Magnetic Resonance Imaging in the Assessment of Surgical and Transcatheter Aortic Valve Replacement:-The impact on neurocognitive function and myocardial reverse remodelling

Akhlaque Uddin

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The University of Leeds
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Abstract

Background: Aortic valve stenosis is the most common degenerative valve disease affecting the Western elderly population. Medical therapy is ineffective at treating the mechanical obstruction of blood flow. Surgical Aortic Valve Replacement (SAVR) is the current recommended treatment for symptomatic severe AS but often high risk patients are declined for this. Transcatheter Aortic Valve Implantation (TAVI) allows the percutaneous delivery of the prosthetic valve but this novel approach is associated with complications.

Aims: This thesis aims to focus on the effects of TAVI and contemporary SAVR on patients' quality of life, neurocognitive function and the left ventricular reverse remodelling.

Methods: High risk patients with symptomatic aortic stenosis were studied at baseline, 30 days, 6 month and 12 months after intervention. Cerebral MRI with diffusion weighted imaging for micro-embolism was conducted before and after intervention and again at 6 months. Cardiac MR was conducted at baseline and 6 months. Health related quality of life and a comprehensive battery of neurocognitive functional assessments were also conducted across 3 and 4 time points respectively.

Results: The incidence (54(77%) vs. 17(43%), p=0.001) and number (3.4±4.9 vs. 1.2±1.8, p=0.001) of new micro-infarcts was greater after TAVI compared to SAVR. Physical component scores (PCS) in TAVI increased after 30 days (32.1±6.6 vs. 38.9±7.0, p<0.0001) and 6m (40.4±9.3, p<0.0001); the improvement occurred later in SAVR (baseline: 34.9±10.6, 30d: 35.9±10.2, 6m: 42.8±11.2, p<0.001).

At 12 months, the majority of neurocognitive function tests did not show a significant change in the proportion of patients categorised as having impaired NCF compared to baseline in the TAVI or SAVR groups.

After 6 months, there were significant improvements in indexed end-diastolic volumes (TAVI: 100±25mls vs. 87±26mls, p<0.001; SAVR 91±28mls vs. 82±17mls, p<0.05)

Extracellular volumes were similar for both groups at baseline (range 22.8 to 24.6%). There was no significant change in ECV after 6 months (TAVI, 24.0±9% vs. 29.3±11%, SAVR, 23.8±7 vs. 23.5±9, p= 0.76).

Conclusions: TAVI patients experience higher numbers of cerebral micro-infarcts than contemporary SAVR patients, but this appears to have no effect on HRQoL; TAVI patients experienced earlier improvements in quality of life than SAVR patients. There was also no evidence of neurocognitive functional decline after TAVI using a battery of very sensitive neurocognitive function tests.

Both TAVI and SAVR improved cardiac imaging parameters with evidence of reverse LV remodelling but no change in diffuse myocardial fibrosis after 6 months.

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INTRODUCTION

1 Introduction

This thesis shall focus on adults with severe calcific aortic valve stenosis and the effect of the treatment of aortic valve stenosis by conventional surgical aortic valve replacement. The important cardiovascular and neurocognitive differences will be compared to the novel percutaneous technique of transcatheter aortic valve implantation. This section will cover the important and unique features of the aortic valve and how various disease processes can impact on its effective function.

1.1 Aortic Valve Anatomy and Function

The aortic and pulmonary valves are also known as the semi-lunar valves as they are formed at junction of the truncus and conus from mesenchymal cushions. A septum forms between the common outflow tracts thus forming the left and right ventricular outflow tracts along with further anti-clock wise rotation to take up their final anatomical positions (Teal et al., 1986).

The aortic valve is located between the left ventricular outflow tract and the proximal ascending aorta and normally has three cusps which are thin (<1mm) and mobile. The cusps are described according to the relationship with the coronary ostia: the left cusp near the left coronary artery ostium, the right cusp near the right coronary artery ostium and the non-coronary cusp which is posterior. The cusps have four histological layers; endothelium, fibrosa, spongiosa and ventricularis (Freeman and Otto, 2005). The cusps attach on to the aortic annulus which itself is composed of dense collagen that becomes part of the aortic root. Congenital variations include bicuspid, quadricuspid and unicuspid valves. In a series 932 adults undergoing valve

surgery for non-rheumatic valve disease, 54% had a congenitally malformed valve, of which 90% were bicuspid, 9% unicuspid (Roberts and Ko, 2005).

The function of the aortic valve like all valves is to maintain unidirectional blood flow and thus prevent regurgitation of the stroke volume back in to the left ventricular cavity and therefore prevent volume overloading of the ventricle. Without this mechanism the left ventricle (LV) becomes volume overloaded and persistence of this would lead to ventricular inefficiency and heart failure. The aortic valve experiences the maximal mechanical forces when closed and these forces are obligatorily transmitted to the annulus and aortic root (Thubrikar et al., 1986).

1.2 Calcific Aortic Stenosis

There are several disease processes that can affect the function of the aortic valve causing changes in the valve tips, cusps and annulus. The processes include infection, inflammation and degeneration (Otto et al., 1994). The pathological processes lead onto failure of the valve to function efficiently and this can progress to complications. For example, sub-acute endocarditis of the aortic valve can be caused by bacterial infiltration of the aortic valve. In this situation the valve can lose the ability to close causing regurgitation of blood into the left ventricle and subsequent myocardial dysfunction.

A more gradual process occurs in degenerative aortic valve disease which is the focus of this thesis. Recent evidence has shown that calcific aortic valve is not just a process of mechanical wear but involves active inflammation of the valve and proximal structures. The initial event involves endothelial injury allowing pro-inflammatory cells and lipids to enter the valve, which are followed by macrophages and oxidation of the lipids, mainly low-density

lipoprotein (LDL) (Freeman and Otto, 2005). This cascade of events continues promoting the proliferation of fibroblasts and myofibroblasts. The abnormal dense collagen depositions lead to progressive fibrosis mediated by matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP). The valvular fibrosis has evidence of angiogenesis, lipid cores and significant cellular inflammatory infiltration. This unopposed insult persists, leading to osteoblast recruitment and eventual calcification of the valve. (Rajamannan et al., 2003) The calcification is mediated by osteocalcin, bone morphogenic protein (BMP-2) and alkaline phosphatase (Kaden et al., 2004).

The combination of inflammation, fibrosis and calcification leads to thickening of the valve leaflets and progressive stiffness which effects cusp separation and leads to leaflet restriction. This culminates in the calcification of the valve tips and leaflets causing a narrowing of the valve orifice known as aortic stenosis.

1.3 Severe Aortic Stenosis

1.3.1 Clinical Presentation of Aortic Stenosis

The clinical presentation of aortic stenosis can be with exertional breathlessness (*dyspnoea*) during activities of daily living, chest pain or syncope or acute LV failure requiring emergency hospital treatment. This level of functional impairment can be graded according to the New York Heart Association (NYHA) classification between I to IV (1964). Class I patients have cardiac disease but without resulting limitations of physical activity where as in class IV there is an inability to carry on with any physical activity and symptoms can occur at rest. However, often patients can be

asymptomatic and can be diagnosed incidentally, such as routine pre-operative assessment or screening physical examination.

A general and cardiovascular system examination should be performed in all patients suspected to have aortic valve disease. A physical examination may reveal a slow rising brachial or carotid arterial pulse, a palpable thrill across the praecordium and attenuation of the second heart sound and the presence of an aortic ejection systolic murmur (systolic crescendo-decrescendo). The murmur is caused by the increased velocity of blood flow through the narrowed valve orifice and subsequent turbulence. The murmur may radiate towards the carotid artery and in the elderly may even be audible at the apical area. In addition there may be reverse splitting of the second heart sound and early signs of peripheral and pulmonary oedema(Ross and Braunwald, 1968). The intensity of the murmur does not correlate with the severity of the gradient (Munt et al., 1999).

1.3.2 Diagnosing Severe Aortic Stenosis

The severity of aortic valve stenosis is graded on: the peak and mean pressure differences (gradients) between the LV cavity and aorta, and the valve area. All of the measurements are performed using transthoracic echocardiography which uses M-mode, 2D, continuous and pulsed wave Doppler analysis.

Invasive measurement can be performed during X-ray left heart catheterisation by crossing the aortic valve and measuring LV systolic and end-diastolic pressure as well as measuring pressure during a pullback across the valve. The pressure difference here is a ‘peak to peak’ measurement and the values obtained are similar to gradients obtained by

the mean pressure gradient measured by Doppler in echocardiography. The invasive measurement, although crude does provide interventional cardiologists with immediate assessment before and after implantation of a percutaneous valve.

Severe aortic stenosis is defined by an effective orifice area (EOA) of <1cm^2, Peak velocity of more than 4ms^{-1}, Peak gradient greater than 65mmHg or a mean greater than 40mmHg and associated with early mortality and heart failure (Vahanian et al., 2012). Although all valve diseases increase with age, aortic stenosis has a higher prevalence in the elderly population. Nkomo et al reported sex-adjusted odds ratio of 2.5 (CI 2.02-3.12) with every 10 year increase in age (Nkomo et al., 2006). There was a higher incidence of aortic stenosis in men than in women even after adjusting for age. The EuroHeart survey had also found a substantial burden of valvular disease in Europe due to degenerative disease, older age and increasing life expectancy (Iung et al., 2003).

1.3.3 Natural History of Aortic Stenosis

The progression of aortic stenosis is slow and hence can take many years to become significant enough to cause symptoms in the patient. An observational echocardiographic study of 2131 patients with aortic valve thickening reported that 15.9% developed aortic stenosis with 2.5% progressing to severe aortic stenosis (Cosmi et al., 2002). The factors that determined progression in this study were age, left ventricular hypertrophy and mitral annular calcification. The predictors of progression in established aortic stenosis are age, coronary artery disease, left ventricular dysfunction, left ventricular wall thickness, valvular calcification and the presence of mitral regurgitation (Faggiano et al., 1996). The majority of these factors are

related to the early changes seen in a pressure overloaded left ventricle and represent the abnormal remodelling that occurs.

Most asymptomatic patients are followed up in a cardiology clinic every one or two years. The average annual change in mean pressure gradient is 7mmHg with a reduction in valve area on 0.1 cm^2 (Palta et al., 2000). Currently, it is difficult to accurately predict the future progression in individual patients. However, a study in 123 patients with asymptomatic aortic stenosis; the major predictor of death or aortic valve replacement by surgery was peak velocity on echocardiography (Otto et al., 1997). At 5 years, 74% of the patients had either died or undergone surgical aortic valve replacement (SAVR).

The onset of symptoms is associated with adverse outcomes and indicates valve disease progression. Severe symptomatic aortic stenosis in the elderly patient has the worst prognosis with reported mortality of 51% in those that were managed without any form of valve replacement (Leon et al., 2010a). Although age and severity of aortic stenosis carry very poor prognosis, it is important to consider other co-morbidities that can co- exist, such as ischaemic heart disease, diabetes, chronic obstructive pulmonary disease (COPD) and renal dysfunction in an elderly population.

1.3.4 Risk Evaluation in Aortic Stenosis

The evaluation of risk is important when discussing treatment strategies with patients. This involves comprehensive clinical assessment of disease severity through a combination of invasive and non-invasive testing, as well as the individual patients' co morbidities. In addition to this there are two risk scoring tools available: European System for Cardiac Operative Risk

Evaluation (EuroSCORE) and the Society of Thoracic Surgeons score STS score (Nashef et al., 1999, Wendt et al., 2009).

The logistic EuroSCORE (www.euroscore.org) predicts operative mortality in patients undergoing cardiac surgery and was developed through evaluation over 20,000 patients across Europe (Roques et al., 2003). This identified the key factors that influenced outcome which were: age, gender, Chronic Obstructive Pulmonary Disease (COPD), extra cardiac arteriopathy, neurological dysfunction, previous cardiac surgery, renal failure (creatinine >200µmolL^{-1}), the presence of endocarditis, critical preoperative state, unstable angina, LV dysfunction, recent MI and pulmonary hypertension. The operative factors were: emergency surgery, type of surgery and post MI septal rupture. The logistic EuroSCORE is most commonly used but can over estimate risk in certain patients. As a consequence EuroSCORE II has been developed but has yet to be validated in a larger contemporary population (Nashef et al., 2012).

The STS score risk calculator is more complicated and requires the input of several variables: the procedure, patient demographics, risk factors, previous cardiovascular interventions, preoperative cardiac status, echocardiographic and cardiac catheter findings. The online calculator (www.riskcalc.sts.org) provides the mortality, morbidity, length of stay and risk of stroke, renal failure, infection and re-operation.

1.3.5 Frailty and Activities of Daily Living (ADL)

The definition and measurement of frailty is difficult and has been studied in gerontology (Fried et al., 2004). Frailty is a syndrome with various factors that have to be considered which are biological, psychological and social.

Overall there is a loss of patient reserves encompassing energy levels, physical ability, cognition and health (Hogan et al., 2003). Other workers have focussed on symptoms and signs, such as unintentional weight loss, feeling exhausted, poor grip strength and slow walking speeds, as well as overall reduced physical activity (Fried et al., 2001). There is also evidence to suggest clinical judgement by physicians of frailty based on history taking and clinical examination can be useful to predict outcomes (Jones et al., 2004). A good example is the Clinical Frailty Scale derived from the Canadian Study of Health and Ageing (CSHA), which is on a 7 point measure (very fit=1, severely frail=7) (Rockwood et al., 2005).

1.4 Treatment of Aortic Stenosis

The treatment of aortic stenosis is driven by severity of symptoms and the gold standard for the treatment of severe symptomatic aortic stenosis being surgical aortic valve replacement (SAVR) (Nishimura et al., 2014). Current guidelines recommend SAVR in symptomatic patients with aortic velocity of greater than 4 metres per second and a mean pressure gradient of greater than 40 mmHg. The symptoms covered are dyspnoea, angina and syncope as well as symptoms on exercise testing. The consensus document attributes Class I recommendation and this is supported by a level of evidence: B (Nishimura et al., 2014). There is no specific drug therapy for aortic stenosis but general medical therapy is discussed below. Patients are usually identified in primary care and referred to secondary care for assessment and surveillance by a consultant cardiologist.

1.5 Medical Drug Therapy

1.5.1 Diuretics

Diuretics are drugs that act on the kidney to increase excretion of sodium chloride and water. The renin-angiotensin-aldosterone system usually regulates overall fluid and electrolyte balance. Diuretics are classed according to the site of action, such as thiazides which act on the distal tubule and loop diuretics which act on the thick ascending loop of Henle.

In the emergency situation, a patient can present in acute pulmonary oedema and respiratory failure. Intravenous loop diuretics (Furosemide) have a role in reducing the degree of alveolar oedema and can be used as maintenance oral therapy. Diuretics reduce the preload to the LV so have to be used with caution and the patients renal function should be monitored (Carabello and Paulus, 2009). The adverse metabolic effects are hypokalaemia, hypomagnesemia, hyperglycaemia and hyperuricaemia. Aldosterone antagonist have been used in aortic stenosis with a reduced risk of hypokalaemia, however a randomised control trial did not show any benefit of delaying systolic dysfunction, LV mass regression or delay progression of valve stenosis (Stewart et al., 2008).

1.5.2 Beta-blockers and Vasodilators

Beta adrenoceptor blockers act on β_1 and β_2 receptors and reduce the heart rate, myocardial contractility and have anti-arrhythmic properties (Class II or III). Generally beta blockers should be avoided in severe symptomatic aortic stenosis as the reduction in myocardial contractility may cause acute decompensation in a pressure overloaded left ventricle. In addition vasodilators, such as nitrates and hydralazine, reduce systemic blood pressure and reduce coronary blood flow and therefore have an adverse

effect in patients with severe fixed outflow obstruction (Carabello and Paulus, 2009).

ACE inhibitors block the conversion of angiotensin I to angiotensin II, the latter is a potent vasoconstrictor and also stimulates aldosterone release. Overall their effectiveness of ACE inhibition has been demonstrated in IHD and heart failure with improvement in symptoms and major adverse cardiovascular events (AIRE(1993)). However, they should be used with extreme caution in aortic stenosis as the vasodilatory properties can increase the aortic valve gradient and precipitate angina and syncope. Nevertheless, recent studies have demonstrated safety of ACE inhibitors in severe aortic stenosis (Dalsgaard et al., 2014, Bull et al., 2015). In a study of 44 patients given trandolapril, there was a reduction in LV end-systolic volume and decrease in pro-brain natriuretic peptide, and there was no adverse effects, such as severe hypotension (Dalsgaard et al., 2014). The Ramipril in Aortic Stenosis (RIAS) trial was a prospective double blinded randomised trial against placebo. The was a reduction in LV mass on cardiovascular MR imaging for the Ramipril 10mg group at 6 months and 12 months (Bull et al., 2015). More importantly there were no adverse events. Therefore, there may be a role for supervised use of ACE inhibitors in the management of patients in the early stages of disease.

1.5.3 Statins

The role of statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) in aortic stenosis has been controversial because of conflicting evidence of the effect on progression of calcific AS. Retrospective and prospective studies have shown that patients receiving statins had a slower progression of stenosis than individuals that did not (Novaro et al., 2001, Moura et al.,

2007). However, randomised controlled trial of 165 patients receiving Atorvastatin 80mg did not show a difference in the rate of stenosis after 25 months (Cowell et al., 2005). Overall, statins are used in patients with hyperlipidaemia and coronary heart disease, which often co-exists with aortic stenosis. With the above evidence the current guidelines do not recommend statin therapy for the prevention of haemodynamic progression in aortic stenosis (Nishimura et al., 2014).

In clinical practice, medical therapy is used cautiously in patients with aortic stenosis and the focus is treating the co-existing hypertension, IHD or heart failure. Overall there is a very limited role for medical drug therapy but it does provide relief of some of the symptoms, however the obstructive nature of aortic stenosis warrants relief in order to offer the best long term result.

1.6 Surgical Aortic Valve Replacement

1.6.1 History

The first ever valve replacement was performed in the aortic position by Harken et al in 1962 using a “caged ball” and this was followed later by mitral valve replacement by Starr (Harken et al., 1962, Starr and Edwards, 1961). Prior to this valve surgery was limited to performing blind commissurotomies, however this dramatically changed following the advent of cardio-pulmonary bypass and eventual cardioplegia. Early experience was obstructed with complications related to bleeding, infection and embolism which lead to death and prolonged hospital stay. As experience in the procedure and peri-operative care and post-operative intensive care units developed, the associated complications also decreased.

1.6.2 Indications

Current guidelines recommend surgical aortic valve replacement in patients with severe aortic stenosis and symptoms or in the presence of early LV systolic dysfunction or a rapid change in gradient (Vahanian et al., 2012). The evaluation of the patient is performed by the cardiologist and clinical visits can occur between 6 and 12 months. The LV function assessed by transthoracic echocardiography can prompt surgery if the ejection fraction is <50%. In a proportion of patients the reported symptoms may not be clear and therefore an exercise treadmill test can be conducted. Generally a contraindication of exercise testing is known severe aortic stenosis, however there is evidence that the test is effective at identifying patients that may benefit from surgery. (Das et al., 2005) During exercise testing a positive test is denoted by new symptoms of: syncope or angina, ECG changes of ST depression, ventricular arrhythmia or a greater than 20mmHg fall in blood pressure (Amato et al., 2001). In a study of 66 asymptomatic patients, 66.7% had a positive ETT and 6% experienced sudden cardiac death, all of which also had a positive ETT (Amato et al., 2001). This implies that the response to exercise may have important prognostic implications.

Earlier studies showed that SAVR in aortic stenosis dramatically reduced mortality when compared to medical therapy alone, with 3 year survival of 87% compared to only 21% in the medical group (Schwarz et al., 1982). Over the last 50 years standards and techniques have improved making SAVR very safe and effective. The Society of Cardiothoracic surgery of Great Britain and Ireland quote an in-hospital mortality of 1.85% and 5 year survival of over 80% for the index aortic valve replacement (Bridgewater,

2010). German registry data of 11,000 patients found the mortality to be 3% in all comers across 80 sites (Gummert et al., 2011).

1.6.3 Operative Method

Conventional SAVR is performed under a general anaesthesia and through a full median sternotomy, however minimally invasive options include mini-sternotomy can be achieved (Salenger et al., 2015). After full heparinisation the patient is placed on cardiopulmonary bypass via arterial and venous cannulae. Once stable the aorta is clamped and cardioplegia is achieved. The aorta is opened and the calcified valve cusps are excised. The surgeon uses a sizer to select the appropriate diameter of the prosthesis. Pledgets are sutured to the aortic annulus and brought through the prosthetic sewing ring. The new valve is lowered in to position and all sutures are tied. The aorta is sutured closed and the cross clamp is released. The heart is de-aired and cardioplegia is reversed and the patient is weaned off bypass. Often patient require temporary epicardial pacing and inotropic support to facilitate coming off bypass. The whole operation can take between 2 to 3 hours and patients are subsequently managed on cardiac intensive care units. Once the patient has been extubated from the respirator and has good analgesia, they are monitored for a further 24 to 48 hours and are transferred to a cardiac surgical ward. Epicardial wires remain in-situ in the event of bradycardia or evidence of damage to the native conduction system. AV conduction delays are frequent after cardiac surgery and currently the pacemaker implantation rates are between 1 to 2%, but this significantly increases with age, pre-existing conduction disease and post-operative MI (Del Rizzo et al., 1996).

1.6.4 Surgical Aortic Valve Prostheses

There are varieties of modern biological (xenograft) or mechanical prostheses available to the surgeon. Registry data from Europe and USA shows an increase in the implantation of bioprostheses over time (Brown et al., 2009) (Bridgewater et al., 2011). In the proportion of patients aged 61 to 70 years undergoing isolated SAVR there has been an increase from 49.2% to 73.1% of bioprostheses over a 5 year period (Bridgewater et al., 2011).

Mechanical valves are durable and require lifelong oral anticoagulation with warfarin, which may not be feasible or suitable for certain patients, such as those at high risk of bleeding. The novel oral anticoagulants (NOAC) are contraindicated as there is a risk of valve thrombosis, especially in the mitral valve position. These valves can be tilting discs, bi-leaflet or rarely ball and cage types. The Veteran Affair trial in 394 patients receiving a mechanical (Bjork-Shiley) spherical disc prosthesis or a bioprosthesis (Hancock porcine) had a 15 year follow up period (Hammermeister et al., 2000). This showed a reduction in mortality and primary valve failure as well as a low incidence of re-operation.

The bioprosthetic valves can be stented or stentless and can be made from porcine, bovine, equine or pericardial tissues. In addition homografts and pulmonary autografts can be used in the aortic position. Stentless bioprostheses do increase the EOA and reduce the transvalvular velocities, but do not show an improvement in clinical outcomes(Perez de Arenaza et al., 2005). Bioprosthetic valves do not require long term anticoagulation but have a higher incidence of reoperation due to degeneration. Therefore bioprosthetic valves are preferred in the elderly patient with high long term

bleeding risk and a lower likelihood of requiring re-operation in their remaining life time (Vahanian et al., 2012).

1.7 Transcatheter Aortic Valve Implantation

1.7.1 History of TAVI

Transcatheter aortic valve implantation is a percutaneous method of treating aortic stenosis in the higher risk patient group who cannot have conventional open cardiac surgery. The technique has evolved from balloon aortic valvuloplasty (BAV), which was initially used for the treatment of congenital severe aortic stenosis as a bridge to surgery. Cribier *et al* performed BAV in the 1980s as a possible therapy for calcific aortic stenosis (Cribier et al., 1986). However, this proved to provide short term symptomatic improvement, as there was a higher proportion of recurrence of stenosis and therefore BAV was performed less often and became a palliative procedure. (Lieberman et al., 1995). In 1992 Andersen *et al* performed the first TAVI in the porcine model with a self-made stainless steel stent and a porcine valve sewn on to this stent (Andersen et al., 1992). This used the retrograde transaortic method and the valve was balloon expandable as opposed to the antegrade approach that Cribier used. Early results showed minimal para-valvular regurgitation, but coronary flow was obstructed in 33% as the stent struts lay close to the ostium of the left main coronary artery. Cribier *et al* performed the first human percutaneous implantation in 2002 but used a transvenous antegrade approach which is technically demanding (Cribier et al., 2002). The transaortic retrograde approach was optimised by Webb *et al* in 2005 and uses the femoral artery as the access site and is currently the favoured approach (Webb et al., 2006).

1.7.2 Evidence for TAVI

Over 200,000 TAVI procedures have been performed worldwide and the number is likely to increase as AS becomes more prevalent (Sinning et al., 2012). The seminal paper was the Placement of Aortic Transcatheter Valve Trial (PARTNER) which randomised 358 patients who were not suitable for SAVR to either standard therapy (including BAV) or transfemoral transcatheter implantation of a balloon-expandable valve (Leon et al., 2010a). This was a highly selected patient group with a 30 day mortality risk >50% (PARTNER cohort B). In the standard arm 84% had BAV performed but mortality was significantly lower in the TAVI arm (30.7% vs. 50.7%). The incidence of major stroke (5.0% vs. 1.1%) and major vascular complications (16.2% vs. 1.1%) were higher. At 1 year the NYHA class was lower in the TAVI arm and prosthetic function had not deteriorated. The overall benefits continued after two year follow up and included improvement in all cause mortality, cardiovascular mortality and repeat hospitalisation (Makkar et al., 2012a).

The second group, (PARTNER cohort A) were considered to have high surgical risk with a predicted 30 day mortality of 15% and/or a STS score >10 and were randomised to SAVR or TAVI (Smith et al., 2011a). This trial showed a non-inferiority to SAVR with similar 30 day mortality and stroke events, however major vascular complications were significantly more frequent in the TAVI group, although the SAVR group had higher bleeding complications. At two years there was no difference in mortality rates but the presence of para-prosthetic regurgitation was associated with increased mortality (Kodali et al., 2012a).

The patients in the PARTNER trials received 1st generation Edwards-SAPIEN prosthesis which required large femoral sheaths (22F-24F) and surgical cutdowns to the artery. This may have contributed to the increased bleeding and vascular complication rates.

The UK TAVI registry database reported on 870 patients from all 25 sites (Moat et al., 2011). Two major types of prostheses were used: CoreValve (52%) and Edward-Sapien (48%) with the majority of procedures being performed trans-femorally. The mortality rates across 3 time points were: 7.1% at 30 days, 21.4% at 1 year and 26% at 2 years.

1.7.3 Vascular Access Site for TAVI

The femoral, subclavian, transapical, direct aortic and carotid approaches have been performed for TAVI (Webb et al., 2006, Grube et al., 2007, Lichtenstein et al., 2006, Latsios et al., 2010, Modine et al., 2012). The favoured arterial access route is the common femoral artery (CFA) which has to have a vessel diameter larger than 6mm on imaging usually by CT aortography. The CFA is punctured at the level of the femoral head thus aiming to avoid the bifurcation of the artery in to the deep and superficial branches. Fluroscopic guidance is recommended to locate the femoral head and some centres use ultrasound for vascular access (Garrett et al., 2005). The vessel is assessed for calcification, atheroma and tortuosity which all play a role in success and complications. Earlier TAVI prostheses required larger sheaths necessitating surgical cut down, however current sheaths are smaller and allow for percutaneous access site closure using suture based closing devices (e.g. ProStar XL or PerClose Proglide (Abbott Vascular Devices)). For example, two Proglide devices can be placed once femoral

access is achieved and the guide wire can be reintroduced to allow for the larger sheath insertion.

Transapical access is indicated in patients with severe peripheral vascular disease and requires surgical antero-lateral mini-thoracotomy at the level of the fifth/sixth intercostal space (Lichtenstein et al., 2006). A pericardiotomy is performed to allow direct myocardial puncture and subsequent dilatation to allow access of the delivery sheath. The myocardium is closed with purse string sutures and the chest wall is closed by standard surgical techniques. Currently, balloon expandable prostheses are only used as self expanding CoreValves are not used.

The subclavian approach also requires surgical cut down with the advantage of not requiring ventriculotomy as is in the apical approach (Petronio et al., 2013). This approach is used for patients with severe peripheral vascular disease and is as effective as the transfemoral approach although a direct comparison is awaited (Petronio et al., 2010). Additional caution has to be taken with patient with history of CABG with left internal mammary artery graft as this can be compromised during sheath and device manipulation. The direct aortic approach is novel but involves a small mid-clavicular or right parasternal incision to expose the ascending aorta (Latsios et al., 2010). This allows for direct puncturing for sheath insertion and device delivery but larger studies of efficacy are awaited. The carotid approach has many advantages but experience is limited to a few centres but is feasible and tolerated in patient without significant complications such as stroke (Modine et al., 2012). Recent UK TAVI registry data comparing survival between transapical, subclavian, direct aortic and transfemoral showed that

TA, DA and SC had similar high EuroSCOREs but poorer survival outcomes (Frohlich et al., 2015). TF reported 86.4% one year survival whereas DA and TA had lower survival at 75.2% and 74.7% respectively.

1.7.4 TAVI Device

Since the inception of TAVI several prostheses have achieved safety approval. The most prevalently used prostheses are described here.

1.7.4.1 CoreValve TAVI

The CoreValve TAVI (Medtronic inc, Minneapolis, Minnesota, USA) is a self expanding prosthesis made from nickel-titanium alloy (Nitinol) which anchors its self in the supra annular position. The prosthesis is crimped down into a delivery sheath and when released in position expands with a prominent radial force. (Grube et al., 2006) Cold temperatures are used during crimping of the valve and after deployment expansion will continue at body temperatures. Currently there are four 3rd generation valves available for annular sizes between 18 to 29 mm (23mm, 26mm, 29mm, and 31mm). The CoreValve is retrogradely delivered from the femoral or subclavian approach and can be post dilated but not repositioned by recompression once fully deployed.

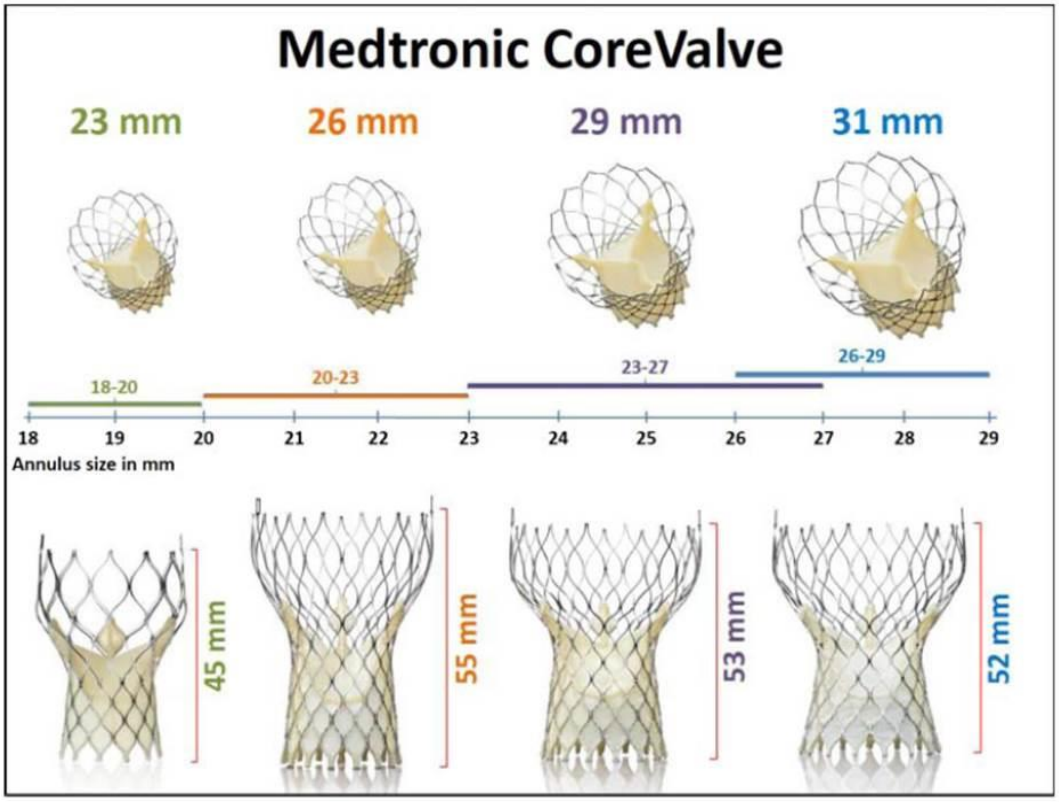


Figure 1-1 CoreValve prostheses (Medtronic Inc, USA)

1.7.4.2 Edward Sapien TAVI

The Edward Sapien (Edwards Life Science, Irvine, USA) valve is a balloon-expandable system that is made from cobalt chromium (Webb et al., 2006). This can be inserted from the femoral, subclavian or transapical approach; there are 4 sizes 20, 23 mm, 26mm and 29 mm. The Edwards Sapien XT has a tubular slotted frame with thinner struts but preserved radial strength. The valve leaflets are bovine pericardium which has been treated with anti-calcification reagent similar to technology used on surgical valves (Webb et al., 2009). The lower frame has a fabric covering to provide an improved seal to the aortic annulus and thus prevent further para-valvular regurgitation. Once positioned the valve is implanted with balloon inflation and can be post dilated.

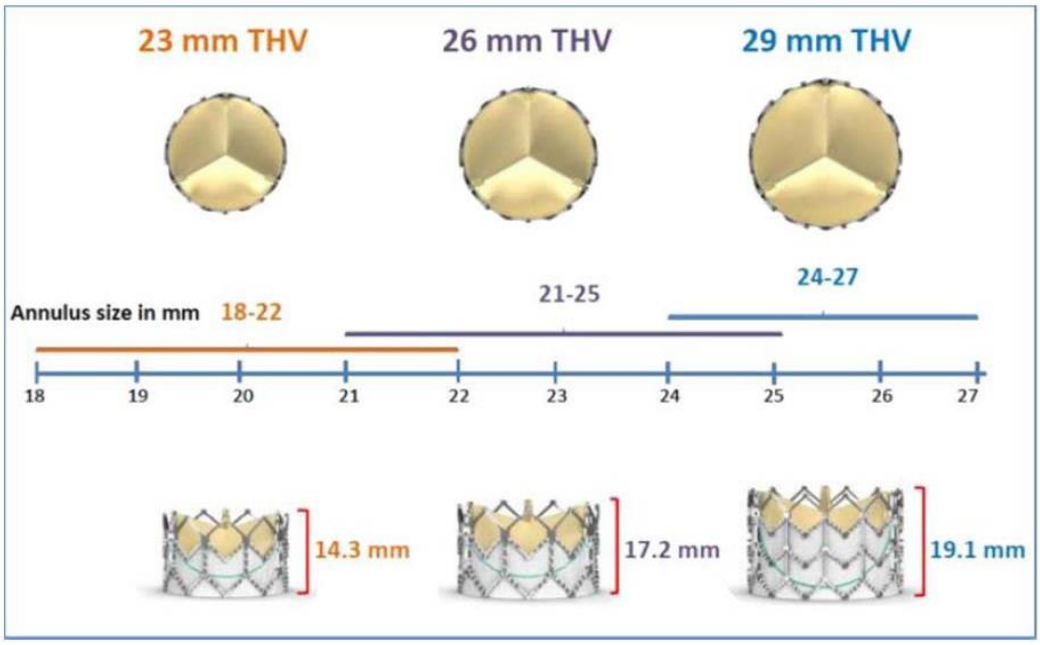


Figure 1-2 Edward Sapien XT prostheses (Edwards Lifesciences, USA)

1.7.5 General Procedure for TAVI

There are several stages during TAVI which requires meticulous planning and a multi-disciplinary approach involving interventional cardiologists, cardiac surgeons, imaging cardiologists, cardiac anaesthetists, catheter lab nurses, and cardiac technicians. The patient undergoes general anaesthesia and arterial lines and central venous catheters are inserted for monitoring. A temporary transvenous pacing wire is placed in the RV to facilitate rapid ventricular pacing during valve intervention. Transesophageal echocardiography (TOE) is also performed to map the aortic valve, LV function and mitral valve. Vascular access is obtained depending on the approach as agreed by the MDT. The large sheath is inserted following serial dilatation over a stiff wire. The aortic valve is crossed with a straight 0.035 wire using a Judkins right catheter or Amplatz 1 or 2. A long exchange length J-tipped wire is then used to swap the standard catheter for a pigtail

catheter. A stiff pre-coiled wire is inserted via the pigtail into the LV cavity. Initially a balloon valvuloplasty is performed under X-ray fluoroscopy and TOE guidance while the RV is rapidly paced at 180 to 190 beats per minute to minimise cardiac motion. The delivery catheter is taken close to the ballooned valve and the prostheses in positioned and deployed again using rapid RV pacing. If there is significant aortic regurgitation detected by contrast aortography and TOE then further balloon dilatation can be performed. The vascular access site is closed and the patient is returned to the coronary care unit for monitoring and recovery from the general anaesthesia.

