

Use of a Repositionable and Fully Retrievable Aortic Valve in Routine Clinical Practice



The RESPOND Study and RESPOND Extension Cohort

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ABSTRACT

OBJECTIVES The authors sought to evaluate 1-year clinical outcomes with the Lotus valve (Boston Scientific, Marlborough, Massachusetts) in a large international, multicenter prospective registry including patients eligible for transcatheter aortic valve replacement (TAVR) based on heart team consensus.

BACKGROUND TAVR is a safe and effective treatment for severe aortic valve stenosis; however, limited data are available on TAVR with the repositionable and fully retrievable Lotus valve in unrestricted contemporary clinical practice.

METHODS The RESPOND (Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes) study enrolled 1,014 patients; 996 patients were implanted with the Lotus valve (mean age 80.8 years, 50.8% female, mean STS score $6.0 \pm 6.9\%$). The primary endpoint was all-cause mortality in the intent-to-treat population at 30 days and 1 year. An Extension cohort of 50 patients was treated with the Lotus valve with Depth Guard including a modified delivery system. Mortality and stroke were independently adjudicated. An independent core laboratory assessed echocardiographic data.

RESULTS One-year clinical follow-up was available for 99.9% of Lotus valve-treated patients. At 1 year, the all-cause mortality rate was 11.7% and 4.1% of patients had experienced a disabling stroke. The permanent pacemaker implantation rate was 32% (37% among pacemaker-naïve patients). Echocardiographic data at 1 year were available for core laboratory assessment in 62.6% of patients. Paravalvular leak was absent or trace in 94.5%, mild in 5.1%, and moderate in 0.4% of patients. Data from the Extension cohort confirmed good clinical outcomes at 30 days with an 18% permanent pacemaker rate (20% among pacemaker-naïve patients).

CONCLUSIONS One-year outcomes from the RESPOND study confirm the safety and efficacy of the Lotus valve when used in routine clinical practice. (Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes [RESPOND]; [NCT02031302](https://doi.org/10.1016/j.jcin.2018.10.052)) (J Am Coll Cardiol Intv 2019;12:38–49) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Transcatheter aortic valve replacement (TAVR) is a safe and effective treatment for patients with symptomatic severe aortic stenosis at intermediate or high surgical risk (1–5). With the expansion of TAVR eligibility to include lower-risk patients, management of procedure-related complications is increasingly important, along with a focus on longer-term outcomes.

Common complications of TAVR include vascular complications, bleeding, valve malpositioning, residual paravalvular leak (PVL) between the native annulus and prosthetic valve frame, and new-onset conduction disturbances. The design of the Lotus valve (Boston Scientific, Marlborough, Massachusetts) helps to mediate a number of these complications. Notably, Lotus uses controlled mechanical expansion to permit optimal placement of the valve, making it fully repositionable and retrievable, and has a unique adaptive seal designed to minimize PVL (6,7). Recent changes to the valve design include the addition of Depth Guard technology, which limits the depth of the valve frame during deployment, reducing the interaction of the valve with the left ventricular outflow tract (LVOT) and conduction system.

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The REPRISE (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System) I and II studies demonstrated the safety and efficacy of TAVR with the Lotus valve in patients at high risk for surgical valve replacement (8,9). The recent REPRISE III (Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement) randomized controlled trial demonstrated comparable safety and efficacy with the Lotus valve and a self-expanding TAVR valve, with significantly less paravalvular regurgitation with the Lotus valve, albeit a greater need for permanent pacemaker implantation (10).

The RESPOND (Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes) post-market registry is unique in that it

evaluated TAVR with the Lotus valve in a large population representative of current clinical practice. Patients in the RESPOND study had excellent clinical outcomes at 30 days, with low rates of all-cause mortality and major/disabling stroke (2.6% and 2.2%, respectively), and negligible PVL (no patients had severe PVL, and moderate PVL was present in only 0.3% of patients at hospital discharge) (11). Approximately one-third of patients required a new pacemaker at 30 days.

Here, we report 1-year outcomes from the RESPOND study, the largest population to date treated with the Lotus valve in clinical practice. Additionally, we report 30-day outcomes from an extension cohort of the RESPOND study treated with the next-generation Lotus valve with Depth Guard.

METHODS

STUDY AND DEVICE DETAILS. The RESPOND study, a prospective, open-label, post-market registry at 41 centers in Europe, New Zealand, and Latin America, enrolled 1,014 patients with symptomatic aortic stenosis at elevated risk of serious surgical morbidity or mortality, per heart team consensus. Study eligibility, enrollment, and data collection in the main patient cohort have been previously described (11). Following completion of enrollment in the main cohort, the RESPOND study also enrolled an Extension cohort ($n = 50$), which allowed for short-term assessment of a modified delivery system and center-driven implantation technique, both intended to reduce pacemaker implantation risk. Patients in the Extension cohort were enrolled at 6 centers in the Netherlands, United Kingdom, and Poland.

The protocol was approved by the locally appointed institutional review boards/ethics committees; the study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles

ABBREVIATIONS AND ACRONYMS

ITT = intent-to-treat

LVOT = left ventricular outflow tract

NYHA = New York Heart Association

PVL = paravalvular leak

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

fees from Boston Scientific and Edwards Lifesciences. Dr. Hildick-Smith has received personal fees from Boston Scientific, Medtronic, and Edwards Lifesciences. Dr. Bleiziffer has received personal fees from Medtronic, Boston Scientific, and JenaValve. Dr. Blackman has received grants and personal fees from Boston Scientific. Dr. Abdel-Wahab has received personal fees from Boston Scientific; and grants from St. Jude Medical and Biotronik. Dr. Gerckens has received personal fees from Boston Scientific and Medtronic as a consultant and proctor. Dr. Linke has received personal fees from Medtronic, Boston Scientific, Edwards Lifesciences, Abbott, Claret Medical (a subsidiary of Boston Scientific), Transverse Medical; has been a consultant for AstraZeneca; has received speaker fees from Edwards Lifesciences, Boston Scientific, Medtronic, Abbott, AstraZeneca, Bayer, and Novartis; and owns stock options from Claret Medical, Transverse Medical Inc., and Emboline. Dr. Ince has received grants from Boston Scientific. Dr. Wenaweser has been a proctor for Boston Scientific, Medtronic, and Edwards Lifesciences. Drs. Allocco and Meredith are employees of and shareholders in Boston Scientific. Dr. Falk has received grants from Boston Scientific, Philips, HeartWare, Berlin Heart, Biotronik, and Edwards Lifesciences; and consulting, lecture, speaking, and other fees from Abbott, Medtronic, and Novartis.

outlined in the Declaration of Helsinki. The study was sponsored by Boston Scientific Corporation and registered with ClinicalTrials.gov (NCT02031302). 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 on the Boston Scientific website. All patients gave written informed consent.

