The effects of transcatheter aortic valve replacement and conventional aortic valve replacement on cardiac mechanics and function in patients with confirmed severe aortic stenosis. Insights from a national echocardiographic core lab

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List of Abbreviations

12M	12-Months Post-Intervention
6W	6-Weeks Post Intervention
ANCOVA	Analysis of Covariance
Ap2Ch	Apical 2-Chamber view
Ap3Ch	Apical 3-Chamber view
Ap4Ch	Apical 4-Chamber view
AS	Aortic Stenosis
AVR	Aortic Valve Replacement (surgical)
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CAD	Coronary Artery Disease
ECL	Echocardiographic Core Lab
EDV	End-diastolic volume
ESV	End-systolic volume
EuroSCORE	European System for Cardiac Operative Risk Evaluation.
GLS	Left Ventricular global longitudinal strain
HR	Heart Rate
ICC	Intraclass Coefficient
LA	Left Atrium
LA Pre-A	Left Atrial Longitudinal Strain at Atrial contraction.
LAPLS	Left Atrial Peak Longitudinal Strain
LFLG	Low-flow Low-gradient (aortic stenosis)
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
PLAX	Parasternal Long Axis
PSAX	Parasternal Short Axis
PV	Pulmonary Vein
RV	Right Ventricle
RVGLS	Right Ventricular Global Longitudinal Strain
STE	Speckle Tracking Echocardiography
STS Score	Society of Thoracic Surgery Risk Score
SVL	Strain Volume Loop
TAVI	Transcatheter aortic valve insertion
TTE	Transthoracic Echocardiogram

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Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application to another degree or qualification at this or any other university or institute of teaching.

Many thanks to William Toff and the UK TAVI trial team for access to the UK TAVI trial echocardiogram image depository.

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To my dear daughter Lottie, whose arrival made everything more chaotic and infinitely better, thank you for being my reminder me that there is life outside the thesis. I hope I have shown you don't need to choose family or career.

Finally, I must acknowledge and thank the UK TAVI trial team, for their collaboration with this project, and allowing me access to the study images for my analysis.

Abstract

Aortic Stenosis (AS) is a progressive disease characterised by increasing aortic valve calcification and thickening, leading to escalating left ventricular afterload, and myocardial damage. This sub-study of the UK TAVI trial investigated myocardial functional recovery post-intervention in subjects with severe AS and intermediate surgical risk, randomised to surgical aortic valve replacement (AVR) or transcatheter aortic valve insertion (TAVI). Speckle tracking echocardiography (STE) was used to assess the deformation of the myocardial wall (strain) in trans-thoracic echocardiographic images (TTE's). Strain was measured pre-intervention (baseline), 6-weeks post-intervention(6W), and 12-months post-intervention (12M) in the left ventricle (LV, n≤142), right ventricle (RV, n=25) and left atrium (LA, n=74). Additionally, strain-volume loops were constructed to explore how the haemodynamic relationship between volume and longitudinal strain in the LV changed pre- to post-intervention after AVR and TAVI (n=48).

The improvement seen from baseline to 12M in TAVI was non-inferior AVR ($P<0.05$) for LV global longitudinal strain, and LA maximum volume, pre-A volume, total emptying fraction and active emptying fraction. Overall, there was evidence of global recovery of the myocardium. Strain volume loops (SVL) for both AVR and TAVI saw a decrease in LV end-diastolic volume at 12M compared to baseline, but only the TAVI SVL saw a reduction in LV end-systolic volume. Overall systolic-diastolic uncoupling recovered in both SVL's but the changes in early vs late diastolic uncoupling varied between the treatment groups; suggesting different myocardial changes. This work was limited by the sample sizes for many of the analyses. A review of the UK TAVI image acquisition and analysis procedures was performed, providing feedback regarding improvements that may initiate greater quality TTE's. Conclusions centred around improving communication pathways and ensuring consistent training of staff. It has previously been established that LV GLS is a sub-clinical predictor of heart function, and long-term outcomes for patients with AS. LA volume is also a well-established predictor of cardiovascular risk. Therefore, the findings of this work that recovery of both LV GLS and LA maximum volume is non-inferior in TAVI compared the AVR suggest that the long-term outcomes will also be non-inferior and supports the use of TAVI to treat severe AS.

Chapter 1 - Background and Literature Review

1.1 Aortic Stenosis

Aortic Stenosis (AS) is a valvular heart disease, most commonly seen in the elderly. Aortic stenosis occurs when calcification causes a progressive narrowing of the aortic valve and obstruction of blood flow across the aortic valve(1). This narrowing causes an increased afterload on the left ventricle (LV) which leads to pathological adaptions if left untreated.

1.1.1. Incidence of Aortic Stenosis

AS is a progressive disease and one that is being seen increasingly in ageing populations. It has become the most prominent of all the valvular heart diseases (1, 2). In the cardiovascular health study, 5201 people over 65 were examined. Of those examined 2% had AS and 26% had aortic sclerosis (where the valve is thickened or calcified but there is no significant obstruction), which is likely to progress to AS over time (1). The cardiovascular health study reported a prominence in men over women (3) but this was not supported by Nkomo *et al* (2006) who reported no difference in the frequency of valvular heart diseases (including both mitral and aortic valve diseases) between men and women (4). The work by Nkomo *et al* was more recent and presented data from the general population, whereas the cohort from Stewart *et al* was smaller (5,201 vs 11 911) and taken from those eligible for Medicaid which resulted in a narrow range of patient ages (75 to 86 years). Notably, there was a clear increase in the incidence of both aortic sclerosis and stenosis as patients increased in age. Aortic sclerosis was present in 20% in patients aged 65–75 years, 35% of those aged 75–85 years, and 48% in patients older than 85 years. In these ages groups, the prevalence of AS was, 1·3%, 2·4%, and 4% respectively (3). Although this study recruited from US locations, comparable figures for the incidence of AS are quoted by the British cardiovascular society; with an overall prevalence of clinically significant AS as approximately 1-3% in those greater than 70 years (5). A prospective population study in Norway followed residents for 14 years and found a prevalence of AS of 3.9% in the 70–79 year's cohort and 9.8% in the 80–89 year's cohort (6), but this study had a

highly defined population and therefore may not be representative of incidence in the wider population.

In contrast to many cardiovascular diseases where a decline in mortality has been seen in recent decades, the incidence of AS has continued to rise. It is expected that the incidence will continue to rise in conjunction with an ageing population and increasing life expectancy (7). Therefore, it is key to study the intervention options available for AS, and the short- and long-term impacts of these interventions.

1.1.2. Aetiology of Aortic Stenosis

Aetiology of AS is varied. The most common cause in patients over 65 years is senile calcific aortic stenosis, which accounts for up to 80% of the cases of AS seen in the US and Europe (8). Calcific AS occurs when calcium deposits build up on the valve leaflets and cause thickening and reduced pliability (pathology further explained in section 1.1.3).

Normal physiology is that the aortic valve is tricuspid, but approximately 1-2% of the population have a congenital Bicuspid Aortic Valve (BAV), where the aortic valve (AV) has only two functional leaflets rather than three (9, 10). The recorded incidence of BAV has that has increased since the introduction of reliable echocardiographic screening, as the previous diagnosis method of auscultation lacked sensitivity and specificity. Those with BAV often have a narrower valve orifice and therefore turbulent trans-valvular flow, which often leads to the development of scarring and calcification and reduced mobility. A bicuspid valve is the most common cause of AS in those 60-75 years, and 50% of patients with severe AS have a bicuspid valve (9), although this figure of 50% relates to all adult cases and those with BAV.

The occurrence of Rheumatic fever, an autoimmune inflammatory response as a result of group A streptococci infection, can damage valve leaflets, increasing turbulence across the valve and the subsequent valvular damage. Rheumatic valve disease is uncommon in the developed world due to the availability of antibiotics to effectively treat infections before rheumatic fever develops (11), and therefore the incidence of rheumatic valve disease is declining in the UK.

This study was conducted as a sub-study of the UK TAVI trial. The inclusion criteria for the UK TAVI trial included a minimum age of 70 years (12). Therefore, it is expected that the majority of patients will have senile calcific AS, and a tricuspid AV as patients with a BAV typically present with symptoms at a younger age.

The pathology of AS development has inflammatory components (as detailed in 1.1.3.1). Therefore, the risk factors for AS, and its progression, have a large overlap with risk factors for other CVD, including age, gender, diabetes, LDL, hypertension and smoking. However, despite shared risk factors, there is a discrepancy in occurrence; only half patients with sAS have significant coronary artery disease (CAD) and most patients with CAD do not have sAS (13).

1.1.3. The Pathology of Aortic Stenosis.

AS is progressive from aortic sclerosis through to severe. Progression occurs over many years and relates to the increasing obstruction of blood flow through the left ventricular outflow tract and aortic valve. Table 1.1 shows the key echocardiographic criteria to guide the diagnosis of AS and the classification of severity. These measurements assess the size of, the flow and the gradient across the AV.

Measurement	**Mild**	**Moderate**	**Severe**
Mean Pressure Drop	<25 mmHg	25-40 mmHg	>40 mmHg
Peak Velocity (across AoValve)	<2.9 m/s	3.0-3.9 m/s	>4 m/s
Valve Area	1.5 - 2.0 cm^2	1.0 – 1.4 cm^2	<1.0 cm^2
VTI Ratio	≥0.5	0.25 – 0.5	≤0.25

Table 1.1 Guidelines for the Classification of Aortic Stenosis Severity via echocardiography*. Based on the characteristics of the aortic valve. Takes into consideration the size of the valve orifice, and the flow and pressure gradient across the valve. (14)*

1.1.3.1 Valvular degeneration

The key characteristic of AS is the progressive calcification and thickening of the aortic valve, resulting in a narrowed valve orifice. As AS progresses the leaflets of the aortic

valve thicken and irregular calcium nodules form of the aortic side of the valve. As the calcium modules become more severe they will protrude out and restrict valve leaflet movement (15).

Although highly correlated with age AS is no longer considered a simple consequence of ageing and 'wear and tear', but rather, an active process involving inflammatory pathways and lipid disposition. In a healthy aortic valve, the valve leaflets appear smooth and thin; they contain very few cells arranged in clearly defined layers. Ageing can lead to thickening of valve leaflet tips, due to thinning tissue layers and an increase in adipose cells. Histological examination of stenosed valves found many features resembling the changes seen in atherosclerosis, which is strongly suggestive of chronic inflammation (16). The AV is chronically exposed to complex shear forces, and calcification is predominately seen on the aortic side of the leaflets where the flow is most turbulent, suggesting that the shear stresses are an aggravating factor (13). Bicuspid aortic valves are less efficient than tricuspid valves at distributing mechanical stress, which is a key component of why these patients often develop AS earlier in life.

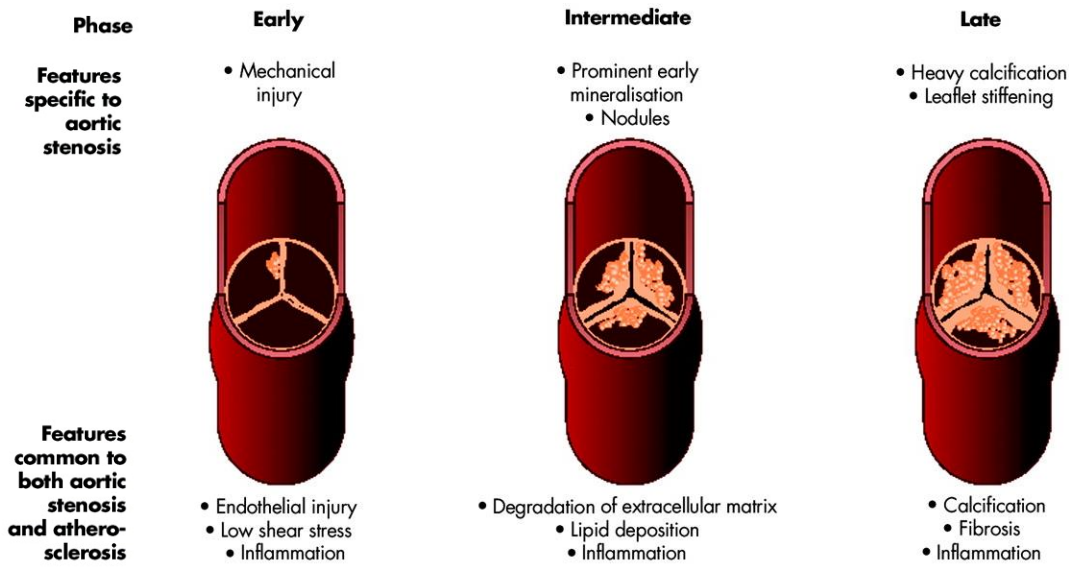

Figure 1.1: Pathogenetic features of the development of aortic stenosis*. As well as the shared inflammatory pathway with over CVD, damage to the valve increases turbulent flow and leads to the development of calcified plaques and nodules which increase, and lead to leaflet stiffening. 'Adapted from Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both?' (16).*

In the early stages of AS it is thought that endothelial disruption may allow lipid penetration into the tissue. The lipoproteins accumulate and undergo oxidative modification. The oxidised lipoproteins are highly cytotoxic and capable of stimulating

inflammatory activity, leading areas of inflammation in the valve leaflets. As seen in figure 1.1, a characteristic feature of AS opposed to vascular plaques and other cardiovascular diseases is the calcification and mineralisation. Occurring nearby areas of inflammation this relies on bone-regulatory protein expression and receptor activation. It is thought that mineralisation is triggered by oxidised lipids or due to cellular degradation following apoptosis (13, 16).

Nagy et al (2011) investigated the leukotriene (LT) pathway in aortic valves. The LT pathway is a lipid signalling proinflammatory pathway. Nagy *et al* dissected surgically removed AV's and extracted RNA from multiple areas of each valve and were able to differentiate normal, thickened, and calcified areas from each valve. Messenger RNA levels of the LT-forming enzyme 5-lipoxygenase increased 1.6-fold in thickened tissue and 2.2-fold in calcified tissue when compared with normal areas of the same valves. This suggests that the upregulation of the LT pathway in AS is one of the inflammatory pathways occurring in AS development (17).

1.1.3.2 Left ventricular adaption

In AS the effective orifice of the aortic valve reduces, leading to increased afterload pressures in the LV. Initially, the LV adapts by the manifestation of concentric LV hypertrophy, ensuring the maintenance of physiological cardiac output. The hypertrophy offsets the raised intracavity pressure and so limits wall stress and maintains normal endocardial shortening. There is also an increase in end-diastolic pressure (EDP). This is unable to be maintained long term, leading to LV fibrosis and eventually systolic and diastolic dysfunction (18). Due to the progressive narrowing of valve opening, there is a steady increase in the transvalvular gradient over time until a point where flow across the valve drops. Reduced myocardial perfusion pressure and flow into the coronary vessels leads to subendocardial ischemia, and resultant myocardial fibrosis and myocardial function impairment. Functional impairment further reduces flow through the valve and leads to worsening ischemia, particularly in the presence of co-morbidities such as systemic hypertension or CAD.

As patients age, many will develop some level of noncompliance of the vascular bed. Reduced systemic arterial compliance (SAC), which frequently occurs in the elderly AS population has been shown to independently contribute to increased afterload and therefore decreased LV function. There was an increase in rates of both diastolic and systolic dysfunction when comparing patients with severe AS with normal and reduced SAC (diastolic dysfunction; 82% and 94% in normal and reduced SAC respectively, and systolic dysfunction; 16% and 31% respectively) (19).

The pathway described above (shown figure 1.2) is known as the classical progression. A subgroup of patients experience severe AS classified by value area but have a lower pressure gradient (<40mm/Hg) across the value suggesting non-severe AS. It is key to identify these patients as their quality of life will likely benefit from intervention. Often low gradient severe AS will be accompanied by low blood flow (< 35mL/m^2) across the valve (LFLG AS), which can occur in patients with both reduced and maintained Left Ventricular Ejection Fraction (LVEF). In patients with LFLG AS and reduced LVEF, there is assumed to be LV systolic dysfunction. This could be from the increased afterload being experienced by the LV and/or other cardiovascular diseases (commonly ischemic heart disease) and is pathophysiologically similar to reduced LVEF heart failure.

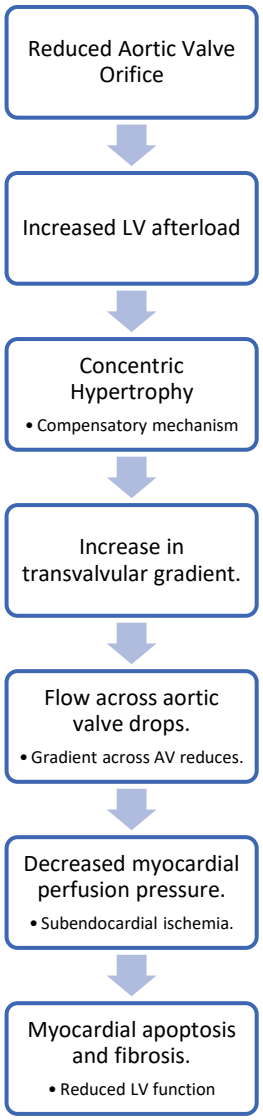

Figure 1.2: The 'Classical' Progression of Aortic Stenosis*. Showing the cascade of events from the reduced valve orifice leading to myocardial fibrosis. Author generated image.*

Patients with LFLG severe AS but a preserved LVEF are diagnosed as having paradoxical LFLG AS. This is a result of reduced LV filling (therefore strike volume), often caused by concentric remodelling of the LV leading to a small LV cavity, and impaired LV diastolic

filling. Co-morbidities such as mitral regurgitation or atrial fibrillation can also reduce LV filling in these patients. The trans-valvular gradient across the value is dependent on flow, therefore in patients with reduced flow, the gradient is pseudo-normalised (20).

Patients with LFLG AS have been shown to have poorer outcomes than comparable patients(21) and this needs to be taken into consideration when deciding when to treat AS. To investigate whether LFLG severe AS is actually an end-stage presentation of severe AS Dahl and colleagues retrospectively looked at the TTE's from the preceding 5 years for 78 patients with LFLG AS. LFLG was only preceded by a high gradient stage in 5% of the patients studied. It was therefore concluded that rather than simply being an end-stage of severe AS LFLG is a distinct presentation with a unique remodelling pathway (22).

There are also some severe AS patients who are classed as having a reduced gradient but normal flow across the aortic valve (NFLG AS). This is due to discrepancies in the definition of severe AS (Aortic Valve Area [AVR] <1.0 cm^2/indexed AVA <0.6 cm^2/m^2, mean gradient <40 mmHg, stroke volume >35 mL/m). An AVA of 1.0 cm^2 does not haemodynamically correlate to a mean gradient of 40mmHg, but approximately 30-35mmHg. Despite this, the AVA cut off for severe AS has remained at 1.0 cm^2 in guidelines, due to this being the optimal cut off to identify mortality risk. (20).

1.1.4 Myocardial Anatomy and Function

1.1.4.1. Left Ventricular Cardiac Mechanics and Function.

The myocardium in the LV consists of three distinct layers; the subendocardium (innermost), the mid myocardium and the subepicardium (outermost) (Figure 1.3). The LV is unique as there is a double-helical myocardial fibre arrangement. The fibres in the subendocardium are arranged in a left-handed helix. The fibres then smoothly transition to a circular arrangement in the midmyocardium and then a right-handed helix in the epicardium (23). Strain is a method of quantifying the deformation of the myocardium during the cardiac cycle (see Ch 1.1.5.1). Additionally, during LV systole, myocardial contraction leads to an anti-clockwise rotation of the LV apex and clockwise rotation of the LV base. This is governed by the subepicardial layer because

of its larger radius and known as twist (see Ch 1.1.5.3). The interaction of these layers and their deformation during the cardiac cycle is crucial in the effective functioning of the LV.

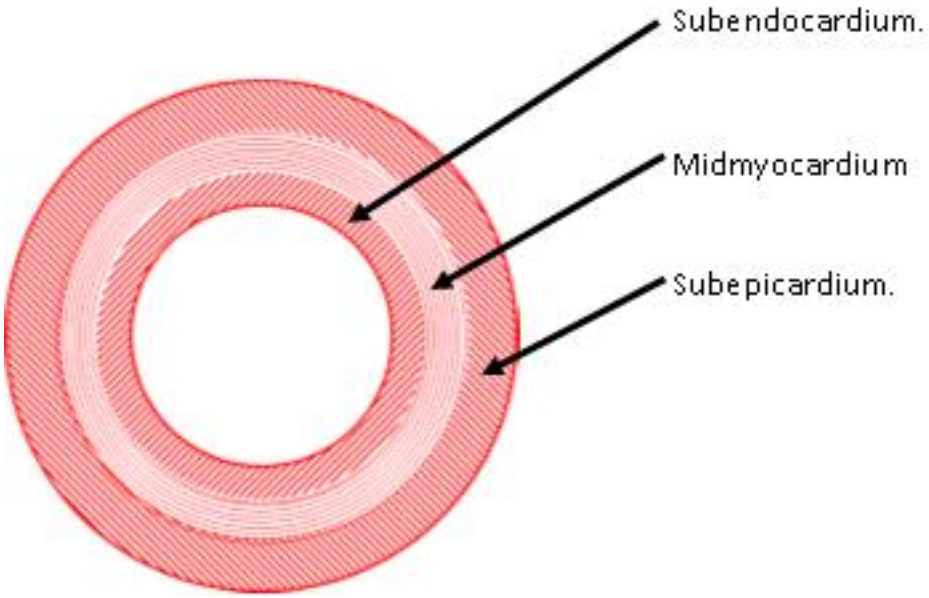

***Figure 1.3**: **Layers of the LV myocardial wall as seen in cross section of the LV.** The fibres are arranged in a left-handed helix in the sub-endocardium, circumferentially in the mid-myocardium, and in a right-handed helix in the sub-epicardium. Author generated image.*

The development of AS has significant effects on the function of the LV, as detailed above. If severe AS (as assessed clinically and by imaging) is not addressed LV function will deteriorate to the stage where LVEF will begin to fall. A reduction in LVEF correlates with poorer patient outcomes and increased mortality, including post aortic valve replacement surgery (AVR) (24, 25). Although, studies have reported that in those with low LVEF (<50%) there was a significant improvement in both LVEF and Global Longitudinal Strain (GLS, see Ch1.1.4.1) 12 months post-TAVI, as detailed in Table 1.2 (26, 27).

		Before TAVI	12-Month FU	P Value
Kamperidis et al, 2014[+]	LVEF (%)	31.9 +/- 8.6	40.0 +/- 13.3	0.02
	LV GLS (%)	-8.2 +/- 2.7	-10.2 +/- 3.6	0.02
Spethmann et al, 2014	LVEF (%)	35.6 +/- 10.8	48.1 +/- 14.8	0.01
	LV GLS	-10.5 +/- 3.1	-13.5 +/- 3.2	0.03

Table 1.2 Recovery of left ventricular ejection fraction and LV global longitudinal strain before TAVI vs 12 Month follow up, in patients with reduced LVEF (<50%). *+ Subjects had low flow, low gradient, severe aortic stenosis. Defined as mean gradient ≤40mmHg and stroke volume ≤35mL/m^2.*

The recovery of LVEF suggests that reduction in LVEF could be, in part, caused by afterload mismatch rather that irreversibly damaged myocardial contractility.

LV function is used as a key indicator of the overall function of the heart and is used in clinical decision making. Therefore, many of the analyses performed in this study focus on aspects and assessments of LV function; such as deformation in the different directions and ejection fraction.

1.1.4.2 Left Atrium

The left atrium (LA) serves a useful purpose in the exploration of cardiac health, as its function reflects long term haemodynamic changes and adaptions.

The left atrium can be considered a smooth-walled sack, apart from the left atrial appendage with its tubular shape and rough walls. The musculature of the LA extends into the pulmonary veins, which allows independent pulsation within the veins and their role in arrhythmias. Although the walls of the LA appear smooth and consistent, they also consist of multiple myocardial fibre layers and vary in thickness and there are more variations seen in the exact arrangement of myocardial fibres in the LA than in other chambers (28). Within the LA the circumferential and longitudinal fibres interact in a multifaceted manner. The circumferential bundles are the most prominent at the base of the atria and in the subepicardium. The main bundle of circumferential fibres transversely crosses the LA anterior wall, and then divides into upper and lower branches by the LA appendage, as seen in Figure 1.4. The upper branch passes in front

of the left pulmonary vein and to the lateral wall of the LA, while the lower branch extends inferiorly to the atrial base. The longitudinal fibre bundles are mostly found in the internal walls of the LA. The left septoatrial bundle of fibres originates on the anteroinferior margin of the septum, passes to the anterior base of the atrium, and attaches to the leaflet of the mitral ring. At which point some of the fibres branch off into a circumferential bundle. The main longitudinal bundle extends between the right and left pulmonary veins; up the superior and posterior walls of the LA. Before branching out and spreading over the posterior wall (29). This leads to mixed fibre orientation in the sub-endocardial layer of the LA (28).

In patients with severe AS LV function is significantly and increasingly impaired due to a negative feedback cycle where pressure gradients across the value lead to reduced myocardial perfusion and resulting ischemia, especially in the subendocardial layers of the LV. Continued and worsening LV dysfunction can lead to LA involvement with AS. Diastolic dysfunction leads to increased end-diastolic volume (EDV) in the LV, and therefore increased afterload in the LA. As shown in Figure 1.5, during early to mid-LV diastole the mitral valve is open exposing the LA to the conditions and pressures of the LV(15). There is progressive LA enlargement and dysfunction in patients, even before the patient becoming symptomatic (30). In contrast to LA afterload which is highly pressure-dependent, LA pre-load is predominantly volume dependant (on the pulmonary return).

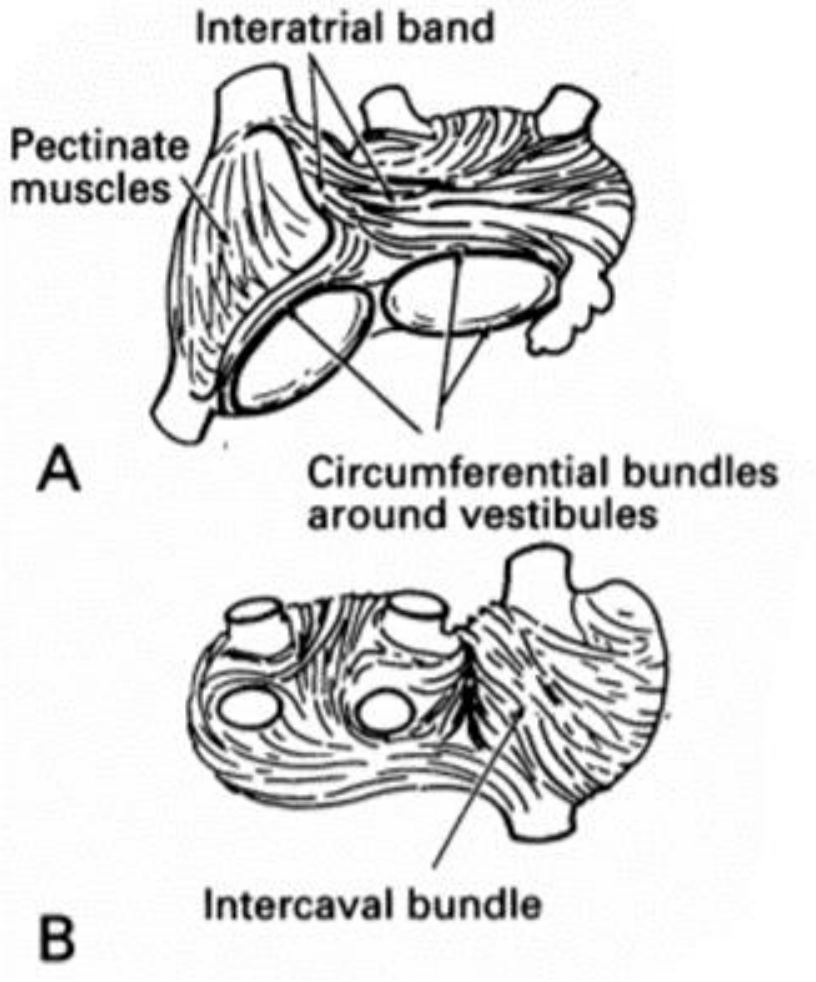

Figure 1.4: Diagrammatic illustration of the front (A) and back (B) views of the right and left atrial musculature *after removal of the epicardium Illustrating the complex anatomy (29)..*

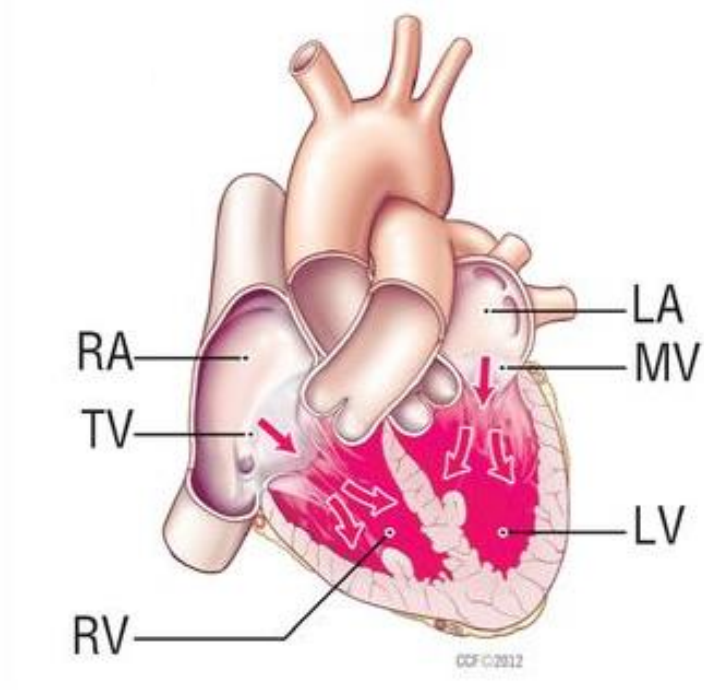

Figure 1.5: Illustration of mitral and tricuspid valves being open during early to mid-diastole*, exposing the each atrium to the conditions of the corraspoding ventricle (15).*

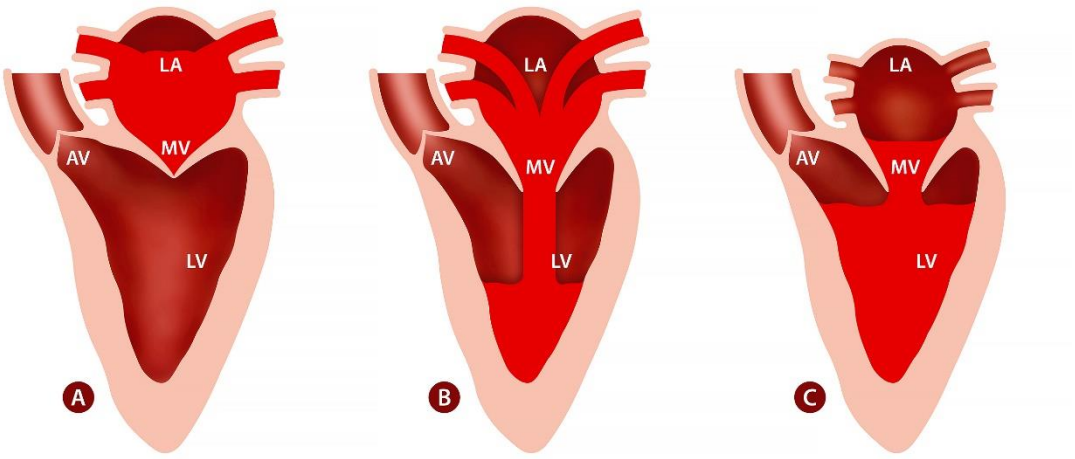

Figure 1.6: Illustration of the three-phase LA function*. A: reservoir phase where the mitral valve is closed as the atrium fills with returning blood. B: conduit phase where the mitral valve is open and the atrium acts as a channel. C: contractile phase, where the atrium actively contracts to expel the remaining blood into the left ventricle. LA: Left Atrium. LV: Left Ventricle. MV: Mitral Valve. AV: Aortic Valve. Author generated image*

The complex arrangement of muscle fibres in the left atrium facilitates a complex electro-mechanical relationship with a tri-phasic function. LA function can be split into reservoir, conduit and contractile phases, as seen in Figure 1.6. The LA acts as a 'reservoir' during ventricular systole and isovolumetric relaxation of the LA; collecting blood that is returning from the pulmonary veins (PV). Moving into early ventricular diastole the LA acts as a channel as the blood passes through from the PV's into the LV (the conduit phase). This is then followed by a time of atrial contraction.

The contributions of the different phases of LA function to LV filling are affected by LV diastolic function. In those with normal diastolic function, the reservoir, conduit and contractile function contribute approximately 40%, 35% and 25% to LV filling respectively(31). As the LV begins to show signs of diastolic dysfunction and relaxation worsens the contributions of the reservoir and contractile functions gradually increase and conduit phase contribution decreases (32). Although, in advanced diastolic dysfunction reservoir and contractile function declines dramatically and the LA serves predominantly as a conduit. This is a result of the compensatory mechanisms failing under increasing pressure from the LV. LA volume measured by speckle tracking echocardiography (STE, see chapter 1.2.3) facilitated the confirmation that in advanced diastolic dysfunction Starlings Law of the heart no longer operates (33). A reduction in

LA reservoir volume has been linked to dyspnoea, a symptom of heart failure (34). Maximum LA volume continues to increase linearly with the increasing severity of diastolic dysfunction.

In a population-based study of those 65 years and older (35) found that LA size is increased and LA emptying decreased, in patients with either systolic or diastolic HF. Age also has an impact on the capacity and function of the LA, with LA volumes being found to slightly but significantly increase with age (33). It has been proposed that this may link with the reduced LV relaxation often observed in, even the healthy, elderly. Age has also been shown as a significant factor in the proportion of passive and active emptying seen in the LA, with active emptying playing a bigger role in elderly patients (36). The changes seen in ageing are mild compared to the changes and remodelling seen in response to diastolic dysfunction.

As the changes seen in the LA reflect the long-term conditions of the heart opposed to acute conditions it is a useful chamber to assess in the assessment of chronic changes to either volume or pressure load. Both AVR and Trans-catheter aortic valve insertion (TAVI) should provide an immediate reduction in LV afterload for patients, which should improve LV diastolic dysfunction and reduce the pathological loads on the LA. Studying LA function pre-and post-intervention will indicate long-term recovery of the heart; a key factor in mortality rates.

1.1.4.3. Right Ventricle

The right ventricle (RV) has a complex geometry that varies in appearance depending on the plane of imaging. The RV appears triangular when viewed from the side, yet in cross-section, it appears crescent-shaped(37). Physiological loading conditions result in the interventricular septum being shaped concavely towards the LV in both systole and diastole. The volume of the RV is larger than that of the LV in a normal healthy adult, but the RV walls are significantly thinner with overall RV mass approximately one-sixth of LV mass(38). The RV myocardium also comprises multiple fibre layers which can be split into the superficial and deep. The deep muscle fibres in the RV are arranged longitudinally, whereas the superficial (sub-epicardial) layers are arranged circumferentially, and parallel to the atrioventricular groove(39). The RV superficial

fibres connect to the myofibers of the LV via the cardiac apex, therefore adding further LV influence over RV deformation. Although RV contraction can be split into three separate functions, the key movement is shortening of the longitudinal fibres, which can be assessed by measuring longitudinal strain. Circumferential and radial strains are not currently routinely measured in the RV, due partially to their smaller influence, and also due to the limitations of current technology to accurately track the thinner walls of the RV. As well as longitudinal shortening, during systole, the RV free wall will move inwards, although this is less significant than in the LV because of the higher surface to volume ratio. Finally, there is traction on the free wall at the points of attachment as a secondary effect of LV contraction (37). As, in a healthy RV, there are no significant layers of obliquely orientated myocardial fibres, there is no significant influence of twist to RV contraction.

The function of the right ventricle (RV) is correlated with that of the LV. Firstly the RV and LV share the interventricular septum, which contributes to RV contractile function. Additionally, RV function will be influenced by the afterload the RV experiences (total pulmonary resistance). Total pulmonary resistance is highly affected by LV end-diastolic pressure. Therefore, when LV function declines in severe AS it is likely to also cause some amount of RV dysfunction. Studies had suggested that right ventricular function is negatively affected by traditional valve replacement, but not TAVI, in the short to medium term (40). More recent work has suggested that although tricuspid annular plane excursion (TAPSE) is reduced post AVR, transverse contraction increased. And overall RV stoke volume, assessed by 3D volumes, remained unchanged (41). This work hopes to add to the body of knowledge regarding RV functional recovery post-AVR and TAVI.

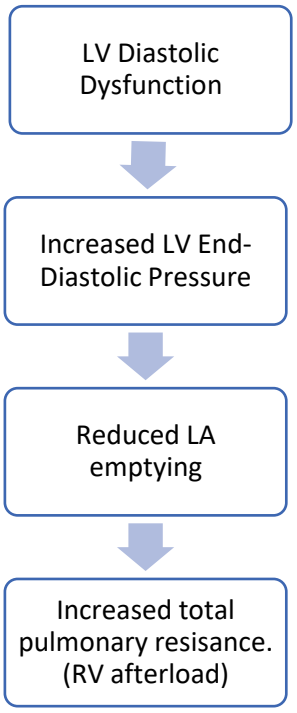

Figure 1.7: Flow Chart illustrating the pathway from LV dysfunction to RV dysfunction. *Author generated image.*

When measuring RV longitudinal strain by STE there is some inconsistency regarding whether to track just the free wall of the RV or whether to include the septal wall and measure global RV longitudinal strain. This is because the septal wall is predominantly controlled by the LV and influenced by LV function. This study will follow current

European guidelines to measure global RV longitudinal strain because although the septal wall is heavily influenced by LV function, it contributes to RV function (42-44).

1.1.5 Cardiac Mechanics and Aortic Stenosis

1.1.5.1. Physiological Cardiac strain

During the cardiac cycle the myocardium deforms; thickening and shortening/lengthening. This is known as strain/stress and can be measured using multiple techniques. This study will investigate strain using speckle tracking echocardiography (STE). As the myocardium is a muscle, with a finite mass in the short term, this deformation is important for the reduction of chamber size and physiological cardiac output.

As the heart is a 3D structure there a six 'strains' on the myocardium; 3 directions of normal strains in the three dimensions, but additionally 3 directions of shear strains produced from the movement of the plane layers over each other in the heart (45). Shear strain provides a key role in both radial thickening and twist in the LV. The gradient of shear strain increases with progression from the sub-epicardium to the sun-endocardium correlates with increasing radial deformation (expressed as percentage radial strain).

STE assesses strain using the Lagrangian description. This method takes one point in time, in cardiac mechanics this is end-diastole, and the tissue dimension at this point represents the unstressed, initial material length that is used as a fixed reference throughout the cardiac cycle. Strain is expressed as a fractional length change, where shortening is a negative valve and lengthening a positive.

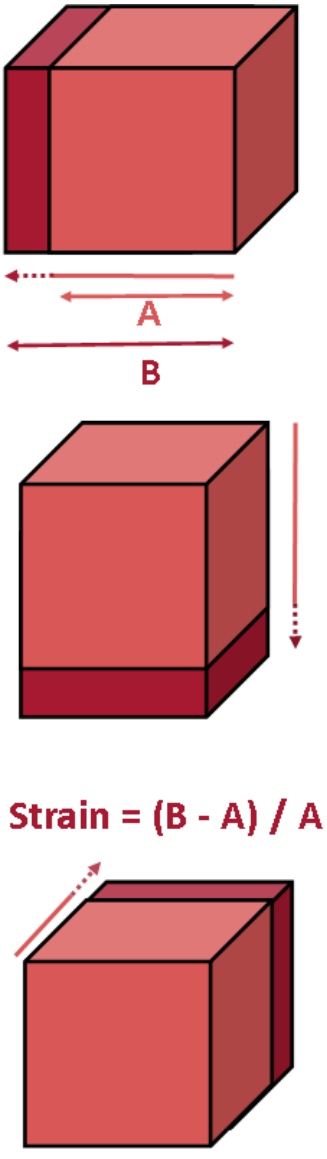

Figure 1.8: Concept of Lagrangian Strain on a 3D object. *Author generated image.*

Figure 1.8 illustrates the concept of 3D strain on a cube. This same concept is applied to the LV where strain is assessed in three directions; longitudinal strain (LS),

circumferential strain (CS) and radial strain (RS). Longitudinal strain measures the change in 'length' of the LV from base to apex, circumferential strain measures the change in the circumference of the LV chamber, and radial strain measures the change in thickness of the LV myocardial wall (See Figure 1.9).

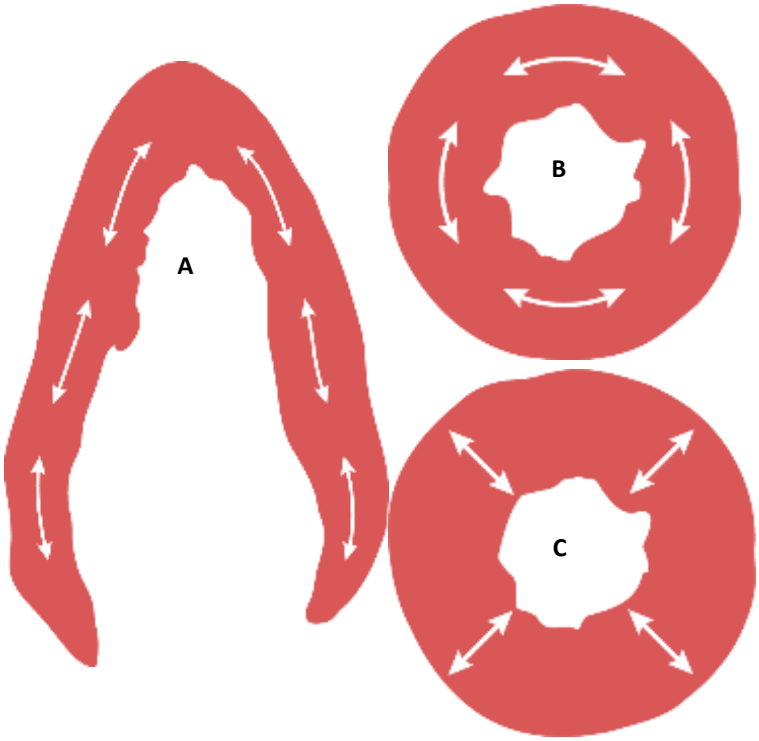

***Figure 1.9: Directions of left ventricular strain**. A- Longitudinal Strain, tracking the 'length' of the LV from base to apex. B- Circumferential strain, measuring the diameter of the LV chamber, C- Radial strain, measuring the thickness of the LV wall. Author generated image.*

The normal ranges of LV strain vary slightly between sources but a meta-analysis of strain in STE studies reported normal values as follows.

LV Strains	Mean Value (%)	95% CI (%)
Global Longitudinal Strain	-19.7	-20.4 to -18.9
Circumferential Strain	-23.3	-24.6 to -22.1
Radial Strain	47.3	43.6 to 51.0

***Table 1.3: Normal Figures for LV strain.** Taken from a meta-analysis by Yingchoncharoen et al, 2013 (46)*

When looking at factors that may affect GLS, vendor, age, and gender meta-regression were not significant determinates, although this should not be misinterpreted to mean they have no effect. Systolic blood pressure was demonstrated to have a significant effect (46). In contrast, in a single centre study, Alcidi *et al* reported that age did have a

significant independent effect on GLS in healthy subjects. GLS in those aged 60 years and over was significantly declined compared to adults aged 20-29 years (23.1 +/- 1.8 vs 22.0 +/- 1.8, P<0.05) (47). Longitudinal strain in the subendocardial and subepicardial layers of the myocardium also showed a statistically significant decline between the 20-29 age group, and 60+ age group (P<0.001). However, care should be taken before generalising these results as the study was limited by a fairly small sample size of 266 subjects, all from a single centre and Caucasian (47).

There were variations in the methodology of papers used to calculate the mean values for CS; some papers measured CS only at the mid apical level in the PSAX view, others measured CS at the basal, mid and apical levels in PSAX and reported the mean of these values. Although this inconsistency is not ideal, CS increases from the basal to the apical levels, therefore, the CS value at the mid-chamber level should be expected to provide a value near the mean.

Although this is the largest and most comprehensive meta-analysis of 2D STE measured LV strain completed thus far, it is worth noting that the data search was completed in 2011. STE software has developed since then and is becoming increasingly reliable, with smaller variations in measurements; especially for non-LV longitudinal strain.

LV Longitudinal strain is measured in multiple apical views and averaged to produce a more robust and reliable measure that reflects all the walls of the LV. GLS measurements using STE have been shown in multiple studies to be a more sensitive marker of myocardial contractility than echocardiographic LVEF (18, 48-50). When assessed as part of a nested Cox model for death in those with known or suspected LV impairment, GLS (HR, 1.45; P<0.001) caused a greater increment in model power than LVEF (HR, 1.23; P=0.03) (51).

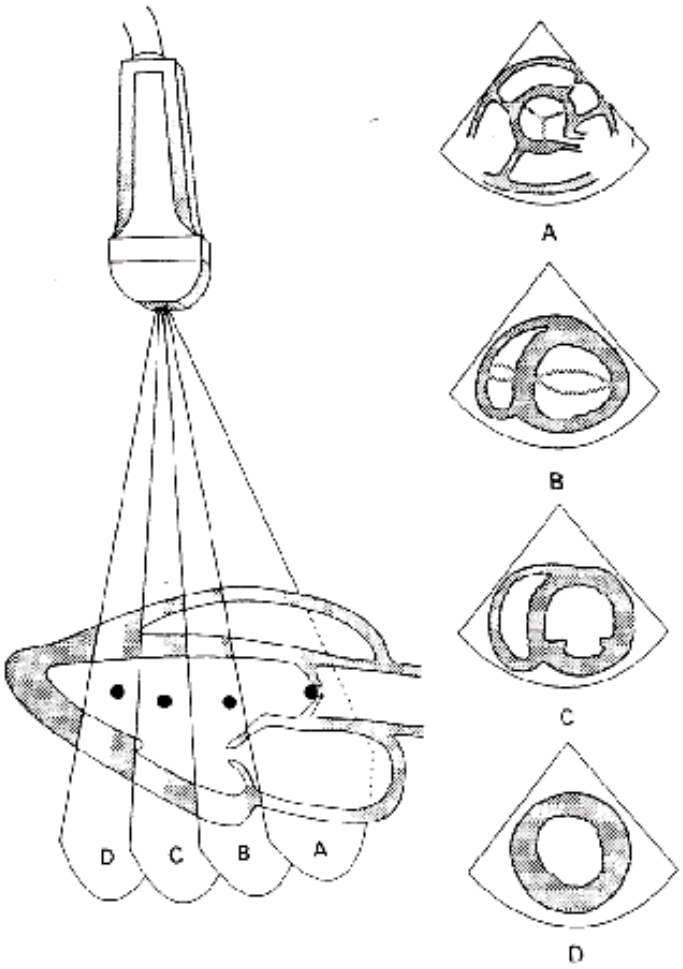

Figure 1.10: The plane of TTE imaging and resulting images acquired from the PSAX view
A: Level of the aortic valve. B: Level of the mitral valve. C: Mid-level in the Left ventricle, where the papillary muscles can be seen. D: Apex of the left ventricle (52).

Circumferential strain represents the circumference of the LV myocardium throughout the cardiac cycle and therefore is also a negative value during systolic contraction. Whereas radial strain represents the thickness of the walls themselves and is a positive valve. Both circumferential and radial strain are measured in the parasternal short-axis view (PSAX); CS at the base, mid-LV and apical levels, and RS only at the mid-LV level. Figure 1.10 shows the different levels at which the ultrasound (US) beam intersects with the myocardium for each of the PSAX views (52). This study does not collect data from the PSAX view at the level of the aortic valve (A).

Although less established clinically longitudinal strain can also be measured for the left atrium and right ventricle. RV longitudinal strain is a negative systolic value, due to the synchronised contraction of both ventricles. LA longitudinal strain is a positive valve, as when the ventricles are contracting the atria are dilating and filling. In subjects in sinus rhythm longitudinal LA strain will have two peaks, representing the peak filling during

LV systole, and then a second peak as it enters the active LA contractile phase (See Figure 1.76. In a meta-analysis Pathan *et al* concluded that the normal range for LA strain was a peak reservoir strain of 39% (95% CI, 38%-41%), and contractile strain of 17% (95% CI, 16%-19%) (53). A recent study investigated the predictive and prognostic value of LA reservoir strain in healthy individuals. 385 participants without atrial fibrillation, heart failure (HF), and ischaemic heart disease (IHD) were followed up for a median of 12.6 years, with an endpoint of a composite of incident IHD, heart failure, or cardiovascular death. The study found that LA reservoir strain is a univariable predictor of cardiovascular morbidity and mortality in the general population, although it is only an independent predictor of outcome in women opposed to men(54).

1.1.5.2 Strain in AS

1.1.5.2.1 Left Ventricular Global Longitudinal Strain.

In their analysis, Yingchoncharoen and team found that age was not independently associated with a change in GLS values in a general linear model. Investigators have looked at strain in patients with varying severities of AS and normal LVEF. In those with severe AS 69% had a GLS that >2SD below the mean of the age-matched controls (48). GLS picks up on subtle changes in LV function and even in those with unchanged LVEF GLS correlates with AS severity and with markers of myocardial damage and increased afterload (49) (55).

Multiple studies have demonstrated that in patients with AS, after adjustment for clinical and echocardiographic variables, baseline GLS was a strong independent predictor of all-cause mortality. With an increasing relative risk of all-cause mortality per 1% impairment beyond a GLS of -15% (56). Table 1.4 shows an overview of the findings of multiple studies regarding the predictive power of GLS in patients with AS.

	Summary
Miyazaki et al, 2012 (48)	In patients with severe AS and preserved LVEF, the mean GLS was −15 ± 3%, which was significantly different from the age-matched controls (P< 0.001).
Ng et al, 2017 (57)	In symptomatic AS patients, with preserved LVEF (>50%) who were treated conservatively (without AVR or TAVI), GLS was independently associated with a higher risk of clinical events (defined as readmission for heart failure, or all-cause death at 2 years), HR= 1.30 (95% CI: 1.06-1.58) P=0.01.
Marwick, 2013 (49)	In patients with AS and preserved LVEF, LV longitudinal strain (measured Ap4Ch only) showed a significant difference between severity groups; mild: 17.1 ± 3.0%, moderate: 16.4 ± 3.0% and severe: 14.5 ± 3.9%. LVEF did not show any significant difference.
Salaun et al, 2018 (58)	Patients with AS and normal LVEF were split according to the median GLS (-14%). Those with preserved GLS (greater in magnitude than -14%) had significantly higher survival rates post AVR (One-year survival 92.3% vs 77.7%). There was no significant difference in survival between those with preserved LVEF but impaired GLS, and those with impaired LVEF (75% survival at 1 year). Univariable and multivariable cox proportional hazard ratio for all-cause mortality for sAS before AVR is HR 1.17 (1.09-1.26), P<0.001.
Pathan et al, 2016 (59)	Patients with moderate/severe AS and preserved LVEF (>50%) were enrolled (n = 582). Those with sAS were split into four subgroups according to their flow and gradient status. By multivariable cox regression analysis, Ap4Ch Longitudinal strain with an absolute value of <13.75 % was independently associated with overall mortality at 2 years (hazard ratio: 1.8; P = 0.045).

Table 1.4: Overview of Study findings regarding the predictive value of GLS in sAS.

1.1.5.2.2. Left Ventricular Circumferential and Radial Strain

Delgado *et al* (2009), conducted a study regarding the recovery of LV strain in patients with severe AS. At baseline, they reported the left ventricular circumferential strain (LVCS) values for healthy controls (n=20), hypertensive subjects with LV hypertrophy (n=20), and subjects with severe AS but preserved LVEF (n=73). Reported mean values were -19.5±2.9% for the healthy controls, -17.0±3.0 for the hypertensive controls, and -15.2±5.0% for those with severe AS (p=0.005 vs healthy controls) (60). This demonstrated that AS causes greater impairment in circumferential strain that LV hypertrophy alone. Also, the variance of LVCS values in the cohort of subjects with severe AS was greater than in the other groups. The recent work of Fung *et al*, correlated with Delgado and team, concluding that LVCS became more impaired at the severity of AS progressed, and reporting a mean LVCS of -14.3 ± 3.5%, in subjects with severe AS (n=52) (61).

Delgado *et al* also reported a decline in left ventricular radial strain (LVRS) in severe AS. Healthy controls had a mean LVRS of 38.9±6.4%, the hypertensive cohort had a mean of 34.4±10,7%, and those with severe AS a mean LVRS of 33.1±14.8%. However, the difference in mean LVRS values between the healthy controls and those with severe AS was not significant (P=0.2)(60).

The mean value reported for both LVCS and LVRS for the healthy controls was lower than that reported in the meta-analysis by Yingchoncharoen and team (LVCS= -23.3%, LVRS= 47.3%), this may be due to the older cohort, as controls were age-matched to the subjects with severe AS (mean age of healthy controls = 65 years) (46). All three directions of normal strain in the LV interact to play an important role in the global function of the chamber, and cardiac output. Therefore, it is key to investigate the impairment of LVCS and LVRS in AS and potential recovery after intervention.

1.1.5.2.3. Left Atrial and Right Ventricular Strain

While there has been less research regarding non-LV STE measured strain in AS there is increasing evidence to show that both peak systolic, and peak contractile atrial longitudinal strain is markedly reduced in patients with sAS. D'Ascenzi *et al* (2013) studied LA remodelling after TAVI and reported baseline LA strain values of 14.4 +/-

3.9% and 8.4 +/- 2.5% for reservoir and contractile strain respectively for the subjects with AS(30). This is significantly reduced compared to reported normal values of 39% for peak reservoir strain, and 17% for contractile strain(53), reflecting major LA functional impairment. A tissue doppler based study conducted by O'Connor and team, supported these conclusions, reporting that all three components of LA function are reduced in those with severe AS, and active LA dysfunction is related to the severity of AS and LV diastolic function(62).

The right ventricle has been studied less through than the LV, but there is an emerging body of work regarding RV function and changes in severe AS. Rigolli *et al* reported on their work using cardiac magnetic resonance imaging to assess RV function; this study found that RV ejection fraction significantly increased with AS severity (severe AS $p<0.001$ compared to controls), as did circumferential and radial strain ($p=0.02$, $p=0.01$), but did not report RV longitudinal strain. Additionally, pre-intervention RVEF strongly correlated to LV mass regression post-AVR ($r=0.61$, $p=0.01$) (63). However, a larger study (Koifman *et al*, 2017) concluded that the presence of RV dysfunction did not correlate with 1-year post-intervention mortality rates in patients with severe AS. Rather than RVEF, this study assessed RV function via fractional area change, tricuspid annular plane systolic excursion (TAPSE), systolic movement of the RV lateral wall by tissue Doppler, and basal and mid-RV diameters (64). A recent study, using STE, investigated RV longitudinal strain in patients with severe AS compared to normal controls. It was reported that there was a significant reduction in RV global strain (measured in both the free and septal walls if the RV opposed to just the free wall) in subjects with severe AS, regardless of if there was concurrent hypertension. In subjects without hypertension, the mean RVGLS was -23.4±3.1% in healthy controls, and -18.8±2.0% in those with severe AS. Subjects with hypertension but no AS had a reported mean RVGLS of -21.8±2.8% and those with both pathologies a reported mean of -17.1±2.0% (65). This study only had a sample size of 64 patients with severe AS, but there were robust methodologies, and the results suggest that the increased circumferential and radial strain reported by Rigolli *et al* is not accompanied by increased longitudinal strain.

1.1.5.3. Physiological Left Ventricular Rotation and Twist

The helical arrangement of the fibres in the LV (detailed in section 1.1.4.1) allows the myocardial layers to interact during systole and create a much larger ejection fraction than the percentage shortening of individual myocytes. Contraction of the fibres in all three layers causes circumferential narrowing, and the LV base and apex to rotate in opposite directions around the long axis. Overall the base rotates in a clockwise direction and the apex in an anti-clockwise direction (23). The calculated difference between apical and basal rotation in the LV is referred to as twist, it can also be normalised against end-diastolic LV length and referred to as torsion (66). Contraction of the fibres stores kinetic energy which can then be realised during relaxation, this 'untwist' causes a diastolic suction, is a key mechanistic link between systole and diastole, and aids early diastolic filling. Twist can be measured by STE, tissue doppler imaging (TDI), vector velocity imaging, MRI, and sonomicrometry (invasive and not used in human studies). This study will use STE due to the availability of echocardiographic images, and TDI being angle dependant. This decision was made with the understanding that STE does have the limitation of a lower temporal resolution. Twist is sensitive to changes in LV loading. Animal studies have concluded that an acute increase in afterload reduces twist, whereas a reduced afterload enhances LV twist, but these studies often had limitations on the thoroughness of their investigations; looking only at apical twist or the epicardial layers. Human studies have also shown support for that changes in LV afterload in relative isolation causes the heart to respond in accordance to Starlings Law; an acute increase in afterload reduces LV twist, while an acute reduction in LV afterload causes an increase in LV twist (23).

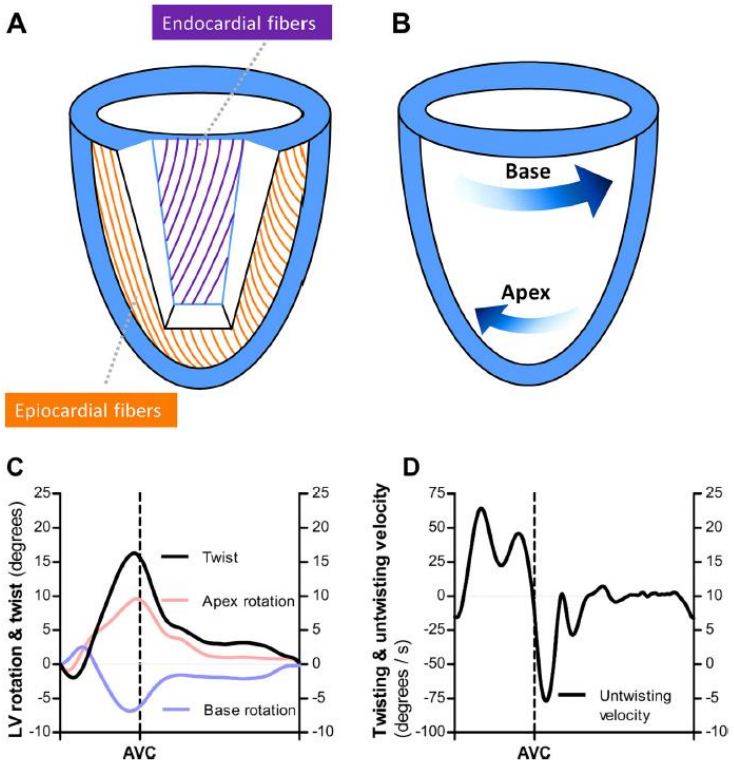

Figure 1.11: Left Ventricle (LV) fibre alignment and systolic twist. *A) LV endocardial and epicardial configuration at end-diastole. B) Rotation directions of Apex and Base of LV. C) Normal rotation and twist for healthy individual in resting conditions Clockwise rotation of the LV base shown as negative rotation, and the anti-clockwise rotation of the apex shown as positive rotation. D) Normal untwisting velocity for a healthy individual throughout the cardiac cycle (23)*

Changes in the physiological environment or needs of the cardio-vascular system (such as ageing or exercise) do not affect a single haemodynamic factor in isolation. Therefore the effects on twist caused by activity or other physiological influences are not always consistent with changes seen in isolated trial conditions (67) (68). When twist is investigated to look for chronic alterations in situations such as exercise training or ageing, changes can be seen.

Studies have demonstrated lower LV twist in those with a high aerobic fitness than controls with a more sedentary lifestyle, but there is some evidence this normalises over time. Regarding ageing; trials have produced consistent results that show that ageing results in increasing LV twist despite increases in afterload which may be expected to reduce twist, which is has been the case when it is measured in isolation (69-71). This suggests that other factors are responsible for the changes seen in ageing,

these could be related to contractile myofiber function (70) and subendocardial ischemia and dysfunction (69). There is still some uncertainty over the mechanisms behind physiological twist adaptation and future research will only act to improve the understanding of pathological changes.

Due to subepicardial fibres having a longer arm of movement they have the overall influence on the direction of the twist. This can be exuberated by subendocardial ischemia, as seen in AS (72).

There is still a lack of consensus in the literature regarding normal values for LV twist, possibly partially due to the influencing factors detailed above. Kocabay *et al* reported a mean value peak LV twist of 20^{o} in healthy subjects(73). Yet the controls of the NORRE study were reported as having a mean peak twist of 7.9^{o}(74).

1.1.5.4 Left Ventricular Rotation and Twist in Aortic Stenosis

AS causes an increase in left ventricular afterload and adaption of the myocardium which presents as increased apical rotation leading to increased twist.

Reduced flow across the valve leads to impaired myocardial perfusion. The subendocardium becomes ischemic and fibrosed. This fibrosis means that the subendocardium is unable to counteract twisting on the subepicardium to the same extent as would be seen in a fully perfused heart. An increase in the apical rotation is seen, whereas basal rotation stays stable due to the tethering effects of a stiffened atrioventricular valvular plane. In a study comparing those with AS (AVA <2.0cm^2) with healthy age-matched controls, the patient population had increased HR, LA size and LV mass compared to the controls. Patients demonstrated normal basal rotation but increased apical rotation, leading to increased twist (72). Maximum apical rotation and twist correlated positively with aortic valve jet velocity and negatively with AVA (indexed to BSA). It has been suggested that the increased twist may be acting as a compensatory mechanism for the reduction in LV contractility often seen due to subendocardial ischemia. Although delayed diastolic untwist will exuberate the diastolic dysfunction seen in patients(72).

1.1.6. Treatment of Aortic Stenosis

1.1.6.1. Medical Management and Balloon Valve Angioplasty

Medical management of AS is somewhat limited in its efficacy. It focuses around treating any co-morbidities; including CAD, and hypertension, and treating the symptoms of heart failure.

There have been some emerging trials looking at patients receiving statins, based on the hypothesis that AS is caused by an inflammatory pathway. Results have been mixed but there has been evidence to suggest that the administration of statins in patients with high Low-density lipoprotein (LDL) concentrations in early disease may slow disease progression (2) (13). However, in a clinical setting patients are rarely co-morbidity free; therefore, many patients who are at risk of developing AS are likely to already be being treated with statins for lipid abnormalities. Therefore, the rate of progression that is seen in a clinical setting may be the slowed rate. An additional study explored the impact of Rosuvastatin in patients with more advanced AS and no clinical indication for cholesterol-lowering drugs. Patients were randomised to Rosustatin or placebo, both arms had a mean gradient >40mmHg at the onset. In this trial, the statin wasn't shown to produce any benefit, suggesting that any potential benefit is only accomplished if the statin is started in early disease state (75). A further double-blind, placebo-controlled study; the SALTIRE (Scottish and lipid-lowering therapy, impact on regression) trial randomised patients with calcified AS to receive either 80 mg of atorvastatin daily or a placebo. They found that although the atorvastatin more than halved serum LDL cholesterol concentrations, it did not halt the progression or induce regression of the valve disease process as measured by Doppler echocardiography or helical CT (76). The SALTIRE study required subjects to have a minimal peak aortic valve jet velocity of 2.5m/s, therefore the subjects recruited all had established AS. Looking at this body of knowledge it could be theorised that although lipid accumulation is involved in the development of AS, other factors are more significant in driving the progression of AS.

Despite ACE inhibition being contraindicated in patients with aortic stenosis, there have been some retrospective studies investigating the effects of ACE inhibitors on AS progression. These have had contradictory results, and further non-retrospective trials

are needed to reach any reliable conclusion, especially in cardiovascular disease with many confounding factors (16).

Overall, studies looking at the potential protective effects of baseline non-steroidal anti-inflammatory drug use found no protective effects regarding the onset of calcification in the aortic valves. Although the Multi-Ethnic Study of Atherosclerosis (MESA) study found a possible link between aspirin use and increased prevalence of aortic valve calcification (RR 1.19 95% CI 0.90 - 1.58) this was only seen when stratified according to diabetic status and wasn't observed in the Heinz Nixdorf Recall Study, which looked at similar measures of calcification as the MESA study. (77).

