients with PPM had a larger body surface area ($1.84 \pm 0.18$ m$^2$ vs. $1.73 \pm 0.18$ m$^2$, $p = 0.003$) and a greater severity of aortic stenosis (indexed valve area $0.35 \pm 0.09$ cm$^2$/m$^2$ vs. $0.40 \pm 0.10$ cm$^2$/m$^2$, $p = 0.005$) than patients without PPM. Patients with PPM demonstrated a slower and smaller reduction in mean transaortic gradient, limited left ventricular (LV) mass regression, and left atrial volume reduction over 6 months compared with patients without PPM. LV filling pressure, measured by E/e′, tended to remain elevated in patients with PPM. Importantly, a higher proportion of patients with PPM did not improve in New York Heart Association functional class compared with patients without PPM (36.7% vs. 1.5%, $p < 0.001$), although major adverse valve-related and cardiovascular events did not differ between the 2 groups.

**Conclusions** PPM may be observed after TAVI and when present may be accompanied by less favorable changes in transvalvular hemodynamics, limited LV mass regression, persistent elevated LV filling pressure, and less improvement in clinical functional status. (J Am Coll Cardiol 2011;58:1910–8) © 2011 by the American College of Cardiology Foundation

Prosthesis–patient mismatch (PPM) can be observed after surgical aortic valve replacement for severe aortic stenosis (AS) (1–4) when the effective orifice area (EOA) of a normally functioning prosthesis is too small in relation to the patient's body size (5). The presence of significant PPM after aortic valve surgery has been associated with worse transvalvular hemodynamics and limited regression of left ventricular (LV) hypertrophy as a result of increased LV afterload (6). In addition, reduced indexed EOA has been reported to negatively affect clinical outcomes (1–4).

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So far, only a few small series (7–9) have described the incidence of PPM after transcatheter aortic valve implantation (TAVI), and little is known about its impact on LV performance and clinical outcomes in these patients. Therefore, we aimed to evaluate the mid-term hemodynamic and clinical impact of PPM in patients with severe

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AS undergoing TAVI with the balloon-expandable Edwards SAPIEN bioprosthesis (Edwards Lifesciences, Inc., Irvine, California).

## Methods

**Patient population.** A total of 190 consecutive patients with symptomatic severe AS who underwent TAVI at Leiden University Medical Center, Leiden, the Netherlands, and Centro Cardiologico Monzino, IRCCS, Milan, Italy, were included. Based on a multidisciplinary team assessment, all patients had severe AS, defined as an aortic valve area <1 $cm^2$ or <0.6 $cm^2/m^2$, and were considered at high operative risk or had contraindications to conventional aortic valve surgery. Patients with previous aortic or mitral prostheses, unsuccessful TAVI, or an echocardiographic follow-up <6 months were excluded from the present analysis.

According to the institutional protocols, all patients underwent clinical and echocardiographic evaluation at baseline, post-procedure (before hospital discharge), and at 6 months follow-up. The incidence of PPM and the hemodynamic and clinical impact of the presence of PPM during follow-up were assessed. Clinical and echocardiographic data were prospectively recorded and retrospectively analyzed.

**TAVI procedure.** The balloon-expandable Edwards-SAPIEN prostheses (Edwards Lifesciences, Inc.) of either 23 or 26 mm was used in all patients when the aortic annulus was 18 to 22 mm and 21 to 25 mm (as confirmed by transesophageal echocardiography), respectively (10). This valve consists of a trileaflet bovine pericardial tissue valve, mounted within a stainless steel balloon-expandable stent. As previously described (11), the device was delivered via either a transfemoral (retrograde) or transapical (antegrade) approach. The transapical approach was performed in patients with unsuitable aortoiliofemoral anatomy such as iliofemoral arteries <7 to 8 mm, marked tortuosity, abdominal aortic aneurysm, porcelain aorta, and/or previous aortoiliac surgery or intervention (12). All procedures were performed under transesophageal echocardiographic and fluoroscopic guidance.

**Transthoracic echocardiography.** Transthoracic echocardiography was performed in all patients at baseline, before hospital discharge, and at 6-month follow-up, using a commercially available ultrasound system (Vivid-7, General Electric, Horten, Norway). All images were digitally stored for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway) and included standard 2-dimensional, color, pulsed, and continuous-wave Doppler acquisitions (13–15). Standard linear LV dimensions were obtained (14), and LV mass was calculated as recommended (14). LV end-diastolic and -systolic volumes were measured from the standard apical views according to the biplane Simpson method (14) and indexed to body surface area (BSA). Next, LV ejection fraction was derived. Similarly, maximal left atrial (LA) volumes were measured using the biplane Simpson method and indexed to BSA (14). Pulmonary artery systolic pressure was estimated from the Doppler spectral signal of tricuspid regurgitation jet (16). The presence of aortic or mitral regurgitation was evaluated using color Doppler, and the severity was assessed according to current guidelines (15).