This technique is continually developing and evidence is merging for procedure to be performed under local anaesthesia with conscious sedation. Studies have shown this to be safe and effective in various centres. This also means that transoesophageal echocardiography is no longer obligatory.

Patients are monitored in a high dependency environment for minimum 24 hours after which venous sheaths for temporary pacing and central venous catheters and arterial lines can be removed. The patients are reviewed daily by the interventional cardiologist and assessed for complications. The aim usually is encouraging early mobilisation of the patient on the ward and safe discharge back to the community.

1.7.6 TAVI Complications

TAVI is performed in a high-risk group of patients which predisposes them to procedure related complications which may be peri-procedural, early prior to discharge or late. The risks of complications are on balance less than various risk associated with conventional aortic valve surgery. Surgical risk

is potentiated by the problems related to prolonged general anaesthesia and the stressor of cardiopulmonary bypass.

The specific complications of TAVI are discussed below focusing on vascular injury, device induced trauma, embolic phenomena and conduction tissue disturbance.

1.7.7 Vascular Access Complications

The femoral artery is the preferred vascular access route to insert delivery sheaths, however the sheaths have a large diameter ranging from 12 to 18F gauge. During vascular access the possible complications include dissection, haematoma and haemorrhage which may progress to a retroperitoneal bleed (Leon et al., 2011). However, the incidence of vascular complications has decreased as delivery sheaths have become smaller and with the wider use of percutaneous suture based closure devices (Barbanti et al., 2015). Nevertheless, in a study comparing Proglide and Prostar devices, there was a high incidence of vascular complication (17.3%) and significant number of patients requiring further peripheral percutaneous intervention (Barbanti et al., 2015). In addition, CT assessment of ileo-femoral arteries for suitability for access has reduced complications (Wuest et al., 2012). Major predictors of vascular injury are vessel tortuosity and calcification and prior peripheral vascular surgery. Major vascular complications can be treated with peripheral intervention with stents or by open vascular surgical repair. In a study comparing access by the surgical or percutaneous method, bleeding complications were significantly higher in the percutaneous approach but overall complications were no different (Spitzer et al., 2015).

1.7.8 Intra-procedural complications

There are several stages of valve implantation that can develop into a serious complication. Cerebral embolism may occur during device delivery up an atheromatous aorta, which will be discussed later (Fairbairn et al., 2012a). There is a risk of myocardial perforation with guide wires and temporary pacing leads which lead on to a haemorrhagic pericardial effusion and tamponade (Katsanos et al., 2015). This effusion must be treated with emergency pericardiocentesis to prevent cardiovascular collapse and cardiac arrest (Lange et al., 2011). Other potential risks are aortic rupture more likely to be seen in patients with a severely calcified aorta called *porcelain aorta*. The rupture could be in the ascending aorta or at the aortic and mitral valve junction. Both scenarios are catastrophic and patients are unlikely to survive despite emergency conversion to open surgery (Eggebrecht et al., 2014). In a registry of balloon expandable valves (Edwards Sapien), the conversion to emergency cardiac surgery was low at 1.2% but the associated 30-day mortality was 52% (Eggebrecht et al., 2014, Thomas et al., 2011). During implantation across the native diseased valve, calcified atheroma can embolise again causing stroke or travel down the coronary arteries resulting in myocardial ischaemia and infarction. As the prostheses is deployed there may be abrupt displacement of the device or the coronary ostia may become occluded which will both require immediate percutaneous coronary intervention (Ribeiro et al., 2013). Occasionally, when there is higher risk of coronary obstruction, some operators may either perform preventive coronary angioplasty such as treating a left main coronary artery stenosis or may place a guide catheter with an angioplasty wire within the coronaries and therefore if a bailout coronary intervention is

necessary then this can be performed swiftly. In a large multi-centre study, coronary obstruction was rare (<1%) and was associated with severe hypotension and electrocardiographic changes. The left coronary artery was involved and associated predictors were low coronary height, prior aortic bioprosthesis and a shallow sinus of Valsalva (Ribeiro et al., 2013).

1.7.8.1 Paravalvular Aortic Regurgitation

The ideal goal is to implant the bioprosthetic valve in the aortic position which is functional without valve incompetence also called regurgitation. The prosthesis may not have complete deployment or expansion of its metal frame resulting in a space between the outer frame of the TAVI device and the native valve. This space allows blood that has been ejected from the left ventricle into the aorta to return into the ventricle. The resulting para-valvular regurgitation is a poor prognostic factor which is a known factor associated with death (Kodali et al., 2012a). If the TAVI device is not appropriately anchored to the aortic wall then there is a risk of device embolisation in to the LV cavity or aorta. This is evident during the procedure but can occur in the first 24 hours leading to cardiac arrest and death (Makkar et al., 2013). During deployment of the valve if rapid pacing does not decrease the aortic pressure, then the TAVI device will be ejected into the aorta. If there is significant regurgitation with the first device, then a second TAVI device may be required to be placed inside the initial prosthesis; this is known as “Valve in Valve”. The use of “valve in valve” and/or the event of valve embolisation is associated with mortality at 1 year (Makkar et al., 2013). Another cause of post procedure aortic regurgitation is a valve leaflet that is adherent to the device frame: a “stuck leaflet”, but this is a rare event.

1.7.9 Pacemakers

The AV node is in close proximity to the aortic annulus and therefore complete heart block may be seen and require permanent therapy with a pacemaker. (Pereira et al., 2013) The need for pacemakers following aortic valve surgery is established and is caused by surgical injury during excision of the native valve (Dawkins et al., 2008). In long term surgical follow up, over two-thirds of patients that required post-operative pacing were dependent on pacing at one year (Merin et al., 2009).

For TAVI the predictors for permanent pacing are pre-existing conduction disease, especially left bundle branch block and also, self-expanding valves (Medtronic CoreValve) have a higher pacing rate compared to balloon expandable (Edwards Sapien) (Jilaihawi et al., 2009, Urena et al., 2012). This observation is primarily related to the difference in valve design.

1.7.10 Other Complications

Acute Kidney Injury (AKI) is defined by a sudden reduction in glomerular filtration rate and is reflected in an increase in serum creatinine (>26µmol/L) or a decrease in urine output (<0.5ml/kg/hour) over a 6 hour period and can be graded on severity (AKI stage 1 to 3) dependent on the urine output and need for dialysis (Bellomo et al., 2004). The mechanisms of kidney injury can be from a variety of sources. Significant haemorrhage can lead to hypovolaemia resulting in pre-renal AKI. Others include, contrast induced nephropathy, renal ischaemia, embolism from calcific or athero-thrombo-embolism (Aregger et al., 2009). In a study of 213 TAVI patients, 11.7% developed acute kidney injury with 1.4% requiring renal replacement therapy (Bagur et al., 2010).

The rates of infection and early and late endocarditis are low in patients treated with TAVI (Leon et al., 2010a). Nevertheless, all patients receive prophylactic antibiotics prior to procedure.

1.7.11 Stroke

Stroke is defined as an acute onset of a focal neurological deficit that last longer than 24 hours otherwise the episode is categorised as a transient ischaemic attack. TAVI has a higher stroke rate in comparison to SAVR which has a poor effect on long term quality of life and prognosis. The major problem is micro-embolisation during deployment which can be observed during transoesophageal echocardiography (TOE) and transcranial Doppler (Kahlert et al., 2012). The reported ranges of strokes are between 2.9 to 10 % (Leon et al., 2010a, Grube et al., 2007). There is a concern that silent embolic cerebral infarcts can affect future cognitive function (Vermeer et al., 2007). The episodes of micro-embolisation can occur during other procedures such as percutaneous coronary intervention (PCI), balloon aortic valvuloplasty (BAV) and atrial fibrillation ablation. Although silent infarcts lack the clinically overt stroke-like symptoms, there has been evidence to show this may contribute to physical and cognitive decline which may be detected by serial neurocognitive assessment (Vermeer et al., 2003).

1.8 Role of MRI in the Assessment of Aortic Stenosis

Magnetic Resonance imaging (MRI) uses the properties of a high field strength electromagnet and radiofrequency impulses to generate images from various tissues. The field strengths used in clinical practice are 1.5 to 3 Tesla. One Tesla is equivalent to approximately 20,000 times the strength of the earth’s magnetic field. (Balaban, 2010) By placing a subject in the bore

of a magnet all the protons align in the direction of the field, then a radiofrequency impulse is delivered to shift them from equilibrium and as the protons recover they emit energy which is detected as a signal. The detected signal is used and post processed to produce an image.

1.8.1 Basic Principles

The human body contains hydrogen atoms in all its parts which is particularly useful for nuclear magnetic resonance imaging. The hydrogen nucleus exhibits a magnetic dipole and a property of spin which is a characteristic of all atoms. Nuclear magnetic resonance refers to the observation where nuclei that have a net magnetic moment can absorb and release electromagnetic energy at specific resonant frequencies.

A magnetic field is a region where particles that are charged will experience an electromagnetic force. Hence if a hydrogen atom is placed in a strong magnetic field then it will align in the direction of the field. However, hydrogen atoms possess their own angular momentum and therefore ‘precess’ around the direction of the externally applied field. Very soon equilibrium is achieved and there is a net magnetisation in the direction of B_0 and is termed M_0.

1.8.2 MR system

In an MR system there are three electromagnetic parts: the main magnet coils, three gradient coils, and a radiofrequency transmitter coil. The main magnet applies the constant strong magnetic field and is denoted by B_0, and clinical systems are generally 1.5 Tesla or 3 Tesla. Conventionally, x, y and z orthogonal planes are used to identify the directions of the magnetic fields; the z direction refers to B_0. The three gradient coils can generate a varying

magnetic field in the direction of B_0 as they can be turned off and on very rapidly. Therefore an object within the bore of the scanner will experience varying forces depending on the location. The units of measure for the gradient field strength are millitesla per metre (mT/m).

The radiofrequency transmitter coils have an important role in signal generation as they produce a radiofrequency magnetic field. The frequency is within the megahertz range which is determined by the main magnet (1.5T or 3T) and the radiofrequency field is conventionally referred to as B_1.

1.8.3 The MR Signal

The combination of a strong static magnetic field and radiofrequency generated fields produce an unique MR signal that can be detected by radiofrequency receiver coils and used to produce the image. The radiofrequency transmitter coil generates a magnetic field to deliver energy to the aligned protons. This is performed at a unique frequency known as the Larmor frequency or the resonance frequency. The Larmor frequency (ω_0) is defined by the Larmor equation:

$$\omega_0 = \gamma \times B_0$$

Where γ is the gyromagnetic ratio (for the proton=42.6MHz/Tesla). Therefore at 1.5T the Larmor frequency is 64MHz. This radiofrequency field is applied as a short time and is known as the *rf* pulse.

At equilibrium, the net magnetisation is M_0 in the line with B_0, but when a *rf* pulse is generated the net magnetisation moves away from M_0. This promotes a rotational motion about M_0, known a precession, which occurs at Larmor frequency. The flip angle refers to the angle between the net magnetic vector and the transverse plane, M_{xy} after the application of a *rf*

pulse. The oscillating magnetic field can induce a current in the receiver coil thus generating the MR signal. As discussed above, the longitudinal component of magnetisation is strong as it aligns with B_0, therefore the MR signal is measured in the transverse (x,y) plane in order to be able to detect changes as a result of the rf pulse.

1.8.4 Radiofrequency pulses

There are several types of radiofrequency pulses used in MR imaging and they are sub-divided by their flip angle and subsequent effect. A saturation pulse, has a 90^o flip angle, which means that the energy is delivered to move protons from the position of equilibrium towards the transverse (x,y) axis. Therefore, the net magnetisation is highest in the x,y plane and least in the z-axis and therefore is the largest transverse magnetisation and largest MR signal. The saturation pulse is an example of an excitation pulse and forms the basis for spin-echo imaging.

When a radiofrequency pulse is applied with an angle that is less than 90^o then the net magnetisation is shared between the x,y plane and z plane, therefore the transverse magnetisation signal has lower energy as opposed to the higher levels seen in the saturation pulse earlier. The low flip angle impulses can be repeated with shorter delays as there will be available protons magnetised in the z plane as they would not have been fully excited. The low flip angle pulses are used in gradient echo imaging.

For 180^o flip angles, the net magnetisation can be aligned to the z axis but after the pulse, there is no signal in the transverse plane (x,y) and thus no detectable signal. This 180^o pulse is known as an inversion pulse and used in inversion recovery sequences such as black blood imaging. Also, this

inversion pulse can be used to restore coherence that may be lost in certain sequences or attributable to magnetic field inhomogeneity.

1.8.5 Characteristics of the MR signal

There are several types of MR signals that are used in clinical practice to show normal anatomy and detect pathologies. A key event after the radiofrequency pulse is the process of relaxation, which occurs as the excited protons return to a state of equilibrium or rest. Relaxation effects net magnetisation in two planes; the longitudinal (z) and transverse(x,y) planes.

T1 relaxation

The longitudinal relaxation time, is referred to as T1 and is the time taken for the z component of magnetisation to return to the equilibrium (63% of its value at equilibrium). The process is exponential and can be described by the following equation:

$$M_z(t) = M_0\,(1 - e^{-t/T1})$$

The magnetisation, M_z recovers to an equilibrium value (M_0), 't' refers to time and T1 is the longitudinal relaxation time decay constant. So initially, recovery is rapid and then the net magnetisation plateaus as equilibrium is approached. The shorter the T1 time constant the faster the relaxation process and return to equilibrium. With T1 relaxation there is a transfer of energy from spinning protons to the surrounding tissues in the form of heat and can also be described as spin-lattice relaxation. As an example, free water has a long T1, however water bound in tissues has a shorter T1 as this can transfer the energy to the surrounding area (lattice).

T2 relaxation

The transverse relaxation process refers to the decrease of net magnetisation in the xy plane as protons rotate about the z axis. This process is longer than longitudinal relaxation. Similarly the magnetisation decay can be defined by the following equation where *T2* is the transverse relaxation time decay constant:

$$M_{xy}(t)=M_{xy}(0)e^{-t/T2}$$

Initially there is coherence of spin and net magnetisation in the xy plane, however, as the protons spin about the z axis and gradually change the phase angles, this results in a net loss of magnetisation in the transverse plane. In a receiver coil this is detected as an oscillating magnetic field that is weakening and is known as Free Induction Decay (FID). There are two relaxation times that are important in the transverse xy plane; T2 and T2*. Both of these detectable signals are a measure of loss of coherence in the spin of protons. T2 relaxation is also known as a spin-spin interaction where a spinning proton transfers energy to another spinning proton. This transient interaction alters the phase angle and thus the Larmor frequency.

The other cause of a loss in coherence of protons is caused by the variations in the applied magnetic field (B_0). These distortions or localised inhomogeneities are inherent to a specific magnet and induced by a body(subject) place in the field itself. T2* relaxation is a combination of T2 relaxation and the effect of variations in the magnetic field.

1.8.6 MR Echoes

There are two major types of echo used in MR imaging that will be discussed here. The first is gradient echo (GE) and the second is spin echo (SE).

Gradient Echo

Gradient echoes are produced by the application on two separate magnetic field gradients. The initiation of the first gradient alters the strength in the magnetic field and spinning protons lose their coherence as they are now precessing at differing phases. The effect in the transverse direction (xy) of magnetisation is that the signal drops to zero. A second magnetic field gradient is applied in the opposite direction to restore phasing of the protons and the free induction decay (FID) signal reappears. This signal generated is known as a gradient echo. The echo time denoted by TE and is the duration between the origin of the radiofrequency pulse, application of the gradient fields and to the maximal amplitude obtained by the gradient echo; this is also the “best” time to sample a signal. The echo time is measured in milliseconds and is unique to the pulse sequence selected by the MR operator.

Spin Echo

The spin echo is generated by first applying an excitation *rf* pulse at 90^{o} followed by a ‘refocussing’ 180^{o} *rf* pulse at half the echo time. After the first pulse the protons will alter their spin phase due to T2 relaxation and as an effect of magnetic field inhomogeneity; the first type of dephasing is irreversible but the second is reversible. The application of the second 180^{o} rf pulse switches positive relative phase changes to a negative; the opposite applies to relative phase changes that were negative. The spins come back into phase which increases the amplitude of the free induction decay signal; the signal that is readout is the spin echo.

1.8.7 Making the image

Slice selection

A slice of tissue will experience the static field (B_0) of the main magnet but if the gradient coils also generate another field (gradient field) then there will be a net field effect across the slice. We recall that the Larmor frequency of protons will vary and depend on the strength of the local magnetic field. Thus the frequency will vary along the applied gradient field (G_s: slice selection gradient). A specific slice can therefore be excited by transmitting a rf pulse with the frequencies within that slice. The rf pulse contains a range of frequencies referred to as a bandwidth. Therefore tissue outside these frequencies will not resonate as they have different Larmor frequencies, and so this gives us slice specificity for a location. In addition the thickness of a slice is determined by the range of the bandwidth, such that a thin slice will have a narrower frequency bandwidth. The slice thickness is also dependent of the strength of the gradient field as this does effect the frequencies of the tissues at a slice.

Phase and frequency encoding

A phase encoding gradient is applied which causes the protons to spin at varying frequencies according to the location along the gradient. Thus the protons in the stronger part of the gradient will spin at a higher frequency than those located at a lower field gradient. When the gradient (G_p) is turned off, this leaves the protons in relatively different phases dependent on where they were located along the gradient. The direction of the applied gradient in this situation is known as the phase encoding direction.

The frequency encoding gradient (G_F) is applied after the phase encoding gradient and is at 90^0 to this. The protons rotate at differing frequencies dependent on the location to the applied gradient, similar to that seen with phase encoding gradients. The unique feature of the frequency encoding gradient is that it is applied for a long period of time and coincides with the signal readout period. The signal is composed of a collection of frequencies (bandwidth) which depends much on the location along the applied gradient.

Additional gradients are applied sequentially following the imaging gradients in order to counteract the dephasing of protons that occurs which effects the MR signal. The dephasing gradients are applied after the imaging gradients but with opposite slopes.

Image reconstruction

The process of image reconstruction is complex and involves several mathematical stages. The data from the MR signal are complicated and have to be broken down into individual components. A mathematical process known as *Fourier transformation* is used where signal or waveform in time can be expressed by its various frequency components. Therefore the frequency encoded MR signal can be converted to a series of frequency components. However, Fourier transformation can only be performed on signals that are time dependent therefore the variation from phase encoding frequencies requires additional steps. The MR signal generation steps are repeated with identical gradients except for the phase encoding gradient, for which the strength of the applied gradient is increased in stages. The time between intervals is known as the repetition time (TR).

What is k space?

K space is a data point that represents a component of spatial frequency for an image. A point in the MR signal contains information about parts of the whole image. There is an inverse relationship between image space and k space. The lines of k space are typically filled in a parallel manner known as Cartesian acquisition. The central region of k space contains the most information regarding image contrast and the peripheral regions contain higher frequencies that provide details of spatial resolution.

1.8.8 Pulse sequences and image contrast

The ability to define normal and abnormal tissue in imaging has to be determined by the quality of the visible differences between tissues. The unique features of MRI are that excellent contrast that can be achieved between blood, muscle and fat to define pathology. We know from earlier that different tissues have individual T1 and T2 relaxation times. In spin echo the varying of TR and TE can impact on the tissues relaxation times on the MR signal. Where as in gradient echo the flip angle, TR and TE alterations can influence the tissues signal.

T1 weighted spin echo

A short TR and TE are used in T1 weighted spin echo imaging to give fat a high signal and appear bright whereas fluid has a lower intensity. T1 weighted imaging is ideal for cardiac anatomical imaging.

T2 weighted spin echo

T2 weighted spin echo utilises a long TR and long TE. The pre-dominant contrast occurs between muscle and fluid which have a short and longer T2 relaxation time respectively. T2 weighted imaging is used to determine fluid

filled areas and depicts myocardial oedema very clearly. Overall spin echo sequences give the “black blood” appearance which provides excellent contrast between tissue and blood. The signal void appears because blood is fast moving through the selected slice and therefore moves thorough after the first rf pulse without being refocused by the second rf pulse.

Spoiled Gradient Echo contrast

Spoiled gradient echo imaging uses a short TR and therefore allows for faster imaging. However, after the first read out the dephasing or a spoiler gradient has to be applied to prevent the initial signal from interfering on the next signal generation.

T1 weighted gradient echo imaging uses a short TR and TE with a low flip angle and provides good cardiac cine imaging. T2* weighted imaging on the other hand uses longer TE and TR to achieve contrast. This form of imaging is used in iron loaded studies or myocardial haemorrhage.

Balanced Steady state free precession

Balanced steady state free precession gradient echo sequences are used widely to assess ventricular function. The transverse magnetisation is not spoiled but instead re-phased after each readout and successively contributes to a steady state signal. The increased signal in SSFP compared to a spoiled gradient echo signal means a higher receiver bandwidth can be used with short TR and TE. However, this sequence is prone to banding artefacts caused by field in-homogeneities.

1.8.9 Contrast Agents

Gadolinium based contrast agents are used in MR imaging which are chelated to prevent toxicity. The agent remains extracellular after

intravenous administration and is excreted renally and is contra-indicated in patients with severe kidney disease and lower glomerular filtration rates. This is because of a disease process called nephrogenic systemic fibrosis (NSF) which occurred in patients with severe renal disease who received linear gadolinium based contrasts. The gadolinium from these early agents displaced in to organs and tissues resulting in subcutaneous fibrosis. Biopsy of tissues confirmed deposition of gadolinium and thus safety concerns were raised. However, modern agents have cyclical chelation and therefore have a reduced risk of displacement of the ion and hence a low risk of NSF. There have been no reports of NSF in recent years and never in patients with normal renal function.

The Gadolinium contrast agent shortens T1 relaxation times and so increases the signal intensity in T1 weighted imaging. The agent is usually administered according to body weight 0.1 to 0.2 mmol/kg.

1.9 Cerebral Magnetic Resonance Imaging

Cerebral MRI is established in acute stroke management and neurovascular disease. The cerebral infarcts appear as focal areas with the same intensity as cerebral spinal fluid. MRI can use diffusion weighted imaging (DWI) to confirm micro-infarcts that have reduced diffusion areas. This helps detect multiple embolic events easily. Other information such as evidence of cerebral atrophy and small vessel ischaemia can be commented upon.

<u>T1 and T2 weighted cerebral imaging</u>

T1 weighted images are used to detect gross anatomical abnormalities and aid detection of older cerebral areas of infarction. On T1 weighted images they can appear hypo-intense and iso-intense in the acute phase. T2 weighted imaging in the early phase of cerebral infarction give a very bright hyper-intense signal and can also detect peri-infarct oedema.

1.9.1 Diffusion weighted imaging

The MR signal is sensitive to random motion of molecules, the latter being known as “self-diffusion”. Therefore when diffusion is obstructed by physical barriers then this can be detected as a signal if diffusion weighted imaging is used. A pulsed gradient spin echo (PGSE) is used by applying a 90º and 180º *rf* pulse along with variable gradients, which allows control and variability on the degree of weighting (b-factor). In general in diffusion weighted imaging a low signal is seen in tissue with normal function and a high signal is detected in disrupted tissues. An apparent diffusion coefficient (ADC) can be calculated from two or more diffusion weighted images (by varying b-factor). The diffusion coefficient is measured in units of mm^2s^{-1}.

1.10 Cardiovascular MRI

Cardiovascular MR imaging has become established as a modality which allows multi-parametric assessment in cardiac disease. CMR uses ECG gating to acquire images over several heart beats and breath holds to reconstruct cine and static images. There are various pulse sequences that allow optimal image acquisition and help to measure disease burden.

1.10.1 LV Function

The gold standard for volumetric analysis is CMR and this is superior to echo and Myocardial perfusion scintigraphy (MPS) and also has the added

benefit of excellent intra and inter-observer reproducibility (Alfakih et al., 2003, Messroghli et al., 2005, Bellenger et al., 2000a). The cine pulse sequence is typically Steady State Free Precession (SSFP) using gated ECG to acquire multiple phases. This uses typical TR 3ms, TE 1.5ms and temporal resolution of 20 to 50ms. This achieves a high signal-to-noise ratio and improved contrast between myocardium and the blood pool. From acquired images the end diastolic phase can be identified and the endocardial border can be contoured using quantitative software (QMass 7.2, Medis, Netherlands). This process is repeated for all LV slices to calculate an End-diastolic volume by the summation of discs method (excluding the papillary muscles). The contouring can be repeated to the end-systolic phase to similarly calculate the end-systolic volume. These measures can be used to calculate the stroke volume (SV), ejection fraction (EF). The mass can be quantified by contouring the epicardial contour and including the papillary muscles.

1.10.2 Late Gadolinium Enhancement

Late Gadolinium Enhancement (LGE) imaging uses an inversion recovery (IR) gradient echo sequence. The Look-Locker method is used after the administration of Gadolinium contrast agent to find the optimal inversion time (TI) to null the myocardium. This allows areas of hyperenhancement to be very well visualised. LGE is described according to distribution within the myocardium and typical patterns include; sub-endocardial hyperenhancement consistent with MI; patchy fibrosis for cardiomyopathy along with mid-wall fibrosis (Kim et al., 1999). Focal areas of hyperenhancement have been reported to vary in patients with severe aortic stenosis and be associated with poor outcome after SAVR (Weidemann et

al., 2009). In this study, cardiac biopsies were analysed along with LGE images, overall there was an improvement in EF but, at 9 months there was no change in the degree of enhancement which suggested AVR did not have an impact of focal fibrosis and this type of fibrosis was permanent.

LGE imaging does not detect diffuse interstitial fibrosis as this relies on comparing the signal intensity between nulled 'normal' myocardium to a relatively hyper-enhanced fibrotic area. This makes accurate quantification difficult as post processing software requires an arbitrary set threshold to differentiate between normal and diseased areas.

1.10.3 Diffuse Fibrosis and T1 mapping

Abnormal left ventricular hypertrophy as seen in aortic stenosis can lead to a diffuse fibrosis developing prior to the severe focal areas. Diffuse fibrosis leads to expansion of the extracellular matrix and volume (ECV) which is mediated by myofibroblasts (Krayenbuehl et al., 1989). New methods of imaging this extracellular space have been developed using T1 mapping.

T1 is the longitudinal relaxation time for the z-component of magnetisation of protons after a radiofrequency pulse; where fat has a shorter T1 time than muscle and fluid has the longest. The T1 time represents 63% of the tissues value at equilibrium. Each tissue contains varying amounts of water molecules which aids differentiation but also pathological processes like fibrosis, oedema and inflammation play a role (Mewton et al., 2011).

1.10.4 Modified Look-Locker Inversion Recovery

T1 mapping techniques have been developed to acquire high spatial resolution images with single breath holding at both 1.5T and 3T field strengths. This allows signal quantification in milliseconds for each

myocardial voxel and therefore does not use an arbitrary scale as in LGE imaging. Messroghli et al developed the technique and validated the method on volunteers and patients with disease (Messroghli et al., 2004). This is performed using the modified Look-Locker Inversion recovery (MOLLI). For each slice, there are 3 successive Look- Locker acquisitions (LL_1, LL_2 and LL_3) with 3 (TI=100ms), 3 (TI=200ms) and 5 (TI=350ms) single shot readouts respectively. For each of the LL acquisitions the first read out occurs at the TI after a non-slice selective adiabatic 180^o pulse and at a delay time (TD) after the previous R wave. Subsequent images are acquired at time TD after the R wave until the required number of images are obtained. A total of 11(3, 3, 5) images are obtained. The images are then post processed using dedicated software (e.g. MR Maps) which sorts the images in order of TI and applies a three-parameter non-linear curve fitting using a Levenberg-Marquardt algorithm (Messroghli et al., 2007) (Messroghli et al., 2010). This produces a T1 map which can be analysed by drawing regions of interest, therefore it is possible to obtain pre-contrast and post-contrast T1 values. The changes in T1 can help differentiate between healthy and diseased myocardium. At 1.5T the healthy normal myocardial pre-contrast T1 is 977±63ms and post contrast T1 is 483±20ms (Messroghli et al., 2006). In comparison, infarct regions have a longer pre-contrast time but the post contrast time is shorter due to retention of Gadolinium.

The studies in this thesis used MOLLI for T1 mapping as this was available on our 1.5T Philips scanner and had been previously validated and several studies had been published using this method. There are several other T1 mapping methods, however, the techniques were not available to our centre as some sequences are vendor dependent, i.e. only available and validated

on Siemens scanners. T1 mapping has been validated using 1.5T and therefore we did not use 3T for the studies in the thesis. An additional restriction was that the TAVI valves had not been declared 3T compatible.

1.10.5 Shortened Modified Look Locker Inversion Recovery (ShMOLLI) and Equilibrium contrast CMR

Other methods of T1 mapping include; Shortened Modified Look Locker Inversion Recovery (ShMOLLI) and Equilibrium contrast CMR. (Piechnik et al., 2010) (Flett et al., 2010)

ShMOLLI acquires 7 (5+1+1) images and therefore shortens the breath hold time and has been shown to correlate with MOLLI, however, does underestimate T1 by 4% and is more prone to noise artefacts (Piechnik et al., 2010).

Equilibrium contrast CMR aims to calculate the volume of distribution of gadolinium in the myocardium and estimate the amount of diffuse fibrosis (Flett et al., 2010). The method involves giving a bolus of gadolinium followed by a dilute infusion over 30 to 60 minutes to achieve contrast equilibrium. The pre-and post-contrast T1 maps are acquired using standard LGE imaging parameters (spoiled gradient echo inversion recovery). The haematocrit is obtained to give the blood volume of distribution and the following equation is used to calculate myocardial volume of distribution (Vd) or extra cellular volume (ECV):

$$Vd = (1 - hct) \times \left(\frac{\left(\frac{1}{T1myo\ post} - \frac{1}{T1\ myo\ pre}\right)}{\left(\frac{1}{T1blood\ post} - \frac{1}{T1\ blood\ pre}\right)}\right)$$

Flett et al were able correlate their method with myocardial biopsies in 18 patients and therefore quantify the diffuse myocardial fibrosis (Flett et al.,

2010). This method was also used in patients with aortic stenosis before and after SAVR, where there was no significant regression of fibrosis, although there was a reduction in LV hypertrophy that was attributed to changes in cell volume (Flett et al., 2012).

Clinical utility of T1 mapping is still in early developmental stages. There have been case reports and short series of T1 mapping to aid diagnoses. Cardiac amyloidosis presenting with heart failure often has cardiac MR assessment and LGE imaging does not allow nulling of the myocardium. Here T1 mapping has been shown to provide diagnostic yield with high T1 values. An inverse effect on would be shortening as seen in Fabry's disease.

1.10.6 Extracellular Volume (ECV)

The ECV can also be measured using MOLLI to obtain the myocardial and blood pool T1 values. Ugander et al showed a difference in patients with MI and atypical LGE patterns, also that ECV changed with age (Ugander et al., 2012). Kellman et al have shown that motion correction and co-registration of the images is important in obtaining accurate ECV values (Kellman et al., 2012). The normal ECV is been reported to be between 20 to 30% (Kellman et al., 2012, Ugander et al., 2012).

Overall, CMR would be able to provide insight into the TAVI and contemporary SAVR patient group. The accurate LV measurement, diffuse fibrosis and late gadolinium patterns may help predict patient outcomes.

1.11 Health Related Quality of Life

Health related quality of life (HRQoL) is a multi-dimensional idea that includes various areas of life known as domains. This concept of HRQoL covers variety of components which are important to the patients' wellbeing and provides a great holistic view of the patients' status. The quality of life notion extends beyond quantitative measures of outcome such as survival after an intervention, a patient's life expectancy or even adverse events due to complications. HRQoL covers domains of physical health, emotional well-being, mental and social functioning. The physical measures refer to what the patient can do or how much pain they are in whereas the mental components refer to the symptoms of low mood and depression or concerns about their future resulting in anxiety.

1.11.1 Measuring Health Related Quality of life

Although absolute measures of outcome are useful when assessing the effect of treatment on a particular disease being able to measure HRQoL can also be valuable. The problem with any measurement is to define the standards that the investigator will use which can be difficult when trying to measure a multi-domain area like HRQoL (Guyatt et al., 1993). In order to achieve accurate measurements several HRQoL scales have been developed and well established examples of these are the Short form 36 item Health survey questionnaire (SF-36) and EurQoL (McHorney et al., 1994). The advantages of an established scale are that the instrument is reliable and validated. Using the SF-36 as an example, this is a patient reported outcome (PRO) which covers 36 items and questions are addressed to cover a variety of aspects. There are 8 domains covering subjective health: physical functioning, role limitations due to physical

problems, role limitations due to emotional problems, social functioning, mental health, energy/vitality, pain and general health perceptions. The reliability of the SF-36 has been shown to be consistent and the validity has been proven across patients with differing health states.

1.11.2 Health Related Quality of Life in Aortic Stenosis

Several studies conducted for valvular disease have shown patient reported outcomes to improve on medical and surgical therapy. Earlier surgical valve replacement research did not record specific HRQoL outcomes perhaps as not all scales had been validated. However, recent randomised control studies do include HRQoL outcomes and have shown significant improvement although emphasis is usually put on survival outcomes and improvement in valvular dynamics. The PARTNER trials for TAVI have recorded HRQoL outcomes and shown an improvement in both arms. Reynolds et al evaluated 628 patients with severe aortic stenosis that were in the high surgical risk arm that were treated with either TAVI or SAVR, known as cohort A (Reynolds et al., 2012). They used the SF-12 which was an abridged version of the SF-36 along with the Kansas City Cardiomyopathy questionnaires and EuroQoL (EQ-5D). Quality of life and health status were measured at baseline, 1 month, 6 months and 1 year. They reported almost 10-point improvement in health status in those treated with TAVI via the femoral route compared to SAVR. There was a significant improvement (>5 points) in SF-12 physical and mental scores at follow up time points in the TAVI arm. However, the surgically treated arm did have significant improvements in the physical score too but with a small point shift (~2 points).

Fairbairn et al showed serial improvement in many domains in patients undergoing TAVI over 12 month period. (Fairbairn et al., 2012b) There were positive changes seen early as 30 days in SF 12 Physical scores and the improved well-being continued up to 12 months. Predictors of improvement in HRQoL scores included male sex and operator experience. (Fairbairn et al., 2012b)

Health related quality of life may be seen as a global indicator of general health. This is an important issue for patients and carers who live with various disease conditions and therefore a key part of medical practice. There are several external factors that can influence HRQoL, such as the procedure patients receive or any consequence related to the procedure. We know micro embolism and stroke are complications of both TAVI and SAVR. Therefore, an important evidence free area is whether stroke and cerebral micro-embolism affect general health status and quality of life.

