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Evaluation of the ventricular assist device programme in the UK

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Abstract

Evaluation of the ventricular assist device programme in the UK

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Objectives: To summarise the relevant clinical effectiveness and cost-effectiveness literature, to collect data on survival, transplantation rates, health-related quality of life (HRQoL) and resource use for ventricular assist device (VAD) and non-VAD transplant candidates in the UK, and to construct cost-effectiveness and cost–utility models of VADs in a UK context. Also to investigate the factors that drive costs and survival.
Design: A comprehensive systematic review was carried out. Data were collected from April 2002 to December 2004, with follow-up to March 2005. Cost-effectiveness and cost–utility models of VAD devices were developed based on UK activity and outcomes collected from April 2002 to March 2005.
Setting: National Specialist Commissioning Advisory Group funded VAD implantation was carried out at the Freeman, Harefield and Papworth transplant centres in the UK.
Participants: Seventy patients were implanted with a VAD as a bridge to transplantation between April 2002 and December 2004. Non-VAD-supported transplant candidates (n = 250), listed at the three centres between April 2002 and December 2004, were divided into an inotrope-dependent group (n = 71) and a non-inotrope-dependent group (n = 179). Although patients in the inotrope-dependent group were closest to the VAD group they were less sick. The last group comprised a hypothetical worst case scenario, which assumed that all VAD patients would die in the intensive care unit (ICU) within 1 month without VAD technology.
Interventions: Patients were included who were implanted with a VAD designed for circulatory support for more than 30 days, with intention to bridge to transplantation. A multistate model of VAD and transplant activity was constructed; this was populated by data from the UK.
Main outcome measures: Survival from VAD implant or from transplant listing for non-VAD patients to 31 March 2005. Serious adverse events and quality of life measures were used. Cognitive functioning was also assessed. Utility weights were derived from EuroQoL responses to estimate quality-adjusted life-years (QALYs). Incremental cost-effectiveness ratios (ICERs) were defined as the additional cost of VADs divided by additional QALYs. Time-horizons were 3 years, 10 years and the lifetime of the patients.
Results: Of 70 VAD patients, 30 (43%) died pretransplant, 31 (44%) underwent transplantation, and four (6%) recovered and had the VAD removed. Five patients (7%) were still supported for median of 279 days at the end of March 2005. Successful bridge-to-transplantation/recovery rates were consistent with published rates. Survival from VAD implantation was 74% at 30 days and 52% at 12 months. There were 320 non-fatal adverse events in 62 patients during 300 months of VAD support, mostly in the first month after implantation. Commonly observed events were bleeding, infection and respiratory dysfunction. Twenty-nine (41%) patients were discharged from hospital with a VAD. The 1-year survival post-transplantation was 84%. For the inotrope-dependent and non-inotrope-dependent transplant candidates, death rates while listed were 10% and 8% and the median waiting times were 16 and 87 days, respectively. For transplant recipients, 1-year survival was 85% and 84%, respectively. Both VAD and non-VAD patients demonstrated similar significant improvements in their New York Heart Association class after transplantation. All patients had poor EQ-5D pretransplantation; after transplantation the groups had similar EQ-5D of 0.76 irrespective of time after surgery. HRQoL was poor in the first month for VAD patients but better for those

who waited longer in all groups. VAD patients reported more problems with sleep and rest and with ambulation in the first month. Symptom scores were similar in all groups pretransplant. After transplantation all groups showed a marked and similar improvement in physical and psychosocial function. Mean VAD implant cost, including device, was £63,830, with costs of VAD support for survivors of £21,696 in month 1 and £11,312 in month 2. Main cost drivers were device itself, staffing, ICU stay, hospital stay and events such as bleeding, stroke and infection. For the base case, extrapolating over the lifetime of the patients the mean cost for a VAD patient was £173,841, with mean survival of 5.63 years and mean QALYs of 3.27. Corresponding costs for inotrope-dependent patients were £130,905, with mean survival 8.62 years and mean QALYs 4.99. Since inotrope-dependent patients had lower costs and higher QALYs than VAD patients, this group is said to be dominant. Non-inotrope-dependent transplant candidates had similar survival rates to those on inotropes but lower costs, also dominant. Compared with the worst case scenario the mean lifetime ICER for VADs was £49,384 per QALY. In a range of sensitivity analyses this ranged from £35,121 if the device cost was zero to £49,384. Since neither inotrope-dependent transplant candidates nor the worst case scenario were considered fair controls the assumption was investigated that, without VAD technology, there would be a mixture of these situations. For mixtures considered the ICER for VADs ranged from £79,212 per QALY to the non-VAD group being both cheaper and more effective.

Conclusions: There are insufficient data from either published studies or the current study to construct a fair comparison group for VADs. Overall survival of 52% is an excellent clinical achievement for those young patients with rapidly failing hearts. However, if the worst case scenario were plausible, and one could reliably extrapolate results to the lifetime of the patients, VADs would not be cost-effective at traditional thresholds. Further randomised controlled trials are required, using current second generation devices or subsequent devices and conducted in the UK.

Contents

List of abbreviations

ACE	angiotensin-converting enzyme
BiVAD	bi-ventricular assist device
BTR	bridge to recovery
BTT	bridge to transplantation
CEAC	cost-effectiveness acceptability curve
CETS	Conseil d'Évaluation des Technologies de la Santé du Québec
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CT	computed tomography
CVA	cerebrovascular accident
CVP	central venous pressure
DCM	dilated cardiomyopathy
DSS	Digit–Symbol Substitution
EQ-5D	EuroQol 5 Dimensions
FLP	Functional Limitations Profile
HADS	Hospital Anxiety and Depression Scale
HRQoL	health-related quality of life
i.v.	intravenous
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IHD	ischaemic heart disease
INB	incremental net benefit
IP	implanted pneumatic
IQR	interquartile range
IVAD	implantable ventricular assist device
LDH	lactate dehydrogenase
LOS	length of stay
LVAD	left ventricular assist device
LVAS	left ventricular assist system
MCS	mental component score
MI	myocardial infarction
MMSE	Mini-Mental State Examination
MUGA	multiple gated acquisition (heart scan)
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
NR	not reported
NSCAG	National Specialist Commissioning Advisory Group
NYHA	New York Heart Association
PCS	physical component score
PVAD	percutaneous ventricular assist device
PSC	Physical Symptoms Checklist
QALY	quality-adjusted life-years

continued

List of abbreviations *continued*

RCT	randomised controlled trial
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
RR	relative risk
RVAD	right ventricular assist device
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form 36
SF-6D	Short Form 6 Dimensions
SGOT (ALT)	serum glutamic oxaloacetic transaminase (alanine aminotransfase)
SGPT	serum glutamic pyrovic transaminase
SIP	Sickness Impact Profile
TIA	transient ischaemic attack
UNOS	United Network for Organ Sharing
VAD	ventricular assist device
VE	vented electric
WAIS	Wechsler Adult Intelligence Scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Medical management of patients with mild to moderate heart failure has substantially improved survival and quality of life in recent years owing to the increased use of angiotensin-converting enzyme inhibitors and β-blockers. For severe heart failure, transplantation is widely accepted as the most effective surgical treatment for suitable patients. However, heart transplantation is rationed by the availability of suitable donor hearts and there has been a steady decline in donor hearts over time.

Ventricular assist devices (VADs) were first used to support transplant candidates with rapidly failing circulation who were considered unlikely to survive until a suitable organ could be found. This situation is described as bridge to transplantation (BTT).

The National Specialist Commissioning Advisory Group (NSCAG) has agreed to support a new national service providing VAD therapy in three centres in the UK. A standard requirement of NSCAG is that such new services should be subject to an appropriate evaluation. Thus, this integrated but independently led health technology assessment was conducted, focusing on the clinical and cost-effectiveness of the use of VADs in the context of bridging to either transplantation or recovery in patients who are appropriate candidates for heart transplantation.

Objectives

This study had four key objectives:

- to summarise the relevant effectiveness and cost-effectiveness literature
- to collect data on survival, transplantation rates, health-related quality of life (HRQoL) and resource use for VAD and non-VAD transplant candidates in the UK
- to construct cost-effectiveness and cost–utility models of VADs in a UK context
- to investigate the factors that drive costs and survival.

Methods

Setting

NSCAG-funded VAD implantation was carried out at the Freeman, Harefield and Papworth transplant centres in the UK.

Participants

The study involved 70 patients implanted with a VAD as a BTT between April 2002 and December 2004. The construction of a fair comparison group was not feasible. To provide bounds on effectiveness/cost-effectiveness of VADs three other groups were studied. The first and second groups consisted of non-VAD-supported transplant candidates (n = 250), listed at the three centres between April 2002 and December 2004. They were divided into an inotrope-dependent group (n = 71) and a non-inotrope-dependent group (n = 179). Although patients in the inotrope-dependent group were closest to the VAD group they were less sick. The final group comprised a hypothetical worst case scenario, which assumed that all VAD patients would die in the intensive care unit (ICU) within 1 month without VAD technology.

Interventions

Patients were included who were implanted with a VAD designed for circulatory support for more than 30 days, with intention to BTT. A multistate model of VAD and transplant activity was constructed; this was populated by data from the UK.

Main outcome measures

The main outcome measure was survival from VAD implant or from transplant listing for non-VAD patients to 31 March 2005. VAD support was considered successful if the patient survived to transplantation or recovered myocardial function to allow removal of the device. Serious adverse events during VAD support and after transplantation were recorded. Pre- and post-transplantation HRQoL for VAD and non-VAD transplant candidates was assessed by the EuroQoL, Short Form 36, Functional Limitations Profile, Physical Symptoms Checklist, Hospital Anxiety and Depression Scale and a VAD-specific questionnaire. Cognitive functioning was also

assessed. Utility weights were derived from EuroQoL responses to estimate quality-adjusted life years (QALYs). Incremental cost-effectiveness ratios (ICERs) were defined as the additional cost of VADs divided by additional QALYs. Time-horizons were 3 years, 10 years and the lifetime of the patients.

Results

Of 70 VAD patients, 30 (43%) died pretransplant, 31 (44%) underwent transplantation and four (6%) recovered and had the VAD removed. Five patients (7%) were still supported for median of 279 days at the end of March 2005. Successful BTT/recovery rates were consistent with published rates. Survival from VAD implant was 74% at 30 days and 52% at 12 months. There were 320 non-fatal adverse events in 62 patients during 300 months of VAD support, mostly in the first month after implant. Common observed events were bleeding, infection and respiratory dysfunction. Twenty-nine (41%) patients were discharged from hospital with a VAD. The 1-year survival post-transplant was 84%.

For the 71 inotrope-dependent and 179 non-inotrope-dependent transplant candidates, death rates while listed were 10% and 8% and the median waiting times were 16 and 87 days, respectively. For transplant recipients 1-year survival was 85% and 84%, respectively.

Both VAD and non-VAD patients demonstrated similar significant improvements in their New York Heart Association class after transplantation.

All patients had poor EQ-5D pretransplantation; after transplantation the groups had similar EQ-5D of 0.76 irrespective of time after surgery. HRQoL was poor in the first month for VAD patients, but better for those who waited longer in all groups. VAD patients reported more problems with sleep and rest and with ambulation in the first month. Symptom scores were similar in all groups pretransplantation. After transplantation all groups showed a marked and similar improvement in physical and psychosocial function.

Mean VAD implantation cost, including device, was £63,830, with costs of VAD support for survivors of £21,696 in month 1 and £11,312 in month 2. Main cost drivers were device itself, staffing, ICU stay, hospital stay and events such as bleeding, stroke and infection.

For the base case, extrapolating over the lifetime of the patients the mean cost for a VAD patient was £173,841, with mean survival of 5.63 years and mean QALYs of 3.27. Corresponding costs for inotrope-dependent patients were £130,905, with mean survival 8.62 years and mean QALYs 4.99. Since inotrope-dependent patients had lower costs and higher QALYs than VAD patients, this group is said to be dominant. Non-inotrope-dependent transplant candidates had similar survival rates to those on inotropes but lower costs, also dominant. Compared with the worst case scenario the mean lifetime ICER for VADs was £49,384 per QALY. In a range of sensitivity analyses this ranged from £35,121 if the device cost was zero to £49,384. Since neither inotrope-dependent transplant candidates nor the worst case scenario were considered fair controls the assumption was investigated that, without VAD technology, there would be a mixture of these situations. For mixtures considered the ICER for VADs ranged from £79,212 per QALY to the non-VAD group being both cheaper and more effective.

Conclusions

There are insufficient data from either published studies or the current study to construct a fair comparison group for VADs. Overall survival of 52% is an excellent clinical achievement for those young patients with rapidly failing hearts. However, if the worst case scenario were plausible, and one could reliably extrapolate results to the lifetime of the patients, VADs would not be cost-effective at traditional thresholds.

Implications for the health service

More reliable information on the effectiveness of VADs compared with alternative treatments is required before robust recommendations can be made. Observational data suggest that VADs are not yet cost-effective for current patients and that there is no cost-effectiveness argument for widespread dissemination of the technology. However, VAD implantation can be justified for selected current cases based on survival, and for future patients on the grounds of maintaining the understanding and skills required for implantation and management.

Recommendations for research

The following areas for further research are suggested.

- Further randomised controlled trials are required, using current second generation devices or subsequent devices and conducted in the UK. Studies could include randomised comparisons with optimal medical management for stable ambulatory patients and/or head-to-head comparisons of different devices for patients with acute-onset severe heart failure.
- Until trials can be conducted, UK activity and results should be carefully monitored and the NSCAG service structured and managed to maximise understanding and skills base for future patients.
- The impact of VADs on the transplant programme requires further modelling work.

Chapter 1

Introduction to the use of ventricular assist devices in the UK

Background

Heart failure

Heart failure is a common disease responsible for high mortality and morbidity. It is a complex process characterised by loss of contractile function and insufficient circulation to support metabolic needs. It has a wide range of aetiologies; approximately two-thirds of patients have ischaemic heart disease and the remaining third are due to a range of conditions such as hypertension, viral cardiomyopathy, postpartum cardiomyopathy, myocarditis or idiopathic dilated cardiomyopathy.[1–3]

Medical management of patients with mild to moderate heart failure has substantially improved survival and quality of life in recent years owing to the increased use of angiotensin-converting enzyme (ACE) inhibitors and β-blockers.[2] For severe heart failure transplantation is widely accepted as the most effective surgical treatment for suitable patients, with 1-, 5- and 10-year post-transplantation survival in the UK of 77%, 67% and 51%, respectively (Hussey J, UK Transplant: personal communication, March 2005). In addition, quality of life after transplantation is significantly improved and is comparable to age- and gender-matched norms.[4] However, heart transplantation is rationed by the availability of suitable donor hearts and there has been a steady decline in donor hearts over time (*Figure 1*). In addition, patients undergoing heart transplantation are prone to rejection of the allograft and to opportunistic infection, so that they are maintained on a range of immunosuppressive and prophylactic drugs for life.

Assessing the size of the heart failure problem is difficult owing to varying age–gender distributions of the populations and varying definitions of heart

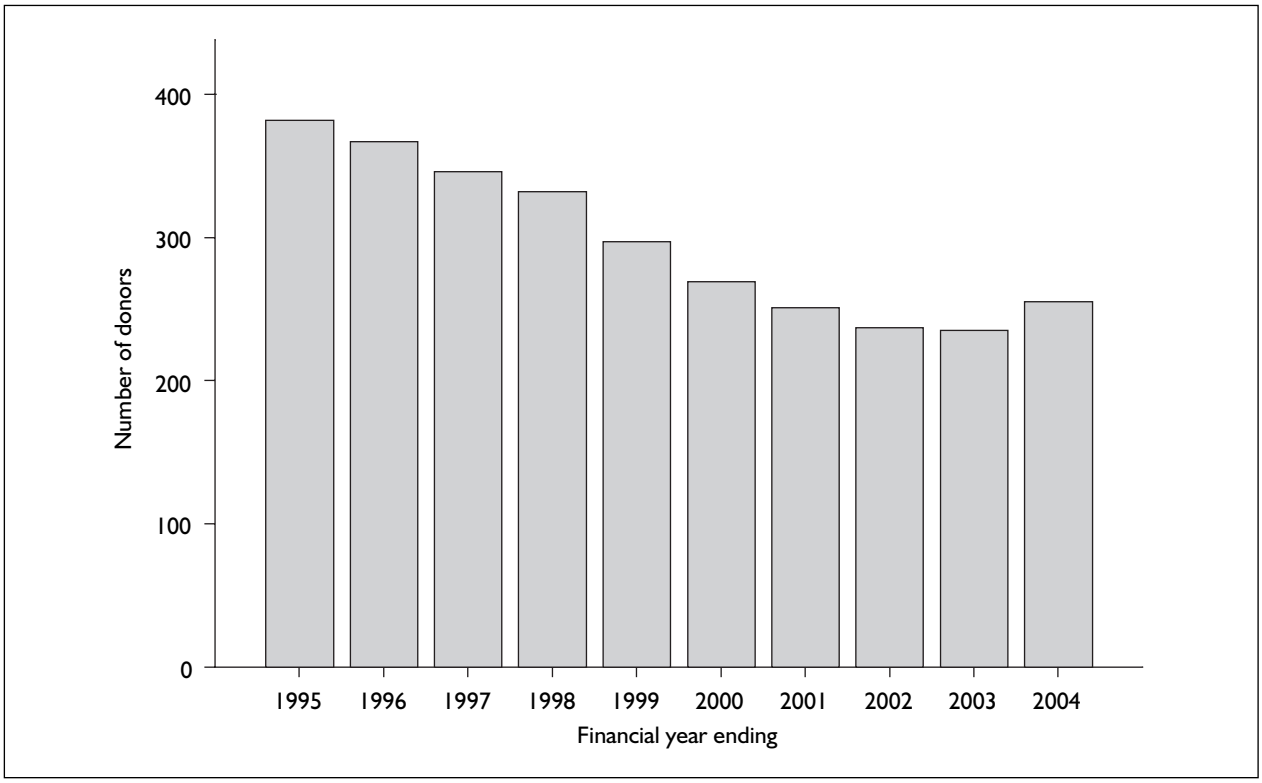

FIGURE 1 *Number of heart donors registered with UK Transplant over time. Source: UK Transplant website (www.uktransplant.org.uk).*

failure used in published studies. In a 2005 review of the incidence and prevalence of heart failure, Clegg and colleagues[5] concluded that there are likely to be between 250,000 and 400,000 people with heart failure in England and Wales, including around 7000–8000 people with severe heart failure, who could potentially benefit from new treatments such as ventricular assist devices (VADs).

Left ventricular assist devices

VADs were first used to support transplant candidates with rapidly failing circulation, who were considered unlikely to survive until a suitable organ could be found. This situation is described as bridge to transplantation (BTT). As a result of growth in clinical experience of VADs, particularly in the USA and Germany, and development of the devices, they have been increasingly used for long-term circulatory support in patients who are ineligible for transplantation. This leads to the question of whether these devices could ultimately be an alternative to heart transplantation. The answer depends on the further development of the devices, batteries and controllers to allow reliable permanent placement while minimising the adverse events associated with their use. Where there has been sufficient recovery of myocardium some VADs have been explanted, termed bridge to recovery (BTR). The challenge in this respect is to identify patients with sufficient myocardial recovery to allow removal of the implanted device.

Over 30 types of VADs have been developed and used, although some are designed for short-term use (<30 days) only or for paediatrics and others are in the early stages of testing. Devices have been termed first, second or third generation.

First generation devices are displacement blood pumps, sometimes described as pulsatile VADs. The most commonly used first generation devices have been the Abiomed BVS 5000, Berlin Heart, HeartMate (IP and VE), Novacor N100 and Thoratec VADs. In these devices an inflow conduit attached to the left ventricle directs blood into a mechanical pump. The pump ejects blood through an outflow conduit to the patient's arterial system. The system is operated and monitored using a controller and is battery powered. The pump is connected to the controller and batteries by two leads which pass through the patient's skin. The main problems with these devices have been VAD size, infection around the driveline and VAD pocket, bleeding and thromboembolism.

Second generation devices are rotary blood pumps, which are designed to address some of the problems with first generation devices. In particular, rotary pumps are smaller and simpler than earlier devices and provide continuous or non-pulsatile flow. The most commonly used second generation devices are the MicroMed DeBakey, the Berlin Incor and the Jarvik 2000.

Third generation devices are in the early stages of clinical testing. These rotary blood pumps have rotors that are suspended between magnets and so do not touch the casing. This should result in fewer complications and better long-term survival on the device.

Assessment of the UK VAD programme

In 2002 the National Specialist Commissioning Advisory Group (NSCAG) agreed to support a new national service providing VAD therapy in three UK centres (the Freeman, Harefield and Papworth Hospitals). A standard requirement of NSCAG is that such new services should be subject to an appropriate evaluation. This resulted in an integrated but independently led health technology assessment focusing on the effectiveness and cost-effectiveness of the use of VADs in the UK in the context of BTT or BTR, in patients who are appropriate candidates for transplantation. Any other VAD patients would not be funded by the NSCAG programme and would therefore not be included in this study.

There is a widely recognised problem in evaluating low-volume, high-cost, but potentially life-saving surgical interventions where randomised controlled trials (RCTs) of sufficient size are often impractical or not feasible. The difficulties in the case of VADs have already been explored by the current research team in reflecting in particular on Papworth Hospital's initial experience in attempting to set up a formal trial.[6] However, VAD technology is a case for which the need for evidence on effectiveness is particularly strong because of its physical and psychological invasiveness to the patient, and its high cost to the NHS.

In evaluating the use of VADs in the UK there is a number of factors to understand. For example, it is important to recognise the emerging nature of the technology and the patient groups who may benefit from implantation. When this evaluation was planned, most of the published literature was in the context of BTT, since at implantation it is not clear whether patients will recover cardiac function sufficiently to allow VAD weaning, and there was very limited information on use of VADs for long-term circulatory support. In general, implantation of an expensive device in a very

high-risk group was not considered acceptable in the absence of a transplant programme. However, in the UK current waiting lists do not include substantial numbers of listed patients requiring VAD implantation, possibly because of selection by referring cardiologists who are aware of the shortage of donor organs, so that interest is directed towards recovery and destination therapy. Unless these devices can be developed for use either as BTR or as destination therapy, they are of limited interest to the health service and, from an economic viewpoint, to the companies.[7]

There is evidence that cardiac function recovers to some degree for most patients following VAD implantation.[8–10] There are also US and European protocols for weaning from VAD, but these are not yet finalised or published. The Harefield approach to BTR has been published.[11] However, markers of successful weaning are still not established.

In addition, since this study began the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial of the HeartMate VAD used as long-term circulatory support has been published and demonstrated significant gains in survival. To date, this is the only RCT.[12]

Although this UK evaluation study does not provide formal trial data, it does provide an opportunity to undertake systematic data collection on a multicentre cohort of patients receiving a VAD and on multicentre cohorts from comparison groups taken from concurrent transplant candidates. A definitive assessment may not be possible, but the UK evaluation aims to provide an indication of whether the new technology already fills or may in future fill the 'cost-effectiveness gap' left by current management before transplant.[13] It also aims to provide an empirical basis, relevant to UK practice, for modelling observed cost-effectiveness and for analysing how future changes in the effectiveness and cost of the technology, or in the mix or management of patients, may change this estimate of cost-effectiveness. In addition, it will provide data on which to build future evaluation studies and from which better to identify those patients who will benefit from VAD implantation and those most likely to be successfully weaned.

Aims of the study

The aims of the study were as follows:

- to summarise briefly the systematic review undertaken by Clegg and colleagues[5] and to include significant publications based on large patient cohorts and device registries
- to record all NSCAG-funded VAD implantation activity in the UK in the period April 2002 to December 2004, with follow-up to March 2005
- to collect and report survival, transplant, myocardial recovery and other clinical outcomes from recipients of VADs in the UK during the study period April 2002 to December 2004, with follow-up to March 2005
- to collect and report health-related quality of life (HRQoL) outcomes from recipients of VADs in the UK during the study period April 2002 to December 2004
- to collect and report individual patient resource use from recipients of VADs in the UK during the study period April 2002 to December 2004
- to collect clinical, HRQoL and resource-use data from non-VAD transplant candidates at centres that undertook VAD implantation in the UK during the study period April 2002 to December 2004
- to construct cost-effectiveness and cost–utility models of VADs based on UK activity and outcomes during the study period April 2002 to March 2005.

This report is arranged as follows. Evidence from clinical studies is reviewed briefly in Chapter 2 and a more comprehensive systematic review of economic studies appears in Chapter 3. The methods for data collection during the study period, April 2002 to March 2005, and clinical outcomes, including survival, are summarised in Chapter 4. HRQoL results, including utilities, from the UK evaluation are provided in Chapter 5 and resource-use data are summarised in Chapter 6. Chapter 7 provides technical details of the cost-effectiveness model and may be ignored without losing the main study methods. A non-technical description of the cost-effectiveness model and the results of the cost-effectiveness and cost–utility analyses appear in Chapter 8. Chapter 9 provides an overview of the UK evaluation and its contribution to the evidence.

Chapter 2

Review of the effectiveness of ventricular assist devices for severe heart failure

Background and methods

This chapter summarises the main results of the 1995 systematic review by Clegg and colleagues,[5] and discusses the results in the context of significant large patient cohorts and device registries. Full details of the search methodology used in the systematic review are in Clegg[5] and are reviewed briefly here.

Sources of information and the search strategy used in the review are given in Appendix 1. The search included studies published in all languages. Studies reviewed involved patients over the age of 16 years with end-stage heart failure who received a VAD implanted as BTT, BTR or long-term circulatory support. Systematic reviews, RCTs, cohort studies, case series, case reports, economic evaluations and cost studies were included. Emphasis was given to comparative studies, such as VADs compared with high-risk transplant candidates. Where evidence from different types of study was available, only those with the most rigorous methods were included in the review. Outcomes of interest were survival to transplantation, survival overall, New York Heart Association (NYHA) class and quality of life. Adverse events were also extracted. Formal meta-analysis of the studies was not undertaken owing to the heterogeneity of study designs and patient groups.

Clegg and colleagues assess methodological quality of studies using standard methods (reference 177 in Clegg). It is not the intention to repeat this exercise here. In addition to the studies identified in Clegg, all large patient cohorts and device registry results published in the same period were reviewed here. The purpose of this part of the review was to assess informally the generalisability of studies included in the systematic review.

Specific devices included are as used in Clegg[5] (see below):

- AB-180 IVAD (implantable)
- Abiomed BVS 5000
- Arrow Lionheart VAD
- Berlin Heart
- Berlin Incor I
- HeartMate IP [implanted pneumatic left ventricular system (LVAS)]
- HeartMate VE (vented electric LVAS)
- Jarvik 2000
- MicroMed DeBakey VAD (Baylor/NASA)
- Nippon-Zeon
- Novacor (Novacor Medical Corporation/Baxter Healthcare, Oakland, CA)
- Thoratec [implantable VAD (IVAD)]
- Toyobo.

Bridge to transplantation

There were 16 studies assessing the clinical effectiveness of VADs as a BTT, in the Clegg systematic review.[5] The present authors identified a further ten recent studies, which included results from large cohorts or device registries. The 26 studies are listed in *Table 1*. There were 17 studies using first generation devices, seven using second generation devices and two recent studies reporting single-centre experience in which a mixture of first and second generation devices was used.

Almost all studies were observational in design and so included biases. Some studies attempted to construct a suitable comparison group, for example other transplant candidates or transplant candidates who were inotrope dependent. In these reports there was little detail to judge the adequacy or relevance of the control groups and so potential for bias remains. Overall, the methodological quality of the 16 studies in the systematic review[5] for assessing the effectiveness of VADs was judged to be weak. The ten large series published since the systematic review were mostly observational studies, did not have comparison groups and provided little information on inclusion criteria. Therefore, the methodological quality of these studies is weak.

Most VAD candidates (89%) were men, with the proportion ranging from 63 to 100% in these studies. The mean age (weighted by size of study) of VAD recipients was 49.1 years [95% confidence

TABLE 1 *Summary of studies of effectiveness of VADs used as a BTT*

Study	Device(s)	Comparator
First generation VADs		
El-Banayosy *et al.*, 2000[14]	Heartmate VE (n = 20)	Novacor N100 (n = 20)
Aaronson *et al.*, 2002[15]	Heartmate IP or VE (n = 66)	Intravenous inotropes (n = 38); post-transplant survival of UNOS status 2 patients (n = 60)
Bank *et al.*, 2000[16]	Heartmate IP (n = 20)	Intravenous inotropes (n = 20)
Massad *et al.*, 1996[17]	Heartmate IP or VE (n = 53)	Medical care (n = 203)
Frazier *et al.*, 1992[18]	Heartmate IP (n = 34)	Historical controls from transplant database (n = 6)
Frazier *et al.*, 1994[19]	Heartmate IP (n = 19)	Patients who met study criteria but no device available (n = 12)
Grady *et al.*, 2001[20]	Heartmate IP or VE (n = 30)	None
Morgan *et al.*, 2004[21]	Heartmate VE (n = 243)	None
Rao *et al.*, 2004[22]	Heartmate VE (n = 131)	Compared three periods
Navia *et al.*, 2002[23]	Heartmate or Novacor N100 (n = 277)	None
Trachiotis *et al.*, 2000[24]	Novacor N100 (n = 10)	Compared patients supported for <30 days with those supported for >30 days
Mussivand *et al.*, 2004[25]	Novacor N100 (n = 1348)	Comparison of centre volumes
Strauch *et al.*, 2003[26]	Novacor N100 (n = 40)	Compared two periods
Holman *et al.*, 1995[27]	Thoratec (n = 1)	None
May *et al.*, 1987[28]	Thoratec (n = 1)	None
Carrier *et al.*, 2004[29]	Thoratec (n = 16)	Routine heart transplant candidates (n = 20)
Masai *et al.*, 1995[30]	Toyobo (extracorporeal) (n = 3)	None
Second generation VADs		
Frazier *et al.*, 2001[31]	Jarvik 2000 (n = 3)	None
Frazier *et al.*, 2003[32]	Jarvik 2000 (n = 22)	None
Noon *et al.*, 2001[33]	Micromed DeBakey (n = 32)	None
Popatov *et al.*, 2000[34]	Micromed DeBakey (n = 6)	None
Wieselthaler *et al.*, 2001[35]	Micromed DeBakey (n = 10)	None
Goldstein *et al.*, 2003[36]	Micromed DeBakey (n = 150)	None
Hetzer *et al.*, 2004[37]	Incor (n = 24)	None
Mixed first and second generation VADs		
Vitali *et al.*, 2004[38]	Thoratec (n = 12), Abiomed (n = 6), Novacor (n = 38), Medas (n = 4), Micromed DeBakey (n = 15), ImpellarRecover (n = 5)	None
Granfeldt *et al.*, 2003[39]	Heartmate IP (n = 17), Heartmate VE (n = 37), Jarvik 2000 (n = 3), Novacor N100 (n = 2)	None

UNOS, United Network for Organ Sharing.

interval (CI) 48.5 to 49.7]. Most patients had either idiopathic dilated cardiomyopathy or ischaemic cardiomyopathy at presentation and were in NYHA class IV.

From *Figure 2* there does not appear to be any relationship between size of study and duration of implant. Average duration of support varied, but was generally less than 6 months. However, in the study comparing HeartMate with Novacor VADs the median time supported was 174.6 (SD 175) and 235.3 (SD 210), respectively. Similarly, the three patients implanted with the Toyobo VAD had an average support time of 206 days. Excluding these studies the mean duration of support ranged from 17 days to 4.6 months. Thus, despite prolonged support in some patients, results from these studies represent short-term use of the devices and simple extrapolation of results to longer term use may not be appropriate.

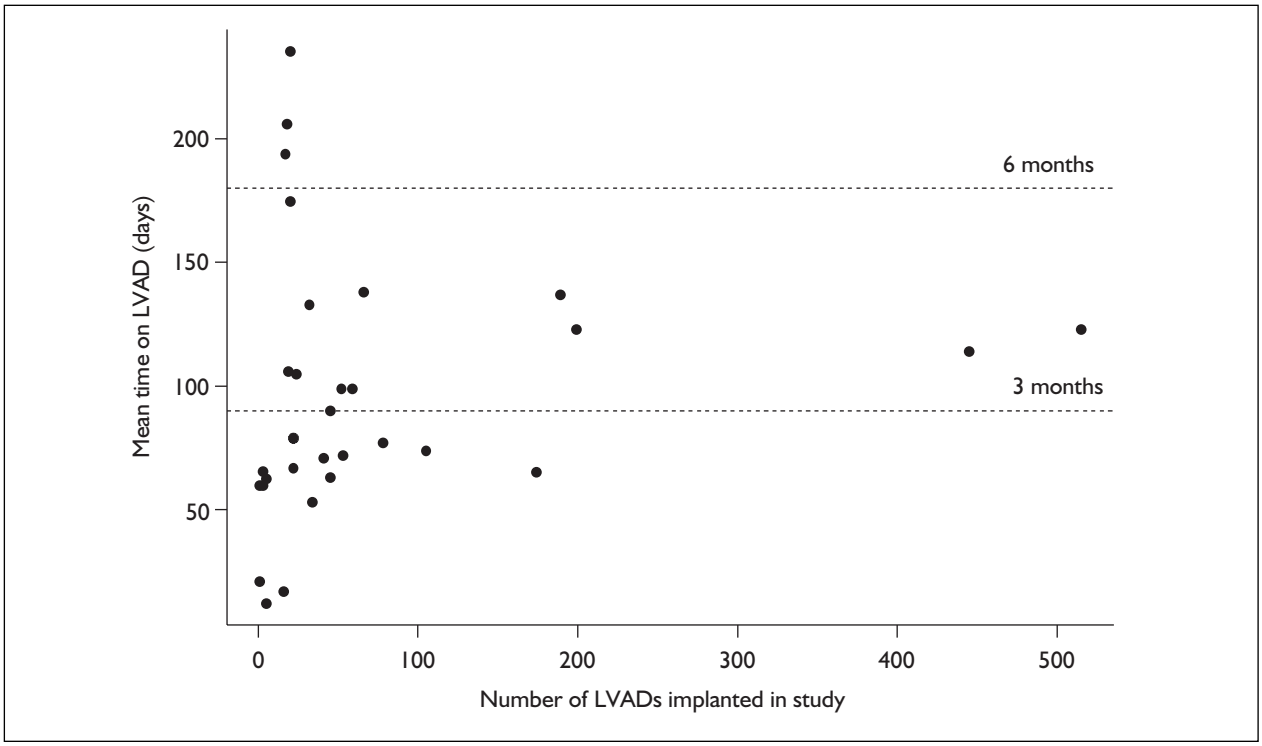

FIGURE 2 *Mean duration of VAD support by number of VADs implanted as a BTT. Where more than one VAD group was studied a separate point was plotted for each group.*

Survival studies

Survival to transplantation or explantation rates are plotted against study size in *Figure 3*. A crude estimate of an overall success rate of 62% was calculated by weighting each study's success rate by the size of the study. In *Figure 3* the dashed lines represent predicted 95% confidence intervals (including overdispersion) around the overall average of 62%. Most studies lie within these limits. However, there is clear publication bias in that 20 out of 22 (91%) studies of fewer than 100 patients have above average survival to transplantation or explantation rates, whereas larger studies are more evenly scattered around the average. Smaller studies were identified in the systematic review[5] and represent the most scientifically rigorous studies of the device. As such, they may be conducted in the most experienced centres. Large cohorts have slightly poorer success rates. These studies are likely to exclude fewer patients and to represent a greater proportion of early cases, although reporting is not sufficiently detailed to make an accurate assessment in most cases.

In the study comparing the HeartMate with the Novacor VAD,[14] survival was similar, with 12 out of 20 (60%) HeartMate patients and 13 out of 20 (65%) Novacor patients surviving to transplantation. These rates were consistent with those reported in case series. For example, in Rao,[22] of 131 patients with HeartMates implanted 93 (71%) were successfully bridged to transplantation and in Morgan[21] transplant rates were 33 of 52 (64%) pneumatic HeartMates, 11 of 17 (65%) dual-lead and 126 of 174 (72%) single-lead devices. In those who received transplants in this study, survival rates were 90.5%, 85.1%, 69.6% and 39.6% at 1, 3, 5 and 10 years after transplantation, respectively. A large series of 264 consecutive cases with VAD implants (HeartMate or Novacor) from Cleveland had similar transplantation rates of 69%, and overall survival rates of 64% at 12 months after VAD implant.[23] A report of 1348 patients from the Novacor registry suggested that 57% of patients had successful BTT or were successfully weaned and that success rates were related to centre volume, although the criteria for reporting to the registry were not described and the extent of selection was not clear.[25] A case series from a single centre using Novacor devices had transplant rates of 68% (15/22) in patients implanted between 1994 and 1998, rising to 89% (16/18) for patients implanted after this time.[26] A private communication with the Thoratec Company indicated that, of 1458 patients implanted with the Thoratec PVAD, who had known outcome by June 2005, 849 (58%) were

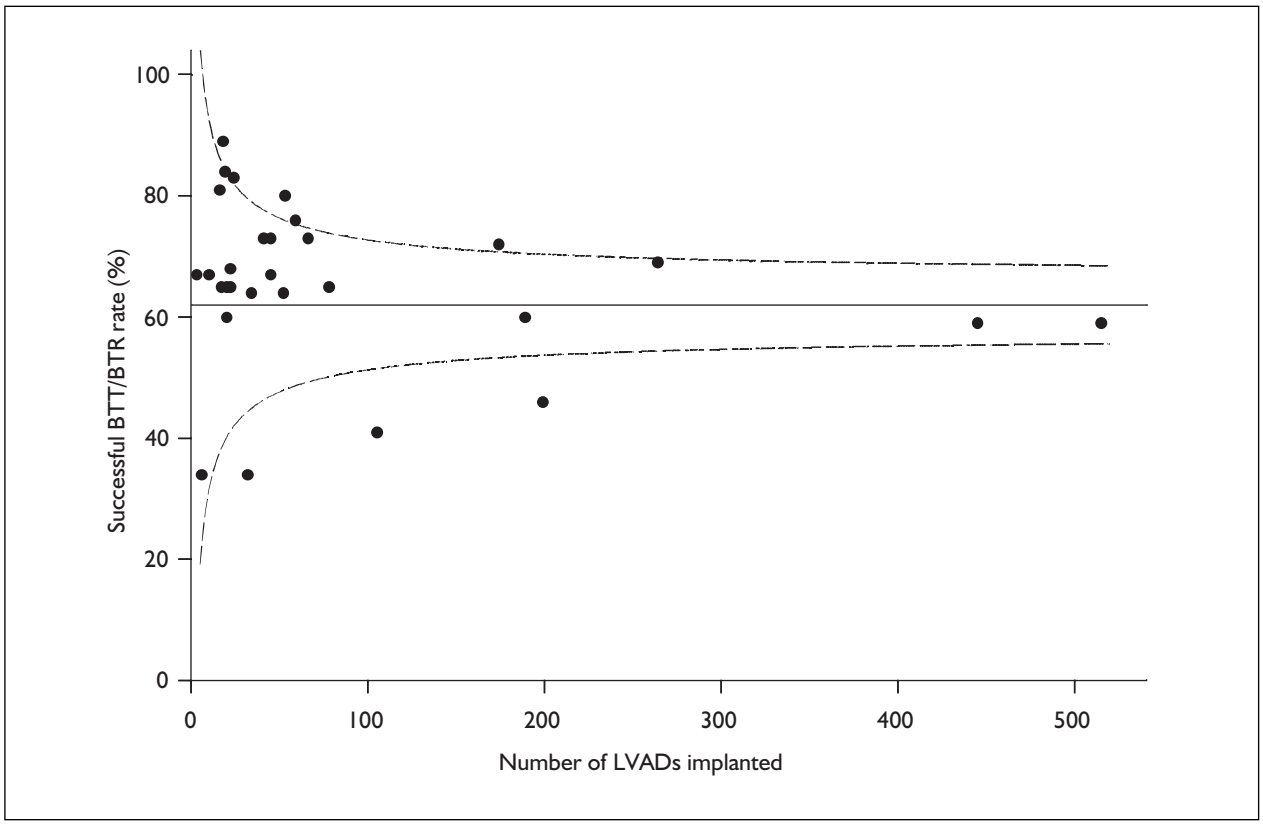

FIGURE 3 *Successful BTT/explantation rate by number of VADs implanted as a BTT. Where more than one VAD group was studied a separate point was plotted for each group.*

successfully bridged to either heart transplant (n = 841) or recovery (n = 8).

Aaronson and colleagues[15] compared 66 HeartMate patients with 38 inotrope-dependent patients and found that the groups had similar survival-to-transplant rates of 73% and 74%, respectively. However, after transplantation HeartMate patients had superior survival compared with inotrope-dependent patients at 1 year (98% versus 74%), 3 years (95% versus 65%) and 4 years (95% versus 65%) (p = 0.007). In addition, HeartMate patients had post-transplantation survival rates that were slightly superior to those of UNOS status 2 patients transplanted during the same period. Bank and colleagues[16] also compared post-transplantation survival for 18 HeartMate patients against 19 inotrope-dependent patients and found a greater 6-month survival rate in VAD patients (89% versus 74%) (p = 0.405).

Three studies compared patients supported with the HeartMate VAD with transplant candidates having routine medical management. In a cohort study, Massad and colleagues[17] showed that the transplant rate of 42 out of 53 (80%) HeartMate patients was close to that for patients on medical care (170/203, 84%). In addition, actuarial survival at 12 months after transplant was 94% in the HeartMate group and 88% in the medical management group. The other two studies were small and came from the same centre, so there may be some overlap.[18,19] Carrier and colleagues[29] conducted a similar study comparing 16 patients implanted with Thoratec devices with 20 routine transplant candidates. The successful transplantation rate was higher in the routine transplant candidates (100% versus 81%), as was actuarial survival at 12 months after transplantation (90% versus 84%).

In general, there was less information on success rates in second generation devices. The largest published series identified was a registry report of 150 patients with MicroMed DeBakey devices implanted, of whom 62 (41%) had successful transplantation and 68 (45%) died on support.[36] Mean support time was 74 days. These results are consistent with single-centre reports. Of 22 patients implanted with the Jarvik 2000 the transplant rate was higher at 59% (n = 13), with a further two patients remaining on support after 92 and 105 days postimplant.[32] Mean duration of support was similar at 67 days.

Functional improvement

Where reported (three studies), almost all patients accepted for VAD implantation were in NYHA class IV, with significant improvement post-transplantation for both first and second generation devices. Frazier and colleagues[18] reported on the 16 HeartMate patients who survived to 60 days after transplantation, at which time 15 were in NYHA class I post-transplantation and one was in class II. A subsequent study from the same group reported similar findings, but the extent of overlap of patients is unclear.[19] Westaby and colleagues[40] reported on ten patients implanted with the Jarvik 2000, all of whom were in class IV before implantation. Three patients died early, but the seven remaining patients were in NYHA class I after implantation.

Health-related quality of life

Published between 1996 and 2005, there were 11 reports identified that recorded some aspect of HRQoL; they came from four groups in the USA: the University of Pittsburgh,[41–43] Rush University Medical Centre, Chicago,[44–47] Columbia Presbyterian Medical Centre, New York,[48,49] and the Texas Heart Institute.[50] With the exception of the study by Miller and colleagues,[50] all studies were of first generation devices. All studies were derived from case series and excluded patients who had died or were too ill to complete self-report instruments. The potential for bias affects the quality of the studies and almost all patients were from US centres, which also limits generalisability. However, the reporting of HRQoL by Dew[41–43] and Grady[20,44–47] used reliable and well-validated instruments. Williams and colleagues[49] used the Short Form 36 (SF-36) and Miller and colleagues[50] used the Minnesota Living with Heart Failure Questionnaire, both well-validated HRQoL instruments. Moskowitz and colleagues[48] elicited utilities at three time-points: preimplantation, postimplantation and post-transplantation.

Grady and colleagues[20] reported changes in HRQoL from before to 2 weeks after HeartMate VAD implantation (n = 30) using the Sickness Impact Profile (12 subscales), the Heart Failure Symptom Checklist, the Rating Question Form, a Quality of Life Index, the Jalowiec Coping Scale and a VAD Stressor Scale. Patients reported more satisfaction with health and functioning and significantly less symptom distress 1–2 weeks after VAD implantation. Patients also reported more self-care disability and more dissatisfaction with social and economic areas of life at this time. This group subsequently performed longer term follow-up studies and noted that quality of life for patients who remained on VAD support was stable from 1 month to 1 year postimplantation. However, attrition was high and of 55 patients available for interview at 1 month only nine were available at 12 months, limiting generalisability.

Dew[41] and Grady and co-workers[46] reported on changes in HRQoL from before to after discharge following VAD implantation. Grady[46] observed good HRQoL both before and after discharge while supported by HeartMate devices, with discharge from hospital associated with increased satisfaction with socio-economic areas of life, decreased overall stress, and decreased overall physical and self-care disability. Dew[41] found that 11 discharged patients reported more concerns about stroke and device noise while trying to sleep, but fewer concerns about infection than inpatients. These studies primarily involve the Novacor and Thoratec devices.

The Pittsburgh group compared HRQoL post-transplant for 63 VAD patients (33 Novacor, 28 Thoratec, two Total Artificial Heart) and 90 non-VAD patients matched by demographic and medical characteristics.[43] Both groups of patients had similar physical functioning and emotional well-being after transplantation, but VAD patients had significantly lower cognitive functioning. The Rush group compared HRQoL before and after heart transplant for 40 BTT patients.[45] Patients were significantly more satisfied with their overall HRQoL, health and functioning, and experienced less physical and self-care dysfunction after transplantation.

Williams and colleagues[49] compared SF-36 scores in three groups: patients with HeartMate VAD support (n = 6), ambulatory status 1 and status 2 transplant candidates (n = 16), and transplant recipients (n = 5). VAD recipients and heart transplant recipients had superior energy, physical functioning and social role scores than other transplant candidates.

Moskowitz and colleagues[48] used a standard gamble technique to elicit utilities in 29 HeartMate patients at three time-points: preimplant, post-VAD implantation and post-transplantation. Mean utility values of 0.548 (SD 0.276), 0.809 (SD 0.136) and 0.964 (SD 0.089), respectively, were derived.

Adverse events

In a comparative study the HeartMate VAD had slightly higher rates of technical problems than

the Novacor.[14] Similarly, a large case series[23] found a higher device failure rate in HeartMate devices (20/218, 9%) than in Novacor devices (1/57, 2%). Device failure was reported in 4 out of 20 (20%) HeartMate patients in an early series,[16] but the Texas Heart Institute reported only a single mechanical failure due to a loose outflow connector in a series of 34 HeartMate implants (4%).[18] HeartMate device malfunction rates varied from 12.8% of cases[21] to 23% of cases.[51] The definition of device failure and malfunction and the detail with which it was reported varied widely.

Infection and thromboembolic events remain the most commonly reported complications. In a controlled comparison of the HeartMate and Novacor devices, the HeartMate had a higher rate of device-related infections (0.096 versus 0.025 per patient-month), particularly in the driveline.[14] Massad and colleagues[17] reported very high rates of septicaemia of 40% (21/53 patients) as a result of device-related infection. Grady and colleagues[51] reported infection rates as high as 83% of patients and Navia and colleagues[23] reported a rate of 1.88 per patient at 6 months after implantation. Most infections appear to have been treated successfully, but death from infection occurred in 5–20% of cases.

Thromboembolic events occurred less frequently than infection episodes, but cerebrovascular accidents (CVAs) remain a major cause of death in VAD patients. El-Banayosy and colleagues[14] reported a thromboembolic event rate of 0.026 per patient-month for Novacor patients, but did not observe these events in HeartMate patients. Similarly, in a large case series from Cleveland, Navia and colleagues[23] found that cerebral infarction rates were more common in patients who received Novacor devices than in HeartMate patients. In a series of 243 HeartMate patients from Columbia (New York), 5.3% (13/243) had a CVA within 30 days of implantation and 11 patients (4.5%) died as a result.[21] In addition, 11 patients (4.5%) had a transient ischaemic attack (TIA). Thromboembolic events were also seen in 73 out of 310 (24%) patients in a study of a subset of Novacor registry patients.[25] Stroke was a reported cause of death in other series of HeartMate patients,[15,22] Novacor patients[26] and Thoratec patients.[29]

Return to theatre for bleeding was a commonly reported adverse event. It occurred in 20% (4/20) of Heartmate patients and 30% of Novacor patients in the study comparing these two devices.[14] Massad and colleagues[17] reported a 6% return to theatre for bleeding rate for HeartMate patients, and Strauch and colleagues[26] reported a higher rate of 33% (13/40) for Novacor patients. Carrier and colleagues[29] reported a 31% rate in a series of 16 patients with a Thoratec device. A similar rate was reported by Granfeldt in a report of a Swedish centre experience using a range of devices.[39]

Right heart failure requiring right ventricular assist device (RVAD) support was reported in 5% of HeartMate and Novacor cases in the study that compared these devices,[14] and in 7%[21] to 12%[22] of other HeartMate series. Right heart failure requiring right ventricular assistance or exhibiting symptoms of severe dysfunction was reported in 21% (7/34) of HeartMate patients in one centre.[18] Right heart failure was reported in 10% (4/40) of Novacor patients.[26]

Published studies of outcomes for second generation devices were few and generally reported small case series. From the MicroMed DeBakey registry report of 150 cases it is clear that mechanical failure (n = 4, 3%), device-related infection (n = 5, 3%), thromboembolic events (n = 16, 11%) and return to theatre for bleeding (n = 48, 32%) were also observed in second generation devices.[36]

Bridge to recovery

There were 11 studies of the clinical effectiveness of VADs used as a BTR, ten using first generation devices and one using the second generation Incor device from Berlin. Seven studies were identified as part of the published systematic review and four were based on (relatively) large case series. These are listed in *Table 2*. Five studies were single case reports, two studies reported two cases and one study reported on six cases, one of whom also received support to the right ventricle; one other study reported on six cases successfully weaned from support and the remaining two recent studies reported on 22 and 28 cases, respectively, the largest series to date.

Overall, of those patients who were weaned 70–75% were men and the age of recipients ranged from 16 to 73 years.

Survival studies

For the case reports and small series of six cases or fewer, all patients survived to discharge, with the exception of the two Toyobo patients reported by Noda[60] and three of the patients described by

TABLE 2 *Summary of studies of effectiveness of VADs used as a bridge to recovery*

Study	Device(s) used
First generation VADs	
Kjellman *et al.*, 2000[52]	HeartMate (*n* = 1)
Pietsch *et al.*, 1998[53]	Novacor (*n* = 1)
Joharchi *et al.*, 2002[54]	Thoratec (*n* = 1)
Ueno *et al.*, 2000[55]	Thoratec (*n* = 1)
Farrar *et al.*, 2002[56]	Thoratec VAD (*n* = 9) or BiVAD (*n* = 13)
Gorcsan *et al.*, 2003[57]	Thoratec VAD (*n* = 3) or BiVAD (*n* = 3)
Marelli *et al.*, 1997[58]	Abiomed BVS 5000 (*n* = 1)
Nakatani *et al.*, 1998[59]	Toyobo (*n* = 5)
Noda *et al.*, 1989[60]	Toyobo (*n* = 2)
Second generation VADs	
Hetzer *et al.*, 2004[37]	Berlin Incor (*n* = 2)
Mixed first and second generation VADs	
Hetzer *et al.*, 2001[8]	Berlin Heart, Novacor, Thoratec, MicroMed DeBakey (*n* = 28)

Nakatani.[59] There were two recent relatively large case series reported. Farrar and colleagues[56] reported on 22 patients weaned from a Thoratec device at an average of 57 days after implantation (range 11–190 days). Of these 19 (86%) were alive at the time of analysis, 17 with their native heart and two after heart transplantation. Three patients died after explant, one who had received a heart transplant. Transplant-free survival postexplant of 86% at 1 year and 77% at 5 years was similar to that of VAD patients who had been bridged to transplantation. Hetzer and colleagues[8] described a cohort of 28 patients who were weaned from VADs in Berlin. Of these, 16 (57%) were alive with normal function 1 month to 5.5 years after explantation. Nine patients had poor LV function after explantation and were subsequently listed for transplantation between 1 and 17 months after explantation; eight survived to receive heart transplantation. Three patients died after VAD explantation and were not listed for transplantation.

There was only one report of weaning from a second generation device. Two patients were weaned from the Berlin Incor, both of whom were alive and transplant free at 4 and 6 months after explant.[37]

There was little information on functional status or HRQoL after weaning in the published studies.

Adverse events

Adverse events on support were rarely the focus of published studies of weaning from VADs and so reports were incomplete. Of the 71 BTR cases reported, 47 (66%) were alive and free of transplantation at last follow-up, although duration of follow-up varied from patient to patient.

Long-term circulatory support

In total, eight reports (seven studies) of the effectiveness of VADs used as long-term circulatory support were identified and these are listed in *Table 3*. Six reports were identified in the published systematic review, one report provided extended follow-up of the only published RCT and one report included a relatively large cohort of 27 patients.

