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ORIGINAL STUDIES

Clinical outcomes of the Lotus Valve in patients with bicuspid aortic valve stenosis: An analysis from the RESPOND study

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Abstract

Aims: Patients with bicuspid valves represent a challenging anatomical subgroup for transcatheter aortic valve implantation (TAVI). This analysis evaluated the clinical outcomes of the fully repositionable and retrievable Lotus Valve System in patients with bicuspid aortic valves enrolled in the RESPOND post-market registry.

Methods and Results: The prospective, open-label RESPOND study enrolled 1,014 patients at 41 centers in Europe, New Zealand, and Latin America, 31 (3.1%) of whom had bicuspid aortic valves. The mean age in the bicuspid patient cohort was 76.4 years, 64.5% were male, and the baseline STS score was 6.0 ± 10.2. Procedural success was 100%, with no cases of malpositioning, valve migration, embolization, or valve-in-valve. Repositioning was attempted in 10 cases (32.3%). There was one death (3.2%) and one stroke (3.2%) at 30-day follow-up. Mean AV gradient was reduced from 48.7 ± 17.0 mmHg at baseline to 11.8 ± 5.1 mmHg at hospital discharge ($P < 0.001$); mean effective orifice area (EOA) was increased from 0.6 ± 0.2 cm^2 to 1.7 ± 0.4 cm^2 ($P < 0.001$). There were no cases of moderate or severe paravalvular leak (PVL) adjudicated by the core laboratory; four subjects (13.8%) had mild PVL, 5 (17.2%) had trace PVL. The rate of pacemaker (PM) implantation for PM-naïve patients was 22.2% (6/27).

Conclusions: Data from the RESPOND registry demonstrate good clinical and echocardiographic outcomes up to 1 year postimplantation in patients with bicuspid aortic valves using the repositionable Lotus Valve.

KEYWORDS

aortic regurgitation, aortic valve stenosis, bicuspid, transcatheter aortic valve implantation, transfemoral

[Correction added on March 25, 2019 after first online publication: affiliation 10 was updated.]

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1 | INTRODUCTION

Bicuspid valves are one of the most common congenital aortic valve anomalies, present in up to 2% of the population.[1,2] Compared to tricuspid valves, bicuspid valves have a larger annulus perimeter, an asymmetrical valve orifice, and more heavily calcified leaflets/raphe.[3,4] Patients with a bicuspid aortic valve are at increased risk for aortic stenosis, aortic dilation, aneurysm, and dissection.[3,4] While transcatheter aortic valve implantation (TAVI) is an established treatment option for patients with symptomatic aortic stenosis who are at high risk for surgical valve replacement,[5,6] patients with bicuspid valves have been excluded from most TAVI clinical trials and bicuspid-TAVI data are limited. Demonstrating safety and efficacy in bicuspid valves is essential for TAVI devices, particularly if TAVI is to be extended into lower risk populations in whom bicuspid anatomy is more prevalent.

Previous data have consistently shown worse outcomes following TAVI in bicuspid anatomy, including increased paravalvular leak (PVL), nonuniform/noncircular valve deployment, reduced procedural success, device migration/embolisation, malfunction, and annular rupture.[7–13] More recent studies have shown that outcomes may be better with newer generation valves.[8] The Boston Scientific Lotus Valve has several features which may be of benefit in patients with bicuspid anatomy, including a sealing skirt to reduce PVL, deployment via gradual mechanical expansion, and full retrievability and repositionability. The **RE**postionable **P**ercutaneous **R**eplacement of stenotic aortic valve through **I**mplantation of Lotus Valve **S**ystem: **E**valuation of safety and performance (REPRISE II)[14] and the **RE**positionable **P**ercutaneous **R**eplacement of stenotic aortic valve through **I**mplantation of Lotus Valve **S**ystem—Randomized Clinical **E**valuation (REPRISE III)[15] trials excluded patients with bicuspid valves.

The RESPOND study evaluated TAVI with the Lotus Valve when used in routine clinical practice, including in patients with bicuspid aortic valve anatomy. This subanalysis of RESPOND evaluates 30-day and 1-year outcomes with Lotus in patients with bicuspid aortic valves.

