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The Effect of Post-Dilatation on Outcomes in the PARTNER 2 SAPIEN 3 Registry

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ABSTRACT

OBJECTIVES The purpose of this study was to understand the effects of balloon post-dilatation on outcomes following transcatheter aortic valve replacement with the SAPIEN 3 valve.

BACKGROUND Hemodynamics and outcomes with balloon post-dilatation for the SAPIEN 3 valve have not been previously reported.

METHODS The effects of balloon post-dilatation (BPD) in 1,661 intermediate (S3i cohort) and high surgical risk (S3HR cohort) patients with aortic stenosis enrolled in the PARTNER (Placement of Aortic Transcatheter Valves) 2, SAPIEN 3 observational study on outcomes, as well as procedural complications, were assessed.

RESULTS 208 of 1,661 patients (12.5%) had BPD during the initial transcatheter aortic valve replacement. Baseline characteristics were similar except BPD had higher STS score ($p < 0.001$), significantly less % oversizing ($p = 0.004$), significantly more ≥moderate left ventricular outflow tract calcification ($p = 0.005$), and severe annular calcification ($p = 0.006$). BPD patients had no increase in permanent pacemaker, annular rupture, or valve embolization. Following transcatheter aortic valve replacement, BPD patients had significantly larger aortic valve area (1.72 ± 0.41 cm^2 vs. 1.66 ± 0.37 cm^2; $p = 0.04$) with no significant difference in prosthesis-patient mismatch ($p = 0.08$) or transvalvular aortic regurgitation ($p = 0.65$), but significantly more paravalvular regurgitation ($p < 0.01$). There was no significant difference in 30-day or 1-year outcomes of all-cause death ($p = 0.65$ to 0.76) or stroke ($p = 0.28$ to 0.72). However, at 1 year, there was a significantly higher incidence of minor stroke in BPD patients ($p = 0.02$). Adjusting for baseline differences, including calcium burden, minor strokes were no longer significantly different between the BPD and NoBPD groups ($p = 0.21$).

CONCLUSIONS BPD is performed more frequently in patients with lower % oversizing and greater calcium burden. BPD is not associated with procedural complications or an increase in 1-year adverse events of death, rehospitalization, or stroke. (J Am Coll Cardiol Intv 2018;11:1710–8) © 2018 by the American College of Cardiology Foundation.

Numerous studies have shown an association between post-procedural paravalvular regurgitation (PVR) and increased late mortality (1–3), generating intense interest in determining predictors or treatment of this complication. Re-ballooning or balloon post-dilatation (BPD) of the transcatheter heart valve (THV) after implantation has been proposed as an effective method to reduce

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post-transcatheter aortic valve replacement (TAVR) PVR (4–6). Potential procedural risks of BPD include THV migration or injury, trauma to the conduction system, rupture of the membranous septum or aorta, and cerebrovascular embolism (5–7). We have previously shown that with a first-generation SAPIEN valve (Edwards Lifesciences, Irvine, California), BPD is associated with reduced rates of moderate or severe prosthesis-patient mismatch (PPM) with no evidence for short-term structural deterioration of the balloon-expandable transcatheter valve (8). BPD, however, was associated with a greater incidence of early stroke with no significant association between BPD and mortality, a finding supported by earlier investigations (6). Evaluation of registries (9) and trial data (10) outcomes of BPD with the CoreValve system (Medtronic, Minneapolis, Minnesota) have not shown significant neurological adverse outcomes, but did show significantly greater acute kidney injury (10). In addition, the need for BPD was nearly 2 times that for the first-generation SAPIEN valve (12% for SAPIEN vs. 24% for CoreValve).

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The third-generation SAPIEN 3 has a new construct that allows for less oversizing (11), more precise positioning (12), and less PVR (13) than prior iterations. Some of these factors may contribute to greater or lesser usage of BPD as a method for reducing intraprocedural PVR. This study will attempt to characterize the patients receiving BPD with the SAPIEN 3 valve and relate this additional intervention to procedural and long term outcomes.

METHODS

STUDY DESIGN AND PATIENTS. The PARTNER (Placement of Aortic Transcatheter Valves) 2 SAPIEN 3 trial incorporated 2 parallel prospective, multicenter, active treatment cohorts of patients with symptomatic (New York Heart Association functional class II or greater), severe aortic stenosis. The S3HR cohort comprised patients considered to be inoperable or high-risk candidates for surgery, as defined by an STS-PROM (Society of Thoracic Surgeons Predicted Risk of Mortality) score of at least 8% and/or by the determination of a multidisciplinary heart team that included at least 1 cardiac surgeon and 1 interventional cardiologist. The S3i cohort comprised patients who were considered to be intermediate-risk candidates for surgery, as defined by STS-PROM score between 4% and 8% or by determination of a multidisciplinary heart team.

The 30-day and 1-year frequencies of all-cause mortality, cardiovascular mortality, rehospitalization, stroke, major vascular complications, major bleeding, myocardial infarction, acute kidney injury, and need for permanent pacemaker were documented according to Valve Academic Research Consortium-2 endpoint definitions (14). An analysis of neurologic events (major defined as a modified Rankin scale score of ≥2, minor as <2) was performed at the time of the event and adjudicated retrospectively by the clinical events committee.

