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Patient-prosthesis mismatch in new generation trans-catheter heart valves: a propensity score analysis

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Aims

When compared with the former Sapien XT (XT-THV), the Sapien 3 trans-catheter heart valve (S3-THV) embeds an outer annular sealing cuff to prevent para-valvular regurgitation (PVR). The consequences of this new feature on valve haemodynamics have never been evaluated. We aimed to compare both types of prostheses regarding patient-prosthesis mismatch (PPM).

Methods and results

Patients who underwent a TAVR for aortic stenosis were retrospectively included. Regression adjustment for the propensity score was used to compare 50 XT-THV patients with 71 S3-THV. At the 1-month follow-up, the mean indexed effective orifice area (iEOA) was $1.12 \pm 0.34 \text{ cm}^2/\text{m}^2$ with XT-THV and $0.96 \pm 0.27 \text{ cm}^2/\text{m}^2$ with S3-THV. The mean gradient was $11 \pm 5 \text{ mmHg}$ and $13 \pm 5 \text{ mmHg}$, respectively. Nine patients had moderate PPM, and two exhibited severe PPM with XT-THV. Nineteen patients had moderate PPM, and seven demonstrated severe PPM with S3-THV. There was a five-fold increased risk of PPM with S3-THV (OR = 4.98; [1.38–20.94], $P = 0.019$). S3-THV decreased the iEOA by $0.21 \text{ cm}^2/\text{m}^2$ [-0.21; (-0.38 to -0.05); $P = 0.012$] and increased the mean gradient by 4.95 mmHg [4.95; (2.27–7.64); $P < 0.001$]. The risk of PPM was increased 15.24-fold with 23 mm S3-THV [15.24; (2.92–101.52); $P = 0.002$] in comparison with the 23 mm XT-THV. PVR were reduced by 98% with S3-THV.

Conclusion

There is an increased risk of PPM with 23mm S3-THV in comparison with 23 mm XT-THV. This may be attributable to the additional sub-annular cuff that avoids the risk of PVR. Regarding the increased vulnerability of younger patients to PPM, we provide essential information on the extension of TAVR indication to the younger population.

Introduction

Trans-catheter aortic valve replacement (TAVR) has become a reliable treatment alternative to surgery for aortic stenosis in patients who are inoperable or at a high surgical risk.¹ Recently, the randomized PARTNER II trial showed similar all-cause death and disabling stroke outcomes of both techniques in intermediate-risk patients,

thus widening the TAVR indication to lower-risk patients.² However, the extension of the indications requires a reduction of several prevalent complications, such as para-valvular regurgitation (PVR), which is associated with a poorer prognosis.³

Recently, the new expandable Sapien 3 trans-catheter heart valve (S3-THV) has replaced the previous generation of Sapien XT trans-catheter heart valve (XT-THV), which was associated with a high

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Table 1 Baseline characteristics

	All n = 121	XT-THV n = 50	S3-THV n = 71	p
Age, years	82.4 ± 6.5	83.3 ± 6.6	81.7 ± 6.4	0.13
Females (%)	73 (60%)	39 (78%)	34 (48%)	<0.001
BSA, m ²	1.70 ± 0.22	1.63 ± 0.17	1.75 ± 0.24	0.04
Mellitus Diabetes	39 (32%)	19 (38%)	20 (28%)	0.25
Hypertension	85 (70%)	39 (78%)	46 (65%)	0.11
Smoke	10 (8%)	3 (6%)	7 (10%)	0.52
Dyslipidaemia	46 (38%)	24 (48%)	22 (31%)	0.05
Coronary artery disease	56 (46%)	26 (52%)	30 (42%)	0.29
Renal insufficiency	23 (19%)	13 (26%)	10 (14%)	0.09
Chronic pulmonary disease	14 (12%)	4 (8%)	10 (14%)	0.3
Cerebrovascular disease	5 (4%)	1 (2%)	4 (6%)	0.4
Porcelain aorta	3 (2%)	1 (2%)	2 (3%)	1
Atrial fibrillation	31 (26%)	10 (20%)	21 (30%)	0.23
NYHA				0.61
I	10 (8%)	4 (8%)	6 (8%)	
II	41 (34%)	15 (30%)	26 (37%)	
III	58 (48%)	24 (48%)	34 (48%)	
IV	12 (10%)	7 (14%)	5 (7%)	
Recent CHF	49 (40.5%)	29 (58%)	20 (28%)	0.001
Haemoglobin (g/L)	119 ± 17	116 ± 17	121 ± 17	0.04
BNP (pg/mL)	417 ± 364	454 ± 358	390 ± 369	0.11
Creatinine (µmol/L)	129 ± 126	131 ± 170	128 ± 82	0.26

