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Predictors of Paravalvular Regurgitation Following Implantation of the Fully Repositionable and Retrievable Lotus Transcatheter Aortic Valve (From the REPRISE II Trial Extended Cohort)

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Running Head: Blackman Predictors of PVL with Lotus

Abstract

Paravalvular leak (PVL) following transcatheter aortic valve replacement (TAVR) is associated with worse long-term outcomes. The Lotus Valve incorporates an innovative adaptive seal designed to minimize PVL. This analysis evaluated the incidence and predictors of PVL following implantation of the Lotus transcatheter aortic valve. The REPRISE II study with Extended Cohort enrolled 250 high-surgical risk patients with severe symptomatic aortic stenosis. Aortic regurgitation was assessed by echocardiography pre-procedure, at discharge and 30 days by an independent core lab. Baseline and procedural predictors of mild or greater PVL at 30 days (or at discharge if 30-day data were not available) were determined using a multivariate regression model (N=229). Among 229 patients, 197 (86%) had no/trace PVL, 30 had mild, and 2 had moderate PVL; no patient had severe PVL. Significant predictors of mild/moderate PVL included device:annulus area ratio (odds ratio [OR]: 0.87 (95% CI: 0.83-0.92); *P*<0.001), LVOT calcium volume (OR:2.85;(1.44-5.63); *P*=0.003), and annulus area (OR:0.89(0.82-0.96); *P*=0.002). When the device:annulus area ratio was <1, the rate of mild/moderate PVL was 53.1% (17/32). The rates of mild/moderate PVL with 0-5%, 5-10%, and >10% annular oversizing by area were 17.5% (11/63), 2.9% (2/70), and 3.2% (2/63), respectively. Significant independent predictors of PVL included device:annulus area ratio and LVOT calcium volume. When the prosthetic valve was oversized by ≥5%, the rate of mild or greater PVL was only 3%. In conclusion, the overall rates of PVL with the Lotus Valve are low and predominantly related to device/annulus areas and calcium; these findings have implications for optimal device sizing.

Key Words: aortic valve stenosis, transcatheter aortic valve implantation, clinical trial, paravalvular regurgitation

Paravalvular leak (PVL) is a significant predictor of mortality following transcatheter aortic valve replacement (TAVR).[1] Reported predictors of PVL post-implantation with first-generation transcatheter aortic valves include annulus/device size mismatch; annulus eccentricity[2]; excessive calcification in the annulus, leaflets or left ventricular outflow tract (LVOT); device implantation depth; baseline aortic or mitral regurgitation; baseline atrial fibrillation; and valve choice (CoreValve versus Sapien).[3-6] The Lotus Aortic Valve (Boston Scientific, Marlborough, MA, USA) incorporates an innovative Adaptive Seal™ designed to minimize PVL. Although the overall incidence of PVL with the Lotus valve is low, mild PVL has been reported in up to 10-15% of patients at 30 days.[7,8] The objective of this analysis was to assess patient, anatomic, and procedural characteristics that predicted PVL following TAVR with the Lotus Valve in the REPRISE II Study with Extended Cohort.

Methods

Key features of the Lotus Valve (Boston Scientific, Marlborough, MA, USA) are shown in **Figure 1**. The valve incorporates bovine pericardium leaflets into a woven nitinol frame and has a central radiopaque marker to enable precise positioning. An Adaptive Seal™ at the base of the valve is designed to prevent PVL by sealing paravalvular interstices between the concentric valve frame and eccentric anatomy. The Lotus Valve is deployed via controlled mechanical expansion, with no rapid pacing required, and functions early in the deployment cycle to facilitate hemodynamic stability. The valve is repositionable and fully retrievable even after full deployment, allowing assessment of paravalvular regurgitation and the need for repositioning if necessary. Two valve sizes, 23mm and 27mm, were available for use in this study. Balloon pre-dilatation was mandated in the study protocol.

The REPRISE II study design and methods have been previously described [7,8]. In brief, the REPRISE II Study Extended Cohort was a prospective, single-arm, multicenter trial designed to evaluate the safety and performance of the Lotus Valve System for the treatment of patients with symptomatic aortic stenosis. Patients aged ≥70 years with New York Heart Association (NYHA) functional class ≥II, and a baseline aortic annulus size ≥20mm but ≤27mm were considered eligible for enrollment if they had a Society of Thoracic Surgery (STS) Score ≥8% or were deemed to be at high surgical risk by the local Heart Team due to comorbidities or frailty. All Heart Team assessments were confirmed by a central case review committee prior to enrollment. One-hundred and twenty patients were enrolled into the original REPRISE II trial, and an additional 130 patients were enrolled in the Extended Cohort for a total of 250 patients. Patients were enrolled between October 2012 and April 2014 at 20 sites in Europe and Australia. Follow-up occurred post-procedure, at hospital discharge or 7 days (whichever came first), and 30 days. Follow-up will continue at 3 and 6 months, and then annually through 5 years.

The primary performance endpoint for the first 120 patients enrolled in REPRISE II was the mean aortic valve pressure gradient at 30 days, as adjudicated by an independent core laboratory. The primary safety endpoint for the REPRISE II trial Extended Cohort was the rate of 30-day all-cause mortality.[9,10] Anatomic measures at baseline, including aortic valve dimensions and calcification, were assessed by computed tomography (CT) in end-systole using a pre-determined standardized system (3mensio Medical Imaging BV, Bilthoven, The Netherlands). Paravalvular leak was assessed by echocardiography at baseline, discharge, and 30 days according to VARC-2 criteria.[9,10] Independent core labs analyzed both CT (Beth Israel Deaconess Medical Center, Boston, USA) and echocardiographic (MedStar, Washington DC, USA) results. An independent clinical events committee adjudicated all adverse clinical events.

