Evaluation of a New Approach to the Management of Advanced Chronic Heart Failure: Use of Implantable Left Ventricular Assist Devices as a bridge to Heart Transplantation in the UK

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Declaration of Originality:

The writing of this thesis consists of my own work, where all else shown here is referenced. All involved with this research and all resources used are acknowledged here or within the body of this work.

Copyright Declaration

Abstract

Introduction: Heart Transplantation (HTx) remains the standard treatment for patients with advanced chronic heart failure (ACHF). Over the last 20 years, despite rising donor numbers, practitioners have observed a decline in the numbers of adult HTx in the UK. Due to this decline and due to increasing waiting times for HTx more patients are requiring a ventricular assist device (VAD) as a bridge to heart transplantation (BTT). This work aims to evaluate VAD practice in the UK and to describe outcomes, which include survival and quality of life.

Methods: A national audit study was undertaken to collect VAD data. The data was recorded in a database and analysed. An audit of quality of life was also undertaken and all adult HTx centres participated. Quality of life (QoL) data was collected from patients who were being medically treated for ACHF; patients who had received a VAD and patients who had received a heart transplant.

Results: 247 patients received VADs within the study period. The use of 3rd-gen devices increased over time. The median duration of support increased from 141 days (interquartile range 80 to 253 days) to 578 days (lower quartile 204 days). Survival improved with device generation (p=0.003). At 1-year, 50.0% of patients receiving a 1st generation device were alive (95% CI 34.9 to 63.3%) compared to 76.9% of patients receiving a 3rd generation device (95%CI 68.0 to 83.6%). 386 patients completed QoL questionnaires. Patients after HTx reported the best QoL; patients with LVADs reported better QoL scores than patients being assessed for HTx and patients listed for HTx on medical therapy.

Conclusions: VAD implantation has improved and increased, and has become a credible option for some patients awaiting HTx. Quality of life for patients with VADs is better than patients being treated with maximal medical therapy.

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* See Appendix 1

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Chapter 1: Introduction

The Heart

"the heart is an exceedingly strong muscle…." Hippocrates (Cheng, 2001)

There are written records of physicians studying the human heart over the last 2,500 years. However, it is only in the last four centuries that the true function of the heart and circulation been appreciated. The story begins with Hippocrates in 400 BC.

Hippocrates' treatise "The Heart" (circa 400 BC) is one of the earliest descriptions of the heart and its vessels. Hippocrates described the anatomical structures of the heart but did not appreciate the difference between the venous and arterial systems. This was the first description of the function of the heart and proved to be a catalyst for centuries of further research (Lloyd, Chadwick & Mann, 1983).

Aristotle (384-322BC) described the heart as central to the vitality of the body. He thought it was the most important organ in the body because of his observation that it was the first organ to form in chick embryos (Hamburger & Hamilton, 1951). He subsequently described it as the seat of intelligence and sensation. He felt that the heart was a hot organ, which was cooled by its surrounding structures (Porter, 1999).

Galen {or Claudius Galenus} (AD 129-217) adopted some of Aristotle's ideas and agreed with his view that that the heart was a source of the body's heat and also the seat of the soul. Galen's main interest was in human anatomy. At that time, Roman law prohibited dissection of human cadavers and therefore Galen used animals, both living and dead, to perform anatomical dissections. Galen, was a proponent of the Hippocratic idea that imbalance in bodily humours (blood, yellow bile, black bile and phlegm) was responsible for differences in human moods. Galen, was an honoured physician and was appointed to the gladiatorial

arena to treat gladiators when he was only 28 years old (Scarborough, 1971; Fullerton & Silverman, 2009). This was a great honour and testament to his skills as a diagnostician and anatomist, and was bestowed upon him by the high priest of Asia (Stewart, Jenkins, Buchan, *et al.*, 2002; Fullerton & Silverman, 2009).

"It is I, and I alone, who have revealed the true path of medicine. It must be admitted that Hippocrates already staked out this path….he prepared the way, but I have made it passable." Galen

Galen was a prolific writer and wrote many manuscripts starting at the age of thirteen. It is reported that he wrote over 2.5 million words in his lifetime. His second and third treatises; *On the Diagnosis of Pulses and On the Causes of Pulsation*, were of particular importance to the development of knowledge of heart function. He explained how to take the pulse and how to interpret the pulse in terms of pulse volume, speed and rhythm.

He described the anatomy of the heart and vessels, and contradicted Aristotle's claim that the heart was the origin of nerves, and considered the heart to be secondary to the liver in terms of importance to the functions of the body. He was convinced that arteries contained blood from the heart. However, he thought that the artery and the heart contracted simultaneously with arterial contraction and expansion being separate active movements (Cowie, Wood, Coats, *et al.*, 1999; Porter, 1999). He maintained that the heart did not drive blood through the arteries and that it was the arteries themselves that had an innate pulsatility that moved the blood (Petersen, Rayner & Wolstenholme, 2002; Fullerton & Silverman, 2009; Hurst & Fye, 2002).

He postulated that in relaxation; atmospheric air was taken into the heart to cool and form vital spirits called *pneuma* by mixing with blood in the heart. Galen thought pneuma was responsible for the pulsatile power within the artery.

Galen thought that blood was made in the liver incorporating ingested foods in the form of chyle; subsequently moving to the peripheries carrying natural spirits to support growth and nutrition. He described dark blood from the liver passing to the right ventricle where it both passed to the lungs via the pulmonary artery and crossed into the left ventricle via inter-septal pores where it mixed with pneuma, became heated and then moved to the peripheries via the aorta. He believed the veins originated in the liver and arteries originated in the heart (McMurray & Adamopoulos, 2012; Porter, 1999).

In the 1500s, a new perspective based on more direct observation began to emerge culminating in William Harvey's exposition of the modern view of the function of the heart and circulation. These changes began with the work of Andreas Vesalius who based his interpretation of the heart's function and circulation based on the dissection of human cadavers.

Andreas Vesalius (1514-1564) was born in Brussels, which was part of the Roman Empire at the time. He studied medicine in Paris and after completing his doctorate in Padua in 1537 was offered the chair of anatomy and surgery.

He championed the study of human rather than animal anatomy as opposed to Galen who was unable to use human cadavers due to Roman prohibition of such practices. In 1539 in Padua, he gained access to a supply of recently dead cadavers of executed criminals and even timed his anatomical dissections and lecture demonstrations around times of execution (McMurray & Adamopoulos, 2012; Klestinec, 2004).

Three years later, in 1542, Vesalius completed his great work *De humani corporis fabrica*

(Vesalius, Dalton & Hartenfels, 1964), which was the first systematic description of human anatomical structure based on dissection and in it he made direct reference to previous misconceptions of Galen's account whose works were based on dissection of primates. Book

VI of the *Fabrica* was devoted to the understanding of the thorax and heart. Vesalius disputed the Galenic speculation of permeability of the inter-ventricular septum.

"We are driven to wonder at the handiwork of the Almighty by means of which the blood sweats from right into the left ventricle through passages which escape the human vision!" Vesalius

Early Development of the Modern Understanding of the Heart

The rejection of the older established idea that blood communicated between the ventricles became a milestone in Renaissance anatomy and encouraged other anatomists including Matteo Realdo Colombo (1515-1559) to discover the pulmonary transit of blood, later to be clarified and developed by William Harvey.

Colombo, an apothecary's son who studied surgery in Padua, described the pulmonary circulation based on hundreds of cadaveric and animal dissections and vivisections. His book, *De re anatomica* describes his original description of the pulmonary circulation. During his vivisection experiments in dogs, Colombo was able to show that blood flowed from the right side of the heart through the lungs to the left side and that the pulmonary veins contained blood and not air as Galen had previously proposed. Blood was exposed to air in the lungs and then returned to the left ventricle of the heart, where it demonstrated the bright red appearance of arterial blood. Colombo described the heartbeat and held the view that the heart acted with greater force in systole (contraction) than in diastole (dilatation) (Hurst & Fye, 2002; Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013).

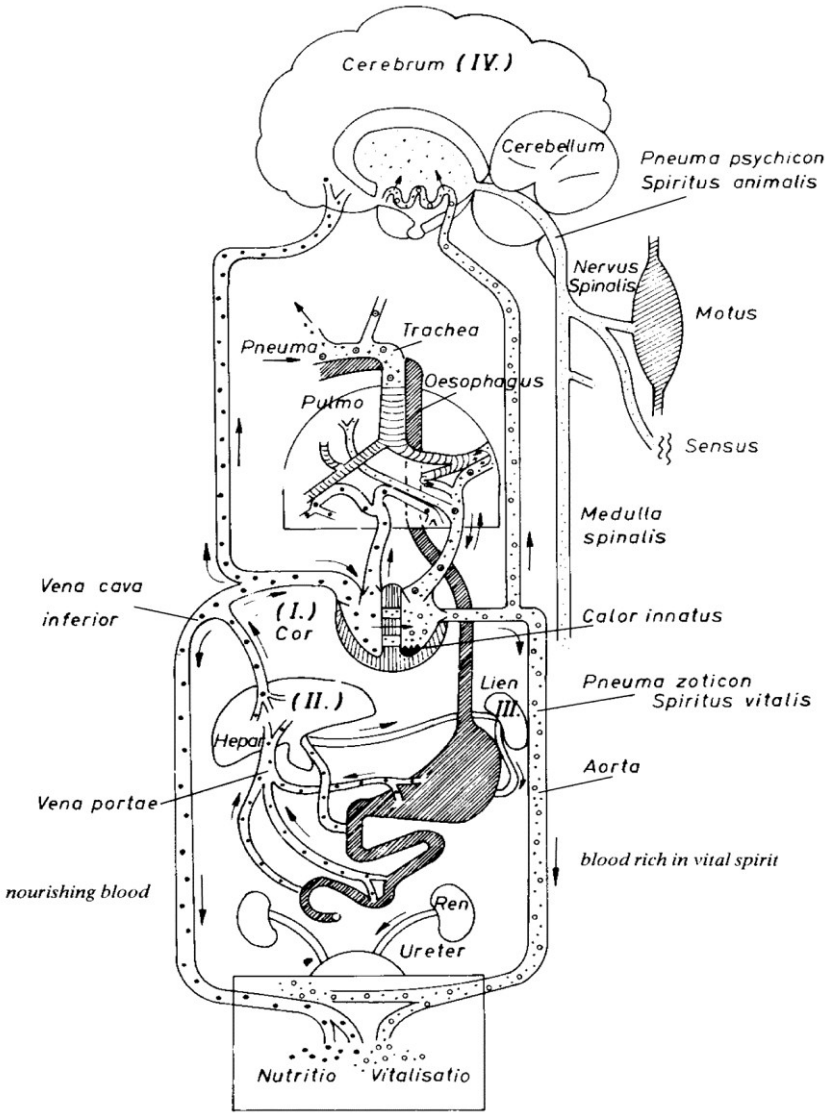
Colombo wrote:

"Between these ventricles there is a septum through which almost everyone believes there opens a pathway for the blood from the right ventricle to the left and that the blood is

rendered thin so that this may be done more easily for the generation of vital spirits. But they are in great error, for the blood is carried through the pulmonary artery to the lung and is there attenuated; then it is carried, along with air, through the pulmonary vein to the left ventricle of the heart. Hitherto no one has noticed this or left it in writing, and it especially should be observed by all." (Lonn & McKelvie, 2000; Hurst & Fye, 2002; Coppola, 1957)

Colombo reached his conclusion independently of two other physicians who had described the pulmonary circulation before him. The 13th century Arabic physician, Ibn al-Nafis of Damascus and Spanish biologist and philosopher, Michael Servetus. Servetus described the pulmonary circulation in his philosophical book in 1553 although there are no surviving copies of the manuscript and he himself was later burnt at the stake in Geneva for heresy. Ibn al-Nafis' description was passed down in Arabic manuscripts but was not contained in a book of his own (Maron & Leopold, 2010; Hurst & Fye, 2002).

Figure 1-1: Galen's view of physiological systems, particularly the heart and great vessels. Note the communication between the right and left ventricles and the independent flows taking place in the venous and arterial vessels (Maron & Leopold, 2010; Schultz, 2002).



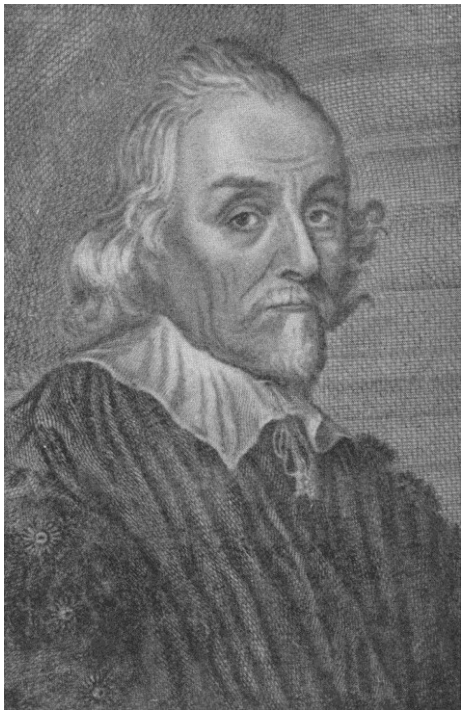
Andrea Cesalpino (1519-1603) supported Galen's earlier idea of pulmonary circulation, and described the function of the heart valves. He started using the term circulation in 1603 (Pitt, Zannad, Remme, *et al.*, 1999; Porter, 1999).

William Harvey

William Harvey (1578-1657) was born on April 1st 1578 in Folkestone and was an English physician. His early studies took place in Folkestone where he studied Latin. He subsequently gained entry into Gonville and Caius College, Cambridge in 1593. Following his graduation as a Bachelor of Arts in 1597 aged 19, he enrolled at the University of Padua where he would study anatomy and physiology under the tutelage of Fabricius who published a description of the venous valves. Harvey graduated as a doctor in 1602 and returned to London where he was able to build a large medical practice. He subsequently married in 1604 and became chief physician at St Bartholomew's Hospital in London. In 1615 he became the Lumleian Lecturer at the Royal College of Physicians (Zannad, McMurray, Krum, *et al.*, 2011; Silverman, 1985). After returning to London, Harvey performed dissections and observed at least 80 species of animal. Harvey wrote:

"**...**the chief function of the heart is the transmission and pumping of the blood through the arteries to the extremities of the body. Thus the pulse which we feel in the arteries is nothing else than the impact of blood from the heart." (Harvey & Sigerist, 1628; Silverman, 1985).

Figure 1-2: William Harvey (1578-1657)



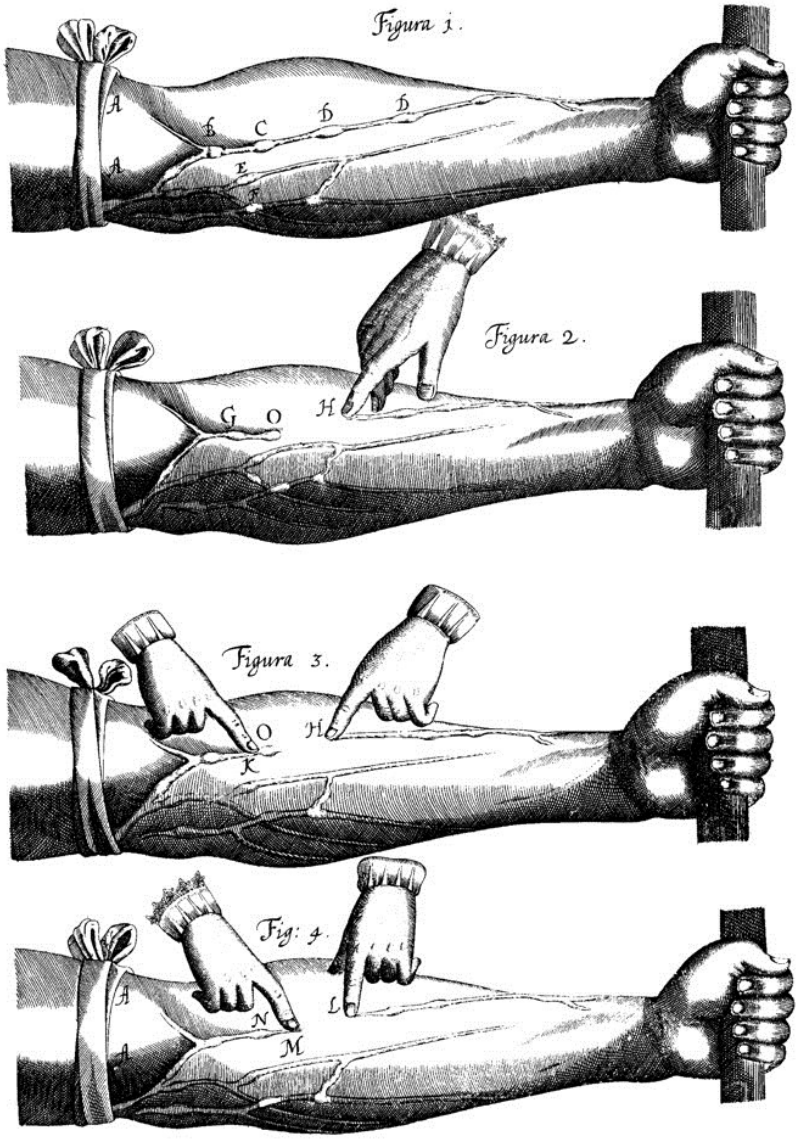
Harvey confirmed Colombo's work on the pulmonary circulation and stated that the heart functioned as a muscle with the ventricles contracting and pumping blood in systole. He decided that the arteries did not pulsate because of any innate ability to do so but rather because of the pressure from the beating heart. In order to prove that the heart pumped blood rather than sucked blood into itself by relation, Harvey needed to show that the heart provided a propulsive force to expel the blood. He noted through observation that the heart after contraction became smaller and thicker, and whilst the ventricles became smaller the pulmonary artery and aorta became dilated. He noted that the arterial pulse would stop if the heart stopped and that blood would spurt from a cut artery in time with each cardiac contraction (Lonn & McKelvie, 2000; Silverman, 1985).

He disproved the 2-way travel between the air and “sooty vapours” that were said to travel separately in the pulmonary vein. He was able to show the action of the auricles and the ventricles using vivisection specimens on frogs.

His most notable achievement was to establish the firm theory of a systemic as well as pulmonary circulatory system.

This concept was a paradigm shift (Kuhn, 1962; 1969; 1957) from Galenist doctrine and was initially difficult to accept. This also cast doubt on Galenist therapeutics particularly the art of bleeding (for example to cool the body of fever). The rationale for bleeding patients with different diseases in a location that varied depending upon the illness was undermined by the discovery that blood circulated around the body.

Figure 1-3: William Harvey's experiment illustrating the venous valves (nodes or portals) and the unidirectional nature of emptying and filling (Harvey & Sigerist, 1628; Hippocrates, Paré, Harvey, *et al.*, 1910; Schultz, 2002).



Harvey was able to infer as to the existence of a connection between arteries and veins, but was not able to see the capillaries with his own eyes. He used a tight ligature around an arm to stop arterial blood flow down the arm. He then loosened it so as to allow arterial flow but

to stop venous blood flow back up the arm. With the ligature very tight, the veins in the arm appeared normal, however with the ligature slightly loosened the veins became swollen, proving that blood had poured from artery into vein, and therefore demonstrating a connection between the two vessels.

Figure 1-4: William Harvey and De Motu Cordis

In his 1628 publication Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus commonly referred to as De Motu Cordis (DiBardino, 1999; Harvey & Sigerist, 1628), Harvey described his model of the motion of the heart and the blood based on the combination of empirical observation and reasoning.

By using simple, clear and easily reproducible experiments Harvey described the two phases of the heart's motion: systole (contraction) and diastole (expansion). Subsequently, by estimating the volume of blood in the left ventricle of the heart and measuring the rate at

which it flowed into the aorta, Harvey concluded that existing explanations of blood movement must be incorrect.

Downgrading the role of the heart from a vital organ directly involved in personality, psyche and spirituality to a mechanical pump had many implications. The de-mystification of the heart reinforced challenges to other received "truths" - such as Charles 1st's divine right to rule England. This seemed contradictory given that he was physician to the King and dedicated his major works to him.

Harvey provided ammunition to the new breed of philosophers rejecting Aristotelian ideas. René Descartes (1596-1650) quickly adopted and championed Harvey's idea of circulation seeing it as a way of removing the soul from the equation and so creating a purely mechanical explanation of the body (DiBardino, 1999; Hurst & Fye, 2003; Stinson, Dong, Clark, *et al.*, 1971).

Perhaps the most lasting influence, however, was brought about due to Harvey's scientific method. Whilst many of Harvey’s ideas are based on traditional Aristotelian thought processes, publication of De Motu Cordis rejected traditional thinking and methods in favour of planned observation and designed experiments using quantitative thinking.

William Harvey’s contribution to medicine paved the way for further research. He established the recognition of the heart as a pump, which led to the idea of heart failure fundamentally being pump failure and also led to the possibility of augmenting or replacing the function of the heart.

William Withering (1741-1799) trained as a physician after studying medicine at the University of Edinburgh. Withering has been credited with the discovery of digitalis. He had been a keen medical student whilst at University, and a member of the Latin society and Masonic Order. After graduation he found a practice in Stafford and married an artist whose

specialty was botanical arrangements, Helena Cooke. Despite expressing a disinterest in botany at University, after marriage, Withering became an avid collector of plants, fruit, rocks and minerals. His book "A Botanical Arrangement of All the Vegetables Naturally Growing in Great Britain with Descriptions of the Genera and Species According to Linnaeus" published in 1776 was the first complete botanical description of flora in Great Britain. He subsequently moved to Birmingham to increase his income at the suggestion of Erasmus Darwin (Grandfather of Charles Darwin). During his travels and visits to patients, Withering learned of a certain herbal tea, which was used as a remedy to dropsy (oedema). He wrote:

"In the year 1775 my opinion was asked concerning a family recipe for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects to perceive, that the active herb could be no other than the Foxglove"(Graham, Rider, Caves, *et al.*, 1974; Withering, 1785). Withering's instinct as a physician compelled him to study the effect of the Foxglove on patients(DiBardino, 1999; Silverman, 1989).

His book was based on 163 cases studies; consisting of his own patients and other case studies that were sent to him. Withering realised that the remedy was especially useful in patients who would be regarded in modern times as suffering with advanced chronic heart failure or atrial fibrillation. His book marks the beginning of modern clinical pharmacology (Borel, 1976; Silverman, 1989).

Since Withering, other Physicians including William Osler also made significant contributions to the understanding of the heart and its function as part of the circulatory system.

Contemporary Epidemiology and Aetiology of Heart Failure

Aetiology

Heart failure is a major health problem worldwide. It is a clinical syndrome that occurs when the heart is no longer able to pump enough blood to meet the demands of the body. More specifically it has been defined by the European Society of Cardiology:

Heart failure may be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures) (DiBardino, 1999; Dickstein, Cohen-Solal, Filippatos, *et al.*, 2008; McMurray & Adamopoulos, 2012).

This can occur when the heart is either damaged or overworked. Cardiovascular disease claims more lives than any other healthcare problem – it is estimated that there are more than 750,000 people in the UK who suffer from heart failure (McGregor, Oyer & Shumway, 1986; MacGowan, Parry, Schueler, *et al.*, 2011), although there are a range of estimates and some put the figure close to 1,000,000 (Thekkudan, Rogers, Thomas, *et al.*, 2010; Stewart, Jenkins, Buchan, *et al.*, 2002). The incidence was 60% higher in males and the highest incidence was in adults of age greater than 75 years. Using the General Practice Research Database (GPRD) data, the BHF estimate 800,000 heart failure sufferers in the UK. A survey conducted in west London involving 220 patients with a new diagnosis of heart failure identified from a denominator of 151,000 patients served by 82 general practitioners showed the predominant causes of heart failure to be ischaemic or coronary heart disease (CHD) (Levy, Mozaffarian, Linker, *et al.*, 2006; Cowie, Wood, Coats, *et al.*, 1999; Metra, Ponikowski, Dickstein, *et al.*, 2007).

It is estimated that the incidence of heart failure will continue to increase by approximately 5% per year (Banner, Bonser, Clark, *et al.*, 2011; Cowie, Wood, Coats, *et al.*, 1999; Petersen, Rayner & Wolstenholme, 2002) leading to a rise in the burden of heart failure and an increase in the number of hospital admissions over the next 20 years.

Symptoms and Signs

Heart failure can be caused by any anatomical or physiological defect of the heart. Common symptoms in heart failure include, shortness of breath on exertion, fatigue, exhaustion and tiredness and ankle swelling. Signs may include tachycardia, tachypnoea, raised jugular venous pressure, peripheral oedema, basal crepitations and pleural effusions.

The diagnosis of heart failure may be difficult because the symptoms are non-specific and there non-discriminating (McMurray & Adamopoulos, 2012). The clinical syndrome of heart failure will include some of these symptoms and signs but an objective measure of structural abnormality of the heart is required to make the underlying diagnosis of heart failure. Investigations include echocardiogram and blood tests (natriuretic peptide).

The commonest cause of heart failure is myocardial disease causing systolic ventricular dysfunction (McMurray & Adamopoulos, 2012), however, ventricular diastolic dysfunction; abnormalities in the valves, pericardium heart rhythm and conduction may also cause heart failure.

Cost

Stewart et al., (Stewart, Jenkins, Buchan, *et al.*, 2002) estimated in the year 2000, that there were 988,000 patients requiring treatment for heart failure in the UK. The estimated health care cost of this burden was 716 million pounds, which constituted approximately 1.83% of total NHS expenditure. The additional costs of associated nursing care in the primary care

setting was 750 million pounds accounting for another 2% of total NHS expenditure. These estimates confirm the importance of heart failure as a major health problem in the UK.

