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Structural

Outcomes With Post-Dilation Following Transcatheter Aortic Valve Replacement

The PARTNER I Trial (Placement of Aortic Transcatheter Valve)

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Objectives This study sought to characterize the patients receiving post-implantation balloon dilation (PD) following transcatheter aortic valve replacement (TAVR) and evaluate procedural outcomes in the PARTNER (Placement of Aortic Transcatheter Valve) I trial.

Background Following TAVR, PD has been used to treat paravalvular regurgitation.

Methods The PARTNER I trial cohort A (n = 304) and cohort B (n = 194) patients randomized to TAVR and the nonrandomized continued access TAVR (n = 1,637) patients were included in the analysis. PD was performed at the discretion of the operator. Clinical events and echocardiographic variables were collected prospectively out to 1 year.

Results The overall incidence of PD was 12.4%. PD patients had significantly less prosthesis-patient mismatch ($p < 0.001$) and larger effective orifice areas ($p < 0.001$) throughout the follow-up period. There were significantly more subacute strokes (occurring <7 days: 4.9% vs. 2.6%; $p = 0.04$) in PD patients but no difference in late stroke, either at 7 to 30 days (0.0% vs. 0.8%; $p = 0.16$) or >30 days (1.9 vs. 1.7%; $p = 0.75$). Although there was no significant increase in early mortality with PD, at 1 year, there was a trend for higher all-cause mortality ($p = 0.054$) and a significant difference in death or stroke ($p = 0.04$). When the subgroup of patients with none/trace paravalvular regurgitation were evaluated, there was no significant association of PD with mortality ($p = 0.61$) and death or stroke ($p = 0.96$). Multivariable analysis failed to show a relationship between PD and mortality.

Conclusions PD is associated with reduced rates of moderate or severe prosthesis-patient mismatch with no evidence for short-term structural deterioration of the balloon-expandable transcatheter valve. Although PD is associated with a greater incidence of early stroke, there is no significant association between PD and stroke beyond 7 days. Multivariable analysis shows no significant association between PD and mortality. (J Am Coll Cardiol Intv 2014;7:781–9) © 2014 by the American College of Cardiology Foundation

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Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to surgical aortic valve replacement for patients with severe aortic stenosis who are at "high risk" or deemed inoperable (1,2) despite a higher incidence of post-TAVR paravalvular regurgitation (PVR) (3). Numerous studies have shown an association between post-procedural PVR and increased late mortality (4–9), generating intense interest in determining predictors or treatment of this complication. Reballooning or post-implantation balloon dilation (PD) of balloon expandable valves after implantation has been proposed as an effective method to reduce post-TAVR PVR (10–13). Potential risks of PD include transcatheter heart valve migration or injury, trauma to the conduction system, rupture of the membranous septum or aorta, and cerebrovascular embolism (11,12,14). Further understanding of the risk of PD would have important consequences to procedural technique and the performance of a potentially life-saving treatment. We thus sought to determine the baseline predictors of PD and the effect of PD on valve hemodynamics and outcomes in the PARTNER I trial.

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CI = confidence interval
EOA = effective orifice area
HR = hazard ratio
LV = left ventricular
NoPD = no post-dilation
PD = post-dilation
PPM = prosthesis-patient mismatch
PVR = paravalvular regurgitation
TAVR = transcatheter aortic valve replacement

Methods

Study design and patient population. Randomized patients from cohort B (inoperable) and cohort A (high-risk) patients of the PARTNER trial with severe, symptomatic aortic stenosis receiving a TAVR with the Edwards Sapien valve (Edwards Lifesciences, Irvine, California), as well as the nonrandomized continued access patients, were studied. Inclusion criteria for this trial included a site-measured echocardiographic aortic valve area of <0.8 cm^2 *plus* either a peak aortic jet velocity ≥ 4 m/s or a mean gradient ≥ 40 mm Hg at rest or during dobutamine infusion. The design, inclusion, and exclusion criteria and primary results of the PARTNER trial have been reported (1,2). Echocardiograms were obtained at baseline, 7 days, 30 days, 6 months, 1 year, and 2 years post-procedure. For this post-hoc analysis, randomized control trial patients from cohort A (n = 304) and cohort B (n = 194), as well as nonrandomized continued access TAVR (n = 1,637) patients, were evaluated.

Procedural method. TAVR was performed as previously described (1). PD was performed at the discretion of the operator, in most cases where PVR was deemed qualitatively more than mild by hemodynamic measurements, fluoroscopic assessment, and/or transesophageal echocardiography immediately after transcatheter heart valve implantation. PD was performed with the same implantation balloon under rapid-pacing runs similar to initial valve deployment. PD was performed using either the same volume or with an additional 0.5 to 2 cc in the inflation syringe as determined by the operator. The balloon was typically positioned slightly more toward the apex for PD. A repeat PD could be performed at the discretion of the operator.

