Transcatheter and Surgical Aortic Valve Replacement for Severe Aortic Stenosis: Insights from Cardiovascular Magnetic Resonance Imaging

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Submitted in accordance with the requirements for the degree of Doctor of Philosophy

The University of Leeds
School of Medicine Leeds Institute of Cardiovascular and Metabolic Medicine
May 2016
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Chapter 1

Publication: Musa TA, Plein S, Greenwood JP. The role of CMR in the assessment of severe aortic stenosis and in post-procedural evaluation following TAVI and surgical AVR.

Accepted for publication March 2016 (Quantitative Imaging in Medicine and Surgery).

Authorship: Individual contributions comprise the following:

TAM - conception and design, drafting and revision of manuscript; SP - revision of manuscript; JPG - conception and design, revision of manuscript.

Chapter 3

Publication: Musa TA, Uddin A, Fairbairn TA, Dobson LE, Sourbron SP, Steadman CD, Motwani M, Kidambi A, Ripley DP, Swoboda PP, McDiarmid AK, Erhayiem B, Oliver JJ, Blackman DJ, Plein S, McCann GP, Greenwood JP. Assessment of Aortic Stiffness by Cardiovascular MR following the treatment of Severe Aortic Stenosis by TAVI and Surgical AVR.

Accepted for publication May 2016 (Journal of Cardiovascular Magnetic Resonance).

Authorship: Individual contributions comprise the following:

TAM: patient recruitment, design, collection of data, data analysis and interpretation, drafting and revision of manuscript. AU, TAF, CDS and LED performed the recruitment of patients and data acquisition. SS and JJO participated in the implementation of the
method of MRI image analysis. DB carried out TAVI implantation and reviewed manuscript. SP and GPM gave input into data interpretation. MM, AK, DR, PS, AKM and BE were involved in critical and intellectual revision of the article. JPG conceived and designed the study and revised manuscript.

Chapter 4

**Publication:** Musa TA, Uddin A, Fairbairn TA, Dobson LE, Steadman CD, Kidambi A, Ripley DP, Swoboda PP, McDiarmid AK, Erhayiem B, Garg P, Blackman DJ, Plein S, McCann GP, Greenwood JP. Right ventricular function following Surgical Aortic Valve Replacement and Transcatheter Aortic valve implantation: a Cardiovascular MRI study. *Accepted for publication August 2016 (International Journal of Cardiology).*

**Authorship:** Individual contributions comprise the following:

TAM patient recruitment, design, collection of data, data analysis and interpretation, drafting and revision of manuscript. AU and TAF performed recruitment of patients, MRI data acquisition and analysis. CDS and LED performed the recruitment of patients and data acquisition. DB carried out TAVI implantation and reviewed manuscript. SP and GPM gave input into data interpretation. AK, DR, PS, AKM, BE and PG were involved in critical and intellectual revision of the article. JPG conceived and designed the study and revised manuscript.

Chapter 5


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TAM: patient recruitment, design, collection of data, data analysis and interpretation, drafting and revision of manuscript. AU analysed MRI data. PPS analysed MRI data and gave input into data interpretation. TAF, CDS, AS and LED performed the recruitment of patients and MRI image acquisition. PG and PH gave input into data interpretation. BE analysed MRI data. SP and GPM were involved in critical and intellectual revision of the article. JPG conceived and designed the study.

Chapter 6

Submitted, undergoing peer-review (Journal of the American College of Cardiology).

Authorship: Individual contributions comprise the following:

TAM patient recruitment, design, collection of data, data analysis and interpretation, drafting and revision of manuscript. AU and LED performed the recruitment of patients, image acquisition and data analysis. TAM and LED analysed MRI data. TAM interpreted the results and drafted the manuscript. DJB and CM performed TAVI implantation and reviewed the manuscript. PPS, PG, JRJF and GJF were involved in critical and intellectual revision of the article. JPG conceived and designed the study.

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Publications Arising From This Work

Abstracts


Acknowledgements

I would like to express my sincere gratitude to Professor John P Greenwood and Professor Sven Plein for the opportunity and privilege of working as a member of their group and benefiting from their invaluable experience and expertise. Their support and enthusiasm were vital to the completion of this project.

I am truly grateful to the patients of West Yorkshire and beyond for their selfless support, time and effort despite frailty and morbidity.

I thank Professor Gerald P McCann and his staff at the University of Leicester for their co-operation and contribution of ideas and patients alike to the project.

I would also like to extend my appreciation to the entire CMR research department. I thank Gavin, Margaret and Caroline for the world-class CMR expertise and support Debbie and Anne for their caring patient-centred approach and Fiona, Petra and Lisa for their outstanding enthusiasm, organisation and commitment.

I am grateful to my colleagues Akhlaque, who afforded me a seemingly effortless transition into the department, Peter, for his invaluable insight into research methods and in particular, his expertise in strain imaging, Laura for her zeal, and Adam, Bara, Pankaj, James and Graham for their cheer, team-spirit and encouragement.

Finally I thank my parents and family for their support and love from a far.
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<th>Description</th>
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<tbody>
<tr>
<td>ACEi</td>
<td>angiotensin converting enzyme inhibitors</td>
</tr>
<tr>
<td>AD</td>
<td>aortic distensibility</td>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AR</td>
<td>aortic regurgitation</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blockers</td>
</tr>
<tr>
<td>AS</td>
<td>aortic stenosis</td>
</tr>
<tr>
<td>AVA</td>
<td>aortic valve area</td>
</tr>
<tr>
<td>BAV</td>
<td>bicuspid aortic valve</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CMR</td>
<td>cardiovascular magnetic resonance</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>CS</td>
<td>circumferential strain</td>
</tr>
<tr>
<td>CSPAMM</td>
<td>complementary spatial modulation of magnetisation</td>
</tr>
<tr>
<td>Cx</td>
<td>circumflex artery</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
</tr>
<tr>
<td>FOV</td>
<td>field of view</td>
</tr>
<tr>
<td>FWHM</td>
<td>full width half maximum</td>
</tr>
<tr>
<td>HLA</td>
<td>horizontal long axis</td>
</tr>
<tr>
<td>HV</td>
<td>healthy volunteer</td>
</tr>
<tr>
<td>LAD</td>
<td>left anterior descending artery</td>
</tr>
<tr>
<td>LGE</td>
<td>late gadolinium enhancement</td>
</tr>
<tr>
<td>LIMA</td>
<td>left internal mammary artery</td>
</tr>
<tr>
<td>LMS</td>
<td>left main stem</td>
</tr>
<tr>
<td>LS</td>
<td>longitudinal strain</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
</tbody>
</table>
LVEDP  left ventricular end diastolic pressure
LVMl  left ventricular mass index
LVOT  left ventricular outflow tract
MACE  major adverse cardiovascular and cerebrovascular events
MDT  multidisciplinary team
MDCT  multi detector computed tomography
MF  myocardial fibrosis
MI  myocardial infarction
MR  mitral regurgitation
NYHA  New York Heart Association
PCI  percutaneous coronary intervention
PG  pressure gradient
PHT  pulmonary hypertension
PLS  peak longitudinal strain
PPM  permanent pacemaker
PWV  pulse wave velocity
RCA  right coronary artery
RF  regurgitant fraction
RFOV  rectangular field of view
ROC  receiver operating characteristic
ROI  region of interest
RV  right ventricle
RVEF  right ventricular ejection fraction
RVESVI  right ventricular end systolic volume index
RVEDVI  right ventricular end diastolic volume index
RWMA  regional wall motion abnormality
SD  standard deviation
SAVR  surgical aortic valve replacement
SNR  signal to noise ratio
SSFP  steady state free precession
STS  Society of Thoracic Surgeons’ risk model
SVG  saphenous vein graft
TAPSE  tricuspid annular systolic plane excursion
TAVI  Transcatheter aortic valve implantation
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>TE</td>
<td>echo time</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>TOE</td>
<td>transoesophageal echocardiography</td>
</tr>
<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>TTE</td>
<td>transthoracic echocardiography</td>
</tr>
<tr>
<td>VARC</td>
<td>valve academic research consortium</td>
</tr>
<tr>
<td>VENC</td>
<td>velocity encoded gradient echo imaging</td>
</tr>
<tr>
<td>VLA</td>
<td>vertical long axis</td>
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<tr>
<td>Zva</td>
<td>valvuloarterial impedance</td>
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Abstract

**Background:** Surgical aortic valve replacement (SAVR) remains first-line treatment for symptomatic severe aortic stenosis, whereas transcatheter aortic valve implantation (TAVI) is indicated in patients who are inoperable or considered too high-risk for surgery. Current focus is centred on differences in the impact of valve replacement upon cardiovascular function to guide patient selection and the development of novel prosthetic valves to improve outcomes. Cardiovascular Magnetic Resonance (CMR) imaging is the investigative modality of choice for such a purpose.

**Objectives:**
To compare the impact of SAVR and TAVI upon aortic stiffness, right ventricular function and myocardial strain, and to compare two vendor designs in the quantity of post-TAVI aortic regurgitation and reverse remodelling.

**Methods:** A prospective study of patients with severe aortic stenosis under surveillance and subsequently requiring SAVR or TAVI, recruited between September 2009 and December 2015. A 1.5 Tesla CMR study was performed pre and 6 months post SAVR, and pre, immediately and 6 months post implantation of Medtronic CoreValve and Boston Lotus TAVI. Aortic distensibility (AD), pulse wave velocity (PWV), right ventricular (RV) volumes, myocardial strain and aortic regurgitation (AR) were quantified.

**Results:** At 6 months, SAVR was associated with a significant worsening in PWV (6.38±4.47 vs. 11.01±5.75ms⁻¹, p=0.001) and ascending AD (1.95±1.15 vs. 1.57±0.68x10⁻³mmHg⁻¹, p=0.044), whereas no change was seen following TAVI. A significant reduction in RV ejection fraction (58±8 vs. 53±8%, p=0.005) was seen flowing SAVR, with no change following TAVI. A significant and comparable decline in LV torsion and twist was observed. Baseline circumferential strain was significantly associated with all-cause mortality (hazard ratio, 1.03; 1.01–1.05; p=0.009). Significantly less AR was seen immediately following Lotus than CoreValve TAVI (4.3±3.4 vs.11.7±8.4%, p=0.001) with equivalent degrees of reverse remodelling observed at 6 months.

**Conclusion:** Compared with TAVI, SAVR is more detrimental upon aortic stiffness and right ventricular function at 6 months. CMR derived circumferential strain is associated with survival following SAVR and TAVI.
Chapter 1 General Introduction

1.1 Aortic Stenosis

Aortic valve stenosis (AS) is the sequela of active valve remodelling which can readily be diagnosed but at present is beyond prevention. At the macroscopic level there is focal subendothelial thickening, inflammatory cell infiltration and subsequent calcification (Rajamannan et al., 2011). There is therefore progressive narrowing of the aortic valve orifice leading to obstruction of left ventricular (LV) outflow with consequential myocardial hypertrophy to preserve wall stress and cardiac performance (Clayton et al., 2014). Decompensation is driven by progressive myocyte death and myocardial fibrosis (Chin et al., 2014b). Increased LV filling pressures and reduced cardiac output lead to exertional dyspnoea. Angina is also frequent from subendocardial ischaemia as a result of an increased LV mass and reduced coronary flow reserve (Julius et al., 1997). Severe aortic stenosis also carries an increased risk of sudden cardiac death (lung and Vahanian, 2014).

Degenerative aortic valvular stenosis is the most common valve disease in the western world (Nkomo et al., 2006). The largest population-based study to date originates from the National Health, Lung and Blood Institute of 11,911 adults across the United States of America. Systematic echocardiographic examination indicated a prevalence ≤ 0.2% before 65 years of age, rising to 2.8% after 75 years (Nkomo et al., 2006). In 2010, there were an estimated 1.2 million people in the USA with at least moderate AS, including 520,000 aged over 75 years (lung and Vahanian, 2012). The European Tromso study included 3,273 patients and reported higher prevalence in the elderly, affecting 9.8% of adults between 80 and 89 years of age. The annual incidence rate (derived from the study period 1974-2008) was 4.9 per 1000 (Eveborn et al., 2013). Aging populations and the absence of any validated prevention method mean that the burden of aortic stenosis is expected to double within the next 50 years (lung and Vahanian, 2012).

The onset of symptoms is a major predictor of mortality; a concept first described by Ross and Braunwald in 1968 (Ross and Braunwald, 1968). The prognosis is particularly poor in the elderly (Leon et al., 2010) in whom there are other significant co-morbidities in more than one-third of cases (lung et al., 2007). In octogenarians with comorbidities, mortality rates between 40% and 50% at 1 year have been reported (lung and Vahanian, 2014). Five-year mortality has recently been reported at 60% after a first hospitalization with a diagnosis of AS (Berry et al., 2013). Two year follow-up data from the PARTNER cohort B study (Kodali et al., 2012) indicated standard medical treatment was associated with a cardiovascular mortality of 62.4% and repeat hospitalisation of 72.5%. Given the lack of effective medical treatment, management
is centred on optimal timing of aortic valve intervention, to reverse hypertrophy, restore systolic and diastolic function, relieve symptoms and ultimately restore prognosis (Thaden et al., 2014).

1.2 Aortic Valve Surgery
Surgical aortic valve replacement (SAVR) is a routine procedure that has been practised for over 50 years and its evidence base places it first-line in the treatment of symptomatic severe aortic stenosis (Walther et al., 2012). The first-in-human heterotopic aortic valve replacement was performed in 1952 by Hufnagel and Harvey, palliating severe aortic regurgitation by implanting an artificial ball prosthesis in the descending aorta (Hufnagel and Harvey, 1953). In 1955, Gordon Murray placed a homograft in the same position (Murray, 1956). The advent of cardiopulmonary bypass facilitated maintenance of procedural haemodynamics and heralded the first sub-coronary mechanical AVR, performed by Starr and Harken in 1960. Two years later, Donald Ross implanted a sub-coronary homograft (Ross, 1962). As a result, surgical AVR emerged as the gold standard for the management of AS. Crucial to the procedure is complete excision of calcified degenerated aortic cusps followed by precise implantation under direct vision of a modern xenograft or mechanical prosthesis using standard suturing techniques. Due to its ability to cure aortic stenosis completely, conventional AVR has long since been considered the gold standard intervention (Walther et al., 2012).

Indeed, despite the intrusive nature, even elderly patients do favourably post SAVR. In a cohort of over 1000 octogenarians, survival rates of 89% and 69% after 1 and 5 years, respectively, were seen (Asimakopoulos et al., 1997). Guidelines from Europe (Joint Task Force on the Management of Valvular Heart Disease of the European Society of et al., 2012) and the USA (Nishimura et al., 2014b) list a Class I recommendation for SAVR in those with symptoms or reduced ejection fraction. However, surgery does carry an associated morbidity and mortality that may be considered prohibitive in elderly patients with multiple comorbidities and frailty. Indeed, in the Euro Heart Survey, one third of 216 patients with symptomatic severe AS aged over 75 years were not referred on for surgery (Iung et al., 2005).

1.3 Transcatheter Aortic Valve Implantation
The concept of a permanent “stent valve”, catheter-mounted, balloon-deployable valve prosthesis dates back over thirty years to animal experimental models (Binder and Webb, 2012). In 2002, the first-in-human transcatheter aortic valve implantation (TAVI) was performed via an antegrade, transvenous approach (Cribier et al., 2002). Later, the retrograde approach, with access via the femoral artery, gained favour and became a reproducible, fully percutaneous procedure (Webb et al., 2006). Since then, the rate of TAVI has risen
enormously, with over 200,000 having been performed worldwide, the vast majority in Europe (Newton et al., 2015).

The early UK experience has been well charted through the construction of the UK TAVI registry (Moat et al., 2011). Data were collected prospectively on 870 patients until 31 December 2009. TAVI was performed with the use of the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota, USA) (52%) or the Edwards-SAPIEN THV (Edwards Lifesciences, Irvine, California, USA) (48%). The majority of the TAVI implants (69%) were performed via the transfemoral approach according to the widespread ‘transfemoral first’ policy. Outcomes of TAVI patients in the UK TAVI Registry at 30 days, 1 year and 2 years were encouraging with mortality rates of 7.1%, 21.4% and 26.3%, respectively.

Health related quality of life measures are an important clinical outcome and are significantly improved following TAVI, with scores maintained out to 1 year (Fairbairn et al., 2012); this is despite silent cerebral microinfarctions which are more frequently seen following TAVI than SAVR (Uddin et al., 2015). In a cost-utility analysis, TAVI was demonstrated to be a cost-effective option in high-risk but operable elderly patients when compared with SAVR (Fairbairn et al., 2013a). TAVI improves survival and functional capacity when compared with standard medical therapy (Leon et al., 2010, Kapadia et al., 2015), and recently data suggests 2 year survival is superior to SAVR in high surgical risk patients (Reardon et al., 2015) and similar at 5 years (Mack et al., 2015). Furthermore, the TAVI procedure is less restricted by patient frailty or confounding surgical considerations such as a “porcelain” aorta or mediastinal adhesions (Rodes-Cabau et al., 2010). Given its transformative benefits, TAVI is now an established intervention in symptomatic patients deemed inoperable or with too high a predicted postoperative mortality (Sorajja and Pedersen, 2014).

1.4 Cardiovascular MR and pre-procedure assessment

Cardiovascular Magnetic Resonance (CMR) imaging is a commonly used technique and determines both morphological and functional information that is crucial to the assessment of valvular heart disease. CMR permits high resolution imaging in any plane and can quantify the severity of the valvular lesions, determine aetiology, assess global and regional cardiac function as well as the anatomy of associated great vessels (Myerson, 2012). Furthermore, myocardial perfusion, myocardial viability, tissue characterisation and proximal coronary anatomy can all be examined within a single study without any ionising radiation (Ripley et al., 2014).

A typical CMR study for evaluating valvular heart disease comprises left ventricular long-axis (2-, 3- and 4-chamber views) and a complete stack of sequential short-axis (every 8-10mm from
base to apex) cine images using a steady-state free precession (SSFP) pulse sequence (Figure 1.1).

![Image of CMR cine imaging demonstrating anatomical and functional information.](image)

**Figure 1.1 CMR cine imaging demonstrating anatomical and functional information.**

A. Short-axis of left ventricle at basal level in diastole indicating mild concentric hypertrophy (white arrow, 14mm)

B. Coronal left ventricular outflow tract (LVOT) view acquired through plane of aortic valve leaflet tips indicating restricted leaflet motility and resultant high velocity jet (white arrow).

C. Cine imaging of a bicuspid aortic valve orifice in systole with A-P closure line. This view permits direct planimetry of valve area in addition to morphological assessment.

D. 4-chamber view allowing visual assessment of ventricular, mitral and tricuspid function and atrial size.

E. Sagittal-Oblique view of aorta throughout its entire thoracic course. F. Cine imaging of heavily stenosed trileaflet aortic valve.

This generates images with an excellent signal-to-noise ratio and high blood-to-myocardium contrast, with a typical in-plane spatial resolution of (1.5-2.0mm) comparable to transoesophageal echocardiography for aortic valve planimetry and assessment of cusp anatomy (Lopez-Mattei and Shah, 2013, Paelinck et al., 2011). CMR facilitates clear visualisation of sub-valvular and supra-valvular aortic stenosis, and also permits assessment of prosthetic valvular function (Figure 1.2).
Figure 1.2 CMR (coronal LVOT) imaging following aortic valve intervention
A. Medtronic CoreValve.
B. Boston Lotus valve.
C. Bioprosthetic Sorin MitroFlow valve.
D. Mechanical 30mm Carbomedics Carbo-Seal Valsalva with 27mm ascending aortic prosthesis.

CMR is the most accurate technique for assessing both left and right ventricular volumes and mass (Bellenger et al., 2000a, Myerson et al., 2002a, Koch et al., 2000). It has been validated against post-mortem studies of animal and human hearts (Childs et al., 2011) and is highly reproducible (Grothues et al., 2002). By providing 3-dimensional datasets, it is also more sensitive and reproducible to changes than one or two-dimensional echocardiographic
measures (Myerson et al., 2002b) and it is independent of geometric assumptions of ventricular morphology. This can be crucial for the surveillance of asymptomatic patients to determine deterioration in ventricular function (Myerson, 2012).

CMR permits direct flow quantification using through-plane phase contrast velocity mapping (Gatehouse et al., 2005). This is a unique advantage of CMR which unlike echocardiography and invasive catheterisation, does not depend upon derivation from complex calculations (Myerson, 2012). The technique measures phase shift of moving protons inside a magnetic field, exploiting their difference to stationary protons. A bipolar gradient pulse pair is applied; the second gradient re-phases the de-phasing caused by the first gradient. Flowing blood has a different phase of transverse magnetization to that of stationary tissue and this difference is proportional to the velocity of the blood in the direction of the applied gradient. VENC refers to the maximum measurable velocity range and is operator defined. Aliasing occurs when the velocity of blood flow exceeds the VENC set, with positive velocities being displayed as negative velocities and vice versa. Modulus and phase images are reconstructed from a gradient-echo flow sequence and post-processing of this data allows an accurate measurement of forward and backward flow across the valve (Figure 1.3) (Gatehouse et al., 2005).
Figure 1.3 Velocity encoded Phase Contrast (PC) imaging to quantify aortic stenosis

A. Short-axis view indicating a bicuspid valve with double-barrelled orifice.
B. Transverse LVOT views obtained using steady state free precession.
C. Coronal LVOT view used to plan imaging planes for PC acquisition.
D. Phase velocity map.
E. Magnitude image
F. Time-velocity curve of aortic flow rate (in this patient peak gradient 53mmHg, RF 14%)

However, the temporal resolution of CMR is typically 25-45ms which is considerably lower than continuous wave Doppler echocardiography (which can be ~2ms) (Myerson, 2012). This in conjunction with turbulent flow artefacts and partial volume effects mean CMR peak velocity measurements may be underestimated compared to echocardiography especially when peak velocities surpass 3.5-4.0 m/s (O'Brien et al., 2008). Indeed, a number of validation studies referencing CMR against echocardiography have indicated good correlation but a trend towards this underestimation by CMR, and clinically the velocity definitions of valvular severity remain echo derived (Cawley et al., 2009).
Accurate measurements of the aortic root and ascending thoracic aorta can be ascertained (Myerson, 2012) which may be dilated, particularly in context of bicuspid aortic valve disease, with important repercussions for subsequent surgical management. Furthermore, in patients with severe LV systolic dysfunction, a dobutamine-stress protocol may be employed to differentiate pseudo from true aortic stenosis and determine contractile reserve (Lopez-Mattei and Shah, 2013).

The European Society of Cardiology guidelines for management of aortic stenosis advocate CMR in particular for more detailed assessment in patients with paradoxical low-flow low-gradient aortic stenosis, assessment of the ascending aorta when enlarged, and for the detection and quantification of myocardial fibrosis. This is in addition to assessment of ventricular volumes and systolic function (Joint Task Force on the Management of Valvular Heart Disease of the European Society of et al., 2012). US guidelines similarly indicate CMR may be required to determine optimal treatment for a patient as an ancillary investigation to transthoracic echocardiography (Nishimura et al., 2014b).

1.4.1 CMR detection of fibrosis and predicting prognosis
Aortic stenosis increases LV afterload and triggers an initial compensatory hypertrophic response. Women develop a concentrically hypertrophied, small cavity LV, whereas men are more prone to the development of eccentric hypertrophy (Dobson et al., 2015). However, left untreated, there is progressive myocyte necrosis and subsequent replacement myocardial fibrosis (Hein et al., 2003). This is associated with abnormal cardiac remodelling and increased ventricular stiffness in both animal and human studies (Mewton et al., 2011) and ultimately culminates in heart failure and a worse prognosis (Chin et al., 2015). Myocardial fibrosis has thus been targeted extensively as a potentially objective marker of LV decompensation that may hold promise in guiding appropriately timed valve intervention.

Historically, the gold standard for validating myocardial fibrosis has been myocardial biopsy but this is invasive, susceptible to sampling errors and does not assess the whole heart (Mewton et al., 2011). There have been varying degrees of interstitial fibrosis reported on histological assessment in patients with severe AS, ranging from 4% to 39% (Krayenbuehl et al., 1989, Flett et al., 2010).

A pivotal and unique strength of CMR is in vivo tissue characterisation, offering a direct visualization, whole-heart assessment of myocardial fibrosis (Ambale-Venkatesh and Lima, 2015) (Figure 1.4). The technique probes the retention of gadolinium-based contrast agents within myocardial tissue, with dead or scarred myocardium appearing bright in contrast to
normal black myocardium on late inversion recovery T1-weighted imaging (Singh et al., 2014). The use of late gadolinium enhancement (LGE) imaging has been validated against surgical biopsy studies in AS (Azevedo et al., 2010), with focal mid-wall enhancement reportedly present in 19-62% of patients (Chin et al., 2015) and with increasing quantities increasing with increasing hypertrophy (Debl et al., 2006).

**Figure 1.4 Late Gadolinium Enhancement CMR imaging**

A. Absence of any hyperenhancement.
B. Typical subendocardial infarction pattern (affecting the inferior interventricular septum and inferior walls, black arrow).
C. Focal (non-infarct) myocardial fibrosis affecting the inferolateral wall (white arrow).

The degree of myocardial fibrosis at histology correlates with worsening NYHA class and impaired longitudinal systolic function, and is inversely associated with the degree of functional improvement following SAVR (Weidemann et al., 2009). In another histology study, fibrosis quantity was strongly associated with increased LV cavity diameters, and reduced LV ejection fraction, a finding also demonstrated from CMR imaging (Nigri et al., 2009). Furthermore, pre-operative fibrosis grade was the strongest independent predictor of mortality post AVR (Milano et al., 2012).

Following on from biopsy observations, LGE imaging has been used to assess the clinical significance of fibrosis in patients with severe AS, both prior to and after valve intervention. The presence of mid-wall fibrosis in this context is associated with raised plasma troponin concentrations (Chin et al., 2014a) and a hypertrophic strain pattern on electrocardiogram tracing (Shah et al., 2014), both of which can provide incremental prognostic information in asymptomatic patients. In a small cohort of patients (n=52, including 24 with aortic regurgitation) the quantity of fibrosis was a multivariate predictor of all-cause mortality and, in a
subset of these patients, predicted lack of improvement of ejection fraction after SAVR (Azevedo et al., 2010). Another study reported that the absence of fibrosis was associated with good prognosis after SAVR for AS and that the extent of LGE did not change after SAVR (Weidemann et al., 2009).

In a larger study of 143 medically treated patients (40% moderate, 60% severe AS), presence of mid-wall hyperenhancement was associated with an 8-fold increase in all-cause mortality in comparison to patients without fibrosis, despite comparable valvular haemodynamics. Half the study population eventually underwent SAVR, and in this group the mortality rate was 53.8 per 1000 patient years in those with mid-wall fibrosis, compared with 13.7 in those without focal fibrosis (Dweck et al., 2011). In a subsequent publication, the incidence of major adverse cardiac events (MACE), stroke and heart block following SAVR were significantly higher in those with mid-wall fibrosis compared to those without. There were no 30-day MACE events, nor patient deaths at 2 year follow-up in those without fibrosis, highlighting the potential use of CMR in predicting risk / outcome prior to AVR for AS (Quarto et al., 2012).