Table 1-1: Classification of Patients with Heart Failure

Class	New York Heart Association Functional Classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause symptoms
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnoea
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation or dyspnoea
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased

The New York Heart Association classification for categorising patients with heart failure was first developed in 1928 and provides a unified classification system that is simple and easy for physicians to apply to their patients (Dolgin, 1994; Raphael, Briscoe, Davies, *et al.*, 2007).

Diagnosis and Treatment options in Heart Failure

Heart failure is diagnosed by assessing the patient both by taking a patient history and performing a physical examination coupled with appropriate investigations. The symptoms

associated with heart failure can often be non-specific and therefore there are no symptoms and signs that are both specific and sensitive for the diagnosis of heart failure.

Investigations including electrocardiography and measurement of B-type natriuretic peptide (BNP) are helpful in making the diagnosis. If these are abnormal, further investigations such as chest radiography to measure the size of the heart (cardiomegaly) and echocardiography to measure ventricular function are undertaken to make the diagnosis(Taylor, Stehlik, Edwards, *et al.*, 2009; Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013). Heart failure treatment can be divided into three broad categories; medical management, electrical or surgical management.

Medical Management for Heart Failure

Pharmacological Management

Diuretics, ACE inhibitors and β blockers are used in patients with heart failure secondary to left ventricular systolic dysfunction as first line therapy (Thekkudan, Rogers, Thomas, *et al.*, 2010; Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013).

Diuretics may be used to alleviate symptoms associated with pulmonary congestion and peripheral oedema secondary to fluid overload. Diuretics are divided into 3 main groups; loop diuretics, thiazide diuretics and potassium sparing diuretics. Diuretics can be prescribed for patients with heart failure who have evidence of fluid overload. Symptoms and signs may include raised JVP; peripheral oedema and ascites and pulmonary congestion. Trials have shown that diuretics are able to control the physical signs of fluid retention and improve cardiac function (Liotta, Crawford, Cooley, *et al.*, 1962; Lonn & McKelvie, 2000).

Aldosterone receptor antagonists are shown to be beneficial in the treatment of congestive heart failure (Liotta, 2008; Maron & Leopold, 2010). The RALES trial showed that Spironolactone reduced mortality by 30% in NYHA III/IV patients when added to an ACE

inhibitor and loop diuretic (Sharples, Buxton, Caine, *et al.*, 2006; Maron & Leopold, 2010) (Rose, Gelijns, Moskowitz, *et al.*, 2001; Pitt, Zannad, Remme, *et al.*, 1999). The EMPHASIS trial showed that Eplerenone reduced the risk of death significantly and hospitalisation among patients with mild symptoms (NYHA II) and systolic heart failure (Sharples, Buxton, Caine, *et al.*, 2006; Zannad, McMurray, Krum, *et al.*, 2011).

Angiotensin converting enzyme inhibitors (ACE) have been shown in large randomised trials to prolong survival and reduce the need for admission to hospital for patients with heart failure (Boettcher, Merkle & Weitkemper, 2003; Lonn & McKelvie, 2000). These agents work by preventing the conversion of Angiotensin I to Angiotensin II, modulating the rennin-angiotensin system and potentiating the effects of bradykinin. ACE inhibitors have been evaluated in many large RCTs and have been shown to reduce morbidity and mortality in patients suffering with heart failure (Pfeffer, Braunwald, Moyé, *et al.*, 1992; Investigators, 1990; Garg & Yusuf, 1995; Julian, Moss, Murray, *et al.*, 1993).

Angiotensin receptor blockers (ARBs) can also be used in these patients to reduce morbidity and mortality (Boettcher, Merkle & Weitkemper, 2003; Banner, Bonser, Clark, *et al.*, 2011; Friedrich & Böhm, 2007).

Beta blockers act by blocking the activation of beta adrenergic receptors and benefit most patients with heart failure due to left ventricular systolic dysfunction by preventing the negative effects if chronic adrenergic stimulation on the heart. Several randomised trials recruiting more than 10,000 participants have shown beta blockers to reduce hospital admissions, reduce the risk of death and prove patients clinical status in patients who were already prescribed ACE inhibitors and diuretics (Bing, 1994; Lonn & McKelvie, 2000).

Patients who do not respond to these agents may require inotropic medications, which alter the force of the muscular contractions. Inotropic agents such as dobutamine and milrinone

may be used in patients that may be resistant to other medical agents such as vasodilators and diuretics; in some circumstances patients can become dependent on inotropic medications whist waiting for a donor heart for transplantation.

While these agents may provide symptomatic relief and improve organ perfusion, they do not improve prognosis.

More recently, newer agents have been shown to be more effective in the treatment of advanced chronic heart failure when compared with traditional regimens. The PARADIGM-HF study investigated the impact of Entresto (Novartis) LCZ696, a combination of an ARB with sacubitril, a neprilysin inhibitor. This was compared with an ACE inhibitor, Enalapril in more that 8000 patients with a left ventricular systolic dysfunction (ejection fraction of less than or equal to 40%). The primary endpoints included death from cardiovascular causes and hospitalisation due to heart failure. The trial was stopped early due to an overwhelming benefit being shown in favour of Entresto in both endpoints. The Entresto group has a significantly reduced risk of death and hospitalisation due to heart failure (McMurray, Packer, Desai, *et al.*, 2014; Bonow & ElGuindy, 2014).

Cardiac Resynchronization Therapy

Cardiac resynchronisation therapy (CRT) aims to treat cardiac dyssynchrony, which complicates or causes heart failure. The retiming of the sequence of contraction can improve cardiac function reducing cardiovascular morbidity and mortality (Gibbon, 1972; Crawford, DiMarco & Paulus, 2009; Bing, 1994). Cardiac dyssynchrony is a term that refers to the disruption of the orderly sequence of contraction and relaxation, which in turn leads to a decline in cardiac efficiency. A delay in the spread of ventricular electrical activation is a common finding in patients with heart failure, and the main cause of dyssynchrony. As much as 60% of patients with heart failure, have cardiac dyssynchrony (Kirklin, Dushane, Patrick, *et al.*, 1955; Saksena & Camm, 2011; Kirklin, Donald, Harshbarger, *et al.*, 1956; Kirklin, Patrick &

Theye, 1957). This can be due to structural abnormalities in the myocardium, which leads to cardiac dyssynchrony by causing asynchronous ventricular contraction (Kouchoukos, Blackstone, Hanley, *et al.*, 2012; Saksena & Camm, 2011). Cardiac dyssynchrony can cause inefficient ventricular performance leading to heart failure.

Cardiac pacing evolved as a method of providing support for patients with heart failure as a result of earlier work with dual-chamber pacemakers, which demonstrated improvement in cardiac function by shortening atrioventricular (AV) delay in these patients (Slepian, Smith & Copeland, 2006; Saksena & Camm, 2011).

CRT involves the placement of a pulse generator in the upper chest with three leads connecting this to the right atrium and both ventricles. The device resynchronises contraction and thereby improves pump efficiency.

CRT can be achieved by using either a biventricular pacemaker (CRT-P) or a biventricular cardioverter defibrillator device (CRT-D).

Heart Transplantation

Patients with severe heart failure that is refractory to both pharmacological and resynchronisation therapies require heart transplantation. This was the first clinically applicable pump replacement therapy.

Transplanting the heart posed a problem for surgeons independent of rejection. The heart would deteriorate minutes after death and therefore was impossible to store. Therefore, to perform the transplant required great speed without the availability of tissue typing. The first attempt at a human heart transplant was undertaken by James Hardy on 23rd January 1964 at the Mississippi Medical Centre (Porter, 1999; Renee C. Fox Annenberg Professor of the Social Sciences University of Pennsylvania Judith P. Swazey President The Acadia Institute, 1992). The potential donor was a young man dying from irreversible brain damage,

whilst the potential recipient was a 68-year-old man suffering from severe heart failure. The potential recipient was put on a heart lung machine whilst Hardy prepared for the transplant. During this period the donor's heart failed. Hardy attempted to use a chimpanzee's heart instead but this was too small and unable to cope and subsequently the patient died. Four years later, it was Christiaan Barnard in December 1967 who performed the first human to human heart transplantation. Barnard transplanted the heart of a young woman, Denise Darvall into 53-year-old Louis Washkansky who had suffered several myocardial infarctions over the previous seven years. Whilst the transplantation was deemed surgically successful, Washkansky died of pneumonia 18 days later (Cooley, 2001; Porter, 1999; Kwan-Gett, Van Kampen & Kawai, 1971; Barnard, 1967).

The year following the first human heart transplant, 102 heart transplants were performed (DeVries, Anderson, Joyce, *et al.*, 1984; DiBardino, 1999). In this early learning curve of heart transplantation, the rate-limiting step to successful transplantation was immunosuppression and the inability to diagnose rejection. Shumway and colleagues published their early experience of heart transplantation in 1971. They showed data pertaining to 26 human heart transplants of which 42% survived more than 6 months. They used electrocardiography, echocardiography and clinical examination as their predominant method of identification of acute rejection episodes and using these criteria were able to diagnose 60 rejection episodes (Mehra & Domanski, 2012; DiBardino, 1999; Stinson, Dong, Clark, *et al.*, 1971). Shumway's group were also the first to describe transvenous endomyocardial biopsy as a method of detecting acute rejection. In 1974, Shumway et al., reported their experience of human heart transplantation in 59 patients. Actuarial survival was 43% at 1 year, 40% at 2 years and 26% at 3 years (Hoshi, Shinshi & Takatani, 2006; Graham, Rider, Caves, *et al.*, 1974). This improvement was in part due to their improved ability to detect acute rejection. The group had added transvenous endomyocardial biopsy to their protocol and this also included serial biopsies in the early post operative period to

diagnose early signs of acute rejection (Dowling, Park, Pagani, *et al.*, 2004; DiBardino, 1999). Further improvement in survival would hinge on the development of better immunosuppression protocols.

Borel first described the immunosuppressive effects of Cyclosporin A in the mid 1970's (Pagani, Long, Dembitsky, *et al.*, 2006; Borel, 1976). Cyclosporin A, which was a fungal metabolite isolated from Swiss soil samples, was the first agent that selectively acted on lymphocytes (Rose, Gelijns, Moskowitz, *et al.*, 2001; DiBardino, 1999). Shumway et al., began using Cyclosporin A in 1980 and subsequently reported actuarial survival rates of 63%, 56% and 52% at 1,2 and 3 years post transplant (Rose, Gelijns, Moskowitz, *et al.*, 2001; McGregor, Oyer & Shumway, 1986). Survival rates subsequently continued to improve until the present day where survival at 1 year is as high as 80% (Thekkudan, Rogers, Thomas, *et al.*, 2010).

Despite the progress of treatments for heart failure, prognosis for patients who progress to advanced heart failure is terrible as is their quality of life (Levy, Mozaffarian, Linker, *et al.*, 2006; Metra, Ponikowski, Dickstein, *et al.*, 2007). In selected patients, heart transplantation offers effective treatment and is shown to improve survival and quality of life (Birks, 2010; Banner, Bonser, Clark, *et al.*, 2011). Data from the international society of heart and lung transplantation on a cohort of over 85,000 heart transplant recipients show that 50% of patients survive for more that 10 years with median survival for those surviving at least 1 year post transplant being 13 years (Taylor, Stehlik, Edwards, *et al.*, 2009; Lund, Edwards, Kucheryavaya, *et al.*, 2014; 2013). Despite this, long-term morbidity following transplantation remains problematic. 10 years after transplant, 97% of recipients have hypertension, 14% have severe renal insufficiency (serum creatinine > 190nmol/L in 7%, dialysis in 4% and renal transplantation in 1.5%), 93% have hyperlipidaemia, 39% have diabetes and 52% have angiographic coronary allograft vasculopathy (Emin, Rogers,

Parameshwar, *et al.*, 2013; Taylor, Stehlik, Edwards, *et al.*, 2009). Heart transplantation is a highly effective treatment for advanced heart failure principally limited by the availability of suitable donor hearts. Most patients achieve a good level of rehabilitation and quality of life.

More than 5000 heart transplants have been performed in the UK (Bartoli, Restle, Woo, *et al.*, 2014; Thekkudan, Rogers, Thomas, *et al.*, 2010).

Ventricular Assist Devices

The first clinical applications of both an intrathoracic and paracorporeal pump took place in the 1960's. Crawford and Liotta implanted the first intrathoracic LVAD into a patient following a cardiac arrest post-surgery (Bartoli, Restle, Woo, *et al.*, 2014; LIOTTA, CRAWFORD, Cooley, *et al.*, 1962). The patient survived for four days. In 1966, DeBakey and Liotta implanted the first clinical LVAD in the paracorporeal position into a patient who developed cardiogenic shock following cardiac surgery (Bartoli, Restle, Woo, *et al.*, 2014; Liotta, 2008).

VAD used as a potential treatment in heart failure

VAD has been shown to be effective in bridging unstable patients with end stage heart failure to heart transplantation (Sharples, Buxton, Caine, *et al.*, 2006). They have also been used in patients who have been ineligible for heart transplantation (Rose, Gelijns, Moskowitz, *et al.*, 2001).

In the UK, patients who are eligible for HTx may be bridged to HTx using VAD therapy if they become unstable whilst waiting for HTx (Sharples, Buxton, Caine, *et al.*, 2006).

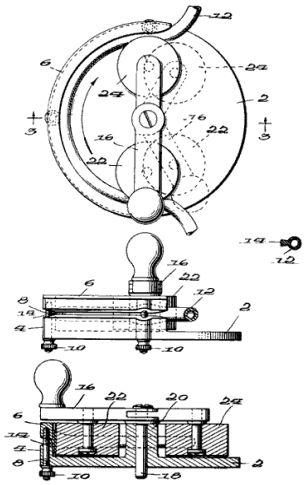
Chapter 2: Mechanical Circulatory Support in the Treatment of Advanced Heart Failure

Early blood pumps and Cardiopulmonary Bypass

The first artificial pump proposed for medical application was described in the middle of the nineteenth century.

In 1855, Porter and Bradley designed a hand operated roller pump, which they suggested could be used for a variety of purposes including that of intravenous injection. In 1887, Allen designed and manufactured the first "surgical pump" which was intended for implementing blood transfusions (Barnes, 2008; Boettcher, Merkle & Weitkemper, 2003). Truax added some modifications to the Allen pump in order to make it more marketable with a broader range of functions, and subsequently he designed and manufactured a double roller in 1899 (Nielsen, Kirklin, Holman, *et al.*, 2008b; Truax, 1899; Nielsen, Kirklin, Holman, *et al.*, 2008a). These innovations would lead to the future widespread use of pumps in medicine.

Figure 2-1: DeBakey Modification of the Porter Bradley Roller Pump



In 1934, DeBakey modified the original Porter Bradley roller pump to prevent movement of the latex rubber tubing by positioning a flange to the outer circumference of the tubing which was then clamped to the housing of the pump. It was with DeBakey's modifications that this pump was used as the basis of the first heart lung machine designed by the surgeon John Gibbon (Rose, Gelijns, Moskowitz, *et al.*, 2001; Boettcher, Merkle & Weitkemper, 2003).

John Gibbon and Cardiopulmonary Bypass

John Gibbon was born in 1904. He began to practice surgery in Philadelphia in 1931. He was inspired to develop the first heart lung bypass machine because of an encounter with a patient whilst undertaking an academic research fellowship at Massachusetts General Hospital. A female patient was admitted after having suffered a massive pulmonary embolism post-operatively. Gibbon watched while his patient deteriorated eventually being taken to theatre by one of Gibbon's colleagues for a pulmonary embolectomy; a procedure which carried a significant mortality. The patient died during the operation. This event was the catalyst for Gibbon to conceive of and develop a cardiopulmonary bypass circuit. He discussed the idea with his colleague and employer Edward Churchill who provided the funds for a research fellowship as well as a technician's salary which would go to Gibbons wife. It is important to note that Gibbon was discouraged from undertaking this project and was warned by even the Professor of Medicine at Massachusetts General. It was thought that the project was too ambitious and that a young surgeon trying to build a surgical career should focus on several smaller projects that could be published regardless of their success (Gordon, Weinberg, Pagani, *et al.*, 2013; Bing, 1994). Several problems were encountered; deciding which fluid to use in the extracorporeal circuit [gum acacia was used], the connection between the vessels and the unit and the decision regarding the type of anaesthesia to use. Oxygenation of the blood in the circuit was handled by developing a screen oxygenator. In 1934, Gibbon and his wife successfully trialled the circuit on an animal

and demonstrated that the animal could be kept alive without having any blood going to its heart or lungs. Gibbon later described the joy that he and his wife had felt when they finally occluded the pulmonary artery with the functioning extracorporeal circuit and observed no change in blood pressure. Gibbon wrote:

"My wife and I threw our arms around each other and danced around the laboratory laughing and shouting hooray….nothing in my life has duplicated that ecstasy and joy of that dance" (Rose, Gelijns, Moskowitz, *et al.*, 2001; Gibbon, 1972; Bing, 1994).

In 1953, Gibbon closed an atrial septal defect whilst his patient was on bypass using a pump oxygenator. His work and contribution led to a completely new line of research and was to later propagate and form the basis for mechanical circulatory support.

Kirklin et al, directed research into pump oxygenators at the Mayo Clinic in the early 1950's (Rose, Gelijns, Moskowitz, *et al.*, 2001; KIRKLIN, DUSHANE, PATRICK, *et al.*, 1955; Stevenson, Miller, Desvigne-Nickens, *et al.*, 2004; KIRKLIN, DONALD, HARSHBARGER, *et al.*, 1956; KIRKLIN, PATRICK & THEYE, 1957). This led to the first use of this kind of device at the Mayo Clinic to successfully repair a ventricular septal defect. The device used was a Mayo-Gibbon pump oxygenator. The use cardiopulmonary bypass subsequently became widespread in cardiac surgery (Rose, Gelijns, Moskowitz, *et al.*, 2001; Kouchoukos, Blackstone, Hanley, *et al.*, 2012; Rose, Moskowitz, Packer, *et al.*, 1999).

Development of Mechanical Circulatory Support

A ventricular assist device (VAD) is used to assist a damaged or weakened heart in pumping blood. VADs have been used to support the circulation following cardiac surgery or as an interim therapy to bridge a patient to heart transplantation or as a long-term 'destination' therapy. VADs can be used to support the left ventricle (LVAD) or the right ventricle (RVAD)

or both ventricles simultaneously (BiVAD). A total artificial heart (TAH) is an implantable device, which totally replaces the heart.

VADs are distinct from artificial hearts; the latter take over the complete function of the heart (and generally require the patient own heart to be removed during the implant procedure). Their development has shared origins but the devices themselves are used differently in the modern treatment of advanced heart failure.

Early attempts to replace cardiac pump function centred on designs for a total artificial heart.

Total Artificial Heart

The rationale for the development of the total artificial heart (TAH) arose from an unmet clinical need for a device that could restore completely the systemic and pulmonary blood circulation and organ perfusion pressure in patients with failing hearts secondary to irreversible biventricular dysfunction (Rose, Gelijns, Moskowitz, *et al.*, 2001; Slepian, Smith & Copeland, 2006). Although this may have been the initial goal for TAH therapy, the parallel rise of heart transplantation secondary to the availability of more effective anti-rejection therapies meant that TAH was more suitable to being used as a bridge to transplant as opposed to a stand-alone therapy.

In 1949 Sewell and Glenn created the first artificial heart pump using parts from children's toys and basic mechanical equipment. They used this to bypass the heart of a dog for more than one hour. Pioneering research into heart pump substitutes at the University of Utah began with Willem Kolff (Stevenson, Miller, Desvigne-Nickens, *et al.*, 2004; Renee C. Fox Annenberg Professor of the Social Sciences University of PennsylvaniaJudith P. Swazey President The Acadia Institute, 1992) and later was continued by Robert Jarvik. In 1957, Willem Kolff implanted an artificial heart into a dog; the dog survived for 90 minutes.

Liotta's work in the 1950's in France and Argentina paved the way for the first clinical application of a total artificial heart in 1969, when accompanied by Cooley, Liotta implanted a mechanical heart into a dying man in Texas as a bridge to transplant. The patient was successfully transplanted 64 hours later although he subsequently died from acute pulmonary infection thought to be a consequence of immunosuppression (Sharples, Buxton, Caine, *et al.*, 2006; Cooley, 2001; Sharples, Cafferty, Demitis, *et al.*, 2007; Kwan-Gett, Van Kampen & Kawai, 1971).

Jarvik made several modifications to Kolff's designs, developing the shape of the device so that it could fit more easily into a patient's chest. In 1982 these modifications culminated in the implantation of the Jarvik 7 device into a 61-year-old dentist who survived for 112 days after the procedure (Clegg, Scott, Loveman, *et al.*, 2005; DeVries, Anderson, Joyce, *et al.*, 1984).

Ventricular Assist Devices

The first clinical applications of both an intrathoracic and paracorporeal pump took place in the 1960's. Crawford and Liotta implanted the first intrathoracic LVAD into a patient following a cardiac arrest post cardiac surgery. The patient survived for four days. In 1966, DeBakey and Liotta implanted the first clinical LVAD in the paracorporeal position into a patient who developed cardiogenic shock following cardiac surgery.

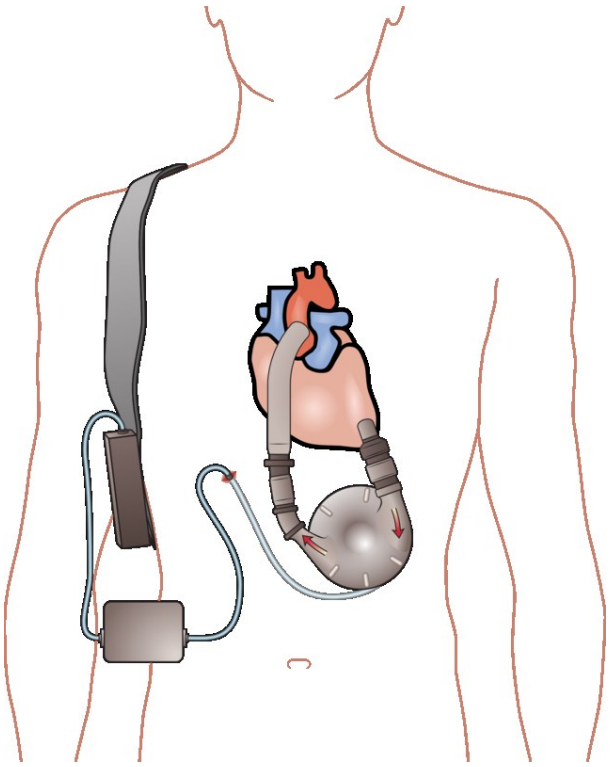
VADs fit broadly into 2 categories; Pulsatile and continuous flow pumps. Early VADs were pulsatile volume displacement pumps where the volume occupied by blood may vary during the pumping cycle and it was assumed that it was an absolute physiological necessity to maintain pulsatility in flow. These devices were larger and bulky and were associated with significant morbidity as a result of infectious, haematological and neurological complications (Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013; Mehra & Domanski, 2012).

Continuous flow devices were developed and were designed to be smaller with the intention of being more durable than pulsatile pumps (Slaughter, Rogers, Milano, *et al.*, 2009). They are divided into centrifugal pumps and axial flow pumps. Centrifugal pumps have rotors, which are designed to pump the blood to the outer rim of the device circumferentially. Axial flow pumps have cylindrical rotors with helical blades which accelerate blood in the direction of the rotor's axis (Strueber, O'Driscoll, Jansz, *et al.*, 2011; Hoshi, Shinshi & Takatani, 2006).

Table 2-1: Implantable LVADs

Manufacturer	Device	Type	Approval
1st Generation			
Berlin Heart	EXCOR	Pulsatile	CE Mark Authorised. FDA approval December 2011.
Thoractec	PVAD	Pulsatile	CE Mark Authorised. Received FDA approval for BTT in 1995.
Thoractec	IVAD	Pulsatile	CE Mark Authorised. Received FDA approval for BTT in 2004.
Thoractec	HeartMate XVE	Pulsatile	FDA approval for BTT in 2001 and DT in 2003. CE Mark Authorised.
2nd Generation			
Thoractec	HeartMate II	Rotor driven, continuous axial flow	Approved for use in North America and EU. CE Mark Authorised. FDA approval for BTT in 2008.
Jarvik Heart	Jarvik 2000	Continuous flow, axial rotor with ceramic bearings	Currently used in the US as a BTT. In Europe, the Jarvik 2000 has earned CE Mark certification
MicroMed	DeBakey	Continuous flow, axial rotor with ceramic bearings	Approved for use in the European Union.
3rd Generation			
HeartWare	HVAD	Centrifugal blood and hydromagnetically suspended rotor	Obtained CE Mark 2009. Obtained FDA approval in the U.S., November 2012.
Thoratec	HeartMate III	Maglev centrifugal flow with suspended rotor	Momentum 3 trial suggests better outcomes at 6 months when comparing maglev centrifugal flow with axial flow devices (Mehra, Naka, Uriel, *et al.*, 2017).
Ventracor (now defunct)	VentrAssist	Continuous flow driven by a hydrodynamically suspended centrifugal rotor.	Approved for use in European Union and Australia.

Figure 2-2: Schematic of LVAD Implant



Left Ventricular Assist Devices in Heart Failure

LVAD therapy has become an established treatment option for patients with advanced chronic heart failure. The indication to use LVAD include: bridge to transplant, destination therapy and bridge to recovery. Over the last 15 years, LVAD therapy has been used successfully to bridge patients to heart transplant in the UK. In the US, VAD devices have also been used as an alternative to transplant (ATT) in patients who are ineligible for transplantation.