The REMATCH multicentre trial published in 2001[12] was the only RCT of VAD use; longer term follow-up of patients in this trial was published in 2005.[61] Some articles published after the initial REMATCH paper described adverse events associated with the technology or specific subgroup analyses.[66–69] The REMATCH trial randomised 129 patients who were not suitable for cardiac transplantation to open-ended support with the HeartMate VE (*n* = 68) or optimal medical management (*n* = 61). Most patients were male with ischaemic cardiomyopathy and mean age was 68 years. Mean duration of support was 235 days (7.8 months).

All other studies were single case studies or small series of cases. Three of these articles reported exclusive use of first generation devices. There was a single case report of the Novacor N100 implanted into a 54-year-old man for 1514 days[62,70] and for another case the Toyobo

TABLE 3 *Summary of studies of effectiveness of VADs used as long-term circulatory support*

Study	Device(s)	Comparator
First generation VADs		
Rose *et al.*, 2001[12] REMATCH	Heartmate VE (n = 68)	Optimal medical management (n = 61)
Park *et al.*, 2005[61] (extended follow-up of REMATCH)	Heartmate VE (n = 68)	Optimal medical management (n = 61)
Dohmen *et al.*, 2001[62]	Novacor (n = 1)	None
Seki *et al.*, 1995[63]	Toyobo (n = 1)	None
El-Banayosy *et al.*, 2003[64]	LionHeart (n = 6)	None
Second generation VADs		
Frazier *et al.*, 2001[31]	Jarvik 2000 (n = 1)	None
Westaby *et al.*, 2002[40]	Jarvik 2000 (n = 7)	None
Mixed first and second generation VADs		
Jurmann *et al.*, 2004[65]	MicroMed DeBakey (n = 15), Berlin Heart (n = 6), LionHeart (n = 4), Novacor (n = 2)	None

provided support for 190 days.[63] El-Banayosy and colleagues[64] described implantation of the LionHeart into six men, mean age 65 years, with duration of support ranging from 17 to 670 days (mean 245 days).

There were three studies in which at least some second generation devices were used. There was one case report of a US man with idiopathic dilated cardiomyopathy, aged 61 years, implanted with the Jarvik 2000.[31] The same device was implanted into four UK and three German patients, all men with mean ages of 64 (UK) and 61 years (Germany).[40] Six patients had idiopathic dilated cardiomyopathy and one had amyloidosis. Duration of support ranged from 95 to 889 days in the four UK patients and 91 to 170 days in the German patients. Jurmann and colleagues[65] reported a single centre's experience of VAD use as open-ended support in 27 patients, 15 of whom had MicroMed DeBakey second generation devices. These patients were aged 66 years (SD 4) at implantation and all were men. Maximum duration of support was 953 days.

Survival studies

The REMATCH trial showed that there was a significant improvement in survival due to the HeartMate VAD.[12] Specifically, survival at 1 and 2 years after implantation was 52% and 23% in the VAD arm, compared with 25% and 8% in the medical management arm. The risk of death for VAD patients relative to controls was 0.52 (95% CI 0.34 to 0.78, p = 0.001). Park and colleagues[61] showed that survival was higher at 1 and 2 years for both VAD and control patients recruited in the second half of the trial.

In the small case series using the LionHeart VAD, all six patients survived the perioperative period, but three cases died of multiorgan failure at 17, 31 and 112 days after implantation.[64] The remaining cases had survived up to 18 months. The Novacor N100 was implanted into a 54-year-old man with contraindications to transplantation. He was supported for 1514 days, during which the pump had to be changed once.[62]

Jurmann and colleagues[65] reported survival at 1, 6, 12 and 24 months of 63%, 30%, 22% and 22%, respectively, in their cohort, lower than that reported in the REMATCH trial, despite use of some second generation devices. Of the eight patients (two studies) implanted with the Jarvik 2000, seven patients survived to discharge from hospital.[31,40] There was no further information on the case from the USA.[31] Two UK patients died at 95 and 382 days and two were alive on support at 642 and 889 days. At the time of analysis all three German patients were alive and supported by the Jarvik 2000 at 91, 93 and 170 days after implantation.

Functional status

There were few reports of functional status after VAD implantation. In an extended follow-up of the REMATCH patients Park and colleagues[61] reported that 126 out of 129 (98%) patients were in NYHA class IV at baseline assessment and that 71% of VAD patients were in class I or II at 12 months compared with only 17% in the medical management group. In a case series of four patients implanted with the Jarvik 2000,[40] all three surviving patients were in NYHA class IV at baseline, with two in class I and one in class II at

4 weeks after implantation. Siegenthaler and colleagues[71] reported that all three German patients implanted with the Jarvik 2000 were in NYHA class I or II at follow-up (range 14–93 days postoperatively).

Health-related quality of life

Only the REMATCH trial has reported HRQoL for patients implanted with a HeartMate VAD for long-term circulatory support.[12] All patients entering the RCT completed baseline assessment using the Minnesota Living with Heart Failure score, the SF-36 and the Beck Depression Inventory. At the 12-month follow-up only a limited number of patients survived and were able to be interviewed (VAD $n = 23$, Medical Management $n = 6$).

Scores on the physical function and role limitations due to emotional problems subscales of the SF-36 and the Beck Depression scale were significantly better in the device group than in the small number of controls surviving to 1 year. The Minnesota Living with Heart Failure score was better in the device group than the medical management group, but this difference was not significant.

Adverse events

The REMATCH study summarised serious adverse event rates for HeartMate and medical management patients.[61] In the medical management arm almost all patients died from causes related to their heart failure. Of 56 patients who died, the cause of death was left ventricular dysfunction in 52 (93%). In contrast, of the 57 HeartMate patients who died during extended follow-up[61] the most common causes of death were sepsis ($n = 21$, 37%), device failure ($n = 11$, 19%) and cerebrovascular disease ($n = 5$, 9%). HeartMate patients were more than twice as likely to have a non-fatal serious adverse event as medical management patients [relative risk (RR) 2.21, 95% CI 1.79 to 2.73, $p < 0.001$]. The excess was primarily due to an increase in non-neurological bleeding, neurological dysfunction and sepsis, as well as device-related events. Medical therapy patients had an excess of ventricular arrhythmias (RR 0.40, 95% CI 0.21 to 0.77, $p < 0.001$).

In a series of six patients receiving the LionHeart device, El-Banayosy and colleagues[64] observed temporary haemolysis and bleeding in three early after surgery, one of whom required reopening. Other early events reported were arrhythmia ($n = 2$), tamponade, gastrointestinal ischaemia and cerebrovascular accident. In addition, there were three device problems recorded, an outflow graft kink, low pump output and requirement for the controller to be changed. In this study there were three readmissions for adverse events, one urinary tract infection, one for bleeding from femoral haematoma and one controller change.

In the case series of 27 patients reported by Jurmann and colleagues,[65] there were 14 deaths within 30 days, mostly from sepsis and multiorgan failure ($n = 11$), and a further seven deaths after 30 days. VAD-associated complications reported were technical defects ($n = 2$), VAD arrests ($n = 4$ in three patients), pump replacements ($n = 6$), VAD component replacements ($n = 5$) and stroke/intracranial bleeding ($n = 8$ in five patients).

Adverse events reported in studies using second generation devices included one case each of dyspnoea, ventricular tachycardia, ventricular arrhythmia and transient ischaemic attack (TIA). In addition, one patient suffered power supply problems, one patient had an infection following a blood transfusion and one patient suffered syncope during battery change.

Summary

Despite the large number of publications, the evidence for effectiveness of VADs used for all indications is limited, with only a single randomised comparison. Overall, the methodological quality of the studies for assessing the effectiveness of VADs as BTT or BTR or for long-term circulatory support was weak.[5] Almost all studies were observational in design and therefore potentially biased. In the few studies with a comparison group there was little detail to judge the adequacy or relevance of the control groups and so potential for bias remains. Although the technology is changing rapidly, the evidence for improved effectiveness of second generation devices has yet to emerge.

For BTT, there was evidence of publication bias in smaller studies. However, from the evidence available, VADs appear to convey improved chance of survival to transplantation, possibly increased survival post-transplantation, improved functional status during the period of support and favourable HRQoL. Between 20 and 40% of patients died during VAD support, typically within the first 30 days, and there was a significant risk of adverse events such as device malfunction, infection, thromboembolic events and bleeding. There was insufficient published evidence on second

generation devices to make robust comparisons with first generation devices.

Overall, there was little information on BTR and most studies provided preliminary information. It was not possible to assess which devices were most effective.

There was one RCT of the HeartMate VE compared with optimal medical management, plus a number of case reports and small case series of VAD use for long-term circulatory support. Patients in these studies were generally older than those who were bridged to transplantation or recovery, with mean ages of over 60 years. In the REMATCH trial there was a significant improvement in survival due to VAD support, with 52% of patients surviving to 1 year after implantation, compared with 25% of medical management patients. The improvement in survival was greater in the second half of the trial (1-year survival of 59% versus 35% in first half of the trial). There was little published evidence from other studies, but these figures were in line with those six patients implanted with the LionHeart VAD (50% survival). There was some evidence of longer survival in patients who had the second generation Jarvik 2000, although this was based on only eight patients. There was evidence of a significant improvement in NYHA class following VAD implant, which was sustained to 1 year. In addition, the REMATCH trial provided some evidence of improved HRQoL. However, VAD use was not without problems in these patients. The most common serious adverse events associated with VAD for long-term circulatory support were device malfunction, sepsis, neurological complications and bleeding.

Chapter 3

Updated systematic review of the costs of left ventricular assist devices for severe heart failure

Introduction

This chapter provides a summary and update of the comprehensive systematic review by Clegg and colleagues,[5] including four new studies published up to March 2005. A brief summary of review methods is given in Chapter 2 and Appendix 1 and full details can be found in Clegg.[5] Owing to the small number of articles and the diversity of information supplied, the review is descriptive.

Studies identified

In total, 17 full studies and seven abstracts were identified and these are listed in *Table 4*. All studies were of first generation devices and there was some overlap between studies. The majority of published studies were based in the USA and involved simple cost estimation for a series of VAD patients. Therefore, these results are unlikely to be directly transferable to the UK context. One study by Skinner and colleagues[72] provided a cost–benefit analysis of antifungal prophylaxis, with no costs of the VAD implantation procedure or subsequent care, and was excluded from the review.

Cost-effectiveness analysis of VADs as BTT

Simple cost analyses

HeartMate

An early study by Cloy and colleagues[74] estimated pretransplant hospital costs for a group of six candidates on conventional medical therapy, six candidates supported by the HeartMate VAD and in hospital and a single patient supported by a HeartMate device at home. The VAD patient who could be discharged from hospital was associated with a cost saving of US$76,191 compared with those patients who could not be discharged. In addition, although the VAD patients spent longer in hospital than the medical therapy patients, the daily hospital charge was less, at US$3178 per day compared with US$5150 per day for non-VAD-supported hospital stay.

Two studies published as abstracts[77,78] both compared the costs of HeartMate VAD with inotrope-based care for status 1 patients at a single centre. The HeartMate group in the two studies had higher total hospital charges of US$291,651 and US$294,087, respectively, compared with US$183,233 and US$194,132 for the inotrope-dependent patients. Morales and colleagues[85] studied 90 consecutive patients implanted with the HeartMate VAD over a period of 6 years and compared those discharged with those who remained in hospital. The estimated mean cost of bridging to transplantation was US$13,200 for discharged patients and US$165,200 for inpatients during the same period (from implantation to transplantation). Costs of the device and implant procedure were not included in this analysis.

Recently, Digiorgi and colleagues[87] evaluated hospital cost and reimbursement for patients in the US who were discharged after HeartMate VAD implantation and returned to hospital for cardiac transplantation. To control for patient-specific variables, the VAD and heart transplant treatments were compared within the same patients (n = 36). To enable the distinction between VAD-related hospitalisation and heart transplant-related hospitalisation, only patients who were outpatients at the time of the heart transplant were included in the analysis. Components of resource use included length of stay (LOS) for all hospitalisations, readmissions and outpatient services and total actual hospital costs were applied (as opposed to hospital charges). Overall, average hospital costs for VAD implantation exceeded those of heart transplantation (US$197,957 versus US$151,646), reflecting longer initial hospitalisation both preoperation and postoperation and more readmissions. The authors acknowledge that a sicker patient population during the period of VAD implantation compared with the heart transplant period may explain these cost differences.

Novacor

Arabia and colleagues[76] studied three patients bridged to transplantation using the Novacor VAD, two of whom had heart transplants while the

TABLE 4 *Published studies of costs and cost effectiveness of VADs*

Study	Origin	Device	Sample
Bridge to transplantation			
Loisance *et al.*, 1991[73]	France	Not specified	37
Cloy *et al.*, 1995[74]	USA	HeartMate	13
Mehta *et al.*, 1995[75]	USA	Pierce-Donachy VAD	43
Arabia *et al.*, 1996[76]	USA	Novacor	3
Mir *et al.*, 1997[77] (abstract)	USA	HeartMate	23
Petty and Ormanza, 1997[78] (abstract)	USA	HeartMate	15
Christopher and Clegg, 1999[79]	UK	HeartMate/Novacor	Model
Couper *et al.*, 1999[80]	USA	ABIOMED BVS 5000	22
Christensen *et al.*, 1999[81] (abstract)	USA	Not specified	12
Kolbye *et al.*, 2000[82] (abstract)	Denmark	HeartMate/Biomedicus	NR
CETS, 2000[83]	Canada	Novacor	Model
Moskowitz *et al.*, 2000[84]	USA	Not specified	Model
Morales *et al.*, 2000[85]	USA	HeartMate VE	90
Schiller and Reichart, 2000[86]	Germany	Novacor N100P LVAS	23
Skinner *et al.*, 2000[72]	USA	HeartMate/Thoratec	36
Digiorgi *et al.*, 2005[87]	USA	HeartMate	36
Long-term circulatory support			
Oz *et al.*, 1997[88]	USA	Not specified	68
Gelijns *et al.*, 1997[89]	USA	HeartMate VE/Pneumatic	62
CETS, 2000[83]	Canada	Novacor	Model
Moskowitz *et al.*, 2000[84]	USA	Not specified	Model
Schulze *et al.*, 2000[90] (abstract)	Germany	Novacor	40
Miller *et al.*, 2002[91] (abstract)	USA, REMATCH	HeartMate VE	45
Oz *et al.*, 2003[92]	USA, REMATCH	HeartMate	52
Blue Cross Blue Shield, 2004[93]	USA	HeartMate (mainly based on REMATCH)	Model
Nelson *et al.*, 2005[94] (abstract)	USA	Not specified	13

CETS, Conseil d'Évaluation des Technologies de la Santé du Québec; NR, not reported.

other patient was discharged home with VAD support. Average hospital costs were compared with projected costs without VAD support and an average cost saving of US$46,893 was reported. The methodology and small sample size limit the generalisability of this study.

A larger study was carried out by Schiller and Reichart[86] to cost the Novacor VAD as a BTT based on 23 patients. The cost from implantation to transplantation was estimated to be €131,117 (approximately US$159,000) and the 3-year cost per day of survival was estimated to be €184 (approximately US$223).

ABIOMED BVS 5000

The study by Couper and colleagues[80] compared 22 patients implanted with the ABIOMED BVS 5000 with historical controls who had centrifugal pumps implanted (types not specified). In BTT patients ($n = 4$), the daily costs associated with the BVS 5000 were lower at US$455 per day compared with US$1271 for the historical controls. However, again the small sample limits the generalisability of the study.

Pierce-Donachy

Mehta and colleagues[75] compared 12 transplant candidates implanted with the Pierce-Donachy VAD on the US status 1 transplant waiting list with 31 concurrent status 1 patients maintained on optimal medical therapy. There was a trend towards improved transplantation rate in the VAD group (92% versus 68%) and there was a significantly higher mean cost for these patients (US$186,131 versus US$100,115, $p < 0.001$).

Unspecified device

One very early study by Loisance and colleagues[73] was based on patients accepted for transplantation between 1986 and 1989. They compared costs of the strategy of bridging using mechanical devices for patients who did not respond to inotropic support ($n = 6$) against continued inotropic support for patients who did respond ($n = 31$). The mechanical devices used in the study included the total artificial heart as well as VADs and bi-ventricular assist devices (BiVADs), limiting generalisability of the findings. However, the cost per patient transplanted at 1 year was US$254,000 for those on mechanical support compared with

US$192,455 for patients on inotropic support. One further abstract[81] compared seven VAD patients (type unspecified) who were discharged to an outpatient hostel with five who could not be discharged. The mean maintenance costs were US$1357 per day in the outpatient group and US$3441 in the inpatient group.

Cost-effectiveness analyses

HeartMate

The study by Kolbye and colleagues[82] was one of the first cost-effectiveness papers to appear, but was published in Danish, with only the abstract available in English. This paper compared the HeartMate VAD with a Biomedicus assist device. In this study the HeartMate was associated with an incremental cost per life-year gained of DKK170,000 (approximately US$28,000).

HeartMate/Novacor

Christopher and Clegg[79] published an early economic model to evaluate the cost–utility of the HeartMate and Novacor devices used as a BTT. Although the work was carried out in the UK, model inputs were mostly derived from Frazier,[95] with utility estimates taken from Moskowitz.[48] Extrapolating to 20 years and using discount rates of 6% for costs and 1.5% for benefits, the incremental cost per quality-adjusted life-year (QALY) for VAD patients was estimated at £39,790 relative to non-VAD. Given the preliminary nature of the inputs and the considerable uncertainty in extrapolating beyond the lifetime of the studies, the variance surrounding the cost-effectiveness estimates is likely to be large. Clegg and colleagues[5] published an economic analysis of the HeartMate as a BTT. The model was estimated using survival data from Aaronson[15] with mean time to implant of 4.6 months for VAD patients and 7.2 months for medical management. Utilities were taken from an American study by Moskowitz and colleagues.[48] Cost estimates were taken from a number of sources, but primarily from communications with the device manufacturers and with Papworth Hospital. The time-horizon was 5 years from implantation. In this study a cost per QALY of £65,242 (95% CI £34,194 to £364,564) was calculated. The estimate was particularly sensitive to the implantation and acquisition costs of the devices.

Novacor

In 2000 CETS conducted a comprehensive economic evaluation of the Novacor VAD when used as either BTT, BTR or long-term circulatory support.[83] Assuming a discount rate of 5% and extrapolating post-transplantation survival to 12 years, the incremental cost per life-year gained for VAD use as a BTT relative to routine care was estimated to be Can$117,197 (approximately US$95,000).

VADs as long-term circulatory support

Simple cost analyses

HeartMate

Gelijns and colleagues[89] calculated the initial hospitalisation and outpatient costs for 12 HeartMate patients and projected these estimates to 12 months. The mean actual cost of HeartMate support over 9.5 months was US$221,313, with the initial hospitalisation accounting for 64% of the costs. The main resource-use and cost components were the device, intensive care unit (ICU) stay and initial hospital stay and readmissions.

Oz and colleagues[88] published a paper in 1997 describing methodology for costing VADs using the REMATCH patients, but did not provide original cost data themselves. Preliminary cost data from the US REMATCH patients appeared in an abstract in 2002.[91] A subsequent paper, in 2003,[92] evaluated the cost of hospital resource use, and its predictors, for a cohort of long-term VAD patients (over 1 year) enrolled in the US REMATCH trial (n = 52). A ratio of cost to charges was calculated for each major resource category, which included the cost of the device, implanting, hospitalisation and readmissions to acute or intermediate care facilities. The mean LOS for the initial implant-related hospitalisation was 43.5 days, yielding a mean cost of US$210,187 (2003 US dollars). The leading resource-use components were days in ICU (average cost of US$50,262) and the device cost (average cost of US$62,308). Multiple regression modelling revealed that sepsis, device-related infection and perioperative bleeding were significant predictors of implantation cost, while for patients who survived the procedure (n = 35), bypass time, perioperative bleeding and late bleeding were the predictors of cost. During the follow-up period there was an average of 4.5 readmissions per patient who survived, with an average readmission cost of US$30,627. The average annual readmission cost per patient for the overall cohort was US$105,326. The authors acknowledge that, because VAD is an evolving technology, there are several opportunities for improvement that may reduce future costs. For example, improvements in the design of devices that may help to reduce

infections, innovative approaches to the management of perioperative bleeding and improvements in patient selection could all help to reduce overall costs of long-term VAD treatment.

The study by Clegg and colleagues[5] also provided a UK-relevant economic model of the HeartMate used for long-term circulatory support. The model estimation relied heavily on the REMATCH trial for survival and costs and derived utilities using a panel-based approach. Baseline cost per QALY was estimated to be £170,616 over 5 years. This figure was robust to a range of sensitivity analyses.

ABIOMED BVS 5000

The study by Couper and colleagues[80] included 12 postcardiotomy patients implanted with the ABIOMED BVS 5000 who might be considered as long-term circulatory support patients. For these patients the mean cost of support with the ABIOMED BVS was US$1146 per day compared with US$1369 per day for historical control on centrifugal VADs. The controls costs were not based on real patient costs and were dependent on a range of assumptions, thus limiting the generalisability of the study.

Novacor

One published abstract[90] reported hospital costs based on ten Novacor VAD patients compared with ten heart transplant patients and 20 patients implanted with a biventricular pacemaker (with or without an implantable cardiac defibrillator). Excluding the device, mean hospital costs were higher for VAD patients, at €62,142 (approximately US$75,000), compared with the other patient groups. Again, the small sample size and lack of detailed information given in the abstract are limitations of this study.

Unspecified device

There was a single abstract reporting on costs associated with VAD use at the most recent meeting of the International Society of Heart and Lung Transplantation.[94] This paper compared 13 patients implanted with VADs after the REMATCH study, with published results from REMATCH (n = 52) and the subset of REMATCH patients after January 2000 (n = 34). The 13 post-REMATCH patients had a significantly lower mean cost of VAD implantation than the REMATCH patients (US$141,000 versus US$210,000, $p < 0.001$), mostly due to earlier discharge from hospital. However, a lack of detail in the abstract limits interpretation of this study.

Cost-effectiveness analyses

HeartMate

A Blue Cross Blue Shield study evaluated the cost-effectiveness of VADs as destination therapy compared with optimal medical management among patients who were ineligible for cardiac transplantation.[93] The economic evaluation involved a Markov model which followed a hypothetical cohort of VAD and medical management patients (numbers not given) over a 3-year period. The main categories of costs included in the model were the VAD implantation costs, readmission costs and outpatient costs. The study assumed that monthly readmission and outpatient costs were the same for patients receiving VADs and medical management. Data on the probability of readmission, VAD implantation costs and monthly readmission costs were obtained from Oz.[92] Monthly outpatient costs were estimated from the studies by Moskowitz and colleagues[96] and Gelijns and colleagues.[89] Survival probabilities were estimated from REMATCH trial data,[12,97] and utility estimates for two quality of life categories: NYHA classes I/II and NYHA III/IV, were taken from Moskowitz[48] in order to produce QALY estimates.

With costs and utilities discounted at 3%, the VAD Markov model produced a total of 0.755 QALYs at a total cost of US$391,900 (2004 US dollars) and the medical management model produced 0.332 QALYs at a cost of US$53,025. The incremental cost per QALY for the VAD group relative to the medical management group was therefore US$802,700 per QALY. The results of one- and two-way sensitivity analyses showed that the incremental cost-effectiveness ratio (ICER) remained fairly stable for changes in most of the underlying variables (e.g. cost of readmission or outpatient care), but was more sensitive to variations in utility for NYHA category I/II and the cost of the VAD implantation.

The authors acknowledge a number of limitations of this analysis. First, the simplicity of the Markov model, which included only two health states (alive and dead), was criticised. The simplicity of the model meant that it was unable to show the impact on quality of life of readmission due to adverse events and device malfunction (which was significantly higher in VAD patients in the REMATCH trial). The utility values used for the NYHA categories in this analysis were derived from BTT patients,[48] which may differ from utility values for destination therapy patients, even within the same NYHA categories. Another issue is that the analysis used monthly readmission and

outpatient cost estimates based only on VAD patients from other published studies and assumed that these costs were the same for both VAD and medical management patients. In terms of readmission costs, this may be rather misleading since results from the REMATCH trial showed VAD patients to have a significantly higher rate of serious adverse events and device malfunctions.[12] Furthermore, outpatient costs were estimated from VAD BTT patients[89,96] and not destination therapy patients. Finally, another limitation of the analysis is that the readmission probabilities used in the model were held constant over time for both patient groups, which is unrealistic.

Novacor

The CETS study[83] also modelled Novacor VAD used as long-term circulatory support. For this indication, assuming a 5% discount rate and extrapolating costs and survival to 12 years, the estimated incremental cost per life-year gained ranged from Can$67,883 (approximately US$55,000) for elective implantation to Can$57,628 (approximately US$46,000) for emergency implantation.

Unspecified device

Moskowitz and colleagues[84] produced a cost–utility analysis based on an economic model and utilities elicited from 29 BTT patients. Utilities of 0.75 were assumed for VAD patients and 0.55 for medical management patients. For patients with hospital stay of 17.5 days the incremental cost per QALY for VADs relative to medical therapy was between US$37,274 and US$46,921 depending on the efficacy of the device. Corresponding figures for patients with hospital stay of 45.5 days were US$45,756 and US$61,762.

Summary

In terms of BTT, there were a few simple cost studies and they focused either on the cost of the initial VAD implant or on the cost of hospital stay compared with discharge to outpatient status. Initial VAD implantation costs ranged from US$159,000[86] to US$294,000.[78] However, the methods used and the cost components included in these studies varied widely. Similarly, after the initial implant, daily costs varied across the studies, although it was clear that patients who could be discharged from hospital with support incurred less cost than those who remained in hospital. The main cost drivers highlighted were the device itself, staffing, ICU stay, duration of hospital stay for initial implantation and adverse events such as bleeding, stroke and infection.

Three economic models of BTT, compared with medical therapy, have been published. These date from 1999 and 2000 and are based on relatively small observational studies. Cost per life-year gained was approximately US$28,000 in Kolbye[82] and US$95,000 in the CETS study. The only study to emerge from the UK[79] used published data from US studies for the model inputs and estimated a cost per QALY gained of approximately £40,000.

For VADs as long-term circulatory support there were three simple cost studies that reported implant costs of US$75,000 (excluding device), US$141,000 and US$210,000, respectively, with the cost of implantation decreasing with date of publication.

Three economic modelling studies of long-term circulatory support, compared with medical therapy, have been published. Two were published in 2000[83,84] and the Blue Cross Blue Shield was published in 2004. The two earlier models are based on observational studies and one lacks detail in terms of the costs, time-horizon and other model inputs.[84] The incremental cost per QALY in this study ranged from US$37,000 to US$61,000. The CETS model was more comprehensive, but used cost per life-year gained rather than QALYs. The results from this analysis yielded a range of ICERs from Can$46,000 to Can$55,000 per life-year gained if costs and death rates were extrapolated over 12 years. The BCBS report was predominantly based on the REMATCH trial. The incremental cost per QALY in this study was extremely high, at over US$800,000.

In summary, there remain relatively few published studies of cost-effectiveness or cost–utility of VADs as either BTT or long-term support. In general, methodology was weak and seven studies were in abstract form only. Further studies based on actual patient resource use, in a UK context, with longer term follow-up, and more comprehensive modelling, are required. One such study was conducted by Clegg and colleagues,[5] but, to date, has yet to be published.

Chapter 4

UK study: methods, population characteristics, survival and clinical results

UK study: methods

The objectives were:

- to summarise all NSCAG-funded VAD activity in the UK in the period April 2002 to December 2004, with follow-up to March 2005
- to summarise transplant listing, procedures and survival for all transplant candidates in the period April 2002 to December 2004, with follow-up to March 2005.

UK study: patients and devices

All VADs implanted into patients in the UK as part of the NSCAG-funded VAD programme during the period April 2002 to December 2004 were included in the study. Implanting centres were Harefield and Papworth from April 2002 and the Freeman, Newcastle, from September 2003. Devices used in the UK during this period were the HeartMate (VE and II), Thoratec [percutaneous ventricular assist device (PVAD) and IVAD] and the Jarvik 2000. Devices designed for short-term support (<30 days) are not included in this report unless they were used in combination with one of the larger VADs.

Current NSCAG recommendations support VAD use as a BTT or BTR. Therefore, for the phase of clinical development in question, the indications for VAD implantation were:

- patients who were appropriate candidates for cardiac transplantation [transpulmonary pressure gradient (TPPG) <14 mmHg, $V\dot{O}_{2max}$ < 14 ml kg^{-1} min^{-1}, cardiac index <2.1 l min^{-1} m^{-2}, no active infection or malignancy, no recent pulmonary embolism] or who would become appropriate for a transplant following a period of VAD support
- who had *rapidly* deteriorating heart function and
- clearly would not survive long enough to be transplant recipients despite the provision of an '*urgent*' category nationally
- to a total activity of around 10% of the total annual cardiac transplantation activity.

UK study: groups

In this context a randomised comparison was considered unethical since the patients in this treatment programme would be very unlikely to survive for long enough to receive a heart transplant, despite the provision of an 'urgent' category nationally. Therefore, several approaches to providing imperfect but appropriate comparative information were taken.

The study groups were:

Group A: the group of primary interest comprised those patients who present with requirement for implantation of a VAD (see list above). One patient during the study period had been listed for transplantation, had subsequently required intravenous inotropic support and finally was given a VAD owing to unstable cardiac function.
Group B: the most similar, readily available group was the subgroup of patients accepted for heart transplantation who had a preoperative requirement for intravenous inotropic support, but did not receive VAD implantation. Survival, HRQoL and resource-use data were recorded for these patients.
Group C: in recognition of the fact that group B may be small or may be difficult to identify prospectively for logistic reasons, the survival experience of routine non-inotrope-dependent heart transplant candidates was also recorded. A random sample of these patients (of similar size to the VAD population) was recruited to compare the resource use and HRQoL of these patients with the VAD-implanted patients before and after transplantation/explantation.
Group D: a hypothetical scenario in which all VAD patients were assumed of very high risk and unable to survive to transplantation, despite the provision of an urgent category, specifically within 30 days of presentation, mean 15 days.

UK study: outcome measures

Outcome measurement for the evaluation was focused on survival and HRQoL, as well as broad indicators of the performance of the VADs in all patients.

The end-point of the study is patient death, irrespective of cause and whether or not the VAD was functioning normally. For the VAD group, measurement of survival time was from implantation and included survival to and following subsequent transplantation or explantation of the VAD. For the non-VAD groups measurement of survival time was from listing for transplantation to the end of the study. Patients were censored at the end of the study period of 31 March 2005. There was no loss to follow-up in this cohort.

The EuroQol 5 Dimensions (EQ-5D)[98] has been used in many studies of cost-effectiveness as a measure of the value that a general population attributes to life in a particular condition.

In addition, generic [SF-36, Functional Limitations Profile (FLP)] and VAD-specific questionnaires were used for the measurement of HRQoL. The questionnaires were administered within 1 month of VAD implantation (group A) or listing (groups B and C), 3-monthly before transplantation and at 3, 6, 12 and 24 months after transplantation until the end of the study period, 31 December 2004. Full details of the HRQoL study are reported in Chapter 5. Specific questionnaires administered are listed in *Table 17* and cover the domains of physical and social functioning, psychological well-being, cognitive functioning and VAD-specific issues.

The study aimed to estimate costs to the NHS. Resource-use information for all three groups was assessed to compare the costs attributed to the three courses of clinical management. Full details of resource use are reported in Chapter 6, technical details of the cost-effectiveness model are described in Chapter 7 and results of the cost-effectiveness analysis are presented in Chapter 8.

UK study: clinical measurements

Information on the key clinical characteristics of patients assessed for VAD implantation was recorded as part of the clinical evaluation. Additional clinical data on VAD patients, and on the technical performance of the device, were collected as part of the integrated data system for the study, but are not the main focus of this study.

The following post-VAD insertion morbidity was recorded where possible:

- device-related bleeding:
  - bleeding requiring surgical exploration for resolution *or* blood transfusion requiring more than 5 units of packed red blood cells within a 24-hour period.
  - cardiac tamponade: accumulation of pericardial fluid resulting in haemodynamic compromise and requiring surgical intervention
  - reoperation: any surgical intervention after the patient has left the operation room postimplantation, excluding reoperation for bleeding or cardiac tamponade
- haemolysis: plasma free haemoglobin level greater than 40 g l^{-1} on two consecutive days
- infection: any positive culture of body tissue or fluid requiring treatment with antibiotics (excluding prophylactic antibiotics) or other antimicrobial medication
- stroke/TIA: constellation of focal neurological deficit, sudden or rapid in onset, clinically demonstrated with or without an identified lesion on computed tomographic (CT) scan, specifically:
  - neurological deficits that persist for at least 24 hours, due to documented disturbance of the cerebral circulation (CVA; specify ischaemic/haemorrhagic)
  - acute onset of neurological deficits, associated with cerebral ischaemia, that resolves completely in less than 24 hours (TIA)
  - focal central neurological deficit that begins abruptly and is not caused by cerebrovascular disease
- thromboembolism: deficit in any non-cerebrovascular organ system (pulmonary, renal, hepatic, splenic or limb) demonstrated to be due to acute vascular occlusion through standard diagnostic assessment or at autopsy
- right ventricular dysfunction: requirement of mechanical support of the right ventricle (RVAD), or central venous pressure (CVP) >18 mmHg with cardiac index <2.0 l min^{-1} m^{-2} despite maximum pharmaceutical support, in a normovolaemic patient in the absence of tamponade, pneumothorax or device failure
- renal dysfunction: serum creatinine greater than 300 µmol l^{-1} after postoperative day 1 or function deterioration requiring replacement therapy (filtration, dialysis) after postoperative day 1
- hepatic dysfunction: increase three times above normal in any two of the four liver indices {bilirubin, serum glutamic pyruvic transaminase [SGPT], serum glutamic oxaloacetic transaminase (alanine aminotransferase), [SGOT (ALT)], or lactate dehydrogenase [LDH]} after postoperative day 3

- cardiovascular dysfunction: abnormal function of the cardiovascular system [e.g. new arrhythmia, new myocardial infarction (MI), systemic hypertension, systemic hypotension, pulmonary hypertension] that occurs more than 24 hours postimplantation.
- respiratory dysfunction: continued ventilator support for more than 5 days postimplantation, or subsequent reintubation for respiratory distress (excluding reoperation or temporary intubation for diagnostic or therapeutic procedures)
- device system failure: mechanical device ceasing to function in the prescribed fashion:
  - blood pump/drive failure: any structural malfunction of the pump/drive unit resulting in the inability of the pump to provide adequate circulatory support
  - control system failure: any malfunction of an external wearable control component (i.e. controller, power pack, monitor or interconnecting cable) that results in the inability to provide adequate circulatory support including, but not limited to, failure to respond to commands, failure to respond appropriately, circuit failure or power supply failure
- time to and rate of discharge to home following VAD implantation
- NYHA dyspnoea score at discharge following VAD implantation and VAD explantation (after transplantation or recovery)
- transplantation rate
- pretransplantation and post-transplantation/explantation mortality
- percentage overall survival at 30 days and 1 year, including median survival (50%) by VAD type
- evidence for recovery of the patient's heart before and after VAD explantation

UK study: statistical methods

Clinical data were collected using standardised data collection forms at each of the three centres and for the period of the evaluation in all patients, except for items specific to VAD patients only. Device-related information was recorded as appropriate. Patient characteristics are summarised as the number (percentage) in each group or the mean and standard deviation for interval measurements.

The Kaplan–Meier product limit method was used to estimate time on the VAD, time listed, survival from listing or device implant and survival post-transplantation. Kaplan–Meier estimates were compared using a log-rank test.

For group A time on the device was calculated from the day of implantation to the day of death or the day of removal, irrespective of the reason for removal, transplant or recovery. Patients alive on VAD support at 31 March 2005 were treated as censored.

For groups B and C time on the transplant waiting list was calculated from the day of listing to the day of death or the day of removal, irrespective of the reason for removal. Patients who were removed from the active waiting list were censored on the day of removal. Patients alive on the waiting list at 31 March 2005 were treated as censored.

For group D mean survival time was fixed at 15 days.

For all groups overall survival was estimated from the day of VAD implantation (group A) or transplant listing (groups B and C) to the day of death or censored at 31 March 2005. Similarly, post-transplantation survival was estimated from the day of the transplant procedure to death, with surviving patients censored at 31 March 2005.

UK study: results – VAD patients

UK study: VAD patients and devices

During the period April 2002 to December 2004 a total of 70 patients had a VAD implant in the UK study cohort, a rate of 25.5 per year. Patient characteristics for the group are summarised in *Table 5*. This table shows that the mean age, gender and primary diagnosis distribution for VAD patients were similar in the three centres involved in the evaluation. However, there were significant differences in the types of device implanted. Specifically, Papworth and the Freeman implanted exclusively Thoratec and Heartmate devices (first generation), while Harefield also implanted 13 Jarvik 2000 devices (second generation), which have more potential as a long-term mechanical circulatory assist device. Patients with right heart failure requiring biventricular support also had an RVAD implanted.

One patient had a HeartMate I VAD explanted after 7 months owing to device malfunction and a second device (Thoratec PVAD) was implanted. On examination the explanted device was infected with candida. For this patient total time supported and total survival time are used in the analysis. The replacement is incorporated into the resource-use analysis.

TABLE 5 *VAD patient characteristics by implanting centre*

Variable	Freeman (*n* = 3)	Harefield (*n* = 39)	Papworth (*n* = 28)	Overall (*n* = 70)
Age (years)				
Mean (SD)	48.57 (11.73)	41.25 (13.65)	42.06 (12.35)	41.89 (12.97)
[range]	[35–57]	[20–63]	[16–59]	[16–63]
Gender, *n* (%)				
Male	3 (100)	32 (82)	24 (86)	59 (84)
Female	0 (0)	7 (18)	4 (14)	11 (16)
Diagnosis, *n* (%)				
DCM	2 (67)	24 (62)	15 (56)	41 (59)
IHD	1 (33)	11 (28)	8 (30)	20 (29)
Other	0 (0.0)	4 (10)	4 (15)	8 (12)
Devices used, *n* (%)				
VAD only	1 (33)	29 (75)	16 (57)	46 (66)
BiVAD	2 (67)	10 (26)	12 (43)	24 (34)
VAD type, *n* (%)				
Heartmate I VE	0	12 (31)	2 (7)	14 (20)
Heartmate II	0	1 (3)	0	1 (1)
Thoratec PVAD	3 (100)	12 (31)	10 (36)	25 (36)
Thoratec IVAD	0	1 (3)	16 (57)	17 (24)
Jarvik 2000	0	13 (33)	0	13 (19)
RVAD type, *n* (%)				
Thoratec PVAD	2 (100)	7 (70)	7 (58)	16 (67)
Thoratec IVAD	0	1 (10)	5 (42)	6 (25)
Levtronix	0	2 (20)	0	2 (8)
Replacements, *n* (%)		1 (3)		1 (1.4)

DCM, dilated cardiomyopathy; IHD, ischaemic heart disease; VE, vented electric.

Figure 4 shows the experience of this cohort of patients up to the end of March 2005. Of the 70 patients, 31 (44%) underwent heart transplantation, four (6%) recovered myocardial function and had the VAD explanted and five (7%) had a VAD in place on 31 March 2005. The remaining 30 patients (43%) died with a VAD *in situ*. Causes of death for these patients are given in *Table 6*. Of the 31 patients transplanted, five (16%) died and 26 (84%) were alive on 31 March 2005. There was no association between cause of death and type of device. The single device-related death was caused by failure of a Jarvik 2000 pump while the patient was discharged from hospital.

There were no significant differences in survival between Harefield and Papworth ($p = 0.288$) (*Figure 5*) and the Freeman only completed three implants. Therefore, all three centres are combined in subsequent analyses.

UK study: patient and VAD survival

Time on VAD

The mean and median time with a VAD were estimated from Kaplan–Meier curves, with the event defined as removal of the device owing to transplantation, myocardial recovery or patient death. Patients alive with a VAD at 31 March 2005 were censored. Time with a VAD implant is summarised in *Table 7* and plotted for the UK study overall in *Figure 6* and by device type in *Figure 7*. The median time on the VAD was 82 days, with Harefield patients supported for significantly longer periods than Papworth patients ($p = 0.004$). The median time with a VAD at Harefield was 57 days if the 13 patients implanted with the Jarvik 2000 are excluded,

TABLE 6 *Causes of death during VAD support*

Cause of death	Number (% of deaths)
Multiorgan failure	15 (50%)
Cerebrovascular accident	7 (23%)
Sepsis/infection	4 (13%)
Device failure	1 (3%)
Congestive cardiac failure/MI	1 (3%)
Respiratory failure	1 (3%)
Haemorrhage	1 (3%)

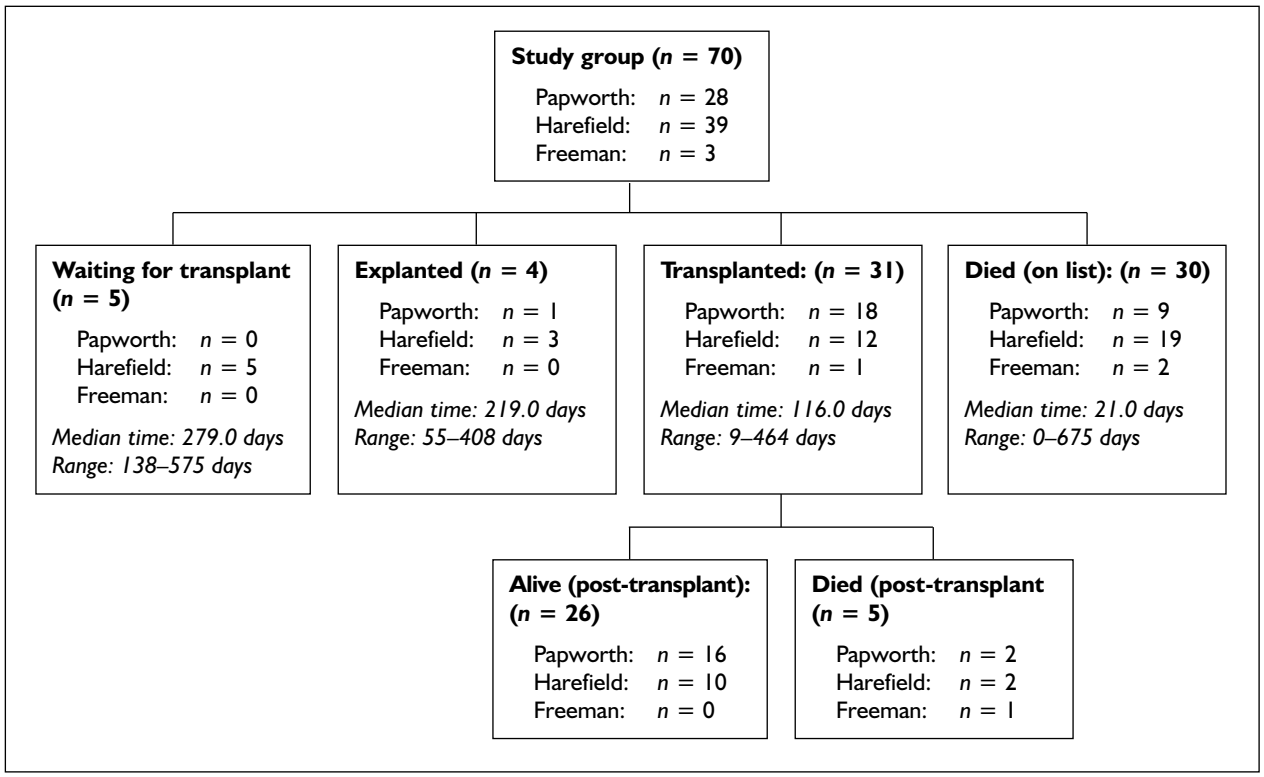

FIGURE 4 *VAD patients CONSORT diagram (n = 70). Implantation dates from 9 May 2002 to 26 December 2004, follow-up until 31 March 2005.*

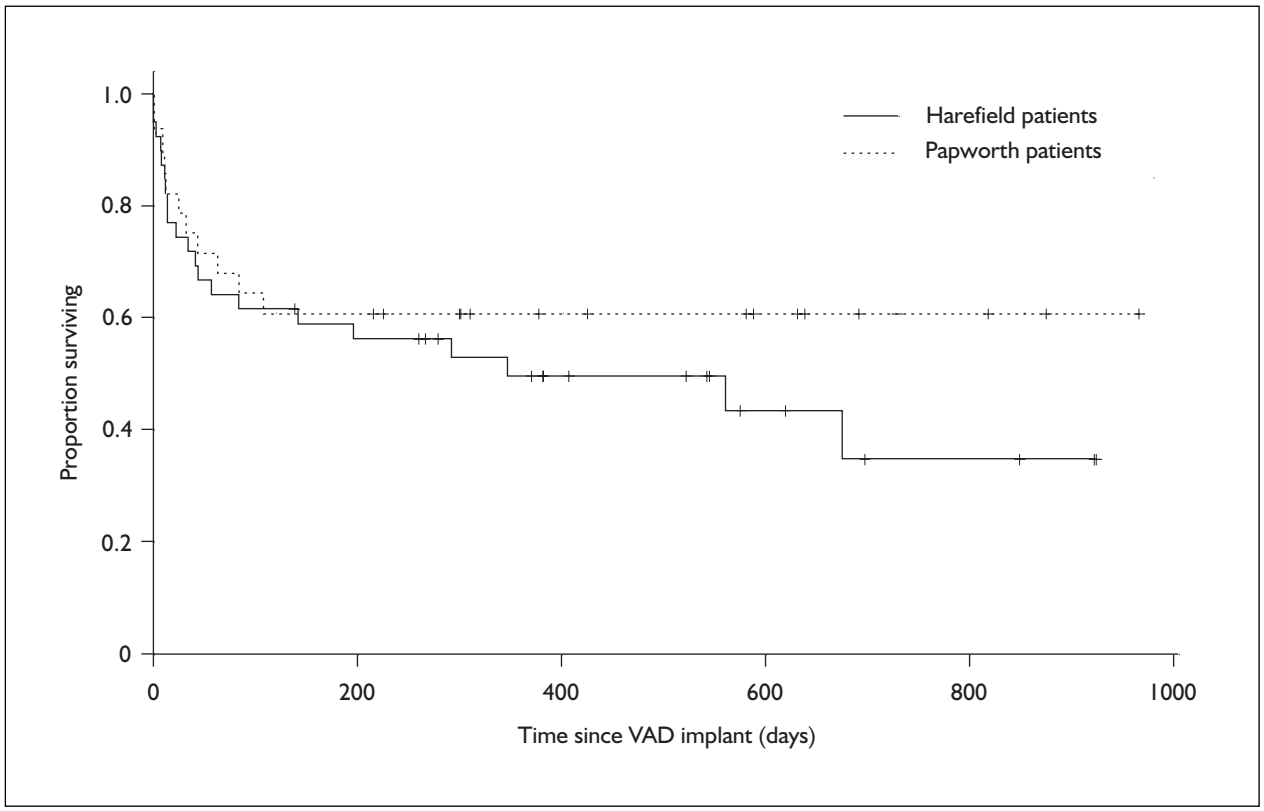

FIGURE 5 *Overall survival of patients by centre*

TABLE 7 *Time (days) with VAD support by implanting centre*

	Freeman	Harefield[a]	Papworth	Overall
Events	3	34	28	65
Median (95% CI)	22 (20 to –)	125 (50 to 292)	63 (32 to 115)	82 (46 to 125)
Mean (SE)	35.3 (11.7)	205.0 (35.0)	87.9 (16.7)	149.0 (21.6)

[a] Includes total time supported for one patient who had a malfunctioning VAD replaced.
NB: A dash (–) indicates that this figure could not be calculated because only a small proportion of patients had died.

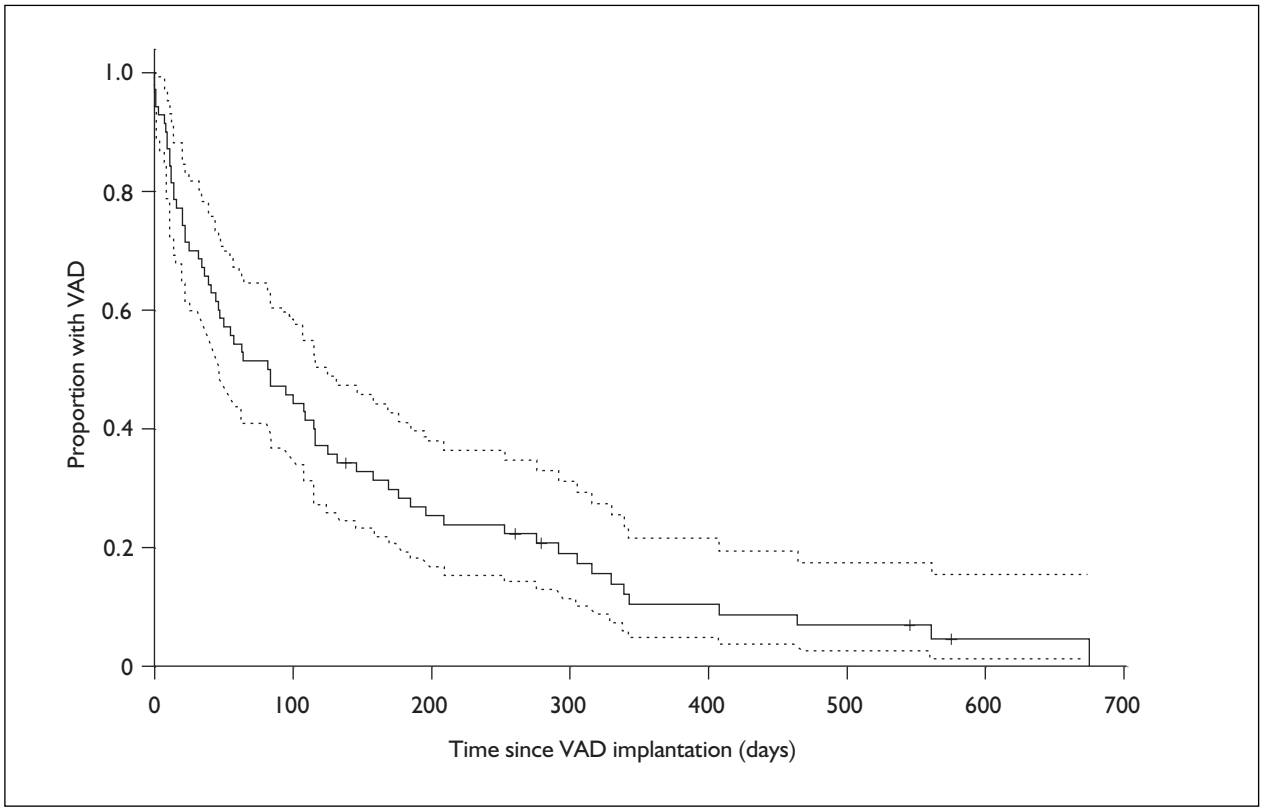

FIGURE 6 *Kaplan–Meier estimates and 95% confidence limits of time supported by VAD (n = 70)*

similar to Papworth patients. The 13 patients implanted with a Jarvik 2000 were supported for a median of 292 days. The Jarvik is a second generation device with a perceived capability for longer term support, so that pressure to transplant was less acute for these patients.

Survival overall

To assess the overall survival experience of patients implanted with a VAD, survival time was calculated for all patients from initial implantation, with death of a patient from any cause the event of interest and all other patients censored at 31 March 2005. The results are summarised in *Table 8* and plotted in *Figure 8*. The proportion alive at 1 year after VAD implantation was 52% (95% CI 41 to 65%). There were no differences in overall survival rates between Papworth and Harefield ($p = 0.288$). There was some evidence that Jarvik 2000 patients had improved median survival (561 days versus 347 days), but the difference was not significant ($p = 0.514$); 12-month survival was 59% for Jarvik and 50% for non-Jarvik patients. Median survival was lower in patients who had BiVADs (108 versus 675 days, $p = 0.735$) and this was expected since they also had right heart failure.