1.12 Neurocognitive Assessment

Neurocognitive testing allows objective assessment of patients who may have a subclinical change in cognitive function as a consequence of brain injury; classically traumatic brain injury. Multiple tests have been developed and validated in brain injury for cognitive assessment and in stroke patients. The recent VARC criteria also set out key areas that neurocognitive functional assessment should address when appraising TAVI and key assessment points; baseline, 30 days, 6 months and 12 months. Due to the nature of TAVI and embolic load, various concerns have been raised with respect to the effect of these silent cerebral infarctions (Fairbairn et al., 2012a, Kahlert et al., 2012). Neurocognitive assessment is used in clinical

practice by Clinical Psychologists to grade degrees of cognitive impairment and assess response to treatment and rehabilitation. Various studies have reported on reliability and validity of these tests.

1.12.1 Neurocognitive assessment in Coronary artery bypass grafting (CABG)

Previously patients having CABG have shown changes in their neuropsychological function after surgery (Zamvar et al., 2002). Possible mechanisms include; cardiopulmonary bypass causing a systemic inflammatory response and micro-embolisation from aortic and cardiac manipulation (Pugsley et al., 1994, Borger et al., 2001). There was some suggestion that off-pump CABG results in less neurocognitive impairment (Zamvar et al., 2002). Another study comparing biological AVR with CABG found that post-operatively there was a reduction in cognitive function, but the CABG group improved at 4 months, however the biological AVR did not (Zimpfer et al., 2002).

Patients undergoing surgery can face a double cerebral insult. There first would be related to cardiopulmonary bypass, cardioplegia and subsequent restoration. The second would be the risk of thromboembolic stroke. Therefore the neuronal cells would experience ischaemia, systemic inflammation and possible infarction. All of which will influence cerebral activity and may have long term health consequences.

Various areas of cerebral function are assessed including executive function, verbal fluency, semantic fluency, immediate and delayed recall, manual dexterity, ability to complete task, evidence of depression or anxiety. What is unknown is the consequences on the micro-infarcts following TAVI, although there are concerns that the events may contribute to vascular dementia.

1.12.2 Neurocognitive function in TAVI

There are limited studies of neurocognitive function in the TAVI patient group. A study in 27 transapical TAVI patients with a 3 month follow up period did not show any decline in 5 cognitive domains (short term memory, working memory, verbal learning, delayed recognition and verbal fluency) (Knipp et al., 2013). However, they did not conduct any paper pencil tests such as, trail making A and B in the TAVI group because of their poor general condition.

A comprehensive assessment neurocognitive assessment will provide information on the significance of the cerebral lesions detected on MRI as TAVI is being considered in the intermediate to high risk groups.

1.13 Aims and Objectives

The aim of the study was to recruit a minimum of 25 patients who were being treated by Transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) and perform a cerebral MRI and cardiac MRI scan at baseline. After intervention a cerebral MRI prior to discharge and at 6 months follow up cardiac MRI were necessary. Also a comprehensive neurocognitive assessment at 4 time points: baseline, 30 days, 6 months and 12 months was conducted.

The primary outcomes are:

1. To assess the relationship of cerebral infarction and the effect on health-related quality of life over 6 months.
2. To assess the relationship of cerebral infarction and the effect on neurocognitive function over 12 months

3. To describe the changes in cardiac reverse remodelling after intervention on aortic stenosis specifically to assess the change in diffuse and focal myocardial fibrosis after TAVI and SAVR.

2 Chapter 2 Methods

The following chapter describes the general methods used during the period of study and further details including ethics are described in the individual study chapters.

2.1 Patient Recruitment

Patients with severe aortic stenosis were prospectively recruited between March 2012 and April 2013. Severe AS was defined by echocardiography with an aortic valve area <0.8cm^2 or a peak velocity of >4ms^{-1} through the aortic valve using continuous wave Doppler. A multidisciplinary team including Cardiac surgeons, Cardiologists and anaesthetists would assess the patients' suitability for TAVI or SAVR. The TAVI patient group are generally >65 years old, with a higher EuroSCORE and/or significant co-morbidities that would prevent safe conventional surgery. Exclusion criteria were: permanent pacemakers, claustrophobia, or being unable to lie in the scanner for 60 minutes.

Patients accepted for TAVI or SAVR were sent a patient information sheet (PIS) by post then a follow up telephone call to discuss any questions. Once verbal consent was obtained an appointment was booked for the baseline visit at which time formal written consent was taken. Baseline visit consisted of: cerebral and cardiac MRI and neurocognitive testing before the TAVI or SAVR. After the procedure the patient would have the second cerebral MRI before discharge from the hospital. Patients who required a permanent pacemaker would no longer continue with the MRI component but would be invited back for neurocognitive assessment at 30 days, 6 months and 12

months. Although MR safe/compatible pacemakers and leads are available, these were not included in the studies. The cerebral scans would have been unaffected, but the cardiac component would have been affected by artefacts. Patients were contacted by telephone to have a follow up cerebral and cardiac MRI at 6 months.

2.2 Patient Risk Factors and Demographics

All patient characteristics were recorded on a study clinical record form (appendix) and transferred to a secure password protected database. The following were recorded: age, sex, height, weight, significant co-morbidities (Hypertension, IHD, MI, DM, Hyperlipidaemia, AF, Stroke/TIA, PVD, and COPD). The EuroSCORE and EuroSCORE II were calculated along with the STS score.

2.3 TAVI procedure

TAVI was performed under general anaesthesia in a dedicated cardiac catheter laboratory. The 18 French third generation CoreValve™ prosthesis (Medtronic, Minneapolis, USA) was used at the Leeds General infirmary. The femoral or subclavian artery was accessed with a valved sheath. The native valve was crossed with a guidewire under x-ray fluoroscopy. A temporary pacing wire was placed in the RV apex for rapid pacing during intervention. Balloon aortic valvuloplasty was performed with rapid pacing. The CoreValve was delivered gradually to maintain satisfactory positioning. The patients were fully heparinised during TAVI and the activated clotting time of >200sec. Patients were on Aspirin 75mg once a day and on day 3

clopidogrel 75mg once a day was initiated for a period of 6 months if there were no bleeding complications.

2.4 SAVR general method

All surgical patients were operated at the Leeds General Infirmary. A midline sternotomy was performed and TOE was used intra-operatively. Following standard heparinisation the aorta was cross clamped and cardiopulmonary bypass was initiated with mild hypothermia. The type and size of the surgical prosthesis was determined by annular size, patient characteristics, surgical and patient preference. Some patients required coronary artery bypass grafting.

2.5 Cerebral Diffusion Weighted Imaging (DWI) for Cerebral Infarction

Before (pre) and after (post) TAVI or SAVR cerebral imaging was performed on the 1.5 Tesla scanner (Intera, Philips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). The patient had to be able to lie supine within a specific head coil for approximately 5 to 10 minutes for the duration of the scan.

Cerebral Protocol: 22 slices, 5 mm thickness, 1 mm gap. The typical field of view (FOV) was 350 and relative FOV 100.

i. Survey

ii. T2 weighted Fast Field Echo (FFE)

iii. Turbo Field echo (TFE)

iv. Diffusion Weighted imaging (DWI)

The images were transferred as DICOM files for analysis. Two experienced Neuroradiologist independently reported the images and were blinded to the clinical data. The numbers of cerebral infarcts were recorded along with the arterial distribution and the infarction volume was quantified using planimetry technique in QMass post-processing software (version 7.2, Medis, Netherlands).

2.6 Cardiovascular MRI protocol

The study was performed on the 1.5 Tesla (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany) for all visits (Baseline, 6 months) using the same imaging protocol.

Protocol:

i. Survey

ii. Localisers: Using cine steady state free precession (SSFP), the vertical long axis (VLA) view and Horizontal long axis (HLA) view are identified. (1 slice, 8mm thickness with 24 phases; FOV 400, RFOV 100.)

iii. Black blood T1 trans-axial acquisition: 24 slices with a thickness of 8mm using 24 phases. (FOV 340, RFOV 80)

iv. LV volumes: These are planned using the VLA and HLA views to identify the short axis of the LV and cine slices are then acquired. Typically 10 to 12 contiguous slices are acquired covering from the mitral valve plane to beyond the apex. (Thickness: 10mm, 0 mm gap, 30 phases. FOV 340, RFOV 100)

v. Left ventricular outflow tract (LVOT): The sagittal/oblique view is acquired first by planning from the LV stack, and then the image plane is rotated 90 degrees to obtain the coronal view. The cine images consist of 3 to 5 slices. (Thickness: 6mm, 0 mm gap, 30 phases, FOV 380, RFOV 100)

vi. AV phase encoded velocity mapping. A through plane scan is planned from the two previously acquired LVOT views at the sino-tubular junction. The initial VENC is set higher at 400cm/s for the baseline scan and assess for aliasing, if present the VENC was increased by 50 cm/s. For follow up studies the VENC was set at 250cm/s and adjusted accordingly. The acquired phase contrast image should be check for aliasing and if present then the VENC should be increased by 50cm/s. Both breath held and non-breath held images are acquired with 40 phases. (1 slice, 10 mm thickness, FOV 350, RFOV 85)

vii. Aortic arch views. SSFP cines are to include the whole arch and are planned through the ascending, transverse and descending aorta. (7 slices, 6mm thickness, 0 gap, 24 phases, FOV 320, RFOV 100)

viii. Aortic Distensibility. Performed using high temporal resolution cine imaging with the imaging plane is perpendicular to the ascending and descending aorta at the level of the bifurcation of the pulmonary artery. (1 slice, 8 mm thickness with 0 mm gap, 50 phases, FOV 320, RFOV 100)

ix. Aortic Pulse Wave Velocity (PWV). A through plane phase encoded velocity mapped image is acquired in the same geometric plane as the distensibility cines. The VENC is set at 250cm/s and increased if there are aliasing pixels seen. Again both breath held (FOV 350 RFOV 85) and non-breath held (FOV 400 RFOV 70) images are acquired. (1 slice, 10 mm thickness, 40 phases)

x. '3 of 5'. The 3 slices will reflect the basal, mid ventricular and apical views in the SA of the left ventricle. The 3 slices are planned from 5 slices with the ventricle in systole using the VLA and 4Ch images. (10 mm thickness, 24 phases, FOV 400, RFOV 100)

xi. Myocardial Tagging. Complementary spatial modulation of magnetization (CSPAMM) pulse sequence is used to generate tags on the apical, mid and basal ventricular slices, using the '3 of 5' technique. (10mm thickness, 18 phases, 2 stacks, FOV 300, RFOV 75)

xii. T1 mapping: This is performed using the modified Look-Locker Inversion recovery (MOLLI) as described by Messroghli (Messroghli et al., 2004). This was selected as it was available on the scanner and had been previously developed and validated, along with 3 clinical studies in aortic regurgitation and ischaemic heart disease. The other t1 mapping techniques were not available during the study period. For each slice, there are 3 successive Look- Locker acquisitions (LL_1, LL_2 and LL_3) with 3

(TI=100ms), 3 (TI=200ms) and 5 (TI=350ms) single shot readouts respectively. A total of 11(3, 3, 5) images are obtained. (3 slices, 3 of 5 technique, 8 mm thickness, FOV 380, RFOV 340). The process is performed pre-contrast, then 5 and 15 minutes after contrast.

xiii. Look-Locker inversion time scout. A single mid ventricular slice to obtain the inversion time (TI) at which the myocardium is nulled. (10mm thickness, FOV 390, RFOV 95)

xiv. Late Gadolinium Enhancement. A T1-weighted segmented inversion-recovery gradient echo pulse sequence is used with the inversion time being adjusted according to the LL scan. Each slice is acquired with one breath hold. (12 SA, 3 VLA, 3 HLA slices, 10mm thickness, 0 gap, FOV 350, RFOV 100)

2.7 Neuropsychological Assessment

The neuropsychological assessment was conducted by trained doctors and trained research nurses. The neuropsychological assessment training was performed by an academic clinical psychologist, who also checked for data quality and consistency of assessment. The assessment was undertaken in a quiet room at a table with chairs for the assessor and patient. The baseline and 6 month visits were conducted before the MRI examination; 30 day and 12 month assessments were conducted at home or hospital. The handedness and years of education for each patient were recorded.

2.7.1 National Adult Reading Test (NART)

This is a quick method to estimate premorbid verbal IQ by testing the correct pronunciation of irregular English words (Nelson and O'Connell, 1978). The number of errors is recorded.

2.7.2 Mini Mental State Examination (MMSE)

This is a screening test for dementia and decline in cognition which is commonly used in clinical practice (Folstein et al., 1975). The MMSE has 11 items that assess orientation, short term memory, attention and visual spatial skills. The total score indicates levels of cognitive impairment: 21-24 is mild, 10-20 is moderate, <10 are severe.

2.7.3 Hopkins Verbal Learning Test (HVLT)

This assesses verbal memory thorough simple list learning, multiple reminder trials and delayed recognition and recall (Brandt, 1991). A list 12 items (semantically grouped) are slowly read out and the patient has to recall them (3 trials). Recognition memory is assessed thorough an additional list with 12 distractor items (6 related and 6 unrelated). After 30 minutes an attempt at recalling the original list should be made for delayed recall score. The immediate recall, total recall and a delayed recall scores are collected. In addition the numbers of related and unrelated errors are recorded.

2.7.4 Rey-Osterrieth Complex Figure test (ROCF)

This assesses the visio-constructive skills of the patient (Rey, 1941). The patient is asked to copy a complicated geometric figure with a HB pencil. Once the patient has completed the drawing, the figures are removed and the patient is asked to redraw the image from memory. After a delay of 30 minutes the patient is asked to redraw the figure from memory. All 3

drawings are scored according to how the lines are placed (poorly placed vs. Properly placed) and whether they are correct or distorted/incomplete or absent/not recognisable.

2.7.5 Trail making A and B

This is a test of psychomotor speed which has been validated (Lezak, 2004). The patient is timed with a digital stopwatch and asked to draw lines with a pencil between the circled numbers (TMT-A) in ascending order as fast as they can. For TMT-B the patient has to alternate between a number and a letter maintaining numerical and alphabetical order. TMT-A includes 1 to 25 digits, TMT-B consists of digits and letters (1-A-2B-3C...-L13). Both times are recorded in seconds.

2.7.6 Controlled oral word association test (COWAT)

This is a test of higher executive function using a verbal and semantic fluency tasks (Tombaugh et al., 1999).

a. **FAS** The patient is asked to say words beginning with, F, A, and S within one minute for each letter. The total number of words for all three letters is recorded along with number of errors.

b. **Semantic fluency** Patient is asked to say words that are within a semantic category within one minute. The total number of words and the number of errors are recorded. The categories for each visit are: animals (baseline and 12 month), clothing (30 days), and foods (6 month).

c. **Switching fluency.** Patient is asked to say words that alternate between two categories. The total number of pairs and errors are recorded.

2.7.7 Letter Number sequencing (LNS)

This is taken from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997). The patient hears a sequence of random letters and numbers and is asked to repeat the numbers and letters back to the assessor but should give the numbers first followed by the letter. Both have to be in numerical and alphabetical order. The sequence increase in length until the patient fails three times. The number of correct responses is recorded.

2.7.8 Digit-symbol substitution test (DSST)

This is taken from the Wechsler Adult Intelligence scale-R (WAIS-R) (Wechsler, 1981).This measures attention, perceptual speed, motor speed, visual scanning and memory. The patient is given a form with 9 symbols corresponding with 9 digits. Below there are rows of digits with empty boxes below. The patient has 2 minutes to fill in as many corresponding symbols as possible. The total number of correct associations is collected.

2.7.9 Grooved Pegboard testing

The grooved pegboard test is a manipulative dexterity test that consisted of 25 holes into which a grooved peg must be placed (Grooved Pegboard, model 32025, Lafayette Instrument, IN, USA. www.lafayetteinstrument.com) (Lezak, 1995). All the pegs are identical. All patients are given the same instructions:

"*This is a pegboard and these are the pegs. All pegs are the same. They have a groove, that is a round side and a square side and so do the holes in*

the boards. What you must do is match the groove of the peg with the groove of the board and put these pegs into the holes like this (The examiner demonstrates). When I say go, begin here and put the pegs into the board as fast as you can using only your dominant hand. Fill the top row then move on to the next row, ready go".

The time to complete the test using the dominant hand is recorded in seconds using a standard stopwatch. The number of dropped pegs is recorded. The pegs are then removed by the examiner and the participant is asked to repeat the test using the non-dominant hand (Instruments, 2003). The grooved pegboard test has been part of other neuropsychological assessment batteries such as the Repeatable Cognitive-Perceptual-Motor battery (Lewis and Kupke, 1992).

Figure 2-1 Grooved Pegboard Test

2.7.10 Modified Rankins Scale

This is a quick 6 point scale that assesses the level of disability (Lyden and Lau, 1991) (Kappetein et al., 2013). This ranges from 0 = no disability, 1=no

significant disability despite symptoms, 2= slight disability, 3=moderate, 4= moderate to severe, 5= Severe disability, 6=Death.

2.8 Health Related Quality of Life

Two generic questionnaires were conducted at each time point (baseline, 30 days, 6 months and 12 months). This was performed at the same time as the neuropsychological assessment.

2.8.1 EQ5D (EuroQoL)

This covers 5 domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Szende et al., 2007). This allows calculation of a utility measure between 0 (death) and 1(full health). The questionnaire is scored using the UK population time-trade off valuation data set. A visual analogue score was also completed by patients indicating their health status as a percentage between 0 (worst imaginable) to 100 (best possible).

2.8.2 Short Form-12

The SF-12 survey (Short Form 12 v2, Quality Metric, Lincoln, Rhode Island, USA) covers 12 questions related to eight multi-item domains which measure: physical functioning, role limitations to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional difficulties and mental health (Ware et al., 1996). The eight domains are combined to produce an average score related to physical (physical component summary PCS) and mental (mental component score MCS). All data are adjusted to give normalised based scores (NBS) using dedicated scoring software (Quality Metric Inc. Lincoln Rhode Island).

2.9 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale is a validated and reliable instrument to identify features of mood disorders in the general population (Zigmond and Snaith, 1983). There are 14 questions to address around the patient's feelings which are scored 0 to 3. After completing the sheet the assessor adds the scores for Anxiety and Depression. A score of less than 7 is normal, 8 to 10=mild, 11-14=moderate and 15 to 21=severe mood affective disorder (Bjelland et al., 2002). HADS was obtained from GL assessments, Swindon (www.gl-assessment.co.uk).

2.9.1 Statistical Analysis

Data will be presented as mean with standard deviations or median and interquartile ranges. Continuous variables will be compared with paired or unpaired t tests and for more than two groups then analysis of variance (ANOVA) will be used. Most of the data will be analysed by ANOVA for repeated measures. Discrete variables will be compared with chi squared test or Mann-Whitney or Wilcoxon signed rank tests.

Further statistical methods were used depending on the individual results chapters such as mixed-effect modelling.

The software packages used during the study were Microsoft Excel and SPSS.

3 Consequence of Cerebral Embolism following Transcatheter Aortic Valve Implantation (TAVI) compared to Contemporary Surgical Aortic Valve Replacement (SAVR): effect on Health-Related Quality of Life (HRQoL) and DWI

3.1 ABSTRACT

Background: The incidence of cerebral micro-infarcts is higher after Transcatheter Aortic Valve Implantation (TAVI) compared to surgical aortic valve replacement (SAVR). It is unknown whether these lesions persist and what direct impact they have on Health-Related Quality of Life (HRQoL). The objective was to identify predictors of cerebral micro-infarction and measure their effect on HRQoL over 6 months after TAVI compared to SAVR.

Methods and Results: Cerebral MR imaging was conducted at baseline, post-procedure and 6m using diffusion weighted imaging (DWI). HRQoL was measured at baseline, 30d and 6m with SF12v2 and EQ5D questionnaires. 111 patients (TAVI n=71; SAVR n=40) were studied. The incidence (54(77%) vs. 17(43%), p=0.001) and mean number (3.4±4.9 vs. 1.2±1.8, p=0.001) of new micro-infarcts was greater after TAVI compared to SAVR. The mean total volume per micro-infarct was smaller in TAVI compared to SAVR (0.23±0.24ml vs. 0.76±1.8ml, p=0.04). The strongest associations for micro-infarction were: TAVI (arch atheroma grade r=0.46, p=0.0001); SAVR (concomitant coronary artery bypass grafting (r=-0.33, p=0.03)).

Physical component scores (PCS) in TAVI increased after 30d (32.1±6.6 vs. 38.9±7.0, p<0.0001) and 6m (40.4±9.3, p<0.0001); the improvement occurred later in SAVR (baseline: 34.9±10.6, 30d: 35.9±10.2, 6m: 42.8±11.2, p<0.001). Following TAVI, there were no differences in the SF12v2 scores according to the presence or size of new cerebral infarction.

Conclusion: Cerebral micro-infarctions are more common post-TAVI compared to SAVR but appear to have no negative effect on early (30days) or medium term (6 month) HRQoL. Aortic atheroma (TAVI) and concomitant CABG (SAVR) are independent risk factors for cerebral micro-infarction.

3.2 INTRODUCTION

Transcatheter aortic valve implantation (TAVI) in patients with symptomatic severe aortic stenosis (AS) is an alternative to medical therapy or surgical aortic valve replacement (SAVR) in those at high surgical risk (Vahanian et al., 2012). TAVI has been shown to reduce mortality, and improve patient symptoms and health related quality of life (HRQoL) (Kodali et al., 2012a, Fairbairn et al., 2012b). Whilst TAVI appears cost-effective compared to SAVR, embolic cerebral infarction remains a concern due to its frequency and the associated morbidity, mortality and healthcare costs (Fairbairn et al., 2013a). This will be increasingly important if TAVI is considered for lower-risk or younger patient populations.

Previous work has shown that embolic cerebral infarction occurs following both TAVI and SAVR, with the majority remaining subclinical (Kahlert et al., 2010, Fairbairn et al., 2012b, Kahlert et al., 2012, Ghanem et al., 2010b, Rodes-Cabau et al., 2011, Stolz et al., 2004). The incidence of cerebral emboli appears to be greater post-TAVI, with no significant difference between the access routes (transfemoral vs. transapical) or valve types (Medtronic CoreValve™ vs. Edwards Sapien™)(Rodes-Cabau et al., 2011). The clinical consequences of these ‘silent infarcts’ and identification of risk factors is yet to be fully established. Two studies have assessed basic cerebral function using a mini-mental state examination (MMSE) pre- and post-TAVI, demonstrating no significant change at 3 months (Kahlert et al., 2010, Kahlert et al., 2012). We have previously described the early (30d) effect of cerebral emboli upon patient HRQoL after TAVI, and identified age and aortic atheroma severity as risk factors (Fairbairn et al., 2012b).

However, there is uncertainty regarding the long-term significance of these silent infarcts, whether their location determines functional status, and how this compares to a contemporary SAVR group.

The principal aim of this study was to compare the incidence and natural history of cerebral embolization and their impact on medium-term HRQoL between a TAVI and SAVR group. A secondary aim was to determine factors associated with cerebral embolization.

3.3 METHODS

3.3.1 Study participants

Patients with severe symptomatic AS were prospectively recruited if they were due to undergo either SAVR or TAVI at a large tertiary surgical centre. Severe AS was defined by transthoracic echocardiography (TTE) with an aortic valve area of $<0.8cm^2$ and a peak velocity of $>4ms^{-1}$. Between May 2008 and February 2013 TAVI patients were selected by a multidisciplinary heart team in accordance with contemporary UK guidance (Kappetein et al., 2012). Older, higher-risk (based on EuroSCORE) SAVR patients with one or more co-morbidities were identified for recruitment so that they more closely represented the TAVI population (complete matching was not possible due to the current UK TAVI guidelines). Exclusion criteria included any contraindication to MRI. Some study patients overlapped as they had quality of life assessments (Ch 3) and neurocognitive assessment (Ch 4).The study was approved by the institutional ethics committee and complied with the Declaration of Helsinki. All patients provided written informed consent.

3.3.2 TAVI procedure

TAVI was performed with the Medtronic CoreValve™ prosthesis by a single experienced, high-volume operator as previously described (Piazza et al., 2008). Briefly, all procedures were performed under general anaesthesia with X-ray fluoroscopy and transoesophageal echocardiographic (TOE) guidance. All patients received heparin to maintain an activated clotting time >200s and were treated with dual anti-platelet therapy (aspirin and clopidogrel) for 3 to 6 months post-procedure.

3.3.3 SAVR operation

Midline sternotomy was performed for all surgical patients using intra-operative TEE guidance. Following standard heparinization the aorta was cross-clamped and cardiopulmonary bypass was initiated with mild hypothermia. The type and size of surgical prosthesis varied dependent upon annulus size, patient characteristics, surgical and patient preference. Coronary artery bypass grafting was concomitantly performed when indicated.

3.3.4 Cerebral MRI

Cerebral magnetic resonance imaging (MRI) was conducted pre- and post-procedure (within 7d) and again at 6m using identical imaging protocols. MRI was performed on the same 1.5T system for all serial scans for any individual patient (Intera, Phillips Healthcare, Netherlands or Avanto, Siemens Medical Systems, Germany). The imaging protocol consisted of T2 weighted fast field echo, T2 turbo field echo and diffusion weighted imaging (DWI) (22 slices, 5mm thick, 1mm gap, FOV 350, RFOV 100). Each scan was independently assessed by three experienced Neuroradiologists, blinded to clinical details. In the case of disagreement, a consensus view

was recorded. Cerebral embolism or micro-infarction was defined as a new restricted diffusion lesion on DWI. New cerebral micro-infarcts were localised to hemisphere and vascular territory. As previously described, infarct diameter was used to categorise patients into small or large lesion sub-groups (<5mm or >5mm; in the case of multiple lesions the largest lesion was used to determine status). The total volume of micro-infarcts (ml) were measured off-line using standard post-processing software (QMass7.2, Medis, The Netherlands).

3.3.5 Neurological assessment and status

A detailed neurological examination was conducted prior to intervention and daily after the procedure by an experienced consultant physician until hospital discharge (typically day 7). A National Institutes of Health Stroke Scale (NIHSS) score was recorded. Transient ischaemic attack was defined as any focal neurological deficit that lasted <24h. Stroke was defined as any persistent focal neurological deficit lasting >24h.

3.3.6 Health related quality of life assessment

Health status was evaluated at baseline, 30 days(30d) and 6 months(6m) (Valve Academic Research Consortium recommended time-points) using two generic health related quality of life (HRQoL) questionnaires: short form-12 health outcomes (SF12v2, QualityMetric, Lincoln, Rhode Island, USA) and EQ5D (©EuroQoL). The SF12v2 survey covers eight domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional difficulties and mental health. Domains are combined to produce an average score related to physical (physical component summary (PCS)) and mental

(mental component summary (MCS)) health. Data are adjusted to give normalised based scores (NBS) using dedicated scoring software (QualityMetric Inc, Lincoln, Rhode Island, USA).

The EQ5D questionnaire covers 5 domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This provides a utility measure between 0 (death) and 1(full health). The questionnaire was scored using the UK population time-trade off valuation data set. A visual analogue score was also completed by patients indicating their health as a percentage between 0 (worst imaginable health) and 100 (best possible health).

3.3.7 Risk factors for embolism

Demographic and procedural risk factors for cerebral embolization were recorded for all patients. The ascending, arch and descending thoracic aorta were imaged using TOE in order to grade severity of atheroma in accordance with a recognised 5-point scale (Barbut et al., 1997): 1=Normal, 2=Severe intimal thickening without protruding atheroma, 3=Atheroma <5mm, 4=Atheroma >5mm, 5=Mobile atheroma of any size. In addition, aortic valve calcification was graded using published criteria: 1=no calcification, 2=mild calcification, 3=moderate calcification, 4=severe calcification (Rosenhek et al., 2000). All patients were having TOE as part of their procedures and so they data was more easily available. CT aortogram for TAVI assessment was not widely performed during the start of this study, but could have given information regarding arch atheroma.

3.3.8 Statistical analysis

Continuous variables are presented as mean±SD and categorical variables as frequency and percentage. Normality was determined by a Shapiro-Wilks test. Comparative statistics were performed using the Student *t*-test or Chi-

squared test. Non-normal data were compared with the Mann-Whitney test or Wilcoxon signed rank test. HRQoL scores (baseline, 30d and 6m) were analysed using linear mixed-effects modelling with an unstructured covariance matrix and time as the fixed effect and Bonferroni post-hoc correction for multiple comparisons. The linear mixed-effects model was used instead of repeated measures ANOVA to overcome any potential impact of missing data and the need for a balanced design.

Our sample size was based on published data to detect a 5 to 10 point difference in SF12v2 summary scores and a 0.1 point difference in EQ5D score. To achieve a power of 80% we needed 33 patients in each group, with an alpha error set at 0.05(two sided) (Ware, 2002).

All analyses were performed using the PASW software (SPSS 19, IBM, Chicago, Ill). Two-sided $p<0.05$ was considered statistically significant. Univariate linear regression analysis was performed using all identified covariates and compared to the number of new infarcts post procedure. Variables with $p\leq0.1$ were entered into a stepwise multivariable regression analysis. Propensity scores (predictive probability) for receiving TAVI were calculated using a binary logistic regression model (TAVI Yes=1, No=0) with confounding variables entered as co-variates (Age, sex, EuroSCORE, STS, BSA, NYHA class, diabetes, hypertension, hypercholesterolaemia, AF, stroke, prior CABG, PVD, porcelain aorta, valve calcification, aortic atheroma grade). Propensity score adjustment for number of new cerebral infarcts was performed by linear regression analysis with number of new cerebral infarcts as the dependent variable and the independent variables were TAVI (yes or no) and the propensity scores

3.4 RESULTS

3.4.1 Patient and procedural factors

One hundred and eleven consecutive patients were recruited (71 TAVI and 40 SAVR). Baseline patient characteristics are presented in Table 3-1. The TAVI group were older (80±6.3 vs. 70.8±8.3 years, $p<0.001$), had higher logistic EuroSCORE, EuroSCORE II and STS scores, with a higher prevalence of AF, CABG, PVD and aortic atheroma (Table 3-1). Overall the two groups are markedly different which is expected given TAVI patients are surgical turndowns and the differences may confound subsequent comparisons. Procedural data for both TAVI and SAVR are detailed in Table 3-2. No major peri-procedural complications were reported in the study population.

Table 3-1 Baseline patient characteristics

Demographics and clinical characteristics	TAVI (n=71)	SAVR (n=40)	p value
Age, years	80.5±6.3	70.8±8.3	<0.0001
Male, n (%)	31 (44)	27 (68)	0.02
BSA, m^2	1.78±0.2	1.9±0.4	0.007
BMI, kgm^{-2}	27.4±4.7	29.2±4.7	0.07
NYHA Class, n (%)			
I	0	1 (2)	0.002*
II	4 (6)	2 (5)	
III	47 (66)	37 (93)	
IV	20 (28)	0	
EuroSCORE, (%)	18.2±10.9	5.9±2.9	<0.0001
EuroSCORE II, (%)	6.1±3.6	1.5±0.6	<0.0001
STS Score (%)	6.0±2.8	2.4±1.7	<0.0001
Hypertension, n (%)	37 (52)	27 (68)	0.16
Diabetes, n (%)	27 (38)	8 (20)	0.06
Hypercholesterolaemia, n (%)	36 (51)	29 (73)	0.03
Atrial fibrillation, n (%)	23 (32)	4 (10)	0.01
Stroke/TIA, n (%)	21(30)	5 (13)	0.06
MI, n (%)	2 (3)	5 (13)	0.10
CABG, n (%)	15 (21)	0	0.0001
PVD, n (%)	24 (34)	3 (8)	0.002
COPD, n (%)	10 (14)	9 (23)	0.29
Creatinine $\mu molL^{-1}$	124±69	85±18	<0.0001
eGFR ml/min/1.73m^2	55±21	88±29	<0.0001
Porcelain Aorta, n (%)	11 (16)	0	<0.0001
Aortic Valve Calcification grade, n (%)			
IV	51 (72)	24 (60)	p=0.46*
III	14 (20)	16 (40)	
II	5 (7)	0	
I	1 (2)	0	
Aortic Atheroma Grade, (median, Q1-Q3)			
Ascending	2 (2–3)	2 (1–2)	<0.0001*
Arch	2 (1–3)	2 (1–2)	0.003*
Descending	2 (2–3)	2 (1–2)	<0.0001*

Data are Mean±SD, n(%). TAVI=Transcatheter Aortic Valve Implantation, SAVR=Surgical Aortic Valve Replacement, BSA=body surface area, BMI=body mass index, NYHA=New York Heart Association, STS=Society of Thoracic Surgery, TIA=transient ischaemic attack, MI=myocardial infarction, CABG=coronary artery bypass grafting, PVD=peripheral vascular disease, COPD=chronic obstructive pulmonary disease, eGFR=estimated glomerular filtration rate. *Mann Whitney U test.

Table 3-2 Procedural and operative data

		n (%)
TAVI		
Medtronic CoreValve size	31mm	2 (3)
	29mm	47 (66)
	26mm	19 (27)
	23mm	3 (4)
Vascular access	Femoral	65 (91)
	Subclavian	5 (7)
	Carotid	1 (1.5)
Procedure-time, (min)		138±71
Fluoroscopy-time, (min)		23±8
Contrast volume, (ml)		157±48
SAVR		
Biological, n (%)		34 (85)
Mechanical, n (%)		6 (15)
Size, (mm)(median, range)		21 (18–29)
Bypass-time, (min)(mean±SD)	All	109±48
	SAVR only	72±46
	SAVR and CABG	100±23
Cross-clamp-time,(min) (mean±SD)	All	82±41
	SAVR only	92±47
	SAVR and CABG	139±32
CABG, n (%)		13 (33)

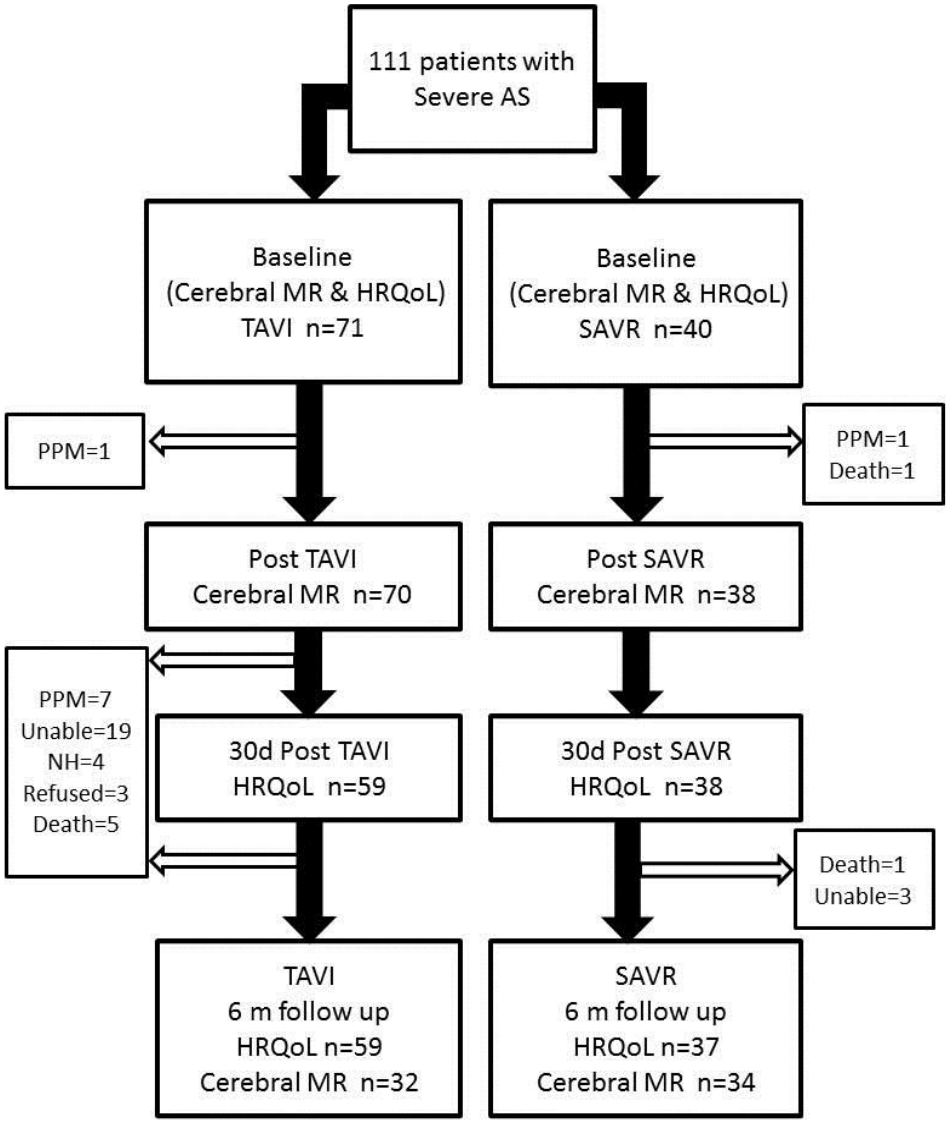
Abbreviations as in Table 3-1

3.4.2 Detection of cerebral emboli

All 111 (TAVI=71, SAVR=40) patients completed the baseline MRI scan. The majority of patients 108 (97%) completed pre-and early post-procedural scans (2 pacemaker implantations (TAVI=1, SAVR=1) and 1 death (SAVR)). Six-month follow-up scans were performed in 66 (59%) patients (TAVI=32, SAVR=34); 38 TAVI patients could not re-attend (physically unable to attend the department due to frailty=19, declined a further MRI scan=3, pacemaker inserted in the follow up period=7) (Figure 3-1). 4 SAVR patients did not have the 6-month scan (death=1, unable to attend due to poor health=3).

