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Transfemoral aortic valve replacement with the repositionable Lotus Valve System in high surgical risk patients: the REPRISE I study

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KEYWORDS

- aortic valve stenosis
- paravalvular regurgitation
- transcatheter aortic valve replacement (TAVR)

Abstract

Aims: To assess outcomes with a new fully repositionable and retrievable valve for transcatheter aortic valve replacement (TAVR).

Methods and results: The Lotus Aortic Valve System is designed to facilitate precise positioning and minimise paravalvular regurgitation. REPRISE I enrolled symptomatic, high-surgical-risk patients with severe aortic stenosis. The primary endpoint (clinical procedural success) included successful implantation without major adverse cardiovascular or cerebrovascular events (MACCE). In all patients (N=11) the first Lotus Valve was successfully deployed. Partial resheathing to facilitate accurate placement was attempted and successfully performed in four patients; none required full retrieval. The primary endpoint was achieved in 9/11 with no in-hospital MACCE in 10/11. There was one major stroke; in another patient, discharge mean aortic gradient was 22 mmHg (above the primary endpoint threshold of 20 mmHg), but improved to 15 mmHg at 30 days. The cohort's mean aortic gradient decreased from 53.9±20.9 mmHg at baseline to 15.4±4.6 mmHg ($p<0.001$) at one year; valve area increased from 0.7±0.2 cm^2 to 1.5±0.2 cm^2 ($p<0.001$). Discharge paravalvular aortic regurgitation, adjudicated by an independent core laboratory, was mild (n=2), trivial (n=1), or absent (n=8). Four patients required a permanent pacemaker post-procedure. There were no deaths, myocardial infarctions or new strokes through one year.

Conclusions: Initial results support proof-of-concept with the Lotus Valve for TAVR.

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Introduction

Transcatheter aortic valve replacement (TAVR) has become a viable alternative for the treatment of severe symptomatic aortic stenosis in selected patients who are poor candidates for surgical valve replacement[1]. Encouraging short- and longer-term data on prosthetic valve function and clinical outcomes have been reported in a number of large observational registries from various countries[2-8]. In the randomised Placement of AoRTic TraNscathetER Valves (PARTNER) trial, patients unsuitable for surgical valve replacement who underwent TAVR experienced significant reductions in mortality and repeat hospitalisation compared to those receiving conventional medical therapy through two years[9]; high-surgical-risk patients receiving either TAVR or surgical replacement had a similar mortality risk[10].

Notwithstanding these favourable results, TAVR with early-generation devices has been associated with increased stroke risk versus surgical valve replacement[10,11], and paravalvular regurgitation more commonly seen with TAVR compared to surgery may be associated with higher early and late mortality[7,10,12,13]. While judicious patient selection may serve to mitigate these risks[14-16], device design improvements may enable more precise placement and minimise or eliminate paravalvular regurgitation. The transcatheter Lotus™ Aortic Valve (Boston Scientific Corporation, Natick, MA, USA) is fully retrievable and repositionable with a unique adaptive seal designed to minimise paravalvular regurgitation. The first human implantation of the initial Lotus Valve has been described previously[17]. We describe here the one-year results with a later version of the Lotus prosthesis in the prospective, single-arm REPRISE I feasibility study which was designed to assess the acute safety and performance of this novel system in patients at high risk for surgical intervention (ClinicalTrials.gov registration number NCT01383720).

Methods

DEVICE DESCRIPTION

The Lotus™ Aortic Valve Replacement System (**Figure 1**; Boston Scientific Corporation) has been described previously[18]. Briefly, the system includes a bioprosthetic aortic valve implant consisting of three bovine pericardial leaflets attached to a braided nitinol frame with a radiopaque marker and a catheter-based system for introduction and retrograde delivery via the femoral artery. One valve size, 23 mm, was available for this study. The valve is pre-attached to the delivery system. The Lotus Valve functions early in deployment, aiding controlled, precise initial positioning, repositioning or full retrieval at any point prior to release if required. Rapid pacing is not required during the implant procedure. The valve is designed to expand radially as the valve shortens during deployment. An adaptive seal surrounds the inflow portion of the device and is designed to minimise paravalvular regurgitation. The device was introduced percutaneously through a dedicated introducer sheath (outer diameter the same size as a conventional 18 Fr sheath) via the femoral artery using conventional percutaneous catheterisation techniques or via a surgical cut-down. Patients with a femoral artery lumen diameter ≥6.0 mm were eligible for inclusion in the trial.