UK study: clinical measurements for VAD patients

Length of ICU and ward stay after the initial VAD implantation was available for 69 out of 70 patients. The mean time in the ICU was 15.8 days, with a median of 10 days (range 0–84 days). Two

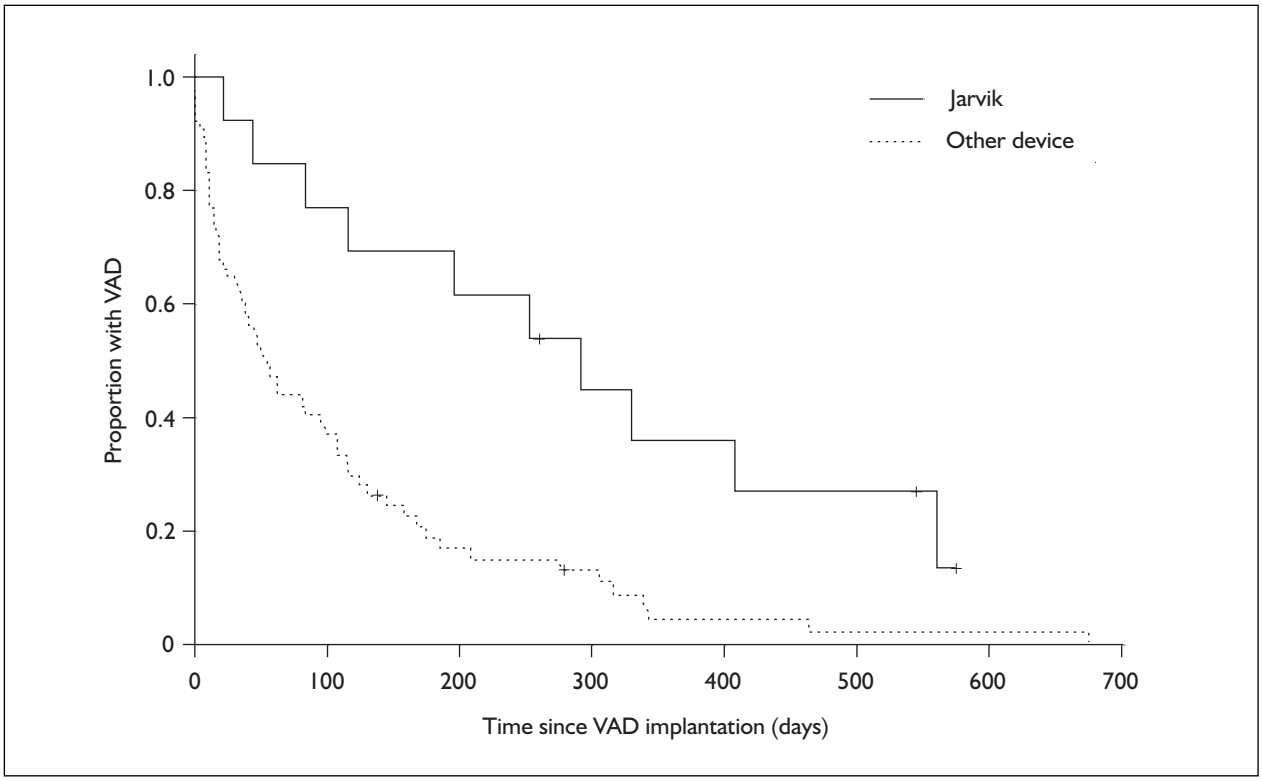

FIGURE 7 *Kaplan–Meier estimates of time supported by the Jarvik 2000 (*n *= 13) compared with other devices (*n *= 57)*

TABLE 8 *Overall survival (days) from VAD implantation to 31 March 2005*

	Freeman	Harefield	Papworth	Overall
Deaths	3	21	11	35
Median (95% CI)	22 (20 to –)	347 (84 to –)	– (84 to –)	561 (25 to –)
Mean (SE)	35.3 (11.7)	453.2 (68.3)	600.4 (86.0)	506.0 (54.8)
% Survival (95% CI)				
30 days	–	74 (62 to 89)	79 (65 to 95)	74 (65 to 85)
6 months	–	59 (45 to 77)	61 (45 to 82)	57 (47 to 70)
12 months	–	50 (36 to 69)	61 (45 to 82)	52 (41 to 65)

NB: A dash (–) indicates that this figure could not be calculated because only a small proportion of patients had died.

patients died on the day of their implantation and so had zero hospital stay. After discharge from the ICU, patients spent a mean of 44.8 days on a cardiac ward (median 36, range 0–187 days). Therefore, mean total hospital stay for the initial procedure was 59.8 days (median 49.5 days, range 0–196 days).

There was some evidence that Jarvik patients had shorter median ICU stay (8 versus 11.5 days, $p = 0.08$) but longer median ward stay (60 versus 26 days, $p = 0.004$). Thus, overall median time in hospital was longer for Jarvik patients (60 versus 41 days, $p = 0.02$). Patients requiring biventricular support spent longer in the ICU (14.5 versus 10 days, $p = 0.06$) and on the ward (41 versus 33 days, $p = 0.064$), reflecting the more complicated management of these patients.

Post-VAD implantation adverse events are recorded in *Table 9*. There were 320 non-fatal events in 62 patients during 300 months of VAD support. Most events (197/320, 62%) occurred in the first 30 days after implantation. The overall rate of serious adverse events (SAEs) was 3.47 per patient-month for the first 30 days, 0.84 per patient-month for months 2–3 and 0.35 per patient-month after the first 3 months. In common with other programmes, haemolysis was not a serious problem in any of the patients. In part, this may be due to the short median time supported of 82 days, but it was also the case for patients supported for longer periods.

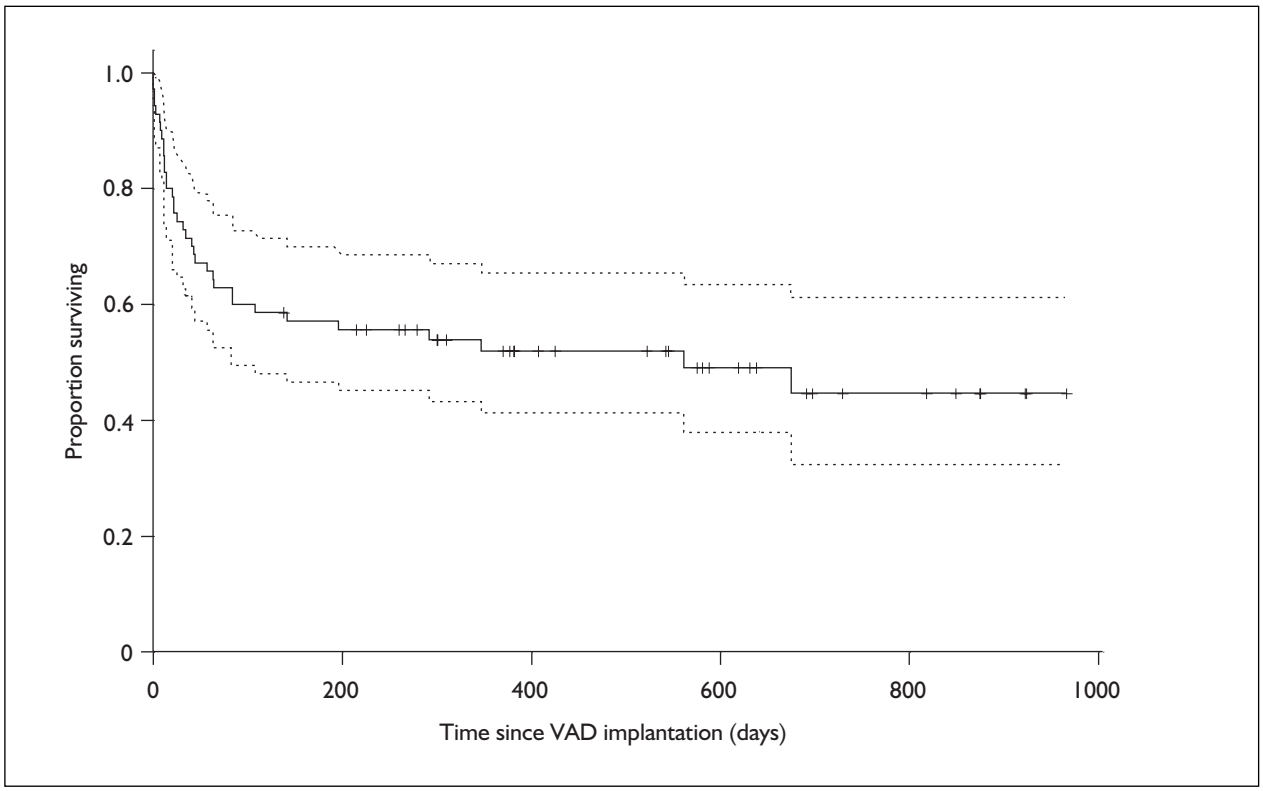

FIGURE 8 *Kaplan–Meier estimates and 95% confidence limits of overall survival from VAD implantation to 31 March 2005 (*n = *70)*

TABLE 9 *SAEs during support with VADs (*n = *70)*

Adverse event	No. of events	Rate per patient-year
Bleeding requiring surgery	52	2.10
Sepsis/infection	72	2.92
Neurological deficit	25	1.01
Thromboembolism	8	0.32
Right ventricular dysfunction	11	0.45
Renal dysfunction	25	1.01
Hepatic dysfunction	5	0.20
Cardiovascular dysfunction	33	1.34
Respiratory dysfunction	52	2.11
Device system failure	19	0.77
Other	18	0.73

The most frequently encountered problems requiring readmission, or prolongation of hospital stay, were related to bleeding, infection and respiratory dysfunction. There was no significant association between type of SAE and type of device, and most events were observed in both first and second generation devices.

Other clinical features

Hospitalisation

Of the 70 VAD patients, 29 (41%) were discharged from hospital after their VAD implantation (*Figure 9*). The median time to discharge for these patients was 66.5 days and ranged between 27 and 190 days postimplantation.

Forty-one VAD recipients (59%) were not discharged from hospital following the initial VAD procedure. There were 26 deaths in hospital following VAD implantation. The median time to death for these patients was 14 days and ranged from 0 to 190 days postimplantation. Of the 26, 22 had never left the ICU following their surgery. Thirteen VAD patients remained in hospital following their surgery until they received a transplant (median time to transplant 56.5 days,

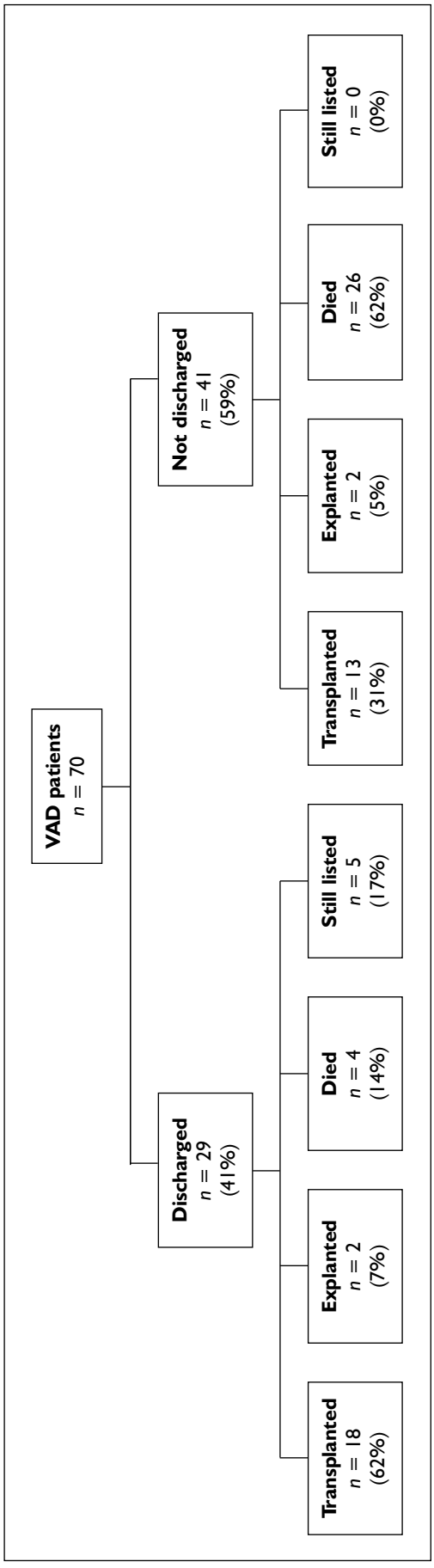

FIGURE 9 *Discharge from hospital following VAD implantation (n = 70)*

TABLE 10 *NYHA class preimplantation, postimplantation and post-transplantation for VAD patients*

NYHA class	Preimplantation	1–30 days postimplantation (%)	≥ 31 days postimplantation (%)	Post-transplantation
I	0	0	0	4 (40)
II	0	2 (6)	10 (36)	6 (60)
III	5 (9)	20 (63)	14 (50)	0
IV	54 (91)	10 (31)	4 (14)	0
Total	59	32	28	10

Data are shown as *n* (%).
One record per patient is taken at each time-point. The record closest to the time of implantation is used and the earliest post-transplantation record is used.

ranging from 9 to 169 days postimplantation) and two remained in hospital until their VAD was explanted (at 55 and 195 days postimplantation).

Of the 29 patients (41%) who were discharged following their VAD implantation, 17 were readmitted while with a VAD on at least one occasion. This includes all readmissions (for SEAs) between the original discharge date and their transplant date, explant date or 31 December 2004, but excludes admissions for transplant surgery itself (where the surgery was not preceded by an SAE). There were 34 readmissions. Nine patients were readmitted once, five patients were readmitted twice, one patient was readmitted three times and one four times, and the final patient was readmitted eight times.

Nine out of 13 Jarvik patients (69%) were discharged, compared with 20 out of 57 non-Jarvik patients (35%) ($p = 0.03$), reflecting the greater capacity for long-term support of these second generation devices. Fewer BiVAD patients were discharged (25% versus 50%, $p = 0.07$), reflecting the more complicated management of these patients. The sample was too small to assess subgroup effects further.

NYHA class for VAD and non-VAD study groups
NYHA class was recorded routinely for those patients who attended follow-up clinics while awaiting transplantation. There was no attempt to elicit information by post or telephone for patients who did not have clinic appointments. Post-transplantation NYHA was not always recorded in the notes and so this information is incomplete and should be considered exploratory.

NHYA class was recorded for 59 patients at referral, of whom five (9%) were in class III and the remaining patients were in class IV (*Table 10*). Following VAD implantation the proportion of patients with NYHA recorded who were in class IV fell from 91% to 31% in the first month and 14% after the first month. After transplantation all patients were in NYHA class I–II.

For non-VAD patients the pattern of change in breathlessness scores was similar, although the number with records in each group was small. Inotrope-dependent patients were predominantly in class IV at acceptance and in class II initially post-heart transplantation (*Table 11*). Non-inotrope-dependent patients were predominantly in class III at acceptance and class I–II post-heart transplantation.

UK study: results – non-VAD patients

During the period April 2002 to December 2004 a total of 250 non-VAD patients was accepted onto the heart transplant waiting list at the Freeman, Harefield or Papworth. *Figure 10* shows the experience of this cohort of patients up to the end of March 2005. Owing to administrative delays in gaining ethical approval and staff recruitment, only 63 of the 250 were recruited for collection of HRQoL and detailed resource use. These are referred to as 'study patients' in the figure. However, transplant and survival experience were available for all 250 patients.

In terms of quality of life and resource use, the 'study patients' may not be completely representative of the whole non-VAD population. HRQoL can only be measured in patients available for interview, so that waiting-list patients who died or were transplanted before they could be interviewed would be under-represented in the study group. Owing to administrative delays non-VAD patients at the Freeman were also under-represented.

TABLE 11 *NYHA class pretransplantation and post-transplantation for non-VAD patients*

NYHA class	Acceptance (within 30 days)	≥ 31 days on list	Post-transplantation
Inotrope-dependent patients (group B)			
I	0	0	0
II	0	0	5 (83)
III	2 (18)	0	0
IV	9 (82)	1 (100)	1 (17)
Total	11	1	6
Non-inotrope-dependent patients (group C)			
I	0	0	2 (14)
II	0	0	11 (79)
III	36 (86)	15 (94)	1 (7)
IV	6 (14)	1 (6)	0 (0)
Total	42	16	14

Data are shown as *n* (%).
One record per patient is taken at each time-point. The record closest to the time of acceptance, the last record while on the list and the earliest post-transplantation records are used.

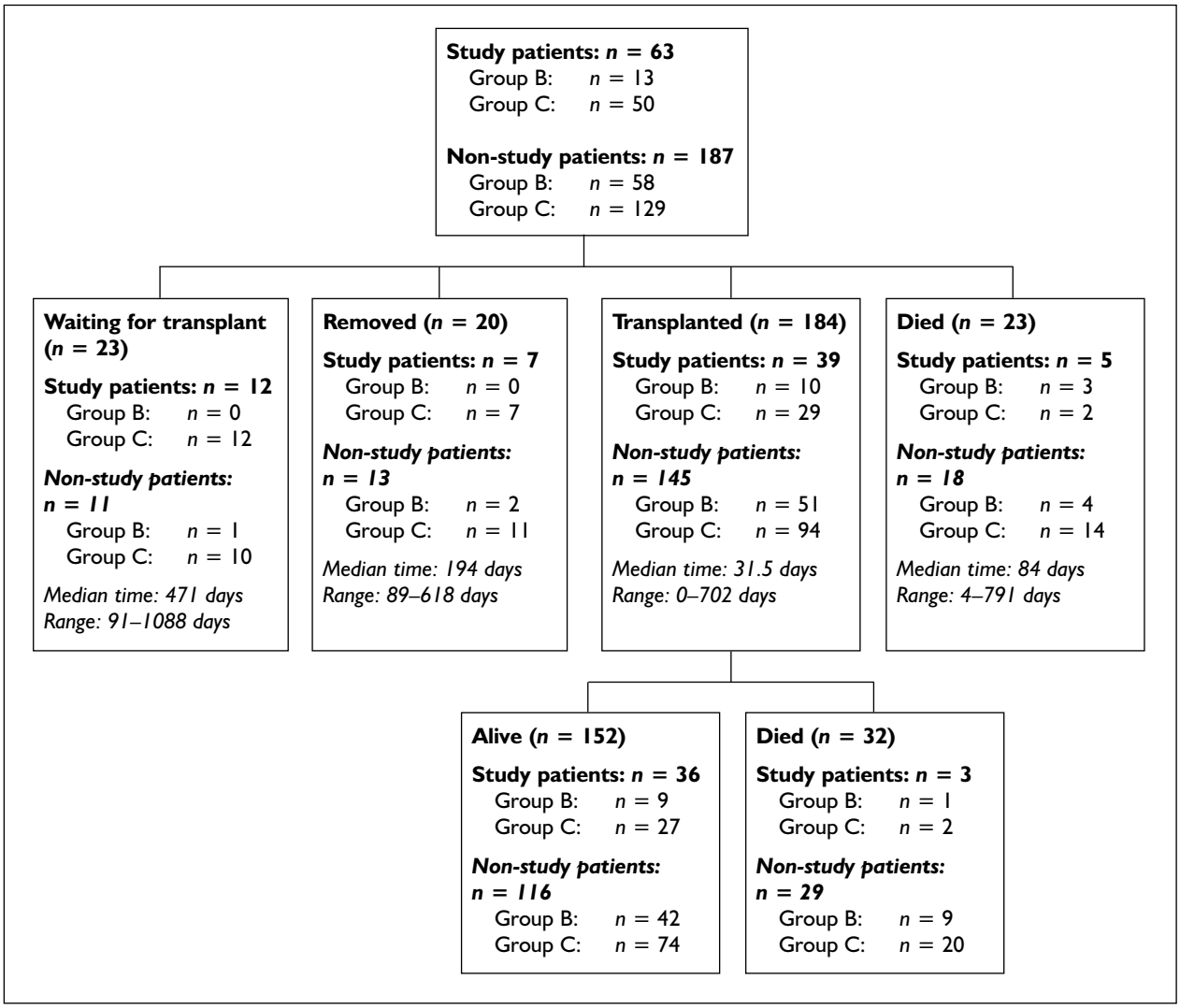

FIGURE 10 *Non-VAD patients CONSORT diagram (n = 250). Accepted onto transplant list between 2 April 2002 and 29 December 2004, follow-up until 31 March 2005.*

TABLE 12 *Characteristics of non-VAD patients accepted for heart transplantation* (n = *250)*

Variable	Group B (inotrope-dependent), *n* = 71			
	Freeman (*n* = 29)	**Harefield (*n* = 18)**	**Papworth (*n* = 24)**	**Overall (*n* = 71)**
Age (years)				
Mean (SD)	40.5 (14.3)	46.9 (17.3)	45.7 (13.2)	43.9 (14.8)
[range]	[18–63]	[19–67]	[22–69]	[18–69]
Gender, *n* (%)				
Female	7 (24)	1 (6)	9 (37)	17 (24)
Male	22 (76)	17 (94)	15 (63)	54 (76)
Diagnosis, *n* (%)				
DCM	16 (55)	6 (33)	17 (71)	44 (62)
IHD	6 (21)	10 (56)	4 (17)	13 (18)
Other	7 (24)	2 (11)	3 (13)	14 (20)
Variable	**Group C (non-inotrope-dependent), *n* = 179**			
	Freeman (*n* = 44)	**Harefield (*n* = 58)**	**Papworth (*n* = 77)**	**Overall (*n* = 179)**
Age (years)				
Mean (SD)	48.7 (12.3)	49.3 (10.7)	48.5 (12.2)	48.8 (11.7)
[range]	[17–68]	[21–63]	[16–65]	[16–68]
Gender, *n* (%)				
Male	7 (16)	13 (22)	15 (20)	35 (20)
Female	37 (84)	45 (78)	62 (80)	144 (80)
Diagnosis, *n* (%)				
DCM	17 (39)	37 (64)	44 (57)	107 (60)
IHD	17 (39)	15 (26)	20 (26)	35 (20)
Other	10 (23)	6 (10)	13 (17)	37 (21)

Of the 250 patients, 71 required intravenous inotropic support or required urgent transplant and are referred to as group B. The remaining 179 patients did not require intravenous inotropic support and are referred to as group C. Groups B and C are non-overlapping. Of the 250, 184 (74%) underwent heart transplantation and 20 (8%) were removed from the list. Twenty-three (9%) were on an active waiting list on 31 March 2005, one of whom had had a VAD implanted between the end of recruitment (31 December 2004) and the end of follow-up (31 March 2005). The remaining 23 patients (9%) died while waiting for a donor heart. Of the 184 patients transplanted, 32 (17%) died and 152 (83%) were alive at 31 March 2005, almost exactly the same crude survival rates as the VAD group.

Patient characteristics for all non-VAD patients accepted for heart transplantation during the study period are summarised in *Table 12*. Within group B there were no significant differences between centres in age ($p = 0.285$), gender distribution ($p = 0.056$) or diagnostic category ($p = 0.051$), with mean age 44 years, 24% female and 80% having either dilated cardiomyopathy or ischaemic heart disease (IHD). Within group C there were no significant differences between centres in age ($p = 0.914$) or gender distribution ($p = 0.714$), but there was significant variation in diagnostic category accepted ($p < 0.001$).

Groups B and C were similar in gender distribution ($p = 0.441$) and diagnostic category ($p = 0.949$), but group C patients were significantly older ($p = 0.014$), with a mean age of 48.8 years.

UK study: non-VAD patients waiting-list time

The mean and median time on the UK waiting list was estimated for all 250 non-VAD patients from Kaplan–Meier estimates with the event defined as transplantation, removal from the list, receiving a VAD implant or death. Patients alive and still listed at 31 March 2005 were censored. Time listed is plotted for the UK study by group in *Figure 11* and according to involvement in quality of life/resource-use study in *Figure 12*. From *Figure 11* it is clear that patients on intravenous inotropes spent much less time on the waiting list than non-inotrope-dependent patients (median 16 days versus 87 days, $p < 0.001$), reflecting the urgent need for transplantation in this group.

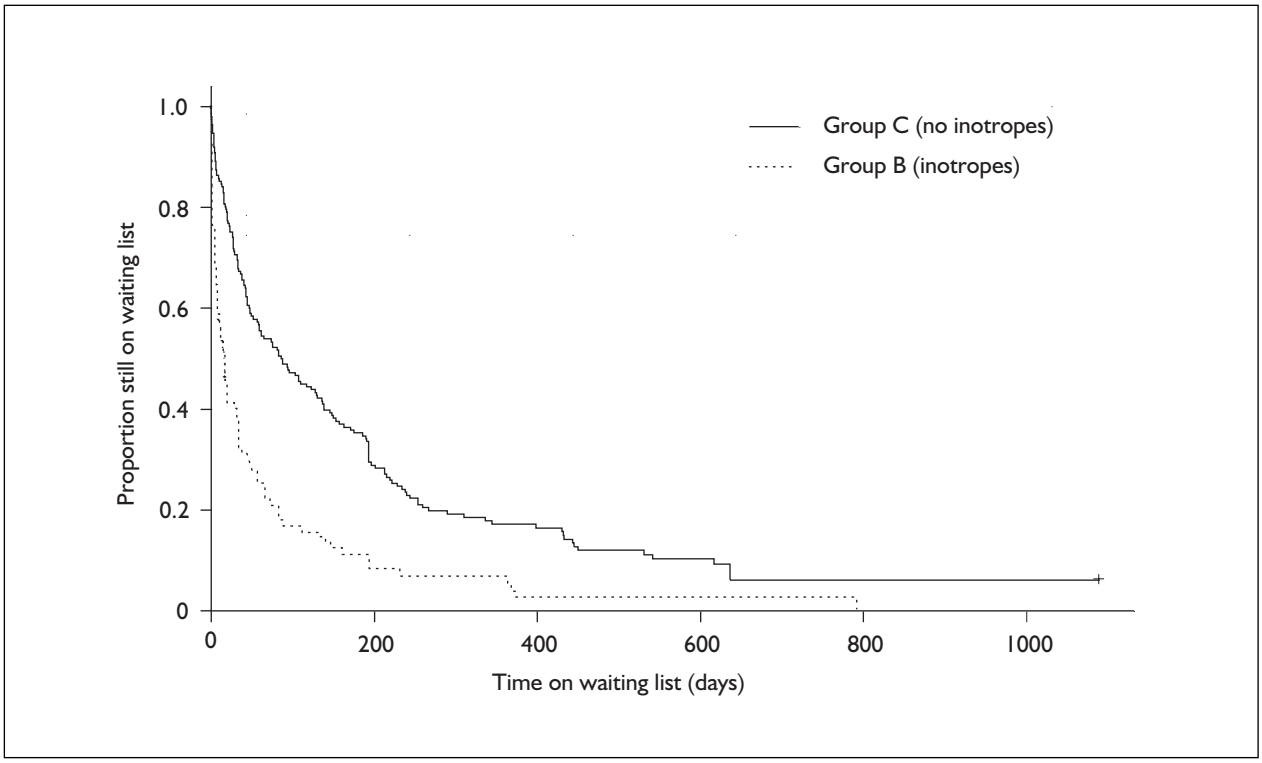

FIGURE 11 *Kaplan–Meier estimates of time spent on the waiting list for non-VAD patients (*n *= 250)*

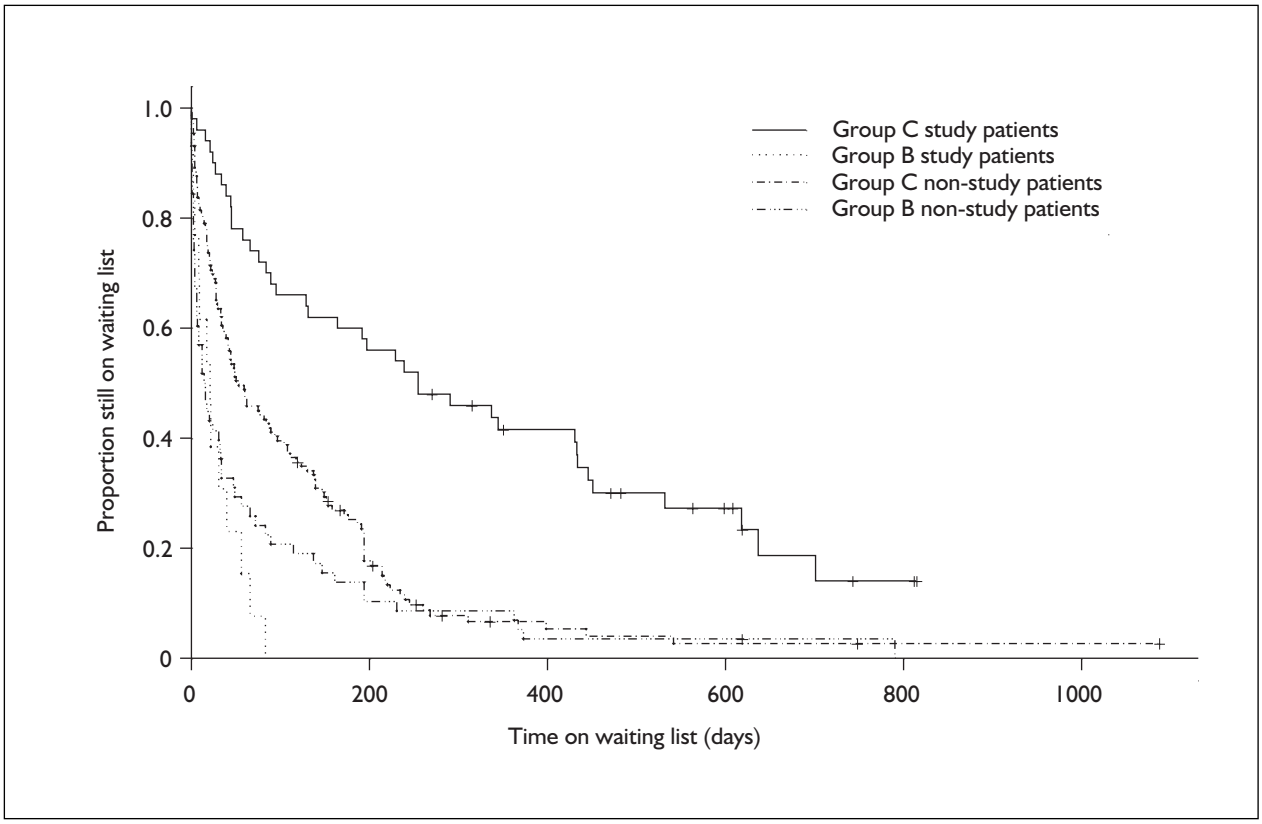

FIGURE 12 *Kaplan–Meier estimates of time spent on the waiting list for non-VAD patients by participation in HRQoL/resource-use study*

TABLE 13 *Waiting times for non-VAD patients*

	Deaths	% listed at 6 months (95% CI)	Median (95% CI)
Inotrope-dependent patients (group B)			
Study patients (n = 13)	13	0	21 (8 to –)
Non-study patients (n = 58)	57	14% (7 to 26)	15 (7 to 34)
Overall (n = 71)	70	11% (6 to 22)	16 (8 to 32)
Non-inotrope-dependent patients (group C)			
Study patients (n = 50)	38	60% (48 to 75)	255 (131 to 446)
Non-study patients (n = 129)	120	25% (19 to 34)	53 (41 to 94)
Overall (n = 179)	158	35% (29 to 43)	87 (59 to 131)

NB: A dash (–) indicates that this figure could not be calculated because only a small proportion of patients had died.

TABLE 14 *Number of deaths and survival estimates from transplant listing to 31 March 2005*

	Deaths	% surviving at 12 months (95% CI)	Median (95% CI)
Group B			
Study patients (n = 13)	4	70% (48 to 100)	– (83 to –)
Non-study patients (n = 58)	13	81% (71 to 92)	– (– to –)
Overall (n = 71)	17	79% (70 to 89)	– (– to –)
Group C			
Study patients (n = 50)	4	96% (91 to 100)	962 (– to –)
Non-study patients (n = 129)	35	75% (67 to 83)	– (– to –)
Overall (n = 179)	39	81% (75 to 87)	– (– to –)

NB: A dash (–) indicates that this figure could not be calculated because only a small proportion of patients had died.

Almost all group B patients were removed from the list rapidly and there was little difference in waiting time between patients for whom detailed clinical and HRQoL data were available and the remaining non-study patients (*Figure 12*). There was more difference in waiting time between study and non-study patients in group C. Non-study patients in group C had shorter waiting times and so may be sicker than those who entered the quality of life and resource-use data collection study. However, all 250 non-VAD patients were included in the survival statistics.

There were significant differences between the centres in waiting times, with patients at the Freeman waiting significantly longer and patients at Papworth having shorter waiting times (p = 0.002). This indicates some differences in the way that centres manage their waiting lists (*Table 13*).

Overall survival from listing

To assess the overall survival experience of patients not implanted with a VAD, survival time was calculated for all 250 patients, with death of a patient from any cause the event of interest and all other patients censored at 31 March 2005. The proportion alive at 1 year after transplant listing was 80% (95% CI 75 to 87%). Kaplan–Meier survival estimates are shown in *Figure 13* for Groups B and C, and according to study participation in *Figure 14*. Deaths are summarised in *Table 14*. There were no significant differences in crude survival rates between the centres (p = 0.209) or between groups B and C (p = 0.513), although this statement is conditional on group B being given priority for transplantation. However, study patients in group C had higher survival rates than non-study patients in group C, since those who died early could not be approached for consent to take part in the study.

Serious adverse events

There were 19 serious adverse events in five patients in group B and 9 events in eight patients in group C while listed for heart transplantation, rates of 1.61 and 0.02 per patient-month respectively. For both groups most events were related to their heart failure.

Alternative scenario for VAD patients

In recognition of the fact that non-VAD transplant candidates are unlikely to be directly comparable

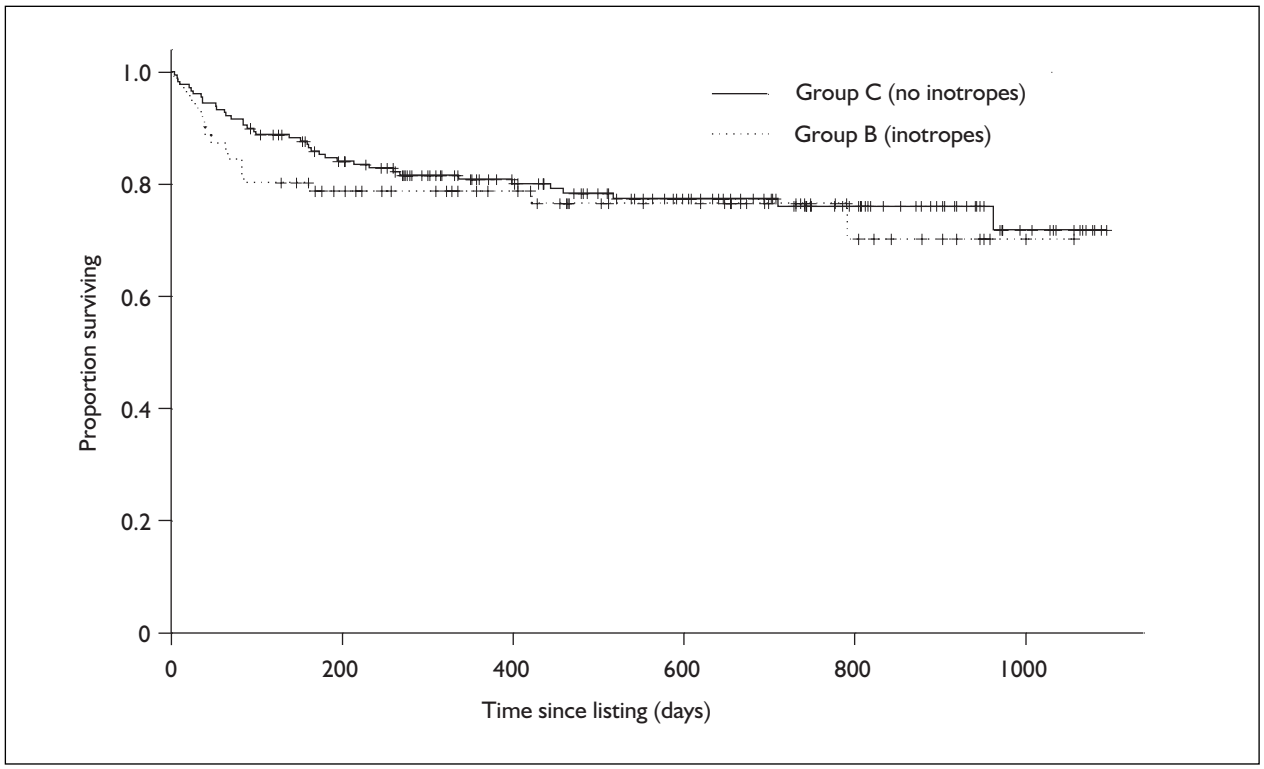

FIGURE 13 *Kaplan–Meier survival estimates for non-VAD patients from transplant listing to 31 March 2005*

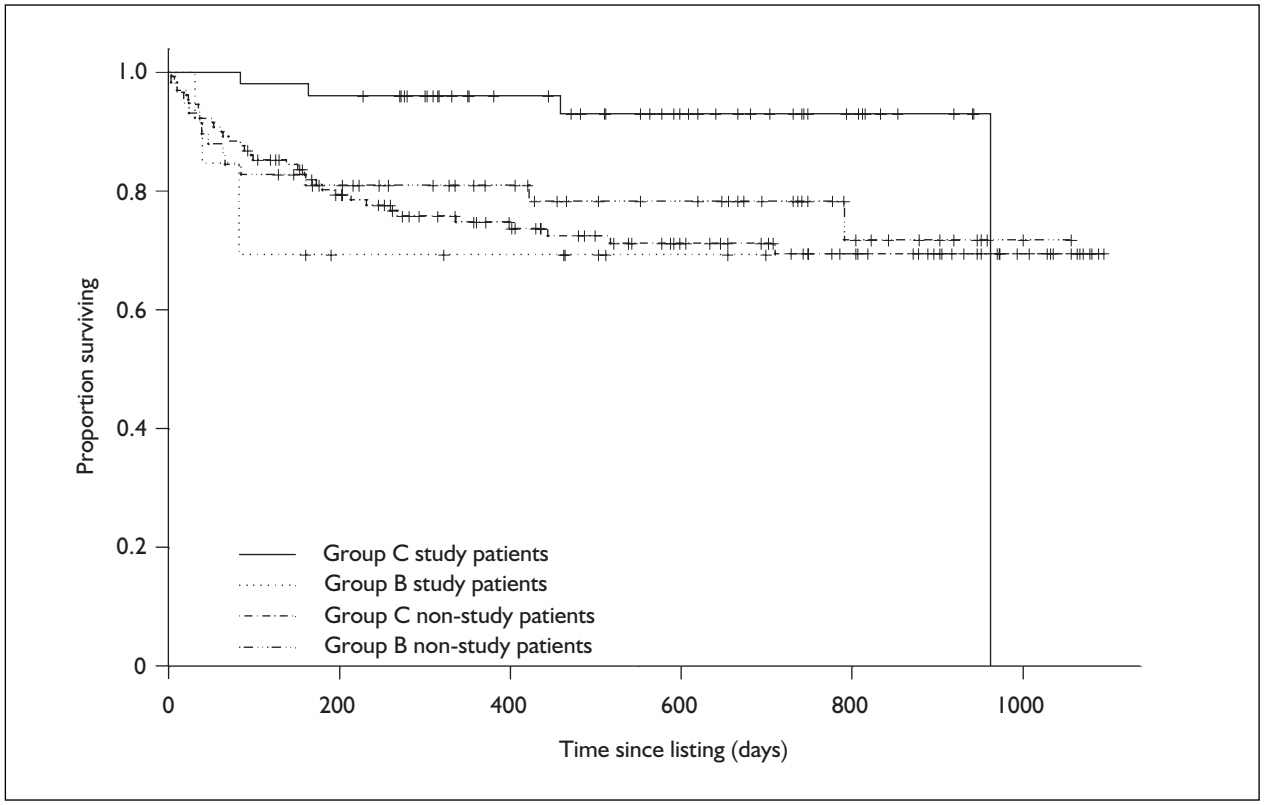

FIGURE 14 *Kaplan–Meier survival estimates for non-VAD patients from transplant listing to 31 March 2005 by study participation*

TABLE 15 *Post-transplantation survival summaries (days) for all patients by group*

	A (n = 31)	B (n = 61)	C (n = 123)	Overall (n = 215)
Deaths	5	10	22	37
Median[a] (95% CI)	–	–	–	–
Mean (SE)	803 (63)	825 (46)	877 (36)	883 (27)
1-year survival (95% CI)	84% (72 to 98)	85% (77 to 95)	84% (78 to 91)	84% (80 to 89)

[a] The median survival could not be calculated since only small numbers of patients died post-transplantation.

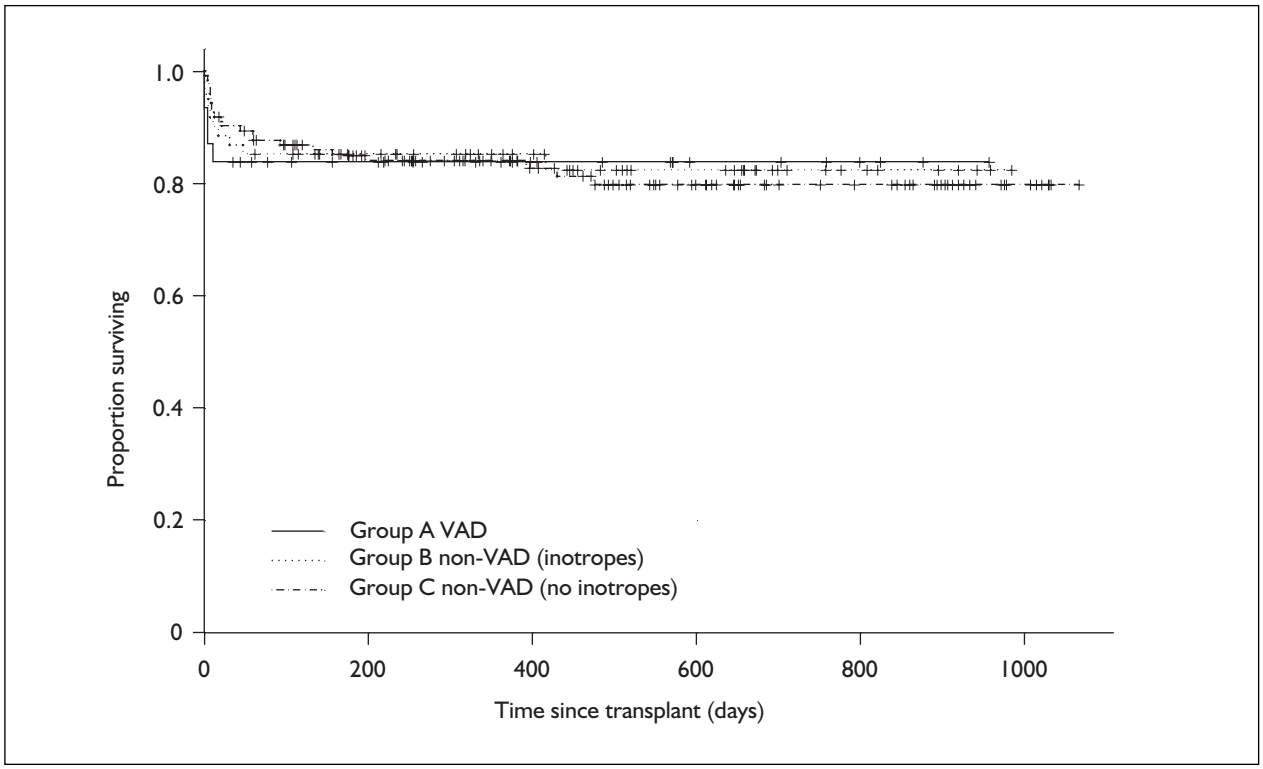

FIGURE 15 *Kaplan–Meier survival estimates from transplantation to 31 March 2005 by group*

to VAD recipients, an alternative scenario was constructed to reflect what might happen if the technology were not available. This alternative scenario was based on discussions with surgeons and cardiologists experienced in treating patients with VADs. In this scenario it was assumed that all VAD-eligible patients who present at one of the three implanting centres would die within 30 days in the absence of a VAD. Thus, expected survival would be 15 days.

The UK Transplant report on the urgent allocation scheme from April 2003 to March 2004 stated that 30 out of 41 adults registered as requiring an urgent transplant received a donor organ and, of these, 19 (63%) waited less than 7 days [CTAG (04) 19 report from UK Transplant; Hussey J: personal communication]. Post-transplantation survival for these patients was comparable to that of non-urgent transplant recipients. Thus, the alternative scenario described above is likely to underestimate survival of these patients in the absence of a VAD. A realistic scenario is that without the VAD programme, patients would have survival rates somewhere between group B and group D. Therefore, in the economic modelling, sensitivity analysis is carried out to assess the effect of altering the proportion of patients in the alternative scenario who, it is assumed, would have died within 30 days without VAD implantation.

Comparison of VAD and non-VAD patients post-transplantation

Survival after transplantation was excellent with all groups achieving a 1-year post-transplantation

TABLE 16 *Post-transplantation SEAs by patient group*

	A (n = 31)	B (n = 10)	C (n = 29)
Bleeding requiring surgery	3 (0.01)	5 (0.05)	8 (0.03)
Infection	15 (0.05)	1 (0.01)	12 (0.04)
Neurological deficit	5 (0.02)	3 (0.03)	4 (0.01)
Thromboembolism	3 (0.01)	2 (0.02)	2 (0.01)
Renal dysfunction	2 (0.01)	5 (0.05)	9 (0.03)
Cardiovascular/graft dysfunction	20 (0.07)	7 (0.07)	20 (0.07)
Respiratory dysfunction	10 (0.03)	2 (0.02)	3 (0.01)
Driveline site repair	1 (0.003)	0 (0)	0 (0)
Post-transplant rejection	2 (0.01)	4 (0.04)	10 (0.04)
Other	3 (0.01)	5 (0.05)	8 (0.03)

survival rate in excess of 80% (*Table 15*, *Figure 15*). For patients who survived to transplantation VAD use did not significantly affect post-transplantation survival (p = 0.983).

SAEs

After transplantation there were 174 SAEs in 50 patients. *Table 16* records the number of events recorded and the rate per patient-month after transplantation. Overall, 20 VAD-supported patients had 64 events during 294 patient-months after transplantation, an overall rate of 0.22 per patient-month. Ten inotrope-dependent patients had 34 events in 101 months, a rate of 0.34 per patient-month, and 20 group C patients had 76 events in 277 months, a rate of 0.27 per patient-month. Thus, provided that VAD patients survive to transplantation there is no evidence that they will have more post-transplantation SAEs than non-VAD transplant recipients.

Discussion

Patients undergoing VAD implantation as a BTT were very sick at presentation. In the REMATCH trial survival in the control groups was poor, at 23% at 1 year and 8% at 2 years after implantation. The patients accepted for VAD implantation as a BTT were considered sicker than those accepted for the REMATCH trial, since they were not expected to survive to heart transplantation, despite the current median waiting time of 16 days for inotrope-dependent patients and the provision of an urgent category. In addition, all were on intravenous inotropic support, compared with 68% of the REMATCH group. Following VAD implantation approximately 57% will recover sufficiently for either heart transplantation, VAD explantation due to myocardial recovery or longer term VAD use, with an overall survival at 12 months after VAD implantation in these patients of 52% (95% CI 41 to 65%). Those patients who subsequently undergo heart transplantation have comparable post-transplantation survival to routine transplant patients.

The BTT experience in the UK is slightly worse than the average rate of 62% derived from previous published series (see Chapter 2), although not significantly so, In addition, the UK BTT/BTR rate is in line with the larger published series, which were less prone to publication bias. The adverse events during VAD support observed in the UK were similar to those reported elsewhere. Thus, the UK evaluation has very good external validity.

Most patients with first generation devices were supported for a median of approximately 2 months. Again, duration of support is similar to other series (see Chapter 2). Those on the Jarvik 2000 second generation device at Harefield were supported for a median of approximately 10 months. The Harefield experience has shown that patients can survive on VAD support for prolonged periods with relatively few adverse events, and indicates that the REMATCH experience could be reproduced, or possibly improved upon using second generation devices in the UK context.

Approximately 8% of non-VAD non-inotrope-dependent transplant candidates died while listed. Of the group who were listed as urgent or who were inotrope dependent 10% died on the waiting list. This is less than is reported in other countries[99] and in previous reports from UK centres. For example, in 1995 Papworth Hospital reported that 25% of candidates died while listed.[100] This represents a change in either referrals or management of the list. There may be several reasons for a decrease in referrals. There

has been a significant improvement in the medical management of heart failure with widespread prescribing of β-blockers and ACE inhibitors.[2] As a result, potential candidates may be referred for transplantation at a later stage in the natural history of their heart failure and so may not be fit enough for transplantation when assessed. In addition, cardiologists who perceive a shortage of donor organs may be operating a more rigorous selection policy than is necessary. Once accepted for heart transplantation patients had a good prognosis, with overall survival at 12 months from acceptance for patients in groups B and C of 81% (95% CI 76 to 87%).

One of the difficulties in assessing the effectiveness of VAD support is the construction of an appropriate comparison group. Transplant candidates who did not have a requirement for mechanical support were less sick than VAD recipients. Even those who were inotrope dependent or who were listed for urgent transplants were considered less sick. However, an alternative (hypothetical) scenario, which assumed that all VAD recipients would have died within 30 days had the devices not been available, is also not directly comparable. The truth is likely to lie somewhere between these two scenarios, so that comparisons between groups A and B and between groups A and D will provide upper and lower bounds for the estimates of effectiveness and cost-effectiveness. The modelling will investigate the sensitivity of the cost-effectiveness summaries to varying the relative proportions of VAD patients who would behave like group B and group D in the absence of the technology.

Summary

In the UK evaluation 70 patients received VAD implants in 2.75 years, a rate of 25.5 per year, all but three at Harefield and Papworth hospitals. Of these, 30 (43%) died at a median of 21 days postimplantation; the remaining patients were BTT (31, 44%) or BTR (4, 6%), or remained on VAD support at a median of 279 days (range 138–575 days) after implantation (5, 7%). Sepsis/infection, bleeding requiring surgery, respiratory and cardiovascular dysfunction and neurological dysfunction were SAEs, and the rate of SAEs was particularly high in the first month of support. Patients who survived the first 30 days had lower rates of SAEs. These figures are consistent with published series. Non-VAD transplant candidates had an 8–10% risk of dying on the transplant waiting list. Inotrope-dependent patients underwent transplantation quickly, with a median waiting time of 16 days, whereas non-inotrope-dependent transplant candidates waited for a median of 87 days. After transplantation, all three groups had excellent and comparable rates of survival and SAEs.

Chapter 5

UK study: health-related quality of life

Background

A review of studies of effectiveness, including HRQoL outcomes, is contained in Chapter 2 of this report.

The majority of published reports investigating the HRQoL of VAD recipients have come from two groups in the USA. The University of Pittsburgh[41–43] studied patients with Novacor and Thoratec devices, and the Rush University Medical Centre, Chicago,[44–47,51] patients with HeartMate devices. Both research groups used well-validated instruments to examine the domains of physical, mental, emotional and social HRQoL. Reports were based on selected case series and had to exclude patients who had died or were too ill to complete self-report instruments. Therefore, all results are potentially biased and may have limited generalisability.

From before to 1 or 2 weeks after VAD implantation, patients reported more satisfaction with health and functioning and significantly less symptom distress, but also reported more self-care disability and more dissatisfaction with social and economic areas of life.[20] Predictors of overall HRQoL at 1 month after VAD implantation were psychological symptoms and stress levels.[44] Quality of life for patients who remained on VAD support and were available for interview was fairly stable from 1 month to 1 year postimplantation.[47]

Discharge from hospital while on VAD support was associated with increased satisfaction with socio-economic areas of life, decreased overall stress and decreased overall physical and self-care disability.[41,46] Some discharged patients reported more concerns about stroke and device noise while trying to sleep, but fewer concerns about infection than inpatients.[41]

After transplantation, VAD patients were significantly more satisfied with their overall HRQoL, health and functioning and experienced less physical and self-care dysfunction.[45] Both VAD and non-VAD patients reported similar physical functioning, emotional and social well-being after transplantation, with improvement from 2 to 12 months post-transplantation.[101] However, VAD patients had significantly lower cognitive functioning post-transplantation than non-VAD patients, and this was associated with a lower return to employment.[101]

UK study: methods

When this UK study was being planned, a main source of information about measures to use with cardiac assist device patients was the protocol on the evaluation of HRQoL produced from a conference organised by the Society of Thoracic Surgeons and the American College of Cardiology.[102] This recommended that in addition to the broad domains of physical, psychological and social function, it was important to consider three subcomponents of particular concern for these patients. They were: specific physical functional limitations in the areas of mobility, ambulation, sleep and body care; cognitive function; patients' reactions to concerns about the device itself. The SF-36 was recommended as the generic health status measure, together with certain dimensions from the Sickness Impact Profile (SIP) to address specific physical function limitations. The British version of the SIP is the Functional Limitations Profile (FLP), which has been translated into British English and rescored using British item weights.[103] Mood state was assessed using the Hospital Anxiety and Depression Scale (HADS), which has been used extensively in the UK. The three cognitive function tests included in the protocol screen for deficits in attention, psychomotor speed, visuospatial processing and memory, and overall mental function: the Trail Making test, the Digit–Symbol Substitution (DSS) task[104] and the Mini-Mental State Examination (MMSE).[105] The device-specific measure recommended was a one-page questionnaire adapted from measures used at three centres in the USA.[106]

In the choice of measures, as well as the recommendations of the American College of Cardiology Conference Protocol, the authors considered the need to be able to compare the results with published data and, from their own experience in working with these and similar

TABLE 17 *HRQoL questionnaires administered*

Construct	Questionnaire
Physical and social function	SF-36 – two dimensions: physical component score; mental component score
	FLP (UK version of SIP) – four dimensions: sleep and rest; bodycare and movement; mobility; ambulation
	PSC
Psychological well-being	HADS – two dimensions: anxiety; depression
Cognitive function	DSS
	Halstead–Reitan Trail Making A&B
	MMSE
VAD Device-Specific Questionnaire	Adapted from Kendell *et al.*, 1993[106] (six questions) and VADQoL (Hallas CN, Wray J, Harefield Hospital, 2003 (15 questions)

PSC, Physical Symptoms Checklist.

patients, the overall burden to the patient. In addition, they considered what would be appropriate for hospital-based as well as home-based patients. [The FLP Manual (1997) specifically mentions how to administer this questionnaire to patients in hospital.]
The SF-36, HADS and MMSE have all been validated in a variety of populations and patient groups and more specifically in heart-failure patients.[107–112]

The battery of questionnaires administered is summarised in *Table 17*. A brief description of each questionnaire is given below. In addition, in this UK study, utility was assessed, to permit the calculation of QALYs; the EQ-5D was used.
The EQ-5D has been recommended for use in the economic evaluation of healthcare technologies in the UK in guidance issued by the National Institute for Health and Clinical Excellence (NICE)[113] and has been used extensively across a wide range of studies within the cardiovascular area.