Figure 3-1. Study flow-diagram of patient recruitment and the 3-cerebral MRI and Health related Quality of Life (HRQoL) time-points.

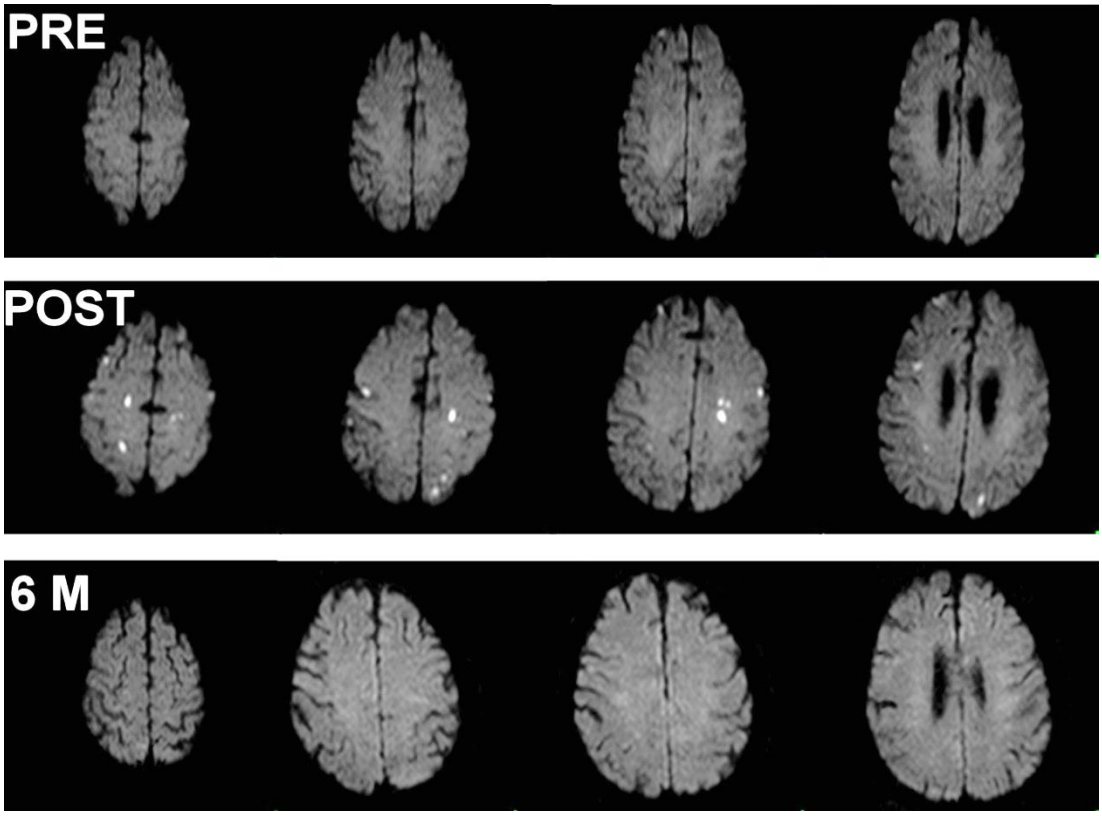
(PPM=permanent pacemaker, NH=nursing home)



Baseline: The cerebral scan showed TAVI patients had greater pre-existing cerebral micro-infarction than the SAVR group (n=26(37%) vs. n=6(15%), p=0.012). There was no difference in the baseline distribution of infarction between TAVI and SAVR (anterior: 86% vs. 44%; posterior: 14% vs. 56%, Chi-square=2.86, p=0.09).

Post-procedure: Figure 2 shows a typical example of new micro-infarction detected by DWI. The incidence of new embolic micro-infarcts on DWI-MRI were higher in TAVI patients compared to SAVR (54(77%) vs. 17(43%), p=0.001). The mean number of new cerebral micro-infarctions per patient was 3.4±4.9 (median=2 (Q1-Q3 1–4)) for TAVI and 1.2±1.8 (median=0 (Q1-Q3 0–3) for SAVR (p=0.001). The mean volume per micro-infarct was significantly smaller in TAVI compared to SAVR (0.23±0.24ml vs. 0.76±1.8ml, p=0.04). However, there was no difference in the mean total volume of new micro-infarction between TAVI (median 0.36ml, Q1-Q3 0.12–1.93) and SAVR (median 0.24ml, Q1-Q3 0.07–1.28, p=0.48) groups. Patients with new micro-infarcts were categorised according to size of the DWI lesion: for TAVI: <5mm, n=32 (46%); >5mm, n=22 (31%); SAVR: <5mm, n=7 (18%); >5mm n=10 (25%). The arterial distribution of new cerebral infarctions post-TAVI and SAVR were similar between the groups (anterior 62% vs. 66%; posterior 38% vs. 34%, p=0.65). (TAVI: anterior cerebral artery (ACA)=17%, middle cerebral artery (MCA)=45%, posterior cerebral artery (PCA)=19%, vertebrobasilar artery (VB)=19%; SAVR: ACA=24%, MCA=42%, PCA=17%, VB= 17%).

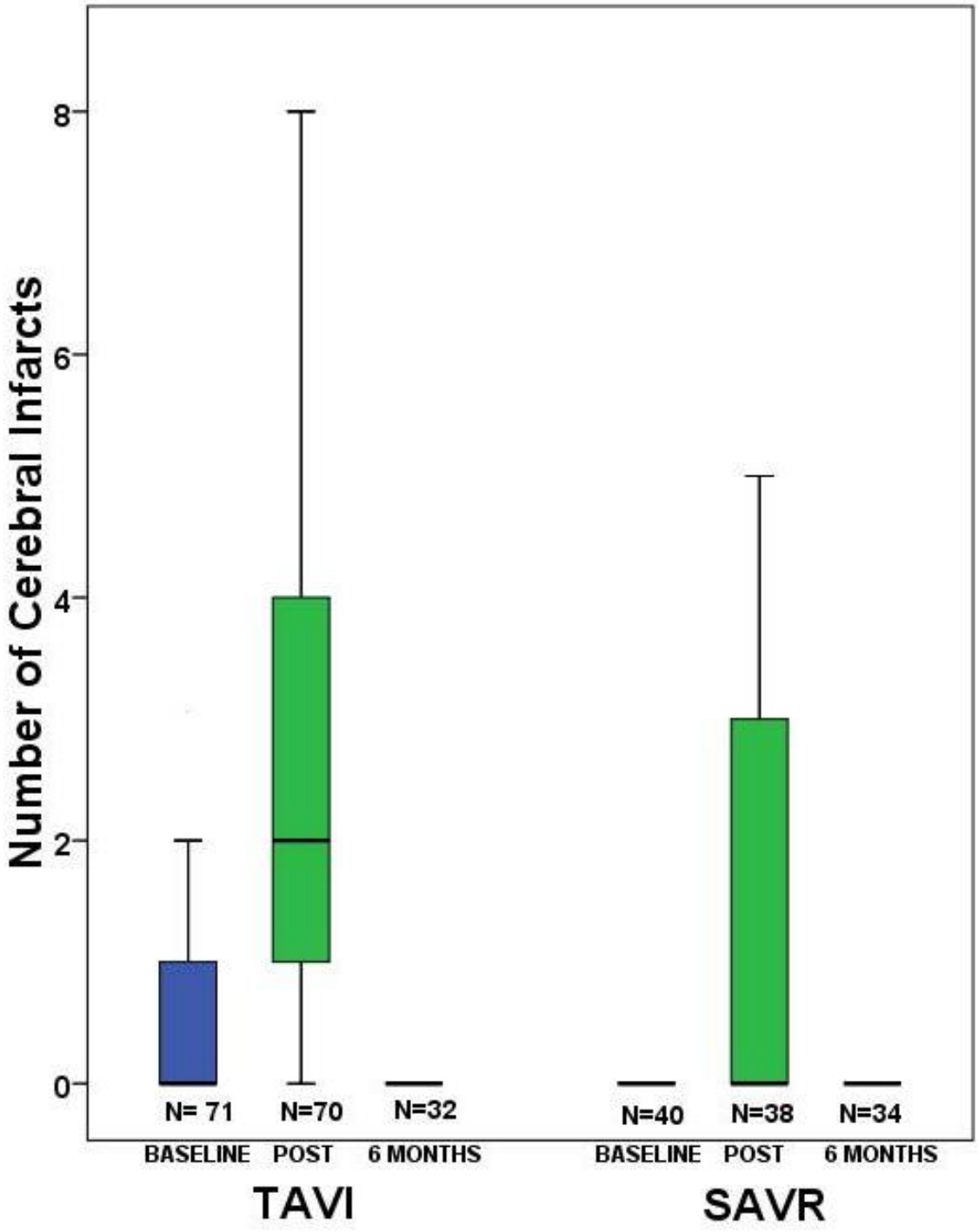
Figure 3-2 DWI before and after TAVI with multiple high-intensity lesions seen in both hemispheres consistent with embolization and their subsequent resolution after 6 months.



6 months follow-up: There were relatively few new micro-infarcts in both groups (TAVI n=2(6.3%) vs. SAVR n=2(5.8%), p=0.68). All previous DWI lesions had resolved in both groups, however, more TAVI patients compared to SAVR had evidence of gliosis (13 (40.6%) vs. 8 (23.5%) p=0.024 respectively). Figure 3-3 shows the absolute number of cerebral micro-infarcts across the three time points for TAVI and SAVR populations.

Figure 3-3 Box and whisker plots of DWI-detected cerebral infarcts (TAVI and SAVR) at baseline, post-procedure and at 6 months.

(Black horizontal line is the median, boxes represent the 2nd and 3rd quartiles, whiskers are 1.5x interquartile range(IQR).)



3.4.3 Neurological assessment

Two (2.8%) TAVI patients had early (<30d) focal and persistent neurological signs such that a diagnosis of minor stroke was made (NIHSS scores 2 and 4). There was 1(2.5%) early stroke in the SAVR group (NIHSS=2). No stroke or TIA occurred in the 6m follow-up period in either group.

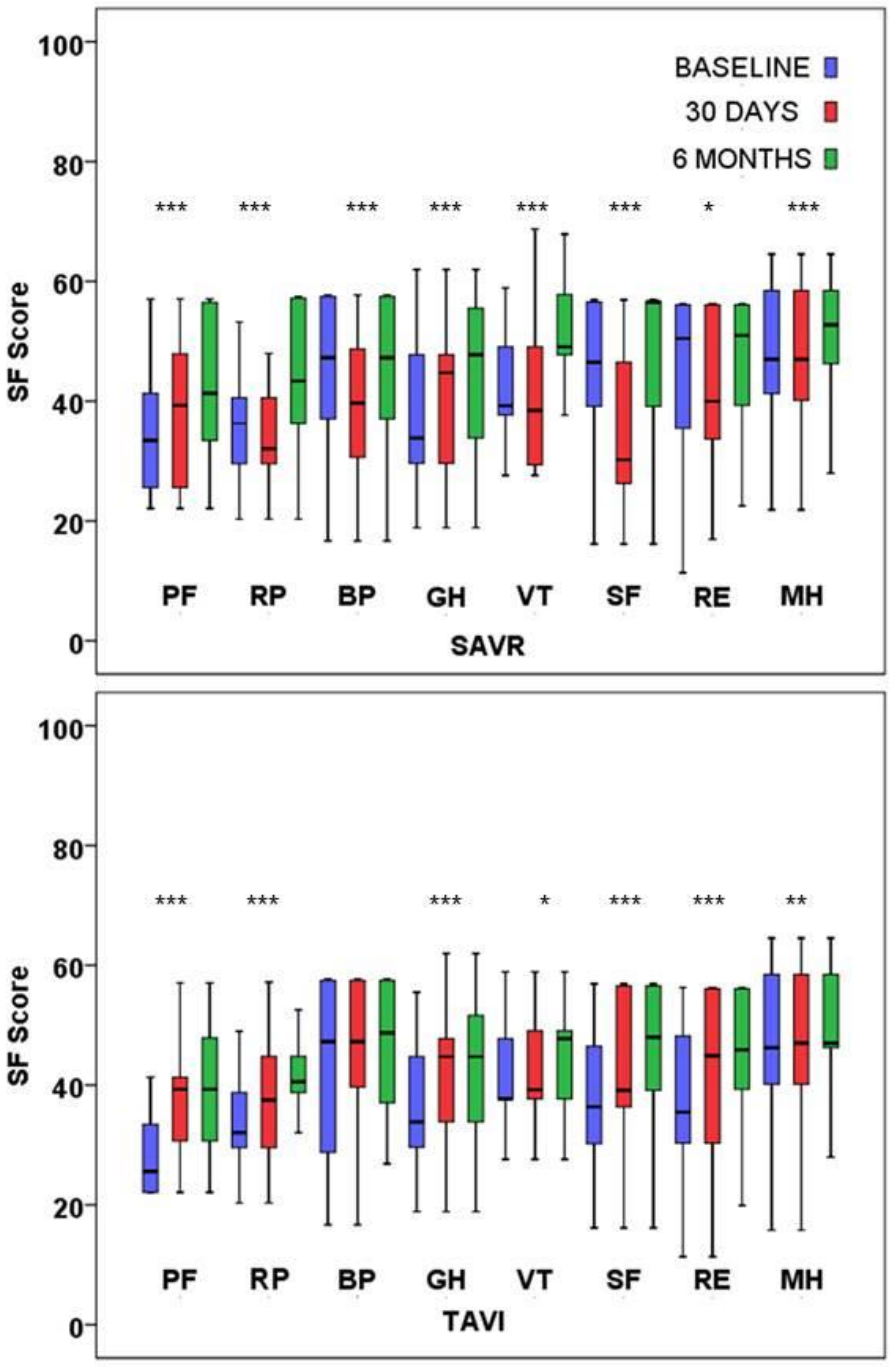
3.4.4 Health Related Quality of Life

HRQoL questionnaires were completed at baseline (n=111(100%); TAVI n=71, SAVR n=40), 30d (n=97(87%); TAVI n=59, SAVR n=38) and 6 months (n=96(86%); TAVI n=59, SAVR n=37).

TAVI HRQoL: In the TAVI group, SF12v2 showed a significant improvement in the Physical Component Score (PCS) over the 3 time points (p<0.0001). PCS improved from baseline to 30d (32.1±6.6 vs. 38.9±7.0, p<0.0001) and 6m (32.1±6.6 vs. 40.4±9.3, p<0.0001). The Mental Component Score (MCS) did not change from baseline after 30d (45.2±11.2 vs. 46.4±11.2, p=0.66), but significantly improved after 6m (baseline vs. 49.3±9.6, p=0.02). The component scores of Physical Functioning (PF), Bodily Pain (BP), General Health (GH) and Mental Health (MH) significantly increased 30d after TAVI (Figure 4). There was no change at 30d for Role Physical (RP), Vitality (VT), Social Functioning (SF) and Role Emotional (RE) (Figure 3-4). After 6m there was a significant improvement in all scores except for MH (Figure 3-4).

Figure 3-4 SF12 scores for TAVI and SAVR patients before and after 30d and 6m.

(Black horizontal line is the median, boxes represent the 2nd and 3rd quartiles, whiskers are 1.5xIQR.) P values derived from linear mixed-effects model, *p<0.05, **p<0.01, ***p<0.001, PF=physical function, RP=role-physical, BP=bodily pain, GH= general health, VT=vitality, SF=social functioning, RE=role-emotional, MH=mental health.)



The EQ5D score and visual analogue score showed a significant improvement over the study period (Table 3-3). There was no significant change in EQ5D at 30d but there was significant improvement by 6m. The VAS significantly improved from baseline to 30d and to 6m, without further significant change between the 30d and 6m time periods (Table 3-3).

SAVR HRQoL: In the SAVR group, the PCS score of SF12v2 showed an improvement only after 6m (baseline, 34.4±10.6 vs. 30d, 35.9±10.2, p=0.67, baseline vs. 6m, 42.8±11.2 p=0.0001). There was a significant decrease in the MCS score at 30d (baseline, 49.7±12.0 vs. 30d, 44.6±11.5, p=0.01) after SAVR which returned to baseline levels at 6m (baseline vs. 6m. 51.1±9.4, p=0.54. At 30d post-SAVR, there was no improvement in any of the component scores, whilst there was a significant reduction in social functioning (baseline, 44.4±12.9 vs. 30d, 35.4±11.3, p=0.001) (Figure 3-4). Nevertheless, at 6m there were significant improvements in all component scores compared to baseline values (Figure 3-4).

The EQ5D and visual analogue scores (VAS) showed a significant difference over the 3 time points (Table 3-3). There was no significant difference for the EQ5D score between baseline and either 30d or 6m; there was however a significant improvement between 30d and 6m. From baseline, the VAS did not change at 30d, but had significantly improved by 6m (Table 3-3).

Table 3-3 EQ5D and VAS scores over 3 time points and US population Norms

	US Norms*	Baseline	30 days	6 months	p value
TAVI		(n=71)	(n=59)	(n=59)	
EQ5D	0.66±0.2	0.63±0.22	0.71±0.25	0.74±0.2†	0.001
VAS	53±7	54.7±15.6	66.1±17.7†	68.1±16.6†	0.0001
SAVR		(n=40)	(n=38)	(n=38)	
EQ5D	0.66±0.2	0.69±0.23	0.66±0.25	0.79±0.22	0.002
VAS	53±7	60.1±18.9	67.1±16.2	76.6±17.1‡	<0.00001

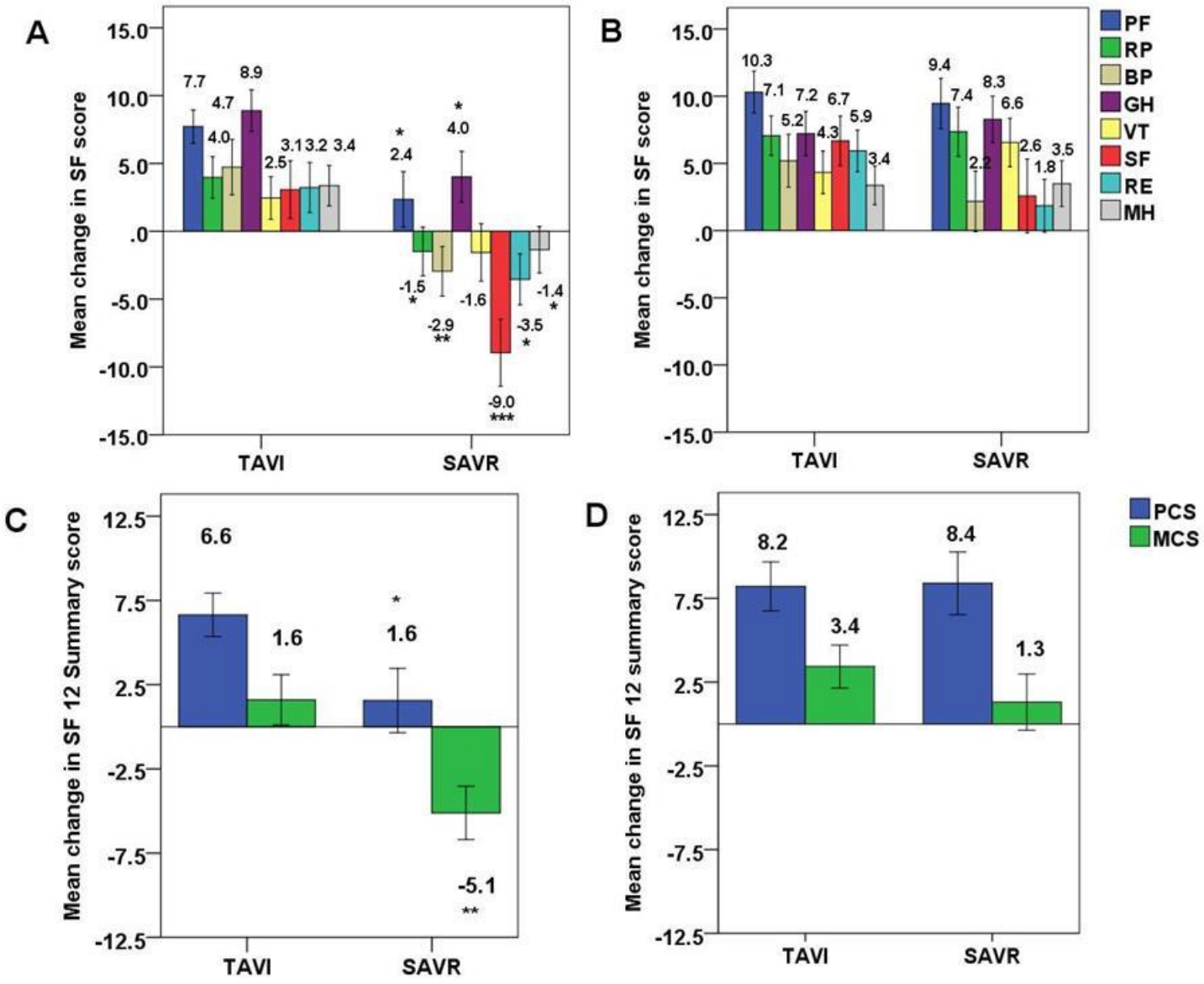
*US norms are reported for a US population stratified according to age (80 to 89 years). †p<0.001, ‡p<0.0001, p values are reported for a change in health for each time point compared with baseline by using linear mixed-effects model with Bonferroni post hoc correction. VAS=visual analogue scale.

Comparison of TAVI and SAVR HRQoL Scores

Figure 3-5 shows the differences in SF-12v2 scores from baseline to 30d and baseline to 6m for TAVI and SAVR. At 30d, mean TAVI scores have improved across all components whilst SAVR score have generally declined; PF and GH did improve but the change was significantly less than in TAVI (Figure 3-5A). At 6m there was a positive improvement in all component scores and there was no statistically significant difference between TAVI and SAVR (Figure 3-5B). The improvement in PCS score at 30d was significantly greater for TAVI than SAVR, whilst there was a significant reduction of MCS score in SAVR compared to TAVI (Figure 3-5C). At 6m there was no statistical difference between TAVI and SAVR (Figure 3-5D). The EQ5D and VAS scores increased over the three time points but there were no statistically significant differences between TAVI and SAVR.

Figure 3-5 Comparison between TAVI and SAVR SF12 questionnaires.

A) Difference in component score between baseline and 30d. B) Difference in component score between baseline and 6m. C) Difference in summary scores between baseline and 30d. D) Difference in summary scores between baseline and 6m. (Line bars represent Standard error (SE), Paired t-test *p<0.05, **p<0.01, ***p<0.001, Abbreviations as in Figure 4



3.4.5 Influence of cerebral emboli on HRQoL scores

The patients that had cerebral MRI and HRQoL assessment were placed into 3 categories: no new infarct, infarcts <5mm or infarcts >5mm (Table 3-4A&B). In the TAVI group, there were no differences in the SF12v2 PCS, MCS or component scores according to the presence or size of new cerebral micro-infarction (Table 3-4A). However in the SAVR group, PCS and the component scores for physical function and bodily pain were significantly lower at 30d in those with smaller (<5mm) infarctions, although these scores had returned to baseline after 6m (Table 3-4B).

Table 3-4 AB SF12 scores at 30 days and 6 months according to the size of infarctions detected by Cerebral DWI after TAVI and SAVR

TAVI (n=59)	Time-point	No infarction (n=13)	<5mm (n=28)	>5mm (n=18)	p value
PF	30d	37.2±10.7	36.0±9.6	37.7±7.6	0.81
	6m	41.9±9.9	38.9±10.9	38.8±9.5	0.74
RP	30d	38.8±12.9	35.6±7.9	39.9±10.1	0.30
	6m	45.5±10.6	40.7±6.9	41.4±8.1	0.35
BP	30d	43.7±14.2	48.1±9.5	45.8±12.6	0.54
	6m	45.4±12.4	46.7±12.3	46.4±10.6	0.96
GH	30d	44.7±7.2	40.7±10.9	45.4±10.3	0.26
	6m	45.9±9.9	42.3±10.7	43.2±12.9	0.75
VT	30d	42.0±11.7	41.0±11.2	45.1±11.2	0.48
	6m	44.4±11.5	43.6±10.4	44.6±8.6	0.95
SF	30d	37.3±16.3	40.7±11.9	45.0±11.2	0.27
	6m	43.4±15.0	46.4±10.1	47.6±11.6	0.68
RE	30d	37.5±17.8	41.7±13.1	44.0±12.9	0.51
	6m	45.3±10.9	45.3±10.3	45.6±12.2	0.99
MH	30d	44.6±17.2	47.9±9.3	50.6±9.9	0.39
	6m	51.6±11.0	48.2±10.7	48.9±7.6	0.69
PCS	30d	40.8±9.8	37.9±7.7	39.6±6.3	0.58
	6m	42.9±9.5	40.2±9.5	39.9±9.8	0.74
MCS	30d	41.7±18.7	46.1±10.2	49.5±10.8	0.27
	6m	48.6±10.2	48.7±9.1	50.0±9.0	0.89

Table 4B

SAVR (n=38)	Time-point	No infarct (n=20)	<5mm (n=8)	>5mm (n=10)	p value
PF	30d	39.1±12.1	26.2±8.9*	37.5±10.1	0.01
	6m	41.6±13.1	43.9±9.2	47.0±13.4	0.42
RP	30d	37.5±9.4	30.2±8.0	34.7±6.1	0.10
	6m	43.7±10.0	42.1±12.1	46.8±12.7	0.56
BP	30d	43.9±10.2	31.2±12.6*	44.8±8.2†	0.01
	6m	48.0±10.6	41.5±15.3	47.9±14.7	0.41
GH	30d	40.3±12.0	41.5±13.0	40.4±11.2	0.95
	6m	45.6±11.1	42.0±11.6	46.2±9.9	0.67
VT	30d	43.9±11.6	39.3±15.7	37.2±6.5	0.31
	6m	49.9±7.5	46.8±11.3	50.5±13.9	0.65
SF	30d	37.9±11.9	36.9±12.9	29.0±6.1	0.10
	6m	48.2±11.1	48.4±13.2	43.8±17.4	0.61
RE	30d	42.9±13.0	40.8±16.9	38.9±11.3	0.80
	6m	47.8±11.0	46.4±12.6	45.3±10.8	0.70
MH	30d	48.5±12.8	46.3±13.8	43.2±6.9	0.52
	6m	52.0±11.6	54.7±11.1	49.9±9.7	0.69
PCS	30d	38.2±10.5	27.3±8.9*	38.7±7.5	0.01
	6m	42.5±10.6	39.5±11.1	47.0±13.2	0.45
MCS	30d	46.4±10.8	48.0±14.6	38.7±8.8	0.25
	6m	52.5±8.7	52.9±11.1	47.7±11.1	0.45

Scores are mean±SD. *=p <0.05 for the change in scores at each time point compared to no infarction using linear mixed-effects model with Bonferroni post hoc correction. †= p <0.05 when comparing between large and small infarcts. PF=physical function, RP=role physical, BP=bodily pain, GH= general health, VT=vitality, SF=social functioning, RE=role emotional, MH=mental health, PCS=Physical component score, MCS=Mental component score.

Overall, there was no difference in EQ5D scores according to the presence or size of new cerebral micro-infarction (Table 3-5). The VAS was significantly decreased in the TAVI group with>5mm) infarcts at 30d (but returned to baseline value by 6m).

Table 3-5 EQ5D scores at 30 days and 6 months according to the size of infarctions detected by Cerebral DWI after TAVI and SAVR

	Time point	**No infarct**	**< 5mm**	**>5mm**	**p value**
TAVI		(n=10)	(n=28)	(n=18)	
EQ5D	30d	0.75±0.31	0.68±0.27	0.69±0.29	0.60
	6m	0.80±0.19	0.76±0.15	0.69±0.27	0.29
VAS	30d	74.0±17.4	65.6±17.4	51.8±16.5*	0.001
	6m	73.3±14.6	67.4±17.4	62.3±16.0	0.20
SAVR		(n=20)	(n=8)	(n=9)	
EQ5D	30d	0.67±0.28	0.67±0.17	0.61±0.25	0.90
	6m	0.83±0.15	0.70±0.29	0.82±0.27	0.40
VAS	30d	70.8±16.4	64.1±19.3	61.9±13.5	0.40
	6m	79.4±13.9	72.8±16.1	77.0±16.7	0.70

Scores are mean±SD. *=p <0.05 for the difference in scores for each group compared to no infarction using linear mixed-effects model with Bonferroni post hoc correction.

3.4.6 TAVI patients without 6 month cerebral imaging

Of the 70 TAVI patients that had a post procedure head scan only 32 had the 6 month follow-up scan. Excluding the 5 deaths, this left 33 patients that did not have a follow-up scan. To look for any potential bias due to this, the early DWI findings and HRQoL scores were compared to those that were scanned (follow-up scan vs. no follow-up scan). There was no difference in the number of infarcts or volumes (new infarcts 3.77±3.4 vs. 5.07±6.6, p=0.37; infarct volumes 0.76±0.8mls vs. 1.75±3.3mls, p=0.31). There were no differences in HRQoL summary scores at baseline (PCS 34.1±6.2 vs. 31.0±6.5, p=0.11; MCS 45.0±10.9 vs. 45.9±11.4, p=0.8) or 30 d. (PCS 41.4±5.5 vs. 36.5±8.5, p=0.08; MCS 45.9±13.2 vs. 47.5±9.0, p=0.66).

3.4.7 Associated factors for new cerebral micro-infarction

Univariate analysis for factors associated with new cerebral micro-infarction are summarised in Table 3-6. In the TAVI group, atheroma in the arch and descending thoracic aorta and fluoroscopic time were the significant univariate factors associated with new cerebral infarction (Table 3-6). In the multivariable analysis (including the univariate predictors ($p \leq 0.1$)), the only significant independent predictor was aortic arch atheroma grade (B=2.33, t=3.06, p=0.004)(r=0.46, p=0.0001). In the SAVR group, there were no baseline or procedural variables from univariate analysis that significantly predicted new cerebral infarction (Table 3-6). Multivariable analysis of univariate factors ($p \leq 0.1$) showed that concomitant CABG at the time of SAVR was the only statistically significant predictor of cerebral infarction (B=-1.67, t=2.16, p=0.04)(r=-0.33, p= 0.03).

Propensity score adjustment for number of new cerebral infarcts showed that despite adjusting for potential confounders, TAVI was still significantly

associated with new cerebral infarction (unstandardized coefficient B±SE=2.26±0.85, standardised β=0.25, p=0.009).

Table 3-6 Univariate regression analysis for the prediction of the number of new cerebral infarcts

Variables	TAVI		SAVR	
	R	**p value**	**R**	**p value**
Age	0.17	0.18	0.15	0.36
EuroSCORE	0.10	0.44	0.06	0.70
EuroSCORE II	–0.24	0.05	0.13	0.42
STS score	0.004	0.97	0.16	0.35
BSA	0.02	0.88	0.20	0.24
BMI	0.02	0.85	0.01	0.95
NYHA class	0.12	0.34	0.002	0.79
Hypertension	0.15	0.24	0.002	0.99
Diabetes	0.13	0.30	0.12	0.48
Hyperlipidaemia	–0.21	0.09	0.10	0.54
Atrial Fibrillation	0.07	0.57	0.12	0.94
Previous MI	0.04	0.77	0.10	0.57
CABG	0.07	0.59	0.08	0.64
Previous PCI	0.05	0.72	0.11	0.51
PVD	0.15	0.21	0.18	0.29
TIA/Stroke	0.16	0.21	0.04	0.84
Creatinine	0.10	0.44	0.12	0.46
eGFR	0.07	0.55	0.12	0.47
COPD	0.01	0.91	0.24	0.14
Porcelain aorta	0.14	0.26		
Aortic Atheroma				
Ascending	0.18	0.14	0.14	0.40
Arch	0.46	0.0001	0.18	0.39
Descending	0.37	0.002	0.18	0.30
Valve Calcification	0.11	0.40	0.08	0.65
TAVI approach	0.10	0.40		
BAV size	0.29	0.06		
CoreValve size	0.22	0.07		
Procedural-time	0.12	0.40		
Fluoroscopy-time	0.30	0.02		
Contrast volume	0.06	0.97		
Bypass-time			0.28	0.10
Cross-clamp-time			0.32	0.07
Valve size			0.02	0.89
CABG performed			0.34	0.07
Valve type			0.21	0.20

TAVI=Transcatheter Aortic Valve Implantation, SAVR=Surgical Aortic Valve Replacement, BSA=body surface area, BMI=body mass index, NYHA=New York Heart Association, STS=Society of Thoracic Surgery, TIA=transient ischaemic attack, MI=myocardial infarction, CABG=coronary artery bypass grafting, PVD=peripheral vascular disease, COPD=chronic obstructive pulmonary disease, BAV=balloon aortic valvuloplasty, eGFR=estimated glomerular filtration rate.

3.5 DISCUSSION

This relatively large prospective study provides evidence that compared to SAVR, TAVI results in a higher burden of post-procedural cerebral micro-infarcts. Aortic atheroma and concomitant CABG were independent predictors of cerebral infarction for TAVI and SAVR respectively. New micro-infarcts had no effect upon the TAVI patients' short or medium term mental and physical quality of life. After SAVR, patients with micro-infarcts had an initial decline in physical health which recovered by 6 months. A major limitation is the significant differences between the baseline characteristics of the two cohorts. Unfortunately this is a significant limitation of early TAVI research as these patients are too high risk for surgery.

The size of the TAVI micro infarcts were smaller than the SAVR micro infarcts mainly related to the mechanism that cause them. The total volumes were not different which is an interesting finding. This suggests the TAVI patients have a broader spread of small cerebral micro-infarcts where the SAVR group have larger localised cerebral infarcts.

Previous studies, including our own have shown high rates (77-84%) of cerebral micro-infarction post-TAVI (Kahlert et al., 2010, Fairbairn et al., 2012b). The mechanism of infarction is believed to be embolic in nature. Transcranial Doppler studies have shown an increase in high intensity transient signals (HITS) during valve alignment and deployment suggesting the main source of embolic material may be atheroma, calcification or even air embolus (Kahlert et al., 2012). We have previously shown a relationship between aortic atheroma and the number of peri-procedural infarcts,

postulating a mechanism of embolization as bulky catheters are manipulated around the aortic arch (Fairbairn et al., 2012b). Two studies have subsequently shown that the trans-femoral and trans-apical approaches have similar rates of embolization (Kahlert et al., 2012, Rodes-Cabau et al., 2011). This finding does not contradict the risk associated with aortic atheroma as with both access techniques cardiac catheters and wires are passed around the aortic arch. In comparison to SAVR group, the embolism is more likely related to be due to thrombotic clot, perhaps even related to paroxysmal AF.