The largest study to date investigating the prognostic importance of CMR defined focal fibrosis involved 194 consecutive patients, all with severe AS undergoing SAVR (n=154) and TAVI (n=40) (Barone-Rochette et al., 2014). This study demonstrated that the presence and extent of myocardial fibrosis detected by CMR imaging predicted increased perioperative risk and worse all-cause mortality in those undergoing SAVR, and increased cardiovascular related mortality in those undergoing SAVR or TAVI. Furthermore, the authors observed a high incidence of sudden cardiac death in those with fibrosis raising the possibility that prophylactic implantable cardioverter-defibrillators may improve long-term survival.

The evidence thus far indicates fibrosis detection using CMR heralds LV decompensation and there are on-going prospective studies to confirm whether this technique holds prognostic importance and could potentially improve patient selection for intervention (https://ClinicalTrials.gov: PRIMID-AS, RELIEF-AS, and NCT01755936).

1.4.2 Myocardial Perfusion Reserve
The myocardial perfusion reserve (MPR) is derived as the ratio of myocardial blood flow during maximal hyperaemia compared to resting conditions (Garcia et al., 2009). In the absence of epicardial disease, it therefore indicates the presence of coronary microvascular dysfunction (Rajappan et al., 2003). Defining this ratio of maximal myocardial flow to baseline has been used to evaluate severity of coronary disease, as well as defects in the myocardial microcirculation associated with other conditions such as diabetes mellitus, hypertension and
hypertrophic cardiomyopathy (Parkka et al., 2006). MPR can be measured using CMR and has been shown in one study to independently predict aerobic exercise capacity in 46 patients with severe AS; with a strong inverse relationship to symptom status (Steadman et al., 2012). However, CMR quantification of MPR is complicated and lacks consensus (Singh et al., 2014). The recently completed PRIMID-AS trial was designed to compare CMR with exercise testing in identifying patients likely to benefit from SAVR, and thus will help clarify the role of CMR MPR in aortic stenosis (Singh et al., 2013).

1.4.3 Assessment of Aortic Stiffness
Aortic function regulates the entire cardiovascular system and changes in aortic wall composition and elasticity are important to the development of cardiovascular disease. Increased arterial stiffness is an independent predictor of adverse outcomes in patients with hypertension, renal failure, diabetes and the elderly (Ripley et al., 2015) and is thus increasingly a clinical focus. CMR permits the measurement of both aortic distensibility (reflecting the systolic expansion of the aorta) and pulse wave velocity (the propagation speed of the pressure wave along the length of the aorta). CMR holds several advantages over conventional ultrasound, but most notably can reproducibly detect more subtle changes in regional stiffness at any operator chosen location (Cavalcante et al., 2011). CMR has been used to study patients with bicuspid aortic valve disease, in whom significantly reduced elasticity of the entire thoracic aorta is observed, even without significant stenosis (Grotenhuis et al., 2007).

1.5 CMR and post-intervention assessment
1.5.1 Detection of myocardial injury
CMR is the gold standard imaging technique for the non-invasive detection and quantification of myocardial infarction (Gibbons et al., 2004), and has been used to investigate myocardial injury following treatment for severe AS (Fairbairn et al., 2013b, Kim et al., 2014). Using LGE CMR, focal fibrosis due to prior myocardial infarction is typically subendocardial in distribution, extending transmurally towards the epicardium the larger the infarct, and confined to a specific epicardial coronary artery territory; a pattern entirely distinct from that of mid-wall myocardial fibrosis (Mahrholdt et al., 2005). In a CMR study of 50 patients (25 SAVR, 25 TAVI), new postoperative sub-endocardial infarction was evident in six individuals (5 SAVR, 1 TAVI, p=0.11). Despite the small numbers, the study was the first to suggest TAVI expansion was not detrimental to the patency of coronary ostia, and that perioperative myocardial protection in severely hypertrophied ventricles could, on occasion, be suboptimal during SAVR (Fairbairn et al., 2013b).
In a larger study of patients undergoing TAVI for severe AS (n=61), new myocardial late enhancement with an ischaemic pattern occurred in 18%; averaging 1.8% of the LV mass in quantity. This was assumed to be embolic in origin, but importantly, did not correlate with cardiac biomarkers of injury, which were ubiquitously elevated in all patients. Furthermore, patients with injury detectable by CMR imaging featured a significant reduction in LV function at discharge (Kim et al., 2014). Further work is needed to evaluate the prognostic significance of new, CMR detected infarction following TAVI, as has been done with elevated serum biomarkers (Sanz and Dangas, 2014).

1.5.2 Reverse Ventricular Remodelling
Aortic valve stenosis increases the afterload of the LV which compensates through alteration in wall geometry to preserve wall stress. Left ventricular hypertrophy is part of this pathophysiological adaptation and a remodelling process is well recognised comprising myocyte degeneration, replacement fibrosis and reduced ventricular performance. SAVR restores valvular function and removes the aorto-valvular impedance and afterload mismatch seen with aortic stenosis. This subsequently drives a “reverse remodelling” defined by mass regression, volumetric reduction and improved function. Indeed, this reverse remodelling underscores the improvement of symptoms and prognosis conferred by SAVR (Fairbairn et al., 2013b).

CMR affords greater precision to 2D echocardiography in the three-dimensional analysis of LV volumes and mass without the requirement for geometric assumptions, and has been used to characterise reverse ventricular remodelling in detail following both SAVR (Fairbairn et al., 2013b) and TAVI (La Manna et al., 2013, Fairbairn et al., 2013b).

In a study of 50 patients (25 SAVR, 25 TAVI) CMR was used to directly compare changes between baseline and 6 months following intervention (Fairbairn et al., 2013b). Both TAVI and SAVR were associated with significant and comparable reduction in the LV end systolic volume and LV mass index, with a greater reduction in LV end diastolic volume seen following SAVR compared to post-TAVI. Myocardial fibrosis reduced post-TAVI (10.9±6% vs 8.5±5%, p=0.03) but not post-SAVR (4.2±2% vs 4.1±2%, p=0.98). It remains undetermined as to whether this reduction in mass reflects an actual change in myocyte size and further work using pre- and post-contrast T1 mapping to determine extracellular volume and estimate cardiomyocyte size is warranted. Overall, adjusting for baseline characteristics, the authors felt global geometric reverse remodelling was unlikely to differ between the two procedures. Interestingly, right ventricular reverse remodelling seemed more favourable following TAVI with a reduction in
volumes and improved function observed. This was in contrast to SAVR, where a decline in RV function was reported, likely reflecting adverse effects of cardiopulmonary bypass during cardiac surgery. In this study, the presence of myocardial scar due to infarction, and not focal myocardial fibrosis, was associated with worse right ventricular function and volumes at 6 months. Statistically, worse baseline measures of LV volumes and mass were independent predictors of reduced reverse remodelling (defined as the LV mass:EDV ratio). These findings again highlight the potential importance of CMR in predicting patient outcomes and those likely to benefit from closer clinical observation.

1.5.3 Quantification of Aortic Regurgitation following TAVI

The TAVI procedure involves destruction of the native aortic valve leaflets, which are crushed by a superimposed bioprosthesis as it is expanded within the aortic annulus. Extensive native valve leaflet calcification, patient/prosthesis mismatch, under expansion of TAVI prosthesis and malposition can preclude a complete sealing of the paravalvular space with resultant paravalvular aortic regurgitation (PAR) (Lerakis et al., 2013). Furthermore, the two frequently used TAVI designs, namely the Medtronic CoreValve and the Edwards SAPIEN, comprise a skirt that covers only the lower part of the TAVI frame, leaving the upper part exposed. The term “supra-skirtal regurgitation” describes leakage through the uncovered part of the prosthesis above the skirt that may occur if the prosthesis is implanted too low in the aortic position (Stahli et al., 2013).

A number of trials and multicentre registries have published data on PAR with an overall incidence ranging between 50 and 85% (Lerakis et al., 2013). A recent meta-analysis including 12,926 TAVI patients reported a pooled estimate incidence of moderate or severe PAR of 11.7% (Athappan et al., 2013).

The significance of PAR post TAVI is in prognostication. Moderate to severe AR is an independent predictor of mortality in the postoperative period to 30 days, at 1 year, and at 2 years (Lerakis et al., 2013). In a recent study of 2,434 patients, the largest single study published, 1 year all-cause mortality, cardiac related mortality and rehospitalisation were significantly increased with worsening PAR. The presence of both mild (hazard ratio 1.27) and moderate-severe PAR (hazard ratio 2.18) were independently associated with higher late mortality on multivariate analysis (Kodali et al., 2015).

The difference in rates of PAR reported after TAVI undoubtedly arises from the variety of imaging methods, time points and grading scales applied to the particular cohort. In clinical practise, 2D transthoracic echocardiography is the most frequently used modality to evaluate
PAR severity given its low cost and availability. However, 2D echocardiography is by its nature largely qualitative and suited to central regurgitation; with image quality susceptible to habitus, prior cardiac surgery or airway disease impeding acoustic windows (Crouch et al., 2015b).

A semi-quantitative assessment is possible but has considerable limitations when applied to eccentric and multiple jets arising from a crescentic irregular orifice, typically seen in the TAVI patient. The Valve Academic Research Consortium (VARC) has defined quantification criteria to improve uniformity in assessment of PAR post TAVI. However, the use of the grading scheme for native valve regurgitation in this post TAVI setting has not been validated (Lerakis et al., 2013).

CMR affords a number of advantages over echocardiography for the assessment of PAR. It permits full quantitation of regurgitant volumes irrespective of valve type, jet number or eccentricity and is unaffected by calcification or prosthesis artefact (Pibarot et al., 2015). Furthermore, a comprehensive evaluation of the consequences of PAR upon LV volumes and function can be determined concomitantly. Indeed the use of CMR to assess both valvular and ventricular function in the post-TAVI setting has been validated (Crouch et al., 2015b).

CMR is susceptible to arrhythmia or poor quality ECG triggering as this generates motion artefact during cine acquisition reflecting variations in the R-R interval. Uncontrolled AF in particular can diminish the accuracy of flow data and is best addressed prior to imaging. Furthermore, for AR the measured regurgitant volume assessment will include diastolic coronary flow (Pibarot et al., 2015). There is also an inherent potential for underestimation of AR as the gap between the image plane of flow mapping and the valve expands in systole; reflecting elastic expansion of the aortic root and sinuses and the movement of the aortic valve towards the LV apex. This can be exacerbated when there is dilatation of aortic sinuses and vigorous longitudinal LV contraction; both of which are associated with AR.

Nonetheless, a recent comparison applying VARC-2 recommendations of 2D, 3D echocardiography and CMR in 71 patients, the intra- and inter-observer variability in determining regurgitant volume was found to be lowest with CMR (2.2±2.0% and 1.5±1.5% respectively) (Altiok et al., 2014). In another recent comparison of quantitative CMR with 2D echocardiography, 27 of 56 (48%) TAVI patients had AR which was at least one grade more severe on CMR than echo indicating echo underestimates the degree of PAR (Crouch et al., 2015b). This may in part explain why even patients with reportedly “mild” PAR from PARTNER exhibited increased mortality (Kodali et al., 2012). Further work is required to determine whether CMR is indeed of superior prognostic value in patients following TAVI.
1.5.4 Assessment of Myocardial Deformation and Strain Imaging

Quantification of myocardial strain and strain rate permits a distinct functional assessment of the radial, longitudinal and circumferential fibres of the LV and can detect contractile dysfunction prior to an overall decline in ejection fraction. Strain imaging has demonstrated prognostic importance in a number of cardiac conditions (Singh et al., 2015). Myocardial tissue tagging using CMR was first introduced in 1988 and remains the current gold standard CMR method to assess strain with proven reproducibility (Swoboda et al., 2014). This technique has been used in patients with symptomatic severe AS in whom pressure overload induces increased systolic wringing motion (thought to be compensatory) that progressively declines as hypertrophy and dilatation worsens. Following SAVR, there is normalisation of LV torsion (Sandstede et al., 2002), but interestingly, this disproportionately favours those without coronary disease (Biederman et al., 2005).

Feature tracking is a novel technique involving more rapid semi-automatic analysis of standard CMR cine images. It has been compared to tissue tagging in patients with AS and consistently produces higher values with excellent reproducibility (Singh et al., 2015). It can detect subtle LV impairment not visible in standard echocardiography and has been used to assess LV performance in patients undergoing TAVI, in whom a trans-apical approach results in significant apical LV dysfunction when compared to a trans-femoral TAVI (Meyer et al., 2014).

1.6 Future applications

1.6.1 CMR Spectroscopy

Myocardial triglyceride content can be quantified using $^1$H CMR spectroscopy, and a number of studies have reported an independent correlation between degree of myocardial steatosis and both systolic and diastolic dysfunction (McGavock et al., 2006, Ng et al., 2010). This technique has been used to demonstrate the presence of myocardial steatosis in patients with severe AS, both with and without symptoms. Myocardial triglyceride content, validated against histological quantification, was independently associated with degree of LV systolic strain impairment, despite a normal ejection fraction. Furthermore, steatosis and strain impairment were reversible following SAVR (Mahmod et al., 2013). Excessive fatty acids are precursors to toxic intermediates that promote apoptosis and ultimately change myocardial architecture (Goldberg et al., 2012). Myocardial lipotoxicity is thus a potentially treatable target which could offset LV dysfunction in aortic stenosis and signal a role for CMR spectroscopy in risk stratification.

1.6.2 4D flow imaging

Two-dimensional phase-contrast CMR imaging has been used for over three decades to evaluate pulsatile blood flow of the heart and great vessels (Stankovic et al., 2014). Further
advances in technology have heralded phase-contrast with flow-encoding in all three spatial directions that is resolved relative to all three dimensions of space, and to the dimension of time along the cardiac cycle (3D + time = 4D); referred to as “4D flow CMR” (Dyverfeldt et al., 2015). 4D flow MRI thus encodes the velocity magnitude and direction of each voxel within the defined volume by acquiring data over multiple cardiac cycles. The 3D velocity dataset obtained therefore reflects an average cardiac cycle and is insensitive to beat-to-beat variations (van der Geest and Garg, 2016). The technique provides full volumetric coverage of any cardiac or vascular region of interest, with subsequent off-line analysis used to quantify total flow, peak velocity or regurgitant fraction amongst other parameters (Figure 1.5) (Markl et al., 2003). Furthermore, deriving advanced haemodynamics such as wall shear stress (Markl et al., 2011), pressure difference (Bock et al., 2011) and turbulent kinetic energy (Dyverfeldt et al., 2009) may facilitate unprecedented assessment of cardiovascular disease beyond simple flow measures (Stankovic et al., 2014).

**Figure 1.5 4D flow acquisition**

Path lines of velocity vectors using 4D flow aortic imaging, segmented on a 2D aortic cine image (sagittal oblique orientation). Flow acceleration in early systole at peak LV ejection (red area) is seen in the ascending aorta in this healthy subject. AAo; ascending aorta, MPA; main pulmonary artery, DAo; descending aorta.
Bicuspid aortic valve disease is associated with an aortopathy and carries a risk of aortic dissection. Aortic dimensions are the principal measurement to guide intervention currently, given no measures of aortic stenosis have proven useful in risk stratification (Nishimura et al., 2014b). 4D flow CMR has offered unique insights into this aortopathy which is an area of significant clinical interest (Stankovic et al., 2014). In an assessment of 30 patients with bicuspid aortic valve (n=15 Right-Left phenotype (BAV-RL), n=15, Right-Non phenotype (BAV-RN)), 4D CMR flow indicated differences in aortopathy expression (Mahadevia et al., 2014). In comparison to controls, the BAV-RL valve phenotype had elevated wall shear stress at the right-anterior wall with aortic enlargement predominantly affecting the tubular portion of the ascending aorta; in contrast to the BAV-RN valve which affected the right-posterior wall with dilatation affecting either the root only or the entire ascending aorta and arch. This unique assessment of haemodynamics with 4D flow CMR indicates a physiological mechanism through which bicuspid AV morphology may impact on aortopathy phenotype.

4D flow CMR has also been used to assess aortic flow following intervention for AS. Rather than physiologic central flow, all stented, stentless and mechanical SAVR prostheses showed eccentric flow jets mainly directed towards the right-anterior aortic wall, with significantly increased local wall shear stress where the flow jet impinged on the aorta (von Knobelsdorff-Brenkenhoff et al., 2014). Furthermore, aortic blood flow following SAVR and TAVI have been directly compared, with both interventions producing similar asymmetric distributions of wall shear stress, but SAVR triggering more extensive vertical and helical (turbulent) flow patterns (Trauzeddel et al., 2015).

1.7 Conclusions
CMR is a well-established imaging technique that is non-invasive and devoid of ionising radiation, offering incremental value in the assessment of patients with aortic stenosis, both prior to and after valve intervention. In a single imaging session, CMR can provide detailed information on cardiac and aortic anatomy, ventricular volumes and mass, myocardial tissue characterisation and valvular morphology and function, both native and prosthetic. There is a growing body of evidence that CMR can predict clinical outcomes in patients undergoing therapy for severe AS and ongoing clinical trials are likely to underscore the importance of CMR in managing this common and high-risk cardiac condition.
1.8 Aims of the Thesis

The emergence of TAVI into clinical practise over the last decade has signalled a dramatic change in the management of patients with symptomatic severe aortic stenosis. Both US and European Society guidelines advocate its use in patients deemed unsuitable by a dedicated heart team for conventional SAVR (Hamm et al., 2016). Short and mid-term data continue to support the durability, economical viability and survival advantage of this revolutionary intervention in patients, in whom previously the options of balloon valvuloplasty or conservative medical management meant a limited survival. TAVI is favoured not only in those inoperable, but also in those with both high- and intermediate-risk, operable symptomatic severe aortic stenosis (Leon et al., 2016). Indeed, the international focus has centred on comparative investigation of TAVI and the gold standard technique of surgical aortic valve replacement (SAVR), with the objective of improving risk stratification and inform patient selection.

This thesis is centred on the use of CMR to investigate accurately and in detail the impact of native severe aortic stenosis, SAVR and TAVI upon cardiac function. In addition, TAVI prosthesis design and technology is continually being updated and the reduction of paravalvular aortic regurgitation post-TAVI is a principal design brief and outcome measure. The assessment of regurgitation post-TAVI is complex but one that CMR is uniquely suited for, given its versatility and direct flow quantification method.

The aims of this thesis are outlined below:

1) To comprehensively evaluate the difference in impact of SAVR and TAVI upon thoracic aortic stiffness through the measurement of two indices; the local ascending and descending thoracic aortic distensibility, and the regional aortic arch pulse-wave velocity (chapter 3).

2) To accurately quantify and contrast the impact of SAVR and TAVI upon right ventricular volumes and function; and determine whether any particular procedural factors where of significance (chapter 4).

3) To characterise circumferential strain using myocardial tagging CMR prior to and following SAVR and TAVI, and determine whether abnormalities in strain were associated with outcome (chapter 5).

4) To compare, using serial CMR, the quantity of aortic regurgitation, following TAVI with two different designs: the established extensively trialled self-expanding CoreValve (Medtronic, Minneapolis, Minnesota) and the novel mechanically expanded Lotus valve (Boston Scientific,
A correlation between non-invasive (CMR derived) and invasive (during TAVI implantation) measures of regurgitation was also investigated as was the impact of regurgitation and valve design upon LV reverse remodelling at mid-term follow-up (chapter 6).

The fundamental approach to these aims was the CMR imaging of patients with severe aortic stenosis at baseline and at 6 months following SAVR and TAVI. In addition, in Chapter 6, patients were also scanned immediately post-TAVI prior to hospital discharge to facilitate early assessment of TAVI prosthetic function and profile the time-course of any changes.

CMR imaging was based on a comprehensively designed protocol including SSFP cine imaging to permit full LV and RV volume and mass quantification and feature tracking analysis, velocity encoded phase contrast imaging of native and prosthetic aortic valves (TAVI and SAVR; both bioprosthetic and mechanical) for flow analysis and quantification of regurgitation, LGE imaging analysis for presence of fibrosis, CSPAMM for circumferential strain quantification, and measures of aortic stiffness (PWV and AD).

Chapter 2 (Standard Methods) details methods common to all five results chapters. Each results chapter includes a dedicated in depth introduction, specific methods (for techniques specific to that particular body of work), results, discussion and conclusion sections with an appreciation of important limitations where appropriate.
Chapter 2. Standard Methods

2.1 Patient recruitment

Patients with severe symptomatic aortic stenosis referred for TAVI and SAVR were prospectively recruited from cardiology and cardiac surgery outpatient departments (performed by myself and other members of the TAVI research team) between January 2009 and April 2015 at two surgical tertiary centres: the Leeds General Infirmary, Leeds, UK and Glenfield Hospital, Leicester, UK (except for the purpose of chapter 6 where patients were undergoing TAVI and exclusively recruited from the Leeds General Infirmary). Severe aortic stenosis was defined on the basis of echocardiography as a peak aortic velocity of >4m/s, a mean pressure gradient >40mmHg, or an aortic valve area ≤1.0cm² in line with standard published criteria (Baumgartner et al., 2009). Baseline echocardiographic data including peak and mean aortic pressure gradients, aortic valve area, left ventricular ejection fraction and estimated pulmonary artery systolic pressures were recorded, as were baseline clinical and demographic data from which the EuroSCORE II (http://www.euroscore.org/calc.html) and Society of Thoracic Surgeons’ risk score for mortality and morbidity were calculated (http://riskcalc.sts.org/STswebRiskCalc/#/calculate). Decision for aortic valve replacement was made by a dedicated Heart Team comprising interventional and imaging cardiologists and cardiac surgeons in line with current guidance (Vahanian et al., 2012).

Inclusion criteria for entry into the study included patients with severe aortic stenosis, aged over 18 years with the willingness and capacity to provide informed consent. Exclusion criteria were essentially any contraindication to CMR, including non-MR conditional permanent pacemaker, prior cerebral aneurysm clips, intra-ocular metal, claustrophobia, and those pregnant. In the case of patients with impaired renal function (defined as an estimated glomerular filtration rate of <30ml/min/1.73m²), gadolinium based contrast was not administered.

The patient invitation and information sheets can be viewed in the Appendix (sections 9.4 and 9.5 respectively). The study was funded by a British Heart Foundation research project grant (PG/11/126/29321), approved by a national research ethics committee (Appendix 9.1, 9.2 and 9.3) and complied with the Declaration of Helsinki, with all patients providing written informed consent (Appendix section 9.6).

2.2 Transcatheter Aortic Valve Implantation

TAVI was performed under general anaesthesia, or conscious sedation and local anaesthesia with X-ray fluoroscopy and echocardiographic (transoesophageal or transthoracic as appropriate) guidance by two experienced high volume operators. The balloon expandable
Edwards Sapien 3, the self-expanding Medtronic CoreValve, Engager and Evolut-R and the mechanically expanded Boston Scientific Lotus TAVI devices were studied, selected primarily on the basis of anatomical considerations. Multi detector computed tomography or 3D transoesophageal echocardiography were used to derive annulus measurements and thus appropriate device sizing. Wherever possible, the femoral artery route was used as a default approach, but in cases of femoral artery stenosis, calcification or tortuosity other routes were adopted (subclavian, carotid, direct aortic and apical LV).

Balloon aortic valvuloplasty, for pre- and post-dilatation and rapid right ventricular pacing were performed during the implant procedure when deemed appropriate. All patients received intravenous heparin via a standardised regimen to maintain an activated clotting time of 150-250s. Dual antiplatelet therapy (typically aspirin 75mg and clopidogrel 75mg) was prescribed for up to 6 months following TAVI with aspirin monotherapy thereafter, or in the need for full formal anticoagulation (atrial fibrillation, previous venous thromboembolism), warfarin monotherapy was administered.

TAVI procedural details, including invasive aortic valve gradient, pre and post TAVI systolic, diastolic and left ventricular end diastolic pressures, TAVI type and size, procedure time, fluoroscopy screening time and contrast dose were recorded for all patients.

2.3 Surgical Aortic Valve Replacement
SAVR was performed by experienced cardiothoracic surgeons using the standard approach of a midline sternotomy incision. Systemic heparinisation with standard aorto-right atrial cannulation was used to establish cardiopulmonary bypass and a mild systemic hypothermia (30-34°C). Cold blood cardioplegic arrest of the heart and pericardial carbon dioxide was used in all cases. The aorta was cross-clamped and aortotomy performed with the size and type of prosthesis being selected according to annulus size, patient characteristics, surgical and patient preference. Concomitant CABG was performed using a combination of left internal mammary artery (LIMA) and saphenous vein grafting (SVG) to significantly diseased major vessels with the aim of complete revascularisation in all patients, where technically possible. Procedural details including valve type and size, cross-clamp and cardiopulmonary bypass time, length of intensive care stay and need for blood transfusion were collected. Aspirin monotherapy was administered for 3 months post-procedure, except in instances of mechanical prosthesis or atrial fibrillation where warfarin monotherapy was prescribed.
2.4 CMR protocol

2.4.1 Cine imaging

Identical CMR scans were obtained on the same imaging platform at baseline and post procedure (for timings of follow up scans see individual methods chapters) using the same 1.5T scanner (Intera and Ingenia, Philips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). Multi-slice, multi-phase cine imaging was performed using a SSFP pulse sequence in the short axis (repetition time (TR) 3msec, TE 1.7msec, flip angle 60°, SENSE factor 2, 8mm slice thickness, 0mm interslice gap, 30 phases, 192 by 192 matrix, typical field of view 340mm) to cover both ventricles. Cine imaging included standard 4 chamber, 2 chamber and short axis views as well as two left ventricular outflow tract views in sagittal-oblique and coronal views (3-5 slices, 6mm slice thickness, 0mm interslice gap, 30 phases, typical field of view 380mm) to permit planning of aortic valve phase contrast imaging.

2.4.2 Aortic valve phase contrast imaging

Through-plane velocity encoded (VENC) phase contrast imaging was then performed perpendicular to the aortic valve jet at the aortic sinotubular junction (repetition time [TR] 4.3 msec, echo time [TE] 2.6 msec, flip angle 15°, slice thickness 6mm, 40 phases, FOV 340mm typical voxel size 1.2x1.2x8mm³, depending on patient size). Aortic flow data were acquired using a free breathing (for regurgitation) and breath-hold (for forward flow) retrospectively gated technique with a VENC limit typically set at 400-500cm/sec on the baseline scan and 250cm/sec post-procedure (individually adjusted/repeated if there was evidence of aliasing). The region of interest was planned at the sinotubular junction (with care taken not to include aortic valve leaflets) or just above the aortic prosthesis post-replacement, orthogonal to the aortic valve jet. For flow measurements following TAVI, through-plane phase contrast imaging was performed perpendicular to the aorta at the sinotubular junction, or at the upper margin of the stent holding the TAVI prosthesis. This position for imaging has been previously described and validated (Salaun et al., 2015). Similarly, if significant turbulence or aliasing was seen in the velocity mapped images, the acquisition was repeated a few millimetres further from the valve, and/or with a higher VENC. In patients with arrhythmia (e.g. atrial fibrillation), 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.

