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Long-term Outcomes of Transcatheter Aortic Valve Replacement With the Lotus Valve vs CoreValve/EvolutR

A Secondary Analysis of the REPRISE III Randomized Clinical Trial

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Abstract

IMPORTANCE Long-term follow-up after transcatheter aortic valve replacement (TAVR) is of interest given that longitudinal data on mortality and durability of transcatheter heart valves are limited. The REPRISE III (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System—Randomized Clinical Evaluation) randomized clinical trial compared the mechanically expanded Lotus valve with the self-expanding CoreValve/EvolutR TAVR platforms.

OBJECTIVE To describe the final 5-year outcomes of the REPRISE III trial.

DESIGN, SETTING, AND PARTICIPANTS This prespecified secondary analysis assessed the final 5-year clinical, functional, and echocardiographic outcomes of 912 patients from the REPRISE III trial, which was conducted at 55 centers in North America, Europe, and Australia between September 22, 2014, and December 24, 2015. Patients had high risk for aortic stenosis or severe or symptomatic aortic stenosis. Data were analyzed from September 22, 2014, to May 21, 2021.

INTERVENTION Lotus valve or CoreValve/EvolutR TAVR platforms.

MAIN OUTCOMES AND MEASURES Valve Academic Research Consortium-2 end points, hemodynamic measures, functional status, and health status were examined through the 5-year follow-up.

RESULTS A total of 912 patients (mean [SD] age, 82.8 [7.3] years; 463 women [50.8%]) were randomized to either the Lotus valve group (n = 607) or CoreValve/EvolutR group (n = 305), with a baseline Society of Thoracic Surgeons risk score of 6.8%. Clinical follow-up data from the REPRISE III trial were available for 581 patients (95.7%) in the Lotus valve group and 285 patients (93.4%) in the CoreValve/EvolutR group. At 5 years, the cumulative event rate for all-cause mortality was 50.9% in the Lotus valve group vs 52.8% in the CoreValve/EvolutR group (P = .59). Disabling stroke was less frequent with the Lotus valve vs CoreValve/EvolutR (cumulative event rates, 8.3% vs 12.2%; P = .04), whereas the cumulative event rates for overall stroke were similar in both groups (14.1% vs 15.3%; P = .38). Insertion of a new permanent pacemaker (38.9% vs 27.3%; P < .001) and detection of prosthetic aortic valve thrombosis (5.8% vs 1.8%; P = .007) were more common in the Lotus valve group than in the CoreValve/EvolutR group. A smaller proportion of patients who received the Lotus valve experienced valve malpositioning (0% vs 2.6%; P < .001) and required the use of a second valve (1.0% vs 3.8%; P < .001) during the procedure compared with those who received the CoreValve/EvolutR. Compared with the Lotus valve group, the CoreValve/EvolutR group had a significantly lower mean (SD) aortic gradient (7.8 [4.2] mm Hg vs 12.6 [6.7] mm Hg; P < .001) and

(continued)

Key Points

Question What are the long-term clinical outcomes in patients who underwent a transcatheter aortic valve replacement with the Lotus valve compared with the CoreValve/EvolutR?

Findings In this secondary analysis of the REPRISE III randomized clinical trial involving 912 patients with high risk for aortic stenosis or severe or symptomatic aortic stenosis, those with the Lotus valve had similar mortality rates, fewer disabling strokes, and similar repeat procedures compared with patients with the CoreValve/EvolutR, although the Lotus valve group had higher gradients, more new pacemaker implantations, and higher incidence of prosthetic aortic valve thrombosis events. Hemodynamics and health and functional status were maintained long term in both cohorts.

Meaning Findings of this analysis suggest that, at the 5-year follow-up, the Lotus valve generally had comparable outcomes to those of the CoreValve/EvolutR, making it a safe and effective treatment for aortic stenosis.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

larger valve areas (1.57 [0.56] cm^2 vs 1.42 [0.42] cm^2; *P* = .10). After 5 years, the proportion of patients with moderate or greater paravalvular leak was not significantly higher with the CoreValve/EvolutR than with the Lotus valve (1.9% vs 0%; *P* = .31); however, the proportion of patients with mild paravalvular leak was higher in the CoreValve/EvolutR group compared with the Lotus valve group (23.1% vs 7.8%; *P* = .006). Long-term, similar improvements in New York Heart Association class and Kansas City Cardiomyopathy Questionnaire score were observed in both groups.

