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Safety and efficacy of a repositionable and fully retrievable aortic valve used in routine clinical practice: the RESPOND Study

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Aims RESPOND is a prospective, open-label, single-arm study evaluating the outcomes following transcatheter aortic valve implantation (TAVI) with the repositionable and fully retrievable Lotus Valve used in routine clinical practice for the treatment of patients with aortic valve stenosis.

Methods and results RESPOND enrolled 1014 patients at sites across Europe, New Zealand, and Latin America; 996 patients received a Lotus Valve (mean age: 80.8 years; 50.8% female; Society of Thoracic Surgeons score: 6.0 ± 6.9). Repositioning was attempted in 29.2% of patients, with 99% success. The rate of all-cause mortality in the intent-to-treat population at 30 days (primary endpoint) was 2.6% ($P < 0.001$ vs. pre-specified performance goal). Thirty-day clinical follow-up was completed for 97.3% of patients. Among patients who received a Lotus Valve, the 30-day overall and disabling stroke rates were 3.0% and 2.2%, respectively. The 30-day permanent pacemaker implantation rate was 30.0% in all patients, and 34.6% in pacemaker-naïve patients. Echocardiographic data at baseline and pre-discharge were assessed by an independent core laboratory. Mean aortic valve gradient declined from 37.7 ± 15.2 mmHg at baseline to 10.8 ± 4.6 mmHg at hospital discharge ($P < 0.001$). Aortic valve area increased from 0.7 ± 0.2 cm^2 at baseline to 1.8 ± 0.4 cm^2 at discharge ($P < 0.001$). At hospital discharge, paravalvular leak (PVL) was absent or trace in 92% of patients; no patients had severe PVL, 0.3% of patients exhibited moderate PVL, and 7.7% of patients had mild PVL. Clinical follow-up in RESPOND will extend to 5 years.

Conclusion The results of RESPOND confirm the safety and efficacy of TAVI with the Lotus Valve in routine clinical practice.

Trial registration ClinicalTrials.gov #NCT 02031302.

Keywords Aortic valve stenosis • Transcatheter aortic valve replacement • Transfemoral • Aortic regurgitation

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Introduction

Transcatheter aortic valve implantation (TAVI) has evolved as a standard treatment option for patients with symptomatic aortic stenosis, particularly for those with elevated surgical risk.[1,2] First generation valves demonstrated good clinical outcomes,[3–5] contributing to the acceptance and adoption of TAVI technology. Based on the strength of data from recent studies, candidacy for TAVI has also been extended to intermediate risk patients.[6,7]

Although the reported incidence of procedure-related complications has substantially decreased, the occurrence of moderate or severe paravalvular regurgitation between the native annulus and the bioprosthetic valve frame remains a concern, as this has been associated with increased short- and long-term mortality.[8–11] The novel repositionable and fully retrievable Lotus Valve utilizes controlled mechanical expansion to permit optimal placement of the valve and has a unique adaptive seal designed to minimize paravalvular leak (PVL).[12,13]

The safety and efficacy of the Lotus Valve was originally demonstrated in the REPRISE I and REPRISE II studies;[14,15] however, the modest size of these studies (11 and 120 patients, respectively) and their strict inclusion/exclusion criteria limit generalizability to a broader patient population. The central hypothesis of RESPOND was to confirm the safety and efficacy of the Lotus Valve in a larger, 'all-comers' patient population that better reflects current clinical practice for TAVI. Pre-specified statistical hypotheses evaluated the rates of all-cause mortality and PVL. Here we report the early (30-day) outcomes of this trial.

Methods

Study design and patient selection

The RESPOND (*Re*positionable Lotus Valve *S*ystem—*P*ost-Market Evaluation of Real World Clinical Outcomes) Study is a prospective, open-label, single-arm, multi-centre, post-market registry from 41 centres in Europe, New Zealand, and Latin America (see Supplementary Material online). Study eligibility was determined by local heart team agreement, including evaluation by a cardiac surgeon, that the subject was likely to benefit from valve replacement, but was at high risk of serious surgical morbidity or mortality per the local standard of practice. Consecutive patients who were candidates for TAVI and were selected to receive a Lotus Valve were enrolled. Data collection occurred at baseline, index procedure, discharge, and 30-day follow-up for all enrolled subjects and will continue annually to 5 years.

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 outlined in the Declaration of Helsinki. The study was sponsored by Boston Scientific Corporation and registered with ClinicalTrials.gov (NCT#02031302). All patients gave written informed consent.

