Incidence and mechanisms of bioprosthetic dysfunction after transcatheter implantation of a mechanically-expandable heart valve

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Abstract

Background: The mechanically-expandable transcatheter valve is no longer commercially available, yet clinical and echocardiographic surveillance is imperative for thousands of patients who received transcatheter aortic valve implantation (TAVI) with this platform.

Aims: We aimed to determine the incidence and mechanism of bioprosthetic valve dysfunction (BVD) following TAVI with mechanically-expandable valves.

Methods: From 2013 to 2020, all 234 patients who underwent TAVI with the LOTUS valve were included. BVD was categorised as (i) structural valve deterioration (SVD), (ii) non-structural valve dysfunction (NSVD), (iii) clinical valve thrombosis and (iv) endocarditis, according to the Valve Academic Research Consortium-3 criteria.

Results: The mean age was 79±7 years, 60% were male, and the mean Society of Thoracic Surgeons score was 4.2±2.9%. The technical success rate was 94% and the 30-day device success rate was 78%. All-cause mortality at 1 year was 15%; median follow-up duration was 36 (IQR 18-60) months during which 47% of patients died. One hundred and three patients had ≥1 type of BVD (44%), which predominantly consisted of NSVD (39%, mostly because of ≥moderate patient-prosthesis mismatch). BVD during follow-up included endocarditis (3.4%), clinical valve thrombosis (3.4%) and SVD (1.3%). Both endocarditis and clinically apparent valve thrombosis occurred early and late after TAVI and resulted in valve-related deaths in 38% and 13% of patients, respectively. Overall, ≥moderate haemodynamic valve deterioration occurred in 5.5% and bioprosthetic failure in 7.3%, leading to valve-related deaths in 36% of cases.

Conclusions: BVD represents a relevant health issue after TAVI with a mechanically-expandable valve. Serious but reversible causes of BVD include endocarditis and clinically apparent valve thrombosis, both carrying a time-independent hazard post-TAVI.

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Abbreviations

BVD   bioprosthetic valve dysfunction
BVF   bioprosthetic valve failure
HVD   haemodynamic valve deterioration
NSVD   non-structural valve dysfunction
SVD   structural valve dysfunction
TAVI   transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve implantation (TAVI) revolutionised the management of aortic valve stenosis and is forecast to be the dominant treatment modality in most patients[1]. The 3 competing transcatheter valve systems are balloon-expandable, self-expanding and mechanically-expandable technologies. However, in 2020 Boston Scientific voluntarily withdrew their mechanically-expandable LOTUS heart valve from the market[2]. Even though the device is no longer available, close follow-up of patients previously treated with a LOTUS valve is needed to monitor valve performance and preserve health outcomes. The controlled implantation of the LOTUS valve, with fully repositionable/retrievable features, high radial force and sealing fabric, made it an attractive platform for more complex anatomies, including bicuspid aortic valve morphologies and severe aortic valve calcification[3]. However, its relatively bulky metallic frame could potentially increase the risk of valve thrombosis[4]. For these reasons the objective of this study was to report the incidence and mechanism of bioprosthetic valve dysfunction (BVD), subsequent valve haemodynamics and clinical outcome in a large single-centre series of patients treated with the LOTUS valve.

Materials and methods

PATIENTS

From September 2013 until November 2020, a total of 234 patients underwent TAVI with the LOTUS valve in the Erasmus University Medical Center, Rotterdam, the Netherlands. All patients underwent multidisciplinary assessment and a structured in-hospital and post-discharge follow-up using a prospective collection of predefined variables. Echocardiographic assessment was performed at baseline, predischarge or at 30 days, and 1 and 3 years. Survival status was checked with the Dutch Civil Registry every year. Institutional review board approval was obtained, and all patients provided informed consent at the end of the pre-TAVI outpatient clinic visit for the TAVI procedure and anonymous data collection for research purposes. The study complies with the Declaration of Helsinki.

DEVICE AND PROCEDURE

The LOTUS valve system consists of a stent frame with woven nitinol wire supporting 3 bovine pericardial leaflets in an intra-annular design and is deployed through mechanical expansion. The device is fully repositionable and retrievable allowing complete deployment and functional assessment of the transcatheter heart valve (THV) before the final release[5]. The LOTUS Edge system (Boston Scientific) (n=68 in this cohort) integrated several design improvements on the former LOTUS design (n=166). All procedures were performed via a transfemoral approach under general anaesthesia until 2015 and local anaesthesia thereafter. Pre- and post-dilatation was performed at the discretion of the operator.