CONCLUSIONS AND RELEVANCE The REPRISE III trial found that, at 5 years, the clinical outcomes of the Lotus valve were comparable to those of the CoreValve/EvolutR and that the Lotus valve was safe and effective.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02202434

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Introduction

Since the first successful transcatheter aortic valve replacement (TAVR) in 2002,[1] use of TAVR has had an explosive growth fueled by randomized trials in high-risk,[2,3] intermediate-risk,[4,5] and low-risk[6,7] patients reporting that this technology is noninferior or superior to surgical aortic valve replacement in the early term. Midterm data are available for the trials with high- and intermediate-risk patients, and these trials have found that TAVR remains noninferior to surgery.[8,9] These findings have led to more TAVR procedures being performed on an annual basis in the US than all surgical aortic valve procedures combined.[10] Current American College of Cardiology/American Heart Association valve guidelines no longer consider surgical risk alone but also focus on age, potential life span, anatomy, and patient preferences.[11] This focus makes longer-term performance data important for all TAVR valves.

The Lotus valve was a mechanically expanded valve designed to allow for a stable deployment without hemodynamic compromise at any point during the deployment. This valve could be fully deployed to the final position and assessed. If the assessment was not satisfactory, the valve could be fully recaptured if needed even from the final deployment position. In addition, the Lotus valve used a sealing skirt to mitigate paravalvular leak (PVL). The REPRISE III (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System—Randomized Clinical Evaluation) trial randomized participants in a 2:1 fashion to the Lotus valve or the self-expanding CoreValve/EvolutR valve. The primary end point and 2-year results of the trial have been previously published.[12-14]

Despite its favorable results, the Lotus valve was withdrawn from the market due to the complexity of the manufacturing process and limited commercial uptake. Before its withdrawal from the market, more than 10 000 patients were treated with the Lotus valve either in this trial or commercially, making its longer-term outcomes important to understand. This study aimed to describe the final 5-year outcomes of the REPRISE III trial.

Methods

Study Design and Participants

This prespecified secondary analysis assessed the results of REPRISE III, a multicenter, randomized clinical trial that compared the Lotus valve (Boston Scientific) and CoreValve/EvolutR (Medtronic) devices. The trial was conducted at 55 centers in North America, Europe, and Australia from September 22, 2014, to December 24, 2015. The institutional review boards at each site approved

the study protocol. The protocol and statistical analysis plan are provided in Supplement 1. All patients provided written informed consent.[12] We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Data were analyzed by independent core laboratories, and a clinical events committee adjudicated major clinical events.

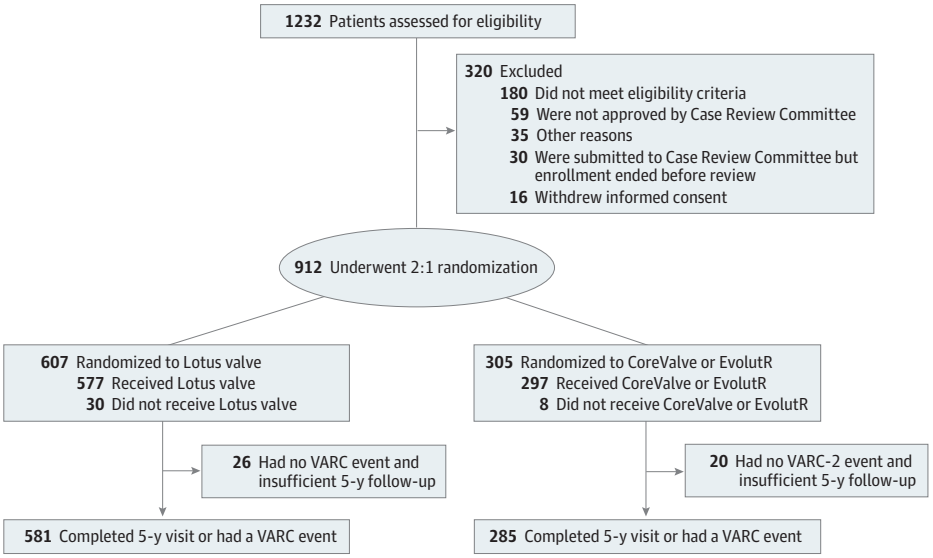
Patients with severe native aortic stenosis with a valve area of 1.0 cm^2 or less (or aortic valve area index ≤0.6 cm^2/m^2) and a mean pressure gradient of 40 mm Hg or greater or jet velocity of 4.0 m/s or higher were eligible for enrollment in the trial if they had a Society of Thoracic Surgeons predicted risk of mortality of 8% or greater or another indicator of high or extreme risk. Agreement among the local heart team and the REPRISE III Case Review Committee regarding risk and suitability for TAVR and eligibility for an available size of both valves was required for enrollment.[12]

Patients were randomized 2:1 to receive the Lotus valve or the CoreValve/EvolutR at the 55 centers worldwide. Clinical and echocardiographic assessments occurred annually through 5 years of the trial (**Figure 1**).

