Cardiovascular Magnetic Resonance assessment of
1st generation CoreValve and 2nd generation Lotus valves

ABSTRACT

Objectives: We sought to compare using serial CMR, the quantity of AR and associated valve haemodynamics, following the first-generation CoreValve (Medtronic, Minneapolis, Minnesota) and the second-generation Lotus valve (Boston Scientific, Natick Massachusetts).

Background: Aortic regurgitation (AR) following Transcatheter Aortic Valve Replacement (TAVR) confers a worse prognosis and can be accurately quantified using cardiovascular magnetic resonance (CMR). Second generation valves have been specifically designed to reduce paravalvular AR and improve clinical outcomes.

Methods: Fifty-one patients (79.0±7.7 years, 57% male) were recruited and imaged at three time points: immediately pre- and post-TAVR, and at 6 months.

Results: CMR-derived AR fraction immediately post-TAVR was greater in the CoreValve compared to Lotus group (11.7±8.4 vs. 4.3±3.4%, p=0.001), as was the frequency of ≥moderate AR (9/24 (37.5%) vs. 0/27, p<0.001). However, at 6 months AR fraction had improved significantly in the CoreValve group such that the two valve designs were comparable (6.4±5.0 vs. 5.6±5.3%, p=0.623), with no patient in either group having ≥moderate AR. The residual peak pressure gradient immediately following TAVR was significantly lower with CoreValve compared to Lotus (14.1±5.6 vs. 25.4±11.6mmHg, p=0.001), but again by 6 months the two valve designs were comparable (16.5±9.4 vs. 19.7±10.5mmHg, p=0.332). There was no difference in the degree of LV reverse remodelling between the two valves at 6 months.

Conclusion: Immediately post-TAVR, there was significantly less AR but a higher residual peak pressure gradient with the Lotus valve compared to CoreValve. However, at 6 months both devices had comparable valve haemodynamics and LV reverse

remodelling.

KEYWORDS: Transcatheter Aortic Valve Replacement, Medtronic CoreValve, Boston Lotus Valve, Cardiovascular Magnetic Resonance, Aortic Regurgitation, Reverse Remodelling

Word count: 4,688 (including references)

Abbreviations list

AR:	aortic regurgitation
AS:	aortic stenosis
CMR:	cardiovascular magnetic resonance
IQR:	interquartile range
LV:	left ventricle
LVEDP:	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
MDCT:	multi detector computed tomography
TAVR:	transcatheter aortic valve replacement
VARC:	valve academic research consortium
VENC:	velocity encoded gradient echo imaging

INTRODUCTION

Transcatheter Aortic Valve Replacement (TAVR) device design has evolved in an attempt to improve both device success rates and clinical outcomes [1]. However, aortic regurgitation (AR) is seen in up to 80% of patients following TAVR, affecting both the balloon-expandable and the self-expanding designs [2]. This typically reflects incomplete circumferential apposition between the circular prosthesis and the oval-shaped aortic annulus [3] and is often compounded by extensive calcification, under-expansion of the TAVR prosthesis or malposition [4]. Clinical trials and registry data have consistently shown that moderate or more paravalvular AR following TAVR is associated with reduced survival at short- and long-term term follow-up with all valve types [5-7].

Cardiovascular magnetic resonance (CMR) is the reference modality for assessing LV mass, volumes and function. In addition, CMR permits full volumetric quantitation of AR that is highly accurate and reproducible [8, 9], independent of the number or eccentricity of regurgitant jets [10], and unlike echocardiography, is not limited by TAVR prosthesis or calcification artefact [3]. CMR has lower intra-observer and inter-observer variability than echocardiography [11, 12] and thus is more suited to serial measurements. Compared with CMR, echocardiography underestimates AR following TAVR [8, 13, 14] and thus CMR offers a potentially superior prognostic assessment of the post-TAVR patient [14].

Little is known about how AR evolves over time, especially with different valve designs, and how this might impact on LV reverse remodelling. Previous studies have indicated a reduction in AR over time with both the CoreValve and Edwards Sapien valve, but these data have been hampered by the limitations of transthoracic echocardiography in the assessment of paravalvular AR. The Boston Scientific Lotus valve has a unique adaptive seal specifically designed to minimise post-TAVR aortic regurgitation (AR) (8), that has proven to be both safe and effective in the REPRISE I [15] and REPRISE II studies [16].