An Institutional Review Board or Ethics Committee approved the protocol at each site prior to patient enrollment. All patients provided written informed consent. The study complied with the principles set forth in the Declaration of Helsinki, and is registered at www.clinicaltrials.gov under the identifier NCT01627691.

Patient baseline and procedural characteristics were compared for patients with and without mild or greater PVL at 30 days (or at hospital discharge if 30-day data were not available) using a 2-sided chi-square or Fisher exact test for categorical variables, as appropriate, and Student t tests for continuous variables. Values were expressed as mean ± standard deviation for continuous variables and percent (n/N) for categorical variables. Clinical, anatomic, electrocardiographic, and procedural characteristics were evaluated as predictors of mild or greater PVL by multivariate analysis; these factors were assessed by logistic regression with Wald's chi-square test and expressed as odds ratios with 95% confidence intervals. Significance was defined as $P<0.05$. Statistical analysis was performed using SAS® software version 9.2 or above (SAS Institute, Cary, North Carolina, USA).

Results

Two-hundred and fifty patients were enrolled in the REPRISE II trial Extended Cohort (**Figure 2**). A total of 243 (97.2%) patients underwent clinical follow-up at hospital discharge or 7 days (7 patients died prior to discharge), and 228 (91.2%) patients had TTE assessment at discharge, of which 201 were considered evaluable for PVL by the core laboratory. For clinical follow-up at the primary endpoint of 30 days, 1 patient withdrew consent at day 11, and 3 patients missed the 30-day follow-up visit with no later follow-up performed, for a total clinical follow-up or death rate of 98.4% (246/250). Thirty-day TTE assessment was performed in 215 patients, of which 177 were considered evaluable for PVL by the core laboratory.

Discharge/7-day PVL data were incorporated into the analysis for those patients who did not have available 30-day PVL data; this resulted in a total of 229 patients with evaluable echocardiograms (Figure 2), of whom 183 (79.9%) had no PVL, 14 (6.1%) had trace PVL, 30 (13.1%) had mild PVL, and 2 (0.9%) had moderate PVL, and thus comprised the analysis population for this manuscript (**Figure 3**).

Baseline patient and anatomic characteristics of patients with and without ≥mild PVL at discharge/30 days are shown in **Table 1**. Patients with ≥mild PVL were significantly more likely to be older, female, have medically treated hyperlipidemia, and have a higher pre-procedure mean aortic gradient. Calcium volume in the LVOT and annulus/leaflets was also significantly greater in patients with ≥mild PVL, particularly with regard to the LVOT (70.6±9.4mm^2 vs 22.4±43.3mm^2 no PVL; *P*=0.008).

Procedural factors for patients with and without ≥mild PVL are shown in **Table 2**. Compared to patients with no PVL, patients with ≥mild PVL were significantly more likely to have received the 23mm valve, to have a lower ratio of the maximum balloon diameter to the valve area, a lower device:annulus area ratio, and a lower device:LVOT area ratio (Table 2). Patients with ≥mild PVL were also more likely to have a less deep implantation; this difference was statistically significant when measured from the left coronary sinus, but not when measured from the non-coronary sinus. The degree of valve oversizing in relation to both the annulus and LVOT was significantly correlated with a decreased rate of PVL (Table 2). Valve repositioning or retrieval during implantation and measured waist (defined as minimum valve diameter divided by maximum valve diameter) were not significantly different between patients with and without PVL.

Mortality was not significantly different between groups in this analysis. Kaplan-Meier rates of all-cause mortality at 1 year were 87.0% in patients with ≥mild PVL versus 91.7% in patients with none/trace PVL (log-rank *P*=0.41), although it should be noted that this comparison is underpowered.

Significant independent predictors of ≥mild PVL by multivariate analysis were the annulus area, the ratio of the device area to the annulus area, and LVOT calcium volume (**Table 3**). Leaflet and annulus calcium volume trended towards being an independent predictor of ≥mild PVL, but the difference did not reach statistical significance (*P*=0.06). Medically treated hyperlipidemia was also a significant independent predictor of decreased PVL (*P*=0.01).

The correlation between various levels of valve oversizing in relation to the annulus and the rate of ≥mild PVL is shown in **Figure 4**. When the valve was undersized (ie, nominal valve area less than the annular area), the rate of ≥mild PVL was 53.1%. In contrast, slight oversizing of the valve (0% to 5%) resulted in a ≥mild PVL rate of 17.5%. Above 5%, there appeared to be a plateau effect, with the rate of ≥mild PVL remaining at ~3% for both 5% to 10% and ≥10% annular overstretch.

The correlation between various levels of valve oversizing and the rate of permanent pacemaker implantation is shown in **Figure 5.** The pacemaker rate trended higher when oversizing of the valve in relation to the annulus was ≥10% (38.5% (25/65) vs 25.5% (47/184), *P*=0.2), although this did not reach statistical significance. The pacing rate was more closely correlated with oversizing in relation to the LVOT, with a significantly higher rate when the valve was ≥10% bigger than the LVOT by area (37.4% (43/115) vs 21.6% (29/134), *P*=0.05).