2 | METHODS

2.1 | Study design and device details

The **RE**positionable Lotus Valve **S**ystem—**P**ost-market evaluatio**n** of real worl**d** clinical outcomes (RESPOND) study is a prospective, open label, single arm, multi-center, post-market registry from 41 centers in Europe, New Zealand, and Latin America. The study design has been previously described.[16] Data collection occurred at baseline, index procedure, discharge and at 30 days and 1 year postprocedure for all enrolled subjects.

The protocol was approved by the locally appointed institutional review boards/ethics committees, and the study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki. All patients gave written informed consent. The study was registered with ClinicalTrials.gov (NCT#02031302). The data and study protocol for this clinical trial may be made available to other researchers in accordance with Boston Scientific's Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

The Lotus Valve System consists of a bioprosthetic aortic valve premounted on a preshaped delivery catheter. Novel features of the Lotus Valve System include an adaptive seal designed to mitigate PVL, controlled mechanical expansion, and the ability to fully recapture or reposition the valve prior to release. Detailed descriptions of the Lotus Valve System have been previously published.[17,18]

2.2 | Outcomes measures

Endpoints were assessed according to Valve Academic Research Consortium (VARC)-2 definitions.[19] The primary endpoint for RESPOND was all-cause mortality at 30 days and 1 year in the intent-to-treat population. Secondary endpoints included in-hospital mortality, the composite of all-cause mortality and disabling stroke at 30 days and 1 year, and grade of paravalvular aortic valve regurgitation at discharge and 1 year. Major clinical events (i.e., all-cause mortality and stroke events) were adjudicated by an Independent Medical Reviewer (IMR). All baseline and follow-up echocardiography data were evaluated by an independent core laboratory (Cardialysis Core Laboratory, Rotterdam, Netherlands).

For this subanalysis, the preliminary identification of bicuspid anatomy was site-reported, and verified on the basis of echocardiography and/or computerized tomography (CT) coronary angiography. Systematic review of CT angiograms was performed by one of the authors (LVG) using 3Mensio software, and each valve was defined as type 0, type 1, or type 2 according to Sievers' valve classification Scheme[20] (Figure 1). Four patients in the bicuspid cohort were initially characterized as having "functional" bicuspid valves; in each of these cases, CT demonstrated fusion between the right—and noncoronary cusps. Thus, these four patients were classified as having Sievers type

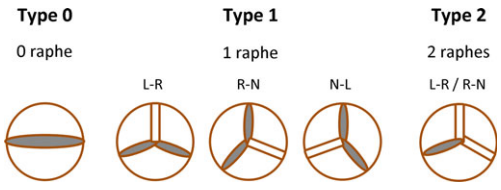

FIGURE 1 Bicuspid valve types. The Sievers' valve classification scheme[20] was used to define each bicuspid valve as type 0, type 1, or type 2 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline patient characteristics

Patient characteristic	Bicuspid cohort N = 31	Tricuspid cohort N = 965	*P*-value
Age, years	76.4 ± 7.9 (31)	80.9 ± 6.4 (965)	<0.001
Gender, male	64.5 (20/31)	48.7 (470/965)	0.083
BMI (kg/m^2)	28.1 ± 4.91 (30)	26.6 ± 4.82 (956)	0.093
STS score	6.0 ± 10.15 (28)	5.9 ± 6.74 (821)	0.948
EuroSCORE 20II	6.1 ± 7.52 (29)	8.0 ± 8.38 (896)	0.233
Diabetes mellitus, medically treated	16.1 (5/31)	22.5 (217/965)	0.403
History of COPD	9.7 (3/31)	15.7 (151/963)	0.458
NYHA class III or IV	66.7 (20/30)	69.6 (623/895)	0.731
History of hypertension	71.0 (22/31)	79.4 (760/957)	0.254
Coronary artery disease, history	25.8 (8/31)	57.1 (550/964)	0.001
Prior PCI	12.9 (4/31)	30.4 (292/962)	0.037
Prior CABG	3.2 (1/31)	12.6 (122/965)	0.163
Prior implanted pacemaker	12.9 (4/31)	13.4 (129/965)	0.100
Atrial fibrillation, history	25.8 (8/31)	34.2 (326/954)	0.333
Porcelain aorta	6.5 (2/31)	4.3 (41/960)	0.394
Hostile chest/unfavorable chest wall anatomy	0.0 (0/31)	1.0 (10/964)	1.000
Annular calcification (site-reported)			
Mild	10.0% (3/30)	19.6% (156/797)	0.192
Moderate	50.0% (15/30)	39.6% (316/797)	0.256
Severe	40.0% (12/30)	40.8% (325/797)	0.932
Cerebrovascular accident, history	16.1 (5/31)	9.3 (89/962)	0.205
Transient ischaemic attack, history	0.0 (0/31)	7.6 (73/958)	0.161

