Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial

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ABSTRACT

BACKGROUND It is unknown whether transcatheter valves will have similar durability as surgical bioprosthetic valves. Definitions of structural valve deterioration (SVD), based on valve related reintervention or death, underestimate the incidence of SVD.

OBJECTIVES This study sought to determine and compare the 5-year incidence of SVD, using new standardized definitions based on echocardiographic follow-up of valve function, in intermediate-risk patients with severe aortic stenosis given transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) in the PARTNER (Placement of Aortic Transcatheter Valves) 2A trial and registry.

METHODS In the PARTNER 2A trial, patients were randomly assigned to receive either TAVR with the SAPIEN XT or SAVR, whereas in the SAPIEN 3 registry, patients were assigned to TAVR with the SAPIEN 3. The primary endpoint was the incidence of SVD, that is, the composite of SVD-related hemodynamic valve deterioration during echocardiographic follow-up and/or SVD-related bioprosthetic valve failure (BVF) at 5 years.

RESULTS Compared with SAVR, the SAPIEN-XT TAVR cohort had a significantly higher 5-year exposure adjusted incidence rates (per 100 patient-years) of SVD (1.61 ± 0.24% vs. 0.63 ± 0.16%), SVD-related BVF (0.58 ± 0.14% vs. 0.27 ± 0.10%), and all-cause (structural or nonstructural) BVF (0.81 ± 0.16% vs. 0.27 ± 0.10%) (p < 0.01 for all). The 5-year rates of SVD (0.68 ± 0.18% vs. 0.60 ± 0.17%; p = 0.71), SVD-related BVF (0.29 ± 0.12% vs. 0.14 ± 0.08%; p = 0.25), and all-cause BVF (0.60 ± 0.15% vs. 0.32 ± 0.11%; p = 0.32) in SAPIEN 3 TAVR were not significantly different to a propensity score matched SAVR cohort. The 5-year rates of SVD and SVD-related BVF were significantly lower in SAPIEN 3 versus SAPIEN XT TAVR matched cohorts.

CONCLUSIONS Compared with SAVR, the second-generation SAPIEN XT balloon-expandable valve has a higher 5-year rate of SVD, whereas the third-generation SAPIEN 3 has a rate of SVD that was not different from SAVR. (The PARTNER II Trial: Placement of AoRTic TranscatheterER Valves - PII A [PARTNERII A]; NCT01314313; The PARTNER II Trial: Placement of AoRTic TranscatheterER Valves II - PARTNER II - PARTNERII - S3 Intermediate [PARTNERII S3i]; NCT03222128) (J Am Coll Cardiol 2020;76:1830–43) © 2020 by the American College of Cardiology Foundation.
transcatheter aortic valve replacement (TAVR) is established for the treatment of symptomatic severe aortic stenosis (AS) in patients deemed to be at high or extreme risk for surgery (1-3). In patients at intermediate or low surgical risk, previous trials have demonstrated that TAVR was either noninferior or superior to surgical aortic valve replacement (SAVR) (4-8), resulting in an expansion of societal guideline recommendations for TAVR (9,10). In the randomized PARTNER (Placement of Aortic Transcatheter Valves) 2 cohort A trial, we previously reported that TAVR with the second generation of balloon-expandable valve, the SAPIEN-XT (Edwards Lifesciences, Irvine, California), was noninferior to SAVR in patients with intermediate surgical risk (4), whereas TAVR with the third generation (i.e., SAPIEN 3) was superior to SAVR in a propensity score analysis of the PARTNER 2A SAVR arm and SAPIEN 3 intermediate-risk registry (5).

Recently, we reported the 5-year outcomes of the PARTNER 2A trial and observed no significant difference in the incidence of death or disabling stroke at 5 years after TAVR compared with SAVR (11). However, in landmark analyses from 2 to 5 years after the procedure, we observed a higher incidence of death from any cause with TAVR than with SAVR (11).