TRANSTHORACIC ECHOCARDIOGRAPHIC DATA. Patients underwent transthoracic echocardiography (TTE) at baseline, discharge, 30 days, and 1 year as evaluated by PARTNER 2 S3 Core Lab Consortium at Québec Heart & Lung Institute (Quebec City, Canada), MedStar Health Research Institute (Hyattsville, Maryland), and Cardiovascular Research Foundation (New York, New York). The process of image reproducibility, analysis, and quality assurance has previously been described (15). Methodology for quantifying chamber size and function was measured using American Society of Echocardiography guidelines for chamber quantification (16). Central, paravalvular, and total aortic regurgitation was measured using an integrative grading scheme (17) as none, trace, mild, moderate, or severe. The effective orifice area (EOA)

ABBREVIATIONS AND ACRONYMS

BPD = balloon post-dilatation
CT = computed tomography
EOA = effective orifice area
LV = left ventricular
NoBPD = no balloon post-dilatation
PPM = prosthesis-patient mismatch
PVR = paravalvular regurgitation
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve
TTE = transthoracic echocardiography

Lifesciences, for which she received no direct compensation. Dr. Weissman has received research grants from Boston Scientific, Edwards, Medtronic, Abbott, and LivaNova; and has had a core lab contract with Edwards Lifesciences, for which he received no direct compensation. Dr. Thourani has been a consultant for Edwards Lifesciences. Dr. Herrmann has received grants to his institution from Edwards Lifesciences, Medtronic, St. Jude Medical, Boston Scientific, Bayer, Corvia, the University of Laval, and Abbott Vascular; and has been a consultant for Edwards Lifesciences. Dr. Webb has been a member of the PARTNER Trial Executive Committee for which he received no direct compensation; and has been a consultant for Edwards Lifesciences. Dr. Leon has been a member of the PARTNER Trial Executive Committee for which he received no direct compensation. Dr. Kodali has been a consultant for Edwards Lifesciences, Merrill Lifesciences, and Claret Medical; has served on the advisory boards of Abbott Vascular, Biotrace Medical, Dura Biotech, Thubrikar Aortic Valve, Duratech, and VS Medtech; and has equity in Thubrikar Aortic Valve, Dura Biotech, and Biotrace Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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was indexed to body surface area and derived from the first echocardiogram obtained after implant (either at discharge or 30 days). No significant PPM was defined as an indexed EOA >0.85 cm^2/m^2, moderate >0.65 cm^2/m^2 and ≤0.85 cm^2/m^2, and severe ≤0.65 cm^2/m^2 (18). SAPIEN 3 implantation depth was measured on follow-up TTE as the length of the proximal stent below the anatomic annulus.

COMPUTED TOMOGRAPHY IMAGING. For computed tomography (CT) analysis, the cohort consisted of intermediate risk patients treated with the SAPIEN 3 valve in a nested registry of the PARTNER 2 trial (19). All CT examinations were reviewed and interpreted in a central core laboratory (St Paul's Hospital, Cardiac CT Laboratory, Vancouver, University of British Columbia). CT image analysis was performed using previously described methods (20). Oversizing was calculated as: (THV nominal area/3-dimensional annular area − 1) × 100. The calculated eccentricity index = 1 − (minimal diameter/maximum diameter). The annular and subannular landing zones were assessed for the presence of calcifications. If present, the distribution of calcification and extension into the left ventricular (LV) outflow tract were also assessed in a semiquantitative fashion as follows: mild, 1 or more nonprotruding nodule of calcium extending <5 mm in any direction and covering <10% of the annular perimeter; moderate, 1 or more nodules, protruding, or extending >5 mm in any direction or covering >10% of the perimeter of the annulus; severe, multiple nodules of calcification of single focus extending >1 cm in length or covering >20% of the perimeter of the annulus. Valve calcification was also measured semiquantitatively as none mild, moderate, and severe.

TAVR PROCEDURE. TAVR was performed as previously described (21). All patients received the SAPIEN 3 balloon expandable valve (22). BPD was performed at the discretion of the operator, in most cases where PVR was deemed qualitatively >mild by hemodynamic measurements, fluoroscopic assessment, and/or transesophageal echocardiography immediately after THV implantation. BPD was performed with the same implantation balloon under rapid-pacing runs similar to initial valve deployment. BPD was performed using either the same volume or with an additional 0.5 to 2 ml in the inflation syringe as determined by the operator. The balloon was typically positioned slightly more toward the apex for BPD. A repeat BPD could be performed at the discretion of the operator.

STATISTICAL ANALYSIS. An as-treated analysis was performed that included all patients proceeding to the operating room for TAVR in the S3HR and S3i cohorts. The first post-implant values are those obtained from the first evaluable echocardiogram obtained at either discharge or 30 days. Patients were stratified on the basis of BPD. Categorical variables were compared by chi-square or Fisher exact test, as appropriate. Continuous variables are presented as mean ± SD and compared using Student's *t*-test. Survival curves for time-to-event variables were constructed using Kaplan-Meier estimates based on all available data and were compared using the log rank test. To study the impact of risk factors on mortality, Cox proportional hazards regression was performed.