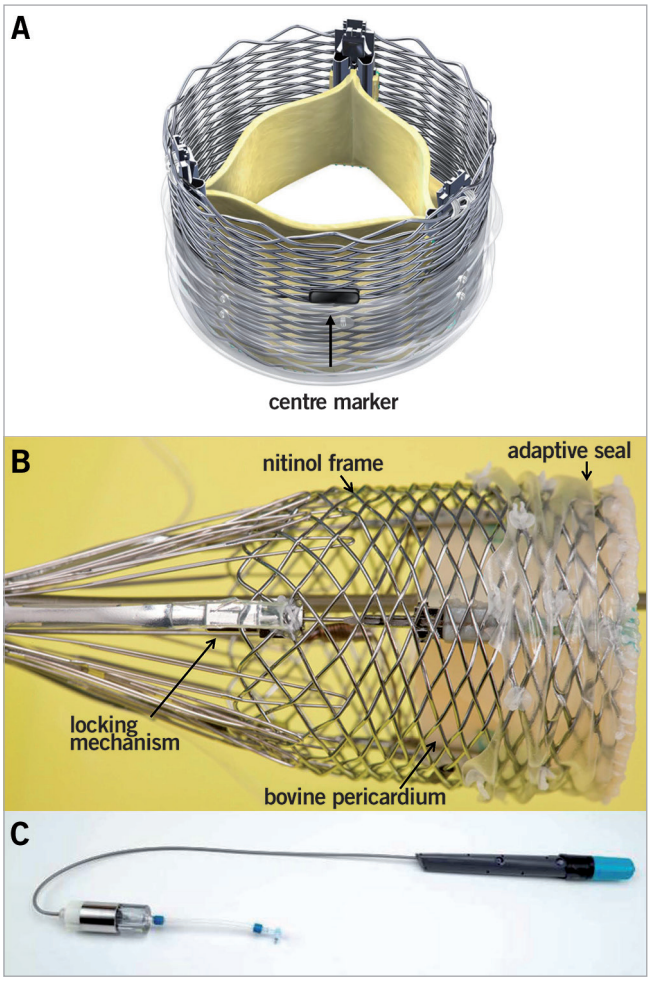

Figure 1. *Lotus Aortic Valve Replacement System. Pictured is the 23 mm Lotus Valve with three bovine pericardial tissue leaflets and a central radiopaque marker to aid positioning (A), a polyurethane/polycarbonate outer seal to minimise paravalvular leakage and a braided nitinol frame with post- and buckle- locking mechanisms for valve stabilisation in vivo (B). The braided structure foreshortens and expands radially when delivered and is locked in position using the post- and buckle- locking mechanism. The Lotus Delivery Catheter has a handle with one control used to deploy the valve, a second control to detach the deployed valve and a guard to prevent inadvertent release (C).*

PATIENT SELECTION

Enrolled patients had symptomatic aortic valve stenosis with New York Heart Association (NYHA) functional Class ≥II and documented calcific aortic valve stenosis, with an initial aortic valve area (AVA) of <1.0 cm^2 (or AVA index of <0.6 cm^2/m^2), and either a mean pressure gradient >40 mmHg, or a jet velocity >4 m/s, as measured by transthoracic echocardiography (TTE). Patients were deemed high-risk based on a Society of Thoracic Surgery score ≥8%[19], a logistic EuroSCORE ≥20%[20] or multidisciplinary Heart Team (including an interventional cardiologist and a cardiothoracic surgeon) agreement that frailty and/or coexisting comorbidities

would be associated with a high surgical risk. Patients had a documented aortic annulus size between 19 and 22 mm (able to accommodate the 23 mm Lotus Valve). Key exclusion criteria included congenital unicuspid or bicuspid aortic valve, acute myocardial infarction (MI), transient ischaemic attack (TIA) or stroke within the previous six months or any permanent neurological defect, severe renal insufficiency, pre-existing prosthetic heart valve (aortic or mitral) or a prosthetic ring in any position, more than moderate (>2+) mitral or aortic regurgitation, untreated clinically significant coronary artery disease likely to require revascularisation after the procedure and documented left ventricular ejection fraction below 30%. Complete inclusion and exclusion criteria are provided in **Online Appendix A**.

The study was approved by the ethics committee at each participating centre and all patients signed written informed consent before undergoing any study-specific tests or procedures. Screening materials from patients identified by the investigators as having met the inclusion and exclusion criteria were reviewed by a Case Review Committee to assess and confirm eligibility. The committee included the study principal investigator (PI), other investigators experienced with TAVR and sponsor representatives. Patients were considered enrolled once an attempt was made to insert the Lotus introducer sheath into the femoral artery.

PROTOCOL

Screening data reviewed by the Case Review Committee included TTE, coronary angiography, computed tomography angiography of the aortic valve and entire aorta, computed tomography angiography or invasive angiography of the iliofemoral system, Society of Thoracic Surgery score, logistic EuroSCORE, modified Rankin Scale score and the Heart Team assessment. Comprehensive frailty assessments were made prospectively including number of falls in the past six months, average maximum grip strength, 5-metre gait speed[21], Katz Index[22], Physical Activity Scale for Elderly[23], Charlson comorbidity index score[24], and the Mini-Cognitive assessment for dementia[25].

All operators and medical personnel completed comprehensive training prior to implanting patients and received on-site proctorship during implant procedures from a trained proctor experienced in TAVR.

Unfractionated heparin was administered before the procedure started and all implants were performed under general anaesthesia with transoesophageal echocardiographic guidance and with a temporary pacing wire inserted into the right ventricle. The Lotus introducer sheath was passed through the femoral and iliac arterial system and positioned in the descending aorta. A super stiff guidewire (Amplatz; Boston Scientific Corporation) was advanced across the aortic valve and into the left ventricle under fluoroscopic guidance. Balloon valvuloplasty was carried out with rapid ventricular pacing and the Lotus Valve subsequently positioned in the aortic valve annulus. Rapid ventricular pacing was not performed during valve implantation. A case study from REPRISE I with images and a detailed description of the Lotus Valve implantation procedure has been published[18]. Valve position was assessed by TTE and contrast aortography and the valve repositioned if necessary prior to final release. After hospital discharge, clinical follow-up was scheduled for 30 days, 3 months, 6 months, 12 months and then annually from two to five years.

Aspirin (≥150 mg) and clopidogrel (75 mg) once a day for five days prior to the procedure or a loading dose of ≥300 mg pre-implant were required. After the procedure, daily aspirin (100 mg) was required for three months and recommended indefinitely. Clopidogrel (75 mg) once a day was required for three months.

DATA MANAGEMENT, ENDPOINTS AND ADDITIONAL MEASUREMENTS

Study monitors verified all case report form data on site. An independent echocardiography core laboratory (Victor Davila-Román, MD; CVR Consulting, PC; St. Louis, MO, USA) reviewed all images for qualitative and quantitative analysis. All 12-lead electrocardiograms were sent to a core laboratory (Peter J. Zimetbaum, MD; Harvard Clinical Research Institute; Boston, MA, USA) for independent analysis.