The aim of this study was to accurately quantify, using serial CMR, the degree of AR over

time following TAVR using the first generation self-expanding Medtronic CoreValve [17-21], and the second generation Boston Scientific Lotus valve, and to determine whether differences in aortic valve regurgitation and haemodynamics impact LV reverse remodelling.

METHODS

Study population

This non-randomised study prospectively recruited 59 patients with severe tri-leaflet degenerative AS who were referred for TAVR at the Leeds Teaching Hospitals NHS Trust, UK, between March 2013 and May 2015. Severe AS was classified by echocardiography as an aortic valve area of ≤1.0cm^2 or peak velocity >4m/s. Decision for TAVR in all cases was taken by a multidisciplinary heart team in accordance with international guidance [22]. In the initial part of the study period only the CoreValve device was available. Subsequently, device selection was made by the TAVI Heart Team according to individual specific patient anatomy and clinical implantation indications. Exclusion criteria included any contraindication to CMR as well as patients with a known bicuspid aortic valve, aortopathy or previous aortic or mitral prostheses. The study was approved by the national research ethics committee, complied with the Declaration of Helsinki and all patients provided written informed consent.

Transcatheter Aortic Valve Replacement

TAVR was performed using either a first generation CoreValve system (Medtronic, Minneapolis, Minnesota, USA) or the Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, MA, USA) employing standard techniques as previously described for both vendors [23, 24]. All patients underwent contrast-enhanced multi-detector computed tomography to assist annular sizing and to assess aortic calcification prior to TAVR. Percutaneous femoral artery access was the default approach, performed under either

general anaesthesia or conscious sedation depending on patient suitability.

CMR Protocol

For each individual patient identical pre- and post-TAVR, and 6-month post-operative scans were performed at 1.5T (Intera or Ingenia, Phillips Healthcare, Best, Netherlands) as previously described (Figure 1) [25, 26]. In brief, multi-slice, multi-phase cine imaging was performed using a standard steady-state free procession pulse sequence in the short axis (8/0mm, 30 phases, typical field of view (FOV) 340mm) to cover the entire left and right ventricle. For flow measurements, through-plane velocity encoded (VENC) phase contrast imaging was performed perpendicular to the aortic valve jet at the aortic sino-tubular junction, at the upper margin of the stent holding the TAVR prosthesis (VENC 200–500cm/s, retrospective gating, slice thickness 6mm, 40 phases, FOV 340mm). This position for imaging has been previously described and validated [9]. If significant turbulence or aliasing was seen in the velocity image, the acquisition was repeated a few millimetres further away from the valve, and/or with a higher-velocity window. In patients with AF, the use of multiple acquisitions and averaging of values, and the application of arrhythmia rejection (in which data points acquired from excessively long or short heart beats are rejected and reacquired) were employed where feasible.

CMR Image Analysis

Image analysis was performed in a blinded fashion, off-line using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada) by two experienced observers. For LV mass and volumes, standard criteria were employed to delineate endocardial and epicardial borders at end-diastole and end-systole and values obtained were indexed to body surface area as previously described [25]. Papillary muscles were included within the LV cavity for the purpose of analysis and excluded from the LV mass. Aortic flow was quantified using cross-sectional phase contrast images with

contouring of the aortic lumen to provide a peak forward flow velocity (m/s), forward flow volume (ml), backward flow volume (ml) for the calculation of trans-valvular pressure gradient (Bernoulli equation) and regurgitant fraction (RF,%). Images were excluded from analysis if artefacts from the TAVR were present on images. Aortic regurgitation was classified as regurgitant fraction of none/trivial ≤5%, mild 6-15%, moderate 16-25%, moderate-severe 26-48%, and severe >48% in line with standard grading criteria [27]. Intra-observer (12 random data sets 6 months apart) and inter-observer (12 data sets) agreement was assessed using the intra-class correlation coefficient.

Sample Size and Statistical Analysis

Based on published data [28] 20 patients per group were required to detect a 10ml change in LVEDV or 10g difference in LV mass regression between the two treatments (90% power and an alpha error of 0.05). A sample size of 16 patients per treatment group was required to adequately power a two-sample comparison of mean aortic regurgitant fraction (again at 90% power and an alpha error of 0.05). Continuous variables are presented as mean±SD. Normality was determined by the Shapiro–Wilk test. Frequencies are reported as number (%). The Student t test and Wilcoxon signed rank test were used to compare continuous variables as appropriate, and $\chi 2$ or Fisher's exact test for categorical comparisons. All statistical analyses were performed using the PASW software package (V.21.0 SPSS, IBM, Chicago, Illinois, USA) with a two-sided significance level of $p<0.05$ was considered statistically significant.