2.4.3 Measures of aortic stiffness

A sagittal-oblique aortic (‘candy cane’) image was acquired (SSFP pulse sequence; repetition time [TR] 3 msec, echo time [TE] 1.7 msec, flip angle 60°, reduction factor 2, 5 slices, 6mm slice thickness, 0 mm interslice gap) to enable the planning of an axial SSFP slice,
perpendicular to the ascending and descending aorta at the level of the pulmonary artery bifurcation. For aortic distensibility, brachial artery blood pressure was recorded by Dinamap (Critikon, Tampa, USA) immediately prior to high temporal resolution multi-phase SSFP cine imaging (retrospective gating, slice thickness 8mm, acquired spatial resolution 1.07x1.8x8mm, acquired temporal resolution 50 phases, TR 3ms, TE 1.5ms, flip angle 60°, breath-held, which for a heart rate of 60 beats per minute was equivalent to 12 seconds) acquired transverse to the ascending and descending thoracic aorta at the level of the pulmonary artery bifurcation. Aortic pulse wave velocity was assessed using identical geometric planning, in order to acquire ascending and descending thoracic aortic blood flow velocity with retrospectively gated, through-plane, phase-contrast velocity encoded images (single slice, 8mm thick, acquired spatial resolution 2.5x2.67x8mm, TR 4.6ms, TE 2.7ms, flip angle 40°, slice thickness 6mm, acquired temporal resolution 50 phases, typical FOV 350, and VENC 200-500cm/s, breath-held, which for a heart rate of 60 beats per minute was equivalent to 13 seconds).

2.4.4 CMR strain imaging using myocardial tissue tagging
Complementary spatial modulation of magnetization (CSPAMM) imaging was carried out during a single breath hold at end expiration in the short axis orientation, at the apex, mid, and basal LV (multishot echo planar imaging, flip angle sweep applied to the radiofrequency excitation pulses of subsequent cardiac phases, two orthogonal line tags acquired per slice, field of view: 300mm, matrix 128x128, slice thickness 10mm, tag separation 8mm, typically 18 phases, TR 30ms, TE 6ms, flip angle 25°). The “3 of 5 technique” was used to minimize variation in slice positioning between visits and has been demonstrated to be highly reproducible (Swoboda et al., 2014).

2.4.5 Tissue characterisation: late gadolinium enhancement imaging
LGE imaging using an inversion recovery-prepared T1-weighted gradient echo pulse sequence (TE 1.79msec; TR 4.8msec; flip-angle 15°, spatial resolution 1.46x1.46x10mm) was performed with inversion time (TI) individually adjusted according to TI scout (Look-Locker pulse sequence). This was planned to cover the entire left ventricle in short axis (10-12 short axis slices, 10mm thickness, no interslice gap, matrix 240x240, typical field of view 350mm), 10 minutes after 0.2mmol/kg of Gadoteric acid (godotere meglumine, Dotarem, Guerbet, SA, Villepinte) or Gadolinium-DTPA (magnevist, Schering, Germany) administered by hand injection. An identical contrast agent was used at both study time-points. Four chamber, two chamber and left ventricular outflow tract (LVOT) views were also obtained. Cross cuts and switching of phase encoding direction were used where necessary to further clarify presence or absence of LGE.
Figure 2.1 depicts the full CMR protocol and a typical time line of its components.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Protocol Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Survey imaging (single shot)</td>
</tr>
<tr>
<td>3</td>
<td>Black blood T1 (transaxial)</td>
</tr>
<tr>
<td>5</td>
<td>Cine localisers (VLA, SAX, 4 chamber)</td>
</tr>
<tr>
<td>8</td>
<td>LV volume SAX stack</td>
</tr>
<tr>
<td>14</td>
<td>LVOT views (sagittal and coronal)</td>
</tr>
<tr>
<td>17</td>
<td>Aortic valve cines</td>
</tr>
<tr>
<td>20</td>
<td>Aortic valve phase contrast imaging</td>
</tr>
<tr>
<td>24</td>
<td>CSPAMM tagging (SAX’3 of 5)</td>
</tr>
<tr>
<td>30</td>
<td>Sagittal Oblique aorta (‘candy cane) view</td>
</tr>
<tr>
<td>32</td>
<td>Aortic distensibility cine</td>
</tr>
<tr>
<td>37</td>
<td>Look-Locker (SAX)</td>
</tr>
<tr>
<td>38</td>
<td>Late Gadolinium Enhancement (SAX stack, 4 chamber, VLA, LVOT)</td>
</tr>
<tr>
<td>48</td>
<td>Phase contrast acquisition (identical geometry to distensibility)</td>
</tr>
<tr>
<td>50</td>
<td>End</td>
</tr>
</tbody>
</table>

**Figure 2.1 Imaging Protocol**

**2.5 CMR image analysis**

2.5.1 Ventricular volume quantification from SSFP cine images

Analyses were performed either using QMass 7.5, Medis Medical Imaging Systems, Leiden, The Netherlands (chapters 3, 4 and 5) and CVI42, Circle Cardiovascular Imaging, Calgary, Alberta (chapter 6). Standard criteria were employed to delineate ventricular endocardial and epicardial borders at end-diastole and end-systole in short-axis to allow the calculation of
ventricular volumes (using the summation of discs methodology) and mass. Papillary muscles were excluded from the LV cavity and included within the LV mass for the purpose of analysis (Figure 2.2).

Figure 2.2 Ventricular chamber quantification in (A) end-diastole and (B) end-systole

LV mass was calculated using Equation 2-1:

\[ \text{LV mass} = (\text{epicardial volume} - \text{endocardial volume}) \times 1.05 \]

Equation 2-1 Calculation of LV mass

All values were indexed to BSA. Structural LV remodelling was defined by LV mass : end diastolic volume ratio as previously described (Gaasch and Zile, 2011).

2.5.2 Quantification of Valvular function

Through-plane phase contrast images were examined to ensure the quality was sufficient and that the VENC chosen was appropriate. Aortic flow was quantified in the Flow module of CVI42 software with contouring of the aortic lumen in both phase and magnitude images (Figure 2.3) to provide a peak forward flow velocity (m/s), forward flow volume (ml), backward flow volume (ml) and regurgitant fraction (%).
Mitral regurgitant fraction (%) was calculated according to Equation 2-2.

\[
\text{Mitral regurgitation fraction} = \left( \frac{\text{LV stroke volume} - \text{aortic stroke volume}}{\text{LV stroke volume}} \right) \times 100.
\]

**Equation 2-2 Calculation of mitral regurgitation fraction**

2.5.3 Quantification of Late Gadolinium Enhancement

All analyses were performed using CVI\textsuperscript{42}, Circle Cardiovascular Imaging, Calgary, Alberta, Canada by two experienced observers (TAM and LED) blinded to procedural and clinical details. LGE images derived from different geometries (VLA, 4 chamber), cross cut and switching of phase encoding direction were used to assist interpretation. Focal myocardial fibrosis and scarring (secondary to myocardial infarction) were differentiated then reported qualitatively as either present or absent. In only those slices deemed to have LGE present, epicardial and endocardial contours were manually drawn, with care taken to exclude artefact, blood pool, fat and pericardium. The auto-identification tool was then applied and an area of normal remote myocardium defined alongside identification of areas with increased signal intensity. Any hyper intense regions felt to be related to artefact were manually excluded and the full-width half max technique was applied to quantify LGE mass (Flett et al., 2011).
2.6 Reproducibility measurements

For the assessment of inter-observer variability, two independent investigators analysed a random selection of 10 patients both pre- and post- valve replacement. For intra-observer variability a similar dataset from 10 patients was analysed twice by the author six months apart. For reproducibility, an intra-class correlation was used and the results can be seen in Table 2.1.

Table 2.1 Observer variability of measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>INTRA – observer variability</th>
<th>INTER – observer variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDV</td>
<td>0.984</td>
<td>0.989</td>
</tr>
<tr>
<td>LV Mass</td>
<td>0.978</td>
<td>0.985</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.982</td>
<td>0.970</td>
</tr>
<tr>
<td>RV EDV</td>
<td>0.995</td>
<td>0.947</td>
</tr>
<tr>
<td>RV ESV</td>
<td>0.996</td>
<td>0.911</td>
</tr>
<tr>
<td>TAPSE</td>
<td>0.939</td>
<td>0.917</td>
</tr>
<tr>
<td>Peak aortic gradient</td>
<td>1.000</td>
<td>0.963</td>
</tr>
<tr>
<td>Aortic Regurgitant Fraction</td>
<td>0.987</td>
<td>0.986</td>
</tr>
<tr>
<td>LGE quantification (%)</td>
<td>0.995</td>
<td>0.979</td>
</tr>
</tbody>
</table>

2.7 Sample Size and Statistical Analysis

CMR is accurate and reproducible and permits hypothesis testing from a considerably reduced number of patients. For this work, sample sizes were based on published data indicating 20 patients per group permit the detection of a 10ml change in LVEDV or 10g difference in LV mass regression between two treatments (90% power and an alpha error of 0.05) (Bellenger et al., 2000b); 30 per group would be sufficient to detect a clinically meaningful 10% absolute difference in aortic peak forward flow velocity or regurgitant fraction (85% power and an alpha error of 0.05)(Fairbairn et al., 2013b). Continuous variables are presented as mean±SD or number (%). Normality was determined by the Shapiro–Wilk test. For normally distributed data, two-tailed unpaired Student’s t tests were used for comparisons between groups, and paired Students t tests were used for intragroup comparisons. For non-normally distributed data, the Related-Samples Wilcoxon Signed Rank Test and independent samples Mann-Whitney U test were used. Changes over time were assessed for differences between the treatment groups and clinical variables by two-way repeated measures analysis of variance (ANOVA). Predictors of functional change were evaluated by a stepwise linear regression model with baseline measurements entered as covariate factors. All statistical analyses were performed using
PASW software (V.21.0 SPSS, IBM, Chicago, USA); two-sided p<0.05 considered statistically significant.
Chapter 3. Assessment of Aortic Stiffness by CMR following the treatment of Severe Aortic Stenosis by TAVI and SAVR

3.1 Abstract

Background: Aortic stiffness is increasingly used as an independent predictor of adverse cardiovascular outcomes. We sought to compare the impact of transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) upon aortic vascular function using cardiovascular magnetic resonance (CMR) measurements of aortic distensibility and pulse wave velocity (PWV).

Methods and Results: A 1.5T CMR scan was performed pre-operatively and at 6m post-intervention in 72 patients (32 TAVI, 40 SAVR; age 76±8yrs) with high-risk symptomatic severe aortic stenosis. Distensibility of the ascending and descending thoracic aorta and aortic pulse wave velocity were determined at both time points. TAVI and SAVR patients were comparable for gender, blood pressure and left ventricular ejection fraction. The TAVI group were older (81±6.3 vs. 72.8±7.0yrs, p<0.05) with a higher EuroSCORE II (5.7±5.6 vs. 1.5±1.0%, p<0.05).

At 6m, SAVR was associated with a significant decrease in distensibility of the ascending aorta (1.95±1.15 vs. 1.57±0.68x10^{-3}mmHg^{-1}, p=0.044) and of the descending thoracic aorta (3.05±1.12 vs. 2.66±1.00x10^{-3}mmHg^{-1}, p=0.018), with a significant increase in PWV (6.38±4.47 vs. 11.01±5.75ms^{-1}, p=0.001). Following TAVI, there was no change in distensibility of the ascending aorta (1.96±1.51 vs. 1.72±0.78x10^{-3}mmHg^{-1}, p=0.380), descending thoracic aorta (2.69±1.79 vs. 2.21±0.79x10^{-3}mmHg^{-1}, p=0.181) nor in PWV (8.69±6.76 vs. 10.23±7.88ms^{-1}, p=0.301) at 6m.

Conclusions: Treatment of symptomatic severe aortic stenosis by SAVR but not TAVI was associated with an increase in aortic stiffness at 6m. Future work should focus on the prognostic implication of these findings to determine whether improved patient selection and outcomes can be achieved.
3.2 Introduction
Degenerative aortic stenosis can be viewed as part of a continuum that comprises not only valvular dysfunction but also a reduction in aortic compliance (Hachicha et al., 2009) which independently contributes to increased afterload (Briand et al., 2005) and decreased left ventricular function. Increased aortic stiffening is detrimental to arterio-ventricular coupling and coronary perfusion and is an independent predictor of future cardiovascular events and mortality in the general population, essential hypertension, diabetes mellitus, end stage renal failure and in the elderly (Ripley et al., 2015). Measurement of aortic stiffness is therefore increasingly used in clinical practice as a prognostic indicator.

CMR offers a robust, reproducible, non-invasive method of assessing both local and regional properties of the aortic wall (Metafratzi et al., 2002). Two standard indices of aortic stiffness can be expressed; aortic distensibility and pulse wave velocity, and there is a strong inverse linear relationship reported between these two measurements (Dogui et al., 2011, Nelson et al., 2009).

The elastic property of the aorta is in part dependent upon the perfusion of the aortic wall via vasa vasorum flow. We hypothesised, based upon the difference in techniques, that more favourable measures of aortic stiffness would be observed following TAVI rather than SAVR. Ultimately, this may herald prognostic implications and guide future patient selection.

The primary aim of this study was to use CMR to serially compare the effects of TAVI and SAVR on aortic stiffness, before and 6m after treatment for severe symptomatic aortic stenosis.

3.3 Methods specific chapter 3
3.3.1 Study population
A total of 127 patients were prospectively recruited with severe AS after being referred for either TAVI (n=77) or SAVR (n=50) at the University Hospitals of Leeds and Leicester, UK, between July 2008 and December 2013. Severe AS was classified according to the criteria in section 2.1. Decision for TAVI was taken by a multidisciplinary heart team in accordance with international guidance. Older, higher-risk (higher EuroSCORE) SAVR patients were preferentially recruited wherever possible to facilitate comparable baseline demographics.

3.3.2 Transcatheter Aortic Valve Implantation
TAVI was performed under general anaesthesia by high-volume operators with >5 years’ experience. Either an 18F CoreValve Revalving system (CVR, Medtronic, Minneapolis,
Minnesota, USA) or an 18F or 20F Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, USA) were deployed as previously described (Piazza et al., 2008, Meredith et al., 2014).

3.3.3 Surgical Aortic Valve Replacement
SAVR was performed by standard midline sternotomy with cardiopulmonary bypass and mild hypothermia. Biological or mechanical prostheses of varying sizes were used according to surgical preference; concomitant coronary artery bypass grafting (CABG) was performed as indicated. No patient underwent aortic root or ascending aortic reconstruction.

3.3.4 CMR Protocol
For each individual patient, identical baseline pre-operative and 6-month post-operative scans were performed on the same 1.5T MR system (Phillips Intera, Best, The Netherlands or Siemens Avanto Erlangen, Germany). Details of the CMR pulse sequence acquisition protocol are outlined in the Standard Methods chapter (sections 2.4.1, 2.4.2 and 2.4.3).

3.3.5 CMR Image Analysis
Image analysis was performed in line with international guidance (Schulz-Menger et al., 2013), blinded to patient details, using off-line commercially available software (QMass V7.5 and QFlow V7.2, Medis, Leiden, The Netherlands). Aortic valve flow indices were quantified using cross-sectional phase contrast images with contouring of the aortic lumen to derive peak forward flow velocity (m/s), and forward and backward flow volumes (ml), for the calculation of trans-valvular pressure gradient and regurgitant fraction(%).

To derive the aortic distensibility of the ascending and descending thoracic aorta, cross sectional measurements were made by manual planimetry of the endovascular-blood pool interface for each phase to determine the maximal and minimal aortic dimensions (Figure 3.1A). Aortic distensibility (mmHg⁻¹) was calculated using Equation 3-1:

\[
\text{Distensibility} = \frac{(\text{Aortic max lumen area} - \text{Aortic min lumen area})}{(\text{Aortic min lumen area} \times [\text{Systolic BP} – \text{Diastolic BP}])}
\]

**Equation 3-1 Calculation of aortic distensibility**

Aortic PWV (m/s) was calculated by dividing the distance separating two locations and the transit time needed to cover this distance (Oliver and Webb, 2003). Analysis was performed using validated software (PMI v0.4, [https://github.com/plaresmedima/PMI-0.4-Runtime-CMRLeeds](https://github.com/plaresmedima/PMI-0.4-Runtime-CMRLeeds)) based on IDL 6.4 (ITT Visual Information Systems, Boulder, USA) (Huber et al., 2012). The distance between the ascending and descending aorta was measured manually
from the sagittal/oblique cines of the aortic arch (Figure 3.1B). Transit time was calculated using the foot-foot delay method from velocity encoded images of the ascending and descending aorta, manually contoured to derive velocity-time curves (Figure 3.1C) (Ibrahim et al., 2010).

3.4 Results
3.4.1 Study population
Seventy-two patients (32 TAVI, 40 SAVR) with paired pre-operative and 6m post-operative CMR scans were included for analysis. Reasons for non-completion of the CMR protocol were varied and are depicted in Figure 3.2.
Figure 3.2 Patient recruitment pathway

Baseline characteristics of the study population are shown in Table 3.1.
Table 3.1 Patient characteristics and baseline data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAVR (n=40)</th>
<th>TAVI (n=32)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.8 ± 7.0</td>
<td>81 ± 6.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>31 (78)</td>
<td>20 (63)</td>
<td>0.151</td>
</tr>
<tr>
<td>EuroSCORE II (%)</td>
<td>1.53 ± 1.0</td>
<td>5.66 ± 5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>STS Mortality (%)</td>
<td>2.01 ± 0.6</td>
<td>5.68 ± 3.8</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kgm(^{2}))</td>
<td>27.9 ± 6.3</td>
<td>26.6 ± 2.8</td>
<td>0.274</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 ± 23</td>
<td>127 ± 28</td>
<td>0.696</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73 ± 11</td>
<td>65 ± 11</td>
<td>0.003</td>
</tr>
<tr>
<td>Resting Heart Rate (bpm)</td>
<td>64 ± 12</td>
<td>65 ± 11</td>
<td>0.713</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.5 ± 0.6</td>
<td>3 ± 1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>5 (13)</td>
<td>6 (19)</td>
<td>0.560</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>1 (3)</td>
<td>10 (31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>0 (0)</td>
<td>12 (38)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>7 (18)</td>
<td>4 (13)</td>
<td>0.667</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>1 (3)</td>
<td>6 (19)</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>4 (10)</td>
<td>8 (25)</td>
<td>0.125</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>24 (60)</td>
<td>20 (63)</td>
<td>0.977</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>4 (10)</td>
<td>6 (19)</td>
<td>0.358</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>1 (3)</td>
<td>8 (25)</td>
<td>0.006</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m(^{2}))</td>
<td>71.7 ± 13.3</td>
<td>61.4 ± 17.1</td>
<td>0.006</td>
</tr>
<tr>
<td>AVA (cm(^{2}))</td>
<td>0.90 ± 0.5</td>
<td>0.62 ± 0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean PG (mmHg)</td>
<td>43 ± 15.8</td>
<td>51 ± 13.7</td>
<td>0.023</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>52±12</td>
<td>52±13</td>
<td>0.961</td>
</tr>
<tr>
<td>ValvuloArterial Impedance (Z(_{va}))</td>
<td>3.88 ± 0.9</td>
<td>4.06 ± 1.6</td>
<td>0.982</td>
</tr>
<tr>
<td>Median prosthetic replacement size (mm)</td>
<td>23</td>
<td>27</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Sinuses of Valsalva dimension indexed to BSA (mm/m$^2$) 17.9±2.2 18.1±2.1 0.615

Proximal ascending aortic dimension indexed to BSA (mm/m$^2$) 17.4±2.8 16.9±2.8 0.505

Values are mean±SD or n (%). *p value for comparison between procedure types.

For both individual groups, key demographic and haemodynamic parameters of the excluded patients were not statistically different to those included for analysis (Table 3.2), indicating that our study patients were representative of the larger population. For the TAVI group (n=32), 9(28%) were taking ACE inhibitors or ARB, 18(56%) β-blockers, 3(9%) spironolactone, 5(16%) calcium antagonists, 1(3%) α-blockers, 23(72%) statins and 16(50%) diuretics. For the SAVR group (n=40), 5(13%) were taking ACE inhibitors or ARB, 5(13%) β-blockers, 1(3%) calcium antagonists, 13(33%) statins and 1(3%) diuretics. None were using spironolactone or α-blockers.

Table 3.2 Comparison of baseline demographics and aortic stiffness between included and excluded TAVI and SAVR patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SAVR Included n=40</th>
<th>SAVR Excluded n=10</th>
<th>p Value</th>
<th>TAVI included n=32</th>
<th>TAVI excluded n=45</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.8±7.0</td>
<td>70.0±8.4</td>
<td>0.261</td>
<td>81±6.3</td>
<td>80.7±7.2</td>
<td>0.593</td>
</tr>
<tr>
<td>STS score (%)</td>
<td>2.01±0.6</td>
<td>2.06±0.9</td>
<td>0.900</td>
<td>5.68±3.8</td>
<td>5.34±2.8</td>
<td>0.693</td>
</tr>
<tr>
<td>EuroSCORE II (%)</td>
<td>1.53±1.0</td>
<td>1.35±0.56</td>
<td>0.116</td>
<td>5.66±5.6</td>
<td>5.18±3.4</td>
<td>0.691</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131±23</td>
<td>127±23</td>
<td>0.557</td>
<td>127±28</td>
<td>132±19</td>
<td>0.524</td>
</tr>
<tr>
<td>Previous MI (n(%))</td>
<td>5(13)</td>
<td>1(10)</td>
<td>0.611</td>
<td>6(19)</td>
<td>4(15)</td>
<td>0.844</td>
</tr>
<tr>
<td>Previous PCI (n(%))</td>
<td>1(3)</td>
<td>2(20)</td>
<td>0.250</td>
<td>10(31)</td>
<td>8(31)</td>
<td>0.872</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (n(%))</td>
<td>1(3)</td>
<td>1(10)</td>
<td>0.531</td>
<td>6(19)</td>
<td>6(23)</td>
<td>0.581</td>
</tr>
<tr>
<td>Diabetes Mellitus (n(%)</td>
<td>4(10)</td>
<td>4(40)</td>
<td>0.163</td>
<td>8(25)</td>
<td>5(19)</td>
<td>0.721</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>24(60)</td>
<td>8(80)</td>
<td>0.925</td>
<td>20(63)</td>
<td>15(58)</td>
<td>0.998</td>
</tr>
<tr>
<td>COPD, n(%)</td>
<td>4(10)</td>
<td>1(10)</td>
<td>0.801</td>
<td>6(19)</td>
<td>5(19)</td>
<td>0.849</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>1(3)</td>
<td>3(10)</td>
<td>0.121</td>
<td>8(25)</td>
<td>5(19)</td>
<td>0.721</td>
</tr>
<tr>
<td>AVA (cm$^2$)</td>
<td>0.90±0.5</td>
<td>0.67±0.2</td>
<td>0.195</td>
<td>0.62±0.2</td>
<td>0.62±0.2</td>
<td>0.941</td>
</tr>
<tr>
<td>AAD (x10$^3$mmHg$^{-1}$)</td>
<td>1.95±1.15</td>
<td>2.12±1.07</td>
<td>0.648</td>
<td>1.96±1.51</td>
<td>1.55±0.61</td>
<td>0.338</td>
</tr>
</tbody>
</table>
The TAVI group were older with a higher predicted 30d mortality risk. The aortic dimensions between the SAVR and TAVI groups were both equivalent and within published normal reference ranges (Evangelista et al., 2010) in keeping with our exclusion criteria (Table 3.1).

3.4.2 Procedural data
For the TAVI group, 25(78%) patients received a Medtronic CoreValve and 7(22%) a Boston Scientific Lotus valve. The femoral access route was used for 30(94%) and the subclavian artery for the remaining 2(6%) patients. Procedural success was 100% with an average catheterisation time of 159±48min, fluoroscopy time of 25±7min and 146±48ml of contrast administered.

In the surgical group, five patients received a mechanical prosthesis (either Sorin Carbomedics or St Jude’s mechanical) and the remaining 35(88%) a tissue bioprosthesis (Sorin mitroflow, Edwards Perimount Magna, Medtronic Hancock, Hancock II and Mosaic, Vascutek Terumo Aspire). Eleven (28%) received concomitant coronary bypass grafting, of which 6 involved use of the left internal mammary artery. For the group as a whole, the average bypass time was 108±50min and average cross clamp time 81±43min. The average length of stay in intensive care was 3.5±2.8days.

3.4.3 Aortic Valve Haemodynamics and LV reverse remodelling
Results of the baseline and 6m CMR scans are shown in Table 3.3. No significant change in arterial pulse pressure was observed following SAVR (58.8±18.6 vs. 61.4±14.4mmHg, p=0.402) or TAVI (63.5±24.0 vs. 69.7±20.3mmHg, p=0.203). There was no significant change in the number of antihypertensive medications used, neither following SAVR (1.3±0.8 vs. 1.4±0.8, p=0.503) or TAVI (1.2±1.0 vs. 1.3±1.0, p=0.161). Reductions in aortic valve pressure gradient, valvuloarterial impedance, LV mass index and end-diastolic volume index were seen 6m following both SAVR and TAVI (Table 3.3).
Table 3.3 Preoperative baseline and 6 month follow-up measurements: SAVR vs. TAVI

<table>
<thead>
<tr>
<th></th>
<th>SAVR (n=40) Baseline</th>
<th>6 months</th>
<th>TAVI (n=32) Baseline</th>
<th>6 months</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>64±12</td>
<td>65±11</td>
<td>65±11</td>
<td>66±15</td>
<td>0.853</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131±23</td>
<td>133±20</td>
<td>127±28</td>
<td>134±22</td>
<td>0.325</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>58±19</td>
<td>61±14</td>
<td>62±24</td>
<td>70±20</td>
<td>0.506</td>
</tr>
<tr>
<td>Number of Medications††</td>
<td>1.3±0.8</td>
<td>1.4±0.8</td>
<td>1.2±1.0</td>
<td>1.3±1.0</td>
<td>0.760</td>
</tr>
<tr>
<td>Systemic Arterial Compliance†††</td>
<td>0.88±0.3</td>
<td>0.74±0.2*</td>
<td>0.81±0.3</td>
<td>0.71±0.2</td>
<td>0.698</td>
</tr>
<tr>
<td><strong>Aortic Valve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak gradient (mmHg)††††</td>
<td>59±20</td>
<td>32±18***</td>
<td>54±14</td>
<td>25±13***</td>
<td>0.439</td>
</tr>
<tr>
<td>$Z_{va}$</td>
<td>3.9±0.9</td>
<td>3.5±0.8*</td>
<td>4.1±1.6</td>
<td>3.0±1.1**</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>Left Ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass Index (g/m²)</td>
<td>80±25</td>
<td>65±16***</td>
<td>82±22</td>
<td>68±18***</td>
<td>0.687</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>95±25</td>
<td>77±14***</td>
<td>95±25</td>
<td>86±19*</td>
<td>0.060</td>
</tr>
<tr>
<td>EF (%)</td>
<td>52±12</td>
<td>57±8**</td>
<td>52±13</td>
<td>55±11</td>
<td>0.651</td>
</tr>
</tbody>
</table>

†Independent samples t-test to compare degree of change seen following SAVR with that seen following TAVI.