Device Classification

Mechanical support devices can be categorised in several ways. They can be categorised in terms of which parts of the heart they provide support to and in terms of the mechanism of support.

Devices are also classified by generation; first, second or third generation devices. In the early days of the first generation devices, pulsatile volume displacement pumps were used which were subsequently replaced with continuous flow rotary impeller drives. Fourth generation devices are currently being assessed in clinical trials. Current practice involves mostly second and third generation mechanical circulatory support devices.

First Generation Devices

HeartMate VE/XVE was a first generation pulsatile-vented electric left ventricular assist device. It was the first mainstream VAD and it has been used to support several thousand patients with advanced chronic heart failure (Xie, Phan & Yan, 2014; Dowling, Park, Pagani, *et al.*, 2004). It was initially conceived as a permanent support device (Kirklin, Naftel, Kormos, *et al.*, 2013; Pagani, Long, Dembitsky, *et al.*, 2006) however was mainly used for bridging therapy. The US FDA approved its use in the context of destination therapy based on trial data from the REMATCH Study (Alba, McDonald, Rao, *et al.*, 2011; Rose, Gelijns,

Moskowitz, *et al.*, 2001). Data from this randomized controlled trial also revealed significant problems with the HeartMate VE LVAS in that it was associated with device failure and significant morbidity and mortality. Rose et al demonstrated that within three months of implantation of the device, the probability of infection was 28%; driveline tract and pocket infection were treated with antibiotics although in severe infection mortality was common. The probability of device failure at 24 months was 35% and the probability of bleeding at 6 months was 42% (Miller, Pagani, Russell, *et al.*, 2007; Rose, Gelijns, Moskowitz, *et al.*, 2001). Despite the trial showing a clear survival benefit for patients with device therapy compared to medical therapy alone, it was obvious that further development of this device and other systems was required to address and attempt to minimize the morbidity associated with mechanical circulatory support.

Second Generation Devices

HeartMate II devices were approved for use in Europe in 2005. This is the second-generation device and operates by using an internal rotator with helically curved blades. The volume of flow generated by this device is determined by the speed of rotation of its rotor and by the difference in pressure that exists across the pump. For a specified speed there was a variance in flow which is inversely proportional to pressure and therefore increasing the differential pump pressure will decrease flow (Slaughter, Rogers, Milano, *et al.*, 2009; HeartMate, 2007).

The device is connected to the circulatory system via an inflow and outflow conduit. The inflow conduit is attached to the left ventricle whilst the outflow graft is attached to the aorta. The device manufacturers have provided extensive information on the functioning of this device along with its physical properties. Laboratory data showed that a decrease in pump differential pressure causes a significant increase in flow, which means that any residual contraction by the left ventricle will subsequently be amplified as a flow pulse

delivered to the aorta. Under most circumstances systemic flow will demonstrate some pulsatility however in the flaccid heart or the fibrillating heart there will be no contribution to flow (Aaronson, Slaughter, Miller, *et al.*, 2012; HeartMate, 2007). This device has been used in more than 3000 patients worldwide (Kirklin, Naftel, Stevenson, *et al.*, 2008; Birks, 2010; Kirklin, Naftel, Kormos, *et al.*, 2013; 2012; 2011).

The Jarvik 2000 operates by using a spinning rotor to propel blood from the apex of the ventricle to the aorta (Jarvik, Frazier, Westaby, *et al.*, 2000). This is a continuous flow pump which was approved for use in Europe as a bridge to transplant and a bridge to destination therapy. The MicroMed Debakey became the HeartAssist 5 and was approved for use for bridging to transplant (Noon & Loebe, 2010). This device is now withdrawn.

Third Generation Devices

Third generation devices include the Berlin Heart 'INCOR', Terumo DuraHeart LVAD, HeartWare HVAD and Thoratec HeartMate III. The Berlin heart System is a magnetic bearing flow pump, which circulates blood from the left ventricular apex to the ascending aorta. The Terumo DuraHeart LVAD is a small continuous radial flow pump connected to a magnetically levitated impeller (Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013). This was one of the first third generation devices to gain approval for use in the European market (Murphy, 2012; Morshuis, Schoenbrodt, Nojiri, *et al.*, 2010). The HeartWare HVAD is currently the most commonly used device United Kingdom (Porter, 1999; Emin, Rogers, Parameshwar, *et al.*, 2013). This is a small implantable centrifugal pump, which drains the left ventricle and pumps blood through the aorta via an outflow graft. This works via a magnetic impeller suspended within the pump. The Thoratec HeartMate III is a new third generation device, which operates via maglev centrifugal flow.

Complications of VAD Therapy

VAD therapy is associated with important complications:

Haemorrhage

Bleeding is one of the commonest complications of mechanical implantation surgery. Haemorrhage may be categorised as early and late; early bleeding being related to the operation whilst late bleeding being associated with anticoagulation and other causes. Early bleeding can result from technical problems creating the inflow or outflow graft anastomoses. Clotting abnormalities as a result of the surgery or as a result of the patients' post-operative status can also cause early haemorrhage. Anticoagulation is required for patients with mechanical circulatory support, and this can be a cause of bleeding at any time.

The literature also describes other causes of non-surgical bleeding in patients with mechanical circulatory support. Impairment of the von Willebrand factor (vWF) pathway in patients with mechanical circulatory support has been implicated as a cause of bleeding in supported patients. Bartoli et al., (Neuhauser, 2002; Bartoli, Restle, Woo, *et al.*, 2014) have shown experimentally that the effect of high shear stress on vWF may reduce high molecular weight vWF multimers and so impair the vWF-platelet aggregation pathway, which in turn leads to bleeding diathesis (Donabedian, 1966; Bartoli, Restle, Woo, *et al.*, 2014). It is suggested that different device types may activate the vWF pathway differently and that the mechanism for this process may involve quantitative and qualitative changes in shear stress. Shear stress profiles differ between pulsatile and continuous flow LVADs (Murphy, 2012; Bartoli, Restle, Woo, *et al.*, 2014).

Organ Failure

Multi-organ failure is also a cause of early morbidity associated with VAD implantation. Patients with advanced chronic heart failure often already have evidence of end organ dysfunction prior to their surgery. This can be exacerbated in the early post-operative period by implant surgery. Right ventricular failure is a recognised complication of VAD implantation. This can occur in a large proportion of LVAD recipients (Porter, 1999; Argiriou, Kolokotron, Sakellaridis, *et al.*, 2014; Silverman, 1985).

Thromboembolic Events

Thromboembolic events are observed in a high proportion of patients. 10-25% of patients may experience these events, which vary dependent on the type of device and anticoagulation regimen (Health, 2002; Barnes, 2008). VAD implantation is associated with consumption of circulating contact proteins and generation of activated contact proteins including Factor XII and high molecular weight kininogen; VAD patients have been shown to have increased platelet activation and hyperfibrinogenaemia which may lead to thrombogenesis (Health, 2001; Nielsen, Kirklin, Holman, *et al.*, 2008b; Health, 2002; Nielsen, Kirklin, Holman, *et al.*, 2008a). Thrombus may originate in the VAD circuit or in the heart.

Chronic Infection

Driveline infections were common with first and second-generation devices. The advent of third generation devices has led to a reduction in these infections. There is a peri-operative risk of deep-seated inflow or outflow graft infection, as well as a risk of infection around the device itself. It is more common however, for drivelines to become infected. Chronic infections in these patients can be difficult to treat and are associated with significant morbidity. Rose et al., 2001 demonstrated that 42% of patients randomized to VAD therapy in the REMATCH study developed sepsis within 1 year of implantation of the first-generation device(Murphy, 2012; Rose, Gelijns, Moskowitz, *et al.*, 2001). Gordon et al., 2013 carried out

a prospective multicentre study of infections in VAD recipients. They showed that 22% (33 patients) experienced VAD infection; 28 out of the 34 infection in 33 patients were associated with the driveline (82%), median time to the first infection was 68 days. 8 out of the 11 centres recruiting patients for the study had patients with an infection episode (Smith, 1998; Gordon, Weinberg, Pagani, *et al.*, 2013).

Device Malfunction

Device malfunction can occur and may necessitate further surgery. Malfunction may be due to failure of a device component or be secondary to pump thrombosis. Further surgery in these cases are often more complex and complicated, causing greater risk for the patient. Rose et al., showed that device failure was common in patients supported with a first-generation device for 2 years or more (Cleland, Dargie, Hardman, *et al.*, 2012; Rose, Gelijns, Moskowitz, *et al.*, 2001).

Randomised Clinical Trial Data

As part of the preparation process for my study I decided to undertake a systematic review of the literature. In the following section I describe the systematic review that I conducted to investigate the available randomised trial data for the use of VAD in treatment of patients with advanced chronic heart failure.

Systematic Review

A systematic review is a type of literature review which attempts to identify, appraise, synthesize and if appropriate combine all high quality data to answer the research question of interest {Centre for evidence based medicine). It differs from other literature reviews because of its systematic methodology, and sequence of steps that lead to the completed review. The results should be reproducible by other researchers.

Method

A systematic review of the literature was undertaken to investigate the evidence base for the use of implantable ventricular assist devices in patients with advanced chronic heart failure. All evidence was included where VAD therapy was used in patients with advanced chronic heart failure irrespective of the indication for VAD support.

The research question for this study was as follows:

Question: Is there high quality randomised trial data to support the use of VAD therapy in patients with advanced chronic heart failure; does VAD therapy improve survival in these patients when compared with other available treatments?

Table 2-2: The PICO approach

P opulation: All patients with advanced chronic heart failure
I ntervention: VAD Implantation
C omparison: Best medical therapy
O utcome: Mortality; short term 30 day mortality and mid term 1 year mortality

Search term and Search Strategy

The search term was formulated to capture all data relating to randomised trials involving VAD therapy in patients with advanced chronic heart failure. Evidence from non-randomised studies were excluded from the study.

Table 2-3: Systematic Review Search Term and Output from OVID Medline

Line	Search Command	Output
1	randomized controlled trial.pt.	399610
2	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	773312
3	(retraction of publication or retracted publication).pt.	6423
4	or/1-3	863363
5	(animals not humans).sh.	3998169
6	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.	3298257
7	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.	47295
8	4 not (5 or 6 or 7)	633174
9	((vad or vads) and (heart or cardiac)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1500
10	(lvas or lvad).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2311
11	Heart-Assist Devices/	9104

12	9 or 10 or 11	9722
13	12 and 8	165
14	mechanical circulatory support.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1369
15	9 or 10 or 11 or 14	10122
16	15 and 8	**170**

The search strategy for this review focussed on finding all relevant randomised trial data available for VAD therapy in the context of treating severe heart failure. Searches were conducted within OVID Medline and EMBASE online databases, as well as searching for evidence within the Cochrane Collaboration Library.

For the purposes of this study, OVID Medline R (1946 to November Week 1 2014) and EMBASE (1974 to 2014 week 46) were chosen for search interrogation.

Searching OVID Medline (using the search parameters in Table 3) provided 170 papers to examine. A similar search of the EMBASE database provided 324 papers to examine.

Identification of publications

Publications were examined using a publication review tool (Papers Version 3.0 for MacOSX). Papers were exported from OVID Medline to the review tool and individually examined.

Ovid Search

170 papers were identified using the search strategy defined in table 3. From 170 publications, 157 were excluded based on the title. 13 publications were included for further analysis. Abstracts were then read for the 13 publications after which a further 10 publications were excluded from the analysis. Full papers were attained for 3 publications. 2 papers are included in the study analysis, one excluded after reading the full paper.

EMBASE Search

324 papers were identified using the previously defined search term. 316 papers were excluded based on title alone. 8 papers were included for further analysis. Abstracts were read for 8 publications – only 2 papers were included in the study analysis. These 2 papers were also identified as valid inclusions after the OVID Medline search.

Publications Included

Only 2 randomised controlled trials were indentified for inclusion in the study. Rose et al., 2001 and Stevenson et al., 2004 (Murphy, 2012; Rose, Gelijns, Moskowitz, *et al.*, 2001; Stevenson, Miller, Desvigne-Nickens, *et al.*, 2004). Stevenson et al., published a subset analysis from the REMATCH study, but has still been included here as the publication is separate and meets the inclusion criteria. The results of this study however will not add further evidence to this systematic review.

Summary of Identified Publications

Rose et al 2001

The REMATCH study published in 2001 (Great Britain & Staff, 2013; Rose, Gelijns, Moskowitz, *et al.*, 2001; Rose, Moskowitz, Packer, *et al.*, 1999). This study randomly assigned 129 patients with end stage heart failure who were ineligible for heart transplantation to receive an LVAD or optimal medical therapy alone. They showed a 48% reduction in the risk of all cause mortality in the VAD group as compared with the medical

therapy group. They demonstrated a 1-year survival rate of 52% in the device group and 25% in the optimal medical therapy group. The authors concluded that LVAD in patients with end stage heart failure resulted in clinically meaningful survival benefit (Rose, Gelijns, Moskowitz, *et al.*, 2001).

Stevenson et al 2004

Stevenson et al., published a subset analysis from the original REMATCH trial and investigated outcomes in patients undergoing inotropic infusions at the time of randomisation. They showed that patients receiving inotropic infusion, despite severe cardiac compromise received a survival benefit and better quality of life from an LVAD (Stevenson, Miller, Desvigne-Nickens, *et al.*, 2004).

Conclusion for Systematic Review

There is a paucity of randomised clinical trial data to support VAD implantation as a potential bridge to transplant, bridge to recovery or alternative to transplantation.

Clinical effectiveness for VAD Therapy: The Available Evidence

Despite the lack of randomised trial data for VAD implantation in patients with advanced chronic heart failure, there is data available from non-RCT sources investigating the clinical effectiveness of VAD implantation.

To investigate this further, a literature review was undertaken with the aim of identifying the key publications on VAD therapy, and in particular, identify, group and summarise the publications according to their quality.

Systematic reviews

EVAD UK study (Sharples, Buxton, Caine, *et al.*, 2006; Sharples, Cafferty, Demitis, *et al.*, 2007) aimed to outline the clinical and cost effectiveness of VAD treatment. Sharples et al, studied 70 VAD patients, 71 inotrope dependent and 179 non-VAD transplant candidates

accepted for transplantation. They showed that the 52% of VAD patients were alive at 1 year. They also showed that the post-HTx survival was similar regardless of pre-HTx VAD implantation although subsequent studies have shown differences in early post-HTx survival between VAD recipients and patients without VAD support. Sharples et al also conducted a systematic review to assess the clinical effectiveness of VAD in patients with advanced chronic heart failure as a bridge to transplant. Clegg et al., conducted the review in 1995; Sharples et al were able to add all large patient cohorts and device registry results available within the same study period to the systematic review conducted by Clegg et al. Clegg et al., identified 16 studies. Sharples et al., identified a further 10 studies within the same period. Of the 26 studies, 17 reported on first generation devices, 7 studies involved second generation devices and 2 studies reported results from a mixture of first and second-generation devices. Most of these studies were observational in nature and methodologically weak further highlighting the lack of good quality data. They reported a crude estimate of overall survival at 1 year of 62%. This figure was calculated by weighing each study's survival rate by the size of the corresponding patient cohort (Health, 2010; Clegg, Scott, Loveman, *et al.*, 2005).

More recently, Sutcliffe et al.,(Murphy, 2012; Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013) undertook a systematic review to investigate clinical and cost effectiveness analysis of second and third generation devices as either bridge to transplant or alternative to transplant for adults who are eligible for heart transplantation. They included studies of VADs with FDA/CE approval; studies with a minimum of 50 participants in the VAD group, studies including both FDA/CE approved and multiple unapproved VADs. They also included studies with control groups and systematic reviews of studies with control groups. Case series were included where adverse events were reported and where they reported on consecutive patients. They identified a potential 4325 records that were potentially relevant. The vast majority of these papers were excluded because they did not meet the inclusion

criteria. After screening, 40 publications were identified as having met the inclusion criteria. They concluded that overall, the study designs of the included publications were not strong and that the studies were likely to be only moderately representative of underlying populations. Publications were grouped by device; outcomes were also reported by device. 29 publications were concerning HMII. They concluded that survival results seemed to improve as experience with the HMII increases. The learning curve lead to improving survival as the cohort of HMII patients grew. Their analysis suggested that survival at 1 year is approximately 75% for HMII patients. Common causes of death included multi-organ failure, right ventricular failure, bleeding and stroke. Sutcliffe et al only identified one study, Strueber et al., which reported on 50 patients implanted with HW VAD as a bridge to transplant. They reported that survival with HW was at least comparable to HMII with a 1-year survival of 85%. When compared with earlier publications for HMII the HW VAD was superior in terms of survival. Causes of death varied evenly between sepsis, multi-organ failure and haemorrhagic stroke (Kenny, Jessop & Gutteridge, 2008; Strueber, O'Driscoll, Jansz, *et al.*, 2011; Kenny & Ashton-Key, 2012).

Xie et al., (Kenny & Ashton-Key, 2012; Xie, Phan & Yan, 2014) investigated the durability of continuous flow devices. They performed a systematic review of the available literature identifying 12 retrospective observational studies with a total of 5471 patients. They reported a mean duration of support 504 days with the incidence of device failure being close to 3.9%. The main cause for device failure was pump thrombosis which represented more that 50% of failures. Lead or cable damage was the second most common cause accounting for 27% of device failures. The reported means however likely do not reflect true practice as the types of LVAD have evolved from 1st generation to the current 3rd generation devices. Recent outcomes in terms of survival and duration of support are better than in older studies (Emin, Rogers, Thomas, *et al.*, 2011; Kirklin, Naftel, Kormos, *et al.*, 2013). Our

use of VADs has also changed as well as the population that is recognised to benefit from VAD support.

Alba et al., (2011) conducted a systematic review to investigate whether VAD supported patients had higher post-transplant mortality (Sharples, Dyer, Cafferty, *et al.*, 2006; Alba, McDonald, Rao, *et al.*, 2011). They were able to identify 31 observational studies which evaluated the effects of VAD on post-transplant outcomes. This study showed the 1 year post-transplant mortality to be significantly higher in patients bridged with an extra-corporeal LVAD compared to non-bridged patients; relative risk 1.8, CI 1.53-2.13. Patients supported with an intra-corporeal LVAD had similar mortality to non-bridged patients (relative risk=1.08 CI 0.9-1.22).

Important Clinical Trials and Cohort Studies

Miller et al., investigated the use of continuous flow VADs in patients awaiting HTx. This was a prospective multicentre study without a concurrent control group (Spilker, 1990; Miller, Pagani, Russell, *et al.*, 2007). 133 patients with advanced chronic heart failure who were on the waiting list for HTx underwent implantation of a continuous flow VAD. Principal outcomes were the proportion of patients who at 180 days had undergone transplantation, had myocardial recovery or had on-going mechanical circulatory support; and quality of life. Miller et al., showed a median duration of support of 126 days with the principal outcomes occurring in 75% (100 patients) of their cohort. Their results showed a 3 month survival whilst on support of 75%; 68% at 6 months, and they were able to conclude that continuous flow LVADs may can provide effective support for a period of at least 6 months.

Slaughter et al., investigated the difference between VAD support provided via a continuous flow LVAD and a pulsatile flow device. They randomised patients who were ineligible for transplantation in a 2:1 ratio to either a continuous flow LVAD (Thoratec HMII) or pulsatile flow LVAD (HeartMate XVE), investigating their primary outcome which was a composite of

survival at 2 years, survival free from disabling stroke and reoperation to repair or replace the device. They also measured quality of life by using 2 disease specific questionnaires; Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaire. 200 patients were assigned in total; 134 to HMII and 66 to HMXVE over a 2 year period. More than 60% of the whole cohort had not responded to cardiac resynchronisation therapy; 80% were on intravenous inotropic medications, and more than 40 patients had already received an intra-aortic balloon pump by the time of their enrolment. The primary composite endpoint was achieved in 46% of patients with a continuous LVAD as opposed to 11% of patients with a pulsatile flow LVAD; hazard ratios 0.38 (CI 0.27-0.54, p<0.001). They showed that actuarial survival was significantly better for patients with a continuous flow LVAD – estimates of the 1 and 2-year survival rates were 68% and 58% in patients with HMII versus 55% and 24% in patients with HMXVE. Improvements in quality of life were seen in both groups (Rose, Gelijns, Moskowitz, *et al.*, 2001; Slaughter, Rogers, Milano, *et al.*, 2009; Slaughter, Pagani, Rogers, *et al.*, 2010).

Aaronson et al conducted the ADVANCE trial which was a multicentre randomised non-inferiority trial comparing a third-generation LVAD (HeartWare HVAD) with a control group from a national registry of commercially approved VADs (second-generation devices). The primary outcome was success deemed to be survival on the originally implanted device, transplantation or explantation for ventricular recovery at 180 days. 140 patients received the third-generation device whilst 499 patients received a commercially available pump. Success occurred in 90.7% of the third-generation device group and 90.1% of the commercially available pump group. This study showed that the third-generation HeartWare HVAD was non-inferior to the commercially available pumps at the time of the study (Sharples, Cafferty, Demitis, *et al.*, 2007; Aaronson, Slaughter, Miller, *et al.*, 2012).

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

INTERMACS is a US registry for patients who are receiving mechanical circulatory support to treat advanced chronic heart failure. The registry was devised as a joint effort between the National Heart, Lung and Blood Institute (NHLBI), the Food and Drug Administration (FDA), clinicians, scientists and industry representatives. To date, there are 158 centres that register their devices with INTERMACS and more than 14,500 have been registered thus far. Participation however is not mandatory. Kirklin et al., recently published the fifth INTERMACS annual report which includes analysis of more than 6000 patients. They report actuarial survival of patients supported with continuous flow devices of 80% at 1 year and 70% at 2 years. This is comparable to 1 year and 2 year survival outcomes in heart transplantation and although there is potentially huge centre bias and selection bias within this dataset, Kirklin and colleagues have demonstrated a result favourable to continuous flow LVAD implantation (Kirklin, Naftel, Stevenson, *et al.*, 2008; Kirklin, Naftel, Kormos, *et al.*, 2013; 2012; 2011).

Table 2-4: Studies identified and their methodological strength.

Publication	Year	Type	Level of evidence	Comments
Sharples	2003	SR and large case-series	2a (SR) 4 (case-series)	Studies identified methodologically weak
Sutcliffe	2013	SR	2a	Moderately representative studies - very little RCT data
Xie	2014	SR	2a	Assesses durability of devices - does not report survival
Alba	2011	SR	2a	Review investigates post HTx outcomes
Miller	2007	Individual Cohort Study	2b	No control group. 133 patients recruited.
Slaughter	2009	RCT	1b	HM XVE vs HMII
Aaronson	2012	RCT	1b	HeartWare HVAD vs HMII
Kirklin	2013	Large Cohort Study	2b	Large multicentre cohort study. Non mandatory reporting

Conclusion

Whilst there are some randomised trial data to support LVAD therapy, there is far more data available from non-randomised trials and large cohort and observational studies which provide evidence for the use of LVAD implantation in patients with advanced chronic heart failure. Unfortunately, however, the other large datasets are prone to selection bias and therefore have limited interpretability.

Further work in the form of randomised clinical trials or unbiased observational and cohort studies will provide evidence to either support or refute the value of LVAD implantation in patients with advanced chronic heart failure. Whilst RCT evidence remains the gold standard, a large cohort audit study with comprehensive case ascertainment would provide high quality data and an excellent snapshot of real world practice.

The Need for More Data

Given the lack of unbiased observational data, there was a need to establish a mandatory system of data collection in the UK for all patients receiving VAD support in the context of heart transplantation. This required standardisation of data collection to ensure collection of high quality, validated and complete data. This took the form of a large observational cohort audit study, the analysis of which would hopefully provide a better understanding of VAD practice and outcomes.

Chapter 3: Methods

Surgical Audit

The aim of a healthcare system is to deliver good outcomes to individuals and populations. Whilst measuring waiting times and numbers of patients seen and treated was the traditional way in which outcomes were recorded in the NHS, what remains important to patients is the clinical outcome of their healthcare intervention and the effect of this delivery of care on their medical and social well-being (Silverman, 1985; Schwartz & Lurie, 1990; Murphy, 2012).

History of Surgical Audit

The first recorded example of an outcome study performed by a surgeon occurred in the middle of the 18th century with a naval surgeon named James Lind (1716-1794). He wrote "A Treatise of the Scurvy" where he reported the discovery that sailors treated for scurvy with citrus fruits recovered and were made better (Murphy, 2012). Subsequently, Florence Nightingale led the way for measuring outcomes. In 1854 during the Crimean War she and her nurses arrived at Scutari where several thousand lay sick and wounded in foul conditions. She coordinated care for the patients but also coordinated an effort to turn the filthy conditions into a cleaner environment. She observed a reduction in mortality from 40% to 2% in the space of six months. She felt cleanliness and hygiene were a panacea to disease. She was a proponent of statistics and data collection and felt that this was "the most important science in the world" (Porter, 1999).

Ernest Codman (1869-1940) was a surgeon in Boston in the USA who kept accurate records of surgical outcomes (Starling, Naka, Boyle, *et al.*, 2011; Neuhauser, 2002). Both Nightingale

and Codman were the earliest proponents of recording and observing outcome data in surgical patients. In more recent times, Donabedian published his landmark paper which recommended assessing healthcare interventions by understanding the structures and processes that have yielded the outcomes (Emin, Rogers, Parameshwar, *et al.*, 2013; Donabedian, 1966).

Why do we need Audit?