The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (device success) without in-hospital major adverse cardiovascular and cerebrovascular events (MACCE, including all-cause mortality, periprocedural MI ≤72 hours, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction) through discharge or seven days post-procedure, whichever came first. Device success, MI, and stroke were defined in accordance with Valve Academic Research Consortium definitions (VARC-1)[26]. Pre-specified secondary endpoints included aortic valve regurgitation and successful repositioning and retrieval of the Lotus Valve System, if attempted.

An independent Clinical Events Committee composed of interventional cardiologists, cardiothoracic surgeons and a neurologist adjudicated death, MI, neurologic events, valve-related dysfunction leading to urgent/emergent conversion to surgery or repeat procedure, bleeding, acute kidney injury, vascular complications, symptomatic coronary obstruction, valve thrombosis, endocarditis, new conduction disturbances and cardiac arrhythmias, requirements for new permanent pacemaker and repeat hospitalisation due to valve- or procedure-related clinical deterioration. Additional measurements at clinical follow-up included valve performance as assessed by TTE, cardiac function as measured by echocardiography, NYHA functional class and health status as evaluated by SF-12 and EQ-5D Quality of Life questionnaires.

Endpoints and measurements are listed in **Online Appendix B** and major endpoint definitions are provided in **Online Appendix C**. Study organisation and oversight committee membership are provided in **Online Appendix D**.

STATISTICAL METHODS

No formal statistical testing was performed for the primary endpoint in this single-arm feasibility study. Subject demographics, clinical history, risk factors, device performance and safety

outcomes are summarised using descriptive statistics for continuous variables and frequency tables for discrete variables. P-values for continuous variables are from the paired Student t-test; p-values for comparison of NYHA class distribution are from the Wilcoxon signed rank test for paired data; p-values for the comparison of repeated measures such as mean aortic gradient are from the repeated measures and random effects ANOVA model. All statistical analyses were undertaken with SAS software (version 8.2 or above; SAS Institute, Inc., Cary, NC, USA).

Results

PATIENTS

Between April 14 and April 20, 2012, 11 patients were enrolled at three investigative sites in Australia **(Online Appendix D)**. There were 15 patients assessed for inclusion and four were deemed not suitable by the Case Review Committee due to aortic annulus too big for a 23 mm valve (n=1), very low take-off of the coronary arteries (n=1), and/or vascular access vessels too small (n=2). **Table 1** shows baseline patient characteristics and echocardiographic assessments. All patients were female and mean age was 83.0±3.6 years. The mean Society of Thoracic Surgeons (STS) score and logistic EuroSCORE were 4.9±2.5% and 9.5±4.4%, respectively. All patients were confirmed by the Heart Team to be at high risk for surgery due to frailty or associated comorbidities **(Table 2)**.

Table 1. Baseline patient characteristics and echocardiographic assessments.

Patient characteristics (N=11)	
Female, no. (%)	11 (100)
Age (years)	83.0±3.6
STS score (%)	4.9±2.5
Logistic EuroSCORE (%)	9.5±4.4
Diabetes mellitus, medically treated, no. (%)	2 (18.2)
NYHA Class II, no. (%)	6 (54.5)
NYHA Class III, no. (%)	5 (45.5)
Hypertension (medically treated), no. (%)	10 (90.9)
Coronary artery disease, no. (%)	5 (45.5)
History of PCI or CABG, no. (%)	2 (18.2)
History of atrial fibrillation, no. (%)	5 (45.5)
History of peripheral vascular disease, no. (%)	1 (9.1)
History of cerebrovascular accident, no. (%)	2 (18.2)
Echocardiographic assessments (N=11)	
Aortic valve area (effective orifice area) (cm^2)	0.68±0.19
Mean aortic valve gradient (mmHg)	53.9±20.9
Left ventricular ejection fraction (%)	62.3±7.6
Aortic regurgitation (moderate or severe), no. (%)	4 (36.4)
Mitral regurgitation (moderate or severe), no. (%)	3 (27.3)

Values are mean±standard deviation or n (%). CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons

Table 2. Baseline frailty/disability/comorbidity assessments.

Assessment	REPRISE I (N=11)	Threshold*
Body mass index (kg/m^2)	27.6±6.0	<19
Serum albumin (g/dL)	3.9±0.4	<3.3
5-metre gait speed (sec)	8.2±4.9	>6
Maximum grip strength average (kg)	15.3±5.7	≤18¶
Katz Index	5.9±0.3	<6
Physical activity scale for elderly (0-400)	85.5±44.7	≤93.4‡
Charlson Comorbidity Index score	1.8±1.7	>3
Mini-Cognitive assessment for dementia	3.3±1.5	<4

Values are mean±standard deviation. *References 41-45; ¶Cut-off for women with BMI <26.1-29; ‡Pre-frailty; BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

OUTCOMES

PROCEDURE

In all patients the first Lotus Valve was successfully deployed. Limited recapture to facilitate accurate final positioning was easily accomplished in all cases attempted (n=4). Valve retrieval was not required and thus not attempted in any patient. Procedure and fluoroscopy time were 110.4±34.7 minutes and 36.9±8.8 minutes, respectively, with 200±74.3 cc of contrast used.

PRIMARY ENDPOINT

The primary endpoint was met in 9/11 patients **(Table 3)**; one patient (Patient A) experienced an in-hospital stroke and one patient (Patient B) experienced device failure. The major ischaemic stroke occurred two days post-index procedure; the modified Rankin Scale score in this patient was 0 at baseline and 3 at one year. Patient B experienced a device failure based on mean aortic valve gradient of 22.1 mmHg and peak velocity of 328 cm/s. Although this event met one of the VARC-1 criteria for device failure, the core lab noted that the valve appeared to be functioning well and the mildly elevated gradient and velocity were likely related to increased flow across the

Table 3. Primary endpoint – discharge/7 days.

