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NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

The Lotus Valve System: an In-depth Review of the Technology

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Abstract

Purpose of Review Innovation for transcatheter aortic valve replacement (TAVR) has transformed a medically complex treatment into a standardized procedure. While Edwards SAPIEN and Medtronic CoreValve occupy the market for TAVR in the United States (US), additional valve systems are being developed. The Boston Scientific Lotus Valve system was recently FDA-approved and will represent the third valve in the US market. This evidence-based review will summarize advantages, disadvantages, and projected impact of this new TAVR system.

Recent Findings The Lotus Valve system demonstrates superiority in terms of rates of paravalvular leak, with similar rates of mortality and disabling stroke. This benefit is at the expense of increased pacemaker implantation rates, though preliminary data from subsequent iterations of the Lotus Valve suggest decreasing rates over time.

Summary There is much anticipation from ongoing trials utilizing the Lotus Edge system, which may perform best for those with pre-existing pacemakers or anatomy that increases likelihood of paravalvular leak.

Keywords Aortic stenosis · TAVR · Lotus Valve · Device development · SAVR

Introduction

There has been a rapid evolution within the transcatheter aortic valve replacement (TAVR) landscape given the demonstrated efficacy across patients of decreasing risk profiles. TAVR has now transitioned from an alternative for the management of aortic valve disease to the standard of care for patients in many with severe symptomatic aortic stenosis [1••, 2–10]. With expansion of TAVR eligibility, it will become increasingly important to mitigate device-related complications, which may vary by device and delivery system. Common complications include vascular complications, bleeding, paravalvular leak, and new-onset conduction abnormalities.

There are three options for transcatheter TAVR use: balloon-expandable (Edwards SAPIEN, Irvine CA), self-expanding (Medtronic CoreValve, Minneapolis, MN), and now, mechanically expandable (Boston Scientific, Lotus, Marlborough, MA) [11]. Based on a multicenter European registry, balloon and self-expandable devices have dominated the market and are being utilized in over 90% of cases. Mechanically expandable valves were utilized in less than 10% of the more than 27,000 TAVRs performed between 2013 and 20 16 [12]. In the face of PARTNER III and Evolut low-risk trials, current and novel transcatheter aortic valves have shown success in meeting primary safety endpoints and will invest in minimizing device-related complications [1••, 2].

From October 2016 to February 2017, Boston Scientific elected to recall the first-generation Lotus and second-generation Lotus Edge system, delaying plans to initiate the pre-market approval from the FDA due to the premature release of a pin that decouples the valve from the delivery system. This created a temporal competitive disadvantage for Boston Scientific, as both the balloon and self-expandable TAVR systems gained traction with significant market share and continued ongoing prospective research demonstrating non-inferiority in high-risk, intermediate-, and low-risk patients.

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In April 2019, the Lotus Edge system was FDA-approved for TAVR use in high-risk patients [13]. As a result, pre-existing TAVR programs are faced with a difficult choice in the face of rapid advancement in transcatheter valve replacement therapy—changing to a new device for primary use, incorporating new devices alongside devices already in practice, or limiting use to established devices in which there is the most user experience. While utilizing established devices may mitigate the impact of learning on patient outcomes, the evolution of a TAVR program with varying options can allow for individualized care based on patient anatomy, comorbid disease, anticipated risk for device-related complications and overall risk profile. Before examining this issue, what follows is a review of the Boston Scientific Lotus Valve System and available clinical data supporting its use.

Mechanism of Lotus Valve System

The Lotus TAVR device utilizes a stent frame with woven nitinol wire, which supports three bovine pericardial leaflets. The device is compressed by the delivery system and utilizes a "buckle and post" system to lock into place. The wire frame undergoes compression at the time of deployment. During the compression of the stent frame, the polyurethrane membrane seal on the basal surface of the device adapts to the intricacies of the valve annulus, aimed to mitigate risk of paravalvular leak. Subsequently, there is outward expansion of the stent frame with significant radial pressure to seat the aortic valve annulus [14].