Device and procedural details

The Lotus Valve System™ consists of a bioprosthetic aortic valve (a braided nitinol wire frame with three bovine pericardial leaflets) premounted on a preshaped delivery catheter. The valve is deployed via controlled mechanical expansion, which enables predictable and precise placement. A detailed description of the implantation procedure is provided elsewhere.[12–14] The lower half of the Lotus Valve is surrounded by an adaptive seal, a polymer membrane designed to fill the space between the native annulus and the prosthetic valve frame, thereby reducing paravalvular leakage. The Lotus Valve begins functioning early in the deployment process, providing haemodynamic stability; rapid pacing is not required. Valvular function can be assessed in the fully expanded position prior to release. Partial or full recapturing/repositioning of the valve, or full retrieval, is possible at any point prior to uncoupling and release.

Three valve sizes were available for RESPOND: 23 mm, 25 mm, and 27 mm (for native annulus sizes ≥20mm to ≤27mm). Multislice computed tomography planning was recommended for aortic annulus sizing and Lotus Valve size selection.

Outcomes measures

Safety and effectiveness were assessed according to Valve Academic Research Consortium (VARC)-2 metrics.[16] The primary end point of the study was all-cause mortality at 30 days and 1 year post-procedure. All-cause mortality at 30 days was compared with a pre-specified performance goal of 14%, based on an expected rate of 10% plus a testing margin of 4%.[17] Study end point-related clinical events (i.e. all-cause mortality and stroke events) reported by study investigators were assessed by an Independent Medical Reviewer (IMR).

The grade of aortic valve regurgitation at baseline and discharge was measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory (Cardialysis Core Laboratory, Rotterdam, Netherlands) according to VARC-2 criteria. The rate of moderate/severe paravalvular aortic regurgitation was compared with a pre-specified performance goal of 16.5% (based on rates observed in the FRANCE-2 Registry).[17]

Additional clinical end points evaluated at 30 days included life-threatening bleeding, acute kidney injury (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complications, valve-related dysfunction requiring a repeat procedure, and permanent pacemaker implantation. Health status was evaluated by the EuroQoL (EQ-5D) quality of life questionnaire at baseline and 30 days, and will be captured at 1-, 3-, and 5-year follow-up. New York Heart Association (NYHA) functional classification was evaluated at baseline, discharge, and 30 days and will be monitored annually to 5 years. A complete list of secondary endpoints and measures is provided in Supplementary Material online.

Statistical methods

The analysis population for the primary endpoint comprises subjects with an attempt to be implanted with or an implanted Lotus Valve [intent-to-treat (ITT) population]. The analysis population for the secondary endpoints includes only subjects who had a Lotus Valve implanted (as-treated population). Thirty-day analyses were performed on data from patients in the as-treated population with available follow-up (i.e. follow-up visit ≥23 days) or an event within 30 days.

Baseline and outcome variables were summarized using descriptive statistics. The 95% confidence intervals (CI) are presented for all safety endpoints. The *P*-value for the primary endpoint of 30-day mortality meeting the performance goal was from a one-sample exact binominal test. *P*-values for improvement in NYHA functional classification were from a generalized McNemar's test; *P*-values for change in haemodynamic parameters from baseline to discharge were derived from a paired *t*-test analysis among patients with echocardiographic data available at both baseline and discharge. All *P*-values were two-sided. Echocardiographic data collected for each subject during the study were independently analysed by the core laboratory in order to control for inter-observer variability and minimize bias and inconsistencies. No imputation of missing data was performed.

