

# Early and late effects of transcatheter aortic valve implantation on myocardial function, myocardial injury and valve haemodynamics

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# Abstract

## Objectives

There remains a paucity of mechanistic data on the effect of transcatheter aortic valve implantation (TAVI) on left and right ventricular function and the clinical impact of these effects. We sought to assess and compare the effects on myocardial function and aortic valve haemodynamics of transcatheter (TAVI) and aortic valve replacement (AVR) utilizing serial cardiovascular magnetic resonance (CMR) and echocardiography. The time points selected were pre-procedure, early post-procedure (<14 days) and late post procedure (12 months). The impact of these changes on clinical endpoints will also be examined. Finally we compared CMR and transthoracic echocardiography (TTE) analysis of pre-operative and post-operative aortic regurgitation in patients undergoing both TAVI and AVR. Paravalvular aortic regurgitation (PAR) following TAVI is well recognised as a complication with a deleterious effect on outcome. Despite improvements, echocardiographic measurement of PAR largely remains qualitative whereas CMR directly quantifies AR with accuracy and reproducibility.

## Methods

To assess early outcomes a prospective comparison study of 47 patients with severe aortic stenosis undergoing either TAVI (26) or high risk AVR (21) was conducted. CMR (for LV/RV function, LV mass, left atrial volume and aortic regurgitation) was carried out pre-procedure and early post-procedure (<14 days). To compare the assessment of PAR, eighty-seven patients with severe aortic stenosis undergoing TAVI (56 patients) or AVR (31) were assessed. CMR (1.5T) and transthoracic echocardiography (TTE) were carried out pre-operatively and a median of 6 days post-operatively. The CMR protocol included regurgitant aortic flows using through-plane phase-contrast velocity. At late follow-up 32 patients (19 TAVI, 13 AVR)

underwent CMR (for LV/RV function, LV mass, AV haemodynamics). Finally late clinical follow-up using a combined endpoint was conducted on 38 patients.

## **Results**

Groups were similar with respect to STS Score across all analyses, however TAVI patients were older. Preoperative left ventricular and right ventricular ejection fractions were similar. In the study of early outcomes post-operative LVEF was preserved in both groups. In contrast, decline in RVEF was more significant in the TAVI group (61% to 54% vs. 59% to 58%,  $p=0.01$ ). Post-procedure aortic regurgitant fraction was significantly greater in the TAVI group (16% vs 4%,  $p=0.001$ ), as was left atrial size (110mls vs. 84mls,  $p=0.02$ ). Further analysis revealed a significant relationship between the increased aortic regurgitant fraction and greater left atrial size ( $p=0.006$ ), and a trend towards association between the decline in RV dysfunction and increased post-procedure AR ( $p=0.08$ ). The analysis of post-procedure aortic regurgitant fraction using CMR demonstrated greater regurgitation in the TAVI group (TAVI  $16\pm 13\%$  vs. AVR  $4\pm 4\%$ ,  $p<0.01$ ). Comparing CMR to TTE, 27 of 56 (48%) TAVI patients had PAR which was at least one grade more severe on CMR than TTE ( $Z = -4.56$ ,  $p < 0.001$ ). Sensitivity analysis confirmed the difference in PAR grade between TTE and CMR in the TAVI group ( $Z = -4.49$ ,  $p < 0.001$ ). Finally the study of late outcomes showed no difference in late LVEF or RVEF between TAVI and AVR. Late regurgitant fraction remained elevated in the TAVI group. In the 38 patients with late clinical follow-up there was an association between the combined endpoint (death, MI, CVA, PPM, Readmission) and impaired LV function and RV function, pre and post-procedure.

## **Conclusion**

There was no significant difference in early left ventricular systolic function between techniques. While RV systolic function was preserved in the AVR group, it was significantly impaired early after TAVI, possibly reflecting a clinically important pathophysiologic consequence of paravalvular aortic regurgitation. Regarding paravalvular aortic regurgitation, TTE underestimated the degree of paravalvular aortic regurgitation when compared to CMR based quantitative analysis. This underestimation may in part explain the findings of increased mortality associated with mild or greater AR by TTE in the PARTNER trial. Paravalvular aortic regurgitation post TAVI assessed as mild by TTE may in fact be more severe. Finally, there was no significant difference in either left or right ventricular function at 12 months. There was however an association between both pre- and early post-procedure left and right ventricular function and a worse late outcome.



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# Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Dr Gareth Crouch

March 2015

## **Preface**

### **Contributors**

This thesis is presented in the manuscript format as two of the three chapters have been accepted for publication. As the author of the thesis I conceived the original study design, undertook data collection, analysis, interpretation of the results and drafted the manuscripts. Mr Jayme Bennetts and Dr Ajay Sinhal assisted with study design and made critical review of the manuscript. Mr Craig Bradbrook and Ms Amy Penhall undertook data collection and provided interpretation of CMR and echocardiographic data. Mr Phillip Tully and Dr Darryl Leong provided statistical analysis and made critical review of the manuscript. Dr Carmine De Pasquale assisted with data interpretation and provided critical review of the manuscript. Professor Selvanayagam and Associate Professor Baker conceived the original study design, made an interpretation of the data and critical revision of the manuscript.

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# List of Abbreviations

AR = Aortic Regurgitation

AS = Aortic Stenosis

AVA = Aortic Valve Area

AVR = Aortic Valve Replacement

CMR = Cardiac Magnetic Resonance

EF = Ejection Fraction

GFR = Glomerular Filtration Rate

HS TnT = High-Sensitivity Troponin T

LV = Left Ventricular

LVEDV = Left Ventricular End-Diastolic Volume

LVESV = Left Ventricular End Systolic Volume

MRI = Magnetic Resonance Imaging

NT-proBNP = N-terminal Pro B-type Natriuretic Peptide

PAR = Paravalvular Aortic Regurgitation

QCA = Quantitative Coronary Angiography

RV = Right Ventricular

TAVI = Transcatheter Aortic Valve Replacement

TOE = Transoesophageal Echocardiography

TTE = Transthoracic Echocardiography



# **Chapter 1: Introduction and Literature Review**

## **1.1 Introduction**

Aortic stenosis (AS) is a disease in which failure of the aortic valve to completely open imposes an abnormally high-pressure load on the left ventricle. Calcific aortic stenosis is a subtype of AS affecting the elderly, and is the most common form of valve disease in the Western world and represents a major healthcare burden [1]. It is the second most prevalent adult valve disease in the United States, occurring in 4% of the population aged more than 75 years, and causes progressive pressure overload leading invariably to life-threatening complications. The aging population of the western world has led to an increase in the number of individuals with AS and a concomitant increase in the number who are older with multiple comorbidities. In the United States alone there has been a doubling in the number of aortic valve procedures performed in the last decade, the majority in patients over age 65 years [1]. Surgical aortic valve replacement (AVR) and, more recently, transcatheter aortic valve implantation (TAVI) effectively relieve the hemodynamic burden and improve symptoms and survival of affected individuals [2-4].

When patients with aortic stenosis develop symptoms such as dyspnoea or syncope, functional limitation is inevitably followed by heart failure and premature death. AVR improves symptoms and is generally accepted to prolong survival on the basis of studies performed over the last 30 years [5]. Despite these encouraging results a significant number of patients may not even be offered operation with multiple studies suggesting up to 40% of patients with severe AS are treated medically [6, 7]. Most often these patients are considered too sick because of associated medical comorbidities or too old to be offered surgery, due to the morbidity associated with both sternotomy and cardiopulmonary bypass. TAVI has been developed as a technique to offer the benefits of aortic valve replacement to patients who were either deemed inoperable or at high surgical risk owing to a combination of advanced age and comorbidities. The first implant of a

transcatheter aortic valve was by Cribier in 2002, with commercially available valve systems becoming available in the late 2000's [8]. The majority of clinical experience worldwide is contained to two different prostheses: the balloon expandable Edwards Sapien Valve; and the self-expanding Medtronic CoreValve. Flinders Medical Centre during the period of this research, has exclusively used the Edwards Sapien system since the first transcatheter procedure there in 2009.

A cornerstone of any procedure intervening on cardiac valvular pathology is peri-procedural imaging. In the modern era a plethora of modalities are available including transthoracic echocardiography (TTE), transoesophageal echocardiography (TOE), cardiac computerized tomography (CCT), single photon emission computed tomography (SPECT), and cardiovascular magnetic resonance (CMR). Despite the recent evolutions of CCT and CMR transthoracic echocardiography remains the primary imaging modality used to evaluate heart valves in both clinical and research practice. The spatial resolution and temporal resolution of echocardiography allow characterisation of valve structure, function and pathology as well as ventricular size and function [9]. Doppler echocardiography is a specific echocardiographic technique, which yields extensive haemodynamic data regarding aortic valve stenosis. Doppler echocardiography is less reliable in quantifying the severity of either valvular or paravalvular regurgitation. Subjective visual assessment of the regurgitant jet with the use of color flow mapping is semi-quantitative and can be affected by several hemodynamic and technical variables [10].

Despite the inherent qualities of TTE, there are significant limitations. The acoustic windows in TTE can be dramatically limited in obese patients and patients with chronic obstructive pulmonary disease to the point of being non-diagnostic. Additionally

echocardiography is limited to secondary measures of right ventricular function and qualitative assessment of aortic regurgitation. Transoesophageal echocardiography overcomes some of these limitations but is invasive, requires sedation, and is subject to complications [11]. High-resolution CMR imaging offers serial assessment of myocardial function and tissue characterisation, and is ideally suited to the periprocedural setting [12-16]. It is non-invasive, does not require sedation and is not restricted by acoustic windows or comorbidities. Given its 3D nature and superior signal to- noise ratio, cine CMR is highly superior to 2D echocardiography and has become the “gold standard” investigation for measurement of left and right ventricular (LV/RV) volumes, mass, and function of both normal and abnormal ventricles [17-20]. Finally, it allows quantitative assessment of both native and prosthetic aortic valve flow dynamics, including parameters such as peak velocity (aortic stenosis) and regurgitant volume (aortic regurgitation) [21].

Whilst significant trial registry data for transcatheter aortic valves has been published, including major adverse clinical events (MACE), there has been a paucity of data on the incidence, extent and temporal sequence of myocardial reversible and irreversible injury. The aim of this thesis is to compare peri-procedural and late myocardial outcomes of patients undergoing either AVR or TAVI. The cohort is a unique group, being either moderate to high risk surgical candidates or those deemed such high risk to have been referred for a percutaneous (transcatheter) procedure. The population was of advanced age, had multiple comorbidities and may have had impaired left ventricular function.

It is hypothesised that there will be significantly less myocardial injury with a percutaneous approach than with an open-arrested heart-bypass approach. We will assess specifically the incidence and extent of myocardial reversible and irreversible injury in transcatheter patients in direct comparison to a high-risk surgical group. To do this we will

utilize CMR with multiple imaging techniques including: cine left ventricular (LV); cine right ventricular; and late gadolinium enhancement (LGE) viability studies. Using these techniques we can compare pre-procedural cardiac status and early post-procedure cardiac outcomes in both groups. We predict the transcatheter patients will have less procedure related myocardial injury, either reversible or irreversible, and therefore comparably better left ventricular (LV) function. Additionally we hypothesise there will be a higher incidence of right ventricular dysfunction in the transcatheter group owing to procedural injury or paravalvular regurgitation. Finally we will conduct late follow-up CMR looking at the key indicators of procedural success such as ventricular function and LV mass regression, expecting to find higher regression rates in the transcatheter group. Additionally the association between late clinical outcomes and periprocedural CMR findings will be examined. We believe reproducible qualitative assessment of the myocardial outcomes of transcatheter valves in comparison to the current gold standard of open valve replacement is a must before this technology gains wide use.

## **1.2 Aortic Stenosis**

### **1.2.1 Epidemiology**

Aortic stenosis (AS) is typically defined as the obstruction to outflow of blood from the left heart caused by narrowing of the aortic valve. It has stages of severity beginning with aortic sclerosis (calcification and thickening of valve leaflets without a significant transvalvular gradient), progressing to mild, moderate and severe stenosis. There are several pathophysiological mechanisms leading to aortic stenosis including degenerative – calcific, rheumatic and congenital abnormalities. Degenerative aortic stenosis is the most common valve disease in the western world and places a significant burden on health

services [22, 23]. One in four individuals over the age of 65 years in the general population have sclerosis of the aortic valve, increasing to 1 in 2 by age 80 [24]. In a North American population study more than 4% of persons age >75 had aortic stenosis [23].

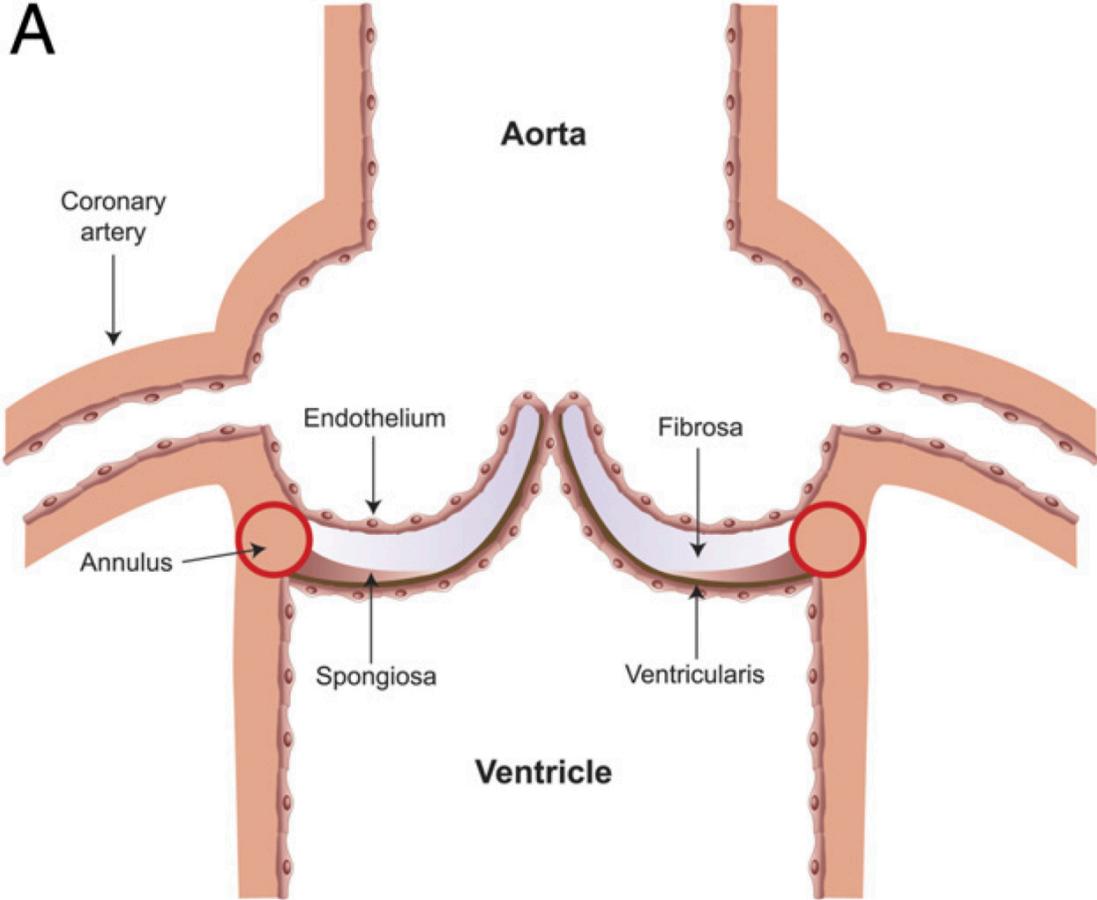
The etiology of the underlying pathologic process of AS has changed along with the age of individuals affected. Passik et al. analysed the valve characteristics in 646 patients with pure AS who underwent valve replacement between 1981 and 1985. During the five years of the study, the relative frequency of rheumatic valve disease decreased from 30% to 18% and the relative frequency of the bicuspid aortic valve changed from 37% to 33%; in contrast, the relative frequency of degenerative - calcific aortic stenosis increased from 30% to 46%. These differences were most frequently seen in persons older than 70 years [25, 26].

### **1.2.2 Anatomy**

The aortic valve is a one way valve at the origin of the aorta that allows blood to flow readily from the left ventricle into the aorta during systole and prevents regurgitation back into ventricle during diastole. It is a passive structure composed of three leaflets each containing a small fibrous nodule at its free edge [27]. The three leaflets are semilunar in shape, having a free edge which opposes the other two cusps when closed, as well as a basal edge which hinges with the aortic annulus [28]. This arrangement of the three leaflets results in even distribution of mechanical stress to the valve ring and the aorta [29]. The leaflets themselves are thin and pliable but inherently strong. Each cusp is approximately 1 mm thick and appears smooth, thin, and opalescent, with very few cells [1]. They are composed of 4 clearly defined tissue layers: the endothelium, fibrosa, spongiosa, and ventricularis (Fig. 1). At their base, the valve leaflets are attached to a

dense collagenous network, called the annulus, which facilitates their attachment to the aortic root and the dissipation of mechanical force.

**Figure 1 – Aortic Valve Anatomy**



(From Dweck et al. 2012 - [1])

### **1.2.3 Pathogenesis**

The pathophysiology of acquired aortic stenosis can be attributed to either calcific degeneration of a normal or congenitally abnormal valve, or a consequence of rheumatic fever. Calcific degeneration and inflammation of a normal trileaflet or an abnormal congenital bicuspid valve is the most common underlying pathology [30, 31]. Degenerative calcification and inflammation is an insidious process that once commenced progresses to increased valve stiffness, reduced cusp excursion, and progressive valve orifice narrowing that contrasts with the cusp fusion seen with rheumatic heart disease [1, 32, 33]. Calcific degeneration occurs in anatomically normal tricuspid aortic valves and is considered a disease of aging, most commonly occurring beyond the age of 65 [24]. The same disease process occurs in congenitally bicuspid aortic valve at a much faster rate, leading to presentation at a younger age. Historically, calcific AS has been attributed to prolonged “wear and tear” and age-associated valvular degeneration and calcification. Recent research however suggests the pathogenesis of AS is an active process that involves a combination of inflammatory activation, increased oxidative stress, fibrosis and calcification which may be amenable to medical therapy {Carabello and Paulus, 2009, #88159; Dweck et al., 2012, #96800}.

Aortic stenosis associated with rheumatic fever is more frequently present in a younger population, and is often associated with mitral valve disease [34]. It is also now rarely seen in the western world owing to the advent of antibiotic treatment for streptococcal infections. Rheumatic disease of the aortic valve is also more likely to be of a “mixed” type, including a regurgitant component as well as stenosis. Taking into account the pathological processes, older patients presenting as high-risk candidates for AV replacement are most likely to have severely calcified tricuspid aortic valves.

#### **1.2.4 Physiology**

The physiological effect of AS regardless of the cause is obstruction of left ventricular (LV) outflow and pressure overload of the left ventricle. This differentiates aortic sclerosis (non-obstructing) from stenosis (obstructing). The ensuing pressure overload results in the manifestation of 2 distinct but overlapping processes [35, 36]. The first is characterized by concentric left ventricular hypertrophy (LVH), and, as demonstrated by the Law of Laplace, the increased wall thickness and mass act to limit the increase in wall stress created by the pressure overload state [36-40].

The presentation of the signs and symptoms of heart failure can be due to either systolic or diastolic dysfunction with the latter usually appearing much earlier in the disease course. Furthermore as the LV wall thickens its compliance is reduced and the coronary arteries feeding the myocardium are compressed. This, in combination with increased afterload and elevated wall strain leads progressively to overwhelming of the compensatory mechanisms and heart failure. The failing pump and outflow obstruction leads to not just early symptoms of shortness of breath and lethargy but also syncopal episodes and angina on physical exertion. In extremis, the reduced outflow, increased myocardial mass and compressed coronary arteries may induce myocardial ischaemia sufficient to cause arrhythmia and sudden death, the risk of which is documented at 1% per year for severe asymptomatic AS [41, 42]. Once a patient develops symptoms mean survival is 2 – 3 years and the risk of sudden death significantly higher than in the asymptomatic group [43, 44].

### **1.3 Treatment of Aortic Stenosis**

Despite its impact on many cardiac diseases, medical therapy has no benefit in terms of survival for AS. The mainstay of treatment for the last 4 decades has been surgical valve replacement, with significant volumes of literature proving its efficacy and safety. The only percutaneous option to date has been balloon valvuloplasty which whilst delaying progression briefly does not impact on outcome {Dweck et al., 2012, #96800}. The aging and increasingly comorbid population has led to the development of a method of replacing the valve which poses less risk than open surgery - transcatheter aortic valve implantation (TAVI). This procedure involves the implantation of a tissue valve via a catheter, most often using a femoral artery approach and without cardiopulmonary bypass. The main concept behind this method is reduced morbidity and mortality by avoiding the effects of sternotomy and cardio-pulmonary bypass, in a group of patients who are considered either inoperable or at high surgical risk because of their age or comorbidities.

Treatment of AS is based on the simple concept of removing the outflow obstruction. Surgical aortic valve replacement is the gold standard treatment for AS and is now the second most common cardiac surgery performed [45]. The procedure is performed via midline sternotomy, on a cross-clamped - arrested heart, with cardiopulmonary bypass. The native valve is excised and the annulus debrided, after which a new valve, either bioprosthetic or mechanical is implanted. This decision on valve type depends on patient factors, largely the longevity required and patients suitability for anti-coagulation. As such, older higher risk patients almost always receive a bioprosthetic valve which does not require warfarin anticoagulation. Relief of the stenosis via excision of the diseased valve and implantation of a prosthesis immediately lowers the pressure gradient across the annulus. Acutely the left ventricle has a reduced workload and in the longer term, in combination with medical therapy, this leads to reduced myocardial mass of the LV, termed LV regression. It is this regression which reverses the mechanisms that lead to

heart failure and thus prolongs survival. The two alternative treatments, balloon valvuloplasty and medical therapy, are of no benefit prognostically [6]. The advent of modern cardiac surgical techniques allows the replacement of an aortic valve with a mortality rate approaching 2% in low risk populations and 8 - 12% in high risk [46].

