Severe Aortic Valve Stenosis and the consequences of Transcatheter and Surgical Aortic Valve Replacement: A cardiovascular magnetic resonance study.

Timothy Andrew Fairbairn

Submitted in accordance with the requirements for the degree of Doctor of Philosophy (PhD)

The University of Leeds

Faculty of Medicine and Health

Leeds Institute of Genetics, Health and Therapeutics

November 2013

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others:

Chapter 2

Publication: Assessment of Valve Haemodynamics, Reverse Ventricular Remodeling and Myocardial Fibrosis following Transcatheter Aortic Valve Implantation compared to Surgical Aortic Valve Replacement: A Cardiovascular Magnetic Resonance Study. Fairbairn TA, Steadman CD, Mather AN, Motwani M, Blackman DJ, Plein S, McCann GP, Greenwood JP.Heart. 2013; 99: 1185-91

Authorship: Individual contributions include.

T.F- design, collection, analysis and interpretation of data, drafting and revision of manuscript; **C.S**- collection, analysis and interpretation of data and revision of manuscript; **A.M**- analysis and interpretation of data and revision of manuscript; **M.M**- analysis and interpretation of data and revision of manuscript; **D.B**- analysis and interpretation of data and revision of manuscript; **S.P**- analysis and interpretation of data and revision of manuscript; **D.B**- conception, design, collection and interpretation of data; revision of manuscript; **G.M**- design, collection, analysis and interpretation of data and revision of manuscript; **J.P.G**- conception, design, collection, interpretation and analysis of data; drafting and revision of manuscript

Chapter 3

Publication: Diffusion-Weighted Magnetic Resonance Imaging Determined Cerebral Embolic Infarction Following Transcatheter Aortic Valve Implantation: Assessment of Predictive Risk Factors and the Relationship to Subsequent Health Status. Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, Blackman DJ, Plein S, Greenwood JP. Heart. 2012; 98(1):18-23

Authorship: Individual contributions include.

T.F- design, analysis and interpretation of data, drafting and revision of manuscript; **A.M**- analysis and interpretation of data and revision of manuscript; **P.B**- design and collection of data and revision of manuscript; **G.W**- analysis and interpretation of data and revision of manuscript; **S.C**- analysis and interpretation of data and revision of manuscript; **A.G**- analysis and interpretation of data and revision of manuscript; **D.B**- conception, design, collection and interpretation of data; revision of manuscript; **S.P**- conception, design and interpretation of data; revision of manuscript; **J.P.G**- conception, design, collection and interpretation of data; drafting and revision of manuscript

Chapter 4

Publication: Serial change in health related quality of life over one year following Transcatheter Aortic Valve Implantation: Predictors of health outcomes. Fairbairn TA, Meads DM, Mather AN, Motwani M, Pavitt S, Plein S, Blackman DJ, Greenwood JP. J Am Coll Cardiol. 2012; 59(19):1672-80

Authorship: Individual contributions include.

T.F- design, collection, analysis and interpretation of data, drafting and revision of manuscript; **D.M**- analysis and interpretation of data and revision of manuscript; **A.M**- analysis and interpretation of data and revision of manuscript; **M.M**- analysis and interpretation of data and revision of manuscript; **S.P**- analysis and interpretation of data and revision of manuscript; **S.P**- analysis and interpretation of data and revision of manuscript; **D.B**- conception, design, collection and interpretation of data; revision of manuscript; **J.P.G**- conception, design, collection and interpretation of data; drafting and revision of manuscript

Chapter 5

Publication: The Cost-Effectiveness of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Patients with Severe Aortic Stenosis at High Operative Risk Fairbairn TA, Meads DM, Hulme C, Mather AN, Plein S, Blackman DJ, Greenwood JP. Heart. 2013; 99(13):914-20.

Authorship: Individual contributions include.

T.F- was involved in the study conception and design; acquisition, analysis and interpretation of data; drafted the article and had final approval of the manuscript; **D.M-** was involved in the study design, analysis and interpretation of data; drafted the article and had final approval of the manuscript; **C.H-** was involved in the study design and interpretation of data; revising the article and had final approval of the manuscript; **A.M-** was involved in the acquisition and analysis of data; revising the article and had final approval of the manuscript; **S.P-** was involved in the study design and interpretation of data; revising the article and had final approval of the manuscript;**D.B-** was involved in the study design and interpretation of data; revising the article and had final approval of the manuscript; **J.G-** was involved in the study conception and design; interpretation of data; drafting and revising the article and had final approval of the manuscript.

Publications arising from this work

Papers

1. Fairbairn TA, Steadman CD, Mather AN et al. Assessment of Valve Haemodynamics, Reverse Ventricular Remodeling and Myocardial Fibrosis following Transcatheter Aortic Valve Implantation compared to Surgical Aortic Valve Replacement: A Cardiovascular Magnetic Resonance Study. ***Heart*** 2013; 99:1185–1191.
2. Fairbairn TA, Meads DM, Hulme C et al. The Cost-Effectiveness of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Patients with Severe Aortic Stenosis at High Operative Risk. ***Heart*** 2013; 99:914-920. (*Editors choice)*
3. Fairbairn TA, Meads DM, Mather AN, et al. Serial Change in Health-Related Quality of Life Over 1 Year After Transcatheter Aortic Valve Implantation: Predictors of Health Outcomes. ***Journal of the American College of Cardiology*** 2012;59(19):1672-80.
4. Fairbairn TA, Greenwood JP, Blackman DJ. Multiple cerebral emboli following dislocation and retraction of a partially deployed corevalve prosthesis during transcatheter aortic valve implantation. ***Catheter Cardiovascular Intervention*** 2011 Online Sep 27.
5. Fairbairn TA, Mather AN, Bijsterveld P, et al. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. ***Heart***. 2012; 98(1):18-23. *(Editors choice)*

Abstracts

Oral Presentations

1. Fairbairn TA, Steadman C, Mather A, et al. The effect of myocardial fibrosis on ventricular remodeling following valve replacement for severe aortic stenosis. A CMR study comparing transcatheter aortic valve implantation and surgical aortic valve replacement. Society of Cardiovascular Magnetic Resonance scientific sessions; *Journal of Cardiovascular Magnetic Resonance. 2012; 14:O71*.
2. Fairbairn T. A., Meads D.M., Mather A.N. et al. Serial change in health related quality of life over one year following transcatheter aortic valve implantation: Predictors of health outcomes. British Cardiovascular Society. *Heart 2012;**98**:Suppl 1 A25*
3. Fairbairn T.A., Steadman C.D., Mather A.N. et al. Assessment of Reverse Ventricular Remodelling, Valve Haemodynamics and Myocardial Fibrosis following Transcatheter Aortic Valve Implantation compared to Surgical Aortic Valve Replacement. A Cardiovascular Magnetic Resonance Study. British Cardiovascular Society. *Heart 2012;**98**:Suppl 1 A26*
4. Timothy A Fairbairn, Christopher D Steadman, Adam N Mather, et al. Reverse Left Ventricular remodelling 6 months post-Transcatheter Aortic Valve Implantation compared to Surgical Aortic Valve Replacement. A Cardiovascular Magnetic Resonance Study. American Heart Association scientific sessions; *Circulation, 2011. 124:A14939*
5. Fairbairn T.A, Mather A.N, Bijsterveld P., et al. Cerebral Embolic Infarcts Following Transcatheter Aortic Valve Implantation: A Diffusion-Weighted Magnetic Resonance Study and the Assessment of Subsequent Health Status. American Heart Association scientific sessions; *Circulation, 2010;122:A17119*. Listed as one of top 5 abstracts from the UK and featured in AHA news.
6. Fairbairn T.A, Greenwood J.P, Goddard AJP, Blackman D.J, Plein S. Magnetic Resonance Imaging for the detection of Cerebral Ischaemic events after Transcutaneous Aortic Valve Replacement. British Cardiovascular Society. *Heart 2010;**96**:Suppl 1 A50.*

Poster Presentations

1. Uddin AU, Fairbairn TA, Motwani MM, Kidambi AK, Steadman CS, Schlosshan DS, Blackman DB, McCann GM, Plein SP, Greenwood JPG. Aortic regurgitation after corevalve TAVI: Assessment by echocardiography and cardiovascular magnetic resonance. British Cardiovascular Society.*Heart* 2013; 99: A85-86
2. Uddin AU, Fairbairn TA, Djoukhader ID, Currie SC, Motwani MM, Kidambi AK, Goddard AG, Blackman DB, Plein SP, Greenwood JPG. A cerebral diffusion weighted MRI study to assess the difference between embolic events following transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR). British Cardiovascular Society.*Heart*. 2013; A85
3. Fairbairn TA, Steadman C, Mather A, et al. A CMR study assessing aortic valve hemodynamics post-transcatheter aortic valve implantation compared to surgical aortic valve replacement. Society of Cardiovascular Magnetic Resonance scientific sessions; *Journal of Cardiovascular Magnetic Resonance*. 2012; 14:P96.
4. Timothy Fairbairn, Christopher Steadman, Adam Mather et al. The effect of myocardial fibrosis on ventricular remodeling following valve replacement for severe aortic stenosis. A CMR study comparing transcatheter aortic valve implantation and surgical aortic valve replacement. British Society Cardiovascular Magnetic Resonance 7th conference, 2012.
5. Timothy Fairbairn, Christopher Steadman, Adam Mather et al. A CMR study assessing aortic valve hemodynamics post-transcatheter aortic valve implantation compared to surgical aortic valve replacement. British Society Cardiovascular Magnetic Resonance 7th conference, 2012.
6. Timothy A Fairbairn, Christopher D Steadman, Adam N Mather, et al. Regional changes in Left Ventricular function and geometry - Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement. Circulation, 2011. 124:A14840

Acknowledgements

This thesis is has come about in no small part due to the support of others. Foremost in this have been Professor John Greenwood and Professor Sven Plein. They gave me the opportunity, the environment and guidance to succeed. I am fortunate to have experienced the ethos, work ethic and academic excellence of their department, in which they lead by example.

The cardiovascular MR research department encompases a multidisciplinary team, all of whom helped in the course of this thesis. I thank Petra, Margaret, Caroline and Fiona for their knowledge, teaching and endurance. I am grateful to my peers Nev and Mani for their positive and friendly approach to team work and to Dr Dan Blackman, without whom we would have no patients to study. Thanks also go to Dr Christoper Steadman and Dr Gerry McCann from the University of Leicester. They contributed more than just numbers. Dr Tony Gooddard and Dr Stuart Currie provided their expertise and time in analysing the cerebral MRI scans, for which I am indebted.

Patients are integral to all research. The readiness of an elderly, frail and unwell population to participate in a demanding study was extraordinary. Their strength and dignity humbles me.

Final acknowledgements must go to my family. To Ciara for her continuing support and understanding, to Ruaridh for his patience and occassional distraction and to my parents for their encouragement.

Table of Contents

List of Tables

List of Figures

List of Equations

Abbreviations

ACE	Angiotensin Converting Enzyme
ADC	Apparent Diffusion Coefficient
AF	Atrial Fibrillation
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
AS	Aortic Stenosis
AR	Aortic Regurgitation
AVA	Aortic Valve Area
BAV	Bicuspid Aortic Valve
B_o	Net magnetic field
BDP	Bodily Pain
BP	Blood Pressure
BSA	Body Surface Area
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Graft
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CKD	Chronic Kidney Disease
CMR	Cardiovascular Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CSA	Cross Sectional Area
CSPAMM	Complementary Spatial Modulation of Magnetization
CT	Computed Tomography
CVA	Cerebrovascular Accident
DW	Diffusion Weighted
ECV	Extra Cellular Volume
EDV	End-Diastolic Volumes
EDWT	End-diastolic Wall Thickness
EF	Ejection Fraction
EQ-5D	EuroQol 5D
ESC	European Society of Cardiology

ESWT	End-systolic Wall Thickness
ESV	End-systolic Volumes
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FID	Free Induction Decay
FLAIR	Fluid attenuated inversion recovery
FLASH	Fast Low Angle Shot
FOV	Field of View
FWHM	Full Width Half Maximum
HITS	High Intensity Transient Signals
HRQOL	Health Related Qaulity of Life
ICER	Incremental Cost-Effectiveness Ratios
ICU	Intensive Care Unit
IVR	Isovolumetric Relaxation
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
EDD	End-Diastolic Dimensions
LVM	Left Ventricular Mass
LVOT	Left Ventricular Outflow Tract
MCS	Mental Component Summary
MHz	Megahertz
M_o	Net Magnetization
M_z	Longitudinal Magnetization
M_{xy}	Transverse Magnetization
MACE	Major Adverse Cardiovascular and Cerebrovascular Events
MCV	Medtronic CoreValve
MF	Myocardial Fibrosis
MH	Mental Health
MI	Myocardial Infarct
MOLLI	Modified Look Locker Inversion
MPG	Mean Pressure Gradient
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging

NICE	National Institute of Clinical Excellence
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Health Association
PARTNER	Placement of Aortic Transcatheter Valves
PF	Physical Functioning
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Summary
POCD	Post Operative Cognitive Decline
PPM	Permanent Pacemaker
PSA	Probabilistic Sensitivity Analyses
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RE	Role Emotional
Rf	Radiofrequency
RFOV	Relative Field of View
ROI	Region of Interest
RE	Role Emotional
RP	Relative Wall Thickness
SAP	Systolic Arterial Pressure
SAVR	Surgical Aortic Valve Replacement
SF-12	Short Form 12
SF	Social Functioning
SSFP	Steady State Free Precession
SNR	Signal to Noise Ratio
STS	Society of Thoracic Surgeons
SV	Stroke Volume
SWT	Systolic Wall Thickening
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TAVI	Transcatheter Aortic Valve Implantation
TE	Echo Time
TA	Transapical

TF	Transfemoral
THV	Transcatheter Heart Valve
TI	Inversion Time
TIA	Transient Ischaemic Attack
TOE	Transoesophageal Echocardiogram
TR	Repetition Time
TTE	Transthoracic Echocardiogram
VARC	Valve Academic Research Consortium
VAS	Visual Analogue Score
VENC	Velocity Encoded Cine
VT	Vitality
VTI	Velocity Time Integral
WTP	Willingness To Pay
Z_{va}	Valvuloarterial Impedance

Abstract

Background: Severe symptomatic aortic stenosis (AS) heralds a poor prognostic outlook and significant co-morbidity, with valve replacement the only definitive cure. Transcatheter aortic valve implantation (TAVI) has developed as an alternative to the standard treatment of surgical aortic valve replacement (SAVR) in high-risk or inoperable AS patients. The clinical and cost effectiveness of TAVI compared to SAVR requires further investigation.

Methods: A prospective study of sixty seven TAVI and twenty seven SAVR patients, recruited from September 2009 to September 2011. Baseline assessments included a cerebral and cardiovascular magnetic resonance scan (1.5 Tesla MRI system) and the completion of two health surveys (EQ 5D and SF 12). Follow-up MRI was performed at 5±2 days (cerebral MRI) and 6 months (cardiovascular MRI) post AVR. Health status was assessed at 30 days, 6 months and one year. A cost-effectiveness analysis was performed using a 10 year Markov model with deterministic and probabilistic sensitivity analyses.

Results: TAVI and SAVR resulted in similar levels of ventricular reverse remodelling. TAVI had a greater reduction in valvular impedance (21±8mmHg vs. 35±13mmHg, p=0.017) and myocardial fibrosis (10.9±6 % vs. 8.5±5%, p=0.03). Cerebral emboli occurred in 77% of TAVI patients. Age (r=0.37, p=0.042), severity of atheroma (r=0.91, p<0.001) and catheterisation time (r=0.45, p=0.02) were predictors of cerebral infarcts. HRQOL significantly improved over 12 months (PCS, p=0.02; EQ-5D, p=0.02; VAS, p=0.01 and SF6D p=0.03). Male gender (SF6D, p=0.01) and increased operator experience (PCS, EQ5D and VAS, p<0.05) predicted an improvement in HRQOL. Despite greater procedural costs, TAVI was cost-effective compared to SAVR over the 10 year model horizon (costs £52,593 vs. £53,943 and QALYs 2.81 vs. 2.75) indicating that TAVI dominated SAVR.

Conclusions: TAVI has comparable cardiac and health benefits to SAVR, but greater cerebral complications. TAVI is likely to represent a clinical and cost effective alternative to SAVR.

1 Introduction

1.1 Aortic Stenosis

1.1.1 Background

Aortic Stenosis (AS) is the most common form of valvular heart disease in Europe and America, constituting approximately 40% of all valvular lesions (Nkomo et al., 2006). AS has profound effects upon patient morbidity and mortality and represents a significant clinical problem within medicine. Symptomatic patients have poor survival, and individuals often present late with pronounced co-morbidities. Asymptomatic patients have a greater event free survival but are still likely to require treatment within 5 years (Nkomo et al., 2006, Rosenhek et al., 2000). The disease remains predominantly one of age. Calcific aortic valve disease is present in approximately 25% of adults aged >65 years, with up to 15% of these individuals progressing to clinically significant AS in the next 2 to 7 years (Owens et al., 2010). The disease prevalence of AS increases from 2.5% at 75 years to 8.1% at 85 years (Lindroos et al., 1993). The incidence of AS is increasing in the United Kingdom (Berry et al., 2013). Given future demographic predictions, AS is set to become a significant public health problem as a greater number of people are diagnosed and require treatment in an ageing population (Iung et al., 2003b).

1.1.2 Aetiology and Pathophysiology

AS is the progressive narrowing of the aortic valve. It is believed to be a degenerative process as a result of several interacting factors. The dominant hypothesis remains changes secondary to 'wear and tear'. The older age of presentation and declining incidence of rheumatic fever (<0.5 per 1000) have contributed to the development of this theory. Mechanical stress from blood flow through the aortic valve creates an inflammatory process at the cellular level resulting in lipid accumulation, calcification and eventual valvular obstruction. Initial sub-endothelial damage from reactive oxygen species results in the accumulation of low-density lipoprotein (LDL), macrophages and T-lymphocytes. These cells stimulate the inflammatory response involving several cytokines: Tumour Necrosis Factor α, Tumour Growth Factor β, C-Reactive Protein and Interleukin 1-β. The renin-

angiotensin system is also involved in disease progression, as Angiotensin Converting Enzyme (ACE) and its product Angiotensin II are found to be present in the lesions of advanced aortic valve disease. Macrophages produce Angiotensin II which contributes to the regulation of the inflammatory process, increasing LDL uptake, smooth muscle adhesion and producing plasminogen activator inhibitor-1 (O'Brien et al., 2002). These signalling pathways are integral in the differentiation of interstitial cells to an osteoblast like phenotype and the subsequent process of valvular calcification (Miller et al., 2011). Fibroblasts become phenotypic osteoblasts that produce matrix proteins including osteopontin and osteocalcin. These stimulate bony differentiation mediated by the Lrp5/Wnt3 signalling pathways, with eventual calcium deposition in the extracellular matrix (O'Brien et al., 2002, Otto, 2006, Rajamannan et al., 2007, Cawley and Otto, 2009).

This cellular response within the aortic valve has histological and pathological features common to the process of atherosclerosis in the arterial vasculature. Risk factors for the development of both diseases are therefore similar; increased age, male sex, hypertension, diabetes mellitus, elevated LDL and smoking (Rajamannan et al., 2007, Otto, 2006, Stewart et al., 1997). Individuals with abnormal valve morphology (bicuspid, unicuspid and quadricuspid) appear to be at a greater risk of this inflammatory process, possibly due to the greater mechanical stress upon the valve. Bicuspid Aortic Valve (BAV) is a congential condition that is present in 0.5% of the population and accounts for approximately 50% of cases presenting for Surgical Aortic Valve Replacement (SAVR). Genetic factors are also believed to play a role but are less clearly defined. The expression of micro-RNA is down regulated and is believed to contribute towards fibrosis. Abnormalities in DNA methylation occur with increased age and are involved in the differentiation of fibroblasts to osteoblasts. A defect in the NOTCH signalling pathway (NOTCH 1 gene) also plays a role in the phenotypic change of fibroblasts by failing to suppress the bone morphogenic protein (BMP2/4) signalling. This gene abnormality has been found in families with both calcified aortic valve disease and bicuspid aortic valves (Miller et al., 2011, Garg et al., 2005).

1.1.3 Haemodynamic severity

The progressive narrowing of the aortic valve can be assessed, quantified and graded according to the degree of left ventricular outflow obstruction. The severity of AS is traditionally assessed by transthoracic echocardiography (TTE). AS is differentiated from 'sclerosis' or valve thickening by the restriction of valve leaflet opening, a raised peak velocity measurement (V_{max}) across the valve and increased transaortic mean pressure gradient (ΔP_{mean}) calculated by the Bernoulli equation (Equation 1). The Doppler waveforms are then combined with the cross sectional area (CSA) of the left ventricular outflow track (LVOT) in the continuity equation to determine the valves aortic valve area (AVA) (Equation 2), (Chambers, 2009).

Equation 1 Bernoulli equation

ΔP_{peak} (mmHg) = $4(V_2^2 - V_1^2)$

ΔP_{peak} = peak pressure gradient; V_1= Subaortic peak velocity; V_2= Transaortic peak velocity

Equation 2 Continuity equation

AVA (cm^2) = (LVOT CSA × VTI_1)/VTI_2

CSA = LVOT cross sectional area (cm); VTI = Velocity Time Integral; VTI_1= velocity time integral at the LVOT; VTI_2= velocity time integral at the aorta.

In small individuals AVA may be more accurate if indexed to the body surface area (BSA). However, this can underestimate the true functional area in obese patients. In these circumstances the ratio of LVOT to aortic velocity is used, with a ratio of 1 normal and 0.25 significantly abnormal.

AS is graded for severity and classified according to the American Heart Association (AHA) and European Society of Cardiology (ESC) working groups' definitions (Table 1-1).

Table 1-1 Aortic Stenosis classification

Aortic stenosis	Velocity (m/s)	Mean gradient (mmHg)	AVA (cm^2)	Other
Mild	2.5-3	10-20	1.5-3	
Moderate	3-4	20-40	1-1.5	
Severe	> 4	>40	<1	AVAi <0.6cm^2/m^2
Critical	>5	>60	<0.6	
Low output, low gradient	3-4	20-40	<1	SVi <35ml/ m^2

AVAi = aortic valve area indexed to BSA; SVi = stroke volume indexed to BSA

Severe AS is defined as an aortic orifice area of less than 1cm^2 (or < 0.6cm^2 indexed to BSA), (Chambers, 2009). As the orifice of the aortic valve narrows, a pressure gradient develops from the left ventricular cavity across the aortic valve to the aorta. This abnormal chronic pressure overload has several consequences primarily on the structure and function of the left ventricular wall, causing it to remodel.

1.1.4 Left ventricular remodelling

1.1.4.1 Normal ventricular structure and mechanics

The normal left ventricle (LV) wall is composed of myofibres that are arranged in a helical formation. The orientation of these fibres change from a leftward direction at the sub-epicardium to a rightward direction in the sub-endocardium. Myofibre contraction causes a circumferential rotation or twist that follows 4 defined phases over time:

Phase 1: Isovolumetric contraction

Phase 2: Systolic ejection

Phase 3: Isovolumetric relaxation

Phase 4: Early diastolic filling

Systolic rotation differs across the myocardial layers. The sub-epicardial fibres rotate in a counter-clockwise direction at the apex and clockwise direction at the base, where as the sub-endocardial fibres rotate clockwise apically and counter-clockwise basally. The global direction of myocardial contraction is controlled by the sub-epicardial layer (apical counter-clockwise and basal clockwise rotation), as its higher mass and longer radius contribute the greatest torque. Electrical activation of this process occurs in a sub-endocardial to sub-epicardial direction from the mid-apical septal wall. Thus in normal systolic contraction the apex initially rotates in a clockwise direction prior to the dominant counter-clockwise motion. The sub-endocardial layer is responsible for the radial thickening and contraction into the LV cavity as well as the longitudinal shortening of the LV (Taber et al., 1996, Sengupta et al., 2008a). In normal individuals most systolic rotation occurs during phase 1 (isovolumetric contraction) with little rotation occurring at systolic ejection (Nagel et al., 2000).

Diastolic untwisting or relaxation is the rotation of the cardiac fibres in the opposite direction to systolic movement (counter-clockwise at base and clockwise at the apex). Potential energy built up and stored in the sub-endocardial fibres during systolic twisting is released. Early in diastole isovolumetric relaxation (IVR) occurs, where the twisted fibres lengthen secondary to elastic recoil without altering the LV volume. Diastolic rotation predominantly occurs during the IVR time (IVRT) with diastolic filling of the LV following this as a separate process (Stuber et al., 1999).

The difference between apical and basal twist is known as ‘Torsion’. Torsion is important in distributing the uneven shortening of sub-endocardial and sub-epicardial fibres equally over the LV (optimisation of strain). If absent during systolic contraction this would result increased endocardial shortening, decreased epicardial shortening, greater wall stress and as a result a higher workload for the ventricle, increased oxygen demand and reduced efficiency (Rüssel et al., 2009) (Sengupta et al., 2008b). Normal torsion is thus essential for a normally functioning LV. Small but significant variations of torsion occur in the normal ventricle, as the inferior and septal walls demonstrate lower levels of torsion compared to the anterior and lateral walls. This is likely an effect of the right ventricular mass displacing the axis of rotation and influencing left ventricular torsion. The clinical implications of this observation are predominantly in the analysis and interpretation of regional rather

than global torsion. Russel *et al* suggest that circumferential segmental (AHA-16-segment model) analysis is less reliable than transmural (whole wall base, mid and apex) analysis (Russel et al., 2008).

1.1.4.2 Twist and Torsion in AS

Systolic twist (rotation) is affected by the loading conditions of the ventricle; an increase in preload exaggerates twist whereas increased afterload attenuates it. Ageing results in reduced sub-endocardial function, increased apical twist and torsion but reduced velocity of untwisting. Physiological hypertrophy (athletes) increases LV wall thickness but maintains the ratio to cavity size, thus developing the same level of twist and torsion (Stuber et al., 1999). In the pressure-overloaded ventricle of AS the increased wall thickness to cavity size ratio produces higher levels of ventricular strain. Basal systolic twist is reduced and apical twist is increased and delayed. Torsion is therefore significantly higher increased compared to normal. This process is believed to be a consequence of sub-endocardial fibre dysfunction that is in part due to reduced endocardial blood flow in AS (Rajappan, 2002).

Diastolic untwisting is also affected in AS. Untwisting is delayed with a reduced peak rotation velocity. The prolonged untwisting results in an overlap of relaxation and filling times and delayed diastolic filling which now occurs in late diastole (Nagel, 2000). The increase in torsion and prolonged untwisting of the LV in AS is related to the severity of the AS (van Dalen et al., 2011) and has been shown to precede any gross remodelling changes of the ventricle. Sandstede *et al* also demonstrated that abnormal twist and torsion have the potential to normalise following AVR (Sandstede et al., 2002).

1.1.4.3 Low-flow AS

Myocardial function may therefore be significantly impaired in the presence of a normal ejection fraction (Pibarot and Dumesnil, 2009). Ejection fraction is a measurement of myocardial fractional shortening (radial movement) and change in cavity size rather than an assessment of the workload and function of the LV wall. Therefore, in a ventricle with altered geometric shape (structural remodelling) a normal ejection fraction does not guarantee normal myocardial function. One third of asymptomatic AS patients with concentric remodelling were found to have impaired mid-wall

shortening, despite a normal ejection fraction (Cramariuc et al., 2009, Dumesnil et al., 2010). This finding is consistent with other observations that approximately one third of AS patients have a reduced stroke volume/body surface area (<35ml/m^2) and low cardiac output (Hachicha et al., 2007, Pibarot and Dumesnil, 2012). These low flow situations may result in a paradoxically low pressure gradient across the valve, leading to an underestimation of the true severity of the stenosis (Pibarot and Dumesnil, 2010). Low flow-low gradient AS is a well recognised clinical scenario which poses difficulties surrounding the appropriateness and timing of treatment.

1.1.4.4 LV structural remodelling

Several physiological and pathological conditions result in the left ventricle altering its geometric shape, size and function (Linzbach, 1960). This structural remodelling has been described and classified according to the pattern of geometric changes in wall thickness, wall mass and cavity volume as recommended by the American Society of Echocardiography (Lang et al., 2005), Table 1-2 (Gaasch and Zile, 2011). These measurements have been validated predominantly in hypertensive populations using angiography (Gaasch et al., 1972), echocardiography (Ganau et al., 1992) and cardiac MRI (Heckbert et al., 2006) with excellent correlation between the techniques.

Table 1-2 Classification of structural remodelling

	RWT	**LVMI***	**LV EDV***	**M/V ratio**
Normal	0.32-0.42	70-90g/m^2	<100ml/m^2	1.1-1.3
Concentric remodelling	>0.42	70-90g/m^2	<100ml/m^2	>1.3
Concentric hypertrophy	>0.42	>90g/m^2	<100ml/m^2	>1.3
Physiological hypertrophy	0.32-0.42	>90g/m^2	<100ml/m^2	1.1-1.3
Eccentric remodelling	<0.32	70-90g/m^2	≥100ml/m^2	≤1
Eccentric hypertrophy	<0.32	>90g/m^2	≥100ml/m^2	≤1

RWT = relative wall thickness; M/V = mass to volume ratio; LVMI = left ventricular mass index

* indexed to Body Surface Area (BSA)

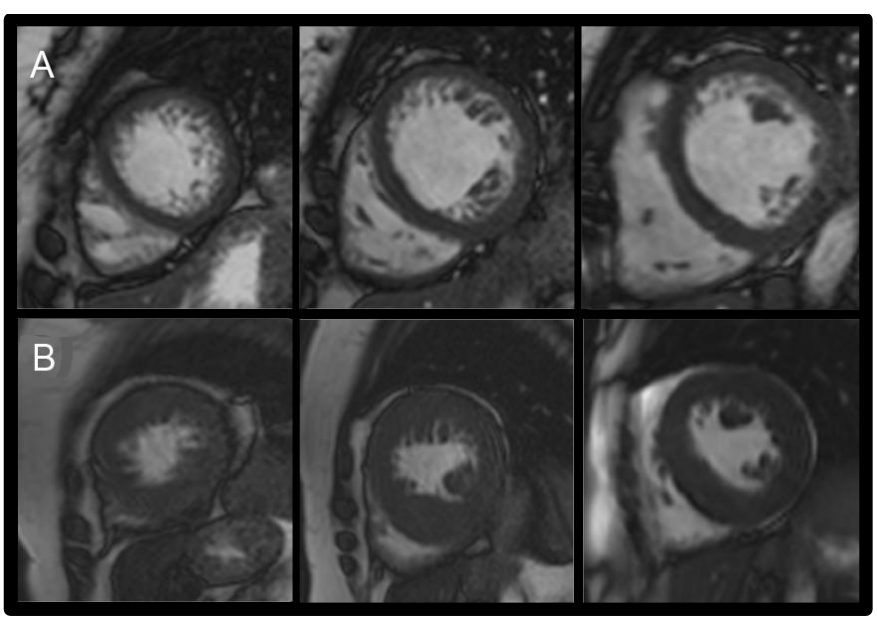
1.1.4.4.1 Concentric hypertrophy

In a pressure overloaded state such as AS the LV compensates for the increased pressure gradient by ventricular hypertrophy in order to maintain a constant after-load, but with no increase in the cavity radius. The increase in absolute and relative wall thickness (RWT) is known as concentric hypertrophy. This compensatory action maintains normal levels of wall stress but results in a late systolic peak compared to the early systolic peak in normal individuals. The rise in LV filling pressures alters the diastolic pressure-volume relationship reduces compliance and decreases ventricular preload capacity and is known as 'diastolic dysfunction' (Hess et al., 1993). Over time the LV starts to decompensate; it becomes scarred as collagen is deposited, cardiac output falls 'systolic dysfunction' and the cavity dilates.

1.1.4.4.2 Eccentric hypertrophy

Eccentric hypertrophy is the structural remodelling process where the geometric changes include: An increase in myocardial mass, peak wall stress and cavity size, with a small increase in absolute wall thickness but normal or reduced RWT. This pattern of remodelling has been classically described in volume overloaded conditions (mitral and aortic regurgitation) but can occur as the LV decompensates at the end stage of a pressure overloaded process (Dweck et al., 2012). Figure 1 represents two different patterns of remodelling as demonstrated by cardiac MRI.

Figure 1-1 Geometric patterns of remodelling



A = eccentric remodelling (increased mass and EDV with reduced RWT). B = concentric remodelling (increased mass and RWT with a lower EDV)

1.1.4.4.3 Mass to volume ratio

The mass to volume ratio (M/V) is easily assessed by cardiovascular magnetic resonance (CMR) imaging and correlates with the RWT of the ventricle. A measurement <1.1 is consistent with eccentric remodelling and >1.3 concentric remodelling. The pattern of ventricular remodelling has been established as important as an independent adverse prognostic marker for cardiovascular events, with concentric hypertrophy the strongest predictor of poor outcomes (Bluemke et al., 2008, Koren et al., 1991). Differences in the geometric structure and remodelling process exist between races (Rodriguez et al., 2010), gender (Piro et al., 2010) and also in response to concomitant factors such as blood pressure (Wang et al., 2011).

1.1.4.5 Valvuloarterial impedance

The left ventricular workload is not solely dependent upon the pressure gradient across the aortic valve but the total pressure generated by vascular and valvular resistance. Given that a large proportion of AS patients (>50%) will have coexisting hypertension and reduced arterial compliance (Nemes et al., 2004), the assessment of global workload is important. Global workload can be estimated by calculating the valvuloarterial impedance (Z_{va}), Equation 3.

Equation 3, Valvuloarterial impedance:

Z_{va} (mm Hg·ml^{-1}·m^2) = (SAP + MPG) / SVI

SAP = systolic arterial pressure; MPG = mean tranvalvular pressure gradient; SVI = stroke volume index

Z_{va} can be categorised as low (≤3.5 mm Hg·ml^{-1}·m^2), intermediate (3.6-4.4 mm Hg·ml^{-1}·m^2) and high (≥4.4 mm Hg·ml^{-1}·m^2). Increased levels of Z_{va} (>3.5 mm Hg·ml^{-1}·m2) can predict systolic dysfunction independent of and superior to the standard measures of AS severity (Briand et al., 2005). It has also been shown to be an independent prognostic marker for mortality in asymptomatic moderate- severe AS patients (Cramariuc et al., 2009) and symptomatic severe AS patients regardless of their therapy (surgical or percutaneous valve replacement and medical therapy) (Hachicha et al., 2007, Katsanos et al., 2013).

1.1.5 Asymptomatic aortic stenosis

Left ventricular remodelling occurs gradually, progressing with the disease severity. In mild and moderate AS patients may remain asymptomatic but as the stenosis becomes severe the high valvuloarterial impedance and increased ventricular workload frequently result in symptoms. The outlook for an asymptomatic patient with severe AS is reasonable at a 20-50% 5-year symptom free survival (Rosenhek et al., 2000). Despite having a better outlook compared to symptomatic patients, the early identification and treatment of asymptomatic individuals may help prevent systolic dysfunction, heart failure and death (Lund, 1990). Several adverse prognostic indicators have therefore been identified to help risk stratify these asymptomatic individuals at an increased risk of symptoms, surgery and cardiovascular death.

Patient characteristics and demographics that represent increased risk include, increased age (especially >80), the presence of coronary artery disease, renal dysfunction, hypertension, dyslipidaemia and diabetes mellitus (Pellikka, 2005, Berry et al., 2013). Echocardiography has been used to identify several high-risk features. The severity of valve calcification (Rosenhek et al., 2009), a very high pressure-gradient (>5m/s) (Otto et al., 1997, Pellikka et al., 2005, Rosenhek et al.) and LV systolic dysfunction (Pellikka et al., 1990) are all independent predictors of increased risk. Newer imaging techniques are being implemented to help identify predictors of adverse outcomes in these asymptomatic individuals. CMR has been used to help identify reduced ejection fraction (Caruthers et al., 2003), increased twist and torsion (Nagel et al., 2000, Stuber et al., 1999) and reduced myocardial perfusion reserve (Steadman et al., 2012). The non-invasive detection and quantification of myocardial fibrosis has also been identified as an independent predictor of mortality in mild-severe AS patients (Dweck et al., 2011). Exercise stress testing is used to risk stratify asymptomatic severe AS patients, with an early positive test predicting the onset of symptoms, aortic valve replacement (AVR) and cardiovascular death (Das et al., 2005, Amato, 2001).

1.1.6 Symptomatic aortic stenosis

Once symptoms develop the prognosis of the patient becomes extremely poor with a mean survival of 23 months (Otto, 2006, Ambler et al., 2005, Horstkotte and Loogen, 1988). Presenting symptoms are frequently a consequence of the LV adaptations, the most common of which are angina, syncope and dyspnoea. Angina tends to be the earliest symptom and heralds an expected life expectancy of 4.5 years. Its mechanism is secondary to the increased myocardial oxygen demand of the left ventricle. Concomitant coronary artery disease, which is present in 30% of AS patients, may contribute to or exacerbate the symptom. When syncope occurs an average survival of 2.6 years is observed. Syncope is usually exertional and is secondary to the LV baroreceptor response to elevated LV pressure causing arterial hypotension and bradycardia. Exertional dyspnoea presents last, indicating a predicted survival < 1 year. This may be due to diastolic dysfunction with high LV end diastolic pressures or systolic dysfunction with the signs of heart failure. The severity of breathlessness is traditionally measured by the New York Heart Association (NYHA) classification, Table 1-3.

Table 1-3 NYHA classification

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity causes fatigue, palpitations, or dyspnoea
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, or dyspnoea.
IV	Unable to carry out any physical activity without discomfort. Symptoms of dyspnoea at rest. If any physical activity is undertaken, discomfort is increased.

1.2 Medical Therapy

Attempts to delay the chronic progressive nature of AS through medical therapies have largely been unsuccessful (Moura et al., 2007, Rossebo, 2008). Trials have concentrated on medications that might influence the pathological process of degenerative valvular calcification. Statins (Rossebo, 2008,

Chan et al., 2010), ACE inhibitors (O'Brien, 2002, O'Brien et al., 2005) and angiotensin receptor blockers (ARB) (Nadir et al., 2011) have all been shown to have no impact upon delaying the progressive calcific degeneration of the valve or altering clinical outcomes.

Medical interventions have therefore concentrated upon reducing the impact of AS and and consequences of pressure overload. ACE inhibitors and ARB have been used to delay the remodelling process and treat any concomitant hypertension (thus reducing the valvuloarterial impedance) with some success, reducing the incidence of heart failure and cardiovascular death (Litwin et al., 1995, Chockalingam et al., 2004). Coronary artery disease (CAD) and atrial fibrillation (AF) are commonly associated co-morbidities, which may require aspirin, beta-blockade or even warfarin anti-coagulation.

1.3 Surgical Aortic Valve Replacement

Aortic valve replacement is the definitive treatment strategy in symptomatic AS, as the evidence supports an improvement in patient survival and quality of life (Vahanian et al., 2006, Kvidal et al., 2000, Bakaeen et al., 2010). Traditionally this has required open cardiac surgery (Surgical Aortic Valve Replacement, SAVR) with either a mid-line sternotomy (if requiring coronary artery bypass grafts (CABG)) or a lateral mini-thoractomy. Mechanical or bioprosthetic valves may be implanted. Mechanical valves were frequently favoured in younger patients due to their better durability. However, there is an increasing trend to greater usage of bioprosthetic valves, even in individuals <65 years (Lee et al., 2011, Brown et al., 2009). This changing pattern likely reflects the improved durability of new valves, patient choice (no anticoagulation) and the availability of a future percutaneous option. Different bioprosthetic valve types are available; bovine pericardial and porcine heterograft or a homograft. The Ross procedure (aortic replacement with pulmonary autograft and pulmonary homograft replacement) is still used in expert centres as another option. No outcome data exists to support the preference of one particular valve type over another; therefore the decision remains that of patient and surgical choice.

1.3.1 Clinical outcomes

Recent data from the Society of Thoracic Surgeons (STS) in North America have shown an increase in the number of SAVRs being performed and a trend towards patients being older with greater co-morbidities. Diabetes, hypertension, obesity and cerebrovascular disease were particularly prevalent conditions amongst the AS population. Cardiothoracic valve surgery is therefore becoming increasingly complicated, and this is reflected by a pattern of higher predicted surgical risk scores (STS surgical risk estimate). However, outcomes following SAVR remain good with 30 day survival between 2.6% (isolated SAVR) and 5.6% (SAVR+ Coronary Artery Bypass Grafting (CABG)), and a risk of stroke of 1.3%. (Brown et al., 2009, Kvidal et al., 2000).

Surgical and patient factors influence patient survival. Observed mortality actually appears to be declining over time, possibly due to improved techniques and better post-operative care. High-volume surgical centres appear to have lower mortality rates, possibly due to surgical competence and overall quality of care (Brown et al., 2009). Patient factors are varied but include; advanced age, NYHA class, presence of atrial fibrillation, concomitant CABG and poor LV function. Frailty and impaired cognition are increasingly recognised as markers of worse outcome but as of yet remain poorly quantified.

1.3.1.1 Surgical risk calculators

In an attempt to estimate surgical risk the surgical societies of America and Europe have devised two risk calculators to approximate an individuals 30-day mortality:

1. STS score (Brown et al., 2009)
2. European System for Cardiac Operative Risk Evaluation (EuroSCORE) (Michel et al., 2003b).

These calculators use patient clinical variables to estimate the 30 day operative risk at the time of surgery from 0-100%, with a higher score indicating a greater risk. They also provide some indication of long-term outcome. The estimation of surgical risk is important to better inform clinicians and patients. It can help guide clinical practice and act as a benchmark allowing comparison between

national and local services. Due to the poor predictive capacity of the previously used Parsonnet score, EuroSCORE was created from the results of data acquired in eight European countries (Nashef et al., 1999). Initially an additive then logistic model (Michel et al., 2003a), EuroSCORE has been extensively validated as a useful predictive model for cardiac surgery (Roques et al., 2003). However, some limitations do exist particularly in reference to the estimation of risk in females, individuals undergoing multiple cardiac operations and those higher risk individuals (Ranucci et al., 2009, Choong et al., 2009). EuroSCORE II was developed in order to address these issues by using more specific data such as poor and very poor ejection fraction and entry of the specific creatinine clearance (Nashef et al., 2012). Validation of EuroSCORE II is ongoing but early results suggest its improved precision for higher-risk individuals and those undergoing combined CABG and AVR (Nashef et al., 2013). Whilst providing some incremental benefit over the original logistic EuroSCORE, questions still remain concerning its accuracy in isolated AVR and CABG (Grant et al., 2012, Chalmers et al., 2013). Additionally, there are no data to establish its role in the estimation of risk for the large number of patient being considered for TAVI.

1.3.2 Decision to operate

A decision to operate remains difficult in severe asymptomatic AS but is mandated when a patient becomes symptomatic. However, in elderly symptomatic patients with multiple co-morbidities, high cardiovascular and operative risk, a ‘simple’ decision process becomes an increasingly complicated one of balancing patient risks and benefits (Grossi et al., 2008, Schueler et al., Schueler et al., 2012).

The European Heart Survey on valvular heart disease investigated this decision-making process. It discovered that up to one third of patients with severe AS and symptoms were not referred for definitive surgical treatment (Iung et al., 2003a). Age and LV dysfunction were two of the main factors stated as the reason for a judgment not to operate. This study highlighted a significant problem in the management of a heterogenous group of elderly complicated patients. Whilst these patients may have the highest absolute risk they equally have the greatest risk-benefit ratio and thus survival, relative to an age matched general population. (Kvidal et al., 2000)

1.4 Transcatheter Aortic Valve Implantation

1.4.1 History of transcatheter valves

The requirement for a less invasive therapy to treat severe AS resulted in the development of a transcatheter based valve system. In the 1980's Cribier *et al* used balloon aortic vavuloplasty (BAV) to treat severe AS (Cribier et al., 1986). This proved successful in initial symptomatic improvement but did not to alter the end outcomes of the disease process (Lieberman et al., 1995). Supra-coronary transcatheter valve devices had been trialled successfully in canine models through the 1960's to the 1980's (Phillips et al., 1976). The first sub-coronary aortic device implantation was demonstrated in pigs by the Aarhus group in Denmark (Andersen et al., 1992). This device was a porcine aortic valve with a balloon expandable surrounding stainless steel stent. A further balloon expandable stent-valve was subsequently developed by Alain Cribier *et al* who went on to perform the first in human implantation in 2002 (Cribier et al., 2002). This equine pericardial and stainless steel, stent-valve was inserted using a balloon expandable technique via an antegrade route. Subsequently the retrograde transfemoral (Webb et al., 2006) and transaxillary approaches have been developed, using both balloon and self-expandable devices (Grube et al., 2005).

1.4.2 Transcatheter aortic valve implantation

The evolution of Transcatheter aortic valve implantation (TAVI) in clinical practice was initially driven by a population requirement rather than good evidence. The first patients were therefore individuals who were deemed very high-surgical risk (calculated logistic EuroSCORE >20) or had inoperable factors such as a porcelain aorta, chronic obstructive pulmonary disease or chronic kidney disease. This approach is in comparison to the normal method for trialling new treatment devices which would commence in the low risk groups and following good results continue in a higher-risk group. (Buellesfeld and Windecker, 2011). On the basis of substantial registry data and one randomised controlled trial (Placement of Aortic Transcatheter Valves (PARTNER) trial) two types of transcatheter valve were given European CE marked approval in 2007:

1.4.2.1 Edwards SAPIEN valve

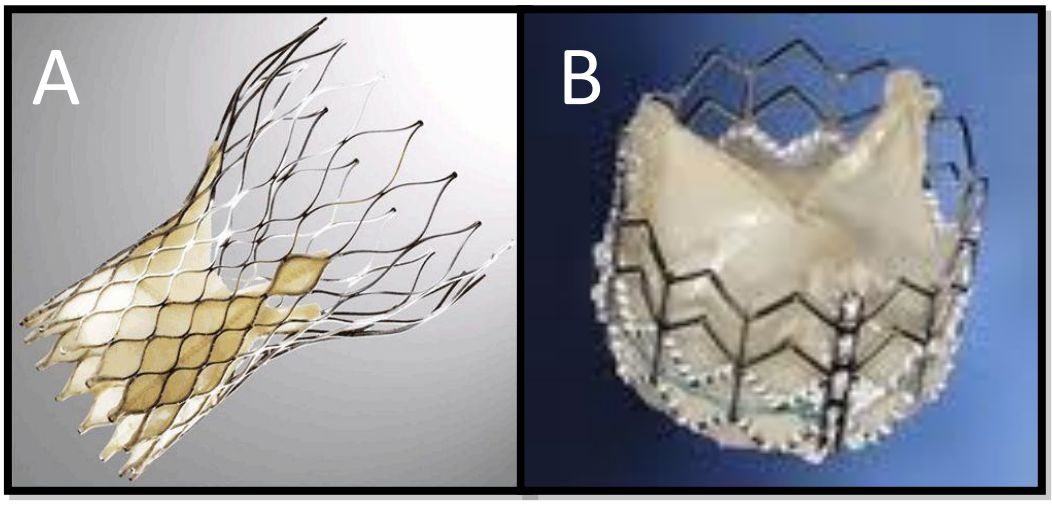
Edwards Transcatheter Heart Valve (THV), (Edwards Lifesiences Inc, Irvine, California, USA) (Figure 1-2) is a bovine pericardial valve leaflet within a cobalt chromium frame. It is suitable for aortic and pulmonary positions and can be deployed via either a femoral or transapical route. The Novaflex (Edwards Lifesiences Inc) delivery system requires a 16-19F sheath and an ileofemoral minimum diameter of 6mm. The valve is available in 20, 23, 26 and 29 mm sizes and is recommended for an annulus diameter of 18-25mm. Once in position the valve is deployed by a balloon expandable system.

1.4.2.2 Medtronic CoreValve

CoreValve™ ReValving system (Medtronic Inc., Minneapolis, MN, USA), (Figure 1-2) is a porcine pericardial leaflet within a nitinol self-expanding frame. It is suitable for both transfemoral and subclavian access but not transapical route. Percutaneous vascular access is required for the 18F delivery sheath which is based on an over the wire catheter system. The device is of either 26, 29 or 31 mm sizes and is recommended for aortic annulus diameters of 20-27mm. The valve is removed from its sheath in the anatomically suitable position using fluoroscopic and transoesophageal echocardiogrphic (TOE) guidance. The frame self-expands and is anchored within the annulus extending superiorly, supracoronary and into the ascending aorta. It can be post-dilated if required and has the potential for retrieval if not fully deployed. Vascular closure is via the Prostar™ suture system.

Patients require several pre-operative assessments to identify whether the patient is technically appropriate for TAVI. Investigations include transoesophageal echocardiography, computed tomography (CT) scanning and coronary angiography to assess coronary anatomy, aortic root and peripheral vascular suitablilty for TAVI. The clinical case is subsequently discussed in a multi-disciplinary forum involving cardiac surgeons, interventional and imaging cardiologists, cardiac anaesthetists and geriatricians. This ‘heart team’ decide upon the appropriateness of any treatments, as to whether a patient is suitable for SAVR, TAVI or if all interventions would be futile. Once a consensus is achieved the potential risks and benefits are conveyed to the patient for a final decision.

Figure 1-2: Transcatheter valves



A = The Medtronic CoreValve; B = The Edwards SAPIEN THV

1.4.3 Evidence for TAVI

The evidence for TAVI will be summarised from two main data sources; registry data and that of the randomised controlled trail, PARTNER.

1.4.3.1 Registry data

Registry data remains the main source of information regarding procedural success, complications and clinical outcomes following TAVI. In Europe early CE approval (2007) resulted in a rapid uptake of the procedure, particularly in Germany where 40% of TAVI's were performed (Binder and Webb, 2012). Thus far over 50,000 patients have been treated worldwide with six national registries published (Piazza et al., 2008, Eltchaninoff et al., 2010, Zahn et al., 2010, Tamburino et al., 2011, Khawaja et al., 2011, Moat et al., 2011). These registries report the short term outcomes of TAVI using both available valve types (THV and MCV) and all of the potential access routes (transapical, transfemoral and subclavian).

1.4.3.2 PARTNER study

One randomised controlled trial has been published comparing TAVI against the current standard clinical care pathway, either SAVR or standard medical therapy. The Placement of Aortic Transcatheter Valves (PARTNER) trial (Clinical trials.gov number, NCT00530894) is a multi-centre RCT recruiting in the USA, Canada and Germany from 2007-2009. There are 4 arms to this study and

2 separate cohorts: In PARTNER cohort A patients were required to have severe AS with clinical symptoms (NYHA class ≥2) and were classified as high-risk (STS ≥10%) but still suitable for surgical intervention. Cohort B patients had similar entry criteria but were not deemed suitable for surgical intervention, due to a calculated 30 day risk of death ≥50% or a serious irreversible illness. Patient suitability was decided by at least two cardiothoracic surgeons. Exclusion criteria included a bicuspid or non-calcified aortic valve, prior acute myocardial infarct, coronary artery disease requiring revascularisation, a left ventricular ejection fraction <20%, an aortic annulus <18mm or >25mm, severe mitral or aortic regurgitation, severe renal insufficiency and a stroke or transient ischaemic attack in the previous 6 months.

The primary outcomes measure for both cohorts was freedom from death at one year (cohort A) and for the length of the study (cohort B) which is estimated to complete in 2014 (5 year follow-up). Secondary endpoints were measured at 30 days, 6 months and 1 year. They included freedom from major adverse cardiovascular and cerebrovascular events (MACCE), improved valve function or evidence of valve dysfunction, length of hospital stay and functional improvement in NYHA class and quality of life. An important note is that the PARTNER trial used only the Edwards-Sapien THV and the manufacturer Edwards Lifesciences were involved in the funding and design of the study.

Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery (PARTNER cohort B) recruited 358 patients with severe AS, randomised to either TAVI (n=179) or standard medical therapy (n=179) and has to date published its one (Leon et al., 2010) and 2 year outcomes (Makkar et al., 2012b).

Transcatheter versus surgical aortic valve replacement in high risk patients (PARTNER cohort A) recruited 699 patients randomised to either TAVI (n=348) or SAVR (n=351), and has also reported its one (Smith et al., 2011) and 2 year results (Kodali et al., 2012b).

A European (Danish) RCT (NCT01057173) using both the THV and MCV devices is presently recruiting (an estimated 280 individuals) and should complete in 2018 with provisional results predicted to be reported in 2014.