**Abbreviations and Acronyms**

**AS** = aortic stenosis
**BSA** = body surface area
**EOA** = effective orifice area
**LA** = left atrium
**LV** = left ventricular
**LVOT** = left ventricular outflow tract
**MAVCE** = major adverse valve-related and cardiovascular event(s)
**NYHA** = New York Heart Association
**PPM** = prosthesis–patient mismatch
**TAVI** = transcatheter aortic valve implantation

To assess LV diastolic function, transmitral early (E-wave) and late (A-wave) velocities and E-wave deceleration time were measured using pulsed-wave Doppler at the mitral leaflet tips (16). Pulmonary venous flow velocities during systole and diastole were also recorded (16). By integrating transmitral and pulmonary venous flow analysis, diastolic dysfunction was classified as follows: 1) impaired relaxation if mitral E/A <0.8 and pulmonary venous systolic velocity > diastolic velocity; 2) pseudonormal filling if mitral E/A = 0.8 to 1.5, E-wave deceleration time = 160 to 200 ms and pulmonary venous systolic velocity < diastolic velocity; and 3) restrictive filling if E/A ≥2, E-wave deceleration time <160 ms, and pulmonary venous systolic velocity < diastolic velocity (16). In addition, peak early diastolic velocities of the septal mitral annulus (e′) were measured by pulsed wave tissue Doppler imaging from the apical 4-chamber view (16). Then, the ratio of E/e′ was calculated. In patients who were not in sinus rhythm, e′ was used as an additional parameter to help determine the degree of LV diastolic dysfunction: impaired relaxation if e′ <10, pseudonormal filling if e′ <8, and restrictive filling if e′ <5 (17).

The aortic annulus was measured in a zoomed-up parasternal long-axis view as recommended (14). Similarly, the left ventricular outflow tract (LVOT) diameter was measured within 5 to 10 mm into the LVOT from the level of the aortic annulus in mid-systole (13). Pulsed-wave Doppler was used for LVOT measurements and continuous-wave Doppler was used for transaortic measurements. Using the continuity equation (13), the aortic valve area was obtained and indexed to BSA. In patients with sinus rhythm, the 3 best available signals were recorded and averaged. In patients who were not in sinus rhythm, a minimum of 5 measurements was averaged (13).

**Definition of PPM after TAVI.** After TAVI, the EOA of the prosthesis was similarly calculated using the continuity equation approach. From the parasternal long-axis view in a zoomed mid-systolic frame, the LVOT was measured just below the ventricular end of the prosthesis (but not inside it) to avoid the area of subvalvular flow acceleration. The EOA was subsequently calculated, assuming a circular geometry

of the LVOT, and indexed to BSA. PPM was defined as an indexed EOA ≤0.85 $cm^2/m^2$ (3,6).

**Follow-up data collection.** Before hospital discharge and at 6-month follow-up, clinical evaluation included the classification of heart failure symptoms according to the New York Heart Association (NYHA) functional class. In addition, all adverse procedural and in-hospital events and mortality were recorded. In particular, major adverse valve-related events, defined as any structural deterioration or nonstructural prosthesis dysfunction, valve thrombosis, embolism, bleeding event, or valve endocarditis, were recorded (18).

During follow-up, major cardiovascular events, such as death, myocardial infarction, stroke, and heart failure, were recorded. A combined endpoint of major adverse valve-related and cardiovascular events (MAVCE) was used for Kaplan-Meier survival analysis.

**Statistical analysis.** Continuous variables are presented as mean and SD unless otherwise specified. Categorical variables are presented as frequencies and percentages. Preprocedural and follow-up data were compared between patients with PPM (indexed EOA ≤0.85 $cm^2/m^2$) and without PPM (indexed EOA >0.85 $cm^2/m^2$). An unpaired Student *t* test or chi-square test or the Fisher exact test was used to compare continuous or categorical variables, as appropriate. A chi-square test was used to compare categorical variables when no cells had an expected count <5, whereas the Fisher exact test was performed when ≥1 cell had an expected count <5. A 2-way repeated-measures analysis of variance was used to evaluate the effects of time (baseline vs. hospital discharge vs. 6-months follow-up) and the presence or absence of PPM on each echocardiographic variable (EOA, transaortic gradient, LV ejection fraction and mass, LA volume, and E/e′), followed by post hoc analyses for significant results performed using Bonferroni correction with 3 pairwise comparisons. In addition, the interaction between group (presence or absence of PPM) and time was also analyzed for each echocardiographic variable and expressed as group-by-time analysis of variance. Finally, the MAVCE-free survival rates were presented as Kaplan-Meier curves, and the log-rank test was used for comparison between groups. A 2-tailed probability value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS for Windows version 16 (SPSS Inc., Chicago, Illinois).

