Cardiovascular magnetic resonance imaging in severe aortic stenosis: impact of surgical and trans-catheter aortic valve replacement on reverse remodelling and fibrosis

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Chapter 1

Publication: Sex differences in Aortic Stenosis and Outcome Following Surgical and Transcatheter Aortic Valve Replacement. Dobson LE, Fairbairn TA, Plein S, Greenwood JP. Journal of Women's' Health. 2015; 24(12):986-95.

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Chapter 5

Publication: Acute reverse remodelling following Trans-catheter Aortic Valve Implantation: a link between myocardial fibrosis and left ventricular mass regression. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Swoboda PP, Erhayiem, B, Foley J, Garg P, Haaf P, Fent GJ, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. Submitted to Canadian Journal of Cardiology. February 2016.

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Publications arising from this work

Papers

1. Sex differences in Aortic Stenosis and Outcome Following Surgical and Transcatheter Aortic Valve Replacement. Dobson LE, Fairbairn TA, Plein S, Greenwood JP. Journal of Women's' Health. 2015; 24(12):986-95.
2. Sex-related differences in left ventricular remodelling in severe aortic stenosis and reverse remodeling following aortic valve replacement; a cardiovascular magnetic resonance study. Dobson LE, Fairbairn TA, Musa TA, Uddin A, Mundie CA, Swoboda PP, Ripley DP, McDiarmid AK, Erhayiem B, Garg P, Malkin CJ, Blackman DJ, Sharples LD, Plein S, Greenwood JP. Am Heart J. 2016. DOI: http://dx.doi.org/10.1016/j.ahj.2016.02.010

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1. Post-procedural myocardial infarction following surgical and trans-catheter aortic valve replacement - insights from cardiovascular magnetic resonance imaging. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Swoboda PP, Erhayiem B, Ripley DP, McDiarmid AK, Garg P, Evans B, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. Submitted to Heart, April 2016.
2. Acute reverse remodelling following Trans-catheter Aortic Valve Implantation: a link between myocardial fibrosis and left ventricular mass regression. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Swoboda PP, Erhayiem, B, Foley J, Garg P, Haaf P, Fent GJ, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. Submitted to Canadian Journal of Cardiology. February 2016.
3. The impact of trans-catheter aortic valve replacement induced left-bundle branch block on cardiac reverse remodeling. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Bebb OJ, Swoboda PP, Haaf P, Foley J, Garg P, Fent GJ, Malkin C, Blackman DJ, Plein S, Greenwood JP.

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Letters

1. Aortic valve replacement and the right ventricle-the plot thickens. Dobson LE, Musa TA, Greenwood JP. J Thorac Cardiovasc Surg. 2015;150(3):742-3.

Abstracts

1. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Bebb OJ, Swoboda PP, Garg P, Fent GJ, Foley J, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. The impact of trans-catheter aortic valve induced left-bundle branch block on cardiac reverse remodelling. Accepted for presentation at EuroCMR, Florence, Italy, May 216.

2. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Bebb OJ, Swoboda PP, Garg P, Fent GJ, Foley J, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. The impact of new left bundle branch block following trans-catheter aortic valve implantation. Is there a TAVI LBBB-induced cardiomyopathy? Insights from cardiovascular Magnetic Resonance Imaging. Accepted for presentation at the British Cardiovascular Society Annual meeting, Manchester, UK, June 2016.

3. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Swoboda PP, Ripley DP, McDiarmid AK, Erhayiem B, Garg P, Evans B, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. Myocardial infarction following surgical and trans-catheter aortic valve replacement. Is peri-procedural revascularisation for TAVI necessary? Accepted for presentation at the British Cardiovascular Society Annual meeting 2016.

4. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Swoboda PP, Ripley DP, McDiarmid AK, Erhayiem B, Garg P, Evans B, Malkin CJ, Blackman DJ, Plein S, Greenwood JP. Post-procedural myocardial infarction following surgical and trans-catheter aortic valve replacement – mechanistic insights from cardiovascular magnetic resonance imaging. J Cardiovasc Magn Reson. 2016: 18 (Suppl 1).

5. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Blackman DJ, Ripley DP, Swoboda PP, Erhayiem B, McDiarmid AK, Garg P, Plein S, Greenwood JP. Left Ventricular Mass Regression Occurs very early following Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis. Heart 2015;101:Suppl 4 A54-A55.

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Contents

List of figures

List of tables

List of equations

Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
AHA	American Heart Association
AKI	Acute kidney injury
AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
AVAi	Indexed aortic valve area
AVR	Aortic valve replacement
BL	Boston Scientific Lotus
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance
DAPT	Dual anti-platelet treatment
ERs	Oestrogen receptors
EuroSCORE	European System for Cardiac Operative Risk
FOV	Field of view
GLS	Global longitudinal strain
ICC	Intra-class correlation

IQR	Interquartile range
LAD	Left anterior descending artery
LAVoli	Indexed left atrial volume
LBBB	Left bundle branch block
LBBB-T	TAVI-induced LBBB
LCx	Left circumflex artery
LGE	Late gadolinium enhancement
LIMA	Left internal mammary artery
LV	Left ventricle
LVEDP	Left ventricular end diastolic pressure
LVEDV	Left ventricular end diastolic volume
LVEDVi	Indexed left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESVi	Indexed left ventricular end systolic volume
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMi	Indexed left ventricular mass
LVOT	Left ventricular outflow tract
MAPSE	Mitral annular systolic plane excursion
MCV	Medtronic CoreValve
MF	Myocardial fibrosis
MI	Myocardial infarction
MOLLI	Modified look-locker inversion recovery
MPG	Mean pressure gradient

MR	Mitral regurgitation
NO	Nitric Oxide
nQRS	Narrow QRS
NYHA	New York Heart Association
OM	Obtuse marginal artery
PDA	Posterior descending artery
PPD	Peak pressure drop
PPM	Permanent pacemaker
RCA	Right coronary artery
RF	Radiofrequency
RFrac	Regurgitant fraction
ROI	Region of interest
SAVR	Surgical aortic valve replacement
SIRS	Systemic inflammatory response syndrome
SNR	Signal to noise ratio
SSFP	Steady-state free procession
STS	Society of Thoracic Surgeons
SVG	Saphenous vein graft
TAPSE	Tricuspid annular plane systolic excursion
TAVI	Trans-catheter aortic valve implantation
TE	Echo time
TI	Inversion time
TR	Repetition time
VARC	Valve Academic Research Consortium

VCG	Vectorcardiogram
VENC	Velocity encoding

Abstract

Introduction: Aortic stenosis (AS) is the commonest valvular lesion in the developed world and is associated with adverse cardiac remodelling. With its excellent accuracy and reproducibility, cardiovascular magnetic resonance (CMR) imaging is an ideal tool to assess cardiac remodelling and reverse remodelling following surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). The aims of this thesis were: 1) to evaluate gender differences in AS and following aortic valve replacement, 2) to evaluate the incidence of post-procedural myocardial infarction following SAVR and TAVI, 3) to describe the immediate effect of TAVI on reverse remodelling and 4) to assess the impact of TAVI-induced left bundle branch block (LBBB) .

Methods: Between January 2009 and April 2015, patients with severe AS undergoing either TAVI or SAVR were prospectively recruited. Patients underwent comprehensive 1.5T CMR evaluation pre-procedure, prior to hospital discharge and 6m post-procedure.

Results: 1) Women with severe AS have a lower indexed left ventricular (LV) mass than men (65.3± 18.4 vs. 81.5±21.3g/m^2, p<0.001). 6m following valve replacement, LV mass regression is similar between genders (men 21.7±10.1 vs. women 18.4±11.0%, p=0.121). 2) Myocardial infarction (MI) is more frequent following SAVR than TAVI (n=10 (26%) vs. n=3 (5%), p=0.004). 3) Over 10% of LV mass regression occurs prior to hospital discharge following TAVI and is more pronounced in the absence of myocardial fibrosis (p=0.005). 4) TAVI-induced LBBB is associated with a reduced LVEF 6m following TAVI compared with those with a narrow QRS (-2.1±6.9 vs. +4.6±7.8%, p=0.002).

Conclusions: TAVI and SAVR are associated with favourable cardiac reverse remodelling which does not differ according to gender and begins prior to hospital discharge. SAVR is associated with a higher incidence of post-procedural MI than TAVI. TAVI-induced LBBB should be avoided where possible due to its unfavourable effects on cardiac reverse remodelling.

Chapter 1: Introduction

1.1. Aortic stenosis

Aortic stenosis (AS) can be defined as obstruction to blood flow at the level of the aortic valve leading to an increase in left ventricular (LV) afterload. It is a progressive, degenerative condition whereby there is calcification and fibrosis of the aortic valve leaflets leading to reduced systolic leaflet excursion and narrowing of the valve orifice. The majority of patients presenting with AS have tri-leaflet valves with equal size and shape of each cusp, whereby there is an equal amount of shear stress distributed to each valve leaflet and the aorta, with blood flow directed centrally through the aortic valve (Figure 1-1). Calcific tri-leaflet AS was traditionally felt to be purely a degenerative phenomenon. However, there is an increasing body of evidence to suggest that the process has an inflammatory [1] and genetic component [2]. Congenitally abnormal valves (the most common being a bicuspid valve affecting around 1-2% of the population) are prone to premature degeneration due to unequal shear stresses on the leaflets. Patients with bicuspid aortic valves typically experience symptoms in their fifth and sixth decades of life with tri-leaflet valves degenerating in the eighth and ninth decades.

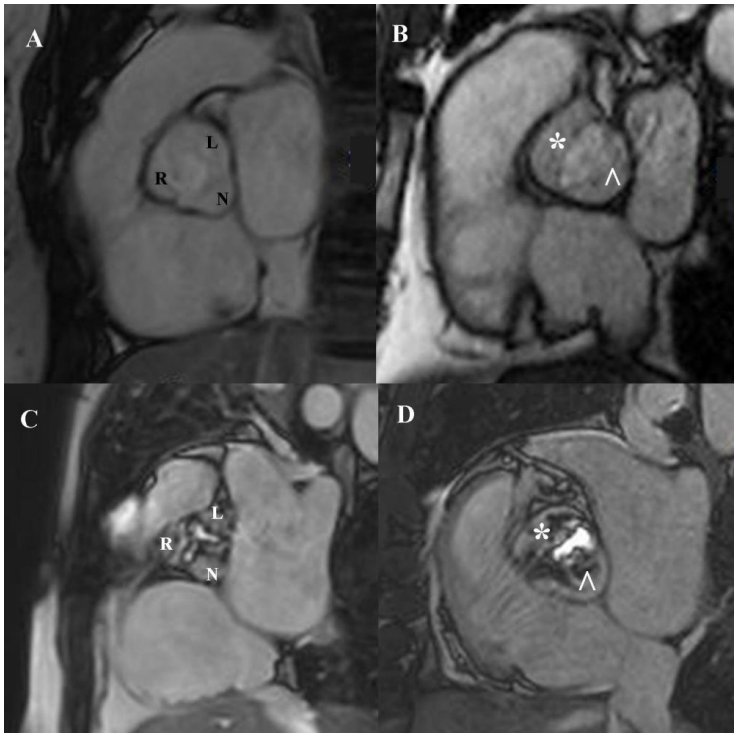

Figure 1-1 Aortic valve morphology

Panel A demonstrates a cardiovascular magnetic resonance steady state free precession image of a normal tri-leaflet aortic valve with unrestricted opening of the right coronary cusp (R), left coronary cusp (L) and non-coronary cusp (N) during ventricular systole. Panel B demonstrates a normally functioning bicuspid aortic valve with the anterior cusp (*) and posterior cusp (^) visible. Panel C demonstrates a heavily calcified tri-leaflet aortic valve with restriction of all three leaflets and a reduced valve orifice. Panel D demonstrates a severely stenosed bicuspid aortic valve.

Aortic stenosis is an increasingly common global problem due to an aging population. It affects around 5% of adults over the age of 75 in the United States [3], with more women than men affected due to their longer life span. It is the most common valvular disease of the developed world now that rheumatic fever has largely been abolished [4]. The onset of symptoms of severe AS heralds a dismal prognosis, with an expected 50% survival at 2 years [5, 6]. Mechanisms for death include sudden cardiac death

and more commonly progressive heart failure. Even those with severe asymptomatic AS are exposed to a 1% annual risk of sudden cardiac death [7], with a higher risk of adverse events seen in those with elevated LV mass [8].

1.1.1. Left ventricular response to AS

Left ventricular hypertrophy is almost ubiquitous in severe aortic stenosis, reflecting myocardial adaptation to chronic elevation of afterload and allowing normalisation of wall stress [9, 10]. At a cellular level, there is an increase in the number of sarcomeres and an increase in myocyte size. Initially the LV adapts to the increase in wall stress by increasing the size of myocytes allowing maintenance of ejection fraction but eventually progressive LV dysfunction occurs, initially affecting diastolic and then systolic function (Figure 1-2). Patterns of hypertrophy can be concentric, eccentric or asymmetric and the degree of hypertrophy seen does not appear to correlate with the severity of AS [11].

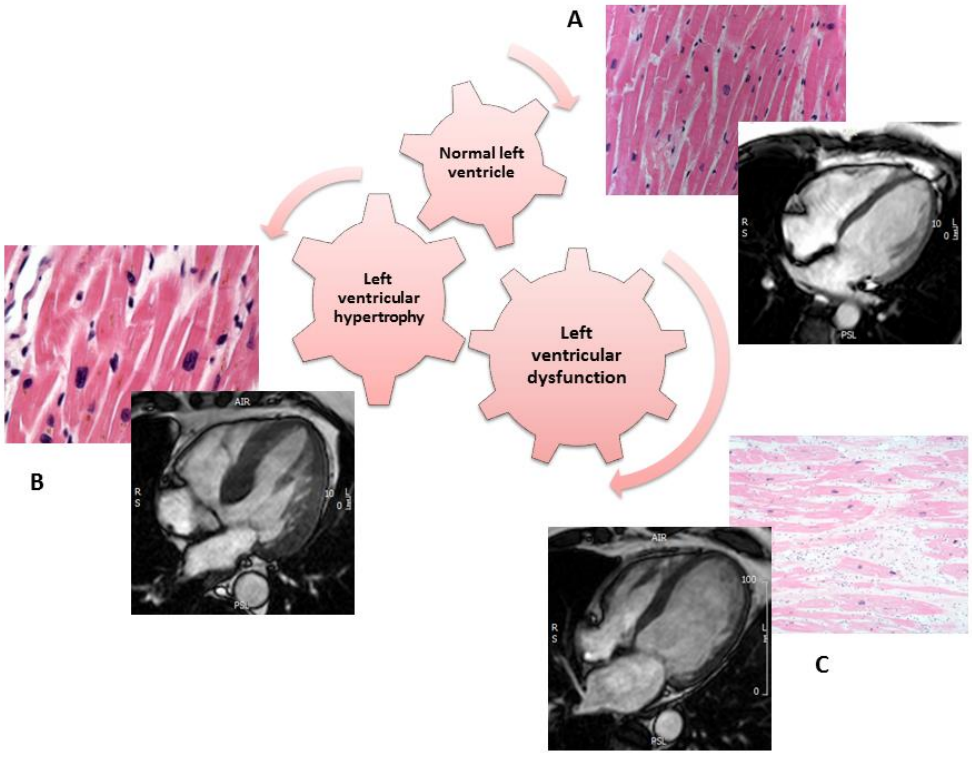

Figure 1-2 The natural history of left ventricular hypertrophy

Panel A: Normal LV mass and myocyte architecture. Myocytes are elongated structures measuring 80-100 x 10-20μm and account for around 70% of myocardial volume. They are surrounded by capillaries and a collagen weave or extracellular matrix. Panel B: With progressive exposure to pressure overload and shear stress, LV mass increases and myocytes become hypertrophied and an increase in sarcomeres leads to an increase in cell width. Eventually LV systolic dysfunction develops due to a combination of subendocardial ischaemia (due to reduced coronary flow reserve) and an inability of the myocyte to normalise wall stress by hypertrophic response alone (Panel C). On a histological level, myocytes are replaced by non-contractile collagen fibres with a resultant increase in extracellular space.

1.1.2. Gender and aortic stenosis

In the normal heart, there are macroscopic and physiological differences between genders. Due to their smaller body size women have smaller hearts and therefore a lower stroke volume than men. Women have higher LV torsion and circumferential shortening compared with males due to an inherent difference in cardiac shape and fibre orientation [12]. Women have reduced sympathetic tone, as reflected by lower peripheral vascular resistance and increased parasympathetic tone in relation to men. Other differences include lower circulating levels of red blood cells (reflected in a lower haematocrit level), noradrenaline and plasma albumin in females, alongside the obvious difference in hormonal profile [13].

The LV responds differently to chronic pressure overload in males and females. Women are found to have lower indexed LV mass, less wall tension, increased trans-valvular gradients, higher pulmonary artery pressure and better left ventricular ejection fraction (LVEF) than their male counterparts [14-20]. Women develop a concentrically hypertrophied, small cavity LV [21] and men are more prone to the development of eccentric hypertrophy [14, 22, 23] (Figure 1-3).

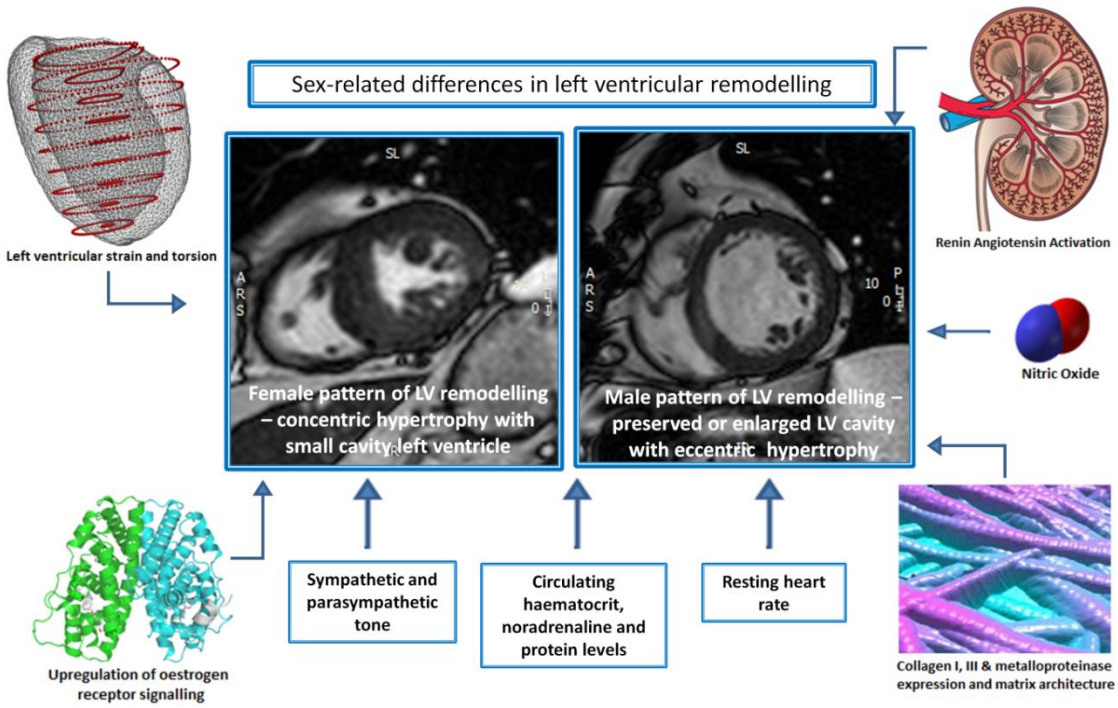

Figure 1-3 Potential mechanisms for differing patterns of LV remodelling between genders in aortic stenosis

The physiological and biochemical basis for myocyte function is different according to gender. Males with severe AS are thought to have increased collagen I, III and metalloproteinases even in the context of normal LVEF [24]. There is increased up-regulation of profibrotic genes and fibrosis in male rodent hearts compared with female rodents following aortic constriction [25]. Petrov et al [26] evaluated biopsies from 10 human hearts with severe AS and compared them with normal controls. Men with AS had higher levels of collagen I, III and MMP-2 gene expression compared to females with AS or controls and this correlated with the degree of hypertrophy and changes in LV geometry. This suggests a different regulation of matrix synthesis and make up of extracellular volume according to gender. In order to further explore this altered extracellular volume in men, the group compared rat cardiac fibroblasts treated with 17β-oestradiol and found a down-regulation of collagen I and III mRNA levels in female rat fibroblasts but increased expression in male rat cells. This is in keeping with the finding that in ageing hearts without AS, there appears to be more fibrosis in male hearts [27]. Women with AS

may therefore develop a different form of remodelled hypertrophy distinguished by less fibrosis in the heart.

Villari et al noted that interstitial fibrosis was more marked in male hearts with AS when compared with female hearts and those of controls without valvular disease [15]. There was no relationship between total collagen volume and systolic function. However there was an inverse relationship between 'cross hatching' (orthogonal collagen fibre meshwork) and LV systolic function. Those with increased cross-hatching also had stiffer hearts. In animal models, male rats were found to have depressed cardiac reserve compared to female rats exposed to pressure overload (aortic banding) despite similar levels of hypertrophy [28]. Therefore it appears that although an increase in the extracellular volume does not relate to reduced LVEF, once abnormal collagen architecture has developed, there is deterioration in systolic and diastolic LV function.

One theory related to the gender differences observed in LV remodelling is the impact of sex hormones on the heart. Oestrogen receptors (ERs) [α and β] can be found in both male and female myocardia and these are felt to be implicated in the development of myocardial hypertrophy [29], with oestrogen binding having genomic effects on gene transcription and non-genomic effects such as protein kinase activation, initiation of intracellular signalling cascades and modulation of growth factor signalling [30]. It has been proposed that rapid signalling of the non-genomic ERα can provide protection from myocyte necrosis and apoptosis, at least in animal models [31].

Testosterone exhibits an anabolic effect on the myocardium inducing myocardial hypertrophy in rodents [32]. Oestrogen modulates the renin-angiotensin system by decreasing renin and angiotensin-converting enzyme (ACE) synthesis and increasing angiotensinogen synthesis. It is well established in animal studies that this impacts on the hypertensive response but may also be implicated in differences in LV remodelling [33]. Gender-related differences in nitric oxide (NO) expression and activity may also play a role. In a rat model of pressure overload, cardiac NO synthase expression is regulated differently between sexes. Male rats subjected to aortic banding experienced more early LV dysfunction and left ventricular hypertrophy (LVH) than their female counterparts which correlated with a greater early

increase in cardiac NO synthase 1 expression in males [34]. Female hearts appear to release less norepinephrine in response to myocardial stress than male hearts [35]. Although a direct link is yet to be established, it is evident that there is a link between circulating catecholamine levels and the development of LVH in the pressure overloaded ventricle [36]. There appears to be gender-related differences in I/D polymorphism of the ACE gene which affects serum ACE activity in patients with AS [37]. In women, absence of DD allele is associated with a higher LV mass whereas the opposite is true for men, with higher LV mass correlating with the presence of a DD genotype. These differences may also impact on reverse remodelling following valve replacement and may at least in part explain the differing patterns of reverse remodelling according to gender seen in a number of studies[38-41], which in turn may be an implicating factor in the improved long term outcomes seen in women following aortic valve intervention[42, 43].

1.1.3. Aortic stenosis and myocardial fibrosis

Myocardial fibrosis (MF) is seen at autopsy in patients with AS [44] where it can be dense replacement fibrosis resulting from myocardial infarction or diffuse, reactive and potentially reversible, more akin to that seen in hypertensive cardiomyopathy [45]. In the normal heart, the extracellular space accounts for around 2-4% of the structural space and is composed of capillaries and a mesh of collagen fibres produced by myofibroblasts, providing support and structure to the surrounding cells. In the pressure overload state of AS, not only is there hypertrophy of the cardiomyocyte, but there is an increase in fibroblast collagen deposition and hence an expansion of the extracellular space. This is manifest clinically as myocardial fibrosis, which is initially of the diffuse reactive type, but eventually becomes focal and dense (akin to that following myocardial infarction) due to cellular death and apoptosis. MF has been reported to be present in between 27 and 63% of patients with severe AS, accounting for 3-4% of LV myocardium [46, 47]. The presence of myocardial fibrosis in patients with severe AS is an independent predictor of mortality [48]. Also, in those undergoing surgical aortic valve replacement (SAVR) it has been found to adversely affect prognosis and may also influence cardiovascular mortality following trans-catheter aortic valve implantation (TAVI) [49].

The association between MF and LV remodelling in AS is still under debate. An early histopathological study suggested that MF burden was associated with LV mass but not LVEF [50], and a CMR late gadolinium enhancement (LGE) study found no correlation between severity of AS and MF, but again found an association with LV mass [46]. Another histopathological study found a direct relationship between the volume of MF and LVEF, with 40% of the myocardial mass composed of MF in those with severely reduced LVEF and almost 10% of cells experiencing autophagic and oncotic cell death [51] .

1.2. Treatment of aortic stenosis

Surgical aortic valve replacement has been available since the 1960s [52] and was for a long time the only available effective treatment for patients with AS. More recently, trans-catheter therapies have become available for those considered inoperable or at high surgical risk [53, 54], revolutionising the care of a generation of elderly patients where previously, palliation was the only option. Prior to the advent of TAVI, balloon valvuloplasty was used in those patients deemed unsuitable for surgery, but the results were disappointing, only impacting on valve gradients for a matter of months [55].

Various trials have been conducted to investigate whether medication can alter the time course of AS. The RIAS trial was a prospective, double-blind randomised control trial investigating the effects of ACE inhibition on LV mass regression in AS [56]. Although a modest reduction in LV mass was observed in the treatment arm, ACE inhibition did not slow the progression of AS or impact on exercise capacity. Early animal studies suggested that statin treatment may be effective at halting the progression of AS due to the anti-inflammatory properties of the drug [57]. Early human studies were promising [58, 59], however, prospective randomised control trials have been negative [60-62]. Bisphosphonates, due to their ability to inhibit vascular calcification, have also been proposed as potential disease modifiers, however, a retrospective observational study has reported negative results [63]. The SALTIRE II trial, a prospective randomised control trial investigating the effects of Denosumab and Alendronic acid on the progression of AS, is ongoing and expected to be completed in 2017.

1.3. Surgical aortic valve replacement

1.3.1. Who should be referred for SAVR?

SAVR remains the gold standard and definitive treatment for severe aortic stenosis and forms a Class I indication in the European Society of Cardiology Guidelines [64] in those with symptoms, those requiring coronary artery bypass surgery (CABG), surgery on another valve or the ascending aorta and those with a LVEF <50%. Class IIa indications for surgery include those with severe AS and an abnormal blood pressure response to exercise, patients with moderate AS undergoing CABG, those with low-flow low-gradient AS with reduced LVEF (if evidence of flow reserve is demonstrated) and, if the surgical risk is deemed to be low, those with very severe asymptomatic AS (peak pressure drop >5.5m/sec) or severe valvular calcification and rapidly progressive disease. SAVR has been shown to benefit patients of all ages, including those in their 10th decade [65]. Age should not be a reason, in its own right, to deny a patient of surgery. Frailty is however, increasingly prevalent with advancing age, and may pertain to a higher peri-operative mortality and morbidity [66]. Pre-operative risk can be reliably estimated using the Society of Thoracic Surgeons (STS) score, however, mortality may be underestimated in high risk patients using the EuroSCORE II scoring system [67].

1.3.2. Surgical AVR technique

The first experience in aortic valve implantation involved a homograft implantation in the descending thoracic aorta [68]. The technique rapidly evolved and the first widespread aortic valve replacement, the Starr-Edwards ball and cage prosthesis, was developed in the 1960's [69, 70]. Mechanical valve design has advanced over the decades, with newer bi-leaflet designs offering improved valvular haemodynamics and requiring lower levels of anticoagulation than earlier models. Bioprosthetic valves, usually fabricated from bovine or porcine pericardium, obviate the need for anticoagulation altogether and although less durable are often the valves of choice in the elderly population. SAVR involves the use of cardiopulmonary bypass and cardioplegia to allow access to the aortic valve via a median sternotomy. Cardioplegia can be delivered in a retrograde or antegrade fashion with differing methods

employed according to the preference of the centre and individual surgeon. Cardioplegic arrest and the systemic inflammatory response associated with cardiopulmonary bypass can cause myocardial injury to the hypertrophied heart of aortic stenosis which is vulnerable to ischaemia/reperfusion injury and is a significant cause of morbidity and mortality following surgery [71]. More modern SAVR techniques including off pump aortic valve bypass and minimal access surgery have been validated in large series but are yet to be adopted into mainstream clinical practice [72, 73].

1.3.3. Gender and SAVR

The effect of gender on outcome following SAVR is difficult to accurately evaluate as most studies are retrospective, comprising a heterogeneous group of patients including those undergoing concomitant bypass grafting. Surgery in women is usually more technically demanding due to smaller annuli size, increased need for aortic enlargement and complications related to cardiopulmonary bypass. Also, women tend to be older and in a more advanced stage of the disease with greater frailty at the time of surgical referral. In the recently published multi-centre OBSERVANT registry that enrolled 2108 patients undergoing TAVI and SAVR (some with concomitant CABG) across 101 heart centres, women represented 44% of the SAVR population [74]. Women were older, frailer and more symptomatic than men with less peripheral and coronary artery disease (CAD). Baseline echocardiography demonstrated a better LVEF, more mitral regurgitation, higher trans-valvular gradients and lower indexed aortic valve area (AVAi) in women with higher post-operative trans-valvular gradients. Female gender was an independent predictor of risk-adjusted 30-day mortality following SAVR compared with males (3.7% female vs. 2.2% male, p=0.043, OR 2.34). Women were more likely to undergo blood transfusions than men (OR 1.47), possibly due to a lower level of haemoglobin pre-operatively. Another large surgical series [75] reported an increased in-hospital mortality in females (3.5% females vs. 1.6% males), however, this difference was not significantly different following propensity matching. Women had shorter cardiopulmonary bypass and aortic cross clamp time, smaller prosthesis size, more tissue bioprostheses and more aortic enlargement procedures than men. Most other studies evaluating isolated SAVR have also failed to show a difference in risk adjusted mortality according to gender [76-78], with

a systematic review of 28 studies failing to demonstrate gender as a prognostic indicator [79]. Females however do appear to have an increased morbidity following SAVR. One recent study of 6809 patients undergoing SAVR found a higher rate of post-operative stroke in women compared with men (3% vs. 2.2%, p=0.031) and various studies have found that women receive more blood transfusions than men [74, 75, 80, 81].

Although a systematic review of the outcomes of SAVR in patients with AS found that gender did not impact on LV mass regression and change in LVEF, the studies analysed were largely historic and included small studies [82]. More recent and larger studies can be seen in Table 1-1. The results are mixed and again contain a heterogeneous group of patients. At least in theory, females' smaller body size requires smaller aortic valves which are associated with a higher post-operative trans-valvular gradient and subsequently less LV mass regression [83].

Table 1-1 Studies investigating LV remodelling according to gender

Reference	No. of patients	Study design	Valve lesion	Valve types	Intervention	Effect of gender
Hanayama et al, 2005 [38]	529 (186 female)	Prospective registry, follow up using echocardiography post-operatively at one year and yearly thereafter	Pure AS or mixed aortic valve disease with predominant stenosis	Stented and stentless bioprosthesis, tilting disk and bi-leaflet mechanical valves	SAVR with or without concomitant CABG	Incomplete LV mass regression occurred less frequently in females; HR 0.44 (95% CI 0.22 – 0.89)
Vaturi et al, 2000 [39]	100 (30 female)	Retrospective study of patients undergoing SAVR for AS or AR. Echocardiograms performed pre- and post-operatively	Aortic stenosis, aortic regurgitation or mixed aortic valve disease.	Tilting disc and bi-leaflet mechanical valves	SAVR with or without concomitant CABG	Male gender was a predictor of LV mass regression on multivariate analysis in patients with pure aortic stenosis.
Petrov et al, 2010 [26]	92 (53 female)	Prospective study with echocardiography performed before and 3-5 days following SAVR	Severe isolated aortic stenosis	Unknown	Isolated aortic valve replacement	Women had more LV mass regression early after surgery than men. Female gender was an independent predictor of postoperative LV mass regression after multivariate adjustment.

AS: aortic stenosis. SAVR: surgical aortic valve replacement. CABG: Coronary artery bypass grafting. AR: Aortic regurgitation. LV: Left ventricular.

1.4. Trans-catheter aortic valve implantation

Transcatheter aortic valve implantation is a procedure that was first performed in man in 2002 [84] whereby a bovine or porcine pericardial aortic valve is delivered via a catheter usually from the femoral, subclavian or apical approach. Large sheaths (typically 14-22 French) are inserted in to the arterial access site and the catheter is delivered to the heart via a steerable delivery catheter. The valve is positioned using fluoroscopic and echocardiographic guidance. Deployment technique depends on the type of valve, but the end point is that the native valve leaflets are displaced towards the wall of the aorta and the new valve is deployed within a metal frame. The procedure originally took place under general anaesthetic with transoesophageal echocardiographic guidance, however, femoral access procedures are now routinely taking place with local anaesthetic under conscious sedation, using only fluoroscopy as guidance. Since their introduction, many different models have become available (Figure 1-4). Some devices such as the Edwards Sapien and Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) comprise a balloon expandable frame with bovine pericardial tissue valve [85]. The Medtronic CoreValve and Evolut-R devices (Medtronic Inc., Minneapolis, MN, USA) are made from porcine pericardium and the nitinol frame is self-expanding [53]. The Boston Lotus device (Boston Scientific Corporation, Natick, MA, USA) is made from bovine pericardium and has an adaptive seal which aims to reduce paravalvular aortic regurgitation at the expense of higher pacing rates, possibly due to increased pressure on the conduction system tissue [86].

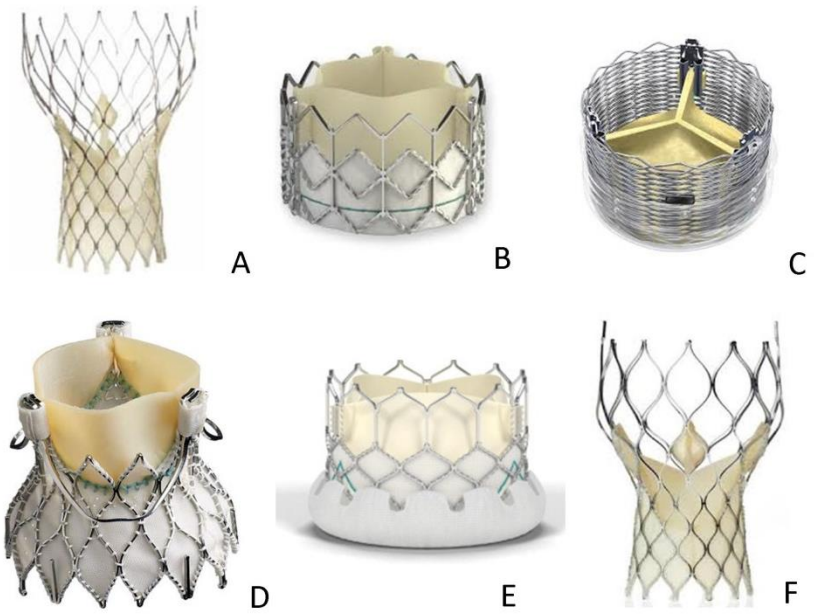

Figure 1-4 Different types of TAVI bioprostheses

Panel demonstrating the different types of TAVI bioprostheses. A: Medtronic CoreValve, B: Edwards Sapien, C: Boston Lotus, D: Medtronic Engager, E: Edwards Sapien 3, F: Medtronic Evolut R.

1.4.1. Patient selection for TAVI

European Society of Cardiology guidelines suggest that TAVI can be considered as an alternative to SAVR in patients deemed to be at high surgical risk by the multidisciplinary heart team [64]. An STS score of >10% has been proposed as the cut-off for considering TAVI over SAVR, with a lower threshold for patients who are frail or with porcelain aorta, patent coronary artery bypass grafts or a hostile mediastinum. Absolute contraindications to TAVI include estimated life expectancy <1 year, severe concurrent valvular disease contributing to symptoms, active endocarditis, inadequate annulus size, LV thrombus, elevated risk of coronary ostial obstruction due to small sinuses, short distance between the annulus and ostia, asymmetric valvular calcification, mobile thrombi in the ascending aorta or arch and inadequate vascular access [64]. Both the EuroSCORE II and STS PROM score have been validated to predict outcome following TAVI[87].