Values are mean ± SD (N) or % (n/N).

1 valves. No specific guidance for the selection of valve size in bicuspid valves was provided and the final decision was at the discretion of the operator. This is the first registry to date to employ the use of an independent clinical event committee as well as to assess both CT and echo data for bicuspid valve validation and characterization.

3 | RESULTS

3.1 | Study participants and baseline characteristics

The RESPOND post-market registry enrolled 1,014 patients between May 2014 and February 2016; 31 of the 996 patients implanted with a Lotus Valve were identified as having bicuspid anatomy. Most baseline characteristics for bicuspid and tricuspid patients from RESPOND were similar. Significant baseline differences existed for average age (76.4 ± 7.9 years bicuspid vs. 80.9 ± 6.4 years tricuspid; $P < 0.001$), history of coronary artery disease (CAD) (25.8% bicuspid vs. 57.1% tricuspid; $P = 0.001$), and percutaneous coronary intervention (PCI) (12.9% bicuspid vs. 30.4% tricuspid; $P < 0.05$) (Table 1).

The majority of the bicuspid patients (74.2% [23/31]) had Sievers type 1 valve anatomy (21 L-R, 2 R-N); 16.1% (5/31) had type 0 valves, 3.2% (1/31; 1 R-N) had type 2 valves, and 6.5% (2/31) were unable to be classified due to scan quality.

Core laboratory-adjudicated baseline echocardiography was significantly different between the two groups. The mean effective aortic orifice area (EOA) was 0.6 ± 0.2 cm^2 for bicuspid and 0.7 ± 0.2 cm^2 for tricuspid ($P = 0.008$) and the mean aortic valve gradient was 48.7 ± 17.0 mmHg for bicuspid and 37.6 ± 15.3 mmHg for tricuspid ($P < 0.001$). There were no significant differences in aortic regurgitation (AR) at baseline (Severe AR: 3.7% for bicuspid, 2.2% for tricuspid; Moderate AR: 18.5% for bicuspid, 14.2% for tricuspid; None-Mild AR: 77.8% for bicuspid, 83.6% for tricuspid; *P*=NS for all). Site-reported aortic valve calcification was not significantly different in patients with bicuspid valves versus patients with tricuspid aortic valves (Table 1), nor was site-reported aortic annulus diameter (25.1 mm for bicuspid, 24.4 mm for tricuspid; $P = 0.085$). Based on preprocedural echocardiography, left ventricular ejection fraction was similar in both groups (50.9 ± 15.3% for bicuspid, 54.8 ± 13.0% for tricuspid; $P = 0.112$). There were 11 (35.4%) aortic root aneurysms (defined as maximum diameter of ascending aorta >40 mm) reported in the bicuspid cohort of the RESPOND registry.