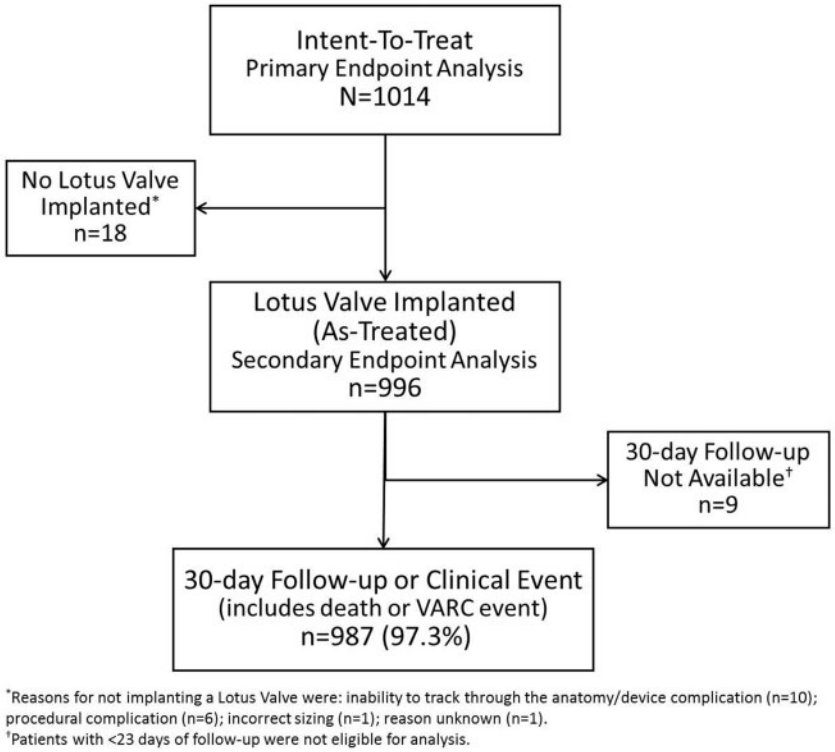

Figure 1 Study flow and patient disposition. One thousand fourteen patients enrolled in RESPOND (intent-to-treat population) and were included in the primary endpoint analysis. The as-treated population comprised 996 patients implanted with a Lotus Valve; of those, 987 patients had sufficient follow-up or had an event by 30 days.

Results

Study participants and baseline characteristics

RESPOND enrolled 1014 patients between May 2014 and February 2016; of these, 996 patients received a Lotus valve and were included in the as-treated population (*Figure 1*). No patient discontinued follow-up prematurely or withdrew from the study. Mean age was 80.8 ± 6.5 years, 50.8% were female, and the mean baseline Society of Thoracic Surgeons (STS) score was 6.0% ± 6.9%. Among patients implanted with a Lotus Valve, 257 (25.8%) received a 23-mm valve, 401 (40.3%) received a 25-mm valve, and 338 (33.9%) received a 27-mm valve. The majority of procedures were performed via transfemoral access (96.6%); in a few cases a subclavian (1.9%) or transaortic (1.5%) approach was used. Balloon predilatation was performed in 53.9% of cases; 8.8% of procedures used embolic protection. At baseline, 11.7% of patients had moderate or severe aortic regurgitation. Additional baseline patient and echocardiographic characteristics are detailed in *Table 1*.

Device performance and safety

Successful vascular access, device delivery, and deployment of the Lotus Valve, and successful retrieval of the delivery system, were achieved in 98.1% of the ITT population. Among patients implanted with the Lotus Valve, 99.7% had correct positioning of one valve in the proper anatomical location. Repositioning of the valve was attempted in 296 patients (29.2%), and was successful (i.e. partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) in 99.0% (*Table 2*). In two patients, repositioning of a 27-mm Lotus valve was attempted, but the valve was ultimately deemed to be too small and was retrieved, and a larger commercially available valve was implanted. In one patient, repositioning was twice unsuccessful due to the inability to unsheathe, lock, and release the Lotus Valve, with persistent PVL; a different 23-mm Lotus Valve was successfully deployed.

Procedural mortality was 0.2% (two patients): one patient underwent a combined coronary artery bypass graft and direct aortic TAVI procedure, and had a peri-procedural myocardial infarction (MI) and subsequent multi-organ failure, resulting in death; one patient experienced MI during the index procedure, complicated by complete heart block, pericardial effusion and cardiac tamponade, resulting in death. During the peri-procedural period (≤72 hr), two patients (0.2%) experienced coronary obstruction (1 of whom died 31 days post-procedure) and cardiac tamponade occurred in 6 patients (0.6%). The average length of hospitalization in RESPOND was 7.3 ± 5.9 days.