††defined as any of: ACE inhibitor, angiotensin II receptor antagonist, β blocker, spironolactone, doxazosin, hydralazine, amlodipine, felodipine or bendrofluazide. †††Derived as stroke volume index / pulse pressure.

†††††Derived from CMR assessment.

Paired $t$ test to compare baseline and 6 months: *$p<0.05$, **$p<0.01$, ***$p<0.001$.

3.4.4 Aortic Stiffness Indices
At baseline there was no difference between the groups in respect to PWV ($p=0.153$) or distensibility; neither of the ascending ($p=0.838$) or descending thoracic aorta ($p=0.306$). Change in indices of aortic stiffness are depicted in Figure 3.3.
Figure 3.3 Bar charts depicting change in indices of aortic stiffness seen pre- and post-SAVR and TAVI

A: pulse wave velocity, B: ascending aortic distensibility, C: descending aortic distensibility. Column height = mean, Bars = standard error.
At 6m, SAVR was associated with a decrease in distensibility of the ascending aorta (1.95±1.15 vs. 1.57±0.68x10⁻³mmHg⁻¹, p=0.044) and of the descending thoracic aorta (3.05±1.12 vs. 2.66±1.00x10⁻³mmHg⁻¹, p=0.018). There was a concomitant increase in PWV observed at 6m (6.38±4.47 vs. 11.01±5.75ms⁻¹, p=0.001) (Table 3.4). These changes were independent of whether or not bypass grafting occurred at the time of valve replacement.

**Table 3.4 Change in mean measurements pre- and post-SAVR and TAVI**

<table>
<thead>
<tr>
<th></th>
<th>SAVR (n=40)</th>
<th></th>
<th>TAVI (n=32)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>p Value*</td>
<td>Pre</td>
</tr>
<tr>
<td>Ascending AD (x10⁻³mmHg⁻¹)</td>
<td>1.95±1.15</td>
<td>1.57±0.68</td>
<td><strong>0.044</strong></td>
<td>1.96±1.51</td>
</tr>
<tr>
<td>Descending AD (x10⁻³mmHg⁻¹)</td>
<td>3.05±1.12</td>
<td>2.66±1.00</td>
<td><strong>0.018</strong></td>
<td>2.69±1.79</td>
</tr>
<tr>
<td>Aortic Arch PWV (m/s)</td>
<td>6.38±4.47</td>
<td>11.01±5.75</td>
<td><strong>0.001</strong></td>
<td>8.69±6.76</td>
</tr>
<tr>
<td>Change in AA area** (mm²)</td>
<td>99±54</td>
<td>80±42</td>
<td><strong>0.032</strong></td>
<td>85±32</td>
</tr>
<tr>
<td>Change in DA area*** (mm²)</td>
<td>87±26</td>
<td>80±27</td>
<td>0.083</td>
<td>73±28</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>58±19</td>
<td>61±14</td>
<td>0.322</td>
<td>63±24</td>
</tr>
<tr>
<td>Length of aortic arch (mm)</td>
<td>139±18</td>
<td>134±20</td>
<td>0.129</td>
<td>126±21</td>
</tr>
</tbody>
</table>

*paired samples t-test

**defined as maximal–baseline cross-sectional ascending aortic area

***defined as maximal–baseline cross-sectional descending aortic area

There was no significant change observed in either the distensibility of the ascending aorta (1.96±1.51 vs. 1.72±0.78x10⁻³mmHg⁻¹, p=0.380) or of the descending thoracic aorta (2.69±1.79 vs. 2.21±0.79x10⁻³mmHg⁻¹, p=0.181) following TAVI. Similarly, TAVI was not associated with any significant change in PWV at 6m (8.69±6.76 vs. 10.23±7.88ms⁻¹, p=0.301).
3.4.5 Demographic and procedural factors associated with change in aortic stiffness

In linear regression analysis, no baseline characteristic (including age, gender, eGFR, surgical risk score or Zva) or procedural variable (including surgical times, CABG and valve type or size) was found to be associated with any index of increased aortic stiffness after SAVR (Table 3.5).

| Table 3.5 Linear regression analysis for the prediction of increased aortic stiffness observed following SAVR |

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PWV (R p Value)</th>
<th>AA Distensibility (R p Value)</th>
<th>Proximal DA Distensibility (R p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.051 0.767</td>
<td>0.157 0.353</td>
<td>0.229 0.172</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.145 0.392</td>
<td>0.181 0.285</td>
<td>0.103 0.544</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.061 0.721</td>
<td>0.105 0.538</td>
<td>0.026 0.880</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.164 0.331</td>
<td>0.018 0.917</td>
<td>0.221 0.189</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>0.175 0.299</td>
<td>0.013 0.940</td>
<td>0.079 0.642</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>0.111 0.513</td>
<td>0.205 0.223</td>
<td>0.058 0.734</td>
</tr>
<tr>
<td>EuroSCORE II (%)</td>
<td>0.356 0.068</td>
<td>0.361 0.064</td>
<td>0.261 0.188</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.080 0.639</td>
<td>0.037 0.827</td>
<td>0.043 0.801</td>
</tr>
<tr>
<td>Mean PG (mmHg)</td>
<td>0.055 0.747</td>
<td>0.085 0.618</td>
<td>0.052 0.761</td>
</tr>
<tr>
<td>ValvuloArterial Impedance (Zva)</td>
<td>0.137 0.420</td>
<td>0.211 0.211</td>
<td>0.043 0.799</td>
</tr>
<tr>
<td>Indexed LV mass</td>
<td>0.007 0.965</td>
<td>0.055 0.747</td>
<td>0.046 0.785</td>
</tr>
<tr>
<td>LV mass:volume ratio</td>
<td>0.020 0.907</td>
<td>0.024 0.890</td>
<td>0.170 0.314</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.183 0.279</td>
<td>0.286 0.087</td>
<td>0.252 0.132</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>0.131 0.438</td>
<td>0.012 0.943</td>
<td>0.183 0.279</td>
</tr>
<tr>
<td>Cross Clamp time (min)</td>
<td>0.142 0.400</td>
<td>0.040 0.815</td>
<td>0.164 0.332</td>
</tr>
<tr>
<td>Valve size (mm)</td>
<td>0.078 0.645</td>
<td>0.132 0.436</td>
<td>0.203 0.229</td>
</tr>
<tr>
<td>CABG at surgery</td>
<td>0.136 0.422</td>
<td>0.067 0.692</td>
<td>0.078 0.647</td>
</tr>
<tr>
<td>Valve type at surgery</td>
<td>0.164 0.333</td>
<td>0.143 0.400</td>
<td>0.037 0.827</td>
</tr>
</tbody>
</table>
3.5 Discussion

Aortic physiology is central to governing the entire cardiovascular network, serving as a conduit and also regulating coronary perfusion and LV performance. Only a limited number of studies have evaluated aortic vascular function following intervention for severe aortic stenosis (Vavuranakis et al., 2012, Nemes et al., 2007, Nemes et al., 2009, Barbetseas et al., 2006, Melina et al., 2002, Schmidtke et al., 2000). The use of M-mode transthoracic echocardiography to determine proximal aortic distensibility has been the exclusive method of investigation; none have measured local and regional indices simultaneously and none have sought to compare SAVR directly with TAVI.

Using CMR we have been able to demonstrate that treatment of severe aortic stenosis with SAVR, compared to TAVI, is associated with an increase in aortic stiffness at 6 months independent of baseline characteristics. This was consistently defined by non-invasive measurement of both local indices (ascending and descending thoracic aortic distensibility) and a regional index (aortic arch pulse wave velocity).

The elastic properties of the aorta relate to its inherent histological structure, the influence of the autonomic nervous system and the perfusion of the aortic wall via vasa vasorum flow (Vavuranakis et al., 2012). In this regard, the fundamental difference in the techniques of SAVR and TAVI could explain our observations.

SAVR involves aortotomy and traumatises aortic wall integrity with destruction of the vasa vasorum. The removal the periaortic fat (containing the vasa vasorum) from the ascending aorta in animal studies has been shown to worsen aortic distensibility acutely due to ischemic medial necrosis and altered fibre composition (Stefanadis et al., 1995). In a porcine model, histological analysis of avascular aorta following surgical manipulation revealed abnormal straightening of the elastin and collagen fibers of the outer media, resulting in increased aortic stiffness under a wide range of stresses (Angouras et al., 2000).

A previous study of 31 patients (mean age 67.2 years) found a significant reduction in ascending aortic distensibility at seven days following mechanical AVR (from 2.21 to 1.01), with a recovery towards pre-operative levels at six months (1.79) (Barbetseas et al., 2006). The authors suggested that the aetiology was due to “aortic root stunning” implicating surgical trauma to the aortic wall via cannulation, cooling, clamping, incising and then suturing, all of which disrupts the aortic wall continuity. None of this occurs during a conventional TAVI procedure and this may underscore the findings of our study.
Our study may have missed the early period of aortic root stunning as we did not examine aortic stiffness acutely and thus cannot comment on temporal trends post SAVR. However our study does suggest that the significant increase in aortic stiffness persists for at least at six months. A decrease in distensibility of the descending thoracic aorta has not previously been reported. This finding suggests the surgical insult affects the aorta more globally, extending beyond the point of local clamp contact.

Interestingly, we found that bypass time, cross clamp time, valve size, valve type and concomitant coronary bypass grafting were not associated with a decline in any of the parameters of aortic stiffness. This suggests the deterioration in aortic stiffness seen at the 6m time point is insensitive to modifiable surgical technique.

Progressive fragmentation of aortic elastin occurs throughout adulthood and underlies a reduction in the Windkessel effect of the aorta, elevating pulse pressures for a given stroke volume (Cavalcante et al., 2011). A recent CMR study measuring both AD and PWV study in healthy subjects reported that aortic segments stiffen with age, but that after the age of 57 years, the ascending aorta is stiffer than the descending thoracic aorta (Devos et al., 2015). We also observed greater distensibility in the descending thoracic aorta compared to the ascending aorta in both groups at baseline which reflects this physiological process.

Measures of aortic stiffness, and PWV in particular, exhibit a strong dependence upon age (2010) which must be factored into the interpretation of our findings. We have studied two groups with an age difference of approximately 9 years; a reflection of current TAVI implantation criteria. Despite this age discrepancy, both baseline PWV and distensibility were statistically comparable between the two groups, at least at the sample sizes we have studied. The ascending AD of the SAVR group and TAVI group were indeed very similar (1.95 vs. 1.96) yet at 6 months, a statistically significant decline from this baseline is seen to a value of 1.57 in the SAVR group; but not following TAVI (to a mean value of 1.72).

It is noteworthy the deleterious effect seen following SAVR was independent of age when entered as a statistical covariate, challenging its potential use in patient selection pre-operatively. Whilst an ascending AD and PWV of 1.72x10^-3mmHg-1 and 10.23m/s may be acceptable and expected in patients aged 80 (post-TAVI), worse values of 1.57x10^-3mmHg-1 and 11.01m/s may not necessarily be acceptable in patients 9 years younger (post-SAVR), undergoing an intervention for prognostic reasons who inherently have a lower surgical risk score.
We and others have shown that lowering of blood pressure can improve aortic stiffness (Ripley et al., 2015, Asmar et al., 1995, Asmar et al., 1988). However in this study, blood pressure and pharmacotherapy were unchanged pre- and post-procedure, suggesting that this was unlikely to account for the difference in impact upon aortic stiffness between TAVI and SAVR. The normal systemic arterial compliance in both groups indicates that baseline haemodynamics were governed predominantly by aortic valve disease without any associated aortic or LV pathology (Briand et al., 2005). Following intervention, SAVR was associated with a limited decrease in Zva as opposed to TAVI. Given a comparable and important reduction in aortic valve gradient (valvular load), the dampened Zva response to SAVR likely reflects an increase in arterial load reflecting a mechanical deterioration in aortic function.

The effect of TAVI upon proximal aortic distensibility has been assessed once previously in 30 patients (mean age 79.9 years) using echocardiography 7 days post-procedure (Vavuranakis et al., 2012). No significant change was observed with an AD of 1.89 pre and 2.05 post TAVI. Our study supports these findings and additionally demonstrates preservation of local and regional aortic stiffness at 6 months post-TAVI. Our study indicates the absence of deterioration in aortic stiffness out to 6 months post-TAVI may favour its usage over SAVR in younger patient populations.

The motivation for this study was to investigate whether TAVI or SAVR is more favourable upon aortic stiffness and thus potentially prognosis. It might be expected that our findings would translate into an increased incidence of adverse cardiovascular events in the surgical population. From a meta-analysis of 17 longitudinal studies comprising 15,877 subjects, an increase in aortic PWV by 1m/s corresponded to an age-, sex-, and risk factor-adjusted risk increase of 15% in all-cause mortality (Vlachopoulos et al., 2010). A dramatic increase in PWV was seen following SAVR in our study although our follow-up data of the surgical group extends to an average of 2.8 years with 95% (n=38) of subjects surviving, such that the numbers are insufficient to make any direct inference.

In the US CoreValve High Risk Study, a higher survival rate at one year in patients undergoing TAVI compared directly with SAVR was likely due to more rapid recovery coupled with relatively lower rates of stroke (Adams et al., 2014). Our findings are noteworthy in this respect as aortic stiffness may be a contributory factor to this observation. Indeed, in a study of 310 patients aged 50 years or more, lower aortic distensibility was shown to be an independent predictor of all-cause mortality in patients presenting with first-ever acute ischemic stroke (Biteker et al., 2015). Larger studies with longer follow-up post AVR are required to determine the precise predictive power of aortic stiffness with respect to mortality and morbidity in this setting.
3.5.1 Study Limitations

The main limitation is the attrition of patients who were unable to complete the CMR protocol at 6 months. This was predominantly in the TAVI population who are a very challenging group to study due to age, frailty and comorbidity. Mortality and pacemaker rates were high, but consistent with large international registries. A small number of TAVI patients declined follow up because of deteriorating health and transfer into long-term nursing care. This is one of the largest studies of its kind and patients not studied at 6m were not statistically different when baseline demographics are considered to those that were, as indicated in Table 3.2. Nonetheless, the potential for bias cannot be excluded as the sickest patients who withdrew may have had higher post-procedural arterial stiffness and worst outcomes. The observed difference between the two treatments may also thus be confounded by the repeatability of the scans as in absolute terms far fewer SAVR patients were lost than for TAVI. Furthermore, the sample size was small, raising the possibility of type 1 and type 2 errors influencing our comparison of means. It is possible that our TAVI population, with an average age of 80 years, may have reached near maximal aortic stiffness. Thus TAVI itself may be deleterious or even beneficial to aortic stiffness, but in our particular population we have not been able to elucidate this.

The difference in baseline demographics between the groups was unavoidable due to current TAVI implantation criteria. However, our study population can be considered a real life reflection, at least of UK national practise (Moat et al., 2011). Finally, this study has not assessed patients undergoing isolated on-pump coronary bypass surgery or direct aortic TAVI.

3.6 Conclusion

In this two centre comparative study using CMR-derived measurements, treatment of symptomatic severe aortic stenosis by SAVR but not TAVI was associated with an increase in aortic stiffness from baseline to 6m. Given aortic stiffness is a marker of adverse cardiovascular events, future work should focus on the potential prognostic benefit of TAVI over SAVR, particularly in younger age-matched populations, as TAVI implantation criteria evolve.
Chapter 4. Right ventricular function following SAVR and TAVI

4.1 Abstract

Background: Right ventricular (RV) function is prognostically important in a variety of cardiovascular conditions. The response of the RV following treatment of aortic stenosis is poorly defined, reflecting the challenge of accurate RV assessment. Cardiovascular magnetic resonance (CMR) is the established reference for imaging of RV volumes, mass and function. We sought to define the impact of transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) upon RV function in patients treated for severe aortic stenosis using CMR.

Methods and Results: A 1.5T CMR scan was performed pre-operatively and 6 months post intervention in 112 patients (56 TAVI, 56 SAVR; 76±8 years) with high-risk severe aortic stenosis at two tertiary cardiac centres. TAVI and SAVR patients were comparable for gender and valvuloarterial impedance, but the TAVI group were older (80.4±6.7 vs. 72.8±7.2 years, p<0.05) with a higher EuroSCORE II (5.8±5.1 vs. 1.6±0.9%, p<0.05). At 6 months, SAVR was associated with a significant increase in RV end systolic volume (33±10 vs. 37±10ml/m², p=0.008), and decrease in RV ejection fraction (58±8 vs. 53±8%, p=0.005) and tricuspid annular plane systolic excursion (22±5 vs. 14±3mm, p<0.001). Longer surgical cross-clamp time was the only predictor of RV end systolic dilatation at 6 months. Post TAVI, there was no observed change in RV volumes or function.

Conclusions: SAVR was associated with RV dysfunction in patients with normal baseline function; attempts to minimise operative cross-clamp time may reduce adverse remodelling seen at 6 months. TAVI had no significant impact upon RV volumes or function.
4.2 Introduction

SAVR was developed in the 1960s and remains first-line therapy for symptomatic patients with severe aortic valve stenosis. TAVI has emerged as a clinical and cost-effective treatment for patients deemed inoperable or with too high predicted postoperative mortality (Fairbairn et al., 2013a). Reverse remodelling of the left ventricle observed following both TAVI and SAVR has been well documented (Fairbairn et al., 2013b, Clavel et al., 2010). However, much less is understood about the response of the right ventricle (RV) in these settings.

RV dysfunction is thought to occur following cardiac surgery for both valvular (Carr-White et al., 1999) and coronary disease (Pegg et al., 2008) and is an independent predictor of late survival and adverse clinical outcomes (Pinzani et al., 1993). The precise mechanism of this dysfunction remains to be elucidated but it is thought incising of the pericardium (and resultant impact upon ventricular coupling), RV contusion, ischaemia and impairment from cytokine release, and right atrial cannulation and subsequent use of an extracorporeal bypass circulation are integral to the pathophysiology. Indeed, a number of theories have been proposed based on conflicting evidence. The EuroSCORE II and the STS models for calculating operative mortality of cardiac surgery do not incorporate preoperative RV dysfunction despite its association with a high mortality (Kempny et al., 2012). This in part reflects the challenging nature of reliably evaluating RV performance (Wenaweser and O'Sullivan, 2012) with its asymmetric and variable 3D geometry, often compounded post-operatively by RV free wall adhesions.

CMR is the established reference modality for imaging of both left and right ventricular volumes and function. CMR can image in any plane, has excellent blood-tissue contrast, can detect subtle wall motion abnormalities and has good reproducibility (Grothues et al., 2004). Furthermore, CMR can be used to quantify tricuspid annular plane systolic excursion (TAPSE). This offers invaluable insight into RV performance, which by the nature of its fibre orientation contracts predominantly longitudinally. This approach is thus an important tool and can identify abnormalities even when overall ejection fraction is normal. Given excellent atrial endocardial border definition, CMR has also been used to study atrial volume and function as a reflection of the duration and severity of diastolic dysfunction (Gulati et al., 2013).

Studies directly comparing the impact of SAVR with TAVI upon RV function are limited (Kempny et al., 2012, Forsberg et al., 2011, Zhao et al., 2011) and have depended upon 2D transthoracic echocardiographic (TTE) parameters with relatively short follow-up. The primary aim of this study was to use CMR to compare the effect of TAVI and SAVR on RV performance at 6 months. We hypothesised that SAVR, but not TAVI (which obviates the need of cardiopulmonary bypass and pericardiotomy), would be associated with decline in RV function.
Furthermore, we sought to elucidate potential mechanisms, by defining the contribution of procedural factors and CMR derived parameters to any observed change in RV performance.

4.2 Methods specific to chapter 4

4.2.1 Study population
This study prospectively recruited 167 patients with severe AS (TTE valve area \( \leq 1.0 \text{cm}^2 \) or peak velocity \( > 4 \text{m/s} \)) who were referred for either TAVI (n=101) or SAVR (n=66) at the University Hospitals of Leeds and Leicester, UK, between July 2008 and June 2014. Contemporary TAVI implantation criteria precluded a randomised, Higher-risk (higher EuroSCORE) SAVR patients were recruited in preference to ensure baseline demographics were more comparable to the TAVI group.

4.2.2 Transcatheter Aortic Valve Implantation
TAVI was performed under general anaesthesia. Either an 18F CoreValve Revalving system (CVR, Medtronic, Minneapolis, Minnesota, USA) or an 18F or 20F Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, MA, USA) were deployed as previously described (Piazza et al., 2008, Meredith et al., 2014).

4.2.3 Surgical Aortic Valve Replacement
SAVR was performed by standard midline sternotomy with cardiopulmonary bypass and mild hypothermia. Biological or mechanical prostheses of varying sizes were used according to surgical preference; CABG was performed as indicated.

4.2.4 CMR Protocol
For each individual patient, identical baseline preoperative and 6 month postoperative scans were performed on the same 1.5T MRI vendor platform (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). Both sites used the identical CMR protocol as previously described (Fairbairn et al., 2013b). Details of the CMR pulse sequence acquisition protocol are outlined in the Standard Methods chapter (sections 2.4.1, 2.4.2 and 2.4.5).

4.2.5 CMR Image Analysis
Quantification of LV and RV volumes and mass was performed blinded off-line, as detailed in section 2.5. Reproducibility was assessed using measurements of intra- and inter-observer variability and is detailed in section Table 2.1 of section 2.2.6. For patients in normal sinus rhythm, the atrial emptying fraction for both the left and right atrium was measured from a 4 chamber SSFP cine image, using Equation 4-1.
Emptying Fraction = (maximum atrial area – minimum atrial area) * 100 / maximum atrial area

Equation 4-1 Calculation of atrial emptying fraction

LV LGE images were analysed as detailed in the methods. For the purposes of Chapter 4, the RV was also assessed qualitatively for the presence or absence of fibrosis from short-axis and 4-chamber delayed enhancement images.

The tricuspid annular plane systolic excursion (TAPSE) was measured as the maximum apical displacement of the lateral tricuspid valve annulus. In the 4 chamber SSFP cine image, atrioventricular motion was measured at the lateral junction points between right atrium and right ventricle at end systole and end diastole. The perpendicular distance between these two points was measured (Figures 4.1A and B).

Figure 4.1 Method for calculation of tricuspid annulus systolic plane excursion

4.2.6 Statistical Analysis
Based on published data, 45 patients per group were required to detect a 7ml change in RVEDV or 2% difference in EF between the two treatments (80% power and an α error of 0.05) (Grothues et al., 2004). Continuous variables are presented as mean±SD. Frequencies are reported as number (%). Normality was determined by the Shapiro–Wilk test. The Student t-test and Wilcoxon signed rank test were used for continuous variables. Changes over time were assessed for differences between the treatment groups and clinical variables by two-way repeated measures ANOVA. Predictors of functional change were calculated by a stepwise multiple linear regression model with baseline measurements entered as covariates. Variables with a univariate p<0.05 were deemed significant.
4.3 Results

4.3.1 Patient population

A total of 112 patients (56 TAVI and 56 SAVR) completed both preoperative and 6 month postoperative scans. Of these, 100 were from Leeds and 12 from Leicester. Reasons for non-completion of the CMR protocol were varied (Figure 4.2).

![Study profile diagram]

**Figure 4.2 Study profile**

Baseline characteristics of the final study population are reported in Table 4.1. For the TAVI group (n=56), 19(34%) were taking ACE inhibitors or ARB, 27(48%) β-blockers, 4(7%) spironolactone, 12(21%) calcium antagonists, 1(2%) α-blockers, 35(63%) statins and 28(50%) diuretics. For the SAVR group (n=56), 13(23%) were taking ACE inhibitors or ARB, 14(25%) β-blockers, 7(13%) calcium antagonists, 31(55%) statins and 8(14%) diuretics. None were using α-blockers and only 1(2%) spironolactone.
Table 4.1 Patient characteristics and baseline echocardiographic data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAVR (n=56)</th>
<th>TAVI (n=56)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.8 ± 7.2</td>
<td>80.4 ± 6.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>38 (72%)</td>
<td>32 (57%)</td>
<td>0.12</td>
</tr>
<tr>
<td>EuroSCORE II (%)</td>
<td>1.51 ± 0.91</td>
<td>5.84 ± 5.10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>STS Mortality (%)</td>
<td>2.13 ± 0.73</td>
<td>5.54 ± 3.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kgm⁻²)</td>
<td>27.6 ± 4.71</td>
<td>27.6 ± 3.81</td>
<td>0.98</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>7 (13)</td>
<td>11 (20)</td>
<td>0.31</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>2 (4)</td>
<td>14 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>0 (0)</td>
<td>16 (29)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>8 (14)</td>
<td>10 (18)</td>
<td>0.61</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>2 (4)</td>
<td>13 (23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>11 (21)</td>
<td>11 (20)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>32 (60)</td>
<td>35 (63)</td>
<td>0.82</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>4 (8)</td>
<td>13 (23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>4 (8)</td>
<td>14 (25)</td>
<td>0.018</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>72.7 ± 13.5</td>
<td>63.7 ± 18.9</td>
<td>0.01</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.82 ± 0.4</td>
<td>0.60 ± 0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean aortic valve PG (mmHg)</td>
<td>46 ± 13</td>
<td>52 ± 18</td>
<td>0.07</td>
</tr>
<tr>
<td>Pulmonary Hypertension**, n (%)</td>
<td>8 (14)</td>
<td>16 (29)</td>
<td>0.05</td>
</tr>
<tr>
<td>Moderate (31-55 mmHg), n (%)</td>
<td>6 (11)</td>
<td>10 (18)</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;55 mmHg), n (%)</td>
<td>2 (3)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>ValvuloArterial Impedance (Zva)</td>
<td>3.86 ± 1.0</td>
<td>3.76 ± 1.4</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**Pulmonary hypertension defined as estimated pulmonary artery systolic pressure by transthoracic echocardiography to be >35mmHg

Values are mean±SD or n (%). *p Value for comparison between TAVI and SAVR groups.