The Lotus valve, a bioprosthetic aortic valve comprising a braided nitinol wire frame with 3 bovine pericardial leaflets, is pre-mounted on a pre-shaped delivery catheter and deployed via controlled mechanical expansion. A detailed description of the implantation procedure is provided elsewhere (6,7,9). A polymer membrane surrounds the lower half of the Lotus valve and reduces PVL by filling the space between the native annulus and the prosthetic valve frame. To provide hemodynamic stability, the Lotus valve functions early in the deployment process, and rapid pacing is not required. Repositioning or retrieval of the valve is possible at any point before uncoupling and release. The RESPOND study evaluated Lotus valve sizes of 23 mm, 25 mm, and 27 mm, for implantation in native annulus sizes ≥ 20 mm to ≤ 27 mm. The Extension cohort was treated with the Lotus valve with Depth Guard. The Depth Guard technology modifies the way the valve is deployed by ensuring early anchoring of the lowest edge of the Lotus valve in the LVOT, and aims to reduce the interaction of the valve with the LVOT and conduction system. In the RESPOND Extension cohort, only the 23-mm and 25-mm valves were available.

OUTCOMES MEASURES. Endpoints were assessed according to Valve Academic Research Consortium (VARC)-2 metrics (12). The primary endpoint of the RESPOND study was all-cause mortality in the intent-to-treat (ITT) population at 30 days and 1-year post-procedure; the primary endpoint for the Extension cohort was all-cause mortality in implanted patients at 30 days post-procedure. Secondary outcomes measured included clinical efficacy and valve safety, and the degree of aortic valve regurgitation. An independent medical reviewer adjudicated all-cause mortality and stroke events. An independent core laboratory (Cardialysis Core Laboratory, Rotterdam, the Netherlands) evaluated all available echocardiography studies at baseline, discharge, and 1-year follow-up for Lotus valve hemodynamic performance and grade of aortic valve regurgitation according to VARC-2 criteria.

STATISTICAL METHODS. The analysis population for the primary endpoint is the ITT population (all enrolled subjects where there was an attempt to

implant the Lotus valve, regardless of whether the Lotus valve was successfully implanted). The analysis population for secondary outcomes includes only subjects who had a Lotus valve implanted (as-treated population). Data from the Extension cohort were not pooled with the main cohort for any data analyses.

Baseline and outcome variables were summarized using descriptive statistics. All *p* values were 2-sided and were derived from either a 1-sample exact binomial test (for safety endpoints), a generalized McNemar's test (for improvement in New York Heart Association [NYHA] functional classification), or a paired *t*-test analysis (for change in hemodynamic parameters among patients with echocardiographic data available at both specified time points). Echocardiographic data collected for each subject during the study was independently analyzed by the core laboratory in order to control for interobserver variability and minimize bias and inconsistencies. No imputation of missing data was performed.

Univariate and multivariate analyses were performed to identify potential predictors for mortality at 1 year. The significance level thresholds for entry and exit of independent variables into the multivariate model were set at 0.1. Parameters with *p* < 0.05 were considered as potential predictors from the multivariate stepwise regression model.

RESULTS

RESPOND STUDY PARTICIPANTS AND BASELINE CHARACTERISTICS. The RESPOND main cohort enrolled 1,014 patients between May 2014 and February 2016; the as-treated population included 996 patients who were treated with a Lotus valve. No patient discontinued follow-up prematurely or withdrew from the study. Baseline patient and echocardiographic characteristics for the main cohort were as described in the 30-day outcomes paper (11), and are presented in brief in Table 1.

CLINICAL OUTCOMES. The rates of all-cause mortality in the ITT population (N = 1,014) at 30 days and 1 year were 2.6% and 12.0%, respectively (primary endpoint, calculated per protocol as binary rates; *p* < 0.001 vs. pre-specified performance goal at 30 days). One-year follow-up data were collected from nearly all patients with a Lotus valve implanted (995 of 996; 99.9%); the minimum follow-up time was 1 year for all patients in this analysis (median [interquartile range] follow-up was 389 [363 to 721] days) (Figure 1A). The cumulative all-cause mortality rate at 1 year was 11.7% (Figure 2, Table 2). In a post hoc subgroup analysis, patients with a higher left

TABLE 1 Baseline Clinical and Echocardiographic Characteristics for the RESPOND As-Treated Population (N = 996)

Age, yrs	80.8 ± 6.5
Female	50.8
STS score*	6.0 ± 6.9
Katz Index Activities of Daily Living Score	5.6 ± 1.0
Diabetes mellitus, medically treated	22.4
COPD, moderate or severe	7.7
NYHA functional class III or IV	69.5
Atrial fibrillation, history	33.9
Coronary artery disease, history	56.1
Prior PCI	29.8
Prior CABG	12.3
Cerebrovascular accident, history	9.5
Prior implanted pacemaker	13.3
Echocardiographic assessments—core lab	
Aortic valve area (effective orifice area), cm ²	0.7 ± 0.2
Mean aortic valve gradient, mm Hg	38.0 ± 15.5
Peak aortic valve gradient, mm Hg	61.9 ± 24.2
Left ventricular ejection fraction, %	49.8 ± 10.5
Aortic regurgitation, moderate or severe†	11.7

Values are mean ± SD or %. *Risk scores were not routinely collected/reported by all study centers. †Severe in 14 patients (1.5%).

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial; STS = Society of Thoracic Surgeons.

ventricular ejection fraction (i.e., >40%) at baseline had a lower likelihood of death at 1 year, whereas history of chronic obstructive pulmonary disease, dialysis-dependent renal failure, or atrial fibrillation were found to be significantly associated with greater mortality (Figure 3).

The rate of disabling stroke at 1 year was 4.1%; 17 patients (1.7%) had experienced a disabling stroke after 30 days. At 1 year, 319 patients had a permanent pacemaker implanted (32.3% among all patients; 37.2% among patients who did not have a pacemaker at baseline); a total of 20 patients required a new pacemaker after 30 days. Additional 1-year safety outcomes for the as-treated population are shown in Table 2.

