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## ► To cite this version:

Alexis Theron, Flora Lavagna, Guillaume Gaubert, Noémie Resseguier, Alizée Porto, et al.. Prosthesis-patient mismatch is an independent predictor of congestive heart failure after transcatheter aortic valve replacement. Archives of cardiovascular diseases, 2021, 114 (6-7), pp.504-514. 10.1016/j.acvd.2020.11.005 . hal-03150052

**HAL Id: hal-03150052**

**<https://hal.science/hal-03150052>**

Submitted on 22 Aug 2023

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## **Prosthesis-patient mismatch is an independent predictor of congestive heart failure after transcatheter aortic valve replacement**

**Abbreviated title:** PPM is a predictor of CHF after TAVR

**Tweet:** #PPMandTAVR

**Alexis Theron<sup>a,\*</sup>, Flora Lavagna<sup>b</sup>, Guillaume Gaubert<sup>c</sup>, Noemie Resseguier<sup>c</sup>, Alizée Porto<sup>a</sup>, Jerome Ferrara<sup>b</sup>, Nicolas Jaussaud<sup>a</sup>, Pierre Morera<sup>a</sup>, Thomas Cuisset<sup>b</sup>, Pierre Deharo<sup>b,d,e</sup>, Frederic Collart<sup>a</sup>**

<sup>a</sup> *Department of Cardiac Surgery, La Timone Hospital, 13005 Marseille, France*

<sup>b</sup> *Department of Cardiology, La Timone Hospital, 13005 Marseille, France*

<sup>c</sup> *EA 3279, Faculty of Medicine, 13385 Marseille, France*

<sup>d</sup> *C2VN, Inserm, Inra, Aix-Marseille University, 13005 Marseille, France*

<sup>e</sup> *Faculty of Medicine, Aix-Marseille University, 13385 Marseille, France*

\* Corresponding author at: Department of Cardiac Surgery, Hôpital de la Timone, 264 rue Saint-Pierre, 13005 Marseille, France.

*E-mail address:* alexis.theron@ap-hm.fr (A. Theron).

## Summary

*Background.* – Little is known about the effect of prosthesis-patient mismatch (PPM) on outcomes after transcatheter aortic valve replacement. We reported previously an increased risk of PPM with the SAPIEN 3 transcatheter heart valve (S3-THV).

*Aims.* – To investigate the association of PPM with 1-year outcomes in patients with severe aortic stenosis (AS) implanted with S3-THV.

*Methods.* – Moderate PPM was defined by an indexed effective orifice area (iEOA)  $\leq 0.85$  cm<sup>2</sup>/m<sup>2</sup>, and severe PPM by an iEOA  $< 0.65$  cm<sup>2</sup>/m<sup>2</sup>. Inclusion criteria were severe symptomatic AS and implantation with S3-THV. The primary endpoint was hospitalization for congestive heart failure (CHF) at 1 year; the secondary endpoint was all-cause mortality.

*Results.* – A total of 208 consecutive patients were included between 2016 and 2018. Male sex was prevalent (53.8%), mean age was  $81.9 \pm 6.2$  years, mean EuroSCORE II was  $4.35 \pm 3.37$ , mean LVEF was  $57.9 \pm 13\%$ . Moderate and severe PPM were observed in 69 (33.2%) and 10 (4.8%) patients. Patients with PPM were younger ( $80.4 \pm 7$  vs  $82.8 \pm 5.41$  years;  $P = 0.006$ ), had a larger BSA ( $1.84 \pm 0.19$  vs  $1.77 \pm 0.19$  m<sup>2</sup>;  $P = 0.01$ ), a lower iEOA ( $0.73 \pm 0.08$  vs  $1.11 \pm 0.22$  cm<sup>2</sup>/m<sup>2</sup>;  $P < 0.001$ ) and a higher mean gradient ( $14 \pm 4.6$  vs  $11.9 \pm 3.9$  mmHg;  $P < 0.001$ ). CHF occurred in 16.5% vs 7% ( $P = 0.03$ ). By multivariable analysis, PPM was independently associated with CHF (hazard ratio [HR] 3.17, 95% confidence interval [CI] 1.17 to 8.55;  $P = 0.032$ ), especially in patients with mitral regurgitation  $\geq 2/4$  (HR  $> 100$ , 95%CI  $> 100$  to  $> 1000$ ;  $P < 0.01$ ). PPM did not correlate with all-cause mortality (HR 0.90, 95%CI 0.22 to 3.03;  $P = 0.86$ ).

*Conclusions.* – PPM after S3-THV implantation is strongly associated with CHF at 1 year, but is not correlated with overall mortality.

## Résumé

*Contexte.* – Les conséquences du mismatch patient prothèse (MPP) après implantation d'une valve TAVI reste débattu. Nous avons préalablement rapporté un risque accru de MPP avec les endoprothèses Sapien 3 (S3-THV).

*Objectifs.* – étudier la corrélation entre MPP et évènements cliniques à un an chez les patients présentant une sténose aortique serrée (RAo) implantés d'une endoprothèse S3-THV.

*Méthodes.* – La PPM modéré était défini par un SVEi  $\leq 0,85 \text{ cm}^2/\text{m}^2$  et la PPM sévère par un SVEi  $< 0,65 \text{ cm}^2/\text{m}^2$ . Critères d'inclusion : RAo serré symptomatique implanté par S3-THV. Critère d'évaluation primaire : hospitalisation pour insuffisance cardiaque congestive (ICC) à un an. Critère d'évaluation secondaire : mortalité toutes causes.