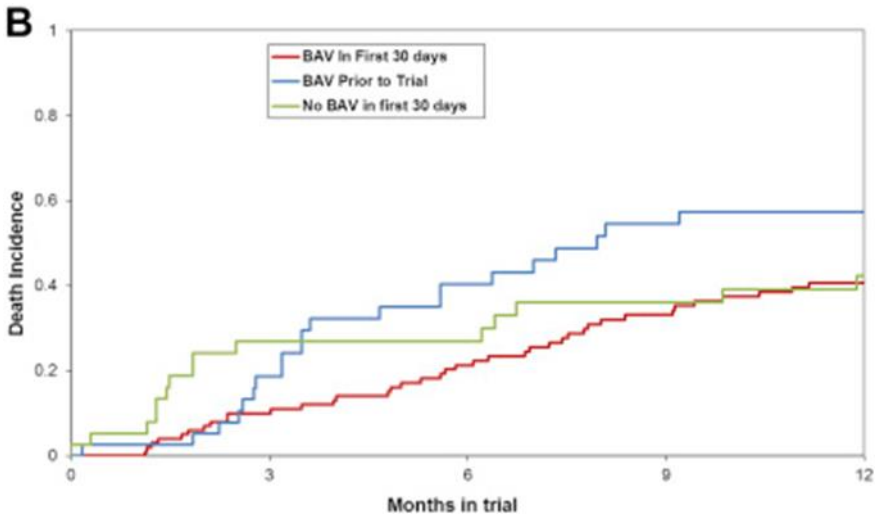

Figure 1.12: Cardiovascular mortality of patients undergoing BAV within 30 days compared with those not undergoing BAV or undergoing BAV before randomization. *Comparing those who had BAV within 3- days of starting the trail and those who didn't, there is no significant different in survival at 6-months. Reproduced from the non-operable cohort of the PARTNER trial (78).*

For those who have symptomatic AS and are inoperable, a balloon valve angioplasty can be performed. An expandable balloon is fed up the patients' vascular system and positioned over the aortic valve. It is then expanded and mechanically forces the valve open wider than it has been. Balloon valve angioplasty (BVA) can relieve symptoms and improve quality of life (QoL) for the patient in the short term. Kapadia et al compared outcomes for inoperable AS patients and found that although those undergoing BVA had improved mortality and QoL at 30-day and 3 months follow up. Survival, at 6 months was not significantly different. This is seen in Figure 1.12. Furthermore, the benefits initially seen in the quality of life scores (measured by

Kansas City Cardiomyopathy Questionnaire Overall Summary Scale and its components) for those who underwent BVA were not sustained at 12-month follow up (78).

1.1.6.2. Valve replacement procedures

1.1.6.2.1. Traditional Aortic Valve replacement

The current gold standard for treatment of AS is surgical aortic valve replacement (AVR). The diseased valve is resected, often along with the aortic root, and is replaced by either a mechanical or biological valve. This results in an immediate increase in AVA and reduction in afterload. The patient will see an improvement in symptoms and outcome.

This method is not without disadvantages though, the surgery is major and accompanied by significant risks, including bleeding, renal damage and stroke-like events. The PARTNER (Placement of Aortic Transcatheter Valves) trial enrolled high operative risk patients (suggested STS score greater than 10%). The SURTAVI (Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients) study ran a similar trial but with patients with a high to intermediate operative risk (STS score 3-15%). Both trials randomised subjects to receive AVR or transcatheter aortic valve insertion (TAVI). Results regarding adverse events for the AVR groups are summarised in Table 1.5.

In those who have a mechanical valve fitted there is the need to take long term anticoagulation therapy. Those who have a biological valve, which is typically a porcine valve over a metal stent, must take into consideration that the healthy life of these valves is 10-15 years, after which repeat surgery is likely to be required.

		PARTNER Trial		SURTAVI Trial	
		30-day (% of pts)	1 Year (% of pts)	30-day (% of pts)	1 year (% of pts)
Death	Any Cause	6.5	26.8	1.7	6.8
	Cardiac Cause	3.0	13.0	1.7	5.5
Stroke-like event	Transient Ischemic Attack	0.3	1.5	1.1	2.0
	Stroke - Minor	0.3	0.7	3.1	3.6
	Stoke - Major	2.1	2.4	2.5	3.9
Myocardial Infarction		0.6	0.6	1.0	2.0
Acute Kidney Injury		1.2[+]	2.7[+]	4.4	
Major Bleeding		19.5	25.7	9.3	
Endocarditis		0.3	1.0		
New Onset Atrial Fibrillation		16.0	17.1		

Table 1.5: Adverse Events in the PARTNER and SURTAVI trials; AVR Group (79, 80). *[+]Defined as creatinine >3mg/dl.*

1.1.6.2.2. Transcatheter Aortic Valve Replacement.

The development of transcatheter aortic valve insertion/replacement (TAVI) allowed the treatment of severe AS in a new sub-set of patients, those previously deemed inoperable. During TAVI a collapsed valve is fed through a delivery system and expanded in the correct position over the location of the diseased valve (Figure 1.13, (81)). The expandable valve sits inside of the diseased valve. Access can be via the femoral artery, the subclavian artery or a direct apical approach (Figure 1.14). The approach used is dependent on the patient's vascular anatomy, and any other previous interventions, although a transfemoral approach is favoured.

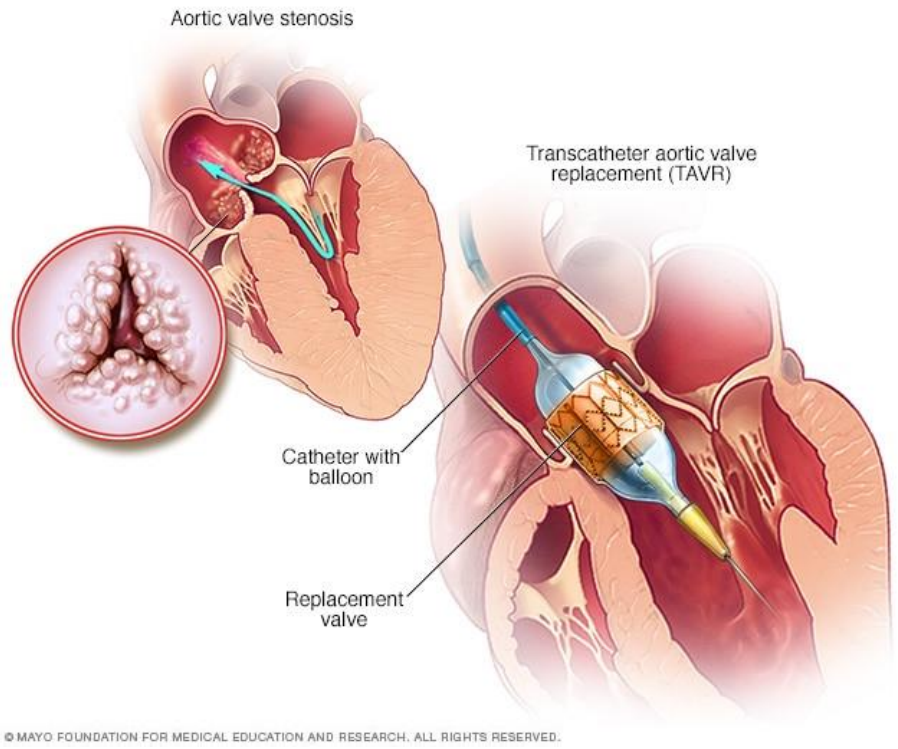

Figure 1.13: Illustration of TAVI valve insertion, *showing the collapsed TAVI valve being positioned within the diseased native valve and then expanded. Valves can be self-expanding or expanded using a balloon as shown in the image. Light blue arrow on upper image is showing the flow of blood though the left side of the heart. Reproduced from Mayo Clinic (81)*

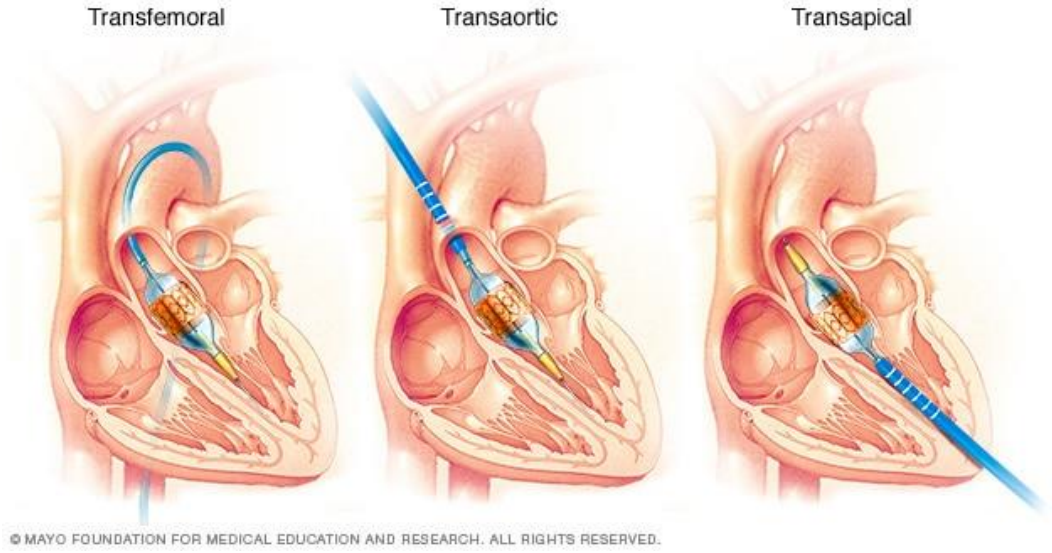

Figure 1.14: Alternative anatomical approaches used for TAVI. *Transfemoral approach involves feeding the catheter and collapsed valve from the femoral artery through the aorta and to the aortic valve. Transaortic approach the aorta is accessed through a puncture site. The approach for transapical is from the apex of the heart and the left atrium. Reproduced from Mayo Clinic (81).*

Trials have illustrated TAVI's superiority to medical treatment in inoperable patients, with the primary outcome of all-cause mortality at one year (82). The PARTNER 1 trial looked at the 5-year outcomes in the inoperable cohort of patients, which also concluded that TAVI had a positive effect on all-cause mortality at 5 years when compared to standard treatment ($p<0.001$)(83). Additionally, in patients classed as having a high surgical risk (guide STS score >10%), TAVI is non-inferior to AVR. Meaning that the upper limit of the one-sided 95% confidence interval for the between-group (AVR vs TAVI) difference in the primary outcome (1-year mortality) was within the limits of clinical equivalence (less than 7.5%) (79). Further, follow up confirmed clinically equivalent mortality rates between AVR and TAVR at 2 and 3 years. At 5 years risk of death was 67·8% in the TAVR group compared with 62·4% in the SAVR group (hazard ratio 1·04, 95% CI 0·86–1·24; p=0·76). Although rates of aortic regurgitation were higher in the TAVI group (14% vs 1%), in the TAVI group this was associated with increased risk of 5-year mortality (p=0.003) (84).

More recently the results of the SURTAVI trial have been presented, this study compared TAVI and AVR in patients with an intermediate operative risk and tried to replicate current clinical practice more closely by allowing surgeons to choose the bio-prosthesis type and size in those randomly allocated to the surgical group. Although most patients allocated to TAVI were treated with the Medtronic Corevalve (84%). This also demonstrated non-inferiority of TAVI to AVR when looking at a primary endpoint of death or disabling stroke at 24 months post-procedure via Bayesian analysis. The estimated incidence of any-cause death or disabling stroke at 24 months was 12.6% for the TAVI group and 14% for the AVR group, with a conditional probability of non-inferiority >0.999 (80). Bayesian analysis is conducted without the full data set available; it uses statistical inference to update the probability for the hypothesis. Therefore, this data is saying that it is very likely that TAVI will be shown to be non-inferior to AVR for the primary outcome, but it cannot say this for sure until all the data is available and analysed. This is a method to allow publication of studies in fast-moving fields as quickly as possible, but as SURTAVI reports such a high value of probability for non-inferiority it suggests that, in this case, the results are reliable.

Bekeredjian *et al* (2019) conducted a review of outcomes after AVR and TAVI in patients with low surgical risk. Data was collected from the German Aortic Valve

Registry, for all patients with an STS risk score <4%, undergoing AVR or TAVI in 2014/2015 (20,549 patients). Once adjusted to take into consideration that those who underwent TAVI were overall significantly older and with more co-morbidities, outcomes showed similar 1-year survival for TAVI and AVR (90.0% vs. 91.2%; P = 0.158) and higher in-hospital survival for TAVI patients (98.5% vs. 97.3%; P = 0.003)(85).

		PARTNER Trial		SURTAVI Trial	
		30-day (% of pts)	1 Year (% of pts)	30-day (% of pts)	1 year (% of pts)
Death	Any Cause	3.4	24.2	2.2	6.7
	Cardiac Cause	3.2	14.3	2.0	4.8
Stroke-like event	Transient Ischemic Attack	0.9	2.3	1.5	3.2
	Stroke - Minor	0.9	0.9	2.2	3.7
	Stoke - Major	3.8	5.1	1.2	2.2
Myocardial Infarction		0	0.4	0.9	2.0
Acute Kidney Injury		1.2[+]	3.9[+]	1.7	
Major Bleeding		9.3	14.7	12.2	
Endocarditis		0	0.6		
New Onset Atrial Fibrillation		8.6	12.1		

***Table 1.6: Adverse Events in the PARTNER and SURTAVI trials; TAVI** Group (79, 80) +Defined as creatinine >3mg/dl.*

Multiple studies have identified that the incidence of many adverse effects, including major bleeds and stroke, have been shown to be reduced in those treated with TAVI (86). Table 1.6 lists the incidences of key major adverse events in the TAVI treated population, as reported from the PARTNER and SURTAVI trials.

Additionally, in their meta-analysis of six studies (745 patients), Takagi *et al* found statistically significant reductions in the rates of moderate (p = 0.03), severe (p = 0.0003), and overall (p = 0.02) patient-prothesis mismatch (PPM) after TAVI relative to

AVR. They also investigated rates of late all-cause mortality after TAVI in patients with PPM versus patients without PPM. This meta-analysis gathered data from five studies (2,654 patients) and found no statistically significant differences in late mortality between patients with PPM and patients without PPM (p = 0.97) (87).

Although, studies have found TAVI to cause a higher rate of paravalvular leaks (88). A significant paravalvular leak is likely to put continued stress on the LV and the results of this need thorough investigation. Interestingly it was recently reported that a BMI in the overweight or obese categories (≥25kg/m^2) was associated with decreased 30-day and 1-year all-cause mortality post-TAVI (89, 90). The potential causation behind this needs further investigation but Abawi *et al* speculate that this may be related to fewer paravalvular leaks or increased energy reserves during the acute recovery phase(89). Although it is tempting to hypothesize that the difference in mortality is related to factors such as AVA, or vessel size it must be remembered that the association seen related to BMI opposed to body surface area ($\sqrt{[(height\ cm\ x\ weight\ kg) \div 3600]}$).

Historically the presence of a bicuspid AV would be considered a contraindication for TAVI. But emerging data, mainly from registries and observational studies, have shown that TAVI can be an effective and viable method for treating sAS in these patients(91). A recent meta-analysis of 13 observational studies containing data on 758 BAV patients showed a device success rate of 95% (95% CI 90.2% to 98.5%). Although even with newer devices there is still increased rates of paravalvular leaks and PPM post-TAVI, due to the bicuspid anatomy. The above meta-analysis identified a moderate to severe paravalvular leak in 12.2% [95% CI 3.1% to 24.8%] and new pacemaker implantation in 17.9% [95% CI 14.2% to 22%] at 30 days post-TAVI (91, 92).

The above studies focused on the direct clinical outcomes of TAVI vs AVR in the comparatively short term. Although these are promising for the use of TAVI in many patients there is still further research to be done. There are few studies looking at outcomes over longer time periods. As life expectancy goes up and TAVI is being offered as a treatment to younger patients with fewer co-morbidities this is of increasing importance. Additionally, there is a need for more research into the cardiac mechanics of severe AS and how these measures are affected by both AVR and TAVI. As cardiac mechanics are so closely tied to function a thorough understanding will shed light on the true impacts of these interventions. It is these cardiac mechanics,

such as longitudinal strain in multiple chambers, and LV rotation and short-axis strain, that this research will explore.

A study considering the cost-effectiveness of trans-femoral TAVI in Australian patients concluded that when considering the quality of life years gained TAVI was a cost-effective procedure for those deemed inoperable. For patients who were classified as high operative risk TAVI was still cost-effective, only if the cost of the device was less than in AVR (93). Although this was an Australian study which does have a higher overall health expenditure as % of GDP (OCED website, 2017) this still stands to demonstrate the positive cost-utility of TAVI. A smaller study conducted retrospectively comparing patients turned down for surgery prior to the availability of TAVI and the first 90 cases of TAVI conducted in South Wales (2009 onwards) reported an incremental cost-effectiveness ratio for TAVI of £10,533 per quality-adjusted life-year (94). This was only a small study so has limitations regarding generalisation but as it was conducted in the UK is it a useful source of data. Additionally; as the TAVI cases were performed were the first in the region it would be expected that as the expertise has improved so have the outcomes for TAVI, therefore potentially lowering the incremental cost. A further systematic review agreed that TAVI was more cost-effective than medical management in high risk symptomatic severe AS patients, while when compared to AVR the results were inconclusive (95). As stated in the studies, a substantial cost during TAVI is the device; and it would be reasonable to speculate that as the TAVI market expands and develops commercial competition will drive down the relative cost of the TAVI device. One of the aims of the UK TAVI study is to evaluate the cost-utility of TAVI in its cohort (12).

1.2 Echocardiography

Transthoracic two-dimensional echocardiography (TTE) was first demonstrated in the late 1950s and since then it has shown itself to be a safe, non-invasive technique with broad clinical utility. The technology of TTE has developed over the years and continues to do so; as can be seen with the recent increase in 3D TTE imaging (96). TTE is more economical and widely available than alternative methods of imaging, such as cardiac MRI or CT. Although the key limitations of echo are its image quality being

dependent on external factors. This includes patient factors such as body habitus and ability to co-operate with instructions and position themselves appropriately. Also the training and expertise of professional performing the scan (97). Both the British and American societies of Echocardiography have structured training problems and accreditation schemes for both individuals and departments performing TTE scans.

1.2.1 Physics of Echocardiography

Echocardiography is a form of ultrasound imaging. Ultrasound waves travel through mediums and are reflected, by detecting the returning waves an image can be constructed. By definition; ultrasound is a form of a sound wave with a frequency (Hz) that is too high to be heard by the human ear (>20kHz), although in TTE the range of wavelengths used is much higher, in the region of 1-8 MHz. Ultrasound waves are diagnostically useful as they can be directed and focused, and because of the short wavelength targets of small size will still reflect US waves and therefore are detected.

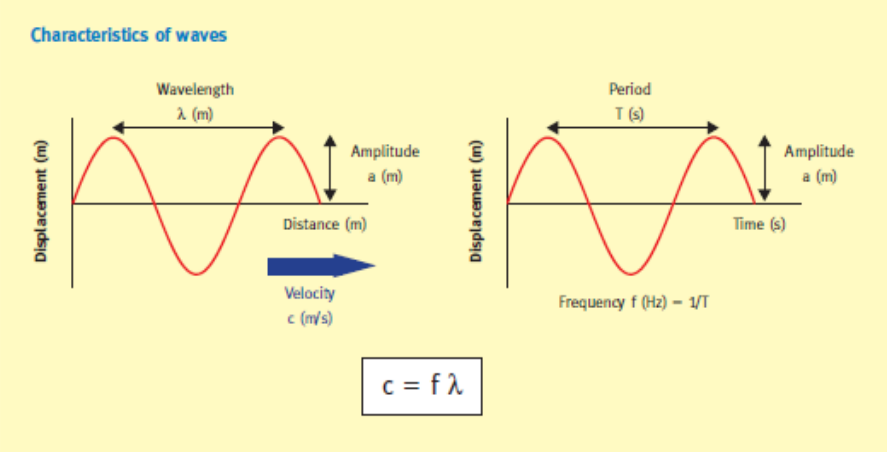

Figure 1.15: The characteristics of an US wave. *Showing frequency, wavelength, and velocity, and the interaction between them. Wavelength and frequency are inversely related, and their product is the velocity of the US wave (99).*

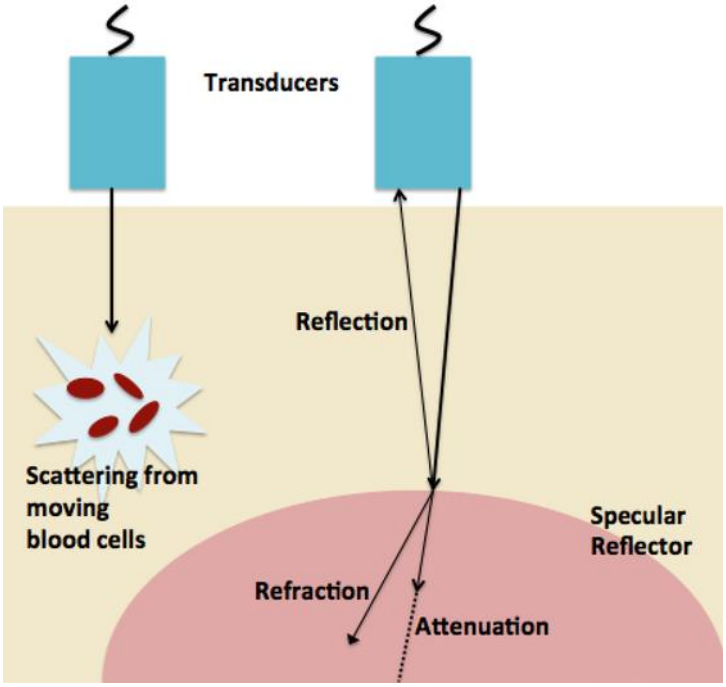

Figure 1.16: Interaction of US waves with surface interfaces: reflection, refraction, and scattering*. As a beam of US waves encounter an interface (any physiology where there is a change in density), some the waves will be reflected, while others will continue but at a refracted angle. There will also be some attenuation of the US waves. It is the combination of the reflected waves and backscatter that is used to generate the US image (100).*

Wavelength and frequency are inversely related (figure 1.15), and their product is the velocity of the wave. This is known as the propagation speed. Propagation speed is constant in any given medium and is subject to the properties of the tissue. Within soft tissue, it can be assumed that the velocity of the US wave is 1.54m/msec. (98). Increasing in less compressible tissues (i.e. bone) and decreasing in more compressible tissues. Ultrasound waves are very poorly conducted through gas, this needs to be taken into consideration and the effects minimised, especially in echocardiography where you are imaging the thoracic cavity. As the US beam hits an interface between two tissues of differing density some waves will continue through at a refracted angle and some will reflect (figure 1.16). The angle of incidence, the surface area of the interface, whether it is a smooth or rough surface, and the impedance mismatch all influences the dissemination of the US beam. If the interface between the two tissues is large and smooth, then there is a large amount of specular reflection (99, 100). This is where the US beam returns towards the source with a direction angle equal to the angle of incidence.

Where there is a small rough interface, which occurs when the US waves interact with anatomy of comparable size, there is a large amount of backscatter. Scatter reflections allow the generation of an image of the structures that are being examined. A higher mismatch between tissues enhances reflection and lower mismatch enhances transmission, therefore; the amplitude of the reflected wave gives information regarding the nature of the tissue interface it has experienced. Assuming a given velocity, the time taken for the wave to return will provide the depth of the interface.

Due to absorption and reflection, the US wave attenuates as it travels through tissue. Attenuation is greater with a higher frequency. In soft tissue, it is assumed the attenuation co-efficient, the rate at which the US waves attenuate, is a constant 0.5 dB/cm/MHz During images formation the US must travel to and from the region of interest which doubles the attention to 1dB/cm/MHz.

The transducers used in US function based on the piezoelectric effect. Every transducer contains a piezoelectric element; this generates US waves because of electricity induced deformation, and conversely generates electricity as a result of the deformation induced by the returning US waves (98). Waves are emitted in pulses, typically with a pulse every 1ms, giving a pulse repetition rate of 100 pulses/second. The transducer is transmitting pulses 1% of the time and receiving returning waves 99% of the time while scanning (99).

1.2.2 Standard Echocardiographic views

The British Society of Echocardiography has realised guidelines to specify the minimum dataset that should be acquired as to ensure a comprehensive echo exam. An exam can be broken down into some key views; each of which shows different compositions of the cardiac chamber and walls.

To acquire parasternal and apical images the patient should be positioned in the left lateral decubitus position. The Parasternal Long Axis is acquired by placing the probe on the patient's chest in the fourth intercostal space; this can be adjusted as needed depending on individual anatomy and acoustic windows. The transducer and beam of US are aimed towards the spine with the plane running between the left costal arch and the axilla. The image acquired is a longitudinal cross-section of the heart. The right ventricle is closest to the probe, with the left heart behind, so the resulting image shows the right ventricle at the top of the screen, as seen in Figure 1.17.1 (101).

The Parasternal short axis view can be visualised by rotating the transducer 90° clockwise so that the imaging plane runs right costal arch to left costal arch. This view shows a cross-section of the heart. If still in the fourth intercostal space the imaging plane should cut through the heart at the level of the aortic valve. Care must be taken to rotate the transducer exactly in the parasternal window as to avoid superimposing

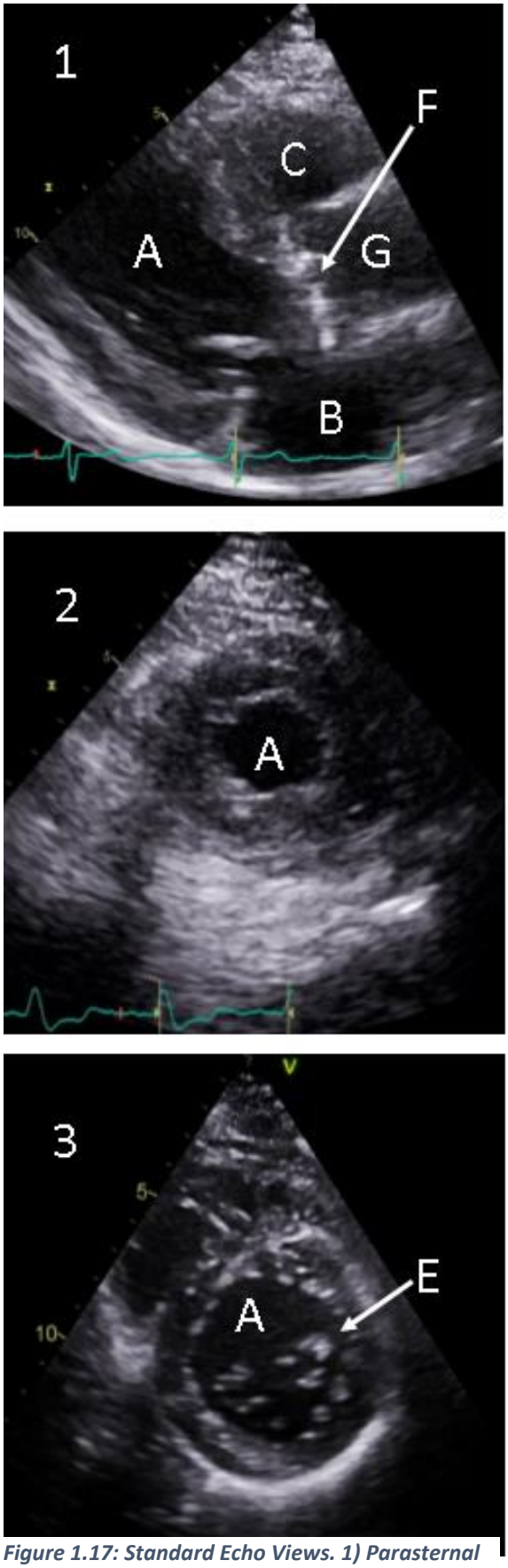

Figure 1.17: Standard Echo Views. 1) Parasternal Long Axis (PLAX) 2) Parasternal Short Axis (PSAX) Apical level, 3) PSAX Mitral valve level. *A= Left Ventricle. B= Left Atrium. C= Right Ventricle, E= Mitral valve leaflets. F= Aortic Valve. G= Aorta.*

lung tissue onto the resulting imaging. To image the mitral valve the transducer should be tilted caudate (towards the right shoulder). Further tilting will move the imaging plane down the LV. Landmarks such as the chordae tendons and papillary muscles guide the positioning of the transducer as seen in figure's 1.17.2 and 1.17.3.

The apical views are obtained by placing the transducer over the location of the apical pulse, normally the 5th intercostal space on the left of the chest and aiming the transducer towards the right shoulder. This imaging plane will run between the left shoulder blade and the right costal arch. The resulting image will show all four main chambers visualised from the apex, the ventricles appearing at the top of the screen and the atria below, right heart on the left of the image and the left heart on the right (101). The apical four-chamber (Ap4Ch) shows the inter-ventricular septum and the lateral wall of the LV (Figure 1.18.1).

By rotating the transducer 60^{o} anti-clockwise the apical 2 chamber (Ap2Ch) view is acquired (Figure 1.19.2). This shows just the left heart. In the LV, the anterior and inferior walls are seen. An additional 60^{o} anti-clockwise rotation will show the apical 3 chamber (Ap3Ch, also known as the apical long-axis) view (Figure 1.18.3). In addition to the LV and atrium, the aortic valve and outflow tract can be seen. In the Ap3Ch view, the anteroseptal and posterior walls of the LV are imaged (101).

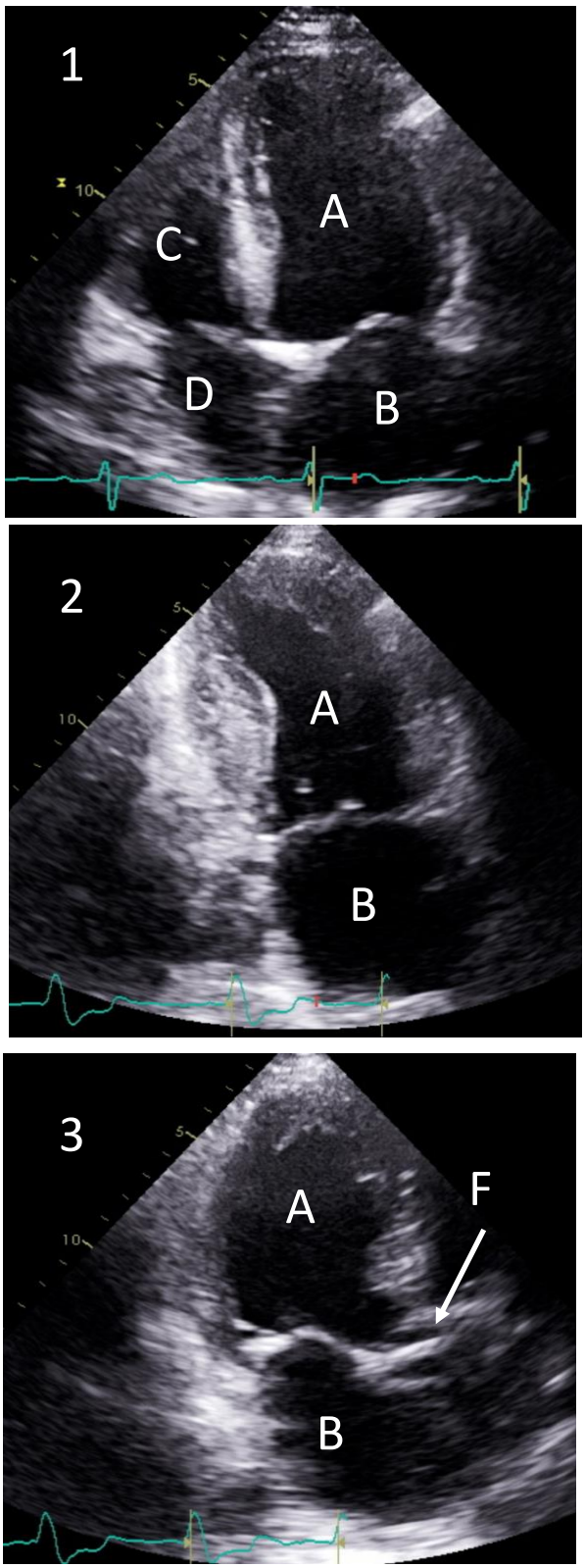

Figure 1.18:Standard Apical Echo Views. 1) 4Chamber view, 2) 2Chamber view, 3) 3Chamber/Apical Long Axis view*. A= Left Ventricle. B=Left Atrium. C= Right Ventricle. D= Right Atrium. F= Aortic Valve*

In a comprehensive examination, the patient would also be examined from the suprasternal and subcostal views.

When performing a TTE, it is important to optimise the image, this includes adjusting the gain, depth and resolution of the image, as well as avoiding artefact (noise) on the image. These factors often need to be balanced in clinical practice. Typically, only 1% of the signal is reflected at any given tissue interface, and as stated above the wave attenuates as it travels through the tissue, in order to detect the returning signal, the US machine amplifies the returning valves using time gain compensation (TGC). TGC is an exponential gain increase after the wave is emitted, resulting in a constant output signal irrespective of the interface depth. If the field of depth is too shallow then the target will not be observed, but if it is too deep the targeted anatomy will be small within the image and hard to assess. The other component to setting an appropriate field of depth is wavelength; objects smaller than the wavelength can not be visualised, but a smaller wavelength leads to a higher frequency and therefore higher rates of attenuation (99). Resolution of the image can be further broken down into temporal resolution (frames per second) and spatial resolution (pixel density). The appropriate balance of temporal resolution, spatial resolution and width of the imaging beam depends on the structure being analysed and outputs being measured. Lowering the spatial resolution can increase the artefactual nature of the image as two adjacent structures have an increased danger of being visualised as one (102).

1.2.3 Speckle Tracking Echocardiography

Speckle Tracking Echocardiography (STE) is an angle independent method of assessing myocardial strain using two-dimensional echo images. Analysis is conducted offline after image acquisition using specialised software. The myocardium is traced, taking care not to include the pericardium or any papillary muscle. This is known as the region of interest (ROI). Within the ROI the image is broken down into clusters of pixels, known as 'speckles'; each containing of a collection of greyscale pixels which together give each speckle a unique fingerprint and so it can be used as an acoustic marker. STE assesses myocardial movement and deformation throughout the cardiac cycle by tracking these speckles (See Figure1. 19).

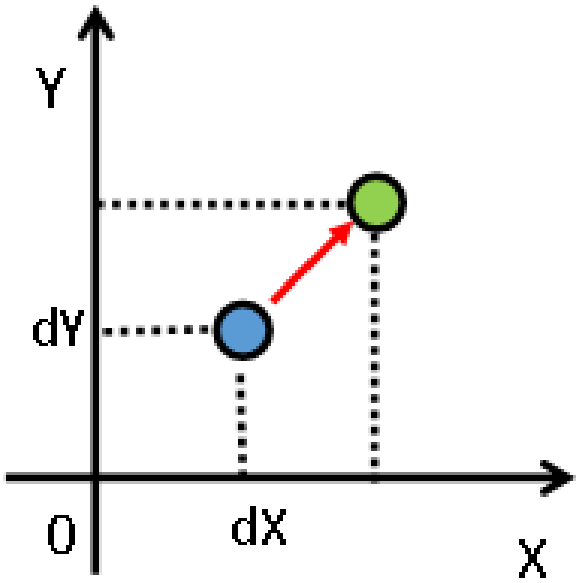

Figure 1.19: Illustration of Speckle Tracking Echocardiography showing a speckle moving from its original location to new location on a 2D axis. *STE software tracks the speckle throughout the cycle and using a sum of differences algorithm calculates the deformation of the myocardium. Author generated image.*

Each speckle is traced through the cardiac cycle and using a sum of differences algorithm Lagrangian strain is calculated, with the end-diastolic frame as the reference point. Twist through the cardiac cycle can also be calculated using STE software. STE has been validated against tagged MRI in human subjects, demonstrating good correlation and agreement of measurements (103, 104). Over recent years STE has been used increasingly in cardiovascular research, and GLS is starting to be used in clinical settings as an additional indicator of LV function. This has worked to validate

further its value as a reliable, non-invasive, and cost-efficient method to calculate myocardial strain. Increased image quality has a positive impact on the reliability of both LVEF and STE strain measurements (105), this will be reflected in the inclusion criteria of this study.

STE has an advantage over tissue doppler analysis of strain because it is angle independent. Tissue doppler strain measurements are dependent on the angle of imaging, therefore to have acceptably accurate strain data the angle deviation of the wave beam from the myocardial wall must be no more than 15-20^{o} (106), meaning that TDI is subject to high interobserver variability. Additionally, because TDI is a one-dimensional method of assessing strain (simplifying the 3D movement of the myocardium) it is prone to error as the myocardium moves out of the plane of imaging during the cardiac cycles. As STE is based on 2D images it can differentiate between myocardial segmental deformation and passive displacement due to neighbouring segments deforming (104). Although it is worth noting that STE is limited in its assessment of strain rate due to the relatively low frame rates used; the temporal resolution is sacrificed for spatial resolution to insure the pixel density is suitable for STE (98).

1.3 Echocardiographic Core Labs

1.3.1 The development and value of ECL's

Transthoracic echocardiography is a highly valuable imaging modality; both clinically and in research. It is non-invasive, versatile, portable, cost-efficient, and can be used for serial monitoring. Although it does have potential limitations associated with the fact that TTE image quality is both patient and operator dependent. Furthermore, there is potential for variation in the analysis of the images, especially if image quality is sub-optimal and the myocardial border unclear(107).

To aid high-quality imaging-based outcomes within a clinical trial it is key that variability of image acquisition and analysis is kept to a minimum. The ECL will receive all the transthoracic echocardiogram's (TTE's) taken as part of the trial, at the specified time points, and conduct the pre-specified analysis. Therefore, ECL's provide a key role

in multi-centre trials by aiming to provide a high level of reliability, consistency, and expertise in the subsequent analysis of data (108-110).

When comparing the assessment of LV dimensions and function post myocardial infarction by local investigators and an ECL Hole *et al* (2002) concluded that the core lab produced measurements that had prognostic value for subsequent clinical endpoints, but the measurements taken by local investigators did not (111). This was due to a larger variation in LV volume measurements due to myocardial border tracking, and occurred despite the core lab staff training the local investigators on the correct measurement technique. It is worth noting though, that this subjects for this study were recruited in 1995-1997, and the quality of TTE images has improved over the last 20 years, which should reduce the uncertainty regarding the positioning of the myocardial border. The addition of an ECL also allows the increased quality of image acquisition via the production of image acquisition guidelines at the beginning of the trial and auditing of image quality being received. Although the ECL cannot eradicate all variables, advocates of the ECL concept believe they can reduce random error (112, 113).

Clear communication between the ECL and the trial sites is crucial for successful research, and if the role of the ECL is not fully explained at the onset of the trial it may lead to confusion among trial sites about the reasoning and value of using an ECL(114). Additionally, as core labs are often located in a different place to the main trial office there can be miss-communication at several levels, which serves to compromise the data being submitted for image review.

1.3.2 Current Guidelines for ECL's.

To facilitate the use of ECL's within clinical trials the American Society of Echocardiography produced an expert consensus document on the topic (114). This guidance has become a key resource when developing a robust ECL. For example, the work outlines the roles of an ECL dependant on the requirements of the trial, image handling and data management. Although, it must be remembered that these guidelines are a consensus document based largely expert opinion, and were written primarily for US trials, which are likely to have some fundamental differences in

structure and staffing levels and roles compared to UK based trials. Many trials in the US are industry-sponsored and of a larger scale. The increased budget and size of these trials often equates to increased staffing and the procurement of the most specific and up to date equipment and information technology support. Information technology within the NHS is compromised due to firewall requirements relating to information governance, privacy and confidentiality. As such, NHS based ECL's do not always have the infrastructure available to employ the most advanced and up-to-date methods seen in the large ECL's within the USA. An example is the difficulties in using cloud-based storage and transfer echocardiographic images to dedicated NHS servers.

Therefore, guidelines that have been written for US-based ECL's make assumptions that are not true within the UK ECL environment and cannot be adequately applied to UK trials, and NHS trial sites.

1.3.3 Surveys within Clinical Trials.

A survey, of which both in-person interviews and questionnaires are types, collect information from a sample of the target population and can be used to measure behaviours and attitudes. As respondents are often asked to report on events in the past in addition to current behaviour/opinions, surveys are generally a retrospective data collection method(115). Cross-sectional studies are those that collect data from the population of interest at one point in time, whereas longitudinal studies are conducted at multiple points in time and aim to investigate cause and effect.

Questionnaires are a frequently used tool in healthcare research, especially to gather options and experiences, they have the potential to provide a wealth of useful and objective information but must be designed and implemented appropriately. A questionnaire must be valid; measuring what it claims to measure, and reliable; producing consistent results, where variation in responses is due to differences in participants not a misinterpretation of the questions or participant response(116). Validity can be broken down into internal and external validity. Internal validity is the degree of confidence the researcher has that there is a causal relationship between the variables being investigated. Whereas external validity relates to the ability to generalise the results of the survey(117).To ensure validity and reliability it is key to

conduct preliminary research, engage with focus groups and pilot the survey. A common criticism of surveys, especially those that are cross-sectional, is that because of the retrospective nature they are prone to recall bias(115) and this must be considered during the analysis of the data and application of the outcomes.

Questionnaires can be structured, semi-structured, or unstructured. The advantage of structured questionnaires, where there are fixed standardised questions, is that the data produced can be analysed quantitatively with relative ease. The disadvantage is that pre-coded responses choices may force respondents to choose an answer that doesn't truly represent their views/experiences. This can be minimised by careful wording and thorough development of the questionnaire.

Telephone interviews have been established as comparable to in-person interviews in multiple studies and of significant less cost enabling greater reach(118, 119), though many of these studies are dated as telephone interviews have become an accepted methodology in recent decades. There are key differences which must be considered when conducting telephone interviews; particularly relevant in this study was the lack of visual aids; such as the image acquisition guidelines(120). Additionally, there is the factor that there may be a different sample that responds to a telephone interview(120). This study opted to perform telephone interviews as it was seen to create less burden on the respondent, it was hoped that this would encourage greater participation. An interview, whether in person or over the telephone, should still be structured, meaning that if it were to be repeated the results would be comparable. Interviews can contain a combination of 'open' and 'closed' questions. Closed questions will have limited and pre-coded responses, whereas open-ended questions allow the respondent to reply in their own words. The wording of questions will affect the responses received; therefore, it is important that all questions are carefully and consistently worded to ensure reproducibility of the results. The interviewer must not change the wording of the question and this may change the meaning or introduce unintentional bias through leading questions. Although it may be appropriate to ask follow-up questions to ensure that the respondent's answer is complete. Interviewees answers should be recorded verbatim(115).

1.4.4 Reproducibility Testing within a research environment.

Due to the nature of TTE and the analysis methods used, there is inherent variability in measurements taken. This is likely to increase as image quality reduces as there is a greater risk of analyst error such as mistaking the location of the myocardial border, or other cardiac features (figure 8.1). ECL's have been demonstrated to be an effective method of minimising this variability; via the production of image acquisition guidelines, the use of a small group of experienced analysts, and through training (108, 109).

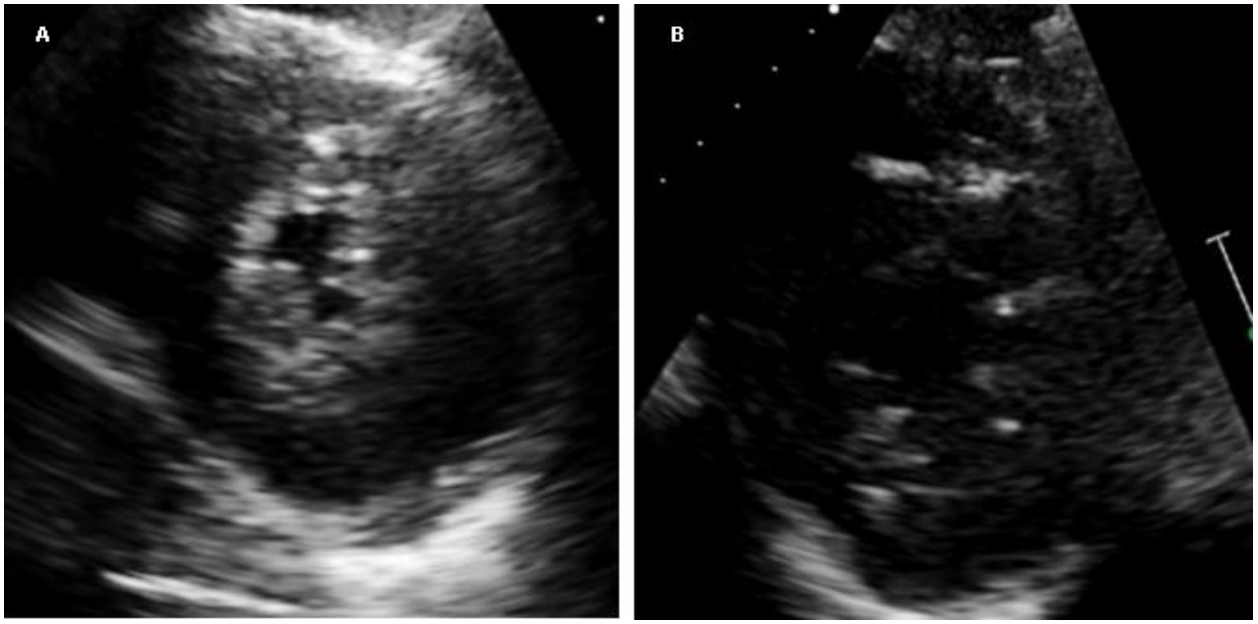

Figure 1.20: Example of good (A) and poor (B) image quality TTE images*. Good quality images contain all the myocardium in the centre of the field with clear myocardial borders. The myocardium in image B is hard to identify and the outer edge moves out of the field of version during diastole.*

Variability; both between different analysts (inter-) and between the same analyst over time (intra-), is a key quality measure. This can be assessed for continuous measures by calculating the ICC, which measures the relative similarity of datasets that share the same units of sampling and measurement process(121). Previous studies have shown encouraging values for ICC within an ECL (108, 113). As expected, Baur et al (109) found that inter-analyst variability was much greater than intra-analyst variability. This is likely due to individual judgements regarding the precise position and thickness of the myocardial wall and supports the use of a small, experienced, ECL team when

conducting research. To ensure that all analysis is being conducted to the optimal level it is recommended that training is ongoing and that ECL's maintain regular variability testing, both inter- and intra- analyst, throughout the trial. This helps the identification and resolution of any inconsistencies. The ECL used in the PARTNER trial classified an acceptable variation of biplane LVEF, within and between analysts, as ≤10%. Variation in aortic valve gradients was acceptable ≤10mmHg, and ≤0.3cm^2 for aortic valve area(108) (Table 8.1). The publication does not state a methodology for how these parameters were decided. Intraclass Correlation (ICC) values between two variables is classified as poor reliability when below 0.5. Values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability and values greater than 0.90 indicate excellent reliability. Although it must be noted that ICC values can be affected by multiple factors, including sample size and the number of analysts being compared(122).

Measurement	Acceptable Intra- and Inter- Analyst Difference.
LVEF (Biplane)	≤10%
Aortic Valve Gradient (Mean and Peak)	≤10mmHg
Aortic Valve area	≤0.3cm^2

Table 8.1: Acceptable Levels of Intra- and Inter-Analyst variation as specified in Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial *(2013).*

1.3 Aims and Objectives

1.3.1. Academic Aims

1. To conduct a detailed assessment of echocardiographic cardiac mechanical and functional characteristics prior to and post Aortic Valve Replacement or Transcatheter Aortic Valve Insertion, in patients who are intermediate or high operative risk with documented severe AS; providing novel evidence regarding the use of TAVI as a first-line intervention.
2. To conduct a thorough evaluation of the reliability of analysis in an Echocardiographic Core Lab (ECL) and the factors that impact on the reliability of data.

1.3.2 Objectives:

1. To measure determinates of cardiac mechanics and function pre-intervention, 6 weeks post and 12 months post-intervention using STE.
2. To assess for statistically significant changes in cardiac mechanical and functional parameters at baseline and post-intervention together with statistically significant differences in the rate of change.
3. To critically compare the two groups, testing for non-inferiority of TAVI compared to AVR in patients with intermediate or high risk operable severe AS.
4. To implement and oversee inter- and intra-analyst reliability testing within an ECL.
5. To survey staff at study sites to understand their views and understanding of the role of the ECL. To explore areas for improvement in the setup and function of an ECL.

Chapter 2 - General Materials and Methods

2.1 Study Design

This study was a sub-study with a longitudinal design, analysing transthoracic echocardiograms (TEE's), conducted in the UK TAVI trial. The UK TAVI trial is a two-arm RCT with 33 active sites across the UK. The patient population had a clinical and cardiac imaging diagnosis of severe symptomatic Aortic Stenosis (AS) needing intervention. All patients were deemed of high or intermediate surgical risk, and suitable for either of the trial interventions by a multi-disciplinary team at their site. It is expected that most enrolled will have an STS score (The Society of Thoracic Surgeons Adult Cardiac Surgery Risk Score) of 4-12%, although the UK TAVI trial did not treat these as strict thresholds and the patients could be included if the MDT felt there was clinical equipoise between the two interventions (AVR and TAVI). Features taken into account when assessing operative risk included clinician assessed frailty, chronic pulmonary disease, previous cardiac surgery, extracardiac arteriopathy (disease of the arteries), neurological dysfunction, impaired renal function, impaired LV function, diabetes mellitus, pulmonary hypertension, and low BMI(12).

Patient randomisation to treatment arm was stratified by site as to minimise bias. The two treatment arms were traditional aortic valve replacement surgery (AVR) or transcatheter aortic valve insertion (TAVI). Severe AS was diagnosed by each centre, guidelines state that for AS to be classified as severe the iAVA (AVA indexed to body surface area) should be $<0.6cm^2$ and the mean gradient across the value >40mmHg(123). Low flow patients were included, these patients have severe AS but with reduced flow across the value and/or without the increased aortic gradient seen in a classic presentation of AS.

This study used the echocardiographic images acquired during the UK TAVI trial and analysed them for measures of cardiac function and mechanics. This analysis was conducted blinded to the intervention, this longitudinal study used images that were collected before the intervention, 6-weeks after intervention (6W) and 12 months after intervention (12M). The echocardiographic scans for 142 patients, from 24 of the UK TAVI sites, were analysed for the primary outcome of change in LV GLS from

baseline to 12M. The subjects were selected from those deemed to have suitable echocardiographic images available for analysis of the primary outcome at baseline and 12-months post-intervention as determined by the below inclusion criteria. From this cohort of 142 participants, TTE scans were assessed for suitability of the images for the assessment of each of the secondary outcomes, and measurements were taken where image quality allowed.

2.2 Patient Selection and recruitment

Potential participants for the UK TAVI trial were identified by clinical teams within the trial sites, patients aged >70 years being referred for intervention for severe AS were identified. Those between 70-80 years who are known to have an increased operative risk and patients older >80 years (regardless of the presence of additional factors as advanced age is a predictor of operative risk) are eligible to be referred to the multi-disciplinary team (MDT) for review (12).

The role of the MDT was to review the clinical data for each patient case and reach an agreement regarding the predicted risk/benefit ratio of both TAVI and conventional AVR. The Logistic EuroSCORE and STS scores, which quantify surgical risk, could be used as guidance as required but the UK TAVI did not specify cut off values for these scores. Although the precise format of the MDT varied from site to site, all would typically contain cardiac surgeons, interventional cardiologists, and experts in cardiac imaging. The MDT were required to assess the following questions;

- Does the patient have severe symptomatic aortic stenosis, and would they benefit from intervention to relieve the stenosis?
- Is conventional surgical AVR clinically appropriate and technically feasible?
- Is the operative risk increased to the extent that, in the current state of knowledge, it is reasonable to consider TAVI as an alternative?
- Is TAVI technically feasible (based on an anatomical assessment) with locally available technologies?
- Is there collective equipoise regarding the relative merits of surgical AVR and TAVI? (12)

If, after consideration of these questions, the MDT concluded that both AVR and TAVI were feasible, comparable in risk/benefit ratio, and met the below inclusion/exclusion criteria, then the patient was eligible to the UK TAVI trial.

Prior to enrolling in the trial, each patient completed informed consent. The patient information leaflet was presented to the patient, detailing the study and the requirements for enrolling in the study, and the use of their data. The patient was allowed as much time as they wish, but no less than 24 hours to consider participation. Written informed consent was then obtained. The person to obtain the consent was required to be suitably qualified and experienced and have the authorisation of the site principal investigator. If informed consent was obtained by someone other than the principal investigator, the principal investigator or a senior clinical co-investigator was required to co-sign the consent. As part of the informed consent, all subjects were assured that they were able to withdraw at any point of the study without affecting the quality of their clinical care (124).

2.2.1 Inclusion and Exclusion criteria for UK TAVI.

The inclusion and exclusion criteria for the UK TAVI trial are listed below. All images for this study were selected from those submitted as part of the UK TAVI trial, and therefore all subjects met these criteria (12).

Inclusion criteria

- Severe symptomatic aortic stenosis referred for intervention
- Age ≥ 80 years OR Age ≥ 70 years with intermediate or high operative risk from conventional AVR. (As determined by the MDT)
- Both conventional AVR and TAVI deemed to be acceptable treatment options.
- Participant is able and willing to give informed consent.
- Participant able (in the investigator's opinion) and willing to comply with all study requirements.

Exclusion Criteria

- Intervention deemed inappropriate due to co-morbidity or frailty.
- Life expectancy less than one year due to co-morbidity.

- Previous AVR or TAVI
- Technically unsuitable for either AVR or TAVI.
- Concomitant CAD requiring revascularisation for which only surgery is considered appropriate.
- Predominant AR.

Coronary artery disease (CAD) itself was not automatically an exclusion criterion; only if it was deemed that surgical treatment was the only appropriate treatment. When assessing a potential subject, the MDT assessed and recorded the extent of any CAD; classifying patients according to whether any major vessel had greater than a 50% stenosis. In those with significant CAD, the MDT considered the fitting treatment approach; if the patient had CAD that did not require treatment or could rationally be treated either by coronary artery bypass graft or percutaneous transluminal coronary angioplasty, the patient was still eligible for the UK TAVI trial.

Further to the above this study also had the following inclusion criteria relating to the echocardiographic images used.

- TTE images must have been saved in a raw DICOM file format to allow analysis.
- The images must be of good quality with a frame rate of 40-90 Hz.
    - Clearly defined myocardial border.
    - No significant artefact on areas of analysis.
    - The whole chamber in view throughout the cardiac cycle.
- The Apical 4,2,3 chamber views must all be present and on-axis, meaning that the angle of interaction between the US waves and the cardiac anatomy was sufficient to show the desired view.
- All scans had been performed on the same brand of machine.

The limitations regarding frame rates for the TTE images were due to the high spatial resolution requirements for speckle tracking echocardiography (STE) analysis. A high spatial resolution limits the temporal resolution possible when acquiring images. Although it was important that the frame rate was not below 40Hz so that the speckles could be effectively tracked from frame to frame.

The quality of images and images being on-axis were assessed visually by the analyst. The primary outcome of the study was; change in GLS from baseline to 12-months

post-intervention, therefore both the baseline scan and 12-month scan were required to meet the above standards for the subject to be included in the analysis. The 6-week post-intervention scan was also analysed if it met the requirements (n=92).

2.3 Sample size

821 subject records were reviewed, figure 2.1 illustrates the review process conducted to reach the final sample size of 142. Firstly, the availability of the DVD containing the images was confirmed; for 262 subjects the baseline and/or 12M TTE scan had not been received from the site. The disks for 33 subjects would not load or when loaded were blank. Along with 8 subjects whose scans had been performed on multiple brands of TTE machine, 3 subjects where trans-oesophageal echocardiograms had been performed, and 1 subject where the intervention was abandoned. Where the disk for the subject was unable to load, or when loaded was blank, the site was contacted to ask them to resend a copy of the images, the above numbers reflect those who did not send a replacement disk, or the replacement disk also did not load correctly. Scans images for 512 subjects were reviewed. Of these 142 subjects had both baseline and 12-month scans that were the correct format and suitable image quality to analyse. The percentage of reviewed subjects that were able to be analysed varied by site; the mean was 18%, with a maximum of 80% and nine sites where none of the subjects had a subject with a data set that was able to be analysed.

Since images for this study were taken from the cohort of participants enrolled in the UK TAVI trial, and the further reduction in available scans due to the inclusion criteria for this study, the sample size was determined by the number of UK TAVI participants with appropriate TTE scans available. Therefore, a power calculation was not deemed appropriate. The design of this study, where a subject's scans were not analysed until both the baseline and 12M scans had been received and deemed to meet the inclusion criteria meant there was no reduction in sample size between the time points. When conducting a non-inferiority trial, the burden of proof is on the hypothesis of non-inferiority; in this case, that the recovery of GLS after TAVI is not less than recovery after AVR. If the evidence is not strong enough then non-inferiority cannot be ruled out.

2.4 Data collection and record-keeping

All disks containing TTE images were anonymised before being sent to the UK TAVI echocardiographic core lab; the images were identifiable only by subject ID and study timepoint. Data (numerical) were entered into a custom-built database on a password-controlled computer and backups kept off-site. All disks were kept on-site at the location of the UK TAVI imaging core lab, in a filing cabinet with restricted access.

The study database was built with expected ranges. If a figure was entered that was outside of the expected range, it was automatically flagged. This is was then reviewed for measurement and input errors. The database was arranged so measurements were split up according to the view in which they were measured for each scan analysed.

2.5 Analyses of Images

Images were acquired at the dedicated study visits using a commercially available ultrasound machine, according to UK TAVI trial guidelines. Patient lay in left lateral position and images were acquired by an experienced and accredited cardiac sonographer. It was requested to record a minimum of three cardiac cycles for each view if the patient was in sinus rhythm or five cycles if the patient was in atrial fibrillation.

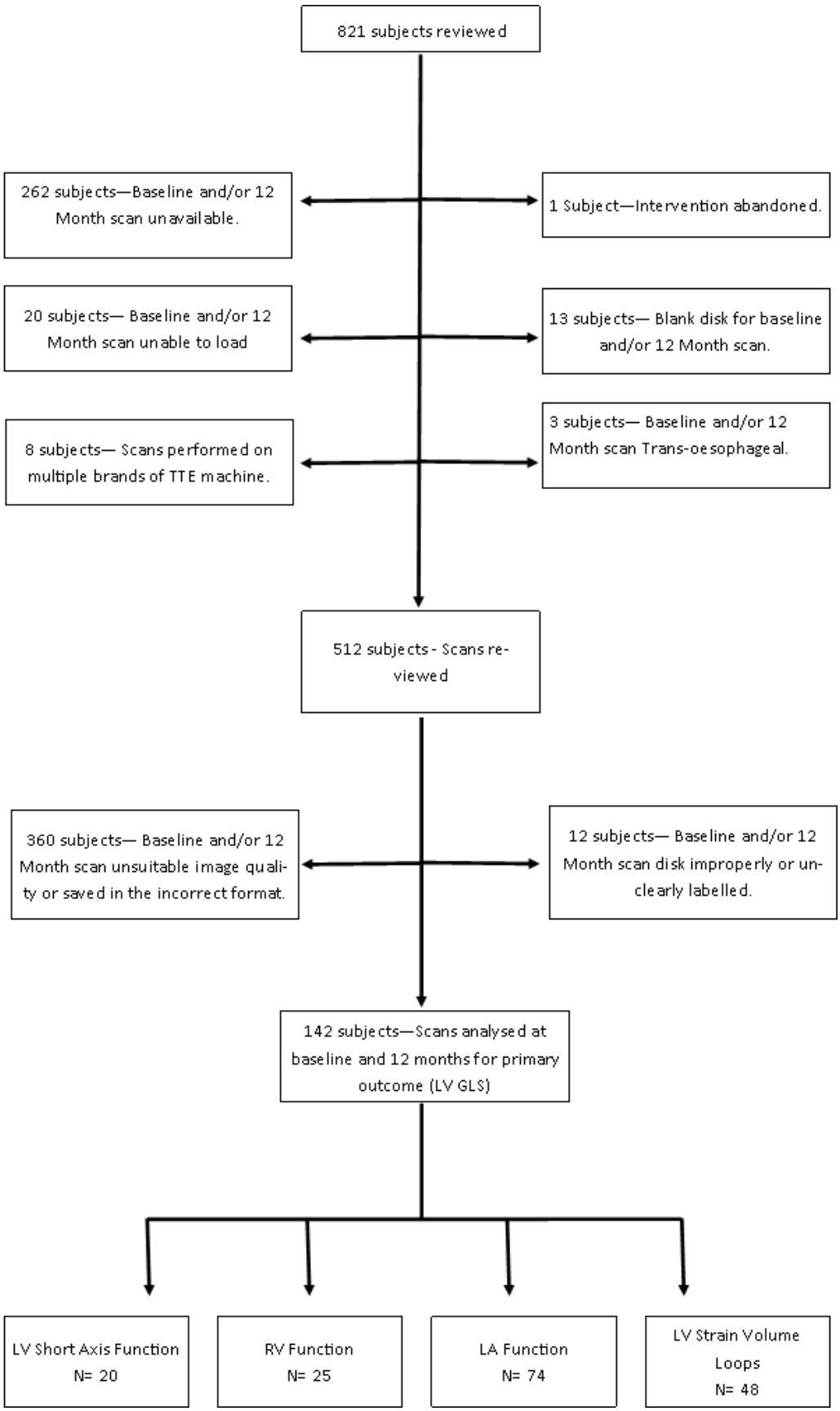

Figure 2.1: Chart of subject selection. *Scan records for 821 subjects were reviewed but only 142 subjects had available scans of suitable format and quality to analyse for the primary outcome The scans for 142 subjects were assessed for suitability to assess secondary trial outcomes. * Site contacted to request a new disk but did not or the new disk had the same issue.*

Analysis of these images using STE and 2D measurements was performed for this study, this was completed offline using TomTec software (TomTec Imaging Systems, Germany, Version 4.6). All measurements were taken blinded to the arm of the study. Measurements were taken by the main researcher and the outcome data was recorded on a secure database. Five percent of studies were randomly allocated to be reviewed by a second analyst to test for variance in the recorded measurements.

2.5.1 Primary Outcome Measure – Global Longitudinal Strain

The primary outcome was to compare the change in Global Longitudinal Strain (GLS) from baseline to 12 months for the two interventions (AVR and TAVI) to test for the non-inferiority of TAVI. GLS is a measure of longitudinal deformation in the left ventricle (LV) (See Chapter 1.4.1). Secondary outcomes included analysis of the rate of change of GLS; comparing changes seen at the 6-weeks and 12-months post time points in each of the two treatment arms.

GLS was assessed at each available time point by speckle tracking echocardiography (STE) using commercially available software (TomTec Imaging Systems, Germany). STE is an echocardiographic based method that works by tracking acoustic markers through-out the cardiac cycle (see Chapter 1.2.3), which has been validated against cardiac MRI and shown to be a reliable way to measure GLS. Apical views were selected from each trial TTE. The longitudinal strain was measured in the apical 4 chamber, apical 2 chamber and apical long-axis (also known as apical 3 chamber) views. To measure peak longitudinal strain (PLS) in each of the apical views, firstly a well visualised, stable R-R interval was chosen, excluding ectopic beats and those beats immediately prior or post. Using the images, and an accompanying ECG where available, the recorded loop was characterised, marking each R wave and the end-systolic and diastolic points of the cardiac cycle in the chosen R-R cycle. The recorded loop was shortened if required to show 3 beats if the subject was in sinus rhythm, or 5 beats if there were any ectopic beats or other signs of an irregular rhythm (Figure 2.2a, 2.3a, 2.4a). The inner edge of the myocardium was then traced to identify the 'region of interest' (ROI) at end-diastole (Figure2.2b, 3.3b, 3.4b). The option to track both the subendocardium and mid-myocardium was selected, and the width of the ROI

adjusted (Figures 2.2c, 2.3c, 2.4c). The ROI included all the myocardium but not the pericardium or papillary muscles. The ROI was then adjusted at the identified point of end-systole (Figures 2.2d, 2.3d, 2.4d). Once the ROI was confirmed the software then automatically tracked the ROI, and the speckles it consisted of, through the cardiac cycle. This tracing was then reviewed to ensure it was accurate and the ROI adjusted if necessary. Once the trace was tracking the ROI well, an output graph was produced, showing strain over the selected time period with the end-diastole dimensions as the reference point, was reviewed (Figure 2.5). The segmental strain of the LV was visually reviewed to confirm all segments of the ROI were tracking successfully. The peak strain the mid-myocardial layer of the myocardium was recorded (negative value). The PLS for each of the three views were averaged to calculate GLS.