1.4.2. Gender and TAVI

Due to the fact that TAVI is a relatively new technique, few long-term data regarding gender differences are available and the findings are discordant. A subgroup analysis of the Placement of Aortic TraNscathetER valves (PARTNER) A trial suggested that women had improved outcomes after TAVI compared with SAVR [88], although it was unclear whether this effect was due to worse surgical outcomes or improved TAVI outcomes, or both, and further research has attempted to explore this relationship. In a prospective registry of 260 patients undergoing TAVI by Hayashida et al [42], women were of similar age to men but with less coronary disease, a higher LVEF and lower EuroSCORE. On Cox regression analysis, women had an improved one-year survival compared with males (76% vs. 65%); however, baseline characteristics between the two groups were not corrected for. Humphries et al [43] recorded a prospective database of 641 patients undergoing TAVI over a 6 year period. Women pre-procedure were more frail but with less comorbidity and a higher LVEF than men. Vascular complications and the need for peri-procedural blood transfusion were seen more frequently in women. There was improved survival in women at 2 years (72.5% in women and 61.7% in men). This mortality benefit was maintained even when demographic, clinical and procedural factors were corrected for (HR 0.55). Buja et al [18] studied 659 high risk patients (55.8% female, mean age 81 ± 6 years) with severe AS undergoing TAVI. At one year follow up there was a 63% relative risk reduction in death, myocardial infarction or major stroke observed in women compared with men. Cardiac reverse remodelling following TAVI may provide late but important differences in cardiac function in women pertaining to improved survival, as this mortality benefit was sustained when cardiovascular death alone was analysed at 12 months (3% men vs. 0.4% women, p=0.048). More recently, Erez et al [89] prospectively followed 224 high risk patients with severe AS undergoing TAVI for a mean of 17 months. Men had an independent two fold increased risk of death at 2 years compared to women. In women, the presence of coronary artery disease was associated with a marked increase in mortality whereas in men the presence of coronary artery disease did not influence survival. In one of the largest registries to date, women were found to have a similar 30 day mortality to men but an improved one year all-cause mortality (HR 0.75 CI 0.57-0.98, p=0.0346) despite being older [90]. Most studies have only evaluated

high risk patients undergoing TAVI, however, a prospective, multi-centre comparison of intermediate risk patients (as defined by STS score of 3-8%) undergoing TAVI and SAVR found that at one year follow up all-cause mortality was similar among both groups, however, women undergoing valve replacement appeared to have an improved survival when undergoing TAVI compared with SAVR, endorsing the findings of the PARTNER A trial [91]. Other studies suggest no difference in all cause and cardiovascular mortality following TAVI according to gender although it is clear that women receive more blood transfusions than men [74, 92-96]. Only one study to date has found female gender to be a predictor of adverse outcome at one year on Cox proportional hazard analysis [97].

Women have been found to have less significant post-procedural (grade ≥ 2) aortic regurgitation than men in several studies [74, 94, 98, 99], likely as a result of their smaller annular size. Significant aortic regurgitation is known to be associated with adverse outcome and this may play a role in apparent gender discrepancies. Differences in LV reverse remodelling and LVEF according to gender following TAVI may help explain this apparent survival advantage in women but has yet to be explored fully in the literature. Stangl et al [41] assessed gender differences in LV reverse remodelling by echocardiography in a prospective cohort of 100 patients following TAVI. Women were older, smaller (both in height, weight and body surface area) and had a smaller aortic annulus size compared with men. They also had an increased ejection fraction, smaller common femoral artery size, lower cardiac output and less comorbidity than men. Although they found no gender difference in mortality, residual aortic regurgitation, pacing rates, cardiovascular or cerebrovascular events at 3 months following TAVI, as with some of the SAVR studies there were differences in LV reverse remodelling according to gender. Women had a significant improvement in LVEF following TAVI whereas men did not, although both genders experienced a similar amount of LV mass regression. This study, to our knowledge, is the only study to have explored in detail gender differences in LV reverse remodelling following TAVI.

1.5. Outcomes following SAVR and TAVI

Published figures for operative mortality in SAVR are low, with overall mortality rates in the region of 3-4% for isolated SAVR and 4-6% for SAVR with CABG [100]. Increasing age has been strongly associated with reduced survival, with mortality rates of >6% reported in the over 80's [100-102]. Peri-operative morbidity also varies according to the patient population. In a young, low risk group of patients (aged 50-70 years) undergoing isolated mechanical or bioprosthetic aortic valve replacement, 30 day stroke rate was 2%, atrial fibrillation (AF) occurred in 13%, acute kidney injury (AKI) in 2% and respiratory failure in 10% [103]. TAVI appears to be non-inferior to SAVR and superior to medical therapy. The first randomised controlled trial results (PARTNER B) were published in 2010 [54] which demonstrated a dramatic reduction in 12 month mortality in those randomised to TAVI compared to those randomised to the optimal medical management arm (30.7 vs. 50.7%, $p<0.001$), at the expense of higher rates of cerebral and peripheral vascular complications. This trial highlighted the dismal prognosis associated with medical treatment of severe AS and paved the way for the expansion of TAVI services worldwide [104]. For the first time, those at prohibitive surgical risk, or those with conditions such as porcelain aorta or a hostile mediastinum due to previous radiotherapy precluding conventional surgery (accounting for around a third of the severe AS population according to the EuroHEART survey) [4], were able to be offered a potentially life-saving treatment. The next PARTNER study (PARTNER A) [85] randomised high surgical risk patients (defined as a society for thoracic surgeons (STS) score of $\geq$ 10%) with severe symptomatic AS to either SAVR or TAVI. At 12 month follow up there were no significant difference in mortality or New York Heart Association (NYHA) classification between patients in the two groups, however, there was a significant increase in vascular complications at 30 days and a trend towards increased major stroke rate at 12 months in the TAVI arm. A more recent randomised control trial comparing self-expanding TAVI with high risk SAVR found that TAVI was associated with a lower mortality at 1 year (14.2 vs.19.1%, $p=0.04$) [53]. Major vascular complication, the need for permanent pacemaker insertion and cardiac perforation were more common following TAVI than SAVR, with major bleeding, AKI and AF higher in the SAVR group. In this study, stroke rates were not significantly different between groups (TAVI 4.9% vs. SAVR 6.2%, $p=0.46$). The recently published NOTION trial randomised all-comers with severe symptomatic AS over the age of 70 years to self-expanding TAVI or SAVR [105]. Mean age of the study participants was 79±5 years

and almost half of them were women. STS score was around 3% and EuroSCORE II around 2%, representing a low to intermediate risk population. At one year follow up there was no difference in all-cause mortality, cardiovascular death or stroke rates between the two groups. Major, life-threatening or disabling bleeding, AF and AKI were more frequent following SAVR. Pacing rates were higher following TAVI, with high rates of 34.1% reported, as was aortic regurgitation (16% of the TAVI cohort had moderate or severe AR at one year) and minor vascular complications. The mortality rate of 4.9% at one year was the lowest reported to date, and may pave the way for a change in guidelines in the low to intermediate risk elderly population.

1.5.1. Myocardial infarction following TAVI and SAVR

Clinically detectable myocardial infarction (MI) appears to be a rare consequence of both TAVI and SAVR. In the PARTNER A study, reported rates of MI were low in both TAVI and SAVR groups; representing 0.4% of the TAVI group and 0.6% of the SAVR group (P=0.69) [85]. In the recent NOTION trial [105], rates of post-procedural MI were numerically higher in the SAVR group but, (possibly due to small numbers) this failed to reach statistical significance both at one month (TAVI 2.8% vs. SAVR 6%, p=0.20) and one year (TAVI 3.5% vs. SAVR 6%, p=0.33). Although clinically detected MI post-TAVI and SAVR is rare, defining peri-procedural MI in this group is challenging, reflected by the change in criterion for diagnosis between the VARC [106] and VARC II guidelines [107]. It does appear however that evidence of MI by CMR LGE has prognostic importance in other settings, even if clinically ‘silent’; those with CMR evidence of new MI following percutaneous coronary intervention or coronary bypass grafting have a >3 fold risk of adverse outcome regardless of peri-procedural troponin rise [108]. . The mechanisms for MI following aortic valve intervention remain incompletely defined but may be embolic, a pathogenesis which is supported by data from an intracoronary Doppler study [109] and possibly relate to differing anticoagulation regimes following surgical and transcatheter valve replacement. The low incidence of reported MI following aortic valve intervention may underestimate the true rate, due to difficulty in post-procedural diagnosis. In the sedated or intubated patient a history of chest pain cannot be established and new conduction defects

on the electrocardiogram such as left bundle branch block (a result of trauma to the cardiac conduction system) mask diagnostic ECG changes [110, 111]. Biomarker release is also often unhelpful, with high levels ubiquitous following both procedures [112, 113]. Silent myocardial infarction, although well described following percutaneous coronary intervention [108, 114], has not been well characterised following SAVR and TAVI. The only study to date using cardiac imaging to detect post-SAVR infarct rates, reported a new MI rate of 16% using technetium-99m pyrophosphate radionuclide scanning [115]. Kim et al [116] reported a new MI rate of 18% following TAVI using CMR-LGE however, the study included a high number of patients undergoing trans-apical TAVI, and it was not clear from the study design whether the inevitable apical scar associated with this approach [117] was classified as new MI.

When considering the risk of post-procedural MI, another pertinent question is that of the need for coronary revascularisation prior to or at the time of aortic valve intervention. Joint American College of Cardiology (ACC) / American Heart Association (AHA) guidelines previously recommended coronary revascularisation at the time of SAVR as a Class I indication in the presence of >70% luminal stenosis and as a Class IIa indication in those with a lumen stenosis above 50% [118]. The updated 2014 guidelines [119] have downgraded the recommendation for revascularisation of luminal stenoses of >70% to a IIa, reflecting the emerging evidence that coronary revascularisation in a number of settings doesn't improve prognosis [120]. Retrospective analyses have suggested a better long-term survival in those with moderate (>50% stenosis) and severe (>70% stenosis) CAD undergoing concomitant CABG at the time of SAVR [121], but evidence from prospective trial data are lacking, and it is not known whether CABG has any impact on the incidence of post-procedural MI. The need for concurrent revascularisation in patients with CAD undergoing TAVI is debated. Initially, full revascularisation was carried out due to concern regarding the risk of peri-procedural MI or myocardial injury, especially in the context of prolonged hypotension as a result of rapid pacing during device deployment [18, 122, 123]. However, these fears appear unfounded, with several studies suggesting that the presence of CAD or non-revascularised myocardium is not associated with an increased risk of adverse events [124, 125].

1.5.2. Conduction system disease

The aortic valve lies close to the electrical conduction system of the heart and is prone to damage at the time of aortic valve intervention, often manifesting as new left-bundle branch block (LBBB). New LBBB is infrequent following SAVR, with reported rates in the region of 5% [126] but much more common following TAVI with rates of up to 65%, depending on valve design [127]. Trauma to the cardiac electrical conduction system at the time of TAVI can be a result of guide wire and catheter manipulation, direct pressure from the valve cage and repeated balloon valvuloplasty (both pre- and post-valve deployment). Given the advanced age of the patients undergoing TAVI, there may be pre-existing conduction system disease and this extra insult at the time of TAVI is the 'final straw' in the deterioration into conduction abnormalities. On a cellular level, the mechanical trauma is thought to result in transient tissue inflammation and oedema. AV nodal ischaemia may also be partially implicated as a result of the transient global hypotension at the time of rapid atrial pacing. Post-mortem studies have demonstrated haematoma of the interventricular septum at the site of valve expansion and resultant compression of the bundle of His following TAVI [128].

Following implantation of the self-expanding Medtronic CoreValve, LBBB has been reported in 29 to 65% [129-143] with high rates of pacemaker implantation also seen with this valve design [129, 133, 136, 143, 144]. The Edwards Sapien valve is associated with a lower rate of LBBB, with an incidence of 16% to 27% reported [129, 131, 144-146]. Pacing rates following Boston Lotus implantation are reported in the region of 29% at 30 day follow up [86], although to date no study has reported the incidence of LBBB in this population. The difference in pacing rates according to device type is not entirely understood. It may relate in part to the differing implant sizes or the differing methods of deployment. The self-expanding nature of the CoreValve may provide a constant pressure (and hence trauma) to the left ventricular outflow tract, long after device deployment occurs, or it may be that the trans-femoral rather than trans-apical approach is to blame, or even the need for balloon valvuloplasty pre-procedure in CoreValve implantation. Depth of TAVI implantation, device type, valve:annulus ratio, male gender and previous myocardial infarction have all been reported as univariate predictors of new LBBB [131, 133, 134, 143, 145]. Only depth of TAVI implantation has been found to be a predictor of post-operative LBBB on multivariable analysis [131]. Guittierez et al [145] found that patients were

more likely to develop post-procedural LBBB if the Medtronic CoreValve cage was located below the hinge point of the anterior mitral valve leaflet. Further insights from post-procedural computed tomography of the Edwards Sapien valve suggests overexpansion of the bioprosthesis >15% of the native aortic annular area and implant depth may be implicated [147]. A short membranous septum (a surrogate of the distance between the aortic annulus and bundle of His), insufficient distance between the membranous septum and implantation depth and basal septal calcification can all predict post-TAVI high degree atrioventricular block [148]. Device landing zone calcification has also been associated with the need for post-procedure PPM implantation in those undergoing Medtronic CoreValve implantation [149]. There does appear to be a resolution of LBBB over time in a significant proportion (50% in one year) following implantation of the Edwards Sapien valve [111]. This does not appear to be the case after Medtronic CoreValve implantation, with no change in rates of LBBB between hospital discharge and 30 day follow up [150]. Data with regard to the Boston Lotus valve are scarce, but given the higher pacing rates reported, the effects on the conduction system are likely to be more akin to the Medtronic CoreValve than the Edwards Sapien [86].

TAVI-induced left-bundle branch block has been linked to reduced survival in a number of studies [151-154] and also increased rates of hospitalisation [111], in keeping with population based studies suggesting reduced overall survival in healthy individuals with LBBB [155] and in patients with heart failure and LBBB [156]. Other studies have failed to establish an association (Table 1-2). In the study by Houthuizen et al, 34.3% of patients developed new LBBB. QRS duration increased from 96ms pre-procedure to 150ms post-procedure and those with new LBBB also had a greater increase in post-procedure PR interval. 12 month all-cause mortality in those with new LBBB was 26.6% in contrast to 17.5% in those without (p=0.006). TAVI-induced LBBB was one of the strongest predictors of mortality (HR 1.54) alongside COPD, female gender, LVEF<50% and baseline creatinine. The effect of TAVI-induced LBBB on mortality was similar between CoreValve and Sapien valve types. The mechanism for this increased mortality is debated. One hypothesis is that LBBB is a precursor to further more lethal conduction abnormalities, supported by pacing studies which reported high degree atrioventricular block on permanent pacemaker (PPM) interrogation of those with TAVI induced LBBB

[157, 158]. The MARE (Ambulatory Electrocardiographic Monitoring for the Detection of High-Degree Atrio-Ventricular Block in Patients with New-onset PeRsistent LEft Bundle Branch Block after TAVI by an Electrophysiological and Remote monitoring Risk-adapted Algorithm' study (NCT02482844)) will attempt to address the optimal management of patients with TAVI-induced LBBB. Another hypothesis is that TAVI-induced LBBB leads to abnormal LV remodelling and ultimately heart failure death via a LBBB-induced cardiomyopathy [159].

Table 1-2 Studies investigating the effect of TAVI-induced LBBB on mortality

Author	Number of patients	Valve type	Excluded	ECG	Follow up	Findings
Houthuizen, 2012 [151]	670 (233 LBBB)	Balloon-expandable (n=292), self-expanding (n=387)	Pre- or post-procedure PPM, pre-existing LBBB	Within 7 days post-procedure	Median 450 days	Significant increase in all-cause mortality in those with new LBBB (37.8 vs. 24.0% at one year, p=0.002). LBBB was independent predictor of all-cause mortality (HR1.54, confidence interval 1.12-2.10)
Urena, 2012 [160]	202 (61 LBBB)	Balloon-expandable	Pre-procedure PPM, prior intraventricular conduction delay	LBBB at discharge	Median 12 months	No increase in all-cause or cardiac mortality at 12 months in LBBB group
Franzoni, 2013 [161]	238 (63 LBBB)	Balloon-expandable (n=151), self-expanding (n=87)	Pre-procedure PPM, Pre-procedure LBBB and RBBB	LBBB at discharge	Median 349 days	Numerical excess of deaths in LBBB (LBBB 8 (20%) vs. nQRS 26 (15.4%), but did not reach significance as under-powered.
Houthuizen, 2014 [153]	476 (175 LBBB)	Balloon-expandable (n=253), self-expanding (n=301)	Pre-procedure LBBB or PPM	LBBB 12 months post-TAVI	Median 915 days	LBBB associated with increased mortality (HR 1.49, 95% CI 1.10-2.03, p=0.01)

Nazif, 2013 [111]	1151 (121 LBBB)	Balloon-expandable	Pre-existing intraventricular conduction abnormalities and pre-procedure PPM	LBBB at 7 days or hospital discharge	1 year	No significant difference in 12 month all-cause or cardiovascular mortality between nQRS and LBBB groups
Testa, 2013 [150]	879 (224 LBBB)	Self-expanding	Pre-existing LBBB, pre or early post-procedure PPM	LBBB at discharge	Median 438 days	LBBB had no effect on mortality at 30 days or 1 year
Urena, 2014 [162]	668 (128 LBBB)	Balloon-expandable	Pre-existing LBBB and pre-procedure PPM	LBBB at discharge	Median 13 months	No increase in all-cause or cardiovascular mortality in LBBB at 12 months

LBBB: Left-bundle branch block, RBBB: right-bundle branch block. nQRS: Narrow QRS. PPM: Permanent pacemaker. TAVI: Trans-catheter aortic valve implantation.

1.6. LV reverse remodelling following aortic valve intervention

Favourable LV reverse remodelling following aortic valve replacement is prognostically important. Enhanced LV mass regression following SAVR has been linked to improved survival [163] and in patients with severe pre-TAVI hypertrophy those with greater mass regression post-procedure have a reduced rate of hospitalisation at 12 months [164]. Improvement in LVEF following SAVR has been associated with improved survival and freedom from heart failure at long term follow up [165].

LV reverse remodelling is the norm following afterload reduction, as is seen following trans-catheter and surgical aortic valve replacement [166]. From a physiological perspective, acute reduction in afterload is associated with a reduction in wall stress and left ventricular filling pressure and, on a cellular level, myocyte shrinkage can be spontaneously seen in hypertensive rats one week after treatment with anti-hypertensive agents [167]. Six months following TAVI and SAVR, there is a reduction in LV end systolic volume and LV mass [166, 168]. Regression of hypertrophy continues over 2 years following TAVI and SAVR, although the rate of regression declines [165, 169]. Echocardiographic studies suggest that following TAVI mass regression starts prior to hospital discharge; Hahn and colleagues reported a reduction of LV mass of 9 grams between baseline and pre-discharge echocardiographic studies [169], and Petrov et al suggested more LV mass regression in women compared with men three days following SAVR [26]. The latter study needs to be viewed with a degree of scepticism, however, as the reduction in mass seen was actually a reflection of a reduction in cavity size rather than a reduction in wall thickness, and highlights once again the pitfalls resulting from the echocardiographic calculation of left ventricular mass. Mass regression has also been reported 2 weeks following SAVR and has been linked to improvement in diastolic indices [170]. These findings have been replicated at 6 month follow up; Vizzardi et al [171] reported mass regression of 31% at 6 months, with baseline LV mass being the strongest predictor of LV mass regression. Diastolic indices were also improved at 6 months, with a reduction in E/E' ratio alongside a reduction in left atrial size. However, echocardiographic data in this setting needs to be interpreted with caution, as numerous

mathematical and geometric assumptions are made when calculating LV mass from M-Mode echocardiography, and the effects of the TAVI and SAVR procedures on cardiac geometry are not completely understood. CMR data on these acute reverse remodelling changes are lacking. Crouch et al [172] investigated 47 patients undergoing TAVI and SAVR using pre and early post-procedure CMR. They reported greater aortic regurgitation and left ventricular end diastolic volume following TAVI compared with SAVR despite similar baseline values. In this study they did not report LV mass, which is surprising given the accuracy of CMR in reporting this information. They reported new LGE in 2 patients in each group, but the nature and distribution of this was not described, nor was the relationship between baseline LGE and cardiac reverse remodelling.

Speckle tracking, tissue Doppler and mitral annular systolic plane excursion (MAPSE) have all been validated as echocardiographic measures of myocardial function in patients with aortic stenosis [173]. Myocardial strain and strain rate have been shown to be predictors of sub-clinical LV dysfunction in patients with severe AS and preserved LVEF [174] and can be used to predict outcomes in this setting [175]. Within a week following TAVI, echocardiographic studies have suggested an improvement in strain when an overt change in LVEF is not seen [176]. Longitudinal strain has also been found to predict LV mass regression after SAVR for severe AS in patients with a preserved LVEF at baseline [177, 178]. Traditionally diastology and strain imaging has been the domain of echocardiography, however, more recently CMR techniques have been developed which are able to evaluate longitudinal LV function and strain [179]. Feature tracking is a novel CMR technique which works in a similar manner to the echocardiographic technique of speckle tracking whereby image features of the myocardium are automatically tracked using dedicated post-processing software. The benefit of this technique is that all analysis can be performed off-line on standard steady state free precession (SSFP) cine images acquired as standard on all CMR examinations, without the need for contrast administration [180]. Reasonable intra and inter-observer variability has been reported [179, 180]. CMR MAPSE has recently been proposed as a simple and easy measure of longitudinal function in healthy volunteers and patients with hypertrophic cardiomyopathy [181].

1.6.1. The impact of TAVI-induced LBBB on cardiac reverse remodelling

Although predictors of TAVI-induced LBBB (LBBB-T) have been extensively studied [127], the impact of LBBB-T on cardiac reverse remodelling is less well described, with studies limited to echocardiographic evaluation and containing a heterogeneous mix of patients including those with pre-existing conduction abnormalities, post-procedure pacemaker insertion and trans-apical access route, all factors which are known to confound reverse remodelling. A PARTNER echocardiographic sub-study investigating the effects of LBBB-T on those undergoing TAVI reported a lower LVEF at 12 months in patients with LBBB on discharge electrocardiogram compared to those with a narrow QRS, however, there was an increased number of those undergoing trans-apical TAVI in the LBBB-T group [111]. A similar failure of improvement in LVEF following balloon-expandable TAVI was seen by Urena et al in 79 patients with LBBB-T at hospital discharge, again with more patients undergoing trans-apical TAVI in the LBBB-T group [162]. Tzikas et al [159] reported unfavourable reverse remodelling in 27 patients (including those with pre-existing conduction defects) following self-expanding TAVI prior to and 6 days post-procedure. They observed an 8% difference in LVEF between the 2 groups. Longitudinal strain was also reduced in those with new conduction abnormalities, however this failed to reach statistical significance, likely due to being under-powered with a small sample size for an echocardiographic study [182]. Hoffman et al [183] investigated 90 patients using 2D and speckle tracking trans-thoracic echocardiography prior to and at 1 and 12 months following Edwards Sapien and Medtronic CoreValve TAVI. Patients with new conduction defects had a significantly larger indexed LV end systolic volume (LVESVi) at 12 months compared with those with a narrow QRS, with less difference in indexed left ventricular end diastolic volume (LVEDVi). New conduction defects and baseline LVEF were independent predictors of reduction in LVEF at 12 months. The inclusion of patients with trans-apical access in the majority of these studies [111, 162, 183] and those with post-procedural pacemaker insertion [111, 159, 162, 183] is a significant confounder, given that trans-apical access has been linked to reduced LVEF in a number of studies [162, 184] and pacing induced LBBB has been shown to cause different patterns of strain to those with idiopathic LBBB [185]. To date, no CMR based study has attempted to investigate the impact of LBBB-T on cardiac reverse remodelling

following TAVI. The large sample sizes required to demonstrate even a small difference in reverse remodelling mean that echocardiography is not ideally placed as a research tool in this setting, with hundreds of patients required to detect a difference in LVEF between groups [186]. The accuracy and excellent reproducibility afforded by CMR SSFP cine imaging in LV quantification means that extremely small sample sizes (in the teens to twenties) can be used to detect treatment differences [187, 188]. Furthermore, it is well established that the strongest predictors of reverse remodelling are the baseline levels of that particular parameter [166]. So, for example, those with the worst LVEF at baseline have a greater improvement in LVEF post-TAVI, and those with the greatest pre-TAVI LV mass have the greatest mass regression post-procedure [166]. Therefore, it is imperative that any study intending to accurately assess the impact of TAVI-induced LBBB is able to account for this by accurately matching subjects for these important parameters at baseline, alongside matching for gender and valve type (which may also impact on reverse remodelling).

1.7. Myocardial fibrosis and aortic valve replacement

Initial studies investigating the natural history of myocardial fibrosis following aortic valve replacement were limited to histopathological studies describing samples taken either at post-mortem or from cardiac biopsies. The results to date are mixed and likely represent the heterogeneous mix of patients included and the different study designs. A long term follow up study evaluated a small number of patients for 6-7 years following SAVR for AS [189]. A regression in fibrosis was seen on serial myocardial biopsy specimens but this was incomplete and never returned to that of the control population. The degree of MF did not correlate with pre-operative LV ejection fraction, however, limited conclusions can be drawn from this study in view of the fact that the late follow up group only included 9 patients. Murine models have also shown increased myocyte fibrosis following aortic banding but in contrast to Krayenbuehl et al [189], did not report regression of fibrosis after aortic debanding [190]. Cardiac biopsies are easy to obtain at the time of SAVR and hence the histopathological basis of fibrosis is well described. Acquiring serial biopsies in humans presents difficulties and therefore is unlikely to form the basis of future longitudinal studies.

The unique ability of CMR to assess for both diffuse fibrosis and focal replacement fibrosis [191] means that it is well placed to investigate the longitudinal changes in MF following aortic valve replacement and in the future it may be able to predict those most likely to gain benefit from valve replacement in terms of LV reverse remodelling. The CMR literature regarding this is in its infancy and to date, differing results have been reported, possibly as a result of differing methodologies according to research group. Fairburn et al [166] found that 53% of patients undergoing aortic valve replacement had evidence of focal myocardial fibrosis (assessed using the CMR full width half max technique) and that the MF as a percentage of myocardial mass was higher in patients undergoing TAVI than SAVR. As with previous studies [46], the degree of aortic stenosis did not correlate with the amount of myocardial fibrosis present, however, MF regression was seen in patients following TAVI but not SAVR. Azevedo et al [191] evaluated the prognostic impact of MF (detected using CMR threshold of two standard deviation technique and myomectomy specimens) in patients with severe aortic valve disease (without concomitant coronary artery disease) undergoing valve replacement. 28 patients had predominantly aortic stenosis. MF was present in 61% of patients with a mean mass of 3.15±1.87% of total LV myocardium was reported in the aortic stenosis group. Most patients had multifocal or widespread MF, but the sites of MF were highly variable. 27 months following SAVR, there was no change in MF expressed as total LV mass (3.13±2.18% to 3.10±2.63%, p=0.93) but a reduction in absolute fibrosis mass (8.9±8.0 to 5.8±6.7g, p=0.005). The amount of MF at baseline inversely correlated with LVEF change over time (r-0.47, p=0.02). MF at baseline was an independent predictor of mortality on Cox regression analysis. The association between MF at baseline and mass regression was not explored. Limited conclusions can be drawn from these follow up data, as only a small subset of the original patient group underwent follow-up CMR scanning. In another prospective follow up study [192]; 58 patients with symptomatic severe aortic stenosis undergoing SAVR were evaluated using myocardial biopsy, echocardiography and CMR. The degree of myocardial fibrosis was determined using myocardial biopsy taken at the time of surgery and patients were categorised into three groups according to the fibrosis index method of classification [193]; no fibrosis, mild fibrosis and severe fibrosis. Those deemed to have severe fibrosis pre-operatively saw a reduction in their LV

ejection fraction post-operatively and also less regression in end diastolic wall thickness and myocardial mass as compared with those with mild or no fibrosis. The majority of patients with severe fibrosis experienced no improvement in NYHA functional class in comparison with those patients with no fibrosis, whom all experienced an increase in NYHA class post-operatively. All 4 patients who died within the follow up period had severe fibrosis. Mitral ring displacement of >7mm classified using echocardiography was able to predict improvement in NYHA status following SAVR whereas ejection fraction and diastolic function (as assessed by echocardiography) were not predictive of a better outcome. This may be explained by the fact that in aortic stenosis, fibrosis tends to be subendocardial. Subendocardial dysfunction is more accurately reflected by abnormal myocardial longitudinal function and only at a very late stage by a reduction in LVEF. In keeping with the results reported by Fairburn et al [166], fibrosis was more prominent in the basal portions on CMR analysis, where regional wall stress is highest due to flatter curvature of the LV [194].

1.8. How does CMR work?

Cardiovascular magnetic resonance imaging is a technique based on the magnetisation of tissues to create images using a strong superconducting magnet cooled in liquid helium. The main strengths of the technique are its ability to produce high spatial resolution anatomical and functional images of the heart with excellent soft tissue contrast (e.g. allowing accurate LV mass and volume data to be derived [188]), without the need for ionising radiation. Additionally, it is able to provide tissue characterisation, information about flow, myocardial perfusion and vasculature, to allow comprehensive (multi-parametric) cardiac evaluation to take place. Gadolinium based contrast agents can be used in a variety of applications, one of which is to delineate focal fibrosis as a result of myocardial infarction (scar) or a number of other replacement fibrotic or infiltrative disease processes.

1.8.1. Generation of images

CMR uses three types of magnetic field; B_0, a strong (typically 1.5 or 3 Tesla), static field generated by the superconducting solenoid, with the field inside the scanner bore aligned parallel to the central axis

(normally denoted the z axis), a gradient field which is switched on and off rapidly and a smaller magnetic field, the radiofrequency (RF) field, known as B_1, typically delivered in short pulses causing resonation of hydrogen nuclei contained within free water and adipose tissue. These three components combine to provide a signal which is transformed into the CMR image. The magnetic field causes the protons to align themselves in a single orientation either towards or away from the magnetic field, B_0, with a slight predominance of protons in a single direction, causing net magnetisation (M). When inside the static field protons resonate at the Larmor frequency (64MHz for 1.5T magnet strength), emitting a small radiofrequency signal. The size of the signal depends on the excess net magnetisation, which is in turn determined by a number of factors including the magnet field strength (B_0), the proton density and the body temperature. In a standard 1.5 Tesla magnet, the excess of protons aligned with the field is approximately 4 per million, assuming a body temperature of 37^{o}C. As the magnetisation is parallel with B_o at equilibrium it is not detected, and therefore of little clinical use. In order to generate a detectable signal, the protons are exposed to a brief radiofrequency (RF) pulse, which flips the protons away from their natural position along the z axis, imparting a transverse component of magnetisation in the x-y plane which rotates around the z axis at the Larmor frequency. The angle of rotation is dependent on the strength of the RF pulse applied. Once the angle of rotation has reached a certain pre-determined point (known as the flip angle), the RF pulse is switched off and magnetisation slowly returns to its equilibrium state (free induction delay), releasing energy which can be detected as a RF signal. This process must be repeated multiple times to allow spatial information to be encoded and images to be generated. The greater the energy delivered by the RF pulse, the greater the flip angle. The 'saturation pulse' is the energy required to create a flip angle of 90^o so that the net magnetisation is at 90^o to the Z axis, i.e. maximum transverse magnetisation, at which point the protons are 'saturated'. Pairs of pulses (a 90^o excitation pulse and a 180^o refocussing pulse) are used to generate spin echo pulse sequences, whereas lower flip angle RF excitation pulses are used without refocussing pulses to generate gradient echo images, which produces a lower signal that can be repeated more rapidly. Static anatomical imaging is usually acquired using spin echo pulse sequences (black-blood imaging) and gradient echo pulse sequences are generally used for cine (bright blood) imaging due to their higher temporal resolution.

1.8.2. T1 and T2 relaxation

There are two distinct relaxation processes; recovery of longitudinal and transverse relaxation. T1 relaxation time represents recovery of approximately two-thirds of the z-component of the magnetization following an RF pulse (longitudinal relaxation), until it reaches its equilibrium (saturation recovery). T1 relaxation time increases with increasing field strength. In the human body, fat has the shortest T1 relaxation time, followed by water-containing tissues with a high macromolecular content such as muscle. Fluid has the longest T1 relaxation time. Spin echo T1 pulse sequences therefore show fat as very bright signal and as such these are useful when characterising fat filled structures such as lipomas or fatty infiltration. T2 relaxation time represents the time taken for transverse relaxation of protons (x-y component relaxation). It is a measure of the spin-spin interaction of protons (protons interfering with the magnetic field of another adjacent proton) and occurs more quickly than T1 relaxation. Body components with dense tissue (such as LV myocardium) contain a high density of macromolecules leading to slower molecular tumbling facilitating proton spin-spin interaction (hence shorter T2 relaxation times and leading to a dark appearance) compared with components such as free water (which appears bright) where the protons tumble very rapidly (faster than the Larmor frequency) with little time for spin-spin interaction. Fat exhibits an intermediate T2 value. T2 values increase when the tissue is inflamed due to increased water content therefore T2 weighted imaging can be a useful modality for the assessment of myocardial oedema. Scanning sequence parameters can be manipulated by the operator in order to affect the relative contribution of different relaxation processes to signal intensity allowing careful tissue characterisation.

1.8.3. Gradient echo

The magnetic field strength can be varied across the imaging region inside the scanner bore by applying magnetic gradients in any direction. This causes spatial variation in the precessional frequency, allowing spatial encoding of the MR signal and also causing dephasing or rephasing of the transverse magnetisation. Echos generated by gradient induced dephasing and rephasing are called gradient echos,

whereas those generated using a refocussing RF pulse are spin echos. The echo time (TE) is the time from the delivery of the RF pulse to the time the echo reaches its maximum amplitude. A RF pulse is generated at the same time as a gradient magnetic field (the direction of which defines the slice selection direction), which defines a slice of tissue and determines the slice thickness. The slice thickness is determined by the frequency of the RF pulse (TR) and the strength of the gradient. Protons dephase at different frequencies when exposed to the gradient echo depending on their position along the gradient, a concept known as phase encoding. A further gradient is then applied at 90^{o}, known as the frequency encoding gradient, allowing another dimension of information about the tissue to be obtained. Through this process therefore, 3 dimensions of imaging have been obtained; the slice selection, the phase-encoding gradient and the frequency-encoding gradient, obtained from the z, y and x axis respectively.

There are two main types of gradient echo; spoiled gradient echo and balanced steady state free precession (SSFP) imaging, the latter being the most widely used for the generation of cine images used for ventricular mass and volume calculation. The spoiled gradient echo pulse sequence typically has a short TR and TE and is partially reliant on the flow of blood to generate contrast. As a result of this the blood signal intensity varies throughout the cardiac cycle due to the speed and direction of flow. This technique can be useful for the quantitative evaluation of jets within the heart such as in the case of valvular regurgitation and shunts. Endocardial definition with this technique can be variable therefore this pulse sequence is less reliable for the quantification of LV mass and volume data [195]. Balanced SSFP pulse sequences ensure that the transverse magnetisation is fully re-phased at the end of each TR period when the next RF pulse is applied, allowing this to be carried over into the next repetition culminating in a steady-state of transverse magnetisation whereby several repetition periods combine to create a much stronger signal. The contrast between blood and tissue generated using SSFP imaging is based on the ratio of the T2/T1 signal in the tissue. Structures with a high fluid or fat content have a higher T2/T1 ratio and hence appear bright. This, combined with the greater signal to noise ratio generated by the combination of transverse magnetisation from a number of TR's allow excellent endocardial definition which is consistent throughout the cardiac cycle.

1.8.4. Data transformation

The information obtained from the application of the magnetic fields is stored in the image space known as '*k-space*'. Each point in k-space data (i.e. each sample of an echo) corresponds to a certain spatial frequency (and contains information from across the full field of view) rather than a spatial position. The location of a particular data point in k-space depends on the strength and duration of each gradient that has been applied from the time of transverse magnetisation generation to that when a particular point is measured. A mathematical algorithm, known as Fourier transformation decodes the frequency and phase data and transforms it digitally into the CMR image.

1.8.5. Image optimisation, signal to noise ratio and artefacts

The matrix size, combined with the field of view and the slice thickness determines the voxel size and hence image resolution. The larger the voxel size, the lower the resolution of the image. On the other hand, in order to increase spatial resolution, the voxel size is reduced, however, this is at the detriment of signal, as the voxel size determines the number of protons that can be magnetised. Signal to noise ratio (SNR) is the ratio of unwanted random 'noise' signal of the patient to the 'wanted' signal from the tissue of interest. The higher the field strength, the higher the signal that is returned from tissue and therefore the higher the SNR and better image quality. Therefore there is always a trade-off between background noise and signal, and settings including the pulse sequence and image acquisition parameters can be adjusted in order to optimise SNR. Artefacts can occur during CMR imaging and are an increasing problem with increasing magnet field strengths. Image *aliasing* can occur when the structure imaged is larger than the pre-determined field of view. These can be minimised by increasing the field of view (at the expense of reduced special resolution), using over-sampling techniques (increasing image acquisition time), changing the phase encoding direction (which may introduce aliasing in the opposite direction) and the use of saturation bands. Respiratory motion leads to ghosting artefacts, whereby motion in the chest as a result of diaphragmatic movement leads to a misplacement of the signal in the image (as the tissue is changing position between each TR). These artefacts can be

reduced by reducing scanning time (hence making breath-hold times shorter), the use of respiratory navigators whereby images are only acquired at a certain part of the respiratory cycle (at the expense of increased acquisition time) and the use of saturation bands. Metallic artefact, such as that of post-CABG sternal wires, metallic valve replacements, pacemaker generators, pacemaker leads and surgical clips, can lead to significant artefact as a result of local field distortion. Spoiled gradient echo pulse sequences cause less image degradation than SSFP pulse sequences and therefore should be considered if the latter yields non-diagnostic imaging [196].