1.4.3.3 Patient population

Baseline characteristics of the registry and PARTNER study populations were similar with a mean age of ≥81 years and approximately 50% female gender. All patients had severe symptomatic AS as defined by the AHA guidelines using TTE Doppler measurements. There were high levels of co-morbid conditions observed in the study populations. These included; prior MI (21%-22%), coronary artery disease (41%-60%), hypertension (60%-75%), previous stroke (7%-10%), Diabetes mellitus (22%-37%) and chronic kidney disease (21%-25%). A significant number of the patients had undergone previous coronary revascularisation by either PCI (28%-34%), CABG (16% -30%). The symptomatic burden was also high with > 75% of patients in either NYHA class III or IV heart failure. The majority of patients had normal or mildly impaired LV function with only 9-14% of the populations having an EF < 30%.

1.4.3.4 Procedural success and complications

The registry and PARTNER procedural success rates were excellent (92.6%-98.7%) with a low rate of conversion to surgery (0.5%-0.8%) (Piazza et al., 2008, Smith et al., 2011). Early complications were principally related to procedural difficulties. Valve embolization (0.6%-1%) and valve-in valve re-implantation (0.5%-2.6%) were uncommon complications of device implantation. A significant proportion of individuals were noted to have some degree of aortic regurgitation (AR) post valve implantation (21-72%). Vascular complications experienced included cardiac tamponade (1.2%-2%) and arterial access dissection or haematoma (1.9%-3.2%). The main risk factor for a vascular complication was the size of the device and arterial access sheath. The Edwards THV and its larger (22-24F) sheath therefore had a greater frequency of vascular problems.

Permanent Pacemaker (PPM) implantation was required in 12%-39% of patients within 30 days of their TAVI procedure, considerably higher than the SAVR complication rate of <10% (Limongelli et al., 2003, Smith et al., 2011). The rate of PPM implantation post-CoreValve is approximately double that following Edwards THV (Zahn et al., 2010, Eltchaninoff et al., 2010). Male sex, greater septal hypertrophy, left axis deviation, right bundle branch block, longer QRS duration and peri-procedural AV block have all been identified as risk factors for the need for permanent pacing. Procedural factors identified were: peri-procedural block, balloon pre-dilatation and the use of the larger Medtronic

CoreValve (29mm) (Khawaja et al., 2011). The likely aetiology of this complication arises secondary to damage to the conduction system of the left ventricle during either valvuloplasty or valve implantation. The left bundle branch sits in the membraneous septum in close proximity to the right and non-coronary leaflets of the aortic valve. In AS leaflet calcification and fusion brings them even closer to the conduction system. Thus during valvuloplasty or valve expansion the thickened valve is compressed against the left bundle branch and the conduction system may become damaged, resulting in an atrio-ventricular block. The higher percentage of PPM post-MCV compared to Edwards THV can be explained by the deployment of its nitinol frame which sits into the left ventricular outflow tract (11.2±4mm), leaving it in direct contact with the inter-ventricular septum and LBB. Thus the potential for peri and post-procedural damage is increased (Khawaja et al., 2011).

Stroke and sub-clinical cerebral infarction are important complications of the TAVI procedure. The UK high-risk TAVI registry reported a stroke risk of 4% at 30 days (Moat et al., 2011). Patients who were randomised to TAVI in the PARTNER B study had an increased likelihood of stroke compared to medical therapy (5% vs. 1.1%), but the composite of death or stroke was still significantly lower in the TAVI group. The PARTNER A study revealed an early increased risk of all neurological events post TAVI compared to SAVR (5.5% vs. 2.4%), but no significant difference in the rate of major stroke. Longer-term follow up has now revealed no difference between the incidence of stroke between TAVI and SAVR at 2 years (Kodali et al., 2012b). The majority of cerebral events diagnosed were ischaemic in origin and are believed to be secondary to emboli from aortic atheroma dislodged during the passage of the bulky delivery apparatus, or degenerative valvular material released during the valvuloplasty and valve deployment. Predictors of cerebral infarcts included previous stroke, increased atherosclerotic burden and the transapical approach (Smith et al., 2011).

1.4.3.5 Patient survival

Early survival is reported as 30 day mortality post TAVI, with late survival data available up to 5 years for registry studies and 2 years from PARTNER (cohort A and B). Early (30 day) mortality rates of approximately 10% (5.4% and 12.7%) are reported from the registry data. The latest survival figures suggest a trend towards a reduction in this mortality to 5%. This improvement is believed to be a consequence of greater procedural experience (the ‘learning curve’), improvements in patient

selection and developments in device technology (Gurvitch et al., 2011, Nuis et al., 2011). Late survival (1 year) ranges from 69% to 85% in the registry data (Thomas et al., 2011, Moat et al., 2011, Tamburino et al., 2011, Kodali et al., 2011). The PARTNER B study found all cause mortality to be similar between TAVI and standard therapy at 30 days (5% vs. 2.8% respectively) but by one-year TAVI was superior (30.7% vs. 50.7%) and was maintained to 2 years (43% vs. 68%). PARTNER A's clinical outcome data (on an intention to treat basis) found no significant difference in all cause mortality between TAVI and SAVR at 30 days (3.4% vs. 6.5%), 1 year (24.2% vs. 26.8%) and 2 years (33.9% vs. 35%). Cardiovascular mortality at the 3 time points was also similar between the groups. TAVI was therefore non-inferior to SAVR on the basis of the studies primary outcome. Longer-term survival data are limited but suggest an expected increase in mortality over time to 50% at 3 years, 58% at 4 years and 65% at 5 years (Kodali et al., 2012b, Toggweiler et al., 2013, Buellesfeld et al., 2011). These survival rates are comparable to the contemporary SAVR data for operations on octogenarians (Vasques et al., 2012, Leontyev et al., 2009, Ashikhmina et al., 2011) and from the randomised PARTNER A cohort (Kodali et al., 2012b). Given the age and co-morbidities of the subject population the mortality observed is not outside of the expected mortality rates of an age matched normal population. Studies suggest that once patients have survived the early-mortality risk that patient death is more frequently non-cardiac or TAVI associated (Buellesfeld et al., 2011, Tamburino et al., 2011).

Predictors of early mortality post TAVI have been identified as predominantly procedural factors; conversion to open heart surgery, cardiac tamponade and vascular access complications (Tamburino et al., 2011). Predictors of late mortality are primarily the pre-procedural patient characteristics or co-morbid risk factors. NYHA functional class, prior stroke, chronic kidney disease and increased mean pressure gradient are all significant independent predictors of mortality (Kodali et al., 2011, Kodali et al., 2012b, Makkar et al., 2012b, Tamburino et al., 2011, Ussia et al., 2012, Moat et al., 2011). Female gender appears to confer a greater cardiovascular risk of death but not all cause mortality (Gotzmann et al., 2012a).

Post-procedural aortic regurgitation (AR) of any kind occurs in up to 58% of cases (Buellesfeld et al., 2011, Unbehaun et al., 2012). Moderate to severe AR (≥ Grade 2) is an important predictor of early

and late mortality (Abdel-Wahab et al., 2011, Gotzmann et al., 2012b, Gotzmann et al., 2012a, Kodali et al., 2012b). The mechanism of AR is believed to be mostly paravalvular, as a consequence of malapposition of the valve to the aortic root due to underestimation of the aortic annulus, extensive valve calcification or poor device placement.

1.4.3.6 Functional change

In an elderly population the functional benefit of TAVI may be more important than greater survival. An improvement in quality of life, functional capacity (NYHA class and 6 minute walk test) have been described post TAVI (Gotzmann et al., 2010, Ussia et al., 2009). In addition, PARTNER demonstrated reduced hospitalisation compared to medical therapy and a shorter hospital stay with greater functional improvement compared to surgery (Smith et al., 2011, Leon et al., 2010).

1.5 Cardiovascular Magnetic Resonance for valvular heart disease

The diagnosis and assessment of valvular heart disease has traditionally been performed using invasive cardiac catheterization and non-invasive echocardiography. Echocardiography in particular remains the dominant force in valvular heart disease management due to its excellent temporal resolution, ready availability and the wealth of historical data. However, the technique is not without its problems. The quality of images is highly dependent upon the acoustic windows available, an issue increasing in size given the obesity epidemic. Difficulties and inaccuracies in quantifying the severity of valve stenosis and in particular absolute regurgitation do occur. Determining the consequences of valvular heart disease also remains problematic. The accurate assessment of left and right ventricular volumes and function are imperative, yet variations in intra and inter-observer variability with echocardiography may limit its sensitivity to small but significant variations.

The technique of CMR imaging has developed extensively over the last 20 years and is now used as standard practice in the assessment of ischaemic heart disease (Bingham and Hachamovitch, 2011, Nagel, 2003, Bekkers et al., 2010, Friedrich et al., 2008), congenital heart disease (Hundley et al., 2010), myocardial disease (Sechtem et al., 2006, Marcus et al., 2010) and imaging of the great vessels. CMR allows non-invasive, non-ionizing imaging of the heart at high levels of temporal and

spatial resolution with an unlimited field of view. Unique information relating to cardiac (myocardial or valvular) anatomy and function can be used to determine the severity and impact of valvular heart disease, thus assisting in the management of these patients.

1.5.1 Principles of magnetic resonance

1.5.1.1 Magnetic fields

The principles of nuclear magnetic resonance underlie magnetic resonance imaging (MRI). Three magnetic fields are generated from three different electromagnetic components: The main *'magnetic coil'* produces a strong constant magnetic field (B_o) in a horizontal direction to the centre of the coil (z axis). The strength of this magnetic field is measured in units of Tesla (T = 20,000 times the earths' magnetic field). Three *'gradient coils'* (inside the main magnet) produce a magnetic field gradient in the same direction as the main magnetic field (B_o). These gradient magnetic fields are measured in units of milliTesla per meter (mT/m). Each gradient coil can be switched on or off altering the strength and direction of the net magnetic field (B_o) in three orthogonal planes depending upon which coil is used. This ability to rapidly change the direction of the electromagnetic field (dB/dt) allows images to be acquired in several orthogonal planes or axes. The third *'radiofrequency (rf) coil'* is integrated inside the main coil and generates a rf magnetic field (B_1). This magnetic field is of low amplitude but oscillates at a resonant (Larmor) frequency measured in megahertz (MHz) at right angles to the B_o (X and Y axes). The rf magnetic field is used to deliver a short rf pulse sequence into the patients tissues.

1.5.1.2 Radiofrequency pulses

Hydrogen is an element which exhibits nuclear magnetic resonance properties and in the form of water is contained in all human tissues. It is made up of a single proton which 'spins' to produce a small magnetic field known as magnetic moments. These magnetic fields are normally randomly orientated, but by applying a magnetic gradient they all align in one direction (that of the magnetic field, B_o). The excess magnetic moments combine to produce a net magnetic field known as *net*

magnetization (M_0). The strength of the net magnetization is proportional to the strength of the underlying magnetic gradient and is in the direction of this field (B_0 or z axis).

The *rf* coil transmits energy in the form of a rf pulse into the tissue hydrogen atoms at the Lamor frequency (ω_o).

Equation 4 Lamor equation

$\omega_o = \gamma \times B_0$

γ = gyromagnetic ratio (42.6 MHz/T)

The *rf* pulse realigns all the magnetic moments (in a process known as coherence), away from its equilibrium at the z axis to a newly directed field in the direction of the x and y axis. As M_0 moves away from its alignment with the B_0 and B_1 fields it starts to rotate around the z axis at the Larmor frequency (precession). Magnetization is now split in to two parts; the z or longitudinal component (M_z) and the xy or transverse component (M_{xy}). The new angle of net magnetization (flip angle) is dependent upon the energy of the rf pulse applied which in turn is dependent upon the length and amplitude of the rf pulse. These pulses are known as excitation pulses. An excitation pulse with a flip angle of 90° (degrees) applies sufficient energy to move net magnetization 90° from the z-axis to the x and y plane (M_{xy}). Net magnetization is now wholly in the in the direction of the transverse component. This is known as a saturation pulse or spin-echo pulse sequence. A smaller flip angle (denoted as α) does not transfer all the net magnetization away from the z axis. Repeated pulse sequences of this type can therefore be used in quick succession and are used in fast imaging sequences known as gradient echo sequences. 180° pulses can also be applied to move the magnetization around 180° from either the xy plane (refocusing pulse) or z plane (inversion pulse). An inversion pulse is frequently used in black blood imaging.

1.5.1.3 T1, T2 and T2 relaxation*

Following a rf pulse, net magnetization immediately attempts to return to its equilibrium. This process is known as relaxation and occurs by two separate actions according to the different components of magnetization, longitudinal (z axis) and transverse (xy) relaxation.

Longitudinal relaxation back toward the z-equilibrium is known as T1 relaxation. This is an exponential recovery with a time constant. The T1 relaxation time constant of a tissue is associated to the rate of energy release from its hydrogen protons. Protons that rotate close to the Larmor frequency (such as fat) have a rapid exchange of energy and the shortest T1 relaxation times. Larger molecules release energy at a slower rate and therefore have longer T1 relaxation times. Additionally, smaller molecules such as water have high levels of molecular motion which is unfavourable for energy transfer and thus have the longest T1 times.

Transverse relaxation is the decay of net transverse magnetization (M_{xy}). This process is known as free induction decay (FID), where protons uniformly aligned following an rf pulse lose coherence and become 'out of phase'. T2 relaxation is the loss of coherence due to the individual protons magnetic field interacting with another proton to change its spin angle resulting in a change in phase direction (dephasing). T2 relaxation is also known as spin-spin relaxation, as small molecules with little spin-spin interaction have long T2 relaxation times (water) compared to the short times of larger static molecules with greater interaction (muscle). Loss of coherence can also occur due to inhomogeneities in the magnetic field (B_0). Variations in the magnetic field result in variations in the protons Larmor frequency and subsequent dephasing. When this is combined with the T2 relaxation the actual FID rate is higher and is known as T2* relaxation.

1.5.1.4 Echoes

The MR signal from FID is generated and detected in the form of an MR echo. Two main types of MR echo exist: Gradient and spin echoes.

1.5.1.4.1 Gradient echoes

Following a 90° rf pulse a magnetic field gradient is applied to dephase the protons in a set direction and reduces the FID to zero. A second magnetic field gradient of equal amplitude but opposite direction results in a re-phasing of the protons and a return of the FID. The MR signal generated from the re-phasing is known as the gradient echo. The echo time (TE) is the time taken from initial rf pulse transverse magnetization to the maximal amplitude of the gradient echo. Altering the echo time

(by applying a more rapid or slower second gradient) can be used to influence the effect of T2* relaxation on the image.

1.5.1.4.2 Spin echoes

Spin echoes use the application of a secondary 180° rf pulse following the initial transverse magnetization 90° rf pulse. This causes the spins dephasing due to field inhomogeneities to refocus (rephase) increasing the amplitude of the FID. The signal generated from the 180° rf pulse is known as the spin echo. As the amplitude of the signal is greater compared to gradient echo, spin echoes produce greater signal quality and are less susceptible to metallic field inhomogeneities

1.5.2 Image acquisition

MR echoes cannot be used in isolation to produce an image. Sequential gradient fields are applied to determine the slice direction, phase encoding direction and frequency encoding direction. Once the slice had been selected the phase encoding gradient shifts the protons in a pre-specified direction. A frequency encoding gradient is then produced at a right angle to the phase encoding direction. Three dimensional imaging becomes possible by using the three gradients in different combinations along the z, x and y axis to produce a transaxial, coronal or sagittal image.

This process is repeated several times to form a pulse sequence. The slice and frequency encoding direction are maintained, but the phase encoding direction is changed in order to alter the phase over time. The MR echoes generated by the frequency encoded gradient therefore vary in amplitude and frequency. The individual frequency and amplitude of each wave is measured to indicate the signal from its original location in a pre-specified field of view. The signal analysis, known as Fourier transformation is dependent upon Nyquist's rule that the sampling frequency should be twice that of the maximum signal frequency.

The time between each repetition of signal echoes is called the repetition time (TR). The spatial resolution of an image (number of pixels) is dependent upon the number of phase encoding steps which in turn relies upon the TR and image acquisition time. Each MR echo signal has its own space or location, known as the *k* space. The spatial location of the *k* space is inversely related to its

frequency, so that higher spatial frequency waves are further away from the centre of *k* space. Gradients of differing length and strength are applied to alter the spatial frequency of a wave and thus sample all areas of the k space from edge to edge (linear order) or from the centre out (centric order). The number of data points acquired are dependent upon the number of phase encoding gradients (x axis) and the number of MR echo signals sampled (y axis). Once all the spatial frequencies have been acquired 2D Fourier transformation converts this into an image space.

1.5.3 Image quality

The quality of a MR image is dependent upon balancing the amount of signal generated to that of the background noise. This relationship is known as the signal to noise ratio (SNR). Several factors influence the SNR: The strength of magnetic field, the receiver coil, the image acquisition parameters and the pulse sequence. Each aspect can be varied in an attempt to improve the SNR. However, improving one factor is almost invariably at the detriment of another.

1.5.3.1 Surface coil

SNR can be improved by the use of a surface coil. This is a small dedicated coil with multiple (normally 5) receiver coils designed to maximize the signal by being closer to the patient and reducing the noise from outside the area of interest. The differently positioned phase array coils also provide spatial distribution information which permits the undersampling of the *k* space to reduce imaging time, in a process known as parallel imaging.

1.5.3.2 Image acquisition parameters

The number of pixels (phase encoding steps) determines the spatial resolution of the image in a set field of view. Increasing the spatial resolution is dependent upon increasing the number of phase encoding repetitions and therefore the image acquisition time. Slice thickness determines the volume of the image (voxel) and therefore the number of protons contributing signal. As spatial resolution increases, voxel volume decreases with a corresponding reduction in protons and signal yet an increase in background noise (decreased SNR).

1.5.3.3 Pulse sequence

The strength of the MR signal from a tissue is influenced by its specific MR characteristics (proton density and relaxation times) and the applied pulse sequence. The recovery of equilibrium (longitudinal magnetization, M_z) depends upon the time given for recovery between pulses (TR), the rate of T1 relaxation and the amount of energy transferred to the transverse component (flip angle). The decay of the transverse magnetization is affected by the rate of T2 and T2* relaxation and the time of signal sampling (TE). For gradient echo a variable flip TR, TE and flip angle can be used to alter the image signal. Spin echo sequences due the 180° refocusing rf pulse are not affected by T2* relaxation nor a variable flip angle. These factors can be changed within a pulse sequence in order to provide different contrast weighting of tissues.

1.5.3.3.1 Long TR Short TE

The long TR allows a full return to equilibrium, where a short TE allows little T2 decay. Therefore all tissues have high signal with little contrast between them. This is useful for anatomical imaging.

1.5.3.3.2 Short TR Short TE

Due to the short TR only tissues with short T1 times recover equilibrium. The effect of T2 relaxation is limited due to the short TE. Therefore images are influenced by the T1 time. This is known as T1 weighted imaging. Signal from fat is high and low from fluid. This produces good signal contrast between tissues.

1.5.3.3.3 Long TR Long TE

The long TR means that most tissues will have recovered equilibrium. The long TE allows greater T2 relaxation, so that the image is dependent upon the T2 and T2* relaxation rates. Fluid has a long T2 relaxation time and therefore appears bright. These sequences are useful for the characterisation of myocardial oedema or haemorrhage (iron loading).

1.5.3.3.4 Short TR Long TE

T1 relaxation has little influence due to the short TR. The long TE also reduces signal secondary to T2 relaxation. This has the effect of reducing the total MR signal and contrast between tissues.

1.5.4 Spin echo and gradient echo imaging

1.5.4.1 Spin echo

As discussed, spin echo pulse sequences use a 90° rf pulse to transfer all magnetization toward the transverse axis and a 180° refocusing pulse to reverse field inhomogeneities. These factors combine to produce high quality images with low susceptibility to magnetic field inhomogeneities. This sequence is known as a black blood sequence, as the blood that was initially magnetized by the excitation pulse has moved out of slice by the time of the 180° refocusing pulse and thus does not contribute towards the MR signal. Black-blood imaging is therefore suited to detailed anatomical assessments. Occasionally a second 180° pulse is used to re-invert magnetization within the slice but leave tissue outside inverted (nulled). The time from inversion pulse to excitation pulse is known as the time from inversion (TI).

1.5.4.2 Gradient echo

The single excitation pulse, low flip angles and short TR of gradient echo pulse sequences make them ideal for rapid imaging. The fast moving blood is therefore visible and this form of imaging is referred to as 'bright blood' imaging. Tissues are frequently saturated (low signal) due to the repeated pulse sequences reducing the time to return to equilibrium. The blood-tissue contrast is therefore good, and combined with the short TR makes this pulse sequence ideal for functional imaging.

1.5.5 Cardiac imaging

The problems and pitfalls of MR imaging are only enhanced in the attempt to image a beating heart. To reduce any motion artefact the imaging time (TR) is kept as short as possible and repeated at identical time points over several cardiac cycles. The ECG R wave is used in order to ensure the timing of the pulse sequence is identical between cardiac cycles. The time from the R wave to the first image acquisition is known as the Trigger delay. This technique can be used to produce both still and moving images.

1.5.5.1 Still imaging

A single line of *k* space data is acquired during each cardiac cycle at the exact same time point as specified by the operator (the trigger delay). This form of imaging is used in:

- Black blood T1 or T2 weighted, spin echo sequences for anatomical assessments.
- Black blood STIR, triple inversion T2w, spin echo sequences to characterise tissues and myocardial oedema.
- Late enhancement, inversion recovery gradient echo sequences for assessment of myocardial scar.

1.5.5.2 Cine imaging

Multiple lines of *k* space data are acquired during each cardiac cycle at different time points (phases). Each phase represents a different image which when reconstructed can be viewed as a movie or cine, permitting functional assessment of the heart. The timing of data acquisition can either be triggered (triggering) after each R wave or be continuous (gating). Data acquired from gating can be used prospectively, where data is given a set time point after each R wave, or retrospectively once all the data has been collected. Retrospective gating is particularly favourable if end-diastolic data is required or if the R-R interval is irregular (arrhythmias).

1.5.5.2.1 Cine gradient echo

Cardiac function is assessed using a bright blood cine gradient echo sequence with retrospective gating. Two different pulse sequences can used:

1. Spoiled Gradient echo (FLASH, T1 FFE): This pulse sequence uses an additional gradient to de-phase any residual transverse magnetization ensuring it does not interfere with the next pulse sequences signal. The imaging is therefore predominantly T1 weighted and relies upon blood movement for contrast between tissues. The greater sensitivity to flow means that this sequence is frequently used in valvular assessments to look for regurgitant or stenotic jets.
2. Steady state free precession (true FISP, bFFE): Three additional gradients are applied to re-phase all the transverse magnetization during each pulse sequence. The transverse magnetization signal following several sequence is increased producing higher signal and providing high quality images with excellent SNR.

1.5.5.2.2 Velocity encoded gradient echo

Spoiled gradient echo can also be utilised to quantify the velocity of blood flow. Unlike static tissues moving blood is not re-phased by the bipolar gradient of the pulse sequence. The blood and tissue therefore have a difference in phase which correlates to the flow velocity of blood in the direction of the applied gradient. As phase changes may be influenced by magnetic field inhomogeneities and flow in more than one direction, two acquisitions are made with separate flow sensitivities to generate a phase map. These phase maps are subtracted to produce a map of phase shifts solely due to velocity changes, a velocity map. The flow sensitivity range or VENC must be set to prevent aliasing where positive velocities are interpreted as negative and vice versa.

1.5.6 Imaging and assessment of the Aortic valve

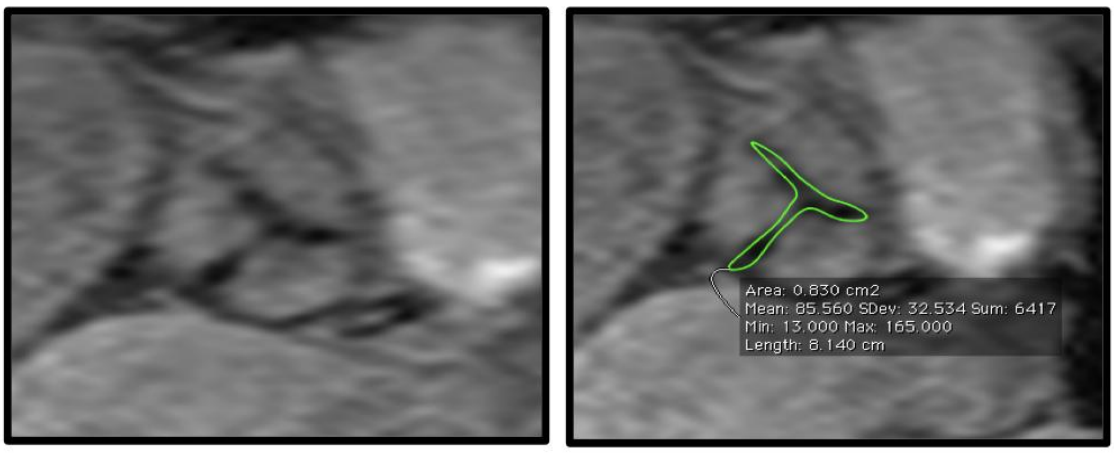
CMR can be utilised to determine the severity of valvular lesions. The severity of AS is assessed and graded using the same classification as TTE. However, CMR does not use the principals of Doppler but makes the use of two distinct techniques; cine functional assessment and phase-contrast imaging.

1.5.6.1 Functional assessment

Direct visualisation of the aortic valve allows the calculation of the AVA by planimetry, Figure 1-3. This technique is useful as it is independent of variations due to flow, which can lead to an under-estimation of valve severity in instances of 'low flow-low gradient AS'. Multi-planar CMR imaging enables the valve and its apparatus to be shown in several orthogonal planes with an unlimited field of view. Two different cine pulse sequences can be used to visualise the valve anatomy: Steady State Free Precession (SSFP) uses multiple phases throughout the cardiac cycle gated from the ECG with a typical repetition time (TR) of 3ms, echo time (TE) of 1.5ms and Temporal Resolution of 25-50ms. This produces a high signal to noise (SNR) ratio with good blood to myocardium contrast. Gradient fast low angle shot (FLASH) sequences differ by using a single shot sequence with a typical TR of 8ms, TE 3.3ms, and Temporal Resolution of 30ms. There are relative advantages and disadvantages to using each sequence. FLASH with its longer TE is subject to spin dephasing artefacts which create a signal void from the stenotic jet, making analysis of the valve margins difficult. SSFP with its

shorter TE is less subject to these dephasing artefacts but is more susceptible to magnetic field inhomogeneities such as valve calcification (Schlosser et al., 2006, Friedrich et al., 2002). CMR planimetry has been compared to TOE (John et al., 2003), TTE (Reant et al., 2006) and cardiac catheterization (Friedrich et al., 2002) with an excellent correlation ($r > 0.8$). CMR is also highly reproducible with estimated intraclass coefficients (ICC) of greater than 0.9 for both intraobserver and interobserver variability (Pouleur et al., 2007, Reant et al., 2006). Whilst CMR planimetry provides better imaging quality compared to echocardiography, it slightly overestimates AVA compared to the Gorlin technique of cardiac catheterisation (Reant et al., 2006). Therefore, recent techniques have concentrated on the estimation of AVA and AS severity by using the technique of phase-contrast MRI.

Figure 1-3 Aortic valve planimetry



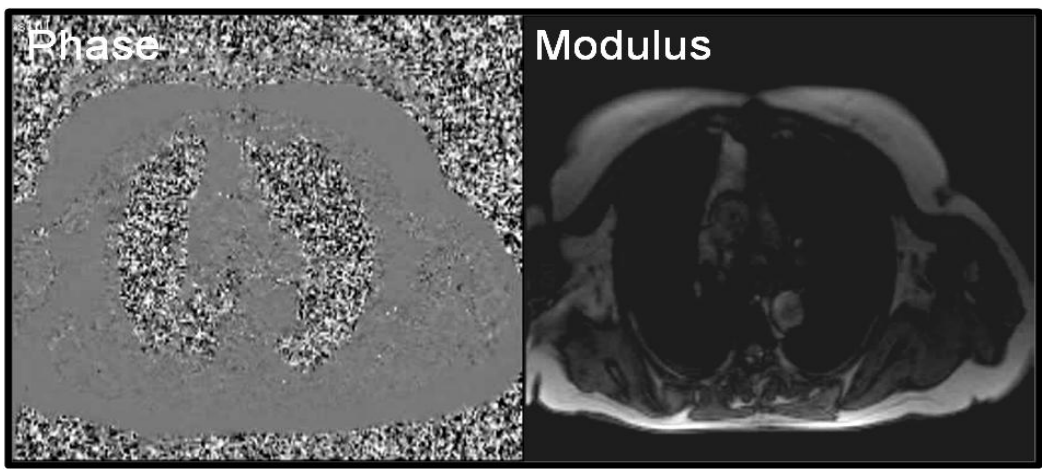
Gradient TFE pulse sequence (4mm slice thickness, 0mm gap, 10 phases. FOV 340, RFOV 60).

1.5.6.2 Phase contrast MRI

Phase contrast pulse sequences (velocity-encoded cine, VENC) can estimate the average flow-velocity of blood in the aorta and use this information to determine the flow-volume of blood. A pulse sequence can detect the phase shift of moving protons by applying a biphasic gradient to them. Stationary protons have no phase shift in a magnetic field, where moving protons have a phase shift that is dependent upon their velocity and distance travelled. The measurement of blood flow velocity can thus be determined by analysing the appropriate region of interest (Lotz et al., 2002). Two images

are produced; a phase contrast and magnitude image, **Figure 1-4**. The phase contrast image displays the velocity map of individual pixels as a greyscale image, with flow towards the phase encoding direction being bright, flow away from the phase encoding direction dark and stationary pixels are grey. The magnitude image is an anatomical bright blood image that allows the delineation of the aortic wall as a region of interest, (ROI),. A contour can then drawn around the vessel in each of its phases, the velocity of each voxel is then measured and averaged over the whole of systole to produce a mean velocity (Cawley et al., 2009). Phase contrast mean velocity measurements correlate well with invasive methods of flow assessment (Evans et al., 1993) and are superior to the non-invasive Doppler ultrasound which tends to overestimate mean flow (Sadek et al., 1996).

Figure 1-4 Phase velocity and modulus maps

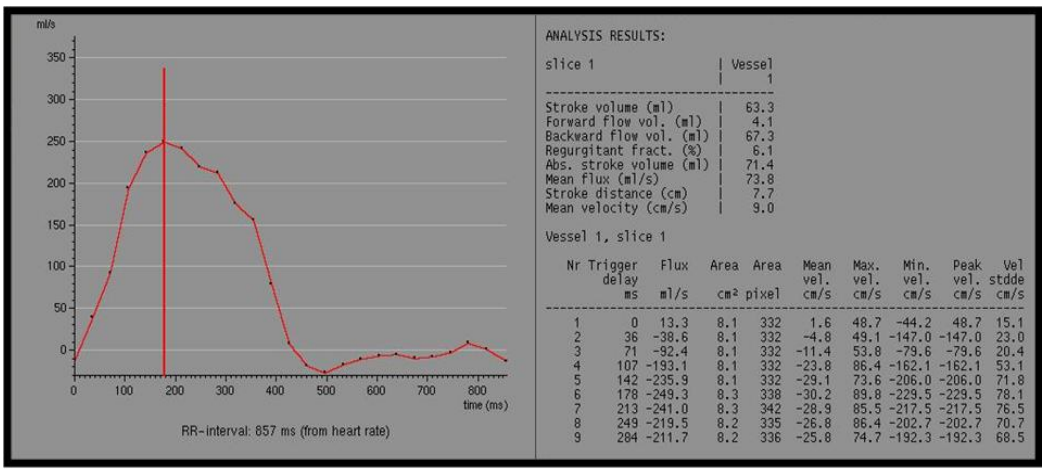


Images can be acquired in either a breath-hold or free breathing technique. Each method uses the cardiac cycle ECG (R wave) to trigger data collection. The breath-holding technique uses prospective gating, in that each R-wave triggers data collection of the subsequent cardiac cycle. Data is used over several cycles to determine the velocity. It does not however acquire data at the end of each cycle (late diastole), as it must wait for the next trigger. The length of acquisition is thus constant, which can be useful if an individual suffers from an irregular heartbeat (arrhythmia) due to this 'arrhythmia rejection window'. A disadvantage of breath-hold images is that any data from late diastole is not acquired. This is a particular problem in valve disease with a regurgitant fraction, as regurgitation

occurs during diastole. Non-breath hold images are attained using retrospective gating of the ECG's R wave. Information is acquired throughout the cardiac cycle and averaged over several cycles for the mean velocity. Any variations in the cardiac cycle are therefore not taken account of and can result in inaccuracies of the final data collected. It does however include diastolic data and is thus useful for any regurgitant blood flow. This technique has been validated for the estimation of AS severity using both VTI measurements and the continuity equation (Pouleur et al., 2007).

Velocity measurements (cm/s) acquired by phase contrast imaging can be multiplied by the aortic area (ROI) to give a flow-volume (ml) measurement, Figure 1-5. Forward and backward flow volumes (ml/heart beat) can be determined by relating the velocity to the timing of the cardiac cycle (systole/diastole). This method of assessment has been used to assess the severity of aortic valve stenosis by Hakki's formula (Puymirat et al., 2010) and regurgitation (regurgitant fraction) (Didier et al., 2000).

Figure 1-5 Flow volume curve



Phase contrast imaging does have several pitfalls and complications which should be accounted for. The encoding velocity (VENC limit) should not be set too high, as this can increase the noise in the velocity image which may affect the accuracy of the peak velocity measurement. Equally it is important not to set the VENC limit below the peak velocity (too low), as this can result in aliasing and an inaccurate velocity estimate. Aliasing occurs when the phase shift is greater than 180°. It can be corrected for in post-processing, but it is simpler to repeat the imaging at a higher VENC (Lotz et al., 2002).

Partial volume averaging may occur, where the peak velocity is underestimated due to an averaging of the vena contracta velocity as its surrounding voxels are included. This is a particular problem if the spatial resolution is too low or the slice thickness to high. Slice thickness should therefore be approximately 4mm (from 8-10mm) in order to reduce the effect of partial volume averaging. A low temporal resolution may also result in the underestimation of flow velocities as a short peak velocity may be missed. Further, the slice position should be perpendicular to the flow (jet) of blood to minimise any inaccuracies (Cawley et al., 2009).

Phase offset errors are background stationary or moving spins, secondary to eddy currents and concomitant (Maxwell) gradients applied from the magnetic field. Small velocity offset errors can result in large flow quantification errors. Post-processing software correction 'background correction', can worsen the phase error as it relies upon uniformity of the gradients (Kilner et al., 2007). In addition each scanner will have its own particular background error (Gatehouse et al., 2010, Rolf et al., 2011). Chernobelsky et al suggested that the technique of 'phantom correction' is the most reliable and effective method of correcting background phase errors (Chernobelsky et al., 2007). Kilner et al have further recommended an acceptable level of error to be less than 0.5% of the velocity encoding limit (Kilner et al., 2007).

1.5.7 Ventricular Function and Volumes

Echocardiography remains the most common non-invasive imaging investigation used to estimate ventricular size and function. It does however depend upon good acoustic windows, clear myocardial definition and certain geometric assumptions. Analysis by M-mode and Simpsons method of discs may result in significant errors estimating cavity size and systolic function. These errors are exaggerated in an abnormally shaped ventricle which is remodelling (Bottini et al., 1995, Semelka et al., 1990a, Teichholz et al., 1976). CMR is a non-invasive, non-ionizing investigation that provides an unlimited field of view combined with high spatial and temporal resolution. It and has thus become the reference standard for the measurement of ventricular volumes, mass, morphology and function.

Cine (bright blood) SSFP imaging with its high signal to noise ratio provides good blood pool to myocardium contrast and excellent image quality. A reproducible LV stack of 10-12 (10mm) short axis cines is acquired, where each image is taken in a single breath hold (Barkhausen et al., 2001). Data acceleration techniques such as parallel imaging can be utilised to improve acquisition time by the theory of spatial undersampling. However, this method may reduce the signal to noise ratio and image quality. Cine images are ECG gated so that each image is the data averaged over several cardiac cycles. Retrospective gating occurs in most instances to ensure full diastolic coverage but prospective gating can be utilised should the ECG R-R interval (rhythm) be irregular.

Several studies have validated the accuracy and reproducibility of left and right ventricular volumes as assessed by MRI. Ex vivo volumetric casts (Longmore et al., 1985) and in vivo stroke volumes (SV) (Kondo et al., 1991) have shown excellent correlation to MR estimates of volumes. Measurements of LV and RV mass have been compared to human and animal autopsy models with high levels of accuracy (Katz et al., 1993). The inter-observer and intra-observer reproducibility of volume and mass measurements using MR is the highest of any imaging modality (Semelka et al., 1990b, Grothues et al., 2004). Furthermore, the high inter-study reproducibility results in small standard deviations (SD) meaning that smaller sample sizes are required for the adequate power design of a study compared to echocardiography (Grothues et al., 2002, Bellenger et al., 2000). CMR is therefore ideally suited to study the serial assessment of a TAVI population, where ventricles are geometrically abnormal and sample sizes are small.

Ventricular function can be described globally or separated into a regional assessment in accordance with the AHA 16 segment model (Duncan et al., 2011). The excellent endocardial and epicardial definition afforded by CMR further permits the assessment of wall thickness and the quantitation of wall dynamics (thickening), (Sheehan et al., 1986). Myocardial tagging is the application of a pre-pulse saturation line (‘tag’) that moves and rotates with the contraction and relaxation of the myocardium. This technique allows the quantitative analysis of endocardial, epicardial and transmural motion, strain and torsion (Reichek, 1999).

1.5.8 Myocardial Fibrosis

Myocardial fibrosis (MF) is recognised in several clinical conditions that are characterised by a dysfunctional ventricle. Myocardial infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy and pressure overloaded ventricles represent different pathological processes that are associated with fibrosis of the failing ventricle. Fibrosis is the deposition of collagen in the myocardial tissue and can take the form of reactive interstitial fibrosis or replacement fibrosis. Replacement fibrosis is the deposition of Type 1 collagen in the place of necrotic myocytes secondary to ischaemic (infarct) or inflammatory (myocarditis) damage. This tends to be focal and irreversible. Reactive fibrosis however involves myofibroblasts depositing collagen in the interstitium (extra-cellular volume, ECV) and is potentially reversible (Mewton et al., 2011). The collagen deposition that occurs with each of these processes results in an increase in the ECV to cardiac myocyte ratio. MF is prevalent in patients with AS, and is believed to be in part a result of activation of the rennin-angiotensin-aldosterone system (Weidemann et al., 2009a, Weber and Brilla, 1991). Focal and diffuse MF alter the T1 relaxation properties of myocardial tissue. CMR can assess the T1 relaxation times and thus MF by two different techniques:

1.5.8.1 Late Gadolinium Enhancement

Late Gadolinium Enhancement (LGE) is an established technique based on the principal that gadolinium accumulates in the increased ECV space of a diseased collagenous myocardium. Gadolinium shortens the T1 relaxation time resulting in late-enhancement of focal fibrotic tissue on a background of normal 'nulled' myocardium. This technique has been validated against the histopathological findings of collagen deposition in animal and human hearts (Weidemann et al., 2009a, Lima et al., 1995, Kim et al., 2000). There is excellent correlation of hyper-enhancement on CMR to the quantity of fibrosis with a high level of sensitivity (Wu et al., 2001). The first studies used a signal intensity threshold of 2 SD above normal myocardium to identify and quantify late gadolinium enhancement (focal fibrosis). This threshold was used predominantly due to the experience in post-myocardial infarction patients. Due to the diffuse nature of fibrosis in non-ischaemic cardiomyopathies accurate quantification of fibrosis poses a greater challenge, particularly in identifying 'normal' nulled myocardium. Several different signal intensity thresholds have been

trialled using 3SD, 5SD and 6SD above the normal myocardium and a full width half maximum (FWHM) technique using visually identifiable focal fibrosis to determine the threshold. Flett et al. compared 7 different quantification techniques in a myocardial infarct and hypertrophic cardiomyopathy cohort and found the FWHM technique to be the most reproducible and accurate (Flett et al., 2011).

1.5.8.2 T1 Mapping

In non-ischaemic cardiomyopathies such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and AS, the type of MF is reactive or diffuse. Whilst LGE-CMR is excellent at defining focal fibrosis it is unable to quantify diffuse fibrosis. In diffuse MF the increased ECV is composed of greater collagen and water content, lengthening the longitudinal relaxation time (T1) of the myocardium. 'T1 mapping' is a developing technique that uses a modified Look-Locker inversion recovery (MOLLI) sequence to detect changes in T1 of the myocardium pre-contrast and following the administration of a gadolinium contrast agent (Iles et al., 2008). This has been compared to a standard Look-Locker sequence with excellent agreement (Nacif et al., 2011). The accuracy and precision of T1 measurements are however dependent upon the number of measurements along the T1-recovery curve, the SNR, the tissue T1 and the method of fitting. Phantom studies have demonstrated small but potentially significant variations may occur with different heart rates, field strengths and MR vendors (Kellman et al., 2013a, Kellman et al., 2013b, Messroghli et al., 2004). Early experience found the MOLLI sequence in practice was further limited by the long breath holds required. A shortened MOLLI (ShMOLLI) sequence was developed to address this issue, reducing the heart rate dependency and breath hold time with good agreement to MOLLI (Piechnik et al., 2010, Messroghli et al., 2006).

T1 mapping has now been used to identify and quantify diffuse MF in several disease groups including post myocardial infarction (Dall'Armellina et al., 2012, Ferreira et al., 2012), AS (Flett et al., 2012), HCM (Flett et al., 2011), DCM (Dass et al., 2012) and amyloid heart disease (Karamitsos et al., 2013). The technique has been validated against histological samples from AS patients (Flett et al., 2012, Bull et al., 2013) and a transplant group (Miller et al., 2013). Normal values and ranges are however yet to be established, and several different methods are currently employed. The T1

calculation is also prone to frequency dependent errors, as the Look Locker correction is based on a spoiled gradient echo sequence despite the fact that T1 mapping uses an SSFP sequence (Kellman et al., 2013b).

1.5.8.2.1 Native T1 mapping

Native T1 mapping measures the T1 values of the myocardium at the level of an individual pixel, prior to the administration of a contrast agent. This removes the need for a defined 'normal' ROI making it more objective, reproducible and thus accurate. Native T1 values have been used in the assessment of myocardial infarction (Ugander et al., 2012a) and diffuse fibrosis with evidence of increased values in normal females and with age (Ugander et al., 2012b, Liu et al., 2013).

1.5.8.2.2 Post contrast T1 mapping

Similar to the principles of LGE, a gadolinium contrast agent is used which small enough to move freely between the vascular (blood) and extracellular compartments but does not enter the cells. Therefore gadolinium accumulates in the expanded ECV and proportionally shortens the T1 relaxation time, which can be detected at a set time point following the administration of contrast agent. Variations in post-contrast T1 can result from differences in drug kinetics, a patients' body composition, renal clearance and haematocrit. The pre and post contrast T1 values can be used to calculate a tissue to blood partition co-efficient, Equation 5 (Flacke et al., 2001). When corrected for the volume of blood contrast distribution (1-haematocrit) this provides a more accurate estimate of ECV (White et al., 2012). The clinical significance of ECV quantification is becoming apparent, as an independent predictor of left ventricular dysfunction (Ugander et al., 2012b), cardiac mortality (Wong et al., 2012) and heart failure (Wong et al., 2013).

Equation 5 tissue to blood partition co-efficient

$$\lambda = \Delta R1_m / \Delta R1_a = (1/T1_{post\ m} - 1/T1_{post\ m}) / (1/T1_{post\ b} - 1/T1_{post\ b})$$

Pre = pre contrast; Post = post contrast; m = myocardial; b = blood

1.6 Aims of the thesis

The trial and registry data have shown TAVI clinical outcomes to be superior to medical therapy and non-inferior to SAVR at two years. TAVI however remains an interventional treatment in its infancy as studies have highlighted several aspects of TAVI that needed greater evidence and further investigation. The Valve Academic Research Consortium (VARC) therefore proposed definitions for clinical endpoints in TAVI in order to aid and improve the quality of research in this area (Leon et al., 2011, Kappetein et al., 2012a). The aim of this thesis was to establish the safety and benefit of the TAVI procedure concentrating on 4 areas of research related to the advancement in knowledge of TAVI as recommended by VARC:

1. Prosthetic valve performance
2. Stroke
3. Quality of life
4. Cost-effectiveness

The following chapters will concentrate on each individual subject of interest with an appropriate introduction, methods, results and discussion sections.

Chapter 2, Prosthetic valve performance: Assessment of valve haemodynamics, reverse ventricular remodelling and myocardial fibrosis following Transcatheter Aortic Valve Implantation compared to Surgical Aortic Valve Replacement.

Chapter 3, Stroke: Diffusion-weighted magnetic resonance imaging determined cerebral embolic infarction following Transcatheter Aortic Valve Implantation: Assessment of predictive risk factors and the relationship to subsequent health status.

Chapter 4, Quality of Life: Serial change in health related quality of life over one year following Transcatheter Aortic Valve Implantation: Predictors of health outcomes.

Chapter 5, Cost-effectiveness: The Cost-Effectiveness of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in patients with severe aortic stenosis at high operative risk.

2 Assessment of Valve Haemodynamics, Reverse Ventricular Remodeling and Myocardial Fibrosis following Transcatheter Aortic Valve Implantation compared to Surgical Aortic Valve Replacement: A Cardiovascular Magnetic Resonance Study.

2.1 Abstract

Background: To compare the effects of TAVI and SAVR on aortic valve haemodynamics, ventricular reverse remodeling and MF by CMR imaging.

Methods: Prospective study of 77 high-risk severe AS patients (age 77±8 years). A 1.5T CMR scan was performed pre-operatively and 6 months post-operatively. Fifty patients (25 TAVI, 25 SAVR) completed both pre and post-operative scans.

Results: Patients were matched for gender and AS severity but not for age (80±6 vs. 73±7yrs, p=0.001) or EuroSCORE (22±14 vs. 7±3, p<0.001). Aortic valve mean pressure gradient decreased to a greater degree post-TAVI compared to SAVR (21±8mmHg vs. 35±13mmHg, p=0.017). Aortic regurgitation (AR) reduced by 8% in both groups, only reaching statistical significance for TAVI (p=0.003). TAVI and SAVR improved (p<0.05) left ventricular (LV) end-systolic volumes (46±18ml/m^2 vs. 41±17ml/m^2; 44±22ml/m^2 vs.32±6ml/m^2) and mass (83±20g/m^2 vs. 65±15g/m^2; 74±11g/m^2 vs. 59±8g/m^2). SAVR reduced end-diastolic volumes (92±19ml/m^2 vs. 74±12ml/m^2, p<0.001) and TAVI increased EF (52±12% vs. 56±10%, p=0.01). MF reduced post-TAVI (10.9±6 % vs. 8.5±5%, p=0.03) but not post-SAVR (4.2±2% vs. 4.1±2%, p=0.98). Myocardial scar (p=0.01) and baseline ventricular volumes (p<0.001) were the major predictors of reverse remodeling.

Conclusions: TAVI was comparable to SAVR at LV reverse remodeling and superior at reducing the valvular pressure gradient and MF. Future work should assess the prognostic importance of reverse remodeling and fibrosis post-TAVI to aid patient selection.

2.2 Introduction

AS is the most common valve disease in the western world (Nkomo et al., 2006), and the onset of symptoms predicts a substantially reduced life expectancy (Otto, 2006). Restricted aortic valve leaflets cause a pressure overloaded LV to compensate by altering its wall geometry in order to maintain wall stress. This hypertrophic remodeling process is pathological, with myocyte degeneration and replacement MF, leading to ventricular dysfunction. Aortic valve replacement removes this aorto-valvular impedance resulting in geometric changes (mass regression, volume reduction and improved function) known as 'reverse remodeling'. This process has been shown to be the essential factor in improving symptoms and prognosis following SAVR (Sandstede et al., 2000, Sandstede et al., 2002, Gaudino, 2004, Lund et al., 1997).

TAVI has emerged as an alternative treatment option for severe AS patients who are unsuitable or too high-risk for SAVR. Randomized trials have shown the two-year mortality following TAVI to be superior to standard medical therapy and non-inferior to SAVR (Makkar et al., 2012a, Smith et al., 2011, Leon et al., 2010, Kodali et al., 2012a), with good registry outcomes at 5 years. TAVI studies have used transthoracic echocardiography (TTE) to demonstrate an improvement in aortic valve haemodynamics and left ventricular function (Clavel et al., 2009). However, TTE has limited reproducibility and relies on mathematical assumptions of left ventricular geometry and cavity size, which may not apply in the remodeled ventricle. In addition, paravalvular aortic regurgitation (AR) is difficult to quantify using TTE yet is common post-TAVI (Smith et al., 2011). Finally, MF has been shown to adversely affect prognosis and functional outcomes following SAVR (Azevedo et al., 2010) but as of yet has not been assessed in a TAVI population.

CMR is the reference standard for the assessment of right and left ventricular mass, volumes and ejection fraction (EF). Aortic stenosis severity can be determined comparably to echocardiography and regurgitant volume assessed with greater precision and reproducibility (Caruthers et al., 2003, Cawley et al., 2013). CMR can also determine the presence, distribution and quantity of MF (Kwong and Farzaneh-Far, 2011).

The primary aim of this study was to use CMR to accurately assess and compare the post-operative changes in aortic valve haemodynamics, reverse ventricular remodeling and MF at 6 months

following TAVI and SAVR. Secondary aims were to identify clinical predictors of impaired 'reverse ventricular remodeling' and to establish the importance of pre-operative myocardial fibrosis on clinical outcomes.

2.3 Methods

2.3.1 Study Population

This study prospectively recruited 77 patients with severe AS who were referred for either TAVI (n=50) or SAVR (n=27) at the University Hospitals of Leeds and Leicester, United Kingdom, between July 2008 and December 2010. Severe AS was classified by TTE as an aortic valve area of $\leq 0.8 cm^2$ or peak velocity >4m/s. Decision for TAVI was taken by a multidisciplinary heart team in accordance with international guidance (Logistic EuroSCORE >20 or inoperable co-morbidities). Higher-risk (higher EuroSCORE) SAVR patients were recruited so that their baseline demographics were more comparable to the TAVI group. Exclusion criteria included any contraindication to CMR. The study was approved by the institutional ethics committee, complied with the Declaration of Helsinki and all patients provided written informed consent.

2.3.2 Transcatheter Aortic Valve Implantation

Patients were screened using echocardiography, CT angiography, invasive coronary angiography and aortography. TAVI was performed using an 18F CoreValve™ Revalving system (CVR, Medtronic, Minneapolis, Minnesota, US). A standard technique was employed for implantation of the CoreValve™ prosthesis. All procedures were performed under general anaesthesia with TEE guidance and aortic balloon valvuloplasty prior to valve deployment.Valve selection (26 or 29mm) depended upon the aortic annulus measurements. Where vascular access was suitable (common femoral artery ≥6mm) a percutaneous femoral route with Prostar® XL (Abbott, Illinois) closure was used. In the presence of significant peripheral vascular disease (PVD) a surgical subclavian artery approach was performed. Following implantation the valve was post-dilated if deemed necessary by the primary

operator. Percutaneous coronary intervention (PCI) of a single vessel was performed in one individual one month preceding TAVI.

2.3.3 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.

2.3.4 CMR Protocol

Identical baseline pre-operative and 6 month post-operative scans were performed on the same 1.5T MRI system (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). An illustration of the full cardiac MR protocol is presented as Figure 2-1. Multi-slice, multi-phase cine imaging was performed using a standard SSFP pulse sequence in the short axis (repetition time [TR] 3 msec, echo time [TE] 1.7 msec, flip angle 60°, reduction factor 2, 10mm slice thickness, 0mm interslice gap, 30 phases, typical FOV 340mm, RFOV 100) to cover the entire left and right ventricles.