Identifying risk factors for cerebral emboli is important as this may influence patient selection and the use of cerebral protection devices (Nietlispach et al., 2010). We assessed a variety of risk factors including baseline demographics, co-morbidity and procedural factors. Aortic atheroma, valvuloplasty balloon size and fluoroscopy time were key factors that influenced the likelihood of TAVI cerebral embolization. Aortic atheroma was an independent predictor of cerebral emboli. This further validates our previous findings and to date remains the only patient-specific risk factor identified for cerebral emboli (Fairbairn et al., 2012a). The use of larger valvuloplasty balloons could result in greater trauma to the aortic atheroma and hence create a substrate for embolism. Similarly, fluoroscopic time can be considered a surrogate marker for procedural complexity and device manipulation against the aortic wall. Nombela-Franco *et al* reported balloon post-dilatation to predict higher acute cerebrovascular events, whereas later events were best predicted from conventional risks such as new onset AF, PVD and cerebrovascular disease (Nombela-Franco et al., 2012).

SAVR is believed to result in cerebral embolization secondary to cannulation of the aorta and stimulation of a systemic inflammatory response induced by cardio-pulmonary bypass (Pugsley et al., 1994). Our results show that duration of cross-clamping time and concomitant CABG are associated with a higher rate of cerebral micro-infarction consistent with this theory. Differences in procedural event rates could represent the greater age and risk factor profile of TAVI compared to SAVR patients, as there has not been a study of matched patients to date. However, following propensity correction our data suggests the TAVI procedure is still an independent risk factor for cerebral emboli.

The clinical impact of cerebral embolism is of significant concern to patients and physicians. TAVI has a greater risk of early stroke and TIA compared to surgery (Smith et al., 2011a), but by two years there appears to be no difference (Kodali et al., 2012b). However, silent cerebral infarcts have been shown to adversely affect patient memory, cognition and be associated with dementia (Blum et al., 2012, Arvanitakis et al., 2011). Quality of life is an important clinical outcome measure and is one of the main reasons that TAVI is conducted (Ussia et al., 2009). As such, anything negatively impacting upon HRQoL, such as silent cerebral emboli, would be of concern. This study has shown that for both TAVI and SAVR new cerebral emboli did not detrimentally affect patient-reported HRQoL at 6 months. Interesting differences occur between the two procedures from baseline to 30 days, with a decline in physical health in the surgical group. This appeared to be in part related to individuals who had developed cerebral emboli but is also likely to reflect the impact that major surgery (sternotomy, bypass, Intensive Care Unit) has upon the early physical condition of the patient thus affecting social

functioning. HRQoL is a global measure of health status and an important clinical outcome measure but is not a test of higher cognitive function; further research is required to identify any subtle effects that silent cerebral micro-embolization may have on neuropsychological function following TAVI or SAVR. Indeed, silent cerebral infarction has been associated with global memory loss (Blum et al., 2012) and post-operative neurocognitive dysfunction following coronary artery bypass grafting(Zamvar et al., 2002) and cardiac procedures such as AF ablation (Medi et al., 2013). For the TAVI procedure, any impact on neurocognitive function will be important to determine if it is to be considered in lower risk and younger patients. Neurocognitive tests are also very specific to an area of the brain and focus on a particular set of functions, such as executive function and verbal fluency and therefore may be able to show more subtle difference that HRQoL may not be sensitive enough to pick up.

3.5.1 Limitations

Due to current TAVI implantation criteria, the groups could not be fully matched for age, co-morbidity or risk factor scores; our findings may be negatively biased against the higher risk TAVI group. Whilst the sample size may appear small, we had adequate power to detect measurable differences in health related QoL scores. Propensity matching would result in a significant reduction in number in each group and is ideally performed in larger studies with more than 1000 patients in each group. There were a number of TAVI patients who could not have follow up scans due to frailty or pacemaker insertion, which may further introduce bias. The use of MR compatible pacemakers would have increase the post cerebral MRI patient numbers. We did not assess frailty pre- and post-procedure as the study

protocol was already considered arduous for this patient group. The cerebral MRI scans were performed at 1.5T which reliably detects DWI infarcts, but higher field strengths (3.0T) may have greater sensitivity. (Medi et al., 2013) However, at the time of our study the CoreValve prosthesis was not approved for 3.0T field strength and on-going clinical trials of cerebral embolic protection devices are at the 1.5T field strength. The study does not explain the full significance of cerebral embolization on patient outcome, in particular the impact on neurocognitive function, and our intention is to follow up this work with dedicated neuropsychological testing. Finally, our study used CoreValve in isolation and the findings and outcomes may be different with other valve prostheses.

3.6 CONCLUSION

Post-procedural cerebral micro-embolic events occur more frequently after TAVI compared to SAVR. Aortic atheroma is the main predictor of cerebral emboli post-TAVI but not post-SAVR, where concomitant CABG remains the dominant risk factor. New cerebral micro-embolization is associated with reduced physical health 30 days post-SAVR, but had no detrimental effect on health following either procedure (TAVI or SAVR) in the medium-term (6 months). Overall conclusions may be confounded by the marked differences in the baseline characteristics of the two groups. Future randomised studies in similar risk groups may be able to delineate in a more robust fashion.

4 Impact of Transcatheter Aortic Valve Implantation and Surgical Aortic Valve Replacement on neurocognitive function following the treatment of severe aortic stenosis

4.1 ABSTRACT

Importance: Transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) is associated with clinically silent cerebral micro-infarction. The medium-term consequences on neurocognitive function (NCF) are unknown.

Objective: To assess serial change in NCF following TAVI and contemporary surgical aortic valve replacement (SAVR) over 12 months.

Design: A longitudinal assessment of NCF using a two-factor mixed design, with treatment type as a between-subjects factor (TAVI vs. SAVR) and time as a within-subject factor (baseline, 30 days, 6 months and 12 months)

Setting: Two tertiary cardiac centres in the UK.

Participants: Ninety patients with severe AS undergoing either TAVI (n=50, 28 males, 81±7 years or SAVR (n=40, 30 males, 73±7 years).

Interventions: TAVI or SAVR as deemed appropriate by the multidisciplinary heart team.

Main outcomes and measures: NCF assessments were conducted over 4 time points. NCF test scores were categorised as ‘impaired’, ‘average or above average’ compared to published age-matched norms. Cerebral MRI with diffusion weighted imaging (DWI) was performed at baseline and post-procedure.

Results: The incidence of cerebral micro-infarction was higher after TAVI compared to SAVR (30(68%) vs. 13(43%), p=0.04). TAVI patients had lower baseline NCF test scores compared to SAVR. At 12 months, the majority of NCF tests did not show a significant change in the proportion of patients categorised as having impaired NCF compared to baseline in the TAVI or SAVR groups, except for the Hopkins Verbal Learning test which showed a significant reduction (TAVI 32(64%) vs. 5(14%), p=0.046; SAVR 17(43%) vs. 6(18%) p=0.019). For both TAVI and SAVR, the proportion of patients with impaired NCF (by any test at 30 days, 6- or 12 months) did not significantly change according to the presence of DWI lesions (all p>0.50)

Conclusions: There was no evidence of short to medium-term cognitive decline following TAVI or SAVR. Although silent cerebral micro-infarcts were more common following TAVI than SAVR, they did not impact on neurocognitive performance.

4.2 INTRODUCTION

The management of severe symptomatic aortic stenosis has changed dramatically with the advent of transcatheter aortic valve implantation (TAVI), particularly in those patients at high surgical risk, resulting in improved quality of life (Fairbairn et al., 2012b). Randomised controlled trials have shown significant survival and symptomatic benefit when compared to medical management, and non-inferiority to surgical valve replacement (Smith et al., 2011b, Makkar et al., 2012b, Adams et al., 2014). With improved TAVI device technology and greater operator experience there has been improved complication rates with a recent meta-analysis showing similar overall complication rates to surgical aortic valve replacement (SAVR) (Jilaihawi et al., 2012). However, significant concern exists relating to the higher incidence of stroke and silent cerebral infarction early following TAVI compared to SAVR (Nombela-Franco et al., 2012).

Cerebral embolisation during device manipulation and delivery is an inherent risk with TAVI and several studies have confirmed a high incidence of cerebral infarction using diffusion-weighted magnetic resonance imaging (DW-MRI) (Ghanem et al., 2010a, Fairbairn et al., 2012a). The vast majority of these cerebral infarcts are small, producing no focal neurological signs, and hence are labelled as silent infarcts. The short, mid and long-term consequences of silent cerebral infarction following TAVI and SAVR are unknown, as conventional clinical and mental state examinations may not detect subtle neuro-functional disturbances. The concept of post-operative cognitive dysfunction (POCD) has been linked to early dementia (Newman et al., 2001) and has been reported after coronary artery bypass grafting

(CABG), carotid stenting and trans-septal AF ablation (Zamvar et al., 2002, Huang et al., 2013, Medi et al., 2013).

In chapter 3, we showed that health related quality of life (HRQoL) improved in both TAVI and SAVR groups but there was no direct influence of cerebral micro-infarction on HRQoL scores. Perhaps as they are generic instruments they may not detect subtle defects. Hence neurocognitive assessment uses tests specifically designed to assess cognitive function. Therefore we may be able to link cerebral infarcts on DWI to neurocognitive function. Neurocognitive tests have been extensively studied, especially in traumatic brain injury and stroke and use reliable and validated tools.

As the current TAVI clinical trials seek to broaden the procedural indications to younger, lower-risk patient groups, it will be important to understand the natural history of neurocognitive function (NCF) following TAVI compared to SAVR and whether patient or procedural factors have an impact on neurocognitive outcomes. The aims of this study were to 1) perform comprehensive, serial, neurocognitive assessments of TAVI and contemporary SAVR patients over a twelve month time period and identify evidence of short to medium term neurocognitive dysfunction; 2) relate the occurrence and extent of new silent cerebral infarction by DW-MRI after TAVI and SAVR to NCF.

4.3 METHODS

4.3.1 Patient selection

Patients with severe symptomatic aortic stenosis were prospectively recruited from two large UK tertiary cardiothoracic centres (Leeds and Leicester) with established high-volume TAVI programmes. All patients were assessed by the multi-disciplinary Heart team and considered suitable for TAVI or SAVR based on contemporary international guidelines. Older, higher-risk (higher EuroSCORE) SAVR patients were preferentially recruited wherever possible, in an attempt to have baseline demographics more comparable to the TAVI group. Inclusion criteria were patients with severe aortic stenosis as defined by echocardiography (mean gradient >40mmHg, peak velocity >4m/s, valve area<1cm^2). Exclusion criteria included any contraindication to MRI or pre-existing severe cognitive impairment (MMSE score<10). The study was approved by the institutional ethics committee (08/H1307/106), complied with the Declaration of Helsinki and all patients provided written informed consent.

4.3.2 Transcatheter Aortic Valve Implantation

In each centre, TAVI was performed by a single experienced (>5years) operator with either an 18F CoreValve Revalving system (CVR, Medtronic, Minneapolis, Minnesota, USA) or Edwards Sapien prosthesis (Edwards Lifesciences Corp. Irvine, California, USA) via the femoral or subclavian artery under general anaesthesia with X-ray fluoroscopy and transoesophageal echocardiographic guidance. All patients received weight-adjusted unfractionated heparin to maintain an activated clotting time >200s

and were treated with dual antiplatelet therapy (aspirin 75mg and clopidogrel 75mg) for a minimum of 6 months.

4.3.3 Surgical Aortic Valve Replacement

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

4.3.4 Neurological assessment and status

A detailed neurological examination was conducted prior to intervention and daily after the procedure by an experienced consultant physician until hospital discharge. A National Institutes of Health Stroke Scale (NIHSS) score was recorded. Transient ischaemic attack was defined as any focal neurological deficit that lasted <24h. Stroke was defined as any persistent focal neurological deficit lasting >24h.

4.3.5 Neurocognitive assessment

The neurocognitive test battery was performed by trained assessors in a quiet comfortable environment at Valve Academic Research Consortium (VARC) recommended time points (baseline, 30 days, 6 month, 12 months). Training of assessors and performance validation was undertaken by an experienced neuropsychologist. Follow-up assessment was conducted at the patient home or the hospital. Total assessment time ranged between 60-90min with appropriate rest periods. Baseline characteristics, hospital anxiety and depression scale (HADS), handedness and years of education

were recorded. The national adult reading test NART was used to calculate the full scale intelligent quotient (FSIQ=123.2-(1.029 x NART error score)). A broad battery of previously validated neurocognitive assessments were performed in all individuals at all time points,(Hachinski et al., 2006) and included: *Global function:* mini mental state examination (MMSE), *Mnemonic function*: Hopkins Verbal Learning Tests (HVLT), Rey-Osterrieth Complex Figure (ROCF), *Executive function*: Controlled Oral Word Association Test (COWAT), Letter Number Sequencing (LNS), Trail-making A and B tests; and *psychomotor function test*: Grooved Pegboard Test (Model 32025, Lafayette Instruments Co, IN, USA), Digit-Symbol Substitution Test (DSST). Scores were compared with age-matched published norms and grouped according to impaired, average or above average function. Cognitive decline was defined as a reduction of the score by 1 SD of the baseline score for all NCF tests (Knipp et al., 2013, Ghanem et al., 2013, Zamvar et al., 2002).

4.3.6 Cerebral MRI

Cerebral MRI was conducted pre- and post-procedure (within 7d) using identical imaging protocols. MRI was performed on the same 1.5T system for all serial scans for any individual patient (Intera, Phillips Healthcare, The Netherlands or Avanto, Siemens Medical Systems, Germany). The imaging protocol consisted of T2 weighted fast field echo, T2 turbo field echo and diffusion weighted imaging (DWI) (22 slices, 5mm thick, 1mm gap, FOV 350, RFOV 100). Each scan was independently assessed by two experienced Neuroradiologists, blinded to all clinical/procedural details. In the case of disagreement, a third blinded Neuroradiologist was consulted and a consensus view was recorded. Cerebral embolism or micro-infarction was

defined as a new restricted diffusion lesion on DWI. New cerebral micro-infarcts were localised to hemisphere and vascular territory. Infarct diameter was used to categorise patients into small or large lesion sub-groups (<5mm or >5mm; in the case of multiple lesions the largest lesion was used to determine status). The total infarct volume (ml) was measured off-line using standard post-processing software (QMass7.2, Medis, The Netherlands) as previously published (Fairbairn et al., 2012a, Uddin et al., 2015).

4.3.7 Statistical Analysis

Data were tested for normality using the Shapiro-Wilks test. Continuous variables were expressed as mean±SD or median (Q2-Q3 or interquartile range (IQR)) and discrete variables as n (%). The changes in test scores (baseline, 30d, 6m and 12m) were assessed using the linear mixed-effects model with an unstructured covariance matrix. Groups (TAVI or SAVR) and time-points were entered as the fixed effect and interactions between group x time-points were measured. Bonferroni post-hoc correction was used for multiple comparisons. This method was used instead of repeated measures ANOVA to overcome potential effects of missing data and need for a balanced design (West, 2009). Fishers exact test or Chi squared test was used for discrete variables. Univariate logistic regression was performed to look for predictors of cognitive impairment (average or above-average=0, impaired=1) at baseline and after the respective procedures. Factors with $p<0.1$ were entered into a multivariate logistic regression analysis in a stepwise method. Odds ratios with 95% confidence intervals were recorded. Sample size to detect cognitive decline (reduction in score by 1SD) was estimated using *IBM SPSS Samplepower version 3*, and using normative

data for the test to have 80% power (alpha 0.05), a minimum of 17 patients were required in each group (TAVI/SAVR).

4.4 RESULTS

4.4.1 Patient Characteristics

A total of 90 patients with severe aortic stenosis were studied (Figure 4-1, Table 4-1). The TAVI group were older with higher surgical risk scores and there was a higher prevalence of prior CABG, PCI, PVD and COPD (Table 4-1). The echocardiographic parameters were similar except for a smaller valve area and higher prevalence of left ventricular systolic dysfunction in the TAVI group (Table 4-1). Overall 70 (78%) of the participants completed the full study protocol. During the study period, 4 deaths occurred in the TAVI group and one in the SAVR group. There are clear and significant differences in the study groups given the differences in co-morbidity, which may confound any findings. This is an expected limitation.

Figure 4-1 Study flow chart

(AS=aortic stenosis, MR=magnetic resonance, NCF=neurocognitive function, PPM=permanent pacemaker, SAVR=surgical aortic valve replacement, TAVI=transcatheter aortic valve implantation)

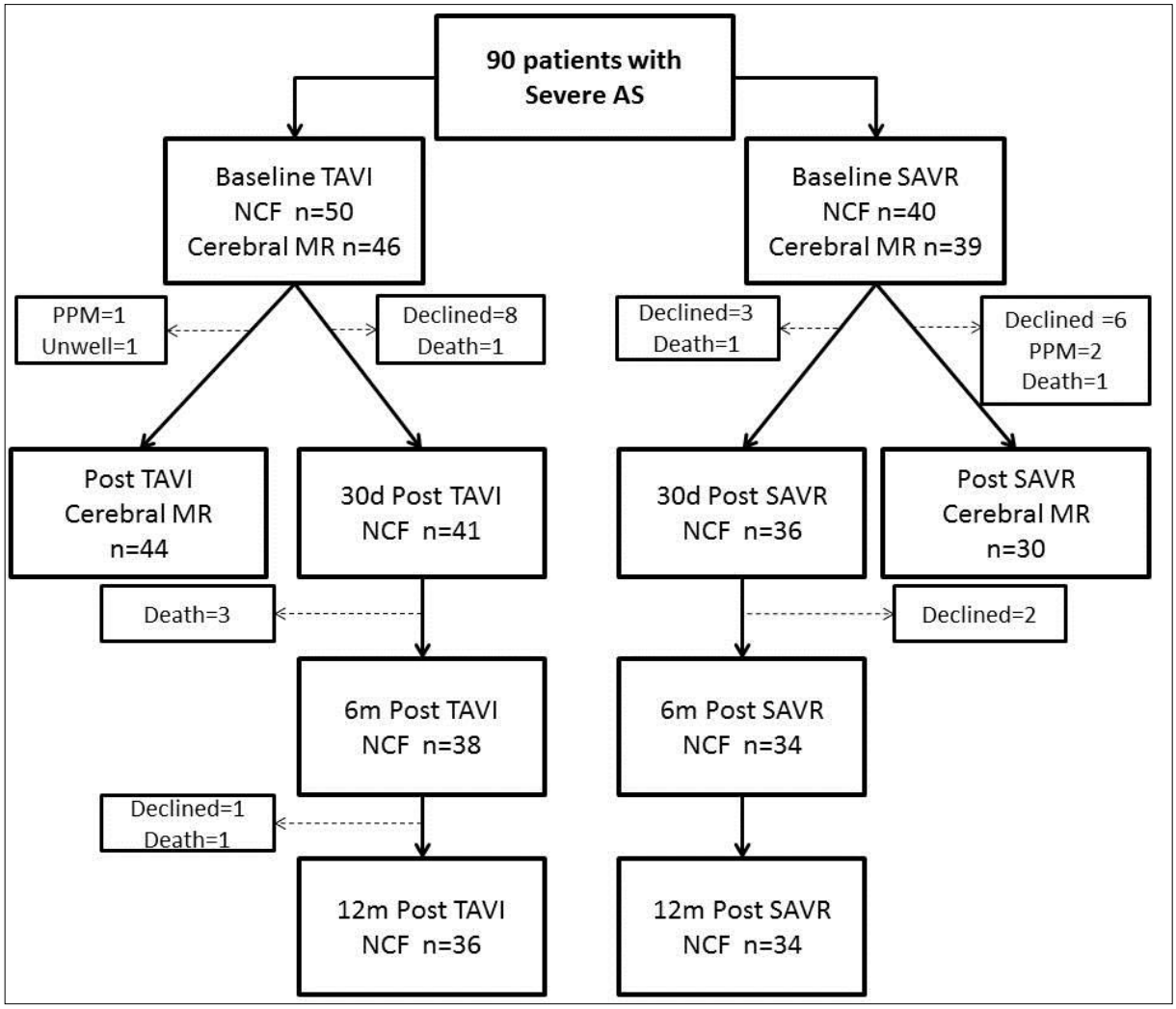


Table 4-1 Baseline patient characteristics

Demographics and clinical characteristics	TAVI (n=50)	SAVR (n=40)	p value
Age, years	81.1±7.0	72.5±7.2	<0.0001
Male, n (%)	28 (56)	30 (75)	0.07
BMI, kgm^{-2}	27.6±5.6	27.9±4.7	0.96
NYHA Class, n (%)			0.0003*
I	0	2 (5)	
II	5 (10)	15 (37)	
III	38 (76)	23 (58)	
IV	7 (14)	0	
EuroSCORE, (%)	20.6±10.1	6.8±7.9	<0.0001
EuroSCORE II, (%)	5.5±3.4	1.5±0.9	<0.0001
STS Score, (%)	5.4±3.1	2.1±0.8	<0.0001
STS Morbidity, (%)	23.8±6.6	15.4±4.4	<0.0001
Hypertension, n (%)	31 (62)	25 (63)	0.42
Diabetes, n (%)	11 (22)	6 (15)	0.61
Hypercholesterolaemia, n (%)	26 (52)	27 (68)	0.21
Atrial fibrillation, n (%)	12 (24)	4 (10)	0.10
Stroke/TIA, n (%)	10 (20)	7 (18)	0.80
MI, n (%)	7 (14)	6 (15)	0.88
CABG, n (%)	13 (26)	0	0.0001
PCI, n (%)	13 (26)	2 (5)	0.009
PVD, n (%)	8 (16)	2 (5)	0.002
COPD, n (%)	12 (24)	2 (5)	0.02
Pulmonary Hypertension n (%)	13 (26)	5 (13)	0.18
eGFR, $ml/min/1.73m^2$	65±17	72±11	0.05
Echocardiographic data:			
Peak AV velocity, ms^{-1}	4.5±0.7	4.4±0.8	0.54
Mean AV gradient, mmHg	48±16	47±17	0.49
Aortic valve area, cm^2	0.6±0.2	0.8±0.4	0.01
LVEF, n (%)			0.004*
Normal	9 (18)	20 (50)	
Mild	29 (58)	18 (44)	
Moderate	5 (10)	1 (3)	
Severe	7 (14)	1(3)	

Data are Mean±SD or n (%). BMI=body mass index, NYHA=New York Heart Association, STS=Society of Thoracic Surgery, TIA=transient ischaemic attack, MI=myocardial infarction, CABG=coronary artery bypass grafting, PVD=peripheral vascular disease, COPD=chronic obstructive pulmonary disease, eGFR=estimated glomerular filtration rate, AV=aortic valve. LVEF=left ventricular ejection fraction. *Mann Whitney test.

4.4.2 Procedural characteristics

TAVI procedural success was 100%, with Transfemoral access being the predominant route. The majority of SAVR patients received a biological valve replacement and 38% had concurrent CABG (Table 4-2).

Table 4-2 Procedural and operative data

		n (%)
TAVI (n=50)		
Medtronic CoreValve, n=46	31mm	8 (16)
	29mm	26 (52)
	26mm	9 (18)
	23mm	3 (6)
Edwards Sapien, n=4	29mm	2 (4)
	26mm	2 (4)
Access route	Femoral	42 (88)
	Subclavian	7 (10)
	Carotid	1 (2)
Procedure time, (min)		147±83
Fluoroscopy time, (min)		24±12
Contrast volume, (ml)		144±76
SAVR (n=40)		
Biological, n (%)		34 (85)
Mechanical, n (%)		6 (15)
Size, (mm) (median, Q1-Q3)		23 (21–24)
Bypass time, (min)	All	124±66
	AVR only	107±54
	AVR and CABG	152±75
Cross clamp time, (min)	All	92±56
	AVR only	83±51
	AVR and CABG	107±61
CABG, n (%)		15 (38)

Data are Mean±SD or n (%).

4.4.3 Baseline education and Intelligence

The majority of patients were right handed (TAVI: 47(94%) vs. SAVR: 38(95%)) The TAVI group had fewer years in education compared to SAVR group (10.5±1.5 vs. 12.2±3.0yrs, p=0.003), but nevertheless were similar in full scale IQ (106±12 vs. 109±10, respectively p=0.27).

4.4.4 Effect of treatment on absolute neurocognitive function scores

Global function (MMSE): The MMSE at baseline was statistically significantly lower for TAVI than SAVR (p=0.0004), but did not change after intervention at 30 days, 6 months and 12m (Table 4-3).

Table 4-3 Summary of neurocognitive test scores at baseline, 30d, 6m, 12m

	Group	Baseline (mean±SD)	30 d (mean±SD)	6 m (mean±SD)	12 m (mean±SD)	p value§
MMSE	TAVI‡	28.4±2.2††	28.3±2.3††	28.4±2.2††	27.9±2.6††	0.44
	SAVR	29.6±0.8	29.2±1.1	29.3±1.1	29.5±0.9	0.41
LNS	TAVI‡	7.6±4.1	7.5±4.1	8.2±4.4	7.9±4.2†	0.70
	SAVR	8.5±3.1	8.6±4.0	9.5±3.7	10.4±3.6*	0.01
DSST	TAVI‡	33±14††	35±14††	37±13††	39±15††	0.12
	SAVR	48±16	52±20	52±18*	52±17*	0.02
HADS						
Anxiety score	TAVI	5±3	6±4	4±4	5±3	0.39
	SAVR	4±4	5±4	4±3	3±3	0.19
Depression score	TAVI	5±3	4±4	4±4	5±3	0.17
	SAVR	4±4	4±3	3±3	4±4	0.17
Groove Pegboard						
Dominant time (sec)	TAVI‡	142±55††	142±66††	137±59††	150±67††	0.46
	SAVR	100±33	98±36	102±89	98±51	0.78
Non-dominant time (sec)	TAVI‡	167±124†	164±61†	169±78†	162±80††	0.64
	SAVR	131±66	128±103	130±100	119±71	0.42

MMSE=mini mental state exam, HVLT=Hopkins Verbal Learning test, ROCF=Rey-Osterrieth complex figure test, LNS=Letter-number sequencing, COWAT=controlled oral word association test, DSST=Digit-symbol substitution test, HADS=Hospital Anxiety Depression Scale. *p<0.05, **p<0.01 vs. baseline score by Bonferroni correction; †p<0.05, ††p<0.01 vs. SAVR score. ‡ p<0.05 for group effect from mixed-effect model. § p values from mixed-effect model for effect of time. ¶p<0.05 vs. 30d

Mnemonic function

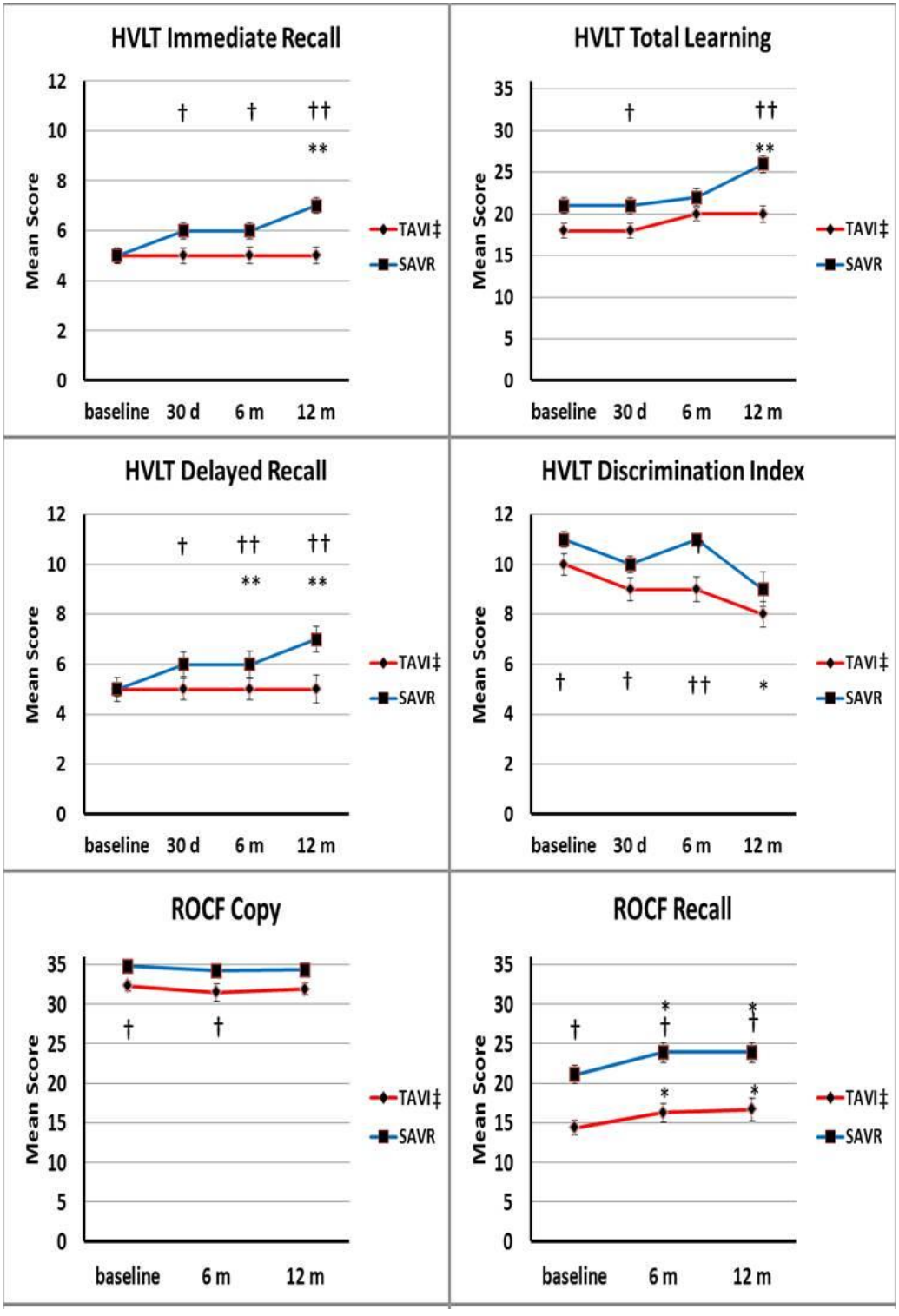
HVLT: Immediate recall of a simple list of words did not change after TAVI but significantly improved after 12 months in the SAVR group (Figure 4-2). Although the TAVI group had a lower total learning score compared to SAVR (p=0.002), there was no change in learning scores after TAVI or SAVR at 30 days and 6 months but a significant increase at 12 months for SAVR only (Figure 4-2). Delayed recall scores improved after 6 months and 12 months in the SAVR group and were higher than the TAVI group at 30 days and 6 months (Figure 4-2). The TAVI group had a lower Discrimination Index (DI) at baseline compared to SAVR group. The DI was worse for TAVI after 6 months and 12 months (baseline: 10±3 vs. 12 months: 8±5, p=0.03). There was a significant improvement in DI between 30 days and 6 months for SAVR (Figure 4-2); there was no deterioration in DI in the SAVR group at 12 months (baseline: 11±2 vs. 12 months: 9±4, p=0.14) (Figure 4-2).

ROCF: At baseline, the TAVI group had significantly lower scores for copying (p=0.001), immediate (p<0.0001) and delayed recall (p<0.001) compared to the SAVR group (Figure 4-2). After 6 months and 12 months, both the TAVI and SAVR groups had significantly improved immediate and delayed recall scores; however the TAVI group remained lower relative to SAVR (Figure 4-2).

Executive function

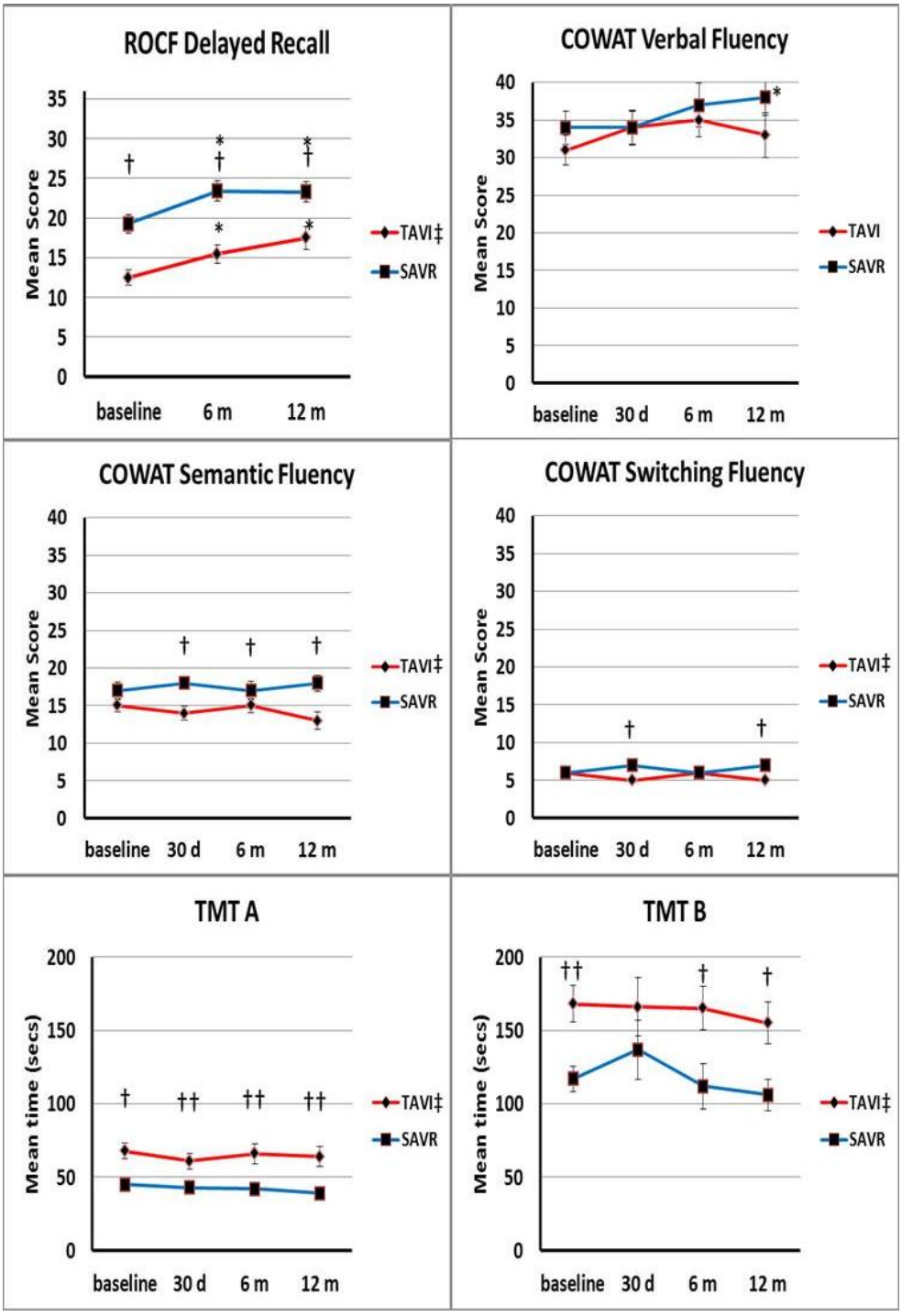
Trail Making Test (TMT) A and B: The TAVI group were slower to complete both trails compared to SAVR (TMT-A: p=0.001), (TMT-B: p=0.005) (Figure 4-2). The recorded times for both tasks did not change after TAVI or SAVR at 30 days, 6 months and 12 months (Figure 4-2).