The revascularisation status of the study patients is detailed in Table 4.2.
Table 4.2 Revascularisation status of study patients

<table>
<thead>
<tr>
<th></th>
<th>SAVR (n=56)</th>
<th>TAVI (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No coronary disease</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>LIMA to LAD</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>SVG to LAD</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>SVG to Cx</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>SVG to RCA</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>LMS</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>LAD</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cx</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>RCA</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>SVG</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>SAVR Procedural CABG:</strong></td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>LIMA to LAD</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>SVG to LAD</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>SVG to Cx</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>SVG to RCA</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td><strong>TAVI Procedural PCI</strong></td>
<td>-</td>
<td>1 (Cx)</td>
</tr>
<tr>
<td>RWMA at baseline</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Anterior</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Septum</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Inferior</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Lateral</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

TAVI patients were older, with a higher STS score and greater frequency of coronary intervention. There was no difference in baseline pulmonary artery systolic pressure, as estimated by echocardiography, between the two intervention groups (p=0.159).
4.3.2 Procedural data
For the TAVI group, 46(82%) patients received a Medtronic CoreValve and 10(18%) a Boston Scientific Lotus valve. The femoral artery was the route of access for 51(91%) patients. Three TAVIs were performed via the subclavian artery, one via the carotid artery and one via a direct aortic approach. Procedural success was 100% with an average catheterisation time of $162\pm53$min, fluoroscopy time $25\pm7$min and $147\pm50$mls of contrast agent. One patient had concomitant PCI at the time of TAVI.

For the surgical group, there was heterogeneity in respect of surgical intervention received; the prosthesis size and type being selected according to annulus size, patient characteristics, surgical and patient preference. Seven patients received a mechanical prosthesis and the remaining 49(88%) a tissue bioprosthesis. Sixteen (29%) received concomitant CABG, of which 9 involved use of the left internal mammary artery. None of the surgical patients received a concomitant tricuspid or mitral valve annuloplasty ring and none underwent surgical closure of the pericardium. For the group as a whole, the average bypass time was $104\pm47$min and cross clamp time $76\pm40$min. The average length of stay in intensive care was $3.1\pm2.5$ days.

4.3.3 Haemodynamics, valvular function and LV reverse remodelling

Baseline and follow-up CMR scan results are shown in Table 4.3.
Table 4.3 Preoperative baseline measurements and postoperative changes in the two procedural groups

<table>
<thead>
<tr>
<th></th>
<th>SAVR Baseline</th>
<th>SAVR 6 months</th>
<th>TAVI Baseline</th>
<th>TAVI 6 months</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>64±11</td>
<td>65±12</td>
<td>66±11</td>
<td>67±14</td>
<td>0.950</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131±22</td>
<td>132±20</td>
<td>127±27</td>
<td>134±25</td>
<td>0.316</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73±10</td>
<td>71±11</td>
<td>64±10</td>
<td>65±10</td>
<td>0.257</td>
</tr>
<tr>
<td><strong>Valves</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV peak PG (mmHg)††</td>
<td>56±19</td>
<td>29±13***</td>
<td>53±15</td>
<td>23±11***</td>
<td>0.485</td>
</tr>
<tr>
<td>AR fraction (%)</td>
<td>19±17</td>
<td>10±10**</td>
<td>17±12</td>
<td>8±7***</td>
<td>0.932</td>
</tr>
<tr>
<td>MR fraction (%)</td>
<td>13±14</td>
<td>6±9**</td>
<td>26±17</td>
<td>16±19**</td>
<td>0.445</td>
</tr>
<tr>
<td><strong>Left Ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>90±26</td>
<td>74±13***</td>
<td>96±23</td>
<td>87±20**</td>
<td>0.09</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>43±22</td>
<td>31±9***</td>
<td>48±24</td>
<td>42±17**</td>
<td>0.06</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54±11</td>
<td>58±8**</td>
<td>52±13</td>
<td>53±11</td>
<td>0.098</td>
</tr>
<tr>
<td>Mass Index (g/m²)</td>
<td>77±24</td>
<td>61±16***</td>
<td>80±20</td>
<td>67±18***</td>
<td>0.694</td>
</tr>
<tr>
<td>LVM/LVEDV (g/ml)</td>
<td>0.88±0.2</td>
<td>0.85±0.2</td>
<td>0.86±0.2</td>
<td>0.79±0.2**</td>
<td>0.224</td>
</tr>
<tr>
<td><strong>Right Ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>78±17</td>
<td>78±16</td>
<td>80±18</td>
<td>77±19</td>
<td>0.334</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>33±10</td>
<td>37±10**</td>
<td>40±15</td>
<td>38±14</td>
<td>0.005</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>58±8</td>
<td>53±9**</td>
<td>52±10</td>
<td>52±10</td>
<td>0.013</td>
</tr>
<tr>
<td>Mass Index (g/m²)</td>
<td>15±4</td>
<td>15±4</td>
<td>15±5</td>
<td>13±4***</td>
<td>0.259</td>
</tr>
<tr>
<td>RVM/RVEDV (g/ml)</td>
<td>0.21±0.07</td>
<td>0.20±0.07</td>
<td>0.20±0.08</td>
<td>0.18±0.06**</td>
<td>0.499</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>22±5</td>
<td>14±3***</td>
<td>19±6</td>
<td>19±7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Paired t test vs baseline: *p<0.05, **p<0.01, ***p<0.001. † Independent samples t-test to compare degree of change seen following SAVR with that seen following TAVI. †† Derived from MRI assessment.

Comparable degrees of reduction in aortic valve gradient and LV reverse remodelling were seen following TAVI and SAVR.
A significant decline in the RA emptying fraction was seen following SAVR (baseline 34.7±8.7% vs. 6m 25.5±9.7%, p<0.001) and increase following TAVI (baseline 31.6±10.8% vs. 6m 35.7±12%, p=0.009). No change in LA emptying fraction was seen following SAVR (baseline 48.5±12.8% vs. 6m 48.7±9.1%, p=0.945) but a significant improvement occurred following TAVI (baseline 36.9±12.6% vs. 6m 43.4±10.4%, p=0.011).

4.3.4 Impact of intervention upon Right Ventricular size and function
No difference existed between the groups’ preoperative indexed measurements of right ventricular EDV (p=0.547) or mass (p=0.462). Although both groups had preserved RV systolic function, the baseline RV ejection fraction (p=0.001) and TAPSE (p=0.026) were significantly higher in the SAVR group. SAVR, but not TAVI, was associated with a statistically significant decrease in RV ejection fraction with a concomitant increase in indexed RVESV at 6 months. Similarly post-operative SAVR TAPSE values were significantly lower than the TAVI group (p<0.001). The effect of intervention upon RV mass at 6 months was comparable between the two groups (p=0.259).

4.3.5 Late Gadolinium Enhancement
LGE imaging was performed in all but three TAVI patients, in whom renal impairment was prohibitive. For the TAVI group, 26(49%) had mid-wall/patchy LV fibrosis and 8(15%) prior myocardial infarction prior to intervention. Only 3(6%) patients had RV hyper-enhancement at baseline with no new cases seen at 6 months. For the SAVR group, 18(32%) had midwall/patchy LV fibrosis and 7(13%) had evidence of previous myocardial infarction. Only two SAVR patients had RV fibrosis at baseline and 4 (7%) had new hyper-enhancement at 6 months. No change in total quantity of scar (% LV myocardium) was seen following SAVR (2.4 vs 2.3%, p=0.759) or TAVI (3.1 vs 3.6%, p=0.795). In the subgroup of SAVR patients without baseline LV scar (n=31(55%)), no significant change was seen in RVEF post-operatively (56.9±7.8% vs. 53.0±8.8%, p=0.071).

4.3.6 Demographic and procedural risk factors associated with RV functional decline
Table 4.4 shows the results of univariate regression analyses of clinical and CMR variables associated with change in RV indices. Surgical cross clamp time statistically was the only factor significantly associated with an increase in RVESV index in the SAVR group at follow up.
### Table 4.4 Univariate regression analysis of clinical and CMR variables for the identification of factors associated with change in RV volume / function indices

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B Coefficient±SE</td>
</tr>
<tr>
<td>RVESVI (ml/m²)</td>
<td></td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>-3.86±2.87</td>
</tr>
<tr>
<td>Bypass time</td>
<td>0.05±0.03</td>
</tr>
<tr>
<td>Cross Clamp time</td>
<td>0.07±0.03</td>
</tr>
<tr>
<td>Mechanical SAVR</td>
<td>5.93±3.63</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>-3.31±3.28</td>
</tr>
<tr>
<td>COPD</td>
<td>2.80±4.73</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td></td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>5.83±3.39</td>
</tr>
<tr>
<td>Bypass time</td>
<td>-0.03±0.03</td>
</tr>
<tr>
<td>Cross Clamp time</td>
<td>-0.05±0.04</td>
</tr>
<tr>
<td>Mechanical SAVR</td>
<td>-5.08 ± 4.36</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>-4.52±3.55</td>
</tr>
<tr>
<td>COPD</td>
<td>-4.08±5.75</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td></td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>0.61±1.74</td>
</tr>
<tr>
<td>Bypass time</td>
<td>0.01±0.02</td>
</tr>
<tr>
<td>Cross Clamp time</td>
<td>0.01±0.02</td>
</tr>
<tr>
<td>Mechanical SAVR</td>
<td>-3.28±2.25</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>0.23±2.37</td>
</tr>
<tr>
<td>COPD</td>
<td>2.20±2.81</td>
</tr>
</tbody>
</table>

Each parameter had a separate regression analysis performed.

#### 4.3.7 Association between RV indices and outcome

Over a maximum 6.3y follow up (median 2.8yrs); there were 19 deaths (all-cause mortality) out of the 112 patients that completed 6 month follow-up imaging. Of the 56 TAVI patients, 18 (32%) died compared to only 1 (1.7%) from the SAVR group (p=0.001). For the TAVI group, there was a significant association between RV mass index at 6 months and all-cause mortality (B 0.306±0.104, p=0.003). This is presumably a reflection of worse outcome in those with right-sided pressure overload from more significant underlying pulmonary disease, despite having received TAVI and restoration of aortic valve haemodynamics.
4.4 Discussion

This prospective two centre study of the right ventricle in aortic stenosis has shown that SAVR resulted in deterioration in RV systolic volumes and function, associated with longer surgical cross-clamp times. In contrast, RV volumes and systolic function were preserved following TAVI.

The prognostic importance of the right ventricle and its contribution to exercise capacity in a number of cardiac conditions is well recognised (Tamborini et al., 2009). Recently it has been demonstrated that RV dysfunction is independently associated with reduced late survival after left heart valve surgery (Kammerlander et al., 2014). There have been inconsistent findings from studies assessing RV function post-TAVI, in part due to the variety of echocardiographic definitions for systolic function being used (Forsberg et al., 2011, Zhao et al., 2011, Quick et al., 2013). This is in contrast to patients receiving SAVR where an early decline in RV ejection fraction appears ubiquitous (Kempny et al., 2012).

TAPSE has been the principal measurement studied in this context. However, TAPSE assessment maybe insensitive to global RV performance and is confounded by paradoxical interventricular septal motion, and particularly following SAVR, thoracic wall pericardial adhesions. Furthermore, TAPSE is an insensitive marker of RVEF unless it falls below 35% (Nijveldt et al., 2008). Even 3D echo can systematically underestimate RV volumes (Crean et al., 2011). CMR is considered the reference investigation for RV morphological and functional assessments. It is reproducible and permits unrestricted imaging of the RV that is variable in configuration and difficult to define geometrically using ultrasound.

We have demonstrated using CMR that there is no change in RV volumes or ejection fraction at 6 months following TAVI. SAVR on the other hand is associated with a significant increase in RV end systolic volume, preserved end diastolic volume and overall reduction in ejection fraction. Consistent with this observation was a significant reduction in TAPSE.

CMR has previously been used to assess RV function in a comparison between off-pump and on-pump techniques for CABG (Pegg et al., 2008). CABG was associated with a significant reduction in RV function 6 days post-operatively which normalised by 6 months. This was independent of surgical technique and thus not compounded by the use of a cross-clamp or cardiopulmonary bypass. The early decline was due to a decrease in the RV end diastolic volume, with the indexed RV end systolic volume remaining unchanged. Our surgical group was on average ten years older than the previously studied CABG cohort with a larger baseline RVESVi. Furthermore, there was no change in indexed LV volumes or mass seen in the CABG studies (Pegg et al., 2008). This is very different to the reverse remodelling seen post-SAVR.
and together suggests our SAVR cohort and the CABG group are not directly comparable.

Our study has uniquely combined CMR volumetric RV analysis with the measurement of TAPSE as part of a comprehensive assessment of systolic function. TAPSE measurement disregards RV dimensions and is less sensitive to subtle RV changes (Nijveldt et al., 2008). This is an important limitation to relying on TAPSE alone to assess treatment response. Our observed combined reduction in both TAPSE and volumetric ejection fraction following SAVR, and not TAVI, implies SAVR confers a genuine functional decline in RV systolic function, and not merely a geometric change post-operatively, such as that described following mitral valve surgery (Tamborini et al., 2009).

Contrary to our findings, a recent study using CMR reported a significant acute decline (mean 4.7±4 days) in RV function following TAVI, possibly mediated through paravalvular aortic regurgitation, whereas no change in RV function was observed following bioprosthetic SAVR (Crouch et al., 2015a). The different timings of the post-procedure CMR scan may account for this observed difference, as in our study repeat CMR was performed at 6 months so that we could study the effect of reverse remodelling on both ventricles. The preservation of RV systolic function in this study early following SAVR is of interest given their surgical operative times were notably shorter than ours, which supports our observation that cardiopulmonary bypass time may be an important factor that influences post-operative RV function. However their study does differ from others, albeit based on echocardiography, that have reported early preservation of RV function following TAVI (Zhao et al., 2011, Puentes et al., 2012, Quick et al., 2013, Ayhan et al., 2014, Keyl et al., 2015) and early deterioration following SAVR (Quick et al., 2013, Keyl et al., 2015, Forsberg et al., 2011, Okada et al., 2014).

Our findings allow us to consider further the pathophysiology of RV deterioration observed following SAVR which remains poorly understood. In our study, LA emptying fraction did not change, mitral regurgitation decreased and LV ejection fraction improved 6 months following SAVR. These findings strongly suggest the pathophysiology of RV systolic decline post SAVR is independent of left heart function.

Our study indicates the increase in RVESV following SAVR is statistically associated with longer aortic cross clamp times at surgery. This is a new, previously undescribed observation. Prolonged cardiopulmonary bypass time is associated with increased mortality and morbidity (Salis et al., 2008). Longer cross-clamp times are associated with a greater risk of myocardial
ischaemia (Liakopoulos et al., 2010) and raised biomarkers of myocardial damage (Chalmers et al., 2014).

Tissue characterisation is a pivotal and unique strength of CMR. However, the thin RV wall, susceptibility to artefact and close association with pericardial fat are all limitations to LGE assessment. Nonetheless, we detected new infarction in only 7% of patients. This is, to our knowledge, the first study to utilise LGE in the assessment of RV response to surgery. Our findings suggest the decline in RV function we observed following SAVR is not fully explicable by suboptimal RV protection during cardiopulmonary bypass. The lack of association with bypass grafting at the time of surgery is also consistent with a process unrelated to epicardial coronary disease.

It is noteworthy that RV dysfunction post operatively is an adverse prognostic marker (Pinzani et al., 1993) and in a small study, patients without LV LGE had no 30-day MACCE events and no deaths up to 2 years following SAVR (Quarto et al., 2012). In our patients without baseline hyperenhancement, SAVR was not associated with a change in RV ejection fraction at 6 months. Further work is needed to investigate the potential role CMR in risk stratifying patients that are potentially most susceptible to RV deterioration following aortic valve surgery.

Incision of the pericardium has been suggested as the principal factor responsible for RV deterioration post-cardiac surgery (Unsworth et al., 2013). A significant decline in RV systolic tissue Doppler velocity occurs within minutes and is sustained, possibly through alterations in pericardial constraint and subsequently RV geometry (Unsworth et al., 2014). Our findings of RV preservation following TAVI which obviates any pericardial insult, supports this hypothesis. Alternatively, a reduction in myocardial strain of the right atrium may confer a reduction in RV inlet long-axis systolic function post-SAVR (Zhao et al., 2011). In experimental canine models, selective RA ischemic injury increases RV free wall dyskinesia (Goldstein et al., 1991). The significant decline in RA emptying fraction following SAVR, and not TAVI, is likely a sequela to traumatic surgical venous cannulation and may contribute to the RV systolic decline observed at 6 months.

Previous studies demonstrating an early decline in RV function following cardiac surgery have implicated an increase in pulmonary vascular resistance (Pegg et al., 2008). It is conceivable that such an increase in afterload could mediate RV dysfunction through end systolic cavity dilatation. The use of mechanical ventilation, anaesthesia and pro-inflammatory cytokines have all been implicated (Honkonen et al., 1997). However, pulmonary vascular resistance is thought to normalize soon after surgery and thus unlikely to fully explain our findings at 6 months (Kwak
et al., 2004). Furthermore, cross-clamping of the thoracic aorta significantly increases mean pulmonary arterial and pulmonary capillary wedge pressures (Kouchoukos et al., 1979). Canine models suggest this is mediated through blood volume redistribution and increased afterload (Stokland et al., 1980). Such an afterload mismatch may contribute to the increased RVESV observed at 6 months and underscore the influence of aortic cross-clamp time at surgery.

4.4.1 Study Limitations
Our study is not randomised and baseline differences in demographics between our study groups are unavoidable due to current TAVI implantation guidelines.

The higher mortality in the TAVI group may have a confounding effect, potentially excluding patients with worse cardiac function from the analysis. There was statistically no difference in the STS score between the included 56 TAVI patients and those that withdrew/died (n=18) (5.54±3.4% vs. 5.28±3.82%, p=0.791). Furthermore, RV function at baseline as assessed by CMR, was also equivalent between these two groups.

Our study did not include patients undergoing trans-apical TAVI. CMR assessment of trans-apical TAVI and its impact upon RV function is warranted to help clarify whether this approach might be less favourable in patients with pre-existing RV dysfunction given the procedural interruption of the pericardium.

Image analysis occurred oblivious to patient details which helped to eliminate bias for pre-operative images. However, post-operative scans inherently appeared different for those with and without sternotomy and thus analysis of 6 month images could not truly be blinded. Furthermore, the heterogeneity in the surgical group in particular may have affected results given that mechanical and bioprosthetic valves with and without concomitant bypass grafting all pose different surgical considerations and procedure duration. However this data does reflect clinical practice.

The requirement for permanent pacing, particularly post TAVI, is a recognised phenomenon likely to result from trauma to degenerative conduction tissue during valvuloplasty. We have not been able to address the impact of pacing upon RV function in the post-intervention setting which is an important and relevant issue in clinical practice.

This present work has not measured LVEDP pre- and post-SAVR and TAVI and this merits attention in future work to determine any contribution of filling pressures towards RV performance.
We have not assessed the impact of tricuspid regurgitation (TR) quantified by CMR upon the changes in RV function seen. The standard method to quantify TR using CMR requires an additional acquisition of flow through the pulmonary valve (subsequently deducting forward flow being from the RV stroke volume to derive TR volume). For the purposes of this research, pulmonary valve assessment was not a component of the protocol. However, in an attempt to account for TR, baseline and follow-up echo imaging was assessed. Based on qualitative echocardiography (grading TR as none, mild, moderate or severe), no significant change in degree of tricuspid regurgitation was seen following TAVI (average interval of 5 months, p=0.144) nor SAVR (average interval of 6 months, p=0.819). We can infer from this that deterioration in RV systolic function is not likely to have been related to post-operative tricuspid regurgitation. The recent suggestion that RV dysfunction, and not significant TR, is independently associated with survival late following a left heart valve operation is noteworthy in this regard (Kammerlander et al., 2014).

4.5 Conclusion

SAVR, but not TAVI, resulted in RV dysfunction that was associated with longer aortic cross clamp times. Further work is needed to determine whether reduction in cross clamp times can preserve RV function following SAVR, and whether TAVI may be the preferable intervention in patients with pre-existing RV dysfunction. Assessment of both left and right ventricular function by CMR may be clinically important when making treatment decisions for high-risk patients with severe aortic stenosis.
Chapter 5. CMR evaluation following TAVI and SAVR for symptomatic severe aortic stenosis: association of myocardial strain and mortality

5.1 Abstract

Background: It is unknown whether circumferential strain is associated with prognosis after treatment of aortic stenosis (AS). We aimed to characterise strain in severe AS, using myocardial tagging cardiovascular magnetic resonance (CMR), prior to and following Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR), and determine whether abnormalities in strain were associated with outcome.

Methods and Results: CMR was performed pre- and 6m post-intervention in 98 patients (52 TAVI, 46 SAVR; 77±8 years) with severe AS. TAVI patients were older (80.9±6.4 vs. 73.0±7.0 years, p<0.01) with a higher STS score (2.06±0.6 vs. 6.03±3.4, p<0.001). Tagged cine images were acquired at the basal, mid and apical LV levels with a complementary spatial modulation of magnetization (CSPAMM) pulse sequence. Circumferential strain, strain rate and rotation were calculated using inTag© software. No significant change in basal or mid LV circumferential strain, or of diastolic strain rate, was seen following either intervention. However, a significant and comparable decline in LV torsion and twist was observed (SAVR: torsion 14.08±8.40 vs. 7.81±4.51, p<0.001, twist 16.17±7.01 vs. 12.45±4.78, p<0.01; TAVI: torsion 14.43±4.66 vs. 11.20±4.62, p<0.001, twist 16.08±5.36 vs. 12.36±5.21, p<0.001). Over a maximum 6.0y follow up, there were 23 (16%) deaths following valve intervention. On multivariable Cox analysis, baseline mid LV circumferential strain was significantly associated with all-cause mortality (hazard ratio, 1.03; 1.01 – 1.05; p=0.009) independent of age, LV ejection fraction and STS mortality risk score. ROC analysis indicated a mid LV circumferential strain > -18.7% was associated with significantly reduced survival.

Conclusion: TAVI and SAVR procedures are associated with comparable declines in rotational LV mechanics at 6m, with largely unchanged strain and strain rates. Pre-operative peak mid LV circumferential strain is associated with post-operative mortality.
5.2 Introduction

The LV responds to pressure overload from aortic stenosis with hypertrophy to offset increased wall stress, in accordance with Laplace’s law (Ozkan et al., 2011). This involves adverse remodelling of the extracellular matrix and altered protein composition which initially leads to a regional reduction in myocardial deformation, with global impairment in contraction occurring later (Kaden et al., 2003).

Myocardial strain, strain rate and twist allow more sensitive characterisation of subtle myocardial performance (Wang et al., 2013) and can all be objectively quantified using myocardial tagging CMR with proven reproducibility (Swoboda et al., 2014, Singh et al., 2015). The myocardium deforms simultaneously in 3 directions and strain measurements can detect pathology prior to decline in conventional indices such as ejection fraction (Galli et al., 2014). Patients with preserved cardiac output and severe AS reportedly exhibit compensatory high circumferential strain with increased apical rotation which are lost with decompensation of LV function (Carasso et al., 2011).

Current guidelines recommend aortic valve replacement with the onset of symptoms or cardiac dysfunction (LVEF<50%) (Vahanian et al., 2012). However, impaired LVEF is a late change indicating significant myocardial damage and poorer outcomes, even after correction of AS (Vaquette et al., 2005). It is notable LVEF is normal in most patients with severe AS, even when symptoms develop and that valve area and transvalvular gradients do not predict clinical outcomes following AVR (Hachicha et al., 2007). The prognostic importance of circumferential myocardial strain in particular on outcome after treatment of aortic stenosis is unknown.

The aims of this study were to 1) characterise LV systolic and diastolic function as measured by CMR tagging in patients with severe symptomatic aortic stenosis prior to and following TAVI and SAVR, and 2) to assess whether CMR measures of strain could hold prognostic importance in those undergoing intervention.

5.3 Methods specific to chapter 5
5.3.1 Study Population
146 patients were prospectively recruited with severe AS who were referred for either TAVI (n=91) or SAVR (n=55) at the University Hospitals of Leeds and Leicester, UK, between July 2008 and March 2014. The duration of follow-up ranged from the initial CMR to July 2014.
Outcomes assessment was based on determining all-cause mortality, confirmed by consulting patient summary care records on the NHS Spine Portal.

5.3.2 Transcatheter Aortic Valve Implantation
TAVI was performed under general anaesthesia. Either an 18F CoreValve Revalving system (CVR, Medtronic, Minneapolis, Minnesota, USA) or an 18F or 20F Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, MA, USA) were deployed as previously described (Piazza et al., 2008, Meredith et al., 2014). A transfemoral route was used preferentially when vascular access was suitable. In the presence of significant peripheral vascular disease, a subclavian artery approach was performed. The invasively measured LV end diastolic pressure was recorded from procedural details.

5.3.3 Surgical Aortic Valve Replacement
SAVR was performed by standard midline sternotomy with cardiopulmonary bypass and mild hypothermia. Biological or mechanical prostheses of varying sizes were used according to surgical preference; concomitant coronary artery bypass grafting was performed as indicated.

5.3.4 CMR Protocol
For each patient, identical preoperative and 6m postoperative scans were performed on the same 1.5T MRI vendor platform (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). Both sites used the identical CMR protocol as previously described (Fairbairn et al., 2013b). Details of the CMR pulse sequence acquisition protocol are outlined in the Standard Methods chapter (sections 2.4.1, 2.4.2, 2.4.4 and 2.4.5).

5.3.5 Image Analysis
CSPAMM analysis was performed for each myocardial slice using a dedicated tagging analysis package (inTag© software, Creatis, Lyon, Fr). Endocardial and epicardial contours were drawn for each slice, and a mid-myocardial contour was automatically calculated; contours were propagated through all cardiac phases. Strain is defined as an index that refers to the amount of myocardial deformation in one direction normalised to its initial dimension. Strain rate is the rate of deformation within a time unit (Ozkan et al., 2011, Wang et al., 2013). Circumferential Lagrangian strain and strain rates (between epicardial and endocardial contours) and rotation were calculated for the three short axis slices. Left ventricular twist was determined as the difference between rotation at the apex and rotation at the base. Torsion was calculated as twist corrected for by length and radius of the LV cavity (Figure 5.1).
Figure 5.1 Directions and quantification of myocardial fibre deformation
A. Schematic representation of circumferential, radial and longitudinal strain demonstrating their directions of motion.
B. Schematic representation of basal clockwise and apical counter-clockwise rotation during systole. The images below show apical, mid LV and basal slices (from left to right) tagged with CSPAMM, with endocardial, mid myocardial and epicardial contours drawn, (LV radius and length measurements derived from cine imaging).

5.3.6 Statistical Analysis
Continuous variables are presented as mean±SD. Normality was determined by the Shapiro–Wilk test. Frequencies are reported as number (%). Changes over time were assessed for differences between the treatment groups and clinical variables by two-way repeated measures analysis of variance (ANOVA). Cox proportional-hazards ratio regression analyses were performed to investigate univariate and multivariate correlates of all-cause mortality. Hazard ratios and 95% confidence intervals (CIs) were reported. Variables with univariate p<0.05 were entered in the multivariate analysis in a stepwise forward approach. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity predictor variables. The cumulative event rates were calculated on the basis of the Kaplan-Meier method, and comparisons between groups were assessed by log-rank test. All statistical analyses were
performed using the PASW software package (V.21.0 SPSS, IBM, Chicago, Illinois, USA) with the exception of ROC analysis that was performed with MedCalc version 9.3.1 (MedCalc Software, Mariakerke, Belgium). A two-sided significance level of p<0.05 was considered statistically significant.