Study End Points

The most current Valve Academic Research Consortium (VARC-2) definitions and end points available at the beginning of the trial were used.[15,16] Safety end points that were adjudicated by an independent clinical events committee included mortality, stroke, major vascular complications, new permanent pacemaker implantation, life-threatening or disabling bleeding, myocardial infarction, repeat procedure for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (New York Heart Association [NYHA] functional class III [indicating marked limitation in activity due to symptoms, even during less-than-ordinary activity; comfortable only at rest] or class IV [indicating severe limitations; experiences symptoms even while at rest and is mostly bedbound]), new onset of atrial fibrillation or flutter, and prosthetic aortic valve thrombosis. The protocol required patients to undergo neurological examinations by a neurology professional at baseline, discharge, 1 year, and after any suspected stroke. Echocardiographic parameters, including aortic regurgitation, mean aortic gradient, and effective orifice area (EOA), were analyzed by an independent core laboratory (MedStar Health Research Institute). Health status was evaluated throughout the 5 years using the Kansas City Cardiomyopathy Questionnaire and 12-Item Short Form quality-of-life questionnaire. Functional status was evaluated using NYHA classification.

Figure 1. Study Flow Diagram



VARC-2 indicates Valve Academic Research Consortium.

Statistical Analysis

The intention-to-treat patient population was analyzed in this secondary analysis. Continuous variables were estimated as mean (SD) and compared with an unpaired, 2-tailed *t* test. Discrete variables were reported as counts and percentages, and differences were assessed by means of the χ^2 or Fisher exact tests. Cumulative event rates were estimated by the Kaplan-Meier method.

A 2-sided $P < .05$ was used to indicate significance. Statistical analyses were performed with SAS software, version 9.3 or later (SAS Institute Inc). Data were analyzed from September 22, 2014, to May 21, 2021.

Results

The REPRISE III trial randomized 912 patients to receive either the Lotus valve (n = 607) or the CoreValve/EvolutR (n = 305). Patients in both groups had a mean (SD) age of 82.8 (7.3) years and included 463 women (50.8%) and 449 men (49.2%).[12] Mean (SD) Society of Thoracic Surgeons risk scores were similar between the Lotus valve and CoreValve/EvolutR cohorts (6.7% [4.0%] and 6.9% [4.1%]). The proportion of patients with symptomatic aortic stenosis (NYHA functional class III or IV) was 71.3% in the Lotus valve group and 67.9% in theCoreValve/EvolutR group. At 5 years, the intention-to-treat analyses included 581 patients (95.7%) who received the Lotus valve and 285 patients (93.4%) who received the CoreValve/EvolutR and either had a VARC-2 event or completed the 5-year clinical follow-up visit (Figure 1).

Clinical Outcomes at 5 Years

All-cause mortality and stroke outcomes at 5 years are shown in **Figure 2** and the **Table**. Cumulative event rates for all-cause mortality were 50.9% in the Lotus valve group and 52.8% in the CoreValve/EvolutR group ($P = .59$) (Figure 2A). Cumulative event rates for all-cause mortality or disabling stroke were 52.8% in the Lotus valve group and 56.0% in the CoreValve/EvolutR group ($P = .24$) (Figure 2B). Overall, cumulative event rates for stroke were 14.1% in the Lotus valve group and 15.3% in the CoreValve/EvolutR group ($P = .38$) (Figure 2C), whereas the rates for disabling stroke were 8.3% in the Lotus valve group and 12.2% in the CoreValve/EvolutR group ($P = .04$) (Figure 2D). Additional clinical end points are shown in the Table.