3.2 | Procedural success and details

Both the bicuspid and tricuspid cohorts demonstrated high rates of procedural success. Pre-dilatation was performed significantly more often in the bicuspid cases than in the tricuspid cases (80.0% [24/30] for bicuspid, 53.0% [500/943] for tricuspid; $P = 0.004$). Correct positioning of a single prosthetic valve in the proper anatomical location occurred in 100% of the bicuspid cases—there were no cases of migration, embolization, or deployment of a second valve. Repositioning was attempted in 10 bicuspid patients (32%) and 299 tricuspid patients (31%). If attempted, repositioning was successful in 9 of 10 attempts (90%) for bicuspid patients and in 287 of 299 attempts (96.0%) for tricuspid patients. In the one bicuspid patient in whom repositioning was deemed unsuccessful, the site had reported "moderate aortic regurgitation

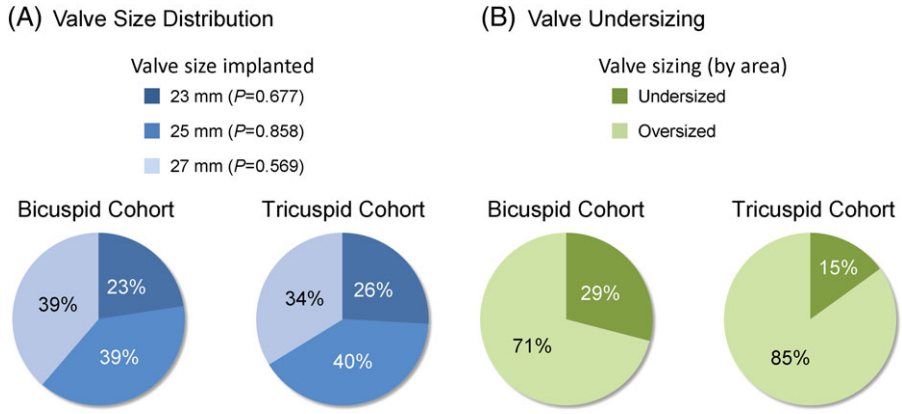

FIGURE 2 Lotus valve sizing. A, The distribution of valve sizes used within the bicuspid and tricuspid patient cohorts was similar. B, Undersizing was more common in patients with bicuspid valves compared to tricuspid valves (29.0% vs. 15.1%; $P = 0.04$) [Color figure can be viewed at wileyonlinelibrary.com]

despite repositioning" following implantation of a 25 mm Lotus valve; the valve was retrieved during the index procedure and a 27 mm Lotus valve was implanted instead. The bicuspid and tricuspid cohorts had a similar distribution of valve sizes (27 mm: 39% for bicuspid, 34% for tricuspid; 25 mm: 39% for bicuspid, 40% for tricuspid; 23 mm: 23% for bicuspid, 26% for tricuspid; *P*=NS for all) (Figure 2A).

3.3 | Haemodynamic performance

The mean aortic valve gradient was statistically different between bicuspid and tricuspid patients at baseline (48.7 ± 17.0 mmHg for bicuspid, 37.6 ± 15.3 mmHg for tricuspid; $P < 0.001$) but was similar at discharge (12.4 ± 4.9 mmHg for bicuspid, 10.8 ± 4.5 mmHg for tricuspid; $P = 0.059$) and 1 year post procedure (13.3 ± 8.2 mmHg for bicuspid, 10.7 ± 4.9 mmHg for tricuspid; $P = 0.167$). The mean EOA measurements were also different at baseline and similar at discharge and 1 year between the groups; both cohorts demonstrated a significant increase in effective orifice area (Baseline EOA: 0.6 ± 0.2 cm^2 for bicuspid, 0.7 ± 0.2 cm^2 for tricuspid; $P = 0.008$. Discharge EOA: 1.6 ± 0.4 cm^2 for bicuspid, 1.8 ± 0.5 cm^2 for tricuspid; $P = 0.052$. 1-year EOA: 1.6 ± 0.4 cm^2 for bicuspid, 1.8 ± 0.5 cm^2 for tricuspid; $P = 0.101$) (Figure 3).

Paravalvular leak was not significantly different between the bicuspid and tricuspid cohorts at either hospital discharge ($P = 0.099$) or 1 year post procedure ($P = 0.131$) (Figure 4).