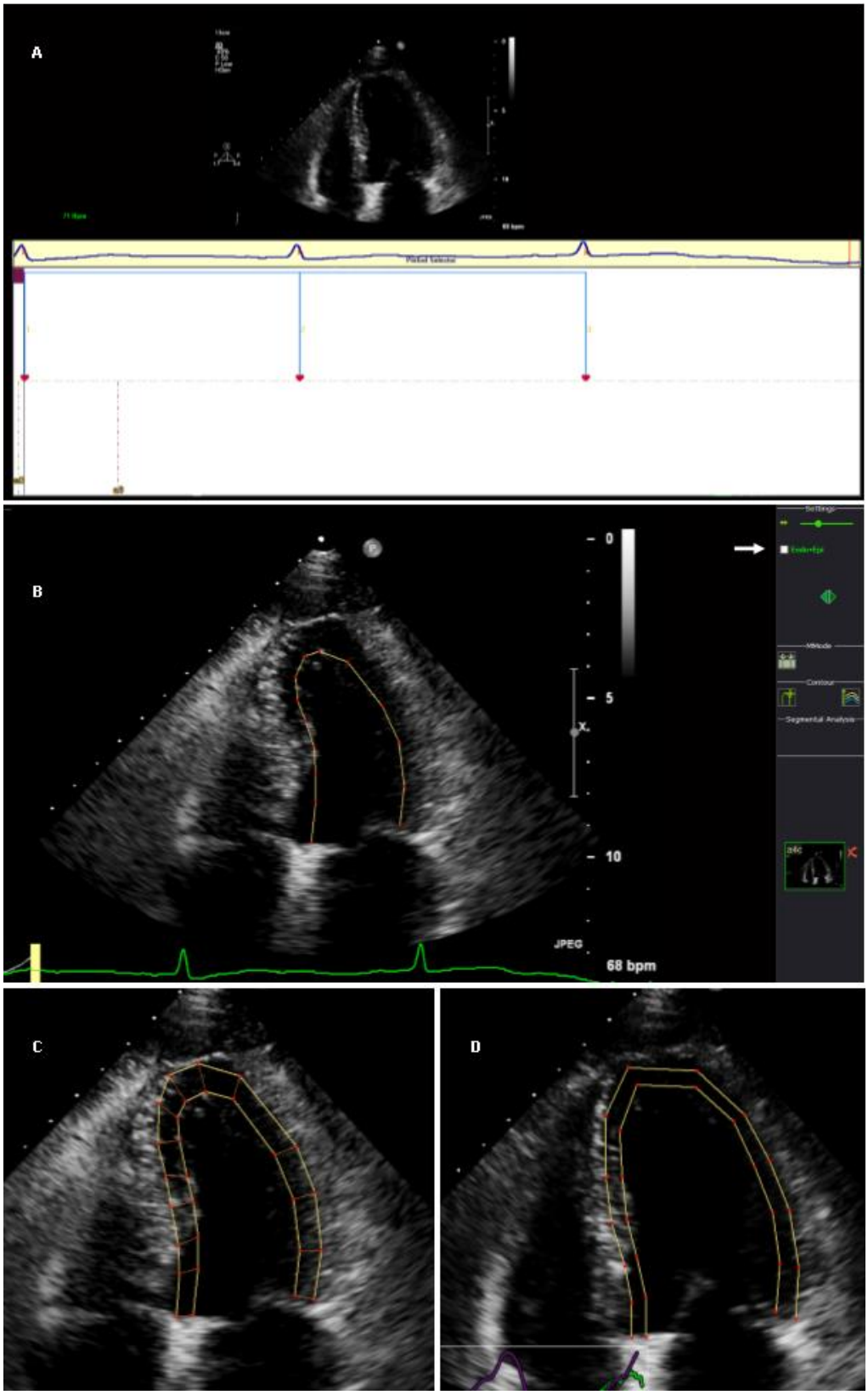

Figure 2.2: Stages of measuring LV longitudinal strain in the apical 4-chamber view*. A - Identify end-diastole and end-systole, using visual assessment and ECG gating B- Trace the inner myocardium at end-systole and select endo/epi. C - Adjust the thickness of the region of interest accordingly. D- Review and adjust the region of interest at end-diastole*

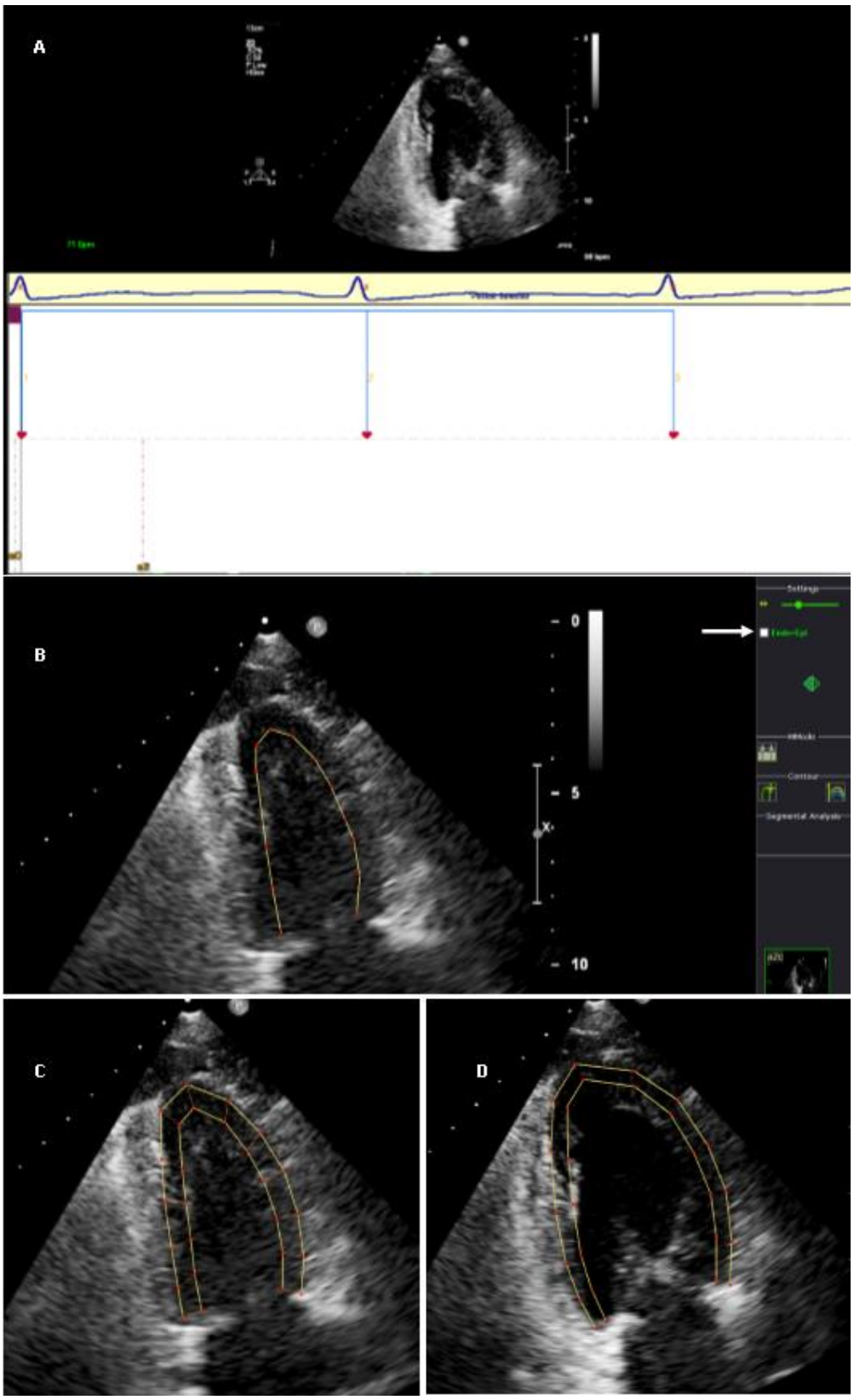

Figure 2.3: Stages of measuring LV longitudinal strain in the apical 2-chamber view*. A - Identify end-diastole and end-systole, using visual assessment and ECG gating. B- Trace the inner myocardium at end-systole and select endo/epi. C- Adjust the thickness of the region of interest accordingly. D- Review and adjust the region of interest at end-diastole*

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Figure 2.4: Stages of measuring LV longitudinal strain in the apical 3-chamber view. *A - Identify end-diastole and end-systole, using visual assessment and ECG gating. B- Trace the inner myocardium at end-systole and select endo/epi. C- Adjust the thickness of the region of interest accordingly. D- Review and adjust the region of interest at end-diastole.*

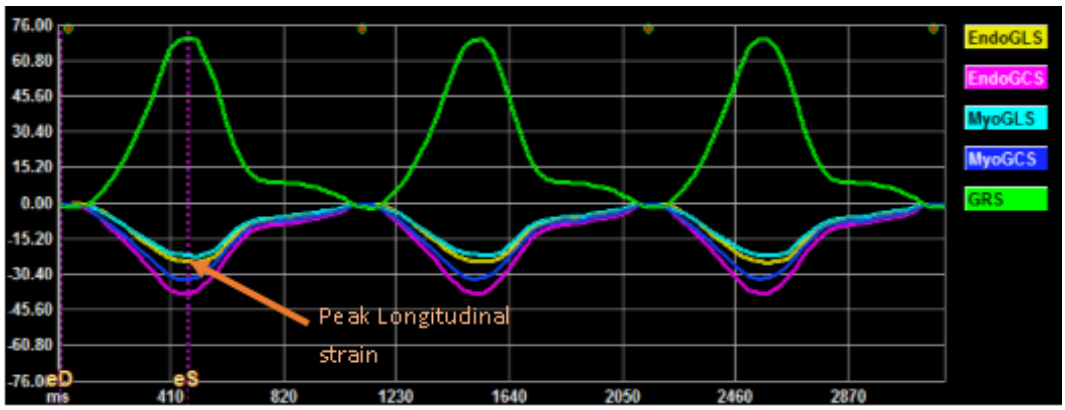

Figure 2.5: Example strain vs time trace of the Left Ventricle, measured in the Apical 4-chamber view. *Peak longitudinal strain was recorded from the aqua blue line, as labelled.*

2.5.2. Secondary Measures

2.5.2.1. Left Ventricular Ejection Fraction

Left Ventricular Ejection Fraction (LVEF) was measured on 2D echo images of the apical 4 and apical 2 chamber views. To calculate LVEF firstly the LV end-diastolic and end-systolic points were identified, visually and by using the ECG. End diastole should coincide with the R-wave on ECG, prior to the mitral valve closing, ventricular systole occurs after the t-wave prior to the mitral valve opening. The LV volume at these two-time points was measured on the 2D image and recorded.

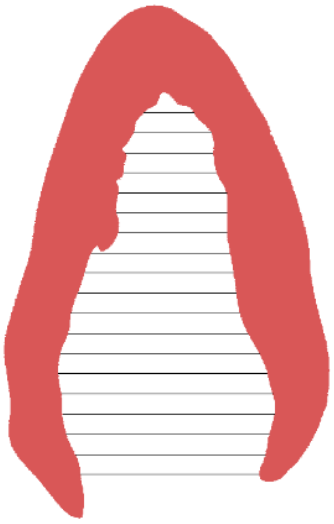

Figure 2.6: Illustration of the stacking disks method used to calculate ventricular volume*. The ventricle is split into 20 'disks' of even thickness and the volume of each disk is calculated on the assumption that it is circular with a diameter of the visualised width. These volumes are combined to provide a total volume. Author generated image.*

To measure the 2D volume the endocardial border was traced in both the apical 2 and apical 4 chamber views as seen in figure 2.7, taking care not to use images where the ventricle had been foreshortened. In each view, the software split the ventricular area

into a series of 20 stacked segments and calculated the area using a mono-plane Simpsons method, based on the assumption that each 'disk' is circular with a diameter equal to the width of the disk (see figure 2.6). The 2-chamber and 4-chamber views of the LV provide complimentary views; the quadratic mean of the volumes measured in each view were calculated, to provide a truer representation of LV volume at end-diastole and end-systole. To ensure maximum accuracy measurements for LVED and LVES were taken in the same cardiac cycle. Once LVED and LVES volumes had been calculated LVEF was calculated using the following formula: LVEF = [(EDV-ESV)/EDV] x 100.

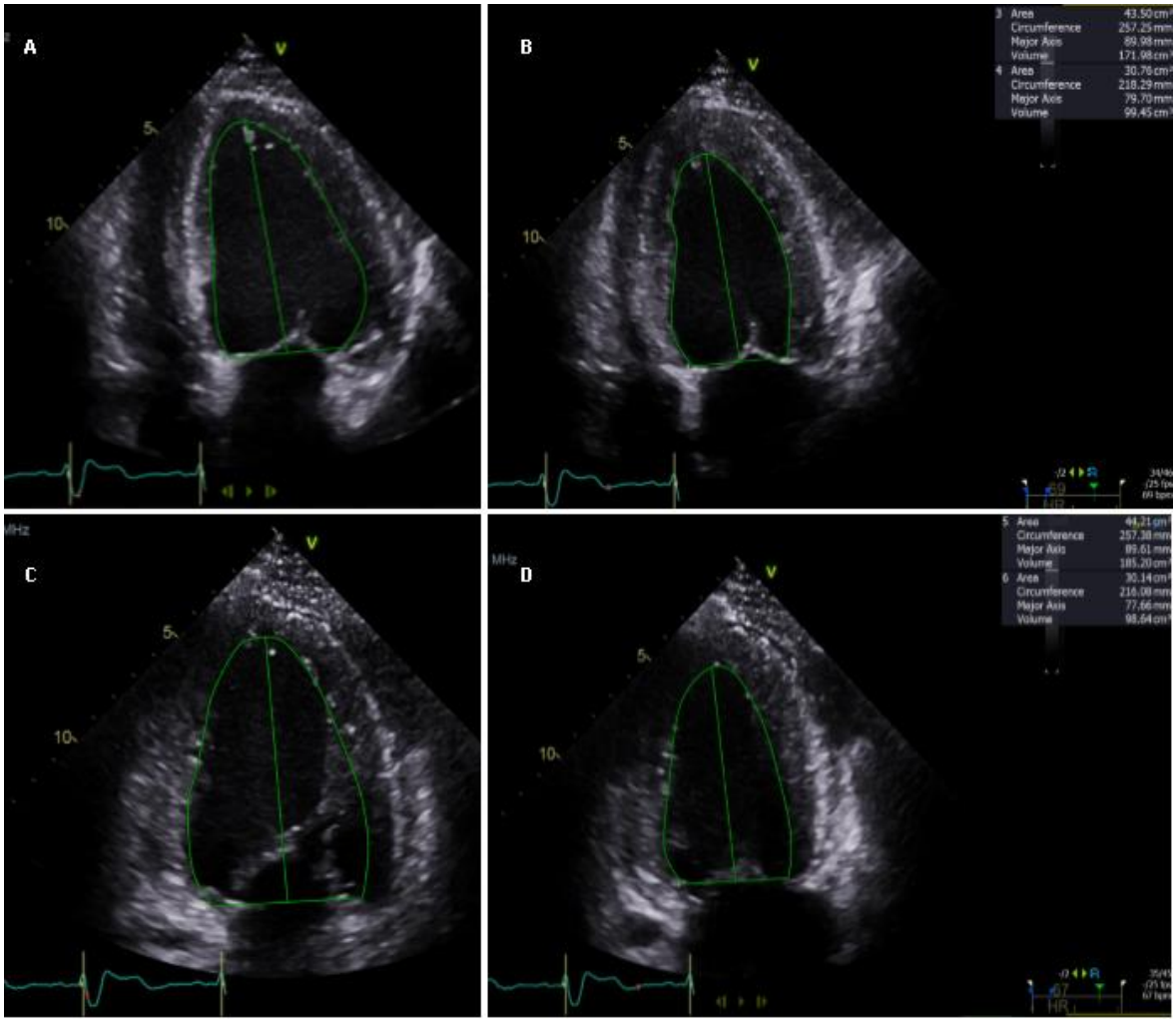

Figure 2.7: Measuring the volume of the Left Ventricle at its maximum volume (A, C) and minimum volume (B, D) in order to calculate Left Ventricular Ejection Fraction. *Measured in both the apical 4 chamber (A, B) and apical 2 chamber (C, D) views. Minimum and Maximum volumes were quadratically averaged across the two views.*

2.5.2.2 Left Ventricular Circumferential and Radial Strain.

Left ventricular circumferential (LVCS) and radial (LVRS) strains were measured using STE. LVCS and LVRS were measured in the parasternal short axis (PSAX) view. The PSAX view visualises a cross-section of the left ventricle, displaying a ring of the myocardium. Where there were suitable available images LVCS was measured in three locations; at the level of MV, level of the papillary muscles and the apex of the ventricle. For each view, the timing of R waves were identified, and end-diastole and systole marked for one R-R interval. The ROI was manually traced by the analyst at both end-diastole (reference point) and end-systole, taking care to include all the myocardium but not any papillary muscles or pericardium (figure 2.8).

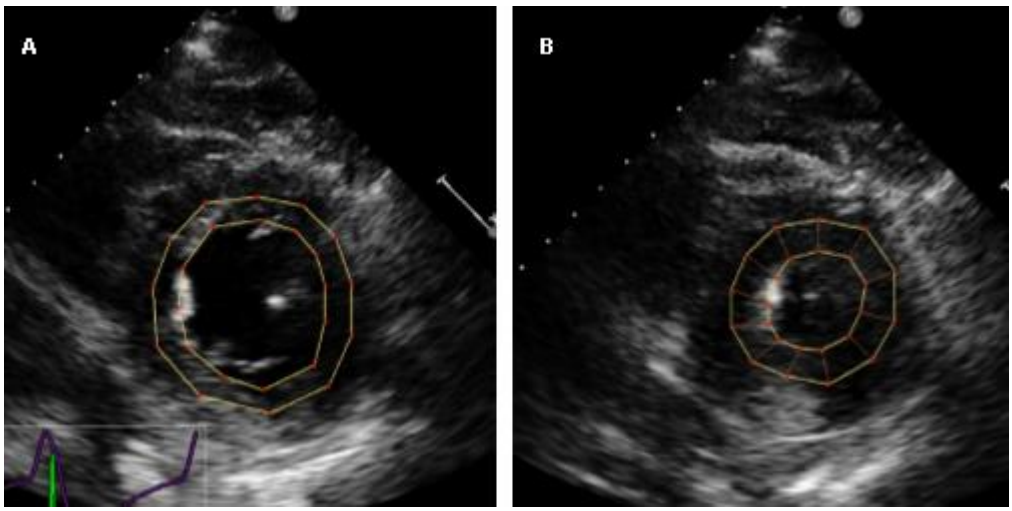

Figure 2.8: Tracking of the myocardium at diastole (A) and systole (B) in the PSAX view at the basal level. *PSAX: Parasternal short-axis view.*

Tracking was reviewed for accuracy before recording the value of peak LVCS (a negative value). LVRS was recorded only at the level of papillary muscles using the same trace as LVCS, peak radial strain is a positive value due to the wall thickening seen during ventricular systole. An example trace can be seen in Figure 2.9. These measurements were taken at baseline, 6 weeks and 12 months where image quality allowed.

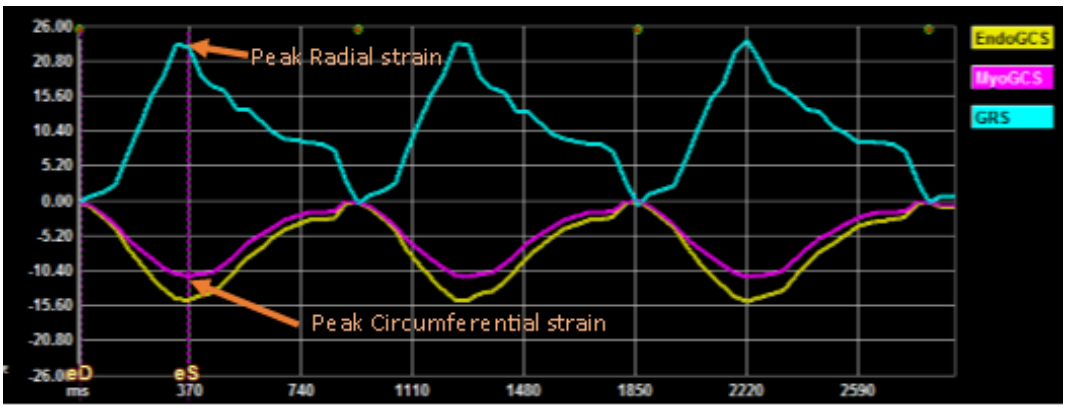

Figure 2.9: Example strain vs time trace, taken in the PSAX view at the level of the papillary muscles*. Illustrating the positive peak of radial strain, and the negative trough of circumferential strain. Circumferential strain is recorded from the pink, mid-myocardial trace.*

2.5.2.3 Left Ventricular twist mechanics.

Using the same Region of Interest generated for the analysis of circumferential strain, peak rotation was recorded at basal and apical levels of the LV in the PSAX view. These measurements were only recorded if the image and tracking were visually assessed to be high quality, with a clear myocardial border, and there was a true apical view (below all the papillary muscles, and on-axis). As seen in figure 2.10 the output generated was a plot of rotation vs time.

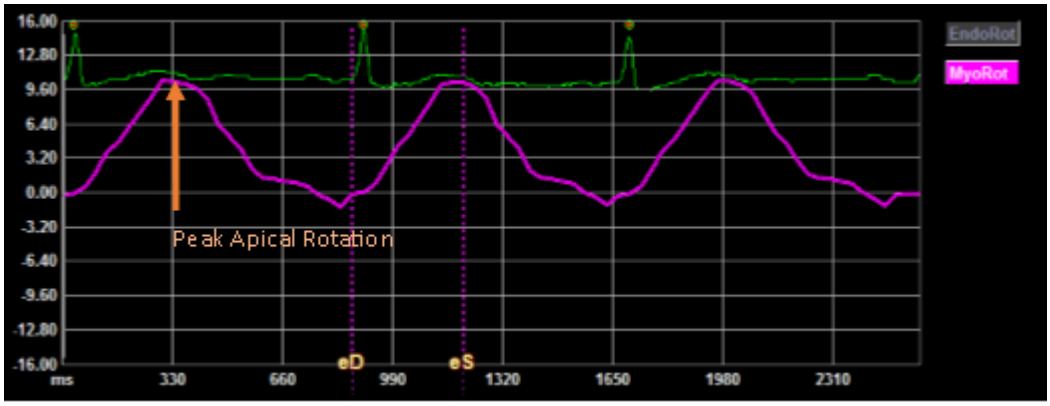

Figure 2.10: Example rotation vs time trace, taken in the PSAX at the apical level. *A positive peak of apical rotation reflects anti-clockwise rotation, measured in degrees*

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2.5.2.4 Right Ventricle Longitudinal Strain

Right ventricular strain (RVGLS) was measured using the same STE technique as LV longitudinal strain and can be seen illustrated in figure 2.11. Firstly end-diastole and end-systole were identified, then the inner edge of the myocardium was traced at both

time points, and adequate tracking throughout the cycle verified before recording the peak strain (negative value) from the output graph (Figure 2.12). Due to the thinner myocardial wall, the strain was measured in the inner layer of the subendocardium, and care had to be taken to make sure the ROI was not too wide. Additionally, RVGLS was analysed only the 4-Chamber apical view as it is not visualised in the other apical views. There is currently some variation in the method used to measure RV longitudinal strain; some authors measure only the free wall of the RV, whereas others measure 6-segment 'global' RV strain, including the septal wall. Review studies have concluded that RV free wall strain and RV 6-segment strain (RVGLS) have excellent correlation, but strain values assessed by RVGLS were lower in absolute value than the strain values assessed from just the RV free wall for the same images(125). Therefore, it is important to be consistent in the method used to assess RV longitudinal strain. At rest, both methods have been shown to be highly reproducible. This study chose to measure RV strain using the global, 6-segment, method, following the recommendations of current EACVI/ASE guidelines (44).

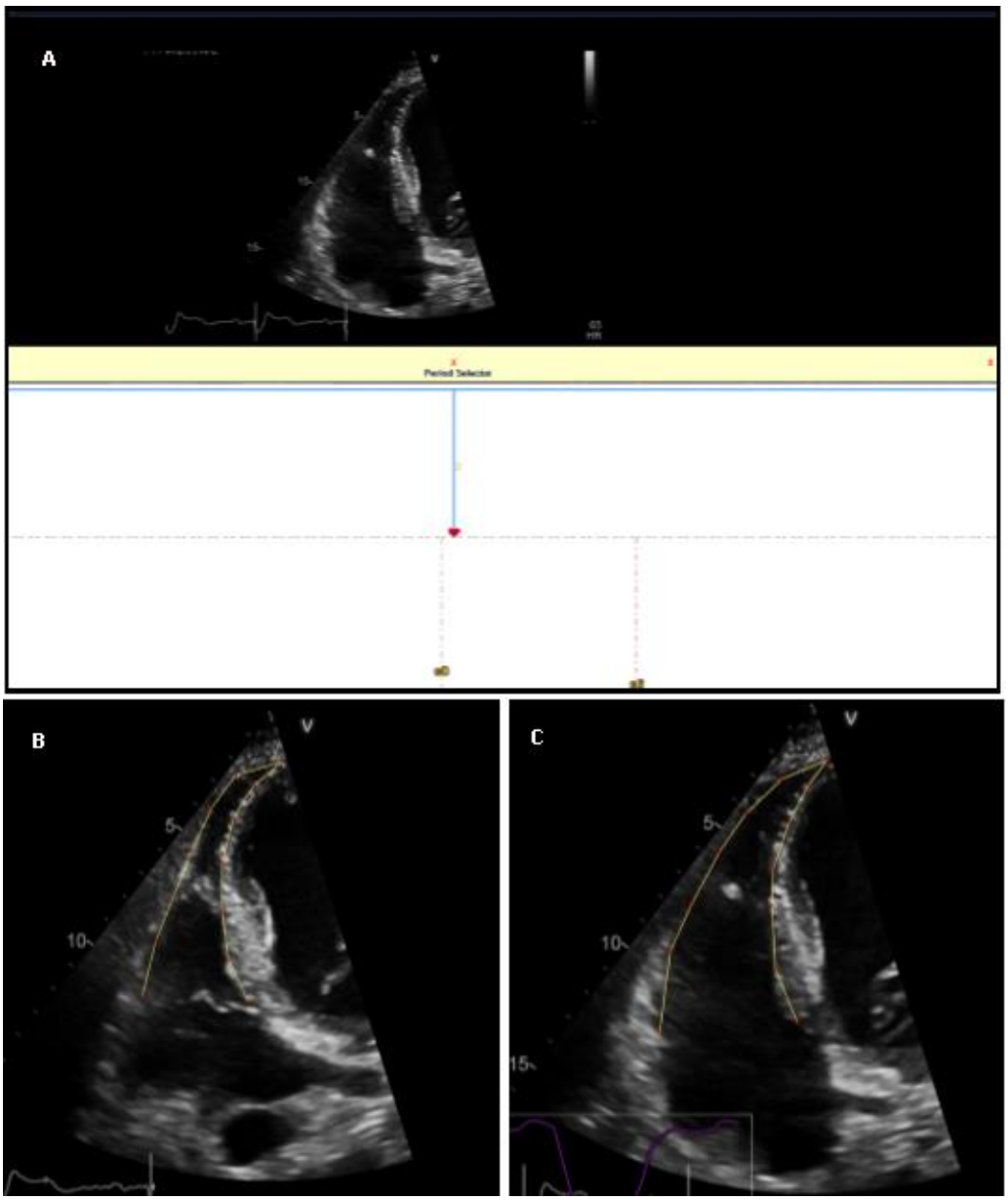


Figure 2.11: Stages of measuring RV longitudinal strain in the apical 4 chamber view. *A - Identify end-diastole and end-systole, using visual assessment and ECG gating. B- Trace the inner myocardium at end-systole. C- Review and adjust the myocardial border tracing at end-diastole.*

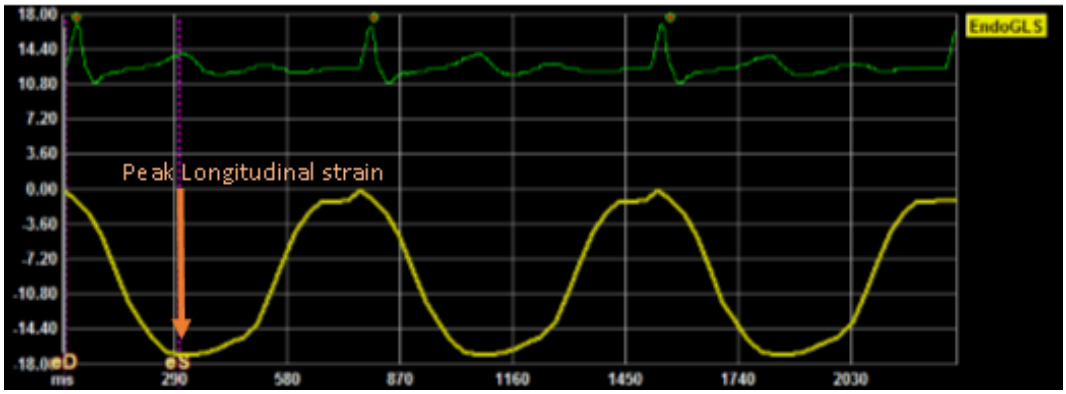


Figure 2.12 Example Strain vs Time trace of the Right Ventricle. *Measured in the Ap4Ch view. Dimensions at end-diastole used as a reference, percentage strain recorded at peak deformation.*

2.5.2.5 Left atrial function.

To explore LA function the LA volume was measured at three points during the cardiac cycle. The minimum LA volume, measured at LV end-diastole, signalled by mitral valve (MV) closure. The maximum LA volume, measured at ventricular end-systole, just before the opening mitral valve. The volume of the LA just before atrial contraction occurs, this was identified using the ECG and the volume measured at the onset of the 'p-wave'. STE derived longitudinal strain was also measured at the point of maximum LA volume, and pre-atrial contraction. Figure 2.13 illustrates the points in the cycle where measurements are taken.

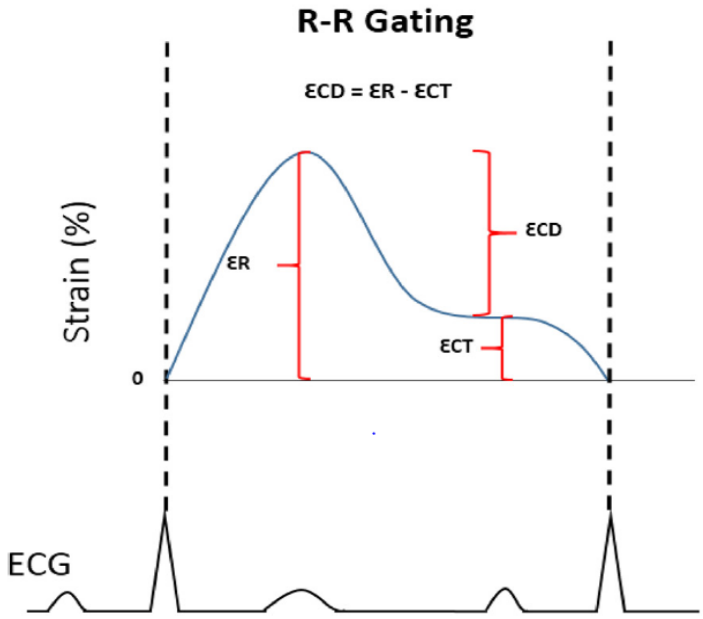


***Figure 2.13 R-R gated LA strain trace**. The R wave and point just prior to mitral valve opening is used at the reference point. εR: Peak strain, also known as reservoir strain. εCT: Pre-A strain, also known as contractile strain), εCD: conduit strain (53).*

Each of these volumes and strains were measured in both the Apical 2 and Apical 4 chamber views (Figures 2.14-2.15), and bi-plane volume calculated. To measure LA volume, firstly ventricular diastole (aligned with R wave on the ECG), and ventricular systole were identified. The inner edge of the myocardium was traced at both time points to identify the 'region of interest'. This was then tracked throughout the cycle and manually reviewed for accuracy.

Reservoir function was assessed via peak LA strain, and by calculating LA total emptying fraction [(Vmax–Vmin)/Vmax.]. Conduit function was assessed by the

calculation of LA passive emptying fraction [(Vmax–Vpre A)/Vmax] and or conduit strain (peak strain – pre-A strain). Finally, LA pump function will be assessed via LA contractile/Pre-a strain (recorded at the p-wave) and the calculation of active emptying fraction ([Vpre A–Vmin]/VpreA). Figure 2.12 illustrates the normal LA strain curve seen on an R-R wave gated analysis, and where the reservoir and contractile strain were measured(53).

In patients with atrial fibrillation, it is not possible to measure the volume just before atrial contraction due to a lack of p-wave on the ECG and co-ordinated atrial contraction, therefore only the minimum and maximum LA volumes were recorded.

Additionally, longitudinal left atrial strain was measured using STE. The myocardium was traced at systole and diastole. And the peak strain recorded (a positive value). If the subject was in sinus rhythm an accurate strain trace will show a second peak during atrial contraction, denoted by the p-wave was, this was recorded. The phasic strain was calculated if the patient was in sinus rhythm, a potentially more sensitive and reliable measure than doppler based assessments of LA function.

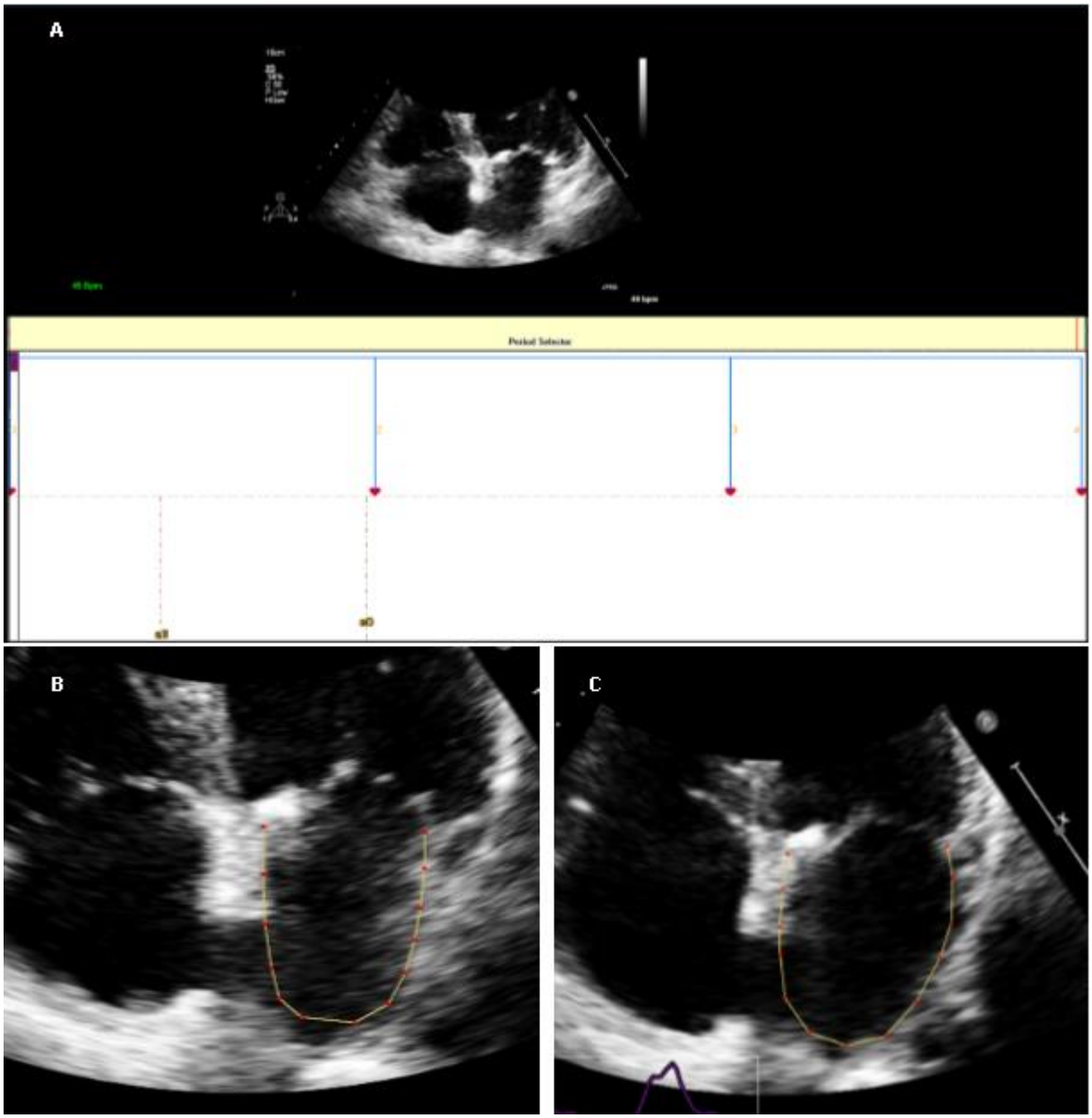


Figure 2.14: Stages of measuring left atrial longitudinal strain in the apical 4 chamber view*. A - Identify end-diastole and end-systole, using visual assessment and ECG gating. B- Trace the inner myocardium at LV end-diastole. C- Review and adjust the myocardial border tracing at LV end-systole.*

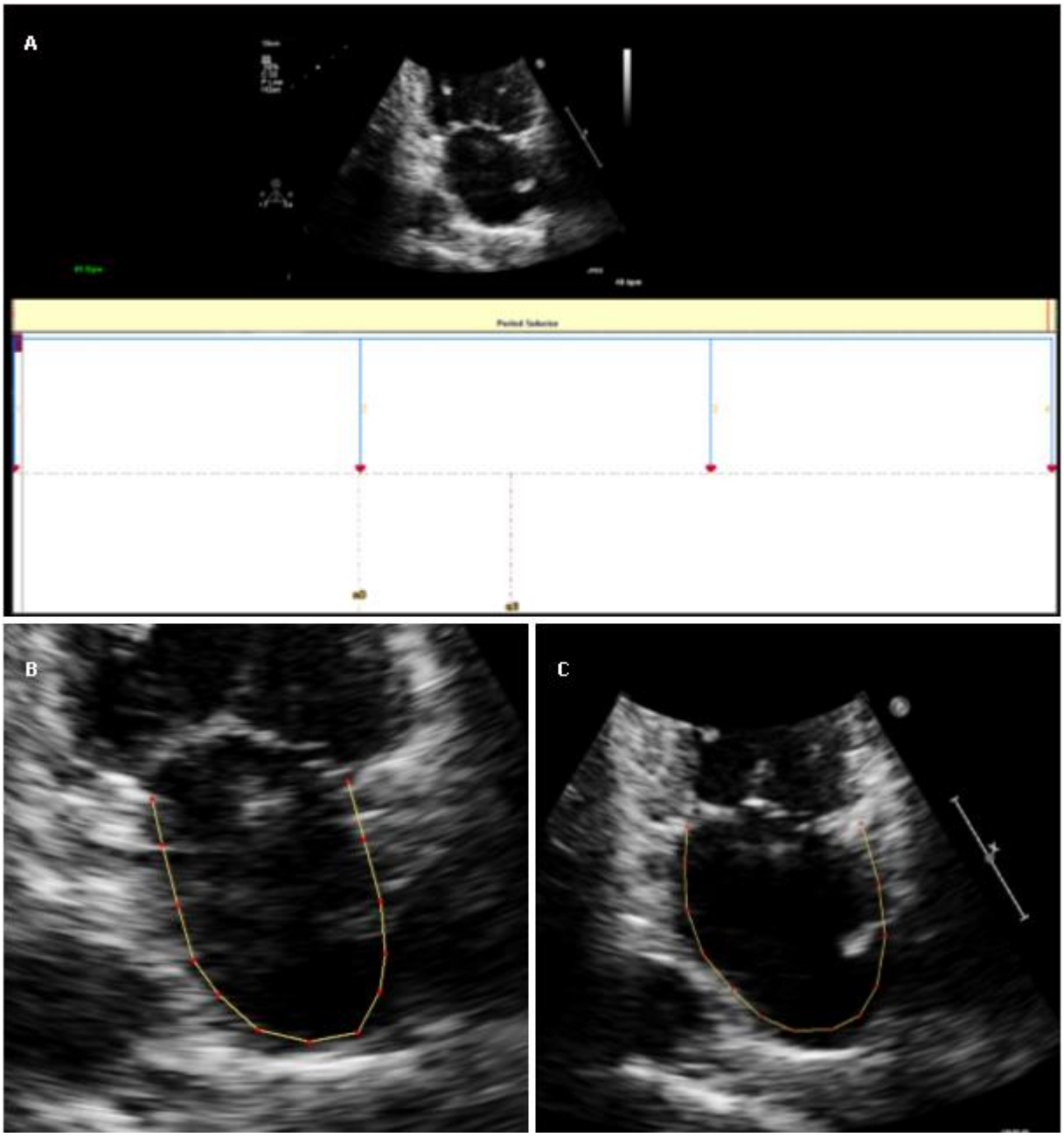


Figure 2.15: Stages of measuring left atrial longitudinal strain in the apical 2 chamber view*. A - Identify end-diastole and end-systole, using visual assessment and ECG gating. B- Trace the inner myocardium at LV end-diastole. C- Review and adjust the myocardial border tracing at LV end-systole.*

2.6 Quality Assurance

To assess the reliability of the measurements being taken for this study both inter- and intra- analyst variation testing was performed.

To test inter-analyst variation twenty of the completed scans (5.2%) were randomly chosen to be re-analysed by the analyst and by an expert analyst. The expert analyst had 20 years of scanning and reporting experience in addition to extensive STE based

research experience. The scans that were to be analysed were generated using a random number generator formula in Microsoft Excel (Microsoft Office, 2013). Once each scan had been allocated a number there were sorted in ascending order of the random number and the top 20 (5.3%) were allocated to be reviewed. For a study to be deemed as having been completed and included in the pool of studies for testing, it must have been analysed for LV longitudinal strain in the three apical views, and LV systolic and diastolic volume in the apical 2 and apical 4 chamber views. No other measurements were required to have been performed. The expert analyst was given a database to record their measurements. It contained just the Study ID, timepoint, and date the TTE was performed, for identification. The database enabled a figure to be entered for all listed analyses independent of whether the initial analyst had performed/recorded value for that measurement. In addition, the author was provided with the same, blank, database and asked to re-analyse the twenty randomly assigned studies.

2.7 Analysis of Data.

Numerical Data was entered into a custom database (Access, Microsoft 2010) and exported for analysis. Statistical analysis was performed using IBM SPSS Statistics v25.

2.7.1 Overall change Baseline – 12 Months Post Intervention

Data for each arm of the study were assessed to look for overall improvement from baseline to 12M via two-tailed paired t-tests. A paired t-test assumes that the data is approximately normally distributed and is based on the mean difference for a series of paired data. The standard deviation for the mean difference was calculated. In large samples, it can be assumed that the t-distribution is equivalent to the normal disruption.

The change seen for each measurement in the two treatment arms was analysed to test for the non-inferiority of TAVI compared to AVR using ANCOVA. The ANCOVA analysis compared the change seen in each treatment arm, taking into consideration the baseline values in each group, and calculated an estimated mean difference, with a 90% confidence interval, of the change seen in the TAVI treatment group compared to

the AVR treatment group. When testing for equivalence between two methods or efficacies the burden of proof rests on the research hypothesis (that there is a significant difference), meaning that if the evidence is not strong enough non-equivalence cannot be ruled out (126). This study tested for non-inferiority; H_1 stating that TAVI is inferior to AVR and H_0 stating that TAVI is not inferior to AVR. When testing for non-inferiority of each measure there was a stated non-inferiority limit, if the lower limit of the 90% two-tailed confidence-interval calculated was within the non-inferiority limit, then the non-inferiority of TAVI could be concluded. A 90% two-tailed confidence interval is equivalent of a 95% one-tailed confidence-interval, in which there is a 95% certainty that the true change in TAVI in no less than the lower limit of the calculated interval. Due to the novel nature of many of the analyses, the non-inferiority limits were based both on current literature and expert consultation regarding a clinically significant change.

2.7.2 Rate of Change and Correlations.

Where data was available for all three timepoints this was analysed to see if there was a difference in the relationship between 6W and 12M data depending on the intervention performed. Rate of change was assessed via ANCOVA analyses on the change seen in each arm taking into consideration the baseline value. ANCOVA were run between the two treatment arms at 6-weeks and 12-months post-intervention for LV and RV measurements.

Data sets were evaluated to look for correlations between continuous sets of data, by calculating a Pearson's correlation coefficient. Correlations were tested between baseline, and 12M values for measures, to explore the effect of baseline impairment on improvement. Additionally, correlations were tested between the improvement in measures to evaluate global cardiac mechanics and the presence of compensatory changes in function mechanics.

2.7.3 Data Reproducibility Testing

Inter- and Intra- reader variability was tested for each measurement using Intraclass Correlation (ICC), and the values for absolute agreement reported. ICC was also used to assess inter- and intra-reader variability for analysts within the UK TAVI ECL, as a component of the objectives of chapter 8. ICC calculates a unitless figure between zero and one. The nearer the figure is to one, the higher the level of agreement between the two sets of data, a value of >0.9 represents excellent reliability and a figure 0.75-0.9 is indicative of a good level of agreement(122).

Additionally, variance will be visually represented using Bland Altman plots for both inter- and intra- analyst variance. A Bland Altman plot shows the mean value and difference between the values for each paired data set, and then also displays the overall mean difference, ± two standard deviations, between the two data groups.

2.8 Ethical Approval

The UK TAVI trial has received national ethical approval, which the subsequent analysis of the TTE images are covered by (First Medical Research Ethics Committee (MREC), 10/04/2013, 13/LO/0451)

Chapter 3 - Change in left ventricular global longitudinal strain and left ventricular ejection fraction post aortic valve intervention.

3.1 Abstract

The increased left ventricular (LV) afterload in severe AS leads to a decline LV function. Left ventricular ejection fraction (LVEF) has historically been used to assess LV function in Aortic Stenosis (AS) and guide the timing of intervention, but recent studies suggest that LV global longitudinal strain (GLS) is a more sensitive marker of LV dysfunction. This study aimed to investigate the recovery of GLS and LVEF in patients with severe aortic stenosis and compare the recovery seen in LVEF and GLS between those who underwent AVR vs TAVI. The non-inferiority of TAVI compared to AVR was investigated. TTE images from 142 subjects, who had been randomised to TAVI or AVR were analysed to measure the GLS using speckle tracking echocardiography (STE) and 2D LVEF. Image analysis was conducted at baseline, 6-weeks, and 12-months post-intervention. There was a significant improvement in GLS from baseline to 12-months post-intervention (12M) in both groups and the improvement in TAVI was non-inferior to AVR ($P<0.05$). At 6-weeks post-intervention (6W) there was an improvement in GLS in the TAVI treatment group, but not in the AVR group. LVEF saw no significant change from baseline to 12M ($P=0.49$) due to the fact the mean LVEF wasn't meaningfully reduced prior to intervention. This study has provided evidence that the recovery of both LVEF and GLS post-intervention is non-inferior in TAVI compared to AVR, as well as adding to the body of knowledge that GLS is a more sensitive marker of LV dysfunction than LVEF.

3.2 Introduction:

In patients with severe AS progressive increases in afterload and reduced myocardial perfusion lead to reduced LV function (see chapter 1.1.3.1). If LV function deteriorates to the stage where LVEF drops, then it is linked to poorer patient outcomes and increased mortality including post aortic valve replacement surgery (AVR)(24, 25).

Global Longitudinal strain (GLS) has also been shown to be an accurate predictor of outcomes such as surgery, mortality, and morbidity, in patients with severe AS(48, 51, 57).

LVEF is a widely used and clinically validated marker of ventricular systolic function. LVEF is also the most widely utilised and studied parameter currently used to guide intervention in asymptomatic severe AS patients(123). In patients with severe AS a reduction in LVEF is correlated with increased mortality prior to and post aortic valve replacement surgery (AVR) (24, 25). Although studies have reported that in those with low LVEF (<50%), there was a significant improvement in LVEF 12-months post-TAVI (26, 27) and AVR(127, 128) (See Chapter 2.1.3.2). This supports the theory that the reduction in LVEF is caused by afterload mismatch rather than irreversible myocardial damage.

Subendocardial fibres are paramount in effective longitudinal LV systolic contraction and are most vulnerable to reduced perfusion. As such, LV longitudinal contractile dysfunction is often the initial mechanical outcome in this patient cohort, detectable before a significant change in overall left ventricular ejection fraction (18, 129). TTE provides a non-invasive and widely available method to monitor overall changes in LV contractile function in a wide variety of clinical populations.

Global Longitudinal Strain (GLS) can be measured using STE (STE) and is an indicator of left ventricular longitudinal myocardial function. It has been shown to be more sensitive detecting a decline in LV systolic function than LVEF for many cardiac diseases (see Chapter 1.1.5.2.1), including severe AS. In this population, reduced GLS is evident in patients with concomitant normal LVEF (>50%) (48, 130). Additionally, GLS has shown predictive valve for morbidity (including heart failure) and post-intervention outcomes post-AVR and TAVI such as hospital re-admissions, recovery, and survival both prior to and after intervention (56, 57, 131). The relative risk of all-cause mortality has been demonstrated to increase with each percentage decline in the absolute value of GLS beyond -15%(56). The current body of research investigating cardiac mechanics and recovery after TAVI is mostly based on very high-risk patients. Therefore, it is not appropriate to compare the recovery of these patients to patients with lower surgical risk and frailty who have undergone AVR.

3.3 Aims:

To investigate the recovery of GLS and LVEF in patients with severe aortic stenosis and of intermediate surgical risk, who had been randomised to either surgical AVR or TAVI.

Evaluate both the overall change from Baseline to 12 months post-intervention and the rate of change comparing baseline, 6 weeks post and 12 months post-intervention.

3.4 Methods:

This study was conducted as a sub-study using the TTE images acquired as part of the UK TAVI trial. Subjects were selected from the cohort of the UK TAVI national trial. All subjects had severe AS and met the inclusion and exclusion criteria of the UK TAVI trial. Subjects had severe AS and were randomised to undergo either surgical aortic valve replacement (AVR) or transcatheter aortic valve insertion (TAVI). Additionally, the TTE images met the specified criteria regarding image quality and format to enable accurate STE tracking (See Chapter 2.2.1). TTE images that had been acquired pre-intervention, 6 weeks post-intervention and 12 months post-intervention, were analysed using STE. Records for 821 subjects were reviewed, after excluding those subjects with uncomplete data or unsuitable image quality, TTE's for 142 subjects were able to be analysed (Figure 2.1, Chapter 2)

3.4.1 Image Analysis

Image analysis was conducted offline using vendor-independent software (TomTec Imaging, Germany, Version 4.6). The average longitudinal strain was measured in the Apical 2-, 3- and 4- chamber views to calculate overall GLS. Based on the ECG and visual tracking of the mitral valve opening and closing, the timepoints of peak LV systole and diastole were identified. The region of interest (ROI) was selected at these timepoints by tracing the myocardium of the LV wall. The ROI was reviewed and manually adjusted as required to ensure accurate tracking throughout the cycle. Figure 3.2 illustrates these steps in the apical four-chamber view. These steps were then repeated in the apical 2 chamber and apical 3 chamber views. Output graphs were

generated by the software (2D CPA. TomTec Imaging, Germany) tracking the longitudinal strain throughout the selected cardiac cycles.

LVEF was calculated by measuring end-diastolic and end-systolic volumes of the LV in the apical 2-chamber and 4-chamber views using the stacked disk method (Figure 3.1). The quadratic mean of the end-systolic and end-diastolic volumes in the Ap4Ch and Ap2Ch views were then calculated and used to calculate percentage ejection fraction (LVEF= [(EDV-ESV)/EDV] x 100, detailed in Chapter 2.5.2.1).

The analysis was performed at baseline (pre-intervention), and 12M as a minimum standard, analysis performed on the TTE 6-weeks post-intervention was also included when the data was available. The change in GLS rather than the absolute valve was used at the primary outcome due to natural variation in GLS which may be influenced by multiple factors including blood pressure, gender, age, and ethnicity (104).

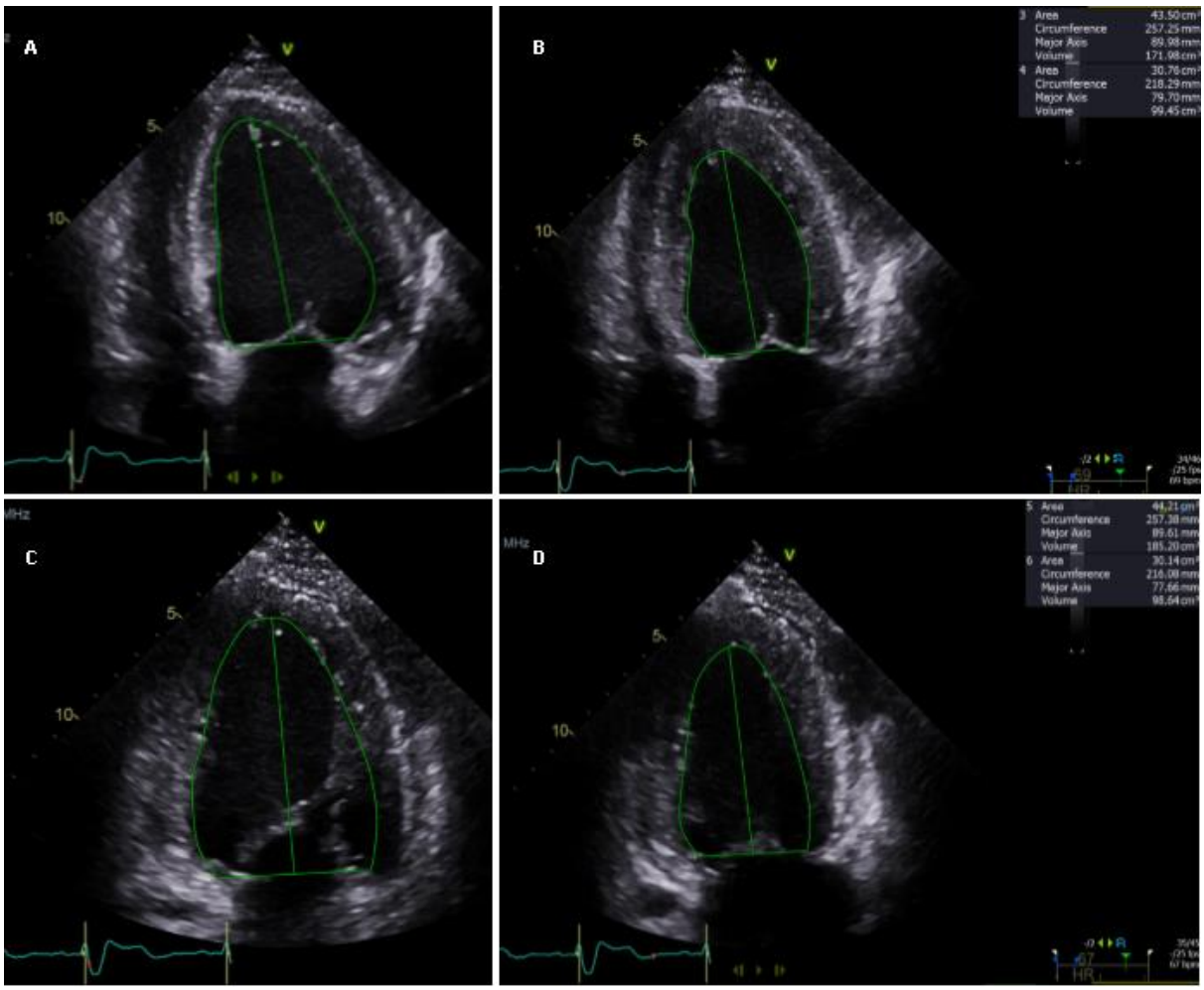


Figure 3.1: Calculation of Left Ventricle Ejection fraction *(LVEF). Measuring the volume of the Left Ventricle at its maximum volume (A, C) and minimum volume (B, D) in order to calculate LVEF. Measured in both the apical 4 chamber (A, B) and apical 2 chamber (C, D) views. Minimum and Maximum volumes were geometrically averaged across the two views.*

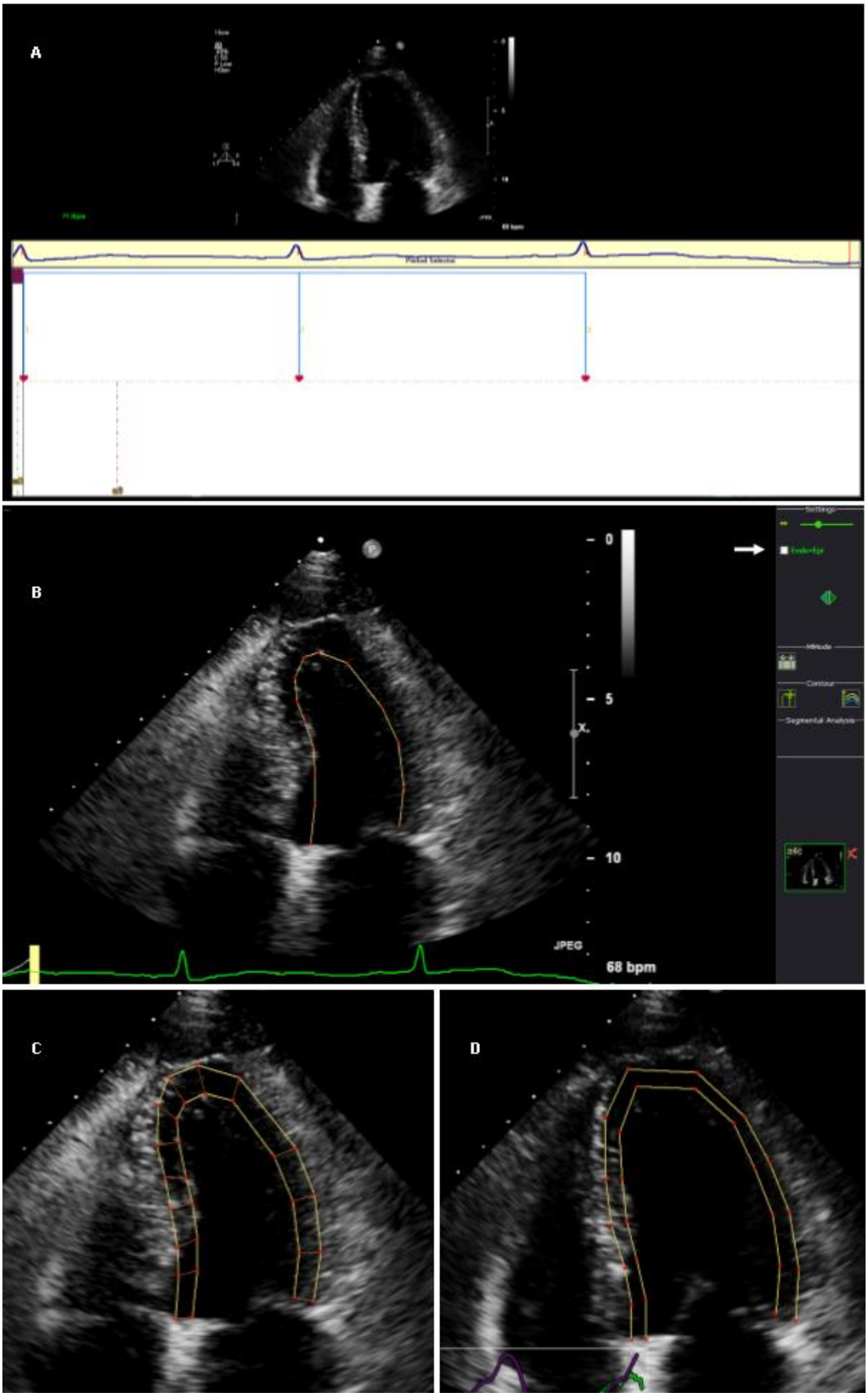


Figure 3.2: Stages of measuring LV longitudinal strain in the apical 4 chamber view*. A - Identify end-diastole and end-systole, using visual assessment and ECG gating. B- Trace the inner myocardium at end-systole and select endo/epi. C - Adjust the thickness of the region of interest accordingly. D- Review and adjust the region of interest at end-diastole.*

3.4.2 Statistical Analysis.

Data for change in GLS and LVEF in each treatment arm were tested for the normality of distribution using the Kolmogorov-Smirnov Test. GLS and LVEF were analysed for overall change from baseline to 12M using paired t-tests and ANCOVA to test for the non-inferiority of TAVI (detailed Chapter 2.7.1). The estimated mean difference for the change in GLS/LVEF between the TAVI and AVR treatment arms was calculated, along with the 90% confidence interval of the mean difference. To accept the non-inferiority of TAVI, the lower limit of the 90% confidence interval needed to be within the non-inferiority limit. Where the 6-week data was available (n=92), the change in GLS from baseline to 6-weeks post-intervention (6W) was also calculated for each treatment arm and compared. Pearson's correlation coefficient was used to assess bivariate correlations between patient demographics and the value of measurements, and between different measurements.

The primary outcome of this study was the change in GLS seen between baseline and 12M. This study was powered to test for the non-inferiority of TAVI compared to AVR. An equivalence limit of 1% was agreed after consultation with a consultant interventional cardiologist with a special interest in valve disease. Additionally, recent research in patients monitored for cardiotoxicity concluded that a relative reduction of <8% compared with baseline GLS indicates the absence of a clinically meaningful deterioration of LV function (132). Although this is investigating the decline of function, opposed to recovery, it supports the expert opinion of a non-inferiority limit of 1% absolute change (equivalent to a relative 8% change for a baseline absolute value of 12.5%).

Due to the design of this study, where a subject's scans were not analysed until both the baseline and 12-month scans had been received and deemed to meet the inclusion criteria, there was no reduction in sample size between the time points. The non-inferiority limit for LVEF was set at 5%. This was based upon the British Society of Echocardiography guidelines regarding the assessment and classification of LVEF (133). These guidelines state that a LVEF of 45-54% indicates mild LV dysfunction, and LVEF of

36-44% indicates moderate LV dysfunction. Therefore 5% is representative of roughly half a classification of LV dysfunction severity. Additionally, multiple studies have concluded that a reduction of 10% in LVEF is indicative of cardiotoxicity(134, 135).

3.5 Results

3.5.1 Baseline Characteristics

Records for 821 subjects were reviewed, of these 512 subjects had both baseline and 12M TTE scans available for assessment, for 360 subjects the baseline and/or 12M scan was unsuitable image quality or saved in the wrong format, for 12 subjects the baseline and/or 12M TTE disk was improperly or unclearly labelled (See figure 2.1 Chapter 2.3). Therefore, TTE's for 142 subjects were analysed for LVEF and GLS at baseline and 12M. Height, weight, blood pressure and heart rate were measured at each study site and provided along with the TTE images.

The AVR group had a mean baseline LVEF of 55.4% (95% CI= 52.5 - 58.3%), and a mean baseline GLS of -13.9% (95% CI = -14.7 - -13.2%). The TAVI group had a mean baseline LVEF of 54.1% (95% CI= 51.7 – 56.5%), and a mean baseline GLS of -14.2% (95% CI = -14.8 - -13.5%) (Table 3.1). There was no statistically significant difference between the treatment arms for either baseline LVEF or GLS (P=0.49 and P=0.66 respectively). Additionally, there was no significant difference in age at intervention between the treatment arms (P=0.43).

All statistics below regarding the change in GLS were calculated using, and refer to, the absolute value of GLS.

	All Subjects	AVR	TAVI	P-Value
Number of Subjects	142	60	82	n/a
Mean Age (years)+	80.6	80.2	80.9	0.43
Mean Body Surface Area +/- 95% CI (m^2) +	1.86 ± 0.03 (n=131)	1.84 ± 0.05 (n=55)	1.87 ± 0.05 (n=76)	0.40
Mean Systolic BP +/- 95% CI (mmHg)+	145.6 ± 3.6 (n=129)	142.7 ± 5.4 (n=54)	147.6 ± 4.9 (n=75)	0.20
Mean Heart Rate +/- 95% CI (bpm)+	69.9 ± 2.3 (n=123)	70.4 ± 3.6 (n=51)	69.5 ± 3.0 (n=72)	0.71
Percentage Male+	54.9	58.3	52.4	0.50
Mean Baseline LVEF +/- 95% CI (%)	54.6 ± 1.8	55.4 ± 2.8	54.1 ± 2.4	0.49
Mean Baseline GLS +/- 95% CI (%)	-14.1 ± -0.49	-13.9 ± 0.71=2	-14.2 ± 0.66	0.66

Table 3. 1: Baseline Characteristics of the subjects undergoing intervention for severe aortic stenosis. *All subjects and split according to intervention. LVEF: Left Ventricular Ejection Fraction. GLS: Global longitudinal strain. %: Percentage. 95% CI: 95% confidence interval. BP: Blood Pressure. mmHg: Millimetres of mercury. Bpm: beats per minute. P-Value: Probability of a true difference between the treatment arms. P<0.05 is considered statistically significant. No statistically significant differences between the baseline characteristics of the two groups. + Source data provided by clinical study sites.*

3.5.2 Overall Change from Baseline to 12-Months Post-Intervention

There was a significant change in GLS from baseline to 12M in the AVR group (n=60, P=0.001, two-tailed paired t-test, figure 3.3). The mean absolute value rose from 13.9% to 15 %, a mean increase of 1.1% (95% CI = 0.50-1.69%). Mean systolic blood pressure in the AVR group rose to 4mmHg to 146.7 (±5.9) mmHg. There was no significant correlation between age (r=0.230, p=0.08) or baseline BSA (r=-0.242, p=0.08) and change in GLS; however, there was a significant positive correlation between change in GLS and both baseline GLS (r=-0.414, p=0.001) and change in systolic blood pressure (r=0.435, p=0.003).

A significant change in GLS from baseline to 12M was also seen in the TAVI group (figure 3.3) (n=82, P=<0.001, two-tailed paired t-test). The mean absolute value rose from 14.2% to 15.2%, a mean increase of 1% (95% CI = 0.49-1.55%). Mean systolic blood pressure in the TAVI group rose to 3.5mmHg to 152.1 (±6.2) mmHg. There was

no significant correlation between change in GLS and age (r=-0.164 p=0.14), BSA (r=-0.115, p=0.32), or change in systolic blood pressure (r=-0.039, p=0.76). There was a statistically significant correlation between baseline GLS and change in GLS (r=-0.296, p=0.007).