VAD patients were scheduled for baseline assessment on transfer from critical care to the ward and at 3-monthly intervals to transplantation/explantation. Post-transplantation/explantation assessment was scheduled for 3, 6, 12 and up to 24 months. Non-VAD study patients were interviewed or asked to complete postal questionnaires soon after acceptance onto the transplant waiting list and at the same intervals as the VAD group before and after transplantation/explantation.

UK study: HRQoL results

All VAD patients (n = 70) and a sample of 63 non-VAD patients gave consent for detailed HRQoL and resource-use data collection. Patient characteristics for non-VAD patients recruited into the detailed data collection study are summarised in *Table 18*. Given the variable nature of HRQoL measurements and the small samples available, further subgroup analyses were not feasible.

There was a total of 231 HRQoL assessment records for 94 patients: 153 pretransplantation in 75 patients and 78 post-transplant in 42 patients. Patients had between one and six assessments (mean 2.46).

The *Tables 19–21* show the number of records for each group and period of assessment.

EUROQoL

The EQ-5D[98] has been used in many cost-effectiveness studies. It defines health in five dimensions: morbidity, self-care, usual activities, pain or discomfort, anxiety or depression. Each dimension has three levels: no problems, a moderate problem, or a severe problem. Health states defined by the level chosen for each dimension can be scored using utility weights reflecting the values from a representative sample of the UK population.[114] These utilities are scaled so that full health = 1 and death = 0, and allow for severe health states for which HRQoL is valued lower than death.

TABLE 18 *Characteristics of non-VAD patients with detailed data collection (n = 63)*

Variable	Group B (inotropes) *n* = 13			
	Freeman (*n* = 0)	**Harefield (*n* = 9)**	**Papworth (*n* = 4)**	**Overall (*n* = 13)**
Age (years)	–			
Mean (SD)		43.42 (17.65)	49.90 (14.56)	45.41 (16.44)
[range]		[19–60]	[37–70]	[19–70]
Gender, *n* (%)	–			
Male		8 (89)	3 (75)	11 (85)
Female		1 (11)	1 (25)	2 (15)
Diagnosis, *n* (%)	–			
DCM		3 (38)	3 (75)	6 (50)
IHD		5 (62)	0 (0)	5 (42)
Other		0 (0)	1 (25)	1 (8)
Variable	**Group C (no inotropes) *n* = 50**			
	Freeman (*n* = 5)	**Harefield (*n* = 25)**	**Papworth (*n* = 20)**	**Overall (*n* = 50)**
Age (years)				
Mean (SD)	52.80 (5.12)	45.98 (11.34)	50.69 (10.48)	48.54 (10.72)
[range]	[45–59]	[21 to 60]	[29–65]	[21–65]
Gender, *n* (%)				
Male	4 (80)	18 (72)	18 (90)	40 (80)
Female	1 (20)	7 (28)	2 (10)	10 (20)
Diagnosis, *n* (%)				
DCM	0 (0)	14 (64)	14 (70)	28 (60)
IHD	2 (40)	4 (18)	3 (15)	9 (19)
Other	3 (60)	4 (18)	3 (15)	10 (21)

Diagnosis information is missing for four Harefield patients.

TABLE 19 *Number of completed questionnaires, before and after transplantation, by study group*

Group	Assessment		Total
	Pretransplantation	**Post-transplantation**	
A	79 (33 patients)	29 (16 patients)	108 (39 patients)
B	6 (6 patients)	11 (5 patients)	17 (10 patients)
C	68 (36 patients)	38 (21 patients)	106 (45 patients)
Total	153 (75 patients)	78 (42 patients)	231 (94 patients)

TABLE 20 *Number of completed questionnaires by time after VAD implantation (group A) or heart transplant listing (groups B and C)*

Group	0–30 days	31–90 days	91–180 days	181–365 days	>1 year
A	13	21	19	18	8
B	6	0	0	0	0
C	4	9	12	23	20

TABLE 21 *Number of completed questionnaires by time after heart transplantation*

Group	0–30 days	31–90 days	91–180 days	181–365 days	>1 year
A	2	8	7	5	7
B	0	1	5	5	0
C	1	11	14	6	6

TABLE 22 *EQ-5D assessments over time pretransplantation*

Group	0–30 days		30–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	13	0.51 (0.21)	21	0.66 (0.14)	45	0.66 (0.14)
B	6	0.50 (0.23)	0	–	0	–
C	4	0.61 (0.07)	9	0.59 (0.20)	55	0.68 (0.16)
B and C	10	0.55 (0.18)	9	0.59 (0.20)	55	0.68 (0.16)

TABLE 23 *EQ-5D assessments over time post-transplantation*

Group	0–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)
A	9	0.76 (0.13)	19	0.78 (0.11)
B	1	0.76 (NA)	10	0.71 (0.08)
C	12	0.74 (0.19)	26	0.78 (0.18)
B and C	13	0.75 (0.18)	36	0.76 (0.16)

NA, not applicable.

Results

Tables 22 and *23* show that VAD patients had low mean HRQoL in the first month after implantation but that there was a significant improvement after the first month, which was maintained for the duration of implantation. There were small numbers of non-VAD cases with EQ-5D measurements early after acceptance for transplantation, However, it was clear that inotrope-dependent patients had similar mean EQ-5D to VAD patients at acceptance. Non-inotrope-dependent transplant candidates had better mean EQ-5D, and this was broadly constant during the pretransplantation period.

After transplantation both VAD and non-VAD patients had a significant improvement in HRQoL (difference in EQ-5D 0.20, 95% CI 0.11 to 0.29, $p < 0.001$ for group A, and 0.16, 95% CI 0.11 to 0.22, $p < 0.001$ for groups B and C). There were no differences in mean EQ-5D between groups and between periods after transplantation.

In order to put the EQ-5D figures in context, the published mean EQ-5D score for a general population with a similar age and gender distribution to the study group (mean age 48 years, 81% male) would be 0.84.[115]

SF-36

SF-36 scales

The SF-36 aims to describe eight dimensions of HRQoL on a scale of 0 (minimum function) to 100 (maximum function). The dimensions are physical functioning, role limitations due to physical problems, pain, energy/vitality, social functioning, mental health, role limitations due to emotional problems, and general health. These scales can be combined into two composite scales named the physical component score (PCS) and the mental component score (MCS) (e.g, Ware[116]). The commonly used standardisation method was adopted, so that for a 'healthy' population the PCS and MCS are centred around 50 with a standard deviation of 10. Lower scores indicate worse physical and mental HRQoL.

It is possible to derive utilities from the SF-6D, a utility instrument based on the SF-36.[117] The SF-6D consists of a multivariate health status classification system with six dimensions: physical functioning, role limitations, social functioning, pain, mental health and vitality, with each dimension consisting of four to six levels. This classification system was developed from 14 items of the SF-36 questionnaire.[118] Health status based on the levels of each dimension is scored using utility weight, scaled so that full health = 1 and dead = 0. The SF-6D is used here to investigate sensitivity of results to the choice of utility measure.

Results

The distributions of the SF-36 scores for the two subscales are presented in the histograms in *Figure 16*. Both scores were, on average, higher post-transplantation. In addition, there was strong positive correlation between the two (physical and mental) component scores, with correlation coefficients of 0.939 and 0.927 before and after transplantation, respectively.

Pretransplant assessments

Table 24 shows pretransplantation summaries for the PCS of the SF-36, by group and by time since implantation (group A) or listing (groups B and C). For all three groups and all time intervals after VAD implantation/listing the mean PCS was significantly lower than the population normal

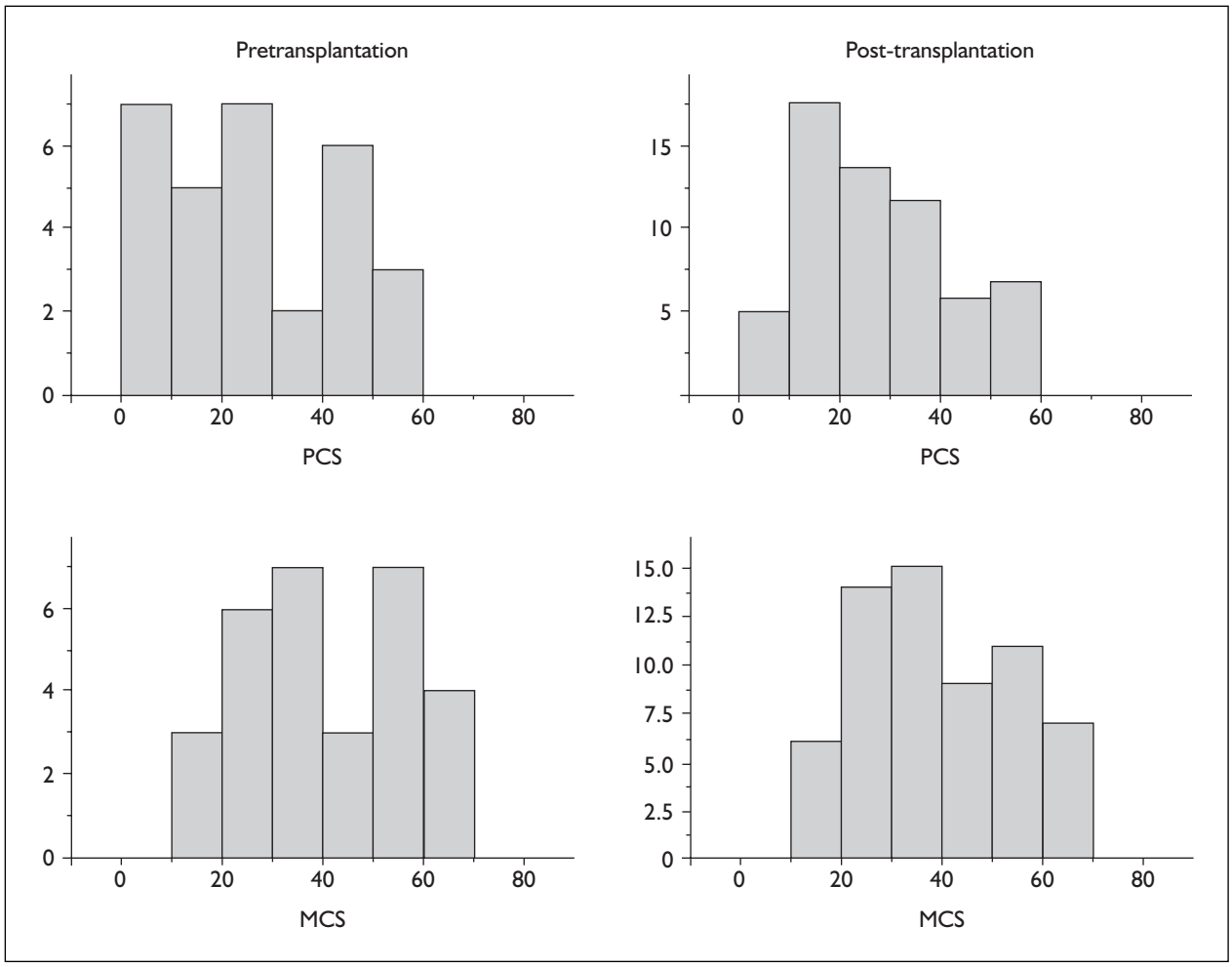

FIGURE 16 *Distribution of SF-36 physical and mental component scores completed before and after transplantation*

TABLE 24 *Pretransplantation time: grouped summaries for the SF-36 physical component score*

Group	0–30 days		31–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	13	14.26 (8.23)	21	17.55 (8.57)	45	28.96 (11.30)
B	6	13.81 (8.62)	0	–	0	–
C	4	13.69 (2.51)	9	17.48 (12.21)	55	24.56 (12.03)
B and C	10	13.76 (6.86)	9	17.48 (12.21)	55	24.56 (12.03)

value of 50. The mean score was higher for patients who waited longer for transplantation, but there was no difference between the three groups.

Table 25 shows pretransplantation summaries for the MCS of the SF-36, by group and by time since implantation (group A) or listing (groups B and C). In common with the PCS, the mean mental component score was lower than the population normal value of 50 for all groups and all time intervals. The mean score was higher for patients with longer time since implantation/listing. The groups had similar mean MCS. The MCS was less impaired than the PCS in all three groups.

Post-transplantation assessments

Physical and mental component scores for the three groups by time interval after transplantation are summarised in *Tables 26* and *27*. In the first 90 days after transplantation there was some evidence that non-VAD patients had better physical functioning but this was not significant. All groups had similar PCS after the first 90 days and similar MCS in both short- and medium-term follow-up.

TABLE 25 *Pretransplant time: grouped summaries for the SF-36 mental component score*

Group	0–30 days		31–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	13	23.51 (10.85)	21	30.70 (9.99)	45	41.17 (13.10)
B	6	17.59 (3.74)	0	–	0	–
C	4	23.38 (4.43)	9	30.45 (14.42)	55	34.50 (12.67)
B and C	10	20.49 (4.91)	9	30.45 (14.42)	55	34.50 (12.67)

TABLE 26 *Post-transplantation time: grouped summaries for the SF-36 physical component score*

Group	0–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)
A	9	33.46 (12.39)	19	39.55 (11.46)
B	1	44.84 (NA)	10	34.19 (11.26)
C	12	38.66 (15.51)	26	43.60 (15.13)
B and C	13	39.17 (14.89)	36	41.17 (14.66)

TABLE 27 *Post-transplantation time: grouped summaries for the SF-36 mental component score*

Group	0–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)
A	9	46.56 (11.27)	19	51.20 (11.97)
B	1	54.08 (NA)	10	45.85 (13.40)
C	12	46.75 (13.95)	26	54.73 (14.21)
B and C	13	47.36 (13.46)	36	52.44 (14.34)

TABLE 28 *SF-6D assessments over time pretransplantation*

Group	0–30 days		31–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	13	0.65 (0.10)	21	0.63 (0.10)	45	0.65 (0.07)
B	6	0.55 (0.11)	0	–	0	–
C	4	0.69 (0.11)	9	0.70 (0.12)	55	0.63 (0.10)
B and C	10	0.61 (0.13)	9	0.70 (0.12)	55	0.63 (0.10)

TABLE 29 *SF-6D assessments over time post-transplantation*

Group	0–90 days		≥ 91 days	
	n	Mean (SD)	*n*	Mean (SD)
A	9	0.71 (0.08)	19	0.62 (0.09)
B	1	0.50 (NA)	10	0.66 (0.08)
C	12	0.59 (0.11)	26	0.63 (0.08)
B and C	13	0.58 (0.11)	36	0.64 (0.08)

For all groups there was a significant improvement in physical and mental component scores due to transplantation. For the 13 VAD patients who had both pretransplantation and post-transplantation measurements, the mean change in PCS was 18.2 (95% CI 5.8 to 30.6, $p = 0.01$). For the 10 non-VAD patients with pretransplantation and post-transplantation measurements, the mean change in PCS was 23.3 (95% CI: 15.5 to 31.0, $p = 0.0001$). Corresponding mean changes in the MCS were 16.1 (95% CI 0.3 to 31.8, $p = 0.05$) for VAD patients and 24.2 (95% CI 15.8 to 32.6, $p = 0.0001$) for non-VAD patients.

SF-6D utilities

Tables 28 and *29* summarise SF-6D utilities before and after transplantation. This measure of utility shows different patterns to the EQ-5D and is generally lower post-transplantation. It shows less variability pretransplantation, which may reflect a lack of sensitivity to between-patient differences. These measurements are used to assess the sensitivity of the cost-effectiveness parameters to the measure of utility (see Chapter 8).

FLP

FLP scales

Four of the 12 FLP subscales were used in this study: sleep and rest (seven questions), bodycare and movement (23 questions), mobility (ten questions) and ambulation (12 questions). All questions are true/false statements for which

TABLE 30 *Sleep and rest subscale over time from implantation/listing*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	13	50.76 (41)	21	25.04 (34)	45	25.04 (47)	79	25.04 (40)
B	6	31.47 (32)	0	–	0	–	6	31.47 (32)
C	4	26.57 (57)	9	26.73 (47)	55	25.04 (36)	68	25.04 (41)
B and C	10	27.41 (26)	9	26.73 (47)	55	25.04 (36)	74	25.04 (38)

TABLE 31 *Bodycare and movement subscale over time from implantation/listing*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	13	22.57 (33)	21	16.19 (23)	45	10.64 (19)	79	12.35 (22)
B	6	20.03 (22)	0	–	0	–	6	20.03 (22)
C	4	13.93 (10)	9	11.26 (20)	55	6.23 (19)	68	7.94 (18)
B and C	10	17.18 (10)	9	11.26 (20)	55	6.23 (19)	74	8.33 (18)

patients score a weighted number of points for every true statement. Scores for each subscale are then calculated as a percentage of the maximum possible score, with higher percentages indicating a poorer quality of life.

Results

The distributions of scores for the four subscales of the FLP are shown in *Figure 17*. In all cases scores were positively skewed. For the pretransplantation period, scores were more spread out, covering the whole scale (0–100%), whereas the post-transplantation scores were more highly skewed and in most cases did not cover the full range.

There were positive correlations between all four of the subscales. Correlations were particularly strong between bodycare/movement, mobility and ambulation.

Pretransplantation assessments

FLP scores were complete for all 153 pretransplantation HRQoL assessments. The following analysis disregarded the time (after VAD implantation/acceptance on the list) at which the assessment was made. Thus, this analysis will average over all measurements taken in a specific period and may be less powerful than analyses that include adjustments for time. These more sophisticated analyses are not possible owing to the small samples within each group/period. This analysis also disregarded the fact that multiple assessments were made for some patients.

For groups A and C, the distribution of scores was very similar in the sleep/rest, mobility and ambulation scales. For bodycare/movement scores were slightly lower (fewer problems), in general, for group C compared with group A, but this was not significant.

For group B, since there were only six observations, it was difficult to say anything conclusive. However, for all four subscales, these patients scored higher (greater problems) than those in groups A and C.

Trends over time pretransplantation

There were no clear trends over time from VAD implantation (group A) or acceptance on to the transplant list (groups B and C) for any of the subscales. However, for mobility and bodycare/movement there was some negative trend, with patients scoring higher (i.e. poorer quality of life) closer to the time of their implantation or acceptance on the list. The corresponding Pearson's correlation coefficients were 0.052 ($p = 0.526$), –0.162 ($p = 0.046$), –0.182 ($p = 0.024$) and –0.159 ($p = 0.049$) for sleep and rest, bodycare and movement, mobility and ambulation, respectively. There were no clear differences between the groups (*Tables 30–33*, *Figures 18–21*).

For the sleep and rest subscale, non-VAD patients had fairly consistent scores across the three time periods. This indicates that non-VAD patients reported similar HRQoL, in terms of sleep and rest, regardless of how long it was since they were accepted on the transplant list. In contrast, VAD

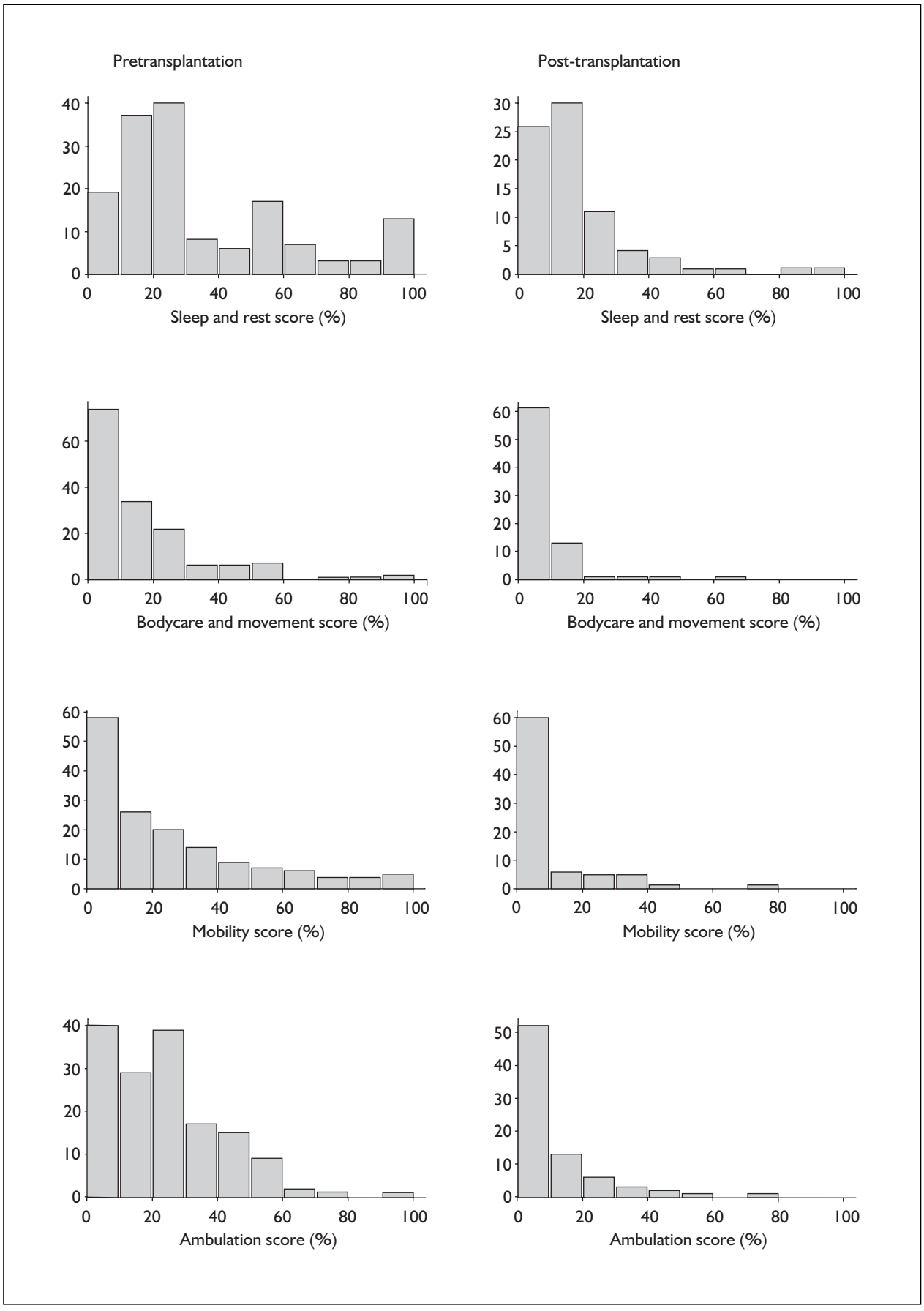

FIGURE 17 *Distributions of FLP scales before and after transplantation*

TABLE 32 *Mobility subscale over time from implantation/listing*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	13	41.27 (42)	21	24.35 (26)	45	7.15 (22)	79	13.89 (41)
B	6	44.77 (28)	0	–	0	–	6	44.77 (28)
C	4	31.50 (31)	9	10.87 (32)	55	14.99 (24)	68	14.99 (26)
B and C	10	38.31 (29)	9	10.87 (32)	55	14.99 (24)	74	17.19 (29)

TABLE 33 *Ambulation subscale over time from implantation/listing*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	13	42.94 (37)	21	24.26 (26)	45	12.03 (26)	79	17.40 (27)
B	6	36.33 (20)	0	–	0	–	6	36.33 (20)
C	4	25.84 (32)	9	21.77 (27)	55	21.77 (22)	68	21.77 (22)
B and C	10	29.92 (21)	9	21.77 (27)	55	21.77 (22)	74	21.77 (21)

patients had poorer sleep/rest scores in the first month after implantation, but beyond this had similar HRQoL to non-VAD patients.

The mean bodycare and movement scores decreased over the three periods for both VAD and non-VAD patient groups, indicating that patients' HRQoL, in terms of bodycare/movement, was better the longer it was since implantation or since they were accepted on to the transplant list. Scores were consistently higher in the VAD patients compared with group C, indicating that they evaluated their HRQoL as worse than those patients without a VAD. Patients on intravenous inotropes reported similar bodycare/movement levels to VAD patients in the first month.

For the mobility scores the trends were less clear. For all groups reported mobility was worse in the first month after VAD implantation or acceptance onto the waiting list and the average scores were similar for the groups. In group C, this was much lower in months 2–3 and did not improve after 3 months. However, in the VAD group HRQoL continued to improve over the periods.

The ambulation scores followed a similar pattern to the sleep and rest scores. Non-VAD patients reported similar HRQoL, in terms of ambulation, regardless of the length of time they had been on the list. VAD patients experienced a poorer HRQoL in the first month after the VAD was implanted, but had a similar HRQoL to non-VAD patients beyond the first month and a lower HRQoL than for non-VAD patients beyond 3 months.

The above results are plotted in *Figures 18–21*.

Post-transplantation assessments

FLP scores were complete for all 78 post-transplantation HRQoL assessments. If one disregards the time (since transplantation) at which the assessment was made and the fact that multiple assessments were made for some patients, there are no clear differences between the three groups in these HRQoL scores. Overall scores are shown in *Tables 34–37*.

Trends over time post-transplantation

There were very weak negative trends over time for all subscales, indicating that patients evaluated their HRQoL as improving over time after transplantation. The corresponding Pearson's correlation coefficients were –0.124 ($p = 0.281$), –0.094 ($p = 0.414$), –0.141 ($p = 0.217$) and –0.009 ($p = 0.936$) for sleep and rest, bodycare and movement, mobility and ambulation, respectively.

There were no clear or significant differences between the groups (*Tables 34–37*, *Figures 22–25*). It was very difficult to determine any trends from these data since so many patients scored 0 on post-transplantation assessments. However, poor HRQoL scores were more frequent in the early period after transplantation. Beyond 3 months

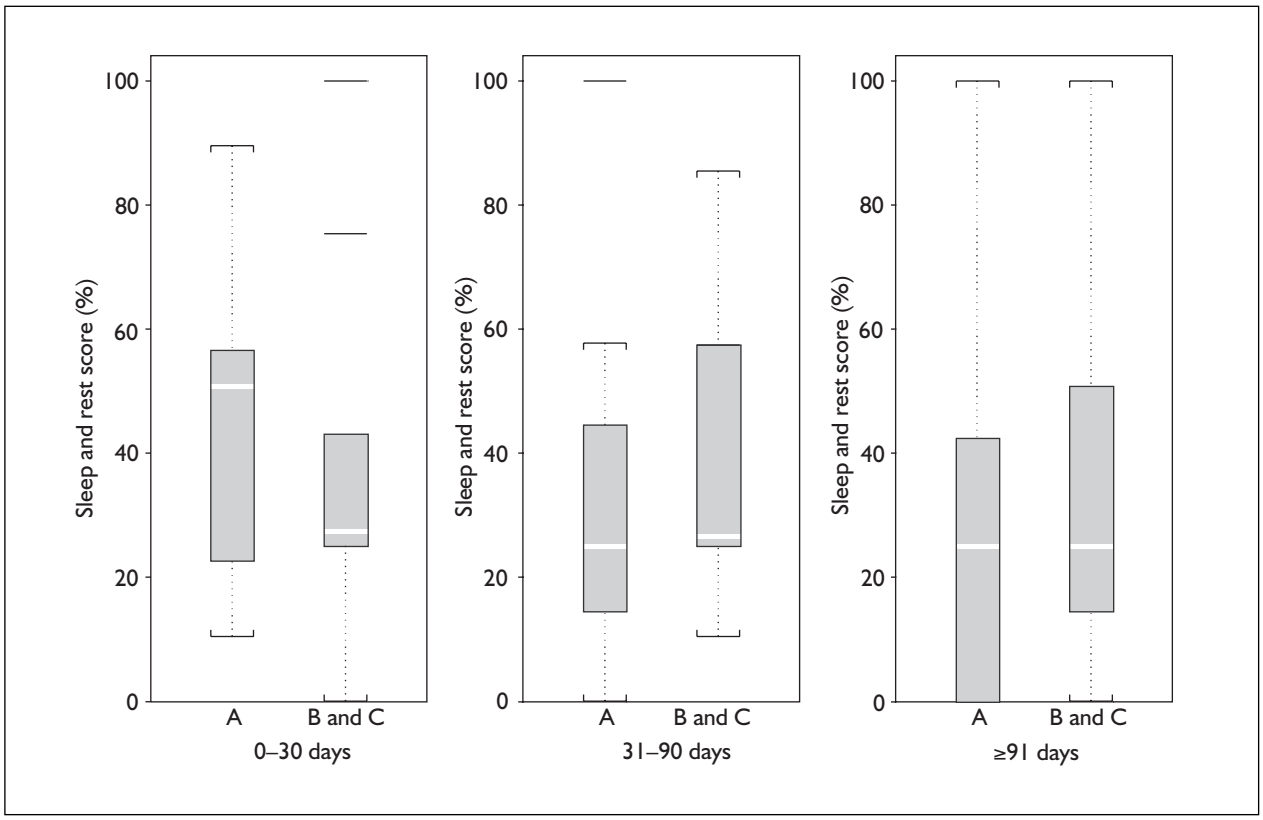

FIGURE 18 *Sleep and rest score by time (since implantation or acceptance) and group*

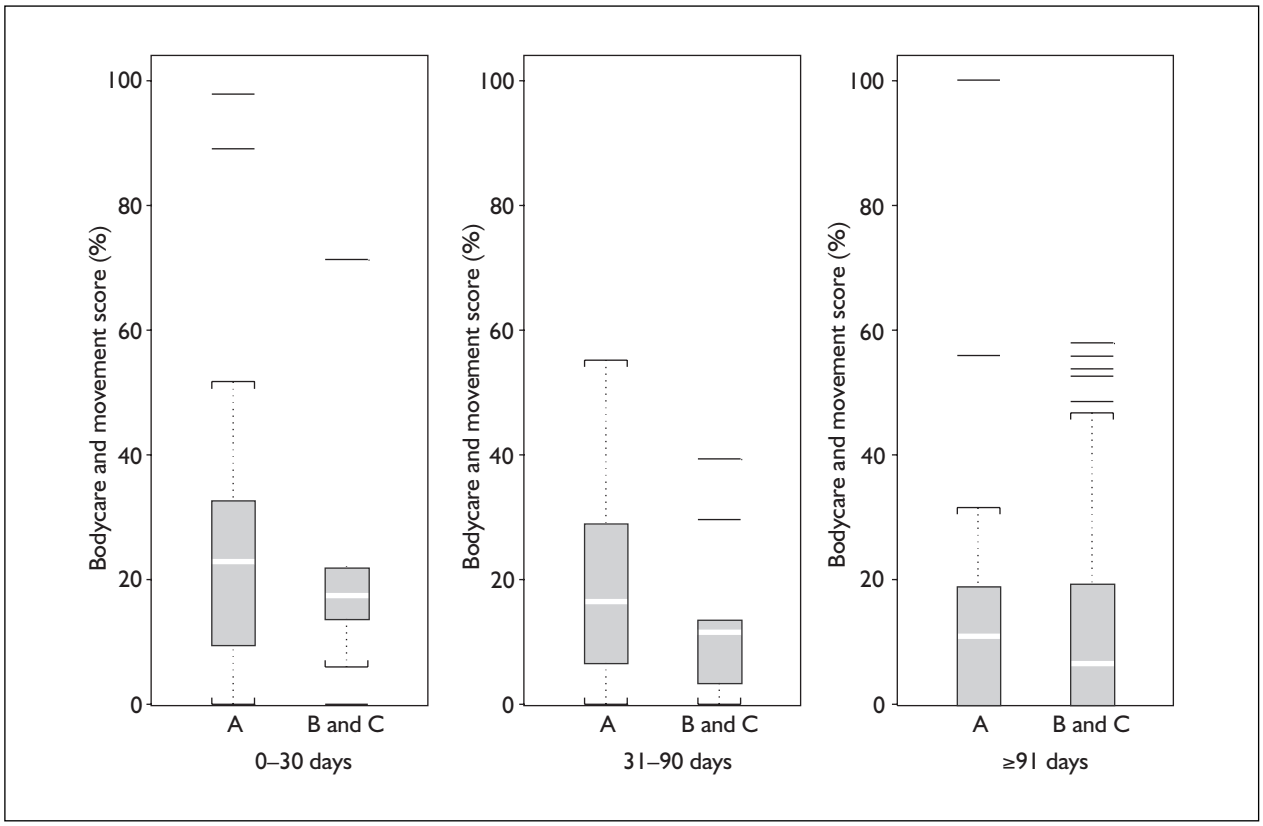

FIGURE 19 *Bodycare and movement score by time (since implantation or acceptance) and group*

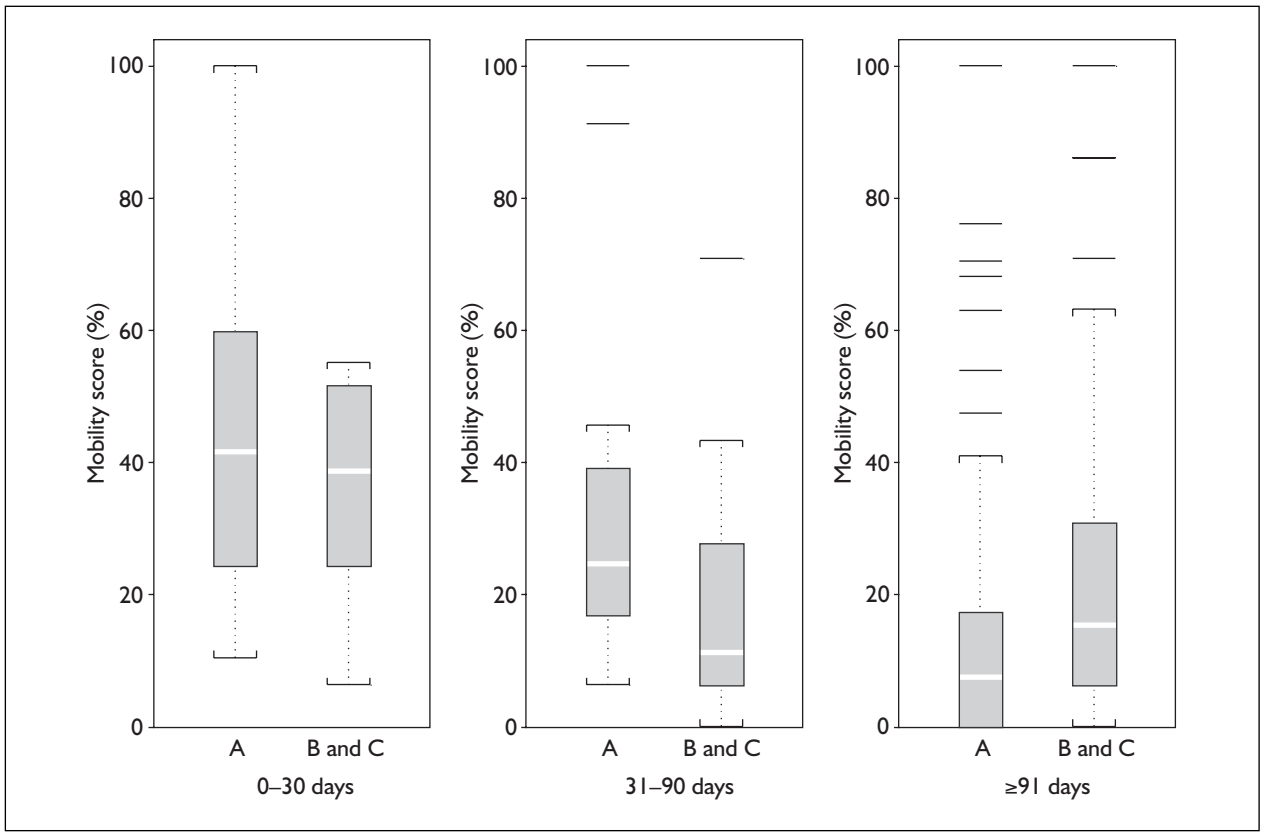

FIGURE 20 *Mobility score by time (since implantation or acceptance) and group*

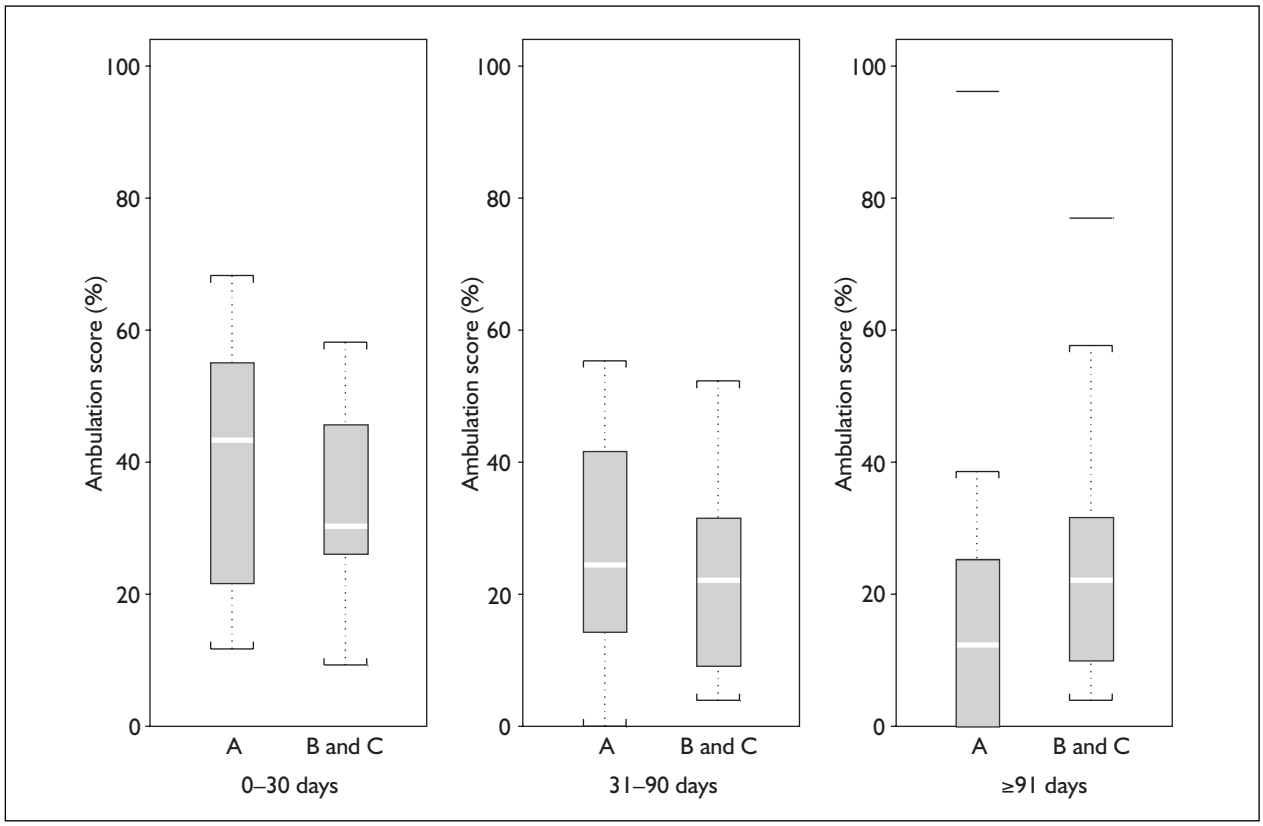

FIGURE 21 *Ambulation score by time (since implantation or acceptance) and group*

TABLE 34 *Sleep and rest over time from transplantation*

Group	0–90 days		≥ 90 days		Overall	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	10	18.61 (18)	19	0 (15)	29	14.55 (25)
B	1	41 (–)	10	5.25 (16)	11	10.49 (28)
C	12	14.55 (16)	26	13.54 (17)	38	14.55 (25)
B and C	13	14.55 (17)	36	12.18 (15)	49	13.54 (25)

The two VAD patients whose assessments were between 0 and 30 days both scored 10. The one group C patient whose assessment was between 0 and 30 days scored 25.

TABLE 35 *Bodycare and movement over time from transplantation*

Group	0–90 days		≥ 90 days		Overall	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	10	3.43 (14)	19	0 (5)	29	2.75 (7)
B	1	0 (–)	10	0 (4)	11	0 (0)
C	12	0 (5)	26	0 (11)	38	0 (8)
B and C	13	0 (4)	36	0 (11)	49	0 (7)

The two VAD patients whose assessments were between 0 and 30 days scored 0 and 3. The one group C patient whose assessment was between 0 and 30 days scored 0.

TABLE 36 *Mobility over time from transplantation*

Group	0–90 days		≥ 90 days		Overall	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	10	0 (11)	19	0 (0)	29	0 (7)
B	1	35 (–)	10	0 (12)	11	0 (28)
C	12	3.16 (16)	26	0 (10)	38	0 (13)
B and C	13	6.33 (26)	36	0 (8)	49	0 (13)

The two VAD patients whose assessments were between 0 and 30 days scored 0 and 24. The one group C patient whose assessment was between 0 and 30 days scored 13.

post-transplantation, most patients felt that they had a good HRQoL (indicated by a score of 0). The highest scores tended to be group C (non-VAD and no inotropes) patients, although this was based on small samples.

In the sleep and rest subscale both VAD and non-VAD (B and C combined) patients reported improvement pretransplantation to post-transplantation and this was significant in the non-VAD group. The mean improvement in the VAD group was 12.6 (95% CI –3.0 to 28.2), $p = 0.10$, and in the non-VAD group was 18.9 (95% CI 2.9 to 34.9), $p = 0.025$).

Both VAD and non-VAD patients reported significant improvements in the bodycare and movement subscale. Mean improvement in this subscale was 18.0 (95% CI 10.1 to 25.0, $p = 0.001$) in the VAD and 6.7 (95% CI 2.2 to 11.3, $p = 0.007$) in the non-VAD group. The extent of improvement was significantly greater in the VAD group ($p = 0.008$).

Mean reported mobility post-transplantation was significantly greater than pretransplantation, in VAD patients 20.6 (95% CI 10.4 to 30.7, $p = 0.001$) and in non-VAD patients 17.1 (95% CI 4.6 to 29.5, $p = 0.011$).

TABLE 37 *Ambulation over time from transplantation*

Group	0–90 days		≥ 90 days		Overall	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	10	12.72 (26)	19	0 (12)	29	6.16 (19)
B	1	13 (–)	10	0 (7)	11	0 (8)
C	12	0 (11)	26	0 (12)	38	0 (11)
B and C	13	0 (12)	36	0 (10)	49	0 (11)

The two VAD patients whose assessments were between 0 and 30 days scored 0 and 4. The one group C patient whose assessment was between 0 and 30 days scored 10.

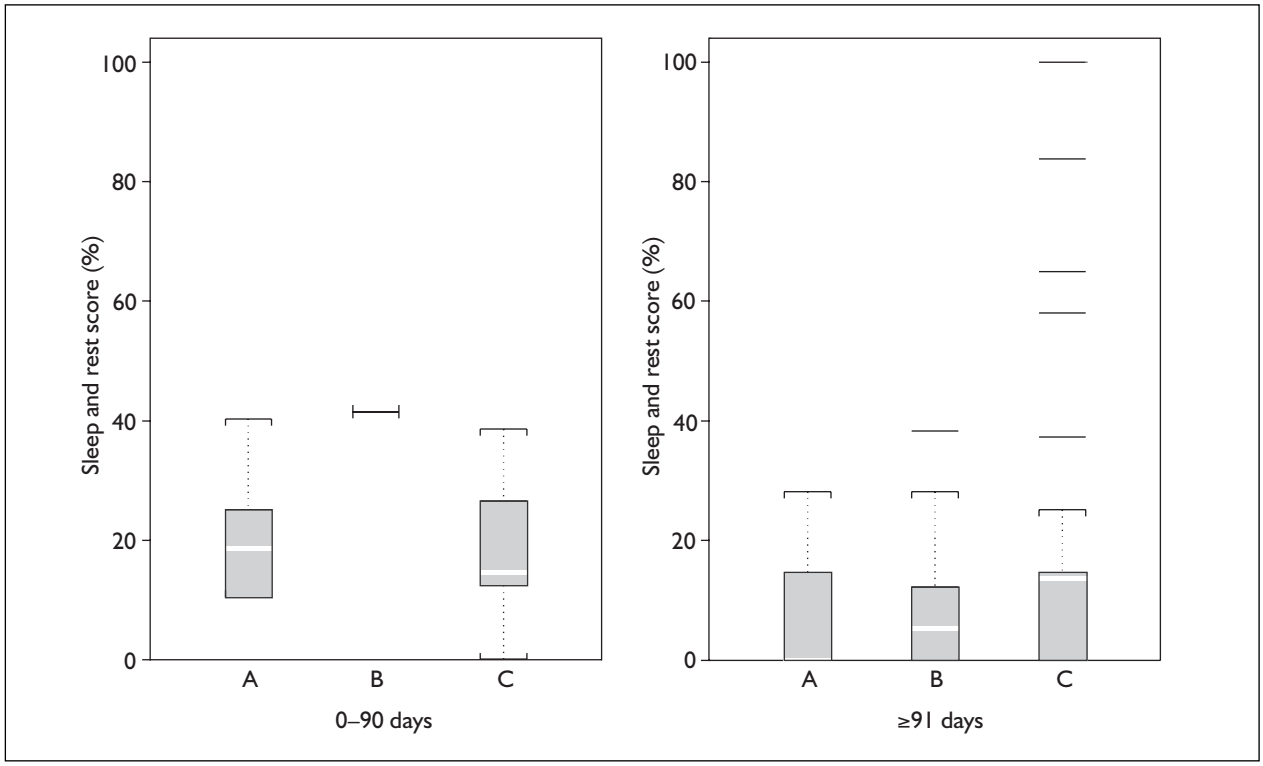

FIGURE 22 *Sleep and rest score by time since transplantation and group*

Similar significant improvements were seen in the ambulation subscale. Mean improvement was 14.5 (95% CI 3.0 to 26.0, $p = 0.0019$) in the VAD group and 19.5 (95% CI 9.5 to 29.5, $p = 0.001$) in the non-VAD group.

PSC

PSC scales

For the PSC, patients completed a questionnaire consisting of 29 items. Each item is a symptom (e.g. fatigue) and patients are required to rate how frequently they experienced the symptom on an ordinal scale of five possible responses, from 'not a problem' to 'occurs daily'. Items are scored from 0 to 4, with high scores indicating high frequency of the symptom. The total scored is calculated as a percentage of the maximum possible score (116), with high percentages indicating more problems.

Results

The distribution of the scores (as a percentage of maximum) is shown in the histograms in *Figure 26*. In both the VAD/medical management assessments and the post-transplantation assessments, scores did not cover the whole range of values (the maximum score was 63 or 54%). Scores for pretransplantation assessments were fairly normally distributed between 0 and 60, whereas

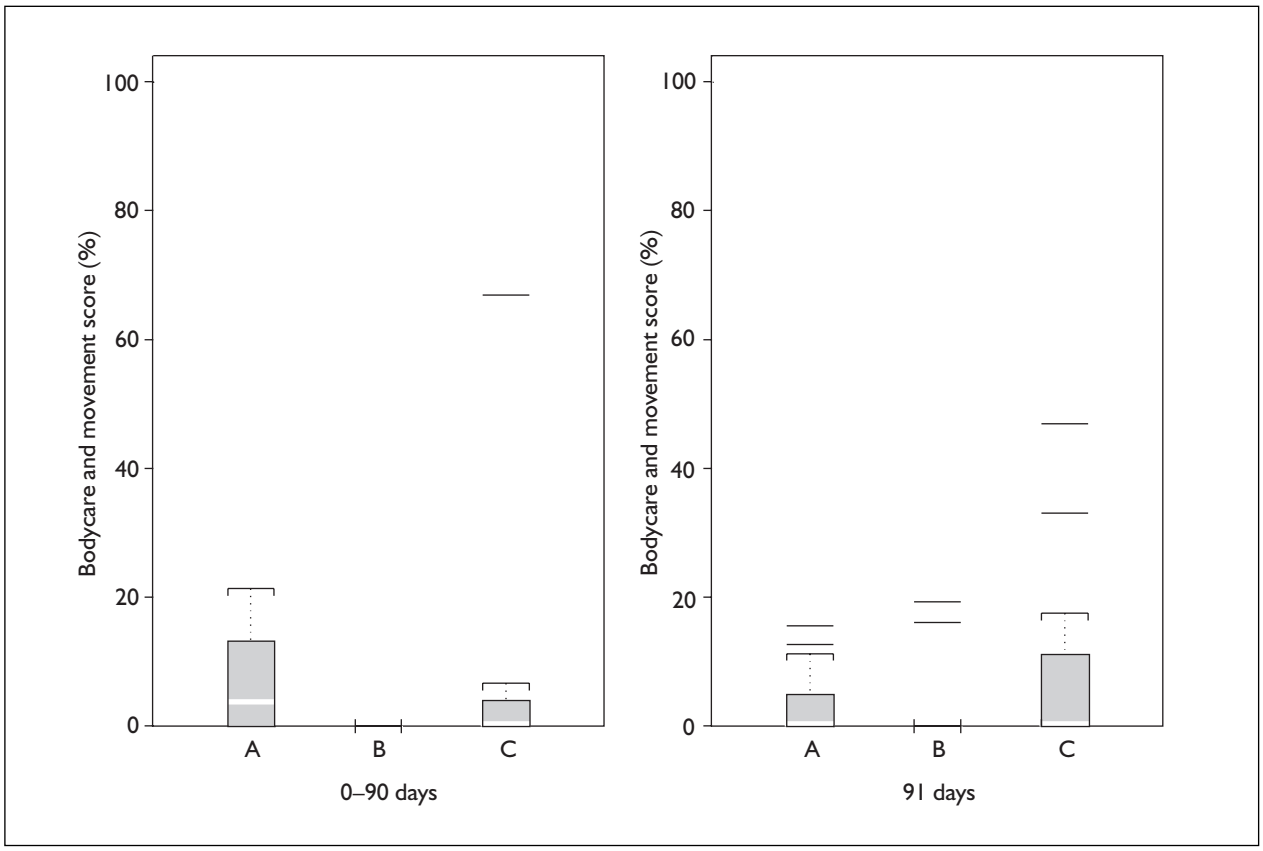

FIGURE 23 *Bodycare and movement score by time since transplantation and group*

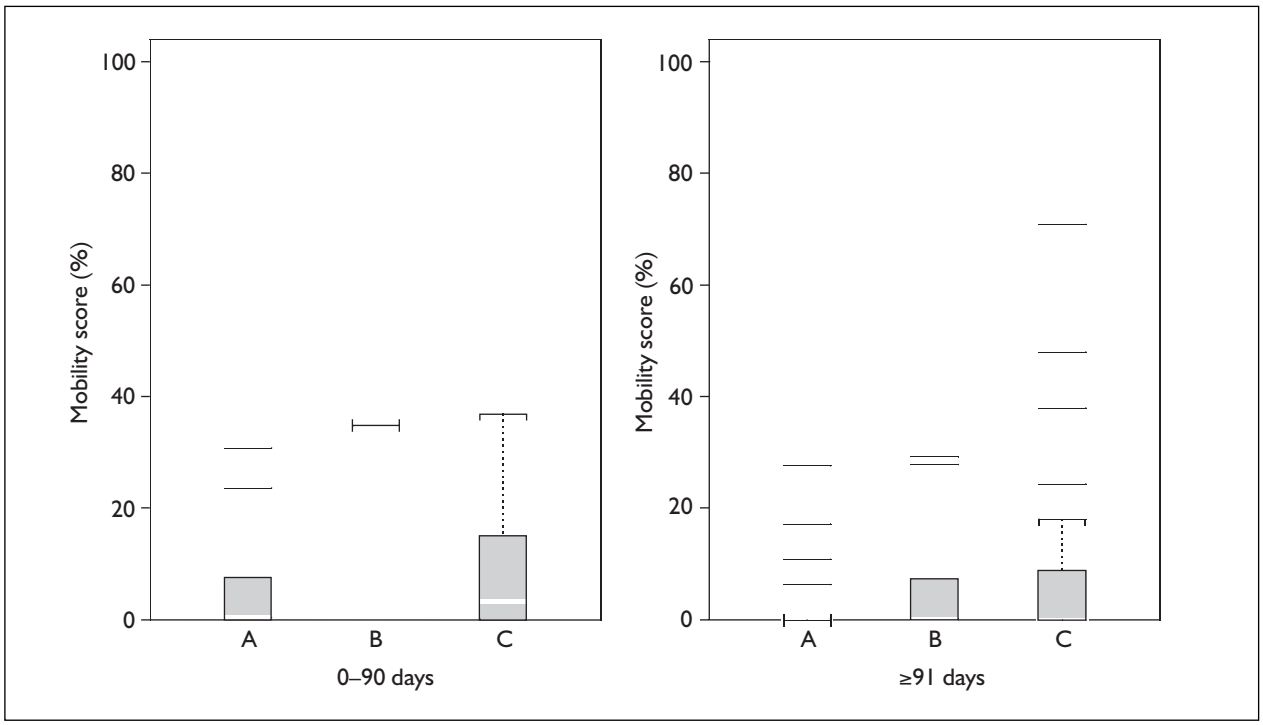

FIGURE 24 *Mobility score by time since transplantation and group*

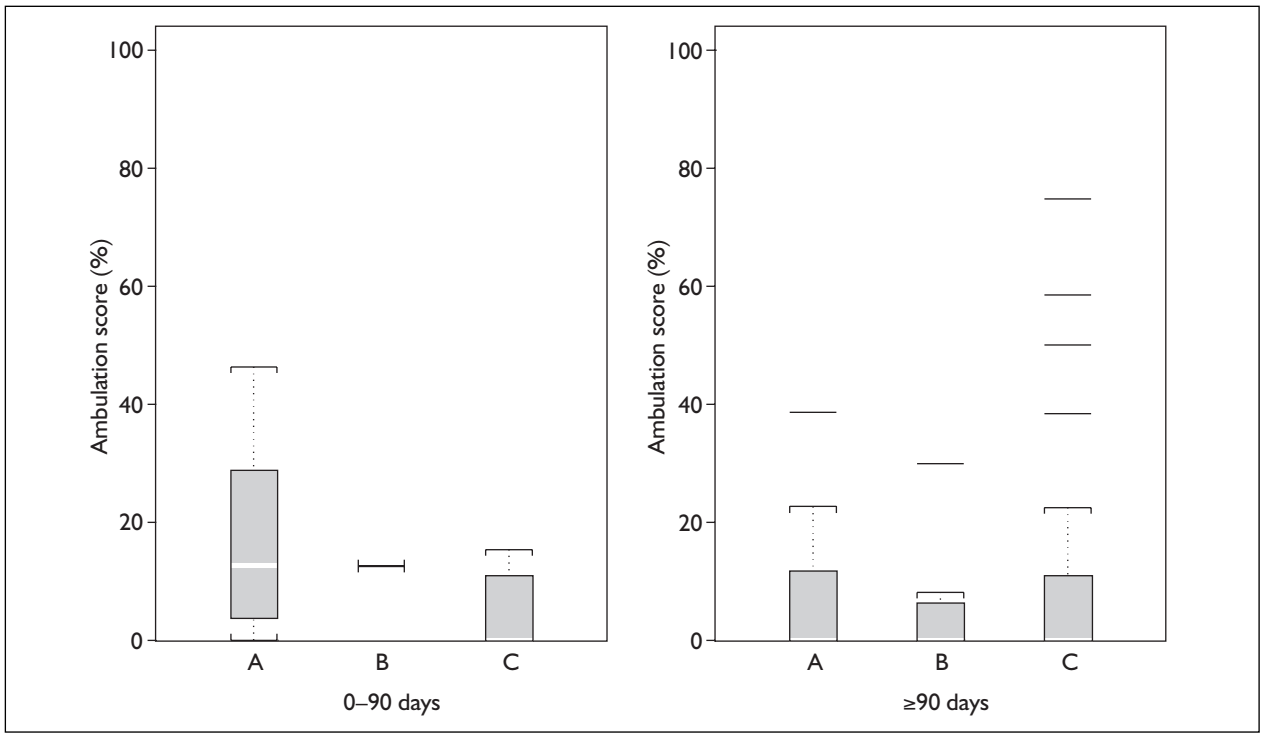

FIGURE 25 *Ambulation score by time since transplantation and group*

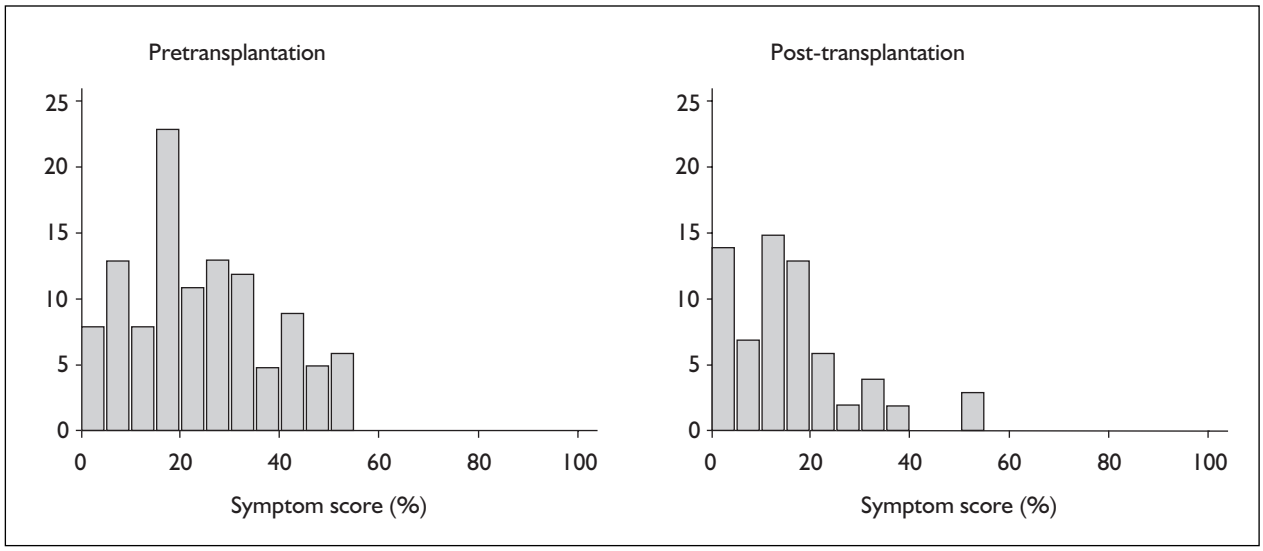

FIGURE 26 *Distribution of PSC scores as a percentage of the maximum possible*

post-transplant scores were positively skewed, with the bulk of assessments indicating a good HRQoL.