BSA, body surface area; CHF, congestive heart failure.

0.001), which is consistent with a lower BSA ($1.63 \pm 0.17 \text{ m}^2$ vs. $1.75 \pm 0.24 \text{ m}^2$, $P = 0.04$), lower haemoglobin rate (116 ± 17 and $121 \pm 17 \text{ g/dL}$, $P = 0.04$), and lower aortic annulus diameter on TTE ($20.2 \pm 1.7 \text{ mm}$ vs. 21.5 ± 1.95 , $P < 0.001$) (Tables 1 and 2).

Procedural characteristics

Among the XT-THV patients, three patients had a 20 mm (6%), 24 had a 23 mm (48%), 21 had a 26 mm (42%), and two had a 29 mm (4%). Among the S3-THV patients, 34 had a 23 mm (48%), 30 had a 26 mm (42%), and six had a 29 mm (10%). Aortic annuli were larger with 23mm and 26mm S3-THV, shown by larger MSCT aortic annulus area ($P < 0.001$) and lower prosthesis to annulus oversizing. Figure 1A and B. There were no differences between the groups regarding procedural events, such as vascular complications or pacemaker implantation.

Clinical follow-up

At 1-month follow-up, five deaths (4%) had occurred, all in the XT-THV subgroup. Seventy-three patients (63%) clinically improved ($P < 0.001$), with a mean improvement of $21 \pm 4.7\%$. No difference was observed between the two prostheses in terms of functional improvement in the NYHA class (25 vs. 15%, $P = 0.6$). Propensity score analysis demonstrated that the S3-THV did not affect functional improvement when compared with the XT-THV [Coefficient = 0.09, (-0.17–0.35), $P = 0.49$].

Haemodynamic follow-up

The overall echocardiographic data and data according to valve type at 1-month follow-up are provided in Table 3. The mean gradient decreased significantly from baseline to 1-month follow-up (51.0 ± 16.0 vs. $12.0 \pm 5.0 \text{ mmHg}$, $P < 0.001$), and LVEF slightly increased (60 ± 12 vs. $56 \pm 13\%$, $P < 0.001$). At 1-month follow-up, the mean EOA was $1.71 \pm 0.52 \text{ cm}^2/\text{m}^2$, which corresponded to a mean iEOA of $1.2 \pm 0.31 \text{ cm}^2/\text{m}^2$. Thirty-seven patients (30.5%) had PPM, of which 28 (76%) had moderate and nine (15%) had severe PPM.

Among the 28 patients with moderate PPM, nine patients (32.1%) received a XT-THV (one with 20 mm, four with 23 mm, and four with 26 mm XT-THV), and 19 patients (67.9%) had S3-THV (12 with 23 mm, 5 with 26 mm, and 2 with 29 mm S3-THV). Among the nine patients with severe PPM, two (22.2%) had a XT-THV (20 mm XT-THV in all), and seven (77.8%) had a S3-THV (six with 23 mm and one with 26 mm S3-THV) Table 4 (see Supplementary data online, Appendix S3A and S3B).

No difference in BSA was observed between patients with and without PPM (BSA = 1.73 ± 0.18 vs. $1.67 \pm 0.19 \text{ m}^2$, $P = 0.12$). The mean trans-prosthetic gradient was significantly higher in patients with PPM vs. no PPM (15.2 ± 5.3 vs. $11.2 \pm 4.5 \text{ mmHg}$, $P < 0.001$) (see Supplementary data online, Appendix S2).