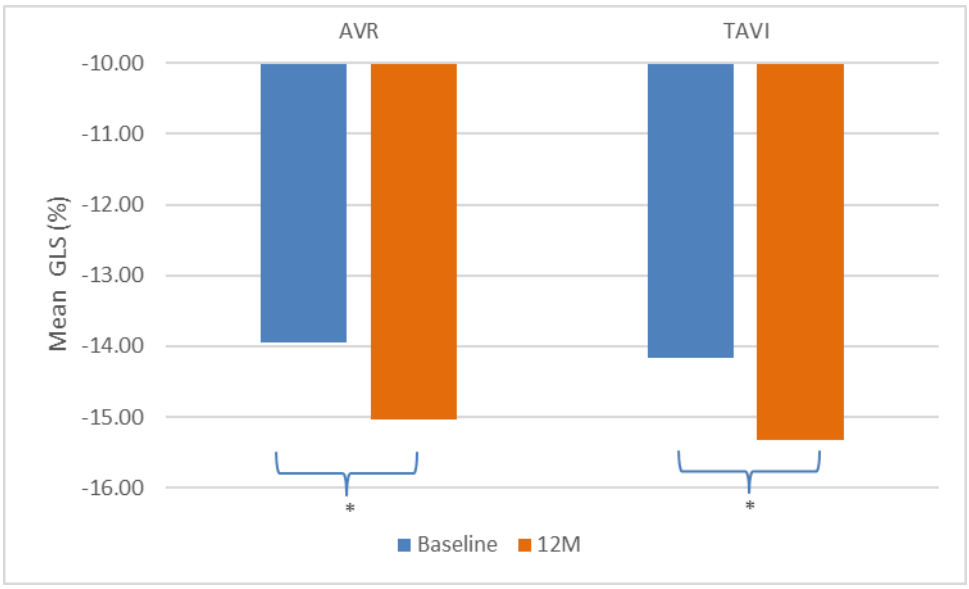


Figure 3.3: Mean Global Longitudinal Strain at Baseline and 12 -months post-intervention *(12M), split according to treatment group. %: Percentage. AVR: Surgical Aortic Value replacement. TAVI: Transcatheter Aortic valve insertion. Significant difference between baseline and 12M in both treatment groups, *=P ≤ 0.001.*

In the TAVI treatment arm, the mean LVEF value rose by 0.45%, from 54.08% to 54.53%. In contrast, there was a decrease of 2% in LVEF from baseline to 12M (55.37% at baseline, 53.36% at 12 months) in the AVR group (figure 3.4). Due to the small changes and larger variance seen in LVEF at both baseline and 12M, it was not possible to conclude that there was a significant difference between the time points in the AVR or TAVI treatment group (all subjects P=0.49, AVR P=0.13, TAVI P=0.69).

There was no statistically significant correlation with the change in LVEF and age (AVR: P=0.56, TAVI: P=0.27), baseline BSA (AVR: P=0.61 TAVI: P=0.45), or systolic blood pressure (AVR: P=0.59, TAVI: P=0.45). There was a statistically significant correlation between change in LVEF and both baseline LVEF (r=0.48, P<0.001), and change in absolute GLS and (r= 0.35, P<0.001). Figure 3.5 illustrates the relationship between baseline LVEF value and the change seen from baseline to 12M. There is a negative correlation (r=0.48, p<0.001) with the y-axis at 53.3%.

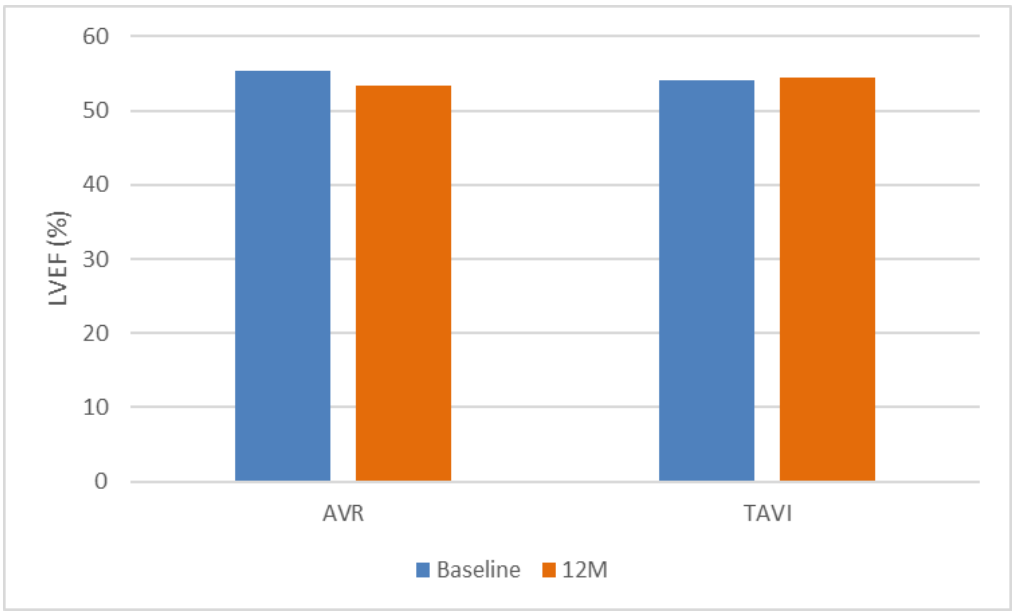


Figure 3.4: Mean Left Ventricular Ejection Fraction at Baseline and 12 -months post-intervention *(12M), split according to treatment group. %: Percentage. AVR: Surgical Aortic Value replacement. TAVI: Transcatheter Aortic valve insertion.*

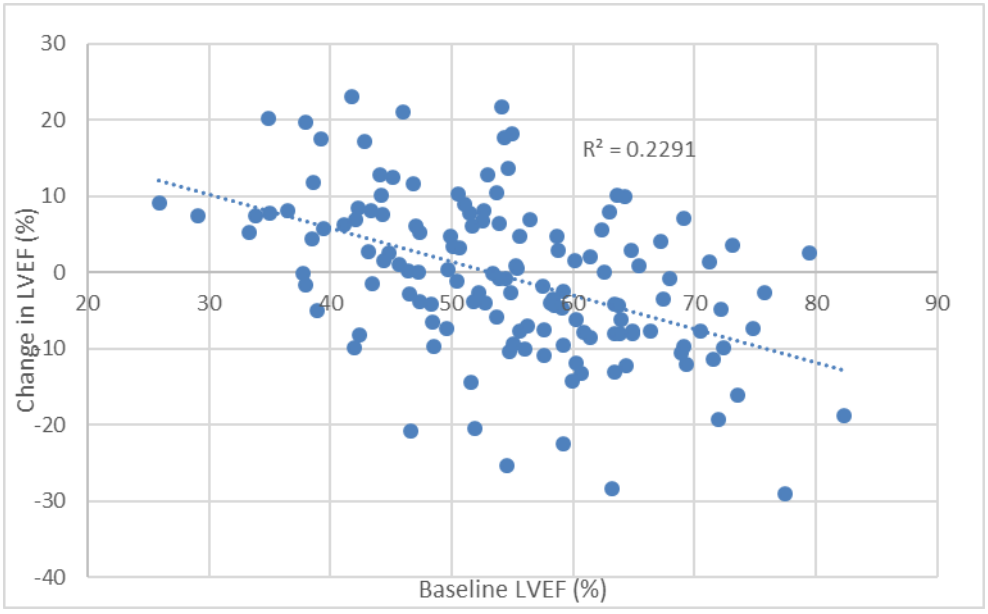


Figure 3.5: Plot of Baseline LVEF vs Change in LVEF for all subjects. *Showing a significant negative correlation between the two data sets (r=0.48, P<0.001). The linear trendline intercepts the y-axis at 53.3%. LVEF: Left Ventricular Ejection Fraction. Change in LVEF = Change in LVEF from baseline to 12-months post-intervention.*

ANCOVA was performed in order to analyse the difference in the recovery of GLS in the two treatment arms. The adjusted mean difference for change in GLS from baseline to 12 months post-intervention was 0.02 (90% CI -0.64-0.61). As the non-

inferiority limit of -1% lies outside of the lower bound of the 90% confidence interview it can be concluded that the recovery of GLS from baseline to 12-months post-TAVI is non-inferior to AVR.

ANCOVA was also performed to assess the difference in the recovery of LVEF between the two treatment arms. The adjusted mean difference for change in LVEF from baseline to 12M was 1.90 (90% CI -0.62-4.42). As the non-inferiority limit of -5% lies outside of this it can be concluded that the recovery of LVEF from baseline to 12-months post-TAVI is non-inferior to AVR.

The 12M TTE was performed a mean of 327 days after intervention in the AVR group and 331 days after intervention in the TAVI group. Ten (16.7%) subjects in the AVR group, and 12 (14.6%) subjects in the TAVI group, had their 12-month TTE performed less than 292 days after the intervention. There was no statistically significant correlation between the timing of the 12-month post-intervention TTE and the change in GLS (P=0.65) or LVEF (0.62).

Kolmogorov-Smirnov test calculated p-values greater than 0.05 for LVEF and GLS in both treatment arms (see Table 3.2), therefore a normal distribution was assumed and independent t-tests between the baseline values were performed.

	Kolmogorov-Smirnov Test P-Value	
	AVR	TAVI
GLS	0.20	0.09
LVEF	0.20	0.20

Table 3. 2 Kolmogorov-Smirnov Test for normality of data distribution. *Testing the distribution of the data for change in LVEF and change in GLS. All measures were normally distributed (P>0.05).*

3.5.3 Rate of Change.

92 subjects had LV GLS and LVEF data for all three time-points; baseline, 6-weeks post-intervention, and 12M. This consisted of 37 subjects in the AVR treatment group and 55 in the TAVI treatment group.

In the AVR treatment group, the mean GLS stayed consistent between the baseline and 6-weeks post-intervention time points at 13.6%. It then increased to 15% at the 12M TTE (Table 3.3). The mean value for GLS in the TAVI treatment group rose at each progressing time point, from 14.2% at baseline, to 14.7% at 6W, and 15.1% at 12M (Table 3.3). The changes in mean GLS for each treatment group and all subjects can be seen in figure 3.6. Despite the visual differences in figure 3.6, there was no statistically significant difference ($P<0.05$) between GLS in the two treatment arms at baseline ($P=0.31$), 6-weeks ($P=0.12$), or 12 months ($P=0.79$). An ANCOVA was run to assess the change in GLS from baseline to 6 weeks post-intervention in the two treatment arms, adjusting for the baseline value. The adjusted mean difference between the two arms for the change in GLS baseline to 6-weeks post-intervention was 0.53 (90% CI -0.18-1.25). This is within the non-inferiority limit of -1%, but as the confidence interval includes zero, we cannot conclude that the recovery after TAVI is superior to the recovery after AVR at 6W.

	All Subjects (n=92)	AVR (n=37)	TAVI (n=55)
Baseline GLS (%)	-14.0 (±2.8)	-13.6 (± 2.6)	-14.2 (± 2.9)
6-Weeks Post GLS (%)	-14.2 (±3.2)	-13.6 (± 3.0)	-14.7 (± 3.3)
12-Months Post GLS (%)	-15.1 (±3.1)	-15.0 (± 2.6)	-15.1 (± 3.4)

Table 3. 3 LV GLS values at each study time point. *Mean values for GLS pre-intervention, 6-weeks post, and 12-months post-intervention (± 95% standard deviation).*

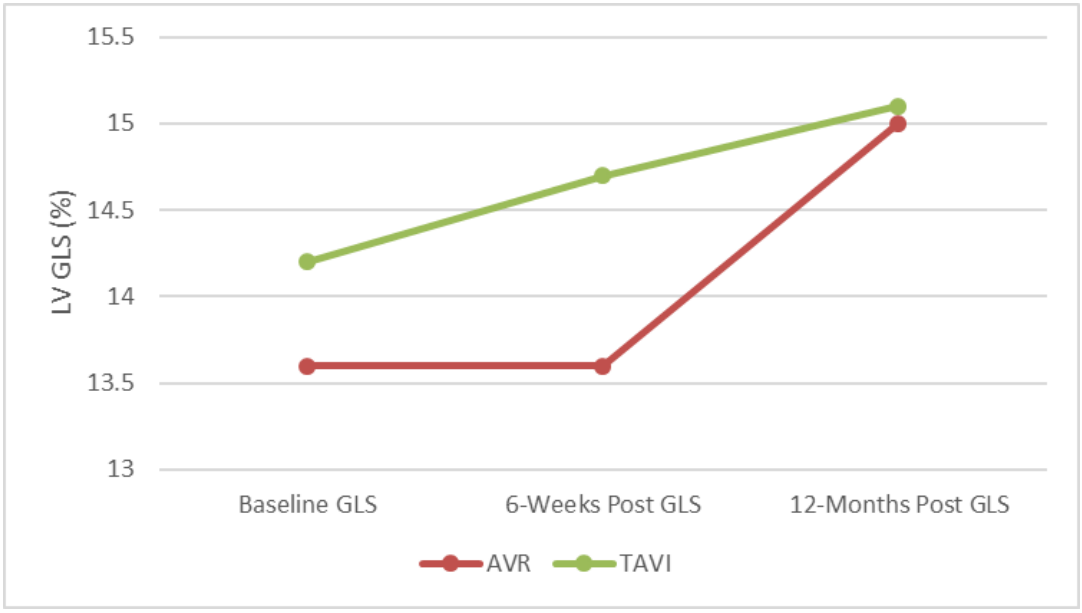


Figure 3.6: Change in Left Ventricular GLS over study timepoints. *Mean LV GLS for each treatment arm at baseline, 6-weeks, and 12-months post-intervention.*

Figure 3.7 displays a box and whisker plot for the value of GLS at each timepoint. Both AVR and TAVI had changing levels of variance depending on the time point. Additionally, the range of each quartile of data is not always even, which suggests the data is skewed opposed to normally distributed. There is a large variance in GLS at each time point, in comparison with the inter-timepoint differences, which supports the decision to assess the mean change seen between timepoints opposed to the mean absolute value.

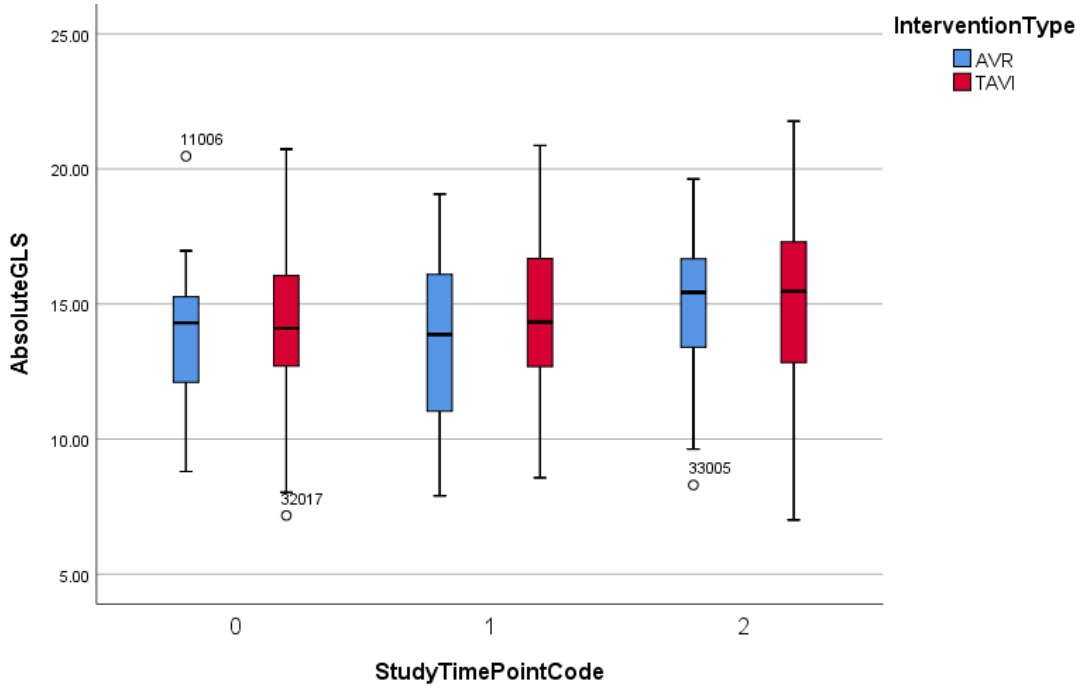


Figure 3.7: The mean and variance of absolute GLS at each timepoint for TAVI and AVR. *Data gathered only from the subjects with GLS values at every timepoint. The mid-point represents the median of the data set, the box contains the central quartiles and the whiskers the outer quartiles. Any outliers were identified and are represented on the graph by a dot and the study ID. Timepoint 0=Baseline, 1= 6-Weeks post-intervention, 2=12-months post-intervention. Outliers are labelled by study ID.*

Mean LVEF for both treatment groups followed the same pattern. There was a reduction from baseline to 6-weeks post-intervention, accompanied by an increased width of the 95% confidence interval which indicates greater variability in the measurements (Figure 3.8). There was no statistically significant correlation between the number of days post-intervention that the 6-week TTE was taken, and the change in LVEF (P=0.35). Between the 6-week post-intervention and 12M TTE's the mean LVEF for both treatment arms rose again, to a slightly higher value than baseline. Mean LVEF values are listed in table 3.4 and shown in figure 3.8. There were no statistically significant differences (P<0.05) between LVEF in the two treatment arms at baseline (P=0.10), 6-weeks (P=0.24), or 12 months (P=0.09). An ANCOVA was run to assess the change in LVEF from baseline to 6 weeks post-intervention in the two treatment arms, adjusting for the baseline value. The adjusted mean difference between the change seen in the two arms was 1.75 (90% CI -1.93-5.43), as this excludes the non-inferiority limit of -5% the non-inferiority of TAVI regarding recovery of LVEF baseline to 6-weeks can be concluded.

	All Subjects (n=92)	AVR (n=37)	TAVI (n=55)
Baseline LVEF	54.2 (±10.6)	52.0 (± 9.6)	55.7 (± 11.0)
6-Weeks Post LVEF	52.1(±12.5)	49.5 (± 12.3)	53.8 (± 12.4)
12-Months Post LVEF	54.7 (±11.2)	52.3 (± 7.7)	56.4 (± 12.9)

***Table 3. 4 LVEF values at each study time point**. Mean values for LVEF pre-intervention, 6-weeks post, and 12-months post-intervention (± Standard deviation).*

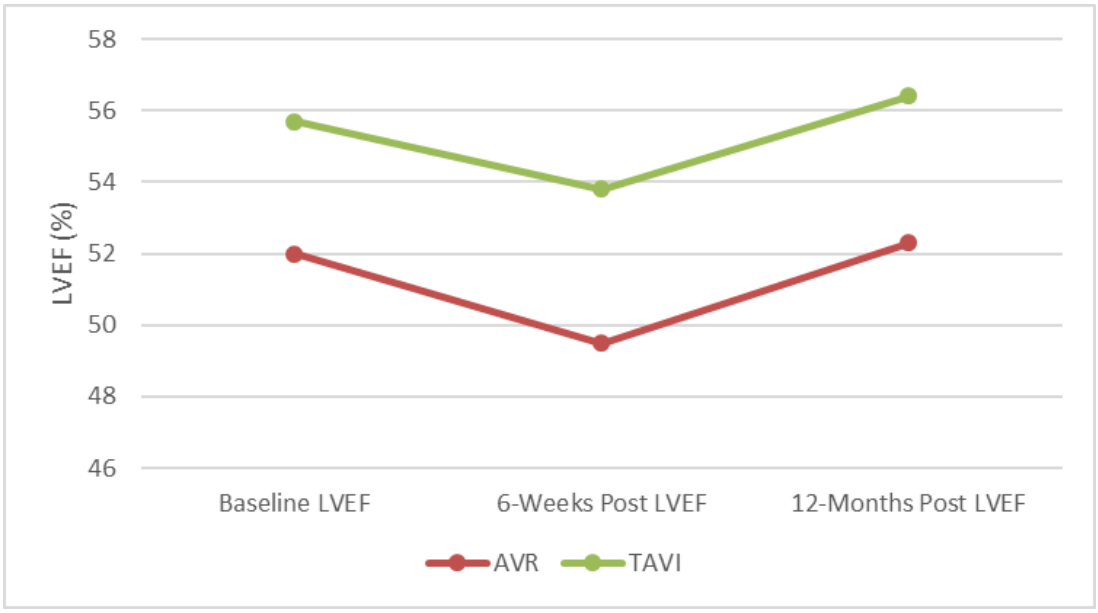


***Figure 3.8: Change in LVEF over study timepoints**. Mean LVEF for each treatment arm at baseline, 6-weeks, and 12-months post-intervention.*

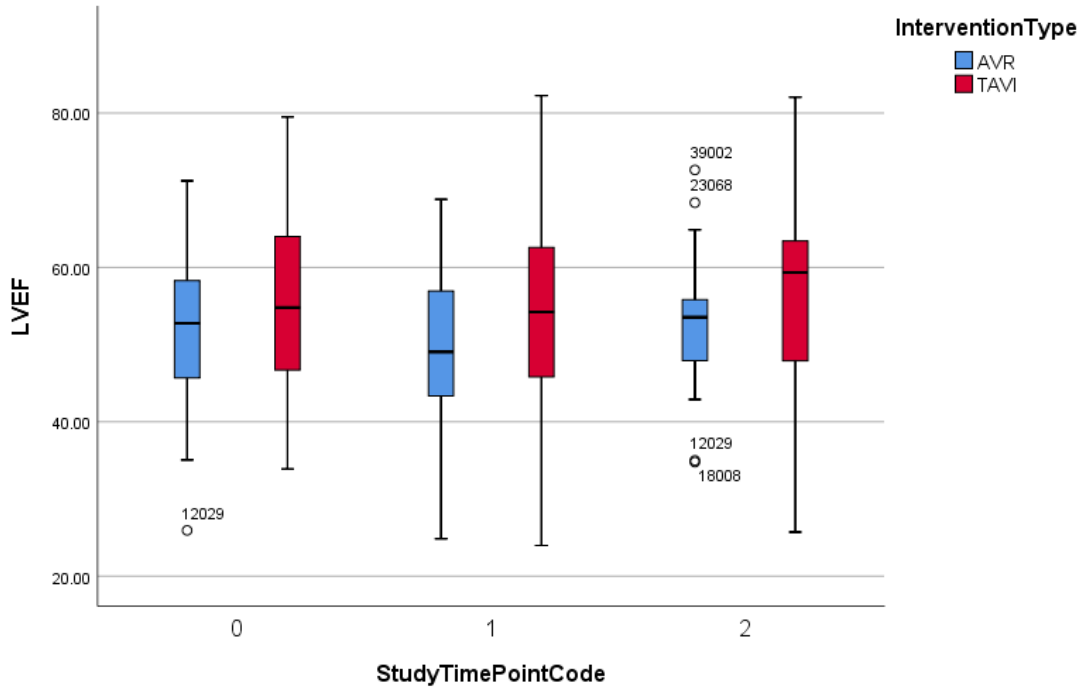


Figure 3.9: The mean and variance of LVEF at each timepoint for TAVI and AVR. *Data gathered from only the subjects with GLS values at every timepoint. The mid-point represents the median of the data set, the box contains the central quartiles and the whiskers the outer quartiles. Any outliers were identified and are represented on the graph by a dot and the study ID. Timepoint 0=Baseline, 1= 6-Weeks post-intervention, 2=12-months post-intervention. Outliers are labelled by study ID.*

Figure 3.9 displays a box and whisker plot for the value of LVEF at each timepoint. Both AVR and TAVI had negatively skewed data at the 12-month time point. Again, there is a large variance in values at each time point, in comparison with the inter-timepoint differences, which supports the decision to assess the mean change seen between timepoints opposed to the mean absolute value.

3.5.4 Quality Assurance

20 scans were assessed for both intra-analyst variation and compared to the 'gold standard' of an expert analyst, with 20 years of TTE scanning and reporting experience plus STE research experience, for GLS & LVEF.

The ICC for intra-analyst variation of GLS was 0.91 (95% CI 0.77-0.96), a value greater than 0.9 indicates an excellent level of agreement between the two sets of

measurements(122). The mean difference between the two reads was 0.56% with a standard deviation of 1.57%.

The ICC figure for comparison between the main analyst and expert for GLS was 0.99 (95% CI 0.97-0.998). The mean difference between GLS measurements was 0.28% with a standard deviation of 0.34%. Figures 3.10 and 3.11 show the Bland-Altman plots for the intra- and inter- analyst variability of GLS. These illustrate the range of values reported and the difference between the two reported values for each pair of data, along with the mean difference of reported values.

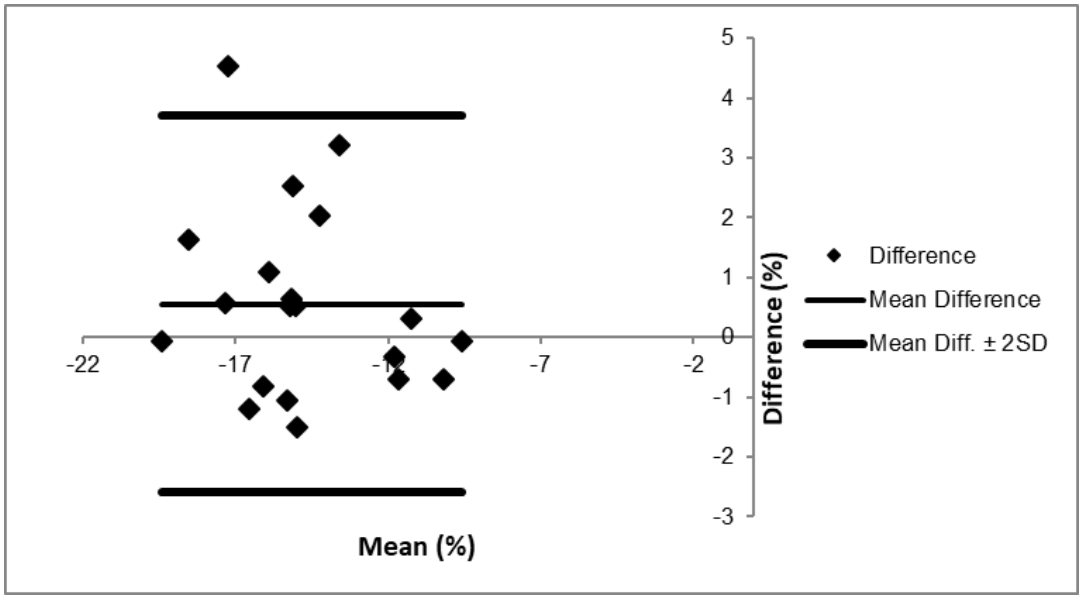


***Figure 3.10**: **Bland Altman Plot Intra-Analysis Variability for GLS**. Mean difference = 0.56%. Standard Deviation = 1.57%.*

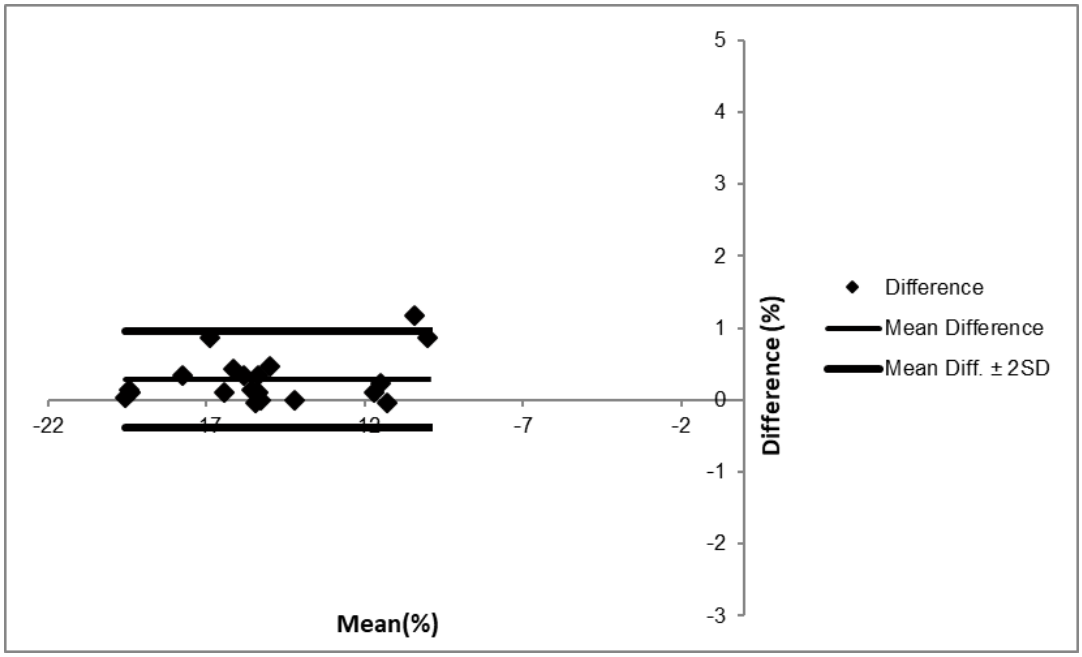


***Figure 3.11: Bland Altman Plot of GLS measurements vs expert analyst**. Mean difference= 0.28%. Standard Deviation = 0.34%.*

For LVEF the ICC for intra-analyst variation was 0.87 (95% CI 0.66-0.95) which is classified as a good level of reliability(122). The ICC value for absolute agreement between the analyst and expert was 0.99 (95% CI 0.97-0.995), indicating an excellent level of agreement between the two analysts(122). Figures 3.12 and 3.13 show the Bland-Altman plots for the intra- and inter- analyst variability of LVEF. These illustrate the range of values reported and the difference between the two reported values for each pair of data, along with the mean difference of reported values. LVEF is known to be prone to high levels of variability, therefore these high levels of reliability are encouraging to see.

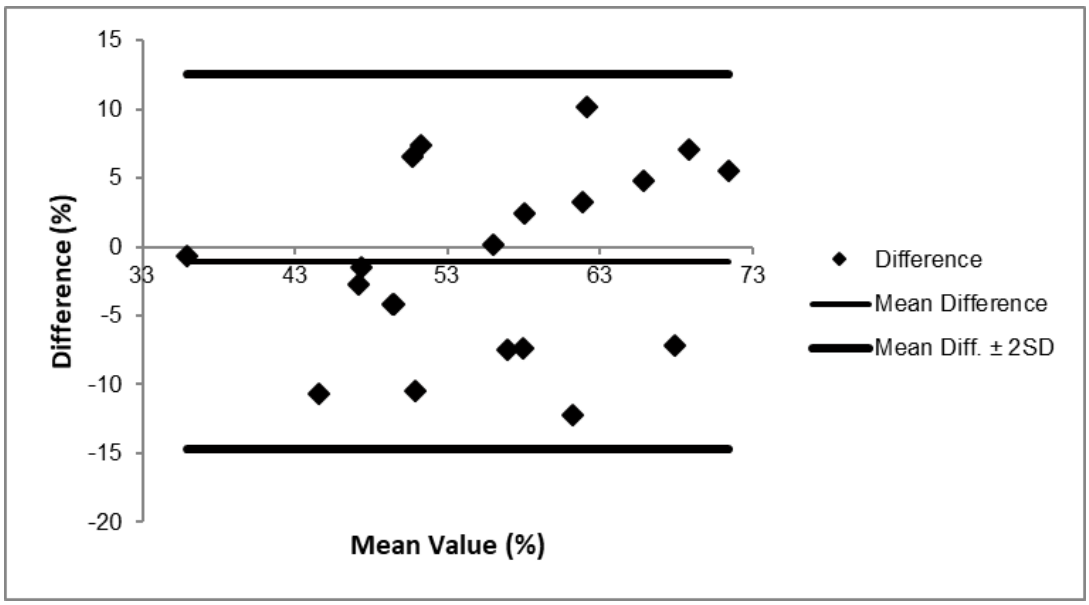


***Figure 3.12*: Bland Altman Plot of the intra-reader variance of LVEF.** *Mean Difference = 1.08%, Standard Deviation = 6.8%*

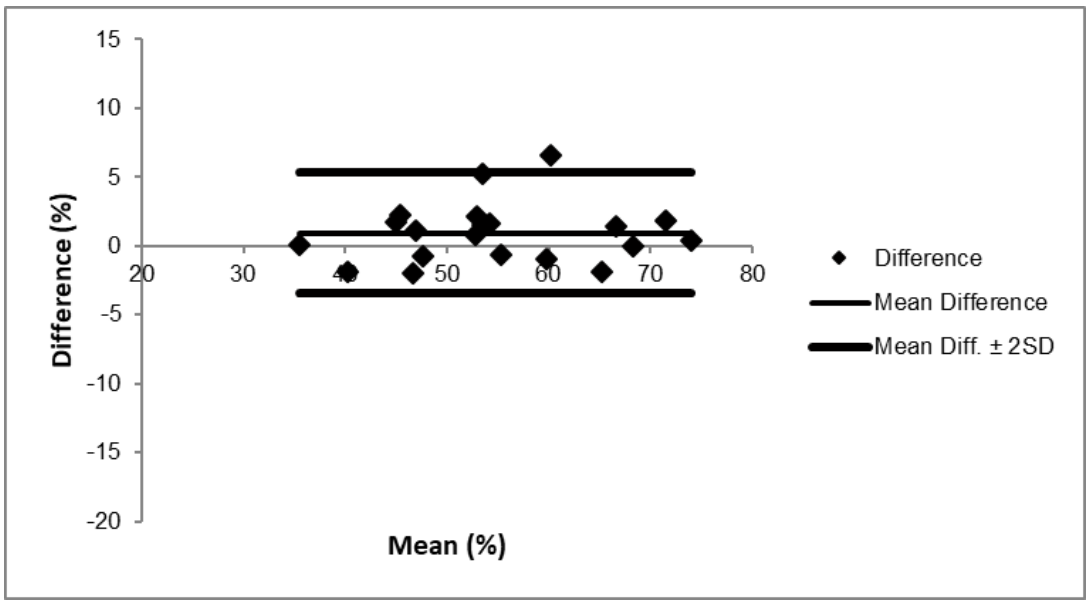


Figure 3.13: Bland Altman Plot of LVEF measurements vs expert analyst. *Mean Difference = 0.92%, Standard Deviation =2.19%*

3.6 Discussion and Conclusions.

The results of this study support previous work which demonstrates that GLS is often impaired in patients with severe AS, even when LVEF remained in the healthy range (48, 49, 57). Furthermore, it also supports previous studies that have shown that an improvement in GLS is often seen after AVR (61). This study demonstrates the non-inferiority of TAVI compared to AVR regarding the recovery of both GLS and LVEF. Both

treatment arms; AVR and TAVI, undergo improvement in GLS from baseline to the 12-month post-intervention, and the 95% confidence interval adjusted mean difference between the two groups did not contain the non-interiority limit of-1%. Therefore, ANCOVA tests comparing the change in LVEF seen in each treatment arm were able to conclude that TAVI was non-inferior to AVR. Although, due to the larger standard deviation seen in the LVEF measurements for both groups, there was no statistically significant improvement in LVEF after intervention for either treatment arm.

Testing for correlations between the change in GLS from baseline to 12M and other metrics identified that although there was a highly significant correlation with the change in systolic blood pressure in those who underwent AVR, there was no such correlation in the TAVI treatment arm. It is possible that this could be related to the smaller aortic valve orifice area seen after TAVI. To investigate this, correlation with the mean aortic valve gradient could be analysed, but this data is not currently available.

The lack of significant change in LVEF after intervention may have been influenced by the variation in measurements, and the associated error. Yet the high values for ICC (O.87 and 0.99 for intra- and inter-analyst respectively) suggest that there is a high level of agreement and reliability in the LVEF measures, therefore the variation in LVEF measures is largely down to a true difference opposed to an inconsistency in analysis technique. As the baseline figures for LVEF are not largely impaired there is limited opportunity for improvement in LVEF within this cohort. This is supported by the negative correlation between baseline LVEF and change in LVEF. The trendline for the scatter chart intercepts the y-axis (change in LVEF) at a baseline value of 53.3%, meaning baseline values below this can be expected to see an increase at 12M, but baseline LVEF values above this can be expected to see a decrease from baseline to 12M. Additionally, the work of Dimitriadis *et al* investigated left ventricular adaption after TAVI and reported that there was only a significant improvement in LVEF in those with a baseline LVEF <40%(136). This is particularly pertinent once the other comorbidities that the UK TAVI cohort may have are taken into consideration. Although this study did not have access to the clinical history of subjects enrolled in the UK TAV trial it would be expected that a large proportion of this cohort may have comorbidities such as hypertension and coronary artery disease which can have

negative effects of LVEF. Additionally, drugs such as beta-blockers, commonly used to treat atrial fibrillation, can affect the contractility of the heart.

A study by Chen *et al*, using 3D STE to assess GLS prior and post-AVR in 20 subjects with severe AS, found that although GLS saw some improvement at 1 week and 1-month post-AVR, this was not significant until 3-months post-AVR. The cohort did not include subjects undergoing TAVI so intervention-dependant comparisons cannot be drawn(137). Even though the difference in the improvement of GLS at 6 weeks post-intervention between the two treatment wasn't statistically significant this is not to mean that it is not clinically relevant. Preliminary results of the SURTAVI trial show reduced estimated rates of stoke (both disabling and nondisabling, 3.4% vs 5.6%), MACCE (major adverse cerebrovascular and cardiovascular event, 5.7% vs 7.4%), and hospitalization for aortic-valve related disease (2.9% vs 4.2%), at 30 days post-intervention in TAVI compared to AVR. This supports the concept that recovery from TAVI, which is a less invasive procedure, may be quicker. Although, it must be noted that the 30-day figure for death from any cause was slighter higher in the TAVI group compared to the AVR group (2.2% vs 1.7%)(80). Data for the 12-month follow up demonstrated a reduction in the estimated differences between the treatment arms for all the above clinical outcomes; the rates for MACCE (13.2% TAVI vs 12.8% AVR) and hospitalization for aortic-valve related disease (8.5% TAVI vs 7.6% AVR) were slighter larger for TAVI(80). The reduction of difference in clinical outcome aligns with the finding of this study, that the recovery of GLS 12M was very similar between the treatment arms.

There was no significant difference between the key baseline characteristics of the two treatment arms, highlighting a key advantage of this study. Many of the studies investigating the recovery of cardiac mechanics post-TAVI have patient cohorts of high or very high surgical risk, and there is very limited work comparing the recovery of markers of LV function in randomised patients undergoing TAVI or AVR. This study, using randomised patients allows novel insight into the effect of different interventions on myocardial recovery while minimising the effects of both known and unknown confounding factors.

In conclusion, an investigation into the change in GLS and LVEF post-intervention demonstrated the non-inferiority of TAVI compared to AVR for both measures at 6-

weeks and 12M. There was a lack of long-term significant change in LVEF in either treatment arm, which is likely due to the fact that LVEF wasn't meaningfully reduced prior to intervention. There was recovery in GLS from baseline to 12M in both treatment arms and the potential superiority of TAVI for the recovery of GLS at 6-weeks post-intervention warrants further investigation and presents further evidence that GLS may be a more sensitive marker of LV recovery than LVEF.

Chapter 4 - The Assessment of Change in Short Axis Left Ventricular function.

4.1 Abstract

It is well established that severe aortic stenosis (AS) has negative effects on Left Ventricular (LV) function due to increased afterload and compensatory concentric hypertrophy. This dysfunction is seen in all three dimensions of LV deformation. This study investigated the impairment and recovery of LV circumferential and radial strain, and rotation, in patients of moderate surgical risk, with severe AS undergoing intervention. TTE scans from twenty subjects enrolled on the UK TAVI trial were analysed at pre-intervention, 6 weeks post-intervention(6W) and 12 months post-intervention (12M). Speckle Tracking Echocardiography (STE) was used to track regions of interest visualised in the Parasternal Long Axis (PSAX) views, at multiple ventricular levels. There was a significant difference (P=0.006) between mid-ventricular LV circumferential strain (LVCS) at baseline and 12M, but no significant correlations between the change in absolute circumferential strain and age (P=0.35), BSA (P=0.58), baseline LVCS (P=0.10), change in LVEF (P=0.22), or change in absolute GLS (P=0.94). The gradient of increase in LVCS from the base to the apex of the LV increased post-intervention. There was a statistically significant increase in left ventricular radial strain (LVRS) at 12M (P<0.001), but no correlation between change in radial strain and age (P=0.95), BSA (P=0.28), change in LVEF (P=0.40), or change in absolute GLS (P=0.99). The relationship between baseline LVRS and the change in LVRS was classed as statistically significant with a negative correlation (r=-0.437, P=0.05). It was not possible to conclude that there was a significant difference between 6W data and either baseline or 12M data for LVCS or LVRS, although mean values for both decreased in magnitude. There was a statistically significant decrease in apical rotation post-intervention (P=0.04) but not in basal rotation (P=0.39). The improvements seen in both LVCS and LVRS indicate that the LV dysfunction seen in these subjects is, at least partially, reversible with timely intervention. The change seen in short-axis function at 6W may be related to myocardial damage and recovery, but further studies are needed. The cohort of this study being a mix of subjects undergoing TAVI and AVR is more representative of the current clinical environment and provides applicable

findings. The key limitation of this study lay in the small sample size, which limited the statistical power of analyses.

4.2 Introduction:

LV function is a key component of overall cardiac function. Patients with severe AS encounter significantly increased afterload pressures in their LV due to the narrowed aortic valve orifice. This is compensated for by the development of concentric hypertrophy in the LV myocardium, as the subsequent increase in contractile force helps reduce systolic wall stress. Therefore, cardiac output will remain within a normal range(129). As the stenosis worsens and blood flow across the aortic valve drops the LV can no longer compensate, wall stress becomes elevated due to 'afterload mismatch' and LV function declines(129).

Myocardial strain assessment using STE an angle independent measure of chamber wall deformation during the cardiac cycle. STE can be used to assess the function of the LV in three contrasting directions; longitudinal, circumferential and radial (See chapter 2.1.4.1). The assessment of global longitudinal strain (GLS) in the LV is detailed in chapter 3. Circumferential strain tracks the circumference of the LV, and radial strain tracks the thickening of the myocardial wall itself and is analysed in the PSAX view. A progressive decline in short-axis function, dependent mostly on the circumferentially aligned mid-myocardial fibres, is associated with severe AS(138).

During ventricular systole the base and apex of the LV rotate in opposite directions, resulting in twisting of the LV, this can be measured in the PSAX views during TTE (72). LV twist and untwist is a key systolic-diastolic link and important in maintaining LV function and LV ejection fraction (LVEF)(139). It is known that in patients with severe AS LV twist is increased, due to increased apical rotation while basal rotation stays within the normal range(72, 130). The increased apical rotation is likely linked to subendocardial dysfunction and therefore the reduced influence of those fibres aligned in a right-handed helix (detailed in Chapter 2.1.4) and it has been shown to normalise after surgical AVR(72, 130, 139) and TAVI(140, 141). Many of the studies investigating the recovery of cardiac mechanics post-TAVI have patient cohorts of high or very high surgical risk(140). Uddin et al (2014) reviewed a cohort of patients where

the cohort undergoing TAVI had a EuroSCORE (European System for Cardiac Operative Risk Evaluation) of 22 ± 14 and those undergoing AVR a EuroSCORE 7 ± 3 (141). With such discrepancies of the surgical risk and patient health, comparisons cannot be drawn between the recover after AVR and TAVI. This study will provide novel data regarding the recovery of LV short-axis deformation (strain and twist) in a mixed group of patients of intermediate surgical risk who were randomised to receive either AVR or TAVI. As the cohort is deemed of intermediate risk by a MDT (see chapter 2.1) opposed to set cut off on a scoring system, this study is more representative of clinical practice in the UK.

4.3. Aims:

To assess the change in LV circumferential and radial strains and basal and apical rotation after intervention by AVR and TAVI.

To evaluate both the overall change from Baseline to 12M and the short-term change seen at 6W.

4.4 Methods:

Subjects were selected from the cohort of the UK TAVI national trial. All subjects had severe AS and met the inclusion and exclusion criteria of the UK TAVI trial. Subjects had severe AS and were randomised to undergo either surgical aortic valve replacement (AVR) or transcatheter aortic valve insertion (TAVI). Additionally, the TTE images met the specified criteria regarding image quality and format to enable accurate STE tracking (See Chapter 2.2.1). From the cohort of subjects where LV global longitudinal strain had been assessed short-axis LV function was also assessed when TTE image quality allowed. LV short-axis function was assessed via the measurement and analysis of circumferential strain, radial strain, apical rotation, and basal rotation. Of the TTE scans for 142 subjects that were reviewed, of these only 20 subjects had suitable image quality to allow for assessment of circumferential and radial strain at both baseline and 12M. 11 subjects had suitable image quality to allow for assessment of LV rotation at baseline and 12M. Image quality assessment was made by the analyst

and was based on the presence of on-axis PSAX images, lack of artefact and the myocardium being clearly visible throughout the cardiac cycle. Height, weight, blood pressure and heart rate were measured at each study site and provided along with the TTE images.

4.4.1 Image Analysis.

LV short-axis function was assessed in the parasternal short-axis view. Circumferential strain was measured primarily at the mid-ventricular level, but also at the apical and basal levels were image quality allowed. Radial strain was measured only at the mid-ventricular level, while rotation was measured at apical and basal levels. Analysis of the scans was conducted offline using vendor-independent software (TomTec Imaging, Germany, Version 4.6). Based on the ECG and visual tracking of the myocardium, the timepoints of peak LV systole and diastole were identified. The region of interest (ROI) was selected at these timepoints by tracing the myocardium of the LV wall. The ROI was reviewed and manually adjusted as required to ensure accurate tracking throughout the cycle. Figure 4.1 illustrates these steps in the PSAX view at the basal level. These steps were then repeated at the apical, and mid-ventricular levels. Output graphs were generated by the software (2D CPA. TomTec Imaging, Germany) tracking circumferential and radial strains, and rotation throughout the cardiac cycle. Peak strain values were recorded from STE output graphs for each applicable view.

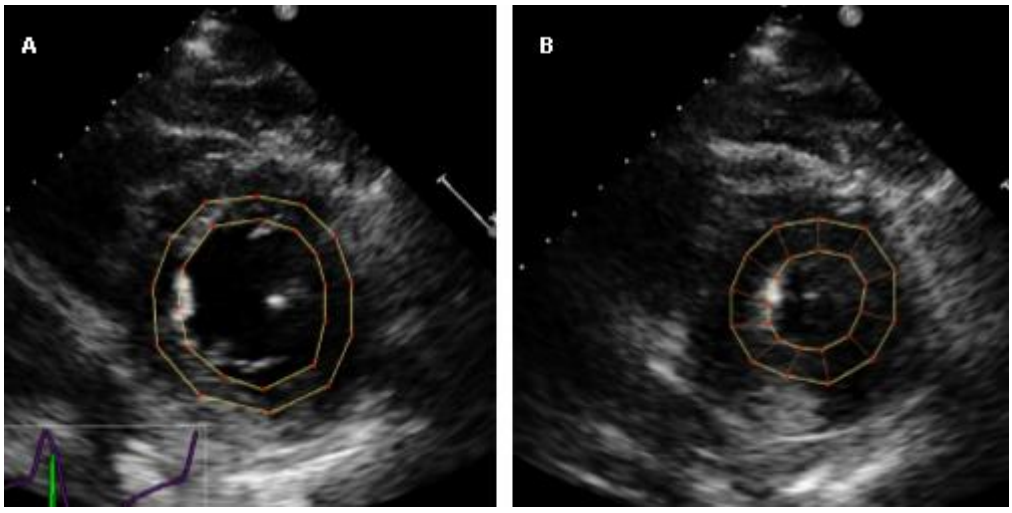


Figure 4.1: Tracking of the myocardium at diastole (A) and systole (B) in the PSAX view at the basal level. *PSAX: Parasternal short-axis view.*

4.4.2 Statistical Analysis

Data was tested for normality using the Shapiro-Wilk test, the null hypothesis that the data was normally distributed was accepted if $p>0.05$. Statistical analyses were conducted using IBM SPSS (Version 26). Continuous measures were expressed as mean ±standard deviation and analysed for overall change from baseline to 12-months post using paired t-tests (detailed 3.7.1). $P<0.05$ was considered statistically significant. Pearson's correlation coefficient was used to assess bivariate correlations between patient demographics and the value of measurements, and between different measurements.

4.5 Results

4.5.1 Changes in Left Ventricular Circumferential Strain

LV circumferential strain was analysed in the PSAX view, at the level of the papillary muscles in 20 subjects (Mean age 82.3 years, 55% male, mean systolic BP 153.7 mmHg, mean BSA 1.82m^2). In 7 subjects this data was also able to be measured at the 6W timepoint.

Mean LVCS rose from 20.8% at baseline to -23.5% at 12M (P=0.006) (Table 4.1, Figure 4.2). There were no significant correlations between the change in absolute circumferential strain and age (P=0.35), baseline BSA (P=0.58), baseline LVCS (P=0.10), change in LVEF (P=0.22), or change in absolute GLS (P=0.94). The data for change in LVCS from baseline to 12M was normally distributed (P=0.98).

Due to the smaller sample size and larger standard deviation of the 6-week post-intervention data, it was not possible to conclude that there was a significant difference between 6-week data and either baseline or 12-month data.

	Baseline	6 weeks post-intervention (n=7)	12 months post-intervention
Mean (%)	-20.81 *	-18.26	-23.53 *
Standard Deviation (%)	4.89	7.33	5.02

Table 4.1 Circumferential strain measured at the papillary muscle level in the PSAX view. *Pre and Post Intervention for severe aortic stenosis. * Significant Difference between baseline and 12-months post-intervention (P=0.006).*

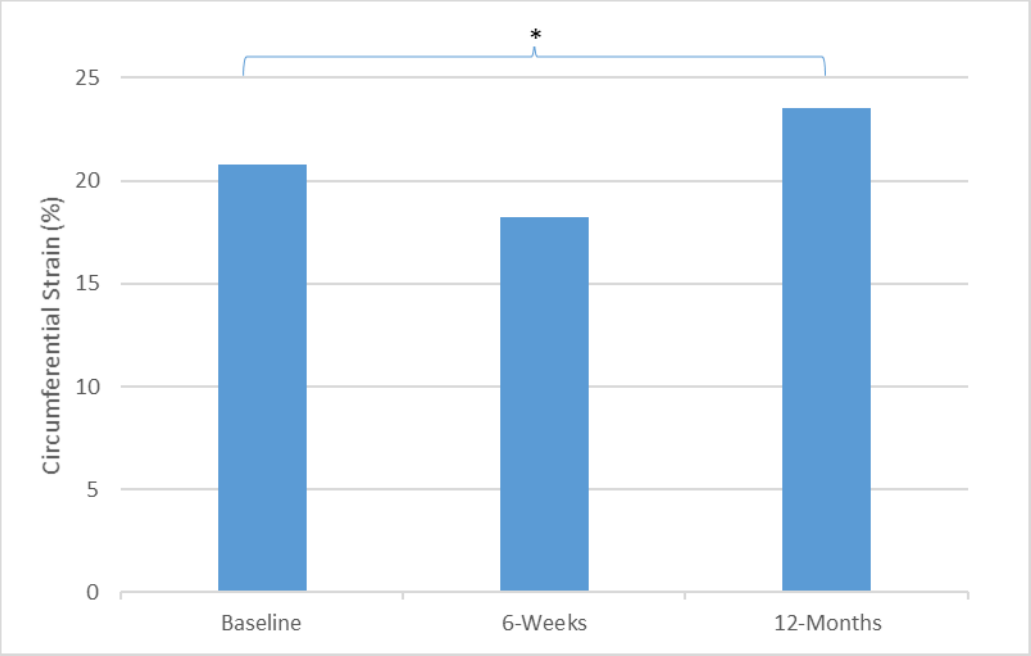


Figure 4.2: Absolute Values of circumferential strain at baseline, 6W and 12M timepoints*. Baseline and 12M N=12, 6W N=7. * = Significant difference between baseline and 12M (P=0.006). Unable to conclude that there was a significant difference between 6-week data and either baseline or 12-month data.*

The sample size was not large enough to conduct meaningful statistical tests comparing the subjects and recovery after AVR and TAVI. Figure 4.3 displays the mean absolute value for circumferential strain at baseline and 12M for each treatment group. Those who underwent AVR saw a mean increase in the magnitude of LVCS of 3.1% (21.68 to 24.74%), and those who underwent TAVI saw a mean increase in the magnitude of LVCS of 2.6% (20.52 to 23.11).

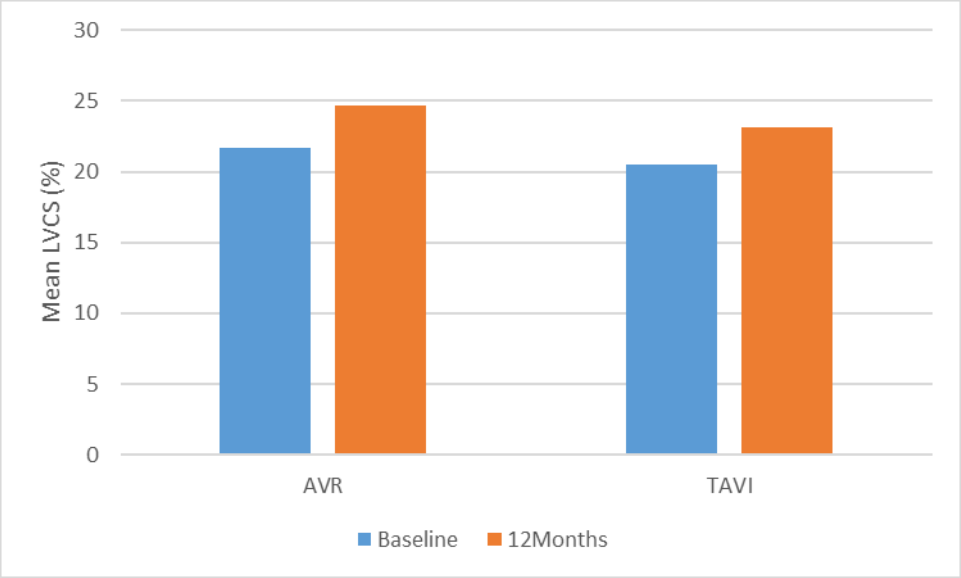


Figure 4.3: Mean absolute value of Left Ventricular Circumferential Strain (LVCS) at baseline and 12-Months Post-Intervention for subjects undergoing AVR and TAVI*. AVR: N= 5. TAVI: N=15*

To further explore LV circumferential strain, it was measured at all three levels of the LV in the PSAX view; basal, mid, and apical where image quality allowed (n=7). Both pre- and post-intervention, the magnitude of LVCS increases as you progress from the base of the LV, at the mitral valve, through to the apex of the chamber. Pre-intervention, mean basal LVCS was -19.8%, increasing to -21.3% at the mid-level (7.5 % increase), and -25.1% at the apical level (26.8 % increase from basal level) (Table 4.2, Figure 4.4). The gradient of LVCS increase was greater 12M; mean basal LVCS was -17%, increasing to -25.2% at the mid-level (48.2 % increase), and -28.3% at the apical level (66.5 % increase from basal level) (Table 4.2, Figure 4.4). The difference between basal and apical LVCS was not significant pre-intervention (P=0.11), but there was a strong statistical difference between basal and apical CS at 12M (P=0.005).

	Baseline	12-Months Post-Intervention
Base (%)	-19.8 ±5.9	-17.0 ±4.0
Mid-Level (%)	-21.3 ± 3.7	-25.2 ±2.6
Apex (%)	-25.1 ± 4.5	-28.3 ±5.3

Table 4.2 Circumferential strain measured at basal, mid and apical levels in the PSAX view *(Mean ± SD). Pre- and 12-Months Post-Intervention for severe aortic stenosis.*

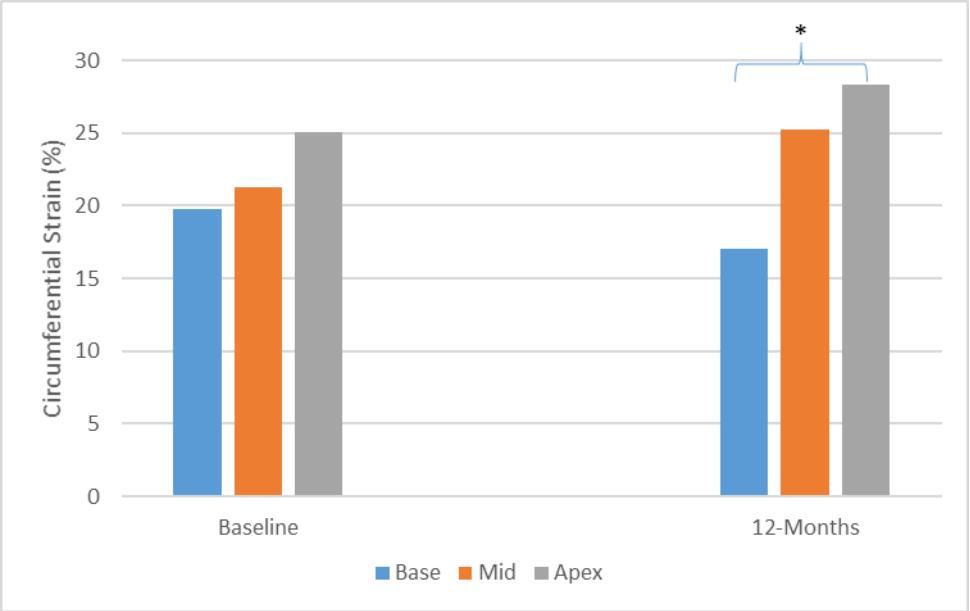


Figure 4.4: Circumferential Strain in the Left Ventricle. *Absolute values. Measured at three levels in the LV, in the PSAX view, pre- and post-intervention. N=7. Paired t-tests concluded there was no significant difference in basal and apical CS at baseline (P=0.11), but there was at 12M post-intervention (P=0.005)*

4.5.2 Changes in Left Ventricular Radial Strain

LV radial strain was analysed at baseline, and 12M in the PSAX view, at the level of the papillary muscles in the same cohort of 20 subjects as circumferential strain. Radial strain was also able to be analysed in the 6-week post-intervention TTE for 7 subjects. The mean radial strain was 37.4% (±11.9%) at baseline, this reduced to 35.2% (±15.9%) at 6W, before increasing to greater than baseline levels (47.2 ±10.9%) at 12M (Table 4.3). A paired t-test was conducted between the data sets for baseline and 12-month post-intervention data, demonstrating statistical significance with $p<0.001$ (Figure 4.5). There was no significant correlation between change in radial strain and age (P=0.95), BSA (P=0.28), change in LVEF (P=0.40), or change in absolute GLS (P=0.99). The relationship between baseline radial strain and the change in radial strain was statistically significant with a negative correlation (r=-0.437, P=0.05). Indicating that the higher the baseline value the smaller the expected increase in value between baseline and 12M. There was no statistically significant difference between the values for radial strain at baseline and 6-weeks (P=0.72) for subjects with available data (N=7,

TAVI=6, AVR=1). The data for change in LVRS from baseline to 12M was normally distributed (P=0.06).

	Baseline (n=20)	6 weeks post intervention (n=7)	12 months post intervention (n=20)
Mean (%)	37.4	35.2	47.2
Standard Deviation (%)	11.9	15.9	10.9

***Table 4.3 Radial Strain measured at papillary muscle level in the PSAX view**. Pre and Post Intervention for severe aortic stenosis.*

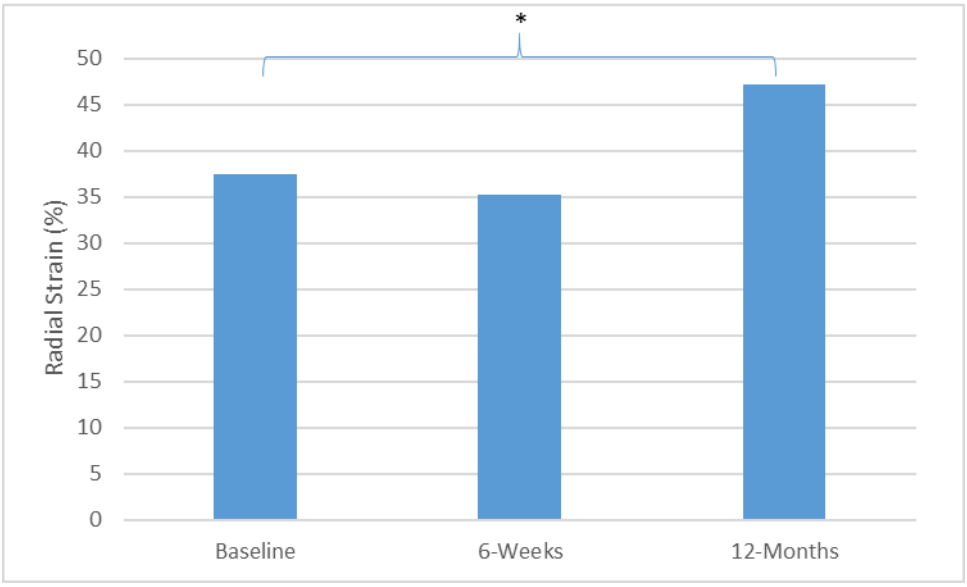


***Figure 4.5 Values of radial strain at baseline, 6W post, and 12M post-intervention**. Significant difference between baseline and 12M timepoint (*P<0.001)*

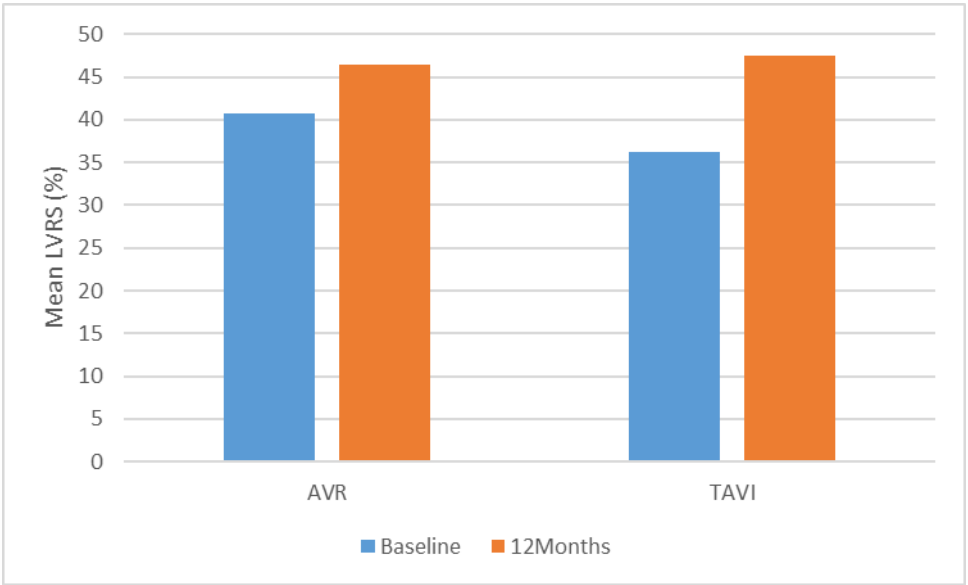


***Figure 4.6: Mean Left Ventricular Radial Strain (LVRS) at baseline and 12-Months Post-Intervention for subjects undergoing AVR and TAVI.** AVR: N=5, TAVI N=15.*

Figure 4.6 displays the mean values for radial strain at baseline and 12M for each treatment group. Those who underwent AVR had a higher mean baseline value (40.8 AVR vs 36.2% TAVI), but both treatment arms saw an increase in mean radial strain. The mean increase baseline to 12M was 5.6% for the AVR treatment arm and 11.3% in the TAVI treatment arm.

4.5.3 Changes in Left Ventricular Rotation

11 subjects had suitable images from analysis of apical rotation in both the baseline and 12-month post-intervention scans (mean age 82.7 years, 27.3% male, mean systolic BP 156.8 mmHg, mean BSA 1.77m^2). The mean value for apical rotation pre-intervention was 9.34^o (±3.35^o). This decreased by a mean of 2.76^o (±3.97^o) from baseline to 12M (P=0.04) (table 4.4).

	Baseline (n=12)	12 months post intervention (n=12)
Mean (^{o})	9.34	6.57
Standard Deviation (^{o})	3.35	3.02

Table 4.4 Apical Rotation measured in the PSAX view, Pre- and Post-Intervention for severe aortic stenosis.

Basal rotation was not able to be measured in one of the above subjects. For the remaining 10 subjects, basal rotation mid-ventricular. The mean basal rotation increased in absolute value slightly between baseline and 12-month post-intervention scans from -6.65 ^{o} to -7.50 ^{o}, this was not deemed statistically significant (p=0.39) (Table 4.5).

	Baseline (n=11)	12 months post intervention (n=11)
Mean	-6.65	-7.50
Standard Deviation	2.64	3.39

Table 4.5 Basal Rotation measured in the PSAX view, *Pre- and Post-Intervention for severe aortic stenosis*

Data was normally distributed for both change in apical (P=0.52) and basal rotation (P=0.58). There was no significant correlation between baseline apical rotation and change in GLS (r=-0.07, p=0.83), change in LVEF (r=0.186, p=0.56), or change in apical rotation (r=-0.424, p=0.17). Although the Pearson's correlation coefficient (r-value), does show a relationship between baseline apical rotation and the change seen, that the greater the baseline value, the larger the reduction.