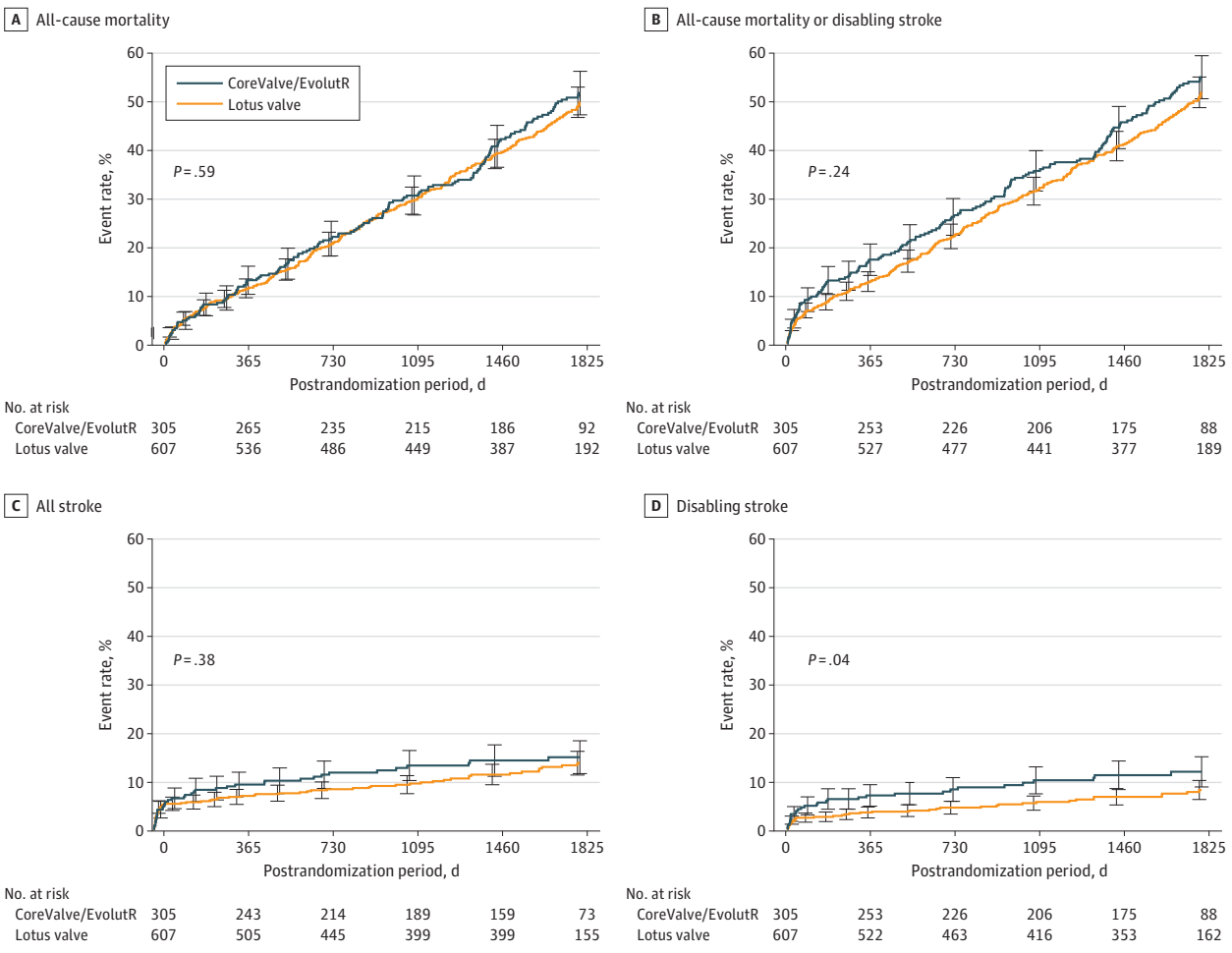
At 5 years, incidences of major vascular complications, life-threatening or disabling bleeding, myocardial infarction, rehospitalization, and new onset of atrial fibrillation or flutter were not significantly different between the valve cohorts (Table). Cumulative event rates for permanent pacemaker implantation were 38.9% in the Lotus valve group and 27.3% in the CoreValve/EvolutR group ($P < .001$). Most new pacemakers were received within the first year of follow-up; 3.5% of patients in the Lotus group compared with 6.7% of patients in the CoreValve/EvolutR group received new pacemakers ($P = .04$). Cumulative event rates for repeat procedures were 1.8% in the Lotus valve group and 2.9% in the CoreValve/EvolutR group ($P = .09$).

The proportion of patients with prosthetic aortic valve thrombosis was 5.8% in the Lotus valve group and 1.8% in the CoreValve/EvolutR group ($P = .007$). Prosthetic aortic valve thrombosis was generally detected during routine echocardiographic follow-up as an increase in the transvalvular gradient. One patient who received the Lotus valve was diagnosed with moderate focal hypoattenuating abnormalities on the leaflets, and the patient's medication was switched to clopidogrel and apixaban. Seven days later, this patient experienced a disabling hemorrhagic stroke and had a modified Rankin score of 3 (indicating moderate disability; patient needs some external help but c an without assistance) at 5 years. A second patient who received the Lotus valve showed leaflet thickening a few months after discontinuing apixaban and underwent a valve-in-valve procedure with a Sapien 3 valve. No other prosthetic aortic valve thromboses required reintervention or resulted in a stroke or death.