1.8.6. Assessment of aortic valve disease using cardiovascular magnetic resonance imaging

CMR is the reference standard for LV mass and volume quantitation using SSFP imaging, with low observer and inter-study variability [197]. The cine images obtained can be contoured using post-processing software in order to derive an accurate assessment of left ventricular mass and volume which has advantages over echocardiography in that it is angle independent and not reliant on acoustic windows. With careful planning, aortic valve planimetry can also be performed [198]. Turbulent flow such as that caused by a stenotic or regurgitant aortic valve can be appreciated on SSFP imaging, but for quantification purposes through-plane phase contrast velocity mapping imaging is used. This spoiled gradient echo technique is able to map the velocity of individual protons as they move within the magnetic field with moving protons acquiring a phase shift proportional to their velocity. Their movement can be compared with that of stationary protons and as a result of this phase shift an average velocity can be derived for each pixel. A thin scan line is planned perpendicular to the flow of interest, in the case of the aortic valve this is usually at the level of the sinotubular junction (Figure 1-5).

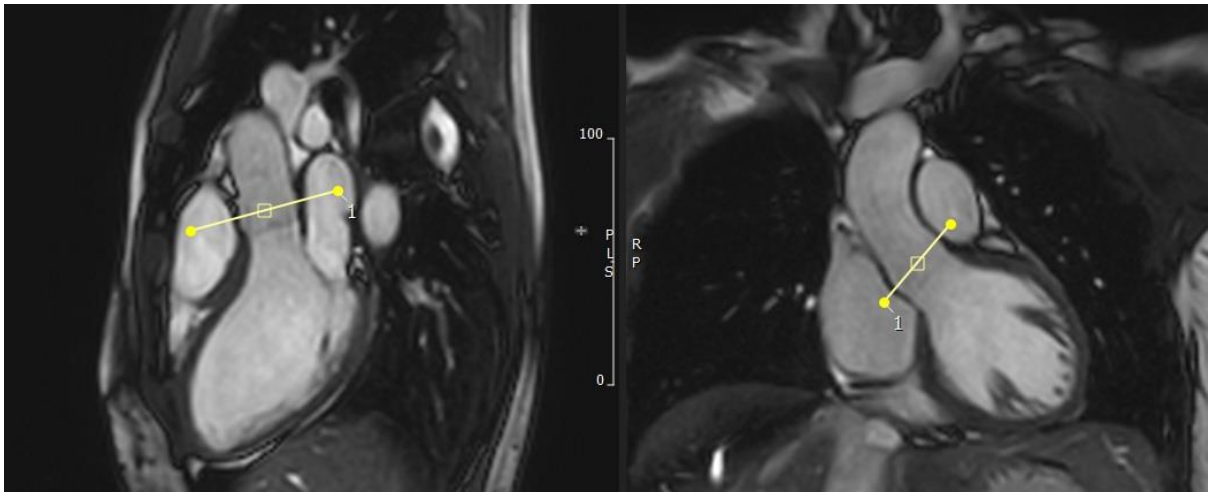

Figure 1-5 Planning views for aortic valve phase contrast acquisition

Image panel showing the two left ventricular outflow tract views used for planning an aortic valve phase-contrast acquisition. The yellow line represents the planning which takes place in the sagittal-oblique and coronal views. The vessel of interest (in this case the aorta) should be perpendicularly intersected in 2 planes. In the case of eccentric jets from stenotic valves (such as in the case of bicuspid aortic valve disease), off-axis planning may be required to ensure that the jet is intersected in an orthogonal manner.

The aliasing velocity needs to be set by the operator according to the estimated peak velocity of the blood at the sampling site. If the blood velocity exceeds this velocity, aliasing occurs (due to the phase shift exceeding 180^0) and can lead to artefactual flow results. Hence, it is imperative that this is recognised at the time of scanning and a repeat phase contrast acquisition takes place at progressively higher velocity encoding (VENC) speed until no aliased pixels are present. If the VENC is set too high the SNR is reduced which can lead to an underestimation of flow. Acquisition is triggered to the R wave on the Vectorcardiogram (VCG) and can be either prospectively acquired (in the case of breath held imaging) or retrospective (in the case of free breathing acquisitions). In prospective (breath held) phase-contrast imaging, information from late diastole is not acquired which can lead to underestimation of aortic regurgitant fraction so it is recommended that free-breathing acquisitions are used for this purpose. Typically prospective breath held images are used for the quantification of forward flow. Therefore it

is imperative that studies involving flow measurements are performed by an operator with an in-depth understanding of the CMR evaluation of valvular heart disease. Like most CMR acquisitions, phase-contrast imaging is susceptible to artefacts. Small errors can combine to give significant inaccuracies in flow [199]. The technique is also limited by reduced temporal resolution (in comparison with Doppler echocardiographic imaging), can be inaccurate in the case of turbulent flow such as that occurring distal to a stenotic aortic valve, and is susceptible to phase shift errors [200]. For these reasons, and due to partial volume averaging effects, peak velocities derived from phase contrast imaging across stenotic valves are usually lower than those seen with echocardiography and the two measures cannot be used interchangeably [201]. In view of this, stroke volume may be underestimated in the context of severe AS, and if this is used to calculate the mitral regurgitant volume, this in turn may be overestimated and is a limitation to all CMR studies reporting mitral regurgitation in the context of AS. Phase contrast imaging works well in the context of aortic regurgitation, and is an established technique for the assessment of aortic regurgitation following TAVI, where both transoesophageal and transthoracic echocardiography underestimate the degree of regurgitation due to the eccentric nature of the aortic regurgitant jet [203, 204]. As example of phase contrast imaging can be seen in Figure 1-6.

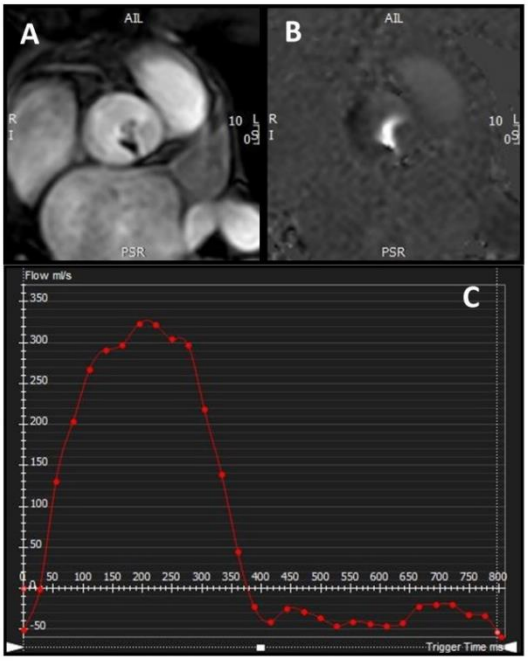

Figure 1-6 Assessment of aortic flow using CMR

Panel A depicts a typical modulus image of the aortic valve in cross section. This is used to allow the CMR analyst to contour around the aorta in each phase of the cardiac cycle, with care being taken to exclude any artefact, in order to derive the region of interest (ROI). Panel B depicts the velocity map of the individual pixels during systole. Stationary tissue appears grey, with forward flow appearing white and backward flow represented by darker shades. The bright white in the centre of the image depicts the high velocity at the centre of the stenotic jet. Panel C depicts the flow curve generated by contouring of the modulus image. The positive deflection represents forward flow velocity in cm/sec (which in this case is elevated due to the stenotic valve) and the negative deflection represents aortic regurgitation, which in this case is pan-diastolic. Quantitative measures such as peak pressure gradient can be calculated using the Bernoulli equation, and regurgitant volume and fraction can also be easily derived using post-processing software.

1.9. The use of CMR for fibrosis assessment

Until the advent of CMR, histological diagnosis (either at autopsy or from myocardial biopsy) was relied upon for research into myocardial fibrosis. Its invasive nature meant that its use as a research tool was limited, rendering longitudinal studies of MF almost impossible. CMR scanning allows *in vivo* assessment of myocardial fibrosis by means of late gadolinium enhancement imaging and more recently, myocardial longitudinal relaxation (T1) mapping. LGE imaging is based on the principle that Gadolinium-based contrast enters the extracellular matrix and then is ‘washed out’ of the extracellular space by capillary blood flow. In areas of fibrosis there is an increase in extracellular space due to myocyte shrinkage or cellular necrosis/apoptosis and therefore increased gadolinium concentration coupled with reduced capillary blood flow and hence accumulation of gadolinium contrast over a period of 8-15 minutes. Gadolinium based contrast agents reduce the T1 relaxation time and hence produce more signal on the image such that areas of delayed contrast washout appear ‘bright’ on CMR images

using inversion-recovery gradient echo pulse sequences in contrast to the normal 'nulled' healthy myocardial tissue which appears dark. Semi-automated computer software allows these areas of myocardial scar/fibrosis to be quantified using different threshold techniques, which are based on the difference in signal intensity between normal nulled myocardium and abnormal fibrosed or scarred regions [205]. Different methods of LGE quantification have been described in a wide range of settings, and no consensus has been reached in the literature regarding the optimal thresholding methods to be used, however, it is likely that computer aided algorithms improve accuracy compared with visual assessment [206]. This variation in methods often leads to the differing mass of fibrosis or infarct LGE reported in the literature [49, 167, 193].

CMR LGE for the assessment of fibrosis has been validated using histopathological studies in patients with AS [193, 207]. Nigri et al [207] performed a baseline 1.5T CMR on 35 patients with severe symptomatic AS who subsequently had myocardial biopsy taken at the time of SAVR. The presence of LGE was assessed by two observers blinded to clinical and histological data. Regions of increased fibrosis were defined as areas of distinct hyperenhancement on subjective visual assessment. When compared with the histological diagnosis, CMR had a sensitivity and specificity of 67% and 82% respectively for the identification of myocardial fibrosis. Azevado et al [192] have validated CMR LGE fibrosis quantification in patients with severe AS undergoing aortic valve replacement. They used the threshold of 2 standard deviations technique and compared values with specimens obtained from myomectomy at the time of surgery. There was good agreement of MF measurements in 20 patients with a mean difference of 0.10% (95% CI -0.29 to 0.49%). They also reported excellent inter- and intra-observer variability. The threshold of 5 standard deviation approach has been found to correlate best with visual assessment of diffuse/focal fibrosis in a large population of patients with non-ischaemic cardiomyopathy [208]. MF quantified using the full width at half maximum technique has been shown to be a predictor of mortality in patients with AS [49]. The threshold of 2 standard deviations method may be the best method to use for the quantification of myocardial infarction as it has been shown to be a powerful predictor of all-cause mortality in patients with ischaemic cardiomyopathy [209], however, it may overestimate infarct mass compared with other techniques [210].

More recently, T1 mapping has been developed to more accurately measure diffuse myocardial fibrosis by quantification of extracellular volume. This technique quantifies the T1 relaxation time of each voxel of the displayed image using a standard scale in order to allow the practitioner to understand the properties of the myocardial tissue independent of function and assess for the presence of diffuse fibrosis. T1 maps can be acquired in a single breath hold using material-enhanced modified Look-Locker inversion recovery (MOLLI) imaging at both 1.5 and 3 Tesla magnet strengths [211-213]. Native T1 values can be derived from non-contrast MOLLI imaging without the need for contrast. Although native T1 values have the potential to more accurately quantify the diffuse fibrosis associated with pressure overload states, the technique is limited by a lack of uniform reference ranges, and the fact that values differ according to vendor, pulse sequence and magnet strength [212]. Although various techniques have been developed to try and improve reproducibility and image quality such as better inversion pulses, motion correction and curve fitting [214], the pitfalls including artefact from partial voluming and reliance on good breath holding (a particular problem in the elderly aortic stenotic population) mean that to date, its use is limited, The addition of 15 minute post-contrast MOLLI imaging allows the extracellular volume fraction to be calculated provided that the blood haematocrit level at the time of the scan is known. Myocardial fibrosis is associated with increased T1 values on pre-contrast imaging and reduced T1 values on post-contrast imaging, corresponding to an increased measured extra-cellular volume. T1 mapping is still however considered a research technique due to variations in absolute values according to vendor, pulse sequence, timing of image acquisition and method of gadolinium administration [212]. T1 mapping has been used to characterise diffuse fibrosis in patients with aortic stenosis at both 1.5 and 3T field strengths [215-218] but longitudinal data on changes following valve replacement are lacking.

1.10. Aims of the thesis

With the advent of TAVI, there has been a renewed interest in aortic valve disease but studies of cardiac remodelling in AS and the response of the LV to aortic valve replacement are mainly limited to the more qualitative technique of echocardiographic assessment [187]. The unique ability of CMR to assess for fibrosis and myocardial infarction (using LGE quantitation), alongside the ability to assess flow (especially in the context of aortic regurgitation post-TAVI, where echocardiographic assessment is challenging [204]), and the novel technique of feature tracking allowing assessment of global longitudinal strain and dyssynchrony, mean that it is ideally placed to comprehensively study the effects of AS and valve replacement on cardiac reverse remodelling.

The aims of the thesis are outlined for each chapter:

Chapter 3: 1) To use CMR to comprehensively evaluate the differences in cardiac remodelling in AS according to gender, including characterisation of the differing patterns and distribution of myocardial fibrosis and predictors of cardiac remodelling at baseline and 2) to evaluate cardiac reverse remodelling at 6 months following aortic valve replacement according to gender.

Chapter 4: 1) To describe the patterns of myocardial fibrosis at baseline in patients with AS undergoing TAVI and SAVR and 2) to compare rates of post-procedural myocardial infarction between the two groups and investigate its impact on post-procedural LVEF.

Chapter 5: To assess acute reverse cardiac remodelling within the first week following TAVI and its link to baseline myocardial fibrosis.

Chapter 6:To evaluate the impact of TAVI-induced left bundle branch block on cardiac reverse remodelling 6 months post-procedure using standard SSFP imaging and the novel technique of CMR Feature Tracking to assess for cardiac dyssynchrony and global longitudinal strain.

This was achieved by obtaining CMR scans of patients with severe AS undergoing either surgical or trans-catheter aortic valve replacement at baseline (pre-procedure) and post-procedure at two discrete timepoints (prior to hospital discharge to assess for early reverse remodelling and 6 months post-procedure for investigation of the remaining hypotheses). A comprehensive CMR was obtained, including cine imaging (to allow quantitation of cardiac mass, volume, function and feature tracking analysis), velocity encoded phase contrast imaging of the aortic valve and, in the case of the baseline and 6 month scans, late gadolinium enhancement imaging for the assessment of myocardial infarction and fibrosis.

Methods common to all four chapters have been outlined in Chapter 2 (General Methods). Each topic has been studied and discussed in depth and forms a results chapter in its own right, with an appropriate introduction, methods (describing any methods specific to that particular chapter), results and discussion section.

Chapter 2: Methods

2.1. Patient selection and recruitment

Between January 2009 and April 2015 (recruitment January 2009 to March 2014; performed by other members of the TAVI research team, see pages 2-5), patients with severe AS undergoing either TAVI or SAVR with or without concomitant coronary artery bypass grafting (CABG), at a single tertiary center (Leeds General Infirmary, Leeds, UK) were recruited from the cardiology and cardiac surgery out-patient departments. As the patients undergoing TAVI are inherently older, frailer and at higher surgical risk than those undergoing SAVR, attempts were made to recruit SAVR patients which more closely matched the TAVI cohort, by selectively recruiting older patients and those with higher baseline co-morbidity. Severe AS was defined as an echocardiographically derived aortic valve area of $\leq 1.0 cm^2$, peak aortic velocity of >4m/sec or mean pressure gradient of >40mmHg using standard criteria outlined by the American Society of Echocardiography [219]. Baseline echocardiographic data including aortic valve area, peak pressure gradient, mean pressure gradient, left ventricular ejection fraction and pulmonary artery pressure were recorded for all patients. Decision for aortic valve intervention was made by a dedicated heart team including interventional and imaging cardiologists and cardiac surgeons [65]. In general, patients were recommended for TAVI over SAVR in the case of elevated surgical risk, previous coronary artery bypass surgery with patent grafts, porcelain aorta, hostile mediastinum from prior radiotherapy or frailty. Inclusion and exclusion criterion for entry into the TAVI study can be seen in Table 2-1. **Error! Reference source not found.** In the case of renal failure with an estimated glomerular filtration rate of $<30 ml/min/1.73m^2$, patients were still recruited to take part in the study but intra-venous Gadolinium based contrast was not given due to the theoretical risk of nephrogenic systemic fibrosis [220].

Table 2-1 Inclusion and exclusion criteria

Inclusion	Exclusion
Severe AS undergoing TAVI or SAVR	Contraindication to CMR e.g. non-MRI compatible pacemaker, intra-orbital metal, claustrophobia
Age >18 years	AS not the predominant lesion
	Pregnancy or breastfeeding
	Weight >130kg
	Inability to lie flat for 60 minutes
	Inability to provide informed consent

AS: Aortic stenosis. CMR: Cardiovascular magnetic resonance. MRI: Magnetic resonance imaging. TAVI: Trans-catheter aortic valve implantation. SAVR: Surgical aortic valve replacement

Clinical, demographic and echocardiographic data were collected prospectively. All patients provided written informed consent. The patient information sheet and consent form can be seen in the Appendix. The study was approved by the institutional ethics committee (08/H1307/106 see Appendix) and complied with the declaration of Helsinki.

2.2. Surgical aortic valve replacement

SAVR was performed using a standard technique on cardiopulmonary bypass via a midline sternotomy incision and mild systemic hypothermia (30-34^{o}C) using intraoperative transesophageal echocardiography. Systemic heparinisation with standard aorto-right atrial cannulation was used to establish cardiopulmonary bypass. 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 characteristics including valve type and size, cross clamp time and cardiopulmonary bypass time were collected for all patients. Aspirin monotherapy was prescribed for 3 months post-procedure, except in the case of atrial fibrillation or mechanical valve implantation, where warfarin monotherapy was administered.

2.3. Trans-catheter aortic valve implantation

TAVI was performed under general anesthetic with X-ray fluoroscopy and transoesophageal echocardiography guidance using the self-expanding Medtronic CoreValve, Engager and Evolut-R devices, the balloon expandable Edwards Sapien 3, and the mechanically expanded Boston Lotus valve by two experienced, high volume operators performing over 150 implants/year. Valve sizing was achieved by annulus measurements taken from gated cardiac computed tomography or 3D transoesophageal echocardiography. Trans-femoral approach was preferred but other approaches (subclavian, carotid, direct aortic and apical) were used if the femoral vessels were found to be unsuitable due to calcification, stenosis or tortuosity. Balloon valvuloplasty was performed before device deployment in the majority of cases and patients typically underwent 2-3 bouts of rapid right ventricular pacing during the implant procedure. For implants prior to 2014, general anaesthetic with transoesophageal and fluoroscopic guidance was used. From 2014 onwards, the majority of femoral implants were performed under local anaesthetic with conscious sedation using transthoracic echocardiographic and fluoroscopic guidance. All patients received heparin via a standardized regimen to achieve and maintain an activated clotting time of >250s. Dual anti-platelet therapy (aspirin 75mg/day and clopidogrel 75mg/day) was administered for 3-6 m post-procedure with aspirin monotherapy thereafter, or in the case of need for full anticoagulation (such as AF, previous venous thromboembolism etc.), warfarin monotherapy was prescribed. Procedural characteristics including invasive valve gradient, pre and post procedure diastolic blood pressure and left ventricular end diastolic pressure, valve type and size, procedure time, screening time and contrast dose were recorded for all patients.

2.4. CMR protocol

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 60^0, 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 including standard 4 chamber, 2 chamber and short axis views were also obtained. Two left ventricular outflow tract views were obtained in sagittal-oblique and coronal views (3-5 slices, 6mm slice thickness, 0mm interslice gap, 30 phases, typical field of view 380mm) to allow planning of aortic valve Q flow imaging. Aortic flow data were acquired using a free breathing (for regurgitation) and breath-hold (for forward flow) retrospectively gated phase contrast velocity encoding technique, sensitized for flow in the through plane direction (TR 4.3ms, TE 2.6ms, flip angle 15^o, slice thickness 6mm, 40 phases, number of signal averages 1, typical voxel size $1.2x1.2x8mm^3$, depending on patient size). 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. VENC was typically set at 400-500cm/sec on the baseline scan and 250cm/sec post-procedure. If aliasing occurred at the pre-set VENC, sequential phase contrast imaging was performed at increasing VENC settings until the aliasing artefact had disappeared.

LGE imaging using an inversion recovery-prepared T1-weighted gradient echo pulse sequence (TE 1.79msec; TR 4.8msec; flip-angle 15^o, spatial resolution 1.46 x 1.46 x 10mm) was performed with inversion time (TI) individually adjusted according to TI scout (Look-Locker sequence, single mid-ventricular slice, 11mm thickness, field of view 390mm). This was planned to cover the entire left ventricle in short axis (10-12 short axis slices, 10mm thickness, no interslice gap, matrix 240 x 240, typical field of view 350mm), 10-15 minutes after 0.2mmol/kg of Gadoteric acid administered by hand injection (godoterate meglumine, Dotarem, Guerbet, SA, Villepinte). This agent was specifically chosen as it has never been reported to be associated with nephrogenic systemic fibrosis and hence felt to be the safest to be used in our elderly population [221]. Four chamber, two chamber and left ventricular outflow tract (LVOT) views were also obtained as standard. Cross cuts and phase swap imaging were used where necessary for further clarification of the presence/absence of LGE.

2.5. CMR analysis

CMR analysis was performed by a single operator with 5 years' experience in CMR blinded to clinical and echocardiographic data, using dedicated computer software (CVI[42], Circle Cardiovascular Imaging, Calgary, Alberta, Canada). LV endocardial and epicardial contours were manually traced (with trabeculation and papillary muscles excluded) in systole and diastole in order to derive end diastolic volume and end systolic volume measurements using the summation of discs methodology [222]. LV mass was calculated using Equation 1, a technique which has been validated using autopsy studies and has been shown to have excellent reproducibility and inter-study variability[223]. All values were indexed to body surface area. LV mass was quantified without papillary muscles and trabeculations as it is the method used clinically in our centre and hence the method with which the investigator had most experience. In order to demonstrate that LV mass calculation was more reproducible without the inclusion of papillary muscles, inter and intra-observer reproducibility was performed on 10 randomly selected patients with and without the inclusion of papillary muscles. The co-efficient of variation was calculated by dividing the standard deviation of the differences between measurements divided by their general mean and expressed as a percentage. Intra-observer variability without papillary muscle contouring was 3% for LV end diastolic volume (LVEDV) and 5% for LV mass (LVM) and 9% for LVEDV and 8% for LVM when papillary muscles were included. Similarly, inter-observer variability was reduced with exclusion of papillary muscle contouring (LVEDV 2%, LVM 5%) than the method with papillary muscles included (LVEDV 13%, LVM 9%).

$$\text{LV mass} = (epicardial\ volume - endocardial\ volume)x\ 1.05$$

Equation 1 LV mass calculation

Septal and lateral wall thickness were measured on the mid-ventricular short axis cine using calliper measurements of the septal and lateral wall at the point of maximal thickness at end diastole. Left atrial volume was calculated as per Equation 2 [224] from the left atrial area and length measured on the 4 chamber and 2 chamber cine imaging.

Left atrial volume (ml) = 8 (2 chamber LA area) (4 chamber LA area) / 3πL

Where L is the shorter of the two left atrial length measurements

Equation 2 Left atrial volume calculation

Longitudinal LV and RV function (MAPSE and tricuspid annular plane systolic excursion (TAPSE)) was assessed by using mitral and tricuspid annular excursion. In the 4 chamber SSFP cine image, atrioventricular motion was measured at the lateral junction points between the left and right atrium and ventricle at end systole and end diastole. The perpendicular distance between these two points was measured (Figure 2-1).

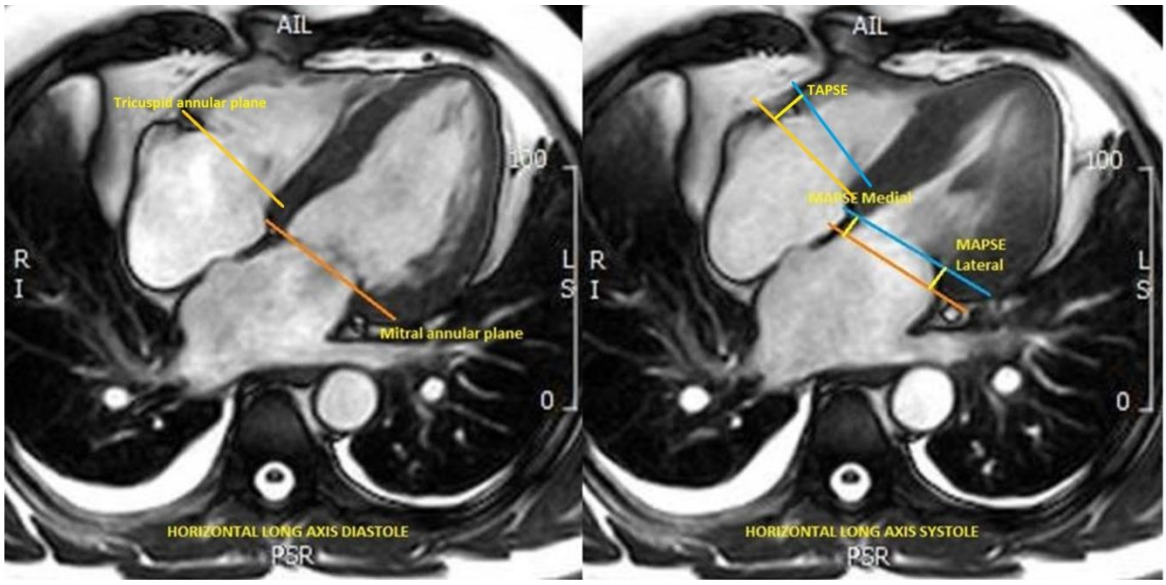

Figure 2-1 Assessment of longitudinal function

End diastole was identified and a reference line was drawn across the atrioventricular valve plane and forwarded across all phases of the cine image (left hand panel). A further line is drawn in end-systole. The distance between the two points at the tricuspid annulus (TAPSE), medial mitral valve annulus (MAPSE medial) and lateral mitral valve annulus (MAPSE lateral) was measured and expressed in mm.

Aortic flow was quantified using a combination of prospectively gated breath held (for flow measurements) and retrospectively gated free-breathing (for regurgitant measurements) cross-sectional phase contrast images with contouring of the aortic lumen to provide a peak forward flow velocity (m/sec), regurgitant volume (ml) and regurgitant fraction (%). Mitral regurgitation fraction was calculated according to Equation 3.

$$\text{Mitral regurgitation fraction} = [(LV\ stroke\ volume - aortic\ stroke\ volume)/ LV\ stroke\ volume]*100$$

Equation 3 Calculation of mitral regurgitation fraction

For analysis of the LGE images, each short axis slice was visually inspected for the presence or absence of LGE by 2 operators independently blinded to clinical and procedural data. Any discrepancy between the two operators was reviewed by a third operator to reach a consensus decision. Phase swap, cross cut and other geometry images were used in order to assist in decision making where required. The pattern of LGE was classified as either focal/mid-wall pattern or infarct pattern. Patients with a mixed pattern of LGE were assigned to the group according to the predominant pattern of LGE. Presence of new LGE was determined by direct comparison of pre and post-procedure scans. In those slices deemed to have LGE present, epi 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. The number and location of segments containing LGE were classified according to the AHA 17 segment model [225]. LGE quantification methods and a justification for their use are described in individual chapters.

2.5.1. Inter- and intra-observer variability

For the assessment of inter-observer variability, two independent investigators analysed LV volume, mass and function on 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 one month apart. The co-efficient of variation was calculated by dividing the standard deviation of the differences between measurements divided by their general mean and expressed as a percentage. Intra-observer variability for LV quantitation was 2.6%, 5.0% and 2.6%for LVEDV, LVM and LVEF respectively. Inter-observer variability 1.4%, 4.5% and 3.7% for LVEDV, LV mass and LVEF respectively. These findings are in keeping with reproducibility data published investigating patients with left ventricular systolic dysfunction and hypertrophy [188, 189]. Bland-Altman plots can be seen in Figure 2-2**.**

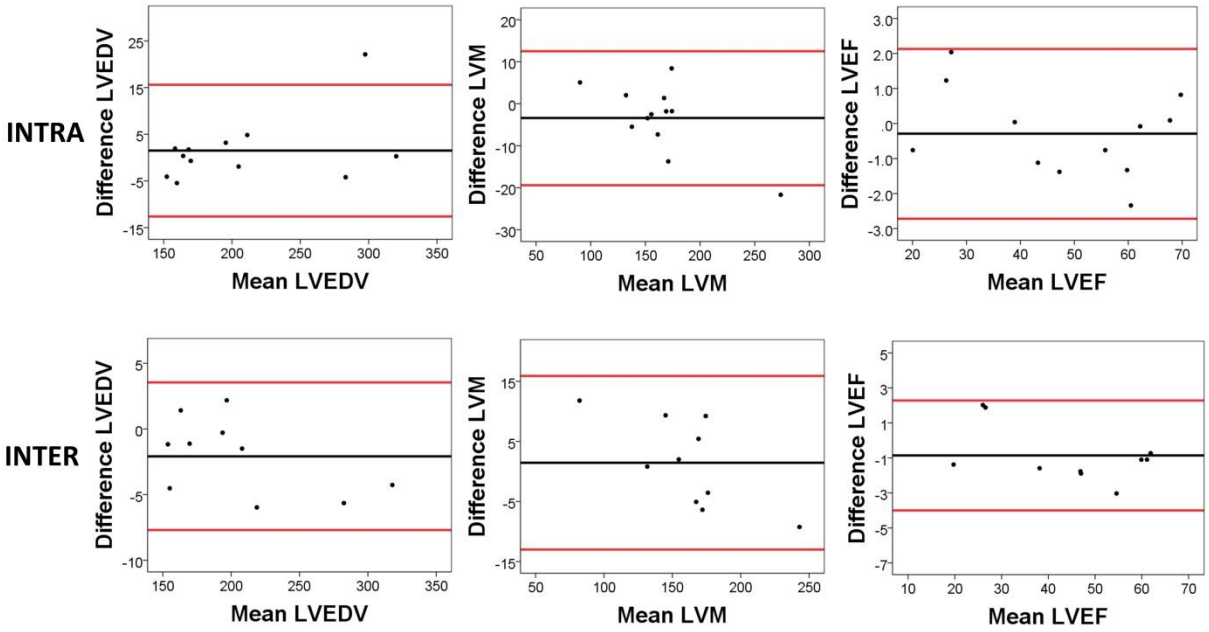

Figure 2-2 Bland Altman plots for LV volume, mass and function reproducibility

Bland-Altman Plots showing Intra- and inter-observer variability for LVEDV, LV mass and LVEF. The black line represents the mean of the differences between measurements and the red lines represent the 95% confidence intervals for the mean of the differences between measures.

For reproducibility of LGE and aortic flow quantification, an intra-class correlation was used in order to compare it with values from previously published studies [226, 227]. For LGE reproducibility 10

studies including a mixture of those with mid-wall/focal fibrosis and infarct pattern LGE were chosen at random using the threshold of 5 standard deviations technique. For the aortic flow reproducibility, 9 baseline studies were chosen at random with regurgitant fraction reproducibility performed on the non-breath held acquisitions and peak velocity figures derived from the breath held acquisitions. For intra-observer variability, the same dataset was analysed by the author 1 month following the first analysis. The intra-class correlation (ICC) for LGE quantification was 0.979 for inter-observer variability and 0.995 for intra-observer variability, which is in keeping with other studies of LGE quantification [226]. The inter-observer ICC for aortic flow quantification was 0.963 for peak velocity and 0.986 for aortic regurgitant fraction. The intra-observer ICC for aortic flow quantification was 1.00 for peak velocity and 0.983 for aortic regurgitant fraction, again these figures being congruous with the current published literature [202, 227]. Graphical representation of this can be seen in the Bland Altman plots displayed in Figure 2-3.

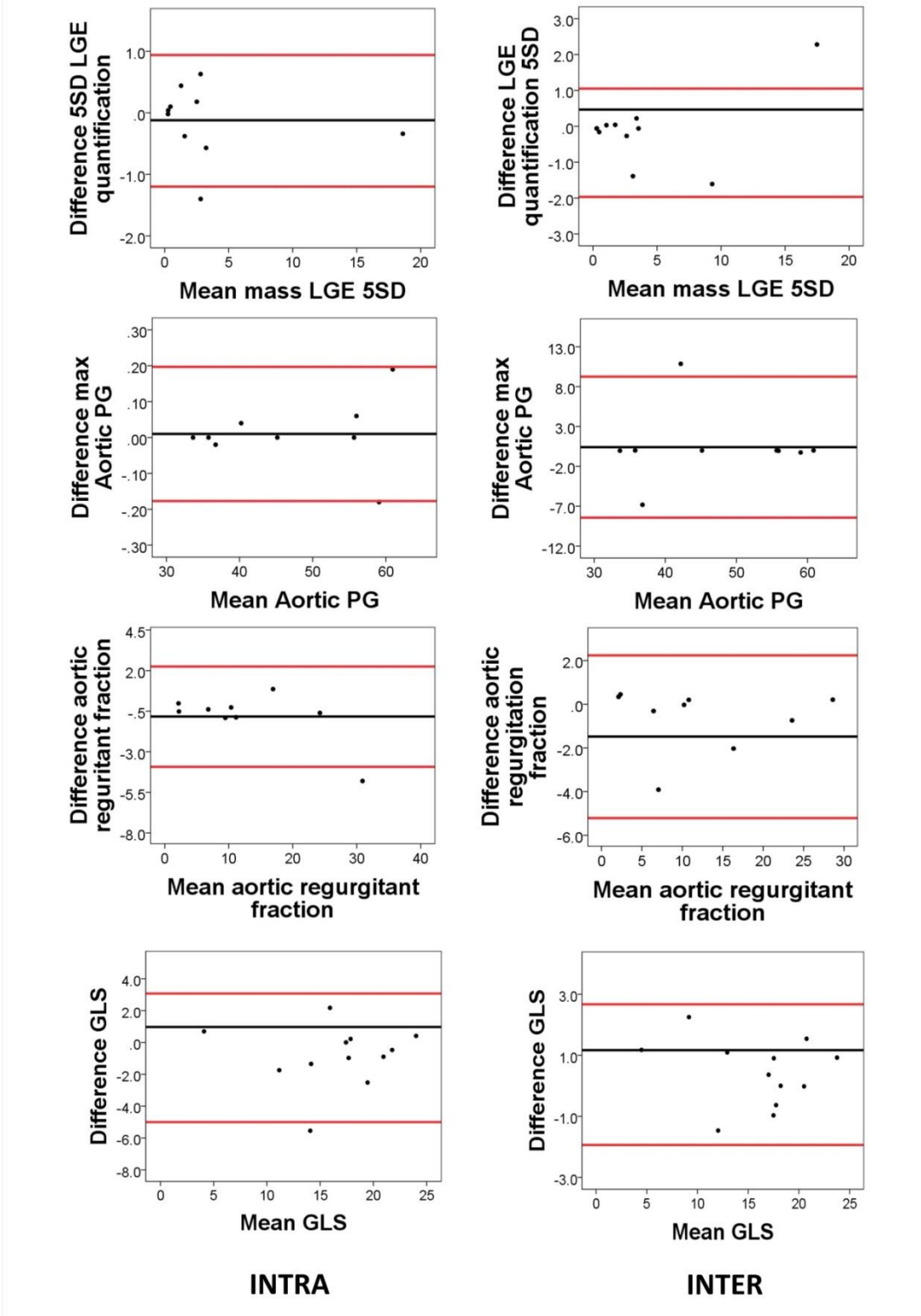

Figure 2-3 Bland Altman plots of flow, LGE and GLS reproducibility

Bland-Altman plots demonstrating reproducibility of LGE, aortic flow and GLS quantification. The black line represents the mean of the differences and the red lines represent the 95% confidence intervals.