Two left ventricular outflow tract SSFP acquisitions in coronal and sagittal-oblique views (5 slices, 6mm slice thickness, 0mm interslice gap, 30 phases, FOV 380mm, RFOV 100mm) were obtained to allow the planning of an aortic valve cine and the aortic valve phase encoded velocity. Aortic valve cines were performed using a spoiled gradient echo pulse sequence (repetition time [TR] 8.5 msec, echo time [TE] 5.1 msec, flip angle 35°, 8 slices, 4mm slice thickness, 0mm interslice gap, FOV 340mm, RFOV 60mm) with retrospective ECG gating over multiple breath holds. Through-plane velocity encoded (VENC) phase contrast imaging was then performed perpendicular to the aortic valve jet at the aortic sinotubular junction (repetition time [TR] 4.3 msec, echo time [TE] 2.6 msec, flip angle 15°, slice thickness 6mm, 40 phases, FOV 340mm), with VENC limit of between 250-500cm/s and retrospective ECG gating. A sagittal-oblique aortic ‘candycane’ image was acquired (SSFP sequence; repetition time [TR] 3 msec, echo time [TE] 1.7 msec, flip angle 60°, reduction factor 2, 5 slices, 6mm slice thickness, 0 mm interslice gap) to enable the planning of an axial SSFP

slice, perpendicular to the ascending and descending aorta at the level of the pulmonary artery bifurcation. Aortic distensibility was calculated using a high temporal resolution single SSFP slice (repetition time [TR] 3 msec, echo time [TE] 1.6 msec, flip angle 60°, 1 slice, 8mm slice thickness, 50 phases, FOV 320mm, RFOV 100mm). Through-plane velocity encoded phase contrast imaging (repetition time [TR] 16.8 msec, echo time [TE] 2.7 msec, flip angle 40°, slice thickness 6mm, 50 phases, FOV 340mm, RFOV 70mm, VENC limit 250cm/s) was then performed in an identical image position in order to acquire the ascending and descending thoracic aortic blood flow velocity for calculation of aortic arch pulse wave velocity.

Myocardial tagging was conducted on three separate slices (apical, mid and base) planned from a '3 of 5'. Five slices are planned in systole where the first and last slices are at the base and apical tip respectively. These are then reduced to 3 slices with an equal distance factor (Messroghli et al., 2005). The tagging sequence used was CSPAMM (repetition time [TR] 30 msec, echo time [TE] 6 msec, flip angle 25°, slice thickness 10mm, FOV 300mm, RFOV 75mm).

LGE imaging (10-12 short axis slices, 10mm thickness, matrix 240x240, typical FOV 340mm, RFOV 100mm) was performed following a Look-Locker sequence (inversion time scout, Single mid-ventricular slice, 11mm thickness, FOV 390mm, RFOV 95mm), 10 minutes after the administration of 0.2mmol/kg of Gadoteric acid (Dotarem, Guerbet, SA, Villepinte) or Gadolinium-DTPA (Magnevist, Schering, Germany). An identical contrast agent was used at both study time-points.

Figure 2-1 Cardiac MR protocol

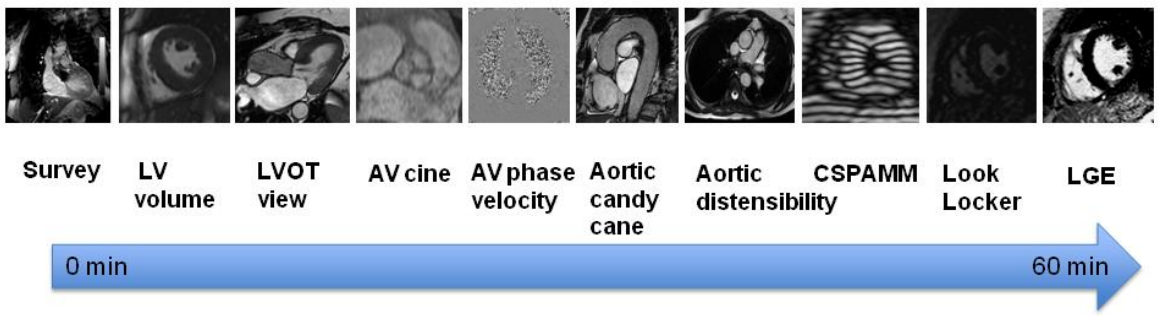
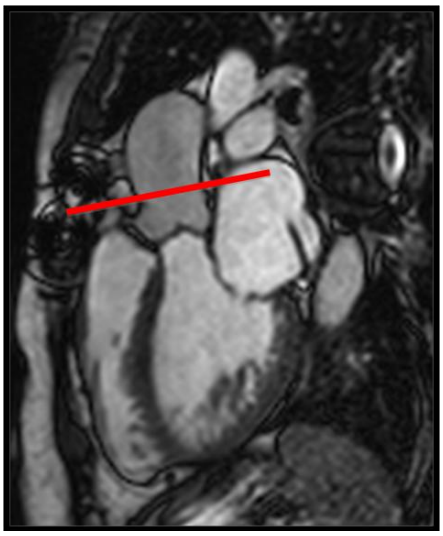


Figure 2-2 Aortic flow planning



2.3.5 CMR Analysis

Endocardial and epicardial borders were manually contoured at end-diastole and end-systole to allow the calculation of ventricular volumes (summation of discs methodology) and mass (epicardial volume - endocardial volume multiplied by myocardial density ($1.05 g/cm^3$)); values were indexed to BSA. Structural remodeling was defined by LV mass/end diastolic volume ratio as previously described (Gaasch and Zile, 2011). A reference point was placed at the inferior right ventricular insertion for automatic segmentation of the LV, enabling regional geometric analysis according to the AHA 16 segment model, Figure 2-3. End-diastolic (EDWT) and end-systolic (ESWT) wall thickness were used to calculate systolic wall thickening (SWT% = (ESWT-EDWT)/EDWT * 100). Wall motion (mm) was calculated as the radial displacement of the mid-ventricular marker. Aortic valve area (AVA) was measured from a cine image (gradient TFE pulse sequence, 4mm thickness, FOV 340mm) by manual planimetry of the smallest orifice at the time of maximal opening in early systole. Aortic flow was quantified using cross-sectional phase contrast images with contouring of the aortic lumen (Figure 2-4) to provide a peak forward flow velocity (m/s), forward flow volume (ml), backward flow volume (ml) for the calculation of trans-valvular pressure gradient (Bernoulli equation) and regurgitant fraction (%). Mitral regurgitant fraction (%) was calculated as (LV stroke volume–aortic stroke volume)/LV stroke volume * 100.

Focal MF and scarring (secondary to infarction) were differentiated then reported qualitatively as either present or absent. Quantitative assessment was performed by semi-automated signal intensity analysis according to the FWHM technique. All analyses were performed using QMass or QFlow (V7.2, Medis, Leiden, The Netherlands) by two experienced observers, blinded to the clinical details.

Figure 2-3 Myocardial wall contouring

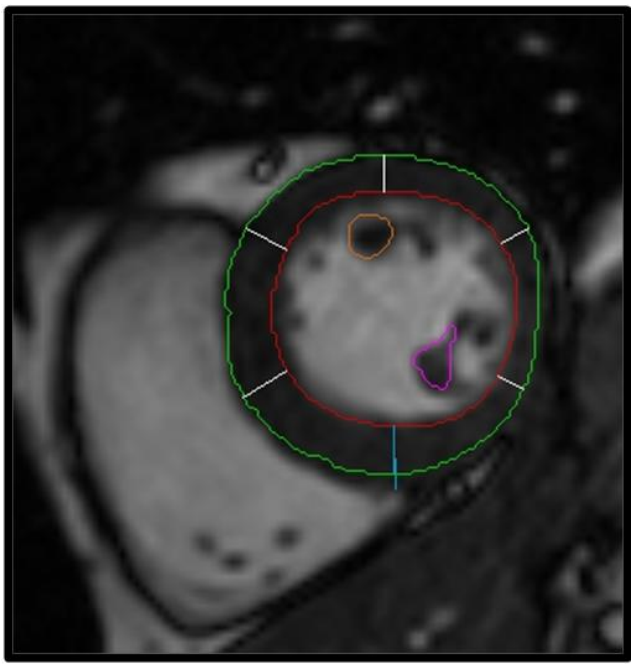
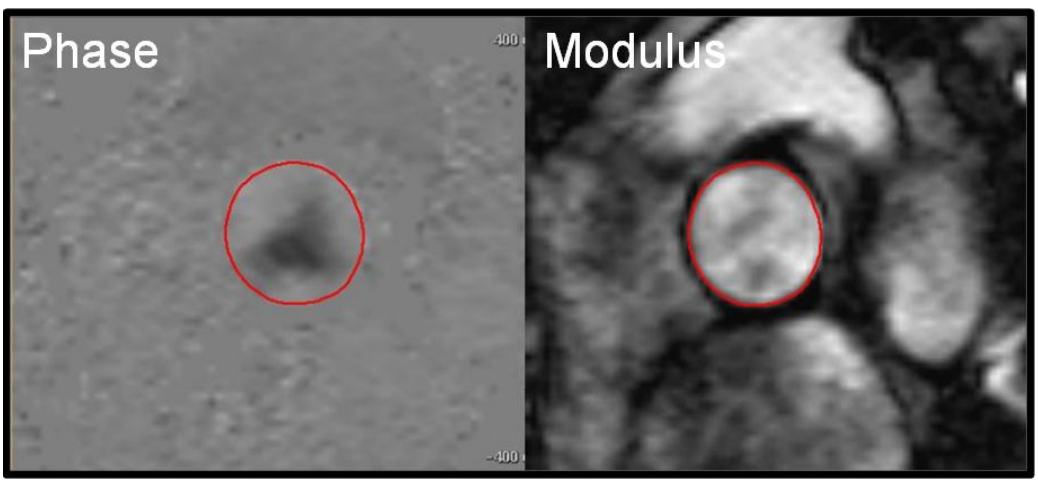


Figure 2-4 Aortic valve flow quantification



A ROI is contoured around the aorta using the modulus image through each of the phases

2.3.6 Sample Size and Statistical Analysis

Based on published data (Bellenger et al., 2000), 20 patients per group were required to detect a 10ml change in LVEDV or 10g difference in LV mass regression between the two treatments (90% power and an alpha error of 0.05); 30 per group would be sufficient to detect a clinically meaningful 10% absolute difference in aortic peak forward flow velocity or regurgitant fraction (85% power and an alpha error of 0.05). Data are presented as mean ± SD (continuous) or median ± Interquartile range (IQR). Normality was determined by Shapiro-Wilks test. Frequencies are reported as number (%). The Student t-test and Wilcoxon signed rank test were used for continuous variables and chi-squared or Fisher's exact test for categorical comparisons. Changes over time were assessed for differences between the treatment groups and clinical variables by 2-way repeated measures ANOVA. Predictors of functional change were calculated by a stepwise multiple linear regression model with baseline measurements entered as covariate factors. Variables with a univariate $P<0.1$ were entered into the multivariable analysis. Intraobserver reliability was calculated using a one-way two measures intraclass correlation co-efficient. All statistical analyses were performed using the PASW software package (version 17.0 SPSS, IBM, Chicago, Il, US) with a two-sided significance level of $p<0.05$ considered statistically significant.

2.4 Results

Fifty patients (25 TAVI and 25 SAVR) completed both the pre-operative (TAVI group, median 1 day (IQR 1-1); SAVR group median 32 days (IQR 10-62)) and 6-month post-operative scans (TAVI group, median 182 days (IQR 176-184); SAVR group median 180 days (IQR 179-184)). Reasons for non-completion of the CMR protocol were varied and are depicted in Figure 2-5 Patient recruitment pathway. The procedural details of both SAVR and TAVI techniques are reported as Table 2-1. The baseline characteristics of the final study population are reported in Table 2-2 Patient and echocardiographic characteristics. The TAVI group were older but comparable in terms of gender and body mass index to the SAVR group. Co-morbidities were equally prevalent in the two groups, except for a greater frequency of atrial fibrillation, coronary and peripheral artery disease in the TAVI group. Procedural success was 100% for both TAVI and SAVR. There were no reported major adverse

cardiac events. Stroke occurred in 1 (4%) patient from each group. The SAVR group experienced a greater number of peri-operative complications (hemorrhage 1 (4%), transfusion 3 (12%), acute kidney injury 1 (4%) and significant pericardial effusion 1 (4%)) compared to no events in the TAVI group during the study period.

The data presented in this thesis include the left and right ventricular function, aortic and mitral valvular function and the myocardial fibrosis results. The additional data acquired as part of the cardiac MRI protocol (tagging, aortic distensibility and pulse wave velocity) will not be reported as further data are being collected for future analysis and presentation.

Figure 2-5 Patient recruitment pathway

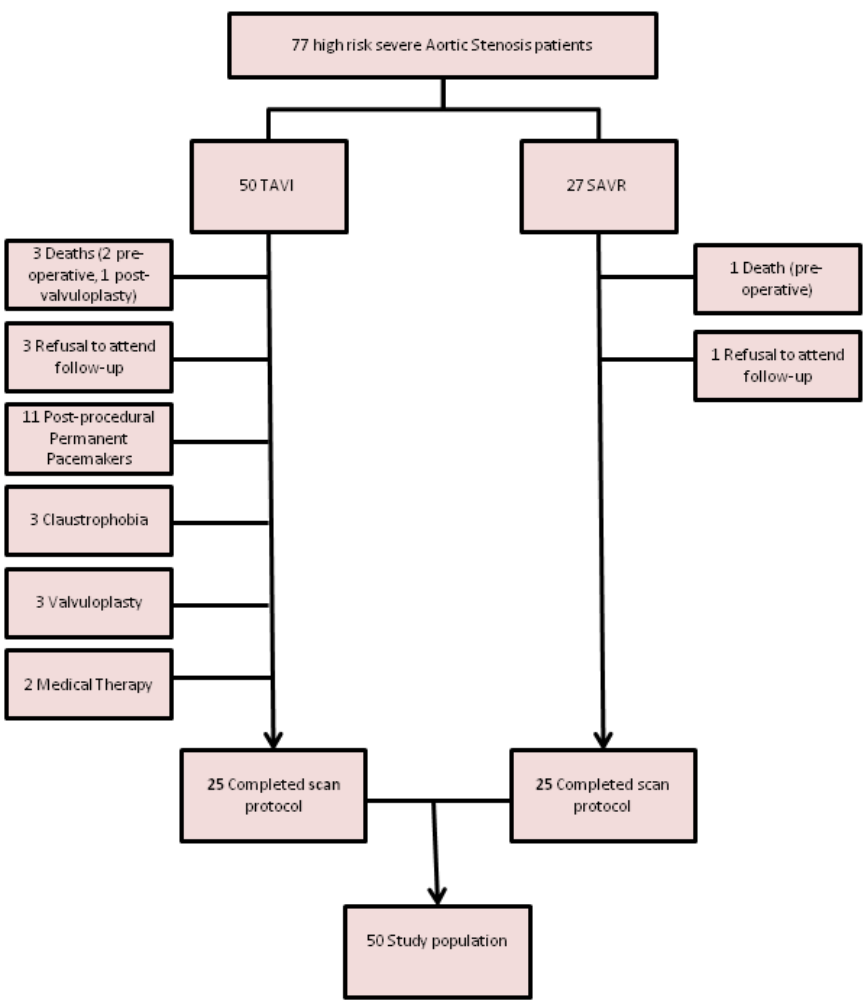


Table 2-1 TAVI and SAVR procedural details

		TAVI (n=25)		SAVR (n=25)
Valve type		**CoreValve**	**Bioprosthetic**	**Mechanical**
		25 (100)	24 (96)	1 (4)
Valve size (mm)				
18		-	1 (4)	-
19		-	2 (8)	-
20		-	1 (4)	-
21		-	7 (28)	-
23		-	10 (40)	1 (4)
25		-	2 (8)	-
26		5 (20)	1 (4)	-
27		-	-	-
29		20 (80)	-	-
Procedure time (min)	**Catheterisation**	72 ±37	**Bypass**	83 ±5
	Fluoroscopy	24 ±8	**Cross Clamp**	61 ±17
Revascularization*	**PCI**	1 (4)	**CABG**	3 (12)

Values are mean ± SD or n (%). TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement; PCI = percutaneous intervention; CABG = coronary artery bypass grafting.

* Prior to or during valve replacement; no patient underwent subsequent revascularisation during the study period.

Table 2-2 Patient and echocardiographic characteristics

Characteristics	**Total (n=50)**	**TAVI (n=25)**	**SAVR (n=25)**	***P* value***
Age	77±8	80±6	73±7	0.001
Male gender, n (%)	31 (62)	14 (56)	17 (68)	0.56
Body Mass Index (kg/m^2)	27±4	27±3	27±5	0.77
Body Surface Area (m^2)	1.86±0.2	1.84±0.2	1.89±2	0.33
Systolic Blood Pressure (SBP, mmHg)	139±24	136±28	142±20	0.48
Diastolic Blood Pressure (DBP, mmHg)	73±11	67±10	77±9	0.002
Valvuloarterial impedance (Z_{va})	4.0±1	3.98±1	4.01±1	0.94
EuroSCORE (%)	16±15	22±14	7±3	<0.001
CV History				
NYHA Class	2.38±0.7	2.48±0.7	2.28±7	0.30
Coronary artery disease (%DS)				0.004
< 50%	29 (58)	9 (36)	20 (80)	
50-70%	8 (16)	5 (20)	3 (12)	
>70%	13 (26)	11 (44)	2 (8)	
Prior PCI, n (%)	5 (10)	4 (16)	1 (4)	0.17
Prior CABG, n (%)	9 (18)	8 (32)	1 (4)	0.01
Prior MI, n (%)	8 (16)	5 (20)	3 (12)	0.70
Co-morbidities				
Hypertension, n (%)	35 (70)	15 (60)	20 (80)	0.22
Hypercholesterolemia, n (%)	26 (52)	16 (64)	10 (40)	0.16
Diabetes, n (%)	13 (26)	7 (28)	6 (24)	0.75
CKD, n (%)	2 (4)	2 (8)	0 (0)	0.49
Atrial Fibrillation, n (%)	7 (14)	6 (24)	1 (4)	0.04
Previous Stroke, n (%)	6 (12)	4 (16)	2 (8)	0.39
Peripheral vascular disease, n (%)	7 (14)	6 (24)	1 (4)	0.04
COPD, n (%)	7 (14)	5 (20)	2 (8)	0.23

Echocardiographic data

AVA (cm^2)	0.62±0.3	0.58±0.2	0.68±0.4	0.24
MPG (mmHg)	51 (41-61)	57±22	47±13	0.05
LV Ejection Fraction, n (%)				
Good (>50%)	34 (68)	15 (60)	19 (76)	0.48
Fair (30-50%)	11 (22)	7 (28)	4 (16)	
Poor (<30%)	5 (10)	3 (12)	2 (8)	

Values are mean ± SD or n (%).* *P*-value for comparison between procedure types. Zva = Valvuloarterial impedance (systolic arterial pressure + mean transvalvular gradient / stroke volume index); NYHA = New York Heart Association; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; MI = myocardial Infarct; CKD = Chronic kidney disease (eGFR<30); COPD = chronic obstructive pulmonary disease; AVA = aortic valve area; MPG = mean pressure gradient.

2.4.1 Aortic and mitral valve haemodynamics

The severity of pre-operative aortic valve stenosis was similar between the TAVI and SAVR groups. Post-operatively the trans-valvular pressure gradient at 6 months was significantly lower in both groups; compared to SAVR the TAVI group had a significantly greater reduction in their pressure gradient. The baseline AR fraction (%) was similar between the groups. Valve replacement resulted in an absolute 8% reduction of AR following both procedures, reaching statistical significance in the TAVI (p=0.003) but not in the SAVR group (p=0.09). ANOVA comparison of the two techniques showed no difference in the efficacy of the two procedures to reduce AR.

Mitral regurgitation (MR) pre-operatively was greater in the TAVI (mild) compared to the SAVR (trivial) group. At follow-up, mitral regurgitant fraction (%) had significantly reduced post-TAVI and remained unaltered post-SAVR, Table 2-3.

Table 2-3 Reverse remodelling, valve haemodynamics and myocardial fibrosis.

	TAVI		SAVR		*ANOVA*
	Baseline	**6 Months**	**Baseline**	**6 Months**	**P- value**
Left Ventricle					
LVEDVI (ml/m^2)	94±18	90±20	92±19	74±12 [b]	0.04
LVESVI (ml/m^2)	46±18	41±17 [a]	44±22	32±6 [a]	0.19
LVSVI (ml/m^2)	48±10	50±10	49±8	42±7 [a]	0.14
LVEF (%)	52±12	56±10 [a]	55±11	57±8	0.57
LVM (g)	153±48	120±38 [c]	143±57	114±42 [c]	0.53
LVMI (g/m^2)	83±20	65±17 [b]	74±11	59±8 [b]	0.35
LVM/LVEDV (g/ml)	0.88±0.2	0.73±0.2 [c]	0.80±0.1	0.81±0.2	0.001
Right Ventricle					
RVEDVI (ml/m^2)	77±19	74±13	78±14	76±17	0.60
RVESVI (ml/m^2)	38±13	35±10 [a]	31±7	34±10	0.80
RVSVI (ml/m^2)	39±9	39±9	47±11	41±14	0.37
RVEF (%)	51±9	53±10	60±8	54±11 [a]	0.63
RVMI (g/m^2)	19±4	16±3 [b]	18±4	17±4	0.17
Aortic Valve					
Mean PG (mmHg)	58 (43-73)	21±8 [c]	51 (37-66)	35±13 [b]	0.017
AR Fraction (%)	16±11	8±6 [a]	18±7	10±11	0.46
Mitral Valve					
MR Fraction (%)	20±16	14±23	2±8	2±6	0.007
Late gadolinium enhancement					
Focal MF					
Mass (g)	14.1±8	8.6±5 [c]	5.9±3	5.1±3	0.005

Percentage myocardium (%)	10.9±6	8.5±5 [a]	4.2±2	4.1±2	0.02
Myocardial infarction					
Mass (g)	20.6±12	13.8±11 [a]	22.7	18.0	0.80
Percentage myocardium (%)	15.6±10	11.2±9	10.0	10.0	0.12

Values are mean ± SD or median (inter-quartile range).

ANOVA repeated measure overtime with procedure as covariate. Paired *t*-test vs. Baseline: [a] $P<0.05$, [b] $P<0.01$, [c] $P<0.001$.

LV = left ventricle; RV = right ventricle; EDVI = end diastolic volume indexed to body surface area; ESVI = end systolic volume indexed; SVI = stroke volume indexed; EF = ejection fraction; LVM = left ventricular mass; Mean PG = peak pressure gradient; AR = aortic regurgitation; MR = mitral regurgitation

2.4.2 Left ventricular reverse remodelling

Results of the baseline and follow-up CMR scans are shown in Table 2-3. No difference existed between the groups pre-operative indexed measurements of end-diastolic volume (EDVI), end-systolic volume (ESVI), stroke volume (SVI), mass (LVMI), mass to volume ratio (LVM/LVEDV) and EF. Post-operatively, the TAVI group significantly decreased their ESVI, LVMI, LVM/LVEDV ratio and increased their EF. EDVI had reduced and SVI increased but did not reach statistical significance. The SAVR group experienced significant reductions in EDVI, ESVI and LVMI, post-operative SVI decreased and no significant change occurred in EF or LVM/LVEDV ratio. ANOVA analysis showed the greater reduction in EDVI post-SAVR compared to post-TAVI was statistically significant, yet TAVI appeared superior at reversing the structural LV remodeling. Intraobserver variability for left ventricular measurements are reported in Table 2-4. The coefficient of variation was 0.28 ±0.1 (range 0.21-0.55). ESV had a lower ICC and greater variability but all measurements showed significant correlation.

Table 2-4 Intraobserver variability

	Analysis 1 Mean ± SD	Analysis 2 Mean ± SD	Correlation coefficient	Intraclass correlation coefficient	Variability (1-ICC)	p value
EDV (ml)	192 ± 40	185 ± 45	0.99	0.96	0.04	<0.001
ESV (ml)	96 ± 32	78 ± 43	0.74	0.65	0.35	0.005
SV (ml)	96 ± 27	99 ± 26	0.95	0.91	0.09	<0.001
EF (%)	51 ± 12	54 ± 11	0.90	0.86	0.14	<0.001
LVM (g)	171 ± 41	161 ± 41	0.96	0.93	0.07	<0.001

ICC = Intraclass correlation coefficient

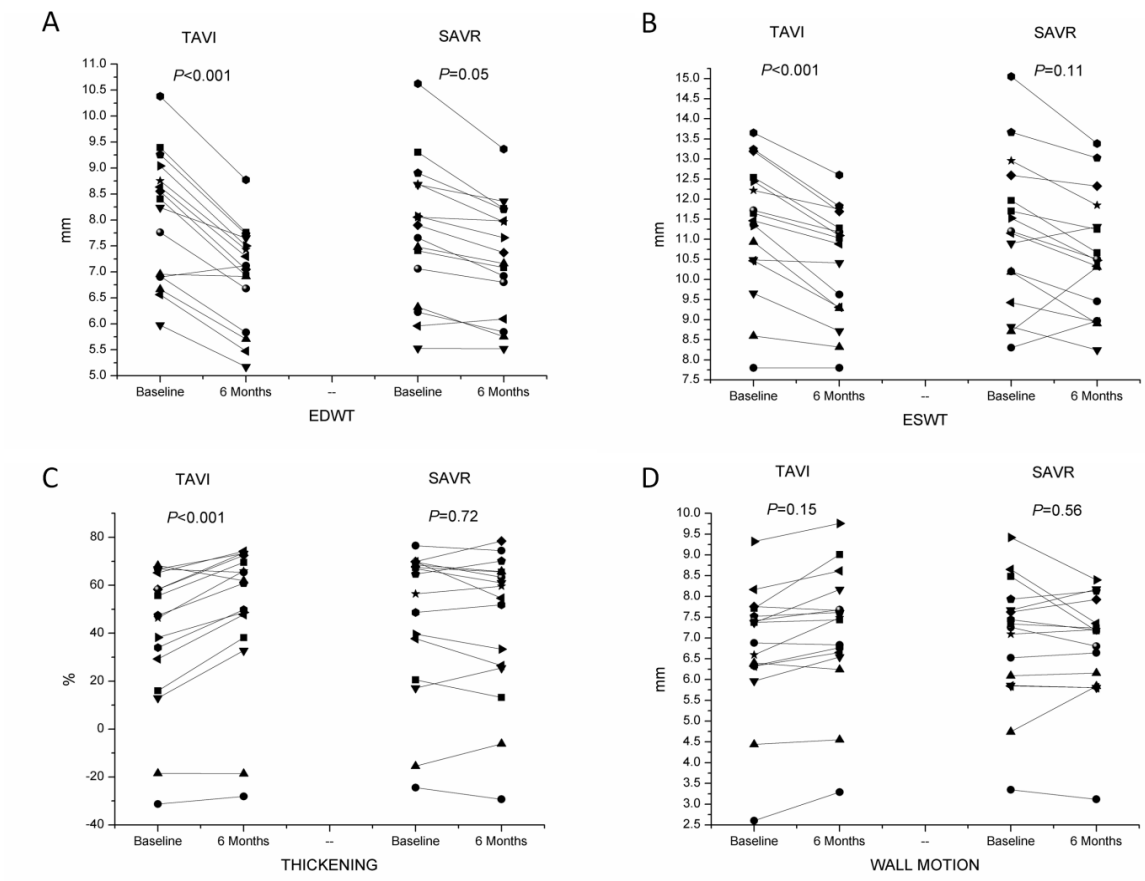
2.4.3 Left Ventricular wall geometry

The study populations baseline LV wall measurements were typical of the concentric hypertrophy that occurs in AS. No difference existed between the TAVI and SAVR groups wall thickness, thickening or wall motion: EDWT (p=0.64), ESWT (p=0.82), wall thickening (p=0.13) and wall motion (p=0.75). Post-operative changes are represented on a segmental level in Figure 2-6 LV wall geometric changes post-TAVI and SAVR. EDWT reduced significantly (p<0.05) in 13/16 (81%) segments post-TAVI and 5/16 (31%) segments post-SAVR group. ESWT reduced significantly in 9/16 (56%) segments post-TAVI compared to 5/16 (31%) post-SAVR. Wall thickening improved in 10/16 segments (63%) post-TAVI but failed to improve significantly in any segment post-SAVR. Wall motion post-TAVI and SAVR significantly improved in only 2/16 (13%) and 4/16 (26%) segments respectively. Global EDWT and ESWT reduced significantly from baseline to 6 months post-TAVI (7.9±2 vs. 6.8±2mm, p<0.001 and 11.4±3 vs. 10.3±3 mm, p<0.001 respectively), but not post-SAVR (7.7±2 vs. 7.3±2 mm, p=0.05 and 11.1±3 vs. 10.7±3 mm, p=0.11 respectively). LV wall thickening

also improved significantly post-TAVI (38.8±13 vs. 50.5±13%, p<0.001), but reduced post-SAVR (46±17 vs. 44±13, p=0.72). Wall motion did not change significantly in either group.

MF was assessed for a relationship to LV wall geometry and post-operative change. The amount (%) of scar at baseline had no relationship to EDWT or ESWT but was inversely associated with the wall thickening (β -0.74, p=0.001) and wall motion (β -0.52, p=0.037) of each segment. Increased baseline MF by LGE predicted reduced post-operative improvement of EDWT (β -0.50, p=0.047), ESWT (β –0.34, p=<0.001) and wall motion (β -0.14, p=0.005). Wall thickening was not significantly affected (β -0.28, p=0.30).

Figure 2-6 LV wall geometric changes post-TAVI and SAVR



The p values represent the difference in global change, where individual segmental changes (AHA 16-segment model) are represented by lines.

2.4.4 Right ventricular reverse remodelling

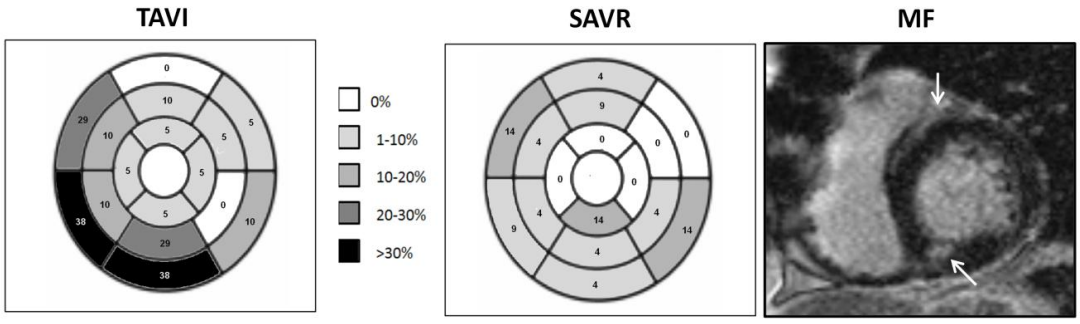
Baseline right ventricular (RV) volumes and mass were similar between the groups Table 2-3. Post-operatively, TAVI resulted in a significant decrease in RV ESVI, RVM and a trend towards an increase in RVEF (p=0.07). SAVR resulted in non-significant reductions in EDVI, RVMI, an increase in ESVI (p=0.09), and an overall significant reduction in RVEF (p=0.04) at 6 months.

2.4.5 Myocardial fibrosis and infarction

MF was assessed by LGE in 47 patients (3 TAVI patients were not given contrast agent due to severe chronic kidney disease). Pre-operative MF was detected in 25 (53%) patients; 13 (59%) TAVI and 12 (48%) SAVR (p=0.38). Fibrosis was predominantly distributed in the basal region and the septal segments for both groups, Figure 2-7 Distribution and frequency (%) of focal myocardial fibrosis (MF). The MF percentage of myocardial mass was greater in the TAVI group compared to the SAVR group (10.9±6 vs. 4.2±2%, p=0.003) at baseline. The severity of AS (aortic valve area and pressure gradient) had no relationship to the amount of MF, but increased Z_{va} was associated with greater mass (g) of MF (β6.4, p=0.019). Post-operatively, MF decreased post-TAVI (10.9±6 % vs. 8.5±5%, p=0.03) but not post-SAVR (4.2±2% vs. 4.1±2%, p=0.98), Table 2-4.

Sub-endocardial LGE consistent with previous MI (scar) was observed in 5 TAVI patients compared 1 SAVR at baseline (p<0.001). Myocardial scar (g) appeared to reduce following TAVI, but the actual scar percentage did not decrease. Post-SAVR, scar mass (g) and percentage showed no difference from baseline, Table 2-3. New post-operative sub-endocardial infarction was evident in 6 individuals (1 TAVI and 5 SAVR, p=0.11). No variable (including procedure type, p=0.09) increased the risk of new post-operative myocardial infarction.

Figure 2-7 Distribution and frequency (%) of focal myocardial fibrosis (MF)



Represented as a 16 segment AHA model. MF was greatest in the basal and septal regions and was significantly higher in the TAVI group. A typical example of MF (as highlighted by the white arrows) is shown on a single mid-ventricular LGE image.

2.4.6 Predictors of left ventricular reverse remodeling

Clinical variables including patient demographics, co-morbidities and pre-operative cardiac measurements were analysed to determine predictors of reverse remodeling, Table 2-5 Regression analysis for the prediction of left ventricular reverse remodelling. Worse individual baseline LV parameters (EDVI, ESVI, EF and LVMI) were independent predictors of reduced reverse remodeling following valve replacement. MF (mass and %) at baseline had no association to the degree of subsequent reverse remodeling, but increased myocardial scar (%) did, resulting in higher EDVI, ESVI and reduced EF post-operatively. TAVI procedure, aortic regurgitation, mean pressure gradient and peripheral vascular disease were also predictors of adverse reverse remodeling, Table 2-5 Regression analysis for the prediction of left ventricular reverse remodelling.

Table 2-5 Regression analysis for the prediction of left ventricular reverse remodelling

Variables	Univariate analysis				Multivariable analysis			
	B Coefficient ±SD	R^2	95% CI	*P*-value	B Coefficient ±SD	*T*	95% CI	*P*-value
EDVI (ml/m^2)								
EDVI	0.57±0.12	0.32	0.33-0.81	<0.001	0.53±0.1	4.56	0.29-0.76	<0.001
TAVI procedure	15.5±3.8	0.50	7.9-23.1	<0.001	10.43±3.7	2.78	2.8-18	0.008
CAD	11.5±4.3	0.42	3.0-20.1	0.009	1.87±4.1	0.45	-6.5-10.2	0.65
Hypercholesterolaemia	11.9±4.1	0.43	3.7-20.2	0.005	6.41±3.7	1.73	-1.1-13.9	0.09
PVD	14.4±6.2	0.39	1.8-26.9	0.03	6.31±4.9	1.28	-3.6-16.3	0.20
AR (%)	0.34±0.19	0.38	0.39-0.71	0.08	0.3±0.1	2.18	0.02-0.57	0.04
Scar (%)	2.01±0.34	0.68	1.31-2.70	<0.001	1.25±0.3	3.79	0.58-1.91	0.001
ESVI (ml/m^2)								
ESVI	0.44±0.08	0.63	0.28-0.59	<0.001	0.21±0.06	3.20	0.07-0.34	0.003
TAVI procedure	8.12±2.8	0.49	2.4-13.8	0.006	3.50±2.5	1.37	-1.6-8.6	0.17
CAD	5.23±3.1	0.44	-0.97-11.4	0.09	1.66±2.6	0.65	-3.5-6.8	0.52
AF	8.97±4.3	0.45	0.25-17.7	0.04	5.29±3.3	1.59	-1.4-11.9	0.12
PVD	10.6±4.2	0.47	2.1-19.2	0.02	7.05±3.3	2.12	0.35-13.7	0.04
Scar (%)	1.61±0.3	0.71	1.0-2.20	<0.001	1.30±0.2	5.43	0.81-1.78	<0.001
EF (%)								
EF	0.49±0.8	0.66	0.33-0.65	<0.001	0.51±0.08	6.78	0.36-0.66	<0.001
MPG	0.14±0.05	0.53	0.05-0.23	0.005	0.14±0.05	2.98	0.05-0.23	0.005

LVMI (g/m^2)								
LVMI	0.64±0.07	0.67	0.51-0.77	<0.001	0.69±0.07	9.88	0.55-0.83	<0.001
NYHA	4.66±2.5	0.74	0.48-9.81	0.07	4.3±2.5	1.74	-0.73-9.34	0.09
CVA	3.77±2.2	0.69	-0.71-8.24	0.09	3.66±2.2	1.69	-0.72-8.05	0.1

[a] Individual variables with a significance level of $P<0.1$ were entered in to the multivariable model. Each parameter of change had a separate multiple regression analysis performed.

EDVI = end diastolic volume indexed to body surface area; ESVI = end systolic volume indexed; SVI = stroke volume indexed; EF = ejection fraction; LVM = left ventricular mass; LVEF = left ventricular ejection fraction; MPG = mean pressure gradient; CAD = coronary artery disease; CVA = cerebrovascular accident; PVD = peripheral vascular disease; AR = aortic regurgitation; MF = myocardial fibrosis; NYHA = New York Health Association;

2.5 Discussion

This study is the first using the reference standard of CMR to show that in an older, higher risk AS population, TAVI when compared to SAVR resulted in similar levels of overall LV reverse remodeling by 6 months post-procedure. This was associated with a greater post-operative reduction in trans-aortic pressure gradient and myocardial fibrosis in the TAVI group and an equivalent reduction in AR compared to SAVR.

Our study population demonstrated baseline concentric and eccentric structural LV remodeling processes consistent with severe AS (Gaasch and Zile, 2011). No significant difference existed between the two treatment groups' baseline LV parameters, aortic valve haemodynamics or the majority of co-morbidities. An 'afterload mismatch' process is known to alter ventricular geometry, raise LVM and progress to diastolic and systolic dysfunction. These factors are recognized adverse prognostic markers pre and post-SAVR (Lund, 2003, Gaudino, 2004, Lund et al., 1997). Removing

the valvular impedance allows the ventricle to 'reverse remodel' and thus improve patient symptoms and prognosis (Biederman et al., 2005). This study used CMR with its greater accuracy and reproducibility to assess these factors in a TAVI population. Whilst comparisons of reverse remodeling between TAVI and SAVR have been previously conducted using echocardiography (Clavel et al., 2010, Forsberg et al., 2011) the limitations of this technique in remodeled ventricles restricts their conclusions.

Improved valvular haemodynamics are markers of procedural success and influence ventricular remodeling. The superior reduction of trans-valvular pressure gradient post-TAVI has been previously noted at 6 months using echocardiography. This can be partially explained by a lower incidence of patient prosthesis mismatch compared to SAVR and may reflect smaller valve sizes inserted at surgery compared to those implanted during TAVI (Clavel et al., 2009).

AR is an important complication following TAVI and has been identified as an independent predictor of mortality (Tamburino et al., 2011). Quantifying valvular and paravalvular regurgitation is however difficult using echocardiography. CMR assesses total (paravalvular and valvular) regurgitation with high levels of accuracy. In this study TAVI actually improved 'total' AR from baseline and was comparable to SAVR at 6 months. As may be expected in a pressure overloaded ventricle, mitral regurgitation decreased post-TAVI, although any comparison to SAVR remains difficult due to differences in the severity of baseline regurgitation.

The reverse remodeling changes observed following TAVI are consistent with the current surgical aortic valve replacement literature (Sandstede et al., 2002, Biederman et al., 2011) and include new important observations. Similar levels of LV reverse remodeling occurred between transcatheter and surgical procedures except for small differences in EDV and EF. The smaller reduction in EDV post-TAVI could be secondary to the greater burden of coronary artery disease and myocardial infarction in this sub-group, as both were predictors of reduced EDV reverse remodeling. The significant increase in EF following TAVI but not SAVR may be attributed to the greater reduction in aortic valvular impedance and wall stress post-TAVI (Clavel et al., 2009). This greater reduction in ventricular workload could also explain the differing structural pattern of reverse remodeling

(mass/volume) which only reduced post-TAVI. However, the smaller EDVI reduction in the TAVI group (secondary to greater myocardial infarction and coronary disease) is a more probable explanation for this observation. Therefore structural remodeling which is an important predictor of stroke, myocardial infarction, heart failure and all cause mortality (Gaasch and Zile, 2011) is unlikely to differ between the procedures. Global ventricular work is not just dependent upon valvular but also vascular load. Z_{va} has been shown to adversely effect outcomes in AS patients. Our groups had similar levels of baseline Z_{va} indicating that this was not a confounding factor in influencing reverse remodeling between the groups.

LV wall geometric measurements provide supplementary information about the function of the LV, particularly when the EF appears normal. Wall thickening is a clinical indictor of wall stress, representing the circumferential twist and longitudinal shortening of the LV. In thick hypertrophied ventricles with a normal EF it is a more sensitive marker of myocardial function and strain (Dumesnil and Shoucri, 1991). When compared to an AS population studied by Sandstede et al,(Sandstede et al., 2000) the baseline wall thickness of our study group is similar but wall thickening was significantly lower, suggesting our patients had markedly impaired LV function despite only a mild reduction in EF. The TAVI group when compared to SAVR had a greater improvement in wall thickness and thickening on a segmental and global level. TAVI appears to result in a superior post-operative reduction in LV wall stress and improved strain and twist when compared to SAVR. This procedural difference could be the result of the greater reduction in trans-aortic valve impedance and wall stress following TAVI, as well as its earlier haemodynamic changes and less invasive nature (Clavel et al., 2009, Dumesnil and Shoucri, 1991). These findings will need to be confirmed by a technique more sensitive to changes in LV strain and torsion, such as speckle tracking (echocardiography) or myocardial tagging (CMR).

Right ventricular reverse remodeling appeared more favourable post-TAVI, as volumes and mass reduced and function improved compared to an actual decline in RV function following SAVR. This may reflect a post-bypass phenomenon but does require further research to establish if there is a specific role for TAVI in individuals with significant right heart disease. The high pacemaker

implantation rate post-TAVI meant some of our TAVI cohort could not undergo follow up scans. As a consequence the impact of pacing on left and right ventricular reverse remodeling could not be established.

Focal MF secondary to AS has been reported in a similar frequency and distribution to the MF in our study (Rudolph et al., 2009, Weidemann et al., 2009b, Nigri et al., 2009). MF is an adverse prognostic indicator and is associated with reduced reverse remodeling post-SAVR (Azevedo et al., 2010, Dweck et al., 2011). In this study it was the quantity of baseline myocardial infarction, not focal MF that was associated with worse post-operative ventricular volumes and function. Following multivariate analysis the baseline LV parameters also remained significant predictors of reverse remodeling. This observation supports the theory that MF does not predict reduced reverse remodeling (Krayenbuehl et al., 1989), but is associated with poor baseline volumes and function, which are the true independent predictors of adverse reverse remodeling. Fibrosis has been found not to regress substantially post-AVR using histological (Krayenbuehl et al., 1989) and diffuse equilibrium measurements (Flett et al., 2012). Our study using a less specific but well validated technique of LGE found similar results post-SAVR but evidence of regression post-TAVI. This finding needs to be validated using a more sensitive technique such as T1 mapping, as it may reflect greater reverse remodeling post-TAVI at the cellular level rather than a true reduction in fibrosis.

Post-procedural subendocardial myocardial infarction occurred more frequently in the SAVR group compared to the TAVI group. This has not been previously described and its clinical significance is limited by the small patient numbers involved. However, concerns related to covering the coronary ostia with the CoreValve^{TM} device and crushing the calcified native aortic valve leaflets do not seem to result in myocardial infarction as detectable on CMR. Equally it may suggest that peri-operative myocardial protection in severely hypertrophied ventricles is suboptimal in surgically treated patients.

2.6 Limitations

Although this was a small study population, comparisons between the two groups using the highly reproducible technique of CMR meant it was appropriately powered. Patients in the two treatment

groups had similar risk factor profiles, but due to the nature of current guidelines for TAVI patient selection, they could not be matched for age or EuroSCORE. Despite the positive selection of higher risk SAVR candidates this hampers our direct comparison of SAVR versus TAVI. Finally, quantification of fibrosis on LGE images was analysed using a semi-automatic, signal intensity threshold method rather than the newer T1 mapping techniques, as the latter were not widely employed at the time of patient recruitment. However, as of yet there is no consensus as to which of the multitude of T1 mapping techniques should be employed in myocardial interstitial disease.

2.7 Conclusions

This study provides evidence of significant reverse remodeling post-TAVI in a high-risk AS population with multiple adverse prognostic factors such as old age, high LVM, reduced LV systolic function and substantial MF. TAVI was comparable to SAVR in terms of global LV reverse remodeling. Baseline LV measurements and myocardial scar (infarction) were the dominant factors predicting change in reverse remodeling for both TAVI and SAVR. TAVI significantly reduced the trans-aortic pressure gradient and aortic regurgitation at 6 months, and when compared to SAVR produced a greater reduction in focal MF.

3 Diffusion-Weighted Magnetic Resonance Imaging Determined Cerebral Embolic Infarction Following Transcatheter Aortic Valve Implantation: Assessment of Predictive Risk Factors and the Relationship to Subsequent Health Status

3.1 Abstract

Background: 'Silent' cerebral infarction and stroke are complications of TAVI. The occurrence of cerebral infarction was assessed to identify predictive risk factors and assess the impact upon patient health related quality of life (HRQOL).

Methods: Cerebral Diffusion Weighted-Magnetic Resonance Imaging (DW-MRI) of 31 AS patients undergoing MCV TAVI. HRQOL assessed at baseline and 30 days by SF-12v2 and EQ5D questionnaires.

Results: New cerebral infarcts occurred in 24 of 31 patients (77%) and Stroke in 2 (6%). Stroke was associated with a greater number and volume of cerebral infarcts. Age ($r=0.37$, $p=0.042$), severity of atheroma (arch and descending aorta; $r=0.91$, $p<0.001$, $r=0.69$, $p=0.001$ respectively) and catheterisation time ($r=0.45$, $p=0.02$) were predictors of the number of new cerebral infarcts. HRQOL improved overall: SF-12v2 Physical Component Summary increased significantly (32.4±6.2 vs. 36.5±7.2; $p=0.03$) with no significant change in Mental Component Summary (43.5±11.7 vs. 43.1±14.3; $p=0.85$). The EQ5D score and Visual Analogue Scale showed no significant change (0.56±0.26 vs. 0.59±0.31; $p=0.70$, and 54.2±19 vs. 58.2±24; $p=0.43$).

Conclusions: Multiple small cerebral infarcts occurred in 77% of TAVI patients. The majority of infarcts were 'silent' with clinical stroke being associated with a both higher infarct number and volume. Increased age and the severity of aortic arch atheroma were independent risk factors for the development of new cerebral infarcts. Overall HRQOL improved and there was no association between the number of new cerebral infarcts and altered health status.

3.2 Introduction

TAVI has rapidly developed as an effective treatment for patients with severe symptomatic AS who are not suitable for SAVR. With over 50,000 patients treated worldwide using the MCV, it reflects the increasing prevalence of AS in an ageing population and observations that 30% of individuals with severe AS are not offered surgery (Iung et al., 2005b). TAVI outcome data have demonstrated superior clinical outcomes to standard medical therapy, 97% procedural success, 6.4-8% 30 day and 22-31% 1 year all cause mortality (Piazza et al., 2008, Rodes-Cabau et al., Leon et al.). Stroke however is an important complication that occurs in 0.6-5% of TAVI patients compared to 1.1% of patients treated with standard medical therapy (Zajarias and Cribier, 2009, Leon et al.). Stroke is believed to be secondary to ischaemic embolic events, either from aortic atheroma during the passage of a delivery catheter or degenerative valvular material released during the valvuloplasty and valve deployment. Procedural cerebral infarction can occur more frequently than is clinically apparent (Busing et al., 2005, Lund et al., 2005, Omran et al., 2003). These 'silent' ischaemic events have been documented post-cardiac surgery (Restrepo et al., 2002b, Stolz et al., 2004b) and are associated with neurological dysfunction and future cognitive decline (Goto et al., 2001). They may have a substantial effect upon an individual's quality of life, potentially affecting patient selection and treatment recommendations, particularly if TAVI is expanded to a larger, younger, lower risk patient group.

Computed tomography (CT) and T2w MRI are conventionally used to diagnose stroke and distinguish haemorrhagic from ischaemic stroke. Cerebral imaging also helps identify the location and size of a stroke aiding in its classification. However, during acute stroke CT and T2w MRI have false-negative rates of between 30-60% in the first 24 hours, thus limiting their usefulness. Cerebral ischaemia causes damage to the cellular N^+/K^+ ATP pump, cytotoxic oedema and a reduction in the diffusion capacity of protons (water) in the brain (Schaefer et al., 2000). This reduction in water diffusion can be detected by diffusion weighted magnetic resonance imaging (DW-MRI) within 5 minutes of symptom onset (Reith et al., 1995). DWI has the advantage of being able to differentiate ischaemic from nonischaemic and acute from chronic lesions with greater sensitivity (false negative rate of 5%)

compared to conventional T2w, Fluid attenuated inversion recovery (FLAIR) and proton density MRI (Lutsep et al., 1997, van Everdingen et al., 1998).

The aim of this study was to determine the incidence of new cerebral infarction on DW-MRI after TAVI, identify demographic and procedural risk factors for clinically apparent and silent cerebral infarction and to assess the impact upon patients' subsequent health status.

3.3 Methods

Between May 2008 and August 2010, 85 patients underwent TAVI at our institution. Each individual was assessed by a multidisciplinary team (cardiothoracic surgeon, cardiologist, cardiac anaesthetist) in accordance with international guidelines (Vahanian et al., 2008a). Severe AS was defined as an aortic valve area of less than 0.8cm² or a peak velocity of >4m/s on echocardiography. All patients were ≥65 years of age, and had a logistic EuroSCORE >20, or co-morbidities that precluded cardiac surgery. Exclusion criteria for the study were MRI incompatible factors including pacemaker, claustrophobia or an inability to lie flat. The study complied with the declaration of Helsinki, was approved by the local research ethics committee and all patients provided written informed consent.

3.3.1 Transcatheter Aortic Valve Implantation

Patients were screened using echocardiography, invasive coronary angiography and aortography. Data collected included patient demographics, co-morbidity and potential risk factors for cerebrovascular accident (CVA). EF, LV End-Diastolic Dimensions (LVEDD) and aortic valve pressure gradient were recorded by transthoracic echocardiography (TTE). Aortic atheroma was assessed in the ascending, descending and arch of aorta by transoesophageal echocardiography (TOE) then graded for severity (1-5) by an experienced reader according to previously published criteria (Hartman et al., 1996). Aortic valve calcification was assessed by a combination of TTE and TOE and graded for severity: I-No calcification; II-mild calcification; III-moderate calcification; IV-severe calcification (Rosenhek et al., 2000). TAVI was performed in all patients using the third-generation 18-Fr MCV Revalving™ system. A standard technique was employed for implantation of the Corevalve™ prosthesis as

previously described (Piazza et al., 2008). All procedures were performed under general anaesthesia with TOE guidance and aortic balloon valvuloplasty prior to valve deployment. Patients received dual antiplatelet therapy with aspirin 75mg and clopidogrel 75mg daily, continued for a minimum of 6 months post-operatively. Heparin was administered during the procedure to maintain an activated clotting time (ACT) >200 seconds.

3.3.2 Cerebral MRI

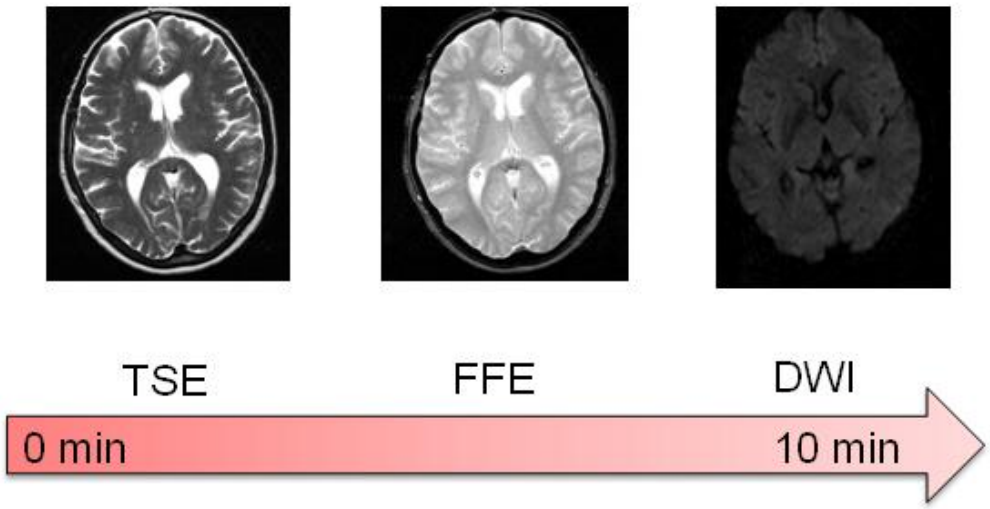
3.3.2.1 MR protocol

Cerebral-MRI was performed using a 1.5Tesla system (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). Baseline and post procedural scans were performed on the same scanner using an identical imaging protocol.

