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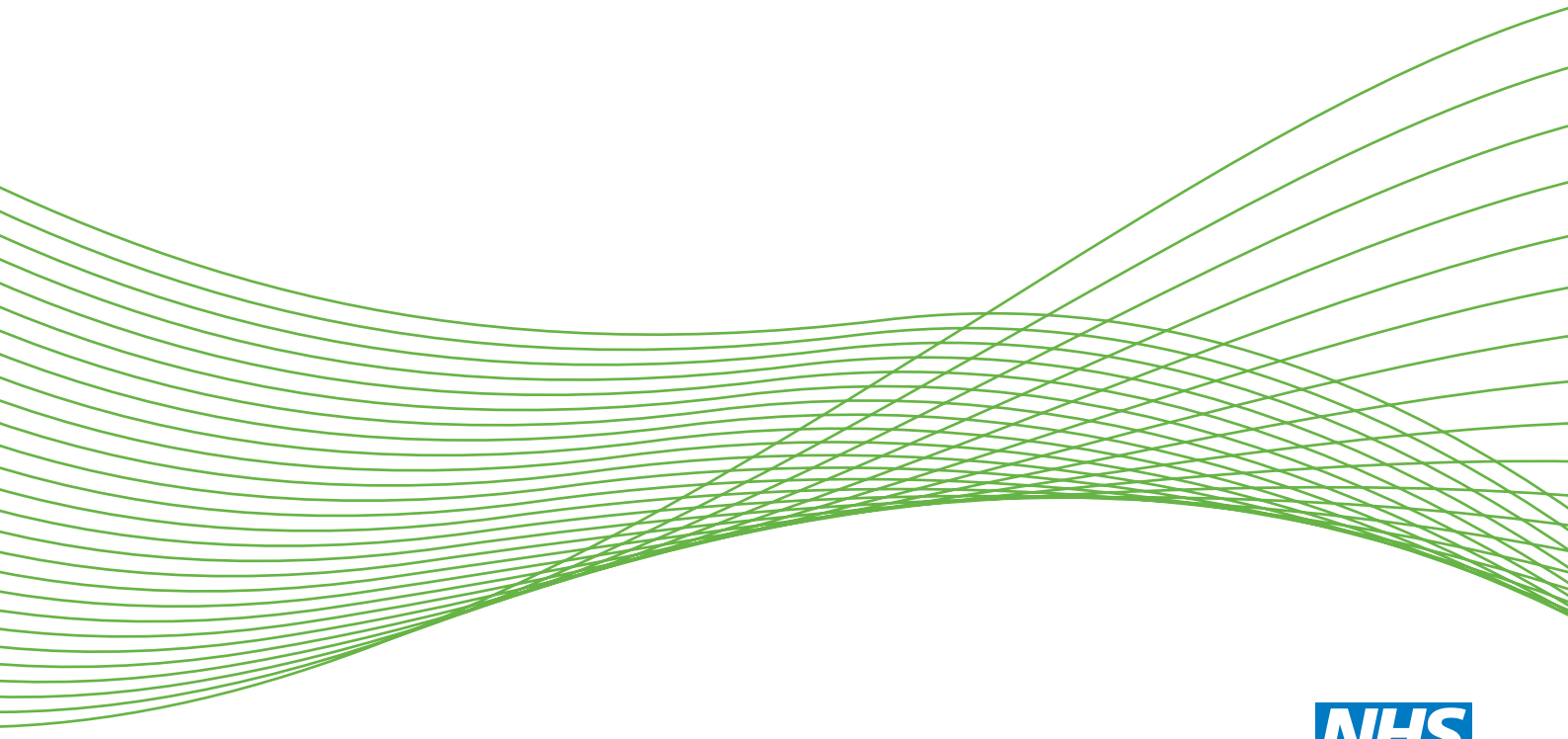

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Abstract

Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model

P Sutcliffe, M Connock, R Pulikottil-Jacob, N-B Kandala, G Suri, T Gurung, A Grove, D Shyangdan, S Briscoe, H Maheswaran and A Clarke*

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Background: Advanced heart failure (HF) is a debilitating condition for which heart transplant (HT) offers the best treatment option. However, the supply of donor hearts is diminishing and demand greatly exceeds supply. Ventricular assist devices (VADs) are surgically implanted pumps used as an alternative to transplant (ATT) or as a bridge to transplant (BTT) while a patient awaits a donor heart. Surgery and VADs are costly. For the NHS to allocate and deliver such services in a cost-effective way the relative costs and benefits of these alternative treatments need to be estimated.

Objectives: To investigate for patients aged ≥ 16 years with advanced HF eligible for HT: (1) the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as BTT compared with medical management (MM); and (2) the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as an ATT in comparison with their use as BTT therapy.

Data sources: Searches for clinical effectiveness studies covered years from 2003 to March 2012 and included the following data bases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), HTA databases [NHS Centre for Reviews and Dissemination (CRD)], Science Citation Index and Conference Proceedings (Web of Science), UK Clinical Research Network (UKCRN) Portfolio Database, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and National Library of Medicine (NLM) Gateway, Cochrane Central Register of Controlled Trials (CENTRAL), Current Controlled Trials and ClinicalTrials.gov. Reference lists of relevant articles were checked, and VAD manufacturers' websites interrogated. For economic analyses we made use of individual patient data (IPD) held in the UK Blood and Transplant Database (BTDB).

Review methods: Systematic reviews of evidence on clinical effectiveness and cost-effectiveness of second- and third-generation US Food and Drug Administration (FDA) and/or Conformité Européenne (CE) approved VADs. Publications from the last 5 years with control groups, or case series with 50 or more patients were included. Outcomes included survival, functional capacity (e.g. change in New York Heart Association functional classification), quality of life (QoL) and adverse events. Data from the BTDB were obtained. A discrete-time, semi-Markov, multistate model was built. Deterministic and probabilistic methods with multiple sensitivity analyses varying survival, utilities and cost inputs to the model were used. Model outputs were incremental cost-effectiveness ratios (ICERs), cost/quality-adjusted life-years (QALYs)

gained and cost/life-year gained (LYG). The discount rate was 3.5% and the time horizon varied over 3 years, 10 years and lifetime.

Results: Forty publications reported clinical effectiveness of VADs and one study reported cost-effectiveness. We found no high-quality comparative empirical studies of VADs as BTT compared with MM or as ATT compared with BTT. Approximately 15–25% of the patients receiving a device had died by 12 months. Studies reported the following wide ranges for adverse events: 4–27% bleeding requiring transfusion; 1.5–40% stroke; 3.3–48% infection; 1–14% device failure; 3–30% HF; 11–32% reoperation; and 3–53% renal failure. QoL and functional status were reported as improved in studies of two devices [HeartMate II® (HMII; Thoratec Inc., Pleasanton, CA, USA) and HeartWare® (HW; HeartWare Inc., Framingham, MA, USA)]. At 3 years, 10 years and lifetime, the ICERs for VADs as BTT compared with MM were £122,730, £68,088 and £55,173 respectively. These values were stable to changes in survival of the MM group. Both QoL and costs were reduced by VADs as ATT compared with VADs as BTT giving ICERs in south-west quadrant of the cost effectiveness plain (cost saving/QALY sacrificed) of £353,467, £31,685 and £20,637 over the 3 years, 10 years and lifetime horizons respectively. Probabilistic analyses yielded similar results for both research questions.

Limitations: Conclusions about the clinical effectiveness were limited by the lack of randomised controlled trials (RCTs) comparing the effectiveness of different VADs for BTT or comparing BTT with any alternative treatment and by the overlapping populations in published studies. Although IPD from the BTDB was used to estimate the cost-effectiveness of VADs compared with MM for BTT, the lack of randomisation of populations limited the interpretation of this analysis.

Conclusions: At 3 years, 10 years and lifetime the ICERs for VADs as BTT compared with MM are higher than generally applied willingness-to-pay thresholds in the UK, but at a lifetime time horizon they approximate threshold values used in end of life assessments. VADs as ATT have a reduced cost but cause reduced QALYs relative to BTT. Future research should direct attention towards two areas. First, how any future evaluations of second- or third-generation VADs might be conducted. For ethical reasons a RCT offering equal probability of HT for each group would not be feasible; future studies should fully assess costs, long-term patient survival, QoL, functional ability and adverse events, so that these may be incorporated into economic evaluation agreement on outcomes measures across future studies. Second, continuation of accurate data collection in the UK database to encompass QoL data and comparative assessment of performance with other international centres.

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Contents

Glossary

Alternative to transplant Refers to the use of a ventricular assist device in patients who, although eligible for heart transplant, are given a ventricular assist device as an alternative. Alternative to transplant was a term developed by the authors in order to distinguish this procedure from use of ventricular assist devices in patients ineligible for transplant as destination therapy.

Bridge to recovery Bridge to recovery is used to refer to a situation where a ventricular assist device is implanted temporarily to allow the heart to recover from a condition such as post-myocardial infarction or post-cardiotomy shock. The ventricular assist device is then removed without the need for transplant.

Bridge to transplant Bridge to transplant is used to refer to the use of a ventricular assist device for a short duration of time to increase survival, while waiting for a suitable heart to become available for transplantation.

Conformité Européenne The Conformité Européenne marking is a mandatory conformity mark for products placed on the market in the European Economic Area.

Destination therapy When recovery is impossible and patients are ineligible for heart transplant, then ventricular assist devices are used as destination therapy. This is distinguished from alternative to transplant because patients are ineligible for heart transplant.

Food and Drug Administration This is an agency of the US Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices and veterinary products.

Heart failure A disease characterised by a decline in the heart's ability to pump blood around a person's body at normal filling pressures so as to meet its metabolic needs.

Incremental cost-effectiveness ratio An equation used in health economics to support decision-making regarding health interventions. The incremental cost-effectiveness ratio is the ratio of the differences in costs between the intervention and comparator divided by the difference in benefits between intervention and comparator; benefits are often measured in terms of quality-adjusted life-years.

Medical management In this report medical management refers to the range of medical therapies used to treat patients with advanced heart failure in the absence of operative intervention. Examples include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and intravenous inotropes for those with severe heart failure.

New York Heart Association functional classification The severity of heart failure is often assessed using the New York Heart Association functional classification which is based on the severity of symptoms patients develop in relation to physical activity. There are four New York Heart Association grades classified according to symptom severity.

Quality-adjusted life-year According to the National Institute for Health and Care Excellence, this is 'a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life-year is equal to 1 year of life in perfect health. Quality-adjusted life-years are calculated by estimating the years of life remaining for a patient

following a particular treatment or intervention and weighting each year with a quality of life score (on a zero to one scale). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance' (National Institute for Health and Care Excellence. *Glossary*. URL: www.nice.org.uk/website/glossary/glossary.jsp?alpha=Q).

Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) This is a published randomised controlled trial of destination therapy with a left ventricular assist device compared with medical management for patients who were not eligible for heart transplant.

UK Blood and Transplant Database Individual patient data set provided by NHS Blood and Transplant from the UK Transplant Registry maintained on behalf of the UK transplant community as part of the NHS National Specialist Commissioning Advisory Group ventricular assist device programme. The data set is known in this report as the UK Blood and Transplant Database.

Ventricular assist device A mechanical circulatory device either used as short- or long-term support in patients awaiting hear transplant. Ventricular assist devices have been classified as (a) first-generation pulsatile volume displacement pumps; (b) second-generation axial continuous flow (CF) pumps; and (c) third-generation bearingless CF pumps.

List of abbreviations

ACE	angiotensin-converting enzyme
AIC	Akaike information criterion
AICD	automatic implantable cardioverter defibrillator
ARB	angiotensin receptor blocker
ATT	alternative to transplant
BiVAD	biventricular assist device
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BTDB	UK Blood and Transplant Database
BTNR	NHS Blood and Transplant National Registry
BTR	bridge to recovery
BTT	bridge to transplant
CCU	critical care unit
CDSR	Cochrane Database of Systematic Reviews
CE	Conformité Européenne
CEAC	cost-effectiveness acceptability curve
CF	continuous flow
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CRT	cardiac resynchronisation treatment
CSS	clinical summary score
CVA	cerebrovascular accident
CVP	central venous pressure
DARE	Database of Abstracts of Reviews of Effects
DT	destination therapy
ECMO	extra-corporeal membrane oxygenation
EQ-5D	European Quality of Life-5 Dimensions
FDA	US Food and Drug Administration
GFR	glomerular filtration rate
GJNH	Golden Jubilee National Hospital
HF	heart failure
HM	HeartMate
HRQoL	health-related quality of life
HT	heart transplant
HTA	Health Technology Assessment
HW	HeartWare
IABP	intra-aortic balloon pump
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
INB	incremental net benefit
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPD	individual patient data
ISHLT	International Society for Heart & Lung Transplantation
KCCQ	Kansas City Cardiomyopathy Questionnaire
K–M	Kaplan–Meier
LV	left ventricle
LVAD	left ventricular assist device
LVAS	left ventricular assist system
LYG	life-year gain/gained
MCD	mechanical circulatory device
METs	metabolic equivalent task score

MLWHF	Minnesota Living With Heart Failure Questionnaire
MM	medical management
NC	neurological complication
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NSCAG	National Specialist Commissioning Advisory Group
NSCT	National Specialist Commissioning Team
NSRC	national schedule of reference costs
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
NUT	Newcastle upon Tyne Hospital NHS Foundation Trust
NYHA	New York Heart Association
OSS	overall summary score
PCWP	pulmonary capillary wedge pressure
PVAD	percutaneous ventricular assist device
QALY	quality-adjusted life-year
QoL	quality of life
RB	Royal Brompton & Harefield NHS Foundation Trust
RCT	randomised controlled trial
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
RR	relative risk
RV	right ventricle
RVAD	right ventricular assist device
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SHFM	Seattle Heart Failure Model
TAH	total artificial heart
TP	transition probability
UHSM	University Hospital of South Manchester NHS Foundation Trust
UNB	University Hospital of Birmingham NHS Foundation Trust
UNOS	United Network for Organ Sharing
VAD	ventricular assist device
VAS	visual analogue scale
WL	waiting list

Scientific summary

Background

Heart failure (HF) is a debilitating condition. Surgery and devices are costly. For the NHS to allocate and deliver its services, relative costs and benefits of various treatments need to be estimated. We aimed to investigate ventricular assist devices (VADs) used as a bridge to transplant (BTT) and as an alternative to transplant (ATT) for patients in the UK for patients with advanced HF who are eligible for heart transplant (HT). There are a number of newer devices and it is important to know the comparative cost-effectiveness of devices used in this way, relative to medical management (MM).

We know that historically HT has offered the best treatment option in terms of both length and quality of life (QoL) for these patients. However, HT is dependent on supply of donor hearts, whose availability appears to be diminishing while the design of VADs has been improving.

Research questions

In patients aged ≥ 16 years with advanced HF who are eligible for HT:

1. What is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as a BTT compared with MM?
2. Where data permit, what is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as an ATT in comparison with their use as a BTT therapy?

Objectives

1. To summarise previously published Health Technology Assessment (HTA) reports by Clegg *et al*. [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)] and Sharples *et al*. [Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*. *Evaluation of the ventricular assist device programme in the UK. Health Technol Assess* 2006;**10**(48)] on VADs.
2. To undertake a systematic review and evidence synthesis of the relevant clinical effectiveness and cost-effectiveness literature.
3. To further develop the cost-effectiveness and cost–utility models developed in the 2006 HTA: *Evaluation of the ventricular assist device programme in the UK* [Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*. *Evaluation of the ventricular assist device programme in the UK. Health Technol Assess* 2006;**10**(48)] and where possible to compare the use of VADs as a BTT first with MM and second as an ATT.
4. To investigate the factors that drive cost-effectiveness estimates.
5. To report on findings and make recommendations for future research.

Methods

Clinical effectiveness review methods

A systematic review of the evidence for each included VAD was undertaken following the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta Analyses statement.

The search strategy comprised the following main elements:

- searching of electronic bibliographic databases
- contact with experts in the field
- scrutiny of references of included studies
- screening of manufacturers' websites for relevant publications.

Databases included

Databases included MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effects (DARE); NHS Economic Evaluation Database (NHS EED); HTA databases [NHS Centre for Reviews and Dissemination (CRD)]; Science Citation Index and Conference Proceedings (Web of Science); UK Clinical Research Network Portfolio Database; Cumulative Index to Nursing and Allied Health Literature; PsycINFO; and the National Library of Medicine Gateway (US Meeting Abstracts and Health Services Research Projects in Progress). The following trial databases were also searched: Cochrane Central Register of Controlled Trials; Current Controlled Trials and ClinicalTrials.gov. In addition, the reference lists of relevant articles were checked, and the manufacturers' websites screened for relevant publications and other websites such as the Medicines and Healthcare products Regulatory Agency.

Inclusion criteria

Study design

- Studies with control groups [i.e. randomised controlled trials (RCTs), cohort studies, case–control studies], systematic reviews of studies with control groups.
- Case series were included if they included over 50 participants and were published in the last 5 years.

Population

- Participants (aged > 16 years) with advanced HF and considered suitable for receipt of a left ventricular assist device (LVAD), right ventricular assist device (RVAD) or biventricular assist device (BiVAD) as BTT or as potential long-term alternative to HT. Studies which reported BTT and destination therapy (DT) participants, but did not distinguish outcomes according to therapy, were included for purposes of completeness of information, but outcomes data were not included in the main text.

Intervention

- Second-generation axial continuous flow (CF) pumps.
- Third-generation bearingless CF pumps.
- LVAD, RVAD and BiVAD currently approved by the US Food and Drug Administration (FDA) and/or Conformité Européenne (CE) and in current clinical use in the UK as a BTT or as a potential long-term alternative to HT for participants with advanced HF.
- Studies with a mixture of different generation devices were considered if data for second- or third-generation devices could be identified separately from those for first-generation devices.

Comparators

- MM.
- Studies comparing HT with other interventions listed above.
- Studies comparing two different interventions listed above.
- Studies comparing first-generation devices with second- or third-generation devices were used to extract data on second- or third-generation devices only.

Outcomes

- Survival, functional capacity [e.g. change in New York Heart Association (NYHA) functional classification], QoL and adverse events.

Exclusion criteria

- Percutaneous ventricular assist device (PVAD) and total artificial heart (TAH).
- First-generation pulsatile volume displacement pumps.
- Devices yet to be FDA or CE approved.
- Devices for 'bridge to decision'.
- Studies not in English.
- Studies before the year 2003.

Searches were undertaken in March 2012.

Review methods
Quality criteria were applied independently by two reviewers using a recognised quality assessment checklist; disagreements were resolved by independent assessment by a third reviewer.

Methods of analysis/synthesis
Data were tabulated and discussed in a narrative review based on the type of VAD.

Cost-effectiveness review methods
A systematic review of cost-effectiveness publications of VADs was undertaken using the same search strategies and methods as the clinical effectiveness review but including relevant costs search terms. Data from the UK Blood and Transplant Database (BTDB) were obtained from the UK Transplant Registry maintained on behalf of the UK transplant community. The data set has been maintained as part of the National Specialist Commissioning Advisory Group (NSCAG) funded VAD programme and data are included from May 2002 to December 2011. The data are collected for patients from six UK centres (listed below) which are responsible for carrying out VAD implantation surgery:

- Royal Brompton & Harefield NHS Foundation Trust (RB)
- Papworth Hospital NHS Foundation Trust
- the Newcastle upon Tyne Hospital NHS Foundation Trust (NUT)
- the Glasgow Golden Jubilee National Hospital (GJNH)
- University Hospital of Birmingham NHS Foundation Trust (UNB)
- University Hospital of South Manchester NHS Foundation Trust (UHSM).

A semi-Markov multistate economic model was developed; the model was adapted from a previous HTA report and was updated with patient experience recorded in the UK BTDB during the period April 2005 to November 2011. The aim of the model was to estimate cost-effectiveness, first, of BTT relative to MM in patients with advanced HF and, secondly, of ATT relative to BTT in patients with advanced HF. The comparison of BTT with ATT represented a 'virtual' scenario to examine the impact of lack of availability of donor hearts. Model outputs are reported as incremental cost-effectiveness ratios (ICERs) as cost/

quality-adjusted life-year (QALY) gained and as cost/life-year gained (LYG). A discount rate of 3.5% was applied to both costs and benefits and time horizons of 3, 10 and 50 years (lifetime) were explored. The analyses were undertaken from the perspective of the NHS. A number of sensitivity analyses were undertaken varying survival in the MM control group (median survival ranged between 3.9 and 16.5 months) as well as other important input variables.

Results

Clinical effectiveness results

We identified 40 relevant publications. There were no randomised studies in our defined patient group (eligible for HT). The majority of included publications described single-arm prospective or retrospective case studies. No publication compared BTT outcomes with those for concurrent controls involving MM or best supportive care. Observations were often based on small numbers of patients from single centres who were participating in multicentre clinical studies. Overall, the study designs were not strong: studies were likely to be only moderately representative of underlying populations, there were no randomised trials and blinding of outcomes assessors was weak.

Analyses of included publications suggested the following estimates for baseline characteristics of participants in BTT studies: the majority were white (78–94%), male [84.2%, 95% confidence interval (CI) 79.4% to 88.0%] and middle aged [mean age was estimated at 50.8 years (95% CI 49.3 to 52.4 years)]. Mean body mass index (BMI) was estimated at 26.5 kg/m^2 (95% CI 25.7 to 27.3 kg/m^2); one-quarter of patients, 25.2% (95% CI 17.4% to 35.1%), were estimated to have diabetes mellitus; study participants had very severe HF with 83.5% (95% CI 78.0% to 87.9%) overall rated as NYHA class IV; most participants were supported with inotrope medication, 80.8% (95% CI 50.9% to 94.5%), and had low mean systolic blood pressure (BP), 97.3 mmHg (95% CI 92.8 to 101.7 mmHg).

By 12 months patients had suffered a variety of serious complications. Studies reported the following wide ranges for adverse events: 4–27% bleeding requiring transfusion; 1.5–40% stroke; 3.3–48% infection; 1–14% device failure; 3–30% HF; 11–32% reoperation; and 3–53% renal failure. Publications reported results from a variety of QoL and functional status measures. Statistically significant improvements in QoL and functional status were reported in studies of two devices [HeartMate II® (Thoratec Inc., CA, USA) and HeartWare® (HeartWare Inc., Framingham, MA, USA)]. There is still insufficient published evidence on second- and third-generation devices to draw robust conclusions about survival, adverse events and QoL for patients receiving these devices compared with MM without VAD.

UK Blood and Transplant Database individual patient data analysis

Using the UK BTDB, which has a large sample size reflecting UK practice, we identified 235 patients who had received a VAD. These patients were also mostly male, 80.4% (95% CI 74.77% to 84.99%), but were somewhat younger, mean age 44 years (95% CI 42.72 to 45.28 years), with a less severe NYHA class rating, class IV 58.1% (95% CI 39.07% to 75.45%), than in the published literature and were also more likely to be white, 89.7% (95% CI 81.80% to 90.86%), as compared with patients in published literature studies. Median survival with a VAD in this population was 32.1 months.

Just over three-quarters of these patients had been treated with inotropes prior to surgery, as compared with published BTT registry studies, which give slightly higher rates at 80%. In contrast, only just over 20% (307) of the 1496 UK BTDB MM patients were categorised as using inotrope treatment, supporting the use of the 'inotrope' subcategory of BTDB patients for the base-case (MM) comparator group in the economic model. Modelling of survival for these BTDB inotrope MM patients yielded a median survival of 9.1 months.

Cost-effectiveness results

- For research question 1, VADs used as BTT had higher mean costs in comparison with medically managed patients with higher survival and QoL benefits. This was the case for all the various scenarios examined for BTT patients and for all time horizons considered [3 years, 10 years and 50 years (lifetime)]. Probabilistic and deterministic results were confirmatory.
- In the base-case scenario for VAD patients compared with medically managed patients, the lifetime ICER was £55,173/QALY in the deterministic model. For a shorter time horizons of 3 years and 10 years the ICERs were £122,730/QALY and £68,088/QALY respectively. The base-case lifetime probabilistic ICER was £53,527/QALY.
- For research question 2, patient mean costs were lower for VADs used as ATT as compared with VADs used as BTT, but mean benefits were also reduced. Over the 3-year, 10-year and lifetime study horizons the ICERs (cost/QALY) were £353,467, £31,685 and £20,637 respectively (these ICERs are distributed in the 'south-west' quadrant of the cost-effectiveness plane); both costs and benefits for the VAD as ATT group were reduced relative to those for VAD as BTT. Probabilistic analysis confirmed these findings.

Conclusions and recommendations for future research

Our findings of a relative lack of cost-effectiveness for VADs as BTT relative to MM given standard levels of willingness to pay for a QALY in the NHS concur with those of other researchers. However, it is clear that devices are changing and improving and in the base-case analysis, cost-effectiveness over a lifetime horizon approaches that for interventions adopted by the NHS as end of life treatments. The cost of VADs would need to be reduced by 15% in order to bring the base-case lifetime time horizon ICER to £50,000 per QALY and by 76% to bring the ICER to £30,000 per QALY.

Future research

No RCT has been published allowing comparison of BTT with VADs versus MM. For ethical reasons a RCT offering equal probability of HT for each group would not be feasible. Therefore, attention should be directed towards:

1. How any future evaluations of second- or third-generation VADs might be conducted. Future studies should fully assess costs, long-term patient survival, QoL, functional ability and adverse events, so these may be incorporated into economic evaluation.
2. Agreement on outcome measures across future studies, in particular length of follow-up, time points for data collection, agreed QoL and functional ability measures.
3. Consideration of support for the UK BTBD so as to ensure that full and accurate records of all patients are kept, and that regular analyses and comparative assessments of performance with other international centres are undertaken.
4. Consideration of extending the UK BTDB data collection process so as to include QoL data [e.g. using the European quality of life-5 dimensions (EQ-5D)], and to include resource-use data in order to facilitate future cost-effectiveness evaluation.
5. Development of guidance in the use of VADs as technology and management continue to change. It will be important to monitor and update this assessment regularly.

Funding

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Chapter 1 Background

Introduction

Heart failure (HF) is a common condition in which the heart does not pump blood properly limiting an individual's quality of life (QoL) and length of life.[1] This chapter describes definition, epidemiology, causes, classification and management of HF.

Definition of heart failure

There are many definitions of HF[2] which have changed over the years. Changes have caused difficulties in undertaking epidemiological studies in this area.[2]

In 1989, HF was defined as a 'syndrome which develops as a consequence of cardiac disease and is recognised clinically by a constellation of symptoms and signs produced by complex circulatory and neurohormonal responses to cardiac dysfunction'.[3] A Health Technology Assessment (HTA) report published in 2005 described HF as 'a disease characterised by a decline in the heart's ability to pump blood around a person's body at normal filling pressures to meet its metabolic needs'.[4]

Symptoms of HF typically include shortness of breath at rest or during exertion and/or fatigue, signs of fluid retention such as pulmonary congestion and ankle swelling, and objective evidence of an abnormality of the structure or function of the heart at rest (*Box 1*).[5,6] Over time, as HF advances, the severity of symptoms worsens. The condition is sometimes known as advanced or end-stage HF. For consistency in this report we will refer to advanced HF.

Epidemiology of heart failure

Heart failure is a major health problem worldwide. It has a considerable impact on health-care costs and patients' lives. It has been estimated that there are currently approximately 750,000 people with HF in the UK.[1] According to the General Practice Research Database, the overall incidence rates of HF are 37.5 and 23 per 100,000 person-years for men and women, respectively, and there are an estimated 27,000 new cases of HF per year in the UK.[7] The overall prevalence of HF in the UK at age 65–74 years is 1 in 35 people, which increases to 1 in 15 in those aged 75–84 years, and just over 1 in 7 in those aged $\geq$ 85 years.[8] Parameshwar *et al.* found that the prevalence of HF in the UK in patients aged $<$ 65 years was 0.6 per 1000 patients but rose to 27.2 per 1000 in those aged $\geq$ 65 years.[9] Similarly, the Hillingdon Heart Failure Study, a contemporary population-based study, identified the median age at presentation of HF as 76 years[10] indicating that risk increases with increasing age. This is in accordance with recorded higher rates of hospital admission for HF at older ages in the UK.[11]

In the year 2000, the direct health-care costs of HF to the NHS were estimated to be £0.75B annually. Total expenditure was estimated to be approximately 4% of the total health-care expenditure in the UK.[11] The impact on health-care costs in the UK is owing to the high prevalence of cardiovascular diseases in older age groups coupled with ageing of the population.[4]

Over the last 10 years HF admission rates in England increased by around 5% and 4% in men and women respectively.[12] It has been predicted that the burden of HF will rise over the next 20–30 years. Hospital admissions due to HF are estimated to increase by approximately 50% in the next 25 years.[12,13]

BOX 1 Definition of HF (adapted from European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure, 2008)[6]

Heart failure is a clinical syndrome in which patients have the following features:

- symptoms typical of HF: breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling; and
- signs typical of HF: tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly; and
- objective evidence of a structural or functional abnormality of the heart at rest: cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration.

Aetiology and pathophysiology of heart failure

Any anatomical or physiological conditions which affect ventricular function can cause HF. In a survey conducted in Hillingdon, West London, which included a population of 151,000 people, researchers found that the most common cause of HF was ischaemic or coronary heart disease (CHD).[10] Similarly, in a UK-based population, a study of coronary artery angiography in new patients aged < 75 years,[14] CHD was found to be the commonest cause of HF. Other causes of HF include hypertension, valvular heart disease, myocardial toxins, myocarditis and cardiomyopathy.[4,10,14]

The final common pathway for all pathophysiology of HF (CHD, poorly controlled hypertension, cardiomyopathy or valvular heart disease) is ventricular dysfunction. The left ventricle (LV) is most commonly affected with eventual myocardial injury and remodelling leading to a dilated ventricular chamber with a low ejection fraction, activation of non-cardiac factors such as the neurohormonal systems with vasoconstriction and renal sodium retention, and further symptoms such as dyspnoea, fatigue and oedema (*Figure 1*).[15,16] This can lead to episodes of arrhythmia, increasing pump failure and, finally,

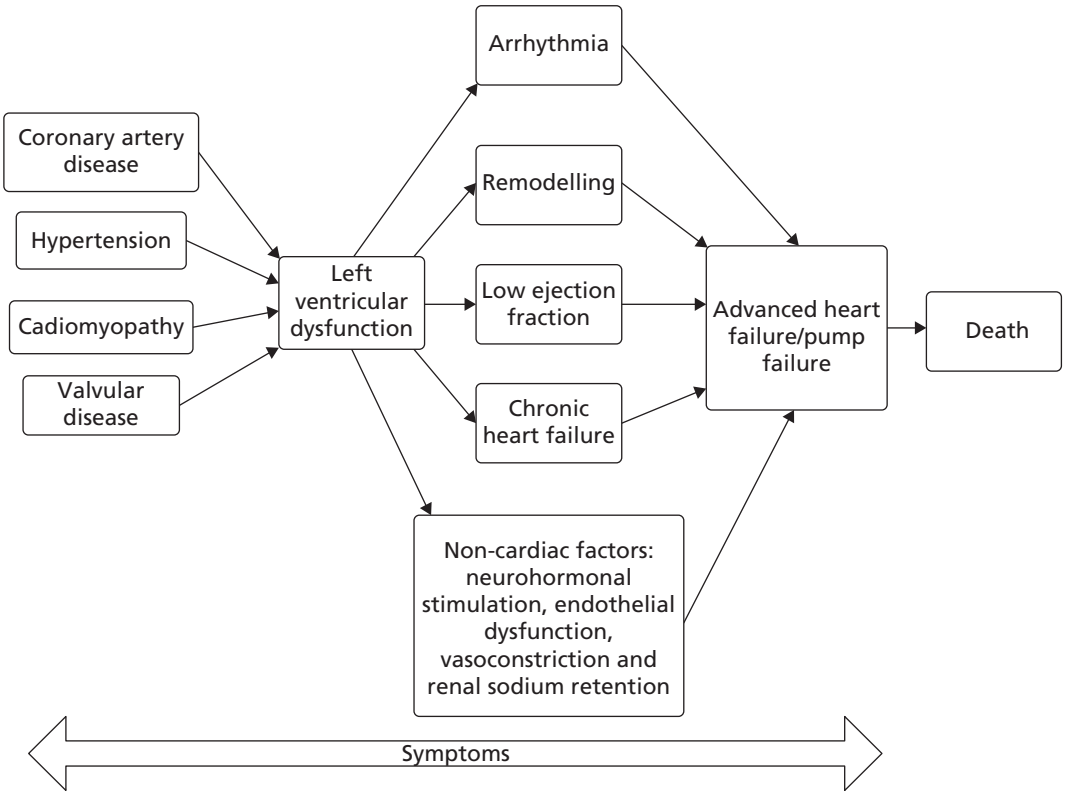


FIGURE 1 The pathophysiology of progression of HF (redrawn and adapted from Cohn[16]).

premature death. However, aetiology of HF varies by age group, as also do the criteria used to identify its presence.[10,17]

Symptoms and signs of heart failure

The most common symptoms of HF are breathlessness, tiredness, loss of appetite, and signs of peripheral oedema, raised jugular venous pressure, tachycardia or tachypnoea.[5,6] The severity of HF is usually assessed using the New York Heart Association (NYHA) functional classification, which is based on the severity of symptoms patients develop in relation to physical activity. Severity of HF can be classified into four grades using the NYHA classification. Patients with NYHA class I are considered to be less severely affected and can perform ordinary physical activity without developing symptoms of HF. Patients with NYHA class IV have advanced HF, are unable to carry out any physical activity and have symptoms at rest (*Box 2*).

Diagnosis of heart failure

There is no 'gold standard' for diagnosis of HF. Initially, it is assessed by patient history and physical examination.[8] In addition, there are no signs and symptoms that are both sensitive and specific for the diagnosis of HF.[19] Investigations such as electrocardiography, measurement of B-type natriuretic peptide (BNP) or both are recommended depending on the condition. If the above tests are abnormal then echocardiography (to measure ventricular performance) and chest radiography (to detect cardiomegaly, pulmonary congestion and pleural fluid accumulation) are undertaken to confirm the diagnosis of HF. BNP and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) are useful biomarker hormones in the diagnosis of HF. Levels of these biomarkers are raised in patients with HF and the concentrations vary with NYHA class.[5,19,20] *Figure 2* gives a schematic representation of recommendations on the diagnosis of HF (adapted from Sutherland).[21]

Quality of life and prognosis of heart failure

People with HF are often heavy users of primary care services.[17,22] The mortality rate of HF is comparable to that of cancer.[17,23] de Giuli *et al.*[24] studied primary care patients in the UK and found that people with HF have a very poor prognosis, especially the elderly. The Hillingdon Heart Failure study also reported that around 40% of people die within 1 year of a diagnosis of HF.[10] In the Echocardiographic Heart of England Screening Study, QoL was measured by Short Form questionnaire-36 items (SF-36), and impairment in

BOX 2 Classification of HF by symptoms relating to functional capacity (NYHA) (adapted from European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure, 2008)[6]

Severity based on symptoms and physical activity

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.

Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.

Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation or dyspnoea.

Class IV: Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Adapted from the Criteria Committee of the NYHA, *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*.[18]

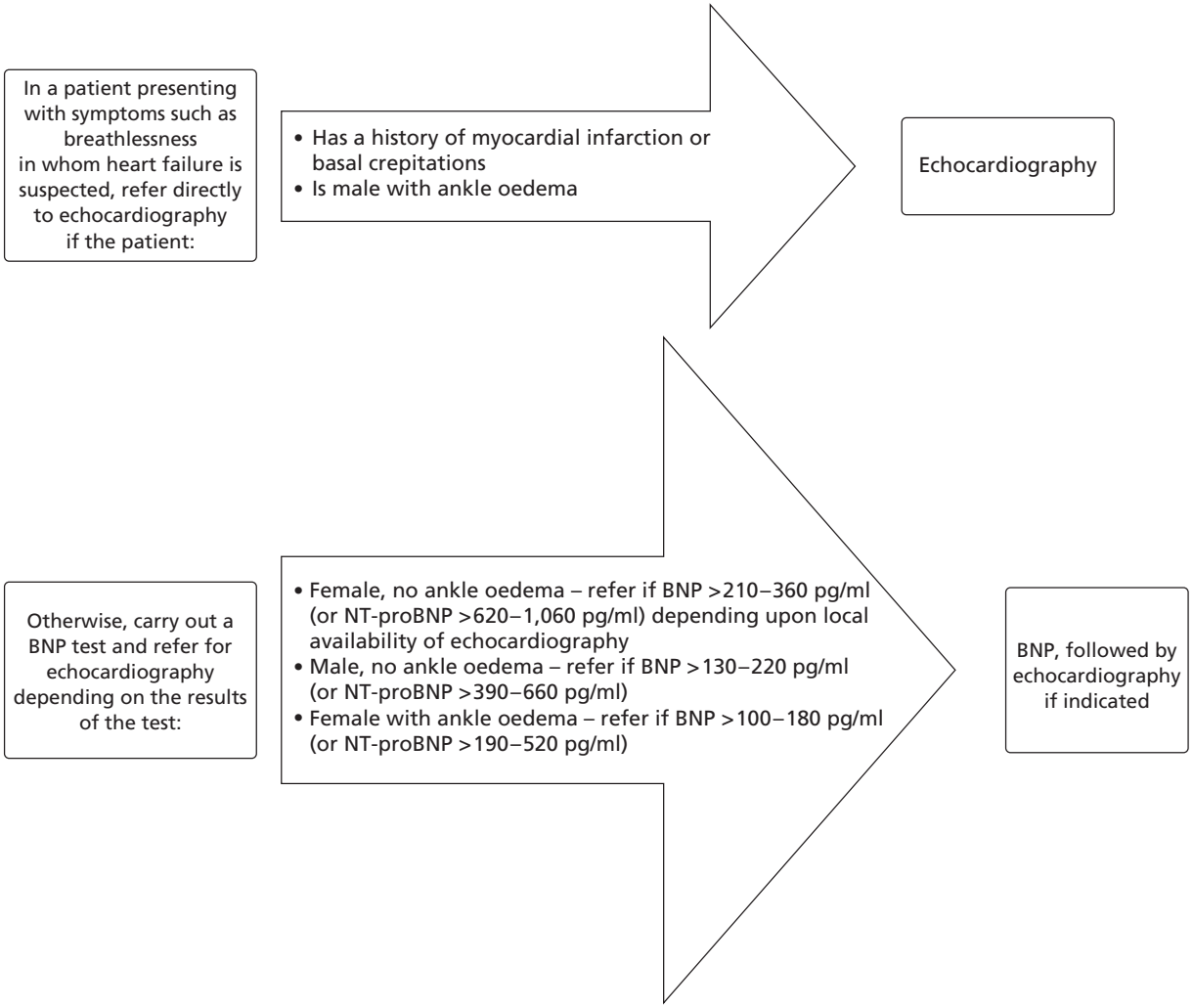


FIGURE 2 A schematic diagram of HF diagnosis recommendations (redrawn and adapted from Sutherland[21]).

both mental and physical QoL was reported. Impairment was found to be worse in those with more severe HF as measured by NYHA severity assessment class[25] and reduction in QoL was particularly evident among elderly people.[21]

Management of heart failure

Treatment of patients with HF depends on type and stage of HF.

Medical management

Medical therapy is beneficial and used for symptomatic relief in patients with HF.[26] Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are recommended as first-line therapy in patients with chronic HF caused by systolic LV dysfunction. Alternatively, angiotensin receptor blockers (ARBs) can be given to patients to reduce morbidity and mortality.[5,27,28] Other drugs, such as beta-adrenoceptor antagonists, inhibitors of the renin–angiotensin system and aldosterone antagonists, can also be used. Diuretics such as thiazides or loop diuretics are given for symptomatic benefit.[6] Simultaneously, it is important to control intake of fluid and sodium in these patients. In severely ill patients who do not respond to other medical treatment, inotropic drugs, such as dobutamine (Dobutrex®, Abbott Healthcare Pvt. Ltd), milrinone (Primacor®, Sanofi-Aventis) or enoximone (Perfan®, Hoechst Marion Roussel), may be considered.[27,28] In England, for example, inotropic drugs are given only on specialist advice for treatment of decompensating HF to reduce hypoperfusion or congestion and if patients are resistant to vasodilators and/or diuretics.[5,6] Some patients can become inotropic dependent while waiting for a donor heart to become available.

Electrical device treatment and heart transplant

Cardiac resynchronisation treatment (CRT) is recommended to improve symptoms and survival of patients with HF, but there remains a subgroup of patients who, despite optimal medical therapy, progress to more severe HF equivalent to NYHA class III or IV.[26]

The prognosis for patients with advanced HF who do not respond to pharmacological and electrical resynchronising therapies is poor. Therefore, heart transplant (HT) is the ultimate surgical approach for the treatment of patients with advanced HF. HT can increase long-term survival for these patients. Patients with NYHA class III or IV are eligible for HT.[28] Survival after HT is estimated at approximately 50% at 10 years. In contrast, for similar patients who do not receive a HT, survival is < 50% at 1 year.[29] In the UK HT has been offered to patients with advanced HF over the last 30 years. However, overall numbers and rates of HT have decreased more recently, i.e. over the last 10 years.[1]

It has been estimated that, although approximately 30,000 patients are waiting for a HT worldwide, only 3500 donor hearts are available annually.[26] The increasing number of patients with HF coupled with the shortage of donor hearts has led to an increased mortality rates among patients waiting for HT. It is estimated that approximately 30% of patients die while waiting for a HT.[26] Following HT, patients are at high risk of developing complications such as infection, bleeding, lung congestion, liver congestion, renal failure, neurological complications (NCs) and device failure. In order to prevent allograft rejection,[6] patients are also given a variety of immunosuppressant and prophylactic drugs, which in turn increases their susceptibility to opportunistic infection.[30]

Mechanical circulatory devices (MCDs) have increasingly been used in the last decade or so in order to increase survival and QoL for patients awaiting HT.[4,30] These devices are used as either short- or long-term support in patients awaiting HT.[31] When a VAD is implanted for a short duration of time, while the patient waits for a suitable heart to become available for transplantation, the procedure is called bridge to transplant (BTT). VADs are currently approved as BTT in the UK. When a VAD is implanted temporarily to support blood flow to allow the heart to recover from a condition, such as post-myocardial infarction or post-cardiotomy shock, the procedure is known as bridge to recovery (BTR). When recovery is impossible and patients are ineligible for HT, then VADs are used as destination therapy (DT).[32] Currently the NHS does not fund VADs as DT;[28] however, VADs are increasingly used for this purpose in some non-UK countries.[33]

Unfortunately, not all patients are eligible for HT. As reported in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) study,[34] contraindications to HT can be due to either modifiable or non-modifiable factors. In the INTERMACS study, the most commonly reported contraindications included advanced age, renal dysfunction or high body mass index (BMI). It should be noted that > 50% of the contraindications identified in the INTERMACS study were modifiable. Approximately 10% of patients originally considered unsuitable for HT and selected for DT subsequently improved sufficiently to undergo HT after 12 months.[34]

In this report, we are considering only patients who are eligible for HT. We are investigating two situations:

- The use of VADs as BTT in patients eligible for HT.
- The use of VADs as an alternative to transplant in patients who are eligible for transplant – a procedure not currently used in the UK. We have coined a new acronym for this situation, 'alternative to transplant' (ATT). ATT should be clearly distinguished from DT as patients receiving ATT are eligible for HT. Patients receiving VADs as DT are not eligible for HT.

Mechanical circulatory devices or ventricular assist devices

Mechanical circulatory devices or VADs are categorised into (a) left ventricular assist devices (LVADs), (b) right ventricular assist devices (RVADs) or (c) devices designed to support both ventricles (biventricular assist devices; BiVADs). Other types include the percutaneous ventricular assist device (PVAD) and the total

artificial heart (TAH). Device use depends on the patient's condition and the type of HF. As mentioned above, indications for the use of MCD are:

1. BTT
2. BTR
3. DT
4. ATT.

Descriptions of ventricular assist devices

An LVAD has inflow and outflow cannulae which help to regulate blood flow from the LV or left atrium to the ascending aorta. Similarly, in the RVAD, an inflow cannula regulates blood from the right ventricle (RV) or right atrium to the pulmonary artery.

Left ventricular assist devices help to pump blood from the LV of the heart to the rest of the body in patients with advanced HF.[35] In the UK, LVAD patients with advanced HF wait for a donor heart to become available.[1,36] These devices as are not currently licensed for use as DT in the UK, although they are approved in the USA and in parts of Europe.[1,35] LVADs can be broadly categorised as generation I, generation II and generation III (*Figure 3*).

Second- and third-generation LVADs are magnetic continuous flow (CF) rotary pumps whereas first-generation LVADs are pulsatile volume displacement devices.[35,37] Compared with first-generation devices, second- and third-generation devices are smaller, quieter and more reliable. Second- and third-generation devices are inserted through a small dissection. They are easier to insert and less traumatic than previous types and are associated with less bleeding and infection. Third-generation LVADs are attached with an impeller which uses magnetic forces or hydrodynamic levitation without mechanical contact. They therefore have greater durability, with no mechanical wear and tear compared with second-generation LVADs.[35,37] In this report the interventions of interest are second- and third-generation devices which have either US Food and Drug Administration (FDA) or Conformité Européenne (CE) approval or both; therefore, this section will describe characteristics only of these devices.

Table 1 shows the VADs which have FDA or CE approval.

Second-generation devices

HeartMate II

This is the only CF axial device. It has an internal rotator with helical blades which curve around the central shaft. It is reported that the device has been implanted in more than 3000 patients worldwide.[35] According to Thoratec Inc., HeartMate (HM) II received FDA approval as a BTT and DT in April 2008 and on 20 January 2010 respectively. The device received CE approval in November 2005, allowing its commercial sale in Europe.[35,38]

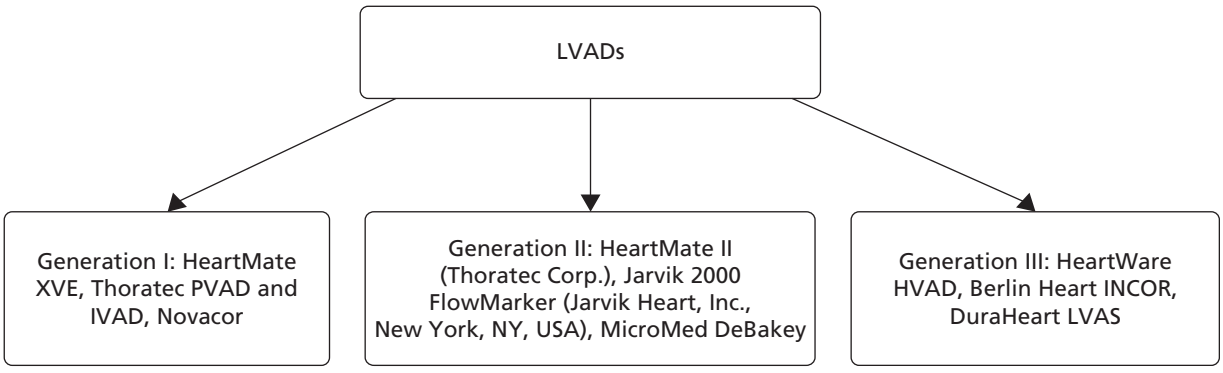


FIGURE 3 A schematic diagram of HF diagnosis recommendations.

TABLE 1 Second- and third-generation devices that have been approved by FDA and/or CE

Name of devices	Manufacturer
LVADs	
MicroMed DeBakey VAD (HeartAssist 5®)	MicroMed, Uden, Netherlands
DuraHeart LVAS®	Terumo Heart Inc., Ann Arbor, MI, USA
HeartMate II®	Thoratec Inc., Pleasanton, CA, USA
[a]HeartWare HVAD®	HeartWare Inc., Framingham, MA, USA
INCOR®	Berlin Heart, Berlin, Germany
[b]Jarvik Heart 2000®	Jarvik Heart Inc., New York, NY, USA
RVADs	
[b]Jarvik 2000 Flow Maker®	Jarvik Heart Inc., New York, NY, USA
BiVADs	
[b]Jarvik 2000®	Jarvik Heart Inc., New York, NY, USA
[a]HeartWare HVAD®	HeartWare Inc., Framingham, MA, USA

LVAS, left ventricular assist system.
a HeartWare HVAD can be used as an LVAD or as a BiVAD.
b Jarvik 2000, Jarvik 2000 flow marker and Jarvik Heart 2000 flow marker are the same device. It can be used as a LVAD, RVAD or BiVAD as required.

Jarvik 2000

This is a long-term implantable, axial, CF pump and has been approved by both the FDA and the CE as a BTT and as a DT in Europe only. It is inserted intrapericardially, regulating blood flow from the LV apex to either the ascending or descending aorta.

MicroMed DeBakey

The design of MicroMed DeBakey has been improved over the years and it is now marketed as HeartAssist 5, which has both CE and FDA approval as a BTT.[39] HeartAssist 5 represent the new-generation device that includes new features such as flow accurate diagnostics and heart assist remote, which provide direct online measurement of blood flow. This is an improvement over MicroMed DeBakey in terms of designs, prevention of pump thrombosis and power fluctuation. In 2002, the MicroMed DeBakey was used in the USA as a BTT.[39]

Third-generation devices

Berlin Heart 'INCOR'

The INCOR LVAD is a magnetic bearing, flow pump with axial design which circulates blood from the LV apex to the ascending aorta. This device was first implanted in 2002 at the German Heart Institute. After this, the device gained CE approval in 2003. Since then it has been implanted in more than 500 patients worldwide. At present, the device is not available in the USA.[37,40]

DuraHeart left ventricular assist system

The DuraHeart left ventricular assist system (LVAS) is a small continuous, radial flow pump connected to a magnetically levitated impeller which helps pump blood from the left side of the heart, improving circulation throughout the body.[37,40,43] The device is generated in such a way that magnetic levitation uses electromagnetic coils to position the movement of impeller within the pump to generate 'gentle and consistent blood flow' as the manufacture suggests.[41] According to the review published by

Morshuis *et al.*,[42] DuraHeart LVAS is the world's first third-generation implantable LVAS to obtain market approval (CE) in February 2007.

HeartWare HVAD

The HeartWare® (HW) HVAD is a small, implantable centrifugal pump, designed to draw blood from the LV and pump it towards the ascending aorta with the help of an outflow graft. The pump has only one moving part, a wide-blade impeller suspended within the pump housing by the combination of passive magnetic and hydrodynamic bearing systems. A thin blood film created by the hydrodynamic thrust bearing prevents physical contact between the housing and the impeller.[37,40,43] The first human implant was performed in March 2006[43] and a clinical trial began in 2008 in the USA, which consisted of 150 participants for whom the device was indicated as a BTT. The device received CE mark approval in 2009.[37,40,43]

The most frequently used CF left VADs in the UK are the HMII and HW.[44] *Table 2* summarises characteristics of second- and third-generation devices.

Randomised controlled trials of left ventricular assist devices

Two randomised controlled trials (RCTs)[45,46] have been performed which examined the effectiveness of LVADs. In each of these the LVAD was used as DT for patients who were not eligible for HT and in whom

TABLE 2 Characteristic of second- and third-generation devices

	Devices	Type	Weight gram (g)	Size (cm)		Circulatory support	
				Length	Diameter	RPM	Flow (l/minute)
Second generation							
A	Thoratec HMII	CF axial blood pumps with magnetically suspended axial flow rotor. The device is placed just below the diaphragm in the abdomen	350	7.0	4.0	6000 –15,000	10
B	Jarvik Heart 2000 Flow Maker	CF axial blood pump which placed in the ventricular cavity	85	5.5	2.4	8000–12,000	7
C	MicroMed DeBakey VAD	Continuous axial flow rotary pump, implants above the diaphragm	92	7.1	3.8	10,000	2–10
Third generation							
D	Berlin Heart INCOR	CF pumps with an axial design, with free floating impeller with magnetic connection	200	3.0	3.0	5000–10,000	5
E	Terumo DuraHeart LVAS	A CF centrifugal pump with a magnetically levitated impeller implanted in an abdominal pocket	540	7.2	4.5	1200–2600	2
F	HW HVAD	Small CF, centrifugal pump inserted in the pericardial space	145	< 2.0	4.0	1800–3000	10

RPM, revolutions per minute.

HT was contraindicated, and these studies therefore do not satisfy the remit for the current report. However, these studies are included here as they provide the only randomised evidence on VADs. Results from the first trial, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH), were published by Rose *et al.*[45] The study compared the pulsatile HMXVE® device (Thoratec Inc., Pleasanton, CA, USA) ($n = 68$) with optimum medical management (MM) ($n = 61$) for patients described as having 'end stage heart failure' (all participants were classified as experiencing NYHA class IV HF). Kaplan–Meier (K–M) analysis of death by any cause was superior in the HMXVE group [relative risk (RR) 0.52, 95% confidence interval (CI) 0.34 to 0.78; $p = 0.001$]. The survival rate at 1 year was 52% and 25% in the LVAD and MM groups respectively ($p = 0.002$). Similarly, 2-year survival rates were 23% in the LVAD group and 8% in the MM group ($p = 0.09$). Adverse events (infection, bleeding and device failure) were 2.35 times more common in the LVAD group (95% CI 1.86 to 2.95), partly reflecting greater time at risk. The QoL according to the Minnesota Living With Heart Failure Questionnaire (MLWHF), the SF-36 and the NYHA classification was improved in the LVAD group at 1 year after implant. Stevenson *et al.*[46] recently reported results from post-hoc analyses of the REMATCH data in which participants were stratified according to inotrope use at baseline. K–M analysis indicated poorer survival for MM patients receiving inotrope treatment at baseline than for MM patients who did not receive inotropes at baseline.

Slaughter *et al.*[47] extended the REMATCH study design to compare the CF HMII device ($n = 134$) with the HMXVE pulsatile flow device ($n = 66$). Again, in this study, LVADs were used as DT for patients for whom HT was contraindicated. The primary end point was survival, freedom from disabling stroke and reoperation for repair or replacement of the device. At 2 years this outcome was significantly superior for the HMII group (46% vs. 11%). The hazard ratio comparing treatments for this outcome was 0.38 (95% CI 0.27 to 0.54; $p < 0.001$). The actuarial survival rate at 2 years was superior for the HMII group (58% vs. 24%; $p = 0.008$). Rates of adverse events and of repeat hospitalisations were lower for the HMII group. Post-implant improvement in the QoL and functional status were similar in both groups.

Complications of ventricular assist devices

This section summarises papers by Potapov *et al.*[48] and Barnes,[49] which describe complications which can occur for patients with VADs. Complications in patients with VADs can be categorised as acute or late.

Acute complications

Acute complications occur shortly after implantation of the device and include thromboembolism, haemorrhage, right ventricular failure and altered immune response.

Thromboembolism: The incidence of thromboembolism after VADs implantation ranges between 10% and 25%. The risk depends on many factors such as presence of infection, type of device used and type of anticoagulation regimen used.[49] Most thromboembolic events in this situation are reported as cerebrovascular. Contact between the surface of the device and the patient's blood is the cause of the thromboembolism. This interaction triggers immune cells and coagulation pathways, thus ultimately causing clot formation. Because of this risk, it is important to administer adequate anticoagulation therapy in these patients. Recent HM devices have a special coating and patients implanted with these devices are considered to need only antiplatelet therapy.

Haemorrhage: Haemorrhage is common post-operatively. It has been reported in more than half of patients with VADs. It also occurs in those undergoing reoperation to treat haemorrhage (~ 20–40% of patients). Risk of bleeding can be increased by anticoagulation, prolonged surgery with cardiopulmonary bypass and extensive surgical incision. Some of the CF devices cause arteriovenous malformation, leading to increased gastrointestinal bleeding.[50] Early and appropriate intervention to control bleeding is important. If untreated, this may lead to further complications such as multiple organ failure. Patients with haemorrhage are given blood transfusion; however, fluid overload can be a problem for some, potentially causing right heart problems and right HF.

Immune response: The interaction between the surface of the device and the patient's blood can activate defective proliferation of T cells, causing activation-induced cell death. This can affect a patient's immunity, and thus he/she may become more susceptible to infection or thromboembolic events. The foreign material of the device can also cause B cell hyperactivity, thus activating an autoimmune reaction. These patients also have an increased risk of post-transplantation organ rejection.

Multiorgan failure: Multiorgan failure is a cause of death after VADs use. It occurs because patients with advanced heart disease in a compromised health state may already have reduced kidney and liver function. Some may also have reduced pulmonary function and may be on mechanical ventilation. It has been suggested that multiple mechanisms and events may be responsible for the development of multiorgan failure including inflammatory reactions, infection, prolonged surgery time, blood transfusion and hypothermia.

Right ventricle failure: RV failure occurs in approximately a tenth of patients receiving VADs. It may develop suddenly after implantation or may already be present in some patients, becoming apparent only after VAD implantation. Various mechanisms can lead to right ventricular failure. One possibility is that the intraventricular septum bulges into the LV, decreasing right ventricular efficiency or the increased efficiency of the LV may increase venous return to the right side of the heart causing failure. Other causes are thought to include myocardial stunning, ischaemia, arrhythmias and increased pulmonary vascular resistance.

Long-term complications

Infection: This occurs commonly and may present as pneumonia, mediastinitis, urinary tract infections or line sepsis. Some infections may also be device related, such as driveline or pump pocket infections, endocarditis or sepsis. After surgery, patients' immunity is considerably reduced, and this can make them susceptible to infection. In addition, existing diseases such as diabetes mellitus and chronic obstructive pulmonary disease (COPD) can increase susceptibility. Risk of infection increases as some parts of the devices are exposed to external pathogens. Some devices may have cavities and pockets which can harbour pathogens. *Staphylococcus* species, *Pseudomonas aeruginosa* and *Candida* are the most common pathogens. It is very important to treat infection early. If not treated, it can increase the risk of other complications such as thromembolic events and strokes.

Abdominal complications: Risk of abdominal complications increases when VAD hardware is placed in the abdomen. Abdominal hardware infection is the most common complication and is usually acquired in hospital. Other abdominal complications include fistula formation, gastrointestinal haemorrhage, bowel obstruction and abdominal herniation (incisional or diaphragmatic hernia). Diaphragmatic hernia usually occurs after the VAD is removed and a heart has been transplanted. Serious abdominal complications such as cholecystitis, pancreatitis, gastric ulceration and perforation can also occur.

Device malfunction: Over the years, modifications to the devices have been made to reduce this complication. However, patients implanted with VADs can still suffer significant morbidity and mortality. It has been estimated that device failure occurs in approximately 35% of patients during the 24 months after implantation. In half of these, external components such as the controller, batteries or the Y-connector are involved, whereas in the remaining patients internal VAD components such as inflow or outflow cannulae are involved. Malposition of the inflow cannula can occur over time as a result of pericardial changes or inappropriate preparation of the pocket for the pump causing partial blockage of the cannula and haemolysis, low pump flow, arrhythmias and, finally, right ventricular failure due to reduced LV loading.[50]

Malnutrition: Almost half of patients with HF are already malnourished. The term ‘cardiac cachexia’ is used to describe this condition, in which the body's inflammatory and metabolic response leads to malnutrition, muscle wasting and weight loss. Implantation of VADs further increases the risk of malnutrition. Other

factors, such as poor appetite, delayed gastric emptying, nausea and vomiting, also contribute to malnourishment.

Psychosocial issues: In most patients, VADs have been found to improve QoL. However, some patients and carers are found to be anxious and concerned about physical limitations and complications which may occur as a result of the device. Some patients deteriorate with time and some may develop more severe psychiatric problems.[50]

In conclusion, driveline infection, post-operative bleeding and thromboembolism are the main complications related to use of LVADs.[50] The use of modern technology and new materials has ensured that complications have reduced in recent years.

Current service provision

With increasing demand for HT, the United Network for Organ Sharing (UNOS) has coded waiting list (WL) patients as Status 1A, 1B or 2 on the basis of medical urgency. Patients who are in a clinically stable condition and patients with LVAD-related complications (infection, thromboembolism or device malfunction) are categorised as Status 1A patients for 30 days. Status 1B is assigned to patients supported by LVAD who do not meet the criteria for Status 1A. Status 2 patients are those receiving long-term LVAD support.[51]

In the UK, WL management is based on the urgent and non-urgent WL, developed by the Cardiothoracic Advisory Group of NHS Blood and Transplant (*Box 3*).[28]

Evolving LVAD technology from first generation to second and third generation has led to development of devices which are considerably smaller, more durable and associated with fewer adverse events. As pulsatile and first-generation LVADs have been modified to CF devices, the improvements have been marked with a lower incidence of infection and complications. Use of these devices as a BTT has led to considerable improvements in QoL among patients with advanced HF.[52,53]

Patient pathways for management of heart failure

Treatment of patients with HF depends on the type and stage of HF. The following examples of patient pathways indicate how patients are treated at different stages: BTT to VAD (*Box 4*), BTT to HT (*Box 5*) and MM (*Box 6*). The National Protocol for Assessment of Cardiothoracic patients lists below the medical indications for patients eligible for a HT.

BOX 3 Cardiothoracic Advisory Group of NHS Blood and Transplant criteria for urgent listing for HT

Need for:

- continuous inotropic treatment at high dose or in combination
- IABP with or without inotropic support
- mechanical circulatory support with a short-term device including venoarterial extracorporeal membrane oxygenation
- long-term LVAD support with device-related complications.

Or:

- exceptional cases outwith these criteria may be listed with permission from the chair of the advisory group.

IABP, intra-aortic balloon pump.

- End-stage heart disease with a life expectancy of between 12 and 18 months.
- NYHA class III or IV.
- Refractory to medical therapy, including, if necessary, cardiac resynchronisation therapy. (This assessment should be made by a cardiologist with a special interest in HF.)
- Usually < 60 years of age as there is an increase in comorbidity with the ageing process. However, consider biologically fit older patients.

In the next section of this report we describe the decision problem and research questions.

BOX 4 Pathway for BTT to VAD

Indication

Patients who are on the WL with rapidly deteriorating heart function and would not survive to get a HT or who are at increased risk of adverse events after HT.

Ventricular assist device implant

Patients receiving a VAD implant as a semi-elective procedure stay in an ICU approximately 3–5 days and spend 2 weeks in the ward. At the end of the second week they are discharged and called for regular follow-up.

Follow-up procedure

1. Drug treatment for heart failure

Patients are treated with the following drugs: diuretics, ACE inhibitors, angiotensin II receptor antagonist, beta-blockers, spironolactone (Aldactone®, Pharmacia Ltd), warfarin, statins, digoxin.

2. Follow-up visit

Fortnightly visits occur for 1 month, and then the patient has monthly visits for 3–4 months and then every 3 months.

Serious adverse events

Patients' post-VAD implant survive with relatively few adverse events. Ten per cent of the patients present with bleeding from either nose or gut and they get admitted and are transfused with blood products for 4–5 weeks. Incidence of infection is relatively rare and occasionally patients present with infection at the VAD exit site are treated with intravenous antibiotics for 1 week.

ICU, intensive care unit.

BOX 5 Pathway for HT

Indication

Appropriate candidate for HT.

Heart transplant

Patients' post-HT stay in an ICU for approximately 3–5 days and spend 2 weeks in a ward. At the end of the hospital stay they are discharged and called for regular follow-up visits.

Follow-up procedure

1. Follow-up medication

Patients are treated with the following drugs: patients receive antiviral prophylaxis against cytomegalovirus, valganciclovir (Valcyte®, Roche) 900 mg once daily for 3 months (about one-third of the patients will need it for 6 months). All patients receive rabbit antithymocyte globulin, three doses per day, tacrolimus (Prograf®, Astellas Pharma US, Inc.) 1 mg per day, mycophenolate mofetil (Cellcept®, Roche) 2.5 g per day and prednisolone 12.5 mg per day.

2. Follow-up visits

Fortnightly visits occur for 1 month, then monthly visits for 3–4 months and after that visits are every 3 months.

3. Investigations

Patients have approximately 12–14 endomyocardial biopsies per year and coronary angiography is usually performed once a year.

Serious adverse events

Adverse events post HT are relatively rare. A patient may experience rejection or infection in the first year and is treated with methylprednisolone 750 mg per day and ganciclovir (Cytovene®, Roche) 5 mg/kg. Fifteen per cent of patients post HT are at risk of getting skin cancer and as the overall survival increases, patients are prone to coronary artery disease in 6–10 years' time.

ICU, intensive care unit.

BOX 6 Pathway for MM patients

Patients are medically managed at home with oral medications while awaiting HT. Forty-five per cent of patients are admitted to hospital with severe HF and are treated with intravenous inotropes. They are admitted to the ICU approximately once per 6 months and either improve or are given urgent VAD implant in 10–15% of cases.

1. Patients are medically managed at home with oral medications

Patients are treated with the following drugs: diuretics, ACE inhibitors, angiotensin II receptor antagonist, beta-blockers, spironolactone, warfarin, statins, digoxin.

Some HF patients are managed with implantable cardioverter defibrillators and biventricular pacemaker.

2. Patients who are admitted to hospital are managed with intravenous inotropes

Enoximone 5 µg/kg/minute and dopamine 5 µg/kg/minute.

Fifty per cent of patients admitted to ICU with acute HF are treated with an IABP, 30% require haemofiltration and a few patients with end stage HF are treated with extracorporeal membrane oxygenation.

IABP, intra-aortic balloon pump; ICU, intensive care unit.

Chapter 2 Definition of the decision problem

The purpose of this section is to specify the decision problem and to translate it into research objectives. A copy of the protocol is included in *Appendix 1*.

Decision problem

In patients with advanced HF who are eligible for HT, VADs are used as a BTT in patients in the UK. There are a number of newer devices and it is important to know the cost-effectiveness of devices used in this way in comparison with MM.

Research suggests that HT is likely to offer the best treatment option in terms of both improved survival and QoL for these patients.[1] However, HT is dependent on the availability of donor hearts and availability appears to be diminishing. Therefore, it is valuable to know the comparative cost-effectiveness of VADs used as an ATT compared with HT. (Note: it is our understanding that VADs are currently funded for use in the UK as a BTT and not as an ATT or as a DT.) Outcomes to be investigated include survival, adverse events, reasons for death, QoL and functional status.

Research questions

In patients aged ≥ 16 years with advanced HF who are eligible for HT:

1. What is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as a BTT compared with MM?
2. Where data permit, what is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as an ATT in comparison with their use as a BTT therapy?

Overall aims and objectives of assessment

Objectives

1. To summarise previously published HTA reports by Clegg *et al.*[4] and Sharples *et al.*[30] on VADs.
2. To undertake a systematic review and evidence synthesis of the relevant clinical effectiveness and cost-effectiveness literature.
3. To further develop the cost-effectiveness and cost–utility models developed in the 2006 HTA: *Evaluation of the ventricular assist device programme in the UK* and where possible to compare the use of VADs as BTT firstly to MM and secondly as ATT.
4. To investigate the factors that drive cost-effectiveness estimates.
5. To report on findings and make recommendations for future research.

Chapter 3 Review of clinical effectiveness

In this chapter we describe the methods and results of the clinical effectiveness systematic reviews.

Methods for reviewing clinical effectiveness

Identification of literature

Identification of publications

Initial scoping searches were undertaken to assess the volume and type of literature relating to the assessment question. A search strategy was then developed which focused the searches on VADs meeting the inclusion and exclusion criteria (see *Inclusion criteria* and *Exclusion criteria*). All searches were undertaken in February and March 2012.

Scoping searches were undertaken to inform the development of the search strategy. An iterative procedure was used, with input from clinical advisors and previous HTAs (e.g. Clegg *et al*.[4] and Sharples *et al*.[30]).

A copy of the search strategy that was used in each of the major databases is provided in *Appendix 2*. This search strategy developed for MEDLINE was adapted as appropriate for other databases. The strategy was designed to capture generic terms for VADs and the specific product names of second- or third-generation, FDA- or CE-approved devices. The search was date limited from 2003 to February/March 2012 (this avoided the retrieval of a large number of literature concerning first-generation VADs, which were outside the remit of the report; see Clegg *et al*.[4] and Sharples *et al*.[30] for further information on first-generation VADs). Studies of patients aged < 16 years and non-English-language studies were excluded. There were no limits for study design at the searching stage. All retrieved papers were screened for potential inclusion.

The search strategy involved the following main elements:

- searching of electronic bibliographic databases
- contact with experts in the field
- scrutiny of references of included studies
- screening of manufacturers websites for relevant publications.

Databases searched

Databases searched included MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database [including Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and HTA databases]; Science Citation Index and Conference Proceedings (Web of Science); UK Clinical Research Network (UKCRN) Portfolio Database; Cumulative Index to Nursing and Allied Health Literature (CINAHL); PsycINFO; and the National Library of Medicine (NLM) Gateway (US Meeting Abstracts and Health Services Research Projects in Progress) were searched. The following trial databases were also searched: Cochrane Central Register of Controlled Trials (CENTRAL); Current Controlled Trials; and ClinicalTrials.gov.

In addition, the reference lists of relevant articles were checked, and the manufacturers' websites screened for relevant publications. Also, the online resources of various regulatory bodies, health services research agencies and professional societies were consulted via the Internet. These included:

(a) HTA organisations (including the National Institute for Health Research and the National Research Register Archive)

(b) INTERMACS
(c) NHS Blood and Transplant (including the Cardiothoracic Transplant Advisory Group)
(d) Ventricular Assist Device Forum, National Specialised Commissioning Team
(e) The International Society Heart & Lung Transplantation
(f) Eurotransplant
(g) Scandiatransplant
(h) US Transplant
(i) The Transplantation Society
(j) British Transplantation Society
(k) Medicines and Healthcare products Regulatory Agency
(l) US FDA.

Citation searches of included studies were undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles were also checked.

Inclusion criteria

Study design

We included:

1. studies of VADs with FDA/CE approval
2. studies with a minimum of 50 participants in the approved VAD group
3. studies including both FDA/CE-approved and multiple unapproved VADs

    i. approved VADs had to be recorded and analysed separately or
    ii. if they were not analysed separately, at least 80% of the included devices had to be FDA/CE approved.

Studies with control groups (i.e. RCTs, cohort studies, case–control studies) and systematic reviews of studies with control groups were included. Case series were included if they reported on adverse events and if they reported on consecutive patients.

Interventions

Interventions included second-generation axial CF pumps and third-generation bearingless CF pumps; LVADs, RVADs and BiVADs currently approved by the FDA and/or CE and in current clinical use in the UK as a BTT; and LVADs, RVADs and BiVADs currently approved by FDA and/or CE and used as potential long-term ATT for people with advanced HF. Studies with a mixture of generation devices were considered if data for second- or third-generation devices were presented separately to first-generation devices (see *Study design*).

Comparators

Comparators included MM and HT; studies that compared two different VADs approved for intervention were also included. Studies comparing first-generation devices with second- or third-generation devices were used to extract data on second- or third-generation devices only.

Population

Participants (aged $\geq$ 16 years) with advanced HF and considered suitable for receipt of a LVAD, RVAD and BiVAD as a BTT or as potential long-term ATT. Studies which reported BTT and DT participants, but which did not distinguish outcomes according to therapy, were included for purpose of complete information, but outcome data were not included in the main text.

Outcomes

We investigated survival, adverse events, reasons for death, QoL and functional status (e.g. change in NYHA functional classification).

Exclusion criteria

The following exclusion criteria were applied:

(a) studies in which 20% patients were known to be receiving VADs as DT
(b) PVAD
(c) TAH
(d) first-generation pulsatile volume displacement pumps
(e) devices yet to be FDA or CE approved
(f) devices for 'bridge to decision'
(g) post-transplant mechanical circulatory support devices for primary graft failure
(h) studies involving VADs in conjunction with other interventions where it was not possible to separate out the effects of the different interventions on outcomes
(i) animal models and post-mortem studies
(j) preclinical and biological studies
(k) editorials and opinions
(l) reports published as meeting abstracts only, where insufficient methodological details were reported to allow critical appraisal of study quality
(m) studies not in English
(n) studies before the year 2003
(o) case series reports with < 50 cases or where patient recruitment was not consecutive.

Data abstraction strategy

A record of all papers rejected at full-text stage and reasons for exclusion was documented. Titles and abstracts of retrieved studies were examined for inclusion by two reviewers independently. Disagreement was resolved by retrieval of the full publication and consensus agreement.

The full data were extracted independently by one reviewer using a data extraction form informed by the NHS Centre for Reviews and Dissemination (CRD)[54] and previous HTA reports[4,30] (see *Appendix 3* for the complete data extraction forms, this includes publications which did not separate outcomes for BTT patients from DT patients and which are not included in the main text of the report). All studies were checked by a second researcher, and any disagreements were resolved by discussion. Further discrepancies were resolved with involvement of a third reviewer. Data were extracted to allow quality assessment of the included studies.

Critical appraisal strategy

Quality criteria were applied independently by two reviewers and an agreed overall quality assessment was determined for each paper. Any disagreements were resolved by independent assessment by a third reviewer. Included studies were assessed using the following recognised quality assessment scales and/or checklists. Systematic reviews were assessed using criteria developed by NHS CRD.[54] Experimental and non-experimental studies were assessed using an adapted set of criteria developed by Thomas *et al*.[55] Each study was scored according to (a) selection of participants; (b) study design; (c) confounders; (d) blinding; (e) data collection methods; (f) withdrawal and dropout; and (g) integrity and analysis (see *Appendix 4* for further details on quality assessment).

Methods of data synthesis

Data were tabulated and discussed in a narrative review based on indication for treatment, type of VAD, quantity and quality of research evidence, representativeness and outcomes. The remit of this report was to consider BTT but not DT. Some publications presented aggregate results for both groups; such aggregate results are not relevant to BTT, but for completeness we report such results in *Appendix 3*.

Where data specific to BTT patients could be extracted from any publication these are also included in the main text of the report. Outcome results are given for BTT patients with published data selected so as to avoid double counting from overlapping populations.

We analysed patient populations in each included study for overlap between studies, and developed a 'family tree' to ascertain which data set included the most recent data on the largest number of unique patient records (as earlier, smaller studies fed into larger, later studies). For each device, we used the largest/latest data set of separately identifiable patients to report baseline characteristics and adverse events.

Baseline characteristics were listed as means for continuous variables and percentages for binary variables. Ninety-five per cent CIs were calculated. Where possible, the reported data for subgroups were combined to obtain a value for the whole study population. Pooling of study baseline characteristic values was undertaken using a random-effects model in MetaAnalyst Version Beta 3.13 (Tufts Medical Centre, Boston, MA, USA) software. Narrative syntheses were used to describe outcomes.

Clinical effectiveness results

Outcomes for each device are reported separately. Outcomes assessed included adverse events, causes of death, functional status and QoL. Again, we adjusted our reporting for double counting caused by inclusion of multiple, overlapping patient populations in studies. Survival analyses findings were included as reported and are further described in the results section by device.

Quantity and quality of research available

A flow chart describing the process of identifying relevant literature on the clinical effectiveness of VADs can be found in *Figure 4*. Following the removal of duplicates, our searches identified 4325 potentially

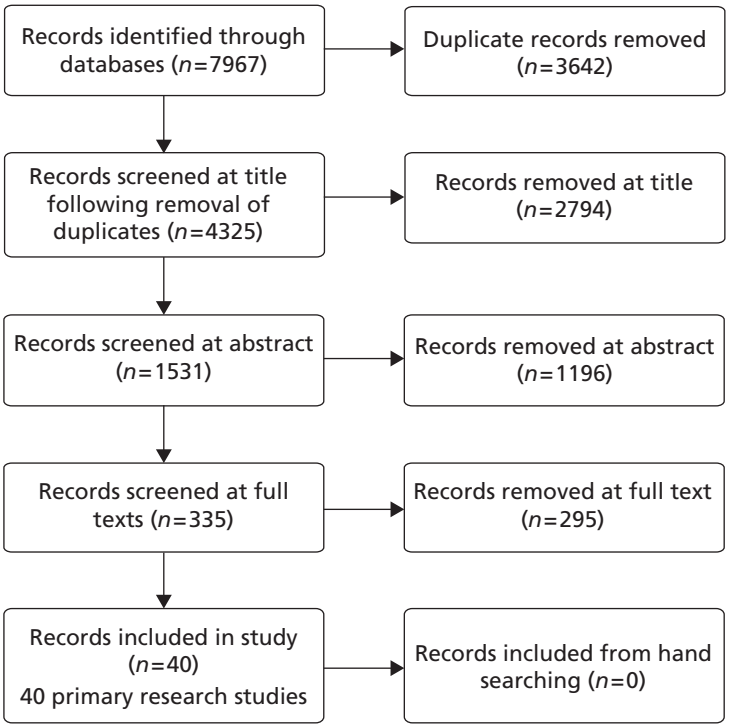


FIGURE 4 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram: summary of study selection and inclusion.

relevant articles. We removed 2794 articles which did not meet our inclusion criteria at title sift, leaving 1531 articles to be screened at abstract sifting stage. A total of 1196 articles were removed at abstract sift because they did not meet inclusion criteria, leaving 335 articles to be sifted at full-paper stage. A total of 40 publications[42,52,53,56–92] met the current inclusion criteria and reported findings on the following devices: HMII ($n = 29$);[52,53,56–82] HW ($n = 1$);[83] Berlin Heart INCOR ($n = 1$);[86] DuraHeart ($n = 2$);[42,85] MicroMed DeBakey ($n = 1$);[84] and mixed devices ($n = 6$).[87–92] Included papers were published between 2003 and 2012.

Seven systematic reviews were identified. After full investigation it was concluded for each one that the majority of their included studies and patients did not meet the inclusion criteria and these reviews were therefore rejected.

A list of the 288 articles that were excluded at full paper sift with reasons for exclusion is provided in *Appendix 5*.

Tables 3–8 provide a summary of the 40 included publications by type of VADs reported and reasons for VAD use.

Types of device used

Of the 29 included studies[52,53,56–82] involving HMII, 22 studies[53,56–59,61–65,67–71,73–75,77–80] presented data on HMII alone. Five studies[60,72,76,81,82] compared HMXVE with HMII. One study[66] compared HMI with HMII, and a further study[52] compared HMII with other devices (type not reported). One study[83] reported on HW only, one study[84] involved MicroMed DeBakey VAD only, one study[86] involved Berlin Heart INCOR only, and two studies[42,85] involved DuraHeart only.

A further six studies[87–92] reported a mixture of devices but data by device were not reported separately.

Reasons for use of ventricular assist devices in included studies

Studies reported mixed reasons for use of VADs. For example, of the 29 HMII studies,[52,53,56–82] 12 studies[52,57,58,64,65,67,70,71,73–75,82] reported that treatment was for BTT, 12 studies[53,56,59,60,62,72,76–81] reported that treatment was for BTT and DT, one study[68] reported that treatment was for BTT or DT or BTR and the remaining four studies[61,63,66,69] did not report reason for treatment.

Delineating multiple overlapping populations between publications

Many of the identified publications investigated overlapping populations; this was especially true for studies of HMII, most of which were conducted in the USA. Also, in some studies the patient group received different devices and authors did not report results separately for each of the several devices investigated. There were many studies in which different patients were given bridge or destination therapies; however, in most of these outcomes were not reported according to indication.

The US HMII publications can be classified as (a) from single centres ($n = 14$); (b) deriving from the multicentre FDA approval study and its extension ($n = 12$); and (c) multicentre registry studies.

Starling *et al.*[52] and John *et al.*[65] reported on HMII, while Nativi *et al.*[89] indicated the number of HMII recipients but reported data for a mix of different VADs. In 12 of the single-centre studies[53,56,59,60,62,72,76–81] both DT and BTT patients were included, or indication was not clearly defined; none of these analysed results separately for BTT patients. The other two single-centre publications (Petrucci *et al.*[74] and John *et al.*[64]) reported results for BTT patients, but these single centres appear to have contributed participants to the FDA approval group of multicentre publications. The FDA approval study publications reflect the gradual accrual of more patients and multiple publications have been produced for overlapping groups of patients. Five of these publications[58,59,65,67,82] report on the same 469–486 participants by either dichotomising the population by various criteria,[67,82] focusing on a particular outcome,[58] combining BTT patients with HMII DT patients,[59] or not separating the outcome data according to therapy received. Registry studies, including John *et al.*[65] and Starling *et al.*,[52] reported on post-approval HMII BTT patients

TABLE 3 Studies involving HMII and reason for treatment (*n*=29)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Adamson	2011	USA	56	55	HMII only	Both DT and BTT Results NR separately
Bogaev	2011	USA	57	465	HMII only	BTT
Boyle	2009	USA	58	331 (from 469 HMII population)	HMII only	BTT
Brewer	2012	USA	59	896 (486 BTT)	HMII only	Both DT and BTT BTT: underweight 23 (48%); normal 305 (51%); obese 108 (66%); extremely obese 50 (57%)
Cowger	2010	USA	60	78	HMXVE and HMII	Both DT and BTT BTT: 69 (88%) [HMII: 54 (90%); HMXVE: 21 (84%)]
Demirozu	2011	USA	61	172	HMII only	NR
Hasin	2012	USA	62	83	HMII only	Both DT and BTT BTT: overall sample 27/83 (32%); GFR < 60 ml/minute/1.73 m^2 group 15/54 (28%); GFR > 60 ml/minute/1.73 m^2 group 12/29 (41%)
John	2010	USA	63	486, of whom 250 underwent HT	HMII only	NR
John	2011	USA	64	102	HMII only	BTT
John	2011	USA	65	1982	HMII only	BTT
Kato	2012	USA	66	342	HMI and HMII	NR
Kormos	2010	Unclear	67	484	HMII only	BTT
Lahpor	2010	European countries	68	184	HMII only	DT, BTT and BTR BTT (73%); DT (21%); BTR (6%)
Martin	2010	USA	69	145	HMII only	NR
Miller	2007	USA	70	133	HMII only	BTT
Pagani	2009	USA	71	281	HMII only	BTT
Pak	2010	USA	72	130	HMXVE and HMII	Both DT and BTT 13 HMXVE patients (19.4%) and 10 HMII patients (15.9%) received devices with DT as the initial goal ($p = 0.530$)

TABLE 3 Studies involving HMII and reason for treatment (*n*=29) (*continued*)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Pal	2009	USA	73	281	HMII only	BTT
Petrucci	2009	USA	74	93	HMII only	BTT
Rogers	2010	USA	53	655	HMII only	Both DT and BTT BTT 281; DT 374
Russell	2009	USA	75	309	HMII only	BTT
Schaffer	2011	USA	76	133	HMXVE and HMII	Both DT and BTT BTT 93/133; DT 40/133 Results NR separately
Schaffer	2009	USA	77	86	HMII only	Both DT and BTT 57/86 BTT; 29/86 DT Results NR separately
Starling	2011	USA	52	338 (169 HMII)	HMII compared with other devices (not specified)	BTT
Strueber	2008	Multiple	78	101	HMII only	Both BTT and DT (split for survival only)
Topilsky	2011	USA	79	110	HMII only	Both DT and BTT 47 DT; 29 BTT
Topilsky	2011	USA	80	76	HMII only	Both DT and BTT RCM/HCM: 6/8 BTT; I/D: 21/75 BTT; others DT
Uriel	2010	France	81	79	HMXVE and HMII	Both DT and BTT Results NR separately
Ventura	2011	USA	82	1157	HMXVE and HMII	BTT

D, dilated cardiomyopathy; GFR, glomerular filtration rate; HCM, hypertrophic cardiomyopathy; I, ischaemic heart disease; NR, not reported; RCM, restrictive cardiomyopathy.

TABLE 4 Studies involving HW and indication for treatment (*n*=1)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Strueber	2011	Multiple	83	50	HW only	BTT

TABLE 5 Studies involving MicroMed DeBakey VAD and indication for treatment (*n*=1)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Goldstein	2003	European countries	84	150	MicroMed DeBakey VAD	BTT

TABLE 6 Studies involving DuraHeart VAD and indication for treatment (*n*=2)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Morshuis	2009	Multiple	85	68	DuraHeart only	BTT
Morshuis	2010	Multiple	43	82	DuraHeart only	BTT

TABLE 7 Studies involving INCOR (Berlin Heart) and indication for treatment (*n*=1)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Schmid	2008	Multiple	86	216	INCOR (Berlin Heart)	Both DT and BTT

TABLE 8 Studies involving a mixture of devices (where data by device were not reported separately) and indication for treatment (*n*=6)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Drews	2010	Germany	87	174	Berlin Heart EXCOR® (Berlin Heart, The Woodlands, TX, USA), Novacor® (World Heart Corp., CA, USA), LionHeart LVD 2000® (Arrow International, PA, USA), HMI, Berlin Heart INCOR, MicroMed DeBakey, HMII, DuraHeart and Jarvik 2000	All devices were implanted primarily for long-term support and not as a BTT
Klotz	2006	Germany	88	130	Continuous LVAD: MicroMed DeBakey or INCOR Berlin Heart Pulsatile LVAD: Novacor or HM	NR
Nativi	2011	USA	89	8557	Pulsatile LVAD: HMIP® (Thoratec Inc., Pleasanton, CA, USA), HMVE® (Thoratec Inc., Pleasanton, CA, USA), HMXVE, Novacor PC® (Novacor, Oakland, CA, USA), Novacor PCq® (Novacor, Oakland, CA, USA), Thoratec® (Thoratec Inc., Pleasanton, CA, USA) and Toyobo® (Toyobo-National Cardiovascular Centre, Osaka, Japan) Continuous LVAD: HMII, Jarvik 2000, MicroMed DeBakey and VentrAssist® (Ventracor Ltd, Sydney, Australia)	BTT

TABLE 8 Studies involving a mixture of devices (where data by device were not reported separately) and indication for treatment (n=6) (*continued*)

First author	Date	Country	Reference number	*n*	VADs reported	Reason for VAD use
Oswald	2010	Germany	90	61	HMII and HW	NR
Sandner	2009	Austria	91	86	MicroMed DeBakey VAD, HVAD® (HeartWare Inc., Miami Lakes, FL, USA) and DuraHeart LVAD	BTT
Sandner	2009	Austria	92	86	MicroMed DeBakey VAD, HVAD and DuraHeart LVAD	BTT

NR, not reported.

who were not participants in the FDA extension study. We consider it likely that the 169 patients reported in Starling *et al*.[52] are participants in the analysis by John *et al*.[65] The International Society for Heart & Lung Transplantation (ISHLT) registry report by Nativi *et al*.[89] included 417 patients who received later generation LVADs for BTT. Of these, 291 were implanted with the HMII device and some were likely to also be participants in the FDA approval study or its extension although outcome results for HMII were not reported.