STUDY ENDPOINTS AND DEFINITIONS

The primary objective was to investigate the type of BVD and any associated haemodynamic valve deterioration (HVD) and/or bioprosthetic valve failure (BVF) in accordance with the latest Valve Academic Research Consortium-3 (VARC-3) criteria[6]. The types of BVD were categorised as: (i) structural valve deterioration (SVD: intrinsic, permanent changes to the prosthetic valve), (ii) non-structural valve dysfunction (NSVD: any abnormality not intrinsic to the prosthetic valve resulting in valve dysfunction, such as patient-prosthesis mismatch or inappropriate positioning), (iii) clinically significant thrombosis and (iv) endocarditis. Prosthesis-patient mismatch (PPM) was classified as moderate (index aortic valve area 0.65 to 0.85 cm^2/m^2, if BMI $\geq$30 kg/m^2 0.56–0.70 cm^2/m^2) or severe (index aortic valve area <0.65 cm^2/m^2, if BMI $\geq$30 kg/m^2 $\leq$0.55 cm^2/m^2). In 6 out of 8 patients with suspected clinical valve thrombosis, a confirmatory multislice computed tomography (MSCT) was performed to assess for reduced leaflet motion (RLM) and/or hypoattenuated leaflet thickening (HALT) in accordance with the Society of Cardiovascular Computed Tomography consensus document[7]. For another 23 patients without suspected clinical valve thrombosis, the available MSCT studies obtained in the framework of post-TAVI surveillance were also analysed for presence of RLM/HALT or other signs of early BVD. In patients with BVD, the severity of HVD was classified as stage 1 (morphological valve deterioration without haemodynamic change), stage 2 (moderate haemodynamic deterioration) or stage 3 (severe haemodynamic deterioration). The clinical consequence of BVD was classified as BVF stage 1 (symptoms or echocardiographic signs of pressure/volume overload), stage 2 (valve reintervention) or stage 3 (valve-related death). The VARC-3 proposed device-related composite endpoints to further include:

(i)   technical success, defined as freedom from mortality at exit from the procedure room with successful access, delivery and retrieval of the valve delivery system, correct valve positioning, and no need for surgery or intervention related to the device or to a major vascular or cardiac-related complication;

(ii)   device success at 30 days, defined as freedom from mortality with technical success and no need for surgery or intervention related to the device or to a major vascular- or cardiac-related complication, and with the intended performance of the valve (mean gradient <20 mmHg, peak velocity <3 m/s, Doppler velocity index $\geq$0.25, and less than moderate aortic regurgitation).

Native aortic valve anatomy was considered complex in the presence of one of the following conditions: severe aortic valve calcification, moderate-severe left ventricular outflow tract (LVOT) calcification, bicuspid aortic valve morphology, degenerated surgical

bioprosthesis or pure aortic regurgitation[3]. Semi-quantitative computed tomography evaluation categorised the aortic valve and LVOT calcifications as mild, moderate or severe.

STATISTICAL ANALYSIS

Categorical variables were presented as frequencies and percentages and were compared with the chi-square test or the Fisher's exact test. Normal and skewed continuous variables were presented as means (±standard deviation) and medians (interquartile range [IQR]), respectively. Continuous variables were compared using the Student's t-test or Mann-Whitney U-test when appropriate. BVD, HVD and BVF were reported as cumulative incidence; to account for the competing risk of death, HVD and BVF were also analysed using a cumulative incidence function. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science for Windows (IBM), version 21.

Results

Baseline patient characteristics of the entire cohort are presented in **Table 1**.

The mean age was 79±7 years, 60% were male and the mean Society of Thoracic Surgeons (STS) Predicted Risk of Mortality was 4.2±2.9 percent. Thirty-nine percent of patients were considered to have complex valvular anatomy. Technical success was 94% and 30-day device success was 78% **(Table 2)**. Reasons for not achieving device success were unfavourable haemodynamic valve performance (11%), absence of technical success (6%) and/or death <30 days (6%). All-cause mortality at 1 year was 15%. The median follow-up duration was 36 (IQR 18-60) months, during which 47% of patients died.

OVERALL HAEMODYNAMIC VALVE PERFORMANCE DURING FOLLOW-UP

Post-TAVI echocardiography data were available in all but 3 patients because of death during the procedure due to a fatal annular rupture, left ventricular wire perforation and major vascular complication in the abdominal aorta. A 1-year echocardiographic assessment was available in 90% of 1-year survivors. From baseline to post-TAVI, the effective orifice area (EOA) and mean gradient improved significantly (EOA: 0.77 vs 1.67 cm²; mean gradient: 41 vs 13 mmHg; p<0.001) and remained stable at 1 year (EOA: 1.72 cm²; mean gradient: 12 mmHg). PPM was present at the first echocardiogram post-procedure in 38% of patients, with 29% with moderate and 9% with severe PPM.

BIOPROSTHETIC VALVE DYSFUNCTION

Patient-level details of the type, timing and management of bioprosthetic valve dysfunction and failure are presented in **Supplementary Table 1** and summarised in the **Central illustration**. One hundred and three patients had ≥1 type of BVD (44%; 91 patients had 1 and 12 patients had 2 types of BVD). The main contributor to this endpoint was NSVD (39%), secondary to PPM in almost all cases

Table 1. Patient characteristics.