ECHOCARDIOGRAPHIC OUTCOMES. Transthoracic echocardiography assessment at 1 year was available for core laboratory evaluation in 62.6% of RESPOND patients (551 of 880 surviving patients) and demonstrated that the improvement in valve hemodynamics observed post-TAVR was sustained at 1 year (Figure 4). Aortic valve area (effective orifice area) improved from 0.7 ± 0.2 cm² at baseline to 1.8 ± 0.5 cm² at discharge and 1.8 ± 0.4 cm² at 1 year ($p < 0.001$ vs. baseline). Mean aortic valve gradient declined from 38.0 ± 15.5 mm Hg at baseline to 10.8 ± 4.6

mm Hg at hospital discharge ($p < 0.001$ vs. baseline), and remained 10.8 ± 5.1 mm Hg at 1 year ($p < 0.001$ vs. baseline; $p = 0.42$ vs. discharge). PVL was absent or trace in 94.5% of patients at 1 year (Figure 5A). There were no patients with severe PVL; 0.4% of patients exhibited moderate PVL, and 5.1% of patients had mild PVL. Paired analysis of the change in PVL over time was performed in patients with available transthoracic echocardiography at discharge and 1 year ($n = 531$). Mild or less PVL was recorded at hospital discharge in 528 of the patients in the analysis and was maintained over the course of the year; only 1 patient (0.2%) was assessed as having moderate PVL at 1 year. Conversely, of the 3 patients in the analysis with moderate PVL at discharge, 2 (66.7%) exhibited only mild PVL at 1 year.

NYHA FUNCTIONAL STATUS AND HEALTH STATUS.

At baseline, 62.4% of patients were NYHA functional class III; an additional 7.1% were class IV (Figure 6A). The significant improvement in NYHA functional class at 30 days post-procedure was maintained at 1 year, with nearly 90% of surviving patients classified as NYHA functional class I or II; 79% and 31% of patients had improved at least 1 or 2 classes, respectively, relative to baseline ($p < 0.001$ for both). Health-related quality of life, as measured by the self-rated EuroQoL EQ-5D questionnaire, was significantly improved from baseline at 30 days post-procedure, with improvements sustained through 1 year (Table 3). The change in patients' self-reported score on the Visual Analog Scale was representative of a clinically meaningful change in overall quality of life (13).

RESPOND EXTENSION COHORT. The RESPOND Extension cohort enrolled 50 patients between June 2016 and October 2016 (Figure 1B); baseline patient and echocardiographic characteristics are shown in Table 4. Patients enrolled in the Extension cohort were generally similar to those in the main study cohort, with the exception of having a slightly lower baseline Society of Thoracic Surgeons (STS) score. Successful vascular access, delivery, and deployment, and successful retrieval of the delivery system were achieved in 100% of patients. Valve repositioning was attempted in 16 of 50 patients (32%), with 100% success.

Thirty-day clinical follow-up was available for all patients. There were no procedural deaths, and no deaths at 30 days. The overall stroke rate was 6.0%; 2.0% of patients experienced a disabling stroke. The permanent pacemaker implantation rate at 30 days was 18.0% among all patients, and 20.0% among patients who did not have a pacemaker at baseline.

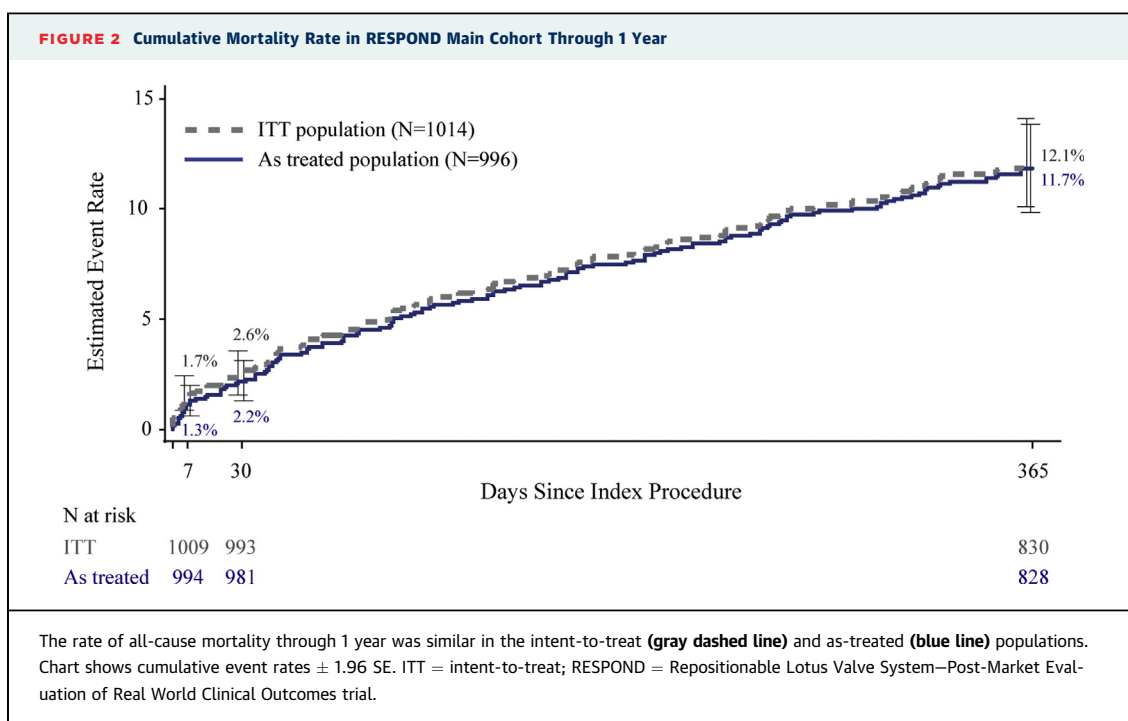
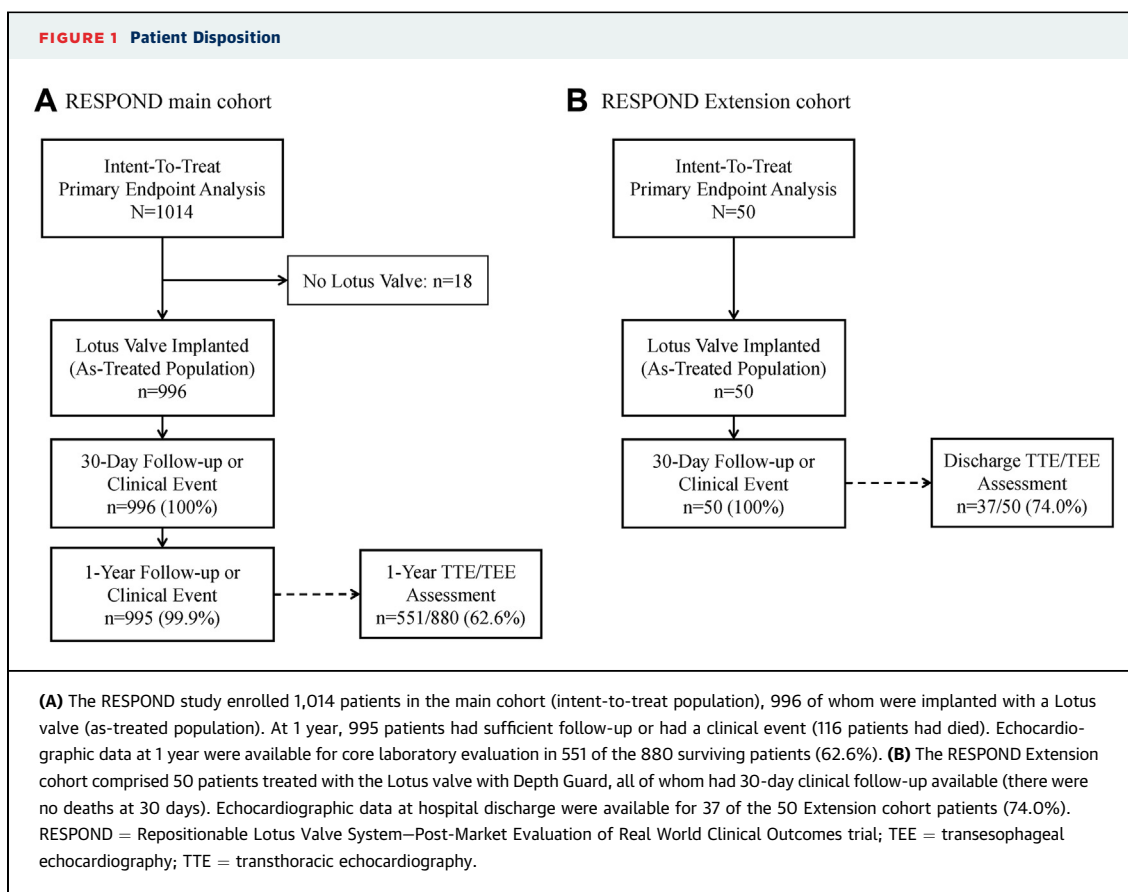


