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CLINICAL RESEARCH
*Valvular heart disease*

# Paravalvular Regurgitation after Transcatheter Aortic Valve Replacement with the Edwards Sapien Valve in the PARTNER trial: characterizing patients and impact on outcomes

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**Aim** The impact of paravalvular regurgitation (PVR) following transcatheter aortic valve replacement (TAVR) remains uncertain. In this analysis, we sought to evaluate the impact of varying degrees of PVR on both mortality and changes in ventricular geometry and function.

**Methods and results** Clinical and echocardiographic outcomes of patients who underwent TAVR from the randomized cohorts and continued access registries in the PARTNER trial were analysed after stratifying by severity of post-implant PVR, which was graded as none/trace in 52.9% ($n = 1288$), mild in 38.0% ($n = 925$), and moderate/severe in 9.1% ($n = 221$). There were significant differences in baseline clinical and echocardiographic characteristics. After TAVR, all the patients demonstrated increase in left ventricular (LV) function and reduction in the LV mass index, although the magnitude of mass regression was lower in the moderate/severe PVR group. The 30-day mortality (3.1 vs. 3.4 vs. 4.5%, $P = 0.56$) and stroke (3.4 vs. 3.7 vs. 2.3%, $P = 0.59$) were similar in all groups (none/trace, mild, and moderate/severe). At 1 year, there was increased all-cause mortality (15.9 vs. 22.2 vs. 35.1%, $P < 0.0001$), cardiac mortality (6.1 vs. 7.4% vs. 16.3%, $P < 0.0001$) and re-hospitalization (14.4 vs. 23.0 vs. 31.3%, $P < 0.0001$) with worsening PVR. A multivariable analysis indicated that the presence of moderate/severe PVR (HR: 2.18, 95% CI: 1.57–3.02, $P < 0.0001$) or mild PVR (HR: 1.37, 95% CI: 1.14–1.90, $P = 0.012$) was associated with higher late mortality.

**Conclusion** Differences in baseline characteristics in patients with increasing severities of PVR may increase the risk of this complication. Despite these differences, multivariable analysis demonstrated that both mild and moderate/severe PVR predicted higher 1-year mortality.

**Keywords** Transcatheter aortic valve replacement • Aortic stenosis • Paravalvular regurgitation



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# Introduction

Over the past decade, transcatheter aortic valve replacement (TAVR) has rapidly emerged as an alternative to surgical aortic valve replacement (SAVR) in high-risk patients and the treatment of choice for inoperable patients with severe, symptomatic aortic stenosis (AS).[1–6] In recent years, there has been explosive growth in the clinical adoption of TAVR worldwide. With this increasing role, research efforts have focused on understanding and reducing procedural complications, such as paravalvular regurgitation (PVR). Numerous studies have shown significant rates of moderate-to-severe PVR following TAVR ranging from 0 to 24%.[7–19] In addition, the presence of moderate or severe PVR has been associated with higher 1-year mortality.[20–22] Several recent studies have also suggested that mild PVR may also be an important predictor of mortality.[7,10,12,22] Mortality in this patient population is complex and whether PVR is causative or is simply associated with it remains to be seen. Characterizing clinical and echocardiographic differences between patients with varying degrees of PVR, as well as determining the effect of PVR on remodelling, could further increase our understanding of the relationship between PVR and mortality. In this study, we present an in-depth analysis of patients from the PARTNER trial evaluating PVR and its impact on clinical and echocardiographic outcomes.

# Methods

The PARTNER trial was a multicentre, randomized, clinical trial comparing TAVR with SAVR for high-risk patients (cohort A)[2] and TAVR with medical therapy for inoperable patients (cohort B).[1] Following completion of the randomized trial and prior to commercial approval of the Edwards SAPIEN valve, additional patients were treated in a randomized continued access registry (RCA), as well as in a non-randomized continued access (NRCA) registry, with the same inclusion and exclusion criteria as the randomized trial. All the patients had severe native trileaflet AS documented on a screening transthoracic echocardiogram (TTE) within 30 days of enrolment and were evaluated by two surgeons for the assessment of risk with SAVR. Important exclusion criteria included bicuspid disease, ejection fraction <20%, renal failure, severe mitral regurgitation (MR), severe aortic regurgitation (AR), recent gastrointestinal bleeding, or recent neurological event. Complete inclusion and exclusion criteria have been presented in the supplementary appendix to a previous publication.[2]