4.5.4 Quality Assurance:

Five scans were assessed for both intra-analyst variation and compared to the 'gold standard' of an expert analyst. The ICC value for circumferential strain, measured at the mid-ventricular level, was 0.944 for intra-analyst reliability and 0.908 For inter-analyst reliability. The ICC values for radial strain were slightly lower for intra-analyst variability 0.913, and 0.964 for inter-analyst comparison. The ICC values for basal rotation were 0.834 for intra-analyst reliability and 0.957 for inter-analyst reliability. Finally, for apical rotation, the ICC values were 0.918 and 0.924 for intra- and inter-analyst reliability respectively (Table 4.6). ICC values are on a scale of 0-1, an ICC value of 0.75-0.9 indicates good reliability, and a value >0.9 indicates excellent agreement between the data sets. The variability of each of the measurements was also assessed via Bland-Altman plots (Figures 4.7-4.14). These allow visualisation of the data and the identification of any outliers. A mean difference that is small compared to the mean value of the data demonstrates that there was no systemic shift in the measurement method.

	Intra-analyst reliability	Inter-analyst reliability
Circumferential Strain	0.944	0.908
Radial Strain	0.913	0.964
Basal Rotation	0.834	0.957
Apical Rotation	0.918	0.924

Table 4.6 ICC Values for left ventricle measurements taken in the PSAX view. *A value of 0.75-0.9 indicates good reliability, and a value >0.9 indicates excellent reliability.*

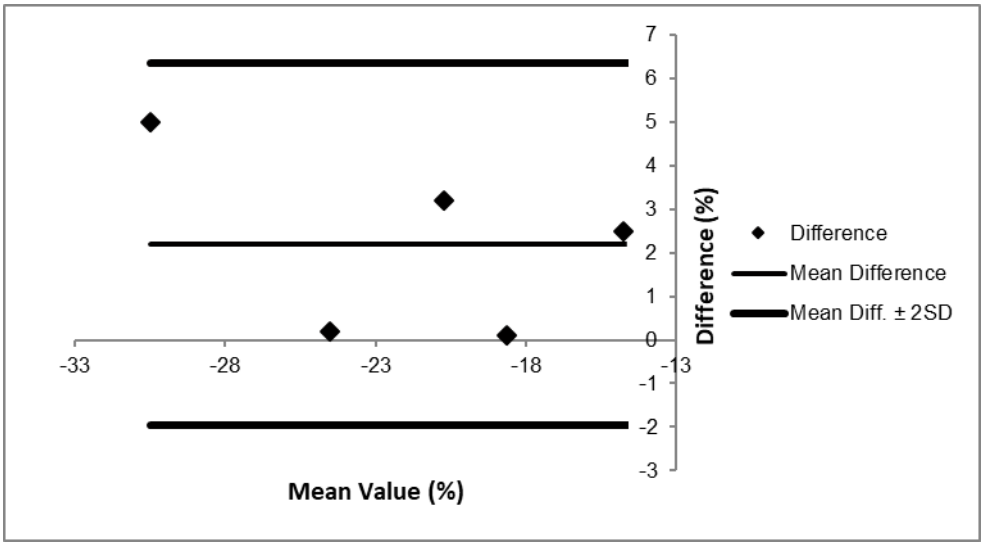


Figure 4.7: Bland Altman Plot of the intra-reader variance of LV circumferential strain. *LVCS was measured at the mid-ventricular level in the PSAX view. Mean difference = 2.2%, Standard Deviation = 2.08%.*

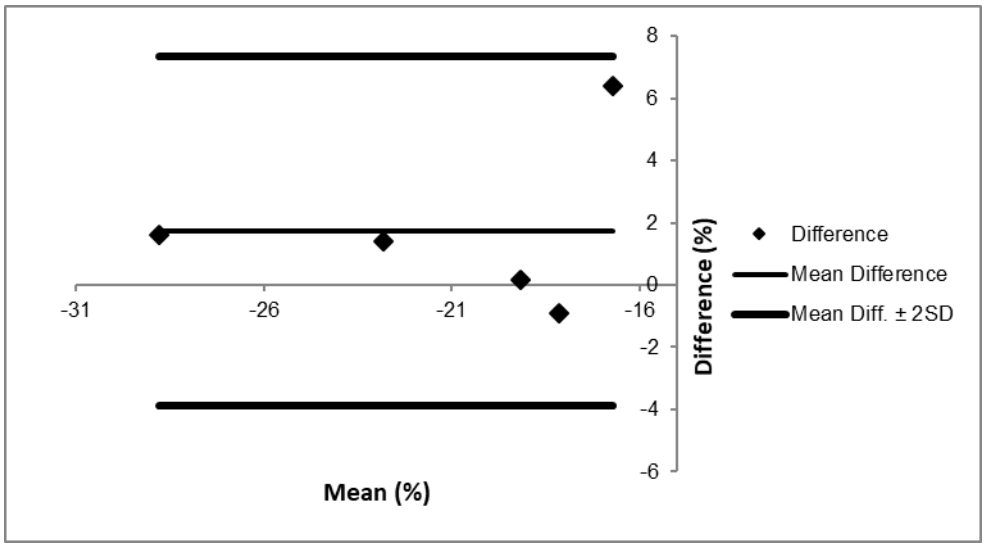


Figure 4.8: Bland Altman Plot of the inter-reader variance of LV circumferential strain. *LVCS was measured at the mid-ventricular level in the PSAX view. Mean difference = 1.7%, Standard Deviation = 2.8%. Each data point represents one set of paired data.*

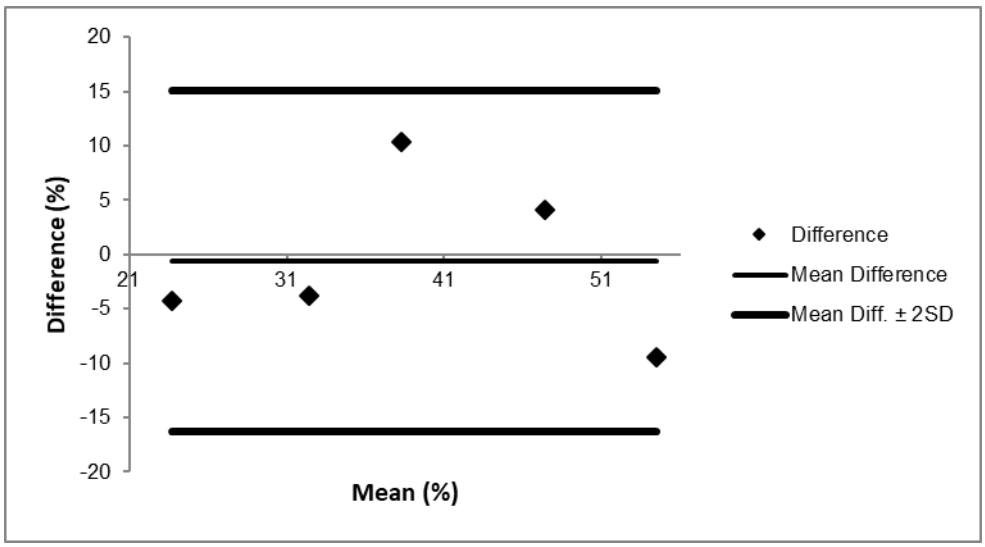


Figure 4.9: Bland Altman Plot of the intra-reader variance of LV radial strain. *LVRS was measured at the mid-ventricular level in the PSAX view. Mean difference = -0.6%, Standard Deviation = 7.8%. Each data point represents one set of paired data (read one and two).*

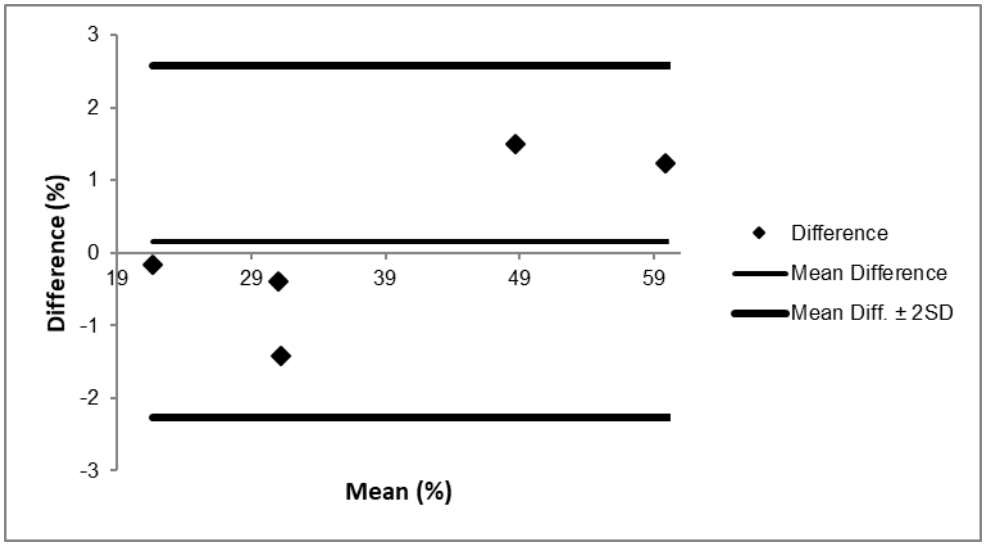


Figure 4.10: Bland Altman Plot of the inter-reader variance of LV radial strain*. LVRS was measured at the mid-ventricular level in the PSAX view. Mean difference = 0.2%, Standard Deviation = 1.2%. Each data point represents one set of paired data.*

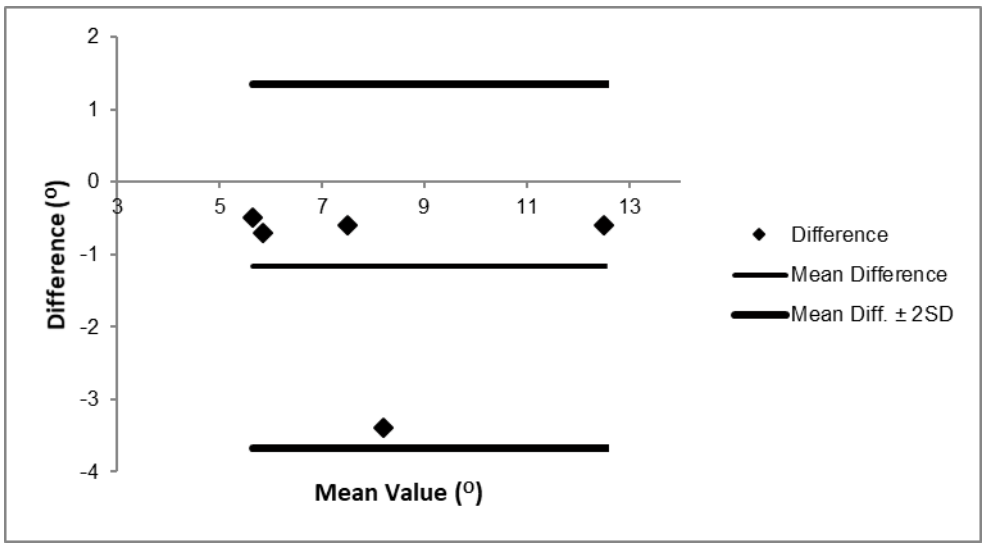


Figure 4.11: Bland Altman Plot of the intra-reader variance of LV apical rotation. *Measured at the level of the mitral apex of the LV in the PSAX view. Mean difference = 1.2º, Standard Deviation = 1.3º. Each data point represents one set of paired data (read one and two)*

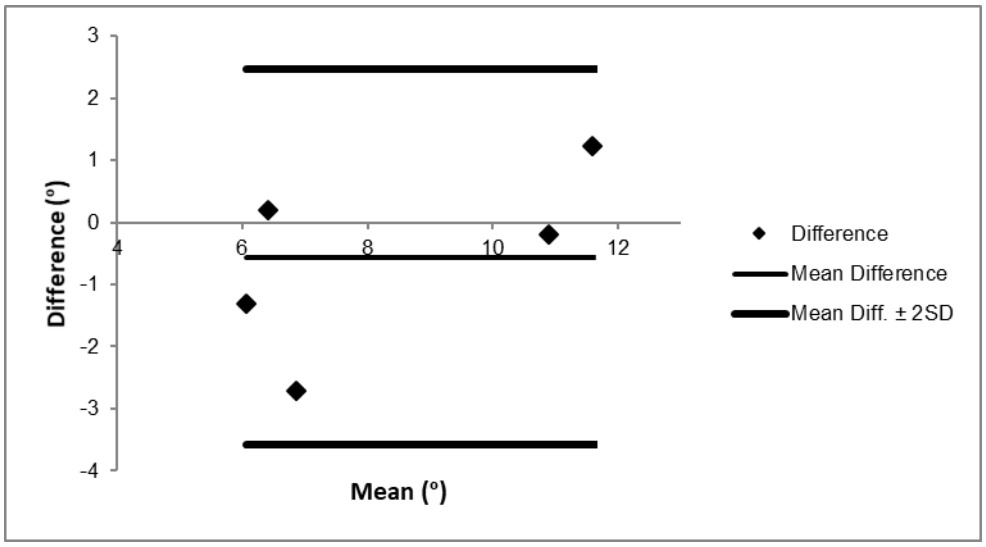


Figure 4.12: Bland Altman Plot of the inter-reader variance of LV apical rotation. *Measured at the level of the mitral apex of the LV in the PSAX view. Mean difference = -0.6º, Standard Deviation = 1.5º. Each data point represents one set of paired data.*

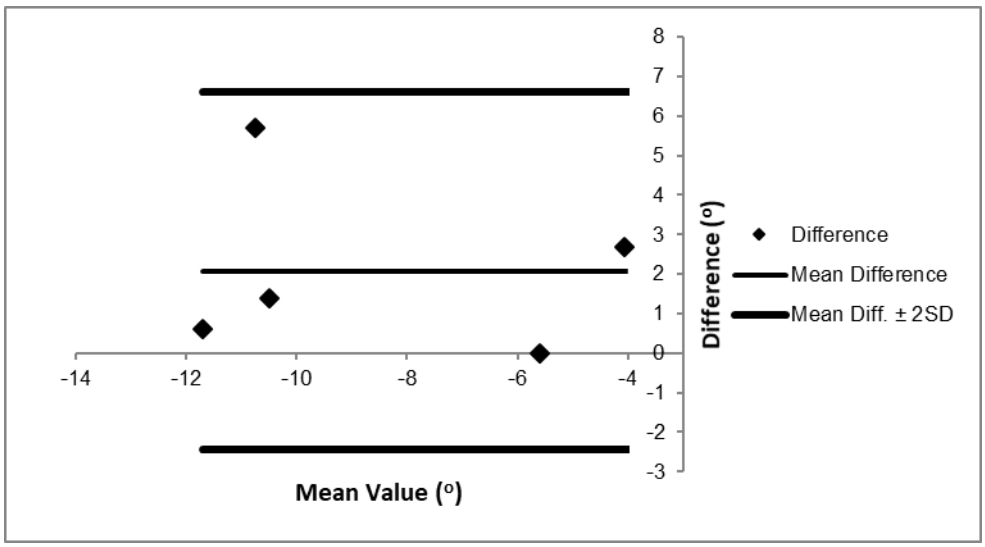


Figure 4.13 Bland Altman Plot of the intra-reader variance of LV basal rotation. *Measured at the level of the mitral valve in the PSAX view. Mean difference = 2.1°, Standard Deviation = 2.3°. Each data point represents one set of paired data (read one and two).*

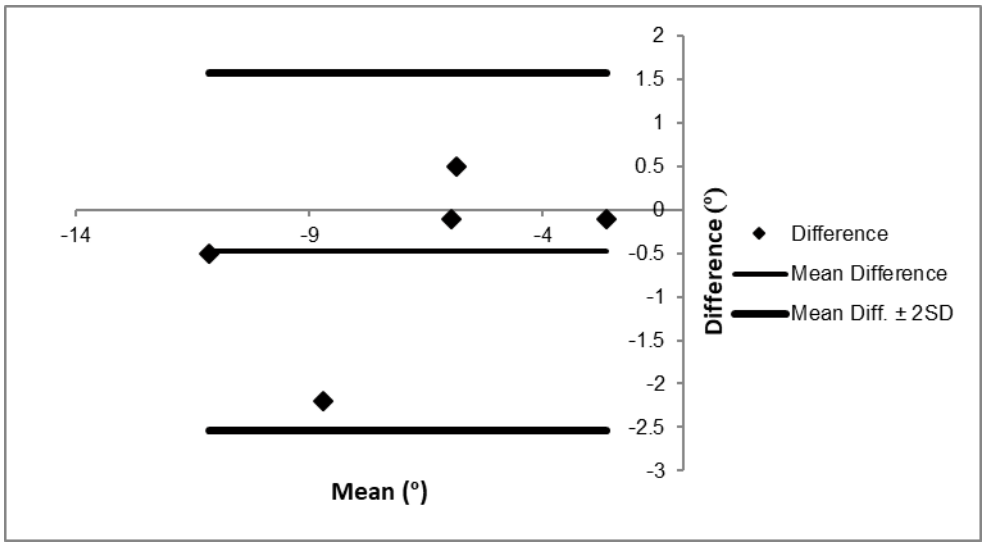


Figure 4.14: Bland Altman Plot of the inter-reader variance of LV basal rotation. *Measured at the level of the mitral valve in the PSAX view. Mean difference =-0.5º, Standard Deviation =1.0º. Each data point represents one set of paired data (read one and two).*

4.5 Discussion and Conclusions.

This study found that both circumferential and radial LV strain improved at 12M, compared to the baseline values. The magnitude of circumferential strain increased to near normal values (46, 74). These improvements indicate that at least some of the LV dysfunction is reversible in this cohort. When considering the directions of strain in the LV, it is key to remember that because of the complex muscle fibre arrangement each

direction of strain is not controlled by only one layer of myocardial muscle. For example; the helical fibres of the subendocardium, not just the circumferential mid myocardial fibres, contribute to circumferential shortening. The contribution of circumferential, radial and longitudinal LV strain to overall ventricular function has not yet been fully established. This may be due to contrasting methodologies in in-vivo studies. Using computer modelling Maciver (2012), concluded that although reducing either longitudinal or circumferential shortening in the LV lead to a reduction LVEF and stroke volume, the reduction of LVCS had approximately twice the impact of reducing longitudinal shortening (142). If these findings stand true in the human model than this illustrates the importance of the recovery of LVCS after an intervention.

Due to the small sample size of this study, the recovery of LVCS and LVRS in AVR and TAVI were not statistically compared but figures 4.3 and 4.6 show visual comparisons of the two interventions. There were no striking differences between the treatment groups for baseline and 12M values for LVCS. Those who underwent TAVI experienced a larger mean increase in LVRS than the subjects who underwent AVR, but further data is required to explore if this is a true difference in recovery.

Although not statistically significant in both CS and RS the mean value dropped from baseline to 6-weeks post. Before increasing again at 12-months. One reason that the short axis strain reduces at 6W may be because it is no longer required to compensate for impaired LV longitudinal strain. Although, the CS was not supra-normal at baseline, and the mean value at 12M is greater than at baseline. Taking this into consideration, and the large standard deviation of CS at 6W, it is more likely that the drop seen is down to myocardial damage and recovery from intervention. Chen *et al* studied the recovery of GLS and LVCS in a cohort of 20 subjects with severe AS undergoing AVR, they reported that LVCS declined a 1-week post-AVR compared to pre-AVR figures, rising slightly by 1-month post-AVR, but a significant improvement compared to baseline wasn't reported until 3-months post-AVR(137).

In healthy individuals, the magnitude of circumferential strain increases from the base to the apex of the LV(74). This can be demonstrated by measuring LVCS at the level of the mitral valve, papillary muscles and LV apex. In subjects where there was adequate image quality to measure LVCS as all three levels (n=7), there was a striking increase in the gradient of LVCS between pre-intervention and 12M data. The insertion of a

prosthetic valve, whether via AVR or TAVI, will affect the flexibility of the basal region of the LV, making it stiffer. Therefore, this would explain the decrease in basal LVCS. The increase seen in mid-level and apical LVCS may reflect both myocardial recovery, and compensation for the reduced basal deformation.

The results demonstrate that pre-intervention apical rotation is exaggerated, and thus LV rotation is greater than in quoted normal values. There is some discussion in the literature regarding the 'normal' values, although it is accepted that physiological LV twist changes with age. Data collected from the NORRE study control subjects provided a mean value for LV twist of 7.9^{o}[74]. In contrast, Kocabay *et al* reported values for -6.9^{o} for basal strain, and 13^{o} for apical strain in their cohort of healthy adults which equates to a twist of up to 19.9^{o} (73). However, that study recruited adults with a mean age of 44 years, and it is known that twist increases with age.

As twist is governed by subepicardial fibres, subendocardial ischemia caused by reduced myocardial perfusion in severe AS has a large effect on LV twist by further reducing the opposing forces of the subendocardial fibres. Additionally, exaggerated twist in severe AS may act as a compensatory mechanism for the reduced long axis function, also caused by subendocardial ischemia, to help maintain global LV function Previous papers have shown that LV twist correlates positively with aortic valve jet velocity, and mean gradient (72).

The improvement seen in LV twist aligns with the improvement in LV longitudinal function seen in patients undergoing intervention for severe AS (see Chapter 4.4).

In this small cohort the results correlated with the current body of knowledge regarding the recovery of twist in patients after intervention for severe AS (130, 143). Whereas many previous papers had cohorts purely of AVR, this study recruited a mixed cohort undergoing both AVR and TAVI. This is more representative of the current clinical environment where both procedures are commonly undertaken. The key limitation of this sub-study lay in the small number of subjects. Images were acquired as part of a multi-site trial and retrospective analysis conducted; therefore, the image quality was not able to be fully controlled. Although, the very strong levels of inter- and intra-analyst reproducibility demonstrate the reliability of the results. The small sample size limited the power of statistics run and made it unwise to reduce the

sample sizes further by splitting the subjects according to intervention. Therefore, intervention dependent recovery cannot be investigated. It does provide a detailed examination of the short axis deformation in the LV pre- and post-intervention for AS and will provide a basis for future, intervention specific, studies.

In conclusion; intervention has a positive effect on the short axis function of the LV in patients with severe AS. Due to the complex interaction of the multiple myocardial layers in the LV myocardium, all three dimensions of myocardial deformation are key in ensuring good LV function, cardiac output, and clinical outcomes.

Chapter 5 - The Assessment of change in Right Ventricular Strain.

5.1 Abstract

The function of the right ventricle (RV) in severe aortic stenosis (AS) has had little focused research. Yet due to its sensitivity to pulmonary resistance, and the shared interventricular septum between the Left ventricle (LV) and RV, RV function is likely to be negatively affected by LV dysfunction that occurs in severe AS. This study aimed to quantify RV function in severe AS, pre- and post-intervention, using STE measured RV global longitudinal strain (RVGLS), and compare the recovery seen after TAVI and AVR. TTE scans taken pre- and 12-months post-intervention, from 25 subjects in the UK TAVI trial were analysed using speckle tracking echocardiography. The overall mean baseline RVGLS was -16.3% and had a significant correlation with both GLS (P=0.005) and LVEF (P=0.003). There was no significant difference in baseline RVGLS according to gender (P=0.91) or treatment arm (P=0.26). The mean RVGLS increased in magnitude from -15.1% to -16.1% in the AVR treatment arm, and -17.0% to -17.2% in the TAVI treatment group. The non-inferiority of TAVI to AVR regarding the recovery of RVGLS could not be concluded (Adjusted mean difference= -0.458 (90%CI -3.03-2.12)). There was also an absence of evidence that there is a significant difference between the two treatment arms (P=0.62). RVGLS dropped in absolute value from baseline to 6W in both treatment arms. This reduction was more dramatic in the AVR group, but not significantly so, there was a 2.6% reduction in RVGLS in the AVR treatment group compared to 1.1% reduction in the patients in the TAVI group (P=0.47). Although there was an absence of statistically significant findings (P<0.05), this work provides preliminary data regarding the comparison of the recovery of RVGLS in patients with severe AS after intervention. The data suggested that there was no significant difference in the recovery seen at 12-months post-intervention, but that there is a potential difference at 6-weeks, with subjects undergoing TAVI experiencing less of a decline in RVGLS before recovery. Due to the limited sample size, further testing, with the aim of establishing statistical significance, should be conducted.

5.2 Introduction

LV function in AS has been extensively investigated, but there has been scarce work regarding the RV. RV function is influenced by multiple factors and is not independent of LV function. The RV and LV share the interventricular septum, the contraction of which contributes to RV systolic function. Additionally, RV function will be influenced by the afterload it experiences in the form of pulmonary resistance. Total pulmonary resistance is highly affected by LV end-diastolic pressure. Therefore, when LV function declines in severe AS, it is likely to also cause some degree of RV dysfunction. Additionally, the superficial fibres in the RV myocardial wall connect to the myofibers of the LV via the cardiac apex, therefore adding further LV influence over RV deformation(37).

The function of the RV not only plays an important role in pulmonary perfusion but also there is interdependence between the ventricles. Not only does LV function affect the RV but RV dysfunction may affect LV function, as it will limit LV preload and the effects of the intraventricular septum(144). Additionally, RVEF has been shown to be an independent predictor of survival in patients with moderate chronic heart failure(145). Therefore, it is likely to have an important role in cardiac function in those with severe AS, where heart failure develops as the disease progresses.

When measuring RV longitudinal strain by STE there is some inconsistency regarding whether to track only the free wall of the RV or to include the septal wall and measure global RV longitudinal strain. This is because the septal wall is predominantly controlled by the LV and influenced by LV function. This study will measure global RV longitudinal strain, in line with current EACVI/ASE guidelines(44) as although the septal wall is heavily influenced by LV function, it contributes to RV function (42, 43).

A review and recommendation document from the American Society of Echocardiography proposed that global longitudinal RV free wall strain > −20% (<20% in absolute value) should be considered abnormal(146). However, this was concluded from the results of only two, single-centre, studies, and is therefore not very robust compared to the well-established normal figures for LV global longitudinal strain (GLS). Tadic et al (2019) reported a mean RVGLS value of -18.8±2.0% in subjects with severe AS but no arterial hypertension, and -17.1±2.0% in subjects with both pathologies (65).

Forsberg et al (2011), concluded that RV function is negatively affected by traditional valve replacement, but not TAVI, in the short to medium term (40). Seventeen TAVI patients were matched by gender, age (±10 years), and LV function to patients undergoing AVR at the same site. Interestingly the TAVI patients were all deemed high risk and unsuitable for AVR and had a mean EuroSCORE 17 ± 9%, compared to the SAVR group with a mean EuroSCORE of 7 ± 5%. Therefore, the results seen could have been affected by the lower pre-procedural RV function in the TAVI group and must be interpreted with care especially as the sample size was small(40). More recent work has suggested that although tricuspid annular plane excursion (TAPSE) is reduced post AVR, transverse contraction increased. And overall RV stoke volume, assessed by 3D volumes, remained unchanged (41). This work hopes to add to the body of knowledge regarding RV functional recovery post-AVR and TAVI.

5.3 Aim:

To quantify RV function in severe AS, pre- and post-intervention, using STE measured RV global longitudinal strain (RVGLS). To compare the recovery in RVGLS after surgical AVR and TAVI at 6 weeks and 12 months post-intervention.

5.4 Methods

Subjects were selected from the cohort of the UK TAVI national trial. All subjects had severe AS and met the inclusion and exclusion criteria of the UK TAVI trial. Subjects had severe AS and were randomised to undergo either surgical aortic valve replacement (AVR) or transcatheter aortic valve insertion (TAVI). Additionally, the TTE images met the specified criteria regarding image quality and format to enable accurate STE tracking (See Chapter 2.2.1). From the cohort of subjects where LV global longitudinal strain had been assessed RV longitudinal strain was also assessed when TTE image quality allowed (n=25). Images were deemed unsuitable for analysis if there was no RV focused apical 4-chamber view, the RV apex was cut off, or the myocardium was poorly defined due to image quality

5.4.1 Image Analysis

Using commercially available software (2DCPA, TomTec Imaging v4.6, Germany), RV longitudinal strain was measured in the Apical 4 chamber view. To measure strain by STE firstly peak systole and diastole were identified and marked on the image loop, the inner edge of the myocardium was then traced at these two time-points. The software then tracked the myocardium throughout the cardiac cycle. The tracking was visually reviewed for accuracy and adjusted as needed before approval (see figure 5.1) Once approved an output was produced that showed a trace of Strain vs Time for the selected region of interest (ROI) and time frame. From this, peak strain could be recorded.

5.4.2 Statistical Analysis

RV global longitudinal strain (RVGLS) was analysed for overall change from baseline to 12-months post-intervention using paired t-tests and non-inferiority testing (n=25, detailed Chapter 2.7.1).

ANCOVA was used to assess the rate of change in both study arms and assess for differences in the 6-week recovery of RVGLS in subjects who underwent TAVI compared to those to underwent AVR (n=15).

Data for change in RVGLS was tested for the normality of distribution in both treatment groups using the Shapiro-Wilk Test. Pearson's correlation coefficient was used to assess bivariate correlations between patient demographics and the value of measurements, and between different measurements.

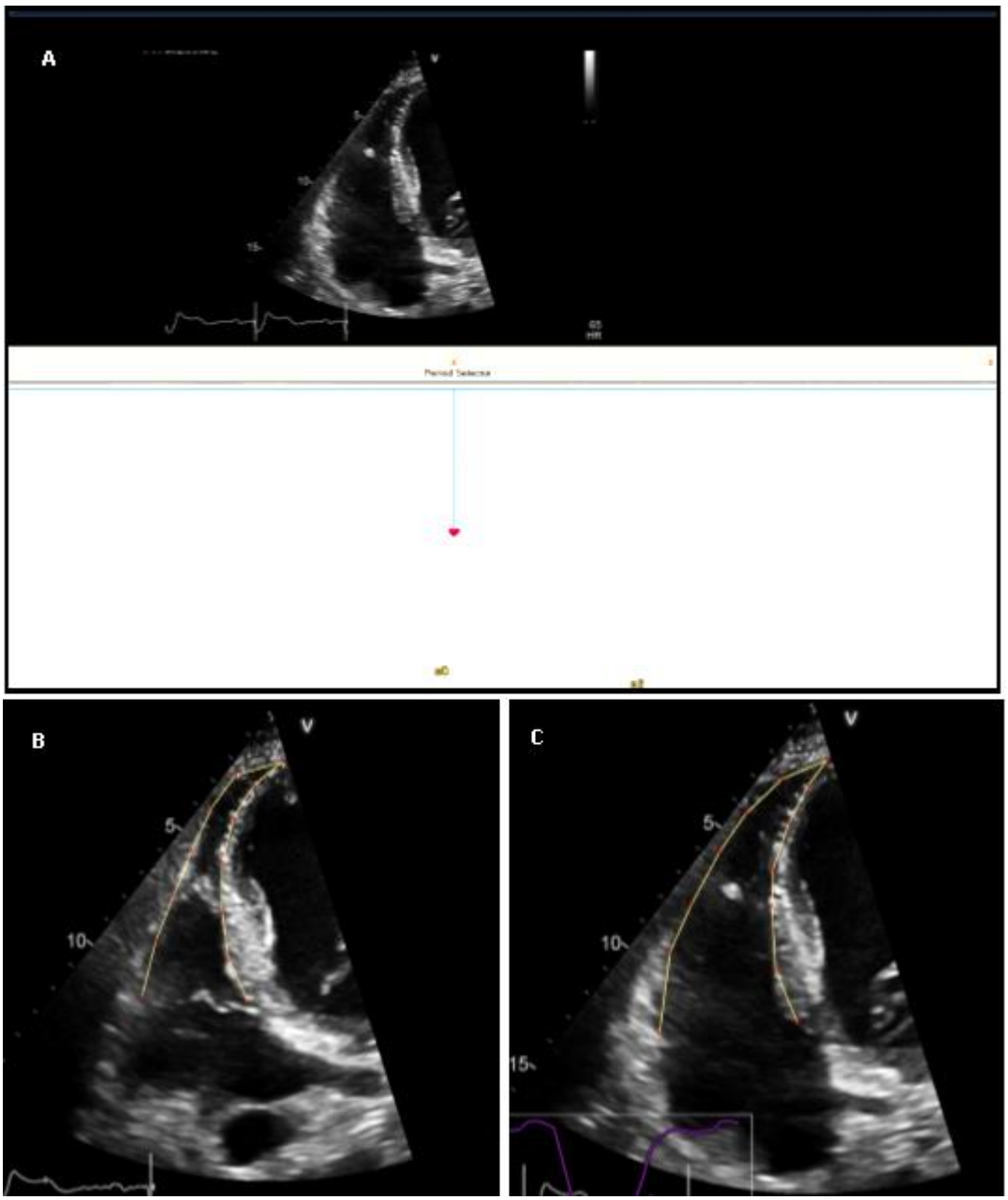


Figure 5.1: Stages of measuring RV longitudinal strain in the apical 4 chamber view using speckle tracking echocardiography. *A - Identify end-diastole and end-systole. B- Trace the inner myocardium at end-systole. C- Review and adjust the myocardial border tracing at end-diastole. (2DCPA, TomTec Imaging v4.6, Germany)*

5.5 Results

5.5.1 Baseline Characteristics

Baseline characteristics can be seen in table 5.1. The overall mean baseline RVGLS was -16.3% and had a significant correlation with both GLS (P=0.005) and LV ejection fraction (P=0.003), but not with subject age (P=0.889). Nor was there a significant

difference in baseline RVGLS according to gender (P=0.91) or treatment arm (P=0.26). There was a statistically significant difference in mean baseline heart rate between the two treatment arms (p=0.01).

	All Subjects (n= 25)	AVR (n=9)	TAVI (n=16)	P-Value
Mean Age (years)	80.2	79.9	80.4	0.79
Mean Body Surface Area +/- 95% CI (m^2) +	1.88 ± 0.07 (n=22)	1.82 ± 0.07 (n=8)	1.91 ± 0.10 (n=14)	0.18
Mean Systolic BP +/- 95% CI (mmHg) +	140.0 ± 8.66 (n=22)	136.4 ± 16.69 (n=8)	142.0 ± 10.1 (n=14)	0.55
Mean Heart Rate +/- 95% CI (bpm) +	68.5 ± 6.24 (n=20)	78.0 ± 10.59 (n=8)	62.1 ± 5.4 (n=12)	0.01*
Percentage Male (%)	56.0	44.4	63.0	0.06
LVEF +/- 95% CI (%)	53.1 ± 4.47	52.4 ± 8.25	53.5 ± 5.41	0.82
GLS +/- 95% CI (%)	-14.6 ± 1.38	-13.8 ± 2.51	-15.0 ± 1.64	0.43
Peak RVGLS +/- 95% CI (%)	-16.3 ± 1.56	-15.1 ± 3.21	-17.0 ± 1.64	0.26

Table 5.1 Baseline Characteristics for subjects analysed for RV Longitudinal strain (RVGLS). *Mean +/- 95% confidence interval. P-Value for the difference between the treatment arms, derived from an independent samples t-test. LVEF: Left Ventricular Ejection Fraction. RVGLS: Right ventricular global longitudinal strain, tracking both the free and septal walls, measured in Apical 4 chamber view. BP: blood pressure. *Significant difference between treatment arms*

5.5.2 Overall Change Baseline to 12 Months Post-intervention

In the AVR treatment group the mean RVGLS increased in magnitude from -15.1% to -16.1%. The TAVI treatment group had a higher mean absolute RVGLS baseline value of -17.0% (P=0.26, no statistically significant difference) but this only increased to -17.2%. There was not a statistically significant correlation in either treatment arm between the change in RVGLS and baseline RVGLS (AVR r=0.271 [p=0.48], TAVI r=0.127 [p=0.64]), age (AVR r=-0.497 [p=0.174], TAVI r=0.137 [p=0.61]), or change in GLS (AVR r=-0.353 [p=0.35], TAVI r=-0.057 [p=0.84]).

When subjects where split according to if the baseline RVGLS was impaired (<-20% or >=-20%)(146, 147) there was a non-statistically significant (P=0.3) difference between the mean change in RVGLS, although the group with baseline absolute RVGLS >=20% saw a mean decrease in RGVLS of 1.15%, whereas the group with impaired RVGLS (<20%) had a mean increase of 0.82%.

Table 5.2 shows the RVGLS values at baselines and 12-months post-intervention, for all subjects and split according to intervention (AVR or TAVI). There was no statistically significant difference in the valve of RVGLS at baseline and 12M, for either treatment group. The mean change in the absolute value of RVGLS was 0.98±2.64% in the AVR treatment group, and 0.24±3.85% in the TAVI treatment group. Data for change in RVGLS was normally distributed (AVR:P =0.54, TAVI: P=0.43).

	Baseline	12M Post-Intervention	P Value
All subjects (%)	-16.32 ± 3.99	-16.83 ± 4.75	0.47
AVR (n=9) (%)	-15.1 ± 4.92	-16.09 ± 4.91	0.30
TAVI (n=16) (%)	-17.0 ± 3.34	-17.24 ± 4.77	0.80

Table 5.2: Baseline and 12-Month post-intervention RVGLS values for AVR and TAVI*. Shown as mean +/- Standard Deviation. P-Value for the difference between the time points, calculated using an independent samples t-test. RVGLS: Right ventricular longitudinal strain*

ANCOVA was used to test the difference in change in RVGLS taking into consideration the baseline values. The adjusted mean difference was -0.458 (90%CI -3.03-2.12). As the lower limit of the 95% confidence interval is outside of the stated non-inferiority limit of 10% of the mean baseline value (1.63%), it could not be concluded that TAVI is non-inferior to AVR. There is also an absence of evidence that there is a significant difference between the two treatment arms (P=0.62). Therefore, more data is needed to be able to conclude if there is a difference in recovery between the groups or not.

5.5.3 Rate of Change

RVGLS was assessed at 6-weeks post-intervention in 15 subjects (6 who underwent AVR and 9 who underwent TAVI). This subgroup had a mean baseline LVEF of 53.3% and baseline RVGLS of -16.67%. The mean age at randomisation was 80.1 years.

	Baseline	6W Post-Intervention	P-Value B-6W	12M Post-Intervention	P-Value B-12M
All subjects	-16.7 ± 4.04	-14.9 ± 4.00	0.09	-16.9 ± 4.95	0.81
AVR	-16.0 ± 5.64	-13.4 ± 3.94	0.19	-16.8 ± 4.80	0.58
TAVI	-17.1 ± 2.84	-16.0 ± 3.89	0.32	-17.0 ± 4.80	0.90

Table 5.3: Baseline, 6 Weeks Post-Intervention, and 12-Month Post-Intervention data for right ventricle longitudinal strain (%). *Shown as mean +/- Standard Deviation. P Value; Probability of a true difference between baseline and 6-weeks/12-months post-intervention, calculated using an independent samples t-test*

RVGLS dropped in absolute value from baseline to 6W in both treatment arms. Although this reduction was greater in the AVR group; a 2.6% reduction in RVGLS compared to 1.1% mean reduction in the patients in the TAVI group. The difference between the treatment arms in the reduction of RVGLS from baseline to 6W was not statistically significant (P=0.47). Nor was there a significant difference in the value of RVGLS at any of the time points (Baseline P=0.599, 6W P=0.224, 12M P=0.931). ANCOVA was performed, taking into consideration the baseline value, to look for differences in absolute RVGLS value at 6-weeks post-intervention. The adjusted mean difference was 1.99% (90%CI -1.18-5.15%). The lower limit of the confidence interval is within the non-inferiority limit of -1.63%, therefore, we can conclude that the function of the RV, assessed by RV GLS, is non-inferior 6 weeks post-TAVI compared to 6-weeks post-AVR.

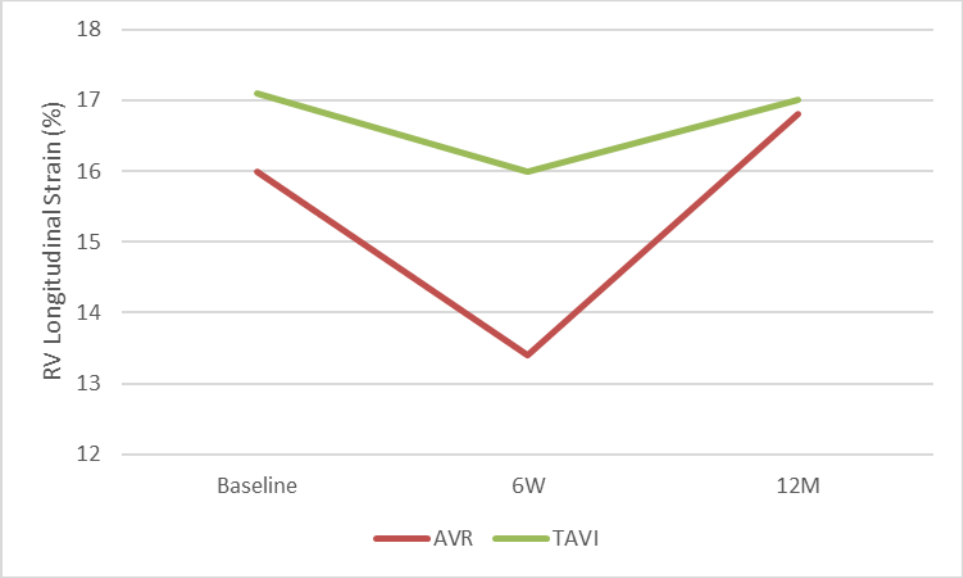


Figure 5.2 RVGLS at Baseline, 6W and 12M post-intervention. *The mean absolute values. Split according to treatment arm. AVR: N=6, TAVI: N=9. RVGLS: Right Ventricular Global Longitudinal Strain.*

5.5.4 Quality Assurance

Comparing the measurements between the main analyst and the expert reviewer the ICC value to RV longitudinal strain was 0.993 (95% CI= 0.934-0.999). The ICC value for intra-analyst variability was 0.865 (95% CI= 0.662-0.947). This is classified as excellent (inter-analyst) and good (intra-analyst) levels of agreement between the data sets(122).

5.6 Discussion and Conclusions

Although the mean value for RVGLS improved from baseline to 12-months post-intervention in both treatment arms, it was not possible to conclude that there had been a statistically significant change ($p<0.05$) in either treatment group. Neither was it possible to conclude that the recovery post-TAVI was non-inferior to after AVR. RVGLS dropped in absolute value from baseline to 6-weeks post-intervention in both treatment groups. Although the decline was greater post-AVR, the difference between the treatment arms was non-significant. It was possible to conclude the non-inferiority of TAVI at 6-weeks post-intervention.

The mean baseline RVGLS in the patient cohort was -16% (-15.1% AVR group, -17.0% TAVI group). Which is significantly impaired compared to American Society of Echocardiography guidelines (<20% in absolute value considered abnormal) (146), and slightly greater impairment than reported by Tardic *et al* (2019)(65). The reasons for this discrepancy are unclear but may be related to inter-vendor differences in the analysis of RVGLS.

The lack of a statistically significant change in RVGLS post-intervention found in this work was heavily influenced by the large standard deviations of the changes seen. While in some subjects RVGLS improved (became larger in magnitude) in others it continues to worsen. This may suggest that the adaption of the RVGLS due to chronic afterload pressures is not reversible in some patients and would fit with the concept of the heterogeneity of RV hypertrophy. Ryan and Archer (2011) report that RV hypertrophy can be adaptive or maladaptive(148). This variation in RV adaption may explain the variation in RVGLS seen, but it would be unwise to state such conclusions without further larger and complementary studies.

Additionally, it is key to take into consideration that the RV has a complex geometry and the RV myocardium, like that of the LV, consists of multiple fibre layers which can be split into the superficial and deep. The deep muscle fibres in the RV are arranged longitudinally, whereas the sub-epicardial layers are arranged circumferentially, and parallel to the atrioventricular groove(39). As this study looked only at the longitudinal function of the RV, any changes in circumferential fibres may not have been fully reflected. However, the key overall deformation in the RV is considered to be the shortening of the longitudinal fibres during ventricular systole(149).

The subjects undergoing TAVI experienced a smaller mean increase in the absolute value of RVGLS. This could have been to the larger baseline values, although, Pearson's correlation shows only a weak correlation between baseline value and change in RVGLS. On the other hand, comparing that change in RVGLS in subjects with impaired vs non-impaired baseline RVGLS calculated showed a striking difference between the two groups. While the mean RVGLS increased from baseline to 12-months post-intervention in the impaired baseline RVGLS group, the means value for RVGLS in the subjects with non-impaired RVGLS at baseline reduced. It was not possible to conclude that this difference was statistically significant, likely due to the limited sample size. However, the variation in baseline values was accounted for by running an ANCOVA with the co-variant of baseline RVGLS when assessing the change seen in each treatment arm. Further studies will be needed in this novel area of research before conclusions regarding the longer-term recovery of RVGLS after intervention for AS.

Although there was a statistically significant difference in baseline heart rate between the two treatment arms, this was highly influenced by some outliers in the small data sets. While heart rhythm has been demonstrated to have some influence on RV function(37) this has not been demonstrated for heart rate. Therefore, it would not be wise to suggest this is clinically significant without further studies. The work of Hashemi et al (2018), studied the recovery of RV longitudinal strain in patients with severe AS, randomised to undergoing traditional AVR or minimally invasive AVR (MiAVR). The reported that RV longitudinal strain had reduced in magnitude at 40 days post-intervention compared to baseline in both treatment groups [AVR (−27.4±2.9% vs −18.8%±4.7%, $p<0.001$) and MiAVR (−26.5±5.3% vs −20.7%±4.5%, $p<0.01$)], however, the reduction seen post-MiAVR was less(150). MiAVR is a different procedure to TAVI

but supported the findings in this study that there is a smaller short-term decline in RV longitudinal function after a less invasive procedure. Additionally, the larger decrease in the magnitude of RVGLS at 6-weeks post-intervention seen in the AVR group compared to the TAVI treatment group mirrors the changes seen in the LV (Chapter 3). This difference may be due to the more invasive nature of AVR and the myocardium taking longer to recover from the trauma. Lee et al (2014) reported evidence of postoperative myocardial injury in 90 of the 314 patients that underwent isolated AVR in their study (28.7%)(151). This was supported by the historical work of Rossiter et al (1974) who investigated the incidence of ischemic myocardial injury in patients undergoing combined AVR and coronary artery bypass grafts. This study concluded that Cross-clamp times should be kept to a minimum and no greater than 70 minutes(152).

The absence of evidence to be able to conclude either a significant difference between the treatment arms or the non-inferiority of TAVI regarding RVGLS at 12-months post-intervention was likely due in part to the small sample size. The good levels of reproducibility seen in ICC testing demonstrate that the recorded values are reliable, and inaccuracy should not have a large effect in the width of the confidence intervals. Due to the nature of the design of this study the sample size could not be fully controlled.

This study provides preliminary data regarding the comparison of the recovery of RVGLS in patients with severe AS after intervention. Despite variations in baseline RVGLS, there was no significant change in the value of RVGLS between baseline and 12-months post-intervention for either treatment arm. The data suggested that there was no significant difference in the recovery seen at 12-months post-intervention, but that there is a potential difference at 6-weeks, with TAVI subject experiencing less of a decline in RVGLS before recovery. Neither of these conclusions were able to be supported statically ($P<0.05$). Due to the limited sample size, further testing, with the aim of establishing statistical significance, should be conducted. The availability of data regarding the clinical characteristics of participants, such as the presence of atrial fibrillation or pulmonary hypotension, would also strengthen further studies.

Chapter 6 - The Assessment of Change in Left Atrial function.

6.1 Abstract

Left Ventricular (LV) function in severe aortic stenosis (AS), and its recovery post-intervention has been widely studied. The function of the left atrium (LA) is also affected by this disease and provides a reflection of the long-term haemodynamic pressures but is less well investigated. This study sought to investigate the function of the LA in patients with severe AS and compare the recovery seen after surgical AVR and TAVI. Transthoracic Echocardiogram (TTE) images from 74 subjects of intermediate surgical risk, who had been randomised to receive AVR or TAVI, were analysed to assess the LA volume and peak longitudinal strain, also recording the volume and strain during atrial contraction where this was possible (n=38). Baseline characteristics showed no significant differences between the two treatment groups. There was a mean reduction in maximum LA volume of 5.03ml (±12.7ml) after AVR and 6.22ml (±14.1ml) after TAVI. There was not a statistically significant difference in the reduction between the treatment arms, although it could be concluded that the improvement seen in max LA volume post-TAVI was non-inferior to that after AVR ($P<0.05$). Regarding the recovery of phasic volume measures the non-inferiority of TAVI could be concluded for pre-a volume, total emptying fraction and active emptying fraction, but not for minimum LA volume or passive emptying fraction. A recovery of peak, and pre-a, longitudinal LA strain was seen in both treatment arms and suggests clinical equivalence, but statistically, the non-inferiority of TAVI could not be concluded. The statistical power analyses were limited by the sample size and comparatively high levels of variance in recovery. Further work with a larger sample size would enable the thorough investigation of co-variants that may be influencing the recovery of the LA.

6.2 - Introduction:

In patients with severe AS the narrowed aortic valve (AV) orifice leads to increased afterload on the LV and progressive LV dysfunction (Chapter 2.1.3.2). During diastole the mitral valve is open, and the LA acts as an extension of the LV and exposed to the

same loads. Therefore LA size and function are influenced by the conditions of the LV (30).

LV function has been shown to have the potential to recover in an acute time frame once the valve has been replaced and the afterload reduced. In a cohort of 209 patients with severe AS undergoing TAVI, there was a significant improvement in echo measured LVEF ($P<0.001$) and GLS ($p=0.008$) at 10 day follow up(153). Although recovery of GLS has been shown to take longer in patients who have AVR opposed to TAVI(137, 154). In contrast, LA function is an indicator of the long-term haemodynamic conditions within the heart, so would not be expected to recover as quickly.

By quantifying the function of the LA, the recovery of the long-term haemodynamic conditions of the heart can be monitored. It is already established that GLS of the LV is a more sensitive marker of LV dysfunction than LVEF, with a reduction in GLS in sAS patients with preserved LVEF (18, 50). Therefore, it follows that there is the potential for LA longitudinal strain to also provide a sensitive and accurate representation of LA function. A recent study investigated the predictive and prognostic value of LA reservoir strain in healthy individuals. The study found that LA reservoir strain is a univariable predictor of cardiovascular morbidity and mortality in the general population, although it is an independent predictor of outcome in women, but not men(54).

LA function during the cardiac cycle can be split into three phases; the reservoir phase where it is relaxed during ventricular systole and filling with blood from the pulmonary veins. The conduit phase where the mitral valve is open and the LA is acting as a channel for the returning blood to pass through and into the LV. And finally, the contractile phase where the LA contracts to expel any remaining blood through the open mitral valve and into the LV (see figure 1.7) (155). In a healthy individual, the contractile phase provides approximately 25% of the total blood volume to the LV (31). As the LV begins to develop diastolic dysfunction, relaxation worsens, and therefore the contributions of the reservoir and contractile functions gradually increase while conduit phase contribution decreases. Although in severe diastolic dysfunction reservoir and contractile function declines dramatically and the LA serves predominantly as a conduit (156, 157). Changes in the relative contributions of LV filling of the conduit and contractile phases can indicate diastolic dysfunction, beyond

that seen just be assessing maximum LA volume which increases linearly with the increasing severity of diastolic dysfunction.

This study will analyse LA strain and phasic functional parameters to provide insight into the long-term haemodynamic recovery after aortic valve intervention. Providing novel data on the comparisons of recovery of LA function in a cohort randomised to undergo AVR or TAVI to treat severe AS.

6.3 Aims

To assess LA peak and phasic strain and volumes in patients with severe AS. To compare the changes seen after intervention in subjects who have been randomised to TAVI and AVR.

6.4 Methods:

Subjects were selected from the cohort of the UK TAVI national trial. All subjects had severe AS and met the inclusion and exclusion criteria of the UK TAVI trial. Subjects had severe AS and were randomised to undergo either surgical aortic valve replacement (AVR) or transcatheter aortic valve insertion (TAVI). Additionally, the TTE images met the specified criteria regarding image quality and format to enable accurate STE tracking (See Chapter 2.2.1). From the cohort of subjects where LV global longitudinal strain had been assessed LA function was also assessed when TTE image quality allowed. LA function was assessed via the measurement and analysis of LA volume and longitudinal strain measurements. The sample size was 74, each subject had a pre-intervention, and 12-month post-intervention TTE, therefore, a total of 148 scans were analysed. Height, weight, blood pressure and heart rate were measured at each study site and provided along with the TTE images.

6.4.1 Image Analysis

LA volumes were measured in the Apical 4 and Apical 2 chamber views, and the quadratic mean for each measurement calculated. Peak and pre-A longitudinal strain were also measured in the apical 2 and 4 chamber views using speckle tracking

technology (2DCPA, TomTec Imaging, Germany. See Chapter 2.2.3) and the mean calculated. Based on the ECG and visual tracking of the mitral valve opening and closing, the timepoints of peak LV systole and diastole were identified. The region of interest (ROI) was selected at these timepoints by tracing the myocardium of the LA wall at the points of peak systole and peak diastole. The ROI was reviewed and manually adjusted as required to ensure accurate tracking throughout the cycle. Figure 6.1 illustrates these steps in the apical four-chamber view. These steps were then repeated in the apical 2 chamber view. Output graphs were generated by the software (2D CPA. TomTec Imaging, Germany) tracking the longitudinal strain, and the volume of the LA throughout the selected cardiac cycles (figure 6.2).

Where possible phasic measurements were recorded for both the apical 2-chamber and apical 4-chamber view and the mean calculated. The measurements included maximum, minimum, and pre-A volumes, as well as peak and pre-A strain (detailed in 2.5.2.6). Pre-A strain and volume were recorded at the point prior to atrial contraction. This is represented by the p-wave on the ECG and by a second opening of the mitral valve leaflets. An example trace and measurement points can be seen in figure 6.2. In patients who were in atrial fibrillation, and therefore had no defined p-wave in their ECG or visual indication of atrial contraction on the echo images, only maximum volume, minimum volume, and peak strain were recorded.

Peak strain represented the strain during the reservoir phase, pre-A strain represented the strain in the contractile phase, and the difference between peak strain and pre-A strain was recorded as conduit strain. The volume measurements were used to calculate further measures of LA function. These were; maximum, pre-a, and minimum LA volume, LA total emptying fraction [(Vmax–Vmin)/Vmax.], LA passive emptying fraction [(Vmax–Vpre A)/Vmax], and LA active emptying fraction [(Vpre A–Vmin)/Vpre A].

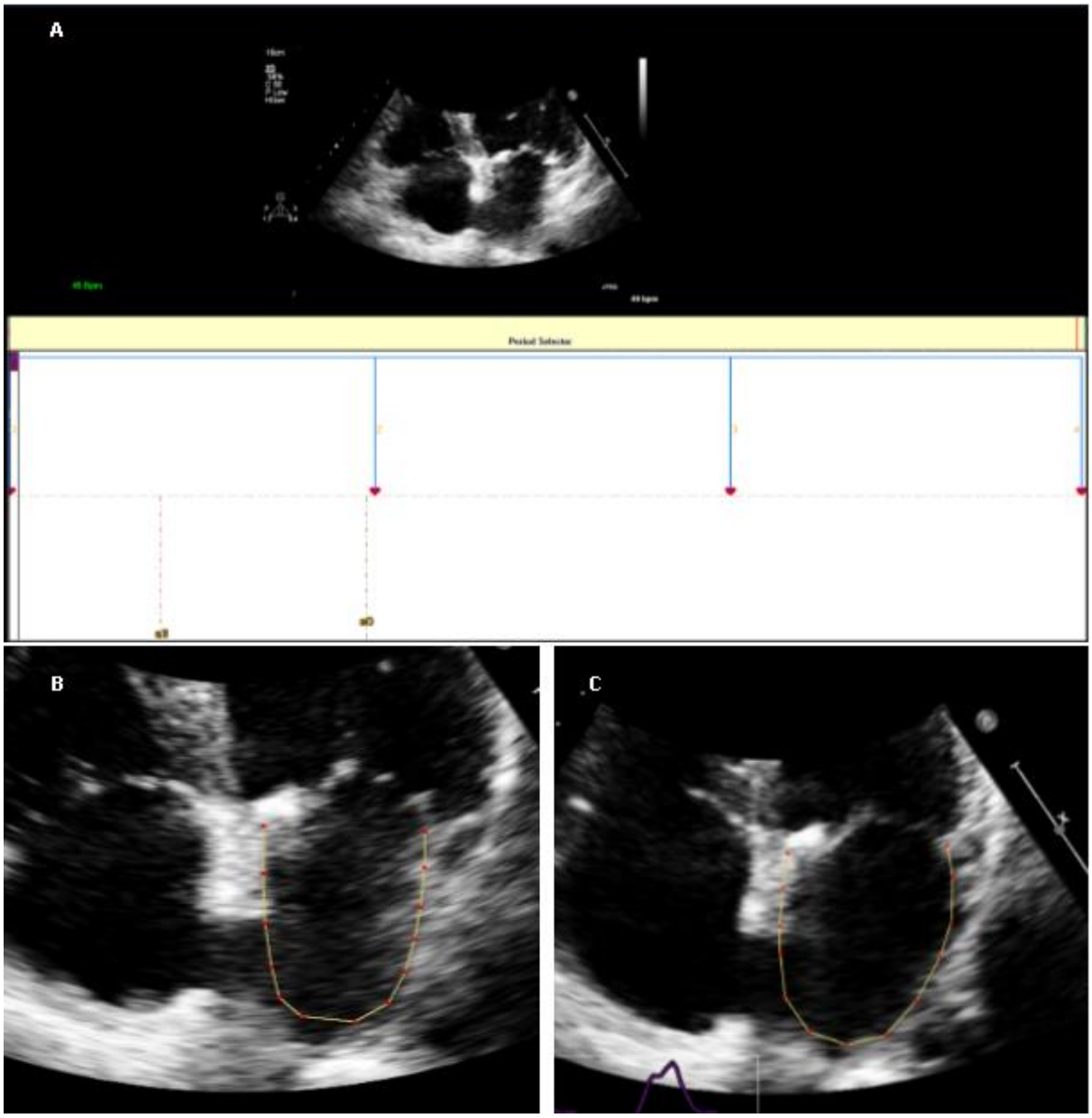


Figure 6.1: Stages of measuring left atrial longitudinal strain in the apical 4 chamber view. *A - Identify end-diastole and end-systole. B- Trace the inner myocardium at LV end-diastole. C- Review and adjust the myocardial border tracing at LV end-systole.*

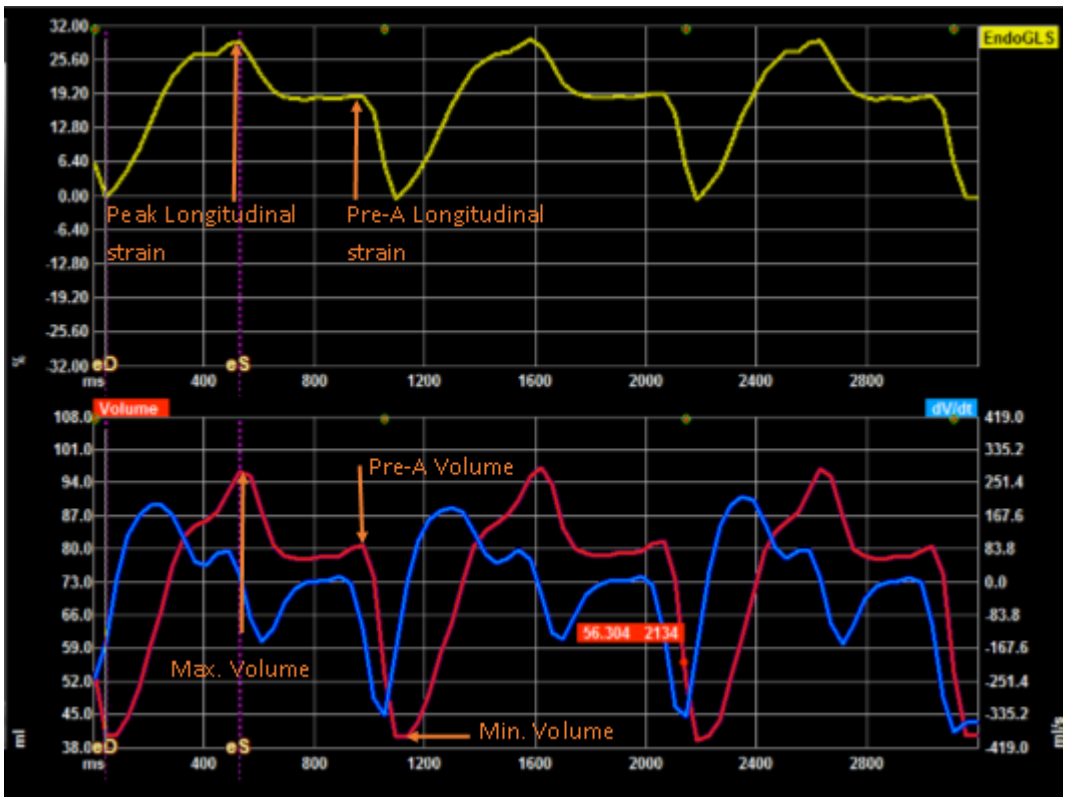


Figure 6.2: Example strain vs time and volume vs time plots of the Left Atrium. *Showing the measurement point for maximum, minimum, and pre-A volumes, as well as peak and pre-A longitudinal strain.*

6.4.2 - Statistical Analysis:

Data for change in LA max volume and peak strain in each treatment arm were tested for the normality of distribution using the Kolmogorov-Smirnov Test. In subjects where phasic data was available, the volume measurements detailed above (Ch 6.3.1.) were calculated. The phasic strain was also analysed to establish the relationship between the three phases of function, and the contributions of passive and active emptying to overall LA contraction.

All measures were analysed for overall change from baseline to 12-months post using paired t-tests (detailed Ch 2.7.1). Data were split according to the intervention received and measurements were tested for the non-inferiority of recovery after TAVI compared to AVR by running an ANCOVA analysis, analysing the changes seen in each treatment arm baseline to 12-months post-intervention, taking into consideration the baseline values. The non-inferiority limit for maximum LA volume was set at 5ml, this was agreed upon after consultation with clinical academics, as it represents half the width of a classification category for LA enlargement. In the absence of relevant guidelines for the clinically relevant reductions in LA Pre-A or minimum volumes, the

non-inferiority limits were scaled down according to the normal values for the LA volume at each time point. In a review published by the European society of cardiology, the normal value for LA minimum volume was half of that of the maximum volume (22ml/m2 vs 11ml/m2), and the normal value for LA pre-A volume was 68% of the normal maximum value (15ml/m2). Therefore, the non-inferiority limits were set at 2.5ml and 3.4ml for minimum and pre-a LA volumes respectively. Based on the literature surrounding LVEF the non-inferiority limit for LA EF was set at 5%. Based on the literature based on clinical relevant changes in LV GLS, and expert consultation with a consultant cardiologist with an interest in TTE and valve disease, the non-inferiority limits for peak and pre-a strain were set at 10% of the baseline value.

6.5 - Results

6.5.1 Baseline Characteristics

73 subjects had suitable TTE images to allow for measurement of maximum and minimum LA volumes at baseline and 12 months post-intervention (AVR n=31, TAVI n=42).

	All Subjects (73)	AVR (31)	TAVI (42)	P-Value
Age (years)+	80.7	80.7	80.7	0.98
Mean Body Surface Area +/- 95% CI (m^2) +	1.84 ± 0.05 (n=66)	1.81 ± 0.06 (n=28)	1.87 ± 0.07 (n=38)	0.22
Mean Systolic BP +/- 95% CI (mmHg)+	145.9 ± 5.4 (n=66)	141.6 ± 8.6 (n=28)	149.0 ± 6.9 (n=38)	0.18
Mean Heart Rate +/- 95% CI (bpm)+	69.1 ± 3.1 (n=64)	69.5 ± 4.9 (n=28)	68.9 ± 4.2 (n=36)	0.86
Percentage Male+	48.6 %	51.1 %	47.6%	0.81
Maximum LA volume (ml)	84.5 ± 20.4	84.4 ± 22.9	84.2 ± 18.8	0.97
Maximum LA Volume Indexed to BSA (ml)	46.5 ± 10.6 (n=66)	47.5 ± 11.2 (n=28)	45.6 ± 10.3 (n=38)	0.48
LA EF	41.3 ± 12.7	40.9 ± 14.1	41.6 ± 11.7	0.83
Peak Strain (%)	20.8 ± 7.9	20.8 ± 9.0	20.9 ± 7.3	0.96

***Table 6.1: Baseline Characteristics for subjects analysed for LA Volumes**. Mean +/- 95% confidence interval. P Value: Probability of a true difference between the treatment groups. LA; Left Atrium. BSA: Body Surface area. EF: Ejection Fraction. + Source demographic data collected by study sites.*

The baseline data (Table 1) were very similar for both treatment arms. The mean peak strain varying by only 0.1%, and the maximum LA volume by only 0.2ml. Although when you index the max to BSA there is a slightly larger difference, this is not statistically significant (P=0.48). Neither were there any statistically significant (P<0.05) differences for any of the other baseline characteristics. LA ejection fraction was significantly impaired compared to normal values in both treatment groups(158, 159), and was weakly correlated with indexed maximum LA volume (r=-0.325, p=0.007).