It is estimated that one third of those with symptomatic severe AS are not referred for surgery or turned down owing to an unacceptably high-risk profile [47]. This increasing number of inoperable and high-risk surgical candidates has created a need for less-invasive, non-surgical treatment option and led to the development of transcatheter aortic valve implantation [48]. This technique involves a percutaneous approach via the femoral artery under general anaesthetic, with balloon valvuloplasty to dilate the stenotic valve. This is followed by implantation of a tissue valve supported by an expanding metal stent. This technique avoids both sternotomy and cardiopulmonary bypass, two factors often implicated in adverse outcomes. Currently there are a number of systems available, the most common have been the Medtronic 'CoreValve' (Medtronic, MN, USA) and Edwards 'Sapien' (Edwards Lifesciences, Irvine, USA) device. Unlike percutaneous coronary artery stenting which started in the simplest, fittest patients, TAVI is only approved for use in patients deemed very high surgical risk or inoperable. The mid-term randomized trial data of TAVI vs surgical AVR has only recently been reported and has demonstrated non-inferiority with LV regression equivalent to an open procedure when assessed by echocardiography [6] (17,21). To date there is no published data using CMR in the early and mid-term assessment post TAVI.

#### **1.4 Imaging Aortic Valve Disease**

### 1.4.1 Echocardiography

Whilst clinical examination may reveal the presence of a typical AS murmur, it is cardiac imaging which allows a formal diagnosis to be made. 2-Dimensional TTE is well validated in the assessment of valvular heart disease, in particular AS and is considered the clinical standard [49]. It remains a cost-effective, simple, and accurate tool for assessing left ventricular function, valve leaflet function, and calculated aortic valve gradients [46]. Flow characteristics including trans-valvular gradient, flow velocities and aortic valve area (AVA) can be calculated or derived using Doppler. The inherent weaknesses of transthoracic echocardiography (TTE) are its inter-user variability and its reliance on calculated flow measurements and valve area, rather than direct quantitative measurements. In assessing AS doppler assessment makes use of the modified Bernoulli equation ( $\text{gradient} = 4 \times \text{velocity}^2$ ) to assess the severity. This technique relies on the concept that as blood flows from the body of the LV across the stenotic valve, the flow rate must accelerate for the volume to remain constant.

The acquired data is utilized to classify the stenosis to mild, moderate or severe. The key parameters used are aortic valve area ( $\text{cm}^2$ ), mean gradient and jet velocity, with values of  $<1.0\text{cm}^2$ ,  $>40\text{mmHg}$  and  $>4.0\text{ m/s}$  respectively, being diagnostic of severe AS (8). Once categorized as severe, the presence or absence of symptoms and LV function determine patients whose risk benefit ratio is in favour of intervention. Trans-oesophageal echocardiography (TOE) and cardiac catheterization add to patient assessment providing more detailed analysis of the valve and ventricular function. TOE is able to provide accurate measurement of the effective orifice area of the aortic valve by direct planimetry, similar to CMR, rather than calculating it from geometric assumptions [50]. Cardiac angiography can also provide a transvalvular gradient by comparing pressures in the left

ventricular outflow tract and aortic root. It also the investigation of choice for concurrent coronary artery disease, a pathology not infrequent in this population.

#### **1.4.2 Cardiac Magnetic Resonance**

The well documented limitations of echocardiography has initiated the investigation of alternative modalities [51]. Cardiovascular magnetic resonance (CMR) is considered the gold standard in the evaluation of volumes, mass and systolic function of both normal and abnormal left ventricles, owing to its high spatial resolution, excellent signal-to-noise ratio, and its ability to image the heart in a three-dimensional manner [52]. CMR-based assessment of LV function has both diagnostic and prognostic utility in patient evaluation. During the same scan, information on myocardial fibrosis, viability, perfusion and valvular function can be ascertained, affording considerable versatility in patient assessment. CMR is highly superior to 2D echocardiography when examining global LV function and allows for follow-up of patients in a temporal manner without cumulative radiation exposure. Its accuracy and reproducibility in the evaluation of volumes, function and mass makes it the standard of reference for all imaging modalities. It utilises multiple imaging techniques to provide an integrated, non-invasive evaluation of valvular heart disease [10].

Cardiac magnetic resonance imaging as with all MRI is based on the detection of signals from hydrogen nuclei which are in very high concentration within the body (approximately 100 molar) [53]. Because of this abundance of hydrogen atoms, nuclear magnetic resonance signal can be used to create an image through magnetic resonance imaging [54]. Within a MRI scanner, hydrogen nuclei in the body align with the axis of the magnetic field rather than spinning randomly. This precession can be perturbed by

application of additional small magnetic field pulses [52]. By applying these pulses in a controlled manner in the form of “pulse sequences,” signals can be received and processed to produce an image of the spatial distribution of the spins or protons within the body. The availability of multiple different pulse sequences for imaging that can define cardiac structure, characterize tissue, or measure cardiovascular function is an important feature of CMR.

Whilst CMR is capable of a broad array of image sequences there are a core set of sequences necessary to acquire information when targeting periprocedural assessment of aortic valve replacement. These include scout images, morphology images, cine images, viability images and flow velocity images. The goal of scout images is to establish the correct image planes for both the short and long axis and orient the body position within the scanner [54]. Morphology images provide information regarding gross thoracic anatomy. The assessment of ventricular function is an essential component of CMR, with cine imaging providing this data. Specifically it provides a highly accurate and reproducible assessment of ventricular volume, ejection fraction and ventricular mass in 3-D [54]. Viability imaging is one of the key strengths of CMR and refers to the assessment of myocardium for evidence of irreversible injury or “scar”. This sequence requires the administration of gadolinium contrast agent intravenously and uses T1-weighted images. It has been shown in numerous studies to be effective in identifying the presence, location, and extent of acute and chronic irreversible myocardial injury [55, 56]. Finally phase-contrast velocity mapping is a method utilised to assess valve stenosis, valve regurgitation or cardiac shunts, that has been validated and found to be reproducible and versatile [57]. With this technique a series of cine series of greyscale images reflecting blood flow within the vessel is acquired, with the grey level proportional to the velocity. Both scanner

software and post-processing software can then analyse the images to ascertain valvular haemodynamics.

In this thesis cardiovascular magnetic resonance assesses both left and right ventricular function using “cine” images, short video loops of 1 -2 cardiac cycles taken in various planes. This allows subjective and objective assessments of ventricular geometry and function. Aortic stenosis and regurgitation will also be assessed using phase-contrast velocity mapping. Aortic valve planimetry can further quantify AS by directly measuring valve area, using cine images. Cine images will also be used to identify the presence of and quantify left ventricular hypertrophy. Regression of left ventricular hypertrophy (LVH) has been extensively demonstrated after aortic valve replacement and the persistence of LVH is associated with negative outcomes and follow-up imaging is important in prognostication [58, 59]. In patients having undergone valve replacement assessment of potential myocardial injury caused by inadequate cardioplegia, aortic cross-clamping or embolisation of valve calcium remnants is vitally important. Late gadolinium enhancement (LGE) identifies focal areas of infarction if present. These areas of infarction are likely due to underlying coronary disease or valvuloplasty emboli in the TAVI group and cardioplegia, cross-clamp emboli, air or underlying coronary artery disease in the AVR group.

### **1.4.3 MRI Safety Considerations**

The performance of CMR requires particular precautions to be taken owing to the high static and gradient magnetic fields. Unlike computerised tomography (CT) there are no risks associated with ionising radiation. The biological effects of magnetic resonance are limited to the experiences of warming from radio-frequency (RF) power deposition, or peripheral nerve stimulation from rapidly switching magnetic fields. The effect of

magnetic fields, in the strength used by MRI scanners, on all body systems has been investigated without any evidence of effect [54]. Cardiac specific studies have shown no effect on cardiac contractility or function [60].

A very relevant consideration in this thesis is the safety of ferromagnetic objects in the MRI environment. Ferromagnetic objects are those in which a strong magnetic field can be induced when they are exposed to an external magnetic field [54]. The cohorts in this thesis were more likely than the general population to have had metallic medical implants owing to their advanced age and comorbidities. This required thorough safety assessments prior to every scan. Additionally given the focus of the study was the effect of aortic valve replacement the safety of these implants in the MRI environment was also paramount.

Many heart valve prostheses and annuloplasty rings have been evaluated for MR issues, especially with regard to the presence of magnetic field interactions associated with exposure to MR systems operating at field strengths of as high as 4.7 Tesla [61]. Of these, the majority displayed measurable yet relatively minor magnetic field interactions. That is, because the actual attractive forces exerted on the heart valve prostheses and annuloplasty rings were minimal compared to the force exerted by the beating heart (i.e., approximately 7.2-N). CMR is not considered to be hazardous for a patient with a prosthetic heart valve provided it is scanned in a field less than that tested [62]. There has been no reported adverse event with prosthetic heart valves in MRI.

There are two groups of device under examination in this study, standard bioprosthetic aortic valves and transcatheter aortic valves. The transcatheter valve being the Edwards Sapien XT and the surgical valves being one of Medtronic Mosaic, Edwards Perimount, or St Jude Epic. All valves have documented MRI safety from their manufacturers at 1.5T

(appendix) and are approved up to 3.0T. In addition to the standard safety data, additional data regarding the timing of scans relatively short periods after device implantation was sought, which confirmed MRI safety from time of implantation for all valves according to the manufacturers.

Gadolinium chelates are widely used MRI contrast agents and were approved for use in MRI by the FDA in the United States in 1988. The prevalence of adverse events associated with gadolinium is very low at approximately 2% [54]. Side-effects such as headache, nausea and local burning can occur. Contrast allergy manifesting in anaphylaxis is very rare at less than 1 in 100 000 patients. The restriction of gadolinium contrast in patients with severe renal impairment arises from the rare complication of nephrogenic systemic fibrosis (NSF). The sequelae of this condition range from skin thickening and joint contracture through to multi-organ failure and death. Those at risk are patients on dialysis where the incidence may be high as 10%, and those with a glomerular filtration rate of  $<30\text{ml}/\text{min}/\text{m}^2$  [63]. The cohort for this thesis were excluded from receiving gadolinium contrast if their creatinine clearance was  $< 45\text{mL}/\text{min}/\text{m}^2$  with all patients required to have a serum creatinine level within 6 weeks of the scan. The majority of the cases of NSF associated with gadolinium have been with a particular contrast agent - 'Omniscan', which is not used at Flinders Medical Centre [64].

Overall there is a significant gap in the current literature in terms of accurately assessing the full extent of early and late myocardial outcomes in patients undergoing intervention for aortic stenosis. This combined with introduction of a new method of aortic valve replacement has created an opportunity to utilize CMR to conduct an observational

comparator trial of patients undergoing transcatheter and open aortic valve replacements for aortic stenosis.

## 1.5 Hypotheses

1. TAVI would result in significantly less peri-procedural LV injury compared with AVR resulting in comparably greater LV function post-procedure.
2. Right ventricular function would be impaired post TAVI
3. TTE would systematically underestimate the severity of PAR in TAVI patients compared with CMR and this underestimation would be more pronounced in the TAVI group owing to the complexity of the paravalvular regurgitation.
4. CMR measured ventricular function early post procedure would be a predictor of late clinical outcome
5. The presence of paravalvular regurgitation would be associated with worse left and right ventricular indices at 12 months.
6. Left ventricular mass regression would be greater in the TAVI group



## **Chapter 2**

### **Materials and Methods**

*The methods for each study are provided in the corresponding chapter.  
Provided below is a methodological overview for the entire thesis*

## **2.1 Subject Selection**

All patients with severe aortic stenosis waitlisted at Flinders Medical Centre or Flinders Private Hospital for transcatheter aortic valve implantation (TAVI) were eligible for inclusion in this study. Additionally a select group of patients with severe aortic stenosis referred for open aortic valve replacement (AVR) who were deemed to be of higher operative risk were also eligible[65]. This second group was to provide a control group for the TAVI cohort. The open group had all elected for an aortic valve bioprosthesis and there were no exclusions for the use of a mechanical heart valve. The fact that those patients referred for TAVI are of recognised higher operative risk required multiple inclusion criteria to be applied to the AVR group. These factors included older age, multiple or more significant comorbidities and higher risk scores as calculated by extensively validated risk scoring systems (EuroSCORE and STS score) [66, 67]. These two risk scores calculate an overall mortality risk by accounting for factors such as age, comorbidities and the type of surgery to be undertaken. To maintain homogeneity between and within groups several exclusion criteria were also applied. The majority of these were technical relating to the MRI such as incompatible implants or metallic foreign bodies, claustrophobia, and symptoms precluding laying flat for sixty minutes. Cardiac specific exclusions were applied across both groups to maintain homogeneity and limit confounding factors. These included significant concomitant valve disease (moderate or greater stenosis or regurgitation) or a requirement for an additional procedure such as coronary artery bypass grafting.

### **2.1.1 Inclusion criteria**

All patients accepted for transcatheter aortic valve replacement and patients accepted for open aortic valve replacement who were high-risk candidates. High risk candidates were identified by the presence of age >70 years and one or more of the following:

- Logistic EuroSCORE >15 or
- STS score >4
- Type 2 diabetes (HbA1c >6.0)
- COPD mild - moderate (FEV1 50 – 80%)
- Active smoker
- LV dysfunction of <50%
- Dilated cardiomyopathy with LVEDV >60mm
- NYHA Class III or IV symptoms
- Previous TIA or CVA
- Cerebrovascular disease
- Pulmonary hypertension
- Peripheral vascular disease

### **2.1.2 Exclusion criteria**

1. Inability to give informed consent
2. Severe claustrophobia
3. Implantable cardiac devices (not including valve prostheses) and other contraindications to MRI (i.e. metal in eyes, incompatible implants)
4. Inability to lie flat for 1 hour
5. Patients with GFR < 45mL/min (excluded from gadolinium contrast only)
6. Concurrent valve disease either stenotic or regurgitant >mild
7. Undergoing concurrent cardiac procedures i.e. CABG or MVR

## 8. Non-elective cases

Patients meeting the aforementioned criteria were identified from the cardiothoracic surgery wait list at Flinders Medical Centre and Flinders Private Hospital. These patients were then contacted either by telephone pre-procedure or at the preoperative assessment clinic to ascertain their interest in participating. A full explanation of the study and the requirements of participation were provided in person (Gareth Crouch), and consent obtained. All TAVI patients approached consented to participate and only one AVR patient declined participation owing to claustrophobia. A thorough medical history was obtained from the patient and medical records and operative risk calculated using online calculators for both EuroSCORE and STS Score.

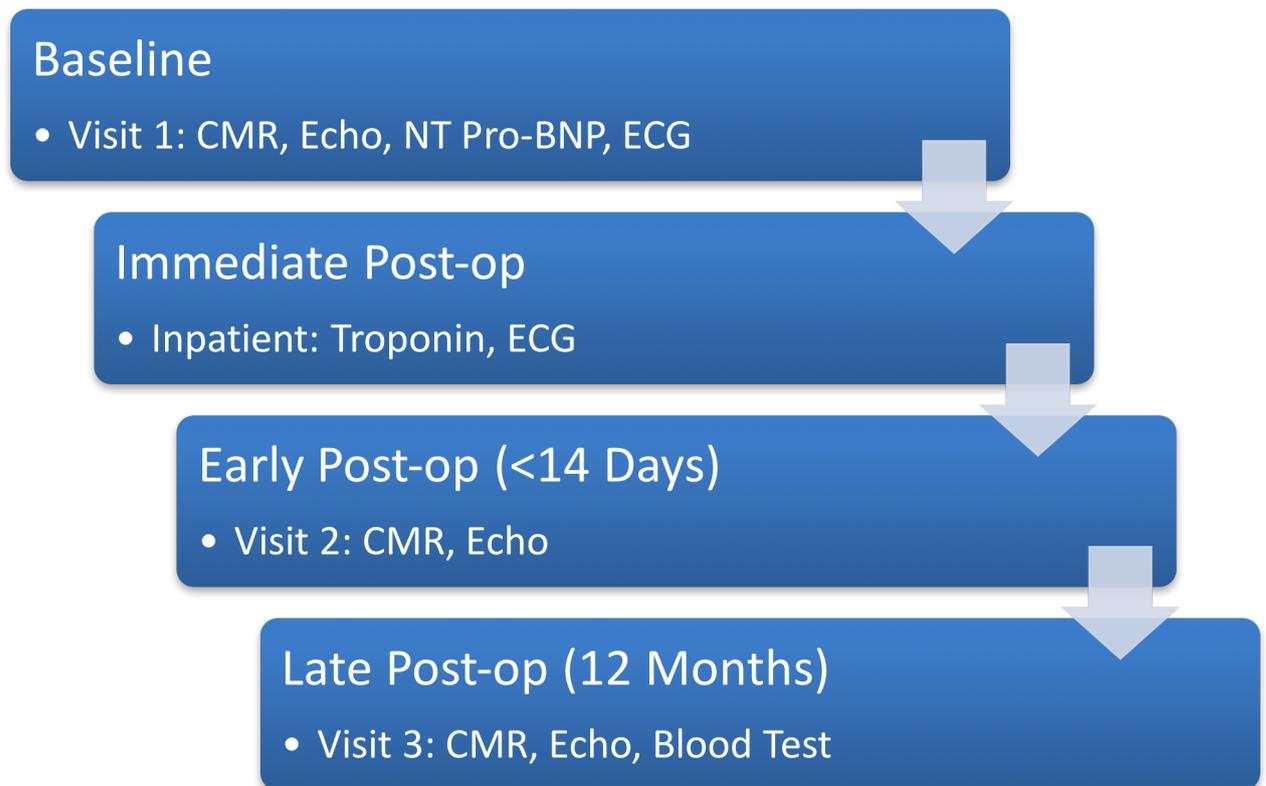
Patients undergoing TAVI and AVR had data collected pre-procedure to allow the EuroSCORE and STS Score to be completed. Additionally ECG, and biochemical markers including troponin T and BNP were also collected. TTE was conducted pre-procedure either immediately before or after the CMR. CMR was conducted within 14 days of the procedure date and included: cine MRI for the assessment of global and regional LV function; T2 weighted oedema images; aortic valve flow by phase contrast velocity mapping; and late gadolinium enhancement images with infusion of contrast agent gadobutrol (Gadovist, Bayer Schering, Germany) at a dose of 0.1mmol/kg.

Patients then underwent either aortic valve replacement or transcatheter aortic valve implantation as decided by the heart team. Post surgery troponin T levels were taken at 6, 12, 24 and 72 hours and ECG's done on day 1 and 2. TTE was routinely conducted for all valve patients regardless of this study, therefore enrolled patients required a slightly more extensive echocardiographic study. Again, this was on the same day as the post-procedure

CMR. Within 14 days of the their valve procedure all patients underwent CMR using an identical image sequence to pre-procedure. Only one patient was excluded owing to permanent pacemaker implantation (an exclusion criteria for safety reasons). This early post-procedure scan was done either whilst the subject was still an inpatient or outpatient if they had already been discharged.

At 12 months patients who had not developed an exclusion criteria were invited for a final CMR which was conducted again using an identical study sequence. TTE was also completed with a routine 12 month post-operative assessment. Patients were followed for major adverse cardiovascular events (MACE), including heart failure, myocardial infarction, re-hospitalisation with cardiac event, cerebrovascular event, heart failure and death to twelve months post-procedure.

**Figure 2 - Study Design**



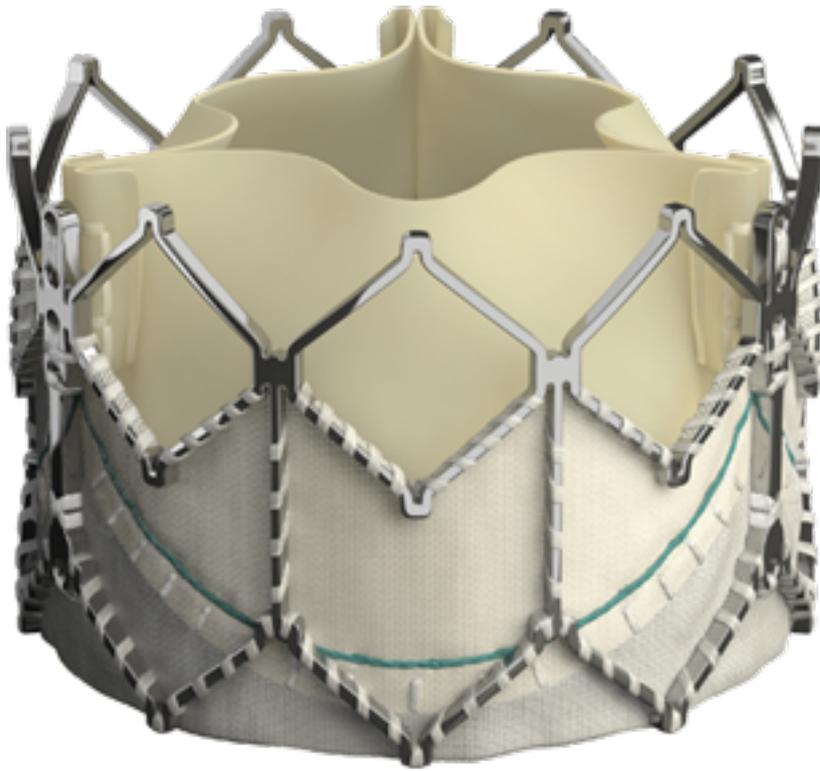
## **2.2 Transcatheter Aortic Valve Implantation**

Only patients planned to receive the Edwards Sapien XT prosthesis (Edwards Lifesciences, California USA) deployed via the transfemoral route were recruited for the study. This device is one of two that were commercially available at the commencement of the study and was the only device used at Flinders Medical Centre during this time. Patients receiving the Edwards Sapien XT prosthesis deployed via the transapical route were excluded to maintain homogeneity as this method requires a degree of myocardial injury at the apex of the heart which may invalidate any findings.