1. T2 weighted Turbo Spin Echo sequence (repetition time [TR] 5016 msec, echo time [TE] 120 msec, flip angle 90°, 20 axial slices, 7mm slice thickness, 0.7mm interslice gap, 1.2 minute acquisition time, FOV 350, RFOV 100).
2. T2 weighted Fast Field Echo sequence (repetition time [TR] 701 msec, echotime [TE] 23 msec, flip angle 18°, 22 axial slices, 5mm slice thickness, 1mm interslice gap, FOV 350, RFOV 100).
3. Diffusion weighted spin echo sequence (repetition time [TR] 4348 msec, echotime [TE] 89 msec, flip angle 90°, 22 axial slices, 5mm slice thickness, 1mm interslice gap, FOV 350, RFOV 100). The apparent diffusion coefficients (ADC) were calculated for each pixel and displayed as an ADC map.

The patients' heads were supported in a head coil with wedges to reduce movement artefact. Ten minutes was required to complete the head protocol with 5 minutes allocated to the DWI.

Figure 3-1 Cerebral MRI protocol



3.3.2.2 Image analysis

Two experienced neuroradiologists (A.G and S.C) blinded to the clinical and procedural details independently reported the scans. A consensus reading was agreed upon if any conflicts in reporting occurred. Ischaemic lesions appear as areas of abnormal hyperintensity on the ADC maps. These hyperintense (white) areas were contoured by direct planimetry on each slice using the post-processing software (Qmass, v7.0, Medis, The Netherlands). The area was then multiplied by the slice thickness and interslice gap to give volume (ml) of cerebral ischaemia. Total cerebral infarct volume was calculated by the summation of all individual lesions volume to determine clinical significance. Finally, the location (hemisphere and cerebral arterial territory) and size (< or ≥ 5mm) of lesions were recorded.

3.3.3 Neurological and Health Status Assessment

Clinical examination of patients post TAVI (day 1 and 2) was performed by an experienced medical physician to assess for neurological signs according to the National Institutes of Health Stroke Scale (NIHSS). Symptoms and signs of <24 hours duration were defined as a Transient Ischaemic Attack (TIA) and if they persisted over 24 hours they were classified as a stroke.

No disease specific questionnaire exists for patients with AS, therefore health status was assessed using two well validated, generic Health Related Quality of Life (HRQOL) Questionnaires: SF-12v2 and EQ5D. Each questionnaire was administered by a trained nurse or doctor with the patient pre-procedurally (baseline) and at 30 days post-procedure by postal or telephone survey. The SF-12v2 health outcomes questionnaire (©QualityMetric, Lincoln, RI, USA) assesses HRQOL using 8 dimensions each with a score of 0-100. It is a shorter, simpler version of the well validated SF-36 (Ware et al., 1996a) and is thus more suited to an elderly population. This produces 1) a physical component summary (PCS) of: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BDP) and General Health (GH). 2) A mental component summary (MCS) score of Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). EQ5D (©EuroQOL) uses 5 dimensions to measure HRQOL: mobility, self care, usual activities, pain/discomfort and anxiety/depression. Scoring is from 0 (death) to 1 (full health). The second component of the EQ5D is a Visual Analogue Scale (VAS) of 0-100 (worst imaginable health to best possible health).

3.3.4 Statistical analysis

Statistical analysis was performed using the PASW software package (version 17.0 SPSS, Chicago, Ill, US). Continuous data are presented as mean ± SD, categorical data as frequencies and percentages. Test for normality was assessed using the Shapiro-Wilks goodness-of-fit test and Q-Q plots. Continuous variables were compared using the paired t-test. Categorical variables were compared using the Mann-Whitney or Fishers exact tests. Linear regression analysis was used to identify the relationship between patient and procedural factors and the number of new cerebral infarctions following TAVI. Univariate analysis was used to identify individual predictors. Variables with a univariate significance of $p<0.1$ were entered into a multiple stepwise regression analysis to determine the independence of these predictors. Multivariate analysis was also performed using number of new infarcts and stroke as two dependent variables and the univariate predictors as factors and covariates. A two-sided significance level of $p<0.05$ was considered statistically significant.

3.4 Results

3.4.1 Patient population

Forty of the eighty five patients consented for recruitment into the study and underwent baseline pre-procedure DW-MRI in order to identify any pre-existing lesions, Figure 3-2. Of these, 31 (78%) completed paired head scans pre- (median 1 day, IQR 1-2) and post-TAVI (median 5 days, IQR 4-6). Of the remaining 9 patients, TAVI was not performed on 4 individuals, and 5 individuals underwent TAVI but could not complete the MRI study due to: 3 patients requiring permanent pacemakers post-valve implantation, 1 claustrophobic patient and 1 unable to lie flat in the scanner. The demographic and echocardiographic details of the 31 patients (mean age 81±5.9yrs; female 65%, Table 3-1) are representative of a typical unselected TAVI population.

Figure 3-2 Patient Recruitment.

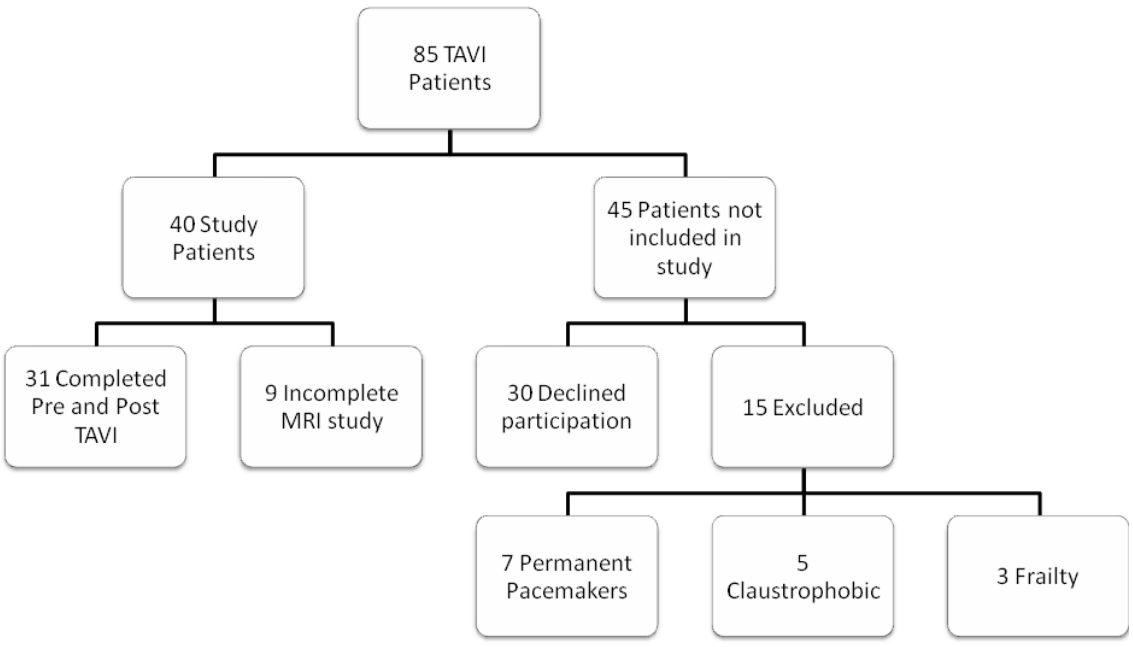


Table 3-1 Baseline Patient Characteristics of the Study Population

Study population (n= 31)	
Age	81 (±5.9)
Female Gender, n (%)	20 (65)
BMI (kg/m²)	27 (±4.3)
Logistic EuroSCORE (%)	23.9 (±16.4)
AV Pressure Gradient (mmHg)	62.2 (±23.9)
AV EOA (cm²)	0.55 (±0.13)
LV Ejection Fraction, n (%)	
Good	18 (58)
Moderate	12 (39)
Poor	1 (3)
LV EDD (mm)	47 (±7.3)
Creatinine (µmol/L)	114 (IQR 90-178)
Hypertension, n (%)	14 (45)
Hypercholesterolaemia, n (%)	20 (65)
Diabetes, n (%)	9 (29)
Atrial Fibrillation, n (%)	7 (23)
Cerebrovascular disease, n (%)	3 (10)
Peripheral Vascular Disease, n (%)	7 (23)
Porcelain Aorta, n (%)	9 (29)

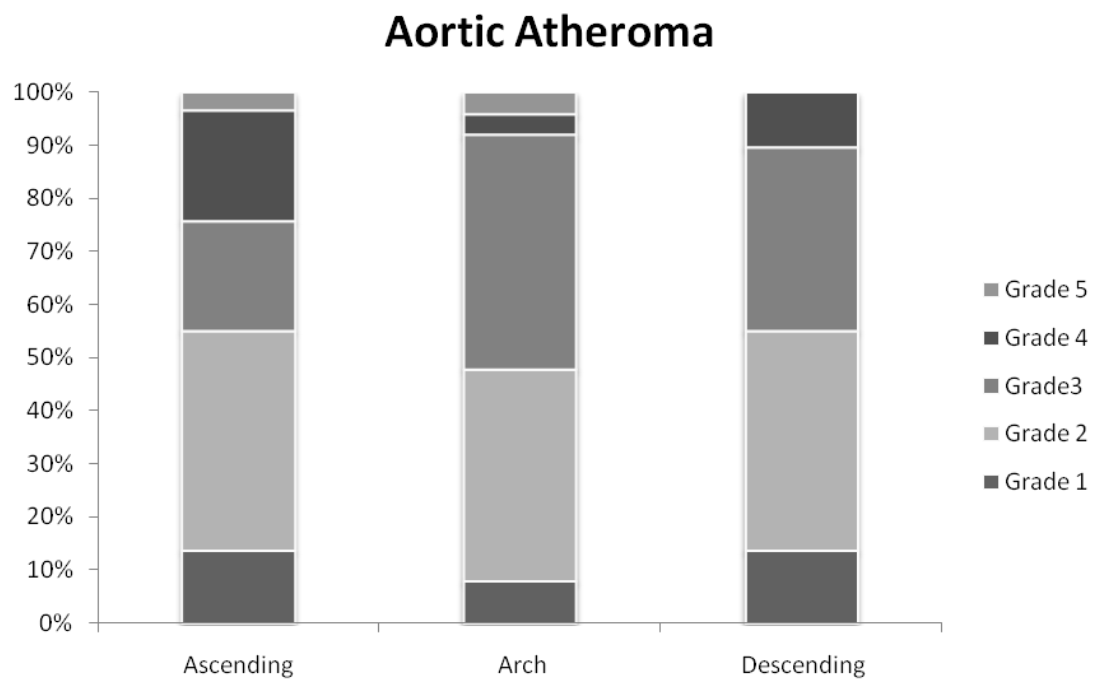
BMI - Body Mass Index, AV- Aortic Valve, EOA- Estimated Orifice Area,

LV - Left ventricle, EDD- end-diastolic dimension

3.4.2 Procedural data

A 26mm MCV was deployed in 11 (35%) cases and a 29mm in 20 (65%), via either the femoral 26 (84%) or subclavian 5 (16%) artery. Procedural success was 98%, with an average catheterisation time of 68±26 minutes, fluoroscopy time of 22±6 minutes and 150±47ml of contrast given. Valve dislocation and retrieval occurred in only 2 (7%) individuals. Despite this low occurrence, this resulted in a significantly longer catheterisation and fluoroscopy time (64±22 vs. 106±48, p=0.02 and 21±5 vs. 35±9, p=0.05 minutes respectively). Post-dilatation of the self expanding valve was required in 11 (35%) cases, with no significant increase in either catheterisation or fluoroscopy times compared to those without post-dilatation (61±15 vs. 77±37, p=0.18 and 22±5 vs. 23±8, p=0.77 minutes respectively). TOE identified aortic valve calcification in all individuals, 20 (64%) patients had severe aortic valve calcification, 7 (23%) moderate and 4 (13%) mild. Aortic atheroma classification and grading are reported in Figure 3-2. Increased age was significantly related to the severity of aortic atheroma (p=0.016).

Figure 3-3 Aortic atheroma

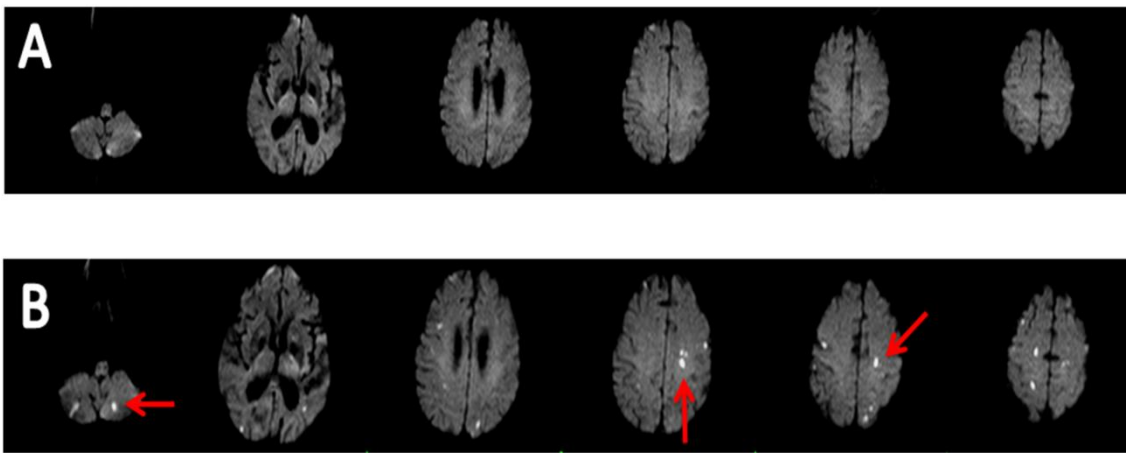


Classified as ascending, arch or descending aorta then graded: 1- Normal to mild intimal thickening; 2 -severe intimal thickening; 3 - atheroma <5mm; 4 - atheroma ≥5mm; 5 - mobile atheroma of any size.

3.4.3 Cerebral Infarction on Diffusion-Weighted Imaging

New cerebral infarction occurred in 24 (77%) patients. A total of 131 new infarcts occurred, distributed equally between the cerebral hemispheres (left 53%, right 47%), in multiple territories but predominantly in the regions of the following cerebral arteries: Anterior 7%, Middle 59%, Posterior 14% and Vertebrobasilar 20%. The number of infarcts per patient was a mean of 4.2±6.5 and median of 2 (IQR 1-5), with an average infarcted tissue volume of 2.05±3.5ml. These were mostly of a small size (<5mm, n=19, 79%). The number of new lesions significantly correlated to the overall volume of infarct ($r=0.82$, $p<0.001$), but interestingly not to the size of the individual infarcts ($p=0.61$). An example of new cerebral infarction using DW-MRI is shown in Figure 3-4.

Figure 3-4 Cerebral DW-MRI images



Trans-axial slices of the entire cerebrum including cerebellum at: A- Baseline. B- post-TAVI procedure. This patient had multiple new cerebral infarcts (highlighted by the red arrows).

New neurological signs were observed in 2 patients (6%). The first presented with an expressive dysphasia and scored 4 on the NIHSS, whilst the second developed gait ataxia and scored 2. DWI confirmed 26 new lesions in each of these individuals, distributed over several territories. These neurological deficits were diagnosed post-operatively on day 1, persisted at day 2 (>24 hours) and were therefore classified as a stroke. When compared to those patients without neurological signs, individuals with new neurological signs demonstrated a significantly higher number (26±0 vs. 2.7±3,

p=0.004) and volume (11.9±6ml vs. 1.1±1.1ml, p=0.007) of new cerebral infarcts, although patient numbers are small.

3.4.4 Demographic and Procedural Risk Factor Assessment

Risk factors were assessed for a relationship to the number of new infarcts, as reported in Table 3-2. Increased age was significantly related to a higher number of new infarcts (r=0.37, p=0.042). There were no associations between the co-morbidities of hypertension, hypercholesterolaemia, diabetes mellitus, atrial fibrillation, cerebrovascular disease, peripheral vascular disease and a porcelain (heavily calcified) aorta, to the number of new infarcts or the development of a clinical stroke. Risk calculation using logistic EuroSCORE had no predictive relationship to the number of new cerebral infarcts (r=-0.08, p=0.69) or clinical stroke. Atheroma burden in the arch and descending thoracic aorta (but not in the ascending aorta, r=0.4, p=0.35), was significantly associated with the number of new cerebral infarcts (r=0.91, p<0.001; r=0.69, p=0.001). The severity of aortic valve calcification was not related to the number of new cerebral infarcts (p=0.33).

Procedural risk factor analysis revealed that increased catheterisation time was associated with the number of new infarcts (r=0.45, p=0.02) whereas increased fluoroscopy time did not reach statistical significance (r=0.36, p=0.05). All other procedural variables including the size of Corevalve^{TM} (26 or 29mm, p=0.19) had no relationship to the number of infarcts or presence of clinical stroke. Corevalve post-dilatation or dislocation and retrieval did not effect the number of new infarcts observed (p=0.22 and p=0.93 respectively).

The univariate variables (age, fluoroscopy time, catheterisation time, arch and descending aortic atheroma) were then entered into a multiple regression model, where age and aortic arch atheroma remained independent predictors of new cerebral infarcts (p=0.036 and p=0.023 respectively), Table 3-3. Multivariate analysis was used to determine if the univariate variables could predict the occurrence of stroke as well as the number of new infarcts. Aortic arch atheroma was the only variable to significantly predict both (F=7.16, p=0.008).

Table 3-2 Predictors of new cerebral infarcts.

Risk Factor		Univariate analysis	
		R	P value
Age		0.37	0.042
BMI (kg/m^2)		0.01	0.974
EuroSCORE (Logistic)		-0.075	0.69
AV Pressure Gradient (mmHg)		0.11	0.57
AV EOA (cm^2)		-0.26	0.17
Ejection Fraction (%)		0.12	0.52
LV EDD (mm)		-0.28	0.14
Creatinine (µmol/L)		-0.02	0.90
Hypertension		0.19	0.30
Hypercholesterolaemia		0.11	0.55
Diabetes		0.1	0.59
Atrial Fibrillation		0	0.93
Cerebrovascular disease		0.2	0.28
Peripheral Vascular Disease		0.06	0.73
Porcelain Aorta		0.25	0.17
Aortic atheroma	Ascending	0.40	0.352
	Arch	0.91	< 0.001
	Descending	0.69	0.001
Aortic Calcification		0.28	0.327
Fluroscopy time (min)		0.36	0.05
Catheterisation time (min)		0.45	0.02
Contrast dose (ml)		-0.12	0.53
Heparin dose (u)		0.24	0.19

BMI- Body mass index, AV EOA- Aortic Valve Estimated Orifice Area,

LV - Left ventricle, EF- ejection fraction, EDD- end-diastolic dimension

Table 3-3 Multiple regression analysis

Univariate predictor	Multivariable analysis*		
	B	**t**	**p value**
Age	0.50	2.2	0.035
Fluroscopy time (min)	0.23	1.1	0.27
Catheterisation time (min)	0.10	0.5	0.61
Aortic arch atheroma	3.97	2.4	0.02
Descending aortic atheroma	0.33	1.7	0.11

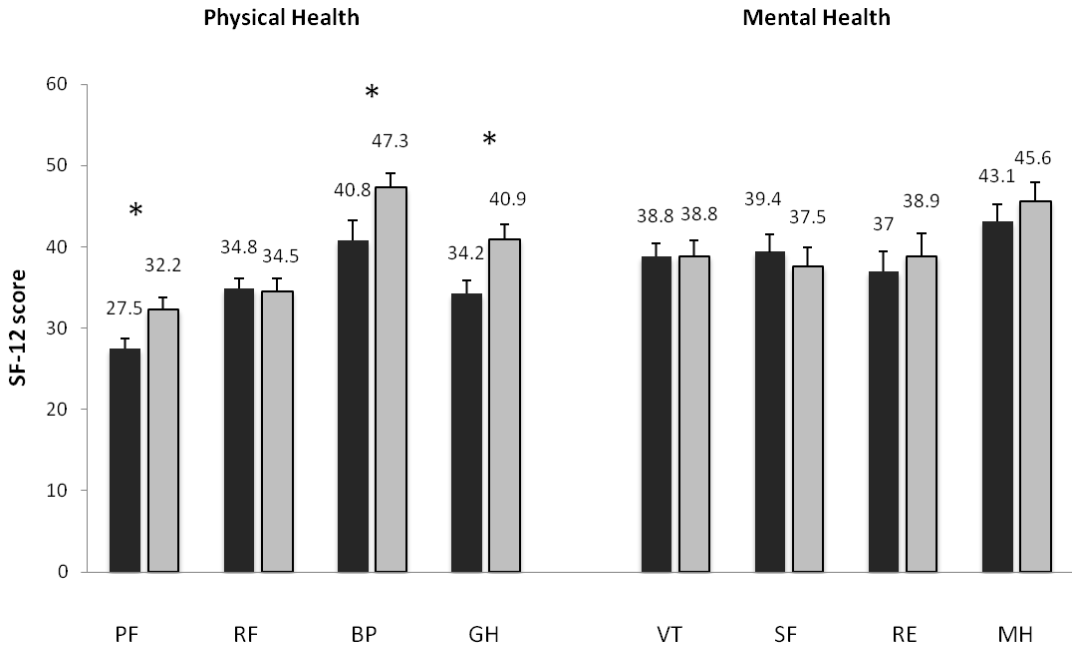
* Univariate variables with a p value <0.1 were included in the model

3.4.5 Health Status

The HRQOL scores should be interpreted in comparison to the average score for a UK population matched for age and gender. These relevant scores were; PCS (36-38), MCS (50-51), EQ5D (0.69-0.71) and VAS (70-75) (Hanmer et al., 2006).

The SF-12v2 individual components that showed a significant increase from baseline were; physical functioning, bodily pain and general health (p=0.003, p=0.03 and p=0.003 respectively), Figure 3-5. A comparison of the summary scores revealed that the PCS increased significantly from baseline 32.4±6.2 to 30 days 36.5±7.2, (p=0.03) with no significant change in MCS from 43.5±11.8 to 43.1±14.3 (p=0.85), Figure 3-6. The PCS and MCS scores at 30 days showed no relationship to the number of new infarcts (r=0.19, p=0.33; r=-0.08, p=0.69 respectively), and were not significantly different between the stroke and non-stroke groups (PCS, p=0.39 and MCS, p=0.98).

Figure 3-5 Health Related Quality of Life- SF12

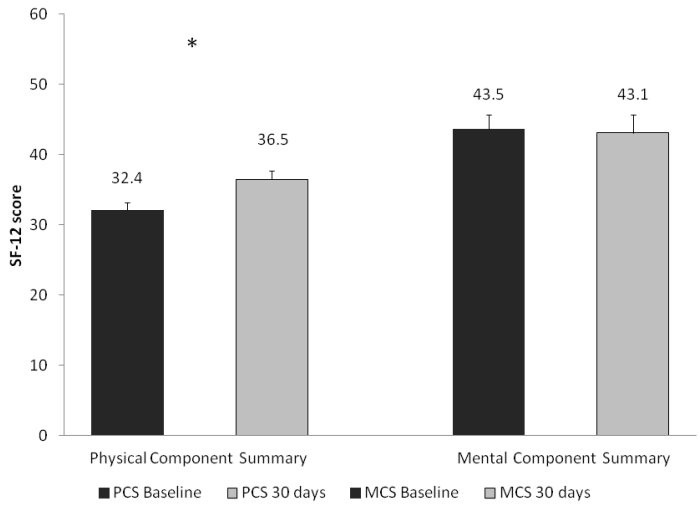


Population mean scores (and standard error) at baseline (dark grey) and 30 days (light grey).

Physical health: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH). Mental Health: Vitality (VT), Social Functioning (SF), Role Emotional (RE), Mental Health (MH).

* P <0.05

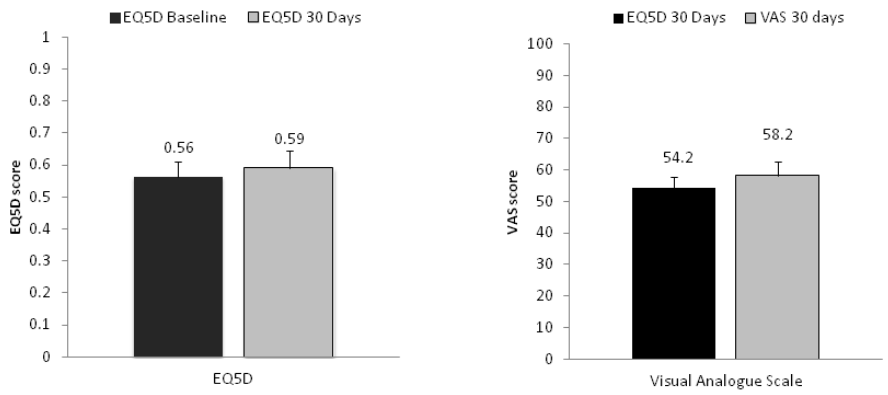
Figure 3-6 Physical and Mental component summary scores



PCS= physical component summary; MCS= mental component summary. * p = 0.03

The mean EQ5D score showed a non-significant increase from baseline to 30 days (0.56±0.26 to 0.59±0.31, p=0.70). Similarly, there was a non-significant increase in the VAS component of the assessment at 30 days (54.2±19 to 58.2±24, p=0.43), Figure 3-7. The EQ5D and VAS scores at 30 days showed no relationship to the number of new cerebral infarcts (r=0.11, p=0.95; r= -0.085, p=0.65, respectively) and were not significantly different between the stroke and non-stroke groups (p=0.85 and p=0.44 respectively).

Figure 3-7 EQ5D and VAS scores at baseline and 30 days.



EQ5D is scored from 0-1 and VAS is a self -rated score of 0-100.

3.5 Discussion

Previous studies have described the incidence of cerebral infarcts post TAVI but have been unable to identify any significant risk factors (Ghanem et al., 2010, Kahlert et al., 2010). This study is to our knowledge the first to demonstrate that increased age and aortic arch atheroma severity are independent predictors for the number of new cerebral infarcts following TAVI. In addition, this is the first study to assess the impact of these new cerebral infarcts on HRQOL.

The small size, high number and distribution of new cerebral infarcts suggest an embolic source. It has been demonstrated in previous cardiac catheterisation studies that embolisation can occur through the contact of a catheter against aortic atheroma, (Segal et al., 2001) and that the risk of stroke

increases with the duration of procedure, fluoroscopy time and contrast dose (Busing et al., 2005, Lund et al., 2005). Our findings that prolonged catheterisation and fluoroscopy time are univariate predictors of infarct number support this as a mechanism of action in TAVI patients, reflecting the increased contact of a catheter or valve apparatus against the aortic wall and atheroma whilst moving around the aortic arch.

An important finding is that the number of new cerebral infarcts is related to the severity of aortic atheroma. Evidence from non-TAVI populations have shown that atheroma plaques >4mm in the aortic arch are associated with an increased risk of stroke and death (Amarenco et al., 1994, Di Tullio et al., 2009). In this TAVI study the presence of atheroma ≥5mm thickness or mobile atheroma in the arch and descending thoracic aorta was significantly associated with greater infarct number and clinical stroke. The association of descending thoracic aortic atheroma to new cerebral infarcts likely reflects its relationship to the severity of arch atheroma rather than as an independent causative factor, as atheroma increases in thickness and complexity progressively from ascending to descending aorta (Meissner et al., 2004). The relationship of atheroma severity to infarct number could potentially be explained by an association with age as atherosclerotic plaques increase in thickness and complexity with advanced age. However in this study age and aortic arch atheroma remained independent predictors of infarct number following multivariate analysis.

Our results did not identify any relationship to support the theory that embolisation occurs during balloon valvuloplasty or valve implantation. Conventional stroke risk factors such as atrial fibrillation or prior cerebrovascular disease and surgical risk (logistic EuroSCORE) were not significant predictors of new cerebral infarction or clinical stroke.

New cerebral infarcts occurred in 77% of our cohort, yet only 6% developed clinical stroke. The multiple infarcts demonstrated on these two individuals were all small (<5mm) except for one lesion whose anatomical distribution would not have accounted for the neurological presentation. Recent literature has demonstrated similar rates of DWI-determined cerebral infarction and clinical symptoms (Kahlert et al., 2010, Ghanem et al., 2010). The clinical significance of ‘silent’ infarcts remains uncertain, as concern exists related to higher cognitive and neuropsychological changes such as

memory, mood and personality. New cerebral infarcts have been reported in 30% of individuals after CABG (Restrepo et al., 2002a) and 40% following SAVR; (Floyd et al., 2006, Stolz et al., 2004a) these were 'silent' in 67% of cases. These cerebral infarcts have been linked to post-operative cognitive decline (POCD), (Newman et al., 2001, Knipp et al., 2005) as well as possible dementia (Yoshitake et al., 1995).

HRQOL is an important method of assessing patient outcomes and is particularly relevant for TAVI patients, as older age and multiple co-morbidities make long-term prognostic benefit less relevant (Gurvitch et al., 2011). The SF-12v2 MCS looks at mood, emotional well being and social functioning, all of which could be affected by POCD. Importantly overall health status improved and the reported mental health of our patients was not affected by the number of cerebral infarcts. Whilst an improvement in HRQOL post-TAVI has been reported previously at 30 days (Gotzmann et al., 2010), 3 months (Krane et al., 2010) and 5 months (Ussia et al., 2009), this is the first study to assess the impact of new cerebral infarction on HRQOL in a TAVI population.

3.6 Limitations

This was a relatively small patient cohort with no direct surgical comparison group. It is however difficult to recruit comparable surgical patients, given that TAVI patients by their nature are older with greater co-morbidity and high surgical risk. No complex neurocognitive testing was undertaken and the health status follow up was only out to 30 days. Our institution uses only the Corevalve^{TM} for TAVI and thus did not assess the Edwards-Sapien valve or the transapical route. Interpretation of the findings related to stroke are limited by the small number of patients presenting with clinical signs. Larger studies are warranted in the future with appropriate cognitive assessment and long term follow up, to fully inform in a patient specific manner the associated risks of the TAVI procedure.

3.7 Conclusion

This study found that increased age and aortic arch atheroma independently predict the number of cerebral infarctions following TAVI, irrespective of patient co-morbidities or calculated surgical risk. The presentation of neurological signs was associated with an increased number and volume of cerebral infarcts. Aortic arch atheroma severity was the only predictor of both infarct number and stroke. Health status and quality of life improved at 30 days post TAVI with no functional mental decline. Although TAVI data demonstrates superiority to standard medical therapy, stroke remains a significant problem (Leon et al., 2010). The frequent and dispersed nature of cerebral infarcts following TAVI does suggest an embolic process, for which protection devices are already being trialled (Nietlispach et al., 2010). The identification of individuals at high risk of multiple cerebral emboli is important as it may help patient selection for the use of a protection device against stroke and POCD.

4 Serial change in health related quality of life over one year following Transcatheter Aortic Valve Implantation: Predictors of health outcomes.

4.1 Abstract

Background: Severe AS reduces the length and quality of a patient's life. TAVI is superior to standard medical therapy and non-inferior to SAVR for 2-year mortality. HRQOL is an important outcome measure, for which there is limited evidence in TAVI populations.

Methods: One hundred and two patients (age 80 ±0.6yrs, female 51%) attending for TAVI consented to participate. Two HRQOL questionnaires, the SF12v2 with physical and mental component summaries (PCS and MCS) and the EQ-5D (with Visual Analogue Scale; VAS) were completed at baseline, 30 days, 6 and 12 months as per the VARC recommendations. A SF-6D utility measure was calculated from the SF12 survey.

Results: HRQOL significantly improved over 12 months (PCS, $p=0.02$; EQ-5D, $p=0.02$; VAS, $p=0.01$ and SF6D $p=0.03$) becoming similar to age adjusted US population norms. The greatest change occurred from baseline to 30 days ($p<0.001$) with further significant improvements to 6 months ($p<0.01$). An insignificant decline occurred between 6-12 months ($p>0.05$), but a linear pattern of change remained for PCS, EQ5D and VAS ($p<0.05$). Male gender (SF6D, $p=0.01$) and increased operator experience (PCS, EQ5D and VAS, $p<0.05$) were independent predictors of a greater improvement in HRQOL.

Conclusions: HRQOL significantly improves early following TAVI and is maintained out to one year. Patient factors, procedural complications and operator experience are predictors of health benefit at 1 year may help patients and physicians make a fully informed decision during the TAVI selection process.

4.2 Introduction

Symptomatic AS reduces the quality and duration of an individual's life. TAVI is indicated as a treatment for the large number of severe AS patients unsuitable for SAVR (Vahanian et al., 2008b). Clinical trial and registry data have demonstrated high procedural success, significantly improved survival compared to medical therapy, and non-inferiority in mortality to SAVR at two years (Zahn et al., 2011, Smith et al., 2011, Leon et al., 2010, Makkar et al., 2012b). HRQOL assessments are important clinical outcome measures of medical treatments. The VARC recommended that quality of life questionnaires be used as a TAVI clinical benefit end-point and that they should be conducted over four separate time-points (baseline, 30 days, 6 months and 12 months) (Leon et al., 2011). Quality of life is particularly relevant for TAVI patients, as in an elderly population with multiple co-morbidities absolute survival benefit may be less substantial, increasing the importance of quality attained years. In addition the identification of particular risk factors and predictors of HRQOL would allow the 'heart team' to better inform patients of their likely individual benefits from this high-risk procedure.

Health utility values are a measure of preferences for health states, which are essential for the calculation of quality-adjusted life years (QALYs) within the framework of cost-utility analyses. Cost-utility analyses are the preferred approach, with QALYs the preferred metric of organisations charged with evaluating the cost-effectiveness of medical technologies for the purpose of healthcare resource allocation and decision making.

Quality of life data on TAVI populations are sparse (Gotzmann et al., 2010, Ussia et al., 2009), and at the time of writing only the PARTNER study has published HRQOL results over the range of recommended time-points (Reynolds et al., 2011), with no reports of health utility values for this patient group. Health utility values, especially multiple assessments over a long time period, are important to allow cost-effective analyses and decision analytical modelling to be undertaken.

The aims of this study were to 1) assess serial changes in HRQOL and health utility at 30 days, 6 months and 1 year after TAVI, 2) Identify the clinical variables that predict patient benefit.

4.3 Methods

One hundred and two patients who underwent TAVI at our institution between May 2008 and May 2010 provided informed written consent to the study, which was approved by the institutional ethics committee and performed in accordance with the declaration of Helsinki. Patient selection for TAVI was performed by a multi-disciplinary 'heart team' which included a cardiologist, cardiothoracic surgeon and cardiac anaesthetist. Severe AS was defined as a peak velocity >4m/s or a calculated aortic valve area <0.8cm^2 by echocardiography. All individuals were symptomatic and deemed unsuitable for SAVR due to high calculated surgical risk (EuroSCORE >20) or in-operable co-morbidities. Pre-operative assessments included invasive angiography of the coronary and iliac arteries and TOE. Patients were deemed unsuitable for TAVI if the aortic annulus was <20 or >27mm. Exclusion criteria were the inability to comprehend English language or impaired cognition.

4.3.1 Transcatheter Aortic Valve Implantation

TAVI was performed under general anaesthesia using the 18F MCV Revalving system (Medtronic, Minneapolis, Minnesota) as previously described (Piazza et al., 2008). A transfemoral approach was used where possible, with percutaneous access and closure. A surgical subclavian approach was performed in patients without suitable femoral access (<6mm diameter). Aortic valvuloplasty under rapid pacing control was followed by CoreValve^{TM} implantation (26 or 29mm) with post-dilatation as required. The primary operator was identical for all procedures and the results reflect all cases sequentially performed following proctorship.

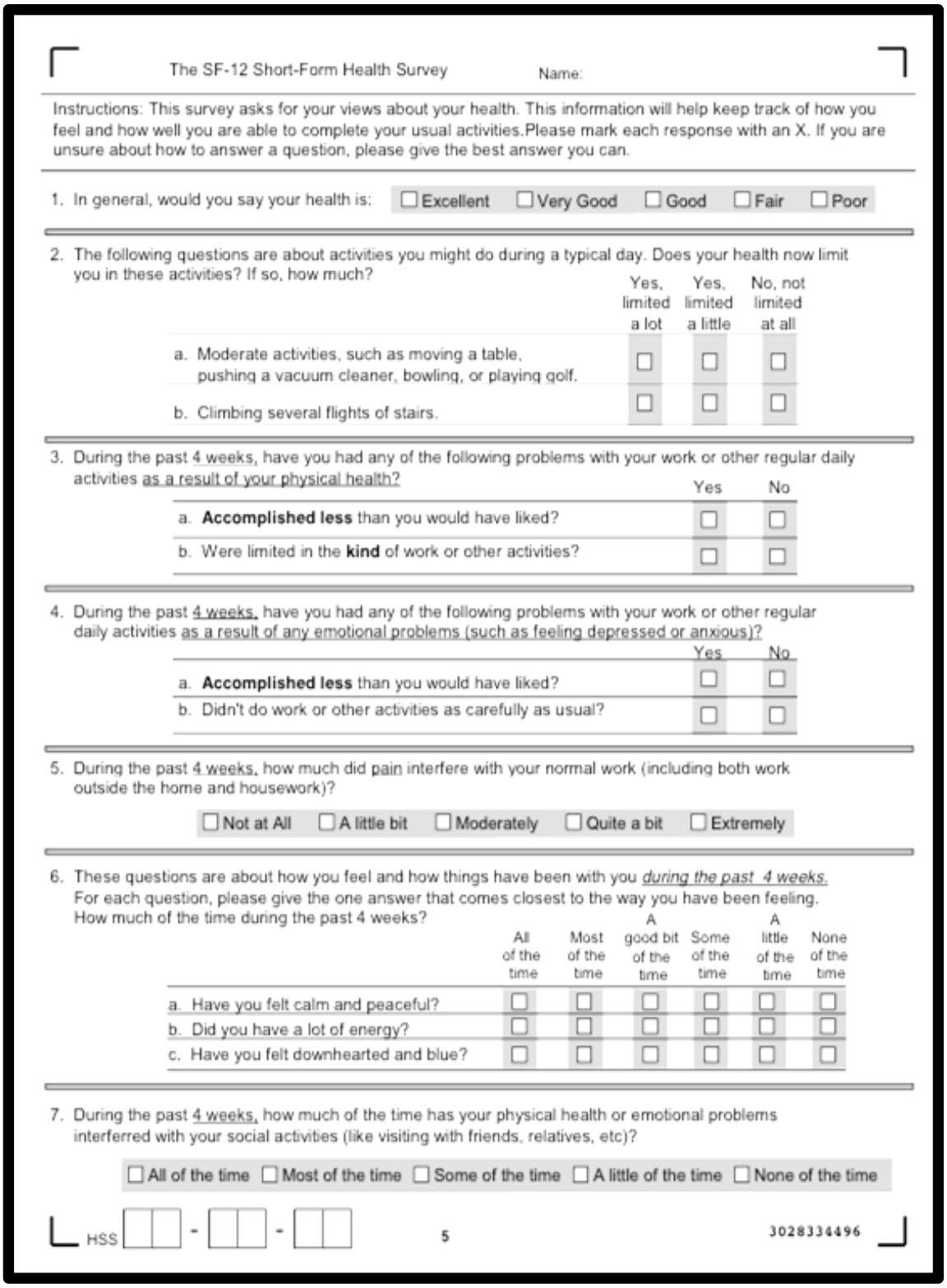
4.3.2 Quality of Life Assessments

HRQOL was assessed using two generic, validated questionnaires; SF-12v2 health outcomes questionnaire (©QualityMetric, Lincoln, RI, USA) and the EQ-5D questionnaire (©EuroQOL). Each patient completed a questionnaire at baseline, 30 days, 6 and 12 months. The initial survey was conducted by interview with a trained health care specialist and later time-points completed by postal or telephone survey. Exclusion criteria were the inability to comprehend English or impaired cognition. Patient characteristics, co-morbidities, NYHA class, procedural risk factors and variables

were collected prior to TAVI. Post-operative complications (e.g. vascular haemorrhage, permanent pacemaker implantation) and mortality were collected post-TAVI.

The short form (SF) 36-item health survey was developed to enable the standardized practical assessment of general health as a medical outcome (Ware, 2000). It has been validated in chronic disease states in comparison to psychometric testing, clinical criteria and medical interviews (Ware et al., 1996b). The information attained is robust, unambiguous and an accurate representation of a patients' medical and psychiatric health. The SF-12 health survey is based on the SF 36-item health survey but is shorter with fewer response categories, and is thus simpler to complete and more suitable to an elderly population (Brazier and Roberts, 2004). Evidence suggests that the results obtained by the SF-12 survey correlate highly with those from SF-36, providing an accurate estimate of health (Lundberg et al., 1999). However, the relative validity coefficient is approximately 10% lower. This greater variance may become important in smaller sample sizes but does not apply in larger samples (i.e. >100). The survey asks for single and ranked responses to questions pertaining to the individuals' health over the preceding 4 weeks, Figure 4-1. It uses 8 dimensions to assess physical and mental health; Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). The individual responses are then graded and scored from 0-100. These scores are normalised to a US or UK population (mean 50, SD 10), where a higher score reflects a better HRQOL. Additionally, two separate component summary scores are reported, distinguishing between physical (PCS; physical component score) and mental (MCS; mental component score) health.

Figure 4-1 SF – 12 version 2 health survey



The SF-12 Short-Form Health Survey Name:

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to complete your usual activities. Please mark each response with an X. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: ☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐	☐	☐
b. Climbing several flights of stairs.	☐	☐	☐

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. **Accomplished less** than you would have liked?	☐	☐
b. Were limited in the **kind** of work or other activities?	☐	☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. **Accomplished less** than you would have liked?	☐	☐
b. Didn't do work or other activities as carefully as usual?	☐	☐

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at All ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

6. These questions are about how you feel and how things have been with you *during the past 4 weeks.* For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks?

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
b. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
c. Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interferred with your social activities (like visiting with friends, relatives, etc)?

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

HSS ☐☐ - ☐☐ - ☐☐ 5 3028334496

EQ-5D and SF-6D are two health-based utility measures (Brazier et al., 2004). Utility measures typically provide an index (quality of life weighting) between zero and one, where one reflects full health and zero, death. Utility values are combined in economic evaluation with survival data to calculate QALY gains from new treatments and technologies. The EQ-5D survey was developed by the EuroQol group (www.euroqol.org) as a standardised measure of health for clinical and economic evaluations (Rabin and de Charro, 2001). It is a straightforward questionnaire that is suitable for self-completion via postal survey or via direct interview. The EQ-5D descriptive system uses 5 domains to assess health states; mobility, self care, usual activities, pain/discomfort and anxiety/depression. Each question has 3 potential responses: no problems, some problems, severe problems Figure 4-2. A single response is required for each domain, resulting in a scoring number (1, 2 or 3). This scoring system allows the identification of 245 health states (from no problems [11111], to dead or unconscious [33333]). The EQ-5D health state can be converted in to a single summary index by a formula that 'weighs' each domains score. The appropriate values are derived from a 'normal' UK population sample to reflect local societal perspective. The conversion is applied in a time-trade off valuation exercise: 1 – the index value (Dolan, 1997). Patients also completed an EQ Visual Analogue Score (VAS) of self-rated health, Figure 4-3 (Robinson et al., 1997). The scale is from worst imaginable (0) to best possible (100) health, and is used as a quantitative assessment of subjective health. Answers applied to the day of completing the questionnaire. SF-6D is a utility-based measure that is calculated using the SF-12 scores converted to SF-6D utility scores using a UK tariff (Brazier et al., 2002). This provides an additional domain (vitality) and different recall period (4 weeks) to the EQ-5D. Differences in the change of scores suggest that SF-6D has a higher sensitivity in severe disease processes (Quercioli et al., 2009, Brazier et al., 2004).

In this TAVI population of generally poor health, the use of both EQ-5D and SF-12 surveys is complementary; EQ-5D is more suitable for a population with poor health as it demonstrates a ceiling effect in moderately severe health conditions, whereas SF-12 is reported to underestimate the severity of health status in poorer health groups but does not demonstrate a ceiling effect (Quercioli et al., 2009).

Figure 4-2 EQ 5D survey

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

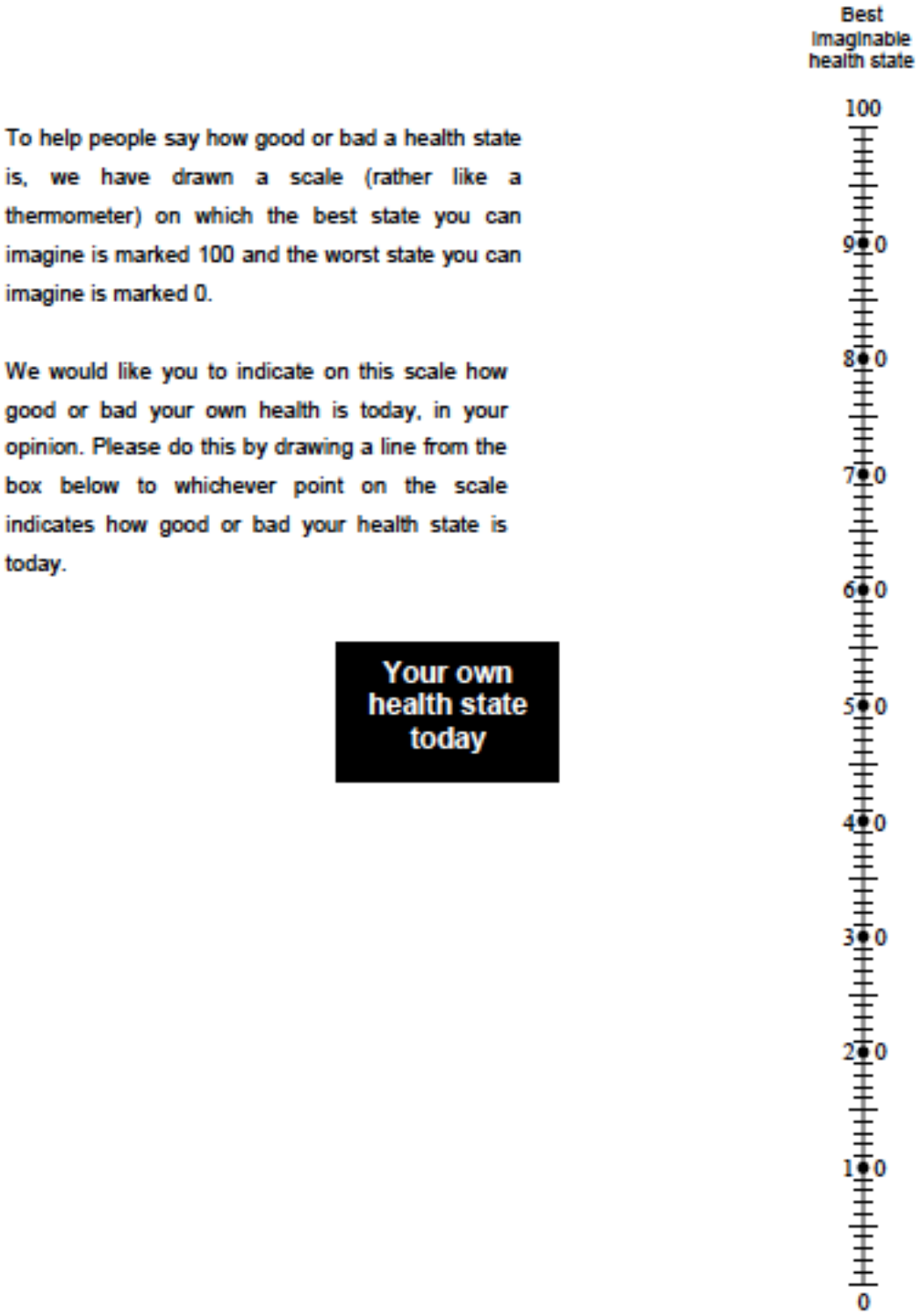
Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Figure 4-3 EQ visual analogue scale



4.3.3 Statistical Analysis

Continuous data are presented as mean ±SD and categorical as frequency and percentage. Normality was determined by Shapiro-wilks test and Q-Q plots. Comparative statistics used were student *t*-test and Wilcoxon signed rank test as appropriate. All paired comparisons between baseline measurements and the various time-points were performed analysis by analysis, excluding un-paired results. Chi-squared test was used for categorical comparisons. Repeated measures ANOVA general linear model was applied to detect changes over the four time-points and differences between subject factors. Predictors of the one year health scores were assessed by individual linear regression analysis with baseline scores entered as a covariate factor. Individual variables with a p value <0.1 were entered into the multivariate general linear model. All statistical analyses were performed using the PASW software package (version 17.0 SPSS, IBM, Chicago, Ill, US) with a two-sided significance level of $p<0.05$ considered statistically significant.

4.4 Results

All 102 patients completed baseline HRQOL questionnaires. Three patients had valvuloplasty instead of TAVI giving a 97% procedural success. The study population therefore consisted of 99 patients (age 80±6yrs, 49% male), whose clinical and procedural characteristics are reported in Table 4-1. All cause mortality was consistent with the published literature; 3 (3%) at 30 days, 7 (7%) at 6 months and 20 (20%) at one-year (Tamburino et al., 2011). Three patients (3%) were unable (due to cognitive decline) and 4 (4%) unwilling to complete all 4 time-point questionnaires. Incomplete questionnaires including those as a result of patient death, were excluded from subsequent time-point ANOVA analysis. Table 4-2 shows the health score results for each survey according to the VARC recommended time points, with the US population norms stratified for age (80-89yrs) to allow comparison to an equivalent age group of healthy individuals (Hanmer et al., 2006).

Table 4-1 Demographic, clinical and procedural characteristics of the TAVI population

Variables	(n=99)
Clinical characteristics	
Age	80 ±6
Male	48 (49)
EuroSCORE (logistic %)	20 ±13
Smoker	
Never	34 (35)
Ex-smoker	63 (64)
Smoking	2 (1)
Diabetic	33 (33)
Renal disease ¶	9 (9)
MI	39 (39)
AF	26 (26)
COPD	23 (23)
CVD	9 (9)
PVD	15 (15)
CABG	28 (28)
Angina (CCS class)	
0	62 (62)
1	4 (4)
2	12 (12)
3	18 (19)
4	3 (3)
NYHA class	
1	0 (0)
2	13 (13)
3	60 (60)
4	26 (27)
Pulmonary Hypertension	15 (15)
Porcelain aorta	15 (15)
Procedural variables	

Access	
Subclavian	8 (8)
Femoral	91 (92)
Valve	
26mm	26 (26)
29mm	73 (74)
Mortality (30 day)	3 (3)
Peri-procedural MI	0 (0)
Stroke	2 (2)
Vascular haemorrhage	4 (4)
Transfusion	26 (26)
Acute Kidney Injury	1 (1)
Permanent Pacemaker	20 (20)

Values are mean ±SD or number (%). COPD = Chronic Obstructive Pulmonary Disease, CVD = Cerebrovascular disease, PVD = Peripheral Vascular Disease, CABG = Coronary Artery Bypass Graft, CCS = Canadian Classification Score of angina, NYHA = New York Heart Association, ¶ = eGFR <30 ml/min/1.73m^2

Table 4-2 Health scores according to VARC time-points

Paired comparisons		**Time-point**			
Health Survey	**US Norm†**	**Baseline n=99**	**30 Days n=90**	**6 Months n=70**	**12 Months n=65**
PCS	37.3 ±3	29.5 ±9	36.3 ±9***	38.3 ±11**	34.4 ± 10*
MCS	51 ±3	45.4 ±12	46.4 ±13	47.4 ±11	46.9 ±11
EQ-5D	0.66 ±0.2	0.54 ±0.3	0.65 ±0.3**	0.68±0.3*	0.65 ±0.3*
VAS	0.53 ±7	51.1 ±21	61.4 ±21***	68.2 ±20**	61.5 ±21*
SF-6D	0.72 ±0.1	0.60 ±0.1	0.66 ±0.1**	0.68 ±0.1**	0.63 ±0.1*

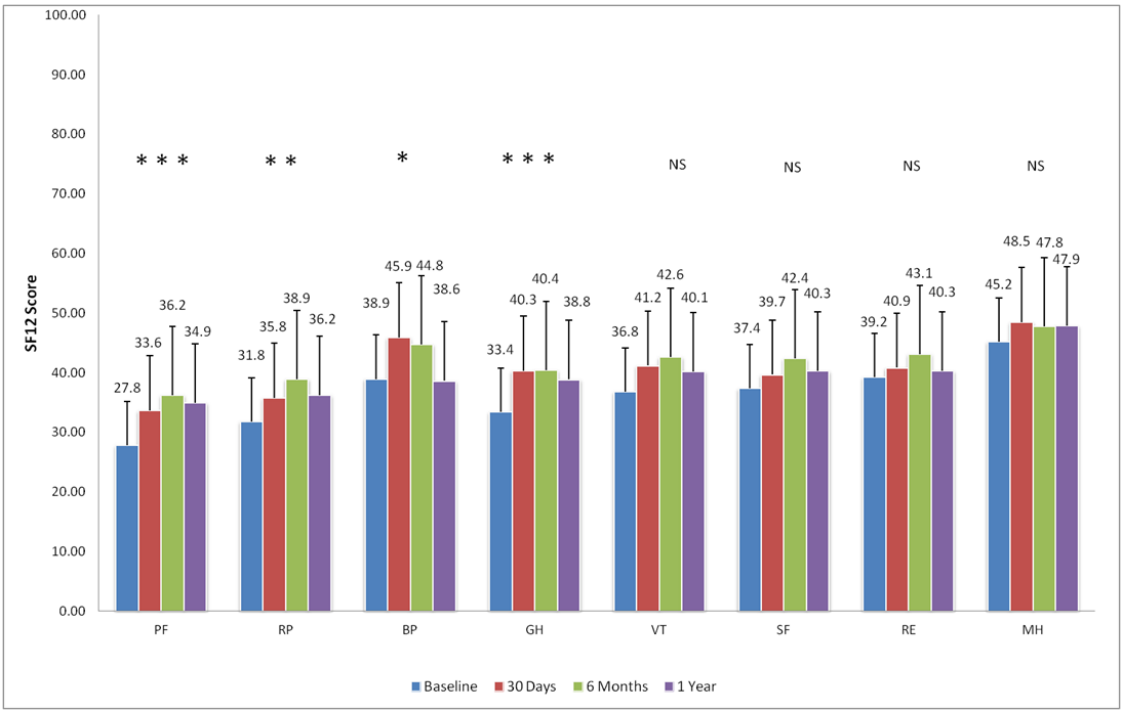
Values are mean ± SD. * $p < 0.05$, ** $p < 0.01$, $p < 0.001$. p values are reported for a change in health for each time point compared to baseline by paired t-test. † US Norms are reported for a US population stratified by age (80-89 years).