Where subject BSA was available indexed LA maximum, volume was reported. A joint statement from the American Society of Echocardiography and the European Association of Cardiovascular Imaging classifies a normal indexed LA volume as 16-34ml/m^2, mildly enlarged as 35-41ml/m^2, moderately enlarged as 42-48ml/m^2, and severely enlarged as ≥48ml/m^2 (146). Of the 28 subjects undergoing AVR with BSA data; four had a normal LA volume, seven had a mildly enlarged LA volume, four had a moderately enlarged LA, and thirteen had a severely enlarged LA. Of the 39 subjects undergoing TAVI with BSA data; six had a normal LA volume, seven had a mildly enlarged LA volume, ten had a moderately enlarged LA, and fifteen had a severely enlarged LA (Table 2).

	AVR (n=28)	TAVI (n=38)
Normal LA Volume	4	6
Mildly enlarged	7	7
Moderately enlarged	4	10
Severely enlarged.	13	15

Table 6.2: Number of subjects in each classification of LA enlargement according to baseline value of LA maximum volume. *Normal indexed LA volume=16-28ml/m2, mildly enlarged=29-33ml/m2, moderately enlarged=34-39ml/m2, and severely enlarged= ≥40ml/m2*

Thirty-six subjects had an unidentifiable p-wave at one or both time points, therefore thirty-seven subjects were analysed for phasic LA function. Table three lists the baseline valve for all measurements for the subjects with phasic volume measurements. There was no difference between the treatment arms for any of the baseline LA phasic volume measures (P values 0.44-0.70). Nor was there a significant

difference between the baseline peak (P=0.63) or pre-A LA longitudinal strain (P=0.39) between the treatment arms.

	All Subjects (n=37)	AVR (n=15)	TAVI (n=22)	P-Value
Max Volume (ml)	80.0 ± 18.1	77.1 ± 20.0	81.1 ± 16.9	0.52
PreA Volume (ml)	68.4 ± 15.8	65.4 ± 17.1	69.5 ± 14.8	0.45
Min Volume (ml)	43.1 ± 12.1	40.7 ± 13.5	43.8 ± 10.4	0.44
Total emptying fraction	0.46 ± 0.09	0.47 ± 0.08	0.46 ± 0.09	0.56
Passive emptying fraction	0.14 ± 0.05	0.15 ± 0.05	0.14 ± 0.05	0.70
Active emptying fraction.	0.37 ± 0.09	0.38 ± 0.08	0.37 ± 0.10	0.62
Peak Strain (%)	23.2 ± 6.1	23.9 ± 6.4	22.9 ± 6.0	0.63
Pre-A Strain (%)	14.8 ± 4.9	15.8 ± 4.7	14.4 ± 5.0	0.39

Table 6.3: Baseline LA Phasic Volumes and Strain *for subjects with data for maximum, pre-A, and minimum LA volume. Mean +/- SD. P-Value: Probability of a true difference between the treatment groups.*

6.5.2. Change in Left Atrial Volumes and Phasic Relationship.

In the whole cohort (n=74) the mean maximum LA volume reduced by 5.71 ml (±13.5 ml). When split according to treatment arm the mean reduction for those who underwent AVR was 5.03ml (±12.7ml), and for TAVI it was 6.22ml (±14.1ml). Despite the difference in mean reduction, there was not a statistically significant difference between the change seen in the two groups (P=0.53), as the standard deviation was high. This did not change once the number of days post-intervention that the 12M TTE was performed had been accounted for.

Figure 6.3 displays the change in mean maximum LA volume for both treatment arms; there was a significant difference between the mean baseline and 12-month post-intervention figures for both AVR (P=0.04) and TAVI (P=0.007). There was no significant correlation between change in LA max volume and age (r=0.078), baseline LVEF (r=0.054), or baseline GLS (r=-0.104), and no significant difference according to gender (P=0.54). Although there was a negative correlation between baseline maximum LA volume and the change in maximum volume (r= -0.442, P<0.001). Meaning at small

baseline volumes there was some increase in LA volume, but overall the larger the baseline maximum LA volume the larger decrease seen between baseline and 12 months. Additionally, there is a statistically significant correlation between change in max LA volume, and change in LV end-diastolic volume (P=0.008, r=0.31). Change in LA max volume was normally distributed (AVR: P=0.20, TAVI P=0.18).

Running an ANCOVA the adjusted mean difference between TAVI and AVR for the change in LA maximum volume from baseline to 12-months post-intervention, taking into consideration the baseline value, was 2.19ml (90% CI –4.2-6.5ml), this is inside the non-inferiority of -5% so it can be concluded that TAVI is non-inferior to AVR. A two-tailed 90% confidence interval is equivalent to 95% one-tailed confidence interval in a pre-specified direction. ANCOVA was also run to assess the difference in LA EF improvement between the treatment groups; the mean difference was 0.63% (90% CI -2.7-4.0%). The lower limit of the confidence interval is within the non-inferiority limit of 5% meaning that non-inferiority of TAVI can be concluded.

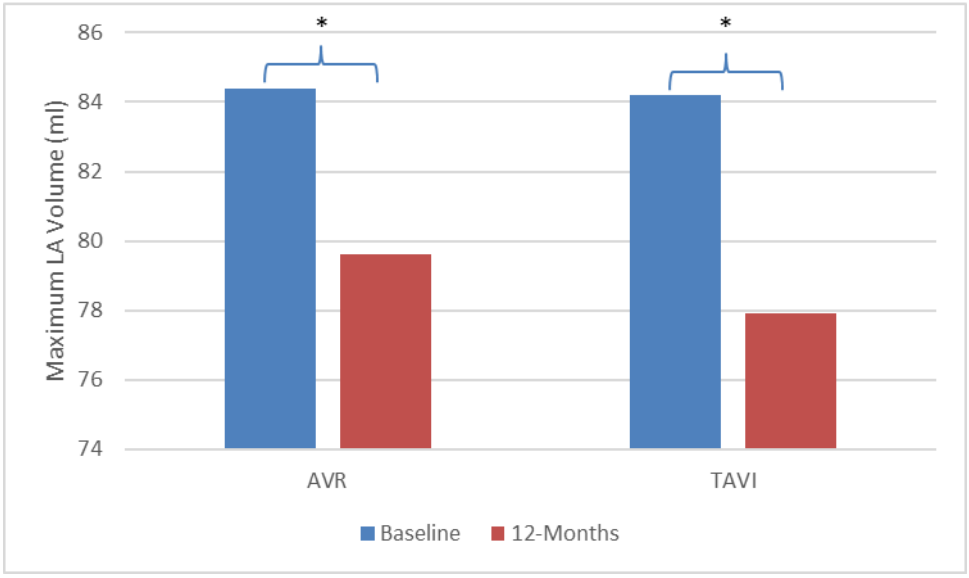


Figure 6.3: Mean Maximum LA Volume at baseline and 12-months post-intervention *split according to intervention. *Significant difference between values in a paired t-test. AVR; P=0.04, and TAVI; P=0.007.*

Comparing pre- and post-intervention phasic volume data, there were statistically significant decreases in LA Max volume (P=0.014), and LA Pre-A volume (P=0.004). The changes seen were not significant for LA min volume (P=0.17), total emptying fraction (p=0.93), passive emptying fraction (P=0.07) and active emptying fraction (P=0.14).

Table 6.4 list the changes seen in the phasic volume measurements split according to intervention, for the cohort where phasic measurements were able to be taken (n=37). Despite the visual differences, as seen in figure 6.4, none of the differences were statistically significant between the treatment arms. Table 6.5 also shows the lower bound of the 90% two-tailed confidence interval for the difference between the treatment arms for change in each factor

	All Subjects (n=37)	AVR (n=15)	TAVI (n=22)	P-Value TAVI vs AVR
Max Volume (ml)	-5.3 ± 11.5	-2.77 ± 11.9	-6.58 ± 11.9	0.35
PreA Volume (ml)	-5.8 ± 11.0	-2.62 ± 11.0	-7.75 ± 11.0	0.17
Min Volume (ml)	-2.2 ± 9.1	-1.25 ± 8.4	-2.76 ± 9.87	0.63
Total emptying fraction	-0.002 ± 0.08	0.00 ± 0.08	0.00 ± 0.07	0.95
Passive emptying fraction	0.02 ± 0.07	0.01 ± 0.09	0.03 ± 0.06	0.42
Active emptying fraction.	-0.02 ± 0.08	-0.01 ± 0.07	-0.03 ± 0.08	0.50

Table 6.4: Mean change in LA Phasic Volumes from baseline to 12-months post-intervention ± Standard Deviation*. Split according to intervention type. P Value; Probability of a true difference between the treatment groups.*

	Lower bound of a 90% confidence interval for the difference in change.	Non-Inferiority limit
Max Volume (ml)	-2.9*	-5.00
PreA Volume (ml)	-1.1*	-2.50
Min Volume (ml)	-3.8	-3.41
Active emptying fraction.	-0.03*	-0.04
Passive emptying fraction	-0.02	-0.01
Total emptying fraction	-0.04*	-0.05

Table 6.5: Lower bound of the 90% confidence interval for the difference between treatment groups for the magnitude of change seen in phasic volumes, for subjects with phasic LA data. *Change seen was a decrease in Max, PreA, and Min volume, and active emptying fraction. But an increase in passive and total emptying fraction. *Non-Inferiority of the recovery after TAVI can be concluded.*

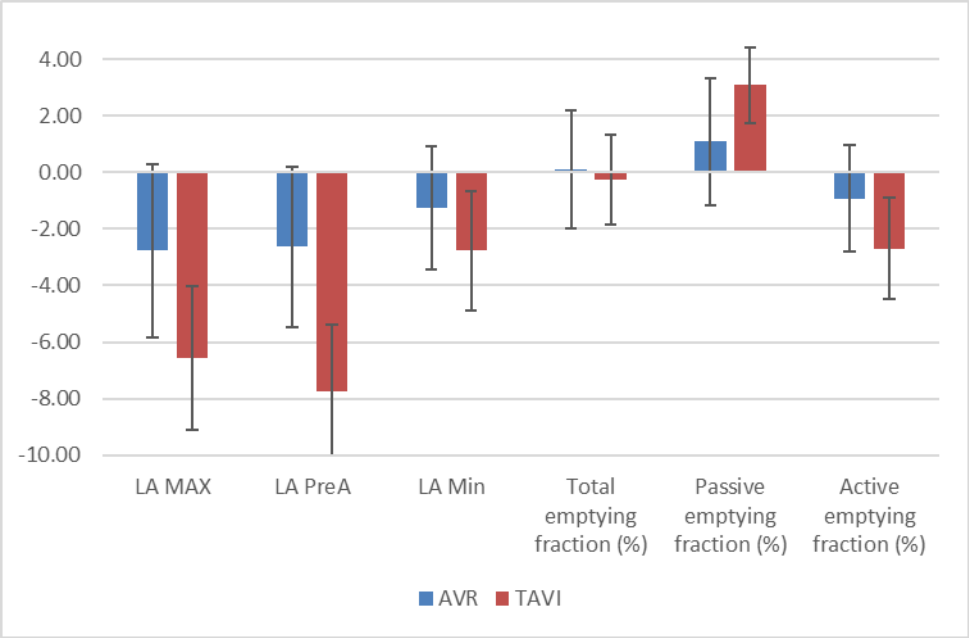


Figure 6.4: Change in LA phasic volume measurements baseline to 12-months post-intervention. *Emptying fractions expressed as a percentage, not a fraction. Error bars represent standard error of the mean. No significant difference between the treatment arms for any measures.*

The limit of the 90% two-tailed confidence interval (equivalent to a 95% one-tailed confidence interval) was within the non-inferiority limit for all factors apart from minimum LA volume and passive emptying fraction. For both minimum LA volume and passive emptying fraction, the mean change seen in TAVI was greater than the mean change seen in AVR, yet there were larger variances in the changes seen. There was no correlation between age at randomisation or gender and change in any of the phasic volume measures.

6.5.3. Change in Left Atrial Strain and Phasic Relationship

In all subjects with LA data the peak strain rose from a mean of 20.8% to 21.2% in the AVR treatment group (p=0.71), and 20.8% to 21.4% in the TAVI treatment group (p=0.74) (figure 6.5). There was no significant correlation between change in LA PLS and age (P=0.90) or change in LV GLS (P=0.12). There was a correlation between baseline peak LA strain and change in LA strain (r= -0.305, P=0.009). Change in LA peak strain was normally distributed (AVR: P=0.20, TAVI: P=0.20). Running an ANCOVA

assess the change in LA PLS from baseline to 12M, taking into consideration the baseline value, the adjusted mean difference for change in LA peak strain between the two treatment arms was 0.19 (90% CI -2.35-2.74). The lower limit of the 90% CI is outside of the predetermined non-inferiority limit of -2.1% (10% of the mean baseline value), therefore we are not able to reject the null hypothesis and conclude the recovery of LA PLS in TAVI is non-inferior to AVR. Although, when testing for a significant difference between the two-treatment groups the calculated p-value was P=0.9, meaning that there is a 90% probability any difference observed between the groups is just by chance opposed to a true difference in recovery.

Figure 6.5: Left Atrial Peak Longitudinal strain (LA PLS) at baseline and 12-months post-intervention *for subjects undergoing AVR and TAVI. No significant change (p<0.05) in either treatment arm.*

Analysing just those patients with phasic LA strain data, again, a larger change in peak LA strain was seen in the AVR treatment arm compared to the TAVI treatment arm. Peak LA strain increased a mean of 1.75% in the AVR group vs 1.07% in the TAVI group. Pre-a strain reduced by a mean of 0.15% post-AVR and 0.27% post-TAVI (figure 6.6). Both treatment arms had a small increase in the contribution of the conduit phase to overall LA function, assessed via the balance of contractile strain vs conduit strain (figure 6.7).

ANCOVA was run to assess the change in LA PLS between the two treatment arms in the sub-group of subjects with phasic LA data; the mean difference was -0.68 (90% CI -

4.51-3.15). The lower limit of the 90% confidence interval is outside of the predetermined non-inferiority limit of 2.1%, therefore, it cannot be concluded that the improvement in LA PLS seen in TAVI is non-inferior to that seen in AVR. When ANCOVA was run to assess the change in LA pre-A strain; the mean difference between the two treatment arms was 0.12 (90% CI -2.72-2.97). As the lower limit of the 90% confidence interval was outside of the specified non-inferiority limit of -1.48% the null hypothesis that recovery of LA longitudinal strain 12 months post-TAVI is inferior to recovery 12-months post-AVR cannot be rejected.

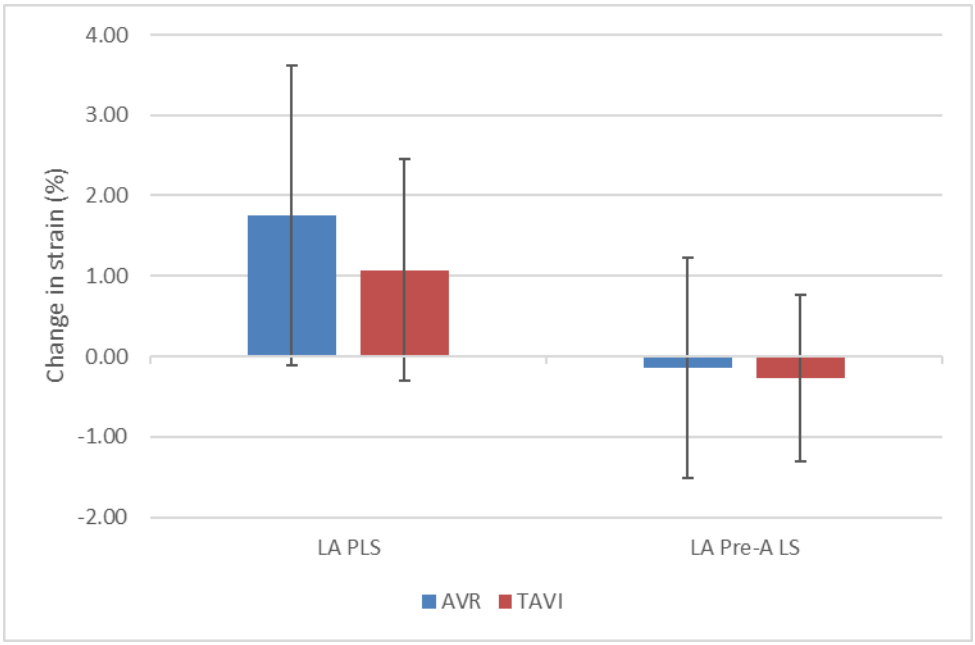


Figure 6.6: Change in LA longitudinal strain for subjects with phasic LA function data*. Baseline to 12-months post-intervention. PLS = Peak Longitudinal strain. Pre-A LS = Longitudinal strain immediately prior to atrial contraction. Error bars represent the standard error of the mean. The non-inferiority of TAVI could not be concluded for either measure.*

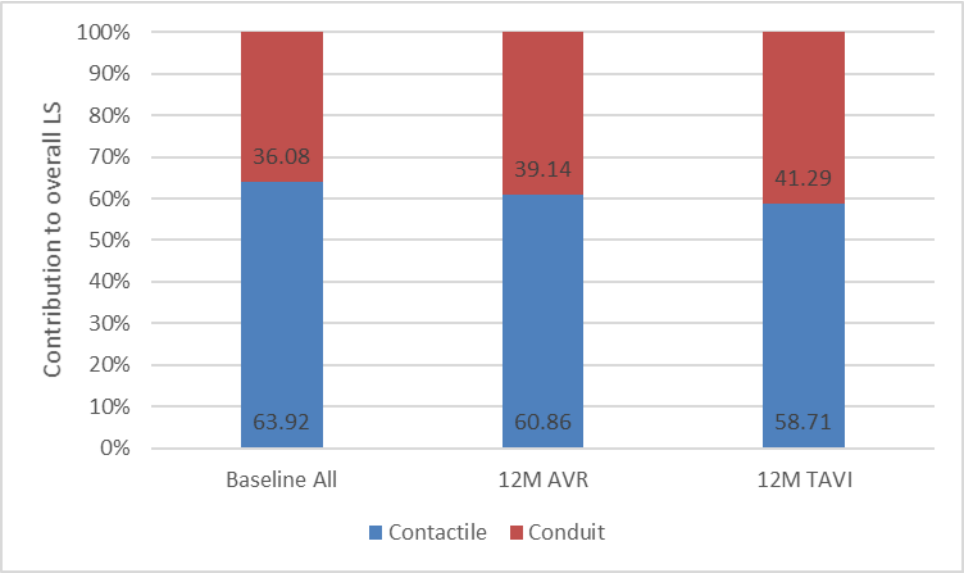


Figure 6.7: Contribution of contractile and conduit strain. *Baseline data for all subjects, 12-month data according to intervention. Conduit strain calculated at the difference between peak (reservoir) strain and pre-A (contractile) strain.*

6.5.4 Quality Assurance.

The ICC value for maximum LA volume was 0.891 for intra-analyst reliability and 0.683 for inter-analyst reliability, an ICC value of 0.75-0.9 indicates good levels of absolute agreement. The lower ICC value for inter-analyst variability was strongly influenced by one subject where there was a large difference in the measured LA volume. Excluding this case, the ICC value rose to 0.874. LA peak longitudinal strain also had strong reliability; the ICC values were 0.904 and 0.986 for intra- and inter- analyst reliability respectively. ICC values greater 0.9 indicate an excellent level of agreement between the data sets.

6.6 Discussion and Conclusions

There was an overall decrease in LA maximum volume in both treatment groups from baseline to 12-months post-intervention. This indicates some recovery in LA structure and function. However; only small improvements were seen in LA GLS and LA EF, and they remained significantly impaired compared to normal values(53, 158, 159); demonstrating limited improvements in dynamic function. A reduction in volume and reverse myocardial re-modelling would be expected to be seen prior to improvements in LA deformation. Therefore, it may be that further LA recovery would have been seen

if longer-term follow up was conducted. The non-inferiority of TAVI could be concluded for the reduction in LA max volume, but not for either peak LA strain, or Pre-a strain.

Baseline data illustrated that the majority of subjects had enlarged LA max volume pre-intervention, which will be a contributing factor to the reduced LA EF seen at baseline(158). Todaro et al (2016) also found that patients with asymptomatic AS had severely enlarged LA volume and impaired LA peak strain compared to age and gender-matched controls (P<0.001)(160). There is a wide basis of research to support that, independent of valve disease, or history of atrial fibrillation, LA enlargement is related to the development of adverse cardiovascular outcomes. This includes; an increased risk of developing atrial fibrillation, stroke, and mortality(161, 162). O'Connor et al (2011) also concluded that tissue doppler derived LA strain was significantly reduced, and LA volumes significantly increased, in patients with severe AS(62). Previous studies of patients with asymptomatic AS found an association between reduction in the LA peak strain and a lower aortic valve area (indexed to BSA, P=0.02), low-flow AS (P=0.01), and lower GLS (P<0.001). Left atrial peak strain, but not pre-a strain, was found to have predictive value in the development of symptoms in subjects, (160, 163). In agreement with this study, the Dallas heart study also found a weak correlation between indexed LA Max and LAEF(164). The mean reduction in LA Max volume of 5.7ml represented a 7% decrease in volume, a change that could be argued to be clinically significant in the context of current research and guidelines(14, 146). A large retrospective review of 36, 561 patients with preserved LVEF calculated that for every millilitre per meter squared increase in indexed LA maximum volume, mortality risk independently increased by 0.9% (P<.001)(165).

When reviewing the results of this study the difference between statistically and clinical significance must be considered. Many measures had a large confidence interval, which hindered the ability to make statistically significant conclusions. The width of the confidence interval is dependent on both sample size and the variance of data. This variation is also demonstrated by the large values for standard error of the mean (SEM) seen in figures 6.4 and 6.6. The subjects undergoing TAVI had a strikingly larger decrease in LA size, both maximum and pre-a volume, indicating a greater

recovery if it was a true difference, although it was only possible to conclude non-inferiority, opposed to superiority, of TAVI for maximum and pre-a LA volumes.

The strong positive correlation between a reduction in LV end-diastolic volume and LA max volume supports the current understanding that the size and function of the two chambers are closely linked, due to the open mitral valve during ventricular filling, and atrial conduit phase(157). The correlations between baseline maximum volume/peak strain and the change seen in these measures demonstrate that the less impaired the LA is at baseline the smaller the improvements seen are.

The mean of LA peak strain rose slightly more in the AVR treatment arm than the TAVI treatment arm, but the changes seen were small, and the calculated p-value when testing for a significant difference between the two groups was very high (P=0.9). This provides evidence to the theory that the two treatments are likely clinically comparable regarding improvement in LA strain, even in the statistical equivalence cannot be concluded. It is interesting to note that regardless of intervention there was a greater improvement of LA peak strain in the subject where phasic data could be analysed. This is the group of patients with defined atrial contraction and p-wave on their ECG and aligns with the current body of knowledge as atrial fibrillation causes dyssynchronous contraction of the LA, limiting LA recovery.

Analysing the phasic strain through the cardiac cycle in the subjects, conduit strain increased slightly from baseline to 12-months post-intervention. The increase in passive function (passive emptying fraction and conduit strain) suggests that the LA wall is not as stiff anymore and so the LA is not having to 'push' blood out to such an extent. But the contribution of the conduit phase, represented by the strain, was still much lower than normal values reported in a meta-analysis by Pathan *et al* (AVR 39.1 vs TAVI 41.3 vs 'normal' 58.4%)(53).

A notable limitation of this work is the absence of data regarding the participants' clinical history, and clinical outcomes post-intervention. In particular; atrial fibrillation (AF) has well documented negative effects of LA function and emptying, which in turn affect global cardiac function. The availability of clinical information to confirm the imaging findings and class participants according to the presence of AF or not would have provided further valuable analyses.

In conclusion; the data collected in this trial suggests that the changes seen, reflecting the recovery of the LA, are comparable in AVR and TAVI. At 12-months post-intervention there were still abnormalities in the phasic function of the LA in both treatment arms, demonstrating that the reverse remodelling had not been able to fully restore the physiological function of the LA. The non-inferiority of TAVI was statistically significant for maximum LA volume, pre-a atrial volume, total emptying fraction, active emptying fraction. Due to the limited sample sizes and the statistical power of many of the analyses were limited and it was not possible to conclude that TAVI was non-inferior to AVR regarding the change in minimum LA volume, passive emptying fraction, peak strain or pre-a strain. The large variance in the change seen suggests that there may be some confounding variables that are affecting recovery. Potential confounding variables should be investigated in further work. Along with the longer-term recovery of the LA, and testing for correlation between recovery of LA mechanics and clinical outcomes such as cardiac events (myocardial infarction, stroke), and development of atrial fibrillation.

Chapter 7 - The Development and Analysis of Strain Volume Loops.

7.1 Abstract

Global Longitudinal strain (GLS) is a sensitive measure of left ventricular (LV) function, it only provides information regarding the point of peak deformation. Strain Volume Loop's (SVL's) are a novel measure that track the volume-strain relationship throughout the cardiac cycle. It is hoped that SVL's will be able to provide detailed and disease-specific data throughout the cardiac cycle. This study used SVL's to look at the changes in the volume-strain relationship throughout the cardiac cycle and how that altered after surgical aortic valve replacement (AVR) and transcatheter aortic valve insertion (TAVI), comparing the two interventions. Forty-eight subjects with high-quality echocardiographic apical 4-chamber (Ap4Ch) strain traces were analysed to produce a SVL. Numerical data from the Ap4Ch LV longitudinal analysis were exported into Excel (Microsoft Word, 2010) and cubic spline interpolation used to calculate the volume and strain at 100 points in systole and 100 points in diastole. These points were plotted to create a graph of volume vs strain throughout the cardiac cycle. SVL's were created from the mean data set for baseline and 12-month post-intervention data for AVR and TAVI. Each SVL was examined using five parameters; the peak strain, early systolic strain, systolic gradient, and early and late diastolic uncoupling. The baseline SVL composed on the mean AVR group data had a peak strain of -16.37%, an early systolic strain of -2.65%, and a systolic gradient of 0.317 %/ml. The SVL composed on the mean TAVI group data had a peak strain of -15.36%, an early systolic strain of -2.36%, and a systolic gradient of 0.279 %/ml. There were no statistically significant differences ($p<0.05$) for any of the SVL metrics between the two treatment groups. Although both treatment arms had a reduced end-diastolic volume at 12-months post-intervention, only the TAVI treatment arm had a reduced end-systolic volume. Overall both treatment arms had reduced systolic-diastolic uncoupling. Post-TAVI the uncoupling during early diastole stayed constant at 3.3, and all the reduction in total uncoupling was the result of a 77% decline in late diastolic uncoupling. In contrast, in the AVR treatment group, the reduction in uncoupling was driven by a reduction in

early diastolic uncoupling, while late diastolic uncoupling increased. Early diastole uncoupling is indicative of delayed relaxation, and a delay/dysfunction key systolic-diastolic link of LV untwisting and is known to happen in chronic overload situations such as aortic stenosis (AS). Late diastolic uncoupling represents the stage in the cardiac cycle that coincides with active atrial contraction. Uncoupling of systolic and diastolic strain at this point suggests LV remodelling and a reduction of chamber compliance. One cause for the differences between the treatment arm could have been a difference in blood pressure between the groups, as hypertension will limit the reduction of afterload after an intervention. The nature of AVR means that there is a rigid ring annulus sown into the left ventricular outflow tract, which would limit the regional compliance of the LV. Also, if there is AF present the lack of synchronised atrial contraction will influence the filling pattern and diastolic strain of the LV. In conclusion; although more work is needed in this novel area to support the findings of this study and further investigate the intervention-specific changes seen, SVL's provide a useful and detailed reflection of LV haemodynamics and warrant further development.

7.2 Introduction

Although GLS has been shown to be a sensitive measure of LV function it only provides data on one moment within the cardiac cycle; the point of peak deformation. Therefore, although it can identify global LV dysfunction GLS is not particularly disease-specific(166, 167). By examining the relationship between LV volume and longitudinal strain throughout the cardiac cycle it is hoped that strain volume loops will provide novel data on the haemodynamic condition of the heart in disease. Hulshof *et al* published a proof of concept paper concerning strain-volume loop's, reporting values for a small group of patients with no pathology, AS, or aortic regurgitation. This work demonstrated the utility of SVL's in illustrating haemodynamic changes, beyond that seen by just GLS, in both AS and aortic regurgitation when compared to healthy individuals and was able to distinguish between the two pathologies(166). Previous studies have shown that healthy individuals have similar strain values for any given LV volume in systole and diastole(168), but that this 'coupling' of systolic and diastolic strain can become dissociated if the cardiac load is altered outside of normal

ranges(169). Severe AS leads to increased afterload forces on the LV and therefore has been demonstrated to cause a degree of systolic-diastolic uncoupling(166).

Chapter 3 in this thesis demonstrated the non-inferiority of the improvement in GLS post-TAVI compared to the gold standard of AVR. This chapter will build on this and the work of Hulshof *et al*, analysing the SVL's in patients with severe AS, and how the SVL changes post-intervention. This will provide novel, detailed, data on the detailed haemodynamic changes post-AVR and post-TAVI, and intervention dependent changes which could affect long-term recovery.

7.3 Aims

To examine the strain volume loop in patients with severe aortic stenosis. To assess the changes in five key parameters of the SVL pre- and post-intervention for severe aortic stenosis, comparing the changes seen in TAVI and AVR.

7.4 Methods

In a selection of subjects (n=48) where the image quality was high strain volume loops (SVL's) were created using LV longitudinal strain data from the baseline and 12-month post images.

LV longitudinal strain was measured in the apical 4-chamber view, as detailed in Chapter 2.5.1. The numerical data from this trace was exported into Excel (Microsoft Word, 2010). The time point for each frame (ms) and the volume and myocardial strain that those points were extracted from the exported data. The cardiac cycle was split into 100 equally spaced time points in systole and 100 equally spaced time points in diastole. Using cubic spline interpolation, the volume and strain were calculated for each time point (170)(Figure 7.1). This was recorded for each subject at baseline and 12 months, which could then be plotted in a volume vs strain scatter graph as in figure 7.2.

Raw Data				Interpolated Data		
Time	Volume	Strain		Time	Volume	Strain
0	90.194	0		0	90.194	0
33.33	89.455	-0.429		3.704	90.07755	-0.0482
66.67	89.234	-1.052		7.408	89.96368	-0.0964
100	86.442	-2.418		11.112	89.85495	-0.1445
133.33	82.877	-3.623		14.816	89.75395	-0.1924
166.66	77.944	-5.059		18.52	89.66326	-0.2403
200	71.306	-6.915		22.224	89.58543	-0.2879
233.33	66.353	-8.402		25.928	89.52306	-0.3352
266.66	62.608	-9.941		29.632	89.47872	-0.3823
300	58.937	-11.497		33.336	89.45498	-0.4291

Figure 7.1: Raw and Interpolated Data for an example SVL. *Ten rows of example data illustrating the raw and interpolated data, all one cardiac cycle data sets were split into 200-time points.*

Strain Volume Loop (SVL) data sets were created using baseline and 12-month post-intervention (12M) data for each subject, producing a total of 96 data sets. The data sets were firstly split into baseline data, and 12M data and the volume and strain at the 200 data points were averaged across the data sets. This then was used to create a baseline SVL's using the mean data. Subjects were then grouped according to intervention. SVL's were then constructed using the mean data for baseline, and 12-months post-intervention according to intervention.

Each SVL was examined using five parameters as shown in figure 7.2; the peak strain, early systolic strain, systolic gradient, and early and late diastolic uncoupling. The early systolic strain was calculated as the longitudinal strain at 90% of the end-diastolic volume during the systolic phase; providing data on the diastolic-systolic link, and isovolumetric LV contraction. A linear regression line was added to the systolic phase of the SVL, and the gradient of the regression line recorded to calculate the S-gradient. This will allow quantitative comparisons between the treatment groups regarding the overall volume/strain ratio.

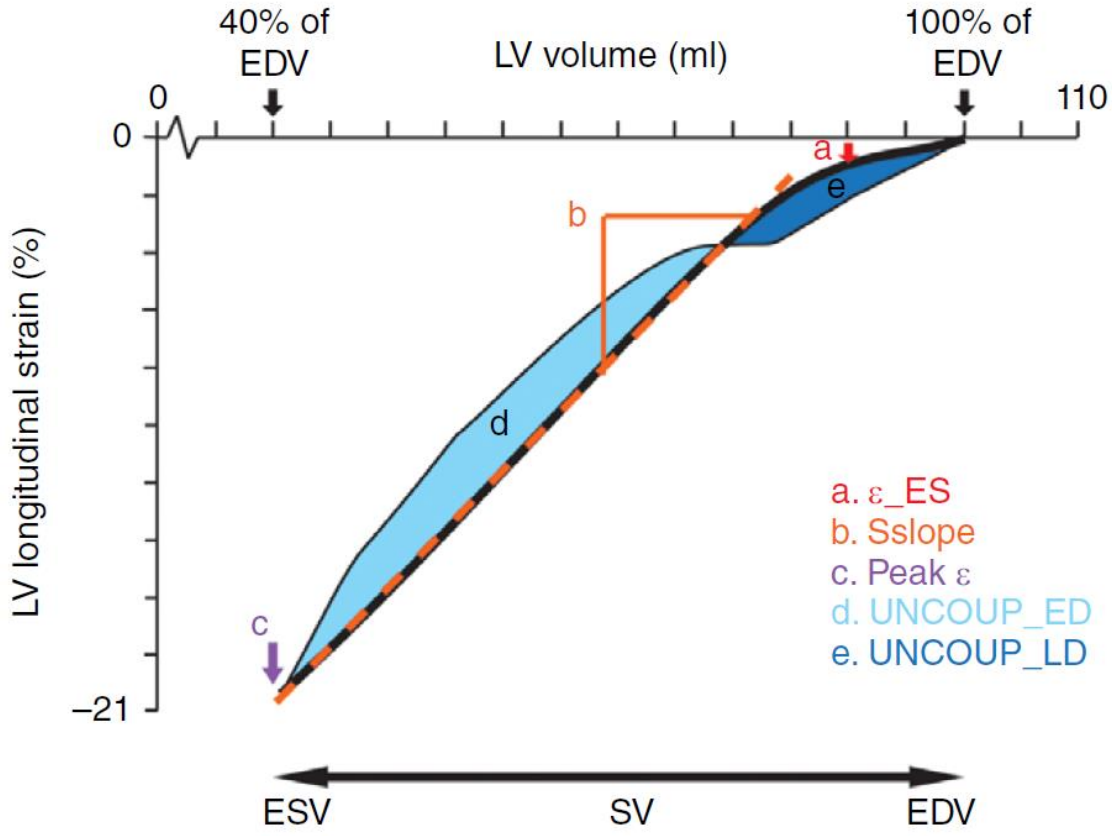


Figure 7.2. Example SVL Plot Schematic. *A: Early Systolic strain measured at 90% of end-diastolic volume. B: Systolic slope, the linear regression line of the strain/volume relationship during systole. C: Longitudinal strain during peak systole. D: Uncoupling during the upper 30% of the working range. E: Uncoupling during the lower 70% of the working range. Image taken from Hulshof et al, 2017(166).*

To assess the uncoupling of the systolic and diastolic strain (the difference between diastolic and systolic strain during the filling of the LV), the working range of the LV (EDV minus ESV) was calculated and split into 10% increments. For each volume, the associated strain during systole and diastole was calculated using cubic spline interpolation. Diastolic strain was then subtracted from systolic strain at each 10% volume increment. Late diastolic uncoupling was classified as the sum of the differences for the upper 30% of the working range of the heart (difference at 100%, 90%, 80%, and 70% of the working range), whereas early diastolic uncoupling was classified as the sum of the differences at 10% increments of the lower 70% of the working range (lower boundary, 10%, 20%, 30%, 40%, 50%, and 60% of working range of the LV). A large degree of systolic-diastolic uncoupling can be suggestive of diastolic dysfunction in the LV. Early diastole uncoupling is indicative of delayed relaxation, and

a delay/dysfunction key systolic-diastolic link of LV untwisting(166, 171). LV untwisting is affected by systolic function; delayed/prolonged LV untwisting us known to happen in chronic overload situations such as AS(23, 171). Late diastolic uncoupling represents the stage in the cardiac cycle that coincides with active atrial contraction. Uncoupling of systolic and diastolic strain at this point suggests LV remodelling and a reduction of chamber compliance(172). This is due to the fact that less compliant ventricles have an impaired ability to adjust strain according to the volume as the atrium actively ejects blood into the LV(171).

7.5 Results

7.5.1 Baseline Characteristics.

Pre- and Post-intervention strain volume loops were calculated for 48 subjects; 15 who underwent AVR and 33 who underwent TAVI. The average at intervention was 81 years, and 47.8% of subjects were male. Table 1 details the baseline characteristics of the SVL's.

The all-subjects baseline SVL had peak strain of -15.6%, an early systolic strain of -2.46%, and a systolic gradient of 0.290 %/ml (figure 7.1). When split according to the intervention, the SVL composed on the mean AVR group data had a peak strain of -16.38%, an early systolic strain of -2.65%, and a systolic gradient of 0.317 %/ml. The SVL composed on the mean TAVI group data had a peak strain of -15.37%, an early systolic strain of -2.36%, and a systolic gradient of 0.279 %/ml. Although the mean value for end-systolic volume was lower and the mean end-systolic strain greater in the AVR group, there was no statistically significant difference between either the baseline end-systolic strain (P=0.38) or end-systolic volume (P=0.14) between the two treatment arms. Nor was there a significant difference in age between the two groups (P=0.27), end-diastolic volume (P=0.21), or LVEF (P=0.29)

	All Subjects (n=48)	TAVI (n=33)	AVR (n=15)	P-Value
Mean Age	80.98	81.87	80.58	0.27
Percentage Male	47.8	54.5	26.7	N/A
Mean Body Surface Area +/- 95%CI (m^2) $^+$	1.81 ± 0.06 (n=45)	1.83 ± 0.08 (n=32)	1.76 ± 0.09 (n=13)	0.33
Mean Systolic BP +/- 95%CI (mmHg)$^+$	147.8 ± 5.8 (n=45)	147.3 ± 6.6 (n=32)	149.1 ± 12.5 (n=13)	0.79
Mean Heart Rate +/- 95%CI (bpm)$^+$	68.4 ± 4.2 (n=44)	67.7 ± 5.6 (n=31)	70.2 ± 4.8 (n=13)	0.59
Mean End Diastolic Volume (+/- 95% CI) ml	99.79 ± 10.6	104.4 ± 13.6	89.59 ± 15.6	0.21
Mean End Systolic Volume (+/- 95% CI) ml	45.09 ± 6.8	48.47 ± 8.8	37.38 ± 8.4	0.14
Mean LVEF (+/- 95% CI) %	56.00 ± 3.1	54.85 ± 4.0	58.54 ± 4.3	0.29
Mean End Systolic Strain (+/- 95% CI) %	-15.68 ± 1.02	-15.37 ± 1.32	-16.38 ± 1.51	0.38

Table 7.1: Summary statistics of baseline data*. Mean ± 95% Confidence Interval. LVEF: Left Ventricular Ejection Fraction. P Value for the difference between treatment arms.*

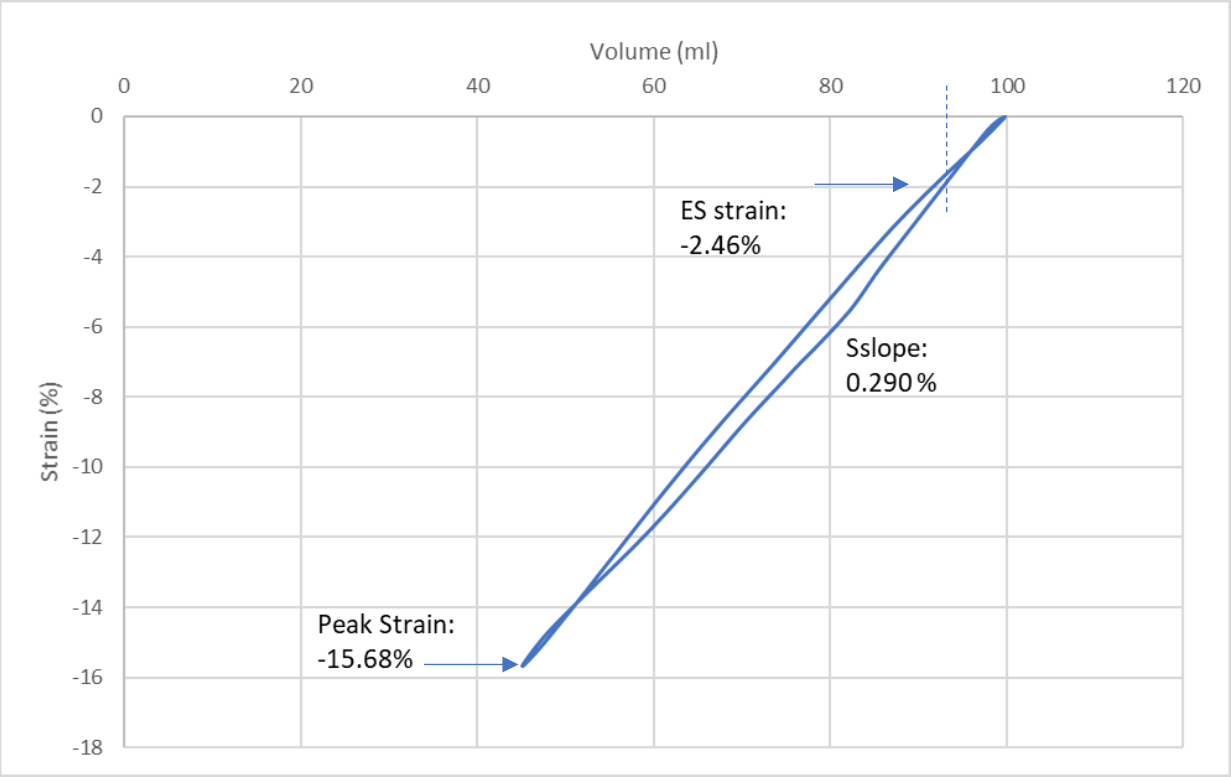


***Figure 7.3: Strain Volume Loop calculated from the mean baseline data for all subjects**. Showing the longitudinal strain, and volume in the LV throughout the cardiac cycle. ES Strain = Early systolic strain, measured at 90% of end-diastolic volume. Sslope = gradient of the systolic strain/volume slope.*

7.5.2 Changes Baseline to 12-Months Post-Intervention

In the AVR arm, the baseline peak strain was -16.38%, this value did not change at 12-months post-intervention. Mean end-diastolic volume reduced slightly from baseline to 12 months post-intervention, and the mean end-systolic volume increased. This reduction of ejection fraction caused the systolic gradient to increase from 0.32%/ml to 0.36%/ml. The systolic gradient also increased from baseline to 12-months post-intervention in the TAVI treatment arm, although not as much. This was caused by an increase in the magnitude of the peak strain from -15.4% to -16.5%, while the LVEF rose from 53.4% to 56.3%.

	AVR		TAVI	
	Baseline	12-Months Post	Baseline	12-Months Post
End-diastolic Vol (ml)	89.6	85.8	104.4	100.0
Ejection Fraction (%)	58.1	55.5	53.4	56.3
S-Slope (%/ml)	0.317	0.358	0.279	0.296
Peak Strain (%)	-16.4	-16.4	-15.4	-16.5
Early Systolic Strain (%)	-2.6	-2.3	-2.4	-2.5

Table 7.2: Baseline and 12M data from the mean SVL loops for AVR and TAVI.

Figures 7.2 and 7.3 illustrated the changing SVL for each treatment group. Although both treatment arms had a leftward shift at end-diastole, only the TAVI treatment arm had a leftward shift at end-systole. Overall both treatment arms had reduced uncoupling.

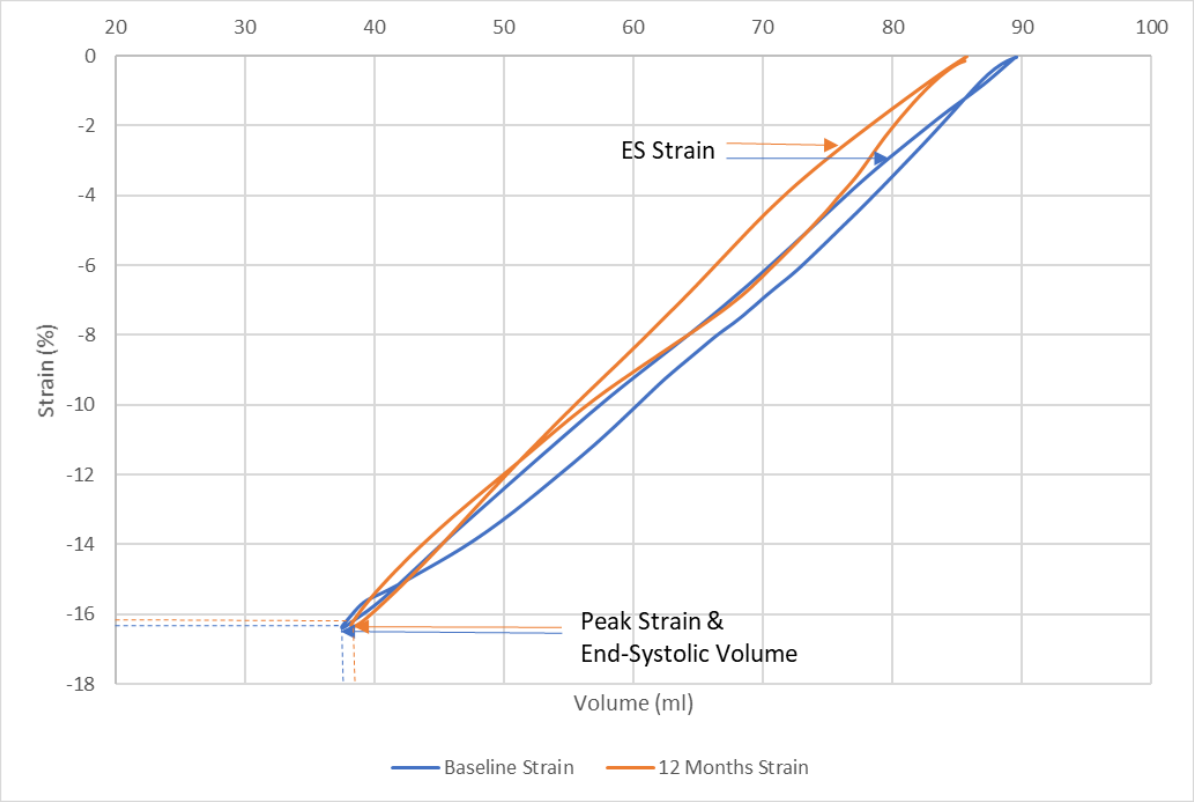


Figure 7.4: Strain Volume Loops Pre- and Post- Aortic Valve replacement*. Baseline: Peak Strain -16.4%, Early systolic strain: -2.6%, Systolic Gradient 0.317%/ml. Uncoupling: 5.9. 12-Months: Peak Strain -16.4%, Early systolic strain: -2.3%, Systolic Gradient 0.358%/ml. Uncoupling: 5.5. Strain: Longitudinal left ventricular strain, measured in the apical 4-chamber view, %: Percentage, ml: Millilitres.*

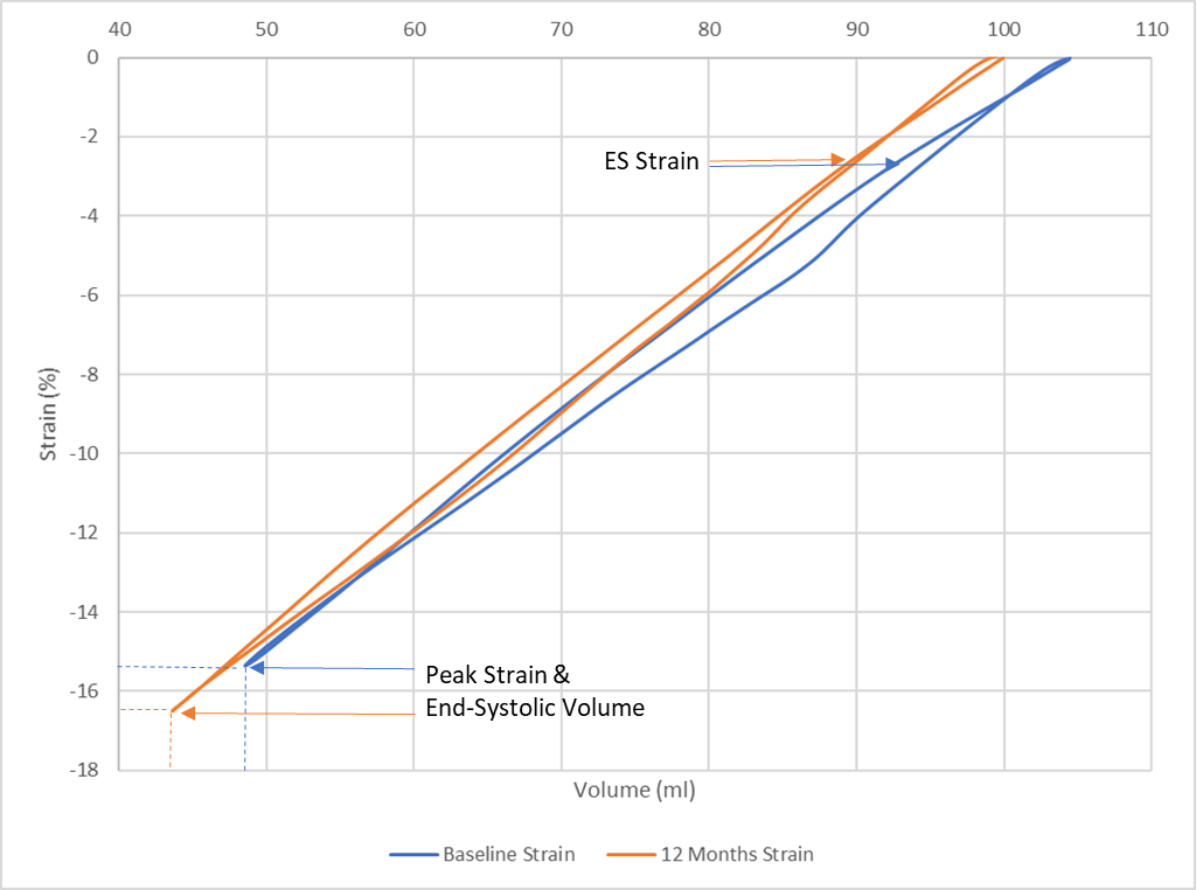


Figure 7.5: Strain Volume Loops Pre- and Post- TAVI*. Baseline: Peak Strain -15.4%, Early systolic strain: -2.4%, Systolic Gradient 0.279%/ml. Uncoupling: 4.9. 12-Months: Peak Strain -16.5%, Early systolic strain: -2.5%, Systolic Gradient 0.296%/ml. Uncoupling: 3.7. Strain: Longitudinal left ventricular strain, measured in the apical 4-chamber view, %: Percentage, ml: Millilitres.*

As seen in figure 7.6A, in the AVR treatment arm the total systolic-diastolic uncoupling reduced from 5.9 to 5.5. This was primarily driven by a reduction in early diastolic uncoupling (4.2 to 2.0), while late diastolic uncoupling increased from 28.6% to 64.1% of the total uncoupling (figure 7.6A, 1.7 to 3.5).

Although the total systolic-diastolic uncoupling also reduced in the TAVI treatment arm from 4.9 to 3.7 (Figure 7.6B), the relationship between early and late diastolic uncoupling contrasted that of the AVR group. The uncoupling during early diastole stayed constant at 3.3, and all the reduction was the result of a 77% decline in late diastolic uncoupling between baseline and 12-months post-intervention (1.6 to 0.4). Despite the overall drop in uncoupling, late diastolic decreased from 32.8% to 10.1% of the total uncoupling (figure 7.6B).

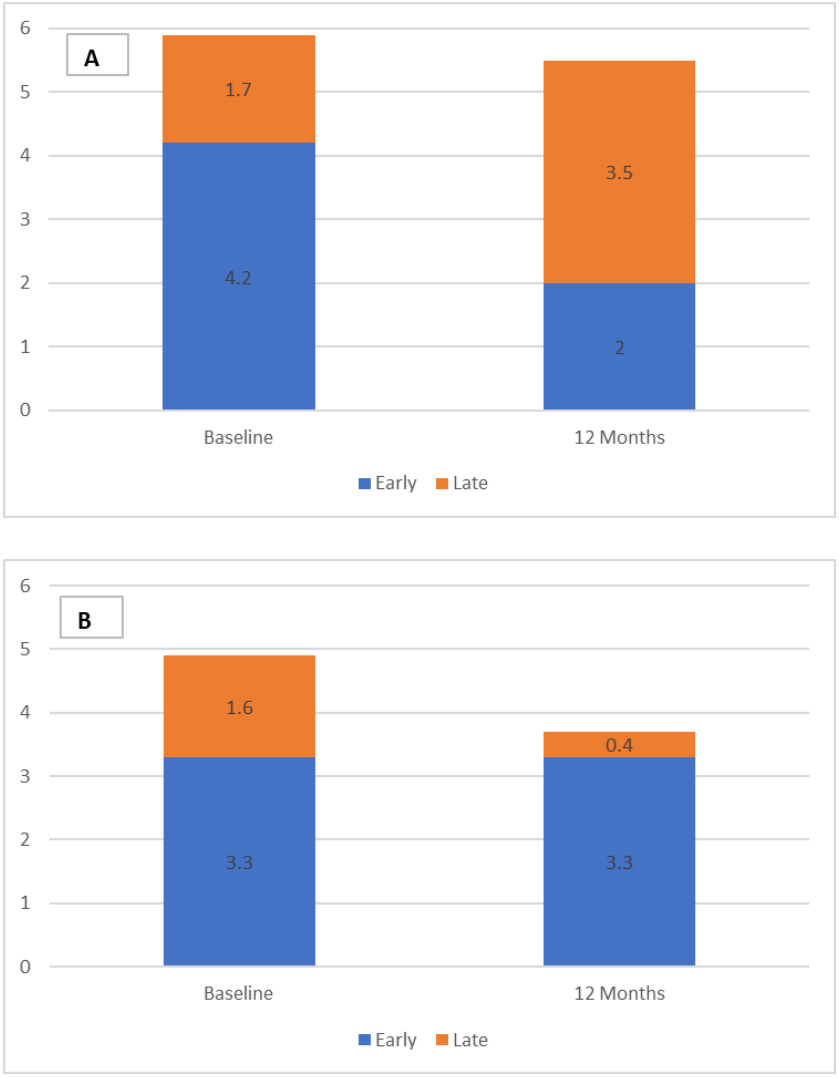


Figure 7.6: Early and late diastolic uncoupling, pre- and post-intervention for AVR and TAVI*. A: AVR treatment arm. B: TAVI treatment arm. Early diastole = First 30% of stroke volume. Late Diastole = Last 70% stroke volume. Uncoupling is a unitless measure used to represent the difference between systolic and diastolic deformation throughout the cardiac cycle.*

7.6 Discussion and Conclusions

Strain Volume loops are a recently developed method to assess the haemodynamic relationship of the LV, therefore there is limited previous work published to act as a body of knowledge. The work by Hulshof *et* al (2017) constructed SVL's using only 20 data points (10 in systole and 10 in diastole)(166), whereas this study calculated a total of 200 data points for each strain volume loop. This aimed to provide more accurate

tracking of the relationship throughout the cardiac cycle, and therefore a more reliable SVL.

Compared to the normal patients reported by Hulshof *et al* (166), the baseline values of the subjects in this study had a very similar mean early systolic strain, but a smaller (less negative) value for peak strain and Sslope. This reflects the LV dysfunction seen in severe AS, and the values for peak strain and Sslope align with the reported values for the subjects with severe AS in the pilot study. However, Hushof and team reported a much smaller value for early systolic strain than this study (-1.4 vs -2.5). The reasons for this difference may be related to the differing patient demographics, particularly in relation to age. The mean age of up subjects with AS in the study by Hulshof et al was 47 ± 11 years, compared to 81 years in this study. Although not specified such a comparatively young cohort with severe AS is suggestive of a high prevalence of bi-cuspid aortic valves(166). Subsequent work by the same team, with a cohort with severe AS and an average age of 67 years, reported a mean early systolic strain value of -1.8±1.4%(171).

Reviewing the baseline data, although the mean EDV is 14.8ml larger in the TAVI group compared to the AVR group, this was not statistically significant due to the larger standard deviation of the EDV's. EDV is affected by many factors; a subject's body surface area, heart rate, venous return, and the compliance of the LV which itself can be affected by co-morbidities such as coronary artery disease. Key is the fact that despite the difference in baseline EDV the change in mean EDV from baseline to 12-months post-intervention is consistent between the two treatment arms (a reduction of 4.1ml AVR, and 4.4ml TAVI). Despite the reduced GLS at baseline, LVEF is preserved (>50%), this is likely due to a compensatory increase in circumferential strain(173, 174). The leftward shift of EDV from baseline to 12-months post-intervention in both treatment arms indicates a reduction in EDV and the associated recovery of LV function. After AVR septal function often becomes dyskinetic. This will affect the LVEF, especially when measuring from the Ap4Ch view as the ESV will be larger. Additionally, pacemaker implantation can also lead to LV desynchrony, although the rates of pacemaker implantation in this cohort is not known, so it is not possible to say if this could be a factor in the lack of reduction in ESV in the AVR cohort.

Systolic-Diastolic uncoupling reduced post-intervention in both treatment cohorts. A previous study investigating changes in SVL's post-AVR and the relation to LV remodelling concluded that reduced uncoupling was significantly correlated to a decline in LV mass and that improvements in the dynamic function of the LV are linked to long-term remodelling of the LV(171). However, although total uncoupling reduced in both treatment arms, there were striking differences in the changes seen in systolic-diastolic uncoupling between the two treatment groups. One cause for the differences between the treatment arm could have been a difference in blood pressure between the groups, as hypertension will limit the reduction of afterload after an intervention. If the LV is still in a pressure overload situation this would limit the recovery of early diastolic uncoupling. However, the mean systolic blood pressure 12-months post-intervention was 152mmHg in the AVR treatment group and 149.9mmHg on the TAVI treatment group. Another factor to take into consideration if the inherent patient-prothesis mismatch seen in TAVI. As the TAVI valve sits inside the diseased native valve, the aortic valve area is going to be smaller than would be seen in a healthy native valve. This will limit the recovery of pressure overload in the LV. If the LV is still experiencing chronically elevated afterload that would explain why no reduction was seen in early diastolic uncoupling in the TAVI treatment arm.

The reduction in late diastolic uncoupling in the TAVI treatment arm but not in the AVR treatment arm suggests that the LV recovered to a more compliant state after TAVI. Multiple factors may have influenced this. The nature of AVR means that there is a rigid ring annulus sown into the left ventricular outflow tract, which would limit the regional compliance of the LV. The SURTAVI trial reported that at 30-day post-intervention the estimated incidence of AF was 12.9% in the TAVI treatment group, and 43.4% in those who had AVR(80). This study did not gather data on the presence or absence of sinus rhythm in subjects, but the presence of atrial fibrillation and therefore a lack of synchronised atrial contraction would influence the filling pattern and diastolic strain of the LV.

The post- AVR alternations in systolic-diastolic uncoupling reported by Hulshof *et al* aligned with the same as the changes seen in the TAVI treatment arm in this group, therefore contrasting the changes seen in the AVR treatment arm(171). This warrants further study, with the aim of reaching a consensus. Despite this, both studies agree

that the changes seen in SVL after intervention for severe AS demonstrate the recovery of the haemodynamic function of the LV, therefore SVLs have the potential to be clinically useful in the future if the process is automated.

This study was limited by a comparatively small number of subjects, and as the findings do not fully agree with previous work, further studies are needed to enhance the body of knowledge. Additionally, the construction of an SVL is based entirely on the original STE tracking of the myocardial wall, therefore it is on the uppermost importance that this is accurate. In this study the STE tracking was taking from a single cardiac cycle for each subject and conducted as a sub-study of the UK TAVI trial, so investigators did not have complete control over the image quality and it is not known how precisely the UK TAVI image acquisition guidelines were followed (for image acquisition guidelines see appendix 1).

Chapter 8 - Review of, and insights from, a national echocardiographic core lab

8.1 Abstract

To aid high-quality outcomes within trials using imaging, it is key that variability of image acquisition and analysis is kept to a minimum. Echocardiographic Core Labs (ECL's) provide a key role in multi-centre trials by aiming to provide a high level of reliability, consistency, and expertise in the subsequent analysis of data. The ECL receives all the transthoracic echocardiogram's (TTE's) taken as part of the trial, at the specified time points, and the team of experienced analysts conduct the pre-specified analysis. This work reviewed the analysis of the 2D ECL for the UK TAVI trial, and the reliability of the analyses conducted, as well as surveying trial sites to acquire feedback on the sites experiences of the ECL. Exploring their understanding and experiences regarding TTE imaging for the trial and working with the ECL.

Inter- and Intra- reader variability testing was conducted to assess ECL reliability. The testing examined the range of core echocardiographic measurements required for the trial; including Doppler assessment, dimension and volume measurements and visual assessment of regurgitation. Each analyst was assigned twenty random studies; 10 of which they had analysed originally to test for intra-analyst variability, and 10 which both analysts re-read to compare for inter-analyst variability. For each data set variation was analysed by calculating the intra-class correlation coefficient and constructing Bland-Altman plots. Initial results highlighted high levels of variability for left ventricular ejection fraction. The causal factors were identified and addressed, and a second round of testing was conducted to clarify if the variability had declined. To survey the UK TAVI sites, initially, contacts at each site were sent a web-based questionnaire. Respondents to the questionnaire were invited to participate in a semi-structured telephone interview to expand on their responses.

Overall, the levels of both intra- and inter-analyst variability were very good. Intraclass correlation coefficient's (ICC's) for the continuous variables were 0.91 (95% CI 0.89 - 0.93) and 0.93 (95% CI 0.91 - 0.94) for intra-analyst variability and 0.9 (95% CI 0.87 - 0.92) for inter-analyst variability. An ICC over 0.9 is deemed to be indicative of

excellent reproducibility. LVEF had noticeably lower levels of reproducibility, a large proportion of this error resulted from inconsistencies between the analysts' decision-making regarding the quality of image for analysis. Retesting, of LVEF where all images were deemed acceptable quality to analyse saw the ICC values increase from 0.62/0.49/0.10 to 0.87/0.99/0.97. The questionnaire of UK TAVI trial sites received a response rate of 20.4% (n=23). The results were overall positive but highlighted the potential for improving communication regarding image formatting requirements, feedback, and query resolution. The questionnaire also identified room for improvement in the process of sending images to the ECL. The four telephone interviews conducted illustrated a range of familiarity with the trial. A key theme was that there had been a delay with feedback, but this had improved since the implementation of a new system in 2017. One respondent spoke of the role of the ECL to 'review' the measurements; a misunderstanding that has the potential to bias the analysts.

Respondents provided constructive feedback that can feed into future trial design; highlighting the importance of clear guidelines, and formalised processes for ensuring the training of new site staff that join the trial team partway through. The overall strong figures for the variability of measurements within the 2D ECL support the hypothesis that the random error rates in the ECL are low; leading to more reliable data and the ability to come to statistically significant conclusions with smaller sample sizes. The lower levels of reproducibility seen for LVEF, especially in the first round of testing, demonstrate the importance of high-quality TTE images and consistent, training of ECL analysts

8.2 Introduction and Background

TTE is a highly useful modality of clinical imaging. However, there is the disadvantage that image quality is dependent on multiple factors; including operator skill, and machine quality (see section 1.2). Poor quality images increase the potential for variation in the analysis of the images (107). To aid high-quality imaging-based outcomes within a clinical trial it is key that variability of image acquisition and analysis is kept to a minimum. ECL's have been demonstrated to be an effective method of

minimising this variability; via the production of image acquisition guidelines, the use of a small group of experienced analysts, and through training (108, 109).

The UK TAVI trial had a dedicated ECL that received and analysed the TTE images for the UK TAVI trial outcomes, to standardise the analysis and remove unnecessary variation. (These TTE outcomes and ECL analysis were done separately to the novel research outputs described in chapters 3-7 in this work).

During study set up, all sites were provided with a set of trial-specific image acquisition guidelines (appendix 1). This detailed the quality requirements for images and which images in each TTE view were required to be captured during the scan. However, the UK TAVI ECL analyst team reported sample sizes for multiple measurements were limited by poor image quality or lack of appropriate view in many of the received TTE scans. These issues were also encountered when performing the analyses in chapters 3-7 in this thesis, again limiting the available sample size.

Therefore, the reliability of the UK TAVI ECL with current study conditions was evaluated to assess the current levels of variation between the analysts. In addition, study staff at UK TAVI sites were surveyed to explore their understanding and experiences regarding TTE imaging for the trial and working with the ECL, with a focus on the identified issues around poor image quality and non-compliance with the acquisition guidelines.

8.3 Aims

To assess the inter- and intra-analyst reliability for the core measurements taken by the 2D ECL for the UK TAVI trial under current conditions. To survey, via questionnaire and telephone interview, staff involved in the acquisition and sending of TTE data at UK TAVI trial sites. Exploring their understanding and experiences regarding TTE imaging for the trial and working with the ECL, in order to identify areas for improvement and change in best practice.