Multivariable analysis was performed for 1-year mortality using the baseline variables that differed between BPD groups ($p \leq 0.10$) with post-dilatation as a forced variable. Predictors of BPD were evaluated using a stepwise model selection performed using 0.10 significance level for effect entry/stay in the model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 1,661 patients were included in this study, with a median (interquartile range) follow-up of 427 (385 to 666) days. Pre-dilatation before TAVR implantation was performed in 93.5% of procedures with no pre-dilatation in 6.5%. The overall incidence of BPD was 12.5% (208 of 1,661). No additional volume was added to the balloon in 14.2% of patients. Up to 1 ml of additional volume was added in 71.6% of patients, and up to 2 ml of volume added in 11.6% of patients. The following analyses were performed on the BPD group compared with the patients not receiving BPD (NoBPD).

BASELINE CLINICAL, CT, AND ECHOCARDIOGRAPHIC CHARACTERISTICS. Baseline clinical characteristics of BPD compared with NoBPD patients are shown in Table 1. The groups were similar in age, sex, body morphometrics, and other cardiac risk factors except for a higher STS score ($p < 0.001$), more frequent history of immunosuppressive therapy ($p = 0.02$), and worse pulmonary capacity ($p = 0.02$) in the BPD group.

Baseline CT data for the 2 groups is shown in Table 2. There was no significant difference in systolic annular area ($p = 0.06$) although the annular shape was more eccentric ($p = 0.02$). The BPD group had a significantly lower % oversizing by systolic area (5.41 ± 9.25% vs. 8.53 ± 10.40%; $p < 0.005$), and significantly greater moderate/severe subannular

calcification (p = 0.007) (Figure 1), but no significant difference in valvular calcification or annular calcification.

On baseline echocardiography (Online Table 1), there was no significant between-group difference in baseline LV size or function (p = 0.49 to 0.91), stroke volume (p = 0.28), or measures of baseline aortic stenosis severity (p = 012 to 0.76). Baseline valvular regurgitation was also similar: aortic p = 0.69, mitral p = 0.96, and tricuspid p = 0.92.

PROCEDURAL OUTCOMES. Procedural differences between BPD and NoBPD patients are shown in Table 3. BPD patients were more like to receive a 20-mm THV (p = 0.008) and less likely to receive a 29-mm valve (p = 0.008). Otherwise, there was no significant difference in the type of anesthesia (p = 0.51), total procedural time (p = 0.65), fluoroscopy time (p = 0.10), the use of pre-dilatation (p = 0.48), or duration of hospital stay (p = 0.43). BPD patients were more likely to have a second valve implanted (p = 0.002). Importantly, there were no conversions to surgical AVR in the BPD group and a 0.4% rate of conversion for the NoBPD group (p = 0.61).

ECHOCARDIOGRAPHIC OUTCOMES. Echocardiographic variables following TAVR are listed in Online Table 2. Implant depths of BPD versus NoBPD patients were 0.70 ± 0.21 cm versus 0.67 ± 0.20 cm; p = 0.08. There were no significant differences in LV size or function; however, the BPD group had significantly larger EOA and indexed EOA compared with NoBPD (p = 0.04 and 0.03, respectively). There was a trend toward lower incidence of any PPM (41.3% vs. 48%; p = 0.08), but no difference in the incidence of severe PPM (8.7% vs. 10.6%; p = 0.42). The severity of PVR following TAVR was greater in the BPD group (p < 0.01) (Figure 2).

CLINICAL OUTCOMES. In-hospital and 1-year clinical outcomes are listed in Table 4. There were no between-group differences for in-hospital outcomes, including major and minor strokes. At 1 year, there was no difference between BPD and NoBPD patients in all-cause mortality, cardiovascular mortality, stroke, repeat hospitalizations, or combined outcomes. At 1 year, there was a significant difference in minor strokes (p = 0.02) and aortic valve reinterventions (p = 0.02) (Online Table 3).

On multivariable analysis adjusting for STS score, current or previous immunosuppressive therapy, and current or previous chronic obstructive pulmonary disease, aortic valve re-interventions were not statistically different between groups (p = 0.06) (Table 5); however, minor strokes at 30 days