Outcome	REPRISE I (N=11)
Clinical procedural success (per patient), no. (%)	9 (81.8)
Device success, no. (%)	10 (90.9)
Successful access, delivery, deployment, valve positioning, delivery system retrieval, no. (%)	11 (100)
Intended valve performance, no. (%)*	10 (90.9)
One valve implanted, no. (%)	11 (100)
No MACCE through discharge or 7 days, no. (%)¶	10 (90.9)

*Aortic valve area >1.0 cm^2 plus either a mean aortic valve gradient <20 mmHg or peak velocity <3 m/sec, without moderate/severe prosthetic valve aortic regurgitation; ¶Major adverse cardiovascular or cerebrovascular events including all-cause mortality, periprocedural myocardial infarction ≤72 hours, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction

aortic valve. The AVA was 1.6 cm^2 and the left ventricular outflow tract/ascending aorta time-velocity integral ratio was 0.51 at discharge. At 30-day and one-year follow-up, the mean transvalvular gradients were 15.0 and 20.0 mmHg, respectively, and the peak velocities were 279 cm/s and 301 cm/s, respectively.

CLINICAL OUTCOMES

Table 4 shows clinical outcomes at discharge, 30 days, and one year. There were no additional MACCE events beyond the primary endpoint. The VARC-1 combined safety endpoint, including MACCE, life-threatening/disabling bleeding, major vascular complications, and Stage 3 acute kidney injury[26], was 3/11 through one year. Patient A experienced a small left femoral dissection that was successfully treated with balloon inflation during the procedure but qualified as a VARC-1 major vascular complication due to the balloon inflation. There were two life-threatening/disabling bleeds through 30 days; neither was related to valve implantation and both resolved. In one case, the patient was successfully treated with pericardiocentesis on day 14 for an event considered related to permanent pacemaker implantation on day four. Another patient had a gastrointestinal bleed on day 20 and received transfusion of multiple units of packed red blood cells. There were also two major bleeding events that occurred in the periprocedural period; neither was associated with TAVR access. One patient developed a haematoma at the site of a left brachial arterial line and another developed one at the site of the right internal jugular sheath. In Patient B and three other patients, conduction disturbances led to implantation of a permanent pacemaker before discharge; two of these four patients had paced rhythm at one year **(Table 5)**. A single REPRISE I patient experienced new-onset atrial fibrillation, which occurred at day 52 post-procedure. While all REPRISE I patients were NYHA Class II (n=6) or III (n=5) at baseline, this distribution was significantly improved between baseline and 30 days (three in Class I, seven in Class II, one in Class III; p=0.02) and baseline and one year (five in Class I, six in Class II; p=0.004).

Table 4. Clinical outcomes at discharge, 30 days and 1 year.

Outcome (N=11)	Discharge	30 days	1 year
MACCE, no. (%)	1 (9.1)	1 (9.1)	1 (9.1)
Death, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction ≤72 hours, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)
Major stroke, no. (%)	1 (9.1)	1 (9.1)	1 (9.1)
Urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular complications			
Major, no. (%)	1 (9.1)	1 (9.1)	1 (9.1)
Minor, no. (%)	1 (9.1)	1 (9.1)	1 (9.1)
Bleeding			
Life-threatening/disabling, no. (%)*	0 (0.0)	2 (18.2)	2 (18.2)
Major, no. (%)¶	2 (18.2)	2 (18.2)	2 (18.2)
Acute kidney injury			
Stage 1, no. (%)	1 (9.1)	1 (9.1)	1 (9.1)
Stage 2 or 3, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)
Conduction disturbance requiring new pacemaker, no. (%)	4 (36.4)	4 (36.4)	4 (36.4)
Myocardial infarction >72 hours, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)
Minor stroke or transient ischaemic attack, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)

*Not related to valve implantation; ¶Not related to TAVR access; MACCE: major adverse cardiovascular or cerebrovascular events; TAVR: transcatheter aortic valve replacement

ECHOCARDIOGRAPHY

Valve performance data as determined by independent core lab analyses of TTE outcomes are shown in **Table 6** and **Figure 2**-**Figure 4**. Changes in peak aortic velocity, mean and peak aortic valve gradient and effective orifice area were statistically significant from baseline to discharge, baseline to 30 days and baseline to one year (p<0.001 for each paired analysis). **Figure 2** shows mean aortic valve gradient and **Figure 3** shows effective orifice area by patient at baseline and at each time point. There was no moderate or severe paravalvular aortic regurgitation observed in any patient at any time point **(Figure 4)**. At one year, one patient had mild regurgitation, one patient had trivial and nine patients had none.

Discussion

This feasibility study assessed the acute safety and performance of the fully repositionable transcatheter Lotus Aortic Valve Replacement System in symptomatic high-risk surgical patients with calcific aortic valve stenosis. The prosthetic valve was positioned successfully in all patients (N=11) with no moderate or severe aortic regurgitation after placement or through one year. Clinical procedural success was achieved in 9/11 patients (one major stroke and one device failure based on a slightly elevated

Table 5. Conduction disturbances requiring new pacemaker.

Baseline				Pacemaker implant day*	Indication	Paced rhythm at 1 year
Rhythm	PR (ms)	QRS (ms)	IV conduction			
Sinus	180	84	Normal	5	CHB	No
Sinus	221	76	Normal	4	CHB	No
AF	180	150	RBBB	0	AF with slow ventricular rate	Yes
Sinus	151	113	LAFB	4	LBBB and sinus bradycardia	Yes

*Days post-index procedure; AF: atrial fibrillation; CHB: complete heart block; LAFB: left anterior fascicular block; LBBB: left bundle branch block; RBBB: right bundle branch block

Table 6. Transthoracic echocardiography data.