Bioprosthetic valves used for SAVR or TAVR have limited durability due to structural valve deterioration (SVD). Valve durability becomes a major issue as TAVR is expanding to lower-risk and younger populations with longer life expectancy. It is unknown whether TAVR bioprosthetic valves will have similar durability as surgical valves. Historical definitions of SVD, based on valve reintervention or valve-related death, markedly underestimate the actual incidence of SVD (12-16). Recent statements redefined SVD based on identification of structural and hemodynamic valve deterioration at echocardiographic follow-up (12,15).

We therefore developed new definition and analysis standards for valve durability based on echocardiographic follow-up of valve structure and function.

**ABBREVIATIONS AND ACRONYMS**

AS = aortic stenosis
BVF = bioprosthetic valve failure
SAVR = surgical aortic valve replacement
SVD = structural valve deterioration
TAVR = transcatheter aortic valve replacement
and we applied these standards to report and compare the 5-year incidence of SVD in intermediate-risk patients with severe AS given SAPIEN XT transcatheter aortic valve replacement (TAVR), SAPIEN 3 TAVR, or SAVR in the PARTNER 2A trial and registry.

**METHODS**

**STUDY DESIGN AND POPULATIONS.** In this analysis, we used the populations from the PARTNER 2A randomized trial (NCT01314313) (4,11) and the PARTNER 2 SAPIEN 3 intermediate-risk observational study (NCT03222128) (5,17). These 2 prospective, multicenter studies enrolled patients with symptomatic, severe AS who were considered to be at intermediate risk for 30-day surgical mortality. Surgical risk status was evaluated by a heart team, and patients were considered at intermediate risk based on clinical assessment or if their Society of Thoracic Surgeons predicted risk of operative mortality score was 4% or higher. In those with a Society of Thoracic Surgeons score lower than 4%, the heart team deemed patients to be intermediate risk if they had risk factors not present within the predictive score (e.g., liver disease, frailty, and pulmonary hypertension).

In the PARTNER 2A trial, patients were randomly assigned to receive either SAVR or TAVR using the SAPIEN XT (Figure 1) (4). In the SAPIEN 3 single-arm study, all TAVR patients who were eligible to receive a SAPIEN 3 valve were presented on a conference call in which a screening committee reviewed imaging and clinical data and approved patients prior to enrollment. Inclusion and exclusion criteria for the PARTNER 2A trial and SAPIEN 3 registry (4,5,17) were the same. Key exclusion criteria were a congenitally bicuspid aortic valve, severe aortic regurgitation, left ventricular ejection fraction lower than 20%, severe renal insufficiency, and estimated life expectancy <2 years. Both trials were approved by the Institutional Review Boards of each participating site, and written informed consent was provided by all patients.

For this analysis, we used the SVD-assessed cohorts, which correspond to the valve-implanted populations of the PARTNER 2A randomized trial (n = 1,438) and of the PARTNER 2 SAPIEN 3 Intermediate-Risk registry (n = 891) with echocardiographic data available at 30 days and subsequent follow-up (at least 1 echocardiogram) to allow assessment of SVD (Figure 1). All cases of BVF were also included in these SVD-assessed cohorts, regardless of whether echocardiographic data were available or not. Furthermore, the rate of all-cause BVF was reported in the valve-implanted cohorts.

**TAVR AND SAVR PROCEDURES.** Pre-procedural valve sizing for TAVR was determined by multidetector computed tomography or 3-dimensional transesophageal echocardiography. These images were independently analyzed by core laboratories in patients enrolled in the SAPIEN 3 study but not in those enrolled in the PARTNER 2A trial. Access was via transfemoral, transapical, or transaortic routes, depending on pre-procedural peripheral vascular assessments. Post-operative dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 1 month, at the heart team’s discretion. Warfarin was also recommended in patients with atrial fibrillation, based on patient tolerance. The co-principal investigators and other members of the executive committee had access to the data after the database was locked and prepared the paper. The same executive committee was used for the PARTNER 2A trial and SAPIEN 3 study, and this committee attests to the completeness and accuracy of the data and adherence of the studies to the protocol.