All the patients undergoing TAVR received either a 23 or 26 mm balloon-expandable Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, CA, USA) from either the transfemoral (TF) or transapical (TA) approach based on vascular access. Annular assessments to determine valve size required were site determined utilizing TTE, transoesophageal echo (TEE), or multi-slice CT scans (MSCT). All the patients underwent TTE prior to discharge and at clinical follow-up time-points including 1 month, 6 months, and 1 year. All echocardiograms were analysed at an independent core lab with methodology described previously.[23] Important clinical events (including death, stroke, and re-hospitalization) were adjudicated by an independent clinical events committee (CEC).

This analysis utilized an as-treated population of patients with either discharge or 30-day echoes evaluable for PVR severity. Paravalvular regurgitation was graded as none/trace, mild, moderate, or severe utilizing semi-quantitative criteria previously described.[19] Briefly, PVR after TAVR/SAVR was graded in accordance with the ASE recommendations for native valves[24] with one exception. Because of the often eccentric, irregular jet and the frequent non-cylindrical 'spray' of the paravalvular jet contour, the parasternal short-axis view(s) was weighted more heavily than other signals in providing an integrated assessment, as follows: *None*, no regurgitant colour flow; *Trace*, pinpoint jet in AV; *Mild*, jet arc length is <10% of the annulus circumference; *Moderate*, jet arc length is 10–30% of the annulus circumference; *Severe*, jet arc length is >30% of the annulus circumference. The cover index is defined as: 100 × [(THV diameter − TEE annulus diameter)/THV diameter].[8]

## Statistical methods

Patients were stratified by severity of PVR to evaluate impact on clinical outcomes. Multivariable analysis was performed to evaluate impact of PVR on 1-year mortality. Only paired data for patients with discharge or 30-day and 1-year echoes were evaluated for changes in the following: indexed effective orifice area (iEOA), LV diastolic volume (LVDV), LV systolic volume (LVSV), LV ejection fraction (EF), LV mass index.

Categorical variables were compared using the $\chi^2$ test. Since regurgitation is an ordinal variable, most comparisons involving this variable use the exact Jonckheere–Terpstra test. However, in survival models, PVR was used as a categorical variable. Continuous variables were presented as means ($\pm$ SD) and compared using Student's *t*-test; comparisons with baseline values used the paired sample *t*-test. For multiple comparisons, Bonferroni correction was employed. The impact of PVR severity on mortality was evaluated using a Cox proportional hazards model, and all Cox models were tested to assure that the proportional hazards assumption was met. Log-rank tests were performed to compare survival distributions. $P < 0.05$ was used to declare statistical significance, unless multiple comparison adjustments were used. All statistical tests were two-sided.

Stepwise multivariable analysis was performed for 1-year mortality using the baseline variables that differed between PVR groups ($P \leq 0.10$) as well as baseline variables that were predictors of 1-year mortality on univariate analysis. Age, gender, PVR severity, and mode of access were forced into the model. Variables were entered with entry/stay criteria of 0.1/0.1 in a forward stepwise fashion.

Data are based on an extract date of 18 February 2014. All statistical analyses were performed in SAS®, version 9.2.

# Results

## Patient population and baseline characteristics

A total of 2515 patients underwent TAVR with valve implantation as part of the randomized trial ($n = 496$), RCA registry ($n = 40$), or the NRCA registry ($n = 1979$). Eighty-one patients were excluded from this analysis due to missing echocardiograms at discharge and at 30 days, which resulted in a total population of 2434 patients. In this population, PVR was graded as none/trace in 52.9% ($n = 1288$), mild in 38.0% ($n = 925$), and moderate/severe in 9.1% ($n = 221$).