	Total (n=234)
Baseline characteristics	
Age, years	79±7
Male	119 (51)
Body mass index, kg/m²	27.7±5.1
Body surface area, m²	1.91±0.22
Hypertension	190 (81)
Diabetes mellitus	76 (32)
Current or recent smoker	104 (44)
Peripheral vascular disease	85 (36)
Previous cerebrovascular event	53 (23)
Previous coronary artery bypass graft	28 (12)
Previous percutaneous coronary intervention	67 (29)
Creatinine, μmol/L	94 (78-116)
Permanent pacemaker	27 (12)
Atrial fibrillation	78 (33)
Platelet inhibitors	113 (48)
Oral anticoagulant	74 (32)
New York Heart Association Class ≥III	137 (59)
Society of Thoracic Surgeons score (percent)	4.2±2.9
Complex valve anatomy	92 (39)
Bicuspid valve morphology	17 (7)
Degenerated bioprosthesis	5 (2)
Severe valve calcification	78 (33)
Severe left ventricular outflow tract calcification	8 (3)
Pure aortic regurgitation	3 (1)
Echocardiography	
Left ventricular ejection fraction	55±12
Mean gradient	42±15
Aortic valve area, cm²	0.78±0.28
Aortic regurgitation ≥moderate	38 (16)
Mitral regurgitation ≥moderate	48 (21)
Tricuspid regurgitation ≥moderate	41 (18)
Data are presented as n (%), mean±standard deviation or median (interquartile range)	

(29% moderate PPM, 9% severe PPM and/or 3% other). Other contributors – in descending order of incidence – were endocarditis (3.4%), clinical valve thrombosis (3.4%) and SVD (1.3%).

Overall, clinically relevant valve thrombosis was diagnosed in 8 patients, of which 4 (50%) occurred within 1 year and the other 4 (50%) between 1 and 5 years after TAVI. MSCT confirmed HALT and/or RLM in all but 2 patients in whom MSCT was not performed. None of the patients were on anticoagulants at the time of the event, except one who was on a reduced dose of direct oral anticoagulant therapy for atrial fibrillation. Initiation of anticoagulants (vitamin K antagonist or unfractionated heparin) returned the bioprosthetic haemodynamics to baseline in all but

Table 2. Procedural and 30-day outcomes.

		Total (n=234)
Procedural characteristics		
Local anaesthesia		161 (68)
LOTUS		165 (70)
LOTUS Edge		69 (30)
Valve size, mm	23	79 (34)
	25	87 (37)
	27	68 (29)
Predilatation		55 (24)
Post-dilatation		8 (3)
Valve embolisation		1 (0.4)
Need for second valve		0
Conversion to surgery		2 (1)
Technical success (at exit from procedure room)		
Yes		219 (94)
No (death)		4 (2)
No (surgical/percutaneous device intervention or major vascular/access site or cardiac structural complication)		11 (5)
30-day outcomes		
Death		14 (6)
Stroke[a]		6 (3)
Transient ischaemic attack		5 (2)
Major vascular complication		12 (5)
BARC type ≥2 bleeding complication		18 (8)
Permanent pacemaker[b]		56 (24)
Device success at 30 days		
Yes		183 (78)
No, related to death or no technical success		22 (9)
No, related to surgical/percutaneous device intervention or major vascular/access site or cardiac structural complication (after exit procedure room)		3 (1)
No, intended valve performance not met[c]		26 (11)
Echocardiography		
Left ventricular ejection fraction		54±13
Aortic mean gradient		13±5
Aortic valve area, cm²		1.68±0.47
Aortic regurgitation ≥moderate		12 (5)[d]
Mitral regurgitation ≥moderate		40 (18)
Tricuspid regurgitation ≥moderate		26 (12)

Data are presented as n (%) or mean±standard deviation. [a]Fatal stroke (n=2), stroke with disability (n=2), stroke without disability (n=2). [b]For the indication of 2nd or 3rd degree AV block (n=47), sick sinus syndrome (n=4), other (n=5). [c]Mean gradient >20, peak velocity >3 m/sec and Doppler velocity index ≥0.25 (n=14), ≥moderate aortic regurgitation (n=12). [d]Only 3 out of the 12 patients with ≥moderate aortic regurgitation post-TAVI were counted as non-structural valve dysfunction because severity of regurgitation reduced to mild in the other 9 patients on subsequent echocardiography.

1 patient (1 valve-related death). There was no HALT or RLM in the 23 patients who underwent an MSCT in the framework of post-TAVI surveillance (median: 3.5 months).