In both the PARTNER 2A trial and SAPIEN 3 study, a transthoracic echocardiogram was performed at baseline prior to the procedure, at 30 days, and annually thereafter until 5 years. All echocardiograms were analyzed independently by a consortium of echocardiography core laboratories. Mean transvalvular pressure gradient, aortic valve area, and Doppler velocity index were calculated as previously described (18). The severity of prosthesis-patient mismatch (PPM) was graded using the aortic valve area indexed to body surface area with absence of mismatch defined as >0.85 cm²/m², moderate mismatch >0.65 and ≤0.85 cm²/m², and severe mismatch ≤0.65 cm²/m² (19). If the patient was obese (body mass index ≥30 kg/m²), lower cut-off values of indexed valve area were used to define moderate (>0.55 and ≤0.70 cm²/m²) and severe (>0.55 cm²/m²) PPM. Aortic regurgitation was assessed before and after the procedure using a multiparameter integrative approach and was graded as: none/trace, mild, moderate, or severe, and classified as transvalvular or paravalvular (20,21).

**STUDY OUTCOMES.** The primary endpoint was the incidence of SVD, which was defined as the composite of hemodynamic valve deterioration stage ≥2 during echocardiographic follow-up and/or BVF related to SVD at 5 years (Supplemental Tables 1 and 2). The secondary endpoints were: 1) SVD-related BVF; and 2) all-cause BVF related to SVD, nonstructural
valve dysfunction, valve thrombosis, or valve endocarditis (Supplemental Table 1).

Potential hemodynamic valve deterioration was identified based on the changes in echocardiographic parameters of hemodynamic valve function from the 30-day (or discharge, if 30-day not available) echocardiogram and follow-up echocardiograms. All potential cases were then adjudicated by a group of 4 experts (P.P., J.T., E.S., R.T.H.) for confirmation of the presence, stage, and etiology of valve deterioration. The stages of SVD were categorized as: SVD, thrombosis, or valve-related death. All valve-related events (reintervention or death) were adjudicated. The etiology of hemodynamic valve deterioration was categorized as: SVD, thrombosis, or endocarditis. SVD implied irreversible structural change to the prosthetic valve (Supplemental Table 1).

BVF was defined according to 2017 European (15) and Valve Academic Research Consortium 3 standardized definitions (Supplemental Table 1): 1) any bioprosthetic valve dysfunction with clinically expressive criteria or irreversible stage 3 (severe) hemodynamic valve deterioration; 2) valve reintervention; or 3) valve-related death. All valve-related events (reintervention or death) were adjudicated. The etiology of BVF was classified as: 1) SVD; 2) nonstructural valve dysfunction (paravalvular regurgitation,
prosthesis-patient mismatch, or valve migration); 3) thrombosis; or 4) endocarditis (Supplemental Table 1).

**STATISTICAL ANALYSES.** Continuous variables are presented as mean ± SD and were compared using the Student’s t-test. Categorical variables are presented as proportions and were compared using the chi-square or Fisher exact tests.