Baseline clinical characteristics stratified by severity of post-implant PVR are shown in *Table 1*. There were differences in several important baseline characteristics. Patients with none/trace PVR were more often female and had a smaller body surface area but higher BMI. The logistic EuroSCORE was higher in the moderate/severe PVR group, but there was no difference in the STS score between PVR groups. Patients with moderate/severe PVR were

**Table 1 Baseline clinical parameters of patients by severity of paravalvular regurgitation**

| Baseline parameters | Severity of paravalvular regurgitation | | | *P*-value (all groups) |
|---|---|---|---|---|
| | None/trace ($n = 1288$) | Mild ($n = 925$) | Moderate/severe ($n = 221$) | |
| Age | 84.17 ± 7.05 | 84.71 ± 7.22 | 85.04 ± 7.52 | 0.10 |
| Male, % | 44.3 | 59.8 | 70.6 | <0.0001 |
| Body surface area | 1.78 ± 0.24 | 1.83 ± 0.25 | 1.82 ± 0.24 | <0.0001 |
| Body mass index | 27.17 ± 6.45 | 26.53 ± 6.09 | 25.12 ± 5.52 | <0.0001 |
| Logistic EuroSCORE | 25.74 ± 16.06 | 26.42 ± 16.24 | 29.79 ± 17.05 | 0.004 |
| STS score | 11.56 ± 4.32 | 11.31 ± 3.85 | 11.10 ± 3.50 | 0.17 |
| Diabetes, % | 37.6 | 37.8 | 30.9 | 0.14 |
| Carotid disease, % | 27.1 | 26.4 | 17.1 | <0.01 |
| Prior coronary artery bypass grafting, % | 43.3 | 41.5 | 44.5 | 0.60 |
| Prior balloon aortic Valvuloplasty, % | 24.1 | 23.0 | 19.6 | 0.34 |
| Renal disease (Cr ≥ 2), % | 14.8 | 18.3 | 18.6 | 0.059 |
| Major arrhythmia, % | 46.9 | 54.7 | 60.0 | <0.0001 |
| Permanent pacemaker, % | 20.1 | 22.4 | 26.4 | 0.08 |
| Smoking, % | 47.8 | 50.9 | 44.5 | 0.15 |
| Chronic obstructive pulmonary disease, % | 43.9 | 45.6 | 40.3 | 0.33 |
| Pulmonary hypertension, % | 37.6 | 38.6 | 48.0 | 0.02 |

**Table 2 Baseline echocardiographic characteristics of patients by severity of paravalvular regurgitation**

| Baseline parameters | Severity of paravalvular regurgitation | | | *P*-value (all groups)[a] |
|---|---|---|---|---|
| | (a) None/trace ($n = 1288$) | (b) Mild ($n = 925$) | (c) Moderate/severe ($n = 221$) | |
| LVEDD (cm) | 4.41 ± 0.74 | 4.60 ± 0.77 | 4.68 ± 0.74 | <0.0001 |
| LVESD (cm) | 3.20 ± 0.92 | 3.35 ± 0.94 | 3.51 ± 0.92 | <0.0001 |
| Stroke volume (cc) | 64.2 ± 19.6 | 68.5 ± 21.4 | 67.6 ± 25.0 | 0.01 |
| Cardiac output | 4.38 ± 1.41 | 4.62 ± 1.54 | 4.57 ± 1.59 | 0.08 |
| LV EF (%) | 53.7 ± 12.4 | 51.4 ± 13.2 | 50.2 ± 13.9 | <0.0001 |
| LV mass (g) | 238.7 ± 74.1 | 260.3 ± 78.3 | 267.2 ± 73.6 | <0.0001 |
| LVOT diameter (cm) | 1.98 ± 0.18 | 2.04 ± 0.18 | 2.06 ± 0.19 | <0.0001 |
| Annulus diameter (cm) | 21.27 ± 1.86 | 21.64 ± 1.83 | 21.91 ± 1.88 | <0.001 |
| EOA ($cm^2$) | 0.65 ± 0.19 | 0.66 ± 0.19 | 0.65 ± 0.19 | 0.25 |
| Aortic regurgitation | | | | |
| None/trace | 44.7% | 42.8% | 34.2% | 0.02 |
| Mild | 46.5% | 46.8% | 41.2% | 0.36 |
| Moderate/severe | 8.6% | 10.3% | 24.4% | <0.0001 |
| Mitral regurgitation | | | | |
| None/trace | 29.9% | 25.8% | 17.8% | 0.001 |
| Mild | 50.7% | 51.7% | 46.1% | 0.37 |
| Moderate/severe | 19.5% | 22.5% | 36.1% | <0.0001 |

[a]Comparisons performed using an exact Jonckheere–Terpstra test.

less likely to have significant carotid artery disease, but more likely to have pulmonary hypertension.