Figure 5 attempts to summarise the 'family tree' of the large number of US HMII VAD publications. As publications lacked sufficient detail, these relationships between publications cannot be stated with total certainty and it would be valuable to confirm this diagram with the authors. A similar situation of overlapping patient populations applies to the other included publications. These reported on a single device other than HMII, or reported results from studies conducted at European centres employing a mix of LVADs or the HMII device. There were two publications about HMII use with European patients;[68,78] these included both BTT and DT patients. In Lahpor *et al*.[68] outcomes were not stratified by therapy and in Strueber *et al*.[78] the only outcome reported according to therapy was survival. The relationship between these is summarised in *Figure 6*. The European multicentre study of patients implanted with the HMII device for BTT, DT or BTR, by Lahpor *et al*.[68] (n = 184), included the patients (n = 101) reported separately by Strueber *et al*.,[78] and possibly some of the patients in the mixed VAD studies by Drews *et al*.[87] and Oswald *et al*.[90] The two BTT publications by Sandner *et al*.[91,92] examined the same 86 patient population (who received an amalgam of several devices which did not include HMII and results were not stratified according to device). The source of patients for the multiple device studies by Klotz *et al*.[88] and Drews *et al*.[87] were single German centres. Two publications of the DuraHeart (Morshuis *et al*.[42,85]) investigated almost identical patient populations differing slightly in size (n = 68[85] and n = 82[42]). A single-centre publication describing 79 HMII patients (BTT n = 64, BTT and DT n = 15) did not identify the centre and it was uncertain if this was a French or US study.[81]

The overlapping inter-relationship of populations described above, especially notable for HMII studies, renders any summary of baseline characteristics or of outcome results problematic if double counting is to be avoided. Therefore, where duplication of patients was judged to occur we have included the largest and/or most recent study of the cohort, conditional on availability of data. However, because of the multicentre nature of many of the HMII studies and authors' contention that experience with LVADs over time has influenced study results for some outcomes, we have occasionally also discussed earlier and smaller studies. We have organised baseline characteristics and outcome results according to device; in the main text we have not considered results for DT patients, or where results combine DT and BTT patients, or where this distinction was unclear. For full data on all baseline characteristics, and on outcome results irrespective of therapy, please consult *Appendix 3*.

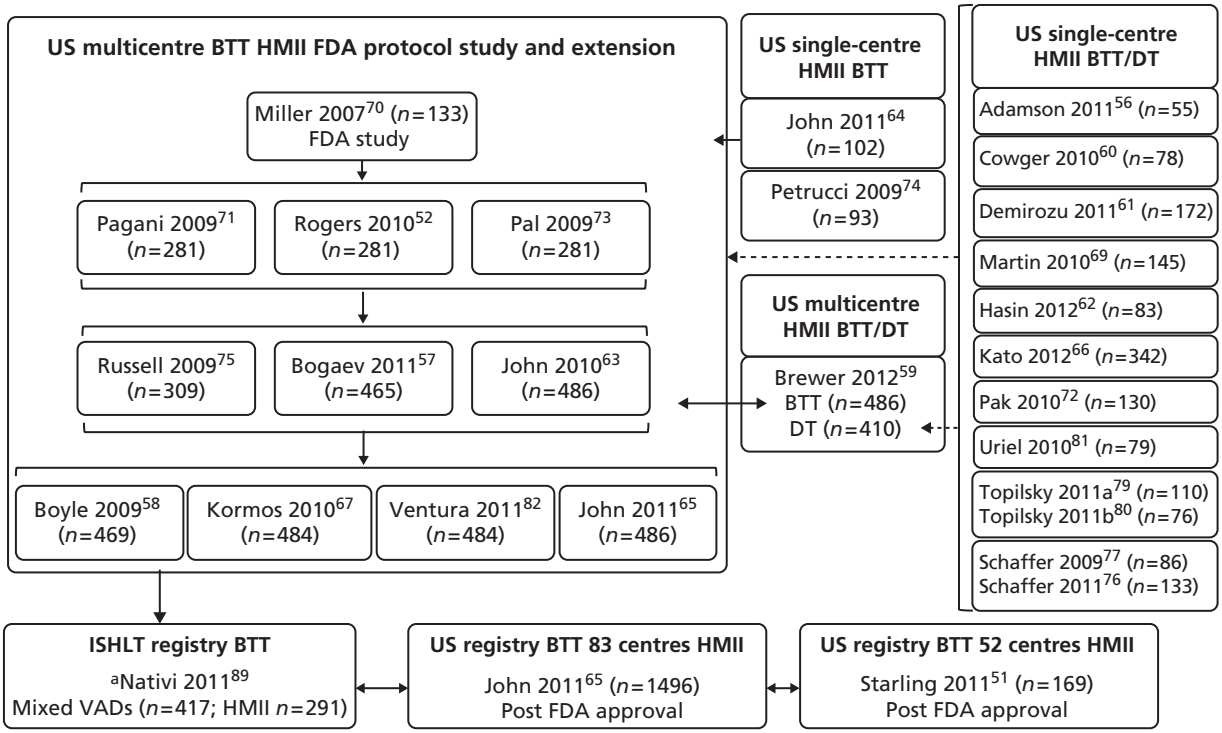


FIGURE 5 Summary of relationships between the included US HMII publications. All US multicentre BTT HMII FDA protocol publications shared patients with each other; the John 2010[63] publication reported on 250 patients who received a HT out of 486 BTT participants. The multicentre study by Brewer 2012[59] combined the 486 FDA study patients with 410 DT patients but did not report results separately according to therapy, some of the DT patients may have come from the single-centre studies. Among the US HMII single-centre publications, those of Petrucci 2009[74] and John 2011[64] contributed patients to the multicentre BTT HMII FDA protocol study. All other US HMII single-centre studies ($n = 12$) included both BTT and DT patients in single analyses (i.e. results not separated according to therapy) or did not state if patients received BTT or DT (Demirozu 2011,[61] Martin 2010[69] and Kato 2012[66]). The two studies of Topilsky 2011[79,80] investigated overlapping populations as also did the two studies by Schaffer 2009,[77] 2011.[76] The Nativi 2011[89] registry study may have included HMII patients from the FDA protocol study extension and may have included patients common to John 2011[65] which in turn included the patients from Starling 2011.[52] Solid arrows indicate publications that almost certainly shared participants and dashed arrows represent publications that probably shared patients. Numbers of patients are shown in brackets. a, CF VAD numbers only, data for HMII not reported separately; pulsatile VADs ($n = 1980$) excluded.

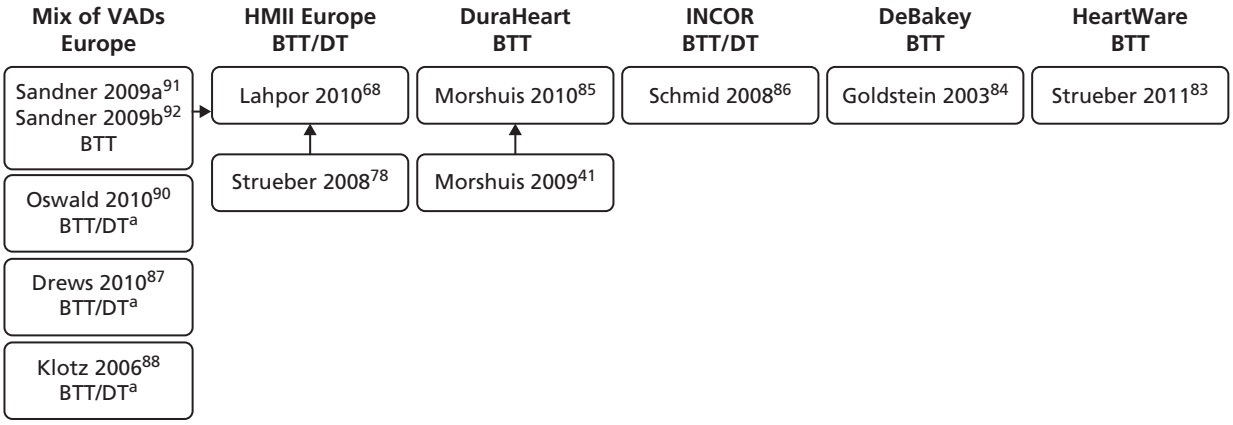


FIGURE 6 Summary publication relationships: non-HMII single-device publications and European centre studies. One single-device publication was included for each of the INCOR, HW (centres in Europe and Australia) and MicroMed DeBakey devices. The INCOR study included both BTT and DT patients but results were not reported by therapy. The two DuraHeart publications had overlapping populations. Solid arrows indicate publications that almost certainly shared participants and dashed arrows represent publications that probably shared patients. a, The Drews 2010[87] population was 'relatively contraindicated for HT'; the reports of Oswald 2010[90] and Klotz 2006[88] were also unclear on proportions BTT or DT patients.

Overall quality assessment

The 40 primary included publications[42,52,53,56–92] were each quality assessed using an adapted set of criteria developed by Thomas *et al*.[55] For completeness, see *Appendix 4* for copies of the quality assessment sheets for each publication.

Selection of participants

The methodological strength of the studies in terms of population representativeness and selection bias varied: 38 studies[42,52,53,56–58,60–89,91,92] were rated moderate and two studies[59,90] were rated weak. Individuals selected to participate in the studies were considered to be 'somewhat likely' to be representative of the target population in just under half of the studies ($n = 17$).[52,53,56,59,64–67,70,71,73–75,82–84,87] Two studies[69,88] were not likely to be representative, and in 21 studies[42,57,58,60–63,68,72,76–81,85,86,89–92] it was not possible to tell.

Study design

There were no RCTs included in the 40 publications.[42,51,52,56–92] No publications reported on a comparison group who received MM or best supportive care. Likewise, no publications reported on direct comparisons between VADs and HT. Some publications reported outcomes (e.g. on clinical functioning or functional assessment/QoL) using patients as their own controls (before–after designs) or within-study comparison on the basis of baseline characteristics such as age > 70 years.

Fourteen publications[42,52,53,63,64,70,71,73–75,83–85,90] used a prospective design; mostly these were single-arm studies either using routine-collected data in registry studies or collecting de novo data. Some of these prospective studies reported used a mixture of data collection methods including both prospective and retrospective data.

Twenty-five publications[42,52,53,63,64,70,71,73,74,75,83–85,90] reported a retrospective design (e.g. based on retrospective case note review).

Confounders

Two publications[73,80] were rated as strong in relation to dealing with confounding factors and 33[42,52,53,56–67,69–71,75–79,82–88,91,92] of the 40 publications were rated as moderate overall. Problems related to important differences between groups prior to the intervention and the percentage of relevant confounders that were adjusted for in analysis. Five publications[68,72,81,89,90] were rated weak on this quality criterion.

Blinding

It was considered that 37[42,52,53,56–73,76–81,83–92] of the 40 publications had weak overall blinding, one publication[82] was rated moderate and two publications[74,75] as strong. In the 37 publications[42,52,53,56–73,76–81,83–92] the outcome assessor was aware of the intervention or exposure status of participants. Interestingly, only 12 publications[42,57,61,63,65,70,71,73,74,83–85] reported that participants were aware of the research question.

Data collection methods

Overall, the data collection methods of eight[42,73,75,76,85,89,91,92] of the studies were rated strong, of 23[52,53,56,57,59–65,67,70–72,74,79,82–84,86,87,90] as moderate and of nine as weak.[58,66,68,69,77,78,80,81,88] In 24 publications[42,52,53,56,59,62–64,67,69–76,83–85,89–92] the data collection tools were shown to be valid; in the other 16 publications[57,58,60,61,65,66,68,77–82,86–88] it was not possible to tell. Eighteen publications[42,52,63,64,70,71,73–76,79,83–86,89,91,92] reported that the data collection tools were shown to be reliable, three were not reliable,[58,60,80] and in the remaining 19 publications[53,56,57,59,61,62,65–69,72,77,78,81,82,87,88,90] it was not clear.

Withdrawal and dropout

Thirty-seven publications[42,52,56–81,83–86,88–92] reported an 80–100% completion rate for study participants. Of these, 15 studies[57–60,62–65,70–74,83,90] detailed numbers of dropouts and reasons. Overall, the methodological considerations relating to dropouts were considered strong in 17 publications,[57–65,70,71,73,74,83,84,87,90] moderate in 21 publications[42,52,66–69,72,75–82,85,86,88,89,91,92] and the remaining two weak.[53,56]

Integrity

In all but one study 80–100% of participants received the intervention of interest.[42,52,53,56–82,84–92] Two publications[62,89] measured the consistency of intervention, five[56,65,69,85,87] did not and in 33 publications[42,52,53,57–61,63,64,66–68,70–84,86,88,90–92] it was not possible to tell either way. Eighteen publications[42,56,66,68,69,72,76–81,85,86,88,89,91,92] reported that participants were likely to have received an unintended intervention that may have influenced the results. In the remainder it was not possible to tell.[52,53,57–65,67,70,71,73–75,82–84,87,90]

Analysis

This section of quality assessment included unit of allocation, unit of analysis, use of appropriate statistical method and whether the analysis was performed by intervention allocation status rather than the actual intervention received. In all 40 publications,[42,52,53,56–92] the unit of allocation and analysis was the patient. Twenty-eight publications[42,52,53,56,57,59,61,62,64–67,69–76,80,83–85,87,89,91,92] reported statistical methods that were deemed appropriate, in four[60,63,68,88] statistical methods were not appropriate and in eight[58,77–79,81,82,86,90] it was not possible to tell. In 30 publications[42,57–71,73,76–81,85–87,89–92] it was not possible to tell how the analysis was performed.

Summary

For the 40 included publications, overall quality ratings were as follows: one study was rated strong,[75] 15 studies as strong to moderate,[42,52,53,64,70,71,73,76,80,83–85,89,91,92] 13 studies as moderate,[56,57,59,62,63,65–67,74,79,82,86,87] 10 studies as moderate to weak[58,60,61,68,69,72,77,78,88,90] and one study as weak.[81]

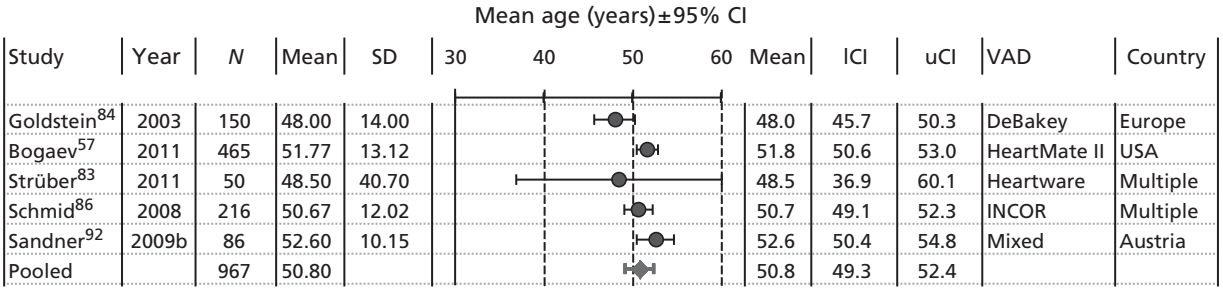
Overall, the study designs were not strong: studies were likely to be only moderately representative of underlying populations, there were no randomised trials and blinding of outcomes assessors was weak. Most patients received the intervention they were anticipated to receive although this criterion is not relevant for the 25 retrospective designs. Data collection methods and recording of withdrawal and dropout were moderate. Analysis was deemed appropriate for the majority of studies and most studies attempted to deal with confounding. Detailed quality assessment reports for each study are presented in *Appendix 4*.

Baseline characteristics

An apparent 19,161 participants were described in the 40 included publications; however, please see *Delineating multiple overlapping populations between publications*, which explains the issue of multiple reporting of patients by publications. The majority of the studies took place in the USA ($n = 27$); others were listed as taking place in Germany ($n = 3$), Europe specifically ($n = 2$), Austria ($n = 2$), unclear ($n = 1$) and multiple counties ($n = 5$).

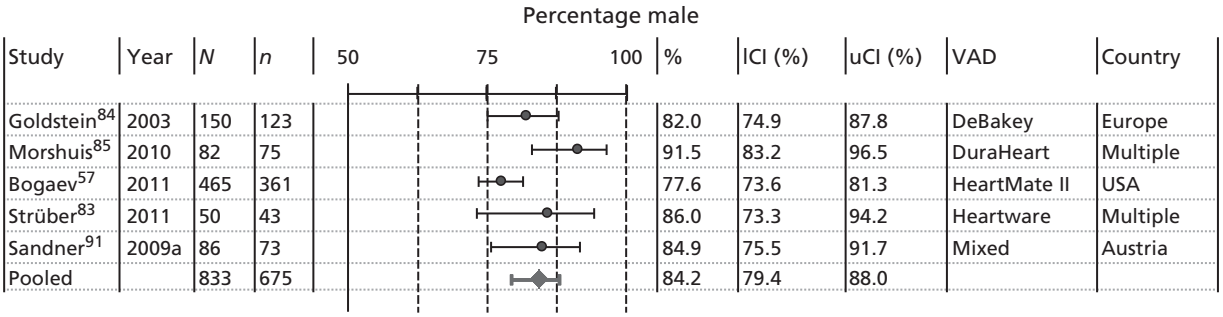
All included studies reported some baseline characteristic values for the population investigated, one study reported five[84] baseline characteristics while two others reported 43.[79,80] Method of reporting varied; for example, age was reported as a mean (standard deviation; SD), a median with range, a proportion or percentage within each of several defined age bands or as a combination of these methods. Some authors reported data for subgroups only but, where possible, subgroups have been combined to provide a value for the whole study population. Authors frequently used baseline characteristics in regression analyses attempting to identify factors that influence outcomes of particular interest in their study (e.g. aortic insufficiency,[60,72] renal function[62] and stroke[58,81]).

The baseline characteristics of BTT patients are presented in *Figures 7–13*. To avoid double counting caused by overlapping populations, the largest or most recent publication from each known cohort, conditional on the availability of data, has been included. Pooled estimates are provided. If the two large registry studies by Nativi *et al*.[89] and John *et al*.[65] were to be included in pooling then pooled estimates would merely reflect their input; therefore, these have been omitted from pooling but where possible have been compared with the pooled estimate. A further difficulty concerns whether or not mixed-device



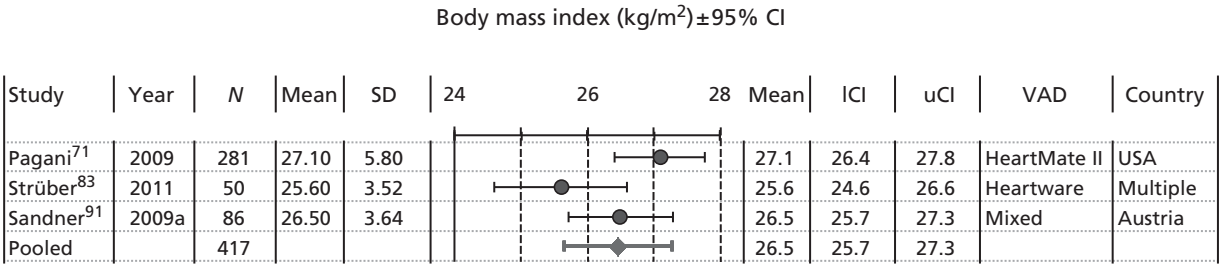
Study	Year	*N*	Mean	SD	Mean	lCI	uCI	VAD	Country
Goldstein[84]	2003	150	48.00	14.00	48.0	45.7	50.3	DeBakey	Europe
Bogaev[57]	2011	465	51.77	13.12	51.8	50.6	53.0	HeartMate II	USA
Strüber[83]	2011	50	48.50	40.70	48.5	36.9	60.1	Heartware	Multiple
Schmid[86]	2008	216	50.67	12.02	50.7	49.1	52.3	INCOR	Multiple
Sandner[92]	2009b	86	52.60	10.15	52.6	50.4	54.8	Mixed	Austria
Pooled		967	50.80		50.8	49.3	52.4		

FIGURE 7 Mean age at baseline for individual studies. (Note: studies with minimal population overlap with other studies; only BTT patients included.) There was statistical heterogeneity between studies ($I^2 = 64\%$). lCI, lower CI; uCI, upper CI.



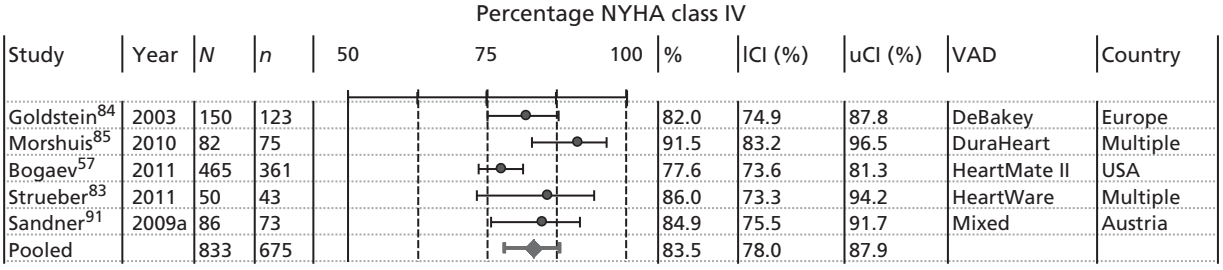
Study	Year	*N*	*n*	%	lCI (%)	uCI (%)	VAD	Country
Goldstein[84]	2003	150	123	82.0	74.9	87.8	DeBakey	Europe
Morshuis[85]	2010	82	75	91.5	83.2	96.5	DuraHeart	Multiple
Bogaev[57]	2011	465	361	77.6	73.6	81.3	HeartMate II	USA
Strüber[83]	2011	50	43	86.0	73.3	94.2	Heartware	Multiple
Sandner[91]	2009a	86	73	84.9	75.5	91.7	Mixed	Austria
Pooled		833	675	84.2	79.4	88.0		

FIGURE 8 Baseline number (%) of patients reported to be male. (Note: studies with minimal population overlap with other studies; only BTT patients included.) lCI, lower CI; uCI, upper CI.



Study	Year	*N*	Mean	SD	Mean	lCI	uCI	VAD	Country
Pagani[71]	2009	281	27.10	5.80	27.1	26.4	27.8	HeartMate II	USA
Strüber[83]	2011	50	25.60	3.52	25.6	24.6	26.6	Heartware	Multiple
Sandner[91]	2009a	86	26.50	3.64	26.5	25.7	27.3	Mixed	Austria
Pooled		417			26.5	25.7	27.3		

FIGURE 9 Baseline BMI (kg/m²). (Note: studies with minimal population overlap with other studies; only BTT patients included.) lCI, lower CI; uCI, upper CI.



Study	Year	*N*	*n*	%	lCI (%)	uCI (%)	VAD	Country
Goldstein[84]	2003	150	123	82.0	74.9	87.8	DeBakey	Europe
Morshuis[85]	2010	82	75	91.5	83.2	96.5	DuraHeart	Multiple
Bogaev[57]	2011	465	361	77.6	73.6	81.3	HeartMate II	USA
Strueber[83]	2011	50	43	86.0	73.3	94.2	HeartWare	Multiple
Sandner[91]	2009a	86	73	84.9	75.5	91.7	Mixed	Austria
Pooled		833	675	83.5	78.0	87.9		

FIGURE 10 Baseline number (%) of patients with NYHA IV classification. (Note: studies with minimal population overlap with other studies; only BTT patients included.) lCI, lower CI; uCI, upper CI.

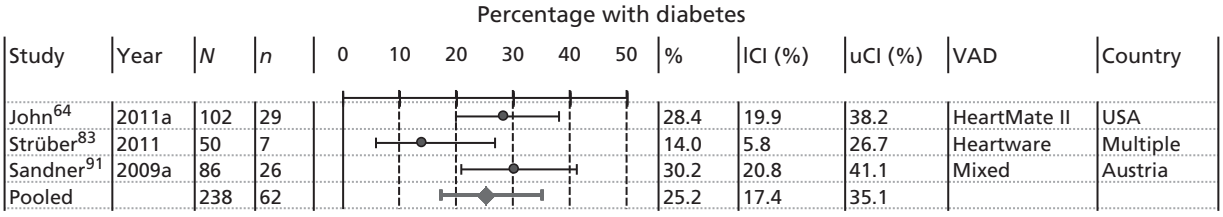


FIGURE 11 Baseline number (%) of patients with diabetes mellitus. (Note: studies with minimal population overlap with other studies; only BTT patients included.) lCI, lower CI; uCI, upper CI.

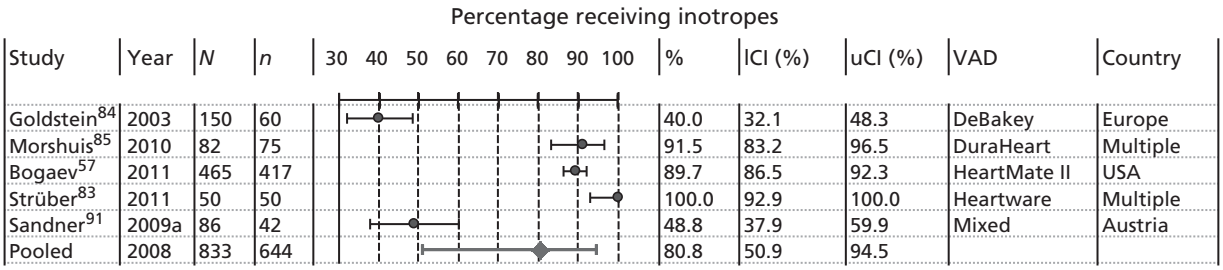


FIGURE 12 Baseline number (%) of patients using inotropes in non-overlapping studies of BTT patients. lCI, lower CI; uCI, upper CI.

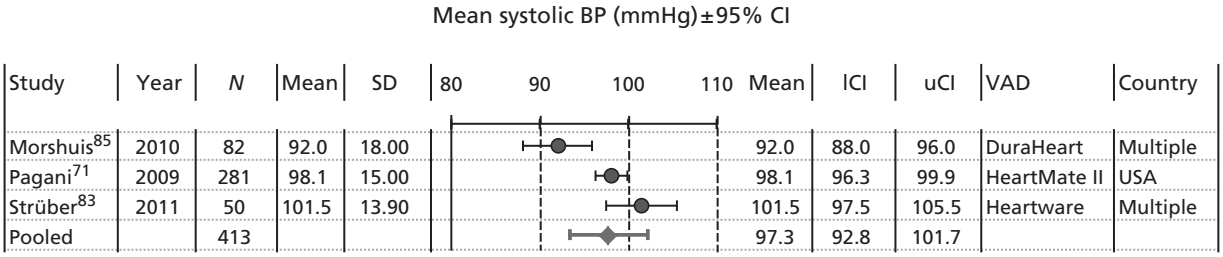


FIGURE 13 Baseline systolic BP (mmHg). (Note: Studies with minimal population overlap with other studies; only BTT patients included.) lCI, lower CI; uCI, upper CI.

studies should be included. We have included data from Sandner *et al*.[91,92] when reported, as overlap with other studies is likely to be minimal. Pooled estimates should be treated with extreme caution as they:

(a) may miss studies that should be included
(b) may not be representative either of all included studies or of all patients within a particular VAD study (most studies defined sampling frames and patient selection methods poorly)
(c) may include clinical heterogeneity and missing information (not all studies provided analysable information and we excluded studies with fewer than 50 patients).

Nevertheless, pooled estimates provide a picture of baseline characteristics of relevant populations receiving VADs.

Age

Where mean age was reported it varied between 45 years (Klotz *et al*.[88]) and 65 years (Adamson *et al*.[56]). Two large studies involving 1157[82] and 8557[89] participants reported comparable mean ages of 51 years. The distribution of mean age in the included non-overlapping studies of BTT patients is summarised in *Figure 7*. The pooled estimate was 50.8 years, and this is similar to the large registry study by Nativi *et al*.[89] of 8557 BTT LVAD patients, which found mean ages of 50.1, 50.2, 50.8, 51.4 and 51.8 years, respectively, in patients who received pulsatile first-generation LVADs, pulsatile second-generation LVADs, continuous second-generation LVADs and for second-generation patients (no LVADs) on inotropes and second-generation patients (no LVADs) not on inotropes.

Gender

The percentage of males in all these studies ranged from 68.5% (Lahpor *et al*.[68]) to 91.5% (Morshuis *et al*.[85]) (summarised in *Figure 8*).

The pooled estimate was 84% with moderate heterogeneity ($I^2 = 40\%$). Again, the combined result is similar to the large registry study of 8557 LVAD BTT patients reported by Nativi *et al*.[89] which found percentages of males to be 85.5%, 86.1%, 82.3%, 75.0% and 74.9% for pulsatile first-generation LVADs, pulsatile second-generation LVADs, continuous second-generation LVADs, second-generation patients on inotropes and second-generation patients not on inotropes respectively.

Race

White or Caucasian patients constituted 44.2% (Schaffer *et al*.[77]) to 95.1% (Oswald *et al*.[90]) of patient populations. The proportion of African American or black patients ranged between 6.6% (Topilsky *et al*.[79]) and 22.6% (Miller *et al*.[70]). All studies reporting race were undertaken in the USA. Studies were overlapping in terms of population and most reported a mix of destination and bridged therapies. Overall, there was limited reporting of race across all devices. The large registry studies (Nativi *et al*.[89] and John *et al*.[65]) ($n = 1496$) did not report race of patients.

Body mass index

Fourteen studies[59,62–65,71,72,77,81,83,86,88,89,91] reported baseline BMI (kg/m^2) of patients. All but one of the studies reported BMIs suggestive that patients were overweight.[59,62–65,71,72,77,81,83,86,89,91] The results reported in non-overlapping studies of BTT patients are shown in *Figure 9*.

The pooled estimate of 26.5 kg/m^2 is similar to the value in the large registry study of 8557 LVAD patients reported by Nativi *et al*.,[89] which found values of 26.7, 27.4, 26.8, 26.2 and 26.3 kg/m^2, respectively, for BTT patients who received pulsatile first-generation LVADs, pulsatile second-generation LVADs, continuous second-generation LVADs, and for second-generation patients on inotropes and second-generation patients not on inotropes. A somewhat larger value of 28.8 kg/m^2 was reported by John *et al*.[65] for 1496 registry patients. It should be noted that in HF BMI may be misleading, owing to the underlying fluid retention of HF.

New York Heart Association functional classification of the extent of heart failure

A minority of studies ($n = 16$) reported baseline information on the NYHA functional classification of patients and where this was reported, the majority of patients were reported as having NYHA class IV. Overall, there was limited reporting of NHYA classification across all devices. Four-fifths (83.5%) of BTT patients had a rating of NYHA class IV assessed from non-overlapping studies (*Figure 10*).

There was some heterogeneity among studies ($I^2 = 38\%$). Neither large registry study[65,89] included usable NYHA class information.

Diabetes mellitus

A total of 12 studies reported the number of patients with diabetes mellitus at baseline (HMII, $n = 8$; HW, $n = 1$; mixed devices, $n = 3$). The percentage of patients with diabetes mellitus at baseline in these studies ranged from 14% (Strueber *et al*.[83]) to 38.5% (Pak *et al*.[72]). In some studies, subgroups with different rates of diabetes mellitus were reported at baseline [e.g. Sandner *et al*.[91] reported 17.9% compared with 53.3% (group 1 aged < 60 years vs. group 2 aged > 60 years respectively)]. *Figure 11* summarises results reported in non-overlapping studies of BTT patients.

The pooled value of 25.2% is similar to reported values, ranging between 20.5% and 28.3%, for patients who received pulsatile first-generation LVADs, pulsatile second-generation LVADs or continuous second-generation LVADs, and for second-generation patients taking inotropes and second-generation patients not taking inotropes, in the large registry study of 8557 LVAD patients (Nativi *et al*.[89]).

Inotropes

The baseline numbers (and percentages) of patients receiving inotropes in non-overlapping studies of BTT patients are shown in *Figure 12*.

There was heterogeneity between studies ($I^2 = 49\%$) and percentage values ranged widely, from 40% to 100% of patients receiving inotropes; the pooled estimate of 81% is similar to the value of 80.4% reported for 1496 HMII patients in the large registry study by John *et al*.[65]

Systolic blood pressure

Baseline systolic blood pressure (BP) was reported in 15 studies.[42,52,53,56,59,63,65,70,71,74,75,79,80,83,85] *Figure 13* summarises the results reported in non-overlapping studies of BTT patients. Systolic BP can be seen to be low compared with normal physiological levels, reflecting the severity of HF in these patients, with a pooled estimate of 97.3 mmHg.

Heterogeneity ($I^2 = 83\%$) between studies arose mainly from the study by Morshuis *et al*.[85] The pooled estimate is similar to the value of 100.9 mmHg reported for 1496 HMII patients in the large registry study by John *et al*.[65] Nativi *et al*.[89] did not report this characteristic for registry patients.

Summary of baseline characteristics

In so far as it was possible to separately identify non-overlapping groups of patients, we identified the following baseline characteristics. The majority of patients were white (78–94%), male [84.2% (95% CI 79.4% to 88.0%)] and middle aged [mean age 50.8 years (95% CI 49.3 to 52.4 years)]. Mean BMI was in the overweight range [mean BMI 26.5 kg/m^2 (95% CI 25.7 to 27.3 kg/m^2)] and about one-quarter of patients [25.2% (95% CI 17.4% to 35.1%)] had diabetes mellitus. Study patients had very severe HF, with 83.5% (95% CI 78.0% to 87.9%) overall rated as NYHA class IV. This was supported by the proportion receiving inotrope medication [80.8% (95% CI 50.9% to 94.5%)] and the low mean systolic BP of 97.3 mmHg (95% CI 92.8 to 101.7 mmHg).

Outcomes by device

In this section we describe outcomes including adverse events, survival, causes of death and QoL for each device.

Outcomes for HeartMate II

A total of 29 studies[52,53,56–82] met the current inclusion criteria concerning HMII (see *Table 3*).

Adverse events

Twenty-three studies[52,56–61,64–73,75,76,78,79,82] reported adverse events or complications during the follow-up of HMII implantation. Given the problems of reporting on overlapping populations within studies (see *Delineating multiple overlapping populations between publications*), adverse events for HMII are best described by John *et al*.[65] (*Table 9*).

Adverse events with HMII affect high proportions of patients. Twenty-one per cent of patients had bleeding requiring re-exploration; 20% had percutaneous lead infection and 3% pump pocket infection. Stroke is a very serious adverse event affecting approximately 10% of patients (it is assumed the ischaemic and haemorrhagic stroke did not occur in the same patient). Event rates per year should be treated with caution as follow-up rates are variable and events are highest in the first year after surgery.

Survival

Table 10 summarises the K–M survival results as reported in the HMII studies (see *Table 3*).

The most recent and largest study of survival in the HMII BTT programme for HF appears to be that of John *et al*.,[65] who included 486 patients from the extension of the HMII FDA approval study and 1496 post-approval patients in the INTERMACS registry. This analysis indicated superior survival for the latter

TABLE 9 Adverse events. Adapted from John *et al.*[65]

	John *et al.*[65] trial group ($n = 486$), 511.1 patient-years	
Adverse event	**Incidence (% of patients)**	**Event rate/patient-year**
Bleeding requiring re-exploration	21	0.23
Infection		
Percutaneous lead infection	20	0.33
Pump pocket infection	3	0.03
Right-side HF requiring RVAD	7	0.06
Stroke		
Ischaemic	5	0.05
Haemorrhagic	5	0.05
Other	0	0.00
Device replacement	5	0.06

TABLE 10 Summary of K–M survival results reported in HMII studies

			% (SE) alive			
Study	**Population**	***n***	**Month 1**	**Month 6**	**Month 12**	**Month 18**
[a]Bogaev 2011[57]	Women	104	96 ± 2	87 ± 4	76 ± 3	73 ± 3
[a]Bogaev 2011[57]	Men	361	93 ± 1	83 ± 2	74 ± 5	73 ± 5
John 2011[65]	HMII FDA approval trial extension	486	NR	83.8 ± 1.8	75.6 ± 2.4	NR
John 2011[65]	INTERMACS post-FDA approval	1496	NR	89.4 ± 0.9	84.9 ± 1.1	NR
[a]Kormos 2010[67]	With early RV failure	65	89 ± 4	66 ± 6	59 ± 7	NR
[a]Kormos 2010[67]	Without early RV failure	386	94 ± 1	87 ± 2	78 ± 3	NR
[b]Miller 2007[70]	HMII FDA approval trial	133	90	75	68.5	NR
Pagani 2009[71]	HMII FDA approval trial extension	281	92 ± 2	83 ± 3	73 ± 3	72 ± 3
[a]Pal 2009[73]	Concurrent cardiac procedures	111	89 ± 4	77 ± 5	66 ± 7	NR
[a]Pal 2009[73]	No concurrent cardiac procedures	271	94 ± 2	84 ± 3	77 ± 4	NR
[b]Starling 2011[52]	INTERMACS post-approval study for FDA[c] (first 169 patients post Miller 2007[70])	169	96	90	85	NR

NR, not reported; SE, standard error.
a These studies dichotomised the patients from the FDA approval study extension.
b Starling 2011[52] and Miller 2007[70] did not report an error value.
c The first 169 HMII patients post Miller 2007,[70] FDA approval study; almost certainly these patients were among the 1496 registry patients in John 2011.[65]

patients ($p < 0.0001$ for log-rank test comparison). These results led the authors to propose that increasing experience with the HMII device has led to a gradual improvement in survival (*Figure 14*).

Earlier publications in the HMII FDA approval series included those of Miller *et al.*,[70] with 133 patients, and Pagani *et al.*,[71] with 281 patients; they represent samples from John *et al.*,[65] a growing cohort of the HMII

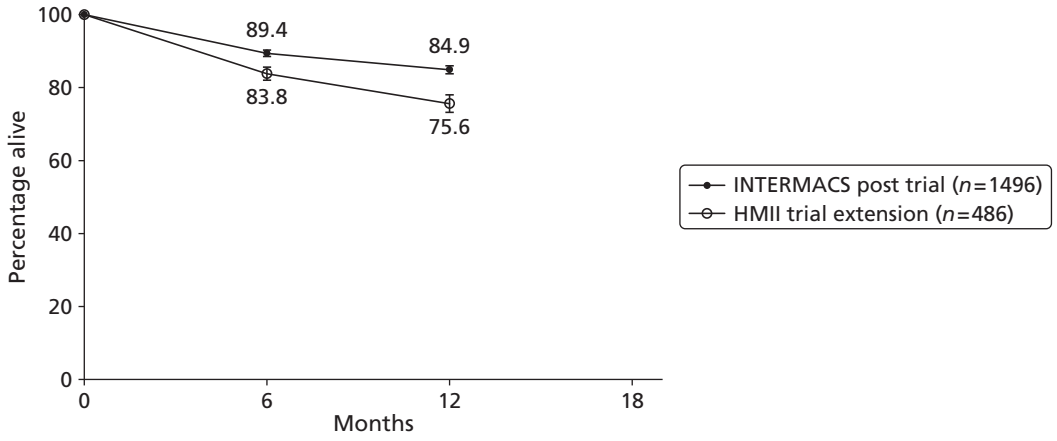


FIGURE 14 Kaplan–Meier survival results reported by John *et al.*[65] for patients who received an HMII LVAD.

approval study patients which accumulated 486 patients. The survival results reported are shown in *Figure 15* together with those for the first 169 post-approval patients analysed in Starling *et al.*[52] The results tend to support the proposition that a so-called learning curve leads to improving survival as the cohort grows. Survival at 1 year was 68.5% in Miller *et al.*,[70] 73% in Pagani *et al.*,[71] 75.6% in John *et al.*[65] and 85% in Starling *et al.*[52] as well as for the 1496 registry post-approval patients in John *et al.*[65]

Greater experience with the device offers one explanation for the apparently improving survival; however, the similarity of these populations at baseline is difficult to gauge.

Three publications reported survival for subgroups of patients in the extension of the HMII FDA approval study (Bogaev *et al.*,[57] Kormos *et al.*[67] and Pal *et al.*[73]). In each of these studies participants were dichotomised according to a single variable. The results are summarised in *Figure 16*. No significant difference was observed between genders, although early RV failure was associated with poorer survival ($p = 0.026$), as were concurrent cardiac procedures undertaken ($p = 0.048$).

In summary, publications suggest that survival at 1 year is approximately 75% but may improve with gain in surgical experience. These K–M analyses censor patients when they receive a HT. The problem here is that if the chance of receiving a donor heart depends on a patient's prognosis, for example if more seriously ill patients are selectively removed from follow-up and receive priority for transplantation, then survival estimates are susceptible to informative censoring and may thereby represent overestimates.

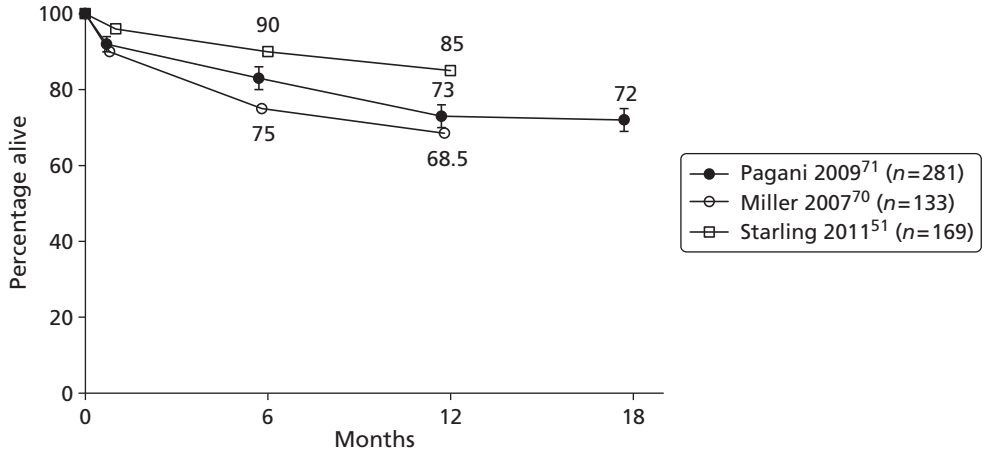


FIGURE 15 Kaplan–Meier survival results for the HMII FDA approval trial and registry patients.

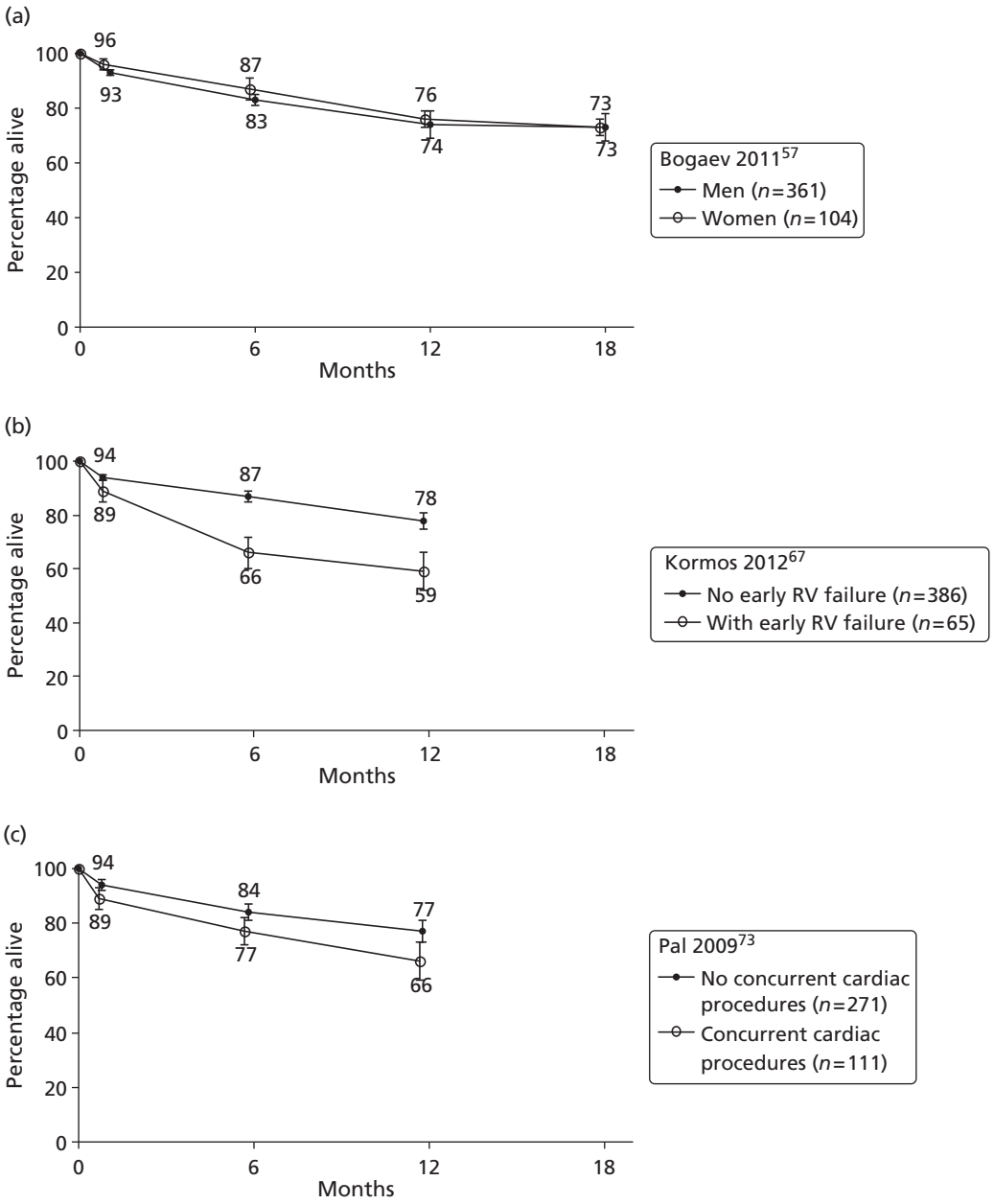


FIGURE 16 Kaplan–Meier results reported for subgroups of patients receiving HMII LVAD.

Causes of death

Twelve of the included HMII papers reported causes of death.[56,57,64,68,70–73,78–80,82] Of these, the most recent and largest publication reporting this outcome in the HMII BTT programme for HF appears to be that of Bogaev *et al*.[57] This publication dichotomised participants according to gender. The reported leading causes of death in men were sepsis (3.9%), right HF (2.8%) and multisystem organ failure (2.2%). The leading causes of death in women were multisystem organ failure (3.8%), haemorrhagic stroke (2.9%), ischaemic stroke (1.9%), right HF (1.9%) and external component device malfunction (1.9%; percutaneous lead trauma in one patient and pump disconnection in another).[57] *Table 11* provides a summary of the causes of death reported in the 12 HMII studies.

Common causes of death included (a) multiorgan failure ($n = 12$ studies), (b) right heart (ventricular) failure ($n = 8$ studies), (c) bleeding ($n = 7$ studies) and (d) stroke and cerebrovascular accident (CVAs) ($n = 9$ studies).

TABLE 11 Causes of death reported in included HMII papers

First author	Date	Country	Causes of death
Adamson[56]	2011	USA	Anoxic brain injury, cardiomyopathy, sepsis, respiratory failure, multiorgan failure, ischaemic stroke, haemorrhagic stroke, device thrombosis, patient disconnected power, cancer, withdrawal of support, unknown causes
Bogaev[57]	2011	USA	Sepsis, right HF, multisystem organ failure, ischaemic stroke, haemorrhagic stroke (thrombi, pump disconnection, twisted inflow graft, pump pocket infection, loss of power, percutaneous lead trauma), respiratory failure, cardiac failure, bleeding, cancer, elective withdrawal of support, death during transplantation, unknown causes
John[64]	2011a	USA	Multisystem organ failure, subclavian vein haemorrhage, ventricular fibrillation, respiratory failure, RV failure, intracranial bleed
Lahpor[68]	2010	Europe	Multiorgan failure mainly occurring as a result of septic complications or right-HF, CVAs
Miller[70]	2007	USA	Sepsis, ischaemic stroke, multisystem organ failure, haemorrhagic stroke, anoxic brain injury, right HF, miscellaneous other causes, device-related death caused by an inflow graft that was accidentally twisted during implantation
Pagani[71]	2009	USA	Sepsis, stroke (ischaemic, haemorrhagic), right HF, device related, multiorgan failure, anoxic brain injury, bleeding, cancer, respiratory failure, hyperthermia, air embolism
Pak[72]	2010	USA	Aortic insufficiency onset of multiorgan system failure
Pal[73]	2009	USA	Bleeding, sepsis, driveline infection, ventricular arrhythmias, perioperative stroke, renal failure
Strueber[78]	2008	Multiple	Multiorgan failure, right HF, CVAs, respiratory failure, driveline disconnection, bleeding after ventricular rupture, suffocation after epistaxis (nose bleed)
Topilsky[79]	2011a	USA	Multiorgan failure, intractable right HF, hyperperfusion brain injury, sepsis, uncontrollable bleeding
Topilsky[80]	2011b	USA	Uncontrolled right HF, multiorgan failure, intracerebellar bleeding, traumatic head trauma injury, haemorrhagic stroke, unexplained sudden death, RV failure, embolic stroke, complication of myocardial biopsy after transplant, patient withdrawal of support owing to persistent RV failure and need for dialysis
Ventura[82]	2011	USA	Graft failure, infection, cardiovascular, cerebrovascular, multiorgan failure, haemorrhage, malignancy, unknown causes

Quality of life

The HMII studies used several instruments for monitoring QoL and functional status of HF patients. *Table 12* provides a summary of HMII studies indicating which QoL measures were used.

For this variety of QoL measures, data were presented as group means at various time points, change in group mean from baseline, or as change in mean or median for paired measures for individual patients. The number of patients investigated during individual studies gradually diminished as a result of death, transplantation with a donor heart and loss to follow-up or withdrawal. Baseline values were not always complete because some patients may not have been sufficiently well to participate. Full QoL results can be found in *Appendix 3*.

Five of the nine studies (Rogers *et al.*,[53] Bogaev *et al.*,[57] John *et al.*,[65] Miller *et al.*[70] and Pagani *et al.*[71]) contribute to the multicentre HMII BTT FDA approval programme with overlapping populations. By far the fullest QoL information was provided in Rogers *et al.*[53] ($n = 281$). Although the largest BTT patient groups were investigated in Bogaev *et al.*[57] ($n = 465$) and John *et al.*[65] ($n = 486$), relatively limited results were presented and neither report paired measures; therefore, here we focus on the data presented in Rogers *et al.*[53] (for this study information in Pagani *et al.*[71] can be used to gauge the completeness of the reported

TABLE 12 Quality of life and functional status outcome measures reported for HMII

First author	Date	Country	MLWHF	KCCQ	METs	VAS	NYHA functional class	6-minute walk test
Rogers[53]	2010	USA	✓	✓	✓		✓	✓
Topilsky[79]	2011	USA					✓	
Topilsky[80]	2011	USA					✓	
Adamson[56]	2011	USA	✓	✓	✓		✓	✓
Bogaev[57]	2011	USA	✓	✓	✓		✓	✓
John[65]	2011	USA		✓		✓		✓
Miller[70]	2007	USA	✓	✓			✓	✓
Pagani[71]	2009	USA	✓	✓			✓	✓
Starling[52]	2011	USA				✓		

KCCQ, Kansas City Cardiomyopathy Questionnaire; METs, metabolic equivalent task score; VAS, visual analogue scale.

data). Rogers *et al.*[53] presented results separately for 281 BTT and 374 DT patients; the DT results were similar to those for BTT patients. (They are not considered further here but can be found in *Appendix 3*.) In the following section, the QoL results presented by Rogers *et al.*[53] are summarised and considered separately according to the investigatory instrument. Comments on the results from Bogaev *et al.*[57] and John *et al.*[65] should be viewed in the knowledge that the populations in these studies included participants from Rogers *et al.*[53]

Minnesota Living With Heart Failure Questionnaire

Scores on the MLWHF questionnaire ranged from 0 to 105, with lower values signifying improved QoL. Scores reported by Rogers *et al.*[53] decreased over time relative to baseline scores (–10 points at 1 month and –29 points at 6 months; median per cent improvement at 6 months of 38%), indicating an improvement in QoL ($p < 0.05$). These results for MLWHF scores at 1, 3 and 6 months for BTT patients are summarised in *Figure 17*.

Reading from the graph in Pagani *et al.*[71] the number of patients supported on HMII at 6 months was about 132, so that the return of 115 questionnaires at 6 months represents a data set approximately 87% complete.

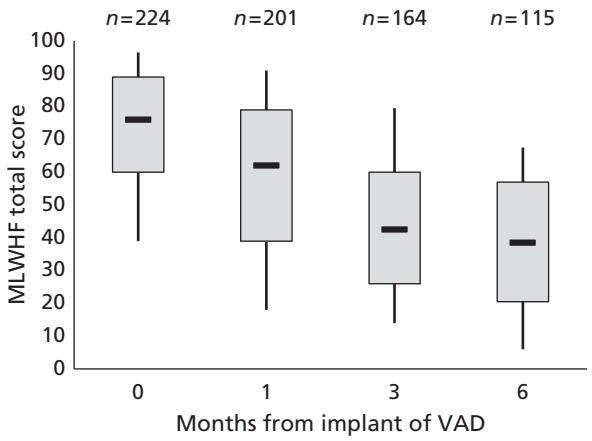


FIGURE 17 Changes in MLWHF for the BTT group over time (Rogers *et al.*[53]). Bars indicate 25th, 50th and 75th percentiles, and the whiskers indicate fifth and 95th percentiles.

Rogers *et al.*[53] also reported paired change (i.e. mean change from baseline for patients with measures at both time points) (*Table 13*).

Borgaev *et al.*,[57] who subdivided the population by gender, reported similar results: a significant improvement (both genders group) between baseline and 6 months (female: 73 ± 22 to 35 ± 22; male: 71 ± 22 to 40 ± 23). There was no significant difference between the sexes ($p = 0.661$).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS) and clinical summary score (CSS) improved during HMII support. The median KCCQ OSS showed improvements at 1, 3 and 6 months compared with baseline and ($p < 0.05$ at each time point). KCCQ group OSS also showed similar improvements ($p < 0.05$ at each time point) (*Figure 18*).

TABLE 13 Paired changes in MLWHF scores reported in Rogers *et al.*[53]

BTT				
Month	***n***	**Mean ± SD**	**Median [25th, 75th percentiles]**	**% improvement of median**
1	167	−12 ± 27	−10 [−28, 4]	13
3	126	−24 ± 31	−30 [−47, −4]	39
6	87	−28 ± 28	−29 [−50, −9]	38

$p < 0.001$ for improvement in median score.

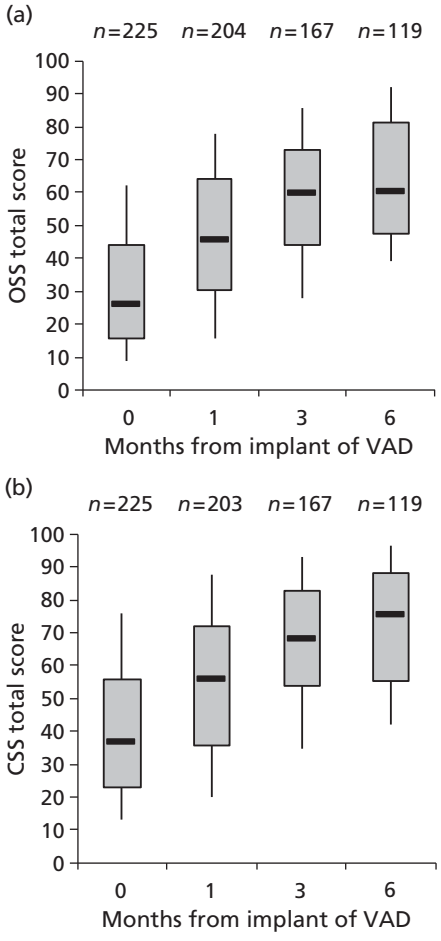


FIGURE 18 Kansas City Cardiomyopathy Questionnaire scores (Rogers *et al.*[53]). Bars indicate 25th, 50th and 75th percentiles, and the whiskers indicate fifth and 95th percentiles. (a) OSS; and (b) CSS.

Rogers *et al*.[53] reported paired KCCQ score changes (i.e. mean of change from baseline for patients with measures at both time points). These results are summarised in *Table 14*.

Again, paired measures support the evidence for an improvement in QoL for patients surviving after implant of the HMII VAD (*p*-value and statistical significance were not reported).

Borgaev *et al*.,[57] who subdivided the population by gender, reported significant improvements for both men and women in mean values on the KCCQ OSS and CSS between baseline and 6 months (there was no significant difference between the sexes).

Metabolic equivalent task score

The metabolic equivalent task score (METs) measures patient-reported exercise ability. Rogers *et al*.[53] presented serial assessments of METs following HMII (*Figure 19*). At baseline, > 90% of patients described their level of function as low or very low. At 6 months, about two-thirds of patients described their level of function as moderate to very high ($p < 0.001$ vs. baseline).

Borgaev *et al*.[57] found no significant difference between males and females in METs improvements ($p = 0.348$).

Quality of life visual analogue scale

Rogers *et al*.[53] did not report on this outcome. For purposes of completeness, results from other studies are reported here. The data presented by Starling *et al*.[52] for the first 169 post-FDA-approval HMII patients are summarised in *Figure 20*. Visual analogue scale (VAS) scores (scale 0–100; best QoL = 100) improved at 3, 6 and 12 months relative to baseline. Changes were large, but *p*-value and statistical significance were not reported. Results were based on 253 tests (50%) completed in 508 potential test sessions.

John *et al*.[65] presented METs QoL data for a sample from the INTERMACS registry BTT post-approval HMII patients (*Table 15*). Improvements of 32 points at 3 months were sustained at 12 months. The authors provided limited discussion of these findings. The overlapping underlying populations preclude development of a summary estimate combining results with those of Starling *et al*.[52]

Functional status

New York Heart Association Rogers *et al*.[53] reported that at baseline patients were classified as NYHA class IV, by 1 month 59% had improved to NYHA class I or II, and at 6 months 82% were NYHA classified as class I or II (*Figure 21*). Relative to baseline scores, highly significant improvements in NYHA functional class were observed at all study intervals ($p < 0.001$).

Bogaev *et al*.[57] reported significant improvements from baseline in the proportion of patients classified as NYHA functional class I/II for both women [0–49 (83%)] and men [0–147 (85%)] ($p < 0.001$). No significant differences were observed between men and women ($p = 0.55$).

6-minute walk test At baseline, Rogers *et al*.[53] reported that of 281 BTT patients 38 (14%) were able to perform the 6-minute walk test. Baseline distance walked for was 214 ± 125 metres. At 6 months the distance walked was 372 ± 199 metres although only 97 patients completed the test. There was a statistically significant improvement over time.

Bogaev *et al*.[57] reported that before LVAD implantation, many patients were unable to walk and could not provide baseline values. Group means exhibited significant change for both women and men at 1, 3, and 6 months. Distance walked at all times was further for men ($p = 0.037$). Registry data for the 6-minute walk test results reported by John *et al*.[65] similarly indicated improvement from baseline. No statistical analysis was reported.

TABLE 14 Paired changes in KCCQ OSS and CSS

OSS					CSS				
Month	*n*	Mean ± SD	Median [25th, 75th percentiles]	Improvement of median	Month	*n*	Mean ± SD	Median [25th, 75th percentiles]	Improvement of median
1	172	13 ± 25	14 [–3, 29]	0.54	1	170	12 ± 27	11 [–6, 31]	0.3
3	132	22 ± 26	20 [9, 42]	0.77	3	132	21 ± 28	21 [4, 42]	0.57
6	90	27 ± 28	28 [7, 45]	1.08	6	90	25 ± 31	24 [8, 43]	0.65

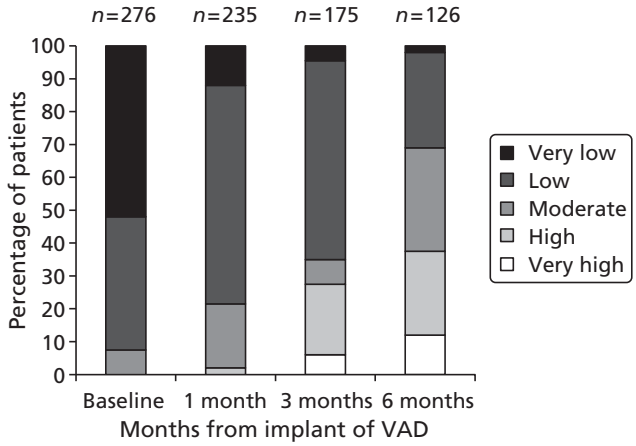


FIGURE 19 Summary of METs. BTT FDA study: data from Rogers *et al.*[53]

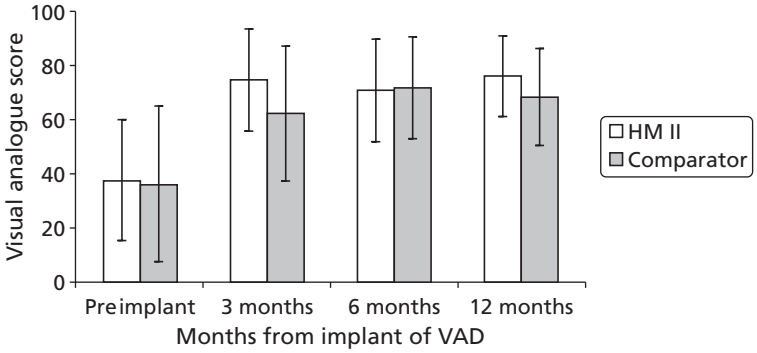


FIGURE 20 Visual analogue scale for HMII and comparator VADs at different time points (Starling *et al.*[52]). Note: the comparator group consisted of patients who received other LVADs than HMII approved for BTT.

TABLE 15 Visual analogue scale results for the post-trial cohort. Adapted from John *et al.*[65]

Item	Pre implant	3 months	6 months	12 months
n (at risk)	1498	1142	822	393
n (completing test)	777	617	432	192
Per cent (completing test)	52	54	53	49
VAS score	42	74	75	76

Summary of quality-of-life results The results presented by Rogers *et al.*[53] provide a persuasive indication that those patients who survive implantation of the HMII device as BTT experience an improvement in QoL by 3 months sustained at 6 months. Some of the changes are substantial and statistically significant (e.g. improvements in MLWHF, KCCQ, NYHA and METs in Rogers *et al.*[53]), but data sets were not complete and this may have skewed results.

These results were supported in other publications with somewhat larger populations and where measures are extended to 12 months.

Summary of outcomes for HeartMate II

The relatively modest quality and diversity of reporting of outcomes and the occurrence of overlapping populations in the 29 publications of HMII have precluded numerical synthesis of results. Outcomes for HMII overall show a profile of substantial adverse events. One in five patients had bleeding requiring re-exploration and almost one in three patients had infection. Stroke is a very serious adverse event

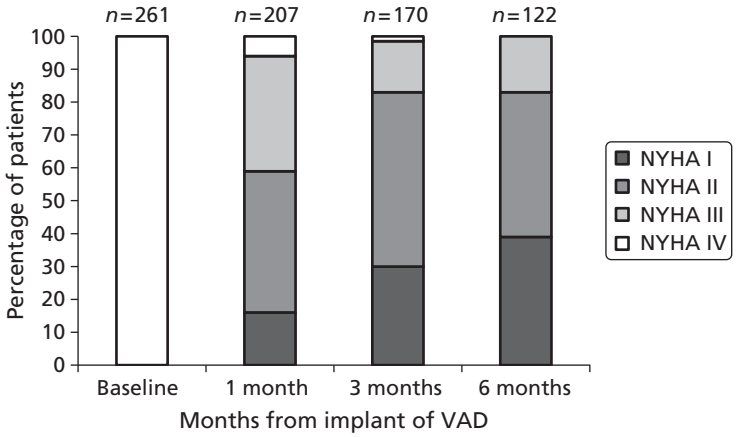


FIGURE 21 Summary of NYHA classification at each time point reported (Rogers *et al.*[53]). Ratings were determined by an independent clinician.

affecting 1 in 10 patients. The K–M estimates of survival post implant of the HMII device suggest improvement with growing experience. The best 1-year survival estimate for this device was 85%. It should be borne in mind that in estimating survival of BTT patients during VAD support using K–M analyses, those patients who receive a HT are censored at the time of transplant; if these patients have poorer prognosis than uncensored patients then survival may be overestimated (or vice versa). Furthermore, any comparison between device types for any outcome may be confounded by differences in underlying populations (e.g. owing to geography, time period, eligibility criteria).

Set against this, however, is reported improvements in QoL and functional status reported using a number of different measures in a number of different studies.

Outcomes for HeartWare

One study reporting on 50 patients implanted with a HW VAD as a BTT fulfilled our inclusion criteria (Strueber *et al.*[83]).

Adverse events

Adverse events were reported in detail and are shown in *Table 16*. Overall, 22 infections occurred among 50 patients; 20% of patients required repeat surgery for bleeding. Six of the 50 patients suffered from stroke and seven device replacements were required. Other important adverse events suffered by smaller numbers of patients included renal and hepatic dysfunction, haemolysis and right HF. Some patients may have experienced multiple events; therefore, summing percentages within categories may be misleading.

Survival

Table 17 provides a summary of the K–M survival results for patients who received the HW VAD in the study by Strueber *et al.*[83]

Strueber *et al.*[83] reported K–M survival results for HW BTT patients ($n = 50$; *Figure 22*). Relative to HMII studies (shown in *Figures 14* and *15*), survival with HW appears to be at least comparable, with 85% of patients alive at 1 year after implant. When compared with the earlier HMII publications, survival appears superior for HW. Strueber *et al.*[83] also provided a survival curve for a 'virtual control' group; this was based on the application of the Seattle Heart Failure Model (SHFM) to the baseline characteristics of the intervention group. This virtual control data fits well when a SHFM score of 2.416 is applied. These results are summarised in *Figure 22*.

Causes of death

Reports on nine deaths from the 50 eligible patients in the HW study[78] suggested that three were caused by sepsis, three by multiorgan failure and three were thought to be caused by haemorrhagic stroke.

TABLE 16 Adverse events for patients with a HW device. Adapted from Strueber *et al.*[83]

Adverse events	Patients with events (%)	Number of events, overall	Number of events, 0–30 days	Number of events, > 30 days
Infection				
Localised non-device related	7 (14)	7	2	5
Sepsis	5 (10)	5	1	4
Driveline exit site	9 (18)	10	0	10
Bleeding				
Requiring surgery	10 (20)	11	8	3
Requiring transfusion ≥ 2 units	2 (4)	2	1	1
Requiring hospital stay	3 (6)	3	1	2
Ventricular arrhythmias	2 (4)	2	1	1
Neurological dysfunction				
Ischaemic stroke	2 (4)	2	2	0
Haemorrhagic stroke	4 (8)	4	0	4
TIA	2 (4)	3	0	3
Pulmonary dysfunction	8 (16)	9	8	1
Device replacement				
Manufacturing defect	2 (4)	2	2	0
Left heart embolus	4 (8)	4	1	3
Inflow occlusion	1 (2)	1	1	0
Pleural effusion	6 (12)	7	5	2
Right HF				
RVAD	3 (6)	3	2	1
Intravenous inotropes	3 (6)	3	1	2
Other serious adverse events				
Renal dysfunction	5 (10)	5	5	0
Hepatic dysfunction	3 (6)	3	1	2
Haemolysis	1 (2)	1	1	0
HF	3 (6)	3	1	2
Chest pain	1 (2)	1	0	1
Femoral embolism	2 (4)	2	1	1

TIA, transient ischaemic attack.

TABLE 17 Kaplan–Meier survival results for patients who received the HW VAD

Study population	Group	*n*	Month 6	Month 12	Month 18	Month 24
Strueber *et al.*[83] BTT (patients from Europe and Australia)	HW	50	90%	85%	NR	79%
	Virtual control	50	73%	58%	48%	40%

NR, not reported.

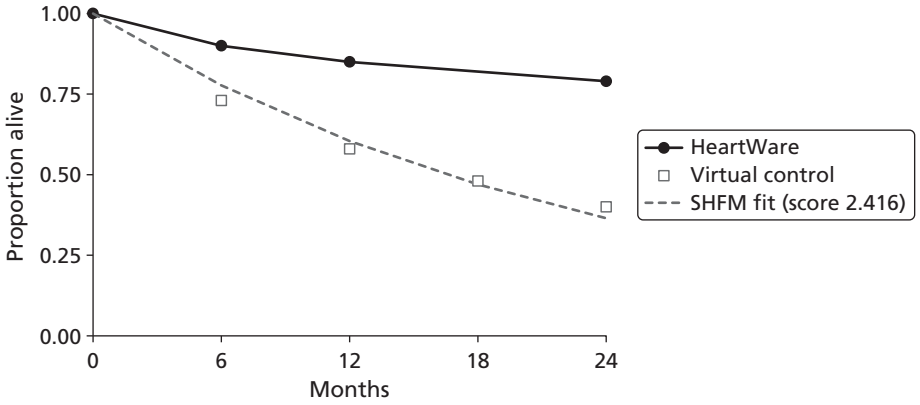


FIGURE 22 Survival of BTT patients implanted with the HW. Reported by Strueber *et al.*[83]

Quality of life

Strueber *et al.*[83] reported KCCQ data for stated sample sizes of 38, 37, 36 and 21 presurgery and 1, 3 and 6 months post surgery for the 50 patients in their study. Results are summarised in *Figure 23*. It was unclear if these were paired data.

Health-related quality of life (HRQoL) improved significantly by 1 month for all subscales of the KCCQ. The authors found statistically significant ($p = 0.05$) improvement in physical limitations, QoL, symptom burden, and overall functional status across all time points. Greater improvements were found during the first 30 days following the HW implant.

Summary of outcomes for HeartWare

Only one small publication reported on the HW VAD; there is a profile of substantial adverse events and mortality due to infection, bleeding and stroke, and one in seven patients with a HW device was reported as requiring the device to be replaced. Although it is possible that mortality within the first year is slightly less than as reported in HMII analyses published during earlier years of experience with that device (e.g. Miller *et al.*[70] and Pagani *et al.*[71]), it should be borne in mind that the K–M estimates are subject to censoring for receipt of a HT. Significantly improved QoL and functional status were reported over the first 6 months after a HW implant.

Outcomes for the Berlin Heart INCOR

One study by Schmid *et al.*[86] of the Berlin Heart INCOR fulfilled our inclusion criteria. This study reported on 138 patients who received a short cannula device and 78 patients who received a long cannula device.

Adverse events

Table 18 shows adverse events for the Berlin Heart INCOR. Nearly one in four patients (23.2%) with a short cannula suffered a thromboembolic stroke. This rate appeared to be significantly lower in the smaller group of patients with a long cannula (3.8%). The authors distinguished stroke from intracerebral bleeding, again finding higher rates in the short cannula group – although not significantly so.

Survival

Kaplan–Meier analysis of survival was performed for 78 patients with a short cannula device and 138 who received a long cannula device in this study.[86] Survival reported at 12 and 24 months for each device type is summarised in *Table 19*, showing that even in the improved survival (long cannula) group, 39% of the patients had died by 12 months.

Causes of death

In this study there were 92 deaths including 48 from multiorgan failure; 13 due to a cerebrovascular event; eight from right ventricular artery failure; two owing to cancer; two to trauma; and one each from

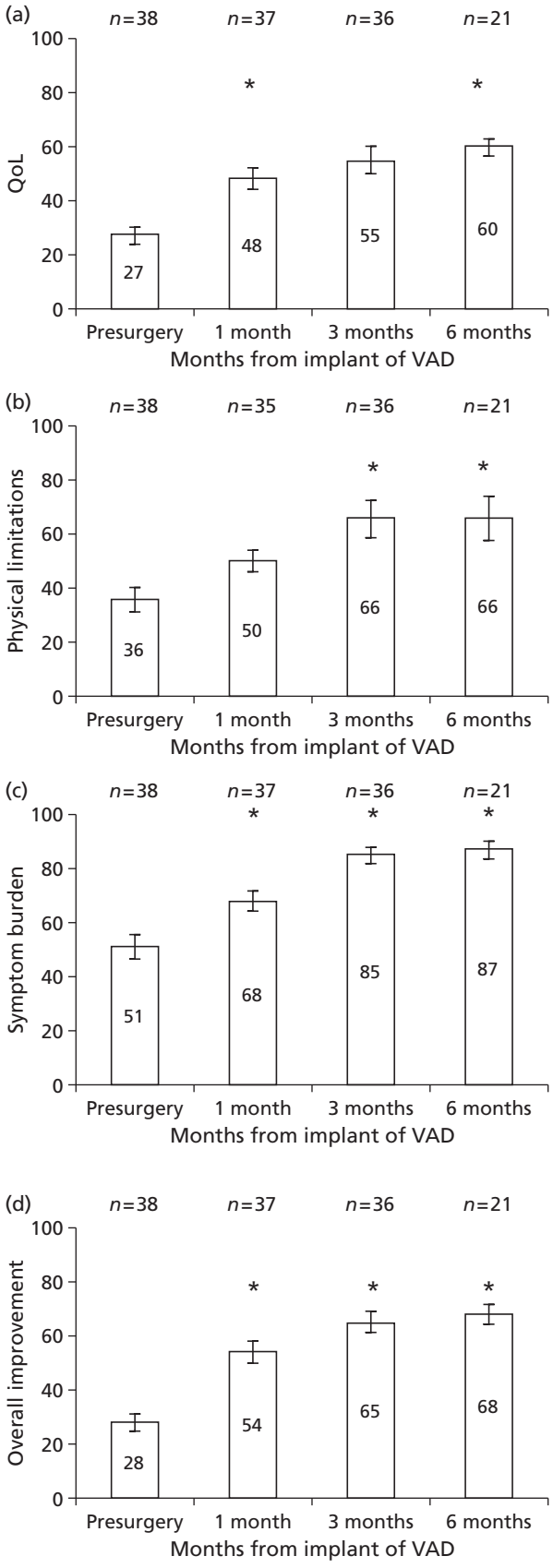


FIGURE 23 Group mean scores for the KCCQ (Strueber *et al.*[83]). Bars indicate means with 95% CIs and asterisks indicate 90th percentiles. *Statistically significant improvement reported in KCCQ score at $p < 0.05$.

TABLE 18 Adverse events. Adapted from Schmid *et al.*[86]

Adverse events	Short cannula (*N* = 138)	Long cannula (*N* = 78)	*p*-value
Thromboembolic stroke, *n*	35	4	
Patients affected, *n* (%)	32 (23.2)	3 (3.8)	< 0.001
Events/patient-year	0.5	0.11	
Time to event (days), mean (range; SD)	73 (2–429; ± 86)	38 (4–66; ± 31)	
Intracerebral bleeding, *n*	15	4	
Patients affected, *n* (%)	14 (10.1)	4 (5.1)	0.152
Events/patient year	0.21	0.11	
Time to event (days), mean (range; SD)	118 (18–330; ± 110)	271 (15–933; ± 442)	

Cerebral bleeding confirmed by computerised tomography scan.

TABLE 19 Kaplan–Meier survival analysis for patients who received a Berlin Heart INCOR VAD

Study	Population	*n*	Month 12 survival (%)	Month 24 survival (%)
Schmid *et al.*:[86] long cannula	BTT unclear	78	61	50
Schmid *et al.*:[86] short cannula	BTT unclear	138	53	33

pulmonary artery embolism and bleeding. Seventeen additional deaths were reported with 'other' or 'unknown' cause.

Quality of life and functional status

No data were reported on QoL or functional status.

Summary of outcomes for the Berlin Heart INCOR ventricular assist device

Only one relatively small study reported on the Berlin Heart INCOR VAD with a profile of substantial adverse events caused by intracerebral bleeding and stroke. Mortality within the first year was high. No data were reported on QoL and functional status.

Outcomes for the DuraHeart ventricular assist device

Two publications fulfilled our inclusion criteria.[42,85] These reported on overlapping populations.

Adverse events

The 2010 study (Morshuis *et al.*[42]) reported adverse events in more detail and these are shown in *Table 20*. Almost all patients (31/33; 94%) suffered at least one serious adverse event. There were 114 serious adverse events in all, equivalent to each patient suffering nearly four events. Infections, cardiovascular complications and bleeding were the most commonly reported.

Survival

Both publications reported K–M survival results for BTT patients who received the DuraHeart VAD.[42,85] Populations in the studies overlapped. The 2009 study[85] provided survival results for the greater number of patients (*n* = 68) as follows: 87% (95% CI 77% to 94%) at 3 months, 81% (95% CI 67% to 89%) at 6 months and 77% (95% CI 34% to 78%) at 1 year.

These figures are comparable with studies reporting early experience with the HMII VAD.

TABLE 20 Incidence of serious adverse events. Adapted from Morshuis *et al.*[42]

Serious adverse events	Patients with events (%)	Number of events, overall	Number of events, 0–30 days	Number of events, > 30 days
All serious adverse events	31 (94)	114	50	64
Infection				
Local non-device-related infection	14 (42)	14	6	8
Driveline infection	5 (15)	7	1	6
Pocket infection	1 (3)	1	1	0
Sepsis	6 (18)	6	3	3
Cardiovascular complications				
Right HF requiring RVAD	1 (3)	1	1	0
Right HF extended inotropes	9 (27)	10	7	3
Ventricular arrhythmia[a]	8 (24)	8	5	4
Myocardial infarction[a]	0	0	0	1
Cerebrovascular complications				
Ischaemic CVA	2 (6)	2	2	0
Haemorrhagic CVA	4 (12)	4	1	3
TIA	5 (15)	5	1	4
Bleeding				
Total bleeding	8 (24)	11	4	7
Bleeding requiring surgery	4 (12)	4	2	2
Other				
Renal failure	5 (15)	5	3	2
Respiratory failure	4 (12)	4	3	1
Pump replacement	2 (6)	2	0	2
Hepatic dysfunction	2 (6)	2	2	0

TIA, transient ischaemic attack.
a The total number of events in the original report did not tally with the number in < 30 days + the number in > 30 days.

Causes of death

Morshuis *et al.*[86] reported on 20 deaths from 82 eligible patients, 13 of which were adjudicated by the Clinical Event Committee. The causes of death in the 13 patients were as follows: CVA, six patients (four haemorrhagic; two ischaemic); sepsis, three patients; non-traumatic subdural haematoma, one patient; accidental fall, one patient; acute myocardial infarction, one patient; and one patient was unknown.

Quality of life and functional status

No data were reported on QoL or functional status.

Summary of outcomes for the DuraHeart ventricular assist device

Two relatively small publications with overlapping populations reported on the DuraHeart VAD with a profile of substantial serious adverse events. Major causes of adverse events and death were CVA bleeding and infection, as with the other devices. Mortality within the first year was apparently similar to that

reported in the publications describing earlier experience with the HMII device. No data were reported on QoL and functional status.

Outcomes for the MicroMed DeBakey ventricular assist device

One relatively small international study of 150 patients in 14 centres (of which 11 centres were European) by Goldstein[84] reported on the MicroMed DeBakey VAD.

Adverse events

Table 21 shows adverse events in this study. One-third of patients required reoperation for surgery and one-third suffered a thromboembolic event. Adverse event reporting in this study was mainly restricted to those related to the device. Complications not directly related to the device were not reported.

Survival

This study[84] did not provide K–M survival data.

Causes of death

Unclear.

Quality of life and functional status

No data were reported.

Summary of outcomes for the MicroMed DeBakey ventricular assist device

Only one study reported on this device with a profile of substantial adverse events. No data were reported on survival or on QoL or functional status. Little can be concluded on outcomes from this device as yet.

Outcomes for the publications reporting on mixed devices

This section reports findings from six studies[88–93] of different VADs (where > 80% of patients received a VAD type which met the inclusion criteria and where results are not reported separately by VAD type).

Adverse events

Table 22 provides a list of the adverse events and complications reported in the six studies[88–93] concerning a mixture of devices. All six studies reported adverse events or complications. The most common adverse events reported were death ($n = 4$ studies), bleeding ($n = 2$ studies), stroke ($n = 3$ studies), renal failure ($n = 2$ studies), and right heart (RV) failure ($n = 2$ studies).

Drews *et al.*[87] reported details of device malfunction. Pump thrombosis occurred in five patients (four patients fitted with the MicroMed DeBakey LVAD; one patient who received the Jarvik 2000 device) and

TABLE 21 Adverse events. Adapted from Goldstein[84]

Adverse event	Incidence	Rate/patient-year
Reoperation for bleeding	32.0% (48/150)	2.03
Haemolysis[a]	12.0% (18/150)	0.61
Device infection	3.3% (5/150)	0.16
Thromboembolic event[b]	10.7% (16/150)	0.61
Pump thrombus	11.3% (17/150)	0.61
Mechanical failure	2.7% (4/150)	0.13

TIA, transient ischaemic attack.
a Defined as plasma-free haemoglobin > 40 mg/dl.
b Composite of embolic stroke, TIA and peripheral embolism.

three patients had pump-stop due to technical failure (MicroMed DeBakey, Berlin Heart INCOR) or due to pannus on inflow cannula (DuraHeart). Two patients had bearing problems (Berlin Heart INCOR), one patient had a broken driveline and in five patients pump exchange was performed. Two patients died and four patients underwent successful HT.

Among 86 patients common to both Sandner *et al*. publications,[91,92] 22 episodes of bleeding requiring surgery, 19 strokes, 30 instances of renal failure requiring continuous venovenous haemofiltration, and five cases of right HF requiring a RVAD were reported; these outcomes were reported by risk groups according to baseline age and glomerular filtration rate (GFR) status (see *Table 22*). The studies by Oswald *et al*.[90] and by Nativi *et al*.[89] reported adverse events post HT; these are listed in *Table 22*.

Survival

Of the six studies,[88–93] two studies[88,90] did not provide survival results. The population in Drews *et al*.[87] mostly received the VAD as DT patients and results could not be separated for BTT patients; post-HT survival only was reported. Likewise, Nativi *et al*.[89] reported post-HT survival only. Results for the remaining two studies, Sandner *et al*.[91,92] are summarised in *Table 23*. The two studies[91,92] appear to have analysed the same populations which were dichotomised according to age in one study and according to renal function status in the other. It was unclear if patients were censored on receipt of a donor heart. Survival appears to be worse for younger patients,[91] but these findings are not adjusted for severity or case mix and these studies lack power; numbers are too small to provide definitive information.

Causes of death

All six of the included papers[83–93] reporting on a mixture of devices provided information on the causes of death. *Table 24* summarises the causes of death. Common causes of death included (a) multiorgan failure; (b) right heart (ventricular) failure; (c) bleeding; and (d) stroke/CVA. Because the proportion of different devices varied from study to study, or was not reported, events rates could not be attributed to a particular device.

Quality of life and functional status

None of the included studies with mixed devices reported QoL or functional status measures.

Summary of outcomes for studies reporting on more than one ventricular assist device

Among these studies, outcomes were not reported by device and the mixture of devices varied from study to study. Therefore it was difficult to derive meaningful conclusions. Overall rates of survival and adverse events are in line with findings reported earlier in this chapter. None of the studies reported on QoL or functional status.

Summary of clinical effectiveness findings

We have reported outcomes for the 40 included publications (for full details see *Appendix 3*). The lack of prospective comparative study design, modest study quality, diversity of reporting of outcomes, and overlap between populations investigated, render it difficult to draw firm overall conclusions. The only comparisons between devices reported were between early generation VADs and second-/third-generation devices. (See also *Appendix 3*.)

For all the devices there was a profile of substantial serious adverse events caused by infection, thrombosis, bleeding and stroke, and of mortality from various causes in this already frail population. By 12 months patients had suffered a variety of serious complications. Studies reported the following ranges for adverse events: 4–27% bleeding requiring transfusion; 1.5–40% stroke; 3.3–48% infection (sepsis); 1–14% device failure; 3–30% HF; 11–32% reoperation; and 3–53% renal failure. *Table 25* gives a summary of the range of rates of the main adverse events by device type per patient-year demonstrating these high rates of adverse events.