8.4 Methods

8.4.1 ECL Variability Testing.

Inter- and Intra- reader variability testing was conducted as a method of assessing ECL reliability.

All analysts were required to engage with the reader variability program, which aimed to assess inter and intra-reader variability. The variability was examined across the range of core echocardiographic measurements required for the trial. This included Doppler assessment, dimension and volume measurements and visual assessment of regurgitation. The full list of measurements can be found in appendix 2.

8.4.1.1. Data Collection

Using Excel (Microsoft Office, 2016) the RAND() function was used to assign each TTE that had been read, excluding those read in the previous 3 months, a random number. TTEs were then sorted in ascending order by the previous randomly assigned number. The list was reviewed in this pre-determined order with each reader being allocated the first 10 TTEs that had been previously analysed by themselves in order to assess intra-reader variability. Allocations were reviewed to ensure the availability of the DVD containing the raw data of the TTE without any saved measurements. If the disk was not available, then it was excluded from the analysis and a replacement allocated. Following this allocation, the subsequent 10 TTE's were distributed to both core ECL analysts to test the inter-reader variation. Each analyst was provided with a personalised data entry spreadsheet and a time slot to work independently on reading the studies. The DVDs containing the images were separated into a specific file to aid identification and ensure a smooth process. Analysts were asked measure all the 25 measurements taken as part of their ECL role, both core and supplementary.

Due to the initial analysis highlighting high levels of variability for left ventricular ejection fraction (Simpson's biplane method), further investigation was required to identify causal factors. A review of the data sets suggested that the major cause of variation was due to decision making regarding whether the image was of suitable quality to analyse. A second round of testing 6-months post the initial round was

conducted to investigate this. An independent expert analyst (a consultant cardiologist) reviewed a selection of echocardiograms and selected 12 studies of varying quality but that were deemed analysable by themselves and a senior echocardiographer. The details of these studies, along with the specific images in the scan series to analyse were sent to both ECL analysts to test inter-reader variability. Additionally, analysts were asked to re-measure the LVEF for the 10 TTE's they had previously analysed for intra-reader variability. All documents containing previous measurements were removed from the analysis computer.

8.4.1.2 Data Analysis

To test the intra-reader variability, the measurements taken and recorded as part of this quality testing were compared to the original measurements that were recorded in the trial database by that same operator. To test the inter-reader variability the measurements taken and recorded as part of this quality testing by each analyst were compared to each other without reference to the originally recorded measurements. In total there were 540 paired comparisons for each analyst; 27 analyses (25 measured plus the 2 calculated outputs) for each of 20 studies. For each data set (intra-reader 1, intra-reader2, and inter-reader) variation was analysed by calculating the intra-class correlation coefficient (ICC) as detailed in section 2.7.3. The ICC was a two-way mixed model, with a 95% confidence interval, testing for absolute agreement. Bland Altman graphs were used to visualize the variation in key measurements (detailed section 2.7.3).

Results for the second round of LVEF only testing were also analysed with ICC and Bland Altman plots as previously detailed.

8.4.2 Survey of Trial Sites.

8.4.2.1 Questionnaire Development and Distribution

Senior staff in the ECL and the UK TAVI trial management team formed a committee that was consulted regarding key areas of the ECL structure and processes that they felt influenced the image quality of scans being provided by trial sites, and a pilot

questionnaire was constructed based on this consultation. The pilot questionnaire was reviewed by clinical academic staff and ECL staff members in the form of a focus group, and appropriate changes made before sending to the main UK TAVI trial office for review, and subsequent approval by trial management. The questionnaire was based around closed questions with a 6-point Likert scale and a 'not applicable' option. A 6-point Likert scale was used to remove the option for a neutral response. There were also questions regarding the respondent's job role and how long they had been involved with the UK TAVI trial. Finally, there was an optional open-ended question to allow participants to voice additional comments. A copy of the questionnaire can be found in Appendix 4.

Following final approval of the questionnaire, it was transferred onto a web-based service (onlinesurveys.ac.uk) to ensure the greatest ease of access and clear formatting. This was with the intention of encouraging a high response rate. Prior to disseminating the questionnaire, the UK TAVI trial office corresponded with each site to ensure they had current email addresses for the staff at that site involved with the trial. To distribute the questionnaire and email was sent by the UK TAVI chief investigator, introducing the questionnaire and explaining its purpose (see Appendix 3). This email contained a hyperlink to the webpage where the questionnaire was hosted. The questionnaire was sent to the staff at UK TAVI sites that were involved in TTE acquisition, processing and dispatch of data to the ECL. The questionnaire was live, and invitees able to respond, for 3 weeks. A reminder email was also sent from the trial office 5 days before the questionnaire closed for submissions. The questionnaire was sent to 113 staff across the 33 UK TAVI sites. Table 8.1 documents the range of staff roles of those who were invited to complete the questionnaire.

Job category	n
Clinical Echo Lead (Consultant Physiologist or Cardiologist)	3
Lead Trial Coordinator/ Research Nurse	36
Lead Cardiac Physiologist	26
Sonographer	48
Total:	113

Table 8.1: Job roles of recipients of the UK TAVI site questionnaire invitation email

Completion of the questionnaire was deemed as informed consent to participate. Additionally, upon completion of the questionnaire respondents were invited to partake in a follow-up phone interview to expand on their views and experiences. If they wished to complete a telephone interview, they were requested to contact the listed email.

8.4.2.2 Telephone Interview Development and Delivery.

Initially, only one member of UK TAVI site staff responded to the request for participants to partake in a follow-up telephone interview. Therefore, an email was sent to the same cohort of staff members as the questionnaire request had been sent to, to ensure everyone was aware of the opportunity and with the aim of recruiting further participants. An additional three site staff responded, giving a total of 4 telephone interviews that were conducted. All four interviewees were physiologists/sonographers who performed TTEs at individual research sites.

The questionnaire responses were reviewed and used to identify themes and potential areas to explore during the telephone interviews. Questions with a less positive response overall, or more variance in opinion were expanded and addressed via the telephone interview. In addition, the analysts in the ECL had raised concerns that not all sites were following the trial image acquisition guidelines therefore this was also addressed during the telephone interviews. The purpose of the telephone interviews was to further explore the views of sites, and aspects of the ECL that are identified as areas for development. This was with the overall aim of being able to identify the

knowledge and resources that trial sites required to facilitate the transfer of the highest quality images possible to the ECL.

The telephone interviews followed a semi-structured format. There were seven main questions with a series of follow- up questions to expand on the participants' responses, as listed in Figure 8.1. At the beginning of each call, permission was requested to record the conversation using a dictation device.

1) What do you understand the role of the UK TAVI ECL to be?
    a) Why do you think that UK TAVI has an ECL?
2) How familiar are you with the echo acquisition guidelines for the UK TAVI trial?
    a) What is your opinion on the guidelines? Their structure, format, and ease to follow?
3) Whom at you site saves the scan images and prepares them to be sent to the ECL?
    a) IF THEY send the images: How do you find the process? Are there changes you would suggest?
    b) IF NOT: How does your site/that person find the process? Are there changes you would like to see?
4) What are your opinions on the current web-based method of feedback from the 2D ECL?
5) What has been you experience of the feedback from the 2D ECL? Has it been timely and helpful?
    a) Do you have any suggestions for improvements to this process?
6) Have you had the need to contact trial staff with a problem or query relating to the Echo's for UK TAVI?
    a) IF YES: Who did you contact? How was that experience?
    b) IF NO: If you needed to how would you do so?
7) Do you have any other feedback regarding the echo Core Lab you would like to share?

Figure 8.1: Questions from the semi-structured telephone questionnaire of UK TAVI site staff.

8.4.2.3 Survey Data Analysis

With the exception of the free comments box, questionnaire responses were coded to allow for quantitative analysis (1= Strongly Agree, 2= Agree, 3= Slightly Agree, 4 = Slightly Disagree, 5 = Disagree, 6 = Strongly Disagree). The mean response and variance of responses were then calculated. The responses for each question were then split according to the role of the respondent; to evaluate any differences. Comments left in the free comments box at the end of the questionnaire were reviewed for themes and associations

Recorded telephone interviews were subsequently transcribed. The interview transcripts (appendix 5) were reviewed for common themes and areas of disagreement between participants.

8.4.3 Ethical Approval

As this work was a component of quality assurance, maintenance of imaging standards and improving ECL function, it did not require additional ethics approval outside that of the UKTAVI trial approval (175).

8.5 Results

8.5.1 Reader Variability

The core two readers in the ECL were assessed for intra-reader variability. Overall, ICC's for the continuous variables calculated were high; 0.91 (95% CI 0.89 - 0.93) and 0.93 (95% CI 0.91 - 0.94). An ICC over 0.9 is deemed to be indicative of excellent reproducibility. Similarly, the ICC for the inter-reader variability was 0.9 (95% CI 0.87 - 0.92).

	Analyst 1 Intra- (95% CI)	Analyst 2 Intra - (95% CI)	Inter-reader (95% CI)
LVOT Diameter	0.95 (0.78 - 0.99)	0.74 (0.06-0.93)	0.81 (0.19 - 0.95)
LVEF (Biplane)	0.62 (0* – 0.90)	0.49 (0*- 0.88)	0.10 (0*- 0.79)
AV CW Mean PG	0.98 (0.94 – 1.0	0.99 (0.98 - 1.0)	0.99 (0.99-1.0)
All measurements	**0.91 (0.89 - 0.93)**	**0.93 (0.91 - 0.94)**	**0.90 (0.87 - 0.92)**

Table 8.2: Intraclass correlation values for intra- and inter- analyst variability of TTE analysis in the UK TAVI ECL*. *SPSS calculated a negative value for the lower bound of the 95% confidence interval.*

Table 8.2 also provides the ICC values for specific measurements key to the main trial dataset. These include left ventricle outflow tract (LVOT) diameter, left ventricle ejection fraction and the aortic valve peak gradient. LVOT diameter and aortic valve mean gradients show high levels of reliability. LVOT diameter ICC values were 0.81 for inter-reader variability and a mean of 0.85 intra-reader variability. Aortic valve mean gradient measurements had ICC values of 0.99 for inter-reader variability and mean intra-reader variability. LVEF had much lower ICC values (0.1 and 0.56 for inter- and mean intra-reader variability respectively), an indication of lower levels of agreement between the data set. This was subsequently investigated in order to detect the possible root cause.

Bland Altman plots to visually representing the variance seen for LVOT, LVEF, and AV CW mean gradient can be seen in figures 8.2-8.4 (analyst 1, analyst 2 and intra-analyst respectively). The mean differences (detailed in table 8.3) were small in absolute value when compared to the mean values (x-axis) this illustrates that there was no systemic increase or decrease in the measurements. The Bland Altman plots show the mean difference +/-two standard deviations. Assuming a normal distribution of data, 95% of data will lie between these boundaries. To test the assumption of normal distribution the kurtosis and skewness of each data set was calculated, with acceptable values between -2 and 2(176). The data for aortic valve peak gradient for intra-reader variability, both analyst one and two, had kurtosis values of 2.1 and 2.1. This means these data sets have more data in the tails of the distribution (the extremity) than a normally distributed data set, and the calculated standard deviation is not truly representative of the spread of the data and should be interpreted with care.

	Intra- Reader 1		Intra- Reader 2		Inter- Reader	
Mean difference (μ) *Standard deviation (σ)*	μ	σ	μ	σ	μ	σ
LVOT Diameter (mm)	0.02	0.10	-0.07	0.15	0.01	0.18
LVEF (Biplane) (%)	12.8	28.4	5.1	41.5	-7.2	43.6
Ao Valve CW Mean Gradient (mmHg)	-1.03	4.66	-0.45	2.29	-1.02	3.88

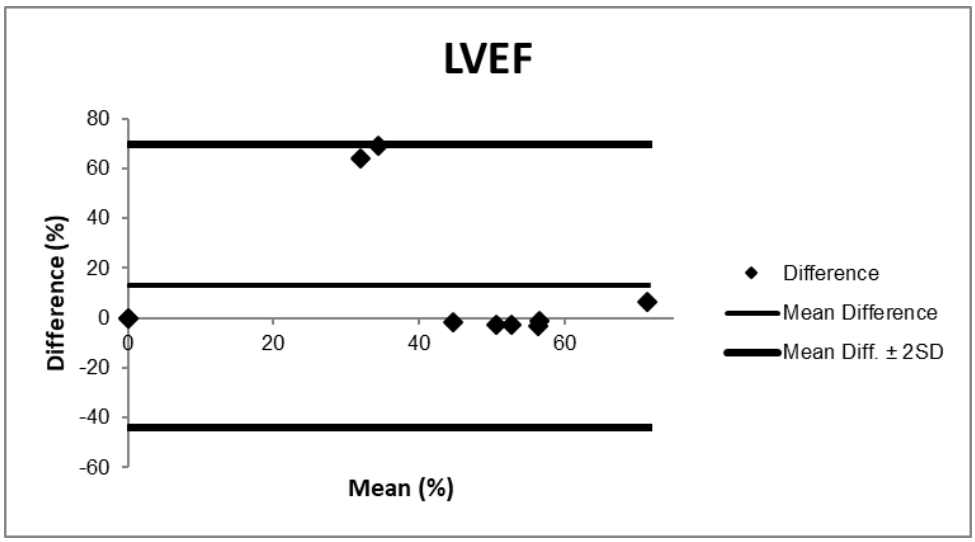
Table 8.3: Mean and Standard Deviation of the difference for LVOT diameter, LVEF, and Aortic Valve mean gradient during intra- and inter- analyst variability testing.

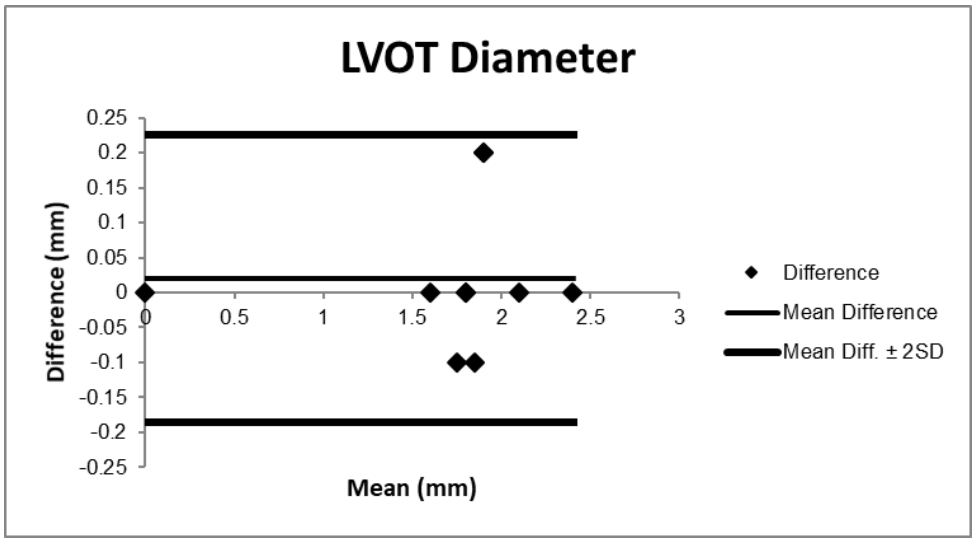
Although the mean difference provides useful insight into whether the measurements analysed have a consistent skew between timepoints (intra-analyst variability) or analysts (inter-analyst variability) but can be somewhat misleading as the negative and positive changes act to neutralise each other. Therefore, the mean absolute differences are displayed in Table 8.4.

	Intra- Reader 1	Intra- Reader 2	Inter-Reader
LVOT Diameter (mm)	0.26	0.13	0.13
LVEF (Biplane) (%)	22.8	25.8	25.1
Ao Valve CW Mean Gradient (mmHg)	5.7	1.5	2.8

Table 8.4: Mean Absolute differences Intra- and Inter-Analyst for key measurements.

All inter-reader variability data were reviewed individually to calculate their ICC valve, values varied between a value of 1.0 (95% CI 0.998-1.000) for RV TDI s', to the lowest value LVEF (0.10 95% CI 0- 0.79). The second-lowest ICC was TR V max, 0.76 (95% CI 0.114-0.938). ICC values between 0.75 and 0.9 indicate good reliability and those greater than 0.9 indicate excellent reliability.





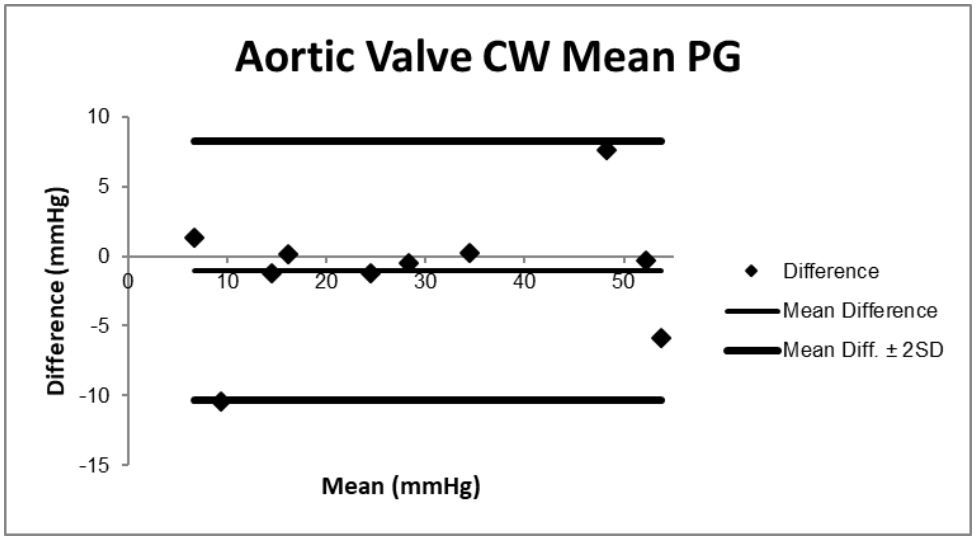


Figure 8.2 – Bland Altman Graphs for Reader 1 intra-reader variability*. Illustrating the mean difference and standard deviation of measurements for Left Ventricular Ejection Fraction (LVEF), Left Ventricular Outflow Tract Diameter (LVOT), and Aortic Valve Peak Gradient. Each data point is represented by a diamond; plotted as the mean value on the X-axis and the difference between the two values on the Y-axis. The outliers seen in LVEF plot occurred due to the measurement being taken at only one of the timepoints.*

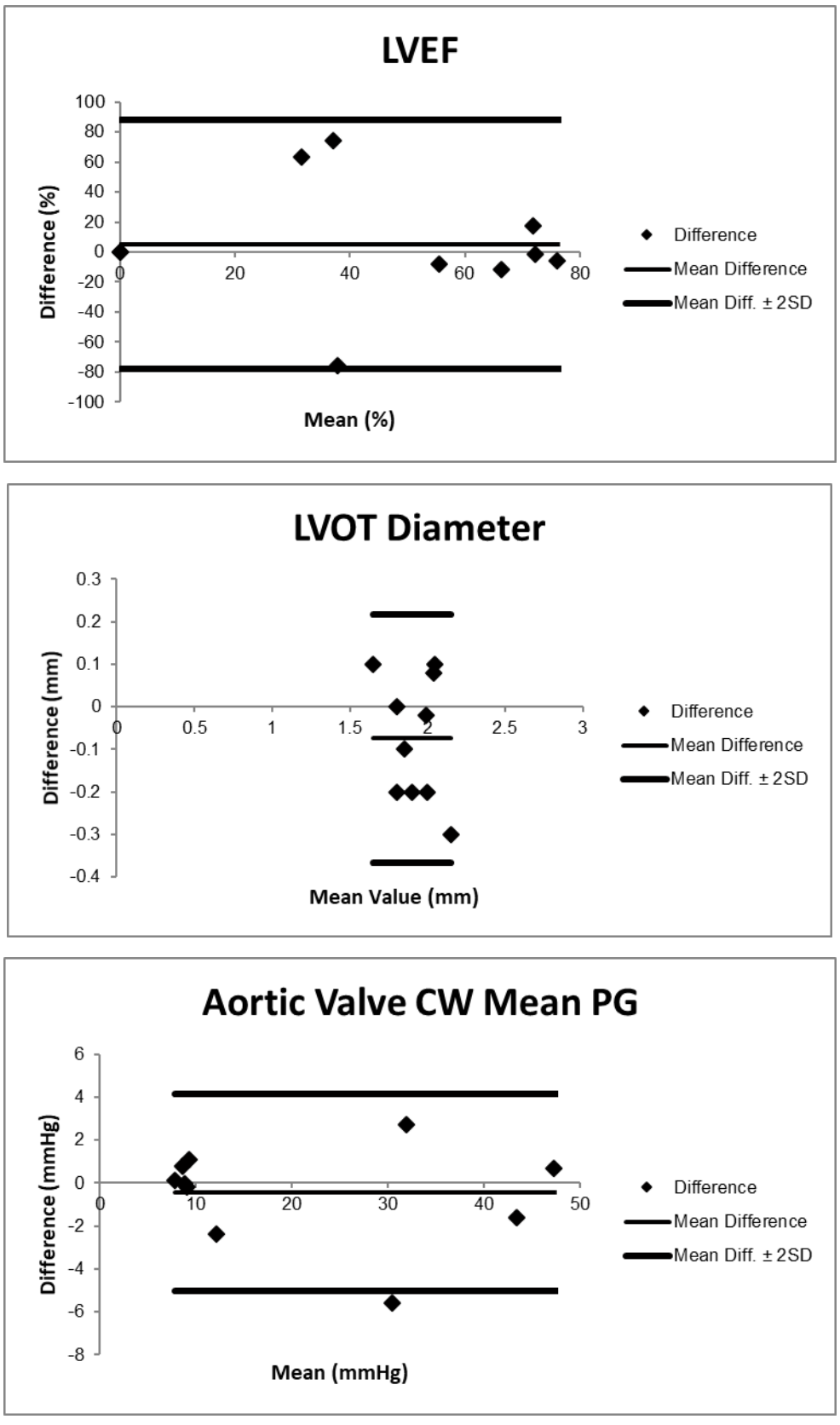
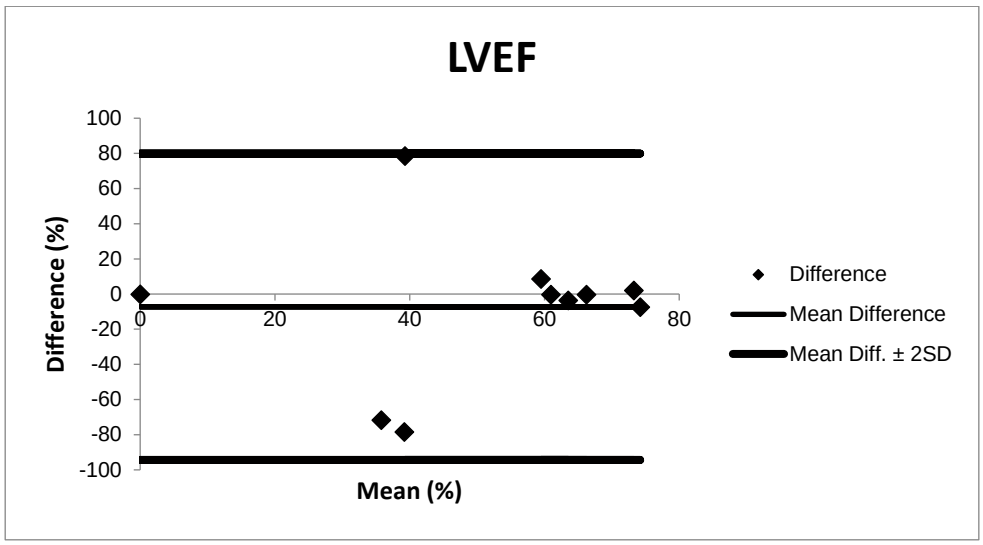
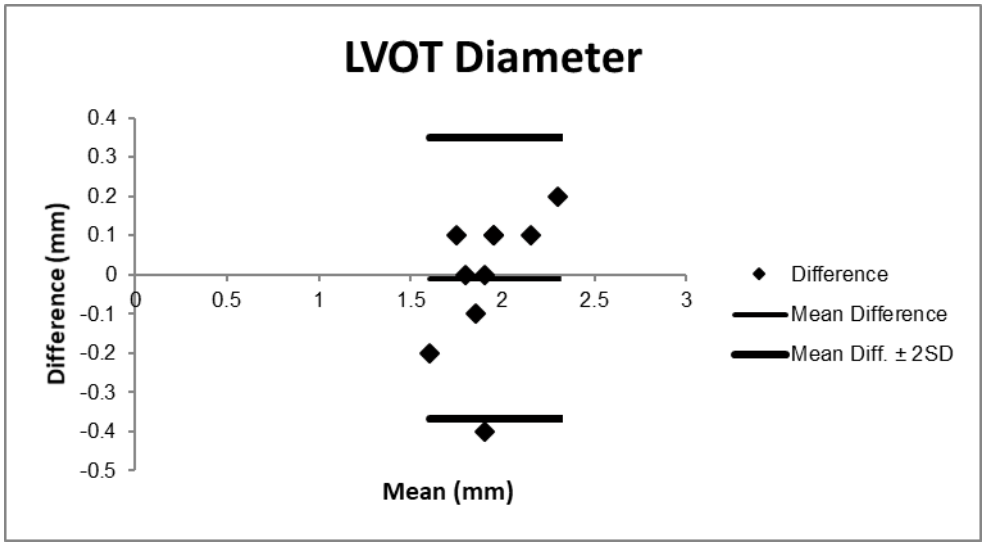


Figure 8.3 - Bland Altman Graphs for Reader 2 intra-reader variability*. Illustrating the mean difference and standard deviation of measurements for Left Ventricular Ejection Fraction (LVEF), Left Ventricular Outflow Tract Diameter (LVOT), and Aortic Valve Peak Gradient. Each data point is represented by a diamond; plotted as the mean value on the X-axis and the difference between the two values on the Y-axis. The outliers seen in LVEF plot occurred due to the measurement being taken at only one of the timepoints.*





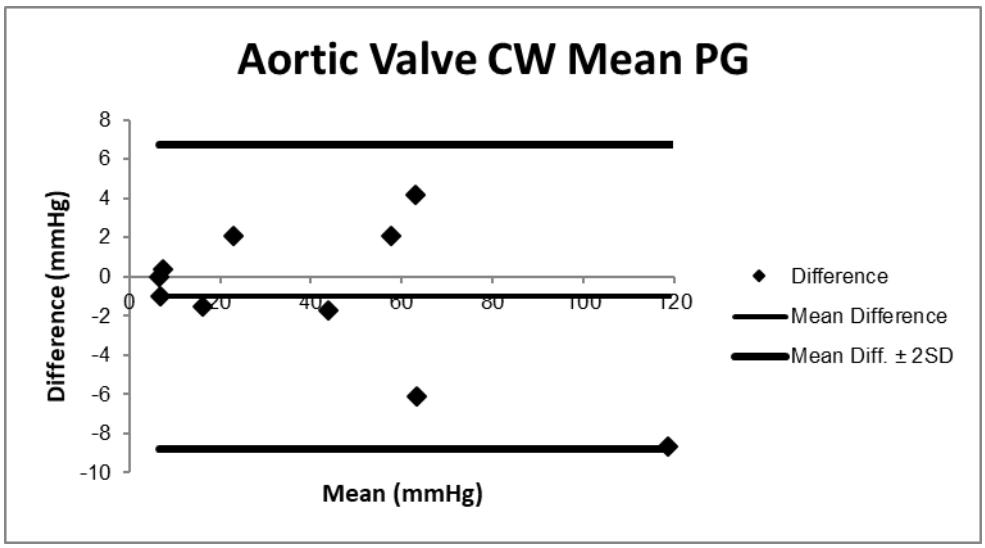


Figure 8.4- Bland Altman Graphs for inter-reader variability*. Illustrating the mean difference and standard deviation of measurements for Left Ventricular Ejection Fraction (LVEF), Left Ventricular Outflow Tract Diameter (LVOT), and Aortic Valve Peak Gradient. Each data point is represented by a diamond; plotted as the mean value on the X-axis and the difference between the two values on the Y-axis. The outliers seen in LVEF plot occurred due to the measurement being taken at only one of the timepoints, and one scan where LVEF was measured at neither timepoint.*

A large proportion of the error for LVEF resulted from inconsistencies between the operators' decision-making regarding the quality of image for analysis. Therefore, analysing only those scans with measurements submitted for both reads, the ICC values rose to 0.966, 0.532, and 0.992 and the mean absolute difference reduced to 2.91, 9.0, and 3.7 for reader 1 intra-, reader 2 intra- and inter-reader variation respectively. A second round of variability analysis for LVEF was conducted, and the results illustrated much lower levels of variation, both inter- and intra-analyst (0.87, 0.99, and 0.97 for reader 1 intra-, reader 2 intra- and inter-reader variation respectively). Table 8.5 displays the ICC values for the inter-reader variability for the second round only. Intra-reader variability compares the LVEF figures only between rounds one and two of testing for each reader.

	Reader 1 Intra (95% CI)	Reader 2 Intra (95% CI)	Inter-reader (95% CI)
LVEF (Biplane)	0.87 (0.52 - 0.97)	0.99 (0.98- 0.1.0)	0.97 (0.89- 0.09)

Table 8.5: Intraclass correlation values for intra- and inter- analyst variability of TTE analysis in the UK TAVI ECLs - Second round testing of LVEF only.

The Bland Altman plots in figure 8.5 visualise the spread of data and mean difference for the re-testing of LVEF variance. The standard deviations of the difference and mean absolute difference can be seen in table 8.6. The mean difference and standard deviation for reader one were heavily influenced by one scan where the measurement had been taken in one round of testing but not the other. Removing this scan from the analysis the standard deviation reduces to 2.86% and the absolute mean difference reduces to 1.84%.

	Intra- Reader 1		Intra- Reader 2		Inter- Reader	
	Mean Difference	Standard Deviation	Mean Difference	Standard Deviation	Mean Difference	Standard Deviation
LVEF (Biplane) (%)	7.71	19.32	3.4	4.32	2.4	3.14

Table 8.6: Mean Absolute difference and Standard Deviation of the difference of LVEF measurements during the re-testing of LVEF analyst variation. *Standard deviation calculated using the true difference not the absolute value of the difference between the two points.*

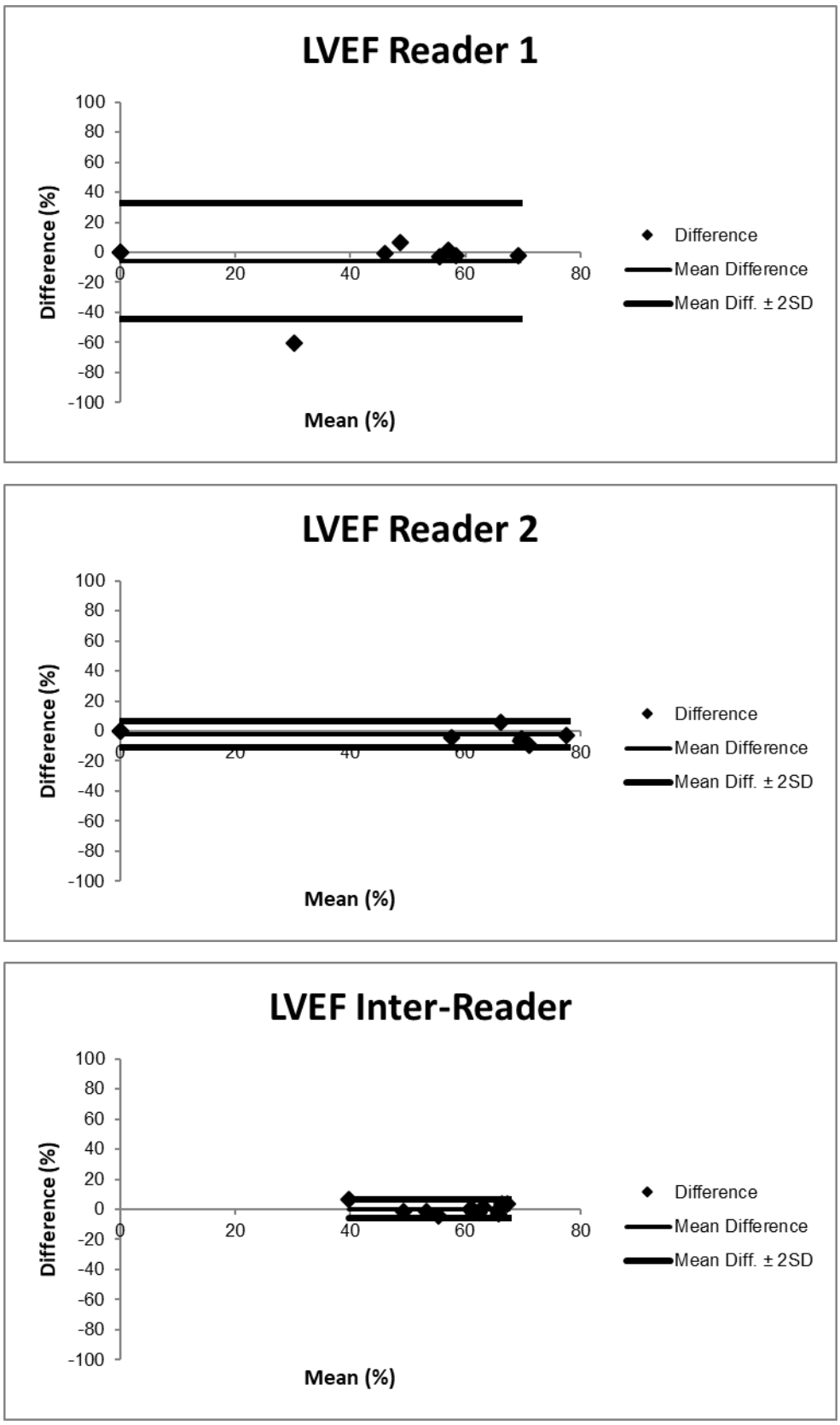


Figure 8.5 – Bland Altman graphs displaying the results for the retesting of reader variability for Left Ventricular Ejection Fraction (LVEF). *Illustrating the mean difference and standard deviation of measurements. Each data point is represented by a diamond; plotted as the mean value on the X-axis and the difference between the two values on the Y-axis.*

8.5.2 Questionnaire Survey of Trial Sites.

The questionnaire sent to UK TAVI sites received 23 responses: a response rate of 20.4%. The response rate varied between the roles; 31.3% of Echocardiographers, 13.9% of research nurses, and 10.3% of those with other roles responded.

Figure 8.6 shows the jobs roles of subjects who completed the questionnaire.

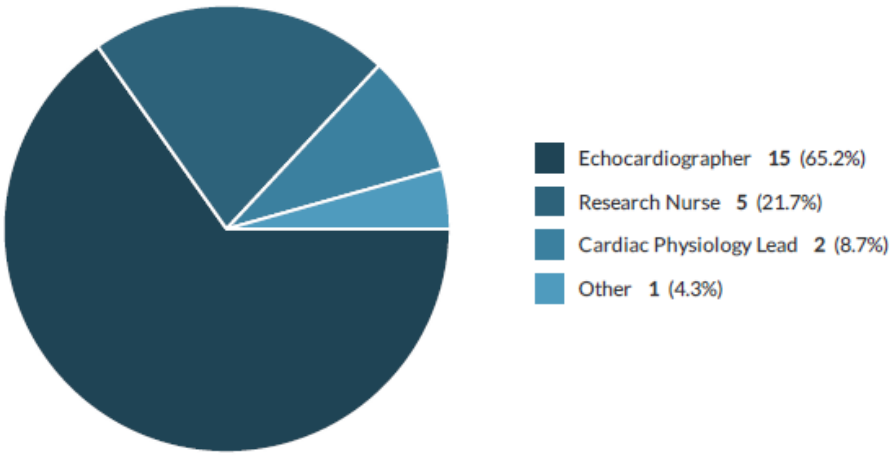


Figure 8.6. Job Roles of those who responded to the UK TAVI site survey. *The number of each job role, and percentage of the sample population.*

The responses received were mainly positive. Responses were coded to assist quantitative analysis, 1 for Strongly Agree through to 6 for Strongly Disagree. Excluding responses of N/A, the mean coded value for the responses to questions 2-11 varied between 1.6 and 2.8 (See Table 8.7). A value of between one and three represents a positive response.

Question	Mean Coded Response
I understand the purpose of the ECL	1.83
I believe the addition of ECL is useful for the trial	1.73
Staff working in the ECL are experts in their roles.	1.84
I have reviewed and understood the imaging acquisition guidelines provided for the UKTAVI trial.	1.60
The image formatting requirements have been clearly explained to me.	2.14
The items that need to be sent to the ECL at each study time point have been clearly explained	1.86
Sending the images to the ECL is convenient.	2.80
Feedback from the ECL is timely	2.67
Feedback from the ECL is relevant and helpful	2.39
If I have queries, I know who to contact and how to do so.	2.55

Table 8.7: Mean responses to UK TAVI site survey questions. *Coded 1= Strongly Agree, 2= Agree, 3= Slightly Agree, 4 = Slightly Disagree, 5 = Disagree, 6 = Strongly Disagree.*

Figures 8.7 – 8.19 show the range of responses received for each question in the survey.

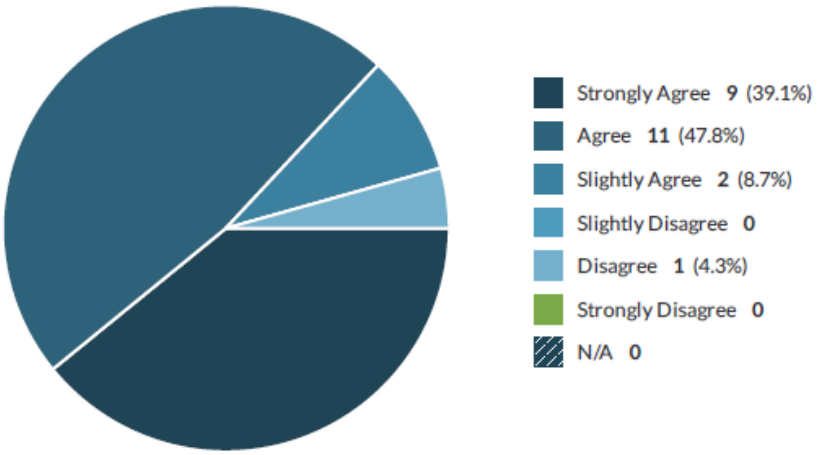


Figure 8.7 Responses to the question 'I understand the purpose of the ECL'

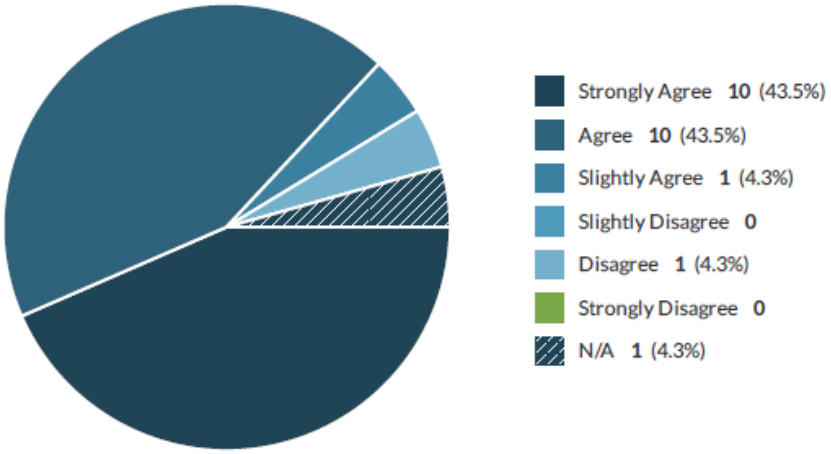


Figure 8.8. Responses to the question 'I believe the addition of an ECL is useful for the trial.'

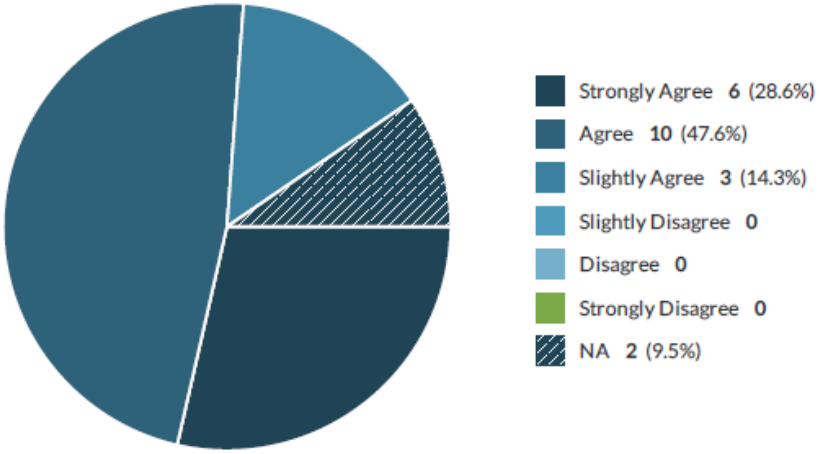


Figure 8.9. Responses to the question 'Staff working in the ECL are experts in their role.'

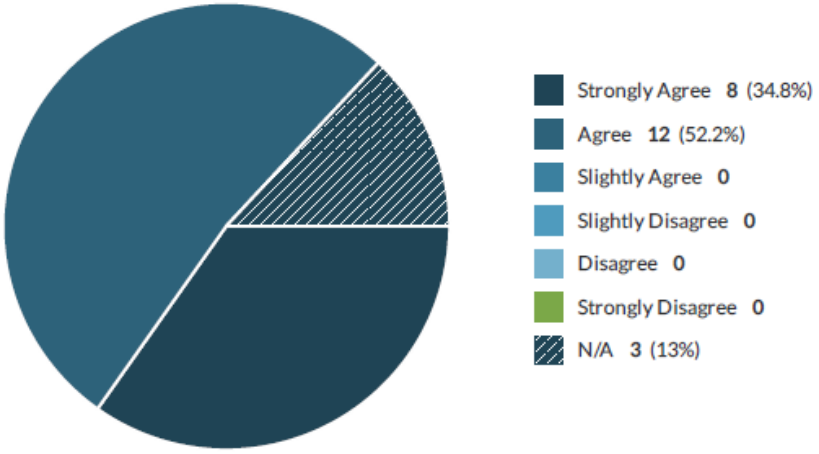


Figure 8.10. Responses to the question 'I have received and understood the image acquisition guidelines provided for the UK TAVI trial.'

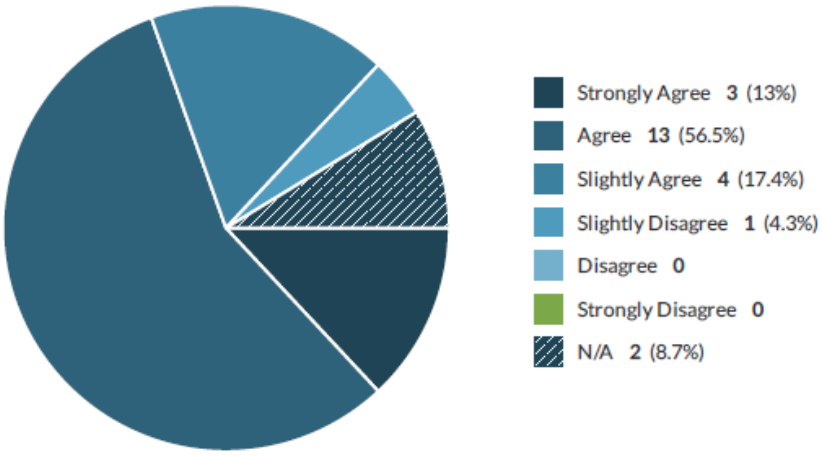


Figure 8.11. Responses to the question 'The image formatting requirements have been clearly explained to me.'

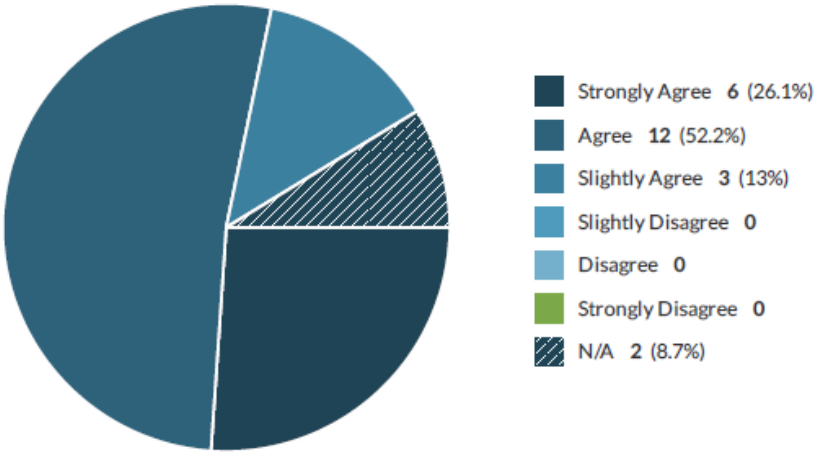


Figure 8.12. Responses to the question 'The items that need to be sent to the ECL at each study time point have been clearly explained.'

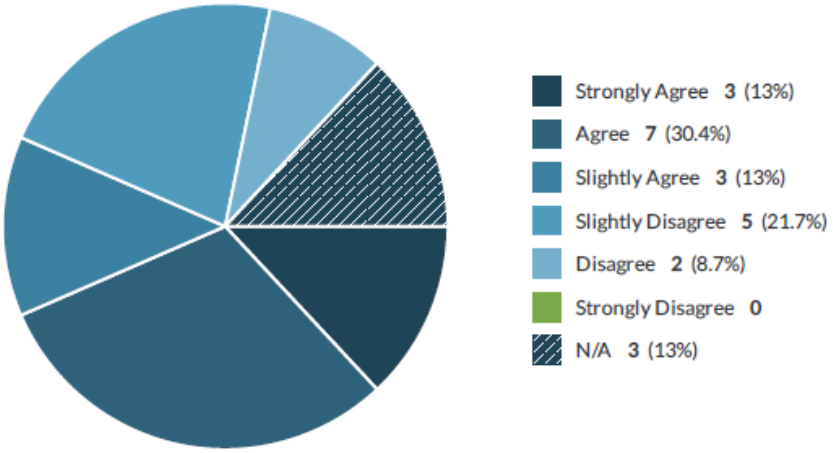


Figure 8.13. Responses to the question 'Sending images to the ECL is convenient.'

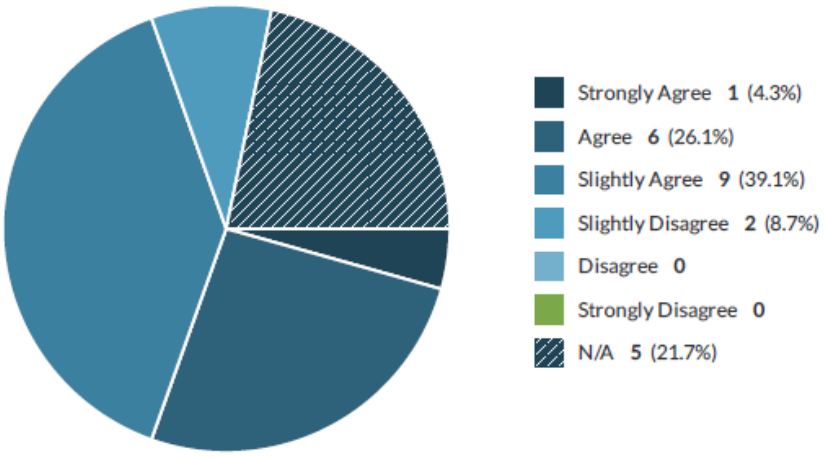


Figure 8.14. Responses to the question 'Feedback from the 2D ECL is timely.'

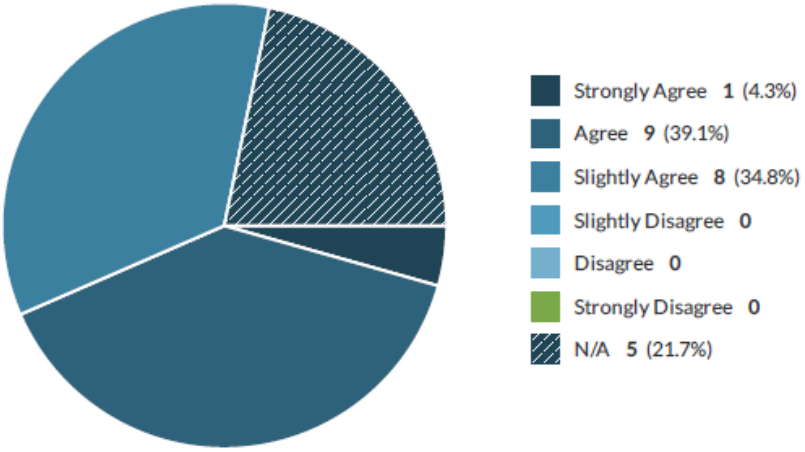


Figure 8.15. Responses to the question 'Feedback from the 2D ECL is relevant and helpful.'

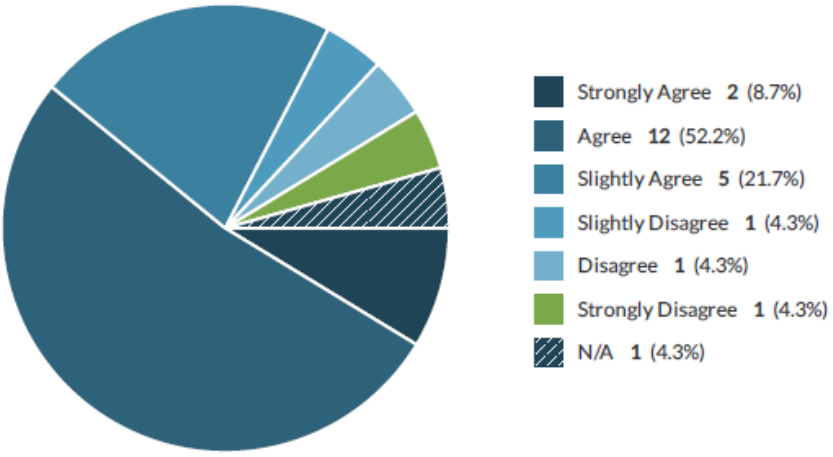


Figure 8.16. Responses to the question 'If I have queries, I know who to contact and how to do so.'

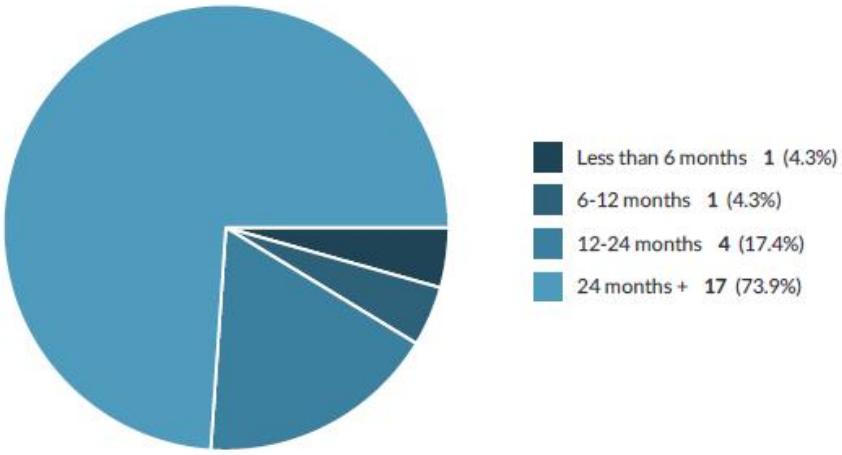


Figure 8.17. Responses to the question 'How long have you been working on the UK TAVI trial?'

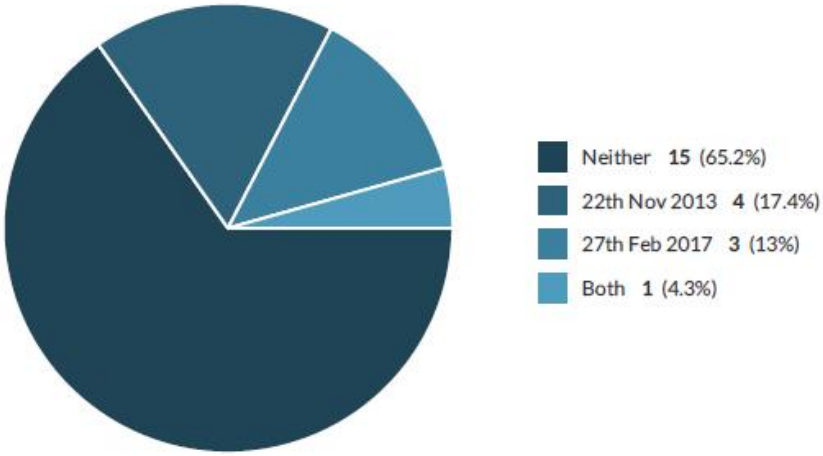


Figure 8.18. Responses to the question 'Did you attend the echo train days on either 22nd November 2013 or 27th February 2017?'

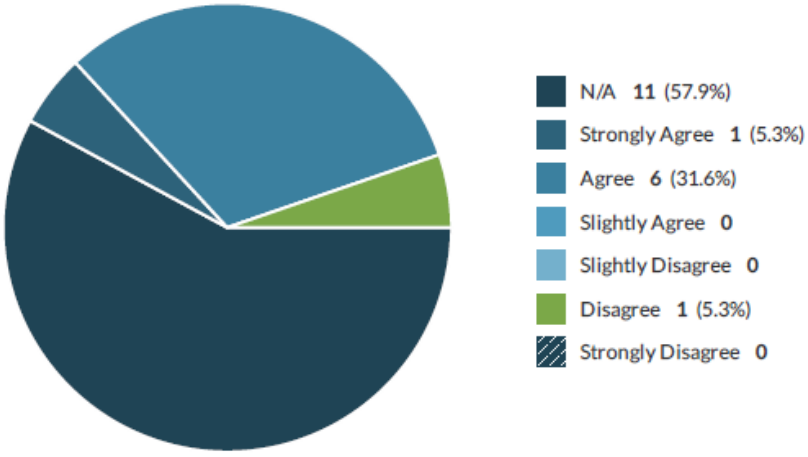


Figure 8.19. Responses to the question 'Attending the echo days affected my practices' regarding acquiring and sending UK TAVI trial images.'

All but one respondent said they were aware of the ECL prior to this questionnaire. This participant answered all the remaining questions regarding the 2D ECL and selected that they had been working on the UK TAVI trial for over 24 months. Therefore, it would be reasonable to suggest that selecting no to question 1 was a user error. Respondents felt that they understood the role of the ECL, with 67% selecting 'strongly agree' or 'agree' with the statement 'I understand the purpose of the ECL', and only one respondent selecting 'disagree'. The statements 'I believe the addition of an ECL is useful for the trial' and 'staff working n the ECL are experts in their role' also both received a majority of positive responses. Those who responded regarding the image acquisition and formatting deadlines; provided a more mixed response, but positive overall. Questions regarding the feedback from the 2D ECL also received a mixed response. Therefore, these were themes that were identified to be explored in telephone interviews. When asked, five respondents (22%) selected N/A, in response to the statement 'Feedback from the 2D ECL is timely/is relevant and helpful', yet the feedback should be relevant to both the research nurses and those performing the TTE's. While most respondents (74%) had been working on the trial for more than 24months, there was a significant minority who had become involved more recently, it is important that these staff members have been given full and appropriate training. How long the respondent had been working on the UK TAVI trial was correlated with the responses to 'The image formatting requirements have been clearly explained to me' (r=-0.74) and 'the items that need to be sent to the ECL at each study time point have been clearly explained' (r=-0.53). The longer a respondent had been working on the trial the more positive their responses were likely to be. The one respondent who has been working on the trial for less than 6-months was the only respondent to select 'slightly disagree' in response to 'The image formatting requirements have been clearly explained to me'.

Of those who attended at least one of the echo training days 87.5% (7/8) either 'strongly agreed' or 'agreed' with the statement that doing so had affected their practices. Although this is not supported by statistically significant correlations between attending the training day(s) and responses to other questions. This is likely, at least in part, to the very small sample sizes involved, as only 8 of the respondents had attended at least one of the training sessions.

Due to the small sample sizes, it was decided that traditional statistics were of limited utility. Therefore, to investigate the potential relationship between job role and the responses the mean coded response for each question is shown in Table 8.8.

Question	Mean Coded Response Echocardiographer	Mean Coded Response Research Nurse	Mean Coded Response Other
I understand the purpose of the ECL	1.80	2.00	1.67
I believe the addition of ECL is useful for the trial	1.57	2.00	2.00
Staff working in the ECL are experts in their roles.	1.83	1.75	2.00
I have reviewed and understood the imaging acquisition guidelines provided for the UKTAVI trial.	1.57	1.33	2.00
The image formatting requirements have been clearly explained to me.	2.27	1.67	2.00
The items that need to be sent to the ECL at each study time point have been clearly explained	2.00	1.5	1.67
Sending the images to the ECL is convenient.	2.92	2.4	3.00
Feedback from the ECL is timely	2.91	2.25	1.67
Feedback from the ECL is relevant and helpful	2.45	2.25	2.33
If I have queries I know who to contact and how to do so.	2.67	2.00	2.00
Attending the echo training days affected my practices' regarding acquiring and sending UK TAVI trial images.	2.33	N/A	2.00

Table 8.8: Coded mean responses to UK TAVI site survey questions, by job role. *Coded 1= Strongly Agree, 2= Agree, 3= Slightly Agree, 4 = Slightly Disagree, 5 = Disagree, 6 = Strongly Disagree. A mean value of ≤3 represents an overall positive response. A mean value > 3 represents an overall negative response.*

The questions where response varied by job role most noticeably were; 'Sending the images to the ECL is convenient ', 'The image formatting requirements have been clearly explained to me', 'Feedback from the ECL is timely' and 'If I have queries I know who to contact and how to do so'.

8.5.3 Survey of Individual Trial Sites - Telephone Interviews.

The four interviews conducted with trial staff at sites illustrated a range of understanding and familiarity with the trial.

The interviews started with a question regarding the role of the ECL and its value within the trial. There were discrepancies in the answers provided for this question. Interviewee two (I2) did not seem to understand the question, despite attempts to clarify so their responses will not be discussed in relation to this question. Interviewee's 1 (I1) and 3 (I3) demonstrated a good understanding of the role of the ECL; discussing key factors such as 'continuity of measurements', reduced inter-observer variability, and elimination of bias. Interviewee 4 (I4) spoke of the ECL role being that of 'reviewing' and being a 'second analyst' saying that the role of the ECL was to "*review the results we send in*". I4 also brought up the reduction of bias that having an ECL provided, saying that it allows great accuracy because *"…you are taking that element of bias or inaccuracy out. Or at least highlighting areas of inaccuracy or bias"*. When asked about their familiarity with the echo acquisition guidelines all respondents demonstrated awareness of them. I1, I2, and I4 spoke of referring to the guidelines each time they did a scan, to try and ensure adherence. Overall the feedback was that the guidelines were clear and easy to follow, I3 described them as "…very clear, very concise", and I2 as "pretty straight-forward". In regards to potential improvements, I1 suggested the addition of a one-page summary or quick list that could be referred to with ease while scanning the patient. I4 spoke of the order of the guidelines saying that they were not in 'chronological order' in their opinion, and they found themselves *"jumping around a little bit"* between different echocardiographic views. Upon review of the image acquisition guidelines, they were already grouped by the echocardiographic view, apart from the guidelines referring to the collection of 3D data. This is due to the fact that not all sites had the ability to collect 3D images.

At all sites interviewed it was the staff member who performed the scan that saved the images onto a disk in preparation to be sent to the ECL. Only one interviewee (I1) spoke of any difficulties with this process, saying *"So, I was doing it [saving the images] wrong, and I kind of got into doing it wrong. And by the time the TAVI trial assessors got to my disks, I think we had lost a couple of the studies because I had done them*

wrong at the beginning." I1 identified that if the images had been reviewed in a timelier manner, they would have been able to have addressed the issue quicker.

When asked about the feedback process from the ECL I3 also spoke of delay saying that when the trial first started the feedback was 'very behind' but that it is 'much better' now. While I1 and I2 seemed overall happy with the current feedback process, I3 spoke of frustration with the language used. I3 spoke of how there are factors that affect image quality that are outside of their control and how when they review the feedback, they "...*often see that when it says not to protocol, it's often because of poor body habitus, or the patient just doesn't have good enough 3D views for me to do…. I put that on the information sheet and I just feel that rather than just writing 'Not to Protocol' …..that they could re-iterate on that….. Because when you just read that 'Sub-optimal, not to protocol' it …..makes you feel quite like, like you haven't done a good enough job."* One interviewee (I4) was not aware of the feedback system for scans sent to the ECL at all stating they *'had never seen [the emails*]'.

The penultimate question in the telephone interviews asked respondents who they would contact regarding queries about the UK TAVI trial echocardiograms. The answers varied with I2 and I3 speaking finding contact details for the UK TAVI trial office, whereas I1 and I4 saying they would look to contact the ECL directly.

The telephone interviews concluded with an invitation to share any other feedback regarding the ECL they wished to share. I3 spoke of wishing to know their sites performance metrics compared to other sites, and the factors that could be affecting this, saying "… *it might be nice to know how our centre compares to other centres. Are we doing a good enough job, what could we do to improve? ... Now how [do] one department, get all their studies to be excellent? Is that because they are allocated a lot more time? Do they have better machines?".*

Full transcripts of the interviews are provided in appendix 5. Overall the interviewees showed a good understanding of the ECL processes and acknowledged improvements that had been made; such as the increased efficiency of TTE quality feedback. Although there were some areas of misunderstanding; such as the role of the ECL as the primary analysts and who to contact with questions, that has the potential to damage the

blinding and impartiality of the ECL. Interviewees also provided constructive feedback that can feed into future trial design.

8.6 Discussion and Conclusions

8.6.1 Reader Variability

Optimal accuracy and reliability of measurements within a trial require high-quality image acquisition, review and analysis. The use of a dedicated ECL within a trial allows adds control to the quality of review and analysis, but all variation cannot be excluded. Overall the core analysts in the ECL reviewed the echoes with excellent reliability in the measurements tested, as demonstrated by the ICC values which al exceeded 0.9 when assessed as a complete study and showed comparable reliability with the work of Douglas *et al* (2013) where the ICC values for inter- and intra- analyst variance ranged from 0.89-0.99, and 0.56-1.00 across the five continuous variables tested in the quality assurance framework (See Figure 8.20)(108). Again, this paper demonstrated higher levels of variability in the measurement of biplane LVEF than the other continuous variables analysed.

Reader type	Analysis	Biplane LVEF	Visual LVEF	Mean AV gradient	Peak AV gradient	AVA
Sonographer	Intraobserver	0.70-0.87	0.95-0.99	0.99-1.00	1.00	0.91-1.00
	Interobserver	0.89	0.88	0.97	0.97	0.90
Physician	Intraobserver	0.56-0.94	0.98-0.99	0.99-1.00	0.99-1.00	0.95-0.97
	Interobserver	0.92	0.95	0.99	0.99	0.95

Figure 8.20: Intraclass correlation coefficient (ICC) values for a range of continuous variables analysed by ECL staff for the PARTNER trial *(108).*

Initially, the results for LVEF with Simpsons bi-plane method showed a low level of reproducibility (ICC values of 0.62[Intra-1], 0.49[Intra-2], and 0.10[Inter-analyst] for absolute agreement). Further review of the data suggested that a significant cause of the inter-reader variability related to disagreement about whether the images were of suitable quality to measure the ventricular volumes. Further inter-analyst testing was conducted purely on studies of adequate quality to measure LV volumes, this saw the ICC rise from 0.10 -0.97 which is a remarkable change. When analysts re-evaluated LVEF on the scans used for intra-reader variability testing 6 months after the initial round and the two rounds compared for variability the ICC also markedly improved. As the first round included studies that had been analysed at the beginning of the trial

this suggests that there is a learning curve for the reliable measurement of LVEF. In-person interviews with the ECL analysts confirmed that they would agree with this. Particularly they acknowledged that they had become more confident in measuring LVEF on sub-standard images, and critically evaluating the figure provided in conjunction with a visual evaluation. The variation could, therefore, be minimised if the images submitted were of optimal quality, as there would be a clear endocardial border for tracing and minimal disagreement regarding if the image was of suitable quality to analyse. A recent study investigated the effect of both expertise and image quality on LVEF measurements. High levels of inter-observer reliability were reported, with ICC values ranging from 0.85-0.89, however, this study excluded any TTE where any of the three observers felt they could not accurately measure LVEF. This study concluded that improved TTE image quality reduced observer variability in all levels of expertise(105).

De Geer *et al* investigated the inter-analyst variability for LVEF and GLS between two analysts in patients with septic shock. The study only included subjects that had adequate TTE images to be analysed accurately. The reported ICC values for LVEF were 0.87 (95% CI 0.77 – 0.93) and 0.84 (95% CI 0.75 – 0.90) for inter- and intra-observer variability respectively(177), which is comparable but slightly lower than the ICC values found in this study when LVEF was re-tested.

The small sample size that was taken (ten studies for each comparison) is likely to be a key contributor to the wider confidence interval seen for many of the individual variables(178), particularly as the confidence intervals for the overall ICC (including all measurements so a significantly larger sample) is much narrower.