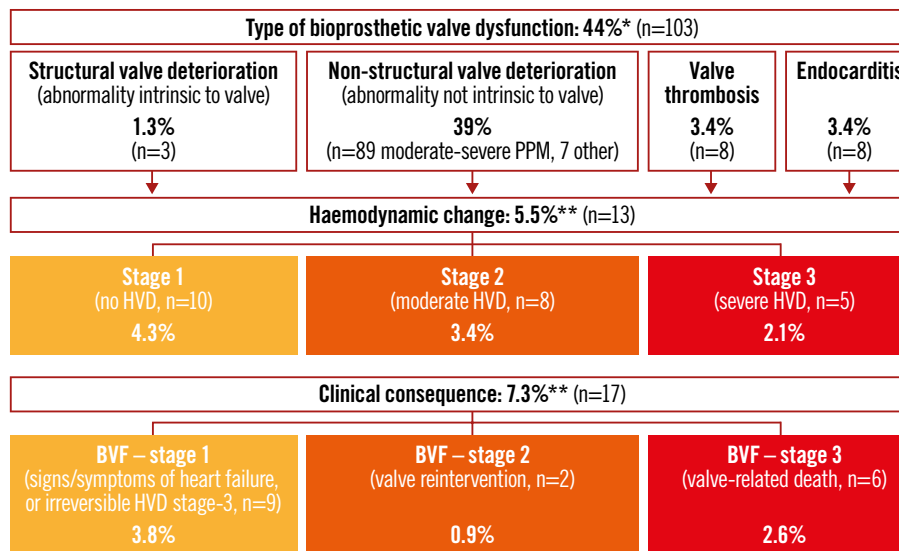## BIOPROSTHETIC VALVE FAILURE

Any stage of BVF occurred in 7.3%. In cumulative incidence function, the rate of any BVF was 4.5% at 3 years. Stage 3 BVF (valve-related death) occurred in 6 patients (2.6%) due to uncontrolled infection secondary to endocarditis (n=3), cardiogenic shock due to clinical valve thrombosis (n=1), cardiogenic shock after valve dislodgement (n=1) and death upon induction of anaesthesia for a TAVI-in-TAVI procedure to treat structural degeneration of the LOTUS valve (n=1). Stage 2 BVF (valve reintervention) occurred in 2 patients. In 1 case, haemodynamic valve deterioration that was secondary to endocarditis required surgical valve replacement (n=1), whereas another patient with rapid structural valve degeneration underwent successful TAVI-in-TAVI therapy with a 23 mm balloon-expandable valve.

Discussion

The main findings of this longitudinal follow-up study of the performance of bioprostheses after TAVI with the mechanically-expandable LOTUS valve are as follows **(Central illustration)**: 1) ≥1 type of BVD occurred in 44% of the patients at a median of 36 (IQR 18-60) months post-TAVI. This was predominantly driven by moderate PPM. NSVD occurred in 39% of patients, endocarditis in 3.4%, clinical valve thrombosis in 3.4% and SVD in 1.3%. 2) The cumulative incidence of BVF was 7.3% and resulted in valve-related death in one third of cases.

The retirement of the Boston Scientific LOTUS platform in 2020 diminished research related to the mechanically-expandable TAVI technology. Although early safety and efficacy of the LOTUS valve has been established before[3,8-10], longer-term data are lacking. Dedicated studies investigating LOTUS BVD during follow-up are particularly scarce. Bridging this knowledge gap is essential to ensure a good outcome in LOTUS recipients. Also, it is conceivable that certain device-host interactions that are common in the LOTUS population may catalyse early BVD. Of note, the fully repositionable/recapturable yet bulky metallic LOTUS system was frequently reserved for more complex anatomies, possibly with resultant suboptimal frame expansion and haemodynamic stress, and subsequent early BVD[11]. The herein reported 44% BVD rate is challenging to compare with previous studies because of differences in patient-risk profiles, follow-up duration and endpoint definitions. **Table 3** provides an overview of prior studies that reported HVD and BVF rates using VARC-3 equivalent definitions (definitions according to consensus criteria by the European Association of Percutaneous Cardiovascular Interventions[12]). The NOTION trial reported a 62% BVD rate (moderate/severe PPM in 44%) in a low-risk population at 8 years after CoreValve (Medtronic) implantation[13]. The risk of (VARC-3 defined) ≥stage 2 haemodynamic valve deterioration varies between 3.2-17.9% at 3-6 years after balloon-expandable TAVI[14-21] and between 1.5-9.5% at 4-8 years after self-expanding TAVI[16,17,19,20,22-25] **(Table 3)**. Although these data imply better haemodynamic sustainability of the self-expanding valve, it is not associated with a lower incidence of BVF when compared with balloon-expandable valves

CENTRAL **ILLUSTRATION** Type, haemodynamic change and clinical consequences of bioprosthetic valve dysfunction during a median of 3 years after mechanically-expandable heart valve implantation.