Pretransplantation

The PSC data were only complete for 113 of the 153 pretransplantation HRQoL assessments.

If one disregards the time (after VAD implantation/acceptance on to the list) at which the assessment was made and the fact that multiple assessments were made for some patients, there was no clear difference between the VAD and non-VAD patients in symptom score. The distributions of symptom scores in groups A and C look to be very similar.

Trends over time pretransplantation

There was some weak negative correlation between symptom score and time since VAD implantation

TABLE 38 *Symptom score (%)*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	8	24.14 (24)	17	28.45 (22)	32	18.97 (16)	57	22.41 (18)
B	4	35.78 (28)	0	–	0	–	4	35.78 (28)
C	3	31.90 (–)	7	29.31 (24)	42	19.40 (25)	52	21.12 (23)
B and C	7	31.90 (21)	7	29.31 (24)	42	19.40 (25)	56	24.14 (23)

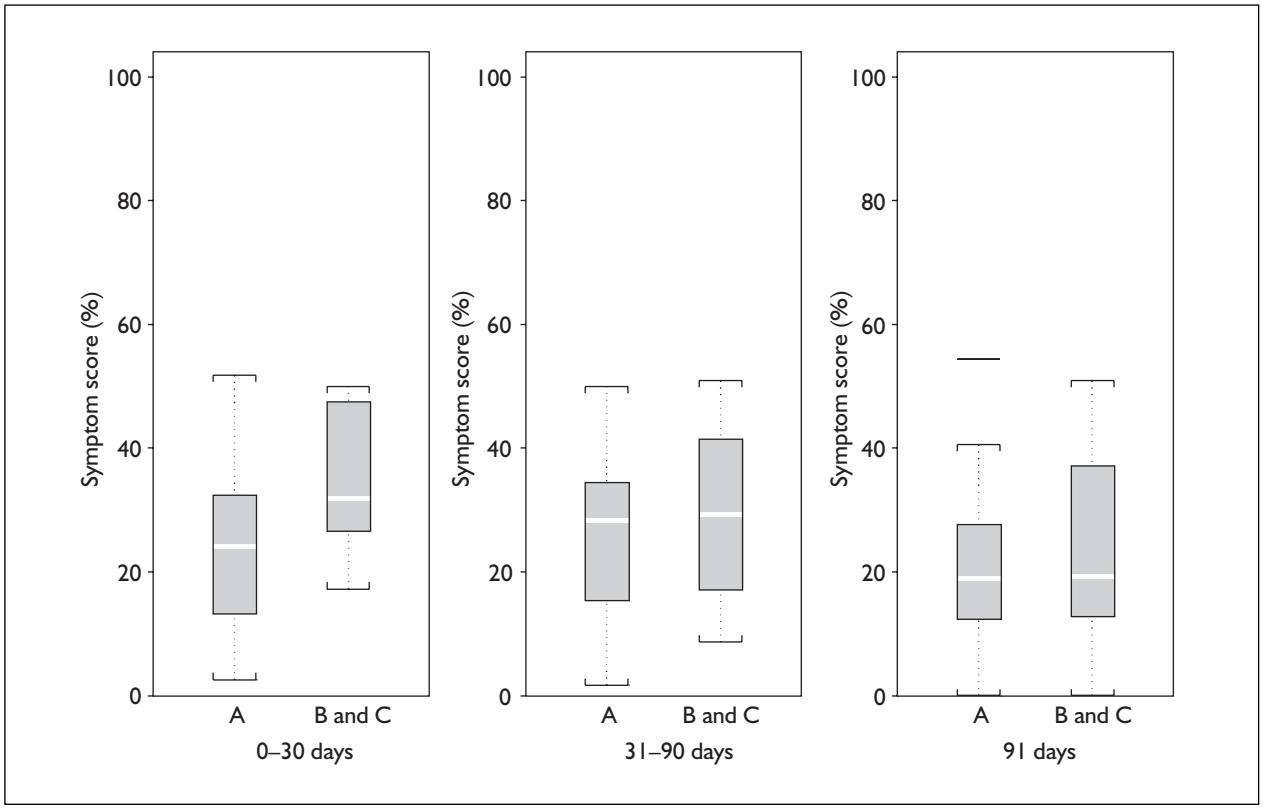

FIGURE 27 *Symptom score by time (since VAD implantation or acceptance on to the list) and by group*

or acceptance on to the list. The corresponding Pearson's correlation coefficient was $r = -0.191$ ($p = 0.042$). This indicates that patients who had had the VAD longer or were on the transplant waiting list longer were likely to have fewer physical symptoms.

In *Table 38* and *Figure 27* symptom scores were lower in the final time interval (i.e. beyond 3 months after implantation/acceptance on to the list). However, there were no differences between groups.

Post-transplantation assessments

PSC data were complete for only 66 of the 78 post-transplantation HRQoL assessments.

Disregarding the time after transplantation at which the assessment was made and the fact that multiple assessments were made for some patients, there were no clear differences in symptom scores between groups A and C. Scores for group B (non-VAD, with inotropes) were lower, but there were eight observations for this group of patients, so it is difficult to draw conclusions.

Trends over time post-transplantation

There was a very weak negative correlation with time pretransplantation, indicating that patients experienced fewer physical symptoms the longer it was since transplantation. The corresponding Pearson's correlation coefficient was $r = -0.131$ ($p = 0.293$).

TABLE 39 *Symptom score (%)*

Group	0–90 days		≥ 90 days		Overall	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
A	10	17.24 (27)	17	13.79 (19)	27	15.52 (22)
B	1	2 (–)	7	11.21 (7)	8	10.34 (9)
C	10	15.95 (11)	21	14.66 (16)	31	14.66 (15)
B and C	11	13.79 (15)	28	12.93 (15)	39	13.79 (15)

The two VAD patients who had assessments between 0 and 30 days after transplantation scored 3% and 5% on the physical symptoms checklist. The one patient in group C who had a HRQoL assessment between 0 and 30 days after transplantation did not have a complete symptom score record.

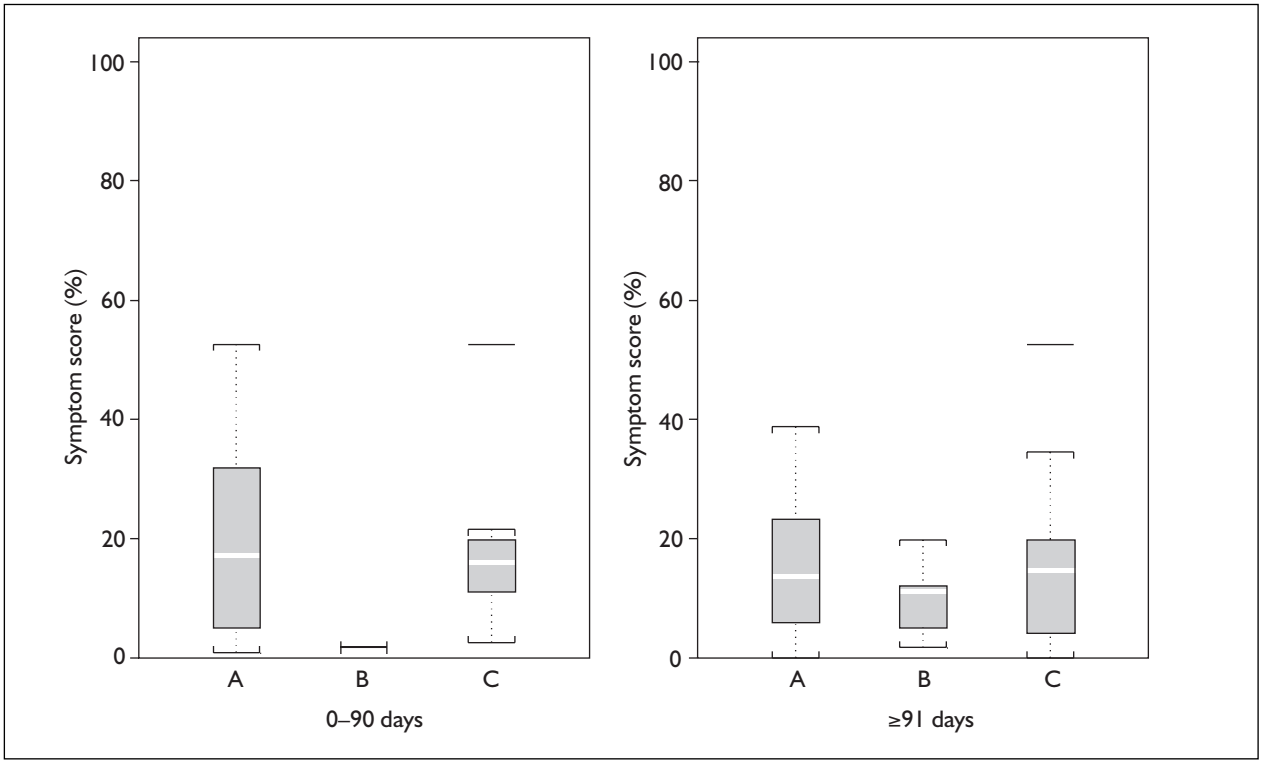

FIGURE 28 *Symptom score by time since transplantation and group*

From *Table 39* and *Figure 28* there were no clear differences across time or between the groups in PSC. The median scores beyond 3 months post-transplantation were lower than those in the first 3 months post-transplantation for all three groups, but the differences were small.

In comparing scores before and after transplantation, owing to the amount of missing data there were only eight patients in the VAD group and ten patients in the non-VAD group with scores both pretransplantation and post-transplantation. Despite this, both groups reported significant improvements from before to after transplantation. The mean improvement in the VAD group was 5.7% (95% CI 0.3 to 11.1%, $p = 0.042$) and in the non-VAD group was 13.8% (95% CI 7.4 to 20.2%, $p = 0.001$). There was weak evidence of a greater improvement in the non-VAD group, ($p = 0.047$).

HADS

HADs subscales

The HADS consists of 14 multiple-choice questions. These are split into two subscales, 'anxiety' and 'depression', of seven questions each.

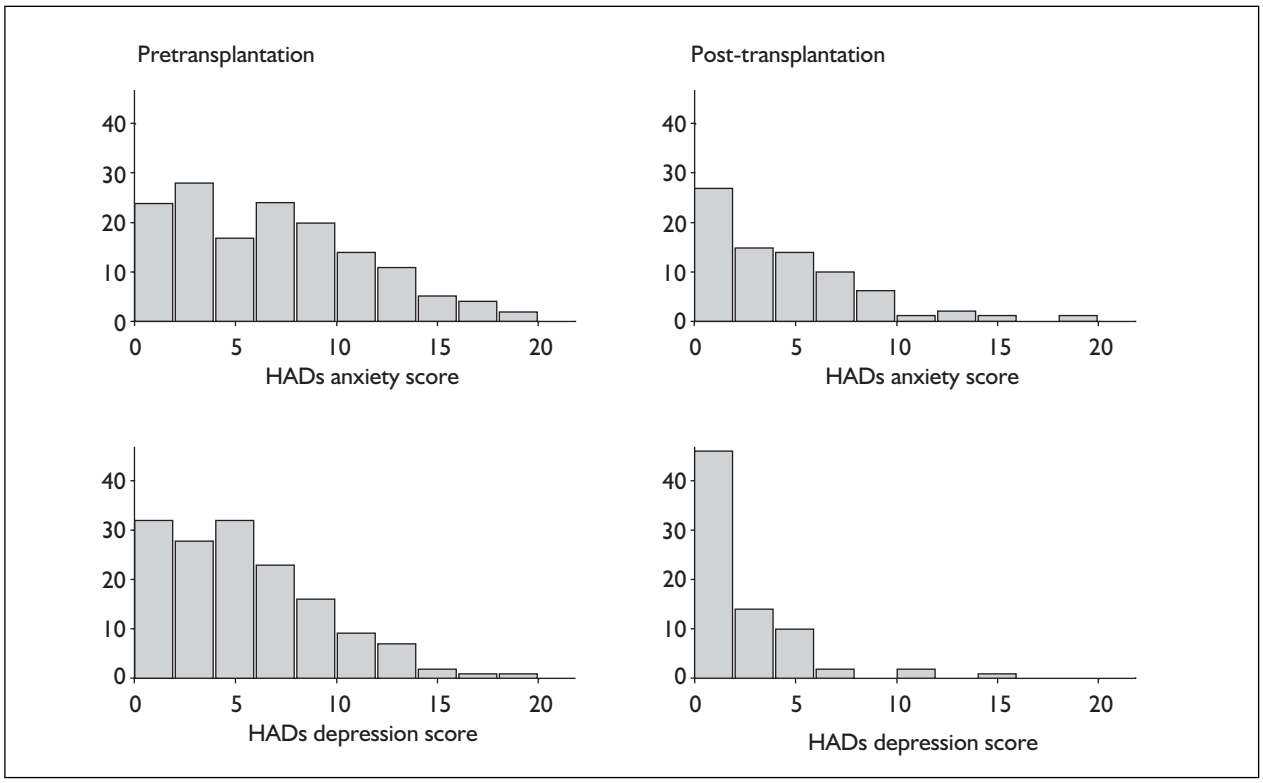

FIGURE 29 *Distribution of HADs anxiety and depression scores*

Each question has four possible answers and these are scored 0–3. Thus, for each subscale, the patient receives a score out of 21, with higher scores indicating a higher level of anxiety/depression. Patients were classed as 'no problem' (scores 0–7), 'borderline' (scores 8–10) or 'anxious/depressed' (scores 11–21).

Results

The distributions of HADs scores for the two subscales are shown in the histograms in *Figure 29*. For both subscales, the non-VAD/VAD assessment scores covered the full range of values, with an approximately normal distribution. For the post-transplantation assessments, however, scores were much more positively skewed, with very few patients scoring over 15 on either scale.

In addition, there was evidence of positive correlation between the two subscales. For pretransplant assessments Pearson's correlation coefficient was $r = 0.579$ ($p < 0.001$) and for post-transplant assessments, $r = 0.589$ ($p < 0.001$).

Pretransplantation

Of the pretransplantation questionnaires, four anxiety assessments and two depression assessments were incomplete and so scores could not be calculated. Disregarding the time (after implantation/acceptance on to the list) at which the assessment was made and the fact that multiple assessments were made for some patients, there were no clear differences between the groups in anxiety or depression scores (*Tables 40–43*). For anxiety there appeared to be more group C patients with scores above 10, but this was not statistically significant ($p = 0.24$). For depression, group B patients appeared to have higher mean scores, but this was based on a very small sample.

Trends over time pretransplantation

There were no obvious trends over time for either subscale (Pearson $r = 0.126$, $p = 0.125$ for anxiety and $r = -0.142$, $p = 0.082$ for depression) and no obvious differences between the groups (*Tables 40–43*, *Figures 30* and *31*).

Post-transplant assessments

Of the post-transplantation questionnaires, one anxiety assessment and three depression assessments were incomplete and so scores could not be calculated.

Disregarding the time (after implantation/acceptance on to the list) at which the assessment was made and the fact that

TABLE 40 *Anxiety subscale over time on VAD/waiting list (%)*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	11	8 (7)	20	6 (6)	44	5 (7)	75	5 (6)
B	6	7.5 (5)	0	–	–	–	6	7.5 (5)
C	4	8 (4)	9	7 (8)	55	7 (8)	68	7 (8)
B and C	10	7.5 (3)	9	7 (8)	55	7 (8)	74	7 (7)

TABLE 41 *Grouped anxiety subscale over time on VAD/waiting list*

Group	No problem	Borderline	Anxious
0–30 days			
A	4 (36.4%)	4 (36.4%)	3 (27.3%)
B	3 (50.0%)	2 (33.3%)	1 (16.7%)
C	2 (50.0%)	1 (25.0%)	1 (25.0%)
B and C	5 (50.0%)	3 (30.0%)	2 (20.0%)
Total	9 (42.7%)	7 (33.3%)	5 (23.8%)
31–90 days			
A	14 (70.0%)	4 (20.0%)	2 (10.0%)
C	5 (55.6%)	2 (22.2%)	2 (22.2%)
Total	19 (65.5%)	6 (20.7%)	4 (13.8%)
≥ 91 days			
A	28 (63.6%)	7 (15.9%)	9 (20.5%)
C	28 (50.9%)	9 (16.4%)	18 (32.7%)
Total	56 (56.6%)	16 (16.2%)	27 (27.3%)

TABLE 42 *Depression subscale over time on VAD/waiting list*

Group	0–30 days		31–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	12	7.5 (7)	20	7 (5)	45	3 (4)	77	5 (5)
B	6	10 (10)	0	–	–	–	6	10 (10)
C	4	8 (4)	9	6 (5)	55	5 (5)	68	6 (5)
B and C	10	9.5 (6)	9	6 (5)	55	5 (5)	74	6 (6)

multiple assessments are made for a given patient, there were no differences between the groups in anxiety and depression scales after transplantation.

Trends over time post-transplantation

There was some weak negative correlation with time for both subscales (Spearman $r = -0.084$, $p = 0.467$ for anxiety and $r = -0.080$, $p = 0.493$ for depression), indicating that patients became less anxious and depressed as time went on after transplantation.

There were no differences between the groups (*Tables 44–47*, *Figures 32* and *33*).

For the HAD questionnaire, owing to missing data, there were only 12 patients in the non-VAD group and ten in the VAD group who had measurements both before and after transplantation.

For the anxiety subscale there was no clear evidence to suggest that VAD patients had become less anxious following transplantation and only weak evidence that non-VAD patients were less

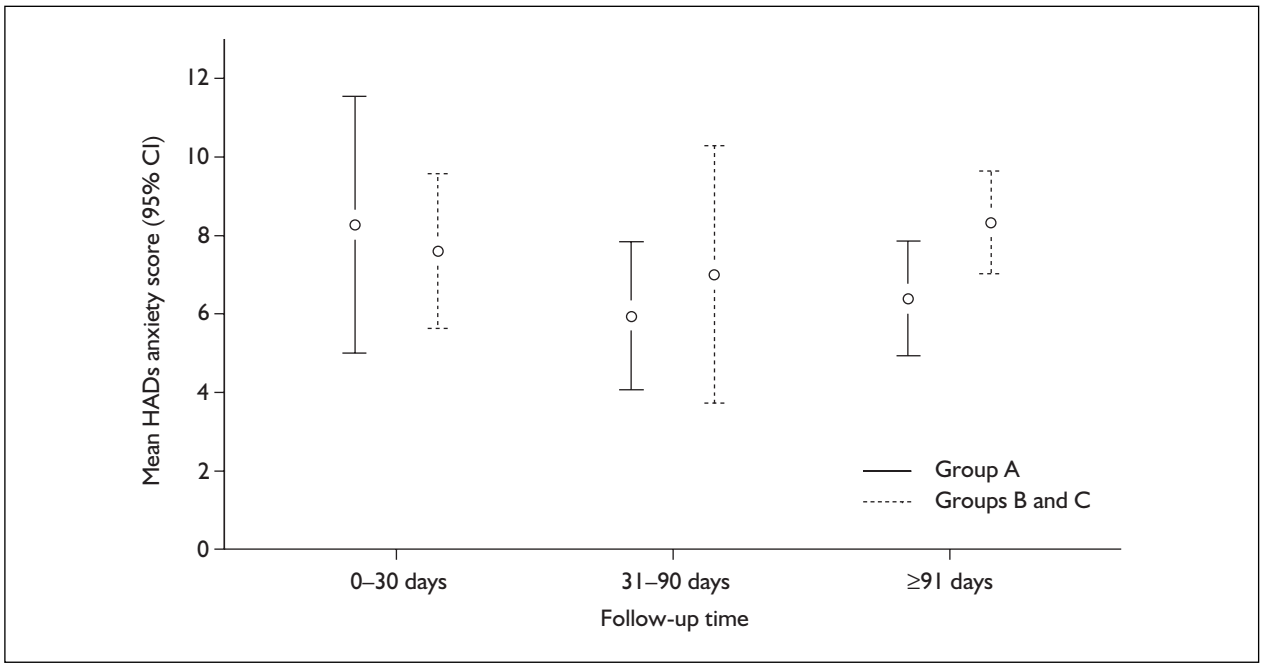

FIGURE 30 *HADs anxiety subscale over time pretransplantation*

TABLE 43 *Grouped depression subscale over time on VAD/waiting list*

Group	No problem	Borderline	Depressed
0–30 days			
A	6 (50.0%)	2 (16.7%)	4 (33.3%)
B	2 (33.3%)	1 (16.7%)	3 (50.0%)
C	2 (50.0%)	2 (50.0%)	0 (0%)
B and C	4 (40.0%)	3 (30.0%)	3 (30.0%)
Total	10 (45.5%)	5 (22.7%)	7 (31.8%)
31–90 days			
A	12 (60.0%)	6 (30.0%)	2 (10.0%)
C	6 (66.7%)	3 (33.3%)	0 (0%)
Total	18 (62.1%)	9 (31.0%)	2 (6.9%)
≥ 91 days			
A	38 (84.4%)	4 (8.9%)	3 (6.7%)
C	40 (72.7%)	7 (12.7%)	8 (14.5%)
Total	78 (78.0%)	11 (11.0%)	11 (11.0%)

anxious. The mean improvement in the VAD group was 2.2 points (95% CI –0.4 to 4.8, $p = 0.086$) and in the non-VAD group was 2.9 points (95% CI 0.0 to 5.8, $p = 0.048$).

For the depression subscale both groups reported significant improvements pretransplantation to post-transplantation. The mean improvement in the VAD group was 3.0 points (95% CI 0.8 to 5.2, $p = 0.014$) and in the non-VAD group was 4.3 points (95% CI 1.2 to 7.3, $p = 0.011$). There was no evidence that one group had improved more than the other in either subscale.

VAD-specific questionnaire

Source and description of the questionnaire

The VAD-specific HRQoL questions were developed over the course of the present study and were derived from two sources. The device-specific measure recommended by the Society of Thoracic Surgeons and the American College of Cardiology[102] was a one-page questionnaire

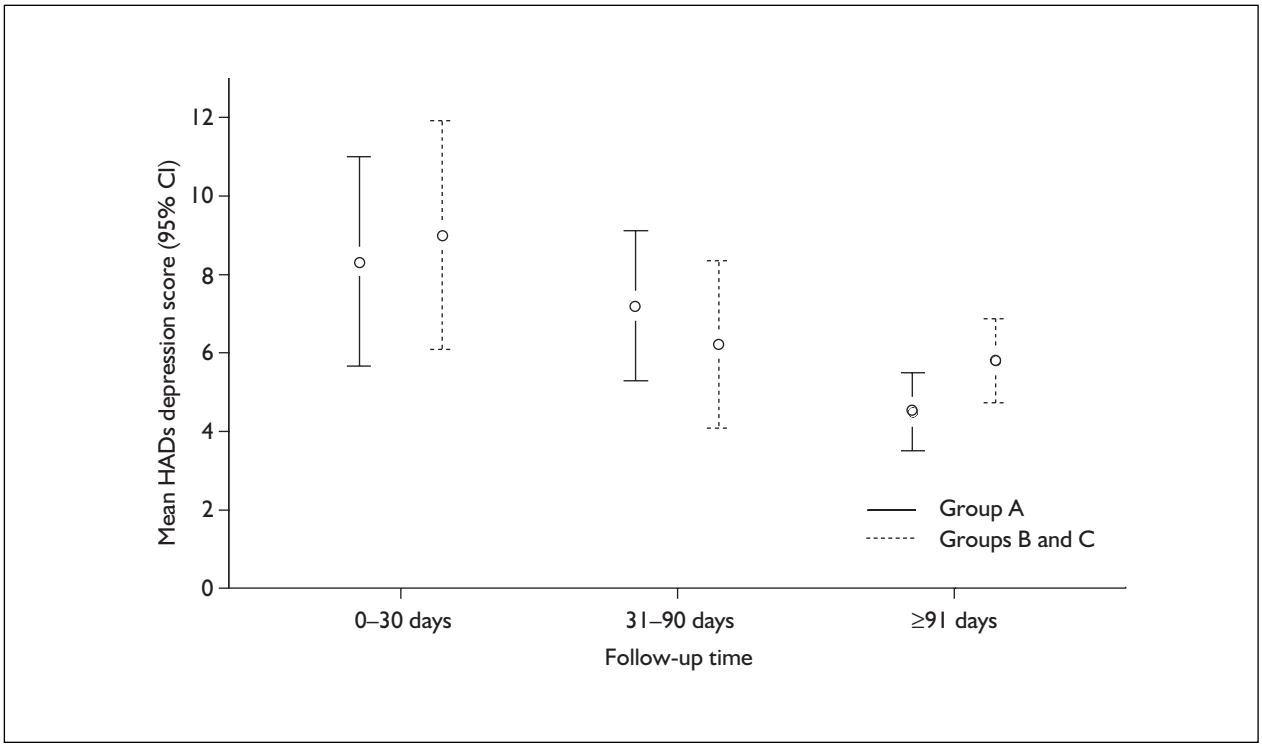

FIGURE 31 *HADs depression subscale over time pretransplantation*

TABLE 44 *Anxiety subscale over time post-transplantation*

Group	0–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	10	4 (5)	19	4 (4)	29	4 (4)
B	1	2 (–)	10	3.5 (9)	11	3 (8)
C	11	5 (6)	26	2.5 (5)	48	4 (5)
B and C	12	4.5 (6)	36	3 (6)	36	4 (6)

TABLE 45 *Grouped anxiety subscale over time post-transplantation*

Group	No problem	Borderline	Anxious
0–90 days			
A	8 (80.0%)	1 (10.0%)	1 (10.0%)
B	1 (100%)	0 (0%)	0 (0%)
C	7 (63.6%)	4 (36.4%)	0 (0%)
B and C	8 (66.7%)	4 (33.3%)	0 (0%)
Total	16 (72.7%)	5 (22.7%)	1 (4.5%)
≥ 9 days			
A	15 (78.9%)	2 (10.5%)	2 (10.5%)
B	6 (60.0%)	3 (30.0%)	1 (10.0%)
C	22 (84.6%)	3 (11.5%)	1 (3.8%)
B and C	28 (77.8%)	6 (16.7%)	2 (5.6%)
Total	43 (78.2%)	8 (14.5%)	4 (7.3%)

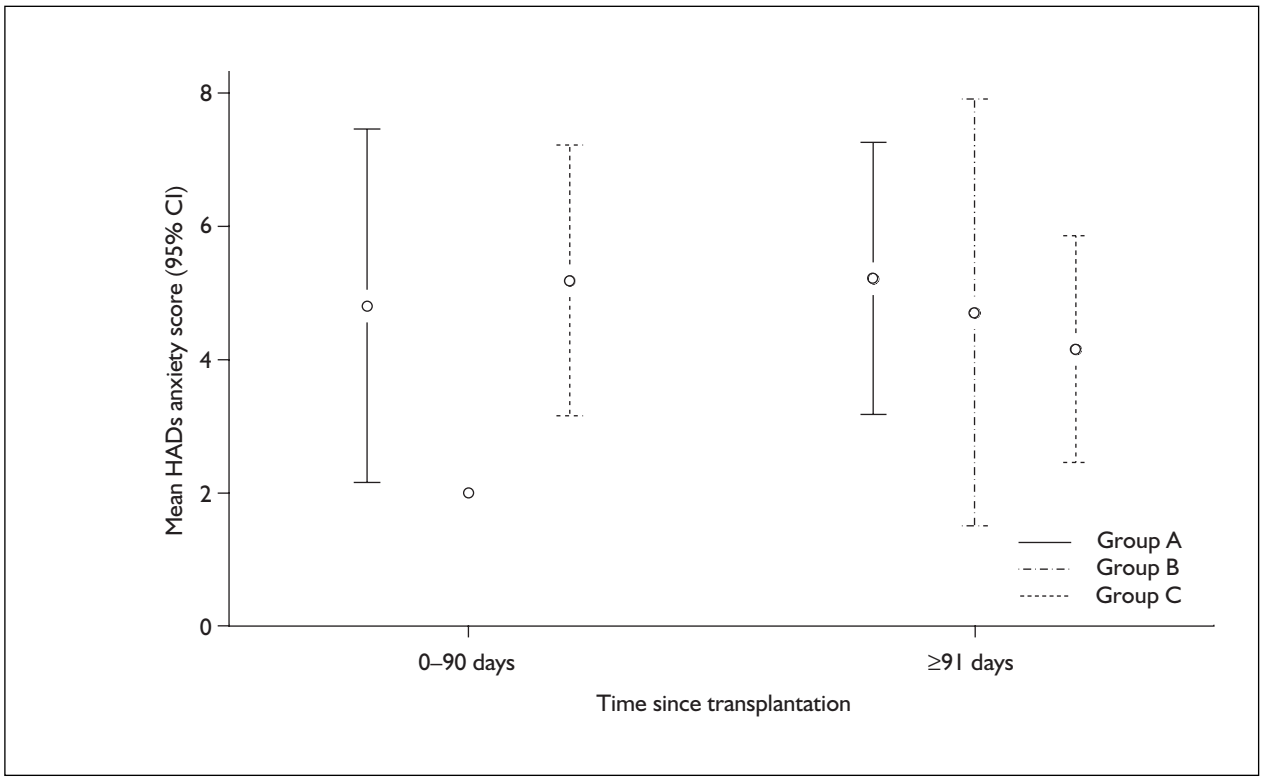

FIGURE 32 *HADs anxiety subscale over time post-transplantation*

TABLE 46 *Depression subscale over time post-transplantation*

Group	0–90 days		≥ 91 days		Overall	
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
A	9	4.5 (5)	19	2 (3)	28	2 (3)
B	1	2 (–)	10	3.5 (3)	11	3 (3)
C	11	1 (4)	25	1 (2)	36	1 (2)
B and C	12	1.5 (4)	35	2 (3)	47	2 (4)

TABLE 47 *Grouped depression over time post-transplantation*

Group	No problem	Borderline	Depressed
0–90 days			
A	9 (100%)	0 (0%)	0 (0%)
B	1 (100%)	0 (0%)	0 (0%)
C	10 (90.9%)	1 (9.1%)	0 (0%)
B & C	11 (91.7%)	1 (8.3%)	0 (0%)
Total	20 (95.2%)	1 (4.8%)	0 (0%)
≥ 91 days			
A	19 (100%)	0 (0%)	0 (0%)
B	10 (100%)	0 (0%)	0 (0%)
C	22 (88.0%)	1 (4.0%)	2 (8.0%)
B and C	32 (91.4%)	1 (2.9%)	2 (5.7%)
Total	51 (94.4%)	1 (1.9%)	2 (3.7%)

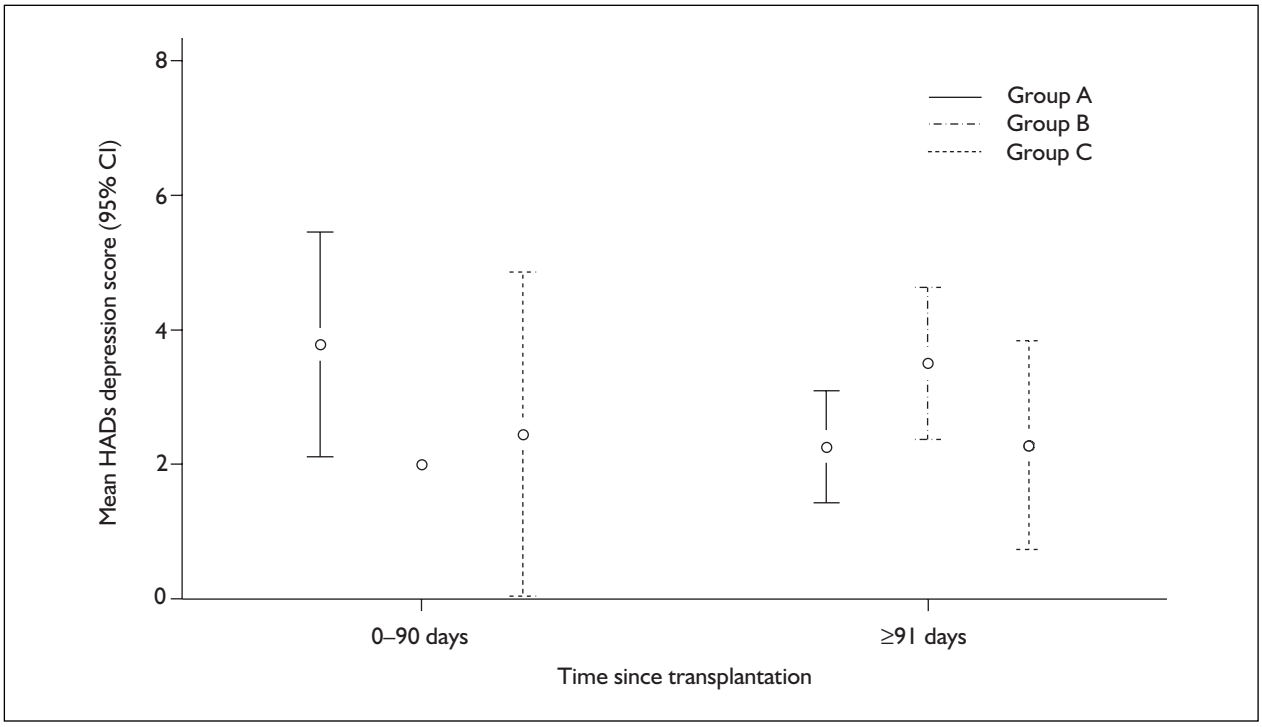

FIGURE 33 *HADs depression subscale over time post-transplantation*

adapted from measures used at three centres in the USA.[106] It was the present authors' original intention to use this questionnaire to compare their results with those from the USA. However, a UK VAD-specific quality of life questionnaire was being developed by psychologists at Harefield Hospital (VADQoL; Hallas and Wray, 2003) based on qualitative interviews with UK VAD patients. A final questionnaire was developed that retained five out of 13 questions from the US questionnaire (reported in *Table 48* Q8–11, Q21 in Appendix 3) and incorporated 16 questions developed by the Harefield Group. The questions were administered in a slightly different order over the course of the study and between hospitals, but the wording remained the same throughout. Questions reported as numbers 1–19 had a five-point response set: always, very often, sometimes, rarely or never. In addition, there were two open questions: 'If you could change anything on the VAD system, what would it be?' and 'If you have any other comments about living with a VAD then please write them below'.

Completed questionnaires

Sixty VAD-specific questionnaires were completed by 30 patients, with between one and four records each. Questionnaires were completed between the day of VAD implantation and 637 days after implantation, with the mean time being 168 days postimplantation. There was no clear evidence of trends over time. Owing to the categorical nature of the questions and the small sample who completed the questionnaires, detailed analysis of periods or patient subgroups was not feasible.

The remaining two questions were open questions and the comments are tabulated in Appendix 3. Note that the same patients made comments at different times when completing the questionnaire and these comments have been grouped. In response to the questions 'If you could change anything on the VAD system, what would it be?' and 'If you have any other comments about living with a VAD then please write them below', most patients wanted a smaller, lighter VAD system that was more comfortable to wear and allowed maximum mobility. Two patients who had had a device for 9 and 16 months reported that they were beginning to 'feel trapped' and 'increasingly aware of the restrictions associated with the VAD'.

UK study: cognitive functioning test results

Since most cognitive function tests have to be administered face to face, few pretransplantation assessments were available for routine waiting-list patients. One of the *a priori* hypotheses was that

TABLE 48 *Number of responses (%) to the VAD-specific quality of life questionnaire*

		Always or very often	Sometimes	Rarely or never
Q1:	I think that my future health is more certain with a VAD	36 (68)	12 (23)	5 (9)
Q2:	I worry about having medical problems whilst I have a VAD	10 (19)	19 (36)	24 (45)
Q3:	I cope well living with a VAD	41 (80)	5 (10)	5 (10)
Q4:	I feel that my family understands what it is like for me to live with a VAD	32 (62)	14 (27)	6 (12)
Q5:	I feel positive about being part of a new medical programme	41 (77)	8 (15)	4 (8)
Q6:	I find other people's reactions to my VAD difficult to deal with	5 (10)	7 (14)	39 (76)
Q7:	I find the frequency of medical tests and dressing changes difficult to deal with	8 (15)	11 (21)	34 (64)
Q8:	I worry about the VAD breaking or malfunctioning	9 (15)	22 (37)	29 (48)
Q9:	The VAD noise bothers me	5 (8)	13 (22)	22 (70)
Q10:	I feel that I can function better since I received my VAD	48 (82)	6 (10)	5 (8)
Q11:	I have a brighter outlook on life since I received my VAD	44 (75)	10 (17)	5 (8)
Q12:	I feel there are restrictions on my daily routine[a]	15 (44)	13 (38)	6 (18)
Q13:	I am bothered by the demands of the VAD on my daily life[a]	9 (27)	10 (29)	15 (44)
Q14:	I am worried about the restrictions that living with a VAD has on my life[a]	7 (21)	10 (29)	17 (50)
Q15:	I am worried about the restrictions that living with a VAD has on my carer/companion[a]	16 (47)	9 (26)	9 (26)
Q16:	I feel in control of my everyday life[a]	23 (68)	6 (17)	5 (15)
Q17:	My relationship with my carer/companion is more positive since having the VAD[a]	22 (69)	7 (22)	3 (9)
Q18:	I restrict my social life because I feel self-conscious with my VAD[a]	3 (9)	7 (21)	24 (71)
Q19:	I am satisfied with the amount of independence that I have[a]	15 (45)	12 (36)	6 (18)

[a] For Q12–19, 22 patients were excluded who, at the time of completing the questionnaire, had not yet left hospital following implantation. This leaves a total of 37 questionnaires.

post-transplantation, patients who had received a VAD implantation followed by transplantation, and had therefore been subject to two major procedures involving periods of cardiopulmonary bypass, may experience more impaired cognitive function than non-VAD transplant recipients. Therefore, the post-transplantation cognitive function assessments for VAD patients are compared with non-VAD patients in *Table 49*. Thirty-four patients completed a total of 55 assessments, between 12 and 722 days post-transplantation, with a mean 178 days (*Table 49*).

TABLE 49 *Number of cognitive function assessments (patients) post-transplantation*

Group	0–90 days	≥ 91 days	Total
A	7 (7)	14 (12)	21 (13)
B and C	10 (9)	24 (17)	34 (21)
Total	17 (16)	38 (28)	55 (34)

Figures given are the number of assessments (number of patients).

Wechsler's DSS

DSS scales

The DSS test is part of the Wechsler Adult Intelligence Scale (WAIS). It is a commonly used test of visual–motor coordination and visual perception of abstract stimuli and measures the speed of processing information. The test takes 90 seconds to complete and involves writing in symbols that match numbers in a grid by copying from a given code. The score is the number of correct consecutive substitutions completed in the given time. Possible scores range from 0 to 100, with a higher score representing better performance.

Scores are likely to be affected by the age of the patient, with lower scores expected for older patients.[119,120] The mean (SD) age of the group was 44.6 (14.0) years, with ages ranging from 21 to 70 years. The mean age for each group is given in *Table 50*. The difference in mean age for the people who completed tests after the first 90 days post-transplantation was

TABLE 50 *Mean (SD) age for patients with cognitive functioning studies*

Group	0–90 days	≥ 91 days	Total
A	39.6 (12.0)	38.9 (10.5)	39.8 (10.7)
B and C	37.4 (12.9)	51.5 (14.1)	47.7 (15.0)

significant, with non-VAD patients being older than VAD-supported patients. However, no adjustment has been made for differences in age in the results.

Results

Post-transplantation results on the DSS are summarised in *Table 51*. There were no significant differences between the groups in the first 3 months after transplantation ($p = 0.742$) or after this period ($p = 0.220$). The lower score for non-VAD patients may reflect the older mean age of this group in this study.

Halstead–Reitan Trail Making A and B

Halstead–Reitan Trail Making scales

The Halstead–Reitan Trail Making tests A and B[121] are sequential problem-solving and concentration tests. The Trail A test requires the subject to connect sequentially (i.e. 1–2–3–4) randomly placed consecutively numbered circles. The Trail B test is similar to but more complex than the Trail A test, in that the subject is required alternately to connect randomly placed consecutively numbered then consecutively lettered circles (1–A–2–B–3). Patients are asked to complete the tasks as quickly as possible and each task is timed. Therefore, higher scores indicate a poorer performance.

If the participant makes a mistake during the test, the examiner points it out and the patient corrects the error and resumes the task. The time includes the time for this to take place and so penalises for errors. Therefore, it is not thought necessary to report numbers of errors (although they have been indicated in the results below). However, this also means that scores are affected by the examiner's reaction time, which may differ from one examiner to the next.

Finally, since this is a timed exercise, age will have an effect on the times recorded, with slower responses expected for older patients. The mean (SD) age of the group was 44.6 (14.0) years, with ages ranging from 21 to 70 years. The mean age for each group is given in *Table 50*. No adjustment has been made for differences in age in the results.

Results

Results: Trail Making A

Overall, the mean time to complete trail A was 38.6 seconds (SD 14.6) and times ranged from 16 to 100 seconds (*Table 52*). One patient in group B made six errors when he was assessed at 84 days post-transplantation and one error when he was assessed again at 236 days post-transplantation. No other errors were made in any of the tests. Although patients in groups B and C had a higher mean time to complete trail A than group A, the differences were not significant ($p = 0.117$, 0–90 days, and $p = 0.064$, ≥ 91 days) and reflect the older age of non-VAD patients in this study.

Results: Trail Making B

Overall, the mean time to complete trail B was 75.2 seconds (SD 29.3) and times ranged from 30

TABLE 51 *Post-transplantation results of the DSS test for VAD- and non-VAD-supported patients*

Group	0–90 days		≥ 91 days		Overall	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
A	48.0 (14.4)	30–73	53.2 (15.4)	28–80	51.5 (14.9)	28–80
B and C	45.6 (14.4)	30–69	47.9 (10.9)	29–70	46.0 (11.0)	29–70

TABLE 52 *Time taken to complete the Trail Making Test A*

Group	0–90 days		≥ 91 days		Overall	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
A	36.1 (7.1)	25–46	31.6 (10.0)	16–57	33.1 (9.2)	16–57
B and C	52.2 (24.5)	22–100	38.3 (10.5)	23–65	43.8 (16.5)	22–100

TABLE 53 *Time taken to complete the Trail Making Test B*

Group	0–90 days		≥ 91 days		Overall	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
A	68.7 (20.3)	40–93	63.8 (23.1)	30–106	65.4 (21.8)	30–106
B and C	98.0 (47.8)	41–185	75.1 (22.0)	40–120	84.7 (28.8)	40–185

TABLE 54 *Time taken to complete the MMSE*

Group	0–90 days		≥ 91 days		Overall	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
A	28.9 (1.2)	27–30	29.0 (1.2)	26–30	29.0 (1.2)	26–30
B and C	27.5 (2.5)	22–30	28.7 (1.6)	25–30	28.3 (1.9)	22–30

to 185 seconds (*Table 53*). The group B patient who made errors in trail A also made one error in each of the trail B assessments. In addition, two group C patients (one assessed at 0–90 days and one at ≥ 91 days) made one error each and, similarly, two group A patients (one assessed at 0–90 days and one at ≥ 91 days) made one error each. Finally, one group C patient, assessed at 104 days post-transplantation, made five errors. As in trail A, groups B and C took longer to complete the test than group A, but the difference was not significant and, again, reflects age differences between the groups.

MMSE

MMSE scales

The MMSE[105] is designed to assess orientation, language, copying, memory, calculation and attention. It contains 11 tasks and summing the points assigned to each successfully completed task gives a score of 0–30, with low scores indicating cognitive impairment. Scores of less than 22 are associated with cognitive decline equivalent to that of elderly patients with dementia. It has been suggested that a score of 23 or less for an individual with more than 8 years' education may be considered evidence of cognitive impairment.

Results

For the MMSE overall the mean score was 28.6 (SD 1.7) and scores ranged from 22 to 30 points (*Table 54*). There were no significant differences between the groups.

Only one patient scored 23 points or less. This was a group C patient assessed 67 days after transplantation who scored 22 points. This patient had also failed to complete the DSS test and the Trail Making tests.

TABLE 55 *Questionnaires with a score of ≤ 26 points*

Group	0–90 days	≥ 91 days	Total
A	0	1 (7%)	1 (5%)
B and C	2 (20%)	3 (13%)	5 (15%)

The number (percentage) of questionnaires with a score of 26 points or less is indicated in *Table 55*.

Discussion

The two main groups with experience in the evaluation of HRQoL of LVAD patients are Pittsburgh and Rush (Chicago) Universities. The REMATCH trial of LVAD as destination therapy,[12] initiated by Columbia University, was conducted in 20 US centres; this protocol has a similar package of HRQoL measures to that used in Pittsburgh. In this study of the UK VAD programme, the protocol for the evaluation of HRQoL was derived from these US groups, together with the valuable experience gained by psychologists at Harefield Hospital in interviews with heart failure and VAD patients. This is therefore the first report of the HRQoL of UK patients, measuring both physical and psychological dimensions of function, before and after transplantation.

The main finding from this study was that there was either no or little difference between the three groups before and after transplantation. This supports a previous report,[43] where both VAD and

non-VAD patients reported similar physical functioning, emotional and social well-being, after transplantation, with improvement from 2 to 12 months post-transplantation. In contrast, Grady and colleagues[45] found that VAD patients were significantly more satisfied with their overall HRQoL, health and functioning, and experienced less physical and self-care dysfunction, after transplantation, than non-VAD patients.

In contrast to the US patient experience,[43] cognitive impairment was not found to be more common in VAD patients than non-VAD patients after transplantation. Indeed, there was a tendency for non-VAD patients to have poorer cognitive function, but this may be explained by the fact that non-VAD patients completing cognitive function tests were older than those who had been on VAD support.

A very important aspect of the evaluation of HRQoL in these patients was the experience of living with the device. The vast majority of patients said that they were coping well living with the VAD (80%), they had a brighter outlook on life since receiving the device (75%) and they felt positive about being part of a new medical programme (77%). A significant number of patients (52%) were worried about the VAD breaking or malfunctioning, at least some of the time, and 30% of patients were bothered about the noise at least some of the time. Most patients who commented on changes they would like to see to the device wanted a smaller, lighter VAD system that was more comfortable to wear and allowed maximum mobility. Two patients who had had a device for 9 and 16 months reported that they were beginning to 'feel trapped' and 'increasingly aware of the restrictions associated with the VAD'.

One limitation of this study was the size of the patient sample which, when combined with the intrinsic variability in HRQoL, precludes detailed study of changes over time, and identification of reasons for patient heterogeneity.

Summary

Following VAD implantation, overall HRQoL, including utility assessed by the EQ-5D, was poor in the first month, but improved over time. In particular, VAD patients experienced additional limitations in the first month, in the sleep and rest, mobility, bodycare and ambulation dimensions of the FLP. After transplantation, all groups showed a marked improvement in utilities and both physical and psychosocial function; there was no difference between the three groups in these functions or in cognitive function. Most patients were coping very well living with their VAD, but there is scope for further technical improvements, which would reduce the size and the noise of the device.

Chapter 6

Analysis of patient-specific data on resource use and costs

Introduction

This chapter provides an overview of the resource use and cost components to be used as inputs for the cost-effectiveness model, as described in Chapter 8. In terms of VAD patients, resource-use data were collected from the date of VAD implantation while for inotrope-dependent transplant candidates, data were collected from the date the patient was accepted on to the transplant waiting list. For all three patient groups, patient-specific resource-use data were collected until the study cut-off date (1 January 2005). All costs reported in this chapter were based on 2004/05 prices unless specified otherwise.