TABLE 2 Clinical Outcomes at 1 Year in the RESPOND As-Treated Population (N = 996)

All-cause mortality	116 (11.7)
Cardiovascular mortality	74 (7.6)
All stroke	48 (4.9)
Disabling stroke	40 (4.1)
Major vascular complications	34 (3.4)
Life-threatening or disabling bleeding	35 (3.6)
Acute kidney injury (stage 2 or 3)	17 (1.7)
Myocardial infarction	18 (1.9)
Repeat procedure for valve-related dysfunction	2 (0.2)
Hospitalization for valve-related symptoms or CHF	78 (8.3)
New onset atrial fibrillation or atrial flutter	33 (3.3)
Prosthetic valve thrombosis	8 (0.8)
Prosthetic valve endocarditis	13 (1.4)
Permanent pacemaker implantation	
Among all patients	319 (32.3)
Among patients without pacemaker at baseline (n = 864)	319 (37.2)

Values are n (%) based on Kaplan-Meier rates.

CHF = congestive heart failure; RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial.

Additional safety outcomes for the RESPOND Extension cohort are shown in Table 5.

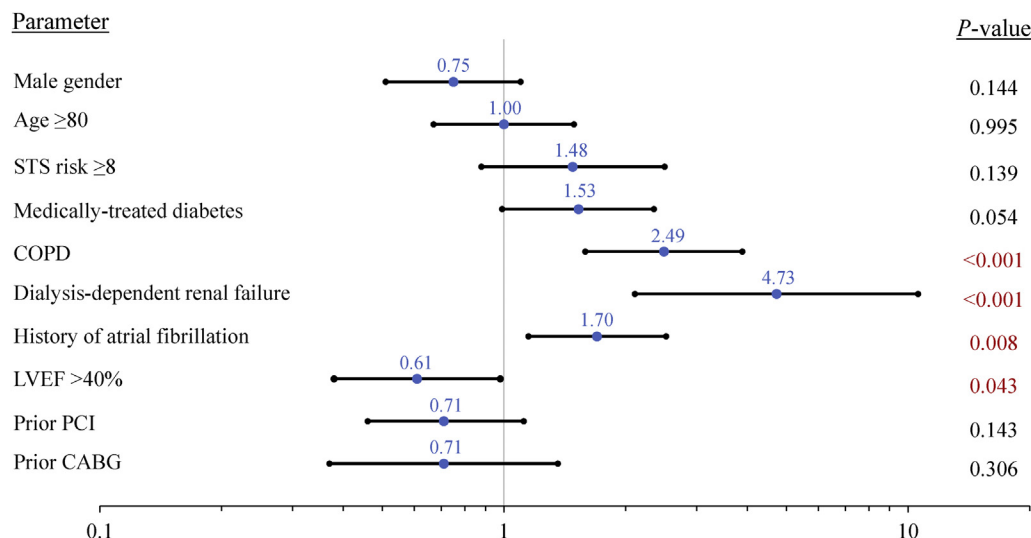
Echocardiographic data at hospital discharge were available for 37 of 50 patients (74%). Aortic valve area (effective orifice area) was $0.7 \pm 0.2 \text{ cm}^2$ at baseline

and $1.7 \pm 0.3 \text{ cm}^2$ at discharge ($p < 0.001$). Mean aortic valve gradient declined from $39.8 \pm 13.7 \text{ mm Hg}$ at baseline, to $11.8 \pm 4.4 \text{ mm Hg}$ at discharge ($p < 0.001$). There were no patients in the Extension cohort with moderate or severe PVL; 86.5% of patients exhibited no or trace PVL, and 13.5% of patients had mild PVL (Figure 5B). At baseline, 51.0% of patients were NYHA functional class III, and 2.0% were class IV (Figure 6B). At 30 days post-procedure, over 95% of surviving patients were classified as NYHA functional class I or II, with 72.3% and 27.7% of patients having improved at least 1 or 2 classes, respectively ($p < 0.001$ for both).