Figure 4-2 Summary of neurocognitive function test scores at baseline, 30 d, 6 m and 12 m



‡ p<0.05 for group effect from mixed-effect model. *p<0.05, **p<0.01 vs. baseline score by Bonferroni correction; †p<0.05, ††p<0.01 vs. SAVR score. HVLT=Hopkins Verbal Learning test, ROCF=Rey-Osterrieth complex figure test, COWAT=controlled oral word association test, TMT=Trail Making Test. Bars represent standard error.

Figure 4.2 (continued) Summary of neurocognitive function tests scores at baseline, 30 d, 6 m and 12 m.



‡ p<0.05 for group effect from mixed-effect model. *p<0.05, **p<0.01 vs. baseline score by Bonferroni correction; †p<0.05, ††p<0.01 vs. SAVR score. HVLT=Hopkins Verbal Learning test, ROCF=Rey-Osterrieth complex figure test, COWAT=controlled oral word association test, TMT=Trail Making Test. Bars represent standard error.

Letter Number Sequencing task (LNS): TAVI patients had lower scores at baseline compared to SAVR (p=0.01), and did not change after 30 days, 6 months and 12 months. However, the SAVR groups score significantly increased at 12 months (Table 4-3).

Verbal fluency (COWAT): There was no effect of group (p=0.10) on verbal fluency at baseline. Whilst there was no significant change in verbal fluency scores after TAVI at 30 days, 6 months and 12 months, the SAVR group increased their scores significantly after 12 months (Figure 4-2).

Semantic fluency (COWAT): The TAVI group had lower scores compared to SAVR at baseline (p=0.002), and the scores for both groups did not change after 30 days, 6 months and 12 months (Figure 4-2).

Switching fluency (COWAT): The TAVI group had comparable baseline score to SAVR and there was no change in scores for either group with time (Figure 4-2).

Psychomotor speed

DSST: The TAVI group had significantly lower scores at baseline compared to SAVR (p<0.001) (Table 4-3), and did not change at 30 days, 6 months and 12 months. The SAVR scores however increased significantly after 6 months and 12 months (Table 4-3).

Mood

HADS: Both TAVI and SAVR groups had normal scores (normal<8) with no evidence of anxiety and depression at baseline or at 30 days, 6 months and 12 months (Table 4-3).

Fine motor co-ordination and speed (grooved pegboard test (GPT): The TAVI group were consistently slower at the task with the dominant hand, across the 4 time points when compared to SAVR (p<0.001) (Table 4-3).

There were similar differences with the non-dominant hand (p=0.004). Overall there was no detectable change after TAVI or SAVR at 30 days, 6 m and 12 months (Table 4-3).

4.4.5 Grade of Cognitive impairment at baseline and after TAVI and SAVR

Table 4 shows the proportions of patients that were graded as “impaired” vs. “average or above” across the four measured time points according to published norms:

Mnemonic function

HVLT grade: For both the TAVI and SAVR groups, there was evidence of significant reduction in the percentage of impairment for total learning over 12 months. The TAVI group did not change on delayed recall but in the SAVR group there was a significant reduction in the percentage who were graded impaired (Table 4-4). The percentage of patients with an impaired discrimination index did not change across the 12 months in either group. The TAVI group had higher percentage of impairment at baseline compared to SAVR for total learning (Table 4-4, p=0.005), but there were equivalent levels of impairment for delayed recall and discrimination indices.

ROCF grade: The TAVI group had a greater proportion of patients with impairment of visuospatial memory at baseline compared to SAVR (p=0.01). For both TAVI and SAVR, there was no change in the proportion of impairment over 12 months for copy and recall grades, except for a significant reduction of impairment in delayed recall grade in the TAVI group only (Table 4-4).

Executive function

TMT-A and B: For both TAVI and SAVR groups, there was no statistically significant change in the proportion of patients with an impaired grade after treatment at 30 days, 6 months and 12 m (Table 4-4). However, across the 12 months the TAVI group had a higher proportion of impaired patients than SAVR (baseline, TAVI vs. SAVR: TMT-A, p=0.0001; TMT-B, p=0.006).

For the letter number sequencing task (LNS), and verbal and semantic fluency (COWAT), the TAVI group compared to SAVR had similar proportions of impaired patients at baseline and this did not change significantly out to 12 months (Table 4-4). For the perceptual and motor speed and visual memory (DSST) and the fine motor co-ordination and speed (GPT), the TAVI group had a greater proportion of impaired patients compared to SAVR at baseline, but there was no change within groups out to 12 months (Table 4-4).

Table 4-4 Proportion of patients graded as impaired function according to published norms for neurocognitive tests across four time points:

(baseline, 30d, 6m and 12m).

	Group	Baseline TAVI n=50 SAVR n=40 n (%)	30 days TAVI n=41 SAVR n=36 n (%)	6 months TAVI n=38 SAVR n=34 n (%)	12 months TAVI n=36 SAVR n=34 n (%)	p value*
HVLT						
Total learning	TAVI	32(64)**	26(63)	17(45)	5(14)	0.046
	SAVR	17(43)	19(53)	15(44)	6(18)	0.019
Delay Recall	TAVI	21(42)	20(49)	15(40)	16(44)	0.88
	SAVR	22(55)	21(58)	12(35)	7(21)	0.005
Discrimination Index	TAVI	35(70)	25(61)	24(63)	23(64)	0.81
	SAVR	30(75)	27(75)	30(88)	26(77)	0.44
ROCF						
Copy	TAVI	6(12) **	-	8(21)	8(22)	0.39
	SAVR	1(2.5)	-	5(15)	1(3)	0.07
Recall	TAVI	6(12) **	-	6(14)	5(13)	0.95
	SAVR	2(5)	-	1(3)	1(3)	0.85
Delayed Recall	TAVI	18(36) **	-	6(16)	4(11)	0.02
	SAVR	4(10)	-	1(3)	1(3)	0.29
Trail Making Tests						
A	TAVI	27(54)	17(41)	18(48)	15(42)	0.59
	SAVR	10(25)	8(22)	10(29)	6(18)	0.79
B	TAVI	24(48)	13(32)	16(42)	16(44)	0.39
	SAVR	11(28)	10(28)	6(18)	7(21)	0.73
LNS	TAVI	22(44)	20(49)	16(42)	20(56)	0.65
	SAVR	12(30)	15(42)	8(24)	8(24)	0.29
COWAT						
Verbal fluency	TAVI	14(28)	7(17)	10(26)	13(36)	0.38
	SAVR	11(28)	11(30)	7(21)	9(27)	0.78
Semantic fluency	TAVI	18(36)	16(41)	13(34)	19(50)	0.55
	SAVR	9(23)	7(19)	12(35)	7(21)	0.44
DSST	TAVI	40(80)**	33(81)	29(76)	26(72)	0.90
	SAVR	22(55)	15(42)	14(41)	12(35)	0.36
Grooved Pegboard						
Dominant hand	TAVI	41(82)**	32(78)	29(76)	26(72)	0.74
	SAVR	19(48)	14(39)	7(21)	10(30)	0.095
Non-dominant hand	TAVI	42(84)**	36(88)	31(82)	24(66)	0.20
	SAVR	17(43)	13(36)	13(38)	12(35)	0.96

HVLT=Hopkins Verbal Learning test, ROCF=Rey-Osterrieth complex figure test, LNS=Letter-number sequencing, COWAT=controlled oral word association test, DSST=Digit-symbol substitution test,*p values from Chi squared test, **p value form Fishers Exact test, TAVI vs. SAVR.

4.4.6 Cerebral MRI

Seventy-four patients (82%) (TAVI, n=44, SAVR, n=30) completed baseline and post-procedure cerebral MRI. Four TAVI and one SAVR patient chose to have the neurocognitive assessment only (Figure 4-1).

Baseline: There was a trend towards a higher proportion of patients in the TAVI group having evidence of previous stroke (TAVI: 10(23%) vs. SAVR: 2(8%), p=0.06) and peri-ventricular ischaemia (TAVI: 16(36%) vs. SAVR: 8(26%) p=0.16). There was evidence of recent micro-infarction on cerebral DWI in four (9%) TAVI patients but none in the SAVR group. The mean volume±SD of baseline micro-infarction in the TAVI group was 0.26±0.33ml.

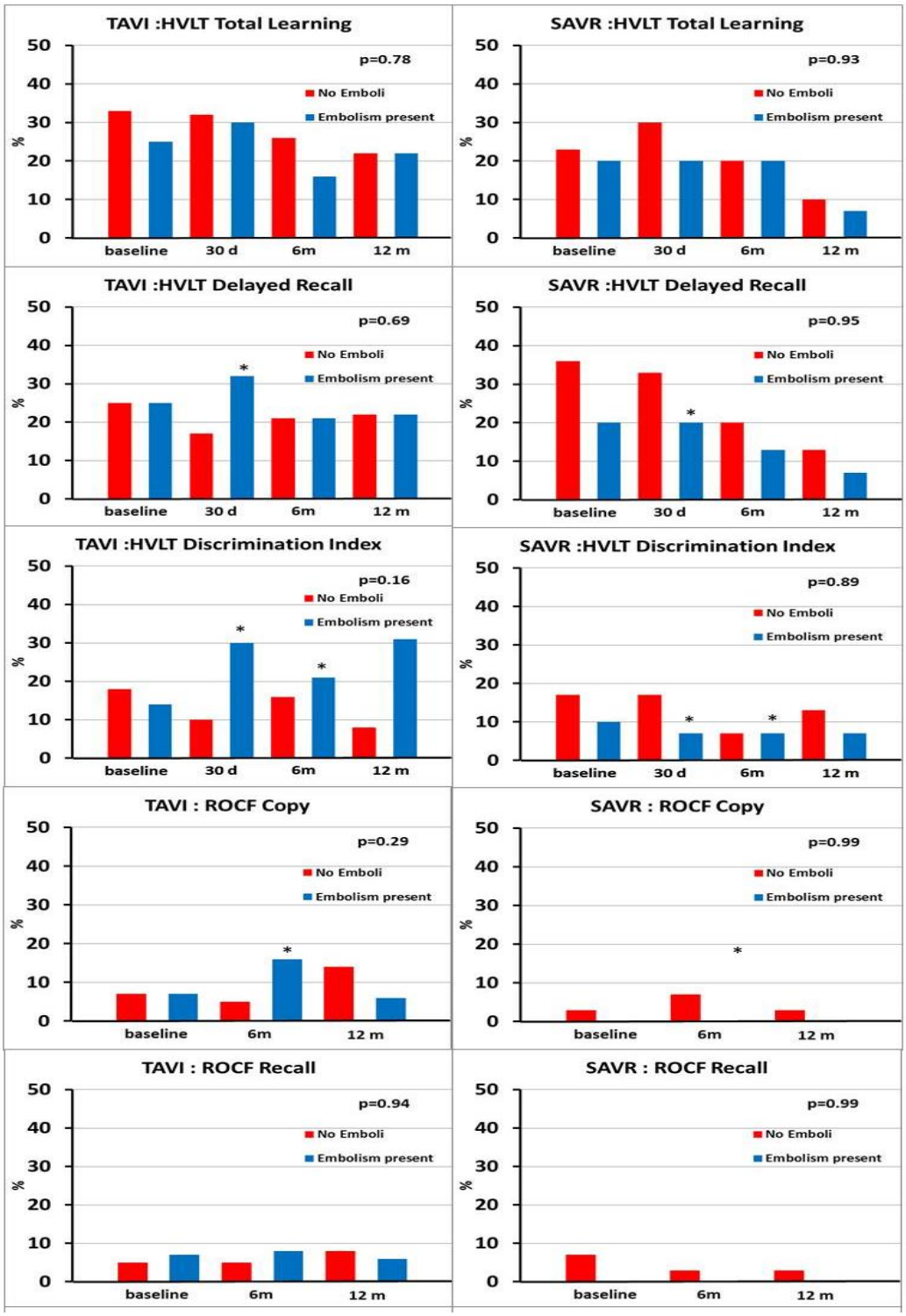
Post-procedure: Post-procedure time to scan was earlier for TAVI compared to SAVR patients (Median (Q1–Q3), TAVI: 4(4–5) vs. SAVR: 6(5–7) days, p=0.001). The incidence of new micro-infarction on DWI-MRI was higher post TAVI compared to SAVR (30(68%) vs. 13(43%), p=0.04). The number of new cerebral micro-infarcts per patient was higher for TAVI (mean±SD; 2.1±2.7 (median=1, Q1-Q3, 0–4) than SAVR (mean±SD, 0.69±0.99 (median=0, Q1–Q3, 0–1) (p=0.006)). The mean volume per micro-infarct was significantly smaller for TAVI patients compared to SAVR patients (0.11±0.08 vs. 0.94±1.9ml, p=0.0001). There was no difference between TAVI and SAVR according to the categorical size of micro-infarcts on DWI: (TAVI: <5mm: 14(32%), >5mm: 6(14%), both: 10(23%); SAVR: <5mm: 5(17%), >5mm: 5(17%) both 6(20%), χ^2=1.32, p=0.52). The TAVI group had a greater number of patients with micro-infarcts in the middle cerebral artery (MCA) and posterior cerebral artery (PCA) territory compared to SAVR (MCA:TAVI 15(34%) vs. SAVR 7(23%), p=0.008; PCA: TAVI 12(27%) vs. SAVR 2(6%), p=0.037). There was no statistical difference between the

number of micro-infarcts in the anterior cerebral artery (ACA) or vertebrobasilar artery (VBA) (ACA: TAVI 9(20%) vs. SAVR 7(23%), p=0.75; VBA: TAVI 10(23%) vs. SAVR 7(23%), p=0.54).

4.4.7 Influence of Cerebral Emboli on Neurocognitive function

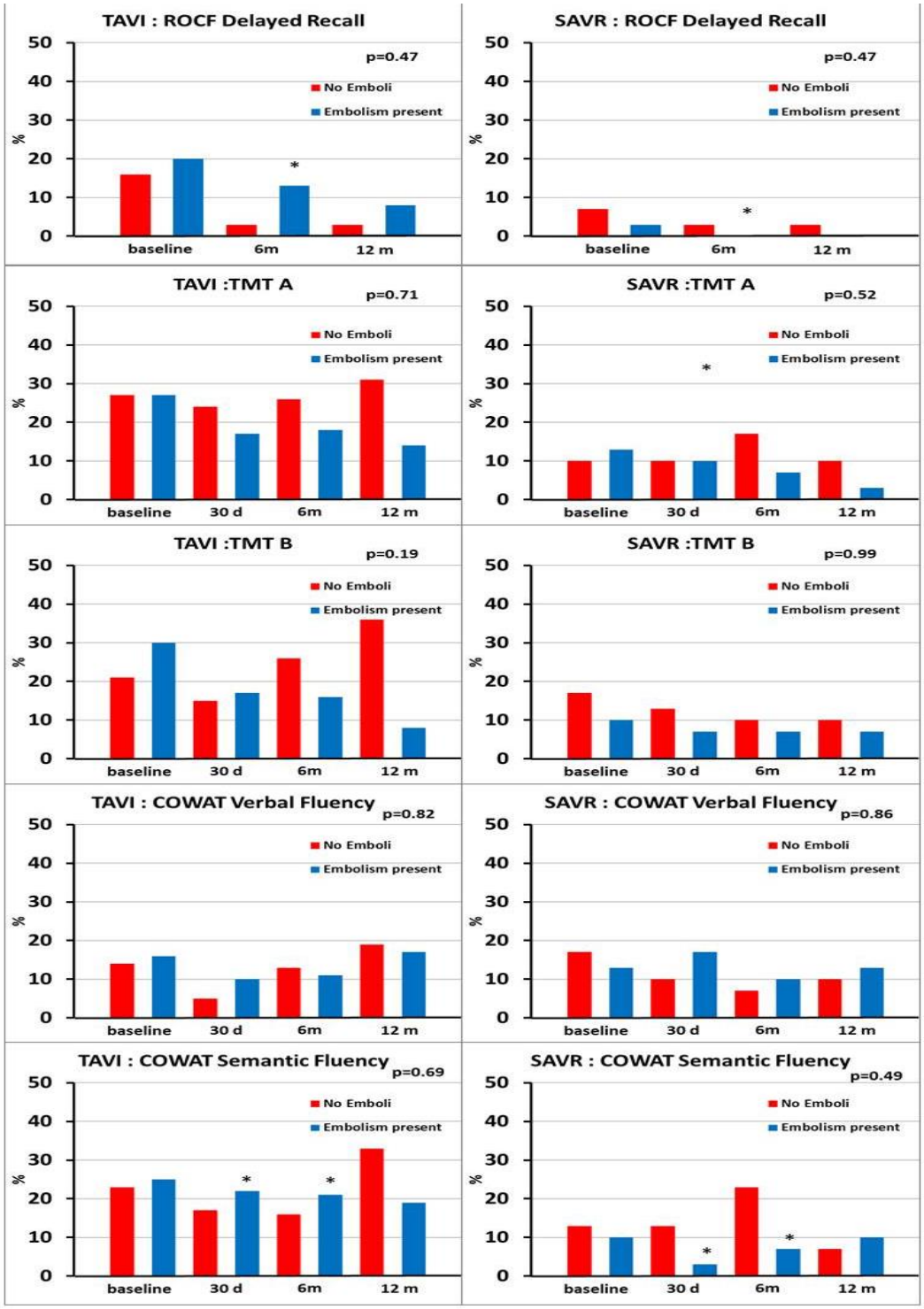
Figure 4-3 and Table 4-5 show the proportion of patients with impaired NCF tests, with and without evidence of cerebral embolism after TAVI and SAVR, over the 4 time points. For those patients that had detected cerebral embolism, there were no significant differences in their baseline test scores compared to those that had none (Figure 4-3 and Table 4-5). Overall within each treatment group (TAVI or SAVR) there was no difference in the proportion of patients with impaired NCF at 30 days, 6 months and 12 months, whether or not they had new cerebral embolism (Figure 4-3 and Table 4-5). In patients with DWI lesions, there was a significantly higher proportion with NCF impairment in the TAVI group compared to the SAVR group at 30 days (according to delayed recall, discrimination index and semantic fluency) and at 6 months (according to DI, ROCF and semantic fluency), but these differences were no longer present by 12 months (Figure 4-3 and Table 4-5). There were no significant differences between groups over the study period in trail making, letter number sequencing, digit symbol substitution tests and grooved peg board tests (Figure 4-3 and Table 4-5).

Figure 4-3 Proportion of patients with impaired neurocognitive function tests with and without cerebral embolism on DWI following TAVI and SAVR over 4 time points



TAVI=Transcatheter aortic valve implantation, SAVR=Surgical aortic valve replacement, DWI=Diffusion weighted imaging, HVLT=Hopkins verbal learning test, TL=total learning, DR=delayed recall, DI=discrimination index, ROCF=Rey Osterrieth complex figure, COWAT=Controlled oral word association, VF=verbal fluency, SF=semantic fluency, P values are from χ^2 test for effect of DWI lesions across 4 time points. Fishers exact p<0.05: comparing groups vs lesions present *at 30d, at 6m, at 12m.

Figure 4-3 (continued) Patients with impaired neurocognitive function tests with and without cerebral embolism on DWI following TAVI and SAVR over 4 time points



TAVI=Transcatheter aortic valve implantation, SAVR=Surgical aortic valve replacement, DWI=Diffusion weighted imaging, HVLT=Hopkins verbal learning test, TL=total learning, DR=delayed recall, DI=discrimination index, ROCF=Rey Osterrieth complex figure, COWAT=Controlled oral word association, VF=verbal fluency, SF=semantic fluency, P values are from χ^2 test for effect of DWI lesions across 4 time points. Fishers exact p<0.05: comparing groups vs lesions present *at 30d, at 6m, at 12m.

Table 4-5 Proportion of patients with impaired neurocognitive function tests with and without cerebral embolism on MRI after TAVI and SAVR over 4 time points

	Group	Baseline TAVI n=44 SAVR n=30 n (%)		30 days TAVI n=41 SAVR n=30 n (%)		6 months TAVI n=38 SAVR n=30 n (%)		12 months TAVI n=36 SAVR n=30 n (%)		p*
DWI lesions **		none	≥1	none	≥1	none	≥1	none	≥1	
LNS	TAVI	10(23)	11(25)	11(27)	10(24)	11(29)	6(16)	14(39)	7(19)	0.54
	SAVR	5(17)	4(13)	6(20)	5(17)	4(13)	2(7)	3(10)	3(10)	0.96
DSST	TAVI	20(46)	16(36)	18(44)	15(37)	18(47)	12(32)	17(47)	11(31)	0.97
	SAVR	10(33)	7(23)	6(20)	5(17)	6(20)	4(13)	6(20)	3(10)	0.92
GPT										
D	TAVI	19(43)	18(41)	19(46)	14(34)	15(40)	15(40)	10(28)	16(44)	0.63
	SAVR	10(33)	4(13)	7(23)	3(10)	3(10)	2(7)	4(13)	3(10)	0.83
Non-D	TAVI	20(46)	17(39)	20(49)	17(42)	16(42)	16(42)	12(33)	13(36)	0.99
	SAVR	8(27)	4(13)	6(20)	4(13)	4(13)	5(17)	4(13)	4(13)	0.60

TAVI=Transcatheter aortic valve implantation, SAVR=Surgical aortic valve replacement, DWI=Diffusion weighted imaging, LNS=Letter number sequencing, DSST=Digit symbol substitution test, GPT=grooved pegboard test, D=dominant hand. *P values are from χ^2 test for effect of DWI lesions across 4 time points. **DWI lesions on post procedure cerebral MRI.

Predictors for Cognitive Impairment

Baseline impairment: Univariate and multivariate logistic regression analysis for predictors of cognitive impairment at baseline are shown in Table 4-6. For TAVI, significant univariate factors of AF, prior CABG, COPD and creatinine were entered into the multivariate analysis. Only AF (OR 8.31, 1.1-60.9, p=0.037) and creatinine (OR 1.03, 1.0-1.05, p=0.02) were statistically significantly associated with impaired baseline NCF. For the SAVR group the predictors were hypertension and baseline creatinine but were not statistically significant in the multivariate analysis (Table 4-6).

Table 4-6 Univariate and multi-variate logistic regression analysis for predictors of baseline cognitive impairment

Risk factors	Unadjusted odds ratios	95% CI	p value	Adjusted odds ratios*	95% CI	p value
TAVI						
Age	0.98	0.92 to 1.05	0.63			
male	0.97	0.36 to 2.57	0.94			
BMI	0.97	0.88 to 1.07	0.56			
EuroSCORE	1.00	0.95 to 1.05	0.83			
EuroSCORE II	0.94	0.82 to 1.08	0.39			
STS Score	0.93	0.79 to 1.09	0.37			
STS Morbidity	1.02	0.95 to 1.10	0.61			
Hypertension	0.61	0.22 to 1.67	0.33			
Diabetes	2.97	0.75 to 11.7	0.12			
Hypercholesterolaemia	0.47	0.17 to 1.30	0.14			
AF	5.79	1.20 to 28.05	0.03	8.31	1.1 to 60.9	0.037
Stroke/TIA	1.27	0.38 to 4.25	0.70			
MI	0.57	0.15 to 2.20	0.41			
CABG	0.37	0.12 to 1.10	0.07	0.29	0.08 to 1.0	0.056
PVD	0.82	0.23 to 2.90	0.75			
PCI	0.93	0.31 to 2.82	0.90			
COPD	3.70	0.95 to 14.45	0.06	2.72	0.5 to 14.1	0.24
Creatinine	1.02	0.99 to 1.03	0.07	1.03	1.00 to 1.05	0.02
PHT	1.48	0.48 to 4.62	0.50			
Cerebral MRI						
PVI	0.68	0.20 to 2.32	0.54			
DWI	1.11	0.18 to 6.79	0.91			
SAVR						
Age	1.01	0.91 to 1.10	0.87			
male	1.0	0.21 to 4.77	1.0			
BMI	1.08	0.93 to 1.24	0.32			
EuroSCORE	1.17	0.91 to 1.52	0.23			
EuroSCORE II	1.99	0.50 to 7.76	0.33			
STS Score	1.57	0.59 to 4.11	0.36			
STS Morbidity	1.15	0.95 to 1.40	0.16			
Hypertension	3.43	0.79 to 14.85	0.10	3.16	0.7 to 14.6	0.14
Diabetes	0.78	0.12 to 5.05	0.80			
Hypercholesterolaemia	2.92	0.66 to 12.99	0.16			
AF	1.06	0.1 to 1.59	0.46			
Stroke/TIA	2.86	0.30 to 27.02	0.36			
MI	0.78	0.12 to 5.05	0.79			
CABG	-	-	-			
PVD	-	-	-			
PCI	-	-	-			
COPD	-	-	-			
Creatinine	1.04	0.99 to 1.10	0.09	1.04	0.99 to 1.1	0.11
PHT	1.82	0.18 to 18.41	0.61			
Cerebral MRI						
PVI	0.68	0.13 to 3.47	0.65			
DWI	-	-	-			

BMI=body mass index, STS=Society of Thoracic Surgery, AF=atrial fibrillation, TIA=transient ischaemic attack, MI=myocardial infarction, CABG=coronary artery bypass grafting, PVD=peripheral vascular disease, PCI=percutaneous coronary intervention, COPD=chronic obstructive pulmonary disease, PHT=pulmonary hypertension, MRI=magnetic resonance imaging, PVI=periventricular ischaemia, DWI=diffusion weighted imaging.*Odds adjusted for TAVI (AF, CABG, COPD, creatinine) and SAVR (Hypertension, creatinine)

Post-procedural cognitive impairment at 12 months: Univariate logistic regression for the associations of cognitive impairment at 12 months was conducted (Tables 4-7). For both TAVI and SAVR, there were no major associations for the development of impaired NCF after considering extensive cardiovascular risk factors, co-morbidities, surgical risk scores and procedural factors. The only exception was hypercholesterolaemia in the TAVI group. Importantly, there was no association with cerebral-DWI micro-infarcts, either by number of new lesions or total lesion volume (Table 4-7).

Table 4-7 Univariate logistic regression analysis for the associations with cognitive impairment at 12 months

Risk factors	Unadjusted odds ratios	95% CI	p values
TAVI			
Age	0.97	0.89 to 1.06	0.54
Male	0.97	0.12 to 1.42	0.16
BMI	0.97	0.91 to 1.04	0.41
EuroSCORE	0.97	0.91 to 1.04	0.41
EuroSCORE II	0.99	0.83 to 1.18	0.92
STS Score	0.85	0.68 to 1.07	0.17
STS Morbidity	0.96	0.88 to 1.06	0.47
Hypertension	1.02	0.91 to 1.14	0.70
Diabetes	0.83	0.22 to 3.13	0.78
Hypercholesterolaemia	0.24	0.07 to 0.84	0.026
AF	1.6	0.43 to 5.96	0.48
Stroke/TIA	0.84	0.21 to 3.43	0.81
MI	0.81	0.14 to 4.54	0.81
CABG	0.36	0.08 to 1.66	0.19
PVD	0.85	0.18 to 3.92	0.85
PCI	1.42	0.34 to 5.91	0.63
COPD	1.60	0.43 to 5.95	0.48
Creatinine	1.00	0.98 to 1.01	0.97
PHT	3.05	0.67 to 13.77	0.15
Number of DWI lesions	1.19	0.86 to 1.63	0.29
Volume of lesions	2.07	0.26 to 16.52	0.49
TAVI size	1.16	0.86 to 1.56	0.80
Femoral access	0.82	0.10 to 6.40	0.84
Procedure Time	1.00	0.99 to 1.01	0.38
Fluoroscopic time	1.03	0.97 to 1.08	0.35
Contrast volume	0.99	0.99 to 1.00	0.88
SAVR			
Age	1.01	0.90 to 1.20	0.78
Male	0.84	0.79 to 8.88	0.88
BMI	0.88	0.62 to 1.25	0.48
EuroSCORE	0.88	0.62 to 125	0.49
EuroSCORE II	0.47	0.56 to 3.99	0.49
STS Score	1.68	0.51 to 5.53	0.39
STS Morbidity	0.98	0.78 to 1.23	0.85
Hypertension	0.71	0.10 to 4.59	0.71
Diabetes	0.83	0.22 to 3.13	0.78
Hypercholesterolaemia	0.49	0.05 to 4.95	0.54
AF	0.46	0.03 to 6.06	0.55
Stroke/TIA	1.00	0.09o 11.02	1.00
MI	1.00	0.09 to 11.03	1.0
Creatinine	0.99	0.93 to 1.04	0.99
No of DWI lesions	1.15	0.44 to 3.04	0.77
Volume of lesions	1.37	0.91 to 2.06	0.13
Bypass time	0.99	0.97 to 1.01	0.43
Cross clamp time	0.98	0.96 to 1.02	0.38
Valve size	1.0	0.61 to 1.64	1.00
CABG performed	1.6	0.27 to 9.53	0.60

4.5 DISCUSSION

This study shows that TAVI and SAVR have no significant detrimental effect on neurocognitive function in the short to medium-term. New silent cerebral micro-infarction, which was more frequent after TAVI had no relationship neurocognitive function at 12 months. However, unfortunately the baseline characteristics are significantly different and therefore may well confound the differences observed. Using a comprehensive battery of validated tests to cover a wide variety of important higher neurocognitive faculties across 4 defined time points, there was a steady improvement in absolute test scores and a quicker performance in timed tasks. The SAVR group showed improvement in immediate memory recall and delayed memory recall over 12 months. Both the TAVI and SAVR groups showed improvement in delayed visual recall and drawing tasks over 12 months. The TAVI and SAVR groups had similar levels of IQ and therefore cognitively would be expected to perform in a similar fashion. However, the TAVI group were impaired in several areas at baseline, such as MMSE, but this did not deteriorate further post-TAVI. The greater prevalence of baseline NCF impairment in the TAVI group likely reflects their advanced age and significant comorbidities. Thus in the TAVI group cognitive function might be expected to decline with time, as in the general population, but this was not seen in our study.

Both TAVI and SAVR groups improved in visuospatial memory tasks indicating genuine improved cognitive performance rather than a learning effect, as the tests were 12 months apart. In the trail making and grooved pegboard tasks the TAVI group was significantly slower, but this may have been related to visual impairment or manual dexterity being limited by age related frailty.

When categorising the patients into “impaired” and “average or above” according to published norms for age and levels of education, the TAVI group overall had higher percentages of “impaired” patients. This again may be related to other significant co-morbidities contributing negatively to cognitive function. However, in our study

there was no evidence following TAVI or SAVR that more patients became neurocognitively impaired out to 12 months.

In the previous chapter we observed significant improvements in health-related quality of life (HRQoL) parameters across time, however, during neurocognitive assessment, this was not seen. This is because HRQoL looks at global health status and well-being, whereas neurocognitive assessment is looking for deteriorations in memory function. Therefore, given the cerebral insults by micro-infarction, we would be concerned with a decline. Also, cognitive function does tend to decline gradually with time especially in the elderly, which we did not observe in our study, suggesting a beneficial effect of intervention.

Both TAVI and SAVR are significant life changing events that patients may find difficulty adjusting to. However, in our study there was no evidence of pre-existing anxiety or depression. Moreover, our two groups of patients were routinely assessed using HADS and did not develop any evidence of psychological disturbance, which undetected can affect neurocognitive function.

Several studies have confirmed a higher incidence of new cerebral micro-infarction after TAVI compared to SAVR(Uddin et al., 2015, Fairbairn et al., 2012a, Kahlert et al., 2010, Ghanem et al., 2010a, Stolz et al., 2004). However, the incidence of micro-infarction was marginally lower in comparison to the findings in chapter 3 ; 68% vs 77% in the TAVI arm and 43% vs 43% for SAVR. The potential mechanisms are related to device manipulation around atheromatous aortas, as well as embolisation of valvular or atheromatous material during balloon aortic valvuloplasty and prosthesis deployment (Kahlert et al., 2012). The TAVI technique is newer than established SAVR and so there is an operator experiential effect which may be observed in the difference in the two chapters, as Chapter three was studied first and this chapter was a differing cohort. Although there were frequent new cerebral micro-infarctions detected in our study, there was no significant impact on NCF in the TAVI patients out to 12 months, as evidenced by the absence

of change in the proportion of patients being graded as ‘impaired’ over time. However, we did see an early (30 days and 6 months) transient decline in verbal memory recall and executive function in TAVI patients with new silent micro-infarction when compared to SAVR patients. This may be due to transient neuronal dysfunction post-procedure directly related to the higher numbers of DWI lesions in the TAVI group, which recovered with time. A degree of neuronal remodelling may occur following an ischaemic insult, there may be gradual neuronal cell death and areas of oedema that recovery by forming new neuronal network connections.

In our study, we identified AF and renal function to be predictors of baseline cognitive impairment, which may both be associated with embolic and diffuse cerebrovascular disease. Interestingly, new silent cerebral micro-infarction and operative (TAVI and SAVR) procedural factors were not significantly associated with impaired NCF, suggesting that the invasive insult does not have a negative impact on short to medium-term cognitive function. Whilst vascular dementia is a significant cause of cognitive disability worldwide, its cause is multifactorial. Prior studies have not shown a direct negative effect on cognition after TAVI although the consequences of silent cerebral infarction remain a concern (Ghanem et al., 2013). Knipp et al studied transapical TAVI and SAVR patients and showed early decline in the surgical patients but no association with cerebral emboli or ischaemia (Knipp et al., 2013). However, this study only looked at follow up to 3 months and did not perform any pencil and paper tests which could have provided additional information for comprehensive neuropsychological evaluation. The differences seen between patients could be related to “cognitive reserve”; which is the ability to maintain cognitive function by making new neuronal connections following a neurotoxic insult.

Embolic protection devices to reduce post-procedure stroke may have an important role and have also been shown to reduce the number of silent cerebral micro-infarcts, with a high procedural success rate and safety profile (Baumbach et al.,

2015). The direct effect on neurocognitive function will be difficult to assess, however early results from DEFLECT III have shown an improvement in delayed recall and overall improvement in cognition using the Montreal Cognitive assessment (Lansky et al., 2015). As TAVI is now being evaluated in randomised trials against SAVR in patients with moderate to high surgical risk, our findings suggest that the higher rate of silent cerebral micro-infarcts after TAVI may not have an observable negative effect on short-medium term NCF.

4.5.1 Limitations

The study groups could not be completely matched due to current international guidelines reserving TAVI for patients that are inoperable or deemed to be at high surgical risk; this is a limitation of all current non-randomised studies in this disease area (Joint Task Force on the Management of Valvular Heart Disease of the European Society of et al., 2012). Therefore the differences that we have demonstrated could be influenced by bias related to differences in baseline characteristics. The TAVI group were older and may have had more limited cognitive reserve in comparison to the SAVR group, who were younger and with less medical co-morbidity. Although the study was prospectively powered with an appropriate sample size, a larger study population would allow greater confidence in the findings. Complete follow up and evaluation to 12 months was not possible in all patients, which again may have introduced bias. The TAVI group in particular are elderly and frail, with a high annual mortality rate, making this population exceptionally hard to study in the medium term (Nielsen et al., 2012).

The study was limited to two high-volume TAVI centres which may not be sufficient to overcome centre selection bias for TAVI or SAVR treatment, and trans-apical TAVI was not evaluated. Neurocognitive function was assessed at the four VARC recommended time points, but we are unable to comment on the longer-term consequences on NCF beyond 12 months. This may be especially important if TAVI is to be considered in younger lower-risk patients, who have a longer life

expectancy. The cerebral MRI scans were performed at 1.5T whereas higher field strengths may have detected more subtle embolic events. However, at the time of our study the CoreValve prosthesis was not approved for 3.0T field strength and on-going clinical trials of cerebral embolic protection devices are at the 1.5T field strength. Nevertheless we were unable to demonstrate an association between new cerebral micro-infarction and a decline in cognitive performance.

4.6 CONCLUSION

There was no evidence of short to medium-term cognitive decline following TAVI or SAVR for severe aortic stenosis. Although silent cerebral micro-infarcts were more common following TAVI than SAVR, there was no impact on neurocognitive performance.