Advantages and Disadvantages of Lotus Valve

Adaptive Seal Technology

The Adaptive Seal technology, proprietary to the Lotus Valve System, is considered beneficial for those with variable anatomy and significant annular calcification by virtually eliminating significant paravalvular leak. Given initial concerns for downward migration of the valve apparatus into the left ventricular outflow tract, subsequent iterations of the Lotus Delivery system allowed for shortening of the valve apparatus from the top portion of the valve, instead of from both sides of the valve, aimed to mitigate downward migration [14, 15].

Reposition and Recapture Capability

Valve malposition, although rare, can have significant implications on both short- and long-term outcomes of TAVR patients. In the periprocedural window, TAVR valve migration or embolization occurred in only 1.0% of patients; however, this complication accounted for greater than 25% of all cases requiring emergent conversion to open heart surgical intervention [16]. Additionally, valve malposition, in conjunction with other patient and procedural variables, may play a role in the development of paravalvular leak, coronary obstruction, and the development of conduction abnormalities. The ability to reposition the Lotus valve after deployment can help mitigate any sequelae of valve malposition. Valve opening and closing occurs during deployment and eliminates the need for rapid ventricular pacing, allowing for stable hemodynamics for serial assessment and repositioning if needed. In a single-center series, valve repositioning was utilized in 76 of 125 patients, most commonly to alter depth or angulation of initial implantation (69.7%), to reduce paravalvular leak (13.2%), or to correct new or evolving complete heart block (7.9%). There was no increased risk of major adverse cardiovascular events with a signal towards decreased rates of pacemaker implantation after repositioning [17]. Similar features are noted in self-expandable valves including Medtronic's Evolut R and Pro systems and Abbott's Portico Valve system.

Stent Frame Compression and Depth Guard Technology

The impact of TAVR implant depth on procedural outcomes has been well studied across varying delivery systems [17–21]. In a recent analysis utilizing computer simulation of pre-operative CT imaging, low implantation depth was associated with increased pressure on the atrioventricular conduction system, with subsequent post hoc analyses supporting low-implantation depth as an independent predictor of need for permanent pacemaker implantation [17, 22, 23]. Subanalyses of Lotus Valve implant data corroborated this concept, as baseline right bundle branch block (OR 12.7; 95% CI 4.5, 36.2; $p < 0.001$) and left ventricular outflow tract overstretch greater than 10% (OR 3.4; 95% CI 1.7, 6.7; $p < 0.001$) were independent predictors of pacemaker implantation [24]. There was a trend towards lower 30-day pacemaker implantation rates in those with implant depth less than 5 mm (23.9% ≤ 5 mm vs. 36.9% > 5 mm depth from LCS; $p = 0.06$) [24]. Boston Scientific developed Depth Guard technology, which facilitates precise deployment and minimizes placement of the valve in the left ventricular outflow tract. These additions, in conjunction with procedural modifications to improve annular sizing, were evaluated in the RESPOND Extension study, which demonstrated decreased pacemaker implantation rates [25]. The second-generation Lotus Edge system will include this technology, in addition to a more flexible catheter, one-view locking with radio-opaque markings, and a tri-fold expandable design with a lower profile to reduce the risk of vascular injury [26].