"*If you do not know what you are doing and how well you are doing it, then you have no right to be doing it at all.*" Sir Bruce Keogh

In the UK, the impetus for collecting national audit data came as a result of the Bristol hearts inquiry in the early 1990s. The inquiry occurred after Dr Steve Bolsin, a cardiac anaesthetist collected and disclosed data which revealed Bristol's higher than expected mortality for paediatric cardiac surgery (Kirklin, Naftel, Kormos, *et al.*, 2012; Murphy, 2012; Kirklin, Naftel, Kormos, *et al.*, 2011; 2010). The subsequent inquiry was followed by publication of a document entitled "Learning from Bristol'' which underlined the significant findings from the inquiry (Slaughter, Pagani, Rogers, *et al.*, 2010; Health, 2002; Slaughter, Tsui, El-Banayosy, *et al.*, 2007; Kirklin, Naftel, Kormos, *et al.*, 2012). The inquiry demonstrated systematic problems leading to poor organisation; failures in communication, lack of leadership, paternalism and a 'club' culture, and a failure to put patients at the centre of care. These led to an excessive mortality in a number of children undergoing cardiac surgery between 1984 and 1995. The inquiry concluded that "*the framework for setting, delivering and monitoring standards should be made more explicit*"[1] (Rose, Gelijns, Moskowitz, *et al.*, 2001; Health,

[1] Learning from Bristol: The DH Response to the Report of the Public Inquiry into children's heart surgery at the Bristol Royal Infirmary 1984-1995; Executive Summary 2002

2001; 2002). Patient safety was felt to be central to improving the NHS. The report reiterated the importance of transparency in the NHS and thus provided the catalyst that created the national audit framework.

The mortality of paediatric cardiac surgery in Bristol fell from 30% in 1994 to approximately 4% within a 2 year period (Slaughter, Pagani, Rogers, *et al.*, 2010; Murphy, 2012). This improvement is thought to be due to several factors, which include a culture change, which saw consultant surgeons assist each other with cases and a better availability of support from related specialties including cardiology and radiology.

Following the Bristol Heart inquiry, Smith et al., published an editorial in the British Medical Journal, which summarised the changes following the catastrophic occurrences in the mid-1990's:

"The Bristol case has already accelerated the move to provide patients with data on the performance of doctors and hospitals and this has to be a good outcome. Cardiothoracic surgeons have already taken impressive steps, but they are way ahead of the pack. Doctors in other specialties, particularly non-surgical ones, are going to have to think hard and fast about how to gather and present data on their performance. Neither gathering nor interpreting the data is easy, and experts on improvement emphasise that such data are best used as a source of knowledge for improvement rather than for judgement." (Aaronson, Slaughter, Miller, *et al.*, 2012; Smith, 1998).

This statement summarises perfectly the problems that are still faced by all healthcare services following the Bristol Hearts scandal.

In the following years, the Society of Cardiothoracic Surgery (SCTS) led the way for collecting, analysing and publishing outcomes in cardiothoracic surgery. Detailed outcome data is published via the Congenital Heart Disease web portal, which was developed in collaboration with the Information Centre for the NHS (IC) and University College London (UCL) (Terracciano, Miller & Yacoub, 2010; Cleland, Dargie, Hardman, *et al.*, 2012). Interactions between the SCTS and the Care Quality Commission (CQC) and Government has made way for publication of mortality results for each surgical team performing adult cardiac surgery in the UK since 2005 (Grady, Jalowiec, White-Williams, *et al.*, 1995; Murphy, 2012; Grady, Jalowiec & White-Williams, 1998; Grady, 1993; Hsich, Naftel, Myers, *et al.*, 2012; Dew, Kormos, Winowich, *et al.*, 2001; Sharples, Dyer, Cafferty, *et al.*, 2006).

Audit is now mandatory for all medical practitioners as set out in the clinical governance guidelines provided by the General Medical Council (GMC) in their document "Good Medical Practice" (Spilker, 1990; Great Britain & Staff, 2013).

"You must take part in systems of quality assurance and quality improvement to promote patient safety" (Great Britain, 2006; Anon, 2001; Great Britain & Staff, 2013).

Measuring Outcomes

In 2010, the Department of Health published its white paper titled "Equity and Excellence; Liberating the NHS". The reforms consisted of 3 major points:

1. Putting patients first and "transforming the relationship between citizen and service through the principle of *no decision about me without me*"
2. Focus on improvement in outcomes; "orientating the NHS towards focussing on what matters most to patients – high quality care"

3. "Making NHS services more directly accountable to patients and communities." (Huber, Knottnerus & Green, 2011; Health, 2010)

Local and regional hospital audit involve comparing current practice against national guidelines and standards, and then after making an improvement in the audited service to complete the audit cycle with a repeat audit to assess the change in practice.

National audit involves comparison between centres where centres are measured against each other with an often agreed target or guideline, although in many circumstances there may not be a guideline for comparison. Often national audit processes need to establish national guidelines, which become the standard for comparison.

There are complex issues that need to be addressed when measuring outcomes and quality of service delivery. Difficulties include how to set criteria for quality; whether these criteria are empirical or normative and finally who should be involved in the decision making to set the criteria (McDowell, 2006; Murphy, 2012).

Apart from the general complexities in national audit, there are also specific problems that can arise when monitoring low volume highly specialised services such as heart transplantation, especially when there is a rapid change in technology and the pattern of care such as with the introduction of LVADs as bridges to transplantation. This evolution of technologies makes comparative audit more difficult and harder to interpret.

My Role as Royal College Fellow

I was appointed as a National Audit fellow in the Clinical Effectiveness Unit (CEU) at the Royal College of Surgeons of England (RCS), in September 2009, for a period of 3 years. The

mandate for my employment included managing the national heart and lung transplantation audit; and to undertake the implementation of a national VAD audit.

When I first arrived in post, I familiarised myself with the UK Cardiothoracic Transplant Audit (UKCTA); one of many national audits presided over by the RCS.

The CEU is a department that is responsible for all the research and audit activity at the RCS. The department, which is affiliated to the London School of Hygiene and Tropical Medicine (LSHTM), liaises with other organisations including the Information Centre (IC) and NHS Blood and Transplant (NHSBT), and are responsible for coordinating several national audit projects across a wide variety of surgical specialties.

As the National Audit fellow my remit was to coordinate the national cardiopulmonary transplantation audit and maintain and maintain the standards of the audit. I was also tasked with developing a national VAD audit to collect and analyse data and examine UK trends in the use of VADs.

National audit infrastructure and National Commissioning

The UK has some highly specialised areas of surgery that are centrally funded, centrally planned and centrally monitored. One of these is heart and lung transplantation and VAD implantation in both adults and children. The National Specialised Commissioning Team (NSCT) was responsible for planning monitoring and funding these services in NHS England (McDowell, 2006; Kenny, Jessop & Gutteridge, 2008; Sharples, Dyer, Cafferty, *et al.*, 2006; Kenny & Ashton-Key, 2012; Dyer, Goldsmith, Sharples, *et al.*, 2010).

Cardiothoracic transplantation has been nationally commissioned since 2002 in the UK. The service is currently provided by the following trusts:

- Great Ormond Street Hospital for Children NHS Trust
- Royal Brompton and Harefield NHS Trust
- Papworth Hospital NHS Foundation Trust
- University Hospital of South Manchester NHS Foundation
- University Hospitals Birmingham NHS Foundation Trust
- The Newcastle upon Tyne Hospitals NHS Foundation Trust (adults and children)
- The Golden Jubilee Hospital, Greater Glasgow and Clyde NHS Foundation Trust

NHS Blood and Transplant, a special health authority within the NHS, is

"*dedicated to saving and improving lives……by encouraging and supporting individuals to donate blood, stem cells and organs"* NHS Blood and Transplant 2015.

Systems for monitoring mortality are linked with data routinely collected by NHSBT (Pae, Anderson & Blackstone, 1998; Kenny & Ashton-Key, 2012).

The United Kingdom Cardiothoracic Transplant Audit (UKCTA) has accrued data on all patients in the UK receiving a first, heart or lung transplant since 01 July 1995.

Audit Data Collection

The audit data collection is mandatory for all centres. Each year, the national audit fellow coordinates the audit and assists in the analysis of the data collected by NHSBT from all UK cardiothoracic transplantation centres. The national audit report is produced and disseminated to the UKCTA Steering Group. During my tenure as the national audit fellow

the Steering Group has consisted of representatives from each of the national centres, the representatives from the RCS and representatives from NHSBT and National Commissioning Group (NCG) (Pae, Anderson & Blackstone, 1998; Emin, Rogers, Thomas, *et al.*, 2011). The lists of Steering and Project Group members can be found in Appendix 1.

The objective of the audit process was to provide a rigorous method by which the national cardiothoracic transplantation service could be monitored and evaluated. The audit is updated every year, with the results subsequently disseminated directly to each centre. As a result of the audit process there have been several national level reviews conducted at centres that have been shown to have a higher than expected rate of mortality. Audit at this level also requires expert statistical input and support to ensure that analyses are performed correctly and the outcomes and interpretation of the results are performed in a consensual fashion. Risk adjustment for case mix is an important aspect of national audit and is key to providing insight into centre practice.

VAD implantation as a bridge to transplantation has been commissioned since 2002. Sharples (Pae, Anderson & Blackstone, 1998; Sharples, Dyer, Cafferty, *et al.*, 2006) performed the first clinical and cost effectiveness study of VAD implantation as a bridge to transplant in the UK. The study suggested that patients with advanced chronic heart failure awaiting heart transplantation might benefit from receiving a VAD in terms of medium term survival and quality of life.

The NHS commissioners subsequently agreed to continue to provide funding for VAD implantation only for use as bridging therapy for patients eligible for heart transplantation.

The centres agreed at this time that auditing VAD practice in the UK would be an essential part of providing this new treatment option to patients.

Early implanted VADs were bridges to HTx; implanted devices were tracked by NHSBT, who recorded device and patient details including type of device; indication for support, centre trust and long-term or short-term. They also recorded some basic patient demographic details including age, sex and hospital number.

As VAD implantation increased and gradually became more widespread in its use for bridging unstable patients on the heart transplant waiting list, it became essential to collect more comprehensive LVAD data in order to provide a robust method of evaluating the service. A database was designed to capture the data relating to each implant and patient in a national VAD registry similar to the UKCTA transplant database.

The database was designed and created by NHSBT with guidance from the UK Cardiothoracic Transplant Project and Steering Groups. It was designed specifically to mirror the INTERMACS database, which accrues data for implants in the USA although the scope of data collection was reduced to ameliorate the burden of data collection in individual hospitals. The aim was to allow comparison of UK and International data and to allow the UK to participate in International studies. When I was appointed at the RCS, the database had not yet become available to the centres for data accrual.

One of my remits as national audit fellow was to firmly establish a routine for each of the 6 national adult cardiothoracic transplant centres to collect data for the national VAD registry.

National VAD Registry

The national VAD registry was launched in October 2009. The data collected for each implant is extensive. Each patient undergoing VAD implantation requires several audit forms to be completed. The forms are completed online via a secure NHSBT server to ensure data protection. The complexity and quantity of the data required demanded dedicated audit administrative staff to collate and enter the data. Each centre used a different method of doing this. The database was created to record data prospectively as the VADs are implanted, however, this would not be possible for VADs implanted prior to the VAD database launch. The National Commissioning Group (NCG) allowed funds to become available so that each centre could facilitate backfilling of the database with VADs implanted prior to October 2009.

Table 3-1: Summary of National VAD Registry Data Collection Forms

Form	Collection Parameters	Potential Variable Count
Implant	Demographics, Device Strategy, Pre-implant Clinical Condition, Medications immediately prior to implant, Pre-implant comorbidity, Pre-implant echo, Pre-implant haemodynamics, Pre-implant investigations, Operative information	164
7 day follow up	Patient status, Current medical condition, Lab tests at 7 days, Key adverse events, other adverse events	111
Follow up on Support	Patient status, Current medical condition, Rehospitalisation, Medications, Echo, Haemodynamics, Lab tests at 7 days, Key adverse events, other adverse events1 & 2	213
Mortality	Key adverse events	81
Explant or Transplant	Explant/transplant details, Key adverse events	80
Follow up after all VADs Explanted	Patient status, Rehospitalisation, Current clinical state	15
Patient Transfer Form	Location of transfer, Date of transfer	5
		Total Variable Count = 669

My responsibility was to facilitate both prospective and retrospective data collection. This involved travelling to each of the 6 adult cardiopulmonary transplantation centres in person and coordinating and trouble-shooting the data collection by ensuring the local administrative staff responsible for recording and entering the data understood the requirements for the national registry.

I developed close relationships with each centre and identified a point of contact at each centre. After the centres were visited and the data collection started, I contacted each centre monthly to ensure the data collection process was being adhered to. I was able to provide centres with monthly progress reports to show how many data collection forms were still outstanding. There are 7 forms in total for each implant. These include 7-day

follow-up forms and follow-up on support forms completed at 3-monthly intervals. There are a total of over 600 variables in the VAD dataset making this one of the most exhaustive and comprehensive national data registries in the UK and Europe. All adverse events including infection episodes are recorded.

Table 3-2: Example of monthly data monitoring reports produced by NHSBT and RCS and sent to the centres as a marker of progress. 1st October 2009 – 31st March 2011 (prospective data entry).

Number of forms reported on the monthly spread sheets and forms started in the VAD database

Form	Harefield No. reported (no. started)	Newcastle No. reported (no. started)	Papworth No. reported (no. started)	Manchester No. reported (no. started)	Birmingham No. reported (no. started)	Glasgow No. reported (no. started)	Total No. reported (no. started)
Implant	46 (46)	45 (41)	26 (26)	8 (5)	4 (2)	12 (1)	141 (121)
7 day FOS	41 (39)	45 (36)	25 (25)	7 (2)	3 (1)	10 (0)	131 (103)
Follow-up on support	158 (146)	195 (127)	58 (48)	32 (2)	4 (2)	17 (0)	464 (325)
Death	12 (12)	11 (10)	11 (11)	0 (0)	0 (0)	6 (0)	40 (33)
Explant	8 (8)	1 (1)	3 (2)	0 (0)	1 (1)	2 (0)	15 (12)
Transplant	3 (3)	3 (1)	3 (2)	1 (0)	2 (0)	1 (0)	13 (6)
F-up after explant	8 (7)	3 (1)	4 (4)	0 (0)	0 (0)	3 (0)	18 (12)
Total forms	**276 (261)**	**303 (217)**	**130 (118)**	**48 (9)**	**14 (6)**	**51 (1)**	**822 (612)**
%	95	72	91	19	43	2	74

No. of forms started as at 22 November 2011

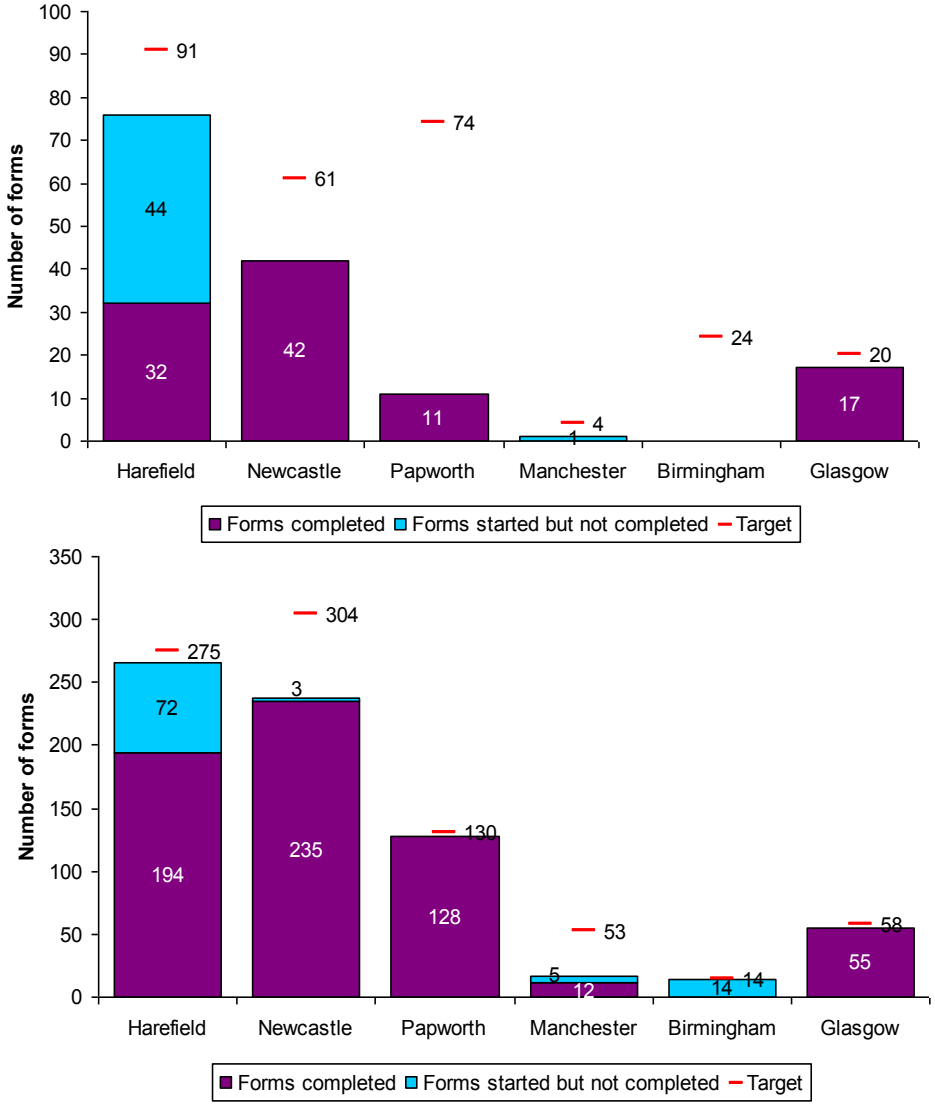
Table 3-3: Example of monthly data monitoring reports produced by NHSBT and RCS and sent to the centres as a marker of progress. Retrospective VAD implants - Harefield, Newcastle and Papworth - BRIDGING implants, 1 January 2005 - 30 September 2009 (LT) and 9 May 2002 - 30 September 2009 (ST).

Number of forms reported on the monthly spreadsheets and forms started in the VAD database

Form	Birmingham No. reported (no. started)	Glasgow No. reported (no. started)	Manchester No. reported (no. started)	Total No. reported (no. started)
Implant	7 (4)	1 (0)	9 (3)	17 (7)
7 day FOS	7 (3)	1 (0)	8 (3)	16 (6)
Follow-up on support	0 (0)	0 (0)	2 (1)	2 (1)
Death	2 (1)	1 (0)	3 (1)	6 (2)
Explant	1 (1)	0 (0)	1 (0)	2 (1)
Transplant	4 (1)	0 (0)	4 (2)	8 (3)
F-up after explant	5 (5)	0 (0)	5 (0)	10 (5)
Total forms	**26 (15)**	**3 (0)**	**32 (10)**	**61 (25)**
%	58	0	31	41

No. of forms started as at 22 November 2011

Figure 3-1: Examples of NHSBT/RCS Graphical Representation Used to Assist Centres in Completion of Outstanding Data Forms - All VADs implanted in the UK, 1 April 2011 to 31 October 2011



Validation of Data Entered into the Database

My duties included a responsibility to ensure that the data collected was accurate. This was required in order to maintain a validated dataset, which was accurate and complete minimising the potential bias from missing data. Validation of the data involved auditing the data entered for a random sample of patients at each centre. I examined each set of case notes and ensured the data entered in the database was accurate. A document was then submitted to the UKCTA Project and Steering Groups notifying of any errors identified.

The accuracy of data entered in the database when validated was greater than 95%, with almost no errors being identified. Errors were highlighted and were thought to be secondary to the inherent difficulties in completing the online data forms and confusion generated by ambiguity in certain questions.

Each centre assigned a team to be responsible for data provision for the UK VAD audit. Monthly meetings were held with NHSBT and each month a document monitoring data completion was submitted to each centre with a list of outstanding documents that were still to be completed. These documents were generated using NHSBTs record of all VAD activity in the UK to date, which was 100% accurate as it was related to funding for each device.

After a period of focussed data collection, validation and monitoring, a comprehensive national VAD database was populated with data and made available for analysis.

A New Audit Project

Quite separate from my duties of maintaining and coordinating the data collection for the National VAD Registry, I was also charged with instituting another national audit project. Quality of life (QoL) measurement is now a routine outcome in patients with advanced chronic heart failure. The

measurement of QoL itself allows patients to be involved in directing and improving their own care (Sharples, Buxton, Caine, *et al.*, 2006; Spilker, 1990). Although QoL in patients receiving VAD implants in the UK was measured during the clinical and cost effectiveness study conducted by Sharples et al in 2006, it had not subsequently been measured routinely apart from short studies conducted by the centres themselves. Quality of life is an important outcome to measure particularly because in nearly all instances, VAD implantation does not cure heart failure and therefore, the meaningful outcomes of interest must include survival, morbidity and quality of life. The long-term prognosis and outcome of advanced chronic heart failure is very poor. The main priorities in managing patients with advanced chronic heart failure are; to control and reduce symptoms of heart failure and to keep patients alive. However, as the heart failure worsens the priorities must focus on maintaining a good quality of life.

With the new national VAD Registry accruing data for the first time, and in order to truly evaluate VAD as a potential treatment for advanced chronic heart failure, the UKCTA Steering Committee suggested that quality of life outcomes in patients with VAD should be measured on a National Scale.

Designing a National Audit

The objective of this national audit project was to assess the effect of VAD implantation on quality of life. It was essential to identify the best way to achieve this objective, taking into consideration the inherent difficulties in attempting to establish a national project. National audit studies are multicentre cohort studies. The success of this audit would depend on the willingness of each centre to be involved and to participate in the study and their willingness to follow a centrally determined study protocol in order to standardise data accrual. The study protocol and QoL instrument designs were presented at the VAD Forum with representatives at each centre.

UKCTA Study Day

In order to maximise both the compliance of the centres and feedback mechanism between the centres and the RCS, a study day was arranged and all centre coordinators were invited to attend. This served 2 purposes; firstly as a method of bringing together all coordinators involved in data collection and data entry so that any problems with the aforementioned could be dealt with in a personal and efficient way. Trouble shooting and encouragement were the main reasons for arranging the study day and it also served as a method to highlight the importance of collecting the data and to provide education to all the important individuals at the centres who were responsible for much of the ground work for the audit. Secondly, it was a forum in which I could introduce the QoL study and the importance of the study to the centre coordinators.

People management and liaison between the RCS and the national centres was a large part of my remit as the national cardiopulmonary transplant fellow.

Figure 3-2: UKCTA Study Day Flyer Produced and Distributed to the Centres

UK Cardiothoracic Transplant Audit Study Day

ON BEHALF OF THE UKCTA STEERING GROUP

October 20th 2010

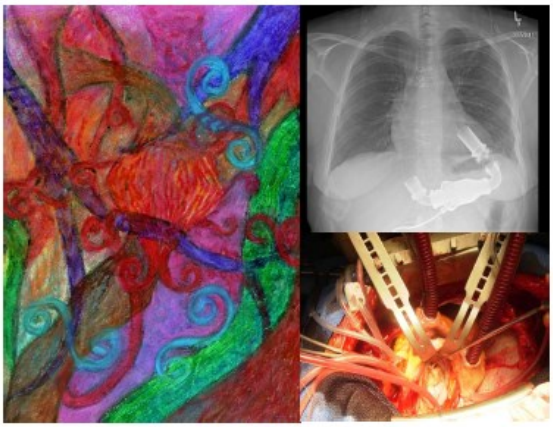
9:30—16:00

@

NHSBT, Bristol

This event is free

(£5 will be charged for an optional lunch—please specify when booking a place. Cheques payable to The Royal College of Surgeons of England)



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Stoke Gifford
BRISTOL
BS34 8RR

To book places for this event (with or without lunch), or for any enquiries please contact:
Mr. Akan Emin MRCS, RCS Fellow:
Phone: 0207 869 6629
Fax: 0207 869 6644
E-mail: aemin@rcseng.ac.uk

RCS
ADVANCING SURGICAL STANDARDS

Quality of Life Instruments

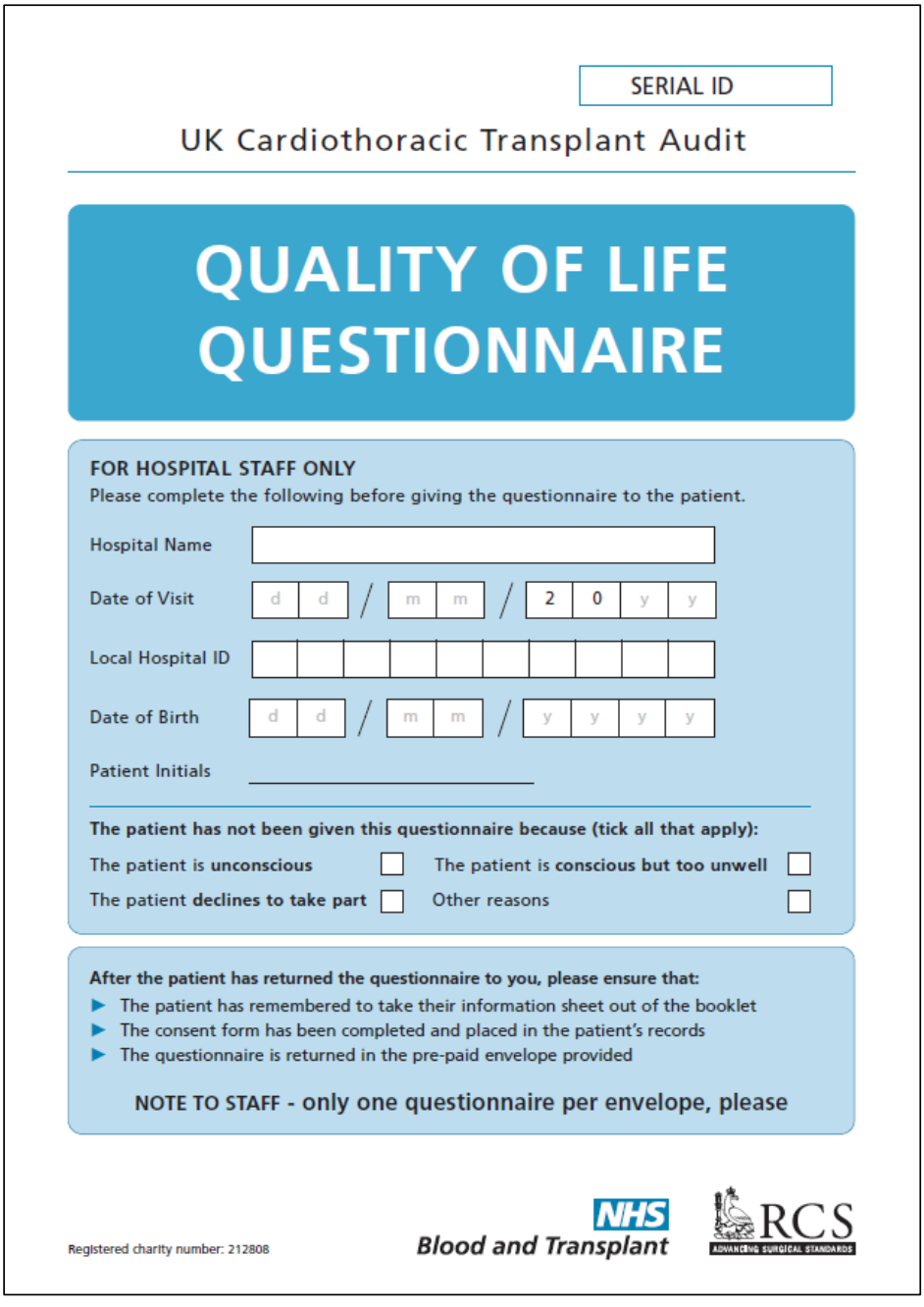
The UKCTA QoL questionnaire included 2 health-related QoL measures: The Kansas City Cardiomyopathy Questionnaire (disease specific) and the EQ-5D (generic). The rational for deciding which quality of life instruments to use is detailed in Chapter 5.