For the assessment of inter-observer variability for the Feature Tracking analysis, two independent investigators analysed LV GLS and time to peak radial strain on a random selection of 10 patients. For intra-observer a similar dataset from 10 patients was analysed twice by one investigator, one month apart. The coefficient of variation was calculated by dividing the standard deviation of the differences between measurements by their mean and expressed as a percentage. Intra-observer variability was 6.8% and 9.1% and inter-observer variability was 9.2% and 12.6% for GLS and time to peak radial strain respectively.

2.6. Statistical analysis and sample size

All statistical analysis was performed using the PASW software package (V21, SPSS, IBM, Chicago, Illinois, USA). Data are presented as mean±SD, median (interquartile range, IQR) or frequency (percentage). Data were tested for normality using the Shapiro-Wilks 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. To compare between groups an analysis of variance (ANOVA) and Tukey *post-hoc* tests were used. The Chi-squared test was used for comparing categorical variables. Pearson's correlation coefficients were used to assess the correlation of dependent and independent variables. P values <0.05 were considered statistically significant. Based on the published data by Bellenger et al [189], the group size required to detect a 10ml change in LVEDV is 12 patients, 10 patients to detect a 10ml change in LVESV, 15 to detect a 3% change in LVEF and 9 to detect a 10g change in LV mass.

Chapter 3: Gender differences in cardiac remodelling in severe aortic stenosis and reverse remodelling following aortic valve replacement

3.1. Abstract

Background: Cardiac adaptation to AS appears to differ according to gender but reverse remodelling following aortic valve replacement has not been extensively described. The aim of the study was to determine using CMR imaging, whether any gender-related differences exist in AS in terms of LV remodelling, myocardial fibrosis and reverse cardiac remodelling after valve replacement.

Methods: One hundred patients (men, n=60) with severe AS undergoing either trans-catheter or surgical aortic valve replacement underwent CMR scans at baseline and 6 months following valve replacement.

Results: Despite similar baseline co-morbidity and severity of AS, women had a lower indexed LV mass than men (65.3 ± 18.4 vs. 81.5±21.3g/m^2, p<0.001) and a smaller LVEDVi (87.3±17.5 vs. 101.2±28.6ml/m^2, p=0.002) with a similar LVEF (58.6±10.2 vs. 54.8±12.9%, p=0.178). Total myocardial fibrosis mass was similar between genders (2.3±4.1 vs. 1.3±1.1g, p=0.714) with a differing distribution according to gender. Following aortic valve replacement, men had more absolute LV mass regression than females (18.3±10.6 vs. 12.7±8.8g/m^2, p=0.007). When expressed as a percentage reduction of baseline indexed LV mass, mass regression was similar between the genders (men 21.7±10.1 vs. women 18.4±11.0%, p=0.121). There was no gender-related difference in post-procedural LVEF or aortic regurgitation. Gender was not found to a predictor of LV reverse remodelling on multiple regression analysis.

Conclusions: There are significant differences in the way that male and female hearts adapt to AS. At 6 m following aortic valve replacement, there are no gender-related differences in reverse remodelling.

3.2. Introduction and study aims

Gender related differences in LV remodelling in response to a wide range of diseases have been extensively explored [228], but the impact of gender on AS and following aortic valve replacement (AVR) is less well described. AS is the commonest valve lesion in the developed world, and with an ageing population its incidence is increasing [4]. AVR has been shown to reduce mortality, and improve patient symptoms and health related quality of life [229-231]. Evidence suggests that women have higher pre-operative morbidity and mortality [232] and lower referral rates [233]. It remains controversial as to whether gender impacts on survival following SAVR , however, females appear to have improved long term survival following TAVI [10, 43, 44]. The longer life expectancy of women or other factors such as LV remodelling and myocardial fibrosis may be implicated. Echocardiographic and CMR studies suggest that men and women remodel differently to the pressure overload of AS [16, 234] and may also reverse remodel differently following AVR [26, 42]. Moreover, gender-related differences in MF may play a key role in any reverse remodelling [167]. The primary aim of this chapter was to determine whether any gender-related differences exist in severe AS in terms of LV remodelling in response to the valve lesion, reverse remodelling after valve replacement and MF.

3.3. Methods specific to this chapter

3.3.1. Patient recruitment

Between January 2009 and April 2014, 135 patients with severe AS undergoing eith er SAVR with or without concomitant coronary artery bypass grafting or TAVR at a single tertiary centre (Leeds General Infirmary, Leeds, UK) were prospectively recruited.

3.3.2. CMR protocol and analysis

Identical CMR scans were obtained on the same imaging platform at baseline (median 1 day pre-procedure, IQR 14 days) and at a median of 6 m (IQR 1 m) following aortic valve intervention using the same 1.5T scanner.

For the purposes of categorising aortic regurgitation fraction, a threshold of >16% was used to delineate significant AR [235]. Significant mitral regurgitation was defined as >40% as per the American Society of Echocardiography guidelines [236]. A threshold of 5 standard deviations method was used for LGE quantitation in this study for the quantification of focal and replacement fibrosis, as it has been previously validated in patients with non-ischaemic cardiomyopathy [208], and in our opinion was able to best evaluate for the presence of both focal and replacement fibrosis (Figure 3-1).

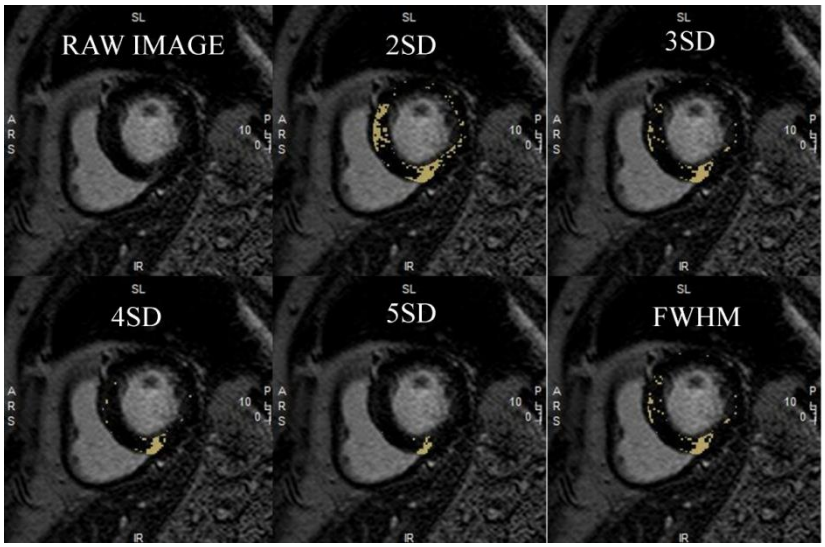

Figure 3-1 Differing methods of LGE quantification

Panel showing the different methods of LGE quantification. The upper left hand panel shows the raw image, a single mid-ventricular short axis LGE slice, with evidence of focal fibrosis in the left ventricular septum at the inferior right ventricular insertion point. The following five panels show the differing techniques of automatic quantification. The threshold of 2 standard deviations and full-width half maximum technique appeared to overestimate the volume of fibrosis compared with visual assessment. The threshold of 5

standard deviation technique most closely matched visual assessment and was therefore chosen for this results chapter.

3.3.3. Statistical methods specific to this chapter

Linear regression analysis was used to identify the main predictors of LV remodelling at baseline and reverse remodelling following AVR and to derive parameter estimates for those predictors and for the differences in gender. First, univariate regression analysis was performed using baseline measurements entered as covariate factors. All clinically significant variables and those with a $P<0.1$ on univariate analysis were subject to exploratory analysis to exclude those with weak or no correlation with the dependent variable, before entering them into a stepwise multiple linear regression model to identify the main predictor or combination of predictors in a multivariable model. Where multiple predictors were identified, the main predictor was determined through further analysis of correlations between variables and robustness of parameter estimates to model specification. Finally, the main predictor was entered with gender in a multivariable linear regression model and the resulting parameter estimates in the final multivariable model were compared with those for the relevant variables in the univariate analysis. Based on the paper by Bellenger et al [189], the sample size to detect a 10ml difference in LVEDV and LVESV, a 3% change in LVEF and a 10g change in LVM with a power of 90% and $p<0.05$ using CMR is 12, 10, 15 and 9 respectively.

3.4. Results

135 patients were recruited into the study. 60 men and 40 women with severe AS completed both baseline and 6-month post-procedure CMR scans. Reasons for non-completion were varied and are depicted in Figure 3-2.

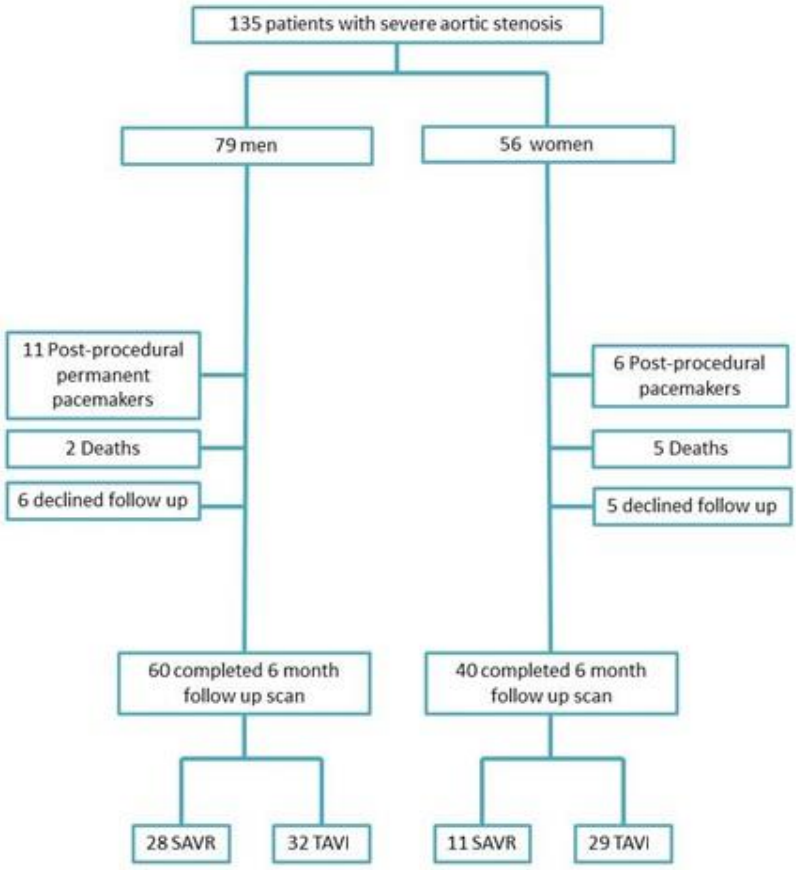

Figure 3-2 Patient recruitment pathway

SAVR: Surgical aortic valve replacement. TAVI: Trans-catheter aortic valve implantation.

There was no significant difference between the group that completed the 6 month CMR protocol indicating that the demographics of the analysed patients were representative of the larger population (Table 3-1). Baseline demographic, clinical and echocardiographic characteristics of the final study population can be seen in Table 3-2.

3.4.1. Baseline left heart characteristics

At baseline, women with severe AS had lower indexed LV mass (LVMi) than men (65.3± 18.4 vs. 81.5±21.3g/m2, $p<0.001$) alongside smaller LVEDVi (87.3±17.5 vs. 101.2±28.6ml/m2, $p=0.002$) and LVESVi (37.3±16.6 vs. 47.9±25.6ml/m2, $p=0.036$). A typical example of the different patterns of remodelling can be seen in Figure 3-3. Further baseline differences according to gender can be seen in Table 3-3. Men had more aortic regurgitation (AR) at baseline (regurgitant fraction (RFrac) men

15.1±12.4 vs. women 9.6±9.2%, p=0.013). Significant AR (defined as RFrac >16%) at baseline was seen in 23 (38%) men and 7 (18%) women (p=0.026). There was a significant correlation between baseline LVMi and AR fraction in men (r=0.455, p<0.01) and in women (r=0.577, p<0.001). There was also a relationship between AR fraction and LVEDVi in men (r=0.433, p<0.001), but not in women (r=0.140, p=0.400). When those with significant baseline AR were excluded, men still had greater LVMi than women (LVMi men 77.1±16.5 vs. women 61.9±13.8g/m^2, p=<0.001). Mitral regurgitation (MR) was similar for both genders (RFrac men 33.8±19.8 vs. women 26.9±21.3%, p=0.09). Significant MR was seen in 24 (40%) men and 10 (25%) women at baseline (p=0.121). Baseline MR fraction was associated with baseline LVMi and LVEDVi on univariate analysis (Table 3-4), but was not found to be an independent predictor of baseline remodelling on multivariate analysis (Table 3-5). Gender and baseline aortic and mitral regurgitation fraction were univariate predictors of baseline LVMi and baseline LVEDVi (Table 3-4). Gender and baseline AR remained independent predictors of baseline LVMi on multiple regression analysis. Only baseline AR fraction was an independent predictor of baseline LVEDVi (Table 3-5).

Table 3-1 Baseline characteristics of the recruited and analysed population

	Recruited patients			Patients completing 6m follow up		
	Total (n= 135)	**Men (n=79)**	**Women (n= 56)**	**Total (n=100)**	**Men (n=60)**	**Women (n=40)**
Age	77.5±7.9	75.6±7.1	80.1±8.4	77.0±8.2	75.3±7.2	79.9±8.90
Systolic blood pressure, mmHg	131 ± 22	130 ± 22	134 ± 23	131 ± 23	129 ± 22	134 ± 24
NYHA	3.0 ± 0.6	2.9 ±0.6	3.1 ± 0.6	2.9 ± 0.6	2.9 ± 0.6	3.0 ± 0.6
EuroSCORE II, %	4.3 ± 4.1	3.9 ± 3.6	4.8 ± 4.8	4.0 ± 4.3	3.9 ± 3.7	4.5 ± 5.1
Hypertension	72 (53)	40 (51)	32 (57)	55 (55)	31 (52)	24 (60)
Diabetes	32 (24)	20 (25)	12 (21)	21 (21)	11 (18)	10 (25)
Atrial Fibrillation	29 (22)	17 (22)	12 (21)	19 (19)	13 (22)	6 (15)
Previous myocardial infarction	25 (19)	18 (23)	7 (13)	15 (15)	9 (15)	6 (15)
Previous CABG	25 (19)	18 (23)	7 (13)	19 (19)	14 (23)	5 (12.5)
Pulmonary hypertension	37 (27)	21 (27)	29 (52)	24 (24)	15 (25)	9 (22.5)
Echocardiographic data						
AVAi, cm/m^2	0.33 ± 0.1	0.33 ± 0.10	0.34 ± 0.10	0.35 ± 0.09	0.35±0.09	0.35 ± 0.10
Aortic valve PPD, mmHg	87 ± 23	84 ± 21	91 ± 25	86 ± 22	85 ± 21	87 ± 23
Aortic valve MPG, mmHg	50 ± 14	48 ± 13	52 ± 15	48 ± 13	48.3±12.3	49.0 ± 13.8

Data expressed as mean±SD or number (%). NYHA: New York Heart Association. CABG: Coronary artery bypass grafting. AVA: Aortic valve area. AVAi: Indexed aortic valve area. PPD: Peak pressure drop. MPG: Mean pressure gradient. P values comparing total baseline population and analysed population all non-significant.

Table 3-2 Baseline characteristics of the analysed population

	Total (n=100)	Men (n=60)	Women (n=40)	P value for gender difference
Age at intervention, years	77. ± 8	75 ± 7	80±9	0.004
Length of stay, days	8.3±4.7	7.9±3.0	8.8±6.5	0.883
BSA, m^2	1.86 ± 0.2	1.96 ± 0.18	1.71 ± 0.16	<0.001
Systolic blood pressure, mmHg	131 ± 23	129 ± 22	134 ± 24	0.20
NYHA	2.9 ± 0.6	2.9 ± 0.6	3.0 ± 0.6	0.724
Logistic EuroSCORE, %	14.5 ± 12.7	14.1 ± 12.4	16.0± 13.8	0.182
EuroSCORE II, %	4.0 ± 4.3	3.9 ± 3.7	4.5 ± 5.1	0.340
Hypertension	55 (55)	31 (52)	24 (60)	0.412
Hypercholesterolaemia	67 (67)	44 (73)	23 (57.5)	0.10
Diabetes	21 (21)	11 (18)	10 (25)	0.42
Atrial Fibrillation	19 (19)	13 (22)	6 (15)	0.41
Previous myocardial infarction	15 (15)	9 (15)	6 (15)	1
Previous CABG	19 (19)	14 (23)	5 (12.5)	0.176
Any coronary artery stenosis >50%	53 (53)	38 (63)	15 (38)	0.011
Pulmonary hypertension	24 (24)	15 (25)	9 (22.5)	0.774
Peripheral vascular disease	16 (16)	11 (18)	5 (12.5)	0.436
Cerebrovascular disease	15 (15)	11 (18)	4 (10)	0.253
COPD	16 (16)	13 (22)	3 (7.5)	0.058
Echocardiographic data				
Indexed aortic valve area, cm/m^2	0.35 ± 0.09	0.35 ± 0.09	0.35 ± 0.10	0.928
Peak pressure drop, mmHg	86 ± 22	85 ± 21	87 ± 23	0.847
Mean pressure gradient, mmHg	48±13	48±12	49±14	0.974

Data are expressed as mean±SD or number (%). BSA: Body surface area. NYHA: New York Heart Association. CABG: Coronary artery bypass grafting. COPD: Chronic obstructive pulmonary disease.

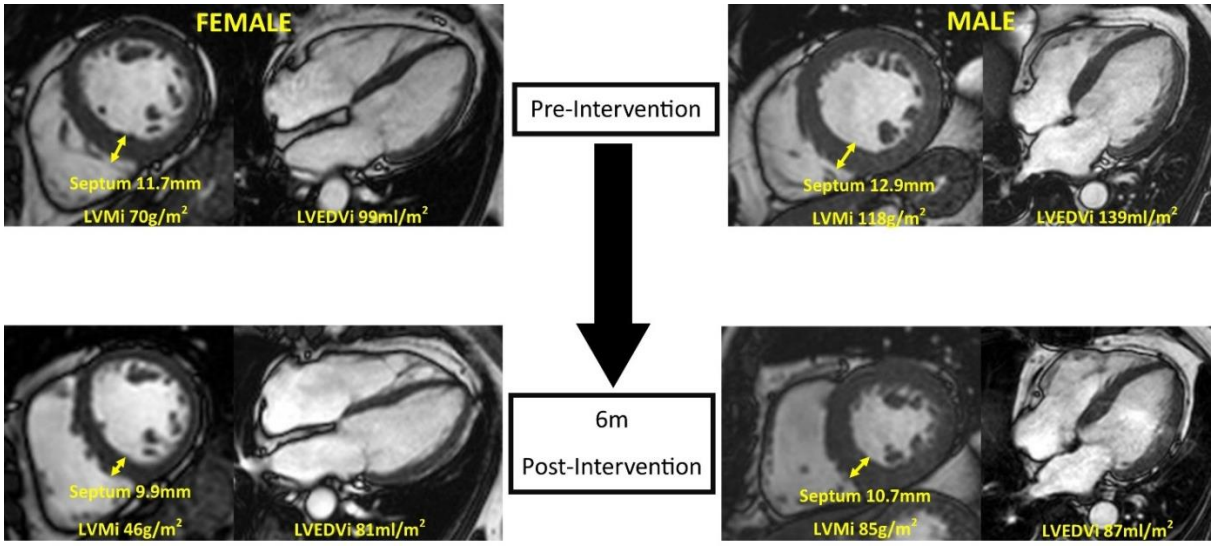

Figure 3-3 Typical male and female ventricular remodelling in AS

Short axis and 4 chamber cardiac magnetic resonance images of the left ventricle acquired at end diastole. The left sided panel depicts the typical female ventricle in severe aortic stenosis with a lower LV mass and a small LV cavity size (top image) and subsequent LV mass regression 6 months (bottom image). The right sided panel shows a typical male pattern of remodelling with increased LV cavity size and greater LV mass at baseline (top image) and then reverse remodelling 6 months following valve replacement (bottom image). Both male and female ventricles exhibit reverse remodelling with LV mass regression 6 months following valve replacement.

Table 3-3 CMR data pre- and post-intervention grouped according to gender

	Total n=100	Men n=60	Women n=40	P Value for gender difference
Indexed left ventricular mass, g/m^2				
Pre-intervention	75.1± 21.6	81.5±21.3	65.3±18.4	<0.001
Post-intervention	59.0±15.9	63.2±15.8	52.6±14.0	<0.001
P Value	<0.001	<0.001	<0.001	
Left ventricular mass/volume				
Pre-intervention	0.80±0.16	0.82±0.15	0.76±0.17	0.068
Post-intervention	0.69±0.15	0.72±0.15	0.65±0.14	0.006
P Value	<0.001	<0.001	<0.001	
Septal thickness, mm				
Pre-intervention	12.2±3.1	13.3±2.8	10.5±2.8	<0.001
Post-intervention	10.5±2.7	11.2±2.6	9.3±2.5	<0.001
P Value	<0.001	<0.001	<0.001	
Lateral wall thickness, mm				
Pre-intervention	8.0±2.2	8.6±2.1	7.1±2.1	<0.001
Post-intervention	7.0±1.9	7.8±1.8	5.9±1.6	<0.001
P Value	<0.001	0.001	<0.001	
Septal:Lateral wall thickness ratio				
Pre-intervention	1.58±0.41	1.56±0.36	1.55±0.48	0.458
Post-intervention	1.57±0.47	1.49±0.38	1.68±0.58	0.174
P Value	0.314	0.020	0.270	
LVEDVi, ml/m^2				
Pre-intervention	95.6 ±25.6	101.2±28.6	87.3±17.5	0.020
Post-intervention	86.5±20.7	89.6±21.2	81.9±19.2	0.075
P Value	<0.001	<0.001	0.019	
LVESVi, ml/m^2				
Pre-intervention	43.7±23.0	47.9±25.6	37.3±16.6	0.036
Post-intervention	37.9±17.1	40.1±17.1	34.4±16.9	0.045
P Value	<0.001	<0.001	0.088	
Left ventricular ejection fraction, %				
Pre-intervention	56.4±12.1	54.8±12.9	58.6±10.6	0.177
Post-intervention	58.0±10.8	56.5±10.5	60.2±11.0	0.042

P value	0.021	0.093	0.129	
Indexed left atrial volume, ml/m^2				
Pre-intervention	67.2±20.8	67.8±21.8	66.2±19.3	0.578
Post-intervention	62.3±20.9	60.1±20.5	65.7±21.3	0.136
P Value	<0.001	<0.001	0.477	
Absolute myocardial fibrosis mass (g)				
Pre-intervention	2.0±3.3	2.3±4.1	1.3±1.1	0.714
Post-intervention	1.6±3.9	2.3±4.7	0.4±0.8	0.034
P value	0.022	0.412	0.010	
Myocardial fibrosis (% LV mass)				
Pre-intervention	1.2±1.5	1.2±1.8	1.2±1.1	0.435
Post-intervention	1.2±2.4	1.6±2.9	0.5±0.9	0.114
P Value	0.263	0.716	0.026	
Aortic max pressure gradient, mmHg				
Pre-intervention	42±36	46±43	36±16	0.171
Post-intervention	21±12	21±11	20±13	0.323
P value	<0.001	<0.001	<0.001	

Data are expressed as mean±SD. LVEDVi: Indexed left ventricular diastolic volume. LVESVi: Indexed left ventricular end systolic volume. LV: Left ventricular.

Table 3-4 Univariable analysis for baseline remodelling

	Unstandardised coefficient	Standard Error	P Value	95% CI	Standardised Coefficient (Beta)
Baseline LVMi (g/m^2)					
Gender	-16.15	4.122	<0.001	-24.33 to -7.97	-0.368
Baseline AR fraction (%)	0.981	0.164	<0.001	0.657 to 1.31	0.522
Baseline MR fraction (%)	0.461	0.097	<0.001	0.269 to 0.654	0.437
Hypertension	-0.503	4.365	0.909	-9.165 to 8.159	-0.012
Previous MI	9.223	6.010	0.128	-2.703 to 21.150	0.153
Systolic blood pressure, (mmHg)	0.142	0.097	0.147	-0.051 to 0.335	0.148
AVAi (cm^2)	-43.06	24.655	0.084	-92.058 to 5.934	-0.183
Baseline LVEDVi (ml/m^2)					
Gender	-13.851	5.053	0.007	-23.878 to -3.824	-0.267
Baseline AR fraction (%)	0.904	0.208	<0.001	0.491 to 1.317	0.405
Baseline MR fraction (%)	0.434	0.120	<0.001	0.196 to 0.672	0.347
AVAi (cm^2)	-16.323	28.769	0.572	-73.495 to 40.848	-0.060
Hypertension	1.829	5.160	0.725	-8.419 to 12.059	0.036
Previous MI	-7.162	7.157	0.319	-21.364 to 7.041	-0.101

LVMi: Indexed left ventricular mass. AR: Aortic regurgitant. MR: Mitral regurgitant. MI: Myocardial infarction. AVAi: Indexed aortic valve area.

Table 3-5 Multiple regression analysis - baseline remodelling

	Unstandardised coefficient	Standard Error	P Value	95% Confidence interval	Standardised Coefficient (Beta)
Baseline LVMi (g/m^2)					
Baseline AR fraction (%)	0.878	0.180	<0.001	0.520 to 1.237	0.445
Gender	-13.37	4.139	0.002	-21.60 to -5.138	-0.295
Baseline LVEDVi (ml/m^2)					
Baseline AR fraction (%)	0.904	0.208	<0.001	0.491 to 1.317	0.405

LVMi: Indexed left ventricular mass. AR: Aortic regurgitation. LVEDVi: Indexed left ventricular end diastolic volume.

3.4.2. Reverse remodelling following aortic valve replacement

There was a similar length of post-procedure hospital stay between genders (men 8±3 vs. women 9±7days, p=0.883). Reverse remodelling parameters according to gender can be seen in Table 3-3 and Figure 3-4. Following valve replacement there was a significant reduction in LVMi in both groups. Men experienced greater absolute LV mass regression than women (18.3±10.6 vs. 12.7±8.8g/m2, p=0.007), however, when expressed as a percentage reduction of baseline LVMi, mass regression was similar between the genders (men 21.7±10.1 vs. women 18.4±11.0%, p=0.121). A gender difference in absolute LV mass regression was still evident when those with significant baseline AR were excluded from the analysis (men 16.2±10.4 vs. women 11.4±8.2g/m^2, p=0.034).

There was no gender-related difference in post-procedural AR (RFRac men 8.4±8.0% vs women 6.9±6.8%, p=0.406). Significant post-procedural AR was seen in 9 (15%) men and 4 (10%) of women (p=0.347). Men experienced a significant reduction in MR following valvular intervention whereas women did not (men 33.8±19.8 to 17.6±18.1%, p<0.001, women: 26.9±21.3 to 20.5±19.6%, p=0.102). Significant post-procedural MR was seen in 5 (8%) of men and 6 (15%) women (p=0.297).

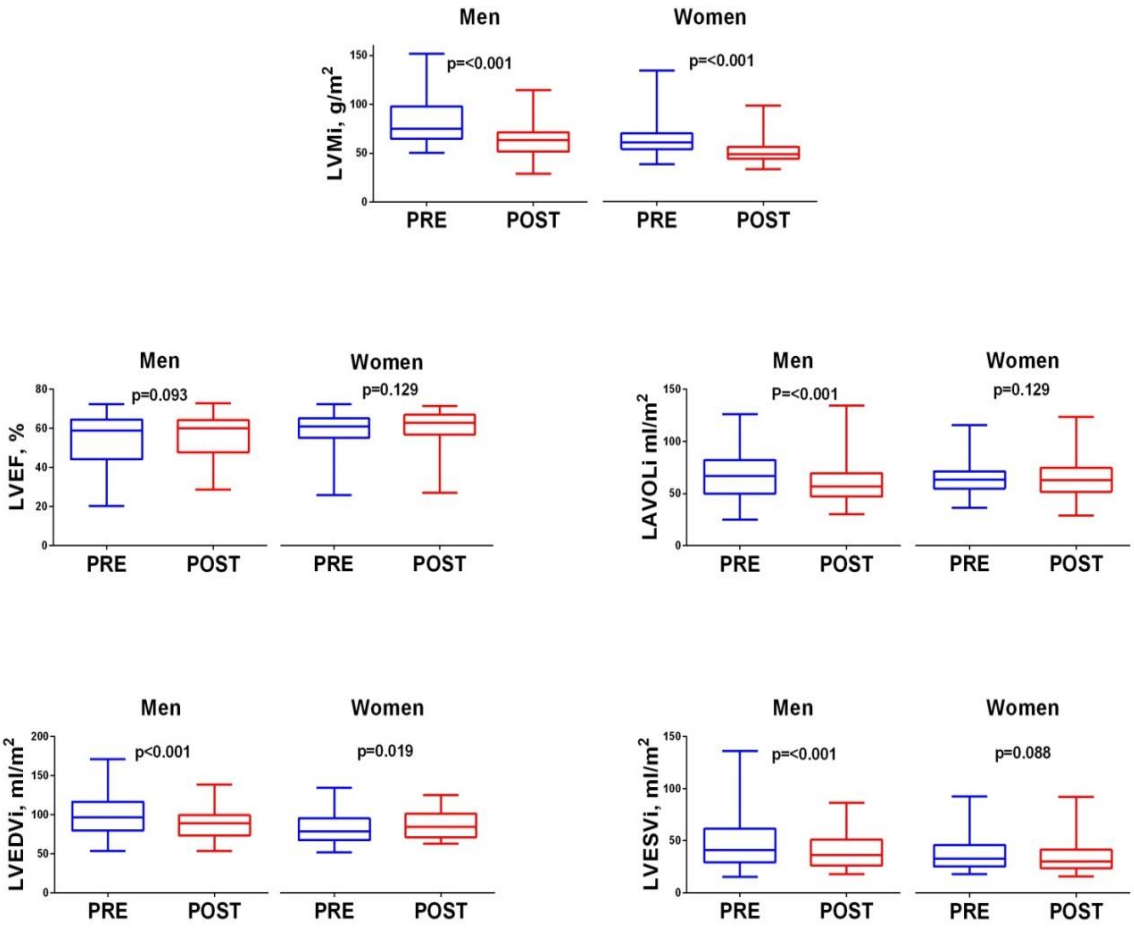

Figure 3-4 Values according to gender pre- and post-valve replacement

Values according to gender pre- and post-aortic valve replacement. Boxplots show median values (line within box), 50th percentile values (box outline) and maximum and minimum values (whiskers). LVMi: Indexed left ventricular mass. LVEF: Left ventricular ejection fraction. LAVOLi: Indexed left atrial volume. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume.

Results according to gender and procedure type can be seen in Table 3-6. As prior myocardial infarction has been reported to affect reverse remodelling following TAVI, a further subgroup analysis was performed, excluding those with infarct pattern LGE at baseline, the results can be seen in Table 3-7 .

Table 3-6 Pre and post-procedure CMR values according to gender and procedure type

	Total SAVR (n=39)	Total TAVI (n=61)	P Value	SAVR men (n=28)	TAVI men (n=32)	P value	SAVR women (n=11)	TAVI women (n=29)	P value
LVMi, g/m^2									
Pre-intervention	74.0 ± 22.7	75.7 ± 21.1	0.701	80.3 ± 21.4	82.47 ± 21.5	0.696	57.8 ± 17.7	68.2 ± 18.1	0.113
Post-intervention	57.8 ± 14.9	59.7 ± 16.6	0.579	61.7 ± 13.5	64.48 ± 17.8	0.500	48.0 ± 14.7	54.3 ± 13.6	0.207
P Value	<0.001	<0.001		<0.001	<0.001		0.006	<0.001	
LVEDVi, ml/m^2									
Pre-intervention	91.2 ± 27.2	98.5 ± 24.3	0.164	95.6 ± 29.1	106.0 ± 27.6	0.166	79.7 ± 18.0	90.2 ± 16.7	0.090
Post-intervention	79.1 ± 16.2	91.3 ± 21.9	0.004	80.7 ± 16.9	97.4 ± 21.7	0.002	75.2 ± 14.3	84.5 ± 20.4	0.173
P Value	<0.001	0.003		0.001	0.021		0.155	0.059	
LVESVi, ml/m^2									
Pre-intervention	39.6 ± 23.0	46.3 ± 22.7	0.151	42.6 ± 24.7	52.5 ± 25.9	0.136	31.7 ± 16.4	39.4 ± 16.4	0.190
Post-intervention	32.7 ± 12.7	41.1 ± 18.8	0.016	33.6 ± 12.9	45.9 ± 18.4	0.004	30.4 ± 12.5	35.9 ± 18.2	0.359
P Value	0.010	0.009		0.010	0.047		0.656	0.081	
LVEF, %									
Pre-intervention	59.0 ± 11.2	54.7 ± 12.5	0.084	57.8 ± 11.5	52.3 ± 13.7	0.123	61.9 ± 10.1	57.4 ± 10.6	0.103
Post-intervention	60.2 ± 9.3	56.6 ± 11.5	0.103	59.2 ± 8.9	54.2 ± 11.4	0.103	62.8 ± 10.2	59.2 ± 11.3	0.157
P value	0.402	0.021		0.524	0.184		0.374	0.206	
LA Voli, ml/m^2									

Pre-intervention	61.1 ± 17.6	71.1 ± 21.8	0.018	61.2 ± 18.2	73.5 ± 23.3	0.027	60.8 ± 16.8	68.3 ± 20.0	0.277
Post-intervention	57.3 ± 16.5	65.5 ± 22.8	0.056	55.1 ± 15.2	64.3 ± 23.4	0.132	62.6 ± 19.1	66.9 ± 22.3	0.576
P Value	0.033	0.004		0.007	0.001		0.484	0.556	
AR fraction, %									
Pre-intervention	14.7±14.4	11.9±9.1	0.707	17.7±15.6	12.7±8.2	0.382	6.2±4.6	10.8±10.1	0.317
Post-intervention	9.5±8.5	6.8±6.8	0.098	10.8±9.1	4.1±1.8	0.033	6.1±5.7	7.2±7.2	0.669
P Value	<0.001	<0.001		0.072	<0.001		0.717	0.096	

Data are expressed as mean±SD. SAVR: Surgical aortic valve replacement. TAVI: Trans-catheter aortic valve implantation. LVMi: Indexed left ventricular mass. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume. LVEF: Left ventricular ejection fraction. LAVoli: Indexed left atrial volume. AR: Aortic regurgitation.

Table 3-7 CMR values pre and post-procedure with prior infarct patients excluded

	Men (n=46)	Women (n=33)	P Value for gender difference
Indexed left ventricular mass, g/m^2			
Pre-intervention	78.7±19.1	64.1±17.7	<0.001
Post-intervention	60.9±14.3	51.1±13.0	<0.001
P Value	<0.001	<0.001	
Septal thickness, mm			
Pre-intervention	13.5±2.8	10.2±2.8	<0.001
Post-intervention	10.9±2.1	9.1±2.3	<0.001
P Value	<0.001	0.004	
Lateral wall thickness, mm			
Pre-intervention	8.6±2.2	7.3±2.2	<0.001
Post-intervention	7.6±1.8	6.0±1.7	<0.001
P Value	<0.001	<0.001	
LVEDVi, ml/m^2			
Pre-intervention	94.4±24.8	83.2±15.8	0.039
Post-intervention	83.4±17.2	77.5±16.2	0.126
P Value	<0.001	0.039	
LVESVi, ml/m^2			
Pre-intervention	41.7±21.7	32.5±10.5	0.037
Post-intervention	35.5±13.4	29.7±9.7	0.051
P Value	0.006	0.214	
Left ventricular ejection fraction, %			
Pre-intervention	57.5±11.4	61.6±6.4	0.183
Post-intervention	58.3±9.6	63.0±7.2	0.023
P value	0.604	0.386	
Indexed left atrial volume, ml/m^2			
Pre-intervention	66.3±23.1	64.8±18.8	0.698
Post-intervention	59.6±21.7	64.5±21.0	0.164
P Value	0.002	0.675	

Aortic max pressure gradient, mmHg			
Pre-intervention	47.1±48.2	36.9±15.6	0.266
Post-intervention	20.5±9.3	16.5±8.1	0.060
P value	<0.001	<0.001	

Data are expressed as mean±SD. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume.

There was a reduction in RV longitudinal function in men and in women (Table 3-8). Change in TAPSE was significantly different according to procedure type (men SAVR -8.3±4.7 vs. TAVI 0.4±4.9mm, p<0.001, women SAVR -8.4±3.5 vs. TAVI 0.6±4.7mm, p<0.001).

Table 3-8 Change in right ventricular longitudinal function

	Total	**Men (n=60)**	**Women (n=40)**	**P Value**
TAPSE, mm				
Pre-intervention	20.05 ± 5.83	19.86 ± 5.77	20.33 ± 5.98	0.697
Post-intervention	16.82 ± 6.18	16.22 ± 5.77	17.73 ± 6.73	0.341
P Value	<0.001	<0.001	0.005	

Data are expressed as mean±SD. TAPSE: Tricuspid annular excursion.

