Defining long term morbidity and mortality in adult survivors of congenital heart disease

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Abstract

Over the past thirty years there has been a dramatic improvement in the survival of children with congenital heart disease, and the vast majority can now expect to reach adulthood. However it is rare that a lesion can truly be described as "cured" even with everything that modern surgery can offer. Often lesions are palliated instead, and this subjects patients to a variety of complications in later life. These include residual haemodynamic lesions necessitating further surgical or percutaneous intervention, cardiac arrhythmia, and heart failure. All of these are potentially lethal, and result in a steady decline in survival, functional status and quality of life in later years.

In order to care for these patients a new medical subspecialty has emerged - that of Adults with Congenital Heart Disease (ACHD). Although the provision of highly specialist management for this population has allowed many significant clinical improvements to be made, healthcare practitioners working in this field face significant challenges. The long term prognosis for these patients is uncertain, making it difficult to know how to counsel young people who wish for employment, a family, and a future. Whilst powerful tools for the non-invasive assessment of cardiovascular structure and function exist, their role in clinical decision making is often poorly defined, and the nature and timing of repeat intervention are frequently based on expert opinion rather than robust evidence from large well conducted clinical trials, and consequently the true benefit of such procedures is unclear. Furthermore, to my knowledge, there has never been a serious attempt to characterise outcomes in ACHD patients in Scotland.

Because of the sheer heterogeneity of congenital cardiac conditions I decided to focus on outcomes in two distinct, relatively easily defined cohorts of adult patients with repaired congenital heart disease - patients with a systemic right ventricle, and patients with repaired Tetralogy of Fallot (TOF), both characterised by the presence of an abnormal right

ventricle. In chapter 3 I outline what is currently known about mortality and morbidity in each condition, based on what has been reported globally by other congenital cardiac centres. I then report the survival and adverse outcomes experienced by patients followed up by our centre: for patients with a systemic right ventricle in chapter 4, and for patients with repaired TOF in chapter 5. I assess these outcomes both in relation to the published literature internationally, and also to the general Scottish population. Finally, in chapter 6 I assess the clinical utility of parameters derived from cardiac MRI and cardiopulmonary exercise testing to establish whether this can improve clinical risk stratification for patients with repaired TOF.

Declaration

The design of this thesis was that of the author, Dr. Nikolaos Tzemos, and Dr. Hamish Walker. The author performed all data collection and manuscript preparation. Advice on the appropriate statistical techniques to use for Chapter 5 was provided by Mr. Nitish Ramparsad and Dr. Alex McConnachie at the Robertson Centre for Biostatistics, although all the statistical analysis and output in this thesis were performed by myself. During my initial year of registration with the University of Glasgow from 2011-12 I was employed in a clinical fellow post at the Golden Jubilee National Hospital which had part funding from Actelion Pharmaceuticals (Allschwil, Switzerland), however there were no associated commercial or research obligations. This work has not been submitted for any other degree at the University of Glasgow or any other institution.

Dr. Richard Dobson 30th July 2017

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Publications and presentations arising from this thesis

Publications

- Dobson R, Danton M, Walker N, Walker H. The natural and unnatural history of the systemic right ventricle in adult survivors. *Journal of Thoracic and Cardiovascular Surgery* (2013). 145:1493-1503
- Dobson R, Tzemos N, Walker H. Relationship between socioeconomic status and survival in Scottish adults with Tetralogy of Fallot. *Heart* (2014). 100:A28
- Dobson R, Mordi I, Danton M, Walker N, Walker H, Tzemos N. Late gadolinium enhancement and adverse outcomes in a contemporary cohort of adult survivors of Tetralogy of Fallot. *Congenital Heart Disease* (2017). 1:58-66

Presentations

- The natural and unnatural history of the systemic right ventricle in adult survivors (plenary presentation). American Association for Thoracic Surgery 92nd Annual Meeting, April 2012
- Relationship between socioeconomic status and survival in Scottish adults with Tetralogy of Fallot (poster presentation). British Cardiovascular Society annual meeting, June 2014
- Ultra long term outcomes in adult survivors of tetralogy of Fallot (oral presentation). American Association for Thoracic Surgery 95th Annual Meeting, May 2015.

List of abbreviations

6MWT Six Minute Walk Test

ACEI Angiotensin Converting Enzyme-Inhibitor

ACHD Adults with Congenital Heart Disease

ADMA Asymmetric Di-Methyl Arginine

AF Atrial Fibrillation

ANP Atrial Natriuretic Peptide

A2RB Angiotensin 2 Receptor Blocker

AVR Aortic Valve Replacement

ASD Atrial Septal Defect

AVSD Atrio-Ventricular Septal Defect

bpm Beats Per Minute [heart rate]

BT Blalock-Taussig [shunt]

CCTGA Congenitally Corrected Transposition of the Great Arteries

CI Confidence Intervals

CMR Cardiac Magnetic Resonance

CNP C-type Natriuretic Peptide

CPET Cardio-Pulmonary Exercise Test

CRT-D Cardiac Resynchronisation Therapy-Defibrillator

DCCV DC Cardioversion

DDD Dual sensing, Dual pacing, Dual response (pacemaker)

DS Down Syndrome

ECG Electrocardiogram

ECV Extra-Cellular Volume

EDVi End Diastolic Volume (indexed per ml body surface area in m^2)

EF Ejection Fraction (%)

ESVi End Systolic Volume (indexed per ml body surface area in m^2)

HASTE Half-Fourier Acquisition Single shot Turbo-spin Echo

HR Heart Rate or Hazard Ratio

HRR Heart Rate Reserve

HW Hamish Walker

ICD Implantable Cardioverter Defibrillator

IQR Interquartile range (25th centile to 75th centile)

LA Left Atrium

LGE Late Gadolinium Enhancement

LV Left Ventricle

LVOT Left Ventricular Outflow Tract

LVOTO Left Ventricular Outflow Tract Obstruction

ml/m2 Millilitres per metre squared [of body surface area]

MRI Magnetic Resonance Imaging

MRA Mineralocorticoid Receptor Antagonist

NYHA New York Heart Association [classification of heart failure symptom severity]

OPCS Office of Population Censuses and Surveys

PA Pulmonary Artery

PFO Patent Foramen Ovale

PAPVD Partial Anomalous Pulmonary Venous Drainage

PDA Patent Ductus Arteriosus

PSIR Phase Sensitive Inversion Recovery

PVP Pulmonary Venous Pathway (in patients post Mustard or Senning repair)

PVR Pulmonary Valve Replacement

RA Right Atrium

RD Richard Dobson

REV Réparation a l'Étage Ventriculaire

RF Regurgitant Fraction

RV Right Ventricle

RVOT Right Ventricular Outflow Tract

SACCS Scottish Adult Congenital Cardiac Service

SAVV Systemic Atrio-Ventricular Valve (tricuspid valve in a systemic RV)

SD Standard Deviation

SE Standard Error

SMR Standardised Mortality Ratio

SRV Systemic Right Ventricle

SSFP Steady State Free Precession

SVC Superior Vena Cava

SVP Systemic Venous Pathway (in patients post Mustard or Senning repair)

TGA Transposition of the Great Arteries

TOF Tetralogy of Fallot

TR Tricuspid Regurgitation

TVR Tricuspid Valve Replacement

VATER Vertebral anomalies, Anal atresia, Tracheoesophageal fistula, Esophageal atresia, Radial/Renal anomalies

VE Minute ventilation L/min

VF Ventricular Fibrillation

VO2 Oxygen uptake during CPET L/min

VO2i VO2 indexed to body weight ml/kg/min

VCO2 Peak carbon dioxide output during CPET L/min

VSD Ventricular Septal Defect

VT Ventricular Tachycardia

VVI Ventricular sensing, Ventricular pacing, Inhibited response (pacemaker)

y Year

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Chapter 1 Introduction

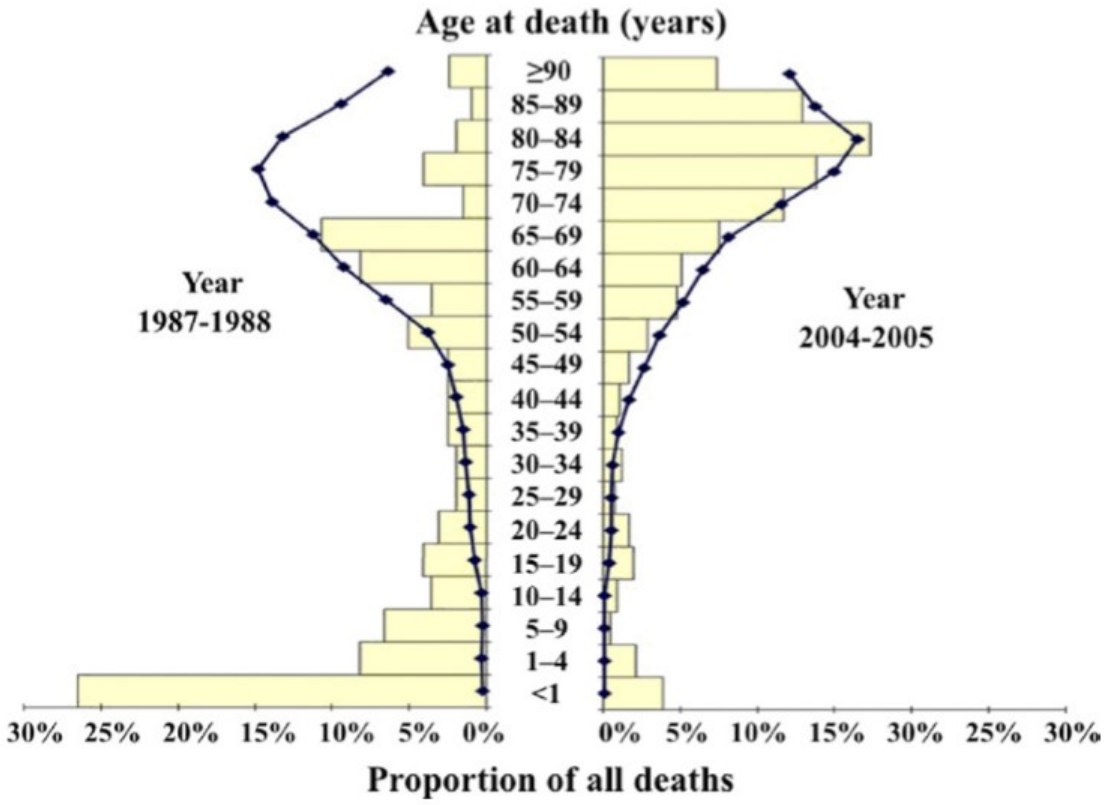
1.1 Preamble

Congenital heart disease is the commonest form of birth defect, with a reported incidence of 7-11 per 1000 live births. Furthermore, this appears to be increasing in the contemporary era, due to improved recognition and detection in infancy, and also improvements in neonatal intensive care (Marelli et al., 2014, Egbe et al., 2015, van der Linde et al., 2011).

Congenital heart defects vary greatly in their effect on circulatory function and physiology, and by extension survival. Mild defects may cause no appreciable clinical signs at all for many years, on the other hand more severe defects are ultimately lethal without urgent intervention. Until the second half of the 20th century such intervention was not possible, leading to a bleak prognosis for children with these more severe lesions. However phenomenal progress in paediatric cardiac surgery since the second half of the 20th century, starting with the introduction of the Blalock-Taussig-Thomas shunt in the 1940s and cardiopulmonary bypass in the 1950s, has set the stage for successive life-extending intervention and transformed the outlook for these children.

Overall survival to age 16 of children with congenital heart disease now exceeds 90%, and there are now more adults than children with repaired congenital heart disease; the proportion of adults being as high as 66% as life expectancy continues to rise, as shown in Figure 1.1 (Marelli et al., 2014, Khairy et al., 2010). As operative mortality in paediatric cardiac surgery continues to fall to as low as 2.9% in the most recent published UK data (Brown et al., 2015), this will only increase. Care for these patients represents, and will continue to represent, an increasing challenge for modern healthcare services.

Figure 1-1 Changing mortality in congenital heart disease in a regional cohort of patients from Quebec, Canada. Figure from (Khairy et al., 2010)[1]



Histogram bars demonstrate the proportion of deaths (x-axis) for the corresponding age group(y-axis) in the period 1987-88 compared to 2004-05. The graph (dotted line) shows the proportion of deaths for the general population in Quebec for the relevant period.

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1.2 Definition and classification

Broadly speaking, an adult with congenital heart disease is an individual over the age of 16 years with any form of congenital heart defect, either repaired or unrepaired. Congenital heart defects can be classified in different ways. They can be divided according to the different structures affected, such as those outlined in the International Classification of Disease version 9 (ICD-9) codes, although this results in a somewhat daunting array of different diagnoses, some of which are specified below (Table 1.1):

Table 1-1 ICD 9 codes for congenital heart disease

Code	Descriptor
745.0	Common truncus
745.10	Complete transposition of the great vessels
745.11	Double outlet right ventricle
745.12	Corrected transposition of the great vessels
745.19	Other transposition of the great vessels
745.2	Tetralogy of Fallot
745.3	Common ventricle
745.4	Ventricular Septal Defect
745.5	Ostium secundum type Atrial Septal Defect
745.60	Endocardial cushion defect unspecified type
745.61	Ostium primum defect
745.69	Other endocardial cushion defect
745.9	Other unspecified defect of septal closure
746.00	Congenital pulmonary valve anomaly unspecified
746.01	Atresia of pulmonary valve congenital
746.02	Stenosis of pulmonary valve congenital
746.09	Other congenital anomalies of pulmonary valve
746.1	Tricuspid stenosis and atresia congenital

746.2	Ebstein anomaly
746.3	Congenital stenosis of aortic valve
746.4	Congenital insufficiency of aortic valve
746.5	Congenital mitral stenosis
746.6	Congenital mitral insufficiency
746.7	Hypoplastic left heart syndrome
746.81	Subaortic stenosis congenital
746.82	Cor triatriatum
746.83	Infundibular pulmonary stenosis congenital
746.84	Congenital obstructive anomalies of the heart not elsewhere specified
746.89	Other specified congenital anomalies of heart
746.9	Unspecified congenital anomaly of heart
747.0	Patent ductus arteriosus
747.10	Coarctation of the aorta
747.11	Interruption of the aortic arch
747.41	Total anomalous pulmonary venous connection
747.42	Partial anomalous pulmonary venous connection
747.89	Other specified congenital anomalies of circulatory system
747.90	Unspecified congenital anomaly of circulatory system

It is immediately obvious that confusion may arise in the case of certain examples (e.g. 745.60 and 745.69), and there is a danger that the non-specialist may not classify lesions in sufficient detail, perhaps opting for 746.9 when a more detailed review of the information might allow a patient to be classified with greater accuracy. The system is further complicated by the fact that different ICD classifications are used over different time periods, for example ICD-10 replaced ICD-9 in 2008, and is itself due to be replaced by ICD-11 in 2017. And finally the ICD system refers only to the initial diagnosis and not any subsequent surgical correction of anatomy. So, for example, there is no ICD code for patients with a Fontan circulation. A separate system, the OPCS (Office of Population Censuses and Surveys)

classification of interventions and procedures, is required to code operations. This is subject to similar limitations and complicates classification still further.

In an effort to expand upon this, and based on earlier work from the 1996 Canadian Consensus Conference on ACHD, the 2001 Bethesda conference divided all defects into defects of simple, moderate and great complexity (Warnes et al., 2001). The main drive to classify defects in this way was to outline the extent to which ACHD patients require review by subspecialist ACHD centres, i.e. none, periodic and regular follow-up for the simple, moderate and great complexity defects respectively. The classification is not perfect as some lesions such as Ebstein anomaly exhibit a wide spectrum of severity in their own right, and a degree of overlap exists between a number of the other specified lesions. However, it serves as a useful framework for reference, is conceptually easy to understand, and is pragmatic.

Table 1-2 Bethesda classification of congenital cardiac lesions

Complexity		Diagnoses
Simple	Native	Isolated congenital aortic valve disease Isolated congenital mitral valve disease Isolated PFO or small ASD Isolated small VSD Mild pulmonary stenosis
	Repaired	Previously ligated or occluded PDA Repaired secundum or sinus venosus ASD without residual defect Repaired VSD without residual defect
Moderate	Aorto-left ventricular fistula Anomalous pulmonary venous drainage (partial or total) Atrio-ventricular canal defects (partial or total) Coarctation of the aorta Ebstein anomaly Ventricular Outflow Tract obstruction of significance PDA (not closed) Pulmonary regurgitation (moderate or severe) Pulmonary stenosis (moderate or severe) Sinus of Valsalva fistula or aneurysm Sinus venosus ASD Subvalvar or supravalvar aortic stenosis Tetralogy of Fallot VSD complicated by: • Absent valve • Aortic regurgitation • Coarctation of the aorta • Mitral valve disease • Right ventricular outflow tract obstruction • Straddling tricuspid/mitral valve	

	• Subaortic stenosis
Great	Presence of a surgical conduit (valved or non-valved) Cyanotic congenital heart disease (all forms) Double outlet ventricle Eisenmenger syndrome Fontan procedure Mitral atresia Single ventricle Pulmonary atresia Pulmonary vascular obstructive disease Transposition of the Great Arteries Tricuspid atresia Truncus arteriosus (including hemitruncus)

1.3 Investigation and follow-up of patients with ACHD

The vast majority of patients with ACHD require regular assessment and follow-up, it is only in rare instances that a patient can be regarded as "cured" , for example a small haemodynamically insignificant VSD that resolves spontaneously. As described above any patient with a congenital defect of moderate or great complexity requires at least some input from a specialist ACHD centre with access to the full range of complex imaging and cardiac catheterisation. Clinical assessment is based on the following modalities:

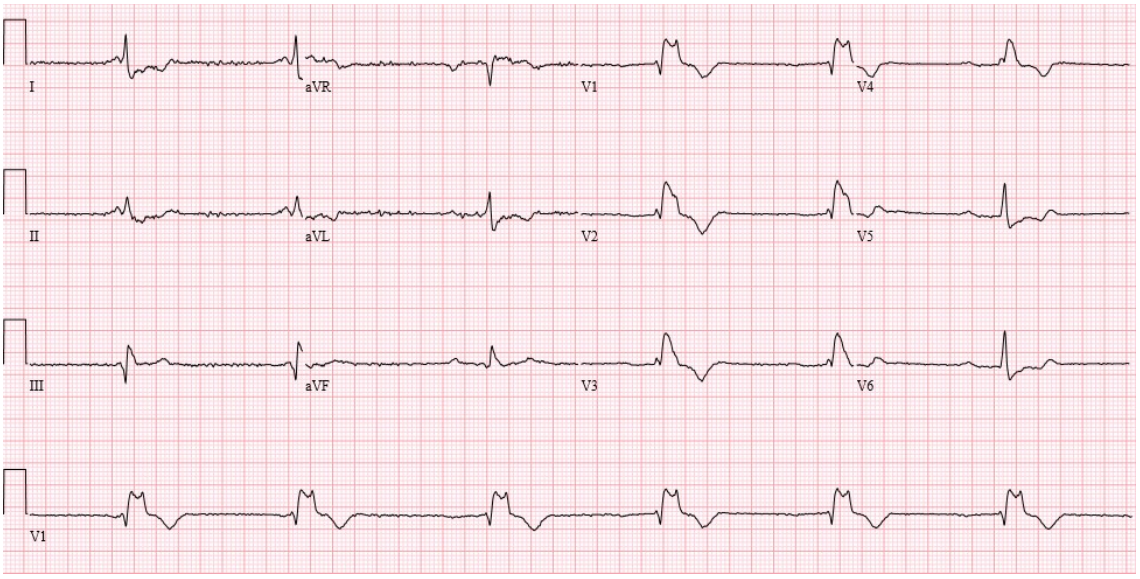
1.3.1 Clinical examination

Documentation of parameters such as heart rate, non-invasive systemic arterial blood pressure, and pulse oximetry. A full cardiovascular and respiratory examination will assess for the presence of scars, cardiac devices, elevated jugular venous pulse, parasternal heave, murmurs or bruits, oedema, and pleural fluid, all of which can indicate the presence of underlying haemodynamically significant lesions or heart failure.

1.3.2 Electrocardiography

The 12-lead surface ECG (Figure 1.2) is a straightforward and widely available tool that provides a wealth of information regarding electrical conduction through the heart. The ECG is rarely normal in congenital heart disease, and will often reflect the underlying structural lesion or lesions, for example for patients with a systemic right ventricle there will be evidence of right axis deviation and right ventricular hypertrophy, and for patients with a dilated right ventricle right bundle branch block is frequently present. The presence of an atrial or ventricular arrhythmia is clearly of immediate relevance in an emergency situation. Furthermore, some parameters are of longer term prognostic significance e.g. the duration of the QRS complex in repaired Tetralogy of Fallot (Gatzoulis et al., 2000).

Figure 1-2 Twelve lead ECG showing sinus rhythm with first degree heart block and marked right bundle branch block in a patient with surgically repaired Tetralogy of Fallot

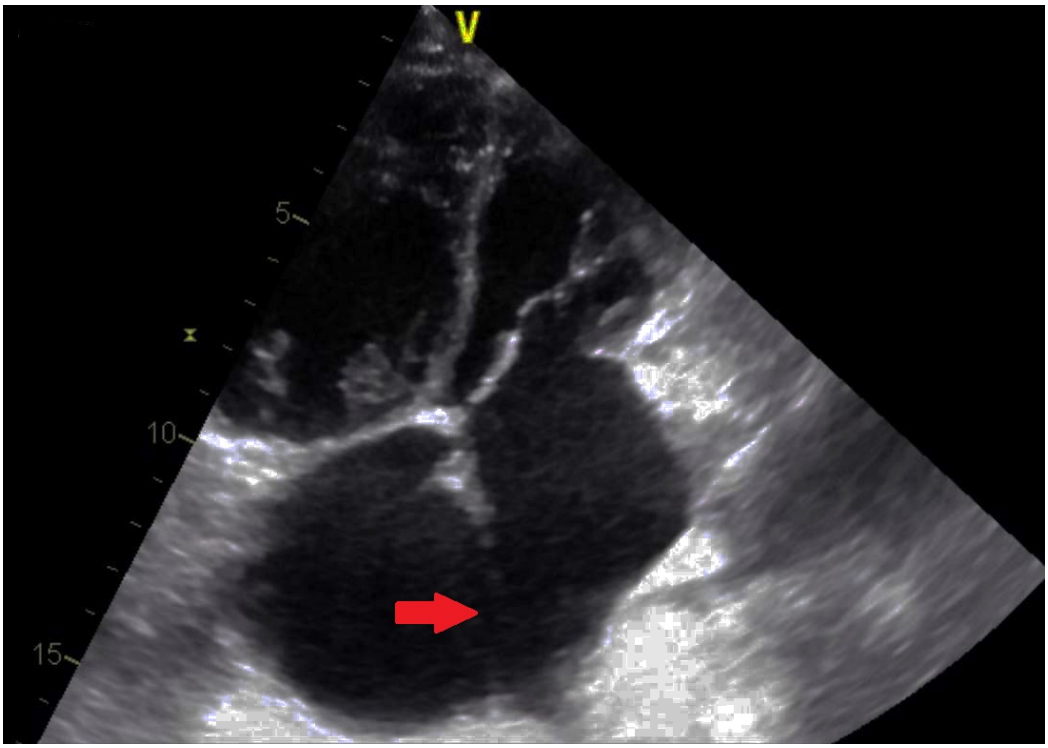


1.3.3 Echocardiography

This technique employs a piezoelectric crystal to generate an ultrasonic beam which is reflected by the heart and related structures, the analysis of which allows real-time two- and three-dimensional digital reconstructions of structures as they move throughout the cardiac cycle together with analysis of the flow of blood through the heart, and by extension the function of valves and conduits (Figure 1.3). Transthoracic probes are most commonly used as they are non-invasive, widely available and cheap to use, although transoesphageal probes provide better visualisation of more posterior structures, and specialist intracardiac and epicardial echo can be invaluable to guide percutaneous and cardiac surgical intervention respectively. The main disadvantage of echocardiography in congenital heart disease is that the highly variable anatomy found in more complex conditions does not lend itself easily to interpretation in conventional echo views, the presence of scar tissue resulting from prior cardiac surgery degrades image quality, and some structures may not be possible to visualise at all. Furthermore, data regarding reference ranges for normal values is often lacking, limiting the utility of quantitative data obtained. Whilst some conditions have been

studied with respect to the prognostic value of certain parameters - for example tricuspid annular plane systolic excursion, atrial dilatation, and the ratio of right ventricular systolic to diastolic duration and the prediction of mortality in Eisenmenger syndrome (Moceri et al., 2012) - most have not.

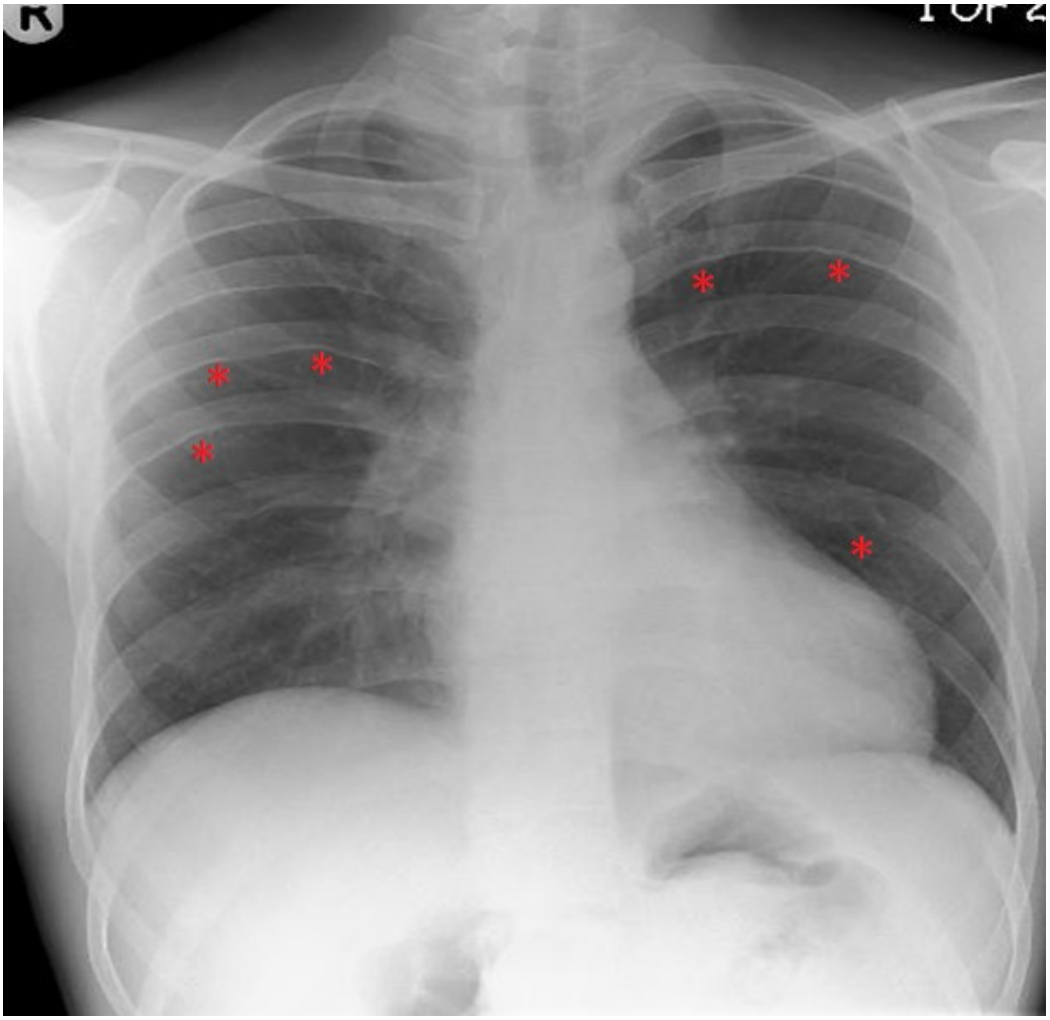
Figure 1-3 Apical four chamber view in a patient with a secundum atrial septal defect (arrowed)



1.3.4 Plain film chest radiography

Often underrated, this provides a quick, cheap, and readily reproducible image of the heart, mediastinum and lung (Figure 1.4). A normal chest radiograph in adulthood is reassuring, and often suggests that an underlying structural lesion is unlikely to be haemodynamically significant (Steiner et al., 1995, Dimopoulos et al., 2013). In the acute setting it allows rapid recognition of pathology such as pulmonary oedema. And finally, subtle changes in the cardiac outline over time can hint at more slowly progressive pathology and guide further investigation.

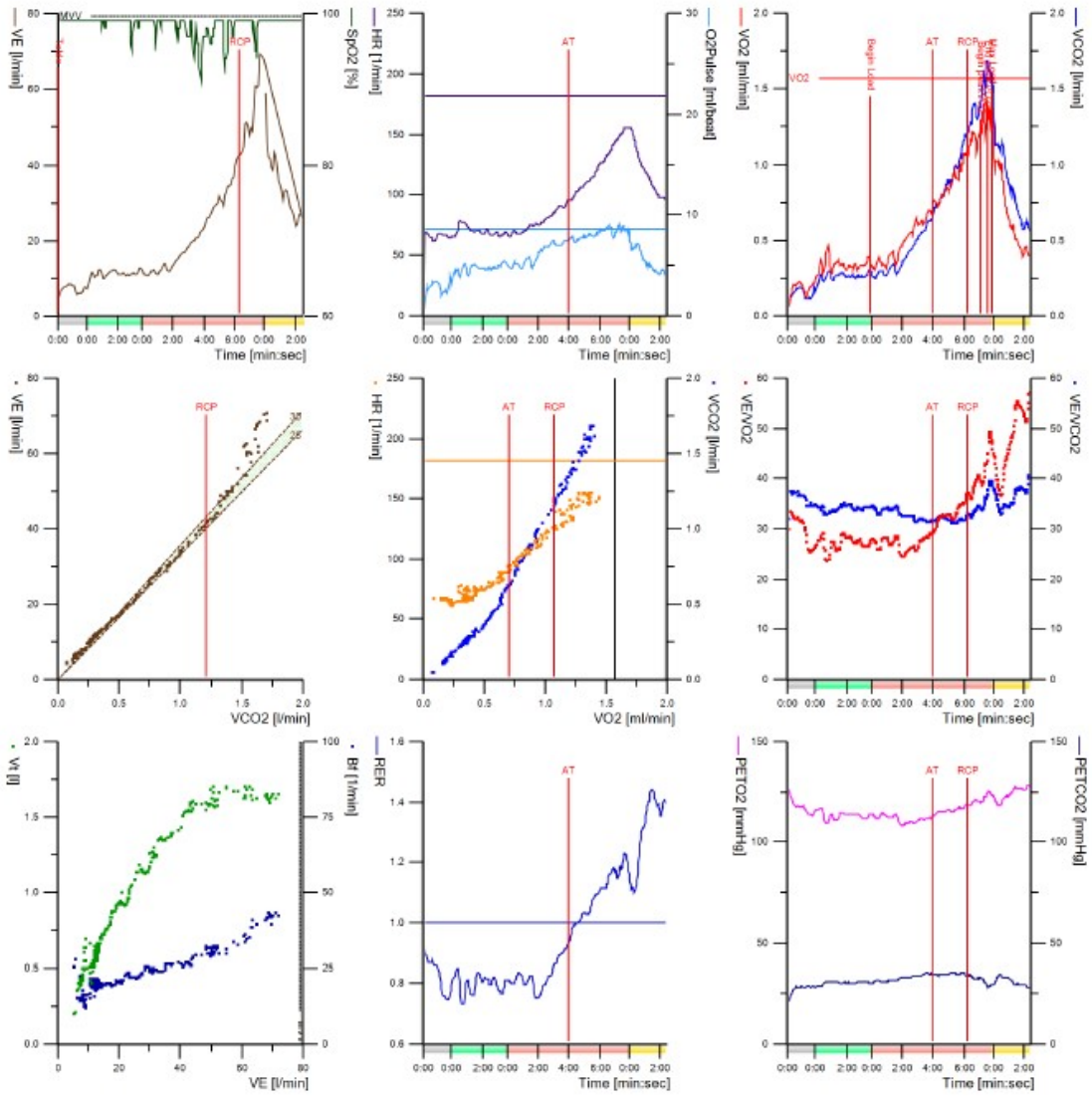
Figure 1-4 Chest X-ray in a patient with unrepaired aortic coarctation, demonstrating inferior rib notching (asterisks)



1.3.5 Cardiopulmonary exercise testing

An established incremental increase in workload, generally by treadmill or cycle ergometer, allows the measurement of the maximum oxygen uptake during exercise and thus quantification of the subject's aerobic exercise capacity. Serial changes in the VO2 over time can establish functional decline before the development of symptoms, furthermore more detailed analysis of response to exercise allows the determination of whether the main limiting factor to exercise occurs on the cardiovascular, respiratory or gas exchange axes (Figure 1.5).

Figure 1-5 Nine-panel plot from CPET performed by a patient post pulmonary valve replacement[2]



[2] From left to right the panels show: top row - minute ventilation against time, oxygen pulse (blue) and heart rate (purple) against time, oxygen uptake and carbon dioxide output against time; middle row - minute ventilation against carbon dioxide output (the VE/VCO2 ratio), heart rate (orange) and carbon dioxide output (blue) against oxygen uptake, ventilatory equivalents (VE/VO2 and VE/VCO2 ratios against time); bottom row - tidal volume (green) and respiratory rate (blue) against time, respiratory exchange ratio (ratio of oxygen uptake to carbon dioxide output) against time, and the end tidal oxygen and carbon dioxide partial pressures against time. Where time is the x-axis this is colour-coded as green: warm-up, red: exercise, and yellow: cool-down.

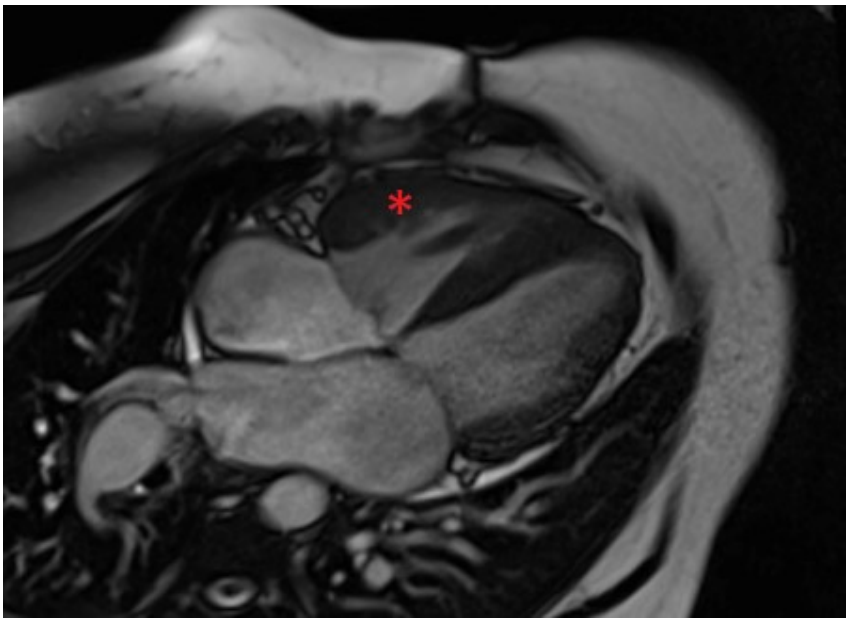
Reference ranges for peak VO2 have been established for one large cohort of ACHD patients (Kempny et al., 2012), and it can be helpful to review the range of exercise capacity seen amongst patients with the same diagnosis, and then compare this to the ranges described for other congenital cardiac diagnoses. For example, patients who have undergone the arterial switch operation for transposition of the great arteries have a mean peak VO2 of 89% of the predicted value, whereas for patients with Eisenmenger physiology the corresponding value was 43%. Furthermore, a number of parameters derived from CPET carry prognostic weight. These include peak VO2, the ratio of minute ventilation to carbon dioxide output, heart rate response to exercise and chronotropic incompetence, and the oxygen uptake efficiency slope (Diller et al., 2005, Dimopoulos et al., 2006, Diller et al., 2009, Giardini et al., 2009b).

1.3.6 Cardiac magnetic resonance imaging

This is regarded as the gold standard technique for imaging of the heart in the setting of repaired congenital heart disease. Many atomic nuclei, for example Hydrogen-1 and Carbon-13 - both widely present in the human body - exhibit a property known as 'spin', where application of a strong external magnetic field causes the nuclei to align in the same axis. Application of a radiofrequency pulse to the nuclei causes them to change their alignment, the degree of change is known as the flip angle. Analysis of the signals emitted from each nucleus following repeated applications of external radiofrequency energy and using different external gradients of magnetic fields in three dimensions allows the digital reconstruction of each nucleus' position inside a virtual space known as k-space. This information can be processed digitally to create a cross-sectional image of the heart in any conceivable plane (Figure 1.6). Discrimination of different tissue types due to different water content in the case of Hydrogen-1 is highly accurate and reproducible. For the heart a series of images throughout the whole cardiac cycle can be obtained by acquiring images at different times, gated to the vector cardiogram or VCG. Further information can be gleaned from the use of Gadolinium contrast, time of flight three-dimensional MRI angiography, and T1, T2 and T2 star mapping. The disadvantages of the technique in congenital heart disease arise if MRI is contraindicated for example due to the presence of a non-MRI conditional cardiac device (although more recent research has suggested that some of these device may be safe for scanning at 1.5 Tesla), the presence of metallic artefact due to implanted material such as prosthetic valve replacements, the long time required to acquire and then analyse the images obtained, problems with claustrophobia and poor patient tolerance, and the difficulty of assessing the heart in the setting of an irregular heart rhythm. As will be seen in the forthcoming chapters, in certain situations the quantitative data derived from MRI carries prognostic significance and can be invaluable to clinical decision making. Most of the evidence applies to adults with repaired tetralogy of Fallot, simply by virtue of the fact that this is the commonest form of congenital heart disease. Accurate estimation of RV end diastolic volume

can help to determine the timing of pulmonary valve replacement (Therrien et al., 2005, Oosterhof et al., 2007), and the presence of late gadolinium enhancement (Babu-Narayan et al., 2006, Wald et al., 2009) or left ventricular dysfunction (Geva et al., 2004) can help to identify patients at risk of adverse outcomes. Fewer published data relate to other conditions such as atrial septal defect, transposition of the great arteries and single ventricle physiology, however the insights each scan can provide in helping to understand the precise anatomy and physiology of a patient's heart carry great merit on a case-by-case-basis.

Figure 1-6 Steady state free precession sequence in horizontal long axis (four chamber view) in a patient with Eisenmenger physiology. Note the right ventricular hypertrophy (asterisk)



1.3.7 Cardiac catheterisation

Fluoroscopic imaging of the heart and great vessels with the use of X-ray contrast provides invaluable information to assess for the presence of abnormal flow of blood from one structure to another or guide subsequent percutaneous intervention e.g. device closure of an ASD or balloon angioplasty. Direct measurements of pressure and the withdrawal of blood samples for analysis of oxygen saturation allows assessment of haemodynamic severity of obstructive lesions or shunts, as well as the calculation of cardiac output and pulmonary vascular resistance. Invasive electrophysiological studies can also be performed, allowing the identification of abnormal pathways and re-entry, three-dimensional voltage mapping of complex arrhythmias, and ventricular stimulation studies to provide information regarding the inducibility of ventricular tachycardia in highly selected patient subgroups to help guide the choice of candidates for primary preventative ICD therapy.

1.4 Treatment

The mainstay of treatment for congenital heart disease involves correction of the underlying haemodynamic lesion or lesions. Thus, as mechanical problems require mechanical solutions, in practice this means invasive intervention. This may be performed through cardiac catheterisation or open cardiac surgery, but in some cases a hybrid approach may be used. Invasive treatment for moderate or great complexity lesions typically involves one or more procedures in early life, following which patients will eventually require further intervention to address any residual and progressive haemodynamic lesions, generally in early adulthood and beyond. Patients with simple congenital cardiac lesions may not undergo any intervention in their early life, but particularly in cases where they may have been undetected in childhood (for example a secundum atrial septal defect, which may cause no symptoms and have only very subtle signs to find on examination in early life), they may go on to exert a progressive effect on cardiac function over time and threaten to cause life-limiting sequelae such as arrhythmia, heart failure or pulmonary arterial hypertension, thus leading to a need for intervention which may not be until the fourth or fifth decade of life and beyond.