Doppler-echocardiographic measurements. All baseline and follow-up echocardiograms were interpreted by an independent core laboratory housed at the Duke Clinical Research Institute. Study workflow, reproducibility testing, image acquisition and analysis, and quality assurance data have been published (15). Ventricular size and function and valvular function were measured according to previously published guidelines (16). The stroke volume was measured in the left ventricular (LV) outflow tract with the use of the diameter and velocity measured just underneath the prosthesis stent (17). The effective orifice area (EOA) was calculated as the LV outflow tract stroke volume divided by the aortic jet velocity time integral and was indexed for body surface area (18). The Doppler velocity index was calculated

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as the ratio of the LV outflow tract and transaortic velocity-time integrals. An integrative, semiquantitative approach was used to assess the severity of native valve regurgitation (19) and PVR (20). The severity of prosthesis-patient mismatch (PPM) was graded using indexed EOA as previously described (20) with the absence of PPM defined as an indexed EOA >0.85 cm^2/m^2, moderate PPM defined as an indexed EOA between 0.65 and 0.85 cm^2/m^2, and severe PPM as an indexed EOA <0.65 cm^2/m^2. The cover index was calculated as the percentage of difference between the nominal transcatheter heart valve diameter and the site-reported systolic annular diameter, divided by the nominal transcatheter heart valve diameter (21).

Clinical endpoints. The primary and secondary endpoints for the PARTNER trial have been previously described (1,2). Of note, major stroke was defined by a score of ≥2 on the modified Rankin scale performed at the time of the event (which ranges from 0 to 6, with higher scores indicating greater disability) in a retrospective analysis of neurologic events adjudicated by the clinical events committee. Timing of strokes was also determined and defined as: acute <24 h, subacute >24 h but <7 days, and late >7 days.

Statistical analysis. The study population was the actual valve implant population who received and retained the transcatheter heart valve. Because of the difficulty in imaging patients immediately following intervention, the first post-implantation values are those obtained from the first evaluable echocardiogram obtained at either discharge or 7 days.

Categorical variables were compared using Fisher exact test. Both regurgitation and New York Heart Association functional class are ordinal variables and comparisons involving these variables use the Mann-Whitney *U* test. Continuous variables were presented as means ± SD and compared using Student *t* test or analysis of variance. A 2-way analysis of variance with repeated measures in one factor (mixed-model analysis of variance) was used to compare between group differences over time. 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 PD groups ($p \leq 0.10$) with PD as a forced variable.

Data are based on an extract date of February 14, 2013. All statistical analyses were performed in SAS (version 9.2, SAS Institute, Cary, North Carolina).

Results

Baseline clinical, procedural, and echocardiographic characteristics. The overall incidence of PD was 12% (261 of 2,123) in the pooled cohort, 15% in cohort A (46 of 259), 7.6% in cohort B (12 of 145), and 12.4% in non-randomized continued access patients (207 of 1,469). PD patients were more likely to be male ($p < 0.0001$); have larger body surface area ($p < 0.0001$); and to have a history

Table 1. Baseline Clinical Characteristics

	PD	NoPD	p Value
Age, yrs	84.30 ± 6.98 (264)	84.43 ± 7.27 (1,869)	0.64
Male	72.7 (192/264)	49.8 (931/1,869)	<0.0001
BSA, m^2	1.88 ± 0.29 (264)	1.79 ± 0.25 (1,863)	<0.0001
BMI, kg/m^2	26.17 ± 6.34 (264)	26.74 ± 6.41 (1,863)	0.23
STS score	11.49 ± 3.55 (263)	11.53 ± 4.26 (1,867)	0.7
Logistic EuroSCORE	27.28 ± 16.34 (245)	26.83 ± 16.25 (1,821)	0.6
Diabetes	34.8 (92/264)	38.3 (716/1,869)	0.28
Hyperlipidemia	83.7 (221/264)	83.7 (1,565/1,869)	0.99
Smoking	61.0 (161/264)	45.8 (856/1,869)	<0.0001
Hypertension	91.3 (241/264)	92.1 (1,721/1,868)	0.64
Cerebrovascular disease	24.6 (61/248)	27.1 (499/1,841)	0.4
Peripheral vascular disease	39.9 (105/263)	43.7 (807/1,848)	0.25
Porcelain aorta	2.3 (6/264)	3.9 (72/1,866)	0.2
CHF	97.7 (257/263)	98.3 (1,836/1,868)	0.46
NYHA functional class I	0.0 (0/264)	0.1 (2/1869)	
NYHA functional class II	4.9 (13/264)	4.6 (86/1,869)	
NYHA functional class III	54.9 (145/264)	46.3 (865/1,869)	
NYHA functional class IV	40.2 (106/264)	49.0 (916/1,869)	
Angina	20.1 (53/264)	21.5 (401/1,869)	0.61
CAD	82.6 (218/264)	77.1 (1,441/1,868)	0.05
Previous CABG	53.4 (141/264)	41.4 (773/1,868)	0.002
Pulmonary hypertension	45.0 (113/251)	38.0 (674/1,775)	0.03
Major arrhythmia	57.2 (151/264)	49.5 (924/1,868)	0.02

Values are mean ± SD (n) or % (n/n).

BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NoPD = not receiving post-dilation; NYHA = New York Heart Association functional class; PD = post-dilation; STS = Society of Thoracic Surgeons.

Table 2. Baseline Echocardiographic Characteristics

	PD	NoPD	p Value
LVED, cm	4.67 ± 0.75 (232)	4.48 ± 0.75 (1,685)	0.0007
LV mass, g	270.15 ± 77.29 (232)	247.32 ± 76.57 (1,683)	<0.0001
LV EF, biplane Simpson method, %	50.42 ± 13.06 (258)	52.96 ± 12.86 (1,830)	0.003
Stroke volume, ml	68.56 ± 19.32 (121)	65.57 ± 21.19 (882)	0.09
Cardiac output, l/min	4.65 ± 1.46 (121)	4.45 ± 1.48 (880)	0.12
Aortic annulus, cm	1.98 ± 0.28 (197)	1.90 ± 0.27 (1,445)	<0.0001
STJ, cm	2.50 ± 0.37 (168)	2.34 ± 0.38 (1,252)	<0.0001
Mean gradient, mm Hg	44.6 ± 13.0 (256)	44.1 ± 14.4 (1,813)	0.44
EOA, cm^2	0.66 ± 0.19 (249)	0.65 ± 0.19 (1,790)	0.42
EOAi, cm^2/m^2	0.35 ± 0.10 (249)	0.37 ± 0.11 (1,782)	0.14

Values are mean ± SD (n).

EF = ejection fraction; EOA = effective orifice area; EOAi = effective orifice area indexed for body surface area; LV = left ventricle; LVED = left ventricular end-diastolic dimension; STJ = sino-tubular junction; other abbreviations as in Table 1.

of smoking ($p < 0.0001$), coronary artery disease ($p = 0.05$), coronary bypass surgery ($p = 0.002$) (Table 1), pulmonary hypertension ($p = 0.03$), and major arrhythmias ($p = 0.02$). There were no between-group differences in Society of Thoracic Surgeons score or Logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), or other cardiovascular risk factors.

On echocardiography (Table 2), there was no significant difference in baseline mean gradient ($p = 0.44$) or indexed EOA ($p = 0.14$); however, PD patients had larger LV dimensions and volumes ($p < 0.01$), greater LV mass ($p < 0.0001$), worse LV function ($p < 0.01$), larger annular diameters ($p < 0.0001$), and larger aortic root diameters ($p < 0.0001$).

Procedural differences between PD and no post-dilation (NoPD) patients were also seen (Table 3). PD patients were more like to receive a 26-mm valve ($p < 0.0001$) and had significantly longer total procedural time ($p < 0.001$), time in the catheterization laboratory ($p < 0.01$), and fluoroscopy time ($p < 0.001$). The cover index for PD patients was significantly smaller ($10.93 \pm 5.47\%$ vs. $12.42 \pm 5.47\%$, $p < 0.001$). The PD rates were not significantly different in the transfemoral versus transapical access patients (13.4% vs. 10.9%, $p = 0.10$).

Echocardiographic outcomes. Echocardiographic variables following TAVR are listed in Table 4. Ventricular volumes and mass continued to be larger in the PD patients at 2 years follow-up. Ejection fraction was lower in the PD patients at baseline (Table 2), as well as immediately following TAVR ($52.5 \pm 11.6\%$ vs. $54.4 \pm 11.7\%$, $p = 0.004$); however, ejection fraction was not significantly different at 1 year ($56.7 \pm 10.0\%$ vs. $55.9 \pm 9.8\%$, $p = 0.28$) and 2 years ($56.0 \pm 9.28\%$ vs $55.8 \pm 9.7\%$, $p = 0.90$) following the procedure. The PD group had larger EOA and indexed EOA than did the NoPD group ($p < 0.001$) (Fig. 1). PVR at discharge or 7 days was greater in the PD group ($p < 0.0001$): none/trace, 38.7% versus 54.9%; mild, 49.2% versus 36.8%; moderate/severe, 12.1% versus 8.2% (Fig. 2). Patients who underwent PD had significantly ($p < 0.001$) less PPM at 30 days (overall: 31%; moderate: 22%; severe: 9%) than did patients with NoPD (overall: 46%; moderate: 32%; severe: 14%). A multivariable analysis was performed to determine whether PD was independently associated with less PPM using the covariates of sex, body surface area, annulus diameter, prosthesis size, cover index, baseline EOA, and PD. In this analysis, PD remained a predictor of less PPM ($p = 0.002$). A smaller EOA, larger body surface area, and use of the 23-mm valve were predictive of severe PPM ($p < 0.001$). Over time, there was no significant change in mean gradients ($p = 0.21$ for PD and $p = 0.74$ for NoPD) or EOA ($p = 0.35$ for PD and $p = 0.58$ for NoPD).