TABLE 1 Baseline Clinical Characteristics of Patients Receiving BPD and NoBPD

	BPD	NoBPD	p Value
Age, yrs	82.33 ± 7.26 (208)	82.17 ± 7.16 (1,453)	0.76
Male	59.1 (123/208)	60.6 (881/1,453)	0.68
BSA	1.90 ± 0.25 (208)	1.91 ± 0.25 (1,453)	0.58
BMI	28.34 ± 5.94 (208)	28.63 ± 6.38 (1,453)	0.54
STS score	7.22 ± 3.33 (208)	6.40 ± 2.82 (1,453)	0.0008
Logistic EuroSCORE	6.92 ± 5.77 (208)	6.47 ± 5.76 (1,451)	0.29
Diabetes	33.7 (70/208)	34.3 (498/1,453)	086
Renal insufficiency	11.5 (24/208)	8.8 (128/1,453)	0.20
Smoking	48.6 (101/208)	49.4 (718/1,453)	082
Hyperlipidemia (requiring medication)	79.8 (166/208)	80.2 (1,166/1,453)	0.88
Coronary artery disease	68.8 (143/208)	72.4 (1,052/1,453)	0.27
Hypertension	94.7 (197/208)	92.7 (1,347/1,453)	0.29
CVA or TIA	18.3 (38/208)	17.5 (255/1,453)	0.80
Peripheral vascular disease	26.9 (56/208)	31.2 (453/1,453)	0.21
CHF			
NYHA functional class I and II	16.3 (34/208)	22.0 (320/1,452)	0.06
NYHA functional class III and IV	83.7 (174/208)	78.0 (1,132/1,452)	0.06
Current or previous immunosuppressive therapy	10.6 (22/208)	6.1 (89/1,453)	0.02
Pulmonary disease			
FEV1, l	1.66 ± 0.58 (121)	1.79 ± 0.61 (935)	0.02
DLCO, %	56.56 ± 27.48 (97)	62.57 ± 25.03 (778)	0.03
Atrial fibrillation or flutter	34.1 (71/208)	41.2 (598/1,453)	0.053

Values are mean ± SD (N) or % (n/N).

BMI = body mass index; BPD = balloon post-dilatation; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cardiovascular accident; NoBPD = not receiving balloon post-dilatation; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

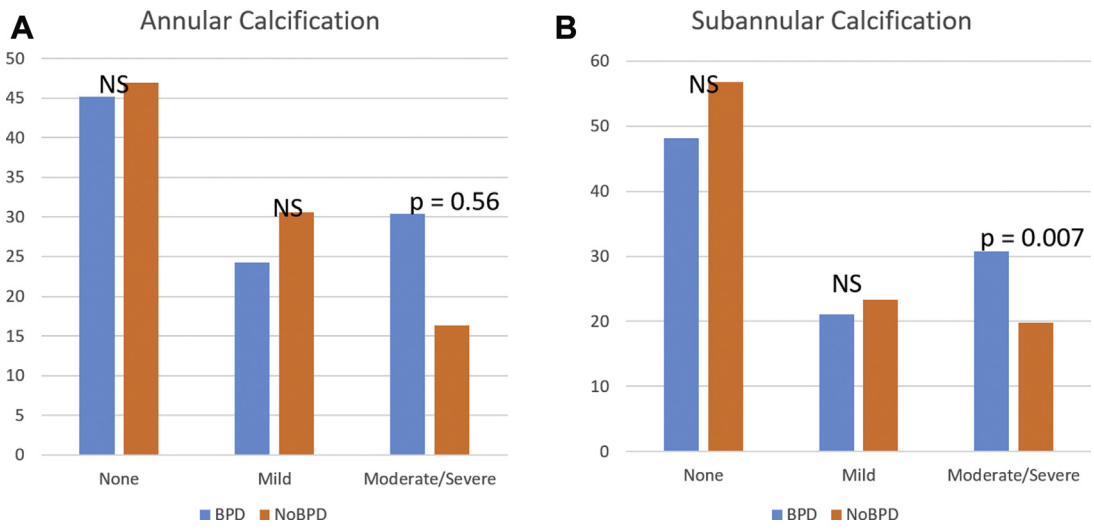
TABLE 2 Baseline CT Data of Patients Receiving BPD and NoBPD

	BPD	NoBPD	p Value
Eccentricity index	0.21 ± 0.06 (101)	0.20 ± 0.06 (851)	0.02
Annulus area, systole	448.96 ± 90.54 (101)	465.89 ± 84.01 (850)	0.06
Annulus calcification			
None	45.2 (52/115)	46.9 (435/927)	0.73
Mild	24.3 (28/115)	30.6 (284/927)	0.16
Moderate	17.4 (20/115)	16.3 (151/927)	0.76
Severe	13.0 (15/115)	6.1 (57/927)	0.006
LVOT calcification			
None	51.3 (58/113)	66.4 (613/923)	0.002
Mild	24.8 (28/113)	19.6 (181/923)	0.20
Moderate	19.5 (22/113)	9.1 (84/923)	0.0006
Severe	4.4 (5/113)	4.9 (45/923)	0.002
Valve calcification			
None	0.0 (0/115)	0.3 (3/927)	1.00
Mild	39.1 (45/115)	34.3 (318/927)	0.31
Moderate	56.5 (65/115)	61.4 (569/927)	0.31
Severe	4.3 (5/115)	4.0 (37/927)	0.80

Values are mean ± SD (N) or % (n/N).

LVOT = left ventricular outflow tract; other abbreviations as in Table 1.

FIGURE 1 Calcium Burden as Assessed by Baseline CT



Calcium burden for patients with balloon post-dilatation (BPD) and those without (NoBPD) are shown for annular calcification **(A)** and subannular calcium **(B)**. CT = computed tomography; NS = not significant.

remained significantly greater in the BPD group (p = 0.01). If the multislice CT measurements of moderate-severe annulus or subannular calcification, % oversizing by systolic area, and eccentricity index were added to the models, there was no longer a significant difference in the rate of minor strokes at 1 year (p = 0.21).