Discussion

In the REPRISE II Trial Extended Cohort, overall rates of PVL with the Lotus valve were very low, with 86% of patients having no or trace PVL, as assessed by an independent core lab. Significant independent predictors of mild/moderate PVL included the ratio of device area to annulus area, LVOT calcium volume, and annulus area. When the nominal valve area was smaller than the annulus, i.e. device:annulus area ratio <1, the rate of mild or moderate paravalvular regurgitation was 53.1%. The rates of mild/moderate paravalvular regurgitation with 0-5%, 5-10%, and >10% annular oversizing by area were 17.5%, 2.9%, and 3.2%, respectively, suggesting that optimal valve oversizing to minimize PVL is >5% by area. While sizing was universally performed using CT in this study, trans-esophageal echocardiography (TEE) including 3D TEE could also be employed.

General predictors of PVL following TAVR have been previously identified as annulus/device size mismatch[3-5]; TAVR access route[5,11]; annulus eccentricity[2]; calcification in the annulus, leaflets or LVOT[3,12]; device implantation depth[3,4]; valve post-dilatation[13]; moderate baseline aortic or mitral regurgitation[4,5,13]; baseline atrial fibrillation[5]; and the use of CoreValve versus Sapien/Sapien XT[3-5,13,14]. In studies of valve-specific PVL predictors, predictors of PVL following CoreValve implantation include LVOT diameter,[15] annulus/device size mismatch,[15,16] and depth of implantation.[15,16] For the Edwards Sapien valves (Sapien, Sapien XT, Sapien 3), significant predictors of PVL include size mismatch[6,17,18] and annular/leaflet/LVOT calcification.[6,17-19]

The mechanism for the contribution of annulus/valve size mismatch to the development of PVL is intuitive; moreover, overall annulus or LVOT size as independent predictors are likely to be related to size mismatch given that all valve manufacturers have only a discrete number of valve sizes available. Depth of implantation with CoreValve is likely related to PVL by also

affecting the annulus/valve diameter ratio, given the conical nature of the device.[16] In the current analysis, annulus/size mismatch and annulus size also emerged as independent predictors of PVL for the Lotus Valve, a finding that was likely exacerbated by the fact that only 2 valve sizes (23mm and 27mm) were available for the study. Data from the RESPOND registry, in which a 25mm valve was also available, demonstrated even lower rates of PVL with Lotus, with mild or greater PVL in only 8.0% of patients, potentially reflecting the ability to select a more optimal valve size across a greater range of patient anatomies.[20] Specifically, in the REPRISE II cohort, a number of patients with annular diameters above 23mm were treated with an undersized 23mm Lotus, increasing the risk of PVL. Balloon pre-dilatation was less frequently performed in the RESPOND registry than in this study (53.9% vs 100% in REPRISE II Extension), though how this might have impacted on the relative rates of PVL is less clear.

In contrast, annulus eccentricity and calcification contribute to PVL by preventing full apposition of the device against the aortic wall, allowing the development of paravalvular jets. The Adaptive Seal of the Lotus Valve was developed to address this issue and the Lotus valve has the lowest reported PVL rates of currently available valves, although even with the Adaptive Seal, calcification continues to remain a significant predictor of PVL. We found that calcium in the LVOT was a stronger predictor of PVL than was annular calcium. This raises the possibility that sealing in the LVOT may be more important than sealing at the level of the annulus and leaflets. Patients with ≥mild PVL did have a less deep implant (5.2±2.7mm) than those without (6.7±2.8mm; P=0.007), although depth of implant did not emerge as an independent predictor of PVL. It is unclear why hyperlipidemia or its treatment would be a preventative factor for PVL with Lotus. This finding will require further evaluation in larger studies including the ongoing REPRISE III pivotal trial.

Based on this study and others reported in the literature, optimal valve sizing for the prevention of PVL varies according to valve type. With all transcatheter valves, undersizing results in significantly increased PVL, leaving in question the appropriate degree of oversizing for each. With the Lotus valve, the current results imply that 5% to 10% oversizing results in ~3% ≥mild PVL, with no further benefit in terms of PVL with oversizing greater than 10% by area, suggesting that minimal oversizing of the Lotus valve is needed to prevent PVL. In contrast, for Sapien 3, 5% to 10% oversizing has been suggested as the optimal sizing and is associated with 13.3% ≥mild PVL[6]; similarly, for Sapien XT, >10% oversizing was associated with ≥20% mild PVL).[6] Although valve sizing has not been studied in terms of mild or greater PVL for CoreValve, one study has noted that 15% to 25% oversizing of the valve was associated with the lowest rates of PVL, resulting in ≥6.3% rates of moderate PVL.[21]

It is important to note that oversizing of a TAVR valve in relation to the LVOT and/or annulus diameters has also been associated with an increased need for a permanent pacemaker,[22,23] which implies there is a need to balance the degree of oversizing to prevent these two different adverse outcomes (PVL or pacemaker). This analysis found that the permanent pacemaker rate increased with valve oversizing of ≥10% in relation to the annulus, although this finding was not statistically significant; there was no difference in pacing rate with sizing ratios below this threshold. This strongly suggests that optimal oversizing of the Lotus valve to minimize risk of both PVL and pacemaker rate is 5-10%. It should be noted, however, that frequency of permanent pacemaker implantation is more closely correlated with overstretch in the LVOT, and that although annular rupture due to oversizing was not observed in the REPRISE II study plus Extended Cohort, it has been reported in approximately 0.3% to 0.8% of patients undergoing TAVR.[24]