*Résultats.* – Un total de 208 patients consécutifs ont été inclus entre 2016 et 2018. Le genre masculin était prédominant (53,8 %), l'âge moyen était de  $81,9 \pm 6,2$  ans, IMC moyen =  $26,43 \pm 5,29 \text{ kg}/\text{m}^2$ , l'EuroSCORE II moyen était de  $4,35 \pm 3,37$ , la FEVG moyenne était de  $57,9 \pm 13$  %. Les MPP modérés et sévères ont été observées chez 69 (33,2 %) et 10 (4,8 %) patients. Les patients atteints de MPP étaient plus jeunes ( $80,4 \pm 7$  vs  $82,8 \pm 5,41$  ans ;  $P = 0,006$ ), présentaient une plus grande surface corporelle ( $1,84 \pm 0,19$  contre  $1,77 \pm 0,19 \text{ m}^2$  ;  $P = 0,01$ ), une SVEi plus basse ( $0,73 \pm 0,08$  contre  $1,11 \pm 0,22 \text{ cm}^2/\text{m}^2$  ;  $P < 0,001$ ) et un gradient moyen plus élevé ( $14 \pm 4,6$  contre  $11,9 \pm 3,9$  mmHg ;  $P < 0,001$ ). L'incidence de l'ICC était significativement plus élevée au bout d'un an de suivi (16,5 % contre 7 % ;  $P = 0,03$ ). En analyse multivariée, la PPM était indépendamment associé à l'ICC (HR 3,17, IC95 % 1,17 à 8,55 ;  $P = 0,032$ ). Le risque d'ICC était prohibitif chez les patients avec MPP présentant une IM non traitée  $\geq$  grade 2/4 (HR  $> 100$ , IC95 %  $> 100$  à  $> 1000$  ;  $P < 0,001$ ). Cependant, la MPP n'était pas corrélé à la mortalité toute cause à un an de suivi (HR 0,90, IC95 % 0,22 à 3,03 ;  $P = 0,86$ ).

*Conclusions.* – La survenue d'un PPM après implantation d'une endoprothèse S3-THV est fortement associée au risque d'ICC à un an mais n'est pas corrélée à la mortalité toute cause.

## **KEYWORDS**

Aortic stenosis;

TAVR;

SAPIEN 3;

Patient-prosthesis mismatch;

Congestive heart failure

## **MOTS CLÉS**

Sténose aortique ;

TAVI ;

SAPIEN 3 ;

Mismatch patient prothèse ;

Insuffisance cardiaque

*Abbreviations:* BMI, body mass index; BSA, body surface area; CHF, congestive heart failure; CI, confidence interval; EOA, effective orifice area; IEOA, indexed effective orifice area; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; OR, odds ratio; PPM, patient-prosthesis mismatch; PVR, paravalvular regurgitation; SAVR, surgical aortic valve replacement; S3-THV, SAPIEN S3 transcatheter heart valve; TAVR, transcatheter aortic valve replacement.

## Background

Patient-prosthesis mismatch (PPM) occurs when the effective orifice area (EOA) of the implanted prosthesis is small relative to the patient body size [1]. The severity of PPM is defined according to the estimation of the indexed effective orifice area (iEOA) by transthoracic echocardiography; it is considered as moderate if the iEOA is between 0.65 and 0.85 cm<sup>2</sup>/m<sup>2</sup>, and severe when the iEOA is < 0.65 cm<sup>2</sup>/m<sup>2</sup> [2].

The results from several clinical studies have demonstrated the negative effect of PPM on life expectancy after surgical aortic valve replacement (SAVR) [3]. Some subgroups of patients are considered as “vulnerable” to the residual afterload caused by PPM, including those aged < 80 years, and those with impaired left ventricular ejection fraction (LVEF), severe left ventricular (LV) hypertrophy, concomitant moderate/severe mitral regurgitation (MR) or paradoxical low flow/low gradient aortic stenosis [4].

Currently, data in the literature focusing on the impact of PPM after transcatheter aortic valve replacement (TAVR) are scarce. Compared with SAVR, early generation transcatheter heart valves tended to have a better EOA because of the absence of material in the annular space [5]. First haemodynamic results from the PARTNER A cohort showed that the risk of PPM was dramatically decreased with the SAPIEN and SAPIEN XT valves (Edwards Lifesciences LLC, Irvine, CA, USA) at the expense of a prohibitive risk of paravalvular regurgitation (PVR) [6, 7]. Neither moderate nor severe PPM was a predictor of mortality in the TAVR arm of the PARTNER A cohort, whereas PPM was a powerful predictor of mortality in the surgical arm [7].

The new-generation SAPIEN S3 transcatheter heart valve (S3-THV; Edwards Lifesciences LLC, Irvine, CA, USA) has an outer annular skirt embedded, which limits the risk of PVR [8]. However, this additional material leads to turbulence during LV ejection, which increases the transprosthetic gradient. We observed previously that patients implanted with S3-THV experienced a 5-fold increased risk of PPM compared with an early generation transcatheter heart valve (SAPIEN XT). Meanwhile, the occurrence of PVR was dramatically reduced in patients with S3-THV [9].

By limiting the risk of PVR, we assume that S3-THV may reveal the true effect of PPM on outcomes after TAVR implantation. Hence, we investigated the association of PPM with 1-year outcomes in patients with severe aortic stenosis implanted with S3-THV.

## Methods

### Study population

This retrospective single-centre study was performed from 2015 to 2017 at La Timone Hospital, Marseille, France. We included all consecutive patients with severe symptomatic aortic stenosis who underwent TAVR with S3-THV after heart team endorsement. International review board approval was obtained. Patients who denied authorization for the anonymous publication of their clinical data for research purposes were excluded.

### Procedure

Suitable access sites and aortic annulus size were assessed by a computed tomography scan, and endorsed by the heart team [10]. Sizing of the S3 valve was based on native valve annulus size, as measured by computed tomography [11]. General or local anaesthesia was performed following heart team decisions. Fluoroscopic guidance was used for prosthesis positioning. Valve implantation was performed under rapid ventricular pacing. Prosthesis position and function were evaluated with angiography, aortic index measurement, transoesophageal echocardiography in case of general anaesthesia and transthoracic echocardiography in case of local anaesthesia.