DISCUSSION

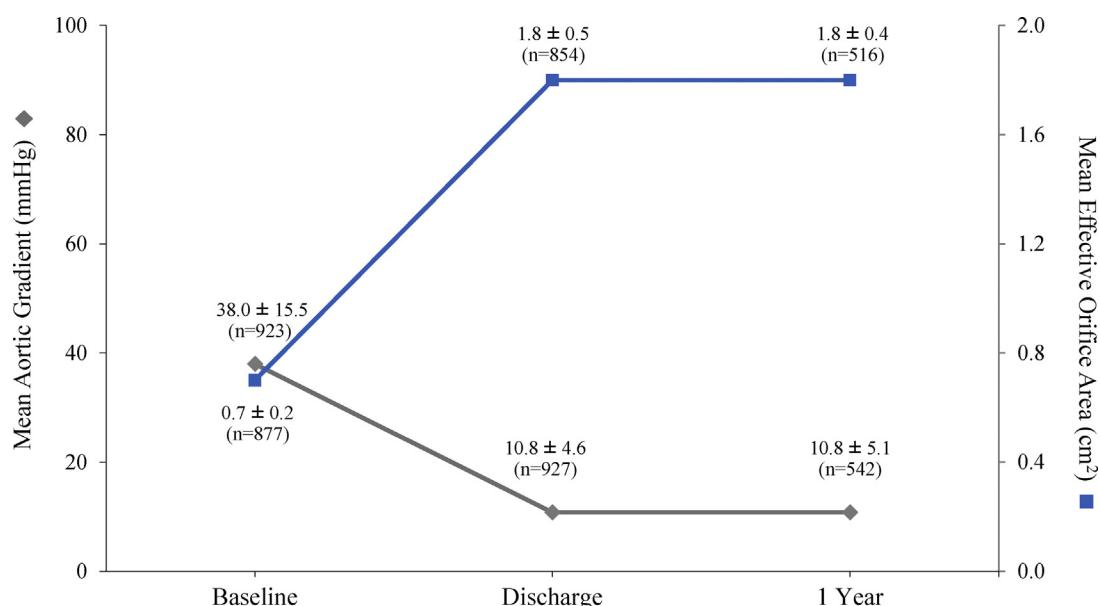
One-year outcomes from the RESPOND study confirm the safety and efficacy of the Lotus valve when used in contemporary clinical practice (Figure 7). The mortality rate in the implanted population was 11.7%, and patients maintained excellent valve hemodynamics with minimal paravalvular regurgitation. One-year post-TAVR, 99.8% of patients who had been assessed as having mild or less PVL at hospital discharge maintained mild or less PVL over the course of the year; no patients had severe PVL, and only 0.4% of patients exhibited moderate PVL.

FIGURE 3 1-Year Mortality Across Patient Subgroups in the RESPOND Main Cohort



An analysis was performed across different patient subgroups to identify baseline variables potentially associated with death at 1 year; p value is from the Wald test. CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial; STS = Society of Thoracic Surgeons.

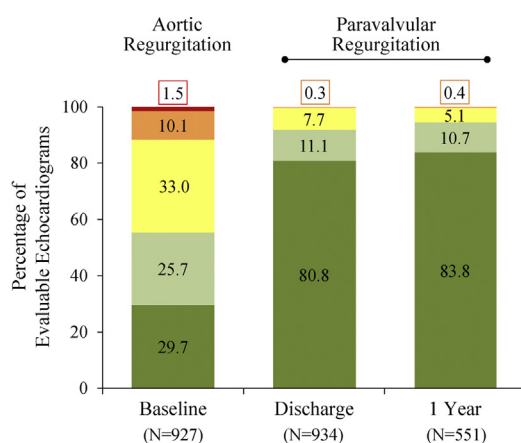
FIGURE 4 Valve Hemodynamics in the RESPOND Main Cohort



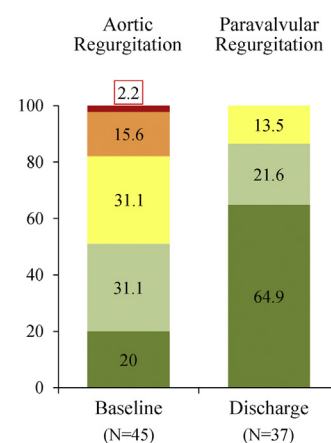
Improvements from baseline in mean aortic valve pressure gradient and mean aortic valve area were maintained at 1 year ($p < 0.001$ for both). Echocardiographic data were independently assessed by a core laboratory. Data are mean ± SD; p values are derived from a paired t -test analysis among patients with data available at both baseline and 1 year. RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial.

FIGURE 5 Aortic Valve Regurgitation

A RESPOND main cohort



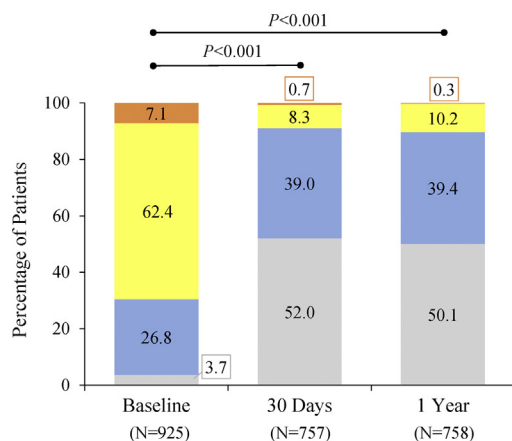
B RESPOND Extension cohort



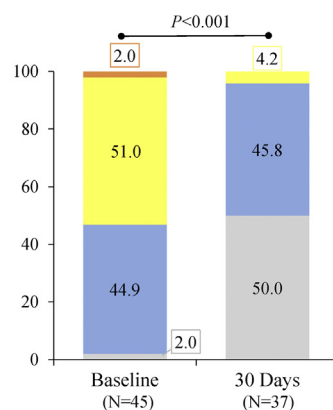
Echocardiographic data were independently assessed by a core laboratory in the RESPOND main cohort (**A**) at baseline, hospital discharge, and 1 year post-procedure, and in the RESPOND Extension cohort (**B**) at baseline and hospital discharge. In both cohorts, the majority of patients exhibited no/trace paravalvular leak (PVL) following Lotus valve implantation. RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial.

FIGURE 6 Change in NYHA Functional Status

A RESPOND main cohort



B RESPOND Extension cohort



(A) In the RESPOND main cohort, the improvement in NYHA functional class at 30 days post-procedure was maintained at 1 year. (B) The majority of patients in the RESPOND Extension cohort also exhibited improved NYHA functional status at 30 days. NYHA status was not recorded at all sites for all patients. Improvement from baseline to 30 days or 1 year was evaluated for patients with data available at both time points; p value is from a generalized McNemar's test. NYHA = New York Heart Association; RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial.