Medical or pharmacologic therapy has a limited application in ACHD, and is essentially pragmatic, for example the use of diuretics in heart failure or beta blockers in tachyarrhythmias. Unlike other cardiac conditions such as coronary artery disease there are no treatments proven to slow the progression of underlying pathology or modify the risk of late complications, and patients may respond poorly or not at all to prognosis-modifying drugs used in the setting of acquired left ventricular systolic dysfunction for example Angiotensin Converting Enzyme inhibitors and Mineralocorticoid Receptor Antagonists.

One extremely important aspect of managing ACHD patients includes the provision of expert cardiac and obstetric care to female patients throughout all stages of conception, including advice on contraception, pre-pregnancy

counselling and genetics assessment, pre-natal care including delivery planning, and safe and effective post-natal care and follow-up. Another key aspects of care to consider is that as the ACHD population ages so patients may develop acquired cardiac conditions such as coronary artery disease, however their comorbidity (difficult vascular access, abnormal coronary anatomy, need for ongoing anticoagulation, etc.) means treatment may not be straightforward. Additionally there is increasing recognition of the burden of psychological morbidity in ACHD patients, which may manifest itself as health anxiety, low mood and other progressively more severe mental health disorders such as severe depression.

And finally, there is the problem of the extensive socioeconomic effects of these conditions. Extensive time spent in hospital limits educational attainment and can also lead to problems successfully applying for and holding down employment. Many congenital cardiac defects lead to outright exclusion from applying for professions such as the armed forces, and the sequelae of congenital heart disease can lead to a ban from even more professions (e.g. a patient with ACHD who holds a category 1 driving licence in the United Kingdom will automatically lose this if they subsequently undergo implantation of an ICD). The uncertainty regarding survival and long-term prognosis in ACHD patients may result in an inability to gain life insurance and loans. "Treatment" of all of these issues is arguably as important as the surgical and medical management of ACHD patients.

1.5 Prognosis in ACHD

1.5.1 Survival

As described above, advances in paediatric care have transformed the outlook for patients with congenital heart disease. Survival since the 1970s has consistently improved for patients with congenital heart disease regardless of severity, with a large study of almost 7500 patients from Belgium demonstrating that survival from birth to adulthood has increased from 81% for patients born in 1970-1974, to 88.6% for those patients born in 1990-1992. Most of the mortality arises from patients with forms of univentricular heart, particularly hypoplastic left heart syndrome. Survival to adulthood for the patients with simple or moderate complexity lesions in the 1990-1992 birth cohort was as high as 98% and 90% respectively(Moons et al., 2010). A decrease in early mortality has been further corroborated by data from the USA, Quebec, Norway and the UK (Jortveit et al., 2016, Brown et al., 2015, Gilboa et al., 2010, Khairy et al., 2010)

1.5.2 Morbidity

As expected morbidity in this population group is high, but less well documented compared to overall survival. Complications include infective endocarditis, arrhythmia, heart failure, pulmonary arterial hypertension, cardioembolic stroke, and reoperation. The incidence of stroke appears to be particularly high, with one study estimating that 1 in 11 of all male patients from age 18-65 will experience a stroke (Lanz et al., 2015). Furthermore, as patients become older, so they experience the full range of conditions associated with the aging process such as ischaemic heart disease and malignancy. Another important cause of morbidity is that resulting from pregnancy, and indeed in cases where the mother has congenital heart disease there is a significantly greater risk of both maternal and fetal adverse outcomes (Drenthen et al., 2007)

1.5.3 Hospital admissions

Contemporary data suggests an increase in hospital admissions of adult patients with congenital heart disease in England and Wales, the USA and the Netherlands, consistent with the increase in size of the ACHD population (Billett et al., 2008, Verheugt et al., 2010, Opotowsky et al., 2009). The age of patients admitted appears to be increasing, and the commonest reason for emergency admission is arrhythmia (Verheugt et al., 2010). All of this suggests an increase in healthcare utilisation for this patient group.

1.6 Problems in defining prognosis for a contemporary cohort of ACHD patients

As alluded to in the previous section, data regarding prognosis in any group of ACHD patients is hampered by a host of different factors. Perhaps the most important is that even in a single diagnostic category, e.g. patients with repaired Tetralogy of Fallot (TOF), there exist a wide range of baseline variables which are difficult to adjust for. First and foremost, the severity of the underlying haemodynamic lesions will differ from patient to patient. Patients with milder lesions (a smaller VSD, less overriding of VSD by the aorta, less outflow tract obstruction) will thrive more in the first few weeks of life so they have a higher weight preoperatively, and they may also require a less radical surgical repair which will decrease operative risk and reduce the likelihood of needing repeat intervention in the future. On the other hand, patients with more severe lesions will have a higher operative risk, require more extensive surgery at the time of initial repair, and will be more likely to have significant residual haemodynamic lesions which will need to be addressed in the future. In the case of repaired TOF a further demonstration of this principle can be made by considering the issue of where the right ventricular outflow tract obstruction occurs. If this is at the level of the infundibulum then the patient may require only an infundibular resection, leaving the pulmonary valve intact. On the other hand the patient with obstruction at the level of the valve may require a transannular patch repair, which destroys the valve. This leaves them with free pulmonary regurgitation, and so the need for pulmonary valve replacement at a later date is effectively guaranteed.

As well as the underlying anatomy, it must be remembered that patients under follow-up by any centre will have been operated upon at different ages and in different eras, and this will also affect prognosis. A patient who underwent primary repair of TOF in the late 1990s at a few months of age will have a very different outlook to the patient who was operated on as a teenager in the 1970s after one or two palliative shunt procedures.

Yet another problem is that there is no standardised way for reporting survival in these patient groups. Some centres report survival across their entire cohort of patients (i.e. as a whole for all patients operated upon from as early as the late 1950s to the current era), whereas others present survival according to groups who underwent surgery within specified chronological periods, however with this approach there is no consensus on how long these intervals should be. Another point of interest is that of differences in operative mortality between different surgical centres and individual surgeons, which will impact upon long term results if included in a survival analysis. In some places this variation is likely to be negligible - for example in the UK the publication of the Bristol Inquiry in 2001 (Kennedy, 2001) resulted in congenital cardiac centres and surgeons in the UK becoming subject to national audit and perhaps the heaviest scrutiny amongst any medical specialty, thus ensuring the upholding of accepted standards in surgical outcomes. However this does not always apply internationally, or indeed historically.

Another key issue is the lack of follow-up into adulthood. Some centres worldwide, of which Scotland is now one, can offer a centralised congenital cardiology service which follows up patients from infancy all the way through to adult life and beyond. However this is not universal. In other places children may attend the congenital cardiac centre for their initial corrective surgery, but may be followed up at a different institution. Whilst it is usually straightforward to find out whether these patients are at least still alive in the longer term, this is not always the case. Furthermore, survival is often the only parameter which can be easily assessed, and it can prove very difficult to get even basic information on functional status and the results of various cardiac investigations performed at follow-up. There is a particular dearth of information regarding the results of advanced investigations such as CPET and cardiac MRI in the published literature.

The final issue relates to the problem of assessing prognosis for the exclusively adult patients with congenital heart disease. The prognosis for a 16 year old with a univentricular heart who has undergone a Fontan repair

will not be the same as a neonate with unrepaired univentricular heart. In many ways the patients who have survived to their adult years represent an "elite" group of survivors who have survived the peak of early mortality, and quoting overall survival statistics for them from birth is of limited relevance: there may well be 70% survival to age 30 for their birth cohort, but as they have already survived to age 16 their chances of reaching age 30 will be proportionately higher. This leads to the problem of deciding upon a suitable baseline for performing survival analysis, and furthermore one must also find a way of accounting for "left-censoring", i.e. the patients who have already experienced the outcome of interest before the baseline of 16 years.

1.7 The situation in Scotland

Scotland is uniquely placed to answer questions relating to long term prognosis for adult survivors of congenital heart disease. In the early 2000s all paediatric cardiac surgery and percutaneous intervention moved to a single centre based at the Royal Hospital for Sick Children in Glasgow, and in fact even before this the vast majority of this workload was performed in Glasgow. Then in 2006 the provision of adult cardiology care for patients with congenital heart disease was reformed with the creation of the Scottish Adult Congenital Cardiac Service (SACCS), and this was fully established and functional by 2009, based at the Golden Jubilee National Hospital in Clydebank, just to the west of Glasgow. This employed the "hub-and-spoke" model widely accepted to be the gold standard in management of patients with moderate or great complexity congenital heart disease, and was the only tertiary centre in country which could offer the full range of congenital cardiac services to ACHD patients. Patients with the most complex forms of ACHD would undergo almost all of their cardiac care at the single national centre, and patients with moderate complexity ACHD would undergo periodic review at the national centre, with all of their advanced investigations such as cardiac MRI and cardiopulmonary exercise testing, and all of their cardiac surgical or percutaneous intervention performed in this single location. This means that all ACHD patients with moderate or great complexity lesions are under regular follow-up by this single centre, and collection of data on outcomes has been assisted by the creation of a locally held database.

Through nationalised data collection on hospital admissions performed by the Information and Statistics Division of NHS Scotland information on rates of hospitalisation and comorbidity can be corroborated, although there remain the problems of coding for complex congenital cardiac diagnoses, and the results of clinical parameters derived from various cardiac investigations will not be documented (so, for example, one could not use the ISD dataset to assess whether the QRS complex duration on an ECG is associated with adverse clinical outcomes). If this can be overcome then

this could also provide a unique and valuable resource for studying this population group - especially with regards to hospital admissions and outcomes extending back before 2009, and the establishment of SACCS and the locally held database.

1.8 How might our understanding of the prognosis for patients with ACHD be improved using the Scottish data?

The most comprehensive and robust data on clinical outcomes for ACHD patients in Scotland exists for patients with moderate and great complexity congenital cardiac lesions as by virtue of their underlying diagnosis all such patients must pass through the national congenital cardiac centre, both for periodic review and also for any form of intervention. For patients with "simple" congenital defects the situation is complicated by the fact that the bulk of their follow-up will be at a non-specialist or local centre, and so there will be a large number of patients missing from our database who have never presented to the national centre.

At the same time it is important to ensure that the diagnostic groups assessed are relatively homogenous. So for example it would be difficult to study patients with an ASD, as although they account for a large population they differ greatly in their presentation. Some patients may present to the attention of cardiac services only during middle age when they develop problems such as atrial arrhythmia (having been asymptomatic beforehand), some patients with a small ASD may never present to secondary care, and there is also the problem of adjusting for the type and timing of intervention, e.g. whether or not and at what age the patient has undergone open surgical repair or device closure of an ASD.

The best groups of patients to study will be those who are easily classified into a particular diagnostic group, who have conditions of sufficient complexity they will all be followed up at the national centre with advanced cardiac investigations such as cardiac MRI, and who form a large enough group that their management and outcomes will be of relevance to clinicians involved in the care of ACHD patients. Two groups that appear to meet this criteria are those patients with a systemic right ventricle, either as a result of congenitally corrected transposition of the great arteries (CCTGA) or atrial inversion surgery for transposition of the great arteries (TGA), and patients with repaired TOF.

1.9 Aims of the thesis

This thesis aims to address the issue of defining long term outcomes and prognosis for Scottish adults with congenital heart disease by addressing the following five questions:

1. What is already known about the long term prognosis for adult patients with a systemic right ventricle?
2. What is already known about the long term prognosis for adult patients with repaired Tetralogy of Fallot?
3. What does the Scottish data tell us about long term outcomes for long term adult patients with a systemic right ventricle in comparison to other centres?
4. What does the Scottish data tell us about long term outcomes for long term adult patients with repaired Tetralogy of Fallot in comparison to other centres?
5. Can data from cardiac MRI and cardiopulmonary exercise testing help to identify the reasons for any differences in outcomes?

Chapter 2 Methods

2.1 Preamble

This chapter outlines the methodology common to all subsequent chapters of this thesis. Where more specialised techniques were used, a more detailed explanation follows in the relevant chapter.

2.2 Patient selection

Since 2009 all care for adult patients with congenital heart defects of moderate or greater complexity in Scotland has been centralised. Care is provided by the Scottish Adult Congenital Cardiac service which is based at the Golden Jubilee National Hospital in Clydebank. All patients in the greater Glasgow area are followed up at this location on a regular basis; patients who are more geographically remote may undergo routine follow-up up at a secondary care centre closer to their place of residence, however they would still attend the national centre every 2-3 years for a more comprehensive clinical review which would normally include the use of advanced imaging and investigation. Furthermore all congenital cardiac surgery and percutaneous procedures are performed at the national centre. All patients were registered in a clinical database and coded according to diagnosis. All patients with following diagnoses were eligible for inclusion:

- Systemic right ventricle:
    - Congenitally corrected transposition of the great arteries (CCTGA)
    - Transposition of the great arteries status post atrial switch operation - either a Mustard or Senning operation (TGA atrial switch)
- Tetralogy of Fallot (TOF) post surgical repair

2.3 Ethical approval

This was a purely descriptive study assessing long term outcomes in congenital heart disease in the Scottish population compared to outcomes in other populations of congenital heart disease patients. Advice from the West of Scotland Research Ethics Service was sought regarding the need for Research Ethics Committee approval. As the project involved the use of previously collected routine clinical data and compared outcomes in our cohort to those of other centres it was felt to be more in keeping with audit, and so this requirement was waived (see Appendix). At the time of initial data collection in 2011 there was no process to register the study locally as an audit with the Golden Jubilee National Hospital, however when it became apparent that further data was required for the TOF cohort in 2015 this had changed, and so the project was formally registered as such (local registration number 1518).

To guarantee patient confidentiality and anonymity all patient identifiable data were stored on an encrypted, password protected NHS drive at the Golden Jubilee National Hospital. Initial data were entered into a Microsoft Excel spreadsheet, each patient was assigned an computer generated random identification number, and then any unique personal identifiable data (e.g. name, date of birth, postcode) was removed prior to converting the spreadsheet into an SPSS Statistics Data Document file to allow statistical analysis of the resultant fully anonymised data. Caldicott guardian approval was discussed and agreed before each round of data collection; in 2011 and 2015.

2.4 Data collection

All patients were tracked through the SACCS central database which contains a summary of their basic anatomy, previous interventions and current diagnoses as well as links to the most recent clinic letters and results of investigations. Clinic letters included data regarding current NYHA status and medication. If clarification was required, these records could be corroborated with information held in the national Scottish Care Information (SCI) Store or by an application to the National Records of Scotland (NRS), which succeeded the General Register Office for Scotland in 2011. If there was no original operation note on the database for a patient who underwent their original surgery in the west of Scotland we also attempted to trace the hard copy of the operation note which was held in an archive at the Royal Hospital for Sick Children at Yorkhill in Glasgow.

2.5 Clinical investigations

2.5.1 Electrocardiogram

Standard surface 12 lead ECGs (stored electronically) were performed and analysed for the following parameters

- Heart rate: expressed as beats per minute or bpm and calculated from the R-R interval (the time between each preceding R wave in milliseconds) according to the following formula: HR = 60000 / R-R. Where the R-R interval was irregular this could be averaged over a duration of 10 seconds.
- Heart rhythm: this was analysed manually and categorised into sinus rhythm, paced rhythm, atrial fibrillation, atrioventricular block (first, second or third degree), or bigeminy.
- QRS interval: this was defined as the duration in milliseconds between the point of initial deflection from the baseline (either a positive R wave or negative Q wave) and the point at which the terminal deflection of the S wave crossed the baseline. This was analysed in the lead with the most obvious and widest complex.

2.5.2 Transthoracic echocardiography

Standard two-dimensional cardiac ultrasound was performed in patients at a variety of centres and with different equipment, furthermore its limitations in the assessment of patients with congenital heart disease are well recognised - specifically reduced image quality secondary to scarring from previous surgery, the difficulty in imaging a complex three-dimensional structure such as an abnormal right ventricle by purely two-dimensional means, the lack of consensus on the best variables by which to assess the severity of a particular abnormality, and the consequent difficulty in obtaining precise and reproducible measurements. The decision therefore was made to utilise the semiquantitative reports to characterise cardiac chambers and valves. All sonographers at the Golden Jubilee National Hospital are accredited nationally with the British Society for

Echocardiography, thus providing adequate quality assurance. The qualitative measurements recorded were:

- Right and left ventricles:
    - Chamber size: mild, moderate, severe dilatation
    - Systolic function: mild, moderate, severely systolic dysfunction
- Valve function:
    - Documented for the four valves: pulmonary, aortic, tricuspid and mitral
    - Categorised as normal, replaced, regurgitant (trivial, mild, moderate or severe), or stenosed (mild, moderate or severe)
    - In the case of a replaced valve if the residual stenosis or regurgitation was present and felt to be moderate or greater this was characterised as "replaced - stenosed" or "replaced - regurgitant"
- Residual ventricular septal defect: presence or absence

2.5.3 Cardiopulmonary exercise testing

All cardiopulmonary exercise testing was performed using a bicycle ergometer (Medisoft, Sorinnes, Belgium). All patients followed a standard protocol of a 2 minute rest period, 3 minutes of unloaded exercise, and then the commencement of incremental workload of 10-20 watts per minute. A fixed cadence of 60 rotations per minute was used. Tests were performed in accordance with standards as defined by the European Society of Cardiology (Mezzani et al., 2009). Variables measured were:

- Height and weight
- Heart rate
- Surface ECG
- Noninvasive blood pressure measurement
- Capillary oxygen saturation or SpO2
- Minute ventilation
- Concentration of inspired and expired oxygen and carbon dioxide

From this data the following variables could be calculated:

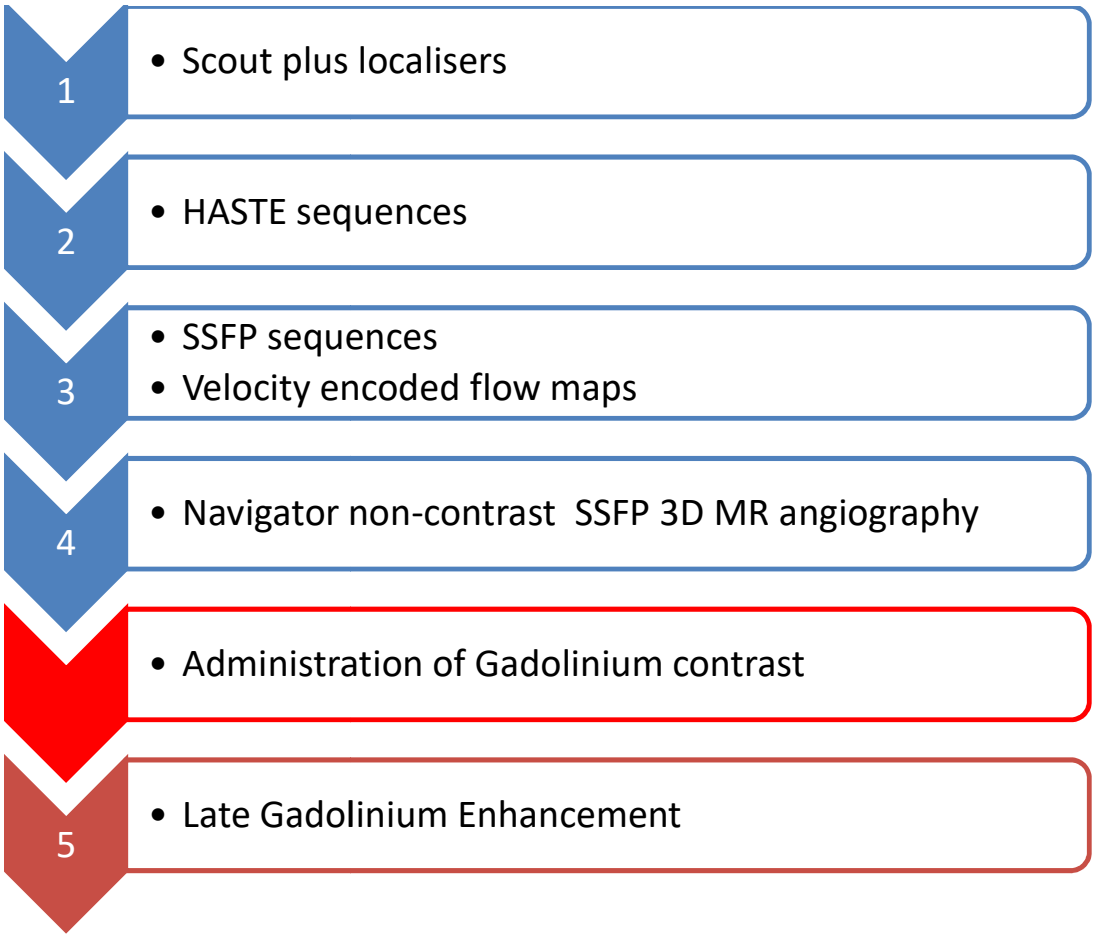
- Peak oxygen uptake VO2, which could be expressed as an absolute value in L/min, a value indexed to body surface area as ml/kg/min, or as a percentage of the predicted value in healthy individuals matched for age, gender and height (Jones et al., 1985)
- The VE/VCO2 slope. This is the ratio between minute ventilation and carbon dioxide output during exercise, and is calculated by linear regression from the start of the exercise test to the VCO2 at anaerobic threshold. This parameter is dimensionless, and a value of less than 30 is considered to be normal. It is a marker of ventilatory efficiency which has previously been shown to be more strongly predictive of mortality and adverse outcomes in patients with repaired congenital heart disease (Dimopoulos et al., 2006).
- Heart rate reserve (HRR), which was expressed as the difference between the maximum heart rate at peak exercise and the *predicted* maximum heart rate at peak exercise. The predicted maximum heart rate at peak exercise was calculated according to the formula 220 - age in years (Tanaka et al., 2001). This has also been shown to be of prognostic value in adult congenital heart disease (Diller et al., 2006).

2.5.4 Cardiac MRI

All cardiac MRI scans were performed at the Golden Jubilee National Hospital. Images were acquired at a field strength of 1.5 Tesla with a Siemens Magnetom Avanto (Siemens AG, Erlangen, Germany) utilising a 12 element phased array surface coil designed for cardiac imaging. Continuous ECG monitoring was employed for every case and full resuscitation facilities were available. Figure 2.1 outlines the imaging protocol used. Steps 1-4 were performed in every case; where the administration of Gadolinium was indicated steps 5 was performed as well. The decision to administer

Gadolinium was a purely clinical one and was made by the consultant (HW) responsible for the congenital cardiac MRI scans at our institution, generally any patient with a congenital cardiac condition characterised by a risk of sudden cardiac death (i.e. including those patients with a systemic RV and repaired TOF) and no contraindication to the administration of Gadolinium would have this administered as part of their index scan at our institution, although this was not generally repeated for subsequent scans.

Figure 2-1 Cardiac MRI protocol



Once the patient was ready for scanning initial localiser sequences were obtained followed by HASTE (Half-Fourier Acquisition Single shot Turbo-spin Echo) sequences. These characterised gross cardiac anatomy specifically visceral and cardiac situs, atrioventricular and ventriculo-arterial connections, and the relationships of the great vessels as well as any overt abnormality of cardiac chamber size. Typical settings were as follows: voxel size 2.3 x 1.3 x 6.0mm with repetition time (TR) 700ms, echo time (TE) 43ms, flip angle 160 degrees, and slice thickness 6.0mm.

The next step in the protocol included steady state free precession (SSFP) images in the following long axis planes: vertical long axis (LV 2 chamber),

horizontal long axis (LV 4 chamber), LV outflow tract (LV 3 chamber), aortic arch, RV outflow tract (in two orthogonal planes), RV 2 chamber, and RV inflow-outflow (RV 3 chamber views). A short axis stack of 10mm slices through the left and right ventricles from base to apex was also obtained. Typical settings were: voxel size 1.5 x 1.3 x 6.0mm with TR 48.79ms, TE 1.21ms, flip angle 80 degrees. To assess function of the aortic and pulmonary valves phase-contrast velocity encoded flow mapping was performed in through-plane short axis views during breath holding, with an appropriate velocity envelope selected (generally 100 cm/s for a low velocity regurgitant jet). Settings for these sequences were voxel size 1.3 x 1.3 x 5.0mm, TR 29.90ms, TE 2.18ms, flip angle 30 degrees.

Once this was performed a non-contrast magnetic resonance angiogram was obtained. This prospectively gated sequence uses a free breathing navigator at the apex of the right hemidiaphragm together with ECG monitoring to allow the acquisition of data over a large field of view in end-expiration and end-diastole. Settings were: voxel size 1.5 x 1.4 x 0.8mm, TR 285.54ms, TE 1.56ms, flip angle 90 degrees.

The final stage in the scan involved the acquisition of late gadolinium enhancement (LGE) images. Single shot SSFP acquisitions were made 10-15 minutes after the administration of 0.15mmol/kg of Gadolenic acid (Dotarem®) through a peripheral intravenous cannula. The entire LV and RV were imaged using a phase sensitive inversion recovery (PSIR) sequence in contiguous short axis views from the level of the AV valves to the apex, and then in long axis views (VLA, HLA, LV 3-chamber, RV outflow tract, and RV inflow-outflow). Typical imaging parameters were as follows: voxel size 3.5 x 1.8 x 8.0mm, TR 23.49ms, TE 1.12ms, flip angle 30 degrees. Inversion time was optimised to null normal myocardium.

Post-procedure analysis was performed using a Siemens Argus workstation. Volumetric analysis was calculated from the short axis stack dataset via assisted planimetry. Firstly end-diastole and end-systole were defined, and the most basal slice designated for both the LV and RV. Endocardial contours were traced for both chambers at end-diastole and end-systole in

each 10mm short axis slice, and the resultant two-dimensional area was used to calculate the corresponding blood pool volume for each 10mm short axis. The volumes for each short axis slice were added together to give the end diastolic volume (EDV) and end systolic volume (ESV) in ml for both the LV and the RV. These values were indexed to body surface area giving the LVEDVi, LVESVi, RVEDVi and RVESVi in ml per m2, and allowed the calculation of ejection fraction (EF) according to the formula:

$$EF = \frac{(End\ Diastolic\ Volume \cdot ml - End\ Systolic\ Volume \cdot ml)}{End\ Diastolic\ Volume \cdot ml} \times 100$$

The practice at our institution is to exclude papillary muscles from analysis of LV volumes, but to incorporate trabeculations into analysis of RV volumes. To analyse pulmonary regurgitant fraction the velocity encoded sequences were used. The valve orifice was defined with planimetry throughout the cardiac cycle, and the forward and reverse flow through the valve calculated. This allowed the calculation of the regurgitant fraction (RF) according to the expression:

$$RF = \frac{Regurgitant\ Volume \cdot ml}{Stroke\ Volume \cdot ml} \times 100$$

2.6 Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, New York). Continuous variables were expressed as mean and standard deviation for normally distributed data, and median and interquartile range for non-normally distributed data. Comparison between groups was performed using an independent samples T-test, Mann Whitney U test or Chi squared test as appropriate. Assumption of normality or non-normality was derived from graphical representation by means of a histogram, or the Shapiro-Wilk test of normality. A *p*-value of less than 0.05 was considered significant.

Survival analysis is outlined in more detail in chapters 4-6. Briefly, cumulative survival was estimated using the life table method, and graphically represented using Kaplan Meier curves. Comparisons between survival curves were made using the log rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model.

Chapter 3 Long term morbidity and mortality in Tetralogy of Fallot and Systemic Right Ventricle: a literature review

3.1 Introduction

As outlined in chapter 1 the birth prevalence of congenital heart disease is increasing (van der Linde et al., 2011), and combined with advances in the prenatal diagnosis and surgical management of children with congenital heart disease of there has been a dramatic improvement in overall survival to adulthood. However, beyond this point, the prognosis for adults with congenital heart disease is uncertain. Life expectancy is poorly defined, furthermore as outlined in the previous chapter corrective surgery is often palliative rather than curative, and this results in extensive morbidity. There are a host of recognised long term sequelae following surgical repair, some of these may be generic, for example endocarditis and arrhythmia, whilst others relate to the specific surgical technique involved, for example severe pulmonary regurgitation in the case of transannular patch repair of Tetralogy of Fallot. Some of these complications have been recognised only recently, e.g. aortic root dilatation in Tetralogy of Fallot (Mongeon et al., 2013), raising the possibility of more as yet under-recognised complications in later adult life. Furthermore, as patients age so they are at risk of developing acquired cardiovascular disease, and it is unclear whether or not they are at greater risk of this than their contemporaries (Tutarel, 2014).

In this chapter I characterise what is already known about the long term mortality and morbidity in the two cohorts of ACHD patients relevant to my thesis; those with a systemic right ventricle and those with surgically repaired Tetralogy of Fallot. These conditions are rare - birth prevalence per 1000 live births has been reported at 0.34 for TOF and 0.31 for TGA (van der Linde et al., 2011), and at less than 0.07 for CCTGA (McCombe et al., 2016), but they are among the more common of the congenital cardiac conditions of at least moderate complexity, and for the reasons outlined in chapter 1 comprise a well defined population with regular follow-up.

3.2 Methods

I undertook a literature search of Ovid MEDLINE and Embase (1980 to November 2016 week 3) to identify papers relating to long term prognosis in systemic right ventricle and repaired Tetralogy of Fallot. Eligibility criteria included:

1. Must refer to outcomes in:
    a. Transposition of the Great Arteries post atrial switch surgery
    b. Congenitally Corrected Transposition of the Great Arteries
    c. Surgically repaired Tetralogy of Fallot
2. Must provide longitudinal data on mortality and morbidity into adulthood, i.e. papers were excluded if they related exclusively to outcomes in neonatal or paediatric patients
3. Include at least 50 patients
4. English language publication

Three search queries were run: a subheading search specific to each of Medline and Embase, and a textword search run simultaneously for both Medline and Embase. Terms used included "congenital heart disease", "survival", "mortality", "morbidity", "transposition of the great arteries", "congenitally corrected transposition of the great arteries", "systemic right ventricle", "D-TGA", "L-TGA", "Mustard", Senning", "atrial inversion", "tetralogy", and "Fallot". I screened titles and abstracts, and if an article was deemed to be relevant then the full text was reviewed to see if the paper met the eligibility criteria outlined above.

It became apparent in the course of the project that some centres published outcomes from the same cohort of patients on more than one occasion, and if the dates of follow-up overlapped then there was of course the risk of duplicating the same data. In these cases generally the most up

to date paper was used, an important exception being if it had fewer years of patient follow-up owing to the subject of interest being a specific subgroup of that cohort. Additionally in the TGA-atrial switch and CCTGA groups care had to be taken that the cohort included patients with a systemic right ventricle; therefore papers were excluded if they related exclusively to patients undergoing surgical correction of TGA or CCTGA that resulted in the left ventricle being placed in the systemic or subaortic position. Examples of such procedures include the Arterial Switch (Jatene) procedure for TGA, the Rastelli, REV (Réparation a l'Étage Ventriculaire) and Nikaidoh procedures for TGA complicated by the presence of a VSD and pulmonary stenosis, and combinations of these procedures with an atrial switch operation for complex CCTGA - a "double switch" or "anatomical" repair. Papers were also excluded if they related to patients with the most severe form of TGA and CCTGA who were palliated by means of a univentricular repair, with the end result being the formation of a Fontan circuit. These patients, even though the right ventricle is in the systemic position, have a very different physiology to those patients with a functionally biventricular heart, and so outcomes and prognosis are not readily comparable to their contemporaries. If a paper related to patients with TGA or CCTGA who underwent various types of repair then an attempt was made to exclude any data relating to those patients who did not have a systemic right ventricle. In the case of TGA this was often straightforward as the results were typically presented separately, unfortunately for the papers relating to CCTGA data was often presented for the cohort as a whole, and therefore was much more difficult to disentangle. In this case I made the decision to include these papers and present them as published, as in general the number of patients undergoing an anatomic repair or Fontan was small, and if I instead excluded these papers outright there would have been no papers relating exclusively to adult patients with CCTGA whatsoever.

The following data were extracted according to diagnosis: centre name, number of cases, anatomical subtype or type of surgical repair, ratio of male/female patients, age at surgical repair (where applicable), surgical era (earliest and latest year of initial surgery), baseline for the purposes of follow-up, mean/median follow-up duration, number of deaths, cumulative survival at 1-5 year intervals, incidence of morbidity, and risk factors associated with mortality. Centres differed in their reporting of perioperative or early postoperative mortality (generally defined as a death occurring within 30 days of surgery). Where possible this was highlighted in the results tables, furthermore if early mortality was not included in the survival analysis the number of patients in the cohort as baseline was adjusted to ensure it accurately reflected this.

Morbidity outcomes were lesion specific but where relevant included incidence of reoperation, device implantation, arrhythmia, and heart failure. Morbidity information was expressed as a percentage of the whole cohort, unless follow-up was incomplete and some patients had missing data. If this was evident then the denominator was adjusted to reflect the number of patients for whom follow-up was available. Risk factors for mortality were included if they were statistically significant (defined as p less than or equal to 0.05) on a multivariate analysis.

Some papers summarised data regarding more than one congenital cardiac diagnosis. Where this occurred the data was stratified according to diagnosis. The diagnosis-specific data had to include more than 50 patients, relate to adult patients, and also correlate with one of the diagnostic groups outlined in the data collection (so data was excluded if for example the study reported outcomes for a group of patients with TGA but did not distinguish between patients with an atrial or arterial switch).

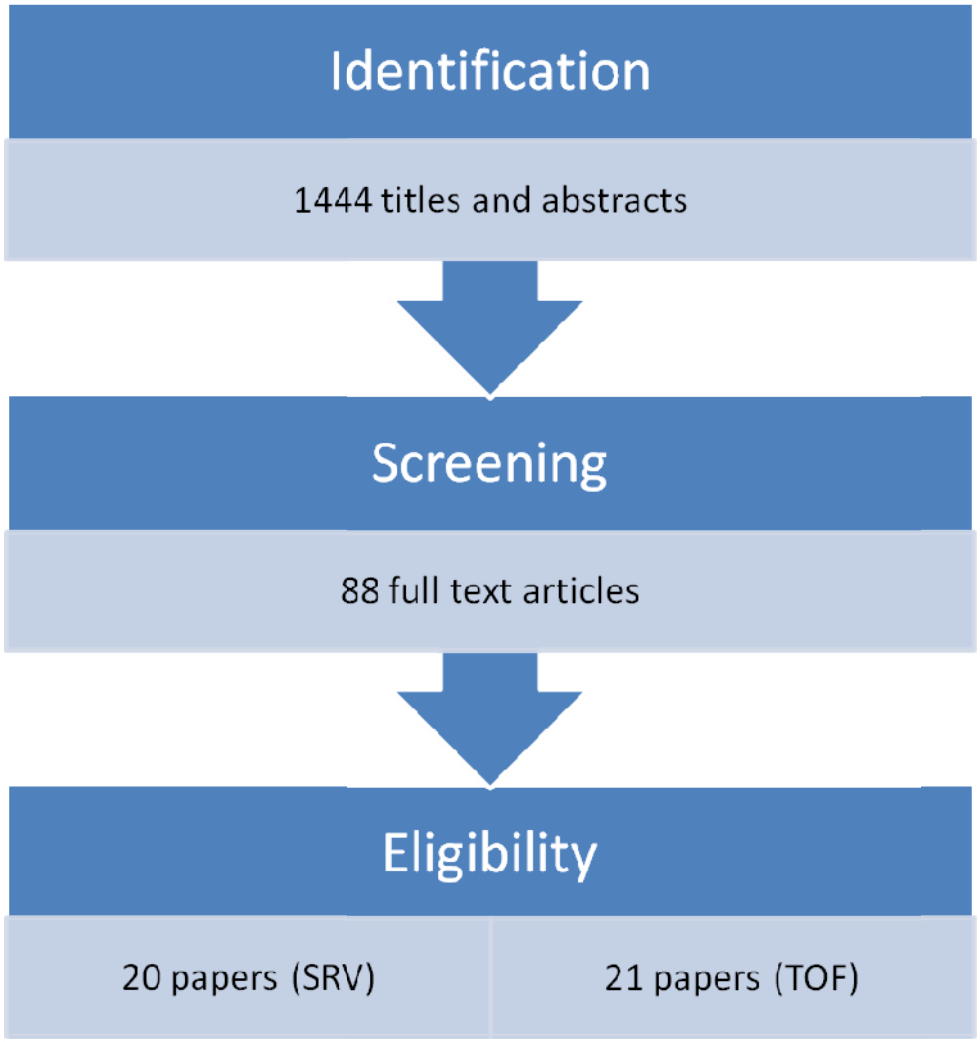
Data were tabulated; no meta-analysis was attempted as the studies were sufficiently heterogeneous that it would not have been possible to adjust for crucial underlying differences between each study population.

3.3 Results

3.3.1 Data collection

The initial search of Medline and Embase using the three search strategies yielded 1444 records (Figure 1). Following title and abstract screening to remove papers which were obviously not relevant, duplicates, and non-English publications a total of 88 full text articles were retrieved. Of these papers 49 were excluded: 15 overlapped with another paper from the same centre, 6 reported outcomes for paediatric patients only, 3 had cohort sizes of less than 50 patients, and 20 did not report survival data or did not report it in a way that allowed comparison with other studies (for example they did not present results according to congenital heart disease subtype). This generated 39 papers for detailed review, of which 1 contained data regarding both TGA-atrial switch and TOF, 1 contained data regarding systemic RV and TOF, and 1 contained data regarding TGA-atrial switch and CCTGA. This gave a total of 20 articles relating to patients with a systemic RV and 21 relating to patients with repaired TOF.

Figure 3-1 PRISMA flowchart (Liberati et al., 2009)



3.3.2 Systemic right ventricle

There were a total of 20 papers which referred to outcomes in patients with a congenital cardiac condition characterised by the presence of a systemic right ventricle (tables 3.1 - 3.3). Of these 14 referred to patients with TGA-atrial switch, 4 referred patients with CCTGA, 1 referred to patients with both TGA-atrial switch and CCTGA, and 1 referred to data for "systemic right ventricle", with no differentiation of the patients within that cohort. Lesion-specific information is outlined as follows:

3.3.2.1 TGA-atrial switch

Baseline demographics:

There were a total of 15 papers reporting outcomes in 2898 patients. Where patient gender was reported, 23-46% were female. The selected baseline for long-term follow-up of these patients was exclusively the time of original atrial switch surgery. Median follow-up ranged from 11.7 - 35 years, those studies published more recently naturally tended to have the greater period of follow-up. Era of surgical repair was generally from the mid 1960s to early 1990s, although some centres were still performing atrial switch surgery for selected patients as late as the early 2000s (Lange et al., 2006, Vejlstrup et al., 2015). Mean / median age of surgical repair was relatively consistent at less than 2 years, with the exception of one paper from Zurich, which in fact included some of the very first patients to have undergone the Senning operation (Turina et al., 1989).

Mortality:

The estimated cumulative survival varied from 61% at 15 years in an early cohort (earliest operation date 1958) to 91% at 20 years in a more recent cohort of patients with simple TGA (Morris and Menashe, 1991, Dos et al., 2005). Sudden death in patients with repaired congenital heart disease is a subject of particular interest, and up to 71% of those patients who died, died in this way. It is worth noting that the lowest percentage of 7% was

reported in a paper which included 62 perioperative deaths (Moons et al., 2004), thus heavily weighting the analysis in favour of early surgical mortality. Papers which did not include early surgical mortality generally quoted sudden death as occurring in over 40% of the patients who died during the follow-up period. Multivariable models to identify risk factors for mortality were generally the exception rather than the rule, however early surgical repair and the presence of associated congenital cardiac lesions such as VSD were identified as conferring a worse prognosis from baseline (Cuypers et al., 2014, Vejlstrup et al., 2015).