The exposure-adjusted incidence rates of SVD, SVD-related BVF, and all-cause BVF were reported in each of the 3 cohorts at each follow-up year until 5 years (22). The exposure-adjusted incidence rate is defined as the number of subjects exposed to the device (i.e., the aortic bioprosthetic valve) and experiencing an event (SVD or BVF) divided by the total exposure time of all patients who are at risk of event, and it is expressed per 100 patient-years (22). The 5-year cumulative rates of SVD and BVF were also reported as Kaplan-Meier curves. The rates of events between SAPIEN XT TAVR versus SAVR and SAPIEN 3 TAVR versus SAVR were compared using hazard ratio and log-rank test. We also used a propensity score matching analysis to compare the rates of SVD and BVF from the SAPIEN 3 TAVR cohort with those of similar intermediate-risk patients in the SAVR arm of the PARTNER 2A trial. First, a logistic regression model was performed on 25 baseline characteristic variables (Supplemental Methods) to calculate the propensity score for each patient. Missing baseline values were imputed using the Markov-Chain Monte Carlo method prior to modeling. Propensity scores represent the likelihood that the patient was in the SAPIEN 3 TAVR group. Patients of the SAPIEN 3 TAVR cohort were matched 1:1 to patients of the PARTNER 2A SAVR cohort and 1:1 to patients in the PARTNER 2A SAPIEN XT cohort according to the propensity score using the greedy nearest neighbor matching algorithm according to a caliper width of 0.2 SD of logit of propensity score (Figure 1). After propensity score matching, the absolute standardized difference was <10% for all baseline variables (Supplemental Figure 1). Propensity score was used to weight each subject of the SAPIEN 3 TAVR and SAVR cohorts by the inverse probability of treatment (stabilized inverse propensity score as weight) and generate an inverse probability treatment weighting (IPTW).

The association between baseline and procedural factors and risk of SVD and BVF was examined in the whole cohort and within each of the 3 cohorts. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

**RESULTS**

**INCIDENCE OF SVD IN TAVR AND SAVR.** The baseline and procedural characteristics of the SAVR, SAPIEN XT TAVR, and SAPIEN 3 TAVR cohorts with echocardiographic data available (i.e., SVD-assessed populations) are presented in Table 1. The median (interquartile range) time from 30-day to last follow-up echocardiograms and to the primary endpoint (SVD) was similar in the 3 cohorts: SAVR: 4.06 years (2.17 to 5.00 years); SAPIEN XT: 3.99 years (2.16 to 4.98 years); and SAPIEN 3: 3.99 years (2.12 to 4.98 years). The number of patients with SVD and SVD-related BVF are presented in Figure 1.

**SAPIEN XT TAVR versus SAVR.** The 5-year Kaplan-Meier cumulative rates of SVD were significantly higher (p < 0.001) in SAPIEN XT TAVR (9.5%; 95% confidence interval [CI]: 7.0% to 12.7%) versus SAVR (3.5%; 95% CI: 2.1% to 5.8%) (Figure 2). The 5-year exposure adjusted incidence rates per 100 patient-years of SVD (1.61 ± 0.24% vs. 0.63 ± 0.16%) and SVD-related BVF (0.58 ± 0.14% vs. 0.12 ± 0.07%) were also significantly (p < 0.01) higher in SAPIEN-XT TAVR versus SAVR (Figure 3, Central Illustration).

**SAPIEN 3 TAVR versus SAPIEN XT-TAVR.** Compared with the SAPIEN-XT TAVR matched cohort, the SAPIEN 3 TAVR cohort had lower exposure-adjusted incidence rates of SVD (0.63 ± 0.16% vs. 1.76 ± 0.27%; p = 0.0001) and SVD-related BVF (0.21 ± 0.09% vs. 0.65 ± 0.16%; p = 0.03) at 5 years (Supplemental Figures 2 and 3).