PCS = Physical Component Score, MCS = Mental Component Score, VAS = Visual Analogue Score .

4.4.1 SF-12 Health scores

The separate health component scores over the 4 different time-points are shown in Figure 4-4. Components that increased significantly from baseline to 30 days included: Physical functioning (PF, 27.8 ±7 vs. 33.6 ±9, p<0.001), Role Physical (RP, 31.8 ±8 vs. 35.8 ±10, p=0.006), Bodily Pain (BP, 38.9 ±14 vs. 45.9 ±12, p=0.001), General Health (GH, 33.4 ±10 vs. 40.3 ±11, p<0.001), Vitality (VT, 36.8 ±9 vs. 41.2 ±10, p=0.006) and Mental Health (MH, 45.2 ±11 vs. 48.5 ±11, p=0.027). Social Functioning (SF, 37.4 ±14 vs. 39.7 ±13, p=0.22) and Role Emotional (RE, 39.2 ±12 vs. 40.8 ±15, p=0.75) improved but not significantly. At 6 months there was a further increase from 30 days in PF (36.5 ±12, p<0.001), RP (39.3 ±10, p<0.001), VT (43 ±11, p=0.002), SF (42.8 ±15, p=0.06) and RE (42.6 ±13, p=0.67). BP and GH scores did not increase further but remained significantly higher than baseline (45.4 ±13, p=0.02 and 40.8 ±11, p=0.001). One year measurements revealed a non-significant (p> 0.05) decrease in all components when compared to 6 month scores, with a sustained improvement compared to baseline scores in PF (34.9 ±10, p<0.001), RP (36.2 ±10, p=0.03), GH (38.8 ±11, p=0.003) and VT (40.2 ±10, p=0.03). Repeated measures ANOVA showed a significant improvement over the four time-points to one year for all physical component scores (PF, RP, BP, GH) but not for the mental component scores (VT, MH, SF, RE).

Figure 4-4 Changes in SF 12 health component scores following TAVI



Time-points are represented by different coloured bars. P values by repeated measure ANOVA analysis are: *** = p<0.001, ** = p<0.01, * = p<0.05; NS = Not significant. PF = Physical Functioning, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role Emotional and MH = Mental Health.

The summary score for physical health (PCS) increased from baseline (29.5 ±9) to 30 days (36.3 ±9, p <0.001) and 6 months (38.3 ±11, p<0.001). One year PCS whilst lower than the 6-month score was still significantly higher compared to baseline (34.4 ±10, p=0.02), Table 4-2. Repeated measures ANOVA in those patients that completed surveys at all 4 time points (n=65) demonstrated a significant linear (p=0.03) and quadratic (inverted U shaped curve, p<0.001) relationship over time,

Table 4-3. Overall mental health (MCS) showed no significant change from baseline to any of the individual time-points (30 days, p= 0.47, 6 months, p=0.71 and 1 year, p=0.58; Table 4-2) which was confirmed on repeated measures ANOVA (p= 0.13,

Table 4-3).

Table 4-3 Serial change in health scores

	Time-point				*p value	
Health Survey	**Baseline n=65**	**30 Days n=65**	**6 Months n=65**	**12 Months n=65**	**Quadratic**	**Linear**
PCS	32.2 ±9	37.4 ±9	40.5 ±11	36.5 ± 11	< 0.001	0.03
MCS	45.2 ±10	45.8 ±13	46.7 ±11	47.2 ±11	0.15	0.13
EQ-5D	0.59 ±0.3	0.70 ±0.3	0.71 ±0.3	0.67 ±0.3	0.02	0.04
VAS	52.8 ±19	64.6 ±20	64.8 ±21	63.3 ±21	0.002	0.02
SF-6D	0.61 ±0.1	0.67 ±0.1	0.69 ±0.1	0.64 ±0.1	0.004	0.14

Values are mean ± SD. * p values are reported for a change in health and were calculated by repeated measures ANOVA. Quadratic p values reflect a inverted U shaped curve, where linear p values represent a linear trend. PCS = Physical Component Score, MCS = Mental Component Score, VAS = Visual Analogue Score.

4.4.2 Utility assessment scores

EQ-5D and VAS scores increased significantly from baseline to 30 days (0.54 ±0.3 vs. 0.65 ±0.3, p< 0.001 and 51.1 ±21 vs. 61.4 ±21, p<0.001 respectively). They improved further at 6 months (0.68 ±0.3, p=0.006 and 68.2 ±20, p=0.008) with a small insignificant decrease at 1 year (0.65 ±0.3, p=0.94 and 61.5 ±21, p=0.70), Table 4-2. One year measures remained significantly higher than baseline for both EQ5D and VAS scores (p=0.02 and p=0.01 respectively). Repeated measures ANOVA demonstrated a significant linear and quadratic relationship over the four time-points for both EQ-5D (p=0.04 and p=0.02 respectively) and VAS (p=0.02 and p=0.002 respectively) scores,

Table 4-3. SF-6D increased from baseline to 30 days (0.60 ±0.1 vs. 0.66 ±0.1, p=0.001) and was maintained at 6 months (0.68 ±0.1, p=0.001) and one year (0.63 ±0.1, p=0.03) (Table 4-2). Repeated

measures ANOVA once more showed a significant quadratic relationship over the 4 time-points (p=0.004),

Table 4-3.

4.4.3 HRQOL changes related to patient and procedural characteristics

All variables were assessed for predictors of change in HRQOL from baseline to one year using a general linear model. Age was considered as a linear variable as well as being categorised into groups of < or ≥80 years. Independent predictors of HRQOL change at one year are reported for the separate questionnaires in Table 4-4. MCS values have not been reported as there were no significant predictors of change.

Male gender was an independent predictor of greater improvement in HRQOL at one year (SF-6D), Table 4-4. There was no gender difference in HRQOL scores at baseline, but at 1 year males had significantly higher HRQOL compared to females (SF-6D: 0.69 ±0.1 vs. 0.58 ±0.1, p=0.001),Figure 4-5. Males had significantly worse baseline LVEF (p=0.004) and higher incidence of previous MI (p<0.001), with no difference between other characteristics (EuroSCORE, age, operation order).

Health changes also differed between age groups, Figure 4-6. The younger age group (<80 years) compared to the older group (≥80 years) reported lower baseline health scores (EQ-5D 0.45 ±0.3 vs. 0.58 ±0.3, p=0.04; VAS 43 ±25 vs. 54 ±20, p=0.02 and SF-6D 0.56 ±0.1 vs. 0.61 ±0.1, p=0.03) with no difference between their health scores at one year (EQ-5D 0.67 ±0.3 vs. 0.63 ±0.3, p=0.51; VAS 58 ±21 vs. 64 ±20, p=0.29 and SF-6D 0.64 ±0.1 vs. 0.63 ±0.1, p=0.70).

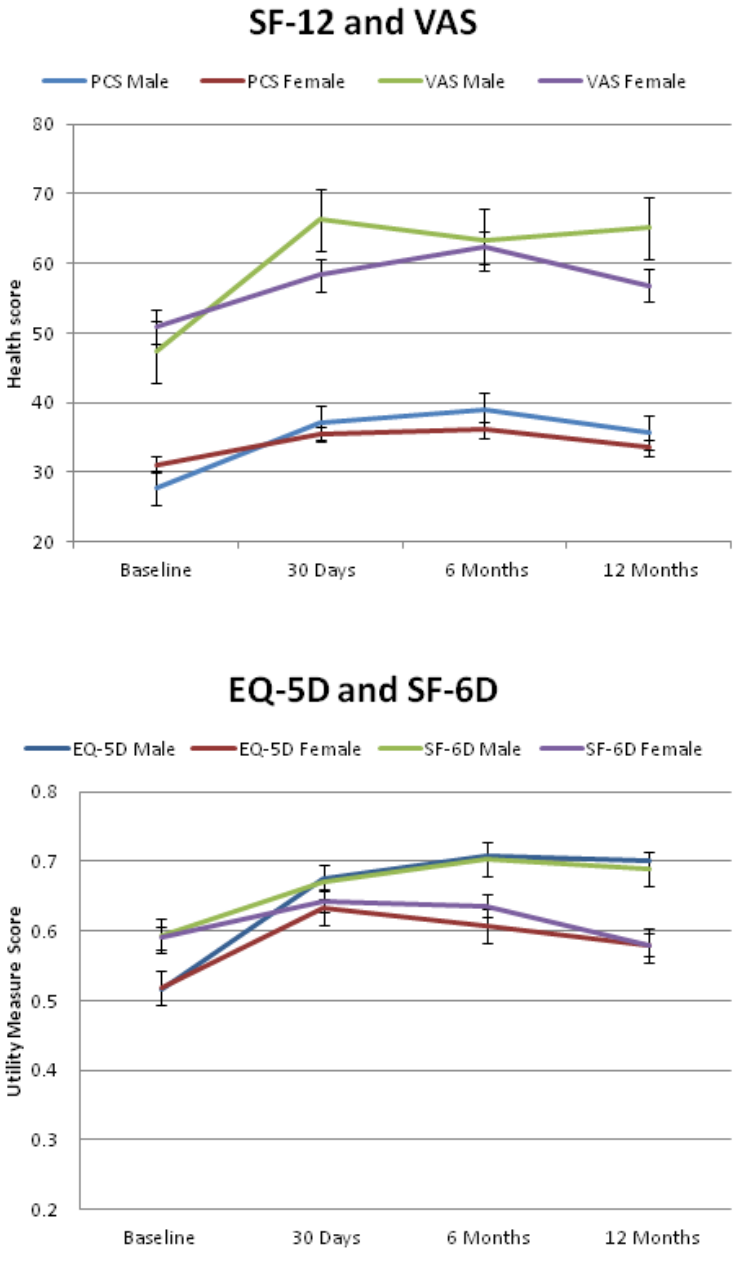
Other than prior CABG predicting a greater improvement in HRQOL, no other specific pre-existing co-morbidity predicted one year HRQOL. Those patients with higher baseline NYHA and angina class had a lower baseline HRQOL, but not significantly (p=0.55 and 0.48). Pre-operative NYHA class III-IV patients did however experience a smaller increase in their HRQOL score compared to those individuals in class I-II, Table 4-4.

Table 4-4 Predictors of one year Quality of Life

	Univariate Analysis		Mutivariate Analysis	
	B coefficient	**p value**	**B coefficient**	**p value**
PCS				
Age group	3.33	0.07	3.01	0.09
Operation order	10.9	0.002	4.05	0.05
CABG	4.56	0.04	3.47	0.07
NYHA class	4.00	0.02	1.83	0.18
EQ5D				
Operation order	12.6	<0.001	4.017	<0.001
Male gender	3.06	0.09	0.69	0.41
Vascular complication	5.94	0.02	9.68	0.03
NYHA class	2.81	0.07	2.14	0.13
VAS				
NYHA class	2.69	0.07	2.05	0.14
Operation order	5.74	0.02	4.97	0.03
SF6D				
Operation order	7.08	0.01	1.11	0.34
Male gender	10.1	0.003	2.84	0.01
NYHA Class	4.947	0.01	2.53	0.09

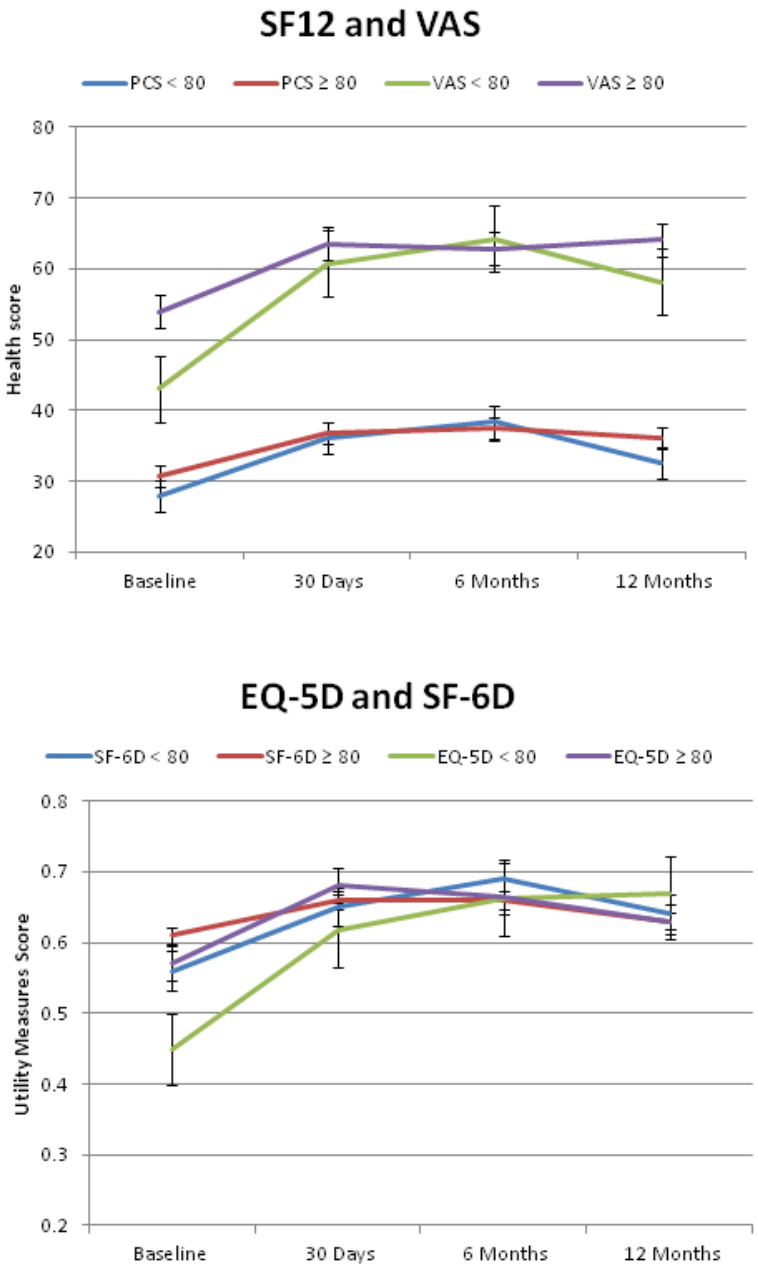
P values represent the univariate and multivariate general linear regression model and the beta standard coefficients. Individual variables were entered in to a multivariable model if the p significance <0.1. CABG = Coronary Artery Bypass Grafting, NYHA = New York Heart Association

Figure 4-5 Gender



Change over time for SF-12, EQ-5D, VAS and SF-6D by gender

Figure 4-6 Age group



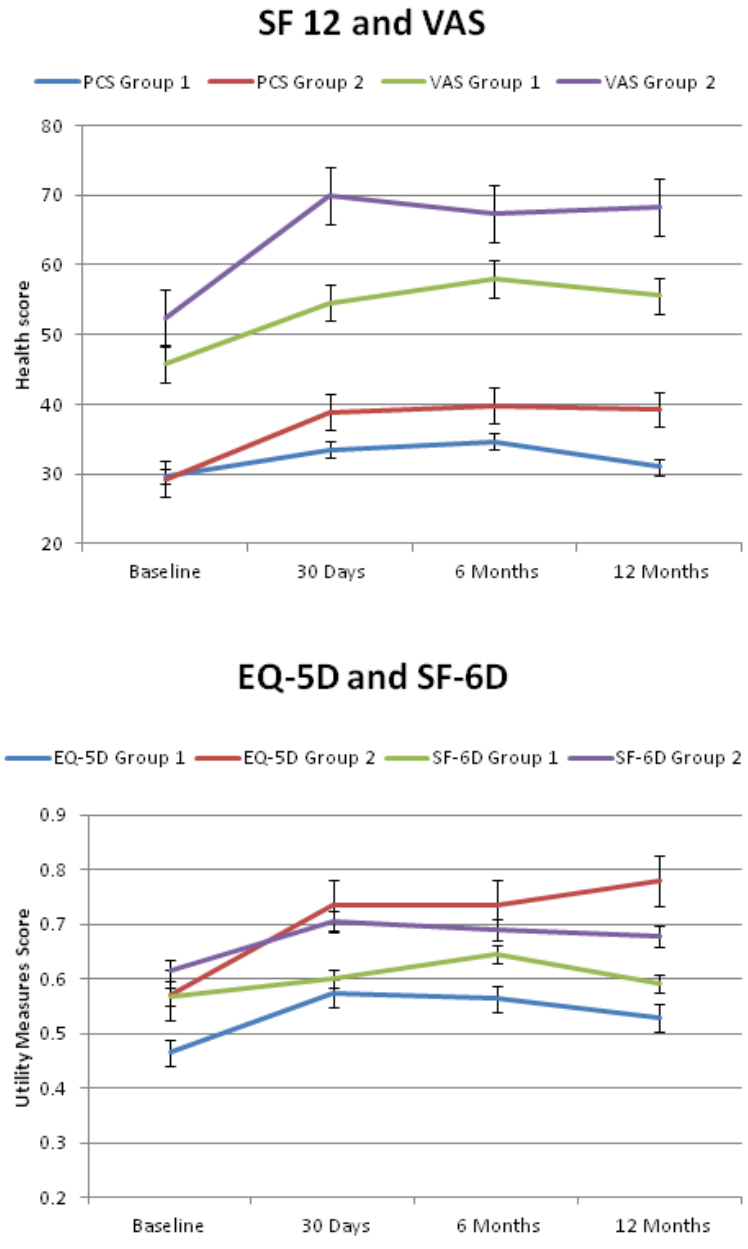
Change over time for SF-12, EQ-5D, VAS and SF-6D for individuals < or ≥ 80 years

4.4.4 HRQOL changes related to operative variables

Operator experience impacted on HRQOL, Table 4-4. Operative order was separated into two; the first 50 (group 1) and subsequent 49 (group 2) procedures. Patients in group 2 had a greater increase in all four health survey scores (PCS, EQ5D, VAS and SF6D) at 12 months. Group 2 patients had insignificantly higher baseline health scores compared to group 1, which increased further becoming

significantly different at 12 months (PCS, p=0.003; VAS, p=0.02; EQ-5D, p<0.001; and SF-6D, p=0.01), Figure 4-7. Vascular haemorrhage was an independent predictor of lower EQ5D at 12 months, with no other specific procedural complication (transfusion or aortic regurgitation) resulting in a significant decline in HRQOL scores, Table 4-4.

Figure 4-7 Operation order



Change over time for SF-12, EQ-5D, VAS and SF-6D by operation order (Group 1 = first 50 cases, Group 2 = last 49 cases)

4.5 Discussion

In a high-risk AS population, we have shown serial improvements in quality of life sustained over 12 months following TAVI. Benefit was seen early at 30 days post-procedure and increased further at 6 months. An insignificant drop in health status occurred between 6 months and one-year which appeared to be related to both patient and procedural factors. Male gender was an independent predictor of a greater increase in health score from baseline to one year. We have also shown for the first time that the 'learning curve' of operator experience impacted upon the health benefits for patients, independent of other procedural factors or complications.

Quality of life is an important clinical outcome measure of TAVI as patients are elderly, often frail and have multiple co-morbidities. This study has demonstrated the change in HRQOL over time post-TAVI, with the greatest change from baseline being observed at the 30-day time-point. This may be explained by certain early benefits from the less invasive nature of TAVI (compared to SAVR), such as shorter hospital stay, rapid haemodynamic response and reduced mortality (Smith et al., 2011, Clavel et al., 2009). Health scores increased further from 30 days to 6 months with an insignificant decline between 6 months and one year for all surveys. In separate studies, HRQOL post-TAVI has previously been shown to improve at the individual time points of 30 days, 5 months, or 12 months (Gotzmann et al., 2010, Gotzmann et al., 2011, Ussia et al., 2011) and over a series of time-points (Reynolds et al., 2011), but ours is the first study to show a pattern of health change over time as recommended by VARC for both health and utility measures. When compared to the age matched general US population norms, the baseline health of our TAVI population appears considerably worse. This improves up to 6 months where the average health is better than the general US norm for PCS, EQ-5D and VAS with similar scores in MCS and SF-6D. The small drop in reported health between 6 months and one year whilst statistically insignificant may reflect a decline in health that could become significant over a longer time period (e.g. 2 years). This observation is important in determining the health outcome post-TAVI and would suggest that future studies should involve long-term (>1 year) follow-up.

An important finding of this study is that different subgroups within the TAVI population had different health responses. One of the major driving forces in the development of TAVI was to aid in the treatment of elderly patients with severe AS, who with high levels of morbidity and mortality were not receiving SAVR (Iung et al., 2005a). This observation was in spite of the evidence that SAVR improves relative survival (Kvidal et al., 2000, Krane et al., 2011) and quality of life in octogenarians (Sundt et al., 2000). Our study is concordant with that of Bekeredjian et al., showing that HRQOL improves post-TAVI in individuals ≥80 years (Bekeredjian et al., 2010). In addition, we have demonstrated that younger patients (<80yrs) actually have lower baseline health scores yet gain equal benefits from the procedure. This is important as in the future, TAVI may be performed on a younger population. Higher baseline health scores in the older age group may appear counterintuitive, but age itself does not affect HRQOL. It is the associated diseases and loneliness which prevail in the elderly that reduce HRQOL (Brazier et al., 2002). Our age groups (<80, ≥80yrs) had similar baseline co-morbidities and thus the elderly population may perceive their health to be relatively higher due to lower expectations.

Females with AS have a decreased survival compared to males that is predominantly due to lower referral rates for SAVR, as once operated on they have similar mortality outcomes (Hartzell et al., 2011). TAVI data have not demonstrated any gender differences in clinical outcomes such as mortality or stroke, but no one has previously assessed this in relation to HRQOL as an outcome measure. Despite having a slightly higher rated baseline health, females improved less significantly than their male counterparts, with the difference becoming significant at 12 months. This was not related to any differences in baseline demographic characteristics or to the operative procedure. Although not formally assessed in this study it may reflect a greater prevalence of frailty in elderly females.

Operator experience has been reported to adversely affect cardiovascular outcomes and 30-day survival following the TAVI procedure, as a result of a 'learning curve' and device developments (Gurvitch et al., 2010, Gurvitch et al., 2011). We describe for the first time the impact of this learning curve on HRQOL as a clinical outcome. Identical device technology was used in all subjects by a single primary operator, and although baseline characteristics differed, in 3 out of 4 health surveys

multivariate analysis showed operator experience to be independent of all other variables. This provides further evidence to support the training and performance of TAVI in high volume centres with experienced operators to maximise the improvement in patient outcomes.

Patient selection remains one of the most challenging areas of TAVI practice. Our results provide evidence that a higher NYHA class predicts a less substantial improvement in health, whereas previous CABG patients gained a greater improvement in HRQOL. These factors may contribute towards the 'heart teams' TAVI patient selection criteria and aid the decision making process for the individual patient.

The published TAVI data have demonstrated improvement in patient survival and symptoms, but it remains a costly procedure with a significant post-procedural risk of death, vascular haemorrhage and stroke. Cost-effectiveness and the calculation of QALY's will therefore form an important part of health policy planning and outcome measurement in TAVI clinical practice. Until now no health utility measures have been reported in a TAVI population. In our study, a significant improvement occurred over 12 months for both utility measures which also showed a similar pattern of change. Further investigation is required to establish if the improvement in health of our study population, when combined with improved mortality rates will indicate a health economic benefit of TAVI.

4.6 Limitations

Although the study cohort was representative of a typical TAVI population, this was a single centre study in the UK and like all quality of life studies should be interpreted in the context of the local population. A surgical comparison group was not recruited given the difficulty in matching to a TAVI population for age, co-morbidities and risk factors, as a consequence of the current guidelines for TAVI patient selection. Incomplete questionnaires secondary to cognitive decline (3%) may indicate a reduced quality of life that has not been calculated. This study was not designed to perform a cost-effectiveness analysis or calculate QALY's from the health utility data. Ideally any future study

should combine both aspects in a multicentre, international registry to provide more comprehensive information to allow future health policy planning.

4.7 Conclusions

Quality of life improves early following TAVI and is maintained out to one year. Population sub-groups respond differently to TAVI, as females have lower health improvements. Increased operator experience is a predictor of greater health response independent of other patient or procedural variables. Health utility measures showed a similar pattern of increased health out to one year, and could in the future be combined with mortality data to produce a comprehensive health benefit model for TAVI.

5 The Cost-Effectiveness of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Patients with Severe Aortic Stenosis at High Operative Risk

5.1 Abstract

Background: To determine the cost-effectiveness of TAVI compared to SAVR in a high-risk AS United Kingdom population.

Methods: A cost-utility analysis employing the NICE reference case design for technology appraisals from the perspective of the UK National Health Service. TAVI and SAVR effectiveness was taken from the PARTNER A randomised controlled trial. Costs were modelled over a 10 year horizon using a Markov model. Incremental cost-effectiveness ratios (ICER) and cost-effectiveness acceptability curve (CEAC) were calculated with reference to the NICE willingness to pay per QALY gain threshold. Deterministic and probabilistic sensitivity analyses performed.

Results Despite greater procedural costs (£16,500 vs. £9,256), TAVI was cost-effective compared to SAVR over the 10 year model horizon (costs £52,593 vs. £53,943 and QALYs 2.81 vs 2.75), indicating that TAVI dominated SAVR. This appeared to be due to greater post-surgical costs, related to the length and cost of hospital stay. The results appeared robust to a number of deterministic sensitivity and probabilistic analyses. The CEAC indicated that at the NICE £20,000 willingness to pay threshold per QALY gained, TAVI had a 64.6% likelihood of being cost-effective, compared to 35.4% for SAVR.

Conclusions TAVI is likely to be a cost effective treatment for high-risk AS patients compared to the reference standard of SAVR. However, uncertainty surrounding the long-term outcomes for TAVI patients remains; this could have a substantive impact on estimates of cost-effectiveness.

5.2 Introduction

AS is the most common valvular heart disease in the western world. As a predominantly degenerative process the disease prevalence increases with age, affecting 4% of individuals aged 85 years and older (Nkomo et al., 2006, Carabello and Paulus, 2009). The onset of symptoms predict a poor prognostic outlook and a reduced quality of life, with valve replacement the only successful treatment option (Pellikka, 2005, Kvidal et al., 2000). The European Heart Survey demonstrated that a third of suitable patients did not receive definitive surgical treatment due to factors such as age, left ventricular dysfunction and associated co-morbidities (Iung et al., 2005a). Transcatheter aortic valve implantation (TAVI) developed as an alternative procedure for those individuals deemed at high-risk or inoperable for conventional SAVR. TAVI improves survival, functional capacity and quality of life compared to standard medical therapy (Leon et al., 2010) and at 2 years is non-inferior to SAVR (Smith et al., 2011, Kodali et al., 2012b). Despite its wide practice, there remains a question regarding the cost-effectiveness of this intervention in an elderly high-risk population. To date, no economic evaluations have conducted a comparison of TAVI and SAVR in high-risk patients suitable for conventional surgery from the perspective of the UK health service.

The aim of this study was to determine whether TAVI is a cost-effective alternative to SAVR in a high-risk group by developing a decision-analytic economic model using the available published evidence and values that reflect UK costs and clinical practice. We aim to provide an estimate of the average cost-effectiveness of TAVI across access site (Transfemoral (TF) or Transapical (TA)) and valve brands (Edwards-SAPIEN™ and Medtronic CoreValve™) with sensitivity analyses to cover differential performance according to these factors; this is to ensure model results reflect an overall viewpoint for the patient, clinician and purchaser in a health care system, where differential practice may occur.

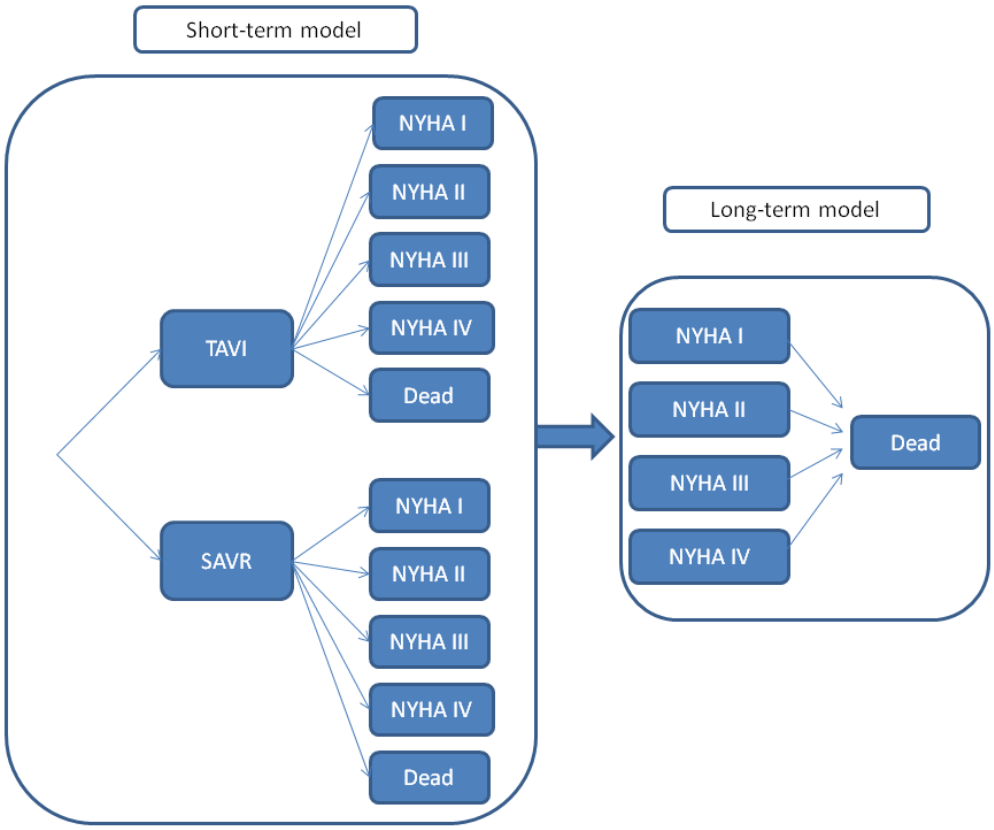
5.3 Methods

To determine the cost-effectiveness of interventions, health costs and outcomes relating to TAVI and SAVR were assessed by decision analytical modelling combining health related quality of life data from a UK AS population with data extracted from published randomised and registry studies.

5.3.1 Analyses and model structure

A cost-utility analysis was conducted with benefits expressed in terms of quality adjusted life years (QALYs) (Richardson and Manca, 2004), costs presented from the perspective of the UK health care provider and results expressed as incremental cost-effectiveness ratio (ICERs) (Reed et al., 2005). A decision tree was constructed to capture the costs and benefits of the interventions from baseline to 2 years and a cohort Markov Model with annual cycles was used to propagate the costs and benefits over a 10 year time horizon, Figure 5-1. A Markov Model assumes that patients exist in one of several possible health states at any time and can move (or transition) between these health states over a time period or cycle. The probability of moving from one health state to another is calculated over several cycles, where the sum of each transition probability must equal 1. The Markov Model ends at a pre-defined state (i.e. dead or time period). A supplementary analysis was based on life years provided by the interventions. Markov modelling requires that values are assigned to each health state in the form of costs and utilities. The costs and outcomes are summed at the end of each cycle according to the proportion of patients expected to be in each health state. Costs and benefits after year 1 were discounted at the National Institute of Clinical Excellence (NICE) preferred rate of 3.5%. Analyses were conducted in Microsoft Excel© (Microsoft Corporation, Redmond, WA, USA).

Figure 5-1 Structure of the decision model



5.3.2 Outcomes and Utility

Health benefits were based on NYHA class transitions with each class ascribed a mean EQ-5D (EuroQoL, 1990) health utility value generated from a UK study population previously described (Fairbairn et al., 2012). This population data did not include any NYHA category I patients, therefore EQ-5D values for this group were taken from UK population norms for the age group (Kind P, 1999). The utility value is multiplied by the unit of measure (life-years gained) in order to report the primary outcome measure (Quality Adjusted Life Years, QALY's). As the only randomised study of TAVI versus SAVR in high-risk patients, PARTNER A was used as the basis of the patient outcomes data (Kodali et al., 2012b). The NYHA proportions from the trial publication were employed with the local NYHA mean EQ-5D values, to generate baseline to 2 year QALYs. As NYHA transition may not capture all the impact of complications additional utility decrements were calculated by subtracting mean utility values associated with complications in published literature from the mean EQ-5D scores for NYHA III. These were adjusted to 80% to reflect the proportion of patients with complications that would die. The NYHA proportions at 2 years were subject to the proportional changes observed

in NYHA classes by Kodali *et al* from 1 to 2 years. The changes from 1 to 2 years were employed as constant proportional changes (with half-cycle correction) in NYHA classes for the 10 year time horizon of the cohort, Table 5-1. To illustrate, the population of NYHA category I was reduced by 12% annually. Using this approach and considering the percentage reductions from the other NYHA categories, the annual mortality rate was set at 40%.

Table 5-1 Utility scores and NYHA proportional changes

EQ5D utility scores			**Annual NYHA Changes from 2 years**		**Utility decrements**		
NYHA		**Reference**	**% change**	**Reference**	**Complication**	**Decrement**	**Reference**
I	0.73	UK Norm (Kind-1999)	-0.12	Kodali (2012)	Major stroke	0.39	Solomon (1994)
II	0.63	Fairbairn (2012)	-0.14	Kodali (2012)	Vascular complication	0.06	Morgan (2006)
III	0.56	Fairbairn (2012)	-0.06	Kodali (2012)	Renal replacement therapy	0.11	Lee (2005)
IV	0.46	Fairbairn (2012)	-0.08	Kodali (2012)			
Dead	0	N/A	40	Kodali (2012)			

5.3.3 Costs

Costs were based on national UK values, Table 5-2. The TAVI procedure was charged at a standard NHS tariff payment-by-results fee. This fee covered the device costs, procedural costs (medical professionals, theatre time), post-operative recovery (coronary care unit) and 4 days general ward hospital stay. The TAVI care pathway incorporated 4 additional days general ward hospital stay, ambulatory monitoring, two echocardiograms, ECG's, a vascular surgery consultation, and three follow-up visits as 1, 6 and 12 months. The SAVR clinical pathway was similar except that this group had 5 days in an intensive therapy unit bed, 7 days in a general ward bed. Long-term costs up to 2

years included cost of the procedure, valve re-dos, length of hospital stay, complications and medication requirements. Future costs were calculated per NYHA category based on weekly care package and subsequent hospitalisation tariffs calculated using a previously published hospitalisation annual hazard per NYHA category (Caro et al., 2006).

Table 5-2 Costs of TAVI and SAVR

Unit Cost (source)	**TAVI**	**SAVR**
Standard Procedure (NHS tariff)		
Procedure	£16,500.00	£9,256.00
Cardiology - Ambulatory Monitoring	£25.65	£25.65
Vascular Surgery - Follow Up Attendance - Single Professional	£120.00	NA
CT Angio- aortic and peripheral	£148.14	NA
Trans Thoracic Echo (Ultrasound)	£27.64	£27.64
Cardiology - Ultrasound Trans Oesophageal Echo	£128.24	£128.24
Cardiology – ECG	£33.00	£33.00
Chest physiotherapy	£1,641.00	£1,641.00
Cardiology follow-up attendance	£113.00	£113.00
General Ward bed day cost	£280.00	£280.00
Intensive Care Unit bed day cost	£1,360.00	£1,360.00
Complication unit costs (NHS Ref costs)		
Pacemaker Implant	£2,886.00	£2,886.00
TIA	£1,252.00	£1,252.00
Minor stroke	£3,479.00	£3,479.00
Major stroke	£3,479.00	£3,479.00
Myocardial Infarct	£2,305.00	£2,305.00
Vascular Complication	£3,772.34	£3,772.34
Major Bleed	£3,772.00	£3,772.00

RR for Kidney fail	£1,421.00	£1,421.00
Endocarditis	£5,261.00	£5,261.00
Repeat Hospitalisation	£1,359.00*	£1,359.00*
Cost of care per NYHA category (PSSRU) β		
Dead	£0.00	£0.00
I	£55.00	£55.00
II	£141.00	£141.00
III	£223.00	£223.00
IV	£626.00	£626.00
Annual Medication costs (BNF)β		
Clopidogrel for stroke, TIA and MI	£30.00	£30.00
Secondary care anticoagulation services for AF	£649.00	£649.00
Beta Blockers for MI	£19.66	£19.66
Simvastatin	£12.09	£12.09
ACE Inhibitors for MI	£14.75	£14.75

*One night non-elective stay; β per person per annum

PSSRU = personal social services research unit (Curtis, 2011) (excludes accommodation);

BNF = British National Formulary (Britain.)

5.3.4 Event probabilities

The majority of event probabilities were taken from the PARTNER A study, Table 5-3. Due to variations in pacemaker implantation post-TAVI according to the valve type an average of probabilities was taken from previous studies to reflect mean event rates.

Table 5-3 Event probabilities and their reference source

	TAVI		SAVR	
	Probability	**Reference**	**Probability**	**Reference**
Procedural outcomes				
Conversion to SAVR/TAVI	0.007	(Moat et al., 2011)	0.003	(Smith et al., 2011)
Multiple valve (≥ 2 implanted)	0.02	(Smith et al., 2011)	0	N/A
Intensive Care Unit bed days (n)	0.5	LTHT Expert opinion*	5	(Dimarakis et al., 2011, Smith et al., 2011)
Coronary care bed days (n)	3	LTHT Expert opinion*	0	LTHT Expert opinion*
General ward bed days (n)	4	LTHT Expert opinion*	7	(Dimarakis et al., 2011) LTHT Expert opinion*
2 Year complications				
New Permanent Pacemaker	0.15	Mean MCV/ESV	0.05	(Smith et al., 2011)
TIA	0.036	(Kodali et al., 2012b)	0.020	(Kodali et al., 2012b)
Stroke	0.077	(Kodali et al., 2012b)	0.049	(Kodali et al., 2012b)
Myocardial Infarction	0.004	(Kodali et al., 2012b)	0.015	(Kodali et al., 2012b)
Major Vascular Complication	0.116	(Kodali et al., 2012b)	0.038	(Kodali et al., 2012b)
Major Bleed	0.19	(Kodali et al., 2012b)	0.295	(Kodali et al., 2012b)
RR for Kidney failure	0.062	(Kodali et al., 2012b)	0.069	(Kodali et al., 2012b)
Endocarditis	0.015	(Kodali et al., 2012b)	0.01	(Kodali et al., 2012b)
New Atrial Fibrillation	0.12	(Smith et al., 2011)	0.17	(Smith et al., 2011)

Hospitalisation hazard by NYHA		
I	0.26	(Caro et al., 2006)
II	0.42	(Caro et al., 2006)
III	0.79	(Caro et al., 2006)
IV	1.81	(Caro et al., 2006)
Dead	0	N/A

* LTHT = Leeds Teaching Hospitals NHS Trust; MCV = Medtronic CoreValve™; ESV = Edwards-SAPIEN™

Long-term data relating to the outcomes of TAVI patients or the longevity of the valve are not yet available, hence a number of assumptions were necessary: 1) The TAVI valve retains functionality for the lifetime of the patient. 2) Implanted pacemakers do not require replacement. 3) TAVI and SAVR patients are subject to the same NYHA proportional change rate after 2 years. In addition, it was also assumed that utility decrements associated with complications were experienced for the first 2 years only, as patients with serious complications are more likely to die early in the model.

5.3.5 Sensitivity analyses

Deterministic and probabilistic sensitivity analyses were conducted to evaluate the sensitivity of the results to the assumptions made and parameter values chosen (Maliwa et al., 2003) and to determine the level of uncertainty surrounding the base case estimates. Sensitivity analyses use the average estimates of utilities, cost and transition probabilities to test the robustness of the model. Variations in any of these variables can be performed in order to determine risk. Deterministic analyses utilise a set threshold to identify any effect upon results. Probabilistic analyses use the probability distribution of variables to (Monte Carlo simulations) to identify variations in results. Since the increased likelihood of early major stroke is a concern with the TAVI procedure, additional sensitivity analyses were run to explore the impact of this complication on the cost-effectiveness results.

For the probabilistic sensitivity analyses (PSA), distributions for parameter values were specified and 10,000 Monte Carlo simulations run using random draws for each parameter distribution and for each run incremental costs and benefits calculated, Table 5-4. The outcomes of the PARTNER A trial (the NYHA transitions from baseline to 2 years) were assumed to be fixed. The PSA allowed the NYHA lifetime changes to vary independently for TAVI and SAVR. The uncertainty surrounding the analyses were represented as incremental benefit and cost plots for each simulation run on a cost-effectiveness plane. Net benefit was calculated and a cost-effectiveness acceptability curve (CEAC) (Fenwick et al., 2001) was generated to determine the probability that TAVI was cost-effective versus SAVR given a range of values of willingness to pay for an additional QALY.

Table 5-4 Sensitivity analyses parameter values

Parameter	Analysis	Source
Costs		
Procedural costs	-/+ 25%	N/A
Complication costs	-/+ 25%	N/A
Weekly care costs by NYHA	-/+ 25%	N/A
TAVI Length of ICU stay	2	Zahn (2010)
TAVI tariff price	£25,000	N/A
Utility		
Alternative Utility values by NYHA		
I	0.85	Maliwa (2003)
II	0.71	Maliwa (2003)
III	0.57	Maliwa (2003)
IV	0.43	Maliwa (2003)
Complication utility decrement	+25%	
TAVI Event probabilities		
UK Registry data		Moat et al (2011)

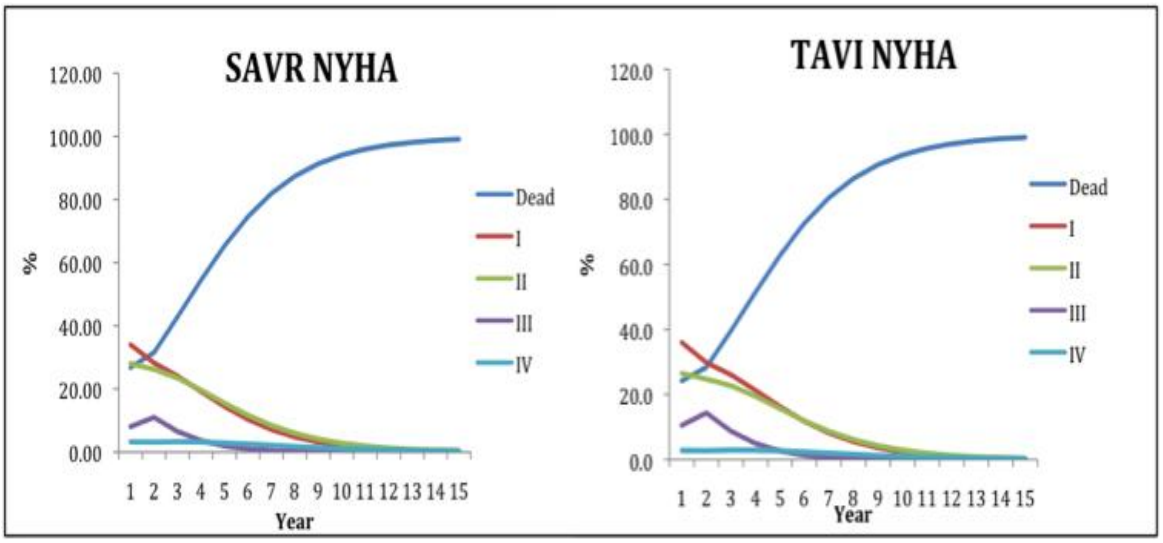
TAVI extreme values ('worst case' scenario):		
Multiple valve	0.036	Tamburino et al (2011)
Permanent pacemaker	0.393	Zahn et al (2011)
Major stroke	0.1	Buellesfeld et al (2010)
Myocardial Infarction	0.086	Gurvitch et al (2010)
Vascular complication	0.324	Leon et al (2011)
Major bleed	0.032	Tamburino et al (2011)
Renal replacement for kidney failure	0.017	Leon et al (2011)
New Atrial Fibrillation	0.0	Leon et al (2011
Hospitalisation hazard rate by NYHA	-/+ 25%	
Discount rate	1%/6%	N/A

5.4 Results

5.4.1 Base case analysis

The NYHA proportions and mortality for the two groups over the 10-year horizon are shown as Figure 5-2. As the NYHA proportional changes were assumed the same across TAVI and SAVR the differential in costs and effects remains relatively constant after year 1 and across the model time horizon. TAVI ranges between £1,350 and £1,600 per patient cheaper than SAVR annually. After year 1 the annual QALY differences between interventions are negligible (around 0.003-0.005 in favour of TAVI). After Year 3 there was little difference between interventions in terms of mortality. By Year 10 in the simulations, 75% and 76% of the cohort were dead in the TAVI and SAVR groups, respectively. At 2 years TAVI was found to confer QALY gains of 0.956 compared to 0.925 provided by SAVR. After 10 years the average QALY gains per person were 2.81 and 2.75, respectively providing a modest incremental benefit for TAVI of 0.063 QALYs.

Figure 5-2 New York Health Association classification proportions over a 10 year horizon



Procedural costs were estimated to be £19,368 for TAVI and £20,380 for SAVR. While the TAVI tariff was substantially more than the SAVR tariff, the surgical intervention incurred greater length of stay and time in intensive care which are significant drivers of cost, Figure 5-3. Complication costs were similar across the interventions though slightly higher in SAVR presumably due to the high costs associated with endocarditis and new atrial fibrillation (both more likely in SAVR). The long term care and hospitalisation costs over the 10 year time horizon were similar in TAVI and SAVR which is unsurprising as they were based on the NYHA proportions. The slightly lower long-term costs in SAVR may be due to the higher mortality in this group. Total 10 year per person costs, benefits (QALYs and life years) and the respective ICER are included in Table 5-5. The base case analysis figures indicate that TAVI dominates SAVR – i.e. is cheaper and more effective – over the time horizon.

Figure 5-3 Hospital and admission costs of TAVI and SAVR

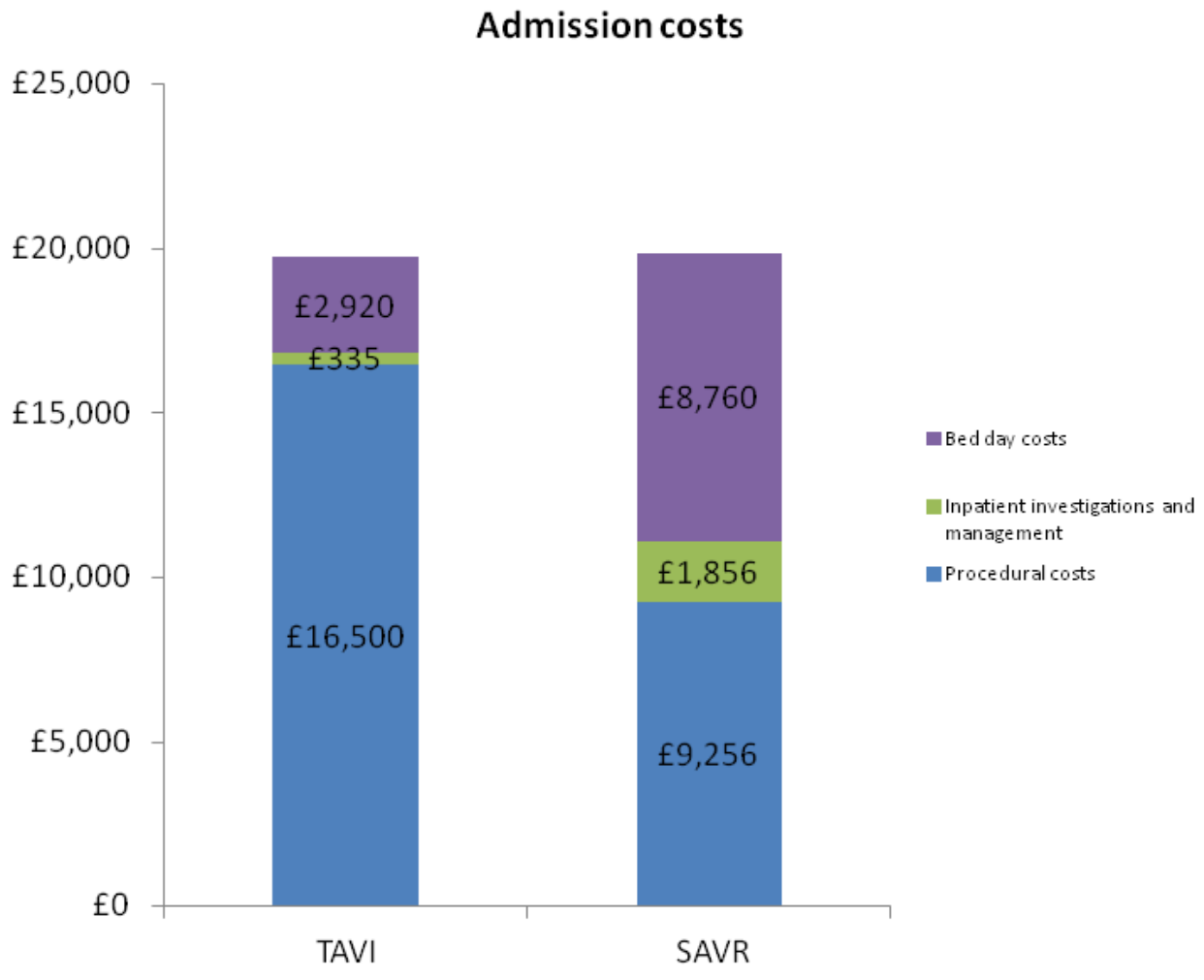


Table 5-5 10 year deterministic and sensitivity analyses

	Costs*	QALYs **	ICER †
Base case			
TAVI		2.81	
Procedural and re-do costs	£19,368.32		
Complication costs (after 2 years)	£2,125.14		
Annual medication costs (after 2 years)	£82.63		
Long term care and re-hospitalisation costs	£31,422.01		
TAVI total 10 year cost	£52,593.02		
SAVR		2.75	
Procedural and re-do costs	£20,380.03		
Complication costs	£2,709.60		
Annual medication costs	£113.62		
Long term care and re-hospitalisation costs	£31,095.10		
SAVR total 10 year costs	£53,943.40		
Incremental QALY	-£1,350.38	0.063	TAVI Dominates
Life Years	4.42	4.30	
Incremental Life Years	-£1,350.38	0.13	TAVI Dominates

Deterministic Sensitivity Analyses	**Incremental QALY**		
Costs	**Incremental cost**	**Incremental benefit**	**ICER**
Procedural Costs +25%	-£1,689.63	0.063	TAVI Dominates
Procedural Costs -25%	-£1,011.13	0.063	TAVI Dominates
TAVI Tariff price £25,000	£7,294.12	0.063	£116,231.63
TAVI Procedure costs +25%	£3,393.00	0.063	£54,067.41
TAVI Length of stay alternative values	£689.62	0.063	£10,989.06
Complication costs +25%	-£1,497.51	0.063	TAVI Dominates
Complication costs -25%	-£1,203.25	0.063	TAVI Dominates
Hospitalisation costs +25%	-£1,336.36	0.063	TAVI Dominates
Hospitalisation costs -25%	-£1,364.40	0.063	TAVI Dominates
Weekly care costs by NYHA +25%	-£1,264.95	0.063	TAVI Dominates
Weekly care costs by NYHA -25%	-£1,435.81	0.063	TAVI Dominates
Utility			
Alternative utility values	-£1,350.38	0.066	TAVI Dominates
Complication utility decrement +25%	-£1,350.38	0.058	TAVI Dominates
Event probabilities			
TAVI extreme (‘worst case’) scenario complication Probabilities	£99.95	0.009	£11,307.18
UK Registry TAVI complication Probabilities	-£1,715.18	0.076	TAVI Dominates
Hospitalisation rates by NYHA +25%	-£1,336.36	0.063	TAVI Dominates
Hospitalisation rates by NYHA -25%	-£1,364.40	0.063	TAVI Dominates
Other			
Time horizon = 5 years	-£1,452.91	0.045	TAVI Dominates
Discount rate 1% for costs and QALYs	-£1,323.06	0.067	TAVI Dominates
Discount rate 6% for costs and QALYs	-£1,373.57	0.059	TAVI Dominates

Probabilistic sensitivity analysis – mean

Monte Carlo simulation results

TAVI	£52,593.08	2.82	
SAVR	£54,004.89	2.75	
Incremental	-£1,411.09	0.066	TAVI Dominates

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve implantation; NYHA = New York Heart Association classification. *All costs at 2011 prices; ** Quality adjusted life years. †Incremental cost-effectiveness ratio

5.4.2 Deterministic sensitivity and scenario analyses

Deterministic and probabilistic sensitivity analyses are presented in Table 5-5. These suggest the base case results are robust to changes in input parameters, yielding similar ICERs. Only analyses where parameter values for one intervention changed (and the other held the same) appeared to have a substantive effect on the ICER value. Thus using a worst case scenario 1 year complication probabilities for TAVI yielded an ICER of £11,307 – in this case TAVI is now more expensive but still offers incremental benefit. Increasing the TAVI procedural costs by 25% increased the ICER to just over £54,000. Allowing for 2 bed days in intensive care (Zahn et al., 2010) for TAVI patients increases the ICER to around £11,000- still below the NICE cost-effectiveness threshold. Including 3 days of intensive care for TAVI yields an ICER of £32,660. The cost of the SAVR tariff would have to drop to £6,632 (ceteris paribus) or alternatively incur only around 3 intensive care bed days before the ICER exceeds the £20,000 threshold. TAVI tariff costs would have to be around £19,000 or £9,800 more expensive than the SAVR tariff, for the ICER to exceed £20,000. The alternative utility values did not significantly affect results, yielding slightly higher incremental benefits (0.066 vs. 0.063) for TAVI. Reducing the time horizon to 5 years and alternating discount rates did not substantively affect results.