5.4 Results

Ninety-eight patients (52 TAVI, 46 SAVR) with paired pre-operative and 6m post-operative CMR scans were included for analysis. Reasons for non-completion of the CMR protocol were varied and are depicted in Figure 5.1.

![Flowchart](image_url)

**Figure 5.1 Study profile**

At baseline, 15 patients did not undergo LGE imaging due to impaired renal function. Baseline characteristics of the study population are shown in Table 5.1 and grouped according to treatment received. As expected the TAVI group were older with a higher predicted 30 day mortality and greater frequency of prior coronary artery intervention.
### Table 5.1 Patient characteristics and baseline echocardiographic data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAVR (n=46)</th>
<th>TAVI (n=52)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.0 ± 7.0</td>
<td>80.9 ± 6.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>34 (74)</td>
<td>28 (54)</td>
<td>0.041</td>
</tr>
<tr>
<td>STS Mortality (%)</td>
<td>2.06 ± 0.6</td>
<td>6.03 ± 3.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kgm(^{-2}))</td>
<td>27.5 ± 4.4</td>
<td>27.0 ± 3.8</td>
<td>0.709</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>6 (13)</td>
<td>9 (17)</td>
<td>0.560</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>1 (2)</td>
<td>14 (27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>1 (2)</td>
<td>17 (33)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>6 (13)</td>
<td>8 (15)</td>
<td>0.742</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>1 (2)</td>
<td>10 (19)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (70)</td>
<td>25 (48)</td>
<td>0.032</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>7 (15)</td>
<td>10 (19)</td>
<td>0.602</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>23 (50)</td>
<td>31 (60)</td>
<td>0.342</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>4 (9)</td>
<td>12 (23)</td>
<td>0.056</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>3 (7)</td>
<td>15 (29)</td>
<td>0.005</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m(^{2}))</td>
<td>73.3 ± 13.8</td>
<td>59.8 ± 18.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AVA (cm(^{2}))</td>
<td>0.83 ± 0.46</td>
<td>0.59 ± 0.17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean aortic valve PG (mmHg)</td>
<td>46.9 ± 13.4</td>
<td>53.2 ± 19.2</td>
<td>0.102</td>
</tr>
<tr>
<td>Pulmonary Hypertension**, n (%)</td>
<td>7 (15)</td>
<td>15 (29)</td>
<td>0.110</td>
</tr>
<tr>
<td>ValvuloArterial Impedance (Z(_{va}))</td>
<td>3.73 ± 0.99</td>
<td>3.71 ± 1.09</td>
<td>0.734</td>
</tr>
</tbody>
</table>

Values are mean±SD or n(%). *p Value for comparison between TAVI and SAVR groups. **Pulmonary hypertension defined as estimated pulmonary artery systolic pressure by transthoracic echocardiography to be >35mmHg. Zva, valvuloarterial impedance (systolic arterial pressure + mean transvalvular gradient / stroke volume index).

For the TAVI group (n=52), 16(31%) were taking ACE inhibitors or ARB, 25(48%) β-blockers, 4(8%) spironolactone, 11(21%) calcium antagonists, 1(2%) α-blockers, 33(63%) statins and 25(48%) diuretics. For the SAVR group (n=46), 8(17%) were taking ACE inhibitors or ARB,
9(20%) β-blockers, 5(11%) calcium antagonists, 24(52%) statins and 5(11%) diuretics. None were using spironolactone and only 1(2%) α-blockers.

5.4.1 Procedural data
Procedural data are summarised in Table 5.2. For TAVI, 40(77%) patients received a Medtronic CoreValve and 12(23%) a Boston Scientific Lotus valve. A 29mm valve was the most frequently used size (n=26, 50%). In the surgical group, six patients received a mechanical prosthesis and the remaining 40(87%) a tissue bioprosthesis from various manufacturers. The modal valve size was 23mm (n=17, 37%). Twelve (26%) patients received concomitant coronary bypass grafting.
### Table 5.2 Procedural and operative data

<table>
<thead>
<tr>
<th><strong>TAVI</strong></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic CoreValve size (n=43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31mm</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>29mm</td>
<td>28 (65)</td>
<td></td>
</tr>
<tr>
<td>26mm</td>
<td>9 (21)</td>
<td></td>
</tr>
<tr>
<td>23mm</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Boston Lotus size (n=9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23mm</td>
<td>3 (33)</td>
<td></td>
</tr>
<tr>
<td>27mm</td>
<td>6 (67)</td>
<td></td>
</tr>
<tr>
<td>Vascular access</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>48 (92)</td>
<td></td>
</tr>
<tr>
<td>Subclavian</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>Procedure-time, (min)</td>
<td>156±52</td>
<td></td>
</tr>
<tr>
<td>Fluoroscopy-time, (min)</td>
<td>25±7</td>
<td></td>
</tr>
<tr>
<td>Contrast volume, (ml)</td>
<td>150±49</td>
<td></td>
</tr>
</tbody>
</table>

| **SAVR**                      |   |   |
| Biological, n (%)             | 40 (87) |
| Mechanical, n (%)             | 6 (13) |
| Size, (mm)(median, range)     | 23 (18–30) |
| Bypass-time, (mean±SD)        |   |   |
| All                           | 105±49 |
| SAVR only                     | 96±50 |
| SAVR and CABG                 | 132±38 |
| Cross-clamp-time, (mean±SD)   |   |   |
| All                           | 78±43 |
| SAVR only                     | 73±46 |
| SAVR and CABG                 | 91±27 |
| CABG, n (%)                   |   |   |
| All                           | 12 (26) |
| LIMA                          | 6 (13) |
5.4.2 Aortic Valve Haemodynamics and LV reverse remodelling
Results of the baseline and 6m CMR scans are shown in Table 5.3. Significant reductions in peak aortic valve pressure gradient resulted in comparable reverse remodelling post-SAVR and TAVI; with reductions in both indexed LV EDV and mass.

Table 5.3 Preoperative baseline measurements and postoperative changes in the separate procedural groups.

<table>
<thead>
<tr>
<th></th>
<th>SAVR</th>
<th>TAVI</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>63±9</td>
<td>64±12</td>
<td>67±12</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136±21</td>
<td>133±20</td>
<td>133±25</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75±10</td>
<td>72±11</td>
<td>66±10</td>
</tr>
<tr>
<td><strong>Valvular Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic Peak PG (mmHg)††</td>
<td>52±18</td>
<td>30±13***</td>
<td>52±16</td>
</tr>
<tr>
<td>MR fraction (%)</td>
<td>20±18</td>
<td>8±10**</td>
<td>26±16</td>
</tr>
<tr>
<td><strong>Left Ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>94±25</td>
<td>76±13***</td>
<td>94±21</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58±12</td>
<td>61±11*</td>
<td>52±11</td>
</tr>
<tr>
<td>Mass Index (g/m²)</td>
<td>76±22</td>
<td>61±16***</td>
<td>79±21</td>
</tr>
<tr>
<td>LVM/LVEDV (g/ml)</td>
<td>0.82±0.2</td>
<td>0.81±0.2</td>
<td>0.86±0.2</td>
</tr>
<tr>
<td><strong>Peak Circumferential strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base (%)</td>
<td>-19.8 ± 5.2</td>
<td>-18.6 ± 4.9</td>
<td>-17.6 ± 5.8</td>
</tr>
<tr>
<td>Mid (%)</td>
<td>-21.1 ± 5.3</td>
<td>-20.0 ± 4.3</td>
<td>-19.3 ± 6.1</td>
</tr>
<tr>
<td>Apex (%)</td>
<td>-20.0 ± 6.4</td>
<td>-17.5 ± 6.8**</td>
<td>-18.8 ± 6.7</td>
</tr>
<tr>
<td><strong>Peak mid-ventricular strain rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (S⁻¹)</td>
<td>-0.032 ± 0.010</td>
<td>-0.034 ± 0.009</td>
<td>-0.029 ± 0.008</td>
</tr>
<tr>
<td>Diastolic (S⁻¹)</td>
<td>0.028 ± 0.016</td>
<td>0.028 ± 0.018</td>
<td>0.022 ± 0.015</td>
</tr>
<tr>
<td><strong>LV torsion</strong></td>
<td>14.08 ± 8.40</td>
<td>7.81 ± 4.51***</td>
<td>14.43 ± 4.66</td>
</tr>
<tr>
<td><strong>LV twist (°)</strong></td>
<td>16.17 ± 7.01</td>
<td>12.45 ± 4.78**</td>
<td>16.08 ± 5.36</td>
</tr>
</tbody>
</table>
5.4.3 Measures of strain by CMR

At baseline, both groups undergoing SAVR and TAVI had comparable LV circumferential strain of the base (p=0.081) mid (p=0.128) and apex (0.318) with overall preserved LV ejection fraction. Similarly LV torsion (p=0.845) and twist (p=0.879) were comparable between groups. However, both systolic (p=0.039) and diastolic (p=0.037) strain rates were higher in the SAVR group.

At baseline for the TAVI group, there was moderate correlation between increasing LV end diastolic pressure (measured invasively during TAVI implantation) and both a deterioration in peak basal circumferential strain (r=0.4, n=33, p=0.04, two-sided) and diastolic peak mid-ventricular strain rate (r=-0.5, n=33, p=0.003, two-sided).

No significant change in basal or mid-LV circumferential strain or of diastolic strain rate was seen following intervention, either post-SAVR or TAVI. A significant decline in peak apical circumferential strain following SAVR and an increase in circumferential systolic strain rate following TAVI were noted.

Both SAVR and TAVI were associated with a significant and comparable decline in LV twist and torsion at 6 months following intervention (Figure 6.2).
Fig. 5.3 Change in twist and mid-LV circumferential strain
Twist pre and post-SAVR (A) and pre and post-TAVI (B).
Circumferential strain pre and post-SAVR (C) and pre and post-TAVI (D).

Analysing the total severe AS patient population (n=98), no change in LV strain at any level was seen following aortic valve intervention (Base: -0.186±0.056 vs. -0.186±0.054, p=0.961; Mid: -0.201±0.058 vs. -0.199±0.006, p=0.714; Apex: -0.194±0.065 vs. -0.182±0.064, p=0.05).

5.4.4 Predictors of Mortality following Intervention
Over a maximum 6.0y follow up (median 2.5yrs); there were 23 deaths (all-cause, of which 14 had completed follow-up imaging). Stepwise logistic regression identified a number of demographics and measures of cardiac function that were associated with mortality. Notably, the presence of baseline myocardial fibrosis (detected by LGE imaging), indexed LV mass, mean aortic pressure gradient and history of myocardial infarction were not significantly associated with prognosis. In multivariate analysis, baseline mid LV circumferential strain remained independently associated with all-cause mortality (Table 6.4).
Table 5.4 Cox proportional hazard analysis for prediction of all-cause death following valve intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>p-Value</td>
<td>Hazard ratio (95% CI)</td>
<td>p-Value</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.125 (1.043 – 1.215)</td>
<td>0.002</td>
<td>1.084 (0.935 - 1.256)</td>
<td>0.286</td>
</tr>
<tr>
<td>STS score (per %)</td>
<td>1.238 (1.037 – 1.477)</td>
<td>0.018</td>
<td>1.365 (0.943 - 1.976)</td>
<td>0.099</td>
</tr>
<tr>
<td>eGFR (per ml/min/1.73m²)</td>
<td>0.963 (0.936 – 0.991)</td>
<td>0.010</td>
<td>0.988 (0.947 – 1.053)</td>
<td>0.953</td>
</tr>
<tr>
<td>Baseline Mid LV CS (per %)</td>
<td>1.016 (1.007 – 1.024)</td>
<td>0.001</td>
<td>1.029 (1.007 – 1.052)</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Baseline LVEF (per %)</td>
<td>0.962 (0.926 – 0.999)</td>
<td>0.046</td>
<td>1.031 (0.949 – 1.119)</td>
<td>0.473</td>
</tr>
<tr>
<td>TAVI procedure</td>
<td>3.776 (1.283 – 11.109)</td>
<td>0.016</td>
<td>0.397 (0.043 – 3.646)</td>
<td>0.414</td>
</tr>
<tr>
<td>Myocardial Fibrosis (LGE +ve)</td>
<td>1.670 (0.615 – 4.541)</td>
<td>0.315</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baseline LVMI</td>
<td>1.014 (0.993 – 1.035)</td>
<td>0.189</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.611 (0.148 – 2.516)</td>
<td>0.495</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean Aortic PG</td>
<td>1.018 (0.91 – 1.046)</td>
<td>0.182</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ROC analysis indicated the optimal threshold for pre-procedure mid LV circumferential strain to be -18.7%, from which a Kaplan-Meier graph was derived (Figure 5.4).
Figure 5.4 Association of circumferential strain with survival

A) ROC curve for baseline mid LV circumferential strain showing optimal discrimination value (-18.69%) and an AUC of 0.74.

B) Kaplan-Meier survival curves for AS patients undergoing valve intervention stratified by mid LV circumferential strain more positive than -18.7% (n=67, green) or more negative than -18.7% (n=40, blue).

5.5 Discussion

This prospective multicentre study has demonstrated that in severe symptomatic AS patients with abnormal strain and torsion, a reduction in torsion but no recovery in circumferential strain is seen post-valve replacement (with either TAVI or SAVR). In addition, reduced baseline mid-LV circumferential strain was associated with a higher post-operative mortality, independent of age, STS predicted mortality and LVEF.

Previous studies in patients with symptomatic severe AS and preserved LV ejection fraction have reported uniformly reduced longitudinal strain (Pibarot and Dumesnil, 2010, Attias et al., 2013, Becker et al., 2007, Iwahashi et al., 2006). Sustained severe AS culminates in hypertrophic LV remodelling and an elevation in LVEDP. This predisposes to subendocardial ischaemia and impairs longitudinal subendocardial fibre contractility (Lancellotti et al., 2010) reducing global systolic function (Ross, 1976). Our study is the first to define an inverse relationship between invasively measured LVEDP and CMR derived circumferential strain and diastolic strain rate in aortic stenosis.
Higher circumferential strain in patients with preserved LVEF, and increased apical rotation in patients with mild LV dysfunction are thought to indicate compensatory mechanics serving to maintain radial strain. These compensatory mechanisms are reduced as LV performance declines (Carasso et al., 2011) and their loss appears to occur at the time of symptom onset (Lancellotti et al., 2010) indicating their potential use for surveillance and timing of surgery (Carasso et al., 2015).

At baseline, our severe AS population had abnormally low circumferential strain with normal twist values compared with echocardiography derived reference ranges (Kaku et al., 2014). This is indicative of failing dynamic LV compensation consistent with their symptomatic status, despite an overall preserved LVEF. Our findings are thus a novel contribution, distinct from prior published work (Biederman et al., 2005, Grabskaya et al., 2011, Carasso et al., 2009, Carasso et al., 2011), in reporting the impact of treatment in a study population with more advanced LV dysfunction as a consequence of severe AS.

Our study population had particularly severe indices of AS severity and the observed reduced baseline strain may reflect diminished coronary flow reserve (Biederman et al., 2005) and repetitive ischaemic myocardial injury (Grabskaya et al., 2011). Improved valvular function following intervention is thought to confer improved transmural myocardial perfusion and subsequent improved LV mechanics (Delgado et al., 2009) but this was not seen in our study; neither following TAVI, SAVR, or as a treated AS population in its entirety. It is notable coronary heart disease is thought to blunt recovery of myocardial mechanics following SAVR (Meimoun et al., 2011). Both the TAVI and SAVR groups were heterogeneous in their degree of coronary disease and established infarction, with over a quarter of SAVR patients also receiving revascularisation. It is challenging to estimate the impact of revascularisation in comparison to valve correction in our study; but in a sub analysis of our entire AS population excluding those with diseased epicardial vessels, we still failed to observe any improvement in circumferential strain at any LV level following treatment.

Conflicting changes in LV strain rates have been reported, with both improvements (Delgado et al., 2009, Rost et al., 2010, Becker et al., 2007) and a decline (Carasso et al., 2009) following SAVR; and either no change (Grabskaya et al., 2011) or an improvement following TAVI (Poulin et al., 2014). Our study demonstrates neither SAVR nor TAVI was associated with improvement of peak circumferential strain at any level, or of diastolic strain rate. In a sub analysis of our entire AS population excluding those with late gadolinium hyperenhancement, we still failed to observe any improvement in circumferential strain at any LV level following treatment. This lack of improvement indicates a degree of irreversible decompensation at baseline which may have
potential future implications for surveillance of systolic function and timing of intervention in severe AS.

Our study provides unique insight into the assessment of LV rotational mechanics, which remains largely unaddressed by previous studies; both in the context of symptomatic AS and following aortic valve intervention. LV torsion and twist are integral components of ventricular contractility and diastolic filling (Sengupta et al., 2008). Previous CMR studies have reported changes in rotation in the context of AS, but inferences were confounded by very small sample sizes (largest n=13) (Nagel et al., 2000, Stuber et al., 1999). An increase in LV twist has been described in severe AS with preserved LVEF as compensation for impaired systolic longitudinal function (Meimoun et al., 2011). The baseline LV twist in our patients was notably lower than those awaiting SAVR from published echo studies (Lindqvist et al., 2011), again suggesting failure of compensation and a more advanced stage of disease (Poulin et al., 2014).

Our study indicates that significant and comparable reductions in both torsion and twist, similar to that reported by others, occurs following SAVR (Lindqvist et al., 2011) and TAVI (Poulin et al., 2014). Twist is an energy saving process reflecting the helical orientation of cardiac fibres which offsets afterload mismatch, generating high intra-cavity pressure with minimal fibre shortening (Nagel et al., 2000). The reduction observed following intervention likely reflects the relief of afterload previously imposed by severe AS. Torsion is dependent on LV shape and falls with declining concentric hypertrophy, representing reduced leverage from epicardial fibres (Young and Cowan, 2012). In our study, both TAVI and SAVR precipitated comparable reverse LV remodelling with significant reductions in both indexed LVEDV and LV mass, consistent with the equivalent changes in torsion observed.

Patients with severe aortic stenosis and reduced LV ejection fraction carry a high risk of mortality following both SAVR (Monin et al., 2003) and TAVI (Sannino et al., 2014). However, deteriorating ejection fraction is a late occurrence and significant interest remains in identifying advanced objective predictors of mortality when ejection fraction is above 50%. This study is, to our knowledge, the first to demonstrate circumferential strain derived by CMR is independently associated with all-cause postoperative mortality in symptomatic patients with severe AS and preserved LVEF undergoing intervention.

Previous studies have hypothesised the prognostic value of longitudinal strain in AS may reflect the impact of myocardial fibrosis and provide the link to poor outcome (Dahl et al., 2012, Kusunose et al., 2014). This study has tested for an association between myocardial fibrosis and strain with respect to outcome, and demonstrates the prognostic importance of
circumferential strain measurement is unrelated to late gadolinium hyperenhancement. This is inconsistent with previous reports; but the follow-up period of 6 years is notably longer than that of others (Dweck et al., 2011) and this study assessed all-cause rather than cardiovascular-specific causes of mortality. In this study, circumferential strain did not improve following SAVR / TAVI which may not have been the case in other studies of younger patients; in whom LGE thus may be more influential with respect to outcome. This study is thus noteworthy but cannot definitively conclude on the importance of fibrosis, whether it be mid-wall or ischaemic, in this context. Lower circumferential strain in severe AS is independently associated with myocardial triglyceride accumulation (Mahmod et al., 2013). It is possible this lipotoxicity, which is undetectable using conventional LGE imaging, is important to the link between strain and outcome. However, our findings are not fully explicable by myocardial steatosis which has been shown to regress following SAVR, albeit in younger patients than our study (Mahmod et al., 2013).

Based on our work, patients with severe AS, even in the context of preserved LVEF, are at high risk for mortality when baseline mid-LV circumferential strain is >18.7%. It is noteworthy this association occurs despite the relief of index aortic stenosis with SAVR or TAVI, and thus these patients in particular may benefit from greater scrutiny in follow-up. Measurement of circumferential strain using CMR is a non-invasive and reproducible modality by which a single, breath-held acquisition can potentially provide prognostic information independent of age, LVEF and surgical risk score.

5.5.1 Limitations
Our study population included patients with coronary artery disease and hypertension, rather than being restricted to pure aortic stenosis. This is however, generalisable to real world clinical practise and reduces the effect of selection bias. CMR assessment of cardiac rotational mechanics is sensitive to atrial fibrillation and regional wall motion abnormalities which can impair image quality. However, our quantification of strain using myocardial tagging CMR has demonstrated good reproducibility (Swoboda et al., 2014).

Image analysis occurred oblivious to patient details which helped to eliminate bias for pre-operative images. However, post-operative scans inherently appeared different for those with and without sternotomy and thus analysis of 6 month images could not truly be blinded.

Our sample size is small with relatively few events carrying a risk of potential statistical over fitting. Also, we have reported all-cause mortality rather than cardiac mortality. Thus our findings
need to be viewed with caution and validated in larger outcome studies. Finally, we only enrolled patients with symptomatic aortic stenosis and further work is required to determine whether the prognostic importance of strain assessment can be extended to those who are asymptomatic; and thus potentially influence surgical timing.

5.6 Conclusions
Patients with symptomatic severe AS and preserved LVEF undergoing aortic valve intervention have reduced peak circumferential strain and systolic strain rates. At 6m, TAVI and SAVR procedures were associated with comparable declines in rotational LV mechanics, with largely unchanged strain and strain rates. Pre-operative peak mid LV circumferential strain was associated with post-operative total mortality and requires further investigation as to its use as a risk stratification tool.
Chapter 6. Aortic Regurgitation post-TAVI: a CMR comparison of two vendor designs

6.1 Abstract

Background: Transcatheter Aortic Valve Replacement (TAVI) is an established treatment for patients with symptomatic severe aortic stenosis. Paravalvular aortic regurgitation following implantation confers a worse prognosis and can be accurately quantified using CMR. Second generation valves have been specifically designed to reduce paravalvular regurgitation and improve device implantation success.

Objectives: To compare, using serial CMR, the quantity of aortic regurgitation, following TAVI with two different designs: the self-expanding CoreValve (Medtronic, Minneapolis, Minnesota) and the mechanically expanded Lotus valve (Boston Scientific, Natick Massachusetts).

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

Results: Valve Academic Research Consortium defined device success was achieved in 94% of the Lotus and 63% of the CoreValve patients (p=0.004), the difference predominantly due to differing rates of ‘at least moderate’ aortic regurgitation. The CMR derived aortic regurgitant fraction immediately post-TAVI was greater in the CoreValve group (11.7±8.4 vs. 4.3±3.4%, p=0.001), with equivalent 6 month values (6.4±5.0 vs. 5.6±5.3% respectively, p=0.623). The residual peak pressure gradient immediately following CoreValve implantation was significantly lower (14.1±5.6 vs. 25.4±11.6mmHg, p=0.001), with comparable values at 6 months (16.5±9.4 vs. 19.7±10.5mmHg, p=0.332). CoreValve and Lotus patients were equivalent in the degree of LV reverse remodelling observed at 6 months.

Conclusion: In the immediate post-TAVI period, there was significantly less aortic regurgitation but a higher residual peak pressure gradient with the Boston Lotus valve compared to the Medtronic CoreValve. However at 6 months post-TAVI, both devices had comparable valve haemodynamics and extent of LV reverse remodelling.
6.2 Introduction

Transcatheter Aortic Valve Replacement (TAVI) is endorsed by both US (Nishimura et al., 2014a) and European (Vahanian et al., 2012) guidelines to improve survival and quality of life in patients with symptomatic severe aortic stenosis deemed inoperable or too high surgical risk. Over 200,000 patients worldwide have received TAVI across ~400 centres. TAVI device design continues to evolve in order to improve implantation success rates and clinical outcomes (Gooley et al., 2015).

However, paravalvular AR is seen in up to 80% of patients following TAVI, affecting both the balloon-expandable and the self-expanding designs (Pibarot et al., 2015). This reflects incomplete circumferential apposition between the circular prosthesis and the oval-shaped aortic annulus (Sinning et al., 2013) and is often compounded by extensive calcification, under expansion of the TAVI prosthesis or malposition (Stahli et al., 2013).

Clinical trials and registry data indicate AR following TAVI is associated with increased mortality at short term follow-up (Smith et al., 2011, Ussia et al., 2012, Webb and Wood, 2012). In a recent analysis of the PARTNER-IA continued access cohorts, mild AR post-TAVI independently predicted an increase in all-cause mortality (HR 1.37) after adjustment of other co-morbidities (Kodali et al., 2015). The dimensionless Aortic Regurgitation Index is derived from invasive measurement during TAVI implant, and a value of less than 25 has been shown to predict 1-year survival (Sinning et al., 2012). There is thus a need to accurately quantify post-procedure AR in order to assess implantation success and to study new generation valves designed to reduce this important complication (Pibarot et al., 2015).

CMR is the reference standard modality for assessing LV mass, volumes and function (Ribeiro et al., 2014). In addition, CMR permits full volumetric quantitation of AR that is highly accurate and reproducible (Crouch et al., 2015b, Salaun et al., 2015), independent of the number or eccentricity of regurgitant jets (Sherif et al., 2011), and unlike echocardiography, is not limited by TAVI prosthesis or calcification artefact (Sinning et al., 2013). CMR has lower intra-observer and inter-observer variability than echocardiography (Cawley et al., 2013, Altıok et al., 2014) and thus is more suited to serial measurements (Merten et al., 2013). Compared with CMR, echocardiography underestimates AR following TAVI (Ribeiro et al., 2014, Crouch et al., 2015b, Hartlage et al., 2014) and thus CMR offers potentially superior prognostic value in the post-TAVI patient (Hartlage et al., 2014).

Little is known about how AR evolves over time when compared between different TAVI designs, or whether in turn this produces meaningful differences in LV structure and function.
The Boston Scientific Lotus valve comprises a unique adaptive seal specifically designed to minimise post-TAVI aortic regurgitation (AR) (8), that has proven in the REPRISE I (Meredith et al., 2014) and REPRISE II (Meredith Am et al., 2014) studies to be both safe and effective.

The aim of this study was to accurately quantify, using serial CMR, the degree of AR following TAVI using two different commercial prosthesis, the extensively trialled Medtronic CoreValve (Adams et al., 2014, Tamburino et al., 2011, Linke et al., 2014, Abdel-Wahab et al., 2014, Popma et al., 2014) and the novel Boston Scientific Lotus valve, and determine whether a particular design had greater predilection for more favourable LV reverse remodelling.

6.3 Methods specific to chapter 6

6.3.1 Study population
This study prospectively recruited 59 patients with severe AS who were referred for TAVI 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 ≤1.0 cm² or peak velocity >4 m/s. Decision for TAVI in all cases was taken by a multidisciplinary heart team in accordance with international guidance (Vahanian et al., 2008). Exclusion criteria included any contraindication to CMR as well as patients with a known bicuspid aortic valve, aortopathy or previous aortic or mitral prostheses.