RESULTS

Patient population

A total of 51 patients (24 CoreValve and 27 Lotus valve) underwent both the pre-operative (median 1 day pre-procedure, IQR 14 days) and immediate post-TAVR (median 4 days, IQR 4 days) CMR scans with 44 of these (19 CoreValve and 25 Lotus) finally completing

6-month post-TAVR scans. Reasons for non-completion of the CMR protocol were varied and are depicted in Figure 2. The final analysis population (n=44) was not different from the whole population (n=51) studied pre-TAVR (comparable in age (p=0.871), EuroSCORE II (p=0.724) and STS predicted operative mortality (p=0.736)). Baseline characteristics of the final study population are reported in Table 1.

Measurement Variability

Calculation of intra-class correlation coefficients indicated good intra- and inter-observer reproducibility of CMR measurements respectively: LVEDV (0.984, 0.989), LV mass (0.978, 0.985), LVEF (0.982, 0.970), peak aortic TAVR gradient (1.000, 0.963) and aortic regurgitant fraction post-TAVR (0.987, 0.986).

Procedural data

All of the Lotus valves were implanted via the femoral artery, as were the majority of CoreValves (67% femoral, 29% subclavian, 4% direct aortic). The size and frequency of device replacement is detailed in Table 2. Invasive resting trans-aortic pressure gradients were equivalent between the two groups, in keeping with baseline imaging. The implant procedure for a Lotus valve involved significantly longer fluoroscopy times, despite a significantly greater proportion of CoreValve TAVR receiving post-dilatation (0% vs. 28%, p=0.003). Equivalent volumes of contrast were used for each TAVR device (Table 2).

VARC-defined device success [29] was achieved in 94% of the Lotus cohort and 63% of the CoreValve cohort (p= 0.004) at the immediate post-TAVR time point. The components of this measure were the absence of procedural mortality (94% vs. 96%, p=0.177), a mean gradient across the TAVR prosthesis of <20mmHg (100% vs. 100%, p=0.999), correct positioning of a single TAVR prosthesis (100% vs. 96%, p=0.290), and no more than mild aortic regurgitation (100% vs. 63%, p=0.001) in the Lotus and CoreValve groups respectively. However, at the 6 month time-point, VARC defined success was

equivalent between the two iterations; 91% Boston Lotus Vs. 89% for Medtronic CoreValve (p=0.827). The absolute rate of new pacemaker insertion was similar between the 2 groups (22% Lotus vs. 15% CoreValve, p=0.424).

Haemodynamics

The severity of pre-operative aortic valve stenosis was similar between the Lotus and CoreValve groups (Table 1). Systolic blood pressures (an important measure of LV afterload) remained comparable between the CoreValve and Lotus group both immediately (132±23 vs. 134±22mmHg, p=0.784) and at 6 months (141±25 vs. 127±16mmHg respectively, p=0.161). Immediately post-TAVR, a significant reduction in peak aortic pressure gradient was observed in both Lotus (94.3±28.7 vs. 25.4±11.6mmHg, p<0.001) and CoreValve (88.5±27.4 vs. 14.1±5.6mmHg, p<0.001) groups. However, the residual peak pressure gradient measured by CMR immediately following Lotus valve replacement was significantly higher than that following CoreValve (25.4±11.6 vs. 14.1±5.6mmHg, p=0.001). At 6 months post-TAVR, the peak pressure gradient of the CoreValve remained unchanged from the immediate post-TAVR time point (16.5±9.4 vs. 15.0±5.5mmHg respectively, p=0.457); however a significant reduction was observed in the Lotus group (25.8±12.1 vs. 19.7±10.5mmHg, p=0.022) (Figure 5A). As such, in comparison between CoreValve and Lotus patients, the residual peak pressure gradient at 6 months was equivalent (16.5±9.4 vs.19.7±10.5mmHg, p=0.332) (Table 3).