S3-THV was significantly associated with lower iEOA (0.96 ± 0.27 and $1.12 \pm 0.34 \text{ cm}^2/\text{m}^2$, $P < 0.01$) and higher mean trans-aortic gradient (13 ± 5 vs. $11 \pm 5 \text{ mmHg}$, $P = 0.002$) than the XT-THV group in univariate analysis.

Using a linear regression adjustment of the propensity score, S3-THV decreased the iEOA by around $-0.21 \text{ cm}^2/\text{m}^2$ [Coefficient = -0.21 , (-0.38 to -0.05), $P = 0.013$] and increased the mean trans-prosthetic gradient by $+4.95 \text{ mmHg}$ [Coefficient = 4.95, (2.27–7.64), $P < 0.001$] compared with XT-THV. Figure 2 Sensitivity analysis using a linear regression with IPTW of the propensity score had similar results for both decreasing the iEOA [-0.11 (-0.21 to -0.02), $P = 0.019$] and increasing the mean trans-prosthetic gradient [4.38, (2.88–5.88), $P < 0.001$]. Consistent with these findings, S3-THV implantation was significantly associated with a higher risk of PPM [OR = 4.98, (1.38–20.94), $P = 0.019$] using logistic regression adjustment of the propensity score. Figure 3A Sensitivity analysis also identified a higher risk of PPM with S3-THV implantation in comparison with XT-THV [OR = 7.24, (3.62–15.38), $P \leq 0.00001$]

The same modalities of regression were used in the subgroup analysis with regard to prosthesis size. Among patients with a size of 23 mm, S3-THV decreased the iEOA by around $0.26 \text{ cm}^2/\text{m}^2$ [coefficient = -0.26 , (-0.44 to -0.08), $P = 0.005$] and increased the mean trans-prosthetic gradient by around 5.63 mmHg [coefficient = 5.63, (2.8–8.45), $P < 0.001$] compared with the 23 mm XT-THV. There was a 15-fold increased risk of PPM with 23 mm S3-THV vs. 23 mm XT-THV [OR = 15.24, (2.92–101.52), $P = 0.002$]. Figure 3B Sensitivity analysis supports these results and also identified a lower iEOA [-0.16, (-0.28 to -0.04), $P = 0.008$], a higher mean trans-prosthetic gradient [5.91, (4.11–7.71), $P < 0.00001$] and a 25-fold increased risk of PPM [25.95 (9.43–86.90), $P < 0.00001$] in the 23 mm S3-THV compared with the 23mm XT-THV

Among patients with 26 mm-THV, no significant difference was found concerning the EOAi [coefficient = -0.13 , (-0.31 to 0.06), $P = 0.18$] or PPM risk [OR = 1.77, (0.312–11.27), $P = 0.068$]. Figure 3C

Table 2 Echocardiography data at baseline

	All n = 121	XT-THV n = 50	S3-THV n = 71	P
LVEF (%)	56 ± 13	55 ± 13	56 ± 13	0.61
LVEF < 50% (%)	31 (25%)	12 (24%)	19 (26.7%)	0.4
LV septum diameter (mm)	14.8 ± 2.4	14.5 ± 2.4	15 ± 2.4	0.46
LV diastolic diameter (mm)	46.8 ± 6.7	48.3 ± 7.2	45.5 ± 6	0.16
LV systolic diameter (mm)	32 ± 6.9	33.6 ± 7	31 ± 6.7	0.32
LV mass (g/m ²)	178 ± 52	190 ± 51	168 ± 51	0.08
Aortic annulus diameter (mm)	20.9 ± 1.95	20.2 ± 1.7	21.5 ± 1.95	<0.001
EOA (cm ²)	0.69 ± 0.22	0.65 ± 0.19	0.71 ± 0.23	0.057
iEOA (cm ² /m ²)	0.41 ± 0.13	0.4 ± 0.12	0.42 ± 0.14	0.44
Mean trans-aortic gradient (mmHg)	51 ± 16	52 ± 16	51 ± 16	0.66
Aortic regurgitation	63 (52%)	35 (70%)	28 (39%)	<0.001
Aortic regurgitation grade				0.001
Trivial	40 (63%)	23(66%)	17 (61%)	
Mild	13 (21%)	5(14%)	8 (29%)	
Moderate	4 (6%)	4(11%)	0	
Severe	6 (4.9%)	3(9%)	3 (10%)	
Mitral regurgitation	57 (47%)	33(66%)	24 (34%)	<0.001
Mitral regurgitation 3–4	4 (3.3%)	1(2%)	3 (4.2%)	0.46
Systolic pressure of pulmonary artery	42 ± 14	44 ± 14	39 ± 15	0.08

LVEF, left ventricular ejection fraction; LV, left ventricle; EOA, effective orifice area; iEOA, indexed effective orifice area.