## Results

**Patient population.** A total of 190 patients were initially included. Of these patients, 25 patients were excluded for different reasons. Eight patients were excluded due to previous aortic or mitral prostheses, and 4 patients did not have a successful implantation procedure. Nine patients died before 6 months and were subsequently excluded from further analysis. These events were due to in-hospital deaths from massive stroke (n = 1), pulmonary disease (n = 2), heart failure (n = 3), and deaths within 6 months from end-stage lung disease (n = 1), chronic renal disease (n = 1), and myocardial infarction (n = 1). They were unrelated to PPM as none of these patients demonstrated PPM post-TAVI. In addition, a further 4 patients were excluded due to extremely poor acoustic windows and echocardiographic images unsuitable for accurate interpretation. Therefore, a total of 165 patients composed the final study population.

The incidence of PPM (indexed EOA ≤0.85 $cm^2/m^2$) post-TAVI was 18.2% (n = 30), as assessed by transthoracic echocardiography before hospital discharge. Baseline clinical and echocardiographic characteristics of patients with and without PPM are summarized in Tables 1 and 2. Patients with PPM had a significantly larger BSA (Table 1) (19). In addition, patients with PPM had a greater severity of AS at baseline (indexed aortic valve area 0.35 ± 0.09 $cm^2/m^2$ vs. 0.40 ± 0.10 $cm^2/m^2$, p = 0.005) compared with patients without PPM, although the calculated valve areas were not significantly different. There was also a trend toward a smaller LVOT, sinotubular junction, and ascending aorta in patients with PPM. However, the aortic annulus diameter, on which the prosthesis sizing was based, did not differ between the 2 groups (Table 2).

**Hemodynamic impact of PPM assessed by echocardiography.** Echocardiographic Doppler data at baseline, hospital discharge, and 6-month follow-up are summarized in Figure 1. Per the definition, patients with PPM were characterized by a smaller EOA at discharge and 6-month follow-up compared with those without PPM (Fig. 1A). Accordingly, patients with PPM demonstrated a slower and smaller reduction in mean transaortic gradient post-TAVI, resulting in a higher transvalvular gradient at 6-month follow-up (16 ± 8 mm Hg vs. 10 ± 4 mm Hg, p < 0.001) compared with patients without PPM (Fig. 1B).

Small improvements in LV ejection fraction were noted in both groups of patients with and without PPM post-TAVI, and no significant difference in LV ejection fraction was observed between the 2 groups (Fig. 2A). However, in terms of LV mass regression, patients with PPM had a smaller LV mass regression 6 months post-procedure (with a reduction in LV mass index of −7.2 ± 4.6% vs. −21.1 ± 10.6%, p < 0.001) compared with patients without PPM (Fig. 2B). Similarly, patients with PPM had a smaller reduction in LA volume 6 months post-TAVI (with a reduction in LA volume index of −8.0 ± 9.7% vs. −26.0 ± 10.5%, p < 0.001) compared with patients without PPM (Fig. 2C).

With regard to LV filling pressure, E/e′ remained elevated in patients with PPM at 6 months despite TAVI (Fig. 2D). In contrast, TAVI resulted in the significant reduction of LV filling pressure in patients without PPM (with a reduction in E/e′ of −29.7 ± 7.0% vs. −4.6 ± 21.4%, p < 0.001) (Fig. 2D). When LV diastolic function was analyzed according to diastolic dysfunction grade, a higher proportion of patients without PPM showed improvement in LV diastolic function than those with PPM (47.4% vs. 10%, p < 0.001) (Fig. 3A).