Clinical Data and Evolution of the Lotus Valve System

Initial assessment of the Lotus Valve system started with a feasibility study in the REPRISE I study [27]. Patients in REPRISE I had severe aortic stenosis, defined by the following echocardiographic parameters: aortic valve area (AVA) of < 1.0 cm^2 (or AVA index of < 0.6 cm^2/m^2) with mean pressure gradient > 40 mmHg or a jet velocity > 4 m/s. Additionally, patients were considered only if they were high risk for SAVR, as determined by a Society of Thoracic Surgery (STS) score ≥ 8%, a logistic EuroSCORE ≥ 20%, or the consideration of a multidisciplinary team consisting of a cardiothoracic surgeon and interventional cardiologist. Enrolled patients were required to have aortic annulus size between 19 and 22 mm for the 23-mm valve size. Key exclusion criteria included congenital anatomy (unicuspid or bicuspid aortic valve), pre-existing prosthetic heart valve or ring in any position, significant mitral or aortic regurgitation (at least moderate), non-revascularized coronary artery disease, left ventricular ejection fraction less than 30%, recent acute myocardial infarction, transient ischemic attack (TIA), or stroke within 6 months of enrollment, severe renal dysfunction. The primary endpoint was successful procedural implantation without major adverse cardiovascular or cerebrovascular event (MACCE). Fifteen patients were considered for this study based on inclusion criteria; however, four patients were excluded due to large annulus size, low coronary takeoff, or limited vascular access. In terms of baseline characteristics, all patients were female, the average STS score was 4.9 ± 2.5% and the mean aortic gradient was 53.9 ± 20.9 mmHg. The primary endpoint was met in 9 of 11 patients, as one patient suffered an in-hospital stroke and one patient suffered a device failure, defined by mean aortic valve gradient of 22.1 mmHg and peak velocity of 328 cm/s. There were no additional MACCE with 100% survival at 1 year. Three of the 11 (27.3%) patients enrolled in REPRISE I met the Valve Academic Research Consortium (VARC) combined safety endpoint, including MACCE, life-threatening bleeding, major vascular complications, and stage 3 acute kidney injury, as one patient suffered a left femoral dissection and two patients suffered life-threatening, transfusion-dependent bleeding. Four of 11 (36.4%) patients suffered conduction disturbances that warranted permanent pacemaker implantation. Four patients (36.4%) underwent successful repositioning of the Lotus Valve, allowing for more optimal annular positioning. In terms of echocardiographic data, no moderate to severe paravalvular leak was noted post procedure, and hemodynamic improvements were sustained over time [27]. Five-year outcomes of the patients enrolled in REPRISE I, demonstrated 63.6% survival at 5 years, cumulative major stroke rates of 9.1% with no additional permanent pacemaker implants needed and sustained hemodynamic performance of the valve was noted (mean aortic gradient at 5 years was 14.1 ± 4.1 mmHg (versus 53.9 ± 20.9 mmHg at baseline, $p < 0.001$; vs 13.7 ± 3.7 mmHg at discharge, $p = 0.744$), mean effective aortic orifice area at 5 years was 1.6 ± 0.4 cm^2 (versus 0.7 ± 0.2 cm^2 at baseline, $p < 0.001$; versus 1.5 ± 0.2 cm^2 at discharge, $p = 0.84$) [28].

The safety and efficacy data allowed for proof-of-concept and provided the foundation for REPRISE II. In this prospective, single-arm, multicenter study, patients who were deemed high surgical risk with STS score ≥ 8% with severe aortic stenosis as previously defined by echocardiographic parameters in REPRISE I and at least NYHA class II symptoms were enrolled [15]. In this study, CT imaging was evaluated by a core laboratory to determine valve size. There were two primary endpoints in REPRISE II, a primary safety endpoint of 30-day all-cause mortality and a device performance endpoint of mean aortic valve pressure compared to a performance goal pre-determined as 18 mmHg (15 mmHg + 3 mmHg test margin given prior data on CoreValve and SAPIEN systems). Additional VARC-2 endpoints were utilized for safety, effectiveness and valve performance. For baseline characteristics, the average STS score was higher in comparison to REPRISE I at 7.1 ± 4.6%, and the mean aortic gradient was 46.4 ± 15 mmHg. All 120 patients underwent successful deployment of the Lotus Valve system, with 31 patients requiring successful repositioning and 6 patients requiring retrieval. Adverse event rates were consistent with those reported from high-risk patient cohort data from balloon and self-expandable TAVR trials. The all-cause mortality rates were 4.2%, 10.9%, and 16.9% at 30 days, 1 year, and 2 years respectively, while the disabling stroke rates, as adjudicated by a neurologist, were 1.7%, 3.5%, and 3.5% at 30 days, 1 year, and 2 years, respectively [15]. At 2 years follow-up, 40 patients (34.2%) required new permanent pacemaker implantation. Yet again, there was no evidence of moderate or severe paravalvular leak in the studied cohort at 2 years with over 87% of patients without any signs of paravalvular leak. In regard to symptoms, patients had significant and sustained improvement NYHA class, with only 6.6% of patients with class III symptoms or higher at 2 years compared with 75.9% of patients with either class III or IV symptoms prior to TAVR. The mean aortic valve gradient at 30 days was 11.5 mmHg, lower than the performance goal of 18 mmHg ($p < 0.001$) [15].