However, the 26 mm S3-THV increased the mean trans-prosthetic gradient by 4.54 mmHg [coefficient = 4.54, (1.64–7.44), $P = 0.002$] compared with the 26 mm XT-THV.

Sixty-one patients (53%) had a PVR at the 1-month follow-up, including 37 patients (82%) in the XT-THV group and 24 patients (34%) in the S3-THV. Among these patients, 47 (77%) had trivial PVR, twelve (20%) had mild/moderate PVR and 2 (3%) had severe PVR. Among the XT-THV group, 26 patients (70%) had trivial PVR, 9 (24%) had mild/moderate PVR and 2 (6%) had severe PVR. Neither moderate nor severe PVR were observed in the S3-THV group, whereas 21 (88%) had trivial PVR and 3 (12%) had mild PVR.

Using a logistic regression adjustment of the propensity score, the odds of a para-prosthetic leak were 98% reduced with S3-THV compared with XT-THV [OR = 0.02, (0.002–0.095), $P < 0.001$]. Figure 4 Sensitivity analysis results for PVR were consistent [OR = 0.03 (0.01–0.06), $P < 0.00001$] with much narrower confidence intervals.

Discussion

The aim of this study was to compare the occurrence of moderate and severe PPM with the new balloon-expandable S3-THV vs. the preceding XT-THV generation in TAVI for severe AS. The main findings were (i) a higher risk of PPM for S3-THV, (ii) a 15-fold increased risk of PPM with the smallest size of S3-THV prosthesis in comparison with the same size XT-THV prosthesis, and (iii) a similar degree of left ventricular mass regression and NYHA functional improvement with both valves.

The clinical effect of PPM after surgical aortic valve replacement (SAVR) has been a matter of controversy since the first description

by Rahimtoola in 1978.⁵ PPM occurs if the EOA of the implanted bio-prosthesis is small relative to the patient body size.

PPM is considered severe when the iEOA is < 0.65 cm²/m² and moderate if the iEOA is between 0.65 and 0.85 cm²/m². The occurrence of PPM post-SAVR is well recognized and ranges from 20 to 70% for moderate PPM and from 2 to 10% for severe PPM.¹² The adverse effects of PPM include functional impairment, reduced LV mass regression and a significant reduction of early and intermediate survival, particularly in severe PPM.¹³ A recent meta-analysis of 34 studies with 27 186 patients confirmed a significantly negative effect of PPM on long-term survival, particularly in cases of vulnerability, such as impaired LVEF, severe LV hypertrophy, concomitant mitral regurgitation, and/or paradoxical low flow/low gradient aortic stenosis.¹⁴

When compared with SAVR, the previous prostheses used for TAVR, such as Edwards Sapien and Sapien-XT, tend to have better haemodynamic performance, thus contributing to a reduction in PPM.¹⁵ In a randomized comparison of 699 patients from the PARTNER trial A cohort, TAVR was significantly associated with less PPM (46.4 vs. 60.0%, $P < 0.001$) and severe PPM (19.7 vs. 28.1%, $P < 0.001$) compared with SAVR.⁷ This study was also the first to identify an important relationship between PPM after TAVR implantation and 2-year mortality, but this relationship was found only in the TAVR nonrandomized continued access arm. The difference in severe PPM was particularly important in patients with small aortic annuli (<20 mm), assuming that the thinner stent frame and absence of a sewing ring in the annular space provide less blood flow obstruction. However, this study was based on the former generation of SAPIEN/SAPIEN XT-THV, and none of these haemodynamic results could be extended to the new S3-THV generation, which embedded supplementary annular space material.

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