Table 3. Procedural and Post-Procedural Characteristics

	PD	NoPD	p Value
Valve size			<0.0001
23 mm	38.4 (99/258)	54.2 (1,004/1,852)	
26 mm	61.6 (159/258)	45.7 (847/1,852)	
Cover index, %	10.93 ± 5.47 (258)	12.42 ± 5.47 (1,850)	<0.0001
Time in cath lab, min	235.36 ± 101.59 (264)	228.80 ± 70.43 (1,867)	0.004
Total procedure time, min	132.32 ± 71.97 (262)	119.82 ± 62.46 (1,866)	0.0003
Fluoroscopy time, min	22.55 ± 13.82 (253)	20.39 ± 14.88 (1,781)	0.0009
Days in hospital	44.75 ± 53.78 (159)	45.18 ± 58.02 (1,195)	0.49
Days in hospital post-TAVR	6.47 ± 2.88 (159)	6.43 ± 11.03 (1,195)	0.27
Procedure success	78.4 (207/264)	81.2 (1,520/1,871)	0.27
NIH stroke score at discharge	0.24 ± 0.87 (262)	0.26 ± 0.83 (1,860)	0.65
Baseline 6-min walk, m	147.10 ± 103.66 (189)	167.52 ± 107.16 (1,145)	0.01
30-day 6-min walk, m	181.26 ± 97.32 (170)	193.86 ± 112.73 (1,145)	0.28

Values are % (n/n) or mean ± SD (n).
cath lab = catheterization laboratory; NIH = National Institutes of Health; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

Table 4. Post-TAVR Echocardiographic Variables

	PD	NoPD	p Value
Discharge			
LVED, cm	4.68 ± 0.77 (233)	4.48 ± 0.78 (1,667)	0.0001
LV mass, g	268.13 ± 79.03 (232)	240.65 ± 74.96 (1,665)	<0.0001
LV EF, %	52.50 ± 11.64 (263)	54.41 ± 11.67 (1,865)	0.004
Stroke volume, ml	74.13 ± 25.02 (87)	67.29 ± 22.04 (628)	0.01
Cardiac output, l/min	5.23 ± 1.82 (394)	4.89 ± 1.48 (410)	0.004
Mean gradient, mm Hg	9.56 ± 4.04 (258)	10.79 ± 4.77 (1,806)	<0.0001
EOA, cm^2	1.82 ± 0.53 (247)	1.61 ± 0.47 (1,749)	<0.0001
EOAi, cm^2/m^2	0.96 ± 0.30 (230)	0.91 ± 0.28 (1,553)	0.003
30 days			
LVED, cm	4.74 ± 0.76 (225)	4.50 ± 0.77 (1,540)	<0.0001
LV mass, g	255.75 ± 76.78 (223)	230.43 ± 73.91 (1,539)	<0.0001
LV EF, %*	52.41 ± 10.63 (239)	54.72 ± 11.15 (1,670)	0.0007
Stroke volume, ml†	77.78 ± 23.31 (100)	68.89 ± 21.73 (646)	0.0003
Cardiac output, l/min	5.21 ± 1.63 (100)	4.74 ± 1.62 (644)	0.004
Mean gradient, mm Hg	8.44 ± 3.36 (234)	9.31 ± 3.84 (1,645)	0.0006
EOA, cm^2	1.85 ± 0.51 (232)	1.69 ± 0.49 (1,606)	<0.0001
EOAi, cm^2/m^2	1.00 ± 0.29 (219)	0.96 ± 0.28 (1,543)	0.01
1 year			
LVED, cm	4.65 ± 0.85 (86)	4.43 ± 0.79 (650)	0.01
LV mass, g	256.87 ± 92.45 (86)	219.23 ± 74.83 (650)	0.0002
LV EF, %	56.73 ± 9.99 (92)	55.86 ± 9.84 (728)	0.28
Stroke volume, ml	82.82 ± 23.68 (44)	66.71 ± 21.58 (271)	<0.0001
Cardiac output, l/min	5.40 ± 1.66 (44)	4.39 ± 1.46 (270)	<0.0001
Mean gradient, mm Hg	9.79 ± 4.99 (92)	10.11 ± 4.05 (718)	0.13
EOA, cm^2	1.78 ± 0.48 (90)	1.60 ± 0.44 (692)	0.0002
EOAi, cm^2/m^2	0.96 ± 0.27 (87)	0.90 ± 0.27 (676)	0.02

Values are mean ± SD (n). *Calculated by biplane Simpson method. †Calculated by Doppler method.
Abbreviations as in Tables 1 to 3.