3.4.3. Myocardial fibrosis

LGE imaging was available for 95 patients. 5 patients (male, n=4) were not given a Gadolinium-based contrast agent due to pre-existing renal failure with an estimated glomerular filtration rate of <30ml/min/1.73m^2. Patients were classified at baseline according to whether they had no LGE (men n=14 (25%), women n=16 (41%)), infarct pattern LGE (men n=14 (25%), women n=7 (18%)) or mid-wall/focal fibrosis pattern LGE (men n=28 (50%), women 16 (41%)).

The presence or absence of infarct pattern LGE did not impact on change in LVEF (men: infarct-LGE(+) 4.8±7.3 vs. infarct-LGE(-) 0.7±8.0%, p=0.099; women: infarct-LGE(+) 2.6±3.4 vs. infarct-LGE(-) 1.4±7.1%, p=0.670) or LVEDVi (men: infarct-LGE(+) 13.4±22.6 vs. infarct-LGE(-) 11.0±19.8ml/m^2, p=0.702; women: infarct-LGE(+) 3.7±19.4 vs. infarct-LGE(-) 5.8±13.1ml/m^2, p=0.726).

Of the patients with mid-wall/focal fibrosis pattern LGE at baseline, there was a different distribution according to gender (Figure 3-5) but comparable total amounts when expressed as a percentage of LV mass (Table 3-3). Following valve replacement, only women experienced a significant reduction in total fibrosis burden as a percentage of LV mass (men 1.2±1.8 to 1.6±2.9%, p=0.716, women 1.2±1.1 to 0.5±0.9%, p=0.026). The presence (MF(+)) or absence (MF(-)) of MF did not impact on change in LVEF (men: MF(+) 1.2±9.3 vs. MF(-) 2.6±6.5%, p=0.292; women: MF(+) 2.4±9.3 vs. MF(-) 1.2±3.9%, p=0.767), LVEDVi (men: MF(+) 13.5±19.4 vs. MF(-) 12.1±21.0ml/m^2, p=0.823; women: MF(+) 13.4±19.4 vs. MF(-) 12.1±21.0ml/m^2, p=0.053) or LVMi (men: MF (+) -17.7±10.0 vs. MF (-) -19.4±11.6g/m^2, p=0.936; women MF (+) -14.7±6.8 vs. MF (-) -11.8±9.9 vs. -14.7±6.8g/m^2, p=0.311).

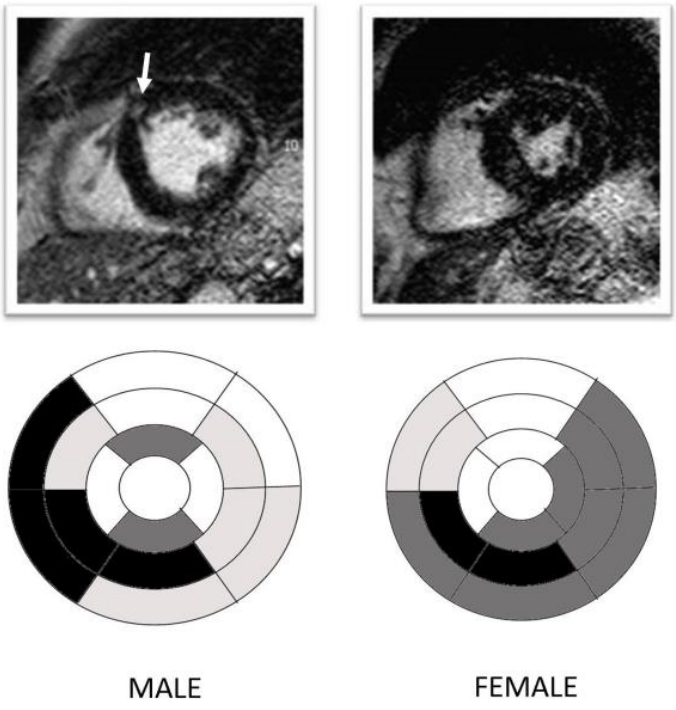

Figure 3-5 Distribution of MF according to gender

The distribution and frequency of focal mid-wall MF for 28 men and 16 women with severe AS represented using the 17-segment AHA model. Focal fibrosis was greatest in the basal and septal regions in men (arrow) whereas women appeared to have a more varied

distribution. The shaded diagram represents the proportion of patients with fibrosis in each numbered segment; <4% white, 4-8% light grey, 8-12% dark grey, >12% black.

3.4.4. Predictors of reverse remodelling

Clinical variables including patient demographics, co-morbidities and pre-operative cardiac measurements were analysed to determine predictors of cardiac reverse remodelling. These variables were each used as dependent variables in linear regression analysis. The results of the univariate analysis can be seen in Table 3-9. For every dependent variable, the baseline level of the same measure emerged as the main predictor in a multivariable model (Table 3-10). The relationship between each dependent and its baseline level is shown in Figure 3-6. Gender was only implicated as a factor for left atrial reverse remodelling but did not appear to influence LV reverse remodelling, and its inclusion in the multivariable model had minimal impact on the parameter estimates for the relevant baseline. Procedure type or the presence of coronary artery disease did not appear to predict reverse remodelling on univariate analysis. Baseline AR fraction was an independent predictor of change in LVMi alongside baseline LVMi, but was not an independent predictor in the multivariate model for any other reverse remodelling parameter. Results of the multiple regression analysis can be seen in Table 3-10.

Table 3-9 Univariable analysis - predictors of LV reverse remodelling

	Unstandardised coefficient	Standard Error	P Value	95% CI	Standardised Coefficient (Beta)
Change in LVMi (g/m^2)					
Baseline LVMi (g/m^2)	0.342	0.033	<0.001	0.276 to 0.408	0.719
Baseline LVEDVi (ml/m^2)	0.194	0.036	<0.001	0.123 to 0.264	0.482
Baseline LVESVi (ml/m^2)	0.139	0.043	0.002	0.054 to 0.225	0.311
Baseline fibrosis mass (g)	0.944	0.393	0.021	0.152 to 1.735	0.344
Baseline AR fraction (%)	0.400	0.082	<0.001	0.237 to 0.562	0.446
Gender	-5.59	2.032	0.007	-9.622 to -1.558	-0.268
Procedure type	-0.111	2.118	0.958	-4.314 to 4.092	-0.005
Any CAD >50%	-0.613	2.069	0.767	-4.719 to 3.492	-0.030
Post-procedure PPD (mmHg)	0.011	0.090	0.907	-0.168 to 0.189	0.012
Post-procedure MR fraction (%)	0.005	0.056	0.928	-0.106 to 0.116	0.009
Post-procedure AR fraction (%)	0.151	0.137	0.272	-0.120 to 0.422	0.112
Change in LVEDVi (ml.m^2)					
Baseline LVEDVi (ml/m^2)	0.43	0.06	<0.001	0.31 to 0.54	0.600
Baseline LVESVi (ml/m^2)	0.4	0.069	<0.001	0.262 to 0.538	0.503
Baseline LVMi (g/m^2)	0.355	0.077	<0.001	0.202 to 0.509	0.421
Baseline LVEF (%)	-0.408	0.146	0.006	-0.698 to -0.117	-0.271
Baseline fibrosis mass (g)	1.92	0.79	0.02	0.32 to 3.51	0.346
Baseline AR fraction (%)	0.608	0.149	<0.001	0.311 to 0.904	0.384
Gender	-6.17	3.69	0.09	-13.4 to 1.16	-0.166
Procedure type	-4.81	3.73	0.2	-12.2 to 2.58	-0.129
Any CAD >50%	-1.938	3.671	0.599	-9.223 to 5.348	-0.053
Post-procedure MR fraction (%)	-0.076	0.100	0.447	-0.274 to 0.122	0.447
Baseline AR fraction (%)	0.221	0.245	0.369	-0.265 to 0.707	0.091
Change in LVESVi (ml/m^2)					
Baseline LVEDVi (ml/m^2)	0.374	0.047	<0.001	0.281 to 0.467	0.627
Baseline LVESVi (ml/m^2)	0.442	0.05	<0.001	0.342 to 0.541	0.665
Baseline LVMi (g/m^2)	0.294	0.065	<0.001	0.166 to 0.423	0.417

Baseline LVEF (%)	-0.62	0.11	<0.001	-0.839 to -0.410	-0.494
Baseline AR fraction (%)	0.457	0.127	<0.001	0.206 to 0.709	0.346
Gender	4.884	3.088	0.117	-11.012 to 1.243	0.158
Procedure type	-1.678	3.136	0.594	-7.901 to 4.545	-0.054
Any CAD >50%	0.768	3.068	0.803	-5.321 to 6.857	0.025
Post-procedure MR fraction (%)	-0.054	0.083	0.515	-0.220 to 0.111	-0.066
Baseline AR fraction (%)	0.168	0.205	0.413	-0.238 to 0.574	0.083
Change in LVEF (%)					
Baseline LVEDVi (ml/m^2)	0.098	0.028	0.001	0.043 to 0.153	0.337
Baseline LVESVi (ml/m^2)	0.153	0.029	<0.001	0.095 to 0.210	0.472
Baseline LVMi (g/m^2)	0.103	0.033	0.299	0.037 to 0.939	0.299
Baseline LVEF (%)	-0.291	0.054	<0.001	-0.399 to -0.183	-0.476
Baseline AR fraction (%)	0.097	0.064	0.134	-0.031 to 0.225	0.152
Gender	-0.094	1.523	0.951	-3.116 to 2.927	-0.006
Procedure type	0.677	1.528	0.658	-2.355 to 3.709	0.045
Any CAD >50%	0.921	1.492	0.538	-2.039 to 3.881	0.062
Post-procedure MR fraction (%)	-0.043	0.040	0.292	-0.123 to 0.037	-0.107
Baseline AR fraction (%)	-0.061	0.100	0.540	-0.260 to 0.137	-0.062
Change in LA Voli (ml/m^2)					
Baseline LVEDVi (ml/m^2)	0.157	0.05	0.002	0.058 to 0.256	0.305
Baseline LVESVi (ml/m^2)	0.155	0.057	0.008	0.042 to 0.268	0.268
Baseline LVMi (g/m^2)	0.120	0.061	0.052	0.001 to 0.241	0.197
Baseline LA Voli (ml/m^2)	0.205	0.061	0.001	0.084 to 0.327	0.324
Baseline AR fraction (%)	0.282	0.117	0.017	0.051 to 0.514	0.242
Gender	-7.031	2.657	0.010	-12.314to -1.759	-0.261
Procedure type	2.004	2.759	0.469	-3.469 to 7.481	0.074
Any CAD >50%	2.831	2.685	0.294	2.500 to 8.162	0.107
AVAi (cm/m^2)	-26.162	15.012	0.084	-56.094 to 3.583	-0.184
Post-procedure MR fraction (%)	0.001	0.075	0.986	-0.148 to 0.150	0.002
Baseline AR fraction (%)	0.031	0.179	0.862	-0.324 to 0.387	0.018

LVMi: Indexed left ventricular mass. AR: Aortic regurgitant. MR: Mitral regurgitant. CAD: Coronary artery disease. LVEDVi: Indexed left ventricular end diastolic volume LVESVi: Indexed left ventricular end systolic volume. LA Voli: Indexed left atrial volume. LVEF: Left ventricular ejection fraction. AVAi: Indexed aortic valve area.

Table 3-10 Multivariable analysis

	Unstandardised coefficient	Standard Error	P Value	95% CI	Standardised Coefficient (Beta)
Change in LVMi (g/m^2)					
Baseline LVMi (g/m^2)	0.342	0.051	<0.001	0.239 to 0.445	0.719
Change in LVEDVi (ml/m^2)					
Baseline LVEDVi (ml/m^2)	0.429	0.088	<0.001	0.251 to 0.607	0.600
Change in LVESVi (ml/m^2)					
Baseline LVESVi (ml/m^2)	1.713	0.298	<0.001	1.122 to 2.305	2.595
Baseline LVEF (%)	1.655	0.339	<0.001	0.982 to 2.328	1.320
Baseline LVEDVi (ml/m^2)	-0.490	0.150	0.002	-0.788 to -0.192	-0.827
Change in LVEF (%)					
Baseline LVEF (%)	-0.291	0.054	<0.001	-0.399 to -0.183	-0.487
Change in LA Voli (ml/m^2)					
Baseline LA Voli (ml/m^2)	0.197	0.061	0.002	0.076 to 0.319	0.322
Gender	-6.440	2.721	0.020	-11.851 to -1.028	-0.236

LVMi: Indexed left ventricular mass. AR: Aortic regurgitant. LVEDVi: Indexed left ventricular end diastolic volume LVESVi: Indexed left ventricular end systolic volume. LA Voli: Indexed left atrial volume. LVEF: Left ventricular ejection fraction. AVAi: Indexed aortic valve area.

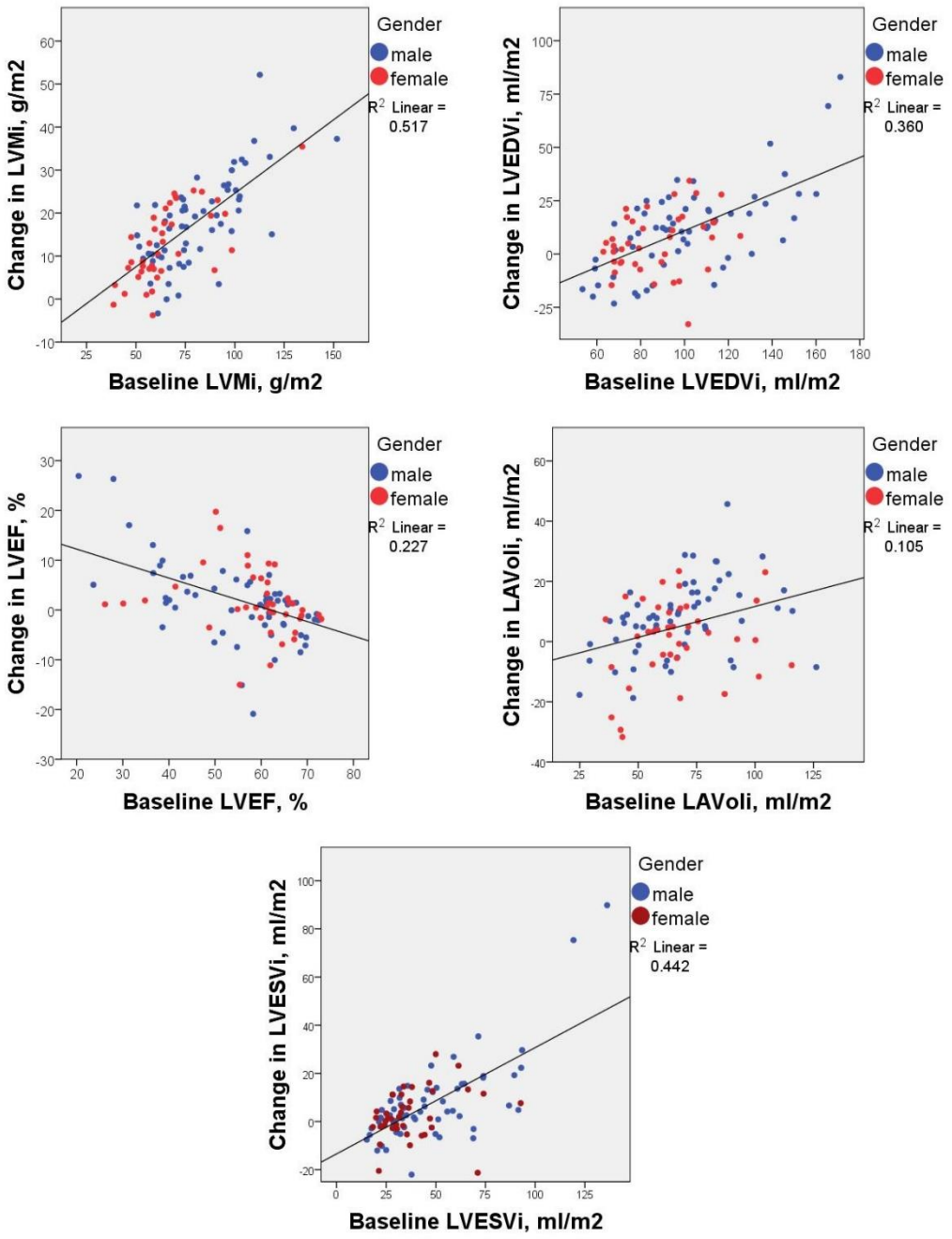

Figure 3-6 Relationship between cardiac remodelling parameters

Relationship between cardiac reverse remodelling parameters following aortic valve replacement and baseline parameters displayed according to gender. A. Relationship between change in LVMi and baseline LVMi. B. Relationship between change in LVEDVi and baseline LVEDVi. C. Relationship between change in LVEF and baseline LVEF. D. Relationship between change in LAVoli and baseline LAVoli. E. Relationship between change in LVESVi and baseline LVESVi.

3.5. Discussion

This study is the first using the reference standard of CMR to accurately assess the influence of gender on differences in LV remodelling in AS and the impact on reverse remodelling following AVR.

3.5.1. Baseline cardiac remodelling in AS according to gender

The baseline CMR results demonstrating differing patterns of ventricular remodelling in response to AS are consistent with the published echocardiographic and CMR literature [14, 16, 234]. We have demonstrated that men and women with severe AS and similar co-morbidities remodel in different ways; women exhibit lower LV mass with a smaller LV cavity size, whereas men are prone to the development of a larger cavity size, greater LV wall thickness and increased LV mass. This pattern of remodelling is seen despite similar valvular gradients between groups but may be in part related to differing degrees of baseline aortic regurgitation. Hormonal influences may also be involved, with oestrogen limiting hypertrophy up to the menopause and its subsequent lack leading to accelerated (and possibly therefore different) patterns of hypertrophy in post-menopausal women compared to men [237].

3.5.2. Reverse remodelling according to gender

In contrast to other studies evaluating gender in AS, our male and female groups were similar in terms of co-morbidity, cardiac risk score, NYHA classification and echo derived valve gradients. Only age, baseline aortic regurgitation and, expectedly, coronary artery disease prevalence and body size differed between the two groups. Previous reports of referral bias for men over women are seen again in our population, with males accounting for 74% of the SAVR population [233]. In our study, men and women had similar reverse remodelling 6 months following valve replacement. Multiple regression analysis suggested that the main predictor of reverse remodelling for each category was the baseline level of that variable. So, the greater absolute LV mass regression seen in men was a result of the fact that men have more LV mass at baseline than their female counterparts, rather than a gender-related difference *per se*. Stangl et al found a better LVEF at baseline and a more favourable LV remodelling

response in women upon serial echocardiography following TAVI, but their female population had higher pre-TAVI aortic valve gradients than men, which may explain the greater degree of mass regression seen [42]. In an echocardiographically based study of 92 patients undergoing SAVR for isolated AS, Petrov et al [26] found a similar LVMi at baseline in men and women, but a greater degree of LVM regression in women after SAVR. This study was based on measurements taken only 3 days post-SAVR. The change in LVM reported was a reflection of a change in cavity size rather than a change in wall thickness and it could be that the LVM regression reported was actually a reflection of the mathematical assumptions made by the echocardiographic estimation of LVM. Our study provides more robust data than that of Petrov et al; CMR is a well validated and accurate technique for LVM quantification, which does not rely to the same extent on mathematical assumptions and is independent of any change in cardiac geometry which may take place in the peri-operative period. Furthermore, the follow up of 6m (rather than 3 days), our larger sample size and the inclusion of other parameters of hypertrophy assessment in our study such as wall thickness, means that more robust conclusions about gender-related differences in reverse remodelling can be drawn.

AR has previously been suggested as a modulator of reverse remodelling following valve replacement and has been proposed as a mechanism for less favourable outcomes in men in the TAVI literature [238]. In our study, men had more AR at baseline which may in part contribute to their increased LV cavity size and mass pre-intervention. The AR regurgitant fraction following valve replacement was similar between genders which may explain why our findings differ from those of Stangl et al where rates of residual AR were much higher in men than women [42]. A significant reduction in valve gradients was observed in both genders, with no significant difference in CMR derived peak valve gradient according to gender, suggesting that patient prosthesis mismatch was not an implicating factor in remodelling parameters according to gender. Furthermore, post-procedure valve gradient was not associated with change in LVMi on univariate analysis. A reduction in mitral regurgitation was seen in men but not women. This, alongside the reduction in left atrial size seen in men but not women, may reflect a greater improvement in LV cavity pressure, trans-mitral gradient and mitral valve tethering forces in men. The assessment of mitral regurgitation in the context of severe aortic stenosis can be

unreliable due to the underestimation of stroke volume using Q flow methodology and it is therefore possible that the reduction in MR seen in men was a result of this rather than a true finding. However, one would expect that these limitations should apply to both men and women equally, adding weight to the argument that this is a true, rather than artefactual observation.

3.5.3. Right ventricular function

Men and women both experienced a reduction in right ventricular longitudinal function. However, subgroup analysis revealed that this was due to the procedure type (SAVR) rather than a gender related effect. It is well described that SAVR causes a reduction in right ventricular function [167, 239], although the cause is not entirely clear, it may be linked to loss of pericardial support, prolonged cardiopulmonary bypass or right ventricular ischaemia (or a combination of all three). TAVI, at least in most studies, does not appear to impact on right ventricular function [167, 239], although reports are contradictory [173]. Our female group, likely due to their advanced age and possibly due to referral bias, comprised a higher proportion undergoing TAVI than the male group. Given the strong association of procedure type on right ventricular function and the uneven split of procedure type in each gender group, any inferences to gender in this setting may be inaccurate.

3.5.4. Myocardial Fibrosis

Myocardial fibrosis has been implicated in adverse clinical outcomes following both TAVI and SAVR [49, 50]. Men and women had similar levels of MF at baseline, in keeping with findings from previous studies [192, 193] but with differing distributions. Our study shows that females develop a varied pattern of MF whereas men display most fibrosis in the basal and septal regions, suggesting that the pathogenesis may differ. The proportion of patients with MF was in keeping with those reported in previous studies; Rudolph et al [47] investigated 21 patients with AS and found MF in 62% once infarct pattern LGE had been excluded. Our absolute values for MF were lower than in previously reported studies [47, 49], however, these studies used different methods of MF quantification which most likely accounts for the increased values reported, rather than a true difference in absolute levels of MF.

Following AVR, there was a significant reduction in absolute MF and also MF as a proportion of LV mass in women but not in men. This finding is surprising given the greater degree of absolute LV mass reduction in the male cohort. Further studies exploring gender differences in MF are required to explain this finding. It is possible that the MF regression is different according to gender, with the more varied distribution 'female' pattern showing an early tendency to regress. It is also possible that the regression in females is a reflection of the fact that more females underwent trans-catheter rather than surgical valve replacement, as it has previously been suggested that MF regression is seen following TAVI but not SAVR [167]. Failure of MF regression following AVR has been reported previously. Weidemann et al found no fibrosis regression following SAVR and also reported LV mass regression regardless of MF or MF burden [193]. Moreover, in our study the MF burden accounted for a very small proportion of total LV mass at both baseline and follow-up, so one may not expect such a small amount of fibrosis to impact significantly on reverse remodelling. Given the limitations of MF quantification using CMR, it is also possible that the finding could have been artefactual; larger studies and those including ECV calculation may help further explore this.

3.6. Limitations

Patients in the two groups were similarly matched in terms of co-morbidities and clinical characteristics but were not comparable in terms of age. Due to age and referral patterns, the proportions of each gender undergoing TAVI and SAVR were different thus hampering any direct comparison between the procedures. Due to their differing implant techniques and flow dynamics, there may be important differences between remodelling parameters in SAVR and TAVI, however, the procedure type did not influence reverse remodelling on univariate analysis. There was numerically (but not statistically significant) greater post-procedural AR in those undergoing TAVI compared with SAVR and therefore it is possible that this influenced findings given the different proportion of men and women undergoing each procedure. A quarter (26%) of the study population did not complete the study protocol mainly due to permanent pacemaker implantation, which may have introduced bias, although the analysed

population did not differ in terms of baseline characteristics from the original population. The post-procedure scan occurred 6 months following valve replacement; although it is well documented that the majority of reverse remodelling occurs within the first 6 months [240], this could still be too early to detect any subtle differences between the genders. The follow up may also be too short to demonstrate reversal of MF. Caution may need to be exercised in the interpretation of mitral regurgitation pre-intervention. Mitral regurgitant fraction in the context of severe AS may be overestimated using CMR phase contrast imaging due to underestimation of aortic forward flow when sampling high velocities [202]. Any inferences related to MF are restrained to the technique of LGE imaging with its limited spatial resolution and variable inter-scan reproducibility. Our inter and intra-observer variability were in keeping with the published literature, supporting the notion that the MF findings are genuine, however, we accept that this is a valid limitation of any paper reporting quantification of MF mass. T1 mapping is superior at detecting the often diffuse fibrosis seen in the pressure overloaded ventricle. T1 mapping was not widely performed at the time of the study design and absolute T1 values can vary between vendors, software release, pulse sequence and contrast agent making comparisons difficult in multivendor studies. This study was not designed as a clinical outcomes trial, but larger-scale mortality data would be useful to identify any independent prognostic markers between the sexes.

Chapter 4: Post-procedural myocardial infarction following surgical and trans-catheter aortic valve replacement – insights from cardiovascular magnetic resonance imaging

4.1. Abstract

Background: Myocardial injury assessed using cardiac biomarker release is ubiquitous following SAVR and TAVI, preventing accurate discrimination between focal MI and global injury. Cardiovascular magnetic resonance late gadolinium enhancement imaging, a more sensitive method of detecting post-procedural MI, was used to compare rates of new MI following trans-catheter and surgical aortic valve replacement.

Methods: Identical CMR scans were obtained at baseline and 6 months post-procedure in ninety-six patients undergoing SAVR (n=39) and TAVI (n=57).

Results: The rate of new MI was greater following SAVR than TAVI (SAVR, n=10 (26%) vs. TAVI, n=3 (5%), p=0.004). Infarct mass was similar between groups (SAVR 1.1±0.6 vs. TAVI 2.0g±1.4g, p=0.395), as was infarct mass as a percentage of LV mass (SAVR 1.0±0.4% vs. TAVI 2.2±1.3%, p=0.268). None of the SAVR and one of the TAVI infarcts were detected clinically. New MI did not impact on LVEF in either group (SAVR: LGE(+) 2.2±4.7% vs. LGE(-) 0.90±8.0%, p=0.437, TAVI: LGE(+)-0.9±6.0 vs. LGE(-) 2.0±7.8%, p=0.420). 34 patients (60%) in the TAVI group had non-revascularised coronary artery disease at the time of TAVI, of whom 3 (9%) had new MI.

Conclusions: MI is an infrequent complication of TAVI but may be more common following SAVR. Infarct size is small following both procedures and does not impact on change in LVEF. The low new infarct rate in TAVI, especially in the context of high rates of non-revascularised CAD, is reassuring and strengthens the notion that coronary revascularisation prior to TAVI may be unnecessary.

4.2. Introduction

Surgical aortic valve replacement remains the recommended technique for those with severe symptomatic AS. However, trans-catheter aortic valve implantation is now a viable alternative for those at high surgical risk [65], with thousands of implants taking place annually [241]. Myocardial injury assessed using cardiac biomarker release is associated with an adverse outcome following both cardiac surgery [242] and trans-catheter intervention [243]. Mechanisms for myocardial injury during SAVR and TAVI are varied and depicted in Figure 4-1. Cardiac biomarker release is almost ubiquitous in patients following both procedures [113, 114] preventing accurate discrimination between release due to focal myocardial infarction and global/diffuse myocardial injury. Furthermore, the importance of coronary artery disease and completeness of revascularisation prior to TAVI is debated [244]. Cardiovascular magnetic resonance imaging is the reference standard imaging test to evaluate the incidence of post-procedural MI using the late gadolinium enhancement technique [245, 246], and can be relied upon to detect even tiny amounts of myocardial scar [118]. As well as quantification of scar mass, infarct transmurality can be determined alongside accurate localization of infarct territory. Our study aimed to compare rates of new MI, using CMR LGE imaging before and 6 months following TAVI and SAVR.

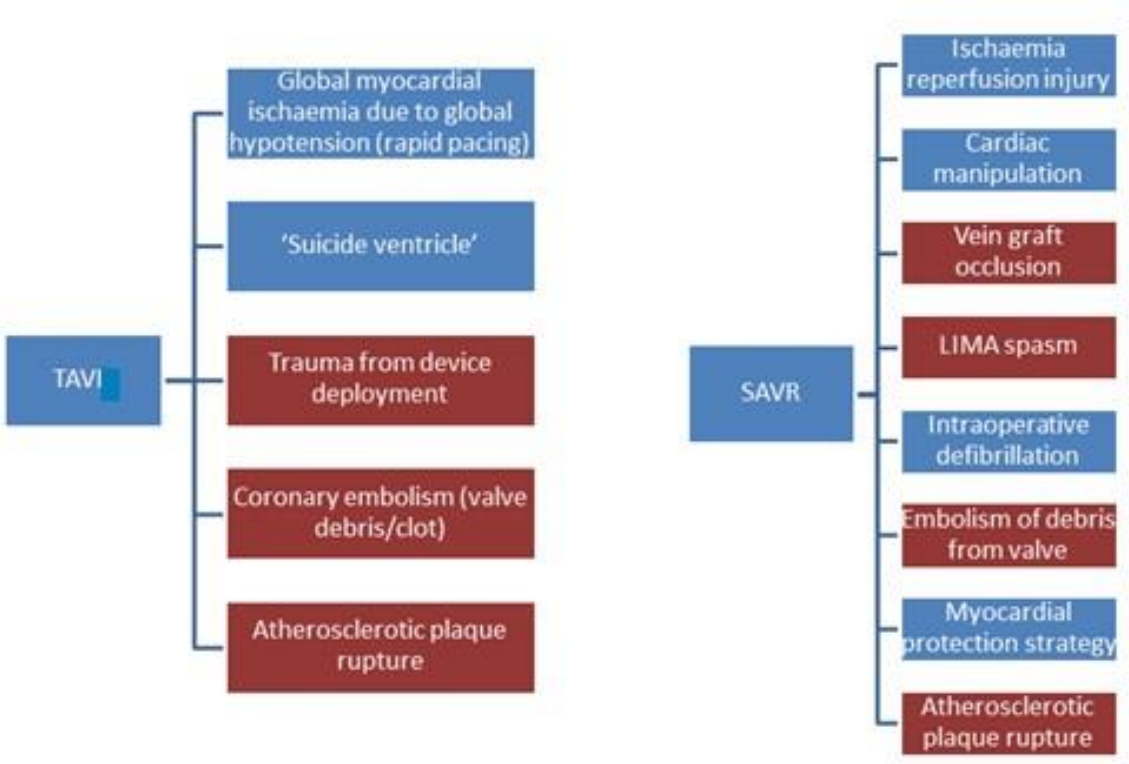

Figure 4-1 Mechanisms of myocardial injury following TAVI and SAVR

Potential mechanisms for myocardial injury following TAVI and SAVR. All mechanisms of myocardial injury can lead to a cardiac biomarker release. Mechanisms which can lead to focal MI and can be assessed using LGE CMR are shown in red.

4.3. Methods specific to this chapter

Between January 2009 and April 2014, 130 patients with severe AS undergoing either SAVR or TAVI with or without concomitant coronary artery bypass grafting at a single tertiary centre (Leeds General Infirmary, Leeds, UK) were prospectively recruited. The presence of significant CAD was determined by the occurrence of >50% stenosis by visual estimation in any major epicardial vessel (>2.5mm diameter) on a pre-procedural coronary angiogram. Angiographic data were acquired from the report of the clinician performing the angiogram. Patients unable to receive Gadolinium based contrast due to renal dysfunction (estimated glomerular filtration rate <30ml/min/1.73m^2) were excluded from this study.

4.3.1. CMR protocol

Identical CMR scans were obtained on the same imaging platform at baseline (median 1 day pre-procedure, interquartile range (IQR) 14 days) and at a median of 6 months (IQR 1 month) following aortic valve intervention using the same 1.5T scanner (Intera, Philips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany).

4.3.2. CMR analysis

The location and transmural extent of LGE according to the 17-segment American Heart Association model was recorded. Quantification of MI was performed using computer-assisted planimetry (cmr^{42}, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Pixels with image intensities of >2SD above the mean of image intensities in a remote myocardial region in the same image were considered to represent infarction. Infarct mass was expressed in grams of tissue and as percentage of overall LV mass as determined by cine imaging. The threshold of two standard deviations method was chosen due to evidence suggesting that this method is most closely linked with prognosis in chronic myocardial infarction [209].

4.4. Results

4.4.1. Patient demographic, procedural and clinical data

130 patients were recruited into the study. 96 patients with severe AS undergoing either TAVI (n=57) or SAVR (n=39) completed both baseline and 6 month post-procedure CMR scans. Reasons for non-completion of the CMR protocol were varied and are depicted in Figure 4-2.

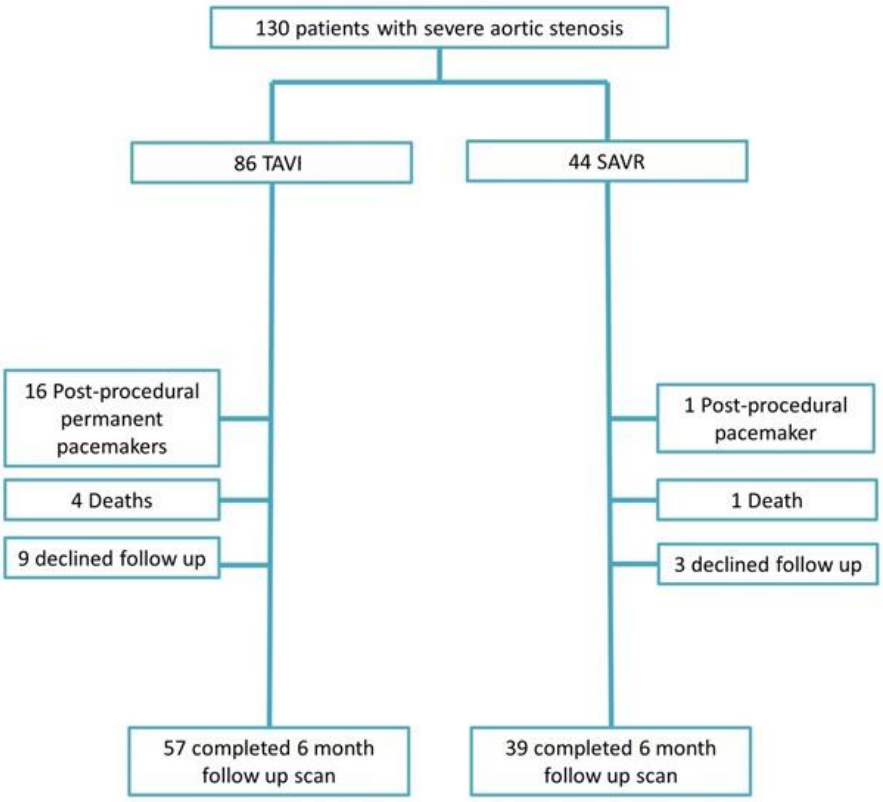

Figure 4-2 Patient recruitment pathway

TAVI: Transcatheter aortic valve implantation. SAVR: Surgical aortic valve replacement

There was no significant difference between the recruited and analyzed study population in terms of age (p=0.204), length of stay (p=0.621), gender (p=0.459), indexed aortic valve area (p=0.556) or EuroSCORE II (p=0.210), indicating that our analyzed patients were representative of the larger population. No patients had a hospital admission with acute coronary syndrome or underwent any revascularisation procedure between hospital discharge and the 6 months follow up scan. Demographic, clinical, angiographic and echocardiographic data can be seen in Table 4-1. Patients in the SAVR group were younger, less symptomatic, with less co-morbidity and were at lower surgical risk than their TAVI counterparts. The SAVR group had less 3 vessel disease than those undergoing TAVI and were less likely to be taking beta-blockers or ACE inhibitors at the time of recruitment. 16 patients (41%) in the SAVR group underwent concurrent CABG. The mean cross-clamp time and cardiopulmonary bypass time was 79±38min and 108±45min respectively. The majority of SAVR patients underwent

bioprosthetic (n=34, 87%) rather than mechanical (n=5, 13%) aortic valve replacement; with a mean valve size of 22±2mm.

In the TAVI group, access was most commonly via the femoral route (n=49, 86%) with 5 (9%) procedures performed via the subclavian approach and one performed by each of direct aortic, apical and carotid arterial access routes. The majority of TAVI implants were Medtronic CoreValve (n=45, 79%) with the remaining implants being Boston Lotus (n=11, 19%) and Medtronic Engager (n=1, 2%).