Table 1 Baseline patient characteristics and echocardiographic assessments

Patient characteristic	As-treated population
Age, years	80.8 ± 6.5 (996)
Gender, female	50.8 (506/996)
STS score[a]	6.0 ± 6.9 (841/996)
EuroSCORE II[a]	8.0 ± 8.4 (919/996)
Diabetes mellitus, medically treated	22.4 (222/991)
COPD—moderate or severe	7.7 (77/994)
NYHA Class III or IV	69.5 (643/925)
Coronary artery disease, history	56.1 (558/995)
Prior PCI	29.8 (296/993)
Prior CABG	12.3 (123/996)
Prior implanted pacemaker	13.3 (132/996)
Atrial fibrillation, history	33.9 (334/985)
Porcelain aorta	4.3 (43/991)
Hostile chest/unfavourable chest wall anatomy	1.0 (10/995)
Cerebrovascular accident, history	9.5 (94/993)
Transient ischaemic attack, history	7.4 (73/989)
Frailty assessments	
5-meter gait speed, s	7.5 ± 3.7 (257/996)
Grip strength—maximal, kg	21.2 ± 9.2 (307/996)
Katz index activities of daily living score	5.6 ± 1.0 (493/996)
Eligibility	
Tricuspid aortic valve stenosis	94.2 (938/996)
Bicuspid aortic valve stenosis	3.1 (31/996)
Low flow/low gradient aortic stenosis	3.0 (30/996)
TAV-in-valve[b]	0.8 (8/996)
Echocardiographic assessments—core lab	
Aortic valve area (effective orifice area), cm^2	0.7 ± 0.2 (877/995)
Mean aortic valve gradient, mmHg	38.0 ± 15.5 (923/995)
Peak aortic valve gradient, mmHg	61.9 ± 24.2 (923/995)
Left ventricular ejection fraction	49.8 ± 10.5 (624/995)
Aortic regurgitation—moderate or severe[c]	11.7 (108/927)
Mitral regurgitation—moderate or severe[d]	14.9 (135/906)

Values are mean ± standard deviation (*n*/*N*) or % (*n*/*N*).
CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TAV, transcatheter aortic valve.
[a]Risk scores were not routinely collected/reported by all study centres.
[b]TAV implanted in surgical aortic valve in 6 patients; TAV-in-TAV in 2 patients.
[c]Severe in 14 patients (1.5%).
[d]Severe in 13 patients (1.4%).

Data for 30-day clinical follow-up were available for 97.3% of patients ($n = 987$). At 30 days, the rate [95% CI] of all-cause mortality was 2.6% [1.7%, 3.8%] in the ITT population ($P < 0.001$ vs. prespecified performance goal) and 2.2% [1.4%, 3.4%] in the as-treated population. Among patients who received a Lotus Valve, the 30-day overall stroke rate was 3.0% [2.1%, 4.3%]; the rate of disabling stroke was 2.2% [1.4%, 3.4%]. Preliminary analyses suggest that stroke was not related to repositioning of the valve ($P = 0.90$). The incidence of repeat procedure was 0.1% [0.0%, 0.6%] ($n = 1$; TAV-in-TAV for elevated gradient, 8 days after initial procedure). The 30-day permanent pacemaker implantation rate was 30.0% [27.1%, 33.0%] among all patients, and 34.6% [31.4%, 37.8%] among patients who did not have a pacemaker at baseline. Additional pre-discharge and 30-day safety outcomes for the as-treated population are shown in *Figure 2* (for safety outcomes in the ITT population, see Supplementary Material online).

Haemodynamic parameters and paravalvular regurgitation

Patients exhibited significantly improved valve haemodynamics compared with baseline following implantation of the Lotus Valve. Pre-discharge TTE assessment was available in 92.5% of patients; complete core laboratory-adjudicated echo analyses, including data at both baseline and discharge, were available for 89.7% of patients. In a paired analysis, mean aortic valve gradient declined from 37.7 15.2 mmHg at baseline to 10.8 4.6 mmHg at hospital discharge ($P < 0.001$), and aortic valve area (effective orifice area) increased from 0.7 0.2 cm^2 at baseline to 1.8 0.4 cm^2 at discharge ($P < 0.001$) (*Figure 3*). Paravalvular leak was absent or trace in 92.0% of patients who underwent TTE at hospital discharge (*Figure 4*). There were no patients with severe PVL; 0.3% of patients exhibited moderate PVL and 7.7% of patients had mild PVL. The rate of moderate/severe PVL (0.3%) was significantly below the predetermined performance goal of 16.5% ($P < 0.001$).

New York Heart Association functional class and health status

At baseline, 62.4% of patients were NYHA Class III; an additional 7.1% were Class IV (*Figure 5*). At 30 days post-procedure, 91% of surviving patients were NYHA Class I or II; 78% and 35% of patients had improved at least one or two classes, respectively, relative to baseline ($P < 0.001$ for both). Health-related quality of life significantly improved from baseline according to the self-rated EQ-5D questionnaire. Patients' self-reported score on the Visual Analog Scale improved from 57.2 ± 18.0 at baseline to 66.7 ± 19.0 at 30 days ($P < 0.001$), representing a clinically meaningful change in overall quality of life.[18]

Discussion

The RESPOND Study is the largest experience to-date evaluating the safety and efficacy of TAVI with the Lotus Valve, and is unique in that it represents an 'all-comers' population. RESPOND reflects current clinical practice, including the trend in the extension of candidacy for TAVI to a more intermediate-risk patient population.