This study has the usual limitations implicit in a single-arm, open-label study; however, a key strength was that all angiographic and echocardiography results from this trial were adjudicated by independent core labs. As noted previously for the REPRISE II study,[25] only two valve sizes (23mm and 27mm) were available at the time of the study, while a 25mm valve is now also available in clinical practice. The reduced rate of echocardiographic follow-up compared with clinical follow-up is also a common limitation in current TAVR trials,[26] which was addressed in this analysis by using discharge data where 30-day information was not available. Further, the limitations of TTE itself in assessing PVL must be considered [27]; however, this is the standard for all published valve studies and therefore is broadly applicable. Finally, the rate of mild or greater PVL with the Lotus Valve is <15%, meaning that the analysis population for predictors of PVL in this study is relatively small and these results should be regarded as hypothesis-generating until confirmed in a larger trial.

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Declaration of interest:

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Lifesciences and proctor fees from Medtronic. Dr. Darren L. Walters reports receiving grant support or research contracts from Edwards Lifesciences, Boston Scientific, and St Jude, consultant fees for advisory board participation for Edwards Lifesciences, and proctoring for Edwards Lifesciences and Boston Scientific. Dr. Jan Harnek reports receiving proctor fees from Boston Scientific. Dr. Stephen G. Worthley reports receiving grant support or research contracts from Medtronic, St. Jude Medical, and Boston Scientific, and honoraria from Medtronic and St. Jude Medical. Dr. Gilles Rioufol reports receiving consultant fees or honoraria from Medtronic and St. Jude Medical, and grant support from Hexacath. Dr. Thierry Lefèvre reports receiving consultant fees or honoraria from Boston Scientific, Edwards Lifesciences, Sanofi, and Tryton, and grant support or research contracts from Boston Scientific, Direct Flow, Symetis, and the Medicines Company. Drs. Vicki M. Houle, Dominic J. Allocco and Keith D. Dawkins are full-time employees of and have equity interest in Boston Scientific. Dr. Didier Tchétché reports that he has no relationships relevant to the contents of this paper to disclose.

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Figure Titles and Legends

Figure 1. The Lotus Valve

Figure 2. Study Flow

Figure 3. Aortic regurgitation over time.

Figure 4. Effect of valve sizing on paravalvular leak. Overstretch was defined as the nominal valve area divided by the annular area.

Figure 5. Effect of valve sizing on newly implanted permanent pacemaker (PPM) through 30 days. A) Rate of new PPM by annulus overstretch; B) Rate of new PPM by left ventricular outflow tract (LVOT) overstretch. Overstretch was defined as the nominal valve area divided by the annular or LVOT area.