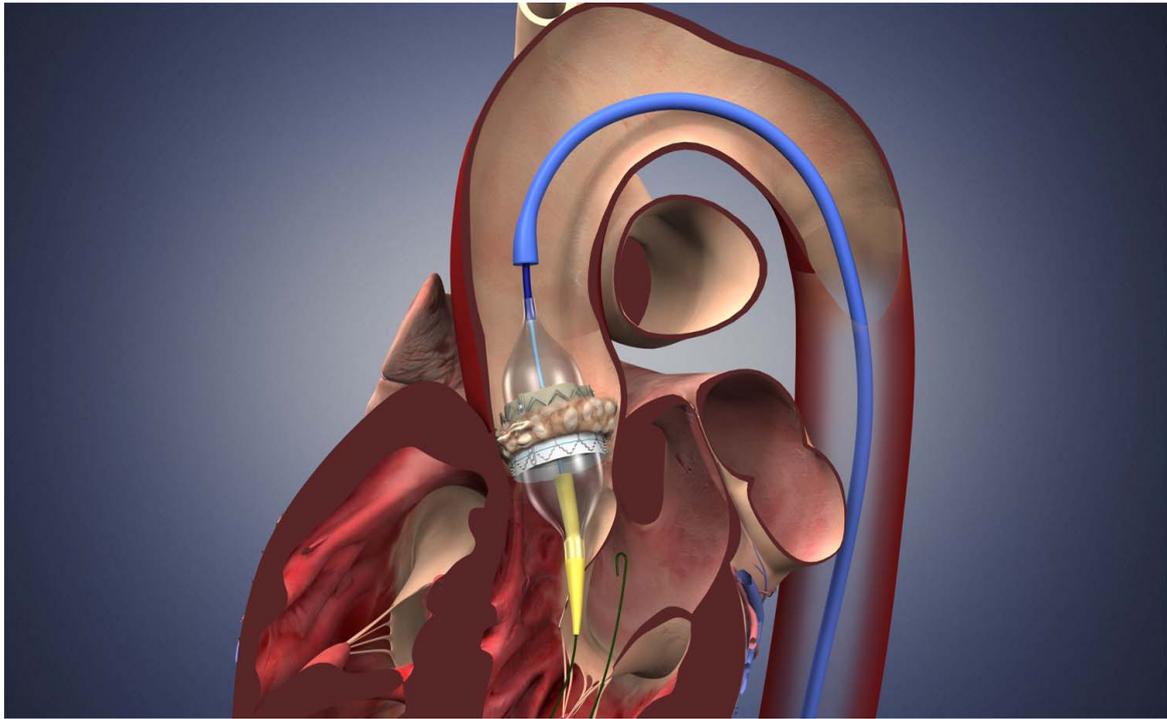
All transcatheter valve procedures were performed by a team including an interventional cardiologist (Ajay Sinhal), cardiac surgeon (Jayme Bennetts), vascular surgeon and cardiac anaesthetist with implantation experience of 80 valves prior to this study. All TAVI procedures were performed using general anaesthesia and combined angiography and transoesophageal echocardiography (TOE) guidance. Vascular access was achieved via the insertion of vascular sheaths into both femoral arteries and the left femoral vein under image guidance. A right ventricular pacing wire was placed into the apex of the right ventricle via the venous sheath. A pigtail catheter was placed in the aortic root via one of the femoral arterial sheaths. A valvuloplasty balloon was then passed via the other femoral arterial sheath and placed across the aortic valve. Balloon aortic valvuloplasty was then performed using rapid ventricular pacing. The balloon was withdrawn and the valve deployment catheter inserted. This was carefully positioned using combined echocardiographic and angiographic guidance. The valve was then deployed into the aortic annulus using rapid ventricular pacing and the deployment catheter withdrawn. Positioning and haemodynamic performance were then checked via echocardiography and

the procedure completed. Patients were then extubated and taken to intensive care for monitoring and support as necessary.

**Figure 2 - Edwards Sapien XT Transcatheter Valve**



([www.edwards.com](http://www.edwards.com))



**Figure 4: Deployment of Edwards Sapien XT Transcatheter Heart Valve via the Transfemoral Route**

([www.edwards.com](http://www.edwards.com))

### **2.3 Aortic Valve Replacement**

As per the inclusion criteria all patients recruited in the Aortic Valve Replacement (AVR) arm elected for a bioprosthesis. Three different bioprostheses were used: Medtronic Mosaic® - Medtronic Inc., Minnesota USA; St Jude Medical Epic™ and Trifecta™, St Jude Medical Inc., Minnesota. All of these valves are common, commercially available prostheses. All surgeons were experienced in their insertion and preference for type was at the discretion of the operating surgeon.

All open surgery was performed by one of three experienced cardiothoracic surgeons. Operative techniques were similar between surgeons. Before aortic cannulation, heparin was given at a dose of 300IU/kg to achieve a target activated clotting time (ACT) of 400 seconds or above before commencement of cardiopulmonary bypass. After median sternotomy, cardiopulmonary bypass was instituted using ascending aortic and two-stage right atrial cannulation. Cardiopulmonary bypass was performed utilizing roller pumps (Sorin Stockert S3 or S5), the circuit included a hard shell membrane oxygenator (Terumo RX25, Terumo Corporation, biopassive tubing (SMARxT®, Cobe Cardiovascular, Arvada, CO) and a 40 micron arterial line filter. Routine CPB protocol included non pulsatile arterial flow rate of 1.8-2.4 lpm/m<sup>2</sup>, alpha-stat pH management, gravity venous drainage, and tepid systemic temperature management (34°C). Myocardial protection was achieved by using intermittent antegrade hyperkalemiac tepid blood cardioplegia (30-36°C). An initial or induction dose was given followed by maintenance doses approximately every 20 min as required. The heart was arrested and following opening of the aorta the native aortic valve was excised and the aortic annulus debrided. The annulus was sized to the chosen prosthesis type and the new valve secured using interrupted sutures. The aorta was then closed and the patient weaned from cardiopulmonary bypass. At the end of surgery

patients were transferred to the intensive care unit (ICU) and managed according to unit protocol.

## **2.4 Cardiac Magnetic Resonance Imaging (CMR)**

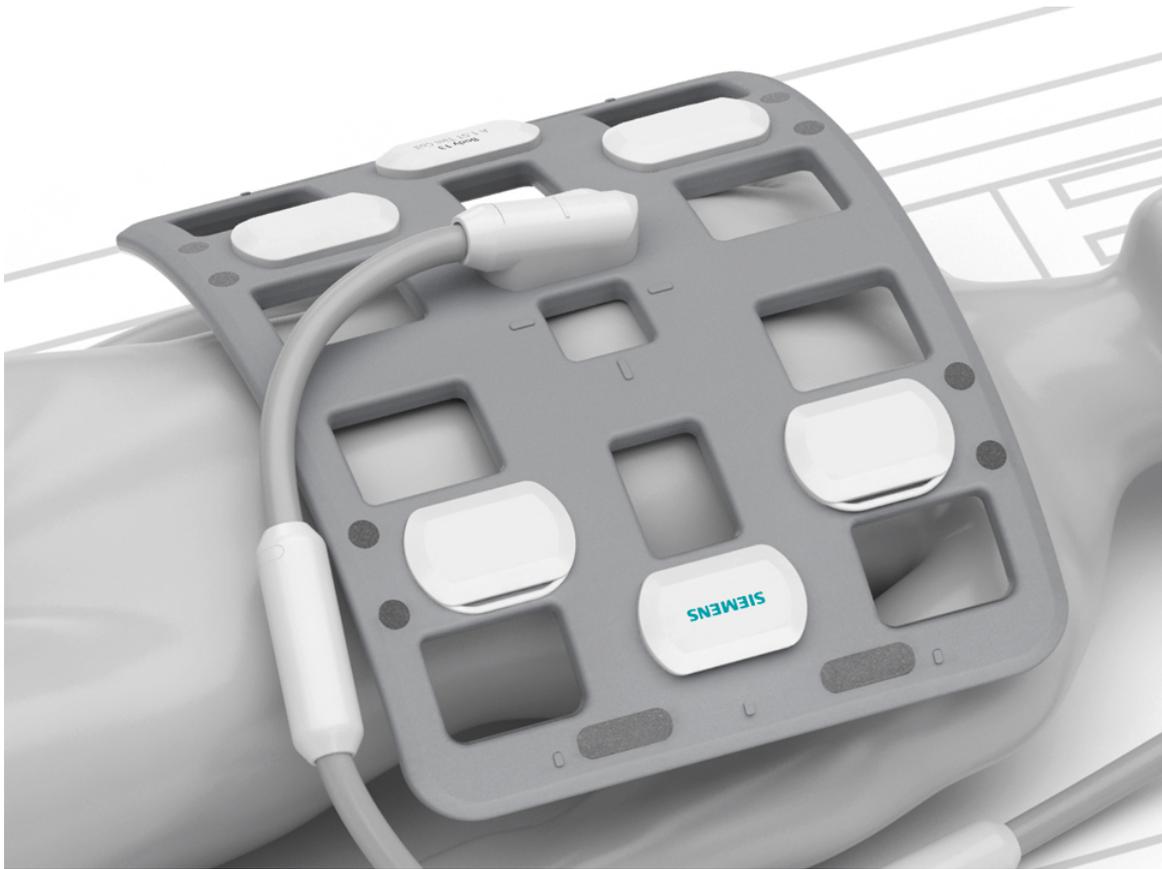
All patients underwent CMR pre- and early post-procedure. A majority of patients also underwent late CMR imaging at twelve months post-procedure. Patients were studied in a 1.5-T clinical MRI scanner (Siemens Aera) at Flinders Medical Centre. All scans were performed by an experienced CMR technician (Craig Bradbrook) and scan time was typically 45 minutes. All patients underwent a thorough pre-scan briefing to explain the CMR environment and conduct required such as breath holds. All participants were also advised they could ask for either a break or to terminate the scan at any time should they develop claustrophobia. Those patients receiving gadolinium contrast had intravenous access established via peripheral cannulation and all were dressed in a hospital gown as per hospital protocol.

A standard set of scout images were acquired to facilitate image planning. Electrocardiographically gated steady-state free precession cine images (TE/TR 1.5/3.0 ms, flip angle 60°) were acquired in 2 long-axis and 8 to 10 short-axis views. The acquisition of short-axis views began 1 cm below the level of the mitral valve insertion plane and continued in 1-cm increments through the left and right ventricles. Forward and regurgitant aortic flows were measured using through-plane phase-contrast velocity mapping (free breathing, retrospective gating). The image plane was placed  $\approx 0.5$  cm above the aortic valve at end-diastole, and maintained throughout the cardiac cycle. Commercially available gadolinium-based contrast agent (Gadovist 1.0<sup>TM</sup>, Gadobutrol,

Bayer Healthcare) was given to those patients with a glomerular filtration rate (GFR)  $>45\text{ml/min/m}^2$ . Images were acquired after a 6-minute delay with the use of an inversion-recovery segmented gradient echo sequence. LGE images were acquired in identical long- and short-axis planes to the cine images, except for the most apical short-axis slice, which was excluded. Regional wall motion analysis was performed by two blinded observers using a 16 segment AHA model and the following 0 to 4 scale: 0 – normal, 1 – mildly hypokinetic, 2- severely hypokinetic, 3 – akinetic, 4 – dyskinetic.



**Figure 5: Magnetic Resonance Imaging Scanner FMC – Siemens Aera 1.5 Tesla**



**Figure 6: Cardiac MRI Coil – Siemens 13 channel body coil**

([www.siemens.com](http://www.siemens.com))

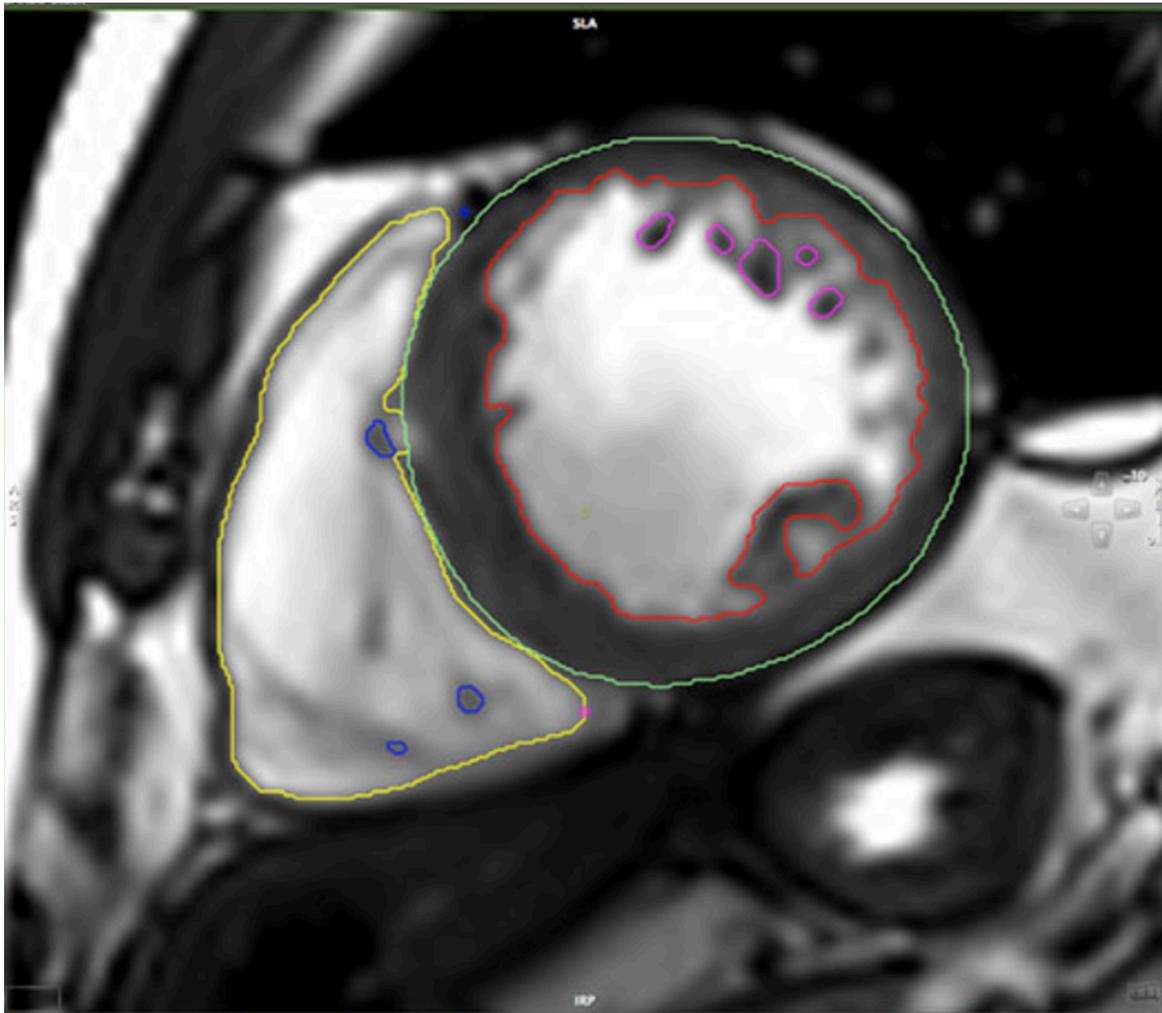
## 2.5 CMR Post-processing Analysis

All CMR scans were downloaded from the MRI scanner and uploaded to a password secured, dedicated laptop (Macbook Pro Retina, Apple, California). CMR image analysis was performed using commercially available software CVI42 (Circle Cardiovascular Imaging, Alberta, Canada). A standardized method for analyzing and calculating LV and RV volumes was used which has been previously validated [68]. All image analysis was conducted by a single observer (Gareth Crouch) and cross-checked by a second experienced observer (Suchi Grover).

Manual tracing of the endocardial and epicardial borders of successive short-axis slices at end-diastole and end-systole (image with the smallest left and right ventricular cavity) was performed. Both epicardial and endocardial borders were traced on the end-diastolic frame, with only an endocardial border on end-systolic frame. The basal slice was selected for end-diastole and for end-systole for the left ventricle when at least fifty percent of the blood volume was surrounded by myocardium. The apical slice was defined as the last slice showing blood pool. For the right ventricle, volumes below the pulmonary valve were included. From the inflow tract, RV volumes were excluded if the surrounding muscle was thin and not trabeculated, suggestive of right atrium [68].

Papillary muscles were excluded in the mass and excluded from the volume calculations. The interventricular septum was included as part of the left ventricle. From these data, the mass, ejection fraction, end-systolic and end-diastolic volumes could be calculated. Functional parameters, normalised to body surface area were also calculated. Left atrial volume was measured using the biplane area-length method utilizing CMR two and four chamber views [69]. Preoperative CMR LV short axis images were analysed for regional

wall motion abnormalities using a standard 17 segment AHA model grading wall motion from 0 - 4 according to previously published criteria [14]. Areas of myocardial infarction were quantified using the 5 SD method [70].



**Figure 7: Post processing software - CVI42, Circle CVI, showing assessment of ventricular volume and function. Yellow contour – right ventricle. Red and green contoure – left ventricle. Purple contour – papillary muscles**

## 2.6 Echocardiography

In the study of early outcomes (Chapter 3) transthoracic echocardiography (TTE) was performed pre-procedure, and post procedure concurrent with CMR, to examine LV diastolic function. Vivid E9 ultrasound machines were used and analysed offline using EchoPAC PC Version 7 (General Electric-Vingmed Ultrasound, Milwaukee, WI, USA). Transmitral E- and A-wave velocities were measured using pulse wave Doppler at the mitral valve leaflet tips. Mitral E' was measured using pulse wave Tissue Doppler by positioning the sample volume at the septal mitral annulus.

In addition to the above in the comparison of CMR and TTE for assessing PAR (Chapter 4) data were analysed by 2 experienced echocardiography trained cardiologists. Aortic valve regurgitation was graded using a combined approach of semi-quantitative and qualitative parameters. For post-operative assessment this included visual assessment of the number of jets, jet width and the circumferential extent for paravalvular regurgitation, as per existing guidelines and the more recent VARC-2 criteria [71, 72]. Regurgitation was classified as none/trivial '0', mild '1', moderate '2' and severe '3' [71]. Parasternal short and long-axis views and five chamber views were used to assess the quantity and qualities of AR jets as well as the extent into the ventricle. Jet width was measured just below the ventricular side of the valve stent frame for PAR sufficient to avoid artefact and graded according to % width of the left ventricular outflow tract (LVOT). The circumferential extent (%) of PAR was assessed in the parasternal short-axis view and graded according to the following definition: none/trivial (no or pinpoint jet), mild (jet <10%), moderate (10%– 29%) and severe ( $\geq 30\%$ ) [71]. Aortic flow reversal was assessed from multiple windows including suprasternal notch and sub-costal views, and used for both PAR and pre-operative AR assessment. Pre-operative AR was assessed using standard imaging

techniques [73]. Where disagreement existed between echocardiographic parameters an additional blinded assessor was utilised and a consensus reached.

## **2.7 Serum Markers**

All patients prior to receiving gadolinium (MR contrast agent), had blood analysis for serum creatinine. From the serum creatinine level creatinine clearance was calculated (Mediquations, Apple App Store) using the Cockcroft-Gault equation [74]. Those patients with a calculated creatinine clearance less than  $45\text{ml}/\text{min}/\text{m}^2$  were excluded from receiving gadolinium contrast during their CMR scan.

Pre-procedure blood was also tested for the level of N-Terminal Pro B-Type Natriuretic Peptide (NT Pro-BNP). This peptide has been validated as a marker of heart failure and was used to compare the incidence of heart failure in each group pre-procedure[75].

## **2.8 Clinical Assessment**

A 12 lead electrocardiograph (ECG) was performed on all participants pre-procedure, at the time of early CMR (<14 days) and at late follow-up (12 months).

## **2.9 Data Collection**

Clinical data were recorded on specifically designed data collection forms after being acquired directly from the patient and from the medical record. This data was then entered in a spreadsheet (Excel, Microsoft Corporation) stored on the same password protected, dedicated laptop as the CMR scans.

De-identified data files in Excel format were forwarded to the statisticians (Phil Tulley and Darryl Leong) via secure electronic transfer. These were converted to SPSS format (SPSS, IBM Corporation) and stored on password-protected computers.

## **2.10 Statistical Analysis**

The specific methods used are discussed in the relevant chapter. All statistics were performed using either SPSS® 20.00 (SPSS Inc., Chicago, IL) or STATA (StataCorp, Texas, USA). Values are expressed as mean (+/-SD) or median (interquartile range) as appropriate.

## **2.11 Ethics**

This study was approved by the Human Research Ethics Committee of Flinders Medical Centre (Approval No. 237.11, 13 July 2011) and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.