Table 4-1 Baseline demographic, clinical, echocardiographic and angiographic characteristics

	SAVR n=39	**TAVI n= 57**	**P Value**
Age, years	72±7	80±7	<0.001
Length of hospital stay, days	8.8±2.9	7.7±4.2	0.003
Gender, male, n (%)	28 (72)	31 (54)	0.085
Body surface area, m^2	1.96±0.19	1.80±0.20	<0.001
Body mass index, kg/m^2	28.4±4.2	27.4±3.9	0.252
NYHA classification	2.6±0.5	3.1±0.5	<0.001
Echocardiographic parameters			
Indexed aortic valve area, cm^2/m^2	0.32±0.15	0.34±0.10	0.528
Mean pressure drop, mmHg	46±11	50±15	0.328
Clinical risk score			
Logistic EuroSCORE	5.58±2.79	19.93±13.50	<0.001
EuroSCORE II	1.35±0.49	5.70±4.85	<0.001
Angiographic data			
Any epicardial stenosis >50%, n (%)	16 (41)	34 (60)	0.121
3 vessel disease, n (%)	2 (5)	15 (26)	0.008
LAD stenosis >50%	11(28)	26 (46)	0.103
LCx stenosis >50%	7 (18)	20 (35)	0.078
RCA stenosis >50%	8 (21)	21 (37)	0.102
Co-morbidity			
Hypertension	27 (69)	26 (46)	0.022
Diabetes	7 (18)	13 (23)	0.565
Hypercholesterolaemia	30 (77)	35 (61)	0.110
Atrial fibrillation	5 (13)	15 (26)	0.110

Previous myocardial infarction	4 (10)	10 (18)	0.320
Prior cardiac surgery	1 (3)	18 (32)	<0.001
Previous PCI	3 (8)	15 (26)	0.022
Peripheral vascular disease	2 (5)	14 (25)	0.012
Cerebrovascular disease	7 (18)	9 (16)	0.780
Pulmonary hypertension	3 (8)	20 (35)	0.002
Medication			
Beta-blocker	11 (28)	32 (56)	0.012
ACE inhibitor	24 (62)	22 (39)	0.019
Statin	22 (56)	43 (75)	0.072

Data expressed as mean ± SD or number (%). SAVR: Surgical aortic valve replacement. TAVI: Trans-catheter aortic valve replacement. NYHA: New York Heart Association. LAD: Left anterior descending artery. LCx: Left circumflex artery. RCA: Right coronary artery. PCI: Percutaneous coronary artery. ACE: Angiotensin converting enzyme.

4.4.2. Baseline late gadolinium enhancement imaging

24 (42%) patients in the TAVI group had infarct pattern LGE at baseline with an average mass of 14.2±10.4g or 10.0±7.9% of total LV mass. Of these only 7 (12%) had a clinical history of MI with a further 8 (14%), 13 (23%) and 10 (18%) having a history of percutaneous coronary intervention, CABG and atrial fibrillation respectively. 9 (23%) SAVR patients had infarct pattern LGE at baseline with a mean mass of 19.7±14.3g or 11.3±6.9% of total LV mass. Of these only 2 (5%) had a history of MI and a single (3%) patient had a history of atrial fibrillation.

4.4.3. New infarct rate following SAVR and TAVI

The rate of new MI defined by LGE (LGE (+)) was greater in the SAVR group than the TAVI group (SAVR, n=10 (26%) vs. TAVI, n=3 (5%), p=0.004). Absolute mean infarct mass was similar between the two groups (SAVR 1.1g±0.6g vs. TAVI 2.0g±1.4g, p=0.395) as was infarct mass as a percentage of LV mass (SAVR 1.0±0.4% vs. TAVI 2.2±1.3%, p=0.268). Details of individual new infarct patients can be seen in Figure 4-3. Baseline and 6 month cardiac parameters according to LGE status are shown in Table 4-2. Two of the TAVI LGE (+) patients had pre-existing infarct pattern LGE on the baseline scan. In both these cases the pre-existing infarct was in the inferior (RCA) territory, with the new post-

procedure infarcts occurring in the left anterior descending artery (AHA segments 1 and 7) and left circumflex artery (AHA segments 11 and 12) territories respectively. None of the SAVR LGE (+) patients had infarct pattern LGE on their baseline scans.

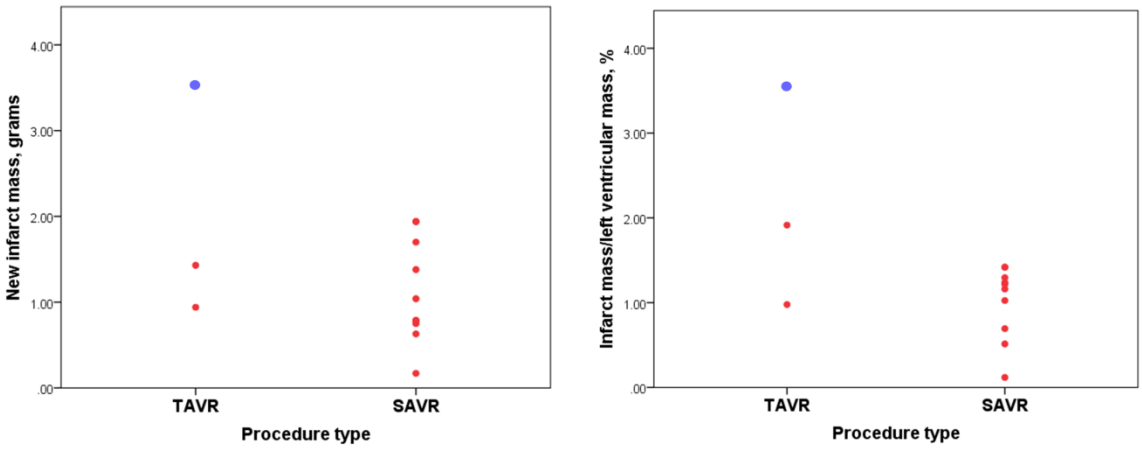

Figure 4-3 New myocardial infarction according to procedure type

New infarct mass expressed in absolute terms and as a percentage of left ventricular mass according to procedure type. The red dots represent individual patients and the blue dot represents the only clinically detected MI according to VARC criteria.

Table 4-2 Basic clinical, echocardiographic and CMR characteristics according to new LGE status

	SAVR LGE(+) n=10 (26%)	SAVR LGE(–) n=29 (74%)	P value	TAVI LGE(+) n=3 (5%)	TAVI LGE(–) n=54 (95%)	P value
Length of hospital stay, days	7.1±1.5	9.4 ± 3.0	0.047	14.7±11.6	7.5±3.3	0.059
Male, n (%)	7 (70)	21 (72)	0.884	2 (67)	29 (54)	0.412
Age, years	73.7±6.8	70.8±7.6	0.273	83.3±9.1	80.1±6.5	0.423
NYHA Class	2.7±0.5	2.6±0.6	0.812	3.3±0.6	3.1±0.5	0.575
EuroSCORE II	1.38±0.51	1.35±0.49	0.831	6.14±3.29	5.46±5.19	0.648
Previous PCI, n (%)	1 (10)	2 (7)	0.751	2 (67)	13 (24)	0.103
Echocardiographic parameters						
Indexed aortic valve area, cm^2/m^2	0.35±0.09	0.37±0.09	0.712	0.28±0.14	0.34±0.10	0.307
Mean pressure drop, mmHg	50±9	45±11	0.120	50±14	51±14	0.978
Baseline CMR findings						
LVMi , g/m^2	76.4±21.4	73.4±23.7	0.815	64.8±6.6	76.4±21.9	0.483
LVEDVi, ml/m^2	90.5± 24.6	91.7±28.8	0.962	88.6±21.8	100.2±24.5	0.427
LVESVi, ml/m^2	34.7±13.3	41.2±25.5	0.862	33.4±14.3	47.2±22.9	0.274
LVEF, %	62.2±7.0	57.9±12.3	0.692	63.1±7.8	54.5±12.4	0.361
LA Voli, ml/m^2	62.8±13.2	60.4±19.2	0.696	72.4±4.7	73.0±23.3	0.964
6 m post-procedure CMR findings						

LVMi, g/m^2	62.4±17.0	56.8±14.4	0.446	48.5±5.1	60.2±17.0	0.203
LVEDVi, ml/m^2	82.6±9.1	78.8±17.7	0.579	76.6±28.9	91.6±21.2	0.243
LVESVi, ml/m^2	28.7±6.5	34.1±14.1	0.456	30.8±20.4	41.2±17.6	0.307
LVEF, %	64.4±5.4	58.8±10.0	0.120	62.2±10.6	56.5±11.1	0.290
LA Voli, ml/m^2	63.2±11.4	55.4±17.5	0.224	63.6±5.5	67.3±24.0	0.794

Data expressed as mean±SD unless otherwise stated. SAVR: surgical aortic valve replacement. LGE: Late gadolinium enhancement. TAVI: Trans-catheter aortic valve implantation. NYHA: New York Heart Association. PCI: Percutaneous coronary intervention. CMR: Cardiovascular Magnetic Resonance Imaging. LVMi: Indexed left ventricular mass. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume. LVEF: Left ventricular ejection fraction. LAVoli: Indexed left atrial volume.

4.4.4. TAVI

There were 3 new infarcts in the TAVI population (Table 4-3); all 3 patients had significant pre-existing CAD, and all three patients were taking beta-blockers pre-procedure. One patient underwent simultaneous PCI during the TAVI procedure. Only one TAVI patient had a clinically detectable post-procedural MI according to Valve Academic Research Consortium (VARC) criteria [107] (Figure 4-3 & Figure 4-4). Change in LVEF according to new MI status was similar between groups (LGE (+) -0.9±6.0 vs. LGE (-) 2.0±7.8%, p=0.420). Valve size (LGE (+) 27±4 vs. LGE (-) 28±2mm, p=0.933), procedure time (LGE (+) 135±23 vs. LGE (-) 161±51min, p=0.511), contrast dose (LGE (+) 126±51 vs. LGE (-) 143±48ml, p=0.343), fluoroscopy time (LGE (+) 26±6 vs. LGE (-) 25±8min, p=0.454) or valvuloplasty rate (LGE (+) 100% vs. LGE (-) 91%, p=0.581) were not different according to LGE status.

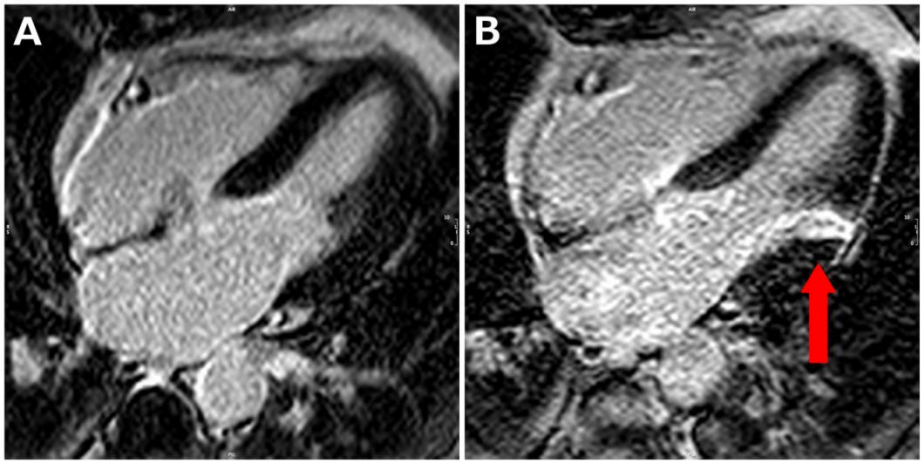

Figure 4-4 Example of new MI demonstrated using LGE CMR

Panel A depicts a horizontal long axis late gadolinium enhancement image of the left ventricle prior to TAVI, the septal and lateral left ventricular walls are seen, with no evidence of scar, depicted by the uniform dark appearance of the myocardium. Panel B shows the same patient 6 months following TAVI with an area of trans-mural hyperenhancement (LGE) indicative of MI (red arrow).

Table 4-3 Characteristics of patients undergoing TAVI and SAVR with new MI on 6 month follow up CMR

	Sex	Age	AF	DM	CAD >50%	Valve type	Grafts	AHA segment	Trans-murality of infarct	Further information
TAVI 1	M	82	N	Y	Y	MCV	-	1, 7	25-50%	Severe LAD lesion not amenable to PCI
TAVI 2	F	93	Y	N	Y	MCV	-	15	25-50%	PCI to LCx at time of TAVI procedure
TAVI 3	M	75	N	N	Y	BL	-	11,12	>75% (Figure 4-4)	Clinical MI according to VARC criteria; chest pain post-procedure with new lateral wall hypokinesis and Troponin I elevation of 26,548ng/L. Previous CABG with occluded LCx and patent SVG to OM on pre-TAVI angiography.
SAVR 1	M	81	N	N	N	Tissue	N	5	25-50%	
SAVR 2	M	77	N	N	N	Tissue	N	17	>75%	
SAVR 3	M	75	N	N	N	Tissue	N	14	>75%	
SAVR 4	M	66	N	N	Y	Tissue	N	14	>75%	Previous CABG with 3 x patent grafts at time of SAVR
SAVR 5	M	70	N	N	N	Tissue	N	13	25-50%	Previous PCI to LAD. Patent stent at time of SAVR
SAVR 6	F	82	N	N	N	Mechanical	N	15	25-50%	
SAVR 7	M	79	N	N	N	Tissue	N	14	50-75%	
SAVR 8	F	77	N	N	N	Tissue	N	13	25-50%	

SAVR 9	F	62	N	N	N	Tissue	N	13	>75%	
SAVR 10	M	68	N	Y	Y	Tissue	Y	9	25-50%	LIMA to LAD and SVG to OM at time of SAVR

AF: Atrial fibrillation. DM: Diabetes Mellitus. CAD: Coronary artery disease. AHA: American Heart Association. TAVI: Trans-catheter aortic valve implantation. MCV: Medtronic CoreValve. TF: Trans-femoral. LAD: Left anterior descending artery. PCI: Percutaneous coronary intervention. LCx: Left circumflex artery. BL: Boston Lotus. MI: Myocardial infarction. VARC: Valve Academic Research Consortium. CABG: Coronary artery bypass grafting. SVG: Saphenous vein graft. OM: Obtuse marginal. LIMA: Left internal mammary artery. SVG: Saphenous vein graft

4.4.5. SAVR

There were 10 new infarcts in the SAVR population, one of whom had significant CAD and was revascularised at the time of surgery. Individual SAVR patient characteristics of those with new LGE confirmed MI are shown in Table 4-3. None of the SAVR LGE (+) events were detected clinically. Patients undergoing CABG were less likely to have a new MI than those not requiring concurrent revascularisation (CABG 6% vs. no CABG 39%, p=0.021) There was no difference in change in LVEF according to new LGE status (LGE (+) 2.2±4.7% vs. LGE (-) 0.90±8.0%, p=0.437). Mean cardiopulmonary bypass time (LGE (+) 88.5±31.1 vs. LGE (-) 114.5±47.4min, p=0.112) and aortic cross clamp time (LGE (+) 66±25 vs. LGE (-) 84±42min, p=0.164) were similar. There was no difference in baseline AS severity (peak pressure drop LGE (+) 87±18 vs. LGE (-) 79±20mmHg, p=0.120), baseline LVEF (LGE (+) 62.2±7.0 vs. LGE (-) 57.9±12.3%, p=0.692) or beta-blocker use (LGE (+) n=3 (30%) vs. LGE (-) n=12 (41%), p=0.666) between the groups.

4.5. Discussion

This study is the first to demonstrate comparative post-procedural MI rates following TAVI and contemporary SAVR using LGE CMR imaging. We have shown that TAVI was associated with a significantly lower rate of post-procedural MI than SAVR, despite the TAVI population being older with more co-morbidity. We have also demonstrated a low new MI rate in those undergoing TAVI with non-revascularised coronary artery disease, suggesting that TAVI may be safely performed in patients with significant CAD without prior percutaneous coronary intervention.

4.5.1. TAVI

Despite high rates of non-revascularised CAD, the rate of new MI in the TAVI population was low. Out of 34 patients undergoing TAVI with non-revascularised CAD at the time of the TAVI

procedure, only 3 (9%) had new MI on 6 month follow up, one of which may have been a result of concomitant percutaneous revascularisation during the TAVI procedure rather than due to the TAVI procedure itself. This study suggests that the risk of MI being precipitated by periods of global hypotension during TAVI in the context of coronary stenosis is lower than previously thought. Our findings are consistent with other studies suggesting that coronary revascularisation pre-TAVI does not improve outcome. For example, Rodes-Cabau et al [243] did not find any influence of the presence of prior CAD and pre-procedural revascularisation completeness on myocardial injury (defined using biomarker release) following TAVI. Masson et al [125] found that the presence of CAD or non-vascularised myocardium was not associated with an increased risk of adverse events. Although pre- and peri- TAVI revascularization does not appear to be warranted on the grounds of preventing myocardial damage, it may still be considered in patients whereby symptoms could be attributed to coronary stenoses rather than the aortic valve disease. In this case, and especially in the context of anginal symptoms, it may be that percutaneous coronary intervention results in relief of symptoms saving the patient (and the healthcare economy) the potential risk and cost of the more invasive TAVI procedure.

Our new infarct rate of 5% in the TAVI arm was much lower than the 18% suggested by a similar sized study by Kim et al [117]. Their study included a large number of patients (43%) with a trans-apical access route and it is not clear from their methodology whether scar related to the trans-apical access site was included in their LGE quantification. Trans-apical TAVI is associated with a 2-4 times increased level of post-procedure troponin release compared with the trans-femoral route [243] and apical LGE has been found to be almost universal on CMR imaging following trans-apical TAVI, with a mean mass of 2.8±1.6g [118]. The new infarct mass described by Kim et al [117] was almost double that observed in our study. However, the post-procedure scan was performed 7 days rather than 6 month post-procedure as in our study, which may account for some differences as mass of infarcted myocardium can be overestimated in the acute phase by CMR LGE imaging [115]. Kim et al [117] also reported a reduction in LVEF in those patients with new infarct pattern LGE. This was not found in our study. The fact that a

1.8% loss of LV myocardium pertained to a 10% reduction in global LVEF in their study is surprising and suggests that the presence of new LGE was a surrogate marker for other adverse procedure-related factors. Our new infarct TAVI population did not show a significant difference in LVEF according to LGE status; this could simply reflect the small sample size, however, other studies have also failed to demonstrate a correlation between myocardial injury and ejection fraction [113, 247].

Our low new infarct rate in the TAVI group is further corroborated by a recent study by Kahlert et al [110] which investigated 15 patients undergoing trans-femoral TAVI using a Doppler wire positioned in the left anterior descending artery for the entire TAVI procedure. They described micro-embolic coronary artery showers (High-intensity Transient Signals) at all stages of the procedure. On pre- and post-procedural CMR scanning, only one patient had a detectable MI, which was described as a tiny mid-myocardial area of LGE in the lateral wall. There was no correlation between the number of High-intensity Transient Signals and troponin release; however, there were positive correlations between post-procedural troponin elevation and the duration of rapid pacing and time to blood pressure recovery.

As there were only 3 new infarcts in our TAVI group, mechanistic insights are difficult to derive. Histopathological specimens of embolic debris captured during TAVI suggest that the debris consists of a mixture between thrombotic material and aortic wall/valve debris [248] and therefore embolic or atherosclerotic plaque rupture at the time of the procedure are both plausible explanations. Emboli formed on the valve post-procedure (the greatest risk for this being the first few weeks post-operatively when the valve surface is yet to endothelialise) could also be implicated. Only one patient (2%) in the TAVI group had a clinically detected MI which fulfilled VARC criteria, with none in the SAVR group. This finding is in keeping with the low rates of clinically detected peri-procedural MI observed in the PARTNER study [86].

4.5.2. SAVR

To our knowledge the new infarct rate using CMR LGE following SAVR has not been previously investigated. Our new infarct rate of 26% is in keeping with the small study of 28 patients by Lim et al, who found a CMR LGE new infarct rate of 32% 6 months following CABG [249] and a small radionuclide study reporting an new infarction rate of 16% following SAVR [116]. Whilst the infarcts were small with no significant effect upon LVEF, our study is able to offer novel insights into the cause of new MI during SAVR. Only one of the SAVR LGE (+) patients had a mechanical valve. Given the higher thrombogenicity of metal valves, it is plausible that improper anti-coagulation post-procedure was implicated in this case, however, the remaining 9 infarcts were in patients undergoing bioprosthetic valve implantation. Spasm of the left internal mammary artery graft has been postulated as a cause [250] but only 1 of 10 patients in the SAVR LGE (+) group underwent arterial grafting, ruling this out as an important mechanism. In fact, only 3 of the SAVR LGE (+) patients had pre-existing CAD, and those in the SAVR LGE (+) group were less likely to undergo concomitant CABG than those in the SAVR LGE (-) group, meaning that bystander coronary disease or the CABG procedure itself are unlikely to represent significant contributing factors. None of the patients in the SAVR LGE (+) group had atrial fibrillation, making an embolic (left atrial) source of infarction also unlikely. The systemic inflammation response syndrome (SIRS) is more common following SAVR than TAVI [251] and SIRS is associated with a 11-13% rate of myocardial injury [252]. Considering all these factors, embolism from valve debris at the time of valve excision, or embolism from the bioprosthetic valve leaflets at some point following surgery (in the context of the hypercoagulable state associated with SIRS [253]) may thus be the most plausible mechanism.

In the SAVR group, all of the infarcts were small, with a mean overall mass of just over one gram. Perhaps it is not surprising, therefore, that those with new infarcts had no significant deterioration in LVEF compared with those without. Interestingly, and in agreement with the findings of Lim et al [249], there was no difference in aortic cross clamp time, cardiopulmonary bypass time or pre-procedure beta blocker rates between the two groups.

4.5.3. Baseline late gadolinium enhancement

The rates of pre-existing MI were high in both the TAVI and SAVR population, representing 42% and 23% respectively. Many of those with evidence of pre-existing infarct pattern LGE had no clinical history of MI, despite the mean mass of infarct accounting for over 10% of myocardial mass. Kim et al [117] found an even higher pre-existing infarct rate of 66% in a group of patients undergoing TAVI, again with the majority of patients not having a clinical history of MI.

4.5.4. Anticoagulation strategy

Unless there was another indication for warfarin at the time of discharge (such as atrial fibrillation or mechanical valve implantation), patients were discharged on aspirin and clopidogrel dual anti-platelet (DAPT) regime in the case of TAVI and aspirin monotherapy in the case of SAVR. This is an inherent difference between the groups and could possibly account for the differing rates of MI observed. A study of over 400 patients undergoing tissue aortic valve replacement demonstrated clinically detected embolic (the majority comprising retinal or cerebral emboli) event rates of 12% following SAVR bioprosthesis implantation [254], with a quarter of those being on aspirin at the time of the event. The mechanism for the embolisation is not entirely established, but may be related to lack of endothelialistaion of the valve leaflets, which exposes the patient to an elevated risk in the early post-operative period, especially as there may be a hypercoagulable state at this time-point due to a systemic inflammatory response [253]. A study of the Carpentier-Edwards porcine valve following up patients on no anticoagulation over a period of 12 years reported a major neurological event in 5% patients, almost half of which occurred in the first 5 days of surgery [255]. A prospective comparison of warfarin against ticlopidine, suggested a lower rate of thromboembolism with ticlopidine (0.5% pt-year) compared with warfarin (3% pt-year) following SAVR, at the expense of higher bleeding rates [256]. The efficacy of a dual anti-platelet regime (DAPT) following bioprosthetic SAVR compared with aspirin monotherapy in the prevention of embolic events has never been tested. In a study of 135 patients with a mechanical aortic valve receiving DAPT, a thrombosis rate of 2.5% per pt-year

was reported [257]. Interestingly in this study, 8 patients died from myocardial infarction, although whether this was a result of atherosclerotic plaque rupture and subsequent coronary artery thrombosis or embolism from the valve itself was not clear.

Anti-coagulation strategies have been more thoroughly investigated following TAVI. Currently, empirical DAPT following TAVI is the norm. However, recent studies comparing DAPT with aspirin monotherapy challenge the need for this aggressive anti-platelet strategy. A recent meta-analysis comparing the two treatment strategies has shown low rates of 30 day stroke (DAPT 2.4% vs aspirin only 1.4%, p=0.56) and 30-day spontaneous MI (DAPT 0.3% vs aspirin monotherapy 0.8%, p=0.59) in both groups [258]. Findings at 6 months were similar. The failure of these trials to show benefit of DAPT over aspirin alone mean that the differences in MI rates following TAVI and SAVR may not be adequately explained by the varied anticoagulation regimes. Indeed, our low new infarct rate at 6 month follow-up compared with higher rates on early CMR scans previously reported [114], suggests that late post-procedure valve embolism is unlikely to be a significant contributing factor. Only a head to head randomized control trial comparing aspirin and DAPT following SAVR and TAVI will help establish whether the post-procedure anticoagulation strategy impacts on embolisation.

It also warrants discussion that a numerically larger (but not statistically significantly different) number of patients in the TAVI arm had atrial fibrillation and hence were warfarinised at the time of discharge. It may be that that warfarin in this setting afforded better embolic protection and could have influenced the findings of the study.

4.5.5. Clinical context

The impact of new infarct pattern LGE following aortic valve intervention is not yet known. Although it may be a benign condition, especially given the small percentage of myocardium affected, the presence of LGE following coronary revascularisation has been linked to reduced survival (26) and evidence of even a small amount of LGE (mean LV mass 1.4%) in patients

presenting with signs or symptoms of coronary artery disease has been associated with a >7-fold risk of major adverse events [259]. Further studies are required to explore whether the presence of LGE following aortic valve intervention is associated with an adverse outcome, and if this is found to be the case, strategies for improved myocardial protection at the time of surgery or reduced embolisation in the post-procedure phase should be developed.

Biomarker release is almost ubiquitous following aortic valve intervention due to the global insult to the ventricle from a number of mechanisms (Figure 4-1). Barbash et al [113] found elevated troponin in 98% of 150 patients following TAVI. The high sensitivity of the cardiac biomarkers impedes their ability to detect focal MI following valve intervention [247]. This combined with the fact that non-ischaemic ECG changes develop frequently following valve implantation due to trauma to the myocardial conduction system [111, 112], makes the detection of true peri-procedural MI as suggested by the VARC definition [107] challenging. Thus our study demonstrates the potential clinical utility of CMR LGE in the diagnosis of peri-procedural MI. Our findings also serve to reassure operators that TAVI is not associated with high rates of MI, even in the context of non-revascularised CAD, and that the strategy of proceeding to TAVI without prior percutaneous revascularisation is unlikely to expose the patient to excessive risk.

4.6. Limitations

As with all observational studies of SAVR and TAVI at the current time, the groups are not matched in terms of age, co-morbidity or surgical risk, due to the current selection criteria for TAVI implantation. The death rate 6 months following TAVI was double that of the SAVR population, which reflects the increased frailty of the TAVI population. Autopsy data were not available and therefore this may be a source of bias. The high post-procedural permanent pacemaker rate following TAVI is a common limitation to all CMR based TAVI studies [117]. Nonetheless, it is also a potential source of significant bias. Our study did not include biomarker data, as it has been shown to have little relationship with myocardial infarction in the post-TAVI

and SAVR period, however, these data may have been helpful in delineating the timeline of the myocardial infarctions observed. Our follow up scan was at 6 months following the procedure, therefore it is difficult to be certain that the infarcts occurred at the time of the procedure and not in the 6 month follow-up, although none of our patients had an admission with acute coronary syndrome or underwent coronary revascularisation in the time between hospital discharge and follow up CMR.

Chapter 5: Acute cardiac reverse remodelling following Trans-Catheter Aortic Valve Implantation

5.1. Abstract

Introduction: Despite the wealth of data demonstrating the positive effects on cardiac reverse remodelling at medium and long term follow up, the immediate effects of the reduction of afterload afforded by TAVI are yet to be comprehensively described using CMR imaging. Also, the link between myocardial fibrosis (MF) and acute LV mass regression is unknown.

Methods: Fifty-seven patients with symptomatic severe AS undergoing TAVI underwent paired CMR scans prior to and 4 days post-procedure. LV mass, volume and function were measured. LGE imaging was performed to assess for the presence of and pattern of MF.

Results: Fifty-three (95%) patients experienced an acute reduction in LV mass. LVMi regressed by 10.1±7.1% from 76±15.5 to 68.4±14.7g/m^2 (p=<0.001). Those with no LGE experienced the most post-procedure mass regression (13.9±7.1%) compared to those with mid-wall/focal fibrosis pattern LGE (7.4±5.8%) and infarct pattern LGE (7.2±7.0%) (p=0.005). There was no overall change in LVEF (55.1±12.1 to 55.5±10.9%, p=0.867), however a significant improvement in LVEF was seen in those with abnormal (<55%, n=24 (42%) baseline LVEF (43.2±8.9 to 46.7±10.5%, p=0.027). Longitudinal function also improved following TAVI in those with no fibrosis (9.68±1.99 to 11.17±2.77mm, p=0.046) whereas in those with mid-wall/focal fibrosis LGE (10.79±2.82 to 10.29±1.75mm, p=0.499) and infarct pattern LGE (10.69±3.78 to 11.69±3.15, p=0.161) there was no change. Baseline LVMi (p=0.005) and MF (p<0.001) were strong independent predictors of early LVMi regression.

Conclusions: LV reverse remodelling occurs within the first week following TAVI, with significant LV mass regression in the total population and an improvement in LVEF in those with pre-existing LV impairment. Those without MF at baseline experience greater LV mass regression than those with fibrosis.

5.2. Introduction

Left ventricular hypertrophy is almost ubiquitous in severe aortic stenosis, reflecting myocardial adaptation to chronic elevation of afterload allowing normalisation of wall stress [9, 10]. At a cellular level, there is an increase in the number of sarcomeres and an increase in myocyte size. Increased LV mass is associated with reduced survival [260]. SAVR and more recently TAVI have been shown to lead to LV mass regression at medium and long term follow-up [167, 261]. Early mass regression following TAVI is associated with reduced hospitalisation [165] and the degree of regression of hypertrophy after aortic valve replacement is a positive prognostic indicator [164]. Despite the wealth of data demonstrating the positive effects on cardiac reverse remodelling at medium and long term follow-up, the acute effects of the reduction of afterload afforded by TAVI are yet to be comprehensively described using CMR imaging. From a physiological perspective, acute reduction in afterload is associated with a reduction in wall stress and left ventricular filling pressure and at a cellular level, myocyte shrinkage can be seen within the first week in animal models [168]. In view of this, the accurate nature of CMR LV mass quantification would be well placed to assess this response in humans and test the hypothesis of early mass regression following acute afterload reduction. The relationship between baseline myocardial fibrosis and LV reverse remodelling remains poorly understood [193, 262, 263]. The unique ability of CMR LGE imaging to assess for myocardial fibrosis may allow us to predict which patients are most likely to derive an immediate benefit from TAVI.

The aim of this study was to describe the acute changes seen in left ventricular systolic performance, as well as changes in LV mass seen within the first week following TAVI and its link with myocardial fibrosis.

5.3. Methods specific to this chapter

Sixty-five patients with severe symptomatic aortic stenosis undergoing TAVI were enrolled between December 2012 and April 2015 at a single tertiary centre (Leeds General Infirmary, Leeds, UK).

5.3.1. TAVI Procedure

Patients underwent Medtronic CoreValve or Evolut R (Medtronic Inc., Minneapolis, Minnesota) or Boston Lotus (Boston Scientific Corporation, Natick, MA) valve implantation. Trans-femoral was the default approach with other techniques (subclavian and direct aortic) chosen in the case of unsuitable femoral access. Descriptions of the devices and technical aspects of the procedure have been described elsewhere [85, 254-256]. Valve sizing was achieved by annulus measurements taken from gated cardiac computed tomography or 3D transoesophageal echocardiography. All procedures were performed by two experienced operators. Left ventricular end diastolic pressure (LVEDP) was measured invasively both at the beginning and at the end of the procedure. A clinically significant reduction in LVEDP was defined as ≥5mmHg.

5.3.2. CMR Protocol and analysis

CMR scans were performed on the same imaging platform (Philips Healthcare, Best, Netherlands) pre-procedure (median 1 day, IQR 0 days) and immediately post-procedure (median 4 days, IQR 1 day), prior to hospital discharge. The pre-procedure scan included late gadolinium enhancement imaging as described in the general methods section. The immediate post-procedure scan protocol was a shortened protocol which was designed to acquire cardiac mass, volume, function and flow data at an acceptable scan length, given the fact that patients were in the early stages of recovery from a major intervention. Therefore immediately post-procedure, the scan protocol consisted of multi-slice, multi-phase cine imaging using a SSFP pulse sequence in the short axis (8mm thickness, 0 mm gap, 30 phases, matrix 192x192, typical field of view 340mm) to cover both ventricles, standard 2, 3 and 4 chamber SSFP cine images and through-plane velocity encoded phase contrast imaging planned just above the TAVI bioprosthesis valve cage (typical VENC

250cm/sec, retrospective gating, slice thickness 6mm, 40 phases). LGE imaging was not performed for the immediate post-procedure scan.

5.3.3. Statistical analysis

As per the paper by Bellenger et al [189], 9 patients are required to detect a 10g change in LV mass using CMR with a power of 90% and $p<0.05$. In the same study, the number of patients required to detect a 3% change in LVEF was 15.

5.4. Results

Of the recruited patients, 57 (88%) completed both pre-procedure and early post-procedure scan protocols. Reasons for non-completion of the study protocol included pacemaker implantation (n=3), peri-procedural death (n=2), poor image quality due to arrhythmia (n=1) and claustrophobia (n=2). The analysed study population did not differ from the drop-out population in terms of age (79±8 vs. 79±7yrs, p=0.916), baseline indexed aortic valve area (0.33±0.09 vs. 0.34±0.09cm/m2, p=0.747) or EuroSCORE II (4.47±3.40 vs. 4.55±3.46%, p=0.891), indicating that the demographics of the analysed patients were representative of the larger population. Basic demographic, clinical and echocardiographic characteristics of the final study population can be seen in Table 5-1. Procedural characteristics can be seen in Table 5-2.

Table 5-1 Basic demographic, clinical and echocardiographic characteristics

	Analysed population (n=57)
Age, years	79±8
Length of stay, days	7.2±7.0
Gender, male (%)	30 (53)
NYHA classification	3.0±0.4
Logistic EuroSCORE, %	18.4±11.3
EuroSCORE II, %	4.6±3.5
Body surface area, m^2	1.84±0.23

Body mass index, kg/m2	27.9±4.80
Atrial Fibrillation	11 (19)
Diabetes Mellitus	9 (16)
Hypertension	24 (42)
Previous myocardial infarction	15 (26)
Previous coronary artery bypass grafting	12 (21)
Prior percutaneous coronary intervention	17 (30)
Peripheral vascular disease	14 (25)
Pulmonary hypertension	23 (40)
Echocardiographic data	
Indexed aortic valve area, cm/m^2	0.34±0.09
Peak aortic valve velocity, m/sec	4.7±0.6
Aortic valve mean pressure gradient, mmHg	51±13
Peak aortic velocity >5m/sec	14 (25)

Data are expressed as mean ±SD or number (%). NYHA: New York Heart association.

Table 5-2 Procedural characteristics

	Analysed population, n=57
TAVI type	
Medtronic CoreValve	26 (45.6)
Boston Lotus	26 (45.6)
Medtronic Evolut-R	5 (8.8)
TAVI access route	
Femoral	49 (86)
Subclavian	7 (12)
Direct aortic	1 (2)
Procedure details	
Valve size, mm	27±3
Procedure time, mins	171±120
Contrast volume, mls	132±52
Invasive haemodynamics	
Invasive aortic valve gradient pre-TAVI, mmHg	53±21
Systolic blood pressure pre-TAVI, mmHg	133±23
Diastolic blood pressure pre-TAVI, mmHg	50±9

Diastolic blood pressure post-TAVI, mmHg	52±10

Data are expressed as mean±SD or number (%). TAVI: Trans-catheter aortic valve implantation.

5.4.1. Baseline CMR characteristics

Baseline LVEF was 55.1±12.1% and mean indexed LV mass was 76.2±15.5g/m^2 with an LV mass:LVEDV ratio of 0.80±0.15. There was no difference between baseline LVMi or LVEF according to severe (aortic peak velocity <5m/sec) or very severe (peak velocity >5m/sec) aortic stenosis (LVMi severe 74.9±14.8 vs. very severe 80.2±17.5g/m^2, p=0.272, LVEF severe 54±13 vs. very severe 57±8%, p=0.725). LGE imaging was available for 53 patients. 4 (7%) patients did not receive a Gadolinium-based contrast agent due to pre-existing renal failure with an estimated glomerular filtration rate of <30ml/min/1.73m^2. 14 patients (26%) had evidence of myocardial infarction pattern LGE, 19 patients (36%) had mid-wall/focal fibrosis pattern LGE and the remaining 20 (38%) had no evidence of LGE. Examples of the differing patterns of LGE can be seen in Figure 5-1.