TABLE 22 List of adverse events and complications in included papers reporting a mixture of devices (*n*=6)

First author, year, country	Reference number	Adverse events and complications
Drews, 2010, Germany	87	Population (*n* = 110) received non-pulsatile devices

Technical complications	*n* (%)
Device failure	2 (2)
Pump thrombosis	5 (4.5)
Inflow-thrombosis	1 (1)
Bearing problem	2 (2)
Driveline broken	1 (1)
Total	11 (10)
Pump exchange	5 (5)
Rehospitalisation (patient/year)	3.6

Klotz, 2006, Germany	88	Reported that risk of severe rejection post HT was higher for pulsatile than non-pulsatile devices
Nativi, 2011, USA	89	Post-HT adverse events included: treated rejection, stroke, hypertension, hyperlipidaemia, diabetes mellitus, vasculopathy, malignancy, severe renal dysfunctions
Oswald, 2010, Germany	90	Population (*n* = 61) received HMII or HW LVAD

Patient safety and complications	*n* (%)
Non-lethal cerebrovascular event	3 (5)
Death from thromboembolic events	9 (15)
LVAD cable infection (total)	14 (23)
Conservatively managed	13 (21)
Requiring surgical revision	1 (2)

Sandner, 2009, Austria	91	Data as: *n* (%); *p*-value for difference between age groups

Adverse events	Group aged < 60 years, *n* = 56	Group aged ≥ 60 years, *n* = 30	*p*-value
Death < 30 days	4 (7.1)	3 (10.0)	0.644
Bleeding requiring surgery	15 (26.8)	7 (23.3)	0.727
Stroke	11 (19.6)	8 (26.7)	0.454
Ischaemic	*5 (8.9)*	*4 (13.3)*	*0.525*
Haemorrhagic	*6 (10.7)*	*4 (13.3)*	*0.718*
Renal failure requiring CVVHD	14 (25.0)	16 (53.3)	0.009
HF requiring RVAD	2 (3.6)	3 (10.0)	0.225

TABLE 22 List of adverse events and complications in included papers reporting a mixture of devices (*n*=6) (*continued*)

First author, year, country	Reference number	Adverse events and complications
Sandner, 2009, Austria	92	Data as: *n* (%); *p*-value for difference between renal function groups

Adverse event	GFR > 60, *n* = 46	GFR < 60, *n* = 40	*p*-value
Bleeding requiring surgery	11 (23.9)	11 (27.5)	0.704
HF requiring RVAD	2 (4.3)	3 (7.5)	0.533
Stroke	6 (13.0)	13 (32.5)	0.03
Ischaemic	*4 (8.7)*	*5 (12.5)*	*0.565*
Haemorrhagic	*2 (4.3)*	*8 (20.0)*	*0.024*
Renal failure requiring continuous venovenous haemofiltration	13 (28.3)	17 (42.5)	0.167

CVVHD, continuous venovenous haemodialysis.

TABLE 23 Kaplan–Meier survival results for populations who received more than one type of VAD

			% survival		
Study	Population	*n*	Month 1	Month 3	Month 6
Sandner 2009[91]	BTT (Austria) aged ≥ 60 years	30	92.9	79.9	74
Sandner 2009[91]	BTT (Austria) aged < 60 years	56	90.0	62.0	37.0
Sandner 2009[92]	BTT (Austria) normal renal function	46	91.3	79.9	72.6
Sandner 2009[92]	BTT (Austria) abnormal renal function	50	92.5	66.5	47.9

TABLE 24 List of causes of death reported in included papers reporting a mixture of devices

First author	Date	Country	Reference number	Causes of death
Drews	2010	Germany	87	Cardiomyopathy, ischaemic cardiomyopathy, other heart diseases
Klotz	2006	Germany	88	Multiorgan failure, cerebral, right HF, sepsis, bleeding, rejection
Nativi	2011	USA	89	Head trauma, stroke, infection, graft failure, CAV, acute rejection, technical, multiorgan failure, renal failure, pulmonary, cerebrovascular, malignancy
Oswald	2010	Germany	90	Thromboembolic events and haemorrhage, in particular stroke
Sandner	2009	Austria	92	Sepsis, haemorrhagic stroke, multiorgan failure, ischaemic stroke, unknown causes

TABLE 25 Range of main adverse events by device type (% of patients with event)

Device[a]	Bleeding requiring transfusion	Stroke	Infection (sepsis)	Device failure	HF	Reoperation	Renal failure
HMII	11–21%	4–40%	17–48%[b]	1–10%	3–28%	11–27%	3–40%
HW (one study only[83])	4%[c]	12%	10%	14%	6%	20%[c]	10%
MicroMed DeBakey (one study only[84])	NR[d]	12%[e]	3.3%[f]	3%	NR	32%[d]	NR
DuraHeart (two studies[42,85])	24%	18%	18%	6%	30%	NR	15%
Mixture of devices (six studies[83–93])	23–27%	1.5–32%	NR	2%	3.6–10%	24–28%	6–53%

NR, not reported; TIA, transient ischaemic attack.
a Those studies reporting data for BTT patients.
b Range from Pagani 2009[71] and Adamson 2011.[56]
c 20% bleeding requiring surgery.
d Reoperation for bleeding 32%.
e Composite of embolic stroke, TIA and peripheral embolism.
f Device infection.

The wide range of rates for stroke, with a very high upper end, represents data from a variety of studies. Higher rates of stroke emanate from shorter studies, as stroke is more likely to occur in the first 3 months after an implant (*Figure 24*).

Early follow-up data (e.g. at 1–3 months) cannot reliably be extrapolated to longer time periods (e.g. over 6 months) owing to the changing adverse event profile over time. Also, as few of the papers reported outcomes beyond 12 months, numbers and percentages in *Table 25* represent the best estimate of adverse events likely in the first year after the VAD intervention, but cannot reliably be extrapolated to later years after the intervention.

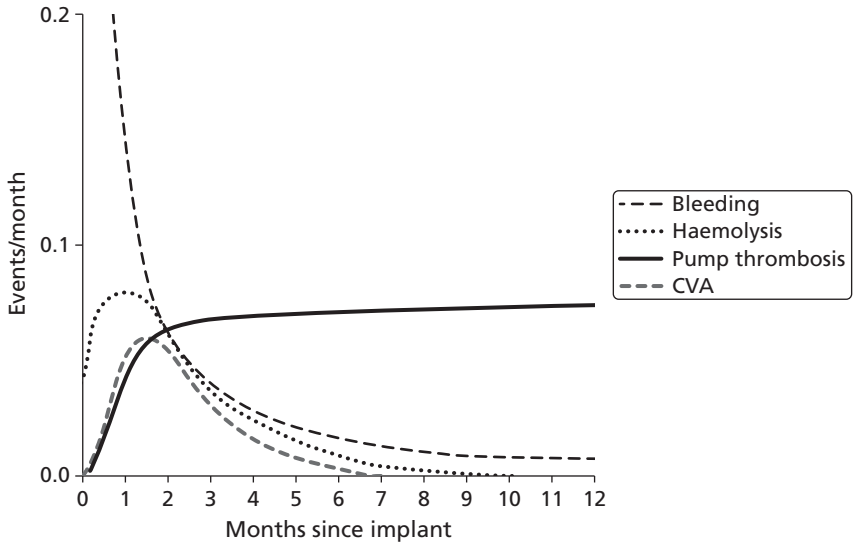


FIGURE 24 Hazard analysis depicting varying incidence over time of four major adverse events: stroke, reoperation for bleeding, pump thrombus and haemolysis (redrawn from Goldstein 2003[84]).

Kaplan–Meier estimates of survival post implant of the HMII device suggest improvement with growing experience. The best 1-year survival estimate for this device was 85%. A similar estimate of 85% survival at 1 year was reported for 50 HW patients (investigated at centres in Europe and Australia). While preparing this report, Aaronson *et al*.[94] published a larger study of 140 US HW patients and estimated survival at 1 year to be 86%. Estimates of survival at 1 year for other devices as reported in the included publications were less impressive (INCOR 61% and DuraHeart 76%). It should be borne in mind that in estimating survival of BTT patients during VAD support using K–M analyses, those patients who receive a HT are censored at the time of transplant; if these patients are unrepresentative of the overall population studied (e.g. have a poorer prognosis than uncensored patients) then survival may be overestimated (and vice versa). Furthermore, any comparison across device types for any outcome may be confounded by differences in underlying populations (e.g. geography, time period, eligibility criteria, case mix, etc.)

Quality of life and functional status, where these were measured for patients who were still alive, showed a trajectory of improvement in the first year after implant for all groups of patients especially over the first 3 months. Improvements at 6 months were statistically significant in studies of HW and HMII.

In the next chapter we describe the individual patient data (IPD) set provided by the NHS Blood and Transplant National Registry (BTNR) from the UK Blood and Transplant Database (BTDB) maintained on behalf of the UK transplant community and explain derivation of parameters for the Warwick Evidence cost-effectiveness model.

Chapter 4 Individual patient data set

This chapter provides a narrative description of the IPD set provided by the BTNR form the BTDB maintained on behalf of the UK transplant community as part of the National Specialist Commissioning Advisory Group (NSCAG)-funded VAD programme. The data set is known here as the BTDB. Data are included from May 2002 to December 2011. The data are collected for patients from six UK centres (listed below) which are responsible for carrying out VAD implantation surgery:

1. Royal Brompton & Harefield NHS Foundation Trust (RB)
2. Papworth Hospital NHS Foundation Trust
3. Newcastle upon Tyne Hospital NHS Foundation Trust (NUT)
4. Glasgow Golden Jubilee National Hospital (GJNH)
5. University Hospital of Birmingham NHS Foundation Trust (UNB)
6. University Hospital of South Manchester NHS Foundation Trust (UHSM).

Within this report VADs used for BTT in the UK have been considered. This chapter explains the BTDB data sets used for calculating parameter values in order to evaluate cost-effectiveness of the VAD economic model. For the purpose of this report and in line with the scope, information and analyses have not been stratified by centre.

Selection of patients

Ventricular assist devices are implanted in patients who have deteriorating advanced HF according to NSCAG's service specification. The clinical guidance recommends VAD implantation for patients as a BTT until a suitable heart donor becomes available. The specified indications are for patients with:

- Low cardiac output (cardiac index < 2.2 l/minute/m^2) despite an adequate preload [central venous pressure (CVP) > 12 mmHg or pulmonary capillary wedge pressure (PCWP) > 16 mmHg] and who require inotropic and/or intra-aortic balloon pump (IABP) support for:
  - symptomatic hypotension (systolic BP < 90 mmHg)
  - secondary organ dysfunction (especially renal and hepatic).
- Better haemodynamic status than mentioned above, but in a rapid rate of deterioration such that the patient is unlikely to survive until transplantation.

Structure of the database

The clinical data were collected at different centres and at different time intervals and have been collated into four categories. These data sets are:

1. Waiting list – MM group
2. VADs surgery
3. VADs follow-up

} BTT patients

4. HT

The WL constitutes all the advanced HF patients who are registered for a HT. This data set contains patient information regarding previous medical history and baseline characteristics of the patients. This information

is then matched with donor hearts to decide on the feasibility of HT. A hypothetical comparator group was formed by removing the BTT patients from the WL. This group constitutes the MM group.

The information for the VAD patients in the BTDB is entered in two subsets. The first data set in the BTDB is a consolidated representation of all VADs surgery and outcomes. This data set contains basic information for VADs patients such as unique reference number, diagnosis details, implant details, dates, current status, etc. All this information relates to the VADs surgery phase. The second data set in the BTDB gives further information for patients in each time phase from VAD implant until the end of follow-up or explant (if the patient is still alive and has not received a HT), HT (if transplanted), or death. A diagrammatic representation of the second data set is shown in *Figure 25*. The second data set was useful for derivation of transition probabilities between health states for use in the economic model.

The HT data set pools information on patients from the BTT group as well as the MM group along with others, for which registration details were missing, although they received a HT. The next section provides detailed numbers. This data set also provides patient information at different time intervals (i.e. registration, transplant and follow-up post HT). The patient information includes both clinical measurements as well as demographic information.

Contents of the database

In order to evaluate cost-effectiveness of VADs, we identified two patient groups: BTT and MM.

1. BTT. This group includes patients who fulfilled the eligibility criteria for VAD implants (see indications above) who received a VAD implant as a BTT.
2. MM. This group includes patients who fulfil the eligibility criteria for HT but who do not receive a VAD and who are supported on MM until a suitable heart donor becomes available.

On the basis of clinicians' suggestions, we divided the patients in the MM data set into three subcategories (*Figure 26*). These categories are listed below:

(a) patients who had not received inotropes (non-inotrope)
(b) patients who had received inotropes (inotrope)
(c) a third group (others for whom no information was available about inotrope treatment).

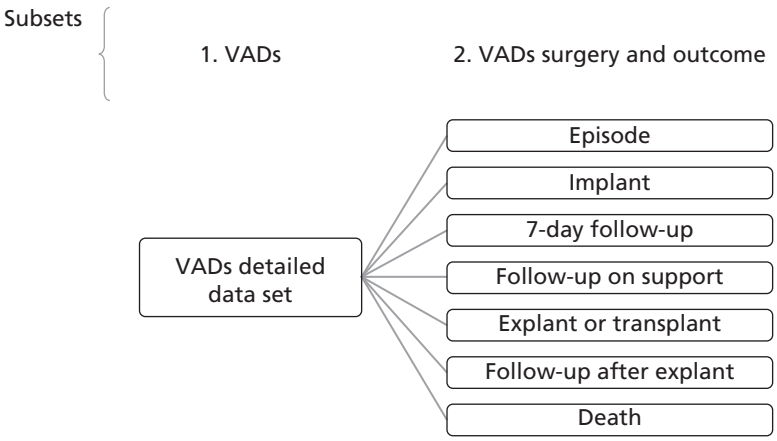


FIGURE 25 Ventricular assist devices detailed data set.

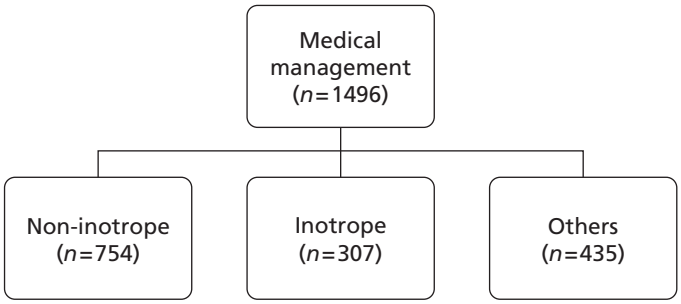


FIGURE 26 Classification of MM patients.

Results

Waiting list patients

The WL data set reported analysable registration data for 33 BTT patients and 1496 MM patients collected during the period January 2002 to December 2011. *Figure 27* illustrates the outcomes for the MM subgroup as reported in the data set.

Of the 1496 MM patients, 1005 (67.18%) patients received a HT (*Transplanted*) and 154 (10.3%) patients died while on the WL (*Died on WL*) before receiving a HT. The data set included 207 (13.84%) patients who were completely removed from the WL because of substantial improvement in their condition, deterioration in their condition or through patient choice. These patients were referred to as *Removed from WL* in the data set. Of the remaining 130 (8.69%) patients, some were temporarily removed (*Suspended*) from the WL due to serious illness such that a HT was inadvisable or because further medical testing was required, while others (*Active*) were still waiting for a transplant.

The next section gives outcomes for the various subgroups identified in the MM arm.

Baseline characteristics for the non-inotrope group (*Figure 28*) are reported in *Table 26*. The median reported age of the patients in this non-inotrope group was 48 years. Almost three-quarters of the group were male. These patients had poor health as evidenced by their NYHA class. More than 95% of the

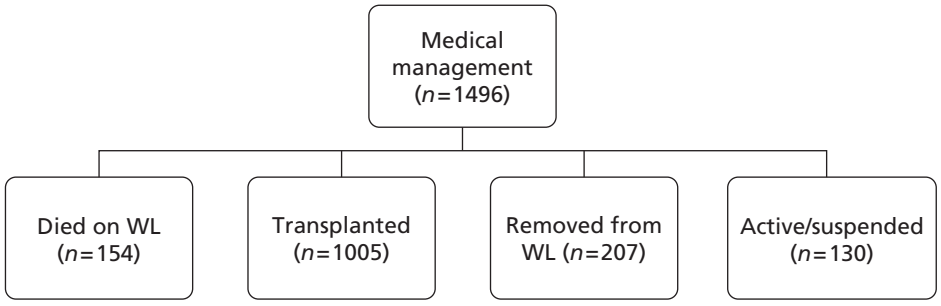


FIGURE 27 Medical management patients.

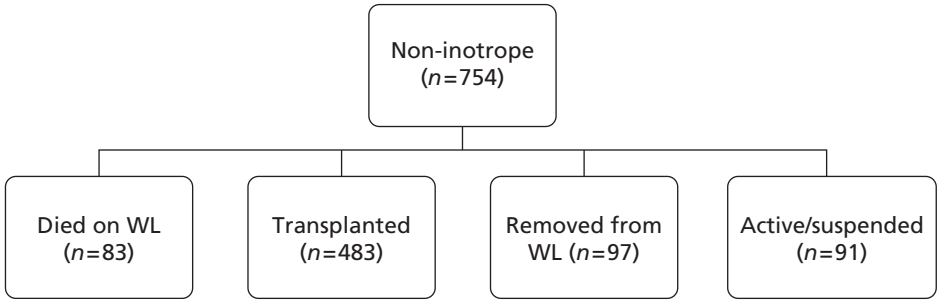


FIGURE 28 Non-inotrope subgroup.

TABLE 26 Summary table for all MM patients

Characteristics	Subcategory	Non-inotrope, *n* (%)	Inotrope, *n* (%)	Others, *n* (%)
Age (years)	Mean	45.34	41.98	47.89
	Median	48	58	50
	SD	13.49	14.16	12.18
	Range	16–68	16–66	16–68
Gender	Male	564/754 (74.8)	236/307 (76.87)	318/435 (73.1)
	Female	190/754 (25.2)	71/307 (23.13)	117/435 (26.9)
Ethnicity	White	676/754 (89.66)	266/307 (86.64)	395/435 (90.8)
	Asian – Asian British	41/754 (5.44)	26/307 (8.47)	26/435 (5.98)
	Black – Black British	28/754 (3.71)	6/307 (1.95)	10/435 (2.3)
	Others	9/754 (1.2)	9/307 (2.93)	4/435 (0.92)
NYHA class[a]	I	2/753 (0.27)	1/307 (0.33)	2/422 (0.47)
	II	40/753 (5.31)	1/307 (0.33)	12/422 (2.84)
	III	504/753 (66.93)	43/307 (14.01)	307/422 (72.75)
	IV	207/753 (27.49)	262/307 (85.34)	101/422 (23.93)
Previous open heart surgery[b]	None	493/750 (65.73)	244/305 (80)	316/424 (74.53)
	1 or more	257/750 (34.27)	61/305 (20)	108/424 (25.47)
AICD		247/754 (32.76)	58/307 (18.89)	114/435 (26.21)
Hypertension		142/754 (18.83)	43/307 (14.01)	96/435 (22.07)
Diabetes mellitus		25/754 (3.32)	7/307 (2.28)	22/435 (5.06)
Previous HT		12/754 (1.59)	2/307 (2.39)	3/435 (0.69)

AICD, automatic implantable cardioverter defibrillator.
a NYHA was not reported for one patient in the non-inotrope group and 13 patients in the 'others' group.
b Previous open heart surgery was not reported for four patients in the non-inotrope group, two patients in the inotrope group and 11 patients in the 'others' group.

patient groups were categorised either NYHA class III or class IV. Approximately one-third of the patients had had an automatic implantable cardioverter defibrillator (AICD) before registration for a HT. Hypertension was present in a fifth of the patients. One-third of the patients in this subgroup had already had open heart surgery. Just over 3% of patients had diabetes mellitus prior to HT registration.

Patients in the inotrope group were older than those in non-inotrope group; the median age in the inotrope group was 58 years. Almost three-quarters of patients were male. The patients in this subgroup had much poorer health than the non-inotrope group. The NYHA class confirm this, as > 99% of the patients were either NYHA class III or class IV. Almost a fifth of the patients had AICD before registration. A small number (22%) of patients had already undergone open heart surgery and a very small number had already undergone a previous HT. *Table 26* reports the baseline characteristics of the 'other' group illustrated in *Figure 29*.

Patients in the 'other' group have a median age of 50 years. Three-quarters were male. Approximately three-quarters of the patients (~ 73%) in this group belonged to NYHA class III with fewer (~ 24%) belonging to NYHA class IV. There were some patients for whom NYHA class was not reported. One-quarter of these patients had already had an open heart surgery and three patients had already undergone HT surgery.

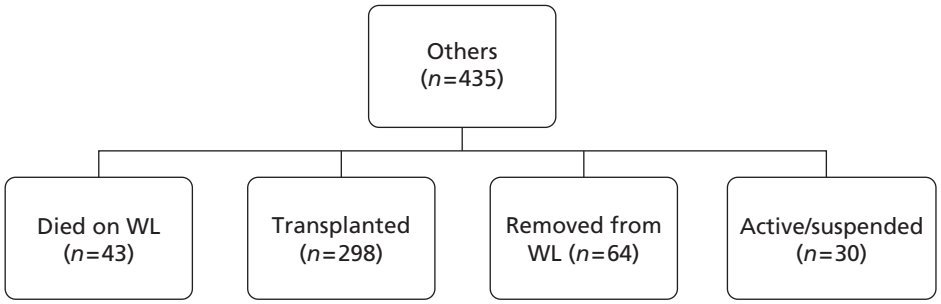


FIGURE 29 The 'other' group.

Summary table

Baseline characteristics for each of the three groups of MM patients are given in *Table 26*.

Baseline characteristics for inotrope patients (*Figure 30*) are reported in *Table 26*.

Bridge to transplant patients

To gain a better understanding of the BTT patients the data were cleaned and merged. Individual identifiers in separate data sheets were matched and then combined so that individual patient characteristics of patients who received a VAD implant were amenable for further analysis.

Figure 31 illustrates the case mix of patients who had received a VAD. The cleaned data set included 235 of the total 389 VAD patients. All these patients were further categorised into three main categories depending on the current status of their VAD implant. If patients still had a VAD and were awaiting HT they were categorised as *VAD patients*; just over three-quarters of the patients ($n = 181$; 77%) belonged in this category. Thirty-three patients (14%) had received a HT and are referred to as *Transplanted*. The remaining patients had had their VAD removed and are referred to as *Explanted*.

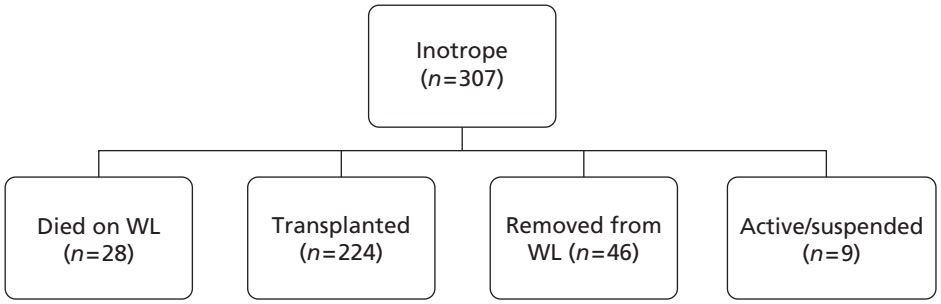


FIGURE 30 Inotrope subgroup.

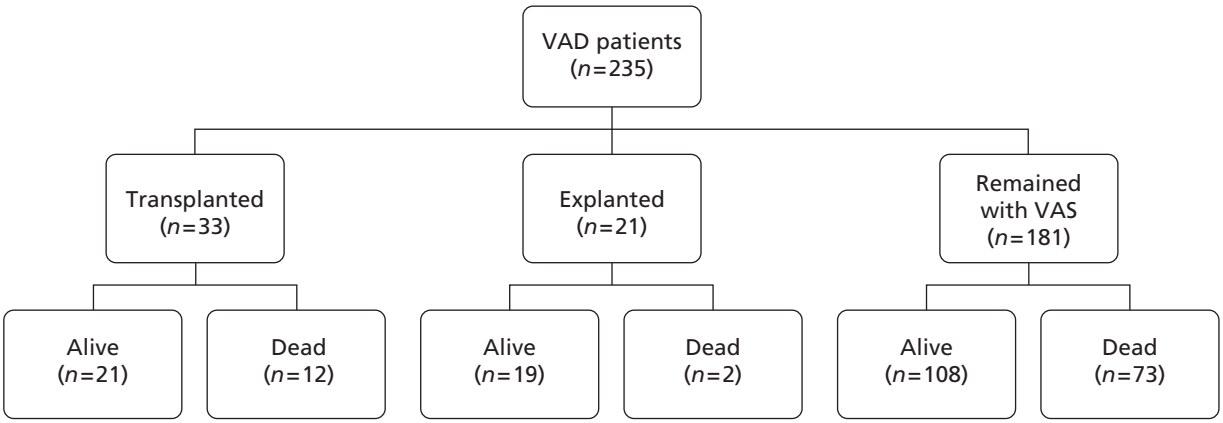


FIGURE 31 Ventricular assist device patient set.

The number of VAD implants has grown with an overall eightfold increase over a period of 10 years and with significant growth over the last 3 years. The year-over-year graph (*Figure 32*) illustrates this trend.

Current practice in the UK is to use a second- or higher-generation VAD implant in patients. *Table 27* lists the second or higher generation FDA-/CE-approved VADs used for the UK patient cohort. The two most commonly used VADs are HW and HMII.

Baseline characteristics of VAD patients are reported in *Table 28*. Information mainly includes patient demographics, past medical history and some clinical measurements. The median age for VAD patients was 47 years and > 80% were male. Almost three-quarters of VAD patients had received intravenous inotrope therapy. ARB use was reported for 10% of patients. Beta-blockers were used in more than one-third of the patients, as were ACE inhibitors.

Previous medical history also included previous VAD implant, use of IABP or extracorporeal membrane oxygenation (ECMO). Just over 25% of VADs patients already had IABP before implant. A very small number (~ 3%) of the patients were on ECMO support during the pre-operative phase.

Within the first 7 days a number of adverse events were reported in BTT patients. These are shown in *Table 29*. Right HF as well as renal failure were the most common problems faced by these patients. Infection and neurological dysfunction were other prominent adverse events which occurred in the VAD-supported patients. A few patients ($n = 3$) also suffered from device malfunction.

Adverse events reported during the follow-up period post 7 days VAD implant are reported in *Table 30*. Infection was the most common, ~ 15% patients suffered with infection. Other patients had neurological dysfunction and right HF. During the follow-up period two patients were rehospitalised each due to infection and right HF.

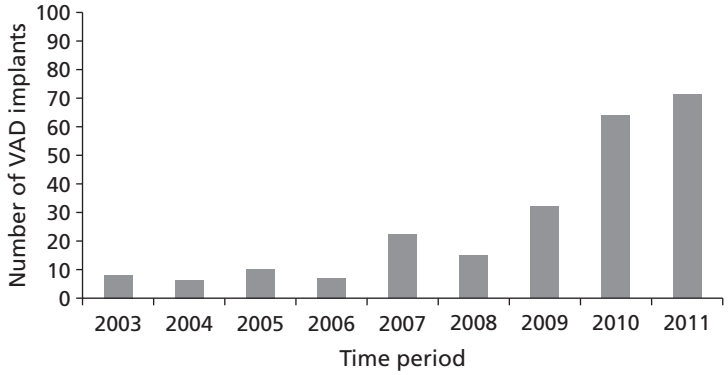


FIGURE 32 Trends of rising VAD implants over a period of 10 years.

TABLE 27 Ventricular assist devices used for chronic patients

Rank of commonly used devices	Types of devices	Number used
1	HW	125
2	HMII	82
3	Jarvik 2000 LVAD	23
5	MicroMed DeBakey	5
Total		235

TABLE 28 Baseline characteristics of the VAD and HT patients

Patient characteristic	Subcategory	VAD, mean number (%)	HT, mean number (%)
Age (years)	Mean	44	45.46
	Median	47	48
	SD	13.41	13.12
	Range	16–66	15–68
Gender	Male	189/235 (80.43)	814/1101 (73.93)
	Female	46/235 (19.57)	287/1101 (26.07)
Ethnicity[a]	White	204/225 (90.67)	991/1101 (90.01)
	Asian – Asian British	10 (4.44)	71/1101 (6.45)
	Black – Black British	7/225 (3.11)	18/1101 (1.63)
	Others	4/225 (1.78)	21/1101 (1.91)
NYHA class[b]	I	0 (0)	1/1089 (0.1)
	II	1/31 (3.23)	30/1089 (2.75)
	III	12/31 (38.71)	549/1089 (50.41)
	IV	18/31 (58.06)	509/1089 (46.74)
Systolic BP	Mean	97	
	Median	97	
	SD	14.07	
	Range	60–130	
Inotrope use		180/235 (76.6)	305/1101 (27.70)
Beta-blocker use		106/235 (45.1)	
ARB use		25/235 (10.64)	
ICD use		112/235 (47.7)	
Pre IABP		68/235 (28.94)	
Pre VAD		15/235 (6.39)	
Pre ECMO		8/235 (3.4)	
Ace inhibitors		94/235 (40)	

ECMO, extra-corporeal membrane oxygenation; ICD, implanted cardiac device.
a Ethnicity is not reported for 10 VAD patients.
b NYHA class is based on 31 VAD patients and 1089 HT patients.

Some of the VAD explanted patients had adverse events. Infection ($n = 3$) and neurological disorder ($n = 3$) were the two main adverse events among patients after the VAD explant surgery.

During follow-up period of the VADs patients received a HT while some remained on VAD implants. Some patients ($n = 68$) died. The main reasons reported for death are given in *Table 31*.

Heart transplant patients

Figure 33 explains patient mix of the HT patients. There were 1101 patients, including BTT patients as well as MM patients, on the WL for HT. Of these, 33 of the patients were in the BTT arm and had received a VAD implant later followed by a HT. The majority of patients (91.2%), however, were from the MM subgroup. Almost half were in the non-inotrope patient subgroup. The remaining half was shared

TABLE 29 Adverse events within 7 days of VAD implants

Adverse events after VAD implant	No. (%) of patients (*n* = 235)
Infection	26 (11.06)
Neurological dysfunction	10 (4.26)
Device malfunction	3 (1.28)
Haemolysis	1 (0.4)
Right HF	32 (13.62)
Renal failure	46 (19.57)

TABLE 30 Adverse events during follow-up period after 7 days of VAD implantation

Adverse events after VAD implant	No. (%) of patients (*n* = 235)
Infection	38 (16.17)
Neurological dysfunction	10 (4.3)
Device malfunction	7 (2.98)
Haemolysis	3 (1.28)
Right HF	9 (3.83)
Hypertension	1 (0.43)

TABLE 31 Reasons for death

Reasons listed for death	No. (%) of patients (*n* = 235)
Pulmonary	3 (1.28)
Bleeding	14 (5.96)
Cardiovascular	6 (2.55)
Infection	7 (2.98)
Liver failure	2 (0.85)
Other	34 (14.47)
Device malfunction	1 (0.43)
CNS	1 (0.43)

CNS, central nervous system.

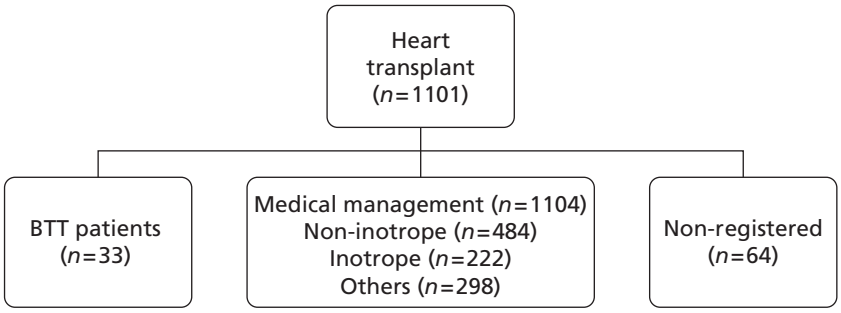


FIGURE 33 Heart transplant patients.

between the inotrope and the 'other' subgroup. There were 64 unregistered patients who spent no time on the WL but went straight to a HT.

Baseline characteristics for the HT patients are given in *Table 28*. The reported median age for a HT patient was 48 years. Almost three-quarters of the patients were male. Almost all the patients belonged to either NYHA class III or class IV, although there were a few in NYHA class I and class II. Of note are the differences in NYHA classification between transplant patients and VAD patients in *Table 28*, with very different inotrope usage (~ 75% for the VAD patients compared with ~ 25% for the HT patients).

Intra-aortic balloon pump use was reported in almost 10% of transplant patients and ECMO support in 1% of transplant patients during the pre-transplant phase.

Assessment of the utility and quality of the UK Blood and Transplant Database

This section considers the utility and quality of the data set from the perspective of the requirements for the present report. Unsurprisingly, the database structure of this resource was not tailored specifically for the task in hand. Therefore, to extract relevant information for the economic model required some readjustment and modification. The strengths and weakness of the data sets are briefly summarised below.

Strengths

1. The database was comprehensive in that it contained information on all patients listed for HT within the six designated UK NHS centres between May 2002 and December 2011.
2. It was possible to identify which VAD had been implanted into BTT patients.
3. It was possible to distinguish between BTT and MM patients. The patients who fulfilled the eligibility criteria (see *Appendix 6*) for HT were clearly registered for HT.
4. The data set reported information about the various important events occurring at different time intervals during the BTT and post-transplant phases.
5. Mortality and time of transplant were recorded in an efficient manner in that patients were followed up routinely and at each time point, current transplant and mortality status were reported. It has therefore been possible to make reasonable estimates of transition probabilities between health states necessary for economic modelling.

Limitations

1. The data set had no information about patients during the pre-VAD phase. Assumptions about clinical treatment and events during that phase had to be made in order to carry out economic modelling.
2. The data set had missing values for some of the important covariates for some of the patients. It had been hoped to use the full set of SHFM covariates in order to make use of the SHFM[95] to model survival

for VADs patients in the database, but because of incompleteness of data it was necessary to undertake modelling with those few covariate values that were available in the database.
3. A few of the patients ($n = 15$) in the data set had an apparent negative waiting time for receipt of a donor heart. This happened because such patients are taken off the WL on receiving a VAD and then put on the WL for receiving a HT, and only recent registration dates are available.
4. NYHA stage was not reported for all BTT patients. A full data set for this variable would have allowed a more rigorous assessment of QoL and utility values for use in the economic model.
5. In the systematic review of clinical effectiveness the adverse events were considered according to the type of device. However, we have described here adverse events experienced post-VAD implantation for all devices as the BTDB data did not clarify these in an interpretable format after 7 days of implantation.
6. There were no cost data in the database.
7. It was hoped to use the database to estimate resource-use incidence and intensity for each health state so that an estimate of current costs associated with the NHS transplant programme could be made in conjunction with NHS reference costs and based on the BTDB. However, as data sets were not complete in terms of resource use – especially for hospital stay and duration, and frequency of medication use in the different health states – alternative modelling procedures were necessary.

Quality assessment

Quality assessment of the BTDB was carried out[96] (*Table 32*). It should be noted that the four data sets were updated over a period of 10 years.

Quality assessment was carried out with the help of the statisticians at the BTNR. The completeness of recruitment is very high for all data sets. Three data sets reported 97% catchment of the target population, and one data set captured most of them (90–97%). However, there is some concern about completeness of data in all the data sets. As already mentioned, several important covariates ($n = 16$) of the SHFM[95] model were not reported and only 5 of the total of 21 covariates used for SHFM analysis were reported. The data sets used explicit definitions for covariates which were well explained for each of the four data sets. Three data sets reported thorough range, consistency and validity checks.

Comparison of individual patient data with literature estimates

Table 33 gives a comparison of the BTDB individual patient baseline characteristics for the 235 UK VAD patients with values for similar patients reported in the international literature (see *Chapter 3*). The UK population implanted with VADs and awaiting a donor heart appear to be younger in mean age, with a less severe NYHA class rating and are more likely to be white.

The proportion of patients using inotropes is of particular relevance to the economic model used in this report. More than three-quarters of BTDB VAD recipients used inotropes, whereas the pooled estimate for published BTT studies with non-overlapping populations and the estimate reported in the registry study by John *et al*.[65] was slightly higher, at 80%. Just over 20% (307) of the 1496 BTDB MM patients were categorised as using 'inotrope' treatment; this lower use of inotropes relative to the BTDB BTT patients tends to support the use of the 'inotrope' category group patients for the base-case comparator group in the economic model.

Conclusion

The BTDB provides valuable information about patient subgroups and the timing of important events for all patients listed for HT under the UK transplant programme for the period May 2002 to December 2011. There were insufficient complete data to estimate resource use or costs associated with the programme.

The following chapter reports the cost-effectiveness review of the literature. The subsequent chapters describe further analysis of this database for use in the Warwick Evidence model.

TABLE 32 Quality assessment of the data sets based on previous quality assessment tool. Adapted from Black *et al.*[96]

Quality criterion	Subcategory	No. of data sets
Completeness of recruitment	Few (< 80%) or unknown	0
	Some (80–89%)	0
	Most (90–96%)	1
	All or almost all (≥ 97%)	3
Completeness of data	Few (< 80%) or unknown	1
	Some (80–89%)	0
	Most (90–97%)	1
	All or almost all (≥ 97%)	2
Use of explicit definitions of the variables	None	0
	Some	0
	Most (90–97%)	0
	All or almost all (≥ 97%)	4
Independence of observations of the primary outcome	Observer not included	N/A
	Observer neither independent nor included	N/A
	Independent observer not blinded	N/A
	Independent observer blinded or outcome is objective	N/A
Extent of data validation	No validation	1
	Range or consistency checks	0
	Range and consistency checks	0
	Range and consistency checks and validity checks	3

N/A, not applicable.

TABLE 33 Comparison of baseline characteristics from different sources

Baseline characteristics	BTDB (VAD) estimate (95% CI)	Pooled published studies estimate (95% CI)	Registry studies (Nativi 2011[89] or John 2011[65]) estimate (95% CI)
Age (mean, years)	44.00 (42.72 to 45.28)	50.80 (49.30 to 52.38)	50.80 (49.84 to 51.76)
Gender (% male)	80.40 (74.77 to 84.99)	84.20 (79.40 to 88.00)	82.30 (78.24 to 85.81)
% NYHA (class IV)	58.10 (39.07 to 75.45)	83.50 (78.00 to 87.90)	Not available
Ethnicity (% white)	89.70 (81.80 to 90.86)	69.20 (60.60 to 76.90)[a]	Not available
% use of inotropes	76.60 (70.65 to 81.85)	80.10 (50.90 to 94.50)	80%
% use of beta-blockers	45.10 (38.63 to 51.71)	38.30 (30.10 to 47.20)[a]	Not available
% use of ACE inhibitors	40.00 (33.69 to 46.57)	30.10 (22.40 to 94.50)[a]	Not available
% use of systolic BP	97.00 (95.71 to 98.28)	97.30 (92.80 to 101.71)	Not available

a Based on single study of Miller *et al.*[70]

Chapter 5 Review of cost-effectiveness publications

Introduction

A previous HTA report by Clegg *et al*.[4] investigated LVADs as a BTT, as a BTR or as a long-term chronic support for people with advanced HF. The authors undertook a systematic review with searches up to 2003. Sixteen studies assessed VADs as BTT, with the majority relating to first-generation devices. The methodological quality of studies was considered to be weak. The authors found limited differences in survival between different types of VADs.

Clegg *et al*.[4] found that patients receiving the pulsatile HM 'experienced some benefit in actuarial survival' and functional status when compared with inotropic agents. They considered that there is a paucity of data in this area. The authors also undertook a systematic review of cost–utility analyses, identifying no relevant cost-effectiveness studies. They developed two models to evaluate the use of VADs: (1) as a BTT and (2) as long-term chronic support for patients suffering from advanced HF, finding that VADs were not cost-effective for either of the indications.

They found the baseline cost per quality-adjusted life-year (QALY) of the first-generation HM to be £170,616. Sensitivity analyses had little effect on this value. Clegg *et al*.[4] suggested that, given the decline in the number of hearts available for transplant that rather than further developing VADs, researching how to improve organ donation may be more prudent and valuable.

In 2006, Sharples *et al*.[30] undertook an evaluation of the VADs programme in the UK.[30] The objectives of the study included summarising the relevant clinical effectiveness and cost-effectiveness literature and constructing cost-effectiveness and cost–utility models of VADs in a UK context, using data on outcomes (including survival, transplantation rates, HRQoL and resource use) to assess the factors that drive costs and survival.

Sharples *et al*.[30] updated the Clegg *et al*.[4] review. Most of the included studies were of first-generation VADs, with only a few reporting mixed use of first- and second-generation devices. Sharples *et al*.[30] found the evidence for effectiveness of VADs used for all indications 'limited'.[30] They reported that the 'methodological quality of the studies for assessing the effectiveness of VADs as a BTT, a BTR or a long-term circulatory support was weak' because of the small-scale observational nature of the studies and their potential for bias. They concluded that evidence for second-generation devices was not yet available. As far as studies of the cost-effectiveness or cost–utility of VADs were concerned, at that time the authors concluded that both for BTT or for longer-term support methodology was also weak and that further studies based on actual resource use were needed.

Sharples *et al*.[30] developed cost-effectiveness and cost–utility models using IPD from the UK NHS funded VAD programme on all 70 patients with VADs implanted during the period April 2002 to December 2004.[30] Comparator groups were drawn from those on the WL for HT [non-VAD-supported transplant candidates ($n = 250$)] who were divided into two groups – those on standard supportive MM ($n = 179$) and those on inotropic support alongside MM ($n = 71$). A final hypothetical group was used in models, which comprised a worst case scenario, where, without VAD technology, all eligible patients would otherwise die in the intensive care unit (ICU) within 1 month. Individual patient-based QoL and resource data were collected and a multistate model of VAD and transplant activity was constructed populated with the data described.

The authors found that survival after a VAD was 74% at 30 days and 52% at 12 months which compared with a survival at 12 months after a transplant of 84%. VAD patients experienced on average between five and six adverse events each, mostly in the first month after VAD implant. Main adverse events were respiratory problems, bleeding and infections. Subsequent HT had similar outcomes for both VAD and MM (non-VAD) groups in terms of survival at 1 year, functional status (NYHA) and European Quality of Life-5 Dimensions (EQ-5D).

At that time, the mean VAD implantation cost, including the device and the main cost drivers (e.g. staffing, lengths of ICU and hospital stay and adverse events), was £63,830. Sharples *et al.*[30] concluded that for the base case:

- For a VAD patient, extrapolating over the patient's lifetime, mean cost was £173,841, with a mean survival of 5.63 years and mean QALYs of 3.27.
- For MM inotrope-dependent patients, costs were £130,905, with a mean survival of 8.62 years and mean QALYs of 4.99 (this intervention was considered to be dominant).
- For non-inotrope-dependent patients who had a HT, similar survival rates to patients on inotropes with lower costs meant that this scenario was also dominant.
- For the 'worst case scenario' the mean lifetime incremental cost-effectiveness ratio (ICER) for VADs was £49,384 per QALY. However, as neither the inotrope-dependent transplant candidates nor the worst case scenario were considered fair controls, a mixture of these scenarios was investigated, here the ICER for VADs ranged from £79,212 per QALY to the non-VAD group being both cheaper and more effective.[30]

The authors concluded that there were 'insufficient data from either published studies or the current study to construct a fair comparison group for VADs', but that in as far as comparisons could be made, VADs would not be cost-effective at traditional thresholds. They suggested, however, that VADs could be justified in selected cases based on survival and for maintaining 'skills required for implantation and management'.[30]

Cost-effectiveness studies: literature searches

The HTA reports by Clegg *et al.*[4] and Sharples *et al.*,[30] as well as the economic studies which they describe, concerned first-generation or a mixture of first- and second-generation devices.[4,30] We therefore searched for cost-effectiveness studies of second- and third-generation VADs. The keyword search strategies developed in the review of clinical effectiveness were used. The same limits and restrictions used in the review of clinical effectiveness were employed (see *Chapter 3*). Search filters were applied to restrict the search results to economic and cost-related studies. The search strategy is described in *Appendix 2*. Searches were undertaken in February and March 2012.

Two reviewers independently screened all titles and abstracts for inclusion. Disagreements were resolved through discussion. The full texts of papers considered potentially relevant were retrieved for further assessment.

Studies were selected for inclusion if they reported cost-effectiveness estimates for BTT which employed second- or third-generation VADs. Studies which reported insufficient detail or which failed to provide an estimate of cost-effectiveness were excluded. Data were extracted by one reviewer using a predefined extraction form, and were checked by a second reviewer. The quality of the included study was investigated by a single reviewer using the Drummond assessment tool.[97]

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart is summarised in (*Figure 34*). One identified study, Moreno *et al.*,[98] satisfied the inclusion criteria and is summarised below.[98]

Aim of analysis

The authors aimed to estimate the cost-effectiveness of the HMII using the most robust and recently published evidence about its comparative performance compared with conventional therapy for patients with advanced HF.

Model structure

The model was a semi-Markov discrete-time multistate model with monthly cycles; the model design was the same as used by Sharples *et al*.[30] The health states were:

1. support on VAD to HT
2. support on conventional care to HT
3. support in the HT state
4. dead.

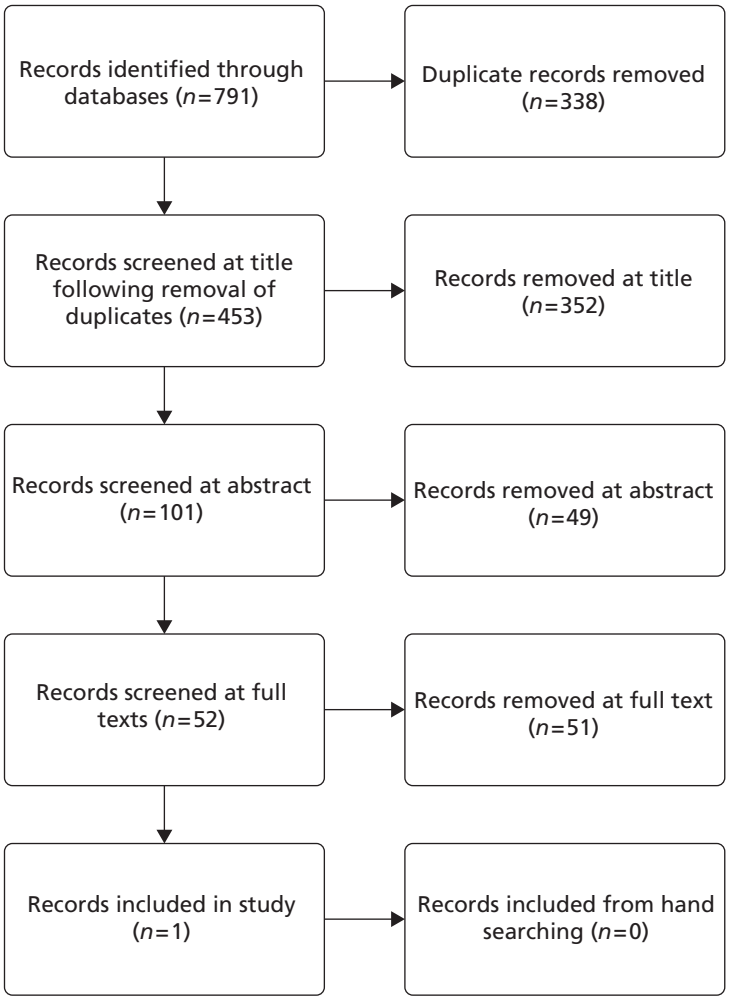


FIGURE 34 Flow chart for identification of cost-effectiveness studies.

Model inputs

Transition probabilities between health states 1 and 4 (VAD to dead), 2 and 4 (conventional care to dead) and 3 to 4 (transplanted to dead) were based on data in published studies describing survival rates: these are summarised in *Table 34*.

For the base-case analysis, all patients alive in each arm at 6 months received a HT [92% and 76%, respectively, for BTT with VAD and conventional therapy patients; transition probability (TP) at 6 months = 1]. For sensitivity analyses receipt of a transplant took place at 12 months or at 18 months. In this way the model did not require extrapolation of survival for patients with BTT or conventional care beyond the observed 18 months of data. Survival after HT was fitted with exponential distributions at 3 months and 7 years using data from Russo *et al.*,[100] extrapolated to a lifetime horizon.

The utilities attached to the health states used by Moreno *et al.*[98] were taken from Sharples *et al.*[30] and are summarised in *Table 35*.[30]

TABLE 34 Survival rates and published sources used for economic modelling

Time from VAD or HT	Mean survival rates (%)	SE	Beta distribution used for probabilistic sensitivity analysis		Source
Conventional therapy					
6 months	76	N/A	N/A	N/A	Lietz *et al.* (2007)[99]
6–12 months	69	N/A	N/A	N/A	
12–18 months	63	N/A	N/A	N/A	
LVAD implant					
1 month	92	0.016	258	23	Pagani *et al.* (2009)[71]
1–6 months	82	0.033	109	24	
6–18 months	72	0.059	42	16	
Post-HT survival					
3 months	93	N/A	N/A	N/A	Russo *et al.* (2009)[100]
7 years	65	N/A	N/A	N/A	

N/A, not applicable; SE, standard error.

TABLE 35 Utilities used by Moreno *et al.*[98]

Health state (time)	Mean	SE	Beta distribution for probabilistic sensitivity analyses	
Conventional therapy	0.500	0.092	6.5	6.5
LVAD implant				
Month 1	0.510	0.056	35.7	34.3
Month 2+	0.660	0.015	46.2	23.8
Post HT	0.760	0.015	58.5	18.5

SE, standard error.

Cost inputs (*Table 36*) were based on those of Sharples *et al.*[30] inflated to 2012 prices with the cost of the HMII device set at £94,200, the remaining cost items were given gamma distributions for the probabilistic sensitivity analysis.

Discounting of costs and benefits used a rate of 3.5% and results were expressed as ICERs calculated as cost per life-year gained (LYG) and cost per QALY.

TABLE 36 Cost inputs used by Moreno *et al.*[98] (adapted from a table in Moreno *et al.*[98])

Event	Mean (£)	SE (£)
HMII device	94,200	N/A
LVAD implant procedure	19,628	2120
Post LVAD implant		
Month 1	25,601	1669
Month 2	13,348	1297
Month 3	5075	759
Month 4	3810	602
Month 5	3226	457
Month 6	2310	354
Month 7+	1880	901
Conventional therapy		
HT assessment		
Treated Month 1	12,133	2526
Treated Month 2	6350	1320
Treated Month 3+	5925	423
HT surgery (both groups), perioperative/post operative	16,933	N/A
Theatre for HT		
LVAD patient	16,550	N/A
Conventional therapy patient	11,317	N/A
Post-HT patients		
LVAD, month 1	15,471	1667
Conventional therapy, month 1	13,120	969
Post HT, both groups		
Month 2	4301	694
Month 3	2591	407
Month 4	2808	226
Month 5	2164	374
Month 6	1634	119
Month 7+	1401	154

N/A, not applicable.

Results

The base-case results (HT received at 6 months) are summarised in *Table 37*.

Probabilistic sensitivity analysis of the base case indicated a 50% probability of cost-effectiveness at a willingness to pay of £247,000 per QALY. Other sensitivity analyses used 12- and 18-month intervals before receipt of a donor heart. The deterministic results for these are summarised in *Table 38*.

Base-case results were also reported for a 10-year time horizon; the ICER was £411,227 per QALY. A further analysis was undertaken in which the HMII was provided free of charge; this reduced the lifetime horizon ICER from £133,860 per QALY to £24,063 per QALY when the waiting time for transplant was set at 18 months, indicating that a major driver in these analyses is the cost of the device.

Authors conclusions

The authors concluded that HMII implantation does not offer better value for money than conventional MM and that it is unlikely to be cost-effective with current cost of the device. For a 50% probability of being cost-effective with 6 month transplant delay and lifetime horizon, a payer would need to be willing to pay about £247,000 per QALY.

Quality assessment and comment

This was a good-quality study using model inputs taken wholly from the published literature (refer to authors for full quality assessment according to the Drummond *et al*. assessment tool[97]). The clinical effectiveness studies used for input to the model did not derive from a systematic review of the literature; however, in comparing the studies discussed in the study with those which we identified in our own review of the literature it appears that appropriate and relevant studies were identified.

TABLE 37 Base-case deterministic results reported by, and adapted from Moreno *et al*.[98]

Base-case[a] results	
Intervention	***Survival in life-years (95% CI)***
LVAD	9.19 (8.48 to 9.91)
Conventional therapy	8.54
Diff. survival (LYG)	0.65 (–0.06 to 1.36)
Intervention	***QALYs (95% CI)***
LVAD	6.93 (5.94 to 7.93)
Conventional therapy	6.38 (5.61 to 7.16)
Diff. QALYs	0.55 (–0.01 to 1.11)
Intervention	***Costs (£) (95% CI)***
LVAD	350,939 (311,726 to 390,151).
Conventional therapy	208,444 (178,835 to 238,053)
Diff. costs	142,495 (116,413 to 168,578)
Economic outcome	***Mean ICER (£/LYG or £/QALY)***
For a LYG	219,705
For a QALY gained	258,922

Diff., difference.
a Waiting time for HT; 6-month interval; time horizon = lifetime; device cost = £94,200.

TABLE 38 Sensitivity analyses around interval to receipt of transplant

Waiting time for HT	12-month interval (95% CI)	18-month interval (95% CI)
(Time horizon; device cost)	Lifetime horizon; £94,200	Lifetime horizon; £94,200
Survival (life-years)		
LVAD	8.99 (8.34 to 9.65)	8.87 (7.84 to 9.91)
Conventional therapy	8.19	7.95
Diff. survival (LYG)	0.8 (0.15 to 1.46)	0.92 (–0.11 to 1.96)
QALYs		
LVAD	6.76 (5.84 to 7.69)	6.62 (5.54 to 7.69)
Conventional therapy	6.04 (5.31 to 6.78)	5.76 (5.04 to 6.48)
Diff. QALYs	0.72 (0.16 to 1.28)	0.86 (0.02 to 1.69)
Costs (£)		
LVAD	347,216 (313,018 to 381,414)	344,170 (303,118 to 385,222)
Conventional therapy	218,630 (190,796 to 246,464)	229,638 (198,472 to 260,804)
Diff. costs	128,586 (108,801 to 148,371)	114,532 (80,689 to 148,376)
Mean ICER (£)		
For a LYG	160,388	124,066
For a QALY gained	178,829	133,860

Diff., difference.

A weakness of this study that is common to all studies of VADs for BTT for advanced HF is the lack of a randomised comparative study in which an appropriate population of patients is randomised to each treatment strategy. A critical element in these economic studies therefore concerns the choice of the comparator population and its associated prognosis (i.e. survival). In the Moreno *et al.*[98] analysis 76%, 69% and 63% of conventional care patients survived to 6, 12 and 18 months respectively. This survival is somewhat inferior to that of the total MM population in the BTDB, but considerably superior to that of BTDB 'inotrope' patients when their survival is modelled on the robust part of the observed K–M survival plot.

A further noteworthy element of the Moreno *et al.*[98] study is the allocation of a donor heart with equal probability to both groups of live patients; this contrasts with the analysis of Sharples *et al.*,[30] in which MM patients received a donor heart with much greater probability than BTT patients.[30] It appears sensible for the purposes of a fair comparison between treatment options that each should have an equal opportunity of receiving benefits of a transplant; however, in medical practice, MM patients do in fact receive transplants much earlier than BTT patients, mainly because it makes little sense to remove a VAD from a patient who is doing relatively well to give them a donor heart which is much more urgently required by other patients. Once the premise that equal opportunity of transplant should prevail for both BTT and MM patients is accepted, then the issue becomes one of 'At what rate should this be set?' In the Moreno *et al.*[98] base case all live patients received a transplant at 6 months; in the BTDB the proportion of live BTT patients who had received a donor heart by 6 months was < 20%. It appears possible that the 18-month delay to transplant used by Moreno *et al.*[98] in sensitivity analysis is more likely to represent a real-world likelihood of receiving a transplant and may have represented a better choice for the base-case analysis (this reduces the estimated ICER to nearly half).

In the next chapter we describe design of the Warwick Evidence model.

Chapter 6 Description of model including definition of scenarios

Overview

This chapter describes the structure of the economic model, the scenarios evaluated and the probabilistic sensitivity analysis. The main assumptions of the model are also presented in this section. The underlying model is based on the study by Sharples *et al*.[30] which has been adapted for our decision problem and updated with new data. For more detailed information, readers are referred to *Chapter 7* and *8* in the Sharples *et al*.[30] report.

Model structure

An economic model was developed based on a multistate model of patient experience from the UK during the period April 2005 to November 2011. The aim of the economic model was to compare BTT with MM treatment for patients eligible for HT.

The model is a semi-Markov, multistate model as shown in *Figure 35*. In the model each patient can be in one of three mutually exclusive health states, namely alive with VAD (or MM) support (state 1), alive after HT (state 2) or dead (state 3). Each individual may move between health states or remain in the same state. State 3 (dead) is an absorbing health state. The transition between each of these health states, referred to as the TP, is represented by the quantities $p12$, $p13$ and $p23$. Transition probabilities are not fixed but depend on time t since the VAD was implanted ($p12$, $p13$) or the time t^* since transplantation ($p23$).[30] For patients on MM support, a precisely similar model was constructed, with different estimates of pre-transplantation transition probabilities ($p12$, $p13$), but the same estimates of post-transplantation transition probabilities ($p22$ and $p23$).

Cycle length was set at 1 month and transition between each health state occurs at the end of each cycle.

The model was evaluated over several time horizons. For the base-case scenario, a lifetime horizon, spanning approximately 50 years, was used. The model was also run for shorter time horizons of 3 and 10 years. The model evaluates costs from the perspective of the NHS. Thus, only direct costs related to VAD implants have been included and indirect costs are excluded. All costs are at 2010/11 UK prices in pounds sterling (£). Health outcomes were measured in QALYs. In accordance with current UK guidelines,[101] an annual discount rate of 3.5% was applied to both costs and health outcomes. Both deterministic and probabilistic approaches were used to estimate the cost-effectiveness of VADs. The probabilistic approach was used to account for uncertainty in the various variables within the model.

Base-case analysis

For the base-case analysis we used observed survival data from the BTDB. We hypothesised that although survival rates are different for each group (patients who received a second- or third-generation approved VAD as a BTT or patients who received MM support to transplant), they would have common post-transplant survival rates, with a constant death rate for months 3–12. In the base-case analysis survival up to 3 years from VAD implantation/listing were estimated using data from the BTDB based on constant death rates beyond 6 months post transplantation. Several assumptions were made when estimating longer-term survival rates after 42 months (see *Chapter 7*).

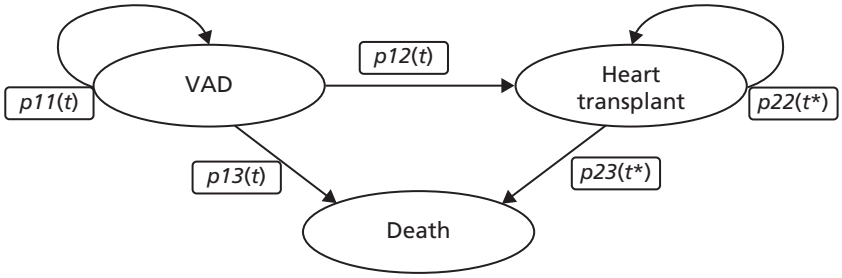


FIGURE 35 Discrete-time, semi-Markov, multistate model of health states for VAD patients. For patients on MM instead of a VAD, a precisely similar model was constructed, with different estimates of the pre-transplantation transition probabilities ($p12$, $p13$), but the same estimates of post-transplantation transition probabilities ($p22$ and $p23$). $p11(t)$, transplantation listing t in state 1; $p22(t^*)$, time since HT t^* in state 2.

Structural assumptions

Disease state/pathways

Two pathways were modelled for this economic evaluation of VADs. In the base case, patients with more severe HF (based on inotrope medication) either followed the VAD pathway or were allocated to the MM pathway. In both pathways patients received a HT after a certain period of time (which was varied according to different sensitivity analyses). Some of the patients died before receiving a HT.

Strategies/comparators

For the two research questions we compared:

- use of VADs as a BTT with MM using the inotrope subgroup of patients as the comparator group
- use of VADs as an ATT with use of VADs as a BTT. For an ATT, transition probabilities were kept the same as for patients in the BTT base-case arm, except that the probability of receiving a donor heart was set to zero.

For the sensitivity analyses we included comparisons of:

- use of the HW only, as a BTT with MM using the inotrope subgroup of patients as the comparator group as in the base case
- use of VADs as a BTT with all MM patients (both inotrope and non-inotrope)
- use of VADs as a BTT with an artificially constructed MM group using the VAD patients as their own controls. (Based on predicted survival of the VADs group – had they been treated with MM not VADs. Predictions were made using the SHFM; see *Chapter 7, Selection of comparator group and sensitivity analyses*.)

Cost-effectiveness summaries

Incremental costs and QALYs gained were estimated and summarised as the 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:

$$\text{ICER} = C_A - C_B/Q_A - Q_B \quad (1)$$

The mean costs and benefits for each group were estimated from the economic model using data from the BTDB.

The joint distribution of incremental mean costs and benefits was plotted on the cost-effectiveness plane and used to estimate both the incremental net benefit (INB), for example:

$$\text{INB}(\lambda) = [\lambda(Q_A - Q_B) - (C_A - C_B)] \quad (2)$$

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

$$\text{CEAC}(\lambda) = \text{prob}[(\lambda Q_A - Q_B) - (C_A - C_B)] > 0) \quad (3)$$

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

Estimation of model parameters

Three types of input were considered for the economic analysis: transition probabilities estimated from the BTDB, utilities derived from the published literature, and costs computed from UK data. The following assumptions were made in the base-case analysis and subsequent scenarios.

Transitions to the HT state were assumed to occur at monthly intervals and a whole month of pre-transplantation survival and costs were included. However, in practice, a transplant may take place at any time during the month and, on average, at the mid-point of the relevant month. Also, costs and utilities associated with death were assigned zero. A half-cycle correction was added to reflect the fact that a death could occur at any time during the month, although transitions were assumed to occur at monthly intervals. Thus, a transition to death would result in a reduction in survival time of 0.5 months. For the month in which death occurred no reduction in costs was required, as only costs up to death were included in these months.

In summary, for the economic model, a simple discrete-time, discrete-state model was constructed. Cost-effectiveness summaries of interest were estimated by weighting time in each state of the model by the utility and cost associated with that state. Transition probabilities, costs and utilities have been estimated using data from the NHS BTDB (see *Chapter 7*).

Quality of life and utilities

Health-related quality of life remains relatively static in HF patients who are medically managed,[102] and improves after receiving a VAD[53,103,104] or HT,[104–106] with improvements maintained for several years.[103,105,107–109] Recipients of HT report better HRQoL than recipients of VAD.[104] In the model, health outcomes were measured in QALYs, in accordance with current UK guidelines.[101] The EuroQoL EQ-5D[110] is the preferred measure of decision-making bodies such as the National Institute for Health and Care Excellence (NICE).[101] The literature revealed two applicable sources of EQ-5D utility scores derived from patients suffering from chronic HF: Sharples *et al*.[30] and Gohler *et al*.[111]

Sharples *et al*.[30] derived EQ-5D utility scores from UK patients suffering from chronic HF who were either implanted with a VAD or medically managed while waiting for HT. A subset of the group were reassessed post HT. *Table 39* shows the extracted data.

Gohler *et al*.[111] collected EQ-5D data on a subsample of the Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial (EPHESUS) trial participants. EPHESUS was a multinational RCT which investigated the effect of the aldosterone antagonist eplerenone (Inspra®, Pharmacia) in patients with chronic HF after acute myocardial infarction. Responses to the EQ-5D descriptive system were used to generate an EQ-5D utility score by applying the appropriate tariff based on participant's country of origin. Univariate and multivariate analyses were used to investigate the association of EQ-5D utility scores with NYHA class.

TABLE 39 European Quality of Life-5 Dimensions utility scores derived from Sharples *et al.*[30] (adapted from Sharples *et al.*[30])

Group	EQ-5D utility score (95% CI)
Medically managed	
All months	0.50 (0.32 to 0.68)
Post VAD	
Month 1	0.51 (0.40 to 0.62)
Month 2+	0.66 (0.63 to 0.69)
Post HT	
All months	0.76 (0.73 to 0.79)

The findings highlight the utility loss associated with worsening NYHA class, with excellent model fit found in the multivariate models. The association between NYHA class and HRQoL, including EQ-5D utility scores, is supported in the literature.[25,112,113] *Table 40* shows the relationship between NYHA class and utility.

For the purposes of this analysis we used the data provided by the BTBD to determine EQ-5D utility scores for health states in the model. The HT data set recorded NYHA class for 1011 patients who received a HT (from 2002 till the end of 2011). NYHA class was entered at initial registration and 3 months after VAD implant (for the 83 of 235 patients who subsequently received a HT). For those who received a HT, NYHA class was recorded post transplant at their 3, 12 and 24 months outpatient visits. The BTDB suggests that there is some improvement in NYHA class after HT; however, this translates into very minor changes in the weighted EQ-5D utility scores over time. *Table 41* summarises the data.

TABLE 40 European Quality of Life-5 Dimensions utility scores by NYHA class (adapted from Gohler *et al.*[111])

NYHA class	EQ-5D utility score (95% CI)
I	0.855 (0.845 to 0.864)
II	0.771 (0.761 to 0.781)
III	0.673 (0.665 to 0.690)
IV	0.532 (0.480 to 0.584)

TABLE 41 New York Heart Association class of patients post-VAD implantation and post HT

NYHA class	Post VAD				Post HT			
	3 months		3 months		12 months		24 months	
	n	%	*n*	%	*n*	%	*n*	%
	83	100.0	931	100.0	832	100.0	719	100.0
I	18	21.7	710	76.3	683	82.1	615	85.5
II	36	43.4	175	18.8	116	13.9	90	12.51
III	21	25.3	25	2.7	24	2.9	10	1.4
IV	8	9.6	21	2.3	9	1.1	4	0.6

For the model, the weighted derived EQ-5D utility score was based on the proportions of patients for each NYHA class for VAD patients (3 months post implant) and HT patients (3 months post transplant) (see *Table 41*). Thereafter, utility was assumed to remain constant.

A weighted EQ-5D utility score for all MM patients and for those MM patients receiving inotropes was similarly determined using NYHA data recorded at registration (*Table 42*) and, as with previous analysis, EQ-5D utility score was assumed to remain constant thereafter (*Table 43*). *Table 43* shows the EQ-5D utility scores used for the base-case analysis. For the sensitivity analysis, data reported by Sharples *et al*.[30] were used (see *Table 39*).

In the next chapter we describe derivation of transition probabilities between model states in more detail.

TABLE 42 New York Heart Association class of inotrope MM patients and all MM patients

NYHA class	Inotrope		All MM	
	n		*n*	
	225	%	978	%
I	0	0	2	0.2
II	0	0	40	4.1
III	24	10. 7	528	54.0
IV	201	89.3	408	41.7

TABLE 43 European Quality of Life-5 Dimensions utility scores for base-case analysis

	EQ-5D			
Group	Mean	Low[a]	High[a]	Distribution
All medically managed patients: all months	0.62	0.59	0.65	Beta
Medically managed receiving inotropes: all months	0.55	0.50	0.6	Beta
Post VAD: all months	0.74	0.73	0.76	Beta
Post HT: all months	0.83	0.82	0.84	Beta

a Low and high values represent the weighted score based on the 95% CI of extracted data[111] and therefore do not represent the true 95% CI of the sample mean.

Chapter 7 Transition probabilities between health states

This section describes the derivation of the transition probabilities between health states used in the economic model.

The transitions required are:

1. supported on VAD to death
2. supported on MM to death
3. supported on VAD to supported on HT
4. supported on MM to supported on HT
5. supported on HT to death.

For the purposes of this report survival after HT is assumed to be the same whether preceded by VAD support or MM support.

The main source of information is the BTDB. In addition, published literature sources and UK population survival data are used, especially for extrapolation beyond observed data, for sensitivity analyses and to place the current analyses in context.

Transition from support on ventricular assist device to death (bridge to transplant)

The BTDB contained analysable data for 235 patients who had received an approved second- or third-generation VAD. The mortality of these patients while on VAD support was investigated using K–M analysis in which patients were censored at the time of receiving a HT, at the time alive at last follow-up while on VAD support, or at the time of explantation of the VAD. This was necessary because there are no observed survival data for a cohort of UK patients who receive a VAD but who never receive a donor heart. The K–M plot is shown in *Figure 36*. Median survival was 32.1 months; < 25 (~ 10%) patients remained at risk after 23 months.

Because patients are removed from the cohort as they receive a HT, and because these patients are likely to be unrepresentative of original cohort (perhaps either more or less ill), then estimated survival is likely to be biased. Clinical opinion varies, but one of our clinical advisors suggested that more severely ill patients are more likely to receive a transplant and therefore the estimated survival shown in *Figure 36* may be an overestimate; on the other hand, patients must be deemed well enough to benefit from HT and this bias will also operate in the comparator (MM) arm.

Most patients had received HMII ($n = 82$) or HW ($n = 125$) devices. There were sufficient data for these patients to be analysed separately; the results are shown in *Figures 37* and in *38* respectively.

Median survival with HMII was 23.95 months but was not reached for HW, 75% of patients with the HW survived to 12 months.

As previously observed by others, survival over the first 90 days post VAD implant was poor relative to the remaining time span. For the whole population ($n = 235$), in common with previous economic analyses (Sharples *et al.*[30] and Moreno *et al.*[98]), we explored fitting a constant hazard for the first 3 months and a second constant hazard for the period 3–23 months (~ 700 days beyond which fewer than 10% of

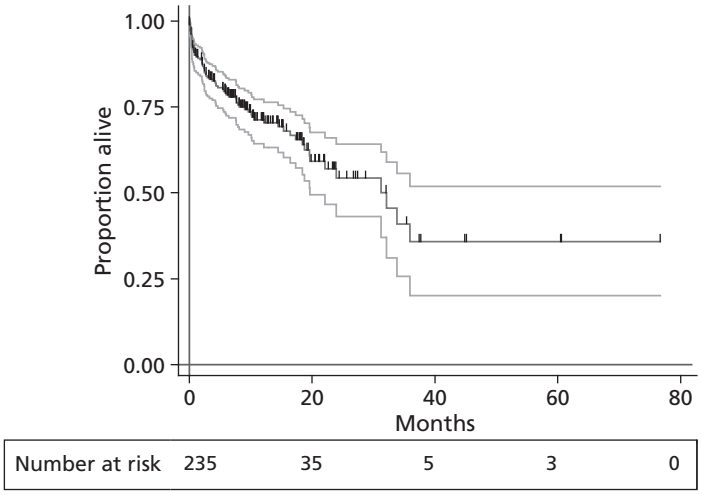


FIGURE 36 Observed survival and 95% CI while supported on a VAD. Two hundred and thirty-five BTDB patients receiving second- or third-generation approved VADs. Patients were censored on receipt of transplant, device removal, or if alive at end of follow-up without receiving a transplant.

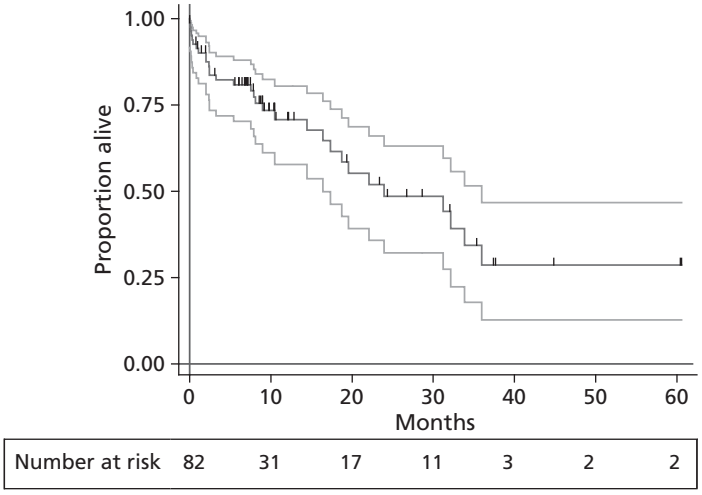


FIGURE 37 Survival while supported by HMII. Patients were censored on receipt of transplant, device removal or if alive at end of follow-up without receiving a transplant.

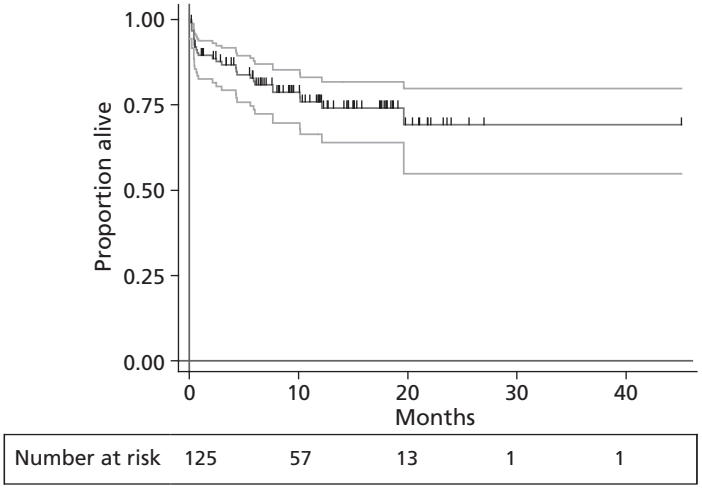


FIGURE 38 Survival while supported by a HW VAD.

patients remained at risk and the observed data were more uncertain). The fit produced relative to observed survival is shown in *Figure 39a*.

Several options were considered for extrapolation beyond 23 months observed data. The simplest extrapolation was to retain the constant hazard fitted from 3 months to 23 months to lifetime horizon.

This generated the extrapolation shown in *Figure 39b* and the monthly probability of death, conditional on surviving to the start of the month, as shown in *Table 44*. These probabilities for the more recent analysis of VAD recipients indicates superior prognosis to the probabilities reported by Sharples *et al.*[30] and this presumably reflects improved performance of the second- and third-generation devices together with the cumulative experience of procedures. This constant hazard model was selected for the base-case analysis.

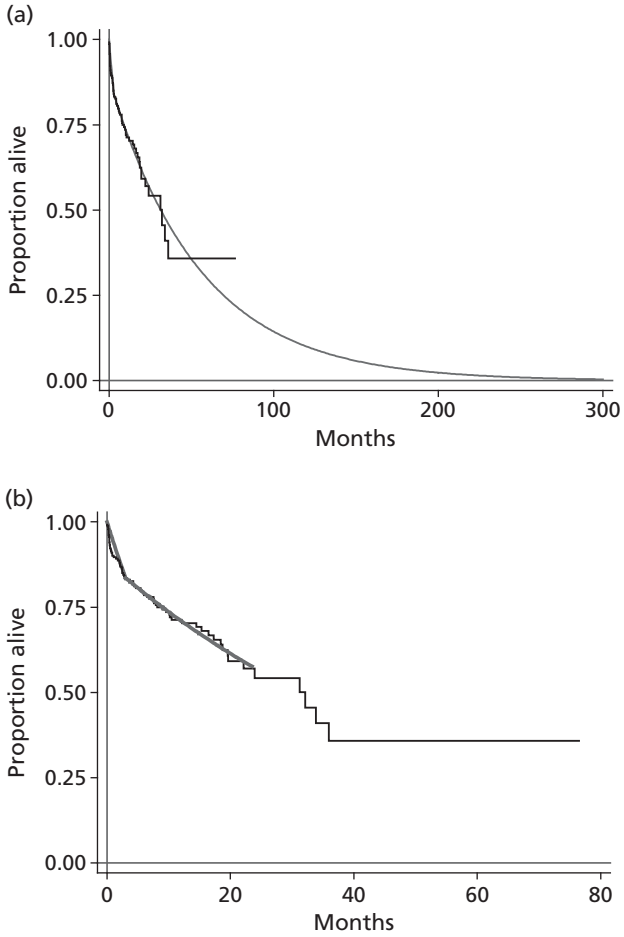


FIGURE 39 All BTDB BTT patients. (a) Survival curve derived from corresponding transition probabilities; and (b) exponential fits to observed data month 3 and from month 3 to 23.

TABLE 44 Monthly transition probabilities (VAD support to death; all VAD patients)

Present model input		Sharples *et al.*[30] model input	
Month	TP	Month	TP
1	0.0577197	1	0.20
2	0.0577197	2+	0.04
3	0.0577197	3	0.04
4+	0.0179873	4+	0.04

For sensitivity analysis, an alternative approach of employing a parametric fit was explored. Weibull, exponential, log-normal, log-logistic and Gompertz distributions were all fitted to the observed data, with the Weibull producing the lowest Akaike information criterion (AIC) values. The Weibull fit is illustrated in *Figure 40*. As the Weibull fit generated a hazard that decreased with time, a better survival was obtained than with the exponential distribution. Decreasing hazard extending to 50 years appears implausible. Therefore, the Weibull distribution was adjusted at the time when the probability of death became less than that for the UK general population matched by age and gender,[114] after which the extrapolation followed the survival for the latter; this made insubstantial difference to the extrapolated curve. These extrapolated survival curves are summarised in *Figure 40*.

For further sensitivity analysis, the observed survival for the 125 BTDB patients who received a HW device was investigated. Weibull and log-normal fits provided the lowest AIC values for goodness of fit, but generated implausible proportions of survivors after extrapolation to 50 years because of continuously decreasing hazard. An alternative approach was adopted in which an exponential distribution was used to fit the K–M survival at 1 month and at 3 months, and then a second exponential distribution was fitted to the K–M function from either 1 month or 3 months, respectively, to 10 months when ~ 10% of patients remained at risk, this latter constant hazard was then extrapolated beyond 10 months. This generated the transition probabilities shown in *Table 45* and the extrapolation shown in *Figure 41*.

Transition from support on medical management to death

We explored survival for the BTDB MM patients to try and establish transition probabilities for MM to death using an appropriate comparison group. There are no observed survival data for a cohort of MM patients suitable for HT who never receive a donor heart.

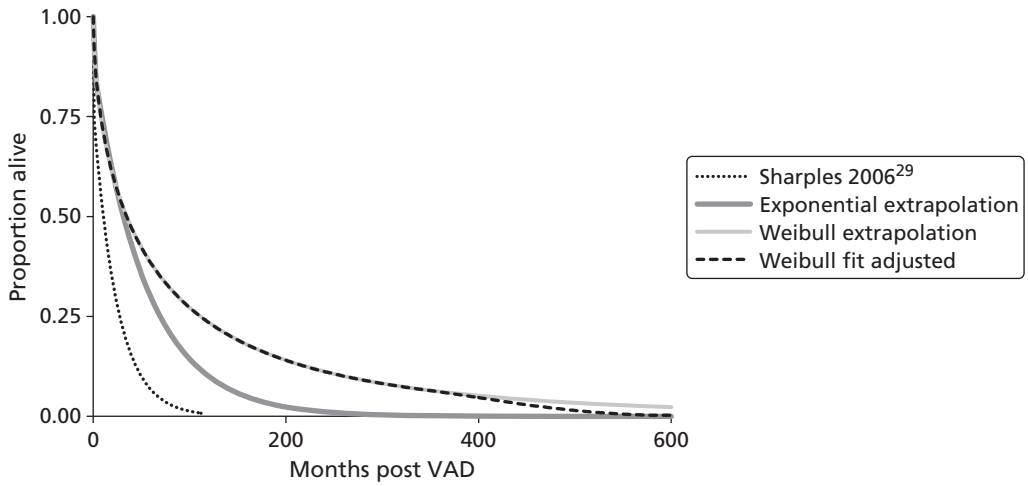


FIGURE 40 Extrapolated constant hazard and Weibull fits for survival of 235 VAD patients. The Weibull curve also shows the adjustment to that of the general population after 380 months. The modelled survival curve for VAD patients employed by Sharples *et al.*[30] is included for comparison.

TABLE 45 Sensitivity analysis monthly transition probabilities (VAD support to death based on survival of patients who received a HW device)

Based on fit to month 1 and months 1–10		Based on fit to month 3 and months 3–10	
Month	**TP**	**Month**	**TP**
1	0.103196666	1, 2 and 3	0.046859463
2+	0.016531431	4+	0.016966028

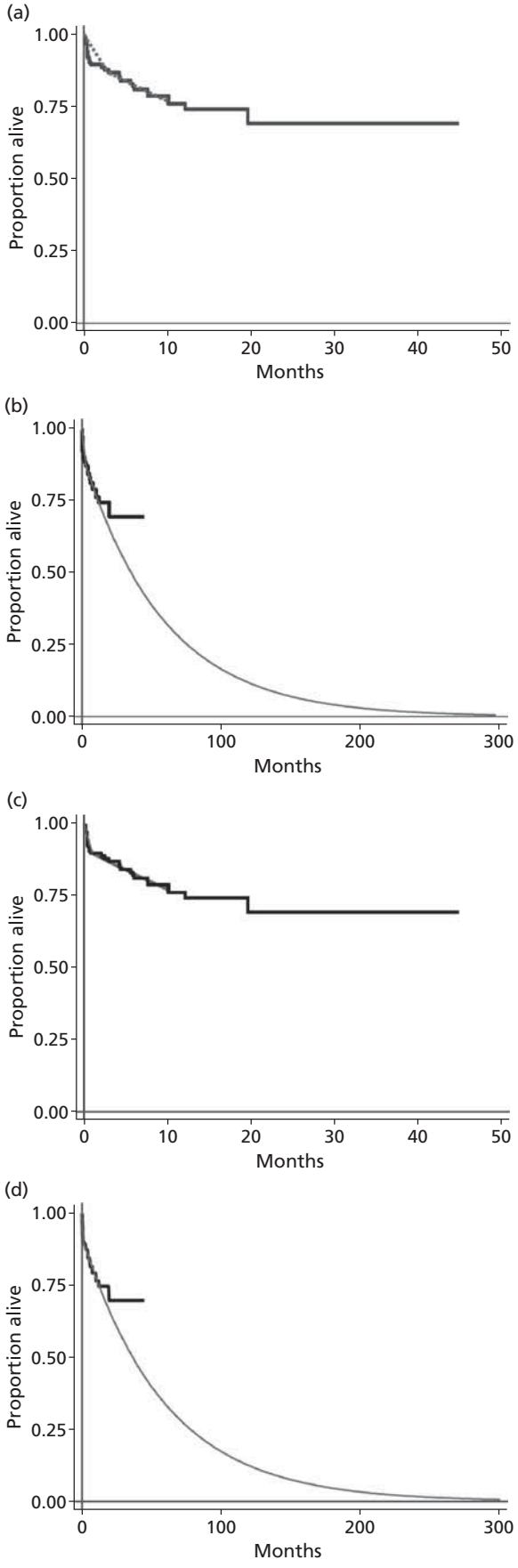


FIGURE 41 HeartWare VAD. Exponential fits to observed data. (a) Extrapolation fit to month 3 and from months 3 to 10; (b) extrapolation derived from corresponding transition probabilities; (c) fit to month 1 and months 1 to 10; and (d) extrapolation derived from corresponding transition probabilities.

The estimate of survival may be biased as a subcategory of patients, possibly those who are more ill, are lost from the cohort to HT.

The BTDB contained data for nearly 1500 patients registered for HT while supported on MM; patients were censored at the time of receiving a HT and at the time alive at last follow-up while on MM support. The K–M analysis for these patients is shown in *Figure 42*; median survival was not reached, 75% survived to 19.5 months. Fewer than 10% of patients remained at risk after about 17 months.

It is recommended by the NICE Decision Support Unit[115] that the same modelling approach for survival should be applied for compared groups (in this case BTT and MM). Therefore, the K–M survival at 3 months was fitted with an exponential distribution, and a second exponential was fitted to the K–M function for the time period from 3 months until 10% of patients remained at risk. This exponential was used to extrapolate beyond the observed data to a lifetime horizon. The fit is shown in *Figure 43*. The resulting survival curve is shown in *Figure 43* and, in *Figure 44* is compared with the survival for medically managed 'inotrope-dependent' and 'non-inotrope' patients as modelled by Sharples *et al*.[30] The monthly transition probabilities are shown in *Table 46*.

The survival of the three BTDB database subgroups (inotrope, no inotrope, or unknown) is shown in *Figure 45*. The survival of the 'inotrope' group ($n = 307$) appears less good than that of either the 'no inotrope' or 'unknown' groups; the median survival for the inotrope group was 28.2 months, but uncertainty at this time was extreme, with only two patients remaining at risk after this time.

The K–M plot for 'inotrope' patients shows distinct phases (*Figure 46*): in the first 2 weeks there was poor survival; between 2 weeks and 2 months survival improved slightly; and after 2 months the plot is increasingly associated with great uncertainty. Of a total of 28 events, only five occurred after 2 months. Fewer than 10% of 'inotrope' patients remained at risk after 4 months and uncertainty in the plot then becomes very substantial. We judged, therefore, that the data beyond 4 months was too unreliable to be used for modelling survival of the 'inotrope' population.

When Weibull and exponential distributions were fitted to all the observed 'inotrope' patients' data, the survival curves generated were poorly related to the more robust part of the K–M plot. Therefore, for consistency of approach, exponential distribution fits to the K–M function to 2 months, 3.4 months and 4 months were explored (*Figure 47*). Up to 4 months the fitted curves correspond well with the K–M data. Transition probabilities are shown in *Table 47*.

In addition, because the early part of the observed survival exhibited two distinct phases, to 2 weeks and 2 weeks to 2 months, these were fitted separately with exponential distributions and the latter (2 weeks to

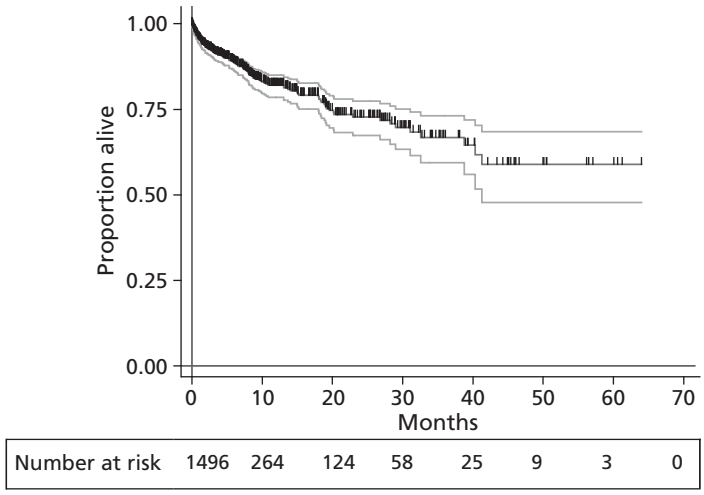


FIGURE 42 Observed survival and 95% CI while supported on a MM (1496 BTDB patients).