Type of bioprosthetic valve dysfunction: 44%* (n=103)			
Structural valve deterioration (abnormality intrinsic to valve) **1.3%** (n=3)	**Non-structural valve deterioration** (abnormality not intrinsic to valve) **39%** (n=89 moderate-severe PPM, 7 other)	**Valve thrombosis** **3.4%** (n=8)	**Endocarditis** **3.4%** (n=8)

Haemodynamic change: 5.5%** (n=13)		
Stage 1 (no HVD, n=10) **4.3%**	**Stage 2** (moderate HVD, n=8) **3.4%**	**Stage 3** (severe HVD, n=5) **2.1%**

Clinical consequence: 7.3%** (n=17)		
BVF – stage 1 (signs/symptoms of heart failure, or irreversible HVD stage-3, n=9) **3.8%**	**BVF – stage 2** (valve reintervention, n=2) **0.9%**	**BVF – stage 3** (valve-related death, n=6) **2.6%**

*A total of 103 patients had BVD (44%), of whom 91 patients had one type of BVD and 12 patients two types of BVD (i.e., moderate or severe PPM and another type of BVD). **The BVD resulted in a haemodynamic change (≥stage 2 HVD) in 5.5% and bioprosthetic valve failure in 7.3% (≥stage 1 BVF) during a median follow-up of 36 (IQR: 18-60) months (cumulative incidence). By cumulative incidence function, haemodynamic change (HVD stage ≥2) was found in 3.9% and bioprosthetic valve failure in 4.5% (BVF stage ≥1) at 36 months. BVD: bioprosthetic valve dysfunction; BVF: bioprosthetic valve failure; HVD: haemodynamic valve deterioration; NSVD: non-structural valve dysfunction; PPM: patient-prosthesis mismatch; PVL: paravalvular leakage*

(reported BVF rate 2.5-8% after self-expanding and 0.6-2.8% after balloon-expandable TAVI, **Table 3**). Also, data from the PARTNER 2 trial in aggregate with the SAPIEN 3 registry indicate that contemporary balloon-expandable device systems carry a 3-fold lower risk of haemodynamic deterioration as compared to older-generation balloon-expandable valves[15]. In the present study, we found a 5.5% ≥stage 2 HVD and a 3.5% ≥stage 2 BVF risk in a substantially shorter time-window (median 3 years). The LOTUS mechanically-expandable valve may be more susceptible to bioprosthetic dysfunction in comparison to other platforms. Therefore, the herein reported insights on BVD incidence and mechanisms may help inform best practices for LOTUS recipients who currently take part in post-TAVI care programs.

The main contributor to BVD was NSVD, which is a bioprosthetic abnormality due to extrinsic factors such as paravalvular aortic regurgitation (PAR), device malpositioning or PPM. In our study, almost all cases of NSVD consisted of moderate or severe PPM (38%); the rate of significant PAR and device malpositioning was low, reflecting the favourable mechanically-expandable technology allowing for complete deployment and functional assessment of the valve prior to the final release. The rate of ≥moderate PPM in our series was similar as compared to the NOTION trial (38 vs 44%, respectively). When using the same PPM definition as in the NOTION trial (≤0.85 cm²/m² not corrected for BMI), the rate of ≥moderate PPM in this study would be 46%[13]. This

is a somewhat surprising finding since patients in the NOTION trial were at low risk and received a self-expanding valve with a supra-annular design which is typically associated with lower rates of PPM[26]. Although NSVD results from any abnormality not intrinsic to the bioprosthesis, the presence of NSVD may accelerate intrinsic bioprosthetic degeneration and, thus, SVD[6,27]. SVD is an irreversible process manifested by gradual degeneration such as leaflet calcification, thickening and pannus formation that ultimately leads to BVF with aortic regurgitation and/or stenosis, and haemodynamic compromise. Clinically manifested SVD is uncommon within 5 years after valve implantation[24,28]. In our study, SVD occurred in 1.3% of cases, although this should be interpreted with caution because of the low number of patients with >5 years of follow-up.

Clinical valve thrombosis was detected in 3.4% of the patients, which corroborates other TAVI series (ranging between 0.6 and 2.8%, and up to 4.5% after balloon-expandable valve implantation[29,30]). The general factors that mediate clinical valve thrombosis are diverse and include, among others, prothrombotic states, high platelet activity and inadequate antiplatelet therapy. In the subset of LOTUS recipients, additional device- and host-specific factors might inflate the thrombosis risk. The bulky metallic frame interacting with excess calcium deposits in the aortic valvular complex may lead to areas of stagnant flow due to underexpansion and/or poor endothelialisation of the stent frame[21,29]. Also,

Table 3. Incidence of VARC-3 defined haemodynamic valve deterioration and bioprosthetic valve failure after balloon- and self-expanding TAVI.