Outcome (N=11)	Baseline	Discharge	30 days	1 year
Peak aortic velocity (cm/s)*	471.0±85.0	257.8±31.2	235.4±31.0	264.5±29.3
Peak aortic gradient (mmHg)*	90.5±30.6	27.0±6.8	22.4±5.9	28.1±6.4
Mean aortic gradient (mmHg)*	53.9±20.9	13.7±3.7	11.7±3.0	15.4±4.6
Effective orifice area (cm^2)*	0.68±0.19	1.53±0.18	1.59±0.14	1.51±0.22
LVEF (%)	63.1±7.1	64.0±6.7	64.3±5.8	65.3±6.0
LV end-systolic volume (mL)	24.9±6.6	24.5±6.2	23.3±6.2	23.1±5.2
LV end-diastolic volume (mL)	66.9±11.6	67.5±7.7	64.6±9.6	66.8±11.5
Mitral regurgitation (mod/sev)	3 (27.3)	3 (27.3)	3 (27.3)	1 (9.1)¶

* Significant change (p<0.001) from baseline to discharge, baseline to 30 days and baseline to 1 year (paired Student's t-test); † No severe mitral regurgitation; Values are mean±standard deviation or n (%); LVEF: left ventricular ejection fraction

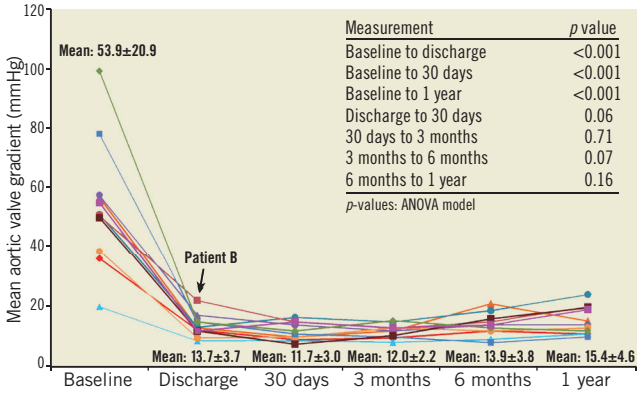

Figure 2. *Mean aortic valve gradient per patient by transthoracic echocardiography. Data are shown for each of the 11 patients at the five time points; cohort mean values at each time point include standard deviation.*

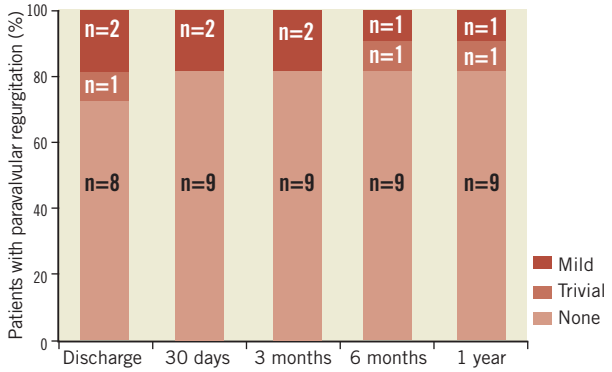

Figure 4. *Paravalvular aortic regurgitation. There were no cases of moderate or severe paravalvular regurgitation.*

aortic gradient/velocity which improved with time), with no additional MACCE through one year. All patients were alive at one year and there was a marked improvement in functional class across the cohort compared to baseline. Thus, these results support proof of concept with the Lotus Valve in TAVR in this patient subset.

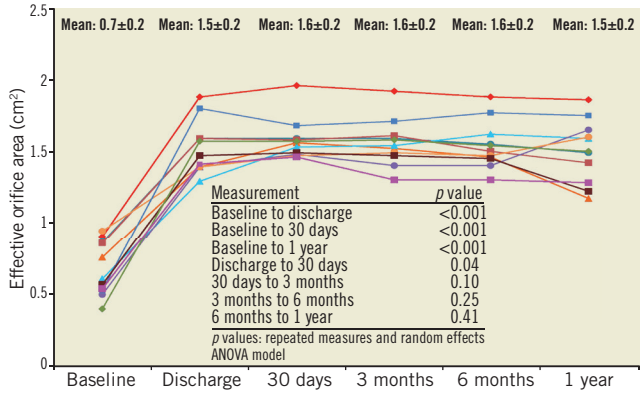

Figure 3. *Effective orifice area per patient by transthoracic echocardiography. Data are shown for each of the 11 patients at the five time points; cohort mean values at each time point include standard deviation.*

PATIENT SELECTION

As existing risk scores imperfectly characterise risk, each centre's Heart Team considered other comorbidities and patient frailty **(Table 2)** in addition to using STS and EuroSCORE. While not captured well by any of the standard risk scores, these added measures helped to more fully characterise a patient population that potentially benefits from TAVR.

VALVE FUNCTION

The novel Lotus Valve System incorporates several features intended to improve upon early-generation devices. The valve functions early in deployment, providing haemodynamic stability and allowing controlled, precise deployment, recapture and subsequent repositioning/redeployment or removal as necessary. Repositioning was successful in all attempted cases (n=4), with no requirements for full retrieval. As described in a REPRISE I case study, the capacity to retrieve and reposition the device easily allowed for more optimal annular positioning even when initial valve placement was considered acceptable[27]. Clinical procedural success was high (9/11) and comparable to results reported with other bioprosthetic aortic valves[2,3,28-30]. The one patient with device failure had a gradient that was slightly above the VARC-1 threshold, and this failure was likely due to increased flow across the aortic valve as

opposed to any valve dysfunction. Mean transvalvular gradient and peak velocity for this patient improved at later time points. In the overall cohort, there was a significant improvement in valve function from a mean aortic gradient of 53.9±20.9 mmHg at baseline to 15.4±4.6 mmHg at one year ($p<0.001$).