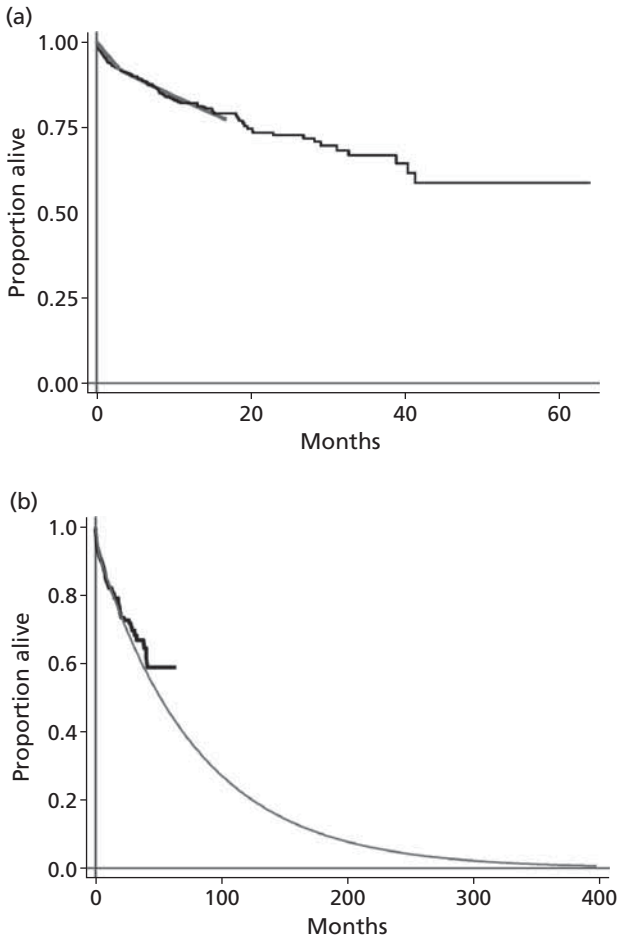


FIGURE 43 Medical management, all patients. Exponential fits to observed data. (a) Fit to month 3 and from months 3 to 17; and (b) extrapolation derived from corresponding transition probabilities.

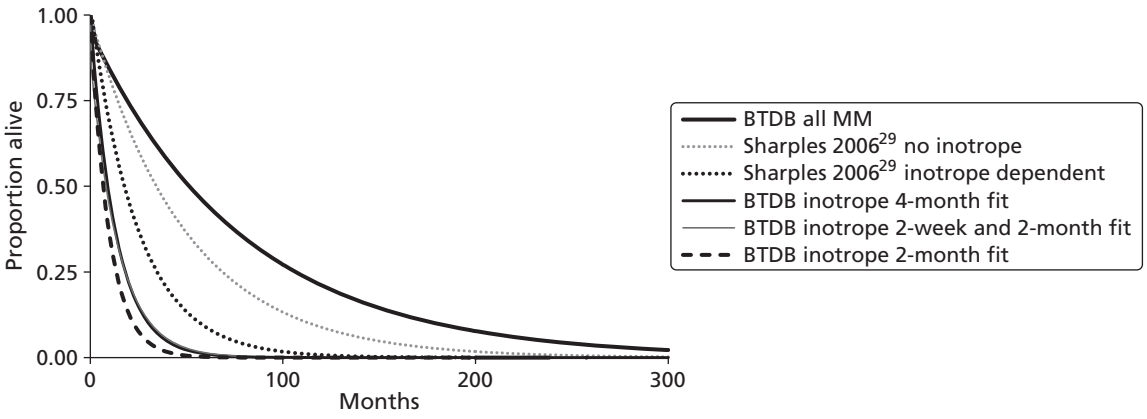
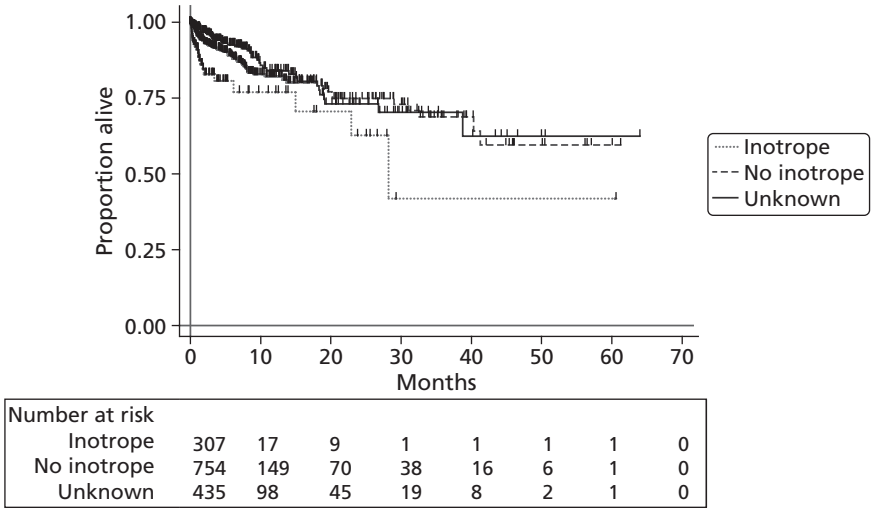


FIGURE 44 Extrapolated survival for 1496 BTDB MM patients. Comparison with MM patients modelled by Sharples *et al.*[30] and 307 BTDB 'inotrope' patients. (Note: 4-month and 2-week/2-month BTDB fits overlap). Sharples *et al.*[30] curves were calculated from the reported monthly transition probabilities.

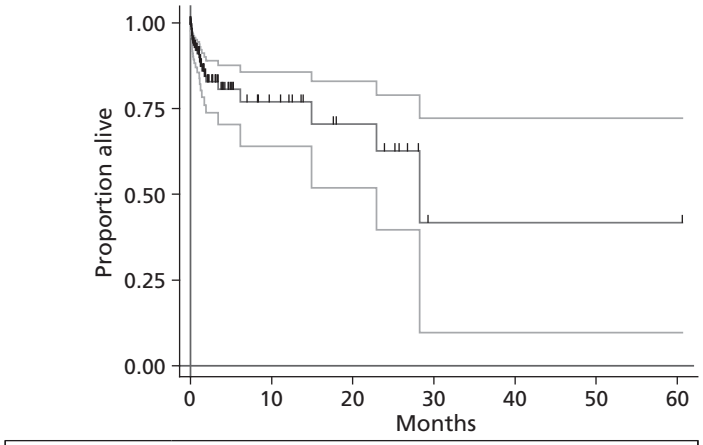
TABLE 46 Monthly transition probabilities (exponential fit all MM patients)

Month	TP
1, 2 and 3	0.027716183
4+	0.012493303



Number at risk								
Inotrope	307	17	9	1	1	1	1	0
No inotrope	754	149	70	38	16	6	1	0
Unknown	435	98	45	19	8	2	1	0

FIGURE 45 Survival of MM patients according to inotrope classification. Seven hundred and fifty-four 'no-inotrope' patients, 307 'inotrope' patients and 435 'unknown' patients.



Number at risk	307	17	9	1	1	1	1

FIGURE 46 Observed survival and 95% CI for BTDB inotrope patients.

2 months) used for extrapolation. The results are shown in *Figure 48* and transition probabilities in *Table 48*. The extrapolated curve is almost the same as that using the 4-month fit described above.

Selection of comparator group and sensitivity analyses

As mentioned above, the absence of a RCT in which patients have been randomised to VAD or to MM makes it difficult to select an appropriate MM group to act as a comparator for VAD implantation. Of the 1496 BTDB HT-listed patients who received MM, the poorest prognosis (survival) was associated with those patients who were categorised as 'inotrope' (see *Figure 45*). Without randomised evidence it is uncertain if these are equivalent to the 235 BTDB patients who were selected to receive a VAD as BTT; however, in view of comments in the literature (Slaughter and Rogers[116]) and from our clinical advisors, it is clear that patients who are selected for BTT are perceived as being less well than the generality of patients who are supported with MM.

For this reason the 'inotrope' subgroup was selected for the base case in the present economic analysis. This follows previous analysis by Sharples *et al.*[30] Furthermore, among the MM BTDB patients only 20% were categorised as 'inotrope', whereas among BTDB BTT patients 77% were classified as 'inotrope' at baseline; this implies that the inotrope subgroup of MM patients may represent a reasonable comparator group for VAD recipients. Sharples *et al.*[30] found that 'inotrope-dependent' patients in their study were associated with greater costs than their 'no inotrope' subgroup (mainly because of hospital stays).

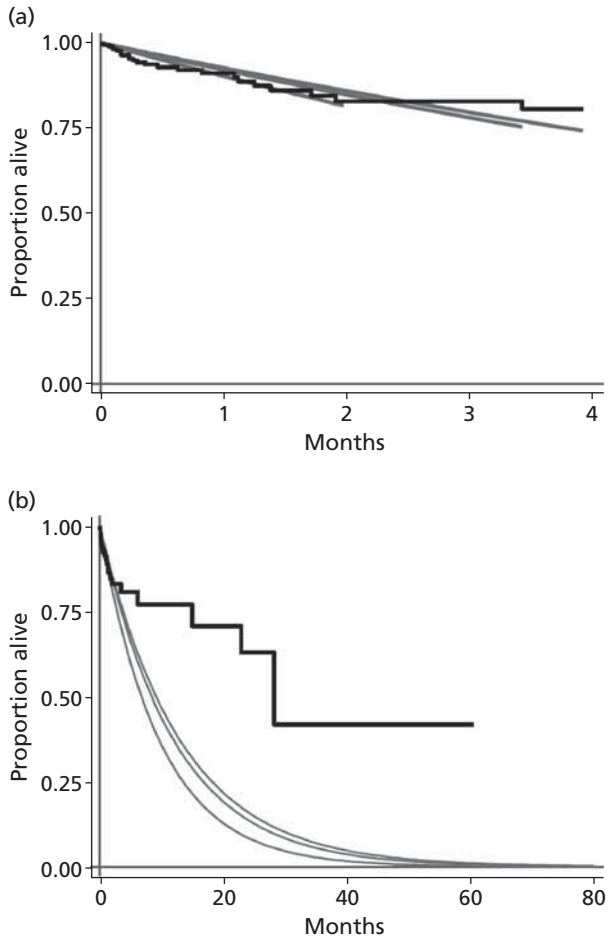


FIGURE 47 Exponential fits to observed data for 'inotrope' BTDB patients. (a) Fit to 2, 3.4 and 4 month K–M function; and (b) extrapolated curves.

TABLE 47 Transition probabilities based on exponential fits to the 'inotrope' K–M function data

Month	Monthly TP
2-month fit	0.097618
3.4-month fit	0.079359
4-month fit	0.073344

Therefore, with minor adjustment, we have used Sharples *et al.*[30] costs for this subgroup, assessed in the light of information provided by Dr Mark Petrie of GJNH, Glasgow. Clinical experts advised that medications used will have remained similar as the previous analysis (Dr Jayan Parameshwar, Papworth Hospital NHS Foundation Trust, 2012, personal communication).

Several options of choice of MM comparator group were selected for sensitivity analysis:

(a) All MM: using the K–M function for all MM patients with a constant hazard fitted to 3 months and from 3 months to the time when 10% of patients remained at risk. The monthly transition probabilities are shown in *Table 46* and the resulting extrapolation in *Figure 46*.
(b) Exponential fit to 2 months: using exponential distribution fit to 2 months K–M survival for the 'inotrope' patients (see *Table 47*).
(c) Predicted survival using the SHFM: survival based on the SHFM (Levy *et al.*[95]).

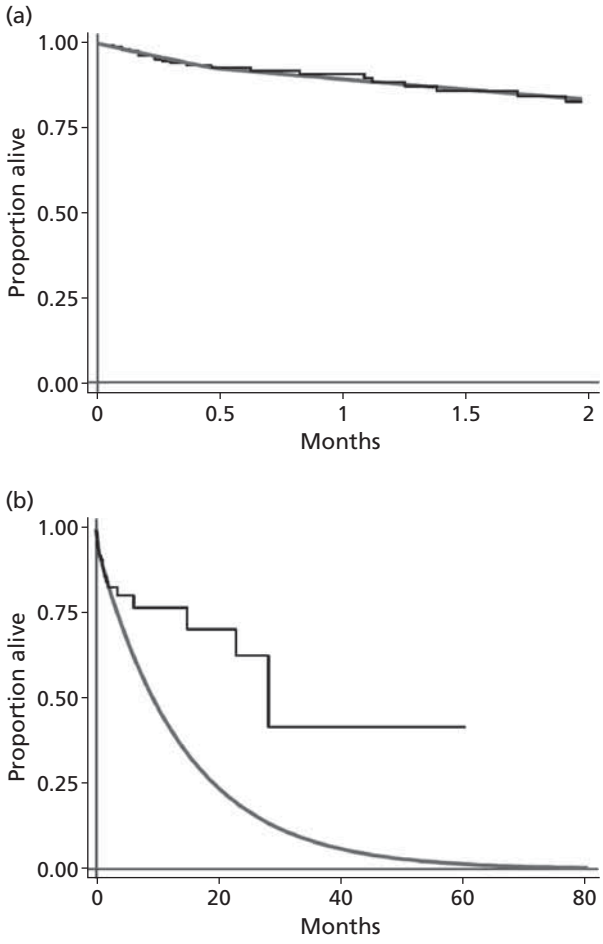


FIGURE 48 Exponential fits to observed data for 'inotrope' BTDB patients. (a) Exponential distributions fit to 2 weeks and from 2 weeks to 2 months; and (b) extrapolation derived from corresponding transition probabilities.

TABLE 48 Transition probabilities based on exponential fits to 2 weeks and 2 weeks to 2 months

Month	TP	Lambda (months)	SE
0.5	0.148552692 × 0.5	0.160817662	
0.5 to 1.5+	0.067042844	0.069396	0.0019133

SE, standard error.

In this analysis we constructed an artificial 'MM' comparator group using the characteristics of the BTDB VAD patients so that the VADs patients could, in effect, act as their own controls. The assumption underlying this use of SHFM scores calculated from baseline characteristics for patients who go on to receive a VAD is that patients with this score would represent the most appropriate comparator group.

The SHFM score is based on multiple baseline covariates and survival may be predicted according to the following equation (Levy *et al.*[95]):

$$S(t) = \exp(-0.045 \times t \times \exp(SC)) \quad (4)$$

where t is in years and SC is the mean SHFM for a group of patients. This may be modified to predict monthly survival:

$$S(t \text{ months}) = \exp(-0.045/12 \times t(\text{months}) \times (\exp(SCm)). \quad (5)$$

Given an SHFM score it is possible to predict survival in order to be able to compare survival with and without a VAD. An SHFM score was obtained for representative populations of VAD patients in the following three ways:

1. Schaffer: Shaffer *et al*.[77] reported the frequency of SHFM scores at baseline among all VAD patients at a single centre for the period June 2000 to May 2009. The results reported were used to calculate a mean score of 3.036. The resulting survival curves are shown in *Figure 49*.
2. Strueber: Strueber *et al*.[83] presented survival to 24 months for a 'virtual' comparator group for patients who were implanted with the HW VAD; the survival estimate was based on the SHFM score. These data fitted the equation above when the score was set at 2.416 and generated the curve shown in *Figure 49*.
3. BTDB SHFM: some covariates required for the calculation of an SHFM score were available at baseline for VAD patients in the BTDB. These were used to estimate a mean score using a Cox's model by using the probability value of ≤ 0.05. The SHFM score was evaluated from the outcomes of the multivariate model, by using the products of the variables, and their β coefficients (natural log of the hazard ratio) were summed. The resulting score was 3.372. Baseline survival was estimated using the equation above and the resulting curve is shown in *Figure 49*.

The monthly transition probabilities for each of these sensitivity analyses are provided in *Table 49*.

Informative censoring

Clinical experts advised that among MM patients, those most likely to receive a donor heart are those with the poorest prognosis. This means that censoring these patients in the analysis of survival under MM may

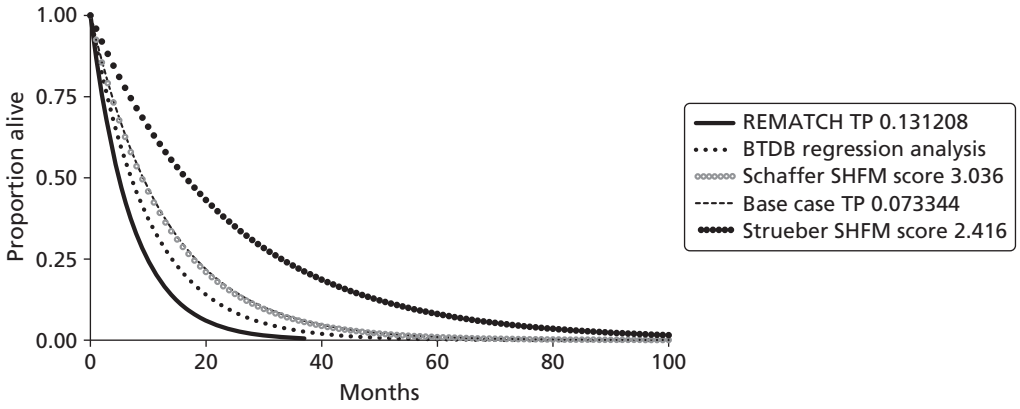


FIGURE 49 Modelled survival using SHFM and REMATCH control group.

TABLE 49 Seattle Heart Failure Model derived monthly transition probabilities

Source	SHFM score	Median survival (months)	Monthly TP
Base-case inotrope MM	3.011[a]	9.1	0.073344
Schaffer *et al*.[77]	3.036[b]	8.9	0.075111
Strueber *et al*.[83]	2.146[c]	16.59	0.041134
BTDB SHFM	3.372[d]	6.343	0.09366
REMATCH MM	3.625[e]	4.9	0.13121

a Calculated from modelled median survival.
b Based on distribution of SHFM scores reported by Schaffer *et al*.[77]
c Based on the virtual control group survival reported by Strueber *et al*.[83]
d Calculated using regression analysis using available data in the BTDB.
e Calculated from the median density reported by Rose *et al*.[45]

represent informative censoring (i.e. those not transplanted would have better prognosis leading to an over estimate of survival).

The distribution of times between listing for transplant and receiving a transplant for the inotrope MM patients is shown in *Figure 50*. About one-quarter were transplanted within 2–3 days of being listed, half were transplanted within a week of listing and 86% within 4 weeks.

This is a short delay to transplant and it seems unlikely to reflect variations in likely survival. However, we further investigated the presence of informative censoring and whether or not it is likely to cause a problem in our analysis by considering the sensitivity analysis approach described by Collet[117] in which patients censored for transplant were (a) assumed instead to die 1 day after their date of transplant; and (b) assumed instead to die at the last event time for uncensored patients. The resulting K–M plots exhibited median survival times of 0.39 months and 28 months, respectively, clearly indicating a large effect on survival estimates if censoring times are equated to predicted survival (*Figure 51*).

The median survival in graph *Figure 51a* mostly reflects the short time between being listed for transplant and receipt of a transplant for those patients transplanted. Although this could be indicative of informative censoring, this could, however, also be partly due to delayed listing of eligible patients so that recorded times between listing and transplantation were too close. Thus, the deviation between the two K–M curves seen is unlikely to be caused by poor prognosis of transplanted patients only, but may also be caused by delayed entry onto the transplant list; this might be interpreted as lead-time bias.

In view of a possible overestimate of survival for the MM group we followed advice from clinical experts to explore the use of the 'optimum MM' group from the REMATCH RCT (Rose *et al.*[45]) as our control group. In the REMATCH trial the median survival for optimum MM patients (for whom HT was contraindicated) was 150 days (4.93 months), the data were mature (54 deaths among 61 patients), most were receiving inotropes at baseline, and there was little censoring. Using this median survival value we calculated the exponent (lambda) for a constant hazard fit: $\lambda = (\ln 0.5)/4.93 = 0.14065$; the fit to observed data is shown in *Figure 52* and the corresponding monthly TP of 0.131207633 was used in our economic model for sensitivity analysis. *Table 49* and *Figure 52* show the survival curve and TP together with other sensitivity analyses.

Stevenson *et al.*[46] performed a post-hoc analysis of survival data from the REMATCH trial. Patients were stratified by baseline treatment with inotropes. Among MM patients, survival was poorer for those receiving inotropes; median survival was 120 days (3.94 months). When fitted with a constant hazard model this provided a monthly TP of 0.161217 which was also used for sensitivity analysis in our economic model.

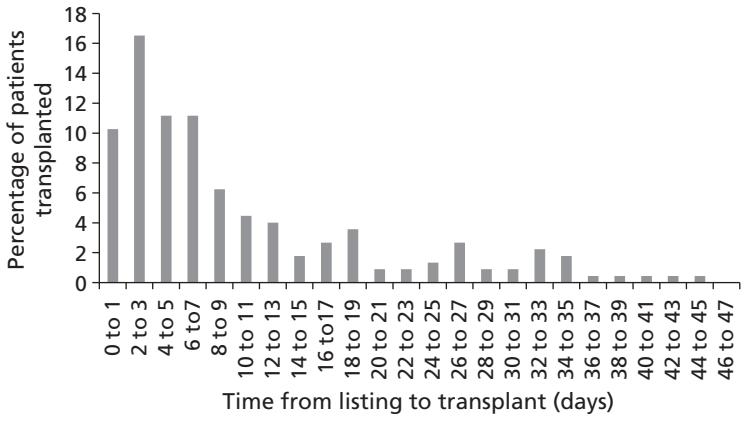


FIGURE 50 Distribution of times from listing to transplant for BTDB MM patients receiving inotropes.

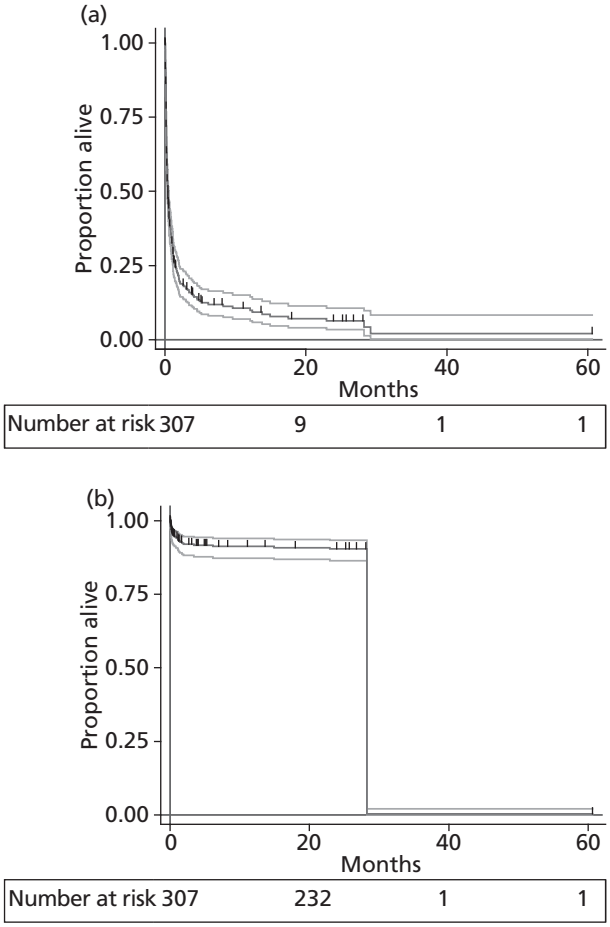


FIGURE 51 Analysis of inotrope MM patients' survival using modified censoring according to Collet. (a) HT recipients assumed instead to die 1-day post-HT date; and (b) HT recipients assumed instead to die at time of last observed

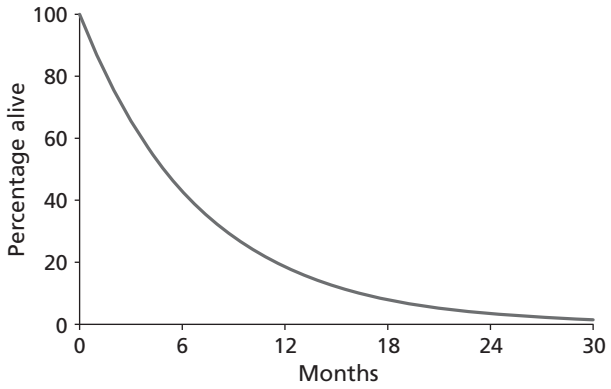


FIGURE 52 Constant hazard fit to REMATCH control group based on median survival of 150 days.

Transition to heart transplant from ventricular assist device or medical management

The BTDB provided sufficient data for analysis of time to HT for 1731 patients. Of these, 235 BTT patients with approved second- or third-generation VADs provided sufficient data for analysis. K–M analysis of time to transplant for all 1731 patients is shown in *Figure 53*.

The median time to transplant was 4.76 months; by 40 months fewer than 2% of patients remained at risk. After 42 months no further patients received a donor heart except for an atypical cluster. Clinical

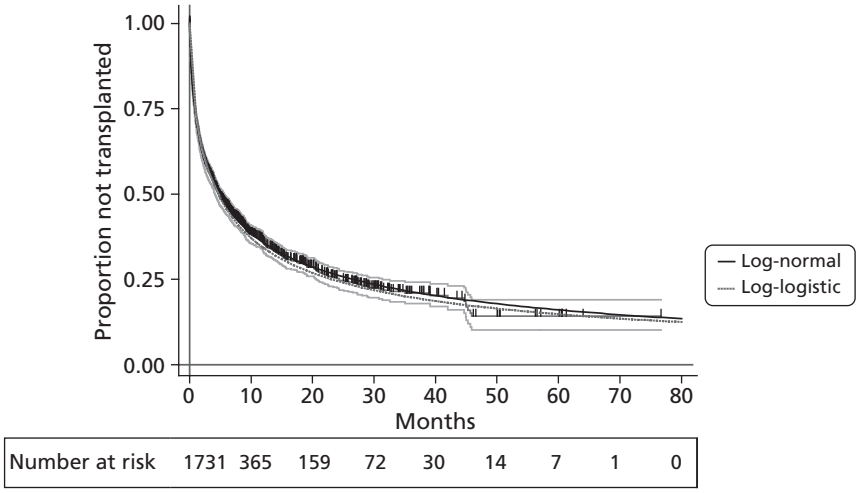


FIGURE 53 Time to HT for all patients in the BTDB with log-logistic and log-normal distribution fits.

advisors suggested that transplantation beyond 42 months was unlikely and for this reason the model set the probability beyond this time as zero.

The log-logistic and log-normal distributions yielded the lowest AIC values (*Table 50*) for parametric fits to the observed data. And these distributions generated almost indistinguishable fits (see *Figure 53*). For sensitivity analysis transition probabilities were calculated from the log-normal distribution.

The time to receipt of a HT in the BTDB was considerably longer for VAD patients (median time to transplant was 44.7 months) than for MM patients (median time to transplant was 3.25 months) (*Figure 54*), and similar results were reflected in the inputs used in the Sharples *et al*.[30] economic analysis. However, in the recent analysis proposed by Moreno *et al*.[98] the probability of receiving a donor heart was kept the same for both VAD (BTT) and MM patients.

For MM patients only, log-logistic and log-normal distributions exhibited the lowest AIC values and a good fit to the observed data (as for all BTDB patients; *Figure 55* and *Table 51*).

For the BTT patients exponential and Weibull parametric distributions provided similarly low AIC values (*Table 52*), these and log-normal fitted curves are shown in *Figure 56*.

For the base-case analysis the same probability of transition to the transplanted state was used for both arms and was calculated from the exponential distribution for the BTT patients; see *Figure 56*). This is in line with Moreno *et al*.[98] and is judged to allow a fairer comparison between management strategies.

The effect of using transition probabilities based on time to HT for all BTDB patients (log-normal fit) for both compared groups was explored in sensitivity analysis. Further sensitivity analyses used transition

TABLE 50 Akaike information criterion values for parametric fits to time to transplant for all BTDB patients

AIC	BIC	Distribution
5963.861	5974.795	Weibull
5915.031	5925.966	Log-normal
5906.04	5916.974	Log-logistic
6863.469	6868.937	Exponential

BIC, Bayesian information criterion.

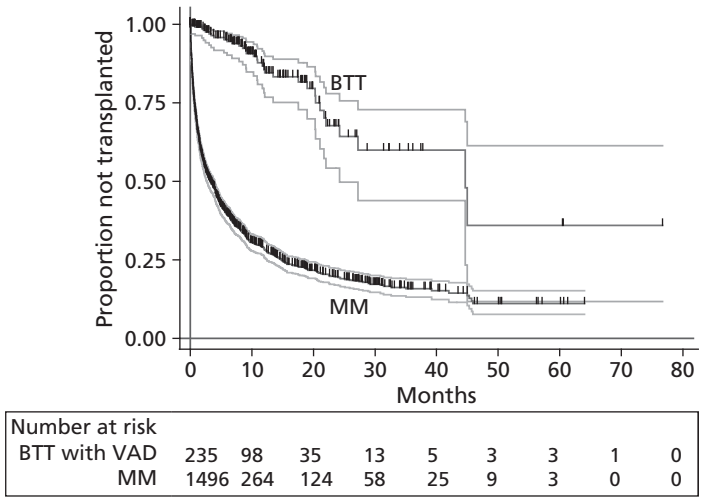


FIGURE 54 Time to HT for BTT (BTT with VAD) and MM patients.

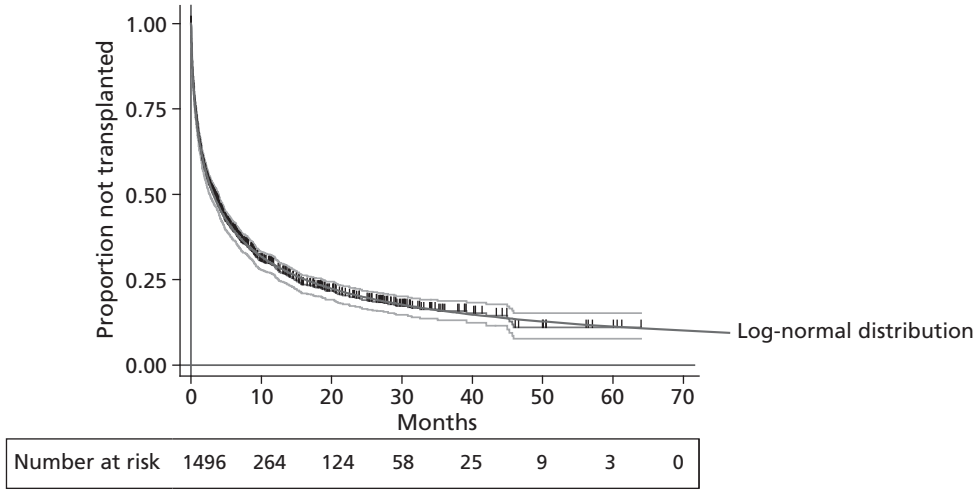


FIGURE 55 Log-normal distribution fitted to time to transplant for MM patients.

TABLE 51 Akaike information criterion values for fits to time to transplant for MM patients

AIC	BIC	Distribution
5413.291	5423.912	Weibull
5361.457	5372.078	Log-normal
5342.205	5352.826	Log-logistic
6277.83	6283.14	Exponential

BIC, Bayesian information criterion.

TABLE 52 Akaike information criterion values for fits to time to transplant for BTT patients

AIC	BIC	Distribution
224.4692	231.3883	Log-normal
217.4888	224.4079	Weibull
217.2066	220.6661	Exponential

BIC, Bayesian information criterion.

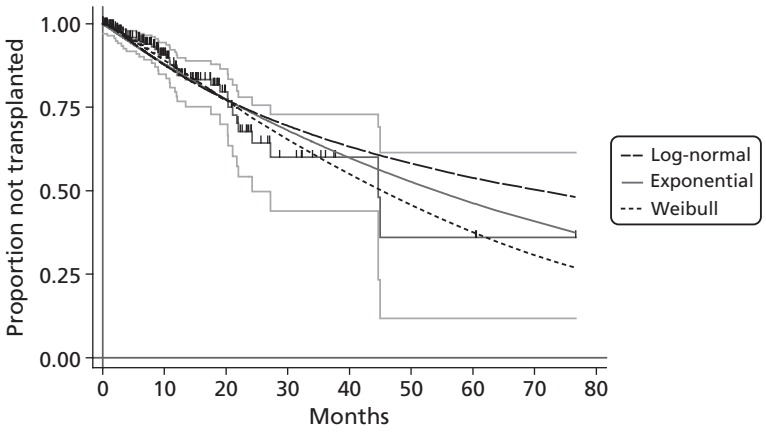


FIGURE 56 Time to HT. Log-normal, Weibull and exponential distributions fitted to time to HT for VAD patients.

probabilities based on time to HT for all BTDB patients (log-normal fit) for the MM arm and TP based on the exponential fit to the time to transplant for BTT patients for the BTT arm.

Transition from heart transplant support to death

The BTDB provided appropriate data for K–M analysis of post-transplant survival for 1101 patients. The plot is shown in *Figure 57*.

Median survival was not reached, 75% survived to 45.6 months. The K–M survival curve follows two phases, an initial phase of poor survival during the first few months post surgery, followed by good survival for up to about 10 years of follow-up. A similar pattern has been reported for 25 years of follow-up for patients transplanted at Papworth Hospital NHS Foundation Trust (Goldsmith *et al.*[118]). In the Goldsmith *et al.*[118] study about 20–25% of patients died within the first 3 months (depending on the era for analysis). At 3 months K–M survival was about 85% for the BTDB patients. We compared BTDB patients with the survival from 3 months reported by Goldsmith *et al.*[118] by assuming 85% survival at 3 months for the latter (*Figure 58*). The recent economic analysis by Moreno *et al.*[98] used post-transplant survival data from the study of Russo *et al.*;[100] the Russo *et al.*[100] data are also shown in *Figure 58*.

Extrapolating survival beyond the observed data is problematic because the K–M plot extends to only about 68% survival and is flat. To remain consistent with previous approaches we fitted a constant hazard to the K–M at 3 months and a second fit to the K–M function from 3 months to 7 years (at which time the proportion of patients at risk has depleted to near 10%). The fits are shown in *Figure 59a*. This generated TP for the first 3 months of 0.070366726, and for months 4–84 of 0.002980948. A second constant hazard fit was made to 6 months and from 6 to 84 months (see *Figure 59a*). Extrapolation beyond 84 months with the 3–84 month and 6–84 month exponentials generated unrealistic proportions of survivors by 50 years. The probability of death after 24 years was less than that for the UK general

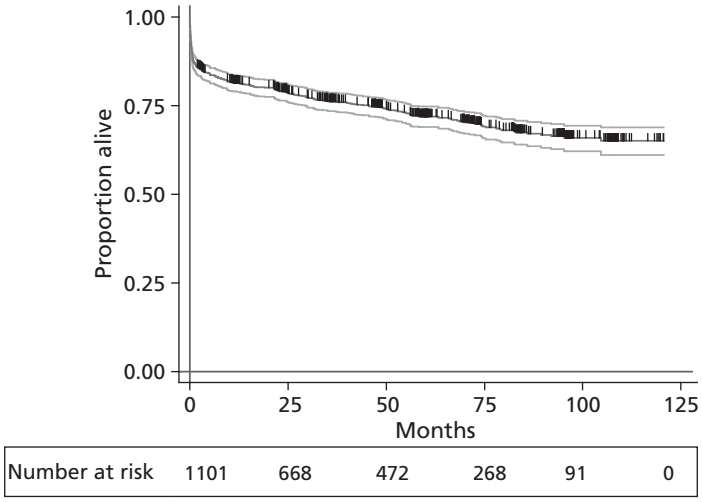


FIGURE 57 Post-HT survival for patients in the BTDB.

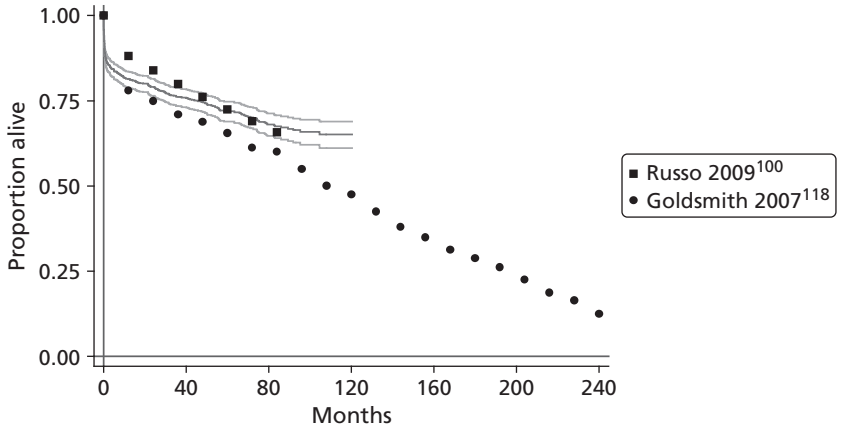


FIGURE 58 Post-HT survival of BTDB patients. Comparison with that reported for Papworth patients by Goldsmith *et al.*[118] and that by Russo *et al.*[100] (modelled by Moreno *et al.*[98]).

population matched according to gender and age (corresponding to the BTDB mean age at transplant + 7 years). Therefore from that time, the probability of death was taken to be the same as the UK general population (matched by age and gender). The curves generated from the transition probabilities are shown in *Figure 60*. The 3–84-month model was used for the base-case analysis.

The transition probabilities between health states employed for the base case and for sensitivity analyses are summarised in *Tables 53* and *54*.

Sensitivity analyses around transition probabilities are designated I for purposes of reporting results. The following analyses were applied for transition probabilities:

- I A] for the transition from MM support to death.
- I B] for the transition from VAD support to death.
- I C] for transition from VAD or MM support to HT.
- I D] bivariate sensitivity analyses.

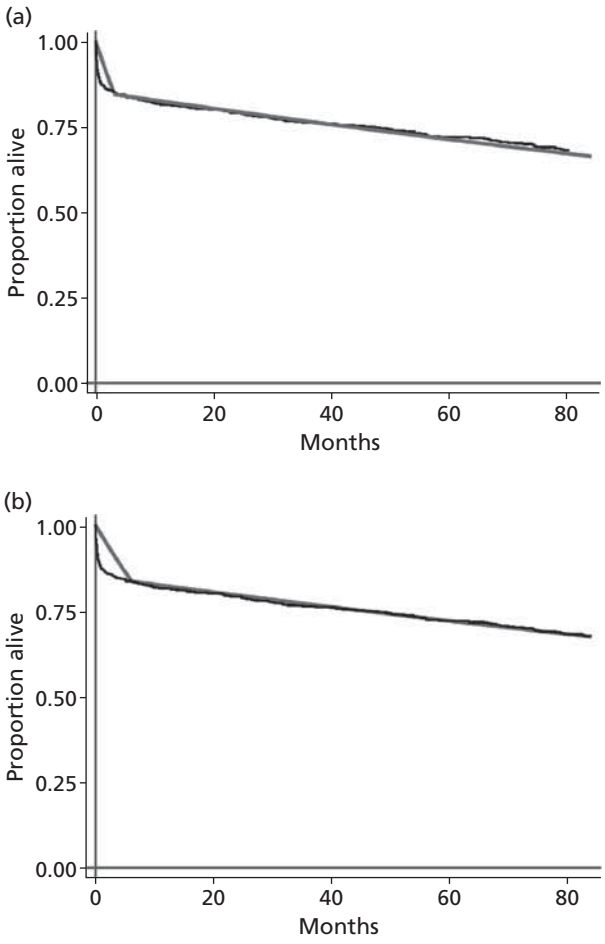


FIGURE 59 Post-HT survival of BTDB patients: exponential distributions fitted to observed data. (a) Exponential distributions fit to 3 months and 3–84 months; and (b) exponential distributions fitted to 6 months and 6–84 months.

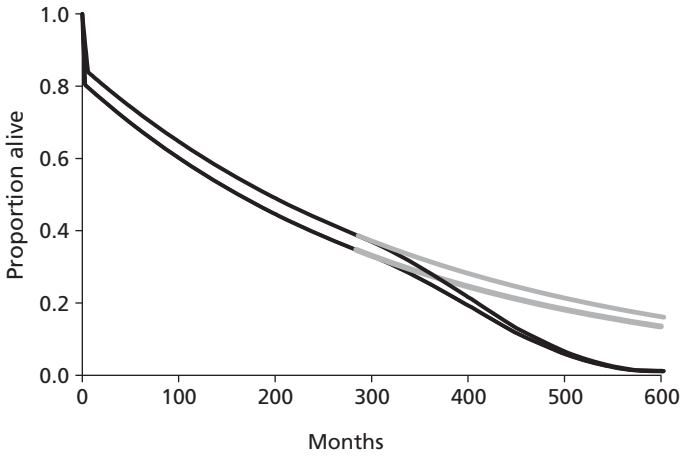


FIGURE 60 Modelled post-HT survival of BTDB patients. The upper curve refers to the 6-month plus 6–84 months-fit to observed data and the lower curve refers to the 3-month plus 3–84-months fit to observed data. The grey lines indicate survival if the constant hazard continued to operate beyond 24 years. The black lines beyond 24 years (288 months) indicate survival according to the probability of death for the UK general population (matched by age and gender).

TABLE 53 Summary of the transition probabilities input for the base-case economic analysis

Health state transition	Monthly TP	Source
VAD support to death	Months 1–3: 0.0577197 Months 4+: 0.0179873	Constant hazard fit to K–M at 3 months, and exponential fit to the K–M function from 3 months until 10% of patients remain at risk for all BTDB VAD recipients[a] (see *Figure 39*)
MM support to death	Months 1+: 0.073344	Constant hazard fit to K–M function to 4 months for inotrope BTDB MM patients (see *Figure 47*)
MM and VAD support to HT	All months: 0.012745641	Exponential parametric fit to observed time to HT for BTDB BTT patients (see *Figure 56*). Probability set at zero after 42 months
Support on HT to death (both BTT and MM groups)	Months 1–3: 0.070366726 Months 4–284: 0.002980948 Months 284+: as UK population (matched for age and gender; available from authors on request)	Constant hazard fit to K–M at 3 months and exponential fit to the K–M function from 3 months until 10% of patients remain at risk (84 months) for those BTDB patients who received a HT (see *Figure 59*). Office of National Statistics survival data[114]

a Second- or third-generation approved VADs.

Two bivariate sensitivity analyses were conducted:

- [I D1] Survival supported by MM based on constant hazard fit to K–M function to 2 months for inotrope patients (as I A3], and for survival on VAD support using Weibull fit to data for all VAD patients (as I B1]).
- [I D2] Survival supported by MM based on Schaffer *et al*.[77] data, SHFM (as I A2 i]) and survival on VAD support based on Weibull fit to data for all VAD patients (as B1).

Probabilistic sensitivity analysis was undertaken for the base case. Details of the inputs are provided in *Table 70*.

Research question 2 (alternative to transplant compared with bridge to transplant)

What is the cost-effectiveness of second- and third-generation VADs used as an alternative to HT in comparison with their use as a BTT therapy for patients with advanced HF who are eligible for HT?

In the intervention arm for this comparison, patients with HF and eligible for HT receive a VAD as an alternative to proceeding with VAD as a BTT. Although RCTs for patients *not* eligible for HT (REMATCH study[119] and Slaughter *et al*.[47]) have been undertaken, no comparative evidence is available for a population eligible for transplant. For this research question the comparator arm patients eligible for HT receive a VAD as a bridge to future intended transplant with a donor heart, whereas the intervention arm patients are also eligible for a HT and receive a VAD as an ATT.

For economic modelling of the comparator arm (BTT) we adopted the base-case TP inputs listed above for the BTT arm of the first research question (as listed in *Table 53*; corresponding costs and utilities also applied). For the intervention arm (ATT) all inputs were the same as the comparator except that the probability of receiving a donor heart was set at zero.

The difference in costs between arms derives from the cost of HT in the comparator arm for BTT patients who survive long enough to receive a donor heart. The intervention (ATT) will therefore always remain cost

TABLE 54 Summary of transition probabilities for univariate sensitivity analysis inputs

Input parameter	Monthly TP	Source
I A1] MM support to death	Months 1–3: 0.027716183 Months 4+: 0.012493303	Constant hazard fit to K–M at 3 months and to K–M function from 4 months to 10% at risk for all MM patients
I A2] MM support to death		Based on SHFM[95] analyses using data from:
	(i) 0.075111	(i) Mean SHFM score derived from Schaffer *et al.*,[77] single-centre study of patients given VADs
	(ii) 0.041133	(ii) Mean SHFM score derived from the 'virtual' comparator group for HW VAD patients reported by Strueber *et al.*[83]
	(iii) 0.09366	(iii) Mean SHFM score derived from Cox regression analysis of baseline covariates for 34 BTDB patients who received a VAD
I A3] MM support to death	Months 1+: 0.097618	Constant hazard fit to K–M function to 2 months for BTDB MM inotrope patients (see *Figure 47*)
I A4] MM support to death	(i) Months 1+: 0.131210	Constant hazard fit to REMATCH all MM arm
	(ii) Months 1+: 0.161217	Constant hazard fit to REMATCH inotrope MM patients
I B1] VAD support to death	Available from authors on request	Weibull distribution fitted to the observed survival for all BTDB VAD patients, with correction after 420 months to survival for age- and gender-matched UK population
I B2] VAD support to death	Months 1–3: 0.046859463 Months 4+: 0.016966028	Constant hazard fit to K–M at 3 months and from 4 months to 10% at risk for those BTDB patients who received a HW VAD
I C1] VAD or MM support to HT	(i) For MM: log-normal fit to time to HT for all BTDB patients (available on request) For BTT patients: months 1+ 0.012745649	For MM patients (log-normal fit to time to HT all BTDB patients); for BTT patients as base case (i.e. based on exponential fit to time to HT for BTT patients)
	(ii) For both MM and BTT: log-normal fit to time to HT for all BTDB patients (available on request)	For both arms log-normal parametric fit to observed time to HT for all listed BTDB patients (see *Figure 53*). Probability set at zero after 42 months

saving (unless donor hearts cease to become available, in which case the two arms become identical). At present, survival is more favourable after receiving a donor heart, therefore the comparator (BTT) is likely to remain more effective than the intervention (ATT) until survival with a VAD becomes as favourable as that after receiving a donor heart. The ICER for this comparison estimates the savings to the payer for each QALY sacrificed, should ATT be adopted in favour of BTT.

Transition probabilities summary and comment

Kaplan–Meier survival plots of BTDB patients supported by VADs and post HT exhibited two phases – a poor survival for several months post surgery and a following longer phase of better survival. Similar poor short-term survival, though less pronounced, was also seen for MM patients. When log-normal or Weibull distributions were fitted to these data they tended to generate implausible proportions of long-term survivors. Therefore, following the approaches of Sharples *et al.*[30] and Moreno *et al.*[98] we used constant hazard fits to segments of the K–M plots up to the time when the proportion of patients at risk was depleted to about 10%.

Time to HT was very different between BTDB MM and BTT patients. In order to retain an equitable comparison between treatment strategies we employed the same transplant probability for both groups. It appears sensible for the purposes of a fair comparison between treatment options that each should have an equal opportunity of receiving benefits of a transplant; however, in clinical practice MM patients do in fact receive transplants much earlier than BTT patients, mainly because it makes little sense to remove a VAD from a patient who is doing well to give them a donor heart much more urgently required by other patients.

Once the premise that equal opportunity of transplant should prevail in economic modelling for both BTT and MM patients then the issue becomes one of 'at what rate should this be set?' In the base case we used data for the BTT group because the much higher probability observed for the MM patients in the BTDB was judged inappropriate as it would dictate that within only about 4 months of receiving a VAD implant, most BTT patients would have undergone device removal so as to receive a donor heart.

In the absence of randomised evidence the selection of an appropriate MM population as comparator is open to debate. Modelling K–M data from the BTDB inotrope MM patients yielded a median survival of 9.1 months. This was almost the same as that calculated from the distribution of SHFM scores reported in Schaffer *et al*.[77] for a series of BTT patients at a single US centre. Aaronson *et al*.[94] reported median survival of 9.86 months for a MM 'virtual comparison' group, again, using the SHFM with data for 140 HW recipients in a multicentre US study. Similar methods used by Strueber *et al*.[83] for 50 HW recipients (at European and Australian centres) yielded a median survival of 16.5 months. Some clinical advisors asserted their opinion that median survival of 9 months was excessively generous, and suggested the poorer survival observed for MM patients in the REMATCH trial of 4.9 months for all REMATCH controls and of 3.94 months for the inotrope subgroup of MM patients, respectively, as more appropriate. These have therefore been employed within sensitivity analyses.

In the next chapter we describe resource and cost inputs to the model.

Chapter 8 Overview of resource and cost inputs to the model

Nature of the inputs required

Resource use and associated costs are required for the following health states

1. Support on BTT with VAD until HT.
2. Support on MM until HT.
3. Support on HT.

States 1 and 3 have two phases:

(a) a short-term phase associated with preparation for surgery and the immediate aftermath of surgery
(b) a prolonged phase of maintenance.

Sources of cost inputs; base case and summary of sensitivity analyses

In our economic evaluation, resource use and costs were estimated from the perspective of the NHS. All costs reported in this chapter are based on 2010/11 prices unless otherwise specified.

Base case

Our main source of information on cost and resource use was from a previous HTA report undertaken by Sharples *et al*.[30] In the Sharples *et al*.[30] study, patient-specific resource-use data were collected for VAD implant, HT, and patients on MM while awaiting transplant. For all three patient groups, costs were collected as monthly costs from the date of VAD implantation, or the date the patients were accepted on to the transplant WL, until the study cut–off date. Post-transplantation and VAD monthly cost were assumed to be constant from month 7 onwards in all groups. Importantly, the study recorded actual costs incurred by patients and, hence, provides a more accurate representation of costs. For our model, these costs were inflated to current levels by applying the projected health services costs.[120] VAD costs were obtained from five UK centres operating under the auspices of the National Specialist Commissioning Team (NSCT), which commissions the VAD programme. We did not include the cost of the VAD supplied by GJNH which was based on a single VAD used at this centre; however, this was used in scenario analysis. The base-case cost inputs for the three health states are summarised in *Table 55*. It is worth mentioning that Sharples *et al*.[30] estimated resource use from the perspective of the NHS and centre. In such settings, the cost does not include setting-up costs for a new centre and we would emphasise that setting up a new service would incur additional set-up costs.

State 1: Support on bridge to transplant with a ventricular assist device until heart transplant

This health state consists of an early short-term phase associated with the VAD implant procedure cost which includes the cost of the device, theatre cost and cost of immediate post-operative hospital stay, and a second long-term follow-up phase that includes the costs of outpatient visits, adverse events and rehospitalisation.

TABLE 55 Base-case costs for each health state. Summary of cost inputs for the base-case economic analysis – 2010/11 prices

Item	Period	Mean cost (£)	SE	Gamma distribution parameter	
				α	β
Supported by VAD					
VAD		80,569[a]	N/A	N/A	N/A
VAD implant procedure		3728[b]	N/A	N/A	N/A
Post-VAD hospital stay and follow-up	Month 1	25,777	2518	2029.08	55.90
	Month 2	13,440	1306	105.95	126.84
	Month 3	5110	764	44.69	114.32
	Month 4	3836	607	40.00	95.89
	Month 5	3248	460	49.89	65.09
	Month 6	2326	356	42.69	54.48
	Months 7+	1893	907	4.35	434.97
Supported by MM					
Support on MM (inotrope)[c]	Month 1	12,216	1156	111.67	109.39
	Month 2	6393	604	112.03	57.06
	Months 3+	5965	193	951.25	6.27
Supported by HT					
HT theatre cost					
BTT		16,663	N/A	N/A	N/A
MM		11,395	N/A	N/A	N/A
HT assessment cost					
BTT		0	N/A	N/A	N/A
MM		1633	N/A	N/A	N/A
Post-HT hospital stay and follow-up	Month 1: BTT	15,577	1117	832.97	38.70
	Month 1: MM	13,211	961	730.39	33.68
Post-HT hospital stay and follow-up	BTT and MM				
	Month 2	4331	802	29.18	148.40
	Month 3	2609	470	30.77	84.79
	Month 4	2828	260	117.87	23.99
	Month 5	2179	432	25.42	85.70
	Month 6	1646	138	142.69	11.53
	Months 7+	1410	177	62.91	22.41

N/A, not applicable; SE, standard error.

All data based on Sharples *et al.*'s[30] data inflated to current prices except:

a Based on current cost of devices recorded at UK centres.

b Based on GJNH finance department.

c Sensitivity analyses included the use of all MM patients from the BTDB for whom the monthly cost is less.

We obtained costs of VADs from five centres (listed below) providing long-term VAD support:

- NUT
- Papworth Hospital NHS Foundation Trust
- RB
- UNB
- UHSM.

The base-case cost per VAD (£80,569) was a weighted value according to the number of devices used by BTDB BTT patients and costs of different devices. Details of unit cost of VADs used in this study are given in *Table 56*.

Device maintenance cost

The costs of maintaining the VAD per patient and associated costs of replacing batteries, cables and other hardware are not incorporated in any of the published cost-effectiveness models. We contacted two long-standing VAD manufacturers, who suggested that the yearly VAD maintenance and other hardware costs were trivial. Although we obtained costs of VADs from six centres, only two centres provided an annual maintenance cost (of £4000/year from year 2 onwards). All other centres reported that the purchase price of the device included a maintenance element and that they did not incur any additional cost on maintenance. We again contacted the device manufactures to verify the maintenance element, but no response was forthcoming. We therefore did not adjust the Sharples *et al*.[30] estimate for the cost of device maintenance.

We estimated the VAD implant procedure cost based on a GJNH finance department costings (£3728.20) supplied to us on request. Detailed information on this is given in *Table 57*.

State 2: Support on medical management until heart transplant

The input required is an estimate of the average monthly cost while patients are medically managed. This includes medication, such as inotropes, and follow-up assessment as inpatient or out-patient visits.

An inotrope-dependent patient subgroup of BTDB MM patients was selected for the base-case analysis. We consulted our clinical advisors and they advised that medications and inotropes used will have remained similar as the previous analysis.[30] The intravenous inotropes used were enoximone 5 μg/kg/minute and dopamine 5 μg/kg/minute. We inflated the cost of inotrope-dependent patients'

TABLE 56 The cost of VADs

Name of device	Average cost/device (£)	Source
HMII	89,831[a]	NHS designated provider cost (Dr Mark Petrie, Golden Jubilee National Hospital, 2012, personal communication)
HW	80,076	NHS designated provider cost (Dr Mark Petrie, Golden Jubilee National Hospital, 2012, personal communication)
Jarvik Heart	50,273	Clegg *et al*.[4]
MicroMed DeBakey/(HeartAssist 5)	80,400	NHS designated provider cost (Dr Mark Petrie, Golden Jubilee National Hospital, 2012, personal communication)

a We did not include the cost of the VAD supplied by GJNH which was based on a single VAD used at this centre; however, this was used in scenario analysis.
The cost of Jarvik Heart was unavailable from the NHS designated providers and hence sought from the literature.
The device cost was reported by Clegg *et al*.[4] and inflated to 2011 prices by applying the projected Health Services Cost Index.[121]

TABLE 57 Pre-VAD implant preparation and theatre costs (GJNH finance department)

Resource area	Description of resource	Number of hours required per average patient	Number of units/ tests required per average patient	Estimated average cost per hour/cost per case (£)	Estimated % of patients requiring this input	Total estimated average cost for VAD (£)
Assessment by medical staff						
Cardiac MDT	Referred to AHF clinic	0.85		528.26	50	224.51
Pre-VAD tests/checks	Consultant surgeon	0.21		68.32	100	14.35
	SPR	0.21		22.18	100	4.66
	Consultant anaesthetist	0.42		61.80	100	25.95
Surgical procedure						
Theatre – pay	Theatre nursing team	5.00		78.00	100	390.00
Theatre – average consumables		1.00		755.85	100	755.85
Hardware	Pump		1	250.00	100	250.00
Perfusion – pay	Perfusionist – Band 7	7.50		35.31	100	264.85
Perfusion – supplies	Consumables per average case		1.00	798.44	100	798.44
Surgeon		6.25		61.80	100	386.22
Anaesthetist		6.25		61.80	100	386.22
Pharmacy (theatre)	Drugs costs		1.00	227.15	100	227.15
Total cost per VAD implant: £3728.20						

AHF, advanced heart failure; MDT, multidisciplinary team; SPR, specialist registrar.

medications to 2011 prices by applying the projected Health Services Cost Index.[120] The resulting monthly costs with distribution parameters where appropriate are shown in *Table 55*.

State 3: Support on heart transplant

The cost inputs include average presurgery preparatory cost, procedural cost and short-term post-surgery cost. The transplantation procedure cost was considered to be different between groups to address the increase in theatre time for VAD explant. Post-transplant monthly costs were assumed to be the same for both groups from month 2 onwards. Post-HT support costs include follow-up outpatient visits, investigation, blood test and drugs (see *Table 55*).

Clinical experts advised that the costs of the transplant donor procedure were trivial and we therefore did not include this cost in our model.

Sources of cost inputs: summary of sensitivity analyses

Sensitivity analyses around cost inputs

A sensitivity analysis (I A1] in *Table 54*) was conducted around the TP for MM to death which assumed the MM group was constituted of all BTDB MM patients (both 307 inotrope patients and 1189 non-inotrope patients). The monthly cost for these is shown in *Table 58*.

The monthly cost of all MM was a weighted value according to the number of both inotrope and non-inotrope patients from the BTDB. We used previously reported costs[30] for inotrope- and non-inotrope-supported MM patients, inflated to 2010/11 prices for the sensitivity analysis *Table 59*.

Sensitivity analyses II A and II B around cost inputs

In univariate sensitivity analyses, the cost of the VAD was varied from that in the base case as shown in *Table 60*. This analysis is designated II A in the results section.

In a further sensitivity analysis (designated II B) the cost of patient maintenance on a VAD was decreased from base case by 30%.

This was undertaken because clinical experts advised that patients on second- and third-generation VADs experience relatively fewer adverse events than those supported with earlier VAD designs. To address the potential cost savings of reduced adverse events, we lowered the monthly post-VAD implantation cost by 30% in sensitivity analysis.

TABLE 58 Cost inputs for patients on MM (both inotrope and non-inotrope)

Event	Components of cost	Mean cost/patient (£)
All MM	Month 1[a]	4517
	Month 2	1673
	Month 3	1759
	Month 4	329
	Month 5	220
	Month 6	245
	Months 7+	287

a Includes transplant assessment cost of £1633.

TABLE 59 Cost inputs for patients medically managed with inotropes and without inotropes

Event	Components of cost	Mean cost/patient (£)
MM – inotrope-dependent	Transplant assessment cost	1633
	Month 1	12,216
	Month 2	6393
	Months 3+	5965
MM – non-inotrope-dependent	Transplant assessment cost	1633
	Month 1	475
	Month 2	454
	Month 3	672
	Month 4	413
	Month 5	277
	Month 6	308
	Months 7+	361

TABLE 60 Summary of costs used in univariate sensitivity analyses

Analysis II A: input parameter	Cost (£)	Source
VAD cost (% reduction)		
10	72,513	Base-case inputs cost of £80,569
15	68,484	
20	64,456	
30	56,399	
40	48,342	
50	40,285	
60	32,228	
76	19,337	
Analysis II B: VAD immediate and long-term monthly cost reduced by 30%		
Month 1	102,342[a]	Base-case inputs
Month 2	9408	
Month 3	3577	
Month 4	2686	
Month 5	2274	
Month 6	1628	
Months 7+	1325	

a Includes VAD and implant cost.

Sensitivity analyses (II C and II D) around costs for both arm using Golden Jubilee National Hospital and national schedule of reference costs data

Further sensitivity analyses used a detailed list of resource use and associated costs which were supplied from Glasgow the Glasgow centre, the GJNH, one of the UK centres operating with the NSCT (analysis II C). The GJNH cost data and definitions used are all presented exactly as provided by GJNH. This provided information on all three health states. In addition, we also sourced the mean cost for three health states from the national schedule of reference costs (NSRC) 2010/11 (analysis II D).[122] These alternative sources are described in further detail below.

Support on medical management until heart transplant

Resource-use data from the Glasgow GJNH finance department were collected on hospital stay, drugs, investigations and outpatient visits for patients with advanced HF. The GJNH finance department reported a total cost of £10,111.66 per hospital stay per patient with advanced HF for the year 2009/10, based on a total of 92 patients costing £842.63 (£10,111.66/12) per patient in month 1. Further detailed information on the resource use and costs supplied by GJNH involved in managing patients in hospital with advanced HF is shown in *Table 61*.

From the cost provided by the GJNH finance department, it was not possible to identify the drugs and inotropes used in hospital at the time of admission. We assumed that patients admitted to hospital for advanced HF were inotrope-dependent and patients at home on the WL were non-inotrope-dependent (Dr Mark Petrie, GJNH, 2012, personal communication).

Patients at home and on the WL were seen in the HF clinic every third month. The cost per initial visit was £437.79, and after 3 months patients are reassessed by a multidisciplinary team consisting of a cardiologist, a cardiac surgeon and a specialist nurse. The cost for every other consecutive follow-up was £160.11 per visit.

We also sourced the mean cost of MM (from the NSRC) 2010/11 and these were explored in the sensitivity analysis (see *Table 66*).

Support on bridge to transplant with a ventricular assist device until heart transplant

A detailed description of resource-use data and unit cost estimates were collected for VAD implant from the GJNH finance department. Resource-use data were collected on VAD assessment cost, implant procedure cost, cost associated with ward and ICU stay, follow-up outpatient visits, investigation, blood test and drugs. The cost was based on one long-term VAD (HMII) patient for 2009/10. We recommend caution in interpreting this result partly because of this and partly as we believe that the cost from the GJNH might be overestimated (as throughput for this intervention is at present insufficient for economies of scale to be in evidence). However, the GJNH data give us details of the cost component for immediate post-operative hospital stay following VAD implant, and are shown in *Table 62*.

Following a VAD implant, patients were requested to attend fortnightly for a follow-up visit for 1 month, then to visit monthly for 3–4 months and then to visit 3-monthly for 6 months. Outpatient follow-up visit was estimated at £894.06 per visit (an outpatient visit post VAD is resource intensive with several invasive tests and non-invasive test undertaken during a follow-up visit).

We also sourced the mean cost of VAD implantation from the NSRC 2010/11 and this was explored in the sensitivity analysis (see *Table 66*).

Support on heart transplant

We determined the transplantation procedure cost for both VAD and MM patients from the GJNH finance department. The theatre cost of retrieving a donor heart was reported as £16,811.66. This includes the cost of surgical support for organ retrieval and does not include the cost of investigations; *Tables 63* and *64* summarise HT theatre cost and immediate post-operative hospital stay cost following four

TABLE 61 Cost of hospital stay for advanced HF (GJNH finance department)

Resource area	Description of resource	Number of OBD per average patient	Number of units/ tests/hours required per average patient	Estimated average cost per hour/cost per case (£)	Estimated % of patients requiring this input	Estimated average cost for HT (£)
Medical assessment and review on admission	Consultant surgeon		0.42	68.32	100	28.70
	Consultant physician		20.00	68.32	100	1366.44
	Anaesthetist/intensivist		0.43	61.80	100	26.57
	Cardiology registrar		1.25	22.18	100	27.72
Inpatient stay (excluding drugs)	Ward staffing and supplies	12.30		461.25	77	4368.49
	Outlier ward staffing and supplies	6.90		194.74	23	309.05
	ITU staffing and supplies	6.67		1268.54	15	1269.17
	HDU staffing and supplies	5.70		420.18	8	191.60
	CCU staffing and supplies	1.50		448.67	2	13.46
	IABP		2	696.32	23	320.30
Drugs	Prescribed in hospital					226.82
Tests	Radiology					459.26
	Cardiology/catheterisation laboratory					608.04
	Respiratory medicine					24.85
	Laboratory					572.83
AHP contact	Physiotherapy staff – Band 6		11.33	17.83	100	202.01
	Cardiology rehabilitation staff – Band 3		3.00	10.16	100	30.48
	Occupational therapy staff – Band 6		3.00	17.83	100	53.49
	Occupational therapy rehabilitation staff – Band 3		1.00	10.16	100	10.16
	Clinical nutrition – Band 7		0.10	22.15	100	2.22
Total cost: £10,111.66						

AHP, Allied Health Professional; CCU, critical care unit; HDU, high dependency unit; ITU, intensive treatment unit; OBD, occupied bed-days.
All salary based on mid-point of the scale.

TABLE 62 Cost of immediate post-operative hospital stay following VAD implant (GJNH finance department)

Resource area	Description of resource	Number of OBD per patient	Number of units/tests/ hours required per patient	Estimated average cost per hour/cost per case/cost per OBD (£)	Estimated % of patients requiring this input	Total estimated cost for VAD (£)
Inpatient stay (excluding drugs)	ITU staffing and supplies	14.66		1268.54	100	18,596.79
	ITU specialist consumables incurred by VAD patients		1	3882	100	3882.00
	Ward staffing and supplies	12.67		461.25	100	58,440.03
	IABP		2	696.32	66	919.14
Medical staff rounds to VAD patients	Surgeon		51.25	61.80	100	3167.00
	Junior surgeon		51.25	22.18	100	1136.65
	Consultant cardiologist		27	61.80	100	1668.47
	Junior cardiologist		25	22.18	100	554.46
	Anaesthetist/intensivist		1.25	428.05	100	535.06
Pharmacy	Surgery drugs – ITU		1	149.53	100	149.53
	Surgery drugs – ward		1	43.51		39.55
Tests	Radiology					132.33
	Laboratory					310.91
AHP contact	Physiotherapy staff – Band 6		25.17	17.83	100	448.78
	Cardiology rehabilitation staff – Band 3		7.67	10.16	100	77.93
	Occupational therapy staff –Band 6		10.50	17.83	100	187.22
	Occupational therapy rehabilitation staff – Band 3		3.33	10.16	100	33.83
Total cost per VAD implant: £37,683.71						

AHP, Allied Health Professional; ITU, intensive treatment unit; OBD, occupied bed-days.
All salary based on mid-point of the scale.

TABLE 63 Pre-HT preparation and theatre cost (GJNH finance department)

Resource area	Description of resource	Number of hours required per average patient	Number of units/tests required per average patient	Estimated average cost per hour/cost per case (£)	Estimated % of patients requiring this input	Total estimated cost attached to HT (£)
Donor heart retrieval						
Organ Retrieval team	Transplant co-ordinator call-outs[a]		1	6311.66	100	6311.66
	SAS surgeon transport of recipient and donor organ		1	10,500.00	100	10,500.00
Theatre cost						
Theatre	Theatre nursing team	15.00		78.00	100	1170.00
	Theatre consumables and drugs				100	2770.77
	Consultant transplant surgeon	15.00		68.32	100	1024.83
	Consultant anaesthetist	15.00		61.80	100	926.93
	Perfusionist – Band 7	22.50		35.31	100	794.56
	Perfusion consumables			1603.44	100	1603.44
	Cardiac physiologist – switch-off device	3.00		26.90	100	80.70
Total cost per HT: £25,182.88						

SAS, specialty and associate specialist.
a Includes five to six senior nurses, perfusionists and co-ordinators.
All salary based on mid-point of the scale.
Perfusionist: one in each theatre and one for cover.

TABLE 64 Costs of immediate post-operative hospital stay following HT (GJNH finance department)

Resource area	Description of resource	Number of OBD per average patient	Number of units/tests/ hours required per average patient	Estimated average cost per hour/cost per case (£)	Estimated % of patients requiring this input	Total estimated average cost for HT (£)
Inpatient stay (excluding drugs)	ITU staffing and supplies	3.50		1268.54	100	4439.89
	HDU staffing and supplies	3.00		420.18	25	315.13
	Ward staffing and supplies	19.00		461.25	100	8763.75
	Outlier ward staffing and supplies	3.00		194.74	50	292.11
Medical staff rounds to transplant patients	Surgeon		51.25	61.80	100	3167.00
	Junior surgeon		51.25	22.18	100	1136.65
	Consultant cardiologist		27	61.80	100	1668.47
	Junior cardiologist		25	22.18	100	554.46
	Anaesthetist/intensivist		1.25	428.05	100	535.06
Drugs	Post operative					15,700.76
Tests	Radiology					141.96
	Laboratory					358.38
	Cardiac physiology					528
AHP contact	Physiotherapy staff – Band 6		25.17	17.83	100	448.78
	Cardiology rehabilitation staff – Band 3		7.67	10.16	100	77.93
	Occupational therapy staff – Band 6		10.50	17.83	100	187.22
	Occupational therapy rehabilitation staff – Band 3		3.33	10.16	100	33.83
Discharge element	Hotel stay	2.50		45.00	100	112.50
	Transport			15.00		15.00
Total cost per patient: £27,136.95						

AHP, Allied Health Professional; HDU, high dependency unit; ITU, intensive treatment unit; OBD, occupied bed-days.
All salary based on mid-point of the scale.
Note: GJNH has a hotel attached to accommodate patients.

HTs. We recommend caution in interpreting this result partly because of these small numbers and partly as we believe that the cost from the GJNH might be overestimated owing to lack of economies of scale.

Following a HT, the follow-up management for both VAD and MM patients was assumed to be the same. The transplant management guidelines from the GJNH detailing follow-up outpatient visits, blood tests, chest radiograph and the biopsy regimen are provided in *Table 65*.

We also sourced the mean cost of HT from the NSRC 2010/11 and this was explored in the sensitivity analysis. These are summarised in *Table 66*.

Model assumptions for transition probabilities, utilities and cost inputs

A summary of the transition probabilities, utilities and cost inputs to the cost–utility model is detailed in *Table 67*. We also include here a list of model assumptions.

Model assumptions – transition probabilities

- The model was simplified by assuming all patients have the same survival post HT despite receiving a donor heart at different times (up to maximum of 42 months) and despite different treatment (VAD or MM) prior to transplant. The assumption is supported by data published by Russo *et al*.[100] and Nativi *et al*.[89] The same assumption has been made in previous economic analyses.[30,98]
- In our base-case analysis < 1% of patients are alive supported by a VAD beyond 70 months.
- In the base case, the model assumes that for an equitable comparison of the compared therapies the same probability of receiving a donor heart should be applied for both treatment and comparator groups.
- In the base case, survival of BTDB MM and VAD-supported patients who were censored on receipt of a HT was assumed to represent survival of patients eligible for HT who never received one; the impact of this was examined in extensive sensitivity analysis. Furthermore, constant hazard extrapolations were assumed to be reasonable estimates for extension of survival beyond the observed data. The same assumption has been made in previous economic analyses.[30,98]
- It is assumed that the MM patients in the BTDB who were classified as baseline users of 'inotropes' represent a distinct subpopulation of all MM patients in the database.
- The model assumes that post-HT survival remains the same irrespective of previous therapy (BTT with VAD or MM) and can be estimated from observed survival of UK BTDB patients who receive a donor heart.

TABLE 65 Scottish National advanced HF service transplant management guidelines recommendations for post-transplantation patients

Time after transplant	Clinic visits	Biopsy (endomyocardial)
0–6 weeks	Weekly	Weekly
6 weeks to 3 months	Fortnightly	Fortnightly
3 months to 1 year	6-weekly	6-weekly
Year 1 to year 2	3-monthly	Regular biopsies will cease at 1 year
Year 2+	6-monthly	

Clinic visits involve physical examination, chest radiograph and blood test [cyclosporine level, full blood count, urea and electrolytes, creatinine, liver function test, plasma creatine kinase, glucose lipids (6-monthly with cytomegalovirus monitoring)].

TABLE 66 Summary of cost inputs for sensitivity (analyses II C and IID) based on the GJNH finance department and NSRC– 2010/11 prices

Item	Period	Mean cost based on GJNH finance department 2011 price (£)	Period	Mean cost based on NSRC 2010/11 price (£)
VAD		78,877		N/A
VAD implant procedure		3728		N/A
Post-VAD implant support	Month 1	120,289[a]	Month 1	67,003[b]
	Month 2	1788.12	Month 2	N/A
	Month 3	894.06	Month 3	N/A
	Month 4	894.06	Month 4	N/A
	Months 5+	298.02	Month 5	N/A
			Month 6	N/A
			Months 7+	N/A
Support on MM (inotrope)	Month 1	843	Months 1+	1479
	Month 2	438		
	Months 3+	160		
HT assessment and theatre cost	BTT and MM	25,183	BTT and MM	N/A
Post-HT hospital stay and follow-up	Month 1	27,137	Month 1	37,871
	Month 2	3576	Month 2	N/A
	Month 3	1788	Month 3	N/A
	Months 4+	894	Months 4–7+	N/A

N/A, not available; data not available and replaced with base-case inputs; OBD, occupied bed-days.
a Includes device cost and implant procedure cost and month 1 support costs.
b Includes cost of device and average length of stay cost for 11.40 days (NSRC does not provide detailed breakdown of cost components).
Note: the cost of VAD implant was based on one VAD patient and 27 OBD in hospital.

Model assumptions – costs

- The model assumes that, other than for VAD cost, resource use associated with MM and VAD support have remained essentially the same as the previous analysis[30] so that relative costs merely require inflating to current prices. Expert clinical advice supported this assumption.
- We simplified assumptions on adverse event costs occurring in the long term (due to lack of reliable data).
- For costing we assumed that patients on second- and third-generation VADs rarely require a VAD replacement within a 7-year period; this was based on personal communication with HW manufacturers (Mr Timothy Homer, Global Market Access, 2012, personal communication).

Model assumptions – utilities

- It was assumed that in the absence of direct EQ-5D information, the modelling of utilities for health states using from NYHA classification of patients in the BTDB represents a reasonable compromise.

The base-case model assumptions were explored in sensitivity analyses. In the next section we describe results from the cost-effectiveness model.

TABLE 67 Summary of transition probabilities, utilities and cost inputs to the cost–utility model

Health state transition	Period	Monthly TP	SE	Beta distribution parameter	
				α	β
VAD support to death *p13*	Months 1–3	0.0577197	0.028	3.91	63.93
	Months 4+	0.0179873	N/A	N/A	N/A
MM support to death *p13*	Months 1+	0.073344	0.058	7.38	93.35
Time to HT[a] *p12*	Months 1–42: probability set to zero after 42 months	0.012745641	N/A	N/A	N/A
Support on HT to death *p23*	Months 1–3	0.070366726	0.0163	17.20	227.25
	Months 4–284	0.002980948	N/A	N/A	N/A
Utility inputs					
Health state	**Period**	**Mean utility**	**SE**	**Beta distribution parameter**	
				α	β
MM[b] (inotrope)	All months	0.55	0.023	237.89	194.63
Post VAD	All months	0.74	0.075	24.57	8.63
Post HT	All months	0.83	0.005	4683.69	959.31
Item	**Period**	**Mean cost (£)**	**SE (£)**	**Gamma distribution parameter**	
				α	β
Cost inputs (2011 prices)					
VAD		80,569	N/A	N/A	N/A
VAD implant procedure		3728	N/A	N/A	N/A
Post-VAD implant support[c]	Month 1	110,075	2518	2029.08	55.90
	Month 2	13,440	1306	105.95	126.84
	Month 3	5110	764	44.69	114.32
	Month 4	3836	607	40.0	95.89
	Month 5	3248	460	49.89	65.09
	Month 6	2326	356	42.69	54.48
	Months 7+	1893	907	4.35	434.97
Support on MM (inotrope)[d]	Month 1	12,216	1156	111.67	109.39
	Month 2	6393	604	112.03	57.06
	Months 3+	5965	193	951.25	6.27
HT theatre cost	BTT	16,663	N/A	N/A	N/A
	MM	11,395	N/A	N/A	N/A
HT assessment cost	BTT	0	N/A	N/A	N/A
	MM	1633	N/A	N/A	N/A

TABLE 67 Summary of transition probabilities, utilities and cost inputs to the cost–utility model (*continued*)

Health state transition	Period	Monthly TP	SE	Beta distribution parameter	
				α	β
Post-transplant hospital stay and follow-up	Month 1: BTT	15,577	1117	832.97	38.70
	Month 1: MM	13,211	961	730.39	33.68
	BTT and MM				
	Month 2	4331	802	29.18	148.40
	Month 3	2609	470	30.77	84.79
	Month 4	2828	260	117.87	23.99
	Month 5	2179	432	25.42	85.70
	Month 6	1646	138	142.69	11.53
	Months 7+	1410	177	62.91	22.41

N/A, not applicable; SE, standard error.
a Both groups.
b In sensitivity analysis utility for all MM patients was 0.62.
c Includes device and procedure.
d In sensitivity analysis monthly cost for MM were: month 1 £4517; month 2 £1672; month 3 £1758; month 4 £328; month 5 £220; month 6 £224; months 7+ £287.

Assessment of quality of cost inputs

The Sharples *et al.*[30] study was a good-quality study estimating cost inputs by combining two methods: direct observation of patients cost and cost estimated from NHS finance departments. The estimated unit costs were specific to the intervention and events of interest, and were generalisable to the study population. The resource use was measured for all three patient groups from the perspective of the NHS until the study cut-off date. Quality and validity of the cost data are good in relation to criteria suggested by Drummond *et al.*[97] The study by Sharples *et al.*[30] was the only study to report patient-specific resource-use data for the VAD procedure and subsequent stay in ICU and cardiac ward. The unit cost reflected the level of resource aggregation for procedure and itemised subsequent costs appropriately (e.g. stay in ICU and cardiac ward; device cost; HT procedure and associated ICU and ward stay; transplant assessment; follow-up readmission to ICU or ward; outpatient visits; investigation and drugs). A weakness of the study for the purposes of the current report is that it describes the results of a mixture of first- and second-generation VADs; however, it is the only available comparable study with the most recent resource-use data and unit cost estimates published in the UK setting.

Chapter 9 Results from the cost-effectiveness model

We present here deterministic and probabilistic results for the two research questions. For the base case(s) we also present probabilistic results plotted on the cost-effectiveness plane showing the joint distribution of differences in costs and QALYs, and CEACs indicating the probability that the interventions (BTT or ATT) are cost-effective at different thresholds of willingness to pay.

We adopted 3-, 10- and 50-year time horizons for both research questions. The 3-year horizon approximately reflects the period over which eligible patients are likely to receive a transplant, the 10-year horizon approximately reflects the maximum follow-up of BTT patients, and the 50-year horizon follows recommendations by NICE that the time horizon should be sufficiently extended to capture all benefits likely to accrue from the intervention. As about 60% of BTDB patients remained alive 10 years after transplant, a 50-year horizon was judged appropriate.

Results for research question 1

In patients aged ≥ 16 years with advanced HF who are eligible for HT:

1. What is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as BTT compared with MM?

Base-case deterministic results: research question 1

For the base case we compared the cost-effectiveness of BTT based on all VAD recipients compared with the MM patients in the BTDB who were classified as 'inotrope'. Derivation of utilities is reported in *Chapter 4*, transition probabilities between health states in *Chapter 7*, and resources and costs are reported in *Chapter 8*. Model inputs are summarised at the end of *Chapter 8*.

Results are tabulated (*Table 68*) in terms of mean cost, mean LYG and mean QALYs gained in each treatment group for 3-year, 10-year and lifetime (50-year) horizons. Also presented are the ICERs for these time horizons. The perspective is from the UK NHS and discounting of benefits and costs at 3.5% was undertaken according to UK guidelines.[115]

For VAD patients compared with the inotrope subgroup of the MM patients the ICER is £122,730 per QALY over a 3-year time horizon. At the 10-year time horizon the ICER increases to £68,088 per QALY, and at a lifetime horizon of 50 years the ICER is £55,1730 per QALY.

The cost of the VAD and of the implantation procedure together make a substantial contribution to the costs. The impact of this and of other inputs is explored in sensitivity analysis. Undiscounted LYG in the BTT and the MM arms are summarised in *Figures 61* and *62*.

Base-case probabilistic results: research question 1

Base-case probabilistic inputs are shown in *Table 67*. The base-case probabilistic results summarised in *Table 69* indicate a lifetime horizon ICER of £53,527 per QALY. Deterministic and probabilistic ICER estimates are similar for all three time horizons with the ICER increasing as the time horizon decreases.

The joint distribution of the difference in costs and the differences in QALYs for the three time horizons is shown in *Figure 63*. Each point is a simulation from the joint distribution; the plot illustrates the uncertainty surrounding incremental costs and benefits for the two groups being compared.

TABLE 68 Base-case deterministic results

Time horizon	Mean cost (£)	Mean years survival	Mean QALYs
3-year time horizon			
VAD	176,594	1.95	1.48
MM	79,637	1.13	0.69
Difference	96,957	0.82	0.79
ICERs (£/LYG)	117,728		
ICERs (£/QALY)	122,730		
10-year time horizon			
VAD	212,648	3.81	2.95
MM	91,450	1.72	1.17
Difference	121,198	2.09	1.78
ICERs (£/LYG)	57,989		
ICERs (£/QALY)	68,088		
Lifetime model			
VAD	239,832	5.40	4.26
MM	104,106	2.47	1.80
Difference	135,726	2.93	2.46
ICERs (£/LYG)	46,322		
ICERs (£/QALY)	55,173		

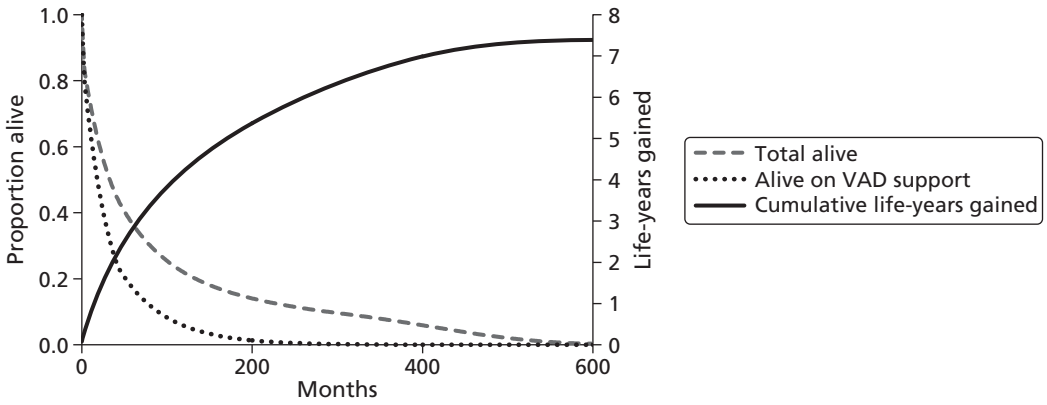


FIGURE 61 Undiscounted LYG with VAD – BTT.

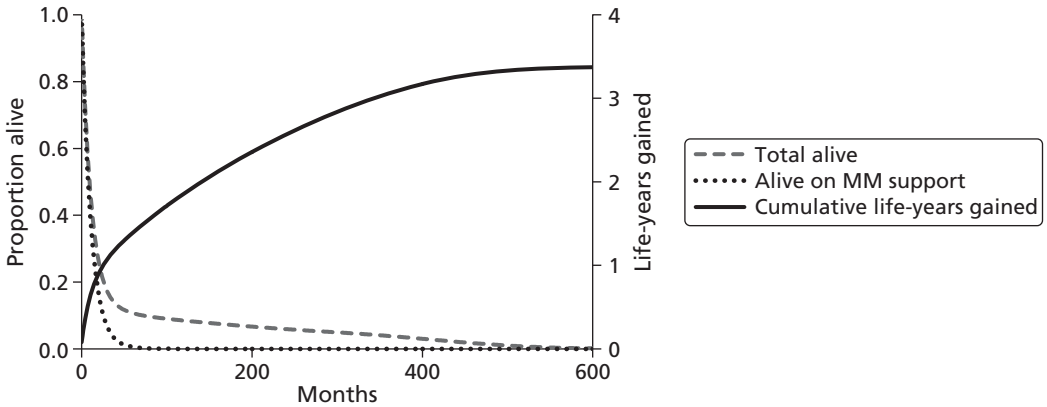


FIGURE 62 Undiscounted LYG with MM support.