TABLE 3 Procedural and Post-Procedural Characteristics of Patients Receiving BPD and NoBPD

	BPD	NoBPD	p Value
Type of anesthesia used			
General	83.2 (173/208)	84.7 (1,229/1,451)	0.57
Sedation	16.8 (35/208)	15.3 (222/1,451)	0.57
Valve size			<0.0001
20, mm	6.3 (13/208)	2.8 (40/1,448)	0.008
23, mm	38.0 (79/208)	32.2 (466/1,448)	0.10
26, mm	41.8 (87/208)	42.2 (611/1,448)	0.92
29, mm	13.9 (29/208)	22.9 (331/1,448)	0.008
Pre-dilatation performed	94.7 (196/208)	93.4 (1,342/1,453)	0.48
% Oversizing by systolic area	5.41 ± 9.25 (101)	8.53 ± 10.40 (847)	0004
Procedure time, h	3.18 ± 0.82 (204)	3.15 ± 0.94 (1,445)	0.65
Fluoroscopy time, min	20.58 ± 10.23 (206)	18.94 ± 26.66 (1,437)	0.10
Conversion to AVR	0.0 (0/208)	0.4 (6/1,453)	0.61
Valve dislodged	0.0 (0/208)	0.1 (2/1,453)	1.00
Annulus rupture	0.0 (0/208)	0.1 (2/1,453)	1.00
Other	0.0 (0/208)	0.1 (2/1,453)	1.00
Number of THV deployed			
0	0.0 (0/208)	0.2 (3/1,450)	1.00
1	97.6 (203/208)	99.5 (1,443/1,450)	0.01
2	2.4 (5/208)	0.3 (4/1,450)	0.002
Duration of hospitalization, days	3 (2-5)	3 (2-5)	0.43

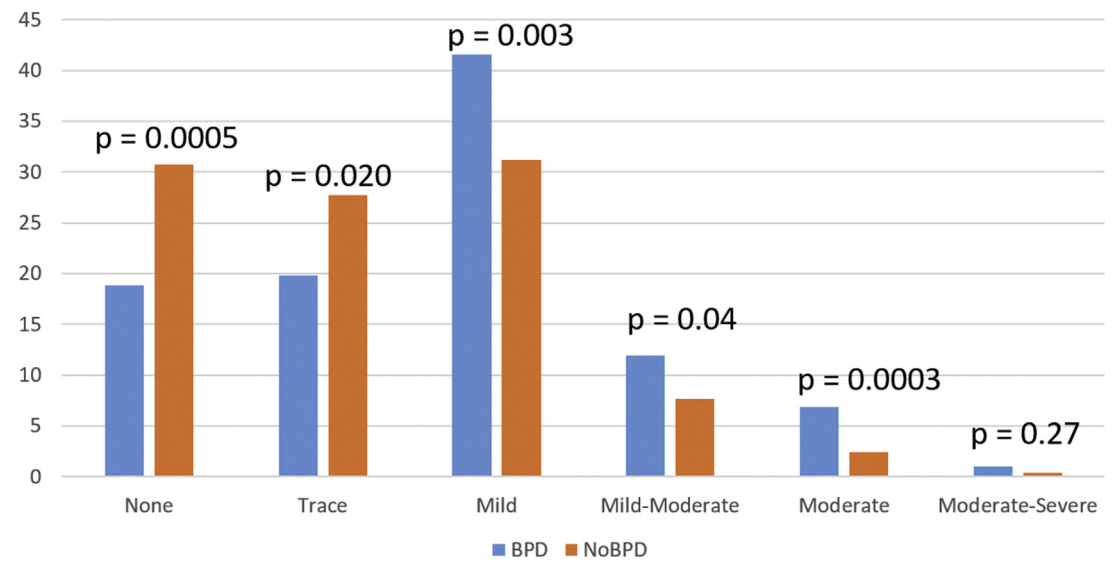
Values are % (n/N), mean ± SD (N), or median (interquartile range).
TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve; other abbreviations as in Table 1.

PREDICTORS OF BPD. A multivariate analysis using a stepwise model was performed to determine the predictors of BPD. Variables in the analysis included STS score, use of immunosuppressive therapy, history of chronic obstructive pulmonary disease, moderate or severe annular calcium, moderate or severe subannular calcium, combined annular + subannular calcium, % oversizing, and ellipticity (per 0.01 increase). Table 6 shows the results of the analysis: use of immunosuppressive therapy, moderate or severe subannular calcium, % oversizing, and ellipticity were all significant predictors of BPD.

DISCUSSION

The main findings of this study are that compared to NoBPD patients: 1) BPD patients receiving a SAPIEN 3 valve have at baseline greater subannular calcification, a more elliptical annulus, and lower % oversizing; 2) BPD patients did not have a significant difference in procedural or in-hospital outcomes including stroke; 3) BPD patients have significantly larger post-TAVR EOA and more PVR; and 4) at 1 year, BPD patients have more minor strokes and more aortic valve reinterventions, however, on multivariable modeling that included differences in baseline calcium burden, minor strokes was no longer significantly different.