6.3.2 Transcatheter Aortic Valve Replacement
TAVI was performed using either a third-generation 18F CoreValve ReValving system (CVR, Medtronic, Minneapolis, Minnesota, USA) or an 18F, 20F or 22F Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, MA, USA) employing standard techniques as previously described for both vendors (Piazza et al., 2008, Meredith et al., 2012). All patients underwent multidetector computed tomography to assist annular sizing and to assess aortic calcification prior to TAVI. Percutaneous femoral artery access was the default approach and the AR index, derived invasively at the time of TAVI, was determined by ([Diastolic BP - LVEDP] / Systolic BP) x100). For the purposes of analysis, an AR index cut-off of 25 was chosen given previous work indicating this threshold holds prognostic importance (Sinning et al., 2012).

6.3.3 CMR Protocol
For each individual patient, identical pre-, immediately post-TAVI, and 6-month postoperative scans were performed at 1.5T (Intera or Ingenia, Phillips Healthcare, Best, Netherlands) (Figure 6.1). The cardiac imaging of patients immediately post-TAVI required a notice of amendment and ethical approval which was duly granted (Appendix 9.2).
Details of the CMR pulse sequence acquisition protocol are outlined in the Standard Methods chapter (sections 2.4.1 and 2.4.2).

For flow measurements, through-plane velocity encoded (VENC) phase contrast imaging was performed perpendicular to the aortic valve jet at the aortic sinotubular junction, at the upper margin of the stent holding the TAVI prosthesis (VENC 200–500 cm/s, retrospective gating, slice thickness 6 mm, 40 phases, FOV 340 mm). This position for imaging has been previously described and validated (Salaun et al., 2015). If significant turbulence or aliasing was seen in the velocity image, the acquisition was repeated a few millimetres further from the valve, and/or with a higher-velocity window.

6.3.4 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. Aortic flow was quantified to provide a peak forward flow velocity (m/s), forward flow volume (ml), backward flow volume (ml) and regurgitant fraction (%). Images were excluded from analysis if artefacts from the TAVI 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 CMR standard grading criteria (Gelfand et al., 2006).
6.3.5 Statistical Analysis
Spearman correlation coefficient were calculated to investigate the relationship between aortic regurgitant fraction measured by CMR and that derived invasively at time of TAVI implantation. Based on published data (Bellenger et al., 2000a), 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); 30 per group would be sufficient to detect a clinically meaningful 10% absolute difference in aortic peak forward flow velocity or regurgitant fraction (85% power and an alpha error of 0.05).

6.4 Results
6.4.1 Patient population
A total of 51 patients (24 Medtronic CoreValve and 27 Boston Lotus) underwent the preoperative and immediate post-TAVI CMR scans with 44 of these (19 CoreValve and 25 Lotus) finally completing 6 month post-TAVI scans. Reasons for non-completion of the CMR protocol were varied and depicted in Figure 6.2.

Figure 6.2 Study profile

The final analysis population (n=44) was not different to the whole population (n=51) studied pre-TAVI (comparable in age (p=0.871), EuroSCORE II (p=0.724) and STS predicted operative
mortality (p=0.736)). The baseline characteristics of this final study population are reported in Table 6.1.

### Table 6.1 Patient characteristics in those with 6 month follow up

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (n=19)</th>
<th>Lotus (n=25)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79.6±6.3</td>
<td>78.6±8.7</td>
<td>0.693</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (63)</td>
<td>14 (56)</td>
<td>0.414</td>
</tr>
<tr>
<td>STS score (%)</td>
<td>3.58±1.9</td>
<td>3.89±2.6</td>
<td>0.669</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.6±4.8</td>
<td>28.7±5.3</td>
<td>0.484</td>
</tr>
<tr>
<td>NYHA, (modal group)</td>
<td>3</td>
<td>3</td>
<td>0.327</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (47)</td>
<td>8 (32)</td>
<td>0.239</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (11)</td>
<td>5 (20)</td>
<td>0.441</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>12 (63)</td>
<td>15 (60)</td>
<td>0.659</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>4 (21)</td>
<td>4 (16)</td>
<td>0.609</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>3 (16)</td>
<td>6 (24)</td>
<td>0.520</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>7 (37)</td>
<td>7 (28)</td>
<td>0.458</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>5 (26)</td>
<td>5 (20)</td>
<td>0.556</td>
</tr>
<tr>
<td>Previous Stroke, n (%)</td>
<td>3 (16)</td>
<td>6 (24)</td>
<td>0.564</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>6 (32)</td>
<td>7 (28)</td>
<td>0.710</td>
</tr>
<tr>
<td>Pulmonary Hypertension, n (%)</td>
<td>6 (32)</td>
<td>10 (40)</td>
<td>0.587</td>
</tr>
<tr>
<td>Peripheral Vascular Disease, n (%)</td>
<td>6 (32)</td>
<td>3 (12)</td>
<td>0.094</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m$^2$)</td>
<td>61±27</td>
<td>72±19</td>
<td>0.135</td>
</tr>
<tr>
<td>AVA (cm$^2$)</td>
<td>0.61±0.21</td>
<td>0.60±0.18</td>
<td>0.965</td>
</tr>
<tr>
<td>Mean Aortic PG (mmHg)</td>
<td>50±12</td>
<td>55±19</td>
<td>0.292</td>
</tr>
<tr>
<td>AR Regurgitant Fraction (%)</td>
<td>12.5±11.7</td>
<td>11.9±9.6</td>
<td>0.852</td>
</tr>
<tr>
<td>LV EDVI (ml/m$^2$)</td>
<td>98.2±28.6</td>
<td>89.4±34.9</td>
<td>0.379</td>
</tr>
</tbody>
</table>
### Procedural data

All of the Boston Lotus valves were implanted via the femoral artery, as were the majority of CoreValves (68%). Fifteen patients (54%) in the Lotus group were treated with smaller Lotus devices (23 or 25mm), whereas only 5 (20%) of the CoreValve group received the smaller CoreValve prostheses (23 or 26 mm) (p=0.030).

Invasive resting 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 TAVI receiving post-dilatation (0% vs. 28%, p=0.003). Equivalent volumes of contrast were used for each TAVI type (Table 6.2).
Table 6.2 Catheterisation data for TAVI implant procedures

<table>
<thead>
<tr>
<th>TAVI size (n(%))</th>
<th>CoreValve (n=24)</th>
<th>Lotus (n=27)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVI size (n(%))</td>
<td></td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Small</td>
<td></td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>(23 &amp; 26mm CoreValve, 23 &amp; 25mm Lotus)</td>
<td>23mm (2 (8%))</td>
<td>23mm (7 (25%))</td>
<td>0.030</td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>(29 &amp; 31mm CoreValve, 27mm Lotus)</td>
<td>29mm (14 (56%))</td>
<td>27mm (13 (46%))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31mm (5 (20%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral route, n (%)</td>
<td>17 (68)</td>
<td>28 (100)</td>
<td>0.003</td>
</tr>
<tr>
<td>Resting PG (mmHg)</td>
<td>51±24</td>
<td>57±27</td>
<td>0.419</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>23±7</td>
<td>28±8</td>
<td>0.017</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>152±51</td>
<td>159±43</td>
<td>0.589</td>
</tr>
<tr>
<td>Contrast (ml)</td>
<td>144±49</td>
<td>120±44</td>
<td>0.068</td>
</tr>
<tr>
<td>Pre-dilatation BAV, n (%)</td>
<td>20 (80)</td>
<td>22 (79)</td>
<td>0.899</td>
</tr>
<tr>
<td>Post-dilatation, n (%)</td>
<td>7 (28)</td>
<td>0 (0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

VARC-defined device success (Leon et al., 2011) was achieved in 94% of the Lotus cohort and 63% of the CoreValve cohort (p=0.004). The components of this measure were the absence of procedural mortality (94% vs. 96%, p=0.177), a mean gradient across the TAVI prosthesis of < 20mmHg (100% vs. 100%, p=0.999), correct positioning of a single TAVI 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.

The rate of new pacemaker insertion was non-statistically different between the Lotus and CoreValve groups (22% vs. 15%, p=0.424).
6.4.3 TAVI haemodynamics

The severity of preoperative aortic valve stenosis was similar between the Lotus and CoreValve groups (Table 7.1). 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 6 months (141±25 vs. 127±16mmHg respectively, p=0.161) post-TAVI. Immediately post-TAVI, 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) patients of a comparable magnitude (-68.9±27.8 vs. -74.4±29.0mmHg respectively, p=0.497). However, the residual peak pressure gradient immediately following Lotus valve implantation was significantly higher than that following CoreValve (25.4±11.6 vs. 14.1±5.6mmHg, p=0.001). At 6 months post-TAVI, the peak pressure gradient of the CoreValve remained unchanged from the immediate post-TAVI 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 7.3A).
Figure 6.3 Comparison of change over time in valvular and ventricular parameters between Lotus and CoreValve
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 6.3).

**Table 6.3 Comparison of LV parameters and aortic valve haemodynamics immediately and 6 months post-TAVI from 2 vendors**

<table>
<thead>
<tr>
<th></th>
<th>Immediate post-TAVI</th>
<th>6 months post TAVI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CoreValve (n=24)</td>
<td>Lotus (n=27)</td>
</tr>
<tr>
<td><strong>Valvular Function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic RF, (%)</td>
<td>11.7±8.4</td>
<td>4.3±3.4</td>
</tr>
<tr>
<td>Aortic Peak PG</td>
<td>14.1±5.6</td>
<td>25.4±11.6</td>
</tr>
<tr>
<td></td>
<td>(mmHg)</td>
<td></td>
</tr>
<tr>
<td><strong>Left Ventricle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m$^2$)</td>
<td>94.7±17.7</td>
<td>91.8±21.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.2±11.5</td>
<td>54.3±10.9</td>
</tr>
<tr>
<td>Mass Index (g/m$^2$)</td>
<td>65.8±13.6</td>
<td>69.6±16.2</td>
</tr>
<tr>
<td>LVM/LVEDV (g/ml)</td>
<td>0.71±0.14</td>
<td>0.80±0.30</td>
</tr>
</tbody>
</table>

At baseline, the aortic regurgitant fraction comparison between CoreValve and Lotus patients was equivalent (12.5±11.7 vs. 11.9±9.6% respectively, p=0.852) highlighting that degenerative severe aortic stenosis was the predominant valvular pathology prior to TAVI in both groups. Immediately post-TAVI, the aortic regurgitant fraction was statistically greater in the CoreValve group (11.7±8.4 vs. 4.3±3.4%, p=0.001). The classification of AR immediately following TAVI in the two groups is depicted in Figure 6.4.
Figure 6.4 AR classification immediately post-TAVI

There was a significantly higher percentage of patients with mild (p=0.017) and moderate AR (p=0.001) following TAVI with CoreValve than Lotus. 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 6.3B). As such, comparison between CoreValve and Lotus patients at 6 months showed the residual total aortic regurgitant fraction was equivalent (6.4±5.0 vs. 5.6±5.3% respectively, p=0.623) (Table 6.3).

6.4.4 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 characteristics between the two groups, immediately and at 6 months post-TAVI, is also summarised in Table 6.3. Immediately post-TAVI, there was no change in indexed LVEDV or 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 TAVI (75.4±15.0 vs.
65.8±13.6g/m², p<0.001) that was not seen following Lotus (70.8±25.0 vs. 69.6±16.2g/m², p=0.811). Compared to baseline, the LVEF and indexed LVEDV values at 6 months were unchanged, regardless of the TAVI vendor. However, a significant and comparable regression in the indexed LV mass was observed in both TAVI groups (Table 6.4, Figure 6.3C and 6.3D).

**Table 6.4 Comparison of aortic valve function and LV reverse remodelling post-TAVI**

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (n=19)</th>
<th>Lotus (n=25)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Valvular Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic RF, (%)</td>
<td>12.5±11.7</td>
<td>6.4±5.0</td>
<td>11.9±9.6</td>
</tr>
<tr>
<td>Aortic Peak PG (mmHg)</td>
<td>88.6±27.4</td>
<td>16.5±9.4***</td>
<td>95.3±28.7</td>
</tr>
<tr>
<td><strong>Left Ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>98.2±28.6</td>
<td>87.2±17.8</td>
<td>89.4±34.9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.2±12.8</td>
<td>56.4±8.6</td>
<td>51.0±19.0</td>
</tr>
<tr>
<td>Mass Index (g/m²)</td>
<td>75.4±15.0</td>
<td>56.8±13.2***</td>
<td>69.2±25.9</td>
</tr>
<tr>
<td>LVM/LVEDV (g/ml)</td>
<td>0.80±0.16</td>
<td>0.67±0.17**</td>
<td>0.73±0.27</td>
</tr>
</tbody>
</table>

**6.4.5 Correlation of AR Index with CMR and impact upon LV reverse remodelling**

There was a moderate negative correlation between invasive AR index and CMR aortic regurgitant fraction (Spearman’s correlation coefficient = -0.5, N=51, p=0.001) (Figure 7.5).
Figure 6.5 Scatter plots demonstrating correlation of invasive and CMR quantification of AR

A: All patients, grouped according to their CMR class of AR. Line of best fit with 95% confidence intervals shown, indicating a negative correlation.

B: All patients grouped according by vendor of TAVI received. Horizontal line indicates AR index of 25.

The mean AR index following Lotus TAVI was non-significantly higher than that following CoreValve TAVI (25.0± 6.3 vs. 23.0±8.7, p=0.145), with an equivalent proportion of patients in each group with an AR index below 25 (59% Lotus vs. 71% CoreValve, p=0.517) (Figure 7.5).

Analysing the final study population as a whole (n=44), the LV mass:volume ratio did not change between the immediate post-TAVI and 6 month scans, in patients with an AR index ≤25 (0.74±0.27 vs. 0.71±0.21g/ml, p=0.382) unlike those with >25 (0.79±0.18 vs. 0.69±0.21g/ml, p=0.003). Furthermore, significantly less LV mass regression was seen between the immediate post-TAVI and 6 month scans in patients with an AR index ≤25 when compared with those >25 (-8.4±11.0 vs. -15.3±9.8 g/m², p=0.046).

6.5 Discussion
This is the first study to use CMR to directly and systematically compare two distinct TAVI designs for aortic valve haemodynamics and impact on LV reverse remodelling over time.

We have shown in this single-centre non-randomised study that compared with the Boston
Lotus, TAVI with the Medtronic CoreValve is associated with a significantly greater quantity of aortic regurgitation immediately post-implantation, but with lower residual peak pressure gradients. At 6 months post-TAVI, both valves perform equally with respect to aortic valve peak pressure gradient and regurgitant fraction, with an equivalent degree of LV mass regression observed from baseline. This is consistent with published studies with longer follow-up that have demonstrated excellent outcomes with both TAVI designs (Reardon et al., 2015, Meredith et al., 2014).

In our study, we observed high rates of procedural success with both CoreValve and Lotus TAVI. However, in direct comparison, the VARC-defined primary composite outcome of device success was significantly higher in the Lotus group, driven principally by the absence of “moderate or more” aortic regurgitation. The Lotus valve has been compared with the CoreValve previously using echocardiography (Gooley et al., 2015). However, the echocardiographic grading criteria suggested by VARC lacks validation post-TAVI (Lerakis et al., 2013). Quantification of regurgitation remains challenging and echo may inherently underestimate AR post-TAVI (Ribeiro et al., 2014, Crouch et al., 2015b, Sherif et al., 2011). In a recent comparison of 2D echocardiography, 3D echocardiography and CMR, applying VARC metrics post-TAVI, the observer variability in determining AR was superior by CMR (Altik et al., 2014). This is the first study to our knowledge to assess device success using CMR and supports a genuine superiority of the Lotus valve over Medtronic CoreValve.

There is growing evidence suggesting a significant association of post-procedural AR with short- and long-term mortality (Kodali et al., 2012, Tamburino et al., 2011, D’Onofrio et al., 2015). In the PARTNER-IA study, even mild AR following TAVI was associated with increased mortality at 2 years (Kodali et al., 2012). In our study, all patients underwent MDCT which is crucial for optimal annular sizing and subsequent TAVI function (Oh et al., 2015). This is distinct to other studies in which only a minority of TAVI procedures were planned using MDCT (Kodali et al., 2015, Linke et al., 2014). We observed a significantly lower quantity of AR following Lotus valve implantation compared to CoreValve, which most likely reflects integral differences in TAVI prosthesis design rather than device undersizing.

The Lotus valve is mechanically expanded, fully retrievable and repositionable, and carries a central radiopaque positioning marker. This allows assessment of TAVI function and haemodynamics prior to final deployment, which in part explains the longer fluoroscopy time we observed with this device. Furthermore, it has an adaptive seal comprising polyurethane/polycarbonate which seals the frame against the native aorto-ventricular interface, thus minimising paravalvular AR (Gooley et al., 2013, Meredith et al., 2012). The CoreValve is a
self-expanding device with a flared inflow segment designed to anchor the TAVI within the native annulus (Gooley et al., 2015). Accurate initial positioning is vital to its placement, alongside device oversizing, to optimise annular occlusion. Notably, the rate of post-dilatation in the CoreValve group (28%) was comparable to those in other studies using the same prosthesis (Adams et al., 2014, Gooley et al., 2015).

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 (Meredith et al., 2014) and REPRISE II (Meredith Am et al., 2014), both of which used echocardiography for surveillance. However, over the same time period, we observed a reduction in quantity of AR following CoreValve, and this is consistent with findings reported in a randomised trial (Adams et al., 2014) and from a large multicentre registry which showed no further deterioration (Tamburino et al., 2011). Furthermore, a recent observation from the multicentre CoreValve US pivotal trial indicated over 80% of patients exhibited an improvement of at least 1 grade of regurgitation at 1 year, again based on echocardiography (Oh et al., 2015). A recent CMR study did suggest a slight increase in AR at 6 months post-TAVI; however this study combined measurements of the CoreValve with those of another TAVI design (Merten et al., 2013). Our observation of further reduction in AR at 6 months may reflect positive geometric annular remodelling (Lerakis et al., 2013), further outward expansion of the bulky CoreValve frame (Oh et al., 2015), or occlusion of residual defects over time by fibrous tissue, similar to that described from another TAVI design (Bauer et al., 2010, Ewe et al., 2015).

The aortic regurgitation index is a dimensionless measure of haemodynamics following TAVI which has shown an inverse correlation with the severity of paravalvular AR. A value ≤ 25 independently predicts 1-year mortality (Sinning et al., 2012). To our knowledge, this is the first study to confirm negative correlation between the invasive AR index and aortic RF measured non-invasively by CMR. Furthermore, in patients with an AR index ≤ 25, the LV mass:volume ratio remained unchanged at 6 months with significantly less LV mass regression compared to those with a higher AR index post-TAVI. A prior CMR study suggested LV mass remained unchanged at 6 months in patients with greater than mild AR following TAVI (Merten et al., 2013) in keeping with our results. Our observation is important given geometric remodelling is associated with heart failure and all-cause mortality (Gaasch and Zile, 2011). It is noteworthy that the degree of LV mass regression, and concomitant recovery of diastolic function after surgical and transcatheter aortic valve replacement, is a positive prognostic indicator (Ali et al., 2011, Rader et al., 2015), whereas residual hypertrophy after aortic valve replacement is thought to be detrimental (Beach et al., 2014). Our CMR study therefore corroborates and may explain the worse outcomes previously described in patients with lower AR index post-TAVI.
Immediately post-TAVI, we observed a lower residual aortic pressure gradient following CoreValve implantation, which was associated with a mean reduction in LV mass of 10 grams/m². In contrast, with the Lotus valve there was a mean residual gradient 10mmHg higher, and no significant LV mass regression was noted. Whilst this may reflect the significantly higher proportion of smaller sized Lotus valves being implanted in our study, our reported values are comparable to those reported in REPRISE II at discharge and 30 days (Meredith Am et al., 2014). Similarly, our CMR measures of residual pressure gradient post-CoreValve implantation are consistent with echocardiographic data from prior studies at comparable time points (Spethmann et al., 2012, Gooley et al., 2015, Linke et al., 2014). These findings may have clinical implications given that early LV mass regression following TAVI is associated with improved diastolic function (Vizzardi et al., 2012), lower B-type Natriuretic Peptide levels and reduced readmission to hospital for heart failure (Lindman et al., 2014). Therefore whilst compared to CoreValve, less immediate aortic regurgitation occurs following Lotus valve implantation, a higher residual valve gradient and the absence of immediate LV mass regression may be a disadvantage. Further work to validate these findings and directly compare the clinical course following these two TAVI designs is thus required.

6.5.1 Clinical Implications
The evidence base for TAVI implantation is extensive. The potential application in lower-risk patients underscores the drive for further improvements in TAVI design to reduce complications, with the need to demonstrate prosthesis durability being crucial. It is noteworthy that despite superior success according to the VARC criteria for device deployment with the Lotus valve, we found comparable haemodynamics and equivalent LV reverse remodelling at 6 months following implantation of both prosthesis designs. This is consistent with published studies with longer follow-up that have demonstrated excellent outcomes with both TAVI designs (Reardon et al., 2015, Meredith et al., 2014).

6.5.2 Limitations
This was a small single-centre non-randomised comparison. Only patients clinically stable enough to participate in the CMR study were included and thus those with more severe AR or impaired LV function may have been excluded. Not all patients were able to complete the 6 month scan, predominantly due to pacemaker implantation or death which may have introduced bias; although the final analysed population was not different to the recruited population in terms of demographics and comorbidities.
VARC-2 criteria includes a measure of Patient-Prosthesis Mismatch; defined as absent when the TAVI effective regurgitant orifice area (EOA) is >0.85 cm$^2$/m$^2$ (Kappetein et al., 2013). We have assessed TAVI performance by VARC criteria (Leon et al., 2011) as our CMR protocol did not include imaging from which TAVI EOA could be ascertained. The VARC criteria are nonetheless an accepted end point, forming the basis of a recent randomised clinical trial directly comparing two different TAVI systems (Abdel-Wahab et al., 2014).

We used CMR to quantify the total AR seen following TAVI, which is a composite of paravalvular and transvalvular regurgitation. Total aortic regurgitation following TAVI has been demonstrated as an important marker of mortality (Costopoulos et al., 2013) and central transvalvular regurgitation is usually minor and a physiological feature by virtue of prosthesis design (Lerakis et al., 2013). Furthermore, VARC-2 criteria advocate a combined measurement of “total” aortic regurgitation (AR) reflecting the total regurgitant volume load imposed on the LV (Kappetein et al., 2013).

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 TAVI (Salaun et al., 2015, Sherif et al., 2011).

6.6 Conclusions
A significantly lower quantity of aortic regurgitation but higher residual peak pressure gradient was seen immediately following Boston Lotus TAVI compared to Medtronic CoreValve implantation. However, by 6 months TAVI haemodynamics were comparable and there were similar degrees of LV reverse remodelling seen with both valve designs.
7. Final Conclusions

Aortic stenosis is the commonest valvular lesion in the elderly with a prevalence of around 5% in those over 75 years. This is anticipated to rise sharply over the next few decades given an aging population. For the vast majority the disease remains latent, but the onset of symptoms heralds a sinister natural history with a 50% mortality rate at 2 years without intervention.

SAVR has been practised widely for over 50 years with developments in valve technology and surgical techniques underscoring the excellent outcomes of modern day. However, the elderly still face a mortality risk of 20% at 1 year and thus a notable proportion are deemed prohibitively high-risk and managed conservatively (Ruparelia and Prendergast, 2015). The advent of TAVI signalled a global shift in approach towards such patients. TAVI has demonstrated clinical superiority over medical therapy with results comparable to SAVR in those at high-risk. The recently published results from the PARTNER 2 trial have indicated TAVI is non-inferior to SAVR with respect to outcomes at 2 years in intermediate-risk patients (Leon et al., 2016). Furthermore, shorter hospital stay, lower bleeding rates and dysrhythmia were notable findings, particularly given the TAVI-arm of the trial employed a now outdated device. The ongoing UK TAVI and SURTAVI trials are also designed to address the role of TAVI in intermediate risk patients who are typically younger. Further studies are addressing “off-label” indications for TAVI, including its use for AR, bicuspid valves and the treatment of failing surgical bioprostheses (termed “valve-in-valve” procedures).

A key recommendation to both European and US guidance is that each individual patient should be discussed within a multidisciplinary “Heart Team” to address comprehensively patient, procedural and risk factors pertaining to SAVR and TAVI. This typically comprises interventional cardiologists, imaging cardiologists, cardiac anaesthetists, cardiothoracic surgeons and general physicians. This “Heart Team” needs to appreciate the intense focus on the comparative benefits of SAVR and TAVI and tailor a decision on a case by case basis.

Evidence that can guide patient selection and thus clinical practise is fundamental to characterising the precise role of TAVI and SAVR in treating the growing problem of symptomatic severe aortic stenosis. This thesis advances the comparative effects of SAVR and TAVI by contributing original evidence regarding the impact of each intervention upon cardiovascular function, assessed using CMR.

The elasticity of the aorta is important to the regulation of coronary blood flow, left ventricular function and the compliance of the entire cardiovascular network. This elasticity is sensitive to
any factors that can induce histological or functional change in the aortic wall. Importantly, arterial stiffness is an independent predictor of cardiovascular risk and mortality in a range of conditions, and much work has been directed to modalities of measurement and formulation of reference ranges to bring this powerful tool into clinical use (2010). There are two principal measures of aortic stiffness; the regional pulse wave velocity which is the velocity at which a pressure wave propagates down a vessel, and the local distensibility which is the ability of the aorta to expand during systole. There is a strong negative linear relationship between the two measures, both of which can accurately and reproducibly made using CMR.

The impact of TAVI and SAVR on aortic pressure gradient and LV performance is well documented. However, there has only been limited work assessing aortic stiffness following intervention for severe aortic stenosis. These studies have exclusively used echocardiography to measure AD and focused on one intervention type. Our work is the first to use CMR specifically to analyse simultaneously PWV and AD in a direct comparison between SAVR and TAVI. We have demonstrated SAVR but not TAVI is associated with an increase in aortic stiffness from baseline at 6 months following intervention. TAVI and SAVR are fundamentally different techniques; in particular SAVR disrupts vasa vasorum flow and traumatises aortic wall integrity whereas TAVI does not. Animal studies have indicated that ischaemic insult to the aortic wall results in histological change and increased stiffness and this is the likely explanation of our findings. We were unable to demonstrate any association between any variables of cardiothoracic surgery and the decline in measures of aortic stiffness, but interestingly our findings do suggest the entire thoracic aorta is affected following SAVR rather than just the focal point of clamp contact and surgical incision.