The 1-year survival data from the RESPOND study are comparable to 1-year clinical outcomes in other large TAVR trials/registries of patients with similar risk (mean baseline STS score in the RESPOND study was 6.0%). In the PARTNER 2A (Placement of AoRTic TraNscatheter Valves) intermediate-risk patient cohort (N = 1,011; mean STS: 5.8%) (4) mortality at 1 year was 12.3% in patients treated with the SAPIEN XT valve (Edwards Lifesciences, Irvine, California), and 3.4% of patients had moderate PVL. Patients treated transfemorally with the SAPIEN 3 valve in the SOURCE 3 (Observational Study to Evaluate Safety and Performance of SAPIEN 3 THV System in Real Life Practice) post-market registry (N = 1,694; median logistic EuroSCORE 13.96) (14) had a 12.6% mortality

rate at 1 year, and moderate PVL was observed in 2.7% of patients (an increase from the 1.2% observed at discharge). In a multivariate analysis of the SOURCE 3 data, the strongest baseline characteristics predictive of 1-year mortality were log EuroSCORE, renal insufficiency, moderate to severe tricuspid regurgitation, and atrial fibrillation. Among patients treated with the CoreValve System (Medtronic, Minneapolis, Minnesota) in the ADVANCE registry (CoreValve Advance International Post Market Study) (N = 1,015; median STS: 5.3%) (15), mortality was 17.9% at 1 year, and 12% of patients had moderate or greater PVL. And in the large, multivalve GARY registry (German Aortic Valve Registry) (16), patients who underwent transvascular TAVR (N = 2,694; mean log EuroSCORE

TABLE 3 Health Status in RESPOND Main Cohort as Evaluated by EQ-5D Quality of Life Questionnaire

	Baseline	30 Days	1 Year	p Value		
				Baseline to 30 Days	30 Days to 1 Year	Baseline to 1 Year
EQ-5D Index values (U.K.-based population algorithm)	0.64 ± 0.24 (715)	0.71 ± 0.26 (720)	0.71 ± 0.26 (704)	<0.001	0.946	<0.001
EQ Visual Analog Scale	57.2 ± 18.0 (719)	66.7 ± 19.0 (719)	68.0 ± 18.2 (707)	<0.001	0.172	<0.001

Values are mean ± SD (n). p value is from a paired t-test for continuous variables.

EQ-5D = EuroQol 5D; RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial.

TABLE 4 Baseline Clinical and Echocardiographic Characteristics for RESPOND Extension Cohort (N = 50)

Patient characteristics	
Age, yrs	80.9 ± 8.2
Female	54
STS score*	4.4 ± 3.1
Katz Index Activities of Daily Living Score	5.9 ± 0.4
Diabetes mellitus, medically treated	30
COPD, moderate or severe	2
NYHA functional class III or IV	52
Atrial fibrillation, history	34
Coronary artery disease, history	62
Prior PCI	28
Prior CABG	14
Cerebrovascular accident, history	12
Prior implanted pacemaker	10
Echocardiographic assessments, core lab	
Aortic valve area (effective orifice area), cm ²	0.7 ± 0.2
Mean aortic valve gradient, mm Hg	39.8 ± 13.7
Peak aortic valve gradient, mm Hg	64.0 ± 19.5
Left ventricular ejection fraction, %	50.2 ± 9.3
Aortic regurgitation, moderate or severe†	17.8
Procedural characteristics	
Valve system implanted	
23 mm	17 (34)
25 mm	33 (66)
Vascular access	
Transfemoral	48 (96)
Transaortic	2 (4)
Subclavian	0 (0)

Values are mean ± SD, %, or n (%). *Risk scores were not routinely collected/ reported by all study centers. †Severe in 1 patient (2.2%).
Abbreviations as in Table 1.

TABLE 5 Clinical Outcomes at 30 Days in the RESPOND Extension Cohort (N = 50)

All-cause mortality	0 (0)
Cardiovascular mortality	0 (0)
All stroke	3 (6)
Disabling stroke	10 (2)
Major vascular complications	1 (2)
Access site related	1 (2)
Life-threatening or disabling bleeding	0 (0)
Acute kidney injury (stage 2 or 3)	1 (2)
Myocardial infarction	0 (0)
Repeat procedure for valve-related dysfunction	0 (0)
Hospitalization for valve-related symptoms or CHF	0 (0)
Prosthetic aortic valve malapposition*	0 (0)
Coronary obstruction (periprocedural)	0 (0)
Cardiac tamponade (periprocedural)	0 (0)
Prosthetic valve thrombosis	0 (0)
Prosthetic valve endocarditis	0 (0)
New onset atrial fibrillation or atrial flutter	2 (4)
Permanent pacemaker implantation	
Among all patients (n = 50)	9 (18)
Among patients without pacemaker at baseline (n = 45)	9 (20)

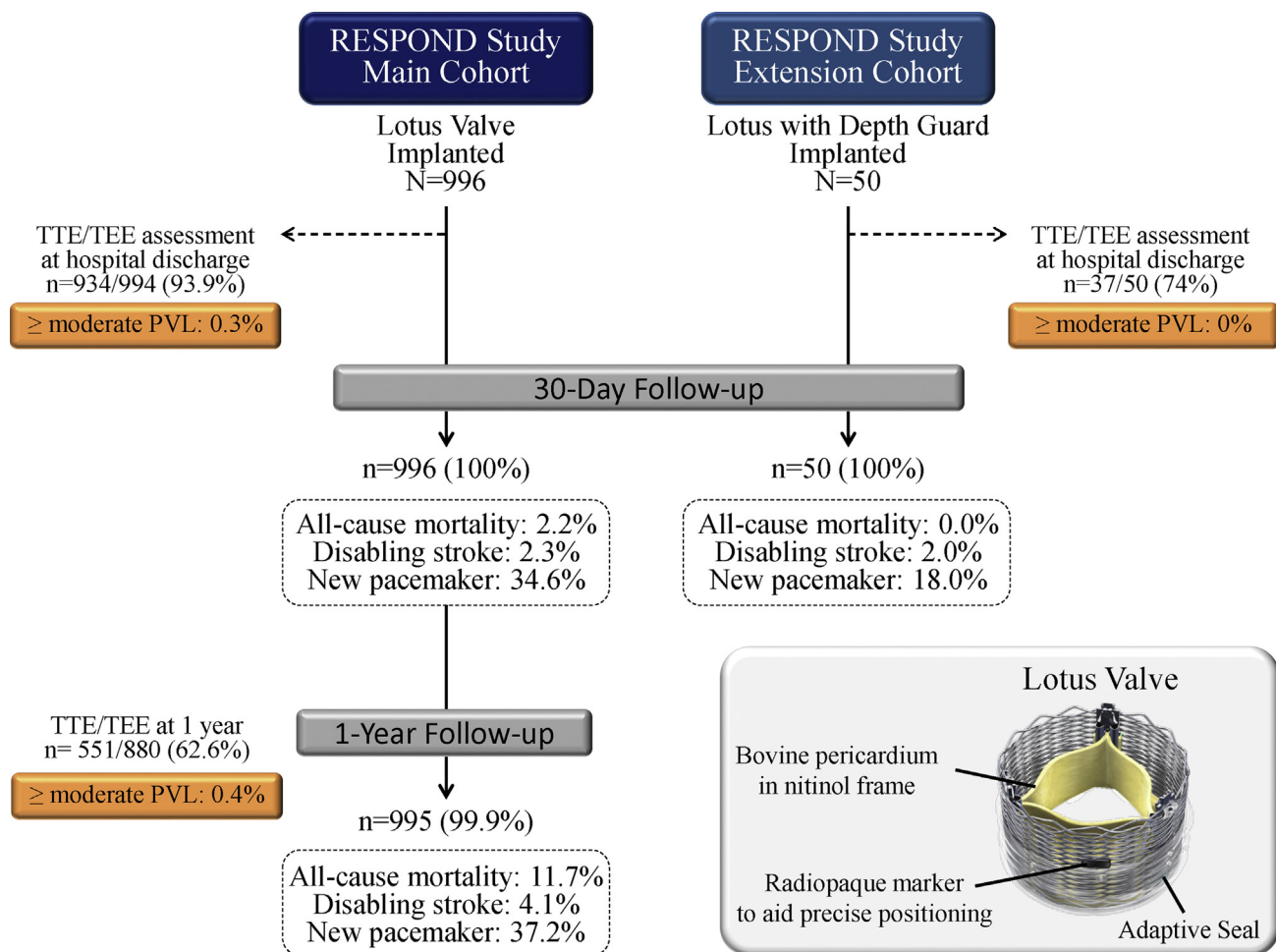
Values are n (%) and are binary rates among patients with sufficient clinical follow-up or death, or who had an adverse event. *Includes valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment.
Abbreviations as in Table 2.