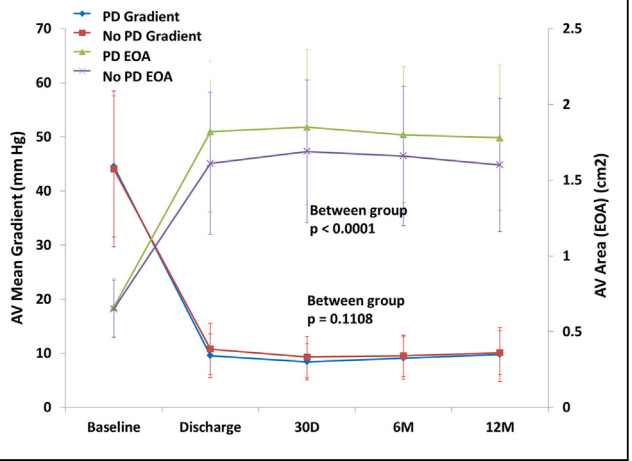

Figure 1. Echocardiographic Hemodynamics

The mean gradient and aortic valve area in the post-dilation (PD) and no post-dilation (NoPD) groups are shown from baseline to 1 year. Over time, there is no significant within group differences in mean gradient or aortic valve area from discharge to 1 year. AV = aortic valve; EOA = effective orifice area.

Clinical outcomes. In-hospital, 30-day, and 1-year clinical outcomes are listed in Table 5. There was no difference between PD and NoPD patients in all-cause mortality, cardiovascular mortality, or mortality + repeat hospitalization in the immediate post-procedure (30-day) time frame. There was a trend toward increased in-hospital stroke in the PD patients (4.9% vs. 2.9%, p = 0.08); however, no significant difference was seen at 30 days (4.9% vs. 3.4%, p = 0.19) or at 12 months (6.8% vs. 5.0%, p = 0.20) (Fig. 3A). There is a trend (25.4% vs. 20.3%, p = 0.054) toward increased all-cause mortality at 1 year in the PD group (Table 5, Fig. 3B), with a significant increase in death or stroke by 1 year (28.2% vs. 23.0%, p = 0.04) (Fig. 3C). When only patients with none/trace PVR were evaluated, however, there was no significant difference in death, or death or stroke (Figs. 4A and 4B).

Multivariable analysis was performed for 1-year mortality using the baseline variables of sex, body surface area, smoking, New York Heart Association functional class, coronary artery disease, coronary artery bypass graft (CABG), pulmonary hypertension, major arrhythmia (atrial fibrillation), LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, LV mass, annulus diameter, PD, and post-TAVR PVR (Table 6). Major arrhythmia (hazard ratio [HR]: 1.58 [95% confidence interval (CI): 1.26 to 1.98], p = 0.0001), baseline annular diameter (HR: 2.03 [95% CI: 1.37 to 3.01], p = 0.0004), and PVR (moderate-severe regurgitation HR: 2.36 [95% CI: 1.72 to 3.24], p < 0.0001) were significant predictors of 1-year mortality. PD was not a significant predictor of mortality.

A similar multivariable analysis was performed for 1-year mortality or stroke (Table 7). Baseline annular diameter (HR: 1.85 [95% CI: 1.32 to 2.59], p = 0.0003) and PVR (moderate-severe regurgitation HR: 2.35 [95% CI: 1.75 to 3.17], p < 0.0001) were significant predictors of mortality or stroke. Absence of previous CABG was associated with a lower risk of mortality or stroke in both models. PD was not a significant predictor of mortality or stroke in either model.

Kaplan-Meier estimates of 1-year stroke rate (major and minor strokes) analyzed by timing of the stroke and stratified by PD showed no significant difference between groups for acute stroke (HR: 1.71 [95% CI: 0.75 to 3.91], p = 0.19), but there was an increased risk of subacute stroke in the PD group (HR: 1.90 [95% CI: 1.03 to 3.49], p = 0.04). There was no increased risk of late stroke, either between 7 and 30 days (p = 0.16) or >30 days (p = 0.75). A multivariable analysis was performed for acute/subacute stroke (<7 days) using covariates of baseline annular diameter, prior CABG, approach (transfemoral vs. transapical), major arrhythmia, baseline-indexed EOA, and PD (Table 8). Only PD was a significant predictor of acute/subacute stroke (HR: 1.90 [95% CI: 1.03 to 3.50], p = 0.041).

Discussion

The main findings of this study are as follows: 1) PD patients had significantly more baseline comorbidities with larger ventricular and annular dimensions, and worse ventricular function; 2) PD patients did not have a significantly higher risk of stroke at 30 days or 1 year, although there was a higher incidence of acute/subacute (<7 days) neurologic events; and 3) when adjusted for residual PVR, PD did not affect short-term mortality.

Given the association between post-procedural PVR and increased late mortality (7), determining ways of treating this procedural complication may have a significant impact on outcomes. A recent meta-analysis (9) identified 3 primary predictors of PVR: valve position; Agatston calcium score; and valve undersizing. In the current study, PD patients had larger aortic annular and aortic root dimensions and were more likely to receive a 26-mm transcatheter valve than were NoPD patients. Because only 2 valve sizes were available (23 mm and 26 mm), patients in the higher annular size range may have been significantly undersized. This is supported by the lower cover index seen in the PD patients. In this study, sizing was initially performed using a single sagittal dimension on echocardiography, with 3-dimensional measurements adopted late in the study. Three-dimensional sizing algorithms for the annulus are now accepted as the more accurate measure of annular size. Whether by multislice computed tomography (22–25) or 3-dimensional transesophageal echocardiography (26–30), the increased accuracy of either technique (31) is likely to reduce sizing inaccuracies and may possibly reduce the rate of PD.