Questionnaire design

The questionnaire was a challenge to design. The study participants for the audit were potentially very unwell patients who would struggle to complete a simple questionnaire. It was necessary for the questionnaire to combine together the instruments chosen for the QoL audit and put them both into a similar format that was easy to read, short and easy to complete. Patient reported outcome measures have traditionally used specific typeface and certain fonts for questionnaires that were thought to improve study compliance. I examined previously designed questionnaires for the RCS National Orthopaedic and National Oesophagogastric Cancer audits and decided to use a similar format for my patient population.

Patient identifiers were decided to include; patient initials, local hospital number, NHS Trust, date of birth.

Figure 3-3: Front page of Questionnaire



SERIAL ID

UK Cardiothoracic Transplant Audit

QUALITY OF LIFE QUESTIONNAIRE

FOR HOSPITAL STAFF ONLY

Please complete the following before giving the questionnaire to the patient.

Hospital Name

Date of Visit d d / m m / 2 0 y y

Local Hospital ID

Date of Birth d d / m m / y y y y

Patient Initials _____

The patient has not been given this questionnaire because (tick all that apply):

The patient is **unconscious** ☐ The patient is **conscious but too unwell** ☐

The patient **declines to take part** ☐ Other reasons ☐

After the patient has returned the questionnaire to you, please ensure that:

- The patient has remembered to take their information sheet out of the booklet
- The consent form has been completed and placed in the patient's records
- The questionnaire is returned in the pre-paid envelope provided

NOTE TO STAFF - only one questionnaire per envelope, please

Registered charity number: 212808

NHS Blood and Transplant

RCS ADVANCING SURGICAL STANDARDS

I gained some insight into the potential usefulness and usability of the questionnaire seeking advice from a small cohort of test patients. This occurred at one of the national centres where I was allowed the opportunity to meet patients with VAD implants in situ.

Designs of the questionnaire were circulated to the VAD coordinators and specialist nurses that would be responsible for administering the questionnaires prior to production. This was an essential part of the process enabling me to act upon opinions and insight gained from people who would be administering and completing the questionnaires.

Finally the designs were circulated to UKCTA Steering and Project groups for opinion prior to manufacture.

Study Design

Quality of life instruments would be sent to centres for administration to patients within 2 main study arms:

[1]: Prospective and longitudinal measurement of QoL in patients as they enter the HTx and VAD pathway

[2]: Cross-sectional measurement of QoL in patients who have received a VAD or HTx or who are on the transplant waiting list.

The study population comprised the following 4 patient groups:

1. Patients being assessed for HTx/VAD
2. Patients listed on medical therapy
3. Patients with a VAD implant
4. Patients who have received a heart transplant between January 2009 and December 2010.

The recruitment period for the study started on January 17th 2011 and ended August 31st 2012.

Involvement of National Transplant Centres

Discussions with all national transplant centres occurred at the local level. Each centre was contacted and visits were arranged to correspond with local HTx and VAD multi disciplinary team meetings. These involved all key transplant staff members at each centre. Presentations to the centres introduced the possibility of QoL data collection. Feedback from each centre was considered and was used to facilitate the improvement of research methodologies and questionnaire design. A VAD and quality of life study day was arranged at the RCS with coordinators from all the centres invited. This was to provide a forum for feedback with regards to both the National VAD registry data and the QoL study.

Table 3-3: Populations to be studied

Group	Patient Description	Study Type
1	All patients assessed for HTx/VAD	Longitudinal
2	All patients listed for HTx on medical therapy	Cross sectional and then longitudinal follow up
3	All patients with an LVAD	Cross Sectional and longitudinal
4	Post HTx	Cross sectional

Estimated Sample Size and Statistical Analysis

Due to small numbers of HTx and VAD implantation each year, the numbers of patients contributing QoL data on more than one occasion (i.e. followed longitudinally) was anticipated to be limited. Based on data submitted to the UKCTA since the audit began, we estimated that approximately 150 patients are listed for HTx in the UK every year. The number of VAD implantations and HTx vary from year to year. In the year 2009, there were 93 adult HTx (68 in patients listed during 2009) and 64 VAD implantations (29 inpatients of whom were listed during 2009). VAD implantation increased in

2010 to 85. Based on these estimates the projected numbers of patients for each group is shown in the table below:

Table 3-4: Expected numbers of patients by population

	Group1 Assessment	**Group2** On List	**Group3** VAD[2]	**Group4** Post HTx	**Total**
Total Numbers of Pts	150	126	60	151	487

Group 1 includes all patients assessed for HTx at a transplant centre. We estimated of 150 patients based on the number of patients listed for HTx per year; however this population would also include those patients who were discharged after HTx assessment; therefore this may have been an underestimate.

The estimated total number of patients expected for recruitment was 487. The anticipated number of completed questionnaires is approximately 500 questionnaires.

Some preliminary analysis was to be undertaken aiming to describe the QoL in these patient populations, and to quantify the uncertainty around these estimates, rather than to test statistical hypotheses.

Receiving the Questionnaires at the RCS

Once questionnaires were completed by the audit participants they would be sent back to the RCS for analysis. These would usually arrive in batches from each of the centres. A database was designed to capture the data from the questionnaires. The data from each questionnaire was

[2] This group is comprised of VAD patients not already listed for HTx

entered onto the database, which was designed to minimise errors in data entry by performing computational checks on the data as entered. Furthermore, a validation process took place using an independent researcher who selected a random sample of 20 questionnaires to test the validity of the database. This was done after most of the data was used to populate the dataset. This exercise showed that there was no data entry errors found in the dataset suggesting high validity.

Linkage

Purpose of Linkage

The linkage process is dependent on patient identifiers. The QoL dataset, UKCTA dataset and VAD dataset hold common patient identifiers enabling linkage if the datasets and combination of all data leading to an extremely comprehensive dataset.

Linkage would allow us to access important clinical information about patients who had participated in the QoL study such as when they received their VAD or HTx, and when they were listed for transplant. It also allowed us to confirm the patient group.

Aims and objectives

The aim of my work was to improve the national audit infrastructure for VAD implantation in the UK and to evaluate VAD therapy is the context of advanced chronic heart failure and heart transplantation. This evaluation also included establishing a method of measuring quality of life outcomes in this population and reporting preliminary cross sectional and longitudinal results.

Chapter 4: Trends in VAD activity in the United Kingdom[3]

Introduction

The technology available for circulatory support has developed rapidly during the last decade, with a progression from first to second and, now, third generation devices (See Chapter 2). For patients in end-stage heart failure, survival on support has been found to exceed that on medical therapy (Ware, Snow, Kosinski, *et al.*, 1993; Rose, Gelijns, Moskowitz, *et al.*, 2001; Ware & Gandek, 1994; Slaughter, Pagani, Rogers, *et al.*, 2010); but, as yet, such therapy has not been deemed cost-effective by the criteria established by the United Kingdom National Health Service (NHS) and the longer-term outcome of such treatment remains to be established. While the use of left ventricular assist devices (LVADs) has been restricted to bridging patients to transplantation in the UK (Dyer, Goldsmith, Sharples, *et al.*, 2010; Sharples, Cafferty, Demitis, *et al.*, 2007), limited heart transplant activity has resulted in patients receiving longer periods of mechanical support. More recently however, the National Institute for Health and Care Excellence (NICE) has provided guidance on implantation of VAD in patients for destination therapy[4].

In the United States trends in LVAD activity and outcome have been documented in the INTERMACS Registry (Kirklin, Naftel, Kormos, *et al.*, 2012; 2013) but this only includes devices implanted after final approval by the US Food and Drug Administration (FDA) and so excludes newer devices(Sharples, Buxton, Caine, *et al.*, 2006; Starling, Naka, Boyle, *et al.*, 2011). LVAD Registries have been established in Europe but are voluntary and so are not comprehensive.

[3] See Appendix 7 for published manuscript and abstracts
[4] National Institute for Health and Care Excellence (2015) Implantation of a left ventricular assist device for destination therapy for people ineligible for heart transplantation

In the UK, nearly all LVAD implants have been performed in NHS hospitals as part of the bridge-to-transplant programme.

Having coordinated national data collection at all heart transplantation centres, I performed an analysis of trends in UK activity and outcomes after implantation of long term (LT) LVADs with the oversight of a project group with representatives from each of the UK VAD centres (UKCTA Project and Steering Groups).

The VAD Dataset

As previously described in Chapter 3, data were accrued in the dataset both prospectively and retrospectively, capturing all new LVAD implants from April 2002 onwards, as well as all historical LVAD implants, including those recruited for the EVAD study analysis (implants between April 2002 and December 2004).

The dataset was closed for analysis in 31st March 2012. At the time of closure, all but 4 implant forms were complete (See Chapter 3: Table 3-1 - Summary of National VAD Registry Data Collection Forms).

The progress reports circulated monthly to each centre specified precisely which data forms were outstanding for each implant. At closure of the dataset, outstanding forms mainly consisted of follow up forms for a small number of devices (see Table 4-1).

Data Collection

Data from patients receiving mechanical circulatory support is collected at implant, 7 days post implant, 1 months post implant, 3 months post implant and every 3 months thereafter until explant, transplant or death. HTx audit data collected at listing, at transplant, at 3 months and annually

thereafter until the patient's death are processed by NHSBT and submitted monthly to the audit. A linkage protocol allows data from the VAD and HTx registries to be combined.

VAD DATA PROVISION PROGRESS REPORT
Prospective VAD implants - since database launched
LT devices (includes patients who received a LT device and then a ST PGF device)
1 October 2009 - 31 March 2011

Number of forms reported on the monthly spreadsheets and forms started in the VAD database

Form	Harefield No. reported (no. started)	Newcastle No. reported (no. started)	Papworth No. reported (no. started)	Manchester No. reported (no. started)	Birmingham No. reported (no. started)	Glasgow No. reported (no. started)	Total No. reported (no. started)
Implant	**47 (46)**	**49 (47)**	**18 (18)**	**7 (6)**	**2 (2)**	**4 (4)**	**127 (123)**
7 day FOS	40 (39)	45 (41)	17 (17)	6 (6)	1 (1)	3 (3)	112 (107)
Follow-up on support	188 (183)	241 (194)	75 (52)	36 (31)	6 (5)	15 (15)	561 (480)
Death	12 (12)	15 (13)	7 (7)	1 (1)	0 (0)	0 (0)	35 (33)
Explant	9 (9)	6 (6)	0 (0)	1 (1)	1 (1)	2 (2)	19 (19)
Transplant	3 (3)	4 (2)	2 (2)	1 (1)	0 (0)	1 (1)	11 (9)
F-up after explant	4 (4)	5 (1)	0 (0)	2 (0)	0 (0)	3 (1)	14 (6)
Total forms	**303 (296)**	**365 (304)**	**119 (96)**	**54 (46)**	**10 (9)**	**28 (26)**	**879 (777)**
%	98	83	81	85	90	93	88

No. of forms started as at 19 July 2012

Table 4-1: Late stage progress report showing almost complete data collection (produced by NHSBT and RCS).

Analysis

The completeness of this database enabled detailed analysis of long term LVAD implantation in the UK.

As previously stated, the dataset contained more than 600 variables for devices with multiple records per device. Analysing the dataset required organisation of the data with indicators to identify each record; each patient may have multiple VAD implants, multiple records per device and different indications for VAD support.

Data were obtained from NHSBT in the form of several data files; each file related to a different form completed for each VAD implant at different time intervals. A master data file was created for the main analysis by combining the files together so that all the data were accessible for each implant.

For the different analyses, the structure of the data within the master data file required extensive data cleaning and restructuring before any statistical or descriptive analysis could take place. This involved using a coding file for STATA 11.2. The complexity of the dataset can be seen in table 4-2.

Table 4-2: Excerpt from dataset. The columns show an extracted table from the dataset. The 4 records in red are patients without a transplant ID and therefore they had not had a transplant in situ when they received VAD support.

VAD ID	Transplant ID	Episode start	Episode end	Implant Date	Indication for Implant	Device type
1034		16-Mar-10	23-Mar-10	16-Mar-10	Bridge to transplant	LVAD
1058		12-Oct-07	14-Oct-07	12-Oct-07	Bridge to decision	BiVAD
1062	135997	08-Dec-07	20-Dec-07	08-Dec-07	Bridge to decision	BiVAD
1100	140513	12-Aug-08	21-Aug-08	12-Aug-08	Rescue of transplant (primary graft failure)	BiVAD
1101	134751	15-Jan-08	24-Feb-08	15-Jan-08	Rescue of transplant (primary graft failure)	BiVAD
1102	131386	06-Dec-07	31-Dec-07	06-Dec-07	Bridge to transplant	BiVAD
1103	127598	08-Sep-07	23-Oct-07	08-Sep-07	Rescue of transplant (primary graft failure)	BiVAD
1107	115100	29-May-05	01-Jun-05	29-May-05	Rescue of transplant (primary graft failure)	RVAD
1108	124248	16-Apr-07	21-Apr-07	16-Apr-07	Rescue of transplant (primary graft failure)	BiVAD
1109	143869	04-Feb-09	28-Feb-09	04-Feb-09	Rescue of transplant (primary graft failure)	BiVAD
1114		23-Dec-07	02-Jan-08	23-Dec-07	Bridge to transplant	BiVAD
1115	126309	23-Jul-06	24-Jul-06	23-Jul-06	Rescue of transplant (primary graft failure)	BiVAD
1129	132511	21-Jun-07	04-Jul-07	21-Jun-07	Bridge to transplant	BiVAD
1130	132293	01-Aug-07	02-Aug-07	01-Aug-07	Rescue of transplant (primary graft failure)	BiVAD
1131	134093	21-Oct-07	29-Oct-07	21-Oct-07	Rescue of transplant (primary graft failure)	LVAD
1137	128572	25-Oct-06	30-Oct-06	25-Oct-06	Rescue of transplant (primary graft failure)	RVAD
1162	145748	27-May-09	05-Aug-09	27-May-09	Bridge to transplant	BiVAD
1167	148083	24-Sep-09	12-Oct-09	24-Sep-09	Rescue of transplant (primary graft failure)	BiVAD
1168		14-Mar-08	02-Apr-08	14-Mar-08	Bridge to transplant	BiVAD

Methods

Study Population

All adults (age>16 years) who received a LT implantable VAD between May 2004 and April 2011 were included in the analysis. Exclusions were patients who received isolated short-term support, with a device such as the Levitronix CentriMag, or who received ECMO without prior or subsequent long term VAD support. The database was closed for analysis on 31st March 2012.

Patients were grouped into three eras according to the date of the first implant: Era1: February 2004 – March 2006, Era2: April 2006 – March 2009 and Era3: April 2009 – March 2011.

Statistical Methods

Continuous variables are summarized using a mean and standard deviation or median and interquartile range if the distribution was skewed, and categorical variables were reported as a number and percentage. Groups are compared using the t test, Wilcoxon rank sum, chi-square or Fisher's exact tests as appropriate.

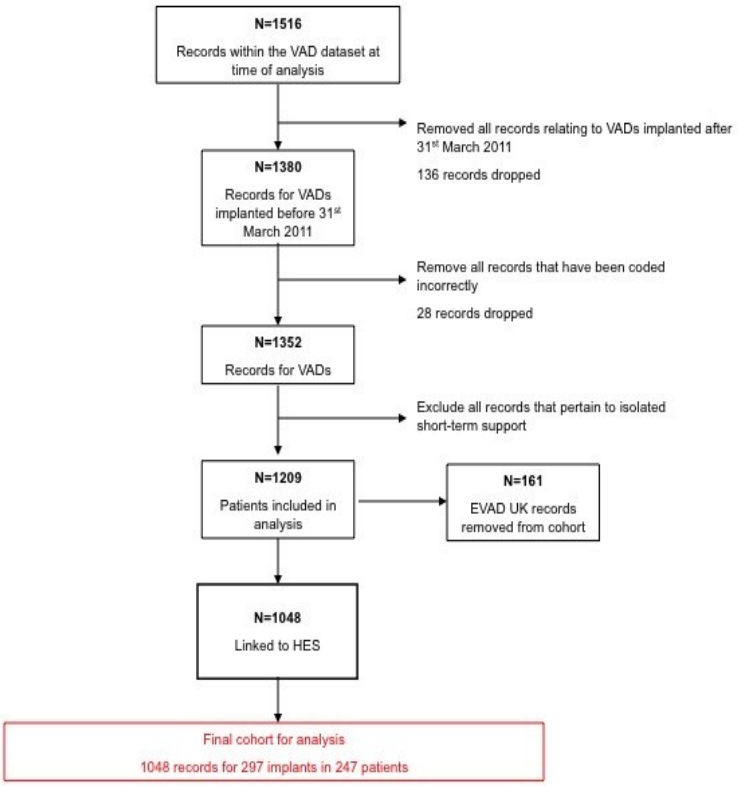
Patient survival and duration of VAD support is estimated by the Kaplan-Meier method and compared using the log rank test. The duration of support was defined as the time from first implant to explant, transplant or death. Any device replacement was included in the overall duration of support. Patient survival for patients alive at the time of analysis was censored at last known follow-up. The cumulative incidence of different causes of recipient death was estimated in the presence of competing risks.

Patient survival, adjusted for generation of VAD device, age, gender, explant without a transplant and HTx after VAD support was compared using Cox proportional hazards regression, with explant

and transplant modelled as time dependent covariates. To capture the changing risk of death post HTx, the hazard was estimated separately for days 0 to 7, 8 to 30, 31 to 90 and days 90+ after HTx.

Analyses are carried out using Stata version 11.2

Figure 4-1: Flowchart describing exclusions before analysing data for LT LVAD implants



Results

LVAD Support

A total of 247 patients received VAD implants for left ventricular failure during the study period, 36 in Era 1, 88 in Era 2 and 123 in Era 3. Fourteen patients had received prior ST support and five patients received replacement LVADs, three due to device malfunction. Overall, 202 patients received LVAD support alone and 45 received BiVAD support. Fifteen patients were implanted with the intention to bridge to a decision and 232 patients were implanted with the intention of bridging to transplant. Patient characteristics by era are described in Table 4-3. The majority of patients (157, 63.6%), had a diagnosis of non-ischaemic dilated cardiomyopathy and were in INTERMACS category 2/2A (114, 46.2%). The proportion of patients in INTERMACS category 1/1A has decreased over time, while the proportion in category 3/3A has increased.

The VAD devices used are summarised in Table 4-4; 46 patients received a 1st generation device, 80 a 2nd generation device and 121 a 3rd generation device. Device use has changed over time, the number of 1st generation devices used has decreased and 3rd generation devices have become more common (Figure 4-2). In Era 1 the median duration of VAD support was 141 days (interquartile range 80 to 253 days), compared with 269 days (interquartile range 74 to 596 days) in Era 2 and 578 days (lower quartile 204 days) in Era 3 (Figure 4-3, $p<0.001$).

Patient Survival

Patient survival to 2-years after implant is shown in Figure 4-4. Survival, unadjusted for patient risk, transplantation or explant, has not changed significantly by era ($p=0.36$), but has improved with device generation ($p=0.003$). At 1-year, 50.0% of patients receiving a 1st generation device were alive (95% CI 34.9 to 63.3%) compared to 68.1% of patients receiving a 2nd generation device (95%CI

56.5 to 77.2%) and 76.9% of patients receiving a 3rd generation device (95%CI 68.0 to 83.6%). The corresponding survival estimates at 2-years were 43.4% (95%CI 28.9 to 57.0%), 54.5% (95%CI 42.3 to 65.2%) and 60.4% (95%CI 46.4 to 71.8%) for the 1st, 2nd and 3rd generation devices respectively.

Outcome of Support

The outcome of support, explant, transplant or death, is shown in Figure 4-5. The numbers of patients receiving a transplant after their VAD implant has reduced significantly over time, with many fewer transplants in Era 3 ($p<0.001$). The cumulative incidence of explant and of death whilst on VAD support had not changed significantly with time ($p=0.26$ and $p=0.40$ respectively).

Fifteen patients with RVAD support were explanted; fifteen were transplanted and fifteen died.

Patient Survival adjusted for risk

Patient survival by era, adjusted for generation of VAD device, age, gender, explant without a transplant and HTx after VAD support is summarised in Table 4-5. Again survival differences by era were not found ($p=0.58$), and differences by device generation remained ($p=0.0026$). As anticipated, the risk of death increased with age and was greatest in the early post-HTx period. After 90 days post-HTx the risk of death was lower than for patients on LVAD support without a transplant.

Causes of death

At the time of analysis 103 of the 247 study patients had died. Causes of death by generation of device are shown in Table 4-6, and the cumulative incidence of death due to bleeding, infection, central nervous system (CNS) causes and others are shown in Figure 4-6. Deaths due to infection were most common with 1st generation devices and there are fewer early deaths due to bleeding with the 3rd generation devices.