Morbidity

Up to 39% of patients required surgical reoperation, where the reason for this was outlined in the manuscript this was generally for haemodynamic problems arising from the interatrial baffles. Arrhythmia occurred in up to 40% of patients, with the lowest prevalence of 7-8% being reported in the earliest studies (Morris and Menashe, 1991, Turina et al., 1989). Most arrhythmias were supraventricular, and where ventricular arrhythmia was reported this occurred in 6% of patients (Cuypers et al., 2014). Permanent pacemaker was required in up to 33% of patients, however the proportion of patients with an ICD was not well described. Only two papers documented this, and both reported it at 5-6% (Cuypers et al., 2014, Wheeler et al., 2014). Systemic tricuspid valve repair or replacement occurred in up to only 2.7% of patients when reported (Sarkar et al., 1999), despite the reported prevalence of severe tricuspid regurgitation of up to 38% in one of the most recent publications (Cuypers et al., 2014).

Differences between Mustard and Senning cohorts:

Three papers assessed whether there was a difference in outcomes between those patients who underwent a Mustard procedure, and those who underwent a Senning repair (Moons et al., 2004, Sarkar et al., 1999, Lange

et al., 2006). Two reported worse survival with a Mustard repair (Lange et al., 2006, Sarkar et al., 1999), and all reported a higher incidence of baffle obstruction and / or reintervention for the Mustard group. However it is important to note that this was based on a univariate comparison. In all three centres the Senning repair was generally introduced after 1980, with the majority of Mustards performed before this date, thus introducing surgical era / birth cohort effect as an important confounding factor.

3.3.2.2 CCTGA

Baseline demographics:

There were five studies reporting outcomes for 609 patients, of which 34-40% were female. Two studies reported outcomes for all patients with CCTGA (Dobson et al., 2013, Rutledge et al., 2002), the remaining three reported outcomes only in patients who had undergone some form of corrective cardiac surgery (Lim et al., 2010, Hraska et al., 2005, Yeh et al., 1999). Associated lesions were extremely common, with estimates of VSD prevalence ranging from 65-86%, pulmonary stenosis from 37-64%, and pulmonary atresia from 15-31% (higher in the three surgical cohort studies).

Mortality:

Cumulative survival was estimated at 59-83% at 20 years, and 48-55% at 30 years. The cohort study reporting the lowest cumulative survival of 48% at 30 years had a higher median age of first corrective surgery, and spanned an earlier operative era, with the first operations being performed in 1959. On the other hand the study reporting the highest survival of 83% at 20 years included exclusively patients undergoing a biventricular repair, of whom a large proportion (26%) underwent an anatomical repair (atrial switch plus arterial switch, Rastelli, or REV procedure). The proportion of deaths which were sudden were reported as 13-31%. Risk factors for late death included systemic RV dysfunction, the presence of a complete AVSD, preoperative pulmonary artery banding and prolonged aortic cross clamp time at surgical repair (Lim et al., 2010, Rutledge et al., 2002).

Morbidity:

Atrial tachyarrhythmia occurred in up to 18% of patients, heart failure in up to 14%, pacemaker implantation in up to 31%, and tricuspid valve surgery in up to 34% of patients, although the latter was often performed at the time of initial surgery rather than as a later procedure in isolation.

3.3.2.3 Systemic RV

A single study reported outcomes for 279 patients with any form of a systemic RV, as part of a larger study assessing mortality in all ACHD patients followed up at a single centre (Diller et al., 2015). Data were not differentiated further with respect to the underlying anatomy, i.e. it was not known how many patients were TGA-atrial switch and how many were CCTGA. Within the cohort 45.9% patients were female. Of the deaths occurring only 13% were sudden, and in fact the commonest cause of death was heart failure (66%). The authors adopted a different approach to reporting mortality compared to the other papers reviewed. Standardised mortality ratios (SMRs) were used, and instead of expressing survival as a function of time (e.g. time from initial surgery or birth), they expressed it as a function of age, i.e. for each congenital cardiac diagnosis they quoted life expectancy by expressing it as the age subgroup of the general population with the same mortality. So for patients with a systemic RV at age 40, mortality was the same as a subject from the general population at age 59. The SMR was 4.88 (95% CI 3.33 - 7.16), and this was the fourth-worst of all the congenital cardiac diagnoses studied (Eisenmenger syndrome, "complex" CHD e.g. unpalliated univentricular hearts, and Fontan patients experienced higher mortality).

Table 3-1 Long term outcomes in TGA-atrial switch

Centre	Year published	Study description	N	% Female	Era of initial surgical repair	Baseline	Mean / median age at baseline	Mean / median follow-up	Survival	N deaths (% sudden or presumed arrhythmic)	Morbidity	Risk factors for late mortality (multivariate analysis)
Zurich(Turina et al., 1989)	1989	Retrospective single centre cohort	220	33.6	1964-84	Atrial switch repair	3.9y	-	83% at 20y	25 total 7 (28%) sudden	PPM 10.5% at 15y Reoperation 9.1% Baffle intervention 6% TVR/repair 1.4% Heart failure 12% at 15y	-
Oregon(Morris and Menashe, 1991)	1991	Retrospective population-based registry	148	23.0	1958-89	Atrial switch repair	-	-	61% at 15y	-	-	-
New York (Myridakis et al., 1994)	1994	Retrospective single centre cohort	76[3]	-	1971-81	Atrial switch repair	0.3y simple 0.6y complex	-	At 20y 86% simple 64% complex	16 total 2 (13%) sudden	SVT 13% Reoperation 9% Severe TR 11%, TVR/repair 0%	-
Helsinki(Kirjavainen et al., 1999)	1998	Retrospective single centre cohort	100	-	1978-91	Atrial switch repair	0.6y simple 0.6y complex	12.8y	At 16y 90% simple 70% complex	10 total 4 (40%) sudden	SVT 8% PPM 24% Reoperation 3% Severe TR 9%	-
New Zealand(Wilson et al., 1998)	1998	Retrospective single centre cohort	113	-	1964-82	Atrial switch repair	0.5y	-	80% at 20y	19 total 8 (42% sudden)	SVT 10.7% PPM 4.4% Reoperation 8% Baffle intervention 7%	-
London (Sarkar et al., 1999)	1999	Retrospective single centre cohort	358	-	1965-92	Atrial switch repair	2.2y	11.7y	At 15y 94% Senning 77% Mustard	62 total 44 (71%) sudden	SVT 38.9% PPM 8.8% Reintervention 31% TVR/repair 2.7%	-
Parma(Agnetti et al., 2004)	2004	Retrospective single centre cohort	70[3]	38.4	1978-87	Atrial switch repair	0.5y	19y	-	5 total 2 (40%) sudden	SVT 10% Reoperation 1.4%	-
Belgium(Moons et al., 2004)	2004	Retrospective multicentre cohort	283[3]	35.4	1970-98	Atrial switch repair	0.3y	17.1y	79.3% at 30y	82 total 6 (7% sudden)	Tachy/bradyarrhythmia 57.6% free at 20y PPM 4.3% Baffle intervention 6% Severe TR 7.4%, TVR/repair 2.5%	-
Barcelona (Dos et al., 2005)	2005	Retrospective single centre cohort	137[3]	40.9	1973-97	Atrial switch repair	1.2y	16.7y	At 20y 91% simple 82% complex	7 total 5 (71%) sudden	SVT 13.1% PPM 5.8% Reoperation 5.1% Baffle intervention 2% Severe TR 9%	-
Munich(Lange et al., 2006)	2006	Retrospective single centre cohort	395[3]	29.7	1974-01	Atrial switch repair	1.2y	19.1y	At 25y 91% Senning 76% Mustard	42 total 15 (36%) sudden	PPM 8.9% Reoperation 16% Baffle intervention 20% TVR/repair 2.3%	-
Hanover(Gorler et al., 2011)	2011	Retrospective single centre cohort	222[3]	-	1973-unspecified	Atrial switch repair	1.4y	16y	78% at 20y	-	PPM 25% Reoperation 39%	-
Glasgow(Dobson et al., 2013)	2013	Retrospective single centre cohort	133	33.1	1971-98	Atrial switch repair	0.7y	-	78% at 30y	24 total (-)	-	-

[3] Excluded early perioperative mortality

Centre	Year published	Study description	N	% Female	Era of initial surgical repair	Baseline	Mean / median age at baseline	Mean / median follow-up	Survival	N deaths (% sudden or presumed arrhythmic)	Morbidity	Risk factors for late mortality (multivariate analysis)
Rotterdam (Cuypers et al., 2014)	2014	Prospective single centre cohort	86[4]	25.2	1973-80	Atrial switch repair	0.7y	35y	77% at 30y	22 total 9 (41%) sudden	SVT 28%, VT/VF 6% PPM 33%, ICD 6% Heart failure 23% severe TR 38%	Repaired pre-1977
Melbourne (Wheeler et al., 2014)	2014	Retrospective single centre cohort	89[5]	46.1	-	Atrial switch repair	1.2y	30y	-	7 total 5 (71%) sudden	SVT 30.3% PPM 25.8%, ICD 5.6%	
Denmark & Sweden (Vejlstrup et al., 2015)	2015	Retrospective multicentre cohort	468	31.8	1967-03	Atrial switch repair	1.9y	26y	60% at 30y	176 total (-)	PPM 15% Reoperation 7%	Repaired pre-1980, presence of associated lesions

[4] Only included patients who survived to at least the age of 10 years and were recruited into the initial cohort prior to publication of the first study in 1990

[5] Excluded patients who died before the age of 18 years

Table 3-2 Long term outcomes in CCTGA

Centre	Year published	Study description	N	% Female	Era of initial surgical repair	Baseline	Mean / median age at baseline	Mean / median follow-up	Survival	N deaths (% sudden or presumed arrhythmic)	Morbidity	Risk factors for late mortality (multivariate analysis)
Toronto (Yeh et al., 1999)	1999	Retrospective single centre cohort (anatomical and physiological biventricular repair)	127	-	1959-97	Initial surgical repair	8y	-	48% at 30y	35 total 11 (31.4%) sudden	VSD 86%, PS 64% SVT 3% PPM 27% TVR/repair 34%	-
Houston (Rutledge et al., 2002)	2002	Retrospective single centre cohort (biventricular and univentricular repair, and unoperated patients)	121	33.9	1952-99	Birth	4.9y	13.2y	55% at 30y	20 total 4 (20%) sudden	VSD 73%, PS 50%, PA 15% SVT 18.2% PPM 24.8% TVR 16% Heart failure 14%	Presence of complete AVSD, moderate-severe RV dysfunction
Boston (Hraska et al., 2005)	2005	Retrospective single centre cohort (physiological biventricular and univentricular repair)	123	39.8	1963-96	Initial surgical repair	4.1y	5.2y	59% at 20y	30 total 4 (13.3%) sudden	VSD 77%, PS 39%, PA 28% SVT 4.9% PPM 37% TVR 22% Heart failure 44%	Ebstein anomaly
Seoul (Lim et al., 2010)	2010	Retrospective single centre cohort (anatomical and physiological biventricular repair)	167	-	1983-2009	Initial surgical repair	4.1y	-	83% at 20y	19 total 4 (21.1%) sudden	VSD 80%, PS 44%, PA 31% SVT 3.6% PPM 16.8% Reoperation 45.8% TVR/repair 16.8%	Preoperative PA band, aortic cross-clamp time
Glasgow (Dobson et al., 2013)	2013	Retrospective single centre cohort (biventricular and univentricular repair, and unoperated patients)	71	35.2%	1978-2009	Birth	-	-	79% at 20y	23 total (-)	VSD 65%, PS 37%, PA 16% SVT 10% PPM 31% TVR 3%	-

Table 3-3 Long term outcomes in systemic RV (includes TGA-atrial switch and CCTGA)

Centre	Year published	Study description	N	% Female	Era of initial surgical repair	Baseline	Mean / median age at baseline	Mean / median follow-up	Survival	N deaths (% sudden or presumed arrhythmic)	Morbidity	Risk factors for late mortality (multivariate analysis)
London (Diller et al., 2015)	2015	Retrospective single centre cohort	279	45.9	-	Age >16y	-	9.1y	SMR 4.88	34 total 13% sudden	-	-

3.3.3 Tetralogy of Fallot

Baseline demographics:

There were 21 papers describing outcomes in 8824 patients. Patient gender was reported by 14 papers, with the overall proportion of female patients ranging from 36-46%. All studies reported outcomes exclusively in patients who had undergone surgical repair. Up to 12% of patients had an associated genetic or chromosomal syndrome, although this was poorly reported with only five studies documenting this (Park et al., 2010, Chiu et al., 2012, Hickey et al., 2009, Jonsson and Ivert, 1995, Bokma et al., 2015). Papers reporting outcomes from an earlier surgical era had a much higher proportion of patients undergoing a palliative shunt, with the highest being 64% (Park et al., 1987).

Mortality:

Cumulative survival ranged from 67% at 25 years in a cohort of operated and unoperated patients (Olsen et al., 2010), to 98% at 30 years in patients undergoing repair by the modern transatrial and transpulmonary approach (Ide et al., 2009). One paper reported survival using SMRs, this was estimated at 2.34 (95% CI 1.73 - 3.17) (Diller et al., 2015). Sudden cardiac death was estimated as accounting for up to 40% of all deaths, although in the large cohort of adult survivors of TOF this was only 6%, again, as for the systemic RV, heart failure was the predominant modality at 40%. Seven papers performed a multivariate analysis to identify risk factors for late mortality. Transannular patch repair and older age at surgery were consistently associated with an increased risk of death (Jonsson and Ivert, 1995, Nollert et al., 1997, Hamada et al., 2002, Bokma et al., 2015)

Morbidity:

Regarding morbidity tachyarrhythmia occurred in up to 15% of patients, and this was mainly supraventricular in origin. Ventricular arrhythmias generally occurred in 3% or less of patients, however one cohort reported it at 5.8% (Bokma et al., 2015). This cohort consisted exclusively of adult patients undergoing PVR, and so

can be assumed to be older and sicker than the other cohorts reporting outcomes in a much younger and broader range of patients. Prevalence of severe pulmonary regurgitation and the need for PVR was not well characterised; the former was often not reported at all, and the latter was often not differentiated from other forms of reoperation in the survival analysis. The highest prevalence of PVR at time of latest follow-up was reported at just under 12% in one study (Luijten et al., 2015). Similarly the presence of tricuspid regurgitation was also poorly described, although one study exclusively of patients undergoing PVR identified preoperative severe tricuspid regurgitation in 10%, furthermore in a multivariate model consisting of age at surgery and indexed RV end systolic volume this conferred a higher risk of adverse postoperative outcomes with a calculated hazard ratio of 2.49 (95% CI 1.11 - 5.52) for a composite endpoint of death, sustained VT, SVT and heart failure (Bokma et al., 2015). Typically 5% or less of patients required PPM, the number of patients undergoing implantation of an ICD was poorly reported.

Table 3-4 Long term outcomes in TOF

Centre	Year published	Study description	N	% Female	Era of initial surgical repair	Baseline	Mean / median age at baseline	Mean / median follow-up	Survival	N deaths (% sudden or presumed arrhythmic)	Morbidity	Risk factors for late mortality (multivariate analysis)
Texas (Park et al., 1987)	1987	Retrospective single centre cohort	117	46.2	1962-83	Initial surgical repair	25y	9.2y	84% at 15y	4 total 0% sudden	Palliative shunt 64% Arrhythmia (any) 22% PPM 1.8% Reoperation 17%	-
Oregon (Morris and Menashe, 1991)	1991	Retrospective population-based registry	425	42.1	1958-89	Initial surgical repair	0.7-6.2y	-	84% at 20y	-	-	-
Niigata (Miyamura et al., 1993)	1993	Retrospective single centre cohort	100[6]	46.0	1965-71	Initial surgical repair	10.4y	-	94% at 20y	14 total 1 (7%) sudden	Reoperation 84% free at 10y	-
Stockholm (Jonsson and Ivert, 1995)	1995	Retrospective single centre cohort	165	43.6	1966-76	Initial surgical repair	7y	19y	84% at 20y	40 total 8 (20%) sudden	Genetic syndrome 3% Palliative shunt 50% VT/VF 1.8% Reoperation 88% free at 10y	Transannular patch repair
Tenri (Okita et al., 1995)	1995	Retrospective single centre cohort	510	-	1966-90	Initial surgical repair	5.6y	8.5y	95% at 20y	13 total (-)	Reoperation 59% free at 20y Severe PR 13%, PVR 8%	-
Munich (Nollert et al., 1997)	1997	Retrospective single centre cohort	490	45.1	1958-77	Initial surgical repair	-	25.3y	89% at 30y	42 total 15 (36%) sudden	Palliative shunt 29%	Transannular patch repair. surgical repair pre-1970
Fukuoka (Masuda et al., 2001)	2001	Retrospective single centre cohort	92	-	1975-99	Initial surgical repair	-	-	98% at 15y	-	-	-
Chiba (Hamada et al., 2002)	2002	Retrospective single centre cohort	167	-	1964-75	Initial surgical repair	6.4y	26y	88% at 20y	24 total 7 (29%) sudden	Palliative shunt 17% SVT 2%, VT 3%	Transannular patch repair, older age at initial repair
Mayo clinic (Dearani et al., 2003)	2003	Retrospective single centre cohort (RV-PA conduit repair only)	411	-	1964-92	Initial surgical repair	9.6y	10.9y	73% at 15y	-	-	
Istanbul (Erdogan et al., 2005)	2005	Retrospective single centre cohort	64	43.8	1985-2002	Initial surgical repair	20.6y	5.2y	89% at 15y	4 total 1 (25%) sudden	Palliative shunt 3% PPM 1.6% Reoperation 6.3% Severe PR 3%, PVR 6%	Associated lesions, need for reoperation
Toronto (Hickey et al., 2009)	2009	Retrospective single centre cohort	1181	40.1	1960-98	Initial surgical repair	6.7y	20y	77% at 40y	208 total (-)	Genetic syndrome 12% Palliative shunt 53%	AVSD, branch PA stenosis, DORV, Down syndrome
Osaka (Ide et al., 2009)	2009	Retrospective single centre cohort	472	-	1960-2007	Initial surgical repair	5.4y	-	98% at 30y	-	-	
Seoul (Park et	2010	Retrospective single	734	39.5	1986-2007	Initial surgical	1.4y	12.5y	93% at 30y	40 total	Genetic syndrome 3.9%	

[6] Excluded early deaths occurring at up to 1 year after initial surgical repair

Centre	Year published	Study description	N	% Female	Era of initial surgical repair	Baseline	Mean / median age at baseline	Mean / median follow-up	Survival	N deaths (% sudden or presumed arrhythmic)	Morbidity	Risk factors for late mortality (multivariate analysis)
al., 2010)		centre cohort				repair				6 (15%) sudden	Palliative shunt 21% SVT 1.2%, VT/VF 0.8% PPM 0.6%, ICD 0.3% Reoperation 47% free at 20y	
Denmark (Olsen et al., 2010)	2010	Prospective population-based registry	381	-	1977-2006	Birth	-	-	67% at 25y	-	-	-
Oslo (Lindberg et al., 2011)	2011	Retrospective single centre cohort	570	-	1952-2008	Initial surgical repair	15.3y	15.8y	At 30y 1952-69 71% 1970-79 73% At 20y 1980-89 96% At 10y 1990-99 98% 2000-09 98%	71 total (-)	-	
Taipei (Chiu et al., 2012)	2012	Retrospective single centre cohort	819	39.0	1970-2002	Initial surgical repair	6.5y	16.9y	91% at 30y	56 total 8 (14%) sudden	Genetic syndrome 5.1% Palliative shunt 15%	MAPCAs, previous palliative shunt
Rotterdam & Nijmegen (Luijten et al., 2015)	2015	Retrospective multicentre cohort	453	36.7	1970-2012	Initial surgical repair	0.6y	15y	92% at 25y	16 total (-)	Palliative shunt 12.8% PPM 1.1% PVR 11.5% Severe TR 0.4%	
Finland (Ylitalo et al., 2015)	2015	Retrospective population-based registry	600	40.0	1962-2007	Initial surgical repair	3.4y	23y	82% at 40y	82 total 13 (16%) sudden	Palliative shunt 25% Reoperation 20.2%	
RBH (Diller et al., 2015)	2015	Retrospective single centre cohort	869	45.9	-	Age >16	-	9.1y	SMR 2.34	54 total 6% sudden	-	
Amsterdam, Leiden, Radboud (Bokma et al., 2015)	2015	Retrospective multicentre cohort	129	38.8	2000-2007	First PVR	33y	8.4y	-	5 total 2 (40%) sudden	Genetic syndrome 7% Palliative shunt 51% SVT 14.7%, VT 5.4% PPM 5% Severe TR (baseline) 10.1% Heart failure 6.2%	Preoperative tricuspid regurgitation, higher RVESV, older age at surgery[7]
Malta (Caruana and Grech, 2016)	2016	Retrospective single centre cohort	75[8]	37.3	-	Initial surgical repair	1.3y	26.4y	88% at 30y	7 total (-)	Reoperation 29%	

[7] Multivariate analysis referred to a composite endpoint of death, arrhythmia (SVT and VT), and heart failure

[8] Excluded deaths occurring within 30 days of initial surgical repair

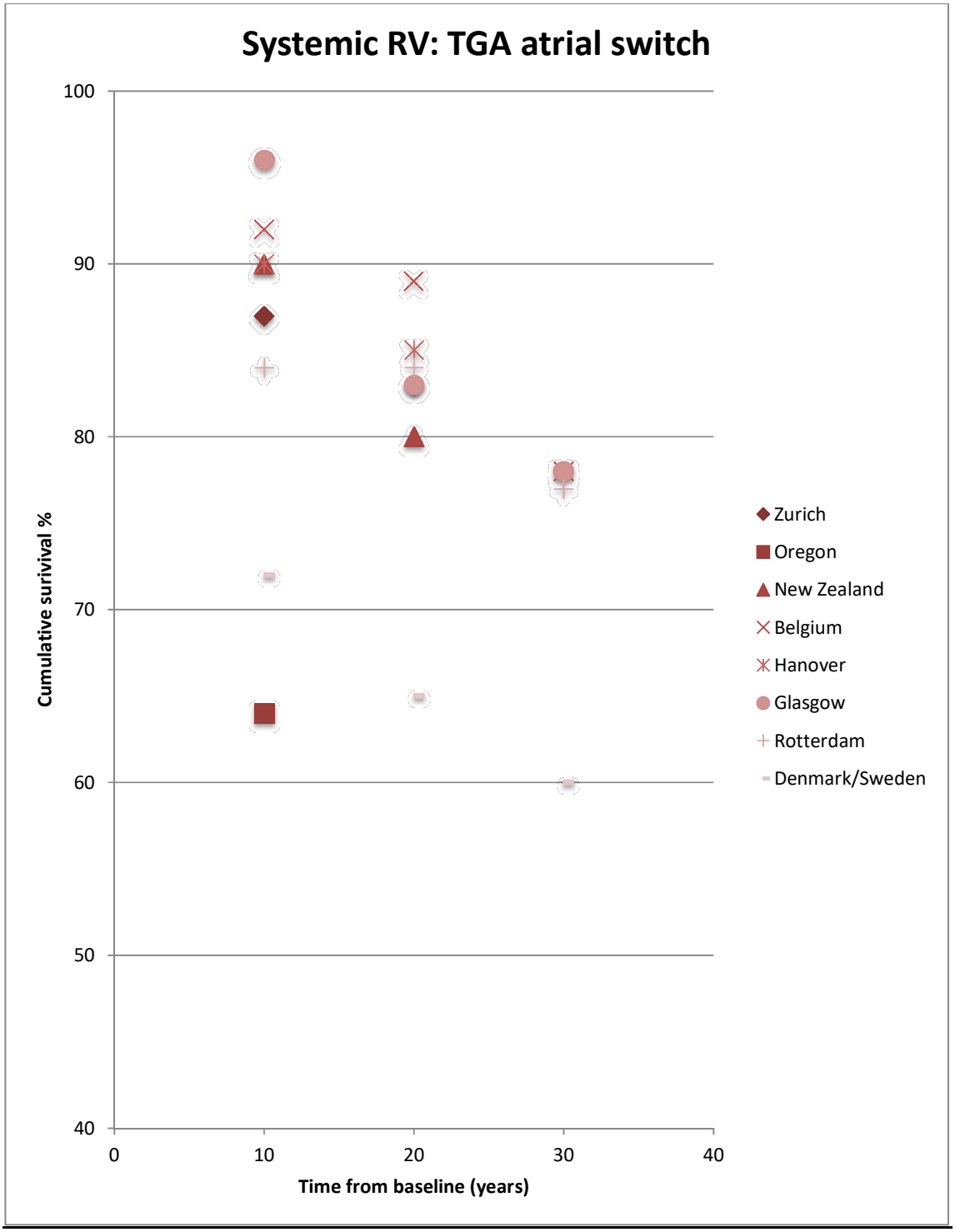
3.3.4. Differences in survival between patients with a systemic right ventricle and repaired Tetralogy of Fallot

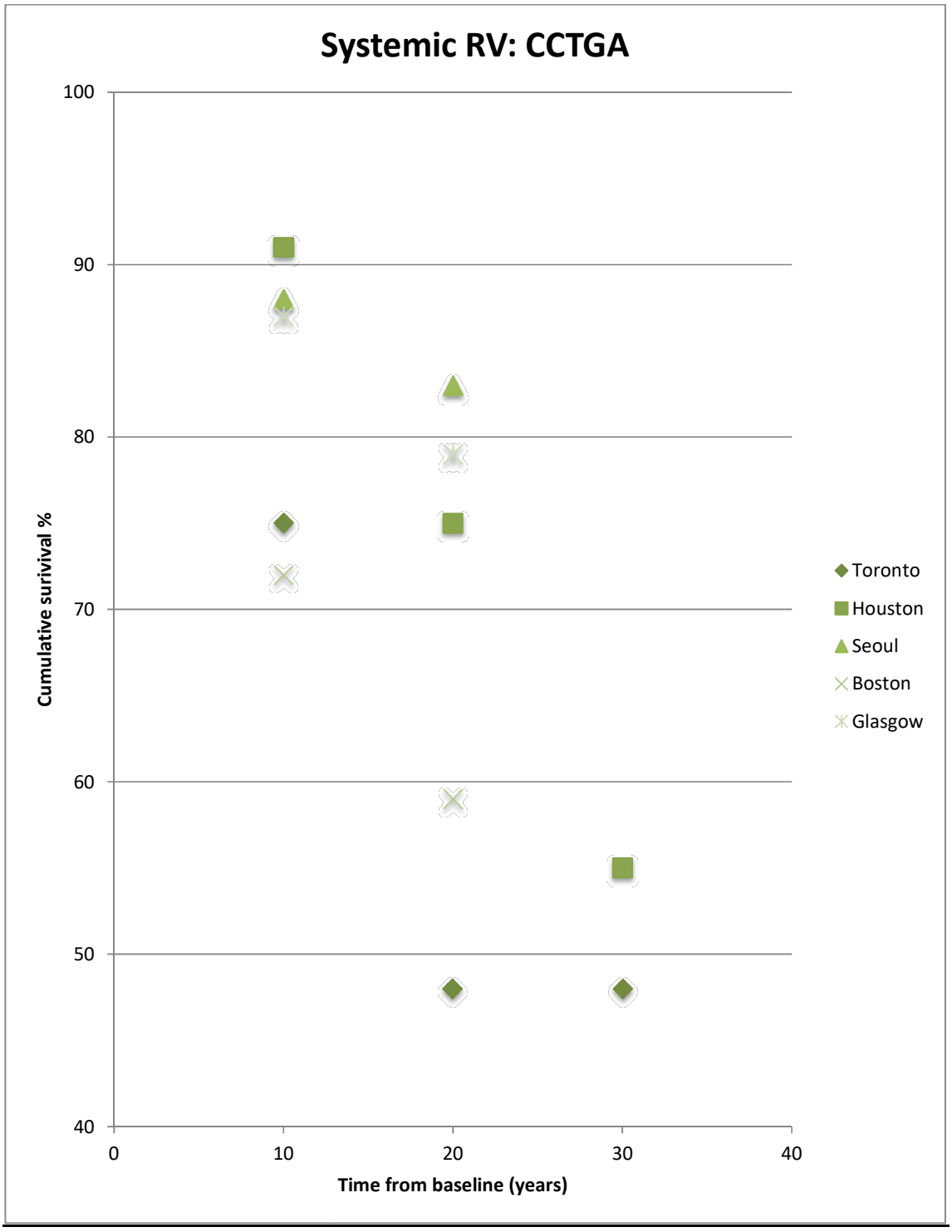
Most studies reported cumulative survival from a baseline of initial surgical repair to 20-30 years of follow up, and it was therefore possible to summarise the differences in median survival for each diagnostic group (Table 3.5 and Figure 3.2). From time of initial surgical correction survival is worse in the systemic RV group, and within this group patients with CCTGA have the higher mortality.

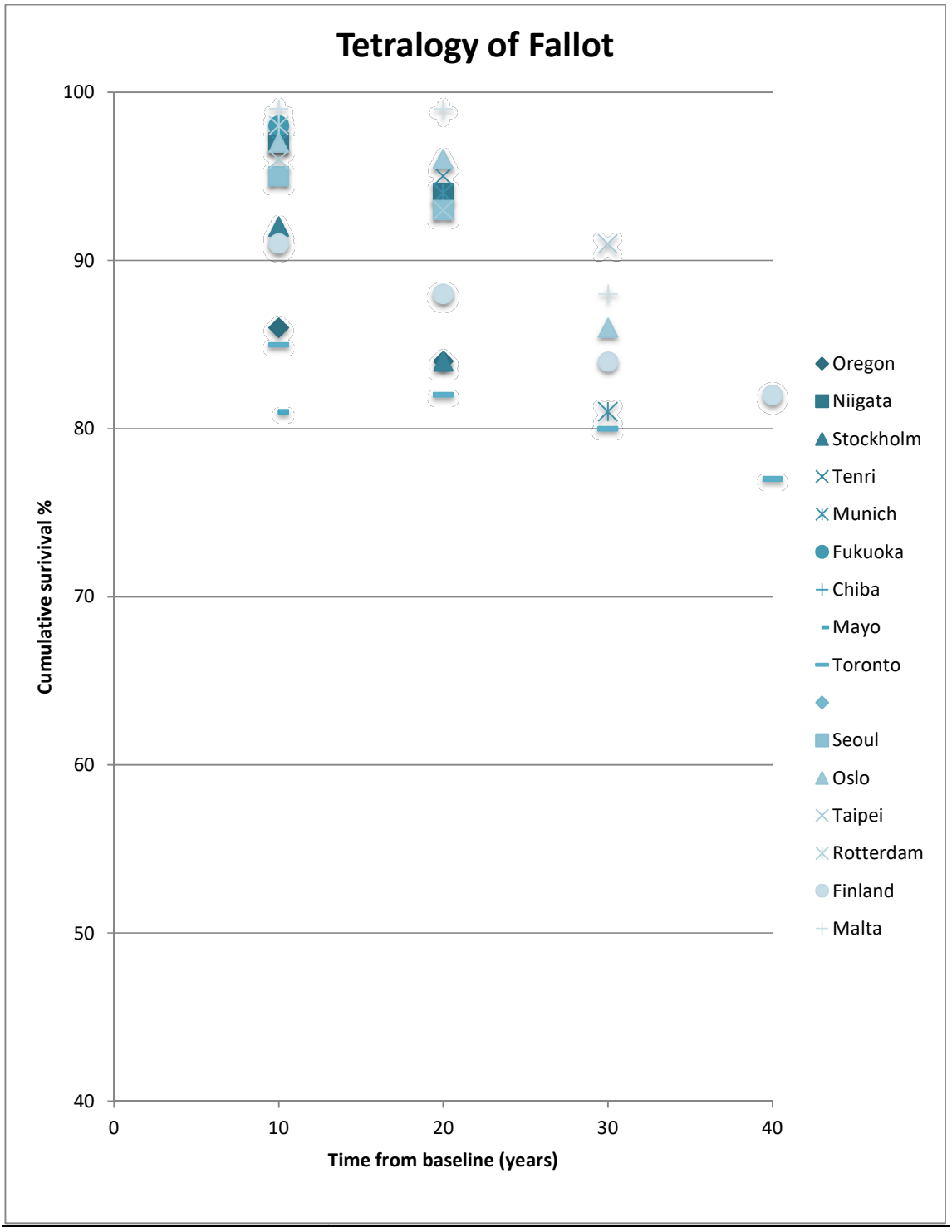
Table 3-5 Cumulative survival from baseline for TOF, TGA-atrial switch, and CCTGA

Diagnosis	Cumulative survival from baseline (years)			
	10	20	30	40
Systemic RV TGA atrial switch				
Zurich (Turina et al., 1989)	87	83		
Oregon (Morris and Menashe, 1991)	64			
New Zealand (Wilson et al., 1998)	90	80		
Belgium (Moons et al., 2004)	92	89	78	
Hanover (Gorler et al., 2011)	90	85		
Glasgow (Dobson et al., 2013)	96	83	78	
Rotterdam (Cuypers et al., 2014)	84	84	77	
Denmark/Sweden (Vejlstrup et al., 2015)	72	65	60	
Median	***88.5***	***83***	***77.5***	
CCTGA				
Toronto (Yeh et al., 1999)	75	48	48	
Houston (Rutledge et al., 2002)	91	75	55	
Seoul (Lim et al., 2010)	88	83		
Boston (Hraska et al., 2005)	72	59		
Glasgow (Dobson et al., 2013)	87	79		
Median	***87***	***75***	***51.5***	
TOF				
Oregon (Morris and Menashe, 1991)	86	84		
Niigata (Miyamura et al., 1993)	97	94		
Stockholm (Jonsson and Ivert, 1995)	92	84		
Tenri (Okita et al., 1995)	95	95		
Munich (Nollert et al., 1997)	97	94	81	
Fukuoka (Masuda et al., 2001)	98			
Chiba (Hamada et al., 2002)	91	88		
Mayo clinic (Dearani et al., 2003)	81			
Toronto (Hickey et al., 2009)	85	82	80	77
Seoul (Park et al., 2010)	95	93		
Oslo (Lindberg et al., 2011)	97	96	86	
Taipei (Chiu et al., 2012)	96	93	91	
Rotterdam (Luijten et al., 2015)	98			
Finland (Ylitalo et al., 2015)	91	88	84	82
Malta (Caruana and Grech, 2016)	99	99	88	
Median	***95***	***93***	***86***	***79.5***

Figure 3-2 Cumulative survival by diagnosis




Systemic RV: CCTGA
100
90
80
70
60
50
40
Cumulative survival %
0
10
20
30
40
Time from baseline (years)
Toronto
Houston
Seoul
Boston
Glasgow


Tetralogy of Fallot
100
90
80
70
60
50
40
Cumulative surivival %
0
10
20
30
40
Time from baseline (years)
Oregon
Niigata
Stockholm
Tenri
Munich
Fukuoka
Chiba
Mayo
Toronto
Seoul
Oslo
Taipei
Rotterdam
Finland
Malta

3.4 Discussion

3.4.1 Mortality

Cumulative survival from date of initial surgical correction as well as the single paper reporting SMRs (Diller et al., 2015) suggest that survival is poorer in patients with a systemic RV versus repaired TOF. This perhaps lends support to the hypothesis that a systemic RV has an innate predisposition to fail prematurely compared to a morphological LV. The reason that CCTGA patients tend to do worse than patients with TGA post-atrial switch can perhaps be explained by the fact that patients with CCTGA often have significant co-existent cardiac lesions, and the papers identified in this review included "all-comers", i.e. it was not possible to express survival purely for patients with CCTGA who did not require any form of additional surgical correction, who would have formed a more natural physiological comparator group to the TGA-atrial switch patients.

With later birth cohorts mortality appeared to decrease, and this is supported by the fact that surgical repair before 1980 was associated with greater risk on multivariate analysis for both systemic RV and repaired TOF patients (Nollert et al., 1997, Vejlstrup et al., 2015, Cuypers et al., 2014). However this is confounded by the fact that papers did not generally report cumulative survival by surgical era, and dates of initial surgical correction tended to be very broad. Establishing whether there was any social or geographical variation in mortality was beyond the scope of this study, mainly owing to the sheer number of potentially confounding variables. However, it is worth noting that the highest cumulative survival for CCTGA and repaired TOF was reported by centres in East Asia (Park et al., 2010, Chiu et al., 2012, Lim et al., 2010, Miyamura et al., 1993, Okita et al., 1995). Interestingly I found no studies from this region reporting long-term prognosis in TGA-atrial switch, although there were a number of studies reporting outcomes in the Arterial Switch Operation for TGA, and these also demonstrated excellent cumulative survival at well over 90% at up to 20 years post-surgical repair (Lim et al., 2013, Masuda et al., 2001). Finally it is worth noting that only one paper reported mortality as SMR. As described previously, by

expressing survival as a function of age rather than time from baseline, one is able to mitigate both the birth cohort effect and also the disproportionate influence of early postoperative mortality. Therefore this method may well be a more accurate way of assessing survival in ACHD patients, and it is surprising that so few centres have adopted this approach.

3.4.2 Morbidity

Morbidity was often not reported, and when it was it was frequently reported in different ways. The commonest way of reporting it was as a cross-sectional "snapshot" at the end of the follow-up period, although for some outcomes, such as arrhythmia or reintervention, survival analysis was undertaken to ascertain the number of patients who were still free from the outcome of interest at a specified point in time from the original baseline. Furthermore, the morbidity outcomes reported tended to relate to outcomes which are generally easy to ascertain such as repeat surgical intervention, rather than more detailed functional assessment such as data derived from non-invasive imaging regarding e.g. the severity of ventricular dysfunction or valve regurgitation. Data were also lacking for morbidity outcomes such as endocarditis, stroke, venous thromboembolism, pregnancy, and acquired cardiovascular disease; again these are outcomes where status is difficult to establish as patients may not present to their original cardiac centre when these occur.

A few general themes came across in the analysis however. The proportion of patients experiencing a morbidity outcome in contemporary publications was higher than that reported by the oldest publications, and this was mainly driven by gradual attrition of patients to developing arrhythmia and haemodynamic lesions requiring repeat intervention. On the whole patients with a systemic RV tended to have higher rates of arrhythmia, pacemaker implantation, and repeat intervention than those with TOF.

3.4.3 Study limitations

The major limitation of this study is the very heterogeneous nature of the cohorts that were reviewed. Despite the same underlying diagnosis, there may be several subtypes within that condition and a number of different operations which can be performed at the time of initial surgical correction. Patients vary in terms of the presence or absence of other associated congenital abnormalities and genetic syndromes, and they may or may not have had a palliative shunt prior to corrective surgery. Whilst all of these parameters can be reported, it is impossible to adjust for them in a meaningful way when performing a standard survival analysis (using time from surgical repair as the baseline) due to the relatively small numbers each subgroup. Another important limitation is that the studies reporting outcomes for the longest period of follow up will inevitably reflect the results of surgery performed several decades ago. This means that the survival data will be less relevant to those patients operated upon in a more contemporary era, and perhaps wider reporting of SMRs could avoid this problem. Other important limitations of this study include the lack of reporting of specific morbidity outcomes for each population, a paucity of functional data, the variation in the definition of a particular adverse outcome between different papers (for example one paper may have defined VT as sustained VT requiring treatment whereas another may have included patients experiencing brief runs of asymptomatic VT identified incidentally on an ambulatory ECG), and wide variations in the proportion of patients for whom morbidity status could be ascertained (sometimes data regarding the presence or absence of arrhythmia was available for less than half of the original cohort). Finally, there was also a degree of selection bias in that by only including papers which included reporting of mortality, it is possible that papers which looked exclusively at a particular morbidity outcome for each diagnosis, for example the need for PVR in TOF, were missed. However this would have added greatly to the complexity of what was already a difficult literature search.

3.4.4 Conclusions

Survival is higher in patients with repaired TOF than those with a systemic RV. Only one paper used SMR to assess survival; this valuable technique is thus under-utilised. Morbidity appears to be high, however there were major differences in the way outcomes were reported, and some outcomes appeared to be significantly under-reported.