Valve Performance at 5 Years

At 5 years of follow-up, mild PVL was less frequent with the Lotus valve compared with the CoreValve/EvolutR (7.8% vs 23.1% patients with mild PVL; $P = .006$), and moderate or greater PVL occurred at a similar rate between cohorts (0% of patients with the Lotus valve vs 1.9% of patients with the CoreValve/EvolutR; $P = .31$) (**Figure 3**A). Mean EOA and mean aortic gradients decreased significantly from baseline in both groups. In the Lotus valve cohort, the mean (SD) EOA increased from 0.69 (0.19) cm^2 to 1.65 (0.47) cm^2 at discharge and was 1.42 (0.42) cm^2 at 5 years (Figure 3B). In the CoreValve/EvolutR cohort, the mean (SD) EOA increased from 0.70 (0.19) cm^2 at baseline to 1.96 (0.52) cm^2 at discharge and was 1.57 (0.56) cm^2 at 5 years. Mean (SD) aortic gradient with the Lotus valve decreased from 44.6 (13.4) mm Hg at baseline to 12.2 (5.2) mm Hg at discharge and was stable at 12.6 (6.7) mm Hg at 5 years (Figure 3B). Mean (SD) aortic gradient also decreased with the CoreValve/EvolutR from 43.9 (12.3) mm Hg to 8.2 (4.0) mm Hg at discharge and was 7.8 (4.2) mm Hg at 5 years. Mean (SD) EOA was significantly lower (1.42 [0.42] cm^2 vs 1.57 [0.56] cm^2; $P < .001$) and mean (SD) aortic gradient (12.64 [6.68] mm Hg vs 7.79 [4.20] mm Hg; $P < .001$) was significantly higher in the Lotus valve group vs the CoreValve/EvolutR group at each follow-up time point except at 5 years. A smaller proportion of patients who received the Lotus valve vs the CoreValve/EvolutR experienced valve malpositioning (0% vs 2.6%; $P < .001$) and required the use of a second valve (1.0% vs 3.8%; $P < .001$) during the procedure.

Figure 2. Cumulative Event Curve for Death and Stroke



Event rates were calculated using the Kaplan-Meier method. Error bars indicate SEs.

Functional and Health Status at 5 Years

At baseline, most patients had an NYHA functional class of III or IV (**Figure 4**A). Of the patients who survived, 91.7% (166 of 181) who received the Lotus valve and 82.4% (70 of 85) who received the CoreValve/EvolutR had an NYHA functional class of I (indicating no limitation of physical activity) or class II (indicating slight limitation of physical activity) at 5 years. Patients in both the Lotus valve and CoreValve/EvolutR groups improved from baseline by 1 or more NYHA classes (81.8% [148 of 181] vs 74.1% [63 of 85]; *P* = .15) or by 2 or more NYHA classes (26.5% [48 of 181] vs 27.1% [23 of 85]; *P* = .93) (Figure 4B). The functional status of patients who were assessed using the Kansas City Cardiomyopathy Questionnaire is shown in Figure 4C and D. There were no significant differences between the 2 cohorts at any time point.

Discussion

In this secondary analysis of the 5-year outcomes of the REPRISE III trial, we found that patients treated with the Lotus valve had similar mortality rates, fewer disabling strokes, and similar repeat procedures compared with those who received the CoreValve/EvolutR. The Lotus valve cohort had higher aortic gradients, more new pacemaker implantations, and higher incidence of prosthetic aortic valve thrombosis events. Hemodynamics and health and functional status were maintained long term in both groups. Overall, the results show that TAVR valves are durable in the midterm, even if the 2 valves studied in the trial are no longer in use.

The Lotus valve was introduced in April 2012 and achieved Conformité Européenne mark in October 2013. The REPRISE III trial was the US investigational device exemption trial and published results at 1 and 2 years.[12,13] The US Food and Drug Administration approved Lotus Edge in April 2019. The Lotus valve was designed to address important limitations of other TAVR valves, most notably related to paravalvular regurgitation.[17,18]

The mechanism of deployment of the Lotus valve was different from either balloon expansion or self-expansion of other valves. The Lotus valve consisted of a bioprosthetic aortic valve that was preattached to the delivery system so as to not require mounting or crimping in the catheterization laboratory or operating room. The valve was progressively unsheathed, deployed, and then locked using a unique mechanical expansion mechanism that foreshortened the valve lengthwise while