Clinical outcomes from RESPOND were comparable to those from studies of patients with a similar level of operative risk, as based on their STS score (i.e. a mean STS score >5, but <8). The rate of all-cause mortality at 30 days in RESPOND was 2.6%, compared with 1.1% in the intermediate risk cohort of the PARTNER II SAPIEN 3 Study[19] (mean STS, 5.3), 3.9% in the PARTNER 2A Intermediate Risk Study[6] (mean STS, 5.8), 4.5% in the CoreValve ADVANCE Registry[20] (mean STS, 5.3), and 7.6% in the TVT Registry[21] (mean STS, 7.0). In the GARY Registry, where the decision for TAVI was made in most cases by a heart team and not based on a particular risk score, the rate of in-hospital mortality was 5.5%;[22] in RESPOND the rate of

Table 2 Device performance

Performance measure	Intent-to-treat population
Successful vascular access, delivery, deployment, and system retrieval	98.1 [97.1, 98.9] (995/1014)
Successful valve repositioning, if attempted ($n = 296$)[a]	99.0 [97.1, 99.8] (293/296)
Successful valve retrieval, if attempted ($n = 47$)	97.9 [88.7, 100.0] (46[b]/47)
Aortic valve malpositioning (includes procedural and pre-discharge events)	
Valve migration	0.0 [0.0, 0.4] (0/1014)
Ectopic valve deployment[b]	0.1 [0.0, 0.6] (1/1014)
Valve embolization[c]	0.1 [0.0, 0.6] (1/1014)
TAV-in-TAV deployment[d]	0.3 [0.1, 0.9] (3/1014)

Values are % [95% CI] (*n*/*N*).
ITT, intent-to-treat; PVL, paravalvular leak; TAV, transcatheter aortic valve; TAVI, transcatheter aortic valve implantation; CI, confidence interval.
[a]Data are for the last valve attempted.
[b]Failure to release valve from delivery system (pin malfunction); valve deployed in the descending aorta (ectopic implantation), with second valve implanted in proper location ($n = 1$).
[c]Valve embolization above the annulus following interaction with delivery catheter upon withdrawal, successfully treated with second Lotus Valve (also recorded as TAV-in-TAV, $n = 1$).
[d]Recurrent aortic valve stenosis with mean gradient of 40 mmHg ($n = 1$), non-study valve implanted; moderate PVL noted following deployment of first Lotus Valve, attempted deployment of second Lotus Valve unsuccessful due to inability to unsheathe, lock, and release the Lotus Valve, a third Lotus Valve was successfully deployed in a position below the aortic root ($n = 1$); valve embolization ($n = 1$; see note above).