### Data collection and follow-up assessments

Clinical follow-up assessments were performed at baseline, at discharge, at 1 month follow-up and at 1 year follow-up, and included formal examination by a cardiologist.

Transthoracic echocardiography was performed at baseline, at discharge and at 1-month follow-up in a core laboratory by experienced cardiologists. A double reading of each echocardiographic examination was performed systematically to improve the accuracy of LV outflow tract diameter measurement. The iEOA was calculated as the EOA divided by the body surface area (BSA). After TAVR implantation, the iEOA was estimated using the LV outflow tract diameter and velocity measured immediately proximal to the stent. Moderate PPM was defined as an iEOA  $\leq 0.85$  cm<sup>2</sup>/m<sup>2</sup>, and severe PPM was defined as an iEOA  $< 0.65$  cm<sup>2</sup>/m<sup>2</sup> [2].

At 1-month follow-up, patients were considered as vulnerable to PPM in the case of age  $< 80$  years, severe LV hypertrophy ( $> 18$  mm), LVEF  $< 50\%$ , untreated MR  $\geq 2/4$  or paradoxical low

flow/low gradient aortic stenosis. An integrative semiquantitative approach was used to assess the severity of PVR [12].

## **Endpoints**

The primary endpoint was the occurrence of hospitalization for congestive heart failure (CHF) 1 year after TAVR. All-cause mortality at 1 year after TAVR implantation was the secondary exploratory outcome. The physician collected all outcomes at each follow-up time point; they were defined according to the Valve Academic Research Consortium-2 definitions [12]. These endpoints were also analysed in the different subgroups of patients who were “vulnerable” to PPM, as described above.

## **Statistical analysis**

Baseline patient characteristics were described and compared according to PPM occurrence. Quantitative characteristics are described by their means  $\pm$  standard deviations or their medians (interquartile ranges), according to their distribution, and were compared using Student's *t* test, when valid, or the Mann-Whitney test otherwise. Qualitative characteristics are described by their numbers and percentages, and were compared using the  $\chi^2$  test, when valid, or Fisher's test otherwise. This analysis was completed by logistic regression models to estimate odds ratios (ORs) and their 95% confidence intervals (CIs), to quantify the association between baseline characteristics and the occurrence of PPM.

Analysis of the endpoints was based on a time-to-event approach. Cumulative incidence of CHF over the first year after TAVR was estimated using the time-to-event approach, taking into account the occurrence of death as a competing endpoint. Univariate Fine and Gray models were built to estimate hazard ratios (HRs) with their 95% CIs to quantify the association between baseline characteristics and CHF risk over the first year after TAVR. A multivariable analysis was performed to estimate adjusted hazard ratios with their 95% CIs. Overall mortality over the first year after TAVR was estimated using the Kaplan-Meier method. Univariate Cox models were built to estimate HRs with their 95% CIs to quantify the association between baseline characteristics and death risk over the first year after TAVR. A multivariable analysis was performed to estimate adjusted HRs with their 95% CIs. As sensitivity analyses, these analyses were performed in patients with vulnerability to PPM. All tests



were performed two-sided, and for all analyses a *P* value < 0.05 was considered statistically significant. All analyses were carried out using R software, version 3.4.3.

## Results

### Baseline characteristics

Among 270 patients who underwent a TAVR procedure from 2015 to 2017, 208 consecutive patients were included in the study (Fig. 1). Baseline characteristics and echocardiography data are shown in Table 1 and Table 2, respectively. The mean age was  $81.9 \pm 6.2$  years, and 112 patients (53.8%) were male. The mean BSA was  $1.79 \pm 0.19$  m<sup>2</sup>, and the mean body mass index (BMI) was  $26.4 \pm 5.29$  kg/m<sup>2</sup>. Ninety-four patients (45.3%) had a BMI < 25 kg/m<sup>2</sup>. Prevalence of obesity (BMI  $\geq$  30 kg/m<sup>2</sup>) and being overweight ( $25 \leq$  BMI < 30 kg/m<sup>2</sup>) were 17.8% (*n* = 37) and 36.5% (*n* = 76), respectively. The mean EuroSCORE II was  $4.35 \pm 3.37$ . The mean LVEF was  $57.9 \pm 13.0\%$ ; 47 patients (22.6%) had an LVEF < 50%. All patients had severe aortic stenosis, with a mean iEOA of  $0.41 \pm 0.10$  cm<sup>2</sup>/m<sup>2</sup> and a mean transaortic gradient of  $50.9 \pm 14.2$  mmHg.

### Procedural characteristics

Procedural data are shown in Table 3. The majority of patients were treated by a transfemoral approach (83.1%) and general anaesthesia (76%). Two patients died intraoperatively, as a result of an aortic annulus rupture, and three died within 30 days of the procedure, which represents an in-hospital mortality rate of 1.8%. None of the patients had a valve-in-valve. Nineteen patients (9.1%) had a vascular complication. Twenty-four patients (11.5%) had pacemaker implantation. The mean length of stay was  $5.6 \pm 8.9$  days. There were no differences between the groups regarding procedural events.

### Haemodynamic follow-up

The mean gradient decreased significantly from baseline to 1-month follow-up ( $50.9 \pm 14.2$  vs  $12.7 \pm 4.3$  mmHg; *P* < 0.001), and LVEF increased slightly ( $58 \pm 13\%$  vs  $62.2 \pm 12.4\%$ ; *P* < 0.001). The mean EOA was  $1.70 \pm 0.45$  cm<sup>2</sup>, and the mean iEOA was  $0.97 \pm 0.25$  cm<sup>2</sup>/m<sup>2</sup>. Table A.1.

Fifty-seven patients were aged < 80 years, 29 had untreated MR  $\geq$  2/4, 18 had severe LV hypertrophy and no patient had paradoxical low flow/low gradient aortic stenosis.

Seventy-nine patients (38%) had PPM, including 69 PPM (33.2%) with moderate PPM and 10 (4.8%) with severe PPM. Postoperative echocardiographic data for patients with severe PPM are shown in [Table A.2](#).