# **Chapter 3**

**Early effects of transcatheter aortic valve implantation and aortic valve replacement on myocardial function and aortic valve haemodynamics: insights from Cardiovascular Magnetic Resonance**

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**Early effects of transcatheter aortic valve implantation and aortic valve replacement on myocardial function and aortic valve haemodynamics: insights from Cardiovascular Magnetic Resonance**

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## **ABSTRACT**

### **Objectives**

There remains a paucity of mechanistic data on the effect of TAVI on early left and right ventricular function and, quantitative aortic valve regurgitation. We sought to assess and compare the early effects on myocardial function and aortic valve haemodynamics of transcatheter (TAVI) and aortic valve replacement (AVR) utilizing serial cardiovascular magnetic resonance (CMR) and echocardiography.

### **Methods**

A prospective comparison study of 47 patients with severe aortic stenosis undergoing either TAVI (26) or high risk AVR (21). CMR (for LV/RV function, LV mass, left atrial volume and aortic regurgitation) was carried out pre-procedure and early post-procedure (<14 days).

### **Results**

Groups were similar with respect to STS Score (TAVI 7.7 vs. AVR 5.9  $p=0.11$ ). Preoperative left ventricular (LVEF: TAVI  $69\% \pm 13$  vs. AVR  $73\% \pm 10$   $p=0.10$ ) and right ventricular ejection fractions (RVEF: TAVI  $61\% \pm 11$  vs. AVR  $59\% \pm 8$   $p=0.5$ ) were similar. Post-operative LVEF was preserved in both groups. In contrast, decline in RVEF was more significant in the TAVI group (61% to 54% vs. 59% to 58%,  $p=0.01$ ). Post-procedure aortic regurgitant fraction was significantly greater in the TAVI group (16% vs 4%,  $p=0.001$ ), as was left atrial size (110mls vs. 84mls,  $p=0.02$ ). Further analysis revealed a significant relationship between the increased aortic regurgitant fraction and greater left atrial size ( $p=0.006$ ), and a trend towards association between the decline in RV dysfunction and increased post-procedure AR ( $p=0.08$ ).

### **Conclusion**

There was no significant difference in early left ventricular systolic function between techniques. While RV systolic function was preserved in the AVR group, it was significantly impaired early after TAVI, possibly reflecting a clinically important pathophysiologic consequence of paravalvular aortic regurgitation.

### 3.1 INTRODUCTION

Aortic stenosis (AS) is an increasingly common condition associated with significant morbidity and mortality, and consequent public health burden [1]. Although surgical aortic valve replacement (AVR) has been the mainstay of treatment over the last 4 decades, transcatheter aortic valve implantation (TAVI) has emerged as an attractive option, especially in patients with high or prohibitive surgical risk [3, 65, 76-78]. Despite widespread clinical use there remains however, limited data on haemodynamics early post-TAVI, which may have important prognostic implications.

Paravalvular aortic regurgitation (AR) in particular has emerged as a potentially important determinant of short and medium term clinical outcomes after TAVI [2] however, there is a paucity of mechanistic data on the effect of TAVI-related AR on left and right ventricular structure and function. Furthermore, the incidence, extent and temporal sequence of myocardial reversible and irreversible injury are poorly characterized after both TAVI and AVR [20, 79]. The few studies to-date that have examined early left ventricular (LV) functional and aortic valve haemodynamic effects following TAVI have used transthoracic echocardiography (TTE), which has substantial limitations related to image quality and sensitivity, especially in a post-procedural setting [80]. Further, TTE is severely restricted in right ventricular (RV) assessment, particularly in the peri-operative setting [81].

High-resolution cardiovascular magnetic resonance (CMR) is a safe, non-invasive technique that allows serial assessment of myocardial function, and tissue characterization in the peri-procedural setting [12, 13, {Selvanayagam et al., 2004, #63922} 15, 16, 20]. Given its 3D nature and superior signal to- noise ratio, cine CMR is highly superior to 2D echocardiography and has become the “gold standard” investigation for measurement of left and right ventricular

(LV/RV) volumes, mass, and function of both normal and abnormal ventricles [17-20]. Finally, it allows quantitative assessment of both native and prosthetic aortic valve flow dynamics, including parameters such as peak velocity and regurgitant volume [21]. Using this highly accurate and reproducible technique, in a single-center prospective cohort trial, we compared the extent of perioperative LV and RV myocardial injury in patients undergoing TAVI with those undergoing high-risk AVR. Furthermore, we sought to characterize the association between post-procedure AR (as assessed by CMR) with effects on the right and left ventricle. We hypothesized that TAVI would result in significantly less LV and RV myocardial stunning compared with AVR. Furthermore, we speculated that the occurrence of paravalvular AR would be correlated with worse myocardial function post-procedure.

## **3.2 METHODS**

### **Ethics**

This study was approved by the Human Research Ethics Committee of Flinders Medical Centre (Approval No. 237.11, 13 July 2011) and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

### **Patient Selection**

Transcatheter aortic valves remain an investigational device in Australia and are approved for use in patients deemed inoperable or high-risk for AVR. Patients with severe symptomatic AS referred for intervention were assessed by the heart team, taking into consideration age, comorbidities, risk scores and frailty. A clinical decision then determined whether the individual proceeded to AVR or TAVI. TAVI patients included were all from the high-risk cohort, with inoperable patients excluded.

To limit bias, a high-risk cohort of AVR patients was selected. Inclusion criteria were euroSCORE >12 or STS score >4, age >70 years and subjective frailty assessment [82]. Additionally, patients with a pre-procedure left ventricular ejection fraction of less than 45% were excluded to maintain homogeneity in peri-procedural functional assessment.

### **Study Protocol**

Consenting patients who met selection criteria had pre-procedural investigation within 14 days of their procedure. This included biochemistry, echocardiography, and CMR. Post-procedure, patients had echocardiography and CMR within 14 days (Figure 2). All patients underwent pre-procedure coronary angiography.

### **AVR and TAVI techniques**

All open surgery was performed by experienced cardiothoracic surgeons. Techniques were similar, being standard median sternotomy and cardiopulmonary bypass with diastolic arrest achieved by antegrade tepid blood cardioplegia. Three tissue valve prostheses were used: Medtronic Mosaic® - Medtronic Inc., Minnesota USA; St Jude Medical Epic™ and Trifecta™, St Jude Medical Inc., Minnesota.

Transcatheter valve procedures were performed by an interventional cardiologist (AS) and cardiac surgeon (JB) with implantation of 80 valves prior to this study. All TAVIs were performed using combined angiography and TOE guidance. All procedures utilized the Edwards Sapien XT prosthesis (Edwards Lifesciences, California USA) deployed transfemorally.

### **CMR Protocol**

Patients were studied in a 1.5-T clinical MRI scanner (Siemens Aera), and steady-state free precession cine images (TE/TR 1.5/3.0 ms, flip angle 60°) were acquired in 2 long-axis and 8 to 10 short-axis views. The acquisition of short-axis views began 1 cm below the level of the mitral valve insertion plane and continued in 1-cm increments through the left and right ventricles.

Forward and regurgitant aortic flows were measured using through-plane phase-contrast velocity mapping (free breathing, retrospective gating). The image plane was placed ≈0.5 cm above the aortic valve at end-diastole, and maintained throughout the cardiac cycle. Commercially available gadolinium-based contrast agent (Gadovist 1.0™, Gadobutrol, Bayer Healthcare) was given to those patients with a glomerular filtration rate (GFR) >45ml/min/m<sup>2</sup>. Images were acquired after a 6-minute delay with the use of an inversion-recovery segmented

gradient echo sequence. LGE images were acquired in identical long- and short-axis planes to the cine images, except for the most apical short-axis slice, which was excluded. Regional wall motion analysis was performed by two blinded observers using a 16 segment AHA model and the following 0 to 4 scale: 0 – normal, 1 – mildly hypokinetic, 2- severely hypokinetic, 3 – akinetic, 4 – dyskinetic.

### **Post-processing Analysis**

A standardized method for analyzing and calculating LV and RV volumes was used. These methods along with their reproducibility have been previously published [83]. Analysis was performed using commercially available software CMR42 (Circle Cardiovascular Imaging, Alberta, Canada). Left atrial volume was measured using the biplane area-length method utilizing CMR two and four chamber views [69]. Preoperative CMR LV short axis images were analysed for regional wall motion abnormalities using a standard 17 segment AHA model grading wall motion from 0 - 4 according to previously published criteria [14]. Areas of myocardial infarction were quantified using the 5 SD method [70].

### **Echocardiography Protocol**

Transthoracic echocardiography (TTE) was performed pre-procedure, and post procedure concurrent with CMR, to examine LV diastolic function. Vivid E9 ultrasound machines were used and analysed offline using EchoPAC PC Version 7 (General Electric-Vingmed Ultrasound, Milwaukee, WI, USA). Transmitral E- and A-wave velocities were measured using pulse wave Doppler at the mitral valve leaflet tips. Mitral E' was measured using pulse wave Tissue Doppler by positioning the sample volume at the septal mitral annulus.

### **Coronary Angiography Analysis**

Severity of coronary artery lesions was quantified using quantitative coronary angiography (QCA) by automated software and assessed visually when not suitable for QCA. A cut-off of >50% diameter stenosis was used to classify single, double or triple vessel disease. Any lesion (>70% diameter stenosis by QCA) that was not revascularised was labelled incompletely revascularised.

### **Statistical Analysis**

Values are expressed as mean (+/-SD) or median (interquartile range) as appropriate. All values were checked for normality and the following transformations were made: pre and post LVEF (inverse), LVEDV (square root), LVESV (log), RVEF (square root), RVEDV (square root), RVESV (square root), BNP (log), regurgitant fraction (log).

Descriptive comparisons (TAVI vs. AVR) were made with independent samples t-test and the chi-square or Fisher's exact test as appropriate. Changes in indices of cardiac function were evaluated with repeated measures analysis of variance (ANOVA). The ANOVA model specified main effects for time, between group effects (TAVI vs. AVR), and interaction effect time X group. ANOVA findings were corroborated using linear mixed effects models, with patient identity incorporated as a random effect. Additionally, in ancillary analysis adjustments were made for propensity score to reduce bias due to the non-randomized TAVI allocation. Calculated with logistic regression, the propensity score determines the likelihood that a patient was treated with TAVI based on demographic and comorbid conditions. Given the small numbers, STS score was chosen as the single characteristic that represented all factors influencing preference for TAVI (e.g. age, reoperation, LV function, COPD and CVA). Given the study focus on RV systolic function, change in RVEF was analysed with repeated measures ANOVA in a full-factorial model and consideration was given to a number of indices selected a priori for their influence on RVEF (age, NT Pro-BNP, post-procedure LVEF and AR).

Covariates were entered as interaction terms (covariate X group X time) in addition to main and between group effects. The area-under-the curve for serial hs TnT measurements was calculated according to Matthews et al [84] and analysed with Mann-Whitney U test. The difference in proportion of patients with NT Pro-BNP values exceeding normal reference range of 125ng/L was analysed with Fisher's exact test. A  $p$ -value of  $\leq 0.05$  was considered significant. Statistical analyses were performed with SPSS® 20.00 (SPSS Inc., Chicago, IL) and STATA (StataCorp, Texas, USA).

### 3.3 RESULTS

#### **Baseline Clinical Characteristics**

A total of 48 patients were recruited, with one exclusion due to pacemaker implantation, leaving 47 patients - 26 TAVI and 21 AVR. The preoperative characteristics of the 2 groups were similar with regards to STS score and comorbidities (Table 1). Patients in the TAVI group were significantly older ( $80 \pm 4$  years vs.  $85 \pm 6$  years,  $p < 0.001$ ). Overall surgical risk factors were similar between cohorts. The TAVI group did have a significantly higher rate of previous cardiac surgery. All patients with prior cardiac surgery had previously undergone coronary artery bypass surgery, with coronary angiography demonstrating patent mammary artery grafts in each. There was no significant difference between groups when comparing incompletely revascularised coronary territories (TAVI 8/78 vs. AVR 3/63,  $p = 0.20$ ). All patients proceeded as clinically indicated to TAVI or AVR intended group.

There was no procedure related mortality in either group. All patients had a successful procedure and no patient in the TAVI group required conversion to AVR in the first 30 days after the procedure. Mean valve size was larger in the TAVI group ( $25.3\text{mm} \pm 1.8$  vs.  $22.6\text{mm} \pm 1.9$ ,  $p < 0.001$ ). In the surgical group the mean cardiopulmonary bypass and cross-clamp times were  $65 \pm 13$  mins and  $50 \pm 11$  mins respectively. Transcatheter patients required between 3 and 4 bursts of rapid ventricular pacing during the procedure.

## **CMR Results**

All patients completed pre- and post-procedure scans. Three patients had inadequate image quality for assessment of aortic valve flow. A total of 47 patients had pre- and post- scans (100%) with 44 (94%) having complete imaging of LV/RV volumes, function and aortic valve flow. Mean time to postoperative scan was  $4.7\pm 4$  days vs.  $5.8\pm 2$  days for TAVI and AVR patients respectively ( $p=0.14$ ).

### **Change to LV/RV Function post TAVI and AVR**

The CMR changes over time are illustrated in Table 2. LVEF was preserved post-operatively in both groups (TAVI  $68\%\pm 12$  vs. AVR  $71\%\pm 13$   $p=0.31$ ) with no significant difference in the group-time interaction ( $p=0.5$ ). There was, however, a significant difference in LV remodelling between TAVI and CMR groups. Despite similar baseline left ventricular end-diastolic volume (LVEDV) ( $129\text{ml}\pm 39$  vs.  $118\text{ml}\pm 27$  respectively,  $p=0.13$ ), LV dilatation was greater following TAVI than AVR (LVEDV  $133\text{ml}\pm 42$  vs.  $97\text{ml}\pm 21$  respectively,  $p<0.001$ ; group-time interaction  $p<0.001$ ) ( $p<0.01$ ).

Right ventricular ejection fraction (RVEF) was similar between groups pre-procedure (TAVI  $61\%\pm 11$  vs. AVR  $59\%\pm 8$   $p=0.6$ ). Unlike LVEF, RVEF decreased more in the TAVI group than the AVR group (post-procedure  $54\%\pm 13$  vs.  $58\pm 8$   $p=0.1$ ; group-time interaction  $p=0.008$ ). This difference was driven by differences in right ventricular end-systolic volume (RVESV) between the groups. Whereas baseline RVESVs were similar between TAVI and AVR groups ( $41\text{ml}\pm 24$  vs.  $40\text{ml}\pm 11$ ,  $p=0.8$ ), post-procedure RVESV was significantly larger in the TAVI group ( $51\text{ml}\pm 31$  vs.  $39\text{ml}\pm 14$ ,  $p=0.05$ ; group-time interaction  $p=0.005$ ). The significant associations between ventricular remodeling/function and procedure type remained significant after adjusting for serum pro BNP concentration.

Sensitivity analysis was performed to determine whether adjustment for propensity score altered the Cine MRI results. The LVEDV main effects were unchanged for group x time interaction ( $p=0.002$ ). The RVEF and RVESV main effects were also unchanged for group x time interaction ( $p=0.009$  and  $p=0.005$ ).

### **Changes to Left Atrial Volume**

LA volume was significantly greater at follow-up in the TAVI group compared with the AVR group ( $110\text{ml}\pm 35$  vs.  $84\text{ml}\pm 24$ ;  $p=0.02$ ). There was a trend towards more favourable reverse remodelling in the AVR group (group-time interaction  $p=0.09$ ).

### **Changes to Aortic Valve flow**

Aortic valve flow parameters on CMR are shown in Table 3. Aortic stenosis, as assessed by aortic valve (AV) peak velocity and aortic valve area (AVA) improved over time and were similar between groups. Post-procedure regurgitant fraction revealed significantly greater AR in the TAVI cohort when compared the AVR group (TAVI  $16 \pm 16\%$  vs. AVR  $4 \pm 2\%$ ,  $p=0.005$ ).

### **Myocardial Injury**

#### Regional wall motion

Thirteen (62%) AVR patients and 14 (54%) TAVI patients had normal regional wall motion in all segments pre-operatively ( $p=0.56$ ). The number of subjects in each group with three or more dysfunctional segments pre-procedure was also similar (TAVI 35%, AVR 29%,  $p=0.65$ ). In addition, there was no difference in the change in segmental wall motion between groups (group-time interaction  $p=0.42$  for wall motion score index).

#### LGE Imaging

Late gadolinium imaging was obtained pre-procedure in 81% and 86% ( $p=0.47$ ) patients and post-procedure in 76% and 86% ( $p=0.73$ ) of AVR and TAVI patients respectively. Preoperatively 9 (45%) TAVI patients and 5 (33%) AVR patients demonstrated late gadolinium enhancement in at least one LV slice ( $p=0.49$ ). Postoperatively there was new LGE in 2 (11%) TAVI patients and 2 (13%) AVR ( $p=0.72$ ).

### **Diastolic LV Function**

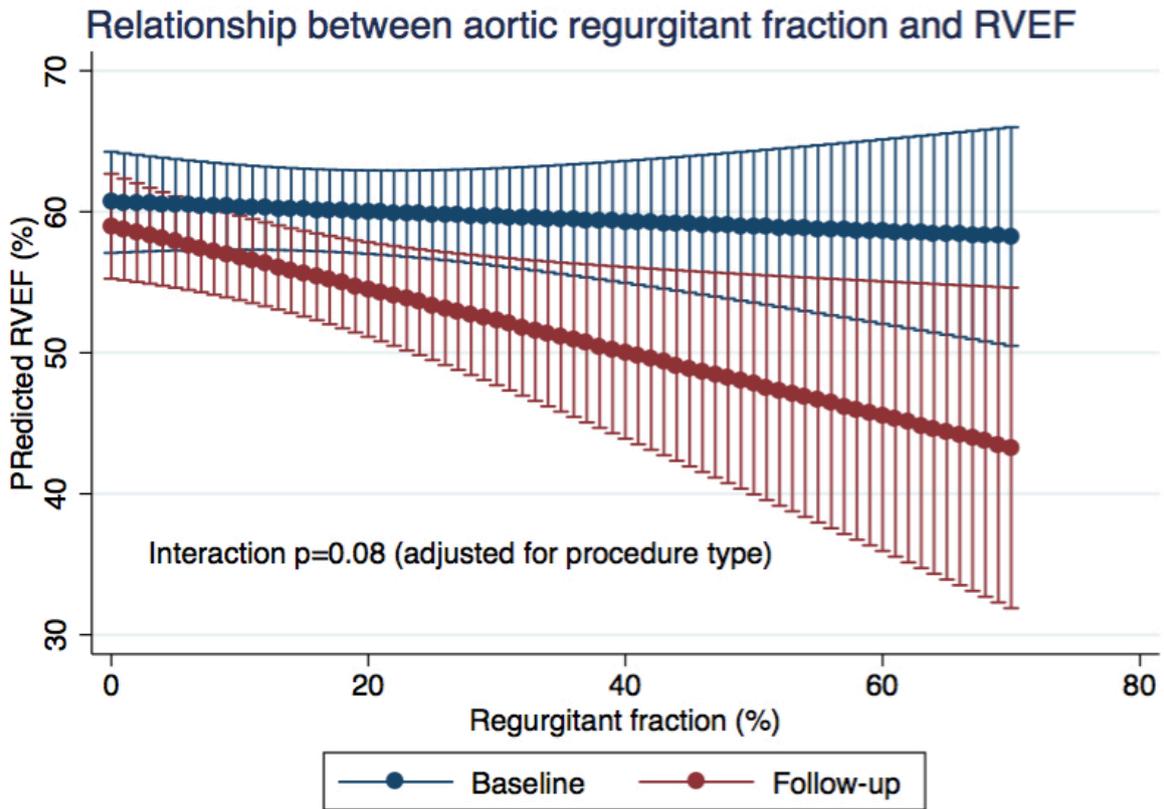
The E/E' ratio – an index of diastolic LV function - showed a significant reduction in the AVR group compared to the TAVI patients (baseline E/E' in the AVR group  $23\pm 9$  vs.  $23 \pm 8$  in the TAVI group,  $p=0.4$ ; post-procedure E/E'  $19\pm 7$  in the AVR group vs.  $23 \pm 7$ , in the TAVI group  $p=0.05$ ; group-time interaction  $p=0.03$ ).

### **Post hoc analyses**

Following the finding of right ventricular dysfunction in the TAVI cohort, ancillary statistical analyses assessed for influences on the change in RV function. There was a trend towards a negative association between regurgitant fraction and RVEF (coefficient  $-0.10$ , 95% CI  $-0.22$  to  $0.011$ ,  $p=0.08$ ) (figure 8). To further assess this finding the TAVI cohort was divided into those with mild or less paravalvular aortic regurgitation (PAR) and those with moderate or greater PAR. There was no significant difference in pre-procedure RVEF between groups ( $\leq$ mild  $62\pm 10\%$  vs.  $\geq$ moderate  $59\pm 13\%$ ,  $p=0.16$ ). Post-procedure there was significantly worse RVEF in those patients with moderate or greater PAR ( $\leq$ mild  $58\pm 11\%$  vs.  $\geq$ moderate  $48\pm 13\%$ ,  $p=0.03$ ). Additionally there was a correlation between change in aortic valve regurgitant fraction and left atrial dilatation post-procedure (coefficient  $2.65$ , 95% CI  $0.75$  to  $4.55$ ,  $p=0.006$ ), although we were unable to show a significant association between, left atrial volume and RVEF. Given the potential for ischaemia induced RV dysfunction further analysis

of the angiographic QCA data was sought. This demonstrated no difference in the number of incompletely revascularised territories ( $p=0.91$ ).

**Figure 8** - Graphic representation of the relationship between aortic regurgitation assessed by cardiovascular magnetic resonance imaging and right ventricle ejection fraction (RVEF) assessed by cardiovascular magnetic resonance imaging.