Chapter 4 Long term outcomes in the systemic right ventricle: adult survivors of atrial switch surgery for transposition of the great arteries, and adults with congenitally corrected transposition of the great arteries

4.1 Introduction

The morphological right ventricle supports the systemic circulation in those individuals with congenitally corrected transposition of the great arteries (CCTGA), and those who have survived atrial switch surgery (the Mustard or Senning procedures) for complete transposition of the great arteries (TGA-atrial switch). Whilst atrial switch is no longer the gold standard for management of TGA, having been superseded by the arterial switch operation in the late 1980s, many adult patients with TGA will have undergone the older procedure.

Patients with either diagnosis are at risk of a host of complications associated with the systemic RV, including premature heart failure, regurgitation through the systemic atrioventricular valve, atrioventricular block and a need for permanent pacing, tachyarrhythmia, and sudden cardiac death (Warnes, 2006).

Contemporary outcomes in patients with an SRV are poorly defined globally, and not at all in Scotland. As outlined in chapter 3, most published cohort studies of patients with TGA-atrial switch focus disproportionately upon early postoperative mortality, and the majority provide follow-up to only 20 years. Patients with CCTGA are the subject of only a handful of cohort studies. The aim of this study was to establish the natural history of the SRV in adult survivors of both conditions in a national population which had not previously been assessed.

Of note some of the work in this chapter formed the basis for a peer-reviewed publication in 2013 (Dobson et al., 2013). Table 4.1, Figure 4.1, and sections 4.3.4, 4.3.6 and 4.3.7 include some of the content of this paper in a modified form. All of this was exclusively my own work, and I have obtained the appropriate permission from the publisher.[9]

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4.2 Methods

Retrospective analysis of 129 individuals aged >18 years with a diagnosis of TGA-atrial switch or CCTGA. Data were collected and anonymised for each individual from the electronic case records database as outlined in chapter 2. Follow-up was from the age of 18 years, and patients were censored at the time of their last clinic review, date of death, or date of cardiac transplant. Patients would also have been censored if they underwent surgery to restore the morphological LV to the systemic circulation however I identified no patients who underwent such a procedure after the age of 18 years. Patient-specific timelines were then constructed to formulate survival curves for time to death, tachyarrhythmia, pacemaker insertion, and surgical or catheter intervention. During each timeline patients underwent regular clinic review which allowed assessment of NYHA and symptom status as well as ascertainment of the occurrence of any clinical events e.g. a hospital admission due to tachyarrhythmia.

For the purposes of this analysis tachyarrhythmia was defined as any supraventricular or ventricular tachyarrhythmia captured on ambulatory or 12-lead ECG recording that was clinically significant i.e. it caused symptoms or required treatment. Cases were excluded if tachyarrhythmia occurred exclusively within 30 days of cardiac surgery. Reintervention was defined as any cardiac surgical or percutaneous cardiac procedure occurring after baseline. Pacemaker insertion was defined as any permanent epicardial or endocardial pacemaker, and included those with cardiac resynchronisation therapy.

Raw data were described and analysed as outlined in chapter 2. Chi square test using linear-by-linear association was used to assess the relationship between severity of tricuspid regurgitation and severity of SRV impairment. The cumulative probability of survival was estimated using the Kaplan Meier and life table method, and differences between groups were evaluated via the log rank test. Survival analysis was performed for the following outcomes: death or transplant, atrial tachyarrhythmia, surgical intervention after baseline, and pacemaker therapy.

Cox proportional hazards models were used to identify predictors for death or cardiac transplant. Standardised mortality ratios for the cohort as a whole as

well as the subgroups of patients with TGA-atrial switch and CCTGA were calculated using the method described by Finkelstein and colleagues (Finkelstein et al., 2003). Cumulative expected mortality was calculated using vital events reference tables published by the National Records of Scotland showing death rates for the year 2011 for age-matched controls (NRS, 2011), and then summating the standardised mortality rates for each year of follow-up for each patient from age 18. All analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, New York).

4.3 Results

4.3.1 Baseline characteristics

There were 97 adult survivors of atrial switch surgery for TGA atrial switch and 32 patients with CCTGA, with a median age of 29 and 33 years respectively at time of latest follow-up. Characteristics are outlined in Table 4.1. There were more male than female patients in both diagnostic groups. Most of the atrial switch patients had undergone a Mustard repair, only 17% had undergone a Senning procedure.

The pattern of surgical intervention in the CCTGA group was more variable and is outlined in Figure 4.1. When surgical repair was performed this was physiological and directed at the correction of haemodynamically significant underlying lesions such as a VSD. No patients in this cohort underwent a double switch (anatomical repair).

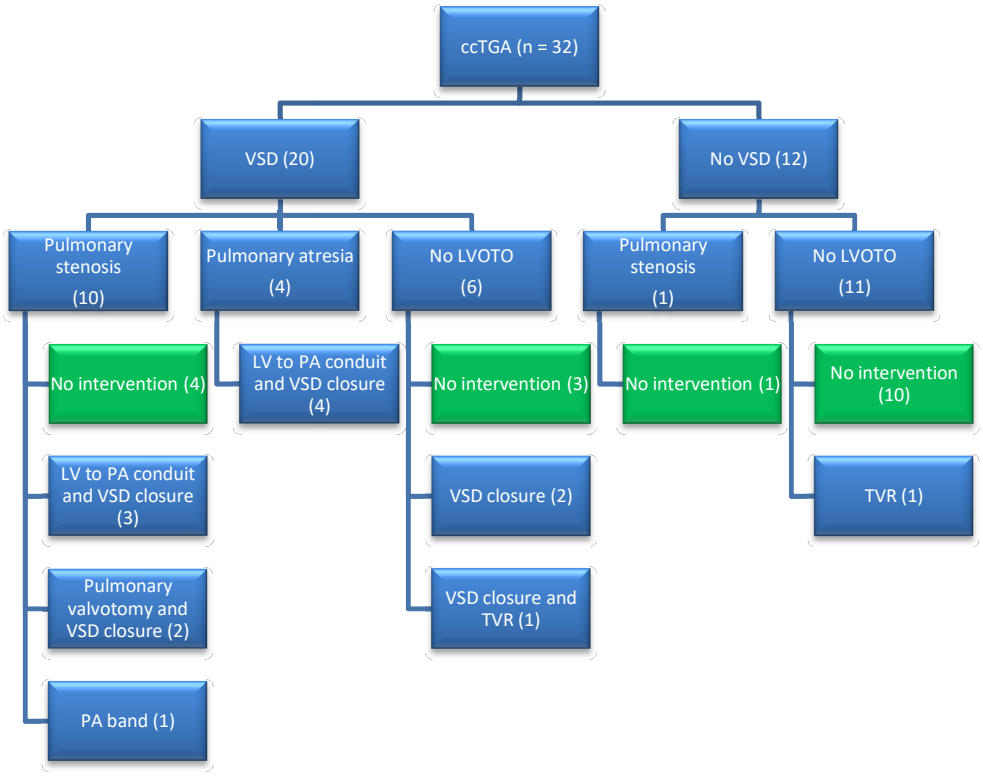
Table 4-1 Baseline characteristics, morbidity and outcomes in patients with TGA-atrial switch and CCTGA

	TGA-atrial switch	CCTGA	P-value
N	97	32	
Female (%)	33 (34)	12 (37.5)	
Age (years)			
Median (IQR)	29 (25 – 32)	33 (23 – 46)	0.331
Years of follow-up from age 18			
Median (IQR)	10.8 (6.5 – 13.9)	13.2 (5.1 – 28.2)	0.256
Atrial switch operation (%)			
Mustard	80 (82.5)	N/A	
Senning	17 (17.5)	N/A	
Palliative shunt (%)	4 (6.2)	6 (18.8)	0.140
Coexistent lesions (%)			
Dextrocardia	0	7 (21.9)	<0.001
VSD	10 (10.3)	20 (62.5)	<0.001
Pulmonary stenosis	13 (13.4)	10 (31.3)	0.002
Pulmonary atresia	0	4 (12.5)	<0.001
Ebstein	0	1 (3.1)	0.08
Coarctation	3 (3.1)	0	0.314
Prior tachyarrhythmia at baseline (%)	7 (7.2)	0	
Prior PPM at baseline (%)	10 (10.3)	6 (18.8)	
Prior baffle reintervention at baseline (%)	17 (17.5)	N/A	
NYHA class			
I	65 (67)	21 (65.6)	
II	20 (20.6)	5 (15.6)	
III	1 (1)	1 (3.1)	
IV	2 (2.1)	1 (3.1)	
Missing	9 (9.3)	4 (12.5)	0.776
Systemic tricuspid regurgitation (echo)			
Nil	42 (43.3)	2 (6.3)	
Mild	40 (41.2)	12 (37.5)	
Moderate	13 (13.4)	9 (28.1)	
Severe	0	3 (9.4)	
Replaced	0	2 (6.3)	
Missing	2 (2.1)	4 (12.5)	<0.001

	TGA-atrial switch	CCTGA	P-value
Systemic RV impairment (echo)			
Nil	26 (26.8)	10 (31.3)	
Mild	32 (33)	13 (40.6)	
Moderate	18 (18.6)	5 (15.6)	
Severe	6 (6.2)	1 (3.1)	
Missing	15 (15.5)	3 (9.4)	0.809
Number of patients assessed by MRI (%)	22 (22.7)	5 (10.6)	
Cardiac MRI data (mean ± SD)			
SRV EDVi ml/m2	111 ± 8.8	127 ± 18.3	0.442
SRV EF %	54 ± 2.3	61 ± 2.6	0.190
LV EDVi ml/m2	79 ± 6.0	92 ± 11.0	0.337
LV EF %	60 ± 2.6	66 ± 3.3	0.220
Number of patients assessed by CPET (%)	33 (34)	17 (53.1)	
CPET (mean ± SD)			
Peak VO_2 ml/kg/min			
Peak VO_2 % predicted	25 ± 1.2 68.5 ± 2.8	25 ± 2.1 62.4 ± 4.3	0.937 0.225
Heart rate reserve (bpm)	29 ± 3.7	35 ± 5.9	0.374
VE/VCO2 ratio	36 ± 1.1	34 ± 1.9	0.196
Female patients with at least one successful pregnancy	7	3	0.787
N (%) PA band	13 (13)	1 (3)	
Median age (IQR)	20.6 (18.0-25.8)	14.2 (N/A)	
Median follow up years post PAB (IQR)	5.8 (4.3-7.2)	6.4 (N/A)	
Median velocity m/s (IQR)	3.4 (2.3-3.9)	3.3 (N/A)	
Median LV:SRV pressure	0.40 (0.16-0.47)	0.32 (N/A)	0.124
Medication[10] (%)			
ACEI or A2RB	15 (15.5)	6 (18.8)	0.662
Betablocker	13 (13.4)	4 (12.5)	0.896
MRA	1 (1)	1 (3.1)	0.406
Digoxin	2 (2.1)	0	0.413
Amiodarone	3 (3.1)	1 (3.1)	0.993
Warfarin	10 (10.3)	3 (9.4)	0.879

[10] ACEI = Angiotensin Converting Enzyme Inhibitor, A2RB = Angiotensin 2 Receptor Blocker, MRA = Mineralocorticoid Receptor Antagonist

Figure 4-1 Coexistent lesions and initial surgery in 32 CCTGA patients



4.3.2 Mortality

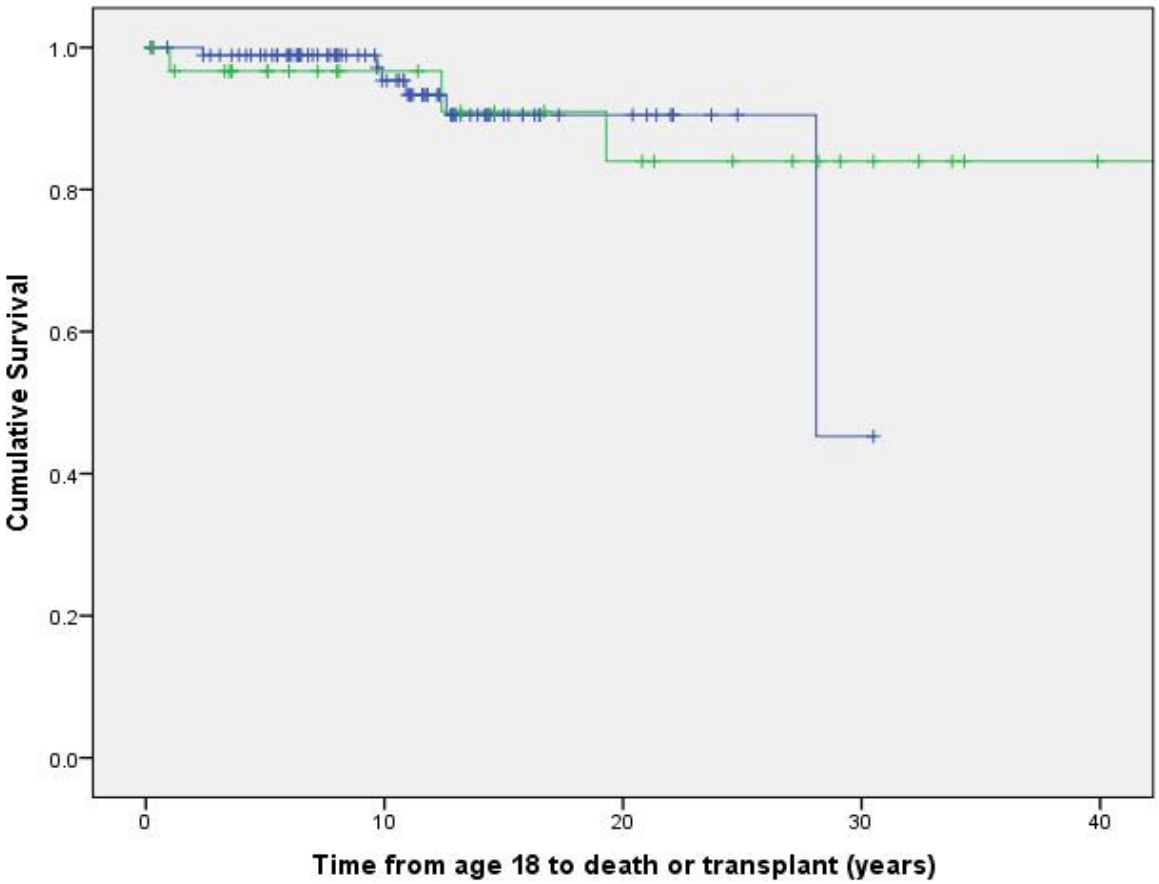
Outcomes and cumulative survival for the 129 patients who reached the age of 18 years are outlined in Table 4.2 and Figure 4.2. There was no significant difference in survival between those patients who were TGA-atrial switch and CCTGA (p = 0.833). For patients with a diagnosis of TGA-atrial switch, cumulative survival from the baseline of 18 years of age from either death or cardiac transplantation was 0.93 +/- 0.03 at 10 years, 0.90 +/- 0.04 at 20 years, and 0.45 +/- 0.32 at 30 years. For patients with CCTGA the corresponding values were 0.97 +/- 0.03 at 10 years, 0.84 +/- 0.09 at 20 years, and 0.84 +/- 0.09 at 30 years. There was no significant difference in survival between Mustard and Senning patients (p = 0.625), although after 27 years of follow-up graphic trends favoured the Senning patients. A univariate analysis with a Cox proportional hazards model was performed to establish risk factors for death or transplant (Table 4.2). A higher NYHA class at baseline or the presence of severe systemic RV impairment were associated with a significant hazard ratio, although the confidence intervals were wide.

The standardised mortality ratio was calculated for TGA-atrial switch and CCTGA, as well as for the SRV cohort as a whole, with results outlined in Table 4.3 and Figure 4.3. There was an overall SMR of 4.18 for the whole cohort, with mortality being lower in the CCTGA cohort versus the TGA atrial switch cohort at 2.54 versus 5.62, although clearly there is considerable overlap between the 95% confidence intervals.

Table 4-2 Clinical outcomes over the follow-up period

	TGA-atrial switch	CCTGA
Status (N %)		
Ongoing follow-up	86 (88.6)	28 (87.5)
Lost to follow-up	5 (5.2)	1 (3.1)
Died or transplanted	6 (6.2)	3 (9.4)
Tachyarrhythmia (%)	12 (12.4)	4 (12.5)
Reintervention (%)	19 (19.6)	3 (9.4)
Pacemaker (%)	6 (6.2)	6 (18.8)
AICD (%)	0	0
CRT (%)	3 (3.1)	1 (3.1)

Figure 4-2 Cumulative survival from age 18 years for patients post atrial switch surgery for TGA and patients with a diagnosis of CCTGA



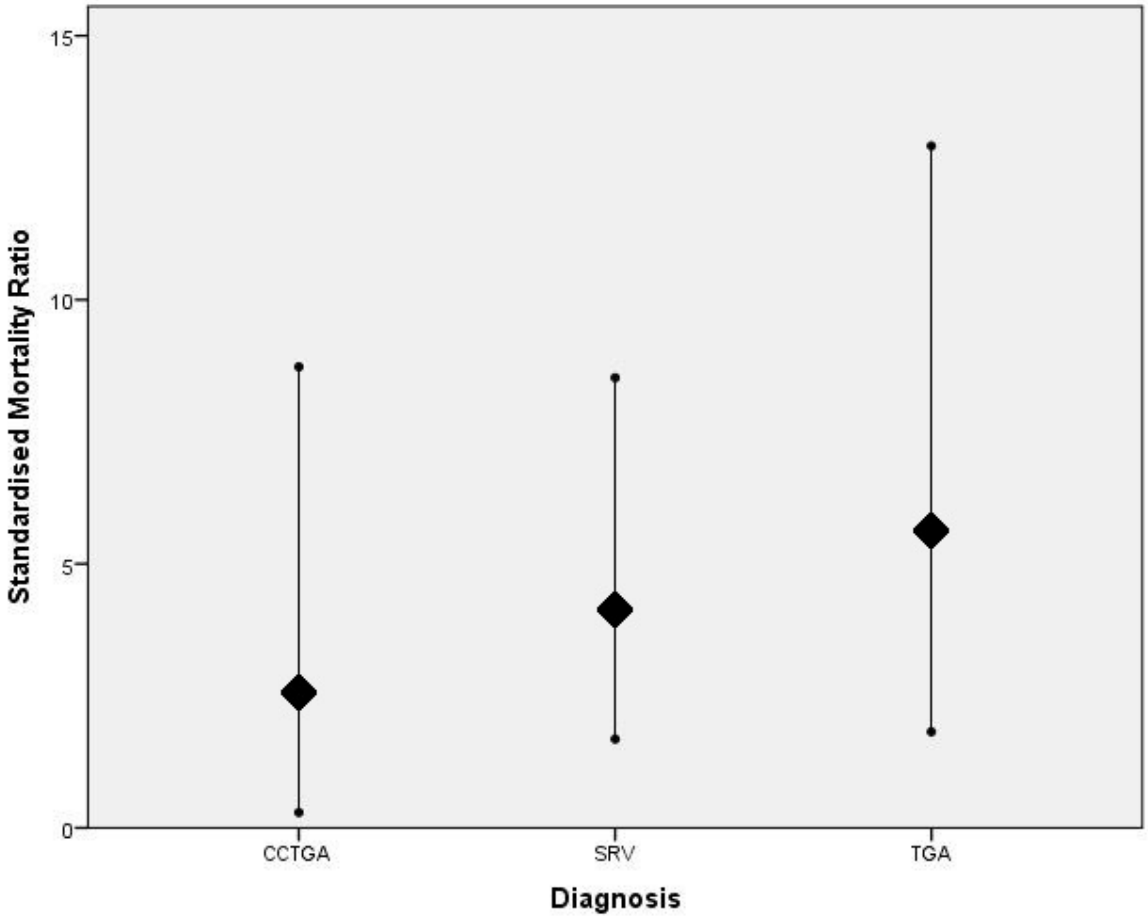
95	52	10	1	-
31	18	12	6	1

Atrial switch
ccTGA

Table 4-3 Univariate analysis for death or cardiac transplant in adult survivors with a systemic RV

Variable	Hazard ratio	95% CI	P
Gender (male)	2.28	0.47, 11.03	0.303
Shunt	1.54	0.18, 12.89	0.692
Initial VSD	2.37	0.62, 9.08	0.208
Pacemaker before baseline	2.39	0.49, 11.61	0.281
Reintervention before baseline	3.65	0.96, 13.87	0.057
NYHA class 2 or higher at baseline	14.39	1.67, 124.06	0.015
At least severe SRV impairment at baseline	10.57	2.13, 52.58	0.004
At least severe TR at baseline	2.33	0.28, 19.28	0.432

Figure 4-3 Standardised mortality ratio with upper and lower 95% confidence intervals for TGA atrial switch, CCTGA, and the systemic RV cohort as a whole



	CCTGA	All SRV	TGA
Expected deaths	0.787	1.676	0.889
Observed deaths	2	7	5
SMR	2.541	4.177	5.624
Lower 95% CI	0.291	1.68	1.82
Upper 95% CI	8.731	8.523	12.915

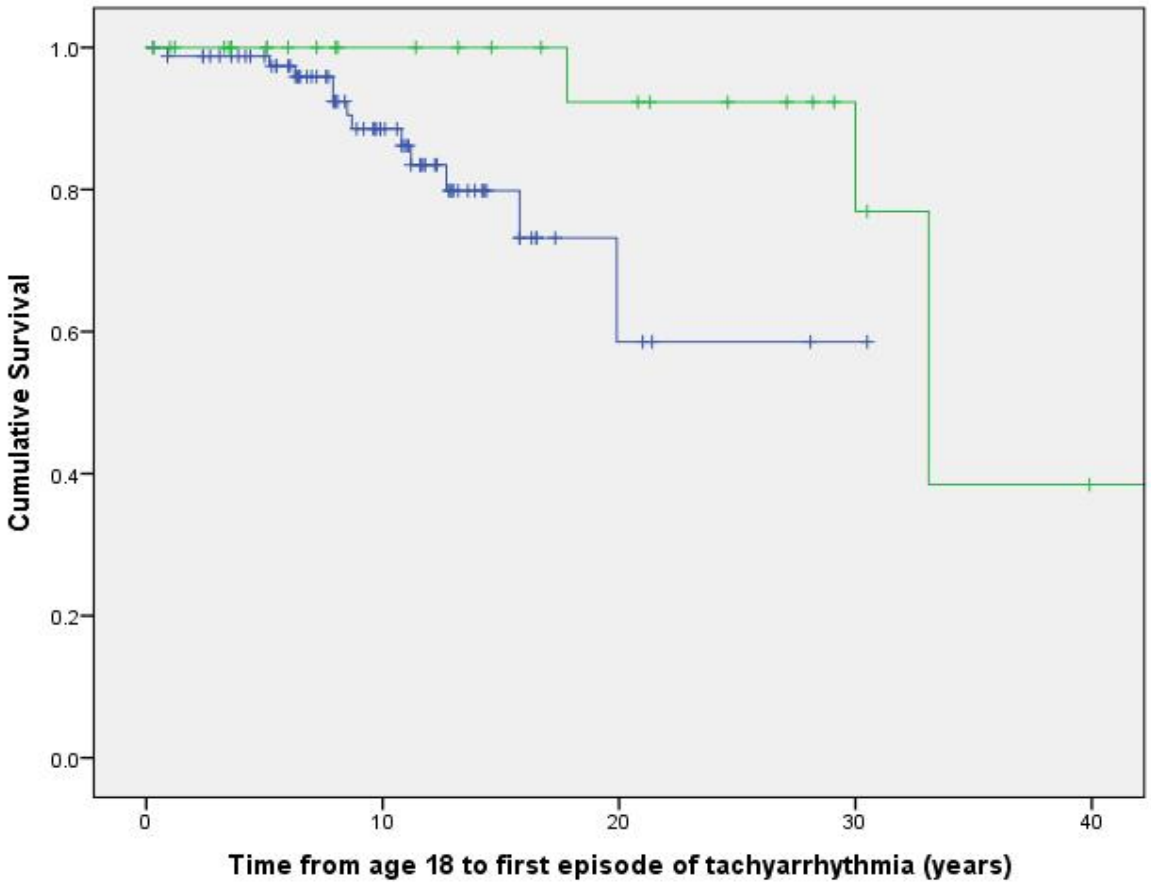
4.3.3 Morbidity

The survival analysis for the three major adverse outcomes of arrhythmia, catheter or surgical intervention, or pacemaker insertion, is outlined below.

4.3.3.1 Arrhythmia

As outlined in Figure 4.4, patients with CCTGA demonstrate low arrhythmia burden with cumulative survival from tachyarrhythmia being 1.00 +/- 0, 0.93 +/- 0.07 and 0.76 +/- 0.16 at 10, 20 and 30 years from baseline. This was significantly better than atrial switch patients, who experienced survival of 0.83 +/- 0.05, 0.58 +/- 0.15 and 0.58 +/- 0.15 at 10, 20 and 30 years (p = 0.028). All documented tachyarrhythmias were supraventricular: there were no recorded instances of ventricular tachycardia causing symptoms or requiring treatment (although of course the four sudden deaths that occurred may have been due to either ventricular tachycardia or fibrillation).

Figure 4-4 Cumulative survival from arrhythmia for patients post atrial switch surgery for TGA and patients with a diagnosis of CCTGA



83	39	4	1	-
30	17	12	6	1

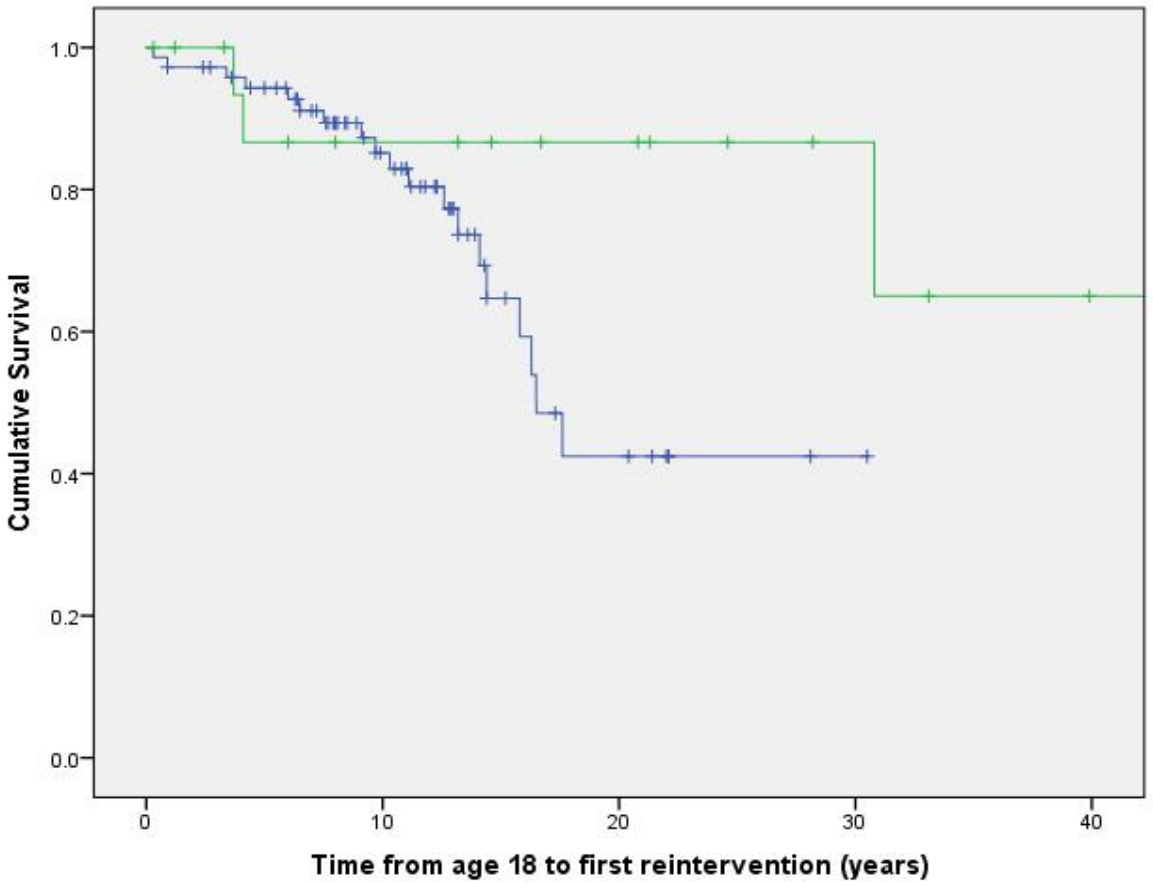
Atrial switch
ccTGA

4.3.3.2 Intervention

Figure 4.5 demonstrates freedom from intervention after baseline of 18. This was 0.80 +/- 0.06, 0.42 +/- 0.11, and 0.42 +/- 0.11 at 10, 20 and 30 years of follow-up for TGA-atrial switch. For the CCTGA patients the corresponding values were 0.87 +/- 0.09, 0.87 +/- 0.09, and 0.65 +/-0.20 (p = 0.056).

In the atrial switch group PA banding (11 patients) and baffle revision (8 patients) accounted for all of the reintervention performed in adulthood. In the CCTGA group intervention was due to TVR in two patients, and closure of a residual VSD in one.

Figure 4-5 Cumulative survival from reintervention for patients post atrial switch surgery for TGA and patients with a diagnosis of CCTGA



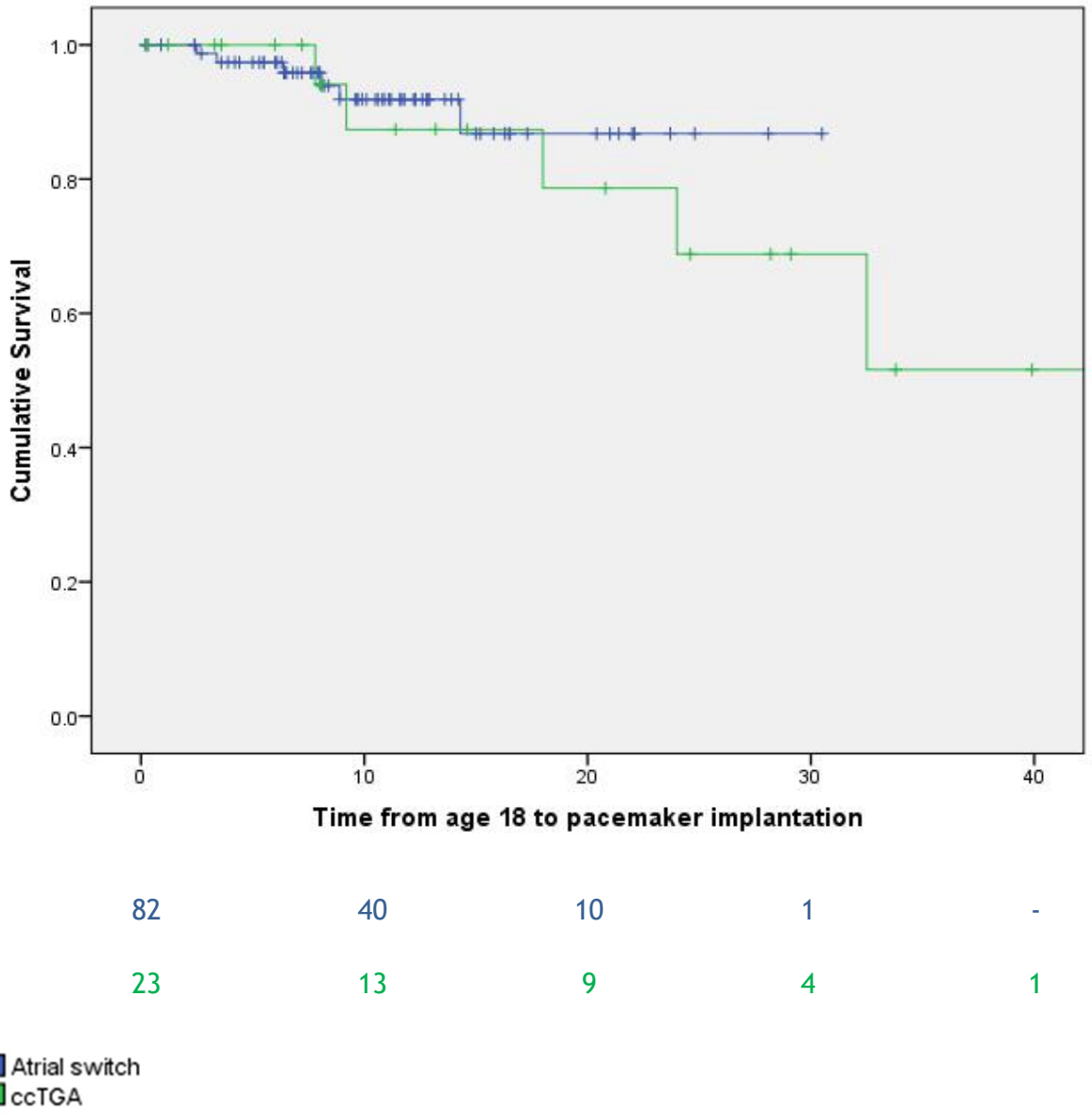
72	38	7	1	-
18	11	8	4	1

Atrial switch
ccTGA

4.3.3.3 Pacemaker insertion

There was no significant difference between the two groups for cumulative survival from pacemaker insertion (p = 0.564), although graphic trends suggest this is more frequent in the CCTGA group (Figure 4.6). Freedom from pacemaker insertion at 10, 20 and 30 years from baseline was 0.92 +/- 0.04, 0.86 +/- 0.06, and 0.86 +/- 0.06 for TGA-atrial switch, and 0.88 +/- 0.08, 0.79 +/- 0.11, and 0.69 +/-0.14 for CCTGA.

Figure 4-6 Cumulative survival from pacemaker implantation for patients post atrial switch surgery for TGA and patients with a diagnosis of CCTGA



4.3.4 Cardiac function and exercise performance

By the end of the follow-up period the majority of patients enjoyed good functional status as assessed by NYHA class, with 98% of atrial switch patients for whom data was available (85/87), and 93% of CCTGA patients (26/28) being in either NYHA class I or II. By transthoracic echo most patients at latest follow-up had no or only mild impairment of SRV function, and no or mild tricuspid regurgitation. More detailed assessment of ventricular function and functional capacity was performed by means of cardiac MRI and cardiopulmonary exercise testing. From cardiac MRI in 27 patients the mean ejection fraction of the SRV was lower in the TGA-atrial switch patients than those with CCTGA (54% versus 61%), although this was not statistically significant. There was no clear relationship between time from baseline and ventricular volumes or ejection fraction. Mean peak oxygen uptake for 50 patients across both groups was 25ml/kg/min, lower than would be expected based on the predicted values for healthy subjects of the same age, height and gender. There was no statistically significant difference between peak oxygen uptake, heart rate reserve and VE/VCO2 ratio between the two cohorts.

4.3.5 Medication

Relatively few patients were prescribed cardiac medication; fewer than 1 in 5 patients were prescribed an ACE inhibitor or Angiotensin 2 receptor blocker which was the most commonly prescribed class of medication, generally in patients with documented systemic ventricular systolic dysfunction. There were 13 patients who were prescribed Warfarin. The indication for this was AF or atrial flutter in 11 patients, the other 2 patients (both CCTGA) had a mechanical tricuspid valve replacement. There was no significant difference in prescribing of each class of medication between the two cohorts.

4.3.6 Analysis of the effect of pulmonary artery banding

Thirteen TGA-atrial switch patients underwent a PA band for treatment of SRV dysfunction, one of whom later died suddenly three years post-banding. For 11 of the 12 surviving patients (1 patient had no up-to-date imaging) the median follow-up period was 5.8 years. The mean gradient through the PA band was 46.2mmHg, and the median SRV to LV peak systolic pressure ratio was 0.4. SRV function was either normal or mildly impaired in 9 patients, moderately impaired in 1 and severely impaired in 1. There was no or mild systemic tricuspid regurgitation in 6/11 patients, with 4 patients having moderate and 1 severe regurgitation. There was only one CCTGA patient who underwent a PA band. None of the PA banding patients were ever deemed suitable for a subsequent double-switch. There was no significant difference in survival between the 14 patients across both groups who underwent PA banding compared to the 115 who did not (p = 0.659).

4.3.7 Systemic RV impairment and tricuspid regurgitation

The relationship between systemic RV impairment and severity of TR was assessed, although the two patients who underwent TVR were excluded from the analysis. The chi-square value for linear-by-linear association between SRV impairment and severity of TR was 10.064 (p = 0.002), implying a statistically significant correlation between the two variables

4.4 Discussion

4.4.1 Mortality

The cumulative probability of survival after 20 years of adult life (i.e. from the baseline of 18 years) was estimated at 90% for TGA-atrial switch and 84% for CCTGA, however the difference was not significant. When compared to the general Scottish population mortality as assessed by SMR is worse for both groups. Risk factors for mortality appeared to be the presence of severe systemic RV impairment or symptoms of heart failure (as evidenced by NYHA class) at age 18. Risk factors which are relevant at birth or in early childhood e.g. the presence of an initial VSD or requirement for a palliative shunt, appear to be less important by the time patients have survived to the age of 18 years.

Regarding the modality of death, of the seven deaths after 18 years of follow-up four were sudden, and two were secondary to heart failure. This is similar to other studies, where sudden death and heart failure accounted for the majority of late deaths (Lange et al., 2006, Moons et al., 2004, Lim et al., 2010). Therefore strategies to identify those at risk of sudden cardiac death, and to manage systemic right ventricular dysfunction, will be crucial to improving outcomes in these patients.

Direct comparison of cumulative survival from baseline between this cohort of adult survivors to those of other centres is difficult. Chapter 3 describes how almost all papers include early postoperative and paediatric mortality which is not relevant to the field of ACHD and the population I studied. However, it is possible to compare the SMR, and in the one paper that reported this the authors documented an SMR of 4.88 (Diller et al., 2015). The SMR of 4.18 for all of our systemic RV survivors was therefore similar. A small variation in the SMR would be expected: with relatively low numbers of patients in both cohorts (compared to e.g. studies of patients with ischaemic heart disease or heart failure), small variations in the absolute number of deaths will have a significant effect on the SMR. Furthermore it should be remembered that it was not possible to adjust for baseline differences such as age at repair, or other comorbidity.

The above all leads to the question of how survival might be improved for patients with a systemic RV. For those patients with TGA, the most elegant solution is simply to avoid having a systemic RV in the first place, and since the 1980s this strategy has been almost universally adopted with the arterial switch operation. Whilst the procedure has its own collection of potential complications, such as problems with flow at the site of the coronary anastomoses and neo-aortic and neo-pulmonary regurgitation, certainly the available data suggests much lower mortality, rates of reintervention and arrhythmia - at least into early adulthood (Lim et al., 2013, Kempny et al., 2013, Tobler et al., 2010, Gorler et al., 2011). It remains to be seen whether the adaptation of an early aggressive strategy for patients with CCTGA, by which the morphological LV is connected to the systemic circulation, results in improved survival into adulthood. However, Brawn reports survival of 90% at up to 9 years in a cohort of 56 patients with CCTGA who underwent both types of double switch (atrial and arterial switch as well as Senning-Rastelli), with an early mortality of 5.6% (Brawn, 2005). Ly and colleagues reported 100% survival at 60 months in 20 complex CCTGA patients who underwent the Senning-Rastelli procedure (Ly et al., 2009). Shinoka and colleagues reported 74.5% survival at 15 years in 15 patients undergoing atrial-arterial switch, and 80% survival at 16 years in 69 patients undergoing the Senning-Rastelli procedure (Shin'oka et al., 2007). However, with longer follow-up of up to 10 years in 65 patients poorer survival was reported in the Senning-Rastelli group compared to the atrial-arterial switch (Gaies et al., 2009) Although these results are encouraging, the prognosis to adulthood and beyond remains to be established.

4.4.2 Morbidity

4.4.2.1 Freedom from arrhythmia, reintervention, and pacemaker insertion

Atrial tachyarrhythmia was common in patients with a systemic RV. However, it occurred significantly earlier in survivors of atrial switch surgery. This may be due to the extensive atrial scar tissue and potential for macro re-entry circuits. The relatively high prevalence of arrhythmia in both cohorts at 40 years is cause for concern: there are few options for pharmacological management, and invasive electrophysiological studies and ablation are rendered challenging by the abnormal anatomy.