Figure 1

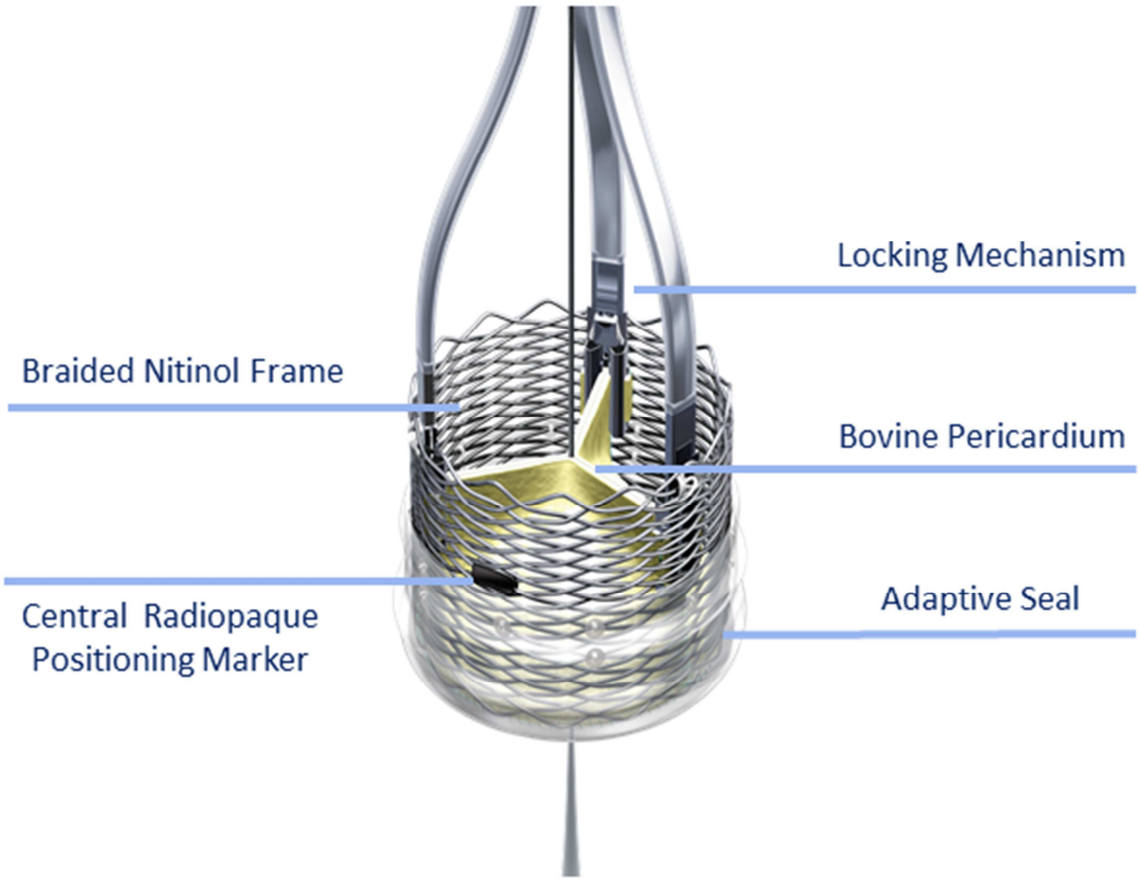

Locking Mechanism
Braided Nitinol Frame
Bovine Pericardium
Central Radiopaque Positioning Marker
Adaptive Seal

Figure 2

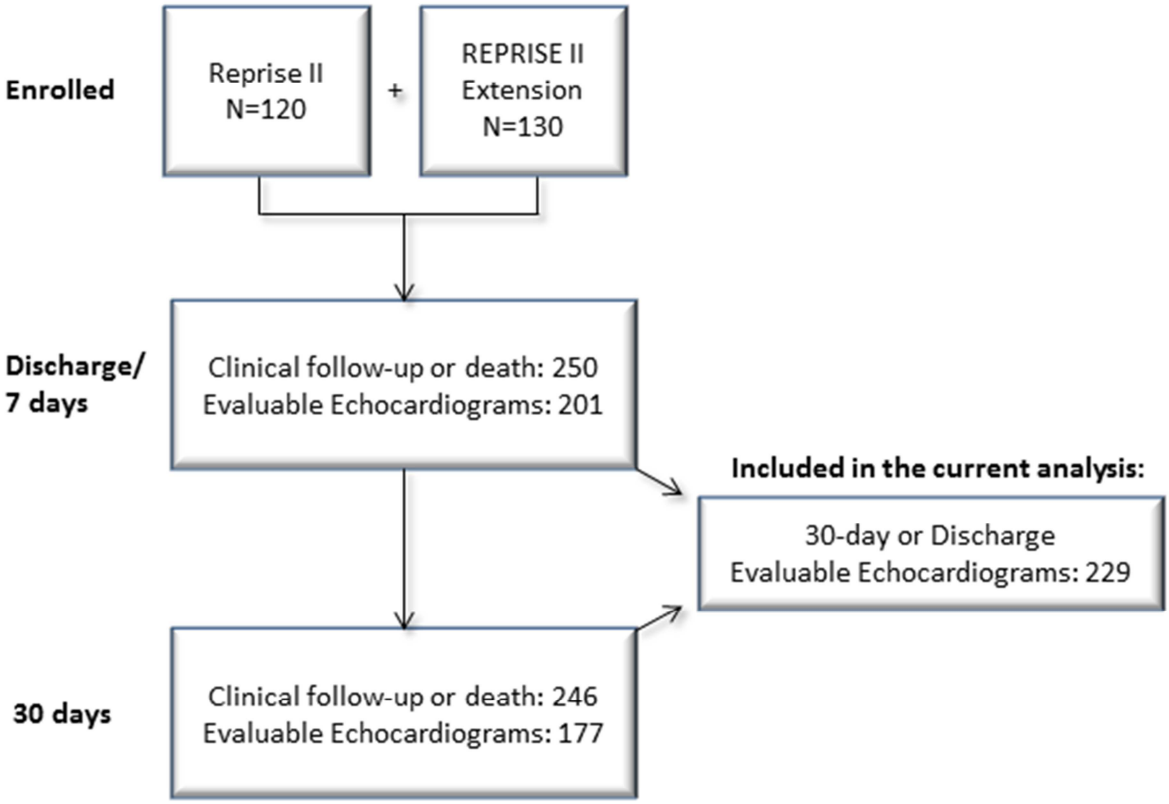

Enrolled
Reprise II
N=120
+
REPRISE II
Extension
N=130
Discharge/
7 days
Clinical follow-up or death: 250
Evaluable Echocardiograms: 201
Included in the current analysis:
30-day or Discharge
Evaluable Echocardiograms: 229
30 days
Clinical follow-up or death: 246
Evaluable Echocardiograms: 177