**Table 1** Baseline Clinical Characteristics

| | PPM (n = 30) | No PPM (n = 135) | p Value* |
|---|---|---|---|
| Age, yrs | 77.8 ± 9.8 | 81.1 ± 6.2 | 0.084 |
| Male | 36.7 | 39.3 | 0.84 |
| Body surface area, $m^2$ | 1.84 ± 0.18 | 1.73 ± 0.18 | 0.003 |
| Body mass index, $kg/m^2$ | 26.6 ± 4.0 | 25.5 ± 5.1 | 0.25 |
| Logistic EuroSCORE | 22.2 ± 9.9 | 21.9 ± 12.3 | 0.91 |
| NYHA functional class | | | |
| II | 23.3 | 17.0 | 0.46† |
| III | 56.7 | 68.2 | |
| IV | 20.0 | 14.8 | |
| Previous myocardial infarction | 16.7 | 16.3 | 1.00 |
| Previous coronary bypass surgery | 23.3 | 18.5 | 0.80 |
| Previous percutaneous coronary intervention | 10.0 | 22.2 | 0.13 |
| Peripheral vascular disease | 26.7 | 28.9 | 0.82 |
| Hypertension | 70.0 | 75.5 | 0.62 |
| Hypercholesterolemia | 43.3 | 36.3 | 0.67 |
| Diabetes | 33.3 | 17.0 | 0.080 |
| Smoking | 20.0 | 31.1 | 0.18 |
| Frailty‡ | 26.7 | 21.5 | 0.81 |
| Heart rhythm | | | |
| Sinus | 80.0 | 81.5 | 0.80 |
| Atrial fibrillation | 10.0 | 14.8 | 0.77† |
| Pacemaker | 10.0 | 3.7 | 0.16† |
| Creatinine clearance, ml/min | 46.8 ± 6.0 | 49.3 ± 21.3 | 0.57 |
| Hemoglobin, g/dl | 11.3 ± 2.5 | 11.6 ± 2.1 | 0.53 |
| Approach | | | |
| Transfemoral | 63.3 | 46.7 | 0.11 |
| Transapical | 36.7 | 53.3 | |
| Prosthesis size, mm | | | |
| 23 | 50.0 | 35.6 | 0.15 |
| 26 | 50.0 | 64.4 | |

Values are mean ± SD or %. *p value for comparison between PPM and no PPM using an unpaired *t* test or chi-square test. †p value by Fisher exact test. ‡Frailty assessed according to Fried et al. (19).

NYHA = New York Heart Association; PPM = prosthesis–patient mismatch.

In terms of aortic regurgitation, there was no difference in the proportion of patients with aortic regurgitation grade ≥2 before hospital discharge (13.3% vs. 23.0%, p = 0.33) and at 6-month follow-up (13.3% vs. 28.1%, p = 0.11) in the group with and without PPM. During 6-month follow-up, the presence of PPM did not have a significant effect on aortic regurgitation post-TAVI. The proportion of patients who did (33.3% vs. 29.6%) or did not improve (66.7% vs. 70.4%, p = 0.83) in terms of aortic regurgitation grade was similar in patients with and without PPM. Similarly, mitral regurgitation was not affected by the presence of PPM. Patients with PPM who did (26.7% vs. 25.2%) or did not improve (73.3% vs. 74.8%, p = 0.82) in terms of mitral regurgitation grade was similar to the group without PPM.

**Clinical impact of PPM.** The majority of patients (n = 152, 92.1%) reported a significant improvement in NYHA functional class at 6 months after TAVI. However, there was a significant proportion of patients with PPM (n = 11, 36.7%) who did not demonstrate an improvement in functional class status. In contrast, among patients without PPM post-TAVI, only a small minority of patients (n = 2, 1.5%) did not show an improvement in functional status (Fig. 3B).

No patients were lost during the follow-up period (mean 17.6 ± 7.0 months) and a total of 18 MAVCE were observed. Three events (10%) occurred in the group with PPM: end-stage lung disease, bleeding event, and infective endocarditis. The remaining 15 events (11.1%) occurred in patients without PPM: 2 deaths (liver cirrhosis, intestinal ischemia), myocardial infarction (n = 3), stroke (n = 2), heart failure (n = 5), and bleeding events (n = 3). Importantly, there was no significant difference between patients with and without PPM in terms of MAVCE (log-rank p = 0.82) (Fig. 4).

## Discussion

The present evaluation demonstrated that PPM is rather common and occurred in 18.2% of patients undergoing TAVI with balloon-expandable valves. In particular, pa-