**SAPIEN 3 TAVR versus SAVR.** The Kaplan-Meier cumulative rates and exposure-adjusted incidence rates of SVD and SVD-related BVF for the SAPIEN 3 TAVR versus SAVR unmatched SVD-assessed cohorts are presented in Figure 2 and Supplemental Figure 4, respectively. In the whole cohort, the 5-year Kaplan-Meier cumulative rates of SVD were similar (p = 0.65) in SAPIEN 3 TAVR (3.9%; 95% CI: 2.5% to 6.0%) versus SAVR (3.5%; 95% CI: 2.1% to 5.8%) (Figure 2). The cumulative and exposure-adjusted rates for the SAPIEN 3 TAVR versus SAVR propensity-score matched cohorts are presented in Supplemental Figure 5 and in Figure 4, respectively. Compared with the SAVR matched cohort, the SAPIEN 3 TAVR cohort had similar exposure-adjusted incidence rates of SVD at 5 years (0.68 ± 0.18% vs. 0.60 ± 0.17%; p = 0.71) (Figure 4, Central Illustration). The 5-year rate of SVD-related BVF was numerically higher but not statistically different in SAPIEN 3 TAVR versus SAVR (0.29 ± 0.12% vs. 0.14 ± 0.08%; p = 0.25). The IPTW analysis in the whole (unmatched) SVD-assessed cohort provided similar results (IPTW-adjusted incidence
rate of SVD at 5 years: 0.78 ± 0.17% vs. 0.64 ± 0.18%; p = 0.37, and of SVD-related BVF: 0.25 ± 0.11% vs. 0.10 ± 0.06%; p = 0.07) (Supplemental Figure 6).

Factors associated with SVD. Baseline and procedural factors associated with SVD were: younger age and female sex in the whole cohort (SAVR + SAPIEN XT TAVR + SAPIEN 3 TAVR); younger age, chronic obstructive pulmonary disease, and smaller transcatheter valve size in the whole TAVR cohort (SAPIEN XT + SAPIEN 3); female sex and smaller transcatheter valve size in the SAPIEN XT TAVR cohort; and younger age, female sex, and diabetes in the SAPIEN 3 TAVR cohort; there were no factors significantly associated with SVD in the SAVR cohort (Supplemental Table 3). After adjusting for age and sex, TAVR with SAPIEN XT was independently associated with higher risk of SVD in the whole TAVR + SAVR cohort (hazard ratio: 2.59; 95% CI: 1.44 to 4.65; p = 0.0015) as well as in the TAVR cohort (hazard ratio: 2.63; 95% CI: 1.56 to 4.55; p = 0.0003).

INCIDENCE AND ETIOLOGY OF BVF IN TAVR AND SAVR. The 5-year Kaplan-Meier cumulative rates and exposure-adjusted incidence rates of all-cause BVF in the whole cohort were higher in SAPIEN XT TAVR (4.7%; 95% CI: 3.1% to 7.1% and 0.56 ± 0.10%, respectively) versus SAVR (1.3%; 95% CI: 0.6% to 2.7% and 0.27 ± 0.10%, respectively) (Figures 2C and 3C). The rates of all-cause BVF were numerically but not statistically (p > 0.10) higher in SAPIEN 3 TAVR (2.6%; 95% CI: 1.7% to 4.2% and 0.56 ± 0.13%, respectively) versus SAVR (Supplemental Figure 4C). Comparison in matched SAPIEN 3 TAVR versus SAVR cohorts provided similar results (Figure 4C), but the IPTW-adjusted incidence rate of all-cause BVF was significantly higher in SAPIEN 3 TAVR versus SAVR (0.50 ± 0.12% vs. 0.21 ± 0.08%; p = 0.004).

In the SAVR cohort, most BVFs were related to endocarditis (50%), followed by SVD (37.5%) (Figure 5, Central Illustration). In the SAPIEN XT TAVR cohort, BVF was related to SVD in 64% of the cases and paravalvular regurgitation in 20%. In the SAPIEN 3 TAVR
FIGURE 2  Comparison of the 5-Year Kaplan-Meier Cumulative Rates of Structural Valve Deterioration and Bioprosthetic Valve Failure in the SAPIEN XT TAVR, SAPIEN 3 TAVR, and SAVR Populations

(A) SVD: that is, a composite of hemodynamic valve deterioration or valve failure (BVF) related to structural valve deterioration. (B) BVF related to structural valve deterioration. (C) All-cause BVF related to structural valve deterioration or nonstructural valve dysfunction. Data are from the SVD-assessed cohort (A and B) and from the whole cohort (C) (see Figure 1). CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.
FIGURE 3  Comparison of the Exposure-Adjusted Incidence Rates of Structural Valve Deterioration and Bioprosthetic Valve Failure in the SAPIEN XT TAVR Versus SAVR Cohorts