FIGURE 2 PVR Post-TAVR



The percentage of patients with each grade of paravalvular regurgitation (PVR) severity is shown for patients with BPD and NoBPD. Note: there were no patients with severe PVR. PVL = paravalvular leak; TAVR = transcatheter aortic valve replacement; other abbreviations as in Figure 1.

The third-generation SAPIEN 3 has a new construct that allows for less oversizing (11) and more precise positioning (12) with a lower incidence of PVR (11,23). In addition, poor outcomes occur with ≥moderate PVR and not with lesser degrees of regurgitation (24). The extent and location of calcium in the transcatheter heart valve landing zone, % oversizing, and ellipticity of the annulus have all been implicated as etiologies of PVR (4,25-27). Because BPD is primarily performed to reduce PVR (4-6,28), the current finding of increased BPD use in patients with more subannular calcification, less % oversizing and more elliptical annuli, parameters also associated with PVR, is not surprising. Although less oversizing has been advocated for the SAPIEN 3 valve (11), the severity of PVR is clearly still related to lower % oversizing or "undersizing" (29). Because annular area and perimeter are more discordant with greater ellipticity (smaller areas for any given perimeter) (20,30), oversizing using annular area likely represents less oversizing in an elliptical annulus compared with a more circular annulus, and this fact should be taken into account when determining the acceptable % oversizing for an individual patient. Finally, whereas the current study shows that BPD is a safe procedure when post-TAVR PVR requires treatment, avoiding very low % oversizing (i.e., ≤4.2% as suggested by Yang et al. (11)) should also be considered.

TABLE 4 Outcomes for Patients Receiving BPD and NoBPD

	BPD (n = 208)	NoBPD (n = 1,453)	p Value
In-hospital			
Death from any cause	1.0 (2)	0.7 (10)	0.65
Death from cardiovascular cause	0.5 (1)	0.6 (9)	1.0
Bleeding (VARC II)	22.6 (47)	25.1 (365)	0.43
Acute kidney injury (VARC II)	7.2 (15)	6.3 (91)	0.60
Pacemaker	12.0 (25)	11.1 (161)	0.74
Aortic valve reintervention, any	0.5 (1)	0.0 (0)	0.13
Stroke/TIA	3.4 (7)	2.1 (30)	0.21
TIA	0.5 (1)	0.2 (3)	0.41
Stroke (VARC I)	2.9 (6)	1.9 (27)	0.29
Major (disabling) stroke	1.4 (3)	0.8 (11)	0.40
Minor stroke	1.4 (3)	1.1 (16)	0.72
Death or stroke	2.4 (5)	1.4 (20)	0.23
1-yr adjudicated events (combined in and out of hospital)			
Death from any cause	10.8 (22)	9.9 (142)	0.76
Death from cardiovascular cause	5.5 (11)	5.9 (84)	0.76
Repeat hospitalization	17.3 (35)	13.9 (194)	0.41
Aortic valve reintervention, any	2.0 (4)	0.5 (7)	0.02
Stroke/TIA	7.9 (16)	6.0 (84)	0.28
TIA	1.5 (3)	2.1 (28)	0.63
Stroke	6.4 (13)	4.2 (59)	0.15
Major (disabling) stroke	1.9 (4)	2.4 (33)	0.75
Minor stroke	4.5 (9)	1.8 (26)	0.02
Death or stroke	16.1 (33)	12.7 (183)	0.21
Death or repeat hospitalization or stroke	27.2 (56)	22.5 (325)	0.14

Values are % (n). Event rates are Kaplan-Meier estimates.
VARC = Valve Academic Research Consortium; other abbreviations as in Table 1.

TABLE 5 Multivariate Models of the Risk for 1-Year Clinical Outcomes With BPD

	Number of Patients in Adjusted Model	Unadjusted		Adjusted	
		HR (95% CI)	p Value	HR (95% CI)	p Value
Aortic-valve reintervention*	1,657	4.00 (1.17–13.66)	0.03	3.33 (0.96–11.54)	0.057
Aortic-valve reintervention†	945			8.25 (1.09–62.42)	0.04
Minor stroke‡	1,657	2.42 (1.14–5.17)	0.02	2.59 (1.21–5.57)	0.01
Minor stroke§	945			2.05 (0.67–6.24)	0.21

Event rates were estimated by Kaplan-Meier and compared by the log-rank test. Cox proportional hazards regression model was used to estimate and compare hazard ratios. *Multivariable adjustments made for the following variables: STS score, current or previous immunosuppressive therapy, current or previous COPD. †Multivariable adjustments made for the following variables: STS score, current or previous immunosuppressive therapy, current or previous COPD, moderate-severe annulus or subannular calcification, % oversizing by systolic area, eccentricity index. ‡Multivariable adjustments made for the following variables: STS score, current or previous immunosuppressive therapy, current or previous COPD. §Multivariable adjustments made for the following variables: STS score, current or previous immunosuppressive therapy, current or previous COPD, moderate-severe annulus or subannular calcification, % oversizing by systolic area, eccentricity index.