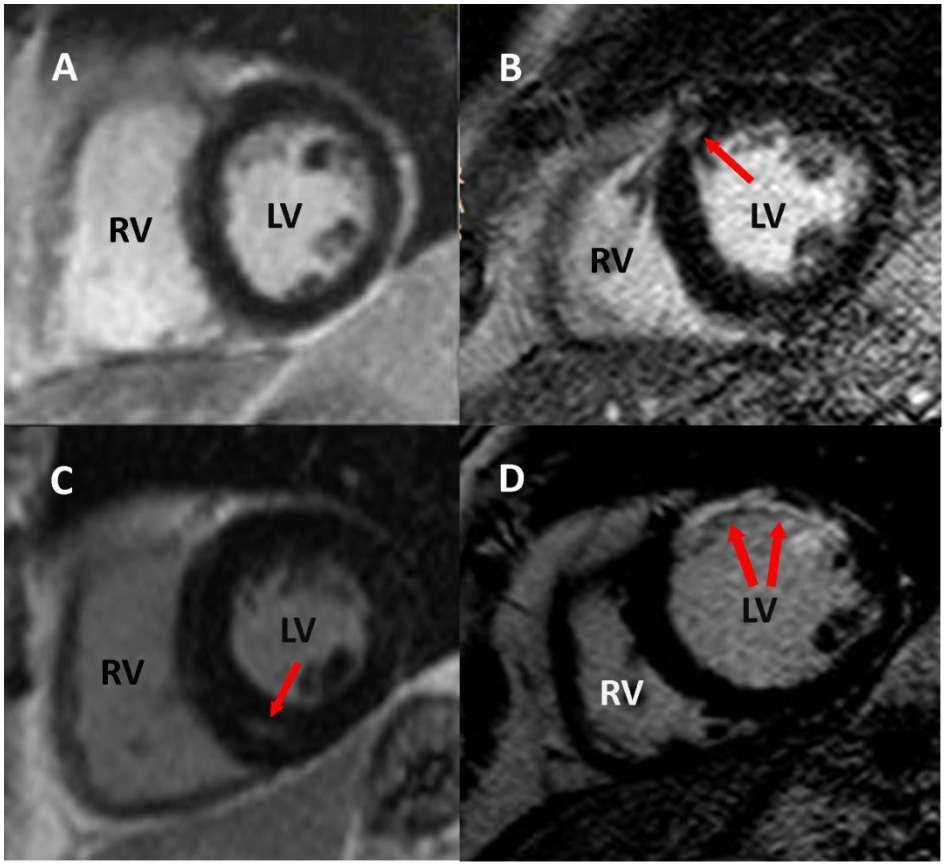

Figure 5-1 Differing patterns of myocardial fibrosis

LV short axis CMR images demonstrating the different patterns of LGE. Panel A. The LV myocardium appears black with no evidence of LGE. Panel B: The red arrow depicts focal fibrosis at the anterior right ventricular insertion point. Panel C: A typical mid wall LGE pattern (red arrow). Panel D: Infarction pattern LGE, with the red arrow demonstrating an anterior myocardial infarction of around 50% trans-murality. LV: Left ventricle. RV: Right ventricle.

Those with no fibrosis at baseline had a lower pre-procedure LVEDP (18±5mmHg) than those with infarct pattern LGE (21±8mmHg) and mid wall/focal fibrosis LGE (24±8mmHg), one-way ANOVA (F=3.249, p=0.047) but there was no significant difference between the different fibrosis groups in terms of baseline LVMi (no LGE 74.3±15.7, mid-wall/focal fibrosis LGE 77.6±55.8, infarct pattern LGE 73.1±13.7g/m^2, F=0.390, p=0.679) or baseline LVEF (no LGE

57.8±10.7, mid-wall/focal fibrosis LGE 55.8±14.5, infarct pattern LGE 51.3±10.6%, F=1.162, p=0.321).

5.4.2. Invasive pressure measurements

There was a moderate positive correlation between baseline LVMi and pre-implant LVEDP (r=0.367, p=0.005) (Figure 5-2), but no relationship between pre-implant LVEDP and LVEF (r=-0.067, p=0.619) or AVAi (r=0.002, p=0.986). TAVI was associated with a minorreduction in LVEDP from 21±8mmHg at the start of the procedure to 19±6mmHg following device deployment (p=0.009). Those with a clinically significant reduction in LVEDP (defined as >5mmHg) had a greater baseline LVMi (LVEDP reduction 85.6±14.1 vs. no LVEDP reduction 72.2±14.5g/m^2, p=0.002) and had a significant reduction in LV cavity size (LVEDVi) post-procedure (LVEDP reduction: 8.7±16.0 vs. no LVEDP reduction 0.24±11.4ml/m^2, p=0.028) compared to those without a reduction in LV filling pressure. There was no relationship between post-procedure LVEDP and post-procedure aortic regurgitation fraction (r=0.186, p=0.173).

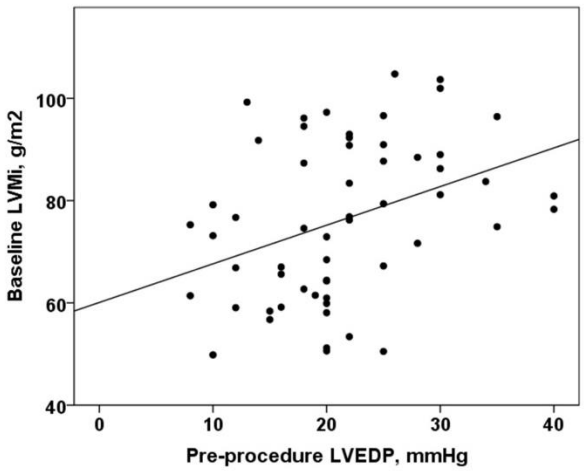

Figure 5-2 Relationship between baseline LVMi and LVEDP

Scatterplot demonstrating the relationship between baseline indexed left ventricular mass (LVMi) and pre-procedure left ventricular end diastolic pressure (LVEDP).

5.4.3. Post-procedure CMR

CMR derived values pre and early post-procedure can be seen in Table 5-3.

Table 5-3 Pre and post-procedure CMR characteristics

	Pre-procedure N=57	Post-procedure N=57	P Value
Mitral annular displacement, mm	10.3±2.8	11.0±2.6	0.134
LVEDVi, ml/m^2	97.8±24.3	95.1±18.9	0.226
LVESVi, ml/m^2	45.7±22.6	43.6±18.3	0.268
LVSVi, ml/m^2	52.1±11.0	51.2±9.1	0.454
LVEF, %	55.1±12.1	55.5±10.9	0.867
LVMi, g/m^2	76.2±15.5	68.4±14.7	<0.001
LV mass/LVEDV	0.76±0.15	0.73±0.15	<0.001
Indexed left atrial volume, ml/m^2	75.4±24.7	70.4±23.1	0.042
Max pressure gradient, mmHg	44±15	18±9	<0.001
Aortic regurgitation fraction, %	12.3±9.4	7.6±6.5	0.005

Data are expressed as mean±SD. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume. LVSVi: Indexed left ventricular stroke volume. LVEF: Left ventricular ejection fraction. LVMi: Indexed left ventricular mass.

Fifty-three (95%) patients experienced an acute reduction in LV mass. Indexed LV mass regressed by 10.1±7.1% from 76±15.5 to 68.4±14.7g/m^2 (p=<0.001). Those in the highest quartile of baseline LVMi had more absolute LVMi regression than those in the lowest quartile (10.5±5.8 vs. 6.4±1.3g/m^2, p=0.045). LV mass regression did not differ according to sex (men 7.8±5.4 vs. women 7.7±6.0g/m^2, p=0.980) or classification of aortic stenosis (severe 8.0±5.7 vs very severe 7.0±5.5g/m^2, p=0.556). Baseline AVAi (r=0.126, p=0.348), post-procedural aortic regurgitation (r=-0.136, p=0.321), post-procedural valve gradient (r=-0.005, p=0.969), or systolic blood pressure (r=-0.041, p=0.767) did not appear to be associated with LV mass regression. Patients with a history of hypertension (n=24 (42%)) experienced more LV mass regression than those with no hypertension (9.6±5.1 vs. 6.4±5.8g/m^2, p=0.038). 9 (16%) patients had significant post-procedure aortic regurgitation (defined as an AR fraction >16% [235]). There was a trend towards greater LVMi regression in those without significant post-procedural aortic regurgitation (LVMi regression significant AR 4.5±5.4 vs. no significant AR 8.5±5.6g/m^2, p=0.051).

There was no overall change in LVEF (Table 5-3), however, when split according to baseline LVEF, classified as normal (baseline LVEF>55%, n=33 (58%)) and abnormal (baseline LVEF<55%, n=24 (42%)), a significant improvement in LVEF was seen in those with an abnormal baseline LVEF (43.2±8.9 to 46.7±10.5%, p=0.027), mainly driven by an increase in LVESVi (Figure 5-3).

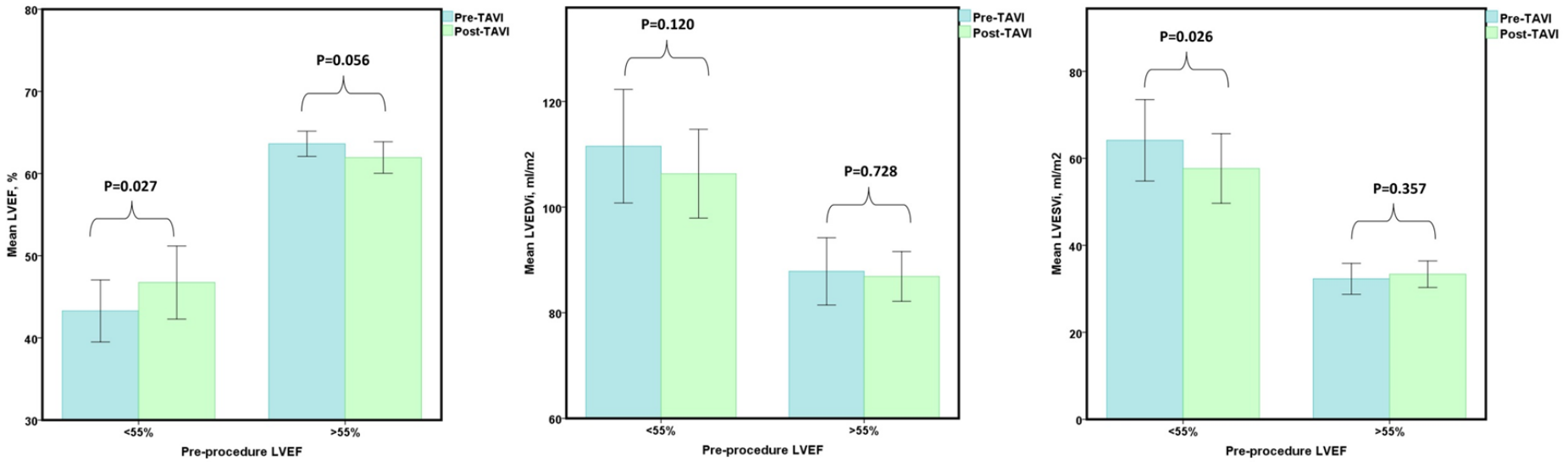

Figure 5-3 Bar graphs showing reverse remodelling according to baseline LVEF

Bar graphs depicting change in LVEF, LVEDVi and LVESVi according to baseline LVEF pre and post-TAVI. The error bars depict the 95% Confidence Intervals. LVEF: Left ventricular ejection fraction. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Left ventricular end systolic volume. TAVI: Trans-catheter aortic valve implantation.

5.4.4. Late gadolinium enhancement

Those with no LGE at baseline experienced the most post-procedure LV mass regression (13.9±7.1%) compared to those with mid-wall/focal fibrosis pattern LGE (7.4±5.8%) and infarct pattern LGE (7.2±7.0%) (One-way ANOVA p=0.005). A Tukey *post-hoc* test revealed that there was a statistically significant difference between those with no fibrosis and mid-wall/focal fibrosis (p=0.011) and the no fibrosis and infarct pattern groups (p=0.017) but no difference in terms of mass regression between those with mid-wall/focal fibrosis and infarct pattern LGE (p=0.997). Longitudinal function also improved following TAVI in those with no fibrosis (9.68±1.99 to 11.17±2.77mm, p=0.046) whereas in those with mid-wall/focal fibrosis LGE (10.79±2.82 to 10.29±1.75mm, p=0.499) and infarct pattern LGE (10.69±3.78 to 11.69±3.15, p=0.161) there was no change.

5.4.5. Predictors of LV mass regression

Variables including patient demographics, relevant clinical history, procedural characteristics and baseline cardiac measurements were analysed to determine univariable predictors of reverse remodelling (Table 5-4). Multivariable regression analysis revealed only baseline LVMi and the presence of LGE to be independent predictors of early LV mass regression.

Table 5-4 Univariable and multivariable regression analysis

	Unstandardised coefficient	Standard Error	P Value	95% CI
Univariable analysis – change in LVMi (g/m^2)				
Baseline LVMi (g/m^2)	0.119	0.047	0.014	0.025 to 0.212
Gender	-0.037	1.514	0.980	-3.072 to 2.997
Age (y)	0.032	0.097	0.747	-0.163 to 0.227
Hypertension	3.126	1.472	0.038	0.176 to 6.076
AVAi (cm/m^2)	7.968	8.426	0.348	-8.919 to 24.855
SBP (mmHg)	-0.010	0.033	0.767	-0.077 to 0.057
Reduction in LVEDP >5mmHg	1.740	1.609	0.284	-4.965 to 1.485
TAVI size (mm)	0.418	0.287	0.151	-0.158 to 0.993
Presence of fibrosis	-5.042	1.467	0.001	-7.987 to -2.097
Type of fibrosis	2.562	0.847	0.004	0.860 to 4.263
Post-procedural AR (%)	-0.120	0.120	0.321	-0.360 to 0.120
Post-procedural aortic valve gradient (mmHg)	-0.004	0.091	0.969	-0.186 to 0.179
Multivariable regression analysis – change in LVMi (g/m^2)				
Baseline LVMi	0.126	0.043	0.005	0.040 to 0.212
Presence of fibrosis	-5.190	1.362	<0.001	-7.926 to -2.454

LVMi: Indexed left ventricular mass. AVAi: Indexed aortic valve area. SBP: Systolic blood pressure. LVEDP: Left ventricular end diastolic pressure. TAVI: Transcatheter aortic valve implantation. AR: Aortic regurgitation.

5.5. Discussion

This study is the first using CMR, the reference standard technique for LV volume and mass quantification, to comprehensively describe the acute changes in left ventricular mass and function within the first week after TAVI and its relationship to myocardial fibrosis. We have shown that LV reverse remodelling begins very early, with around 10% of LV mass regression occurring within the first week and LVEF improving in those with a reduced baseline ejection

fraction. Furthermore, we have demonstrated that those without fibrosis at baseline experience more early LV mass regression and an improvement in longitudinal left ventricular function.

5.5.1. Remodelling in aortic stenosis and acute reverse remodelling following TAVI

Our baseline characteristics were similar to other TAVI-based studies, representing a population with high levels of co-morbidity at elevated surgical risk [264]. Our patients were elderly with an equal gender split in keeping with other studies of patients undergoing TAVI, reported by both our group and elsewhere [167, 169]. Our rates of baseline mid-wall/focal and infarct fibrosis are congruent with those reported in other centres. Dweck et al [49] reported rates of mid-wall/focal fibrosis in 38% of patients and infarct pattern LGE in 28% of patients with moderate or severe aortic stenosis. Weidemann et al reported rates of fibrosis in 62% of patients undergoing aortic valve replacement for aortic stenosis [193]. In our population, there was no association between baseline LVMi and presence or type of fibrosis in keeping with Weidemann's study, although differing from the results of Dweck et al [49] who found that those with mid-wall fibrosis had an elevated LV mass at baseline. In our study, those with fibrosis had a higher pre-implant LVEDP, suggesting that those with fibrosis may have more severe disease at baseline, with a stiffer, less compliant left ventricle leading to elevated filling pressures. In our patient population there was no overall acute change in LVEF which is in keeping with other CMR studies [173], however, those with a reduced baseline LVEF did derive a significant improvement, suggesting that acute afterload reduction does have a favourable effect on LVEF in those with an abnormality at baseline.

This study offers further insight into the timeline of LV mass regression following TAVI for aortic stenosis. It is well described in the literature that most mass regression occurs within the first 6 months of TAVI, with mass regression rates of 18-22% reported [167, 169] and a slower rate of regression thereafter [261]. In this study we have been able to show that favourable reverse remodelling occurs almost immediately, with around 10% of mass regression occurring within the first week post-TAVI. Similar findings been suggested by echo studies following TAVI [165]

and SAVR [26, 265] and early LV mass regression following TAVI has been associated with reduced hospitalisation [165]. An echocardiographic sub-study of the PARTNER A trial comparing surgical and trans-catheter aortic valve replacement in high risk patients with aortic stenosis and severe baseline LV hypertrophy, reported mass regression of 17% at one year following TAVI, with around half of this occurring within the first 30 days [165]. Christakis et al investigated 57 patients before and 5 days following surgical aortic valve replacement, and reported very similar results with a mean LV mass reduction of 10% [265].

Assessment of LV mass by echocardiography is calculated on the basis of a number of anatomical and mathematical assumptions, potentially reducing accuracy that may be compounded by the higher inter-operator variability rendering them relatively inaccurate [266]. Due to the excellent endocardial definition and the 3D nature of the technique, LV mass quantification using modern CMR SSFP pulse sequences are highly correlated with autopsy studies (r=0.95) [267] and therefore can give an acute assessment of LV mass pre- and post-TAVI. CMR LV mass quantitation is also more reproducible than by echo, as evidenced by the low inter and intra-observer variability reported in this study and in others [268] allowing smaller sample sizes to detect a treatment effect.

The mechanism for acute LV mass reduction remains poorly understood. A number of mechanisms are possible; it is conceivable that the decreased afterload leads to an acute reduction in myocyte stretch and hence a decrease in myocyte diameter and volume. Other mechanisms may relate to a reduction in oedema or an overall reduction in extra-cellular volume. Evidence from animal models support the notion that LV mass regression occurs acutely; a regression in myocyte volume and myocyte cross sectional area has been demonstrated in hypertensive rats one week following the initiation of anti-hypertensive treatment [168], and novel CMR techniques using tissue characterisation have been developed to investigate cardiomyocyte size in murine models of hypertension. If this is successfully translated into humans, it may allow

future investigation into the pathogenesis of the mass regression, discriminating between an acute reduction in myocyte size or a reduction in extracellular volume [269].

5.5.2. Myocardial fibrosis

Myocardial fibrosis manifests as a result of myocyte apoptosis and subsequent replacement fibrosis and expansion of the extra-cellular volume [52]. It is a well-defined phenomenon in patients with severe AS [193] although the pathogenesis of the myocyte death remains unclear. Potential mechanisms include sub-endocardial ischaemia as a result of chronic supply demand mis-match in the context of LVH [270], myocardial stretch as a result of increased systolic wall stress [271] and angiotensin II mediated cell damage [272]. Myocardial fibrosis is important; it has been found to be an adverse prognostic marker in patients with aortic stenosis, with a 6-8x risk of mortality, incremental to that of baseline LVEF [49]. Postulated mechanisms of this excess in mortality include fibrosis associated arrhythmogenicity and adverse ventricular remodelling. Our study provides further insights into the mechanism of excess mortality. Although LV mass regression was seen in all 3 groups of patients, those without fibrosis at baseline had more acute LV mass regression than those with both focal/mid wall fibrosis and infarct pattern fibrosis. This favourable LV mass regression in those without fibrosis may allow a mechanistic explanation for the survival advantage seen by Dweck et al [49]. The lack of relationship between myocardial fibrosis and LVEF is perhaps not surprising, as LVEF is derived predominantly from radial contraction, which is not significantly contributed to by the sub-endocardial layers. Sub-endocardial fibres are the most sensitive to myocardial ischaemia (resulting from supply-demand mismatch) and systolic wall stress [273] and are responsible for longitudinal function [274]. This is therefore a plausible explanation for the improvement in longitudinal function seen in our group with no fibrosis and the lack of improvement in longitudinal function in both the mid-wall/focal and infarct pattern fibrosis groups.

5.6. Limitations

As with many studies investigating ‘real world’ patients, our study population included a heterogeneous patient mix including those with and without coronary artery disease and differing baseline LVEF, which may have influenced the results. Although the dropout rate was low for a CMR based study and the recruited population did not appear to differ from the analysed population, there is still the potential for bias. Although we were careful to include all possible factors in the study that may have influenced LV reverse remodelling, there may have been other factors involved. Specifically, no echocardiographic data regarding post-procedure valve gradients was acquired as a part of this study. However, we were able to report CMR derived values for post-procedural valve gradient and did not find this to be a predictor of LV mass regression on univariate analysis. CMR derived flow gradients are less accurate than echocardiographically derived Doppler gradients and therefore an in-depth analysis of any influence of patient-prosthesis mismatch was not possible. This study was not designed as an outcome study, nonetheless, demonstrating a link between acute LV reverse remodelling and mortality would strengthen these data.

Chapter 6: The impact of trans-catheter aortic valve implantation induced left bundle branch block on cardiac reverse remodelling

6.1. Abstract

Background: Left bundle branch block is common following TAVI and has been linked to increased mortality, although whether this is due to less favourable cardiac reverse remodelling is unclear. Using CMR prior to and 6 months following TAVI and a carefully matched patient population, we investigated the impact of TAVI-induced LBBB on cardiac reverse remodelling.

Methods: 48 patients undergoing TAVI for severe aortic stenosis were evaluated. 24 patients with new LBBB (LBBB-T) following TAVI were matched with 24 patients with a narrow post-procedure QRS (nQRS). Patients underwent CMR imaging prior to and 6 months post-TAVI. Measured cardiac reverse remodelling parameters included LV size, LVEF and global longitudinal strain (GLS). Inter- and intra-ventricular dyssynchrony was determined using time to peak radial strain derived from CMR Feature Tracking.

Results: Change in LVESVi, LVEF and GLS was significantly different between the two groups (LVESVi: nQRS -7.9±14.0 vs. LBBB-T -0.6±10.2ml/m2, p=0.020, LVEF: nQRS +4.6±7.8 vs LBBB-T -2.1±6.9%, p=0.002; GLS: nQRS -2.1±3.6 vs. LBBB-T +0.2±3.2%, p=0.024). The nQRS group had a significant improvement in LVEF (54.1±11.5 to 58.7±9.0%, p=0.010) and GLS (15.6±3.9 to 17.7±2.7, p=0.010) at follow-up. There was significant post-procedure inter- and intra-ventricular dyssynchrony in the LBBB-T group (inter: LBBB-T 130±73ms vs. nQRS 23±86ms, p=<0.001; intra: LBBB-T 118±103ms vs. nQRS 13±106ms, p= 0.001). Post-procedure QRS duration was an independent predictor of change in LVEF and GLS at 6 months.

Conclusion: TAVI-induced LBBB is associated with less favourable cardiac reverse remodelling at medium term follow-up. In view of this, every effort should be made to prevent TAVI-induced LBBB, especially as TAVI is now being extended to a younger, lower risk population.

6.2. Introduction

The aortic valve lies close to the electrical conduction system of the heart and is prone to damage at the time of aortic valve intervention, often manifesting as new left-bundle branch block. New LBBB is infrequent following SAVR [127], but much more common following TAVI with reported rates of up to 65%, depending on valve design [128]. TAVI-induced left-bundle branch block (LBBB-T) has been linked to reduced survival [152-155] and increased hospitalisation [112], in keeping with population based studies suggesting reduced overall survival in healthy individuals with LBBB [156] and in patients with heart failure and LBBB [157]. The mechanism for this increased mortality is debated. One hypothesis is that LBBB-T is a precursor to further more lethal conduction abnormalities, suggested by studies reporting high levels of atrioventricular block on those receiving post-TAVI permanent pacemaker insertion [158]. Another hypothesis is that LBBB-T leads to adverse LV remodelling and ultimately heart failure death via a LBBB-induced cardiomyopathy [160]. Even in normal hearts it is recognised that the mechanical dyssynchrony of LBBB results in an increase in left ventricular end systolic volume, a reduction in stroke volume and a reduction in LVEF, leading some to believe that it is the LBBB itself that provokes cardiomyopathy in a certain sub-set of patients rather than an intrinsic cardiomyopathic process triggering the LBBB [275]. Over the long term, a similar mechanism may exist in patients with TAVI-induced LBBB.

Current evidence on the impact of LBBB-T on cardiac reverse remodelling is limited to echocardiographic studies, with a heterogeneous patient mix including those with post-procedural permanent pacemaker implantation, trans-apical access route and unmatched patient groups [160, 184, 276], all of which are potential confounders in the reverse remodelling process. The impact

of LBBB-T on cardiac reverse remodelling has never been investigated using CMR imaging. Furthermore, the novel technique of CMR feature tracking allows accurate estimation of global longitudinal strain and inter- and intraventricular dyssynchrony which are of interest in this population [277].

6.3. Methods specific to this chapter

6.3.1. Patient selection

90 patients undergoing either Boston Lotus or Medtronic CoreValve TAVI for severe symptomatic aortic stenosis were recruited at a single tertiary centre from April 2009 to April 2015. Exclusion criterion included pre-existing QRS prolongation (>120ms), pre-TAVI pacemaker implantation or contra-indication to CMR scanning. Patients were excluded from the analysis in the case of new right bundle branch block, post-procedural myocardial infarction and post-procedural permanent pacemaker implantation.

6.3.2. Matching

24 patients with LBBB-T were identified. These were matched with 24 patients with a narrow post-procedure QRS for sex, valve type, and CMR variables known to impact on reverse remodelling following TAVI including baseline LVEF, baseline LVMi and baseline LVEDVi. The results of Chapter 3 (gender differences) suggested that it was the baseline variable which most strongly predicts the change in that variable following valve replacement, therefore by matching for baseline CMR variables, the true effect of the QRS prolongation could be determined by reducing as many of the confounding factors as possible. The sample size did not permit true propensity matching, however, patients were matched on a case by case basis so that were of the same valve type and sex, and that each baseline variable was within 10% of the nQRS patient that they were matched with.

6.3.3. Electrocardiographic data

12-lead electrocardiogram recordings, acquired immediately prior to TAVI and at the time of post-procedure, hospital discharge were reviewed by a reader (OJB) blinded to clinical and procedural data. Heart rhythm, PR interval and QRS duration were recorded. LBBB-T was defined as post-procedural v1-negative QRS complex with a duration of >120ms and a notched or slurred R wave in at least one of the lateral leads according to international guidelines (I, aVL, V_5, V_6) [278].

6.3.4. CMR protocol

Details of the CMR pulse sequence acquisition protocol are outlined in the Methods chapter. Briefly, identical CMR scans were obtained at baseline (median 1 day pre-procedure, IQR 1) and at a median of 181 days (IQR 20 days) following TAVI using a 1.5T scanner (Intera, Philips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany).

6.3.5. CMR analysis

CMR analysis was performed by a single operator (LED) with 5 years' experience in CMR, blinded to clinical data using dedicated computer software (cmr^{42}, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada). Feature tracking analysis was performed on cine imaging of the mid ventricular short axis slice at the papillary muscle level to determine time to peak LV and right ventricular radial strain and the 4 chamber cine to measure global longitudinal strain as previously described [279]. Endo- and epicardial LV borders were manually drawn and a reference point was established to mark the inferior and anterior right ventricular insertion point. Borders were also traced around the right ventricle in short axis to generate time to peak radial strain values for the right ventricular free wall. The level of the mitral valve was demarcated and the left ventricular apex highlighted to allow longitudinal segmentation of the ventricle. Strain and strain rate curves were then generated for both longitudinal and radial strain parameters. If these were of sub-optimal quality, the endo- and epicardial contours were manually adjusted to

allow accurate tracking of the endocardial border. LV global longitudinal strain was calculated form the 4 chamber cine image. Time to peak strain was generated from the short axis mid ventricular cine slice. Interventricular dyssynchrony was calculated as the difference between time to peak radial strain of the right ventricular free wall and the lateral LV wall (an average of segments 11 and 12 of the American Heart Association 17 segment model). Intraventricular dyssynchrony was calculated as the difference between time to peak radial strain of the LV septal (an average of AHA segments 8 and 9) and LV segments (an average of AHA segments 11 and 12), as recommended by Gorksan et al [280]. Segments with LGE suggestive of previous myocardial infarction were excluded from strain analysis. Direct comparison of LGE images pre and post-procedure scans was performed by a single operator blinded to clinical and procedural data to determine the presence of new myocardial infarction.

6.3.6. Statistical analysis

Linear regression analysis (Enter model) was performed to establish univariate and multivariate predictors of change in LVEF and GLS post-procedure. Univariate predictors with $P<0.1$ were included in the multivariate analysis. According to the paper by Bellenger et al[183], 15 patients are required to detect a 3% change in LVEF with a power of 90% and an α error of 0.05 using 1.5T cine imaging. From the paper by Singh et al[180], a sample size of 14 is required to detect a 10% difference in global longitudinal strain with a 90% power and an α error of 0.05 using 1.5T SSFP cine imaging.

6.4. Results

90 Patients were recruited into the study. Patients undergoing post-procedure permanent pacemaker implantation (n=12), those with post-procedure right bundle branch block (n=2) and those with CMR LGE evidence of post-procedural myocardial infarction (n=3) were excluded from analysis. In addition, 3 patients died within the 6 month follow-up period and 5 patients declined follow-up. 24 patients with LBBB-T and 41 patients with a narrow QRS (nQRS) on

discharge electrocardiogram completed both baseline and 6 month scans and were available for retrospective matching in a 1:1 fashion for variables known to effect reverse remodelling following TAVI including sex, valve type, baseline LVEF, baseline LVMi and baseline LVEDVi. 48 patients were included in the final analysis, 24 with LBBB-T and 24 with nQRS. Demographic, clinical, procedural and baseline CMR details for each group can be seen in Table 6-1. 14 (29%) patients underwent Lotus valve and 34 (71%) patients underwent Medtronic CoreValve implantation. Balloon valvuloplasty was performed in 43 (90%) patients. Mean valve size was 28±2mm, procedure time 164±52 mins and contrast dose 153±61ml. Access approach was femoral in 43 (90%) patients, subclavian in 4 (8%) patients and carotid in one patient.

Table 6-1 Demographic, clinical and baseline CMR details of the nQRS and LBBB-T groups

	nQRS (n=24)	LBBB-T (n=24)	P value
Demographic details			
Age, years	80.5±6.2	79.6±9.6	0.670
Gender, male	13 (54)	13 (54)	1
Body surface area, m^2	1.82±0.29	1.86±0.19	0.332
Clinical details			
STS Mortality, %	4.5±2.4	5.1±2.8	0.397
STS Morbidity/mortality, %	21.7±7.5	24.5±8.8	0.452
Systolic blood pressure, mmHg	134±25.9	138±18	0.558
Atrial fibrillation	2 (8.3)	5 (20.8)	0.220
Hypertension	12 (57.1)	9 (37.5)	0.383
Cerebrovascular disease	4 (16.7)	4 (16.7)	1
Previous myocardial infarction	5 (20.8)	2 (8.3)	0.220
Chronic obstructive pulmonary disease	6 (25)	5 (20.8)	0.731
Peripheral vascular disease	6 (25)	7 (29.2)	0.745
Diabetes mellitus	4 (16.7)	8 (33.3)	0.182
Any epicardial coronary stenosis >50%	9 (37.5)	13 (54.2)	0.247
Pre-procedure CMR characteristics			
Baseline LVEF, %	54.1±11.5	56.6±10.5	0.386
Baseline GLS, %	-15.6±3.9	-16.1±4.2	0.638

Baseline Indexed left ventricular mass, g/m^2	74.3±14.7	73.3±17.4	0.650
Baseline LVEDVi, ml/m^2	97.8±22.8	93.4±22.1	0.500
Baseline aortic regurgitation fraction, %	9.6±8.7	10.7±5.9	0.444
Infarct pattern LGE	6 (26)	4 (18)	0.391

Data are expressed as mean±SD or number (%). STS: Society of Thoracic Surgeons. CMR: Cardiovascular magnetic resonance. LVEF: Left ventricular ejection fraction. GLS: Global Longitudinal Strain. LVEDVi: Indexed left ventricular end diastolic volume. LGE: Late gadolinium enhancement.

6.4.1. Electrocardiographic Characteristics

Mean heart rate at baseline was 67±11bpm and at 6 months was 68±13bpm. 7 patients (15%) (nQRS n=2, LBBB-T n=5) had atrial fibrillation at baseline. There were no new cases of post-procedural AF. For those in sinus rhythm, mean PR interval remained similar pre and post procedure in both the nQRS group (179±33 to 191±39ms, p=0.053) and the LBBB-T group (181±30 to 192±37ms, p=0.171). In the nQRS group there was no change in QRS duration (93±17 to 96±11ms, p=0.098). In the LBBB-T group, QRS duration increased from 96±14 to 151±12ms (p=<0.001).

6.4.2. Reverse remodelling according to post-procedure QRS duration

Change in LVEF and GLS was significantly different between the two groups (LVEF: nQRS +4.6±7.8 vs LBBB-T -2.1±6.9%, p=0.002 and GLS: nQRS -2.1±3.6 vs. LBBB-T +0.2±3.2%, p=0.024) (Figure 6-1). The change in LVEF was driven by a reduction in LVESVi in the nQRS group not seen in the LBBB-T group (nQRS -7.9±14.0 vs. LBBB-T -0.6±10.2ml/m^2, p=0.02). Pre- and post-procedure values for all CMR characteristics can be seen in Table 6-2. Change in indexed left ventricular mass was similar between the two groups (nQRS -15.9±10.4 vs LBBB-T -13.3±9.6g/m^2, p=0.367) as was change in LVEDVi (nQRS -7.3±17.4 vs LBBB-T -3.2±14.5ml/m^2, p=0.373). Neither group experienced any change in right ventricular longitudinal function (nQRS 21.7±7.0 to 21.5±6.2mm, p=0.817, LBBB-T 18.9±5.8 to 18.6±5.8mm, p=0.773). Post-procedure aortic regurgitant fraction was similar between groups (nQRS 5.4±5.7 vs LBBB-

T 5.5±3.3%, p=0.948). The relationship between post-procedure QRS duration and change in LVESVi, LVEF and GLS can be seen in Figure 6-1.

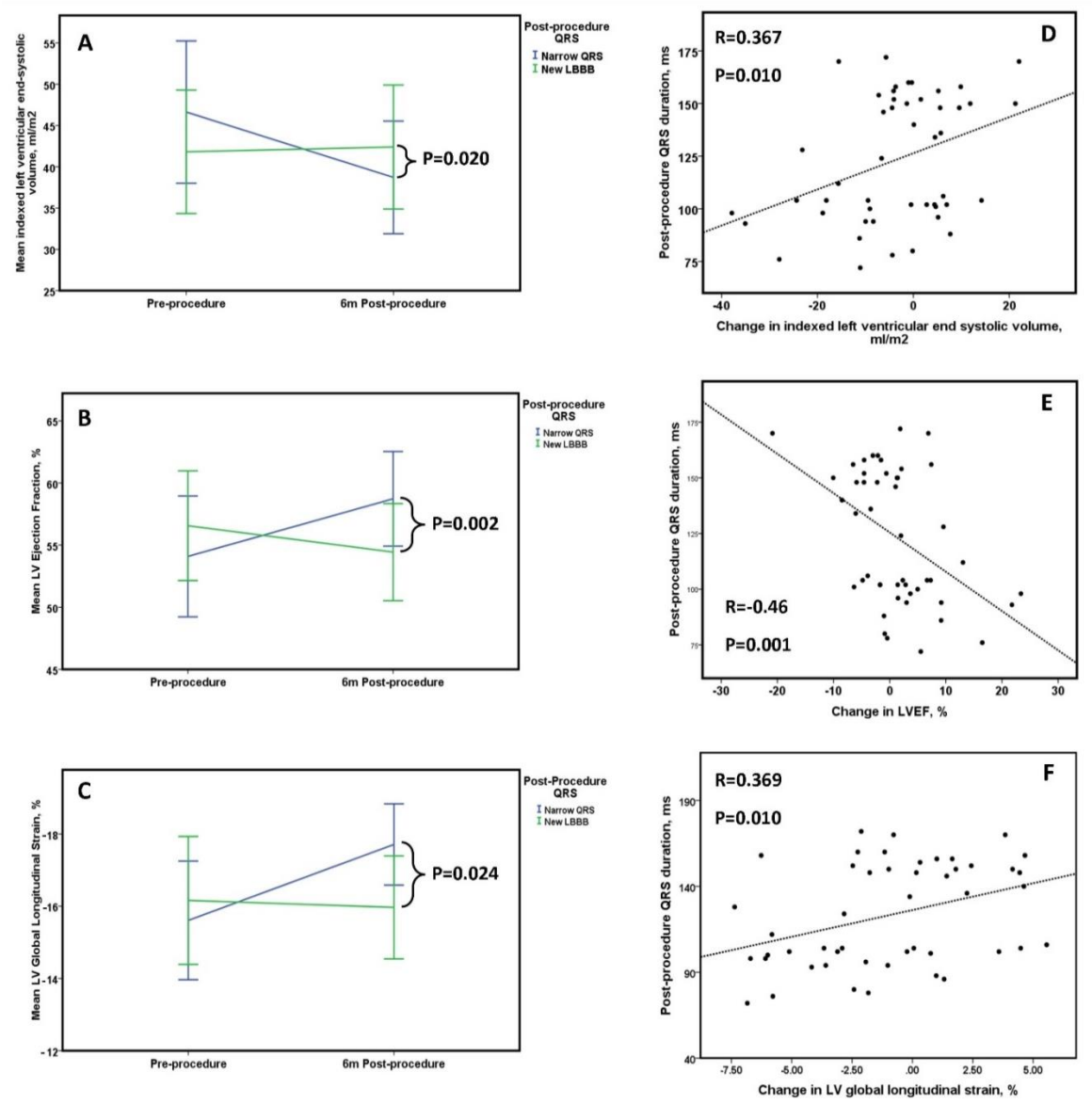

Figure 6-1 Line graphs and scatterplots

Line graphs depicting change in LVESVi (Panel A), LVEF (Panel B) and global longitudinal strain (Panel C) before and 6 months following TAVI according to post-procedure QRS duration, the vertical lines represent the 95% confidence intervals. Panels D, E and F demonstrate the relationship between post-procedure QRS duration and change in LVESVi, LVEF and GLS.