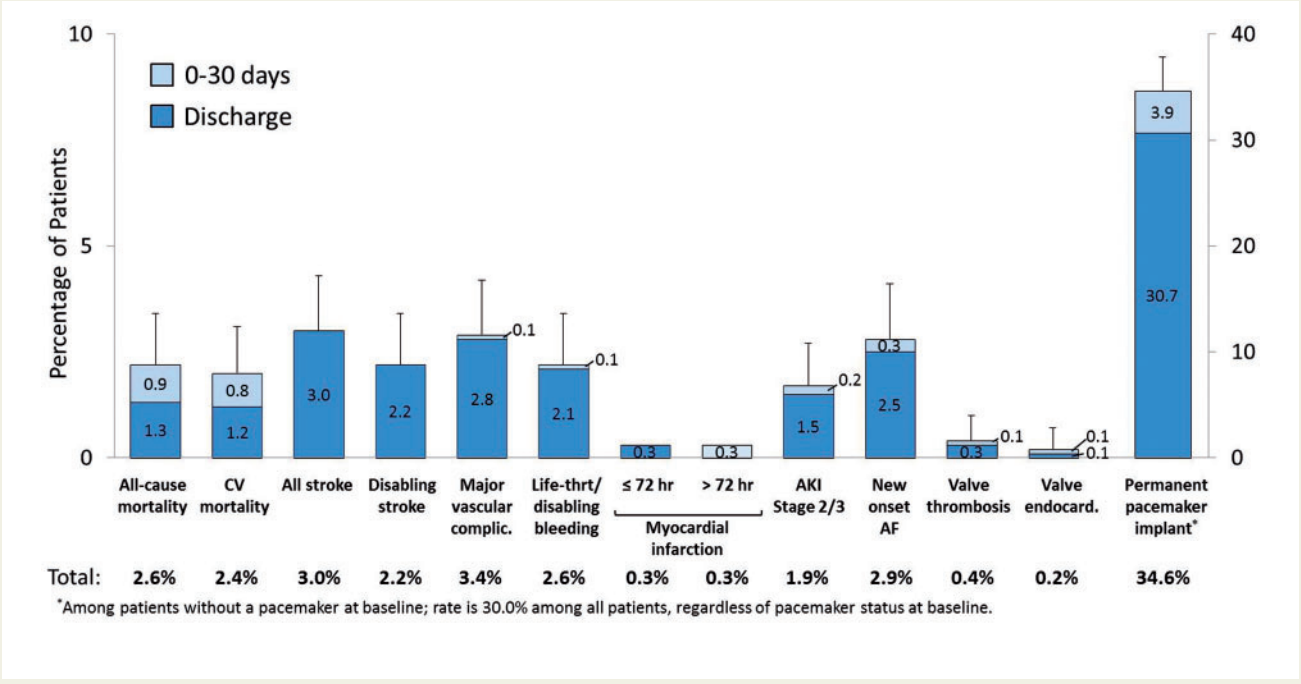

Figure 2 Clinical outcomes at discharge and 30 days. Event rates are shown for hospital discharge (dark blue) and 30 days post-procedure (light blue bars). Data are percentage of patients; bar indicates 95% confidence interval. AF, atrial fibrillation; AKI, acute kidney injury; CV, cardiovascular.

all-cause mortality at hospital discharge was 1.3%. Likewise, the 2.2% risk of major/disabling stroke at 30 days in RESPOND is well within the range of rates (1.0–3.2%) observed in these contemporary studies.[6,19–22]

Patients in RESPOND had a very low rate of paravalvular regurgitation at hospital discharge—PVL was negligible in 92% of patients, as assessed by an independent core laboratory. No patients exhibited severe PVL, and moderate PVL was present in only 0.3% of patients. The pre-discharge rate of moderate/severe PVL in RESPOND was much lower than that observed at 30 days in the CoreValve ADVANCE Registry[20] (13.1%), the SAPIEN 3 CE Mark Study[23] (3.5%), or the Direct Flow DISCOVER[24] Study (1.2%). Additionally, the rate of mild PVL in RESPOND was 7.7%—the lowest reported for any TAVI system, and approaching rates seen with surgical valve

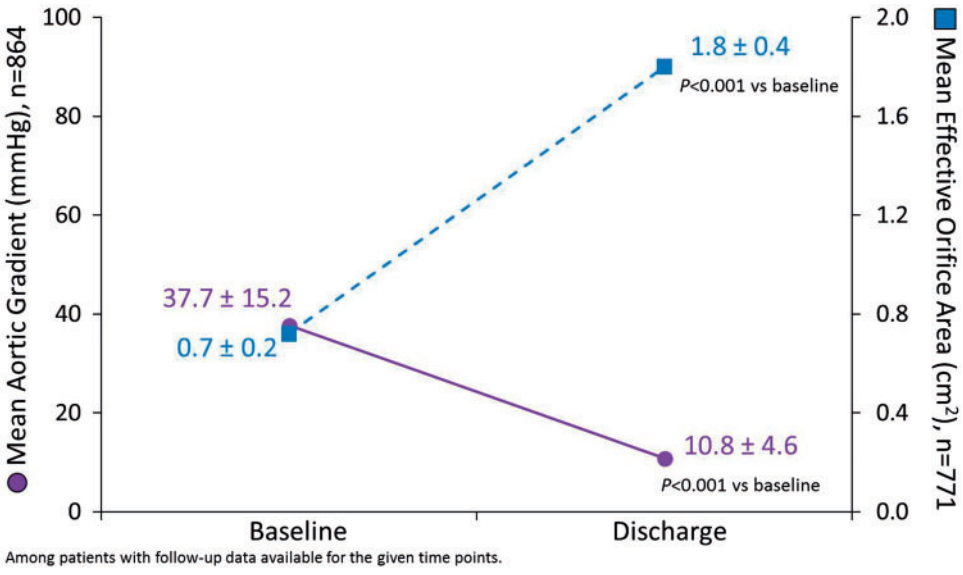

Figure 3 Haemodynamic parameters. Mean aortic valve pressure gradient and mean aortic valve area improved significantly from baseline to discharge ($P < 0.001$ for both). Echocardiographic data were independently assessed by a core laboratory. Data are mean ± standard deviation; *P*-values are derived from a paired *t*-test analysis among patients with data available at both baseline and discharge.