**Table 2** Baseline Echocardiographic Characteristics

| | PPM (n = 30) | No PPM (n = 135) | p Value* |
|---|---|---|---|
| Aortic valve area, $cm^2$ | 0.64 ± 0.16 | 0.69 ± 0.17 | 0.096 |
| Aortic valve area index, $cm^2/m^2$ | 0.35 ± 0.09 | 0.40 ± 0.10 | 0.005 |
| Left ventricular outflow tract, cm | 19.8 ± 2.1 | 20.4 ± 1.9 | 0.065 |
| Aortic annulus, cm | 21.2 ± 2.1 | 21.9 ± 2.2 | 0.15 |
| Aortic sinus, cm | 32.7 ± 4.7 | 32.7 ± 4.1 | 0.99 |
| Sinotubular junction, cm | 26.0 ± 4.0 | 27.5 ± 4.2 | 0.067 |
| Ascending aorta, cm | 32.0 ± 4.8 | 33.0 ± 4.2 | 0.062 |
| Mean transaortic gradient, mm Hg | 44 ± 18 | 49 ± 17 | 0.081 |
| Left ventricular end-diastolic volume index, $ml/m^2$ | 68 ± 31 | 61 ± 20 | 0.23 |
| Left ventricular end-systolic volume index, $ml/m^2$ | 32 ± 28 | 27 ± 16 | 0.13 |
| Left ventricular ejection fraction, % | 52 ± 16 | 55 ± 11 | 0.30 |
| Left ventricular mass index, $g/m^2$ | 149 ± 50 | 151 ± 38 | 0.84 |
| Left atrial volume index, $ml/m^2$ | 48 ± 11 | 52 ± 15 | 0.095 |
| E-wave, cm/s | 92 ± 24 | 92 ± 29 | 0.96 |
| A-wave, cm/s | 96 ± 44 | 100 ± 33 | 0.64 |
| Mitral E/A ratio | 1.20 ± 0.78 | 1.02 ± 0.61 | 0.20 |
| Mitral deceleration time, ms | 219 ± 82 | 222 ± 77 | 0.86 |
| E′, cm/s | 4.4 ± 0.9 | 4.7 ± 1.1 | 0.19 |
| E/e′ | 22.2 ± 8.3 | 20.6 ± 7.1 | 0.28 |
| Diastolic function | | | |
| Impaired relaxation | 30.0 | 43.0 | 0.38† |
| Pseudonormal filling | 53.3 | 45.9 | |
| Restrictive filling | 16.7 | 11.1 | |
| Pulmonary artery systolic pressure, mm Hg | 45 ± 7 | 42 ± 9 | 0.100 |
| Aortic regurgitation grade | | | |
| 0 | 20.0 | 19.3 | 0.63† |
| I | 50.0 | 58.5 | |
| II | 26.7 | 15.6 | |
| III | 3.3 | 6.7 | |
| Mitral regurgitation grade | | | |
| 0 | 20.0 | 13.3 | 0.57† |
| I | 56.7 | 53.3 | |
| II | 16.7 | 27.4 | |
| III | 6.7 | 5.9 | |

Values are mean ± SD or %. *p value for comparison between PPM and no PPM using unpaired *t* test or chi-square test. †p value by Fisher exact test.
PPM = prosthesis–patient mismatch.

tients with PPM were accompanied by less favorable changes post-TAVI compared with patients without PPM, with higher transvalvular gradient, limited LV mass regression, and LA volume reduction, and with persistent elevated LV filling pressures. Finally, more patients reported a lack of clinical improvement in the group with PPM, although the MAVCE-free survival did not differ between the 2 groups.

**Incidence of PPM in patients undergoing TAVI.** To minimize paravalvular regurgitation and to ensure adequate annular sealing, it is generally recommended that the implanted prosthesis be slightly larger than the native aortic annulus for the currently applied percutaneous systems (20). For example, in the balloon-expandable delivery system of the Edwards SAPIEN valves, the 23-mm valve is used for aortic annulus between 18 and 22 mm, whereas the 26-mm valve is used for aortic annulus between 21 and 25 mm (10,21). Despite these indications, the current study showed that PPM developed before hospital discharge in 18.2% of patients who underwent Edwards SAPIEN valve implantation.

Using the definition of an indexed EOA ≤0.85 $cm^2/m^2$, the incidence of PPM post-TAVI has been reported to be higher (32% to 39%) in patients who underwent CoreValve implantation (8,9). This difference can be partially explained by the fact that only 1 size of the device (26 mm, the smallest) was available at the time of TAVI in one-fourth of the patients (27%) in the reported series (9). In addition, the differences in prosthesis design may play a role. The Edwards SAPIEN valve is a trileaflet valve mounted on a balloon-expandable stainless stent frame that is 14.5 mm or 16 mm in height (for the 23- or 26-mm valve, respectively) and is implanted intra-annularly (21). Conversely, the CoreValve (designed for supra-annular implantation) has a longer frame of 53 or 55 mm (for the 26- or 29-mm device, respectively), with the lower third sitting within the LVOT