Table 4-3: Patient Demographics

Variable	Overall N (%)	Era1 N (%)	Era2 N (%)	Era3 N (%)	p value
Patients within the study period	247	36	88	123	
Demographics					
Age in years (mean (SD))	44.8 (13.3)	43.9 (13.8)	42.1 (13.9)	46.9 (12.4)	0.030
Male gender	197 (80.0)	29(80.6)	69(78.4)	99(80.5)	
Co-morbidities					
Diabetic	33 (13.8)	3 (9.1)	10 (11.5)	20 (16.8)	0.39
Smoking status					
Smoker <= 5 per day	123 (60.0)	19 (67.9)	47 (63.5)	57 (55.3)	0.58
Ex-smoker > 6 months	61 (29.8)	6 (21.4)	19 (25.7)	36 (35.0)	
Still Smoking (> 5/day in last 6 mths)	21 (10.2)	3 (10.7)	8 (10.8)	10 (9.7)	
COPD	2 (0.85)	0 (0)	0 (0)	2 (1.7)	0.36
Previous vascular disease	3 (1.3)	1 (3.2)	2 (2.4)	0 (0)	0.20
Neurovascular Disease					
Previous ischemic stroke	10 (5.2)	1 (3.9)	3 (4.4)	6 (6.3)	0.21
Previous transient ischaemic attack	11 (5.8)	4 (15.4)	2 (2.9)	5 (5.2)	
None	170 (89.0)	21 (80.8)	64 (92.8)	85 (88.5)	
Hypertension	21 (9.8)	3 (9.7)	4 (5.0)	14 (13.5)	0.16
Ascites	24 (11.1)	1 (3.7)	9 (11.5)	14 (12.6)	0.41
HLA sensitized	26 (17.0)	2 (10.0)	9 (15.5)	15 (20.0)	0.53
Previous myocardial infarction	64 (28.1)	11 (33.3)	15 (19.0)	38 (32.8)	0.08
Number of previous sternotomy[5]					
0	159 (82.4)	23 (82.1)	46 (79.3)	90 (84.1)	0.38
1	29 (15.0)	3 (10.7)	10 (17.2)	16 (15.0)	
2	5 (2.6)	2 (7.1)	2 (3.5)	1 (0.9)	
Number of previous thoracotomy					
0	174 (98.3)	26 (100)	55 (98.2)	93 (97.8)	0.85
1	2 (1.1)	0 (0)	1 (1.8)	1 (1.1)	
2	1(0.6)	0 (0)	0 (0)	1 (1.1)	
Previous IABP	83 (35.9)	19 (59.4)	29 (35.4)	35 (29.9)	0.021
Previous ECMO	6 (2.6)	0 (0)	3 (3.6)	3 (2.6)	0.55
Diagnosis at Implant					
Ischaemic heart disease	66 (26.7)	11 (30.6)	10 (11.4)	45 (36.6)	0.001
Non ischaemic dilated cardiomyopathy	157 (63.6)	23 (63.9)	67 (76.1)	67 (54.5)	
Restrictive cardiomyopathy	8 (3.2)	1 (2.8)	5 (5.7)	2 (1.6)	

[5] Sternotomy and thoracotomy data missing in 21% & 28% of records respectively

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Hypertrophic cardiomyopathy	7 (2.8)	0 (0)	2 (2.3)	5 (4.1)	
Congenital heart disease	3 (1.2)	0 (0)	0 (0)	3 (2.4)	
Valvular heart disease	1 (0.4)	0 (0)	1 (1.1)	0 (0)	
Other	5 (1.6)	1 (2.8)	3 (3.4)	1 (0.8)	
INTERMACS Profile at First Implant					
Prior SHORT TERM Support	14 (5.7)	3 (8.3)	8 (9.1)	3 (2.4)	0.016
INTERMACS 1/1A	37 (15.0)	8 (22.2)	11 (12.5)	18 (14.6)	
INTERMACS 2/2A	114 (46.2)	16 (44.4)	47 (53.4)	51 (41.5)	
INTERMACS 3/3A	47 (19.0)	2 (5.6)	11 (12.5)	34 (27.6)	
INTERMACS 4/4A/5/6/7	35 (14.2)	7 (19.4)	11 (12.5)	17 (13.8)	

Figure 4-2: Stacked Bar-chart showing changes in VAD Generation by Year

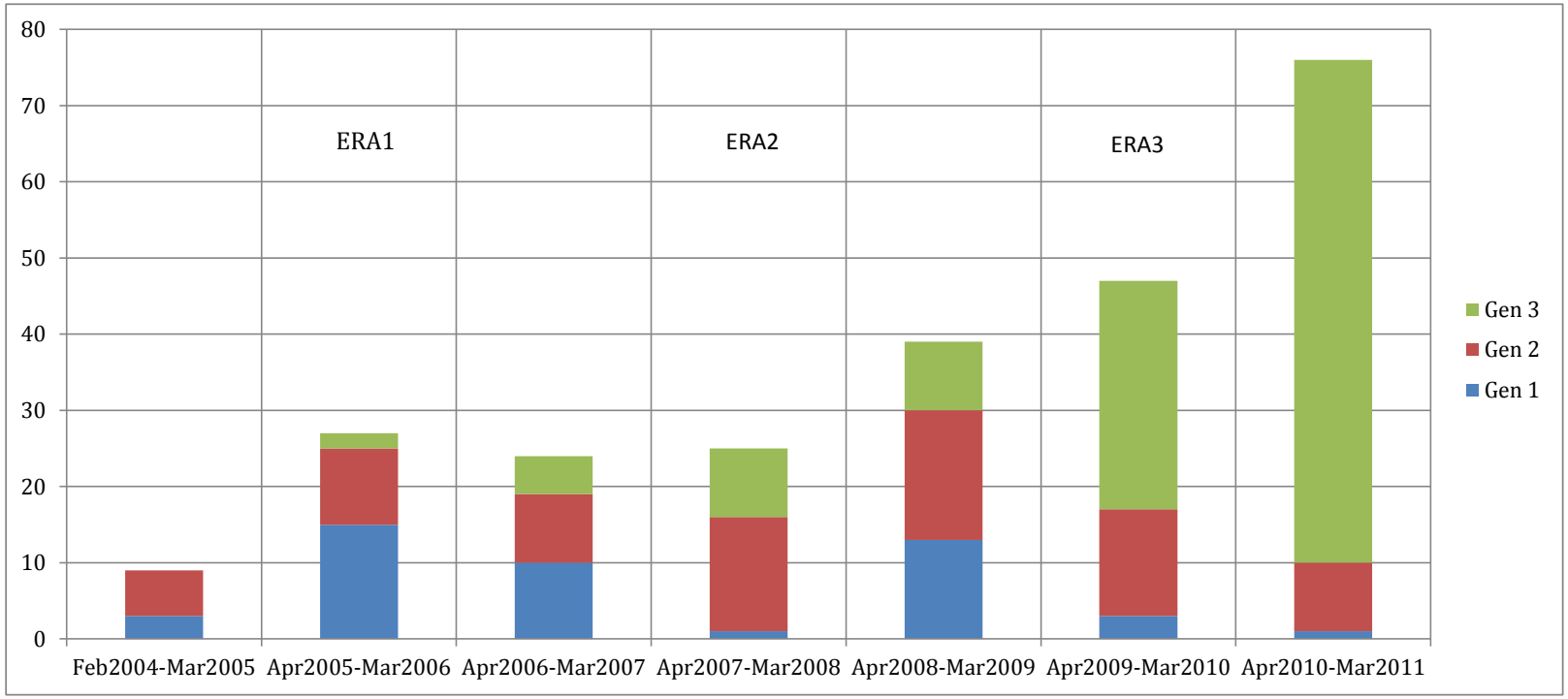

Table 4-4: VAD Type at first LVAD implant

			N	%
Manufacturer*	**Device**	**Generation**		
Berlin Heart	EXCOR	1st	17	6.9
Thoratec	PVAD	1st	13	5.3
Thoratec	IVAD	1st	9	3.6
Thoratec	HeartMate XVE	1st	7	2.8
Thoratec	HeartMate II	2nd	64	25.9
Jarvik Heart	Jarvik 2000	2nd	13	5.3
Micromed	DeBakey	2nd	3	1.2
HeartWare	HVAD	3rd	94	38.1
Ventracor	VentrAssist	3rd	27	10.9

Table 4-5: Multivariate cox proportional hazards model for time to death

Variable	**Hazard Ratio**	**95% CI**	**P-value**
Era			0.58
1	1.00		
2	1.32	0.74 to 2.36	
3	1.48	0.70 to 2.88	
Generation of VAD			0.0026
1	1.00		
2	0.70	0.40 to 1.24	
3	0.34	0.18 to 0.65	
Age (per 10 years)	1.27	1.07 to 1.49	0.004
Female gender	1.24	0.75 to 2.05	0.40
Explant without transplant	0.25	0.06 to 1.08	0.063
Transplant			<0.0001
0-7 days post HTx	11.1	4.41 to 27.7	
8-30 days post HTx	7.68	3.38 to 17.5	
31-90 days post HTx	1.43	0.43 to 4.74	
90+ days post HTx	0.12	0.04 to 0.39	

* Thoratec HeartMate XVE has been discontinued

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Figure 4-3: Median Duration of Support for Patients with Long Term LVAD by Era

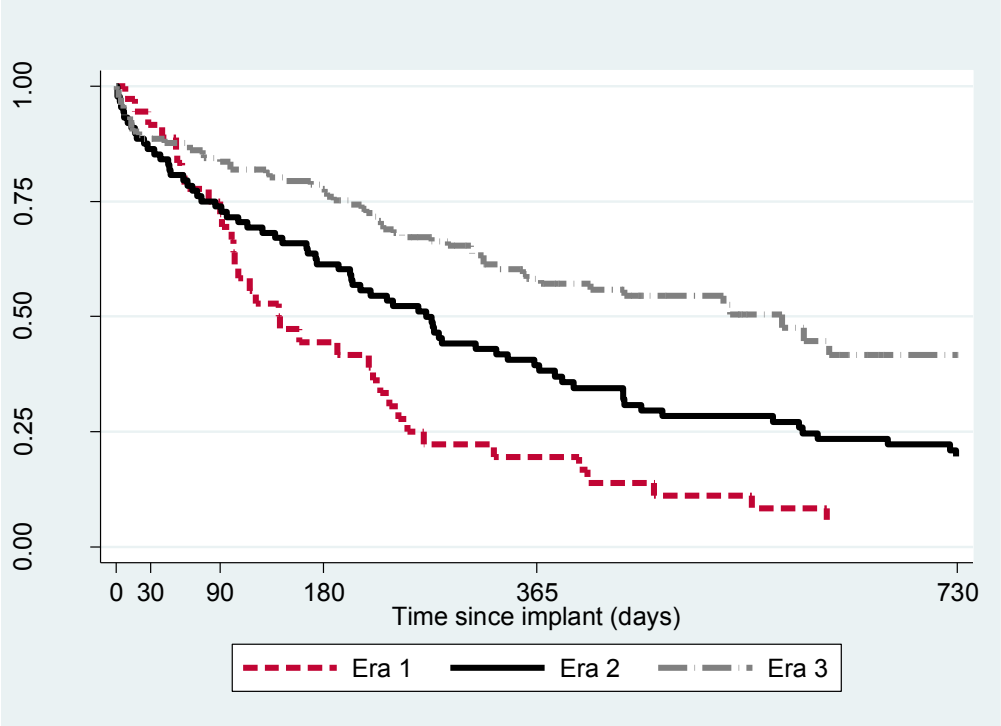


Figure 4.4: Patient survival after VAD implant by Era and Device Generation

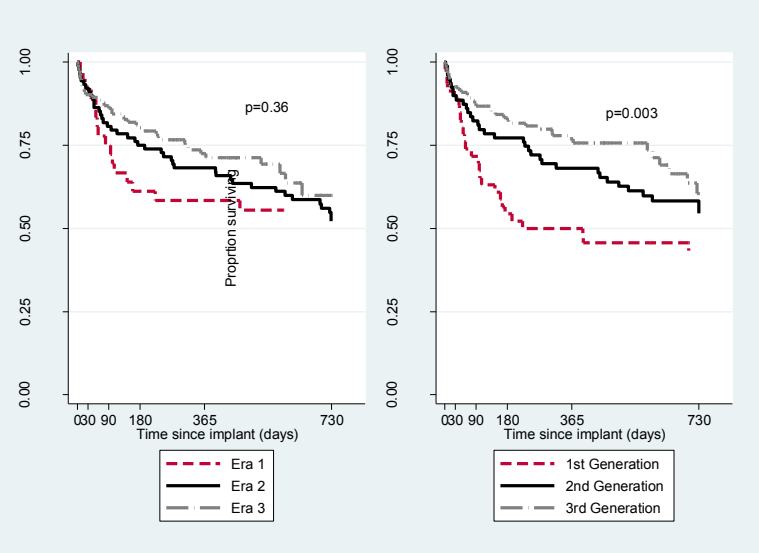


Figure 4-5: Cumulative incidence of Explant, Transplant & Death by Era

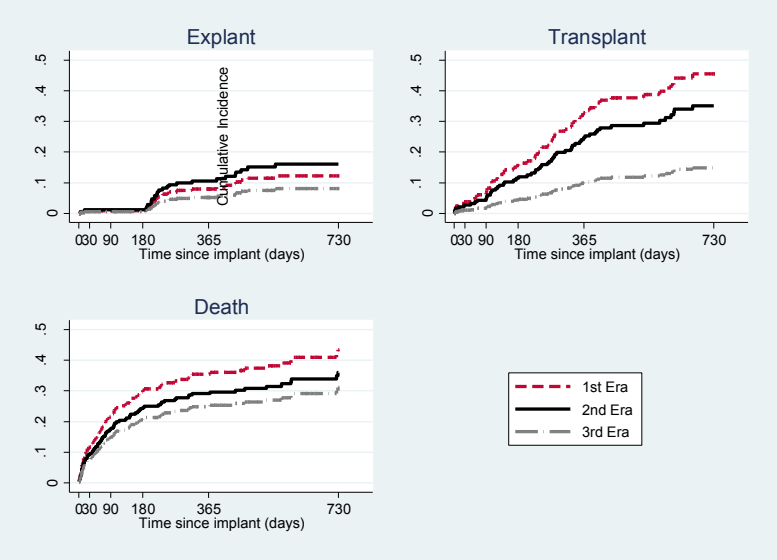


Figure 4.6: Cumulative incidence of different causes of death by Device Generation

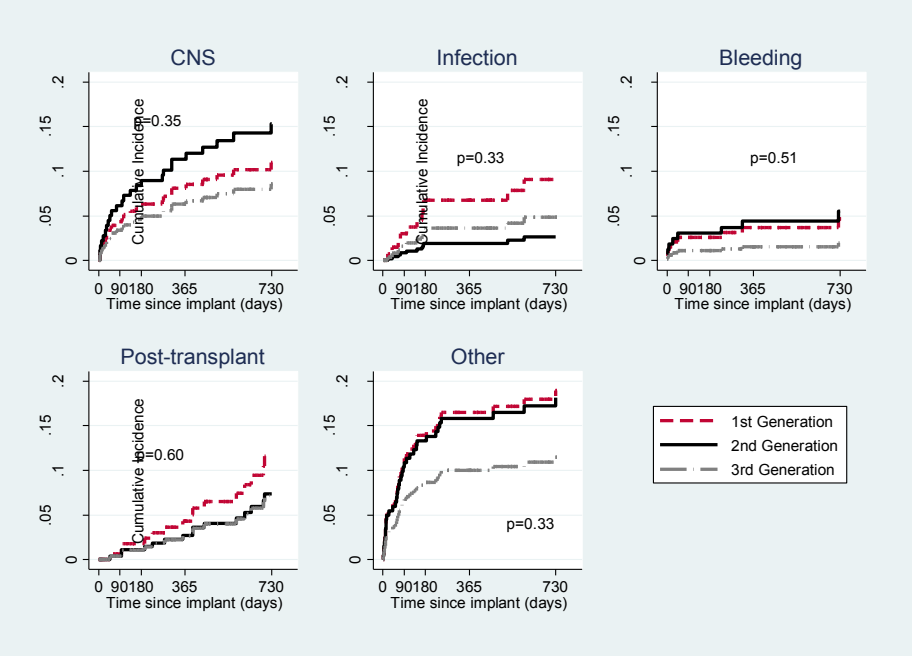


Table 4-6: Cause of death by device generation

	Generation of VAD device			
	1st	**2nd**	**3rd**	**Total**
Person years of follow-up	97.2	161.4	164.6	423.2
Primary Cause of Death	**N (%)**	**N (%)**	**N (%)**	**N (%)**
CNS	5 (18.5)	12 (30.0)	9 (25.0)	26 (25.2)
Infection	4 (14.8)	2 (5.0)	5 (13.9)	11 (10.7)
Bleeding	2 (7.4)	4 (10.0)	2 (5.6)	8 (7.8)
Cardiovascular	3 (11.1)	3 (7.5)	2 (5.6)	8 (7.8)
Multi Organ Failure	4 (14.8)	4 (10.0)	0	8 (7.8)
Embolic	1 (3.7)	2 (5.0)	1 (2.8)	4 (3.9)
Device Malfunction	0	1 (2.5)	1 (2.8)	2 (1.9)
Thrombosis	0	0	1 (2.8)	1 (1.0)
Post HTx	7 (25.9)	7 (17.5)	7 (19.4)	21 (20.4)
Other	0	2 (5.0)	6 (16.7)	8 (7.8)
Unknown	1 (3.7)	3 (7.5)	2 (5.6)	6(5.8)
Total	**27**	**40**	**36**	**103**

Renal Function

The dataset contains physiological and biochemical data for each VAD patient at multiple time points.

For the this cohort, serum creatinine levels were recorded at time of implant, 7 days following implant at subsequently at 3 months. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease formula (MDRD) = 32788 × serum creatinine (measured in µmol/litre)$^{-1.154}$ × age$^{-0.203}$ × [1.210 if black] × [0.742 if female].

The serum creatinine at implant was recorded in 238 patients; at 7 days 229 patients had a recorded serum creatinine and at 3 months 174 patients had a recorded serum creatinine. Table 4-7 shows the change in eGFR after implantation of LT LVAD. A trend of increasing eGFR after implantation was seen.

Table 4-7: Summary of eGFR calculated using the MDRD formulae for patients with VAD implants

Renal Function	Mean	SD	Median	Interquartile Range
eGFR at implantation	71.8	33.7	66.0	39.8
eGFR 7days post implant	93.6	52.2	85.9	59.3
eGFR 1 month post implant	90.9	56.0	78.7	50.3

Discussion

This report from a now comprehensive UK national database of long-term mechanical circulatory support for advanced heart failure, has documented a change in clinical practice with increasing activity and a progressive shift from 1st to 3rd generation LVADs. Despite the initial indication being bridge to transplantation, the scarcity of suitable donor hearts has resulted in a lengthening of the duration of support with the maximum survivor now being supported with VAD therapy for more than 8 years. The probability of receiving a HTx whilst on mechanical circulatory support has declined progressively, and survival has significantly improved with the introduction of the newer generation of devices (Dyer, Goldsmith, Sharples, *et al.*, 2010; Emin, Rogers, Parameshwar, *et al.*, 2013).

The UK VAD registry collects data from all devices and so is up to date with current VAD technology whereas the US INTERMACS registry only includes devices after FDA approval (Carter, Bobbitt, Bergner, *et al.*, 1976; Kirklin, Naftel, Kormos, *et al.*, 2012; 2011; 2010). European registries are voluntary whereas the UK database is comprehensive and data collection is linked to NHS reimbursement. The data is independently validated; case note

validation is performed at the centres and computerised validation checks are performed during data entry. Thus, this data is unique in its completeness and in reflecting clinical practice with the newer generation of devices.

LT LVADs implanted during Era1 were mainly large 1st generation pulsatile volume displacement pumps. These were progressively replaced by 2nd generation axial impeller devices and, currently, the majority of LVADs implanted are 3rd generation devices. These are smaller centrifugal pumps, which can be implanted within the pericardium obviating the need for further surgery to create a space or pocket to accommodate the device. The drivelines of second and third generation devices are smaller and may reduce the chance of infection (see Chapter 2). The data shows a progressive improvement in survival. There have been few deaths due to infection in patients with 3rd generation devices despite median duration of support being longer in this group than in patients implanted with 1st and 2nd generation devices. Similar improvements in survival have been seen in other randomised and non-randomised studies (McDowell, 2006; Slaughter, Pagani, Rogers, *et al.*, 2010; O'Brien, Banner, Gibson, *et al.*, 1988; Slaughter, Tsui, El-Banayosy, *et al.*, 2007; Kirklin, Naftel, Kormos, *et al.*, 2012).

Survival has improved with time, albeit not significantly, with overall survival in Era 3 approaching 70% at 1-year. One factor leading to better survival is improved LVAD technology. The REMATCH trial established a survival benefit for patients implanted with a 1st generation device when compared with medical therapy (Green, Porter, Bresnahan, *et al.*, 2000; Rose, Gelijns, Moskowitz, *et al.*, 2001). The HeartMate II trial showed a further improvement in survival with a 2nd generation device (Rector & Cohn, 1992; Slaughter, Pagani, Rogers, *et al.*, 2010). The ADVANCE study has recently shown similar short to

medium term survival after the use of a 3rd generation device as after 2nd generation devices in the bridge to transplantation indication (Zuluaga, Guallar-Castillón, López-García, *et al.*, 2010; Aaronson, Slaughter, Miller, *et al.*, 2012). In the present study, actuarial 1-year survival in an unselected group of patients with 3rd generation devices was 77%, which is comparable to reported survival rates in the United States. However, survival for the cohort as a whole; 69% at 1-year, 56% at 2-years; is lower than that reported in clinical trials, due to the unselected nature of the cohort, the longer follow-up and the higher proportion of patients in INTERMACS classes 1 and 2.

Subsequent HTx or VAD explant (due to myocardial recovery) (Parissis, Nikolaou, Farmakis, *et al.*, 2009; Terracciano, Miller & Yacoub, 2010) had a significant impact on patient survival. After the initial increased risk, HTx lowered the hazard for death, reflecting the relatively high risk of late mortality with on-going VAD support, compared to HTx. Similarly, the risk of death after explant was lower than for a patient with on-going VAD support.

Causes of death during VAD support were predominantly haemorrhage, embolic and infective events. Cause varied depending upon time since VAD implantation. The majority of early deaths were due to bleeding, cerebrovascular events including intracranial bleeding and sepsis.

The median duration of support has increased significantly over time; 141 days in Era 1 to 533 days in Era 3. This increase is partly due to improving survival on support and partly because continued support was necessitated by a lack of available donor hearts for transplantation. In Era1 the proportions of patients receiving a transplant and patients who

died on support within a year of implantation were similar. In contrast, in Era 3 the likelihood of HTx reduced significantly and patients had a higher chance of death than HTx.

Implications for practice

VAD therapy has increased significantly in the UK since 2002. Third generation devices are now preferred to 1st and 2nd generation devices due to their easier surgical implantation and improved survival. Device durability is excellent with few deaths due to device malfunction. With the shortages of donor hearts, the initial intentions to bridge patients to HTx have not been realised and long-term VAD support is becoming an alternative to HTx. Although the long term outcomes after VAD are not as good as after HTx, the results are improving and this treatment is not limited by donor availability.

Limitations

This study is limited by its observational nature. There was no standardisation of practice across centres and treatment was determined by the treating physician and surgeon. However, this data comes from a newly established, comprehensive national registry thereby avoiding any bias due to case selection or in the publication of results. To date, this is the most complete study of VAD outcomes from a single country.

Conclusions

Donor heart availability has decreased resulting in fewer transplants and an increase in the number of VADs implanted into patients with advanced heart failure. VAD technology has evolved rapidly and there has been a progressive improvement in outcome, VAD therapy has become an excellent short-term alternative to HTx and with similar survival rates at 1- year

for those with 3rd generation devices to HTx. However, there still appears to be a long-term survival benefit for VAD patients who subsequently undergo HTx.

Chapter 5: Quality of Life in Patients with Advanced Chronic Heart Failure

Quality of life in heart failure

The goal of heart failure treatment is to keep patients alive with a good quality of life. Therefore measuring quality of life outcomes became an important determinant of success for treatments in patients with advanced chronic heart failure.

Quality of life (QoL) has been shown to improve after LVAD implantation and after HTx (Dew, Kormos, Winowich, *et al.*, 2000; Grady, Jalowiec, White-Williams, *et al.*, 1995; Dew, Kormos, Winowich, *et al.*, 2001; Grady, Jalowiec & White-Williams, 1998; Grady, 1993; Hsich, Naftel, Myers, *et al.*, 2012; Sharples, Dyer, Cafferty, *et al.*, 2006). However, a direct comparison of transplant candidates receiving medical therapy, LVAD support and after HTx has not been undertaken.

Here I report the results of a multicentre cohort study of QoL in ACHF patients.

Definition of Quality of Life

Quality of life can be defined as the functional effect of an illness and its treatment upon a patient, as perceived by the patient (Grady, Jalowiec & Grusk, 1991; Spilker, 1990; Grady & Jalowiec, 1998; Grady, Meyer & Dressler, 2003; Grady, Meyer, Mattea, *et al.*, 2003; Grady & Jalowiec, 1996; Grady, Meyer, Mattea, *et al.*, 2001; 2002; Grady, Jalowiec & White-Williams, 1999). The assessment of QoL is an essential step in assessing "Health" according to the definition of health by the World Health Organisation (WHO):

"A state of complete physical, mental and social wellbeing and not merely absence of disease or infirmity" (Grady, Meyer, Mattea, *et al.*, 2002; Huber, Knottnerus & Green, 2011).

Interest in measuring QoL is the result of the success in treating many diseases and the resultant prolongation of life but often without restoration to complete health. QoL outcomes can be inconvenient to address, as conventional medical treatments do not always take QoL into account. Despite this however, it is obvious that patients would prefer to live life with a good quality, rather than having their lives prolonged with a poor quality of life.

QoL metrics are now routinely being applied to outcome evaluation (Grady, Meyer, Dressler, *et al.*, 2004; McDowell, 2006). The benefit of including QoL measurement in health research is that it broadens the scope of outcome measures and provides a way for patients' to become involved in the assessment of, and perhaps influence, their own treatments. QoL measurement may be particularly important where studies demonstrate little or no other evidence of improvement although more commonly QoL changes parallel with other changes clinical outcome (Chapman, Parameshwar, Jenkins, *et al.*, 2007; McDowell, 2006; Sharples, Dyer, Cafferty, *et al.*, 2006; Dyer, Goldsmith, Sharples, *et al.*, 2010).

Pae et al (Rose, Gelijns, Moskowitz, *et al.*, 2001; Pae, Anderson & Blackstone, 1998) concludes that there is growing evidence to support the measurement of QoL. They describe two categories of instruments, which are key in assessment of QoL; some are disease specific, while others are generic (Jacob, Copley, Lewsey, *et al.*, 2005; Pae, Anderson & Blackstone, 1998; Braun, Teren, Wilms, *et al.*, 2009). Disease specific questionnaires focus on measuring QoL in the context of the disease; a heart failure specific questionnaire might

tackle symptoms specific to heart failure such as dyspnoea or leg swelling. Generic questionnaires are used in all contexts and examine disease states in a generalised way.

The best instrument for assessment of QoL should contain the following characteristics (Green, Porter, Bresnahan, *et al.*, 2000; Pae, Anderson & Blackstone, 1998):

1. The instrument must be multidimensional
2. Both elements of generic and disease-specific measures need to be included
3. The measures must be based on evidence demonstrating their sensitivity to clinical change in the population being investigated
4. The indices must be simple to compute and easy to compare to normative data
5. The instrument must be brief so as to minimise its burden on patients and investigators
6. The instrument must be easily administered where specialist administrative training is unavailable or unfeasible

The EVAD UK study (Spertus, 2008; Sharples, Buxton, Caine, *et al.*, 2006; Green, Porter, Bresnahan, *et al.*, 2000) used these recommendations to design a QoL assessment tool. Pae et al recommended the SF-36 measure as a core, generic instrument together with the Sickness Impact Profile for the specific physical function limitations (British version of SIP is the Functional Limitations Profile (FLP) which is translated into British English and rescored). Mood state was assessed using the Hospital Anxiety and Depression Scale (HADS). 3 cognitive function tests included the MMSE, the Trail Making Test and the Digit-Symbol Substitution task (DSS). They also recommended an adaptation of a single page

questionnaire to assess the device specific concerns. VAD patients were assessed on transfer to ward and at 3-monthly intervals to transplantation/explantation. Post transplantation/explantation assessment was at 3, 6, 12, and 24 months. The non-VAD patients were interviewed or asked to complete a postal questionnaire at similar intervals.