Study	Period	No. of patients	Age and surgical risk	5-year mortality	Follow-up (years)	Haemodynamic valve deterioration ≥ stage 2		Bioprosthetic valve failure ≥ stage 2
						%	% per valve generation	
Balloon-expandable valves								
Eltchanichoff et al 2018 Single centre observational study[14]	2002-2012	378	83 yrs, Log EuroSCORE 23%	68%	3	3.2%	PVT/CE: not reported SAPIEN-XT: not reported SAPIEN-3: not reported	0.6%
Pibarot et al 2020 PARTNER-2A trial and registry[15]	2011-2013	1,366	81 yrs, STS 5.8%	na	5	4.2%	SAPIEN-XT: 6.3% SAPIEN-3: 2.1%[d]	2.8%
Durand et al 2019 Multicentre observational study[16]	2002-2011	1,058	83 yrs, Log EuroSCORE 21%	60%	3.9	4.3%	PVT/CE (n=70): not reported SAPIEN-XT (n=512): not reported SAPIEN-3 (n=475): not reported	Not reported (1.9% at 7 yrs for both BE and SE)
Blackman et al 2019 UK TAVI registry[17]	2007-2011	80	79 yrs, Log EuroSCORE 20%	na	5.8	11.2%	SAPIEN-1: 8.9% SAPIEN-XT: 14.2%	Not reported
Aldalati et al 2018 Single centre observational study[18]	2005-2015	259	82 yrs, Log EuroSCORE 21%	55%	2.8	13.7%	SAPIEN-1: not reported SAPIEN-XT: not reported SAPIEN-3: not reported	<0.1%[e]
Didier et al 2018 FRANCE-2 registry[19]	2010-2012	2,774	83 yrs, Log EuroSCORE 22%	61%	5	17.9%	Not reported	Not reported
Barbanti et al 2018 Single centre observational study[20]	2007-2012	48	81 yrs, STS 8.1%	45%	8	Not reported	Not reported	Not reported (4.5% for both BE and SE)
Self-expanding valves								
Durand et al 2019 Multicentre observational study[16]	2002-2011	199	83 yrs, Log EuroSCORE 21%	60%	3.9	1.5%	CoreValve: 1.5%	Not reported (1.9% at 7 yrs for both BE and SE)
Panico et al 2019 Single centre observational study[22]	2007-2013	278	82 yrs, STS 6.2%	55%	6.8	3.6%	CoreValve: 3.6%	2.5%
Sondergaard et al 2019 NOTION trial[23]	2009-2013	139	78 yrs, Log EuroSCORE 2.0%, STS 3.0%	28%	6	4.8%	CoreValve: 4.8%	7.5%
Blackman et al 2019 UK TAVI registry[17]	2007-2011	149	79 yrs, Log EuroSCORE 20%	na	5.8	8.1%	CoreValve: 8.1% Portico: 0%	Not reported
Didier et al 2018 FRANCE-2 registry[19]	2010-2012	1,413	83 yrs, Log EuroSCORE 22%	61%	5	8.9%	Not reported	Not reported
Gleason et al 2018 CoreValve US Pivotal High-Risk Trial[24]	2011-2012	391	83 yrs, STS 7.3%	55%	4.2	3.9-9.5%[c]	CoreValve: 3.9-9.5%	3%
Barbanti et al 2018 Single centre observational study[20]	2007-2012	238	81 yrs, STS 8.1%	45%	8	Not reported[a]	Not reported	Not reported (4.5% for both BE and SE)
Holy et al 2018 Single centre observational study[25]	2007-2011	152	81 yrs, Log EuroSCORE 21%, STS 4.4%	50%	6.2	Not reported[b]	Not reported	8%

[a]Not reported per TAVI technology. [b]Only HVD stage 3 reported in 0%. [c]In this study a major component of HVD was mean gradient >20 mmHg at any time after the procedure (5.4%), which in itself is not classified as HVD according to the VARC-3 criteria. Therefore, the reported HVD rate in the CoreValve Pivotal high-risk trial ranges between 3.9-9.5% according to VARC-3 criteria. [d]Propensity-matched analysis. [e]Valve-related deaths not recorded, and endocarditis cases excluded. BE: balloon-expandable; HVD: haemodynamic valve deterioration; na: not applicable; SE: self-expanding; STS: Society of Thoracic Surgeons risk score; VARC-3: Valve Academic Research Consortium-3 criteria

repetitive repositioning and recapturing during LOTUS implantation attempts may impose microscopic leaflet injury potentially creating a prothrombotic milieu. The finding that clinical valve thrombosis occurred both early and late after TAVI and was detected by routine echocardiography prior to the development of symptoms in 2 cases signifies the importance of frequent clinical and echocardiographic post-TAVI surveillance. A correct diagnosis early in the disease process allows for timely administration of corrective anticoagulant therapy. Conversely, failure to detect the erratic disease state during early phases may cause rapid clinical deterioration and (valve-related) death. Although oral anticoagulant therapy prevents the development of both subclinical and clinically overt valve thrombosis, further studies are needed to identify candidates for such a strategy.

Infective endocarditis is an important reversible cause of bioprosthetic dysfunction. Our cumulative incidence of 3.4% corroborates surgical (4.9-5.9%) and transcatheter series (4.4-5.8%)[23,31] and also equals the 1.1% per person-year incidence previously reported in a large collaborative study[32].

Limitations

This study reports on the incidence, type and timing of bioprosthetic dysfunction as recorded by clinical and echocardiographic assessment at predefined time points after TAVI. It is possible that patients who did not undergo a clinical and echocardiographic assessment during follow-up (10% at 1 year) might have had bioprosthetic dysfunction. The fact that all 234 study subjects underwent TAVI over the course of a long time period (8 years) may have introduced heterogeneity into the study population which could have affected study results. As mentioned above, few patients exceeded the 5-year follow-up threshold, beyond which degenerative changes of the bioprosthesis may become clinically relevant, and, therefore, no conclusions on the rate of SVD can be drawn from this study. Nevertheless, this study design, streamlined to the recently released VARC-3 criteria, provides valuable insight into the mode and incidence of bioprosthetic dysfunction in LOTUS recipients that will inform best practices after LOTUS TAVI.