There was relatively high attrition from reintervention in both cohorts, with cumulative probability of freedom from reintervention being 57% in atrial switch and 53% in CCTGA patients at 30 years. In the TGA-atrial switch cohort the relatively high rate of baffle reintervention may be explained by the fact most patients had undergone a Mustard repair, and this technique is associated with a higher incidence of baffle obstruction than the Senning repair (Khairy et al., 2004). There have been no systemic AV valve replacements, and there were no adult patients who underwent a subsequent arterial switch procedure. In the CCTGA cohort physiological repair of coexistent cardiac lesions accounted for most intervention. Most surgery was performed during childhood, with intervention after 18 years being far less common than intervention prior to 18 years.

Both the TGA atrial switch group and CCTGA group had relatively high rates of pacemaker insertion. Although not statistically significant there was a trend towards this being more common in the CCTGA group. One possible reason for this is that the prevalence of VSD was much higher in the CCTGA group (62.5% versus 10.3%), and surgical repair of this can often result in AV block due to the proximity of the VSD to the His-Purkinje system. Furthermore the anatomy of the AV node and His-Purkinje system in CCTGA can be highly variable (Warnes, 2006).

4.4.2.2 Current functional status, systemic RV impairment and tricuspid regurgitation, and the management of heart failure

In keeping with the other cohort studies described previously both atrial switch and CCTGA patients continue to enjoy good functional status. Formal cardiopulmonary exercise testing demonstrated reduced maximum oxygen uptake compared to peak predicted, with mean peak VO_2 being 25ml/kg/min for both atrial switch and CCTGA patients. This is in keeping with previous studies assessing exercise performance in patients with a systemic RV (Hechter et al., 2001, Fredriksen et al., 2001). There was also evidence of an abnormally high heart rate reserve and increased VE/VCO2 ratio, again in keeping with previous work (Diller et al., 2006, Diller et al., 2005, Diller et al., 2009)

At the time this study was performed the vast majority of patients in both cohorts exhibited insignificant or mild SRV impairment and TR. However severe SRV impairment not surprisingly was a significant risk factor for death, there was a clear correlation between severity of SRV impairment and severity of TR - in keeping with the published literature elsewhere (Warnes, 2006, Scherptong et al., 2009) - and as described previously most patients who died, died from heart failure. Within the cohort there was no difference between mean SRV function (as measured by ejection fraction from cardiac MRI) in the patients with CCTGA and those post TGA-atrial switch (p = 0.190).

Approaches to management of SRV failure are controversial. Early intervention to a regurgitant systemic tricuspid valve has been advocated in view of its correlation with SRV failure. However results are poor in patients who have pre-existing SRV impairment, and therefore this is a prophylactic strategy rather than a valid treatment option for those patients who already have a failing SRV. Furthermore long-term prognostic data is lacking, and there are no large scale case-control studies (Scherptong et al., 2009, Mongeon et al., 2011, van Son et al., 1995). Generally tricuspid valve replacement rather than repair is advocated if the RV is planned to remain in the systemic circulation, but this is challenging even in structurally normal hearts (Scherptong et al., 2009, Acar et al., 1998). The atrial-arterial double switch or Senning-Rastelli procedures – if performed early enough in a centre with sufficient expertise – eliminate the problem of systemic RV

dysfunction and indeed tricuspid regurgitation. However results are unfavourable in adult patients (Benzaquen et al., 2004, Metton et al., 2010, Brawn, 2005).

It is theoretically possible to train the LV through the placement of a PA band and use this effect as a treatment in its own right: higher LV pressures avoid septal dyskinesis which exacerbates SRV impairment, and could prevent tricuspid annular dilatation, thus lessening the severity of tricuspid regurgitation. From the small sub-cohort in our group of patients undergoing PA banding certainly most maintained normal or only mildly impaired SRV function. However there was no overall improvement in the degree of tricuspid regurgitation, where pre-PA band data existed. This is confirmed by two relatively large studies of 39 and 20 patients respectively (Winlaw et al., 2005, Cools et al., 2012), although some older, smaller trials suggest a modest beneficial effect on tricuspid regurgitation (Acar et al., 1998, van Son et al., 1996, Langley et al., 2003). The biggest problem appears to be the development of subpulmonary LV dysfunction (Langley et al., 2003, Winlaw et al., 2005).

Another potential option includes the use of classes of medication more usually employed in patients with left ventricular systolic dysfunction in structurally normal hearts. However few patients in this cohort were prescribed these, and this almost certainly reflects the complete absence of randomised control trials assessing the survival benefit of beta-blockers and renin-angiotensin system blocking drugs in patients with an SRV. The decision to prescribe such medication is therefore made on a case-by-case basis, where the theoretical benefits of prescribing for systemic RV impairment are balanced against the risks and side effects, and the patient is made fully aware of the lack of evidence.

Regarding device therapy only a handful of patients underwent cardiac resynchronisation therapy; again there is a lack of evidence for this intervention in patients with a systemic RV, and it may also be associated with the development of dysfunction of the subpulmonary left ventricle (Dubin et al., 2005, Kiesewetter et al., 2008). Interestingly there were no AICD insertions. Although there is a high risk of sudden cardiac death there are no established guidelines for formal risk assessment, and AICD insertion in patients with a systemic RV is based on a

“common sense” approach, extrapolated from studies in other populations (Baumgartner et al., 2010).

Finally cardiac transplantation is an effective treatment for end stage heart failure in this population, however there is the problem of limited donor organ availability in many parts of the world, and the additional risk conferred by the complexity of abnormal anatomy and previous surgical intervention. Despite its efficacy, transplantation is sadly likely to be a realistic option for only a minority of patients.

4.4.3 Limitations

As with all retrospective studies our study is limited by those patients lost to follow up both before and after the age of 18 years, although fortunately these numbers were relatively small. Another group of patients missing from the analysis are those with asymptomatic uncomplicated CCTGA, who either have yet to present to medical services or are not recognised as having cardiac anatomy consistent with CCTGA. However, based on our own experience very few patients with CCTGA present after the age of 18 years, and clearly all longitudinal cohort studies of CCTGA have the same problem. The analysis of SMR, whilst useful, must always be interpreted with caution when low numbers of patients means that individual deaths can have a large impact on the final calculation.

Functional data regarding ventricular function as assessed by cardiac MRI is missing for a relatively large number of patients. Some patients had undergone a scan without formal volumetric analysis of ventricular function being performed (e.g. due to arrhythmia artefact), some may have been genuinely intolerant of the MRI scanner, and for others MRI was contraindicated owing to the presence of a pacemaker - none of the cardiac devices for our patients at the time the study was performed were MRI conditional. This will hopefully become less of an issue in the future as it now appears safe to scan even non-MRI conditional devices at 1.5 Tesla (Russo et al., 2017), although the problem of metallic artefact from leads and generators degrading image quality will be more difficult to address. There will of course be other reasons, which may include factors as mundane as administrative error, patient non attendance and claustrophobia. However it should be possible to improve upon all of these. Similar issues apply to CPET. Whilst some patients may genuinely be unable to exercise, again this will not apply for the majority, and although the percentage of patients who actually underwent CPET was higher than for MRI this could also be improved.

4.4.4 Conclusion

Overall mortality in adult survivors of atrial switch surgery for TGA and CCTGA is similar, but is still higher than age and sex matched controls in the general population. This suggests that for the majority of patients it is actually the systemic RV itself, rather than the nature of any prior surgery, that determines long term prognosis. Systemic RV dysfunction and a higher NYHA class increase overall hazard for death or transplant, and most deaths are due to heart failure.

Morbidity is substantial, with a high incidence of tachyarrhythmia, surgical or catheter intervention, and pacemaker insertion. Tachyarrhythmia is a particular problem for TGA-switch patients, occurring significantly earlier than in those with CCTGA. More reassuringly however significant SRV dysfunction, TR, and functional impairment are relatively rare at up to 40 years of age.

Risk stratification for sudden cardiac death, and the identification of suitable strategies to manage SRV impairment, will be key to improving survival in the future. In view of the high morbidity associated with SRV impairment any corrective surgery which can avoid the RV having to support a systemic circulation is inherently attractive, and by performing this surgery in early life one may achieve a more favourable prognosis to early adulthood and beyond. It will be interesting to see whether, similar to the transition from a strategy of atrial switch surgery to arterial switch surgery for TGA, in those CCTGA patients who require surgical repair in childhood, there will be a paradigm shift to an early anatomical repair. For the asymptomatic patient with uncomplicated CCTGA however, it is likely that there will always be a dilemma between this and conservative management.

Chapter 5 Long term outcomes in a national cohort of adult survivors of Tetralogy of Fallot

5.1 Introduction

Survival for children with Tetralogy of Fallot (TOF) has improved dramatically, to the extent that in modern cohorts over 90% of patients can expect to survive to adulthood (Ide et al., 2009, Okita et al., 1995, Park et al., 2010). These survivors progress to make up a significant and increasing proportion of the group of patients cared for by adult congenital cardiac services. However, the long term mortality, morbidity and functional status experienced by these patients after adulthood is less well defined, and despite high rates of interventions such as pulmonary valve replacement there is no single therapy that has yet been shown to definitively modify prognosis in this group. Most papers outlining the long term prognosis for patients with TOF have performed survival analysis from time of initial surgical correction (Hamada et al., 2002, Nollert et al., 1997, Park et al., 2010, Okita et al., 1995, Jonsson and Ivert, 1995, Hickey et al., 2009, Lindberg et al., 2011, Chiu et al., 2012), and therefore their results and conclusions are heavily influenced by early mortality in infancy (i.e. perioperative mortality at the time of initial repair), and because they typically analyse all patients operated on at a single institution over several decades, there is a disproportionate "birth cohort" effect, with the estimates of survival for the longest specified time period based on patients operated upon in the 1960s and 1970s. This means that any analysis is likely to underestimate survival for those patients with TOF who have already survived to adulthood, and will be of less relevance to those involved in the care of adult survivors of CHD. Furthermore, when identifying potential models for late mortality and morbidity there is a disproportionate focus on baseline parameters derived from the timing of the initial repair surgery (e.g. aortic crossclamp time), and comparatively little information regarding measures of current functional and performance status for example parameters derived from cardiac MRI and cardiopulmonary exercise testing. There is therefore a large unmet need for a paper assessing prognosis for exclusively adult patients with repaired TOF, using contemporary information derived from modern investigative techniques. And as with the systemic RV patients, the Scottish population has yet to be characterised to any extent.

The aim of this chapter is therefore to define the baseline characteristics of a large national cohort of adult patients with repaired TOF, explore the adverse outcomes experienced over a specified time period, identify risk factors which might identify patients at greater risk of these adverse outcomes, and assess the impact of pulmonary valve replacement.

5.2 Patients and methods

5.2.1 Inclusion criteria

Since 2004 a national cardiac service for the provision of care to those patients with adult congenital heart disease (ACHD) has been established in Scotland, serving patients from a total population of 5.3 million. All surgical and catheter based interventions, advanced imaging and functional testing have been delivered through a single centre since 2009, and a computerised database capturing outcomes for all adult patients exists. Retrospective review of all 341 patients with Tetralogy of Fallot who were alive and known to our service from 1st April 2009 until the time of data collection at 22nd September 2015 was undertaken.

5.2.2 Follow-up

Status at baseline was documented along with details of past surgical history. Clinical events and the results of investigations including ECG, echo, cardiac MRI and cardiopulmonary exercise tests (CPET) were collated over the period of follow-up, and clinical status at the time of end of follow-up was recorded. Where patients had more than one investigation, changes in key parameters were documented. All investigations, including cardiac MRI and CPET, were performed according to the basic protocols outlined in chapter 2.

5.2.3 Statistical analysis

Data were described as frequency, median, and mean values with interquartile range and standard deviation as appropriate. A Cox proportional hazards assumption was used to establish risk factors for adverse outcomes. It became apparent early on that there were very few events for some of the adverse clinical outcomes when taken in isolation, thus invalidating any attempt at creating a multivariate model. Furthermore some of the outcomes recorded, such as ICD and PVR, were premeditated clinical decisions rather than spontaneous events, and thus assessment of "risk" for these outcomes was somewhat misleading. The decision was therefore made to use a composite endpoint of

death, ventricular arrhythmia, and atrial arrhythmia. A univariate analysis was undertaken for each parameter in the first instance. Significant parameters were then combined in a stepwise approach to find the best fitting multivariable model, assuming none of the principles of a regression analysis were violated e.g. with multicollinearity between variables.

Calculation of SMR was performed according to the same method described in chapter 3 (Finkelstein et al., 2003), however the National Records of Scotland reference tables for 2014 were used as this reflected the later period of data collection (NRS, 2014).

5.3 Results

5.3.1 Baseline characteristics

As demonstrated in Table 5.1, 341 adult survivors of repaired TOF were identified (145 female, 42.5%). Mean age at entry was 31.6 years (SD 12.3). The majority of patients (91.1%) had the classical form of TOF with the remaining 8.9% having a variant such as TOF with pulmonary atresia or TOF with AVSD. Mean age at repair was 4.9 years (SD 6.8), older than would be expected in contemporary practice but representative of the fact that, as adults, most of our patients were initially repaired in the 1970s and 1980s. There were 124 patients (36.4%) who had undergone at least one palliative shunt procedure prior to their, and 37 patients (10.9%) who had been diagnosed with an underlying genetic syndrome, of whom the majority had either Down's (n = 16) or Di George syndrome (n = 10). We assessed socio-demographic status by means of the Carstairs deprivation score, and this showed a normal distribution, similar to the general Scottish population (Dobson et al., 2014).

Prior to entry into the study 26.7% of patients (n = 91) had already undergone some form of surgical or catheter based intervention since their original surgical repair, the median age of first post-repair intervention being 15.4 years (IQR 8.2- 26.3). For the majority of patients this took the form of surgical intervention (n = 80), and the single most common intervention performed was a pulmonary valve replacement (PVR). Regarding other morbidity outcomes 8.5% of patients had already suffered at least one documented episode of cardiac arrhythmia, with 6.2% experiencing an atrial arrhythmia and 3.2% experiencing a ventricular arrhythmia (some patients experienced both). Arrhythmia occurred relatively late, with a median age of 31.9 years (IQR 24.1 - 44.5) for first episode of atrial arrhythmia and a median age of 32.7 years (IQR 19.3 - 37.2) for the first episode of ventricular arrhythmia. There were 13 patients who had already undergone implantation of a cardiac device (n = 6 dual chamber PPM, n = 2 ventricular single chamber PPM, n = 5 ICDs), and this occurred at a median age of 34 years (IQR 22.7 - 41.3). The vast majority of patients were in NYHA class 1, however response to exercise capacity was abnormal (reduced peak VO2, elevated VE/VCO2 slope and reduced heart rate

response). The VE/VCO2 slope was significantly higher in females than males, but in contrast to what would be expected with this relationship female patients had a higher median peak VO2. However, on review of the raw data it appears this was due to three female outliers with supra-normal peak VO2, and when these patients were removed there was no significant difference (p=0.187). By cardiac MRI the mean indexed RV and LV volumes were increased across the cohort, and median RV and LV ejection fraction were reduced relative to a reference population (Kawel-Boehm et al., 2015). The difference was more marked for the RV: for patients <60 years of age mean RVEDVi in males and females was 134 and 118ml/m2 versus 87 and 78ml/m2, RVESVi was 75 and 61ml/m2 versus 32 and 28ml/m2, and RVEF was 46 and 50% versus 64 and 64%. By Mann Whitney U test there was a significant difference in the distribution of ventricular volumes and EF between males and females.

Table 5-1 Baseline characteristics

	All	Male	Female	P-value
N (%)	341 (100.0)	196 (57.5)	145 (42.5)	
Age at entry y				
Median (IQR)	28.2 (21.4, 39.3)	28.1 (21.2, 38.2	28.2 (22.2, 40.4)	0.392
Age at repair y				
Median (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	3.0 (1.1, 6.0)	0.346
Time since repair y				
Median (IQR)	24.2 (18.5, 32.2)	24.1 (18.4, 32.2)	24.2 (19.5, 32.2)	0.675
Era of initial surgery				
N (N missing)	322 (19)	187 (9)	135 (10)	
N (%) Pre-1970	27 (8.4)	16 (8.6)	11 (8.1)	
N (%) 1970s	76 (23.6)	41 (21.9)	35 (25.9)	
N (%) 1980s	126 (39.1)	72 (38.5)	54 (40.0)	
N (%) 1990 onwards	93 (28.9)	58 (31.0)	35 (25.9)	0.425
Tetralogy subtype				
N (N missing)	338 (3)	195 (1)	143 (2)	
N (%) Classical	308 (91.1)	180 (92.3)	128 (89.5)	
N (%) Non-classical	30 (8.9)	15 (7.7)	15 (10.5)	0.661
Carstairs deprivation category[11]				
N (N missing)	336 (5)	192 (4)	144 (1)	
N (%) 1	21 (6.2)	10 (5.2)	11 (7.6)	
N (%) 2	36 (10.7)	23 (12.0)	13 (9.0)	
N (%) 3	66 (19.6)	41 (21.4)	25 (17.4)	
N (%) 4	81 (24.1)	49 (25.5)	32 (22.2)	
N (%) 5	64 (19.0)	28 (14.6)	36 (25.0)	
N (%) 6	38 (11.3)	23 (12.0)	15 (10.4)	
N (%) 7	30 (8.9)	18 (9.4)	12 (8.3)	0.514
N (%) Genetic syndrome	37 (10.9)	23 (11.7)	14 (9.6)	0.542
N (%) Palliative shunt prior to entry into cohort	124 (36.4)	68 (34.7)	56 (38.6)	0.734
N (%) Redo surgery or intervention prior to entry into cohort	91 (26.7)	51 (26.0)	40 (27.6)	0.643
Age at first redo surgery or intervention prior to entry into cohort y				
N (N missing)	88 (3)	51 (0)	37 (3)	
Median (IQR)	15.4 (8.2, 26.3)	15.2 (8.5, 23.9)	16.6 (7.9, 27.6)	0.172
N (%) Prior arrhythmia	29 (8.5)	19 (9.7)	10 (6.9)	0.360

[11] 1 = least deprived, 7 = most deprived

	All	Male	Female	P-value
Age at first arrhythmia y				
N (N missing)	27 (2)	19 (0)	8 (2)	
Median (IQR)	31.8 (20.6, 42.0)	31.8 (20.6, 45.0)	32.8 (23.1, 40.0)	0.811
N (%) Prior atrial arrhythmia	21 (6.2)	16 (8.2)	5 (3.4)	0.073
Age at first atrial arrhythmia y				
N (N missing)	20 (1)	16 (0)	4 (1)	
Median (IQR)	31.9 (24.1, 44.5)	30.5 (20.7, 50.0)	35.5 (30.3, 40.0)	0.820
N (%) Prior ventricular arrhythmia	11 (3.2)	6 (3.1)	5 (3.4)	0.841
Age at first ventricular arrhythmia y				
N (N missing)	10 (1)	6 (0)	4 (1)	
Median (IQR)	32.7 (19.3, 37.2)	33.4 (27.6, 37.2)	25.3 (15.0, 36.0)	0.610
N (%) Prior cardiac device	13 (3.8)	7 (3.6)	6 (4.1)	0.787
Age at first cardiac device y				
N (N missing)	13 (0)	7 (0)	6 (0)	
Median (IQR)	34.0 (22.7, 41.3)	35.0 (30.1, 39.6)	28.2 (21.6, 40.9)	0.534
N (%) Prior PVR	62 (18.1)	35 (17.9)	27 (18.6)	0.857
Age at first PVR y				
N (N missing)	60 (1)	36 (0)	24 (1)	
Median (IQR)	17.7 (13.8, 27.8)	16.3 (13.7, 25.5)	23.0 (14.5, 27.8)	0.304
Prescribed classes of medication N (%)				
ACE/A2RB	24 (7)	18 (9.2)	6 (4.1)	0.121
Betablocker	49 (14.4)	32 (16.3)	17 (11.7)	0.267
MRA	8 (2.3)	4 (2)	4 (2.8)	0.439
Loop diuretic	16 (4.7)	11 (5.6)	5 (3.5)	0.612
Warfarin	24 (7)	17 (8.7)	7 (4.8)	0.318
Antiarrhythmic	12 (3.5)	8 (4.1)	4 (2.8)	0.495
NYHA class				
N (N missing)	334 (7)	190 (6)	144 (1)	
N (%) class 1	323 (96.7)	183 (96.3)	140 (97.2)	
N (%) class 2	8 (2.4)	5 (2.6)	3 (2.1)	
N (%) class 3	3 (0.9)	2 (1.1)	1 (0.7)	
N (%) class 4	0	0	0	0.645
Peak VO2 % predicted				
N (N missing)	182 (159)	98 (98)	84 (61)	
Mean (SD)	0.69 (0.18)	0.67 (0.17)	0.73 (0.19)	0.049
VE/VCO2 slope				
N (N missing)	172 (169)	93 (103)	79 (66)	

	All	Male	Female	P-value
Median (IQR)	33.0 (29.8, 36.0)	31.0 (28.0, 34.0)	34.0 (31.9, 37.0)	<0.001
Peak HR% predicted				
N (N missing)	174 (167)	94 (102)	80 (65)	
Median (IQR)	0.84 (0.75, 0.89)	0.85 (0.73, 0.91)	0.82 (0.77, 0.88)	0.657
RVEDVi ml/m2				
N (N missing)	200 (141)	111 (85)	89 (56)	
Median (IQR)	122 (100, 149)	127 (105, 158)	117 (99, 141)	0.008
RVESVi ml/m2				
N (N missing)	195 (146)	108 (88)	87 (58)	
Median (IQR)	63 (49, 79)	70 (52, 86)	59 (46, 74)	0.004
RVEF %				
N (N missing)	196 (145)	109 (87)	87 (58)	
Median (IQR)	47 (42, 54)	47 (40, 53)	49 (44, 55)	0.013
LVEDVi ml/m2				
N (N missing)	192 (149)	106 (90)	86 (59)	
Median (IQR)	79 (69, 91)	81 (72, 94)	76 (66, 86)	0.007
LVESVi ml/m2				
N (N missing)	189 (152)	104 (92)	85 (60)	
Median (IQR)	31 (25, 40)	33 (28, 42)	29 (23, 34)	0.001
LVEF %				
N (N missing)	189 (152)	104 (92)	85 (60)	
Median (IQR)	60 (54, 65)	58 (54, 62)	62 (56, 67)	0.003

5.3.2 Adverse outcomes over the follow-up period:

Clinical outcomes which occurred over the study period are outlined in Table 5.2.

Table 5-2 Clinical outcomes from 2009 - 2015

Outcome	Number of events	Person y follow up	Event rate per 100 person y
Death	7[12]	1248.7	0.56
Arrhythmia (any)	35	1069.7	3.27
Ventricular arrhythmia	14	1206.4	1.16
Atrial arrhythmia	25	1162.1	2.15
Cardiac device[13]	16	1203.6	1.33
PVR[14]	70	1034.7	6.77

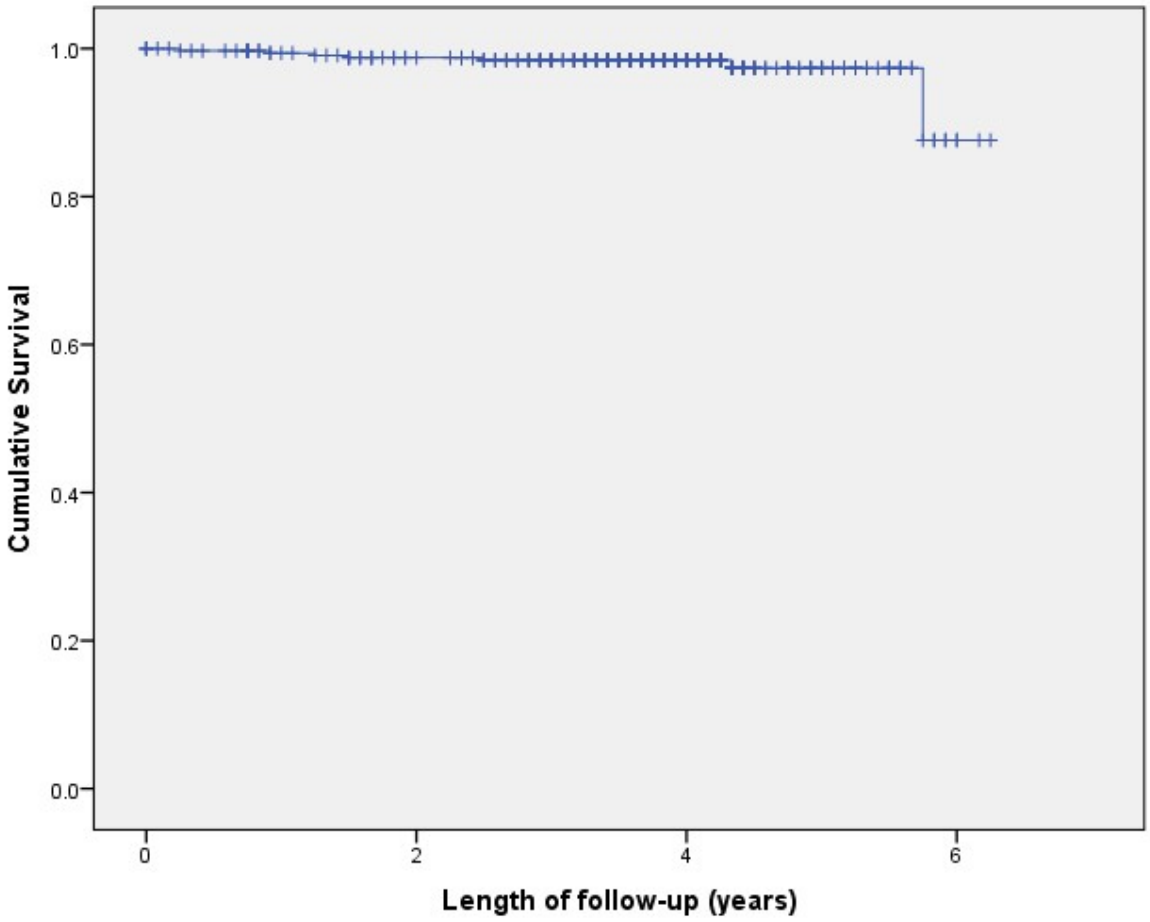
Kaplan Meier curves were employed to visually represent the cumulative survival from each of the clinical outcomes over the study period. Mortality for the cohort was low at 0.98 +/- 0.01, 0.97 +/- 0.01, and 0.93 +/- 0.04 at 2,4 and 6 years of follow-up (Figure 5.1). The corresponding cumulative survival from tachyarrhythmia was 0.91 +/- 0.02, 0.84 +/- 0.03 and 0.80 +/- 0.05, from cardiac device insertion was 0.96 +/- 0.01, 0.93 +/- 0.02 and 0.93 +/- 0.02, and from PVR was 0.80 +/- 0.02, 0.59 +/- 0.04 and 0.52 +/- 0.06 at 2,4 and 6 years (Figures 5.2 - 5.4).

[12] Of the seven deaths the causes were stroke (1), pneumonia (1), heart failure (3), sudden presumed arrhythmic (1), and postoperative following PVR (1). Of these patients 2 were female and 5 were male. Median age at death was 56.9 years

[13] 11 devices were ICDs and 5 were dual chamber pacemakers

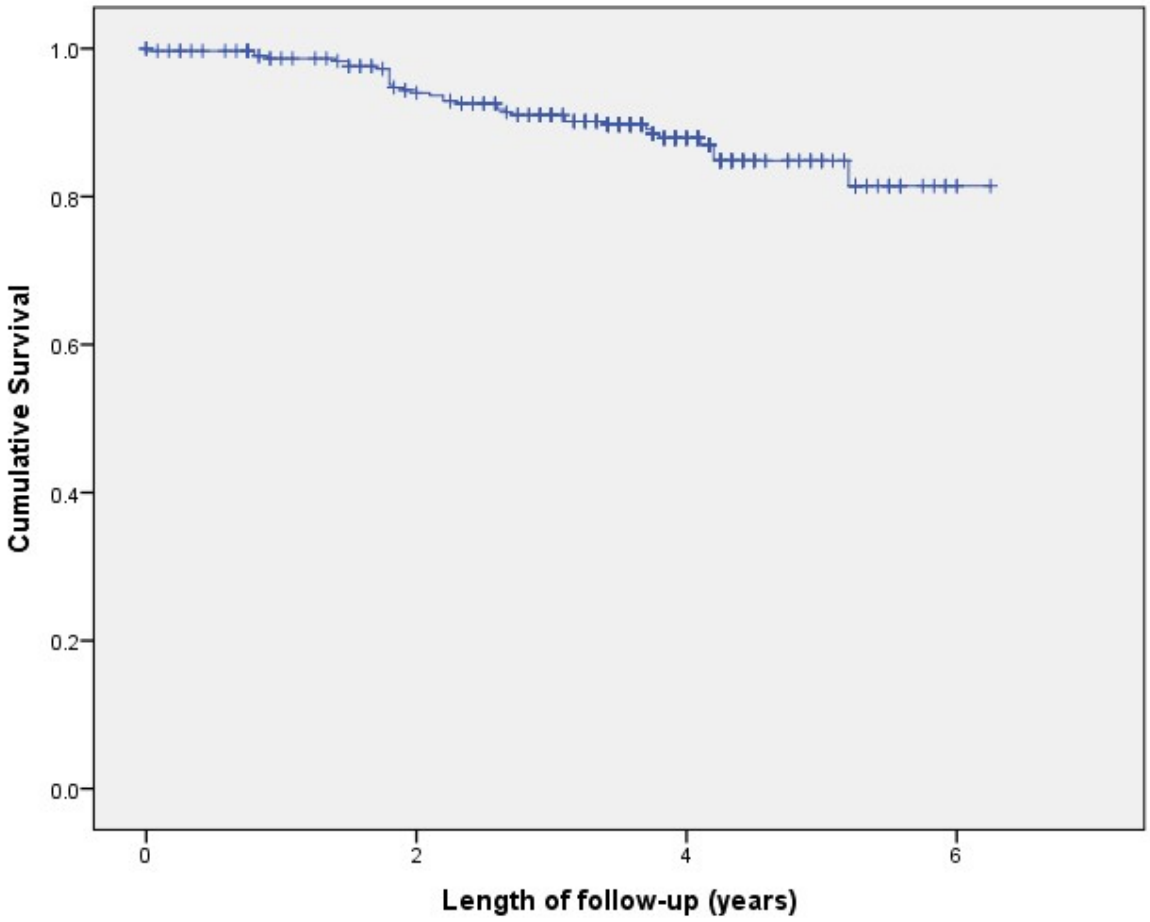
[14] The overwhelming number of interventions were PVR. Only 4 patients had surgery which involved another procedure (aortic root, aortic valve, or tricuspid valve surgery). Of the percutaneous intervention performed all were percutaneous PVRs apart from in 6 patients (these other procedures included pulmonary artery angioplasty, pulmonary balloon valvuloplasty, and percutaneous device closure of an ASD).

Figure 5-1 Cumulative survival from baseline



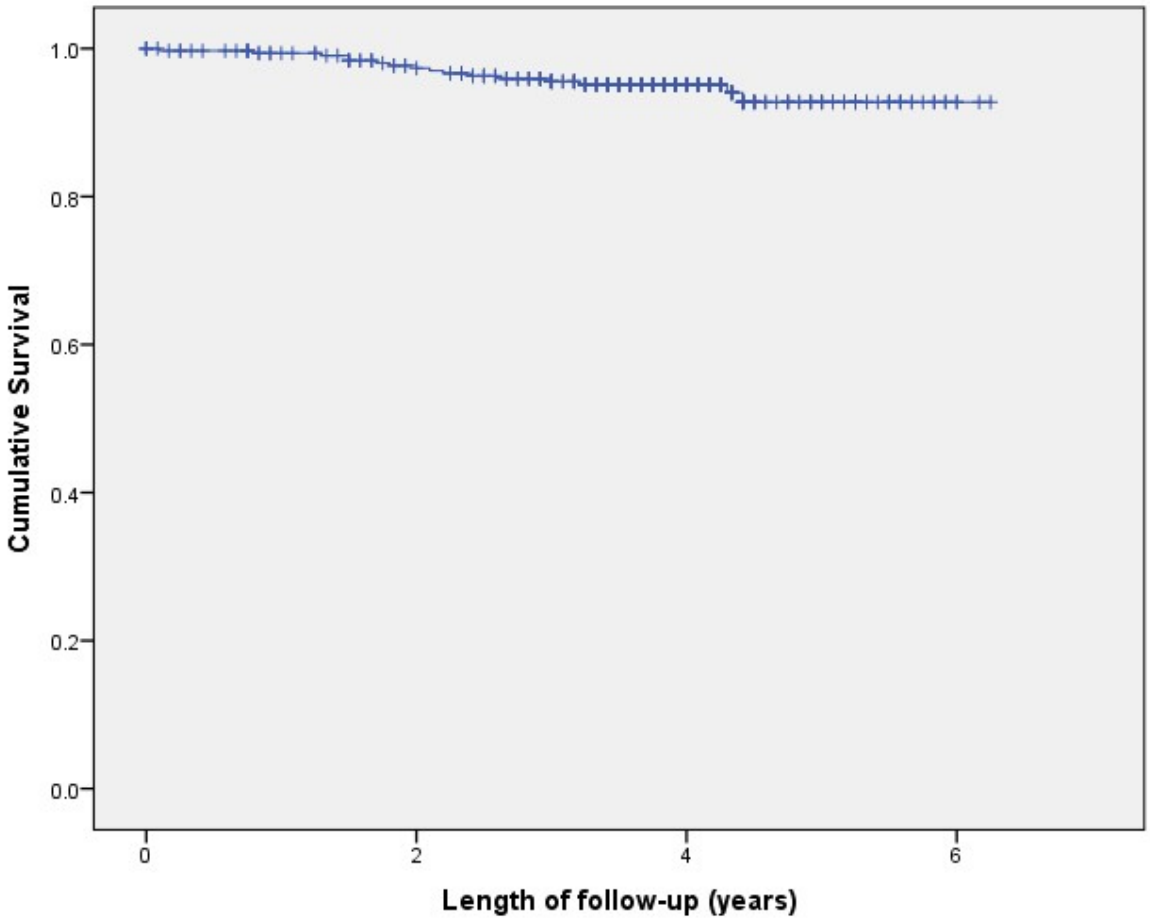
N at risk	341	299	151	4

Figure 5-2 Cumulative survival from tachyarrhythmia (any)



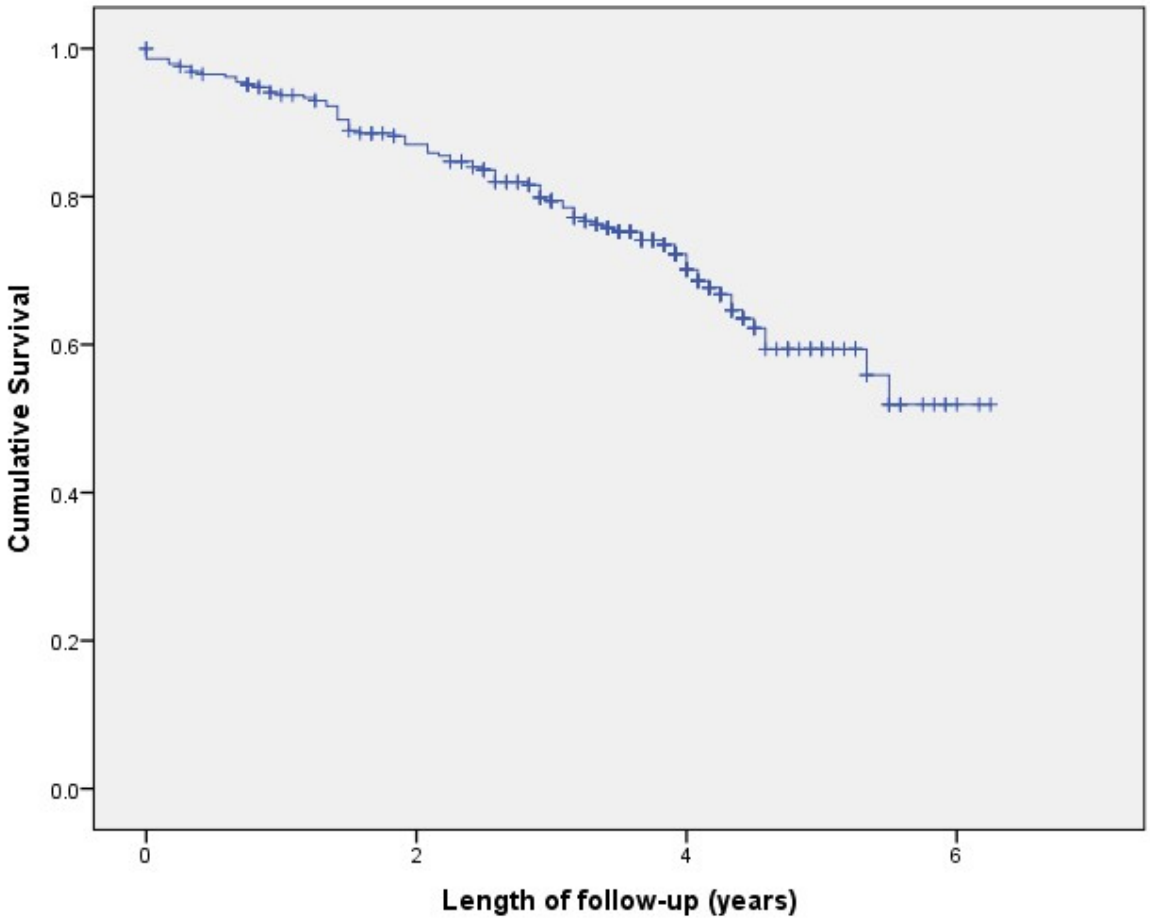
N at risk	312	260	119	3

Figure 5-3 Cumulative survival from cardiac device insertion



N at risk	328	281	139	4

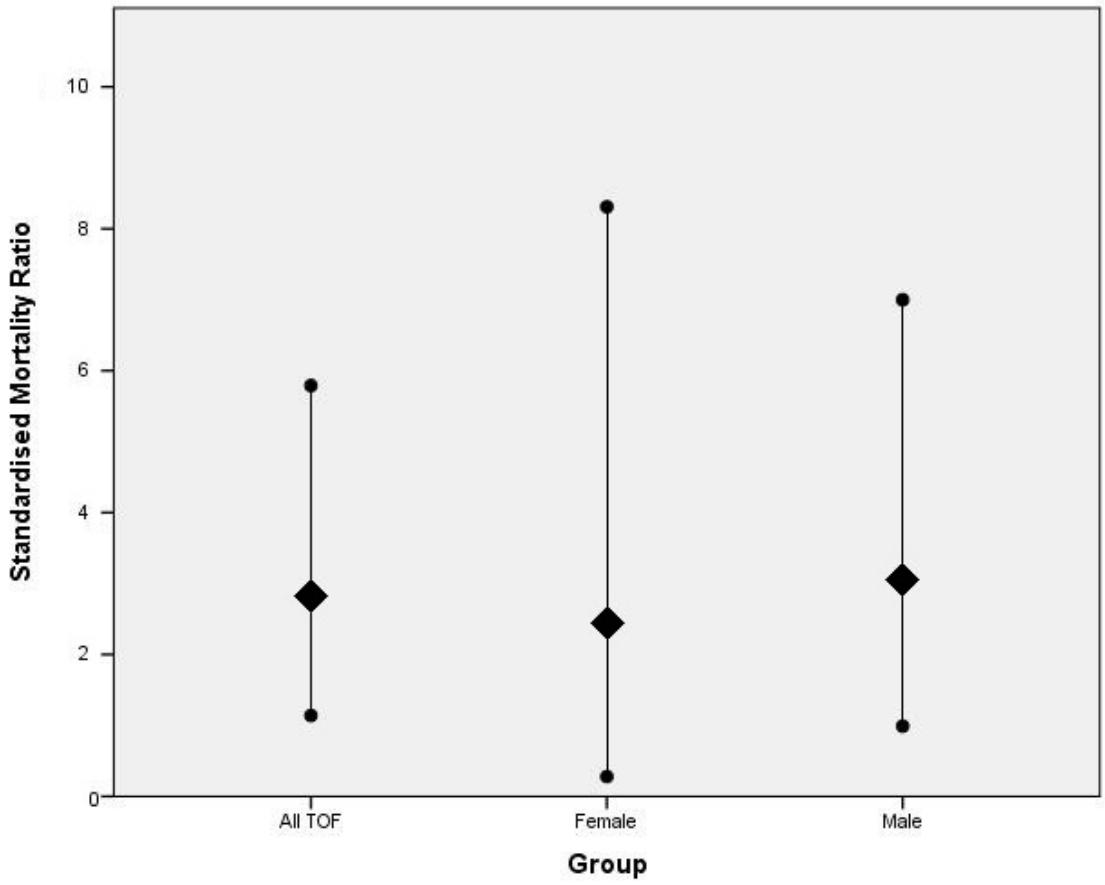
Figure 5-4 Cumulative survival from PVR



N at risk	280	229	102	3

The standardised mortality ratio was calculated for the cohort using the method described previously in chapter 4 (Finkelstein et al., 2003). This gave an SMR of 2.84 (95% CI 1.14 - 5.79) for the whole cohort; when analysed according for gender it was higher for males at 3.05 (95% CI 0.99 - 7) than females at 2.42 (95% CI 0.28 - 8.31), however note the wide overlapping confidence intervals (Figure 5.5).