TABLE 69 Base-case probabilistic results: (estimated using Monte Carlo method of 1000 simulations)

Time horizon	Mean cost (£) (95% CI)	Mean years survival (95% CI)	Mean QALYs (95% CI)
3-year time horizon			
VAD	177,009 (154,922 to 210,495)	1.96 (1.60 to 2.22)	1.49 (1.14 to 1.80)
MM	83,010 (49,888 to 124,933)	1.18 (0.68 to 1.81)	0.72 (0.42 to 1.12)
Difference	93,999 (45,307 to 139,435)	0.78 (0.09 to 1.36)	0.77 (0.26 to 1.21)
ICERs (£/LYG)	114,631 (78,800 to 374,982)		
ICERs (£/QALY)	120,510 (79,560 to 251,285)		
10-year time horizon			
VAD	212,000 (175,724 to 264,432)	3.83 (3.07 to 4.41)	2.95 (2.26 to 3.55)
MM	99,240 (57,026 to 169,449)	1.87 (1.05 to 3.19)	1.27 (0.73 to 2.15)
Difference	112,760 (33,076 to 179,395)	1.96 (0.55 to 2.97)	1.68 (0.63 to 2.51)
ICERs (£/LYG)	57,530 (35,881 to 99,572)		
ICERs (£/QALY)	67,119 (38,756 to 116,681)		
Lifetime model			
VAD	240,193 (196,411 to 306,883)	5.46 (4.29 to 6.56)	4.32 (3.31 to 5.31)
MM	112,802 (65,086 to 197,666)	2.67 (1.49 to 4.59)	1.94 (1.07 to 3.33)
Difference	127,391 (36,782 to 179,736)	2.79 (0.61 to 4.33)	2.38 (0.78 to 3.59)
ICERs (£/LYG)	45,659 (30,159 to 86,586)		
ICERs (£/QALY)	53,527 (31,802 to 94,853)		

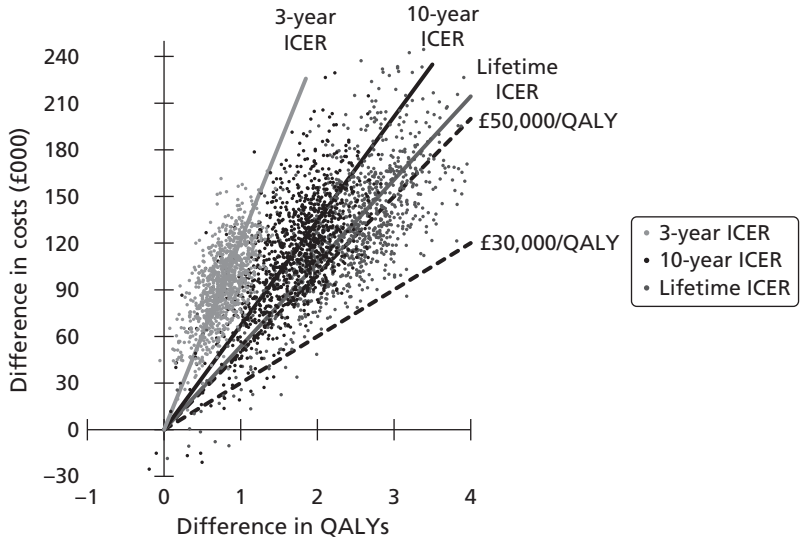


FIGURE 63 Cost-effectiveness plane for 3-year, 10-year and lifetime horizons: base-case probabilistic results.

Figure 64 presents the CEACs for the 3-year, 10-year and 50-year time horizons. NICE guidance,[101] although not explicit, suggests a benchmark of approximately £30,000 per QALY as the usual upper limit for the NHS. At a willingness to pay of £50,000 per QALY BTT approaches cost-effectiveness compared with MM (see *Figure 63*). Although, again not explicit, NICE appears to have applied a threshold of £50,000 per QALY for interventions which satisfy recommended criteria as end of life treatments. These include:

- predicted survival of < 2 years in the absence of the intervention
- the intervention prolongs survival by at least 3 months
- a small population eligible for the treatment.

Sensitivity analyses: base-case analysis-research question 1

Sensitivity analyses were conducted by altering base-case inputs to the model. Several types of sensitivity analysis were explored encompassing changes to:

1. I] TPs between health states (I A to I D)
2. II] inputs for costs (II A to II D)
3. III] utility inputs for health states.

I] Impact of changing the transition probabilities between health states

The results for these sensitivity analyses are summarised in *Table 70*.

In analyses A2, the survival under MM was modelled according to the SHFM score after Levy *et al*.[95] for BTT patients. Using data from Schaffer *et al*.[77] and from Strueber *et al*.[83] the resulting modelled median survivals were 8.9 months and 16.5 months, respectively, providing values both higher and lower than that modelled for the BTDB inotrope patients (9.1 months). The resulting lifetime ICERs of £55,058 per QALY and £51,731 per QALY differed little from the deterministic base-case value of £55,173 per QALY. More recently Aaronson *et al*.[94] reported that the SHFM predicted 43% survival at 1 year for a MM group equivalent to the 140 BTT patients investigated in a HW study. This equates to a median predicted survival of 9.86 months, again very close to that modelled from our BTDB inotrope patients. Thus, when survival under MM is modelled according to these SHFM scores, the ICER estimates remain similar to that of the base case.

Some UK clinical experts expressed the view that a median survival of 9 months was too generous an estimate for inotrope-dependent MM patients entered onto UK lists for HT. On their suggestion sensitivity analysis was therefore undertaken in which the TP for MM to death was modelled on the survival of the optimum MM control group of the REMATCH trial (median survival 4.94 months); the resulting lifetime ICER (£55,203/QALY) was hardly different to that in the base case. The reason for this is that although the

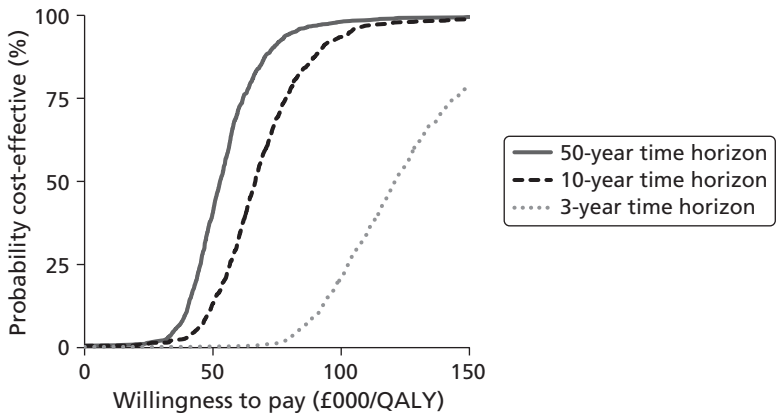


FIGURE 64 Cost-effectiveness acceptability curves for 3-year, 10-year and lifetime models.

TABLE 70 Sensitivity analyses based on changes to TPs between health states

Input parameter	Horizon (years)	ICER[a] (£/QALY)	Difference in QALYs	Difference in costs (£)
A1] TP MM to death based on K–M for all BTDB MM patients ($n = 1496$) using constant hazard fit to 3 months and then 3 months to 10% at risk (costs input appropriate for mix of inotrope and non-inotrope patients)	3	7,423,100	−0.02	148,462
	10	−430,700[b]	−0.37	159,359
	50	−207,054[b]	−0.76	157,361
A2 i] TP MM to death from SHFM[95] making use of data from Schaffer *et al.*[77]	3	122,814	0.80	98,251
	10	68,268	1.80	122,882
	50	55,058	2.50	137,644
A2 ii] TP MM to death from SHFM[95] making use of data from Strueber *et al.*[83]	3	129,178	0.50	64,589
	10	61,539	1.17	72,001
	50	51,731	1.55	80,183
A2 iii] TP MM to death from SHFM[92] making use of BTDB MM patients' data	3	121,309	0.90	109,781
	10	68,967	1.99	137,302
	50	55,148	2.79	154,125
A3] TP MM to death based on K–M for BTDB inotrope MM patients using constant hazard fit to 2 months	3	121,560	0.92	111,835
	10	69,196	2.02	139,776
	50	55,074	2.85	156,961
A4 i] TP MM to death based on the optimum MM arm of the REMATCH trial using constant hazard fit to reported median survival of 150 days	3	119,305	1.05	125,270
	10	69,413	2.24	155,484
	50	55,203	3.17	174,994
A4 ii] TP MM to death based on the optimum MM arm of the REMATCH trial using constant hazard fit to reported median survival of 120 days	3	118,968	1.12	133,244
	10	69,723	2.36	164,547
	50	55,178	3.36	185,398
B1] TP VAD to death based on Weibull fit to survival for all BTDB VAD patients	3	128,556	0.75	96,432
	10	69,947	1.73	121,030
	50	56,221	2.40	134,853
B2] TP VAD to death based on K–M for BTDB HW patients, using hazard fit to 4 months, and from 4 months to 10% at risk (with associated HW costs)[c]	3	115,794	0.86	99,032
	10	64,663	1.95	126,064
	50	52,344	2.72	142,545
C1i] TP MM to HT based on log-normal fit to data for all BTDB transplant recipients (MM and BTT); TP VAD to HT based on exponential fit to data for BTDB BTT transplant recipients	3	627, 644	0.16	100,423
	10	−404,858[b]	−0.24	97,166
	50	−54,168[b]	−1.37	74,210
C1ii] TP from MM or VAD to HT based on log-normal fit to data for all BTDB transplant recipients (i.e. equal opportunity of donor heart in both arms based on log-normal fit)	3	283,924	0.38	107,891
	10	135,726	0.88	119,439
	50	96,319	1.34	129,068

continued

TABLE 70 Sensitivity analyses based on changes to TPs between health states (*continued*)

Input parameter	Horizon (years)	ICER[a] (£/QALY)	Difference in QALYs	Difference in costs (£)
Bivariate sensitivity analysis				
D1] TP MM to death based on K–M for BTDB inotrope MM patients using constant hazard fit to 2 months to death using a constant hazard fit to 2 months (A3] above)TP VAD to death based on Weibull fit to survival for all BTDB VAD patients (as B1] above)	3	125,880	0.88	111,309
	10	70,621	1.97	139,419
	50	56,172	2.78	155,897
D2] TP MM to death based on SHFM using data from Schaffer *et al.*[77] (as A2i] above) TP VAD to death based on Weibull fit to survival for all BTDB VAD patients (as B1] above)	3	128,300	0.76	97,725
	10	70,026	1.75	122,686
	50	56,224	2.43	136,744

a ICERs do not correspond to the exact differences in cost by differences in QALYs owing to rounding of the difference in QALYs to two decimal places.
b BTT is dominated by MM, being more expensive while delivering less benefit.
c Note: the cost for the HW device was £80,076 (base-case cost for VADs was £80,569).

poorer survival of the MM arm results in an increase in the difference in QALYs between BTT and MM this poorer survival also results in lower costs in the MM group and an increase in the difference in costs between BTT and MM, and these factors tend to cancel out when calculating the ICER. It is interesting that under the base-case scenario, varying the survival of the MM arm between 3.9 and 16.5 months has negligible impact on the resulting lifetime ICER.

When the comparator population is constituted from the whole BTDB MM population (analysis A1), the ICER indicates that BTT is dominated, that is BTT is found to be more costly and less beneficial than MM. Similarly when a high probability of receiving a HT is applied to both groups (C1i), or if the MM arm is allocated a high probability but the BTT arm a low probability as in previous analyses (C1ii), BTT is dominated or the ICER becomes extremely large. These results indicate the critical importance of both the selection of an appropriate comparator population and of ensuring that an equal opportunity of receiving a HT is allocated to both groups.

These alternative scenarios have been modelled over the lifetime of the patient (i.e. until all patients have died). As in the base case, models with shorter time-horizons result in higher ICERs.

II] Impact of changing inputs for cost

Analysis II A change to device cost

We reduced the mean cost of the VAD by 10–76% to identify its impact on the ICER. The largest reduction in ICER was noticed at 76% reduction, where the 10-year and lifetime horizons of the model were more cost-effective (*Table 71*). Although the device has already been priced and marketed, this sensitivity analysis may inform reimbursement agencies in identifying the maximum price they may be willing to accept on the basis of cost-effectiveness.

These results indicate that under the base-case scenario a modest reduction in device cost of 15% reduces the ICER to a threshold of ~ £50,000 per QALY, which is close to values used by NICE for treatments which satisfy end of life criteria. To bring the ICER to a threshold of £30,000 per QALY requires a very substantial reduction to the cost of the device of 76%.

TABLE 71 Incremental cost-effectiveness ratio based on reduced VAD cost (analysis II A): BTT vs. MM

% reduction in device cost	Time period	VAD mean cost (£)	New ICER (£/QALY)	Deterministic base-case ICER (£/QALY)
10	3 years	168,537	112,605	122,730
	10 years	204,591	63,613	68,088
	Lifetime	231,774	51,739	55,173
15	3 years	164,509	107,502	122,730
	10 years	200,563	61,348	68,088
	Lifetime	227,746	50,106	55,173
20	3 years	160,481	102,400	122,730
	10 years	196,534	59,083	68,088
	Lifetime	223,718	48,474	55,173
30	3 years	152,424	92,194	122,730
	10 years	188,477	54,553	68,088
	Lifetime	215,661	45,209	55,173
40	3 years	144,367	81,989	122,730
	10 years	180,420	50,023	68,088
	Lifetime	207,604	41,943	55,173
50	3 years	136,310	71,784	122,730
	10 years	172,364	45,493	68,088
	Lifetime	199,547	38,678	55,173
76	3 years	115,361	45,250	122,730
	10 years	151,415	33,715	68,088
	Lifetime	178,599	30,189	55,173

Note: the base-case cost of the device was £80,569.

Analysis II A: Change to patient maintenance cost supported on ventricular assist device

A sensitivity analysis considered that patients implanted with second- and third-generation VADs rather than first-generation devices experience fewer adverse events. The base-case monthly cost of immediate and long-term follow-up under VAD support was based on appropriately adjusted data from a previous study obtained in an era of transition between use of early and later generation devices. A reduction of 30% to this base-case cost resulted in an ICER of £42,914 over a lifetime time horizon (*Table 72*). It should be borne in mind that to date there are no firm data to support a conclusion that patients experience 30% fewer adverse events after implantation of second- and third-generation VADs. However, one publication identified in the clinical effectiveness systematic review (Ventura *et al.*[82]) reported a non-randomised comparative study of HMII ($n = 484$) compared with the pulsatile HMXVE ($n = 673$) finding a significantly higher rate of hospitalisation for infection post implant for the pulsatile device. In addition, the RCT of DT with patients ineligible for HT conducted by Slaughter *et al.*,[47] comparing HMII with the pulsatile HMXVE device, reported lower risk in the HMII group for a wide range of adverse events (bleeding, stroke, rehospitalisation) and statistically lower rates of infection.

TABLE 72 Incremental cost-effectiveness ratio based on reduction in immediate and long-term monthly costs of VADs by 30%: comparison BTT vs. MM support

Time period	Mean cost (£)	Cost difference (£)	New ICER (£/QALY)	Base-case ICER (£/QALY)
3-year time horizon				
VAD	153,381			
MM	79,637	73,744	94,529	122,730
10-year time horizon				
VAD	183,939			
MM	91,450	92,488	51,960	68,088
Lifetime model				
VAD	209,998			
MM	104,106	105,892	42,914	55,173

Analysis II C: Sensitivity analysis around costs for both arms using Golden Jubilee National Hospital data

Sensitivity analysis used variations on cost inputs for both arms based on the GJNH finance department costs; results are shown in *Table 73*. All ICERs (3 year, 10 year and lifetime) are higher than base case with these alternative costings.

Analysis II D: Sensitivity analysis around costs for both arms using national schedule of reference costs data

In this sensitivity analysis we altered costs for both arms using variations in cost inputs based on the NSRC for 2010/11;[122] results are shown in *Table 74*. All ICERs (3 year, 10 year and lifetime) are higher than base case with these alternative costings.

III] Impact of changing utility values for health states

Univariate sensitivity analysis was undertaken replacing base-case utilities by those reported by Sharples *et al.*;[30] no large deviation in ICER was noticed (*Table 75*).

TABLE 73 Incremental cost-effectiveness ratio based on health states cost sourced from the GJNH finance department 2010/11: comparison BTT vs. MM support

Time period	Mean cost (£)	Cost difference (£)	New ICER (£/QALY)	Deterministic base-case ICER (£/QALY)
3-year time horizon				
VAD	145,431			
MM	12,954	132,477	167,692	122,730
10-year time horizon				
VAD	159,856			
MM	19,048	140,808	79,106	68,088
Lifetime model				
VAD	175,303			
MM	27,069	148,234	60,014	55,173

TABLE 74 Incremental cost-effectiveness ratio based on health states cost sourced from the NSRC: comparison BTT vs. MM support

Time period	Mean cost (£)	Cost difference (£)	New ICER (£/QALY)	Deterministic base-case ICER (£/QALY)
3-year time horizon				
VAD	134,907			
MM	25,832	109,075	138,158	122,730
10-year time horizon				
VAD	171,016			
MM	35,879	135,137	75,980	68,088
Lifetime model				
VAD	198,200			
MM	48,533	149,667	60,654	55,173

TABLE 75 Incremental cost-effectiveness ratio based on changes in utility score: comparison BTT vs. MM support

Time period	Mean QALY	QALY difference	New ICER (£/QALY)	Deterministic base-case ICER (£/QALY)
3-year time horizon				
VAD	1.31			
MM	0.63	0.69	141,360	122,730
10-year time horizon				
VAD	2.65			
MM	1.07	1.58	76,823	68,088
Lifetime model				
VAD	3.85			
MM	1.64	2.21	61,536	55,173

Tornado diagram

In sensitivity analysis the sources of all major base-case inputs were retained, but their values were raised and lowered at a fixed rate of 30% from their original values. For each parameter change, the percentage impact on the ICER is shown graphically in the form of a tornado diagram (*Figure 65*).

These analyses indicate that the most influential inputs were the monthly cost on BTT support, the monthly cost on MM support, and utility on VAD support. The probability of death while supported with a VAD was not influential in this over a ± 30% range of change. These results coincide with findings from the previous sensitivity analyses except that the time to HT is not influential in this analysis. This is because here the opportunity of receiving a donor heart has been kept the same for both VAD (BTT) and MM arms.

Base-case results for research question 2

Where data permit, what is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as ATT in comparison with their use as BTT therapy? This comparison addresses a

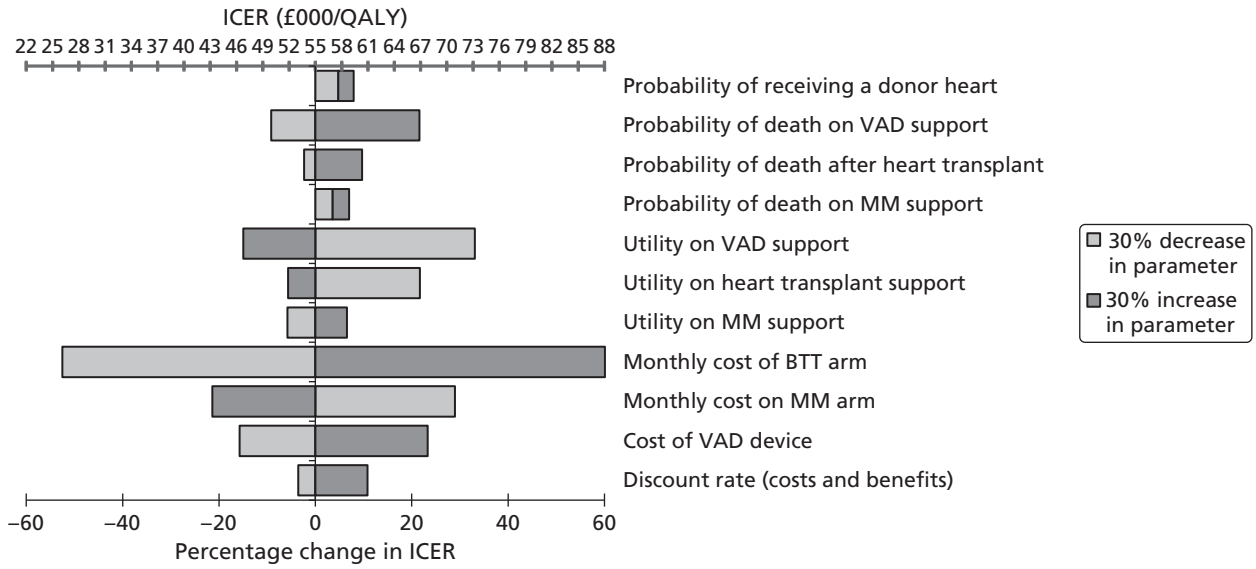


FIGURE 65 Tornado diagram. The bars indicate the effect on the base-case deterministic ICER (£55,173/QALY) of a 30% increase or decrease in input values for each of the input parameters listed on the right-hand side of the figure. Note: change to monthly cost of the BTT and MM arms included 30% increase or decrease to both pre-HT and post-HT costs.

hypothetical scenario in which VAD recipients in one arm (ATT) have no opportunity of receiving a donor heart, whereas the BTT arm retains the same chance of a transplant as observed for BTDB BTT patients.

Base-case deterministic results: research question 2

The base-case TP inputs as listed for BTT VAD recipients for research question 1, and corresponding costs and utilities were applied to the comparator arm. For the ATT arm all inputs were the same as for the BTT arm except that the probability of receiving a donor heart was set to zero. It is recognised that ATT for patients suitable for HT is not currently a therapeutic option for the UK HF patients.

The base-case results for the deterministic model are represented for 3-year, 10-year and lifetime time horizons of the model, and these are tabulated in *Tables 76* and *77*. We have also presented results on a cost-effectiveness plane together with a CEAC (see *Figures 66* and *67*).

The ICERs (cost/QALY) for VAD as an ATT compared with VAD as a BTT over the 3-year, 10-year and lifetime study periods are £353,467, £31,685 and £20,637, respectively, but it should be noted that ATT costs less than BTT and delivers reduced benefit.

Over 3 years the ATT arm cost £10,604 less than the BTT arm and generated 0.03 fewer QALYs. At 10 years the ATT arm cost £15,329 less than the BTT arm and generated 0.48 fewer QALYs, and over a lifetime the VAD as ATT arm cost £32,813 less and generated 1.59 fewer QALYs. Thus, over a 50-year time horizon 1.59 QALYs are sacrificed at a cost saving rate of £20,637 per QALY.

Base-case probabilistic results: research question 2

Base-case probabilistic results are summarised in *Table 77* and indicate a lifetime horizon ICER of £21,393 per QALY. The ICER falls mainly across the south-west quadrant, with a few results in the north-west quadrant, indicating that a VAD as an ATT is less effective and in some of the simulations is more costly. VADs as an ATT is, on the whole, cheaper – but confers less health gain. These findings are illustrated graphically in *Figures 66* and *67*. The cost-effectiveness plane for 3-year, 10-year and lifetime probabilistic estimates for VAD as an ATT compared with VAD as a BTT are shown in *Figure 66* and base-case results are presented as CEACs for 3-year, 10-year and lifetime time horizons of the model in *Figure 67*.

TABLE 76 Deterministic results for VAD-ATT compared against VAD-BTT

Time horizon	Mean cost (£)	Mean survival (years)	Mean QALYs
3-year time horizon			
VAD – ATT	165,990	1.96	1.45
BTT	176,594	1.96	1.48
Difference	–10,604	0	–0.03
ICERs (£/LYG)	Cannot be calculated		
ICERs (£/QALY)	353,467		
10-year time horizon			
VAD – ATT	197,319	3.33	2.47
BTT	212,648	3.81	2.96
Difference	–15,329	–0.48	–0.48
ICERs (£/LYG)	31,685		
ICERs (£/QALY)	31,685		
Lifetime model			
VAD – ATT	207,019	3.62	2.60
BTT	239,831	5.41	4.27
Difference	–32,812	–1.79	–1.59
ICERs (£/LYG)	18,331		
ICERs (£/QALY)	20,637		

Please note an ICER can be unstable if the denominator is close to zero.

TABLE 77 Probabilistic results for VAD as ATT compared with VAD as BTT

Costs	Mean cost (£)	Mean survival (years)	Mean QALYS
3-year time horizon			
VAD – ATT	167,400	1.97	1.46
BTT	177,430	1.97	1.50
Difference	–10,030	0	–0.04
ICERs (£/LYG)	Cannot be calculated		
ICERs (£/QALY)	309,561		
10-year time horizon			
VAD – ATT	195,745	3.34	2.48
BTT	213,626	3.84	2.97
Difference	–17,881	–0.49	–0.50
ICERs (£/LYG)	36,490		
ICERs (£/QALY)	35,760		

continued

TABLE 77 Probabilistic results for VAD as ATT compared with VAD as BTT (*continued*)

Costs	Mean cost (£)	Mean survival (years)	Mean QALYS
Lifetime Model			
VAD – ATT	206,153	3.62	2.68
BTT	241,023	5.47	4.32
Difference	–34,870	–1.85	–1.63
ICERs (£/LYG)	18,849		
ICERs (£/QALY)	21,393		

Please note an ICER can be unstable if the denominator is close to zero.

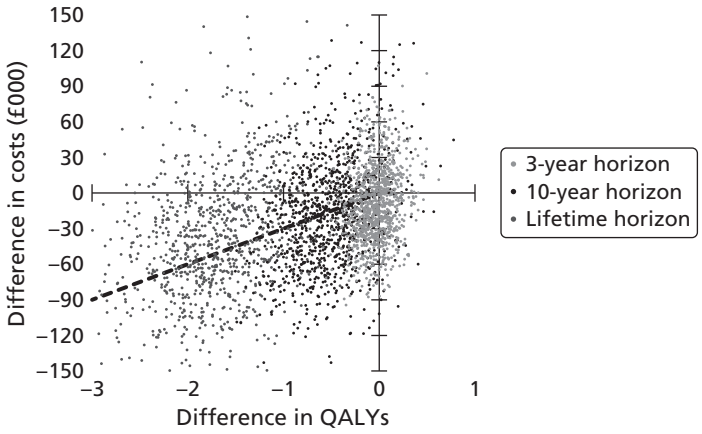


FIGURE 66 Cost-effectiveness planes for 3-year, 10-year and lifetime time horizons. The dashed line indicates a saving of £30,000 for the sacrifice of 1 QALY.

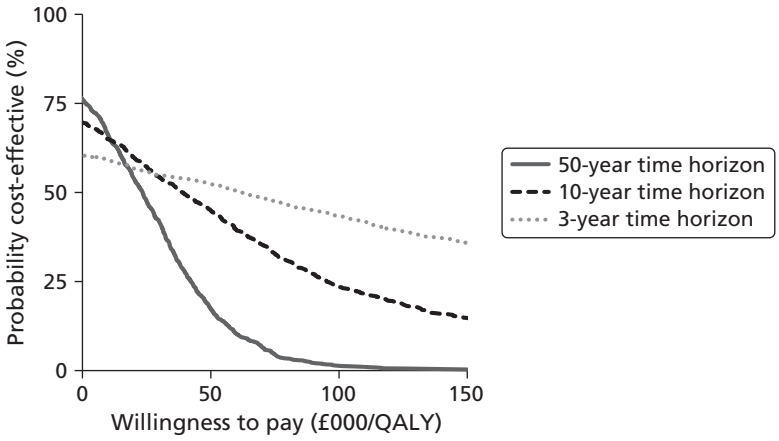


FIGURE 67 Cost-effectiveness acceptability curve for VAD as an ATT vs. VAD as a BTT.

These findings tell us that, relative to VAD for a BTT, VAD as an ATT over a 10-year or lifetime time horizon costs less and confers less benefit. At 10 years the intervention is just above ~ £30,000 per QALY plane – albeit mainly within the 'south-west' rather than the 'north-east' quadrant.

In the final chapter we summarise our findings, discuss the strengths and limitations of the work and make recommendations for future research.

Chapter 10 Discussion

Summary of research questions and methods

We aimed to answer two research questions:

In patients aged ≥ 16 years with advanced HF who are eligible for HT:

1. What is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as a BTT compared with MM?
2. Where data permit, what is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as an ATT in comparison with their use as a BTT therapy?

Our objectives were:

1. to summarise previously published HTA reports by Clegg *et al*.[4] and Sharples *et al*.[30] on VADs
2. to undertake a systematic review and evidence synthesis of the relevant clinical effectiveness and cost-effectiveness literature
3. to further develop the cost-effectiveness and cost–utility models developed in the 2006 HTA: *Evaluation of the ventricular assist device programme in the UK*[30] and where possible to compare the use of VADs as a BTT firstly with MM and secondly as an ATT
4. to investigate the factors that drive cost-effectiveness estimates
5. to report on findings and make recommendations for future research.

We summarised previous research in the area and undertook systematic reviews of the evidence on the clinical effectiveness and cost-effectiveness of second- and third-generation VADs, including studies which had control groups, or were case series with ≥ 50 patients. Studies had to relate to patients with advanced HF suitable for receipt of an LVAD, RVAD or BiVAD as a BTT or as potential long-term alternative to HT. We investigated potential comparators. Patient outcomes included survival, functional capacity (e.g. change in NYHA functional classification), QoL and adverse events. We used recognised quality assessment methods and produced a narrative review.

Data from the NHS BTDB were obtained from the BTNR maintained on behalf of the UK transplant community. We used review findings and IPD to build a model to compare costs and effectiveness of VADs firstly used as a BTT with MM and secondly used as an ATT. To estimate quality-adjusted survival a discrete-time, semi-Markov, multistate model was developed. The discount rate was 3.5%, the time horizon varied (with 3-year, 10-year and lifetime time horizons investigated) and the analysis was undertaken from the perspective of the NHS. We reported the findings using both deterministic and probabilistic methods and undertook multiple sensitivity analyses varying survival, utilities and costs inputs to the model.

Summary of clinical effectiveness evidence

A total of 40 observational publications[42,52,53,56–92] were included; 29[52,53,56–82] involved HMII, one[83] involved HW, one[84] involved the MicroMed DeBakey VAD, one[86] involved Berlin Heart INCOR, two[42,85] involved DuraHeart, and six further studies reported on a mixture of devices. Nineteen studies reported that the patients received a BTT; the remaining studies reported results for a mix of patients some receiving a BTT and some DT. In some studies the reason for VAD implantation was not clearly reported.

No direct comparative evidence was found for the clinical effectiveness of second- and third-generation VADs used as a BTT compared with MM or best supportive care. Furthermore, there was no direct evidence for the clinical effectiveness of second- and third-generation VADs used as an ATT in comparison with their use (1) as a BTT and (2) with MM and subsequent HT. This is in line with previous findings on first-generation devices (Clegg *et al*.[4] and Sharples *et al*.[30]).

The 40 included publications reported outcomes for repeatedly overlapping populations. Therefore, to avoid double counting, the results presented have focussed on the study or studies with the largest relevant population that reported on outcome results with sufficient rigour and coverage. The results from such studies are difficult to interpret in an assessment of the clinical effectiveness of BTT.

The majority of studies were rated as of moderate quality or less. In over half of the studies, it was not possible to tell if the participants were representative of the target population. This was mainly due to limited or no information on baseline characteristics.

All included studies were observational in design and were potentially at risk of bias. Studies were mostly non-comparative, always non-randomised, non-blinded and often retrospective. Although several studies did compare the findings of different VADs (e.g. HMII vs. HMXVE and HMII vs. HMI) these studies often provided insufficient detail to judge the adequacy or relevance of the comparator groups and so the potential for bias remained. The technology is changing rapidly in this area. We have highlighted the evidence currently available on the effectiveness of second- and third-generation devices. However, with the exception of HMII, evidence is limited although we are aware of a recently published study of HW by Aaronson *et al*.[94]

Analyses of included publications suggested the following estimates for baseline characteristics of participants in BTT studies: the majority of participants were white (78–94%), male 84.2% (95% CI 79.4% to 88.0%) and middle aged [mean age was estimated at 50.8 years (95% CI 49.3 to 52.4 years)]; mean BMI was in the overweight range, estimated at 26.5 kg/m^2 (95% CI 25.7 to 27.3 kg/m^2); one-quarter of patients, 25.2% (95% CI 17.4% to 35.1%) were estimated to have diabetes mellitus; study participants had very severe HF, with 83.5% (95% CI 78.0% to 87.9%) overall rated as NYHA class IV; most participants were supported with inotrope medication (80.8%; 95% CI 50.9% to 94.5%) and had low mean systolic BP (97.3 mmHg; 95% CI 92.8 to 101.7 mmHg).

By 12 months patients had suffered a variety of serious complications. Studies reported the following ranges for adverse events: 4–27% bleeding requiring transfusion; 1.5–40% stroke; 3.3–48% infection (sepsis); 1–14% device failure; 3–30% HF; 11–32% reoperation; and 3–53% renal failure. Publications reported results from a variety of QoL and functional status measures; these indicated that patients supported by HMII and HW VADs for up to 6 and 12 months, respectively, experienced an improved QoL and functional status relative to their condition pre implantation. Overall, patients who were supported by a VAD and survived appeared to have an improved QoL and functional status from before implantation of the device.

The adverse event rates reported (including, for example, stroke and renal failure) are high. However, this needs to be read in the context of patients with advanced HF, whose vascular and renal function are likely to have been poor prior to intervention, and whose QoL and life expectancy are poor (e.g. a substantial chance of dying within a year with conventional therapy without VAD; see *Chapters 6* and *10*). These patients are receiving VADs as a BTT, their options without the intervention may be limited and they may be prepared to accept a high risk of adverse events in an attempt to achieve a better QoL post transplant.

Strengths of systematic review of clinical effectiveness evidence

Our review was rigorous and followed clear systematic methods to ensure robust coverage and quality assessment of available evidence. We were informed by clinical and methodological experts who advised about the development of the research protocol and the report.

Limitations of systematic review of clinical effectiveness evidence

Studies in this area reported on heterogeneous populations, were of modest or poor quality and reported on diverse outcomes over diverse time periods. This made synthesis and/or pooling of study data problematic and use of meta-analysis of outcome measures was not an option.

Mixed populations receiving destination and bridge to transplant therapies

The reason for VAD use varied across the 40 publications. It was not always clear what the indication for treatment was. Although every attempt was made to identify papers concerned with BTT, in those studies that involved both a BTT and a DT, results were frequently not reported separately.

Different numbers of patients at each period

Analysis of different time periods in several publications was undertaken on different numbers of participants. This was likely to be attributable to several factors (e.g. death and transplantation). It was also noted that outcomes (e.g. survival) were often reported at different follow-up time points across the included studies, which presented difficulties when analysing findings. Attrition rates were difficult to determine. Some studies did report missing data and withdrawals. However, owing to the nature of the studies (i.e. retrospective), there was limited reporting of dropouts and their reasons.

Duplication of data and heterogeneity

As many publications reported on patients who were participants in other studies, the extent of duplication was difficult to determine precisely. We were unable to contact authors to clarify overlaps.

Summary of cost-effectiveness evidence

Using rigorous systematic review methods we identified only one relevant study of cost-effectiveness of second- and third-generation VADs.[98] This was a good-quality, cost-effectiveness modelling study which allocated equal probability of receiving a HT to both groups of patients (VADs and MM); this contrasts with the analysis of Sharples *et al*.[30] in which MM patients received a donor heart with much greater probability than BTT patients reflecting actual UK clinical practice. It appears sensible for the purposes of a fair comparison between treatment options that each should have an equal opportunity of receiving the benefits of a transplant.

Our model was built using data from a UK database (BTDB) with large sample size reflecting UK practice and under a range of model scenarios and sensitivity analyses. We investigated cost-effectiveness of BTT for patients implanted with a second- or third-generation VAD, compared with MM candidates. BTT patients had higher mean costs with higher survival benefit. This was the case for nearly all the various scenarios examined for BTT patients compared with MM patients and for all time horizons considered (3 years, 10 years and lifetime), exceptions occurring when the MM arm was represented by all BTDB MM patients or when chance of a transplant was much greater for MM patients than for BTT patients. Both our probabilistic and deterministic results were confirmatory of these results.

In the base-case scenario with a deterministic analysis, for the lifetime model, the ICER for VAD patients compared with MM patients was £55,173. For a shorter time horizon of 3 years the ICER was much higher at £122,730. Using a wide range of model assumptions and scenarios the three time horizons gave us costs per QALY in the range £55,173–122,730 in the base case. The base-case probabilistic lifetime ICER was £53,527 per QALY. The base-case ICER was notably stable to sensitivity analyses in which the median survival during MM was varied between 3.9 and 16.5 months.

We found that, relative to currently employed willingness-to-pay thresholds, VADs as a BTT cannot be considered cost-effective compared with MM. However, for the lifetime horizon the ICER approaches willingness-to-pay thresholds that have been applied by NICE under specified end of life criteria. The cost

of VADs would need to be reduced by 15% in order to bring the base-case lifetime ICER to £50,000 per QALY. To bring the ICER to £30,000 per QALY would require a reduction in device cost of 76%.

Sensitivity analyses demonstrated that the model inputs most influential in affecting the estimated ICER of BTT with a VAD compared with MM to transplant were:

- *The choice of the comparator population* For the base case we selected BTDB MM patients classified as 'inotrope' as the comparator population and the resulting ICER was £55,173 per QALY. This choice can be justified on the following grounds: (a) there was no direct comparative or randomised evidence to inform choice of comparator; (b) 77% of BTT patients in the BTDB were using inotropes at baseline, while only 20% of MM patients were classified as using inotropes; (c) the SHFM[95] score for VAD patients taken from the published literature (Schaffer *et al*.[77] and Strueber *et al*.[83]) and for BTT patients, the BTDB predict survival that is consistent with that of the 'inotrope' MM patients; (c) clinical advice and published opinion[116] indicate that patients who receive BTT therapy have poorer prognosis than the generality of MM patients. This choice was critical in determining the cost-effectiveness estimate; this was demonstrated when all MM patients were compared with all BTT patients – the former exhibited superior delivery of benefit and was less costly. It should be noted that varying median survival from 3.9 months to 16.5 months had little impact on the estimated ICER under base-case conditions.
- *The probability of receiving a donor heart* For the base case we adopted an equal probability of receiving a donor heart for both arms and based this on the probability of HT observed for the BTDB BTT patients. However, in current clinical practice BTT patients have a much longer waiting time to transplant than patients supported on MM. When these probabilities are applied in the economic model, MM was cheaper and yielded more QALYs than VADs as a BTT therapy.
- *Cost of the VAD* When the cost of the device is reduced by 30% the ICER reduces by 18%.
- *Cost of lifetime treatment for BTT* When the overall cost of VAD support was reduced by 30% the ICER was halved to £42,914 per QALYs.

One of the 'fairest' comparisons made, modelling a situation nearest to a RCT, was to use the SHFM[95] to predict the BTDB VADs patients' survival using data from their own baseline values in order to construct an artificial 'matched' control group. Even with this comparison, VADs were not cost-effective at standard levels of willingness to pay, with an ICER of £55,148 at a lifetime time horizon.

For research question 2 we investigated the cost-effectiveness of VADs used as an ATT compared with VADs used as a BTT. The ICERS (cost/QALY) for a VAD as an ATT compared with a VAD as a BTT over the 3-year, 10-year and lifetime study periods were £353,467, £31,685, and £20,637, respectively, but these should be viewed carefully as ATT was cost saving while delivering less benefit than BTT. Probabilistic analysis yielded similar results over the lifetime horizon.

Strengths of the cost-effectiveness analysis

We undertook a rigorous systematic review of cost-effectiveness studies of VADs. The individual patient database from the BTDB was used for the derivation of the prediction model and for transition probabilities between health states. The use of IPD from the NHS for > 1000 patients provided substantial key clinical characteristics of patients for VAD implantation and relevant associated mortality.

All patients in the UK receiving a relevant VAD and included in the BTDB database until 2011 were included in the study. First-generation VADs were excluded. Compared with Sharples *et al*.[30] the BTDB database now has a large sample size to provide more robust clinical effectiveness estimates for patients from UK VADs practice. We built a discrete-time, semi-Markov, multistate cost-effectiveness model and undertook both deterministic and probabilistic analysis and extensive sensitivity analyses.

Limitations of the cost-effectiveness analysis

No randomised or controlled evidence was available to inform the choice of an appropriate MM population to act as a comparator to BTT with a VAD. The ongoing long-term cost of support with modern VADs is uncertain. It is difficult to establish the cost of adverse events experienced by patients who receive the newer generation VADs. There was a lack of sufficient IPD resource-use data; however, we have been able to update device costs and certain other costs related to resources. In some cases, when there was a complete lack of data, we have used Sharples *et al.*'s[30] costs and inflated them to the current prices. The GJNH was the only centre that shared its cost data with us. GJNH provided detailed cost for immediate and post-operative hospital stay following VAD implant and HT, but the cost was based on one VAD implant and four HT cases. Hence, we used the cost only as a scenario analysis.

The length of follow-up of patients supported by either MM or a VAD was short and required extrapolation to model survival. We extrapolated survival data beyond observed data (especially post HT), leading to uncertainty regarding the estimation of transition probabilities in the longer term. The use of a simple constant hazard model may also be problematic in analysis. The problem is a result of poor parametric fits to the biphasic survival data seen post surgery.

We made a number of assumptions in the model, although the base-case model assumptions were explored in sensitivity analyses. The disadvantage of the BTDB is that limited clinical variables were reported for the patients in this data set to allow us to use published predictive survival models (e.g. the SHFM).[95] In addition, the BTDB did not collect information on QoL measures such as the EQ-5D or EuroQoL. The lack of individual QoL data for individuals from the BTDB meant that we had to use values from the literature for different health states. This will continue to hamper economic evaluations of VADs in the UK until these data can be routinely collected as part of the BTDB.

Conclusions and recommendations for future research

Despite the lack of randomised trials and the consequent weak design of effectiveness studies, the systematic review of clinical evidence provides support for an improvement in QoL and functional status for patients who survive implantation of a HMII or HW second-/third-generation LVAD. The lack of a comparator means that survival advantage from VAD implantation remains to be demonstrated unequivocally. There is randomised evidence from the REMATCH study that VAD implantation improves survival in patients ineligible for transplant.[119] A lack of survival benefit for some BTT patients would therefore be surprising.

We found that VADs considered as a BTT yields ICERs of £122,730, £68,088 and £55,173, respectively, when compared with MM. We found that at a lifetime time horizon, using VADs as an ATT rather than as a BTT was complex. VADs as an ATT has a reduced cost and reduced QALYs. When considered over a lifetime horizon ATT as compared with BTT is £20,637 cheaper for each QALY lost.

Future research

No RCT has yet been conducted comparing BTT with MM for patients eligible for HT; furthermore, the long-term survival after these therapies is uncertain. For ethical reasons a RCT offering equal probability of HT for each group would not be feasible. The REMATCH randomised trial[119] made the comparison of VADs with MM, but only for patients for whom HT was counterindicated. REMATCH also employed a pulsatile VAD of an earlier generation than those currently used. In the context of the results from the REMATCH trial, and from a UK NHS perspective, Girling *et al.*[123] explored the expected value of further information (i.e. from a RCT) and considered that a further RCT was likely to be justified only for devices that cost < £60,000.

Although the REMATCH result cannot be applied for second-generation devices, and in any case was based on results from a population ineligible for transplant, it indicates that although a RCT can provide the best information on effectiveness it would need to be justified in terms of the value of information provided to bodies responsible for reimbursement decisions. However, an adequately powered trial of BTT with VAD compared with BTT with MM (or alternative VAD) with second- and third-generation devices would, if undertaken, provide far superior information for decision-makers than that currently available.

Therefore attention should be directed towards:

1. How any future evaluations of second- or third-generation VADs might be conducted. Future studies should fully assess costs, long-term patient survival, QoL, functional ability, adverse events so these may be incorporated into economic evaluation.
2. Agreement on outcome measures across future studies; in particular, length of follow-up, time points for data collection, agreed QoL and functional ability measures.
3. Consideration of support for BTBD so as to ensure that full and accurate records of all patients are kept, and that regular analyses and comparative assessments of performance with other international centres are undertaken.
4. Consideration of extending the BTDB data collection process so as to include QoL data (e.g. using the EQ-5D), and to include resource-use data in order to facilitate future cost-effectiveness evaluation.
5. Development of guidance in the use of VADs as technology and management continue to change. It will be important to monitor and update this assessment regularly.

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Contributions of authors

Paul Sutcliffe (Associate Professor), **Martin Connock** (Senior Research Fellow) and **Aileen Clarke** (Professor of Public Health and Health Services Research) co-ordinated the clinical effectiveness and cost-effectiveness systematic reviews.

Tara Gurung (Research Fellow) wrote the background section of the report.

Simon Briscoe (Information Specialist) developed the search strategy and undertook searches.

Paul Sutcliffe and **Martin Connock** screened search results and with **Deepson Shyangdan** (Research Fellow) screened retrieved papers against inclusion criteria, appraised the quality of papers and abstracted data from papers.

Gaurav Suri (Research Associate) and **Ngianga-Bakwin Kandala** analysed and critiqued the BTDB.

Martin Connock, **Ngianga-Bakwin Kandala** (Principal Research Fellow) and **Gaurav Suri** analysed the data and developed transition probabilities.

Ruth Pulikottil-Jacob, **Martin Connock** and **Aileen Clarke** developed the economic model and **Hendramoorthy Maheswaran** (Academic Clinical Fellow) assisted in developing and analysing the economic model.

Aileen Clarke provided advice on design and analysis, wrote the abstract, summary and discussion and with **Amy Grove** (Research Project Manager) co-ordinated the project.

All authors were involved in writing draft and final versions of the report.

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Appendix 1 Protocol: National Institute for Health Research Health Technology Assessment programme project number 12/02/01

1. Research questions

In patients aged 16 years and over with end-stage heart failure who are eligible for heart transplant:

(a) What is the clinical and cost-effectiveness of second and third generation ventricular assist devices used as bridge to transplant compared to medical management?
(b) Where data permit, what is the clinical and cost-effectiveness of second and third generation ventricular assist devices used as destination therapy (alternative to transplant (ATT)) in comparison to their use i) as bridge to transplant therapy ii) with medical management and subsequent heart transplant?

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3. Plain English Summary

Heart failure is the debilitating condition when the heart does not pump blood properly thereby limiting an individual's life activities. End-stage heart failure (ESHF) is life threatening but heart transplant (HT) offers a last resort treatment for patients not well controlled on medical therapies. Unfortunately donor hearts are in short supply and some patients are not suitable to receive one for a variety of reasons. Patients receive medicines aimed at reducing symptoms, improving quality of life and slowing progression of disease.
If these fail, and a donor heart is not available, they may have surgery to receive a device (a 'ventricular assist device', VAD) which partly or wholly takes over the job of the heart. There are many types of device and this report aims to find out how successful they are in prolonging survival and providing good quality of life. If data permit, we will consider which devices are best. Patients who are suitable for a HT may receive a device until a donor heart becomes available. This latter option is called bridging therapy or bridge to transplant (BTT). There have been technical advances in device design and it would be useful to know which are best for bridging. Surgery and devices are expensive treatments. For the NHS to best allocate and deliver its services, relative costs and benefits of various treatments need to be estimated. Therefore another aim of this report is to relate patient's extra benefits from these treatments to the costs of the treatments and to reach an idea of their cost-effectiveness.

4. Decision problem

- In patients with ESHF who are eligible for HT, VADS are used as BTT in patients in the UK. There are a number of newer devices and it is important to know the comparative cost-effectiveness of devices used in this way, and to know how the use of devices compares to medical management (MM).
- Research suggests that HT is likely to offer the best treatment option in terms of both length and quality of life for these patients. However, HT is dependent on availability of donor hearts whose availability appears to be diminishing. Therefore, it will be valuable to know the comparative cost-effectiveness of VADs used as alternative to transplant (ATT) in comparison to their use as BTT. (Note: VADs are currently used in the UK as BTT and are not commissioned as ATT. This means that UK data may not be available for populating models to investigate question 1b. We will therefore use published international data where available, to make direct comparisons between VADs i) used as bridge to transplant therapy ii) with medical management and subsequent HT).

Objectives:

To:

i. Summarise previously published HTA reports[1,2] on ventricular assist devices (VADs).
ii. Undertake a systematic review and evidence synthesis of the relevant clinical and cost-effectiveness literature.
iii. Further develop the cost-effectiveness and cost-utility models developed in the 2006 HTA: "Evaluation of the ventricular assist device programme in the UK" using findings from objectives i. and ii. and NHS Blood and Transplant, Organ Donation and Transplant Directorate data.
iv. Where data permit, compare the use of VADs as ATT in comparison to their use as BTT and with medical management and subsequent HT.
v. Investigate the factors that drive costs and survival.
vi. Report on findings and make recommendations on future research.

4.1 Background

Heart failure is defined as '*a disease characterised by a decline in the heart's ability to pump blood around a person's body at normal filling pressures to meet its metabolic needs*'.[1] Any anatomical or physiological condition that affects the function of ventricle can cause heart failure. This mainly includes coronary heart disease.[1] Other causes include hypertension, valvular heart diseases, myocardial toxins, myocarditis, or idiopathic dilated cardiomyopathy.[1] The severity of heart failure is usually assessed using the New York Heart Association (NYHA) functional classification which is based on the severity of symptoms patients develop after undertaking physical activity. The severity of the heart failure is classified into four grades of increasing severity using the NYHA classification. NYHA grade I heart failure is the least severe category.[1]

Heart failure can have a considerable impact on patients' lives and also on overall health care costs.[3] In 2005, it was estimated that there would be between 250,000 and 400,000 people with heart failure in England and Wales, with approximately 7,000 to 8,000 people with ESHF.[1] The impact on overall health care cost to the NHS is high as the incidence and prevalence of heart failure is increasing due to the ageing population and the high prevalence of cardiovascular diseases.[1]

Medical management with inotropic agents, ACE inhibitors, beta-blockers, angiotensin 2 inhibitors and aldosterone antagonists together with resynchronisation therapy has improved the survival of many with heart failure, but there remain a subgroup of patients who, despite optimal medical therapy, progress to NYHA Class III or IV heart failure.[3,4]

HT offers the best effective surgical treatment for long-term survival in suitable patients with ESHF.[4] The number of HTs is severely limited by the availability of suitable donor hearts. It has been estimated that approximately 30,000 patients are waiting for HT, with approximately 3,500 donor hearts being available in the whole world annually.[4]

When heart failure occurs, patients may show signs and symptoms of inadequate cardiovascular functioning, pulmonary or peripheral oedema and under perfusion of other organs such as the kidney and liver. Pulmonary hypertension can make patients ineligible for HT. Even if patients undergo HT, there is a chance of allograft rejection. In order to prevent this, patients are given variety of immunosuppressant and prophylactic drugs which in turn increases their susceptibility to opportunistic infections.[2]

In order to increase survival and quality of life among selected patients waiting for HT (BTT) VADs are increasingly being used.[1–3] These include: a) left ventricular assist device (LVAD), b) right ventricular assist device (RVAD) and c) Biventricular assist device (BiVAD). Destination therapy (DT) describes a course of treatment for severe (e.g., NYHA stage IV/ACC stage D) heart failure patients using a mechanical circulatory support in place of HT. Devices are increasingly used in some non-UK countries as DT in these patients.[3,5] However, since devices are used in this way when patients are no longer eligible for HT, DT is outside the scope of this review.

As the number of donor hearts available for transplant is decreasing, there is a suggested need within the UK to determine the place of VAD as ATT in the clinical management of patients with ESHF (see Figure 1).[6]

4.2 Scoping searches

The aim of the scoping searches was to establish all known devices and determine their approval status with the Conformité Européenne (CE) and Food and Drug Administration (FDA). Scoping searches were undertaken in MEDLINE (2000 to date) and on identified VAD manufacturer websites in February 2012. The scoping searches identified a range of VADs and manufacturers, which were discussed with our clinical advisors. The following tables provide a summary of the findings.

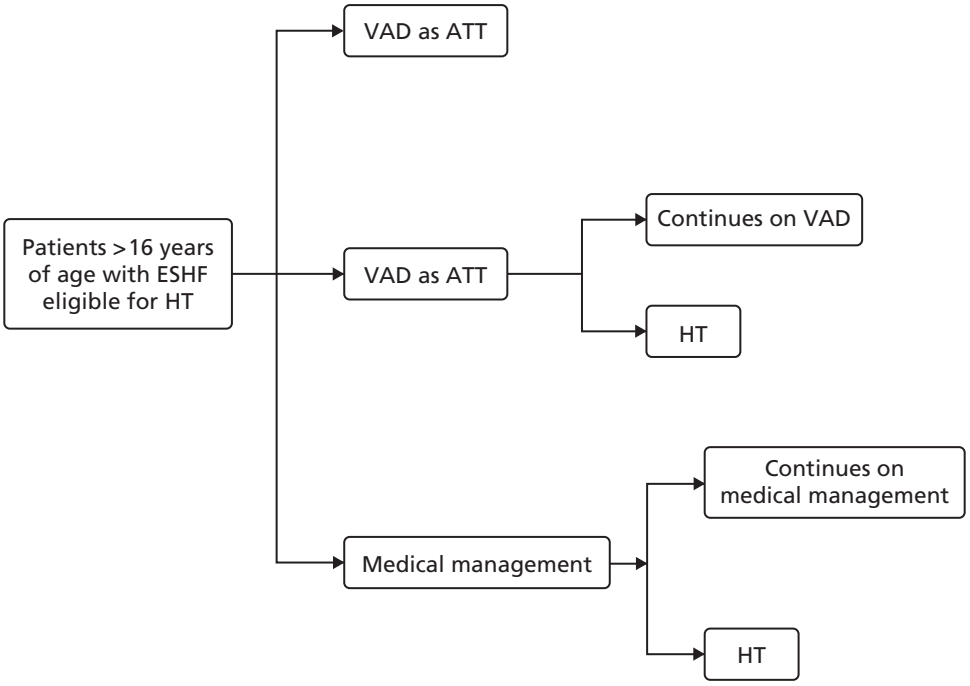

FIGURE 1 Schematic representation of research questions. HT: heart transplant, BTT: bridge to transplant, VAD: ventricular assist device, ESHF: end-stage heart failure, ATT: alternative to transplant.

TABLE 1 Names and manufacturers for all Left Ventricular Assist Devices (LVAD)

Name of Device	Manufacturer
Coraide	Arrow International Inc
C-Pulse	Sunshine Heart
CircuLite Synergy Pump	CiculLite
DeBakey VAD	MicroMed
DuraHeart LVAS	Terumo
Evaheart LVAS	Evaheart Medical
HeartAssist5	MicroMed
HeartMate II	Thoratec
HeartMate III	Thoratec
HeartMate X	Thoratec
HeartMate XVE, VE, and IP1000	Thoratec
HeartQuest	MedQuest Products
Heartware MVAD	HeartWare Inc
HVAD	HeartWare Inc
INCOR	Berlin Heart
Implantable Ventricular Assist Device (IVAD)	Thoratec
Jarvik 2000	Jarvik Heart
Levacor VAD	World Heart Inc
LionHeart	Arrow International Inc
MTIHeartLVAD	MiTiHeart Corporation
Novacor	World Heart Inc
Procyon circulatory assist device (CAD)	Procyon Inc
Rotary VAD	World Heart
Symphony	SCR Inc
Synergy	CircuLite Inc
TandemHeart	Cardiac Assist
Thoratec PVAD or IVAD	Thoratec
VentrAssist	Ventracor

NB: devices highlighted in grey have received FDA and/or CE approval and are second or third generation VAD.

TABLE 2 Names and manufacturers for all Right Ventricular Assist Devices (RVAD)

Name of Device	Manufacturer
Jarvik 2000 Flow Maker	Jarvik
IVAD	Thoractec
DexAide RVAD	Cleveland Heart
Impella Recover RD	Abiomed
Impella Right Peripheral	Abiomed

NB: devices highlighted in grey have received FDA and/or CE approval and are second or third generation VAD.

TABLE 3 Names and manufacturers for all Percutaneous Ventricular Assist Devices (pVAD)

Name of Device	Manufacturer
Impella Recover LP 2.5	Abiomed
TandemHeart	Cardiac Assist

NB: devices highlighted in grey have received FDA and/or CE approval and are second or third generation VAD.

TABLE 4 Names and manufacturers for all Biventricular Assist Devices (BiVAD)

Name of Device	Manufacturer
Abiomed BVS5000 and AB5000	Abiomed
Thoratec PVAD and IVAD	Thoratec
Berlin Heart EXCOR	Berlin Heart
Medos HIA-VAD	MEDOS Medizintechnik
Levitronx CentiMag	Levitronx
Jarvik 2000	Jarvik
HeartWare HVAD	HeartWare Inc
CorAide/DexAide	Arrow International Inc
Korean AnyHeart	BiomedLab Co
Gyro	Baylor College of Medicine, Miwatec, NEDO
BiVACOR BV Assist	BiVACOR Pty Ltd

NB: devices highlighted in grey have received FDA and/or CE approval.

The current scoping searches identified seven LVAD, one RVAD, two pVAD, and two BiVAD that have been approved by the FDA and/or CE.

Report methods for synthesis of clinical evidence

A systematic review of the evidence for each included VAD will be undertaken following the general principles recommended in the PRISMA statement.[7,8] Previous systematic reviews of included VAD will be identified and summarised in the current report.

5.1 Identification and selection of studies

Initial scoping searches were undertaken to assess the volume and type of literature relating to the assessment question. A search strategy was then developed which focuses the searches to ventricular assist devices meeting the inclusion and exclusion criteria (see below). All searches will be undertaken in February and March 2012.

5.1.1 Search strategy for clinical effectiveness

Scoping searches have been undertaken to inform the development of the search strategy. An iterative procedure was used, with input from clinical advisors and previous HTAs (e.g. Clegg et al., 2005[1]; Sharples et al., 2006[2]). A copy of the draft search strategy that is likely to be used in the major databases is provided in Appendix A. This search strategy developed for MEDLINE will be adapted as appropriate for other databases. The strategy has been designed to capture generic terms for VADs and the specific product names of second or third generation and FDA or CE approved devices. The search will be date-limited from 2003 to current. Studies of patients under 16 years and non-English language studies will be excluded. There will be no limits for study design at the searching stage. All retrieved papers will be screened for potential inclusion.

The search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases.
- Contact with experts in the field.
- Scrutiny of references of included studies.
- Screening of manufacturers websites for relevant publications.

Databases will include: MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database (including Cochrane Systematic Reviews, DARE, NHS EED, and HTA databases); Science Citation Index and Conference Proceedings (Web of Science); UKCRN Portfolio Database; CINAHL; PsycINFO; and NLM gateway (US Meeting Abstracts and Health Services Research Projects in Progress). The following trial databases will also be searched: CENTRAL; Current Controlled Trials; and ClinicalTrials.gov.

In addition, the reference lists of relevant articles will be checked, and the manufacturers' websites will be screened for relevant publications. Also the online resources of various regulatory bodies, health services research agencies and professional societies will be consulted via the Internet. These are likely to include:

- HTA organisations, including the NIHR and the National Research Register (NRR) Archive.
- Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).
- NHS Blood and Transplant, including the Cardiothoracic Transplant Advisory Group.
- Ventricular Assist Device Forum, National Specialised Commissioning Team.
- International Society Heart and Lung Transplantation.
- Eurotransplant.
- Scandia Transplant.
- US Transplant.
- The Transplantation Society.
- British Transplantation Society.

- Medicines and Healthcare products Regulatory Authority (MHRA).
- US Food and Drug Administration.

Citation searches of included studies will be undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles will also be checked.

5.1.2 Inclusion of relevant studies

Study design:

- Studies with control groups (i.e. randomised controlled trials, cohort studies, case controlled studies), systematic reviews of studies with control groups.
- Case series will be included if they report adverse events and if they report on consecutive patients. In the first instance we will limit the inclusion of case series to those including over 50 patients and published since 2003.

Population:

- People (aged > 16 years) with ESHF and considered suitable for receipt of an LVAD, RVAD and BiVAD as BTT or as potential long-term ATT.

Intervention:

- Second generation axial continuous flow pumps.
- Third generation bearingless continuous flow pumps.
- LVAD, RVAD and BiVAD currently approved by FDA and/or CE and in current clinical use in the UK as a BTT.
- LVAD, RVAD and BiVAD currently approved by FDA and/or CE and used as potential long-term ATT for people with ESHF.
- Studies with a mixture of generation devices will be considered if data for second or third generation devices are presented separately to first generation devices.

Comparator:

- Medical management.
- Studies comparing HT with other interventions listed above.
- Comparing two different interventions listed above.
- Studies comparing first generation devices with second or third generation devices will be used to extract data on second or third generation devices only.

Outcomes:

- Patient outcomes will include survival, functional capacity (e.g. change in NYHA functional classification), quality of life (QoL) and adverse events.

5.1.3 Exclusion criteria

- pVAD.
- Total artificial heart (TAH).
- First generation pulsatile volume displacement pumps.
- Devices yet to be FDA or CE approved.
- Devices for "bridge to decision".
- Post-transplant mechanical circulatory support devices for primary graft failure.

- Studies involving VADs in conjunction with other interventions where it is not possible to separate out the effects of the different interventions on outcomes.
- Animal models and post-mortem studies.
- Preclinical and biological studies.
- Editorials and opinions.
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.
- Studies not in English.
- Studies before the year 2003.
- Case series reports with less than 30 cases or where patient recruitment is not consecutive.

5.2 Review methods

A record of all papers rejected at full text stage and reasons for exclusion will be documented. Titles and abstracts of retrieved studies will be examined for inclusion by two reviewers independently. Disagreement will be resolved by retrieval of the full publication and consensus agreement.

5.3 Data extraction strategy

The full data will be extracted independently by one reviewer using a data extraction form informed by the NHS Centre for Reviews and Dissemination[9] and previous HTA reports (e.g. Clegg et al., 2005[1]; Sharples et al., 2006[2]; see Appendix B). Studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion. Further discrepancies will be resolved with involvement of a third reviewer when necessary. Summary tables will detail information about study design, participant, intervention, comparator and outcomes. In addition we will provide a summary of the findings and authors conclusions.

Data will be extracted to allow quality assessment of the included studies (see below).

5.4 Quality assessment strategy

Quality criteria will be applied independently by two reviewers, with any disagreements resolved by independent assessment by a third reviewer. Included studies will be assessed using recognised quality assessment scales and/or checklists. Systematic reviews will be assessed using criteria developed by NHS Centre for Reviews and Dissemination (CRD).[10] Experimental and nonexperimental studies will be assessed using the criteria developed by Thomas *et al*.[11] See Appendix C.

5.5 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review through subgroup analysis based on the indication for treatment, type of VAD and quality of studies. Each device will be looked at separately for the VAD categories (e.g. LVAD, RVAD and BiVAD). Subanalyses will be undertaken (if possible) of the different populations captured in the studies (e.g. demographics, reasons for VADs, co-morbidities such as diabetes mellitus). It is unlikely that a meta-analysis will be appropriate due to clinical heterogeneity. However, if appropriate studies are available, meta-analyses will be undertaken using random effect models using STATA software.[12] The possibility of using mixed treatment comparison (MTC) methods will be considered if appropriate studies are available using WINBUGS.

Report methods for synthesising evidence of cost-effectiveness

The structure of the economic evaluation will be informed by previous work undertaken by Clegg et al. (2005)[1] and Sharples et al. (2006).[2] Therefore the content of this section has been adapted from their protocols and published reports.

6.1 Published economic studies

Published economic studies of HT and second and third generation VADs in the treatment of ESHF will be identified. The keyword search strategy developed in the review of clinical effectiveness of VADs will be used and an additional two searches will be conducted for studies on HT and ESHF. The same limits and

restrictions used in the review of clinical effectiveness will be applied. Search filters will be applied to restrict the search results to economic and cost-related studies (Appendix A). The primary objective will be to investigate second and third generation VADs currently approved by FDA and/or CE and in current clinical use in the UK as a BTT. However, additional searches will be undertaken to identify high-quality evidence on second and third generation VADS which do not have FDA/CE approval to provide controls for cost-effectiveness models, where appropriate. All searches will be undertaken in February and March 2012. Two reviewers will independently screen all titles and abstracts for inclusion. Disagreement will be resolved through discussion. The full text of papers considered potentially relevant will be retrieved for further assessment. Studies will be selected for inclusion if they report cost-effectiveness estimates for second or third generation VADs. Studies considered methodologically unsound, that report insufficient detail or that fail to provide an estimate of cost-effectiveness, will be excluded. The quality of included economic studies will be investigated by a single reviewer using the Drummond assessment tool (Appendix C).[13]

6.2 Approach to economic evaluation

Availability of requisite data permitting, we will undertake an economic evaluation through a decision analytic approach to estimate: a) the incremental cost effectiveness of second and third generation VADs used as BTT compared to medical management; and b) the incremental cost effectiveness of second and third generation VADs used as ATT in comparison to their use as BTT.

The models will take the form of EXCEL spreadsheets and will be transparent in order that changes/ updates to any attribute of provision can be incorporated and the model can be continually updated.

Our analyses will involve the following data:

- The clinical pathways for the different patient groups will need to be clarified with support from our clinical advisors.
- The different treatment options will need to be defined (i.e. HT, LVAD, RVAD, BiVAD, usual care on WL or best supportive care [BSC]).
- All cause mortality according to treatment received.
- The resources and costs required to manage the care of the patients.

The analyses will be informed by previous models completed by Clegg et al. (2005)[1] and Sharples et al. (2006)[2] for the UK HTA programme and will be guided and informed by advice from the authors of the Sharples model. Our initial intention is to provide estimates for a life time horizon from the perspective of the NHS and Social Services. Information for the analysis will be identified through searching for literature and support from clinical experts and manufacturer's of devices. This will be supplemented with data from NHS Blood and Transplant, Organ Donation and Transplant Directorate, Bristol, if individual patients' data (IPD) is available, appropriate and accessible within the predicted time scale.

If UK NHS Blood and Transplant VAD database data are adequate, the report will include an analysis of data on survival from listing for transplant, transplantation rates, post-transplant survival, and resource use for patients with and without mechanical circulatory support. Analysis of the database will be undertaken in collaboration with our clinical advisors.

Key inputs will be costs (of devices, of surgery, of associated medications and adverse events, of device maintenance, of consumables, of specialist staff pay costs, of infrastructure including staff training/skill maintenance); life years gained; frequency of cost-incurring events; and the utility associated with health states. All resource-use data will be in monetary terms using UK unit costs. Costs will be presented in a base year with discounting of costs and benefits in subsequent years.

Where available, outcomes will be analysed for different subgroups, the type of VAD used and the severity of the patient condition, to allow assessment of the most appropriate treatment for the different patient

groups. The underlying assumptions and robustness of the developed models will be examined through sensitivity and threshold analyses.

6.3 Effectiveness of treatment

The model will use efficacy data extracted from the studies included in the systematic review of clinical effectiveness and/or IPD provided by NHS Blood & Transplant. Outcomes will be extracted for patients receiving VADs and for the comparators of HT and WL/supportive care.

The primary effectiveness end-point for the economic evaluation will be patient survival defined in terms of mean (or possibly median) life-years. In addition, the economic evaluation may use information on functional capacity and QoL if available to assess utilities of health states following various interventions.

Studies of QoL for people with ESHF undergoing different types of treatment will be identified concurrently with cost-effectiveness studies (Appendix A and section 6.1). Initial scoping searches suggest the information on QoL may be limited. In addition, searches will be made to identify whether any studies have mapped measures of functional status, such as the NYHA values, with utility weights. If necessary information from the literature may be supplemented by patient-, clinician- and/or expert based estimates of utility by patient perception data held by NHS Blood and Transplant and by published UK population norms for the EQ-5D. The nature and quality of the data will be assessed and, if adequate, will be used to inform the economic evaluation.

6.4 Cost and resource use

Costs will be identified from published sources, supplemented by contact with NHS Blood and Transplant, the National Specialised Commissioning Team, and advice from clinical experts. Costs can be divided into a number of categories: materials; operational or implantation procedures; maintenance; hospitalisation. Material costs include the costs of the VAD devices, up-to-date costs of these, including discounts available, will be obtained from manufacturers; LVADs are not reused. The cost and frequency of device re-implantation following failure will be considered. Drug costs associated with treatments will be obtained from the British National Formulary. Cost of HT will be obtained from the National Specialised Commissioning Team. Other procedural costs will include the costs of implantation and removal of the LVAD. Hospitalisation will incorporate length of inpatient/outpatient attendance for implantation, side-effects, infection, complications, drugs, maintenance of the VADs and routine check-ups. Patients may require home visits by GPs or district nurses. These costs will be obtained from published data.[14] For simplification, costs of side-effects (e.g. haemorrhage, thromboembolism, infections) will be aggregated depending on their likelihood.

Resource use will require the patients' clinical and treatment pathways for the different treatment options to be clarified. Literature searches and advice from experts will provide the evidence to construct the appropriate scenarios. Where applicable, survival analysis or the DEALE method[15,16] will be used to estimate prospective resource use over patients' lives. Likewise, UK NHS Blood and Transplant will be approached for data on WL patients.

Expertise in this TAR team

Warwick Evidence is a newly developed technology assessment group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work includes: Dr Paul Sutcliffe, Dr Deepson Shyangdan, Dr Martin Connock, Dr Pam Royle, Dr Tara Gurung and Professor Norman Waugh who are experienced systematic reviewers; Dr Helen Hall and Mr Simon Briscoe, information specialists; Professor Aileen Clarke, Dr Kandala Ngianga-Bakwin, Ms Ruth Jacobs, Mr Gaurav Suri provide modelling and health economic expertise; Mr Steven Tsui, Professor John Wallwork, Dr Jayan Parameshwar, Professor Stephan Schueler, Dr Guy MacGowan, Dr Mark Petrie, Mr Saleem Haj-Yahia provide clinical advice; Professor Martin Buxton and Dr Linda Sharples provide methodological modelling and economic advice; and Ms Amy Grove will provide project management support.

Competing interests of authors and advisors

None of the authors have any competing interests. One of our clinical advisors holds consultancy agreements with a number of LVAD manufacturers.

Timetable/milestones

The project will be undertaken in phases, including: literature search, study selection, data extraction and critical appraisal, evidence synthesis, and dissemination of the results. A progress report including a draft clinical effectiveness section will be submitted on the 30 March 2012, this is conditional upon the rapid approval of the protocol. The final assessment report including the clinical and cost-effectiveness sections will be submitted on 31 May 2012. There will be fortnightly team meetings and correspondence with the clinical advisors will take place every 2–3 weeks via email.

Draft protocol finalised: 21 February 2012
Commissioning decision: TBC
Progress report including draft clinical effectiveness section: 30 March 2012
Final assessment report including clinical and cost-effectiveness sections: 31 May 2012

10. Team members' contributions

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10.1 Methodological advisors

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Dr Linda Sharples, MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Robinson Way, Cambridge. UK.

Contribution of methodological advisors: previous experience of modelling in this area, multistate models, general evidence synthesis, statistics issues in health economic modelling, application of statistical methods to cardiothoracic medicine and surgery.

10.2 Clinical Advisors

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Professor John Wallwork, retired transplant surgeon.

Dr Jayan Parameshwar, Consultant Respiratory, Transplant Physician, Papworth Hospital NHS Foundation Trust.

Professor Stephan Schueler, Cardiothoracic Surgeon, Freeman Hospital, The Newcastle Upon Tyne Hospitals NHS Foundation Trust.

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Dr Mark Petrie, Consultant Cardiologist, The GJNH, Glasgow.

Mr Saleem Haj-Yahia, Consultant Cardiac and Transplant Surgeon, The GJNH, Glasgow.

Contribution of clinical advisors: protocol development, help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness and review of report drafts.

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Appendix A Search strategies

Search for clinical-effectiveness of VADs

1. *Heart-Assist Devices/
2. (lvad or biVAD or bvad or vad or vads or rvad).tw.
3. (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*).tw.
4. (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart).tw.
5. 2 or 3
6. 1 and 5
7. 4 or 6
8. limit 7 to (English language and yr="2003 -Current")

Search for cost effectiveness of VADs

Lines 1–8 as above

9. "costs and cost analysis"/
10. "cost of illness"/
11. exp Economics/
12. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
13. exp "Quality of Life"/
14. exp "quality adjusted life years"/
15. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw
16. (quality adj2 life).tw
17. ("resource use" or "resource utili?ation").tw
18. (utilit* or hrql or hrqol).tw
19. health status/
20. (health state* or health status).tw
21. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 8 and 21

Searches for cost-effectiveness and quality of life for heart transplantation

1. (heart and transplant*).ti,ab and *HEART TRANSPLANTATION/ [limit to human only]
2. "costs and cost analysis"/
3. "cost of illness"/
4. exp Economics/
5. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
6. exp "Quality of Life"/
7. exp "quality adjusted life years"/
8. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw

9. (quality adj2 life).tw
10. ("resource use" or "resource utili?ation").tw
11. (utilit* or hrql or hrqol).tw
12. health status/
13. (health state* or health status).tw
14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 and 14
16. limit 15 to (English language and yr="2003 -Current")

Searches for cost-effectiveness and quality of life for end-stage heart failure

1. ("heart failure" and ("end stage" or "end-stage")).mp and heart failure/
2. "costs and cost analysis"/
3. "cost of illness"/
4. exp Economics/
5. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
6. exp "quality of Life"/
7. exp "quality adjusted life years"/
8. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw
9. (quality adj2 life).tw
10. ("resource use" or "resource utili?ation").tw
11. (utilit* or hrql or hrqol).tw
12. health status/
13. (health state* or health status).tw
14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 and 14
16. limit 15 to (English language and yr="2003 -Current")

Searches for prospective studies, cohort studies and RCTs of specific product names of VADs that do not have FDA/CE approval to provide controls for cost-effectiveness models, where appropriate

1. *Heart-Assist Devices/
2. (lvad or biVAD or bvad or vad or vads or rvad).tw.
3. (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*).tw.
4. (CircuLite Synergy Pump or Coraide or Evaheart LVAS or HeartMate III or HeartMate X or HeartQuest or Heartware MVAD or Levacor VAD or MTIHeartLVAD or Procyon circulatory assist device or Rotary VAD or Symphony or Synergy or VentrAssist or DexAide RVAD or Impella Right Peripheral or CorAide or DexAide or BiVACOR BV Assist).tw.
5. 2 or 3
6. 1 and 5
7. 4 or 6
8. limit 7 to (English language and yr="2003 -Current")
9. random$.mp
10. 8 and 9
11. Epidemiologic studies/
12. Exp case control studies/
13. Exp cohort studies/
14. Case control.tw.
15. (cohort adj (study or studies)).tw.

16. Cohort analy$.tw.
17. (Follow up adj (study or studies)).tw.
18. (observational adj (study or studies)).tw.
19. Longitudinal.tw.
20. Retrospective.tw.
21. Cross sectional.tw.
22. Prospective.tw
23. Cross-sectional studies/
24. Or/11-23
25. 8 and 24
26. 10 or 25

Appendix B Data extraction form

Data extraction form for primary studies

Name of the reviewer:

Study details

Study ID (Ref man):

First author surname:

Year of publication:

Country:

Study design:

Study setting:

Number of centres:

Duration of study:

Follow-up period:

Funding:

Aim of the study:

Participants

Total number of participants:

Sample attrition/dropout:

Inclusion criteria:

Exclusion criteria:

Characteristics of participants:

Mean age:

Mean sex:

Race:

Diagnosis:

Intervention
Indication for treatment:
Type of device used:
Any comparison:
Duration of treatment:
Other interventions used:
Any FDA or CE approval: Yes/No; which one?

Outcomes
Primary outcomes:
Secondary outcomes:
Method of assessing outcomes:
Timing of assessment:
Study end point:
Survival analysis: Yes/No
Mortality: Yes/No
Physiological data: Yes/No
Adverse event: Yes/No
HRQoL: Yes/No; which measures used?
Length of follow-up:

Number of participants	Intervention	Comparator, if present
Screened		
Randomised/included		
Excluded		
Missing participants		
Withdrawals		

Patient's baseline characteristics	Intervention	Comparator, if present
Age, years		
Sex		
BSA, m^2		
Weight, kg, BMI		
Ischaemic causes of heart failure		

APPENDIX 1

Survival data	Intervention	Comparator, if present
Actuarial survival		
Overall survival		
Kaplan-Meier estimates		
Survival by era (at 5 year intervals)		
Heart transplantation without prior mechanical circulatory support		
Mechanical circulatory support without subsequent heart transplantation		
Mechanical circulatory support with subsequent heart transplantation		
Physiological data	**Intervention**	**Comparator, if present**
New York Heart Association class		
Six minute walk test		
American United Network for Organ Sharing classification		
Short-term complications		
Long-term complications		
Adverse events	**Intervention**	**Comparator, if present**
Bleeding		
Stroke		
Hypertension		
Infection		
Heart failure		
VAD failure		
Renal failure		
Haemorrhagic stroke		
Other neurological dysfunction		
Haemolysis		
Cause of death		
≤12 months		
≥12 months		
Quality of life	**Intervention**	**Comparator, if present**

Authors conclusion

Reviewer's conclusion

Data extraction form for economic studies[1]

Name of the reviewer:

Study intervention (clearly defined?)

Objective (clearly defined?)

Design

Analytical framework (type of model):

Patient population:

Comparator (clearly defined?)

Analytic horizon:

Perspective:

Setting:

Clinical measures:

Effectiveness measures:

Economic measures:

Methods

Health care system:

Model description:

Data sources (efficacy, resource use, costs, appropriately measured, all costs included?:

Data collection (primary data collection, if appropriate):

Probabilities:

Healthcare use:

Sensitivity analysis (allowance made for uncertainty):

Discounting (costs/benefits?):

Results (incremental analysis of costs and consequences?)

Conclusion:

Assessment:

Authors conclusion

Reviewer's conclusion

Data extraction form for systematic reviews

Name of the reviewer:

Study details

Study ID (Ref man):

First author surname:

Year of publication:

Country:

Funding:

Aim of the study:

Methods

Databases searched:

Last date of search:

Inclusion criteria:

Participants:

Interventions:

Comparators:

Outcome measures:

Types of studies included:

Quality assessment criteria used:

Application of methods:

Methods of analysis:

1. narrative, 2. meta-analysis, 3. indirect comparison, 4. others

Results

Quantity and quality of included studies:

Treatment effect:

Economic evaluation:

Conclusions:

Implications of the review:

Methodological comments

Search strategy:

Participants:

Inclusion/exclusion criteria:

Quality assessment of studies:

Method of synthesis:

General comment

Generalisability:

Funding:

Authors conclusion

Reviewer's conclusion

Appendix C Quality assessment forms

Quality assessment form for primary studies

[Based on the quality criteria given by Thomas *et al.* 2004][11] – *Used by Clegg et al. 2005*[1]

Name of the reviewer:

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?)	80–100%	60–79%,	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	Moderate	Weak		
B. Study design					
1. What was the study design?	1. Randomised Controlled Trial 2. Controlled Clinical Trial 3. Cohort Analytic (two group pre + post) 4. Case–control 5. Cohort [one group pre + post (before and after)] 6. Other – specify 7. Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 and 4 below	Yes	No			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	Moderate	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. race, sex, marital status, age, income, social class, education, health status)	Yes	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	Moderate	Weak		

D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	Weak		
E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	< 60%)	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest	80–100%	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	Cannot tell		
3. Is it likely that subjects received an unintended intervention that may influence the results	Yes	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design	Yes	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Cannot tell		

Global rating for study (overall methodological strength of study – based on section A–F)	Strong	Moderate	Weak
Overall rating (To be assessed following discussion by two reviewers)			
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	No	
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study
FINAL DECISION OF REVIEWERS	**Strong**	**Moderate**	**Weak**

The different criteria were rated following the guidelines provided by *Thomas and colleagues*. Where criteria are rated as weak, moderate, or strong, it relates to the study's methodological control of the criteria. As such, if a study is rated as strong it indicates that there is a low risk of bias for the particular criteria.

Quality assessment criteria for systematic reviews:

[Based on NHS CRD Report 4][10] – *used by Clegg et al. 2005*[1]

Question	Score
1. Are any inclusion/exclusion criteria reported to the primary studies which address the review question?	Yes or No
2. Is there evidence of a substantial effort to search for all relevant research?	Yes or No
3. Is the validity of included studies adequately assessed?	Yes or No
4. Is sufficient detail of the individual studies presented?	Yes or No
5. Are the primary studies summarised appropriately?	Yes or No

Quality assessment criteria for economic studies: Drummond checklist (Drummond, 1996)[13]

Item	Yes	No	Not clear	Not appropriate
Study design				
1. The research question is stated.				
2. The economic importance of the research question is stated.				
3. The viewpoint(s) of the analysis are clearly stated and justified.				
4. The rationale for choosing alternative programmes or interventions compared is stated.				
5. The alternatives being compared are clearly described.				
6. The form of economic evaluation used is stated.				
7. The choice of form of economic evaluation is justified in relation to the questions addressed.				

Item	Yes	No	Not clear	Not appropriate
Data collection				
8. The source(s) of effectiveness estimates used are stated.				
9. Details of the design and results of effectiveness study are given (if based on a single study).				
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).				
11. The primary outcome measure(s) for the economic evaluation are clearly stated.				
12. Methods to value benefits are stated.				
13. Details of the subjects from whom valuations were obtained were given.				
14. Productivity changes (if included) are reported separately.				
15. The relevance of productivity changes to the study question is discussed.				
16. Quantities of resource use are reported separately from their unit costs.				
17. Methods for the estimation of quantities and unit costs are described.				
18. Currency and price data are recorded.				
19. Details of currency of price adjustments for inflation or currency conversion are given.				
20. Details of any model used are given.				
21. The choice of model used and the key parameters on which it is based are justified.				
Analysis and interpretation of results				
22. Time horizon of costs and benefits is stated.				
23. The discount rate(s) is stated.				
24. The choice of discount rate(s) is justified.				
25. An explanation is given if costs and benefits are not discounted.				
26. Details of statistical tests and confidence intervals are given for stochastic data.				
27. The approach to sensitivity analysis is given.				
28. The choice of variables for sensitivity analysis is justified.				
29. The ranges over which the variables are varied are justified.				
30. Relevant alternatives are compared.				
31. Incremental analysis is reported.				
32. Major outcomes are presented in a disaggregated as well as aggregated form.				
33. The answer to the study question is given.				
34. Conclusions follow from the data reported.				
35. Conclusions are accompanied by the appropriate caveats.				

Appendix 2 Search strategies

MEDLINE via Ovid interface

Search for clinical effectiveness of ventricular assist devices

1. *Heart-Assist Devices/
2. (lvad or biVAD or bvad or vad or vads or rvad).tw.
3. (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*).tw.
4. (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart).tw.
5. 2 or 3
6. 1 and 5
7. 4 or 6
8. limit 7 to (English language and yr="2003 -Current")

(2350 results, search run 22 February 2012.)

Search for cost-effectiveness of ventricular assist devices

Lines 1–8 as above.

9. "costs and cost analysis"/
10. "cost of illness"/
11. exp Economics/
12. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
13. exp "Quality of Life"/
14. exp "quality adjusted life years"/
15. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw
16. (quality adj2 life).tw
17. ("resource use" or "resource utili?ation").tw
18. (utilit* or hrql or hrqol).tw
19. health status/
20. (health state* or health status).tw
21. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 8 and 21

(243 results, search run 22 February 2012.)

Search for cost-effectiveness and quality of life for heart transplantation

1. (heart and transplant*).ti,ab and *heart transplantation/ [limit to human only]
2. "costs and cost analysis"/
3. "cost of illness"/
4. exp Economics/
5. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
6. exp "Quality of Life"/
7. exp "quality adjusted life years"/
8. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw

9. (quality adj2 life).tw
10. ("resource use" or "resource utili?ation").tw
11. (utilit* or hrql or hrqol).tw
12. health status/
13. (health state* or health status).tw
14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 and 14
16. limit 15 to (English language and yr="2003 -Current")

(388 results, search run 23 February 2012.)

Search for cost-effectiveness and quality of life for end-stage heart failure

1. ("heart failure" and "end stage" and "end-stage").mp and heart failure/

   Lines 2–16 as above.

(172 results, search run 23 February 2012.)

MEDLINE In-Process & Other Non-Indexed Citations via Ovid interface

Search for clinical effectiveness of ventricular assist devices

1. (lvad or biVAD or bvad or vad or vads or rvad).tw.
2. (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*).tw.
3. (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart).tw.
4. 1 or 2
5. 3 or 4
6. limit 5 (english language and yr="2003 –Current)

(363 results, search run 23 February 2012.)

Search for cost-effectiveness of ventricular assist devices

Lines 1–6 as above.

7. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
8. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw
9. (quality adj2 life).tw
10. ("resource use" or "resource utili?ation").tw
11. (utilit* or hrql or hrqol).tw
12. (health state* or health status).tw
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 14

(33 results, search run 23 February 2012.)

EMBASE via Ovid interface

Search for clinical effectiveness of ventricular assist devices

1. *heart assist device/
2. (lvad or biVAD or bvad or vad or vads or rvad).tw.
3. (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*).tw.
4. (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart).tw.
5. 2 or 3
6. 1 and 5
7. 4 or 6
8. limit 7 to (English language and yr="2003 -Current")

(2330 results, search run 29 February 2012.)

Search for cost-effectiveness of ventricular assist devices

Lines 1–8 as above.

9. "cost"/
10. "cost benefit analysis"/
11. "cost of illness"/
12. exp Health Economics/
13. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw
14. exp "quality of life"/
15. exp quality adjusted life year/
16. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw
17. (quality adj2 life).tw
18. ("resource use" or "resource utili?ation").tw
19. (utilit* or hrql or hrqol).tw
20. health status/
21. (health state* or health status).tw
22. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 8 and 22

(320 results, search run 29 February 2012.)

Cumaltive Index to Nursing and Allied Health Literature via EBSCOhost interface

Search for clinical effectiveness of ventricular assist devices

1. (MM "Heart Assist Devices")
2. TI (lvad or biVAD or bvad or vad or vads or rvad) OR AB (lvad or biVAD or bvad or vad or vads or rvad) OR TI (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*) OR AB (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*)

3. TI (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart) OR AB (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart)
4. (S1 and S2)
5. S3 or S4
6. S3 or S4 [**Limiters** - Published Date from: 20030101-20121231; English Language]

(387 results, search run 22 February 2012.)

Search for cost-effectiveness of ventricular assist devices

Lines 1–6 as above.

7. (MH "Costs and Cost Analysis")
8. (MH "Economic Aspects of Illness")
9. (MH "Economics+")
10. (MH "Quality of Life+")
11. (MH "Quality-Adjusted Life Years+")
12. (MH "Health Status")
13. TI (pharmacoeconomic* or pharmaco-economic* or cost* or economic*) OR AB (pharmacoeconomic* or pharmaco-economic* or cost* or economic*) OR TI (qaly* or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol) OR AB (qaly* or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol) OR TI quality N2 life OR AB quality N2 life OR TI ("resource use" or "resource utili?ation") OR AB ("resource use" or "resource utili?ation") OR TI (utilit* or hrql or hrqol) OR AB (utilit* or hrql or hrqol) OR TI (health state* or health status) OR TI (health state* or health status)
14. S7 or S8 or S9 or S10 or S11 or S12 or S13
15. 6 and 14

(81 results, search run 22 February 2012.)