The prevalence of obesity was 26.6% (21/79) in the PPM group and 13.2% (17/129) in the no PPM group, without significant difference between these groups ( $P = 0.14$ ). The prevalence of PPM in obese patients was 52.6% (20/38).

Postoperative data for the population overall and according to PPM are shown in [Table 4](#). Patients with PPM had a significantly lower LVEF ( $59.2 \pm 14.0\%$  vs  $64.0 \pm 10.9\%$ ;  $P = 0.02$ ), lower iEOA ( $0.73 \pm 0.08$  vs  $1.11 \pm 0.22$  cm<sup>2</sup>/m<sup>2</sup>;  $P < 0.001$ ) and higher mean transprosthetic gradient ( $14.0 \pm 4.6$  vs  $11.9 \pm 3.9$  mmHg;  $P < 0.001$ ). The prevalence of patients with LVEF  $< 50\%$  was 27.8% (22/79) in the PPM group and 19.3% (25/129) in the no PPM group, without significant difference between groups ( $P = 0.13$ ). The incidences of untreated MR  $\geq 2/4$  (18.9% vs 11.4%;  $P = 0.74$ ) and PVR  $\geq 2/4$  (2.5% vs 5.4%;  $P = 0.83$ ) were similar between the PPM and no PPM groups.

## Predictors of PPM

Multivariable logistic regression was used to identify predictors of PPM. The use of single antiplatelet therapy ( $P = 0.78$ ) or dual antiplatelet therapy ( $P = 0.50$ ) or a vitamin K antagonist/non-vitamin K antagonist oral anticoagulant ( $P = 0.75$ ) at discharge was not associated with the occurrence of PPM in the univariate analysis. Significant predictors included larger BSA (OR 5.9, 95% CI 2.6 to 9.9;  $P < 0.001$ ), lower LVEF (OR 1.06, 95% CI 1.01 to 1.12;  $P = 0.01$ ), 23 mm prosthesis size (OR 1.63, 95% CI 0.22 to 3.22;  $P = 0.02$ ) and female sex (OR 2.44, 95% CI 1.11 to 3.88;  $P < 0.03$ ).

## Outcomes

### Hospitalization for CHF

Twenty-two patients (10.8%) experienced at least one episode of CHF requiring hospitalization: 13 patients (16.5% of patients with PPM) in the PPM group and nine patients (7% of patients without PPM) in the no PPM group ( $P = 0.03$ ). By multivariable analysis adjusted for age, sex, PVR  $\geq 2/4$ , preoperative LVEF and BMI, PPM was independently associated with recurrent CHF after TAVR implantation in competing risk analysis (HR 3.17, 95% CI 1.17 to 8.55;  $P = 0.032$ ) ([Fig. 2](#)).

Among the 29 patients with untreated MR  $\geq 2/4$ , four patients, who belonged exclusively to the PPM group, experienced at least one episode of CHF.

By multivariable analysis adjusted for age, sex and PVR  $\geq 2/4$ , PPM was strongly associated with CHF in the subgroup of vulnerable patients with untreated MR  $\geq 2/4$  (HR  $> 100$ , 95% CI  $>100$  to  $> 1000$ ;  $P < 0.001$ ), but was not associated with an increased risk of CHF in patients aged  $< 80$  years (HR 4.53, 95% CI 0.49 to 42.04;  $P = 0.14$ ), with LVEF  $< 50\%$  (HR 2.17, 95% CI 0.36 to 13.06;  $P = 0.31$ ) (Fig. 3) or with severe LV hypertrophy (HR 0.5, 95% CI 0.01 to 100;  $P = 0.5$ ).

### All-cause mortality

Eleven patients (5.3%) died during follow-up. Six patients (2.9%) died from cardiovascular causes, and five (2.4%) from non-cardiovascular causes – mainly cancer (80%). Four deaths (1.9%) occurred in the PPM group and seven (3.4%) in the no PPM group. All patients who died in the PPM group had moderate PPM.

By Kaplan-Meier analysis, 1-year overall mortality was 5.29% in the total population, 5.4% in the no PPM group and 5% in the PPM group, without significant difference between the groups ( $P = 0.98$ ). By multivariable analysis, adjusted for age, sex, PVR  $\geq 2/4$  and preoperative LVEF and BMI, PPM was not independently associated with overall mortality at 1-year follow-up (HR 0.90, 95% CI 0.22 to 3.03;  $P = 0.92$ ) (Fig. 4).

Among patients with vulnerability to PPM, six deaths (4.8%) occurred: two (1.6%) in the PPM group and four (3.2%) in the no PPM group. By multivariable analysis adjusted for age, sex and PVR  $\geq 2/4$ , PPM was not associated with overall mortality (Table 5).

## Discussion

The present study aimed to retrospectively investigate the association of PPM and 1-year outcomes in patients with severe aortic stenosis implanted with S3-THV. The main results were as follows: (1) PPM was prevalent after S3-THV implantation, occurring in 38% of patients; (2) the main predictors of PPM included larger BSA, lower LVEF, valve prosthesis  $\leq 23$  mm and female sex; (3) PPM was associated with CHF after S3-THV implantation, but did not correlate with 1-year overall mortality; (4) patients with untreated MR  $\geq 2/4$  could be particularly vulnerable to the haemodynamic consequences of PPM.

The clinical impact of PPM following aortic valve replacement has been a controversial issue since its first description by Rahimtoola [1]. PPM is considered moderate when the iEOA is  $\leq 0.85$   $\text{cm}^2/\text{m}^2$  and severe when the iEOA is  $< 0.65$   $\text{cm}^2/\text{m}^2$  [2]. The incidence of PPM after SAVR has been widely described, ranging from 20% to 70%, depending on the series [3].

PPM leads to less LV mass regression after SAVR as a result of the persistence of a residual afterload. Previous studies demonstrated an adverse impact of PPM on outcomes, especially in case of severe PPM or vulnerability [3, 4].