Immediately post-TAVR, the aortic regurgitant fraction was significantly greater in the CoreValve group (11.7±8.4 vs. 4.3±3.4%, p=0.001). Similarly, the proportion of patients with ≥moderate AR was significantly higher with CoreValve than Lotus (9/24 (37.5%) vs. 0/27 (0%), p<0.001) (Figure 3). Between the immediate and 6 month scans, the aortic regurgitant fraction in the Lotus group remained unchanged (4.0±3.5 vs. 5.6±5.3%, p=0.267). However, a significant reduction was observed in the CoreValve patients

(11.7±7.2 vs. 6.4±5.0%, p=0.002) (Figure 5B). As such, comparison between CoreValve and Lotus patients at 6 months showed that the residual total aortic regurgitant fraction was equivalent (6.4±5.0 vs. 5.6±5.3% respectively, p=0.623) (Table 3). Importantly, of the 19 CoreValve patients who were imaged at 6 months, all of the 7 patients with ≥moderate AR immediately post-TAVR reduced to only mild AR, while three changed from mild to none/trivial AR There were no Lotus valve patients with ≥moderate AR at any time point (Figure 4).

LV reverse remodelling

There were no significant differences in indexed LV end diastolic volume (LVEDV) (p=0.379), indexed LV mass (p=0.357), LV ejection fraction (LVEF) (p=0.306) or LV mass:volume ratio (p=0.329) between the groups at baseline. A direct comparison of LV morphology and function between the two groups, immediately and at 6 months post-TAVR, is summarised in Table 3. Immediately post-TAVR, there was no change in indexed LVEDV or in LVEF in the Lotus group (p=0.550 and 0.498) or the CoreValve group (p=0.461 and 0.847) respectively. However, a significant reduction in the indexed LV mass occurred following CoreValve TAVR (75.4±15.0 vs. 65.8±13.6g/m^2, p<0.001) that was not seen following Lotus (70.8±25.0 vs. 69.6±16.2g/m^2, p=0.811). Compared to baseline, the LVEF and indexed LVEDV values at 6 months were unchanged, regardless of the valve type. However, at 6 months, a significant and comparable regression in the indexed LV mass was observed in both TAVR groups (Table 4, Figure 5C and 5D).

DISCUSSION

This is the first study to use CMR to directly and systematically compare two distinct TAVR designs for aortic valve regurgitation, haemodynamics and impact on LV reverse remodelling over time. The principal findings were as follows: 1. TAVR with the Medtronic CoreValve is associated with a significantly greater quantity of aortic regurgitation

immediately post-replacement, with over a third of patients having at least moderate AR, compared to none with Lotus valve. 2. AR improves significantly with CoreValve over time, such that none of the patients with ≥moderate AR immediately post-TAVR were left with more than mild AR at 6 months, and there was no longer a difference between valve types in mean aortic regurgitant fraction at 6 months. 3. The Lotus valve is associated with a significantly higher residual peak gradient than the CoreValve immediately post-TAVR. 4. Peak TAVR gradient fell significantly with the Lotus valve over time, with no difference between the valves at 6 months. 5. Despite the differences in aortic valve haemodynamics immediately post-TAVR, left ventricular reverse remodelling at 6 months was equivalent. This is consistent with published studies with longer follow-up that have demonstrated excellent outcomes with both TAVR prostheses [15, 30].

Procedural Success

In direct comparison, the VARC-defined primary composite outcome of device success was significantly higher in the Lotus group at the immediate post-TAVR time point, driven principally by the absence of ≥moderate aortic regurgitation. The Lotus valve has been compared with the CoreValve previously using echocardiography [1]; however these grading criteria suggested by VARC lack validation post-TAVR [31]. In a recent comparison of 2D and 3D echocardiography and CMR, applying VARC metrics post-TAVR, the observer variability in determining AR was superior by CMR [12]. This is the first study to our knowledge to assess device success using CMR, and using VARC criteria suggests superiority of the Lotus valve over CoreValve immediately post deployment. However, device success by the 6 month time point in our study was equivalent.

Aortic Regurgitation following TAVR

There is growing evidence suggesting a significant association of post-procedural AR with short- and long-term mortality [18, 32, 33]. In a meta-analysis of 12,926 patients from 45 studies (a majority using Edwards SAPIEN devices), moderate or more AR was associated with a 2.3-fold increase in 1 year mortality following TAVR [34]. Our study used CMR to study the evolution of AR over time. No significant change was seen in the Lotus group from post-implant to 6 months, in line with REPRISE I [15] and REPRISE II [16]. However, we did observe a significant reduction in AR at 6 months following CoreValve replacement. This is consistent with prior echocardiography studies, including the multicentre CoreValve US Pivotal Trial which indicated over 80% of patients exhibited an improvement of at least 1 grade of regurgitation at 1 year [35]. A recent CMR study did suggest a small increase in AR at 6 months post-TAVR; but this study combined measurements of the CoreValve with those of another TAVR design [36]. Our study is the first to use CMR to demonstrate a significant and clinically important improvement in AR over time; all patients with at least moderate AR immediately post-TAVR having mild or less at 6 months. This may reflect continued outward expansion of the nitinol CoreValve frame [35], in contrast to the fixed mechanically locked Lotus frame. Interestingly, analysis of the large UK TAVR registry showed ≥moderate AR after CoreValve, in contrast to the SAPIEN valve, was not associated with increased long-term mortality [37], our finding that ≥moderate AR post-TAVR had resolved at 6 months in all cases may explain these findings.