Table 6-2 CMR parameters pre and 6 months post-TAVI according to post-procedure QRS status

	nQRS (n=24)	LBBB-T (n=24)
Left ventricular ejection fraction, %		
Pre-procedure	54.1±11.5	56.6±10.5
Post-procedure	58.7±9.0	54.4±9.3
P Value	0.010	0.092
Global longitudinal strain, %		
Pre-procedure	-15.6±3.9	-16.2±4.2
Post-procedure	-17.7±2.7	-15.9±3.4
P Value	0.009	0.771
Indexed left ventricular mass, g/m^2		
Pre-intervention	74.3±14.7	73.3±17.4
Post-intervention	58.4±12.6	60.0±13.7
P Value	<0.001	<0.001
Indexed left ventricular end diastolic volume, ml/m^2		
Pre-intervention	97.8±22.8	93.4±22.1
Post-intervention	90.5±21.0	90.3±21.0
P Value	0.051	0.298
Indexed left ventricular end systolic volume, ml/m^2		
Pre-intervention	46.6±20.4	41.8±17.7
Post-intervention	38.7±16.2	42.4±17.8
P Value	0.011	0.886
Indexed left ventricular stroke volume, ml/m^2		
Pre-intervention	51.2±10.3	51.4±10.5
Post-intervention	51.8±8.7	47.9±8.5
P Value	0.742	0.035
Indexed left atrial volume, ml/m^2		
Pre-intervention	67.9±19.2	72.9±23.3
Post-intervention	60.0±18.2	67.9±23.8
P Value	0.002	0.180
Septal thickness , mm		
Pre-intervention	12.18±2.61	12.00±4.00

Post-intervention	10.49±2.98	9.22±2.52
P Value	0.002	<0.001
Lateral wall thickness , mm		
Pre-intervention	7.55±1.65	7.25±2.00
Post-intervention	6.75±1.78	6.44±1.75
P Value	0.017	0.022

Data are expressed as mean±SD. nQRS: Narrow QRS post-procedure. LBBB-T: New LBBB post-procedure.

6.4.3. Inter- and intra-ventricular dyssynchrony

A typical LV contraction pattern in nQRS and LBBB-T can be seen in Figure 6-2. There was evidence of significant inter- and intra-ventricular dyssynchrony in the LBBB-T group at 6 months compared with the nQRS population (Inter: LBBB-T 130±73 vs. nQRS 23±86ms, p=<0.001, intra: LBBB-T 118±103 vs. nQRS 13±13ms, p=0.001). There was a correlation between post-procedure QRS and inter- and intra-ventricular dyssynchrony (r=0.57, p=<0.001 and r=0.49, p=<0.001 respectively).

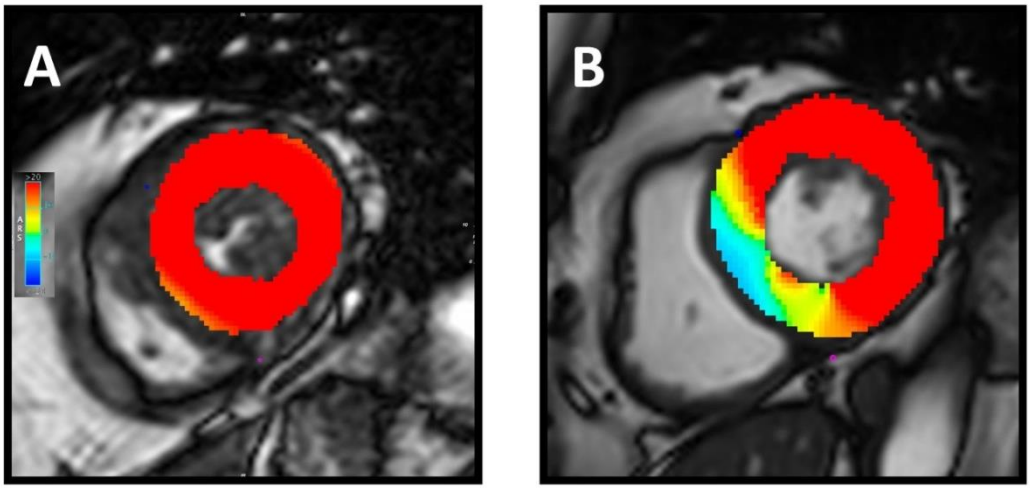

Figure 6-2 Radial strain in nQRS and LBBB-T

Radial strain in the mid-ventricular short axis cine. Panel A shows the typical contraction pattern in a patient with a narrow post-procedure QRS, the red colour depicts positive radial strain occurring in all segments of the left ventricle at end systole. Panel B depicts radial strain at end systole in a patient with TAVI-

induced LBBB. Peak positive septal radial strain occurs in early systole and therefore by end-systole the septum is relaxing (negative strain), depicted by the blue colour.

6.4.4. Reverse remodelling according to narrow, intermediate and broad post-procedure QRS

Table 6-3 shows reverse remodelling characteristics with the LBBB-T split into intermediate QRS duration (iQRS 120-150ms) and very broad QRS (bQRS, >150ms).

Table 6-3 CMR parameters according to post-procedure QRS duration

	nQRS <120ms (n=24)	**iQRS 120-150ms (n=12)**	**bQRS >150ms (n=12)**
Change in LVEF, %	4.6±7.8	-2.1±5.5*	-2.1±7.3*
Change in GLS, %	-2.1±3.6	0.48±3.5*	-0.10±3.06
Change in LVMi, g/m^2	-15.9±10.4	-9.5±9.3*	-17.0±8.6
Post-procedure septal thickness, mm	10.5±3.0	8.9±2.4	9.6±2.7
Post-procedure lateral thickness, mm	6.8±1.8	5.5±1.4*	7.3±1.6†
Change in septal thickness, mm	-1.69±2.3	-1.39±2.88	-4.2±2.4*†
Change in lateral wall thickness, mm	-0.79±1.50	-0.70±1.84	-0.92±1.43
Post-procedure interventricular dyssynchrony, ms	23±86	109±77*	149±19*
Post-procedure intraventricular dyssynchrony, ms	13±106	112±130*	124±72*

Data expressed as mean±SD. nQRS: Narrow QRS. iQRS: intermediate QRS. bQRS: Broad QRS. LVEF: left ventricular ejection fraction. GLS: Global Longitudinal Strain. LVMi: Indexed left ventricular mass. *P<0.05 compared with nQRS (<120ms). †p<0.05 compared with iQRS (120-150ms).

6.4.5. Predictors of change in LVEF and change in GLS

Baseline variables which may affect cardiac reverse remodelling following TAVI (including clinical, baseline CMR characteristics and post-procedural AR) were analysed to determine univariable predictors of change in LVEF and GLS (Table 6-4 and Figure 6-3). Baseline LVEF

(beta -0.414, p=0.015) and post-procedure QRS (beta -0.422, p=<0.001) remained significant independent predictors of change in LVEF on multiple regression analysis. Baseline LVEF (beta=-0.502, p=0.001), baseline GLS (beta -1.02, p=<0.001) and post-procedure QRS (beta=0.322, p=0.001) were independent predictors of a change in GLS at 6 months. Infarct pattern LGE at baseline did not impact on post-procedural change in LVEF or change in GLS on univariate analysis.

Table 6-4 Univariate and multivariate analysis

	Unstandardised coefficient	Standard Error	P Value	Unstandardised coefficient	Standard error	P Value
	Univariate analysis – change in LVEF (%)			**Multiple regression analysis – change in LVEF (%)**		
Age (y)	-0.201	0.141	0.160			
Sex	2.844	2.246	0.212			
Diabetes mellitus	-1.092	2.624	0.679			
Infarct pattern LGE at baseline	1.647	2.819	0.562			
STS PROM (%)	-0.020	0.448	0.965			
Post-procedure QRS duration (ms)	-0.119	0.034	0.001	-0.110	0.028	<0.001
AVAi (cm/m^2)	7.888	14.638	0.593			
Baseline GLS (%)	-0.963	0.249	<0.001	-0.292	0.319	0.365
Baseline LVEF (%)	-0.393	0.088	<0.001	-0.295	0.117	0.015
Baseline fibrosis mass (g)	-0.007	0.242	0.975			
Post procedure aortic regurgitation fraction (%)	0.089	0.252	0.725			
	Univariate analysis – change in GLS (%)			**Multiple regression analysis – change in GLS (%)**		
Age (y)	0.090	0.064	0.167			
Sex	-1.161	1.028	0.265			
Diabetes mellitus	-0.467	1.197	0.698			
Infarct pattern LGE at baseline	-0.078	1.291	0.952			
STS PROM (%)	-0.108	0.204	0.600			
Post-procedure QRS duration (ms)	0.044	0.016	0.010	0.038	0.011	0.001

AVAi (cm/m^2)	-4.954	6.658	0.461			
Baseline GLS (%)	-0.588	0.098	<0.001	-0.904	0.122	<0.001
Baseline LVEF (%)	0.094	0.046	0.046	-0.163	0.044	0.001
Post-procedure aortic regurgitation fraction (%)	-0.015	0.116	0.895			
Baseline fibrosis mass (g)	-0.004	0.112	0.970			

LVEF: Left ventricular ejection fraction. LGE: Late gadolinium enhancement, STS PROM: Society of thoracic surgeons predicted risk of mortality. AVAi: Indexed aortic valve area. GLS: Global longitudinal strain

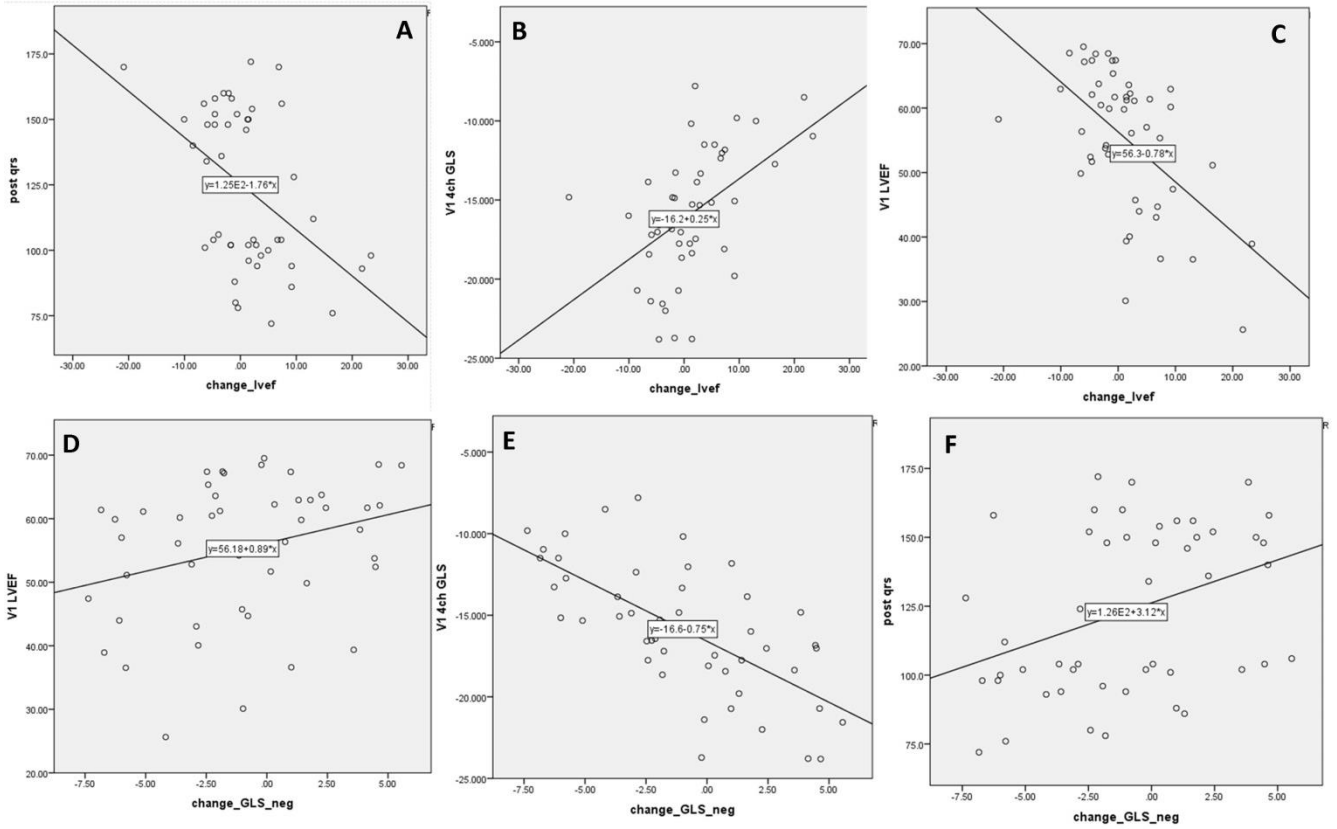

Figure 6-3 Scatterplots showing main predictors of change in LVEF and GLS

Relationship between change in LVEF and post-procedure QRS duration (Graph A), baseline GLS (Graph B), and baseline LVEF (Graph C). Relationship of change in GLS and baseline LVEF (Graph D), baseline GLS (Graph E) and post-procedure QRS duration (Graph F). Note that a more negative GLS is a favourable finding, and that a negative value for change in GLS represents positive reverse remodelling. The line represents a line of best fit.

6.5. Discussion

This is the first study using CMR to investigate the impact of TAVI-induced LBBB on cardiac reverse remodelling. The main findings of this study are: 1) Patients with a narrow QRS post-TAVI have better LVEF and GLS compared to those with LBBB-T 6 months post-procedure, 2) Patients with TAVI-induced LBBB exhibit significant inter- and intra-ventricular dyssynchrony compared with those with narrow QRS and 3) Post-procedure QRS duration remained a significant independent predictor of change in LVEF and GLS following TAVI on multivariable analysis.

6.5.1. Impact of TAVI-induced LBBB on cardiac reverse remodelling

TAVI-induced LBBB is common, occurring in 16 to 65% patients depending on valve type [128]. Although predictors of LBBB-T have been extensively studied [128], the impact of LBBB-T on cardiac reverse remodelling is less well described, with studies limited to echocardiographic evaluation and containing a heterogeneous mix of patients. A PARTNER echocardiographic sub-study investigating the effects of LBBB-T on those undergoing TAVI reported a lower LVEF at 12 months in patients with LBBB on discharge electrocardiogram compared to those with a narrow QRS, however, there was an increased number of those undergoing trans-apical TAVI in the LBBB-T group [112, 158]. A similar failure of improvement in LVEF following balloon-expandable TAVI was seen by Urena et al in 79 patients with LBBB-T at hospital discharge, again with more patients undergoing trans-apical TAVI in the LBBB-T group [163]. Tzikas et al [160] reported unfavourable reverse remodelling in 27 patients (including those with pre-existing conduction defects) following self-expanding TAVI prior to and 6 days post-procedure. They observed an 8% difference in LVEF between the 2 groups. Longitudinal strain was also reduced in those with new conduction abnormalities, however this failed to reach statistical significance, likely due to being under-powered with small study numbers for an echocardiographic study [183]. Hoffman et al [184] investigated 90 patients using 2D and speckle tracking trans-thoracic echocardiography prior to and at 1 and 12 months following Edwards Sapien and Medtronic

CoreValve TAVI. Patients with new conduction defects had a significantly larger LVESVi at 12 months compared with those with a narrow QRS, with less difference in LVEDVi, mirroring the findings in our study. New conduction defects and baseline LVEF were independent predictors of reduction in LVEF at 12 months. The inclusion of patients with trans-apical access in the majority of these studies [112, 163, 184] and those with post-procedural pacemaker insertion [112, 160, 163, 184] is a significant confounder, given that trans-apical access has been linked to reduced LVEF in a number of studies [163, 185] and pacing induced LBBB has been shown to cause different patterns of strain to those with idiopathic LBBB [186].

Our study adds further insight into the impact of LBBB-T on cardiac reverse remodelling. Groups were matched for clinical and baseline CMR characteristics, all parameters which have been found to strongly influence reverse remodelling following valve intervention [167]. None of the patients in our study received trans-apical TAVI or permanent pacemaker insertion and the unique ability of CMR LGE imaging allowed us to identify and exclude any patients who had a post-procedural myocardial infarction, another factor that may have confounded the earlier echocardiographically based studies. Finally, the two groups experienced similar amounts of post-procedural aortic regurgitation, which is an important modulator of post-TAVI reverse remodelling [281] and which was not reported in many of the echocardiographic studies [112, 160, 184]. This group of patients may be able to provide unique insight into whether there is a LBBB-induced cardiomyopathy; it is certainly suggestive in the intermediate term that LBBB induced unfavourable effects on reverse remodelling. It would be interesting to study this group of patients over a longer period of time to investigate whether these unfavourable effects are sustained, or indeed continue to worsen with time.

6.5.2. Inter and intra-ventricular dyssynchrony

The novel use of CMR feature tracking allows us to report values for intra- and inter-ventricular dyssynchrony. In LBBB, the normally functioning right bundle conducts the electrical impulse to the right ventricle prompting early right ventricular contraction followed by activation of the

interventricular septum and finally lateral wall contraction resulting in inter- and intra-ventricular dyssynchrony. Inter-ventricular dyssynchrony leads to the classical abnormal septal motion pattern of contraction seen in LBBB which is felt to impair LV filling and ejection in its own right. This dysynchronous contraction leads to an increase in LVESVi, as seen in our LBBB-T group and it is this, rather than a change in LVEDVi, that is the largest driver of reduction in LVEF. We have also shown that LBBB-T impacted on change in GLS, with no improvement in this group compared to a significant improvement in the nQRS group. Although GLS may be affected by dyssynchrony [282], this, coupled with the reduction in left atrial volume in the nQRS, but not the LBBB-T group, and the reduction in LV stroke volume in those with LBBB-T, suggests that the effects of LBBB-T may go beyond that of simple mechanical dyssynchrony.

6.5.3. Patterns of reverse remodelling

With the accurate information that CMR is able to provide on LV wall thickness, our study offers new insights into reverse remodelling patterns in LBBB-T. Those with the broadest QRS (>150ms) had greater regression of septal hypertrophy compared with those with a narrower post-procedure QRS. Asynchronous electrical activation, similar to that seen in LBBB, leads to redistribution of mechanical load within the left ventricle and chronic pacing has been shown to produce thinning of the early activated wall and thickening of the late activated wall in dogs, resulting in asymmetrical left ventricular wall thickness [283]. In our study numbers were small and follow up was short but this is hypothesis generating and would be interesting to investigate in a larger, longer term follow-up study.

6.5.4. Conduction system damage during TAVI

It is well established that TAVI is associated with a high rate of conduction abnormality [128]. On a cellular level, the mechanical trauma is thought to result in transient tissue inflammation and oedema and autopsy studies report haematoma formation compressing on the bundle of His [129]. The LV outflow tract where the conduction fibres lie has the potential to be traumatised at multiple time-points during the TAVI procedure; from damage by the guidewire, to during

balloon valvuloplasty, device manipulation and deployment. It is likely that the different valve designs can cause differing degrees of compression to the conduction system, with the lower cage design of the self-expanding CoreValve felt to cause more compression to the LV outflow tract than the balloon expandable Edwards Sapien device [161]. The unique design of the mechanically expandable and repositionable Lotus valve with its adaptive seal, may also be associated with more conduction system trauma, although reports to date are limited [284]. Global ischaemia during rapid pacing required for valve deployment may exacerbate the issue [128]. Other procedure-related factors felt to be implicated include pre-implant valvuloplasty, deep implant, low ratio of the annulus:balloon or annulus:prosthesis and operator experience [285].

6.5.5. Clinical implications

The impact of TAVI-induced LBBB on mortality is a subject of debate, however, it has been shown in many studies to be a predictor of mortality [152-155] and has been associated with increased hospitalisation [112]. Other studies have failed to demonstrate a link [151, 163, 276]. Nonetheless, LVEF is a strong independent predictor of long term survival [286]. This study has shown that TAVI-induced LBBB results in reduced global longitudinal and radial systolic function compared with those with a narrow post-procedure QRS, which could partially explain the link with mortality. Given the adverse effect of TAVI-induced LBBB on cardiac reverse remodelling, restoring inter- and intra-ventricular dyssynchrony using cardiac resynchronisation therapy, could be considered, especially if another conventional indication for device therapy exists [287]. Every effort should be made by the operator, in terms of device selection, avoidance of valvuloplasty and device positioning and sizing, to reduce the risk of TAVI-induced LBBB given the adverse effects on ventricular remodelling seen. As newer devices are being developed, designs should be focused on minimising damage to the electrical conducting system in order to prevent the deleterious effects on the LV that this entails.

6.6. Limitations

Although patients were recruited in a prospective manner, they were matched retrospectively and hence the study is prone to the selection bias of this type of study. Patients with LBBB-T were matched according to those factors known to influence cardiac reverse remodelling but other factors may be unaccounted for. Specifically, patients with coronary artery disease and previous myocardial infarction were included in the study, however, numbers in each group were similar and infarct pattern LGE at baseline was not a univariate predictor of change in LVEF or GLS. Group allocation was based on the discharge electrocardiogram and not re-confirmed at 6 months, however, there are evidence to suggest (at least in patients undergoing CoreValve implantation) that virtually all those with LBBB at discharge have persistent LBBB at 30 days [151]. Furthermore, the demonstration of ongoing dyssynchrony at 6 month follow up in the LBBB-T group suggests that the conduction abnormality was persistent.

Given the low temporal resolution of CMR, strain measurements are only able to give estimate values, and echocardiographic values may allow a more detailed assessment of dyssynchrony, albeit with their own but differing set of limitations. Finally, only limited conclusions can be made from the sub-group analysis of the QRS width as the groups were small, and any statements pertaining to differing remodelling patterns are merely hypothesis generating.

Chapter 7: Conclusion

This body of work is an important collection of findings with conclusions going beyond those of simply investigating patterns of reverse remodelling following aortic valve intervention. From the work presented here, the clinician can be confident that men and women experience similar positive reverse cardiac remodelling as a result of aortic valve intervention and in view of this, referral patterns should not differ according to gender. It has also been demonstrated that there is improved early cardiac reverse remodelling in those without myocardial fibrosis; this supports data linking fibrosis with adverse outcome, and takes us one step closer to understanding which patients are more likely to benefit from TAVI from the outset. It also reassures clinicians that myocardial infarction is rare following TAVI, even in the context of non-vascularised coronary artery disease, and adds further weight to the argument that coronary revascularisation prior to TAVI may be unnecessary. Finally, it robustly demonstrates that TAVI-induced left bundle branch block is associated with unfavourable cardiac reverse remodelling. This is especially important given the high rates of LBBB associated with certain valve types as TAVI is extended to a younger population.

Aortic stenosis is the commonest valvular lesion of the developed world and its incidence is expected to grow due to the ageing population [4]. The left ventricle adapts to the increased afterload by developing hypertrophy which allows normalisation of wall stress and maintenance of cardiac output. Eventually, however, the left ventricle starts to fail with a resultant reduction in cardiac output leading to the signs and symptoms of heart failure. The onset of symptoms resulting from aortic stenosis heralds a dismal prognosis, with 2 year survival rates of 50% if left untreated [5]. Surgical aortic valve replacement is the standard treatment option and has been the standard treatment option for nearly 5 decades. Trans-catheter aortic valve implantation was first performed in 2002 and since its inception, has been widely adopted to offer a permanent treatment option to those considered too frail or high risk for conventional surgery [288]. It has been an important development as previously, up to a third of those with severe AS were left

untreated given that AS is predominantly a disease of advanced age [288]. Although TAVI is less invasive than SAVR, it is still associated with significant morbidity and mortality [54, 86, 106]. Common complications of both approaches are stroke as a result of cerebral emboli, with an excess of bleeding, acute kidney injury and AF seen following surgical replacement and increased vascular complications, significant aortic regurgitation and need for pacemaker implantation seen following TAVI. Despite the different co-morbid complications, contemporary randomised controlled trials suggest that survival is similar between the two techniques [54, 86, 106]. Rates of clinically detected myocardial infarction are low following both procedures but silent infarcts may go undetected, both due to the lack of ability of patients to report symptoms (as the patient is under the influence of general anaesthetic or heavy sedation at the time of TAVI and SAVR) and due to conduction abnormalities (such as LBBB) masking important ischaemic changes. Biomarker levels are ubiquitously raised following both procedures and therefore prove to be unhelpful [113, 114]. CMR LGE allows infarction to be directly visualised and as such, using direct comparison of pre- and post-procedure scans is a useful tool to accurately define the true incidence of post-procedural MI according to procedure type. Whilst MI assessed by CMR LGE is an infrequent complication of TAVI it appears to be more common following SAVR. Absolute infarct size is small following both procedures and does not impact on post-procedural LVEF. The importance of bystander coronary artery disease at the time of TAVI is further explored by the results presented in this thesis. Initially, it was feared that the period of global hypotension experienced during TAVI may lead to myocardial infarction in the context of significant epicardial coronary artery stenoses. This study has demonstrated that the new MI rate is low following TAVI in the context of non-revascularised coronary artery disease, reassuring the operator that pre-implant percutaneous intervention may be unnecessary.

Gender differences in the left ventricular response to aortic stenosis have previously been described [14, 22, 289], however, the studies reporting this to date have compared men and women with differing valvular gradients (typically higher in women) which may confound results. This study compares a population with matched AS severity at baseline, but greater aortic regurgitation in men, and demonstrates that men exhibit differing remodeling patterns in the face

of aortic stenosis. Men have a larger LV cavity size, greater LV mass, greater LV wall thickness and the same amount but a differing pattern of fibrosis than women. The referral bias of men over women is again seen in our study, with more men undergoing SAVR than TAVI. Following aortic valve replacement, both genders experienced a significant reduction in left ventricular mass and a similar reduction in aortic valve gradient, but there was more absolute mass regression in men, but similar amounts when expressed as a percentage of mass reduction. Multivariate analysis found baseline LV mass, but not gender, to be a predictor of LV mass regression. This difference was still apparent if those with significant baseline AR was excluded. It was therefore the more adverse remodelling profile at baseline seen in men, rather than gender *per se*, that was a predictor of reverse remodelling following valve replacement. Males also had a reduction in mitral regurgitation and left atrial size, suggestive of greater benefits in diastology than females, possibly reflecting the greater absolute mass reduction. There was no significant difference in post-procedural AR following valve replacement.

Therefore, there were no significant differences in cardiac reverse remodelling following aortic valve replacement according to gender, suggesting that the improved medium and long term survival seen in women following aortic valve replacement is due to factors other than cardiac reverse remodelling.

Cardiac reverse remodelling occurs in virtually all patients following valve intervention. It is well established by both CMR and echocardiographic studies that mass regression occurs at intermediate follow up [167, 169], with most mass regression occurring within the first year and continuing at a slower rate thereafter [166, 170]. Mass regression is associated with improved survival and reduced heart failure hospitalisation following both SAVR and TAVI [164, 165]. The link between myocardial fibrosis and mass regression is less clear, with differing reports in the limited studies where it is described [167, 190, 191]. The results presented in this thesis show that at least half of the LV mass regression occurs prior to hospital discharge, which supports the findings of previously published echocardiographic studies [26, 170].

The ability of CMR LGE to assess for myocardial fibrosis permits further insight to be gained with regard to early reverse remodelling. Those with no fibrosis experience more acute LV mass regression than those with either myocardial infarct pattern or mid-wall/focal fibrosis pattern LGE, suggesting that the process may begin earlier in those without fibrosis at baseline. We have also demonstrated that in those with an abnormal LVEF at baseline, there is an acute improvement in LVEF, suggesting that the afterload reduction seen acutely following TAVI is associated with favourable acute cardiac reverse remodelling.

Left bundle branch block is commonly seen following TAVI, with rates differing according to valve design and procedural factors such as valve positioning and valve over-expansion [128]. It is thought to occur due to damage to the cardiac conduction fibres contained within the left ventricular outflow tract which lies adjacent to the aortic valve annulus. The conduction fibres have the potential to be damaged at many points during the TAVI procedure, with the constant pressure of the self-expanding TAVI design felt to lead to more permanent damage, especially in the context of pre-existing conduction system degeneration.

Some registry studies suggest reduced survival and increased hospitalisation in those with TAVI-induced LBBB [112, 152]. The mechanism for this excess mortality may relate to less favourable reverse remodelling in this group. We have demonstrated in a matched group of patients undergoing TAVI that those with TAVI-induced LBBB have ongoing inter- and intra-ventricular dyssynchrony 6 months following TAVI and that this is associated with reduced LVEF compared to those with a narrow QRS at 6 months, driven by a reduction in LV end-systolic volume in those with a narrow QRS not seen in those with TAVI-induced LBBB. The differences in LVESVi between the groups is perhaps not surprising given the clear LBBB-induced dyssynchrony, however, those with TAVI-induced LBBB also exhibited reduced global longitudinal strain compared with those with a narrow post-procedure QRS, suggesting that the negative effects may go beyond that of simple dyssynchrony. Post-procedure QRS duration remained an independent predictor of change in LVEF and change in GLS on multivariable analysis, confirming the negative effects of this. As TAVI is extended to a lower risk population,

it is important therefore that LBBB is avoided where possible in order to maximise positive cardiac reverse remodelling. The operator should therefore be mindful of this both during device selection and at the time of implantation, to maximise the chance of maintaining normal cardiac electrical conduction.

This body of work presents a comprehensive assessment of remodeling in aortic stenosis and reverse remodelling and the impact of fibrosis following aortic valve intervention, using cardiovascular magnetic resonance imaging. As TAVI is extended to a younger, lower risk population, the findings of this thesis help further the understanding of the cardiac response to AS and aortic valve replacement.

7.1. Future directions

Although this body of work sheds light on some of the unanswered questions with regard to the cardiac response to aortic stenosis and its treatment, there is still scope for further research. One of the limitations of this thesis is the limited study size, inherent to many CMR based studies, and the lack of outcome data presented. In order to fully understand the true impact of aortic stenosis and myocardial fibrosis on cardiac remodelling, and the relationship to outcomes, larger scale studies are required. The 'British Society of Cardiovascular Magnetic Resonance Imaging' AS-700 study is currently underway, whereby data from several centres' across the United Kingdom are being collated. This will allow the analysis of over 700 CMR scans of patients with severe AS. Large scale data like this will allow robust conclusions to be made about the importance CMR can have in predicting outcome in AS and further insights into topics such as the importance of myocardial fibrosis and gender differences will be possible.

Although now a widely used and accepted technique, the literature regarding TAVI is still in its infancy. Due to the fact that the initial cohort of TAVI patients treated were frail and elderly, long-term outcome data, including long-term effects on mortality, cardiac remodelling and valve durability are still relatively unknown and will be an interesting focus of future research, especially as the technology has recently been extended to a younger, lower surgical risk cohort. The extension of the technology to this group will allow for prospective studies comparing SAVR and TAVI to be better matched for co-morbidity, gender and age, a factor which has been a limitation in inter-group comparisons in this and many other studies to date. Also, as more valve designs become available, the operator is left with a bewildering choice of designs, each with their own pros and cons. CMR has a role to play in the evaluation of these different TAVI valve designs; from the differing effects on cardiac reverse remodelling and aortic regurgitation to the impact on cerebral embolisation and should be a focus for future investigation to help facilitate the decision making process.

The data presented in this thesis regarding acute remodelling are of particular interest and was a surprising finding of the study. The mechanism for acute LV mass reduction is unknown but may be related to an acute reduction in extracellular volume or indeed an acute shrinkage in myocyte size. The mechanism for this could be further explored using CMR. Extracellular volume can be estimated from T1 Mapping techniques. T1 Mapping works by allowing the T1 relaxation time of each voxel of the myocardium to be calculated and quantified on a standardised scale to directly evaluate the composition of myocardial tissue. Using State-of-the-art techniques, high resolution TI mapping can be readily performed during a single breath hold using modified Look-Locker inversion recovery (MOLLI) imaging [211, 290]. TI mapping is usually performed at a pre-specified timepoints pre and post gadolinium contrast administration. Extracellular volume can then be estimated via a mathematical equation which takes into account of the circulating haematocrit levels [291]. More recently, CMR has been used to detect cardiomyocyte size in murine models with hypertension [269]. Via mathematical modelling, T1 relaxation times following gadolinium contrast agent were obtained in order to calculate the intracellular lifetime in water. This technique demonstrated a non-invasive measure of cardiomyocyte size. To our knowledge, T1 mapping to calculate extracellular volume or cardiomyocyte size has not been performed acutely following TAVI or SAVR for AS, and would be an interesting topic of future research to help delineate the pathophysiology behind the acute reduction in LV mass observed in our study.

TAVI is now an accepted treatment option, with excellent short to medium term outcome data [54] leading to its adoption worldwide and inclusion in international guidelines [65, 292]. The huge success of transcatheter aortic valve technology opens the door for the development of new approaches in the treatment of other valvular heart disease. Mitral regurgitation is the second most prevalent valve lesion requiring surgery in the developed world [4] and is associated with significant morbidity and mortality [293]. To date, the only catheter based therapy in widespread use had been the Mitraclip device, although results in the only head-to-head trial to date have been disappointing [294] possibly due to the design of the device (an Alfieri stitch-like mechanism) offering only a partial resolution of the regurgitation. The short term results of the

first in-man transcatheter mitral valve replacement have recently been reported [295] and are promising. CMR, with its capabilities to provide robust evaluation of cardiac mass, volume, scar, fibrosis and flow data, alongside more novel techniques such as 4D flow [296] and T1 mapping, is ideally placed to evaluate the impact these new devices have on the heart, and it will be interesting to use this as a tool to evaluate these therapies as they become more widespread.

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Appendix

Leeds (West) Research Ethics Committe
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09 October 2008

Dr John P Greenwood
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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

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

Document	*Version*	*Date*
Participant Consent Form	1.0	14 August 2008
Participant Information Sheet	1.0	14 August 2008
GP/Consultant Information Sheets	1.0	14 August 2008
Compensation Arrangements		24 September 2007
Letter from Sponsor		20 August 2008
Protocol	1.0	18 August 2008
Investigator CV		20 August 2008
Application		11 August 2008
Response to Request for Further Information		25 September 2008
Letter of invitation to participant	1.1	25 September 2008

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

NHS
Health Research Authority
NRES Committee Yorkshire & The Humber - Leeds West
Room 001, Jarrow Business Centre
Rolling Mill Road
Jarrow
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NE32 3DT

Tel: 0191 4283548

18 March 2015

Ms Petra Bijsterveld
Senior Research Nurse & MRI MRF manager
Cardiovascular Imaging
LICAMM
University of Leeds
Leeds Teaching Hospitals NHS Trust

Dear Ms Bijsterveld

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:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	5	17 February 2015
Research protocol or project proposal	1.5	17 February 2015

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 clots 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; and 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 periodical 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:

Ms Fiona Richards / Ms Petra Bijsterveld
Cardiovascular Research
Leeds General Infirmary
LS1 3EX
Tel: 0113 392 5224 / 0113 392 5481

or

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

cmrresearch@leeds.ac.uk

Patient Study Number: ..... Date of Birth: .....

Hospital Number: ..... Initials: .....

CONSENT FORM – Version 1.3 November 30 2012

MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation

	Name of Researcher: Prof John Greenwood	Please initial box
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.	☐

Signature.....

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

Signature of witness.....

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

.....

I am interested in hearing more about this study. (study code: TAVI)

I give permission for a researcher to contact me by telephone to discuss the study further.

My phone number is.....

Name.....

Address.....

.....

Please return this slip to us in the stamped addressed envelope provided.

Thank you.