Figure 5-5 Standardised mortality ratio with upper and lower 95% confidence intervals by gender, and for the TOF cohort as a whole



	All TOF	Female	Male
Expected deaths	2.47	0.83	1.64
Observed deaths	7	2	5
SMR	2.84	2.42	3.05
Lower 95% CI	1.14	0.28	0.99
Upper 95% CI	5.79	8.31	7.00

As described previously the decision was made to identify variables conferring additional hazard for a composite endpoint of death, ventricular arrhythmia and atrial arrhythmia. The results of the univariate analysis and best fitting multivariable model are outlined in table 5.3. Note that for continuous variables (RVEDV, RVESV, VE/VCO2, peak VO2%, peak HR% and ECG QRS duration) the hazard ratio is per unit increase of the variable in question.

Table 5-3 Univariate and multivariate predictors of a combined endpoint of death, ventricular arrhythmia and atrial arrhythmia

Univariate				Multivariate		
Variable	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
Gender (male)	0.63	0.34, 1.19	0.159	0.23	0.09, 0.58	0.002
Shunt	1.26	0.65, 2.43	0.491			
Syndrome	0.22	0.03, 1.60	0.135			
Surgery post-1980	3.47	1.79, 6.74	<0.001			
Age at repair	1.08	1.05, 1.11	<0.001	1.11	1.02, 1.21	0.022
Classical TOF	1.02	0.24, 4.21	0.985			
Reintervention of surgery before entry	1.07	0.52, 2.19	0.861			
RVEDV at baseline	1.01	1.01, 1.02	<0.001	1.02	1.01, 1.02	<0.001
RVESV at baseline	1.01	1.01, 1.02	0.001			
VE/VCO2 at baseline	1.12	1.03, 1.21	0.007			
Peak VO2% at baseline	0.73	0.08, 6.75	0.778			
Peak HR% at baseline	0.10	0.02, 0.66	0.018			
ECG QRS interval at baseline	1.02	1.00, 1.03	0.038			

As can be seen the best fitting multivariable model identified greater indexed RVEDV at baseline, female gender, and older age at repair as conferring increased risk for the primary outcome.

5.3.3 Medication

The prevalence of prescribed cardiac medication was low; the most commonly prescribed class of medication was a betablocker and this was in less than 15% of patients in the entire cohort. Most of these patients had a history of arrhythmia. Only 7% of patients were formally anticoagulated with Warfarin (data collection was carried out before the widespread introduction of newer direct oral anticoagulants), and in most cases this was due to the presence of AF or atrial flutter. Prescribing of renin-angiotensin system inhibitors and loop diuretics was even lower, and only 3.5% of patients were prescribed a dedicated antiarrhythmic drug (defined as a Vaughan Williams class I drug e.g. Flecainide, or a class III drug e.g. Amiodarone).

5.3.4 Analysis of the effect of pulmonary valve replacement on functional status

There were 70 patients who underwent PVR over the study period. Where patients had paired data for particular investigations (i.e. at the beginning and at the end of the follow-up period) the changes in ventricular volumes, exercise performance and electrical conduction within the ventricles (as measured by QRS interval duration on ECG) were assessed for those patients who underwent PVR relative to those who did not to gain an impression of the effects of this intervention (Table 5.4). There were too few adverse outcomes in each group to be able to reliably assess the effect of PVR on clinical endpoints such as mortality and arrhythmia.

Table 5-4 Influence of PVR on ventricular volumes and exercise performance over the specified follow-up period

Variable		No PVR during follow-up period	Had PVR during follow-up period
Mean LVEDVi (SD)	N	22	22
	Baseline	80.4 (18.6)	81.2 (22.7)
	Follow-up	81.9 (17.4)	80.8 (15.2)
	Change	1.5 (10)	-0.4 (16.2)
	P	0.489	0.917
Mean LVESVi (SD)	N	20	22
	Baseline	32.1 (12.6)	36.3 (16.8)
	Follow-up	34.3 (9.6)	35.6 (9)
	Change	2.2 (9.7)	-0.8 (10.6)
	P	0.335	0.735
Mean LVEF (SD)	N	19	22
	Baseline	58.2 (6)	56.1 (9.6)
	Follow-up	57.6 (8.3)	56.6 (5.5)
	Change	-0.6 (6.9)	0.5 (6.8)
	P	0.720	0.757
Mean RVEDVi (SD)	N	23	27
	Baseline	116.1 (29.6)	144.5 (28.2)
	Follow-up	116.0 (26.4)	112.4 (37.2)
	Change	-0.1 (19.7)	-32.1 (32.3)
	P	0.983	<0.001
Mean RVESVi (SD)	N	21	27
	Baseline	62.1 (20.1)	80.0 (21.8)
	Follow-up	60.6 (20.1)	62.4 (24.2)
	Change	-1.5 (13.6)	-17.7 (17.3)
	P	0.625	<0.001

Mean RVEF (SD)	N	21	27
	Baseline	47.9 (7.9)	45.6 (8.8)
	Follow-up	49.8 (10)	44.1 (13.1)
	Change	1.9 (5.7)	-1.5 (11)
	P	0.132	0.489
Peak VO2 as a % of predicted (SD)	N	37	34
	Baseline	0.73 (0.17)	0.65 (0.16)
	Follow-up	0.67 (0.16)	0.63 (0.15)
	Change	-0.05 (0.15)	-0.02 (0.18)
	P	0.032	0.583
VE/VCO2 slope (SD)	N	34	34
	Baseline	32.7 (4.5)	34.7 (5.6)
	Follow-up	30.7 (5.5)	33.2 (4.5)
	Change	-2.0 (4.9)	-1.5 (4.6)
	P	0.021	0.070
Peak HR as a % of predicted (SD)	N	36	34
	Baseline	0.81 (0.10)	0.83 (0.11)
	Follow-up	0.81 (0.11)	0.81 (0.1)
	Change	0 (0.1)	0 (0.1)
	P	0.840	0.111
ECG QRS interval (SD)	N	143	70
	Baseline	143.7 (23.4)	153.7 (25.4)
	Follow-up	144.9 (25.4)	149.8 (28.0)
	Change	1.2 (10)	-3.8 (13.3)
	P	0.146	0.019

As can be seen, with no PVR during follow-up there was no significant change in ventricular volumes or ejection fraction. In patients who underwent PVR over the follow-up period there was a significant reduction in both RVESV and RVEDV, although the combined effect of this appeared to cancel out any significant change in RVEF. PVR was not associated with a significant change in LV volumes or EF.

Regarding exercise test data, peak VO2 declined significantly in those patients who did not undergo a PVR over the follow-up period, but did not change significantly in those that did. Interestingly VE/VCO2 slope decreased slightly in both groups, although this was not significant for the PVR group. There was no significant change in peak HR as a percentage of the predicted value in either group. On review of ECG data interventricular conduction delay (as measured by QRS interval duration) decreased significantly following PVR, and displayed a trend towards increasing in those who did not undergo PVR.

5.4 Discussion

5.4.1 Survival and morbidity

Over a follow-up period of over 6 years the number of deaths in a large cohort of patients with repaired TOF was low, corresponding to an event rate of 0.56 per 100 person-years. Morbidity was much higher, with event rates of documented arrhythmia of 3.27 per 100 person-years, ventricular arrhythmia of 1.16 per 100 person-years, atrial arrhythmia of 2.15 per 100 person-years, device implantation of 1.33 per 100 person-years, and PVR of 6.77 per 100 person-years.

The variables associated with adverse outcomes in the multivariate analysis were indexed RVEDV, female gender, and older age at repair. A higher RVEDV is the inevitable consequence of a volume loaded RV in the setting of severe pulmonary regurgitation, and as the RV dilates so there is adverse cardiac remodelling, greater scarring and fibrosis. This creates the substrate for macro-reentrant circuits and arrhythmia, and deleterious RV-LV coupling ultimately results in the development of left ventricular dysfunction and biventricular failure (Babu-Narayan et al., 2006, Apitz et al., 2009). In fact RVEDV is already a key determinant in when to offer a patient PVR, since as RV volumes increase past a threshold of 150-160ml/m2 so the RV is less likely to normalise even with PVR (Geva, 2013, Buechel et al., 2005, Geva et al., 2010, Frigiola et al., 2008).

Regarding female gender it must be remembered that this is a single cohort, the confidence intervals were relatively wide, and this only became significant with indexed RVEDV in the model. However, it is an interesting finding, and certainly worthy of further study. There have been comparatively few papers to identify a link between gender and adverse outcomes in ACHD as a whole, let alone TOF in isolation. However there is compelling evidence to suggest that even when indexed to body surface area there are significant gender differences in ventricular dimensions and function as well as electrical conduction through the ventricles, and perhaps this is the mechanism by which female patients are more likely to experience outcomes such as arrhythmia (Sarikouch et al., 2011) . One of the few studies which has looked at the effects of gender in ACHD identified that women with ACHD were more likely to have pulmonary hypertension, and less likely to

receive an ICD compared to men (Verheugt et al., 2008). The mechanisms for this are likely to be complex, however in the field of acquired heart disease it is well established that women are at greater risk of sudden cardiac death, often present with atypical symptoms, and may be subject to gender bias (the Yentl effect).

With older age at repair patients will have been exposed to cyanosis and increased blood flow through the pulmonary circulation for a longer period of time, they are also more likely to have been repaired in an older era with less advanced myocardial protection intraoperatively, and will almost certainly have experienced a degree of failure to thrive. All of the above might reasonably be expected to increase myocardial scar, have a deleterious effect on cardiac function, and indeed this variable has been identified as conferring hazard in other TOF cohorts (Nollert et al., 1997, Bokma et al., 2015, Hamada et al., 2002).

It is also worth noting that although it was not robust enough to be included in the multivariable model, there was a univariate association between VE/VCO2 and the primary outcome. The VE/VCO2 ratio is a marker of reduced efficiency of ventilation and gas exchange during exercise, is thus associated with sicker hearts, and has been consistently associated with adverse outcomes in repaired TOF in a number of previous studies (Giardini et al., 2007, Giardini et al., 2009a, Buys et al., 2012), and of all the parameters derived from CPET the VE/VCO2 ratio appears to be the most powerful at establishing prognosis.

Finally, comparatively few patients were prescribed cardiac medication when compared to contemporary cohorts of patients with acquired conditions such as ischaemic heart disease. This reflects the absence of any evidence for the use of such medication in improving outcomes in repaired TOF. In this cohort generally the only patients for whom these medications were prescribed were older patients who had developed secondary pathology for which these medications were indicated; such as LV systolic dysfunction, ischaemic heart disease and tachyarrhythmia. It would be interesting to ascertain whether patients with repaired TOF and an indication for such treatments respond as well to these drugs as those patients without TOF but who with the same indication.

5.4.2 The effect of pulmonary valve replacement

Any interpretation of the results in table 5.4 needs to take into the account that the decision to proceed to elective PVR – as with other major surgical operations – is nuanced, and based on multiple clinical parameters. Both the European and American guidelines (Baumgartner et al., 2010, Warnes et al., 2008) suggest that this should be based on the presence of symptoms (including an objective reduction in exercise capacity as measured by CPET), haemodynamic parameters such as the degree of RV dilatation or a reduction in systolic function, and the development of arrhythmia. These factors must be balanced against other factors such as comorbidity, the number of previous sternotomies, and of course individual patient preference regarding intervention. Thus the two groups of patients can be characterised as follows: the group of patients who underwent PVR will have had severe pulmonary regurgitation, a dilated RV, and reduced exercise capacity. On the other had in the group of patients who did not undergo PVR will exhibit a dichotomy between those patients who have reaped the benefits of an excellent surgical repair (with minimal pulmonary regurgitation and RV dilatation, and good exercise capacity), and those patients who technically meet the indications for PVR (and will thus have the same characteristics as the PVR group), but due to factors such as comorbidity, patient preference, or loss to follow-up did not undergo PVR over the follow-up period.

At baseline the PVR group had higher indexed RVEDV and RVESV, slightly lower RVEF, and lower peak VO2 than the non-PVR group. Over the follow-up period, the effect of PVR was to bring about a significant decrease in RVEDV and RVESV, and also a reduction in ECG QRS duration – as RV volumes decrease so there is less delay in depolarisation throughout the ventricle, and less electromechanical decoupling from the LV. This confirms findings from other cohorts (Cavalcanti et al., 2013, van Huysduynen et al., 2005).

The effect of PVR on the left ventricle and exercise capacity has been less well studied. In this cohort PVR brought about no significant change in LV volumes or function, in contrast to one single centre study of 39 patients which saw an improvement in LVEF driven by a reduction in LVESV - however it should be noted that this increase was only significant in patients with an LVEF of less than 45%

preoperatively - significantly lower than mean LVEF of 56% in this cohort (Tobler et al., 2012). I found only two papers which reported data from CPET post PVR. One described a very small reduction in VE/VCO2 but no change in peak VO2 (Frigiola et al., 2008), another found no change in peak VO2 (Ho et al., 2015). Neither paper assessed change in exercise parameters in a control group. I found no significant change in either peak VO2 or VE/VCO2 in the PVR group. Although peak VO2 decreased significantly in the no-PVR group, which might suggest that PVR at least helps to halt the decline in exercise capacity that may occur in untreated pulmonary regurgitation, this is not supported by the change in VE/VCO2, which decreased in the non-PVR group (i.e. one would expect it to increase if there was a genuine reduction in peak VO2 due to cardiovascular limitation of exercise). Ultimately, there is no evidence to suggest that exercise capacity is dramatically improved by PVR, regardless of the undeniable improvement in RV volumes.

5.4.3 Study limitations

The study used a composite endpoint due to the low event rate over the follow-up period. Whilst this is a valid way of increasing statistical power, and has been employed previously in contemporary studies of adult survivors of TOF (Gatzoulis et al., 2000, Bokma et al., 2015) there remain the problems of weighting the analysis in favour of some adverse outcomes over others, and increasing the likelihood of a type 1 error.

This study was based upon retrospective data, and thus the univariate and multivariate predictors of adverse outcomes need to be validated through prospective follow-up of a larger cohort. Finally, not all of the patients had cardiac MRI and CPET performed, and for those patients who underwent PVR it was not always the case that paired CPET and MRI data were available (that is to say that a patient had both MRI and CPET performed before and after valve replacement). In some cases this was unavoidable, for precisely the same reasons as outlined in chapter 4 - artefact preventing quantitative ventricular analysis, presence of a non-MRI conditional cardiac device, patient claustrophobia, etc. The other issue is that these were all clinical rather than research tests, and in a resource limited environment such as the NHS clinical elective investigations may of course at times be postponed or cancelled in favour of more urgent cases. However, improving the proportion of patients who undergo these recommended investigations is clearly an important issue which has become evident as a result of this study, and one which the service must address in the future.

5.4.4 Conclusion

In a large cohort of adult survivors of repaired TOF mortality is low, although event rates of morbidity outcomes such as arrhythmia, cardiac device insertion, and especially PVR are relatively high. Consistent markers for adverse outcomes are the presence of RV dilatation as assessed by indexed RVEDV, older age at primary repair, and female gender. PVR - by far the commonest intervention - was associated with a significant reduction in RV volumes and interventricular conduction delay, and by extrapolation could conceivably avoid adverse clinical outcomes such as arrhythmia. However due to the low mortality rate in this cohort, and with a high number of confounding factors, proof that PVR definitively modifies prognosis in this patient group is likely to remain elusive.

Chapter 6 Improving risk stratification of patients with repaired Tetralogy of Fallot using cardiac MRI and cardiopulmonary exercise testing

6.1 Introduction

In the previous chapter I described the natural course of adult patients with repaired TOF, and defined the adverse outcomes experienced over the follow-up period. It became apparent that it was difficult to risk stratify patients, and in particular those patients who were likely to develop sustained ventricular arrhythmia, which can be devastating as it may present as sudden cardiac death (SCD). The electrophysiological mechanisms behind this are likely to be multifactorial, however ventricular scar and fibrosis can provide the substrate for this to develop (Friedli, 1999, Steeds, 2004, Khairy et al., 2009).

Cardiac MRI is regarded as the gold standard for the serial non-invasive assessment of patients with TOF: it provides detailed and reproducible information on the structure and function of the heart post surgical repair, and crucially, with respect to ventricular arrhythmia, it allows the determination of the presence and extent of myocardial fibrosis as assessed by Late Gadolinium Enhancement (LGE). LGE has been associated with a greater risk of adverse outcomes in patients with repaired TOF in other cohorts (Babu-Narayan et al., 2006), however the data is relatively old and relates to patients who were repaired in an earlier surgical era - perhaps with less perioperative myocardial protection during repair. A significant proportion of patients with repaired TOF in this Scottish cohort had undergone cardiac MRI, but no formal attempt had been made to establish whether or not LGE could improve the recognition of patients at risk of adverse outcomes.

The aim of this study therefore was to quantify the amount of RV and LV LGE in adult survivors of TOF in a contemporary cohort, and together with the other parameters derived from cardiac MRI and CPET establish its utility in identifying those patients at greater risk of adverse clinical endpoints. Of note tables 6.1-6.3, and figures 6.1-6.4, whilst exclusively the work of the author, have been published elsewhere (Dobson et al., 2017) and so the appropriate permissions were sought and granted by the publisher[15].

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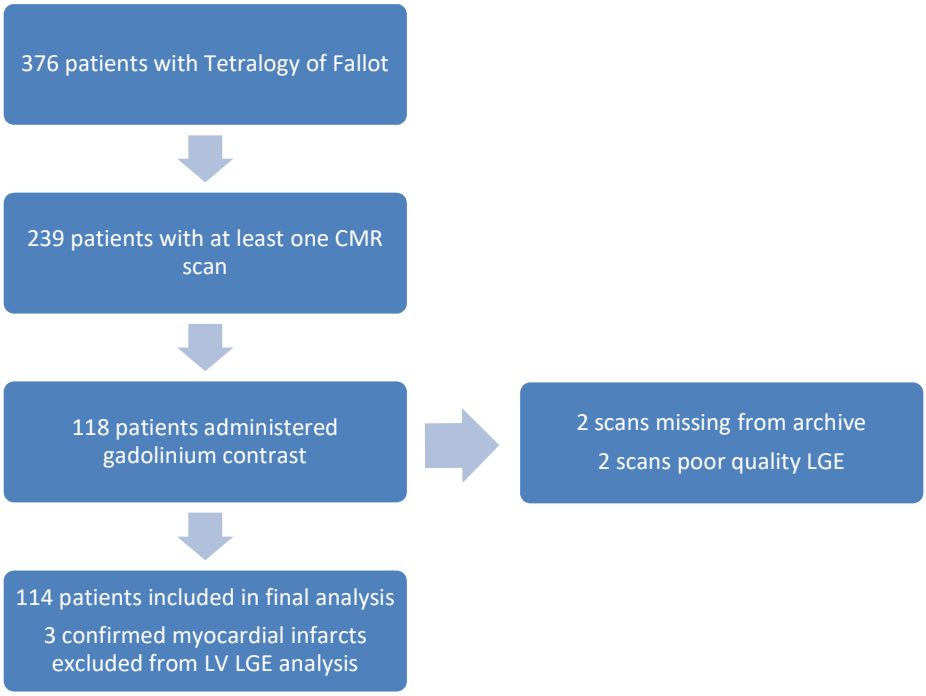
6.2 Methods

6.2.1 Patient eligibility and data collection

This was a single centre cohort study. At the time of data collection there were 376 adult survivors of TOF. Of these patients 239 had undergone CMR scanning, and 118 of these had contrast enhanced CMR with the administration of Gadolinium as Gadolenic acid (Dotarem®), with 114 scans of sufficient quality to include in the final analysis (Figure 6.1).

Figure 6-1 Eligibility criteria



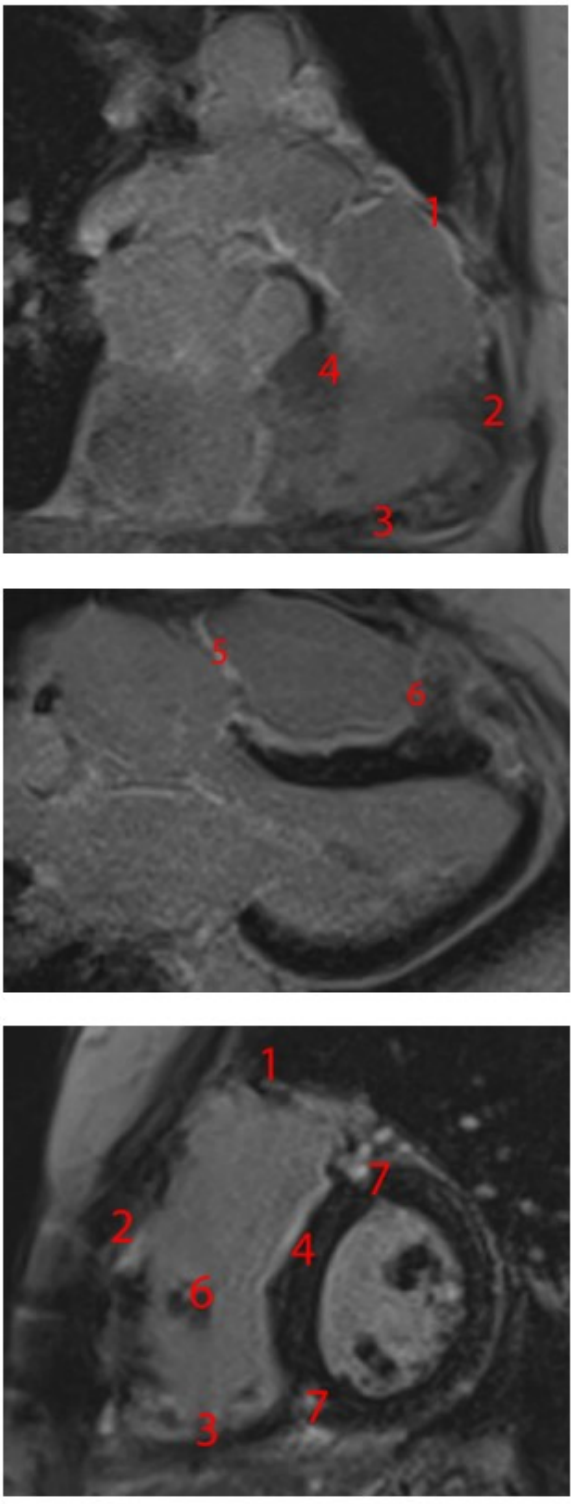
Baseline demographics included date of birth, gender, details of surgical repair including palliation, and date of death or last review. Morbidity outcomes

documented were atrial arrhythmia (defined as sustained atrial tachycardia, supraventricular tachycardia, atrial flutter, or atrial fibrillation), clinically significant ventricular arrhythmia (defined as sustained ventricular tachycardia or ventricular fibrillation), the need for cardiac device insertion (permanent pacemaker or implantable cardioverter-defibrillator), and the need for percutaneous or cardiac surgical reintervention. Information on functional status included NYHA class and parameters derived from ECG, echocardiography, CMR and cardiopulmonary exercise testing (CPET).

6.2.2 Cardiac MRI

All CMR scans were performed at the host institution at 1.5 Tesla field strength using a Siemens Magnetom Avanto (Siemens AG, Erlangen, Germany) with a 12-element phased array cardiac surface coil. A standard imaging protocol was followed for all patients as outlined in chapter 2. Following this, LGE images were obtained 10-15 minutes after the administration of 0.15mmol/kg of Gadolenic acid (Dotarem®). The entire LV and RV were imaged using a phase sensitive inversion recovery sequence in contiguous short axis views from the level of the AV valves to the apex, and then in long axis views (Mordi et al., 2014). LV and RV volumes at end diastole and end systole had been quantified using computer assisted planimetry and indexed to body surface area by a single analyst with over 5 years of CMR experience (HW). Pulmonary regurgitant fraction was calculated as a percentage of regurgitant volume divided by RV stroke volume on the flow-mapping sequences. LV LGE was formally quantified as late Gadolinium mass and expressed as a percentage of the total LV mass using the 5 SD from remote myocardium method (Mordi et al., 2014). The degree of RV LGE was expressed using the semiquantitative RV seven segment model proposed by Babu-Naryan and colleagues, as shown in Figure 6.2 (Babu-Narayan et al., 2006).

Figure 6-2 Quantification of RV LGE



Scoring system to semiquantitatively estimate degree of RV LGE. Images obtained using a phase-inversion recover sequence 10-15 minutes following the administration of gadolenic acid. Regions 1 to 5 were graded as 0 = no enhancement, 1 = less than 2cm, 2 = 2-3cm, 3 = greater than 3 cm. Trabecular bands were graded as 0 = no enhancement, 1 = LGE seen in one trabecular band, 2 = LGE seen in 2-4 bands, 3 = LGE seen in more than 4 bands. Insertion points graded as 0 = no LGE, 1 = LGE present (1 point for each insertion point). Adapted from Babu Naryan et al[8]

1. Anterior wall of RVOT (0 - 3)
2. Anterior wall of RV (0 - 3)
3. Inferior wall of RV (0 - 3)
4. RV surface of septum (0 - 3)
5. VSD patch region (0 - 3)
6. Trabecular bands (0 - 3)
7. RV insertion points (0 - 2)

Total score 0 - 20

6.2.3 Statistical analysis

The first part of the study involved a cross-sectional analysis of the cohort at the end of the study period. Means, medians and distributions were compared using the techniques described in chapter 2. Correlation for normally distributed data was assessed using the Pearson product-moment correlation coefficient, and the Spearman rank correlation coefficient if non-normal. Tests of association between nominal and continuous data were performed using one way ANOVA or the Kruskal Wallis test according to whether the distribution of the data was normal or non-normal.

The second part comprised a survival analysis from the date of CMR scan to the end of the follow-up period. This was initially undertaken using a univariate Cox regression model from the date of CMR scan. Because of the low number of adverse events (and no deaths) over the follow-up period I decided to use a composite outcome, which included atrial arrhythmia, sustained ventricular arrhythmia, ICD implantation or heart failure admission. PVR was not included in this composite outcome, for the reasons outlined in chapter 5. If a baseline variable was associated with a greater risk of the composite outcome in the univariate model to a level of significance of $p < 0.2$, the analysis was repeated with age at the time of scan as a covariate in order to adjust for the effect of older age on the likelihood of experiencing an adverse event - the reasons for this became apparent during the course of the study and are outlined below. Due to the relatively low number of adverse outcomes it was not possible to use more than two covariates in the model.

6.3 Results

6.3.1 Baseline characteristics

Characterisation of the cohort at the end of the study period is presented in table 6.1. As mentioned previously, an adverse event was defined as an episode of atrial arrhythmia, sustained ventricular arrhythmia, ICD implantation or heart failure admission. The breakdown of these adverse outcomes was as follows: atrial arrhythmia in 15 (13.2%), sustained ventricular tachycardia in 4 (3.5%), ICD implantation in 6 (5.3%) and heart failure admission in 3 (2.6%), i.e. a total of 27 adverse events occurred in 21 patients.

Table 6-1 Characteristics of cohort

	All patients	Patients with no adverse events	Patients with adverse events	*P*
N (%)	114	93 (81.6)	21 (18.4)	
Male/Female	64/50	51/42	13/8	0.557
Median age at repair y (IQR)	2 (1 - 4)	2.5 (1.3 - 4.2)	3.7 (1.9 - 9.8)	0.029
Median age at scan y (IQR)	29.5 (23.3 - 38.8)	26.8 (22.3 - 36.7)	42.7 (32.1 - 46.7)	<0.001
TOF subtype N (%)				
Classical	107 (93.9)	86 (92.5)	20 (95.2)	
Non-classical	7 (6.1)	7 (7.5)	1 (4.8)	0.656
Era of initial surgical repair N (%)				
1960-1969	3 (2.6)	2 (2.2)	1 (4.8)	
1970-1979	29 (25.4)	20 (21.5)	9 (42.9)	
1980-1989	45 (39.5)	36 (38.7)	9 (42.9)	
1990-1999	29 (25.4)	29 (31.2)	0	
2000-	2 (1.8)	2 (2.2)	0	
Missing	6 (5.3)	4 (4.3)	2 (9.5)	0.001
Palliative shunt N (%)	46 (40.4)	37 (39.8)	9 (42.9)	0.275
Number of redo sternotomies (%)				
0	52 (45.6)	44 (47.3)	8 (38.1)	
1	52 (45.6)	43 (46.2)	9 (42.9)	
2	8 (7.0)	5 (5.4)	3 (14.3)	
3	2 (1.8)	1 (1.1)	1 (4.8)	0.223
Had at least one PVR (%)	60 (52.6)	47 (50.5)	13 (61.9)	0.348
NYHA class N (%)				
1	107 (93.9)	90 (96.8)	17 (81.0)	
2	5 (4.4)	3 (3.2)	2 (9.5)	
3	1 (0.9)	0	1 (4.8)	
4	0	0	0	0.032
ECG median resting HR (IQR)	72 (62 - 79)	74 (62 - 80.5)	68 (61.5 - 75)	0.117
ECG QRS duration ms (IQR)	150 (134 - 164)	148 (133 - 161)	165 (141 - 186.75)	0.023
CPET median VO2 as % predicted (IQR)	71 (60.25 - 80)	72 (62 - 80.5)	63 (49 - 75)	0.078
CPET median VE/VCO2 slope (IQR)	32 (28.63 - 35.75)	31.5 (28 - 34.6)	35 (32 - 37.8)	0.012
CPET median peak HR as % predicted (IQR)	82 (75.5 - 89)	83.5 (77 - 89)	73 (67 - 90)	0.091

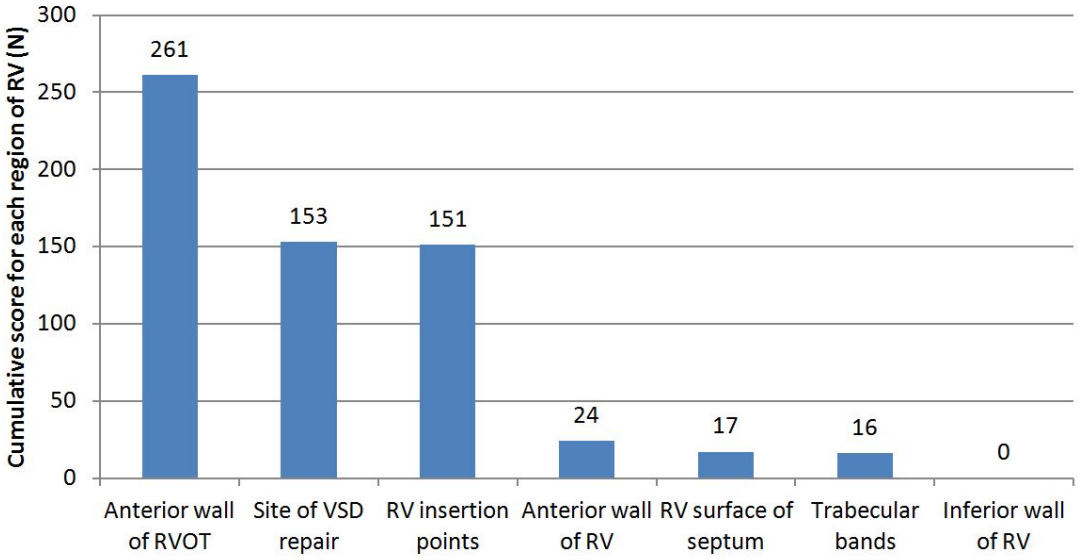
CMR median RVEDVi ml/m2 (IQR)	125 (100 - 152)	121 (99 - 144)	141 (121 - 168)	0.048
CMR median RVESVi ml/m2 (IQR)	64 (49.75 - 83)	61 (46.5 - 77.5)	79 (55.5 - 99)	0.036
CMR median RVEF % (IQR)	48 (43 - 54)	49 (44 - 54.5)	47 (37 - 53)	0.092
CMR median LVEDVi ml/m2 (IQR)	80.5 (72 - 93)	80 (70.5 - 91)	85 (74.5 - 108.5)	0.071
CMR median LVESVi ml/m2 (IQR)	32 (27 - 41)	31 (27 - 40)	37 (29 - 51)	0.022
CMR median LVEF % (IQR)	59 (54.75 - 64)	60 (55.5 - 65)	56 (52 - 60)	0.025
Median pulmonary regurgitant fraction % (IQR)	28.5 (10.75 - 38.5)	28 (10.5 - 36.5)	31 (12.5 - 46)	0.163
Median RV LGE score /20 (IQR)	6 (5 - 7)	6 (4 - 6.5)	6 (5 - 7.5)	0.069
Median LV LGE mass % (IQR)	1.75 (0.7 - 3.23)	1.55 (0.5 - 2.95)	2.9 (1.7 - 4.2)	0.008

The majority of patients were male, most were repaired in the 1980s, and under half had received a palliative shunt prior to complete repair. Symptomatic dyspnoea was rare, with almost 95% of patients in NYHA class 1. Across the cohort both the median peak VO2 and heart rate response to exercise were reduced compared to the predicted values, and median VE/VCO2 was slightly elevated at 32. Regarding CMR data, the median indexed RV volumes were elevated in comparison to a reference population (Maceira et al., 2006, Kawel-Boehm et al., 2015) although median LV volumes were comparable, with a slight reduction in LVEF driven by a rise in LVESVi. Approximately 22% of patients had negligible pulmonary regurgitation (RF <5%), either due to prior PVR which still retained good function, or an initial surgical repair which preserved the function of the pulmonary valve. The remainder had significant pulmonary regurgitation with a median regurgitant fraction of almost 30%.

6.3.2 Distribution and extent of LGE

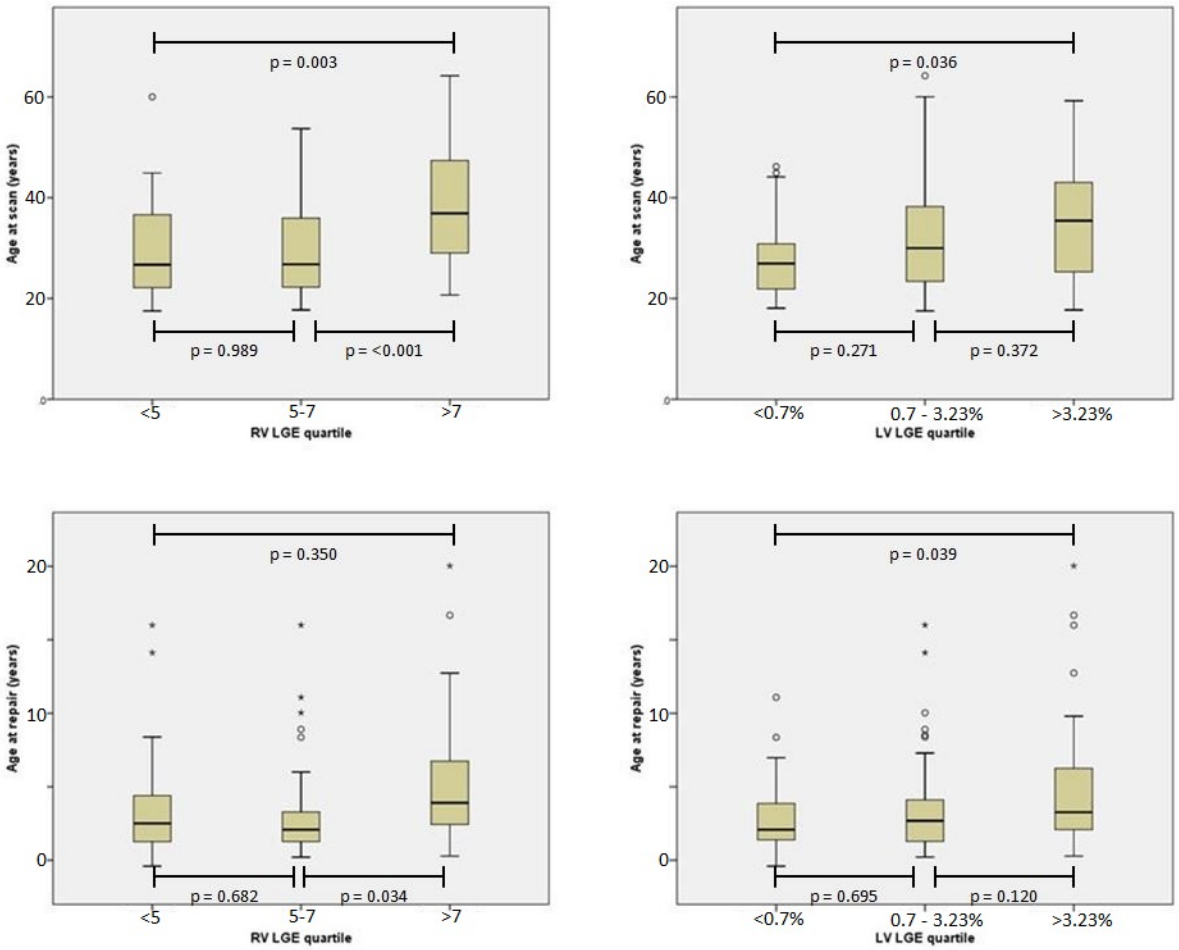
All patients had at least some RV LGE evident. Median RV LGE score was 6/20, and the pattern of LGE was consistent, being almost always seen at the surgical sites of the RVOT and VSD patch, and the insertion points of the RV on to the LV (Figure 6.3). Median LV LGE mass expressed as a percentage of total LV myocardial mass was low at 1.75%, and in almost all cases LGE was confined to in or around the insertion points of the RV on the interventricular septum. Only 9 patients had no LV LGE evident. There were three patients with overall significantly higher LGE mass than the remainder of the cohort, all of whom had undergone myocardial infarction.

Figure 6-3 Distribution of LGE within the right ventricle



As outlined in figure 6.4, when the cohort was divided into quartiles[16], there was a clear relationship between the RV LGE score and age at scan and age at repair. There was also a statistically significant difference between the LV LGE mass and age at scan and age at repair.

Figure 6-4 Relationship between age at scan / age at repair and right and left ventricular LGE



[16] For each panel, from left to right, the data is presented as the lowest quartile (Q1), the interquartile range (Q2 and Q3), and the highest quartile (Q4)

The Spearman rank coefficient was used to identify whether there was any correlation between parameters derived from CMR and from CPET. There was no significant correlation between either RV LGE score and LV LGE mass and the following variables: peak VO2, peak VO2 as a percentage of the peak predicted value, VE/VCO2 slope, and peak HR as a percentage of the peak predicted value. There was weak negative but significant correlation between RV LGE score and RVEF (r = -0.193, *p*=0.036). LV LGE score and LVEDVi were weakly correlated (r = 0.216, *p*=0.021), as were LV LGE score and LVESVi (r = 0.201, *p*=0.032). RV LGE score and LV LGE mass weakly correlated with each other (r = 0.267, *p*=0.004).