3.3.1 | Safety

The primary endpoint of all-cause mortality was not significantly different between the bicuspid and tricuspid cohorts at 30 days (3.2% vs. 2.2%, respectively; $P = 0.51$) or 1 year (9.7% vs. 11.7%, respectively;

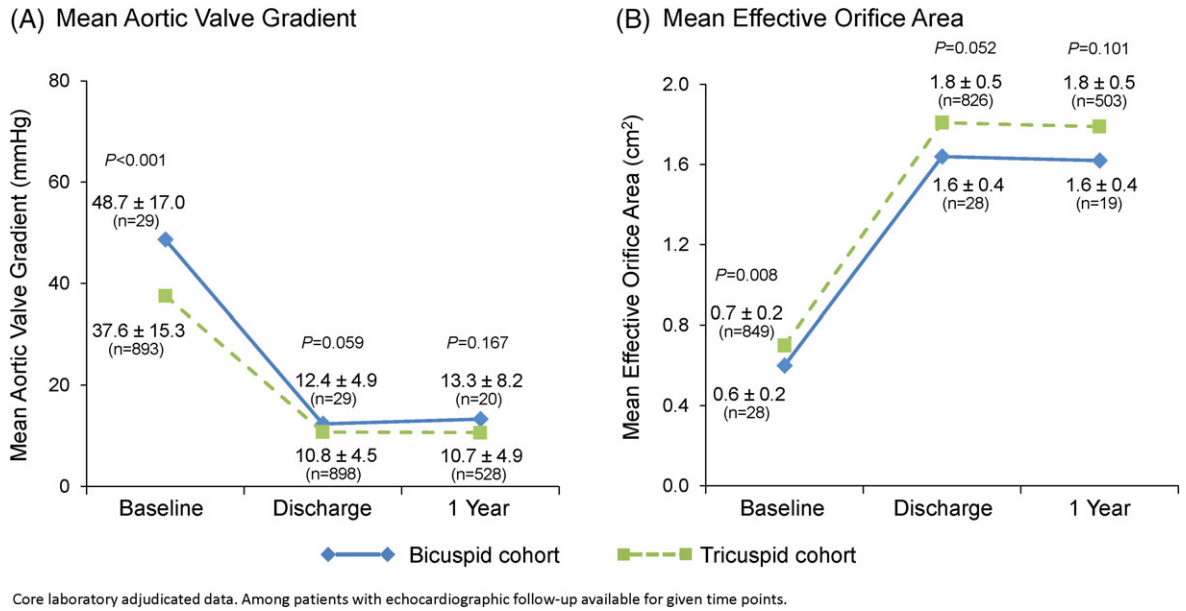

FIGURE 3 Mean aortic valve gradient and effective orifice area. Bicuspid and tricuspid patients both demonstrated a significant change in mean aortic valve gradient and effective orifice area (EOA) from baseline to discharge, which was maintained at 1 year. Baseline measurements for mean aortic gradient and mean EOA were different between the bicuspid and tricuspid cohorts at baseline, with no significant difference observed between groups at discharge or 1 year post-TAVI. Data is core laboratory adjudicated [Color figure can be viewed at wileyonlinelibrary.com]