25.9%) had a 1-year mortality rate of 20.7%. Although this higher mortality rate reflects a somewhat earlier TAVR experience (procedures were performed in 2011), data from the GARY registry do provide insight into the influence of PVL on mortality: long-term survival was worst in patients with severe PVL (50.0%), and patients with mild PVL had greater mortality (25.3%) compared with those with trace (23.3%) or no (21.2%) PVL.

The outcomes in the RESPOND population are also comparable to those recently observed with the Lotus valve in the REPRISÉ III randomized controlled trial (N = 607; mean STS 6.7) (Figure 8) (10). In the REPRISÉ III study, the cumulative 1-year mortality rate in Lotus-treated patients was 11.4%, 4.0% of patients had experienced a disabling stroke, and moderate PVL was observed in 0.9% of patients. The rates of major vascular complications or bleeding were numerically lower in the RESPOND study compared with REPRISÉ III, which may reflect a

greater familiarity and experience with the Lotus valve among operators in the RESPOND study compared with the REPRISÉ III study. Because the RESPOND study was a post-market registry, most operators had experience implanting the Lotus valve before enrolling patients. By contrast, most REPRISÉ III sites did not have prior experience with the Lotus valve before enrolling patients in the trial. Additionally, patients in the REPRISÉ III study were slightly older and had a slightly higher STS score at baseline compared with patients in the RESPOND study. Such differences in baseline risk may also have contributed to the lower rates of vascular complications and bleeding events in the RESPOND study. A higher overall stroke rate was recorded in the REPRISÉ III study compared with the RESPOND study, perhaps due to differences in reporting requirements (the REPRISÉ III protocol specified a neurological exam at discharge and 1 year; the RESPOND protocol did not). These differences aside, the similarity in the overall performance of the Lotus valve in the highly selected REPRISÉ III population versus the RESPOND registry, which more closely approximates unrestricted

FIGURE 7 Key Findings From the RESPOND Study and RESPOND Extension Cohort



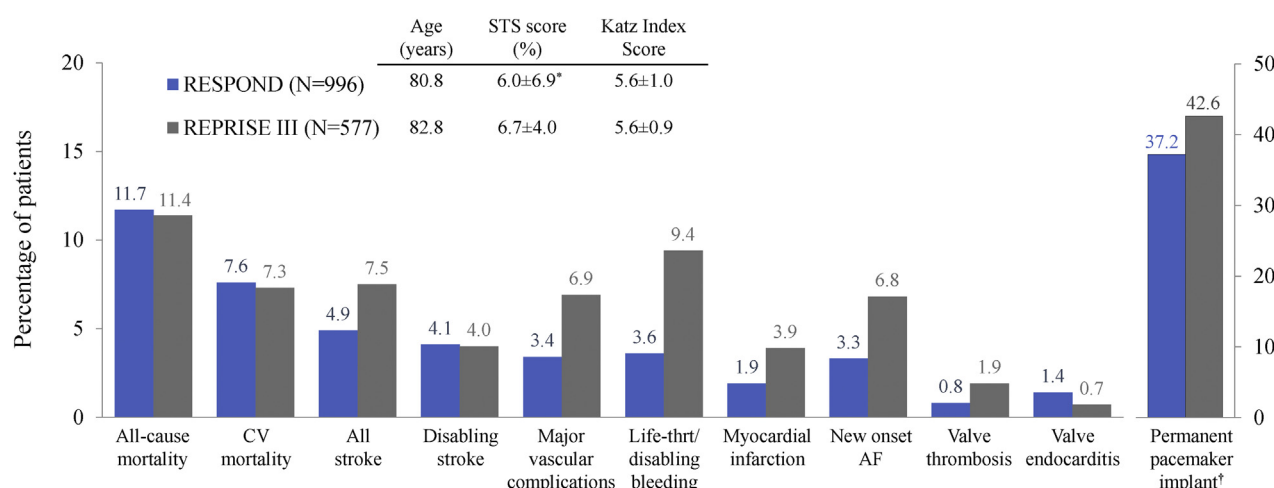
In the RESPOND post-market registry and RESPOND Extension cohort, patients with severe aortic stenosis underwent transcatheter aortic valve replacement with, respectively, the Lotus valve (n = 996) or the Lotus valve with Depth Guard (n = 50). Clinical follow-up 30 days post-implantation was available for all patients in both groups; 1-year follow-up was available for 99.9% of patients in the RESPOND main cohort (1-year follow-up was not required per protocol for the Extension cohort). Patients in both study cohorts exhibited a low mortality rate and excellent valve hemodynamics with minimal paravalvular regurgitation, as assessed by an independent core laboratory. The outcomes from the RESPOND study and RESPOND Extension confirm the safety and efficacy of the Lotus valve when used in contemporary clinical practice. Additionally, the observed rate of permanent pacemaker implantation at 30 days was lower in the Extension cohort (18%) compared with the main cohort (34.6%), suggesting that modifications to the valve design (i.e., Depth Guard technology) and to the implant technique may aid in lowering the pacemaker rate. PVL = paravalvular leak; RESPOND = Repositionable Lotus Valve System—Post-Market Evaluation of Real World Clinical Outcomes trial; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

clinical practice, underscores the suitability and adaptability of Lotus across the TAVR population.