TAVI remained dominant in the instance of increasing the probability of major stroke after TAVI (from 0.051 to 0.10) or increasing the utility decrement associated with stroke (from 0.39 to 0.70). Finally, if all values remain constant as per the base case, the cost of stroke would have to be increased to over £100,000 (from £3,479) before the ICER exceeded £20,000.

5.4.3 Probabilistic sensitivity analyses

Figure 5-4 is the cost-effectiveness plane plotting 10,000 incremental cost and benefit estimates from the Monte Carlo simulations. Most of the estimates are in the North-East and South-East quadrants indicating TAVI is more costly and more effective or cheaper and more effective.

Figure 5-4 Cost effectiveness plane TAVI versus SAVR

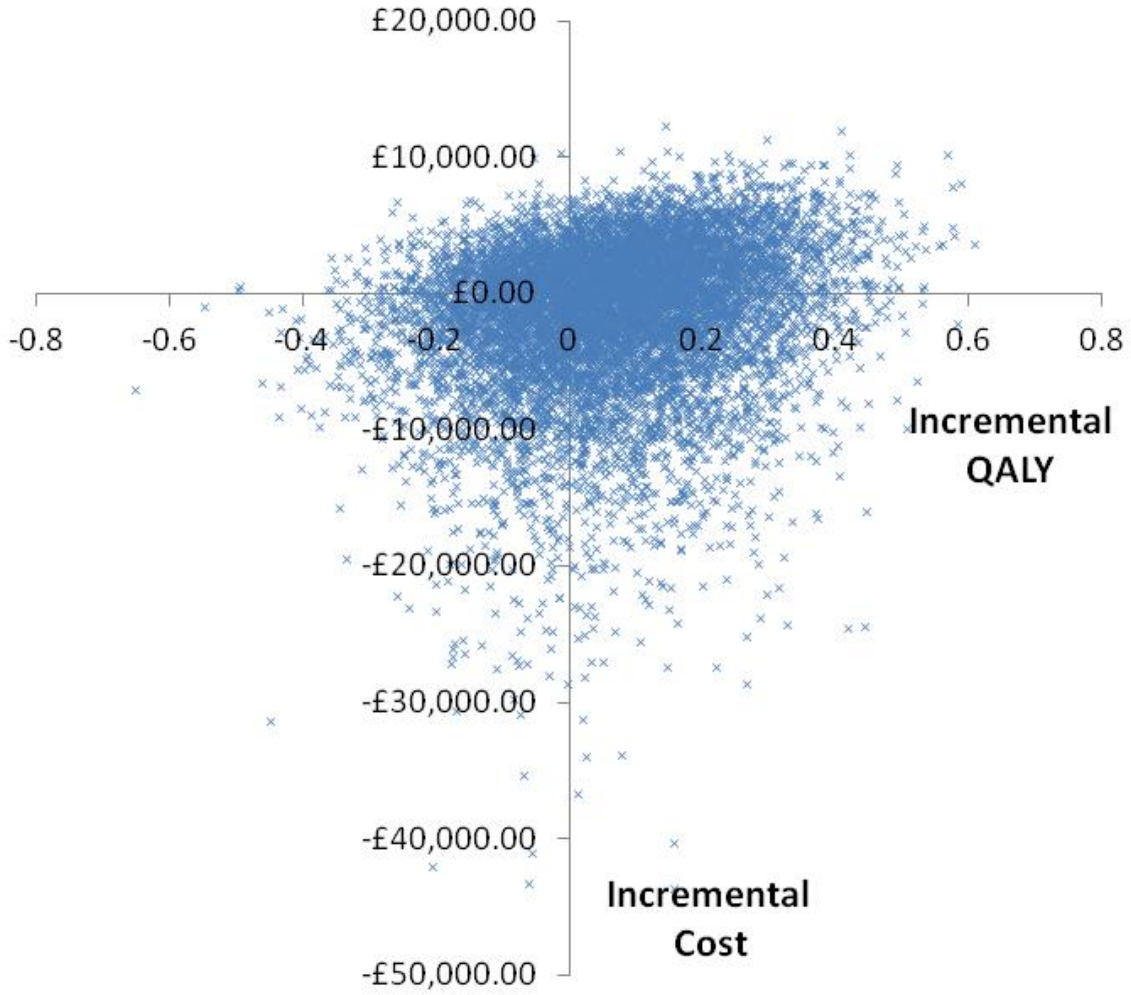
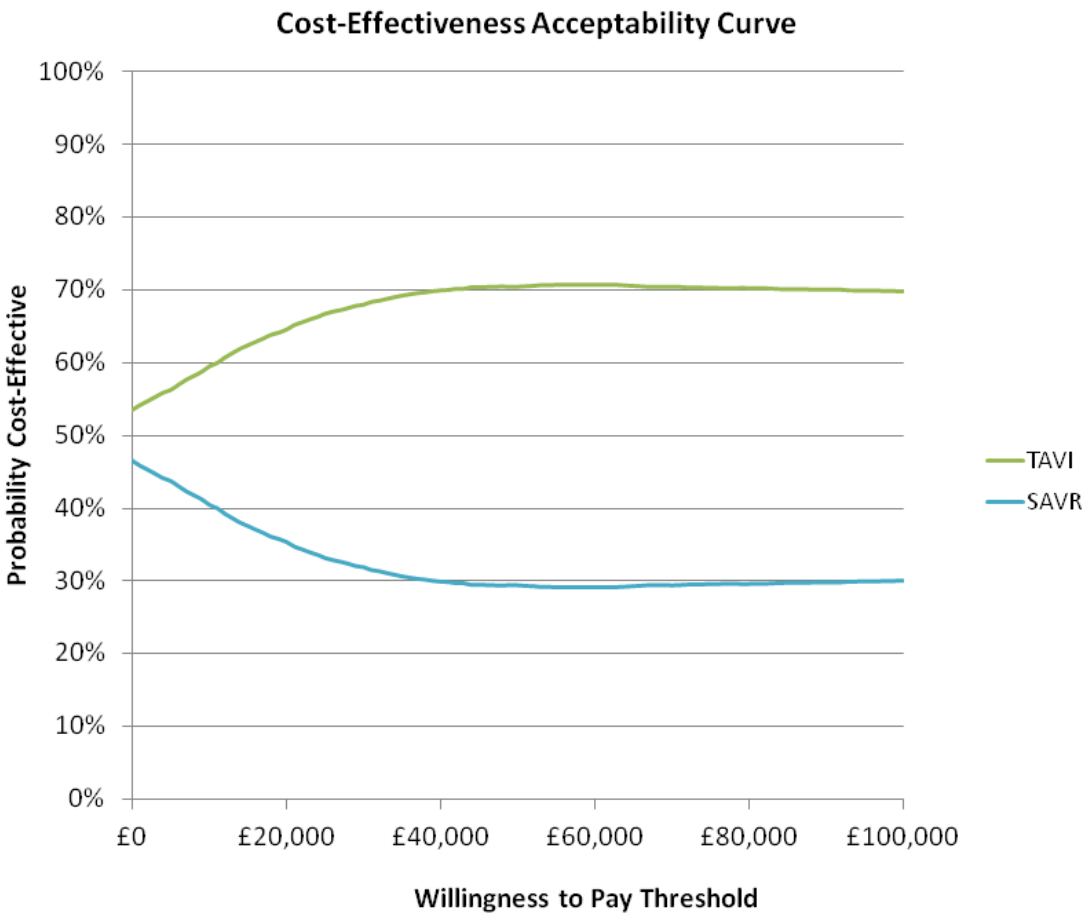


Figure 5-5 is the cost effectiveness acceptability curve (CEAC), indicating TAVI is cost-effective regardless of the incremental QALY willingness to pay threshold. At the NICE threshold of £20,000 TAVI has a 64.6% likelihood of being cost-effective, compared to 35.4% for SAVR. The mean incremental costs and benefits from the Monte Carlo simulations were very similar to the base case estimate, Table 5-5.

Figure 5-5 Cost-effectiveness Acceptability Curve



5.5 Discussion

The economic analysis in this study suggests that from the UK healthcare provider perspective, TAVI is a cost-effective option in high-risk but operable elderly patients when compared to SAVR. Over a 10 year horizon, the model yielded both incremental cost and QALY benefits for TAVI over SAVR. These results appear robust to numerous sensitivity analyses including those targeting major stroke. TAVI conferred only marginal quality of life benefits over SAVR with similar costs for both interventions. Therefore, results were sensitive to changes in costs and benefits when they occurred in either intervention arm in isolation. The additional device costs for TAVI appears outweighed by the greater length of stay cost (and intensive care stay) in the SAVR group. The probabilistic sensitivity analyses and CEAC suggest that TAVI is probably cost-effective regardless of the QALY willingness to pay threshold.

The cost-effectiveness of TAVI versus medical therapy has been previously assessed in a UK population ineligible for surgery (Watt et al., 2012), but this analysis is the first UK study to compare the costs and benefits of TAVI and SAVR in a high-risk but operable AS group. The recently published PARTNER study cost-effectiveness analysis report a significant cost benefit at one year towards TF-TAVI with similarly higher procedural but lower hospitalisation costs compared to SAVR (Reynolds et al., 2012a). Procedural costs are likely to differ between studies (US versus UK costs) but health benefits (QALY's) should remain universal. The one year incremental QALYs in both analyses are 0.027 supporting our model design, but this study reports lower QALY gains with TAVI. This may be a consequence of our combined TF and TA assessment as TA-TAVI resulted in lower quality adjusted life expectancy and was deemed economically unattractive in the PARTNER study. Another cost-analysis by Neyt *et al* (Neyt et al., 2012) concluded that TAVI was cost-effective in inoperable patients but not in high-risk operable patients. However, their conclusions are limited by a lack of health utility data. Doble *et al* (Doble et al., 2012) performed a comprehensive analysis of TAVI versus medical and surgical therapy concluding that TAVI may not be cost-effective compared to SAVR over a 20 year horizon. This observation was determined predominantly by the higher

procedural costs of TAVI. However, their SAVR costs were estimated using a lower risk, 70 year-old population rather than the older, higher risk population in this study and that of PARTNER. In addition there is no mention of the length or cost of hospital stay, a major driver in our own cost analysis. This study has shown that despite a greater procedural cost, TAVI remained cost-effective compared to SAVR due to lower post-procedural costs (length and cost of hospital stay). Our TAVI group had a mean ICU stay of 0.5 days and 3 further days in a coronary care unit. In the PARTNER A study there was a median ICU stay of 3 days reflective of US practice. If outcomes are in part a function of the intensity of care received, it is possible we overestimated outcomes or underestimated the costs for TAVI depending upon individual practice and national guidance. However, including 2.4 days of intensive care for TAVI patients in this analysis still yields an ICER below £20,000. Additionally, the ICU stay post-SAVR in PARTNER A may be considered longer than is 'normal' for a standard SAVR post-operative recovery. The nature of high-risk cardiothoracic surgery in this older age group with a number of associated co-morbidities, results in a longer ICU and over-all hospital stay, thus driving up costs (Dimarakis et al., 2011). This study used the UK TAVI tariff as an average national procedural cost with sensitivity analysis to allow for variations which may occur locally. Transcatheter device costs are of particular concern as a driver of high procedural costs. Our results suggest that TAVI is no longer cost-effective when device costs rise above £19,000 (when the QALY gain willingness to pay threshold is £20,000).

Post-TAVI we predicted no valve re-do's after 12 months and that the integrity of valves were maintained for the model time horizon. Thus our results would be sensitive to any future evidence suggesting differential rates of valve failure and re-do procedures between SAVR and TAVI. Due to the uncertainties of long-term data, our model time horizon was performed at a conservative 10 years rather than a lifetime model. In their lifetime comparison of TAVI vs. standard medical therapy, Reynolds *et al* (Reynolds et al., 2012b) found significant cost benefits of TAVI within the first year, which were subsequently lost over long term follow-up due to the burden of incurred costs over an extended life time in an elderly population. This issue may not apply in a younger population with less co-morbidity, as studies have demonstrated that most long-term deaths post-TAVI are non-cardiac in origin (Buellesfeld et al., 2011, Tamburino et al., 2011, Zahn et al., 2011). However, the

shorter timeframe of the model and uncertainty in terms of outcomes, device longevity and need for future valve replacements post-TAVI, mean that extrapolation of our findings to a younger-lower risk age group remains difficult. Stroke is a significant clinical concern post-TAVI (Smith et al., 2011). As a major contributor to hospital and social care costs, (Luengo-Fernandez et al., 2009) stroke could additionally impact upon the cost-effectiveness of the TAVI procedure. However, our analysis suggests that TAVI still dominates SAVR in cost-effectiveness even in the presence of a doubling of the stroke rate. This finding is reassuring, particularly when considering the latest evidence from PARTNER which suggests that the 2 year stroke rate is not significantly different between TAVI and SAVR.

Our findings offer a perspective based on UK clinical practice, costs and local health utility values. The results provide useful information to local health care commissioning agencies and national policy makers regarding the relative cost-effectiveness of TAVI and SAVR in elderly high-risk patients. The clinical effectiveness of TAVI has been demonstrated in the PARTNER A trial; our study provides additional evidence that compared to SAVR, TAVI is likely to be a cost-effective approach in an elderly high-risk AS population.

There is a clear requirement for longer term outcome data in TAVI patients. Such data will become available as the TAVI procedure becomes more common in clinical practice and large data registries are published. Avenues for future research in health economics include the employment of the value of information framework and the calculation of total decision uncertainty (expected value of perfect information) (Brennan et al., 2007) for parameters and samples. This information will help identify the parameters that are driving economic decision uncertainty and guide future research and trial planning.

5.6 Limitations

As TAVI is a relatively new procedure there are limited data available to populate the decision model. Hence a number of assumptions were necessary which increase the level of uncertainty in the results. However, sensitivity analyses suggest our results are relatively unaffected by changes in parameter values.

Whilst we have based costs on the UK care pathway for this population we have based the benefits on US data (PARTNER A). The PARTNER A trial employed both transapical and transfemoral implantation approaches but only the Edward Sapien device was used. Reliance on the PARTNER A study efficacy data may limit extrapolation of our findings outside of the studies recruitment criteria, in particular related to the Medtronic CoreValve system. In addition the PARTNER A cost-effectiveness study report a 0.068 QALY gain with TF-TAVI, but 0.070 loss with TA-TAVI. This suggests a potential weakness in our methodology of reporting an average cost-effectiveness despite the use of deterministic and probabilistic sensitivity analyses. Future research should explore the differential cost-effectiveness of transapical and transfemoral approaches in the UK.

5.7 Conclusions

With any new treatment, the medical community must ask first if it is safe and clinically effective and secondly if it is cost-effective. In comparison to the accepted reference standard treatment SAVR, TAVI appears likely to be cost-effective in a high-risk elderly population. TAVI was cheaper and more effective than SAVR according to the base case analysis. Sensitivity analysis using the NICE threshold of £20,000 showed TAVI to have a 64.6% likelihood of being cost-effective, compared to 35.4% for SAVR. Whilst the findings cannot be extended to other populations of different age or surgical risk, the evidence provided should help clinicians and commissioning groups in future decision making policies and resource allocation.

6 Final Discussion

In the near future the United Kindgom is set to experience an AS epidemic (Berry et al., 2013). Demographic changes in the population indicate that this disease is set to pose an increasing challenge to clinicians managing valvular heart disease and represent a greater burden on the health care system (Nkomo et al., 2006). SAVR remains an excellent operation, delivering good prognostic and quality of life benefits. However, the real world situation exposed by the European heart survey (Iung, 2005) highlighted the need for an alternative. Since its inception TAVI has rapidly become the alternative treatment of choice for the inoperable patient and those at high operative risk. It has been shown to be a procedural success and significantly improves the survival and quality of life of a patient. Its benefits over medical therapy are substantial, with comparable results compared to SAVR in high-risk patients. Despite significant progress, TAVI remains a new technology only recently practised. Due to the high-risk nature of the procedure, limited resources and substantial associated costs, TAVI is unlikely to be a suitable treatment for all high-risk patients. Additionally, the usefulness of TAVI in an intermediate risk population is yet to be proven. Evidence that can guide patient selection and thus clinical practice will be essential to fundamentally establish the role of TAVI in the treatment of severe symptomatic AS.

This thesis advances the practice of TAVI by contributing original evidence of the clinical and cost-effectiveness of the procedure from the perspective of the patient as well as the health care provider. It comprehensively assesses several of the key areas of research as recommended by the international VARC (Kappetein et al., 2012b). However, there remain areas of research that were not possible to explore during the time of this thesis, yet they are relevant to our conclusions and merit inclusion in the final discussion.

6.1 Haemodynamics

6.1.1 Reverse remodelling

The unique attributes of MRI allowed us to assess ventricular reverse remodelling in the context of changes in valvular function, myocardial infarct and fibrosis. Post TAVI we have demonstrated that significant reverse remodelling of the left ventricle occurs due to reduced ventricular wall stress following a significant decrease in valvular pressure gradient and valvulo-arterial impedance. Our data are consistent with the available published echocardiography data (Clavel et al., 2009, Ewe et al., 2010, Hahn et al., 2013), but do not rely upon the geometric assumptions inherent with the technique of echocardiography. As an appropriately powered study using the 'gold standard' technique, our data provide the most robust evidence to date of the haemodynamic benefits of TAVI. One recently published manuscript also used the technique of CMR to examine the changes in LV mass and volumes, 6 months following TAVI (La Manna et al., 2013). They observed similar levels of LV mass reduction and geometric changes (reduced LV mass/volume ratio), but did not demonstrate any change in volumes or function. This finding is in contrast to our own observations and those of the echocardiography studies. It also represents a disparity to the reverse remodelling effects established in the SAVR literature (Sandstede et al., 2000). The authors conclude that this may represent a difference in reverse remodelling processes between the procedures, but accept the limitation of a lack of surgical comparator group. Their conclusions are further limited by a lack of valvular haemodynamic data, nor do they assess the effects of myocardial fibrosis and scar. Comparing our two studies reveals differences in the TAVI population baseline characteristics. Our patient group had greater pre-procedural volumes (EDVi 94±18 ml/m^2 vs. 87±35 ml/m^2; ESVi 46±18 ml/m^2 vs. 34±29ml/m^2), poorer function (EF 52±12% vs. 64±15%) and thus in all likelihood a greater severity of AS. As demonstrated by the results of our linear regression analyses the potential for reverse remodelling is greater in the instances of more advanced remodelling, providing a possible explanation for any differences observed.

6.1.1.1 Early versus late reverse remodelling

A potential drawback in the design of our valve haemodynamics and ventricular reverse remodelling study was the limitation of imaging time points to baseline and 6 months. Conclusions regarding early and late changes in valvular and ventricular function are therefore restricted. However, we do know from echocardiography studies that post TAVI there is an immediate reduction in valvular pressure gradient and wall thickness (< 1 week) (Clavel et al., 2009), with changes in ventricular volumes occurring later (6 months – 2 years) (Hahn et al., 2013). In comparison following surgery, cavity volumes and SV are immediately reduced with no change in EF and late changes in RWT (Hahn et al., 2013). These echocardiographic findings appear to substantiate our own observations and contribute towards any conclusions. The immediate improvement in transvalvular pressure gradient and a lower incidence of patient prosthesis mismatch post TAVI results in a rapid decline in wall stress and ventricular workload (Clavel et al., 2009, Hahn et al., 2013, Kodali et al., 2012b). As a consequence ventricular twist and torsion are expected to improve early. Speckle tracking echocardiography studies have confirmed this in a small number of patients (Schueler et al., 2012, Delgado et al., 2013) but no comparison has been made to SAVR. Our results suggest that the earlier pressure reduction and greater AVA post TAVI has subtle but sustained benefits on LV wall thickness and thickening and potentially in strain and torsion compared to SAVR at 6 months. The difference may not be sustained in the long term (≥2 years) as the early advantage of TAVI is lessened with time. This subject matter needs further research, using a more accurate method of analysis (speckle tracking echocardiography or myocardial tagging study) to compare the effects of TAVI against SAVR.

6.1.1.2 Reduced Ejection Fraction

A major factor in the refusal of patients for surgical AVR was found to be a reduced EF (Iung, 2003). This is an area of particular concern, given the higher percentage of TAVI patients with a reduced EF and the uncertain nature of reverse remodelling in the impaired ventricle. The evidence from our work suggests that reduced EF does not by itself imply reduced capacity to reverse remodel post surgical or transcatheter aortic valve replacement. Indeed the individuals with the greatest change from baseline were those with the lowest function. Rather it is the percentage of myocardial scar and reduced

viability which influence inferior reverse remodelling. Evidence is beginning to indicate a specific role for TAVI in the severe AS patient with a reduced EF, as the reverse remodelling outcomes appear superior when compared to SAVR (Clavel et al., 2010, Bauer et al., 2013). The improved outcomes post-TAVI in this group may be related to the associated co-morbidities and risk factors, as our evidence suggests either procedure is a viable option and that the important factor is the assessment of scar burden. As TAVI expands identifying who is not a suitable candidate may become a more relevant issue than who is fit for intervention. CMR could thus be useful in aiding future patient selection.

6.1.2 Coronary Artery Disease

Given the prevalence of CAD in severe AS (25-50%) (Kvidal et al., 2000) substantial interest has been generated concerning the clinical impact and significance of CAD post TAVI. This question remains unanswered by PARTNER as patients with significant non-revascularised CAD were excluded from the study. The importance of CAD in the SAVR population is better recognised. Whilst CABG increases the surgical and mortality risk in the short term, non-revascularised CAD detrimentally effects long-term outcomes (Lund et al., 1990). Non-randomised TAVI studies suggest there is no significant effect of CAD upon procedural outcomes or early death (Thomas et al., 2011, Rodes-Cabau et al., 2010). We identified the adverse effects of significant CAD (>50% degree stenosis) in the reverse remodelling process post TAVI and SAVR, independent of the drop in valvuloarterial impedance. This adverse relationship was related to the amount (g and %) of myocardial infarct and associated viability of the ventricle as the main determinant of reduced reverse remodelling. This evidence is supported by the inferior long-term outcomes of patients with CAD described post TAVI (Masson et al., 2010, Dewey et al., 2010). Individuals with concomitant CAD (>50%) suffer from increased cardiac mortality, and lower ventricular EF improvement 9 months following TAVI (Rodes-Cabau et al., 2011b).

The incidence and consequences of new peri-procedural myocardial infarct is still uncertain, as markers of myocardial damage are frequently elevated with little consensus or uniformity amongst the studies (Goel et al., 2013). VARC have attempted to clarify this matter by recommending a standardised definition of MI post TAVI, but results are still pending (Kappetein et al., 2012b). In a

small population, using the technique of LGE we established that the incidence of peri-procedural infarct is small post-TAVI and SAVR and has no clinical significance on reverse remodelling.

Managing TAVI patients with significant CAD therefore remains a conundrum. If the presence of CAD is a marker of worse outcomes it raises the question, 'should these patients be revascularised'? As of yet no evidence exists to suggest revascularisation of significant CAD provides protection against peri-operative MI or improved clinical outcomes (Rodes-Cabau et al., 2010). The appropriateness of PCI, its timing and type of stent is therefore still an unanswered question. Nevertheless, staged PCI revascularisation is occurring, in particular in instances of proximal CAD with a suspected high ischaemic burden. This is believed to minimise the risk of infarct and instability during TAVI, whilst limiting the contrast dose. Randomised controlled trials (ACTIVATION, SURTAVI and PARTNER 2) will go some way towards answering these questions, but CMR could play a pivotal role in any future research surrounding this topic. Adenosine stress CMR can identify myocardial ischemia and viability as pre-operative adverse markers, assisting in the management of CAD pre-TAVI and aiding patient selection. In addition, it could be used to assess reverse remodelling as a clinical endpoint.

6.1.3 Patient survival

This thesis concentrated on assessing post-operative functional cardiac recovery as a clinical endpoint. We did not explore the impact of haemodynamic measurements on other clinical outcomes, in particular patient prognosis. Although mortality was not a primary outcome measure the available literature suggests our study findings have relevance to patient survival, specifically in relation to the severity of post-operative AR.

6.1.3.1 Aortic Regurgitation

Several studies have identified post-TAVI AR as an important predictor of increased mortality (Kodali et al., 2012b, Gotzmann et al., 2012a, Toggweiler et al., 2013, Moat et al., 2011, Gilard et al., 2012). A majority of patients appear to have some degree of AR post-TAVI compared to very little post SAVR (Abdel-Wahab et al., 2011). Trivial or mild AR has no significant consequence on either

reverse remodelling or survival. Moderate to severe regurgitation is however independently associated with a reduced patient survival (Tamburino et al., 2011). The paravalvular nature of regurgitation makes the accurate grading of total AR technically challenging but important in order to gage procedural success and predict patient outcomes. Angiographic (Sellers criteria) and haemodynamic (AR index) assessments are useful and have some predictive capacity (Sinning et al., 2012), but are subject to significant variability and dependent upon external factors such as the use of ionotropes or the presence of a catheter across the heart valve (Sinning et al., 2013). Echocardiography and in particular TOE are used most frequently to determine the severity of AR. However, conventional semi-quantitative methods of grading AR do not apply in paravalvular AR, as the jet is not central but annular and eccentric. Quantitative assessment of total AR may represent a more precise method of assessing AR and the associated risk. CMR phase contrast imaging allows the quantification of total AR (regurgitant %) with greater accuracy and reproducibility when compared to echocardiography. Our study and that of Sherif *et al* unequivocally prove that this technique can be applied in a TAVI population (Sherif et al., 2011, Fairbairn et al., 2013). Whether this can then be used to provide prognostic data still needs to be established. The implications of post-operative AR have heralded an increase in the pre-operative multi-modality assessment of the patients' aortic root in order to minimise the risk of developing this complication.

6.1.3.2 Aortic Root assessment

The prevention of post operative AR is therefore vital to improve patient survival. The causes of paravalvular regurgitation are believed to be predominantly due to mal positioning, under deployment, or under sizing of the device (Takagi et al., 2011). Severe aortic valve calcification is also thought to be implicated. Non-invasive imaging techniques are being increasingly used to provide detailed information about the size of the aortic root and burden of calcification. 2D TOE has traditionally been the imaging technique used to assess the size of the aortic root and degree of paravalvular regurgitation. However, the aortic route is frequently oval shaped and TOE underestimates the annular size and quantity of AR. 3D TOE improves the accuracy of these measurements but is still limited by low volume rates (Jilaihawi et al., 2013). Multislice computed tomography has developed as the 'gold standard' technique for preoperative aortic root assessment.

The aortic root can be assessed at multiple planes and levels with substantial evidence supporting its utility in predicting and reducing AR (Jilaihawi et al., 2012, Willson et al., 2012). The anatomic detail afforded by CT is excellent but the functional information is limited. In comparison, CMR has been shown to be as accurate as CT in the anatomic assessment of the aortic annulus using multislice, multiplanar SSFP imaging and has the additional benefit of providing functional detail, in particular total AR (Jabbour et al., 2011). This is undoubtedly an issue that could and should be answered in any future TAVI CMR research.

6.2 Stroke

In our assessment of cerebral embolic infarcts following TAVI we established the incidence cerebral infarcts and identified age and aortic atheroma as independent risk factors. To date this remains the only published data in the literature to establish risk factors for the number and volume of cerebral infarcts and therefore stroke. Limitations of our study include; the inability to establish the timing of embolisation and the failure to include TAVI patients with transapical access. Nor did we have a surgical comparator group. Furthermore, cerebral protection devices were not available at the time and were thus not trialled. Finally, whilst examining the effects on quality of life no detailed cognitive assessment was made. These factors are important to consider given the 5% risk of stroke following TAVI and the significant co-morbidity and mortality associated with the condition.

6.2.1 Transfemoral versus Transapical route

The mechanism of cerebral emboli during TAVI is thought to be secondary to bulky catheter devices dislodging aortic atheroma whilst moving around the aorta and releasing calcific debris whilst crossing the aortic valve. This theory was developed from previously established evidence concerning conventional stroke risk factors (Di Tullio et al., 2009), (Russo et al., 2009) and studies involving cardiac catheterisation (Lund et al., 2005, Busing et al., 2005). The relationship of aortic atheroma severity to the number of cerebral infarcts identified in our research would support this mechanism of

action. The TA access route could therefore be expected to result in a lower rate of infarcts and hence stroke, given the reduction in the number of catheters moving around the aorta and avoidance of the retrograde crossing of the aortic valve (Himbert et al., 2009). Two studies have examined this subject and have discovered no difference in the number of new infarcts between TF and TA TAVI (Rodes-Cabau et al., 2011a, Astarci et al., 2011). The explanation provided for this unexpected observation was that cerebral emboli are in fact a consequence of microbubbles developed during the exchange of cardiac catheters. The incidence of cerebral emboli would therefore not differ between the two approaches, particularly as the TA approach requires a large 24F sheath to be inserted into the LV and the exchange of multiple catheters. They support this statement by demonstrating no relationship of aortic atheroma or calcification to the number of infarcts, in contrast to the findings of our own study. Whilst air embolism may contribute to the mechanism of cerebral infarcts both studies failed to prove the timing of emboli corresponding with the exchange of catheters. They also do not acknowledge that during both procedures stiff wires, balloons and valvular devices are moved across the valve and into the ascending aorta and around the arch.

6.2.2 Transcranial Doppler and the timing of embolisation

The timing of embolisation is thus important to help identify the aetiology of cerebral infarcts, determine associated risk factors and aid preventative measures. Transcranial Doppler can detect the occurrence of cerebral high intensity transient signals (HITS) and is used in standard practice during carotid endarterectomy (Koennecke et al., 1998). Two studies have identified several stages of cerebral embolisation or HITS separated into: (1) Passage of the wire across the valve (antegrade or retrograde), (2) Passage of the super stiff wire into the LV apex (TF) or descending aorta (TA), (3) introduction of the balloon, (4) valvuloplasty, (5) introduction and positioning of the stent valve, (6) valve implantation. HITS were observed in all patients at all stages with no overall difference noticed between the procedural routes (TF and TA) or valve type (THV vs. MCV) (Kahlert et al., 2012, Erdoes et al., 2012). The greatest number of HITS was observed during valve positioning and deployment for both valves via both routes. These peak events corresponded with the longest phase of valve manipulation in the aorta and against the valve. The peak HITS with THV replacement occurred

during valve positioning, which is time consuming but once in place is quick to deploy. In contrast the MCV, which is quick to position but slow to deploy had the greatest number of HITS during valve deployment.

6.2.3 Clinical outcomes

Whilst it is not possible to define the nature of any microbubbles identified during HITS (solid material or air emboli), the collective evidence clearly suggests the predominant cause of cerebral emboli is the manipulation of bulky valves against the atheromatous and calcified valve and ascending aorta (Fairbairn et al., 2011, Kahlert et al., 2010, Kahlert et al., 2012, Ghanem et al., 2010, Rodes-Cabau et al., 2011a). This process is to a point unavoidable, therefore the information may be most useful in identifying risk factors to assist in patient selection and when to use new embolic protection devices (Onsea et al., 2012, Naber et al., 2012). The advantages and clinical application of these embolic protection devices in a TAVI population still needs to be verified using DW-MRI in randomised controlled studies.

If prevention is not possible then a clear understanding of the consequences of cerebral emboli needs to be developed. Our study and others have established that stroke whilst the main complication of these emboli, is still a relatively infrequent one. Clinically 'silent' emboli on the other hand occur in 66-93% of TAVI patients. These markers of acute cerebral ischaemia have been shown to be associated with long-term neurocognitive decline and dementia in non-TAVI populations (Yoshitake et al., 1995) and post cardiac surgery (Knipp et al., 2005). Having determined the clinical impact of cerebral emboli on short-term HRQOL we were unable to assess the impact upon complex cognitive function. Subsequently, one study has investigated cognitive function after TA-TAVI (Knipp et al., 2013). Using 5 cognitive domains (short term memory, working memory, delayed recognition, verbal learning and verbal fluency) they found no evidence of cognitive decline 3 months post TAVI. This single centre study is limited by a small study population (n=27) and the lack of long-term data, but it does suggest that cerebral emboli may not herald cognitive decline. Neurocognitive decline post-TAVI is a topic that will become increasingly important and relevant as the procedure is used in a

lower risk and younger population. Future research in this subject field will need to concentrate on long-term follow up data and comparisons to a matched surgical population.

6.3 Quality of Life

Quality of life is a particularly important clinical outcome measure in an elderly, frail TAVI population where the quality rather than quantity of life attained becomes more relevant. Our research established the improvement in HRQOL post-TAVI, its time course and identified patient and procedural predictors of improvement. The discovery of age, gender and operator experience as predictors of improvement in HRQOL post-TAVI will be used to greater inform patients of procedural outcomes and guide clinicians in deciding which patients are likely to benefit from the procedure.

A pattern of improvement sustained over one year observed in our study has been confirmed in several subsequent HRQOL studies (Reynolds et al., 2011, Grimaldi et al., 2012, Krane et al., 2012, Reynolds et al., 2012c). These studies also highlighted the temporal changes of early (30 days) benefit with a minor 6-month decline then further improvement to 1 year. One study has described quality of life maintained out to 2 years (Taramasso et al., 2012). Evidence with a longer follow up period is necessary in order to have a full understanding of the impact on HRQOL. This data is being collected and should be disclosed in time. The choice of generic SF-12 and EQ5D questionnaires has been endorsed by VARC as an appropriate assessment tool in an AS population (Kappetein et al., 2012b). Alternative quality of life questionnaires have been trialled (Kansas city cardiomyopathy questionnaire and the Minnesota living with heart failure questionnaire) with similar results observed (Arnold et al., 2013). However, these questionnaires are disadvantaged by an inability to provide health economic outcome data.

Our study was limited by a lack of either a TA-TAVI group or a matched SAVR group. Recent evidence suggests that the TA-TAVI approach should be considered separately, as it is performed at a greater cost in terms of lower HRQOL benefit, increased complications and a greater length of

hospital stay (Reynolds et al., 2012c). This may reflect the higher risk nature of this sub-group as testified by their higher calculated risk scores (STS or logistic EuroSCORE) and increased frequency of vascular disease (PVD and CVA). Reynolds *et al* separated TA and TF-TAVI and evaluated them against SAVR. The early (30 day) HRQOL scores improved more substantially post TF-TAVI compared to either the TA route or SAVR. This finding corresponds with the earlier haemodynamic changes observed in TF-TAVI trials. Impaired early LV reverse remodelling, greater post-operative pain and increased vascular complications post TA-TAVI and SAVR may in part explain the lower HRQOL improvement. This difference in 'physical' improvement is further supported by 6-minute walk test distance scores post TAVI compared to SAVR (Gotzmann et al., 2011). Regarding mental health there appears uniform agreement between the studies and investigators that TAVI (TF or TA) and SAVR have no significant impact upon mental health (depression or anxiety) at any time point over a 2 year period.

HRQOL data is utilised to determine the cost-effectiveness of a medical intervention in health economic studies. The differences observed in quality of life following TAVI (TF and TA) and SAVR could imply altered cost-effectiveness of these procedures.

6.4 Health economics

6.4.1 Background

Having established the procedural success and mortality advantages of TAVI over medical therapy the number of procedures performed grew rapidly, particularly in Europe. Whilst UK numbers were significantly fewer than other European countries such as Germany, an increase in the demand for TAVI was developing alongside an increase in the number of patients being referred for SAVR. This reflects the increasing prevalence of a disease in an ageing population but is also a consequence of more patients being identified as potentially treatable whom previously may not have been considered. TAVI has significant health benefits for the affected individual but places a substantial cost burden on national health economies and thus society at large. In the UK the procedure was

therefore restricted to a certain number of procedures per head of population in nominated 'high volume' centres. An urgent demand for health economic data supporting the cost-effectiveness of this new procedure was stated by the department of health, clinicians and NICE (NICE, 2012). Cost-effectiveness analyses (CEA) determine to what degree a medical intervention improves clinical outcomes compared to the best alternative treatment available in the context of the relative costs of the interventions. Health outcomes are normally reported as QALY's. The ICER is a cost-benefit ratio, where the difference in health benefit (QALY) between two treatments is divided by their cost differential. Unlike a cost-benefit assessment, CEA do not assign a specific monetary value to a health outcome. As such no clearly defined threshold exists where a procedure becomes not cost-effective. The willingness to pay (WTP) for a procedure is therefore somewhat dependent upon the healthcare system/provider and the perspective of society at large. WTP is frequently interpreted in comparison to commonly accepted medical interventions. The US uses a WTP threshold of <$50,000 per QALY based on the assumed costs of annual renal dialysis, as an intervention that is universally covered for by the US Medicare insurance system. The UK NICE set a cost-effectiveness threshold of £20,000 per QALY. This acts as a guide to national commissioning groups but is not an absolute benchmark, as variations in local policy do occur.

6.4.2 Cost-effectiveness of TAVI versus medical therapy

Initial CEA concentrated on evaluating TAVI compared to the previously used treatment for 'inoperable' individuals, medical therapy (Watt et al., 2012, Reynolds et al., 2012b, Simons et al., 2013). These studies established the greater early cost of TAVI, predominantly due to cost of devices and the length of hospital stay. However, TAVI resulted in significantly greater QALY gains versus medical therapy (0.7-1.56) over a 10-year period (Watt et al., 2012) and lifetime horizon (Reynolds et al., 2012b, Simons et al., 2013). The PARTNER cohort B CEA (Reynolds et al., 2012b) estimated added life years of 1.9 and improved quality of life by TAVI compared to medical therapy. The initial cost of the procedure was therefore partially offset by lower rates of subsequent hospitalization in the TAVI group. Interestingly however they also observed that due to the increase in life expectancy the lifetime costs of this elderly group were overall greater. This resulted in an ICER of $50,212 per life

year gained, with the authors concluding that TAVI was probably cost-effective and certainly within the accepted range for other cardiovascular therapies. The UK study by Watt *et al* (Watt et al., 2012) modelled their study on the PARTNER B data and similarly found TAVI to be a cost-effective alternative with an ICER of £16,200.

Considerable concern persisted about the validity of these CEA projections, given the changing nature of the TAVI procedure, in particular the reduced early complications but uncertain long-term survival benefit. Simons *et al* designed a piecewise exponential markov model using a hypothetical AS population to look at how variations in patient, procedural and healthcare costs affected the cost-effectiveness of TAVI versus medical management (Simons et al., 2013). The higher base case costs and lower health benefits modelled in their analysis are open to criticism (Reynolds and Cohen, 2013), but their analysis did once more raise the issue of additional long-term healthcare costs in the TAVI group due to increased survival. They modelled several clinical instances where the CEA was prohibitive, concluding that the underlying health status and co-morbidities of the patient were more significant drivers of future cost-effectiveness compared to variations in procedural costs, or patient survival. TAVI was therefore less cost-effective in individuals with greater co-morbidties and healthcare dependency than for a healthier population, such as those patients deemed suitable for SAVR.

6.4.3 Cost-effectiveness of TAVI versus SAVR

Our research sought to answer the question of cost-effectiveness in a high-risk but operable group by comparing TAVI to the 'gold-standard' available treatment, SAVR. It remains the only UK study to report health economic data for this type of population, although other international studies have subsequently been published. The markov model design of our study is similar to that of Watt *et al* in their comparison to medical therapy, but was based predominantly on the health outcomes of the PARTNER A study. Uniquely, health benefit outcomes were modelled on UK quality of life data (chapter 4) and the costs were based on a UK national tariff. An ICER of £20,158 suggests with high probability that TAVI is a cost-effective alternative to SAVR in a high-risk but operable AS

population. The health benefit data of our study closely matches those reported by Reynolds *et al* in their PARTNER A CEA (Reynolds et al., 2012a). Remarkably, despite using different costing data to reflect variations in national practice the two studies report a similar pattern of costs distribution. The greater device cost of TAVI compared to the surgical valve was offset by a greater length and cost of hospital say following surgery, in particular the ICU cost. The health benefits (HRQOL) achieved in our study were similar between procedural groups as per the PARTNER A evidence. Long-term health care costs were also similar between the TAVI and SAVR groups, but were on average lower than was observed in the inflated US healthcare system. An accepted limitation of our study was the 'averaging' of health outcomes for both TAVI devices and procedural routes (TF versus TA). We performed this type of analysis in order to present data that would closely reflect current UK clinical practice. The PARTNER study group by performing sub-group analysis demonstrated lower health benefits post TA-TAVI compared to TF-TAVI or SAVR. As the CEA was dependent upon small variations in either health outcomes or costs, it is likely that we have overestimated the cost-effectiveness of TA-TAVI and underestimated that of TF-TAVI.

6.4.4 Future economic analysis

Health economic analyses can be as precarious as forecasting the weather or the national economy. Variations in the design of an economic model and input characteristics mean that a range of opinions and values are reported. The continued reappraisal of the cost-effectiveness of a technology such as TAVI is necessary, particularly as data are released concerning developments in device technology, improved health outcomes and long-term results. Any medical intervention that extends life is unlikely to be a truly 'cost-effective' option. However, TAVI represents a significant medical advance, which on the basis of evidence from several studies including our own does appear to be affordable. Whether this affordability is deemed acceptable or justified will be dependent upon the view of health care commissioners who are responsible for balancing the various needs of the local population and the societal WTP. TAVI will not be a cost-effective option in everyone. Identifying those individuals in whom TAVI is least beneficial or particularly advantageous, will in all probability allow the selection of the most cost-effective option. As the role of TAVI expands in to an

intermediate risk population the clinical effectiveness may improve (Piazza et al., 2013, Wenaweser et al., 2013), altering the cost-effectiveness of the procedure. Evidence towards improved outcomes, reduced complications and device longevity will reduce the overall cost of TAVI in this lower risk group. Yet the cost of the procedure would remain significant given the high price of the transcatheter device compared to surgical valves. It may prove to be a less favourable option compared to SAVR if the post surgical hospital stay is less protracted in this population (Osnabrugge et al., 2012).

6.5 Conclusion

This thesis provides original evidence supporting the clinical and cost effectiveness of TAVI. We have compared TAVI to the gold standard treatment for symptomatic severe AS, SAVR and found it to be equivalent. In establishing the haemodynamic changes that take place post-TAVI we identified the foundation of future clinical improvement, which was confirmed by the change in quality of life. TAVI significantly improves clinical outcomes for the majority of appropriately selected individuals, as demonstrated by this research and that of others. A theme of this research has been the identification of patient and procedural markers of superior clinical outcome and potential complications. This information should aid the clinician and patient in deciding whether TAVI is the most appropriate and favourable treatment option and help society assess its affordability.

6.5.1 Future Direction

Many questions remain unanswered concerning TAVI, Ongoing trials (including the UK TAVI trial) will address many of the issues, in particular the management of concomitant CAD and the role of TAVI in a younger, healthier, intermediate risk AS population.

This thesis identified several areas of interest. Whilst successfully addressing all of these topics our results did highlight additional questions pertaining to the clinical benefits and costs of TAVI that were not possible to answer during the time of this thesis. Having assessed gross myocardial function

and reverse remodelling, we aim to measure subtle markers of myocardial function (strain and torsion) using the myocardial tagging (CSPAMM) data acquired during the cardiac MRI. A comparison of the effects of TAVI versus SAVR will be possible, to determine whether the greater reduction in valvuloarterial impedance post TAVI translates into a difference in myocardial strain and torsion following the procedures. This information may also help identify individuals at greater pre-operative risk, who appear to have a normal functioning ventricle but actually have markedly abnormal torsion and strain. This has the potential to act as a more sensitive clinical outcome end point, as the absence of change in EF does not necessarily mean a lack of improved myocardial function. There is also the prospect of combining myocardial strain data in a risk stratification model of asymptomatic AS patients in order to aid clinicians in deciding the timing of any AVR.

This study has highlighted the ability of cardiac MRI through its multi-parametric approach to identify markers of adverse outcome in AS (valvular function, LV remodelling and MF) and act as a measure of clinical outcomes. These factors are not just important in the high-risk TAVI sub-group but in all AS patients. Considerable difficulties exist for clinicians and patients in deciding when the right time to operate is. This is particularly relevant in the severe asymptomatic AS group where some patients ventricles decompensate despite the absence of symptoms (McCann et al., 2011). Standard tools of assessment including exercise testing, β-natriuretic peptide and echocardiography have proved ineffective at risk stratifying this group of individuals (Dal-Bianco et al., 2008, Das et al., 2005, Vahanian et al., 2012). Our study was insufficiently big enough to address this issue and involved a high-risk AS sub-group. However, it did identify several areas of possible future research using CMR. In collaboration with other centres we aim to determine the ability of CMR to predict clinical outcomes in a symptomatic and asymptomatic AS population (~500 patients).

The effects of removing valvular impedance on aortic arterial stiffness have yet to be determined. Arterial stiffness is known to increase with age as well as in several cardiovascular (heart failure, stroke and diabetes) and non-cardiovascular (CKD and rheumatoid arthritis) disease (Rogers et al., 2001). It is an important clinical outcome measure as an independent predictor of cardiovascular events as well as cardiovascular and all cause mortality (Vlachopoulos et al., 2010, Laurent, 2006). In addition, increased aortic stiffness has been shown to be associated with greater myocardial fibrosis in

a HCM population and reduced aortic compliance had a significant impact on LV after load and function in an AS population. Aortic stiffness or reduced elasticity can be measured using several different techniques and imaging modalities (Laurent et al., 2006). CMR has the ability to accurately determine arterial stiffness by measuring the aortic distensibility and pulse wave velocity (Grotenhuis et al., 2009, Dogui et al., 2011). Our study included the assessment of these variables in the cardiac MR protocol. Due to limitations in the number of patients studied and statistical power required it is not possible to report the data acquired in this thesis. However, the work is ongoing and we aim to present the changes in arterial stiffness following TAVI compared to SAVR, and their relationship to reverse remodelling and MF regression in the near future.

CMR can measure the aortic root with greater precision to TTE or TOE and with similar accuracy to CT (Jabbour et al., 2011). The frequency and significance of post-TAVI paravalvular regurgitation is believed to be the consequence of inaccurate estimates of aortic root size and thus poor device selection/sizing (Takagi et al., 2011). We aim to address the issue of device sizing and aortic regurgitation by analysing the LVOT and aortic sagittal oblique cine images obtained in our cardiac MR protocol, comparing them to the TOE and TTE assessments and look for a correlation to post-operative 'total AR' as measured by phase contrast MR imaging.

Having identified the incidence and predictors of cerebral emboli post-TAVI, we aim to use cerebral DW MR imaging to compare a TAVI and SAVR population. This will include an assessment of the clinical utility of new embolic protection devices and a comparison of new TAVI valves. Further, having determined no short term effects of cerebral emboli on the health status of an individual we decided to assess the impact of cerebral emboli upon higher cognitive function post-TAVI. This study is presently being undertaken and is due to complete in 2014.

7 References

ABDEL-WAHAB, M., ZAHN, R., HORACK, M., GERCKENS, U., SCHULER, G., SIEVERT, H., EGGEBRECHT, H., SENGES, J. & RICHARDT, G. 2011. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. *Heart,* 97**,** 899-906.

AMARENCO, P., COHEN, A., TZOURIO, C., BERTRAND, B., HOMMEL, M., BESSON, G., CHAUVEL, C., TOUBOUL, P. J. & BOUSSER, M. G. 1994. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med,* 331**,** 1474-9.

AMBLER, G., OMAR, R. Z., ROYSTON, P., KINSMAN, R., KEOGH, B. E. & TAYLOR, K. M. 2005. Generic, Simple Risk Stratification Model for Heart Valve Surgery. *Circulation,* 112**,** 224-231.

ANDERSEN, H. R., KNUDSEN, L. L. & HASENKAM, J. M. 1992. Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *Eur Heart J,* 13**,** 704-8.

ARNOLD, S. V., SPERTUS, J. A., LEI, Y., ALLEN, K. B., CHHATRIWALLA, A. K., LEON, M. B., SMITH, C. R., REYNOLDS, M. R., WEBB, J. G., SVENSSON, L. G. & COHEN, D. J. 2013. Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis. *Circ Heart Fail,* 6**,** 61-7.

ASHIKHMINA, E. A., SCHAFF, H. V., DEARANI, J. A., SUNDT, T. M., 3RD, SURI, R. M., PARK, S. J., BURKHART, H. M., LI, Z. & DALY, R. C. 2011. Aortic valve replacement in the elderly: determinants of late outcome. *Circulation,* 124**,** 1070-8.

ASTARCI, P., GLINEUR, D., KEFER, J., D'HOORE, W., RENKIN, J., VANOVERSCHELDE, J. L., EL KHOURY, G. & GRANDIN, C. 2011. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve. *Eur J Cardiothorac Surg,* 40**,** 475-9.