PARAVALVULAR REGURGITATION

Implantation of the Lotus Valve with its adaptive seal designed to mitigate paravalvular regurgitation resulted in 8/11 patients with no paravalvular regurgitation at discharge and trivial or mild regurgitation in the others. This result was maintained at one year as one patient had trivial, one had mild, and nine had no regurgitation **(Figure 4)**. Reported moderate or severe aortic regurgitation after TAVR has ranged from 6% to 21%[31]. In the FRANCE 2 registry[8], 30-day paravalvular regurgitation of grade 2 or more (on a scale of 0 to 4) post-implantation of commercially available TAVR devices was an independent predictor of one-year mortality. In the Italian CoreValve registry[7], post-procedural paravalvular leak ≥2+ independently predicted mortality between 30 days and one year. While the effect of paravalvular regurgitation on mortality was proportional to its severity in the PARTNER trial, an increased rate of late deaths through two years was seen with even mild regurgitation[10]. The current results with the Lotus Valve compare very favourably to aortic regurgitation outcomes in the first-human-use study of another repositionable valve[32] as well as with other commercially available transcatheter valves[3,4,6-8,33].

PACEMAKER IMPLANTATION

Reported rates for early conduction abnormalities and the need for pacemaker implantation after TAVR have ranged from 3% to 40%[1,6-8,11,33-39]. Of the four REPRISE I patients who required implantation of a new permanent pacemaker before discharge, three had conduction abnormalities at baseline; only two patients had paced rhythm at one year. Pre-existing conduction disease has been identified as a predictor of permanent pacemaker implantation post TAVR[40]. A recent account following transfemoral TAVR noted similar 12-month clinical outcomes among patients with periprocedural permanent pacemaker implantation compared to those without[39].

Study limitations

Limitations of this study include the small number of patients typical of a human feasibility study which was insufficient to provide accurate estimates of clinical event rates, and the absence of a randomised control group. The currently used surgical risk scores imperfectly characterise surgical risk. The centre Heart Team assessment thus included factors not accounted for by these risk scores **(Table 2)**. The absence of mortality through one year could be due, at least in part, to the inclusion of lower-risk patients. The study was conducted with a single, small valve size and as a result all participants were female; thus the results of this trial may not be representative of outcomes in an unselected population. Greater understanding of the impact of this technology on paravalvular leak and the need for permanent pacemakers can only be drawn from a larger study approximating a more normal distribution of aorto-annular dimensions.

Conclusions

In this small feasibility study, the Lotus Valve could be positioned precisely and successfully with minimal aortic regurgitation after placement. Haemodynamic and clinical benefits achieved upon valve implant have been sustained out to one year with a low rate of adverse events in this patient population. The larger REPRISE II study in high-risk surgical patients will further evaluate the safety and efficacy of this novel bioprosthetic aortic valve.

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Boston Scientific Corporation, Natick, MA, USA.

Conflict of interest statement

I.T. Meredith reports receiving consultant fees and honoraria from Abbott Vascular, Boston Scientific, and Medtronic. S.G. Worthley reports receiving consultant fees and honoraria from Medtronic and St. Jude. A.E. Newcomb reports receiving unrestricted educational funding from Boston Scientific. S. Lockwood reports receiving consulting fees from Boston Scientific. Ms. Haratani was a full-time employee of Boston Scientific and a stockholder of Sadra Medical and Boston Scientific Corporation. D.J. Allocco and K.D. Dawkins are full-time employees and stockholders of Boston Scientific Corporation. R.J. Whitbourn, P. Antonis, and J.K. Montarello have no conflicts of interest to declare.

References

The references can be found in the online version of the paper.

Online data supplement

Online Appendix A. REPRISE I inclusion and exclusion criteria.
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Online data supplement

Appendix A. REPRISE I inclusion and exclusion criteria.

CLINICAL INCLUSION CRITERIA
Subject must be at least 70 years of age or older.
Subject has documented calcified native aortic valve stenosis with an initial aortic valve area of <1.0 cm^2 (or AVA index of <0.6 cm^2/m^2) and either a mean pressure gradient >40 mmHg or a jet velocity >4 m/s, as measured by echocardiography.
Subject is considered at high risk for surgical aortic valve replacement with a STS score ≥8% or a EuroSCORE ≥20%, or documented multidisciplinary Heart Team agreement that the subject is at high risk for surgery due to frailty and/or coexisting comorbidities.
Symptomatic aortic valve stenosis with NYHA functional Class ≥II.
Subject has a documented aortic annulus size between 19 and 22 mm (able to accommodate the 23 mm Lotus Valve). Preprocedure measurement by TTE is required. Other imaging modalities (e.g., TEE, CT scan, etc.) can be used in an adjunctive manner.
Subject (or legal representative) understands the study requirements and the treatment procedures and provides written informed consent.
Subject agrees and is capable of returning to the study hospital for all required scheduled follow-up visits.
CLINICAL EXCLUSION CRITERIA
Subject has a congenital unicuspid or bicuspid aortic valve.
Subject with an acute MI within 30 days of the index procedure (defined as Q-wave MI, or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin level elevation [WHO definition]).
Subject has had a CVA or TIA within the past six months or has any permanent neurologic defect prior to study enrolment.
Subject is on dialysis or has serum creatinine level >3.0 mg/dL.
Subject has a pre-existing prosthetic heart valve (aortic or mitral) or a prosthetic ring in any position.
Subject has >2+ mitral regurgitation or >2+ aortic regurgitation (i.e., subject cannot have more than moderate mitral or aortic regurgitation).
Subject has moderate to severe pulmonary hypertension (PA systolic pressure >60 mmHg) as assessed by TTE.
Subject has a need for emergency surgery for any reason.
Subject has a history of endocarditis within 12 months of index procedure or evidence of an active systemic infection or sepsis.
Subject has echocardiographic evidence of intracardiac mass, thrombus or vegetation.
Subject has Hgb <9 g/dL, platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, or WBC count <3,000 cells/mm^3.
Subject is receiving chronic (≥72 hours) anticoagulation therapy (e.g., warfarin, heparin, etc.), and cannot tolerate concomitant therapy with aspirin and clopidogrel (subjects who require chronic anticoagulation must be treated with either aspirin or clopidogrel).
Subject has active peptic ulcer disease, gastrointestinal bleed within the past three months, other bleeding diathesis or coagulopathy or will refuse transfusions.
Subject is contraindicated for TEE.
Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all thienopyridines, heparin, nickel, titanium or polyurethanes.
Subject has a life expectancy of less than 12 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrolment.
Subject has other cardiac devices or hardware which will interfere with study device placement (per physician judgement).
Subject has hypertrophic obstructive cardiomyopathy.
Subject has any therapeutic invasive cardiac procedure within 30 days prior to the index procedure.
Subject has untreated clinically significant coronary artery disease requiring revascularisation.
Subject has documented LVEF<30%.
Subject is in cardiogenic shock or has haemodynamic instability requiring inotropic support or mechanical support devices.
Subject has severe peripheral vascular disease (including aneurysm defined as maximal luminal diameter >5 cm or documented presence of thrombus, marked tortuosity, narrowing of the abdominal aorta, severe unfolding of the thoracic aorta or thick [>5 mm], protruding or ulcerated atheroma in the aortic arch) or symptomatic carotid or vertebral disease.
Femoral artery lumen of <6.0 mm or severe iliofemoral tortuosity or calcification that would prevent safe placement of the introducer sheath.
Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.).
Subject is participating in another investigational drug or device study that has not reached its primary endpoint.
Subject has one of the following pre-existing untreated conduction system disorders: Type II second-degree AV block, bifascicular or trifascicular block.
AVA: aortic valve area; CK: creatine kinase; CT: computerised tomography; CVA: cardiovascular accident; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PA: pulmonary artery; STS: Society of Thoracic Surgeons; TEE: transoesophageal echocardiography; TIA: transient ischaemic attack; TTE: transthoracic echocardiography; WBC: white blood cell; WHO: World Health Organization