(A) SVD: that is, a composite of hemodynamic valve deterioration or BVF related to structural valve deterioration. (B) BVF related to structural valve deterioration. (C) All-cause BVF related to structural valve deterioration or nonstructural valve dysfunction. Data are from the SVD-assessed cohort (A and B) and from the whole cohort (C) (see Figure 1). Error bars represent standard deviation. Abbreviations as in Figure 1.
There was no statistically significant difference between SAPIEN 3 TAVR for all endpoints except for all-cause (i.e., structural or nonstructural dysfunction) BVF with inverse probability treatment weighting (IPTW). BVF = bioprosthetic valve failure; SAVR = surgical aortic valve replacement; SVD = structural valve deterioration; TAVR = transcatheter aortic valve replacement.
cohort, BVF was related to paravalvular regurgitation in 58% of the cases and SVD in 32%. The other and much less frequent causes of BVF were: valve thrombosis in 3 patients (2 in SAPIEN XT and 1 in SAPIEN 3), and valve migration in 3 patients (2 in SAPIEN XT and 1 in SAPIEN 3) (Figure 5). The causes and types of aortic valve reintervention are presented in Supplemental Figure 7 and Figure 5, respectively. In the SAVR cohort, 83% of reinterventions were redo surgery, and 17% were transcatheter valve-in-valve
procedures (Figure 5). In the SAPIEN XT cohort, reintervention was valve-in-valve in 81%, surgical replacement in 14%, and balloon dilation in 5%. In the SAPIEN 3 TAVR cohort, reintervention was valve-in-valve in 76% and surgical replacement in 24%. Mortality at 30 days related to reintervention was high (50%) in the SAVR cohort, and significantly ($p < 0.01$) higher versus the 5% in the SAPIEN XT and 0% in the SAPIEN 3 cohorts.

**DISCUSSION**

The second generation of transcatheter balloon-expandable heart valve, the SAPIEN XT, showed a 2.6-fold higher incidence of SVD, whereas the third-generation, the SAPIEN 3, had similar rates of SVD compared with SAVR (Central Illustration). The rates of all-cause BVF were higher in SAPIEN XT and SAPIEN 3 TAVR versus SAVR. However, the causes of
BVF differed between groups: that is, the majority of BVFs and valve reinterventions were related to SVD in the SAPIEN XT TAVR, paravalvular regurgitation (i.e., nonstructural valve dysfunction) in the SAPIEN 3 TAVR, and endocarditis in the SAVR cohort.

The historical definition of SVD, based on the occurrence of valve reintervention or death related to structural valve failure, markedly underestimates the true incidence of SVD because it only captures the most severe cases of SVD associated with heart failure symptoms (12–16). Furthermore, a substantial proportion of patients with severe SVD may not undergo reintervention because they are deemed to be at high risk for poor outcomes with redo surgery or even with transcatheter valve-in-valve procedure. Several deaths may not be classified as valve-related, although SVD may have directly or indirectly contributed to this adverse event. Recently, more sensitive definitions of SVD based on the documentation of a deterioration of valve structure and function at echocardiographic follow-up have been proposed (12,15). These definitions include 3 stages of SVD: stage 1: morphological SVD with no deterioration in valve hemodynamic function; stage 2: moderate hemodynamic valve deterioration; and stage 3: severe hemodynamic valve deterioration. In a recent SAVR series, the 10-year rate of SVD (stage ≥2) was 41%, whereas the rate of SVD-related BVF was much lower at 3.5% (23). Moreover, the occurrence of stage ≥2 SVD following SAVR was independently associated with a marked increase in the risk of mortality and valve reintervention during subsequent follow-up (23,24).

NEW DEFINITION AND ANALYSIS STANDARDS FOR REPORTING SVD AFTER AORTIC VALVE REPLACEMENT.