Conclusions

Our study suggests that patients treated with the mechanically-expandable LOTUS transcatheter heart valve are at considerable risk for bioprosthetic dysfunction at follow-up. Cardiologists and physicians involved in post-TAVI care of LOTUS recipients should have a heightened awareness for clinical and echocardiographic signs of bioprosthetic dysfunction. These measures will help provide a timely diagnosis of potentially hazardous yet reversible causes of bioprosthetic dysfunction.

Impact on daily practice

The mechanically-expandable LOTUS transcatheter heart valve is no longer commercially available, yet clinical and echocardiographic surveillance in patients previously treated with a LOTUS valve is crucial to maintain health outcomes. Our study indicates that LOTUS valve dysfunction is a common health issue. Potentially dangerous and reversible causes of bioprosthetic dysfunction carry a time-independent hazard after TAVI and, occasionally, can be detected by echocardiography prior to the onset of symptoms. Therefore, clinicians should be at heightened awareness for BVD and maintain a close follow-up early and late after LOTUS valve implantation.

Conflict of interest statement

N. Van Mieghem received research grants from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, Pie Medical, Daiichi Sankyo, PulseCath BV, and Abiomed. J. Daemen received institutional grant/research support from AstraZeneca, Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic, MicroPort, Pie Medical, and ReCor Medical. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Case level overview of the type, haemodynamic change and clinical consequences of bioprosthetic valve dysfunction during a median of 3 (IQR 1.5-5) years after LOTUS implantation.

The supplementary data are published online at: https://eurointervention.pcronline.com/ doi/10.4244/EIJ-D-22-00193

Supplementary Table 1. Case level overview of the type, haemodynamic change and clinical consequences of bioprosthetic valve dysfunction during a median of 3 (IQR 1.5-5) years after LOTUS implantation.

Case	Bioprosthetic valve dysfunction				Management	
	Timing (months post-TAVI)	Type	Haemodynamic valve deterioration stage	Bioprosthetic valve failure stage	Therapy	Therapy success
Structural valve deterioration						
1	48	**Structural valve degeneration**	Stage 2 (increased mean gradient >10 mmHg resulting in mean gradient >20 mmHg with decrease in VTI index >0.1)	Subclinical	No	N.A.
2	52	**Structural valve degeneration**	Stage 3 (cardiogenic shock)	Stage 3 (valve-related death)	Death during induction of anaesthesia prior to re-TAVI	No
3	60	**Structural valve degeneration *** *(MSCT: RLM, TTE: leaflet thickening)*	Stage 3 (increase in MG >20 mmHg resulting in MG>30 with decrease in VTI index >0.1; increase ≥1 grade of intra-prosthetic AR resulting in moderate AR)	Stage 2 (valve reintervention)	Coumadin administration followed by TAV-in-TAV	Coumadin: no TAV-in-TAV: yes
Non-structural valve dysfunction						
4--61	0	**Moderate PPM** *(without other type of BVD)*	No	No	No	N.A.
62--80	0	**Severe PPM** *(without other type of BVD)*	No	No	No	N.A.
81	0	**Moderate PAR since TAVI ***	No	Subclinical	No	N.A.
82	0	**Moderate PAR since TAVI**	No	Subclinical	No	N.A.
83	0	**Moderate PAR since TAVI ****	No	Stage 1 (worsening symptoms)	No	N.A.
84	0	**Inappropriate valve positioning ***	Stage 2 (increase ≥1 grade of intra-prosthetic AR resulting in moderate AR)	Stage 3 (valve-related death)	Reintervention: balloon post-dilatation resulting in valve dislodgement leading to death	No
85	8	**New moderate PAR at follow-up ***	Stage 1 (no haemodynamic deterioration)	Stage 1 (worsening symptoms)	Diuretics	Yes (mildly symptomatic NYHA II)
86	12	**New moderate PAR at follow-up**	Stage 1 (no haemodynamic deterioration)	Stage 1 (worsening symptoms)	No	N.A.
87	12	**New moderate PAR at follow-up**	Stage 1 (no haemodynamic deterioration)	Subclinical	No	N.A.
Clinical valve thrombosis						
88	0-7*	**Probable valve thrombosis **** *(MSCT: RCC leaflet thickening with HALT with extreme stent deformation)*	Stage 2 (increased mean gradient >10 mmHg resulting in mean gradient >20 mmHg with decrease in VTI index >0.1)	Stage 1 (worsening symptoms)	Coumadin administration	Yes (resolution of symptoms and imaging findings)
89	1	**Probable valve thrombosis ****	Stage 3 (cardiogenic shock)	Stage 3 (valve-related death)	Unfractionated heparin	No
90	1	**Probable valve thrombosis** *(MSCT: HALT/RLM in 3 leaflets)*	Stage 2 (increased mean gradient >10 mmHg resulting in mean gradient >20 mmHg with decrease in VTI index >0.1)	Stage 1 (worsening symptoms)	Reduced dose NOAC substituted by vit. K antagonist	Yes (resolution of symptoms and imaging findings)