PsycINFO via ProQuest interface

Search for clinical effectiveness of ventricular assist devices

1. ab(ventricular support OR biventricular support OR ventric* assist device* OR cardiac assist device* or cardiac assist system* or ventric* assist system* OR biventricular assist device* OR ventricular assistance OR heart assist device* OR heartassist* OR debakey OR heartmate II OR HVAD OR incor OR jarvik 2000 OR jarvik flowmaker OR duraheart) OR ti(ventricular support OR biventricular support OR ventric* assist device* OR cardiac assist device* OR cardiac assist system* OR ventric* assist system* OR biventricular assist device* OR ventricular assistance OR heart assist device* OR heartassist* OR debakey OR heartmate II OR HVAD OR incor OR jarvik 2000 OR jarvik flowmaker OR duraheart)
2. Additional limits - Date: After 31 December 2002; Population: Human; Language: English

(151 results, search run 24 February 2012.)

Search for cost-effectiveness of ventricular assist devices

Lines 1–2 as above.

3. EXACT.EXPLODE("Costs and Cost Analysis")
4. EXACT.EXPLODE("Economics")
5. EXACT.EXPLODE("Quality of Life")

6. ab(pharmacoeconomic* or pharmaco-economic* or cost* or economic* or qaly* or EQ5D or EQ-5D or well-being or wellbeing or health state* or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol or utilit* or resource use or resource utili?ation) or ti(pharmacoeconomic* or pharmaco-economic* or cost* or economic* or qaly* or EQ5D or EQ-5D or well-being or wellbeing or health state* or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol or utilit* or resource use or resource utili?ation)
7. ti(quality W/2 life) or ab(quality W/2 life)
8. 3 or 4 or 5 or 6 or 7
9. 2 and 8

(20 results, search run 24 February 2012.)

Cochrane database

Cochrane database includes:

- CDSR (Cochrane reviews)
- DARE (other reviews)
- HTA database (technology assessments)
- NHS EED (economic evaluations).

Search for clinical effectiveness of ventricular assist devices

1. Heart-Assist Devices/
2. (lvad or biVAD or bvad or vad or vads or rvad):ti,ab,kw
3. (ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*):ti,ab,kw
4. (heartassist* or debakey or heartmate II or HVAD or incor or jarvik 2000 or jarvik flowmaker or duraheart):ti,ab,kw
5. 2 or 3
6. 1 and 5
7. 4 or 6
8. limit 7 to (yr="2003 -Current")

(Results: CDSR = 0; DARE = 3; HTA database = 22; NHS EED = 3, search run 27 February 2012.)

Search for cost-effectiveness of ventricular assist devices

Lines 1–8 as above.

9. (pharmacoeconomic* or pharmaco-economic* or cost* or economic* or qaly* or EQ5D or EQ-5D or well-being or wellbeing or health state* or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol or utilit* or resource use or resource utili?ation):ti,ab,kw
10. 8 and 9

(Results: CDSR = 0; DARE = 0; HTA database = 4; NHS EED = 2, search run 27 February 2012.)

Appendix 3 Data extraction form for primary studies

Adamson 2011[56]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Adamson
Year of publication: 2011
Country: CA, USA
Study design: Retrospective case series
Study setting: Small community hospital
Number of centres: Single centre
Duration of study: 5 October 2005 and 1 January 2010
Follow-up period: Patients were followed up until HT, recovery of native heart function with device removal, or withdrawal from the study
Funding: Not reported

Aim of the study

To determine outcomes of LVAD patients aged > 70 years

Participants

Inclusion criteria: All patients studied met the clinical trial enrolment criteria and the general criteria for BTT/DT LVAD implantation as published by the Centres for Medicare & Medicaid Services, including chronic end-stage HF (NYHA functional class IV symptoms, failing to respond to optimal MM, end-stage left ventricular failure for at least 90 days, and a life expectancy of < 2 years), LVEF < 25%, demonstrated functional limitation with peak VO_2 < 12 ml/kg/minute, continued need for intravenous in inotropic therapy, and an appropriate body size to support LVAD implantation
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): < 70 years group 56.7 ± 14.3 (16–69) years; ≥ 70 years group 76.3 ± 3.9 (70–87) years
Median age: Not reported
Age range: See above
Sex: Not reported
Race: Not reported
Diagnosis: HF

Intervention

Indication for treatment: BTT/DT for advanced HF
Type of device used: HMII LVADs
Any comparison: HMII not compared against another device, but all the participants were divided into two groups according to age at the time of implant: (1) aged < 70 years and (2) aged ≥ 70 years
Duration of treatment: Until HT, recovery of native heart function with device removal, or withdrawal from the study
Percentage of patients using inotropes: 17/25 and 18/30
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Groups were compared with regard to pre-operative patient characteristics and outcome measures, including K–M survival, prevalence and incidence of adverse events, QoL metrics (KCCQ CSS and OSS, MLWHF), and functional status (6-minute walk distance, NYHA functional class, and patient activity levels with the METs)
Secondary outcomes: Not applicable
Method of assessing outcomes: Prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: Yes
Length of follow-up: Patients were followed up until HT, recovery of native heart function with device removal, or withdrawal from the study

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported	Not reported
Randomised/included	Aged < 70 years group: $n = 25$	Aged ≥ 70 years group: $n = 30$
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	0	1

Patient's baseline characteristics			
Parameter	**Aged < 70 years ($n = 25$)**	**Aged ≥ 70 years ($n = 30$)**	***p*-value**
Patients enrolled	25 (45%)	30 (55%)	
Age, years (minimum–maximum)	56.7 ± 14.3 (16–69)	76.3 ± 3.9 (70–87)	< 0.001
Ischaemic	15 (60%)	24 (80%)	0.140
BSA (m^2)	1.98 ± 0.21	1.95 ± 0.19	0.671
Weight (kg)	83 ± 15	79 ± 15	0.276
LVEF (%)	21 ± 9	20 ± 6	0.651
Cardiac index (l/minute/m^2)	1.95 ± 0.72	1.67 ± 0.49	0.139
PCWP (mmHg)	27 ± 9	27 ± 9	0.824
Systolic BP (mmHg)	104 ± 19	108 ± 15	0.438
Creatinine (mg/dl)	1.76 ± 1.17	1.47 ± 0.61	0.420
BUN (mg/dl)	34.3 ± 20.1	32.8 ± 15.4	0.939
ALT (U/l)	81 ± 209	62 ± 123	0.205
AST (U/l)	98 ± 165	44 ± 48	0.141
Total bilirubin (mg/dl)	1.08 ± 0.78	0.99 ± 0.53	0.932
Albumin (g/dl)	3.55 ± 0.52	3.76 ± 0.52	0.137
Pre-albumin (mg/dl)	16 ± 7	21 ± 6	0.030
Na (mmol/l)	135.3 ± 5.5	136.9 ± 4.6	0.297
Beta-blockers	6 (24%)	13 (43%)	0.163
ACE inhibitors	2 (8%)	13 (43%)	0.005
Intravenous inotrope agents	17 (68%)	18 (60%)	0.585
Single inotrope	10 (40%)	14 (47%)	0.785
More than one inotrope	7 (28%)	4 (13%)	0.198
CRT	9 (36%)	19 (63%)	0.060
ICD	16 (64%)	25 (83%)	0.128
Ventilator support	5 (20%)	0 (0%)	0.015
IABP	3 (12%)	0 (0%)	0.088
DTRS	10.5 ± 6.3	8.3 ± 5.8	0.205
DTRS low risk	10 (40%)	15 (50%)	0.588
DTRS high/very high risk	5 (20%)	4 (13%)	0.716

Patient's baseline characteristics

BSA, cardiac index, PCWP, systolic BP, albumin, pre-albumin and DTRS were normally distributed and evaluated using the *t*-test. The remaining continuous variables, LVEF, creatinine, BUN, ALT, AST, total bilirubin and Na, were evaluated using the non-parametric Mann–Whitney *U*-test

Survival outcomes reported (by group and/or intervention)

Overall survival
Survival of patients, including those who had a HMXVE replaced with a HMII: K–M survival for both groups were comparable (log-rank $p = 0.806$). Survival rates for the < 70-year age group vs. ≥ 70-year age group were similar at 30 days (96% vs. 97%), 6 months (88% vs. 83%), 1 year (72% vs. 75%) and 2 years (65% vs. 70%)
Survival rates for patients receiving the HMII as their initial device, after excluding those who received it as an exchange for the HMXVE, were also similar ($p = 0.898$) at 1 year (65% vs. 70%) and 2 years (65% vs. 70%) (log-rank $p = 0.898$)

Other specified/relevant outcomes reported (by group and/or intervention)

Average length of stay in the hospital was similar for the < 70-year age group and ≥ 70-year age group (23 ± 14 days vs. 24 ± 15 days, respectively)

Other specified/relevant outcomes reported (by group and/or intervention)

6-minute walk test

	Aged < 70 years					Aged ≥ 70 years				
Parameter	Baseline	1 month	3 months	6 months	*p*-value A	Baseline	1 month	3 months	6 months	*p*-value A
Patients tested at interval, *n*	6	14	18	17	< 0.001	15	17	17	15	0.004
Distance walked (m)	256 ± 96	188 ± 113	354 ± 162	275 ± 135		233 ± 100	162 ± 114	256 ± 100	295 ± 97	

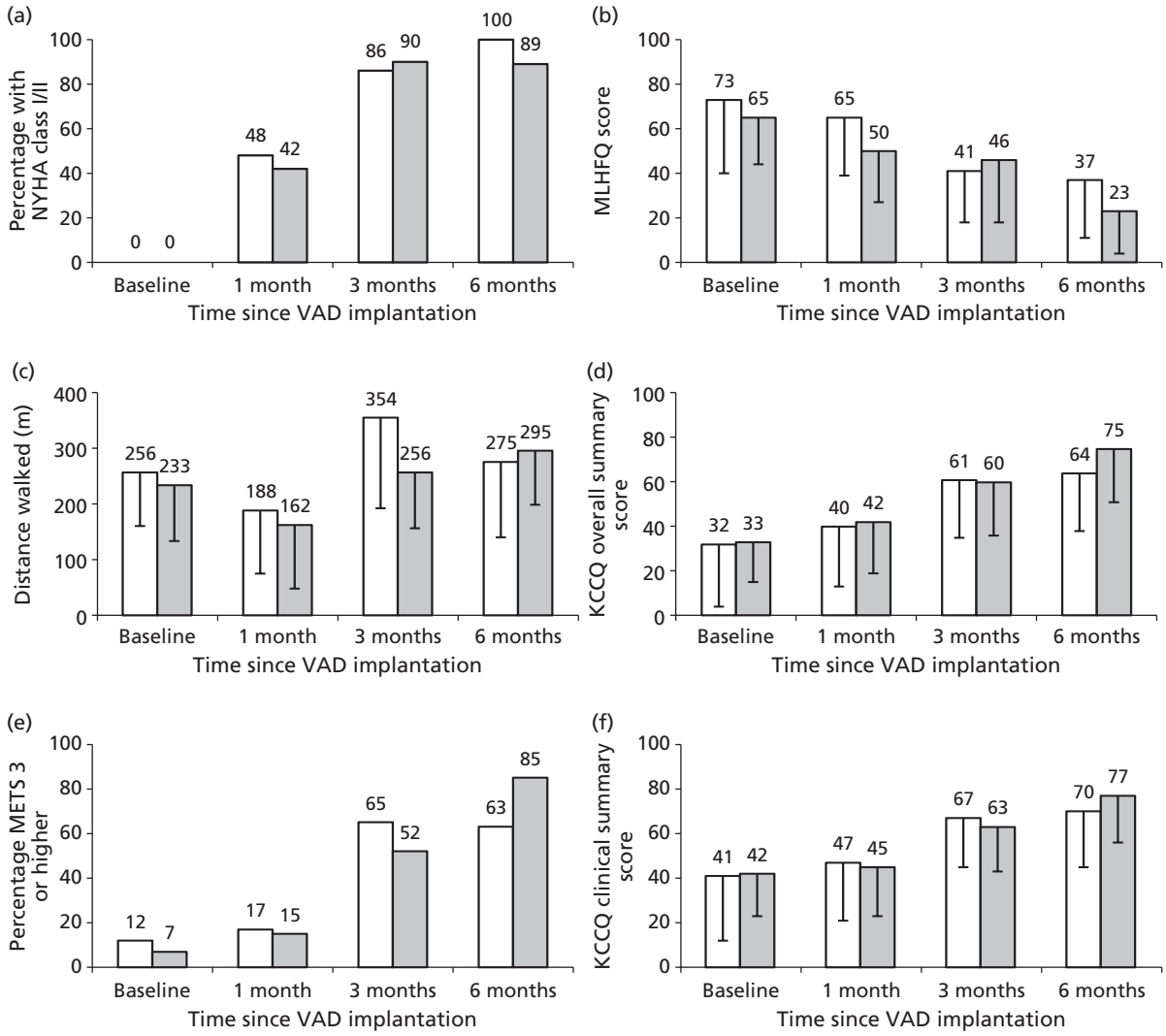
p-value A, change over time. *p*-value older vs. younger = 0.221.

Patient activity levels (METs)

	Aged < 70 years					Aged ≥ 70 years				
Parameter	Baseline	1 month	3 months	6 months	*p*-value A	Baseline	1 month	3 months	6 months	*p*-value A
Patients tested at interval, *n*	25	23	23	19	< 0.001	30	27	23	20	<0 .001
% METs ≥ 3	3 (12%)	4 (17%)	15 (65%)	12 (63%)		2 (7%)	4 (15%)	12 (52%)	17 (85%)	

p-value A, change over time. *p*-value older vs. younger = 0.205.

Other specified/relevant outcomes reported (by group and/or intervention)



Other specified/relevant outcomes reported (by group and/or intervention)

Adverse events reported (by group and/or intervention)

Events	Aged < 70 years (*n* = 25), 38.8 patient-years		Aged > 70 years (*n* = 30), 37.7 patient-years		*p*-value
	Incidence (%)	Rate events/ patient-year	Incidence (%)	Rate events/ patient-year	
Bleeding requiring PRBCs	7 (28)	0.33	9 (30)	0.42	0.591
Bleeding requiring re-exploration	5 (20)	0.15	3 (10)	0.11	0.583
Infection					
Sepsis	12 (48)	0.67	14 (47)	0.72	0.853
Local non-device related	6 (24)	0.21	6 (20)	0.19	0.854
Device related	5 (20)	0.15	5 (17)	0.13	0.813
Cardiac arrhythmias (cardioversion/ defibrillation)	8 (32)	0.26	10 (33)	0.29	0.802
Renal failure	1 (4)	0.03	1 (3)	0.03	0.984
Right side HF	1 (4)	0.03	1 (3)	0.03	0.984
RVAD	0 (0)	0	1 (3)	0.03	0.317
Ischaemic stroke	1 (4)	0.03	1 (3)	0.03	0.984
Haemorrhagic stroke	1 (4)	0.03	2 (7)	0.05	0.557
Other neurological events (TIA, seizures, confusion, etc.)	4 (16)	0.1	3 (10)	0.08	0.746
Haemolysis	0 (0)	0	0 (0)	0	Not reported

Cause of death reported (by group and/or intervention)

Causes of death	Aged < 70 years	Aged ≥ 70 years	*p*-value
< 12 months	**n = *6/25 (24%)***	**n = *7/30 (23%)***	
Sepsis	1 (4%)	1 (3%)	1
Respiratory failure	2 (8%)	1 (3%)	0.586
Multiorgan failure	0 (0%)	1 (3%)	1
Ischaemic stroke	1 (4%)	0 (0%)	0.455
Haemorrhagic stroke	0 (0%)	1 (3%)	1
Device thrombosis	1 (4%)	0 (0%)	0.455
Patient disconnected power	1 (4%)	0 (0%)	0.455
Cancer	0 (0%)	1 (3%)	1
Withdrawal of support	0 (0%)	1 (3%)	1
Unknown	0 (0%)	1 (3%)	1
> 12 months	**n = *2/25 (8%)***	**n = *3/30 (10%)***	
Anoxic brain injury	0 (0%)	1 (3%)	1
Cardiomyopathy	1 (4%)	0 (0%)	0.455
Sepsis	1 (4%)	0 (0%)	0.455
Unknown	0 (0%)	1 (3%)	1
Respiratory failure	0 (0%)	1 (3%)	1

QoL reported (by group and/or intervention)

MLWHF

	Aged < 70 years					Aged ≥ 70 years				
Parameter	Baseline	1 month	3 months	6 months	*p*-value A	Baseline	1 month	3 months	6 months	*p*-value A
Patients tested at interval, *n*	18	20	22	20	< 0.001	26	23	20	17	< 0.001
Score	73 ± 33	65 ± 26	41 ± 23	37 ± 26		65 ± 21	50 ± 23	46 ± 28	23 ± 19	

p-value A, change over time. *p*-value older vs. younger = 0.072.

KCCQ

	Aged < 70 years					Aged ≥ 70 years				
Parameter	Baseline	1 month	3 months	6 months	*p*-value A	Baseline	1 month	3 months	6 months	*p*-value A
Patients tested at interval, *n*	18	20	22	20	< 0.001	25	23	22	18	< 0.001
OSS	32 ± 28	40 ± 27	61 ± 26	64 ± 26		33 ± 18	42 ± 23	60 ± 24	75 ± 24	
CSS	41 ± 29	47 ± 26	67 ± 22	70 ± 25	< 0.001	42 ± 19	45 ± 22	63 ± 20	77 ± 21	< 0.001

p-value A, change over time. *p*-value older vs. younger = 0.587 (OSS), 0.881 (CSS).

NYHA functional class: patients tested at interval class I/II

	Aged < 70 years					Aged ≥ 70 years				
Parameter	Baseline	1 month	3 months	6 months	*p*-value	Baseline	1 months	3 months	6 months	*p*-value A
Patients tested at interval, *n*	24	21	21	20	< 0.001	29	26	20	19	< 0.001
Class I/II	0 (0%)	10 (48%)	18 (86%)	20 (100%)		0 (0%)	11 (42%)	18 (90%)	17 (89%)	

p-value A, change over time. *p*-value older vs. younger = 0.35.

QoL reported (by group and/or intervention)

6-minute walk test by age across time points

	Aged < 70 years					Aged ≥ 70 years				
Parameter	Baseline	1 month	3 months	6 months	*p*-value	Baseline	1 month	3 months	6 months	*p*-value A
Patients tested at interval, *n*	6	14	18	17		15	17	17	15	
Distance walked (m)	256 ± 96	188 ± 113	354 ± 162	275 ± 135	<0.001	233 ± 100	162 ± 114	256 ± 100	295 ± 97	0.004

p-value A, change over time. *p*-value older vs. younger = 0.221.

Author's conclusion

Advanced HF patients receiving an HMII LVAD who were aged ≥ 70 years had outcomes similar to those of patients aged < 70 years. Older patients had acceptable length of hospital stays, adverse events and functional recovery. Advanced age should not be used as an independent contraindication when selecting a patient for LVAD therapy. As this technology continues to improve, increasing numbers of older patients will seek centres for DT. Analysis of the referral data suggests that more patients should be referred for LVAD evaluation at an experienced centre, because good outcomes can be achieved in this patient cohort

Reviewer's conclusion

The population consisted of both DT and BTT patients; results were not reported separately. The results were similar for patients aged < 70 and aged ≥ 70 years

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; DTRS, Destination Therapy Risk Score; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; Na, sodium; PRBC, packed red blood cell; TIA, transient ischaemic attack; VO_2, volume of oxygen consumption.

Bogaev 2011[57]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Bogaev
Year of publication: 2011
Country: USA
Study design: Retrospective
Study setting: Unclear
Number of centres: 35
Duration of study: March 2005 and April 2008
Follow-up period: First 18 months of support
Funding: The HMII BTT trial was sponsored by Thoratec Inc. Dr Bogaev is a consultant to Thoratec Inc. Dr Pamboukian has received honoraria from Thoratec Inc. Dr John has received research support from Thoratec Inc. Dr Moore served on the Clinical Events Committee of the HMII clinical trial while the trial was in progress. Dr Farrar and Dr Sundareswaran are employees and stockholders of Thoratec Inc.

Aim of the study

To compare the survival outcomes, QoL and adverse events in 465 patients (104 women, 361 men) with advanced systolic HF in their first 18 months of support with the HMII CF LVAD for BTT

Participants

Total number of participants: 465
Sample attrition/dropout: Unclear
Inclusion criteria: Patients had NYHA functional class IV symptoms and UNOS status 1a or 1b
Exclusion criteria: Patients were excluded for severe renal (serum creatinine > 3.5 mg/dl or long-term dialysis), hepatic (INR > 2.5, total bilirubin > 5 mg/dl, or transaminases > 2000 U/litre), or pulmonary (severe chronic obstructive or restrictive disease) dysfunction. Patients were also excluded if they had uncontrolled infections, previous strokes, mechanical aortic valves, irreparable aortic insufficiency, aortic aneurysm > 5.0 cm, or other mechanical circulatory support devices, except IABPs
Characteristics of participants:
Mean age (SD): Women 49.6 ± 14.2 years; men 52.4 ± 12.8 years
Median age: Not reported
Age range: Not reported
Sex: 104 women, 361 men
Race: Not reported
Diagnosis: Advanced systolic HF

Intervention

Indication for treatment: BTT patients enrolled in the HMII clinical trial. For patients who underwent transplantation, recovered their native heart function, died, underwent pump explantation, or withdrew from the study before 18 months, data measurements until the date of outcome were used
Type of device used: HMII
Any comparison: Male vs. female
Duration of treatment: 18 months
Percentage of patients using inotropes: Approximately 90% of patients were receiving inotropic support [women $n = 89$ (86%); men $n = 328$ (91%)]
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Differences in outcomes and adverse events between women and men were evaluated at follow-up 18 months
Secondary outcomes: Hospital readmissions and adverse events, causes of death, QoL questionnaires and functional assessments were obtained when possible for all patients before LVAD implantation (baseline) and at 1, 3 and 6 months. Functional status measurements included NYHA functional class, METs and 6-minute walk distances. HF-related QoL was assessed using responses from the MLWHF and KCCQs
Method of assessing outcomes: Medical records and interviews with family members
Survival: Yes
Adverse event: Yes
HRQoL: Yes
Length of follow-up: 18 months

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	465 HF patients	Not applicable
Randomised/included	465 HF patients	Not applicable
Excluded	Not applicable	Not applicable
Missing participants	Not applicable	Not applicable
Withdrawals	Five men underwent pump replacement and were withdrawn	Not applicable

Patient's baseline characteristics

Variable	Women	Men	*p*-value
Patients enrolled	104 (22%)	361 (78%)	
Age (years)	49.6 ± 14.2	52.4 ± 12.8	0.075
Ischaemic cardiomyopathy	32 (31%)	177 (49%)	0.001
BSA (m^2)	1.76 ± 0.27	2.05 ± 0.23	< 0.001
BSA < 1.5 (m^2)	15 (14%)	3 (1%)	< 0.001
Weight (kg)	68.6 ± 18.4	87.3 ± 18.1	< 0.001
LVEF (%)	16.4 ± 7.0	16.5 ± 6.4	0.803
Cardiac index (l/minute/m^2)	2.07 ± 0.62	2.06 ± 0.68	0.699
PCWP (mmHg)	23 ± 7	26 ± 8	0.001
SBP (mmHg)	97 ± 15	99 ± 16	0.230
Creatinine (mg/dl)	1.32 ± 0.52	1.46 ± 0.52	0.006
BUN (mg/dl)	26.9 ± 15.2	31.4 ± 17.1	0.013
ALT (U/l)	106 ± 226	96 ± 250	0.841
AST (U/l)	107 ± 238	77 ± 240	0.007
Total bilirubin (mg/dl)	1.08 ± 0.79	1.31 ± 0.84	0.003
Albumin (g/dl)	3.40 ± 0.58	3.59 ± 1.41	0.037
Pre-albumin (mg/dl)	17.2 ± 6.9	18.3 ± 7.6	0.288
Na (mmol/l)	134.6 ± 5.4	133.4 ± 4.8	0.028
Beta-blockers	30 (29%)	147 (41%)	0.030
ACE inhibitors	26 (25%)	100 (28%)	0.619
Inotropes	89 (86%)	328 (91%)	0.142
CRT	45 (43%)	185 (51%)	0.182
ICD	68 (65%)	287 (80%)	0.004
Ventilatory support	14 (13%)	25 (7%)	0.044
IABP	48 (46%)	147 (41%)	0.367

Patient's baseline characteristics

Continuous data are reported as mean ± SD; categorical data as number (%)
Fewer women had ischaemic cardiomyopathy (31% vs. 49%; $p = 0.001$); women had significantly smaller BSAs (1.76 ± 0.27 vs. 2.05 ± 0.23 m^2; $p < 0.001$); 15 out of 104 women had BSAs < 1.5 m^2 compared with 3 out of 361 men

Survival outcomes reported (by group and/or intervention)

During the 18 months, 21 women (20%) and 70 men (21%) died
No differences in K–M survival (log-rank test $p = 0.855$) during support, with similar survival at 30 days (96% vs. 93%), 180 days (87% vs. 83%) and 365 days (74% vs. 76%) after HMII implantation
No difference in 1-year survival after HT for women (32/37, 86%) or men (157/174, 90%) ($p = 0.553$)
Similar survival rates during device support and lower transplantation rates compared with that of men, more women remained on LVAD support at 18 months (36% vs. 23%; $p = 0.007$)

Other specified/relevant outcomes reported (by group and/or intervention)

During the 18-month period, 42 women (40%) had HT compared with 200 men (55%) ($p = 0.001$)
For women who had HT, median duration of support before transplantation was similar to men (155 vs. 141 days)
No differences in BSA between women who had a HT and those on device support
Five men underwent pump replacement for a different device and were withdrawn from the study
Before LVAD implantation, fewer women were taking P-blockers (29% vs. 41%)
Fewer women had ICDs (65% vs. 80%), and more women required pre-operative ventilatory support (13% vs. 7%)
More than 40% of all patients were receiving IABP support. Cardiac resynchronisation therapy had failed in > 40% of all patients
No difference in pre-operative cardiac index or SBP measurements, although PCWP was lower in women (23 vs. 26 mmHg)
Serum creatinine and BUN levels were lower in women, and serum sodium levels were slightly higher. AST in women was elevated, but men had higher total bilirubin levels
Mean duration of LVAD support was 422 ± 370 days for women (median 238 days; longest duration 4.3 years) and 315 ± 322 days for men (median 184 days; longest duration 4.2 years; $p = 0.003$)
Pulsatility index, measured from pump console, also was higher in women (5.0 ± 0.7 vs. 4.8 ± 0.8; $p = 0.009$)
No difference in average SBP measurement during support (98 ± 12 vs. 96 ± 13 mmHg; $p = 0.317$)
Average pump speed during LVAD support was significantly lower for women (9204 ± 421 vs. 9420 ± 524 RPM; $p < 0.001$)
Mean estimated pump blood flow index was higher in women (2.9 ± 0.4 vs. 2.7 ± 0.4 litre/minute/m^2; $p < 0.001$)
Significant differences were observed between women and men in the transplantation rate ($p = 0.001$) and in ongoing LVAD support ($p = 0.007$). There were no significant differences among other outcomes

Adverse events reported (by group and/or intervention)

Most frequent adverse events were bleeding, arrhythmias and infection (see below)
Average duration of LVAD support before an ischaemic stroke did not differ (207 ± 289 vs. 156 ± 260 days; $p = 0.441$)
No difference in ischaemic stroke rate between sexes (0.06 vs. 0.05 events/patient-year), but the haemorrhagic stroke rate was higher in women (0.10 vs. 0.04 events/patient-year; $p = 0.02$)
Event rates associated with sepsis, non-device-related infections (e.g. central line or urinary tract infections, pneumonias) and right HF requiring the use of a VAD or extended inotropic support (> 14 days) did not differ between sexes
The rate of device-related infection was lower in women (0.23 vs. 0.44 events/patient-year; $p = 0.006$) compared with men
Duration of LVAD support before a haemorrhagic stroke did not differ (170 ± 177 vs. 170 ± 166 days; $p = 0.977$), nor did average systolic BP in patients who had a haemorrhagic stroke (99 ± 15 vs. 98 ± 12 mmHg; $p = 0.891$). At time of haemorrhagic stroke, no difference in mean INR (1.82 ± 0.70 vs. 1.98 ± 0.78; $p = 0.648$), partial thromboplastic time (55 ± 12 vs. 50 ± 27 seconds; $p = 0.197$), or platelet count (229 ± 66 vs. 213 ± 117 × 1000/mm^3; $p = 0.750$)
In BSA-matched subanalysis, haemorrhagic stroke occurred more frequently in women (12%) than in smaller-sized men (4%), but difference in event rates did not reach statistical significance (0.10 vs. 0.06 events/patient-year; $p = 0.317$)

	Women ($n = 104$) 120.1 patient-years		Men ($n = 361$) 311.1 patient-years		
Adverse event	Incidence, patients (%)	Event rate/ patient-year	Incidence, patients (%)	Event rate/ patient-year	*p*-value
Bleeding requiring PRBC	68 (65)	1.4	200 (55)	1.24	0.398
Bleeding requiring re-exploration	23 (22)	0.23	77 (21)	0.27	0.546
Infection					
Local non-device related	49 (47)	0.74	117 (32)	0.69	0.674
Sepsis	20 (19)	0.22	78 (22)	0.34	0.062
Device related	20 (19)	0.23	77 (21)	0.44	0.006
Arrhythmias cardioversion/ defibrillation	59 (57)	0.93	208 (58)	1.15	0.168

Adverse events reported (by group and/or intervention)

Adverse event	Women ($n = 104$) 120.1 patient-years		Men ($n = 361$) 311.1 patient-years		
	Incidence, patients (%)	Event rate/ patient-year	Incidence, patients (%)	Event rate/ patient-year	*p*-value
Renal failure	9 (9)	0.08	42 (12)	0.14	0.145
Right HF	25 (24)	0.22	67 (19)	0.22	0.970
RVAD	7 (7)		22 (6)		
Ischaemic stroke	7 (7)	0.06	16 (4)	0.05	0.788
< 30 days	3 (3)	0.36	9 (2)	0.32	0.886
> 30 days	4 (4)	0.04	7 (2)	0.03	0.704
Haemorrhagic stroke	12 (12)	0.1	12 (3)	0.04	0.020
< 30 days	3 (3)	0.36	2 (1)	0.07	0.086
> 30 days	9 (9)	0.08	10 (3)	0.04	0.109
Other neurological events[a]	13 (13)	0.13	34 (9)	0.13	0.910
Haemolysis	8 (8)	0.1	12 (3)	0.05	0.090

a TIA, seizures, confusion, etc.

Cause of death reported (by group and/or intervention)

In men, the leading causes of death were sepsis (3.9%), right HF (2.8%) and multisystem organ failure (2.2%). The leading causes of death in women were multisystem organ failure (3.8%), haemorrhagic stroke (2.9%), ischaemic stroke (1.9%), right HF (1.9%) and external component device malfunction (1.9%; percutaneous lead trauma in one patient and pump disconnection in another). See below

Cause	Deaths in LVAD patients		
	Women, *n* (%)	Men, *n* (%)	*p*-value
Total	21/104 (20.2)	70/361 (19.4)	
Sepsis	1 (1.0)	14 (3.9)	0.208
Right HF	2 (1.9)	10 (2.8)	1.000
Multisystem organ failure	4 (3.8)	8 (2.2)	0.480
Ischaemic stroke	2 (1.9)	4 (1.1)	0.620
Haemorrhagic stroke	3 (2.9)	3 (0.8)	0.129
Internal components[a]	1 (1.0)	5 (1.4)	1.000
External components[b]	2 (1.9)	2 (0.3)	0.037
Other[c]	6 (5.8)	24 (7.2)	1.000

a Three thrombi, one pump disconnection, one twisted inflow graft and one pump-pocket infection.
b Three loss of power and one percutaneous lead trauma.
c Other causes of death included respiratory failure, cardiac failure, bleeding, cancer, elective withdrawal of support, death during transplantation and unknown causes.

Cause of death reported (by group and/or intervention)

Causes of death at 18 months

QoL reported (by group and/or intervention)

NOTE: Before LVAD implantation, many patients were unable to walk and were therefore omitted from this analysis
Significant improvements from baseline in 6-minute walk distances for both women (219–327 m) and men (247–356 m)
Overall distance walked at all times was further for men ($p = 0.037$). Improvement for both sexes in QoL metrics related to HF
Percentage of patients with NYHA functional class I or II symptoms improved from 0% at baseline to 83% for females and 85% for males at 6 months (see below)
The number of patients achieving METs of ≥ 3 increased from 5% in women and 8% in men at baseline to 67% in women and 74% in men at 6 months

Functional capacity and QoL female

	Women				
Variable	Baseline	1 month	3 months	6 months	*p*-value[a]
NYHA functional class					
Patients tested at interval	98	80	78	59	< 0.001
Class I/II	0 (0)	47 (59)	60 (77)	49 (83)	
6-minute walk test					
Patients tested at interval	15	56	56	47	
Distance walked, metres	219 ± 173	238 ± 108	306 ± 147	327 ± 114	< 0.001
Questionnaires					
MLWHF					
Patients tested at interval	77	78	73	56	
Score	73 ± 22	63 ± 27	44 ± 25	35 ± 22	< 0.001
KCCQ					
Patients tested at interval	75	80	75	59	
OSS	29 ± 21	44 ± 24	57 ± 22	68 ± 21	< 0.001
CSS	37 ± 24	50 ± 25	65 ± 23	74 ± 21	< 0.001
METs					
Patients tested at interval	103	92	79	63	
METs ≥ 3	5 (5)	15 (16)	45 (57)	42 (67)	< 0.001

a *p*-value for changes over time.
Continuous data are presented as mean ± SD; categorical data as number (%).

QoL reported (by group and/or intervention)

Functional capacity and QoL male

Variable	Men					
	Baseline	1 month	3 month	6 month	*p*-value[a]	*p*-value[b]
NYHA functional class						
Patients tested at interval	342	276	227	172		
Class I/II	0 (0)	165 (60)	188 (83)	147 (85)	< 0.001	0.550
6-minute walk test						
Patients tested at interval	59	208	177	152		
Distance walked, m	247 ± 112	275 ± 162	351 ± 163	356 ± 179	< 0.001	0.037
Questionnaires						
MLWHF						
Patients tested at interval	297	268	224	161		
Score	71 ± 22	58 ± 27	42 ± 24	40 ± 23	< 0.001	0.661
KCCQ						
Patients tested at interval	300	304	233	170		
OSS	31 ± 20	46 ± 22	60 ± 21	65 ± 21	< 0.001	0.706
CSS	40 ± 22	54 ± 24	68 ± 21	73 ± 21	< 0.001	0.371
METs						
Patients tested at interval	349	304	233	170		
METs ≥ 3	27 (8)	76 (25)	157 (67)	125 (74)	< 0.001	0.348

a *p*-value for changes over time.
b *p*-value for differences between men and women.

Author's conclusion

BTT women with the HMII were equivalent to that of men, despite significantly fewer women who eventually underwent transplantation. Women had longer wait times for suitable donor hearts, they also had longer LVAD support times and usually continued LVAD support beyond the 18-month period (36% of women vs. 23% of men continued support at 18 months). In addition, there were significant improvements in functional capacity and HF-related QoL metrics for both sexes during LVAD support. CF LV assistance as a BTT was associated with similar survival rates in both women and men. Further research is needed to examine the differences observed in higher stroke rates and fewer infections among women

Reviewer's conclusion

QoL and functional capacity data were reported on different numbers of patients at each period because of several factors (e.g. death and transplantation). Interesting observation of higher stroke rates and fewer infections among women than men. Caution is needed when interpreting the findings as there were differences in baseline characteristics between the male and female samples (e.g. BSA, weight, ischaemic cardiomyopathy)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; ICD, implantable cardioverter-defibrillator; INR, international normalised ratio; LVEF, left ventricular ejection fraction; Na, sodium; RPM, revolutions per minute; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Boyle 2009[58]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Boyle
Year of publication: 2009
Country: USA
Study design: Retrospective
Study setting: Not reported
Number of centres: Not reported
Duration of study: Unclear – 6-month analysis period
Follow-up period: INR was measured monthly for 6 months in all discharged HMII BTT patients and at an event. Three hundred and thirty-one patients had follow-up for at least 1 month since their initial discharge on support and formed the cohort for analysis
Funding: Data from this study were from a clinical trial sponsored and managed by Thoratec Inc. Authors have the following disclosures related to this article: three were consultants to Thoratec Inc.; five received grant support from Thoratec Inc.; and two are employees of Thoratec Inc.

Aim of the study

To evaluate the risk of thromboembolism and pump thrombosis related to the degree of anticoagulation as reflected by the INR in HMII BTT patients after their initial discharge
To assess the frequency of major bleeding events once a patient is discharged and its relationship with the degree of anticoagulation with warfarin

Participants

Total number of participants: 331
Sample attrition/dropout: 1 (0.3%). Of the 469 patients who received an implant, 138 had outcomes before discharge, 46 received a transplant, 3 were exchanged to other types of LVADs and withdrew, 50 died, and 39 remained on device support in hospital
Inclusion criteria: At least 1 month since their initial discharge on support and form cohort for analysis
Exclusion criteria: Blood transfusions for events related to trauma, surgical procedures, or haemolysis were excluded from bleeding analysis
Characteristics of participants:
Mean age (SD): 55 years
Median age: 55 years
Age range: 15–74 years
Sex: Male ($n = 252$, 76%); female ($n = 79$, 24%)
Race: African American 22%
Diagnosis: 45% ischaemic cardiomyopathy

Intervention

Indication for treatment: BTT
Type of device used: HMII LVAD
Any comparison: Comparisons against 469 patients enrolled in BTT arm of US HMII pivotal trial
Duration of treatment: Mean duration of mechanical circulatory support in these patients was 272 ± 201 days (median 211 days; range 31–1088 days), for an accumulated duration of support for entire cohort of 246 patient-years
Percentage of patients using inotropes: Intravenous inotropes, 89.1%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: INR, haemoglobin, platelet count and partial thromboplastin time
Secondary outcomes: Adverse events. Thrombotic events analysed included ischaemic stroke and pump thrombosis. Haemorrhagic events analysed included haemorrhagic stroke, bleeding requiring surgical exploration, and bleeding requiring at least 2 units of PRBC within 24 hours. Stroke was defined as any neurological event lasting longer than 24 hours and then categorised as having a haemorrhagic or thromboembolic aetiology according to the results of intracranial imaging. Pump thrombosis was defined as any thrombus within the device or its conduits associated with clinical signs of impaired pump performance
Method of assessing outcomes: Medical records. INRs recorded at the time of adverse events. Adverse events related to thromboembolism, thrombosis and major bleeding were independently adjudicated by the Clinical Events Committee of the main trial. Adverse events for each INR range during the 6-month analysis period were calculated in events per patient-year
Survival: No
Adverse event: Yes
HRQoL: No

Outcomes

Length of follow-up: 331 participants had follow-up for at least 1 month since their initial discharge on support and form the cohort for analysis

Number of participants	Intervention	Comparator, if present
Screened	469 patients enrolled in the BTT arm of the US HMII pivotal trial	Not applicable
Randomised/included	331 patients who have had follow-up for at least 1 month since their initial discharge on support	Not applicable
Excluded	Not reported	Not applicable
Missing participants	Not reported	Not applicable
Withdrawals	Three patients were exchanged to other types of LVADs and withdrew from the study, 50 patients died	Not applicable

Patient's baseline characteristics

Demographics for patients successfully discharged

Characteristic	Value
Total *N*	331
Sex, *n* (%)	
Male	252 (76)
Female	79 (24)
Age, mean years (range)	55 (15–74)
Ischaemic aetiology (%)	45
African American (%)	22
BSA, mean (range), m^2	2.0 ± 0.3 (1.33–2.62)
LVEF, mean ± SD (%)	16.5 ± 6.5
LVEDD, mean ± SD (mm)	70 ± 12
ACE inhibitors (%)	29
ARBs (%)	5
P-blockers (%)	37.2
CRT (%)	45,3
Intravenous inotropes (%)	89.1
IABP (%)	41
Lab/haematology, mean ± SD	
BUN (mg/dl)	29 ± 16
Creatinine (mg/dl)	1.4 ± 0.5
Total bilirubin (mg/dl)	1.3 ± 0.8
ALT (U/l)	96 ± 246
AST (IU/l)	76 ± 217
INR	1.3 ± 0.4
PTT (seconds)	48.8 ± 31.2
Haemoglobin (g/dl)	11.7 ± 1.9

Patient's baseline characteristics

Characteristic	Value
Flematocrit	35.1 ± 5.5
WBC count (1000/mm^3)	8.7 ± 3.5
Platelets (1000/mm^3)	225 ± 85

Survival outcomes reported (by group and/or intervention)

Overall survival: 30 (9.1%) patients died
Mechanical circulatory support without subsequent HT: 137 (41.4%)
Mechanical circulatory support with subsequent HT: 154 (46.5%)

Other specified/relevant outcomes reported (by group and/or intervention)

Mean duration of mechanical circulatory support was 272 ± 201 days (median 211 days; range 31–1088 days), for an accumulated duration of support for the entire cohort of 246 patient-years
Mean duration of time outside the hospital once a patient was discharged was 221 ± 191 days, or 93% of total support time
Overall cumulative support time after discharge was 200.2 patient-years
Cumulative support period for INR analysis from hospital discharge through 6 months was 111 patient-years

Adverse events reported (by group and/or intervention)

Thrombotic and haemorrhagic adverse events after initial hospital discharge (*n* = 331)

	All events (220 patient-years)			Discharge to 6 month (111 patient-years)		
Events after discharge	Patients (%)	Events	Events/ patient-year	Patients (%)	Events	Events/ patient-year
Thrombotic events						
Ischaemic stroke	8 (2.4)	9	0.041	6 (1.8)	6	0.054
Pump thrombosis	3 (0.9)	3	0.014	3 (0.9)	3	0.027
Haemorrhagic events						
Haemorrhagic stroke	7 (2.1)	7	0.032	6 (1.8)	6	0.054
Bleeding requiring surgery	4 (1.2)	4	0.018	4 (1.2)	4	0.037
Transfusion > 2 units PRBC/24 hours						
For bleeding[a]	40 (12.1)	60[c]	0.273	31 (9.4)	43[d]	0.387
For anaemia[b]	21 (6.3)	42[c]	0.191	17 (5.1)	25[d]	0.225

a With identified sites of bleeding.
b Without identified site of bleeding.
c The combined 60 + 42 = 102 events occurred in 51 patients (15.4%).
d The combined 43 + 25 = 48 events occurred in 40 patients (12.9%).

The frequency of thromboembolic events in HMII patients is extremely low, in patients with INRs > 1.5. The risk of lowering the target INR in selected patients who demonstrated a repeated tendency towards significant bleeding, such as those with recurrent gastrointestinal bleeding, appears to below. The frequency of thromboembolic events in this study was very low despite the infrequent use of clopidogrel (Plavix®, Bristol-Myers Squibb)

Adverse events reported (by group and/or intervention)

Patient outcomes before and after hospital discharge

Variable	Before discharge, *n* (%)	After discharge, *n* (%)
Patients on LVAD support	469	331
Transplantation	46 (9.8)	154 (46.5)
Recovery	0 (0.0)	9 (2.7)
Withdrew from study	3 (0.6)	1 (0.3)
Death	50 (10.7)	30 (9.1)
Ongoing device support	39 (8.3)	137 (41.4)
Transplantation, recovery, or ongoing support device	416 (88.7)	300 (90.6)

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Rates of thromboembolism and pump thrombosis are low with the HMII as a BTT. The low number of thrombotic events appears to be offset by a greater number of haemorrhagic events, particularly in patients with higher INRs. Hence, an appropriate universal target INR to minimise the risk of both thromboembolic and haemorrhagic events appears to be 1.5–2.5 in addition to the routine use of aspirin therapy. In patients with recurrent episodes of bleeding, the risk of lowering the target INR appears to be small. Therefore, a patient's target INR, taking into account their own risk factors for and history of thrombosis and bleeding, may be difficult from the universal target INR and should be individualised to minimise the risks of both thromboembolism and haemorrhage

Reviewer's conclusion

INR levels were recorded at monthly intervals and at time of a clinical event. However, it was noted that INRs for outpatients can change widely and over much shorter time periods according to patient conditions. There is a question of how appropriate it is to assign data into INR ranges. Generalisability of adverse event findings – caution is needed

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; INR, international normalised ratio; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; PRBC, packed red blood cell; PTT, partial thromboplastin time; WBC, white blood cells.

Brewer 2012[59]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Brewer
Year of publication: 2012
Country: USA
Study design: Retrospective analysis of patients enrolled in the multicentre HMII BTT and DT
Study setting: USA
Number of centres: Multicentre
Duration of study: Not reported
Follow-up period: Not reported
Funding: Lead author has received research support and travel reimbursement from Thoratec Inc.; one author has received speaking honoraria and travel reimbursement from Thoratec Inc.; two authors are employees of Thoratec Corporation; and another author has received grant support from Thoratec Inc.

Aim of the study

To assess the association of BMI with survival and major morbidity after CF LVAD implantation

Participants

Total number of participants: 896
Sample attrition/dropout: Four patients were withdrawn: obese 2 (1%); extremely obese 2 (2%)
Inclusion criteria: The authors report that inclusion and exclusion criteria have been published elsewhere (Slaughter *et al.* 2009[47] and Miller *et al.* 2007[70]). To be eligible to participate, patients have to be enrolled in the multicentre HMII BTT and DT trials, and received HMII devices
Exclusion criteria: Patients who received the HMII as an exchange for a HMXVE
Characteristics of participants:
Mean age (SD): Underweight (< 18.5): 53 ± 16 years; normal (≤ 18.5 to < 30): 59 ± 14 years; obese (≤ 30 to < 35): 54 ± 13 years and extremely obese (≥ 35): 49 ± 12 years
Median age: Not reported
Age range: Not reported
Sex: n (%) of females reported – underweight 22 (46); normal 144 (24); obese 32 (20); extremely obese 18 (20)
Race: n (%) reported – Caucasian race, underweight 29 (60); normal 428 (72); obese 125 (76); extremely obese: 62 (70); African American race, underweight 13 (27); normal 117 (20); obese 31 (19); extremely obese 20 (23)
Diagnosis: n (%) reported – ischaemic aetiology, underweight 17 (35); normal 307 (52); obese 91 (55); extremely obese 36 (41)

Intervention

Indication for treatment: BTT and DT [BTT indication, *n* (%) – underweight 23 (48); normal 305 (51); obese 108 (66); extremely obese 50 (57)]
Type of device used: HMII
Any comparison: Patients were divided based on their BMI into four groups: underweight (< 18.5); normal (≤ 18.5 to < 30); obese (≤ 30 to < 35) and extremely obese (≥ 35)
Duration of treatment: Not clear
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Survival; association of BMI group with survival; adverse events
Secondary outcomes: Unclear
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No

Outcomes		
Length of follow-up: 2 years		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported	Not reported
Randomised/included	896: underweight 48; normal 596; obese 164; extremely obese 88	Refer to left column
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Underweight 0 (0%); normal 0 (0%); obese 2 (1%); extremely obese 2 (2%)	Refer to left column

Patient's baseline characteristics

Parameter	Underweight	Normal	Obese	Extremely obese	*p*-value
N	48	596	164	88	
BTT indication (%)	23 (48)	305 (51)	108 (66)	50 (57)	0.007
Age (years)	53 ± 16	59 ± 14	54 ± 13	49 ± 12[a]	< 0.001
Female (%)	22 (46)	144 (24)	32 (20)	18 (20)	0.002
Caucasian race (%)	29 (60)	428 (72)	125 (76)	62 (70)	0.192
African American race (%)	13 (27)	117 (20)	31 (19)	20 (2%)	0.562
BMI (kg/m^2)	17 ± 1[a]	24 ± 3	32 ± l[a]	38 ± 3[a]	< 0.001
BSA (m^2)	1.57 ± 0.18	1.88 ± 0.21	2.16 ± 0.18	2.35 ± 0.23[a]	< 0.001
Ischaemic aetiology (%)	17 (35)	307 (52)	91 (55)	36 (41)	0.024
LVEF (%)	17 ± 7	17 ± 6	17 ± 7	16 ± 6	0.405
Systolic BP (mmHg)	97 ± 18	100 ± 15	102 ± 15	100 ± 16	0.316
Diastolic BP (mmHg)	59 ± 14	61 ± 12	63 ± 12	63 ± 11	0.064
PCWP (mmHg)	21 ± 7	24 ± 8	27 ± 9	27 ± 7	< 0.001
CVP (mmHg)	12 ± 6	12 ± 7	14 ± 6[a]	15 ± 7[a]	< 0.001
Serum sodium (mmol/l)	133.2 ± 5.7	134.1 ± 4.9	134.8 ± 4.5	134.5 ± 4.4	0.478
Serum albumin (g/dl)	3.18 ± 0.60	3.48 ± 1.16	3.57 ± 0.59	3.51 ± 0.64	< 0.001
Pre-albumin (mg/dl)	15.2 ± 5.4	18.2 ± 7.5	19.3 ± 7.3	17.6 ± 16.9	0.011
Cholesterol (mg/dl)	119 ± 36	126 ± 39	126 ± 44	124 ± 41	0.774
Serum creatinine (mg/dl)	1.35 ± 0.59	1.45 ± 0.57	1.53 ± 0.51	1.58 ± 0.62	0.004
Blood urea nitrogen (mg/dl)	30.5 ± 18.6	32.0 ± 19.4	33.1 ± 17.8	32.6 ± 18.3	0.423
ALT (IU/l)	80 ± 185	79 ± 208	67 ± 156	61 ± 92	0.382
AST (IU/l)	72 ± 144	67 ± 186	66 ± 223	49 lt 66	0.742
Total bilirubin (mg/dl)	1.39 ± 1.65	1.27 ± 0.90	1.24 ± 0.80	1.18 ± 0.74	0.845
LDH (mg/dl)	783 ± 1,643	435 ± 942	412 ± 410	330 ± 187	0.696
Haematocrit (%)	33 ± 5	35 ± 6	35 ± 6	36 ± 5	0.001
WBC (× 1000)/ml	8.7 ± 3.4	8.3 ± 3.3	8.7 ± 3.2	8.8 ± 3.2	0.196
Platelets (× 1000)/ml	225 ± 95	216 ± 90	224 ± 82	241 ± 87	0.013
INR	1.35 ± 0.48	1.34 ± 0.64	1.31 ± 0.31	1.33 ± 0.38	0.913

Outcomes

Parameter	Underweight	Normal	Obese	Extremely obese	*p*-value
ACE inhibitors (%)	13 (27)	168 (28)	45 (27)	26 (30)	0.985
Beta-blockers (%)	15 (31)	238 (40)	78 (48)	45 (51)	0.038
CRT (%)	24 (50)	319 (54)	90 (55)	53 (60)	0.622
IABP (%)	13 (27)	200 (34)	52 (32)	25 (28)	0.646
Prior cardiac procedures (%)	12 (25)	165 (28)	48 (29)	17 (19)	0.347

a < 0.001 vs. normal BMI group as control.

Survival outcomes reported (by group and/or intervention)

Actuarial survival: Not reported
Overall survival: Death at 1 year, *n* (%) – underweight 12 (25); normal 149 (25); obese 33 (20); extremely obese 16 (18) ($p = 0.357$)
K–M estimates: 1 year – underweight 73% ± 7%; normal 71% ± 2%; obese 76% ± 4%; extremely obese 79% ± 5%; 2 year – underweight 59% ± 9%; normal 60% ± 2%; obese 66% ± 5%; extremely obese 68% ± 6% ($p = 0.83$)
Proportional hazards regression modelling was used to assess survival compared with the normal BMI group, adjusting for baseline characteristics that differed between BMI groups (age, gender, race, aetiology, CVP, albumin, creatinine, haematocrit, platelet, beta-blocker and BTT/DT indication)
In adjusted analyses there were no differences observed for the underweight patients [HR 1.23 (95% CI 0.72 to 2.10); $p = 0.452$], obese patients [HR 0.94 (95% CI 0.68 to 1.31); $p = 0.723$] or extremely obese patients [HR 1.29 (95% CI 0.85 to 1.97); $p = 0.231$] when compared with normal-weight patients
Using same Cox proportional hazard model, if an age of 59 years is entered (this was the mean age of normal group), predicted 1-year survival for underweight group drops to 69%, obese group remains at 76% and extremely obese group drops to 69%
Higher K–M survival estimate in extremely obese patients is likely owing to confounding variables, primarily related to significantly younger age of patients in extremely obese group

Other specified/relevant outcomes reported (by group and/or intervention)

Comparisons of outcomes at 1 year for the four BMI groups

Outcomes at 1 year	Underweight (%)	Normal (%)	Obese (%)	Extremely obese	*p*-value
Transplantation, ongoing or recovery	36 (75)	445 (75)	129 (79)	70 (80)	0.606
Ongoing	21 (44)	270 (45)	73 (45)	47 (53)	0.512
Transplanted	12 (25)	169 (28)	54 (33)	23 (26)	0.560
Transplanted (BTT)	10/23 (43)	155/305 (51)	48/108 (44)	18/50 (36)	0.208
Transplanted (DT)	2/25 (8)	14/291 (5)	6/56 (11)	5/38 (13)	0.122
Expired	12 (25)	149 (25)	33 (20)	16 (18)	0.357
Explanted[a]	0 (0)	2 (0)	0 (0)	0 (0)	
Recovered[a]	3 (6)	6 (1)	2 (1)	0 (0)	
Withdrawn[a]	0 (0)	0 (0)	2 (1)	2 (2)	

a Total number of events too small to evaluate a meaningful *p*-value.

Other specified/relevant outcomes reported (by group and/or intervention)

Mechanical circulatory support without subsequent HT: (a) ongoing, *n* (%) – underweight 21 (44); normal 270 (45); obese 73 (45); extremely obese 47 (53) ($p = 0.512$); (b) explanted, *n* (%) – underweight 0 (0); normal 2 (0); obese 0 (0); extremely obese 0 (0) ($p = 0.357$)
Mechanical circulatory support with subsequent HT: (a) total transplant, *n* (%) – underweight 12 (25); normal 169 (28); obese 54 (33); extremely obese 23 (26) ($p = 0.560$); (b) BTT, *n*/*N* (%) – underweight 10/23 (43); normal 155/305 (51); obese 48/108 (44); extremely obese 18/50 (36) (p=0.208); (c) DT, *n*/*N* (%) – underweight 2/25 (8); normal 14/291 (5); obese 6/56 (11); extremely obese 5/38 (13) ($p = 0.122$)
No differences between groups in percentage of patients who were transplanted ($p = 0.560$), died ($p = 0.357$) or had ongoing device support ($p = 0.512$) at 1 year

Adverse events reported (by group and/or intervention)

Comparisons of adverse events for the four groups

	Underweight (66.4 patient-years)		Normal (731.8 patient-years)		Obese (192.9 patient-years)		Extremely obese (129.0 patient-years)		
Adverse events	Incidence	Event rate	Incidence	Event rate	Incidence	Event rate	Incidence	Event rate	*p*-value
Bleeding requiring packed red blood cells	31 (65%)	1.67	399 (67%)	1.40	100 (61%)	1.30	57 (65%)	1.12	< 0.001
Bleeding: requiring re-exploration	20 (42%)	0.35	130 (22%)	0.21	41 (25%)	0.22	16 (18%)	0.13	0.010
Infection									
Local non-device related	20 (42%)	0.65	229 (38%)	0.60	66 (40%)	0.72	38 (43%)	0.67	0.660
Sepsis	13 (27%)	0.30	136 (23%)	0.28	43 (26%)	0.33	28 (32%)	0.50	0.032
Device related	10 (21%)	0.29	144 (24%)	0.34	45 (27%)	0.38	31 (35%)	0.51	0.041
Cardiac arrhythmias: cardioversion/ defibrillation	25 (52%)	0.62	339 (57%)	0.79	83 (51%)	0.79	56 (64%)	0.86	0.179
Renal failure	8 (17%)	0.14	60 (10%)	0.09	23 (14%)	0.12	15 (17%)	0.12	0.959
Right HF	11 (23%)	0.17	110 (18%)	0.17	37 (23%)	0.20	24 (27%)	0.21	0.749
RVAD	4 (8%)	0.06	32 (5%)	0.04	13 (8%)	0.07	5 (6%)	0.04	0.403
Ischaemic stroke	6 (13%)	0.09	32 (5%)	0.05	10 (6%)	0.06	9 (10%)	0.07	0.838
Haemorrhagic stroke	3 (6%)	0.05	32 (5%)	0.05	12 (7%)	0.07	5 (6%)	0.04	0.394
Other neurological events (TIA, seizures, confusion, etc.)	9 (19%)	0.14	93 (16%)	0.15	17 (10%)	0.11	11 (13%)	0.10	0.731
Haemolysis	4 (8%)	0.06	22 (4%)	0.03	9 (5%)	0.08	7 (8%)	0.07	0.617
Respiratory failure	21 (44%)	0.45	183 (31%)	0.34	42 (26%)	0.23	33 (38%)	0.35	0.055
Rehospitalisations	33 (69%)	1.91	417 (70%)	2.02	114 (70%)	2.26	67 (76%)	2.54	0.014

p = evaluated based on event rates using Poisson regression.

Adverse events reported (by group and/or intervention)

Adverse event comparisons of four BMI groups are shown above. Extremely obese patients had a higher incidence of sepsis ($p = 0.032$) and device-related infection ($p = 0.041$). Extremely obese patients also had highest rate of rehospitalisation (2.54 hospitalisations/patient-year), which differed significantly from other three groups ($p = 0.014$). In terms of bleeding requiring transfusion, rates were 1.67, 1.40, 1.30 and 1.12 bleeding events per patient-year for same groups respectively ($p < 0.001$). Bleeding was significantly associated with BMI, with underweight patients having highest risk and extremely obese patients having the lowest risk. For bleeding requiring re-exploration, the incidence was 42%, 22%, 25% and 18% in the underweight, normal, obese and extremely obese groups respectively ($p < 0.01$). Incidence of respiratory failure was borderline significant across the four BMI groups ($p = 0.055$), with underweight patients having highest risk (underweight 44%, normal 31%, obese 26%, very obese 38%). No differences were observed in development of cardiac arrhythmias, renal failure, right HF, stroke or haemolysis

Cause of death reported (by group and/or intervention)

Unclear

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

The reported data from the HMII clinical trial suggest both cachectic and obese patients who are appropriately selected and managed can undergo CF LVAD implantation with good intermediate-term results. Extremely obese patients (BMI ≥ 35) can also achieve good outcomes but have a higher risk of infection

Reviewer's conclusion

This was a post-hoc analysis of trial data. The authors did attempt to adjust for factors that might differ across groups. The population looks comparable to other study samples in terms of demographics

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; HR, hazard ratio; INR, international normalised ratio; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; TIA, transient ischaemic attack; WBC, white blood cells.

Cowger 2010[60]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Cowger
Year of publication: 2010
Country: USA
Study design: Retrospective
Study setting: University hospital, UMHS
Number of centres: One
Duration of study: May 2004 and May 2008
Follow-up period: Studies were obtained pre-operatively and at 1, 3, 6, 12, 18 and 24 months after surgery
Funding: National Institutes of Health T32-HL007853

Aim of the study

To examine the temporal trend of AI following LVAD implant and to identify correlates of AI development and progression

Participants

Total number of participants: Echocardiograms ($n = 315$) from 78 subjects undergoing HMXVE [$n = 25$ (32%)] or HMII [$n = 53$ (68%)] implantations
Sample attrition/dropout: All subjects with pre-operative AI of moderate or worse severity undergo intraoperative aortic valve repair, bioprosthetic valve replacement, or patch closure of the aortic valve ($n = 8$) were excluded
Inclusion criteria: Transthoracic or transesophageal echocardiograms from consecutive HMXVE and HMII LVADs implanted at the UMHS between May 2004 and May 2008
Exclusion criteria: Subjects were excluded from the analysis if they did not have a pre-operative echocardiogram plus at least one echocardiogram within 1 year of device placement from which AI could be accurately assessed
Characteristics of participants:
Mean age (SD): Total cohort 54 ± 13; HMII 54 ± 13; HMXVE 52 ± 13
Median age: Not reported
Age range: Not reported
Sex: Male, *n* (%): total cohort 68 (87); HMII 44 (83); HMXVE 24 (96)
Race: Caucasian, *n* (%): total cohort 57 (73); HMII 17 (68); HMXVE 40 (75)
Diagnosis: Not clear

Intervention

Indication for treatment: BTT – 69 (88%) [HMII 54 (90%); HMXVE 21 (84%)]
Type of device used: HMXVE and HMII
Any comparison: HMXVE and HMII
Duration of treatment: Echocardiograms were performed pre-operatively within 30 days of LVAD implant and at approximate intervals of 1, 3, 6, 12, 18 and 24 months post operative or until LVAD explant for any cause
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Temporal trend of AI following LVAD implant and AI development and progression
Secondary outcomes: Device replacement and AI
Method of assessing outcomes: Medical records
Survival: No
Adverse event: Yes
HRQoL: No

Outcomes

Length of follow-up: Echocardiograms were performed pre-operatively within 30 days of LVAD implant and at approximate intervals of 1, 3, 6, 12, 18 and 24 months post operative or until LVAD explant for any cause

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	HMII [*n* = 53 (68%)]	HMXVE [*n* = 25 (32%)]
Excluded	8 participants were excluded from the analysis	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Baseline characteristics and demographics of the total cohort and by LVAD model type (mean ± SD)

Parameter	Total cohort (*n* = 78)	HMXVE (*n* = 25)	HMII (*n* = 53)	*p*-value
Age, years	54 ± 13	52 ± 13	54 ± 13	0.60
Male, *n* (%)	68 (87)	24 (96)	44 (83)	0.16
Caucasian, *n* (%)	57 (73)	17 (68)	40 (75%)	0.41
BSA, m^2	2.0 ± 0.3	2.1 ± 0.2	2.0 ± 0.3	0.36
Diabetes mellitus, *n* (%)	28 (36)	10 (40)	18 (34)	0.62
Hypertension, *n* (%)	34 (44)	10 (40)	24 (45)	0.81
Hyperlipidemia, *n* (%)	52 (67)	15 (60)	37 (70)	0.45
Non-ischaemic HF, *n* (%)	39 (50)	16 (64)	23 (43)	0.14
Pre-operative IABP, *n* (%)	30 (38)	11 (44)	19 (36)	0.62
BTT, *n* (%)	69 (88)	21 (84)	54 (90)	0.46

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

Profile plot of aortic insufficiency for LVAD support subjects are reported

Adverse events reported (by group and/or intervention)

VAD failure = 8 (10%) in the entire cohort, six leading to reoperation

Adverse events reported (by group and/or intervention)

AI grade for the cohort at follow-up. The within-subject change in AI (ΔAI) is also shown

Time	*n*	AI total cohort	ΔAI from baseline	*p*-value[a] ΔAI
Pre operative	78	0.0 [0.0, 0.0]		
1 month	75	0.0 [0.0, 0.5]	0.0 [0.0, 0.5]	< 0.001
3 months	66	0.5 [0.0, 1.0]	0.0 [0.0, 1.0]	< 0.001
6 months	49	1.0 [0.5, 1.5]	0.5 [0.0, 1.0]	< 0.001
12 months	29	1.0 [0.0, 1.5]	1.0 [0.0, 1.0]	< 0.001
18 months	13	2.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.004
24 months	5	2.0 [1.0, 2.0]	1.5 [1.0, 2.0]	0.13

a via Wilcoxon signed-rank tests. Data expressed as median [25th, 75th]; AI was graded: 0 = none, 0.5 = trivial, 1.0 = mild, 1.5 = mild–moderate, 2.0 = moderate, 2.5 = moderate–severe, 3.0 = severe.

Correlates of worsening aortic insufficiency in LVAD supported subjects

Parameter	Change in AI *p*-value, slope ± SE	*p*-value
Age, per 10 years	0.0004 ± 0.002	0.069
Female sex	0.002 ± 0.001	0.010
HMII vs. HMXVE	0.002 ± 0.001	0.039
LVAD flow (l/minute)	0.090 ± 0.044	0.044

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

AI progresses over time in LVAD supported participants. Post-operative progression of AI is likely multifactorial. More studies are needed to determine the clinical significance of these findings

Reviewer's conclusion

This was a single-centre study. There may be potential bias in selection, image interpretation and LVAD management which could impact on AI development and assessment. Caution when interpreting the unadjusted *p*-values. Also failure to apply Bonferroni correction to the multiple comparisons reported

AI, aortic insufficiency; SE, standard error; UMHS, University of Michigan Health System.

Demirozu 2011[61]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Demirozu
Year of publication: 2011
Country: USA
Study design: Retrospective
Study setting: Texas Heart Institute at St. Luke's Episcopal Hospital
Number of centres: One
Duration of study: October 2003 and June 2010
Follow-up period: Unclear
Funding: Not reported

Aim of the study

To identify the prevalence of GI bleeding and the role of AVMs in patients with the CF HMII LVAD

Participants

Total number of participants: 172
Sample attrition/dropout: None
Inclusion criteria: Patients with severe HF associated with compromised systolic left ventricular cardiac function who underwent implantation of a CF HMII LVAD at authors hospital between October 2003 and June 2010
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): GI bleeding group 58 ± 12 years; non-GI bleeding group 49 ± 15 years
Median age: Not reported
Age range: Not reported
Sex: Men/women – GI bleeding group 24/8; non-GI bleeding group 110/30
Race: Not reported
Diagnosis: Ischaemic cardiomyopathy – GI bleeding group 18 (56%); non-GI bleeding group 59 (42%); idiopathic cardiomyopathy – GI bleeding group 14 (44%); non-GI bleeding group 81 (58%)

Intervention

Indication for treatment: CF LVAD support was initiated as therapy for patients with severe HF associated with compromised systolic left ventricular cardiac function
Type of device used: HMII
Any comparison: Two groups – GI bleeding group ($n = 31$) and non-GI bleeding group ($n = 140$)
Duration of treatment: Unclear
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below. Post-operative anticoagulation therapy included aspirin (81 mg/day), dipyridamole (Persantine®, Actavis) (75 mg, three times a day) and warfarin (maintaining an INR of 1.5 to 2.5). A proton pump inhibitor was administered intravenously for peptic ulcer prophylaxis until extubation and then was continued orally
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: GI bleeding
Secondary outcomes: None
Method of assessing outcomes: Medical records
Survival: No
Adverse event: Yes
HRQoL: No
Length of follow-up: Unclear

Number of participants	Intervention	Comparator, if present
Screened	GI bleeding group: $n = 32$	Non-GI bleeding group: $n = 140$
Randomised/included	GI bleeding group: $n = 32$	Non-GI bleeding group: $n = 140$
Excluded	None	None
Missing participants	None	None
Withdrawals	None	None

Outcomes

Patient's baseline characteristics

Demographic and pre-implantation characteristics of patients with and without GI bleeding

Parameter	GI bleeding ($n = 32$)	No GI bleeding ($n = 140$)	p-value
Age (years)	58 ± 12	49 ± 15	0.001
Weight (kg)	81 ± 19	87 ± 21	0.175
BSA (m^2)	1.9 ± 0.3	2.0 ± 0.3	0.234
Men/women	24/8	110/30	0.839
Heart disease			0.211
Ischaemic cardiomyopathy	18 (56)	59 (42)	
Idiopathic cardiomyopathy	14 (44)	81 (58)	
Diabetes mellitus	10 (31)	50 (36)	0.581
Hypertension	21 (66)	72 (51)	0.209
Myocardial infarction	15 (47)	38 (27)	0.049
LVEF (%)	19 ± 4	20 ± 5	0.944
Cardiac index (l/minute/m^2)	1.7 ± 0.3	1.7 ± 0.5	0.224
BUN (mg/dl)	40 ± 29[a]	30 ± 17[a]	0.055
Creatinine (mg/dl)	1.8 ± 1.3	1.3 ± 0.4	0.066
Use of haemodialysis	4 (13)	4 (3)	0.123
Previous cardiac surgery	13 (41)	65 (46)	0.691
HMXVE LVAD implantation	5 (16)	27 (19)	0.819
Pre-implantation support			
IABP	12 (38)	57 (41)	0.893
Tandem heart	1 (3)	18 (13)	0.203
Pre-existing hepatic dysfunction	5 (5)	18 (13)	0.899
Gastric ulcer	4 (4)	11 (8)	0.622

a Normal range 10–26 mg/dl.

Results are presented as mean ± SD or number of patients.

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

Arteriovenous malformations were source of GI bleeding in 10 of 32 (31%) patients; mean duration of LVAD support was 439 ± 315 (range 108–996) days

Average age of 10 AVM patients was 63 ± 7 (range 54–75) years; these patients were significantly older than 162 HMII recipients (mean age 50 ± 15 years, range 14–76 years; $p = 0.0001$)

Eight of the 10 patients with AVMs as cause of bleeding were supported by HMII LVAD at most recent follow-up (mean duration 468 ± 339 days, range 108–996 days). Five of the 10 patients had had recurrent GI bleeding from a different location in each episode: three patients had two episodes of bleeding from a jejunal AVM, and two patients had five episodes of bleeding from a gastric AVM

Adverse events reported (by group and/or intervention)

No thromboembolic events occurred
GI bleeding: 32 (19%); 53 episodes
Upper GI bleeding: 16
Lower GI bleeding: 15
Upper and lower GI bleeding: 1
Compared with 140 patients not having GI bleeding, patients with GI bleeding were significantly older ($p = 0.001$) and had more myocardial infarctions before LVAD implantation ($p = 0.049$)
On multivariate regression analysis, the only significant risk factor was age > 51 years (odds ratio = 2.8, 95% CI 1.1 to 7.3; $p = 0.031$)
The first AVM bleeding episode occurred at an average of 67 (range 17–241) days after device implantation. In 10 patients with bleeding from GI AVMs, 6 had jejuna AVMs and 4 had gastric AVMs. At first GI bleeding episode, mean INR was 1.8 ± 1.0 and mean haemoglobin was 9.0 ± 1.4 g/dl. Two of the 10 patients with AVM bleeding subsequently underwent HT; no GI bleeding occurred after transplantation

Outcomes

Location of GI bleeding in 32 patients after HMII implantation

Location	Number of patients
Upper GI	16
Haemorrhagic gastritis	10
Mallory–Weiss tear	2
Gastric AVM	4
Lower GI	15
Jejuna AVM	6
Diverticulosis	6
Driveline erosion of colon	1
Ischaemic colitis	1
Sigmoid polyp	1
Upper and lower GI	1
Colocutaneous and gastrocutaneous fistula	1

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

AVM-related GI bleeding is a significant but medically manageable complication, the possibility of which should be considered in patients with CF LVADs. The overall incidence of GI bleeding associated with this technology is similar to that associated with other implantable LVADs that require anticoagulation

Reviewer's conclusion

The study provides no information on survival or QoL. The main consideration is that arteriovenous malformations can cause GI bleeding in patients with HMII. Limited statistical analysis was reported

AVM, arteriovenous malformation; BSA, body surface area; BUN, blood urea nitrogen; GI, gastrointestinal; INR, international normalised ratio; LVEF, left ventricular ejection fraction.

Drews 2010[87]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Drews
Year of publication: 2010
Country: Germany
Study design: Retrospective
Study setting: Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin
Number of centres: One
Duration of study: January 1999 and January 2009
Follow-up period: 3 years
Funding: Funding to reproduce the figures in colour was provided by Berlin Heart GmbH

Aim of the study

To find out whether or not pulsatile and non-pulsatile VADs can ensure a low rate of complications for extended periods of time in elderly patients

Participants

Total number of participants: 174 – group A 64; group B 110
Sample attrition/dropout: Not clear
Inclusion criteria: 174 consecutive patients presenting with catecholamine-dependent terminal HF who underwent implantation of a left ventricular MCS system and who were aged > 60 years
Exclusion criteria: Not clear
Characteristics of participants:
Mean age (SD): Group A 65 ± 3; group B: 67 ± 4
Median age: Not reported
Age range, years: Group A 60–73; group B 60–80
Sex (*male/female):* Group A 61/3; group B 98/12
Race: Not reported
Diagnosis: Group A – ischaemic CMP = 33, dilated CMP = 28 and post-cardiotomy syndrome = 3; group B – ischaemic CMP = 50, dilated CMP = 50, acute myocarditis = 2, post-cardiotomy syndrome = 2 and restrictive CMP = 1

Intervention

Indication for treatment: Owing to the shortage of organs available for transplantation, this age is a relative contraindication for HT; therefore, all these patients received the device primarily for permanent support. All devices were implanted primarily for long-term support and not as a BTT
Type of device used: Berlin Heart EXCOR, Novacor, LionHeart, HMI, Berlin Heart INCOR, MicroMed DeBakey, HMII, DuraHeart and Jarvik 2000
Any comparison: Two groups – group A 64 patients who underwent implantation of a first-generation pulsatile system (Berlin Heart EXCOR $n = 39$, Novacor $n = 18$, LionHeart $n = 4$ and HMI3) between January 1994 and October 2008; group B 110 patients with implantation of a second- or third-generation non-pulsatile VAD (Berlin Heart INCOR $n = 65$, MicroMed DeBakey $n = 18$, HMII $n = 14$, DuraHeart $n = 7$ and Jarvik 2000 $n = 6$)
Duration of treatment: Group A were implanted during 1994–2008 and the non-pulsatile devices during 1999–2009
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – Berlin Heart INCOR, MicroMed DeBakey, HMII, DuraHeart and Jarvik 2000

Outcomes

Primary outcomes: Survival
Secondary outcomes: Discharge from hospital, technical complications
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No

Outcomes

Length of follow-up: 3 years

Number of participants	Intervention	Comparator, if present
Screened	943 pulsatile have been implanted in the institution	567 non-pulsatile have been implanted in our institution
Randomised/included	64	110
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Parameter	Group A: pulsatile device	Group B: non-pulsatile device
Patients, *n*	64	110
Age (years)	65 ± 3 (60–73)	67 ± 4 (60–80)
Sex (male/female)	61/3	98/12
Date of implantation	January 1994 to October 2008	January 1999 to January 2009
Heart disease		
Ischaemic CMP	52% (33)	50% (55)
Dilated CMP	44% (28)	45% (50)
Other	4% (3)	5% (5)
Assist device Berlin Heart EXCOR LVAD	61% (39)	
Novacor	28% (18)	
LionHeart	6% (4)	
HMI	5% (3)	
Berlin Heart INCOR		59% (65)
MicroMed DeBakey LVAD		16% (18)
HMII		13% (14)
DuraHeart		7% (7)
Jarvik 2000		5% (6)

Data are presented as mean ± SD (range, minimum–maximum) or % (z).

Survival outcomes reported (by group and/or intervention)

6-month survival rate of pulsatile (group A) was 11% and non-pulsatile (group B) was 42% ($p = 0.0017$)
Differences in survival between the group A and group B:
- The 1-year survival was 15% in group A and 36% in group B
- The 2-year survival was 12% in group A and 26% in group B
- The 3-year survival was 12% in group A and 16% in group B

The difference was significant (log-rank test $p = 0.0017$)
Most deaths occurred during the early post-operative period
In group A 63% of patients died during first 3 months and in group B 42% ($p = 0.0017$). Death was mainly multiorgan failure and infections (significantly more frequent in group A, $p = 0.0036/p = 0.015$). Other reasons included stroke, right ventricular failure and bleeding complications. The rate of stroke, right ventricular failure and bleeding complications did not differ between groups

Other specified/relevant outcomes reported (by group and/or intervention)

Only 17% of patients in group A and 41% in group B could be discharged home ($p = 0.017$)
The mean time to first discharge was 79 ± 38 (33–146) days in group A and 50 ± 33 (9–160) days in group B ($p = 0.007$)
The frequency of rehospitalisation in group A was 2.8 rehospitalisations per patient per year and group B was 3.6 rehospitalisations per patient per year ($p > 0.05$)
Reasons for rehospitalisation were mainly anticoagulation disorders, wound infections and other non-cardiac problems
For group A mean duration of support was 157 ± 343 (1–1836) days (see below); 17 patients (27%) were supported for > 6 months, 7 (11%) for > 1 year; 3 (5%) for > 2 years; and 3 (5%) for > 3 years
For group B patients were on MCS for mean of 281 ± 336 (1–1619) days (significantly longer than group A; $p = 0.0004$); 46 patients (42%) were supported for > 6 months; 34 (28%) for > 1 year; 14 (13%) for > 2 years; and 4 (3.6%) for > 3 years

Duration of support and discharge from hospital

Parameter	Group A: pulsatile device	Group B: non-pulsatile device
Number of patients	64	110
Duration of support, mean (days)	157 ± 343 (1–1836)[a]	281 ± 336 (1–1619)[a]
> 6 months	27% (17)	42% (46)
> 1 year	11% (7)	28% (34)
> 2 years	5% (3)	13% (14)
> 3 years	5% (3)	3.6% (4)
Discharge from hospital		
Number of patients	17% (11)[b]	41% (45)[b]
Mean (days)	632 ± 635 (7–1688)	442 ± 344 (7–1487)
> 6 months	13% (8)	31% (34)
> 1 year	11% (7)	19% (21)
> 2 years	6% (4)	10% (11)
> 3 years	5% (3)	2% (2)
Time to first discharge (days)	79 ± 38 (33–146)[c]	50 ± 33 (9–160)[c]
Rehospitalisation (patient/year)	2.8 ×	3.6 ×

a $p = 0.00043$.
b $p = 0.0173$.
c $p = 0.007$.
Data are presented as mean ± SD (range, minimum–maximum) or % (z).

Adverse events reported (by group and/or intervention)

Technical complications were observed in group B only ($p = 0.0175$), see below. Pump thrombosis occurred in five patients (MicroMed DeBakey LVAD $n = 4$; Jarvik 2000 $n = 1$) and 3 patients had pump-stop due to technical failure (MicroMed DeBakey, Berlin Heart INCOR) and due to pannus on inflow cannula (DuraHeart); two patients had bearing problems (Berlin Heart INCOR); one patient had a broken driveline; five patients pump exchange could be performed; two patients died; and four patients underwent a successful HT

Adverse events reported (by group and/or intervention)

Technical complications and outcome

Parameter	Group A: pulsatile device	Group B: non-pulsatile device
Number of patients	64	110
Technical complications		
Device failure	Not reported	2% (2)
Pump thrombosis	Not reported	4.5% (5)
Inflow-thrombosis	Not reported	1% (1)
Bearing problem	Not reported	2% (2)
Driveline broken	Not reported	1% (1)
Total	0[a]	10% (11)[a]
Pump exchange	Not reported	5% (5)
Outcome		
On device	5% (3)	15% (17)
Transplanted	5% (3)	8% (9)
Weaned	5% (3)	3% (3)

a $p = 0.0175$.
Data are presented as mean ± SD (range, minimum–maximum) or % (z).

Cause of death reported (by group and/or intervention)

Overall, 88 patients had dilated CMP, 78 patients had ischaemic CMP and 8 patients had other heart diseases leading to device implantation. For patients with CMP ($n = 88$): 59 died, 6 were transplanted and 4 were still on the device. For patients with ischaemic CMP: 72 died, 5 were transplanted, 2 were weaned and 9 are still on support. For patients with other heart diseases: 5 died and 2 were weaned. Outcome in relation to differences in aetiology were not significant

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Although pulsatile (Berlin Heart EXCOR, Novacor, LionHeart and HMI) and non-pulsatile VADs (Berlin Heart INCOR, MicroMed DeBakey, HMII, DuraHeart and Jarvik2000) can be used for extended periods of time, non-pulsatile systems resulted in significantly higher survival rate in elderly patients. The authors suggested that this may allow elderly patients additional years of life in their familiar environment. The authors recognised that a limitation of the study was that the pulsatile devices in group A were implanted during an earlier period (1994–2008) and the non-pulsatile devices between 1999 and 2009. Therefore, improved understanding during recent years in the care of these elderly patients on MCS may have contributed to the better results in the non-pulsatile device group

Reviewer's conclusion

All devices were implanted primarily for long-term support and not as a BTT. Devices were implanted during different time periods. Cox proportional hazards were not reported. Caution when interpreting the findings related to survival

CMP, cardiomyopathy; MCS, mechanical circulatory support.

Goldstein 2003[84]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Goldstein
Year of publication: 2003
Country: Europe (Germany, Austria, France, Switzerland and Italy) and USA (Texas, Cleveland and Newark)
Study design: Prospective single arm study
Study setting: Multicentre
Number of centres: Europe (11 centres) and USA (3 centres)
Duration of study: Unclear
Follow-up period: Unclear
Funding: Unclear

Aim of the study

To explore if second-generation VAD, MicroMed DeBakey, can overcome the shortcomings of pulsatile first-generation pumps such as applicability to small patients, noise, and high incidence of infection and pump malfunction

Participants

Total number of participants: 150
Sample attrition/dropout: None
Inclusion criteria: All patients in the US groups ($n = 24$, 3 centres) and in the European groups ($n = 126$, 11 centres) underwent implantation of the MicroMed VAD with the intention of BTT as part of a clinical trial between 13 November 1998 and 7 July 2002
Exclusion criteria: Post-cardiotomy cardiac failure, cardiogenic shock due to acute myocardial infarction of < 48 hours duration, as well as any criteria that contraindicated future cardiac transplantation
Characteristics of participants:
Mean age (SD): 48 ± 14 years
Age range: 12–73 years
Sex: 18% ($n = 27$) were female
Race: Not reported
Diagnosis: The most common aetiology of HF was ischaemic, followed by dilated cardiomyopathy

Intervention

Indication for treatment: BTT
Type of device used: MicroMed DeBakey VAD
Any comparison: 103 patients who had complete data were divided into two groups according to BSA. Outcomes such as mean pump speed, mean pump flow and indices of renal (BUN and creatinine) and hepatic (total bilirubin) function for duration of support were extracted from each patient's datasheet and comparisons were made between small (BSA < 1.9 m^2) and large (BSA ≥ 1.9 m^2) patients
Duration of treatment: Unclear, the authors stated given that the longest support time was 441 days
Percentage of patients using inotropes: 40% of patients were on at least two inotropes
Other interventions used: Unclear
Any FDA or CE approval: Yes – MicroMed DeBakey VAD

Outcomes

Primary outcomes: Adverse events and outcome of the support (BTT, death, ongoing support, recovery)
Secondary outcomes: Not clear
Method of assessing outcomes: Medical records – haemolysis defined as plasma–free haemoglobin > 40 mg/dl. Thromboembolic event is a composite of embolic stroke, TIA and peripheral embolism
Survival: No
Adverse event: Yes
HRQoL: No
Length of follow-up: Longest support time was 441 days. Cumulative support time was 30.4 patient-years. Twelve patients (8%) have been supported for at least 6 months

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Unclear	Not applicable
Randomised/included	150	Not applicable
Excluded	47 patients from the subgroup analysis	Not applicable
Missing participants	Not reported	Not applicable
Withdrawals	Not reported	Not applicable
Patient's baseline characteristics		
Age, years	48 ± 14 years (range 12–73)	Not applicable
Sex	18% ($n = 27$) were female	Not applicable
BSA (m^2)	Range 1.4–2.34	Not applicable
Weight (kg), BMI	Not reported	Not applicable
Ischaemic causes of HF	No data. However, the paper reports that most common aetiology of HF was ischaemic, followed by dilated cardiomyopathy	Not applicable

A baseline characteristics table was not presented. All patients in the US groups ($n = 24$, 3 centres) and in the European groups ($n = 126$, 11 centres) underwent implantation of the MicroMed VAD with intention of BTT as part of a clinical trial. Demographic, adverse event and outcome data were collected for each participant in case report forms

Survival outcomes reported (by group and/or intervention)

Linearisation and hazard function analysis were performed to calculate the incidence of adverse events. *t*-tests were used for comparison of means and a two-tailed probability value < 0.05 was considered significant

Outcomes of 150 patients receiving the MicroMed DeBakey VAD as a BTT

Outcome	Europe	USA	Carmeda[a]	Total
BTT	41	16	5	62
Died	45	8	15	68
Ongoing	1	0	18	19
BTR	1	0	0	1
Total	88	24	38	150

a Pumps with covalently coated heparin, recently available.

Other specified/relevant outcomes reported (by group and/or intervention)

Survival outcomes reported (by group and/or intervention)

Comparison of pump speed, flow and end-organ function between smaller (BSA < 1.9) and larger (BSA ≥ 1.9) patients

	BSA		
Parameter	< 1.9 m² (*n* = 46)	~ 1.9 m² (*n* = 57)	*p*-value
Mean BSA (m²)	1.7 ± 0.1	2.0 ± 0.1	< 0.05
Range BSA (m²)	1.4–1.89	1.9–2.34	
Mean pump speed (RPM)	9500 ± 600	9700 ± 400	0.08
Mean pump flow (l/minute)	4.2 ± 0.9	4.8 ± 0.9	0.005
Mean BUN	26 ± 42	38 ± 31	0.57
Mean serum creatinine (mg/dl)	1.0 ± 0.5	1.4 ± 0.5	0.14
Mean total bilirubin (mg/dl)	2.8 ± 5.3	2.4 ± 2.0	0.009

All figures are average values for duration of MicroMed VAD support.