Appendix B. REPRISE I endpoints and additional measurements.

PRIMARY ENDPOINT
Clinical procedural success defined as successful implantation of a Lotus Valve (device success) without in-hospital MACCE through discharge or seven days post-procedure, whichever comes first.
Device success includes the following, as defined by VARC-1:
Successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system
Correct position of the device in the proper anatomical location
Intended performance of the Lotus Valve (AVA >1.0 cm^2 plus either a mean aortic valve gradient <20 mmHg or a peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation)
Only one valve implanted in the proper anatomical location
In-hospital MACCE includes the following, as defined by VARC-1:
All-cause mortality
Periprocedural MI ≤72 hours after index procedure
Major stroke
Urgent or emergent conversion to surgery or repeat procedure (surgical or interventional) for valve-related dysfunction
SECONDARY ENDPOINTS
Device performance endpoints peri- and post-procedure:
Successful repositioning of the Lotus Valve System if repositioning is attempted
Successful retrieval of the Lotus Valve System if retrieval is attempted
Incidence of aortic valve regurgitation (central and paravalvular)
ADDITIONAL MEASUREMENTS
Information reported peri- and post-procedure, at discharge or seven days post-procedure (whichever comes first), 30 days, 3 months, 6 months, 12 months and annually through five years unless otherwise specified.
VARC-1 safety composite (composite reported at 30 days; individual components reported for all time points)
All-cause mortality
Major stroke
Life-threatening (or disabling) bleeding
Acute kidney injury - Stage 3 (including renal replacement therapy)*
Periprocedural MI (≤72 hours post-index procedure)
Major vascular complication
Urgent or emergent conversion to surgery or repeat procedure (surgical or interventional therapy) for valve-related dysfunction
VARC-1 efficacy composite (composite reported at one year)
All-cause mortality (after 30 days)
Failure of current therapy for aortic stenosis, requiring hospitalisation for symptoms of valve-related or cardiac decompensation (reported for all time points)
Prosthetic heart valve dysfunction (AVA <1.0 cm^2 and either a mean aortic valve gradient ≥20 mmHg or a peak velocity ≥3 m/s, OR moderate or severe prosthetic valve aortic regurgitation; reported for all time points)
New conduction disturbances requiring new permanent pacemaker implantation
Coronary obstruction (periprocedure)
Major bleeding
Spontaneous MI (>72 hours post-index procedure)
Minor stroke
Valve performance as assessed by TTE including effective orifice area, mean and peak aortic gradients, peak aortic velocity and grade of aortic regurgitation
Valve thrombosis
Valve endocarditis
Cardiac function as measured by echocardiography, including pulmonary artery systolic pressure, left atrial dimension, left ventricular diameter and LVEF
Functional status as evaluated by NYHA class
Health status as evaluated by SF-12 and EQ-5D QoL questionnaires at baseline, six months, and one year

* Modified RIFLE classification[46]. AVA: aortic valve area; LVEF: left ventricular ejection fraction; MACCE: major adverse cardiovascular and cerebrovascular events; MI: myocardial infarction; QoL: quality of life; RIFLE: Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease; TEE: transthoracic echocardiography; VARC: Valve Academic Research Consortium[26]

Appendix C. REPRISE I endpoint definitions (major endpoints).

ACUTE KIDNEY INJURY (Modified RIFLE classification)
Change in serum creatinine (up to 72 hours) compared to baseline
Stage 1: Increase in serum creatinine to 150-200% (1.5-2.0 times increase compared with baseline) or increase of ≥0.3 mg/dl (≥26.4 µmol/L)
Stage 2: Increase in serum creatinine to 200-300% (2.0-3.0 times increase compared with baseline)
Stage 3*: Increase in serum creatinine to ≥300% (>3 times increase compared with baseline) or serum creatinine of ≥4.0 mg/d (≥354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L)
*Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
BLEEDING
Life-threatening or disabling bleeding
Fatal bleeding OR
Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR
Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR
Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed RBC transfusion ≥4 units*
Major bleeding
Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC AND
Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding
Any bleeding worthy of clinical mention (e.g., access-site haematoma) that does not qualify as life-threatening, disabling, or major
* Given one unit of packed RBC typically will raise blood haemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated.
DEATH
All-cause death
Death from any cause after a valve intervention.
Cardiovascular death
Any one of the following criteria:
Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure)
Unwitnessed death and death of unknown cause
All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease.
MYOCARDIAL INFARCTION (MI)
Periprocedural MI (≤72 hours after the index procedure)
New ischaemic symptoms (e.g., chest pain or shortness of breath), or new ischaemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, haemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), AND
Elevated cardiac biomarkers (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are >0.6 to 8 hours apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile URL, or a peak value exceeding 5x the 99th percentile URL with new pathological Q-waves in at least two contiguous leads.
Spontaneous MI (>72 hours after the index procedure)
Any one of the following criteria:
Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile URL, together with evidence of myocardial ischaemia with at least one of the following:
ECG changes indicative of new ischaemia (new ST-T changes or new LBBB)
New pathological Q-waves in at least two contiguous leads
Imaging evidence of new loss of viable myocardium or new wall motion abnormality
Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Pathological findings of an acute myocardial infarction.