Longer term outcomes from REPRISE II demonstrated continued low rates of paravalvular leak, mortality, and disabling stroke in addition to stable hemodynamics at 4 years [29]. Of the 59 patients followed at 4 years, the mean aortic valve area was 1.6 ± 0.4 cm^2 and mean valve gradient was 12.4 + 6.9 mmHg, with 84.5% of patients with either no evident or trace paravalvular leak. At 4 years after implantation, 18 of the 120 enrolled patients (15.0%) died of cardiac

etiology, while 5 suffered disabling stroke (4.2%). No patients had valve thrombosis or a repeat procedure for valve-related dysfunction [29].

While this data allowed for CE approval of the device in Europe and pre-market approval in the US market, subsequent analysis of this high-risk population was expanded utilizing an additional cohort of 130 patients in the REPRISE IIE study [24]. This study utilized the initial cohort of 120 patients from REPRISE II and with the extension cohort was more effectively powered to assess safety and device performance outcomes. The primary safety endpoint was 30-day all-cause mortality in the full cohort of 250 patients. Patient inclusion and exclusion criteria were identical to REPRISE II, following the same procedural protocol and use of core laboratory for assessment.

The data from this extended cohort identified a significant limitation of this delivery system which is the need for post-procedural pacemaker implantation. At 30 days, 32.0% of pacemaker-naïve patients required a new permanent device, 25% of such patients on the day of index procedure, predominantly the result of complete atrioventricular block in 81.9% of cases. In evaluating characteristics of those who required permanent pacing after TAVR in comparison to those who did not suffer this complication, such patients were more likely to have a baseline right bunch branch block (24.7% vs. 4.1%, $p < 0.001$), greater degree of LVOT total calcium volume (OR 1.80 per 100 mm^3 increase; 95% CI, 1.03, 3.14; $p = 0.04$), significant (> 10%) LVOT overstretch (58.0% vs. 38.6%, $p = 0.005$) [24]. Lastly, clinical outcomes did not differ between those with and without need for permanent pacemaker implantation, with no significant difference in 30-day mortality (5.6% vs. 3.9%, $p = 0.73$), 1 year mortality (12.3% vs. 12.6%, $p = 0.96$), LVEF at 30 days (53.2 ± 6.8% vs. 54.8 ± 10.0%, $p = 0.41$), or 1 year (50.9 ± 9.0% vs. 53.4 ± 10.4%, $p = 0.24$) [30]. In aggregate, data from both trial and registry sources demonstrate that nearly one-third of patients required pacemaker implantation and was subsequently corroborated in small- to intermediate-sized independent studies, ranging from 24.0 to 38.4% [30–35].

Given the limited generalizability of the data from REPRISE I and II, the initial prospective data utilizing the Lotus Valve system was released in 2017 from the RESPOND trial [36]. In this prospective, open-label, single-arm study, 1014 patients were enrolled in a post-market registry. Study eligibility was determined by local heart team with agreement for high surgical mortality risk per local standard of practice. The primary endpoint was all cause mortality at 30 days and 1 year compared to pre-specified performance goal of 10%, in addition to a 4% test margin, derived from the FRANCE 2 registry [37].

The mean age was 80.8 ± 6.5 years, with almost equal distribution by gender (50.8% female), mean STS score of 6.0 ± 6.9%, with baseline mean aortic valve gradient of 38.0 ± 15.5 mmHg [36]. This trial utilized CT imaging pre-procedurally to guide annular size, with 23 mm, 25 mm, and 27 mm Lotus Valve sizes available for use. In terms of device safety, successful device delivery and deployment occurred in 98.1% of patients. In the 296 patients (29.2%) that required repositioning of the valve, 99% were successful [36].