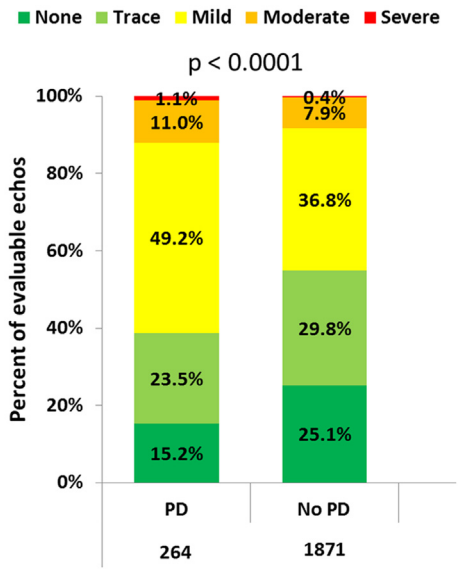

Figure 2. PVR at Discharge or 7 Days (Valve Implant Patients)

The incidence of paravalvular regurgitation (PVR) is shown in patients receiving post-dilation (PD) and those not receiving PD (NoPD) following transcatheter valve replacement (TAVR).

Table 5. Post-TAVR Outcomes

	PD	NoPD	p Value
In-hospital			
Death from any cause	3.0 (8/264)	2.5 (47/1,871)	0.62
Death from cardiovascular cause	1.5 (4/264)	1.3 (24/1,871)	0.77
Stroke	4.9 (13/264)	2.9 (54/1,871)	0.08
Death or stroke	5.7 (15/264)	4.4 (83/1,871)	0.37
30-day adjudicated events (combined in and out of hospital)			
Death from any cause	3.4 (9)	3.3 (61)	0.89
Death from cardiovascular cause	2.3 (6)	1.9 (36)	0.7
Death from any cause or repeat hospitalization	9.5 (25)	9.8 (183)	0.88
Stroke	4.9 (13)	3.4 (63)	0.19
Death or stroke	5.7 (15)	5.5 (102)	0.85
6-month adjudicated events (combined in and out of hospital)			
Death from any cause	9.3 (23)	7.7 (139)	0.39
Death from cardiovascular cause	17.1 (42)	14.8 (263)	0.34
Death from any cause or repeat hospitalization	28.6 (74)	24.2 (451)	0.13
Stroke	6.3 (16)	4.3 (79)	0.16
Death or stroke	20.9 (54)	16.0 (297)	0.05
1-year adjudicated events (combined in and out of hospital)			
Death from any cause	25.4 (63)	20.3 (366)	0.054
Death from cardiovascular cause	16.9 (39)	12.3 (210)	0.051
Death from any cause or repeat hospitalization	37.0 (93)	32.9 (596)	0.14
Stroke	6.8 (17)	5.0 (89)	0.2
Death or stroke	28.2 (71)	23.0 (415)	0.04

Values are % (n/n) or % (n).
Abbreviations as in Tables 1 and 3.

PD may result in improved hemodynamics following TAVR. Compared with NoPD, PD patients in this study had larger EOA and less PPM, which was confirmed on multivariable analysis. In addition, there was no deterioration in the acute hemodynamic changes over the study period. Although PD after TAVR has been proposed as an effective method to reduce PVR (10–13,32–34), there was greater residual PVR in the PD versus the NoPD cohort. Whether this represents an improvement in what would have been worse PVR post-TAVR, or a poor response to PD, cannot be determined in this study. Valve calcium burden has been shown to be a predictor of the need for, as well as a poor response to, PD (12). Although a calcium score is not available in this study, patients who received PD had baseline clinical characteristics such as smoking, coronary artery disease, and previous CABG that may increase the likelihood of valvular calcification and thus PVR. Determining which patients may benefit from PD may help reduce the performance of ineffective reballooning as well as increase the safety of the procedure.

The relationship between PD and acute neurologic events deserves special attention. Early transcranial Doppler studies have suggested that cerebral embolic events may be more frequent during prosthesis positioning and implantation (35,36). Nombela-Franco et al. (14) showed that PD was a predictor of early (≤24 h) cerebrovascular events (14). In their multicenter study of the predictors of cerebrovascular events, timing of the events was meticulously documented (either prospectively or retrospectively). Predictors of acute (≤24 h) events were PD and valve embolization/dislodgement, whereas predictors of subacute (occurring 1 to 30 days after TAVR) events were PD and new onset atrial fibrillation. In the current study, the in-hospital trend of greater neurologic events in the PD group was driven by a significantly higher incidence of <7-day stroke. Although our study failed to show a significant association at the acute stroke, this may be explained in part by the criteria used to differentiate stroke (signs/symptoms lasting >24 h) from transient ischemic attack (signs/symptoms lasting ≤24 h), as well as post-general anesthesia management protocols that may prevent accurate early neurologic assessment. The significant association with <7-day events and PD found in the present study was confirmed by multivariable analysis, but importantly, there is no increased risk for stroke with PD after 7 days and up to 1 year.