AZEVEDO, C. F., NIGRI, M., HIGUCHI, M. L., POMERANTZEFF, P. M., SPINA, G. S., SAMPAIO, R. O., TARASOUTCHI, F., GRINBERG, M. & ROCHITTE, C. E. 2010. Prognostic Significance of Myocardial Fibrosis Quantification by Histopathology and Magnetic Resonance Imaging in Patients With Severe Aortic Valve Disease. *Journal of the American College of Cardiology,* 56**,** 278-287.

BAKAEEN, F. G., CHU, D., RATCLIFFE, M., GOPALDAS, R. R., BLAUSTEIN, A. S., VENKAT, R., HUH, J., LEMAIRE, S. A., COSELLI, J. S. & CARABELLO, B. A. 2010. Severe aortic stenosis in a veteran population: treatment considerations and survival. *Ann Thorac Surg,* 89**,** 453-8.

BARKHAUSEN, J., RUEHM, S. G., GOYEN, M., BUCK, T., LAUB, G. & DEBATIN, J. F. 2001. MR evaluation of ventricular function: true fast imaging with steady-state precession versus fast low-angle shot cine MR imaging: feasibility study. *Radiology,* 219**,** 264-9.

BAUER, F., COUTANT, V., BERNARD, M., STEPOWSKI, D., TRON, C., CRIBIER, A., BESSOU, J. P. & ELTCHANINOFF, H. 2013. Patients With Severe Aortic Stenosis and Reduced Ejection Fraction: Earlier Recovery of Left Ventricular Systolic Function After Transcatheter Aortic Valve Implantation Compared With Surgical Valve Replacement. *Echocardiography*.

BEKEREDJIAN, R., KRUMSDORF, U., CHORIANOPOULOS, E., KALLENBACH, K., KARCK, M., KATUS, H. A. & ROTTBAUER, W. 2010. Usefulness of percutaneous aortic valve implantation to improve quality of life in patients >80 years of age. *Am J Cardiol,* 106**,** 1777-81.

BEKKERS, S. C. A. M., SMULDERS, M. W., PASSOS, V. L., LEINER, T., WALTENBERGER, J., GORGELS, A. P. M. & SCHALLA, S. 2010. Clinical implications of microvascular obstruction and intramyocardial haemorrhage in acute myocardial infarction using cardiovascular magnetic resonance imaging. *European Radiology,* 20**,** 2572-2578.

BELLENGER, N. G., DAVIES, L. C., FRANCIS, J. M., COATS, A. J. & PENNELL, D. J. 2000. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson,* 2**,** 271-8.

BERRY, C., LLOYD, S. M., WANG, Y., MACDONALD, A. & FORD, I. 2013. The changing course of aortic valve disease in Scotland: temporal trends in hospitalizations and mortality and prognostic importance of aortic stenosis. *Eur Heart J,* 34**,** 1538-47.

BIEDERMAN, R. W., DOYLE, M., YAMROZIK, J., WILLIAMS, R. B., RATHI, V. K., VIDO, D., CARUPPANNAN, K., OSMAN, N., BRESS, V., RAYARAO, G., BIEDERMAN, C. M., MANKAD, S., MAGOVERN, J. A. & REICHEK, N. 2005. Physiologic compensation is supranormal in compensated aortic stenosis: does it return to normal after aortic valve replacement or is it blunted by coexistent coronary artery disease? An intramyocardial magnetic resonance imaging study. *Circulation,* 112**,** I429-36.

BIEDERMAN, R. W. W., MAGOVERN, J. A., GRANT, S. B., WILLIAMS, R. B., YAMROZIK, J. A., VIDO, D. A., RATHI, V. K., RAYARAO, G., CARUPPANNAN, K. & DOYLE, M. 2011. LV reverse remodeling imparted by aortic valve replacement for severe aortic stenosis; is it durable? A cardiovascular MRI study sponsored by the American Heart Association. *Journal of Cardiothoracic Surgery,* 6**,** 53.

BINDER, R. K. & WEBB, J. G. 2012. TAVI: from home-made prosthesis to global interventional phenomenon. *Heart,* 98 Suppl 4**,** iv30-6.

BINGHAM, S. E. & HACHAMOVITCH, R. 2011. Incremental Prognostic Significance of Combined Cardiac Magnetic Resonance Imaging, Adenosine Stress Perfusion, Delayed Enhancement, and Left Ventricular Function Over Preimaging Information for the Prediction of Adverse Events. *Circulation,* 123**,** 1509-1518.

BLUEMKE, D. A., KRONMAL, R. A., LIMA, J. A. C., LIU, K., OLSON, J., BURKE, G. L. & FOLSOM, A. R. 2008. The Relationship of Left Ventricular Mass and Geometry to Incident Cardiovascular Events. *Journal of the American College of Cardiology,* 52**,** 2148-2155.

BOTTINI, P. B., CARR, A. A., PRISANT, L. M., FLICKINGER, F. W., ALLISON, J. D. & GOTTDIENER, J. S. 1995. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. *Am J Hypertens,* 8**,** 221-8.

BRAZIER, J., ROBERTS, J. & DEVERILL, M. 2002. The estimation of a preference-based measure of health from the SF-36. *J Health Econ,* 21**,** 271-92.

BRAZIER, J., ROBERTS, J., TSUCHIYA, A. & BUSSCHBACH, J. 2004. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ,* 13**,** 873-84.

BRAZIER, J. E. & ROBERTS, J. 2004. The estimation of a preference-based measure of health from the SF-12. *Med Care,* 42**,** 851-9.

BRENNAN, A., KHARROUBI, S., O'HAGAN, A. & CHILCOTT, J. 2007. Calculating partial expected value of perfect information via Monte Carlo sampling algorithms. *Med Decis Making,* 27**,** 448-70.

BRIAND, M., DUMESNIL, J. G., KADEM, L., TONGUE, A. G., RIEU, R., GARCIA, D. & PIBAROT, P. 2005. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. *J Am Coll Cardiol,* 46**,** 291-8.

BRITAIN., B. M. A. A. R. P. S. O. G. British National Formulary. *BMA,* No 61.

BROWN, J. M., O'BRIEN, S. M., WU, C., SIKORA, J. A., GRIFFITH, B. P. & GAMMIE, J. S. 2009. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg,* 137**,** 82-90.

BUELLESFELD, L., GERCKENS, U., SCHULER, G., BONAN, R., KOVAC, J., SERRUYS, P. W., LABINAZ, M., DEN HEIJER, P., MULLEN, M., TYMCHAK, W., WINDECKER, S., MUELLER, R. & GRUBE, E. 2011. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. *J Am Coll Cardiol,* 57**,** 1650-7.

BUELLESFELD, L. & WINDECKER, S. 2011. Transcatheter aortic valve implantation: the evidence is catching up with reality. *Eur Heart J,* 32**,** 133-7.

BULL, S., WHITE, S. K., PIECHNIK, S. K., FLETT, A. S., FERREIRA, V. M., LOUDON, M., FRANCIS, J. M., KARAMITSOS, T. D., PRENDERGAST, B. D., ROBSON, M. D., NEUBAUER, S., MOON, J. C. & MYERSON, S. G. 2013. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart*.

BUSING, K. A., SCHULTE-SASSE, C., FLUCHTER, S., SUSELBECK, T., HAASE, K. K., NEFF, W., HIRSCH, J. G., BORGGREFE, M. & DUBER, C. 2005. Cerebral infarction: incidence and risk factors after diagnostic and interventional cardiac catheterization--prospective evaluation at diffusion-weighted MR imaging. *Radiology,* 235**,** 177-83.

CARABELLO, B. A. & PAULUS, W. J. 2009. Aortic stenosis. *Lancet,* 373**,** 956-66.

CARO, J. J., GUO, S., WARD, A., CHALIL, S., MALIK, F. & LEYVA, F. 2006. Modelling the economic and health consequences of cardiac resynchronization therapy in the UK. *Curr Med Res Opin,* 22**,** 1171-9.

CARUTHERS, S. D., LIN, S. J., BROWN, P., WATKINS, M. P., WILLIAMS, T. A., LEHR, K. A. & WICKLINE, S. A. 2003. Practical value of cardiac magnetic resonance imaging for clinical quantification of aortic valve stenosis: comparison with echocardiography. *Circulation,* 108**,** 2236-43.

CAWLEY, P. J., HAMILTON-CRAIG, C., OWENS, D. S., KRIEGER, E. V., STRUGNELL, W. E., MITSUMORI, L., D'JANG, C. L., SCHWAEGLER, R. G., NGUYEN, K. Q., NGUYEN, B., MAKI, J. H. & OTTO, C. M. 2013. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. *Circ Cardiovasc Imaging,* 6**,** 48-57.

CAWLEY, P. J., MAKI, J. H. & OTTO, C. M. 2009. Cardiovascular Magnetic Resonance Imaging for Valvular Heart Disease: Technique and Validation. *Circulation,* 119**,** 468-478.

CAWLEY, P. J. & OTTO, C. M. 2009. Prevention of calcific aortic valve stenosis-fact or fiction? *Ann Med,* 41**,** 100-8.

CHALMERS, J., PULLAN, M., FABRI, B., MCSHANE, J., SHAW, M., MEDIRATTA, N. & POULLIS, M. 2013. Validation of EuroSCORE II in a modern cohort of patients undergoing cardiac surgery. *Eur J Cardiothorac Surg,* 43**,** 688-94.

CHAMBERS, J. B. 2009. Aortic stenosis. *European Journal of Echocardiography,* 10**,** i11-i19.

CHAN, K. L., TEO, K., DUMESNIL, J. G., NI, A. & TAM, J. 2010. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation,* 121**,** 306-14.

CHERNOBELSKY, A., SHUBAYEV, O., COMEAU, C. R. & WOLFF, S. D. 2007. Baseline Correction of Phase Contrast Images Improves Quantification of Blood Flow in the Great Vessels. *Journal of Cardiovascular Magnetic Resonance,* 9**,** 681-685.

CHOCKALINGAM, A., VENKATESAN, S., SUBRAMANIAM, T., JAGANNATHAN, V., ELANGOVAN, S., ALAGESAN, R., GNANAVELU, G., DORAIRAJAN, S., KRISHNA, B. P. & CHOCKALINGAM, V. 2004. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS). *Am Heart J,* 147**,** E19.

CHOONG, C. K., SERGEANT, P., NASHEF, S. A., SMITH, J. A. & BRIDGEWATER, B. 2009. The EuroSCORE risk stratification system in the current era: how accurate is it and what should be done if it is inaccurate? *Eur J Cardiothorac Surg,* 35**,** 59-61.

CLAVEL, M.-A., WEBB, J. G., PIBAROT, P., ALTWEGG, L., DUMONT, E., THOMPSON, C., DE LAROCHELLIÈRE, R., DOYLE, D., MASSON, J.-B., BERGERON, S., BERTRAND, O. F. & RODÉS-CABAU, J. 2009. Comparison of the Hemodynamic Performance of Percutaneous and Surgical Bioprostheses for the Treatment of Severe Aortic Stenosis. *Journal of the American College of Cardiology,* 53**,** 1883-1891.

CLAVEL, M. A., WEBB, J. G., RODES-CABAU, J., MASSON, J. B., DUMONT, E., DE LAROCHELLIERE, R., DOYLE, D., BERGERON, S., BAUMGARTNER, H., BURWASH, I. G., DUMESNIL, J. G., MUNDIGLER, G., MOSS, R., KEMPNY, A., BAGUR, R., BERGLER-KLEIN, J., GURVITCH, R., MATHIEU, P. & PIBAROT, P. 2010. Comparison Between Transcatheter and Surgical Prosthetic Valve Implantation in Patients With Severe Aortic Stenosis and Reduced Left Ventricular Ejection Fraction. *Circulation,* 122**,** 1928-1936.

CRAMARIUC, D., CIOFFI, G., RIECK, A. E., DEVEREUX, R. B., STAAL, E. M., RAY, S., WACHTELL, K. & GERDTS, E. 2009. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS Substudy. *JACC Cardiovasc Imaging,* 2**,** 390-9.

CRIBIER, A., ELTCHANINOFF, H., BASH, A., BORENSTEIN, N., TRON, C., BAUER, F., DERUMEAUX, G., ANSELME, F., LABORDE, F. & LEON, M. B. 2002. Percutaneous transcatheter implantation of

an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation,* 106**,** 3006-8.

CRIBIER, A., SAVIN, T., SAOUDI, N., ROCHA, P., BERLAND, J. & LETAC, B. 1986. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet,* 1**,** 63-7.

CURTIS, L. 2011. Unit Costs of Health and Social Care. *Personal Social Services Research Unit,* http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf.

DAL-BIANCO, J. P., KHANDHERIA, B. K., MOOKADAM, F., GENTILE, F. & SENGUPTA, P. P. 2008. Management of Asymptomatic Severe Aortic Stenosis. *Journal of the American College of Cardiology,* 52**,** 1279-1292.

DALL'ARMELLINA, E., PIECHNIK, S. K., FERREIRA, V. M., SI, Q. L., ROBSON, M. D., FRANCIS, J. M., CUCULI, F., KHARBANDA, R. K., BANNING, A. P., CHOUDHURY, R. P., KARAMITSOS, T. D. & NEUBAUER, S. 2012. Cardiovascular magnetic resonance by non contrast T1-mapping allows assessment of severity of injury in acute myocardial infarction. *J Cardiovasc Magn Reson,* 14**,** 15.

DAS, P., RIMINGTON, H. & CHAMBERS, J. 2005. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J,* 26**,** 1309-13.

DASS, S., SUTTIE, J. J., PIECHNIK, S. K., FERREIRA, V. M., HOLLOWAY, C. J., BANERJEE, R., MAHMOD, M., COCHLIN, L., KARAMITSOS, T. D., ROBSON, M. D., WATKINS, H. & NEUBAUER, S. 2012. Myocardial tissue characterization using magnetic resonance noncontrast t1 mapping in hypertrophic and dilated cardiomyopathy. *Circ Cardiovasc Imaging,* 5**,** 726-33.

DELGADO, M., RUIZ, M., MESA, D., DE LEZO CRUZ CONDE, J. S., PAN, M., LOPEZ, J., VILLANUEVA, E. & CEJUDO, L. 2013. Early improvement of the regional and global ventricle function estimated by two-dimensional speckle tracking echocardiography after percutaneous aortic valve implantation speckle tracking after CoreValve implantation. *Echocardiography,* 30**,** 37-44.

DEWEY, T. M., BROWN, D. L., HERBERT, M. A., CULICA, D., SMITH, C. R., LEON, M. B., SVENSSON, L. G., TUZCU, M., WEBB, J. G., CRIBIER, A. & MACK, M. J. 2010. Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. *Ann Thorac Surg,* 89**,** 758-67; discussion 767.

DI TULLIO, M. R., RUSSO, C., JIN, Z., SACCO, R. L., MOHR, J. P. & HOMMA, S. 2009. Aortic arch plaques and risk of recurrent stroke and death. *Circulation,* 119**,** 2376-82.

DIDIER, D., RATIB, O., LERCH, R. & FRIEDLI, B. 2000. Detection and quantification of valvular heart disease with dynamic cardiac MR imaging. *Radiographics,* 20**,** 1279-99; discussion 1299-301.

DIMARAKIS, I., REHMAN, S. M., GRANT, S. W., SARAVANAN, D. M., LEVY, R. D., BRIDGEWATER, B. & KADIR, I. 2011. Conventional aortic valve replacement for high-risk aortic stenosis patients not suitable for trans-catheter aortic valve implantation: feasibility and outcome. *Eur J Cardiothorac Surg,* 40**,** 743-8.

DOBLE, B., BLACKHOUSE, G., GOEREE, R. & XIE, F. 2012. Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: A Canadian perspective. *J Thorac Cardiovasc Surg*.

DOGUI, A., KACHENOURA, N., FROUIN, F., LEFORT, M., DE CESARE, A., MOUSSEAUX, E. & HERMENT, A. 2011. Consistency of aortic distensibility and pulse wave velocity estimates with respect to the Bramwell-Hill theoretical model: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson,* 13**,** 11.

DOLAN, P. 1997. Modeling valuations for EuroQol health states. *Med Care,* 35**,** 1095-108.

DUMESNIL, J. G., PIBAROT, P. & CARABELLO, B. 2010. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. *Eur Heart J,* 31**,** 281-9.

DUMESNIL, J. G. & SHOUCRI, R. M. 1991. Quantitative relationships between left ventricular ejection and wall thickening and geometry. *J Appl Physiol,* 70**,** 48-54.

DUNCAN, R. F., DUNDON, B. K., NELSON, A. J., PEMBERTON, J., WILLIAMS, K., WORTHLEY, M. I., ZAMAN, A., THOMAS, H. & WORTHLEY, S. G. 2011. A study of the 16-Segment Regional Wall

Motion Scoring Index and biplane Simpson's rule for the calculation of left ventricular ejection fraction: a comparison with cardiac magnetic resonance imaging. *Echocardiography,* 28**,** 597-604.

DWECK, M. R., JOSHI, S., MURIGU, T., ALPENDURADA, F., JABBOUR, A., MELINA, G., BANYA, W., GULATI, A., ROUSSIN, I., RAZA, S., PRASAD, N. A., WAGE, R., QUARTO, C., ANGELONI, E., REFICE, S., SHEPPARD, M., COOK, S. A., KILNER, P. J., PENNELL, D. J., NEWBY, D. E., MOHIADDIN, R. H., PEPPER, J. & PRASAD, S. K. 2011. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol,* 58**,** 1271-9.

DWECK, M. R., JOSHI, S., MURIGU, T., GULATI, A., ALPENDURADA, F., JABBOUR, A., MACEIRA, A., ROUSSIN, I., NORTHRIDGE, D. B., KILNER, P. J., COOK, S. A., BOON, N. A., PEPPER, J., MOHIADDIN, R. H., NEWBY, D. E., PENNELL, D. J. & PRASAD, S. K. 2012. Left ventricular remodeling and hypertrophy in patients with aortic stenosis: insights from cardiovascular magnetic resonance. *J Cardiovasc Magn Reson,* 14**,** 50.

ELTCHANINOFF, H., PRAT, A., GILARD, M., LEGUERRIER, A., BLANCHARD, D., FOURNIAL, G., IUNG, B., DONZEAU-GOUGE, P., TRIBOUILLOY, C., DEBRUX, J. L., PAVIE, A., GUERET, P., LEPRINCE, P., BEYGUI, F., COLLET, J. P., HIMBERT, D., NATAF, P., VAHANIAN, A., LEFEVRE, T., ROMANO, M., LITZLER, P. Y., BESSOU, J. P., CRIBIER, A., FAJADET, J., CARRIE, D., BERTHOUMIEU, P., DUMONTEIL, N., TEIGER, E., DUBOIS RANDE, J. L., KIRSCH, M., FABIANI, J. N., SUDRE, A., MODINE, T., DOS SANTOS, P., GUIBAUD, J. P., ROQUES, X., BOSCHAT, J., BEZON, E., SCHIELE, F., CHOCRON, S., MENEVEAU, N., BASSAND, J., RIOUFOL, G., OBADIA, J. F., TIROUVANZIAM, A., ROUSSEL, J. C., CROCHET, D., COLLARD, F., BONNET, J. L., CUISSET, T., WOLF, J. E., BOUCHOT, O. & CHEVREUL, K. 2010. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *European Heart Journal,* 32**,** 191-197.

ERDOES, G., BASCIANI, R., HUBER, C., STORTECKY, S., WENAWESER, P., WINDECKER, S., CARREL, T. & EBERLE, B. 2012. Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. *Eur J Cardiothorac Surg,* 41**,** 778-83; discussion 783-4.

EVANS, A. J., IWAI, F., GRIST, T. A., SOSTMAN, H. D., HEDLUND, L. W., SPRITZER, C. E., NEGRO-VILAR, R., BEAM, C. A. & PELC, N. J. 1993. Magnetic resonance imaging of blood flow with a phase subtraction technique. In vitro and in vivo validation. *Invest Radiol,* 28**,** 109-15.

EWE, S. H., AJMONE MARSAN, N., PEPI, M., DELGADO, V., TAMBORINI, G., MURATORI, M., NG, A. C. T., VAN DER KLEY, F., DE WEGER, A. & SCHALIJ, M. J. 2010. Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis. *American Heart Journal,* 160**,** 1113-1120.

FAIRBAIRN, T. A., GREENWOOD, J. P. & BLACKMAN, D. J. 2013. Multiple cerebral emboli following dislocation and retraction of a partially deployed CoreValve prosthesis during transcatheter aortic valve implantation. *Catheter Cardiovasc Interv*. 82**,** E911-4

FAIRBAIRN, T. A., MEADS, D. M., MATHER, A. N., MOTWANI, M., PAVITT, S., PLEIN, S., BLACKMAN, D. J. & GREENWOOD, J. P. 2012. Serial change in health-related quality of life over 1 year after transcatheter aortic valve implantation: predictors of health outcomes. *J Am Coll Cardiol,* 59**,** 1672-80.

FAIRBAIRN, T. A., STEADMAN, C. D., MATHER, A. N., MOTWANI, M., BLACKMAN, D. J., PLEIN, S., MCCANN, G. P. & GREENWOOD, J. P. 2013. Assessment of valve haemodynamics, reverse ventricular remodelling and myocardial fibrosis following transcatheter aortic valve implantation compared to surgical aortic valve replacement: a cardiovascular magnetic resonance study. *Heart,* 99**,** 1185-91.

FENWICK, E., CLAXTON, K. & SCULPHER, M. 2001. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ,* 10**,** 779-87.

FERREIRA, V. M., PIECHNIK, S. K., DALL'ARMELLINA, E., KARAMITSOS, T. D., FRANCIS, J. M., CHOUDHURY, R. P., FRIEDRICH, M. G., ROBSON, M. D. & NEUBAUER, S. 2012. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson,* 14**,** 42.

FLACKE, S. J., FISCHER, S. E. & LORENZ, C. H. 2001. Measurement of the gadopentetate dimeglumine partition coefficient in human myocardium in vivo: normal distribution and elevation in acute and chronic infarction. *Radiology,* 218**,** 703-10.

FLETT, A. S., HASLETON, J., COOK, C., HAUSENLOY, D., QUARTA, G., ARITI, C., MUTHURANGU, V. & MOON, J. C. 2011. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging,* 4**,** 150-6.

FLETT, A. S., SADO, D. M., QUARTA, G., MIRABEL, M., PELLERIN, D., HERREY, A. S., HAUSENLOY, D. J., ARITI, C., YAP, J., KOLVEKAR, S., TAYLOR, A. M. & MOON, J. C. 2012. Diffuse myocardial fibrosis in severe aortic stenosis: an equilibrium contrast cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging*.

FLOYD, T. F., SHAH, P. N., PRICE, C. C., HARRIS, F., RATCLIFFE, S. J., ACKER, M. A., BAVARIA, J. E., RAHMOUNI, H., KUERSTEN, B., WIEGERS, S., MCGARVEY, M. L., WOO, J. Y., POCHETTINO, A. A. & MELHEM, E. R. 2006. Clinically silent cerebral ischemic events after cardiac surgery: their incidence, regional vascular occurrence, and procedural dependence. *Ann Thorac Surg,* 81**,** 2160-6.

FORSBERG, L. M., TAMAS, E., VANKY, F., NIELSEN, N. E., ENGVALL, J. & NYLANDER, E. 2011. Left and right ventricular function in aortic stenosis patients 8 weeks post-transcatheter aortic valve implantation or surgical aortic valve replacement. *European Journal of Echocardiography,* 12**,** 603-611.

FRIEDRICH, M., SCHULZMENGER, J., POETSCH, T., PILZ, B., UHLICH, F. & DIETZ, R. 2002. Quantification of valvular aortic stenosis by magnetic resonance imaging. *American Heart Journal,* 144**,** 329-334.

FRIEDRICH, M. G., ABDEL-ATY, H., TAYLOR, A., SCHULZ-MENGER, J., MESSROGHLI, D. & DIETZ, R. 2008. The Salvaged Area at Risk in Reperfused Acute Myocardial Infarction as Visualized by Cardiovascular Magnetic Resonance. *Journal of the American College of Cardiology,* 51**,** 1581-1587.

GAASCH, W. H., BATTLE, W. E., OBOLER, A. A., BANAS, J. S., JR. & LEVINE, H. J. 1972. Left ventricular stress and compliance in man. With special reference to normalized ventricular function curves. *Circulation,* 45**,** 746-62.

GAASCH, W. H. & ZILE, M. R. 2011. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *J Am Coll Cardiol,* 58**,** 1733-40.

GANAU, A., DEVEREUX, R. B., ROMAN, M. J., DE SIMONE, G., PICKERING, T. G., SABA, P. S., VARGIU, P., SIMONGINI, I. & LARAGH, J. H. 1992. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol,* 19**,** 1550-8.

GARG, V., MUTH, A. N., RANSOM, J. F., SCHLUTERMAN, M. K., BARNES, R., KING, I. N., GROSSFELD, P. D. & SRIVASTAVA, D. 2005. Mutations in NOTCH1 cause aortic valve disease. *Nature,* 437**,** 270-4.

GATEHOUSE, P. D., ROLF, M. P., GRAVES, M. J., HOFMAN, M. B. M., TOTMAN, J., WERNER, B., QUEST, R. A., LIU, Y., VON SPICZAK, J., DIERINGER, M., FIRMIN, D. N., VAN ROSSUM, A., LOMBARDI, M., SCHWITTER, J., SCHULZ-MENGER, J. & KILNER, P. J. 2010. Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. *Journal of Cardiovascular Magnetic Resonance,* 12**,** 5.

GAUDINO, M. 2004. Survival after aortic valve replacement for aortic stenosis: does left ventricular mass regression have a clinical correlate? *European Heart Journal,* 26**,** 51-57.

GHANEM, A., MÜLLER, A., NÄHLE, C. P., KOCUREK, J., WERNER, N., HAMMERSTINGL, C., SCHILD, H. H., SCHWAB, J. O., MELLERT, F., FIMMERS, R., NICKENIG, G. & THOMAS, D. 2010. Risk and Fate of Cerebral Embolism After Transfemoral Aortic Valve Implantation: A Prospective Pilot Study With Diffusion-Weighted Magnetic Resonance Imaging. *Journal of the American College of Cardiology,* 55**,** 1427-1432.

GILARD, M., ELTCHANINOFF, H., IUNG, B., DONZEAU-GOUGE, P., CHEVREUL, K., FAJADET, J., LEPRINCE, P., LEGUERRIER, A., LIEVRE, M., PRAT, A., TEIGER, E., LEFEVRE, T., HIMBERT, D., TCHETCHE, D., CARRIE, D., ALBAT, B., CRIBIER, A., RIOUFOL, G., SUDRE, A., BLANCHARD, D.,

COLLET, F., DOS SANTOS, P., MENEVEAU, N., TIROUVANZIAM, A., CAUSSIN, C., GUYON, P., BOSCHAT, J., LE BRETON, H., COLLART, F., HOUEL, R., DELPINE, S., SOUTEYRAND, G., FAVEREAU, X., OHLMANN, P., DOISY, V., GROLLIER, G., GOMMEAUX, A., CLAUDEL, J. P., BOURLON, F., BERTRAND, B., VAN BELLE, E. & LASKAR, M. 2012. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med,* 366**,** 1705-15.

GOEL, S. S., IGE, M., TUZCU, E. M., ELLIS, S. G., STEWART, W. J., SVENSSON, L. G., LYTLE, B. W. & KAPADIA, S. R. 2013. Severe aortic stenosis and coronary artery disease-implications for management in the transcatheter aortic valve replacement era: a comprehensive review. *J Am Coll Cardiol,* 62**,** 1-10.

GOTO, T., BABA, T., HONMA, K., SHIBATA, Y., ARAI, Y., UOZUMI, H. & OKUDA, T. 2001. Magnetic resonance imaging findings and postoperative neurologic dysfunction in elderly patients undergoing coronary artery bypass grafting. *Ann Thorac Surg,* 72**,** 137-42.

GOTZMANN, M., BOJARA, W., LINDSTAEDT, M., EWERS, A., BOSCHE, L., GERMING, A., LAWO, T., BECHTEL, M., LACZKOVICS, A. & MUGGE, A. 2011. One-year results of transcatheter aortic valve implantation in severe symptomatic aortic valve stenosis. *Am J Cardiol,* 107**,** 1687-92.

GOTZMANN, M., HEHEN, T., GERMING, A., LINDSTAEDT, M., YAZAR, A., LACZKOVICS, A., MUMME, A., MUGGE, A. & BOJARA, W. 2010. Short-term effects of transcatheter aortic valve implantation on neurohormonal activation, quality of life and 6-minute walk test in severe and symptomatic aortic stenosis. *Heart,* 96**,** 1102-6.

GOTZMANN, M., KORTEN, M., BOJARA, W., LINDSTAEDT, M., RAHLMANN, P., MUGGE, A. & EWERS, A. 2012a. Long-term outcome of patients with moderate and severe prosthetic aortic valve regurgitation after transcatheter aortic valve implantation. *Am J Cardiol,* 110**,** 1500-6.

GOTZMANN, M., LINDSTAEDT, M. & MUGGE, A. 2012b. From pressure overload to volume overload: aortic regurgitation after transcatheter aortic valve implantation. *Am Heart J,* 163**,** 903-11.

GRANT, S. W., HICKEY, G. L., DIMARAKIS, I., TRIVEDI, U., BRYAN, A., TREASURE, T., COOPER, G., PAGANO, D., BUCHAN, I. & BRIDGEWATER, B. 2012. How does EuroSCORE II perform in UK cardiac surgery; an analysis of 23 740 patients from the Society for Cardiothoracic Surgery in Great Britain and Ireland National Database. *Heart,* 98**,** 1568-72.

GRIMALDI, A., FIGINI, F., MAISANO, F., MONTORFANO, M., CHIEFFO, A., LATIB, A., PAPPALARDO, F., SPAGNOLO, P., CIONI, M., VERMI, A. C., FERRARELLO, S., PIRAINO, D., CAMMALLERI, V., AMMIRATI, E., SACCO, F. M., ARENDAR, I., COLLU, E., LA CANNA, G., ALFIERI, O. & COLOMBO, A. 2012. Clinical outcome and quality of life in octogenarians following transcatheter aortic valve implantation (TAVI) for symptomatic aortic stenosis. *Int J Cardiol*.

GROSSI, E. A., SCHWARTZ, C. F., YU, P.-J., JORDE, U. P., CROOKE, G. A., GRAU, J. B., RIBAKOVE, G. H., BAUMANN, F. G., URSUMANNO, P., CULLIFORD, A. T., COLVIN, S. B. & GALLOWAY, A. C. 2008. High-Risk Aortic Valve Replacement: Are the Outcomes as Bad as Predicted? *Ann Thorac Surg,* 85**,** 102-107.

GROTENHUIS, H. B., WESTENBERG, J. J., STEENDIJK, P., VAN DER GEEST, R. J., OTTENKAMP, J., BAX, J. J., JUKEMA, J. W. & DE ROOS, A. 2009. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging,* 30**,** 521-6.

GROTHUES, F., MOON, J. C., BELLENGER, N. G., SMITH, G. S., KLEIN, H. U. & PENNELL, D. J. 2004. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J,* 147**,** 218-23.

GROTHUES, F., SMITH, G. C., MOON, J. C., BELLENGER, N. G., COLLINS, P., KLEIN, H. U. & PENNELL, D. J. 2002. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol,* 90**,** 29-34.

GRUBE, E., LABORDE, J. C., ZICKMANN, B., GERCKENS, U., FELDERHOFF, T., SAUREN, B., BOOTSVELD, A., BUELLESFELD, L. & IVERSEN, S. 2005. First report on a human percutaneous transluminal implantation of a self-expanding valve prosthesis for interventional treatment of aortic valve stenosis. *Catheter Cardiovasc Interv,* 66**,** 465-9.

GURVITCH, R., TAY, E. L., WIJESINGHE, N., YE, J., NIETLISPACH, F., WOOD, D. A., LICHTENSTEIN, S., CHEUNG, A. & WEBB, J. G. 2011. Transcatheter aortic valve implantation: lessons from the learning curve of the first 270 high-risk patients. *Catheter Cardiovasc Interv,* 78**,** 977-84.

GURVITCH, R., WOOD, D. A., TAY, E. L., LEIPSIC, J., YE, J., LICHTENSTEIN, S. V., THOMPSON, C. R., CARERE, R. G., WIJESINGHE, N., NIETLISPACH, F., BOONE, R. H., LAUCK, S., CHEUNG, A. & WEBB, J. G. 2010. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. *Circulation,* 122**,** 1319-27.

HACHICHA, Z., DUMESNIL, J. G., BOGATY, P. & PIBAROT, P. 2007. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation,* 115**,** 2856-64.

HAHN, R. T., PIBAROT, P., STEWART, W. J., WEISSMAN, N. J., GOPALAKRISHNAN, D., KEANE, M. G., ANWARUDDIN, S., WANG, Z., BILSKER, M., LINDMAN, B. R., HERRMANN, H. C., KODALI, S. K., MAKKAR, R., THOURANI, V. H., SVENSSON, L. G., AKIN, J. J., ANDERSON, W. N., LEON, M. B. & DOUGLAS, P. S. 2013. Comparison of Transcatheter and Surgical Aortic Valve Replacement in Severe Aortic Stenosis: A Longitudinal Study of Echocardiography Parameters in Cohort A of the PARTNER Trial (Placement of Aortic Transcatheter Valves). *J Am Coll Cardiol,* 61**,** 2514-21.

HANMER, J., LAWRENCE, W. F., ANDERSON, J. P., KAPLAN, R. M. & FRYBACK, D. G. 2006. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. *Med Decis Making,* 26**,** 391-400.

HARTMAN, G. S., YAO, F. S., BRUEFACH, M., 3RD, BARBUT, D., PETERSON, J. C., PURCELL, M. H., CHARLSON, M. E., GOLD, J. P., THOMAS, S. J. & SZATROWSKI, T. P. 1996. Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study. *Anesth Analg,* 83**,** 701-8.

HARTZELL, M., MALHOTRA, R., YARED, K., ROSENFIELD, H. R., WALKER, J. D. & WOOD, M. J. 2011. Effect of gender on treatment and outcomes in severe aortic stenosis. *Am J Cardiol,* 107**,** 1681-6.

HECKBERT, S. R., POST, W., PEARSON, G. D., ARNETT, D. K., GOMES, A. S., JEROSCH-HEROLD, M., HUNDLEY, W. G., LIMA, J. A. & BLUEMKE, D. A. 2006. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. *J Am Coll Cardiol,* 48**,** 2285-92.

HESS, O. M., VILLARI, B. & KRAYENBUEHL, H. P. 1993. Diastolic dysfunction in aortic stenosis. *Circulation,* 87**,** IV73-6.

HIMBERT, D., DESCOUTURES, F., AL-ATTAR, N., IUNG, B., DUCROCQ, G., DETAINT, D., BROCHET, E., MESSIKA-ZEITOUN, D., FRANCIS, F., IBRAHIM, H., NATAF, P. & VAHANIAN, A. 2009. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. *J Am Coll Cardiol,* 54**,** 303-11.

HORSTKOTTE, D. & LOOGEN, F. 1988. The natural history of aortic valve stenosis. *Eur Heart J,* 9 Suppl E**,** 57-64.

HUNDLEY, W. G., BLUEMKE, D. A., FINN, J. P., FLAMM, S. D., FOGEL, M. A., FRIEDRICH, M. G., HO, V. B., JEROSCH-HEROLD, M., KRAMER, C. M., MANNING, W. J., PATEL, M., POHOST, G. M., STILLMAN, A. E., WHITE, R. D. & WOODARD, P. K. 2010. ACCF/ACR/AHA/NASCI/SCMR 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance. *Journal of the American College of Cardiology,* 55**,** 2614-2662.

ILES, L., PFLUGER, H., PHROMMINTIKUL, A., CHERAYATH, J., AKSIT, P., GUPTA, S. N., KAYE, D. M. & TAYLOR, A. J. 2008. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol,* 52**,** 1574-80.

IUNG, B. 2003. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *European Heart Journal,* 24**,** 1231-1243.

IUNG, B. 2005. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *European Heart Journal,* 26**,** 2714-2720.

IUNG, B., BARON, G., BUTCHART, E. G., DELAHAYE, F., GOHLKE-BARWOLF, C., LEVANG, O. W., TORNOS, P., VANOVERSCHELDE, J. L., VERMEER, F., BOERSMA, E., RAVAUD, P. & VAHANIAN, A. 2003a. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J,* 24**,** 1231-43.

IUNG, B., CACHIER, A., BARON, G., MESSIKA-ZEITOUN, D., DELAHAYE, F., TORNOS, P., GOHLKE-BARWOLF, C., BOERSMA, E., RAVAUD, P. & VAHANIAN, A. 2005a. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J,* 26**,** 2714-20.

JABBOUR, A., ISMAIL, T. F., MOAT, N., GULATI, A., ROUSSIN, I., ALPENDURADA, F., PARK, B., OKOROAFOR, F., ASGAR, A., BARKER, S., DAVIES, S., PRASAD, S. K., RUBENS, M. & MOHIADDIN, R. H. 2011. Multimodality imaging in transcatheter aortic valve implantation and post-procedural aortic regurgitation: comparison among cardiovascular magnetic resonance, cardiac computed tomography, and echocardiography. *J Am Coll Cardiol,* 58**,** 2165-73.

JILAIHAWI, H., DOCTOR, N., KASHIF, M., CHAKRAVARTY, T., RAFIQUE, A., MAKAR, M., FURUGEN, A., NAKAMURA, M., MIROCHA, J., GHEORGHIU, M., STEGIC, J., OKUYAMA, K., SULLIVAN, D. J., SIEGEL, R., MIN, J. K., GURUDEVAN, S. V., FONTANA, G. P., CHENG, W., FRIEDE, G., SHIOTA, T. & MAKKAR, R. R. 2013. Aortic annular sizing for transcatheter aortic valve replacement using cross-sectional 3-dimensional transesophageal echocardiography. *J Am Coll Cardiol,* 61**,** 908-16.

JILAIHAWI, H., KASHIF, M., FONTANA, G., FURUGEN, A., SHIOTA, T., FRIEDE, G., MAKHIJA, R., DOCTOR, N., LEON, M. B. & MAKKAR, R. R. 2012. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol,* 59**,** 1275-86.

JOHN, A. S., DILL, T., BRANDT, R. R., RAU, M., RICKEN, W., BACHMANN, G. & HAMM, C. W. 2003. Magnetic resonance to assess the aortic valve area in aortic stenosis. *Journal of the American College of Cardiology,* 42**,** 519-526.

KAHLERT, P., AL-RASHID, F., DOTTGER, P., MORI, K., PLICHT, B., WENDT, D., BERGMANN, L., KOTTENBERG, E., SCHLAMANN, M., MUMMEL, P., HOLLE, D., THIELMANN, M., JAKOB, H. G., KONORZA, T., HEUSCH, G., ERBEL, R. & EGGEBRECHT, H. 2012. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. *Circulation,* 126**,** 1245-55.

KAHLERT, P., KNIPP, S. C., SCHLAMANN, M., THIELMANN, M., AL-RASHID, F., WEBER, M., JOHANSSON, U., WENDT, D., JAKOB, H. G., FORSTING, M., SACK, S., ERBEL, R. & EGGEBRECHT, H. 2010. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation,* 121**,** 870-8.

KAPPETEIN, A. P., HEAD, S. J., GENEREUX, P., PIAZZA, N., VAN MIEGHEM, N. M., BLACKSTONE, E. H., BROTT, T. G., COHEN, D. J., CUTLIP, D. E., VAN ES, G. A., HAHN, R. T., KIRTANE, A. J., KRUCOFF, M. W., KODALI, S., MACK, M. J., MEHRAN, R., RODES-CABAU, J., VRANCKX, P., WEBB, J. G., WINDECKER, S., SERRUYS, P. W. & LEON, M. B. 2012a. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol,* 60**,** 1438-54.

KAPPETEIN, A. P., HEAD, S. J., GENEREUX, P., PIAZZA, N., VAN MIEGHEM, N. M., BLACKSTONE, E. H., BROTT, T. G., COHEN, D. J., CUTLIP, D. E., VAN ES, G. A., HAHN, R. T., KIRTANE, A. J., KRUCOFF, M. W., KODALI, S., MACK, M. J., MEHRAN, R., RODES-CABAU, J., VRANCKX, P., WEBB, J. G., WINDECKER, S., SERRUYS, P. W. & LEON, M. B. 2012b. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg,* 42**,** S45-60.

KARAMITSOS, T. D., PIECHNIK, S. K., BANYPERSAD, S. M., FONTANA, M., NTUSI, N. B., FERREIRA, V. M., WHELAN, C. J., MYERSON, S. G., ROBSON, M. D., HAWKINS, P. N., NEUBAUER, S. &

MOON, J. C. 2013. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging,* 6**,** 488-97.

KATSANOS, S., YIU, K. H., CLAVEL, M. A., RODES-CABAU, J., LEONG, D., VAN DER KLEY, F., AJMONE MARSAN, N., BAX, J. J., PIBAROT, P. & DELGADO, V. 2013. Impact of valvuloarterial impedance on 2-year outcome of patients undergoing transcatheter aortic valve implantation. *J Am Soc Echocardiogr,* 26**,** 691-8.

KATZ, J., WHANG, J., BOXT, L. M. & BARST, R. J. 1993. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. *J Am Coll Cardiol,* 21**,** 1475-81.

KELLMAN, P., ARAI, A. E. & XUE, H. 2013a. T1 and extracellular volume mapping in the heart: estimation of error maps and the influence of noise on precision. *J Cardiovasc Magn Reson,* 15**,** 56.

KELLMAN, P., HERZKA, D. A., ARAI, A. E. & HANSEN, M. S. 2013b. Influence of Off-resonance in myocardial T1-mapping using SSFP based MOLLI method. *J Cardiovasc Magn Reson,* 15**,** 63.

KHAWAJA, M. Z., RAJANI, R., COOK, A., KHAVANDI, A., MOYNAGH, A., CHOWDHARY, S., SPENCE, M. S., BROWN, S., KHAN, S. Q., WALKER, N., TRIVEDI, U., HUTCHINSON, N., DE BELDER, A. J., MOAT, N., BLACKMAN, D. J., LEVY, R. D., MANOHARAN, G., ROBERTS, D., KHOGALI, S. S., CREAN, P., BRECKER, S. J., BAUMBACH, A., MULLEN, M., LABORDE, J. C. & HILDICK-SMITH, D. 2011. Permanent Pacemaker Insertion After CoreValve Transcatheter Aortic Valve Implantation: Incidence and Contributing Factors (the UK CoreValve Collaborative). *Circulation,* 123**,** 951-60.

KILNER, P. J., GATEHOUSE, P. D. & FIRMIN, D. N. 2007. Flow Measurement by Magnetic Resonance: A Unique Asset Worth Optimising. *Journal of Cardiovascular Magnetic Resonance,* 9**,** 723-728.

KIM, R. J., WU, E., RAFAEL, A., CHEN, E. L., PARKER, M. A., SIMONETTI, O., KLOCKE, F. J., BONOW, R. O. & JUDD, R. M. 2000. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med,* 343**,** 1445-53.

KIND P, H. G., MACRAN S. 1999. UK Population norms for EQ-5D. *York Centre for Health Economics,* University of York

KNIPP, S. C., KAHLERT, P., JOKISCH, D., SCHLAMANN, M., WENDT, D., WEIMAR, C., JAKOB, H. & THIELMANN, M. 2013. Cognitive function after transapical aortic valve implantation: a single-centre study with 3-month follow-up. *Interact Cardiovasc Thorac Surg,* 16**,** 116-22.

KNIPP, S. C., MATATKO, N., SCHLAMANN, M., WILHELM, H., THIELMANN, M., FORSTING, M., DIENER, H. C. & JAKOB, H. 2005. Small ischemic brain lesions after cardiac valve replacement detected by diffusion-weighted magnetic resonance imaging: relation to neurocognitive function. *Eur J Cardiothorac Surg,* 28**,** 88-96.

KODALI, S. K., O'NEILL, W. W., MOSES, J. W., WILLIAMS, M., SMITH, C. R., TUZCU, M., SVENSSON, L. G., KAPADIA, S., HANZEL, G., KIRTANE, A. J. & LEON, M. B. 2011. Early and late (one year) outcomes following transcatheter aortic valve implantation in patients with severe aortic stenosis (from the United States REVIVAL trial). *Am J Cardiol,* 107**,** 1058-64.

KODALI, S. K., WILLIAMS, M. R., SMITH, C. R., SVENSSON, L. G., WEBB, J. G., MAKKAR, R. R., FONTANA, G. P., DEWEY, T. M., THOURANI, V. H., PICHARD, A. D., FISCHBEIN, M., SZETO, W. Y., LIM, S., GREASON, K. L., TEIRSTEIN, P. S., MALAISRIE, S. C., DOUGLAS, P. S., HAHN, R. T., WHISENANT, B., ZAJARIAS, A., WANG, D., AKIN, J. J., ANDERSON, W. N. & LEON, M. B. 2012b. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med,* 366**,** 1686-95.

KOENNECKE, H. C., MAST, H., TROCIO, S. H., JR., SACCO, R. L., MA, W., MOHR, J. P. & THOMPSON, J. L. 1998. Frequency and determinants of microembolic signals on transcranial Doppler in unselected patients with acute carotid territory ischemia. A prospective study. *Cerebrovasc Dis,* 8**,** 107-12.

KONDO, C., CAPUTO, G. R., SEMELKA, R., FOSTER, E., SHIMAKAWA, A. & HIGGINS, C. B. 1991. Right and left ventricular stroke volume measurements with velocity-encoded cine MR imaging: in vitro and in vivo validation. *AJR Am J Roentgenol,* 157**,** 9-16.

KOREN, M. J., DEVEREUX, R. B., CASALE, P. N., SAVAGE, D. D. & LARAGH, J. H. 1991. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med,* 114**,** 345-52.

KRANE, M., DEUTSCH, M. A., BLEIZIFFER, S., SCHNEIDER, L., RUGE, H., MAZZITELLI, D., SCHREIBER, C., BROCKMANN, G., VOSS, B., BAUERNSCHMITT, R. & LANGE, R. 2010. Quality of life among patients undergoing transcatheter aortic valve implantation. *Am Heart J,* 160**,** 451-7.

KRANE, M., DEUTSCH, M. A., PIAZZA, N., MUHTAROVA, T., ELHMIDI, Y., MAZZITELLI, D., VOSS, B., RUGE, H., BADIU, C. C., KORNEK, M., BLEIZIFFER, S. & LANGE, R. 2012. One-year results of health-related quality of life among patients undergoing transcatheter aortic valve implantation. *Am J Cardiol,* 109**,** 1774-81.

KRANE, M., VOSS, B., HIEBINGER, A., DEUTSCH, M. A., WOTTKE, M., HAPFELMEIER, A., BADIU, C. C., BAUERNSCHMITT, R. & LANGE, R. 2011. Twenty years of cardiac surgery in patients aged 80 years and older: risks and benefits. *Ann Thorac Surg,* 91**,** 506-13.

KRAYENBUEHL, H. P., HESS, O. M., MONRAD, E. S., SCHNEIDER, J., MALL, G. & TURINA, M. 1989. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation,* 79**,** 744-55.

KVIDAL, P., BERGSTROM, R., HORTE, L. G. & STAHLE, E. 2000. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol,* 35**,** 747-56.

KWONG, R. Y. & FARZANEH-FAR, A. 2011. Measuring myocardial scar by CMR. *JACC Cardiovasc Imaging,* 4**,** 157-60.

LA MANNA, A., SANFILIPPO, A., CAPODANNO, D., SALEMI, A., CADONI, A., CASCONE, I., POLIZZI, G., FIGUERA, M., PITTALA, R., PRIVITERA, C. & TAMBURINO, C. 2013. Left ventricular reverse remodeling after transcatheter aortic valve implantation: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson,* 15**,** 39.

LANG, R. M., BIERIG, M., DEVEREUX, R. B., FLACHSKAMPF, F. A., FOSTER, E., PELLIKKA, P. A., PICARD, M. H., ROMAN, M. J., SEWARD, J., SHANEWISE, J. S., SOLOMON, S. D., SPENCER, K. T., SUTTON, M. S. & STEWART, W. J. 2005. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr,* 18**,** 1440-63.

LAURENT, S. 2006. Surrogate measures of arterial stiffness: do they have additive predictive value or are they only surrogates of a surrogate? *Hypertension,* 47**,** 325-6.

LAURENT, S., COCKCROFT, J., VAN BORTEL, L., BOUTOUYRIE, P., GIANNATTASIO, C., HAYOZ, D., PANNIER, B., VLACHOPOULOS, C., WILKINSON, I. & STRUIJKER-BOUDIER, H. 2006. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J,* 27**,** 2588-605.

LEE, R., LI, S., RANKIN, J. S., O'BRIEN, S. M., GAMMIE, J. S., PETERSON, E. D., MCCARTHY, P. M. & EDWARDS, F. H. 2011. Fifteen-year outcome trends for valve surgery in North America. *Ann Thorac Surg,* 91**,** 677-84; discussion p 684.

LEON, M. B., PIAZZA, N., NIKOLSKY, E., BLACKSTONE, E. H., CUTLIP, D. E., KAPPETEIN, A. P., KRUCOFF, M. W., MACK, M., MEHRAN, R., MILLER, C., MOREL, M. A., PETERSEN, J., POPMA, J. J., TAKKENBERG, J. J. M., VAHANIAN, A., VAN ES, G. A., VRANCKX, P., WEBB, J. G., WINDECKER, S. & SERRUYS, P. W. 2011. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *European Heart Journal,* 32**,** 205-217.

LEON, M. B., SMITH, C. R., MACK, M., MILLER, D. C., MOSES, J. W., SVENSSON, L. G., TUZCU, E. M., WEBB, J. G., FONTANA, G. P., MAKKAR, R. R., BROWN, D. L., BLOCK, P. C., GUYTON, R. A., PICHARD, A. D., BAVARIA, J. E., HERRMANN, H. C., DOUGLAS, P. S., PETERSEN, J. L., AKIN, J. J., ANDERSON, W. N., WANG, D. & POCOCK, S. 2010. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med,* 363**,** 1597-607.

LEONTYEV, S., WALTHER, T., BORGER, M. A., LEHMANN, S., FUNKAT, A. K., RASTAN, A., KEMPFERT, J., FALK, V. & MOHR, F. W. 2009. Aortic valve replacement in octogenarians: utility of risk stratification with EuroSCORE. *Ann Thorac Surg,* 87**,** 1440-5.

LIEBERMAN, E. B., BASHORE, T. M., HERMILLER, J. B., WILSON, J. S., PIEPER, K. S., KEELER, G. P., PIERCE, C. H., KISSLO, K. B., HARRISON, J. K. & DAVIDSON, C. J. 1995. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol,* 26**,** 1522-8.

LIMA, J. A., JUDD, R. M., BAZILLE, A., SCHULMAN, S. P., ATALAR, E. & ZERHOUNI, E. A. 1995. Regional heterogeneity of human myocardial infarcts demonstrated by contrast-enhanced MRI. Potential mechanisms. *Circulation,* 92**,** 1117-25.

LIMONGELLI, G., DUCCESCHI, V., D'ANDREA, A., RENZULLI, A., SARUBBI, B., DE FEO, M., CERASUOLO, F., CALABRO, R. & COTRUFO, M. 2003. Risk factors for pacemaker implantation following aortic valve replacement: a single centre experience. *Heart,* 89**,** 901-4.

LINDROOS, M., KUPARI, M., HEIKKILA, J. & TILVIS, R. 1993. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol,* 21**,** 1220-5.

LINZBACH, A. J. 1960. Heart failure from the point of view of quantitative anatomy. *Am J Cardiol,* 5**,** 370-82.

LITWIN, S. E., KATZ, S. E., WEINBERG, E. O., LORELL, B. H., AURIGEMMA, G. P. & DOUGLAS, P. S. 1995. Serial echocardiographic-Doppler assessment of left ventricular geometry and function in rats with pressure-overload hypertrophy. Chronic angiotensin-converting enzyme inhibition attenuates the transition to heart failure. *Circulation,* 91**,** 2642-54.

LIU, C. Y., CHANG LIU, Y., WU, C., ARMSTRONG, A., VOLPE, G. J., VAN DER GEEST, R. J., LIU, Y., HUNDLEY, W. G., GOMES, A. S., LIU, S., NACIF, M., BLUEMKE, D. A. & LIMA, J. A. 2013. Evaluation of Age related Interstitial Myocardial Fibrosis with Cardiac Magnetic Resonance Contrast-Enhanced T Mapping in the Multi-ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol*.