5 Extracellular Volume (ECV) in health: Reproducibility of myocardial T1 values and estimation of ECV fraction in healthy adult volunteers using the Modified Look-Locker Inversion recovery (MOLLI) method

5.1 ABSTRACT

Objective: To establish the reproducibility of T1 mapping and ECV calculation in healthy adults.

Methods: Twenty healthy volunteers underwent CMR studies at 1.5T using the identical MOLLI (3,3,5) method with acquisition in 3 short axis slices and 4 chamber. 10 of the volunteers were restudied. Native and post-contrast (0.2mmol/kg of gadoteric acid contrast (Dotarem®) T1 values were obtained for myocardium and blood pool, and ECV calculated. T1 maps were generated offline using MR Maps software.

Results: Mean age 20.6±1.5 years (9(45%) male; BSA 1.86±0.2m^2; Haematocrit 0.44±0.03). All cardiac volumetric measurements were in the normal range (ejection fraction 60±5%; LV mass index 32±4g/m^2). A total of 320 T1 maps (3 slices, 16 segments) were produced from 20 volunteers and graded according to image quality (unusable n=4(1%); poor n=50(16%); adequate n=93(29%); excellent n=174(54%)).

There was no statistical difference in pre-contrast myocardial T1 values between, apex, mid-, base or 4 chamber slices (701±73ms vs. 739±77ms vs. 701±75ms vs. 722±56 ms; ANOVA, p=0.29). Post-contrast myocardial T1 values were also consistent across the slices (apex 422±51ms, mid- 446±41ms, base 431±47ms, 4Ch 439±59ms; ANOVA, p=0.51). Mean ECV values were: apex 22.3±6%, mid- 23.9±3%, base 22.1±6% and 4Ch 23.4±7% (ANOVA F=0.72, p=0.55).

The intra-observer, inter-observer and inter-study variability was fair to good for native myocardial T1. The intra-, inter-observer and inter-study agreement was fair to excellent (inter-class correlation co-efficient ranges (R (0.52 to 0.80), R (0.51 to 0.77) and R (0.52 to 0.81). ECV measurement had variability but excellent agreement (R (0.73 to 0.84).

Conclusions: In healthy young volunteers at 1.5T, native and post-contrast T1 mapping using MOLLI and ECV fraction show good agreement across the myocardium and fair observer and inter-study reproducibility.

5.2 INTRODUCTION

Cardiovascular magnetic resonance imaging has provided a deeper insight into the understanding of various cardiomyopathic processes such as genetic, ischaemic, inflammatory and infiltrative causes (Kuruvilla et al., 2014, Motwani et al., 2014). The advantages of CMR are in the high spatial resolution and multi-planar imaging, as well as contrast enhanced imaging. Late gadolinium enhanced imaging is widely used in clinical practice to investigate cardiomyopathy and detects specific patterns related to disease processes, such as sub-endocardial LGE in myocardial infarction or mid wall enhancement in Dilated cardiomyopathy (DCM) (Kim et al., 2009). LGE imaging is excellent for focal fibrosis or scar but does not highlight diffuse cardiomyopathic processes as well. T1 mapping involves measuring the T1 value (ms) of each voxel within the myocardium (and blood pool) and subsequently generating a parametric map from which regional variations in the T1 relaxation time can be visualised. T1 mapping techniques have developed following investigations of diffuse processes that can occur in infiltrative or valvular heart disease, such as aortic stenosis (Mewton et al., 2011). Various methods of T1 mapping have been developed, but are based around an inversion recovery sequence (Wacker et al., 1999, Flacke et al., 2001). Messroghli et al developed the modified Look-locker inversion recovery method to provided estimations of tissue t1 values (Messroghli et al., 2004). This technique was developed in Leeds on the Phillips 1.5T scanner. MOLLI has been widely studied and published in aortic regurgitation, acute MI, stable CAD and valvular disease(Sparrow et al., 2006). Modifications of the MOLLI method include shortened MOLLI

(ShMOLLI) (Piechnik et al., 2013). We decided to use the original MOLLI as this was only available on our scanner and this had already been validated.

This study aimed to use the original MOLLI sequence using 3,3,5 readout at 1.5T in healthy adult volunteers and confirm reproducibility before using this in patients with severe aortic stenosis.

5.3 METHOD

5.3.1 Study participants

We recruited 20 healthy volunteers who had CMR studies using an identical protocol, 10 of these were randomly selected to have repeat study. Inclusion criteria: age > 18 years. Exclusion criteria: History of any medical problem, recent cold or flu, contra-indication for MRI, claustrophobia, pregnancy. Informed written consent was obtained and this study was approved by the Local ethic committee. An intravenous 20-gauge cannula was placed in the antecubital fossa vein. A full blood count by venesection was obtained for haematocrit.

5.3.2 Scan protocol

The study was performed on 1.5 Tesla (Intera, Philips Healthcare, Best, Netherlands) with Master gradients (30mT/m, 150[$mT.m^{-1}$]/msec) and a five-element cardiac phased array receiver coil with vector cardiogram. Localiser images were obtained using cine steady state free precession for the vertical long axis (VLA), horizontal long axis (HLA) and short axis (SA) of the left ventricle (SSFP, TR 3.0ms, TE 1.5ms, Slice thickness 8mm, FOV 400, RFOV 80, 30 phases). The LV volumes were acquired in the short axis plane using multi-slice and multi-phase cine imaging. Typically 10 to 12 contiguous slices were acquired covering from the mitral valve plane to

beyond the apex (Slice thickness 10mm, 0 gap, 30 phases, FOV 380, RFOV 100). The “3 of 5” technique was used to identify basal, mid- ventricular and apical slices as this has been shown to be reproducible (Messroghli et al., 2005). This is performed by planning 5 parallel short axis slices from the outmost aspect of mitral annulus and LV apex, with the ventricle in systole. The centre 3 slices are used to acquire cine images and later plan MOLLI sequences.

T1 mapping was performed with the MOLLI pulse sequence which was described by Messroghli (Messroghli et al., 2004). For each individual slice (base, mid, apex, 4Ch), there were 3 successive Look-Locker acquisitions (trains). Each of these trains, starts with a specific inversion time (100ms, 200ms and 350ms) after which multiple single shot images are acquired over consecutive heart beats in end-diastole. The 3 trains produce 3, 3 and 5 images (3,3,5 MOLLI). MOLLI was performed pre-contrast (twice), and 5 and 15 minutes after intravenous administration of 0.2mmol/kg of gadoteric acid contrast (Dotarem®, Guerbet, Villepinte). The contrast was followed by a 20mls saline flush.

5.3.3 Image analysis

Left ventricular volumes using the summation of discs method were calculated by manually contouring the endocardial and epicardial borders at end-diastole and again at end-systole in commercially available software (Qmass 6.0, Medis, Netherlands). Mass = epicardial volume – endocardial volume multiplied by the myocardial density (1.05g/cm^3) (Gaasch and Zile, 2011).

T1 maps were generated off-line from source MOLLI data images using published software MR Maps (Messroghli et al., 2010). In the software the images are manually checked and corrected for significant motion before map generation. The software sorts the images in order of effective inversion time (TI) and uses three-parameter non-linear curve fitting using a Levenberg-Marquardt algorithm. A T1 map is generated as a DICOM file which is stored. This T1 map is analysed in Qmass 6.0 (Medis, The Netherlands). A small region of interest is drawn in the myocardial mid septum and mid ventricular blood pool to measure mean signal intensity for the T1 value. A conservative septal ROI has been shown to provided good reproducibility (Rogers et al., 2013). Image quality was assessed by two independent observers and were graded using a Likhart scale (1=unusable, 2=poor, 3=adequate, 4=excellent).

5.3.4 Extra cellular volume (ECV) calculation

The myocardial partition coefficient was calculated using the following equation:

$\lambda = \frac{\Delta R1\ myocardium}{\Delta R1\ blood\ pool}$ where $1 = \frac{1}{T1}$. The $ECV = (1\ - haematocrit) \times\ \lambda$

The haematocrit is measured from the full blood count sample. The 15 min post contrast values were used for ECV.

5.3.5 Statistical analysis

Data are presented as mean±SD or median (IQR). Normality of the continuous data were checked for using the Shapiro-Wilks test and comparisons were made using un-paired or paired Student's t-test or the non-parametric equivalent.

Reproducibility analysis was performed for intra-observer, inter-observer and inter study, using coefficients of variation (CoV) and calculating intra-class correlation coefficients (ICC). Coefficients of variation were calculated by dividing the standard deviations of the differences between two measurements over the mean of the groups. Agreement was considered as follows: Excellent:R≥0.75, Good: R=0.60 to 0.74, Fair:=0.40 to 0.59, Poor R<0.40 (Oppo et al., 1998). Data were analysed using Microsoft Excel 2010 or in SPSS (version 22, IBM, USA) as appropriate.

5.4 RESULTS

All twenty volunteers completed the study protocol along with ten who were re-studied at a median 90 days. The age was 20.6±1.5 years, 9 (45%) males, with a BSA 1.86±0.2. Mean Haematocrit was 0.44±0.03.

5.4.1 LV volumes

All volumetric measurements were in the normal range(Alfakih et al., 2003); Indexed End-diastolic volume=89±15ms/m^2, indexed end-systolic volume= 36±9.8ml/m^2, stroke volume 53ml±9.8ml/m^2, ejection fraction 60±5%, indexed LV mass 32±4g/m^2.

5.4.2 Image quality

A total of 320 T1 maps (3 slices, 16 segments) were produced from 20 volunteers (Grade: unusable n=4(1%), poor n=50 (16%), adequate n=93 (29%), excellent n=174 (54%). The median grade was 4 (IQR 1) for all (apex, mid, base, 4Ch) slices Kruskal Wallis test p=0.96)

5.4.3 T1 measurements and extracellular volume (ECV) estimations

Table 5-1 shows the T1 values of myocardium and blood pool obtained from the 20 healthy volunteers. There was no statistical difference in myocardial T1 value between apex, mid- or base for the first and second pre-contrast measures (pre-contrast 1) (ANOVA F=1.26, p=0.29) & (pre-contrast 2)(F=0.88 p=0.45), 5 mins (F=0.15 p=0.92) or 15 mins (F=0.77 p=0.51) after contrast (Table 5-1). The calculated mean ECV were: Apex 22.3±6%, Mid-23.9±3, Base 22.1±6 and 4Ch 23.4±7 (ANOVA F=0.72, p=0.55).

Table 5-1 T1 measurements of myocardium and blood pool for 20 volunteers

Myocardium	**Apex T1 (ms)**	**Mid T1 (ms)**	**Base T1 (ms)**	**4 Ch T1 (ms)**
Pre-contrast 1	701±73	739±77	701±75	722±56
Pre-contrast 2	713±84	734±93	700±89	741±74
5 mins	388±84	387±44	396±48	399±65
15 mins	422±51	446±41	431±47	439±59
Blood Pool	**Apex**	**Mid**	**Base**	**4 Ch**
Pre-contrast 1	1597±225	1677±257	1664±233	1619±193
Pre-contrast 2	1648±222	1673±258	1678±233	1580±246
5 mins	262±29	281±46	291±355	295±42
15 mins	329±44	362±46	355±45	366±55

5.4.4 Reproducibility and agreement

Reproducibility of T1 measurements was assessed for intra-, inter-observer (two observers) and inter-study variation (two studies) (Table 5-2). The intra-observer for T1 measurement was fair to good for pre-contrast T1 measurements but the post contrast measurements had higher coefficients of variation. The CoV for ECV was high over 10%. The inter-observer variability also had similar coefficient of variation values with lower values for pre-contrast. The inter-study variability was fair but had high coefficients for post contrast T1 measurements. Overall, there was consistency of T1 measurements across ventricular slices (apex, mid-, base and 4 chamber) (Table 5-2). The intra-class correlation coefficients for intra-, inter-observer and inter-study are shown in table 5-3. There was evidence of good to excellent agreement on T1 measurement for intra-, inter-observer and inter-study (Table 5-3). The ECV measurement had excellent agreement for intra-, inter-observer and inter-study.

Table 5-2 Intra-, inter observer and inter study reproducibility of T1 measurements in 10 healthy volunteers

	Apex		**Mid**		**Base**		**4 Ch**	
	Mean diff±SD	CoV	Mean diff±SD	CoV	Mean diff±SD	CoV	Mean diff±SD	CoV
Intra-observer								
Pre contrast 1	-1.4±40	6.5	2.7±35	5.4	3.1±30	5.8	2.8±54	7.4
Pre contrast 2	-2.4±45	8.8	4.5±60	8.3	4.6±57	8.3	5.9±35	6.6
Post contrast								
5 min	-4.6±50	13.1	1.2±58	15.1	1.4±57	14.3	7.9±44	11.0
15 min	-1.7±49	10.4	5.0±40	10.3	4.2±50	11.6	8.3±39	8.9
ECV(%)	-0.1±2	14.9	-0.3±3	13.5	0.3±2	12.1	0.1±2	11.2
Inter-observer								
Pre contrast 1	-3.4±45	6.3	4.7±40	5.4	6.1±40	5.7	-1.8±54	7.4
Pre contrast 2	-3.4±63	8.6	9.9±60	8.2	-9.6±58	8.1	4.9±49	6.6
Post contrast								
5 min	-9.6±50	13.4	-0.2±58	15.1	0.4±57	14.3	-3.9±44	11.0
15 min	-1.6±44	10.3	-4.5±46	10.5	4.1±50	11.6	6.3±39	8.8
ECV(%)	-0.1±4	17.1	-1.8±4	17	-0.3±4	16.0	-0.5±3	14.3
Inter-study								
Pre contrast 1	-13.6±24	3.6	-11.1±80	11.9	-12.8±98	14.3	-8.7±84	11.3
Pre contrast 2	0.4±50	7.2	-1.8±73	10.5	-11.7±63	9.2	-12.7±64	8.8
Post contrast								
5 min	-7.5±51	13.7	2.8±49	12.8	-3.7±69	17.3	-8.4±63	15.3
15 min	-11.3±59	14.2	-5.3±33	7.8	-8.7±84	12.4	-9.6±78	18.0
ECV(%)	0.8±3	11.8	1.8±3	12.1	0.8±2	9.6	0.5±2	9.0

All values show mean difference±SD in T1 (ms). ECV=extracellular volume. 4Ch= 4 chamber slice

Table 5-3 Intraclass correlation coefficient for Intra-, inter-observer and inter-study reproducibility of T1 measurements in 10 healthy volunteers

	Apex		Mid		Base		4 Ch	
	ICC	CI	ICC	CI	ICC	CI	ICC	CI
Intra-observer								
Pre contrast 1	0.70	(0.60–0.80)	0.68	(0.60–0.79)	0.67	(0.57–0.77)	0.59	(0.21–0.87)
Pre contrast 2	0.73	(0.65–0.79)	0.69	(0.35–0.80)	0.70	(0.64–0.80)	0.55	(0.47–0.85)
Post contrast								
5 min	0.75	(0.60–0.90)	0.76	(0.61–0.90)	0.61	(0.56–0.80)	0.58	(0.39–0.82)
15 min	0.80	(0.60–0.96)	0.81	(0.51–0.89)	0.69	(0.32–0.80)	0.52	(0.40–0.69)
ECV	0.73	(0.66–0.86)	0.77	(0.61–0.80)	0.77	(0.61–0.83)	0.77	(0.50–0.88)
Inter-observer								
Pre contrast 1	0.66	(0.61–0.72)	0.64	(0.60–0.71)	0.63	(0.58–0.76)	0.59	(-0.11–0.87)
Pre contrast 2	0.71	(0.65–0.75)	0.59	(0.15–0.84)	0.72	(0.65–0.79)	0.54	(0.47–0.85)
Post-contrast								
5 min	0.64	(0.62–0.77)	0.72	(0.61–0.79)	0.61	(0.56–0.80)	0.51	(-0.50–0.84)
15 min	0.77	(0.61–0.87)	0.64	(0.51–0.82)	0.69	(0.36–0.80)	0.52	(0.40–0.69)
ECV	0.70	(0.66–0.76)	0.76	(0.63–0.79)	0.77	(0.60–0.81)	0.76	(0.49–0.89)
Inter-study								
Pre contrast 1	0.67	(0.63–0.71)	0.66	(0.60–0.81)	0.68	(0.60–0.80)	0.69	(0.24–0.90)
Pre contrast 2	0.60	(0.58–0.68)	0.72	(0.48–0.83)	0.71	(0.49–0.79)	0.71	(0.40–0.89)
Post contrast								
5 min	0.64	(0.63–0.69)	0.79	(0.50–0.85)	0.70	(0.63–0.76)	0.53	(0.43–0.63)
15 min	0.81	(0.78–0.86)	0.75	(0.63–0.81)	0.70	(0.62–0.75)	0.52	(0.42–0.79)
ECV	0.79	(0.62–0.89)	0.84	(0.65–0.93)	0.72	(0.22–0.90)	0.79	(0.61–0.86)

ICC=intraclass correlation coefficient, CI=95% confidence intervals for ICC, ECV=extracellular volume

5.5 DISCUSSION

This study showed that T1 mapping using MOLLI at 1.5T produced good quality T1 maps. The T1 maps of the apex, mid, basal and 4 chamber ventricular slice provided consistent T1 values with fairly acceptable coefficients of variation. Intra-, inter-observer and inter-study reproducibility was good to excellent. The calculation of extracellular volume was consistent across the slices and had fair intra-, inter-study and inter-study reproducibility.

Unfortunately, 16% of the maps generated were of poor quality, which was specifically related to the apical slices and in volunteers with poorly timed breath hold. The need for manual motion correction also added another potential source of error.

These findings are consistent with Messroghli et al at 1.5T who showed good image quality and excellent reproducibility although reproducibility was only assessed in the mid-cavity slice (Messroghli et al., 2006). In addition our study looked at 4 chamber slice and quantified extra-cellular volume. Chin et al performed a similar study but at 3 Tesla with 20 volunteers and reported longer pre-contrast T1 times (approx. 1200±40) but similar ECV(Chin et al., 2014). Also, the normal volunteers were compared with patients with asymptomatic aortic stenosis, but a difference in T1 times nor ECV could be identified.

Equilibrium contrast cardiovascular magnetic resonance (EQ-CMR) is a method to estimate diffuse myocardial fibrosis which uses an infusion of gadolinium contrast to reach steady state. Flett et al reported 13.4% diffuse myocardial fibrosis in healthy volunteers which was lower than the ECV

percentage in our data (Flett et al., 2012). This may be because the EQ-CMR method is validated against patients that underwent myocardial biopsy in order to measure collagen volume fractions (Flett et al., 2010).

Shortened MOLLI (ShMOLLI) acquires the readout over 5,5,1 as opposed to 3,3,5 by MOLLI. Therefore the subject has a shorter breath hold and less likely to experience artefact with the advantage of speedier image acquisition (Piechnik et al., 2010). However, although a robust and reproducible variation to MOLLI, there is a consistent underestimation of T1 by 4%.

T1 mapping using this MOLLI sequence is reproducible but some errors can occur during acquisition due to altered breath holding or poor triggering which can affect the subsequent map generation. For each ventricular slice, the map required 3 separate breath-holds which may slightly alter the position of acquisition. All readout images were manually motion corrected in the MR Maps software. The need for motion correction can introduce error and automated and semi-automated methods of motion correction have been shown to improve T1 mapping (Kellman et al., 2012). The improvements have reduced variability in the T1 value. Off resonance artefact can affect the regional T1 measurement but is more significant at 3T rather than 1.5T (Kellman et al., 2013).

The coefficients of variation for ECV were high and this may be because of existing variability in the measurement of pre- and post-contrast myocardial T1 values combined with the variability of blood pool measurements. A single breath hold MOLLI which was not available on our scanner at the time of study may overcome this potential problems.

Other limitations of this study are that we have studied healthy volunteers with a mean age of 20 years and therefore the normal values obtained may not reflect or represent a control group for older patients. Ideally, a larger sample with a wide stratified age range would be helpful. This study was only performed on 1.5T which has a longer T1 value compared to 3T, nevertheless, T1 mapping is favourably a 1.5T based technique given problems with mapping at 3T.

There are a variety of T1 mapping techniques available which have been studied in normal and diseased states, however, there is a very wide range of normal T1 values which often overlap with ranges quoted for disease processes. Currently this makes it very challenging to differentiate between true normal and a true disease processes.

Also, the post-processing time is long with multiple stages and therefore may not be immediately or easily applicable to clinical patients.

5.6 CONCLUSION

This small study of healthy volunteers showed T1 mapping and ECV calculation to be feasible and reproducible at 1.5T. The intra-, inter-observer and inter-study agreement was fair for both T1 measurement and extracellular volume estimation. However, further studies in diffuse myocardial fibrosis of patients are necessary.

6 Left Ventricular Reverse Remodelling and Changes in Diffuse Myocardial Fibrosis in Severe Aortic Stenosis after treatment with Transcatheter Aortic Valve Implantation and Contemporary Surgical Aortic Valve Replacement

6.1 ABSTRACT

Background: TAVI for severe aortic stenosis has been effective in treating high risk patients with improvement in symptoms and quality of life. There is an improvement in cardiac function through reverse remodelling in Transcatheter Aortic Valve Intervention (TAVI) and Surgical Aortic Valve Replacement (SAVR).

Aim: To determine if 1) extracellular volume (ECV), a measure of diffuse fibrosis, changes after treatment of severe aortic stenosis by TAVI or SAVR; 2) is baseline ECV related to reverse remodelling.

Methods: Cardiovascular MRI was conducted at baseline and 6 months after intervention. Left ventricular volumes, masses and aortic flows were measured. Changes in ECV were measured using T1 mapping using modified Look-Locker inversion recovery (MOLLI).

Results: Seventy patients with severe aortic stenosis were studied (TAVI n=39, SAVR n=31, Age: 80.1±7yrs vs. 73.1±7yrs, p<0.0001, EuroSCORE: 20.6±7 vs. 7.1±8.2, p<0.0001). After 6 months, there were significant improvements in indexed end-diastolic volumes (TAVI: 100±25mls vs. 87±26mls, p<0.001; SAVR 91±28mls vs. 82±17mls, p<0.05) and reduction in

mass for both TAVI (75±16g vs. 55±17g, p<0.001) and SAVR (75±24g vs. 59±59±15g, p<0.001) patients. Only TAVI patients showed a significant reduction in end-systolic volume (48±26mls vs. 40±19mls, p<0.05). Extracellular volumes were similar for both groups at baseline (range 22.8 to 24.6%). There was no significant change in ECV after 6 months (TAVI, 24.0±9% vs. 29.3±11%, SAVR, 23.8±7 vs. 23.5±9, p= 0.76). In multivariate logistic regression only AF and baseline LV mass were significant for cardiac reverse remodelling (Adjusted odds ratio (OR) and confidence intervals (CI), AF: OR, 2.06, CI 1.2 to.3.7, p=0.04; LV mass OR 1.08, CI 1.008 to 1.147, p=0.03)

Conclusion: Significant cardiac reverse remodelling takes place by 6 months after TAVI and SAVR due to cellular changes. ECV does not change after TAVI or SAVR and is not independently associated with LV reverse remodelling.

6.2 INTRODUCTION

Severe aortic stenosis is a progressive disease with associated risk of death from heart failure. This is prevalent in the elderly population who often are deemed unsuitable to receive surgical aortic valve replacement (SAVR) due to high operative risk. Recent large randomised controlled trials and subsequent follow-up studies to 3 to 6 years have shown that Transcatheter Aortic Valve Implantation (TAVI) has survival benefit and is associated with significant improvement in symptoms and quality of life (Leon et al., 2010b, Kodali et al., 2012c, Fairbairn et al., 2012b). UK TAVI six year follow-up showed survival at one year to be 81.7% falling to 37.3% at six years (Ludman et al., 2015). The benefits are possibly due to the obliteration of the valvular obstruction and subsequent improvement in ventricular function through reverse remodelling which has been shown by echocardiography and CMR (Fairbairn et al., 2013b). A possible contributing pathological process is myocardial interstitial fibrosis that is associated with severe aortic stenosis and the related left ventricular hypertrophy (Rudolph et al., 2009). In aortic stenosis there is predominantly a reactive form of interstitial fibrosis which is diffuse and not readily detectable, but can also be focal scar, which can be seen on CMR late gadolinium imaging (Flett et al., 2011, Fairbairn et al., 2013b). The degree of diffuse fibrosis and focal fibrosis (scar) may influence subsequent reverse remodelling after valve surgery or intervention. Fairbairn et al showed focal myocardial fibrosis to be a predictor for reverse re-modelling because the presence of scar was associated with poor baseline volumes and ejection fraction which in turn determined post intervention volumes and function (Fairbairn et al., 2013b). Although TAVI and SAVR are different approaches, both have been shown to improve

ventricular function early as 14 days (Crouch et al., 2015). Studies have shown the increasing importance of patient selection for high risk expensive procedures and there is a need to identify predictors for beneficial outcomes that the Heart MDT may use to influence management decisions (Ludman et al., 2015). The aim of the study was to see if there was a change in diffuse interstitial fibrosis after TAVI and whether it was similar in patients receiving SAVR. Secondly, is diffuse myocardial fibrosis associated with LV reverse remodelling?

6.3 METHODS

6.3.1 Study Participants

Between March 2012 to October 2013, patients with symptomatic severe aortic stenosis were prospectively and consecutively recruited from two large tertiary (Leeds & Leicester) TAVI centres. Severe aortic stenosis was defined by transthoracic echocardiography with a peak aortic velocity of >4ms^{-1} , mean gradient >40 mmHg and a valve area <1.0cm^{2}. All patients were assessed by the multi-disciplinary Heart team and considered suitable for SAVR or TAVI according to contemporary guidance. Complete matching was not possible because of current UK TAVI guidelines, however, Older, higher risk based on the logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) SAVR patients with ≥1 comorbidities were identified for recruitment. Exclusion criteria were: any contraindication to MRI, such as cardiac pacemaker and claustrophobia, end stage renal failure. The study was approved by the Institutional Ethics Committee and complied with the Declaration of Helsinki. All patients provided written informed consent.

6.3.2 TAVI procedure

TAVI was performed by highly experienced consultant interventional cardiologists (>5 years TAVI experience) with the Medtronic CoreValve or Edward Sapien prosthesis according to institutional preference, as previously described (Piazza et al., 2008). In brief, all procedures were performed under general anaesthesia with X-ray fluoroscopy and transoesophageal echocardiographic guidance in the cardiac catheter laboratory. At the time of study conscious sedation was not widely practiced

in the UK. All patients received weight-adjusted unfractionated heparin to maintain an activated clotting time >200secs and were treated with dual antiplatelet (aspirin and clopidogrel) for 6 months post procedure.

6.3.3 SAVR operation

All patients under went general anaesthesia and midline sternotomy with cardiopulmonary bypass and mild hypothermia. The surgical valve prosthesis varied according to annular size, patient characteristics and surgeon/patient preference. Coronary artery bypass grafting was concomitantly performed if indicated.

6.3.4 Scan protocol

Each participant was imaged on the same vendor platform with an identical protocol. The study was performed on 1.5 Tesla (Intera, Philips Healthcare, Best, Netherlands) with Master gradients (30mT/m, 150[$mT.m^{-1}$]/msec) and a five-element cardiac phased array receiver coil with vector cardiogram. Localiser images were obtained using cine steady state free precession for the vertical long axis (VLA), horizontal long axis (HLA) and short axis (SA) of the left ventricle (SSFP, TR 3.0ms, TE 1.5ms, Slice thickness 8mm, FOV 400, RFOV 80, 30 phases). The LV volumes were acquired in the short axis plane using multi-slice and multi-phase cine imaging. Typically 10 to 12 contiguous slices were acquired covering from the mitral valve plane to beyond the apex (Slice thickness 10mm, 0 gap, 30 phases, FOV 380, RFOV 100). The “3 of 5” technique was used to identify basal, mid- ventricular and apical slices as this has been shown to be reproducible (Messroghli et al., 2005). This is performed by planning 5 parallel short axis slices from the outmost aspect of mitral annulus and LV apex, with the ventricle in systole.

The centre 3 slices are used to acquire cine images and later plan MOLLI sequences.

T1 mapping was performed with the MOLLI pulse sequence which was described by Messroghli (Messroghli et al., 2004). For each individual slice (base, mid, apex), there were 3 successive Look-Locker acquisitions (trains). Each of these trains, starts with a specific inversion time (100ms, 200ms and 350ms) after which multiple single shot images are acquired over consecutive heart beats in end-diastole. The 3 trains produce 3, 3 and 5 images (3,3,5 MOLLI). MOLLI was performed pre-contrast, and 5 and 15 minutes after intravenous administration of 0.2mmol/kg of gadoteric acid contrast (Dotarem®, Guerbet, Villepinte). The contrast was followed by a 20mls saline flush.

6.3.5 Image analysis

Left ventricular volumes using the summation of discs method were calculated by manually contouring the endocardial and epicardial borders at end-diastole and again at end-systole in commercially available software (Qmass 6.0, Medis, Netherlands) (Mass = epicardial volume – endocardial volume multiplied by the myocardial density (1.05g/cm^3)). (Gaasch and Zile, 2011).

T1 maps were generated off-line from source MOLLI data images using published software MR Maps (Messroghli et al., 2010). In the software the images are manually checked and corrected for significant motion before map generation. The software sorts the images in order of effective inversion time (TI) and uses three-parameter non-linear curve fitting using a Levenberg-Marquardt algorithm. A T1 map is generated as a DICOM file

which is stored. This T1 map is analysed in Qmass 6.0 (Medis, Netherlands). A region of interest (ROI) is drawn in the myocardial septum and blood pool to measure T1. A conservative septal ROI has been shown to provide good reproducibility (Rogers et al., 2013). Image quality was assessed by two independent observers and were graded Likhart scale (1=unusable, 2=poor, 3=adequate, 4=excellent).

6.3.6 LGE Analysis

Focal areas of hyperenhancement were described according to their number and location and specific pattern (mid wall fibrosis or sub-endocardial infarct type) by three independent observers. Quantitative analysis was performed by semi-automated signal intensity analysis according to the full width half maximum method which has been previously published in severe aortic stenosis (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada) (Fairbairn et al., 2013b).

6.3.7 ECV calculation

The myocardial partition coefficient was calculated using the following equation:

$\lambda = \frac{\Delta R1\ myocardium}{\Delta R1\ blood\ pool}$ where $1 = \frac{1}{T1}$. The $ECV = (1\ - haematocrit) \times\ \lambda$

The haematocrit is measured from the full blood count sample.

6.3.8 Statistical analysis

Data were tested for normality with the Shapiro-Wilks test. Continuous variables were expressed as means±SD or medians (Q1-Q3) and discrete variables as n (%). Continuous variables were compared with ANOVA for repeated measures with Bonferroni correction or independent T tests. The

between subjects' factor was treatment group (TAVI vs. SAVR). Age and sex were entered as co-variates when necessary. Fishers exact or Chi squared was used for comparison of discrete variables. Wilcoxon signed rank test and Mann-Whitney test was used for non-parametric testing.

Univariate linear regression analysis was conducted using clinical and CMR fibrosis variables and compared with the change in LV mass. Variables with $p \leq 0.10$ were entered into a stepwise multivariable regression analysis. Univariate logistic regression analysis was performed for overall LV remodelling (yes=1 or no=0) (LV remodelling=reduction in EDV and ESV by 10mls and reduction in mass by 10g).

Previous CMR studies have shown that to detect a 10ml change in LV volumes then a sample size of n=10-12 would be sufficient and 3% change in EF, n=15 (Bellenger et al., 2000b). To detect a 0.038 change in ECV (Equivalent to 3% histological fibrosis) the sample of n=27 in each group would be necessary for power of 80% and alpha error on 0.05 (Liu et al., 2012).

6.4 RESULTS

6.4.1 Patient characteristics

Seventy patients with severe aortic stenosis were recruited (Figure 6-1). Expectedly, the TAVI group were older with higher surgical risk scores and a higher prevalence of prior CABG, PCI and COPD (Table 6-1). Both groups have similar prevalence of hypertension, diabetes, AF, prior stroke and hypercholesterolaemia. The echocardiographic parameters are shown in table 6-1. The peak velocities were similar but calculated valve areas were significantly smaller in TAVI group and there were also higher proportion of LV impairment (table 6-1). There was a higher dropout in the TAVI group compared to SAVR as they were elderly and had greater co-morbidities.

Figure 6-1 Study Flow Chart

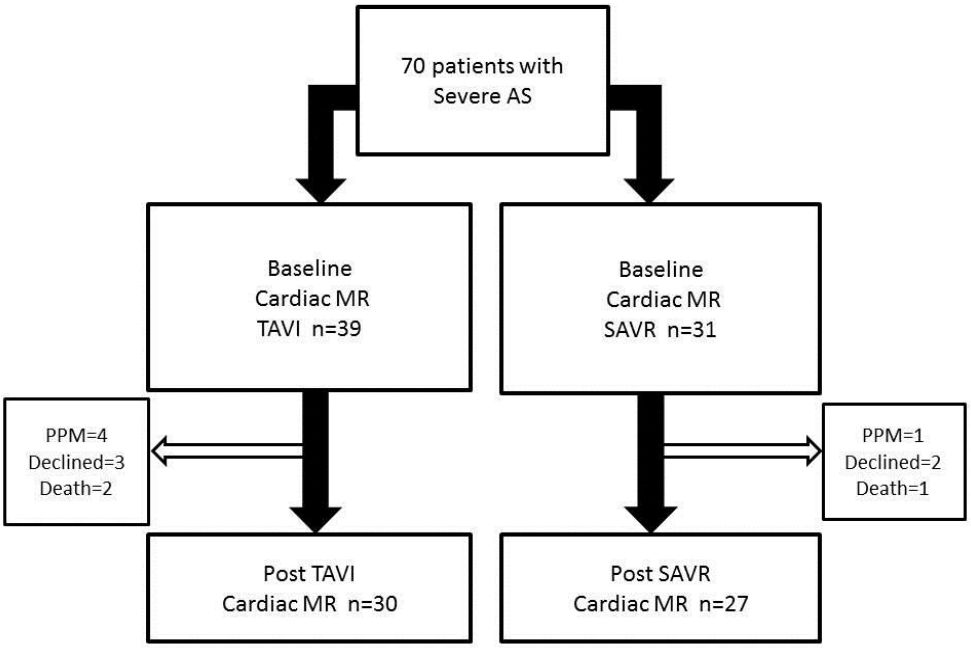


Table 6-1 Patient characteristics

Clinical characteristics	TAVI (n=39)	SAVR (n=31)	p value
Age, years	80.1±6.9	73.1±7.2	<0.0001
Male, n (%)	20 (51)	23 (74)	0.04
BSA, m^2	1.82±0.2	1.97±0.2	0.008
BMI, kgm^{-2}	27.9±4.6	28.4±4.7	0.66
NYHA Class, n (%)			0.0001*
I	0	2 (7)	
II	3 (8)	12 (39)	
III	30 (77)	17 (55)	
IV	6 (15)	0	
EuroSCORE, (%)	20.6±7.1	7.1±8.2	<0.0001
EuroSCORE II, (%)	5.4±3.9	1.5±0.9	<0.0001
STS Score, (%)	5.3±3.4	2.2±0.7	<0.0001
STS Morbidity, (%)	24.0±7.2	15.9±3.7	<0.0001
Hypertension, n (%)	21 (53.8)	21 (67)	0.18
Diabetes, n (%)	8 (21)	6 (19)	0.57
Hypercholesterolaemia, n (%)	22 (56)	24 (77)	0.08
Atrial fibrillation, n (%)	11 (28)	3 (10)	0.07
Stroke/TIA, n (%)	6 (15)	5 (16)	0.99
MI, n (%)	5 (13)	5 (16)	0.75
CABG, n (%)	10 (26)	0	0.002
PCI, n (%)	10 (26)	2 (7)	0.03
PVD, n (%)	8 (21)	2 (7)	0.17
COPD, n (%)	12 (31)	2 (7)	0.02
Pulmonary Hypertension n (%)	8 (23)	4 (13)	0.35
eGFR, $ml/min/1.73m^2$	67±17	75±12	0.03
<u>Echocardiographic data:</u>			
Peak AV velocity, ms^{-1}	4.5±0.6	4.5±1.4	0.88
Mean AV gradient, mmHg	49±14	45±13	0.18
Aortic valve area, cm^2	0.6±0.2	0.8±0.5	0.04
LVEF, n (%)			0.03*
Normal	18 (46)	24 (78)	
Mild	16 (41)	6 (19)	
Moderate	3 (8)	0 (0)	
Severe	2 (5)	1(3)	

Data are Mean±SD or n (%). BMI=body mass index, NYHA=New York Heart Association, STS=Society of Thoracic Surgery, TIA=transient ischaemic attack, MI=myocardial infarction, CABG=coronary artery bypass grafting, PVD=peripheral vascular disease, COPD=chronic obstructive pulmonary disease, eGFR=estimated glomerular filtration rate, AV=aortic valve. LVEF=left ventricular ejection fraction. *Mann Whitney test.