### 3.4 Discussion

The principal findings from this study are: (1). Left ventricular ejection fraction was equally well preserved in both TAVI and AVR groups early following the procedure. (2). Right ventricular systolic function was impaired early after TAVI, and potentially associated with paravalvular aortic regurgitation. Given the prognostic importance of RV dysfunction, our findings provide a potential mechanism for the recent observation of increased mortality in the setting of post TAVI aortic regurgitation.

No previous study has used CMR for serial assessment and comparison of perioperative (< 14 days) myocardial effects of AVR and TAVI. Previous CMR based studies have conducted scans at pre-procedure and 6 months post-procedure offering a mid-term outlook [85, 86]. Our study findings do not support the primary hypothesis that LV function would be better preserved by TAVI when compared to AVR. Imaging at similar intervals post-procedure revealed no significant difference in global left ventricular systolic function (LVEF). Indeed, volumetric measures of LV remodelling favoured AVR. Ewe and co-workers used TTE to assess early ( $\leq 48$  hours) post-procedure LV global function in 147 patients undergoing TAVI and compared this to a retrospective surgical control group of 99 patients. These investigators reported no significant change in LVEF in patients with baseline LVEF  $> 50\%$  who underwent TAVI [87]. Earlier work by Clavel and co-workers in a TAVI population with matched surgical controls revealed similar findings with no significant difference or change in LV function [88]. The majority of patients in our cohort had normal ( $> 55\%$ ) LVEF pre-procedure (85% of TAVI and 95% of AVR). Hence, despite the use of a more sensitive and reproducible technique (CMR), our findings on global LV function support previous echocardiographic studies. Our hypothesis was based on an expected relative decrease in LVEF in the AVR group secondary to the ischemic insult of cardiopulmonary bypass and aortic cross clamping. Our results

suggest that there is no left ventricular functional benefit of a transcatheter approach despite the absence of ischaemic insult.

There were differences in LV volumetric indices between the two groups, but contrary to our initial hypothesis, this favoured the AVR group. Postoperative LVEDV demonstrated a trend favoring the AVR group (figure 9) and this reduction was partially matched by a non-significant reduction in LVESV in the AVR group accounting for the lack of change in LVEF. The presence of reduced postoperative LVEDV can be explained simply by the reduced outflow obstruction leading to a lower end-diastolic pressure and subsequently reduced EDV. Successful resolution of aortic stenosis would be expected to have this effect in both groups however this was not seen in the TAVI group. We propose this may be an effect of acutely increased post-procedure aortic regurgitation increasing end-diastolic pressure. This may offset the benefit that aortic valve obstruction resolution provides and result in static LV volumetric measures post TAVI. Previous echocardiographic studies in TAVI cohorts have not shown any significant reduction in LVEDV (or LV end-diastolic-diameter) early post-procedure in either normal or impaired LVEF [87] [89]. The next generation of TAVI devices may confirm the mechanism of volumetric changes post TAVI should they decrease the incidence and severity of post-procedure AR.

Despite the fact that both groups had preserved RV function at baseline, there was significantly greater right ventricular dysfunction in the TAVI group. RVEF decreased significantly in the TAVI patients compared to the AVR, driven largely by an increase in RVESV in the TAVI patients. The right ventricle is recognised as a thin-walled, highly compliant structure with a primary compensatory mechanism to injury – irrespective of the cause - of dilation [90]. The AVR cohort demonstrated a decrease in both RVEDV and RVESV. To the best of our knowledge this study is the first to report a decrease in RVEF among TAVI patients when

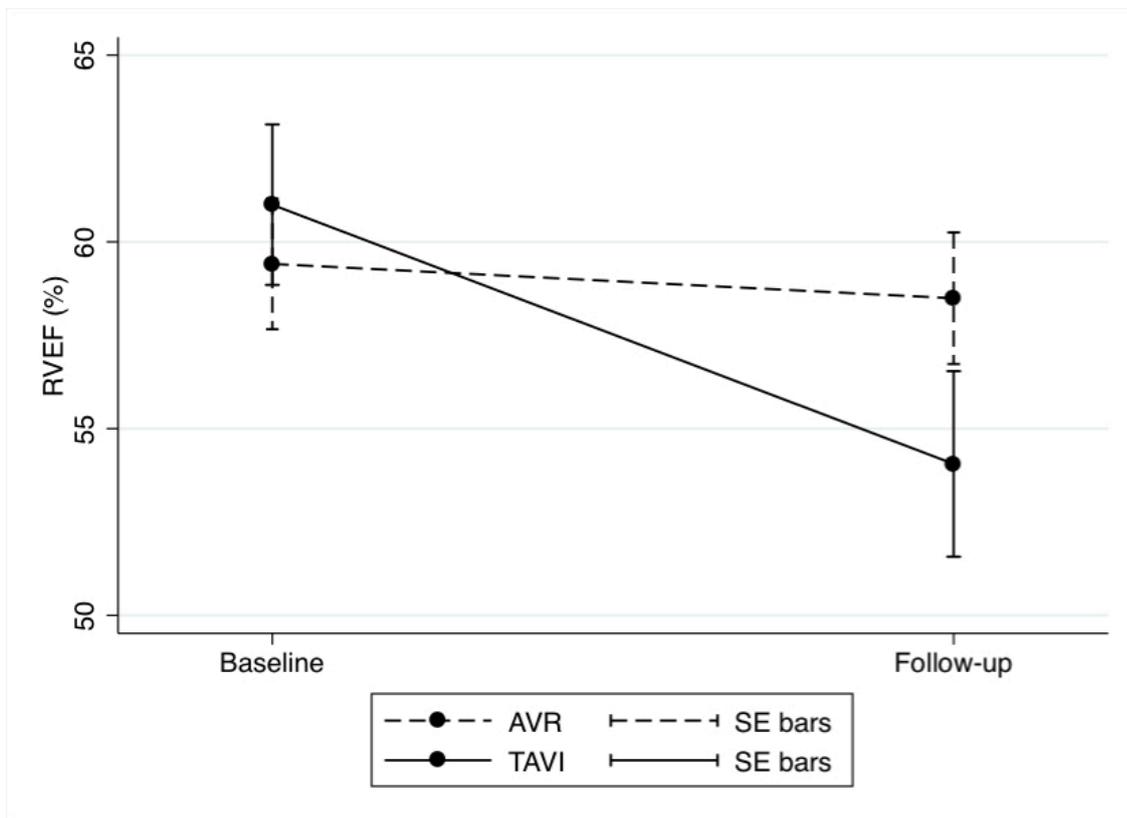
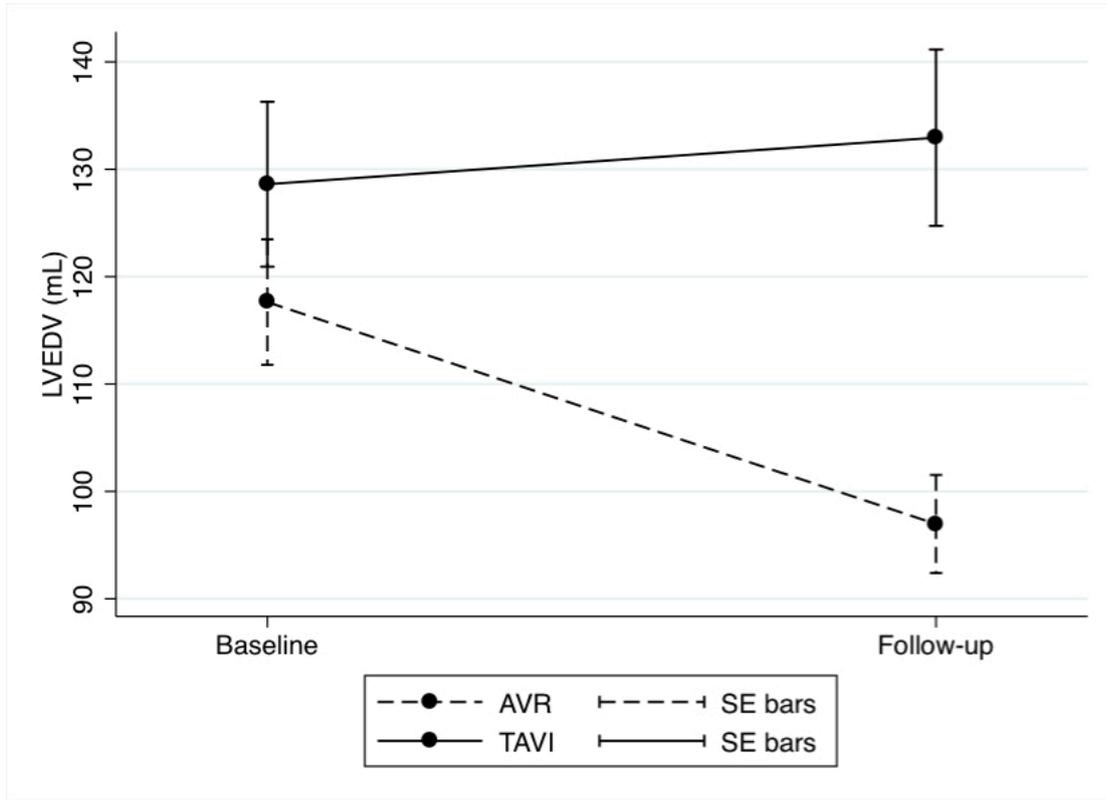
compared to AVR and tellingly the only report of CMR derived RV parameters. None of the large trials or registries has focused on RV function and several small echocardiographic studies did not report significant changes [2, 91]. Kempny et al and Zhao et al had findings contradictory to ours with echocardiography assessed RV function preserved in a TAVI cohort and decreased in a surgical control group [92, 93]. The discrepancy between findings is likely explained by several methodological limitations, namely: unmatched baseline characteristics, mixture of mechanical and bioprosthetic valves, mixture of transfemoral and transapical valves and concomitant bypass surgery in the surgical group. Moreover, the echocardiographic studies reported elsewhere largely utilised secondary measures of RV function such as TAPSE and RV strain; these are inherently difficult to assess particularly in a surgical population owing to difficult image acquisition and variances induced by pericardiotomy and septal function. Furthermore the secondary nature of measurements such as TAPSE mean that while tricuspid excursion may change post-procedure, adaptive mechanisms may maintain RVEF [81]. Finally the increased accuracy of CMR RV interrogation over echocardiographic imaging is well recognized.

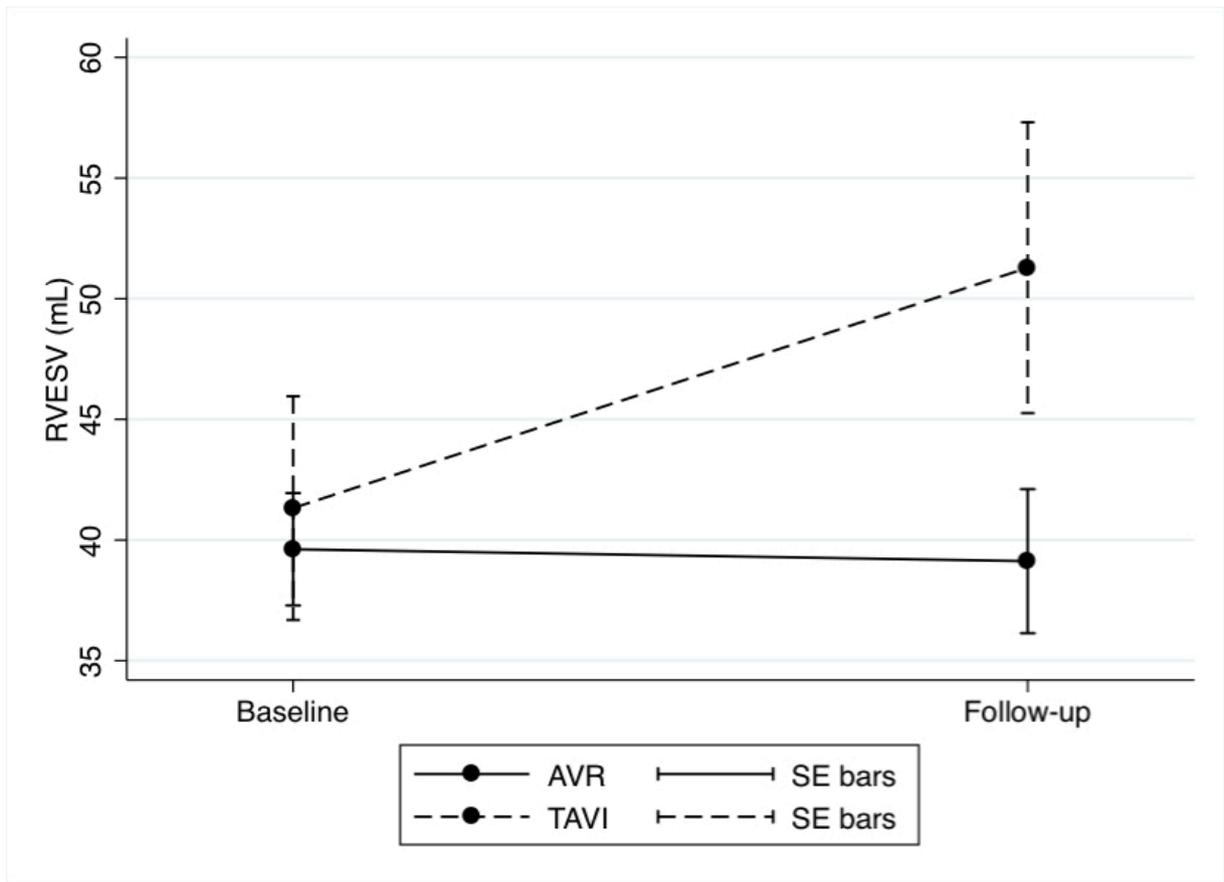
Even after propensity score adjustment and statistical reevaluation to account for the difference in NT Pro-BNP, we found a significant decrease in RVEF in the TAVI cohort compared to AVR. We thought the most likely aetiology of this dysfunction was the increased incidence and severity of paravalvular aortic regurgitation (PAR) in the TAVI group. This hypothesis was supported by ancillary analysis revealing two key findings. The first was a trend correlation between decreased post-procedure RVEF and increased aortic regurgitant fraction ( $p=0.08$ ). The second was the finding of significantly worse RVEF in those TAVI patients with moderate or greater PAR (as assessed by CMR) compared to those with mild or less. The differences in between-group post-procedure  $E/E'$  and  $E/E'$  group-time interaction, suggested a mechanism whereby increased left sided filling pressures secondary to aortic paravalvular

regurgitation potentially leading to an increased load on the right ventricle. Forsberg et al also found E/E' measurements suggested high left ventricular filling pressures in a TAVI cohort compared to surgical AVR [91]. The correlation of increased paravalvular AR to increased left atrial volume, both of which were significantly worse in the TAVI group further supports a potential mechanism for our novel finding. We postulate that the AR associated with TAVI rather than AVR results in a) increased LVEDP (the hypertrophic ventricle being less compliant), increasing left atrial pressure (E/E') and volume (LA volume) leading to b) venous/passive pulmonary hypertension which increases strain on the precariously positioned RV leading to c) reduced RVEF. Given the adverse clinical consequences of RV dysfunction in the syndrome of heart failure, this chain of events resulting in RV dysfunction offers a potential hypothesis for the important clinical observation of increased mortality in patients with AR post TAVI. This hypothesis can be further investigated with medium and long-term data examining both RV function and clinical outcomes. Importantly another potential cause of RV dysfunction, ischaemia, is unlikely given the lack of difference on coronary QCA.

Overall the irreversible myocardial injury rate was low in both groups. Our findings did not support our hypothesis that there would be a significant rate of irreversible injury in both groups. Even with a higher incidence of unrevascularised coronary artery disease in the TAVI group injury rates were similar. Despite using the highly sensitive imaging late enhancement CMR technique, we found that only 8% of TAVI and 10% of AVR patients demonstrated new irreversible myocardial injury (type V AMI) [94]. The PARTNER trial reported infarct rates of 0% and 0.6% for TAVI and AVR respectively, using clinical and biochemical data; and the higher rate reflects the higher sensitivity of the CMR techniques. The clinical significance of these small areas of myocardial injury is uncertain although our previous work in a CABG population indicates may not be entirely benign[95].

**Figure 9** - Differential effects of AVR and TAVI on remodeling and function. A - LVEDV. B – RVEF. C – RVESV. SE, Standard error.





### 3.5 Limitations

The most significant limitation of this trial is the non-randomised design of the study. Regulatory approval limitations mean TAVI remains utilised largely in the inoperable cohort, limiting randomization. As expected, the TAVI group were significantly older as they consisted of both technically and medically high-risk patients. The higher rate of reoperative cases in the TAVI group was attributable to the evolution of TAVI as the preferred treatment for patients with patent bypass grafts and multiple comorbidities. The question of increased susceptibility to periprocedural ischaemic injury in these patients was addressed with the findings that neither QCA nor RWMA assessment demonstrated differences between groups. Despite the difference in age and redo status, the groups were matched regarding STS score, as they were for CMR derived pre-procedure cardiac indices. Moreover, our attempt to adjust for risk factors using propensity score and post-hoc mixed effects regression modelling demonstrated no change in the significant findings. Overall the two groups were sufficiently matched and post-hoc analysis sufficiently robust that results seen in this study reflect the effects of procedural technique rather than pre-existing patient characteristics.

The small cohort numbers is also an obvious limitation. One of the inherent advantages of CMR over echocardiography or other modalities is the accuracy and reduced observer variability it provides, allowing smaller research cohorts. Although the ability to postulate a link between aortic regurgitation and RV dysfunction is hampered by our small numbers we believe this new observation warrants focused study in a future mechanistic study. Finally the inherent effects of cardiovascular loading states need to be considered. Patients were scanned in the early morning and all were at least 48 hours post-procedure with mean time of 6-7 days. The similarity in time of day and time post-procedure to allow for settling of fluid shifts we believe minimizes the variation from cardiovascular loading. This would minimize the impact

on factors such as left atrial volume. We do however acknowledge the difficulties in measuring left atrial volume, regardless of the methodology.

### **3.6 Conclusion**

We have shown that patients undergoing either AVR or TAVI have preserved LV function post-procedure. Furthermore although irreversible injury rates were very low in both groups, they are higher than has been reported using clinical and/or biochemical methods in large trials. However, our results demonstrate for the first time that TAVI is associated with early right ventricular dysfunction, this may reflect the higher incidence of aortic regurgitation with TAVI and explain the recent observation of increased long term mortality in this setting.



**TABLE 1. Baseline Patient Characteristics**

	<b>AVR</b>		<b>TAVI</b>		<b>P</b>
	<b>N = 21</b>		<b>N = 26</b>		
Age, (SD)	79.6	4.0	84.6	5.6	<.001
Male (SD)	8	38.1	17	65.4	.06
STS (SD)	5.9	3.4	7.7	3.9	.11
BNP (log)	1084	1783	2854	4944	<.001
Hypertension (%)	19	90.5	24	92.3	.82
Hypercholesterolemia (%)	15	71.4	21	80.8	.51
Previous MI (%)	4	19.0	6	23.1	1.0
Previous PCI (%)	3	14.3	8	30.8	.30
COPD (%)	9	42.9	11	42.3	.97
Renal impairment (%)	8	38.1	9	34.6	.81
Atrial fibrillation (%)	5	23.8	6	23.1	.95
Diabetes (%)	9	42.9	10	38.5	.76
Redo (%)	-		11	42.3	<.001
Previous CVA/TIA (%)	1	4.8	9	34.6	.02
Angina (%)	10	47.6	8	30.8	.24
NYHA Class (SD)	2.7	0.6	2.5	0.8	.14
PAH (%)	7	33.3	5	17.2	.19
Non-revascularised CAD (%)	3	14.3	8	30.8	.21

BMI – Body Mass Index; CAD – Coronary Artery Disease; COPD - Chronic Obstructive Pulmonary Disease; Neuro CVA- Previous TIA or CVA; Redo – Previous Cardiac Surgery

**Table 2. Preoperative and Postoperative Ventricular Function**

	AVR	TAVI	P For Group X Time Interaction
LVEF, %			0.48
Preop	73±9	69±13	
Postop	71±13	68±12	
LVEDV, ml			<0.01
Preop	118±27	129±39	
Postop	97±21	133±42	
LVESV, ml		±	0.54
Preop	33±15	43±28	
Postop	30±17	44±32	
RVEF %			.01
Preop	59±8	61±11	
Postop	58±8	54±13	
RVEDV, ml			0.28
Preop	98±22	104±37	
Postop	95±27	108±42	
RVESV, ml			<0.01
Preop	40±11	41±24	
Postop	39±14	51±31	

AVR = Aortic Valve Replacement; EDV = End diastolic volume; ESV – End systolic volume;

LV - Left Ventricle; RV - Right Ventricle, EF – Ejection fraction; TAVI = Transcatheter

Aortic Valve Implantation

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**Table 3. Aortic Valve Flow**

	AVR	TAVI	P For Group X Time Interaction
Forward Volume, mls			.07
Preop	59±24	57±22	
Postop	66±24	76±26	
Regurgitant Fraction %			0.51
Preop	12±16	18±15	
Postop	4.0±2.4	16±16	
Peak velocity, m/s			0.71
Preop	3.6±0.81	3.9±1.0	
Postop	2.6±0.62	2.4 ± 0.49	
AVA, cm <sup>2</sup>			.12
Preop	0.74±0.18	0.83±0.21	
Postop	1.8±0.40	1.7±0.29	

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AVR - Aortic Valve Replacement; TAVI - Transcatheter Aortic Valve Implantation;  
AVA – Aortic Valve Area

# Chapter 4

**Quantitative Assessment of Paravalvular Regurgitation Following Transcatheter Aortic Valve  
Replacement**

**Accepted for Publication in the Journal of Cardiovascular Magnetic Resonance**

## **Quantitative Assessment of Paravalvular Regurgitation Following Transcatheter Aortic Valve Replacement**

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## **ABSTRACT**

### **Background**

Paravalvular aortic regurgitation (PAR) following transcatheter aortic valve implantation (TAVI) is well acknowledged. Despite improvements, echocardiographic measurement of PAR largely remains qualitative. Cardiovascular magnetic resonance (CMR) directly quantifies AR with accuracy and reproducibility. We compared CMR and transthoracic echocardiography (TTE) analysis of AR in patients undergoing both TAVI and surgical aortic valve replacement (AVR).