Costs of VAD implantation

For all VAD patients, patient-specific resource-use data were collected for the VAD procedure, including the type of device used and the associated length of stay in ICU and cardiac ward. The total device costs (excluding VAT) for the VADs used in the study, including temporary devices such as the Levtronix and Impella devices, were obtained from the Papworth NHS Trust and Royal Brompton & Harefield NHS Trust Finance departments. Only two temporary devices were used in this patient cohort and both were in combination with larger devices. For the three patients enrolled at Freeman hospital, only the Thoratec PVAD single VAD and BiVAD devices were used, for which costs were unavailable. Therefore, the costs of these devices were estimated using a simple average of the two costs from Papworth and Harefield. The costs of VAD implantation are shown in *Table 56*.

For the VAD implantation procedure itself, an estimate of the average cost was provided by Papworth finance department. No estimates were readily available from the Harefield or Freeman centres. Therefore, the same cost estimate from Papworth was applied to the VAD patients from these two centres. According to Papworth finance department, the cost of the extra implant for BiVAD patients (n = 22) was calculated as £4200, mostly reflecting the extra time in theatre, on average, for these patients. (On average, BiVAD patients spent 429 minutes and single-VAD patients spent 349 minutes in theatre.) A full description of the resource-use and cost components involved in the VAD procedure is given in *Table 57*. Overall, the individual device costs for each patient were added to the fixed cost of the procedure to produce a total cost for the VAD implant. Any associated ICU and cardiac ward stay was costed separately from the VAD implantation procedure.

Costs of heart transplant

Heart transplant costs are shown in *Table 58*. For patients from all three treatment groups who went

TABLE 56 *VAD costs*

VAD device	Papworth cost (£)	Harefield cost (£)	Freeman cost (£)
Thoratec PVAD single VAD	24,000	27,965	26,000
Thoratec PVAD BiVAD	44,000	47,000	45,500
Thoratec PVAD single IVAD	34,000	NA	NA
Thoratec PVAD 2X IVAD	64,500	75,788	NA
Heartmate	55,000	58,706	NA
Jarvik 2000	NA	43,742	NA
Levitronix single VAD	NA	2,500	NA
Levitronix BiVAD	NA	5,875	NA
Impella LV	5,279	NA	NA
Impella RV	6,179	NA	NA

TABLE 57 *VAD procedure costs*

VAD implant procedure resource-use component	Cost (£)
Theatre staff	2,176
Pump	875
Blood consumables	738
Other theatre consumables	1,024
Anaesthetic medical staffing	904
Perfusion	1,433
Pathology	900
Radiology	909
Echocardiogram	75
Drugs[a]	5,500
Physiotherapy	1,300
Technical support	800
Total (Single VAD)	**16,634**
Total (BiVAD)	**20,834**

[a] Reflects the use of epoprostanol, bretylium and haemofiltration for the implantation procedure.

TABLE 58 *Heart transplant costs*

Cost component	Papworth (£)	Harefield (£)	Freeman (£)
Heart transplant assessment (groups B and C patients only)	1,316	1,433	1374
Heart transplant procedure			
Overheads, capital equipment	1,110	NA	NA
Consumables	4,400	NA	NA
Theatre staff	4,081	NA	NA
Total (groups B and C only)	**9,591**	**9,591**	**NA**
Total (VAD)	**14,025**	**14,025**	**NA**

These are lower than National Reference Costs for heart transplant, which include both the transplant procedure and the associated hospital stay. In the present analysis post-transplant hospital stay is included in the month 1 costs.

on to have the heart transplantation procedure, resource-use data were collected on the procedure itself as well as any associated ICU and ward stay. Again, it was only possible to obtain an estimate for the overall cost of the heart transplantation procedure from Papworth finance department. Therefore, this fixed cost was applied across patients from all three centres who underwent the procedure.

For the heart transplant preparatory assessment, no patient-specific resource-use data were collected. However, it was possible to estimate the cost of this assessment for Papworth and Harefield patients based on the heart transplant patient management protocols that were available from both centres. Both assessments at the two centres involved a stay on the cardiac ward for 3–4 days and a range of tests and investigations including chest X-rays, ECGs, lung function tests and MUGA (multiple gated acquisition) scans. Cost estimates were available from both Papworth and Harefield for all of the tests and ward stays, and were applied to all inotrope-dependent transplant candidates during the pretransplantation waiting-list period, irrespective of whether they went on to have the transplant or not. (For more detailed information on the resource use and costs involved in the heart transplant preparatory assessment, see Appendix 4.) It was assumed that patients in the VAD group did not incur these assessment costs since most of those patients who went to have a heart transplant remained in hospital (ICU or ward) following VAD implantation. Once again, no assessment costs were available for the five non-inotrope-dependent transplant candidates at the Freeman. Therefore, a simple average of the two costs from Papworth and Harefield was used.

VAD patients who went on to have the heart transplantation, on average spent longer in theatre for the transplantation procedure than the inotrope-dependent transplant candidates. This was mainly because of the extra time spent on the VAD explantation procedure, which was

TABLE 59 *Follow-up costs*

Post-transplant month	Visits/investigations[a] (£)		Medications[b] (£)		Total costs (£)	
	Papworth	Harefield	Papworth	Harefield	Papworth	Harefield
Month 1	1154	1652	549	431	1703	2083
Month 2	577	1239	549	431	1126	1748
Month 3	577	982	549	431	1126	1413
Month 4	289	491	549	430	837	921
Month 5	289	491	549	430	837	921
Month 6	192	491	549	430	741	921
Month 7	192	246	549	430	741	921
…	…	…	…	…	…	…
Month 12	192	246	549	430	741	921

[a] Cost components include outpatient visits, investigations including cardiac biopsy, chest X-ray, ECG and blood tests. For more detailed information see Appendix 4.
[b] Medication costs based on recommended post-transplant drug treatments including ciclosporin, mycophenolate and prednisolone. Costs were obtained from British National Formulary.[123] For more detailed information see Appendix 4.

TABLE 60 *Bed-day costs*

	Papworth (£)	Harefield[a] (£)	Freeman[b] (£)
ICU	1204	697	1025
Cardiac ward	315	110	134

[a] Based on 2003/04 prices.
[b] Cost estimates obtained from National Reference Costs 2004.[122]

incorporated as part of the total transplantation procedure theatre time. Overall, the mean time in theatre for the transplant procedure was 501 minutes for VAD patients and 342 minutes for non-VAD patients combined. To account for this difference, the cost of the transplantation procedure itself was assumed to be £9591, based on 342 minutes in theatre for inotrope-dependent transplant candidates, and the cost of the transplantation procedure for VAD patients was simply adjusted upwards by the extra 160 minutes spent in theatre to give a total cost of £15,050 [i.e. (501/342) × £9591].

Follow-up costs

Follow-up costs are shown in *Table 59*. Since no resource-use data were collected during the transplant follow-up period (except for adverse events), it was assumed that patients from all three treatment groups who had a transplant followed the routine discharge follow-up as specified in the relevant transplant management guidelines. Both the Papworth and Harefield transplant discharge protocols were similar in terms of the numbers of recommended outpatient visits, investigations, blood tests and drug treatments. (For more detailed information on the resource use and costs involved in the post-transplantation follow-up, see Appendix 4.) If patients were still admitted to hospital (ICU or ward) during the follow-up period, the follow-up costs were adjusted downwards accordingly to avoid double-counting. These costs were not relevant to any of the Freeman patients since the only patient who underwent transplantation died within 1 month of the procedure.

Bed-day costs

For each patient, relevant data were collected on length of stay in ICU or ward during the VAD implantation or heart transplantation episodes and also for any readmissions. Bed-day unit costs were then applied for each centre (*Table 60*).

Adverse event costs

Resource-use data were collected for all serious and non-serious adverse events experienced by patients in each treatment group throughout the

TABLE 61 *Return to theatre costs (for patients with missing theatre times)*

Return to theatre (reason)	Average theatre time (minutes)	Cost (based on £1000 per hour) (£)
Tracheotomy	29	483
Bleeding/sternotomy	157	2617
Laparotomy	119	1983
Wound débridement	79	1317
Device related (VAD patients only)	225	3750

study period. These data included information on the type of event and a brief description of any resource use involved, such as time spent in theatre or length of stay on ward. Cost estimates were then applied. A description of the different types of events experienced by the study patients is given in Chapter 4. Such associated resource use included readmission to hospital (ICU or ward), return to theatre for events such as bleeding and other cardiac-related procedures such as pacemaker insertion and coronary artery bypass grafts.

Costs for all events except for those that involved ICU or ward stay were based on estimates from Papworth finance department. All return-to-theatre costs were based on both the time spent in theatre and on an estimate of £1000 per hour for all return-to-theatre patients from Papworth finance department. [For example, for a patient who spends 120 minutes in theatre, the cost would be (120/60) × £1000 = £2000.] For patients from all three treatment groups with missing return-to-theatre times, an estimate of the time in theatre was calculated based on the type of event and the subsequent procedure. An estimate of the average theatre time was then derived from those patients who did have theatre times recorded (*Table 61*).

Any resource use associated with events that did not occur at the three study centres, such as accident and emergency admissions and GP visits, was costed using estimates from NHS Reference Costs 2004[122] and Netten and Curtis.[124]

For patients who experienced rejection or infection episodes that required drug treatment, no patient-specific resource-use data were collected. Therefore, an estimate of the resource use and cost involved was calculated based on recommendations given in the Papworth and Harefield transplant management guidelines. For rejection episodes, it was assumed that patients would, on average, receive 750 mg i.v. methylprednisolone for 3 days at a total cost of £57.30. For patients who experienced viral infection (cytomegalovirus), it was assumed that they would receive 400 mg twice daily of i.v. canciclovir at a total cost of £63.20 per day. (Medication costs were obtained from the British National Formulary.[123] For more detailed information see Appendix 4.)

Other drug costs

For VAD patients, resource-use and cost data on a variety of medications were collected for a sample of VAD patients (n = 23) at Papworth during the VAD implantation period. (Only detailed information on more expensive drugs such as Aztreonam, Bicaflac, Flucanazole and Remifentanyl was collected during the first 2 months on VAD support.) This sample of patients was fairly representative of the overall cohort, although no medications were collected for the 13 patients implanted with the Jarvik 2000 device at Harefield. Overall, based on this sample, VAD patients had, on average, much lower drug costs in the first month on VAD support than BiVAD patients (average cost: £1137 versus £4492). With these data, it was also possible to estimate mean monthly drug costs for this sample for the first 2 months on VAD support. For the remaining VAD patients (from all three centres) for whom no medication data was collected, a mean estimate of monthly drug costs was calculated based on the patient sample from Papworth. For the first month on VAD support (month 1 VAD implant), the mean drug cost was £2818 (95% CI £1736 to 4846) and for the second month (month 2 post-VAD implant) the mean cost was £2977 (95% CI £684 to 7340) (95% CI non-parametric bootstrap bias corrected method; 5000 replicates).

For inotrope-dependent transplant (inotropic support) patients, resource-use data were collected on the time spent (in days) on intravenous inotropic support while on the transplant waiting list. Based on the transplant management guidelines and clinical opinion, it was assumed

that the patient would receive 0.4 mg per minute of i.v. enoximone and dopamine over a 24-hour period, resulting in a total cost of £103 per day. (Medication costs obtained from British National Formulary.[123] For more detailed information see Appendix 4.)

Post-transplant drug maintenance treatment costs for all three patient groups, as described in the transplant management guidelines, were incorporated into the overall transplant follow-up costs (see the section 'Follow-up costs', p. 69).

Test/investigation costs

Throughout the study period, resource-use data were collected for a number of patients from each treatment group on a variety of tests and investigations. It should be noted that these were not tests or investigations that were recorded as a result of patient adverse events, thus avoiding any double-counting. Although it was not possible to obtain exact dates for each of the individual tests, information was given on the period (start and end dates) within which each investigation or test occurred. With this information, it was possible to separate tests that were carried out in the post-VAD implantation or pretransplantation period from tests that were carried in the post-transplantation period. It was also possible to calculate monthly test/investigation costs based on the number of months the patient spent in each period. This was done by simply dividing the total cost of the investigations carried out for a particular period (e.g. post-transplantation) by the number of months for that period. Cost estimates for each of the tests and investigations were available from both the Papworth and Harefield finance departments. (For more detailed information on the tests and investigations that were included for costing, and their costs, see Appendix 4.)

For patients in the VAD group, who did not have information collected on any tests or investigations, the mean costs based on the patients who did have data collected were applied depending on the particular period. For patients who died within 1 month of the VAD implantation procedure, the mean monthly cost was estimated as £1843 (95% CI £1346 to 2724) based on the similar patient group (i.e. those who died within 1 month of the VAD implantation) for whom data were collected. For the period after the VAD implantation leading up to the heart transplantation, the mean monthly cost was estimated as £917 (95% CI £588 to 1588) and was applied to every month post-VAD implantation leading up to the month of the transplantation. For the post-transplantation period, the mean monthly cost was £800 (95% CI £570 to 1102) and was applied to every month post-transplantation up to 12 months.

For inotrope-dependent transplantation candidates for whom no data on tests and investigations were collected, not enough data were available to provide a reliable estimate of the mean monthly costs in the post-transplantation period (even though these patients did not appear to have any underlying differences in terms of their clinical characteristics). Therefore, the only test and investigation costs applied to these patients were those based on the transplant guidelines for patient follow-up (see the section 'Follow-up costs', p. 69). This may result in an underestimate (approximately £4080 over 12 months) of the test and investigation costs incurred by these patients (compared to VAD patients) during the post-transplantation period.

However, for inotrope-dependent transplant candidates for whom no data were collected for the pretransplantation waiting-list period, it was possible to calculate a reliable estimate of the mean monthly test and investigation costs for this period. This was calculated as £320 (95% CI £206 to 606) for each month that the patient remained on the transplant waiting list.

Cost breakdowns

Tables 62–65 each provide a breakdown of the resource-use and cost components involved during the VAD implantation period (1 month) for VAD patients and the heart transplant period for all three patient groups. For the VAD implantation period (*Table 62*), the largest cost component involved was the device itself, followed by other implant equipment and consumables as well as stay in the ICU. These results appear to corroborate the findings from other published evidence from the USA on the initial costs of VAD implantation.[89,96]

For the heart transplant period, the various resource-use components were similar for all three patient groups. Within each group, the largest cost component was the transplant equipment and consumables, followed by theatre staff and ICU stay. The greater total cost for the VAD patients was due mainly to the higher cost of the transplantation procedure, itself a result of the longer time spent in theatre by the VAD patients.

TABLE 62 *VAD implant month 1 costs (VAD patients)*

Resource-use component	Mean cost per patient (95% CI)[a] (£)	% of total cost
VAD	45,755 (42,601 to 49,174)	54.1
Implant equipment/consumables	12,421 (12,054 to 12,694)	14.7
Implant theatre staff	5,664 (5480 to 5800)	6.7
ICU stay	12,584 (10,290 to 15,164)	14.9
Ward stay	1,914 (1490 to 2511)	2.3
Maintenance drugs	2,698 (2456 to 2778)	3.2
Adverse events	2,525 (1805 to 3358)	3.0
Maintenance tests	957 (822 to 1131)	1.1
Total costs	**84,518 (80,275 to 89,586)**	

[a] 95% CI non-parametric bootstrap bias corrected method: 2000 replicates.

TABLE 63 *Transplant month 1 costs (VAD patients)*

Resource-use component	Mean cost per patient (95% CI) (£)	% of total cost
Transplant equipment/consumables	8,057 (NA)	30.3
Transplant theatre staff	5,968 (NA)	22.4
ICU stay	6,016 (3927 to 10077)	22.6
Ward stay	3,280 (2279 to 4365)	12.3
Adverse events	2,370 (1275 to 4064)	8.9
Maintenance tests	590 (411 to 763)	2.2
Maintenance drugs	336 (0 to 662)	1.3
Total costs	**26,616 (24,143 to 30,604)**	

TABLE 64 *Transplant month 1 costs (inotrope-dependent transplant candidates)*

Resource-use component	Mean cost per patient (95% CI) (£)	% of total cost
Transplant equipment/consumables	5,510 (NA)	26.59
Transplant theatre staff	4,081 (NA)	19.69
ICU stay	6,611 (4260 to 9998)	31.9
Ward stay	2,672 (1731 to 3963)	12.89
Adverse events	1,572 (513 to 3489)	7.58
Maintenance tests	280 (120 to 502)	1.35
Total costs	**20,726 (18,054 to 26,794)**	

TABLE 65 *Transplant month 1 costs (non-inotrope-dependent transplant candidates)*

Resource-use component	Mean cost per patient (95% CI) (£)	% of total cost
Transplant equipment/consumables	5,510 (NA)	28.4
Transplant theatre staff	4,081 (NA)	21
ICU stay	4,741 (3325 to 7084)	24.45
Ward stay	3,087 (2427 to 3896)	16
Adverse events	1,779 (761 to 5180)	9.18
Maintenance tests	187 (92 to 344)	0.97
Total costs	**19,385 (17,237 to 24,574)**	

Chapter 7

Cost-effectiveness model: technical details

Introduction

This chapter contains technical details of the economic model and the probabilistic sensitivity analysis. The model is described for the VAD group, but the structure is identical for non-VAD groups. The main assumptions of the model are repeated in non-technical language in Chapter 8. Readers who are not familiar with health economic modelling may miss this chapter.

The cost-effectiveness model

A cost–utility analysis based on a multistate model of patient experience is adopted. The effectiveness measure of this analysis will be QALYs. To estimate quality-adjusted survival a discrete-time, discrete-state model was used, as depicted in *Figure 34*. In the VAD model each patient can be in one of three states, namely, alive with VAD support (state 1), alive after heart transplantation (state 2) or dead (state 3). Each individual may move between states according to monthly time-units or remain in the same state. Transition probabilities out of the VAD state are dependent on the time since VAD implant t, and transition probabilities from the heart transplant state to death depend on the time since transplantation t^*. For other non-VAD study groups (B, C and D) the structure of the model is the same, with the VAD state replaced by an 'alive-pretransplant' state.

First, a general description of the model is given. Data from the Evaluation of Ventricular Assist Device study are used to populate the model and these will be described in Chapter 8.

A time-discrete model is assumed, made up of T cycles, with cycle length of 1 month. Suppose that within each cycle t a patient remains in one of K states and that transitions occur just before the end of each cycle. Let $X(t)$ be the state occupied at time t. The probability of a patient being in each state at the first cycle $t = 1$ is given by the vector π_1. Patients move between states according to a probability transition matrix $P(t,t^*)$ which, in this application, depends on the time of entry into the current state. The probability of state occupancy at any cycle t can be calculated using the recursive relation $\pi_t = \pi_{t-1}P(t,t^*)$. The probability transition matrix has piecewise constant probabilities that depend on the time since VAD implantation/transplantation listing t in state 1 and time since heart transplantation t^* in state 2. Thus the model is semi-Markov.

For the VAD evaluation the transition probability matrix has the form:

$$P(t,t^*) = \begin{bmatrix} p_{t,11} & p_{t,12} & p_{t,13} \\ 0 & p_{t^*,22} & p_{t^*,23} \\ 0 & 0 & 1 \end{bmatrix}$$

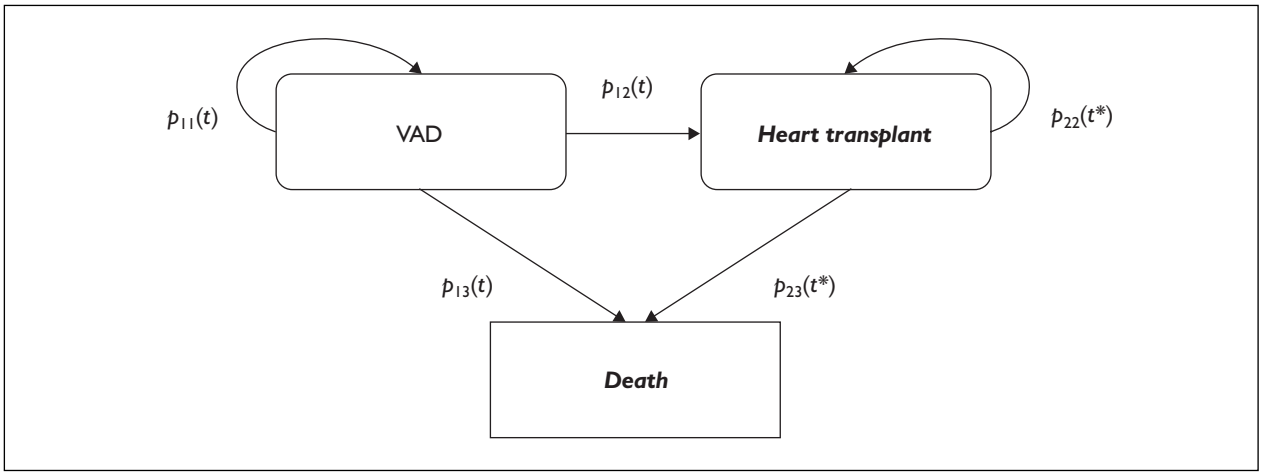

FIGURE 34 *Discrete-time, semi-Markov, multistate model for VAD patients*

where all rows sum to one and where:

$$p_{t,ij} = prob(X(t+1) = j | X(t) = i),\ t = 1, \ldots, T$$

In the VAD application the following assumptions have been made:

- $p_{2,11} = p_{3,11} = \ldots = p_{T,11}$
- $p_{2,12} = p_{3,12} = \ldots = p_{T,12}$
- $p_{2,13} = p_{3,13} = \ldots = p_{T,13}$
- $p_{3*,23} = p_{4*,23} = \ldots = p_{12*,23}$
- state 3 (dead) is an absorbing state.

Thus, conditional on surviving the first month pretransplantation, both transplant rates and survival-on-the-list rates are assumed constant. The rates are assumed to be different for each group. In addition, common post-transplant rates were assumed for all groups, with a constant death rate for months 3–12 (data from current VAD study). In the base-case analysis survival up to 3 years from VAD implantation/listing were estimated using data from the UK evaluation study only and based on constant death rates beyond 12 months post-transplantation. Since there were few cases beyond 12 months post-transplantation, when estimating longer term survival rates, death rates after the first 12 months were estimated from data supplied by UK Transplant.

Since transition probabilities, costs and utilities depend on time of entry to the current state, rather than time of entry to the study, it is convenient to decompose the problem into two simple processes, the first representing time pretransplantation and the second representing post-transplantation.

Pretransplantation

At the start of the study all patients are alive with VAD support, $\pi_1 = (1,0,0)$. When considering the pretransplantation period both heart transplantation and death can be treated as two separate absorbing states, so that backward moves are not allowed (*Figure 35*). This is equivalent to a simple competing risks model with independent causes of failure.

Then the corresponding transition probability matrix has the form:

$$P(t) = \begin{bmatrix} p_{t,11} & p_{t,12} & p_{t,13} \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

As above, the vector of state occupancy at any cycle t can be calculated using the recursive relation $\pi_t = \pi_{t-1}P(t-1)$, $t = 2, \ldots, T$.

Let $\mathbf{u}$ and $\mathbf{c}$ be vectors of parameters, length T, representing utilities and costs in each month for the pretransplantation state, where T is the time-horizon over which cost-effectiveness is to be estimated. In addition, let C_0^{pre} represent the initial costs associated with the VAD implantation procedure. Then, total costs and benefits before transplantation can be estimated as a function of the parameters $\theta = \{\mathbf{p}_{12}, \mathbf{p}_{13}, \mathbf{u}, \mathbf{c}, C_0^{pre}\}$. Specifically, total cost is given by

$$C^{pre} = C_0^{pre} + \left(\sum_t \pi_{t,1} c_t\right)$$

and total quality adjusted survival is given by

$$Q^{pre} = \left(\sum_t \pi_{t,1} u_t\right)$$

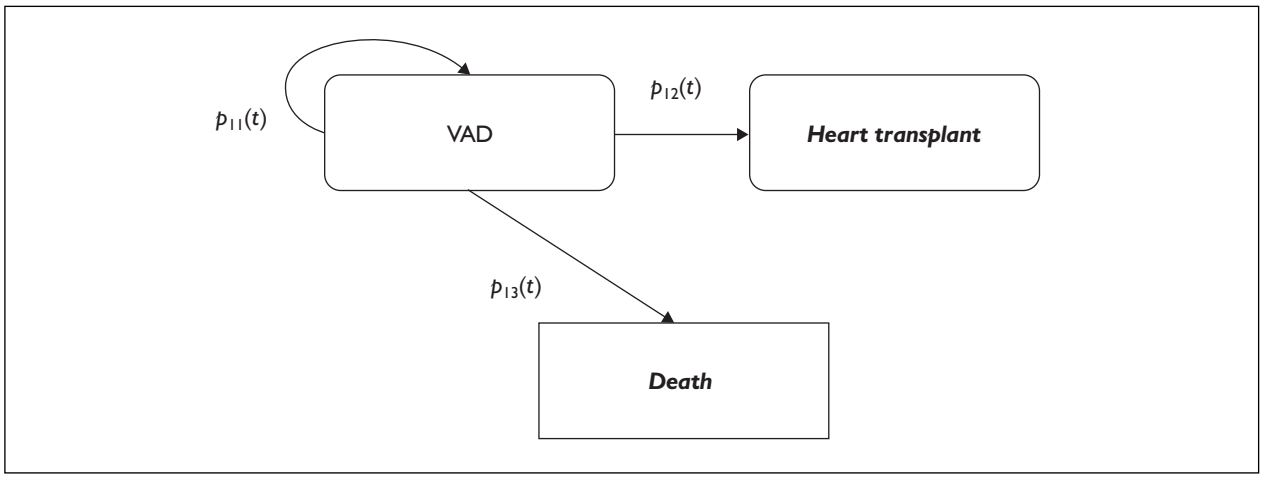

FIGURE 35 *Multistate model for VAD patients up to transplantation*

Pretransplantation experience for groups B, C and D can be represented by models with identical structure but different transition probabilities, costs and utilities.

Post-transplantation

Let *tx* denote the time between VAD implantation and transplantation and let T be the time-horizon for the study. Then the proportion of VAD patients who undergo heart transplantation is equivalent to:

$$p(tx \leq T) = \sum_{t=1}^{T} p_{t,12} \left\{ \prod_{s=0}^{t-1} p_{s,11} \right\}$$

That is, the sum over all periods t up to the time-horizon T, of the probability of having a transplant in month t, conditional on not having died or been transplanted up to time t. Thus, the vector of initial states post-transplantation is:

$$\pi_1^* = (p(tx \leq T), 0)$$

When estimating survival post-transplantation there is a simple two-state (alive with a transplant, dead) model with monthly probabilities of death dependent on time since transplantation t^* (*Figure 36*).

Then the corresponding transition probability matrix has the form:

$$P^*(t^*) = \begin{bmatrix} p_{t^*,22} & p_{t^*,23} \\ 0 & 1 \end{bmatrix}$$

where $p_{t^*,22} = 1 - p_{t^*,23}$.

Again the vector of state occupancy at any cycle t^* can be calculated using the recursive relation $\pi_{t^*}^* = \pi_{t^*-1}^* P^*(t^* - 1)$, $t^* = 2, \ldots, T$.

As above, let $\mathbf{u}^*$ and $\mathbf{c}^*$ be vectors of parameters, length T, representing utilities and costs in each post-transplantation month in the study groups and let C_0^{tx} be the initial costs associated with the transplant procedure. Then, total costs and benefits after transplantation can be estimated as a function of the parameters $\theta^* = \{\mathbf{p}_{23}, \mathbf{u}^*, \mathbf{c}^*\}$. Specifically, total cost is given by

$$C^{post} = C_0^{post} + \left(\sum_t \pi_{t^*,1}^* c_{t^*}^* \right)$$

and total QALYs are given by

$$Q^{post} = \left(\sum_t \pi_{t^*,1}^* u_{t^*}^* \right)$$

Post-transplantation experience for groups B and C is modelled in exactly the same way.

In practice, if one is interested in cost and effects over a finite time T, then the post-transplantation sums above will be taken from transplantation ($t^* = 0$) to the horizon less the time spent on the waiting list ($t^* = T - w$), where w is the mean waiting time.

Total costs and benefits for VAD patients are given by:

$$C_a = C^{pre} + C^{post}$$

and

$$Q_a = Q^{pre} + Q^{post}$$

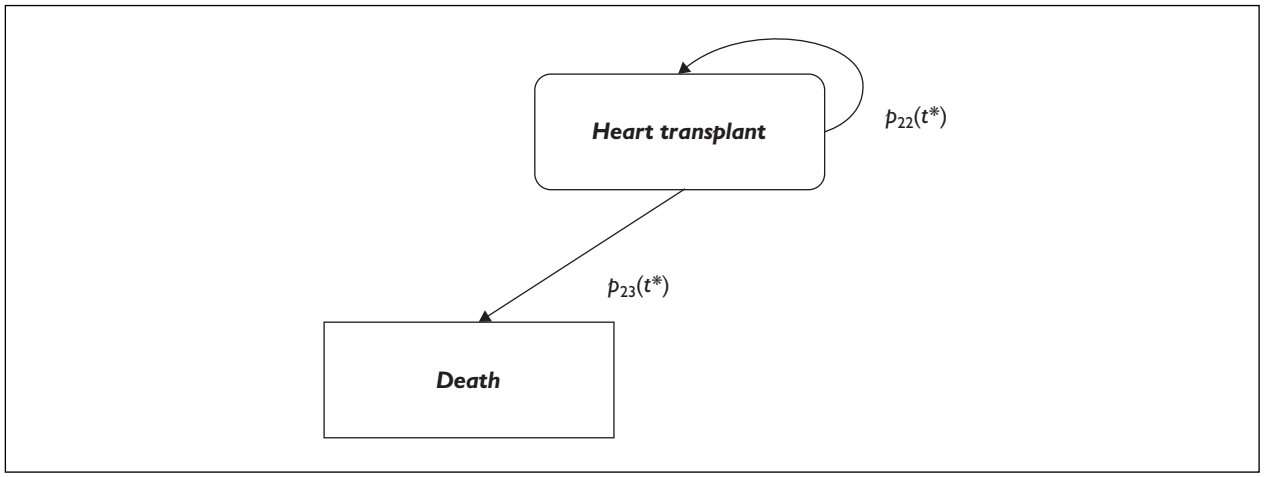

FIGURE 36 *Multistate model for VAD patients post-transplantation*

Discounting

In economic analyses the convention is to discount costs and benefits accrued beyond the first year from entry to the study. This discounting does not fit in well with the decomposition of the model. Calculating discounted costs and benefits pretransplantation is straightforward. If δ is the annual discount rate, the discounted pretransplantation costs and benefits are given by

$$C^{pre} = C_0^{pre} + \sum_t \left((\pi_{t,1} c_t) / (1 + \delta)^{[(t-1)/12]} \right)$$

and

$$Q^{pre} = \sum_t \left((\pi_{t,1} u_t) / (1 + \delta)^{[(t-1)/12]} \right)$$

The square brackets in the above equations indicate the integer value, for example [1.56] = 1.

It is more difficult to calculate discounted costs and benefits post-transplantation since these vary according to the time from entry to the current state rather than the time since entry into the initial state. Since these quantities vary considerably in the first year after transplantation, monitoring the time since study entry as well as the time since current state entry would add considerable complexity to the model implementation. Thus, for discounting a crude approximation is proposed, based on the assumption that transplantation takes place at a fixed time after study entry, w months. The fixed time is set at the average time on the VAD or waiting list. For groups A, B and C the mean time in the study pretransplantation was 5.1, 2.4 and 6.7 months, respectively. Thus, if δ is the annual discount rate and w is the mean number of months spent in the study pretransplantation, then the discounted post-transplantation costs and benefits are given by

$$C^{post} = C_0^{post} * \pi^*_{1,1} + \sum_{t^*} \left((\pi^*_{t^*,1} c^*_{t^*}) / (1 + \delta)^{[(t^* + w - 1)/12]} \right)$$

and total QALYs are given by

$$Q^{post} = \sum_{t^*} \left((\pi^*_{t^*,1} u^*_{t^*}) / (1 + \delta)^{[(t^* + w - 1)/12]} \right)$$

Pretransplantation and post-transplantation estimates are summed to provide total costs and benefits. In this application the annual discount rate for both costs and benefits was set at 3.5% according to current Department of Health guidelines.

Cost-effectiveness summaries

Incremental costs and life-years gained for VAD recipients relative to groups B, C and D were estimated and summarised as the incremental cost-effectiveness ratio (ICER), the additional cost per QALY gained. Specifically, given mean costs C_A, C_B, C_C and C_D and mean benefits (QALYs) Q_A, Q_B,Q_C and Q_D for the groups, the ICER for group A relative to group B, say, is

$$\text{ICER} = \frac{C_A - C_A}{Q_A - Q_B}$$

The mean costs and benefits for each group will be estimated from the economic model, populated by data from the UK VAD evaluation and UK Transplant survival estimates. The joint distribution of incremental mean costs and benefits will be plotted on the cost-effectiveness plane and will be used to estimate both the incremental net benefit (INB), for example,

$$\text{INB}(\lambda) = \lambda(Q_A - Q_B) - (C_A - C_B)$$

and the cost-effectiveness acceptability curve (CEAC), for example,

$$\text{CEAC}(\lambda) = prob(\lambda Q_A - Q_B) - (C_A - C_B) > 0)$$

where λ represents the maximum acceptable cost for one unit of benefit, in this case 1 QALY.

Estimation of model parameters

The economic analysis has three types of inputs, transition probabilities, utilities and costs, all indexed by time since entry into the currently occupied state. In the base-case analysis the following assumptions are made. Let $r_{t,11}$, $r_{t,12}$, $r_{t,13}$ be the number of observed transitions from the VAD state in month t prior to transplantation, with $r_{t,11} + r_{t,12} + r_{t,13} = n_{t,1}$. Then under model assumptions all transitions are *iid* with:

$$(r_{t,11}, r_{t,12}, r_{t,13}) \sim \text{Multinomial}\ (p_{t,11}, p_{t,12}, p_{t,13}, n_{t,1})$$

Then, maximum likelihood estimates of the transition probabilities and corresponding (standard error)^2 are given by:

$$\hat{p}_{t,1j} = \frac{r_{t,1j}}{n_{t,1}} \text{ and } \hat{\sigma}^2_{\hat{p}1} = \frac{\hat{p}_{t,1j}(1 - \hat{p}_{t,1j})}{n_{t,1}}$$

For this model, the four patients who had their VAD explanted were censored at the time of

explantation. Similarly, let $r_{t^*,22}$, $r_{t^*,23}$ be the number of observed transitions from the heart transplant state in month t^* after transplantation, with $r_{t^*,22} + r_{t^*,23} = n_{t^*,2}$. Then all transitions are *iid* with:

$$r_{t^*,23} \sim \text{Binomial}\ (P_{t^*,23}, n_{t^*,2})$$

Maximum likelihood estimates of the transition probabilities and corresponding (standard error)^2 are given by:

$$\hat{p}_{t^*,23} = \frac{r_{t^*,23}}{n_{t^*,2}} \text{ and } \hat{\sigma}^2_{\hat{p}2} = \frac{\hat{p}_{t^*,23}(1 - \hat{p}_{t^*,23})}{n_{t^*,2}}$$

Let $\bar{x}_{ut}$ and $\bar{x}_{ct}$ be observed mean utilities and costs in month t, then in the base-case analysis it was assumed that:

$$\bar{x}_{ut} \sim \text{Normal}\ (u_t, \sigma^2_{ut})$$
$$\bar{x}_{ct} \sim \text{Normal}\ (c_t, \sigma^2_{ct})$$

where σ_{ut} and σ_{ct} are standard errors of utilities and costs in month t. In addition, the following assumptions are made regarding costs and utilities:

- Pretransplantation $u_2 = u_3 = \ldots = u_T$, where the subscript indexes time since VAD implantation/listing.
- Pretransplantation $c_7 = c_8 = \ldots = C_T$, where the subscript indexes time since VAD implantation/listing.
- Post-transplantation $u_1 = u_2 = \ldots = u_T$, where the subscript indexes time since transplantation and these are common to all groups.
- Post-transplantation $C_7 = C_8 = \ldots = C_T$, where the subscript indexes time since transplantation and these are common to all groups after the first month post-transplantation.

Observed mean utilities and costs and corresponding variances are maximum likelihood estimates of the population means and variances.

Model adjustments

In the model, transitions to the heart transplant state are assumed to occur at monthly intervals and a whole month of pretransplantation survival and costs are included. In reality, a transplant may take place at any time during the month, and on average at the midpoint of the relevant month. Therefore, an adjustment must be made such that a transition to the heart transplant state will result in a reduction in pretransplantation survival time of 0.5 months and a reduction in costs of 0.5 times the pretransplantation costs associated with the month in which the transplant occurred.

Both costs and utilities associated with death are zero. However, since transitions are assumed to occur at monthly intervals, an adjustment must be made to reflect the fact that a death can occur at any time during the month. Thus, a transition to death will result in a reduction in survival time of 0.5 months. For the month in which death occurs no reduction in costs is required since only costs up to death were included in these months.

Two-stage approach to estimation

The section 'The cost-effectiveness model' (p. 73) shows how to calculate point estimates of cost-effectiveness summaries using the model parameters. This section describes how to estimate (second order) uncertainty around these point estimates using the two-stage approach (e.g. Spiegelhalter and colleagues[125]). The first stage involves estimation of the distributions of the components of $\theta = \{\mathbf{p}_{12}, \mathbf{p}_{13}, \mathbf{u}, \mathbf{c}\}$ and $\theta^* = \{\mathbf{p}_{23}, \mathbf{u}^*, \mathbf{c}^*\}$ using the assumptions in the section 'Estimation of model parameters' (p. 76) and the data arising from the UK study data and UK Transplant (see Chapter 4 for details). At the second stage a set of 1000 values from $p(\theta, \theta^*)$ was simulated from the joint distribution using Monte Carlo methods. For each simulation the total costs and QALYs were calculated as in the section 'The cost-effectiveness model' (p. 73), to provide a sample of 1000 values from the distribution, from which the predictive distributions of cost-effectiveness summaries can be estimated.

The two-stage approach provides a simple, transparent method of producing estimates of the main cost-effectiveness summaries and was adopted to develop the method.

Integrated estimation/simulation approach to estimation

The two-stage approach separates estimation of $p(\theta, \theta^*)$ and calculation of the cost-effectiveness parameters. Using Markov chain Monte Carlo methods it is possible to combine these two steps to estimate simultaneously the distribution of model parameters, distribution of total costs and benefits and other cost-effectiveness summaries. This method has a number of methodological advantages. For instance, it allows inclusion of the full covariance structure of model parameters in the estimation of cost-effectiveness summaries, without assuming specific distributions. Elements of the economic decision analysis such as the CEAC(λ) are natural products of the integrated approach, as is the inclusion of probabilistic sensitivity analysis. In addition, it is possible to include prior information for parameters should it be available.

The integrated approach to model fitting and estimation was used to provide probabilistic sensitivity analysis, incorporating the covariance structure of the economic model. Since results from the two-stage and integrated analyses were very similar, only those from the integrated analyses are presented in Chapter 8.

Summary

Two simple discrete-time, discrete-state models were constructed to represent the pretransplantation and post-transplantation experience. Cost-effectiveness summaries of interest are the ICER, INB function and the CEAC of the VAD group relative to non-VAD study groups B, C and D. These summaries can be estimated by weighting time in each state of the model by the utility and cost associated with that state. Transition probabilities, costs and utilities are dependent on the time since entry to the currently occupied state and have been estimated using data from the UK VAD evaluation and from longer term survival from UK Transplant (see Chapters 4 and 8). Both two-stage and integrated approaches to estimation were described. Since the results were very similar, those from the integrated approach are presented in Chapter 8.

Chapter 8

Cost-effectiveness model and inputs

Introduction

Chapter 7 gave technical details of the model and statistical analysis. This chapter provides a non-technical description of the economic model and its inputs. Full results of the cost-effectiveness analysis are given in the section 'Base-case results' (p. 83), with sensitivity analysis in 'Alternative scenarios' (p. 89).

Methods

Cost-effectiveness model

The measure of effectiveness in this analysis was QALYs gained. To estimate survival a discrete-time, semi-Markov, multistate model was used to describe the experience of VAD and non-VAD transplant candidates. The multistate model for VAD patients is depicted in *Figure 37*.

In the VAD model each patient can be in one of three states, namely, alive with a VAD, alive after transplantation or dead. After transplantation each individual can be in two states, alive after heart transplantation or dead. Each individual may move between states according to monthly time-units. The probability of moving between each of these states is represented by the quantities p_{12}, p_{13} and p_{23}. The probabilities are not fixed but depend on the time t since the VAD was implanted (p_{12}, p_{13}) or the time t^* since transplantation (p_{23}). For patients who do not have a VAD implant an identical model was constructed, with different estimates of the pretransplantation probabilities (p_{12}, p_{13}), but the same estimates of post-transplantation probabilities (p_{23}). Modelling uses discrete time, with one cycle being equal to 1 month.

Patients who recovered function sufficiently to have their VAD removed were include in the base case up until the time of VAD removal, after which their data were not included. This assumption is examined in sensitivity analysis.

Model inputs

The values used for the transition probabilities and the sources of the estimates are summarised in *Table 66*. In brief, using results from the analysis in Chapter 4 it was assumed that the probability of death in the first month after VAD implantation (group A) or acceptance for transplantation (groups B and C) was higher than in subsequent months. After the first 30 days of support or listing the risk of death was constant over time within each group but different between groups. For group D (hypothetical scenario of no VAD implants) it was assumed that all patients died within the first month, with a mean survival of 15 days.

After transplantation it was assumed that all groups had an identical risk of death and that the risk was constant within the post-transplant periods month 1, month 2 and months 3–12, but

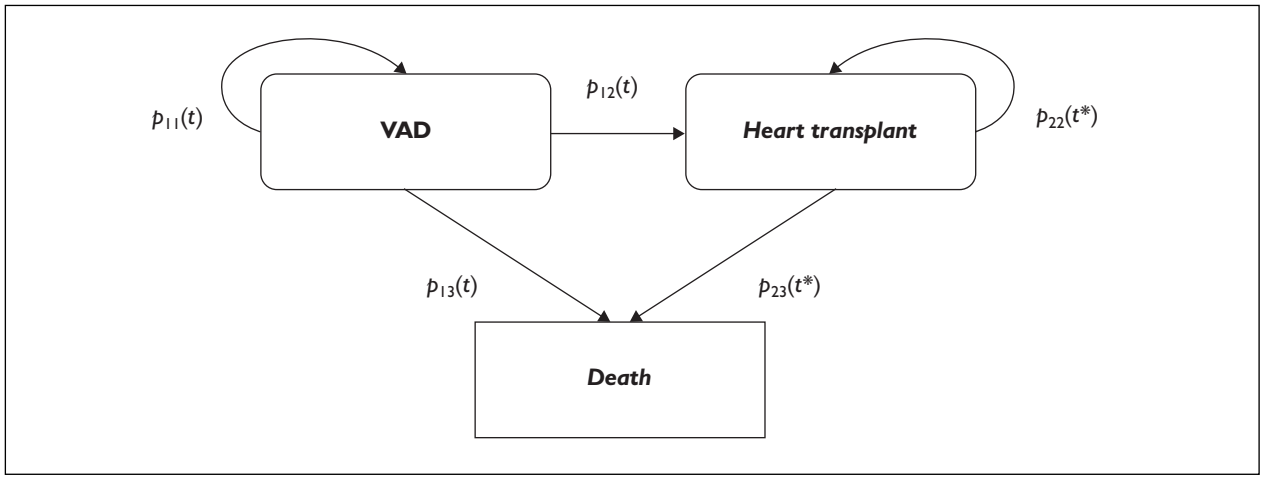

FIGURE 37 *Discrete-time, semi-Markov, multistate model for VAD patients*

TABLE 66 *Effectiveness inputs and sources*[a]

	State	Period	Source of information
Transition probabilities			
VAD implanted (group A)	Month 1	P_{12} = 0.04 (95% CI 0.01 to 0.15) P_{13} = 0.26 (95% CI 0.16 to 0.38)	UK study of 70 patients
	Month 2+	P_{12} = 0.11 (95% CI 0.08 to 0.15) P_{13} = 0.04 (95% CI 0.02 to 0.08)	
Inotrope-dependent patients accepted for heart transplantation (group B)	Month 1	P_{12} = 0.58 (95% CI 0.46 to 0.70) P_{13} = 0.01 (95% CI 0.00 to 0.07)	UK study of 71 patients
	Month 2+	P_{12} = 0.15 (95% CI 0.09 to 0.23) P_{13} = 0.04 (95% CI 0.01 to 0.10)	
Non-inotrope-dependent patients accepted for heart transplantation (group C)	Month 1	P_{12} = 0.27 (95% CI 0.21 to 0.34) P_{13} = 0.02 (95% CI 0.00 to 0.06)	UK study of 179 patients
	Month 2+	P_{12} = 0.10 (95% CI 0.08 to 0.12) P_{13} = 0.02 (95% CI 0.01 to 0.03)	
Hypothetical scenario preheart transplant (group D)	Month 1	P_{12} = 0.00 P_{13} = 1.00	Expert opinion
Postheart transplantation (groups A, B and C)	Month 1	P_{23} = 0.11 (95% CI: 0.07 to 0.16)	UK study of 27 VAD and 178 non-VAD patients
	Month 2	P_{23} = 0.026 (95% CI: 0.01 to 0.06)	
	Month 3–12	P_{23} =0.003 (95% CI: 0.000 to 0.005)	
	Month 13+	P_{23} varies as UK recipients	UK Transplant (Hussey J: personal communication; Appendix 2)
Utilities (see Chapter 4)			
VAD implanted (group A)	Month 1	U = 0.51 (95% CI 0.40 to 0.62)	UK study of 70 patients
	Month 2+	U = 0.66 (95% CI 0.63 to 0.69)	
Inotrope-dependent patients (group B)	Month 1+	U = 0.50 (95% CI 0.32 to 0.68)	UK study of 13 patients
Non inotrope-dependent patients (group C)	Month 1	U = 0.61 (95% CI 0.54 to 0.68)	UK study of 50 patients
	Month 2+	U = 0.67 (95% CI 0.63 to 0.71)	
Hypothetical scenario preheart transplant (group D)	Month 1	U = 0.51 (95% CI 0.40 to 0.62)	Assumed equivalent to VAD patients in first month
Postheart transplantation (groups A, B and C)	All months	U = 0.76 (95% CI 0.73 to 0.79)	UK study of 28 VAD and 49 non-VAD patients

[a] See Chapter 4 for details.
P_{12}, probability of a patient being transplanted in the next month; P_{13}, probability of a VAD/listed patient dying in the next month; P_{23}, probability of a transplant recipient dying in the next month; U mean utility for 1 month in the appropriate state (see the section 'Methods', p. 79).

different between these times. In the base case survival up to 3 years from VAD implantation/listing was estimated using data from the UK study, extrapolating death rates up to 36 months. However, beyond 12 months there were few cases providing survival data. Therefore, to estimate longer term survival, beyond 12 months after heart transplantation it was assumed that these patients would have the same survival rates as 12-month survivors of heart transplantation registered with UK Transplant.

A month spent in a particular state, at a particular time after entry into that state, is associated with a utility, that is a value put on life in that state; utility values range from 1 (maximum health) to 0 (death) and allow for values less than zero, representing quality of life valued lower than death. Utility values were used from the EQ-5D results from the UK study described in the section 'EuroQol' (p. 40) (see *Table 66*). After the first month on VAD support or waiting list, mean utilities were assumed constant within each group but different between groups. For group D patients (hypothetical worst case scenario), HRQoL was assumed to be constant throughout the period spent on the waiting list and taken to be equal to the utility score for VAD patients in the

first month after implant. Given the similarity in post-transplantation utilities over time and between groups (see the section 'Discussion', p. 37), and in the absence of long-term utility measures, a utility value of 0.76 was assumed for all periods after heart transplantation. The amount of time spent on the VAD and the survival time after transplantation are weighted by the utilities of being in each of those states, to estimate QALYs.

Each month in a given state (alive with VAD, alive on transplant list or post-transplantation) was associated with resource use. Cost summaries used in the model and the source of the evidence are summarised in *Table 67*, with full cost details and assumptions in Chapter 6. For VAD patients, costs for the VAD implantation procedure (including the device itself) were separated from the remaining month 1 costs in that state. Monthly costs were assumed to be constant beyond month 6 on VAD support/waiting list. Costs for group B (inotrope-dependent) patients were assumed to be constant beyond month 2 since costs were only available for one patient beyond this point. For group D (hypothetical scenario of no VAD implants) it was assumed that all patients would be in the ICU until death at 1–30 days after admission (median 15 days). Group D monthly costs were based on a standard ICU stay.[122]

For all groups, costs for the transplantation procedure have been separated from the remaining month 1 costs in that state. The groups were allowed to have different costs for the transplantation procedure and for the first month after transplantation to identify any increase in surgical complexity owing to removal of the VAD. Post-transplantation monthly costs were assumed to be constant beyond month 6 and were assumed to be the same in all groups beyond this point. Monthly costs were estimated from UK study patients up to 12 months after transplantation. Beyond 12 months after transplantation the costs were augmented using a combination of extrapolation of event costs and inference from protocols describing transplant patient management. It is likely that adverse events that occur in the medium to long term after heart transplantation (e.g. malignancies, chronic renal dysfunction) have been underestimated. In addition, prophylaxis for cytomegalovirus has not been costed.

An NHS perspective was adopted for the resource use and costs included in the study. It is worth noting that costs were also estimated from the perspective of a centre with an existing NSCAG-funded transplantation programme, so that dissemination of the service to a new centre would incur additional set-up costs not included in this study. In addition, costs of the transplant donor procedure were not included.

According to current Department of Health guidelines,[112,126] an annual discount rate of 3.5% was adopted for costs and benefits.

Model outputs

Results are presented as the total cost and the total QALYs with associated 95% confidence intervals for each group. The joint distribution of cost difference and QALY difference for any comparison between two groups is plotted on the cost-effectiveness plane.

The ICER is the additional cost per QALY gained and is estimated as the cost difference divided by the difference in QALYs. Since the ICER is a ratio the mean estimate can be unstable if the denominator is small (close to zero). Thus, the median ICER and 95% probability interval are also reported.

In traditional cost-effectiveness analyses the ICER is compared with the maximum amount one is willing to pay for 1 additional QALY. Since this threshold may vary depending on the perspective, the INB (Threshold × Difference in effects – Difference in costs) is plotted against the threshold. The INB at a threshold of £1000 is the mean benefit in monetary terms if 1 QALY is worth a maximum of £1000. Thus, positive values indicate cost-effectiveness. The latest NICE guidance suggests a benchmark of approximately £30,000 per QALY as the upper limit of what is acceptable to the NHS. It should be noted that this is not an explicit recommendation. The threshold is somewhat arbitrary and will change over time as the healthcare budget changes. In addition, to date there is insufficient information available on the costs and QALYs of all competing treatments to estimate a fixed ICER threshold.[112]

Since the additional mean cost and mean QALY is not fixed but an estimate, a further useful summary is to plot the probability of a new treatment being cost-effective (INB >0) against the maximum willingness to pay threshold. The resulting plot is named the cost-effectiveness acceptability curve (CEAC).

Cost-effectiveness summaries were calculated for three time-horizons: 3 years to reflect the data

TABLE 67 *Cost inputs and sources*[a]

Event	Components of cost	Source of resource-use data
Pretransplantation		
VAD implantation (group A)	Device costs Implantation theatre costs Total £63,830 (SD 15,032)	UK study of 70 patients
Post-VAD implantation (group A)	Initial ICU stay and hospital ward stay Maintenance and support (includes drugs, investigations, outpatient visits) Readmissions VAD replacement SAEs Total Month 1: £21,696 (SD 11,834) Month 2: £11,312 (SD 9,194) Month 3: £4,301 (SD 5,382) Month 4: £3,229 (SD 4,271) Month 5: £2,734 (SD 3,238) Month 6: £1,958 (SD 2,507) Month 7+: £1,593 (SD 6,389)	UK study of 70 patients
Non-VAD transplantation assessment (groups B and C)	Transplantation assessment costs Total £1,315.5 (Papworth), £1,432.77 (Harefield)	Fixed costs from Papworth and Harefield finance departments
Non-VAD pretransplantation costs (groups B and C)	Maintenance and support (includes drugs, investigations, outpatient visits) Readmissions (ICU and hospital stay) SAEs Total Group B: Month 1: £10,282 (SD 7,718) Month 2: £5,381 (SD 4,034) Month 3: £5,021 (SD 1,291) Group C: Month 1: £400 (SD 698) Month 2: £382 (SD 691) Month 3: £566 (SD 1131) Month 4: £348 (SD 717) Month 5: £233 (SD 93) Month 6: £259 (SD 173) Month 7+: £304 (SD 573)	UK study of 63 non-VAD patients (groups B and C separately)
Hypothetical scenario (group D)	ITU stay (15 days) Total £14,350	Expert opinion, National Reference Costs 2004[122]
Peri- and post-transplantation costs		
Transplantation procedure (groups A, B and C)	Theatre costs Total £14,025 (group A), £9,591 (groups B and C)	Papworth finance department. Group A adjusted upwards owing to longer theatre time
Postheart transplantation (groups A, B and C)	Initial ICU stay and hospital ward stay Maintenance and support (includes drugs, investigations, outpatient visits) Readmissions SAEs Total Month 1: group A: £13,111 (SD 7,866); group B: £11,119 (SD 6,411); group C: £9,737 (SD 8,111) Month 2: £3,645 (SD 5,645) Month 3: £2,196 (SD 3,312)	UK study patients, protocol (groups A, B and C combined)

continued

TABLE 67 *Cost inputs and sources[a] (cont'd)*

Event	Components of cost	Source of resource-use data
	Month 4: £2,380 (SD 1,834) Month 5: £1,834 (SD 3,043) Month 6: £1,385 (SD 970) Month 7+: £1,187 (SD 1,252)	
Discount rates		
All groups from implantation date	Annual 3.5% discount rate for costs and benefits	Current Department of Health guidelines

[a] See Chapter 6 for details.

collection period; 50 years to represent a complete lifetime model for these patients; and 10 years as an indicator of the rate of change in results due to increasing the time-horizon.