Figure 3

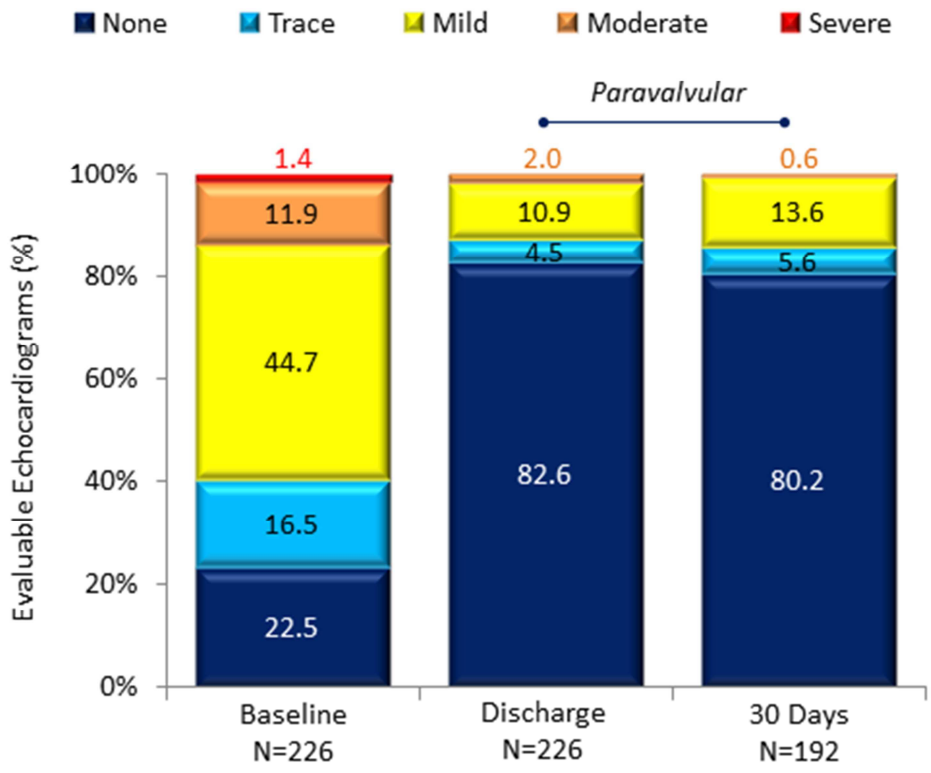

None
Trace
Mild
Moderate
Severe
Paravalvular
1.4
2.0
0.6
100%
80%
60%
40%
20%
0%
Evaluable Echocardiograms (%)
11.9
44.7
16.5
22.5
10.9
4.5
82.6
13.6
5.6
80.2
Baseline
N=226
Discharge
N=226
30 Days
N=192

Figure 4

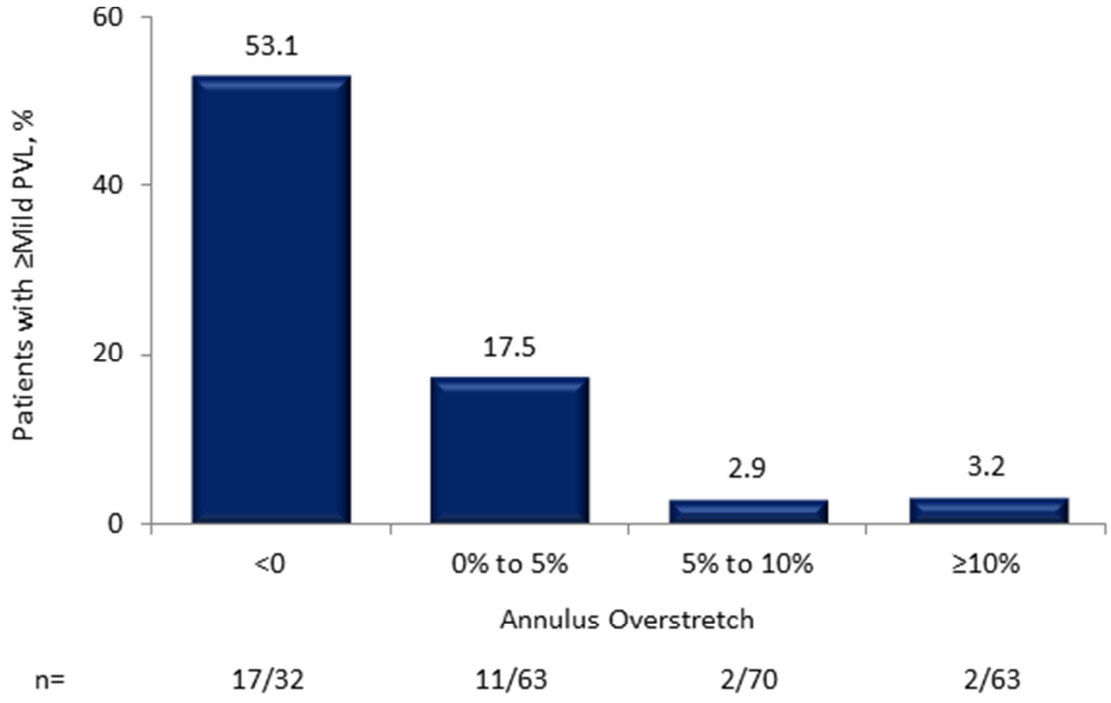
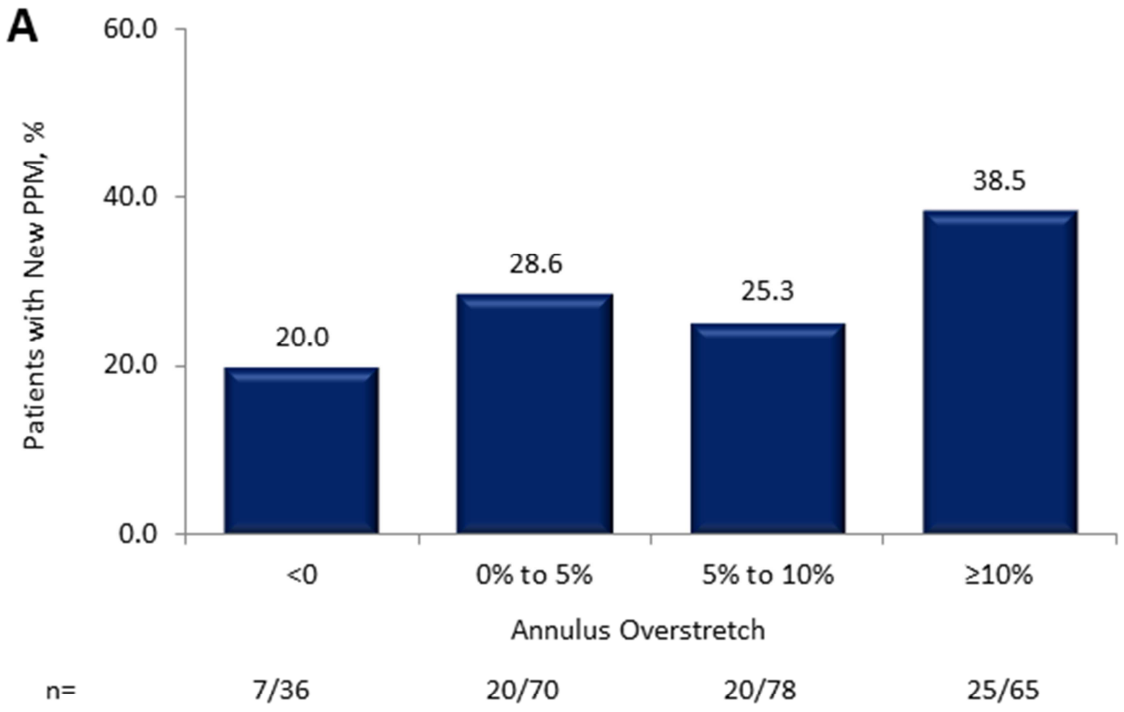