### **Methods**

Forty-six patients with severe aortic stenosis undergoing TAVI (29 patients) or AVR were recruited. CMR (1.5T) and transthoracic echocardiography (TTE) were carried out pre- and <2 weeks post-operatively. The CMR protocol included regurgitant aortic flows using through-plane phase-contrast velocity. None/trivial, mild, moderate, moderate-severe and severe AR by CMR was defined as  $\leq 5\%$ , 6-15%, 16–25%, 26–48%, and  $>48\%$  regurgitant fractions respectively.

### **Results**

Post procedure imaging was conducted at a mean of 5 days for TAVI and 6 days for AVR. Pre- and post-operative left ventricular ejection fraction (LVEF) was similar. Post-procedure aortic regurgitant fraction using CMR was higher in the TAVI group (TAVI  $19\pm 15\%$  vs AVR  $4\pm 3\%$ ,  $p < 0.01$ ). Comparing CMR to TTE, 13 of 29 (45%) TAVI patients had PAR which was at least one grade more severe on CMR than TTE ( $Z = -3.00$ ,  $p = 0.003$ ). Sensitivity analysis confirmed the difference in PAR grade between TTE and CMR in the TAVI group ( $Z = -3.12$ ,  $p = 0.002$ ).

## **Conclusion**

When compared to CMR based quantitative analysis, TTE underestimated the degree of paravalvular aortic regurgitation. This underestimation may in part explain the findings of increased mortality associated with mild or greater AR by TTE in the PARTNER trial. Paravalvular aortic regurgitation post TAVI assessed as mild by TTE may in fact be more severe.

## 4.1 INTRODUCTION

There is now extensive registry and clinical trial data demonstrating an increased incidence of paravalvular aortic regurgitation (PAR) following transcatheter aortic valve implantation (TAVI), and consequently, increased mortality over short term follow-up [65, 96-99]. Despite recent improvements in both hardware and software, transthoracic echocardiographic (TTE) measurement of paravalvular aortic regurgitation (PAR) largely remains qualitative. This is particularly evident in TAVI associated PAR where patient factors such as airways disease and prior cardiac surgery limit acoustic windows, and the regurgitant jets are often multiple and eccentric making traditional TTE assessment techniques more difficult. By contrast to echocardiography, cardiovascular magnetic resonance (CMR) is able to directly quantify aortic regurgitation with high accuracy and reproducibility by using the technique of phase-contrast velocity mapping. CMR is not affected by the location, number or nature of regurgitant jets or thoracic structural patient factors, and therefore offers an ideal technique for assessing the severity of TAVI associated PAR. CMR has previously been well validated in the quantitative assessment of aortic valve regurgitation [100-103]. The assessment of regurgitation severity is identical whether intravalvular or paravalvular.

In a single-center prospective cohort trial, we assessed the extent of early PAR in TAVI and AVR patients using this highly accurate and reproducible CMR technique. We compared the CMR PAR assessment with qualitative TTE assessment, still the most widely used technique worldwide. We hypothesized that TTE would systematically underestimate the severity of PAR in TAVI patients compared with CMR. .

## **4.2 METHODS**

### **Ethics**

This study was approved by the Human Research Ethics Committee of Flinders Medical Centre (Approval No. 237.11, 13 July 2011) and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

### **Patient Selection**

Fifty patients with severe aortic stenosis undergoing either TAVI or high risk (STS Score >4, euroSCORE>10) AVR were enrolled between June 2011 and July 2013. The decision to proceed with either procedural technique was made by the heart team at our institution based on clinical assessment. Four patients were excluded due to inadequate image quality (2 TAVI, 2 AVR), leaving 29 TAVI patients and 17 AVR patients (46 total).

### **Procedure Technique**

All transcatheter valves were Edwards Sapien XT prostheses (Edwards Lifesciences, California USA) inserted via the femoral route. The AVR group all received bioprosthetic valves, access being via a median sternotomy using cardio-pulmonary bypass. Myocardial preservation and implantation techniques were similar in the surgical group. Four different tissue valve prostheses were used: Medtronic Mosaic® - Medtronic Inc, Minnesota USA; St Jude Medical Epic™ and Trifecta™, St Jude Medical Inc, Minnesota; Edwards Perimount Magna, Edwards Lifesciences, California USA.

## **Imaging Techniques**

CMR (1.5T Siemens Aera, Siemens - Germany) and transthoracic echocardiography (TTE, General Electric Vivid E9, GE Healthcare - UK) were carried out pre-operatively and within two weeks post-operatively. Both CMR and echo were performed on the same day (consecutively). in random order and analysed by separate blinded operators. The CMR protocol consisted of standard LV short and long axis views (steady state free precession images) and forward and regurgitant aortic flows using through- plane phase-contrast velocity mapping (free breathing, retrospective gating). The image plane was placed 0.5 cm above the aortic valve at end-diastole, but a position in the aortic root was maintained throughout the cardiac cycle. The severity of regurgitation by CMR regurgitant fraction was stratified according to published criteria: none/trivial <5%, mild 5.1-15%, moderate 15.1–25%, moderate-severe 25.1–48%, and severe >48% [100]. The published criteria was modified with the inclusion of the none/trivial grading equivalent to a regurgitant fraction of <5%. This modification allowed separation of those patients with clearly no or trace regurgitation from the “mild” group and was done pre-analysis. The severity gradings were used to compare CMR and TTE techniques.

Echocardiography was performed in the left decubitus position using commercially available Vivid E9 ultrasound machines (General Electric-Vingmed Ultrasound, Milwaukee, WI, USA). Data were analysed offline using EchoPAC PC Version 7 (General Electric-Vingmed Ultrasound). Paravalvular regurgitation was assessed using a combination of traditional and TAVI specific techniques. These included: jet depth; jet width; aortic flow reversal, and proportion of the circumference of the sewing ring.

Both CMR and TTE image analysis was carried out by two separate, experienced and blinded operators. Data that demonstrated significant variance were analysed by a third experienced clinician.

### **Statistical Analysis**

Data analysis was performed with SPSS<sup>®</sup> 20.0 (SPSS Inc., Chicago, IL). Descriptive comparisons between TAVI and AVR included the independent samples t-test and the chi-square statistic with Fisher's exact test as appropriate. Agreement between grade of PAR ascertained by CMR and TTE was estimated with the Wilcoxon signed-rank test, separately for preoperative and postoperative measures. All statistical tests were two-tailed, an alpha value  $p < .05$  was considered statistically significant and no adjustment was made for multiple comparisons.

### **4.3 RESULTS**

A total of 29 TAVI patients and 17 AVR patients were recruited. Although TAVI patients were older, STS scores were similar between the groups (table 4). Post-operative CMR and TTE were conducted at a mean of 5 days for TAVI and 6 days for AVR ( $p=NS$ ). Mean preoperative left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were similar in the 2 groups using CMR (AVR  $69\% \pm 18$  vs TAVI  $65\% \pm 16$ ,  $p=NS$ ). Post-operative LVEF was also similar in both groups (AVR  $68\% \pm 17$  vs TAVI  $65 \pm 16$ ,  $p=NS$ ).

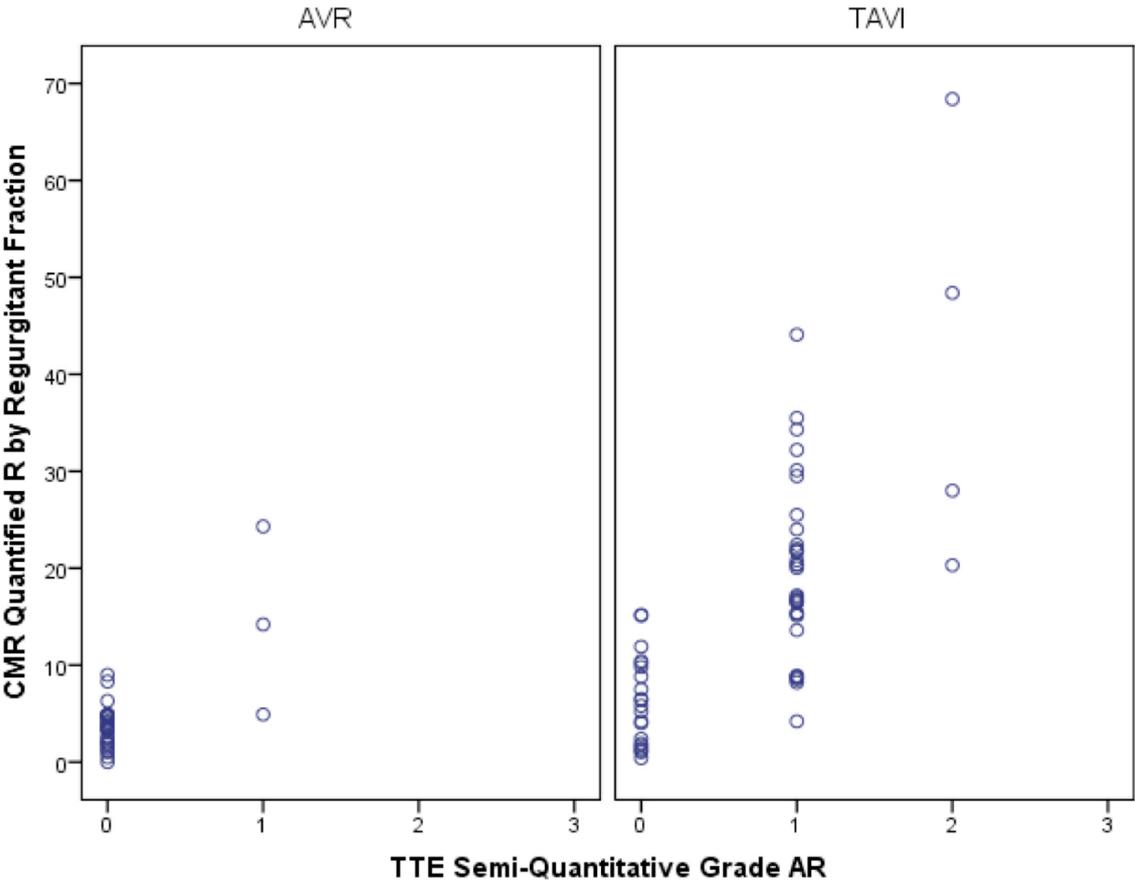
Pre-procedure aortic valve regurgitation was similar between AVR and TAVI when compared using CMR regurgitant fraction (AVR  $14\% \pm 17$  vs TAVI  $18 \pm 16$ ,  $p=NS$ ). Comparing pre-

procedure aortic valve regurgitation grades between imaging techniques, CMR and TTE demonstrated near identical mean values for TAVI (CMR  $1.6 \pm 0.7$  vs TTE  $1.6 \pm 1.0$ ,  $p = \text{NS}$ ) and AVR groups ( $1.2 \pm 1.3$  vs  $1.2 \pm 1.1$ ,  $p = \text{NS}$ ). All regurgitation was valvular in nature and less severe than the predominating stenosis. The Wilcoxon signed-rank test did not indicate a significant difference between CMR PAR grade and TTE ( $Z = -0.323$ ,  $p = .75$ ).

All post-procedure regurgitation was paravalvular in nature when assessed by TTE and intra-operative transoesophageal echocardiography (TOE). Post-procedure mean regurgitant fraction using CMR was higher in the TAVI group when compared to the AVR group (TAVI  $19\% \pm 15$  vs. AVR  $4\% \pm 3$   $p = 0.001$ ). In the AVR group only one patient had PAR which was graded mild (table 5).

In the TAVI group 52% of patients (15/29) had TTE findings which graded PAR at a different value to CMR. In 86.7% (13/15) of these cases the PAR was graded at a lesser value by TTE ( $Z = -3.00$ ,  $p = .003$ ). Sensitivity analysis confirmed that the difference in PAR grade was evident in the TAVI group ( $Z = -3.12$ ,  $p = .002$ ) but not the AVR group ( $Z = 0.00$ ,  $p = 1.0$ ). The CMR grade (continuous) is plotted by TTE grade in Figure 10.

Figure 10 – Correlation between CMR derived regurgitant fraction and TTE grade



#### 4.4 DISCUSSION

Our principle findings show that: (1) using CMR quantitative analysis there was significantly more PAR in the TAVI group than AVR group; (2) transthoracic echocardiography appears to underestimate the degree of paravalvular AR compared to quantitative CMR; (3) there was no difference between CMR and TTE in pre-procedure valvular AR.

To the best of our knowledge CMR has not been reported being used to assess early PAR in the first week post-procedure. It has been compared to echocardiography in the assessment of PAR in only one prior study of 16 patients with the CoreValve prosthesis and not in the Sapien population [104]. This study was conducted 4 weeks post-procedure and showed CMR correlated well with invasive catheter based assessment and poorly with TTE, which again appeared to underestimate the regurgitation. The finding by Sherif et al. [104] concerning consistent agreement between TTE and CMR in pre-procedure aortic valve regurgitation was corroborated here and together highlights the inherent and specific difficulties in transferring valvular regurgitation assessment techniques to the post-procedure transcatheter-paravalvular arena.

Despite the paucity of data in assessing PAR, CMR has been well validated in the assessment of aortic valvular regurgitation [21, 101]. It carries many advantages in addition to being non-invasive and highly reproducible: 1) unaffected by prosthesis artifact or thoracic patient artifact such as sternal wires or COPD, 2) direct quantitative assessment by regurgitant fraction or volume, 3) unaffected by other valvular lesions and 4) offers concurrent information on left and right ventricular size, function and pathology. These factors allow CMR to be the only quantitative and non-invasive method of assessing PAR.

Though increased PAR in the TAVI population has been previously reported this is the first quantitative assessment of PAR by CMR within the first week of procedure. The importance of CMR quantification of PAR is underscored by the finding that, after converting CMR regurgitant fraction to regurgitant grade, 93% of patients were classified as having mild or greater PAR. Moreover, the finding 62% of patients had moderate or greater PAR, exceeding reports with echo in the existing literature, likely indicates systemic underestimation of PAR by TTE. The underestimation of postoperative PAR by TTE was highlighted by several findings. Firstly, 13 of 29 TAVI patients had a regurgitant grade lower on TTE than CMR, secondly the discordance between CMR and TTE was evident by significant Wilcoxon rank-sum test, and thirdly sensitivity analysis corroborated that the difference in TTE and CMR was constrained only to the TAVI group.

Paravalvular aortic regurgitation (PAR) remains a significant and underestimated issue for transcatheter valves despite the impending arrival of third generation devices. Until TAVI can match surgical PAR rates and hence reduce associated increased mortality AVR will remain first line therapy. Furthermore, there is now a large population of patients with transcatheter valves who are affected by mild or greater PAR. It is widely accepted patients with PAR face increased morbidity and mortality and there may be an opportunity to intervene either medically or procedurally should the accurate assessment offered by CMR be broadly adopted [2]. The association of *mild* PAR with increased mortality was a particularly unexpected finding of the PARTNER trial [2]. We speculate from our findings that whilst the causality component of this finding is correct the assessment of mild PAR is not. We suggest that in fact the mild PAR is in fact moderate or greater in severity and this occurs as a result of underestimation by transthoracic echocardiography.

Considering that there is generally no agreed quantitative method for grading regurgitation in this setting by TTE this study was constrained by use of Wilcoxon signed-rank tests by contrast to more established methods such as Altman-Bland plots [64].

## 4.5 CONCLUSION

We propose that PAR can be easily, reproducibly and accurately assessed using CMR. Furthermore we offer a hypothesis that the association of mortality with mild AR in the PARTNER trial may be due to limitations of echocardiography causing underestimation of the degree of PAR.

**Table 4 – Patient Characteristics**

	<b>AVR</b> <b>n = 17</b>		<b>TAVI</b> <b>n = 29</b>		<b>P</b>
Age (SD)	79 (4)		84 (6)		<.001
Male (%)	8	41	20	69	.14
STS Score (SD)	5.9	3.4	7.7	3.9	.11
Hypertension (%)	15	88	26	90	.88
Hypercholesterolemia (%)	11	64	24	83	.17
Previous MI (%)	3	18	6	21	.80
Previous PCI (%)	3	18	10	35	.22
COPD (%)	9	53	11	38	.32
Renal impairment (%)	6	35	11	38	.86
Atrial fibrillation (%)	3	18	8	28	.45
Diabetes (%)	8	47	10	35	.73
Redo (%)	0		13	45	.001
Previous CVA/TIA (%)	3	18	9	35	.22
Angina (%)	8	47	8	28	.18
NYHA Class (SD)	2.6	0.6	2.5	0.7	.22
PAH (%)	8	47	4	14	.01
BMI – Body Mass Index; CAD – Coronary Artery Disease; COPD - Chronic Obstructive Pulmonary Disease; MI – Myocardial Infarction; Neuro CVA- Previous TIA or CVA; PAH – Pulmonary Artery Hypertension; PCI - Percutaneous coronary intervention; Redo – Previous Cardiac Surgery; STS – Society of Thoracic Surgeons Score					

**Table 5 – Comparison of PAR severity**

<b>AVR</b>	<i>None/Trivial</i>	<i>Mild</i>	<i>Moderate</i>	<i>Mod-Sev</i>	<i>Severe</i>
CMR	16 (94%)	1 (6%)	0	0	0
Echo	16 (94%)	1 (6%)	0	0	0
<b>TAVI</b>					
CMR	2 (7%)	9 (31%)	10 (35%)	6 (21%)	2 (7%)
Echo	12 (41%)	12 (41%)	3 (10%)	2 (7%)	0

# Chapter 5

**Late effects of transcatheter aortic valve implantation on myocardial function and early  
Cardiac Magnetic Resonance Predictors of Late Clinical Outcome**

**Late effects of transcatheter aortic valve implantation on myocardial function and early  
Cardiac Magnetic Resonance Predictors of Late Clinical Outcome**

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## **ABSTRACT**

### **Introduction**

Transcatheter aortic valve implantation (TAVI) is now an accepted alternative to surgical aortic valve replacement (AVR) in high risk and inoperable patients with aortic stenosis (AS). Despite large trials and registries there remains a paucity of accurate data on myocardial function late after TAVI. Furthermore, whilst clinical predictors of late outcome are well documented, periprocedural myocardial indices are less well explored. We sought to compare the late myocardial function of patients post TAVI to a control group of high-risk AVR patients. Additionally we aim to identify those peri-procedural myocardial indices which predict a worse late outcome.

### **Methods**

A prospective comparison study of patients with severe AS undergoing TAVI (n = 19) or high-risk AVR (n = 13). CMR (for LV/RV function, LV mass, and aortic regurgitation) was carried out at 12 months post-procedure in addition to pre and early post-procedure (<14 days). Also included were 37 TAVI patients who underwent peri-procedural CMR who had clinical follow-up at twelve months

### **Results**

The groups undergoing CMR late post-procedure were similar with respect to STS Score (TAVI 8.3 vs. AVR 6.5,  $p=0.11$ ), however the TAVI group were older (85 vs. 80 years,  $p<0.01$ ). Mean time to late CMR was 432 days for TAVI and 454 days for AVR ( $p=0.23$ ). Late LVEF was similar between groups ( $70\pm 13$  vs.  $73\pm 10$ ,  $p=0.28$ ) and preserved when comparing to pre-procedure. Similarly RVEF was also similar between groups ( $59\pm 12$  vs.  $59\pm 10$ ,  $p=0.37$ ) and there was no change over time. Late regurgitant fraction was notably higher in the TAVI

group ( $12\pm 8$  vs.  $5\pm 4$ ,  $p<0.01$ ) but demonstrated a reducing trend from early post procedure ( $p=0.06$ ). For the larger cohort of 37 patients with clinical follow-up to 12 months the predictors of a combined endpoint of death, MI stroke, permanent pacemaker and cardiac readmission were impaired LV function pre ( $p=0.04$ ) and early post-procedure ( $p=0.04$ ) as well as impaired RV function pre ( $p=0.02$ ) and early post-procedure ( $p=0.005$ ).

## **Conclusion**

Our findings demonstrate that both left and right ventricular function is preserved at late follow-up after both TAVI and AVR. Similar to other studies we found persistent increased rates of PAR in the TAVI group although it appeared to decrease compared to early post-procedure. The peri-procedural CMR predictors of worse late outcome include impaired left and right ventricular function pre and post-procedure but not increased immediate post-procedure regurgitant fraction.



## 5.1 Introduction

Transcatheter aortic valve implantation (TAVI) is now an accepted alternative to surgical aortic valve replacement (AVR) in high risk and inoperable patients with aortic stenosis (AS). This shift in clinical practice is supported by multiple randomised trials and large registries, which have demonstrated similar clinical outcomes [2, 76, 78, 97]. Despite these large trials there remains a paucity of accurate data on myocardial function pre- and post-procedure, and its effects on either early or late outcome. There are several reasons for this paucity of data including a focus on clinical endpoints and the limitations of echocardiography in the assessment of perioperative cardiac structure and function.