Baseline echocardiographic parameters also differed between the three groups (*Table 2*). Compared with patients with none/trace, patients with mild or moderate/severe PVR had larger LV end-diastolic dimensions (LVEDD), LV end-systolic dimensions (LVESD), and LV mass but lower EF at baseline. Patients with moderate/severe PVR post-implant were more likely to have moderate/severe baseline AR ($P < 0.001$) and MR ($P < 0.01$). Interestingly, the systolic LV outflow tract (LVOT) and aortic annular diameters

**Table 3 Procedural characteristics**

| Characteristic | None/trace ($n = 1288$) | Mild ($n = 925$) | Moderate/severe ($n = 221$) | $P$-value (all groups)[a] |
|---|---|---|---|---|
| Approach (%) | | | | |
| Transfemoral | 48.8 | 67.1 | 75.1 | <0.0001 |
| Transapical | 51.2 | 32.9 | 24.9 | <0.0001 |
| Valve size | | | | |
| 23 mm | 54.7 | 49.5 | 45.9 | 0.01 |
| 26 mm | 45.3 | 50.5 | 54.1 | 0.01 |
| Cover index | 12.74% ± 5.40 | 11.73% ± 5.57 | 10.82% ± 5.73 | <0.0001 |

[a]Comparisons performed using an exact Jonckheere–Terpstra test.

as well as diastolic measurements of the aorta were progressively larger with increasing PVR severity.

Patients undergoing valve implantation via the TA approach compared with the TF approach had significantly less PVR ($P < 0.0001$). Patients with moderate-to-severe PVR were more likely to have received a 26 mm valve and had a lower cover index then those with less PVR (*Table 3*).

## Clinical outcomes

In patients with none/trace, mild or moderate/severe PVR, the 30-day or in-hospital mortality (3.1 vs. 3.4 vs. 4.5%, $P = 0.56$), and stroke (3.4 vs. 3.7 vs. 2.3%, $P = 0.59$) were similar in all groups. At 1-year, there was increased all-cause mortality (15.9 vs. 22.2 vs. 35.1%, $P < 0.0001$), cardiac mortality (6.1 vs. 7.4 vs. 16.3%, $P < 0.0001$), and re-hospitalization (14.4 vs. 23.0 vs. 31.3%, $P < 0.0001$) with higher grades of PVR (*Figure 1*). Patients with moderate/severe PVR showed less improvement in NYHA class at 6months compared with those with none/trace or mild PVR (*Figure 2*).

Multivariable analysis (*Table 4*) evaluating the impact of PVR on 1-year all-cause mortality was performed using the following covariates: age, sex, BMI, STS score, diabetes, smoking history, prior CABG, prior BAV, frailty, renal disease, major arrhythmia, pacemaker, chronic obstructive pulmonary disease, anaemia, 6 min walk distance, LV ejection fraction, LV mass, LVED, LVES, AV annulus diameter, and AV mean gradient. In addition, the following variables were forced into the model: PVR, TF vs. TA, and baseline moderate/severe AR. The presence of moderate/severe PVR (HR: 2.18, 95% CI: 1.69–3.35, $P < 0.0001$) or mild PVR (HR: 1.37, 95% CI: 1.14–1.90, $P = 0.012$) were each associated with higher 1-year mortality.

## Changes in ventricular size and function

*Table 5* shows changes in ventricular size and function between baseline and 1-year using paired data in patients stratified by post-implant PVR. As expected, following valve implantation, iEOA significantly increased from baseline to 1-year, with no significant between group differences. Compared with baseline, there was a significant decrease in LVES and LVED in none/trace and mild PVR groups with no change in LVES and an increase in LVED in the moderate/severe PVR group. Left ventricular ejection fraction significantly increased over time in all groups. The left ventricular mass index improved significantly in all group over time, however, compared with moderate/severe PVR ($-8.4 \pm 26.6$ g/m$^2$) greater reductions were seen in none/trace ($-19.6 \pm 32.8$ g/m$^2$, $P = 0.001$) and mild PVR groups ($-17.3 \pm 33.0$ g/m$^2$, $P = 0.01$).