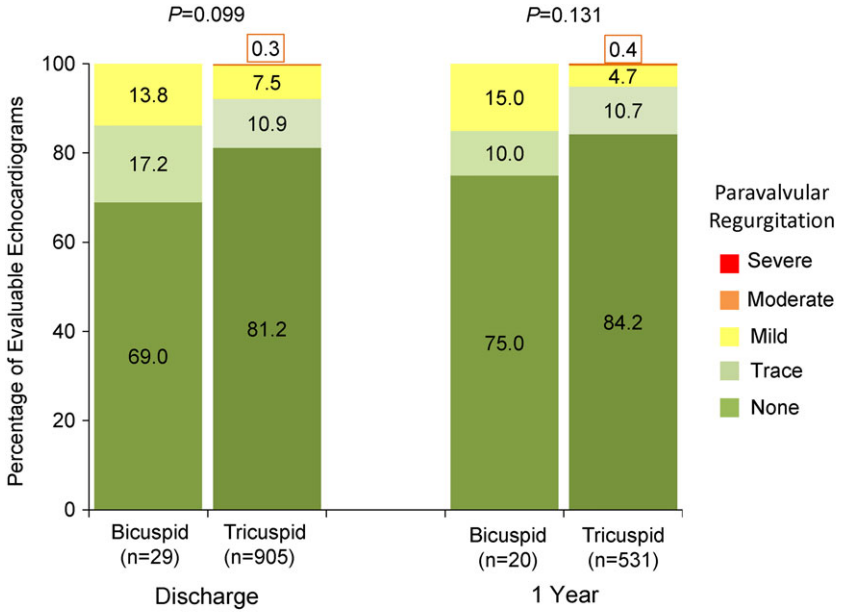

FIGURE 4 Paravalvular aortic regurgitation. There was no severe PVL observed in either the bicuspid or tricuspid cohort, as adjudicated by the core laboratory. At hospital discharge, 86.2% of the bicuspid cohort and 92.1% of the tricuspid cohort had no/trace PVL; absence from PVL was maintained in 85.0% of the bicuspid cohort and 94.9% of the tricuspid cohort at 1 year post-TAVI

P = 0.74). There were no significant differences between groups for other principal safety outcomes through 1 year, including cardiovascular mortality, stroke, hospitalization for valve-related symptoms or worsening congestive heart failure, and pacemaker implantation (Figure 5).

3.4 | Valve sizing in bicuspid anatomy

Annulus diameter measurements were performed by each site and valve sizing was determined at the discretion of the operator. Undersizing was more common in patients with bicuspid valves compared to tricuspid valves (9/31 [29.0%] for bicuspid, 112/744 [15.1%] for tricuspid; *P* = 0.04) (Figure 2B, Table 2). Of the 31 patients with bicuspid anatomy, five had considerable (>10%) undersizing by annulus area. Echocardiographic data indicates that PVL and haemodynamic results were good in these patients (Table 3).

4 | DISCUSSION

The principal finding of this study is that outcomes for patients with bicuspid aortic valves who underwent TAVI with the Lotus Valve in the "real-world" RESPOND registry were comparable to those with

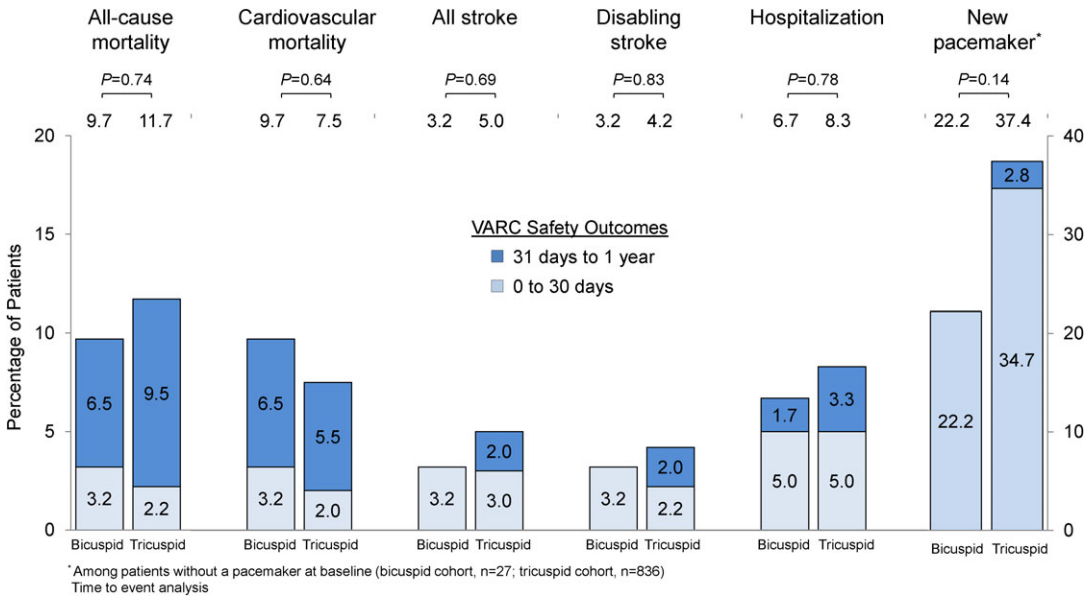

FIGURE 5 Principal VARC safety outcomes at 30 days and 1 year post-TAVI. All-cause mortality (RESPOND primary endpoint) was not significantly different between the bicuspid and tricuspid cohorts at 30 days or 1 year. There were no significant differences between groups for other principal safety outcomes through 1 year