Given the prognostic importance of aortic vascular function our work raises important issues. Impairment of aortic elasticity is accompanied by an increase in risk of future cardiovascular events. In meta-analysis, an increase in PWV by 1 m/s corresponded to a 15% increase in all-cause mortality (Vlachopoulos et al., 2010). Similarly, in a healthy population, a decrease in aortic distensibility was associated with an increase in cardiac death and non-fatal cardiac events by hazard ratios of 1.49 and 1.69 respectively (Maroules et al., 2014). Our comparison therefore raises the possibility TAVI confers a MACE advantage over SAVR. This is perhaps partly reflected by the favourable results for TAVI in high-risk patients from trial data. In addition, our findings support the avoidance of aortic trauma wherever possible and suggest that a direct-aortic TAVI approach would be more detrimental to aortic vascular function that the traditional femoral artery route.
Right ventricular function is a major contributor to exercise capacity, holds prognostic importance in a range of cardiac conditions and RV failure is an important determinant of survival following cardiac surgery (Wenaweser and O’Sullivan, 2012). Previous reports using echocardiography have described deterioration in RV function following SAVR but the mechanisms for this have been poorly defined. Despite this however, pre-operative risk scoring tools do not yet comprise an assessment of RV function. The evaluation of RV performance is challenging given its asymmetric and variable shape, thin free wall, predominant longitudinal systolic motion and location behind the sternum. SSFP CMR is the gold standard modality to quantify RV dimensions and function; it is reproducible, offers excellent blood-tissue contrast and can image in any plane. The findings of this thesis are the first that are statistically powered, using CMR, to directly compare the effects of SAVR and TAVI upon RV volumes and function.

At baseline, our two groups both had preserved RV systolic function. At 6 months a key finding was that SAVR had a significant detrimental impact on RV systolic volume, ejection fraction and systolic longitudinal motion (TAPSE) associated with longer surgical cross-clamp times, whereas TAVI had no such impact on any RV functional indices. These findings raise some pertinent issues. Firstly, it does seem sensible that consideration of RV function should be given by the Heart Team MDT when deciding upon an intervention in high-risk patients. Secondly, given the deterioration in RV performance 6 months following SAVR, patients with pre-existing RV dysfunction and symptomatic severe AS are likely to derive better clinical outcomes with TAVI, although this remains to be proven. Furthermore, the reported increase in end-systolic volume following SAVR was associated with longer cross-clamp time, and unlikely to be related to left heart function or suboptimal protection during cardiopulmonary bypass. Thus, attempts to minimise cross-clamp duration may help optimise post-operative recovery, perhaps by minimising changes in pulmonary vascular physiology.

Degenerative aortic stenosis exerts a chronic pressure overload upon the LV with elevated end-diastolic pressures. This results in LV hypertrophy to compensate for increased wall stress as per Laplace’s law. There follows the potential for subendocardial ischaemia that can impair systolic and diastolic function, even when epicardial coronary vessels are normal. Myocardial fibre length changes in the longitudinal, circumferential and radial directions throughout the cardiac cycle and each of these changes can be quantified independently using CMR strain measurements. Myocardial tissue tagging acquisition is the principal technique employed for this purpose. We have used this techniques in this thesis to determine whether circumferential strain measurements can predict outcomes following SAVR and TAVI.
Chapter 5 of this thesis indicates circumferential strain is associated with survival following valve replacement for severe AS. In particular, those with a pre-operative mid-LV circumferential strain >-18.7% are at higher risk of mortality, even when index aortic stenosis has been relieved with SAVR and TAVI, independent of age, LVEF and surgical risk score. CMR strain imaging is hence an advanced technique that may afford crucial insight into the progression of aortic valve disease and prognosis. It is recognised that reduced LVEF signals a poorer outcome even after intervention (Vaquette et al., 2005) but this is a late change in the disease process. Our findings implicate circumferential strain as a marker of LV decompensation and survival even when ejection fraction is preserved and thus may have important implications again for patient assessment prior to consideration of treatment. Our work advocates the use of CMR strain imaging for a more comprehensive examination of LV performance in patients with severe symptomatic AS, and further work is needed to confirm whether intervening “early” with SAVR or TAVI, based on a measurement circumferential strain, can improve clinical outcomes.

Paravalvular aortic regurgitation following TAVI has been a subject of intense scrutiny and study in recent years. SAVR involves complete excision of calcified aortic valve leaflets. This does not occur during TAVI, with the inherent possibility of paravalvular aortic regurgitation from incomplete sealing between native annular calcification and the TAVI prosthesis. Even mild regurgitation is often poorly tolerated following SAVR. It is however a common finding following TAVI being present in up to 61% of patients (Hamm et al., 2016). Both registry and clinical trial data have consistently indicated moderate and severe paravalvular regurgitation following TAVI is an independent predictor of early and late survival. This is reflection of the poor haemodynamic tolerance of a hypertrophied stiff left ventricle with impaired diastolic function to the volume burden of AR and ensuing increase in end-diastolic pressure. The assessment of regurgitation following TAVI is challenging using conventional 2D echocardiography; but nonetheless is a crucial clinical consideration and part of the VARC recommendations for measuring device success. The overall incidence of moderate and severe regurgitation has been decreasing of recent. This is in part due to improved delivery devices that allow repositioning and optimal deployment of novel TAVI designs with specific features to reduce AR.

The use of CMR following TAVI and SAVR to assess both valve and ventricular function has been validated (Crouch et al., 2015a) and has proven superiority over echocardiography. We used CMR to compare the internationally established self-expanding Medtronic CoreValve with a novel TAVI iteration; the mechanically expanded Boston Lotus valve, both acutely following implantation and then at 6 months. The Boston Lotus valve is repositionable and can avoid the
need for rapid pacing during deployment, with an adaptive seal designed specifically to minimise aortic regurgitation. The results presented in this thesis indicate that significantly less aortic regurgitation, and thus a higher device success by VARC criteria, is seen immediately following implantation of Lotus compared to CoreValve. This is however at the expense of a higher pressure gradient and lack of early LV mass regression. At 6 months follow-up, comparable degrees of LV reverse remodelling was observed with comparable valvular function. The use of CMR in this thesis for such a comparison is unique and informative given it is the reference modality for quantifying ventricular volumes, mass and function, and outperforms echocardiography in the assessment of AR following TAVI. Invasive measurement of AR using the AR index at TAVI implant has been shown to predict mortality; with an index value of 25 being the optimal threshold. We have uniquely shown in this thesis that there is significantly more mass regression in those patients with higher AR index than those less than 25. Our work indicates Lotus procedural success is higher than that of CoreValve but procedural success does not necessarily herald clinical success. The purpose of novel TAVI devices is to afford patients superior health related outcomes and quality of life and it is interesting that at 6 months, the two studied valve types were comparable. The active REPRISE III trial aims to recruit 1,000 patients form over 60 centres to define whether CoreValve or Lotus offers an all-cause mortality advantage. Our findings indicate comparable degrees of cardiac response to TAVI by 6 months and thus we might expect no survival benefit to be demonstrated at the one year follow-up.

7.1 Future Directions
The first TAVI implantation was performed by Cribier in 2002 and in the last decade the procedure has evolved on a global scale to become a standard credible therapeutic option deliverable under only moderate sedation. The fact that over 200,000 procedures have been performed worldwide corroborates its success and acceptance. However, it was 1960 when Harken reported the first SAVR and this remains the gold standard treatment in patients at low or intermediate risk given its proven safety and efficacy over 50 years of clinical practise.

Two contemporary randomised controlled trials will help shape the future indication of TAVI, both with a primary composite end-point of all-cause mortality and disabling stroke at 2 years post-TAVI randomised against SAVR. The SURTAVI (Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) trial is designed to investigate the safety and efficacy of TAVI in intermediate surgical risk (defined as an STS score 4-10% inclusive) with patients being randomised to either SURTAVI or the Medtronic CoreValve. SURTAVI aims to recruit 2500 patients from across 75 global sites with a minimum follow-up of
The recently published PARTNER 2 Trial (Placement of AoRTic TraNscathetER Valves) enrolled 2,032 intermediate-risk patients (STS 4-8%). TAVI was found to be non-inferior to SAVR with respect to outcomes at 2 years, with lower bioprosthetic-valve gradients, risk of bleeding and shorter length of hospital stay (Leon et al., 2016). Whilst the evidence to support the use of TAVI in younger patients gains prominence, the long-term assessment of TAVI durability and performance (i.e. out to 10 years following implantation) remains to be defined.

There is thus an intense international focus on the comparison between TAVI and SAVR. This thesis, using CMR specifically to evaluate the impact of these two therapeutic options upon cardiovascular function, sheds important light on the subject. There are still however distinct areas in which CMR can be used to shape the ongoing debate.

7.1.1 Cerebral Embolism associated with novel TAVI delivery systems
TAVI has historically raised concerns with an increased risk of cerebrovascular events, typically due to embolism intra-operatively or within the first 24 hours. Cerebral MRI has been used to detect new ischaemic lesions following TAVI with between 68-84% of patients being reportedly affected (Hamm et al., 2016). In the PARTNER trial, a significantly higher rate of stroke was observed at 30 days and 1 year following TAVI compared to SAVR. Interestingly, a recent MRI study, confirming cerebral microinfarctions are more common after TAVI compared with SAVR, indicated there were no negative effects on early (30 days) or medium term (6 months) health-related quality of life. Aortic atheroma (TAVI) and concomitant coronary artery bypass grafting (SAVR) are independent risk factors for cerebral microinfarction (Uddin et al., 2015). Valve repositioning and post-TAVI dilatation are associated with higher rates of early stroke post-TAVI and thus embolic protection devices, designed to protect the cerebral circulation from procedural debris, are currently being trialled.

The Boston Lotus valve is a novel valve that is repositionable and delivered via a large 18F sheath. We are currently comparing, using cerebral diffusion-weighted MRI and formal neurocognitive assessments at VARC recommended time-points, the impact of the Lotus and CoreValve TAVI procedures. As further iterations of TAVI technology continue to emerge, such a study is crucial; particularly given their potential extension to increasingly younger candidates.

7.1.2 Balloon Aortic Valvuloplasty
Prior to the emergence of TAVI, balloon aortic valvuloplasty was offered as an alternative to SAVR in those deemed inoperable; accounting for up to 30% of patients in some reports (Costopoulos et al., 2015). Balloon valvuloplasty is associated with a notable increase in AVA
and reduction in pressure gradients immediately following the procedure. Accordingly, current European guidance advocates the use of balloon therapy as a bridge to definitive treatment; whether it be SAVR or TAVI as appropriate, or in patients who require urgent non-cardiac surgery (class IIb, level of evidence C) (Joint Task Force on the Management of Valvular Heart Disease of the European Society of et al., 2012). Reported success rates for bridging from balloon aortic valvuloplasty to definitive treatments varies between 26-74%, with SAVR or TAVI occurring within a median time of 8 weeks to 7 months (Nwaejike et al., 2015).

The incidence of balloon valvuloplasty is increasing given its inherent association with the TAVI procedure, being used both as a pre- and post-dilatation tool to optimise TAVI deployment. However, there is an inherent risk of valve material embolization and residual aortic regurgitation that is poorly tolerated by a typically stiff ventricle with impaired relaxation. We have been studying the impact of balloon valvuloplasty specifically using MRI; with an assessment of cerebral sequelae using diffusion-weighted MRI and neurocognitive assessment, and of cardiac function using CMR to assess valve performance and LV mass and volumes. We aim to compare three groups; those receiving balloon valvuloplasty alone, those with TAVI and associated valvuloplasty as part of the implantation procedure, and those receiving direct TAVI without any valvuloplasty. This will help characterise the neurological safety profile of the three approaches and clarify whether balloon inflatable or valve deployment is more associated with embolism. Furthermore, it will allow an assessment of reverse remodelling following ballooning which will be noteworthy; particularly as drug-coated balloons become more readily available. Balloon valvuloplasty will continue to be an important tool in the future, and such work is thus noteworthy, particularly as interventional therapy extends towards younger populations.

7.1.3 The British Society of Cardiovascular Magnetic Resonance “AS700 study”
CMR offers a unique insight into myocardial tissue characterisation and is gold-standard for the assessment of ventricular volumes, mass and function. A number of smaller studies have examined the importance of LV ejection fraction, mass, myocardial fibrosis and left atrial size in predicting outcomes following TAVI and SAVR. Studies using CMR to predict mortality in severe AS and in response to AVR are few and in the response to TAVI completely lacking. Currently a large multicentre observational study (comprising groups from Edinburgh, Leeds, Leicester, London and Oxford) is under way with the intention of amassing a cohort of patients, all of whom have had CMR prior to receiving SAVR or TAVI for severe AS. The intended period of follow-up is a minimum of 2 years. Such a study is designed to categorically identify specific CMR-derived factors that hold prognostic significance, over and above standard surgical risk models, in patients with severe AS undergoing intervention.
7.1.4 New Valves

There has been, and continues to be an impressive emergence of TAVI iterations since the first in human implantation by Cribier in 2002 (Figure 7.1). A number of vendors have released new (or 2nd generation) products specifically designed to avoid paravalvular leakage, access related complication, stroke and improve durability (Blumenstein et al., 2013). Some devices such as the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) are balloon expandable, with cobalt-chromium stent and thinner struts reducing valve profile and permitting narrower sheath delivery whilst still providing the required radial force when deployed. Others, such as the Medtronic Engager (Medtronic Inc., Minneapolis, MN, USA) comprise a self-expanding nitinol stent with a main frame and support frame mounted together, offering a “predefined” prosthesis suitable to individual patient anatomy. The St. Jude Portico prosthesis (St. Jude Medical, CA, USA) consists of a bovine and porcine pericardial tissue, again mounted on a nitinol stent that is self-expanding. This design holds valve leaflets low in the stent frame with clearance of coronary ostia and is thus intended reduce atrio-ventricular block. The proximal stent also comprises a tissue cuff designed to preclude para-valvular regurgitation. Each of these valves are currently being studied in clinical trials to assess efficacy and complication rates.

Figure 7.1 New (second) generation TAVI designs currently being trialled

A. Edwards SAPIEN XT™.
B. Medtronic Engager™.
C. St. Jude Portico™ prosthesis.

CMR offers a comprehensive assessment of TAVI function, able to accurately quantify valvular function, regurgitation, reverse remodelling, regression of fibrosis and the detection of myocardial injury post procedure, and is thus the ideal imaging modality to compare and contrast in detail such emerging technologies.
7.1.5 CMR guided TAVI

Traditionally, the imaging modalities used in the TAVI procedure involve MDCT for annular sizing prior to, and X-ray fluoroscopy, angiography and TOE during the procedure. Imaging is fundamental to optimal valve positioning across the native aortic valve annulus and to making an assessment of TAVI function and potentially life-threatening complications. This affords only limited soft-tissue contrast and carries inherent radiation exposure, the need for rapid ventricular pacing and nephrotoxic contrast media. Pilot in vivo work has emerged to support the use of real-time CMR to guide the TAVI procedure (Kahlert et al., 2012). Real-time CMR offers real-time image acquisition without any restriction in scan plane to optimise pinpoint axial alignment and TAVI deployment. CMR permits excellent soft-tissue contrast without the need for any contrast and thus may hold a survival advantage in the elderly by obviating the risk of acute kidney injury following TAVI. Recent work in swine has confirmed the deployment of the Medtronic CoreValve via a subclavian approach using a minimally modified delivery system guided by real-time CMR is feasible (Miller et al., 2015). Further work will be needed to determine whether the potential inherent to CMR can be realised, making it a single comprehensive imaging tool to assess anatomy pre-intervention, guide the TAVI procedure, and assess valvular function and any complications post-operatively.
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9. Appendices

9.1 Ethical Approval

Leeds (West) Research Ethics Committee
A/B Floor, Old Site
Leeds General Infirmary
Great George Street
Leeds
LS1 3EX

Telephone: 0113 2065637
Facsimile: 0113 2066772

08 October 2008

Dr John P Greenwood
Senior Lecturer & Consultant Cardiologist
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Full title of study: MRI evaluation of Percutaneous and Surgical Aortic Valve Replacement
REC reference number: 08/H1307/106

Thank you for your letter of 25 September 2008, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by Mr Bush.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites (“R&D approval”) should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

147
The final list of documents reviewed and approved by the Committee is as follows:

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H1307/106 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely
Mr Jon Silcock
Chair

Email: Elaine.hazell@leedsth.nhs.uk

Enclosures:
“After ethical review – guidance for researchers”
Site approval form

Copy to:
Ms Clare Skinner
R&D, LTHT
9.2 Substantial Amendment (addition of immediate post-procedure CMR scan)

19 December 2012

Dr John P Greenwood
Senior Lecturer & Consultant Cardiologist
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study title: MRI Evaluation of Transcatheter and Surgical Aortic Valve Implantation.
REC reference: 08/H1307/106
Amendment number: Four.
Amendment date: 30 November 2012
IRAS project ID: 6033

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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Membership of the Committee
The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

Yours sincerely

Dr Rhona Bratt
Chair

E-mail: markneal@nhs.net

Enclosures:

List of names and professions of members who took part in the review

Copy to:

Ms Anne Bowing, Leeds Teaching Hospitals NHS Trust
Ms Clare Skinner

NRES Committee Yorkshire & The Humber - Leeds West

Attendance at Sub-Committee of the REC meeting on 18 December 2012

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</tr>
<tr>
<td>Mr Marc Neal</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Dr Vera Neumann</td>
<td>Consultant in Rehabilitation Medicine</td>
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9.3 Substantial Amendment (extension to recruitment)

Health Research Authority
NRES Committee Yorkshire & The Humber - Leeds West
Room 001, Jarrow Business Centre
Rope Mill Road
Jarrow
Tyne and Wear
NE32 3DT
Tel: 0101 4203548

18 March 2015
Ms Petra Bijnerveld
Senior Research Nurse & MRI MRF manager
Cardiovascular Imaging
LICAMM
University of Leeds
Leeds Teaching Hospitals NHS Trust
Dear Dr Bijnerveld

Study title: MRI Evaluation of Transcatheter and Surgical Aortic Valve Implantation.
REC reference: 08/H1307/106
EudraCT number: N/A
Amendment number: 5
Amendment date: 17 February 2015
IRAS project ID: 6033

The above amendment was reviewed by the Sub-Committee in correspondence.

Summary of Amendment

The applicants seek approval for an increase in the number of participants to be recruited for this study, and for an extension of the recruitment period to September 2016. This long running study requires a large number of participants in relation to the number of completed datasets. This is due to the study population being elderly with many comorbidities, leading to a high dropout rate. The applicants have obtained some further funding to complement the BHF programme grant and wish to continue recruitment as the applicants have not yet obtained the 60 complete datasets required.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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<tr>
<td>Notice of Substantial Amendment (non-CTIMF)</td>
<td>5</td>
<td>17 February 2015</td>
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<tr>
<td>Research protocol or project proposal</td>
<td>1.5</td>
<td>17 February 2015</td>
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Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R&D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

08/H1307/105: Please quote this number on all correspondence

Yours sincerely

[Signature]

Dr Vera Neumann
Chair

E-mail: nrescommittee.yorkandhumber-leedswest@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Anne Gowing, Leeds Teaching Hospitals NHS Trust

Dr John P Greenwood, University of Leeds

NRES Committee Yorkshire & The Humber - Leeds West

Attendance at Sub-Committee of the REC meeting in correspondence

Committee Members:

<table>
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<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Ms Danni Collingridge Moore</td>
<td>Research Fellow</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Dr Vera Neumann (chair)</td>
<td>Consultant in Rehabilitation Medicine</td>
<td>Yes</td>
<td></td>
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Also in attendance:

<table>
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<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
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<tr>
<td>Miss Christie Ord</td>
<td>REC Assistant</td>
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9.4 Patient Invitation

An information sheet is enclosed which tells you all about a heart research study we are running at this hospital. It is called MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation.

Please read the information sheet carefully and if you are interested in finding out more about the study before your planned admission to hospital then please return the reply slip to us using the prepaid envelope.

You may phone us so that the research team can explain the study to you further and answer any questions you may have. The numbers you can ring are 0113 39 25909 (Dr Tarique Al Musa) or 07733 424 528 (Fiona Richards). Alternatively, once you are admitted to hospital for your valve replacement you will have an opportunity to discuss the study with one of the researchers.

Please note that you are under no obligation to take part and it will not affect your treatment if you decide not to. However we would very much appreciate it if you would let us know. We can reimburse any travelling expenses you incur as part of this study and arrange transport as needed. Potentially it would only involve one extra visit to the LGI approximately 6 months after your TAVI procedure.

Thank you for considering this request.

Yours sincerely

Professor JP Greenwood
Consultant Cardiologist
Cardiovascular and Diabetes Research
Leeds General Infirmary
Leeds
LS1 3EX
9.5 Patient information Leaflet

Leeds Institute of Cardiovascular and Metabolic Medicine
Division of Cardiovascular and Diabetes Research
Sunshine Corridor
Leeds General Infirmary
Great George Street
Leeds, LS1 3EX

UNIVERSITY OF LEEDS

MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation

Patient information Leaflet
Version 1.3 November 30 2012

Chief Investigator: Prof John Greenwood

Dear patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHY HAVE I BEEN CHOSEN?
This study is looking at people like you, who are scheduled by their consultant for replacement of their aortic valve. We are looking at two groups of patients in this study; patients who are going to have a surgical valve replacement (done by a heart surgeon), and patients who are going to have a transcatheter valve replacement, a procedure which replaces the valve without the need for surgery (done by a cardiologist). This second technique is newer and we still need to find out more about the long term results for patients.

How your valve is going to be replaced has been decided by your doctor and is based purely on your health and symptoms. This study is completely separate from the decision of how your valve is going to be replaced.

WHAT IS THE PURPOSE OF THE STUDY?
Patients have their aortic valve replaced because their own valve does not work properly, which causes problems with the function of the heart and with the circulation. After the valve has been replaced the heart function and the circulation will normally improve. In this study we want to compare that improvement in the two groups of patients.
We also like to study the blood vessels in the head. As your doctor will have told you one of the risks of valve replacement is small dots travelling from the heart to the head. It is important for us to find out how often this happens with surgery and with non-surgical replacement, and compare the results.

We want to use Magnetic Resonance Imaging (MRI) in this study to look at the head and the heart. MRI does not involve radiation and is therefore very safe. It gives us very good images of the blood vessels and can tell how well the heart is pumping.
DO I HAVE TO TAKE PART?
It is up to you to decide whether or not to take part. You do not have to decide straightaway; you may discuss the study further with a member of the research team over the telephone, or once you come into hospital. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. Information collected up to the point of your withdrawal may still be used. In the unlikely event of you losing capacity (being unable to make decisions for yourself) you will be withdrawn from the study by us, but information already collected will be kept and used for the purposes of the study.

WHAT WILL HAPPEN TO ME IF I TAKE PART?
All patients in this study will have MRI scans of their head and heart before and after the valve replacement procedure. Before the valve replacement, we will scan your head and heart during one visit to the MRI department; this visit can take place before your admission, or whilst you are already an in-patient in the hospital. This scan will take approximately 60 minutes to complete. After the valve replacement, and before you go home, if you have had a surgical valve replacement (AVR) we will scan your head only, which takes about 10 minutes. If you have had a transcatheter replacement (TAVI), we would like to scan your head (10 minutes) and do a shortened version of the heart scan (15 minutes). Approximately 4-6 months later we will ask you to return to the MRI department so we can scan you heart and your head, which takes about 60 minutes.

The reason why we want to do this scan later is that your heart’s function may continue to improve for some time after the valve replacement. During each scan you lie in a short ‘tunnel’, which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodic loud “banging” noises while we are acquiring the images. We will remain in communication with you throughout the scan. If you have normal kidney function then once during each heart scan, we will inject an MRI contrast medication into a vein in your arm. The needle used for this will feel like a sharp scratch. Usually people are not aware of the contrast dye injection. Should your kidneys be impaired then the injection will not be given.

As part of the study we will ask you to fill out 2 questionnaires which will ask questions about how you feel the quality of your life is. A member of the research team can help you with this if you need assistance. We will ask you to complete these again after 1 month, 6 months, and 1 year. At the same time points we will also ask you to do a number of tests which look at memory and other functions of the brain. These tests will take about an hour on each occasion. If you feel too tired or unwell to come to the hospital we may ask if we can visit you in your own home to do these tests.

WHAT ARE THE RISKS AND DISCOMFORTS?
Magnetic Resonance Imaging (MRI) is safe and no X-rays or radiation are used for this scan. There are no known risks from this technique. Some patients may experience claustrophobia. The staff will provide every possible means to reduce this sensation. The scan will be stopped immediately if you do not wish to carry on with it. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is
equipped to cope with allergic reactions if they happen and medical staff will be on hand to deal with any unforeseen circumstances or problems.

**BENEFITS TO YOU**
There are no particular benefits to you from taking part in this study.

**EXPENSES**
We are able to meet reasonable expenses for costs of travel to and from the hospital for the scans and tests after you have left hospital. Alternatively we can arrange transport by pre-paid taxi for you.

**WILL MY TAKING PART BE KEPT CONFIDENTIAL?**
All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research. All data will be anonymised so that your identity will not be revealed to anybody outside the Cardiac MRI Unit at Leeds General Infirmary.

With your permission, we will inform your General Practitioner (GP) of your participation in this study as well as in the event of an unexpected abnormality on the scan.

**WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?**
When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

**INDEMNITY/COMPENSATION**
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

If you have a private medical insurance please ensure that participation in the study does not affect your cover.

**WHO IS ORGANISING AND FUNDING THE STUDY?**
This is a research project of the Cardiac MRI department at Leeds General Infirmary.

**WHO HAS REVIEWED THE STUDY?**
The study has been reviewed and approved by the Leeds West Local Research Ethics Committee.

*For further information please contact:*

Drs TA Musa
Cardiac MRI Department,
B Floor, Clarendon Wing,
Leeds General Infirmary,
LS1 3EX

Ms Fiona Richards / Ms Petra Bijsterveld
Cardiovascular Research
Leeds General Infirmary
LS1 3EX

Tel: 0113 392 5224 / 0113 392 5481
### 9.6 Consent Form

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<tr>
<th>Name of Researcher: Prof John Greenwood</th>
<th>Please initial box</th>
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1. I [ ] confirm that I have read and understood the information sheet (version 1.3 November 30 2012) for the above study and have had the opportunity to ask questions.

2. I understand that sections of any of my medical notes may be looked at by members of the research team and authorised personnel within the Leeds Teaching Hospitals NHS Trust and the University of Leeds, where it is relevant to the research or to assess that appropriate research standards are being maintained within the study. I give permission for these individuals to have access to my records. I understand that the information about me will be held in the strictest confidence and that my results will not be available to a third party.

3. I give my consent for my General Practitioner to be informed of my participation in the study.

4. I understand that images collected will be stored on a computer system, and, after my name and address have been removed, may be available to researchers at other institutions.

5. I understand that my participation is voluntary; and that I am free to withdraw at anytime, without giving any reason, without my medical care or legal rights being affected.

6. I agree to take part in the study and that the general results of the study will be made available to medical community most likely through publication in a reputable medical journal.
7. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study.

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Signature..............................................................

Name (block capitals)........................................Date.........................................

Signature of witness............................................

Name (block capitals)........................................Date.........................................