Several recent studies (25–29) reported the rates of SVD defined according to the 2017 European standardized definitions (15). In these studies, the cumulative rates of SVD at 5 to 7 years of follow-up after TAVR were between 4.8% and 13.3% (25–29). In the NOTION (Nordic Aortic Valve Intervention) trial (28), the 6-year rate of SVD was lower in TAVR versus SAVR (4.8% vs. 24.0%; p < 0.001), whereas the rate of BVF was similar (6.7% vs. 7.5%; p = 0.89). In the CoreValve U.S. Pivotal High-Risk Trial (29), the 5-year rate of SVD was also lower in TAVR versus SAVR (9.5% vs. 26.6%; p < 0.001), but the rate of valve reintervention was higher in TAVR (3.0% vs. 1.1%; p = 0.04).

In the present study, we developed new definition and analysis standards for SVD, which build on previously proposed standardized definitions (12,15,19) and include the addition or modification of several criteria of SVD (Supplemental Table 2) as well as an adjudication process to provide a more accurate and complete estimation of the overall incidence of SVD following SAVR or TAVR. This new standardized definition scheme mandates the documentation of permanent structural changes to the prosthetic valve leaflets and the occurrence of hemodynamic valve deterioration during follow-up to confirm the presence of SVD. Hence, patients with high residual gradient (≥20 mm Hg) related to prosthesis-patient mismatch and no evidence of structural and hemodynamic valve deterioration during follow-up are not classified as having SVD with these new definitions (Supplemental Tables 1 and 2), whereas these patients would be deemed to have SVD according to the 2017 European definitions (15). Prosthesis-patient mismatch occurs when the effective orifice area of the prosthetic valve is too small in relation to the patient’s body size, thus resulting in high procedural residual gradients, despite normal prosthetic valve function. This entity is a nonstructural valve complication and should therefore not be classified as SVD. In the NOTION and CoreValve U.S. Pivotal High Risk trials, the incidence of severe prosthesis-patient mismatch was higher in SAVR than in TAVR, which may have contributed to the higher rates of SVD reported in these trials at midterm follow-up in SAVR versus TAVR (28,29).

DURABILITY OF THIRD VERSUS SECOND GENERATION OF BALLOON-EXPANDABLE TRANSCATHETER VALVE.

Several potential factors may explain the better durability of the SAPIEN 3 versus the SAPIEN XT observed in the present study. First, computed tomography was not systematically used for valve sizing with the SAPIEN XT, and the 29-mm size of the SAPIEN XT valve was introduced late in the course of the PARTNER 2A trial. Hence, several patients may have received an undersized transcatheter valve, and operators may have elected to overexpand the valve excessively to accommodate. Overexpansion increases valve leaflet tethering and mechanical stress, which may reduce valve durability (30). Second, the SAPIEN 3 valve generally requires less of a degree of valve oversizing than the SAPIEN XT (31,32). More important, oversizing may lead to valve underdeployment, which increases pinwheeling and bending stress of valve leaflets, and may thus predispose to accelerated SVD (33). Third, a greater proportion of patients with the SAPIEN XT versus the SAPIEN 3 (20.9% vs. 11.9%) (Table 1) underwent balloon post-dilation to correct residual paravalvular aortic regurgitation or high gradient at the time of the procedure. Balloon post-dilation may cause damage to the leaflets and valve overexpansion, which may
impart valve durability (34). Fourth, as opposed to the SAPIEN XT, the SAPIEN 3 does not have stent posts, which may allow more complete valve expansion (Central Illustration) (31). Also, the SAPIEN 3 was generally implanted in a higher position than the SAPIEN XT. Both factors may result in lesser leaflet mechanical stress and thus better durability with the SAPIEN 3 versus the SAPIEN XT.