STROKE AND TRANSIENT ISCHAEMIC ATTACK (TIA)
Stroke diagnostic criteria
Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, haemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, haemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences)*
Confirmation of the diagnosis by at least one of the following:
Neurology or neurosurgical specialist
Neuroimaging procedure (MR or CT scan or cerebral angiography)
Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial haemorrhage).
Definitions
Stroke (diagnosis as above, preferably with positive neuroimaging study)
Minor - Modified Rankin Scale score <2 at 30 and 90 days¶
Major - Modified Rankin Scale score >2 at 30 and 90 days
Transient ischaemic attack
New focal neurological deficit with rapid symptom resolution (usually one to two hours, always within 24 hours)
Neuroimaging (if performed) does not demonstrate new tissue injury
*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies. ¶Modified Rankin Scale score assessments made by qualified individuals according to a certification process. If there is discordance between the 30 and 90-day Modified Rankin Scale scores, a final determination of major versus minor stroke will be adjudicated by the CEC.
VASCULAR COMPLICATIONS
Major vascular complication
Any thoracic aortic dissection
Access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischaemia or spinal artery injury causing neurologic impairment)
Distal embolisation (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage
Minor vascular complication
Access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula or pseudoaneurysms requiring compression or thrombin injection therapy, or haematomas requiring transfusion of ≥2 but <4 units) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage.
Distal embolisation treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage.
Failure of percutaneous access-site closure resulting in interventional (e.g., stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4 units), or irreversible end-organ damage.
CEC: Clinical Events Committee; CK-MB: creatine kinase MB; CT: computed tomography; ECG: electrocardiogram; LBBB: left bundle branch block; MI: myocardial infarction; RBC: red blood cells; RIFLE: Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function and End-stage kidney disease[46]

Appendix D. REPRISE I study organisation and processes.

Sponsor	Boston Scientific Corporation, Natick, MA, USA
Study principal investigator (PI)	Ian T. Meredith AM, MBBS, PhD Director, MonashHEART, Southern Health, Melbourne Executive Director, Monash Medical Centre, Clayton, Victoria, Australia
Investigative centres	Ian T. Meredith AM, MBBS, PhD (Center PI) Paul Antonis, MBBS (Secondary Operator) Monash Medical Centre, Clayton, Victoria, Australia (5 patients)
	Stephen G. Worthley, MD (Center PI) Joseph K. Montarello, MBBS (Secondary Operator) Royal Adelaide Hospital, Adelaide, Australia (4 patients)
	Robert J. Whitbourn, MBBS (Center PI) Andrew E. Newcomb, MBBS (Secondary Operator) St. Vincent's Hospital, Victoria, Australia (2 patients)
Clinical Events Committee	Sergio Waxman, MD, Chair Interventional cardiologist; Lahey Clinic, Burlington, MA, USA
	Carey Kimmelstiel, MD Interventional cardiologist; Tufts New England Medical Center, Boston, MA, USA
	Gregory Smaroff, MD Cardiothoracic surgeon; Lahey Clinic, Burlington, MA, USA
	Roberto Rodriguez, MD Cardiothoracic surgeon; Lankenau Hospital, Wynnewood, PA, USA
	Viken Babikian, MD Neurologist; Boston Medical Center, Boston, MA, USA
Case Review Committee*	Ian T. Meredith AM, MBBS, PhD Chair/Study Principal Investigator MonashHEART, Southern Health, Melbourne Monash Medical Centre, Clayton, Victoria, Australia
	Ralf Mueller, MD Independent Physician/Proctor Helios Klinikum Siegburg, Siegburg, Germany
	Stephen G. Worthley, MD Center Principal Investigator Royal Adelaide Hospital, Adelaide, Australia
	Robert J. Whitbourn, MBBS Center Principal Investigator St. Vincent's Hospital, Victoria, Australia
	Sponsor representatives (Boston Scientific Corporation, Natick, MA, USA) Dominic J. Allocco, MD; Blessie Concepcion; Christa Florence, RN; Nicole Haratani, RN, BSN; Kenneth Martin; Stephanie Spainhower, NP
Proctors	Ralf Mueller, MD Helios Klinikum Siegburg, Siegburg, Germany
	Ian Meredith, MBBS, PhD MonashHEART, Southern Health, Melbourne Monash Medical Centre, Clayton, Victoria, Australia
Echocardiography core laboratory	Victor Davila-Román, MD CVR Consulting, PC St. Louis, MO, USA
Electrocardiography core laboratory Boston, MA, USA	Peter J. Zimetbaum, MD Harvard Clinical Research Institute Boston, MA, USA
Data management, biostatistical analysis, safety monitoring	Boston Scientific Corporation, Natick, MA, USA

* The study PI/CRC Chair (or designee/centre PI if study PI is presenting subjects [one vote]), proctor (one vote), and Sponsor (one vote) had to agree to achieve consensus/quorum to confirm suitability of patient enrolment into the study.

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