Instruments for QoL Assessment

This section will describe some of the instruments used to assess QoL in LVAD patients:

Generic Instruments

SF-36

The SF-36 is a self-administered questionnaire, which contains 36 items measuring health on 8 multi-item dimensions. The questionnaire takes approximately 5 minutes to complete. It covers functional status, wellbeing and overall evaluation of health. Five of these dimensions are similar to those found in the Nottingham Health Profile (NHP), however the items within the SF-36 are said to detect positive as well as negative states of health (Miller, Pagani, Russell, *et al.*, 2007; Ware, Snow, Kosinski, *et al.*, 1993; Rogers, Aaronson, Boyle, *et al.*, 2010; Ware & Gandek, 1994).

EQ-5D

The EQ-5D is a generic multi-attribute health state classifier (Green, Porter, Bresnahan, *et al.*, 2000; Dyer, Goldsmith, Sharples, *et al.*, 2010) which defines health in 5 dimensions: morbidity, self-care, usual activities, pain or discomfort, anxiety or depression. Each dimension has 3 options; no problems, a moderate problem or a severe problem. Utility weights reflecting the values from a representative sample of the UK population can be used to score each level chosen for each dimension. These utilities are scaled so that death is

equal to 0, and full health is equal to 1 and allow for severe health states where the QoL is valued as a negative number i.e. lower than death (EuroQol Group, 1990; Sharples, Buxton, Caine, *et al.*, 2006). Dyer et al concluded that the validity and reliability of EQ-5D was supported by the published evidence for its use as an outcome measure in the cardiovascular area (Grady, 1993; Dyer, Goldsmith, Sharples, *et al.*, 2010; Dew, Kormos, Winowich, *et al.*, 2001; Grady, Jalowiec & White-Williams, 1998; Dew, Kormos, Roth, *et al.*, 1993).

EQ-5D is a short and simple measurement, which has gained widespread use in as a QoL measure due to its ease of use and ease of interpretation. It is particularly useful in assessing QoL in patients where it is important to minimise the burden of the questionnaire. The advantages of a generic measure such as EQ-5D are that they allow for calculation of Quality Adjusted Life Years (QALYs) within cost-utility analyses.

Nottingham Health Profile (NHP)

This was an instrument originally intended for use in the primary care setting. Its design was influenced by the Sickness Impact Profile (Grady, Jalowiec, White-Williams, *et al.*, 1995; Carter, Bobbitt, Bergner, *et al.*, 1976; Grady, Jalowiec & White-Williams, 1998; Grady, 1993; Dew, Kormos, Winowich, *et al.*, 2001). The revised NHP contains 2 parts. Part 1 contains 38 items grouped into 6 sections; physical abilities, pain, sleep, social isolation, emotional reactions, and energy levels. Part 2 assesses handicap and contains 7 items that record the effect of health problems on; jobs around the house, occupation, social life, sex life, personal relationships, hobbies and holidays. Positive or negative responses are used throughout the profile. This is a well validated instrument for assessment of QoL and has been used

previously in the HTx population (Jakovljevic, McDiarmid, Hallsworth, *et al.*, 2014; McDowell, 2006; O'Brien, Banner, Gibson, *et al.*, 1988).

Heart Failure Specific Instruments

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a disease specific health state measure comprising of 23 items measuring the impact of heart failure on various areas of general health including; physical function, social limitations, self-efficacy and QoL. Green et al. demonstrated that the KCCQ was the most sensitive measure to reflect clinical change in a multi-centre cohort of 476 patients. The study also suggested that clinically meaningful changes in the status of patients with heart failure may not be detected by other measures such as EQ-5D (Banner, Bonser, Clark, *et al.*, 2011; Green, Porter, Bresnahan, *et al.*, 2000).

Minnesota Living with Heart Failure Questionnaire

This health state measure was designed in 1984 for the purposes of assessing the effects of heart failure and heart failure treatments on QoL. It consists of 21 items and has been shown to be reliable in detection of clinical change when correlated with NYHA class (Thekkudan, Rogers, Thomas, *et al.*, 2010; Rector & Cohn, 1992).

Other Instruments

Other tools that have been used include the Hospital Anxiety and Depression Scale; Digit Symbol Substitution, Halstead-Reitan Trail Making A&B, Mini Mental State Examination and a VAD specific questionnaire.

Previous QoL studies

Zuluaga et al., showed that subscales of the Short Form-36 and Minnesota Living With Heart Failure (MLWHF) questionnaire predicted long term mortality in patients with heart failure. They assessed 416 patients admitted for HF-related emergencies. Cox hazard regression modelling showed that 2 subscales from both instruments predicted long term mortality with a p value of less than 0.05 (Emin, Rogers, Parameshwar, *et al.*, 2013; Zuluaga, Guallar-Castillón, López-García, *et al.*, 2010).

Parissis et al., also examined predictors of long term outcomes in advanced chronic heart failure patients. They surveyed 137 ACHF patients and showed that the Kansas City Cardiomyopathy Questionnaire (KCCQ) score reflected neurohormonal and inflammatory burden (tested by correlating QoL with inflammatory markers such as IL-6) and was an independent predictor of long term event-free survival (Parissis, Nikolaou, Farmakis, *et al.*, 2009).

Dew et al., (Sharples, Buxton, Caine, *et al.*, 2006; Dew, Kormos, Winowich, *et al.*, 2000; Emin, Rogers, Parameshwar, *et al.*, 2013; Dew, Kormos, Winowich, *et al.*, 2001; Thekkudan, Rogers, Thomas, *et al.*, 2010) examined whether LVAD support as a bridge to transplantation was associated with similar QoL outcomes compared with those patients who did not receive pre-transplant VAD support. They used a matched-group design in which LVAD and non-LVAD patients were matched on medical and demographic parameters. 233 adults were assessed using 90-120 minute face-to-face interviews. Patients were assessed at 2, 7 and 12 months post-transplant. LVAD patients' reports of somatic complaints declined more rapidly than non-VAD patients showing a statistically significant lower average than the non-LVAD group at 12 months. Cognitive impairment was shown to be higher in the LVAD group in all

assessments, which may be related to the proportionally higher risk of neurological event in the LVAD group. All patients showed improvements during the year post-transplant in social activity. LVAD patients were significantly less likely to return to employment and showed less involvement in social activities.

Grady et al, described QoL change in both the LVAD and HTx populations (Dew, Kormos, Winowich, *et al.*, 2001; Grady, Jalowiec & Grusk, 1991; Grady & Jalowiec, 1998; Grady, Meyer & Dressler, 2003; Grady, Meyer, Mattea, *et al.*, 2003; Grady & Jalowiec, 1996; Grady, Meyer, Mattea, *et al.*, 2001; 2002; Grady, Jalowiec & White-Williams, 1999). One study examined a non-random sample of adult HeartMate LVAD patients from multiple centres. 40 patients who had paired data at both 3 months after LVAD implantation and 3 months after HTx were investigated. Many instruments were used to assess QoL; Quality of Life Index, Rating Question Form, Heart Failure Symptom Checklist, SIP and Jalowiec Coping Scale. Additionally after LVAD implantation patients completed the LVAD Stressor Scale and at 3 months after transplant they completed the Heart Transplant Stressor scale (Emin, Rogers, Parameshwar, *et al.*, 2013; Grady, Meyer, Mattea, *et al.*, 2002). Grady et al showed that patients seemed more satisfied with their health and functioning 3 months post HTx as compared with 3 months post LVAD implantation. Mobility, physical function and overall functional ability were improved 3 months post LVAD and 3 months post HTx. Neurologic, dermatologic and physical symptom stress was less after LVAD implantation in contrast to work/school and financial stress which was lower after HTx.

Grady et al, also examined longitudinal change in QoL after LVAD implantation. They assessed 78 patients who received a HeartMate VAD who had QoL data at 1, 2, 3, 6, 9, or 12 months after implant. They used linear mixed effects modelling to test for interval changes

in QoL over time. They detected 2 significant differences for patient satisfaction with time. The mean satisfaction with health and functioning increased from 1 month to 2 months after LVAD implantation. In contrast the mean satisfaction with significant others (spouse and children) decreased from 3 months to 6 months (Emin, Rogers, Parameshwar, *et al.*, 2013; Grady, Meyer, Dressler, *et al.*, 2004).

Chapman et al., (Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013; Chapman, Parameshwar, Jenkins, *et al.*, 2007) retrospectively and qualitatively examined 6 patients in a pilot study. They conducted semi-structured face-to-face interviews lasting approximately 1 hour giving the patients the opportunity to share their experiences of health and illness before, during and after LVAD implantation. They described the patients' responses to questions and showed a number of LVAD specific concern. For example, patients described being kept awake at night because of the implant and being concerned that the device may malfunction and stop. Chapman et al used various instruments including the Utility-Based QoL – Heart questionnaire, the Minnesota Living with Heart Failure questionnaire and the SF-36.

Rose et al used the SF-36, Beck Depression Inventory and the MLHFQ to assess QoL in 129 NYHA class IV patients randomly assigned to either receive a LVAD or optimal medical management (Flint, Matlock, Lindenfeld, *et al.*, 2012; Rose, Gelijns, Moskowitz, *et al.*, 2001).

Interestingly, QoL measurement has also been shown to be a predictor of survival in patients receiving liver transplants (Jacob, Copley, Lewsey, *et al.*, 2005; Braun, Teren, Wilms, *et al.*, 2009). Jacob et al showed that functional status was a predictor of post-transplant mortality after risk adjustment.

Table 5-1: Summary of selected studies and their methods of QoL Assessment

Research Group	No. of Pts	Assessment Interval	Assessment type	Instruments
Rose et al., (2001)	129 patients, 24 VAD pts	QoL assessed at 1yr	Self-Report	SF-36, MLHFQ, Beck Depression Inventory
Dew et al. (2001)	202 patients; 170 non-VAD, 63 VAD	2,7 and 12 months post-transplant	90-120 min interviews	SIP, Karnofsky Index, Symptom checklist 90,PTSD module, MMSE, SF-36
Grady et al. (2002)	281 patients, LVAD pts150 in study	3 months after LVAD, 3 months after HTx	Self-report	Quality of Life Index Rating Question Form, Heart Failure Symptom Checklist, Jalowiec Coping Scale, LVAD Stressor Scale, HTx Stressor Scale
Grady et al. (2004)	78 HM II VAD patients	1,2,3,6,9,12 months post implant	Self-Report	QoL Life Index, Rating Question Form, Heart Failure Symptom Checklist, SIP
Miller et al., (2007)	133 patients – underwent VAD for HF	Baseline & 3 months	Self-Report	MLHFQ, KCCQ
Chapman et al. (2007)	6pts, All VAD	Retrospective	Structured interviews	Utility based QoL – heart questionnaire, MLHFQ, SF-36
George et al., (2008)	72 patients, 14 BTR, 29 BTT, 29 Tx	Variable intervals	Self-report	SF-36
Parissis et al., (2009)	137 chronic heart failure patients	Followed up for 250 days	Self-Report	KCCQ, MLHFQ 6MW, Beck Depression Inventory

Methods

This part of my study was launched on 17th January 2011 and includes data accrued until 31st August 2012.

Instrument Selection

Quality of life instruments

The validated QoL instruments used included one disease specific measure: the Kansas City Cardiomyopathy Questionnaire (KCCQ) and one generic measure: the EuroQol 5 dimensions (EQ-5D) (Green, Porter, Bresnahan, *et al.*, 2000). There are no available validated LVAD specific QoL instruments available at present, and therefore my disease specific questionnaire is specific to heart failure.

The KCCQ, a 23-item questionnaire, was developed to describe QoL in patients with HF. It quantifies physical limitation; symptom stability, frequency and burden; QoL; social interference; and self-efficacy. These scores are then used to derive a total symptom score, overall summary score and clinical summary score (KCCQ Questionnaire and method of calculating the KCCQ scores is described in Appendix 3). The KCCQ was chosen in preference to other disease specific measures due to its excellent sensitivity to clinical change in patients with HF and its reliability and validity in the patient population (Spertus, 2008; Green, Porter, Bresnahan, *et al.*, 2000). The KCCQ has been previously been used to assess QoL in patients with VAD (Miller, Pagani, Russell, *et al.*, 2007; Rogers, Aaronson, Boyle, *et al.*, 2010). Miller et al., used both the KCCQ and MLHFQ to assess QoL in a multicentre prospective study. They showed an improvement in QoL at 3 months post-implant. The KCCQ has been shown to have a greater sensitivity than MLHFQ to minimal changes of disease state. A 5 point change in the overall summary score longitudinally is considered to

reflect a clinically significant change in HF status (Green, Porter, Bresnahan, *et al.*, 2000). For all scores, higher values indicate better QoL.

EQ-5D was selected as the generic measure because It is a short and easy to administer instrument; easy to interpret, is validated for use in patients with heart failure, has no cost and is easy to use requiring very little patient effort to complete. The EQ-5D defines health in 5 dimensions: morbidity, self-care, usual activities, pain or discomfort, anxiety or depression, which are combined to give a state score (EuroQol Group, 1990). The EQ-5D has a broader user base than the KCCQ and is well recognised as a generic measure which is short and easy to use for both the administrator and patient. Again, higher state scores represent better QoL. A value of 1 indicates full heath and a value less than zero, a QoL worse than death. The EQ-5D also returns scores from a visual analogue scale, a self-reported percentage where 100% represents full health.

The selection of the instruments for QoL assessment took into consideration the patient populations within this study. Patients with ACHF can be very unwell and can find even the simplest tasks difficult to achieve. Therefore the ideal QoL instruments for these patients would need to be brief and easy to use. Questions regarding return to work and other activities of daily living were also investigated by means of an un-validated set of VAD/HTx candidate specific questions.

Calculation of the QoL Summary scores

Summary scores were calculated using guidance from the KCCQ and EQ-5D implementation manuals. These are included as appendices (Appendices 2 and 3, for KCCQ and EQ-5D respectively).

Participants and Recruitment

Questionnaires were distributed to patients within four defined populations when they attended hospital.

We included all adult patients assessed for heart transplant (HTx) (Group 1: Assessment); all patients listed for HTx without a LVAD in situ (Group 2: LIST on medical therapy); all patients with a LVAD in situ (Group 3: LVAD); and all patients who underwent HTx between 1st January 2009 and 31st December 2010 (Group 4: POST-HTx).

All NHS adult HTx centres participated in the study. These are the Royal Brompton and Harefield Trust, Harefield Hospital (London), Queen Elizabeth Hospital (Birmingham), Papworth Hospital (Cambridge), Freeman Hospital (Newcastle), Wythenshawe Hospital (Manchester) and Golden Jubilee Hospital (Glasgow).

Completed questionnaires were returned to the Royal College of Surgeons of England (RCS) where they were entered into a purpose-designed database (see Chapter 3). The questionnaires included a minimal set of identifiers that allowed the data to be linked to the UKCTA transplant and VAD databases to determine the patient group. The UKCTA transplant database includes all patients listed for or in receipt of a HTx, while the VAD database includes all NHS patients who have had LVAD support. Questionnaires which could not be successfully linked to either database were checked with the centre to confirm they were returned by a patient being assessed for HTx.

Statistical Methods

Continuous variables were summarised using a mean and standard deviation or median and inter-quartile range as appropriate and categorical variables are reported as a number and percentage. Patient characteristics and questionnaire scores were compared using analysis

of variance, the Kruskal Wallis, chi-square or Fisher's exact tests as appropriate. Statistical analyses were carried out using Stata version 11.2

Funding and Ethics

The National Specialised Commissioning Team (NSCT), NHS UK, funded the UK Cardiothoracic Transplant Audit and my post as audit fellow. Although NSCT expressed an interest in my proposed study, its design and implementation were carried out independently of the funder. Ethical approval was not required for this study as confirmed by the UK National Ethics Service.

Results

Questionnaires completed

Questionnaires were received from the 6 HTx centres during the study period. In total, 389 questionnaires were returned, three were excluded from the analysis due to lack of sufficient identifiers to facilitate data linkage, leaving 386 questionnaires. Case ascertainment was not complete; centre coordinators administered questionnaires and patient participation was voluntary. In total 286 patients were listed for HTx within the study period. 204 questionnaires were completed during assessment, 32 were completed while the patient was listed on medical therapy and 127 while the patient was on VAD support. Ninety-six patients completed questionnaires after their HTx. The median time since HTx was 332 days (IQR 168 to 623 days). Median scores and interquartile ranges in the different populations are shown in Figure 5-1.

Patient demographics

Patient demographics of the four patient groups, summarised in Table 5-2. The median age was 50.1 years (IQR 41.1 – 57.8, n=385). Self reported hypertension was more prevalent

amongst post-HTx recipients and previous stroke occurred more frequently in patients with an LVAD. Employment status differed significantly across the groups (p=0.005). Proportionally more patients were in paid employed at assessment (34.8%) and after transplant (34.7%) than at other times (16% if listed on medical therapy, 20% with VAD support).

Table 5-2: Self-reported patient demography and co-morbidity

Variable	**Overall N=386**	Assessment N=194	Listed on medical therapy N=28	LVAD N=82	Post HTx N=82	P value
Age in years (median, IQR)	**50.1 (41.1 – 57.8)**	50.4 (44.1 – 57.9)	47.1 (40.6 – 56.7)	49.6 (39.1 – 55.3)	50.3 (40.2 – 58.5)	0.42
Co-morbidities	**N (%)**	N (%)	N (%)	N (%)	N (%)	
Hypertension	**54 (16.9)**	16 (10.5)	5 (23.8)	7 (9.6)	26 (36.1)	<0.001
Stroke	**26 (8.4)**	8 (5.4)	1 (4.6)	11 (15.3)	6 (8.8)	0.083
Peripheral vascular disease	**58 (18.3)**	31 (20.3)	3 (13.6)	12 (16.7)	12 (17.1)	0.82
Lung Disease	**26 (8.1)**	13 (8.5)	2 (8.7)	6 (8.1)	5 (7.0)	0.98
Diabetes	**43 (13.4)**	20 (12.9)	1 (4.6)	10 (13.7)	12 (16.9)	0.52
Kidney Disease	**26 (8.3)**	15 (9.9)	1 (4.6)	5 (6.9)	5 (7.5)	0.76
Anxiety or depression	**85 (26.2)**	34 (22.1)	9 (37.5)	22 (29.3)	20 (27.8)	0.33
Arthritis	**39 (12.3)**	21 (13.6)	2 (9.5)	9 (12.3)	7 (10.1)	0.88

KCCQ Scores

The ten KCCQ summary scores are shown in Table 5-3. Both patients being assessed for HTx and those listed on medical therapy consistently reported worse scores than patients with LVAD support. The post HTx group reported the best QoL scores in most domains (exceptions being symptom stability and self-efficacy scores). The symptom stability scores were best in the LVAD group; mean 60.9 in the patients with LVAD compared to 54.0 in the post HTx group. Patients with LVAD reported similar self-efficacy scores to the post HTx group.

EQ-5D Scores

EQ-5D index scores are shown in table 5-3 (See Appendix 4 for EQ5D Scoring). Patients in the LVAD group reported better EQ-5D index scores than medically treated ACHF patients or listed patients. There was no significant difference between QoL scores reported by Post HTx patients and LVAD patients although there was a trend towards better QoL in patients who had undergone HTx.

Discussion

There are three main findings of my study. First, patients with ACHF receiving medical therapy, those being assessed for HTx and those awaiting HTx without LVAD had a very poor QoL. Second, HTx is the most effective surgical treatment in terms of QoL achieved. Third, patients receiving LVAD support for ACHF had a better QoL than patients receiving medical treatment despite LVAD patients having been selected because they were refractory to medical treatment.

The different populations in this study were broadly comparable because they were all in the same national referral pathway to heart transplant centres.

Many studies have documented poor QoL in advanced chronic heart failure, and the impact appears to be related to the stage of the disease (Grady, 1993; Dew, Kormos, Winowich, *et al.*, 2001; Grady, Jalowiec & White-Williams, 1998; Dew, Kormos, Roth, *et al.*, 1993). My study confirmed this finding with similar KCCQ and EQ5D results to those presented by others. Previous studies have demonstrated that both HTx and LVAD support can improve QoL in ACHF (Grady, Jalowiec, White-Williams, *et al.*, 1995; Grady, Jalowiec & White-Williams, 1998; Grady, 1993; Dew, Kormos, Winowich, *et al.*, 2001). A recent study showed improved QoL at 3 months following HTx and LVAD implantation, with an associated increase in levels of habitual physical activity. This was compared with a poorer QoL and lower physical activity in ACHF patients not undergoing HTx or LVAD (Jakovljevic, McDiarmid, Hallsworth, *et al.*, 2014). My study is the first to directly compare QoL in ACHF patients receiving medical therapy while awaiting HTx, LVAD support as a bridge to HTx and after HTx.

The study population consisted of ACHF patients within the UK pathway leading to HTx. This pathway involved several stages; referral for HTx assessment and selective listing for HTx, HTx when organs are available or LVAD implantation in the absence of HTx when patients deteriorate (Banner, Bonser, Clark, *et al.*, 2011).

Due to advances in LVAD technology, patients with ACHF refractory to medical therapy now have two options. HTx provides best long-term outcome in selected patients but scarcity of organs means this treatment has a limited availability and the waiting period is long. HTx activity in the UK had decreased in recent years (Thekkudan, Rogers, Thomas, *et al.*, 2010) leading to an increasing need for LVAD support (Emin, Rogers, Parameshwar, *et al.*, 2013). More recently however, we have started to see HTx back on the rise, although VAD implantation continues to increase despite this (Emin, Rogers, Thomas, *et al.*, 2011).

In my study, patients receiving medical treatment for HF and being listed for HTx reported the worst QoL scores in all domains. QoL was best after HTx. QoL scores in patients with HTx were significantly better that all other treatment groups. This reflects the better long-term morbidity and mortality rates in HTx compared with LVAD support (Sharples, Buxton, Caine, *et al.*, 2006; Emin, Rogers, Parameshwar, *et al.*, 2013; Thekkudan, Rogers, Thomas, *et al.*, 2010).

The most important finding in this study was that patients receiving LVAD support reported QoL scores that were better than medically treated patients despite the fact that patients who were being treated medically were deemed to be "too well" to currently require an LVAD. Patients selected for LVAD were refractory to medical therapy, more unwell and less stable prior to LVAD implantation than those who continued on medical therapy. Despite this bias, LVAD patients reported significantly better QoL in all domains. This is compatible with previous studies, which have shown that LVAD implantation improved QoL in ACHF patients (Dew, Kormos, Winowich, *et al.*, 2001).

Patients with LVAD support report worse scores for some specific elements of physical limitation such as showering. This is expected due to the LVAD's percutaneous driveline, which makes showering and washing more difficult for LVAD patients, necessitating special precautions.

Strengths and Limitations

This is the first comprehensive national cohort study of QoL in ACHF patients who are eligible for HTx while receiving medical treatment, LVAD support or after a transplant. As is common with patient completed questionnaires the response rate was incomplete. The limited duration of this study mandated a cross sectional study design. In future, longitudinal

studies may be able to directly observe the effect on QoL of patients moving from medical therapy to LVAD support and ultimately HTx.

We used two of the best-established questionnaires to detect clinical changes in heart failure whilst also trying to keep the instrument battery brief. Patients who have undergone HTx have technically been "cured" of ACHF and this caused some confusion for certain patients when answering questions regarding "their" ACHF. There are no specific questionnaires developed with good validation for LVAD support; any such QoL instrument would focus on elements such as sleep deprivation and background noise (pulsation devices) as well as complications of the skin and infections, which was not covered by the questionnaires used here.