# Discussion

This report from the PARTNER trial represents the largest published single study to evaluate the impact of PVR following TAVR with the Edwards Sapien valve on clinical and echocardiographic outcomes. It is particularly notable for utilizing echocardiography core laboratory data as well as CEC adjudication for important endpoints. The principle findings of this study are the following: (i) there were significant differences in the baseline clinical and echocardiographic characteristics of patients with none/trace, mild, or moderate/severe PVR; (ii) patients with moderate/severe PVR demonstrated increases in LVED and less reduction in the LV mass index when compared with patients with less PVR; (iii) the presence of greater severity PVR was associated with reduced improvement in NYHA class and higher rates of re-hospitalization; (iv) On multivariable analysis, the presence of either mild (HR: 1.37) or moderate/severe (HR: 2.18) PVR resulted in significantly higher 1-year mortality.

There were important differences in the baseline clinical and echocardiographic characteristics between the three groups. Whether these differences are responsible for the severity of PVR remains uncertain. Unfortunately, patients in the PARTNER trial did not have routine 3D imaging of the aortic annulus that would have allowed a more complete analysis evaluating predictors of PVR such as LVOT calcification and annular area. Nevertheless, less oversizing (i.e. lower cover index) as assessed by a 2D measurement of the annulus was associated with in more PVR. Interestingly, patients undergoing TAVR via the TA approach had less severe PVR. The reasons for this are uncertain and may be related to procedural differences as well as important differences in baseline characteristics between the two groups. Despite less PVR, the TA approach resulted in higher 1-year mortality in the multivariable analysis.

Several prior reports have suggested that PVR could negatively impact mid- and long-term prognosis following TAVR.[25–28] A recent meta-analysis by Athappan *et al.* with 1620 patients demonstrated increased 1-year mortality in patients with either moderate/severe