60
40
20
0
Patients with ≥Mild PVL, %
53.1
17.5
2.9
3.2
<0
0% to 5%
5% to 10%
≥10%
Annulus Overstretch
n=
17/32
11/63
2/70
2/63

Figure 5


A
60.0
40.0
20.0
0.0
Patients with New PPM, %
20.0
28.6
25.3
38.5
<0
0% to 5%
5% to 10%
≥10%
Annulus Overstretch
n=
7/36
20/70
20/78
25/65

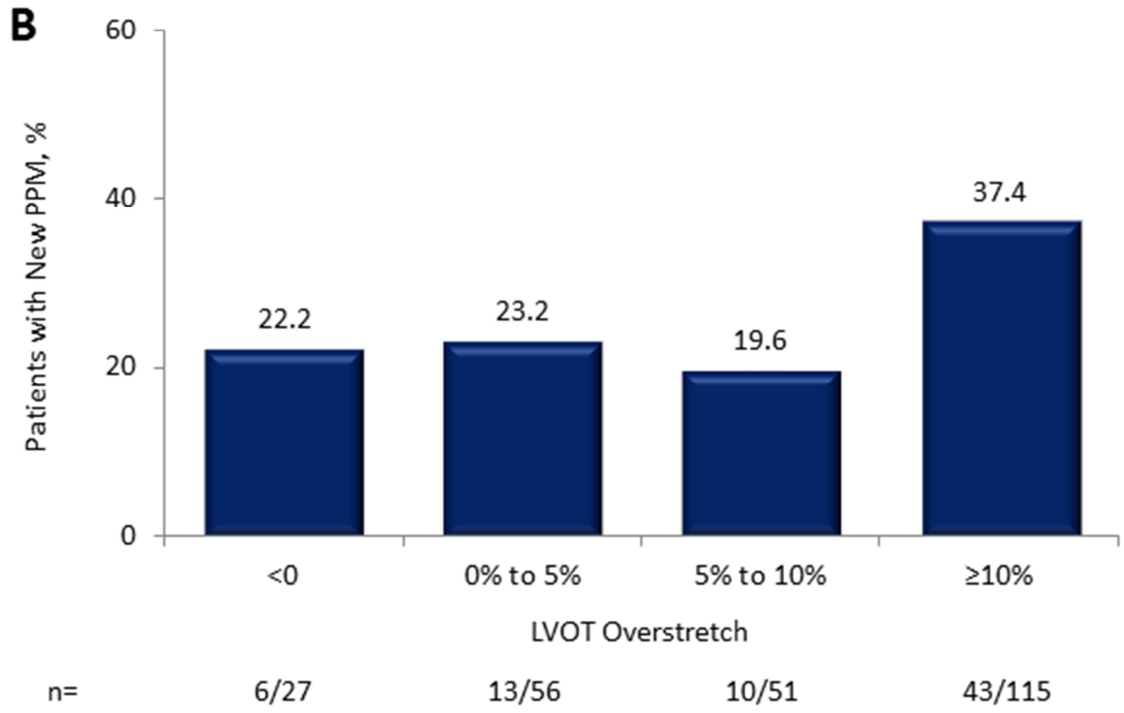

B
60
40
20
0
Patients with New PPM, %
22.2
23.2
19.6
37.4
<0
0% to 5%
5% to 10%
≥10%
LVOT Overstretch
n=
6/27
13/56
10/51
43/115