Table. Time-to-Event Rates for Valve Academic Research Consortium-2 End Points at 5 Years After Randomization in the Intention-to-Treat Population

End point	Patients, No. (%)[a]		Hazard ratio (95% CI)
	Lotus valve (n = 607)	CoreValve/EvolutR (n = 305)	
All-cause mortality or disabling stroke	297 (52.8)	158 (56.0)	0.89 (0.73-1.08)
All-cause mortality	286 (50.9)	146 (52.8)	0.95 (0.78-1.16)
Cardiovascular mortality	180 (35.7)	102 (40.7)	0.85 (0.67-1.09)
Stroke	68 (14.1)	40 (15.3)	0.84 (0.57-1.24)
Disabling	39 (8.3)	31 (12.2)	0.61 (0.38-0.98)
Nondisabling	31 (6.4)	10 (4.0)	1.55 (0.76-3.17)
Major vascular complications	45 (7.5)	19 (6.4)	1.21 (0.71-2.06)
Permanent pacemaker implantation: all patients	219 (38.9)	72 (27.3)	1.71 (1.31-2.23)
Pacemaker-naive patients	219 (48.6)	72 (35.2)	1.67 (1.28-2.18)
Life-threatening or disabling bleeding	103 (21.2)	52 (21.0)	1.00 (0.71-1.39)
Myocardial infarction	50 (11.0)	27 (12.4)	0.90 (0.56-1.44)
Repeat procedure for valve-related dysfunction	7 (1.8)	8 (2.9)	0.43 (0.15-1.17)
Hospitalization[b]	163 (34.7)	78 (31.6)	1.01 (0.77-1.32)
New onset of atrial fibrillation or flutter	41 (6.9)	14 (4.7)	1.50 (0.82-2.74)
Prosthetic aortic valve thrombosis	27 (5.8)	3 (1.8)	4.52 (1.37-14.91)

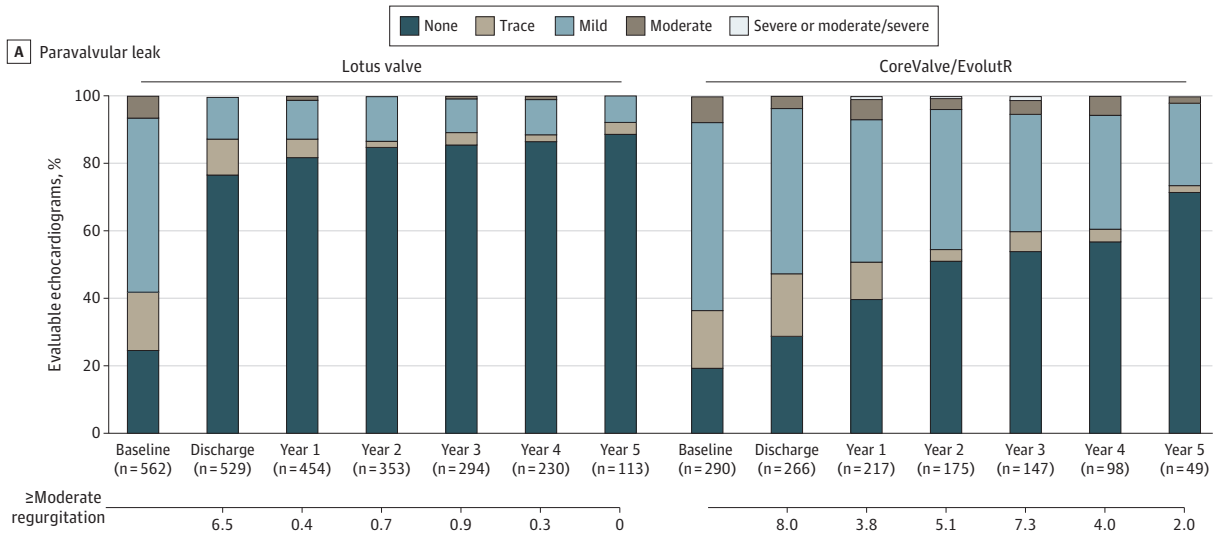
[a] As time-to-event rates, the denominator is the starting patient population. The numbers are not No./total No. because of censoring.