#		Diagnosis	Haemodynamic	Clinical	Treatment	Resolution
91	3	**Probable valve thrombosis ***	Stage 3 (increased mean gradient >20 mmHg resulting in mean gradient >30 mmHg with concomitant decrease in EOA >0.6 cm2)	Stage 1 (worsening symptoms)	Coumadin administration	Yes (resolution of symptoms and imaging findings)
92	12	**Possible valve thrombosis *** *(thrombo-embolic event; MSCT: HALT in 2 leaflets)*	Stage 2 (increased mean gradient >10 mmHg resulting in mean gradient >20 mmHg with decrease in VTI index >0.1)	Subclinical	Aspirin added onto coumadin therapy	Yes (resolution of imaging findings)
93	12	**Probable valve thrombosis** *(MSCT: HALT in 2 leaflets)*	Stage 2 (increased mean gradient >10 mmHg resulting in mean gradient >20 mmHg with decrease in VTI index >0.1)	Stage 1 (worsening symptoms and embolic sequelae: TIA)	Coumadin administration	Yes (resolution of symptoms and imaging findings)
94	36	**Probable valve thrombosis** *(MSCT: HALT and RLM in 3 leaflets)*	Stage 1 (no haemodynamic deterioration)	Stage 1 (embolic sequelae: repetitive NSTEMI's in absence of coronary disease)	Unfractionated heparin	Yes (resolution of symptoms and imaging findings)
95	52	**Probable valve thrombosis** *(TEE: leaflet thickening, MSCT: calcified leaflets)*	Stage 3 (increased mean gradient >20 mmHg resulting in mean gradient >30 mmHg with concomitant decrease in EOA >0.6 cm2)	Subclinical	Coumadin administration	Yes (resolution of symptoms and imaging findings)

Infective endocarditis

#		Diagnosis	Haemodynamic	Clinical	Treatment	Resolution
96	1	**Definite endocarditis *** *2 major: blood culture (s. oralis)+imaging (vegetation); 2 minor: fever+predisposing*	Stage 1 (no haemodynamic deterioration)	Stage 3 (valve-related death)	Antibiotic therapy	No
97	4	**Definite endocarditis** *2 major: blood culture (e. faecalis)+imaging; 2 minor: temp+predisposing. (secondary to mitral valve endocarditis)*	Stage 1 (no haemodynamic deterioration)	Subclinical	Antibiotic therapy	Yes
98	5	**Definite endocarditis *** *2 major: oscillating mass on valve + strept gordoni; 2 minor: temp+TAVI*	Stage 1 (no haemodynamic deterioration)	Subclinical	Antibiotic therapy	Yes
99	9	**Definite endocarditis *** *2 major: blood culture (h. streptococcus)+imaging (vegetations); 2 minor: fever, predisposing*	Stage 2 (increased mean gradient >10 mmHg resulting in mean gradient >20 mmHg with decrease in VTI index >0.1)	Stage 1 (worsening symptoms)	Antibiotic therapy	Yes
100	12	**Definite endocarditis** *2 major: blood culture (s. mitis)+imaging (vegetation); 2 minor: fever +predisposing*	Stage 1 (no haemodynamic deterioration)	Subclinical	Antibiotic therapy	Yes
101	17	**Definite endocarditis** *2 major: blood culture (e. faecalis)+imaging (vegetation, aneurysm); 3 minor (fever, predisposing, vascular phenomena)*	Stage 2 (increase of ≥1 grade of intra-prosthetic AR resulting in moderate AR)	Stage 2 (valve re-intervention)	Antibiotic therapy with surgical aortic valve replacement	Yes
102	33	**Definite endocarditis** *2 major: blood culture (s. sanguinis) imaging (vegetation); 2 minor (fever, predisposing)*	Stage 1 (no haemodynamic deterioration)	Stage 3 (valve-related death)	Antibiotic therapy	No
103	48	**Possible endocarditis** *1 major: s. aureus; 2 minor: temp+TAVI*	Stage 1 (no haemodynamic deterioration)	Stage 3 (valve-related death)	Antibiotic therapy	No

AR: aortic regurgitation; EOA: effective orifice area; HALT: hypoattenuated leaflet thickening; MG: mean gradient; MSCT: multisliced computed tomography; NOAC: new oral anticoagulant; NSTEMI: non-ST-segment elevated myocardial infarction; NYHA: New York Heart Association; PAR: paravalvular aortic regurgitation; PPM: prosthesis-patient mismatch; RLM: reduced leaflet motion; TAVI: transcatheter aortic valve implantation; TOE: transoesophageal echocardiography; TIA: transient ischaemic attack; VTI: velocity time index

* Concomitant moderate PPM
** Concomitant severe PPM