TABLE 2 Valve sizing in RESPOND

Valve sizing range (per area)	Bicuspid cohort (N = 31)	Tricuspid cohort (N = 965)	*P value*
Undersized >10%	16.1% (5/31)	3.6% (27/744)	0.007
Undersized 0 to ≤10%	12.9% (4/31)	11.4% (85/744)	0.773
Oversized 0 to ≤10%	41.9% (13/31)	42.1% (313/744)	0.988
Oversized >10%	29.0% (9/31)	42.9% (319/744)	0.126

Values are % (n/N).

tricuspid aortic valves receiving the Lotus Valve. The bicuspid cohort was significantly younger, which aligns with other descriptions of aortic stenosis in bicuspid valves,[1] and the bicuspid cohort presented with significantly less coronary artery disease. There was no significant difference in clinical outcomes between bicuspid and tricuspid patients, including mortality, stroke, bleeding, vascular complications, and acute kidney injury. Device success in bicuspid patients was 100%, with no cases of migration, embolization, placement of a second valve, or annular rupture. Consistent with the low rates of PVL with the Lotus Valve in tricuspid anatomy, bicuspid patients in RESPOND had 0% moderate/severe PVL and only 13.8% mild PVL, as well as good haemodynamics.

4.1.1 | Challenges of TAVI in bicuspid anatomy

Due to the high level of calcification and eccentric geometry in patients with bicuspid anatomy, TAVI in bicuspid valves may be subject to an increased risk of complications related to irregular and incomplete expansion of the prosthetic valve.[9] Asymmetrical expansion of valves has been observed as high as 38% with the S3 valve in bicuspid anatomy[10] and Zegdi et al. describes noncircular stent deployment as 81% more frequent in bicuspid vs. tricuspid aortic valves.[11] Noncircular or irregular valve expansion may impact valve hemodynamics and durability. Valve haemodynamics following TAVI, including mean gradient and effective orifice area, were no different between bicuspid and tricuspid valves in RESPOND, despite a range of eccentricity from 1.11 to 1.48 in the bicuspid group (Supporting Information Table S1). This similarity may be attributed to the independent mobility of the Lotus valve leaflets. The Lotus Valve is designed such that the leaflets are not sutured to the valve frame, and are therefore not affected by non-circular valve expansion.

Furthermore, heavy calcification and eccentricity of the native annulus increases the risk of device malapposition and consequently of PVL. In a comparative analysis from the German TAVI Registry of bicuspid vs. tricuspid valves, the risk for moderate or greater AR was higher in patients with bicuspid anatomy receiving CoreValve or Sapien.[12] Mylotte et al. similarly reported a high incidence of post-implant AR in 139 bicuspid patients undergoing TAVI with Sapien XT and CoreValve (AR grade ≥ 2 was 28.4%).[13] In tricuspid anatomy, the Lotus Valve has low rates of PVL due to the Adaptive Seal feature. This seal reduces PVL by conforming to irregular anatomic surfaces, which may be a crucial attribute for minimizing PVL in bicuspid anatomy. In this analysis PVL was similar between tricuspid and bicuspid patients; there were no cases of moderate or severe PVL in patients with bicuspid valves, and even mild PVL was seen in only 13.8%. This result is consistent with the findings of Yoon et al. for PVL with current generation TAVI in bicuspid valves.[8]