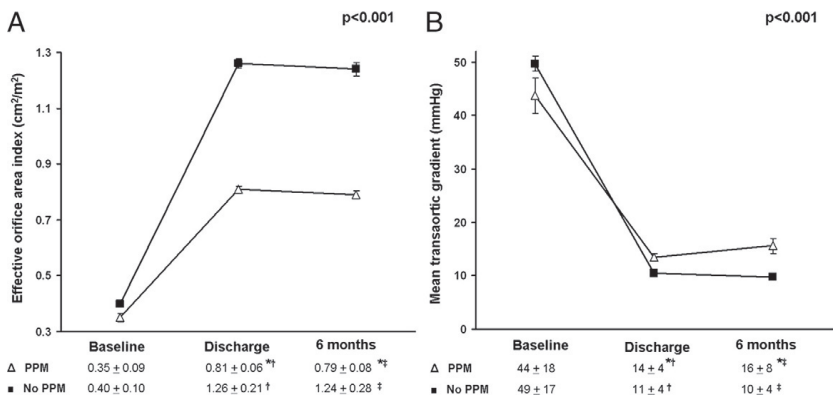


**Figure 1** **Impact of PPM on Transvalvular Hemodynamics**

Comparison of changes in aortic effective orifice area index **(A)** and mean transaortic gradient **(B)** in patients with and without prosthesis–patient mismatch (PPM). The p value is for the group-by-time analysis of variance. **Error bars** denote the SEM. Measurement values (mean ± SD) at the corresponding time point are given **below each graph**. *p < 0.05 between PPM and no PPM. Bonferroni post-hoc test: †p < 0.05 versus baseline. ‡p < 0.05 versus baseline.

(21). These differences may account for a potentially higher incidence of PPM with the CoreValve prosthesis. Finally, optimal prosthesis positioning may be important for good expansion and functioning of the transcatheter aortic bioprosthesis. Recently, Jilaihawi et al. (8) reported that a lower incidence of PPM could be achieved with optimal positioning of the prosthesis compared with suboptimal positioning (16% vs. 48%, p = 0.015) in 50 patients who underwent CoreValve implantation.

Of interest, the incidence of PPM has been reported to be lower with the balloon-expandable transcatheter valve compared with surgical bioprosthesis. In a recent matched study of 50 patients who underwent TAVI with an Edwards SAPIEN valve and 2 other groups of 50 patients who underwent surgery with a stented or a stentless bioprosthesis valve (7), the incidence of severe PPM (defined as an indexed EOA $\leq 0.65$ cm$^2$/m$^2$) was significantly higher in patients with either a stented (26%) or a stentless (28%) bioprosthetic valve than in patients who underwent TAVI (11%). Our findings extended this to a larger population of patients who underwent Edwards SAPIEN valve implantation. The lower incidence of PPM in the TAVI series compared with the surgical series may be partly explained by the absence of a sewing ring and a thinner transcatheter stent frame. Furthermore, sizes of surgical prostheses are generally smaller than transcatheter prostheses, although this might be offset by a routine annular debridement and removal of the native valve before implantation during surgery, which cannot be performed during TAVI (7).

The current study showed that patients with a larger BSA were more prone to the development of PPM post-TAVI. This is probably due to a higher transvalvular flow along with a higher cardiac output required in patients with a larger BSA. Similar findings were observed in the cited study of Jilaihawi et al. (8), including 50 patients who underwent TAVI with a CoreValve prosthesis, in which a larger BSA was observed in patients with PPM compared with patients without PPM (1.8 ± 0.3 vs. 1.7 ± 0.2). It is important to highlight that currently the choice of transcatheter bioprosthesis size depends exclusively on the aortic valve annulus, which was not different between the 2 groups of patients in the present study. These observations suggest that the limited transcatheter prosthesis sizes currently available (for either system) are probably inadequate to avoid PPM, especially in a subset of patients with a larger BSA and taking into account that additional maneuvers, such as removal of the calcified native valve before implantation and root enlargement, cannot be performed. To avoid PPM, a larger selection of transcatheter valve sizes (taking BSA into consideration) and continued improvement of valve design with a better hemodynamic profile (to provide a larger cross-sectional area for blood flow) may be necessary. However, excessive oversizing of the currently used transcatheter prosthesis has to be weighed against the risk of aortic rupture during balloon expansion, especially in patients with a calcified aortic root.