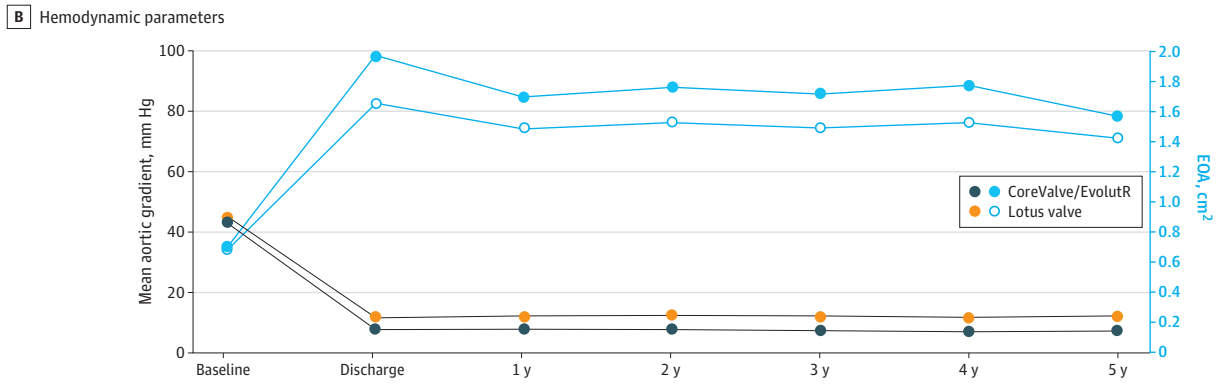
[b] Hospitalization for valve-related symptoms or worsening congestive heart failure (New York Heart Association class III or IV).

expanding its diameter. This mechanism allowed for full repositioning and resheathing, even in the completely expanded position. The valve functioned early in deployment, which provided hemodynamic stability for the patient and enabled the operator to determine if the valve was functioning as desired (if not optimal, the valve could be repositioned for precise device placement). The Lotus valve was the first TAVR valve to employ an adaptive seal, a flexible polyurethane sealing membrane around the lower part of the outer surface of the nitinol frame. The seal was designed to fill any potential space between the native annulus and prosthesis and thus minimize PVL. Sealing skirts have subsequently become popular in new devices, including the Sapien (Edwards Lifesciences Corporation) and Evolut (Medtronic) families.[19-21]

In the REPRISE III trial, prosthetic aortic valve thrombosis occurred more frequently with the Lotus valve than with the CoreValve/EvolutR. Most patients were diagnosed during routine echocardiographic follow-up, and treatment with anticoagulants resolved hemodynamic impact in most cases. More recent studies found that intra-annular valves were associated with a 2-fold increase in the risk of developing subclinical leaflet thrombosis, compared with supra-annular valves.[22,23] Prosthetic aortic valve thrombosis may increase the risk of stroke and transient ischemic

Figure 3. Hemodynamic Parameters From Baseline to 5 Years





Mean aortic gradient							
CoreValve/EvolutR	294	280	220	177	138	107	33
Lotus valve (N)	575	564	465	382	273	243	114
EOA							
CoreValve/EvolutR	280	246	200	168	150	107	43
Lotus valve (N)	541	510	422	327	303	243	94

Aortic regurgitation is shown only at baseline; paravalvular leak is shown at discharge to 5 years. EOA indicates effective orifice area.

attack[24]; however, no increased incidence of stroke associated with prosthetic aortic valve thrombosis was found in the REPRISE III trial.