Device success is typically lower overall for bicuspid TAVI-patients as compared to tricuspid TAVI-patients.[8] The use of balloon-expanded valves has been associated with an increased risk of annular rupture due to overdilation of the prosthesis to treat residual paravalvular regurgitation.[21] The Lotus Valve is fully repositionable and retrievable, allowing precise positioning in asymmetric anatomy, and avoiding risk of device migration or embolization. By virtue of its mechanical expansion and the fact that it does not rely on post-dilatation to mitigate PVL, use of the Lotus Valve may minimize the risk of annular injury inherent in the procedure. In the entire RESPOND population, there was only one case of annular rupture (which occurred in a tricuspid patient following balloon valvuloplasty). Despite frequent aortopathy (35.4% [11/31] of patients with bicuspid valves in RESPOND had aortic root aneurysms), no cases of dissection were seen. The data from this subanalysis support these potential advantages of the Lotus Valve for bicuspid patients as there were no cases of migration, embolization, deployment of a second valve, or annular rupture in this cohort.

4.1.2 | Valve sizing in bicuspid anatomy

For the RESPOND registry, sizing of the valve was at the discretion of the implanter. Some clinicians have hypothesized that routine undersizing may be beneficial in bicuspid anatomy, allowing fixation and sealing within the leaflets, with more complete and symmetrical expansion of the valve frame to optimize haemodynamics and potentially enhance long-term durability. In this analysis five patients received valves that had >10% undersizing by area; all had good outcomes with respect to PVL and valve haemodynamics.

Other studies have shown a tendency to oversize TAVI devices in bicuspid anatomy in an effort to circularize the annulus, prevent malpositioning, and reduce PVL, even though oversizing may increase the

TABLE 3 Cases of considerable undersizing (>10%) in bicuspid valves

Patient	Valve size implanted	Annulus size		Mean aortic gradient (mmHg)		PVL at discharge
		Area (mm^2)	Area-derived diameter (mm)	Baseline	Discharge	
1	27 mm	706	30.0	61.6	NR	NR
2	27 mm	550	25.7	29.0	12.4	Trace
3	27 mm	784	31.6	53.6	12.9	Mild
4	25 mm	604	28.0	48.2	15.8	None
5	27 mm	691	30.0	22.9	12.0	Trace

Values are means.
NR, not recorded due to death of patient (left ventricular perforation, cardiac tamponade) prior to discharge.

risk of rupture.[8] The combination of controlled mechanical expansion and the Adaptive Seal of the Lotus Valve may provide a benefit in addressing these challenges. Specific sizing for bicuspid anatomy with the Lotus Valve will require further investigation.

In a multivariate analysis of patients treated with the Lotus Valve in the REPRISE II study,[22] the ratio of device area to annulus area was shown to be a significant independent predictor of PVL (Odds Ratio [95% CI]: 0.87 [0.83, 0.92]; $P < 0.001$). Other TAVI studies have likewise demonstrated a similar association between valve sizing and PVL.[23–25] However, it is difficult to draw a definitive conclusion regarding the incidence of PVL as a function of valve oversizing among bicuspid patients in RESPOND, chiefly due to the small sample size and low rate of PVL overall in this study. Further examination is needed to determine whether specific baseline and/or procedural characteristics influence the development of PVL in bicuspid patients treated with the Lotus Valve.

4.1.3 | Study limitations

The primary limitation of this study is the small size of the analysis population. Additionally, RESPOND is a single-arm registry, and not a randomized study. Preliminary identification of bicuspid anatomy was site-reported, and although central CT analysis was used to confirm bicuspid anatomy, it was unfortunately not possible to review baseline CT scans for all RESPOND patients. In RESPOND, 3% of patients were identified as having bicuspid aortic valve stenosis; however, other studies have shown an incidence of approximately 20%.[2] It is possible that initial identification via echocardiography failed to capture all patients with bicuspid anatomy, underestimating the true number of bicuspid patients in the population. An additional limitation is that at the time of this study, the largest available Lotus Valve was 27 mm, which limits the results to patients with smaller annular diameters.

5 | CONCLUSIONS

TAVI with the Lotus Valve in patients with bicuspid aortic valve anatomy treated within the RESPOND registry was associated with good procedural, clinical, and haemodynamic outcomes.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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