In regard to device performance, patients exhibited significant hemodynamic improvement with aortic valve effective orifice area increase from 0.7 ± 0.2 cm^2 at baseline to 1.8 ± 0.4 cm^2 post-TAVR ($p < 0.001$), and mean aortic valve gradient decreased from 37.7 ± 15.2 mmHg at baseline to 10.8 ± 4.6 mmHg at time of discharge ($p < 0.001$). The majority had no evidence of paravalvular leak (92.0%), with only 0.3% of patients having moderate paravalvular leak and 7.7% of patients with mild paravalvular leak [36]. The rates of significant (moderate or severe) paravalvular leak with the Lotus valve compare favorably to equivalent studies of alternative TAVR valves, including 13.1% of patients in the CoreValve ADVANCE registry and 3.5% of patients in the SAPIEN 3 CE Mark Study [38, 39]. Patients also noted significant symptom improvement, as 91% of patients were NYHA class I or II, 78% of patients improved at least one NYHA class, 35% of patients improved at least two NYHA functional classes at 30 days from TAVR implantation [36].

In terms of device safety, the all-cause 30-day mortality rate was 2.6% (95% CI 1.7, 3.8, $p < 0.001$) in comparison to pre-specified performance goal), and the rate of disabling stroke was 2.2%. The clinical outcomes in the RESPOND trial are comparable to equivalent studies of similar risk patients, such as the PARTNER II trial (3.9% mortality rate, mean STS 5.8) and CoreValve SURTAVI trial (2.2% mortality rate, mean STS 4.5) [3, 4, 36]. The continued demonstration of low rates of at least moderate paravalvular leak (0.3%) occurred at the expense of permanent pacemaker implantation rates of 34.6% amongst those studied [36].

Given higher rates of pacemaker implantation after Lotus Valve use in comparison with pre-existing TAVR systems, there has been considerable investment in understanding the mechanistic underpinnings for this outcome. Based on sub-analysis from the REPRISE IIE study, procedural variables including implant depth and degree of LVOT stretch were independent predictors of pacemaker implantation [24]. Thus, careful attention to shortening implant depth (< 5 mm) and appropriate annular sizing were considered impactful interventions within the Lotus system that may serve to mitigate pacemaker implantation [30].

As a result, Boston Scientific introduced Depth Guard technology to the Lotus Valve, aimed at earlier anchoring during deployment and decreased valve frame depth, thus reducing LVOT interaction. This modification, in combination with change in valve implant technique, was evaluated in the RESPOND extension study [25]. In this post-market study, 50 patients underwent TAVR with Lotus Valve with Depth

Guard technology, noting 0.0% 30-day all-cause mortality and very low rates of paravalvular leak (0.3%), with only 8 of the 50 patients (16.0%) requiring permanent pacemaker implantation, markedly less than prior REPRISE data [25].