TAVR Pressure Gradients

Immediately post-TAVR, we observed a lower residual aortic pressure gradient following CoreValve by an average of 10 mmHg when compared with the Boston Lotus. Previous studies have consistently shown that the CoreValve is associated with low residual

gradients immediately post valve replacement [17, 19-21], probably due to the supra-annular position of the valve leaflets within the frame, isolating valve function from the surrounding anatomy. Our reported values with the Lotus valve are also comparable to those reported in previous echocardiographic studies [16]. We do not have effective orifice area information as CMR does not permit accurate assessments in this context. Hence the degree of patient - prosthesis mismatch in our study remains unclear and would further clarify whether the pressure gradients represent poor individual sizing or a genuine reflection of TAVR design.

LV Reverse Remodelling

A significant finding of this study is the acute regression in LV mass index observed following the CoreValve but not the Lotus. Our group has previously reported acute reverse remodelling following TAVR with an average reduction in 8 g/m^2 seen within the first week [38]. In a sub-study of the PARTNER A trial, a notable portion of patients exhibited mass regression within the first 30 days [39]. These findings may have clinical implications given that early LV mass regression following TAVR is associated with improved diastolic function [40], lower B-type Natriuretic Peptide levels and reduced readmission to hospital for heart failure [39]. The difference in immediate LV mass regression post TAVR may well be a consequence of the pressure gradients measured; with comparable reverse remodelling observed at 6 months when pressure gradients were similar. Given that the degree of LV mass regression and recovery of diastolic function after TAVR are positive prognostic indicators [41, 42] and residual hypertrophy detrimental [43], further work to validate these findings is merited.

Limitations

This was a small single-centre non-randomised comparison. Only patients clinically stable enough to participate in the CMR study were included. Not all patients were able to complete the 6 month scan, predominantly due to pacemaker replacement or death, which may have introduced bias, although the final analysed population did not differ from the recruited population in terms of demographics and comorbidities. Our study did include patients in atrial fibrillation (18% in total) in whom there was potential quantification error. Whilst the VARC-2 criteria include a measure of Patient-Prosthesis Mismatch, defined as absent when the TAVR effective regurgitant orifice area (EOA) is >0.85 cm^2/m^2 [44], we assessed TAVR performance by the original VARC criteria [29], as our CMR protocol did not include imaging from which TAVR EOA could be ascertained. The VARC criteria are nonetheless widely accepted, forming the basis of a recent randomised clinical trial directly comparing two different TAVR systems [20].

We used CMR to quantify the total AR seen following TAVR, which is a composite of para-valvular and trans-valvular regurgitation. Total aortic regurgitation following TAVR has been demonstrated as an important marker of mortality [45] and central trans-valvular regurgitation is usually minor and a physiological feature by virtue of prosthesis design [31]. Furthermore, the VARC-2 criteria advocate a combined measurement of "total" aortic regurgitation (AR) reflecting the total regurgitant volume load imposed on the LV [44]. Finally, this study utilised a different grading scale for aortic regurgitant fraction to that advocated by VARC-2, which is based primarily on data from native valve AR measurements. Our values are however entirely consistent with studies focusing on AR specifically after TAVR [9, 10].

CONCLUSIONS

Immediately post-TAVR, there was significantly less AR but a higher residual peak pressure gradient with the Lotus valve compared to CoreValve. However, at 6 months

both devices had comparable valve haemodynamics and LV reverse remodelling.

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FIGURE TITLES and LEGENDS

Figure 1: CMR coronal views showing a Medtronic CoreValve (A) and Boston Lotus valve (B).

Figure 2: Study profile.

Figure 3: Aortic Regurgitation classification immediately post-TAVR

Figure 4: Change in TAVR aortic regurgitation over time

Figure 5: Comparison of change over time in valvular and ventricular parameters between the two TAVR designs (mean±SE).