Adverse events reported (by group and/or intervention)

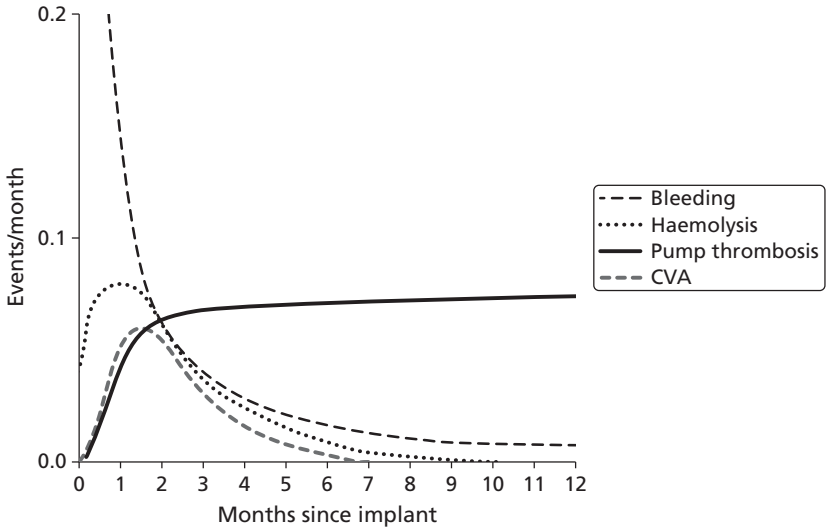
Reoperation for bleeding was most common complication following VAD placement
Low incidence of device-related infection and pump failure
Infections were all related to the driveline site as no real preperitoneal pocket exists
The causes of mechanical failure were: recessed connector pin (*n* = 2); broken wire (*n* = 1); controller failure (*n* = 1)
17 cases of pump thrombus, 11 (64%) cases had a successful resolution with transplantation, pump exchange or thrombolysis
No strokes associated with pump thrombus
Two patients haemolysis was association with pump thrombus
BTT was successful in nearly 50% of patients (European series) and 66% of patients (US cohort)
No statistically significant difference was present with regard to pump speed, larger patients had statistically significant higher pump flows. Renal function did not differ significantly between smaller and larger patients but larger patients had lower total bilirubin levels. Patients with larger BSAs had higher pump output

Incidence and linearised rate of adverse events following MicroMed DeBakey VAD replacement

Adverse event	Incidence	Rate/patient-year
Reoperation for bleeding	32.0% (48/150)	2.03
Haemolysis[a]	12.0% (18/150)	0.61
Device infection	3.3% (5/150)	0.16
Thromboembolic event[b]	10.7% (16/150)	0.61
Pump thrombus	11.3% (17/150)	0.61
Mechanical failure	2.7% (4/150)	0.13

a Defined as plasma-free haemoglobin > 40 mg/dl.
b Composite of embolic stroke, TIA and peripheral embolism.

Adverse events reported (by group and/or intervention)



Hazard analysis depicting varying incidence over time of four major adverse events[a]

Cause of death reported (by group and/or intervention)

Unclear

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

MicroMed DeBakey VAD is promising and supports continued evaluation of axial flow pumps for long-term support. Low incidence of pump failure and infection and pumps are applicable to many patient sizes. The patients appreciate the easy mobility and quiet operation and outpatient support is possible. Incidence of pump thrombus and thromboembolism is being examined through heparin coating to all device surfaces. Many challenges including elucidation of pathogenesis of pump thrombus, its prevention and treatment, as well as better patient selection and development of a physiologically responsive controller remain

Reviewer's conclusion

Did not clearly report the patient baseline characteristics

BSA, body surface area; BUN, blood urea nitrogen; RPM, revolutions per minute; TIA, transient ischaemic attack.

a Stroke (thick dashed line), reoperation for bleeding (dashed descending line), pump thrombus (solid line) and haemolysis (dotted line); adapted from Goldstein 2003.[84]

Hasin 2012[62]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Hasin
Year of publication: 2012
Country: USA (Rochester, MN)
Study design: Retrospective
Study setting: Mayo Clinic (University hospital)
Number of centres: Single centre
Duration of study: February 2007 to June 2010
Follow-up period: 6 months
Funding: Unclear

Aim of the study

To evaluate the effects of LVAD support on renal function in our cohort of BTT and DT patients implanted with CF HMII devices and to identify pre-operative predictors for improved renal function within this population

Participants

Total number of participants: 83
Sample attrition/dropout: None
Inclusion criteria: Patients implanted with HMII CF devices ($n = 83$) from February 2007 to June 2010 in a single centre were followed. Included both BTT and DT patients
Exclusion criteria: 20 patients with other devices (8 with Jarvik 2000, 6 with VentrAssist and 6 with HMXVE were excluded from analysis)
Characteristics of participants:
Mean age (SD): All patients 63.0 ± 12.3 years; GFR < 60 ml/minute/1.73 m^2 65.9 ± 8.8 years; GFR > 60 ml/minute/1.73 m^2: 57.7 ± 15.8 years
Median age: Not reported
Age range: Not reported
Sex: Male – all patients 68/83 (81%); GFR < 60 ml/minute/1.73 m^2 41/54 (76%); GFR > 60 ml/minute/1.73 m^2 27/29 (93%)
Race: Not reported
Diagnosis: Ischaemic aetiology – all patients 46/83 (55%); GFR < 60 ml/minute/1.73 m^2 30/54 (56%); GFR > 60 ml/minute/1.73 m^2 16/29 (55%)

Intervention

Indication for treatment: BTT – all patients 27/83 (32%); GFR < 60 ml/minute/1.73 m^2 15/54 (28%); GFR > 60 ml/minute/1.73 m^2 12/29 (41%)
Type of device used: HMII
Any comparison: Two groups – GFR < 60 ml/minute/1.73 m^2 and GFR > 60 ml/minute/1.73 m^2: 12/29 (41%)
Duration of treatment: Unclear
Percentage of patients using inotropes: 59/83 (71%)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Renal function; predictors of RD
Secondary outcomes: Not relevant
Method of assessing outcomes: Medical records – renal function was assessed at admission for LVAD implantation (determined as baseline renal function), the morning before LVAD implantation, and 1 month (range 14–46 days), 3 months (range 56–120 days) and 6 months (range 150–240 days) after implantation during routine follow-up visits. Stages of RD were determined according to calculated GFR in accordance with established guidelines. A GFR cut-off of > 60 ml/minute/1.73 m^2 was used to differentiate mild or normal renal function from more severe RD. Patients requiring haemodialysis were considered in stage 5 (GFR 15 ml/minute/1.73 m^2). As the actual GFRs in these patients were undetermined, they were considered missing for analysis requiring numerical GFR measurement
Survival: Yes
Adverse event: No. Eight patients developed ARF. In addition, it is reported that 'all patients had significant post-operative complications, including right ventricular dysfunction, infections, bleeding, and need for prolonged inotropic support'.
No data given
HRQoL: No

Outcomes		
Length of follow-up: Unclear		
Number of participants	**Intervention**	**Comparator, if present**
Screened	103	
Randomised/included	83; 80% of adult LVAD implantations	
Excluded	20 patients with other devices (8 with Jarvik 2000, 6 with VentrAssist and 6 with HMXVE were excluded from analysis	
Missing participants	None	
Withdrawals	None	

Patient's baseline characteristics

Demographic characteristics of patients needing chronic dialysis after LVAD implantation

Patient no.	Age (years)	Sex	Medical history	Transplantation candidacy	Small kidney (< 10 cm)	NYHA functional class	Rhythm	LM Score
1	59	Female	HTN, CKD (CVVHD), severe lung disease	BTT	Yes	IV	AF	13
2	62	Male	CKD s/p transplantation, (Fabry), lung disease, s/p TVR	BTT	NA	IIIb	AF	21
3	74	Male	HTN, CKD, IHD	DT	No	IIIb	AF	22
4	61	Male	HTN, DM	DT	No	IV	Sinus	6
5	67	Male	Complex congenital heart disease, recurrent VT, CKD (CVVHD)	BTT	No	IV	Sinus	24
6	73	Male	s/p B-cell lymphoma, s/p CABG, DM, CKD, on continuous milrinone infusion (4 years)	DT	No	IV	AF	4
7	45	Female	Recent mitral repair + Maze procedure, shock, acute renal	BTT	No	IV	AF	20
8	48	Male	Recent mitral repair + Maze procedure, shock, acute renal	BTT	No	III	Paced	10

Outcomes

Baseline characteristics

Characteristic	All patients ($n = 83$)	GFR < 60 ml/minute/1.73 m^2 ($n = 54$)	GFR ≥ 60 ml/minute/1.73 m^2 ($n = 29$)	*p*-value
Demographic				
Age (years)	63.0 ± 12.3	65.9 ± 8.8	57.7 ± 15.8	0.020
Men	68/83 (81%)	41/54 (76%)	27/29 (93%)	0.053
HTN	31/83 (37%)	20/54 (37%)	11/29 (38%)	0.936
HM	24/83 (29%)	19/54 (35%)	5/29 (17%)	0.086
CKD	45/83 (54%)	41/54 (76%)	4/29 (14%)	< 0.001
Ischaemic aetiology	46/83 (55%)	30/54 (56%)	16/29 (55%)	0.973
BTT	27/83 (32%)	15/54 (28%)	12/29 (41%)	0.207
Clinical				
GFR (ml/minute/1.73 m^2)	53.2 ± 21.4	40.5 ± 12.3	76.8 ± 12.7	< 0.001
Pre-operative GFR	64.5 ± 22.5	55.4 ± 18.2	81.3 ± 20.2	< 0.001
Admission to operation time (days)	9.4 ± 9.3 ($n = 83$)	10.8 ± 10.2 ($n = 54$)	6.8 ± 6.6 ($n = 29$)	0.039
BMI (kg/m^2)	28.9 ± 5.6	28.8 ± 5.8	29.2 ± 5.3	0.782
NYHA class IV	50/81 (62%)	31/52 (60%)	19/29 (66%)	0.577
Prior sternotomy	42/83 (51%)	28/54 (52%)	14/29 (48%)	0.756
AF	14/83 (17%)	8/54 (15%)	16/29 (21%)	0.500
Kidney length (cm)				
Left	11.7 ± 1.2	11.5 ± 1.2	11.9 ± 1.3	0.287
Right	11.5 ± 1.1	11.5 ± 1.1	11.5 ± 1.3	0.868
Pre-operative IABP use	28/83 (37%)	20/54 (37%)	8/29 (28%)	0.385
Need for inotropes	59/83 (71%)	41/54 (76%)	18/29 (62%)	0.184
ACE inhibitors or ARBs	54/78 (69%)	34/51 (67%)	20/29 (69%)	0.585
Spironolactone	43/81 (53%)	29/53 (55%)	14/28 (50%)	0.686
Beta-blockers	68/81 (84%)	44/53 (83%)	24/28 (86%)	0.753
Loop diuretic agents	69/75 (92%)	44/48 (92%)	25/27 (93%)	0.887
Digoxin	43/75 (57%)	28/48 (58%)	15/27 (56%)	0.815
Urine protein (mg/dl)	7 (4–23) ($n = 71$)	7 (4–30) ($n = 45$)	7 (4–18) ($n = 26$)	0.756
Haemoglobin (g/dl)	11.9 ± 1.9	11.7 ± 2.0	12.4 ± 1.7	0.100
Platelet count (× 1000)	175.6 ± 70.0	167.1 ± 61.0	191.0 ± 83.0	0.286
Bilirubin (mg/dl)	1.2 ± 0.7	1.2 ± 0.7	1.4 ± 0.8	0.171
NT-pro-BNP (pg/ml)	6004 ± 5812 ($n = 47$)	7521 ± 6578 ($n = 29$)	3559 ± 3143 ($n = 18$)	0.014
Albumin (g/dl)	3.8 ± 0.6	3.7 ± 0.5	3.8 ± 0.7	0.486
BUN (mg/dl)	31.6 ± 16.8	35.2 ± 17.6	25.0 ± 12.9	0.005
Creatinine (mg/dl)	1.6 ± 0.7	1.9 ± 0.7	1.1 ± 0.2	< 0.001
LM score	9.6 ± 6.0	10.3 ± 6.0	8.6 ± 5.7	0.156
VO_2 max. (% predicted)	39.4 ± 11.3 ($n = 42$)	39.6 ± 8.5 ($n = 25$)	39.1 ± 11.8 ($n = 17$)	0.885

Outcomes

Characteristic	All patients ($n = 83$)	GFR < 60 ml/minute/1.73 m² ($n = 54$)	GFR ≥ 60 ml/minute/1.73 m² ($n = 29$)	p-value
Pre-operative echocardiography				
Left ventricular diastolic diameter (mm)	67.2 ± 9.5 ($n = 82$)	67.9 ± 9.4 ($n = 53$)	66.0 ± 9.6	0.379
Ejection fraction (%)	19.8 ± 8.6 ($n = 83$)	19.2 ± 6.3 ($n = 54$)	20.9 ± 11.7 ($n = 29$)	0.908
RIMP	0.6 ± 0.2 ($n = 75$)	0.6 ± 0.2 ($n = 48$)	0.5 ± 0.3 ($n = 27$)	0.440
RV dysfunction more than moderate	54/81 (67%)	40/52 (77%)	14/29 (48%)	0.009
Pre-operative catheterisation				
Mean right atrial pressure (mmHg)	15.4 ± 6.7 ($n = 80$)	15.9 ± 6.5 ($n = 52$)	14.5 ± 7.2 ($n = 28$)	0.388
Mean pulmonary pressure (mmHg)	36.1 ± 9.3 ($n = 80$)	36.8 ± 9.0 ($n = 52$)	34.8 ± 9.9 ($n = 28$)	0.350
RVSWI (g/m²/beat)	7.1 ± 3.9 ($n = 74$)	7.0 ± 3.7 ($n = 49$)	7.3 ± 4.3 ($n = 27$)	0.776
Mean wedge pressure (mmHg)	23.5 ± 6.9 ($n = 77$)	24.6 ± 6.6 ($n = 50$)	21.4 ± 7.1 ($n = 27$)	0.049
Cardiac index (l/minute/m²)	1.9 ± 0.5 ($n = 78$)	1.9 ± 0.6 ($n = 50$)	2.1 ± 0.5 ($n = 28$)	0.073
Operation				
Bypass time (minutes)	103.6 ± 33.7 ($n = 82$)	105.6 ± 32.9 ($n = 54$)	99.8 ± 35.5 ($n = 28$)	0.350
Duration of hospitalisation (days)	21.4 ± 13.3 ($n = 75$)	22.2 ± 14.2 ($n = 47$)	20.1 ± 11.8 ($n = 28$)	0.576

Values are mean ± SD or *n*/*N* (%).

The above table depicts baseline characteristics of 83 patients implanted with HMII LVADs and of the subgroups of patients with baseline GFRs < 60 or > 60 ml/minute/1.73 m²
All comparisons are between patients with baseline GFR < 60 and > 60 ml/minute/1.73 m²
At baseline the mean age was 63 ± 12 years, and majority of patients were men (82%). Majority of LVADs (70%) were DT, and approximately half had ischaemic aetiology
Main reason for DT was older age (median 70 years vs. 55 years for BTT patients; $p < 0.0001$)
Compared with patients with preserved renal function (GFR ml/minute/1.73 m²), those with low baseline GFRs were significantly older, with more CKD and longer pre-operative hospital stays

Outcomes

Pre-operative clinical characteristics of patients needing chronic dialysis after LVAD implantation

Patient no.	GFR (ml/minute/1.73 m^2)	Pre-operative GFR improvement	Hb (mg)	Albumin (g%)	IABP	TR	MR	RVSWI	RAP (mmHg)	Wedge pressure (mmHg)
1	24	+24	9.2	3.1	No	Severe	Moderate to severe	5	25	21
2	20	+10	11.2	2.8		Severe	Moderate	1.3	12	22
3	39	+17	10.2	3.3	No	Mod	None	11.7	11	19
4	38	+0	9.8	3.8	Yes	Mod	None	1.9	34	32
5	32	−13	11.1	3.3	Yes	None	None	NA	NA	NA
6	40	+18	12.4	3.5	Yes	Mod	Mild	5.1	23	27
7	41	+43	9.8	3.3	Yes	Severe	None	2.4	20	25
8	76	+0	10.9	NA	Yes	Mod	Mild	1.4	35	35

Survival outcomes reported (by group and/or intervention)

Of the 51 patients with GFRs < 60 ml/minute/1.73 m^2 before LVAD surviving at 1 month, 34 (67%) improved to GFRs > 60 ml/minute/1.73 m^2. Univariate pre-operative predictors for improvement in renal function at 1 month included younger age ($p = 0.049$), GFR improvement with optimal medical therapy ($p < 0.001$), IABP use ($p = 0.004$), kidney length > 10 cm ($p = 0.023$), no treatment with ACE inhibitors or ARBs ($p = 0.029$), higher bilirubin ($p = 0.002$), higher LM score ($p = 0.019$) and AF ($p = 0.007$). Multivariate analysis indicated pre-operative improved GFR (slope = 0.5 U/unit improved, 95% CI 0.2 to 0.8; $p = 0.003$), AF (slope = 27, 95% CI 8 to 46; $p = 0.006$) and IABP use (slope = 14, 95% CI 2 to 26; $p = 0.02$) as independent predictors

Post-operative characteristics of patients who succumbed to chronic need for haemodialysis

Patient number	Complications	Duration of inotropic support	Hospital stay	Late outcome
1	GI bleeding, pneumonia, prolonged intubation, RV dysfunction, MR (moderate), continued need for dialysis	160	65 days	Died (sepsis) 2.5 years after implantation
2	Early RV failure, sepsis, prolonged intubation, VT	1032	Death 76 days	In-hospital death
3	Early HMXVE failure, emergent HMII implantation, mediastinitis, RV dysfunction	446	28 days	Withdrew support 1.5 years after implantation
4	Early RV failure, prolonged intubation, sepsis, RV dysfunction	504	52 days	Recovered renal function 6 months after implantation
5	Early RV failure, prolonged intubation, recurrent VT encephalopathy, sepsis, ileus, hyperbilirubinemia	1488	Death 37 days	In-hospital death
6	Delayed chest closure, prolonged intubation, encephalopathy, biliary sepsis	1056	Death 44 days	In-hospital death
7	Early RV failure, delayed chest closure, prolonged ventilation	1320	61 days	Recovered renal function 45 days after implantation
8	Chest reopening for severe bleeding, shock	168	Death 7 days	In-hospital death

Other specified/relevant outcomes reported (by group and/or intervention)

Overall, GFR significantly improved 1 month after LVAD implantation (from 53.2 ± 21.4 to 87.4 ± 27.9 ml/minute/1.73 m^2; $p < 0.0001$). GFR partially declined at 3 months in 41 of 66 patients with GFR estimates at both time points (77.6 ± 22.8 ml/minute/1.73 m^2; $p = 0.0001$, compared with 1 month). Between 3 and 6 months, GFR further declined in 36 of 55 patients (71.2 ± 21.0 ml/minute/1.73 m^2; $p = 0.0032$, compared with 3 months). Only six patients had continuous GFR improvements without any decline over the study period (67 had some decline or no recovery of RD, and data were missing for 10 patients)
Overall, GFR remained significantly higher at 6 months compared with pre-operative GFR ($p < 0.0001$)
Eight patients (10%) developed ARF after LVAD implantation necessitating acute haemodialysis. Two died in the early post-operative period, and two recovered renal function. Four patients (5%) continued with chronic haemodialysis
The subset with pre-operative RD had a significant increase at 1 month ($p < 0.0001$), a partial decline (1–3 months, $p = 0.0059$; 3–6 months, $p = 0.0258$), and overall improvement > 6 months ($p < 0.0001$)
For patients with available renal staging at 1 month, 57 patients (72%) improved their RD stages or remained at stage 1
14 patients (18%) remained in their pre-operative renal stages (10 in stage 2, 4 in stage 3), and 8 (10%) deteriorated (2 from stages 4–5, 5 from stages 3–5, and 1 from stages 2–3)

Renal dysfunction stage distribution – all patients

	Baseline		1 month		3 months		6 months	
Renal dysfunction stage (GFR range)	*n*	%	*n*	%	*n*	%	*n*	%
Stage 1 (> 90)	5	6	32	38	15	18	8	10
Stage 2 (60–90)	24	29	29	35	35	42	31	37
Stage 3 (30–60)	42	51	11	13	15	18	18	22
Stage 4 (15–30)	11	13	0	0	1	1	0	0
Stage 5 (< 15)	1	1	7	8	3	4	3	4
Missing	0	0	4	5	14	17	23	28

Renal dysfunction stage distribution – subset with stage 3 at baseline

	Baseline		1 month		3 months		6 months	
Renal dysfunction stage (GFR range)	*n*	%	*n*	%	*n*	%	*n*	%
Stage 1 (> 90)	0	0	13	31	4	10	3	7
Stage 2 (60–90)	0	0	18	43	22	52	17	40
Stage 3 (30–60)	42	100	4	10	7	17	8	19
Stage 4 (15–30)	0	0	0	0	0	0	0	0
Stage 5 (< 15)	0	0	5	12	2	5	2	5
Missing	0	0	2	5	7	17	12	29

Other specified/relevant outcomes reported (by group and/or intervention)

Univariate linear regression analysis for prediction of increase in GFR 1 month after LVAD implantation

Parameter	*n*	Parameter estimate	95% CI	*p*-value
General				
Age	44	−0.8	−1.6 to 0.0	0.049
Male[a]	44	4.2	−12.8 to 21.1	0.630
HTN[a]	44	−0.4	−15.1 to 14.2	0.954
DM[a]	44	−0.6	−15.4 to 14.2	0.936
CKD[a]	44	−11.5	−27.1 to 4.1	0.151
BTT[a]	44	9.1	−6.6 to 24.9	0.256
Ischaemic aetiology[a]	44	4.5	−10.1 to 19.0	0.549
Weight	44	−0.2	−0.6 to 0.2	0.300
BSA	44	−18.1	−46.0 to 9.8	0.204
Diastolic BP	44	−0.2	−1.2 to 0.5	0.474
Systolic BP	44	−0.2	−0.7 to 0.3	0.413
Heart rate	44	0.0	−0.5 to 0.5	0.974
AF[a]	44	31.8	8.8 to 54.7	0.007
NYHA class IV[a]	44	10.0	−4.1 to 24.1	0.163
Small kidney (< 10 cm)[a]	40	−24.7	−46.0 to −3.5	0.023
VO_2 max. (% predicted)	20	0.6	−0.5 to 1.7	0.294
GFR increase, admission to pre-operative	44	0.6	0.3 to 0.9	< 0.001
Scores				
LM score	44	1.6	0.2 to 2.9	0.019
Matthews score	44	2.4	−0.4 to 5.2	0.091
Kormos score	41	3.5	−1.2 to 8.2	0.149
Treatment before surgery				
IABP used[a]	44	20.5	6.7 to 34.2	0.004
Inotropes[a]	43	−2.8	−20.1 to 14.4	0.745
ACE inhibitors or ARBs[a]	44	−15.5	−29.4 to −1.6	0.029
Beta-blockers[a]	44	−5.4	−23.9 to 13.0	0.562
Aldosterone inhibitors[a]	44	5.6	−8.5 to 19.8	0.435
Diuretic agents[a]	40	−14.4	−39.4 to 10.6	0.258
Amiodarone[a]	40	−6.9	−22.8 to 8.9	0.390
ICD/CRT[a]	40	−4.7	−20.0 to 10.7	0.550
Digoxin[a]	40	−8.1	−23.6 to 7.4	0.307
Statins[a]	40	7.0	−9.5 to 23.5	0.404
Laboratory results				
Urine protein	36	0.1	−0.1 to 0.3	0.466
GFR on admission	44	−0.1	−0.7 to 0.4	0.626
Haemoglobin	44	−0.5	−4.0 to 3.0	0.779
Bilirubin	44	14.6	5.6 to 23.7	0.002

Other specified/relevant outcomes reported (by group and/or intervention)

Parameter	*n*	Parameter estimate	95% CI	*p*-value
AST	44	0.0	0.0 to 0.1	0.193
ALT	41	0.0	0.0 to 0.0	0.157
LDH	37	0.0	0.0 to 0.0	0.210
BNP	25	0.0	0.0 to 0.0	0.768
Platelets	44	0.0	–0.1 to 0.1	0.943
BUN	44	0.0	–0.4 to 0.4	0.975
Albumin	43	–13.2	–28.1 to 1.7	0.082
Echocardiography				
RIMP	39	–3.2	–38.5 to 32.2	0.861
TR time (corrected)	42	–0.1	–0.2 to 0.0	0.174
LVEDD	44	–0.4	–1.3 to 0.4	0.320
Mitral E-wave	39	5.3	–17.7 to 28.2	0.653
LA volume index	43	–0.1	–0.5 to 0.4	0.794
EF	44	–0.2	–1.4 to 0.9	0.684
LV mass	34	0.0	–0.1 to 0.0	0.130
TR (more than moderate)	44	–0.5	–14.8 to 13.7	0.941
AR (more than moderate)	44	–7.1	–35.3 to 21.1	0.623
MR (more than moderate)	44	3.5	–10.9 to 17.8	0.633
Catheterisation				
Stroke volume index	42	–0.2	–0.9 to 0.6	0.682
RVSWI	42	–0.7	–2.8 to 1.5	0.537
Cardiac index	42	–2.7	–16.7 to 11.3	0.704
SVR	31	–0.6	–1.5 to 0.4	0.242
PVR	42	–0.4	–2.7 to 2.0	0.757
RA pressure (mean)	43	0.7	–0.5 to 2.0	0.262
Wedge pressure (mean)	41	–0.4	–1.5 to 0.7	0.452
PA pressure (mean)	43	0.1	–0.7 to 0.9	0.821
Surgery and pump settings				
Bypass time	44	0.0	–0.2 to 0.2	0.928
Discharge pump flow	43	0.5	–9.5 to 10.5	0.920
Discharge LVAD pulsatility index	42	12.6	0.5 to 24.8	0.042
Discharge pump speed (200 RPM)	42	7.4	1.8 to 13.0	0.009
Discharge pump speed > 9200 RPM[a]	42	22.0	6.9 to 37.2	0.004

a Categorical predictors were assessed using one-way analysis of variance.

Table shows the results of a univariate linear regression analysis for prediction of increase in GFR 1 month after LVAD implantation. GFR was evaluated as a continuous variable. Authors estimated associations of various pre-operative variables with increased GFR (operative time and LVAD settings were also included). Estimates were calculated depicting the change in mean GFR associated with the variable measured before and 1 month after operation. Estimates for continuous variables are for change in mean per unit increase in evaluated variable.

TR time was corrected for pulse; RIMP = (TR time – RV ejection time)/RV ejection time; RVSWI = [0.0136 × (MPAP – RAP) × stroke volume index]; kidney size was assessed by pre-operative abdominal ultrasound.

Other specified/relevant outcomes reported (by group and/or intervention)

Predictors of improved GFR 1 month after LVAD implantation. Authors used a univariate model for predicting an increase in GFR for 72 patients with available GFR measurements at 1 month. Five significant positive predictors associated with GFR improvement were: (1) use of an IABP before surgery (slope = 17; $p = 0.003$); (2) higher bilirubin (slope = 12.1; $p = 0.002$); (3) alanine transaminase (slope = 0.03; $p = 0.041$); (4) LM score (slope = 1.5; $p = 0.003$); and (5) higher right atrial pressure (slope = 0.97; $p = 0.048$)

An increase in GFR with optimal medical treatment before surgery was associated with further improvement 1 month after surgery (slope = 0.6/ml/minute/1.73 m^2; $p < 0.001$). Higher pump speed at discharge (slope = 5.9/200 RPM increase; $p = 0.01$) was also associated with improved GFR. Negative predictors were: (1) having at least one kidney < 10 cm on ultrasound (slope = –23.7; $p = 0.01$); and (2) treatment with an angiotensin pathway inhibitor before surgery (slope = –15.7; $p = 0.006$)

Multivariate model suggested that LM score (slope = 1.2/unit increase, 95% CI 0.25 to 2.11; $p = 0.013$) having at least one kidney < 10 cm (slope = –21, 95% CI –37.7 to –4.6; $p = 0.012$), and use of an IABP (slope = 11.8, 95% CI 0.8 to 22.8; $p = 0.035$) and were independent predictors

Adverse events reported (by group and/or intervention)

Unclear

Cause of death reported (by group and/or intervention)

See above

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

For most patients with end-stage HF considered for LVAD, RD appears to be reversible. The present study found that ARF after LVAD was less common than previously reported and is related with a complicated post-operative course. Prediction of post-operative improvement in RD should consider the contribution of renal hypo-perfusion and congestion, irreversible renal injury and response to medical treatment pre implant

Reviewer's conclusion

GFR estimates later in the post-implantation course might be biased to healthier patients. No consideration of QoL measures

AF, atrial fibrillation; ALT, alanine aminotransferase; ARF, acute renal failure; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CVVHD, continuous venovenous haemodialysis; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IHD, ischaemic heart disease; LA, left atrial; LDH, lactate dehydrogenase; LM, Lietz–Miller; LVEDD, left ventricular end-diastolic dimension; MPAP, mean pulmonary arterial pressure; MR, mitral regurgitation; NA, not available; PA, pulmonary artery; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RD, renal dysfunction; RIMP, right index of myocardial performance; RPM, revolutions per minute; RVSWI, right ventricular stroke work index; s/p, status post; SVR, systemic vascular resistance; TR, tricuspid regurgitation; TVR, tricuspid valve replacement; VO_2 max., peak oxygen uptake; VT, ventricular tachycardia.

John 2011a[64]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: John
Year of publication: 2011
Country: USA (MN)
Study design: Retrospective (data prospectively collected and retrospectively analysed)
Study setting: Medical Centre at University of Minnestota
Number of centres: One centre
Duration of study: From June 2005 to June 2010
Follow-up period: Total duration of follow-up was 137.5 patient-years
Funding: Not reported

Aim of the study

To report the outcomes in patients receiving the HMII LVAD at a single centre and review lessons learned from this experience

Participants

Total number of participants: 102 BTT patients; pre-FDA approval ($n = 38$) and post-FDA approval ($n = 64$)
Sample attrition/dropout: None
Inclusion criteria: Patients who received the HMII LVAD at the University of Minnesota Medical Centre as BTT therapy from June 2005 through June 2010
Exclusion criteria: DT and exchange therapy for a failed HMXVE
Characteristics of participants:
Mean age (SD): 52.6 ± 12.8 years
Median age: Not reported
Age range: 17–71 years
Sex: 76 male : 26 female
Race: Not reported
Diagnosis: Coronary artery disease 53 (51.9%) [causes of HF – ischaemic 58 (56.8%); non-ischaemic 36 (35.3%); other 8 (7.8%)]

Intervention

Indication for treatment: BTT. HF resulting from causes such as: ischaemic 58 (56.8%); non-ischaemic 36 (35.3%); and other 8 (7.8%; including postpartum cardiomyopathy, myocarditis, congenital heart disease and post-cardiotomy shock)
Type of device used: HMII LVAD
Any comparison: Patients were divided into pre-FDA and post-FDA approval groups
Duration of treatment: Duration of LVAD support (days) 327 ± 286 (range 10–1538 days)
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below. Anticoagulation therapy – initially (first 14 patients) intravenous infusion of unfractionated heparin as a bridge to warfarin therapy was used, titrating dose to an INR of 2–3. However, it was changed to include only warfarin therapy starting on post-operative day 2 or 3, titrating dose to an INR of 1.5–2, in addition to antiplatelet therapy with aspirin
Any FDA or CE approval: Yes – HMII LVAD

Outcomes

Primary outcomes: Haemodynamic and end-organ function; adverse events (BTT therapy); survival; impact of FDA approval on BTT outcomes
Secondary outcomes: Not relevant
Method of assessing outcomes: Medical records, data were also prospectively collected and retrospectively analysed. Baseline and follow-up data were collected, including patient characteristics, blood chemistry analyses, haematological findings, neurological status and concomitant medication use. After discharged from hospital, patients returned for follow-up, device review and clinical assessment. Data were prospectively collected and retrospectively analysed. Continuous data are presented as mean and SD. Categorical data were presented as a percentage. Continuous data were compared with analysis of variance or the *t*-test as indicated. The chi-squared or the Fisher's exact test was used for categorical variables. Survival estimates were based on the K–M method and compared using log-rank statistics. Hospital readmission and patient adverse events were recorded throughout the study period as they occurred, using standardised definitions. After FDA approval, data continued to be collected for all patients using similar definitions
Survival: Yes
Adverse event: Yes
HRQoL: No

Outcomes

Length of follow-up: Total duration of follow-up was 137.5 patient-years. Duration of LVAD support (days) 327 ± 286 (range 10–1538)

Number of participants	Intervention	Comparator, if present
Screened	130 patients	
Randomised/included	102 patients	
Excluded	28 patients – 17 DT patients and 11 exchange patients	
Missing participants	Not reported	
Withdrawals	Not reported	

Patient's baseline characteristics

Baseline demographic and clinical characteristics of BTT patients prior to LVAD implantation (*n* = 102)

Variable	*n* (%)
Mean age (years)	52.6 ± 12.8 (range 17–71)
Gender ratio (male : female)	76 : 26
Aetiology of HF	
Ischaemic	58 (56.8%)
Non-ischaemic	36 (35.3%)
Other	8 (7.8%)
Diabetes mellitus	29 (28.4%)
Hypertension	37 (36.2%)
Coronary artery disease	53 (51.9%)
BMI	28.7 ± 6.8 (range 15–44)
Duration of LVAD support (days)	327 ± 286 (range 10–1538)
Haemodynamics mean ± SD	
Systolic PAP (mmHg)	54.55 ± 14.86
Diastolic PAP (mmHg)	28.11 ± 7.35
Right atrial mean (mmHg)	13.46 ± 6.28
PCWP (mmHg)	24.80 ± 6.58
PVR (Wood units)	3.75 ± 2.14
Cardiac output (l/minute)	3.77 ± 1.11
Cardiac index	1.86 ± 0.49
End-organ parameters (mean ± SD)	
Renal	
Sodium	134.8 ± 5.1
Creatinine	1.39 ± 0.59
BUN	33.4 ± 20.4
Liver	
ALT	80.49 ± 236
AST	79.16 ± 224
Total bilirubin	1.15 ± 1.00

Patient's baseline characteristics

Variable	*n* (%)
INTERMACS profiles (*n* = 97)	
1	17 (17.5)
2	13 (13.4)
3	13 (13.4)
4	16 (16.5)
5	25 (25.7)
6	12 (12.7)
7	1 (1.03)

Survival outcomes reported (by group and/or intervention)

30-day and 6-month survival in 38 patients in the clinical trial (pre-FDA approval) was 97.4% and 88.8%, and were not significant when compared with the 93.7% and 76.2% 30-day and 6-month survival in the 64 patients in the post-FDA approval period ($p = 0.1$)
K–M estimates: 30-day, 6-month and 1-year survival for the BTT patients by K–M estimate was 95.1%, 83.5%, and 78.8%, respectively

Other specified/relevant outcomes reported (by group and/or intervention)

Mechanical circulatory support with subsequent HT: Of 102 BTT patients, 48 had cardiac transplantation with mean duration to transplant period of 329.8 ± 265.6 days (range 96–1230 days)
In pre-FDA approval period, 30 of 38 were patients transplanted with mean duration to transplant period of 331.2 ± 322 days; in post-FDA approval period, 18 of 64 were patients transplanted with mean duration to transplant period of 327.78 ± 132 days (no significant difference in mean duration to transplant between both groups; $p = 0.9$)

Adverse events reported (by group and/or intervention)

Major adverse events among 102 BTT patients included right ventricular failure requiring RVAD support in 5 patients (4.9%), LVAD driveline infections in 25 patients (24.5%), neurological events in 10 patients (9.8%) and gastrointestinal bleeding in 18 patients (17.6%)
One patient had pump thrombosis, and this patient required a device replacement (for pump thrombosis)
Incidence of adverse outcomes in pre-FDA approval group was not statistically different from that in the post-FDA approval group

Adverse events in BTT patients during LVAD support (*n* = 102)

Events	*n* (%)
Neurological	
Stroke/TIA	9 (8.8)
Paraplegia	1 (0.98)
Haemorrhagic	
Gastrointestinal bleeding	18 (17.6)
Mediastinal bleeding requiring reoperation	17 (16.7)
Infectious	
Driveline infection	22 (21.5)
Pocket infection	0
Pump infection	0
RV failure requiring RVAD	5 (4.9)
Pump thrombosis	1 (0.98)
Device malfunction	2 (1.9)
Device replacement	1 (0.98)
Renal failure	2 (1.9)

Adverse events reported (by group and/or intervention)

Adverse events in BTT patients during LVAD support by the US FDA approval status

Events	Pre-FDA approval (*n* = 38)		Post-FDA approval (*n* = 64)	
	n	%	*n*	%
Neurological stroke/TIA	2	5.3	7	10.9
Haematological				
Gastrointestinal bleeding	9	23.7	9	(14.1)
Infectious				
Driveline infection	10	26.3	12	18.8
RV failure requiring RVAD	2	5.3	3	4.7
Pump thrombosis	0		1	1.6
Device replacement	0		1	1.6

Summary of adverse events

Adverse events	Intervention	Comparator, if present
Bleeding	Gastrointestinal bleeding in 18 (17.6%) patients; mediastinal bleeding requiring reoperation 17 (16.7%)	Gastrointestinal bleeding – pre-FDA approval 9 (23.7%) and post-FDA approval 9 (14.1%)
Stroke	Stroke/TIA 9 (8.8%)	Stroke/TIA – pre-FDA approval 2 (5.3%) and post-FDA approval 7 (10.9%)
Hypertension	Some of the patients already had hypertension at baseline	
Infection	Driveline infections in 25 (24.5%) patients; pocket infection 0; pump infection 0	Driveline infection – pre-FDA approval 10 (26.3%) and post-FDA approval 12 (18.8%)
HF	Right ventricular failure requiring RVAD support in 5 (4.9%) patients	RV failure requiring RVAD – pre-FDA approval 2 (5.3%) and post-FDA approval 3 (4.7%)
VAD failure	Device malfunction 2 (1.9%)	
Renal failure	Renal failure 2 (1.9%)	
Other neurological dysfunction	Paraplegia 1 (0.98%)	

Cause of death reported (by group and/or intervention)

There were eight early deaths (≤ 30 days or prior to hospital discharge); four patients with multisystem organ failure, one with subclavian vein haemorrhage, one patient with ventricular fibrillation, one patient with respiratory failure, and one patient with RV failure and intracranial bleed

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Despite significant morbidity, use of HMII LVAD as a BTT provides excellent haemodynamic support and is associated with excellent survival and low mortality. Improvement and focused strategies are needed in areas of gastrointestinal bleeding, driveline infections, and adverse neurological events for devices to provide a long-term alternative to HT

Reviewer's conclusion

Neurological problems were present in approximately 10% patients and around 5% experiencing right ventricular failure requiring RVAD. Survival findings did not reach significance, but note the small numbers used. There was a 12% difference in 1-year survival pre-FDA and post-FDA approval

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalised ratio; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; TIA, transient ischaemic attack.

John 2010[63]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: John
Year of publication: 2010
Country: USA, Canada
Study design: Retrospective
Study setting: Multicentre
Number of centres: 35 centres (abstract states 36 centres)
Duration of study: Between March 2005 and April 2008
Follow-up period: Each centre followed up patients based on their own post-transplant follow-up schedule. Each centre completed a form to document 1-month and 1-year post-transplant survival. Of transplanted patients, 229 patients completed a 30-day follow-up and 190 patients completed a 1-year follow-up
Funding: Not reported

Aim of the study

To determine factors related to post-transplant survival in patients supported with CF LVADs

Participants

Total number of participants: 250
Sample attrition/dropout: Unclear
Inclusion criteria: Patients with end-stage HF and listed for HT at each centre. Patients were required to have NYHA class IV HF symptoms and to be ill enough to have high priority for transplantation (UNOS status 1a or 1b). Detailed inclusion and exclusion criteria published elsewhere (Miller *et al*. 2007[70]). Only patients who underwent cardiac transplantation after VAD support are included in this paper
Exclusion criteria: Severe renal, pulmonary or hepatic dysfunction, active uncontrolled infection, a mechanical aortic valve, aortic insufficiency, an aortic aneurysm, other mechanical circulatory support (except an IABP) and technical obstacles thought by investigator to pose an increase surgical risk
Characteristics of participants:
Mean age (SD): 51 ± 13 years
Median age: 54 years
Age range: Not reported
Sex: Male 204 (82%)
Race: Not reported
Diagnosis: Ischaemic causes of HF – 107 (43%); the paper reports that most of the HF were caused by non-ischaemic cardiomyopathy

Intervention

Indication for treatment: Most frequent aetiology of HF was non-ischaemic cardiomyopathy. All patients had symptoms of advanced HF despite optimal MM with oral medications
Type of device used: HMII LVAD
Any comparison: None
Duration of treatment: Unclear for each centre. Of 468 patients, 250 (53%) underwent cardiac transplantation after a median duration of LVAD support of 151 days (longest 3.2 years). Of the patients undergoing transplantation, 229 patients completed a 30-day follow-up and 190 patients completed a 1-year follow-up
Percentage of patients using inotropes: Intravenous inotrope agents = 91% ($n = 228$); intolerant to inotropes owing to arrhythmias = 9% ($n = 22$)
Other interventions used: See section *Patient's baseline characteristics*, below. After device implantation, a standardised antithrombotic regimen was implemented with initiation of heparin followed by transition to warfarin as well as aspirin. Post-operative MM, including inotropic, antiarrhythmic and HF therapy was performed according to each investigator's preference and usual practice
Any FDA or CE approval: Yes – HMII LVAD

Outcomes

Survival after transplantation at two specific time points: 30 days and 1 year. Survival after transplantation was also compared with the survival for patients continuing on LVAD support, starting at 6 months of support and continuing through 18 months support (censored for transplantation)
Secondary outcomes: The post-transplant survival was also stratified according to age, aetiology, BMI, duration of device support, and by adverse events during support
Method of assessing outcomes: Medical records. This study was supervised by sponsor (Thoratec Inc.). Co-ordinators at each site collected all study data, which were then forwarded to data analysis centre of sponsor. Academic authors vouch for completeness and accuracy of data and analyses. Data and safety monitoring board consisting of four independent physicians and one biostatistician who were not investigators met routinely to review study compliance, adverse events, QoL and outcomes of patients. A clinical events committee of four independent physicians reviewed, classified and adjudicated causes of death and all adverse events
Survival: Yes
Adverse event: No
HRQoL: No
Length of follow-up: 30 days and 1 year (229 patients completed a 30-day follow-up and 190 patients completed a 1-year follow-up)

Number of participants	Intervention	Comparator, if present
Screened	468 patents	Not applicable
Randomised/included	250 (53%) patients that underwent cardiac transplantation	Not applicable
Excluded	Out of 468 patients, 218 patients were excluded: 106 (23%) patients died, 12 (2.6%) patients recovered ventricular function and the device was removed, and 100 (21%) patients were still receiving LVAD support	Not applicable
Missing participants	Not applicable	Not applicable
Withdrawals	Not applicable	Not applicable

Patient's baseline characteristics

Baseline characteristics of the 250 LVAD patients who underwent HT

Characteristic	Mean ± SD or *n* (%) (*n* = 250)
Age (years)	51 ± 13
Male (%)	204 (82)
BMI (kg/m^2)	27 ± 5.6
BSA (m^2)	2.0 ± 0.3
Ischaemic aetiology of HF (%)	107 (43)
LVEF (%)	16.1 ± 6.5
Arterial BP (mmHg)	
Systolic	98.2 ± 15.4
Diastolic	62.3 ± 12.1
PCWP (mmHg)	25.4 ± 8.2
Cardiac index (l/minute/m^2)	2.1 ± 0.7
Heart rate (b.p.m.)	92 ± 18
Pulmonary artery pressure (mmHg)	
Systolic	51.5 ± 13.2
Diastolic	26.7 ± 8.0
Mean	35.8 ± 9.0

Patient's baseline characteristics

Characteristic	Mean ± SD or *n* (%) (*n* = 250)
Pulmonary vascular resistance (Wood units)	2.8 ± 1.4
CVP (mmHg)	12 ± 6
NYHA class	IV (221/250)
Serum sodium (mmol/l)	133.3 ± 5.2
Serum albumin (g/dl)	3.6 ± 1.8
Pre-albumin (mg/dl)	18.5 ± 7.7
Cholesterol (mg/dl)	129 ± 41
Serum creatinine (mg/dl)	1.4 ± 0.5
BUN (mg/dl)	29.8 ± 16.7
ALT (IU/l)	106 ± 278
AST (IU/l)	91 ± 223
Total bilirubin (mg/dl)	1.3 ± 0.8
LDH (mg/dl)	567 ± 1538
Haematocrit (%)	34.8 ± 5.7
White blood count (× 1000/ml)	8.8 ± 3.3
Platelets (1000/ml)	225 ± 87
INR	1.3 ± 0.3
Concomitant medications	
Intravenous inotrope agents	228 (91)
Intolerant to inotropes owing to arrhythmias	22 (9)
Biventricular pacemaker	119 (48)
ICD	192 (77)
IABP	115 (46)
Mechanical ventilation	18 (7)

Of 468 patients, 250 (53%) underwent cardiac transplantation, 106 (23%) died, 12 (2.6%) recovered ventricular function and device was removed, and 100 (21%) were still receiving LVAD support
Of transplanted patients, 229 patients completed a 30-day follow-up and 190 patients completed a 1-year follow-up; 46% of patients had concomitant support with IABP, many had previously received biventricular pacing therapy
Majority of patients were listed at UNOS status 1a

Survival outcomes reported (by group and/or intervention)

Post-transplant survival: Of 468 patients, 250 (53%) patients had cardiac transplantation after LVAD support median duration of 151 days (longest 3.2 years). In patient's receiving transplantation, 229 patients completed a 30-day follow-up and 190 patients completed a 1-year follow-up. Overall 30-day and 1-year survivals are 97% and 87%, respectively. 1-year survival was 88% for men and 82% for women. No significant differences in 30-day and 1-year post-transplant survivals in patients when stratified by demographics (e.g. age, gender, aetiology of HF, and BMI)

Survival outcomes reported (by group and/or intervention)

Post-transplant survival vs. patient demographics

Parameter	Demographic	LVAD duration	Survival at 30 days	*p*-value	Survival at 1 year	*p*-value
Overall	All	151 (3.2 years)	222/229 (97%)		165/190 (87%)	
Aetiology	Ischaemic	152 (13 years)	100/102 (98%)	0.47	74/85 (87%)	1.00
	Non-ischaemic	143 (3.2 years)	122/127 (96%)		91/105 (87%)	
Gender	Male	145 (3.2 years)	182/187 (97%)	0.36	136/155 (88%)	0.41
	Female	159 (1.7 years)	38/40 (95%)		28/34 (82%)	
Age (years)	< 50	131 (3.2 years)	82/85 (97%)	0.92	66/75 (88%)	0.93
	50–59	172 (3.2 years)	79/81 (98%)		56/65 (86%)	
	> 60	151 (1.8 years)	61/63 (97%)		43/50 (86%)	
BMI (kg/m^2)	< 20	131 (1.4 years)	19/21 (91%)	0.10	16/19 (84%)	0.75
	20–29	136 (3.2 years)	136/138 (99%)		99/112 (88%)	
	> 30	173 (3.2 years)	66/69 (96%)		50/59 (85%)	

Patients undergoing transplantation were stratified into four groups on basis of duration of LVAD support ranging from < 30 days to > 180 days (see below). No significant differences in 30-day or 1-year post-transplant survivals among groups

Post-transplant survival vs. LVAD duration

LVAD duration	Median days (maximum)	Survival at 30 days	*p*-value	Survival at 1 year	*p*-value
< 30 days	18 (28)	17/17 (100%)	0.28	16/17 (94%)	0.18
30–89 days	58 (89)	62/62 (100%)		55/59 (93%)	
90–179 days	135 (179)	57/60 (95%)		46/55 (84%)	
180–365 days	227 (363)	64/68 (94%)		37/45 (82%)	
> 365 days	507 (3.2 years)	22/22 (100%)		11/14 (79%)	

No significant difference in 30-day or 1-year post-transplant survivals when patients supported for > 180 days were subdivided into 180–365 days and > 365 days

Survival outcomes reported (by group and/or intervention)

Post-transplant survival vs. adverse events during LVAD support

Adverse event		LVAD duration	Survival at 30 days	*p*-value	Survival at 1 year	*p*-value
Any infection during LVAD support	No	120 (3.2 years)	132/135 (98%)	0.45	102/115 (89%)	0.38
	Yes	192 (2.1 years)	90/94 (96%)		63/75 (84%)	
Percutaneous lead infection during LVAD support	No	126 (3.2 years)	185/189 (98%)	0.10	144/162 (89%)	0.07
	Yes	253 (2.1 years)	37/40 (93%)		21/28 (75%)	
Reoperation for bleeding during LVAD support	No	149 (3.2 years)	180/184 (98%)	0.14	133/152 (88%)	0.60
	Yes	152 (3.2 years)	42/45 (93%)		32/38 (84%)	
Bleeding requiring > 2 units PRBC/24 hours during LVAD support	No	130 (2.1 years)	88/90 (98%)	0.7i	74/79 (94%)	0.03
	Yes	162 (3.2 years)	134/139 (96%)		91/111 (82%)	
Last creatinine value during LVAD support	< 1.7 mg/dl (1.1 ± 0.1)	143 (3.2 years)	202/209 (97%)	1.00	154/175 (88%)	0.12
	> 1.7 mg/dl (2.2 ± 0.5)	194 (1.5 years)	20/20 (100%)		11/15 (73%)	
Last BUN value during LVAD support	< 30 mg/dl (17 ± 5)	143 (3.2 years)	200/206 (97%)	0.53	151/172 (88%)	0.27
	> 30 mg/dl (46 ± 19)	178 (1.3 years)	22/23 (96%)		14/18 (78%)	
Last ALT value during LVAD support	< 40 IU (24 ± 8)	157 (3.2 years)	171/177 (97%)	1.00	124/142 (87%)	0.81
	> 40 IU (62 ± 38)	120 (1.8 years)	51/52 (98%)		41/48 (85%)	

Post-transplant survival was stratified on basis of occurrence of adverse events during LVAD support as well as end-organ function before transplantation (see above). Patients needing > 2 units of PRBCs in 24 hours during LVAD support had a significant decreased 1-year survival (82% vs. 94%) compared with patients not requiring > 2 units of PRBCs in 24 hours during LVAD support ($p = 0.03$). There was lower survival at 1 year (75%) in 28 patients with percutaneous lead infections during LVAD support vs. no infection (89%) ($p = 0.07$), and in 15 patients with last creatinine level before transplant > 1.7 mg/dl (73% vs. 88%) when compared with patients with creatinine level before transplant was < 1.7 mg/dl ($p = 0.12$). No significant differences in 30-day or 1-year post-transplant survivals among other groups (see above)
Post-transplant survival vs. survival after 6 months of LVAD support: 30-day and 1-year survivals for patients continuing on LVAD support were 98% and 87%. This was not significantly different from 30-day and 1-year post-transplant survivals of 97% and 87%. (Note: starting point of 6 months was used for analysis as median duration for timing of transplant on LVAD support was 151 days)

Survival outcomes reported (by group and/or intervention)

Summary of survival data

Survival data	Intervention	Comparator, if present
Overall survival	Overall 30-day and 1-year post-transplant survival was 97% (222/229) and 87% (165/190) respectively. LVAD support duration was 151 days (longest 3.2 years) 1-year post-transplant survival for men was 88% (136/155) and 82% (28/34) for women (LVAD support in men was 145 days, longest 3.2 years; and in women 159 days, longest 1.7 years) There was no statistically significant differences in 30-day and 1-year post-transplant survivals among these patients The 30-day and 1-year survival for patients continuing on LVAD support (starting from 6 months of support, through 18 months, and censored for transplantation) were 98% and 87%. This was not statistically significantly different from the 30-day and 1-year post-transplant survivals of 97% and 87%. The starting point of 6 months for this analysis was used as the median duration of timing of transplant on LVAD support was 151 days	Not applicable
K–M estimates	Not applicable	Not applicable
Survival by era (at 5-year intervals)	Not applicable	Not applicable
HT without prior mechanical circulatory support	Only included patients who had a HT after LVAD support	Not applicable
Mechanical circulatory support without subsequent HT	Only included patients who had a HT after LVAD support	Not applicable
Mechanical circulatory support with subsequent HT	250 patients	Not applicable

Other specified/relevant outcomes reported (by group and/or intervention)

Not reported

Adverse events reported (by group and/or intervention)

Not reported – post-transplant survival was stratified according to adverse events that developed during LVAD support

Cause of death reported (by group and/or intervention)

Not reported – the causes of post-transplant death were unknown

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Post-cardiac transplant survival in patients supported with CF devices such as HMII LVAD was found to be equivalent to that with conventional transplantation. Furthermore, post-transplant survival was not influenced by duration of LVAD support. Improved durability and reduced short- and long-term morbidity associated with HMII LVAD reduced the need for urgent cardiac transplantation, which may have adversely influenced survival in the pulsatile LVAD era. This information may have significant implications for changing current UNOS criteria regarding listing of HT candidates

Reviewer's conclusion

This was a non-randomised study which did not have a risk-adjusted group for direct comparison. The authors stated that the comparison of efficacy of LVADs as a BTT therapy with a medical control group would be unethical. Several key variables not examined in this study could potentially influence transplant survival (e.g. HLA sensitisation and pulmonary vascular resistance). There were no data evaluated on post-transplant morbidity such as rejections, infections, and post-transplant length of stay and hospital readmissions. This study had a limited 1-year post-transplant follow-up. Further multivariate analyses are needed to identify the clinically significant variables: infection, sensitisation, increased duration, or a combination of these risk factors

ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; HLA, human leucocyte antigen; ICD, implantable cardioverter-defibrillator; INR, international normalised ratio; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; PRBC, packed red blood cell.

John 2011b[65]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: John
Year of publication: 2011
Country: Multicentre
Study design: Retrospective analysis of outcome data from 1982 patients supported by the HMII LVAD as a BTT
Study setting: Multicentre
Number of centres: Trial group = 32 centres; post-trial group = 83 centres
Duration of study: Trial group (March 2005 to April 2008) – 6 months; post-trial group (April 2008 to October 2010) – 12 months
Follow-up period: For the trial period patients were followed up at 1, 3 and 6 months; for the post-trial period patients were followed up at 3, 6 and 12 months
Funding: Thoratec Inc.

Aim of the study

To determine changes in post-trial outcomes in widespread commercial use since the clinical trial

Participants

Total number of participants: 1982 patients (trial group 486 patients; post-trial group 1496 patients)
Sample attrition/dropout: Unclear
Inclusion criteria: Patients supported by the HMII LVAD as a BTT between 2005 and 2010
Exclusion criteria: Unclear
Characteristics of participants:
Mean age (SD): aged < 40 years = trial group 96 (20%), post-trial group 255 (17%); aged 40–59 years = trial group 234 (48%), post-trial group 787 (53%)
Median age: Not reported
Age range: Not reported
Sex: Male – trial group 377 (78%); post-trial group 1154 (77%)
Race: Not reported
Diagnosis: Unclear

Intervention

Indication for treatment: BTT
Type of device used: HMII LVAD
Any comparison: Patients were divided into two groups: those supported during the clinical trial (trial group) and those supported after commercial approval by the FDA (post-trial group) as reported to the INTERMACs registry
Duration of treatment: Average support duration for the trial period 12.6 ± 14.0 months; post-trial period 8.7 ± 7.1 months
Percentage of patients using inotropes: $n = 297$ (19.9%) were stable but inotrope dependent. A smaller percentage of post-trial patients (80%) required intravenous inotropes than did trial patients (90%; $p < 0.0001$)
Other interventions used: See section *Patient's baseline characteristics*, below. IABP = trial 204 (42%), post trial 490 (33%); mechanical ventilation = trial 41 (8%), post trial 138 (9%); ACE inhibitors = trial 134 (28%), post trial not reported; beta-blockers = trial 182 (37%), post trial not reported; intravenous inotropic agents = trial 436 (90%), post trial 1203 (80%)
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Overall survival from the LVAD implant, ongoing LVAD support, transplant, device removal after myocardial recovery, and death. Adverse events were recorded (for trial patients KCCQ OSSs and for post-trial patients EuroQol EQ-5D) to assess QoL. 6-minute walk test was used in both groups to assess functional status
Secondary outcomes: Not applicable
Method of assessing outcomes: Medical records. No clear details on how outcomes were assessed. In the trial period, data were collected before implant and 1, 3 and 6 months after implant. In the post-trial period, data were collected before implant and at 3, 6 and 12 months
Survival: Yes
Adverse event: Yes
HRQoL: Yes. For trial patients the KCCQ OSSs; for post-trial patients the EuroQol EQ-5D

Outcomes		
Length of follow-up: For trial patients 6 months; for post-trial patients 12 months		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported	Not reported
Randomised/included	Trial group: 486	Post-trial group: 1496
Excluded	Not applicable	Not applicable
Missing participants	Not applicable	Not applicable
Withdrawals	Not applicable	Not applicable

Patient's baseline characteristics

Baseline characteristics of the trial and post-trial groups

Characteristic	Trial group	Post-trial group	*p*-value
n	486	1496	
Male, *n* (%)	377 (78)	1154 (77)	0.9009
Age (years), *n* (%)			0.4048
< 40	96 (20)	255 (17)	
40–59	234 (48)	787 (53)	
> 60	156 (32)	454 (30)	
Height (cm)	174.7 ± 9.8	174.8 ± 11.5	0.8631
Weight (kg)	83.5 ± 20.1	87.4 ± 21.4	0.0004
BSA (m^2)	1.99 ± 0.27	2.05 ± 0.29	0.0001
BMI (kg/m^2)	27.2 ± 5.9	28.8 ± 10.0	0.0008
BSA (< 1.5 m^2), *n* (%)	18 (3.7)	24 (2)	0.0098
INTERMACS category, *n* (%)			
1 = critical cardiogenic shock	NA	252 (16.8)	
2 = progressive decline	NA	667 (44.6)	
3 = stable but inotrope dependent	NA	297 (19.9)	
4 = resting symptoms	NA	174 (11.6)	
5 = exertion intolerant	NA	42 (2.8)	
6 = exertion limited	NA	33 (2.2)	
7 = advanced NYHA class III	NA	31 (2.1)	
Haemodynamics			
Heart rate (b.p.m.)	91.2 ± 18.6	89.9 ± 18.4	0.1773
Systolic BP (mmHg)	98.5 ± 15.5	100.9 - ± 15.6	0.0032
Diastolic BP (mmHg)	62.3 ± 11.6	63.0 ± 11.6	0.2479
Mean BP (mmHg)	74.4 ± 11.2	75.7 ± 11.4	0.0304
Systolic PAP (mmHg)	51.4 ± 13.5	50.0 ± 115.0	0.0258
Diastolic PAP (mmHg)	26.8 ± 8.2	25.7 it 8.6	0.0133
Mean PAP (mmHg)	35.9 ± 9.4	33.8 ± 10.1	0.0002
Pulmonary wedge pressure (mmHg)	25.5 ± 8.0	24.5 ± 8.6	0.0236

Patient's baseline characteristics

Characteristic	Trial group	Post-trial group	*p*-value
PVR (Wood units)	2.89 ± 1.57	2.76 ± 2.23	0.2973
Right atrial pressure (mmHg)	12.8 ± 6.6	12.8 ± 6.8	1.0000
Cardiac index (l/minute/m^2)	2.06 ± 0.67	2.13 ± 0.66	0.0705
Laboratory			
BUN (mg/l)	30.3 ± 16.7	28.4 ± 18.0	0.0398
Creatinine (mg/l)	1.42 ± 0.52	1.39 ± 0.76	0.4176
Total bilirubin (mg/l)	1.26 ± 0.83	1.49 ± 1.83	0.0074
Sodium (mg/l)	133.6 ± 4.9	134.5 ± 5.1	0.0007
INR	1.34 ± 0.41	1.34 ± 0.46	1.0000
White blood cell count (K/µl)	8.9 ± 3.6	8.8 ± 3.6	0.5948
Platelets (K/µl)	225.7 ± 87.6	206.2 ± 89.7	0.0001
SGOT/AST, (unclear units)	84.0 ± 237.9	83.9 ± 336.8	0.9952
Haemoglobin (mg/dl)	11.6 ± 2.0	11.3 ± 2.0	0.0041
Albumin (mg/dl)	3.5 ± 1.2	3.4 ± 0.68	0.0224
Concomitant procedures, *n* (%)			
IABP	204 (42)	490 (33)	0.0002
Mechanical ventilation	41 (8)	138 (9)	0.6493
ACE inhibitors	134 (28)	Not reported	
Beta-blockers	182 (37)	Not reported	
Intravenous inotropic agents	436 (90)	1203 (80)	0.0001

Survival outcomes reported (by group and/or intervention)

Measure	Trial patients	Post-trial patients
K–M estimates	83.8% at 6 months and 75.6% at 12 months	89.4% at 6 months and 84.9% at 12 months K–M survival significantly improved for the post-trial group ($p = 0.001$) compared with the trial group, with 1-year survival estimates increasing from 76% to 85%
Mechanical circulatory support without subsequent HT	Ongoing support: 53% at 6 months and 32% at 12 months	Ongoing support: 66% at 6 months and 45% at 12 months
Mechanical circulatory support with subsequent HT	32% at 6 months and 48% at 12 months	22% at 6 months and 39% at 12 months
Deaths	30-day operative mortality: 6.6% Deaths: 14% at 6 months and 18% at 12 months	30-day operative mortality: 4.5% Deaths: 10% at 6 months and 13% at 12 months. (Please note 1-year data of only 892 patients available in this group)

Other specified/relevant outcomes reported (by group and/or intervention)

See included tables

Adverse events reported (by group and/or intervention)

Adverse events in the post-trial period were presented using INTERMACS definitions. Adverse events in the trial period were only presented for events having comparable definitions with the INTERMACS registry
Bleeding and infection were the most frequently reported adverse events

Adverse events reported (by group and/or intervention)

Adverse events for the post-trial patients (*n* = 1496)[a]

Adverse event	Patients, *n* (%)	No. of events	Events/patient-year
Arterial non-CNS thromboembolism	8 (1)	9	0.01
Bleeding	539 (36)	1376	1.27
Bleeding requiring surgery	101 (7)	127	0.12
Gastrointestinal bleeding	157 (10)	415	0.38
Cardiac arrhythmia	418 (28)	643	0.59
Device malfunction	156 (10)	225	0.21
Haemolysis	45 (3)	54	0.05
Hepatic dysfunction	59 (4)	63	0.06
Hypertension	78 (5)	94	0.09
Infection[b]	566 (38)	1113	1.03
Driveline	192 (13)	303	0.28
Pump pocket	28 (2)	33	0.03
Pump interior	4 (0)	5	0.00
Blood	167 (11)	233	0.22
Line sepsis	38 (3)	41	0.04
Other infection	386 (26)	653	0.60
Myocardial infarction	10 (1)	10	0.01
Stroke	97 (6)	110	0.10
Haemorrhagic stroke	23 (2)	24	0.02
Ischaemic stroke	57 (4)	62	0.06
Unknown	17 (1)	24	0.02
Other neurological dysfunction	64 (4)	70	0.06
Pericardial drainage	91 (6)	103	0.10
Psychiatric episode	125 (8)	153	0.14
Rehospitalisation	744 (50)	1882	1.74
Renal dysfunction	129 (9)	151	0.14
Respiratory failure	241 (16)	303	0.28
Right-side HF	173 (12)	197	0.18
RVAD	14 (1)	15	0.01
Venous thromboembolism	88 (6)	96	0.09
Wound dehiscence	19 (1)	22	0.02
Device replacement	21 (1)	22	0.02

a Cumulative support = 1081.8 patient-years.
b Infection events can have multiple sites.

Adverse events reported (by group and/or intervention)

Adverse events comparable by definition for trial group (*n* = 486) and post-trial group (*n* = 1496)

Adverse event	Trial (*n* = 486) 511.1 patient-years		Post-trial group (*n* = 1496) 1081.8 patient-years	
	Incidence (%)[a]	Event rate[b]	Incidence (%)[a]	Event rate[b]
Bleeding requiring re-exploration	21	0.23	7	0.12
Infection				
Percutaneous lead	20	0.33	13	0.28
Pump pocket	3	0.03	2	0.03
Right-side HF requiring RVAD	7	0.06	1	0.01
Stroke				
Ischaemic	5	0.05	4	0.06
Haemorrhagic	5	0.05	2	0.02
Other	0	0.00	1	0.02
Device replacement	5	0.06	1	0.02

a Per cent of patients.
b Events per patient-year.

Cause of death reported (by group and/or intervention)

Unclear – bleeding and infection were the most frequently reported adverse events

QoL reported (by group and/or intervention)

For the trial patients, the KCCQ OSSs were used to assess QoL. For post-trial patients, the EuroQol EQ-5D METs, as used by INTERMACS, was used. Functional status was evaluated using 6-minute walk test in both groups. Comparisons over time for functional and QoL measures used linear mixed-effects modelling
Results of 6-minute walk test showed similar improvements in distance walked after LVAD support in both groups. Although using different instruments, similar improvements were found during LVAD support in the KCCQ (used in trial) and the EQ-5D METs

6-minute walk test results for the trial and post-trial groups (data read off histogram)

Parameter	Pre implant		3 months		6 months		12 months
	Trial group	Post-trial group	Trial group	Post-trial group	Trial group	Post-trial group	Trial group
n at risk	1496	486	1147	347	822	258	393
n available data points	1189	486	428	283	469	222	111
n able to do test	139	76	356	253	432	209	91
% able to do test	13	16	83	89	92	94	82
Distance (m)	240	230	340	310	350	370	380

QoL reported (by group and/or intervention)

KCCQ OSSs for the trial group (data read off histogram)

Parameter	Pre implant	1 month	3 months	6 months
n at risk	486	432	342	258
n completing teat	393	369	317	246
% completing test	81	85	93	93
OSS	30	45	60	68

EuroQoL EQ-5D METs results for the post-trial cohort (note: the EuroQoL and KCCQ reporting intervals are different; data read off histogram)

Parameter	Pre implant	3 months	6 months	12 months
n at risk	1498	1142	822	393
n completing test	777	617	432	192
% completing test	52	54	53	49
EuroQoL results	42	74	75	76

Author's conclusion

Results demonstrate that survival rates of BTT patients with HMII LVAD improved since the clinical trial. Findings indicate excellent outcomes have been maintained with dissemination of new LVAD technology from a clinical trial phase to more broad based use in post-market-approval period

Reviewer's conclusion

Limited reporting of QoL measures. Important to note that individual centres may have their own variations in patient selection criteria, implantation techniques, and post-operative management of patients. The authors recognised that this is a limitation of multicentre trials; however, this was not accounted for within the analysis. Furthermore, caution should be made when interpreting the adverse events and QoL results as it is possible that the definitions and tools used may have varied between the clinical trial and INTERMACS registry

AST, aspartate aminotransferase; BSA, body surface area; b.p.m., beats per minute; INR, international normalised ratio; NA, not available; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SGOT, serum glutamic oxaloacetic transaminase.

Kato 2012[66]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Kato
Year of publication: 2012
Country: USA
Study design: Retrospective
Study setting: Columbia University Medical Centre
Number of centres: One
Duration of study: November 2000 to December 2010
Follow-up period: Mean post-operative observation period was 259 ± 304 days. Mean observation periods were 138 ± 224 days (range 3–1434 days) for HMI patients and 277 ± 333 days (range 3–2069 days) for HMII patients
Funding: Unclear. One author reports received consulting fees from Thoratec Inc. and Terumo Heart and another from Thoratec Inc. and Jarvik Heart

Aim of the study

This study was initiated to assess pre-operative and post-operative factors associated with the development of NCs in patients undergoing LVAD placement, and investigated factors associated with NCs after LVAD surgery

Participants

Total number of participants: 307 patients (167 patients with HMI device and 140 patients with HMII device)
Sample attrition/dropout: Not applicable
Inclusion criteria: Patients who underwent placement of a HMI or HMII device were divided into two groups: those with any NC, including TIA (group NC), and those who did not develop NC after the surgery (group non-NC). After excluding patients with only TIA episodes, patients with ischaemic or haemorrhagic CVA were classified as group CVA
Exclusion criteria: Patients who underwent other types of LVAD surgery and patients with only TIA episodes
Characteristics of participants:
Mean age (SD): Overall 54 ± 14 years at time of surgery; group non-NC ($n = 264$) = 53.6 ± 12.6 years; group NC ($n = 43$) = 54.4 ± 13.1 years; group CVA ($n = 35$) = 54.1 ± 15.6 years
Median age: Not reported
Age range: Not reported
Sex: Males: Group non-NC $n = 216$ (79.1%); group NC $n = 33$ (76.7%); group CVA $n = 29$ (82.9%)
Race: Not reported
Diagnosis: Not clear

Intervention

Indication for treatment: Not clear
Type of device used: HMI or HMII
Any comparison: Patients who underwent placement of a HMI or HMII device were divided into two groups: those with any NC, including TIA (group NC), and those who did not develop NC after the surgery (group non-NC). After excluding patients with only TIA episodes, patients with ischaemic or haemorrhagic CVA were classified as group CVA
Duration of treatment: The mean observation periods were 138 ± 224 days (range 3–1434 days) for HMI patients and 277 ± 333 days (range 3–2069 days) for HMII patients
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII patients

Outcomes

Primary outcomes: Factors associated with NC or CVA; variables that discriminated patients with NC or CVA from those without any episodes of NC
Secondary outcomes: Clinical characteristics, haemodynamic and laboratory data were compared among groups
Method of assessing outcomes: Medical records. Pre-operative variables were obtained within 7 days before surgery. Post-operative laboratory data for patients with NC or CVA were collected within 7 days before events, and data for patients without NC were collected within 7 days from end of observation or device removal owing to transplant, recovery or death
Survival: No
Adverse event: Yes
HRQoL: No
Length of follow-up: Mean post-operative observation period was 259 ± 304 days. Mean observation periods were 138 ± 224 days (range 3–1434 days) for HMI patients and 277 ± 333 days (range 3–2069 days) for HMII patients

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported	Not reported
Randomised/included	167	140
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Clinical characteristics

Variables	Group non-NC ($n = 264$)	Group NC ($n = 43$)	*p*-value (non-NC vs. NC)	Group CVA ($n = 35$)	*p*-value (non-NC vs. CVA)
Age, years	53.6 ± 12.6	54.4 ± 13.1	0.701	54.1 ± 15.6	0.830
Male sex	216 (79.1)	33 (76.7)	0.126	29 (82.9)	0.266
BSA, m^2	1.96 ± 0.24	1.91 ± 0.21	0.578	1.93 ± 0.22	0.484
Medical history					
Stroke	41 (15.5)	12 (27.9)	0.046	10 (28.6)	0.054
Diabetes mellitus	77 (29.1)	12 (27.9)	0.866	10 (28.6)	0.941
Hypertension	120 (47.0)	18 (40.9)	0.660	18 (51.4)	0.505
Hyperlipidaemia	84 (31.8)	13 (30.2)	0.836	13 (37.4)	0.527
PVD	29 (11.0)	8 (18.6)	0.225	7 (20.0)	0.124
Renal failure	76 (28.8)	11 (25.0)	0.665	9 (25.7)	0.704
Atrial fibrillation	134 (50.8)	25 (58.1)	0.369	23 (62.8)	0.096
Aetiology of heart disease					
Ischaemic	207 (78.8)	28 (65.1)	0.056	25 (71.4)	0.352
Non-ischaemic	57(21.2)	15 (34.9)	0.056	10 (28.6)	0.352
Type of LVAD					
HMI	143 (54.2)	24 (55.8)	0.804	19 (54.3)	0.989
HMII	121 (55.8)	19 (44.2)	0.804	16 (45.7)	0.989

Patient's baseline characteristics

Results of pre-operative haemodynamic and laboratory examinations

Parameter	Group non-NC ($n = 264$)	Group NC ($n = 43$)	p-value (non-NC vs. NC)	Group CVA ($n = 35$)	p-value (non-NC vs. CVA)
Haemodynamic variables					
Cardiac index (l/minute/m^2)	1.8 ± 0.4	1.7 ± 0.3	0.118	1.7 ± 0.5	0.179
PCWP (mmHg)	28.4 ± 8.1	2.3 ± 8.9	0.268	28.8 ± 10.0	0.790
Mean pressure (mmHg)					
Pulmonary artery	36.2 ± 9.4	38.5 ± 9.7	0.140	37.2 ± 12.0	0.568
Right atrial	12.9 ± 7.9	13.2 ± 7.8	0.817	12.6 ± 8.0	0.833
Atrial	79.1 ± 12.8	76.3 ± 9.6	0.171	77.1 ± 10.0	0.375
Vascular resistance (Wood units)					
Peripheral	3.8 ± 2.2	3.9 ± 2.4	0.785	3.7 ± 2.5	0.804
Systemic	23.1 ± 6.3	23.8 ± 9.2	0.530	23.8 ± 7.9	0.550
Laboratory examinations					
White cell count (× 10^3/pl)	8.2 ± 2.3	9.0 ± 3.9	0.060	9.0 ± 3.8	0.078
Lymphocytes (%)	11.4 ± 5.2	10.9 ± 3.7	0.545	10.3 ± 4.6	0.234
Haematocrit (%)	33.2 ± 5.9	32.4 ± 6.2	0.304	32.1 ± 6.3	0.414
Platelets (× 10^3/111)	191 ± 86	190 ± 80	0.898	189. ± 85	0.876
Bilirubin (mg/dl)					
Total	1.7 ± 1.3	1.8 ± 1.5	0.678	1.6 ± 1.6	0.375
Direct	0.6 ± 0.5	0.7 ± 0.7	0.254	0.7 ± 0.9	0.322
Sodium (mEq/l)	132.1 ± 8.1	129.0 ± 7.0	0.018	129.1 ± 7.1	0.038
Potassium (mEq/l)	4.3 ± 0.5	4.4 ± 0.5	0.225	4.4 ± 0.4	0.257
BUN (mg/dl)	37 ± 18	35 ± 19	0.460	34 ± 18	0.442
Creatinine (mg/dl)	1.6 ± 0.4	1.5 ± 0.9	0.224	1.5 ± 0.7	0.212
Albumin (mg/dl)	3.7 ± 0.6	3.5 ± 0.7	0.049	3.5 ± 0.7	0.030
ALT (IU/l)	99 ± 100	88 ± 96	0.509	91 ± 91	0.661
AST (IU/l)	72 ± 86	55 ± 77	0.231	60 ± 77	0.428
BNP (pg/ml)	1835 ± 1117	2101 ± 1046	0.145	1921 ± 946	0.663
INR	1.4 ± 0.5	1.3 ± 0.4	0.213	1.3 ± 0.3	0.249
Echocardiographic parameters					
LVEDD (mm)	69.5 ± 12.1	71.9 ± 12.8	0.240	70.7 ± 12.5	0.588
LVEF (%)	18.4 ± 10.0	20.0 ± 12.4	0.353	19.1 ± 10.8	0.713

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

Malnutrition and inflammation, pre-LVAD and post-LVAD factors known to be associated with severity of HF were also associated with development of major complications after LVAD placement such as NC and infection. The authors suggest that major complications after LVAD placement, such as NC and infection, may also have a cause-and-effect relationship with each other

Adverse events reported (by group and/or intervention)

51 NC events occurred in 43 patients (14.0%, 0.23 events/patient/year) after a mean of 92 ± 116 days after LVAD surgery, consisting of 27 events in 24 patients (14.4%) with HMI and 24 events in 19 patients (13.6%) with HMII. These 43 patients were classified as those in group NC
A total of 39 CVA events occurred in 33 patients (10.7%, 0.18 events/patient/year) at 80 ± 103 days after surgery, consisting of 22 events in 19 patients (11.4%, 0.34 events/patient/year) with HMI and 17 events in 14 patients (10.0%, 0.16 events/patient/year) with HMII. These patients were classified as those in group CVA
Duration from LVAD surgery to all NC events revealed that 37 of 51 events (72.5%) occurred within 6 months after LVAD surgery
Multiple NCs occurred in six patients (2.0%)
Stepwise forward selection analysis found that history of CVA and post-operative infection was independently associated with the development of NCs after LVAD surgery. A discriminant function test found that a discriminant score (*z*-value), yielded a discriminant probability of 76.6%

Post-operative infection data in all patients

Infection type	Group non-NC (*n* = 264)	Group NC (*n* = 43)	*p*-value (non-NC vs. NC)	Group CVA (*n* = 35)	*p*-value (non-NC vs. CVA)
All forms, *n* (%)	51 (19.3)	17 (39.5)	0.003	13 (37.1)	0.016
Sepsis, *n* (%)	41 (15.1)	9 (20.9)	0.377	7 (20.0)	0.498
LVAD related, *n* (%)	30 (11.4)	10 (23.3)	0.031	7 (20.0)	0.145
Urinary tract, *n* (%)	45 (17.0)	11 (25.6)	0.179	9 (25.7)	0.082
Respiratory, *n* (%)	30 (11.4)	6 (14.0)	0.624	5 (14.2)	0.613
Others, *n* (%)	14 (5.3)	4 (9.3)	0.874	2 (5.7)	0.577

Adverse events reported (by group and/or intervention)

Stepwise forward selection analysis of factors associated with NC and CVA after LVAD placement

Factors	OR (95% CI)	*p*-value
Associated with overall NC development		
History of CVA	2.37 (1.24 to 5.29)	0.011
Pre-operative factor		
Sodium	0.93 (0.90 to 1.12)	0.208
Albumin	0.51 (0.21 to 1.37)	0.079
Post-operative factor		
Haematocrit	0.96 (0.71 to 1.22)	0.184
Sodium	0.84 (0.68 to 1.21)	0.075
Albumin	0.71 (0.46 to 2.42)	0.143
Infection	2.99 (1.16 to 10.49)	0.011
Associated with CVA development		
Pre-operative factor		
Sodium	0.95 (0.92 to 1.01)	0.057
Post-operative factor		
Sodium	0.92 (0.90 to 1.02)	0.060
Albumin	0.43 (0.23 to 0.98)	0.050
Infection	4.24 (1.69 to 14.58)	0.0005

Cause of death reported (by group and/or intervention)

Unclear

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

The overall frequency of NC including TIA was 14.0% after LVAD placement and that the frequency of ischaemic/haemorrhagic CVA was 11.4%; the frequency of NC was not different between patients with HMI vs HMII devices; the history of CVA and post-operative infection were factors independently associated with development of NCs after LVAD placement; the combination of prior CVA, pre-operative sodium and albumin, post-operative sodium, haematocrit and albumin, and post-operative infection could discriminate patients who develop NCs with a discriminant probability of 76.6%; and an analysis done for CVA patients after excluding patients with only TIA yielded similar results. Previous CVA, persistent malnutrition, persistent inflammation, severity of HF, and post-LVAD infections were found to be key factors associated with NC as well as CVA development after LVAD implantation

Reviewer's conclusion

The study did not reveal differences in frequency of NC development between devices in different generation. The authors claim that these findings provide helpful guidance for risk stratification and clinical management strategies of patients with advanced HF receiving LVAD support. Furthermore, previous stroke, persistent malnutrition and inflammation, severity of HF, and post-LVAD infections were considered to be key factors associated with the development of NCs after LVAD implantation. However, owing to limitations of the statistical analyses in terms of a failure to adjust for the large number of multiple analyses caution should be made when interpreting these findings

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalised ratio; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; OR, odds ratio; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Klotz 2006[88]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Klotz
Year of publication: 2006
Country: Germany
Study design: Retrospective
Study setting: University hospital in Münster
Number of centres: One
Duration of study: Unclear
Follow-up period: Unclear
Funding: No information

Aim of the study

To find out if the pre- and post-transplant outcomes of CF LVADs are similar to pulsatile LVADs

Participants

Total number of participants: CF LVAD $n = 50$ (MicroMed DeBakey $n = 30$ and INCOR Berlin Heart $n = 20$); pulsatile LVAD $n = 80$ (Novacor $n = 61$ and HM $n = 19$)
Sample attrition/dropout: Presumably none
Inclusion criteria: Unclear. It included patients receiving pulsatile LVAD from the year 1993 and continuous LVAD from the year 2000 at the Münster University hospital
Exclusion criteria: Patients with extracorporeal LVAD systems and patients aged < 17 years
Characteristics of participants:
Mean age (SD): MicroMed DeBakey 43.0 ± 14.6; INCOR 46.1 ± 11.1; Novacor 45.0 ± 11.9; HM 49.4 ± 7.2
Median age: Not reported
Age range: Not reported
Sex: Male – MicroMed DeBakey 87%; INCOR 70%; Novacor 85%; HM 95%
Race: Not reported
Diagnosis: Dilated cardiomyopathy – MicroMed DeBakey 37%; INCOR 45%; Novacor 51%; HM 42%

Intervention

Indication for treatment: Elective – MicroMed DeBakey 13%, INCOR 30%, Novacor 16%, HM 26%; urgent – MicroMed DeBakey 43%, INCOR 35%, Novacor 54%, HM 42%; emergency – MicroMed DeBakey 44%, INCOR 35%, Novacor 30%, HM 32%
Type of device used: Continuous LVAD – MicroMed DeBakey or INCOR Berlin Heart; pulsatile LVAD – Novacor or HM
Any comparison: Patients with a CF device was compared with an age-, disease-, and LVAD duration-matched control group supported with a pulsatile device. Mortality data compared with patients after cardiac transplantation without previous LVAD support
Duration of treatment: Unclear
Percentage of patients using inotropes: Unclear
Other interventions used: No information
Any FDA or CE approval: Yes – MicroMed DeBakey; INCOR

Outcomes

Primary outcomes: Mortality data compared with patients after cardiac transplantation without previous LVAD support
Secondary outcomes: Adverse events
Method of assessing outcomes: Medical records. No clear information
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Unclear

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported	Not reported
Randomised/included	50 patients with a CF device (MicroMed DeBakey, $n = 30$ and INCOR Berlin Heart, $n = 20$)	LVAD duration-matched control group ($n = 80$) supported with a pulsatile device (Novacor, $n = 61$ and HM, $n = 19$)
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics		
Age, years	CF: MicroMed DeBakey 43.0 ± 14.6; INCOR 46.1 ± 11.1	Pulsatile flow: Novacor 45.0 ± 11.9; HM 49.4 ± 7.2
Sex, male	CF: MicroMed DeBakey 87%; INCOR 70%	Pulsatile flow: Novacor 85%; HM 95%
BSA, m^2	CF: MicroMed DeBakey 1.92 ± 0.18; INCOR 1.91 ± 0.23	Pulsatile flow: Novacor 1.94 ± 0.19; HM 2.02 ± 0.21
Weight, kg, BMI	CF: MicroMed DeBakey 24.5 ± 3.2; INCOR 24.9 ± 3.9	Pulsatile flow: Novacor 24.6 ± 3.6; HM 25.2 ± 4.8
Ischaemic causes of HF	Dilated cardiomyopathy: MicroMed DeBakey 37%; INCOR 45%	Dilated cardiomyopathy: Novacor 51%; HM 42%

Demographics and clinical characteristics at study entry

	CF		Pulsatile		
Demographics	**MicroMed DeBakey**	**INCOR**	**Novacor**	**HM**	***p*-value**
n	30	20	61	19	
Age (years)	43.0 ± 14.6	46.1 ± 11.1	45.0 ± 11.9	49.4 ± 7.2	NS
Gender, male (%)	87	70	85	95	NS
Disease, DCM (%)	37	45	51	42	NS
BMI (kg/m^2)	24.5 ± 3.2	24.9 ± 3.9	24.6 ± 3.6	25.2 ± 4.8	NS
BSA (m^2)	1.92 ± 0.18	1.91 ± 0.23	1.94 ± 0.19	2.02 ± 0.21	
Inotropic agents (%)	83	75	86	79	
IABP (%)	27	25	16	21	
ECC (%)	20	15	16	11	
Status of implantation (%)[30]					NS
Elective	13	30	16	26	
Urgent	43	35	54	42	
Emergency	44	35	30	32	
LVAD duration, days (death prior HT)	69 ± 63	68 ± 34	80 ± 104	68 ± 68	NS
LVAD duration, days (BTT)	240 ± 115	194 ± 177	160 ± 87	195 ± 120	NS

Survival outcomes reported (by group and/or intervention)

Long-term survival was similar in both LVAD groups compared with patients without previous LVAD support
From transplanted patients with prior CF LVAD support who survived longer than 30 days, 89% had rejections equal to or higher than ISHLT grade III
K–M survival analysis for transplanted patient with previous CF LVAD support log-rank = 0.7085

Patients at risk

Intervals	Pulsatile flow	CF	Control group
0	45	25	262
2	29	13	169
4	28	6	146
6	20		115
8	15		87
10	15		58

Other specified/relevant outcomes reported (by group and/or intervention)

Successful BTT was similar with CF in comparison with pulsatile device support (52% vs. 56%; p = NS)
Severe rejections were more frequent in patients with a CF LVAD ($p < 0.001$)
Patients who died during LVAD support were significantly older compared with patients who could be transplanted ($p < 0.05$)
The rate of rejection ISHLT grade III or greater in the pulsatile group was 33% ($p < 0.001$)

Pre transplantation

Overall mortality rate pre transplant was 48% ($n = 24$) in CF group and 44% ($n = 35$) in pulsatile group (p = NS). Time interval from LVAD implantation to death in the CF group was not significant to pulsatile group (68 ± 54 days vs. 76 ± 95 days; p = NS). In analyses of patients who received an LVAD under emergency conditions in acute cardiogenic shock, in 20 patients in CF group, BTT or weaning was possible in $n = 10$ (50%). In pulsatile group this was possible in 14 out of 24 patients (58%) of the emergency implants

Post transplantation

In CF group, 23 patients (46%) transplanted and 3 patients (6%) weaned from device. In pulsatile group, 45 patients (56%) transplanted (p = NS). The time from LVAD implantation to cardiac transplant was 220 ± 147 days in CF group and 167 ± 96 days in the pulsatile group ($p = 0.084$). Post-transplant 30-day mortality was 21.7% in CF group and 22.2% in pulsatile LVAD group
In both groups, age was significantly higher in patients who died during LVAD support
BMI was significantly higher in pulsatile LVAD group in patients who died before cardiac transplant compared with patients who BTT successfully (25.7 ± 4.5 vs. 24.0 ± 3.2 kg/m^2; $p < 0.05$), while there was no difference between the CF LVAD and control groups
Pulsatile LVADs in this study were implanted from the year 1993 to 2000 while CF LVADs were implanted starting from year 2000

Adverse events reported (by group and/or intervention)

The risk of severe rejection was increased threefold after CF LVAD support, compared with pulsatile LVAD support

Cause of death reported (by group and/or intervention)

Reasons for death were similar among the different LVAD groups

Pre transplant

CF device vs. pulsatile device (read off graphs – approximations): multiorgan failure (~ 35 vs. ~ 45 deaths); cerebral (~ 47 vs. ~ 33 deaths); device related (~ 9 vs. 0); right HF (~ 6 vs. ~ 13); sepsis (~ 10 vs. ~ 11); bleeding (~ 0 vs. ~ 6). No significant difference between CF and pulsatile LVAD group

Post transplant

CF vs. pulsatile device (read off graphs – approximations): multiorgan failure (~ 22 vs. ~ 42 deaths); cerebral (~ 42 vs. ~ 0 deaths); right HF (~ 42 vs. ~ 31); rejection (~ 0 vs. ~ 12); sepsis (~ 0 vs. ~ 22). Reasons for death post transplant showed no significant difference between CF and pulsatile LVAD groups. Trend towards lower incidence of rejection, sepsis, and multiorgan failure while the incidence of cerebral accident is elevated

QoL reported (by group and/or intervention)

Not reported

Author's conclusion
New generation of cardiac assist devices with CF pattern has a similar rate of pre- and post-transplant mortality in comparison with pulsatile LVADs. The rate and severity of post-transplant rejection was significantly higher in with CF device group. Further studies are needed to explain the higher rate of severe rejections
Reviewer's conclusion
Overall the analyses generally support the author's conclusions; however, patients were not randomised to different VADs. Authors did use age-, disease- and LVAD duration-match controls. Regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables. Exact *p*-values were not reported

BSA, body surface area; DCM, idiopathic dilated cardiomyopathy; ECC, extracorporeal circulation prior to LVAD implantation; NS, not significant.