Most recent trial data from the REPRISE III trial represents the first head-to-head comparison data between TAVR systems [40••]. This prospective, multicenter, randomized controlled trial compared the self-expanding CoreValve TAVR to the mechanically expanding Lotus Edge Valve. Enrolled patients were included based on aortic annular size (20–27 mm) with symptomatic severe aortic stenosis as previously determined by echocardiographic parameters with at least NYHA class II symptoms, and high or extreme surgical risk. Patients were excluded clinically if they had suffered an acute myocardial infarction within 30 days, stroke or TIA within 6 months, gastrointestinal bleeding within 3 months, had untreated coronary artery disease that warranted revascularization, were in cardiogenic shock or otherwise with hemodynamic compromise, had underlying end-stage renal disease (or GFR < 20 by Cockcroft-Gault), had recent invasive cardiac procedure (other than balloon aortic valvuloplasty or pacemaker implantation), or had less than 1-year life expectancy. Patient were also excluded anatomically if they had bicuspid or unicuspid aortic valve; prior valve prosthesis or ring; significant aortic, mitral, or tricuspid regurgitation; inadequate femoral arterial access; or had significant systolic left ventricular function with left ventricular ejection fraction less than 20% [40••]. This study enrolled 912 patients and randomized in a 2:1 fashion to either Lotus versus CoreValve. Each case was reviewed by the interdisciplinary heart team, case review committee, and neurologic examination and was performed after randomization and again after TAVR implantation. Patients were followed by echocardiography and clinically at discharge, 7 days, 30 days, 6 months, and annually for 5 years after TAVR implantation. All patients received either dual antiplatelet therapy or warfarin and either aspirin or clopidogrel for at least 1 month. The primary composite safety endpoint was all-cause mortality, stroke, life-threatening bleeding, the development of stage II or III acute kidney injury, or major vascular complications at 30 days. The primary composite effectiveness endpoint was death, disabling stroke, or significant paravalvular leak (at least moderate) at 1 year.

Regarding demographics, underlying comorbidities, pre-operative risk assessment, and baseline echocardiographic parameters, both groups were similar [40••]. In the full-study population, the mean age was 82.8 (SD, 7.3) years and 51% of patients were women. The mean STS risk was 6.7% in the Lotus group and 6.9% in the CoreValve group, with 23% of patients considered at extreme risk by STS score. There was procedural variability within the study, most notable for the transition to use of the second-generation self-expandable CoreValve during study enrollment; thus, 51.5% of patients received a CoreValve as opposed to the next generation CoreValve EvolutR, with important design changes.

The Lotus Valve demonstrated non-inferiority in regard to the 30-day primary safety endpoint in comparison to the CoreValve system (20.3% vs. 17.2%, 97.5% CI, $-\infty$ to 8.3%; $p = .003$ for non-inferiority), with no significant difference in all-cause mortality (2.5% vs. 2.3%, $p = 0.86$), disabling stroke (4.8% vs. 4.3%, $p = 0.72$), major bleeding (4.8% vs. 5.9%, $p = 0.48$) or acute kidney injury (2.5% vs. 3.6%, $p = 0.34$). The Lotus system met both the non-inferiority and superiority for the 1-year primary effectiveness endpoint (15.4% vs. 25.5%, difference − 10.1%, 97.5% CI, $-\infty$ to − 4.4%; $p < .001$ for non-inferiority and superiority) [40••]. There was a significant difference in the rates of significant paravalvular leak between groups, evident in 6.9% of patients with CoreValve TAVR as opposed to 0.9% in the Lotus TAVR population (6.9% vs. 0.9%, $p < 0.001$), which met both the non-inferiority and superiority for the Lotus TAVR system. Additionally, 81.7% of Lotus TAVR patients had no evidence of paravalvular leak, compared to 39.7% of CoreValve patients. Permanent pacemaker implantation rates were significantly higher in the Lotus TAVR population at 30 days (35.5% vs. 19.6%; 95% CI 9.4, 22.4; $p < 0.001$) and 1 year (41.4% vs. 23.0%; 95% CI 11.5, 25.3; $p < 0.001$) [40••]. Also, patients who received the Lotus Valve were more likely to have had a valve thrombosis event (1.5% versus 0.0%, $p < 0.001$) [40••]. Although rare, this finding was not associated with a difference in neurologic events such as disabling stroke between groups [40••].

Heterogeneous use of CoreValve systems, with some patients within the CoreValve cohort receiving the second-generation Evolut valve, with lower rates of paravalvular leak (2.6% compared to 10.6% with first-generation CoreValve) and pacemaker implantation, in conjunction with non-inclusion of the balloon-expandable Edwards SAPIEN valve has led to questions about the comparator group [41]. Given the continued evolution of the competitor TAVR valve system, this admixture of valve case mix limited this study's external validity to current clinical practice. The discordance between the low safety and efficacy targets for non-inferiority (10.5% and 40%, respectively) in comparison to the actual event rates may have biased towards non-inferiority in REPRISE III. The study investigators argue that the set rates for efficacy and safety were based on pre-existing data that included the initial operator experiences and early device iterations, thus not accounting for the rapid evolution of procedural advancement. Further concern surrounds the inclusion of paravalvular leak in the composite effectiveness endpoint and exclusion of pacemaker implantation in the composite safety outcome.