Moderate PPM and severe PPM occurred in 25% and 12% of patients, respectively, after TAVR implantation [13]. Several studies have demonstrated improved haemodynamic performances with a TAVR compared with SAVR, leading to a lower incidence of postoperative PPM [7, 14]. However, these studies were mainly based on the early generation SAPIEN XT transcatheter heart valve, and none of their haemodynamic results can be extended to S3-THV [15].

We found previously that S3-THV was associated with a higher risk of moderate and severe PPM than the SAPIEN XT transcatheter heart valve [9]. Miyasaka et al. have corroborated our results, as S3-THV was an independent predictor of PPM occurrence in their recent cohort OCEAN TAVI [16]. The dramatic increase in PPM rate is attributed to the additional subannular cuff that prevents the occurrence of PVR.

A recent registry of 757 patients treated with TAVR highlighted that intra-annular position of balloon-expandable valves could also play a role in the increased occurrence of PPM compared with supra-annular position [17]. However, balloon-expandable valves are still associated with a higher occurrence of PVR than S3-THV.

The consequences of PPM after TAVR remain a matter of debate because of methodological differences and the characteristics of the patients being studied. Pibarot et al. were the first to compare the incidence of PPM in the TAVR arm (including patients implanted with first-generation SAPIEN valves only) and the surgical arm of the PARTNER I cohort A [7]. In this study, PPM appeared as an independent predictor of mortality at 2 years in the SAVR group, but not in the TAVR group.

By comparison, severe PPM was associated with higher mortality and hospitalization for CHF at 1 year in the largest registry, including 62,125 TAVR procedures with several models and generations of valves [13].

To explain these conflicting data, we assume that the high rate of PVR with the early generation SAPIEN valve, which is known to be a strong predictor of mortality and CHF [6], could have masked the negative effect of PPM on outcomes.

Both haemodynamic sequelae (i.e. PPM and PVR) contribute to limit LV hypertrophy regression by exposing patients to a residual LV afterload, diastolic dysfunction and impaired coronary flow reserve [18, 19]. By avoiding the occurrence of the most important confounding factor, such as PVR, S3-THV may have revealed the negative effect of PPM on CHF occurrence.

In our study, obesity was frequent, and prevalence of PPM in obese patients was high (52.6%). It is well established that indexation of EOA to BSA can falsely overestimate the prevalence of PPM, especially in obese patients. Our results are in line with this hypothesis, as BMI and BSA were significantly higher in patients with PPM than in those without PPM.

To date, there is no other way to index EOA that correlates with prognosis [20]. Given the lack of evidence for a new definition of PPM in obese patients, some authors have arbitrarily decided to lower the threshold of iEOA defining PPM in obese patients [12]. Another approach could be to index the EOA to a more effective marker of obesity, such as the abdominal perimeter, but further investigations are still needed to validate novel prognostic markers in this specific subset.

## **Strengths and limitations**

Subclinical leaflet thrombosis occurred frequently after TAVR [21]. Attenuated leaflet motion can increase the transprosthetic gradient, which can mimic PPM. The main limitation is that we did not perform a computed tomography scan systematically after TAVR implantation. The real incidence of subclinical leaflet thrombosis in both groups was consequently unknown. However, all transthoracic echocardiograms were performed by experienced cardiologists, and a computed tomography scan was performed if there was any suspicion of subclinical leaflet thrombosis on transthoracic echocardiography. In addition, antiplatelet therapy and anticoagulants were used similarly in both subgroups, which limits treatment biases.

We did not find any correlation between PPM and 1-year mortality after S3-THV implantation. This can be explained by the short duration of follow-up. Moreover, the population implanted with TAVR was highly selected, with many co-morbidities, which could have masked the negative effect of PPM on survival.

Patients with PPM were significantly younger than those without PPM ( $80.4 \pm 7$  vs  $82.8 \pm 5.41$  years;  $P = 0.006$ ). This can be explained by the fact that younger patients less frequently have undernutrition than older patients, and therefore have a higher BSA ( $1.84 \pm 0.19$  vs  $1.77 \pm 0.19$ ;  $P = 0.01$ ) and lower iEOA. Unfortunately, we did not collect biological markers of undernutrition (albumin, prealbumin, C-reactive protein) to confirm this hypothesis.

Unexpectedly, patients with PPM had mean transprosthetic gradients relatively close to those in patients without PPM ( $14 \pm 4.6$  vs  $11.9 \pm 3.9$  mmHg). Estimation of mean transprosthetic gradient is dependent on stroke volume, and therefore on LV inotropism, LV preload and LV afterload. Patients with PPM had a lower stroke volume ( $39.1 \pm 7.6$  vs  $48.1 \pm 10.3$  mL/m<sup>2</sup>;  $P < 0.001$ ) at 1-month follow-up; they had also higher LV afterload than patients without PPM (systolic blood pressure  $143.7 \pm 17.1$  vs  $136.2 \pm 16.9$  mmHg, respectively;  $P = 0.006$ ). These observations may explain why mean transprosthetic gradients were relatively close in the two subgroups, whereas mean iEOA, which is independent of aortic flow rate, was significantly lower in the PPM group ( $0.73 \pm 0.08$  vs  $1.11 \pm 0.22$  cm<sup>2</sup>/m<sup>2</sup>).

## **Clinical perspective**

We are still facing a trade-off concerning the best transcatheter heart valve to use for TAVR. A balloon-expandable prosthesis avoids the risk of PVR, but is associated with a high risk of PPM. By comparison, a self-expandable prosthesis may have a better haemodynamic performance, but exposes patients to a higher risk of PVR. Both haemodynamic sequelae contribute to limiting LV hypertrophy regression, and further investigations are mandatory to evaluate the respective strength of the effect of each variable on prognosis.