CI = confidence interval; BPD = balloon post-dilatation; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Although we assume that BPD decreased the immediate post-implant severity of regurgitation, this maneuver may not eliminate regurgitation from malapposition of the transcatheter stent with native tissue in regions of noncompressible calcium, particularly in the setting of significant undersizing of the valve or elliptical annuli. In fact the BPD cohort were more likely to receive a second valve during the initial procedure and after adjusting for baseline characteristics and annular anatomy, BPD remains a risk for aortic reintervention at 1 year. This study shows despite these complications, there is no difference in 30 day or 1 year mortality compared to NoBPD patients.

The role of procedural factors is also of interest. Although many investigators have suggested by pre-dilatation may not be necessary for implantation of the balloon-expandable valve (31), other reports suggest an individual approach should still be used because some patients with severe valve calcification may require pre-dilatation for positioning of the valve (32,33). In the SAPIEN 3 registry, a minority of patients did not have pre-dilatation. There was no difference in BPD between patients who did not receive pre-dilatation (5.3% of BPD and 6.6% of NoBPD; p = 0.48); however, the numerical difference suggesting the use of pre-dilatation may reduce the need for BPD requires further study. Although implant depth was measured from TTE imaging, there was a trend toward greater implant depths in the BPD patients.

TABLE 6 Multivariate Analysis of the Predictors of BPD

	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
STS score	1.06 (0.96–1.18)	0.24		
Current or previous immunosuppressive therapy	2.28 (1.13–4.57)	0.02	2.41 (1.18–4.89)	0.02
Current or previous COPD	0.81 (0.50–1.29)	0.37		
Moderate or severe annulus calcification	1.52 (0.97–2.39)	0.07		
Moderate or severe subannular calcification	1.75 (1.11–2.78)	0.02	1.66 (1.04–2.65)	0.03
Moderate or severe annulus or subannular calcification	1.45 (0.93–2.28)	0.10		
% Oversizing by systolic area	0.97 (0.95–0.99)	0.006	0.97 (0.95–0.99)	0.004
Eccentricity index, per 0.01	1.04 (1.01–1.08)	0.02	1.04 (1.01–1.08)	0.01

Abbreviations as in Tables 1 and 5.

Other risks of BPD include possible THV migration, or injury/trauma to the conduction system, rupture of the membranous septum or aorta, and cerebrovascular embolism (5–8). In addition, 1 study of the self-expanding valve showed a high incidence of BPD (24% of cases) with significantly greater acute kidney injury (10). The current study found no association between BPD and acute kidney injury, pacemaker rates, annular rupture, embolization of the valve, or acute stroke (either major or minor).

The association with calcium burden and neurological events was suggested in an early study of BPD (6). The current study shows that the incidence of minor stroke in the BPD cohort increased only at 1 year and is thus unlikely to be related to any procedural factors but rather more likely due to the greater calcium burden in this patient cohort. Multivariable modeling in this study supports this theory because BPD was no longer a risk for minor strokes at 1 year after adjusting for CT calcium burden. Still, an earlier study from the PARTNER 1 trial suggested that BPD was associated with early post-TAVR stroke (8). The current study, using the SAPIEN 3 valve, shows no significant risk for early neurological adverse outcomes with the BPD maneuver.

STUDY LIMITATIONS. Documentation of the number and hemodynamic result of BPD as well as the PVR severity and EOA before BPD was not captured in the procedure database nor was intraprocedural imaging (transesophageal echocardiographic or fluoroscopic) collected. Thus, the effect of the BPD procedure on PVR as well as valve area could not be quantified. Post-procedural CT scans may be useful for determining final valve position and shape; however, these were not performed during the trial. Given variability among sites in rates and reasons for BPD, selection bias may be an issue that cannot be accounted for in this analysis. Finally, although we used data from a large, randomized study with core laboratory echocardiographic data and adjudicated outcome data,

this subanalysis was retrospective and subject to the limitations of an observational study.

CONCLUSIONS

In the SAPIEN 3 registry, BPD is associated with significantly smaller % oversizing and greater calcium burden, without annular ruptures, valve embolizations, central aortic regurgitation, or increased pacemaker rates. Importantly, despite greater post-TAVR PVR, BPD was not associated with an increase in 1-year adverse events of death, rehospitalization, or stroke/transient ischemic attack.

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PERSPECTIVES

WHAT IS KNOWN? Balloon post-TAVR dilatation (BPD) of the stented valve is an intraprocedural maneuver to reduce PVR but has been previously associated with possible adverse outcomes including valve embolization, stroke, annular or septal rupture, heart block, and acute kidney injury.

WHAT IS NEW? The current study of the PARTNER 2, SAPIEN 3 registry shows that although BPD patients continue to have more PVR, this maneuver is not associated with other procedural complications or death, rehospitalization, or stroke/transient ischemic attack.

WHAT IS NEXT? Although associated with larger valve areas, the direct effect of BPD on valve area and PVR requires further study.

REFERENCES

1. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

2. Gotzmann M, Korten M, Bojara W, et al. Long-term outcome of patients with moderate and severe prosthetic aortic valve regurgitation after transcatheter aortic valve implantation. Am J Cardiol 2012;110:1500–6.

3. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585–95.

4. Unbehaun A, Pasic M, Dreysse S, et al. Transapical aortic valve implantation incidence and predictors of paravalvular leakage and transvalvular regurgitation in a series of 358 patients. J Am Coll Cardiol 2012;59:211–21.

5. Daneault B, Koss E, Hahn RT, et al. Efficacy and safety of postdilatation to reduce paravalvular regurgitation during balloon-expandable transcatheter aortic valve replacement. Circ Cardiovasc Interv 2013;6:85–91.

6. Nombela-Franco L, Rodes-Cabau J, DeLarochelliere R, et al. Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol Intv 2012;5:499–512.

7. Nombela-Franco L, Webb JG, de Jaegere PP, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation 2012;126:3041–53.

8. Hahn RT, Pibarot P, Webb J, et al. Outcomes with post-dilation following transcatheter aortic valve replacement: the PARTNER I trial (placement of aortic transcatheter valve). J Am Coll Cardiol Intv 2014;7:781–9.

9. Barbanti M, Petronio AS, Capodanno D, et al. Impact of balloon post-dilation on clinical outcomes after transcatheter aortic valve replacement with the self-expanding CoreValve prosthesis. J Am Coll Cardiol Intv 2014;7:1014–21.

10. Harrison JK, Hughes GC, Reardon MJ, et al. Balloon post-dilation following implantation of a self-expanding transcatheter aortic valve bioprosthesis. J Am Coll Cardiol Intv 2017;10:168–75.

11. Yang TH, Webb JG, Blanke P, et al. Incidence and severity of paravalvular aortic regurgitation with multidetector computed tomography nominal area oversizing or undersizing after transcatheter heart valve replacement with the Sapien 3: a comparison with the Sapien XT. J Am Coll Cardiol Intv 2015;8:462–71.

12. Schymik G, Schrofel H, Heimeshoff M, Luik A, Thoenes M, Mandinov L. How to adapt the implantation technique for the new SAPIEN 3 transcatheter heart valve design. J Interv Cardiol 2015;28:82–9.

13. Nijhoff F, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. Circ Cardiovasc Interv 2015;8:e002408.

14. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

15. Douglas PS, Waugh RA, Bloomfield G, et al. Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial. J Am Soc Echocardiogr 2013;26:348–58.e3.

16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. J Am Soc Echocardiogr 2005;18:1440–63.

17. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. J Am Coll Cardiol Img 2015;8:340–60.

18. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation 2009;119:1034–48.

19. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218–25.

20. Blanke P, Willson AB, Webb JG, et al. Oversizing in transcatheter aortic valve replacement, a commonly used term but a poorly understood one: dependency on definition and geometrical measurements. J Cardiovasc Comput Tomogr 2014;8:67–76.

21. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

22. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic

stenosis who are not candidates for surgery. J Am Coll Cardiol Intv 2015;8:1797–806.

23. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J 2016;37:2252–62.

24. Pibarot P, Hahn RT, Weissman NJ, et al. Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the Sapien 3 valve. JAMA Cardiol 2017;2:1208–16.

25. Koos R, Mahnken AH, Dohmen G, et al. Association of aortic valve calcification severity with the degree of aortic regurgitation after transcatheter aortic valve implantation. Int J Cardiol 2011;150:142–5.

26. Schultz C, Rossi A, van Mieghem N, et al. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. EuroIntervention 2011;7:564–72.

27. Marwan M, Achenbach S, Ensminger SM, et al. CT predictors of post-procedural aortic regurgitation in patients referred for transcatheter aortic valve implantation: an analysis of 105 patients. Int J Cardiovasc Imaging 2013;29:1191–8.

28. Martinez CA, Singh V, O'Neill BP, et al. Management of paravalvular regurgitation after Edwards SAPIEN transcatheter aortic valve replacement: management of paravalvular regurgitation after TAVR. Catheter Cardiovasc Interv 2013;82:300–11.

29. Blanke P, Pibarot P, Hahn R, et al. Computed tomography-based oversizing degrees and incidence of paravalvular regurgitation of a new generation transcatheter heart valve. J Am Coll Cardiol Intv 2017;10:810–20.

30. Papachristidis A, Papitsas M, Roper D, et al. Three-dimensional measurement of aortic annulus dimensions using area or circumference for transcatheter aortic valve replacement valve sizing: does it make a difference? J Am Soc Echocardiogr 2017;30:871–8.

31. Strauch J, Wendt D, Diegeler A, et al. Balloon-expandable transapical transcatheter aortic valve implantation with or without predilation of the aortic valve: results of a multicentre registry. Eur J Cardiothorac Surg 2018;53:771–7.

32. Kim WK, Praz F, Blumenstein J, et al. Transfemoral aortic valve implantation of Edwards SAPIEN 3 without predilatation. Catheter Cardiovasc Interv 2017;89:E38–43.

33. Chan PH, Mario CD, Moat N. Transcatheter aortic valve implantation without balloon predilatation: not always feasible. Catheter Cardiovasc Interv 2013;82:328–32.

KEY WORDS aortic stenosis, echocardiography, post-dilatation, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this paper.