The initial data on the second-generation Lotus Valve has been presented in the Lotus Edge Feasibility Study and REPRISE Edge study [25, 42]. Patients in this study were of

a lower risk profile in comparison to prior Lotus data, with STS scores of 4.3 ± 1.5 and 4.4 ± 1.9, respectively [25, 42]. In Lotus Edge Feasibility study, 21 patients were enrolled with severe symptomatic aortic stenosis, with the primary endpoint as technical success, defined as successful vascular access, delivery, and deployment of the Lotus Edge Valve system in the proper anatomic position with successful retrieval of the delivery system [25]. The REPRISE Edge study enrolled similar patients; however, its primary endpoint was focused on effectiveness, evaluating the mean aortic valve gradient at discharge. When evaluating these studies as a combined cohort, the technical success rate was 100%, and at 1 year, there was a 0.0% all-cause mortality rate with 5.6% rate of disabling stroke. Similar to prior studies, 76.5% of patients improved symptomatically by at least 1 NYHA class, and there were high rates of non-existent paravalvular leak at discharge (94.2%), at 30 days (91.4%), and at 1 year (97.1%) [43]. Most interestingly, the rate of permanent pacemaker implantation was 15.2% in the combined cohort, almost half of the previously seen complication rate in REPRISE I, II, and III [43]. While these two cohorts represent a small sample size, they are promising for upcoming larger trials currently enrolling utilizing the second-generate Lotus Edge system.

Table 1 delineates the pacemaker implantation rates, incidence of moderate to severe paravalvular leak at 1 year and 30-day mortality rates across contemporary studies utilizing the Lotus Valve system. Upcoming trials to evaluate the second-generation Lotus Edge system are currently enrolling, including REPRISE Edge for high-risk patients, REPRISE IV for intermediate risk and bicuspid aortic valve patients (utilizing Edwards SAPIEN 3 as a comparator), and REPRISE V for low-risk patients.

Discussion

Expected Clinical Impact on Pre-existing TAVR Programs and TAVR Market

As the numbers of those eligible for TAVR grows with evidence to support high-, intermediate-, and low-risk patients, increasing competition will provide operators with the opportunity to make individualized decisions on valve type that may be more suitable for certain patients. Additionally, the consistent trend toward favorable outcomes for TAVR has analysts expecting significant growth in the TAVR market to US$12.2 billion globally by 2025 [44].

The major appeal to the Lotus system is the near abolishment of clinically relevant paravalvular leak. Long-term outcomes from PARTNER trial data demonstrated that moderate to severe paravalvular leak occurred in 14% of patients and was associated with increased 5-year risk of mortality (72·4 versus 56·6%; $p = 0{\cdot}003$) [10]. This may prove to be most relevant to those who pose significant risk for paravalvular leak due to anatomic constraints, including those with asymmetric and significant calcification burden, large LVOT-ascending aorta angle, and those with significant annular eccentricity indices [45].

The major barrier to integration of the Lotus Valve into the TAVR market is the disproportionate rates of permanent pacemaker implantation, seen in almost one-third of patients. Post-market data from the RESPOND extension study and EDGE feasibility study demonstrated lower rates of pacemaker implantation at 18.0% and 10.8%, respectively [25, 42]. While there is ongoing refinement of the procedural aspects of the procedure and the device delivery with the Lotus Edge system, clinical data is needed to support decreasing rates of pacemaker implantation in a large, randomized cohort.