Recently there has been an increased interest in the use of artificial intelligence technologies in medical imaging. Recent reviews have suggested that current machine learning models have the potential to provide a rapid, highly accurate and consistent assessment of TTE's, and the results of the analyst variation testing demonstrate that even in a controlled setting there is some inbuilt variation. Currently, though there is a lack of trust in the ability of machine learning technology and there is a need for further validation of their application, therefore it is unlikely that it will be seen in a clinical setting in the near future(179).

8.6.2 Site Surveying – Questionnaire and Telephone Interviews.

Although overall the responses were positive, reviewing the mean ranking and variance of answers from the online question revealed the following areas that have room for improvement within the UK TAVI trial (receiving a mean rank greater than 2, indicating an average response between 'agree' and 'slightly agree').

- Explanation of image formatting requirements for TTE scans.
- The process and convenience of sending images to the ECL.
- Timeliness of ECL feedback.
- How Relevant/Helpful ECL feedback is.
- Contact point for queries.

Both the responses to the questionnaire and the telephone interviews suggest that sites believe they understand the role of the ECL within the UK TAVI trial. But the variety of responses to question 1 of the telephone interviews (What do you understand the role of the UK TAVI 2D ECL to be?), and especially that of I4, suggest that there is some room for further education around the role of the ECL. If sites believe that the role of the ECL is to act as a second analyse/a review, then they may be likely to send TEE images that have measurement data stored on them. If ECL analysts see the site measured data this is likely to influence their measurements, and introduce potential bias, however unintentional.

It should be somewhat concerning that when divided by job role by the echocardiographers had the least positive response to the question 'The image formatting requirements have been clearly explained to me' and in the telephone interviews, the respondents unanimously said that it was themselves as echocardiographers that were saving the images onto the disks to be sent to the ECL. Although the responses regarding having reviewed and understood the imaging acquisition guidelines were more positive.

During in the UK TAVI trial, an online portal was introduced partway through the trial, to address concerns that had arisen regarding ensuring that timely feedback was sent to trial sites and that there was a tracking system to identify any disks that were sent by trial sites but had not been received by the ECL. This provided an ability for the ECL

to confirm that the disk had been received and provide feedback to the sites and trial office regarding image quality, and any problems with the TTE images, file format or physical disk.

The delay in reviewing TTE data sent in was an issue the ECL had been aware of and had taken successful steps to improve during the later stages of enrolment. This included updating the relevant SOP's so that disks underwent a preliminary quality check upon receipt at the ECL and transferring the feedback system onto an online platform. Additional work was also undertaken to reduce the timeframe from disks being received by the ECL and them being analysed. This resulted in more timely feedback overall, but also any disks that had formatting issues or were very clearly unable to be analysed could be highlighted within a few working days of being received. Being able to highlight image formatting issues in a timely manner increases the chances that the issue can be positively resolved.

The comments of one interviewee (I3) regarding feedback from the ECL identifies an area of miscommunication. The ECL must rate the scan quality, regardless of if they are aware of limiting factors so that overall performance metrics can be gathered. So, although ECL analysts have acknowledged that it is helpful to know of limiting factors, they are still required to classify the quality of the scan and if it is 'to protocol' or not. Additionally, the fact that one interviewee was not aware of the feedback system for TTE scans sent to the ECL demonstrated a potential shortfall in the system and area for improvement, because if the feedback is not reaching those performing the scans then it will not be acted upon and overall data quality is likely to be impacted.

Another area for education highlighted by the surveying was who to contact with queries. Sites should not contact the ECL directly as this has the potential to introduce a source of bias into the analysis. Although the telephone interviews varied in their responses and seemed unsure, the questionnaire results suggest more certainty from the research nurses and other members of the site research team regarding this issue.

Telephone interviews do have disadvantages compared to in-person interviews; a loss of rapport and being unable to respond to nonverbal communication may affect the quality of data collected(180). In this study, the practicalities of being able to speak to people over a wider geographical area, and cost confines, outweighed these

limitations. Additionally, telephone interviews allow for increased anonymity of participants, which is likely to reduce and self-consciousness and increase their honesty in responses(180). The small number of telephone interviews conducted means caution must be taken in extrapolating these findings, and it must be remembered that those who were willing to engage in this survey process are likely to be those most engaged with the trial and therefore may have views that are not reflective of the wider experience. Nether the less the responses identified have transferability, there are common themes, and areas for improvement. Therefore they contribute to the audit and review process(181).

8.6.3 Conclusions and Recommendations:

The overall strong figures for the variability of measurements within the 2D ECL illustrate a strength of the UK TAVI ECL; that the random error rates were low. This leads to more reliable data and the ability to come to statistically significant conclusions with smaller sample sizes and strengthens the case for TTE to be used for trial endpoints in cases where analysis is conducted by an ECL. The high levels of reproducibility seen indicate the positive impacts of an ECL where there is ongoing training and a collaborative environment where challenging scans are raised for discussion between team members. The lower levels of reproducibility seen for LVEF, especially in the first round of testing, demonstrate the importance of high-quality TTE images and consistent, thorough, training of ECL analysts. As a result of the work conducted in this chapter, the standard operating procedure within the ECL was updated to mitigate intra-analyst variability by ensuring scans from each study participant are ready by a single analyst.

Surveying of sites for the UK TAVI trial allowed us to gather useful information regarding the operations of the ECL from a different perspective and explore the potential root causes for sub-optimal quality TTE images. The data demonstrated an overall positive attitude to the ECL but varying levels of understanding of best practice regarding image acquisition and processing. This has highlighted the importance of clear guidelines, and open channels of communication. Suggestions for implementing this would include expanding the online feedback portal to include an area where the

relevant guidelines (image acquisition and how to save and send the data) are stored online for easy access. This could also provide a feature to send questions to the site office which could then be passed onto the ECL if required. Furthermore, future trials may benefit from formalised guidelines for the training of new site staff that join the team partway through the trial.

Although this study had a small cohort, a limitation regarding conducting statistical analysis. It provided applicable feedback regarding the ECL from several trial sites and has identified best practise for future collaborations; based on identified areas of strength and weakness of the current core-lab.

Chapter 9 - Discussion, Future Work and Conclusions.

This study has provided data on the changes seen in myocardial mechanics post-intervention for aortic stenosis (AS) in patients of moderate surgical risk. The randomisation of patients to either transcatheter aortic valve insertion (TAVI) or surgical aortic valve replacement (AVR) allowed direct and novel comparisons of the effects of the interventions on the recovery of myocardial mechanics. As TAVI is being performed on moderate and low-risk patients the long-term prospects become increasingly important. The detailed evaluation of myocardial mechanics post-intervention provides insight into the recovery of the heart, which is a key aspect to the long-term cardiac health of patients.

9.1 Key Findings

9.1.1 Global Longitudinal Strain and Left Ventricular Ejection Fraction

The results of chapter 3 demonstrate that left ventricle global longitudinal strain (LV GLS) improves by 12-months post-intervention following AVR and TAVI. The recovery seen in TAVI is non-inferior to that seen in AVR. Mean GLS began to recover by 6-weeks post-intervention in those who underwent TAVI, but not in the those who underwent AVR. Although this change was not statistically significant it is clinically relevant (discussed section 9.2.2).

Left Ventricular ejection fraction (LVEF) was not meaningfully impaired prior to intervention, therefore this is likely why no statistically significant change was seen at 12-months post-intervention in either treatment arm. Both treatment groups saw a decline in LVEF at 6-weeks post-intervention when compared to baseline values. There was a correlation between the improvement of LVEF and GLS at 12-months post-intervention.

9.1.2. Left Ventricular Short Axis Function.

Statistically, significant improvement was seen in both LV circumferential (LVCS) and radial (LVRS) strain 12-months post-intervention. Furthermore, there was an increase in the gradient of LVCS from the base to the apex of the LV from baseline to 12-months post-intervention (12M). Due to the limited sample size, comparative tests could not be run between the treatment arms, but descriptive statistics illustrated an improvement in mean values for both AVR and TAVI. There was a significant reduction in apical rotation at 12M compared to baseline values. Although there was a small increase in basal rotation post-intervention, it was not statistically significant.

At 6-weeks post-intervention (6W) a small, but not statistically significant decline was seen in both circumferential and radial strain. This may be influenced by the recovery of the LV longitudinal function, but as the baseline levels of LVCS and LVRS were not supra-normal it was concluded to be more likely related to the stress of intervention.

9.1.3 Right Ventricular Strain

Chapter 7 provided evidence that although right ventricular global longitudinal strain (RVGLS) declines at 6-weeks post-intervention after both AVR and TAVI, RVGLS 6-weeks post-TAVI is non-inferior to that 6-weeks post-AVR. At 12M RVGLS had recovered in both treatment groups. Although neither the non-inferiority the recovery after TAVI, nor a significant difference between the recovery in the two treatment groups could be statistically concluded.

9.1.4 Left Atrial Function.

Left atrial (LA) function provides information regarding the long-term haemodynamic environment of the heart and resulting adaptions, such as LA chamber enlargement and functional impairment. Therefore; recovery was only investigated at 12M. At baseline, the majority of subjects had an enlarged LA, as classified by the European echocardiography guidelines(146). A statistically significant reduction in LA maximum volume was seen in both treatment groups, and the non-inferiority of TAVI could be concluded. The non-inferiority of TAVI could also be concluded for the recovery of

several of the phasic volume measurements; LA pre-A volume, total emptying fraction and active emptying fraction. The non-inferiority of TVAI could not be concluded for improvement in LA minimum volume or passive emptying fraction; but for both measures, a greater change was seen in TAVI; and the statistical significance was restricted due to small overall changes and limited sample size. The non-inferiority of the recovery of the LA peak strain after TAVI could not be concluded. Peak LA strain rose slightly more after AVR compared to TAVI, but these changes seen were small. There was a much greater recovery in LA longitudinal strain in the subjects with a discernible atrial contraction phase, allowing phasic measurements to be taken.

9.1.5 Strain Volume Loops.

The strain volume loops (SVL) for both AVR and TAVI saw a decrease in LV end-diastolic volume at 12M, compared to baseline, but only the TAVI SVL saw a reduction in LV ESV. Overall systolic-diastolic uncoupling recovered in both SVL's but the changes in early vs late diastolic uncoupling were different between the two treatment groups; suggesting different myocardial changes.

9.2 General Discussion.

9.2.1 Global Myocardial Mechanics.

This work demonstrates a global improvement in function throughout the heart. Although the change in GLS was not significantly correlated with change in longitudinal strain the LA or RV, this association trended towards significance in both chambers (GLS and LA PLS P=0.12, GLS and RV LS P=0.09). Therefore, it is reasonable to suggest that a statistically significant correlation may have been able to be concluded had the sample size had been larger. In addition, the change in LA maximum volume correlated with change in LV end-diastolic volume. This supports the concept that the individual cardiac chambers do not work in isolation. During ventricular filling the mitral and tricuspid valves are open, exposing the atria to any changes in volume or pressure loading that the corresponding ventricles experience. Also, although each chamber has its own specific myocardial structure to enable appropriate contraction, there is a

continuum of the muscle fibres. The Torrent-Guasp model is shown in Figure 9.1, which has been supported by more recent magnetic resonance imaging(182). In this model, the fibres are continuous throughout the myocardium and transition from longitudinal to oblique and then circumferential (183). The descending and ascending muscle loops both have transverse fibres, but in the intact heart the fibres are aligned in opposite directions.

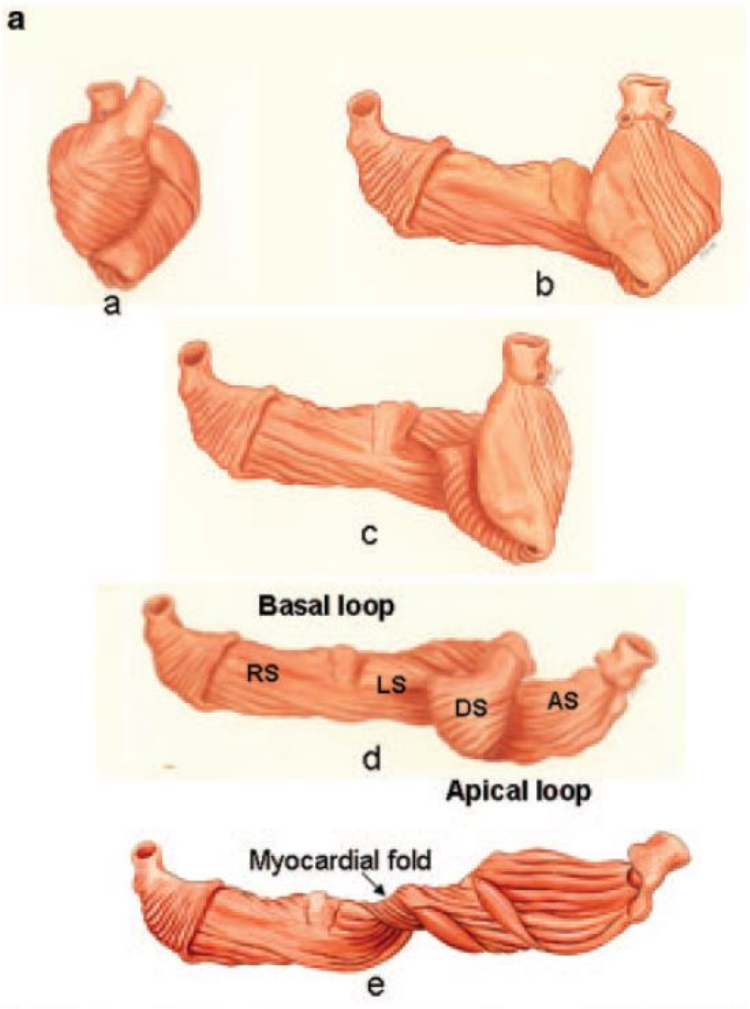


Figure 9.1: Myocardial Fibre Anatomy, the Torrent-Guasp dissection. Taken from Buckberg et al, 2008. *A: The Intact Heart. B: Detachment of the right ventricle free wall. C: The detached rotated apical loop. D: Unwrapped Left helix revealing the descending segment. E: The complete transverse myocardial band, with the central myocardial muscle fold to separate the basal and apical loops. RS: Right basal segment. LS: Left basal segment. DS: Descending segment. AS: Ascending segment. (183)*

9.2.2 6-week recovery after TAVI and AVR

In both the LV and RV there was evidence of quicker recovery after TAVI compared to AVR. This aligns with the findings of the PARTNER trial. PARTNER compared the outcomes of high surgical risk subjects randomised to AVR or TAVI. PARTNER focused on clinical outcomes but recorded some key transthoracic echocardiographic measures. The study reported that although the 30-day recovery in valve characteristics were comparable between the two interventions (aortic valve area and gradient, LVOT diameter), LVEF improved by 18.5% 30-days post-TAVI, but by only 10.4% 30-days post AVR(79). Regardless of the fact that the PARTNER was conducted in patients with higher surgical risk than the cohort in this study (based on clinical opinion, and STS/EuroSCORE values), it provides further evidence that the myocardial recovery may be faster after TAVI. This could be due to the physical stress and damage that occurs to the myocardium during AVR owing to its invasive nature. Another factor to consider is the negative effect ventilation and positive pressure ventilation has on ventricular function, even in patients without cardiac disease (184). However, but there is no evidence that this reduction in function would maintain once the patient was extubated without underlying pulmonary pathology.

9.2.3 12-Month recovery after TAVI and AVR.

A statistically significant improvement ($P<0.05$) in function was seen post-intervention for GLS, LVCS and LVRS, and LA maximum and pre-a volume's. The fact that a statistically significant improvement was seen GLS, but not in LVEF in the same cohort provides further evidence that GLS is a more sensitive marker of LV longitudinal function than the more commonly used LVEF(48, 185, 186). A criticism of GLS is that because it is not as widely used as LVEF it is more prone to operator error, and therefore a lack of reproducibility, but a recent study by Karlsen et al (2019), compared the reproducibility of LVEF and GLS measurements between an expert echocardiographer and a trainee in forty-seven patients with recent Acute Coronary Syndrome. They found that GLS was more reproducible than LVEF between the two analysts (ICC 0.89 vs 0.63)(187). This study reported an ICC value of 0.99 for inter-analyst reproducibility for both GLS and LVEF, but in agreement with Karlsen et al,

found that intra-analyst reproductivity was slightly better for GLS than LVEF (ICC 0.91 vs 0.87). However, further studies will be needed, in larger cohorts with a range of image quality, before reliable conclusions can be reached.

The non-inferiority of TAVI could be concluded for the 12-month recovery of GLS, LVEF, LA max volume, LA pre-a volume, and LA total and active emptying fractions. Non-inferiority could not be statistically concluded for LA peak or pre-a strain, or RVGLS. Although tests for a significant difference in the recovery of the two interventions suggest that there is unlikely a true difference in recovery.

Improvement in LA volume and strain was correlated with baseline values; the greater the impairment at baseline the greater the improvement experienced post-intervention. This demonstrates that the pathology that occurs is reversible to some extent, although the dynamic function of the LA (LAEF and strain) is still strikingly different from the normal values quoted in literature. A similar correlation; between baseline value and recovery was seen for LVEF, GLS (absolute value), and radial strain, but not for circumferential strain.

There was no evidence that LV and LA recovery had any significant correlation with body surface area. In contrast to BMI, which previous work has shown has a link to cardiac surgery outcomes. The obesity paradox is a body of research that shows a link between obesity (high BMI) and positive outcomes post some cardiac surgeries, including short- and long-term survival post-TAVI (188).

9.2.4 Myocardial Mechanics and Clinical Outcomes

GLS has not only been demonstrated to have prognostic value for the need for intervention in AS; but also for long term outcomes(48). The Copenhagen city heart study investigated the prognostic utility of GLS in 1,296 subjects without major cardiac pathology. This study found that lower (absolute) GLS was associated with a higher risk of adverse outcome (a composite of incident heart failure, acute myocardial infarction or cardiovascular death) over a median follow-up of 11 years (HR 1.12 [1.08–1.17], $p<0.001$ per 1% decline). Interestingly this independent association was stronger in men than women; remaining after multivariate adjustment only for men(189). Additionally; a study of symptomatic AS patients, with preserved LVEF (>50%) who

were treated conservatively (without AVR or TAVI), found that GLS was independently associated with a higher risk of clinical events (defined as readmission for heart failure, or all-cause death at 2 years); HR= 1.30 (95% CI: 1.06-1.58, P=0.01)(57).

Indexed LA volume is also well established as a predictor of cardiovascular risk in the general population, including AMI, heart failure and cardiovascular death, and is closely linked to diastolic function(164). The Dallas heart study found that LA EF was independently associated with the risk of mortality, in a study of 1802 participants over a median follow up of 8.1years(190). In a sub-study of elderly participants followed (mean 1.9 years) LA EF remained associated with increased risk even after adjusting for LV function, clinical risk factors and LA volume. The highest risk subjects had LA EF ≤49% and indexed LA max volume ≥38ml/m2(164, 191). Left atrial systolic force (LASF) during the contractile phase of LA function was investigated for prognostic value in a high-risk population, without valvular disease or previous cardiovascular events. LASF was calculated based on the orifice area of the mitral valve, and the volume/acceleration of blood passing through. LASF was associated with a higher rate of cardiovascular events (fatal and nonfatal) during a 60 month follow up (HR = 1.033, 95% CI = 1.005 to 1.061; P = .021)(192). Kaminski *et al* (2011) also concluded that decreased LA contractile function demonstrated strong associations with patient mortality, non-fatal cardiac events(193).

Kocaaslan *et al* (2016) collected quality of life data in a group of patients, 70 years and older, undergoing AVR or TAVI. They found that at 3 months post-intervention scores for physical task difficulty, emotional task difficulty, and mental health had had a greater positive change in the TAVI group. Although subjects were from a single centre and were not randomised regarding intervention, and the decision whether AVR or TAVI was more suitable was made by clinicians taking into consideration the patient's medical history and EuroSCORE (European System for Cardiac Operative Risk Evaluation). However, the patients undergoing TAVI were older and had a higher mean EuroSCORE (P<0.001), and therefore would have been expected to be frailer and struggle to recover from the intervention(194). This suggests that the differences that were seen in both RV and LV longitudinal function 6-weeks post-intervention may translate into differences in quality of life for the patients.

Taking into consideration the above studies; the non-inferiority in the recovery of GLS, LA max volume, and LA active emptying fraction 12-months post-TAVI compared to AVR provides evidence for long-term myocardial recovery and positive clinical outcomes post-TAVI.

9.3 Limitations and Future Work

A significant limitation of this work was the small sample size for many of the analyses. Although some reduction in sample size was expected for the analyses of LV short axis, LA and RV the scale of this was unforeseen and was a result of overall poorer image quality than predicted, and missing data. Guidance for how to improve the completeness of data and quality of images submitted for future trials has been investigated and discussed in chapter 8. This work concluded that more timely feedback regarding image quality and formatting was required, to allow issues to be rectified. This was addressed part-way through the UK TAVI trial. Also, the need to train staff at sites that joined the team part-way through the trial was identified. Finally, better systems for follow up when TTE data was not received as expected from sites. Taking these steps in future trials should lead to an increase in image quality.

Additionally – given the inclusion criteria of this study; that both the baseline pre-intervention TTE and the 12-months post-intervention TTE were available for analysis, this excluded any subjects who died prior to follow up. Although, given the purpose of this study; to investigate the recovery of myocardial mechanics to provide insight into long term recovery, this was deemed acceptable to insure complete and paired data.

Given the limitations that the sample size caused it would be recommended that, where possible, future studies are conducted using a cohort where image quality can be more closely controlled. Larger sample sizes will increase the power of the statistics and allow further insight into the recovery of LA and RV mechanics, as well as the recovery at 6-weeks post-intervention. Continuing to collect data for this study with longer follow up times post-intervention would provide data regarding the continued recovery of the LA and if dynamic recovery followed the recovery in LA volumes demonstrated in this study.

Additionally, collaborating with UK TAVI to link the myocardial mechanics' analyses conducted in this work to aortic valve characteristics such as valve gradients, and the presence or absence of patient-prothesis mismatch would further link to improvements seen in strain to clinical outcomes. Additionally, collaboration with the UK TAVI trial and access to the data regarding clinical outcomes of the participants would enable future studies expanding on the relationship between cardiac mechanics and clinical outcomes in intermediate-risk patients undergoing intervention for severe aortic stenosis.

9.4 Conclusions

In conclusion; the statistical non-inferiority of TAVI was seen for the majority of measures in which it was tested (GLS, LVEF, LA max volume, LA pre-a volume, and LA total and active emptying fractions). Where statistical non-inferiority could not be concluded there was reasonable evidence of clinical equivalence. Given the links between myocardial mechanics and clinical outcomes (discussed in 10.2.4), and the known advantages of a less invasive procedure, this work provides evidence in support of the wide use of TAVI to treat severe AS. Further work will need to be carried out to support these conclusions and further evaluate the non-inferiority of TAVI especially regarding the recovery of LA and RV longitudinal function.

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Appendix 1

UK Transcatheter Aortic Valve Implantation.

(UK TAVI) Trial.

Image acquisition guidelines for echocardiography.

Project:	UK TAVI
Document file name:	Image acquisition quality assurance .
Document revision:	V2
Version date:	16/12/2013

Introduction.

University Hospital South Manchester and Kings College Hospital have developed the following guidelines for the purpose of quality assurance of image acquisition across study centres participating in the UK TAVI Trial.

- **After screening baseline images all parameters should remain constant for all subsequent imaging within the study. Where possible the same sonographer, using the same equipment and settings, should acquire all images for a given study subject at each visit.**

- **Imaging data, including the raw original data, wherever possible should remain digitally archived at the recruitment site.**

- **With regards to quality of the submission, the core lab will provide feedback as required.**

For enquiries regarding these guidelines please contact:

[redacted]

[redacted]

[redacted]

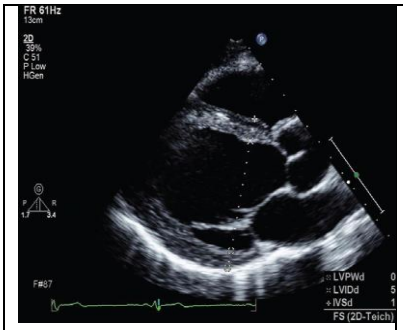
Echo Core Lab Acquisition Guidelines

Study Centre:

Submission/Subject ID:

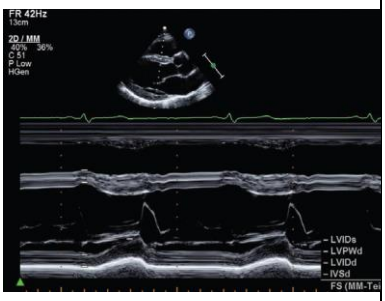
General Instructions:	**Please ensure an adequate ECG tracing is present on each view.** When recording digital images set machine to capture minimum of 3 full cardiac cycles. In cases of frequent premature atrial / ventricular ectopic please attempt to record 3 consecutive normal beats. If not possible the whole study should capture 5 full cardiac cycles. In cases of irregular rhythm (e.g. AF) please capture 5 consecutive beats for all clips and 10 consecutive beats for the apical 4, apical 2 and apical 3 chamber images. Record the clinical measurements specified below prior to each echocardiographic examination.	
Timetable:	**Stage of visit**	

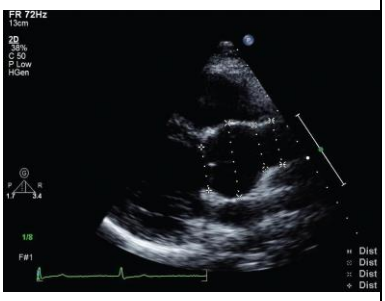
	Screening 6 Weeks 12/12 24/12 >24/12	† † † † †
Measurements:	Weight _____ kilograms Height _____ centimetres Heart rate _____ beats per minute Blood pressure Systolic _____ mmHg. Diastolic _____ mmHg.	†
Echocardiographic Image Planes:		
Parasternal Long-Axis View.	**2D imaging:** 1. 2D PLAX (optimised for depth). 2. PLAX m-mode for LV dimension and wall thicknesses (ensure on-axis). 3. 2D zoom of Ao root. 4. 2D zoom of LVOT.	

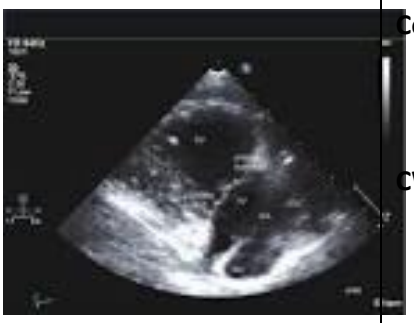
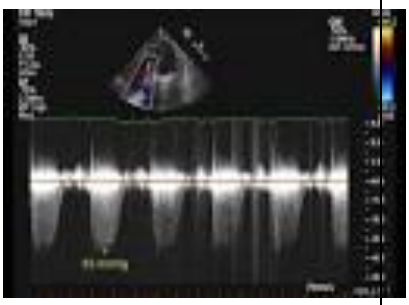
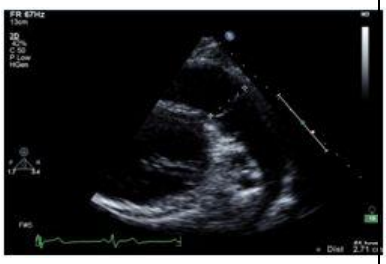


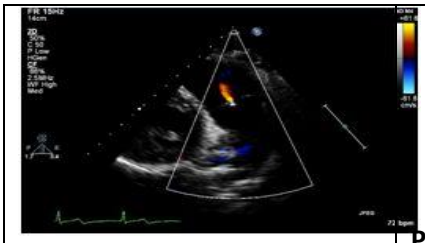
Colour Flow Doppler:

1. CFD for AR standard.
2. CFD for AR zoomed.
3. CFD for AR zoomed with reduced colour flow baseline.
4. CFD for MR standard.
5. CFD for MR zoomed.
6. CFD for MR zoomed with reduced colour flow baseline.



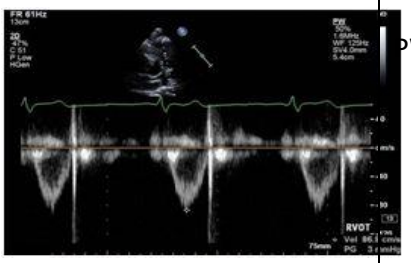


Parasternal Long-Axis View - RV Inflow.  	**2D imaging:** 1. 2D RV inflow optimised for depth. **Colour Flow Doppler:** 1. CFD for TV. **CW Doppler:** 1. CW for TR jet.	
Parasternal Long-Axis View – RV outflow tract. 	**2D imaging:** 1. 2D RV outflow tract optimised for depth. **Colour Flow Doppler:**	



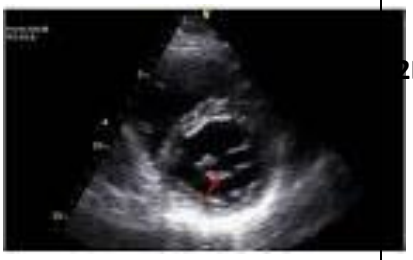
1. CFD for RV outflow

PW Doppler:



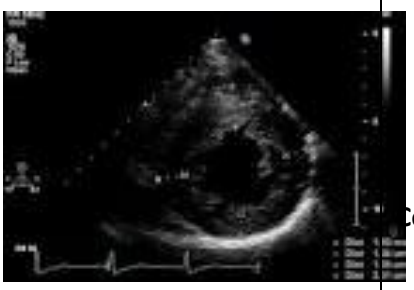
PW for RV outflow.

Parasternal Short-Axis Views.



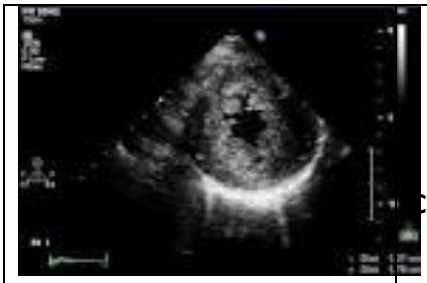
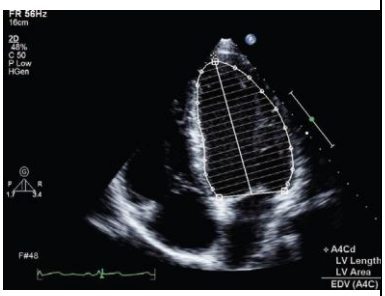
2D imaging:

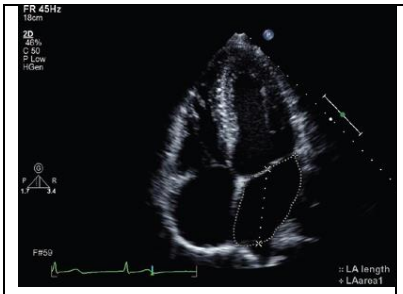
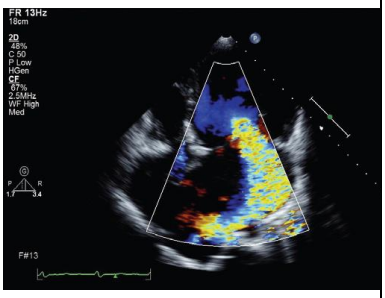
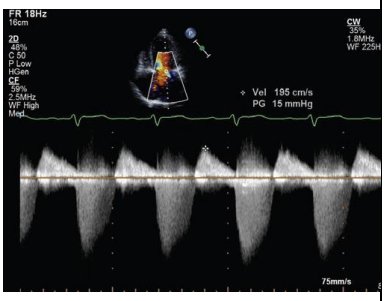
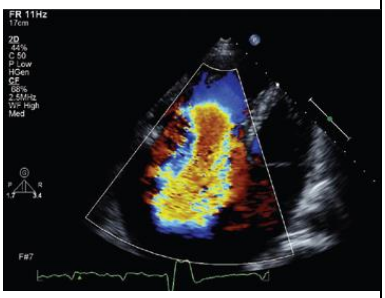
1. PSAX at LV base (MV level).
2. PSAX at mid LV cavity (Papillary level).
3. PSAX at apical LV level.
4. PSAX Ao valve level (morphology).
5. PSAX Ao valve level zoomed.

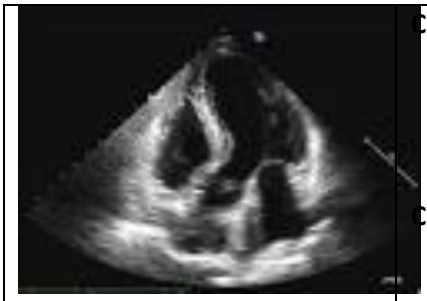
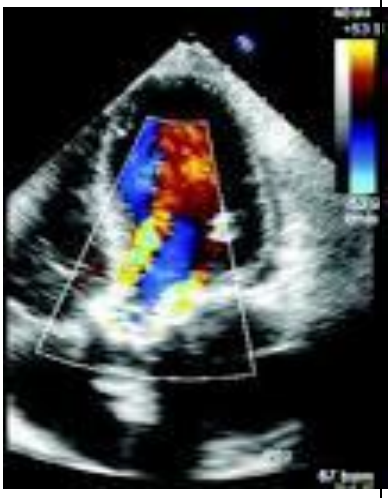
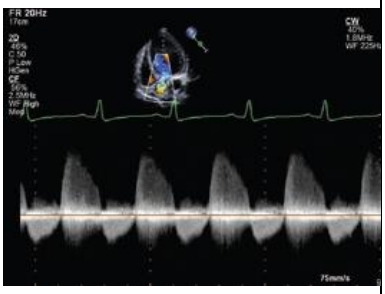


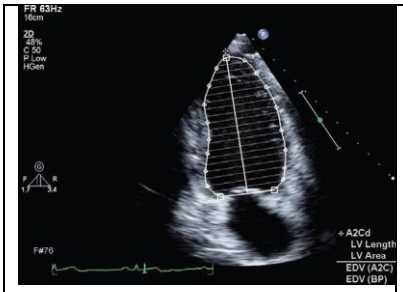
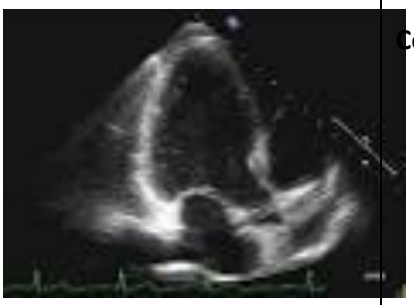
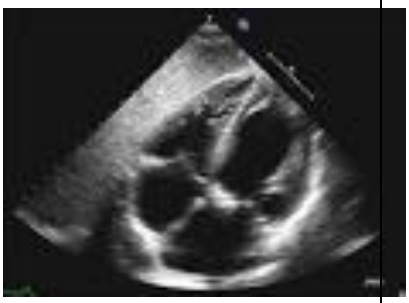
Colour Flow Doppler:

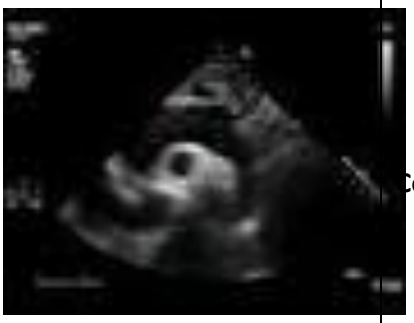
1. CFD Ao valve level.
2. CFD of RV inflow.
3. CFD RV outflow.

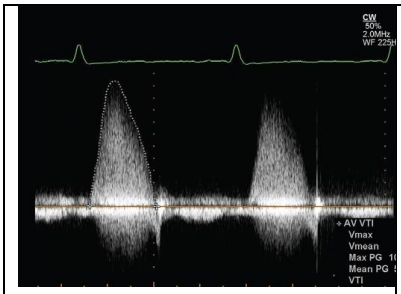
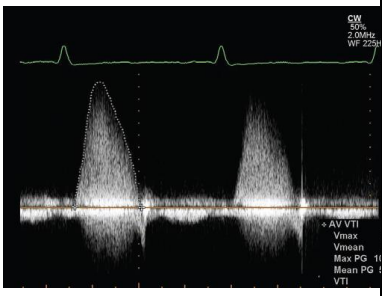
	**CW Doppler:** 1. CW Doppler for TR jet. 2. CW Doppler for PR jet / PA flow.	
Apical Views. **Apical 4 chamber.** 	**2D imaging:** 1. A4C optimised for depth (all 4 chambers). 2. A4C optimised for LV EF assessment. 3. A4C optimised for LA volume assessment. 4. A4C optimised for RV assessment (TAPSE). **Colour Flow Doppler:** 1. CFD of MV (ensure colour propagation within LA demonstrated). 2. CFD zoomed of MR. 3. CFD zoomed of MR with reduced colour flow baseline. 4. CFD of TV (ensure colour propagation within RA demonstrated). **CW Doppler:** 1. CW Doppler for MR jet (optimise scale and baseline). 2. CW Doppler for TR jet (optimise scale and baseline).	

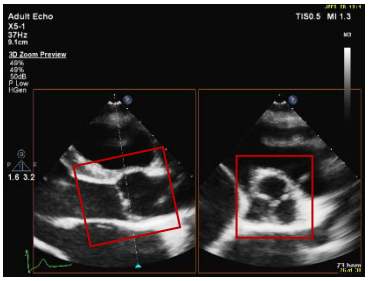
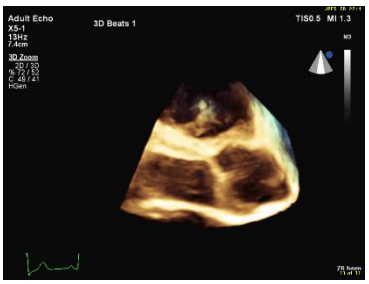
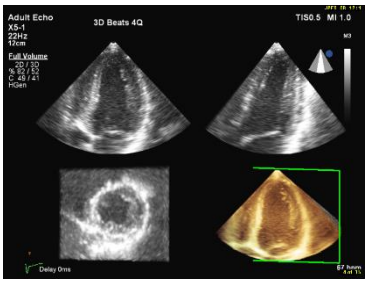
    	**PW Doppler:** 1. PW Doppler of MV forward flow (tips of MV leaflets). **Tissue Doppler Imaging:** 1. Septal MV annulus. 2. Lateral MV annulus. 3. RV free wall at TV annulus.	
Apical 5 chamber.	**2D imaging:** 1. A5C optimised for depth (all 5 chambers).	

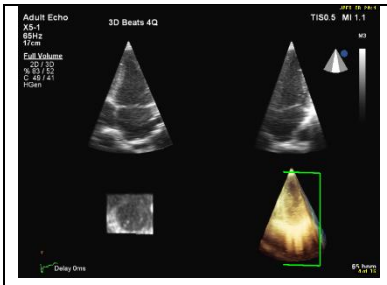
  	**Colour Flow Doppler:** 1. CFD of AR (ensure full propagation into LV). 2. CFD of AR zoomed. **CW Doppler:** 1. CW Doppler of Ao forward flow (optimised scale and baseline). 2. CW Doppler of AR jet (optimised scale and baseline). **PW Doppler:** 1. PW Doppler of LVOT (1cm proximal to Ao annulus – optimised for scale and baseline).	
Apical 2 chamber.	**2D imaging:** 1. A2C optimised for depth. 2. A2C optimised for LV EF assessment. 3. A2C optimised for LA volume assessment.	

		
Apical 3 chamber (long-axis). 	**2D imaging:** 1. A3C optimised for depth. 2. A3C optimised for LV. **Colour Flow Doppler:** 1. CFD of AR (ensure full propagation into LV). 2. CFD of AR zoomed.	
Subcostal View. 	**2D imaging:** 1. Subcostal view (exclude pericardial effusion). 2. IVC diameter. 3. IVC diameter m-mode for respiratory variation.	

		
Suprasternal View. 	**2D imaging:** 1. Ascending Ao, Ao arch and descending Ao. **Colour Flow Doppler:** 1. CFD of ascending Ao. 2. CFD of Ao arch. 3. CFD of descending Ao. **PW Doppler (standard imaging probe).** 1. PW Doppler of descending Ao flow. CW Doppler (Standard imaging probe). 1. CW Doppler of descending Ao flow.	ŦŦŦ

	**CW Doppler (using stand-alone probe).** 1. Suprasternal notch CW Doppler of Asc Ao.	
Right parasternal view. 	**CW Doppler (using stand-alone probe).** 1. Ao forward flow (optimised for scale and baseline).	

3D Zoom of the LVOT / Aortic valve / Aortic root   	**Parasternal Long Axis View:** 1. Set the zoom guides to 2cms below the aortic valve extending to 1cm above the STJ and medial to lateral annulus aspects (in transverse plane) 2. Select 3D zoom mode acquisition. **Note:** Slightly overgain 3D image to avoid drop-off artefact.	
LV 3D Full volume  	**Apical 4 chamber view:** 1. Apical 3D full volume dataset set at a mitral annulus depth for LV acquisition and sector width adjusted to include the entire endocardial and epicardial surface. **Note:** Please use multi-beat acquisition for higher frame rate and suspended respiration to avoid stitching artefact.	
LV 3D Full volume	**Apical 4 chamber view:** 1. Apical 3D full volume dataset set at a depth to incorporate the LA and sector width adjusted to include the LA endocardial surface.	

 Adult Echo X5-1 65Hz 17cm Full Volume 3D Beats 4Q TIS0.5 MI 1.1 M3 Delay 0ms		

Echo Core Lab quality assurance feedback:

Highlight the ECL feedback option below: Enter comments where required.

	2D data	3D data
Excellent		
Good		
Adequate		
Sub Optimal		

	2D data	3D data
Pass		
Reject		
Comments:		

Suggestions:		

Echo Core Lab Demographics Sheet

Please fill in all the relevant sections below and attach with each CD/DVD submission:

SUBMISSION REQUIREMENTS:

Subject Study Number:- ……..

Site Number:……..

Date of Study: ……

Please circle which stage of visit

Test Case Baseline 6 Weeks 12/12 24/12 >24/12

If >24/12 please identify number of months ……

Subject Demographics

Weight _____ kilograms Height _____ centimetres

Heart rate _____ beats per minute

Blood pressure

Systolic _____ mmHg.

Diastolic _____ mmHg.

Appendix 2

Core Measurements for the 2D Echocardiographic Core Lab

Echocardiographic View	Measurement	Units
PLAX	Vena contracta AR	cm
PLAX	Vena contracta MR	cm
PLAX	TR max velocity	cm/s
PLAX	Grade of AR (1,2,3)	N/a
PLAX	LVOT diameter	cm
PSAX	TR max velocity	cm/s
PSAX	AV – tricuspid y/n	N/a
Apical 4-Chamber	LVED volume	ml
Apical 4-Chamber	LVES volume	ml
Apical 4-Chamber	LVEF (4 chamber)	Percentage
Apical 4-Chamber	MR VTI	N/a
Apical 4-Chamber	MR PISA (aliasing velocity)	
Apical 4-Chamber	LVOT VTI mean gradient	
Apical 4-Chamber	LVOT VTI max gradient	
Apical 4-Chamber	AV VTI mean gradient	
Apical 4-Chamber	AV VTI max gradient	
N/A, Calculated	AVA, valve ratio and Zva	cm^2, n/a, mmHg/ml
Apical 4-Chamber	TR max velocity	
Apical 4-Chamber	RVSP from TR	
Apical 4-Chamber	TAPSE	
Apical 4-Chamber	TV TDi S wave	
Apical 2-Chamber	LVED volume	ml
Apical 2-Chamber	LVES volume	ml
Apical 2-Chamber	LVEF (2 chamber)	Percentage
N/A, Calculated	Biplane LVEF.	Percentage
Right Parasternal	CW VTI mean gradient.	
Right Parasternal	CW VTI max gradient.	

AR – Aortic Regurgitation

MR – Mitral Regurgitation

LVED – Left Ventricular End diastolic

LVES – Left ventricular End Systolic

LVEF – Left Ventricular Ejection Fraction

LVOT – Left Ventricular Outflow Tract

AV – Aortic Valve

AVA – Aortic Valve Area

VTI – Volume Time Integral

CW – Continuous Wave

Appendix 3

Accompanying emails sent with the link to the UK TAVI site survey.

First Email:

Dear Colleague,

I am writing to invite you to contribute to some qualitative research that we are supporting relating to the use of an Echo Core Lab in clinical trials such as UK TAVI.

The team in the 2D Echo Core Lab in Manchester are working in collaboration with Katherine Kuyt, a PhD student from Manchester Metropolitan University, to investigate the understanding, attitudes and experience of site staff in relation to the Core Lab and its function.

We would be extremely grateful if you could please complete a brief online questionnaire relating to your personal experience of working with the UK TAVI Echo Core Lab. The questionnaire will take around 10 minutes to complete and can be accessed by clicking on the link: https://mmu.onlinesurveys.ac.uk/exploring-the-role-and-implementation-of-an-echocardiograp

The data from the survey will serve to audit the functioning of the Core Lab and identify areas for improvement. It is intended that aggregated and anonymised data from the survey will be reported in Katherine's PhD thesis and it may also be also presented and published elsewhere.

Your completion of the questionnaire is entirely voluntary but your participation would be very much appreciated, as we are keen to obtain a high response rate to ensure that the data truly represent the views of our study group.

The online survey will be active for 3 weeks, closing at midnight on Friday 19th October but we would be grateful if you could please complete it as soon as conveniently possible. All

responses will be treated in strict confidence. Data will only be shared with the UK TAVI Trial Office team in aggregated and anonymised form, when the work is complete.

If you have any queries, please feel free to contact Katherine directly by email: [redacted].

With many thanks for your help and best wishes,

[redacted]

<u>Follow-up email.</u>

Dear Colleague,

This is just a brief reminder that the online questionnaire regarding your experience of working with the Echo Core Lab will close at midnight on Friday 19th October.

If you have not already responded, we would be extremely grateful if you could please do so as soon as possible. We are keen to know your views and to ensure that the results truly represent the experience of all of the investigators who are involved in the echo process. The questionnaire should only take a few minutes to complete.

If you have already responded, please accept our apologies for troubling you again and disregard this e-mail.

With many thanks for your help and best wishes,

[redacted]

Appendix 4

Questions from the online questionnaire sent to UK TAVI sites.

The below questions relate to the echocardiographic core lab (ECL) for the UK TAVI trial. All responses will be kept confidential and will have no bearing on your future interactions with trial staff. The completion of this questionnaire is voluntary, and responses will be used to maintain and improve core lab standards for the UK TAVI trial and future trials.

Question	**Response Options**
Prior to being contacted for this questionnaire were you aware that there was a separate echo analysis core lab for the trial?	Yes / No
I understand the purpose of the ECL	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
I believe the addition of ECL is useful for the trial	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
Staff working in the ECL are experts in their roles.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
I have reviewed and understood the imaging acquisition guidelines provided for the UKTAVI trial.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
The image formatting requirements have been clearly explained to me.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
The items that need to be sent to the ECL at each study timepoint have been clearly explained to me.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
Sending the images to the ECL is convenient.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
Feedback from the ECL is timely	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA

Feedback from the ECL is relevant and helpful	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
If I have queries I know who to contact and how to do so.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
What is your job role?	Sonographer/Research Nurse/Other
Length of time involved with UK TAVI trial	Less than 6m/6-12m/12m-24m/ 24m +
Did you attend the echo training days on either 22nd Nov 2013 or 27th Feb 2017?	Neither / 22 Nov 2013 / 27 Feb 2017 / Both
Funnel - If Yes to at least one - Attending the echo training days affected my practices' regarding acquiring and sending UK TAVI trial images.	Strongly Agree / Agree / Slightly Agree / Slightly Disagree / Disagree / Strongly Disagree / NA
Any other comments	*Free text field*

If you would be willing to take part in a follow up telephone interview to expand on your experiences, please email ****.

Appendix 5

Interview 1:

K: This is just a follow up from the questionnaire that went out a few weeks ago, obviously that was quite structured yes/no questions. This is a chance to expand on those questions and for you to expand on the answers. It will follow a semi-structured format, there are starter questions but please feel free to expand and justify what you are saying and why you are saying that.

K: What do you understand the role of the UK TAVI ECL to be?

To give an independent assessment of the echo's so that they are not bias according to the centre that is doing them, so they are all analysed in the same way.

K: How familiar are you with the echo acquisition guidelines for the UK TAVI trial?

Umm, yeah, uhh, it's so rare that we do one that I have to get the form out every time. Which then makes it quite hard to do the echo and be trying to read a piece of paper at the same time. So, I think because it is so rare I find it quite hard.

K: But you do tend to get the guidelines out to refer to them?

Yes, Yes.

K: Ok, and umm, is there anything you think would make them better?...

What is your opinion on the guidelines? …Their structure, format, and ease to follow?

Only doing more

K: So you are more familiar?

Yes

K: There is nothing regarding the layout, or..

Well maybe making it on just one page rather than having to turn over. Like a quick list.

Interruption (Knocking at door)

*So, like, once it has all been explained very thoroughly it would be nice if there was just a one page *mutters**

K: A one-page overview?

Yes.

K: Who at you site [Once you have taken the scans] saves the scan images and prepares them to be sent to the ECL?

Umm we do, the people who have done the scan.

K: How do you find the process? Are there changes you would suggest that?

Again, I have to get the thing out and look it up. And at the beginning I think I was doing it wrong. So, I was doing it wrong, and I kind of got into doing it wrong. And by the time the TAVI trial assessors got to my disks I think we had lost a couple of the studies because I had done them wrong at the beginning. So, umm, yeah, that wasn't easy.

K: Ok. Are there any particular changes you would suggest for that process?

I think just having the disks looked at quicker to check they were ok. I appreciate that it is hard to do the whole analysis, but if I had known quicker I would have been able to solve the problem quicker.

K: [Umm,] What are your opinions on the current web-based method of feedback from the 2D ECL?

Umm….

K: Are you aware that there is web-based feedback?

Yeah, yep, I am, and I get an email, and must admit I am not very good at looking at the actual feedback.

K: What has been you Overall was has your experience been of that feedback? from the 2D ECL? (Timely and Helpful?) Has it been timely? Helpful?

Again, it's the same thing. Its that I was doing the saving wrong. So it wasn't very timely, but it was really helpful.

K: Have you had the need to contact trial staff with a problem or query relating to the Echo's for UK TAVI?

Umm, No.

If you needed to how would you go about that? Who would you contact?

*I would chat to Andy *laughs*. I would go through him.*

And just generally, do you have any other feedback regarding the echo Core Lab; the process, your experiences with it, that you would like to share?

I don't think so.

Ok, well thank you very much.

Interview 2:

So I don't know if you are aware of the questionnaire that went out a few weeks ago from the UK TAVI office.

Right

That was mostly closed ended questions. This is just an expansion on that. These questions are semi-structured. It should give you a chance to expand on your views.

Right, I don't think I personally filled that one out. Do I need to have filled that out first?

No, its ok, its fine, its just that these questions pick up on similar things.

Ok. I must say its been 6-12 months since we actually did one, and the numbers are really small for this centre. So I am not sure how much help we will be. That's why that [the questionnaire] wasn't filled out.

That's fine, I will go through the questions, and umm, if you have any opinions to share about them that is great, if not don't worry.

OK.

Firstly - What do you understand the role of the UK TAVI ECL to be?

*Right, I think it's *inaudible* about like a plan study where they go for surgery or for TAVI. And its not just the over 80's, I think there were 70 odd years onwards. That's my understanding.*

It is, yep. Ok specifically, do you know where the core lab and imaging fits into that?

Sorry, what do you mean?

Umm, within the trial, why, why do you think that UK TAVI has a Core Lab? Because you sent your disks off to the core lab to be reviewed, rather than reviewing them on-site?

Umm, yes. We were just looking at the patients who had had TAVI itself, opposed to the surgery. So, I haven't been scanning the surgical patients for this trial.

Ok, do you have been scanning just TAVI patients.

Yes

Ok. How familiar would you say you are with the…are you aware of the Echo acquisition guidelines? Stating what images need to be taken, and what zooms, etc?

As far as the trial goes?

Yes

Yes, we just follow the standard set and layout for each of the images, for the study. Yea we just follow that.

Ok, do you find that fairly easy to follow, is there any feedback you have?

Yeah, that is fine, that's never been an issue. It's pretty straight-forward.

Umm. At your site, once you have taken the images on the echo machine, umm, who at your site saves the images and prepares them to be sent to the core lab? Do you do it yourselves or do the research nurses do it?

We do it ourselves.

Ok, and how do you find that? I there are changes you would make to that process?

Sorry, can you say that again.

How do you find that, the process of saving it to a DVD and sending it?

Not a problem, it's absolutely fine.

Ok. Are you aware of the web based feedback?

Yeah

Do you find that timely and helpful? Do you think that it is a good way to receive feedback on the images?

Yes, yes its been a good way. As I say, we are limited on how much feedback we have received as we have had a small number of patients.

But on those patients, the scans you have sent in, you have got feedback on them?

Yes

Ok. Have you needed to contact trial staff at all with any problems or queries relating to the Echo's for UK TAVI?

Umm contact, no. Just the feedback, just the intial written feedback on the database.

Ok, if you were having a problem with the echos, or had a question regarding them who you would you reach out to? What would be your first port of call?

Uhh depending what the issue was; if it was with the patient then the research nurses here at the centre. Otherwise we would be contacting, I am assuming, Manchester and the core lab itself. I have never had to so…

Yep that's ok. And just finally; do you have any other feedback regarding the core lab or taking the images for the UK TAVI trial?

Umm, not really, they have been very straight forward I have found. I have just been a little bit disappointed that we have been short on numbers to be much help to you.

Every little helps!

Yeah.

Ok, well that's all from me. Thank you very much for taking the time to talk to me.

Interview 3:

The purpose of this phone call, and interview is, I don't know if you are aware of the questionnaire that was distributed a few weeks ago…

Yes, I completed it.

Ok, great, well thank you for that. This interview is just expanding on that. The questions are of a similar theme. It's a chance to expand on your answers and tell us anything else you would like to. Ok?

Ok.

So, I will get started. Firstly, what do you understand the role of the UK TAVI Core Lab to be?

Umm, I understand the role of it to be, basically, they are the people that analyse the echo's that we produce for the UK TAVI Trial.

Yep. And why do you think there is an ECL, a Core Lab? Why does that add value to the trial?

Well, I am presuming it's for continuity of, umm, measurements. So that the same person is measuring the same thing continuously. So you don't have that inter-observer variability, umm, I presume that is the main aim.

Yep, yep that is fine. Umm. How familiar would you say you are with the echo acquisition guidelines?

Umm well, I am being doing the UK TAVI trial, have been the main sonographer, for the whole UK TAVI trial at Brighton, so its been about 5 years. I went last February to a UK TAVI study day, and I did learn quite a few things there that I hadn't been doing, umm, even though obviously I had the whole protocol. It was just little things like when there is 3D you need to collect three volumes, and I don't think that was made clear on the original, umm, protocol. If it was forgive me, but I came away with that information.

Yep, that's fine.

I think it's pretty clear, I do know that when I get the feedback it does say not to protocol. But I think you are going to ask me a question about that later, so I will save that till then.

Laughs That's Fine. Umm. You have mostly answered this now, but I was going to ask what is your opinion on the guidelines? There structure, format, is there anything you think would improve them, make them easier to follow?

Umm, no, I think pretty much anyone who is able to echo to a good standard, a BSE standard. I think they are fine. The way they work everything is very clear, very concise. Umm. Yeah I think it is fine.

Ok, umm. Who at your site, so once you have taken the images, who at your saves the scan images onto the disk and prepares it to be sent to the core lab?

Me.

You. And how to do you find that? That process of saving it onto the DVD and sending it over to the core lab?

*I save it onto the disk and then I give it to the research sister *name* and she sends it to Core Lab.*

Ok.

So once I have given her the disk she then takes ownership of sending it off to you [the ECL].

Yep

And I think we have only had one or two that have come back damaged over the course of the 5 years.

Yeah. So that process has been ok for you as a site?

As far as I know. We don't seem to get feedback regarding …apart from a broken disk at one point…we don't seem to get any poor feedback. And we know we have to do it on RAW data. All of yours are set up to do that on RAW data.

Ok, great, Umm. Coming back to the feedback: what are your opinions on the current web-based method of feedback? So obviously, more recently we have had that web-based method. How do you find that?

I think its ok, umm, I think its quicker. I know when we first started this trial the feedback was, and I think this was one of things we talked about in February last year as well, the feedback was very behind.

Yes

So I would do the echo, I dunno, say January, and I might not get feedback for that echo, not that I am hanging on it, but that would come through maybe 6-9 months later. So quite a long time. But that's much better now. I know that for me to look at the feedback, umm, I like to, well obviously I do read the feedback, and sometimes if I see it says. For instance, I was just going to go back to this question, not to protocol or whatever. I always look at my, I keep a copy of everything myself as well, so I look at my report for that day, and I will often

see that when it says not to protocol, its often because of poor body habitus, or the patient just doesn't have good enough 3D views for me to do.

Yes.

And I put that on the information sheet and I just feel that rather than just writing 'Not to Protocol' and making it, I don't think we have had many sub-optimal, but sometimes it is classed as sub-optimal because its not to protocol. And I feel, and I put this on the web based, on the feedback form, that they could re-iterate on that and say, look the reason its not to protocol was because of ….poor body habitus or whatever it was. Because when you just read that 'Sub-optimal, not to protocol' it makes me feel, umm, as someone who really tries my absolute best to get everything superb, well for every echo I do but especially for the research echo's, umm makes you feel quite like, like you haven't done a good enough job.

Yep.

And as we know, everything is patient dependant.

Yes of course.

And I just feel like if it was just said 'sub-optimal, protocol not followed due to…' and then whatever.

An acknowledgement that sometimes…

An acknowledgement that they realise why I had not done a 3D and it's because of whatever, umm, whatever reason I have put on the form, the report.

Ok.

So that's the only thing I would say. And I know when I get the little email saying, I've had two emails this morning, or last night I think, to say there is some feedback. Now I don't immediately go into that because I haven't got time.

Yep

So what I tend to do, is I have a to-do list every day of things I need to do. And on that to-do list is the UK TAVI feedback and when I have a 15-minute, 20-minute slot I will put into my email search engine UK TAVI feedback and then I have maybe 10 to look at and I will look at all 10 in a batch. As opposed to I get one and I look at it, and I get one and look at it.

Ummhmm

And if there is anything major Jess, the research nurse, she will say to me. Like for instance with the broken disk one, we had to just do another disk. Because what I do is I make sure that the patients aren't deleted from our hard drive, so if we ever have a broken disk or anything, I can still transfer the images via RAW data onto a new disk, several months after the event.

That is great, yeah.

Sorry that was a long-winded answer.

No that was brilliant. I completely understand what you are saying there. Umm, moving on. Have you ever, have you yourself ever had the need to contact the trial staff with a problem or query relating to the echo's for UK TAVI?

I haven't actually contacted them directly, no I haven't.

Ok, if you had, if you did, if you had a query about the echos or the core lab process, how would you do that, what would be your first port of call?

Yeah, I think actually, over the years I may well have emailed, I would have just emailed the UK TAVI, umm, almost the same email you get through all the feedback,

Yep

I will have emailed that. I think I did once email, regarding what I was talking about before, where it had said, I think I had even got a poor, not sub-optimal, it was like poor or inadequate rating. And I got a bit annoyed because it was, I had completely worded on the worksheet the reason why I hadn't done XYZ. I cant remember what it was now, but whatever it was. Umm, and I did email and say 'Look, I have been given a poor and the reasons were…..'.So yes I have contacted once, and I have probably got an answer, which is fair enough. But I cant remember because it was a while ago.

That's fine, that's umm perfect. And then just finally; do you have any other feedback regarding the Core Lab that you would like to share? Any improvements or feedback?

Umm, don't think so, no. I mean I am sure, they must get a huge range of studies and we, we, I don't know how other centres do it. I mean their research studies may well be allocated an entire hour to do everything to the absolute best, and we try to do everything, well we do do everything within our forty minute slot. All the reporting and everything is done afterwards but we spend the entire 40 minutes on the scan, sometimes longer. But I dunno how, I guess it would be quite nice, I dunno it might be nice to know how our centre compares to other centres. Are we doing a good enough job, what could we do to improve?

Yep, Ok.

It seems to be you [the ECL] tell us, 'This is good', 'This is sub-optimal', 'This is poor', 'This is whatever'. Umm, but in the scheme of things, I dunno, another centre every single one of their studies could be poor, or every single one of their studies could be excellent. Now how one study, I mean one department, get all their studies to be excellent? Is that because they are allocated a lot more time? Do they have better machines? That sort of thing I suppose.

Yes, that's really interesting, that is a good point. Ok, umm well that's all from me; thank you very much for your time.

That's alright.

So this is just following on from the questionnaire that went out a few weeks ago.

Ok

The questionnaire questions follow a similar theme but it is a chance for you to expand on your answers and tell us anything else you would like to.

Ok

Umm, so firstly, what do you think, what do you understand the role of the UK TAVI echo core lab to be within the trial?

Umm its difficult, I don't know really, because I haven't worked in research for that long, so I am kind of guessing the answers.

That's ok, there is no wrong or right answers. This is about your views.

Ok. I would have thought that the role was to review the results that we send in and, yeah, second ….umm I have lost the word I am looking for, not investigator, umm second…oh gosh I have lost my words this morning! Umm…

Analyst?

Yes analyst, that will do! Second analyst to look at the results So that its not the second person looking at them. Umm, so, sort of comparison.

That kind of answers the next question: why do you think that UK TAVI has an ECL? How does it add value? You said that comparison?

How does it add value?

Yes, obviously it makes it a little more complicated: why do they [the UK TAVI trial] have an ECL?

Because in the long run there will be greater accuracy of results because you remove any element of bias that be introduced, or any element of inaccuracy by the first analyst. Umm, so if there is widely different results coming out from those two analyses you would be able to see, investigate, where the errors are coming from. So in the long term the results will be more accurate because you are taking that element of bias or inaccuracy out. Or at least highlighting any areas of inaccuracy or bias.

Yep, umm, how familiar are you with the echo acquisition guidelines? For the UK TAVI trial.

Umm, well I have all the guidelines in the folder, so I have got all those guidelines here. So every time I do a scan for UK TAVI I follow the, the protocol that is required. But obviously I don't know if the core lab follow a different one, well I assume it's the same, in terms of their analysis.

Ok. So do you physically get it out to refer to it each time you do a scan?

Umm, yes. Every time. Because at the minute I work on about 10 different studies, so every time I do one I get the actual protocol out. Otherwise I wouldn't know what was required for each ok.

Ok. So what is your opinion on the guidelines? Their structure, or format, ease to follow? Is there anything that could make them better?

*Umm, they're not too bad. They reasonably work in a flowing order. The only thing that *inaudible* a little bit, the don't seem exactly chronological as the protocol requires, sometimes you are jumping around a little bit. For example, umm, I haven't got it in front of me know, sorry I should have brought it round. Umm, when they ask for colour on the mitral valve and then colour on the aortic valve. Then CW on the mitral then CW on the…. Do you see what I mean? You are jumping back and forth. So sometimes, well from our point of view, to do the full assessment on the that valve, then the full assessment on the other valve rather than jumping between the modalities. I don't know if that makes sense?*

Yes, that makes sense. Rather than doing it on the mitral valve, and then going to find the aortic valve, then coming back to the mitral valve.

Exactly, yeah, do everything in that view on that valve, everything in the view on the next value. Then when you go to the next view….do you know what I mean? Sometimes it just jumps around a little. But not too much, not as much as some protocols to be fair.

Ok. Who at your site, once you have taken the images, who at your site saves the scan images onto the DVD and prepares them to be sent to the Core Lab?

I put them on the DVD and then the research nurses send them off…..

Interruption

Interview resumes

So, who at your site, once you have done the scans, saves the images and prepares them to be sent to the ECL. You said you save the images onto the disk?

I save them yep.

And then you pass them onto the research nurse?

That's right, yes.

Ok, and how do you find that process of saving them?

Really straightforward, yeah very easy.

Ok, that's great. Umm. So, umm, currently there is a web-based method of feedback for the echo's.

OK.

I don't know if you are aware of that?

No, Ive never seen that.

You've never seen that? So you don't receive automated emails saying there is some feedback waiting for you?

No

No, Ok, that's not a problem. It might be something which at your site goes to the research nurse.

I would think that would be the case yeah.

OK, umm, so my next question was going to what has your experience been of the feedback from the 2D ECL? Has it been timely and helpful? But ….

Yeah, I can't really answer that one.

That's ok. Have you ever had to contact the trial staff, the UK TAVI trial staff, with any problem or query relating to the echo's?

No.

If you did, if you did have a problem, do you know how you would go about that? What would be your first port of call?

Umm, I am pretty sure in the file, its got the contact details with the protocol.

Ok, yeah.

So they are in there.

Ok, Umm, and just finally: Do you have anything else, regarding the echo core lab or the echo's, or the imaging side of the UK TAVI you would like to share? Any other feedback, things to make it better?

Umm, no not really. I mean if there was a way I could that feedback that would be really helpful, but I don't know if that is something I need to sort at this end rather than your end?

That's probably something that the main UK TAVI office could do for you.

Ok.

If you emailed their standard email; I think its uktavi@nds..... I would have to look it up. But if you emailed them with your email address and that you are taking the scans at your site, they can make you a log on for that system and set it up.

Ok, yeah that would be really useful.

So they are probably the people to contact for that.

Ok

Ok, thank you very much for your time, bye.