Conclusion

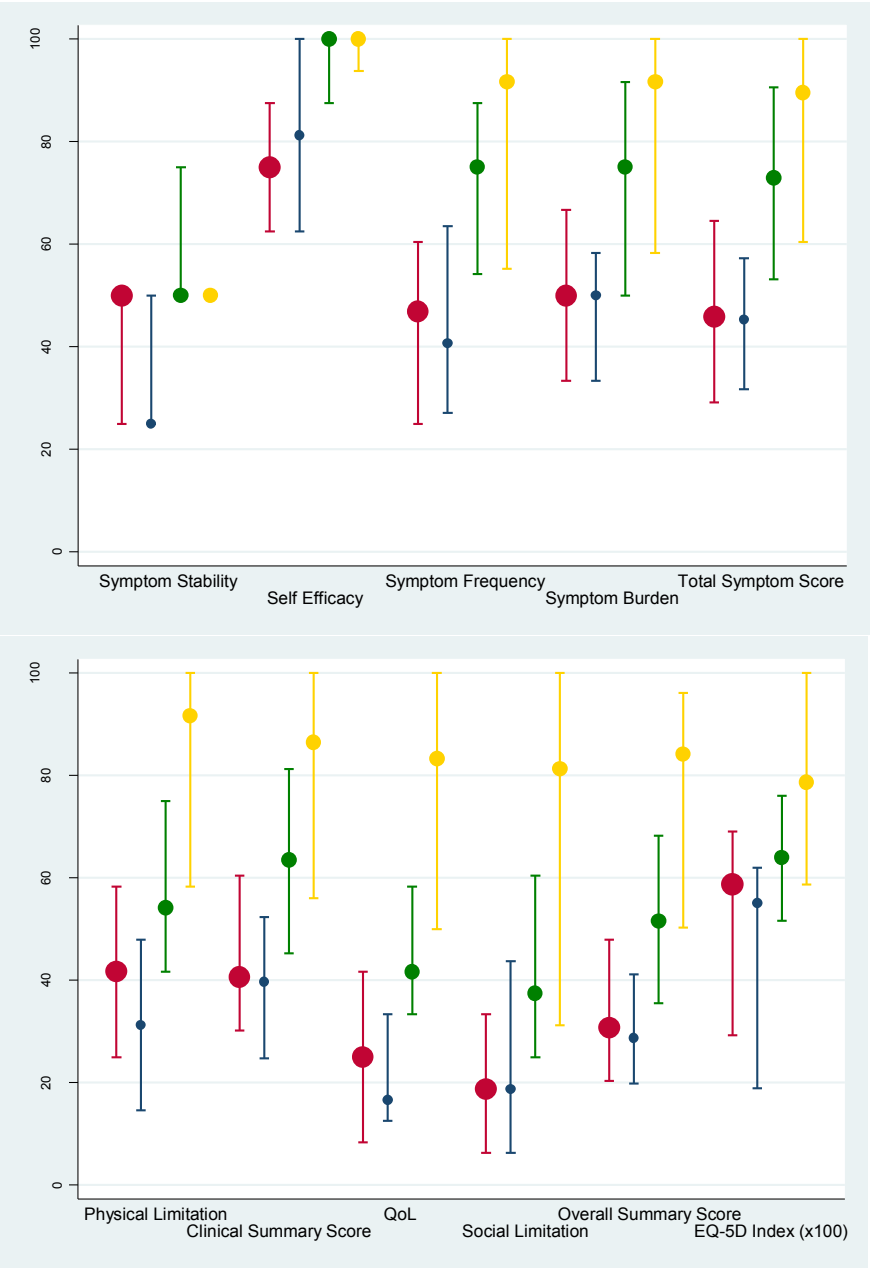
This study has found that ACHF patients receiving LVAD support experienced significantly better QoL while awaiting HTx than those continued on medical therapy. However, HTx recipients had an even better QoL and HTx remains the standard of care for such patients when a suitable donor heart is available.

Table 5-3: KCCQ and EQ-5D scores - Higher scores imply better performance within domains.

QoL Domain Scores[1]					
Score	**Assessment**	**Listed on medical therapy**	**LVAD**	**Post HTx**	**P-value**
KCCQ Domains					
Symptom Stability	47.8 (29.5)	33.9 (23.8)	60.9 (21.7)	54.7 (21.6)	<0.001
Self Efficacy	74.2 (22.2)	79.5 (18.7)	93.8 (11.1)	93.4 (15.0)	<0.001
Symptom Frequency	45.5 (26.8)	43.5 (22.5)	68.5 (25.3)	77.1 (26.3)	<0.001
Symptom Burden	48.5 (25.5)	47.9 (20.7)	69.5 (25.5)	77.8 (25.1)	<0.001
Total Symptom Score	**47.0 (24.9)**	**45.7 (20.6)**	**69.0 (24.7)**	**77.5 (25.1)**	<0.001
Physical Limitation	43.3 (26.7)	34.7 (25.8)	56.5 (25.9)	75.4 (31.1)	<0.001
Clinical Summary Score	**45.0 (23.5)**	**40.2 (22.0)**	**62.6 (23.8)**	**76.6 (26.1)**	<0.001
QoL	27.0 (22.1)	24.4 (20.4)	44.1 (23.2)	71.4 (28.5)	<0.001
Social Limitation	23.7 (23.4)	27.3 (27.2)	41.6 (27.0)	67.0 (34.2)	<0.001
Overall Summary Score	**35.5 (21.5)**	**33.3 (21.1)**	**52.6 (22.0)**	**73.0 (27.2)**	<0.001
EQ-5D Index Score	**0.50 (0.30)**	**0.44 (0.27)**	**0.58 (0.26)**	**0.74 (0.27)**	<0.001

[1] Higher score imply better performance within domains.

Figure 5-1: Median score and interquartile range by study group (assessment group in red, medical therapy in blue, LVAD in green and post HTx in yellow)



Chapter 6: Discussion and Clinical Implications

My personal journey and perspectives

My work as RCS Clinical Audit Fellow was both fascinating and challenging. I had no prior experience of clinical research, national audit or observational cohort studies.

Getting Started

After my appointment, I attended courses in basic research methodology and statistics and statistical programming. Under the supervision of Dr Chris Rogers, I learned how to use STATA to analyse and perform my own data analyses (See Chapters 4 and 5).

I familiarised myself with the operation of the national Cardiothoracic Transplantation Audit including the structure of the data warehoused by NHSBT and the analysis of data extracted for the annual audit report. Part of my role at the RCS was to contribute to the production annual UKCTA report. I used the UKCTA dataset to examine national performance in adult heart transplantation and learnt how to manipulate and analyse large data repositories to perform simple and complex analyses.

Learning how to analyse data and how to use datasets

Large complex datasets can be challenging to analyse. The UKCTA dataset was launched in 1995 (See Chapter 2), and both the layout of the dataset and the number of data that were routinely accrued provided a huge data repository for examination. Analysis required a detailed knowledge of the structure and organisation of the dataset and an appreciation of the completeness of the data. The VAD dataset was established in 2009 (Chapter 2), and this dataset had been designed and structured to be similar in format to the INTERMACS database in the United States. The main problem that I encountered was that the resulting

database had a very complex structure with repeating data accrued at multiple time points The data needed to be reorganised using indicators that defined whether the data was being examined on a per-implant or per-patient basis. Identifying the type of implant (generation of implant and implant manufacturer), type of support (LVAD, RVAD, BiVAD) and reason for support (BTT, BTD, PGF) became more complicated where patients had received multiple implants of different devices at different time points. Where a patient might have received multiple episodes of VAD support, statistical testing became harder to interpret as, multiple episodes of support might suggest that the patient had been ill for longer and more likely to suffer morbidity and mortality.

Even though the level of completeness for the dataset was very high, missing data was hard to identify due to the complexity of the dataset and this required careful examination and where necessary, correction.

Establishing Relationships with the centres

My aim (Chapter 3) was to facilitate the establishment of national VAD data collection and to ensure its accurate accrual as well as to ensure completeness of the data. It was essential for me to establish positive relationships with audit, clinical and data entry staff, in each centre. I needed to educate and motivate key team members to achieve high quality (accurate and complete) data entry in a timely fashion. My role involved liaising with both NHSBT and each centre on a monthly basis providing progress reports to ensure that the data collection was proceeding according to plan (Chapter 3). I found this process challenging but discovered that regular contact with each centre and provision of progress reports to each centre helped facilitate this process. A tally of the complete and incomplete forms was disseminated to each centre so that data collection coordinators could plan their work.

Bimonthly feedback to the UKCTA Project Group and UKCTA Steering Groups was an essential to ensure that encouragement and feedback was provided to the centres, facilitating open discussion. My work to establish bidirectional communication with each centre regarding data accrual and quality, coupled with active engagement with the UKCTA Project and Steering Groups and building personal relationships with key staff in each centre provided me with a sound basis for my Quality of Life study. It was agreed by the UKCTA Project and Steering Groups, that collecting QoL data in patients with VAD implants was an essential part of evaluating the success of VAD implantation.

There were many challenges in establishing the QoL study. It was difficult to standardise the time of questionnaire administration, as each centre had a slightly different way of listing and assessing patients (see strengths and limitations – chapter 5). Postal questionnaires were considered but excluded as the main way of collecting data due to the problem of a likely reduction in case ascertainment.

In order for the study to become established, I needed to not only engage with members of the UKCTA but also with members of the national VAD forum, the NHS Commissioners (NCG/NSCT) and other key individuals in each centre. I was able to directly address concerns and perceived flaws within the study, prior to recruitment of patients, and therefore be able to modify my protocols in accordance with the centres' specific needs.

Designing the Questionnaire Booklet

Each aspect of the questionnaire booklet was very carefully considered. The colour scheme, the font shape and size, and most importantly the layout needed to be easy to read and clear. The patients that would be completing these forms needed to find the questionnaire easy to complete and easy to understand. With advice and guidance from colleagues at the

RCS I was able to carefully put together all of the elements to design a questionnaire booklet that would allow administration of our selected QoL instruments.

I was able to show some designs of the questionnaire to test patients at the Harefield Hospital to gain their insight and perceptions from the questionnaire. The feedback was positive with the 2 patients spoken to, agreeing that the questionnaire seemed reasonably short and easy to complete, easy to read, and easy to understand. The questionnaire was distributed to all VAD and transplant coordinators who were given the opportunity to examine the questionnaire and provide feedback.

A database was created to capture the QoL data that was sent the RCS. I sought advice from dedicated database administrators to receive training in order to complete this task.

Preliminary testing suggested that it was better to construct a database, which looked very similar to the questionnaire itself in the way that the data would be entered and recorded. After testing the database, it was used to capture all QoL data that was returned to the RCS. For analysis of the data, the dataset was then extracted and converted to a format suitable for analysis using the STATA statistical software package.

The database included mechanisms to avoid errors, in order to maximise the quality and accuracy of the data captured. Automatic range checks were put in place to avoid simple typographical errors. Cross validation of data input was achieved using independent data administrators who checked the accuracy of the input data randomly against questionnaires.

Key Results and Clinical Implications

Implications for VAD practice

This thesis demonstrated that it was possible to collect high quality, national, multicentre audit data on patients receiving VAD implants in the context of chronic advanced heart failure and heart transplantation. As a result, this study facilitated the first report on the use of second and third generation implantable LVADs in the UK and enabled the publication of a manuscript (Emin, Rogers, Parameshwar, *et al.*, 2013). The analysis of these data showed that in the UK, we are supporting increasing numbers of patients using LVADs and that the types of device being used for support have changed with time. The median duration of support has increased and survival after LVAD implantation has improved significantly. Short term patient survival for those with 3rd generation LVAD implants was comparable to that seen in the UK heart transplant population and therefore that LVAD implantation has become an excellent short term alternative to heart transplantation. The results also showed that patients with LVAD implants have a significantly higher early mortality if they receive a HTx, when compared to patients on LVAD support who are not transplanted. This last point highlights the difficulties that physicians and surgeons face when they are confronted with a potential heart transplant for one of their LVAD supported patients. The hazard for death in the first 7 days after heart transplantation is 20 times higher than patients with LVAD who are not undergoing heart transplantation, although this hazard is reduced after 90 days following HTx. In the long term there appears to be an overall survival benefit with heart transplantation. I believe that these data and study partially answer the question of whether patients on LVAD support should receive a HTx.

The potential for morbidity associated with LVAD implantation is significant. Complications of implantation include adverse events such as, infection, device thrombosis and

thromboembolism, bleeding and death (Emin, Rogers, Parameshwar, *et al.*, 2013)(Chapter 4). Whilst the potential for complication is undeniable, these results have shown that patients waiting for heart transplantation have a viable alternative treatment available to them for continued support until a HTx becomes available.

Quality of Life

To date this is the first time a study has attempted to compare quality of life in patients who are on medical therapy; patients who have received an LVAD and patients who have received a HTx. I examined the cross sectional differences in quality of life between these patient populations within the heart transplantation pathway.

The first result of the study was expected. I found that patients with HTx had the best QoL. However it was notable that patients with LVAD support had a significantly better QoL than those awaiting HTx on medical therapy and those being assessed for HTx despite the fact that the LVAD patients were a subset of heart failure patients with the most severe heart failure before implant.

What has changed since the study was launched?

Building upon my work to develop the national LVAD database, Sutcliffe et al., (Sutcliffe, Connock, Pulikottil-Jacob, *et al.*, 2013) produced an HTA report examining the clinical and cost effectiveness of second and third generation VADs used as a bridge to transplantation compared with medical management. They developed a semi-Markov economic model to estimate the cost effectiveness of LVAD BTT versus medical management. They were able to calculate estimated cost per quality adjusted life years (QALY). They concluded that VADs used for BTT had higher mean costs that medical management but with better survival and QoL.

VAD implantation is still increasing – as was shown with this work; third generation device implantation is forming the bulk of LVAD usage. The National Institute for Health and Care Excellence (NICE) has provided guidance on implantation of VAD in patients for destination therapy, which has opened the road to using VADs in patients who are ineligible for HTx. This will likely pave the way for increasing usage of VADs subsequently leading to greater experience with these important devices. Whilst cost effectiveness is still in question given the substantial cost of each device, prices of devices may change in conjunction with increased use. This may lead the UK along the same path as the United States where VADs are increasingly being used in the context of destination therapy (Flint, Matlock, Lindenfeld, *et al.*, 2012).

Conclusion

This research found LVAD bridging therapy to be an important and valuable alternative to heart transplantation in the short-term. Patients bridged to HTx with LVAD have a significantly better QoL than patients who are awaiting HTx without support. This data suggests that LVAD support should be made available earlier for patients awaiting HTx, but this strategy would not be cost effective by current NICE criteria.

Appendices

Appendix 1: UKCTA Steering Group and Project Group Members

Steering Group (2009-2011) - *indicates Project Group Member as well

Professor Robert Bonser*	Mr Nizar Yonan
Director, Cardiopulmonary Transplantation	Director, Cardiopulmonary Transplantation
Queen Elizabeth Hospital	Wythenshawe Hospital
Edgbaston	Southmoor Road
Birmingham B15 2TH	Manchester M23 9LT
Professor Paul Corris	Dr Mike Burch
Director, Cardiopulmonary Transplantation	Director, Cardiopulmonary Transplantation
Freeman Hospital	Great Ormond Street Hospital for Children
Freeman Road	Great Ormond Street
Newcastle upon Tyne NE7 7DN	London WC1N 3JH
Mr Peter Braidley	Mr Mark Petrie
Director, Cardiopulmonary Transplantation	Director, Cardiopulmonary Transplantation
Northern General Hospital	Glasgow Royal Infirmary
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Dr Chris Rogers*	Mrs Helen Thomas*
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Professor Dave Collett

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Mrs Rhiannon Taylor*

NHSBT Statistician,

Organ Donation and Transplantation,

Bristol

Mr Akan Emin*

Member of PG and (Honorary) SG member

UKCTA National Audit Fellow

The Royal College of Surgeons of England,

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Dr Jayan Parameshwar*

Transplant Physician

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Cambridgeshire CB3 8RE

Appendix 2: Kansas City Cardiomyopathy Questionnaire and Scoring

Cardiomyopathy Questionnaire (Kansas City)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering or having a bath	☐	☐	☐	☐	☐	☐
Walking 100 yards on level ground	☐	☐	☐	☐	☐	☐
Doing gardening, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Jogging or hurrying (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** are now…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

KCCQ - UK/English

3. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

KCCQ - UK/English

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse (for example, regularly weighing yourself, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I have felt that way **all of the time**	I have felt that way **most of the time**	I have **occasionally** felt that way	I have **rarely** felt that way	I have **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please put an X in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

The Kansas City Cardiomyopathy Questionnaire
Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. **Physical Limitation**

   - Code responses to each of Questions 1a-f as follows:

     Extremely limited = 1
     Quite a bit limited = 2
     Moderately limited = 3
     Slightly limited = 4
     Not at all limited = 5
     Limited for other reasons or did not do = <*missing value*>

   - If at least three of Questions 1a-f are not missing, then compute

     Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

     (see footnote at end of this document for explanation of meaning of "actually answered")

2. **Symptom Stability**

   - Code the response to Question 2 as follows:

     Much worse = 1
     Slightly worse = 2
     Not changed = 3
     Slightly better = 4
     Much better = 5
     I've had no symptoms over the last 2 weeks = 3

   - If Question 2 is not missing, then compute

     Symptom Stability Score = 100*[(Question 2) – 1]/4

3. **Symptom Frequency**

   - Code responses to Questions 3, 5, 7 and 9 as follows:

     Question 3
     Every morning = 1
     3 or more times a week but not every day = 2
     1-2 times a week = 3
     Less than once a week = 4
     Never over the past 2 weeks = 5

3. **Symptom Frequency (cont.)**

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. **Symptom Burden**

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. **Total Symptom Score**

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

7. Quality of Life (cont.)

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Severely limited = 1
  Limited quite a bit = 2
  Moderately limited = 3
  Slightly limited = 4
  Did not limit at all = 5
  Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:
  Physical Limitation Score
  Total Symptom Score
  Quality of Life Score
  Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores:
  Physical Limitation Score
  Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

- If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
  (sum of the responses to those *n-i* questions) / (*n-i*)
  not
  (sum of the responses to those *n-i* questions) / *n*

If doing these calculations seems like too much trouble, consider using one of our tools – available at www.cvoutcomes.org:

- SAS or SPSS code
- Excel spreadsheets
- Web data services

Appendix 3: EQ-5D

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

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

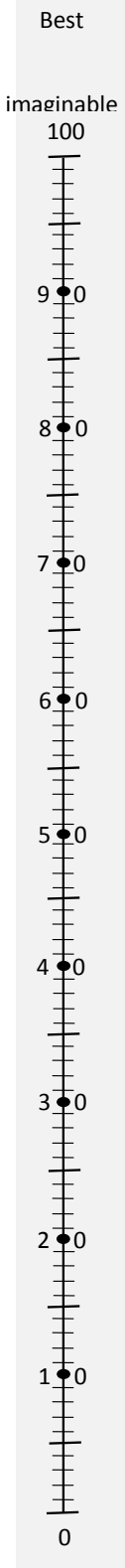
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 4: Questionnaire design

SERIAL ID

UK Cardiothoracic Transplant Audit

QUALITY OF LIFE QUESTIONNAIRE

FOR HOSPITAL STAFF ONLY

Please complete the following before giving the questionnaire to the patient.

Hospital Name

Date of Visit d d / m m / 2 0 y y

Local Hospital ID

Date of Birth d d / m m / y y y y

Patient Initials _____

The patient has not been given this questionnaire because (tick all that apply):

The patient is **unconscious** ☐ The patient is **conscious but too unwell** ☐

The patient **declines to take part** ☐ Other reasons ☐

After the patient has returned the questionnaire to you, please ensure that:

- The patient has remembered to take their information sheet out of the booklet
- The consent form has been completed and placed in the patient's records
- The questionnaire is returned in the pre-paid envelope provided

NOTE TO STAFF - only one questionnaire per envelope, please

Registered charity number: 212808

NHS Blood and Transplant

RCS ADVANCING SURGICAL STANDARDS

The Royal College of Surgeons of England

UKCTA - QUALITY OF LIFE AUDIT

SERIAL ID

PATIENT TO DETACH AND RETAIN FOR INFORMATION

PATIENT INFORMATION

Please tear out and keep for information

We understand that you have been diagnosed with severe heart failure and either (a) are in the process of being assessed for heart transplantation, (b) have been listed for heart transplant, (c) have been implanted with a ventricular assist device (VAD) or (d) have received a heart transplant. We invite you to take part in a national study that is investigating how patients feel during their treatment. By taking part in the study you will be making an important contribution to the improvement of care for patients with severe heart failure in the future.

About the Audit?

This Audit looks at how well the NHS cares for patients with severe heart failure. We are interested in finding out how patients feel during the time of their illness, and how it affects their lives. We are also interested in how we can use your opinions and experiences to improve healthcare services for patients with severe heart failure.

Who is undertaking the Audit?

The Royal College of Surgeons of England and NHS Blood and Transplant have been funded by the Department of Health to undertake the Audit.

Why have I been invited?

All adults listed for **transplantation** and all patients receiving a **VAD** in a number of hospitals in England and Scotland are being invited to take part in the Audit. We are also surveying all patients who have had a **heart transplant** in the last 2 years.

Why should I take part?

The Audit will help us to improve patient care in the future.

Do I have to take part?

Your participation is voluntary and you are free to withdraw from the Audit at any time without giving any reason, without your medical care or legal rights being affected.

Do I have to give my consent?

If you decide to take part, you need to sign a consent form so that your information can be used in the Audit.

Data Protection Notice

All the information that you give to us is strictly confidential. The information you provide will only be available to members of the Audit Team at The Royal College of Surgeons of England and NHS Blood and Transplant. The information will not be released to any outside organisations without your consent. Published reports will not refer to individual patients.

PATIENT TO DETACH AND RETAIN FOR INFORMATION

The Royal College of Surgeons of England

UKCTA - QUALITY OF LIFE AUDIT

What information is being collected?

- How your symptoms are affecting your everyday life. This information will be collected both at the time you are assessed for a heart transplant and at various points during your treatment to see if your symptoms have changed. Patients who have had heart transplants will also be asked to complete a follow-up questionnaire. You will be asked to complete your first questionnaire now.
- It will take about 10 – 15 minutes to answer all the questions.
- Before you receive this questionnaire, some information will be written on the front cover. This will enable us to link the questionnaire data with the clinical information provided by your doctors and with other NHS databases.

What will happen to my information?

Staff at The Royal College of Surgeons of England will describe and compare how patients feel at different stages of treatment. A final report based on the Audit findings will be made available to all hospitals.

Want to know more?

Send an email to:
aemin@rcseng.ac.uk

Write to:
Mr Akan Emin
Clinical Effectiveness Unit
The Royal College of Surgeons of England
35-43 Lincoln's Inn Fields
London WC2A 3PE

Telephone: 020 7869 6629

Visit the NHSBT web site:
www.organdonation.nhs.uk

Thank you for your cooperation

NHS Blood and Transplant

RCS ADVANCING SURGICAL STANDARDS

The Royal College of Surgeons of England

UKCTA - QUALITY OF LIFE AUDIT

SERIAL ID

CONSENT FORM

(Please retain in patient's record)

The Audit needs to collect your personal details and access information held about your treatment by NHS Blood and Transplant and other NHS databases. To do this we need your consent. Please read the following and sign one of the two boxes below:

I agree that my personal details and the information I provide will be held and used by the **UK Cardiothoracic Transplant Quality of Life Audit**, including information held about me by **NHS Blood and Transplant** and other NHS databases.

I also agree that I will receive further questionnaires during the course of my treatment.

I understand that the UK Cardiothoracic Transplant Audit will not release my personal details or the information that I provide, unless required by law or where there is a clear overriding public interest in disclosure. However, I will be told if any disclosure will take place.

Signature _____

Print Name _____

Date _____

I do not wish to participate in the UK Cardiothoracic Transplant Quality of Life Audit.

Signature _____

Print Name _____

Date _____

Once completed, this consent form should be removed from the questionnaire booklet and placed in the patient's notes.

Registered charity number: 212808

PLEASE RETAIN IN PATIENT'S RECORD

PLEASE RETAIN IN PATIENT'S RECORD

The Royal College of Surgeons of England

UKCTA - QUALITY OF LIFE AUDIT

PLEASE PLACE CONSENT FORM IN PATIENT'S RECORD

The Royal College of Surgeons of England

UKCTA - QUALITY OF LIFE AUDIT

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering or having a bath	☐	☐	☐	☐	☐	☐
Walking 100 yards on level ground	☐	☐	☐	☐	☐	☐
Doing gardening, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of steps without stopping	☐	☐	☐	☐	☐	☐
Jogging or hurrying (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** are now...

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

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3. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse (for example, regularly weighing yourself, eating low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

The Royal College of Surgeons of England

UKCTA - QUALITY OF LIFE AUDIT

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I have felt that way **all of the time**	I have felt that way **most of the time**	I have **occasionally** felt that way	I have **rarely** felt that way	I have **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

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UKCTA - QUALITY OF LIFE AUDIT

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

16. **Mobility**

- I have **no** problems in walking about ☐
- I have **some** problems in walking about ☐
- I am **confined to bed** ☐

17. **Self-care**

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

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

- I have **no** problems performing my usual activities ☐
- I have **some** problems with performing my usual activities ☐
- I am **unable to perform my usual activities** ☐

19. **Pain / Discomfort**

- I have **no** pain or discomfort ☐
- I have **moderate** pain or discomfort ☐
- I have **extreme** pain or discomfort ☐

20. **Anxiety / Depression**

- I am **not** anxious or depressed ☐
- I am **moderately** anxious or depressed ☐
- I am **extremely** anxious or depressed ☐

The Royal College of Surgeons of England

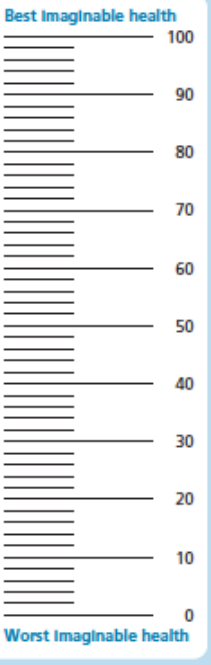
UKCTA - QUALITY OF LIFE AUDIT

21.
Think about how good or bad your own health is today.

This scale may help. The best health you can imagine is marked 100, and the worst health you can imagine is marked 0.

Please write in the box below, the number between 0 and 100 that you feel best shows how good your health is today.

Your own health today



22. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

23. Have you been told by a doctor that you have any of the following? (tick all that apply to you)

	Yes	No
High blood pressure	☐	☐
Problems caused by a stroke	☐	☐
Leg pain when walking due to poor circulation	☐	☐
Lung disease (for example asthma, chronic bronchitis or emphysema)	☐	☐
Diabetes	☐	☐
Kidney disease	☐	☐
Diseases of the nervous system (for example Parkinson's disease or multiple sclerosis)	☐	☐
Liver disease	☐	☐
Cancer (within the last 5 years)	☐	☐
Anxiety and Depression	☐	☐
Arthritis	☐	☐

24. Which of the following best describes your occupation?

Employed ☐ Seeking work ☐

Retired ☐ Other ☐

Keeping house ☐ Unknown ☐

Student ☐

If **other** please specify

25. What is today's date?

d d / m m / 2 0 y y

THANK YOU FOR YOUR ASSISTANCE. PLEASE RETURN THIS QUESTIONNAIRE TO THE PERSON WHO GAVE IT TO YOU

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