**Hemodynamic impact of PPM.** In the present study, a marked reduction in the mean transvalvular gradient was observed in all patients post-TAVI, in line with previously reported TAVI series (11). However, this study highlighted that patients with PPM showed less benefit in terms of mean transvalvular gradient reduction compared with patients without PPM. Similar findings have been described

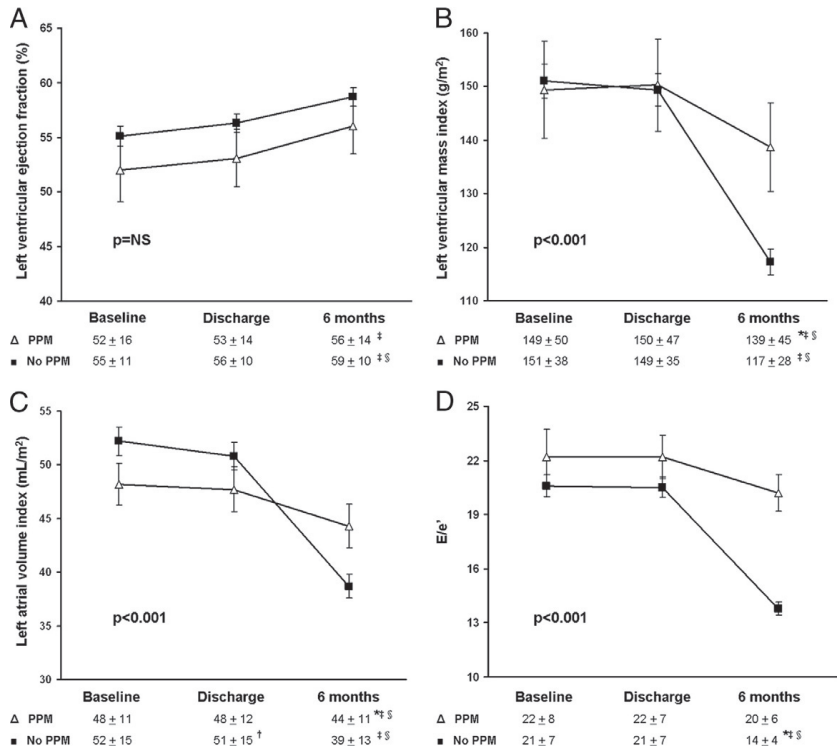


**Figure 2** **Hemodynamic Impact of PPM**

Comparison of changes in left ventricular ejection fraction **(A)**, left ventricular mass index **(B)**, left atrial volume index **(C)**, and E/e' **(D)** in patients with and without prosthesis–patient mismatch (PPM). **Error bars** denote the SEM. Measurement values (mean ± SD) at the corresponding time point are given **below each graph**. *$p < 0.05$ between PPM and no PPM. Bonferroni post-hoc test: †$p < 0.05$ versus baseline. ‡$p < 0.05$ versus baseline. §$p < 0.05$ versus discharge.

for patients with PPM with a surgical prosthesis who showed high transvalvular gradient even in the presence of a normally functioning prosthesis (6).

The impact of small indexed EOA and its residual high post-operative gradient on the delay of LV mass regression has been well documented in patients who underwent aortic valve replacement (22,23). Tasca et al. (23) showed that the extent of LV mass regression was related to the extent of the increase in indexed EOA after aortic valve surgery. Similarly, the current study showed that LV mass regression post-TAVI was more pronounced in patients without PPM, whereas in patients with PPM, the regression of LV hypertrophy was less marked (Fig. 2B). This observation might have important clinical implications because regression in LV hypertrophy has been reported to be an important predictor of survival after aortic valve replacement (24). Whether this finding extends to the TAVI population needs to be determined in future studies. In the current study, patients with PPM were observed also to exhibit a more delayed reduction in LA volume and persistently elevated LV filling pressures at 6 months post-TAVI (Fig. 2) compared with patients without PPM. These observations are presumably the result of a combination of incomplete relief of outflow tract obstruction and of a residual significant LV hypertrophy. Ikonomidis et al. (25) previously showed that abnormal LV relaxation was associated with residual LV hypertrophy in patients with isolated AS who had undergone aortic valve replacement. Accordingly, in the present study, only a small proportion (10%) of patients with PPM had improvement in their LV diastolic grades despite the relief of severe AS, whereas more patients without PPM (47%) exhibited a significant improvement in LV diastolic function.