LONGMORE, D. B., KLIPSTEIN, R. H., UNDERWOOD, S. R., FIRMIN, D. N., HOUNSFIELD, G. N., WATANABE, M., BLAND, C., FOX, K., POOLE-WILSON, P. A., REES, R. S. & ET AL. 1985. Dimensional accuracy of magnetic resonance in studies of the heart. *Lancet,* 1**,** 1360-2.

LOTZ, J., MEIER, C., LEPPERT, A. & GALANSKI, M. 2002. Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. *Radiographics,* 22**,** 651-71.

LUENGO-FERNANDEZ, R., GRAY, A. M. & ROTHWELL, P. M. 2009. Costs of stroke using patient-level data: a critical review of the literature. *Stroke,* 40**,** e18-23.

LUND, C., NES, R. B., UGELSTAD, T. P., DUE-TONNESSEN, P., ANDERSEN, R., HOL, P. K., BRUCHER, R. & RUSSELL, D. 2005. Cerebral emboli during left heart catheterization may cause acute brain injury. *Eur Heart J,* 26**,** 1269-75.

LUND, O. 1990. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis. Reasons for earlier operative intervention. *Circulation,* 82**,** 124-39.

LUND, O. 2003. Regression of left ventricular hypertrophy during 10 years after valve replacement for aortic stenosis is related to the preoperative risk profile. *European Heart Journal,* 24**,** 1437-1446.

LUND, O., FLO, C., JENSEN, F. T., EMMERTSEN, K., NIELSEN, T. T., RASMUSSEN, B. S., HANSEN, O. K., PILEGAARD, H. K. & KRISTENSEN, L. H. 1997. Left ventricular systolic and diastolic function in aortic stenosis. Prognostic value after valve replacement and underlying mechanisms. *Eur Heart J,* 18**,** 1977-87.

LUND, O., NIELSEN, T. T., PILEGAARD, H. K., MAGNUSSEN, K. & KNUDSEN, M. A. 1990. The influence of coronary artery disease and bypass grafting on early and late survival after valve replacement for aortic stenosis. *J Thorac Cardiovasc Surg,* 100**,** 327-37.

LUNDBERG, L., JOHANNESSON, M., ISACSON, D. G. & BORGQUIST, L. 1999. The relationship between health-state utilities and the SF-12 in a general population. *Med Decis Making,* 19**,** 128-40.

LUTSEP, H. L., ALBERS, G. W., DECRESPIGNY, A., KAMAT, G. N., MARKS, M. P. & MOSELEY, M. E. 1997. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. *Ann Neurol,* 41**,** 574-80.

MAKKAR, R. R., FONTANA, G. P., JILAIHAWI, H., KAPADIA, S., PICHARD, A. D., DOUGLAS, P. S., THOURANI, V. H., BABALIAROS, V. C., WEBB, J. G., HERRMANN, H. C., BAVARIA, J. E., KODALI, S., BROWN, D. L., BOWERS, B., DEWEY, T. M., SVENSSON, L. G., TUZCU, M., MOSES, J. W., WILLIAMS, M. R., SIEGEL, R. J., AKIN, J. J., ANDERSON, W. N., POCOCK, S., SMITH, C. R. & LEON, M. B. 2012b. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med,* 366**,** 1696-704.

MALIWA, M. A., VAN DER HEIJDEN, G. J., BOTS, M. L., VAN HOUT, B. A., CASSELMAN, F. P., VAN SWIETEN, H. & VERMEULEN, F. E. 2003. Quality of life and NYHA class 30 years after mechanical aortic valve replacement. *Cardiovasc Surg,* 11**,** 381-7.

MARCUS, F. I., MCKENNA, W. J., SHERRILL, D., BASSO, C., BAUCE, B., BLUEMKE, D. A., CALKINS, H., CORRADO, D., COX, M. G. P. J., DAUBERT, J. P., FONTAINE, G., GEAR, K., HAUER, R., NAVA, A., PICARD, M. H., PROTONOTARIOS, N., SAFFITZ, J. E., SANBORN, D. M. Y., STEINBERG, J. S., TANDRI, H., THIENE, G., TOWBIN, J. A., TSATSOPOULOU, A., WICHTER, T. & ZAREBA, W. 2010. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed Modification of the Task Force Criteria. *European Heart Journal,* 31**,** 806-814.

MASSON, J. B., LEE, M., BOONE, R. H., AL ALI, A., AL BUGAMI, S., HAMBURGER, J., JOHN MANCINI, G. B., YE, J., CHEUNG, A., HUMPHRIES, K. H., WOOD, D., NIETLISPACH, F. & WEBB, J. G. 2010. Impact of coronary artery disease on outcomes after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv,* 76**,** 165-73.

MCCANN, G. P., STEADMAN, C. D., RAY, S. G. & NEWBY, D. E. 2011. Managing the asymptomatic patient with severe aortic stenosis: randomised controlled trials of early surgery are overdue. *Heart,* 97**,** 1119-21.

MEISSNER, I., KHANDHERIA, B. K., SHEPS, S. G., SCHWARTZ, G. L., WIEBERS, D. O., WHISNANT, J. P., COVALT, J. L., PETTERSON, T. M., CHRISTIANSON, T. J. & AGMON, Y. 2004. Atherosclerosis of the aorta: risk factor, risk marker, or innocent bystander? A prospective population-based transesophageal echocardiography study. *J Am Coll Cardiol,* 44**,** 1018-24.

MESSROGHLI, D. R., BAINBRIDGE, G. J., ALFAKIH, K., JONES, T. R., PLEIN, S., RIDGWAY, J. P. & SIVANANTHAN, M. U. 2005. Assessment of regional left ventricular function: accuracy and reproducibility of positioning standard short-axis sections in cardiac MR imaging. *Radiology,* 235**,** 229-36.

MESSROGHLI, D. R., PLEIN, S., HIGGINS, D. M., WALTERS, K., JONES, T. R., RIDGWAY, J. P. & SIVANANTHAN, M. U. 2006. Human myocardium: single-breath-hold MR T1 mapping with high spatial resolution--reproducibility study. *Radiology,* 238**,** 1004-12.

MESSROGHLI, D. R., RADJENOVIC, A., KOZERKE, S., HIGGINS, D. M., SIVANANTHAN, M. U. & RIDGWAY, J. P. 2004. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. *Magn Reson Med,* 52**,** 141-6.

MEWTON, N., LIU, C. Y., CROISILLE, P., BLUEMKE, D. & LIMA, J. A. 2011. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol,* 57**,** 891-903.

MICHEL, P., ROQUES, F. & NASHEF, S. A. 2003a. Logistic or additive EuroSCORE for high-risk patients? *Eur J Cardiothorac Surg,* 23**,** 684-7; discussion 687.

MICHEL, P., ROQUES, F. & NASHEF, S. A. M. 2003b. Logistic or additive EuroSCORE for high-risk patients? *European Journal of Cardio-Thoracic Surgery,* 23**,** 684-687.

MILLER, C. A., NAISH, J. H., BISHOP, P., COUTTS, G., CLARK, D., ZHAO, S., RAY, S. G., YONAN, N., WILLIAMS, S. G., FLETT, A. S., MOON, J. C., GREISER, A., PARKER, G. J. & SCHMITT, M. 2013. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. *Circ Cardiovasc Imaging,* 6**,** 373-83.

MILLER, J. D., WEISS, R. M. & HEISTAD, D. D. 2011. Calcific aortic valve stenosis: methods, models, and mechanisms. *Circ Res,* 108**,** 1392-412.

MOAT, N. E., LUDMAN, P., DE BELDER, M. A., BRIDGEWATER, B., CUNNINGHAM, A. D., YOUNG, C. P., THOMAS, M., KOVAC, J., SPYT, T., MACCARTHY, P. A., WENDLER, O., HILDICK-SMITH, D.,

DAVIES, S. W., TRIVEDI, U., BLACKMAN, D. J., LEVY, R. D., BRECKER, S. J., BAUMBACH, A., DANIEL, T., GRAY, H. & MULLEN, M. J. 2011. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol,* 58**,** 2130-8.

MOURA, L. M., RAMOS, S. F., ZAMORANO, J. L., BARROS, I. M., AZEVEDO, L. F., ROCHA-GONCALVES, F. & RAJAMANNAN, N. M. 2007. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. *J Am Coll Cardiol,* 49**,** 554-61.

NABER, C. K., GHANEM, A., ABIZAID, A. A., WOLF, A., SINNING, J. M., WERNER, N., NICKENIG, G., SCHMITZ, T. & GRUBE, E. 2012. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. *EuroIntervention,* 8**,** 43-50.

NACIF, M. S., TURKBEY, E. B., GAI, N., NAZARIAN, S., VAN DER GEEST, R. J., NOURELDIN, R. A., SIBLEY, C. T., UGANDER, M., LIU, S., ARAI, A. E., LIMA, J. A. & BLUEMKE, D. A. 2011. Myocardial T1 mapping with MRI: comparison of look-locker and MOLLI sequences. *J Magn Reson Imaging,* 34**,** 1367-73.

NADIR, M. A., WEI, L., ELDER, D. H., LIBIANTO, R., LIM, T. K., PAURIAH, M., PRINGLE, S. D., DONEY, A. D., CHOY, A. M., STRUTHERS, A. D. & LANG, C. C. 2011. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *J Am Coll Cardiol,* 58**,** 570-6.

NAGEL, E. 2003. Magnetic Resonance Perfusion Measurements for the Noninvasive Detection of Coronary Artery Disease. *Circulation,* 108**,** 432-437.

NAGEL, E., STUBER, M., BURKHARD, B., FISCHER, S. E., SCHEIDEGGER, M. B., BOESIGER, P. & HESS, O. M. 2000. Cardiac rotation and relaxation in patients with aortic valve stenosis. *Eur Heart J,* 21**,** 582-9.

NASHEF, S. A., ROQUES, F., MICHEL, P., GAUDUCHEAU, E., LEMESHOW, S. & SALAMON, R. 1999. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg,* 16**,** 9-13.

NASHEF, S. A., ROQUES, F., SHARPLES, L. D., NILSSON, J., SMITH, C., GOLDSTONE, A. R. & LOCKOWANDT, U. 2012. EuroSCORE II. *Eur J Cardiothorac Surg,* 41**,** 734-44; discussion 744-5.

NASHEF, S. A., SHARPLES, L. D., ROQUES, F. & LOCKOWANDT, U. 2013. EuroSCORE II and the art and science of risk modelling. *Eur J Cardiothorac Surg,* 43**,** 695-6.

NEMES, A., FORSTER, T. & CSANADY, M. 2004. Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. *J Heart Valve Dis,* 13**,** 567-73.

NEWMAN, M. F., KIRCHNER, J. L., PHILLIPS-BUTE, B., GAVER, V., GROCOTT, H., JONES, R. H., MARK, D. B., REVES, J. G. & BLUMENTHAL, J. A. 2001. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *The New England journal of medicine,* 344**,** 395-402.

NEYT, M., VAN BRABANDT, H., DEVRIESE, S. & VAN DE SANDE, S. 2012. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. *BMJ Open,* 2.

NICE 2012. Transcatheter aortic valve implantation for aortic stenosis (IPG421). *National Institute for Clinical Excellence,* http://guidance.nice.org.uk/IPG421.

NIETLISPACH, F., WIJESINGHE, N., GURVITCH, R., TAY, E., CARPENTER, J. P., BURNS, C., WOOD, D. A. & WEBB, J. G. 2010. An embolic deflection device for aortic valve interventions. *JACC Cardiovasc Interv,* 3**,** 1133-8.

NIGRI, M., AZEVEDO, C. F., ROCHITTE, C. E., SCHRAIBMAN, V., TARASOUTCHI, F., POMMERANTZEFF, P. M., BRANDAO, C. M., SAMPAIO, R. O., PARGA, J. R., AVILA, L. F., SPINA, G. S. & GRINBERG, M. 2009. Contrast-enhanced magnetic resonance imaging identifies focal regions of intramyocardial fibrosis in patients with severe aortic valve disease: Correlation with quantitative histopathology. *Am Heart J,* 157**,** 361-8.

NKOMO, V. T., GARDIN, J. M., SKELTON, T. N., GOTTDIENER, J. S., SCOTT, C. G. & ENRIQUEZ-SARANO, M. 2006. Burden of valvular heart diseases: a population-based study. *Lancet,* 368**,** 1005-11.

NUIS, R. J., VAN MIEGHEM, N. M., VAN DER BOON, R. M., VAN GEUNS, R. J., SCHULTZ, C. J., OEI, F. B., GALEMA, T. W., RAAP, G. B., KOUDSTAAL, P. J., GELEIJNSE, M. L., KAPPETEIN, A. P., SERRUYS,

P. W. & DE JAEGERE, P. P. 2011. Effect of experience on results of transcatheter aortic valve implantation using a Medtronic CoreValve System. *Am J Cardiol,* 107**,** 1824-9.

O'BRIEN, K. D. 2002. Association of Angiotensin-Converting Enzyme With Low-Density Lipoprotein in Aortic Valvular Lesions and in Human Plasma. *Circulation,* 106**,** 2224-2230.

O'BRIEN, K. D., PROBSTFIELD, J. L., CAULFIELD, M. T., NASIR, K., TAKASU, J., SHAVELLE, D. M., WU, A. H., ZHAO, X. Q. & BUDOFF, M. J. 2005. Angiotensin-converting enzyme inhibitors and change in aortic valve calcium. *Arch Intern Med,* 165**,** 858-62.

O'BRIEN, K. D., SHAVELLE, D. M., CAULFIELD, M. T., MCDONALD, T. O., OLIN-LEWIS, K., OTTO, C. M. & PROBSTFIELD, J. L. 2002. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. *Circulation,* 106**,** 2224-30.

OMRAN, H., SCHMIDT, H., HACKENBROCH, M., ILLIEN, S., BERNHARDT, P., VON DER RECKE, G., FIMMERS, R., FLACKE, S., LAYER, G., POHL, C., LUDERITZ, B., SCHILD, H. & SOMMER, T. 2003. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet,* 361**,** 1241-6.

ONSEA, K., AGOSTONI, P., SAMIM, M., VOSKUIL, M., KLUIN, J., BUDDE, R., HENDRIKSE, J., RAMJANKHAN, F., VAN KLARENBOSCH, J., DOESBURG, P., SIESWERDA, G. & STELLA, P. 2012. First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. *EuroIntervention,* 8**,** 51-6.

OSNABRUGGE, R. L., HEAD, S. J., GENDERS, T. S., VAN MIEGHEM, N. M., DE JAEGERE, P. P., VAN DER BOON, R. M., KERKVLIET, J. M., KALESAN, B., BOGERS, A. J., KAPPETEIN, A. P. & HUNINK, M. G. 2012. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg,* 94**,** 1954-60.

OTTO, C. M. 2006. Valvular aortic stenosis: disease severity and timing of intervention. *J Am Coll Cardiol,* 47**,** 2141-51.

OTTO, C. M., BURWASH, I. G., LEGGET, M. E., MUNT, B. I., FUJIOKA, M., HEALY, N. L., KRAFT, C. D., MIYAKE-HULL, C. Y. & SCHWAEGLER, R. G. 1997. Prospective Study of Asymptomatic Valvular Aortic Stenosis : Clinical, Echocardiographic, and Exercise Predictors of Outcome. *Circulation,* 95**,** 2262-2270.

OWENS, D. S., KATZ, R., TAKASU, J., KRONMAL, R., BUDOFF, M. J. & O'BRIEN, K. D. 2010. Incidence and progression of aortic valve calcium in the Multi-ethnic Study of Atherosclerosis (MESA). *Am J Cardiol,* 105**,** 701-8.

PELLIKKA, P. A. 2005. Outcome of 622 Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up. *Circulation,* 111**,** 3290-3295.

PELLIKKA, P. A., NISHIMURA, R. A., BAILEY, K. R. & TAJIK, A. J. 1990. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol,* 15**,** 1012-7.

PELLIKKA, P. A., SARANO, M. E., NISHIMURA, R. A., MALOUF, J. F., BAILEY, K. R., SCOTT, C. G., BARNES, M. E. & TAJIK, A. J. 2005. Outcome of 622 Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up. *Circulation,* 111**,** 3290-3295.

PHILLIPS, S. J., CIBORSKI, M., FREED, P. S., CASCADE, P. N. & JARON, D. 1976. A temporary catheter-tip aortic valve: hemodynamic effects on experimental acute aortic insufficiency. *Ann Thorac Surg,* 21**,** 134-7.

PIAZZA, N., GRUBE, E., GERCKENS, U., DEN HEIJER, P., LINKE, A., LUHA, O., RAMONDO, A., USSIA, G., WENAWESER, P., WINDECKER, S., LABORDE, J. C., DE JAEGERE, P. & SERRUYS, P. W. 2008. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention,* 4**,** 242-9.

PIAZZA, N., KALESAN, B., VAN MIEGHEM, N., HEAD, S., WENAWESER, P., CARREL, T. P., BLEIZIFFER, S., DE JAEGERE, P. P., GAHL, B., ANDERSON, R. H., KAPPETEIN, A. P., LANGE, R., SERRUYS, P. W., WINDECKER, S. & JUNI, P. 2013. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. *JACC Cardiovasc Interv,* 6**,** 443-51.

PIBAROT, P. & DUMESNIL, J. G. 2009. Aortic Stenosis: Look Globally, Think Globally. *JACC: Cardiovascular Imaging,* 2**,** 400-403.
PIBAROT, P. & DUMESNIL, J. G. 2010. Assessment of aortic stenosis severity: when the gradient does not fit with the valve area. *Heart,* 96**,** 1431-3.
PIBAROT, P. & DUMESNIL, J. G. 2012. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol,* 60**,** 1845-53.
PIECHNIK, S. K., FERREIRA, V. M., DALL'ARMELLINA, E., COCHLIN, L. E., GREISER, A., NEUBAUER, S. & ROBSON, M. D. 2010. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. *J Cardiovasc Magn Reson,* 12**,** 69.
PIRO, M., DELLA BONA, R., ABBATE, A., BIASUCCI, L. M. & CREA, F. 2010. Sex-related differences in myocardial remodeling. *J Am Coll Cardiol,* 55**,** 1057-65.
POULEUR, A.-C., LE POLAIN DE WAROUX, J.-B., PASQUET, A., VANCRAEYNEST, D., VANOVERSCHELDE, J.-L. J. & GERBER, B. L. 2007. Planimetric and continuity equation assessment of aortic valve area: Head to head comparison between cardiac magnetic resonance and echocardiography. *Journal of Magnetic Resonance Imaging,* 26**,** 1436-1443.
PUYMIRAT, E., CHASSAING, S., TRINQUART, L., BARBEY, C., CHAUDEURGE, A., BAR, O. & BLANCHARD, D. 2010. Hakki's Formula for Measurement of Aortic Valve Area by Magnetic Resonance Imaging. *The American Journal of Cardiology,* 106**,** 249-254.
QUERCIOLI, C., MESSINA, G., BARBINI, E., CARRIERO, G., FANI, M. & NANTE, N. 2009. Importance of sociodemographic and morbidity aspects in measuring health-related quality of life: performances of three tools: comparison of three questionnaire scores. *Eur J Health Econ,* 10**,** 389-97.
RABIN, R. & DE CHARRO, F. 2001. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med,* 33**,** 337-43.
RAJAMANNAN, N. M., BONOW, R. O. & RAHIMTOOLA, S. H. 2007. Calcific aortic stenosis: an update. *Nat Clin Pract Cardiovasc Med,* 4**,** 254-62.
RAJAPPAN, K. 2002. Mechanisms of Coronary Microcirculatory Dysfunction in Patients With Aortic Stenosis and Angiographically Normal Coronary Arteries. *Circulation,* 105**,** 470-476.
RANUCCI, M., CASTELVECCHIO, S., MENICANTI, L. A., SCOLLETTA, S., BIAGIOLI, B. & GIOMARELLI, P. 2009. An adjusted EuroSCORE model for high-risk cardiac patients. *Eur J Cardiothorac Surg,* 36**,** 791-7.
REANT, P., LEDERLIN, M., LAFITTE, S., SERRI, K., MONTAUDON, M., CORNELOUP, O., ROUDAUT, R. & LAURENT, F. 2006. Absolute assessment of aortic valve stenosis by planimetry using cardiovascular magnetic resonance imaging: Comparison with transœsophageal echocardiography, transthoracic echocardiography, and cardiac catheterisation. *European Journal of Radiology,* 59**,** 276-283.
REED, S. D., ANSTROM, K. J., BAKHAI, A., BRIGGS, A. H., CALIFF, R. M., COHEN, D. J., DRUMMOND, M. F., GLICK, H. A., GNANASAKTHY, A., HLATKY, M. A., O'BRIEN, B. J., TORTI, F. M., JR., TSIATIS, A. A., WILLAN, A. R., MARK, D. B. & SCHULMAN, K. A. 2005. Conducting economic evaluations alongside multinational clinical trials: toward a research consensus. *Am Heart J,* 149**,** 434-43.
REICHEK, N. 1999. MRI myocardial tagging. *J Magn Reson Imaging,* 10**,** 609-16.
REITH, W., HASEGAWA, Y., LATOUR, L. L., DARDZINSKI, B. J., SOTAK, C. H. & FISHER, M. 1995. Multislice diffusion mapping for 3-D evolution of cerebral ischemia in a rat stroke model. *Neurology,* 45**,** 172-7.
RESTREPO, L., WITYK, R. J., GREGA, M. A., BOROWICZ, L., JR., BARKER, P. B., JACOBS, M. A., BEAUCHAMP, N. J., HILLIS, A. E. & MCKHANN, G. M. 2002. Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. *Stroke,* 33**,** 2909-15.
REYNOLDS, M. R. & COHEN, D. J. 2013. The cost-effectiveness of transcatheter aortic valve replacement for nonsurgical candidates: revisionist history or the final word? *Circ Cardiovasc Qual Outcomes,* 6**,** 376-8.

REYNOLDS, M. R., MAGNUSON, E. A., LEI, Y., LEON, M. B., SMITH, C. R., SVENSSON, L. G., WEBB, J. G., BABALIAROS, V. C., BOWERS, B. S., FEARON, W. F., HERRMANN, H. C., KAPADIA, S., KODALI, S. K., MAKKAR, R. R., PICHARD, A. D. & COHEN, D. J. 2011. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation,* 124**,** 1964-72.

REYNOLDS, M. R., MAGNUSON, E. A., LEI, Y., WANG, K., VILAIN, K., LI, H., WALCZAK, J., PINTO, D. S., THOURANI, V. H., SVENSSON, L. G., MACK, M. J., MILLER, D. C., SATLER, L. E., BAVARIA, J., SMITH, C. R., LEON, M. B. & COHEN, D. J. 2012a. Cost-Effectiveness of Transcatheter Aortic Valve Replacement Compared With Surgical Aortic Valve Replacement in High-Risk Patients With Severe Aortic Stenosis: Results of the PARTNER (Placement of Aortic Transcatheter Valves) Trial (Cohort A). *J Am Coll Cardiol,* 60**,** 2683-92.

REYNOLDS, M. R., MAGNUSON, E. A., WANG, K., LEI, Y., VILAIN, K., WALCZAK, J., KODALI, S. K., LASALA, J. M., O'NEILL, W. W., DAVIDSON, C. J., SMITH, C. R., LEON, M. B. & COHEN, D. J. 2012b. Cost-Effectiveness of Transcatheter Aortic Valve Replacement Compared With Standard Care Among Inoperable Patients With Severe Aortic Stenosis: Results From the Placement of Aortic Transcatheter Valves (PARTNER) Trial (Cohort B). *Circulation,* 125**,** 1102-1109.

REYNOLDS, M. R., MAGNUSON, E. A., WANG, K., THOURANI, V. H., WILLIAMS, M., ZAJARIAS, A., RIHAL, C. S., BROWN, D. L., SMITH, C. R., LEON, M. B. & COHEN, D. J. 2012c. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). *J Am Coll Cardiol,* 60**,** 548-58.

RICHARDSON, G. & MANCA, A. 2004. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. *Health Econ,* 13**,** 1203-10.

ROBINSON, A., DOLAN, P. & WILLIAMS, A. 1997. Valuing health status using VAS and TTO: what lies behind the numbers? *Soc Sci Med,* 45**,** 1289-97.

RODES-CABAU, J., DUMONT, E., BOONE, R. H., LAROSE, E., BAGUR, R., GURVITCH, R., BEDARD, F., DOYLE, D., DE LAROCHELLIERE, R., JAYASURIA, C., VILLENEUVE, J., MARRERO, A., COTE, M., PIBAROT, P. & WEBB, J. G. 2011a. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. *J Am Coll Cardiol,* 57**,** 18-28.

RODES-CABAU, J., GUTIERREZ, M., BAGUR, R., DE LAROCHELLIERE, R., DOYLE, D., COTE, M., VILLENEUVE, J., BERTRAND, O. F., LAROSE, E., MANAZZONI, J., PIBAROT, P. & DUMONT, E. 2011b. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. *J Am Coll Cardiol,* 57**,** 1988-99.

RODES-CABAU, J., WEBB, J. G., CHEUNG, A., YE, J., DUMONT, E., FEINDEL, C. M., OSTEN, M., NATARAJAN, M. K., VELIANOU, J. L., MARTUCCI, G., DEVARENNES, B., CHISHOLM, R., PETERSON, M. D., LICHTENSTEIN, S. V., NIETLISPACH, F., DOYLE, D., DELAROCHELLIERE, R., TEOH, K., CHU, V., DANCEA, A., LACHAPELLE, K., CHEEMA, A., LATTER, D. & HORLICK, E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol,* 55**,** 1080-90.

RODES-CABAU, J., WEBB, J. G., CHEUNG, A., YE, J., DUMONT, E., FEINDEL, C. M., OSTEN, M., NATARAJAN, M. K., VELIANOU, J. L., MARTUCCI, G., DEVARENNES, B., CHISHOLM, R., PETERSON, M. D., LICHTENSTEIN, S. V., NIETLISPACH, F., DOYLE, D., DELAROCHELLIERE, R., TEOH, K., CHU, V., DANCEA, A., LACHAPELLE, K., CHEEMA, A., LATTER, D. & HORLICK, E. 2010. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol,* 55**,** 1080-90.

RODRIGUEZ, C. J., DIEZ-ROUX, A. V., MORAN, A., JIN, Z., KRONMAL, R. A., LIMA, J., HOMMA, S., BLUEMKE, D. A. & BARR, R. G. 2010. Left ventricular mass and ventricular remodeling among Hispanic subgroups compared with non-Hispanic blacks and whites: MESA (Multi-ethnic Study of Atherosclerosis). *J Am Coll Cardiol,* 55**,** 234-42.

ROGERS, W. J., HU, Y. L., COAST, D., VIDO, D. A., KRAMER, C. M., PYERITZ, R. E. & REICHEK, N. 2001. Age-associated changes in regional aortic pulse wave velocity. *J Am Coll Cardiol,* 38**,** 1123-9.

ROLF, M. P., HOFMAN, M. B. M., GATEHOUSE, P. D., MARKENROTH-BLOCH, K., HEYMANS, M. W., EBBERS, T., GRAVES, M. J., TOTMAN, J. J., WERNER, B., VAN ROSSUM, A. C., KILNER, P. J. & HEETHAAR, R. M. 2011. Sequence optimization to reduce velocity offsets in cardiovascular magnetic resonance volume flow quantification - A multi-vendor study. *Journal of Cardiovascular Magnetic Resonance,* 13**,** 18.

ROQUES, F., MICHEL, P., GOLDSTONE, A. R. & NASHEF, S. A. 2003. The logistic EuroSCORE. *Eur Heart J,* 24**,** 881-2.

ROSENHEK, R., BINDER, T., PORENTA, G., LANG, I., CHRIST, G., SCHEMPER, M., MAURER, G. & BAUMGARTNER, H. 2000. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med,* 343**,** 611-7.

ROSENHEK, R., ZILBERSZAC, R., SCHEMPER, M., CZERNY, M., MUNDIGLER, G., GRAF, S., BERGLER-KLEIN, J., GRIMM, M., GABRIEL, H. & MAURER, G. 2009. Natural History of Very Severe Aortic Stenosis. *Circulation,* 121**,** 151-156.

ROSSEBO, A. B. 2008. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. *New England Journal Of Medicine,* 11**,** 1343-56.

RUDOLPH, A., ABDEL-ATY, H., BOHL, S., BOYE, P., ZAGROSEK, A., DIETZ, R. & SCHULZ-MENGER, J. 2009. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. *J Am Coll Cardiol,* 53**,** 284-91.

RUSSEL, I. K., GOTTE, M. J., KUIJER, J. P. & MARCUS, J. T. 2008. Regional assessment of left ventricular torsion by CMR tagging. *J Cardiovasc Magn Reson,* 10**,** 26.

RÜSSEL, I. K., GÖTTE, M. J. W., BRONZWAER, J. G., KNAAPEN, P., PAULUS, W. J. & VAN ROSSUM, A. C. 2009. Left Ventricular Torsion: An Expanding Role in the Analysis of Myocardial Dysfunction. *JACC: Cardiovascular Imaging,* 2**,** 648-655.

RUSSO, C., JIN, Z., RUNDEK, T., HOMMA, S., SACCO, R. L. & DI TULLIO, M. R. 2009. Atherosclerotic disease of the proximal aorta and the risk of vascular events in a population-based cohort: the Aortic Plaques and Risk of Ischemic Stroke (APRIS) study. *Stroke,* 40**,** 2313-8.

SADEK, A. G., MOHAMED, F. B., OUTWATER, E. K., EL-ESSAWY, S. S. & MITCHELL, D. G. 1996. Respiratory and postprandial changes in portal flow rate: assessment by phase contrast MR imaging. *J Magn Reson Imaging,* 6**,** 90-3.

SANDSTEDE, J. J., BEER, M., HOFMANN, S., LIPKE, C., HARRE, K., PABST, T., KENN, W., NEUBAUER, S. & HAHN, D. 2000. Changes in left and right ventricular cardiac function after valve replacement for aortic stenosis determined by cine MR imaging. *J Magn Reson Imaging,* 12**,** 240-6.

SANDSTEDE, J. J., JOHNSON, T., HARRE, K., BEER, M., HOFMANN, S., PABST, T., KENN, W., VOELKER, W., NEUBAUER, S. & HAHN, D. 2002. Cardiac systolic rotation and contraction before and after valve replacement for aortic stenosis: a myocardial tagging study using MR imaging. *AJR Am J Roentgenol,* 178**,** 953-8.

SCHAEFER, P. W., GRANT, P. E. & GONZALEZ, R. G. 2000. Diffusion-weighted MR imaging of the brain. *Radiology,* 217**,** 331-45.

SCHLOSSER, T., MALYAR, N., JOCHIMS, M., BREUCKMANN, F., HUNOLD, P., BRUDER, O., ERBEL, R. & BARKHAUSEN, J. 2006. Quantification of aortic valve stenosis in MRI—comparison of steady-state free precession and fast low-angle shot sequences. *European Radiology,* 17**,** 1284-1290.

SCHUELER, R., HAMMERSTINGL, C., SINNING, J.-M., NICKENIG, G. & OMRAN, H, 2010. Prognosis of octogenarians with severe aortic valve stenosis at high risk for cardiovascular surgery. *Heart,* 96**,** 1831-1836.

SCHUELER, R., SINNING, J. M., MOMCILOVIC, D., WEBER, M., GHANEM, A., WERNER, N., NICKENIG, G., GRUBE, E. & HAMMERSTINGL, C. 2012. Three-dimensional speckle-tracking analysis of left ventricular function after transcatheter aortic valve implantation. *J Am Soc Echocardiogr,* 25**,** 827-834 e1.

SECHTEM, U., MAHRHOLDT, H. & VOGELSBERG, H. 2006. Cardiac magnetic resonance in myocardial disease. *Heart,* 93**,** 1520-1527.

SEGAL, A. Z., ABERNETHY, W. B., PALACIOS, I. F., BELUE, R. & RORDORF, G. 2001. Stroke as a complication of cardiac catheterization: risk factors and clinical features. *Neurology,* 56**,** 975-7.

SEMELKA, R. C., TOMEI, E., WAGNER, S., MAYO, J., CAPUTO, G., O'SULLIVAN, M., PARMLEY, W. W., CHATTERJEE, K., WOLFE, C. & HIGGINS, C. B. 1990a. Interstudy reproducibility of dimensional and functional measurements between cine magnetic resonance studies in the morphologically abnormal left ventricle. *Am Heart J,* 119**,** 1367-73.

SEMELKA, R. C., TOMEI, E., WAGNER, S., MAYO, J., KONDO, C., SUZUKI, J., CAPUTO, G. R. & HIGGINS, C. B. 1990b. Normal left ventricular dimensions and function: interstudy reproducibility of measurements with cine MR imaging. *Radiology,* 174**,** 763-8.

SENGUPTA, P., TAJIK, A., CHANDRASEKARAN, K. & KHANDHERIA, B. 2008. Twist Mechanics of the Left VentriclePrinciples and Application. *JACC: Cardiovascular Imaging,* 1**,** 366-376.

SHEEHAN, F. H., BOLSON, E. L., DODGE, H. T., MATHEY, D. G., SCHOFER, J. & WOO, H. W. 1986. Advantages and applications of the centerline method for characterizing regional ventricular function. *Circulation,* 74**,** 293-305.

SHERIF, M. A., ABDEL-WAHAB, M., BEURICH, H. W., STOCKER, B., ZACHOW, D., GEIST, V., TOLG, R. & RICHARDT, G. 2011. Haemodynamic evaluation of aortic regurgitation after transcatheter aortic valve implantation using cardiovascular magnetic resonance. *EuroIntervention,* 7**,** 57-63.

SIMONS, C. T., CIPRIANO, L. E., SHAH, R. U., GARBER, A. M., OWENS, D. K. & HLATKY, M. A. 2013. Transcatheter aortic valve replacement in nonsurgical candidates with severe, symptomatic aortic stenosis: a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes,* 6**,** 419-28.

SINNING, J. M., HAMMERSTINGL, C., VASA-NICOTERA, M., ADENAUER, V., LEMA CACHIGUANGO, S. J., SCHEER, A. C., HAUSEN, S., SEDAGHAT, A., GHANEM, A., MULLER, C., GRUBE, E., NICKENIG, G. & WERNER, N. 2012. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol,* 59**,** 1134-41.

SINNING, J. M., VASA-NICOTERA, M., CHIN, D., HAMMERSTINGL, C., GHANEM, A., BENCE, J., KOVAC, J., GRUBE, E., NICKENIG, G. & WERNER, N. 2013. Evaluation and management of paravalvular aortic regurgitation after transcatheter aortic valve replacement. *J Am Coll Cardiol,* 62**,** 11-20.

SMITH, C. R., LEON, M. B., MACK, M. J., MILLER, D. C., MOSES, J. W., SVENSSON, L. G., TUZCU, E. M., WEBB, J. G., FONTANA, G. P., MAKKAR, R. R., WILLIAMS, M., DEWEY, T., KAPADIA, S., BABALIAROS, V., THOURANI, V. H., CORSO, P., PICHARD, A. D., BAVARIA, J. E., HERRMANN, H. C., AKIN, J. J., ANDERSON, W. N., WANG, D. & POCOCK, S. J. 2011. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med,* 364**,** 2187-98.

STEADMAN, C. D., JEROSCH-HEROLD, M., GRUNDY, B., RAFELT, S., NG, L. L., SQUIRE, I. B., SAMANI, N. J. & MCCANN, G. P. 2012. Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis. *JACC Cardiovasc Imaging,* 5**,** 182-9.

STEWART, B. F., SISCOVICK, D., LIND, B. K., GARDIN, J. M., GOTTDIENER, J. S., SMITH, V. E., KITZMAN, D. W. & OTTO, C. M. 1997. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol,* 29**,** 630-4.

STOLZ, E., GERRIETS, T., KLUGE, A., KLOVEKORN, W.-P., KAPS, M. & BACHMANN, G. 2004. Diffusion-weighted magnetic resonance imaging and neurobiochemical markers after aortic valve replacement: implications for future neuroprotective trials? *Stroke; a journal of cerebral circulation,* 35**,** 888-92.

STUBER, M., SCHEIDEGGER, M. B., FISCHER, S. E., NAGEL, E., STEINEMANN, F., HESS, O. M. & BOESIGER, P. 1999. Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation,* 100**,** 361-8.

SUNDT, T. M., BAILEY, M. S., MOON, M. R., MENDELOFF, E. N., HUDDLESTON, C. B., PASQUE, M. K., BARNER, H. B. & GAY, W. A., JR. 2000. Quality of life after aortic valve replacement at the age of >80 years. *Circulation,* 102**,** III70-4.

TABER, L. A., YANG, M. & PODSZUS, W. W. 1996. Mechanics of ventricular torsion. *J Biomech,* 29**,** 745-52.

TAKAGI, K., LATIB, A., AL-LAMEE, R., MUSSARDO, M., MONTORFANO, M., MAISANO, F., GODINO, C., CHIEFFO, A., ALFIERI, O. & COLOMBO, A. 2011. Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. *Catheter Cardiovasc Interv,* 78**,** 432-43.

TAMBURINO, C., CAPODANNO, D., RAMONDO, A., PETRONIO, A. S., ETTORI, F., SANTORO, G., KLUGMANN, S., BEDOGNI, F., MAISANO, F., MARZOCCHI, A., POLI, A., ANTONIUCCI, D., NAPODANO, M., DE CARLO, M., FIORINA, C. & USSIA, G. P. 2011. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation,* 123**,** 299-308.

TARAMASSO, M., LATIB, A., CIONI, M., DENTI, P., BUZZATTI, N., GODINO, C., CHIEFFO, A., ALFIERI, O., COLOMBO, A. & MAISANO, F. 2012. Quality of life improvement is maintained up to two years after transcatheter aortic valve implantation in high-risk surgical candidates. *EuroIntervention,* 8**,** 429-36.

TEICHHOLZ, L. E., KREULEN, T., HERMAN, M. V. & GORLIN, R. 1976. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol,* 37**,** 7-11.

THOMAS, M., SCHYMIK, G., WALTHER, T., HIMBERT, D., LEFEVRE, T., TREEDE, H., EGGEBRECHT, H., RUBINO, P., COLOMBO, A., LANGE, R., SCHWARZ, R. R. & WENDLER, O. 2011. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation,* 124**,** 425-33.

TOGGWEILER, S., HUMPHRIES, K. H., LEE, M., BINDER, R. K., MOSS, R. R., FREEMAN, M., YE, J., CHEUNG, A., WOOD, D. A. & WEBB, J. G. 2013. 5-year outcome after transcatheter aortic valve implantation. *J Am Coll Cardiol,* 61**,** 413-9.

UGANDER, M., BAGI, P. S., OKI, A. J., CHEN, B., HSU, L. Y., ALETRAS, A. H., SHAH, S., GREISER, A., KELLMAN, P. & ARAI, A. E. 2012a. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. *JACC Cardiovasc Imaging,* 5**,** 596-603.

UGANDER, M., OKI, A. J., HSU, L. Y., KELLMAN, P., GREISER, A., ALETRAS, A. H., SIBLEY, C. T., CHEN, M. Y., BANDETTINI, W. P. & ARAI, A. E. 2012b. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. *Eur Heart J,* 33**,** 1268-78.

UNBEHAUN, A., PASIC, M., DREYSSE, S., DREWS, T., KUKUCKA, M., MLADENOW, A., IVANITSKAJA-KUHN, E., HETZER, R. & BUZ, S. 2012. Transapical aortic valve implantation: incidence and predictors of paravalvular leakage and transvalvular regurgitation in a series of 358 patients. *J Am Coll Cardiol,* 59**,** 211-21.

USSIA, G. P., BARBANTI, M., CAMMALLERI, V., SCARABELLI, M., MULE, M., ARUTA, P., PISTRITTO, A. M., IMME, S., CAPODANNO, D., SARKAR, K., GULINO, S. & TAMBURINO, C. 2011. Quality-of-life in elderly patients one year after transcatheter aortic valve implantation for severe aortic stenosis. *EuroIntervention,* 7**,** 573-9.

USSIA, G. P., BARBANTI, M., PETRONIO, A. S., TARANTINI, G., ETTORI, F., COLOMBO, A., VIOLINI, R., RAMONDO, A., SANTORO, G., KLUGMANN, S., BEDOGNI, F., MAISANO, F., MARZOCCHI, A., POLI, A., DE CARLO, M., NAPODANO, M., FIORINA, C., DE MARCO, F., ANTONIUCCI, D., DE CILLIS, E., CAPODANNO, D. & TAMBURINO, C. 2012. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J,* 33**,** 969-76.

USSIA, G. P., MULE, M., BARBANTI, M., CAMMALLERI, V., SCARABELLI, M., IMME, S., CAPODANNO, D., CIRIMINNA, S. & TAMBURINO, C. 2009. Quality of life assessment after percutaneous aortic valve implantation. *Eur Heart J,* 30**,** 1790-6.

VAHANIAN, A., ALFIERI, O., AL-ATTAR, N., ANTUNES, M., BAX, J., CORMIER, B., CRIBIER, A., DE JAEGERE, P., FOURNIAL, G., KAPPETEIN, A. P., KOVAC, J., LUDGATE, S., MAISANO, F., MOAT, N., MOHR, F., NATAF, P., PIERARD, L., POMAR, J. L., SCHOFER, J., TORNOS, P., TUZCU, M., VAN HOUT, B., VON SEGESSER, L. K. & WALTHER, T. 2008. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J,* 29**,** 1463-70.

VAHANIAN, A., ALFIERI, O., ANDREOTTI, F., ANTUNES, M. J., BARON-ESQUIVIAS, G., BAUMGARTNER, H., BORGER, M. A., CARREL, T. P., DE BONIS, M., EVANGELISTA, A., FALK, V., IUNG, B., LANCELLOTTI, P., PIERARD, L., PRICE, S., SCHAFERS, H. J., SCHULER, G., STEPINSKA, J., SWEDBERG, K., TAKKENBERG, J., VON OPPELL, U. O., WINDECKER, S., ZAMORANO, J. L. & ZEMBALA, M. 2012. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J,* 33**,** 2451-96.

VAHANIAN, A., BAUMGARTNER, H., BAX, J., BUTCHART, E., DION, R., FILIPPATOS, G., FLACHSKAMPF, F., HALL, R., IUNG, B., KASPRZAK, J., NATAF, P., TORNOS, P., TORRACCA, L., WENINK, A., PRIORI, S. G., BLANC, J. J., BUDAJ, A., CAMM, J., DEAN, V., DECKERS, J., DICKSTEIN, K., LEKAKIS, J., MCGREGOR, K., METRA, M., MORAIS, J., OSTERSPEY, A., TAMARGO, J., ZAMORANO, J. L., ANGELINI, A., ANTUNES, M., FERNANDEZ, M. A. G., GOHLKE-BAERWOLF, C., HABIB, G., MCMURRAY, J., OTTO, C., PIERARD, L., POMAR, J. L., PRENDERGAST, B., ROSENHEK, R. & UVA, M. S. 2006. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J,* 28**,** 230-268.

VAN DALEN, B. M., TZIKAS, A., SOLIMAN, O. I., KAUER, F., HEUVELMAN, H. J., VLETTER, W. B., TEN CATE, F. J. & GELEIJNSE, M. L. 2011. Left ventricular twist and untwist in aortic stenosis. *Int J Cardiol,* 148**,** 319-24.

VAN EVERDINGEN, K. J., VAN DER GROND, J., KAPPELLE, L. J., RAMOS, L. M. & MALI, W. P. 1998. Diffusion-weighted magnetic resonance imaging in acute stroke. *Stroke,* 29**,** 1783-90.

VASQUES, F., MESSORI, A., LUCENTEFORTE, E. & BIANCARI, F. 2012. Immediate and late outcome of patients aged 80 years and older undergoing isolated aortic valve replacement: a systematic review and meta-analysis of 48 studies. *Am Heart J,* 163**,** 477-85.

VLACHOPOULOS, C., AZNAOURIDIS, K. & STEFANADIS, C. 2010. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol,* 55**,** 1318-27.

WANG, J., CHEN, W., RUAN, L., TOPRAK, A., SRINIVASAN, S. R. & BERENSON, G. S. 2011. Differential effect of elevated blood pressure on left ventricular geometry types in black and white young adults in a community (from the Bogalusa Heart Study). *Am J Cardiol,* 107**,** 717-22.

WARE, J., JR., KOSINSKI, M. & KELLER, S. D. 1996a. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care,* 34**,** 220-33.

WARE, J. E., JR. 2000. SF-36 health survey update. *Spine (Phila Pa 1976),* 25**,** 3130-9.

WARE, J. E., JR., PHILLIPS, J., YODY, B. B. & ADAMCZYK, J. 1996b. Assessment tools: functional health status and patient satisfaction. *Am J Med Qual,* 11**,** S50-3.

WATT, M., MEALING, S., EATON, J., PIAZZA, N., MOAT, N., BRASSEUR, P., PALMER, S., BUSCA, R. & SCULPHER, M. 2012. Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. *Heart,* 98**,** 370-6.

WEBB, J. G., CHANDAVIMOL, M., THOMPSON, C. R., RICCI, D. R., CARERE, R. G., MUNT, B. I., BULLER, C. E., PASUPATI, S. & LICHTENSTEIN, S. 2006. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation,* 113**,** 842-50.

WEBER, K. T. & BRILLA, C. G. 1991. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation,* 83**,** 1849-65.

WEIDEMANN, F., HERRMANN, S., STORK, S., NIEMANN, M., FRANTZ, S., LANGE, V., BEER, M., GATTENLOHNER, S., VOELKER, W., ERTL, G. & STROTMANN, J. M. 2009. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation,* 120**,** 577-84.

WENAWESER, P., STORTECKY, S., SCHWANDER, S., HEG, D., HUBER, C., PILGRIM, T., GLOEKLER, S., O'SULLIVAN, C. J., MEIER, B., JUNI, P., CARREL, T. & WINDECKER, S. 2013. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J,* 34**,** 1894-905.

WHITE, S. K., SADO, D. M., FLETT, A. S. & MOON, J. C. 2012. Characterising the myocardial interstitial space: the clinical relevance of non-invasive imaging. *Heart,* 98**,** 773-9.

WILLSON, A. B., WEBB, J. G., LABOUNTY, T. M., ACHENBACH, S., MOSS, R., WHEELER, M., THOMPSON, C., MIN, J. K., GURVITCH, R., NORGAARD, B. L., HAGUE, C. J., TOGGWEILER, S., BINDER, R., FREEMAN, M., POULTER, R., POULSEN, S., WOOD, D. A. & LEIPSIC, J. 2012. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. *J Am Coll Cardiol,* 59**,** 1287-94.

WONG, T. C., PIEHLER, K., MEIER, C. G., TESTA, S. M., KLOCK, A. M., ANEIZI, A. A., SHAKESPRERE, J., KELLMAN, P., SHROFF, S. G., SCHWARTZMAN, D. S., MULUKUTLA, S. R., SIMON, M. A. & SCHELBERT, E. B. 2012. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. *Circulation,* 126**,** 1206-16.

WONG, T. C., PIEHLER, K. M., KANG, I. A., KADAKKAL, A., KELLMAN, P., SCHWARTZMAN, D. S., MULUKUTLA, S. R., SIMON, M. A., SHROFF, S. G., KULLER, L. H. & SCHELBERT, E. B. 2013. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. *Eur Heart J*.

WU, E., JUDD, R. M., VARGAS, J. D., KLOCKE, F. J., BONOW, R. O. & KIM, R. J. 2001. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet,* 357**,** 21-8.

YOSHITAKE, T., KIYOHARA, Y., KATO, I., OHMURA, T., IWAMOTO, H., NAKAYAMA, K., OHMORI, S., NOMIYAMA, K., KAWANO, H., UEDA, K. & ET AL. 1995. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology,* 45**,** 1161-8.

ZAHN, R., GERCKENS, U., GRUBE, E., LINKE, A., SIEVERT, H., EGGEBRECHT, H., HAMBRECHT, R., SACK, S., HAUPTMANN, K. E., RICHARDT, G., FIGULLA, H. R. & SENGES, J. 2010. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *European Heart Journal,* 32**,** 198-204.

ZAHN, R., GERCKENS, U., GRUBE, E., LINKE, A., SIEVERT, H., EGGEBRECHT, H., HAMBRECHT, R., SACK, S., HAUPTMANN, K. E., RICHARDT, G., FIGULLA, H. R. & SENGES, J. 2011. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J,* 32**,** 198-204.

ZAJARIAS, A. & CRIBIER, A. G. 2009. Outcomes and safety of percutaneous aortic valve replacement. *J Am Coll Cardiol,* 53**,** 1829-36.

8 Appendices

8.1 Ethical Consent

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)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

8.2 Substantial Amendment

Leeds (West) Research Ethics Committee
Leeds West REC
Yorkshire & Humber REC Office
Millside, Mill Pond Lane
Meanwood, Leeds
LS6 4EP
Tel: 0113 305 0116

20 May 2010

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

Dear Dr Greenwood

Study title: **MRI evaluation of Percutaneous and Surgical Aortic Valve Replacement**
REC reference: **08/H1307/106**
Amendment number: **2**
Amendment date: **24 April 2010**

The above amendment was reviewed at the meeting of the Sub-Committee held on 18 May 2010.

Ethical opinion

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

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form	1.0	01 August 2008
Participant Information Sheet	1.1	20 April 2010
Protocol	1.1	20 April 2010
Notice of Substantial Amendment (non-CTIMPs)		24 April 2010
Covering Letter		25 April 2010

Membership of the Committee

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

R&D approval

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

Statement of compliance

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

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

Yours sincerely

Claire Kelly
Committee Assistant Co-ordinator

E-mail: Claire.kelly@leedspft.nhs.uk

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

Copy to: *Ms Clare Skinner*

8.3 Patient Invitation

We would like to invite you to participate in a research study, called MRI evaluation of Percutaneous and Surgical Aortic Valve Replacement.

Please read the information sheet carefully and if you are interested in finding out more about the study before your planned admission to hospital then please phone us so that the research team can explain the study to you further and answer any questions you may have. The numbers you can ring are 0113 392 5481 or 0113 392 5167, please ask for Dr Tim Fairbairn. Alternatively, once you are admitted to hospital for your valve replacement you will have a chance to discuss the study with one of the researchers.

Please note that you are under no obligation to take part and it will not affect your treatment if you decide not to. However we would very much appreciate it if you would let us know. We will reimburse any travelling expenses you incur as part of this study.

Thank you for considering this request.

Yours sincerely

Dr JP Greenwood
Consultant Cardiologist
Academic Unit of Cardiovascular Medicine
G Floor Jubilee Wing
Leeds General Infirmary
Leeds
LS1 3EX

8.4 Patient Information Sheet

Division of Cardiovascular and Neuronal Remodelling Leeds Institute of Genetics, Health and Therapeutics

Cardiovascular Research G Floor,

Jubilee Building Leeds General Infirmary Great George Street Leeds,

LS1 3EX

T 0113 392 5481

F 0113 392 8611

M 07922 512887

MRI evaluation of Percutaneous and Surgical Aortic Valve Replacement

Patient information Leaflet

Version 1.1 April 2010

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

percutaneous 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; once you come to hospital for your valve replacement you will be able to discuss the study further with a member of the research team. 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, 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, we will scan your head only, which takes about 10 minutes. Approximately 4-6 months later we will ask you to return to the MRI department so we can scan you heart, which takes about 50 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

During the actual valve replacement we will carry out an ultrasound scan of your head. This is a simple non-invasive study using ultrasound waves, with no known risk. You will wear a comfortable head band during the procedure which contains two small ultrasound probes. As you will be either sedated or fully anaesthetized you will not notice the scan.

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, 1 year and 2 years. We will also do a short test (before and after the valve replacement) called the 'mini-mental test' which is a commonly used list of 10 questions which tests your memory.

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 scan 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 Tim Fairbairn

Cardiac MRI Department,

B Floor, Clarendon Wing,

Leeds General Infirmary,

LS1 3EX

Tel: 0113 39 25167

8.5 Consent Form

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

Hospital Number: ……. Initials: ……..

CONSENT FORM – Version 1.1 April 2010

MRI evaluation of Percutaneous and Surgical Aortic Valve Replacement Name of Researcher: Dr John Greenwood Please initial box		
1.	I confirm that I have read and understood the information sheet (version 1.1 April 2010) 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.	