## **Conclusions**

PPM was associated with CHF in patients undergoing TAVR with S3-THV, but did not correlate with 1-year overall mortality. The extension of TAVR indications to younger patients with fewer co-morbidities and higher vulnerability to PPM emphasizes the need for further large prospective studies.

## **Sources of funding**

None.

## **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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## Figure legends

**Figure 1.** Flow chart of patients implanted with a SAPIEN 3 transcatheter heart valve from 2015 to 2017. AS: aortic stenosis; iEOA: indexed effective orifice area; PPM: patient-prosthesis mismatch; TAVR: transcatheter aortic valve replacement.

**Figure 2.** Kaplan-Meier cumulative incidence of hospitalization for congestive heart failure (CHF) in consecutive patients with a SAPIEN 3 transcatheter heart valve according to patient-prosthesis mismatch (PPM).

**Figure 3.** Kaplan-Meier cumulative incidence of hospitalization for congestive heart failure (CHF) in vulnerable patients with a SAPIEN 3 transcatheter heart valve according to patient-prosthesis mismatch (PPM). A. Untreated mitral regurgitation (MR)  $\geq$  2/4. B. Age < 80 years. C. Left ventricular ejection fraction (LVEF) < 50%.

**Figure 4.** Kaplan-Meier curves for 1-year overall mortality in consecutive patients with a SAPIEN 3 transcatheter heart valve according to patient-prosthesis mismatch (PPM).

**Table 1** Baseline characteristics, overall and according to patient-prosthesis mismatch.

Baseline characteristics	Overall ( <i>n</i> = 208)	PPM ( <i>n</i> = 79)	No PPM ( <i>n</i> = 129)	<i>P</i>
Age (years)	81.9 ± 6.2	80.4 ± 7	82.8 ± 5.41	0.006
Male sex	112 (53.8)	38/79 (48.1)	74/129 (57.4)	0.2
BMI (kg/m <sup>2</sup> )	26.4 ± 5.29	27.6 ± 6.53	25.7 ± 4.22	0.01
BMI ≥ 30 kg/m <sup>2</sup>	37 (17.8)	21 (26.5)	17 (13.2)	0.14
BSA (m <sup>2</sup> )	1.79 ± 0.19	1.84 ± 0.19	1.77 ± 0.19	0.01
EuroSCORE II	4.35 ± 3.37	4,66 ± 3.64	4.16 ± 3.20	0.24
Diabetes mellitus	21 (10.1)	6 (7.6)	15 (11.6)	0.34
Hypertension	153 (73.6)	59 (74.7)	94 (72.9)	0.77
Dyslipidaemia	99 (47.6)	39/79 (49.4)	60/129 (46.5)	0.68
Renal insufficiency	36 (17.3)	15 (19)	21 (16.3)	0.61
Smoking	69 (33.2)	24 (30.4)	45 (34.9)	0,50
Coronary artery disease	83 (39.9)	36 (45.6)	47 (36.4)	0.19
Atrial fibrillation	81 (38.9)	24 (30.4)	57 (44.2)	0.04
Stroke	20 (9.6)	10 (12.6)	10 (7.7)	0.24
Previous cardiac surgery	14 (6.7)	9 (11.4)	5 (3.9)	0.03
Pacemaker implantation	26 (12.5)	12 (15.2)	14 (10.8)	0.35
NYHA				0.92
I/II	77/197 (39.1)	30/73 (41.1)	47/124 (38)	
III	105 (53.3)	37/73 (50.7)	68/124 (54.8)	
IV	15 (7.6)	6/73 (8.2)	9/124 (7.2)	

Data are expressed as mean ± standard deviation or number (%). BMI: body mass index; BSA: body surface area; NYHA: New York Heart Association; PPM: patient-prosthesis mismatch.

**Table 2** Echocardiography data at baseline, overall and according to patient-prosthesis mismatch.

Preoperative TTE	Overall ( <i>n</i> = 208)	PPM ( <i>n</i> = 79)	No PPM ( <i>n</i> = 129)	<i>P</i>
LVEF (%)	57.9 ± 13.0	54.6 ± 12.8	59.9 ± 12.8	0.004
LVEDV (mL)	121.8 ± 51.9	132.5 ± 56.5	115.9 ± 48.6	0.14
LVESV (mL)	54.2 ± 37.5	62.9 ± 39.4	49 ± 35.7	0.03
IVSd (mm)	14.4 ± 2.7	14 ± 2.4	14.6 ± 2.8	0.2
Bicuspid aortic valve (%)	3/147 (2.04)	0/60 (0)	3/87 (3.5)	0.27
EOA (cm <sup>2</sup> )	0.73 ± 0.19	0.72 ± 0.18	0.74 ± 0.20	0.79
iEOA (cm <sup>2</sup> /m <sup>2</sup> )	0.41 ± 0.10	0.40 ± 0.10	0.42 ± 0.11	0.05
Mean gradient (mmHg)	50.9 ± 14.2	50.4 ± 15.2	51.2 ± 13.7	0.70
Stroke volume (mL/m <sup>2</sup> )	44.3 ± 13.3	42.2 ± 12.2	45.6 ± 14	0.18
AR ≥ 2/4	31/199 (15.6)	14/75 (18.7)	17/123 (13.8)	0.36
MR ≥ 2/4	29/204 (14.2)	9/78 (11.5)	20/126 (15.8)	0.38
LA volume (mL/m <sup>2</sup> )	48.9 ± 25.3	49.6 ± 23.1	48.3 ± 26.6	0.17
sPAP (mmHg)	38.4 ± 13.7	41.4 ± 14.2	36.6 ± 13.1	0.02

Data are expressed as mean ± standard deviation or number/number (%). AR: aortic regurgitation; EOA: effective orifice area; iEOA: indexed effective orifice area; IVSd: interventricular septum; LA: left atrial; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; PPM: patient-prosthesis mismatch; sPAP: systolic pulmonary arterial pressure; TTE: transthoracic echocardiography.