Table 1. Baseline Patient and Anatomical Characteristics

Variable	Paravalvular Leak		*P* value
	None/Trace (n=197)	≥Mild (n=32)	
Age (years)	84 ± 5 (197)	86 ± 5 (32)	0.048
Woman	93/197 (47%)	22/32 (69%)	0.02
STS Score (v2.73) (%)	6.2 ± 3.8 (197)	6.8 ± 4.6 (32)	0.46
Treated diabetes mellitus	55/197 (28%)	4/32 (13%)	0.06
Treated hypertension	152/197 (77%)	23/32 (72%)	0.51
Treated hyperlipidemia	121/197 (61%)	13/32 (41%)	0.03
Prior coronary artery disease	104/197 (53%)	14/32 (44%)	0.34
Prior cerebral vascular accident	13/197 (7%)	3/32 (9%)	0.47
Baseline LVEF (%)	53 ± 10 (99)	54 ± 13 (18)	0.76
Baseline atrial fibrillation	41/196 (21%)	8/32 (25%)	0.60
Pre-procedure aortic regurgitation (any)	137/175 (78%)	23/29 (79%)	0.90
Pre-procedure mean aortic gradient (mmHg)	44 ± 13 (170)	53 ± 15 (29)	<0.001
Annulus diameter (mm)*	24 ± 2 (196)	24 ± 2 (32)	0.84
Annulus area (mm^2)	444 ± 74 (196)	444 ± 55 (32)	0.96
Annulus eccentricity†	0.8 ± 0.1 (196)	0.8 ± 0.1 (32)	0.65
LVOT diameter (mm)*	23 ± 2 (196)	23 ± 2 (32)	0.80
LVOT area (mm^2)	423 ± 81 (196)	417 ± 61 (32)	0.72
LVOT eccentricity†	0.7 ± 0.1 (196)	0.7 ± 0.1 (32)	0.65
Total LVOT calcium volume (mm^3)	22 ± 43 (196)	71 ± 94 (32)	0.008
Total leaflet & annulus calcium volume (mm^3)	836 ± 589 (196)	1109 ± 620 (32)	0.02

Right coronary cusp leaflet/annulus calcium volume (mm^3)	229 ± 163 (196)	307 ± 217 (32)	0.06
Left coronary cusp leaflet/annulus calcium volume (mm^3)	285 ± 427 (196)	381 ± 233 (32)	0.07
Non-coronary cusp leaflet/annulus calcium volume (mm^3)	322 ± 209 (196)	421 ± 303 (32)	0.08

Values are mean ± standard deviation (n) or n/N (percent). Anatomic characteristics assessed by independent core laboratory angiographic analysis.

*Area-derived

†Eccentricity defined as perpendicular to the maximum annulus diameter divided by the maximum annulus diameter.

Abbreviations: LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract; STS=Society of Thoracic Surgeons

Table 2. Procedural Characteristics

Variable	Paravalvular Leak None/Trace (n=197)	Paravalvular Leak ≥Mild (n=32)	*P* value
Valve size implanted (mm)			
23	79/197 (40%)	24/32 (75%)	<0.001
27	118/197 (60%)	8/32 (25%)	<0.001
Valve repositioned or retrieved	78/197 (40%)	10/32 (31%)	0.37
Maximum balloon diameter:valve area ratio	0.9 ± 0.1 (196)	0.8 ± 0.1 (32)	0.004
Measured waist reduction [min/max] (%)*	12.2 ± 4.8 (91)	13.0 ± 4.9 (17)	0.53
Depth of device implantation, left coronary sinus (mm)	6.7 ± 2.8 (173)	5.2 ± 2.7 (28)	0.007
Depth of device implantation, non-coronary sinus (mm)	5.1 ± 2.5 (171)	4.7 ± 2.8 (27)	0.52
Device area : Annulus area ratio	1.2 ± 0.1 (196)	1.0 ± 0.1 (32)	<0.001
Annulus overstretch†‡			
Any (>0%)	181/196 (92%)	15/32 (47%)	<0.001
≥5%	129/196 (66%)	4/32 (12.5%)	<0.001
≥10%	61/196 (31%)	2/32 (6.3%)	0.004
Device area:LVOT area ratio	1.2 ± 0.2 (196)	1.1 ± 0.2 (32)	<0.001
LVOT overstretch†‡			
Any (>0%)	181/196 (92%)	22/32 (69%)	<0.001
≥5%	141/196 (72%)	13/32 (41%)	<0.001
≥10%	95/196 (49%)	8/32 (25%)	0.01

Values are mean ± standard deviation (n) or n/N (percent). Anatomic characteristics assessed by independent core laboratory angiographic analysis.

*Defined as minimum valve diameter divided by maximum valve diameter

†Area-derived

‡Overstretch defined as the nominal valve area divided by the LVOT or annular area.

Abbreviations: LVOT=left ventricular outflow tract

Table 3. Multivariate Predictors of ≥Mild Paravalvular Leak

Variable	Odds Ratio	95% CI	*P* value
Ratio of device area to annulus area (%)	0.87	0.83, 0.92	<0.001
Annulus area (per 10 mm^2)	0.89	0.82, 0.96	0.002
Treated hyperlipidemia	0.29	0.11, 0.74	0.01
LVOT calcium volume (per $100mm^3$)	2.85	1.44, 5.63	0.03
Leaflet & annulus calcium volume (per $100mm^3$)	1.07	1.00, 1.16	0.06

Abbreviations: CI=confidence intervals; LVOT=left ventricular outflow tract