Although there was no increased risk of procedural (30-day) or short-term mortality, our study, unlike previous studies (12), showed a trend toward increased 1-year mortality with PD. However, further analysis of patients

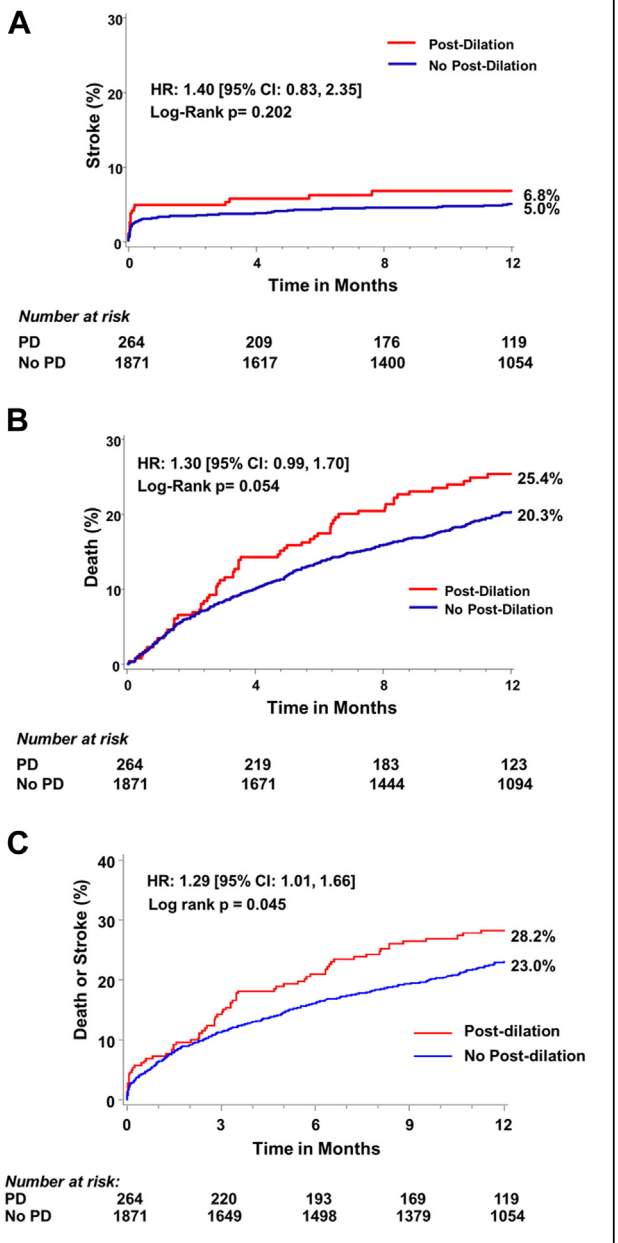

Figure 3. Outcomes in the As-Treated Cohort

Kaplan-Meier curves compare outcomes of patients with post-dilation (PD) and those not receiving post-dilation (NoPD) over 12 months with respect to stroke **(A),** death **(B)**, and death or stroke **(C)**. CI = confidence interval; HR = hazard ratio.

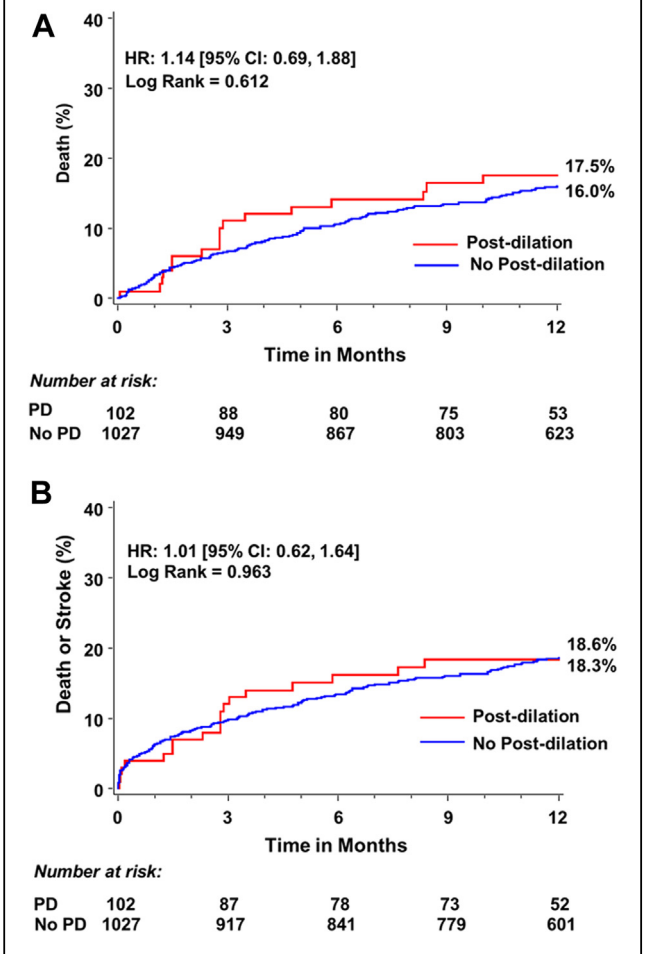

Figure 4. Outcomes in Patients with None/Trace PVR

Kaplan-Meier curves compare outcomes of patients with post-dilation (PD) and those not receiving post-dilation (NoPD) over 12 months with respect to death **(A),** and death or stroke **(B)** in patients. Abbreviations as in Figures 2 and 3.