**Table 3** Procedural data, overall and according to patient-prosthesis mismatch.

	Overall ( <i>n</i> = 208)	PPM ( <i>n</i> = 79)	No PPM ( <i>n</i> = 129)	<i>P</i>
Size of prosthesis				0.07
23 mm	75 (36)	35 (44.3)	40 (50.6)	
26 mm	103 (49.5)	37 (46.8)	66 (51.1)	
29 mm	30 (14.4)	7 (8.8)	23 (17.8)	
Access				0.44
Transfemoral	173 (83.1)	68 (86.8)	105 (81.4)	
Transapical	6 (2.8)	1 (1.2)	5 (3.8)	
Transcarotid	7 (3.3)	4 (5)	3 (2.3)	
Transaortic	18 (8.6)	4 (5.6)	14 (10.8)	
Complications				
Aortic annulus rupture	2 (1)	1 (1.2)	1 (0.7)	0.22
Stroke	3 (1.4)	2 (2.5)	1 (0.8)	0.55
Pacemaker implantation	24 (11.5)	10 (12.6)	14 (10.8)	0.69
Vascular complication	19 (9.1)	11 (13.9)	8 (6.2)	0.06
Anticoagulation <sup>a</sup> at discharge	67 (32.2)	23 (29.1)	44 (34.1)	0.45
Single antiplatelet therapy at discharge	121 (58.1)	45 (56.9)	76 (58.9)	0.78
Dual antiplatelet therapy at discharge	45 (21.6)	19 (24.1)	26 (20.1)	0.50

Data are expressed as number (%). PPM: patient-prosthesis mismatch.

<sup>a</sup> Vitamin K antagonist or non-vitamin K antagonist oral anticoagulant.

**Table 4** Postoperative data, overall and according to patient-prosthesis mismatch.

	Overall ( <i>n</i> = 208)	PPM ( <i>n</i> = 79)	No PPM ( <i>n</i> = 129)	<i>P</i>
LVEF (%)	62.2 ± 12.4	59.2 ± 14.0	64.0 ± 10.9	0.02
IVSd (mm)	13.9 ± 2.5	13.4 ± 2.5	14.2 ± 2.4	0.03
LVEDV (mL)	135.3 ± 43.8	148.3 ± 48.2	126.8 ± 38.5	0.003
LVESV (mL)	52.6 ± 31.8	61.3 ± 36.7	46.9 ± 26.7	0.003
Stroke volume (mL/m <sup>2</sup> )	44.3 ± 10.3	39.1 ± 7.6	48.1 ± 10.3	< 0.001
EOA (cm <sup>2</sup> )	1.70 ± 0.45	1.33 ± 0.19	1.93 ± 0.42	< 0.001
iEOA (cm <sup>2</sup> /m <sup>2</sup> )	0.97 ± 0.25	0.73 ± 0.08	1.11 ± 0.22	< 0.001
<i>V</i> <sub>max</sub> (m/s)	2.3 ± 0.4	2.4 ± 0.4	2.2 ± 0.3	< 0.001
Mean gradient (mmHg)	12.7 ± 4.3	14.0 ± 4.6	11.9 ± 3.9	< 0.001
PVR ≥ 2/4	9 (4.3)	2 (2.5)	7 (5.4)	0.83
MR ≥ 2/4	29 (13.9)	15 (18.9)	14 (11.4)	0.74
sPAP (mmHg)	38.1 ± 11.4	39.9 ± 12.7	37 ± 10.5	0.11

Data are expressed as mean ± standard deviation or number/number (%). EOA: effective orifice area; iEOA: indexed effective orifice area; IVSd: interventricular septum; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; PPM: patient-prosthesis mismatch; PVR: paravalvular regurgitation; sPAP: systolic pulmonary arterial pressure; *V*<sub>max</sub>: peak velocity.

**Table 5** Risk of congestive heart failure and overall mortality according to patient-prosthesis mismatch, in the overall population and in vulnerable patients.

Type of analysis	Primary endpoint: CHF		Secondary endpoint: overall mortality	
	Risk ratio (95% CI)	<i>P</i>	Risk ratio (95% CI)	<i>P</i>
Adjusted for age, sex, PVR $\geq$ 2/4, preoperative LVEF and BMI				
Overall population ( <i>n</i> = 208): PPM versus no PPM	3.17 (1.17 to 8.55)	0.02	0.90 (0.22 to 3.03)	0.86
Adjusted for age, sex and PVR $\geq$ 2/4				
Untreated MR $\geq$ 2/4 ( <i>n</i> = 29): PPM versus no PPM	> 100 (> 100 to > 1000)	< 0.001	1.65 (1.01 to 3.2)	0.7
Age < 80 years ( <i>n</i> = 57): PPM versus no PPM	4.53 (0.49 to 42.04)	0.18	3.36 (< 0.01 to > 100)	0.4
LVEF < 50% ( <i>n</i> = 47): PPM versus no PPM	2.17 (0.36 to 13.06)	0.39	1.52 (0.09 to 25.2)	0.7
Severe LV hypertrophy ( <i>n</i> = 18): PPM versus no PPM	0.5 (0.01 to 100)	0.5	1.94 (0.02 to > 100)	0.5

BMI: body mass index; LV: left ventricular; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; PPM: patient-prosthesis mismatch; PVR: paravalvular regurgitation.