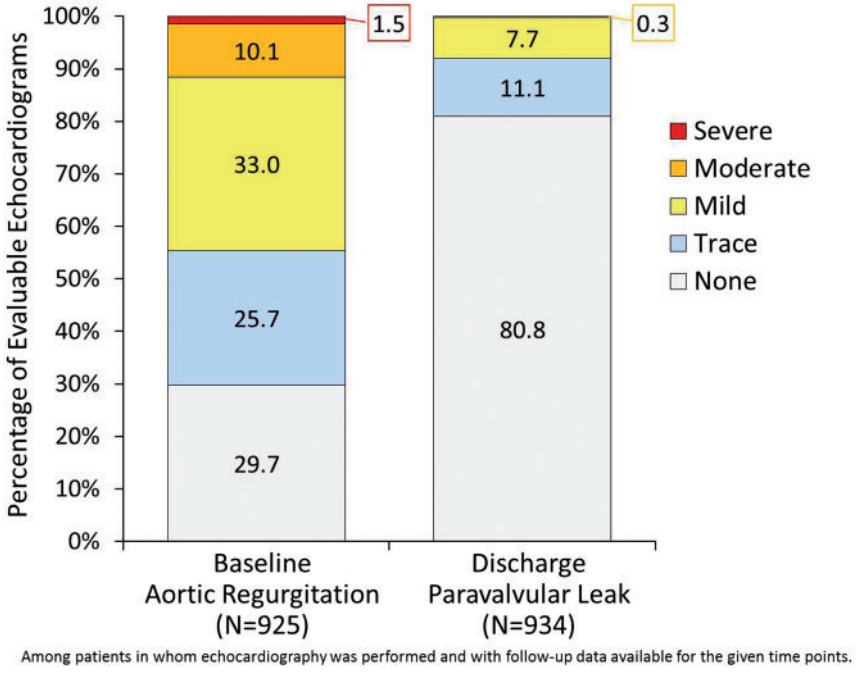

Figure 4 Aortic regurgitation. In the majority of patients, paravalvular leak (PVL) was absent or at trace levels at discharge. Echocardiographic data were independently assessed by a core laboratory.

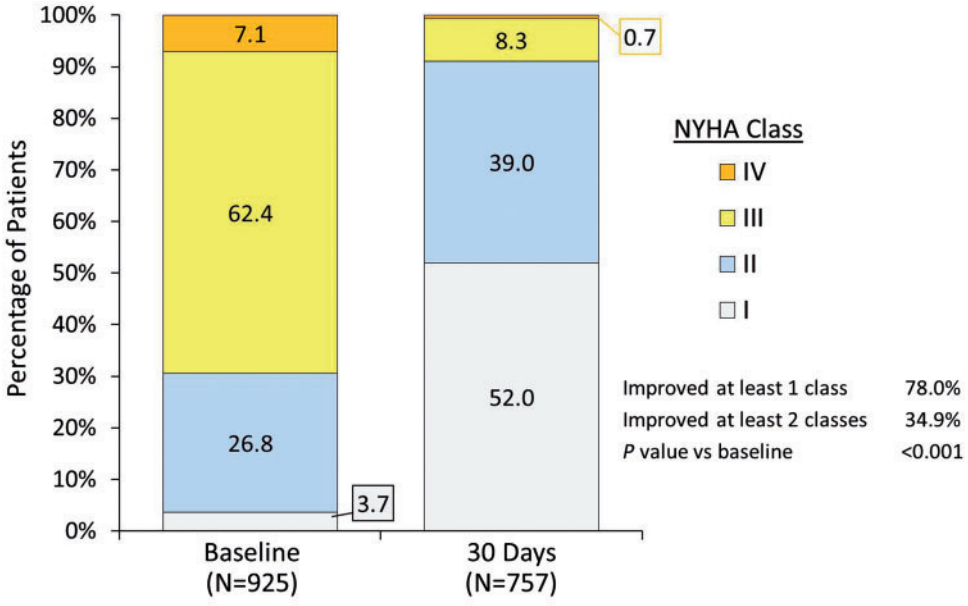

Figure 5 New York Heart Association (NYHA) functional status. The majority of patients exhibited improved NYHA functional status at 30 days post-procedure compared with baseline. By 30 days post-procedure, there were 22 deaths; NYHA Class data were not collected at all sites for all remaining patients. Improvement from baseline was evaluated for patients with data available at both baseline and discharge; *P*-value is from a generalized McNemar's test.