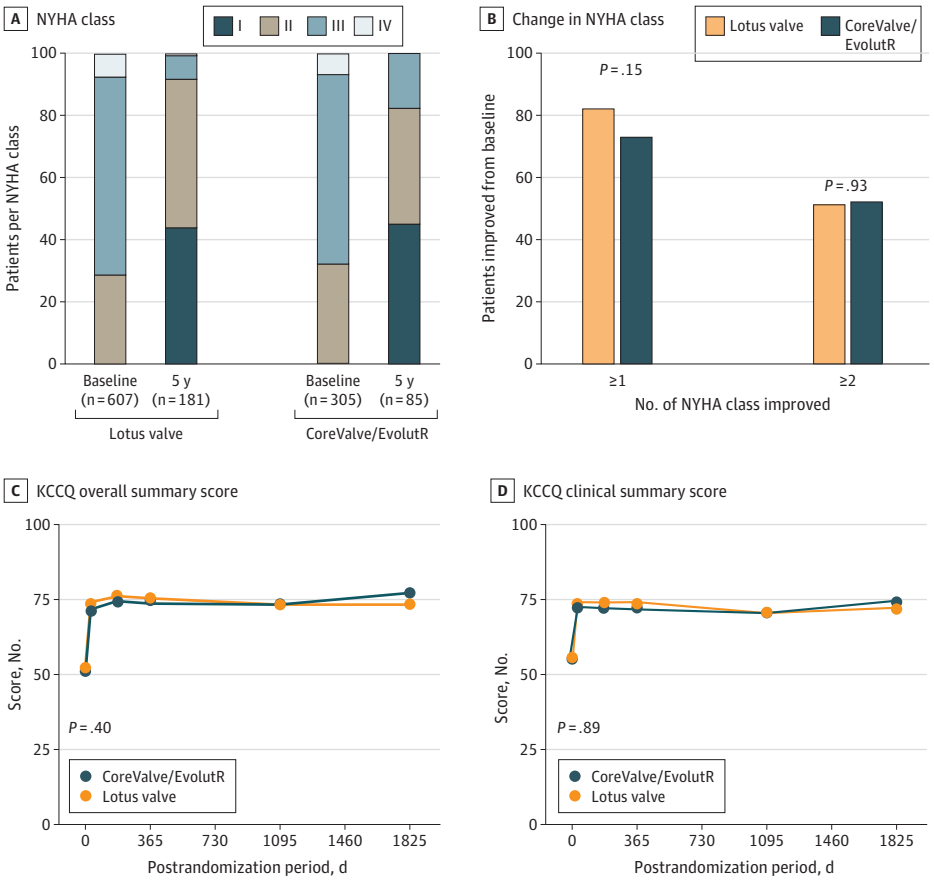
Over 5 years, mean transvalvular gradients remained stable among patients in both groups and within the range observed in previous studies.[25-28] Effective orifice area was lower than expected in the CoreValve/EvolutR cohort (1.66 cm^2 to 2.2 cm^2),[26,29] although the number of patients with hemodynamic data at 5 years was low, which may have influenced the results. Long-term differences in hemodynamics between intra-annular and supra-annular valves have not affected clinical outcomes.[30]

Although the Lotus and Lotus Edge valves were promising new devices, the Lotus valve was withdrawn from the market due to manufacturing challenges, the need for enhancements to the delivery system, and limited market adoption rates. Despite being off the market, the Lotus valve was implanted in more than 10 000 patients. Hence, it is of paramount importance for living recipients of this valve and their physicians to be aware of the long-term follow-up data from a clinical trial of the device.

Limitations

This study has some limitations. The evaluated valves are no longer on the market or have largely been replaced by newer-generation valves. In addition, the REPRISE III trial included only patients with high surgical risk and may not be applicable to other patient populations.

Figure 4. Symptom Status From Baseline to 5 Years



KCCQ indicates Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.

Conclusions

This secondary analysis found that, at 5 years, the clinical outcomes observed with the Lotus valve were generally comparable to outcomes of the CoreValve/EvolutR. The Lotus valve was a safe and effective treatment for aortic stenosis.

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Author Contributions: Drs Reardon and Rizik had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Rizik, Kereiakes, Thourani, Buchbinder, Allocco, Reardon.

Acquisition, analysis, or interpretation of data: Rizik, Rajagopal, Makkar, Bajwa, Kleiman, Linke, Waksman, Stoler, Mishkel, Iyer, Götberg, Bjursten, Reardon.

Drafting of the manuscript: Rizik, Rajagopal, Reardon.

Critical revision of the manuscript for important intellectual content: Rizik, Rajagopal, Makkar, Bajwa, Kleiman, Linke, Kereiakes, Waksman, Thourani, Stoler, Mishkel, Iyer, Buchbinder, Götberg, Bjursten, Allocco, Reardon.

Statistical analysis: Rizik, Makkar, Iyer.

Administrative, technical, or material support: Linke, Kereiakes, Stoler, Iyer.

Supervision: Rizik, Bajwa, Kereiakes, Thourani, Stoler, Iyer, Götberg, Bjursten, Allocco, Reardon.

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outside the submitted work. Dr Thourani reported receiving personal fees from Boston Scientific Corporation outside the submitted work. Dr Stoler reported receiving personal fees from Boston Scientific Corporation and Medtronic during the conduct of the study and personal fees from Edwards Lifesciences Corporation outside the submitted work. Dr Iyer reported receiving grants from Boston Scientific Corporation during the conduct of the study. Dr Götberg reported receiving personal fees from Boston Scientific Corporation during the conduct of the study and personal fees from Medtronic and Philips Healthcare outside the submitted work. Dr Bjursten reported receiving personal fees and grants from Boston Scientific Corporation during the conduct of the study. Dr Allocco reported receiving personal fees from, being an employee of, and holding stock or stock options in Boston Scientific Corporation during the conduct of the study. Dr Reardon reported receiving consulting fees from Boston Scientific Corporation and Medtronic paid to his department outside the submitted work. No other disclosures were reported.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
Data Sharing Statement