High-resolution cardiovascular magnetic resonance (CMR) is a safe, non-invasive technique that allows serial assessment of myocardial function, and tissue characterization in the peri-procedural setting [12-16]. Given its 3D nature and superior signal to- noise ratio, cine CMR is highly superior to 2D echocardiography and has become the “gold standard” investigation for measurement of left and right ventricular (LV/RV) volumes, mass, and function of both normal and abnormal ventricles. Despite numerous publications on TAVI outcomes there is still limited data on the myocardial consequences of TAVI on left ventricular (LV) function and aortic valve haemodynamics. Of the literature published, the nearly all studies use transthoracic echocardiography (TTE), with its inherent limitations related to image quality and sensitivity, especially in a post-procedural setting [80]. Furthermore, TTE is limited in the assessment of right ventricular (RV) function, particularly in the peri-operative setting[81].

We have previously published on the early effects of both TAVI and AVR on cardiac function [105]. In this study we demonstrated significantly more right ventricular dysfunction in the

TAVI group and correlated this to the degree of paravalvular leak. Paravalvular aortic regurgitation (PAR) in particular remains the Achilles heel of TAVI and an important determinant of medium term clinical outcomes after TAVI [2] however, there is a paucity of mechanistic data on the effect of TAVI-related paravalvular aortic regurgitation (PAR) on late left and right ventricular structure and function. CMR offers accurate assessment of PAR using quantitative flow velocity mapping and frequently re-grades TAVI associated PAR as more severe than the echocardiographic assessment [85, 102, 106, 107]. In this single centre prospective cohort study we endeavoured to find which CMR derived parameters of pre or early post-procedure cardiac function predicted late clinical outcome. Using a combination of cardiovascular magnetic resonance and clinical endpoints these outcomes were assessed at 12 months post-procedure and included all cause mortality, cardiac mortality, stroke, permanent pacemaker insertion, NYHA class >2, cardiac readmission and new atrial fibrillation. CMR parameters considered were LV size and function, RV size and function, and aortic valve haemodynamics. We hypothesized that right ventricular dysfunction either pre or post procedure and greater than mild PAR would be associated with a worse outcome represented by a combined MACE endpoint.

## **5.2 METHODS**

### **Ethics**

This study was approved by the Human Research Ethics Committee of Flinders Medical Centre (Approval No. 237.11, 13 July 2011) and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

### **Patient Selection**

Transcatheter aortic valves remain an investigational device in Australia and are approved for use in patients deemed inoperable or high-risk for AVR. Patients with severe symptomatic AS referred for intervention were assessed by a heart team, taking into consideration age, comorbidities, risk scores and frailty. A clinical decision then determined whether the individual proceeded to AVR or TAVI. TAVI patients included were all from the high-risk cohort, with inoperable patients excluded.

To limit bias, a high-risk cohort of AVR patients was selected. Inclusion criteria were euroSCORE >12 or STS score >4, age >70 years and subjective frailty assessment [82]. Additionally, patients with a pre-procedure left ventricular ejection fraction of less than 45% were excluded to maintain homogeneity in peri-procedural functional assessment.

### **Study Protocol**

Consenting patients who met selection criteria had pre-procedural investigation within 14 days of their procedure. This included echocardiography and CMR. Post-procedure, patients had echocardiography and CMR within 14 days (Figure 2). All patients underwent pre-procedure coronary angiography.

Late follow-up was conducted at 12 months post procedure. Patients were assessed for clinical events since their procedure with a focus on MACCE outcomes.

### **AVR and TAVI techniques**

Procedural techniques have been described previously [105]. In summary, all AVR's were conducted by experienced surgeons and all prostheses were commercially available bioprostheses. Transcatheter valve procedures were performed by an interventional cardiologist (AS) and cardiac surgeon (JB) using combined angiographic and TOE guidance. All procedures utilized the Edwards Sapien XT prosthesis (Edwards Lifesciences, California USA) deployed transfemorally.

### **CMR Protocol**

Patients were studied in a 1.5-T clinical MRI scanner (Siemens Aera), and steady-state free precession cine images (TE/TR 1.5/3.0 ms, flip angle 60°) were acquired in 2 long-axis and 8 to 10 short-axis views. The acquisition of short-axis views began 1 cm below the level of the mitral valve insertion plane and continued in 1-cm increments through the left and right ventricles.

Forward and regurgitant aortic flows were measured using through-plane phase-contrast velocity mapping (free breathing, retrospective gating). The image plane was placed  $\approx 0.5$  cm above the aortic valve at end-diastole, and maintained throughout the cardiac cycle. Commercially available gadolinium-based contrast agent (Gadovist 1.0<sup>TM</sup>, Gadobutrol, Bayer Healthcare) was given to those patients with a glomerular filtration rate (GFR)  $>45$  ml/min/m<sup>2</sup>. Images were acquired after a 6-minute delay with the use of an inversion-recovery segmented gradient echo sequence. LGE images were acquired in identical long- and short-axis planes to the cine images, except for the most apical short-axis slice, which was excluded. Regional wall

motion analysis was performed by two blinded observers using a 16 segment AHA model and the following 0 to 4 scale: 0 – normal, 1 – mildly hypokinetic, 2- severely hypokinetic, 3 – akinetic, 4 – dyskinetic.

### **Post-processing Analysis**

A standardized method for analysing and calculating LV and RV volumes was used. These methods along with their reproducibility have been previously published [83]. Analysis was performed using commercially available software CMR42 (Circle Cardiovascular Imaging, Alberta, Canada). Left atrial volume was measured using the biplane area-length method utilizing CMR two and four chamber views [69]. Preoperative CMR LV short axis images were analysed for regional wall motion abnormalities using a standard 17 segment AHA model grading wall motion from 0 - 4 according to previously published criteria [14]. Areas of myocardial infarction were quantified using the 5 SD method [70].

### **Statistical Analysis**

Values are expressed as mean (+/-SD) or median (interquartile range) as appropriate. Descriptive comparisons (TAVI vs. AVR) were made with independent samples t-test and the chi-square or Fisher's exact test as appropriate. Changes in indices of cardiac function were evaluated with repeated measures analysis of variance (ANOVA). The ANOVA model specified main effects for time, between group effects (TAVI vs. AVR), and interaction effect time X group. ANOVA findings were corroborated using linear mixed effects models, with patient identity incorporated as a random effect. A  $p$ -value of  $\leq 0.05$  was considered significant. Statistical analyses were performed with SPSS® 20.00 (SPSS Inc., Chicago, IL) and STATA (StataCorp, Texas, USA).



## 5.3 RESULTS

### Baseline Clinical Characteristics

A total of 37 patients undergoing elective TAVI who had pre- and early post-procedure CMR were eligible for clinical review at 12 months. All patients completed pre and post-procedure imaging and 12 month follow-up either clinically or from medical records. In addition 19 TAVI patients and 13 AVR patients returned for follow-up CMR at 12 months at mean periods of procedure of  $432\pm 81$  and  $454\pm 95$  days respectively ( $p=0.23$ )

Pre-procedure characteristics including comorbidities and STS score were similar (table 6) for those who underwent 12 month CMR. The TAVI cohort was significantly older (85 vs. 80 years,  $p<0.01$ ) and did have a higher incidence of previous cardiac surgery (37% vs. 0%,  $p=0.04$ ). All redo patients had previously undergone coronary artery bypass surgery. As previously published there was no difference between groups when considering the number of incompletely revascularised territories [105].

Transcatheter valve procedural success was 100%, as it was for AVR. There were no in hospital deaths in either group. No patient in the TAVI group required conversion to an open procedure during the primary admission. One patient required conversion to AVR at 3 months post-procedure for severe PAR with intractable heart failure. For those patients having CMR at twelve months mean prosthesis size was larger in the TAVI group ( $26\pm 2$  vs.  $23\pm 2$ mm,  $p<0.01$ ). Mean transcatheter valve size in the 38 patients with clinical follow-up was  $25\pm 2$ mm.

### CMR Results

In the 12 month clinical follow-up group, all patients completed pre- and post-procedure scans. Three patients had inadequate image quality for assessment of aortic valve flow. A total of 38

patients had pre- and post- scans (100%) with 35 (92%) having complete imaging of LV/RV volumes, function and aortic valve flow. Mean time to postoperative scan was  $4.7 \pm 4$  days. In those presenting for 12 month CMR scans imaging was 100% complete across both TAVI and AVR cohorts.

### **Late Change to LV/RV Function post TAVI and AVR**

The CMR derived changes in ventricular size and function over time are illustrated in Table 7. LVEF was similar pre-procedure (TAVI  $68 \pm 16$  vs.  $72 \pm 9$ ,  $p=0.20$ ) and preserved both early and late post procedure with no between group differences. Similarly LVESV was also similar between groups and preserved post-procedure. There was however a difference in post procedure LVEDV. Whilst similar pre-procedure, there were significant between group differences both early (TAVI  $126 \pm 46$  vs. AVR  $94 \pm 20$ ,  $p=0.01$ ) and late (TAVI  $122 \pm 40$  vs. AVR  $102 \pm 24$ ,  $p=0.05$ ). This was driven by a significant drop in LVEDV from pre-procedure to early post-procedure ( $p=0.04$ ) in the AVR group, which persisted at late CMR. Conversely there was no change in LVEDV from either pre to early post-procedure ( $p=0.35$ ) or pre to late post-procedure ( $p=0.45$ ) in the TAVI group. The functional and volumetric changes from early post-procedure to late post-procedure were examined and did not reveal any changes for left ventricular indices.

Right ventricular ejection fraction (RVEF) was similar between groups pre-procedure (TAVI  $60 \pm 12$  vs. AVR  $62\% \pm 6$ ,  $p=0.37$ ). Similar to LVEF, RVEF was preserved post procedure at early and late time points in both groups (TAVI pre to early  $p=0.19$ ; pre to late  $p=0.39$ ) (AVR pre to early  $p=0.20$ ; pre to late  $p=0.22$ ). There were no between group differences. Baseline RVEDV was similar between groups. There was no significant change from pre to early post-procedure or pre to late post-procedure in either the TAVI (pre to early  $p=0.19$ ; pre to late  $p=$

0.15) or AVR groups (pre to early  $p = 0.42$ ; pre to late  $p=0.15$ ). Similarly RVESV did not demonstrate any between group differences nor any change over time in either group (TAVI pre to early  $p=0.16$ ; pre to late  $p = 0.20$ ) (AVR pre to early  $p = 0.35$ ; pre to late  $p=0.09$ ). The functional and volumetric changes from early post-procedure to late post-procedure were examined and did not reveal any changes for right ventricular indices.

### **Changes to Aortic Valve flow**

Aortic valve flow parameters over each time point as measured by CMR are shown in Table 8. There was a between group difference in forward volume at late follow-up (TAVI  $75\pm 16$  vs.  $64\pm 13$ ,  $p=0.04$ ). Regurgitant fraction showed highly significant between group differences, both at early ( $p<0.01$ ) and late follow-up ( $p<0.01$ ). This was due to the decrease in mean regurgitant fraction in the AVR group (AVR pre to early  $13\pm 11$  to  $5\pm 4$ ,  $p=0.01$ ) that was not seen in the TAVI group (TAVI pre to early  $17\pm 16$  to  $19\pm 16$ ,  $p=0.36$ ). While the between group difference remained significant at late follow-up there was a trend towards a reduction in regurgitant fraction from early to late post-procedure in the TAVI group ( $19\pm 16$  to  $12\pm 8$ ,  $p=0.06$ ). As was expected peak velocity showed a significant drop from pre-procedure to late post-procedure in both the AVR ( $p<0.01$ ) and TAVI ( $p<0.01$ ) groups. Concurrently the aortic valve area (AVA) increased significantly for AVR ( $p<0.01$ ) and TAVI ( $p<0.01$ ).

### **Change in LV Mass**

Left ventricular mass demonstrated no between group difference at late CMR (TAVI  $138\pm 44$  vs.  $128\pm 16$ ,  $p=0.21$ ) (Table 10). When indexed to BSA, LV mass showed a trend favouring greater mass regression at late follow-up in the AVR group (TAVI  $78\pm 22$  vs. AVR  $69\pm 7$ ,  $p=0.09$ ). Comparing pre-procedure to late LV mass index demonstrated a significant decrease in the AVR group that was not present in the TAVI group (TAVI pre  $88\pm 21$  to late  $78\pm 22$   $p=0.09$  vs. AVR pre  $85\pm 19$  to late  $69\pm 7$ ,  $p<0.01$ ).

### **CMR Predictors of Late Clinical Events**

The 37 TAVI patients who had pre and early post-procedure CMR and 12 month clinical endpoints taken were examined for an association between these measures. A combined clinical endpoint was formed by including all-cause mortality, CVA/TIA, NYHA Class >II, heart failure readmission. A number of CMR indices were selected a priori for their likely impact on late outcome, and these included pre and post-procedure LVEF <50% and RVEF <50%, pre and post-procedure regurgitant fraction >20% (moderate regurgitation), and post-procedure peak AV velocity >3m/s. Impaired left ventricular function (LVEF <50%) was associated with poorer outcome both pre-procedure (p=0.04) and post-procedure (p=0.04). Similarly impaired right ventricular function was also associated with the combined endpoint pre-procedure (p=0.02) and post-procedure (p=0.005). Neither post-procedure regurgitant fraction of greater than 20% nor an AV peak velocity greater than 3m/s were associated with the clinical endpoint.

## 5.4 Discussion

The principal findings from this study are: (1) Left ventricular ejection fraction was preserved late post-procedure in both TAVI and AVR groups despite a lack of LVEDV reverse remodelling in the TAVI group. (2) Right ventricular function and size was preserved late post procedure in both groups. (3) There was an association between both impaired left and right ventricular function and combined clinical endpoint demonstrating worse outcomes. Notably there was no association with significant paravalvular aortic regurgitation in the TAVI group. (4) There was a significantly greater reduction in left ventricular mass index in the AVR group compared to the TAVI group.

To the best of our knowledge no previous study has utilised CMR for the serial assessment of the myocardial effects of AVR and TAVI at three time points: pre-procedure, early post-procedure (<14 days) and late post-procedure (12 months). Our previous work examined a larger cohort of TAVI and high-risk AVR and examined pre and early post-procedure function [105]. Similar to our earlier work the current study found no significant differences between groups when examining left ventricular function. This was once again in contradiction to our primary hypothesis that TAVI would result in less myocardial injury and therefore would have improved post-procedure function. From the limited number of CMR studies in TAVI cohorts there is general agreement that LVEF is preserved post procedure [85, 86, 108]. Similar findings have been made in echocardiographic studies by Ewe and Clavel [87, 109].

Despite the absence of any significant change in LVEF there were differences in left ventricular indices. The AVR group demonstrated significant reverse remodelling in the form of reduced LVEDV, that would be expected after relief of AS by any means. In contrast the TAVI group showed no change in LVEDV either early or late post procedure. Whilst the

cohort size is too small to offer an associative analysis we speculate this may be due to increased incidence of PAR in the TAVI group. Regurgitant fractions were significantly greater in the TAVI group early and late post-procedure, and mechanistically this would increase end diastolic volume in the left ventricle. Our previous work also demonstrated this finding, correlating the increased PAR with left atrial size and right ventricular dysfunction [105]. Kempney et al. utilised TTE to compare outcome after AVR and TAVI and found no difference LVEDV in either group. These contradictory findings are potentially explainable by the lower sensitivity of TTE and the mixed prosthesis types used in their study. Despite the changes in LVEDV, there were no significant differences in LVESV between groups at 12 months, or within groups over time

Our hypothesis of worse right ventricular function in the TAVI group was proven in our study of early outcomes [105]. Similar to that cohort the preoperative RVEF was similar between groups in the current study. Unlike our earlier work there was no difference in RVEF between groups at either early or late time points. This was supported by a similar absence of difference in either RVEDV or RVESV. The small number of studies which have specifically studied right ventricular function have found it to be preserved at follow-up periods from 30 days to 6 months [91-93]. Although these studies agree with our current data, both are in contradiction to our early outcome study. Reasons for this finding may include: a smaller cohort size; potential follow-up bias due to patients with worse RV function requiring reoperation, dying or being too unwell to return for 12 month CMR; and use of echocardiography by other groups.

Late aortic valve flow assessment by CMR revealed persistently greater PAR in the TAVI group. This was also present at early CMR. Whilst there was no change from early to late CMR in AVR group there was a trend toward less regurgitation in the TAVI group. The reasons for this improvement are unclear. The PARTNER trial found at two years the degree of

PAR as assessed by TTE varied greatly, remaining unchanged in 46%, improving in 32% and worsening in 22% [2]. The authors did not offer any commentary on these findings. It is tempting to speculate that in our study it may be due to follow-up bias. It is now well documented that survival after TAVI is negatively impacted by PAR and there is no reason this would be different in our cohort [2, 65, 110].

Left ventricular mass regression is an important determinant of survival after aortic valve surgery for AS[111]. Our hypothesis that there would be greater mass regression in the TAVI group was not supported by our findings of greater regression in the AVR group. This hypothesis was based on the clinical observation that on average larger valve sizes were implanted via the transcatheter route compare to AVR, therefore leading to better haemodynamics and hence greater regression. Our CMR flow analysis revealed comparable peak AV velocities both early and late post-procedure. Furthermore AVA measured by planimetry was also similar between groups (table 8). From these findings it would have been reasonable to expect equivalent regression. Our finding of superior regression in the AVR group is therefore difficult to explain. One hypothesis is the increased incidence of PAR post-procedure in the TAVI group may prohibit reverse remodelling of the LV and therefore mass regression. Gavina et al. also demonstrated superior regression for AVR over TAVI at 6 months in an echocardiographic study, despite more favourable transvalvular gradients in the TAVI group[112].

The predictors of worse long-term outcome with TAVI have been increasingly documented by large studies and registries [48, 65, 76, 97, 98, 110, 113]. These have included PAR, impaired LV function, stroke and advanced heart failure (NYHA >II). Despite this plethora of clinical predictors there has been little studied regarding the cardiac specific predictors of late outcome. Our relatively small cohort size of 38 patients necessitated the use of a combined endpoint

analysis. This demonstrated an association between several CMR derived indices and worse late outcome. Both pre and post-procedure impaired LVEF were associated with worse outcomes. Furthermore pre and post-procedure RVEF was also associated with an increased incidence of the combined endpoint. Perhaps somewhat surprising was the absence of association between regurgitant fraction and worse outcome. Larger trials have demonstrated the even mild PAR is associated with increased mortality at 12 months. Our small sample size may offer some explanation for this finding.

## **5.5 Limitations**

The most significant limitations of this trial are the small sample size and the non-randomised design of the study. A significant number of patients were either unable or declined to return for late CMR. The reasons included death, pacemaker insertion, remoteness, poor health and unwilling. The loss of significant number of patients to late CMR follow-up must be recognized for its potential impact on our findings.

The non-randomised study design was inherently necessary given regulatory approval limitations. The older age of the TAVI cohort may also have impacted on results and follow-up. The higher rate of reoperative cases in the TAVI group was attributable to the evolution of TAVI as the preferred treatment for patients with patent bypass grafts and multiple comorbidities. Overall the two groups were sufficiently matched and post-hoc analysis sufficiently robust that results seen in this study reflect the effects of procedural technique rather than pre-existing patient characteristics.

## **5.6 Conclusion**

Our findings demonstrate that left ventricular function is preserved at late follow-up. Late RVEF is also preserved and similar between groups. Similar to other studies we found persistently increased rates of PAR in the TAVI group although it appeared to decrease compared to early post-procedure, however this may reflect the survival bias. Left ventricular mass regression was greater in the AVR group despite similar valvular haemodynamics. The peri-procedural CMR predictors of worse late outcome include impaired left and right ventricular function pre and post-procedure but not increased post-procedure regurgitant fraction.