From 01/01/2015 to 01/01/2017  
270 patients implanted with TAVR valve

- 39 Corevalve Evolut
- 3 Sapien XT

228 patients with severe symptomatic  
AS implanted with Sapien 3 valve

- 5 in-hospital deaths
- Aortic annulus rupture (n = 2)
  - Cardiogenic shock (n = 2)
  - Septic shock (n = 1)

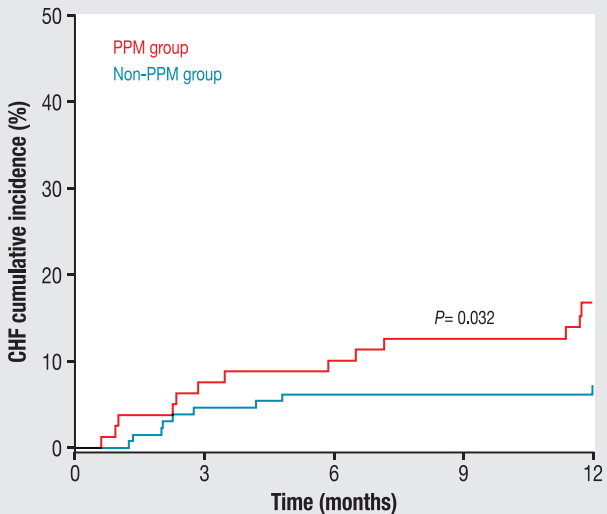
- 15 exclusions
- unavailability of iEOA in all

208 patients with complete echo data  
at 1 month follow-up

PPM group  
n = 79

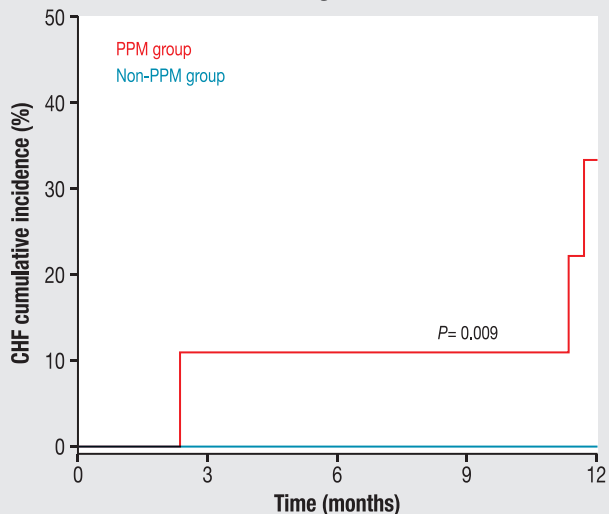
Non-PPM group  
n = 119

### CHF occurrence according to PPM



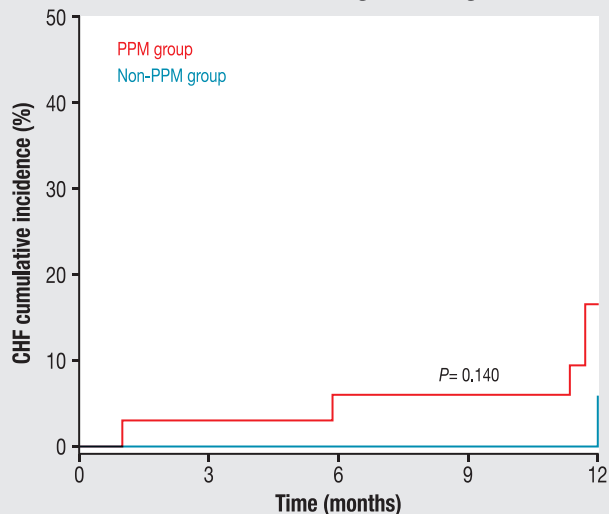
79	73	n - PPM	71	68	44
129	122	n - Non-PPM	119	116	85

CHF occurrence according to PPM - Untreated MR ≥ 2



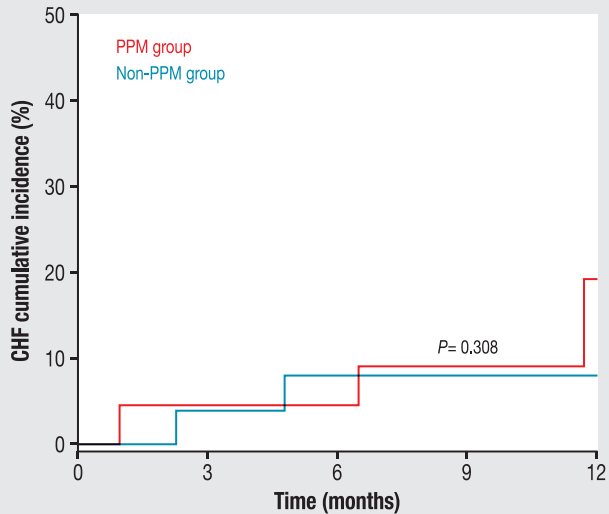
Time (months)	0	3	6	9	12
n - PPM	9	8	8	8	4
n - Non-PPM	20	20	20	20	17

CHF occurrence according to PPM - Age < 80



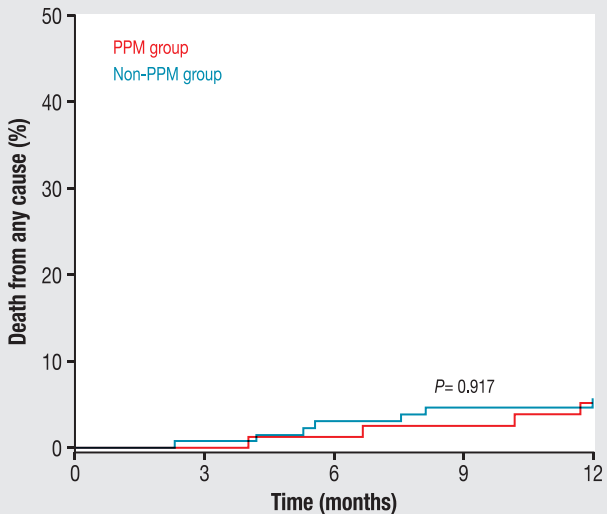
Time (months)	0	3	6	9	12
n - PPM	33	32	31	30	14
n - Non-PPM	24	24	24	23	19

CHF occurrence according to PPM - LVEF < 50%



Time (months)	0	3	6	9	12
n - PPM	22	21	21	19	11
n - Non-PPM	25	24	23	23	16

### Death occurrence according to PPM



n - PPM

79

79

78

76

50

n - Non-PPM

129

128

125

122

89