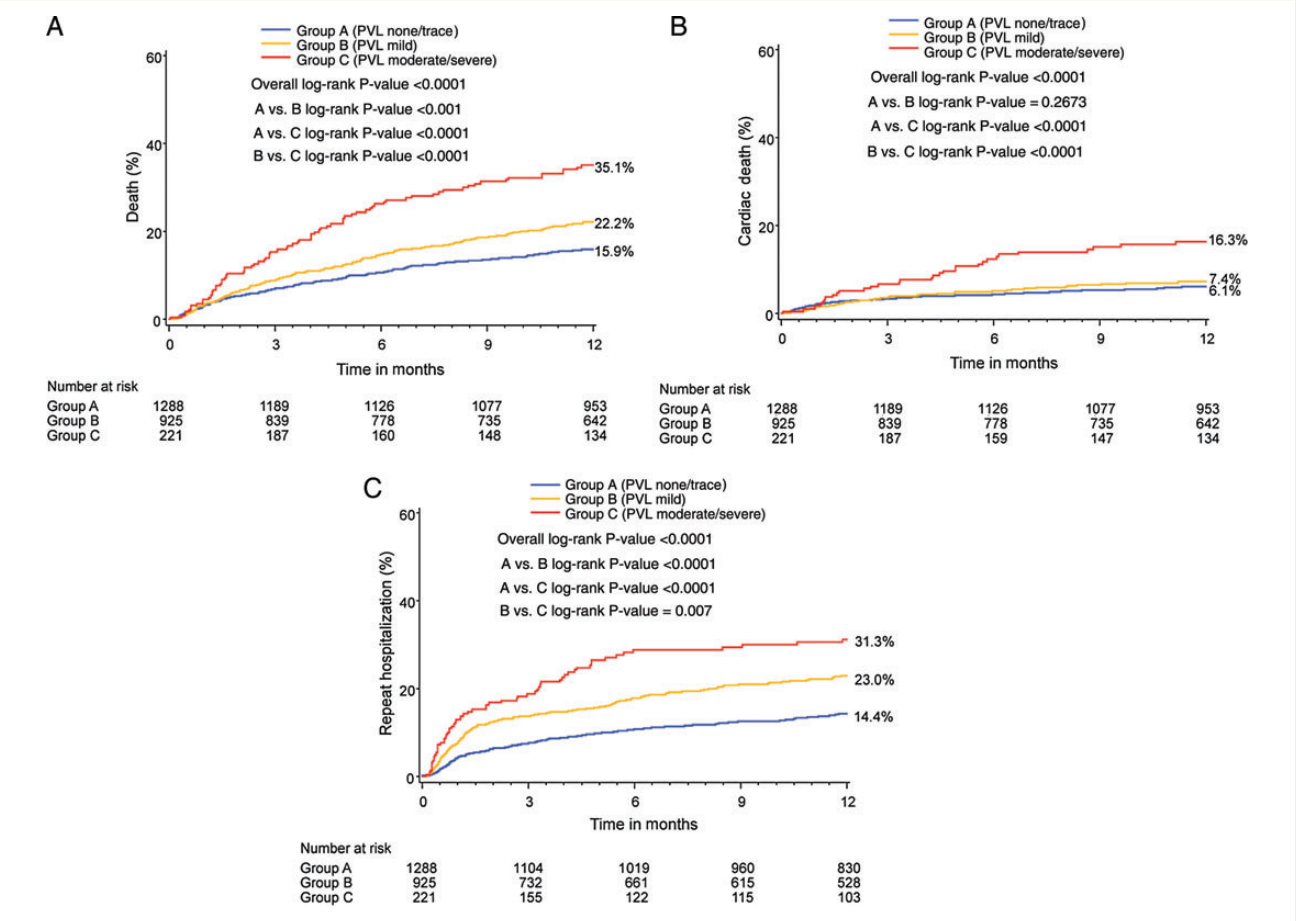


**Figure 1** Differences in all-cause mortality (*A*), cardiac mortality (*B*) and repeat hospitalization (*C*) in patients following transcatheter aortic valve replacement stratified by severity of post-implant paravalvular regurgitation: none/trace (group *A*), mild (group *B*), and moderate/severe (group *C*).

(HR: 2.27) or mild PVR (HR: 1.83). However, on sensitivity analysis, the clinical impact of mild PVR was less certain. Our study confirms that moderate/severe PVR results in higher 1-year mortality with a multivariate hazard ratio (HR: 2.18) similar to that seen in the meta-analysis. In addition, our analysis demonstrates that mild PVR also results in significantly higher 1-year mortality. There are several key differences between the current study and the prior ones. First, in contrast to ours, the studies used in the meta-analysis consisted of both Edwards Sapien and Medtronic CoreValve implants. Also the assessment of PVR in prior studies was variable and included both angiographic and echocardiographic assessment with only one study[29] relying on a core laboratory for grading. Finally, our study with 2434 patients represents one of the largest experiences published to date.

The impact of mild PVR on mortality remains controversial. As noted above, prior studies have not demonstrated a clear association. In the recently presented FRANCE2 registry[30] in which site-graded PVR was analysed, patients with grade 1 or mild PVR did not have increased 1-year mortality when compared with none/trace. One potential explanation for this difference is variability in the assessment of PVR severity. It is often challenging to characterize those patients with mild-to-moderate PVR. In this grey zone, one individual may downgrade the PVR to mild while another may call it moderate. These differences may result in different patient populations between various studies. As an example, in the FRANCE 2 registry, 13% of patients receiving a balloon-expandable valve were graded as having PVR grade 2 (moderate) or greater based on site assessed pre-discharge TTE. In our study, moderate or greater PVR was seen in only 9.1% of patients. It is conceivable that these differences in frequency may be due to different thresholds for what is graded as moderate and whether the grading is performed at the site or by a core laboratory. In our study, using core lab assessed PVR, the differential LVED response of each PVR group ($-0.16 \pm 0.60$ cm in none/trace, $-0.04 \pm 0.60$ cm in mild, and $+0.09 \pm 0.64$ cm in mod/severe) as well as the differential LV mass response of each PVR group, suggest that these groups represent truly different volume loads on the ventricle and support the grading scheme used by the core lab. Nonetheless, a standardized and comprehensive system for assessing PVR, including quantitative assessment as proposed by the recently published VARC-2 guidelines,[31] may help elucidate the true impact of varying severities of PVR.

Another question is whether PVR results in higher mortality or is simply associated with other factors leading to late mortality. Prior studies have suggested that higher PVR rates are seen in patients with certain clinical characteristics such as severe aortic valve

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