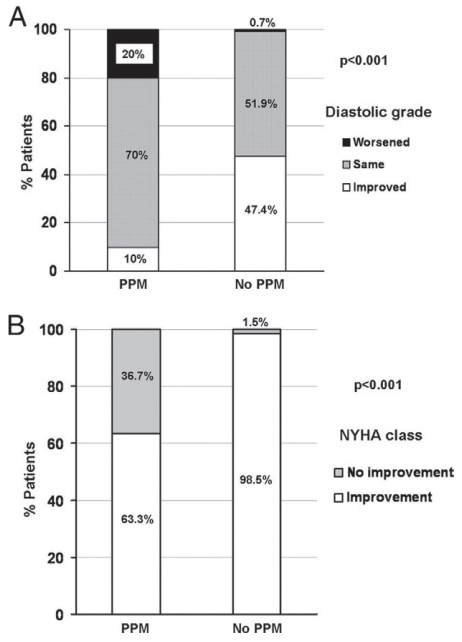


**Figure 3** **Impact of PPM on Left Ventricular Diastolic Function and Symptoms**

Comparison of the proportion of patients with changes in left ventricular diastolic dysfunction grade **(A)** and New York Heart Association (NYHA) functional class **(B)** at 6 months after transcatheter aortic valve implantation in patients with and without prosthesis–patient mismatch (PPM). p value denotes the comparison between patients with and without PPM.

**Clinical impact of PPM.** Another major finding of the present study is that the presence of PPM negatively affected the improvement in NYHA functional class at 6 months post-TAVI. This is in line with previous studies that showed that PPM (defined as an indexed EOA $\leq$0.85 $cm^2/m^2$) was independently associated with limited improvement NYHA functional class after aortic valve replacement with a stented bioprosthesis (26). In 312 patients who underwent bioprosthetic aortic valve replacement, Bleiziffer et al. (27) also observed that patients without PPM could achieve a better physical exercise capacity compared with patients with PPM. The suboptimal improvements in valvular hemodynamics and the higher residual afterload post-TAVI in patients with PPM could have contributed to the lack of clinical improvement. However, a recent study by Tzikas et al. (9), which included 74 patients who underwent TAVI with the CoreValve, reported that the functional status in terms of NYHA functional class did not differ between patients with (n = 12) and without (n = 62) severe PPM. One of the plausible explanations is that this observation was made by comparing the proportion of patients with NYHA functional class I to II versus III to IV 6 months post-TAVI in the 2 groups (9). Examining the paired changes in NYHA functional class from baseline to 6 months post-TAVI (Fig. 3B) may provide more reliable information on the impact of PPM on an individual patient basis.

So far, there are conflicting reports on the impact of PPM on clinical outcome after aortic valve replacement (1,2,4,28,29). Part of the controversy stems from the use of either the in vitro or the in vivo EOA measurement used to define PPM (5). Nonetheless, using the indexed EOA as a parameter to define PPM, recent series (1–4) demonstrated that patients without significant PPM had better early and late mortality benefits. In addition, patients without PPM exhibit more freedom from congestive heart failure after aortic valve replacement (30). However, the present study showed that there was no significant difference in terms of freedom from MAVCE between patients with or without PPM post-TAVI, which is similar to the finding of a recent series of TAVI using the CoreValve system (9).

**Study limitations.** Due to a relatively short follow-up period and few major adverse events observed in the present study, the effect of PPM on clinical outcomes will need to be verified in a larger population with a longer follow-up period post-TAVI.

## Conclusions

In patients with AS who underwent TAVI with balloon-expandable valves, PPM may be observed. When present,

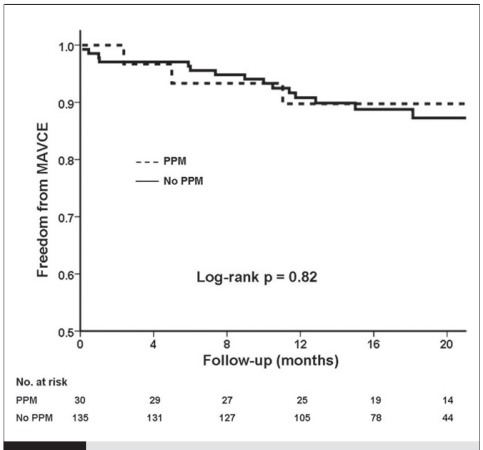


**Figure 4** **Kaplan-Meier Curves for Major Adverse Events After Transcatheter Aortic Valve Implantation**

Kaplan-Meier probability of freedom from combined major adverse valve-related and cardiovascular events (MAVCE) in patients with and without prosthesis–patient mismatch (PPM).

PPM may be accompanied by less favorable changes in transvalvular hemodynamics post-TAVI, together with limited LV mass regression and LA volume reduction and with persistent elevated LV filling pressure. More importantly, PPM may be also associated with less functional improvement after TAVI.

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**Key Words:** aortic valve ■ echocardiography ■ heart valve prosthesis ■ hemodynamics ■ transcatheter aortic valve implantation.