Only the 3-year analysis has a strong evidence base, as extrapolating beyond the range of the data is always uncertain. In this study extrapolating survival rates using UK transplantation curves is justified. There is less justification for extrapolating quality of life and costs.

Alternative scenarios

To explore the potential for cost-effectiveness as the devices develop, the sensitivity analysis considered the following alternative scenarios:

- Explanted patients were included up to the end of their lifetime (mean 72 years) assuming zero costs after explantation.
- One-third of VAD patients would behave like group B and two-thirds like group D in the absence of the technology.
- Two-thirds of VAD patients would behave like group B and one-third like group D in the absence of the technology.
- The cost of the devices was reduced to half the current costs.
- The cost of the devices was reduced to zero.
- Maximum ICU stay was reduced to 7 days and maximum ward stay was reduced to 60 days.
- The 13 second-generation devices implanted in the UK evaluation study were excluded.
- Survival on VAD support was increased to 95% in the first month, with 2% mortality per month thereafter.
- To investigate the effect of increasing waiting times on inotrope-dependent patients, the monthly transplantation rate was reduced to 0.3 in the first month and 0.1 thereafter, and the monthly death rate was increased to 0.3 in the first month and 0.1 thereafter.
- To investigate the effect of increasing waiting times on non-inotrope-dependent transplant candidates, the monthly transplantation rate was reduced to 0.15 in month 1 and 0.05 thereafter, and the monthly death rate was increased to 0.15 in month 1 and 0.05 thereafter.
- To investigate the effect of using a different utility measure, EQ-5D was replaced with SF-6D (see *Table 79*).

All alternative scenarios are modelled over the lifetime of the patient (i.e. until all patients have died). Clearly, models with shorter time-horizons would result in less favourable ICERs.

Base-case results

Three-year time-horizon

Table 68 summarises the total costs and effects for the four study groups over the 3-year study period. As expected, the average costs for the VAD group are higher than those for non-VAD groups. The mean cost over 3 years for a VAD patient was estimated at £131,600 (95% CI £123,000 to 140,200). The majority of the cost was attributable to the VAD implantation and the initial hospital stay (ICU and ward) and this alone almost accounted for the difference in costs between VAD patients and inotrope-dependent patients. After the first month on VAD support the costs decreased. The next biggest component of cost was the transplantation procedure and immediate post-transplantation costs, and these were common to those patients in all three groups who had a heart transplant. VAD patients had higher transplant procedure costs owing to the need to remove the device, and slightly higher immediate post-transplantation care costs. After the first month post-transplantation there was no evidence of a difference in the monthly costs among groups A, B and C.

TABLE 68 *Cost-effectiveness summaries for the 3-year time-horizon*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Costs				
Group A	£131,600	£131,500	£4,399	(£123,000 to 140,200)
Group B	£64,530	£64,400	£3,101	(£58,800 to 71,080)
Group C	£45,410	£45,470	£1,600	(£42,100 to 48,360)
Group D (fixed)	£14,350			
Cost comparisons				
Cost A–B	£67,040	£67,090	£5,372	(£56,440 to 77,390)
Cost A–C	£86,140	£86,110	£4,724	(£76,960 to 95,410)
Cost A–D	£117,250	£117,150	£4,399	(£108,650 to 125,850)
Life-years (mean survival)				
Group A	1.46	1.45	0.148	(1.17 to 1.75)
Group B	2.05	2.05	0.10	(1.84 to 2.24)
Group C	2.15	2.15	0.09	(1.98 to 2.31)
Group D (fixed)	0.04			
QALYs				
Group A	1.026	1.025	0.105	(0.824 to 1.235)
Group B	1.458	1.46	0.073	(1.308 to 1.594)
Group C	1.440	1.44	0.056	(1.324 to 1.547)
Group D (fixed)	0.02			
QALY comparisons				
QALY A–B	–0.432	–0.433	0.128	(-0.6774 to –0.1757)
QALY A–C	–0.414	–0.415	0.12	(-0.648 to –0.176)
QALY A–D	1.006	1.005	0.105	(0.804 to 1.215)
ICERs				
ICER A–B[a]	£41,170	–£154,800	£41,710,000	(–£431,000 to –84,250)
ICER A–C	–£239,100	–£207,100	£474,400	(–£536,500 to –119,100)
ICER A–D	£117,336	£116,650	£8,223	(£103,328 to 135,404)

[a] Since the denominator has a small but non-negligible chance of being zero the mean ICER is unstable.

Inotrope-dependent patients had 3-year costs of £64,530 (95% CI £58,800 to 71,080) and non-inotrope-dependent transplantation candidates had 3-year costs of £45,410 (95% CI £42,100 to 48,360). The difference in costs between these two groups was almost exclusively due to requirement for hospital admission and intravenous drug use pretransplantation for group B patients, since similar numbers survived to transplantation and there was little difference in post-transplantation costs.

During the 3-year study period VAD patients had a mean survival of 1.46 years (95% CI 1.17 to 1.75) and mean QALYs of 1.026 years (95% CI 0.824 to 1.235). For group B patients the corresponding figures were 2.05 years (95% CI 1.84 to 2.24) and 1.458 QALYs (95% CI 1.308 to 1.594) and group C 2.15 years (95% CI 1.98 to 2.31) and 1.440 QALYs (95% CI 1.324 to 1.547).

The relative benefits of groups B and C deserve some discussion. Since inotrope-dependent patients were at higher risk of death than other non-VAD transplantation candidates, one might have expected to see worse survival for this group. However, when donor organs became available priority was given to high-risk patients, so that they were removed from risk earlier. As a result, overall group B survival was equivalent to that of group C. The interpretation is that the waiting lists are being managed appropriately, with all (non-VAD) candidates having the same chance of survival to 3 years, irrespective of risk.

The hypothetical scenario has been constructed so that it results in comparatively little cost and very little survival benefit.

Comparing group A with B or group A with C, it is clear that the non-VAD groups are dominant,

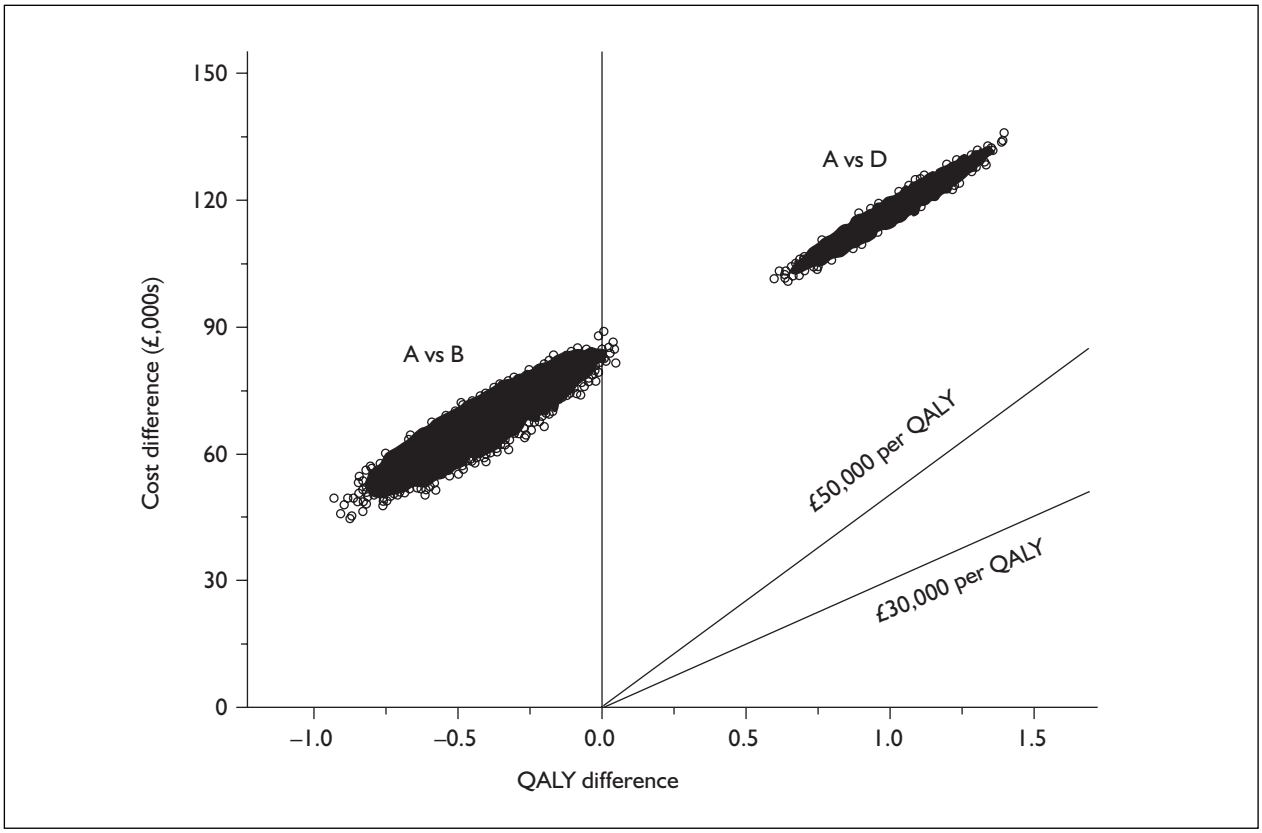

FIGURE 38 *Cost-effectiveness plane for the 3-year time-horizon*

that is, they cost less and result in greater survival benefit. Thus, the upper limit of the cost-effectiveness estimates is one of group B dominating group A. Note that the mean ICER for the comparison of A and B is not reliable owing to the possibility of zero difference in QALYs between the groups; rather, the median is the reliable estimator. Comparing group A with the worst case scenario of group D shows that VAD patients incurred higher costs but resulted in greater survival benefit. Over 3 years the mean ICER per QALY was high at £117,336 (95% CI £103,328 to 135,404) for the comparison between groups A and D.

The comparisons of group A with B and group A with D are plotted in the cost-effectiveness plane in *Figure 38*.

This plot shows the joint distribution of the difference in costs and the differences in QALYs for the two comparisons. Each point is a simulation from the joint distribution and the plot illustrates the uncertainty surrounding the mean incremental costs and benefits for the two comparisons. In addition, the shape of the distributions suggests that incremental costs and QALYs are correlated. The plot demonstrates that, despite some uncertainty surrounding the estimates of mean cost difference and QALYs, there is no evidence that group B is anything other than dominant when compared with VAD patients. The comparison between groups A and D is much more promising in that VAD patients had significantly greater QALYs than group D over 3 years. However, the cost per QALY over 3 years for this comparison was higher than generally considered cost-effective.

Ten-year time-horizon and lifetime model

Clearly, 3 years is a short time in which to observe the full costs and benefits resulting from VAD support. Using long-term transplantation survival estimates from UK Transplant, the analysis was extended to 10 years and to the complete lifetime of these patients, that is, until all patients would have died. Results for these two time horizons are given in *Tables 69* and *70*.

These tables demonstrate similar patterns to the 3-year analysis, but both costs and QALYs increase with the time-horizon. The rate of increase in costs is slower than the increase in QALYs since

TABLE 69 *Cost-effectiveness summaries for the 10-year time-horizon*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Costs				
Group A	£156,200	£156,200	£7,201	(£141,900 to 170,300)
Group B	£130,905	£130,970	£6,488	(£118,170 to 143,630)
Group C	£85,550	£85,640	£3,480	(£78,360 to 92,090)
Group D (fixed)	£14,350			
Cost comparisons				
Cost A–B	£52,790	£52,770	£8,597	(£35,910 to 69,620)
Cost A–C	£70,620	£70,550	£7,908	(£55,310 to 86,100)
Cost A–D	£141,894	£141,850	£7,202	(£127,550 to 155,950)
Life-years (mean survival)				
Group A	3.55	3.55	0.38	(2.18 to 4.30)
Group B	5.37	5.39	0.28	(4.78 to 5.89)
Group C	5.55	5.55	0.24	(5.06 to 6.01)
Group D (fixed)	0.04			
QALYs				
Group A	2.336	2.334	0.256	(1.834 to 2.839)
Group B	4.99	4.99	0.30	(4.408 to 5.577)
Group C	3.568	3.248	0.156	(3.248 to 3.867)
Group D (fixed)	0.02			
QALY comparisons				
QALY A–B	–1.193	–1.197	0.315	(–1.804 to –0.566)
QALY A–C	–1.234	–1.236	0.297	(–1.809 to –0.648)
QALY A–D	2.316	2.314	0.256	(1.814 to 2.819)
ICERs				
ICER A–B	–£51,710	–£43,960	£80,660	(–£122,012 to –20,050)
ICER A–C	–£63,350	–£57,090	£29,200	(–£132,600 to –30,670)
ICER A–D	£61,683	£61,290	£3,910	(£55,251 to 70,487)

according to the model, after 3 years, almost all surviving patients will have received a heart transplant. Thus, the ICERs for the various comparisons decreased in magnitude (moved closer to zero) with time-horizon.

The effect of time-horizon on the joint distribution of costs and effects is demonstrated in *Figure 39* for the comparison of group A with B and in *Figure 40* for the comparison of group A with D.

From *Figures 39* and *40* the uncertainty surrounding the mean incremental costs and effects increases with the length of the time-horizon and this is appropriate. *Figure 39* shows that the mean cost difference decreases with time-horizon, but at the same time the difference in benefit gained increases, since a greater proportion of group B patients survive to transplantation and continue to accrue survival benefit. Thus, group B patients should not be transferred to VAD support unless it is clear that they are unlikely to survive to transplantation, despite the current success of the urgent listing strategy.

Figure 40 demonstrates the effect of time-horizon on the comparison between groups A and D. In this analysis VAD patients continue to gain survival benefit in the long term owing to transplantation and the cost of this continued survival is relatively low. Therefore, the joint distribution moves towards a situation that is generally considered cost-effective. The diagonal lines in the plot represent £30,000 per QALY, and £50,000 per QALY and the proportion of points to the right of these lines gives an estimate of the probability that VADs are cost-effective at these thresholds (conditional on group D being a valid comparison group). This is illustrated more clearly in *Figure 41*, a plot of lifetime estimates for the comparisons of group A with B and group A with D.

TABLE 70 *Cost-effectiveness summaries for the lifetime of the patients*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Costs				
Group A	£173,841	£173,700	£9,269	(£156,000 to 192,200)
Group B	£130,905	£130,970	£6,488	(£118,170 to 143,630)
Group C	£114,400	£114,300	£5,339	(£104,000 to 125,000)
Group D (fixed)	£14,350			
Cost comparisons				
Cost A–B	£42,936	£42,820	£11,305	(£20,750 to 65,150)
Cost A–C	£59,490	£59,520	£10,750	(£38,280 to 80,360)
Cost A–D	£159,491	£159,350	£9,269	(£141,650 to 177,850)
Life-years (mean survival)				
Group A	5.63	5.61	0.688	(4.35 to 7.05)
Group B	8.62	8.55	0.69	(7.49 to 10.29)
Group C	8.96	8.78	0.63	(7.96 to 10.52)
Group D (fixed)	0.04			
QALYs				
Group A	3.270	3.260	0.370	(2.562 to 4.012)
Group B	4.990	4.990	0.300	(4.408 to 5.577)
Group C	5.099	5.092	0.260	(4.608 to 5.629)
Group D (fixed)	0.02			
QALY comparisons				
QALY A–B	–1.717	–1.723	0.474	(–2.637 to –0.783)
QALY A–C	–1.826	–1.827	0.456	(–2.724 to –0.933)
QALY A–D	3.251	3.242	0.370	(2.542 to 3.992)
ICERs				
ICER A–B	–£37,160	–£32,530	£22,080	(–£86,140 to –14,160)
ICER A–C	–£29,969	–£24,920	£60,492	(–£82,970 to –7,875)
ICER A–D	£49,384	£49,135	£2,924	(£44,451 to 55,896)

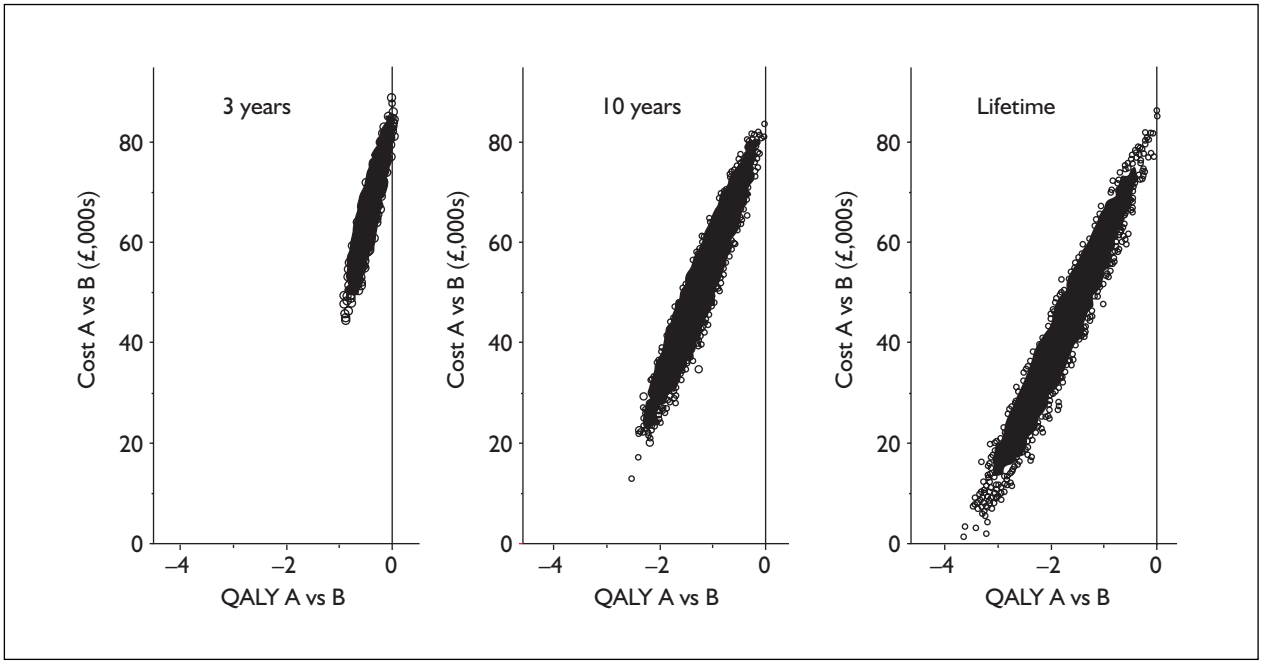

FIGURE 39 *Differences in costs and QALYs between groups A and B by time-horizon*

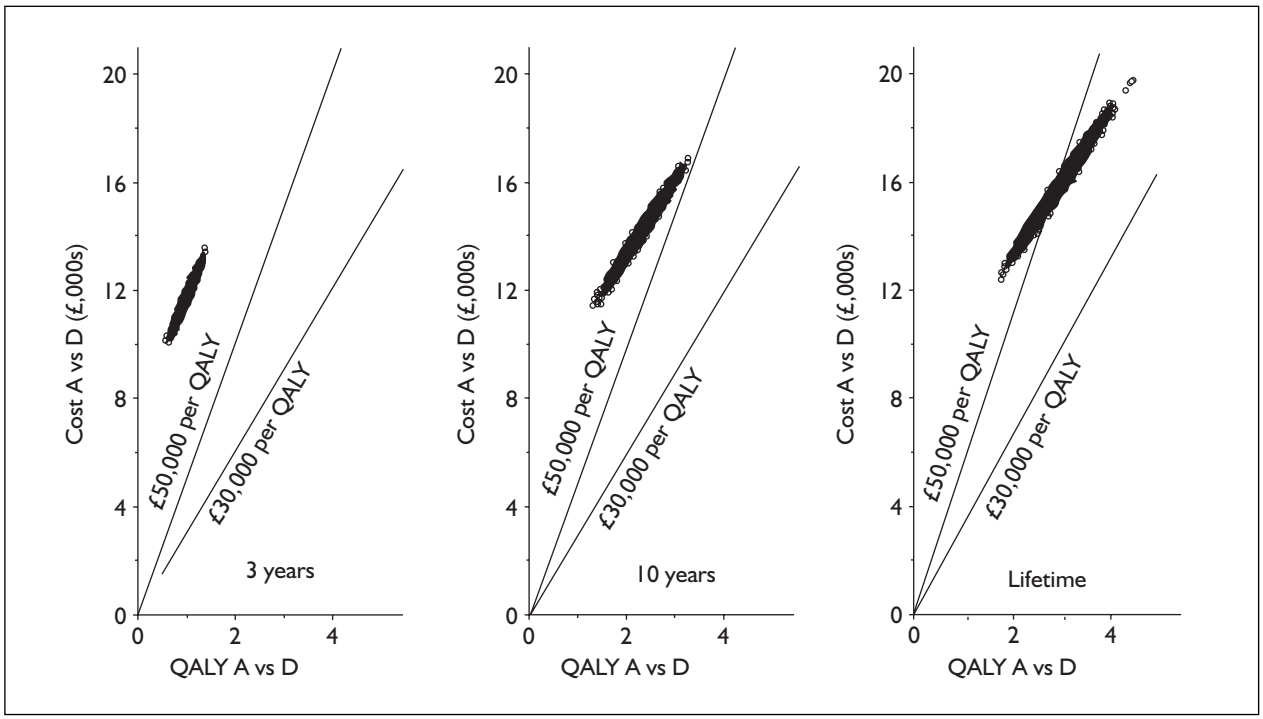

FIGURE 40 *Differences in costs and QALYs between groups A and D by time-horizon*

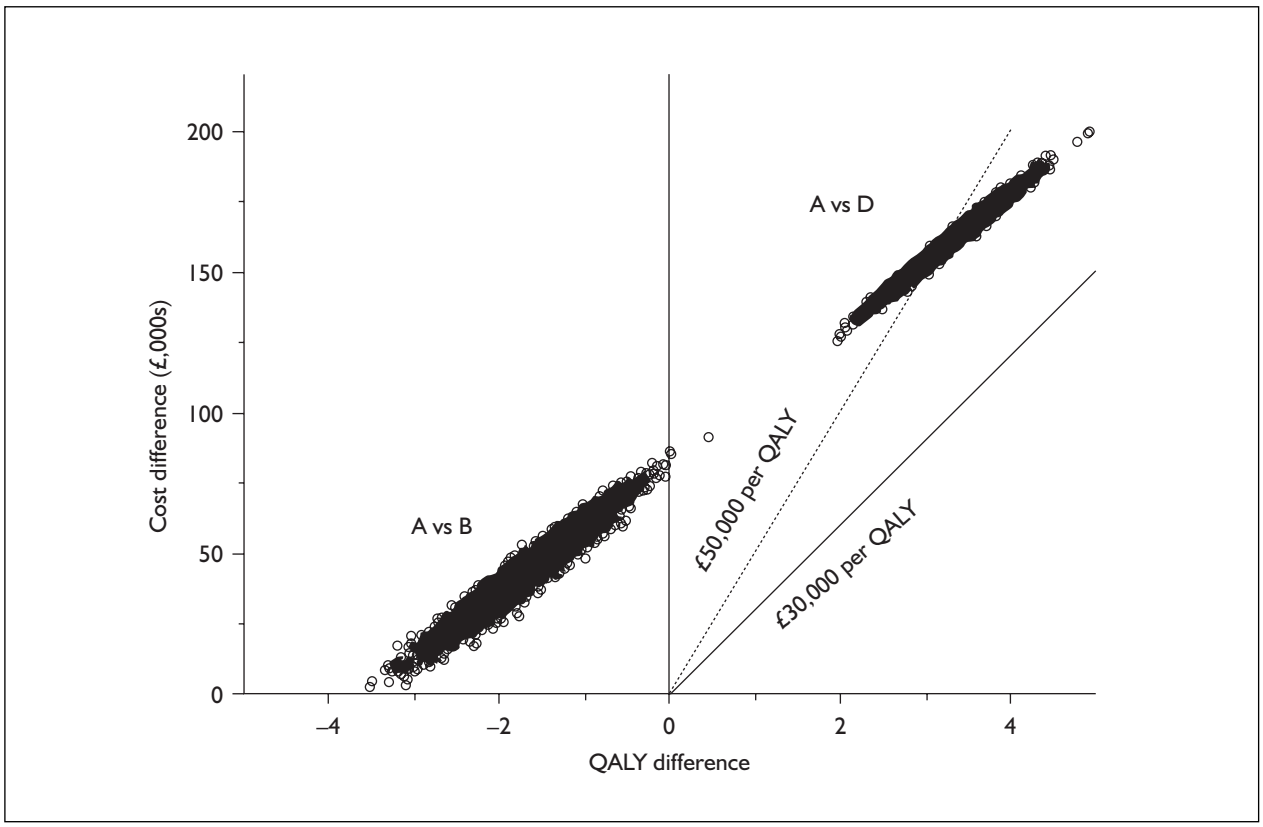

FIGURE 41 *Cost-effectiveness plane for the lifetime model*

TABLE 71 *Cost-effectiveness summaries assuming explantations have zero costs and mortality after transplantation*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
A compared with B				
Cost difference	£44,130	£44,020	£10,659	(£23,211 to 65,075)
QALY difference	–0.78	–0.78	0.45	(–1.65 to 0.10)
ICER	–£37,586	–£51,716	£373,575	(–£600,705 to 367,327)
A compared with C				
Cost difference	£59,742	£59,766	£10,136	(£39,740 to 79,415)
QALY difference	–0.88	–0.88	0.43	(–1.73 to –0.04)
ICER	–£79,649	–£65,546	£390,016	(–£507,762 to –17,932)
A compared with D				
Cost difference	£154,024	£153,892	£8,740	(£137,203 to 171,335)
QALY difference	3.91	3.90	0.35	(3.24 to 4.60)
ICER	£39,552	£39,474	£1,384	(£37,080 to 42,538)

TABLE 72 *Posterior summaries for the lifetime of VAD patients compared with alternative comparison groups*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Alternative comparison group 2/3 B and 1/3 D				
Cost difference	£81,788	£81,663	£10,222	(£62,023 to 101,810)
QALY difference	–0.061	–0.067	0.42021	(–0.867 to 0.766)
ICER	$>10^{10}$	–£96,604	>1010	(–£3,310,676 to 3,035,976)
Alternative comparison group 1/3 B and 2/3 D				
Cost difference	£120,639	£120,497	£9,514	(£102,337 to 139,320)
QALY difference	1.595	1.588	0.384	(0.864 to 2.354)
ICER	£79,212	£75,892	£16,416	(£58,934 to 119,402)

Alternative scenarios

BTR patients

In the base-case analysis the four patients who were bridged to recovery were censored at the time of explantation. Implicitly these patients are assumed to behave as other patients supported for similar lengths of time. With only four cases there are insufficient data to model this arm accurately. Therefore, a best case sensitivity analysis was performed in which all these patients are assumed to survive to their natural lifetime (mean age 72 years) and to incur zero costs.

Changing the assumptions regarding the explantations patients did make a difference to the cost-effectiveness results (*Table 71*). The mean lifetime ICER was reduced from £49,384 per QALY to £39,552 per QALY when compared with the worst case scenario.

Control group characteristics

Clearly, neither inotrope-dependent patients nor the hypothetical scenario of rapid decline to death are appropriate comparisons. In reality, in the absence of the technology one might expect the VAD recipients to be a mixture of these two extremes, but it is not clear what the relevant mixing proportion would be. As an illustration, cost-effectiveness summaries were calculated for two scenarios: a control group comprising two-thirds of group B and one-third of group D, and a control group comprising one-third group B and two-thirds group D (*Table 72*).

For the first control group the difference in QALYs between VAD patients and controls was very small at –0.061 (95% CI –0.867 to 0.7666), so that the ICER was unstable. In this case the analysis should concentrate on cost minimisation. As the mean cost for a VAD patient was £81,788 greater than that for a control patient, the logical decision would be to list the patients for transplantation.

For the second control group with two-thirds group D patients the average VAD patient gained 1.595 QALYs over their lifetime at a cost of

TABLE 73 *Cost-effectiveness summaries for the lifetime of VAD patients assuming that devices costs are halved*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Device costs halved A compared with B				
Cost difference	£20,057	£19,941	£11,304	(–£2,129 to 42,271)
QALY difference	–1.717	–1.723	0.474	(–2.637 to –0.783)
ICER	–£15,262	–£11,601	£44,048	(–£53,288 to £843)
Device costs halved A compared with C				
Cost difference	£36,615	£36,641	£10,750	(£15,401 to 57,481)
QALY difference	–1.826	–1.827	0.456	(–2.724 to –0.933)
ICER	–£23,599	–£20,006	£17,127	(–£61,424 to –5,703)
Device costs halved A compared with D				
Cost difference	£136,612	£136,471	£9,269	(£118,771 to 154,971)
QALY difference	3.251	3.242	0.370	(2.542 to 3.992)
ICER	£42,253	£42,079	£2,096	(£38,683 to 46,910)

TABLE 74 *Cost-effective summaries for the lifetime of VAD patients assuming that device costs are zero*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Device costs zero A compared with B				
Cost difference	–£2,820	–£2,936	£11,305	(–£25,006 to 19,394)
QALY difference	–1.717	–1.723	0.474	(–2.637 to –0.783)
ICER	–£557	£1,717	£27,623	(–£24,415 to 9,596)
Device costs zero A compared with C				
Cost difference	£13,674	£13,644	£10,695	(–£7,156 to 34,644)
QALY difference	–1.826	–1.827	0.456	(–2.724 to –0.933)
ICER	–£8,646	–£7,495	£8,495	(–£27,338 to 3,457)
Device costs zero A compared with D				
Cost difference	£113,735	£113,594	£9,269	(£95,894 to 132,094)
QALY difference	3.251	3.242	0.370	(2.542 to 3.992)
ICER	£35,121	£35,019	£1,282	(£32,895 to 37,959)

£120,639, resulting in an ICER of £79,212, again high by traditional standards.

Reduced device costs

If future device costs were reduced to half the current cost and there was no change in other model inputs, the lifetime ICER per QALY would reduce in magnitude to some extent for all three comparisons (*Table 73*). Since this assumption would not change the relative effect sizes, groups B and C would still remain cheaper and more effective compared with group A. The mean lifetime ICER for the group D comparison would be reduced from £49,384 to £42,253.

If device costs were zero, group C would remain cheaper and more effective than group A since there are significant costs associated with device support, such as hospital stay, intravenous drug use, staffing and adverse events (*Table 74*). However, there would be a small cost saving associated with VADs compared with inotrope-dependent patients. In this analysis one would be paying a median of £1717 for each extra QALY gained by keeping patients on inotropes rather than VAD support. The mean lifetime ICER for the comparison with the worst case scenario would be reduced to £35,121, which is close to traditionally acceptable levels.

Reduced initial ICU and hospital stay

The length of time spent in the ICU and on the hospital wards by VAD patients is an important component of costs. To assess the impact of hospital stay the lifetime model was repeated under the assumption that maximum ICU and ward stay for the initial implantation were reduced to 7 and 60 days, respectively. Results for this scenario are given in *Table 75*.

TABLE 75 *Cost-effectiveness summaries assuming a maximum ICU stay of 7 days and maximum ward stay of 60 days following VAD implantation*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
A compared with B				
Cost difference	£33,010	£33,060	£11,210	(£10,880 to 54,570)
QALY difference	–1.71	–1.71	0.48	(–2.64 to –0.78)
ICER	–£24,770	–£19,400	£105,900	(–£68,660 to –4,149)
A compared with C				
Cost difference	£49,490	£49,360	£10,400	(£29,490 to 69,940)
QALY difference	–1.83	–1.83	0.45	(–2.70 to –0.94)
ICER	–£31,040	–£26,990	£19,040	(–£74,480 to –10,890)
A compared with D				
Cost difference	£149,599	£149,650	£9,099	(£131,950 to 167,652)
QALY difference	3.26	3.26	0.37	(2.53 to 3.99)
ICER	£46,225	£45,970	£2,619	(£41,821 to 52,059)

TABLE 76 *Cost-effectiveness summaries with Jarvik 2000 patients excluded from the analysis*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
A compared with B				
Cost difference	£47,150	£47,140	£12,070	(£23,540 to 65,150)
QALY difference	–1.68	–1.68	0.49	(–2.64 to –0.71)
ICER	–£34,990	–£28,220	£45,650	(–£98,670 to –9,009)
A compared with C				
Cost difference	£63,597	£63,560	£11,431	(£41,149 to 85,750)
QALY difference	–1.83	–1.83	0.46	(–2.70 to –0.87)
ICER	–£37,160	–£32,530	–£22,080	(–£98,892 to –15,340)
A compared with D				
Cost difference	£163,725	£163,750	£10,088	(£143,950 to 183,250)
QALY difference	3.29	3.29	0.39	(4.36 to 7.24)
ICER	£50,081	£49,783	£3066	(£44,983 to 57,049)

This assumption results in reducing the mean lifetime costs for the VAD patients from £173,841 to £163,900. In this case, inotrope-dependent and non-inotrope-dependent transplant candidates (groups B and C) have lower mean lifetime costs and greater survival. The mean lifetime ICER for VAD patients compared with the worst case scenario (group D) is reduced from £49,384 to £46,225.

Excluding second generation devices

There was evidence that patients implanted with the Jarvik 2000 second generation device were supported longer than recipients of first generation devices. The impact of excluding these second generation devices was of interest. Therefore, the lifetime model was repeated with transition probabilities and costs derived from first generation devices only. This had the effect of increasing the mean lifetime costs from £173,841 to £178,100 and also increasing the mean lifetime QALYs from 3.27 to 3.31 years. Therefore, the effect on the ICER was negligible (*Table 76*).

Improvement in survival with VADs

The extent to which survival on the VAD can be improved is difficult to predict. The best case scenario that could be envisaged is one in which the operative mortality was reduced to 5%, similar to other cardiothoracic procedures, and subsequent mortality was reduced to half the observed mortality of 4% per month. Summaries for the case where the model runs for the lifetime of VAD patients are shown in *Table 77*. Here groups B and C continue to cost less and have greater survival benefit since current waiting list mortality is of the order of 8–10% overall. The lifetime ICER for the comparison with the worst case scenario is reduced

TABLE 77 *Cost-effectiveness summaries for the lifetime of VAD patients assuming monthly mortality rates of 5% for the first month and 2% thereafter*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
Improved survival with VAD A compared with B				
Cost difference	£82,610	£82,880	£11,050	(£60,540 to 103,500)
QALY difference	–0.220	–0.209	0.481	(–1.187 to 0.696)
ICER	–£111,500	–£108,700	£12,667,902	(–£3,043,000 to 2,759,000)
Improved survival with VAD A compared with C				
Cost difference	£98,920	£99,200	£10,430	(£77,890 to 118,700)
QALY difference	–0.34	–0.333	0.46	(–1.27 to 0.54)
ICER	–£64,390	£149,600	£50,660,000	(–£3,041,000 to 2,880,000)
Improved survival with VAD A compared with D				
Cost difference	£199,100	£199,300	£8,842	(£180,700 to 215,500)
QALY difference	4.74	4.75	0.37	(3.97 to 5.45)
ICER	£42,110	£41,970	£1,552	(£39,450 to 45,600)

TABLE 78 *Cost-effectiveness summaries assuming lower transplantation rates and higher death rates for non-VAD groups*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
A compared with B				
Cost difference	£89,610	£89,620	£11,990	(£66,130 to 113,200)
QALY difference	0.37	0.37	0.49	(–0.59 to 1.33)
ICER	–£1,026,000	£145,900	£144,500,000	(–£1,756,000 to 1,950,000)
A compared with C				
Cost difference	£106,400	£106,500	£11,130	(£84,870 to 128,100)
QALY difference	0.20	0.20	0.46	(–0.71 to 1.11)
ICER	£330,000	£180,500	£19,250,000	(–£2,948,000 to 3,303,000)

from £49,384 to £42,110. This reduction is less than might be expected since both costs and survival increase in this scenario.

Impact of increased waiting time

The base-case cost-effectiveness analysis reflects current VAD and transplantation activity and favours non-VAD transplant patients owing to the success of the urgent transplant strategy. This results from the relatively short transplant waiting lists, likely because of a reluctance to refer potential candidates in the climate of acute donor organ shortage. Should cardiologists increase referrals, or donor organs become more scarce, then waiting lists and waiting-list mortality would increase. A crude assessment of the impact of this practice was made by approximately halving the monthly transplant probabilities for non-VAD candidates and assuming that the patients who are not transplanted under this scheme would die on the waiting list.

For inotrope-dependent patients the alternative scenarios assumes that both transplant and death probabilities are 30% in the first month and 10% thereafter. This has the effect of reducing the mean lifetime costs for this group from £130,905 in the base case to £84,230 since fewer patients survive to transplantation (*Table 78*). Corresponding mean lifetime QALYs are reduced from 4.99 years to 2.90 years. Thus, in this hypothetical scenario, inotrope-dependent patients had lower costs than VAD patients, but slightly lower QALYs. The mean lifetime ICER was unstable and the median ICER was high at £145,900 per QALY for VAD patients relative to inotrope-dependent patients.

For the non-inotrope-dependent patients, the alternative waiting time scenario assumes that both transplant and death probabilities are 15% for month 1 and 5% thereafter. This has the effect of reducing the mean in the base case to £67,460 (*Table 78*). Again, the main reason for the reduction in costs is the decrease in patients surviving to transplantation and hence incurring longer term costs. There is a corresponding decrease in mean lifetime QALYs from 5.10 years

TABLE 79 *Posterior summaries for the lifetime of VAD patients using the SF-6D utilities*

Parameter	Mean	Median	SD	Equal-tailed 95% CI
A compared with B				
Cost difference	£42,980	£42,880	£11,370	(£20,620 to 65,370)
QALY difference	–1.401	–1.404	0.397	(–2.173 to –0.611)
ICER	–£36,260	–£30,570	£154,042	(–£105,300 to –9535)
A compared with C				
Cost difference	£59, 280	£59,140	£10,750	(£38, 600 to 79,990)
QALY difference	–1.548	–1.551	0.379	(–2.279 to –0.804)
ICER	–£44,100	–£38,090	£51,410	(–£98,840 to –16,830)
A compared with D				
Cost difference	£159,490	£159,351	£9,269	(£141,651 to 177,851)
QALY difference	2.741	2.733	0.312	(2.141 to 3.353)
ICER	£58,186	£58,306	£2,096	(£54,163 to 62,210)

(95% CI 4.61 to 5.63) in the base case to 3.07 years (95% CI 2.55 to 3.63). Thus, in this hypothetical scenario of increased waiting times and pretransplantation mortality the median lifetime ICER for VAD patients relative to non-inotrope-dependent transplant candidates was £180,500 per QALY.

In the analysis shown in *Table 78*, for group B, it was assumed that both death and transplantation rates are 30% in month 1 and 10% beyond month 1. For group C, it was assumed that both death and transplantation rates are 15% for month 1 and 5% beyond month 1.

Use of SF-6D utilities

To assess the influence of the EQ-5D utility measure, the analysis derived from the SF-36 was repeated. In this scenario, pretransplantation utilities were estimated as 0.65 for the VAD group, 0.55 for the inotrope-dependent group, and for routine transplant candidates, 0.69 in the first month after listing, falling to 0.64 thereafter. Since there was no evidence that the groups had different SF-6D results after transplantation a fixed value of 0.63 was assumed for all patients. The effect of these assumptions on cost-effectiveness summaries is shown in *Table 79*. Since the SF-6D is lower than the EQ-5D for most cases, the absolute gain in QALYs is lower and the resulting ICERs are less favourable to VADs. Compared with the worst case, the cost per QALY gain for VADs rose to £58,186.

Selected scenarios comparing VAD patients with the worst case scenario (group D) are illustrated using CEACs in *Figure 42*. The curves are provided for the base case, the case of free devices and the case of waiting-list mortality for VAD patients of 5% in the first month and 2% thereafter. The CEAC plots the probability that the ICER for VADs is less than the maximum one is willing to pay for one QALY. The comparison of VAD patients with controls made up of one-third group B (inotrope-dependent) and two-thirds group D (worst case) is plotted in *Figure 43*.

For the base case VADs are considered cost-effective (probability cost-effective ≥ 0.05) if approximately £50,000 per QALY is considered an acceptable threshold. For the reduced mortality scenario cost-effectiveness is likely at a threshold of £42,000, and if devices were provided free this figure would be reduced to £35,000. This assumes that group D is the appropriate comparator. For the more likely scenario of a control group comprising a mixture of one-third group B and two-thirds group D, VADs are unlikely to be cost-effective unless one is willing to pay approximately £79,000 per QALY.

Summary

In summary, based on a robust statistical model that reflects current UK practice, populated by actual UK data and under a range of model assumptions, VAD patients with an indication of BTT had higher mean costs than other transplant candidates and less survival benefit. The implication from this analysis is that transplant candidates should not undergo VAD implantation unless it is unlikely that they will survive to transplantation under the current urgent listing scheme, or unless they are unable to undergo transplantation until they have a period of

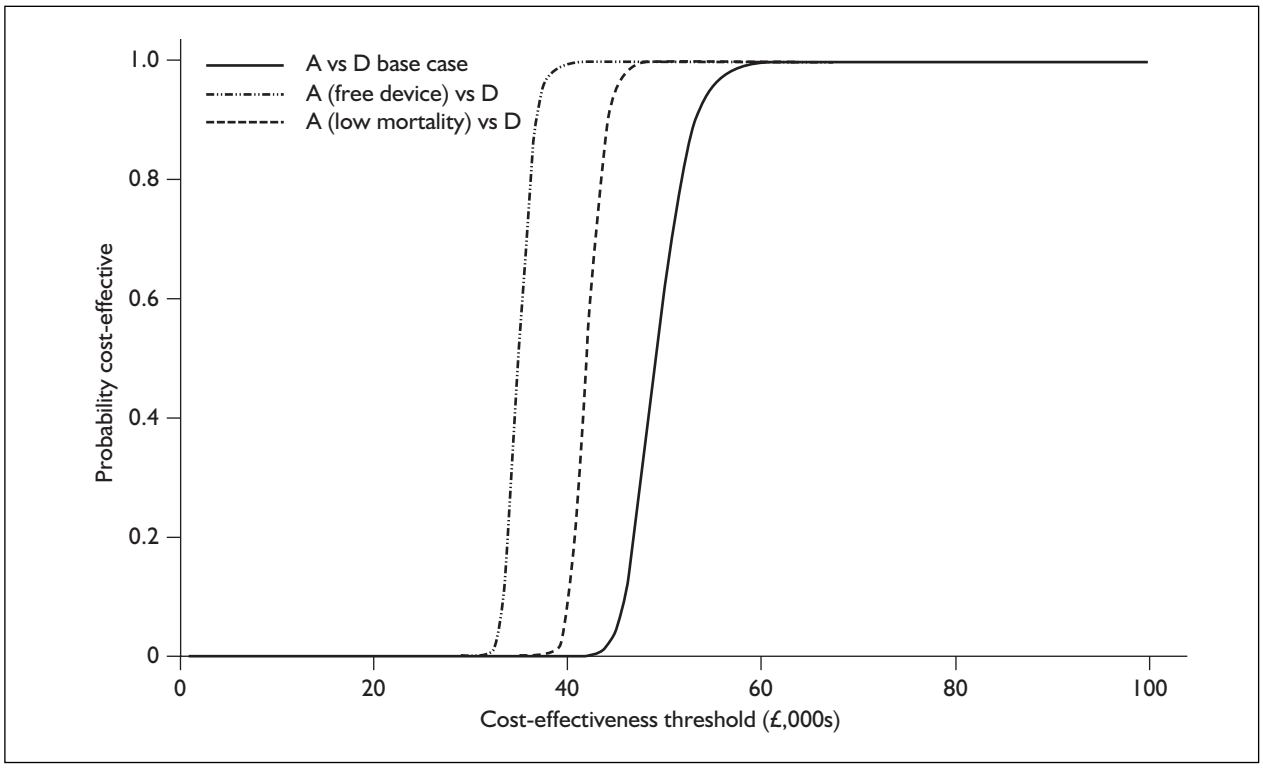

FIGURE 42 *CEACs for VAD patients relative to the death within 1 month on ICU (group D) with base-case assumptions and selected sensitivity analyses*

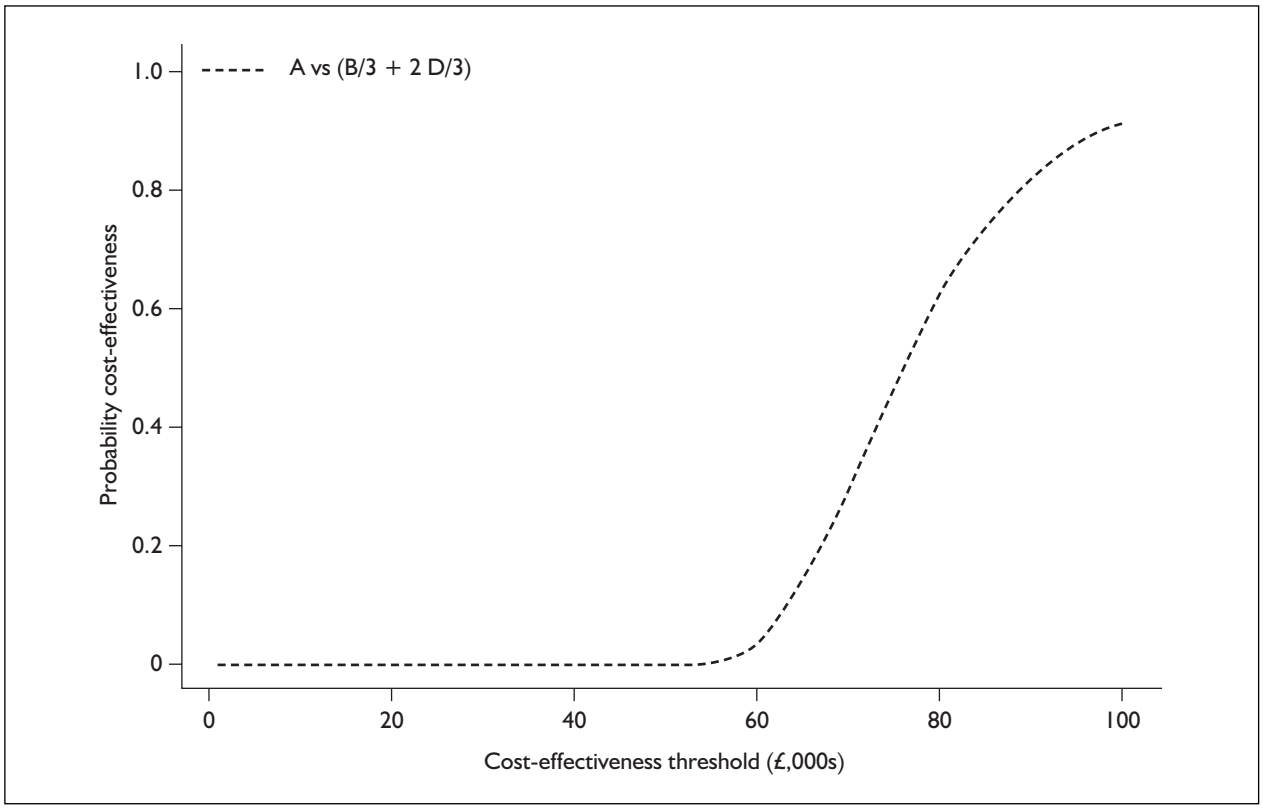

FIGURE 43 *CEACs for VAD patients relative to a group of patients who are a mixture of inotrope-dependent (one-third) and expected to die within 1 month (two-thirds)*

stabilisation using mechanical support. Radical changes in the waiting-list mortality may render VAD implants more effective than continued listing, but the ICER would be high, at £145,900–180,500 in the scenarios considered. Compared with a worst case scenario in which patients would die in the ICU within 30 days without VAD support, the mean cost of a VAD was higher, but significant survival benefit resulted. Depending on model assumptions, the lifetime cost per QALY in this case ranged from £35,121 if the device cost was zero to £49,384 in the base case. A more plausible control group is a mixture of group B and group D patients and in this case the lifetime ICER per QALY ranged from £79,212 to the VAD group being more expensive and less effective than the control group in the mixtures considered.

Chapter 9

Conclusions, implications and recommendations

Clinical effectiveness of VADs

Although it is difficult to obtain precise estimates of the prevalence of severe heart failure, it is likely to exceed greatly the number of cadaveric organ donors in the UK, particularly as the number of donors has decreased in recent years. To have an impact on the heart failure population, researchers need to investigate new treatments such as VADs.

During the period April 2002 to December 2004, 71 patients in the UK received VADs as BTT, equivalent to a rate of 25.5 implants per year, mostly at two established transplant centres, Harefield and Papworth hospitals. The team from the Freeman hospital took some time to set up their VAD programme and at the end of the study period was still on the learning curve, having implanted three VADs. The requirement for implants as a BTT did not increase over the period of study and failed to meet the target of 35 per year agreed by NSCAG. It is likely that extending the service to other centres would increase the activity nationally, since referrals tended to be clustered around the three NSCAG-funded centres.

Patients undergoing VAD implantation as a BTT were young (mean age 41.9 years) and had rapidly failing hearts, with poor prognosis. Survival to transplantation was considered unlikely despite the provision of an urgent listing category nationally, with a median waiting time of 16 days for urgent transplant candidates. Despite this, VAD patients had a 1-year survival of 52% (95% CI 41 to 65%) and had post-transplantation survival rates comparable to routine transplant candidates. Thus, there is little doubt as to the clinical effectiveness of VAD support for these very sick patients.

Successful BTT or BTR rates from the UK study were slightly lower than published case series, with 57% achieving a good outcome. Given the clear publication bias exhibited in the literature review, UK success rates are entirely consistent with those of other centres. In addition, device malfunction, sepsis, bleeding and neurological events continue to affect a significant minority of patients, both in the UK and in published reports. Studies of second generation devices included small samples, were uncontrolled and had short mean follow-up, so that one should beware of drawing conclusions about improvements at this stage. Although a small group of patients can be bridged to recovery, the effectiveness of the VAD programme is heavily influenced by the proportion of patients who survive to transplantation. Both VAD patients and non-VAD-supported transplant candidates had excellent survival of 84–85% at 12 months after transplantation. In addition, the costs associated with heart transplantation were low relative to those for VAD implantation and management. An important message from this study is that significant health gains result from heart transplantation and all efforts to maintain the availability of donor hearts should be encouraged. Investment in encouraging organ donation may provide greater overall benefit for current patients.

Costs

In the UK evaluation, the mean implantation cost, including the device, was estimated to be £63,830, with substantial costs of VAD support for survivors of £21,696 in the first month and £11,312 in the second month (see *Table 67*). These figures are lower than published estimates and there may be a number of reasons for this. For example, in the costing exercise set-up costs were not included. It was assumed that patients receive VADs in an established NSCAG-funded transplant centre, where set-up costs have already been incurred. If new centres were to come on line there would be an additional set-up cost to ensure that adequately trained surgical, cardiological, anaesthetic, nursing and technical staff were in place. In addition, many of the published estimates have been from the USA, which is known to have a less parsimonious approach to healthcare resource use than the UK. However, the main cost drivers highlighted in the literature, including the device itself, staffing, ICU stay, duration of hospital stay for initial implantation and adverse events such as bleeding, stroke and infection, were also observed in UK patients.

In published studies VAD recipients who could be discharged from hospital had significantly lower

costs than those who could not be discharged. In the UK evaluation monthly costs for VAD support decreased substantially over the first 6 months. However, this may not be extrapolated to long-term VAD support uncritically. As the length of support is extended the requirement for VADs to be replaced is likely to increase and this will have cost implications. Although only one patient in the UK series required a replacement VAD, the mean time on the VADs was short. Further evaluation of device reliability in the longer term when used in clinical practice is required.

Implications of the cost-effectiveness results

Three economic models of BTT, compared with medical therapy, have been published. Cost per life-year gained was approximately US$28,000 in the study by Kolbye and colleagues[82] and US$95,000 in the comprehensive study from Canada.[83] An early published UK study[79] estimated a cost per QALY of approximately £40,000. A further study from Clegg and colleagues[5] has recently been published and estimates the ICER for VAD at £65,242 per QALY over 5 years. The data collected in the UK evaluation and presented here suggest that these figures are too low, with the lifetime cost per QALY ranging from approximately £50,000 if the scenario that patients offered LVAD would have died within a mean of 15 days is the more plausible, to the situation that VADs are dominated (i.e. are less effective and more costly) if it is more reasonable to compare these LVAD patients with inotrope-dependent transplant candidates.