**FACTORS ASSOCIATED WITH SVD FOLLOWING TAVR OR SAVR.** Younger age, female sex, and diabetes were associated with higher risk of SVD in the present study. Several previous studies reported that younger age and diabetes are powerful risk factors of SVD following biological aortic valve replacement (23,35,36). Furthermore, Salaun et al. (23) found an independent association between female sex and SVD following SAVR. Women have smaller aortic annuli and are at higher risk for severe prosthesis-patient mismatch and high residual gradient following valve replacement, which may predispose to accelerated SVD (13,23,37). Furthermore, postmenopausal women are predisposed to osteoporosis and may thus be more susceptible than men to develop ectopic calcification, including calcification of bioprosthetic valve leaflets (23).

**CAUSES OF BVF IN TAVR AND SAVR.** Most cases of BVF and valve reintervention in the SAVR cohort were caused by endocarditis and were associated with high mortality, whereas in the TAVR cohorts, none of the BVFs were related to endocarditis. Paravalvular aortic regurgitation was the cause of BVF in 58% of the cases in the SAPIEN 3 cohort versus 20% in the SAPIEN XT cohort. This finding may be explained by the competitive risk associated with SVD-related BVF in the SAPIEN XT group. Also, the SAPIEN 3 intermediate-risk study was conducted after the PARTNER 2A trial. Hence, the treating physicians of the patients included in the SAPIEN 3 study may have been more aware of the detrimental impact of paravalvular regurgitation on outcomes, and may thus have been more aggressive with regard to reintervention (delayed balloon dilation or valve-in-valve procedure) in patients with significant paravalvular regurgitation.

**STUDY LIMITATIONS.** A limitation of this study is that randomization was available for SAPIEN XT versus SAVR comparison but not for that between SAPIEN 3 versus SAVR. A propensity score-matched approach was therefore applied to allow well-balanced comparison of these 2 groups. Another limitation is that the occurrence of echocardiography-defined stage 2 or 3 SVD could not be assessed in 22% of this population because echocardiograms were not available or incomplete. However, the occurrence of BVF was determined in the whole valve-implanted populations. The post-procedural antithrombotic regimen was not systematically collected and adjudicated in PARTNER 2, and so we were not able to assess the effect of this factor on occurrence of SVD and BVF.

**CONCLUSIONS**

The 5-year rates of SVD were higher in SAPIEN XT TAVR and not statistically different in SAPIEN 3 TAVR compared with SAVR. The 5-year rates of all-cause BVF were higher in SAPIEN XT and SAPIEN 3 TAVR versus SAVR. In the SAPIEN XT, the vast majority of BVFs and valve reinterventions were related to SVD, whereas in the SAPIEN 3, most BVFs were related to nonstructural dysfunction (i.e., paravalvular aortic regurgitation). In SAVR, one-half of BVFs and reinterventions were caused by endocarditis versus none in TAVR, and 30-day mortality related to reintervention was higher in SAVR versus TAVR. The second generation of SAPIEN balloon-expandable valves (i.e., the SAPIEN XT) has lower midterm durability compared with SAVR, whereas the third generation (i.e., the SAPIEN 3) has better durability compared with SAPIEN XT. Further studies are needed to determine whether SAPIEN 3 TAVR has similar midterm and long-term durability compared with SAVR.

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**PERSPECTIVES**

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** The second generation balloon expandable valve prosthesis (SAPIEN XT) was associated with lower 5-year durability than SAVR, whereas the third generation SAPIEN 3 prosthesis exhibits midterm durability similar to SAVR, supporting use of the SAPIEN 3 valve as an alternative to SAVR in patients at high, intermediate, or low surgical risk.

**TRANSLATIONAL OUTLOOK:** Longer-term studies are required to characterize more completely the durability of the SAPIEN 3 valve prosthesis after TAVR.
REFERENCES


KEY WORDS: aortic stenosis, bioprosthetic valve, echocardiography, structural valve deterioration, transcatheter aortic valve replacement

APPENDIX: For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.