6.3.3 Adverse events and LGE: a cross-sectional analysis

The next step in the analysis was to compare the characteristics of the 21 patients who had experienced an adverse event at any time (atrial arrhythmia, sustained ventricular arrhythmia, ICD implantation or heart failure admission) with the 93 patients who had not (table 6.1). The patients who had experienced an adverse event were significantly older both at age of repair and age at CMR scan. They were more likely to have symptomatic breathlessness, have a wider QRS duration on ECG, and have a higher VE/VCO2 ratio on CPET. The RVEDVi and RVESVi were significantly higher as was LVESVi, although LVEDVi did not quite approach statistical significance. Consequently LVEF (but not RVEF) was lower in this group. They displayed a higher LV LGE mass, and there was the suggestion that they also had a higher RV LGE score, although this did not reach significance at the 0.05 level.

6.3.4 Survival analysis

The final step was to establish which factors were associated with an increased hazard of a composite outcome of adverse cardiac events at a mean follow up of 2.35 years (SD 1.29) from time of scan, and whether these included RV or LV LGE. Of the 21 patients who experienced an adverse outcome, 10 had experienced it before the time of baseline CMR scan. This left 11 patients who could be included in the survival analysis. The results of the univariate analysis are outlined in table 6.2. A higher RVEDVi, LVEDVi, older age at scan, NYHA class, and LV LGE mass conferred risk for an adverse event, as did a lower RVEF, LVEF and peak HR during CPET (expressed as a percentage of the peak predicted value). Of note RV LGE score did not. As the patients who experienced adverse events tended to be significantly older than those who did not, it was decided to repeat the analysis adjusting for age at scan as a covariate, and the results are shown in table 6.3. Briefly, RVEDVi, LVEDVi, RVEF, LVEF and NYHA class all continued to be significantly associated to the development of adverse outcomes, as well as having a higher number of redo sternotomies or a lower peak VO2 during CPET. LV LGE mass and peak HR as a percentage of the predicted value during CPET trended

towards but did not reach statistical significance at the 0.05 level, and RV LGE score was not significantly associated.

Table 6-2 Prediction of a composite endpoint of atrial arrhythmia, sustained ventricular tachycardia, device insertion, or hospitalisation with heart failure after index CMR scan

	Adverse events N = 11 (9.6%)		
	Hazard ratio	95% confidence intervals	*P*
RV LGE score	1.238	0.928 - 1.65	0.146
LV LGE mass %	1.345	1.035 - 1.749	0.027
RVEDVi	1.013	1.006 - 1.020	<0.001
RVEF	0.933	0.874 - 0.997	0.039
LVEDVi	1.032	1.017 - 1.047	<0.001
LVEF	0.934	0.890 - 0.981	0.006
Male gender	2.156	0.571 - 8.134	0.257
Age at repair	0.997	0.846 - 1.175	0.971
Age at scan	1.073	1.023 - 1.124	0.004
Number prior redo sternotomies	1.837	0.857 - 3.939	0.118
Transannular patch	0.464	0.099 - 2.188	0.332
ECG QRSi	1.024	0.997 - 1.053	0.083
NYHA class	3.987	1.325 - 11.993	0.014
Peak VO2 % predicted	0.966	0.922 - 1.012	0.146
Peak HR % predicted	0.934	0.884 - 0.986	0.014
VE/VCO2 slope	1.066	0.957 - 1.188	0.245

Table 6-3 Prediction of a composite endpoint of atrial arrhythmia, sustained ventricular tachycardia, device insertion, or hospitalisation with heart failure after index CMR scan, adjusting for age at scan as a covariate

Variable	Adverse events N = 11 (9.6%)		
	Hazard ratio	95% confidence intervals	*P*
RV LGE score	1.003	0.742 - 1.357	0.982
Age at scan	1.072	1.015 - 1.132	0.012
LV LGE mass %	1.293	0.980 - 1.706	0.070
Age at scan	1.085	1.028 - 1.144	0.003
RVEDVi	1.011	1.004 - 1.018	0.002
Age at scan	1.065	1.015 - 1.118	0.011
RVEF	0.924	0.865 - 0.987	0.002
Age at scan	1.083	1.029 - 1.139	0.020
LVEDVi	1.027	1.012 - 1.041	< 0.001
Age at scan	1.061	1.008 - 1.117	0.023
LVEF	0.939	0.893 - 0.988	0.015
Age at scan	1.066	1.018 - 1.116	0.006
Number redo sternotomies	2.201	1.022 - 4.740	0.044
Age at scan	1.083	1.028 - 1.140	0.002

ECG QRSi	1.020	0.994 - 1.047	0.132
Age at scan	1.057	0.995 - 1.123	0.075
NYHA class	5.377	1.606 - 18.004	0.006
Age at scan	1.081	1.022 - 1.144	0.007
Peak VO2 % predicted	0.939	0.887 - 0.993	0.028
Age at scan	1.128	1.054 - 1.207	0.001
Peak HR % predicted	0.951	0.898 - 1.007	0.086
Age at scan	1.084	1.024 - 1.147	0.006

6.4 Discussion

6.4.1 Presence and extent of LGE in repaired TOF

The amount of LGE seen in the RV was relatively low in most patients, and almost exclusively consigned to the insertion points of the RV on to the LV, and sites of surgical intervention, namely the RVOT and site of VSD patch repair. This is similar to that reported previously (Babu-Narayan et al., 2006), and is possibly due to increased haemodynamic stress from RV volume in the case of the RV insertion points. With the exception of a small number of outliers who had suffered myocardial infarcts the amount of LV LGE was also low with a median value of 1.75% (IQR 0.7 - 3.23%).

The was a weak relationship between the quantity of RV LGE seen and older age at surgery, older age at time of scan, and repair in an earlier surgical era. There was also a weak relationship between the LV LGE mass, and age at the time of scan and age at repair. These findings are perhaps not unexpected. Patients who underwent surgical repair in the 1960s and 1970s typically underwent repair of the defects through right ventriculotomy, and did not benefit from more modern techniques of myocardial preservation. From the 1980s onwards the preferred technique for repair was a combined transatrial and transpulmonary approach, with no direct incision over the free wall of the RV. This suggests that ventricular fibrosis may be associated with transventricular approach and earlier techniques of myocardial protection.

There was a weak but significant inverse correlation between RV LGE and RVEF, implying that increased fibrosis of the RV is associated with reduced stroke volume and RV systolic impairment. On the other hand, regarding the LV, whilst there was a positive correlation between LV LGE and indexed LV end diastolic volume, no corresponding inverse correlation between LV LGE and LVEF was seen, This perhaps suggests that LV fibrosis may be associated with an increase in LV end diastolic volume initially, with an increase in end systolic volumes and reduction in LVEF occurring later on, i.e. too late to be seen in this cohort over the specified follow-up period. Further work would be required to confirm this hypothesis, although it is well documented that LV dysfunction is typically a very late

complication in repaired TOF (Apitz et al., 2009), and, as a relatively young cohort, this study population may therefore have been too "healthy" to display this relationship in its entirety. The overall impression of all of the above however, is that the amount of LGE is associated with a more dysfunctional ventricle, and this reinforces findings from previous work (Wald et al., 2009, Oosterhof et al., 2005).

This did not however translate into a significant association with adverse markers of exercise performance. This is likely to be because the determinants of exercise performance in individuals with repaired TOF are complex, depending not just on ventricular volumes and contractility - which *could* conceivably be affected by LGE as a marker of ventricular fibrosis - but also factors such as heart rate response, minute ventilation, and abnormalities of gas exchange. Furthermore, it was not possible to adjust for baseline levels of training and fitness in individuals in this cohort, and so varying degrees of physical deconditioning may also have had an effect. Thus LGE in isolation is not likely to prove particularly useful in this regard.

6.4.2 Use of LGE to identify patients at higher risk of adverse outcomes in comparison to other parameters derived from CMR and CPET

LV LGE mass, but not RV LGE score, was predictive of an adverse outcome over the follow-up period at the 0.05 level in a univariate model (Table 3), and interestingly this finding has been also shown by other groups when assessing myocardial fibrosis via the quantification of ECV: Chen and colleagues found that in a group of 84 TOF survivors greater LV ECV, but not RV ECV, was associated with arrhythmia on univariate analysis, although arrhythmia in this context included not just atrial arrhythmia and sustained VT but also frequent ventricular ectopy and non-sustained VT (Chen et al., 2016). Broberg and colleagues looked exclusively at LV ECV in a smaller, older group of 48 TOF survivors, and over a follow-up period of 3.5 +/- 1.5 years reported that of the patients with extensive LV ECV (defined as a fraction >30%), 5/15 experienced the adverse outcome of atrial arrhythmia (3) or death (2), whereas only 2/37 patients experienced atrial arrhythmia in the low LV ECV group, with no deaths (Broberg et al., 2016). This is contrast to the 2006 paper where RV LGE did predict arrhythmia (Babu-Narayan et al., 2006). The reason that RV LGE score, and indeed RV ECV, have not been shown to be

predictive of an adverse outcome since is unclear. There will clearly be a birth cohort effect with the 2006 paper including older patients, furthermore it is difficult to accurately quantify the extent of abnormal areas of enhancement in the thin-walled RV to the same degree of precision as the LV at 1.5 Tesla.

Another key issue to bear in mind is that when a bivariate analysis was performed - adjusting for age at the time of initial surgical repair - LV LGE mass trended towards but did not reach the 0.05 level of significance as a predictor of an adverse clinical outcome (Table 4). This is in contrast to other, more established makers of a poor prognosis in repaired TOF such as indexed RVEDV, LVEF, NYHA class and peak oxygen uptake on cardiopulmonary exercise testing which did achieve this level of statistical significance in this cohort. Again this does bring into question the clinical utility of LGE in TOF.

6.4.3 Limitations

When interpreting these findings a number of limiting factors need to be taken into account. This was a single centre study and included a heterogeneous group of patients. Despite being larger than other published studies of TOF patients undergoing CMR, this cohort was still relatively small and patients experienced a low number of primary outcome events, preventing multivariable analysis. Patients who had already received a pacemaker before they could undergo CMR scanning were by definition excluded, and they could well have been in a higher risk group, thus giving rise to selection bias. The semiquantitative means of estimating RV LGE is likely to be inferior to a formal quantification of RV LGE mass, although as described previously the latter is technically more difficult to achieve. Due to the method of estimating LV LGE mass from the short axis stack it was not possible to quantify any areas of LGE at the apex of the LV, as exemplified by some older patients who underwent insertion of a transmural apical vent at the time of surgery - however the amount of LGE here was likely to be negligible in terms of absolute quantity. Finally the administration of Gadolinium contrast was not repeated in follow up scans for the vast majority of patients, and so it was not possible to determine whether the amount of LGE increases over time and whether rate of change is more significant than the absolute value. However,

given the small amounts of LGE seen overall, it is likely that a large time interval would be required to see any significant difference. It was necessary to exclude patients who had already experienced an adverse outcome at the time of scan from the survival analysis; therefore as with other, similar, studies, the data is subject to the problem of left censoring.

6.4.4 Conclusion

In summary, in a contemporary cohort of patients with repaired TOF, the amount of LGE is lower in younger patients who underwent repair at an earlier age. LGE is rarely seen outwith the sites of surgical repair or the insertion points of the RV on to the LV. It is associated with other markers of ventricular dysfunction such as increased volume and reduced ejection fraction, but not exercise performance. The data presented here suggest that LV myocardial fibrosis as quantified by LGE is useful as a univariate predictor of adverse outcomes in contemporary adult survivors of TOF. However the data does not allow the construction of a robust multivariable model, and in view of the low incidence of hard clinical endpoints in this patient group, it is clear that only a large, prospective, multicentre study with follow up for a much longer period of time would achieve this. If this data can be obtained then the risk of ventricular arrhythmia, heart failure hospitalisation, and death can be more formally quantified, thus helping to guide clinical decision making and perhaps allow the creation of a formal risk scoring system.

Chapter 7 Discussion

7.1 Summary of findings

Chapter 3 summarised the results of a review of a total of 41 papers relating to patients with a systemic RV and repaired TOF. I confirmed that mortality is higher for those patients with a systemic RV, and of those patients with a systemic RV mortality is worse in CCTGA when compared to TGA-atrial switch. Survival to 30 years from baseline (generally taken as the date of initial surgical repair) for repaired TOF and TGA-atrial switch was relatively good at 86% and 78% respectively, but for CCTGA the equivalent figure was only 51% (see Table 3.5 and Figure 3.2). The only consistent risk factor for mortality identified was earlier birth cohort / earlier surgical era, although a transannular patch repair was also identified as conferring a worse prognosis for patients with repaired TOF by three papers. No differences in gender were reported. Geographical variation within countries (and urban versus rural split) was not assessed by any paper I reviewed, however at an international level cohorts from East Asia reported the highest cumulative survival for all diagnostic groups. No studies assessed for the effect of socioeconomic status. Unfortunately with the exception of reintervention morbidity outcomes and functional status were barely reported, despite their clear importance to any patient living with one of these conditions. And even with reintervention, outcomes were often simply reported as a cross-sectional analysis or "snapshot" at the end of the study period, rather than cumulative survival, and so estimates tended to vary considerably. Rates of reintervention tended to be much higher in the more contemporary papers; in the earliest cohorts the mean age of adult patients with these diagnoses was still low and therefore they had not had time to develop some of the later sequelae of their respective diagnoses.

Chapters 4 and 5 describe my own analysis of data relating to cohorts of patients with systemic RV and repaired TOF respectively. This is the first time mortality and morbidity in a contemporary, nationwide population of ACHD patients in Scotland has been reported.

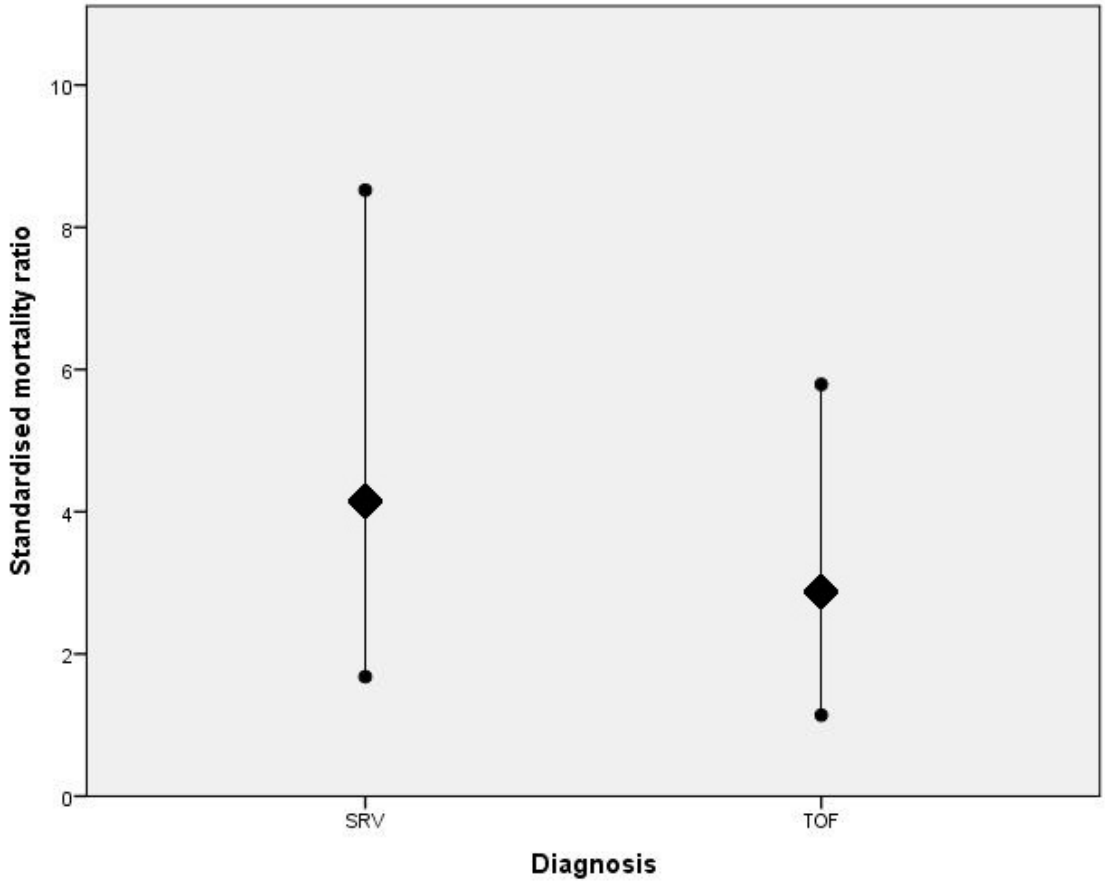
I confirmed that the finding of a higher mortality in SRV patients versus TOF patients appears to apply to Scotland as well, both by using the Kaplan Meier technique to assess cumulative survival, and also by calculating the appropriate

SMRs (Figure 7.1). The SMRs I obtained for the Scottish cohort were similar to those obtained by the only other study I identified which reported SMRs for these groups of ACHD patients in a large tertiary centre elsewhere in the UK (Diller et al., 2015).

Within the SRV cohort, patients with CCTGA did not appear to fare as badly with respect to TGA-atrial switch patients as they did in the papers identified in the literature review. By log rank test there was no significant difference in cumulative survival between these two groups, and furthermore the 95% confidence interval estimates of SMR overlapped considerably. Clearly it would be impossible to conclusively identify why this is the case - at least without comparing patient-level data between all of the studies - however the most obvious hypothesis would be that the other CCTGA papers all included childhood mortality, and therefore would have included children with the most severe forms of CCTGA with multiple associated structural lesions who would have been less likely to survive to adulthood.

Within the TOF cohort cumulative mortality was relatively low, however in a multivariable model increased RVEDV at baseline, older age at repair, and female gender appeared to confer a higher risk of a composite outcome of death and arrhythmia.

Figure 7.1: Comparison of SMR between patients with a systemic RV and patients with repaired TOF



When morbidity outcomes for the SRV group are compared to the TOF group it becomes apparent that crude event rates (expressed as per 100 years of patient follow-up) appear to be higher in the TOF group for arrhythmia and reintervention (Table 7.1). The former appears to be driven largely by the fact that no ventricular arrhythmia was documented in the SRV group at all (although presumably as this group ages and more patients develop severe SRV dysfunction this will change), the latter by the sheer number of PVRs performed in the TOF group. Raw data such as this needs does need to be interpreted with caution however, as clearly the baseline reference point was not the same for each group, and clearly the values obtained will take no account of outcomes that occurred before the follow-up period.

When functional status is compared, this was ostensibly better in the TOF cohort. Almost 97% of TOF patients were in NYHA class 1 compared to 67% in the SRV cohort. This relationship was confirmed by those patients who underwent CPET assessment: peak VO2 as a percentage of the predicted value was higher, and the VE/VCO2 slope was lower in the TOF cohort compared to the SRV cohort (69% versus 66%, and 36 versus 33 respectively, in keeping with results published elsewhere (Diller et al., 2005, Dimopoulos et al., 2006). This lends support to the hypothesis that a morphological RV is less well adapted to support the physiological demands of exercise compared to a morphological LV. Prescribing of cardiac medication in both cohorts was low. The commonest class of drug prescribed in patients with a systemic RV was an ACE inhibitor / A2RB (16% of TGA-atrial switch and 19% of CCTGA patients), whereas in the TOF cohort it was a betablocker - mainly for those patients who had experienced arrhythmia.

Table 7-1 Crude incidence of adverse outcomes in patients with a systemic RV and patients with repaired TOF

Outcome	SRV			TOF		
	N events	Person y follow-up	Event rate per 100 person y	N events	Person y follow-up	Event rate per 100 person y
Death	7	1559.7	0.45	7	1248.7	0.56
Arrhythmia (any)	21	1361.4	1.54	35	1069.7	3.27
Ventricular arrhythmia	0	N/A	N/A	14	1206.4	1.16
Atrial arrhythmia	21	1361.4	1.54	25	1162.1	2.15
Cardiac device[17]	17	1311.6	1.30	16	1203.6	1.33
Reintervention	22	1109.1	1.98	70	1025.4	6.79

Regarding morbidity outcomes within the SRV group, patients with CCTGA tended to experience less arrhythmia and less reintervention after the baseline of 18 years, but a higher incidence of pacemaker implantation. Again one can only speculate as to the pathophysiological mechanisms underpinning this observation, but the greater rates of arrhythmia and reintervention in the TGA-atrial switch group may well have been driven by the fact that by definition the interatrial baffles create scar which leads to electrical re-entry (and hence arrhythmia), and also creates the propensity for stenosis and leaks (which drives the need for reintervention). In CCTGA patients anatomy of the AV node is variable, and VSD is more frequent - both of these factors can result in AV block.

The final results chapter, chapter 6, looked at the role of cardiac MRI in more detail, specifically with regard to establishing prognosis in repaired TOF. To my knowledge this is the largest published series to formally quantify the degree of myocardial fibrosis (as measured by LGE) in the LV and RV, and it showed that increased fibrosis was associated with adverse clinical outcomes, although the

[17] Includes pacemaker, CRT, and ICD implantation

relatively small number of clinical events in the follow up period made it difficult to quantify the nature of this relationship by means of a multivariable analysis.

7.2 Limitations

Ultimately this was a single centre retrospective study, with all the inherent limitations that this entails. Mortality was low, and this made it difficult to create a robust multivariable model to identify those patients at higher risk of death. Following the literature review it became apparent that almost all of the other published literature was subject to the same problem, and owing to the wide variety of ways in which criteria for study entry were specified and clinical outcomes were reported, it would be impossible to carry out a robust meta-analysis to address this. Another problem arises when trying to define the baseline characteristics for the population of interest, specifically with regards to the actual operations undertaken. There are a daunting number of different codes for the various types of congenital cardiac surgery which may be performed, and even if these are entered correctly it may be impossible to try and summarise them in a meaningful way without reference to the original operation note. Actual operation notes are only readily available from the digital era of medical records i.e. after 2007-2008, and prior to this one is faced with the prospect of trying to unearth the original paper based health records, sourcing them from a wide variety of different centres and trying to account for the fact that there may be no standardised unique patient identification number from that era, and that patent's names may have changed in the interim. This leads on to the wider problem of missing data for a host of investigations and clinical outcomes, and how there is a pressing need for this to be improved. Finally, although I collected general data regarding Carstairs deprivation scores for the TOF cohort, I did not gather specific data regarding educational attainment and employment status - arguably this would provide a more nuanced assessment of socioeconomic status in these patients, in addition to being an outcome which is poorly reported in the literature.

7.3 Clinical implications and future directions for research

The ever expanding population of adults with congenital heart disease represents a major challenge to the National Health Service in Scotland, with a high level of morbidity that is not easy to manage even with a comprehensive (and expensive) range of cardiac investigations, procedures and operations. All of the above suggests that we need larger numbers of patients, standardised reporting of baseline characteristics and patient outcomes, and prospective rather than retrospective follow up. Perhaps the best way of achieving this would either be through the creation of a national or international registry. Whilst the Central Cardiac Audit Database (CCAD) reports outcomes for surgical or percutaneous procedures in a standardised way for ACHD patients throughout the UK, the data focuses primarily on 30-day mortality. Far more powerful would be a registry with clearly defined entry criteria for each particular congenital cardiac diagnosis, uniform outcome reporting, case linkage to other national registries such as births, deaths and acute hospital admissions, and regular uploading of data derived from ECG, CMR and CPET for each patient. The sheer volume of data generated from such a program would make it very easy to identify multivariable predictors of mortality and morbidity, document trends in survival over time, and allow the creation of a risk scoring system for specific diagnoses or adverse outcomes. This would also allow data to be collected on the "milder" forms of congenital heart disease such as bicuspid aortic valve and small VSDs, where as described previously patients may not come through the national centre. This is important because these patients form a much larger cohort as a whole, and their prognosis, whilst better than for the moderate and great complexity lesions, is still worse than the general population and not as benign as previously assumed (Videbæk et al., 2015). Yet another advantage of such a system is that it would automatically highlight which patients had not undergone key tests such as cardiac MRI and CPET, thus prompting the clinical team to investigate why - e.g. is there a large proportion of patients who are genuinely unable to undergo these tests, does capacity need to be expanded, and so on. And finally it would be possible to design and test simple clinical scoring systems which may identify which patients could be at higher risk for adverse outcomes, or who might benefit most from a particular

intervention or therapy. This has recently been applied to a large multicentre cohort of patients undergoing catheter-based intervention (Stefanescu et al., 2017), but given sufficient patient numbers similar systems could readily be applied to specific diagnostic groups or those patients undergoing a specific procedure e.g. PVR.

The issue to consider is how mortality and morbidity is reported. For reasons discussed earlier, cumulative survival from baseline using the Kaplan Meier method, whilst useful, is not as generalisable as reporting a standardised mortality ratio. Could morbidity outcomes be reported in the same way - as standardised morbidity ratios - when compared to the general Scottish population? Whilst this would not necessarily be applicable for very specialised outcomes such as PVR, it would certainly be relevant for other more widely reported cardiovascular outcomes such as stroke, myocardial infarction, heart failure, and endocarditis, and if this could be re-assessed at regular intervals (say every 2-3 years) it would provide a useful barometer as to whether the ACHD population as a whole is getting sicker or healthier, and also identify where the clinical need for preventative medicine is greatest for these patients.

With regard to assessing the clinical efficacy and cost effectiveness of an intervention such as PVR, the best way forward would be through the creation of a multicentre randomised control trial - perhaps using different thresholds for when to intervene. However this would be difficult - there would need to be some way of standardising patients by entry criteria, furthermore there would likely need to be at least several years worth of follow-up to show a meaningful difference in hard clinical outcomes rather than surrogate endpoints such as change in RV volumes.

Lastly I have shown that variation in outcomes by gender, socioeconomic status and geographical region are rarely reported. Whilst the Scottish data suggests that, at least for adult survivors of TOF, socioeconomic status is comparable to the general population, there is a suggestion that female patients may do worse when RVEDV is taken into account, and clearly these factors are worthy of dedicated study.

7.4 Conclusion

In this thesis I have demonstrated to the reader just how much uncertainty there is in establishing long term prognosis in ACHD, and how much of what might be regarded as routine clinical data is manifestly absent from the results reported by many congenital cardiac centres across the world. Retrieving and analysing the data in the course of this project has been a useful exercise, and has not just allowed the detailed characterisation of outcomes in two large, contemporary, national ACHD cohorts in Scotland, but also provided insight into how this can be achieved more efficiently and effectively. I have identified significant areas where knowledge gaps exist, and suggested ways in which these might be addressed. All of the above will hopefully allow us to identify where the areas of greatest clinical need are in ACHD, and where we might make the most significant contributions to improving the outlook for this important, complex group of patients.

Chapter 8 References

ACAR, P., SIDI, D., BONNET, D., AGGOUN, Y., BONHOEFFER, P. & KACHANER, J. 1998. Maintaining tricuspid valve competence in double discordance: a challenge for the paediatric cardiologist. *Heart,* 80**,** 479-483.

AGNETTI, A., CARANO, N., CAVALLI, C., TCHANA, B., BINI, M., SQUARCIA, U. & FRIGIOLA, A. 2004. Long-term outcome after Senning operation for transposition of the great arteries. *Clinical Cardiology,* 27**,** 611-614.

APITZ, C., WEBB, G. D. & REDINGTON, A. N. 2009. Tetralogy of Fallot. *The Lancet,* 374**,** 1462-1471.

BABU-NARAYAN, S. V., KILNER, P. J., LI, W., MOON, J. C., GOKTEKIN, O., DAVLOUROS, P. A., KHAN, M., HO, S. Y., PENNELL, D. J. & GATZOULIS, M. A. 2006. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. *Circulation,* 113**,** 405-413.

BAUMGARTNER, H., BONHOEFFER, P., DE GROOT, N. M., DE HAAN, F., DEANFIELD, J. E., GALIE, N., GATZOULIS, M. A., GOHLKE-BAERWOLF, C., KAEMMERER, H., KILNER, P., MEIJBOOM, F., MULDER, B. J., OECHSLIN, E., OLIVER, J. M., SERRAF, A., SZATMARI, A., THAULOW, E., VOUHE, P. R., WALMA, E., VAHANIAN, A., AURICCHIO, A., BAX, J., CECONI, C., DEAN, V., FILIPPATOS, G., FUNCK-BRENTANO, C., HOBBS, R., KEARNEY, P., MCDONAGH, T., POPESCU, B. A., REINER, Z., SECHTEM, U., SIRNES, P. A., TENDERA, M., VARDAS, P., WIDIMSKY, P., SWAN, L., ANDREOTTI, F., BEGHETTI, M., BORGGREFE, M., BOZIO, A., BRECKER, S., BUDTS, W., HESS, J., HIRSCH, R., JONDEAU, G., KOKKONEN, J., KOZELJ, M., KUCUKOGLU, S., LAAN, M., LIONIS, C., METREVELI, I., MOONS, P., PIEPER, P. G., PILOSSOFF, V., POPELOVA, J., PRICE, S., ROOS-HESSELINK, J., UVA, M. S., TORNOS, P., TRINDADE, P. T., UKKONEN, H., WALKER, H., WEBB, G. D. & WESTBY, J. 2010. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *European Heart Journal,* 31**,** 2915-2957.

BENZAQUEN, B. S., WEBB, G. D., COLMAN, J. M. & THERRIEN, J. 2004. Arterial switch operation after Mustard procedures in adult patients with transposition of the great arteries: is it time to revise our strategy? *American Heart Journal,* 147**,** E8.

BILLETT, J., MAJEED, A., GATZOULIS, M. & COWIE, M. 2008. Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. *Heart,* 94**,** 342-8.

BOKMA, J., WINTER, M. M., OOSTERHOF, T., VLIEGEN, H., VAN DIJK, A., HAZEKAMP, M., KOOLBERGEN, D., GROENINK, M., MULDER, B. & BOUMA, B. 2015. Severe tricuspid regurgitation is predictive for adverse events in Tetralogy of Fallot. *Heart,* 101**,** 794-99.

BRAWN, W. J. 2005. The double switch for atrioventricular discordance. *Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual***,** 51-6.

BROBERG, C. S., HUANG, J., HOGBERG, I., MCLARRY, J., WOODS, P., BURCHILL, L. J., PANTELY, G. A., SAHN, D. J. & JEROSCH-HEROLD, M. 2016. Diffuse LV Myocardial Fibrosis and its Clinical Associations in Adults With Repaired Tetralogy of Fallot. *JACC Cardiovascular Imaging,* 9**,** 86-87.

BROWN, K. L., CROWE, S., FRANKLIN, R., MCLEAN, A., CUNNINGHAM, D., BARRON, D., TSANG, V., PAGEL, C. & UTLEY, M. 2015. Trends in 30-day mortality rate and case mix for paediatric cardiac surgery in the UK between 2000 and 2010. *Open Heart,* 2.

BUECHEL, E., DAVE, H., KELLENBERGER, C., DODGE-KHATAMI, A., PRETRE, R., BERGER, F. & BAUERSFELD, U. 2005. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. *European Heart Journal,* 26**,** 2721-2727.

BUYS, R., VAN DE BRUAENE, A., DE MEESTER, P., BUDTS, W. & VANHEES, L. 2012. Predictors of mid-term event-free survival in adults with corrected Tetralogy of Fallot. *Acta Cardiologica,* 67**,** 415-21.

CARUANA, M. & GRECH, V. 2016. A first population-based long-term outcome study in adults with repaired tetralogy of Fallot in Malta. *Congenital Heart Disease,* doi: 10.1111/chd.12439 [Epub ahead of print].

CAVALCANTI, P., SÁ, M., SANTOS, C., ESMERALDO, I., ESCOBAR, R., MENEZES, A., AZEVEDO JR, O., SILVA, F., LINS, R. & LIMA, R. 2013. Pulmonary valve replacement after operative repair of Tetralogy of Fallot: meta-analysis and meta-regression of 3118 patients from 48 studies. *Journal of the American College of Cardiology,* 62**,** 2227-2243.

CHEN, C. A., DUSENBERY, S. M., VALENTE, A. M., POWELL, A. J. & GEVA, T. 2016. Myocardial ECV Fraction Assessed by CMR Is Associated With Type of Hemodynamic Load and Arrhythmia in Repaired Tetralogy of Fallot. *JACC Cardiovascular Imaging,* 9**,** 1-10.

CHIU, S. N., WANG, J. K., CHEN, H. C., LIN, M. T., WU, E. T., CHEN, C. A., HUANG, S. C., CHANG, C. I., CHEN, Y. S., CHIU, I. S., CHEN, C. L. & WU, M. H. 2012. Long-term survival and unnatural deaths of patients with repaired Tetralogy of Fallot in an Asian cohort. *Circulation: Cardiovascular Quality and Outcomes,* 5**,** 120-5.

COOLS, B., BROWN, S. C., LOUW, J., HEYING, R., MEYNS, B. & GEWILLIG, M. 2012. Pulmonary artery banding as 'open end' palliation of systemic right ventricles: an interim analysis. *European Journal of Cardio-Thoracic Surgery,* 41**,** 913-918.

CUYPERS, J., EINDHOVEN, J. A., SLAGER, M. A., OPIĆ, P., UTENS, E., HELBING, W., WITSENBURG, M., VAN DEN BOSCH, A., OUHLOUS, M., VAN DOMBURG, R., RIZOPOULOS, D., MEIJBOOM, F., BOGERS, A. & ROOS-HESSELINK, J. 2014. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *European Heart Journal,* 35**,** 1666-1674.

DEARANI, J. A., DANIELSON, G. K., PUGA, F. J., SCHAFF, H. V., WARNES, C. W., DRISCOLL, D. J., SCHLECK, C. D. & ILSTRUP, D. M. 2003. Late follow-up of 1095 patients undergoing operation for complex congenital heart disease utilizing pulmonary ventricle to pulmonary artery conduits. *Annals of Thoracic Surgery,* 75**,** 399-410; discussion 410-1.

DILLER, G. P., DIMOPOULOS, K., OKONKO, D., LI, W., BABU-NARAYAN, S. V., BROBERG, C. S., JOHANSSON, B., BOUZAS, B., MULLEN, M. J., POOLE-WILSON, P. A., FRANCIS, D. P. & GATZOULIS, M. A. 2005. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation,* 112**,** 828-35.

DILLER, G. P., DIMOPOULOS, K., OKONKO, D., UEBING, A., BROBERG, C. S., BABU-NARAYAN, S., BAYNE, S., POOLE-WILSON, P. A., SUTTON, R., FRANCIS, D. P. & GATZOULIS, M. A. 2006. Heart rate response during exercise predicts survival in adults with congenital heart disease. *Journal of the American College of Cardiology,* 48**,** 1250-6.

DILLER, G. P., KEMPNY, A., ALONSO-GONZALEZ, R., SWAN, L., UEBING, A., LI, W., BABU-NARAYAN, S., WORT, S. J., DIMOPOULOS, K. & GATZOULIS, M. A. 2015. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation,* 132**,** 2118-25.

DILLER, G. P., OKONKO, D. O., UEBING, A., DIMOPOULOS, K., BAYNE, S., SUTTON, R., FRANCIS, D. P. & GATZOULIS, M. A. 2009. Impaired heart rate response to exercise in adult patients with a systemic right ventricle or univentricular circulation: prevalence, relation to exercise, and potential therapeutic implications. *International Journal of Cardiology,* 134**,** 59-66.

DIMOPOULOS, K., GIANNAKOULAS, G., BENDAYAN, I., LIODAKIS, E., PETRACO, R., DILLER, G. P., PIEPOLI, M. F., SWAN, L., MULLEN, M., BEST, N., POOLE-WILSON, P., FRANCIS, D. P., RUBENS, M. B. & GATZOULIS, M. A. 2013. Cardiothoracic ratio from postero-anterior chest radiographs: a simple, reproducible and independent marker of disease severity and outcome in adults with congenital heart disease. *International Journal of Cardiology,* 166**,** 453-457.

DIMOPOULOS, K., OKONKO, D. O., DILLER, G. P., BROBERG, C. S., SALUKHE, T. V., BABU-NARAYAN, S. V., LI, W., UEBING, A., BAYNE, S., WENSEL, R., PIEPOLI, M. F., POOLE-WILSON, P. A., FRANCIS, D. P. & GATZOULIS, M. A. 2006. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation,* 113**,** 2796-802.

DOBSON, R., DANTON, M., WALKER, N. & WALKER, H. 2013. The natural and unnatural history of the systemic right ventricle in adult survivors. *The Journal of Thoracic and Cardiovascular Surgery,* 145**,** 1493-501; discussion 1501-3.

DOBSON, R., MORDI, I., DANTON, M., WALKER, N., WALKER, H. & TZEMOS, N. 2017. Late gadolinium enhancement and adverse outcomes in a contemporary cohort of adult survivors of Tetralogy of Fallot. *Congenital Heart Disease,* 12**,** 58-66.

DOBSON, R., TZEMOS, N. & WALKER, H. 2014. 48 Relationship Between Socioeconomic Status and Survival in Scottish Adults with Tetralogy of Fallot. *Heart,* 100**,** A28.

DOS, L., TERUEL, L., FERREIRA, I. J., RODRIGUEZ-LARREA, J., MIRO, L., GIRONA, J., ALBERT, D. C., GONCALVES, A., MURTRA, M. & CASALDALIGA, J. 2005. Late outcome of Senning and Mustard procedures for correction of transposition of the great arteries. *Heart,* 91**,** 652-656.

DRENTHEN, W., PIEPER, P. G., ROOS-HESSELINK, J. W., VAN LOTTUM, W. A., VOORS, A. A., MULDER, B. J., VAN DIJK, A. P., VLIEGEN, H. W., YAP, S. C., MOONS, P., EBELS, T. & VAN VELDHUISEN, D. J. 2007. Outcome of pregnancy in women with congenital heart disease: a literature review. *Journal of the American College of Cardiology,* 49**,** 2303-11.

DUBIN, A. M., JANOUSEK, J., RHEE, E., STRIEPER, M. J., CECCHIN, F., LAW, I. H., SHANNON, K. M., TEMPLE, J., ROSENTHAL, E., ZIMMERMAN, F. J., DAVIS, A., KARPAWICH, P. P., AL AHMAD, A., VETTER, V. L., KERTESZ, N. J., SHAH, M., SNYDER, C., STEPHENSON, E., EMMEL, M., SANATANI, S., KANTER, R., BATRA, A. & COLLINS, K. K. 2005. Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study. *Journal of the American College of Cardiology,* 46**,** 2277-83.

EGBE, A., UPPU, S., LEE, S., STROUSTRUP, A., HO, D. & SRIVASTAVA, S. 2015. Temporal Variation of Birth Prevalence of Congenital Heart Disease in the United States. *Congenital Heart Disease,* 10**,** 43-50.

ERDOGAN, H. B., BOZBUGA, N., KAYALAR, N., ERENTUG, V., OMEROGLU, S. N., KIRALI, K., IPEK, G., AKINCI, E. & YAKUT, C. 2005. Long-term outcome after total correction of tetralogy of Fallot in adolescent and adult age. *Journal of Cardiac Surgery,* 20**,** 119-23.

FINKELSTEIN, D., MUZIKANSKY, A. & SCHOENFELD, D. 2003. Comparing survival of a sample to that of a standard population. *Journal of the National Cancer Institute,* 95**,** 1434-1439.

FREDRIKSEN, P., THERRIEN, J., VELDTMAN, G., WARSI, M., LIU, P., SIU, S., WILLIAMS, W., GRANTON, J. & WEBB, G. 2001. Lung function and aerobic capacity in adult patients following modified Fontan procedure. *Heart,* 85**,** 295-299.

FRIEDLI, B. 1999. Electrophysiological follow-up of Tetralogy of Fallot. *Pediatric Cardiology,* 20**,** 326-330.

FRIGIOLA, A., TSANG, V., BULL, C., COATS, L., KHAMBADKONE, S., DERRICK, G., MIST, B., WALKER, F., VAN DOORN, C., BONHOEFFER, P. & TAYLOR, A. M. 2008. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? *Circulation,* 118**,** S182-90.