The main difficulty in modelling cost-effectiveness of VADs remains the lack of adequate comparison data. The only level 1 evidence available was from the REMATCH trial for the HeartMate used as destination therapy.[12] Patients in this trial were older than BTT VAD recipients and by definition were not eligible for transplantation. In addition, although REMATCH participants had poor prognosis, as demonstrated by the high mortality rate among the control group, they were less acutely sick than current VAD recipients in the UK, for whom the intention is BTT. In addition, most BTT patients are considered to require a period of stabilisation on VAD support before a transplant can be attempted. Therefore, the REMATCH results cannot be applied in this cost-effectiveness model. Most published BTT evidence was uncontrolled or based on small case series, or had other potential biases. There was also evidence of publication bias, so that reliable control groups could not be derived from the literature.

In the original proposal for this study one of the proposed methods was to construct historical controls based on risk-score predicted survival. Although a range of risk scores is available, all depend on VAD candidates undergoing tests, such as measurement of peak oxygen uptake during a cardiopulmonary exercise test. Given the nature of the VAD candidates and inotrope-dependent patients, it was not feasible to obtain such test data and the proposed risk-matching of VAD patients was not feasible.

In the absence of a suitable control group, concurrent transplant candidates who did not require a VAD were studied to provide an upper limit of cost-effectiveness. A hypothetical worst case scenario was constructed as a lower bound. Results from these models demonstrated that even if the worst case scenario were plausible, and results could be reliably extrapolated to the full lifetime of the patients, VADs are associated with a high ICER per QALY of approximately £50,000. (An alternative scenario of patients otherwise living longer, maintained in the ICU before dying before transplantation, would make VADs seem relatively more cost-effective, but such a scenario, although perhaps relevant in the 1980s,[127] would not be consistent with the current situation in the UK where most urgent patients receive transplants relatively quickly.)

Given the difficulty in identifying a suitable control group and the relatively small number of VAD cases, careful interpretation of the cost-effectiveness results is required. Compared with inotrope-dependent transplant candidates, VAD support was more expensive and less effective. The provision of the urgent listing category has significantly reduced the waiting time of inotrope-dependent candidates for a donor organ and hence their risk of death waiting for transplantation. In current practice, such a patient should not become a VAD recipient unless it became clear that the patient was unlikely to survive to transplantation or would not become eligible for transplantation without a period of VAD support. Should the waiting list change radically owing to an increase in suitable referrals then this could be reassessed.

A further putative argument for use of VADs as BTT has been the suggestion that having been stabilised on VADs before transplantation their

survival after transplantation may be better than it otherwise would have been. These data show no evidence of such an advantage. Thus, with the current technology and the current arrangements for allocation of organs for heart transplantation it is unlikely that a patient service using VADs as BTT can be justified in terms of its cost-effectiveness as a patient service. However, there may well be an effectiveness argument for BTT for selected cases.

Although the cost-effectiveness of the current VAD programme focusing on BTT is not sufficiently encouraging to justify continued funding in terms of the value to current recipients, the more promising application of VADs in the longer term is likely to be for BTR and as destination therapy. The bases for this conclusion are the modelling presented here, the evidence from the REMATCH study, and the cost-effectiveness gap left by the inadequacy of existing medical interventions.[13]

As a result, in the meantime, there may be a significant argument to justify that a funded programme of BTT be continued, in that the use of VADs in that context may provide the most appropriate way of maintaining skills required to implant and manage the devices and to keep abreast of the developing technology, while minimising the risk to recipients of the devices. However, if that is the basis for maintaining a programme then the characteristics of that programme should be those that maximise these long-term research and developmental (R&D) benefits. It is likely that these R&D benefits will be maximised by restricting the programme to a small number of specialist centres, and by ensuring that these cooperate in an active formalised research programme that maximises knowledge gained from the small number of cases.

Strengths and weaknesses of the current evaluation

The main strengths of the current study can be summarised as follows:

- Although the study was integrated into the UK VAD programme it was designed and conducted by independent researchers, with no vested interest in the technology.
- A comprehensive statistical model of patient experience was developed, which included the full uncertainty associated with measures of survival, utilities and costs.
- The model was populated with consistent data from the centres so as to reflect the whole of the UK VAD and transplant programmes. It is therefore both current and directly relevant to the UK.

The study was limited by the following features:

- The biggest weakness was the absence of a directly comparable control group. Groups B and D provided bounds on the cost-effectiveness parameters, but there was a wide range of scenarios between these bounds.
- Any statistical/economic model of patient experience necessarily simplifies the complex reality of the VAD and transplant programmes, with the likely result being an underestimate of the variation associated with cost and QALY estimates.
- VAD activity was low at 25.5 per year, so that there was large variation around some of the cost and effects estimates.
- Owing to the difficulties in obtaining HRQoL data from these very sick people there was considerable variation around the estimates of some model inputs. In particular, only 13 group B patients provided utility and detailed resource-use data.
- Since the emphasis of this study was to conduct and report primary research, the authors have not attempted to reproduce the thorough systematic review reported by Clegg and colleagues.[5]

Recommendations for future research

In summary, the authors' research recommendations are:

1. Formal analysis of the expected benefit from reducing the uncertainty about the cost-effectiveness of this technology, which would be achieved by undertaking further research across the various applications of VADs.
2. An analysis of the consequences of the overall effect of a major BTT VAD programme on the whole heart transplant programme and all of its patients.
3. Formal randomised trials of improved VADs as bridge to recovery and/or destination therapy, initially against medical management and then between devices.
4. Continued systematic monitoring of any VAD activity to maximise resultant R&D learning.

As explained below, these are not in a priority order. Rather, each of the first three is contingent on the development of other plans and policies (1 and 2) or external developments in the technology (3). Recommendation 4 is modest but essential.

It was not within the agreed brief to undertake a formal analysis of the likely payback from further research, either in terms of the normative recommendations that could be produced from a formal value of information analysis that looked at the expected value of sample information as recommended by Claxton and colleagues,[128] or in terms of a more pragmatic positive assessment as recommended by Townsend and colleagues.[129] Thus, the authors' recommendations for future research are made on a less formal basis. Although they believe that there is evidence to support them, the authors would recommend that a formal analysis of potential decision–benefit be undertaken in advance of funding any major and expensive study or trial. This analysis would need to compare and prioritise investment in research on the various possible indications for VADs.

This study provides a fairly conventional cost-effectiveness analysis, focusing on the costs and benefits associated with subsets of potential transplant recipients. The study groups identified are interdependent, rather than independent of each other, and using VADs to increase the number of people who survive to transplantation in one group is likely to increase the average waiting time for all transplant candidates, since the number of transplants is limited by donor availability and (probably) unchanged by the use of VADs. This increases the likelihood that routine transplant candidates will deteriorate on the list (to a greater extent than would have otherwise been the case) and they may then require VAD support. Therefore, the proportion of transplanted patients, who had been supported by VADs, may increase substantially. It is possible that the total lifetime gained from the UK transplant programme will not increase substantially, but the costs will increase according to the cost of VAD support. This requires careful system modelling and this should be the subject of further research, if and when it is thought that a programme could be justified in terms of its cost-effectiveness for a subgroup of transplant patients.

Although BTT is a convenient vehicle for development of devices and their management, unless it leads to greater mean survival post-transplantation across the whole supply of transplant recipients, it cannot have a major impact on patient survival. The real potential value of the technology is likely to be for BTR and for destination therapy. At present it is not possible at the time of implant to predict accurately who will recover sufficient myocardial function to allow explantation. However, early protocols for assessing myocardial recovery during VAD support are available and are being refined through observational studies. For destination therapy the REMATCH trial was a well-conducted study and provided valuable level 1 evidence of the extent of the costs and benefits of VADs.[12] However, it was relatively small, used a first generation device and was completed in 2001. In addition, although significant survival benefit was demonstrated, on average patients gained only about 4.6 months due to VAD support.[61] There is growing evidence that second generation devices can support patients for longer periods, although the low quality of many published reports means that it is difficult to tell whether overall survival rates have improved with these devices. Moreover, most devices are still not fully implantable, so that significant risks of sepsis and haemorrhage remain. It is important that a randomised comparison is carried out when the devices have developed sufficiently to have a good chance of success with fewer adverse events. Further randomised clinical trials will be required in future, in the UK context once it is considered that devices have developed sufficiently to represent a realistic technology for destination therapy. Such studies could include a variety of designs, including randomised comparisons with optimal medical management for stable ambulatory patients and head-to-head comparisons of different devices for patients with acute-onset severe heart failure.

Meanwhile, all UK VAD activity and results should be carefully and consistently monitored, and the NSCAG service should be structured and managed to maximise understanding and to develop the skill-base for future patients, rather than being seen as a service for which the benefits to current patients justify its ongoing costs.

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Contribution of authors

Linda Sharples (MRC Programme Leader in Statistics) undertook the review of clinical studies, supervised the construction of the economic model and the statistical analysis, and led the process of integrating the various contributions into the final draft. Martin Buxton (Professor of Health Economics) supervised the review of economic studies and the analysis of the resource-use data, and advised on the modelling of cost-effectiveness. Noreen Caine (Deputy Director of R&D, Department of Health) supervised the management of all the data collection exercises and led the design and analysis of the health-related quality of life survey. Fay Cafferty (PhD student) undertook the statistical analysis of the clinical and health-related quality of life data. Nikolaos Demiris (MRC Career Development Fellow in Statistics) constructed the economic model and was responsible for estimation of cost-effectiveness parameters. Matthew Dyer (Research Assistant in Health Economics) undertook the review of economic studies and the analysis of the resource-use and cost data. Carol Freeman (Research Officer) was responsible for coordination of the study and management of all data collection. All the authors contributed to the drafting of the report. Linda Sharples, Martin Buxton and Noreen Caine took prime responsibility for producing the final report.

References

1. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, *et al*. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Heart Lung Transplant* 2002;**21**: 189–203.
2. Department of Health. *National Service Framework for Coronary Heart Disease: Modern Standards and service models*. Chapter 6. Heart failure. National Service Frameworks. London: Department of Health; 2003.
3. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, *et al*. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;**20**:421–8.
4. Caine N, Sharples LD, English TA, Wallwork J. Prospective study comparing quality of life before and after heart transplantation. *Transplant Proc* 1990;**22**:1437–9.
5. Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(45).
6. Robert G, Caine N, Sharples LD, Buxton MJ, Large SR, Wallwork J. Assessing low volume, high cost, potentially life saving surgical interventions: how and when? Left ventricular assist devices (LVADs) as a case study. *J Eval Clin Pract* 1999;**5**:387–91.
7. Portner PM. Economics of devices. *Ann Thorac Surg* 2001;**71**(3 Suppl):S199–201; Discussion S203–4.
8. Hetzer R, Muller JH, Weng Y, Meyer R, Dandel M. Bridging-to-recovery. *Ann Thorac Surg* 2001; **71**(3 Suppl):S109–13; Discussion S114–15.
9. Frazier OH, Myers TJ. Left ventricular assist system as a bridge to myocardial recovery. *Ann Thorac Surg* 1999;**68**:734–41.
10. Torre-Amione G, Stetson SJ, Youker KA, Durand JB, Radovancevic B, Delgado RM, *et al*. Decreased expression of tumor necrosis factor-alpha in failing human myocardium after mechanical circulatory support: a potential mechanism for cardiac recovery. *Circulation* 1999;**100**:1189–93.
11. Yacoub MH, Birks EJ, Tansley PD, Henien MY, Bowles C. Bridge to recovery: the Harefield approach. *Journal of Congestive Heart Failure and Circulatory Support* 2001;**2**:27–30.
12. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, *et al*. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;**345**:1435–43.
13. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. *Journal of Health Services Research Policy* 1997;**2**:26–30.
14. El-Banayosy A, Arusoglu L, Kizner L, Tenderich G, Minami K, Inoue K, *et al*. Novacor left ventricular assist system versus Heartmate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. *J Thorac Cardiovasc Surg* 2000;**119**:581–7.
15. Aaronson KD, Eppinger MJ, Dyke DB, Wright S, Pagani FD. Left ventricular assist device therapy improves utilization of donor hearts. *J Am Coll Cardiol* 2002;**39**:1247–54.
16. Bank AJ, Mir SH, Nguyen DQ, Bolman RM III, Shumway SJ, Miller LW, *et al*. Effects of left ventricular assist devices on outcomes in patients undergoing heart transplantation. *Ann Thorac Surg* 2000;**69**:1369–74; Discussion 1375.
17. Massad MG, McCarthy PM, Smedira NG, Cook DJ, Ratliff NB, Goormastic M, *et al*. Does successful bridging with the implantable left ventricular assist device affect cardiac transplantation outcome? *J Thorac Cardiovasc Surg* 1996;**112**:1275–81; Discussion 1282–3.
18. Frazier OH, Rose EA, Macmanus Q, Burton NA, Lefrak EA, Poirier VL, *et al*. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. *Ann Thorac Surg* 1992;**53**:1080–90.
19. Frazier OH, Macris MP, Myers TJ, Duncan JM, Radovancevic B, Parnis SM, *et al*. Improved survival after extended bridge to cardiac transplantation. *Ann Thorac Surg* 1994;**57**:1416–22; Discussion 1421–2.
20. Grady KL, Meyer P, Mattea A, White-Williams C, Ormaza S, Kaan A, *et al*. Improvement in quality of life outcomes 2 weeks after left ventricular assist device implantation. *J Heart Lung Transplant* 2001;**20**:657–69.
21. Morgan JA, John R, Rao V, Weinberg AD, Lee BJ, Mazzeo PA, *et al*. Bridging to transplant with the

HeartMate left ventricular assist device: the Columbia Presbyterian 12-year experience. *J Thorac Cardiovasc Surg* 2004;**127**:1309–16.

22. Rao V, Oz MC, Flannery MA, Idrissi KA, Argenziano M, Edwards NM, *et al*. Changing trends in mechanical circulatory assistance. *J Card Surg* 2004;**19**:361–6.

23. Navia JL, McCarthy PM, Hoercher KJ, Feng J, Jeevantham R, Smedira NG, *et al*. Do left ventricular assist device (LVAD) bridge-to-transplantation outcomes predict the results of permanent LVAD implantation? *Ann Thorac Surg* 2002;**74**:2051–62; Discussion 2062–3.

24. Trachiotis GD, D'Amico C, Johnston TS, Smith AL, Lutz JF, Vega JD, *et al*. Short- or long-term support with left ventricular assist device (LVAD) provides an effective bridge to transplantation. *Journal of Congestive Heart Failure and Circulatory Support* 2000;**1**:119–22.

25. Mussivand T, Hasle DA, Holmes KS. Is center specific implantation volume a predictor of clinical outcomes with mechanical circulatory support? *ASAIO J* 2004;**50**:33–6.

26. Strauch JT, Spielvogel D, Haldenwang PL, Correa RK, deAsla RA, Seissler PE, *et al*. Recent improvements in outcome with the Novacor left ventricular assist device. *J Heart Lung Transplant* 2003;**22**:674–80.

27. Holman WL, Roye GD, Bourge RC, McGiffin DC, Iyer SS, Kirklin JK. Circulatory support for myocardial infarction with ventricular arrhythmias. *Ann Thorac Surg* 1995;**59**:1230–1.

28. May DR, Adams MA. Ventricular assist devices. A bridge to cardiac transplantation. *AORN J* 1987;**46**:633–41, 644–6.

29. Carrier M, Perrault LP, Bouchard D, Pellerin M, Racine N, White M, *et al*. Effect of left ventricular assist device bridging to transplantation on donor waiting time and outcomes in Canada. *Can J Cardiol* 2004;**20**:501–4.

30. Masai T, Shimazaki Y, Kadoba K, Miyamoto Y, Sawa Y, Yagura A, *et al*. Clinical experience with long-term use of the Toyobo left ventricular assist system. *ASAIO J* 1995;**41**:M522–5.

31. Frazier OH, Myers TJ, Jarvik RK, Westaby S, Pigott DW, Gregoric ID, *et al*. Research and development of an implantable, axial-flow left ventricular assist device: the Jarvik 2000 Heart. *Ann Thorac Surg* 2001;**71**(3 Suppl):S125–32; Discussion S144–6.

32. Frazier OH. Implantation of the Jarvik 2000 left ventricular assist device without the use of cardiopulmonary bypass. *Ann Thorac Surg* 2003;**75**:1028–30.

33. Noon GP, Morley DL, Irwin S, Abdelsayed SV, Benkowski RJ, Lynch BE. Clinical experience with the MicroMed DeBakey ventricular assist device. *Ann Thorac Surg* 2001;**71**(3 Suppl):S133–8; Discussion S144–6.

34. Potapov EV, Loebe M, Nasseri BA, Sinawski H, Koster A, Kuppe H, *et al*. Pulsatile flow in patients with a novel nonpulsatile implantable ventricular assist device. *Circulation* 2000;**102**(19 Suppl 3):III183–7.

35. Wieselthaler GM, Schima H, Dworschak M, Quittan M, Nuhr M, Czerny M, *et al*. First experiences with outpatient care of patients with implanted axial flow pumps. *Artif Organs* 2001;**25**:331–5.

36. Goldstein DJ. Worldwide experience with the MicroMed DeBakey ventricular assist device as a bridge to transplantation. *Circulation* 2003;**108** (Suppl 1):II272–7.

37. Hetzer R, Weng Y, Potapov EV, Pasic M, Drews T, Jurmann M, *et al*. First experiences with a novel magnetically suspended axial flow left ventricular assist device. *Eur J Cardiothorac Surg* 2004;**25**:964–70.

38. Vitali E, Lanfranconi M, Bruschi G, Ribera E, Garatti A, Colombo T, *et al*. Mechanical circulatory support in severe heart failure: single-center experience. *Transplant Proc* 2004;**36**:620–2.

39. Granfeldt H, Koul B, Wiklund L, Peterzen B, Lonn U, Babic A, *et al*. Risk factor analysis of Swedish left ventricular assist device (LVAD) patients. *Ann Thorac Surg* 2003;**76**:1993–8; Discussion 1999.

40. Westaby S, Frazier OH, Beyersdorf F, Saito S, Siegenthaler MP, Pigott DW, *et al*. The Jarvik 2000 Heart. Clinical validation of the intraventricular position. *Eur J Cardiothorac Surg* 2002;**22**:228–32.

41. Dew MA, Kormos RL, Winowich S, Nastala CJ, Borovetz HS, Roth LH, *et al*. Quality of life outcomes in left ventricular assist system inpatients and outpatients. *ASAIO J* 1999;**45**:218–25.

42. Dew MA, Kormos RL, Winowich S, Stanford EA, Carozza L, Borovetz HS, *et al*. Human factors issues in ventricular assist device recipients and their family caregivers. *ASAIO J* 2000;**46**:367–73.

43. Dew MA, Kormos RL, Winowich S, Harris RC, Stanford EA, Carozza L, *et al*. Quality of life outcomes after heart transplantation in individuals bridged to transplant with ventricular assist devices. *J Heart Lung Transplant* 2001;**20**: 1199–212.

44. Grady KL, Meyer P, Mattea A, Dressler D, Ormaza S, White-Williams C, *et al*. Predictors of quality of life at 1 month after implantation of a left ventricular assist device. *Am J Crit Care* 2002;**11**:345–52.

45. Grady KL, Meyer PM, Dressler D, White-Williams C, Kaan A, Mattea A, *et al*. Change

in quality of life from after left ventricular assist device implantation to after heart transplantation. *J Heart Lung Transplant* 2003;**22**:1254–67.

46. Grady KL, Meyer PM, Mattea A, Dressler D, Ormaza S, White-Williams C, *et al*. Change in quality of life from before to after discharge following left ventricular assist device implantation. *J Heart Lung Transplant* 2003;**22**: 322–33.

47. Grady KL, Meyer PM, Dressler D, Mattea A, Chillcott S, Loo A, *et al*. Longitudinal change in quality of life and impact on survival after left ventricular assist device implantation. *Ann Thorac Surg* 2004;**77**:1321–7.

48. Moskowitz AJ, Weinberg AD, Oz MC, Williams DL. Quality of life with an implanted left ventricular assist device. *Ann Thorac Surg* 1997;**64**:1764–9.

49. Williams DB, Shapiro PA, Weinberg AD, Richards AF, Rodrigues N, Ianuzzi AM, *et al*. Quality of life and caregiver burden in LVAD, heart transplant and heart failure patients. *J Heart and Lung Transplant* 1996;**15**:S54.

50. Miller K, Myers TJ, Robertson K, Shah N, Delgado RM III, Gregoric ID. Quality of life in bridge-to-transplant patients with chronic heart failure after implantation of an axial flow ventricular assist device. *Congest Heart Fail* 2004;**10**:226–9.

51. Grady KL, Meyer P, Mattea A, Dressler D, Ormaza S, White-Williams C, *et al*. Change in physical and psychosocial domains of quality of life from before to after discharge post left ventricular assist device implantation. *J Heart Lung Transplant* 2001;**20**:203.

52. Kjellman UW, Hallgren P, Bergh CH, Lycke J, Oldfors A, Wiklund L. Weaning from mechanical support in a patient with acute heart failure and multiple sclerosis. *Ann Thorac Surg* 2000;**69**: 628–30.

53. Pietsch L, Laube H, Baumann G, Konertz W. Recovery from end-stage ischemic cardiomyopathy during long-term LVAD support. *Ann Thorac Surg* 1998;**66**:555–7.

54. Joharchi MS, Neiser U, Lenschow U, Schubert J, Kienast W, Noeldge-Schomburg G, *et al*. Thoratec left ventricular assist device for bridging to recovery in fulminant acute myocarditis. *Ann Thorac Surg* 2002;**74**:234–5.

55. Ueno T, Bergin P, Richardson M, Esmore DS. Bridge to recovery with a left ventricular assist device for fulminant acute myocarditis. *Ann Thorac Surg* 2000;**69**:284–6.

56. Farrar DJ, Holman WR, McBride LR, Kormos RL, Icenogle TB, Hendry PJ, *et al*. Long-term follow-up of Thoratec ventricular assist device bridge-to-recovery patients successfully removed from support after recovery of ventricular function. *J Heart Lung Transplant* 2002;**21**:516–21.

57. Gorcsan J III, Severyn D, Murali S, Kormos RL. Non-invasive assessment of myocardial recovery on chronic left ventricular assist device: results associated with successful device removal. *J Heart Lung Transplant* 2003;**22**:1304–13.

58. Marelli D, Laks H, Amsel B, Jett GK, Couper G, Ardehali A, *et al*. Temporary mechanical support with the BVS 5000 assist device during treatment of acute myocarditis. *J Card Surg* 1997;**12**:55–9.

59. Nakatani T, Sasako Y, Kobayashi J, Komamura K, Kosakai Y, Nakano K, *et al*. Recovery of cardiac function by long-term left ventricular support in patients with end-stage cardiomyopathy. *ASAIO J* 1998;**44**:M516–20.

60. Noda H, Takano H, Taenaka Y, Nakatani T, Umezu M, Kinoshita M, *et al*. Treatment of acute myocardial infarction with cardiogenic shock using left ventricular assist device. *Int J Artif Organs* 1989;**12**:175–9.

61. Park SJ, Tector A, Piccioni W, Raines E, Gelijns A, Moskowitz A, *et al*. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg* 2005;**129**:9–17.

62. Dohmen PM, Laube H, de Jonge K, Konertz W. A reliable test to detect impending pump failure during long-term support on the Novacor N100 Left Ventricular Assist System. *Tex Heart Inst J* 2001;**28**:139–41.

63. Seki T, Kitamura S, Kawachi K, Fukutomi M, Kobayashi S, Kawata T, *et al*. Efficacy and limitation of a left ventricular assist system in a patient with dilated cardiomyopathy accompanying multi-organ dysfunction. *J Cardiovasc Surg (Torino)* 1995;**36**:147–51.

64. El-Banayosy A, Arusoglu L, Kizner L, Morshuis M, Tenderich G, Pae WE Jr, *et al*. Preliminary experience with the LionHeart left ventricular assist device in patients with end-stage heart failure. *Ann Thorac Surg* 2003;**75**:1469–75.

65. Jurmann MJ, Weng Y, Drews T, Pasic M, Hennig E, Hetzer R. Permanent mechanical circulatory support in patients of advanced age. *Eur J Cardiothorac Surg* 2004;**25**:610–18.

66. Holman WL, Park SJ, Long JW, Weinberg A, Gupta L, Tierney AR, *et al*. Infection in permanent circulatory support: experience from the REMATCH trial. *J Heart Lung Transplant* 2004;**23**:1359–65.

67. Dembitsky WP, Tector AJ, Park S, Moskowitz AJ, Gelijns AC, Ronan NS, *et al*. Left ventricular assist device performance with long-term circulatory support: lessons from the REMATCH trial. *Ann Thorac Surg* 2004;**78**:2123–9; Discussion 2129–30.

68. Lazar RM, Shapiro PA, Jaski BE, Parides MK, Bourge RC, Watson JT, *et al*. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. *Circulation* 2004;**109**:2423–7.

69. Stevenson LW, Miller LW, Desvigne-Nickens P, Ascheim DD, Parides MK, Renlund DG, *et al*. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). *Circulation* 2004;**110**: 975–81.

70. Dohmen PM, Laube H, de Jonge K, Baumann G, Konertz W. Mechanical circulatory support for one thousand days or more with the Novacor N100 left ventricular assist device. *J Thorac Cardiovasc Surg* 1999;**117**:1029–30.

71. Siegenthaler MP, Martin J, van de Loo A, Doenst T, Bothe W, Beyersdorf F. Implantation of the permanent Jarvik-2000 left ventricular assist device: a single-center experience. *J Am Coll Cardiol* 2002;**39**:1764–72.

72. Skinner JL, Harris C, Aaron MF, McGiffin DC, Kirklin JK, Bourge RC, *et al*. Cost–benefit analysis of extended antifungal prophylaxis in ventricular assist devices. *ASAIO J* 2000;**46**:587–9.

73. Loisance D, Benvenuti C, Lebrun T, Leclerc A, Tarral A, Sailly JC. Cost and cost effectiveness of the mechanical and pharmacologic bridge to transplantation. *ASAIO Trans* 1991;**37**:M125–7.

74. Cloy MJ, Myers TJ, Stutts LA, Macris MP, Frazier OH. Hospital charges for conventional therapy versus left ventricular assist system therapy in heart transplant patients. *ASAIO J* 1995;**41**: M535–9.

75. Mehta SM, Aufiero TX, Pae WE Jr, Miller CA, Pierce WS. Mechanical ventricular assistance: an economical and effective means of treating end-stage heart disease. *Ann Thorac Surg* 1995;**60**: 284–90; Discussion 290–1.

76. Arabia FA, Smith RG, Jaffe C, Wild JC, Rose DS, Nelson RJ, *et al*. Cost analysis of the Novacor left ventricular assist system as an outpatient bridge to heart transplantation. *ASAIO J* 1996;**42**:M546–9.

77. Mir SH, Morton I, Park S, Francis G. Effects of the HeartMate left ventricular assist device on clinical outcomes and cost in status 1 heart transplantation patients. *Circulation* 1997;**96**(8 Suppl):I367–8.

78. Petty M, Kshetty VR, Ormanza S, Bolman RM. Daily costs reduced for status 1 heart transplant (HT) patients following bridge with Heartmate left ventricular assist device (LVAD). *J Heart Lung Transplant* 1997;**16**:57.

79. Christopher F, Clegg A. *Left ventricular assist devices (LVADs) for end stage heart failure*. Southampton: Wessex Institute for Health Research and Development; 1999.

80. Couper GS, Dekkers RJ, Adams DH. The logistics and cost-effectiveness of circulatory support: advantages of the ABIOMED BVS 5000. *Ann Thorac Surg* 1999;**68**:646–9.

81. Christensen DM, Frazier PA, Messner ER, Pae WE Jr, Silber DH, Sun B, *et al*. 48th Annual Scientific Session of the American College of Cardiology, New Orleans, Louisiana, USA, March 7–10, 1999. Save me the money: a cost comparison of inpatient vs. outpatient care of left ventricular assist device patients. *J Am Coll Cardiol* 1999;**33**(2 suppl A):204A.

82. Kolbye A, Sander Jensen KM, Aldershvile J, Hansen PB, Kjersem AM, Nielsen KS, *et al*. [Economic aspects of implementation of the mechanical heart, 'HeartMate']. *Ugeskr Laeger* 2000;**162**:3722–5.

83. Conseil d'Évaluation des Technologies de la Santé di Québec. *Implantable ventricular assist devices: should they be used in Quebec*? Quebec: CETS; 2000.

84. Moskowitz AJ, Williams DL, Tierney A, Levitan RG, Zivin J, Gelijns AC. Economic considerations of left ventricular assist device implantation. In Goldstein DJ, Oz MC, editors. *Cardiac assist devices*. New York: Futura Publishing; 2000. pp. 183–91.

85. Morales DL, Catanese KA, Helman DN, Williams MR, Weinberg A, Goldstein DJ, *et al*. Six-year experience of caring for forty-four patients with a left ventricular assist device at home: safe, economical, necessary. *J Thorac Cardiovasc Surg* 2000;**119**:251–9.

86. Schiller W, Reichart B. Cost-analysis of treatment with the portable Novacor-left-heart-assist-system. In Szucs H, Haverich A, Odar J, editors. *Economics of surgical procedures*. Leipzig: JA Barth; 2000. pp. 33–8.

87. Digiorgi PL, Reel MS, Thornton B, Burton E, Naka Y, Oz MC. Heart transplant and left ventricular assist device costs. *J Heart Lung Transplant* 2005;**24**:200–4.

88. Oz MC, Grewal R, Gelijn A. Cost considerations for long-term mechanical circulatory support. *ASAIO J* 1997;**43**:268–70.

89. Gelijns AC, Richards AF, Williams DL, Oz MC, Oliveira J, Moskowitz AJ. Evolving costs of long-term left ventricular assist device implantation. *Ann Thorac Surg* 1997;**64**:1312–9.

90. Schulze B, Tenderich G, Hansky B, El Banayosy A, Arusoglu L, Deyerling W, *et al*. In hospital costs of left ventricular assist device (Novacor) in comparison to different therapeutical strategies in end stage heart disease. *Int J Artif Organs* 2000;**23**:553.

91. Miller LW, Magovern G, Shannon RP, Mehra M, Van Meter C, HuiLing L, *et al*. Costs of LVAD implantation: lessons from the REMATCH trial. *American Heart Association Scientific Sessions 2002*, 17–20 November 2002.

92. Oz MC, Gelijns AC, Miller L, Wang C, Nickens P, Arons R, *et al*. Left ventricular assist devices as permanent heart failure therapy: the price of progress. *Ann Surg* 2003;**238**:577–83; Discussion 583–5.

93. Blue Cross Blue Shield Association Medical Advisory Panel. *Cost-effectiveness of left-ventricular assist devices as destination therapy for end-stage heart failure*. Chicago: BCBS; 2004.

94. Nelson K, Tong K, Ellman A, Long J. Advances in patient and economic outcomes associated with left ventricular assist devices for destination therapy. *J Heart Lung Transplant* 2005;**24**:S76 (No. 105).

95. Frazier OH, Rose EA, McCarthy P, Burton NA, Tector A, Levin H, *et al*. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. *Ann Surg* 1995;**222**:327–36, Discussion 336–8.

96. Moskowitz AJ, Rose EA, Gelijns AC. The cost of long-term LVAD implantation. *Ann Thorac Surg* 2001;**71**:S195–8; Discussion S203–4.

97. Rose EA, Moskowitz AJ, Packer M, Sollano JA, Williams DL, Tierney AR, *et al*. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. *Ann Thorac Surg* 1999;67:723-30.

98. Kind P. The EuroQol instrument: an index of health-related quality of life. In Spiker B, editor. *Quality of life and pharmacoeconomics in clinical trials*. Philadelphia, PA: Lippincott-Raven; 1996.

99. Deng MC, De Meester JM, Smits JM, Heinecke J, Scheld HH. Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study Group. Effect of receiving a heart transplant: analysis of a national cohort entered on to a waiting list, stratified by heart failure severity. *BMJ* 2000;**321**:540–5.

100. Sharples LD, Roberts M, Parameshwar J, Schofield PM, Wallwork J, Large SR. Heart transplantation in the United Kingdom: who waits longest and why. *J Heart Lung Transplant* 1995;**14**: 236–43.

101. Dew MA, Kormos RL, Winowich S, Stanford E, Carozza L, Griffith BP. Long-term post-transplant quality of life outcomes in patients bridged to transplant with ventricular assist devices. *J Heart Lung Transplant* 2001;**20**:203.

102. Pae WE Jr. Bethesda Conference: conference for the design of clinical trials to study circulatory support devices for chronic heart failure. *Ann Thorac Surg* 1998;**66**:1452–65.

103. Charton JRH. Measuring disability in a longitudinal survey. In Patrick DL, Peach H, editors. *Disablement in the community*. Oxford: Oxford University Press; 1989. pp. 62–80.

104. Lezak M. *Neuropsychological assessment*, 2nd ed. New York: Oxford University Press; 1983.

105. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98.

106. Kendell K, McCarthy P, Sharp J, Vargo R. Quality of life for hospitalized implantable left ventricular assist device patients. *Annual Meeting of the International Society for Heart and Lung Transplantation*, 1–3 April, 1993. Boca Raton, Florida; 1993.

107. Wolinsky FD, Wyrwich KW, Nienaber NA, Tierney WM. Generic versus disease-specific health status measures. An example using coronary artery disease and congestive heart failure patients. *Evaluation and the Health Professions* 1998;**21**:216–43.

108. Berry C, McMurray J. A review of quality-of-life evaluations in patients with congestive heart failure. *Pharmacoeconomics* 1999;**16**:247–71.

109. Sneed NV, Paul S, Michel Y, Vanbakel A, Hendrix G. Evaluation of three quality of life measurement tools in patients with chronic heart failure. *Heart Lung* 2001;**30**:332–40.

110. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997;**63**:509–12.

111. Oldridge N, Perkins A, Hodes Z. Comparison of three heart disease specific health-related quality of life instruments. *Monaldi Arch Chest Dis* 2002;**58**:10–18.

112. Junger J, Schellberg D, Muller-Tasch T, Raupp G, Zugck C, Haunstetter A, *et al*. Depression increasingly predicts mortality in the course of congestive heart failure. *Eur J Heart Fail* 2005;**7**:261–7.

113. National Institute for Clinical Excellence. *Guide to the methods of health technology appraisal*. London: NICE; 2004.

114. Dolan P. Modelling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108.

115. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. Discussion Paper 172. York: Centre for Health Economics; 1999.

116. Ware JE Jr, Gandek B, Kosinski M, Aaronson NK, Apolone G, Brazier J, *et al*. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;**51**:1167–70.

117. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;**21**:271–92.

118. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol* 1998;**51**:1115–28.

119. Salthouse TA. The role of memory in the age decline in digit–symbol substitution performance. *J Gerontol* 1978;**33**:232–8.

120. Salthouse TA. What do adult age differences in the Digit Symbol Substitution Test reflect? *J Gerontol* 1992;**47**:P121–8.

121. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1958;**8**:271–6.

122. Department of Health. *NHS reference costs 2004*. London: Department of Health; 2005.

123. *British National Formulary*. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, No. 49; 2005.

124. Netten A, Curtis L. *Unit costs of health and social care 2004*. University of Kent, Public Social Services Research Unit (PSSRU); 2004.

125. Spiegelhalter DJ, Abrams K, Myles JP. *Bayesian approaches to clinical trials and health care evaluation*. Chichester: John Wiley & Sons; 2004.

126. National Institute for Clinical Excellence. *Guide to methods of technology appraisal*. London: NICE; 2004.

127. Mulcahy D, Wright C, Mockus L, Yacoub M, Fox K. Cardiac transplantation in severely ill patients requiring intensive support in hospital. *Br Med J* (*Clin Res Ed*) 1988;**296**:817–19.

128. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technol Assess* 2004;**8**(31).

129. Townsend J, Buxton M, Harper G. Prioritisation of health technology assessment. The PATHS model: methods and case studies. *Health Technol Assess* 2003;**7**(20).

Appendix 1

Sources of information searched, including databases and search terms

Searches for clinical and cost-effectiveness of LVADs

The databases below were searched for published studies, and recently completed and ongoing research. A broad search strategy about the device was used, and the results were scanned manually for any articles relevant to cost-effectiveness and clinical effectiveness. Copies of all search strategies are available on request.

MEDLINE (2003 to March 2005)

((vad or vads) and (heart or cardiac)) or ((lvas or lvad)) or ((ventricular near assist) and (left or heart or cardiac)) or ((ventricular near support system$)) or ((assist near device$) near (ventricular or heart or cardiac)) or ('Heart-Assist-Devices' / all subheadings)

EMBASE (2003 to March 2005)

('heart-assist-device' / all subheadings) or ((vad or vads) and (heart or cardiac)) or (lvas or lvad) or ((ventricular near assist) and (left or heart or cardiac)) or (ventricular near support system$) or ((assist near device$) near (ventricular or heart or cardiac))

Cochrane Library (Issue 2 2005)

((vad or vads) and (heart or cardiac)) or ((lvas or lvad)) or ((ventricular near assist*) and (left or heart or cardiac)) or ((ventricular near support system*)) or ((assist near device*) near (ventricular or heart or cardiac)) or ('Heart-Assist-Devices' / all subheadings)

PubMed (2003 to March 2005)

lvad OR lvas OR vad OR (ventricular AND assist) OR (assist AND device*)

CINAHL (2003 to March 2005)

('Heart-Assist-Devices' / all topical subheadings / all age subheadings in DE) or ((assist near device$) and (heart or cardiac)) or ((ventricular) near (assist or device$)) or ((lvad or lvas or vad or vads)) and (heart or cardiac)). [All in ti, ab or de].

PsycINFO (2003 to 2005)

lvad or (left ventricular assist device$) or lvas or (left ventricular assist system$)

British Nursing Index (2003 to March 2005)

ventricular assist device$ or lvad or ((vad or vads) and (heart or cardiac))

DH DATA (2003 to March 2005)

ventricular assist device$ or lvad or ((vad or vads) and (heart or cardiac))

King's Fund (2003 to March 2005)

ventricular assist device$ or lvad or ((vad or vads) and (heart or cardiac))

National Research Register (Issue 2 2005)

((vad or vads) and (heart or cardiac)) or ((lvas or lvad)) or ((ventricular near assist*) and (left or heart or cardiac)) or ((ventricular near support system*)) or ((assist near device*) near (ventricular or heart or cardiac)) or ('Heart-Assist-Devices' / all subheadings)

NLM Gateway, including Health Services Research Projects, NLM Meeting Abstracts and ClinicalTrials.gov (2003 to March 2005)

LVAD OR ventricular assist device*

Current Controlled Trials (searched March 2005)

LVAD or "left ventricular assist device%" or "heart assist device%"

Zetoc Conference Search (2003 to March 2005)

LVAD or "left ventricular assist"

Searches for quality of life and end-stage heart failure

MEDLINE (2003 to March 2005)

((heart failure) or (exp Heart Failure, Congestive/)) and ((quality of life) or (exp Quality of Life/))

Additional sources

The bibliographies of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Appendix 2

Post-transplantation survival for 4218 adult first heart only transplants in the UK, 1 January 1985 to 31 December 2004

Interval (years)	No. of deaths	No. censored	Effective no. at risk	Conditional probability of death	Cumulative survival at beginning of interval
0–1	944	157	4139.5	0.2280	1.0000
1–2	104	102	3066.0	0.0339	0.7720
2–3	99	114	2854.0	0.0347	0.7458
3–4	95	131	2632.5	0.0361	0.7199
4–5	94	126	2409.0	0.0390	0.6939
5–6	91	148	2178.0	0.0418	0.6668
6–7	77	158	1934.0	0.0398	0.6390
7–8	91	157	1699.5	0.0535	0.6135
8–9	85	167	1446.5	0.0588	0.5807
9–10	77	131	1212.5	0.0635	0.5466
10–11	70	167	986.5	0.0710	0.5119
11–12	59	122	772.0	0.0764	0.4755
12–13	49	127	588.5	0.0833	0.4392
13–14	32	100	426.0	0.0751	0.4026
14–15	23	83	302.5	0.0760	0.3724
15–16	25	54	211.0	0.1185	0.3441
16–17	21	58	130.0	0.1615	0.3033
17–18	10	42	59.0	0.1695	0.2543
18–19	3	17	19.5	0.1538	0.2112
19–20	1	7	4.5	0.2222	0.1787
20–21			0		0.1390

Source: Hussey J, UK Transplant.

Appendix 3

Health-related quality of life: comments from VAD-specific questionnaire

Patient	Comment	Time with VAD (days)
Q20: If you could change anything on the VAD system, what would it be?		
A	1. Smaller and lighter	42
	2. Lighter – guards over vacuum knob – so it can't be bumped – carrying strap should all be wide – easier to carry – lead to light up site to plug it in – so I can see	119
B	Smaller – laptop size	27
C	Smaller and lighter	46
D	1. Reduce the size, bigger wheels. 5 ft hose isn't enough! Dropped my glasses had to move device as couldn't reach – retractable hose!	20
	2. Could the battery be recharged in the machine instead of taking it out – battery charger is very heavy. Hook on handle of trolley so it does not catch in wheels of trolley	103
E	Smaller – batteries could last longer – they only last 20 mins–3/4hr only	33
F	1. Noise and pulsating sound in head. Too heavy	45
	2. Internal noise and throbbing sometimes to my chest, neck and back of head	156
G	VAD pipe can fall too short – would be better if it was retractable or extendable. If batteries could be charged in machine it would be easier. Smaller and lighter. Pump outside smaller inside. Can be uncomfortable	34
H	Weight – wheels – too small – difficult to pull and attachments difficult. Pipe attachment too short	54
I	More compact – carry on shoulder	30
J	1. Mobility – needs to be off-road friendly – wheels too small	0
	2. How mobile it is – especially as they are staying in longer these days	95
K	1. Make it smaller – everything inside and trolley	76
	2. Make it a lot smaller	189
L	Smaller and lighter – more compact	45
M	1. It would be nice to have it easier to carry/wear. Smaller batteries	36
	2. Outlet – affects life too much – dressing in the way – no baths etc.	146
N	1. Extend the trolley to accommodate both machines. The spare could be pulled along too – bigger wheels!	67
	2. Smaller version	173
Q21: If you have any other comments about living with a VAD then please write them below		
A	I think that all patients should have support slings for their VADS to stop them pulling	42
B	It would have been better if I had had time to understand the VAD before it was put in, but I was too unwell. Would have been nice to meet someone – if we had time. Was surprised at the amount of intrusive equipment	27
E	It's uncomfortable, but needed – you get used to it!	33
G	Exercise bike easier than walking	34
M	Belt has made a difference – more comfortable – holds it all in. Everyone should have three or four so they can be washed	146

continued

Patient	Comment	Time with VAD (days)
N	1. Focus DIY refused entry unless (he) left it outside! 2. Getting pressure sores under external VAD sites now	173 250
O	I have had a VAD for about 16 months and still have people following me around wherever I go. I would like to be on my own sometimes. It makes me feel trapped	462
P	As time goes by I become increasingly aware of the restrictions associated with the VAD and become occasionally impatient to continue fully with the rest of my life	285
Q	1. The fittings to connect the controller and battery should be more robust – they break too easily 2. The Jarvik VAD has enabled me to get back to a virtually normal lifestyle including getting back to work and back to being fit 3. I think the Jarvik 2000 is the most amazing piece of equipment as it allows a return to virtually normal living	68 183 272
R	The questions do not really relate to hospital care or hospitalisation which I am with both L & R VADs	42

Appendix 4

Detailed resource-use summaries

TABLE 80 *Heart transplant preparatory assessment costs*

Papworth resource-use component	Cost (£)	Harefield resource-use component	Cost (£)
Cardiac ward stay (3 days)	945	Cardiac ward stay (4 days)	438
Midstream urine	5	Chest X-ray	25
Nose swab	6	MUGA scan	94
MRSA screen	15	Echocardiogram	40
Chest X-ray	40	Lung function tests	39
ECG	65	Cardiac catheter	797
Lung function tests	50		
MUGA scan	190		
Total	**1316**	**Total**	**1433**

MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 81 *Post-transplantation follow-up outpatient visit costs*

Outpatient visit resource-use component	Papworth cost (£)	Harefield cost (£)
Cardiac outpatient visit	128	128
Cardiac biopsy	270	130
Chest X-ray	40	25
ECG	65	52
Blood tests[a]	74	78
Total outpatient visit cost	**577**	**413**

[a] Blood tests for both centres included urea and electrolytes, liver function tests, immunosuppression level, creatinine, cholesterol, glucose and full blood count.

TABLE 82 *Monthly post-transplantation follow-up outpatient visit costs*

Post-transplant Month	No. of outpatient visits		No. of blood tests		Total cost (£)	
	Papworth	Harefield	Papworth	Harefield	Papworth	Harefield
1	2	4	2	4	1154	1652
2	1	3	1	4	577	1317
3	1	2	1	4	577	982
4	0	1	0	2	289	491
5	1	1	1	2	289	491
6	0	1	0	2	192	491
7	0	0	0	1	192	246
8	1	1	1	1	192	246
9	0	0	0	1	192	246
10	0	1	0	1	192	246
11	1	0	1	1	192	246
12	0	1	0	1	192	246

Papworth Transplant Management Guidelines recommendations for post-transplantation patients

Outpatient clinic visits are scheduled to occur as follows:

- two visits during first month
- one visit during second month
- one visit during third month
- one visit during fifth month

and then 3-monthly up to 2 years and 6-monthly thereafter.

Therefore, it was assumed that in months 4 and 5 the outpatient visit and test costs would be split over 2 months, so the total cost for each month would be: 577/2 = £289.

For months 6–12, it was assumed that the costs would be split over 3 months, so the total cost for each month would be: 577/3 = £192.

If patients remain in hospital or are readmitted (ICU or ward) during the post-transplantation period then these costs are adjusted downwards by £128 (the cost of an outpatient visit) depending on the length of stay in hospital. For example, if a Papworth patient spends the first month post-transplantation in a cardiac ward, the follow-up costs are £1154 – (£128 × 2) = £898. This also applies to patients at Harefield.

Harefield Transplant Management Guidelines recommendations for post-transplantation patients

It was assumed that for months 7–12 the outpatient visit cost would be split over 2 months, so the total cost for each month would be: (335/2) + 78 = £245.5.

Post-transplantation follow-up medication costs

Papworth Transplant Management Guidelines recommendations for post-transplant patients

- ciclosporin (Neoral): 4–10 mg kg^{-1} per day in two divided doses
- mycophenolate mofetil: 2–3 g per day in two divided doses
- prednisolone: 10–15 mg per day

all for at least 3 months post-transplantation.

The total monthly medication cost based on Papworth Transplant Management Guidelines is £548.53. It was assumed that this cost would remain constant over 12 months for all post-transplantation patients at Papworth.

Harefield Transplant Management Guidelines recommendations for post-transplantation patients

- ciclosporin (Neoral): 2–6 mg kg^{-1} per day in two divided doses
- mycophenolate mofetil: 2–3 g per day in two divided doses
- prednisolone: 0.2 mg kg^{-1} per day (max. 15 mg daily) up to 3 months post-transplantation; 0.1 mg kg^{-1} per day (max. 7.5 mg daily) between 3 and 6 months post-transplantation.

The total monthly medication cost based on Harefield Transplant Management Guidelines is £430.61 for months 1–3 post-transplantation and £429.52 for months 4–12.

TABLE 83 *Harefield follow-up visits and tests*

Time after transplant	Clinic visits	Blood tests
0–6 weeks	Weekly	Weekly
6–12 weeks	Fortnightly	Weekly
3–6 months	Monthly	Fortnightly
6–12 months	Every 2 months	Monthly
At 15 months		Every 6 weeks
At 18 months and thereafter	Every 6 months	Every 2 months

TABLE 84 *Papworth follow-up medication costs*

Ciclosporin (Neoral) Assuming a maintenance dose of 7 mg kg^{-1} per day for an 80-kg person; therefore, 560 mg per day				
Item	**Cost per item**	**No. of capsules needed per day**	**Cost for 560 mg per day**	**Cost for 560 mg per day (30-day supply)**
30 capsules of 100 mg each	£50	5	£8.3	£250
30 capsules of 50 mg each	£26.50	1	£0.88	£26.50
60 capsules of 10 mg each	£16.44	1	£0.27	£8.22
			Total cost per month	**£284.72**
Mycophenolate mofetil Assuming a maintenance dose of 2.5 g per day for an 80-kg person				
Item	**Cost per item**	**No. of tablets needed per day**	**Cost for 2.5 mg per day**	**Cost for 2.5 mg per day (30-day supply)**
50 tablets of 500 mg each	£87.33	5	£8.73	£261.99
			Total cost per month	**£261.99**
Prednisolone Assuming a maintenance dose of 12.5 mg per day for an 80-kg person				
Item	**Cost per item**	**No. of tablets needed per day**	**Cost for 12.5 mg per day**	**Cost for 12.5 mg per day (30 day supply)**
28 tablets of 5 mg each	£0.68	2.5	£0.0607	£1.82
			Total cost per month	**£1.82**

TABLE 85 *Harefield follow-up medication costs*

Ciclosporin (Neoral) Assuming a maintenance dose of 4 mg kg^{-1} per day for an 80-kg person; therefore, 320 mg per day				
Item	**Cost per item**	**No. of capsules needed per day**	**Cost for 320 mg per day**	**Cost for 320 mg per day (30-day supply)**
30 capsules of 100mg each	£50	3	£5	£150
60 capsules of 10mg each	£16.44	2	£0.548	£16.44
			Total cost per month	**£166.44**
Mycophenolate mofetil Assuming a maintenance dose of 2.5 g per day for an 80-kg person				
Item	**Cost per item**	**No. of tablets needed per day**	**Cost for 2.5 mg per day**	**Cost for 2.5 mg per day (30-day supply)**
50 tablets of 500mg each	£87.33	5	£8.733	£261.99
			Total cost per month	**£261.99**
Prednisolone Assuming a maintenance dose of 15 mg per day for an 80-kg person (months 1–3 post-transplantation) and a maintenance dose of 7.5 mg per day for an 80-kg person (months 4–12)				
Item	**Cost per item**	**No. of tablets needed per day**	**Cost for 15 mg per day**	**Cost for 15 mg per day (30-day supply)**
28 tablets of 5 mg each	£0.68	3	£0.0728	£2.18
			Total cost per month (months 1–3)	**£2.18**
28 tablets of 5mg each	£0.68	1.5	£0.0364	£1.09
			Total cost per month (months 4–12)	**£1.09**

Adverse event costs

TABLE 86 *Rejection treatment costs*

i.v. methylprednisolone Assuming a dose of 750 mg per day for 3 days				
Item	**Cost per item**	**No. of vials needed per day**	**Cost for 750 mg per day**	**Cost for 750 mg per day (for three days)**
500-mg vial	£9.60	1	£9.60	£28.80
125-mg vial	£4.75	2	£9.50	£28.50
			Total cost (for 3 days)	**£57.30**

TABLE 87 *Infection (cytomegalovirus) treatment costs*

i.v. ganciclovir Assuming a dose of 5 mg kg^{-1} twice daily for an 80-kg person; therefore, 800 mg per day			
Item	**Cost per item**	**No of vials needed per day**	**Cost for 800 mg per day**
500-mg vial	£31.60	2	£63.20
		Total cost per day	**£63.20**

Other drug costs

TABLE 88 *Group B inotropic support costs*

i.v. enoximone Assuming a maintenance dose of 5 μg kg^{-1} per minute for an 80-kg person; therefore, 0.4 mg per minute				
Item	**Cost per item**	**Cost per mg**	**Cost per minute**	**Cost per 24 hours**
20-ml (100-mg) ampoule	£15.02	£0.1502	£0.06008	£86.51
			Total cost per day	**£86.51**
i.v. dopamine Assuming a maintenance dose of 5 μg kg^{-1} minute for an 80-kg person; therefore, 0.4 mg per minute				
Item	**Cost per item**	**Cost per mg**	**Cost per minute**	**Cost per 24 hours**
250-ml (400-mg) container	£11.69	£0.029225	£0.01169	£16.83
			Total cost per day	**£16.83**
			Total inotropic support cost per day	**£103**

Test/investigation costs

TABLE 89 *Test/investigation costs*

Test/investigation	Papworth cost (£)	Harefield cost (£)
Angiography	454	264[a]
CT abdomen	175	145
CT brain	150	145
CT thorax	175	145
Balloon pump (IABP)	300	300
Cardiac biopsy	270	130
Lung biopsy	270	130
Bone-marrow aspiration	400	–
Bronchoscopy	400	223[a]
ECG	65	52
Echocardiogram (Doppler)	140	40
Transoesophageal echo	265	196
MUGA scan	190	94
MRI scan	500	224[a]
Right heart catheter	851	796
Ultrasound (abdominal; kidney, Liver, thoracic)	140	102
Vascular ultrasound (Doppler)	140	162
X-ray chest	40	39
X-ray abdomen	40	25

[a] Costs not available from Royal Brompton & Harefield finance department; therefore, National Reference Costs (2004)[122] used.
CT, computed tomography; MRI, magnetic resonance imaging.

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The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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