**TABLE 6. Late Baseline Patient Characteristics**

	<b>TAVI</b>		<b>AVR</b>		<b>P</b>	<b>TAVI</b>	
	<b>12M</b>		<b>12M</b>			<b>12M</b>	
	<b>CMR</b>		<b>CMR</b>			<b>CLINICAL</b>	
	<b>N = 19</b>		<b>N = 13</b>			<b>N = 37</b>	
Age, (SD)	85	4	80	3	<i>&lt;0.01</i>	85	6
Male (%)	11	57.9	5	38.5	<i>0.28</i>	22	59.5
STS (SD)	8.3	5	6.5	3	<i>0.11</i>	8.1	5.0
Hypertension (%)	14	73.7	10	76.9	<i>0.84</i>	32	86.5
Hypercholesterolemia (%)	14	73.7	9	69.2	<i>0.92</i>	29	78.4
Previous MI (%)	3	15.8	1	7.7	<i>0.90</i>	7	18.9
Previous PCI (%)	7	36.8	1	7.7	<i>0.15</i>	11	29.7
COPD (%)	10	52.6	6	46.2	<i>0.72</i>	14	37.8
Renal impairment (%)	7	36.8	4	30.8	<i>0.99</i>	11	29.7
Atrial fibrillation (%)	4	21.1	2	15.4	<i>0.97</i>	11	29.7
Diabetes (%)	8	42.1	3	23.1	<i>0.46</i>	12	32.4
Redo (%)	7	36.8	0	0	<i>0.04</i>	14	37.8
Previous CVA/TIA (%)	5	26.3	1	7.7	<i>0.39</i>	12	32.4
Angina (%)	3	15.8	6	46.2	<i>0.14</i>	8	21.6
NYHA Class (SD)	2.7	0.6	2.8	0.4	<i>0.31</i>	2.6	0.7
PAH (%)	4	21.1	6	46.2	<i>0.26</i>	7	18.9

CV – Cardiovascular; NYHA – New York Heart Association; MI – Myocardial Infarction; TIA – Transient Ischaemic Attack;  
CVA – Cerebrovascular Accident; AF – Atrial Fibrillation; COPD – Chronic Obstructive Pulmonary Disease; PCI –  
Percutaneous Coronary Intervention

**Table 7. Ventricular Function Pre-Procedure, Early and Late Post-Procedure**

	<b>TAVI</b>	<b>AVR</b>	<b>P</b>
LVEF, %			
Pre	68±16	72±9	0.20
Early	69±15	70±10	0.39
Late	70±13	73±10	0.28
LVEDV, ml			
Pre	121±39	110±26	0.20
Early	126±46	94±20	0.01
Late	122±40	102±24	0.05
LVESV, ml			
Pre	42±35	30±12	0.12
Early	44±35	32±15	0.12
Late	40±31	29±15	0.12
RVEF %			
Pre	60±12	62±6	0.37
Early	57±10	59±9	0.30
Late	59±12	59±10	0.48
RVEDV, ml			
Pre	95±27	97±25	0.38
Early	105±43	95±27	0.24
Late	107±45	108±26	0.48
RVESV, ml			
Pre	39±20	37±9	0.40
Early	45±23	39±15	0.18
Late	46±32	44±14	0.42

AVR = Aortic Valve Replacement; EDV = End diastolic volume; ESV – End systolic volume;

LV - Left Ventricle; RV - Right Ventricle, EF – Ejection fraction; TAVI = Transcatheter

Aortic Valve Implantation

	<b>TAVI</b>	<b>AVR</b>	<b>P</b>
Forward Volume, mls			
Pre	52±20	56±23	0.29
Early	68±24	64±28	0.37
Late	75±16	64±13	0.04
Regurgitant Fraction %			
Preop	17±16	13±11	0.22
Postop	19±16	5±4	<0.01
Late	12±8	5±4	<0.01
Peak velocity, m/s			
Preop	3.2±0.8	3.4±0.9	0.35
Postop	2.3±0.5	2.5 ± 0.5	0.15
Late	2.4±0.5	2.2±0.3	0.21
AVA, cm <sup>2</sup>			
Preop	0.8±0.2	0.7±0.2	0.01
Postop	1.7±0.2	1.8±0.4	0.18
Late	1.8±0.2	1.8±0.2	0.50

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AVR - Aortic Valve Replacement; TAVI - Transcatheter Aortic Valve Implantation;

AVA – Aortic Valve Area

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**Table 9 – Late Clinical Endpoints**

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	<b>TAVI</b>	
	<b>N = 38</b>	
Combined Endpoint 1 (%)	19	51.4
Combined Endpoint 2 (%)	12	32.4
Mortality (%)	6	16.2
CV Mortality (%)	4	10.8
NYHA Class (SD)	1.2	0.7
MI (%)	2	5.4
TIA (%)	0	0
CVA (%)	0	0
New Renal Failure (%)	3	8.1
Cardiac Readmission (%)	5	13.5
New PPM (%)	2	5.4
New AF (%)	3	8.1
Reoperation (%)	1	2.6

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CV – Cardiovascular; NYHA – New York Heart Association; MI – Myocardial Infarction; TIA – Transient Ischaemic Attack; CVA – Cerebrovascular Accident; AF – Atrial Fibrillation

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**Table 10. Late Left Ventricular Mass**

	<b>TAVI</b>	<b>AVR</b>	<b>P</b>
LV Mass			
Pre	160±43	156±34	0.40
Early	153±44	145±28	0.28
Late	138±44	128±16	0.21
LV Mass Index BSA			
Pre	88±21	85±19	0.37
Early	84±79	79±16	0.26
Late	78±22	69±7	0.09

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AVR - Aortic Valve Replacement; TAVI - Transcatheter Aortic Valve Implantation;  
LV – Left Ventricular; BSA – Body Surface Area

# **Chapter 6**

## **Conclusion**

## 6.1 Conclusion

Our findings show that there was similar post-procedure left ventricular function in the TAVI group compared to the AVR group, contrary to our hypothesis. Similarly our second hypothesis that there would be more per-procedural myocardial injury in the AVR group was also not supported with a very low incidence in both groups. Thirdly our hypothesis that the degree of paravalvular aortic regurgitation post TAVI was underestimated by echocardiography was proven correct when it was compared to CMR regurgitant fraction. Finally we demonstrated similar outcomes of ventricular function at late follow-up and also superior left ventricular mass regression in the AVR group, an unexpected finding contrary to our hypothesis.

This thesis has demonstrated the breadth of capability CMR has in the setting of cardiac surgery. It has proven a worthy adjunct to the clinical standard of echocardiography in assessing patients pre-procedure, early post-procedure or late post-procedure. A single CMR scan yields a large amount of data pertaining to ventricular function, myocardial injury and valvular function, all in a highly accurate and reproducible manner. Despite this it will not replace echocardiography in this setting given certain limitations. These include the safety and logistic contraindications to CMR, cost, and limitations of valvular assessment. However it would be an adjunct technique to echocardiography in a number of these patients.



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## Appendices

### Patient Information Sheet and Consent Form:



Government of South Australia  
SA Health



## Participant Information Sheet

### Title:

Comparison of Reversible and Irreversible Myocardial Injury in Patients Undergoing Either Transcatheter or Open Aortic Valve Replacement: A Cardiovascular Magnetic Resonance Study

### Principal Investigator:

Professor Joseph Selvanayagam  
Department of Cardiovascular Medicine  
Flinders Medical Centre  
BEDFORD PARK SA 5042

### Invitation to Participate in Research:

You are invited to participate in this research project but you do not have to be involved, whether you wish to or not is entirely up to you. Whether you take part or not, your medical care will not be affected in any way. Please take your time to read the following information carefully.

### Selection:

You have been invited to participate in this research study because you have been diagnosed with aortic stenosis, which is the abnormal narrowing of the aortic valve in your heart. Based on a medical assessment of your surgical risk, you will have an aortic valve replacement by either open surgery through your chest, or percutaneously by a catheter that goes through a large artery in your groin. The percutaneous valve replacement is a new technique and we are still learning about how it affects the heart compared to the standard technique of open heart surgery. We aim to recruit 30 patients undergoing each method, with a total of 60 patients in this research project.

### Aim:

The aim of this study is to learn more about heart function of patients treated with aortic valve replacement, particularly the newer less invasive methods by using cardiac magnetic resonance imaging (MRI). This will give us a better understanding of the effects of the valve replacement procedure itself and the longer term outcomes of having the stenosis relieved.

### What will happen to me if I take part?

If you decide to take part in this study, you will be followed up at 3 timepoints. Baseline visit will be done before you have the valve replacement, post procedure will be done at 1-2 weeks after your valve replacement, and the final visit at 12 months post. At each of these timepoints you will undergo different tests. At the first visit a short clinical questionnaire will be completed along with a physical examination and medical history. Pulse, blood pressure, height and weight measurements will be also be obtained.

### Blood Tests

Results from routine blood tests taken at baseline and post procedure will be recorded. Just prior to the final 12 month post procedure visit a blood test of approximately 10mls (2 teaspoonsful) will be taken. This will also be to check your renal function before you have your MRI.

### Electrocardiogram (ECG)

Routine ECG will be recorded at baseline, post valve replacement and again at 12 months. This is a painless, paper recording of your heart rate and rhythm and has no risk.

### Echocardiography

This is an ultrasound of your heart and is routine care. This will be performed at all three visits. You will already have had one if not many echocardiograms. It is a non-invasive, painless way of examining the heart using ultrasound waves.

### Cardiac Magnetic Resonance Imaging (MRI)

You will have a cardiac MRI at baseline, 1-2 weeks post procedure and 6 months post procedure. MRI is a safe and painless exam that takes pictures of your heart that shows how your heart is working. There is no x-ray or radiation exposure when having a MRI. The scan takes approximately 45 minutes, where you will be lying on a flat table that is moved inside the doughnut shape of the MRI machine. If you suffer from claustrophobia, please tell the research doctor. During the MRI scan, you will hear a loud rhythmic sound, similar to that of a boat engine or drum beat. You will be asked at times to hold your breath for a maximum of 10 seconds, but you will be talked through this and can have a rest at any time. Please inform your research doctor if you have metallic items or devices in your body (cardiac pacemaker, metallic implants), or difficulty lying on your back. The research nurse or doctor will go through a safety questionnaire with you before you have the test. Your blood results will be checked to make sure your renal function is normal before you have the scan.

### Gadolinium

You will have an intravenous needle inserted to administer dye for this scan. The dye used for CMR is called gadolinium. Some minor allergic symptoms can sometimes accompany the injection of gadolinium, such as an itching sensation, and red skin. Swelling and fainting are rare occurrences. Please inform your research doctor if you are epileptic or have ever had an epileptic seizure.

**There has been a rare, severe, and potentially fatal reaction to the dye used in patients with abnormal kidney function. This has resulted in diffuse scarring of the skin, lungs, and heart. For this reason, if your kidney function is not adequate, you will not be given dye. It is theoretically possible although very rare that this adverse reaction may even occur if your kidneys function is normal.**

### **Commitment:**

If you choose to participate in this research study, you will be followed for 12 months. If you have already been discharged from hospital by 1-2 weeks post procedure, you will be asked to come back to have blood tests, an ECG, echocardiogram and cardiac MRI. You will also be asked to come back at 12 months to have blood tests, a final MRI scan of your heart, and review of any adverse events. These visits will take approximately 3 hours.

### **Benefits:**

There may be no benefit to you by taking part in this research study, but the information gathered may benefit other patients with your specific condition.

### **Risks and Adverse Effects:**

Risks from taking blood and the insertion of the intravenous needle into your vein may include a small amount of pain at the puncture site. In addition, a temporary bruise or "black and blue mark" may develop. Very rarely, the vein in which the needle has been inserted may become inflamed or infected, which can be treated.

There are no risks from the MRI as there is no radiation involved. There is a possibility that the Cardiac MRI scan may discover some (previously unknown) problem in the chest or abdomen. If this happens, you and your treating doctor will be advised and further management and testing will be done as appropriate.

### **Compensation:**

Any injuries that occur whilst taking part in this study are covered by an insurance policy. If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, compensation is not automatic and you may have to take legal action to determine whether you should be paid.

**Confidentiality:**

Your medical records will be accessed only by the study team. All records containing personal information will remain confidential and no information which could lead to your identification will be released, except as required by law.

**Publication:**

The results of this study may be published in scientific journals at a later date but your name will never appear.

**Withdrawal:**

Your participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without giving a reason. If you decide not to participate in this study, or if you withdraw from the study, you may do so freely, without affecting the standard care or treatment you will receive.

**Outcomes:**

At the end of the research project, you will be notified of the outcome of the study.

**Expenses and Payments:**

You will not receive any payment for participation in this study apart from compensation for reasonable travel costs for visits made during the study.

**Contact:**

If you would like any further information on this study, or this research, or in the event of a study related injury, you may contact:

Professor Joseph Selvanayagam on 8404 2195

**Complaints:**

This study has been reviewed by the Southern Adelaide Flinders Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer on 8204 4507 or email [research.ethics@health.sa.gov.au](mailto:research.ethics@health.sa.gov.au)

## CONSENT TO PARTICIPATION IN RESEARCH

I, ..... request and  
*(first or given names)* *(last name)*  
give consent to my involvement in the research project:

### Study of Early and Late Outcomes in Transcatheter and Surgical Aortic Valve Replacement.

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

.....  
*(first or given names)* *(last name)*  
and my consent is given voluntarily.

I acknowledge that the detail(s) of the following has/have been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

1. ECG (baseline & post procedure)
2. Cardiac MRI (baseline, post procedure & 6 mths)
3. Administration of gadolinium as contrast dye during MRI (baseline, post procedure & 6 mths)
4. Echocardiogram (baseline, post procedure & 6 mths)
5. Simple Blood Tests (baseline, post procedure & 6 mths)
6. Access to Medical Records as described in patient information sheet

I have understood and am satisfied with the explanations that I have been given. I have been provided with a written information sheet. I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect. I declare that I am over the age of 16 years. I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

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Signature of Research Participant: \_\_\_\_\_ Date: \_\_\_\_\_

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I, ..... have described to .....  
the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: ..... Date: .....

Status in Project: .....

## Edwards Lifesciences Sapien

Replacement Heart Valve Product Description (Stented Tissue)				Models		Reference			
Edwards SAPIEN transcatheter heart valve				9000TFX		N/A			
<p>Non-clinical testing has demonstrated that the Edwards SAPIEN transcatheter heart valve is MR Conditional. It can be scanned safely under the following conditions:</p> <ul style="list-style-type: none"> <li>• Static magnetic field of 3 tesla or less.</li> <li>• Spatial gradient field of 720 gauss/cm or less.</li> <li>• Maximum whole-body-averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.</li> </ul> <p>In non-clinical testing, the device produced a maximum temperature increase of 0.5 °C at a maximum whole body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of MRI.</p> <p>MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device.</p> <p>The valve's stent frame is composed of stainless steel material. The nominal composition (wt. percent) of the stainless steel material used is as follows:</p>									
Chromium	Nickel	Molybdenum	Manganese	Silicon	Copper	Carbon	Phosphorus	Sulfur	Iron
17.3%	14.4%	2.53%	1.74%	0.54%	0.093%	0.026%	0.017%	0.001%	Bal

## Medtronic Mosaic

		
<p><b>CONDITIONS:</b></p> <ol style="list-style-type: none"> <li>1. Has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use. Field conditions that define the specified MR environment include field strength, spatial gradient, dB/dt (time rate of change of the magnetic field), radio frequency (RF) fields, and specific absorption rate (SAR). Additional conditions, including specific configurations of the item, may be required. The field conditions that define specific MR environment includes field strength (static field = 3.0 T or less), special gradient, radio frequency fields (Spatial Magnetic gradient field = 3.9 T/m), and specific absorption rate (SAR). Maximum whole body SAR of 1.1 w/kg for ≤ 20 minutes as read from MR System.</li> </ol>		
Valves	Model Prefixes	Conditions
AHK 7700	7700	1.
Advantage®	A7760, M7760	1.
Hall-Kaster	AHK, MHK	1.
Hancock®	242, 250, 342	1.
Hancock® II & Hancock II® Ultra	T505C, T505U, T510C	1.
Intact®	705, 805	1.
Medtronic Hall™	A7700 M7700	1.
Melody® Pulmonary Valve	PB10	1.
Mosaic® & Mosaic® Ultra	305C, 305U, 310C	1.



**Medtronic**

CardioVascular LifeLine MRI Letter rev 03.20.2011

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## St Jude Medical Biocor Epic

Non-clinical testing has demonstrated that St. Jude Medical (SJM) heart valves and annuloplasty rings can be scanned safely under the following conditions:

- Static magnetic field of 3 Tesla or less
- Spatial gradient of 525 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0-W/kg for 15 minutes of scanning

This includes the models listed below, as well as earlier models which are no longer manufactured.

<b>Mechanical Valves:</b>	<b>Tissue Valves:</b>	<b>Annuloplasty Rings:</b>
xxAGN-751*	E100-xxA-00 or E100-xxM-00*	AFR-xx
xxAGFN-756*	ESP100-xx-00*	RSAR-xx
xxAHPJ-505 or xxMHPJ-505*	B100-xxA-00 or B100-xxM-00*	SARP-xx
xxAEHPJ-505*	BSP100-xx*	TARP-xx
xxAFHPJ-505*	B10-xxA-00 or B10-xxM-00*	TAB-xx
xxAJ-501 or xxMJ-501*	B10SP-xx*	
xxAECJ-502 or xxMECJ-502*		
xxATJ-503 or xxMTJ-503*		
xxMETJ-504*		
xxA-101 or xxM-101		
xxVAVGJ-515*		
xxCAVGJ-514*		

Please note: "xx" denotes different sizes available (e.g. 23A-101).

SJM heart valves and repair devices produce a temperature rise of less than or equal to 0.5 °C under the conditions listed above. SJM heart valves and repair devices can be scanned safely under the conditions listed above. MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the SJM heart valve or repair device.

**Product Information:**

<b>Replacement Heart Valve Product Description (Stented Tissue)</b>				<b>Models</b>		<b>Reference</b>	
Carpentier-Edwards aortic and mitral porcine bioprostheses				2625, 6625		1	
Carpentier-Edwards S.A.V. aortic and mitral bioprostheses				2650, 6650		1	
Carpentier-Edwards PERIMOUNT pericardial aortic and mitral bioprostheses				2900, 6900		1	
Carpentier-Edwards PERIMOUNT Plus mitral pericardial bioprosthesis				6900P		1	
Carpentier-Edwards PERIMOUNT Theon mitral pericardial bioprosthesis				6900PTFX			
Carpentier-Edwards PERIMOUNT Magna mitral pericardial bioprosthesis				7000TFX		1	
Carpentier-Edwards bioprosthetic valved conduit				4300		1	
Testing of these devices in a magnetic field of 1.5, 3.0, and 8.0 tesla has shown that these devices are safe and compatible during MRI (magnetic resonance imaging) procedures. Valve stent frames are composed of Elgiloy, a corrosion-resistant cobalt-chromium spring alloy. Elgiloy is commonly used in implantable devices because of its rust-resistant and non-magnetic properties. The nominal composition (wt. percent) of Elgiloy is as follows:							
Cobalt	Chromium	Nickel	Molybdenum	Manganese	Carbon	Beryllium	Iron
40%	20%	15%	7%	2%	< 0.10%	< 0.10%	5.8%

<b>Replacement Heart Valve Product Description (Stented Tissue)</b>				<b>Models</b>		<b>Reference</b>	
Carpentier-Edwards PERIMOUNT Magna pericardial aortic bioprostheses				3000, 3000TFX		1	
The device has been shown not to have magnetic interactions at up to 8 tesla. It is also safe with respect to RF heating at 1.2 W/kg for up to 15 minutes. Artifacts have been determined at 1.5 tesla.							
Valve stent frames are composed of Elgiloy, a corrosion-resistant cobalt-chromium spring alloy. Elgiloy is commonly used in implantable devices because of its rust-resistant and non-magnetic properties. The nominal composition (wt. percent) of Elgiloy is as follows:							
Cobalt	Chromium	Nickel	Molybdenum	Manganese	Carbon	Beryllium	Iron
40%	20%	15%	7%	2%	< 0.10%	< 0.10%	5.8%

**Valve Safety Data from MRI safety.com**

<b>Valve</b>	<b>Conditional Status</b>	<b>Field Strength</b>	<b>Ref</b>
Medtronic Mosaic	5	1.5 & 3	Medtronic Heart Valves, Medtronic, Inc., Minneapolis, MN, Permission to publish 3-Tesla MR testing information for Medtronic Heart Valves provided by Kathryn M. Bayer, Senior Technical Consultant, Medtronic Heart Valves, Technical Service
Perimount Magna	5	1.5 & 3	
SJM Biocor	5	3	75. Edwards, M-B, Taylor KM, Shellock FG. Prosthetic heart valves: evaluation of magnetic field interactions, heating, and artifacts at 1.5 Tesla. J Magn Reson Imag 2000;12:363-369.
Edwards Sapien	6	3	
SJM Portico	5	1.5 & 3	

# MRI Safety Questionnaire



## MRI Safety Form

### IMPORTANT

This form must be completed and returned or faxed to (8204 5790) MRI before an exam time can be given.

Patient name: .....

Date of Birth: ..... Height: ..... Weight: .....

When are you next seeing the doctor who sent you for this test?: .....

Where are you seeing your doctor? .....

Have you had a previous MRI scan? .....  YES  NO

**In order to complete the examination safely we need to know the following information. Answer by ticking yes or no to each question. If you answer 'yes' to any implants we need to know the model and type of implant that you have before your arrival in the MRI Department.**

- |                                                                               |                              |                             |
|-------------------------------------------------------------------------------|------------------------------|-----------------------------|
| Have you ever been a metal worker or welder? .....                            | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Have you ever had an eye injury caused by metal? .....                        | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have, or have you ever had a cardiac pacemaker or defibrillator? ..... | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a stent? .....                                                    | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have an artificial heart valve or clip? .....                          | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have an ear or eye implant? .....                                      | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a Neuro stimulator? .....                                         | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a brain aneurysm clip? .....                                      | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have any implanted stimulation or drug infusion devices? .....         | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have an implanted prosthesis or artificial body part? .....            | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a penile prosthesis? .....                                        | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have an intra uterine device (IUD)? .....                              | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Is there a possibility you may be pregnant? .....                             | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Are you breast feeding? .....                                                 | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have any surgical clips or wire sutures? .....                         | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have an embolisation coil? .....                                       | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have an inferior vena cava (IVC) filter? .....                         | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a brain shunt tube? .....                                         | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a joint replacement or prosthesis? .....                          | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have metal pins, screws, wires or mesh in your body? .....             | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have any drug patches on your skin? .....                              | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have any shrapnel, bullets or gun shot in your body? .....             | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have any metallic foreign bodies? .....                                | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Are you claustrophobic? .....                                                 | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Have you had an operation in the last 6 weeks? .....                          | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you suffer from hypertension or high blood pressure? .....                 | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you suffer from diabetes? .....                                            | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have a history of renal disease? .....                                 | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Do you have tattoos or body piercing? .....                                   | <input type="checkbox"/> YES | <input type="checkbox"/> NO |

**If you have answered 'yes' to any of the above questions it is very important that you advise us on 8204 5750 at your earliest opportunity.**

I ..... (Person completing this form)

(if not the patient, please state your relationship to the patient) .....

Acknowledge that to the best of my understanding the above answers are true.

I do/do not consent to contrast if required. (To be discussed at Appointment)

Signature ..... Date .....

Radiographer ..... Date .....

Phase 3 complete

Safe at 1.5T

Safe at 3T