GAIES, M. G., GOLDBERG, C. S., OHYE, R. G., DEVANEY, E. J., HIRSCH, J. C. & BOVE, E. L. 2009. Early and intermediate outcome after anatomic repair of congenitally corrected transposition of the great arteries. *Annals of Thoracic Surgery,* 88**,** 1952-1960.

GATZOULIS, M. A., BALAJI, S., WEBBER, S. A., SIU, S. C., HOKANSON, J. S., POILE, C., ROSENTHAL, M., NAKAZAWA, M., MOLLER, J. H., GILLETTE, P. C., WEBB, G. D. & REDINGTON, A. N. 2000. Risk factors for arrhythmia and sudden cardiac death late after repair of Tetralogy of Fallot: a multicentre study. *The Lancet,* 356**,** 975-981.

GEVA, T. 2013. Indications for pulmonary valve replacement in repaired tetralogy of Fallot: the quest continues. *Circulation,* 128**,** 1855-1857.

GEVA, T., GAUVREAU, K., POWELL, A. J., CECCHIN, F., RHODES, J., GEVA, J. & DEL NIDO, P. 2010. Randomized trial of pulmonary valve replacement with and without right ventricular remodeling surgery. *Circulation,* 122**,** S201-S208.

GEVA, T., SANDWEISS, B. M., GAUVREAU, K., LOCK, J. E. & POWELL, A. J. 2004. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. *Journal of the American College of Cardiology,* 43**,** 1068-1074.

GIARDINI, A., HAGER, A., LAMMERS, A. E., DERRICK, G., MULLER, J., DILLER, G. P., DIMOPOULOS, K., ODENDAAL, D., GARGIULO, G., PICCHIO, F. M. & GATZOULIS, M. A. 2009a. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. *Journal of the American College of Cardiology,* 53**,** 1548-55.

GIARDINI, A., SPECCHIA, S., GARGIULO, G., SANGIORGI, D. & PICCHIO, F. M. 2009b. Accuracy of oxygen uptake efficiency slope in adults with congenital heart disease. *International Journal of Cardiology,* 133**,** 74-9.

GIARDINI, A., SPECCHIA, S., TACY, T. A., COUTSOUMBAS, G., GARGIULO, G., DONTI, A., FORMIGARI, R., BONVICINI, M. & PICCHIO, F. M. 2007. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired Tetralogy of Fallot. *American Journal of Cardiology,* 99**,** 1462-7.

GILBOA, S. M., SALEMI, J. L., NEMBHARD, W. N., FIXLER, D. E. & CORREA, A. 2010. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation,* 122**,** 2254-63.

GORLER, H., ONO, M., THIES, A., LUNKEWITZ, E., WESTHOFF-BLECK, M., HAVERICH, A., BREYMANN, T. & BOETHIG, D. 2011. Long-term morbidity and quality of life after surgical repair of transposition of the great arteries: atrial versus arterial switch operation. *Interactive Cardiovascular and Thoracic Surgery,* 12**,** 569-574.

HAMADA, H., TERAI, M., JIBIKI, T., NAKAMURA, T., GATZOULIS, M. A. & NIWA, K. 2002. Influence of early repair of Tetralogy of Fallot without an outflow patch on late arrhythmias and sudden death: a 27-year follow-up study following a uniform surgical approach. *Cardiology in the Young,* 12**,** 345-51.

HECHTER, S. J., WEBB, G., FREDRIKSEN, P. M., BENSON, L., MERCHANT, N., FREEMAN, M., VELDTMAN, G., WARSI, M. A., SIU, S. & LIU, P. 2001. Cardiopulmonary exercise performance in adult survivors of the Mustard procedure. *Cardiology in the Young,* 11**,** 407-414.

HICKEY, E. J., VELDTMAN, G., BRADLEY, T. J., GENGSAKUL, A., MANLHIOT, C., WILLIAMS, W. G., WEBB, G. D. & MCCRINDLE, B. W. 2009. Late risk of outcomes for adults with repaired Tetralogy of Fallot from an inception cohort spanning four decades. *European Journal of Cardio-Thoracic Surgery,* 35**,** 156-64; discussion 164.

HO, J., SCHAMBERGER, M., HURWITZ, R., JOHNSON, T., STERRETT, L. & EBENROTH, E. 2015. The effects of pulmonary valve replacement for severe pulmonary regurgitation on exercise capacity and cardiac function. *Pediatric Cardiology,* 36**,** 1194-1203.

HRASKA, V., DUNCAN, B. W., MAYER, J., FREED, M., DEL NIDO, P. & JONAS, R. 2005. Long-term outcome of surgically treated patients with corrected transposition of the great arteries *The Journal of Thoracic and Cardiovascular Surgery,* 129**,** 182-191.

IDE, H., ONO, M., BOETHIG, D., SHALHOUB, N., WAGNER, N., HAVERICH, A., SAWA, Y. & BREYMANN, T. 2009. Clinical outcome of patients 30 years after surgical repair of Tetralogy of Fallot: Effects of right ventriculotomy on late results. *Interactive Cardiovascular and Thoracic Surgery,* 9**,** S115-S116.

JONES, N. L., MAKRIDES, L., HITCHCOCK, C., CHYPCHAR, T. & MCCARTNEY, N. 1985. Normal standards for an incremental progressive cycle ergometer test. *American Review of Respiratory Disease,* 131**,** 700-708.

JONSSON, H. & IVERT, T. 1995. Survival and clinical results up to 26 years after repair of Tetralogy of Fallot. *Scandinavian Cardiovascular Journal,* 29**,** 43-51.

JORTVEIT, J., ØYEN, N., LEIRGUL, E., FOMINA, T., TELL, G. S., VOLLSET, S. E., ESKEDAL, L., DØHLEN, G., BIRKELAND, S. & HOLMSTRØM, H. 2016. Trends in Mortality of Congenital Heart Defects. *Congenital Heart Disease,* 11**,** 160-168.

KAWEL-BOEHM, N., MACEIRA, A., VALSANGIACOMO-BUECHEL, E., VOGEL-CLAUSSEN, J., TURKBEY, E., WILLIAMS, R., PLEIN, S., TEE, M., ENG, J. & BLUEMKE, D. 2015. Normal values for

cardiovascular magnetic resonance in adults and children. *Journal of Cardiovascular Magnetic Resonance,* 17**,** 29.

KEMPNY, A., DIMOPOULOS, K., UEBING, A., MOCERI, P., SWAN, L., GATZOULIS, M. A. & DILLER, G. P. 2012. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life-single centre experience and review of published data. *European Heart Journal,* 33**,** 1386-96.

KEMPNY, A., WUSTMANN, K., BORGIA, F., DIMOPOULOS, K., UEBING, A., LI, W., CHEN, S. S., PIORKOWSKI, A., RADLEY-SMITH, R., YACOUB, M. H., GATZOULIS, M. A., SHORE, D. F., SWAN, L. & DILLER, G. P. 2013. Outcome in adult patients after arterial switch operation for transposition of the great arteries. *International Journal of Cardiology,* 167**,** 2588-93.

KENNEDY, I. 2001. Learning from Bristol: the report of the public inquiry into children's heart surgery at the Bristol Royal Infirmary 1984-1995. CM 5207(I).

KHAIRY, P., DORE, A., POIRIER, N., MARCOTTE, F., IBRAHIM, R., MONGEON, F. P. & MERCIER, L. A. 2009. Risk stratification in surgically repaired tetralogy of Fallot. *Expert Review of Cardiovascular Therapy,* 7**,** 755-762.

KHAIRY, P., IONESCU-ITTU, R., MACKIE, A. S., ABRAHAMOWICZ, M., PILOTE, L. & MARELLI, A. J. 2010. Changing mortality in congenital heart disease. *Journal of the American College of Cardiology,* 56**,** 1149-57.

KHAIRY, P., LANDZBERG, M., LAMBERT, J. & O'DONNELL, C. 2004. Long-term outcomes after the atrial switch for surgical correction of transposition: a meta-analysis comparing the Mustard and Senning procedures. *Cardiology in the Young,* 14**,** 284-292.

KIESEWETTER, C., MICHAEL, K., MORGAN, J. & VELDTMAN, G. 2008. Left ventricular dysfunction after cardiac resynchronization therapy in congenital heart disease patients with a failing systemic right ventricle. *PACE,* 31.

KIRJAVAINEN, M., HAPPONEN, J. & LOUHIMO, I. 1999. Late results of Senning operation. *The Journal of Thoracic and Cardiovascular Surgery,* 117**,** 488-495.

LANGE, R., HORER, J., KOSTOLNY, M., CLEUZIOU, J., VOGT, M., BUSCH, R., HOLPER, K., MEISNER, H., HESS, J. & SCHREIBER, C. 2006. Presence of a ventricular septal defect and the Mustard operation are risk factors for late mortality after the atrial switch operation: thirty years of follow-up in 417 patients at a single center. *Circulation,* 114**,** 1905-13.

LANGLEY, S., WINLAW, D., STUMPER, O., DHILLON, R., DEGIOVANNI, J., WRIGHT, J., MILLER, P., SETHIA, B., BARRON, D. & BRAWN, W. 2003. Midterm results after restoration of the morphologically left ventricle to the systemic circulation in patients with congenitally corrected transposition of the great arteries. *The Journal of Thoracic and Cardiovascular Surgery,* 125**,** 1229-1240.

LANZ, J., BROPHY, J. M., THERRIEN, J., KAOUACHE, M., GUO, L. & MARELLI, A. J. 2015. Stroke in Adults With Congenital Heart Disease: Incidence, Cumulative Risk and Predictors. *Circulation*.

LIM, H. G., KIM, W. H., LEE, J. R. & KIM, Y. J. 2013. Long-term results of the arterial switch operation for ventriculo-arterial discordance. *European Journal of Cardio-Thoracic Surgery,* 43**,** 325-34.

LIM, H. G., LEE, J. R., KIM, Y. J., PARK, Y. H., JUN, T. G., KIM, W. H., LEE, C. H., PARK, H. K., YANG, J. H., PARK, C. S. & KWAK, J. G. 2010. Outcomes of biventricular repair for congenitally corrected transposition of the great arteries. *Annals of Thoracic Surgery,* 89**,** 159-67.

LINDBERG, H. L., SAATVEDT, K., SEEM, E., HOEL, T. & BIRKELAND, S. 2011. Single-center 50 years' experience with surgical management of Tetralogy of Fallot. *European Journal of Cardio-Thoracic Surgery,* 40**,** 538-42.

LUIJTEN, L. W., VAN DEN BOSCH, E., DUPPEN, N., TANKE, R., ROOS-HESSELINK, J., NIJVELD, A., VAN DIJK, A., BOGERS, A. J., VAN DOMBURG, R. & HELBING, W. A. 2015. Long-term outcomes of transatrial-transpulmonary repair of tetralogy of Fallot. *European Journal of Cardiothoracic Surgery,* 47**,** 527-34.

LY, M., BELLI, E., LEOBON, B., KORTAS, C., GROLLMUSS, O. E., PIOT, D., PLANCHE, C. & SERRAF, A. 2009. Results of the double switch operation for congenitally corrected transposition of the great arteries. *European Journal of Cardio-Thoracic Surgery,* 35**,** 879-83; discussion 883-4.

MACEIRA, A. M., PRASAD, S. K., KHAN, M. & PENNELL, D. J. 2006. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. *European Heart Journal,* 27**,** 2879-2888.

MARELLI, A. J., IONESCU-ITTU, R., MACKIE, A. S., GUO, L., DENDUKURI, N. & KAOUACHE, M. 2014. Lifetime Prevalence of Congenital Heart Disease in the General Population from 2000 to 2010. *Circulation*.

MASUDA, M., KADO, H., KAJIHARA, N., ONZUKA, T., KURISU, K., MORITA, S., SHIOKAWA, Y., IMOTO, Y., TOMINAGA, R. & YASUI, H. 2001. Early and late results of total correction of congenital cardiac anomalies in infancy. *Japanese Journal of Thoracic and Cardiovascular Surgery,* 49**,** 497-503.

MCCOMBE, A., TOUMA, F., JACKSON, D., CANNIFFE, C., CHOUDHARY, P., PRESSLEY, L., TANOUS, D., ROBINSON, P. & CELERMAJER, D. 2016. Sudden cardiac death in adults with congenitally corrected transposition of the great arteries. *Open Heart,* 3**,** e000407.

METTON, O., GAUDIN, R., OU, P., GERELLI, S., MUSSA, S., SIDI, D., VOUHE, P. & RAISKY, O. 2010. Early prophylactic pulmonary artery banding in isolated congenitally corrected transposition of the great arteries. *European Journal of Cardio-Thoracic Surgery,* 38**,** 728-34.

MEZZANI, A., AGOSTONI, P., COHEN-SOLAL, A., CORRA, U., JEGIER, A., KOUIDI, E., MAZIC, S., MEURIN, P., PIEPOLI, M., SIMON, A., LAETHEM, C. V. & VANHEES, L. 2009. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention and Rehabilitation,* 16**,** 249-67.

MIYAMURA, H., EGUCHI, S. & ASANO, K. 1993. Long-term results of the intracardiac repair of tetralogy of Fallot: a follow-up study conducted over more than 20 years on 100 consecutive operative survivors. *Surgery Today,* 23**,** 1049-52.

MOCERI, P., DIMOPOULOS, K., LIODAKIS, E., GERMANAKIS, I., KEMPNY, A., DILLER, G., SWAN, L., WORT, S., MARINO, P., GATZOULIS, M. & LI, W. 2012. Echocardiographic predictors of outcome in Eisenmenger syndrome. *Circulation,* 126**,** 1461-1468.

MONGEON, F. P., CONNOLLY, H. M., DEARANI, J. A., LI, Z. & WARNES, C. A. 2011. Congenitally corrected transposition of the great arteries ventricular function at the time of systemic atrioventricular valve replacement predicts long-term ventricular function. *Journal of the American College of Cardiology,* 57**,** 2008-17.

MONGEON, F. P., GURVITZ, M. Z., BROBERG, C. S., ABOULHOSN, J., OPOTOWSKY, A. R., KAY, J. D., VALENTE, A. M., EARING, M. G., LUI, G. K., FERNANDES, S. M., GERSONY, D. R., COOK, S. C., TING, J. G., NICKOLAUS, M. J., LANDZBERG, M. J. & KHAIRY, P. 2013. Aortic root dilatation in adults with surgically repaired Tetralogy of Fallot. *Circulation,* 127**,** 172-179.

MOONS, P., BOVIJN, L., BUDTS, W., BELMANS, A. & GEWILLIG, M. 2010. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation,* 122**,** 2264-72.

MOONS, P., GEWILLIG, M., SLUYSMANS, T., VERHAAREN, H., VIART, P., MASSIN, M., SUYS, B., BUDTS, W., PASQUET, A., DE WOLF, D. & VLIERS, A. 2004. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart,* 90**,** 307-313.

MORDI, I., JHUND, P. S., GARDNER, R. S., PAYNE, J., CARRICK, D., BERRY, C. & TZEMOS, N. 2014. LGE and NT-proBNP identify low risk of death or arrhythmic events in patients with primary prevention ICDs. *JACC: Cardiovascular Imaging,* 7**,** 561-569.

MORRIS, C. D. & MENASHE, V. D. 1991. 25-year mortality after surgical repair of congenital heart defect in childhood. A population-based cohort study. *JAMA,* 266**,** 3447-52.

MYRIDAKIS, D. J., EHLERS, K. H. & ENGLE, M. A. 1994. Late follow-up after venous switch operation (Mustard procedure) for simple and complex transposition of the great arteries. *American Journal of Cardiology,* 74**,** 1030-6.

NOLLERT, G., FISCHLEIN, T., BOUTERWEK, S., BÖHMER, C., KLINNER, W. & REICHART, B. 1997. Long-term survival in patients with repair of Tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *Journal of the American College of Cardiology,* 30**,** 1374-1383.

NRS. 2011. *Vital events reference tables 2011* [Online]. Available: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2011 [Accessed 30/01/2017].

NRS. 2014. *Vital events reference tables 2014* [Online]. Available: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/vital-events-reference-tables [Accessed 30/01/2017 2017].

OKITA, Y., MIKI, S., UEDA, Y., TAHATA, T., SAKAI, T., MATSUYAMA, K., MATSUMURA, M. & TAMURA, T. 1995. Early and late results of repair of Tetralogy of Fallot with subarterial ventricular septal defect. A comparative evaluation of tetralogy with perimembranous ventricular septal defect. *The Journal of Thoracic and Cardiovascular Surgery,* 110**,** 180-5.

OLSEN, M., CHRISTENSEN, T. D., PEDERSEN, L., JOHNSEN, S. P. & HJORTDAL, V. E. 2010. Late mortality among Danish patients with congenital heart defect. *American Journal of Cardiology,* 106**,** 1322-6.

OOSTERHOF, T., MULDER, B. J., VLIEGEN, H. W. & DE ROOS, A. 2005. Corrected tetralogy of Fallot: delayed enhancement in right ventricular outflow tract. *Radiology.,* 237**,** 868-871.

OOSTERHOF, T., VAN STRATEN, A., VLIEGEN, H. W., MEIJBOOM, F. J., VAN DIJK, A. P. J., SPIJKERBOER, A. M., BOUMA, B. J., ZWINDERMAN, A. H., HAZEKAMP, M. G., DE ROOS, A. & MULDER, B. J. M. 2007. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation,* 116**,** 545-551.

OPOTOWSKY, A. R., SIDDIQI, O. K. & WEBB, G. D. 2009. Trends in hospitalizations for adults with congenital heart disease in the U.S. *Journal of the American College of Cardiology,* 54**,** 460-7.

PARK, C. S., LEE, J. R., LIM, H. G., KIM, W. H. & KIM, Y. J. 2010. The long-term result of total repair for Tetralogy of Fallot. *European Journal of Cardio-Thoracic Surgery,* 38**,** 311-317.

PARK, I. S., LEACHMAN, R. D. & COOLEY, D. A. 1987. Total correction of Tetralogy of Fallot in adults: surgical results and long-term follow-up. *Texas Heart Institute Journal,* 14**,** 160-9.

RUSSO, R., COSTA, H., SILVA, P., ANDERSON, J., ARSHAD, A., BIEDERMAN, R., BOYLE, N., FRABIZZIO, J., BIRGERSDOTTER-GREEN, U., HIGGINS, S., LAMPERT, R., MACHADO, C., MARTIN, E., RIVARD, A., RUBENSTEIN, J., SCHAERF, R., SCHWARTZ, J., SHAH, D., TOMASSONI, G., TOMINAGA, G., TONKIN, A., URETSKY, S. & WOLFF, S. 2017. Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. *New England Journal of Medicine,* 376**,** 755-764.

RUTLEDGE, J., HIHILL, M., FRASER, C., O'BRIAN-SMITH, E., MCMAHON, C. & BEZOLD, L. 2002. Outcome of 121 patients with congenitally corrected transposition of the great arteries. *Pediatric Cardiology,* 23**,** 137-145.

SARIKOUCH, S., KOERPERICH, H., DUBOWY, K. O., BOETHIG, D., BOETTLER, P., MIR, T. S., PETERS, B., KUEHNE, T. & BEERBAUM, P. 2011. Impact of gender and age on cardiovascular function late after repair of tetralogy of Fallot: percentiles based on cardiac magnetic resonance. *Circulation: Cardiovascular Imaging,* 4**,** 703-11.

SARKAR, D., BULL, C., YATES, R., WRIGHT, D., CULLEN, S., GEWILLIG, M., CLAYTON, R., TUNSTILL, A. & DEANFIELD, J. 1999. Comparison of long-term outcomes of atrial repair of simple transposition with implications for a late arterial switch strategy. *Circulation,* 100**,** 176-181.

SCHERPTONG, R. W., VLIEGEN, H. W., WINTER, M. M., HOLMAN, E. R., MULDER, B. J., VAN DER WALL, E. E. & HAZEKAMP, M. G. 2009. Tricuspid valve surgery in adults with a dysfunctional systemic right ventricle: repair or replace? *Circulation,* 119**,** 1467-72.

SHIN'OKA, T., KUROSAWA, H., IMAI, Y., AOKI, M., ISHIYAMA, M., SAKAMOTO, T., MIYAMOTO, S., HOBO, K. & ICHIHARA, Y. 2007. Outcomes of definitive surgical repair for congenitally corrected transposition of the great arteries or double outlet right ventricle with discordant atrioventricular connections: risk analyses in 189 patients. *The Journal of Thoracic and Cardiovascular Surgery,* 133**,** 1318-1328.

STEEDS, R. P. 2004. Predicting late sudden death from ventricular arrhythmia in adults following surgical repair of tetralogy of Fallot. *QJM,* 97**,** 7-13.

STEFANESCU, S., ARMSTRONG, A., KENNEDY, K., NYKANEN, D., ABOULHOSN, J. & BHATT, A. 2017. Prediction of adverse events after catheter-based procedures in adolescents and adults with congenital heart disease in the IMPACT registry. *European Heart Journal,* 38**,** 2070-2076.

STEINER, R., GROSS, G., FLICKER, S., SALAZAR, A., BARON, M. & LOESSNER, A. 1995. Congenital heart disease in the adult patient: the value of plain film chest radiology. *Journal of Thoracic Imaging,* 10**,** 1-25.

TANAKA, H., MONAHAN, K. & SEALS, D. 2001. Age-predicted maximal heart rate revisited. *Journal of the American College of Cardiology,* 37**,** 153-156.

THERRIEN, J., PROVOST, Y., MERCHANT, N., WILLIAMS, W., COLMAN, J. & WEBB, G. 2005. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *American Journal of Cardiology,* 95**,** 779-82.

TOBLER, D., CREAN, A., REDINGTON, A., VAN ARSDELL, G., CALDARONE, C., NANTHAKUMAR, K., STAMBACH, D., DOS, L., WINTERSPERGER, B., OECHSLIN, E., SILVERSIDES, C. & WALD, R. 2012. The left heart after pulmonary valve replacement in adults late after tetralogy of Fallot repair. *International Journal of Cardiology,* 160**,** 165-170.

TOBLER, D., WILLIAMS, W. G., JEGATHEESWARAN, A., VAN ARSDELL, G. S., MCCRINDLE, B. W., GREUTMANN, M., OECHSLIN, E. N. & SILVERSIDES, C. K. 2010. Cardiac outcomes in young adult survivors of the arterial switch operation for transposition of the great arteries. *Journal of the American College of Cardiology,* 56**,** 58-64.

TURINA, M. I., SIEBENMANN, R., VON SEGESSER, L., SCHONBECK, M. & SENNING, A. 1989. Late functional deterioration after atrial correction for transposition of the great arteries. *Circulation,* 80**,** I162-7.

TUTAREL, O. 2014. Acquired heart conditions in adults with congenital heart disease: a growing problem. *Heart,* 100**,** 1317-21.

VAN DER LINDE, D., KONINGS, E. E., SLAGER, M. A., WITSENBURG, M., HELBING, W. A., TAKKENBERG, J. J. & ROOS-HESSELINK, J. W. 2011. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *Journal of the American College of Cardiology,* 58**,** 2241-2247.

VAN HUYSDUYNEN, B., VAN STRATEN, A., SWENNE, C., MAAN, A., VAN ECK, H., SCHALIJ, M., VAN DER WALL, E., DE ROOS, A., HAZEKAMP, M. & VLIEGEN, H. 2005. Reduction of QRS duration after pulmonary valve replacement in adult Fallot patients is related to reduction of right ventricular volume. *European Heart Journal,* 26**,** 928-932.

VAN SON, J. A. M., DANIELSON, G. K., HUHTA, J. C., WARNES, C. A., EDWARDS, W. D., SCHAFF, H. V., PUGA, F. J. & ILSTRUP, D. M. 1995. Late results of systemic atrioventricular valve replacement in corrected transposition. *The Journal of Thoracic and Cardiovascular Surgery,* 109**,** 642-653.

VAN SON, J. A. M., MOHAN REDDY, V., SILVERMAN, N. H. & HANLEY, F. L. 1996. Regression of tricuspid regurgitation after two-stage arterial switch operation for failing systemic right ventricle after atrial inversion operation *The Journal of Thoracic and Cardiovascular Surgery,* 111**,** 342-347.

VEJLSTRUP, N., SORENSEN, K., MATTSSON, E., THILEN, U., KVIDAL, P., JOHANSSON, B., IVERSEN, K., SONDERGAARD, L., DELLBORG, M. & ERIKSSON, P. 2015. Long-term outcome of Mustard/Senning correction for transposition of the great arteries in Sweden and Denmark. *Circulation,* 132**,** 633-38.

VERHEUGT, C. L., UITERWAAL, C. S., VAN DER VELDE, E. T., MEIJBOOM, F. J., PIEPER, P. G., SIESWERDA, G. T., PLOKKER, H. W., GROBBEE, D. E. & MULDER, B. J. 2010. The emerging burden of hospital admissions of adults with congenital heart disease. *Heart,* 96**,** 872-8.

VERHEUGT, C. L., UITERWAAL, C. S., VAN DER VELDE, E. T., MEIJBOOM, F. J., PIEPER, P. G., VLIEGEN, H. W., VAN DIJK, A. P., BOUMA, B. J., GROBBEE, D. E. & MULDER, B. J. 2008. Gender and outcome in adult congenital heart disease. *Circulation,* 118**,** 26-32.

VIDEBÆK, J., LAURSEN, H. B., OLSEN, M., HØFSTEN, D. E. & JOHNSEN, S. P. 2015. A Long-Term Nationwide Follow-Up Study of Simple Congenital Heart Disease Diagnosed in Otherwise Healthy Children. *Circulation*.

WALD, R. M., HABER, I., WALD, R., VALENTE, A. M., POWELL, A. J. & GEVA, T. 2009. Effects of regional dysfunction and late gadolinium enhancement on global right ventricular function and exercise capacity in patients with repaired tetralogy of Fallot. *Circulation,* 119**,** 1370-7.

WARNES, C. A. 2006. Transposition of the great arteries. *Circulation,* 114**,** 2699-709.

WARNES, C. A., LIBERTHSON, R., DANIELSON, G., DORE, A., HARRIS, L., HOFMANN, J., SOMERVILLE, J., WILLIAMS, R. & WEBB, G. 2001. Task force 1: the changing profile of congenital heart disease in adult life. *Journal of the American College of Cardiology,* 37**,** 1170-1175.

WARNES, C. A., WILLIAMS, R. G., BASHORE, T. M., CHILD, J. S., CONNOLLY, H. M., DEARANI, J. A., DEL NIDO, P., FASULES, J. W., GRAHAM, T. P., JR., HIJAZI, Z. M., HUNT, S. A., KING, M. E., LANDZBERG, M. J., MINER, P. D., RADFORD, M. J., WALSH, E. P., WEBB, G. D., SMITH, S. C., JR., JACOBS, A. K., ADAMS, C. D., ANDERSON, J. L., ANTMAN, E. M., BULLER, C. E., CREAGER, M. A., ETTINGER, S. M., HALPERIN, J. L., KRUMHOLZ, H. M., KUSHNER, F. G., LYTLE, B. W., NISHIMURA, R. A., PAGE, R. L., RIEGEL, B., TARKINGTON, L. G. & YANCY, C. W. 2008. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology,* 52**,** e1-121.

WHEELER, M., GRIGG, L. & ZENTNER, D. 2014. Can we predict sudden cardiac death in long-term survivors of atrial switch surgery for transposition of the great arteries? *Congenital Heart Disease,* 9**,** 326-32.

WILSON, N. J., CLARKSON, P. M., BARRAT-BOYES, B. G., CALDER, A. L., WHITLOCK, R. M. L., EASTHOPE, R. N. & NEUTZ, J. M. 1998. Long-term outcome after the Mustard repair for simple transposition of the great arteries. *Journal of the American College of Cardiology,* 32**,** 758-765.

WINLAW, D. S., MCGUIRK, S. P., BALMER, C., LANGLEY, S. M., GRISELLI, M., STUMPER, O., DE GIOVANNI, J. V., WRIGHT, J. G., THORNE, S., BARRON, D. J. & BRAWN, W. J. 2005. Intention-to-treat analysis of pulmonary artery banding in conditions with a morphological right ventricle in the systemic circulation with a view to anatomic biventricular repair. *Circulation,* 111**,** 405-411.

YEH, T., CONNELLY, M. S., COLES, J. G., WEBB, G. D., MCLAUGHLIN, P. R., FREEDOM, R. M., CERRITO, P. B. & WILLIAMS, W. G. 1999. Atrioventricular discordance: results of repair in 127 patients. *The Journal of Thoracic and Cardiovascular Surgery,* 117**,** 1190-1203.

YLITALO, P., NIEMINEN, H., PITKANEN, O. M., JOKINEN, E. & SAIRANEN, H. 2015. Need of transannular patch in tetralogy of Fallot surgery carries a higher risk of reoperation but has

no impact on late survival: results of Fallot repair in Finland. *European Journal of Cardiothoracic Surgery,* 48**,** 91-7.

Appendix

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland Research Ethics Service
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT

28 OCT 2011

Dr R Dobson
Clinical Research Fellow
Scottish Adult Congenital Cardiac Service
Cardiothoracic Administration
Level 1
Golden Jubilee National Hospital
Clydebank
G81 4DY

Date 26 October 2011
Your Ref
Our Ref WoS ASD 689
Direct line 0141 211 2126
Fax 0141 211 1847
E-mail Judith.Godden@ggc.scot.nhs.uk

Dear Dr Dobson

Full title of project: The natural and unnatural history of the systemic right ventricle in adult survivors of atrial switch for complete transposition of the great arteries and congenitally corrected transposition of the great arteries

You have sought advice from the West of Scotland Research Ethics Service Office on the above project. This has been considered by the Scientific Officer and you are advised that it does not need ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK. The advice is based on the following.

- The project is an audit using only data obtained as part of usual care but note the requirement for Caldicott Guardian approval to permit sharing or publication of anonymised data obtained from patient under the care of the Golden Jubilee National Hospital.

If during the course of your project the nature of the study changes and starts to generate new knowledge and thereby inadvertently becoming research then the changing nature of the study would necessitate REC review at that point, before any further work was undertaken. A REC opinion would be required for the new use of the data collected.

Note that this advice is issued on behalf of the West of Scotland Research Ethics Service Office and does **not** constitute a favourable opinion from a REC. It is intended to satisfy journal editors and conference organisers and others who may require evidence of consideration of the need for ethical review prior to publication or presentation of your results.

However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

Continued...

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS. This letter has been copied to the Golden Jubilee National Hospital R&D Department for their information.

Kind regards

Dr Judith Godden
WoSRES Scientific Officer/Manager

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland Research Ethics Service
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT

28 OCT 2011

Dr R Dobson
Clinical Research Fellow
Scottish Adult Congenital Cardiac Service
Cardiothoracic Administration
Level 1
Golden Jubilee National Hospital
Clydebank
G81 4DY

Date 26 October 2011
Your Ref
Our Ref WoS ASD 688
Direct line 0141 211 2126
Fax 0141 211 1847
E-mail Judith.Godden@ggc.scot.nhs.uk

Dear Dr Dobson

Full title of project: Long term outcomes in a cohort of adult survivors of tetralogy of Fallot and relation to right ventricular function and exercise capacity

You have sought advice from the West of Scotland Research Ethics Service Office on the above project. This has been considered by the Scientific Officer and you are advised that it does not need ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK. The advice is based on the following.

- The project is an audit using only data obtained as part of usual care but note the requirement for Caldicott Guardian approval to permit sharing or publication of anonymised data obtained from patient under the care of the Golden Jubilee National Hospital.

If during the course of your project the nature of the study changes and starts to generate new knowledge and thereby inadvertently becoming research then the changing nature of the study would necessitate REC review at that point, before any further work was undertaken. A REC opinion would be required for the new use of the data collected.

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However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

Continued...

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS. This letter has been copied to the Golden Jubilee National Hospital R&D Department for their information.

Kind regards

Dr Judith Godden
WoSRES Scientific Officer/Manager

Golden Jubilee National Hospital
National Waiting Times Centre Board

NHS SCOTLAND

PROJECT REGISTRATION FORM

Please be advised that it is **mandatory** to complete this form prior to undertaking any audit /project improvement on behalf of Golden Jubilee National Hospital. Failure to complete this form, and Audit-Data Protection Checklist Form (Q-Pulse: COR-EH-IG-HTG-1) or provide sufficient information will **not allow the issue of a registration number** . Please note that a registration number is necessary for the release of medical or information reports.

Thank you for your co-operation in this matter .

1. Project lead			
Name of Project Lead	Richard Dobson	Division	NSD
Designation	Cardiology StR	Department/Ward	SACCS
Email address	richard.dobson@nhs.net		
Contact No	07759147645		

2. Project team		
Name	Job Title	Contact Details (email & phone no)
Richard Dobson	Cardiology StR	As above
Mark Danton	Consultant Cardiac Surgeon	dantonmark@googlemail.com

3. Project details	
Project Title	Long term outcomes in a cohort of adult survivors of tetralogy of Fallot and the relationship with parameters derived from cardiac MRI and cardiopulmonary exercise testing
Project Background	To date the clinical course of survivors of surgical repair of tetralogy of Fallot has been poorly defined beyond adulthood, and no-one has yet looked at this in Scotland.
Project Aim	1.Define the overall mortality and morbidity in adult survivors of tetralogy of Fallot in Scotland 2.Assess the relationship between parameters derived from cardiac MRI and exercise testing and adverse clinical outcomes
Project Objectives	As above
Project Standards	No nationally agreed standards or targets, however we can compare the mortality and morbidity outcomes in our cohort to those published in other centres around the world

4. Reasons for carrying out project (please tick all that apply)	
To confirm that the service is meeting standards	x
To improve patient care or compliance	x
There is a potential for change	☐
New evidence or best practice guidance has recently been published	☐
Problem identified through risk assessment/litigation/risk of litigation	☐
Problem identified through complaint/clinical incidents/near misses	☐
I believe there are a number of cost implications in this area/with this service	x
There is high volume/high frequency for this condition/treatment/procedure	x
It is perceived to be a problem in this area	☐
I believe there is a wide variation in practice	☐
Other(please specify)	

5. Project driver

National	x	Local	☐
1. Mandatory ☐	2. High risk/high profile ☐	3. Division priority ☐	4. Clinician interest x

6. Need for re-audit

If this project is a re-audit, how many cycles have already been completed: 0

Dates of previous audit ____/____/_____ ____/____/_____ ____/____/_____

If a re-audit what changes in practice have been introduced since first/subsequent audit(s)?

7. Evidence / guidance project is based on

Nationally agreed	☐	
Royal College	☐	
Professional body	☐	
Locally agreed	☐	
Other(please specify)		Data published in other centres in the UK and worldwide

8. Staff groups involved in or affected by the project (please tick all that apply)

Nursing	☐	Dietetics	☐
Medical	x	Radiology	☐
Pharmacy	☐	Labs	☐
Occupational Therapy	☐	Ophthalmology	☐
Administration staff	☐	Other (please specify) _____	
Physiotherapy	☐		

Other areas project may impact on

Who have you discussed and agreed this project with?

Name	Job Title	Date agreed
Mark Danton	Consultant Cardiac Surgeon	7/7/15

*Please note: It is **your** responsibility to inform anyone who may be involved, or who may be affected by your results, of your intention to carry out this project.*

9. Methodology

Project Type	Retrospective	x	Prospective	☐
Data collection method	Project tool (proforma)	☐	Case note review	☐
	Patient/staff questionnaire completed in hospital	☐	Postal patient/staff questionnaire	☐
	Structured face-to-face patient/staff interview*	☐	Structured telephone patient/staff interview*	☐
	Data from existing databases(s)	x		
	Other (please specify)			
Sample size criteria	200-400		Project sample size 200-400	
Time period audited: From	Start of database (2004)		Time period audited: To	_July 2014
Do you intend to do a pilot study?	Yes	☐	No	x
Do you intend to involve patients?	**Yes	☐	No	x

*i.e. * using a fixed schedule of questions which is followed rigidly*

10. Project deadline

Start date (begin collection of data)	_July 2015	Proposed finish date (inc. summary / action plan)	August 2015

11. Support required from CGD (please tick all that apply)			
None	x	Facilitation of project group	☐
Advice on methodology	☐	Design of data collection form	☐
Database/spreadsheet design	☐	Data entry	☐
Data analysis	☐	Writing a report	☐
Presentation of your results	☐	Other (please specify)	

Please Note: If you have requested assistance from the CGD you will be contacted and arrangements made to take your project forward to the next stage in the clinical audit / clinical quality improvement process.

12. Authorisation

Project Lead: *By signing this form I agree to ensure that the project is completed, the results disseminated and a report given to the CGD within the anticipated timescales. I understand that non-anonymised (staff/patients) data must not be taken outside the organisation and that the report may be made available to anyone who requests it.*

Name Richard Dobson	Signature	Date 7 / 7 / 2015

Senior Clinician/Manager: *By signing this form I confirm that this project has been agreed as part of the Division work plan and that I will give my support to it. I will ensure dissemination of project results and lead on the development and implementation of an action plan (if necessary) in order to obtain improvements in the quality of care provided.*

Name Mark Danton	Signature	Date 8 / 7 / 2015

Please Note: by signing this form the Project Lead and Senior Clinician/Manager confirm that data will be handled and kept in accordance with the Data Protection Act 1998, Caldicott Guidelines and the Freedom of Information Act.

After completion and sign off (electronically and / or in hard copy) of this form and the audit data protection checklist, your project will be formally registered on the CGD departmental database and given a registration number. The CGD will contact you with this number which should be used in correspondence with any staff about the project e.g. e-health, or requesting case notes. The CGD will require you to submit:

- A copy of your project tool / questionnaire before you begin collecting your data,
- A copy of the final report within one calendar month of completion of your findings.
- A summary and action plan.

The project **will not** be formally completed until a summary / action plan is completed. You can complete a summary / action plan and submit it with your report or shortly after when the action plan has been agreed by the project team or relevant group / committee stating **what** changes will be implemented, **who** will be responsible for carrying them out and **when** this will be done. If agreed, set a date for a re-audit to complete the cycle. Progress updates may be requested during the project.

Marie Rush
Clinical Governance Officer
marie.rush@gjnh.scot.nhs.uk
x. 5355
CGD, Level 2, GJNH, Agamemnon Street, Clydebank G81 4DY

THANK YOU FOR COMPLETING THE FORM

TO BE COMPLETED BY CGD

Date received	___/___/_____
Project Number	

RE: Audit : Long tem outcomes in a cohort of adult survivors of tetralogy of fallot and the relationship with parameters derived from cardiac MRI and cadiopulmonary exercise testing

Mike Higgins [Mike.Higgins@gjnh.scot.nhs.uk]

Sent: 31 July 2015 16:59

To: Stott Sharon (NHS NATIONAL WAITING TIMES BOARD); Rush Marie (NHS NATIONAL WAITING TIMES BOARD)

Sharon, Marie

I'm happy with this as Caldicott

Mike

Dr Mike Higgins
Medical Director
National Waiting Times Centre
Golden Jubilee National Hospital
Agamemnon Street
Clydebank
West Dunbartonshire
G81 4DY

Tel: 0141 951 5957
Mobile: [redacted]

From: Sharon Stott
Sent: 24 July 2015 13:21
To: Marie Rush
Cc: Mike Higgins
Subject: FW: Audit : Long tem outcomes in a cohort of adult survivors of tetralogy of fallot and the relationship with parameters derived from cardiac MRI and cadiopulmonary exercise testing

Hi Marie

I'm happy with this, as it's all anonymous information, but I have copied Mike in if they would like our Caldicott Guardian to have sight of it and agree approval.

Mike, would you mind having a quick look over the attached please?

Many thanks,

Sharon

From: Marie Rush
Sent: 20 July 2015 10:57
To: Sharon Stott
Subject: Audit : Long tem outcomes in a cohort of adult survivors of tetralogy of fallot and the relationship with parameters derived from cardiac MRI and cadiopulmonary exercise testing

Hi Sharon

Is the attached checklist OK?

Also, the have asked about Caldicott guardian approval. I am unsure what the process is for this now, are you able to advise, or point me in the right direction.

Kind regards

Marie