6.4.2 Procedural characteristics

TAVI was successful in all cases with predominant femoral access. Most SAVR patients received biological valves and 14(35%) had concomitant CABG which prolonged bypass time (Table 6-2).

Table 6-2 Procedural details

		n (%)
TAVI (n=39)		
Medtronic CoreValve, n=29	31mm	4 (10)
	29mm	19 (49)
	26mm	3 (8)
	23mm	3 (8)
Boston LOTUS, n=10	27mm	8 (21)
	23mm	2 (5)
Access route	Femoral	38 (97)
	Carotid	1 (3)
Procedure time, (min)		160±76
Fluoroscopy time, (min)		26±13
Contrast volume, (ml)		138±69
SAVR (n=31)		
Biological, n (%)		26 (84)
Mechanical, n (%)		5 (16)
Size, (mm) (median, Q1-Q3)		23 (21–25)
Bypass time, (min)	All	133±72
	AVR only	113±65
	AVR and CABG	158±74
Cross clamp time, (min)	All	99±61
	AVR only	89±61
	AVR and CABG	111±61
CABG, n (%)		14 (35)

Data are Mean±SD or n (%). CABG=coronary artery bypass grafting

6.4.3 Cardiovascular MRI findings

Volumes, mass and flow analysis

Cardiovascular MR volumetric analysis is shown in Table 6-3. There were significant improvements in indexed end-diastolic volumes and reduction in mass for both TAVI and SAVR patients. This was reflected in a statistically significant reduction in mass to volume ratio (LVM/LVEDV) Table 6-3. Only TAVI patients showed statistically significant reduction in end-systolic volumes and stroke volumes (Table 6-3). There was no significant change in ejection fraction for TAVI and SAVR patients. Both treatments resulted in significant reductions in mean aortic pressure gradients and there was no significant post procedural aortic regurgitation (Table 6-3).

Table 6-3 Cardiovascular magnetic resonance volumetric, flow and late gadolinium enhancement findings at baseline and after 6 months.

	TAVI		SAVR		
	Baseline n=39	6m n=30	Baseline n=31	6m n=27	p value†
Left ventricle					
LVEDVI (ml/m^2)	100±25	87±26***	91±28	82±17*	0.002
LVESVI (ml/m^2)	48±26	40±19*	39±22	34±14	0.006
LVSV (ml/m^2)	52±9	47±13*	52±12	48±8	0.005
LVEF (%)	54±13	53±15	60±12	60±10	0.54
LVM (g)	75±16	55±17***	75±24	59±15***	0.001
LVM/LVEDV (g/ml)	0.76±0.3	0.62±0.18**	0.85±0.2	0.73±0.2***	0.04
Aortic valve					
Mean PG (mmHg)	35±16	17±12***	44±21	21±10***	0.0001
AR fraction	16±10	6±6***	15±13	8±8*	0.001
Late gadolinium enhancement					
Mass (g)	4.8±4.7	5.5±5.7	7.2±6.5	6.3±8.3	0.60
Percentage myocardium	3.2±3.1	7.7±7.8**	4.4±3.9	5.3±5.9	0.001
T1 mapping					
Pre-contrast myocardial T1 (ms)					
Base	761±92	760±70	760±83	740±77	0.22
Mid	752±82	767±86	759±90	755±70	0.49
Apex	732±77	764±78	754±84	730±73	0.31
Post-contrast T1 (ms)					
Base	450±80	426±62	447±78	426±55	0.38
Mid	447±86	418±78	451±77	438±78	0.42
Apex	453±50	414±67	431±60	410±56	0.35
Extracellular Volume (%)					
Base	23.5±9	27.3±10	24.6±7	23.7±8	0.38
Mid	24.0±9	29.3±11	23.8±7	23.5±9	0.76
Apex	22.8±8	26.1±10	21.9±7	22.8±8	0.08

Values are means±SD. †Repeated measures ANOVA with treatment group as between subjects' factor. Paired t test vs baseline: *p<0.05, **<0.01, ***p<0.001. For T1 mapping analysis, age was entered as a co-variate in ANOVA. AR=aortic regurgitation, EDVI=end diastolic volume indexed to body surface area, ESVI= end-systolic volume indexed, SV=stroke volume, LV= Left ventricular, EF=ejection fraction, M=mass, PG= peak gradient, SAVR= surgical aortic valve replacement, TAVI=transcatheter aortic valve implantation.

Late gadolinium findings

Sixteen (41%) TAVI and 14 (45%) SAVR patients had evidence of LGE at baseline (p=0.81). There was no statistically significant difference in fibrosis mass at baseline between the two groups (TAVI vs. SAVR, 4.8±4.7g vs. 7.2±6.5g, p=0.20).

At baseline, the basal and mid ventricle had higher proportions of enhancement, but there were no statistically significant differences between TAVI and SAVR (TAVI vs. SAVR; Base, 16/16 (100%) vs. 13/14(93%) (p=0.47), mid 15/16(94%) vs. 10/14(71%) (p=0.16) and apex 8/16(50%) vs. 3/14(21%) (p=0.14). There was also higher proportion of septal wall enhancement at each ventricular level but no difference between TAVI vs. SAVR, (basal septum 10/16 (62%) vs 7/13(54%) (p=0.71), mid septum 9/15 (60%) vs 6/10(60%) (p=0.13) apical septum 3/8(38%0 vs 2/3 (66%). (p=0.9))

There was no change in mean mass of fibrosis 6 months after TAVI and SAVR (Table 6-3). However, the percentage myocardium with scar after TAVI was significantly higher (Table 6-3).

T1 mapping and extracellular volume analysis

There was no difference between baseline pre-contrast T1 measurements between TAVI and SAVR (base, mid and apex all p>0.05) (Table 6-3). Similarly, there were no statistical differences in post contrast measurements (Table 6-3). After 6 months, the T1 measurements did not change for either group (Table 6-3).

The extracellular volumes were similar at baseline for both TAVI and SAVR (range 22.8 to 24.6%) across the base, mid and apex. After 6 months, there

were no statistically significant reductions in ECV for either TAVI or SAVR (Table 6-3) over the 3 slices.

6.4.4 Predictors of LV mass regression and LV reverse remodelling

Clinical variables and baseline cardiovascular MR measures of diffuse and focal fibrosis were analysed using univariate and multivariate regression to detect change in LV mass indexed by BSA (Table 6-4). The significant univariate predictors were gender, PVD and mass of fibrosis on late gadolinium but not diffuse fibrosis as measured by extracellular volume. However, in multivariate analysis these variables did not reach significance (Gender: $\beta=0.05$, $p=0.78$, PVD $\beta=0.24$, $p=0.16$, LGE fibrosis, $\beta=0.24$, $p=0.18$).

Table 6-4 Univariate regression analysis of clinical and CMR variables for prediction of LV mass regression

variables	R	P value
TAVI	0.01	0.98
Age	0.07	0.59
Male	0.28	0.04
BSA	0.19	0.16
NYHA class	0.18	0.18
EuroSCORE	0.02	0.89
EuroSCORE II	0.12	0.38
STS score	0.01	0.98
Hypertension	0.04	0.76
Diabetes	0.08	0.56
Hyperlipidaemia	0.16	0.23
Atrial Fibrillation	0.16	0.23
TIA/Stroke	0.01	0.96
Previous MI	0.21	0.13
CABG	0.09	0.52
Previous PCI	0.06	0.64
PVD	0.26	0.05
COPD	0.05	0.71
PHT	0.17	0.21
GFR	0.11	0.40
LGE fibrosis	0.27	0.10
ECV (mid)	0.09	0.56
T1 (mid)	0.03	0.80
	-	-

TAVI=Transcatheter Aortic Valve Implantation, SAVR=Surgical Aortic Valve Replacement, BSA=body surface area, BMI=body mass index, NYHA=New York Heart Association, STS=Society of Thoracic Surgery, TIA=transient ischaemic attack, MI=myocardial infarction, CABG=coronary artery bypass grafting, PVD=peripheral vascular disease, COPD=chronic obstructive pulmonary disease, BAV=balloon aortic valvuloplasty, eGFR=estimated glomerular filtration rate.

LV reverse remodelling was defined by a reduction in LVEDV and LVESV by 10mls and reduction in LV mass by 10g. Predictors of reverse remodelling were analysed using a logistic regression analysis (Remodelling; yes=1, no=0) (Table 6-5). AF, PVD and baseline CMR volumes and mass were predictors of cardiac reverse remodelling but not late gadolinium enhancement fibrosis or extracellular volume. In multivariate logistic regression only AF and baseline LV mass remained significant factors (Adjusted odds ratio (OR) and confidence intervals (CI), AF: OR, 2.06, CI 1.2 to.3.7, p=0.04; LV mass OR 1.08, CI 1.008 to 1.147, p=0.03).

Table 6-5 Univariate logistic regression analysis of clinical and CMR variables for predictors of left ventricular reverse remodelling

Abbreviations as in table 4.

Risk factors	Unadjusted odds ratios	95% CI	p values
TAVI	1.66	0.58 to 4.75	0.34
Age	1.00	0.95 to 1.05	0.87
Male	2.08	0.70 to 6.2	0.19
BSA	1.60	0.17 to 16.1	0.41
NYHA	1.04	0.46 to 2.36	0.93
EuroSCORE	1.0	0.96 to 1.06	0.73
EuroSCORE II	0.96	0.82 to 1.12	0.57
STS Score	1.02	0.82 to 1.25	0.88
Hypertension	0.67	0.23 to 1.94	0.46
Diabetes	2.00	0.45 to 8.91	0.36
Hypercholesterolaemia	0.63	0.21 to 1.9	0.41
AF	3.1	1.54 to 11	0.02
Stroke/TIA	0.54	0.13 to 2.12	0.38
MI	1.67	0.36 to 7.77	0.55
CABG	2.5	0.44 to 14.1	0.30
PCI	1.44	0.36 to 5.77	0.61
PVD	0.10	0.01 to 0.86	0.04
COPD	1.1	0.29 to 4.12	0.89
PHT	2.40	0.53 to 10.83	0.26
Creatinine	0.99	0.98 to 1.01	0.93
LV EDVi	1.05	1.02 to 1.08	0.001
LV ESVi	1.03	1.01 to 1.06	0.02
LVSV	1.13	1.05 to 1.21	0.002
EF	0.97	0.92 to 1.01	0.14
LV mass	1.08	1.04 to 1.13	0.001
LGE mass	1.10	0.94 to 1.27	0.22
ECV	0.13	0 to 13.9	0.57
T1	1.01	0.99 to 1.00	0.72

DISCUSSION

This study showed that reverse remodelling occurs within 6 months of intervention with both TAVI and SAVR. We showed that both groups had a reduction in end diastolic volumes and LV mass regression, but the TAVI group also had a reduction in end systolic volumes. The latter difference may be related to the differences between the TAVI device and the surgical prosthesis, suggesting TAVI may achieve a greater effective orifice area and hence a lower final end systolic volume. With late gadolinium imaging we showed the presence of scar was similar in both TAVI and SAVR. This study used T1 mapping in patients with severe aortic stenosis who either received TAVI or SAVR dependent on their surgical risk. We showed similar levels of extracellular volumes in both patient groups but there was no significant change after six months. However, a change may not have been detected because of the wide standard deviations. Also, there has been reported overlaps between the ranges of normal T1 values and pathological states. Therefore, larger sized samples may be necessary to detect significant differences. In addition, key factors for predicting mass regression were gender, peripheral vascular disease and fibrosis mass on late gadolinium imaging. When defining revere cardiac remodelling as a reduction in EDV, ESV and mass, we found that the presence of AF and the baseline LV mass were important factors.

The groups are significantly different with regard to their baseline characteristics as we have seen in the earlier chapters. The TAVI group had a smaller aortic valve area which may imply that they had a more severe form of aortic stenosis and thus the results could be confounded.

Focal fibrosis as detected by LGE may not be fixed and can undergo remodelling with time and the patterns can be mid wall or sub endocardial as in myocardial infraction. Previous studies have shown that there was a quantitative reduction after TAVI but not SAVR in myocardial fibrosis (Fairbairn et al., 2013b).

Flett et al showed that diffuse myocardial fibrosis was associated with severe aortic stenosis using the equilibrium contrast CMR method, and fibrosis correlated with functional status. However, the fibrosis volume did not alter after surgical valve replacement but LV hypertrophy receded(Flett et al., 2012). This suggested that cell volume reduction was the key component and interstitial fibrosis is fixed and not dynamic. Similar findings occurred in our study with TAVI patients having a higher fibrosis burden relative to the overall LV mass (% myocardium). This can again be a reflection on the frailer TAVI patient.

Weidemann et al showed that late gadolinium enhanced fibrosis was associated with higher NYHA class in patients undergoing SAVR. Nevertheless, they did not detect a change in this form of fibrosis (scar or replacement fibrosis) when CMR was repeated 9 months later (Weidemann et al., 2009).

The benefits of using CMR with T1 mapping and late gadolinium imaging are: 1) accurate changes in left ventricular volumes and aortic flow measurements can be detected 2) diffuse myocardial fibrosis changes can be identified compared after treatment and 3) fixed irreversible scarring can be highlighted and silent myocardial infarction can be documented.

6.4.5 Limitations

There are several limitations in our study due to technical or practical restrictions. This study was not matched for age, sex or surgical risk due to restrictions and recommendations according to current international guidelines; however future studies may be able to overcome this when TAVI is being considered in a traditionally lower surgical risk setting. Therefore the findings are confounded by the differences in the groups.

Histological myocardial samples were not obtained in this study, however, this has been extensively studied and correlated with CMR fibrosis imaging (Azevedo et al., 2010, Flett et al., 2012). In addition myocardial biopsy during TAVI may pose an additional risk to patients who are already vulnerable to myocardial insults.

Unfortunately some patients would have been excluded from follow up CMR due to pacemaker implantation which is an inherent complication for both TAVI and SAVR, but the study was powered to detect sufficient change in ECV and thus was not influenced by exclusions.

There are a variety of T1 mapping techniques available such as MOLLI and ScMOLLI, but we only had MOLLI available on the study scanner and therefore could not use any other sequence. Perhaps a shortened acquisition would reduce artefact and reduce the amount of motion correction necessary. This would improve the accuracy of the obtained T1 values and subsequent ECV estimations.

6.5 CONCLUSIONS

This study showed that cardiac reverse remodelling after TAVI is similar to contemporary surgical aortic valve replacement, with the additional reduction in end systolic volumes. Although the quantity of diffuse fibrosis as estimated with T1 mapping techniques is similar between TAVI and SAVR patients at baseline, we could not demonstrate a reduction in this after 6 months.

7 Overall Conclusions and Future directions

The advancement of medical therapy has facilitated the prolongation of life and improved the quality of life over the last 100 years. A direct consequence of early achievements has led to the increased prevalence of degenerative conditions affecting various organs and systems. The cardiovascular system is an essential part of the body which influences other organs. With the aging population the diagnosis of calcific aortic stenosis would be such a condition. We know that as life expectancy increases the population will exhibit a significant proportion of patients with this condition. Currently it is estimated that in the over 65 years age range the prevalence of calcific aortic stenosis is between 2 to 7 % (Nkomo et al., 2006, Stewart et al., 1997). Nevertheless a recent Swedish registry highlighted that the prevalence of aortic stenosis may be declining and that there was a gender difference (Martinsson et al., 2015). There was a decline in the age-adjusted incidence from 15.0 to 11.4 per 100000 in men over 10 years and 9.8 to 7.1 for women respectively. These changes may be additional evidence towards general improvement in healthcare and the wider use of risk factor modifications.

Severe aortic stenosis is a progressive degenerative condition which occurs as a result of valve leaflet restriction. There is a reduction in aortic valve area which initiates changes in left ventricular performance and the myocytes undergo remodelling in a pressure overloaded state. The myocardium at the cellular level causes cellular hypertrophy and the mass of the ventricular increases. The patient develops symptoms of exertional dyspnoea, angina

pectoris, syncope and heart failure; the latter being characterised by oedema.

The option of medical therapy is palliative as severe aortic stenosis is a mechanically obstructed condition and drug therapy has limited roles. The patient may be treated with diuretics for symptomatic improvement but other therapies such as beta blockers, statins and ACE inhibition have limited benefit.

The current recommendation for from the American and European cardiovascular societies are that surgical aortic valve replacement should be offered to patients that have symptomatic aortic stenosis (Nishimura, 2014 #923). The difficulty arises when the Heart MDT deems the patient unsuitable for surgical intervention due to high operative risk. The EuroSCORE and STS scores are used to help surgeons risk stratify such patients although the presence of significant medical and surgical co-morbidity may potentiate risk. There is growing evidence that surgery in the elderly can be performed safely and with minimal complication (Jansen Klomp et al., 2016, Kolh et al., 2007). Studies of octogenarians and nonagenarians have reported supporting data, such as similar operative mortality of 2.9% in octogenarians and 1.9% in the younger cohort. The incidence of post-operative delirium in the elderly was high at 11% (Jansen Klomp et al., 2016). However, often the success is limited around specific surgical centres.

Percutaneous aortic valve implantation has been a major advance in cardiology for the 21st century. The procedure is now widely accepted as Transcatheter aortic valve implantation (TAVI). This procedure evolved from palliative balloon aortic valvuloplasty (BAV) which only used a balloon inflation to increase the aortic valve area, however was complicated by severe aortic incompetence or aortic rupture leading to tamponade and death (Dauterman et al., 2003). The other important limitation of BAV was the high six month restenosis rate that was observed.

The initial percutaneous aortic valve prosthesis were either mounted on a balloon known as balloon expandable prosthesis (Edwards Lifesciences). The other prosthesis was on a self-expanding nitinol frame that was released in position after initial BAV (Medtronic CoreValve). The PARTNER trials or Placement of Aortic Transcatheter Valves studies were major randomised control studies that showed significant benefits in the TAVI arm. Firstly those who received TAVI reported reduced symptoms of heart failure and mortality was superior to medical therapy alone. In comparison the high risk SAVR, TAVI exhibited similar 30-day mortality but higher stroke rates. Overall the PARTNER studies supported the use of TAVI devices in this high risk frail group of patients that would die without intervention. The major risks in TAVI were associated with bleeding and post-procedure stroke and post implantation regurgitation. The complication of bleeding has reduced with evolution in vascular access and closure methods. The size of the sheaths has decreased from 24F down to 18F and improvement in suture based closure devices have reduced vascular complications.

The studies in this thesis focussed on the cerebral embolisation that occurs during TAVI and SAVR and the consequence of the cerebral micro-infarctions on the patients with emphasis on the effect on their quality of life and changes in the neurocognitive performance. The implantation or replacement of the aortic valve changes the cardiac function and cardiovascular MRI was used to observe the changes between the diseased state and 6 months after intervention. Particular focus was placed on the process of diffuse fibrosis and the influence it may have on reverse LV remodelling as the ventricle adapts from a pressure overloaded state to a pressure free state.

In Chapter 3 the study found that TAVI resulted in significantly higher number of cerebral micro-infarcts in comparison to the SAVR patients. This used a highly sensitive technique of cerebral MRI and diffusion weighted imaging (DWI). Clearly, the implantation of the TAVI prosthesis generates showers of micro-embolisation which can seed to any organ, but in the brain cause micro-infarction. The DWI lesion did not appear in the follow up scans as they would have resolved by then. The predictors of cerebral micro-infarcts for TAVI was aortic atheroma and for SAVR the co-existing significant coronary artery disease. This suggests that the embolic material is atheromatous in origin in both groups.

Health related quality of life improved earlier at 30 days in TAVI group supported by improvement in the physical scores. There was a lag in improvements in the HRQoL scores in the SAVR group which may be related to the longer recovery period which is associated with this group.

There was no negative effect of cerebral micro-infarction on the HRQoL, even the TAVI mental component scores improved. Interestingly, SAVR patients with micro-infarcts had a lower physical component score at 30 days suggesting a greater influence on physical function. This may be due to additional effects of cardio-pulmonary bypass on neuronal function and perhaps an impaired response to injury. Therefore, although not causing a definite clinical stroke, the embolic event causes an effect on general physical well-being.

Following the finding of this chapter, we wanted to shift the focus of the potential effects of cerebral micro-infarction from overall multi-factorial general health to more specific cerebral functions. In Chapter 4 the focus moved to the effect on neurocognitive function following the treatment of aortic stenosis with either percutaneous valve implantation(TAVI) or open surgical valve replacement (SAVR). Here we used specific tools designed to detect and grade cognitive function over a wide range of areas. The TAVI group had a lower level of neurocognitive function at baseline compared to the SAVR group which is likely to be related to the differences in baseline characteristics and risk factor profile. The neurocognitive functional testing was broad and comprehensive covering areas of global, mnemonic and executive functions as well as psychomotor and dexterity. There was an improvement in neurocognitive function in both TAVI and SAVR groups supporting the beneficial effects of treatment. Although the cerebral micro-infarction was again higher in the TAVI group, the findings suggest that the was no detrimental effect of embolism on neurocognitive function. In addition, patients did not fall into the impaired neurocognitive function group over the 4 assessment points. The predictors of neurocognitive impairment

at baseline were atrial fibrillation, prior CABG and renal function suggesting that chronic disease processes may influence cognitive decline rather than a one off cerebral insult. The findings based on the serial neurocognitive functional testing suggests that TAVI and related cerebral embolisation does not have a negative effect on overall higher cerebral function.

In the thesis there is evidence that the treatment of aortic stenosis with TAVI or SAVR improves heath related quality of life and neurocognitive function. However, the were significant differences in the baseline characteristics of the TAVI group and SAVR group. Overall, the TAVI group as expected given their high surgical risk had greater co-morbidities, were older and more frail. Thus comparisons were confounded by these differences which were unavoidable as the studies were not randomised control trails.
The common but important intervention to both TAVI and SAVR groups was the removal of the obstruction caused by the diseased aortic valve. Therefore it was important to understand the changes in cardiac reverse remodelling that occured after both interventions. In the introduction the superiority of Cardiovascular magnetic resonance (CMR) to echocardiography was highlighted and how it is useful and accurate at assessing ventricular function. CMR allows comprehensive assessment by volumetric analysis, aortic flow measurements and tissue characterisation. Most processes in cardiomyopathy involve fibrosis which can be focal or diffuse. In chapter 5 and 6 the focus was placed on measuring myocardial extra cellular volume (ECV) as a measure of diffuse fibrosis.

In Chapter 5, T1 mapping was conducted in healthy volunteers using the Modified Look-Locker Inversion(MOLLI) method. The study showed that the T1 value was similar across the 3 slices of the left ventricle. In addition the ECV was similar across the 3 slices. The MOLLI method was reproducible with good intra- and inter observer and inter study reproducibility. There were limitations in this study as MOLLI was the only T1 mapping sequence available to the study scanners. However, this MOLLI method had been used before and studied in aortic regurgitation and myocardial infarction within the department. This gave confidence in using this method in the patients with severe aortic stenosis.

In chapter 6 CMR was conducted before and 6 months after TAVI and SAVR. The key findings were that LV mass regression occurred in both groups supporting reverse myocardial remodelling. In addition the End-diastolic volumes decreased. There was no difference in T1 at baseline or after TAVI/SAVR and the ECV did not significantly change. This suggests that reverse remodelling was occurring due to changes in myocyte hypertrophy and rather that the diffuse fibrosis process was fixed or takes longer than 6 months to change. This chapter also highlighted the limitations with current T1 mapping techniques.

The predictors of reverse remodelling were the presence of atrial fibrillation and LV mass. Therefore, patients with aortic stenosis undergo adaptive processes in response to high LV pressures such as higher end-diastolic volumes and higher left atrial pressures. The presences of high LA pressures can lead to atrial dilatation and subsequent AF. The reverse remodelling process relies on intra-cellular adaptation and perhaps the extra-cellular fibrosis causing scarring is irreversible or fixed.

The thesis has contributed towards the treatment of severe aortic stenosis, especially in the recently adopted transcatheter aortic valve implantation population. TAVI improves health related quality of life and does not precipitate neurocognitive dysfunction and the detected cerebral micro-infarction does not bear adverse outcomes. The left ventricle adapts by reverse remodelling and is not limited by diffuse fibrosis. The above findings support the continued expansion of TAVI programme. Currently TAVI is indicated for patients not suitable for SAVR but studies are under way looking at moderate to high surgical risk groups. Also, randomised control trials are recruiting comparing TAVI and SAVR. In the future, TAVI may be equal to SAVR and become available to a wider population. There are already advances in TAVI device technology to reduce vascular access sizes and valve designs to eliminate para valvular regurgitation. The peri-procedural risks are also being reduced by performing implantation under local (regional) anaesthesia with light sedation.

Further research is need in the treatment of aortic stenosis with TAVI. Relative to other cardiovascular interventions TAVI is still new and long term follow up studies about TAVI prosthesis function would be useful.

Cerebral embolisation does occur and strategies to prevent this can be explored. There are devices available that provide embolic protection in the aortic arch at the origins of the carotids. Cerebral MRI studies could be conducted to confirm a reduction in embolic load. In addition, a higher field strength (3T) may further detect DWI lesions not seen at 1.5T. An area not explored in cerebral MRI could involve function MR (fMR) of patients undergoing TAVI and SAVR. The domains assessed in this thesis could be

repeated which may provide fMR data of the consequences of micro-infarction.

CMR continues to evolve with newer scanners and faster processing times. The key properties of CMR are in volumetric analysis and flow measurements through phase contrast imaging. Future work should study new valve designs such as the Boston Lotus and CoreValve Evolut R which have additional material known as ‘skirts’ to reduce para valvular regurgitation. The assessment of regurgitation after TAVI remains challenging and CMR may be able to quantify regurgitant volumes soon after implantation. Further study is required in diffuse fibrosis and other T1 mapping techniques can be explored such as ScMOLLI.

Other techniques that may provide insight in valvular disease may involve “4D flow”. This is 3-dimensional phase contrast imaging that allows acquisition of 3D morphology and time-resolved blood flow velocities in the x-, y- and z axes. These special sequences allow the acquisition of anatomical and directional velocities for each voxel in a 3D volume across the cardiac cycle.

In conclusion, the thesis has explored the aims set out in the earlier chapters. Aortic stenosis is an important degenerative cardiovascular disease that can be treated successfully with surgery or in those with high surgical risk with percutaneous means. Health related quality of life improves for the better and neurocognitive function benefits from intervention. Overall, cerebral micro-infarction does not have any early negative impact on health-related quality of life or neurocognitive function. Following TAVI and SAVR

the left ventricle undergoes reverse remodelling with no detectable change in diffuse fibrosis as estimated by measuring extracellular volumes.

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9 List of Abbreviations

ACE	Angiotensin Converting Enzyme
AF	Atrial Fibrillation
AR	Aortic Regurgitation
AS	Aortic stenosis
ANOVA	Analysis of Variance
AV	Aortic Valve
BAV	Balloon Aortic Valvuloplasty
BMI	Body Mass Index
BP	Bodily Pain
BSA	Body Surface Area
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CFA	Common Femoral Artery
CI	Confidence Intervals
CMR	Cardiovascular Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coefficient of Variation
CT	Computerised Tomography
DI	Discrimination Index
DR	Delayed Recall
DSST	Digit-symbol substitution test
DWI	Diffusion Weighted Imaging
ECG	Electrocardiogram
ECV	Extracellular Volume
EF	Ejection Fraction
EDV	End-diastolic Volume

ESV	End-systolic Volume
EOA	Effective Orifice Area
FFE	Fast Field Echo
FID	Free Induction Decay
FOV	Field of View
GE	Gradient Echo
Gf	Gradient frequency echo
GH	General Health
GPT	Grooved Pegboard test
HADS	Hospital Anxiety Depression Scale
HLA	Horizontal Long axis
HRQoL	Health Related Quality of life
HVLT	Hopkins Verbal Learning Test
ICC	Interclass Correlation Coefficient
IHD	Ischaemic Heart Disease
IQ	Intelligent Quotient
IQR	Interquartile Range
IR	Inversion Recovery
LA	Left Atrium
LGE	Late Gadolinium Enhancement
LNS	Letter Number Sequencing
LV	Left Ventricle
LVM	Left Ventricular Mass
LVOT	Left Ventricular Outflow tract
MCS	Mental Component Score
MDT	Multi-Disciplinary Team
MI	Myocardial Infarction
MH	Mental Health
MMSE	Mini-Mental State Examination

MOLLI	Modified Look-Locker Inversion recovery
MRI	Magnetic Resonance Imaging
NART	National Abbreviated Reading test
NCF	Neurocognitive Function
NYHA	New York Heart Association
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Score
PF	Physical Functioning
POCD	Post-operative Cognitive Dysfunction
PPM	Permanent Pacemaker
PVD	Peripheral Vascular Disease
RE	Role Emotional
ROCF	Rey-Osterrieth Complex Figure test
ROI	Region of Interest
RP	Role Physical
RV	Right ventricle
SA	Short Axis
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
SE	Spin Echo or Standard Error
SF	Social functioning or Semantic Fluency
SSFP	Steady State Free Precession
STS	Society of Thoracic Surgeons
SV	Stroke volume
TAVI	Transcatheter Aortic Valve Implantation
TD	Delay time
TE	Echo time
TFE	Turbo Fast Echo

TI	Inversion time
TIA	Transient Ischaemic Attack
TOE	Transoesophageal Echocardiography
TTE	Transthoracic Echocardiography
TMT	Trail Making Test
TR	Repetition time
VAS	Visual Analogue Scale
VENC	Velocity Encoding
VF	Verbal Fluency
VLA	Vertical Long Axis
VT	Vitality

10 Appendix A
Ethics Letter

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

Telephone: 0113 2065637
Facsimile: 0113 2066772

09 October 2008

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

Dear Dr Greenwood

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

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

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

Confirmation of ethical opinion

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

Ethical review of research sites

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

Conditions of the favourable opinion

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

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

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

Approved documents

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

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

Statement of compliance

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

After ethical review

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

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

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

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

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

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

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

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

Yours sincerely

Mr Jon Silcock
Chair

Email: Elaine.hazell@leedsth.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Site approval form

Copy to: *Ms Clare Skinner*

R&D, LTHT

Leeds (West) Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	08/H1307/106	**Issue number:**	0	**Date of issue:**	09 October 2008
Chief Investigator:	Dr John P Greenwood				
Full title of study:	MRI evaluation of Percutaneous and Surgical Aortic Valve Replacement				

This study was given a favourable ethical opinion by Leeds (West) Research Ethics Committee on 07 October 2008. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes (1)*
Dr John Greenwood	Senior Lecturer & Consultant Cardiologist	The Leeds Teaching Hospitals NHS Trust	Leeds (West) Research Ethics Committee	09/10/2008	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Co-ordinator)
(delete as applicable)

..... (Name)

10.1 Appendix B Patient information Leaflet

MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation

Version 1.3 November 30 2012

Chief Investigator: Prof John Greenwood

Dear patient,

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

WHY HAVE I BEEN CHOSEN?

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

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

WHAT IS THE PURPOSE OF THE STUDY?

Patients have their aortic valve replaced because their own valve does not work properly, which causes problems with the function of the heart and with the circulation. After the valve has been replaced the heart function and the circulation will normally improve. In this study we want to compare that improvement in the two groups of patients.

We also like to study the blood vessels in the head. As your doctor will have told you one of the risks of valve replacement is small clots travelling from the heart to the head. It is important for us to find out how often this happens with surgery and with non-surgical replacement, and compare the results.

We want to use Magnetic Resonance Imaging (MRI) in this study to look at the head and the heart. MRI does not involve radiation and is therefore very safe. It gives us very good images of the blood vessels and can tell how well the heart is pumping.

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. You do not have to decide straightaway; and you may discuss the study further with a member of the research team over the telephone, or once you come into hospital. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. Information collected up to the point of your withdrawal may still be used. In the unlikely event of you losing capacity (being unable to make decisions for yourself) you will be withdrawn from the study by us, but information already collected will be kept and used for the purposes of the study.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

All patients in this study will have MRI scans of their head and heart before and after the valve replacement procedure. Before the valve replacement we will scan your head and heart during one visit to the MRI department, this visit can take place before your admission, or whilst you are already an in-patient in the hospital. This scan will take approximately 60 minutes to complete. After the valve replacement, and before you go home, if you have had a surgical valve replacement (AVR) we will scan your head only, which takes about 10 minutes. If you have had a transcatheter replacement (TAVI), we would like to scan your head (10 minutes) and do a shortened version of the heart scan (15 minutes). Approximately 4-6 months later we will ask you to return to the MRI department so we can scan you heart and your head, which takes about 60 minutes. The reason why we want to do this scan later is that your heart’s function may continue to improve for some time after the valve replacement.

During each scan you lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud “banging” noises while we are acquiring the images. We will remain in communication with you throughout the scan. If you have normal kidney function then once during each heart scan, we will inject an MRI contrast medication into a vein in your arm. The needle used for this will feel like a sharp scratch. Usually people are not aware of the contrast dye injection. Should your kidneys be impaired then the injection will not be given

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

occasion. If you feel too tired or unwell to come to the hospital we may ask if we can visit you in your own home to do these tests.

WHAT ARE THE RISKS AND DISCOMFORTS?

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

BENEFITS TO YOU

There are no particular benefits to you from taking part in this study.

EXPENSES

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

WILL MY TAKING PART BE KEPT CONFIDENTIAL?

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

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

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

INDEMNITY/COMPENSATION

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

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

WHO IS ORGANISING AND FUNDING THE STUDY?

This is a research project of the Cardiac MRI department at Leeds General Infirmary.

WHO HAS REVIEWED THE STUDY?

The study has been reviewed and approved by the Leeds West Local Research Ethics Committee.

For further information please contact:

Dr Akhlaque Uddin

Cardiac MRI department

B Floor, Clarendon Wing

Leeds General Infirmary

LS1 3EX Tel: 0113 392 5224 / 0113 392 5481

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

Hospital Number: ……. Initials: ……..

CONSENT FORM – Version 1.3 November 30 2012
MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation

	Name of Researcher: Prof John Greenwood	Please initial box
1.	I confirm that I have read and understood the information sheet (version 1.3 November 30 2012) for the above study and have had the opportunity to ask questions.	☐
2.	I understand that sections of any of my medical notes may be looked at by members of the research team and authorised personnel within the Leeds Teaching Hospitals NHS Trust and the University of Leeds, where it is relevant to the research or to assess that appropriate research standards are being maintained within the study. I give permission for these individuals to have access to my records. I understand that the information about me will be held in the strictest confidence and that my results will not be available to a third party.	☐
3.	I give my consent for my General Practitioner to be informed of my participation in the study.	☐
4.	I understand that images collected will be stored on a computer system, and, after my name and address have been removed, may be available to researchers at other institutions	☐
5.	I understand that my participation is voluntary; and that I am free to withdraw at anytime, without giving any reason, without my medical care or legal rights being affected.	☐
6.	I agree to take part in the study and that the general results of the study will be made available to medical community most likely through publication in a reputable medical journal	☐
7.	If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study.	☐

Signature.....

Name (block capitals).....Date…….

Signature of witness.....

Name (block capitals).....Date…….