with none/trace PVR showed no difference in mortality. In addition, multivariable analysis revealed a significant relationship between PVR and death but no association between PD and death, strongly supporting the theory that residual PVR, and not PD, is the determinant of mortality.

Given the association of PVR with increased mortality, the small increase in <7-day stroke risk with PD may nonetheless be worth the benefit of reducing PVR and PPM. The indications for PD, however, remain uncertain because previous reports from the PARTNER trial with echocardiographic core lab–assessed aortic regurgitation suggest that even mild PVR is associated with increased mortality (7), whereas recent large registries suggest increased mortality is only associated with more-than-moderate PVR (37,38). These differences are more likely related to the differences in regurgitation grading schemes rather than to differences in the mortality rates between grades. It is, however, abundantly clear that moderate or severe PVR is associated with increased mortality, and the clinical practice of performing PD when it is likely to reduce PVR to less than mild or mild is supported by this study. A better understanding of which patients will respond to PD and which patients are at high risk for complications such

Table 6. Multivariable Cox Regression Model for 1-Year Mortality

	HR (95% CI)	p Value
Major arrhythmia	1.58 (1.26–1.98)	<0.0001
Baseline annulus diameter	2.03 (1.37–3.01)	0.0004
Previous CABG	0.81 (0.65–1.01)	0.0622
Paravalvular aortic regurgitation		
None/trace	1.16 (0.95–1.43)	0.1411
Mild	1.29 (1.02–1.65)	0.0365
Moderate/severe	2.36 (1.72–3.24)	<0.0001
Post-dilation	1.13 (0.82–1.55)	0.461

Model: Potential covariates included male sex, BSA, smoking, NYHA functional class, CAD, CABG, pulmonary hypertension, major arrhythmia, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, LV mass, annulus diameter. Forced in covariates included post-dilation and paravalvular aortic regurgitation (3 grades).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

as stroke will also help define indications for PD and potentially improve outcomes.

Study limitations. Documentation of the number and hemodynamic result of PD as well as the PVR severity and EOA prior to PD was not captured in the procedure database. Thus the effect of PD on PVR as well as valve area could not be quantitated. Given variability among sites in rates and reasons for PD, selection bias may be an issue that cannot be accounted for in this analysis. In addition, in the absence of more precise neurologic assessment and imaging, it is impossible to know whether neurologic events are related to PD or initial valve implantation methods. The PARTNER I trial also did not capture pre-procedural computed tomography data, and therefore an analysis of valve calcium burden or location cannot be made. 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

Although PD is associated with a greater incidence of <7-day stroke, there is no significant association between PD and stroke beyond 7 days. Multivariable analysis shows no significant association between PD and mortality. PD is associated with reduced rates of moderate or severe PPM, with no evidence for short-term structural deterioration of the balloon-expandable transcatheter valve. Improved sizing algorithms to reduce the rate of PVR, as well as defining optimal candidates for successful PD, may improve overall outcomes.

Table 7. Multivariable Cox Regression Model for 1-Year Mortality or Stroke

	HR (95% CI)	p Value
Baseline annulus diameter	1.88 (1.30–2.72)	0.0008
Previous CABG	0.80 (0.65–0.99)	0.0417
Paravalvular aortic regurgitation		
None/trace	1.16 (0.96–1.41)	0.1145
Mild	1.32 (1.06–1.65)	0.0145
Moderate/severe	2.35 (1.75–3.17)	<0.0001
Post-dilation	1.12 (0.83–1.51)	0.4702

Included model covariates as in Table 6.

Table 8. Multivariable Cox Regression Model for Acute Stroke

	HR (95% CI)	p Value
Baseline annulus diameter	0.11 (0.01–1.42)	0.0901
Post-dilation	1.90 (1.03–3.50)	0.0409

Acute stroke is defined as stroke occurring within 7 days of implantation. Model: Potential covariates included baseline annulus diameter, previous CABG, approach (transfemoral vs. transapical), major arrhythmia, baseline AV area index. The forced in covariate was post-dilation.

AV = aortic valve; other abbreviations as in Tables 1 and 6.

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Key Words: aortic stenosis ■ paravalvular regurgitation ■ post-dilation ■ prosthesis-patient mismatch ■ reballooning ■ transcatheter aortic valve replacement.