Table 1 A summary of the contemporary studies on the Lotus Valve system from 2014 to 2018, comparing permanent pacemaker implantation rates, incidence of at least moderate paravalvular leak, and 30-day mortality rate

Study (data)	N	All-cause moratality at 30 days (%)	Moderate to severe PVL (%)	PPM implantation (%)
REPRISE I (2014)	11	0.0	0.0	36.4
REPRISE II (2014)	120	4.2	1.0	30.4
Gooley et al. (2015)	50	2.0	0.0	28.0
Rampat et al. (2016)	228	1.8	0.8	31.8
Nordic Lotus (2016)	154	1.9	0.6	27.9
Worhle et al. (2016)	110	0.9	0.0	24.1
Pilgrim et al. (2017)	140	2.2	0.7	38.4
REPRISE IIE (2017)	250	4.0	0.6	32.0
RESPOND (2017)	996	1.9	0.3	35.5
REPRISE III	601	4.0	0.9	35.5
RESPOND Extension (2018)	50	0.0	N/A	18.0
Lotus Edge FIM (2018)	21	0.0	0.0	10.2

Additionally, with the advent of favorable data in low-risk patients from PARTNER 3 and CoreValve low risk released in 2019, proceduralists and patients alike will be looking towards lower procedural complications as more patients will be offered transcatheter options. This may limit the use of Lotus Valve systems if permanent pacemaker rates remain high in comparison to balloon-expandable and self-expandable TAVR systems, unless the patient has a pre-existing permanent pacemaker. Recent evaluation of long-term outcomes in patients with permanent pacemaker implantation after TAVR were more likely to be have recurrent hospitalization due to heart failure, less likely to have improvement in left ventricular ejection fraction, however had similar mortality rates to those without pacemaker implantation [46].

While previously considered a contraindication to TAVR, patients with bicuspid aortic stenosis are being treated both off label and within clinical trials for this entity. Although this population is younger, and inherently lower risk, prior TAVR use in bicuspid anatomy has been fraught with significant post-procedural moderate to severe paravalvular leak, and the Lotus system will need to be evaluated as a potential alternative for this indication [47]. The controlled expansion provided by the mechanical Lotus apparatus can reduce the risk of elliptical deployment. This mechanism, in conjunction with an adaptive seal that could serve to address paravalvular leak across variable annular anatomy and the ability to reposition prior to final deployment, may prove to of value. Rigorous evaluation in clinical trials will need to be performed prior to its use for this indication.

Given the enthusiasm for TAVR program development, there has been considerable discussion regarding the impact of operator experience, the need for outcomes tracking and the expected requirements for new and ongoing TAVR programs nationally. Existing TAVR programs will be expected to demonstrate competency, in terms of both volume and outcomes [48]. Such guidelines may favor operators with experience utilizing pre-existing TAVR systems to continue to optimize technique as opposed to adopt new delivery systems in an effort to maintain adequate outcomes and support TAVR program growth.

With the introduction of a third competitor into the US TAVR market, the dynamics will be interesting to observe. In large volume TAVR programs, the introduction of another valve may be more easily adopted given the ability to quickly overcome challenges of learning curves and operator experience. With purported benefits of significant reduction in paravalvular leak rates and with lower reported permanent pacemaker rates in next generation technology, larger programs may be able to gain experience and offer this technology in a more streamlined fashion. With a large number of smaller TAVR programs performing less than 40–50 procedures per year in the US, consideration must be given to the value of adding a third valve option to individual lower volume programs. The inability to overcome a learning curve in short order or to become facile with a particular device in a low-volume setting, may hinder its practical adoption in the vast majority of lower volume sites. The alternative to having three valves available is to simply replace a currently used valve type in favor of a mechanically expanding Lotus Valve. This may be a viable strategy in lower volume programs looking to introduce this valve technology so implanting teams can focus more on optimizing learning experience and case volume.

Compliance with Ethical Standards

Conflict of Interest Matthew E. Seigerman and Ashwin Nathan declare that they have no conflict of interest.

Saif Anwaruddin reports the following: Consultant/Speaker/Advisory Board: Medtronic; Consultant/Speaker/Proctor: Edwards; and DSMB: Cardiovascular Research Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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