replacement. The rates of mild and moderate/severe PVL at 30 days were 2.8% and 0.5%, respectively, in the PARTNER IIA surgical group[6], and 3.2% and 1.0%, respectively, in the surgical group of the US CoreValve Study.[25]

Moderate or severe PVL is an independent predictor of mortality after TAVI.[6,8–11,26] As the indication for TAVI continues to expand to patients with moderate- and low-operative risk, every effort should be made to reduce the incidence of PVL. The low rate of PVL observed with the Lotus Valve is promising; however, approximately a third of patients in RESPOND required permanent pacemaker implantation, which is at the high end of the spectrum among TAVI studies. In a recent meta-analysis of predictive factors for pacemaker implantation, the rate ranged from 2% to 51%.[27] Among RESPOND centres enrolling at least 10 patients, the observed pacemaker implantation rate varied from 0% to 70%. These disparate rates could be influenced by varying degrees of experience with the Lotus Valve, differences in implant technique, and differing criteria for pacemaker implantation. Recent data suggest that measures can be taken to achieve a lower pacemaker rate with the Lotus Valve, including procedural adaptations to avoid valve oversizing and implanting the valve in a higher position.[28,29] Design modifications to the Lotus Valve System currently under development include alterations to reduce the interaction of the valve with the conduction system and the left ventricular outflow tract during deployment, and an expanded size matrix, which may help to avoid conduction problems related to valve oversizing. Additional improvements to the Lotus Valve System include a lower delivery profile and more flexible catheter, which may help to mitigate procedural complications related to the ability to navigate tortuous or heavily calcified vessels.

Study limitations

RESPOND is not a randomized study, but rather a single-arm registry, and as such has a number of limitations, including the lack of a direct comparator. Although the statistical hypotheses for mortality and PVL were compared against pre-specified performance goals, these goals were based on historical data and are somewhat outdated relative to data from newer-generation valves. RESPOND enrolled a relatively unselected patient population, which included some patients who may not have been considered high-risk by STS score alone. However, existing surgical risk scores may have limited accuracy in risk estimation of TAVI patients because essential variables like frailty and hostile chest are not considered.[30,31]

Variability in data collection between sites contributed to differences in sample size for some data elements, as not all outcomes and parameters were evaluated for all patients at every time point. There were differences in local standard of practice that may have impacted outcomes, including differences in the use of balloon valvuloplasty for predilation of the aortic annulus, differences in the prescribing of anticoagulation therapies, and differences in the evaluation of conduction disturbances and criteria employed for permanent pacemaker implantation. As RESPOND was a post-market registry, routine CT

scanning or other systematic assessment of valve thrombosis was not required by the protocol; valve thromboses diagnosed in the course of routine clinical care were reported. Per the VARC-2 definition, procedural mortality includes any death occurring within 30 days; cardiovascular mortality includes procedural mortality.[16,32] In RESPOND, and consistent with other studies,[6,19] not all mortality within the first 30 days was adjudicated by the IMR as being cardiovascular in nature; if all procedural deaths were adjudicated as cardiovascular, 30-day cardiovascular mortality would be 2.2%, rather than 2.0%.

Finally, only short-term outcomes up to 30 days are reported to date. Additional follow-up is needed to evaluate the long-term safety and efficacy of the Lotus Valve; follow-up in RESPOND will continue to 5 years.

Conclusion

The RESPOND post-market study confirms the safety and efficacy of TAVI with the Lotus Valve in routine clinical practice. Clinical outcomes at 30 days were excellent with an unprecedented low rate of mild or more PVL, albeit with a relatively high rate of permanent pacemaker implantation. Additional follow-up in RESPOND patients will help to evaluate longer term clinical outcomes with the Lotus Valve.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

V.F., N.V.M., D.J.A., and K.D.D. conceived and designed the research; V.F., J.W., D.H.-S., S.B., D.J.B., M.A.-W., U.G., A.L., H.I., P.W., and N.V.M. participated in data acquisition; V.F., N.V.M., D.J.A., and K.D.D. drafted the manuscript; all authors made critical revision of the manuscript for key intellectual content.

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