It should be noted that the proportion of RESPOND patients who received a new permanent pacemaker within 1 year, 37.2%, remains high compared with other contemporary studies/registries (PARTNER 2A 9.9% [4]; SOURCE 3 13.2% [14]; ADVANCE 26.4% [15]; GARY 26.2% [16]). A recent post hoc analysis of the RESPOND study demonstrated that pacemaker

implantation following TAVR with the Lotus valve was highly correlated with valve implantation depth; however, PVL was not [17]. Thirty-day outcomes from the RESPOND Extension cohort corroborate the following findings: patients treated with the Lotus valve with Depth Guard, which effectively limits valve implantation depth, had excellent clinical outcomes at 30 days (0% mortality, and only 1 incidence of disabling stroke), and no moderate or severe PVL

FIGURE 8 Comparison of 1-Year Outcomes With the Lotus Valve in the RESPOND Main Cohort and REPRISE III



Mortality, cardiovascular mortality, and disabling stroke at 1 year were similar in RESPOND and REPRISE III patients (10), whereas bleeding and vascular complications were relatively more common among REPRISE III patients. Data shown are KM rates. *Risk scores were not routinely collected/reported by all RESPOND study centers.

†Among patients without a pacemaker at baseline. AF = atrial fibrillation/flutter; CV = cardiovascular; REPRISE III = Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement trial; KM = Kaplan-Meier; other abbreviations as in Figure 3.

was observed. Although the Extension cohort represents a small sample of patients treated with the Lotus valve with Depth Guard, the observed rate of permanent pacemaker implantation at 30 days (20.0%) was lower than that seen with the original Lotus valve (34.6%), suggesting it is possible to reduce the pacemaker rate using a combination of modifications to implant technique and valve design.

STUDY LIMITATIONS. The RESPOND study is not a randomized study, and thus lacks a direct comparator. Additionally, echocardiographic follow-up at 1 year was available for only 62.6% of the as-treated population (551 of 880 surviving patients). The rate of echo follow-up in the RESPOND study is similar to that seen in contemporary TAVR studies/registries at 1 year (PARTNER 2A 72.0% [4]; SOURCE 3 60.4% [14]; ADVANCE 60.0% [15]). The RESPOND protocol reflected standard practice, and 1-year echocardiographic follow-up is not the standard of practice at all institutions; it is often difficult to get patients to return to the study site, particularly when they are participating in a post-market registry. Because longer-term echocardiographic data would aid in understanding the impact of PVL on clinical outcomes, the RESPOND study will continue to collect such data at those sites for which annual echocardiographic follow-up is the standard of care.

CONCLUSIONS

The RESPOND post-market study is unique in that, to our knowledge, it is the only prospective TAVR registry presenting data with independent clinical event adjudication and echocardiographic core laboratory assessment at 1 year. One-year outcomes from the RESPOND study confirm the sustained safety and efficacy of TAVR with the Lotus valve in a large population treated in routine clinical practice. Early experience with Lotus with Depth Guard suggests that adaptations to implantation technique, in conjunction with modifications to the valve design, may lower the pacemaker implantation rate.

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PERSPECTIVES

WHAT IS KNOWN? Although transcatheter aortic valve replacement is a valid treatment strategy for patients with symptomatic severe aortic stenosis, additional evidence is warranted as treatment expands to younger patients and those at lower risk.

WHAT IS NEW? This report from the RESPOND post-market registry confirms favorable clinical outcomes and sustained valve performance with the Lotus valve out to 1 year. Patients treated with the Lotus valve exhibited excellent valve hemodynamics with minimal paravalvular

regurgitation, albeit with a high rate of conduction disorders requiring permanent pacemaker implantation.

WHAT IS NEXT? Data from the RESPOND Extension cohort suggest that adaptations to implantation technique, in conjunction with modifications to the valve design (i.e., Depth Guard technology), may lower the pacemaker implantation rate. Further Lotus valve iterations and procedure experience that may help reduce conduction disorders warrant additional research.

REFERENCES

1. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014; 370:1790–8.
2. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012; 366:1696–704.
3. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet* 2016;387:2218–25.
4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016; 374:1609–20.
5. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J* 2016;37: 2252–62.
6. Gooley R, Lockwood S, Antonis P, Meredith IT. The SADRA Lotus Valve System: a fully repositionable, retrievable prosthesis. *Minerva Cardioangiol* 2013;61:45–52.
7. Gooley R, Antonis P, Meredith IT. The next era of transcatheter aortic valve replacement: A case illustrating the benefit of a fully re-positionable, re-sheathable and retrievable prosthesis. *Catheter Cardiovasc Interv* 2014;83:831–5.
8. Meredith IT, Walters D, Dumonteil N, et al. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study. *J Am Coll Cardiol* 2014; 64:1339–48.
9. Meredith IT, Worthley SG, Whitbourn RJ, et al. Transfemoral aortic valve replacement with the repositionable Lotus Valve System in high surgical risk patients: the REPRISE I study. *Euro-Intervention* 2014;9:1264–70.
10. Feldman TE, Reardon MJ, Rajagopal V, et al. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis: the REPRISE III randomized clinical trial. *JAMA* 2018; 319:27–37.
11. Falk V, Wöhrle J, Hildick-Smith D, et al. Safety and efficacy of a repositionable and fully retrievable aortic valve used in routine clinical practice: the RESPOND study. *Eur Heart J* 2017;38: 3359–66.
12. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium -2 consensus document. *J Am Coll Cardiol* 2012;60:1438–54.
13. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007;5:70.
14. Wendler O, Schymik G, Treede H, et al. SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve. *Eur Heart J* 2017;38:2717–26.
15. Linke A, Wenaweser P, Gerckens U, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve: the international multi-centre ADVANCE study. *Eur Heart J* 2014;35:2672–84.
16. Mohr FW, Holzhey D, Mollmann H, et al. The German Aortic Valve Registry: 1-year results from 13,680 patients with aortic valve disease. *Eur J Cardiothorac Surg* 2014;46:808–16.
17. van Gils L, Wöhrle J, Hildick-Smith D, et al. Importance of contrast aortography with lotus transcatheter aortic valve replacement: a post hoc analysis from the RESPOND Post-Market Study. *J Am Coll Cardiol Intv* 2018;11:119–28.

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