Kormos 2010[67]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Kormos
Year of publication: 2010
Country: Unclear
Study design: Presumably retrospective analysis of data from multicentre trial. Data were then divided into different groups and compared against each other
Study setting: Not reported
Number of centres: Multicentre
Duration of study: 1 year
Follow-up period: 1 year
Funding: Unclear

Aim of the study

To evaluate incidence, risk factors and effect on outcomes of RVF in patients implanted with HMII CF LVAD

Participants

Total number of participants: Total $n = 484$ – no RVF $n = 386$ and RVF subgroups $n = 98$ (RVF-RVAD $n = 30$; RVF-early inotropes $n = 35$; RVF-late inotropes $n = 33$). Data from RVF-RVAD and RVF-early inotropes were combined to form an early RVF group ($n = 65$)
Sample attrition/dropout: None
Inclusion criteria: Patients receiving HMII LVAD in the multicentre HMII pivotal clinical trial for BTT between March 2005 and April 2008. Patients were listed as status 1A or 1B on the HT list
Exclusion criteria: Not stated
Characteristics of participants:
Mean age (SD): No RVF 51.8 ± 13.5 years; RVF-RVAD 51.0 ± 13.3 years; RVF-early inotropes 55.0 ± 11.0 years; RVF-late inotropes 48.6 ± 12.0 years
Median age: Not reported
Age range: Not reported
Sex (female): No RV: 80 (21%); RVF-RVAD 7 (23%); RVF-early inotropes 8 (23%); RVF-late inotropes 13 (39%)
Race: Not reported
Diagnosis: Ischaemic cause – no RVF 174 (75%); RVF-RVAD 15 (50%); RVF-early inotropes 15 (43%); RVF-late inotropes 10 (30%)

Intervention

Indication for treatment: BTT
Type of device used: HMII LVAD
Any comparison: RVF was defined in HMII clinical trial as either need for a RVAD. In addition: group 1, need of an LVAD support; group 2, continuous inotropic support for at least 14 days after implantation; group 3, late inotropic support starting 14 days after implantation. Data from groups 1 and 2 were combined to form an early RVF group, whereas group 3 patients were examined separately (late RVF group). Rationale for differentiating early and late occurrences of RVF is that cause of the RVF is likely triggered by different mechanisms
Duration of treatment: Durations of support for all RVADs ranged from 0 to 408 days. Most RVADs were implanted within 24 hours of LVAD surgery. Eight patients received RVAD after 24 hours, with one patient receiving RVAD 38 days after LVAD surgery. Three of these eight patients underwent transplantation, four died and one withdrew
Percentage of patients using inotropes: Inotropes, early 35 (7%); inotropes, late 33 (7%)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Identify the potential risk factors for early RVF, survival on HMII, adverse events (intra- and post-operative complications)
Secondary outcomes: Not relevant
Method of assessing outcomes: Medical records. RVF was defined in HMII clinical trial as either need for a RVAD in addition to LVAD, continuous inotropic support for at least 14 days after implantation, or late inotropic support starting 14 days after implantation
Survival: Yes
Adverse event: Yes – intraoperative and post operative
HRQoL: No
Length of follow-up: 1 year

Number of participants	Intervention	Comparator, if present
Screened	Not reported	
Randomised/included	No RVF $n = 386$ and RVF subgroups $n = 98$ (RVF-RVAD $n = 30$, RVF-early inotropes $n = 35$, RVF-late inotropes $n = 33$); data from RVF-RVAD and RVF-early inotropes were combined to form an early RVF group ($n = 65$)	See column to left
Excluded	Not reported	
Missing participants	Not reported	
Withdrawals	Not reported	

Patient's baseline characteristics

Pre-implantation characteristics for all groups

Parameter	No RVF ($n = 386$)	RVF subgroups			p-value[a]	Any early RVF ($n = 65$)
		RVF-RVAD ($n = 30$)	RVF-early inotropes ($n = 35$)	RVF-late inotropes ($n = 33$)		
Percentage of total patients ($n = 484$)	80	6	7	7		13
Sex, female	80 (21%)	7 (23%)	8 (23%)	13 (39%)	0.10	15 (23%)
Ischaemic cause	174 (45%)	15 (50%)	15 (43%)	10 (30%)	0.37	30 (46%)
Age (years)	51.8 ± 13.5	51.0 ± 13.3	55.0 ± 11.0	48.6 I 12.0	0.12	53.0 ± 12.0
BSA	1.99 ± 0.26	1.94 +.0.28	1.98 ± 0.30	2.11 ± 0.63	0.58	1.96 ± 0.29
Cardiac index	2.1 ± 0.7	2.0 ± 0.6	2.2 ± 0.8	2.0 ± 0.5	0.96	2.1 ± 0.7
PCWP (mmHg)	25 ± 8	26 ± 8	26 ± 8	24 ± 7	0.60	26 ± 6
PAPm (mmHg)	36 ± 9	35 ± 9	35 ± 9	35 ± 11	0.94	35 ± 9
PAPs (mmHg)	52 + 13	49 + 12	50 ± 16	50 ± 17	0.54	50 ± 14
PAPd (mmHg)	27 ± 8	27 ± 8	26 ± 8	26 ± 9	0.87	27 ± 8
CVP (mmHg)	12.3 ± 6.4	16.1 ± 6.4[b]	14.5 ± 7.1[c]	12.9 ± 7.7	0.01	15.2 ± 6.8[d]
CVP/PCWP ratio	0.51 ± 0.46	0.64 ± 0.21	0.57 + 0.27	0.51 ± 0.23	0.10	0.60 ± 0.20[d]
RVSWI (mmHg/ml/m^2)	556 ± 298	391 ± 226[c]	541 ± 344.1	560 ± 335	0.04	477 ± 306[c]
PVR (Wood units)	2.91 ± 1.61	2.93 + 1.41	72.79 ± 1.55	2.94 ± 1.67	0.97	2.85 + 1.48
BPs (mmHg)	99 ± 16	102 ± 18	98 ± 15	95 ± 14	0.51	100 ± 16
Heart rate (b.p.m.)	91 ± 19	98 ± 19	89 ± 17	87 ± 19	0.14	93 1 18
IABP	161 (42%)	18 (60%)	15 (43%)	9 (27%)	0.07	33 (51%)
Ventitatory support	21 (5%)	11 (37%)[d]	5 (14%)[c]	3 (9%)	< 0.001	16 (25%)[d]

Patient's baseline characteristics						
Pacing	188 (49%)	10 (33%)	20 (57%)	18 (55%)	0.23	30 (46%)
Creatinine (mg/dl)	1.41 ± 0.50	1.54 ± 0.52	1.53 ± 0.59	1.47 ± 0.63	0.34	1.53 ± 0.56
BUN (mg/dl)	29.6 + 16.6	36.1 ± 17.5[c]	32.0 ± 13.6	33.1 ± 19.7	0.05	33.8 ± 15.0[c]
AST (mg/dl)	74 + 201	236 ± 557[b]	78 ± 236	89 ± 164[c]	0.02	148 ± 415
TBILL (mg/dl)	1.25 + 0.78	1.39 + 1.43	1.34 ± 0.71	1.25 ± 0.98	0.55	1.36 ± 1.07
Haematocrit (%)	34.9 ± 5.5	33.5 ± 7.4	35.3 ± 6.0	34.5 ± 5.4	0.26	4.5 ± 6.6
WBC (× 10^3/ml)	8.7 ± 3.6	11.2 ± 4.6[b]	9.3 ± 3.2	8.4 ± 3.2	0.01	10.1 ± 4.0[b]
Platelet count (× 10^3/ml)	226 ± 88	221 ± 90	220 ± 74	225 ± 93	0.98	220 ± 81
INR (IU)	1.32 ± 0.33	1.57 ± 1.01	1.35 ± 0.32	1.37 ± 0.44	0.89	1.5 ± 0.71
MRVFRS	1.14 ± 1.88	2.04 ± 2.34	1.34 ± 1.70	1.38 ± 1.80	0.08	0.65 ± 2.00[c]

a p-value for differences between the four subgroups.
b $p < 0.01$.
c $p < 0.05$.
d $p < 0.001$ compared with no-RVF group.

Survival outcomes reported (by group and/or intervention)

Actuarial survival

At 1 year: No RVF 79%; RVF-RVAD 59% ($p = 0.004$); RVF-early inotropes 56% ($p = 0.007$); RVF-late inotropes 75% ($p = 0.81$). Actuarial survival at 1 year was also significantly better for patients without RVF (79%) compared with that in patients requiring RVADs (group 1, 59%; $p = 0.004$) or extended inotropes (group 2, 56%; $p = 0.007$)
No difference for patients with late inotrope use (group 3, 75%; $p = 0.81$)
Overall survival
K–M estimates:
At 0 days: No RVF, remaining at risk 386; RVF, remaining at risk 65
At 30 days: No RVF, remaining at risk 348, 94% ± 1%; RVF, remaining at risk 52, 89% ± 4%
At 180 days: No RVF, remaining at risk 206, 87% ± 3%; RVF, remaining at risk 30, 66% ± 6%
At 365 days: No RVF, remaining at risk 105, 78% ± 3%; RVF, remaining at risk 18, 59% ± 7%
At 1 year: No RVF, 78% ± 3%; RVF-RVAD, 59% ± 9% ($p < 0.01$); RVF-early inotropes, 56% ± 9% ($p < 0.01$); RVF-late inotropes, 75% ± 9%; any early RVF, 59% ± 7% ($p < 0.01$)
Decreased survival for patients with early RVF is evident in grouped K–M survival curve
Patients without RVF, 342 (89%) survived to transplantation, recovery, or continuing support at 180 days. Patients with early RVF had worse survival to same end points ($n = 46$, 71%; $p = 0.001$), with those requiring RVADs having lowest percentage reaching these outcomes ($n = 20$, 67%; $p < 0.001$)
Within RVAD group, 17 (77%) of 22 patients who received a RVAD within first 24 hours survived to primary outcome at 180 days, whereas only 3 (38%) of 8 patients who received a RVAD later survived to the same end point

Other specified/relevant outcomes reported (by group and/or intervention)

Other outcomes

Parameter	Patients ($n = 484$)	Length of stay for discharged patients (days)	Transplant, recovery or ongoing at 180 days	K–M survival at 1 year
No RVF	386 (80%)	22 (8–180)	342 (89%)	78% ± 3%
RVF subgroups				
RVAD	30 (6%)	32 (0–158)	20 (67%)	59% ± 9%
Inotropes, early	35 (7%)	35 (17–73)	25 (71%)	56% ± 9%
Inotropes, late	33 (7%)	32 (12–86)	29 (88%)	75% ± 9%
Any early RVF	65 (13%)	32 (0–173)	46 (71%)	59% ± 7%

Other specified/relevant outcomes reported (by group and/or intervention)

Hospital length of stay for discharged patients was longer for those requiring a RVAD than for those without RVF (32 vs. 22 days; $p < 0.001$). Those who required inotropic support for > 14 days after LVAD implantation and those with late inotropic support had an average length of stay of 35 and 32 days, respectively
Any RVF resulted in a significantly longer hospitalisation time before discharge than seen in those without any RVF ($p < 0.001$)

Univariate analysis

The haemodynamic variables of CVP > 15 mmHg, RVSWI < 300 mmHg/ml/m^2, and a CVP/PCWP ratio > 0.63 were statistically significant predictors that indicated a higher risk of RVF. No statistically significant differences in pulmonary artery pressures or pulmonary vascular resistance between groups
With a baseline CVP of > 15 mmHg, 19% of patients had early RVF compared with 10% of patients with a CVP of < 15 mmHg (OR 2.1, 95% CI 1.2 to 3.6; $p < 0.01$)
22% of patients with a CVP/PCWP ratio of > 0.63 had early RVF compared with 11% with a CVP/PCWP ratio of < 0.63, and 26% of patients with an RVSWI of < 300 mmHg/ml/m^2 had RVF compared with 10% of patients with an RVSWI of > 300 mmHg/ml/m^2
Increased WBC and lower haematocrit values were also statistically significant between those who required RVAD support and those who did not
Patients on pre-operative ventilator support were five times more likely to have RVF compared with those without ventilator support
Multivariate analysis found that CVP/PCWP ratio of > 0.63 (OR 2.3, 95% CI 1.2 to 4.3; $p < 0.009$), need for ventilatory support (OR 5.5, 95% CI 2.3 to 13.2; $p < 0.001$), and a pre-operative BUN value of > 39 mg/dl (OR 2.1, 95% CI 1.1 to 4.1; $p < 0.02$) were the independent pre-operative predictors of early RVF after LVAD implantation
The area under the receiver operating curve was 0.68

Adverse events reported (by group and/or intervention)

No significant differences in bleeding and transfusion requirements during implantation or within the first 48 hours of LVAD implantation for those who eventually had RVF
Patients implanted with a RVAD required a greater number of units of packed red blood cell transfusions compared with those without RVF (14.3 ± 18.9 vs. 5.6 ± 5.8 units; $p < 0.03$) and more often required a reoperation for bleeding (40% vs. 19%; $p < 0.04$)
53% of patients who needed a RVAD required > 6 units of PRBCs during implantation procedure, only 26% of those without RVF required similar transfusion
Cardio-pulmonary bypass times were higher in those requiring a RVAD (149 ± 76 vs. 106 ± 61 minutes; $p < 0.005$)

Cause of death reported (by group and/or intervention)

Unclear

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Rates of RVF and RVAD requirement in patients with HMII were low compared with previous results with pulsatile LVADs and support use of this device in those with end-stage HF. The development of RVF remains difficult to predict. Both clinical and haemodynamic factors affect the development of RVF. RVF in HMII recipients was associated with worse clinical outcomes than in patients without RVF, which highlights the importance of appropriate RVF management and prevention

Reviewer's conclusion

No concurrent control group for comparison with pulsatile devices. It was noted that the late inotrope group (group 3) was excluded from RVF group for most of analyses

AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; INR, international normalised ratio; MRVFRS, University of Michigan right ventricular failure risk score; OR, odds ratio; PAPd, diastolic pulmonary artery pressure; PAPm. mean pulmonary artery pressure; PAPs, systolic pulmonary artery pressure; PRBC, packed red blood cell; PVR, pulmonary vascular resistance; RVF, right ventricular failure; RVSWI, right ventricular stroke work index; TBILL, total bilirubin; WBC, white blood count.

Lahpor 2010[68]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Lahpor
Year of publication: 2010
Country: European countries
Study design: Presumably retrospective analysis of data from a multicentre trial
Study setting: Multicentre study
Number of centres: 64 European institutions
Duration of study: March 2004 until August 2008
Follow-up period: All 411 patients were followed for a minimum of 180 days or until either transplantation, explantation after recovery or death
Funding: Not reported

Aim of the study

Report on the European experience with the HMII as a BTT and as a destination device

Participants

Total number of participants: HMII was implanted in 571 patients at 64 European institutions. 411 patients (72%) had implantation at least 6 months before closing date of the study (1 August 2008)
Sample attrition/dropout: None, although analysis focussed on the 411 patients (72%) that had implantation at least 6 months before end of study
Inclusion criteria: Unclear. Patients suffering from end-stage HF secondary to cardiomyopathy; all patients were NYHA class IIIb or IV and were on maximum medical treatment including intravenous inotropic support
Exclusion criteria: Unclear
Characteristics of participants:
Mean age (SD): mean of 51 ± 14 years
Median age: Not reported
Age range: 14–75 years
Sex: 81% male and 19% female
Race: Not reported
Diagnosis: All patients were NYHA class IIIb or IV and were on maximum medical treatment including intravenous inotropic support

Intervention

Indication for treatment: The intention of support was BTT (73%), DT (21%) and a BTR (6%)
Type of device used: HMII
Any comparison: HMII CE mark study (group A), a European multicentric study (group B), and a Dutch single-centre study (group C)
Duration of treatment: Duration of support ranged from 0 to 1019 days with a mean of 236 ± 214 days and a total of 293 patient-years support time
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below. Patients (19% female, 70% ischaemic aetiology) were on maximum medical therapy, including inotropic support
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Overall survival to transplantation, recovery of the natural heart function with device removal or ongoing device support
Secondary outcomes: Not reported
Method of assessing outcomes: Medical records or prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: All 411 patients were followed for a minimum of 180 days or until either transplantation, explantation after recovery or death

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	571	Not reported
Randomised/included	411	Not reported
Excluded	160	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Patient characteristics and LVAD support duration

Parameter	Group A, $n = 53$	Group B, $n = 101$	Group C, $n = 30$
Mean age (years)	46 ± 12	48 ± 13	45 ± 12
Male (%)	60	71	74
Mean support duration (days)	347 ± 214	166 ± 175	264 ± 192
Range (days)	1–1556	1–972	1–615
Total experience (years)	51.3	44.6	22.4

Survival outcomes reported (by group and/or intervention)

All 411 patients were followed for a minimum of 180 days or until either transplantation, explantation after recovery or death
Overall survival to transplantation, recovery or ongoing device support at end of study was 69% ($n = 284$) with an early mortality of 17.5% and late mortality of 13.5%
Of surviving patients, 23% had been transplanted, 4% had their device removed after recovery of LV and 42% were still ongoing
A total of 249 (61%) patients were supported for > 6 months, 119 (29%) patients for > 1 year and 12 (3.0%) patients for > 2 years
Overall survival to transplantation, recovery of natural heart function with device removal or ongoing device support was 69% (284) at end of study, with an early mortality (30 days) of 18% and late mortality of 13%
Survival rate at 6 months = 74% and at 1 year = 71.5%. Of the surviving patients by end of follow-up period, 23% were transplanted, 4% had device removed after recovery of LV and 42% were still ongoing 6 months following implant
Actuarial survival: taken from curve
Number at risk: 0 days = 409; 90 days = 297; 180 days = 249; 270 days = 181; 360 days = 121
Survival probability (%):180 days = 72% ± 2%; 360 days = 65% ± 3%
Competing-outcomes analysis of survival to transplantation, recovery of the natural heart, or ongoing device (percentage of patients): Recovery at 180 days = 2.5% and 1 year = 5%; transplanted at 180 days = 11% and 1 year = 23%; expired at 180 days = 26% and 1 year = 31%; ongoing at 180 days = 61% and 1 year = 41%; positive outcomes at 180 days = 74% and 1 year = 69%

Other specified/relevant outcomes reported (by group and/or intervention)

No applicable

Adverse events reported (by group and/or intervention)

Adverse events occurred in first 53 patients in original HMII CE mark study (group A), in 101 patients of European multicentric study (group B) and 30 patients in a Dutch single-centre study (group C)
Most common adverse events occurring following implantation of a HM VAD are shown below
NCs occurred primarily in first 6 weeks following implantation
Adverse events included bleeding (ranging from 42% in group C to 59% in group A), percutaneous lead infections (group A 0.19, group B 0.61 and group C 0.18 events/patient-year), pocket infections (group A 0.08, group B 0.07 and group C 0.09 events/patient-year), ischaemic stroke (group A 0.06, group B 0.09 and group C 0.04 events/patient-year), haemorrhagic stroke (group B 0.07 and group C 0.04 events/patient-year) and TIAs (group A 0.08, group B 0.02 and group C 0.13 events/patient-year)
Rethoracotomy or multiple blood transfusions (6 units/24 hours) due to bleeding, mainly due to coagulopathy was found in all groups (e.g. group C = 43% and group A = 59%)
Other frequent adverse events are cardiac arrhythmias, right-HF, renal failure and haemolysis
Pocket infections was a more serious complication with incidences of 0.08, 0.07 and 0.09 events per patient-year

Adverse events reported (by group and/or intervention)

Incidence of sepsis varied from 0.13% (group C) to 0.62% (group B) per patient-year
Isolated percutaneous lead infections were most frequently seen in all three groups with incidences of 0.19, 0.61 and 0.18 per patient-year

Adverse events and events per patient year

	Number of adverse events (events/patient year)		
Adverse events	Group A, *n* = 53	Group B, *n* = 101	Group C, *n* = 30
Bleeding	31 (0.59)	51 (1.14)	13 (0.58)
Ventricular arrhythmias	14 (0.27)	41 (0.92)	3 (0.13)
Infections	47 (0.92)	77 (1.73)	11 (0.49)
Local non-device related	16 (0.31)	19 (0.43)	2 (0.09)
Sepsis	24 (0.47)	28 (0.62)	3 (0.13)
Percutaneous lead	10 (0.19)	27 (0.61)	4 (0.18)
Pump pocket	4 (0.08)	3 (0.07)	2 (0.09)
NCs	7 (0.14)	8 (0.18)	5 (0.22)
Ischaemic stroke	3 (0.06)	4 (0.09)	1 (0.04)
Haemorrhagic stroke	0	3 (0.05)	1 (0.04)
TIA	4 (0.08)	1 (0.02)	3 (0.13)
Device thrombosis	1 (0.02)	1 (0.02)	1 (0.05)
Right ventricular failure	17 (0.33)	10 (0.22)	9 (0.40)
Renal failure	8 (0.16)	18 (0.40)	1 (0.04)
Haemolysis	7 (0.14)	6 (0.13)	4 (0.18)

Cause of death reported (by group and/or intervention)

Most frequent cause of death was multiorgan failure mainly occurring as a result of septic complications or right-HF; the second most common cause was CVAs

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

These results support the use of HMII for long-term support as a BTT and possibly for DT. Future emphasis should focus on minimising adverse events such as infections, bleeding and neurological events. The authors recognise the limitations of the Thoratec Inc. Registry as it is retrospective and does not provide adequate information concerning adverse events and causes of mortality. The data were derived from institutional studies with HMII

Reviewer's conclusion

Limited reporting of baseline characteristics and lack of statistical analyses which suggests caution is needed when interpreting these findings

TIA, transient ischaemic attack.

Martin 2010[69]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Martin
Year of publication: 2010
Country: USA
Study design: Retrospective
Study setting: The OSUMC
Number of centres: Not reported
Duration of study: April 2000 through to March 2009
Follow-up period: Unclear
Funding: Not reported

Aim of the study

Examine a series of LVAD recipients at a single institution to assess the impact of targeted risk factors on the development of infection

Participants

Total number of participants: 145 cases, of which 52 (35.9%) were HMII
Sample attrition/dropout: None
Inclusion criteria: For inclusion in the final analysis, the device had to be in place for > 30 days. The six categories of LVADs identified were: device 1 (HMXVE), device 2 (HMII), device 3 (Thoratec Inc. IVAD), device 4 (VentrAssist LVAS), device 5 [ABIOMED VADs (ABIOMED Inc., MA, USA)], and device 6 (MicroMed)
Exclusion criteria: Not clear
Characteristics of participants:
Mean age (SD): Not reported
Median age: Overall 52 years; HMII details are not provided
Age range: Overall 18–75 years; HMII details are not provided
Sex: Not reported
Race: Not reported
Diagnosis: Unclear

Intervention

Indication for treatment: Not reported
Type of device used: The six categories of LVADs identified were: device 1 (HMXVE), device 2 (HMII), device 3 (Thoratec Inc. IVAD), device 4 (VentrAssist LVAS), device 5 (ABIOMED VADs), and device 6 (MicroMed)
Any comparison: See above devices which were reported in terms of baseline characteristics and risk of infection
Duration of treatment: Unclear, > 30 days
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Risk for infection
Secondary outcomes: None
Method of assessing outcomes: Medical records
Survival: No
Adverse event: Yes
HRQoL: No
Length of follow-up: Unclear

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Through to March 2009, there were 202 LVADs placed in 163 patients at OSUMC since the programme's inception in April 2000. Of the 202 device placements, 150 remained in place for > 30 days. Five had no BMI data	Not applicable
Randomised/included	145 cases for analysis	Not applicable
Excluded	Not reported	Not applicable
Missing participants	Not reported	Not applicable
Withdrawals	Not reported	Not applicable

Patient's baseline characteristics

Comparison between patients with infection vs those without after LVAD placement for long-term support

Parameter	ALL LVAD placements (*n* = 145)	LVAD placements with infections (*n* = 51)	LVAD placements without infections (*n* = 94)	*p*-value[a]
Age, median years (range)	52 (18–75)	50 (20–74)	53 (18–75)	0.316
Male gender	107 (73.8%)	39 (76.5%)	67 (71.3%)	0.351
Median BMI, kg/m^2 (range)	28.41 (14.92–48.35)	29.35 (18.56–47.13)	28.32 (14.92–48.35)	0.372
Underweight	3 (2.1%)	0	3 (3.2%)	Not applicable
Normal weight	39 (26.9%)	12 (23.5%)	27 (28.7%)	0.501
Overweight	41 (28.3%)	14 (27.5%)	27 (28.7%)	0.871
Obese	33 (22.8%)	14 (27.5%)	19 (20.2%)	0.322
Severely obese	15 (10.3%)	5 (9.8%)	10 (10.6%)	0.875
Morbidly obese	14 (9.7%)	6 (11.8%)	8 (8.5%)	0.528
Device type				
1	64 (44.1%)	34 (66.7%)	30 (31.9%)	0.0001
2	52 (35.9%)	8 (15.7%)	44 (46.8%)	0.0001
3	13 (9%)	2 (3.9%)	11 (11.7%)	0.136
4	10 (6.9%)	6 (11.8%)	4 (4.3%)	0.101
5	4 (2.8%)	1 (2%)	3 (3.2%)	0.669
6	2 (1.4%)	0	2 (2.1%)	Not applicable

a *p*-value based on univariate logistical regression analysis.
Please note: device 1 (HMXVE), device 2 (HMII), device 3 (Thoratec Inc. IVAD), device 4 (VentrAssist LVAS), device 5 (ABIOMED VADs), and device 6 (MicroMed).

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

Not reported

Adverse events reported (by group and/or intervention)

The overall time to infection post-device placement was a median 50 days (range 6–524 days)
HMII showed a decreased risk of infection, OR 0.21 with 95% CI 0.09 to 0.50 ($p = 0.0001$). Adjusting for age, gender and BMI as either a continuous variable or by individual weight categories using multivariable logistical regression confirmed this association with infection for both of these devices with device 1 and device 2 (see below)

Results of multivariable regression model on infectious risk and LVAD type

Device type	OR (95% CI)	*p*-value
HMXVE	4.63 (2.14 to 10.03)	0.0006
HMII	0.20 (0.08 to 0.49)	0.0005

Infections among recipients of LVAD long-term support

Infections	Number of infections ($n = 51$)
Source	
Bacteraemia	21 (41.2%)
Driveline	19 (37.3%)
LVAD pocket	5 (9.8%)
Sternal wound	6 (11.8%)
Pathogen	
Staphylococcus aureus	14 (27.5%)
Pseudomonas aeruginosa	7 (13.7%)
Staphylococcus epidermidis	6 (11.8%)
Enteric Gram-negative rods	6 (11.8%)
Enterococcus species	6 (11.8%)
Candida species	5 (9.8%)
Culture negative	5 (9.8%)
Lactobacillus species	1 (2%)
Aspergillus species	1 (2%)

Although the table below does not subdivide the number of infections by device, HMII appeared to have a decreased risk of infection compared with the other device types in the study.

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Certain device types may have an effect infection risk in long-term support. Patients with HMXVE had a greater risk compared with patients with HMII who had a smaller risk. This effect was considered independent of BMI. Understanding risk factors for infection post-LVAD placement for long-term support remains much-needed area of study. Patient selection for long-term LVAD support is a complex decision-making process. In this cohort, there were likely to be a variety of issues that contributed to infectious risk in long-term support

Reviewer's conclusion

This single-centre retrospective analysis presents useful findings related to BMI and infection in patients with various LVADs (including HMII – $n = 52$). Limited information was provided about sample. Caution is needed when comparing the findings as definitions of infections may vary across studies

OR, odds ratio; OSUMC, Ohio State University Medical Centre.

Miller 2007[70]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Miller
Year of publication: 2007
Country: USA
Study design: Prospective study
Study setting: Multicentres in USA
Number of centres: 26
Duration of study: March 2005 to March 2006
Follow-up period: Data on performance of the device and haemodynamics of patients were recorded every 8 hours for 3 days, daily through day 14, and weekly through day 30 while the patient was hospitalised. Physical assessment and laboratory tests and medications were recorded on days 1, 3, 5, 7, 11, 14, 21 and 28 after implantation of the device while the patient was hospitalised. After 30 days, device measurements, laboratory evaluations, and physical assessments were recorded monthly. After discharge, patients were assessed over the telephone at least every 2 weeks; they returned to the investigational study site for follow-up, equipment review, and general status assessment weekly for first 4 weeks and then monthly. Assessment of QoL and a 6-minute walk test were completed at baseline and 1, 3 and 6 months after implantation of device. Deaths of patients and causes of death were determined at autopsy when possible or by examination of medical records or by interviews with family members. Final adjudication was determined by the clinical events committee
Funding: Supervised by the sponsor (Thoratec Inc.) – Investigators in the clinical affairs and biostatistics departments at Thoratec Inc. designed this trial in consultation with FDA and clinical investigators

Aim of the study

To report on results from a large observational clinical study of a CF LVAD

Participants

Total number of participants: 133 patients with end-stage HF
Sample attrition/dropout: Not reported
Inclusion criteria: The following was taken from the supplementary appendix:

1. Patient or their legal representative has signed an informed consent
2. Transplant listed
3. BSA > 1.2 m^2
4. NYHA class IV HF symptoms
5. Female patients of childbearing potential must agree to use adequate contraceptive precautions (defined as oral contraceptives, intrauterine devices, surgical contraceptives or a combination of condom and spermicide) for the duration of the study
6. On inotropic support, if tolerated
7. Despite medical therapy, the patient must meet one of the following criteria:

   (a) No contraindication for listing as Status 1A; or
   (b) No contraindication for listing as Status 1B and meet the following haemodynamic criteria (collected within 48 hours of enrolment):

   - PCWP or PAD > 20 mmHg
   - Cardiac Index < 2.2 l/minute/m^2 or systolic BP < 90 mmHg

Exclusion criteria: Severe renal, pulmonary, or hepatic dysfunction; active uncontrolled infection; a mechanical aortic valve; aortic insufficiency; an aortic aneurysm; presence of other mechanical circulatory support, except for an IABP; and technical obstacles thought to increase surgical risk. Additional information was provided in the supplementary appendix

Patients will be excluded from study participation for any one or more of the following:

1. Aetiology of HF caused by or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy
2. Technical obstacles, which pose an inordinately high surgical risk, in the judgement of the investigator.
3. Existence of any ongoing mechanical circulatory support other than intra-aortic balloon counterpulsation.
4. BMI > 40 kg/m^2
5. Positive pregnancy test if of childbearing potential
6. Presence of mechanical aortic cardiac valve that will not be converted to a bioprosthesis at the time of LVAD implant
7. History of cardiac transplant
8. Platelet count < 50,000/ml

Participants

9. Evidence of an untreated aortic aneurysm > 5 cm
10. Psychiatric disease, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAD management
11. Presence of an active uncontrolled infection
12. Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy the Investigator will require based on the patient's health status
13. Presence of any one of the following risk factors for and indicators of severe end-organ dysfunction or failure:

    (a) An INR > 2.5 which is not attributable to anticoagulant therapy or clopidogrel administration within 5 days
    (b) A total bilirubin that is > 5 mg/dl, or shock liver (e.g. transaminases > 2000), or biopsy proven liver cirrhosis
    (c) History of severe COPD or severe restrictive lung disease
    (d) Fixed pulmonary hypertension, with a most recent PVR > 6 Wood units, that is unresponsive to pharmacological intervention
    (e) History of unresolved stroke or uncorrectable cerebrovascular disease
    (f) Serum creatinine > 3.5 mg/dl or the need for chronic renal replacement therapy (e.g. chronic dialysis)
    (g) Significant peripheral vascular disease accompanied by rest pain or extremity ulceration

1. The patient has moderate-to-severe aortic insufficiency without plans for correction during pump implantation surgery
2. Participation in any other clinical investigation that is likely to confound study results or affect study outcome

Characteristics of participants:
Mean age (SD): 50.1 ± 13.1 years
Median age: Not reported
Age range: Not reported
Sex: Male, *n* = 105 (79%)
Race: White *n* = 92 (69%); Black *n* = 30 (23%)
Diagnosis: Patients with end-stage HF who were on a WL for HT

Intervention

Indication for treatment: BTT
Type of device used: HMII
Any comparison: Not clear – some discussion about comparison with studies involving pulsatile pumps
Duration of treatment: Median duration of support was 126 days (range 1–600 days)
Percentage of patients using inotropes: All patients were receiving intravenous inotropic therapy, with 25% requiring more than one inotrope. 11% of patients could not tolerate inotropes owing to cardiac arrhythmias. Median duration of post-operative inotropic support was 7 days. 17 patients (13%) required inotropic support for > 14 days for right ventricular dysfunction
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Proportions of patients who, at 180 days, had undergone transplantation, had cardiac recovery, or had ongoing mechanical support while remaining eligible for transplantation
Secondary outcomes: Overall survival, survival while receiving device support, survival after transplantation, frequency of adverse events, assessment of functional class by a 6-minute walk test, independent evaluation of NYHA functional class by a physician and QoL
Method of assessing outcomes: Medical records and prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: Yes
Length of follow-up: Data on performance of the device and haemodynamics of patients were recorded every 8 hours for 3 days, daily through day 14, and weekly through day 30 while the patient was hospitalised. Physical assessment and laboratory tests and medications were recorded on days 1, 3, 5, 7, 11, 14, 21 and 28 after implantation of the device while the patient was hospitalised. After 30 days, device measurements, laboratory evaluations and physical assessments were recorded monthly. After discharge, patients were assessed over the telephone at least every 2 weeks; they returned to the investigational study site for follow-up, equipment review and general status assessment weekly for first 4 weeks and then monthly. Assessment of QoL and a 6-minute walk test were completed at baseline and 1, 3 and 6 months after implantation of device. Deaths of patients and causes of death were determined at autopsy when possible or by examination of medical records or by interviews with family members. Final adjudication was determined by the clinical events committee

Number of participants	Intervention	Comparator, if present
Screened	Unclear	
Randomised/included	133	
Excluded	Not reported	
Missing participants	Not reported	
Withdrawals	Three patients underwent replacement of CF pump with a different type of VAD (because of surgical complications that occurred shortly after pump implantation) and were withdrawn from study	

Patient's baseline characteristics

Baseline characteristics of the 133 patients[a]

Characteristic	Value	Characteristic	Value
Age, years	50.1 ± 13.1	Haematologic values	
Sex, male, *n* (%)	105 (79)	Haematocrit, %	34.8 ± 5.2
Race, *n* (%)[b]		White cell count/mm^3	8900 ± 3200
White	92 (69)	Platelets/mm^3	228,000 ± 86,000
Black	30 (23)	Concomitant medications, *n* (%)	
BSA, m^2	2.0 ± 0.3	Inotropic agents	
Ischaemic cause of HF, *n* (%)	49 (37)	Intravenous	118 (89)
LVEF, %	16.3 ± 5.7	Intolerance to inotropic agents owing to arrhythmias	15 (11)
Arterial BP (mmHg)		Two or more inotropic agents	33 (25)
Systolic	95.8 ± 14.6	Diuretic	109 (82)
Diastolic	61.7 ± 11.3	ACE inhibitor	40 (30)
PCWP (mmHg)	26.1 ± 7.9	Angiotensin II-receptor antagonist	7 (5)
Cardiac index (l/minute/m^2)	2.0 ± 0.6	Beta-blocker	51 (38)
Heart rate (b.p.m.)	91.8 ± 18.5	Digoxin	61 (46)

Patient's baseline characteristics

Characteristic	Value	Characteristic	Value
Pulmonary artery pressure (mmHg)		Hydralazine	25 (19)
Systolic	53.0 ± 14.1	Amiodarone	54 (41)
Diastolic	28.2 ± 8.8	Heparin	84 (63)
Mean	36.5 ± 9.7	Warfarin	2 (2)
PVR, Wood units	3.0 ± 1.5	Aspirin	40 (30)
CVP, mmHg	13.5 ± 7.8	Mechanical device, *n* (%)	
RVSWI	564 ± 272	Biventricular pacemaker	64 (48)
NYHA class	IV	ICD	98 (74)
Laboratory values		IABP	55 (41)
Serum sodium (mmol/l)	132.9 ± 5.1	Mechanical ventilation	8 (6)
Serum albumin (g/dl)	3.7 ± 3.3		
Serum pre-albumin (mg/dl)	18.8 ± 8.0		
Serum cholesterol (mg/dl)	126 ± 41		
Serum creatinine (mg/dl)	1.4 ± 0.5		
Estimated creatinine clearance (ml/minute)	75.1 ± 36.8		
BUN (mg/dl)	31.4 ± 17.6		
Serum ALT (U/l)	104 ± 287		
Serum AST (U/l)	67 ± 168		
Serum total bilirubin (mg/dl)	1.2 ± 0.8		
Serum lactate dehydrogenase (mg/dl)	376 ± 371		

a Plus–minus values are means ± SD.
b Race was reported by the patient.

Survival outcomes reported (by group and/or intervention)

Rate of death was 20–25% before transplantation
Overall rate of survival to transplantation, recovery, or continued support with no pump replacement was 75% at 180 days
K–M analysis of survival for patients who continued to receive mechanical support, with data censored for HT and recovery of ventricular function were reported in a figure. Withdrawal from the study was counted as a death. Overall survival of patients who underwent transplantation, recovered cardiac function, or continued to receive mechanical support while remaining a candidate for transplantation was estimated to be 70% at 1 year
Additional estimates of actuarial survival taken from the K–M curve were: 1 month = 89%; 2 months = 88%; 3 months = 84%; 4 months = 79%; 5 months = 75%; 6 months = 75%; 7 months = 74%; 8 months = 74%; 9 months = 74%; 10 months = 74%; 11 months = 68%; 12 months = 68%

Other specified/relevant outcomes reported (by group and/or intervention)

Median duration of support was 126 days (range 1–600 days), with a mean of 168 ± 148 days during a cumulative follow-up of 61.7 patient-years. Median time to transplantation was 97 days (range 15–498 days), and the median time to cardiac recovery for three patients was 347 days (range 161–380 days)
All 133 patients were followed for ≥ 180 days or until transplantation or death: 100 patients (75%) reached HT, cardiac recovery, or survival at 180 days with ongoing mechanical support and eligibility for transplantation
Of 100 patients: 56 underwent a HT, 43 received support and were eligible for transplantation, and one did not need transplantation after recovery of cardiac function and explantation of device
Of 43 patients remaining on device support at 180 days: 32 were on active list for a HT, and 11 remained eligible for transplantation, including four who removed themselves from transplantation list
Among 33 patients with unsuccessful outcomes were 25 patients who died before 180 days of support, with a median time to death of 38 days (range, 6–144) days: five patients became ineligible for transplantation during mechanical support owing to irreversible medical complications, and three patients underwent replacement of the CF pump with a different type of VAD (because of surgical complications that occurred shortly after pump implantation) and were withdrawn from the study

Other specified/relevant outcomes reported (by group and/or intervention)
Two patients who underwent replacement of CF pump with a second identical pump remained in study were alive on mechanical support at 216 and 367 days after replacement Twelve patients (9%) underwent transplantation during their initial hospital stay, and 18 patients (14%) died before discharge while receiving mechanical support. One-hundred patients (75%) were discharged from hospital while receiving mechanical support, with a median hospital stay after surgery of 25 days (range 10–114 days) Median number of days out of hospital before transplantation, readmission, or death was 60 days (range 0–418 days). Forty-four discharged patients required rehospitalisation for complications, with a median duration of rehospitalisation of 4 days (range 0–57 days)

Outcomes of the 133 patients[a]

Outcome	Value
Principal outcomes at 180 days, *n* (%)	100 (75)
HT, *n* (%)[b]	56 (42)
Cardiac recovery with device explanted, *n* (%)[c]	1 (1)
Ongoing device support > 180 days, *n* (%)	43 (32)
On WL for transplantation, *n* (%)[d]	32 (24)
Eligible for transplantation, *n* (%)[e]	11 (8)
Other outcomes, *n* (%)	33 (25)
Death at < 180 days, *n* (%)	25 (19)
Ongoing device support at > 180 days but ineligible for transplantation owing to medical issues, *n* (%)[f]	5 (4)
Device replaced with another LVAD; patient withdrawn from study, *n* (%)	3 (2)
Transplantation, recovery of cardiac function, or ongoing support at 180 days, *n* (%)[g]	105 (79)
With no pump replacement, *n* (%)[h]	100 (75)
Alive with LVAD support, %[i]	
At 1 month	89 ± 3
At 6 month	75 ± 4
At 1 year	68 ± 6
Alive after transplantation, *n* (%)[j]	
At 30 days	64/68 (94)
At 1 year	12/15 (80)

a LVAD denotes left ventricular assist device.
b An additional 12 patients underwent transplantation after 180 days.
c An additional two patients had recovery with the device removed at 347 and 380 days.
d One patient subsequently died at 326 days.
e Of 11 patients who were eligible for transplantation, four removed themselves from the WL owing to a preference to continue mechanical support (one of whom underwent transplantation at 21 months); three were not on the list because of inadequate social support and smoking, alcohol abuse, or a failed drug test; three had reversible illness (one of whom subsequently underwent transplantation at 16 months and one of whom was on the WL at 7 months); and one was being evaluated for potential cardiac recovery but was placed on the WL at 13 months.
f Two patients subsequently died at 184 and 191 days.
g This category includes the 100 patients who met the principal outcomes plus five patients who remained on device support but were not eligible for transplantation owing to medical issues.
h This category includes the 105 patients listed above minus five patients who received pump replacements (three who withdrew from the study and two who remained in the study on CF LVAD support).
i Plus–minus values are means ± SE for actuarial survival.
j For patients who reached the stated interval (actual survival).

Other specified/relevant outcomes reported (by group and/or intervention)

The authors present a figure showing the outcomes of 133 patients after implantation of HMII. It shows all outcomes over time. After 6 months of mechanical support, outcomes were as follows: 56 patients had undergone a HT (42%); 48 patients continued to receive mechanical support (36%), five of whom were ineligible for transplantation; 25 patients had died while receiving mechanical support (19%); three had withdrawn from study; and one patient had recovery of ventricular function after explantation of device (1%). A total of 105 patients (79%) had undergone transplantation, had undergone explantation of device with recovery of ventricular function, or continued to receive mechanical support

Adverse events reported (by group and/or intervention)

Adverse events per patient-year with HMII showed an acceptable risk profile with respect to bleeding requiring surgery (0.78 events/patient-year), driveline infection (0.37 events/patient-year), stroke (0.19 events/patient-year), other non-stroke neurological events (0.26 events/patient-year), and right HF requiring a RVAD (0.08 events/patient-year)
Most common adverse event was bleeding (mainly early post-operative period)
Eight patients (6%) had ischaemic stroke, three (2%) had a haemorrhagic stroke
Five additional patients had TIAs that were completely reversed
Nine patients were reported to have psychological symptoms
Eight patients had other neurological events
Localised infection not related to device implantation occurred in 28% of patients
Device-related infection occurred in 14% of patients, with all infections involving the percutaneous lead and none involving the pump pocket
Five devices were replaced: two for pump thrombosis at 24 and 56 days after implantation and three for complications related to surgical implantation at 1, 15 and 32 days

Adverse events in the 133 study patients[a]

Adverse event	Overall			0–30 days			> 30 days		
	Patients with event (%)	No. of events	Event rate/ patient-year	Patients with event (%)	No. of events	Event rate/ patient-year	Patients with event	No. of with events	Event rate/ patient-year
Bleeding									
Requiring surgery	41 (31)	48	0.78	40	45	4.41	1	3	0.06
Requiring ≥ 2 units of PRBCs only	70 (53)	129	2.09	60	85	8.33	10	44	0.85
Ventricular arrhythmias[b]	32 (24)	49	0.79	24	26	2.55	8	23	0.45
Infection									
Local, not related to device	37 (28)	70	1.13	28	37	3.63	9	33	0.64
Sepsis	27 (20)	38	0.62	18	18	1.77	9	20	0.39
Percutaneous lead	18 (14)	23	0.37	0	0	0.00	18	23	0.45
Pump pocket	0	0	0.00	0	0	0.00	0	0	0.00
Respiratory failure	34 (26)	43	0.70	29	32	3.14	5	11	0.21
Renal failure	18 (14)	19	0.31	15	15	1.47	3	4	0.08
Right HF									
Need for RVAD	5 (4)	5	0.08	4	4	0.39	1	1	0.02
Need for extended inotropic support[c]	17 (13)	17	0.28	12	12	1.18	5	5	0.10

Adverse events reported (by group and/or intervention)

Adverse event	Overall			0–30 days			> 30 days		
	Patients with event (%)	No. of events	Event rate/ patient-year	Patients with event (%)	No. of events	Event rate/ patient-year	Patients with event	No. of with events	Event rate/ patient-year
Stroke									
Ischaemic	8 (6)	8	0.13	5[d]	5	0.49	3	3	0.06
Haemorrhagic	3 (2)	3	0.05	2	2	0.20	1	1	0.02
Spinal cord infarct	1 (1)	1	0.02	0	0	0.00	1	1	0.02
TIA	5 (4)	6	0.10	2	2	0.20	3	4	0.08
Psychological	9 (7)	11	0.18	6	6	0.59	3	5	0.10
Other neurological	8 (6)	10	0.16	3	3	0.29	5	7	0.14
Peripheral non-neurologic thromboembolic event	9 (7)	9	0.15	8	8	0.78	1	1	0.02
Device replacement[e]	5 (4)	5	0.08	3	3	0.29	2	2	0.04
Device thromboses[f]	2 (2)	2	0.03	1	1	0.10	1	1	0.02
Complications of surgical implantation[g]	3 (2)	3	0.05	2	2	0.20	1	1	0.02
Haemolysis	4 (3)	4	0.06	3	3	0.29	1	1	0.02
Hepatic dysfunction	3 (2)	3	0.05	2	2	0.20	1	1	0.02

a The cumulative duration of device support was 61.7 patient-years overall, 10.2 patient-years for 0–30 days, and 51.5 patient-years for > 30 days.
b This event required cardioversion or defibrillation.
c The duration of support was for a period longer than 14 days or starting after day 14.
d All events took place within the first 2 days after implantation.
e Devices were replaced with another HMII in two patients and with another LVAD in three patients
f Events occurred on days 24 and 56.
g Complications included a surgical pledget that was trapped in the pump (day 1), a temporary RVAD that caused a kink in outflow graft (day 15), and malpositioning of the inflow cannula (day 32).

Cause of death reported (by group and/or intervention)

Causes of death in first 180 days after device implantation were: sepsis ($n = 5$); ischaemic stroke ($n = 5$); multisystem organ failure ($n = 4$); haemorrhagic stroke ($n = 3$); anoxic brain injury ($n = 2$; 1 after a protamine reaction and 1 after a hemothorax with cardiac arrest), right HF ($n = 2$), and miscellaneous other causes ($n = 4$). Also one device-related death caused by an inflow graft that was accidentally twisted during implantation

QoL reported (by group and/or intervention)

Most patients who were evaluated at 3 months after device implantation had improvement in two or more NYHA functional classes and improvement in a 6-minute walk test by a distance > 200 m. Measures of QoL significantly improved after device implantation on basis of both survey instruments used ($p < 0.001$)

QoL reported (by group and/or intervention)			
Functional status and QoL[a]			
Variable value	**Baseline**	**3 months**	***p*-value**
NYHA functional class			
Patients evaluated, *n*	133	78[b]	
Mean class	4.0 ± 0.0	1.9 ± 0.7	
Patients with paired measurements, *n*	NA	78	
Class, *n* (96%)			
I	0	25 (32)	
II	0	40 (51)	
III	0	11 (14)	
IV	133 (100)	2 (3)	
Improvement in functional class in paired measurements	NA	2.1 ± 0.7	< 0.001
Distance walked in 6 minutes			
Patients performing test, *n*	25	56	
Patients not performing test, *n*			
Unable for medical reason[c]	105	13	
For other reason[d]	3	13	
Values included in mean distance, *n*	130	69	
Mean distance, m	42 ± 97	292 ± 212	
Patients with paired data			
Patients, *n*	NA	66	
Mean paired change, m	NA	250 ± 232	< 0.001
Patients with improved distance > 200 m, *n*	NA	38 (58)	
QoL			
MLWHF[e]			
Patients completing questionnaire, *n*[d]	114	77	
Mean score	73 ± 25	45 ± 25	
Patients with paired data[f]			
Patients, *n*	NA	61	
Mean paired change in score	NA	–27 ± 26	< 0.001
KCCQ[g]			
Patients completing questionnaire, *n*[f]	113	77	
OSS	33 ± 19	57 ± 20	
CSS	39 ± 22	65 ± 22	

QoL reported (by group and/or intervention)

Variable value	Baseline	3 months	*p*-value
Patients with paired data			
Patients, *n*	NA	60	
Mean paired change in overall score	NA	22 ± 19	< 0.001
Mean paired change in clinical score	NA	25 ± 22	< 0.001

NA, not applicable.
a Plus–minus values are means ± SD.
b Of the 82 patients who were alive at 3 months, four patients did not undergo NYHA evaluation because of issues related to staff availability, scheduling, or oversight.
c Patients in this category were assigned 0 m in distance walked.
d Some patients did not perform the indicated tests or complete the questionnaire because of issues related to staff availability, scheduling, or oversight; other patients underwent a HT or died during the interval.
e Scores on the MLWHF range from 0 to 105, with higher scores indicating a worse QoL.
f Performance was compared with that at baseline measurement.
g Scores on the KCCQ range from 0 to 100, with higher scores indicating a better QoL.

Author's conclusion

HMII provided effective mechanical circulatory support in patients with refractory HF. Circulatory support with this device significantly improved haemodynamic status and improvements in functional status, as assessed with a 6-minute walk test, and in NYHA functional class and QoL, as measured by MLWHF and KCCQs. A CF LVAD can provide effective haemodynamic support for a period of at least 6 months in patients awaiting a HT, with improved functional status and QoL

Reviewer's conclusion

It was noted that the authors were not able to assess the functional status and QoL of all patients, which raises the concern that the estimates of typical benefit with respect to these end points may be subject to ascertainment bias. The criteria for selection of patients for ventricular assist is subjective and may present difficulties in comparison with other studies

ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; ICD, implantable cardioverter-defibrillator; INR, international normalised ratio; LVEF, left ventricular ejection fraction; PAD, pulmonary artery diastolic; PRBC, packed red blood cell; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; TIA, transient ischaemic attack.

Morshuis 2009[85]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Morshuis
Year of publication: 2009
Country: Multiple
Study design: Prospective, multicentre, non-randomised trial
Study setting: Germany, Austria and France
Number of centres: Four
Duration of study: Between 15 January 2004 and 7 March 2007
Follow-up period: All 33 CE mark study patients were followed for ≥ 3 months or until either transplant or death at time of database closure. All 68 patients of both CE mark and post-market studies were followed until 25 August 2008
Funding: Not reported

Aim of the study

Report clinical outcomes of 68 patients implanted with DuraHeart as a bridge to cardiac transplantation in Europe

Participants

Total number of participants: A total of 68 patients were implanted with DuraHeart between January 2004 and July 2008. Of those, 33 patients who met inclusion criteria were enrolled in CE mark study and 35 patients were enrolled in post-market study in four centres (48 patients were enrolled at Heart & Diabetes Centre, North Rhine-Westphalia, Germany, 14 at German Heart Institute Berlin, Germany, five at University of Vienna, Vienna, Austria, and one at Pitie Salpetriere Hospital, Paris, France)
Sample attrition/dropout: Not reported
Inclusion criteria: Patient referred for, and eligible for, cardiac transplantation: BSA 1.1 m^2; NYHA functional class IV; cardiac index 2.2 l/minute/m^2 with either systolic BP 80 mmHg or LAP (PCWP) or PAD ~ 18 mmHg; receiving optimal medical treatment, including inotropes and/or IABP; gives informed consent; all laboratory and physiologic data used for evaluation of patient status were collected within 48 hours of enrolment
Exclusion criteria: Surgical contraindications to LVAD implantation; high-risk cardiothoracic surgery within 30 days of enrolment; myocardial infarction within 30 days of enrolment; aortic regurgitation ~ grade 1; evidence of recent or life-limiting malignant disease; patients with either an implanted mechanical aortic or mitral heart valve; fixed pulmonary hypertension with a PVR ~ 480 dynes/second/cm^5; severe COPD as evidenced by FEV_1 1.5 l/minute; on ventilator support for ~ 1 week within 30 days of enrolment
Characteristics of participants:
Mean age (SD): Not reported
Median age: 58 years
Age range: 29–74 years. Note: 43% of patients were aged > 60 years and 31% were aged > 65 years
Sex: Male 90%
Race: Not reported
Diagnosis: End-stage left ventricular failure

Intervention

Indication for treatment: Bridge to cardiac transplantation
Type of device used: DuraHeart
Any comparison: CE mark study vs. post-market study
Duration of treatment: Unclear – 13 weeks end point and all 68 patients in CE mark and post-market studies were followed until 25 August 2008. The mean support duration was 338 ± 311 days (range 17—1148 days, median 201 days)
Percentage of patients using inotropes: Unclear, all patients were receiving optimal medical treatment (e.g. inotropes and/or IABP)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – DuraHeart

Outcomes

Primary outcomes: Survival of patients either to cardiac transplantation or at 13 weeks (3 months) of device support
Secondary outcomes: Adverse events, device performance, and overall patient status throughout period of DuraHeart support
Method of assessing outcomes: Prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: All 33 CE mark study patients were followed for ≥ 3 months or until either transplant or death at time of database closure. All 68 patients of both CE mark and post-market studies were followed until 25 August 2008

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	Unclear	Not reported
Randomised/included	33 patients were enrolled in CE mark study	35 patients were enrolled in post-market study
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Baseline characteristics of the trial and post-market patients

Characteristics	All (*n* = 68)	Trial (*n* = 33)	Post-market study (*n* = 35)
Age, years (median)	56.7 ± 11.3 (57.6)	55.5 ± 12.5 (57.0)	57.8 ± 10.4 (58.2)
Male (%)	90	85	96
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	2.0 ± 0.2
NYHA class IV (%)	100	100	100
Ischaemic cause of HF (%)	51	42	62
LVEF (%)	20.2 ± 6.9	20.2 ± 6.7	20.2 ± 7.0
LVEDD (mm)	74.6 ± 11.6	74.7 ± 12.9	74.3 ± 9.8
Arterial BP (mmHg)			
Systolic	98.1 ± 16.6	97.2 ± 16.2	99.3 ± 21.7
Diastolic	61.0 ± 13.2	59.2 ± 16.2	63.2 ± 15.6
Cardiac index (l/minute/m^2)		1.8 ± 0.31	
PCWP (mmHg)		22 ± 6.7	
CVP (mmHg)		10.0 ± 4.8	
PVR (dyne/second/cm^5)		265 ± 98	
Blood chemistry values			
Serum albumin (g/dl)	3.4 ± 1.0	3.5 ± 1.0	3.0 ± 0.2
Serum sodium (mmol/l)	132.9 ± 10.4	131.2 ± 12.3	135.4 ± 6.0
Serum creatinine (mg/dl)	1.5 ± 0.7	1.5 ± 0.5	1.6 ± 1.0
BUN (mg/dl)	39.1 ± 24.7	38.7 ± 26.0	39.7 ± 23.4
Serum ALT (U/l)	80.9 ± 231.1	88.9 ± 285.6	67.5 ± 91.8
Serum AST (U/l)	96.7 ± 347.3	114.9 ± 429.3	62.4 ± 53.4
Serum lactate dehydrogenase (mg/dl)	313.7 ± 163.1	294.6 ± 120.3	344.9 ± 215.9
Serum total bilirubin (mg/dl)	1.5 ± 1.6	1.4 ± 1.1	1.7 ± 2.2
Haematologic values			
Haematocrit (%)	36.2 ± 6.3	37.1 ± 6.7	34.8 ± 5.5
Platelets (per mm^3)	198,000 ± 82,000	202,000 ± 91,000	193,000 ± 69,000
INR	1.4 ± 0.5	1.5 ± 0.6	1.3 ± 0.3
Intravenous inotropic support (%)		97	

Patient's baseline characteristics

Characteristics	All (*n* = 68)	Trial (*n* = 33)	Post-market study (*n* = 35)
Mechanical support prior to implant surgery			
ICD/biventricular pacemaker		82	
IABP		18	
Mechanical ventilation		6	

Survival outcomes reported (by group and/or intervention)

Some disagreements in reporting of the overall survival for CE mark study: 'The K–M survival for CE-mark study at time of 15 June 2007 was 81% (95% CI 63% to 91%) at 13 weeks end point and 76% (95% CI 55% to 88%) at 1 year' and 'K–M survival estimates for the CE mark study were 81% (95% CI 63% to 91%) at 3 months, 77% (95% CI 58% to 89%) at 6 months, 72% (95% CI 51% to 85%) at 1 year, and 57% (95% CI 31% to 76%) at 2 years'
The overall K–M survival estimate of all 68 patients was 87% (95% CI 77% to 94%) at 3 months, 81% (95% CI 67% to 89%) at 6 months, 77% at 1 year, and 61% (95% CI 34% to 78%) at 2 years

Other specified/relevant outcomes reported (by group and/or intervention)

The median time to transplantation was 142 days (range 43–497 days); 35 patients (51%) were awaiting HT with a mean support duration of 317 days (range 19–1148 days, median 216 days)
At 1 year of support 16 patients (38%) had undergone transplant, while 13 patients (31%) remained on device support

End-organ function and haemolysis during support

Parameter	Baseline (*n* = 33)[a]	4 weeks (*n* = 30)[a]	13 weeks (*n* = 24)[a]	6 months (*n* = 15)[a]
BUN (mg/dl)	38.7 ± 26.0	22.0 ± 19.6	24.1 ± 21.1	27.9 ± 14.5
Creatinine (mg/dl)	1.5 ± 0.5	1.2 ± 0.4	1.3 ± 0.7	1.4 ± 0.6
Total bilirubin (mg/dl)	1.4 ± 1.1	1.2 ± 2.1	0.7 ± 0.4	0.6 ± 0.2
GOT (U/l)	89 ± 286	36 ± 22	32 ± 10	39 ± 37
GPT (U/l)	115 ± 429	31 ± 23	28 ± 11	21 ± 14
Free haemoglobin (mg/dl)	10.0 ± 10.6	8.1 ± 5.8	11.0 ± 10.0	9.0 ± 7.5
LDH (U/l)	295 ± 120	323 ± 96	267 ± 73	260 ± 77

a Mean ± SD.

Adverse events reported (by group and/or intervention)

Incidence of serious adverse events during support for 33 trial patients

	Overall (*n* = 33) 17.8 patient-years			Initial 11 patients 4.8 patient-years			Last 22 patients 13.0 patient-years		
Serious adverse event	No. of events	No. of patients (%)	Event rate/ patient-year	No. of events	No. of patients (%)	Event rate/ patient-year	No. of events	No. of patients (%)	Event rate/ patient-year
All serious adverse events	92	28 (85)	5.17	34	10 (91)	7.11	58	18 (82)	4.45
Infection, total	24	20 (61)	1.35	8	7 (64)	1.67	16	13 (59)	1.23
Local, non-device related	11	11 (33)	0.62	4	4 (36)	0.84	7	6 (27)	0.54
Driveline	6	5 (15)	0.34	2	1 (9)	0.42	4	4 (18)	0.31
Pocket	1	1 (3)	0.06	0	0 (0)	0	1	1 (5)	0.08

Adverse events reported (by group and/or intervention)

Serious adverse event	Overall ($n = 33$) 17.8 patient-years			Initial 11 patients 4.8 patient-years			Last 22 patients 13.0 patient-years		
	No. of events	No. of patients (%)	Event rate/ patient-year	No. of events	No. of patients (%)	Event rate/ patient-year	No. of events	No. of patients (%)	Event rate/ patient-year
Sepsis	6	6 (18)	0.34	2	2 (18)	0.42	4	4 (18)	0.31
Right HF, total	10	9 (27)	0.56	4	3 (27)	0.84	6	6 (27)	0.46
Requiring RVAD	1	1 (3)	0.06	0	0 (0)	0	1	1 (5)	0.08
Neurological dysfunction, total	10	9 (27)	0.56	7	6 (55)	1.46	3	3 (14)	0.23
CVA	5	5 (15)	0.28	5	5 (45)	1.05	0	0 (0)	0
TIA	5	5 (15)	0.28	2	2 (18)	0.41	3	3 (14)	0.23
Ventricular arrhythmia	7	7 (21)	0.39	2	2 (18)	0.42	5	5 (23)	0.38
Renal dysfunction – acute	4	4 (12)	0.23	3	3 (27)	0.63	1	1 (5)	0.08
Bleeding, total	8	8 (24)	0.45	2	2 (18)	0.42	6	6 (27)	0.46
Requiring surgery	4	4 (12)	0.22	1	1 (9)	0.21	3	3 (14)	0.23
Respiratory failure	4	4 (12)	0.22	1	1 (9)	0.21	3	3 (14)	0.23
Temporary flow interruption	3	2 (6)	0.17	0	0 (0)	0	3	2 (9)	0.23
Hepatic dysfunction	2	2 (6)	0.11	1	1 (9)	0.21	1	1 (5)	0.08
Other, total	16	12 (36)	0.90	5	5 (45)	1.05	11	8 (36)	0.84

Cause of death reported (by group and/or intervention)

Majority of deaths (six patients, 85%) occurred in initial 11 patients enrolled in study. Majority of patients who died had multiple comorbidities
Seven deaths occurred during device support, six before primary end point and one after primary end point
Median time to death was 29 days
One ischaemic and three haemorrhagic CVA were determined to be cause of death in four patients (57%)

Cause of death reported (by group and/or intervention)

Summary of deaths during support

Implant order	Age (years)	Time to death (day)	Cause of death	Other complications	Device relatedness
#2	67	28	Ischaemic CVA	HIT II, Left atrial thrombus, chronic atrial fibrillation	Possibly related
#5	60	29	Haemorrhagic CVA[a]	Multiorgan failure	Possibly related
#6	63	21	Subdural haematoma[a] (non-traumatic bleeding)	Multiorgan failure	Unrelated
#7	73	17	Cardiovascular failure (traumatic fall)	Carotid stenosis, confusion	Possibly related
#10	66	86	Haemorrhagic CVA[a]	Sepsis (*Staphylococcus aureus*)	Possibly related
#11	56	37	Haemorrhagic CVA[a]	Sepsis (*Candida albicans*)	Possibly related
#16	61	178	Sepsis	Multiorgan failure	Unrelated

a Three haemorrhagic CVAs with massive intracerebral bleeding and one subdural haematoma resulted in immediate deaths; likely associated with excessive anticoagulation therapy.

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

The study demonstrated that the DuraHeart LVAS appears to be safe and provides an adequate circulatory support with an acceptable adverse event rate for patients eligible for cardiac transplantation. The device may have a potential for long-term circulatory support not only as a bridge to cardiac transplantation, but also for older patient cohort as a DT

Reviewer's conclusion

Limitations of study include a limited clinical experience with 68 patients and lack of direct randomised comparison with other LVADs or optimal medical therapy

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; FEV_1, forced expiratory volume in 1 second; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ICD, implantable cardioverter-defibrillator; INR, international normalised ratio; LAP, left atrial pressure; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PAD, pulmonary artery diastolic; PVR, pulmonary vascular resistance; TIA, transient ischaemic attack.

Morshuis 2010[42]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Morshuis
Year of publication: 2010
Country: Multiple
Study design: Prospective, multicentre, non-randomised trial
Study setting: Germany, Austria and France
Number of centres: Four
Duration of study: between 15 January 2004 and 7 March 2007
Follow-up period: Adverse events were analysed for CE mark study patients ($n = 33$) for extended follow-up periods of at least 15 months at time of database closure on 15 June 2008
Funding: Not reported

Aim of the study

Review the clinical outcome of 82 patients implanted with DuraHeart LVAS in Europe

Participants

Total number of participants: 82 patients were implanted with the DuraHeart LVAS between January 2004 and May 2009 in Europe. Of these, 33 patients who met inclusion criteria were enrolled in approval CE mark study, and 49 patients were implanted after CE mark
Sample attrition/dropout: Not reported
Inclusion criteria: Patients referred for, and eligible for, cardiac transplantation: BSA 1.1 m^2; NYHA functional class IV; cardiac index 2.2 l/minute/m^2 with either systolic BP 80 mmHg or LAP (PCWP) or PAD ~ 18 mmHg; receiving optimal medical treatment, including inotropes and/or IABP; gives informed consent; all laboratory and physiologic data used for evaluation of patient status were collected within 48 hours of enrolment
Exclusion criteria: Surgical contraindications to LVAD implantation; high-risk cardiothoracic surgery within 30 days of enrolment; myocardial infarction within 30 days of enrolment; aortic regurgitation ~ grade 1; evidence of recent or life-limiting malignant disease; patients with either an implanted mechanical aortic or mitral heart valve; fixed pulmonary hypertension with a PVR ~ 480 dyne/second/cm^5; severe COPD as evidenced by FEV_1 1.5 l/minute; on ventilator support for ~ 1 week within 30 days of enrolment
Characteristics of participants:
Mean age (SD): Not reported
Median age: 57 ± 11 years (59 years)
Age range: Not reported
Sex: Male 91%
Race: Not reported
Diagnosis: End-stage left ventricular failure

Intervention

Indication for treatment: Bridge to cardiac transplantation
Type of device used: DuraHeart
Any comparison: CE mark study vs. post-market study. The authors relate to comparisons of pulsatile devices
Duration of treatment: Median duration of device support was 261 days (range 17–1494 days), with a cumulative duration of 78 patient-years
Percentage of patients using inotropes: Unclear. All patients were receiving optimal medical treatment (e.g. inotropes and/or IABP)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – DuraHeart

Outcomes

Primary outcomes: Survival of patients either to cardiac transplantation or at 13 weeks (3 months) of device support
Secondary outcomes: Adverse events, device performance and overall patient status throughout period of DuraHeart support
Method of assessing outcomes: Prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: No

Outcomes

Length of follow-up: Adverse events were analysed for CE mark study patients ($n = 33$) for extended follow-up periods of at least 15 months at time of database closure on 15 June 2008

Number of participants	Intervention	Comparator, if present
Screened	Unclear	Unclear
Randomised/included	$n = 82$	Trial $n = 33$; post-market study $n = 49$
Excluded		
Missing participants		
Withdrawals	One patient (2%) was withdrawn from study after original device was replaced	

Patient's baseline characteristics

Pre-implant characteristics of the trial and post-market patients

Characteristics	All ± SD ($n = 82$)	Trial ± SD ($n = 33$)	Post-market study ± SD ($n = 49$)	p-value (trial vs. post-market study)
Age, years (median)	57 ± 11 (59)	55 ± 13 (57)	58 ± 10 (59)	0.6462
Male (%)	91	85	96	0.161
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	2.0 ± 0.2	0.8986
NYHA class IV (%)	92	100	85	0.0303
Ischaemic cause of HF (%)	52	42	57	0.1207
LVEF (%)	20 ± 7	20 ± 7	20 ± 7	0.8986
LVEDD (mm)	72 ± 11	75 ± 13	70 ± 10	0.0689
Systolic arterial BP (mmHg)	92 ± 1 8	97 ± 16	76 ± 15	0.0007
Diastolic arterial BP (mmHg)	54 ± 15	59 ± 16	38 ± 14	0.0004
Cardiac index (l/minute/m^2)	2.0 ± 0.5	1.8 ± 0.3	2.2 ± 0.6	0.0018
PCWP (mmHg)	20 ± 6.6	22 ± 6.7	19 ± 6.4	0.165
CVP (mmHg)	9 ± 5	10 ± 5	8 ± 5	0.1762
Pulmonary vascular resistance (dyne/second/cm^5)	232 ± 106	265 ± 98	200 ± 105	0.0068
Blood chemistry values				
Serum sodium (mmol/l)	134 ± 10	131 ± 12	136 ± 6	0.0132
Serum creatinine (mg/dl)	1.5 ± 0.7	1.5 ± 0.5	1.5 ± 0.7	0.9042
BUN (mg/dl)	37 ± 22	39 ± 26	36 ± 19	0.9808
Serum ALT (U/l)	82 ± 287	89 ± 286	57 ± 62	0.0827
Serum AST (U/l)	71 ± 191	115 ± 429	56 ± 68	0.3388
Serum lactate dehydrogenase (mg/dl)	372 ± 288	295 ± 120	437 ± 364	0.0732
Serum total bilirubin (mg/dl)	1.4 ± 1.1	1.4 ± 1.1	1.2 ± 0.8	0.7925
Haematological values				
Haematocrit (%)	35 ± 6	37 ± 7	33 ± 5	0.0152
Platelets per mm^3	199,000 ± 84,000	202,000 ± 91,000	199,000 ± 80,000	0.9311

Patient's baseline characteristics

Characteristics	All ± SD ($n = 82$)	Trial ± SD ($n = 33$)	Post-market study ± SD ($n = 49$)	p-value (trial vs. post-market study)
Inotrope values				
Intravenous inotropic support (%)	91	97	88	0.1329
Number of inotropes/patient	1.8 ± 1.0	1.8 ± 0.8	1.8 ± 1.1	0.9517
Mechanical support prior to implant surgery (%)				
ICD	53	48	56	0.5069
Biventricular pacemaker	37	36	38	1
IABP	26	18	33	0.2033
Mechanical ventilation	10	6	13	0.462

Survival outcomes reported (by group and/or intervention)

20 (24%) patients died on support with a median time to death of 167 days (range 17–1066 days)
70% of deaths occurred within 1 year of support
As of August 2009, 36 patients (45%) were alive using device support, with a median duration of 442 days, with a longest duration of 4.1 years
Overall K–M survival for patients who continued on device support was 90% (95% CI 81% to 95%) at 13 weeks end point; 85% (95% CI 75% to 92%) at 6 months; 79% (95% CI 67% to 87%) at 1 year; and 58% (95% CI 37% to 74%) at 2 years
Overall survival for 62 patients (76% of all patients) implanted at Heart and Diabetes Centre had survival outcome of 85% (95% CI 71% to 92%) at 12 months and 69% (95% CI 48% to 84%) at 24 months; this was significantly better than other centres (log-rank $p = 0.05$ at 12 months and $p = 0.0365$ at 24 months)

Other specified/relevant outcomes reported (by group and/or intervention)

23 patients (28%) received a HT, with a median time to HT of 157 days (range 43–497 days)
87% of patients received a HT within 1 year of device support, 13% received a HT after 1 year
Median age of patients who received a HT was 52 years (range 29–68 years)
Median age of patients with ongoing device support was 60 years (range 30–73 years), with 12 patients (31%) aged > 65 years and 4 patients (11%) aged > 70 years ($p = 0.009$)
Two patients recovered and devices were removed at 283 and 344 days of support
At 1 year, 20 patients (29%) received a HT, 31 patients (46%) remained on device support with median support duration of 1.5 years; 14 patients (21%) died, 2 patients (3%) recovered and underwent device explantation
66 patients (80% of all patients, $n = 82$; 86% survived > 30 days) were discharged from hospital with DuraHeart, with a median hospital stay after implantation of 36 days (range 20–147 days). Median time of out of hospital was 260 days (range 29–410 days)

Adverse events reported (by group and/or intervention)

114 adverse events were observed in 31 patients (94%) during device support
Highest rates of adverse events and deaths were observed within 30 days, and significantly lower levels of adverse events and deaths were observed after 1 month, and further decreased over time during late follow-up periods (91–180 days and > 180 days)
28 infections occurred in 22 patients (67%): 14 (50%) were localised and non-device related (pneumonia, urinary tract infections, respiratory tract infections and decubitus ulceration); six patients (18%) had device-related infections (six driveline and one driveline/pocket infection); and six patients (18%) had sepsis
Events of right HF were found 11 times in 10 patients (30%), and one patient (3%) required a RVAD [Thoratec PVAD™ (Thoratec Inc., Pleasanton, CA, USA)]
A total of 11 neurological events occurred in 10 patients (33%), six were CVA and five were TIAs. Of these six CVAs (four haemorrhagic and two ischaemic), five were determined to be the cause of death. One intracerebral bleeding that followed an accidental fall was resolved without permanent neurological deficit
In the initial 11 patients, five CVAs were reported (1.05/patient-year), whereas only one CVA was found in the last 22 patients (0.04/patient-year) after implementing less intensive anticoagulation and antiplatelet therapy
Five CVAs occurred within the first 3 months and only one haemorrhagic CVA occurred at 549 days post implant
Perioperatively, four patients developed acute renal dysfunction (12%); however, all events resolved within a few days.
One patient (3%) had chronic renal failure and the patient later died of multiorgan failure
Bleeding events occurred 11 times in eight patients (24%)
Four events (two cardiac tamponades and two pump pocket bleedings) required surgical interventions
Three patients (9%) had GI bleeding

Adverse events reported (by group and/or intervention)
Three events of sudden temporary flow interruption occurred in two patients (6%) The authors state that the event rates for major adverse events during DuraHeart support were acceptable in comparison with the first-generation pulsatile and the second-generation axial flow devices. For example, event rate of bleeding requiring surgery (0.14/patient-year) was considerably lower in DuraHeart than first- and second-generation LVADs (1.47/patient-year and 0.78/patient-year, respectively) Three GI bleedings (9%; 0.10/patient-year) at 197, 275 and 113 days after implantation DuraHeart LVAS showed a lower rate of GI bleedings compared with those reported previously with other rotary blood pumps (0.10 vs. 0.63) and comparable to pulsatile pumps Driveline or pocket infection rate was reduced by 90% compared with pulsatile device (0.27 vs. 3.49) and was comparable to the small axial flow devices (0.27 vs. 0.37)

Incidence of serious adverse events of 33 CE mark trial patients for extended duration of support

	Overall ($n = 33$) 28.7 patient-years			0–30 days 2.6 patient years			> 30 days 26.1 patient years		
Serious adverse events	Number of events	Number of patients (%)	Event rate	Number of events	Number of patients (%)	Event rate	Number of events	Number of patients (%)	Event rate
All serious adverse events	114	31 (94)	3.96	50	19 (58)	18.9	64	23 (70)	2.45
Local non-device-related infection	14	14 (42)	0.49	6	6 (18)	2.27	8	7 (21)	0.31
Driveline infection	7	5 (15)	0.24	1	1 (3)	0.38	6	4 (12)	0.23
Pocket infection	1	1 (3)	0.03	1	1 (3)	0.38	0	0	0
Sepsis	6	6 (18)	0.21	3	3 (9)	1.13	3	3 (9)	0.11
Right HF requiring RVAD	1	1 (3)	0.06	1	1 (3)	0.38	0	0	0
Right HF extended inotropes	10	9 (27)	0.35	7	7 (21)	2.65	3	3 (9)	0.11
Ischaemic CVA	2	2 (6)	0.07	2	2 (6)	0.76	0	0	0
Haemorrhagic CVA	4	4 (12)	0.14	1	1 (3)	0.38	3	3 (9)	0.11
TIA	5	5 (15)	0.17	1	1 (3)	0.38	4	4 (12)	0.15
Ventricular arrhythmia	8	8 (24)	0.28	5	5 (15)	1.89	4	4 (12)	0.15
Renal failure	5	5 (15)	0.17	3	3 (9)	1.14	2	2 (6)	0.08
Total bleeding	11	8 (24)	0.38	4	4 (12)	1.51	7	6 (12)	0.27
Bleeding requiring surgery	4	4 (12)	0.14	2	2 (6)	0.76	2	2 (6)	0.07
Respiratory failure	4	4 (12)	0.14	3	3 (9)	1.13	1	1 (3)	0.04
Pump replacement	2	2 (6)	0.07	0	0	0	2	2 (6)	0.08
Hepatic dysfunction	2	2 (6)	0.07	2	2 (6)	0.76	0	0	0
Myocardial infarction	0	0	0	0	0	0	1	1 (3)	0.04
Other, total	34	21 (63)	1.18	3	3 (9)	1.17	20	9 (27)	0.77

Cause of death reported (by group and/or intervention)

Of 20 deaths reported, 13 were adjudicated by the Clinical Event Committee. The primary causes of these 13 deaths were CVA in six patients (four haemorrhagic; two ischaemic) and sepsis in three patients
Other causes included non-traumatic subdural haematoma, accidental fall, acute myocardial infarction and unknown

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Third-generation DuraHeart LVAS combined with a centrifugal pump and active magnetic levitation provided adequate circulatory support with improved survival and reduced adverse event rates during extended follow-up periods for patients who are eligible for transplantation. Better survival outcomes, reduced adverse event rates and long-term device reliability in present study with DuraHeart LVADs compared with first-generation pulsatile LVADs. DuraHeart may have significant potential for long-term circulatory support for both BTT and DT

Reviewer's conclusion

Several limitations were identified including limited clinical experience with 82 patients, with few patients supported beyond 2 years, and lack of a direct, randomised comparison with other LVADs, including second- and third-generation LVAS or optimal medical therapy. These patients appear to have been included in the earlier study by this author

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; FEV_1, forced expiratory volume in 1 second; GI, gastrointestinal; ICD, implantable cardioverter-defibrillator; LAP, left atrial pressure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; PAD, pulmonary artery diastolic pressure; TIA, transient ischaemic attack.

Nativi 2011[89]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Nativi
Year of publication: 2011
Country: USA
Study design: Retrospective
Study setting: Unclear
Number of centres: Unclear. Data taken from ISHLT. The centres participating in data collection were listed on ISHLT website
Duration of study: January 2000 to May 2008
Follow-up period: 4 years
Funding: Part funded by the 2010 ISHLT 'Branislav Radovancevic Memorial' Best Mechanical Circulatory Support Abstract Award

Aim of the study

Determine whether or not post-transplant survival in BTT patients with newer CF LVADs differed from BTT patients bridged with first-generation pulsatile LVADs. Aimed to determine whether or not the era of LVAD implantation influenced survival rates

Participants

Total number of participants: 8557 patients underwent a HT between January 2000 and May 2008. Of these, 2397 required mechanical assist support as a BTT. In first era, 1100 BTT patients were bridged with pulsatile-flow LVADs. In second era, 880 BTT patients were bridged with pulsatile-flow LVADs and 417 BTT patients were bridged with CF LVADs. Control groups consisted of 3432 second-era patients who did not receive LVAD but needed continuous inotropic support before transplant and 2728 patients who did not need LVAD or inotropes
Sample attrition/dropout: None reported
Inclusion criteria: Included adult patients who underwent a HT from January 2000 to May 2008. No further details were provided
Exclusion criteria: 568 patients were excluded from analysis, those who required biventricular support (both LVAD and RVAD or TAH) and those with temporary extracorporeal LVADs [ABIOMED BVS or TandemHeart™ (CardiacAssist Inc., Pittsburgh, PA, USA)]. Excluded patients bridged with CF LVADs transplanted in first era
Characteristics of participants:
Mean age (SD): Pulsatile LVAD 50.1 ± 11.6 years; pulsatile LVAD 50.2 ± 11.7 years; continuous LVAD 50.8 ± 12 years; no LVAD, on inotropes 51.4 ± 12.9 years; no LVAD, no inotropes 51.8 ± 12.6 years
Median age: Not reported
Age range: Not reported
Sex: % male – Pulsatile LVAD 85.5%; pulsatile LVAD 86.1%; continuous LVAD 82.3%; no LVAD, on inotropes 75.0%; no LVAD, no inotropes 74.9%
Race: Not reported
Diagnosis: HF

Intervention

Indication for treatment: BTT
Type of device used: See below

Devices and number

Device	*n*
Pulsatile LVAD, first era	
HMIP, HMVE, HMXVE	1029
Novacor PC, PCq	17
Thoratec	33
Toyobo	12
Other total	9
Total	1100

Intervention

Device	*n*
Pulsatile LVAD, second era	
HM IP, VE, XVE	605
Novacor PC, PCq	58
Thoratec	196
Toyobo	9
Other	12
Total	880
Continuous LVAD, second era	
HMII	291
Jarvik 2000	39
MicroMed DeBakey	34
VentrAssist	31
Other	22
Total	417

Note: first era January 2000 to June 2004; second era July 2004 to May 2008.

Any comparison: Pulsatile LVAD, first era vs. pulsatile LVAD, second era vs. continuous LVAD, second era. Patients who required intravenous inotropes but not LVAD support ($n = 2728$) and patients who did not require either LVAD or inotropes ($n = 3432$) were controls
Duration of treatment: Unclear
Percentage of patients using inotropes: Unclear in the intervention groups. In the control groups: (a) no LVAD, on inotropes ($n = 2728$); and (b) no LVAD, no inotropes ($n = 3432$)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII, Jarvik 2000, MicroMed MicroMed DeBakey

Outcomes

Primary outcomes: All-cause mortality. Secondary analyses focused on
Secondary outcomes: Causes of mortality and non-fatal post-transplant events
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: 4 years

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	First era: Pulsatile LVAD ($n = 1100$) Second era: Pulsatile LVAD ($n = 880$); continuous LVAD ($n = 417$); no LVAD, on inotropes ($n = 2728$); no LVAD, no inotropes ($n = 3432$)	See left column
Excluded	In total 568 patients were excluded from analysis: those who required biventricular support (both LVAD and RVAD or TAH) and those with temporary extracorporeal LVADs (ABIOMED BVS or TandemHeart). In addition, authors excluded patients bridged with CF LVADs transplanted in first era, as significant clinical use of CF devices did not occur until 2004 (n was not reported)	See left column
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Age, years: See below
Sex: See below
BSA, m^2: See below
Weight, kg, BMI: See below
Ischaemic causes of HF: See below

	First era	Second era				
	Pulsatile LVAD ($n = 1100$)	Pulsatile LVAD ($n = 880$)	Continuous LVAD ($n = 417$)	No LVAD, on inotropes ($n = 2728$)	No LVAD, no inotropes ($n = 3432$)	p-values
Recipient						
Age, years	50.1 ± 11.6	50.2 ± 11.7	50.8 ± 12	51.4 ± 12.9	51.8 ± 12.6	< 0.01
BMI	26.7 ± 4.3	27.4 ± 4.6	26.8 ± 4.7	26.2 ± 4.5	26.3 ± 4.4	< 0.01
Gender (% male)	85.5	86.1	82.3	75.0	74.9	< 0.01
PRA (%)b	7.5 ± 20	10.4 ± 24	7.3 ± 19	4.8 ± 15	4.1 ± 14	< 0.01
0–10%	84.7	79.8	84.7	89.0	90.9	< 0.01
> 10–30%	6.7	7.7	6.1	6	4.3	< 0.01
> 30–90%	6.5	9.2	7.9	4.4	4.2	< 0.01
> 90%	2.2	3.2	1.3	0.7	0.7	< 0.01
Blood type						< 0.01
A	36.5	32.6	38.6	41.7	44.2	
B	11.1	12.2	10.1	13.9	15.7	
AB	3.3	3.1	2.6	6.0	7.3	
O	49.1	52.2	48.7	38.4	32.8	
Diagnosis						< 0.01
DCM	45.9	50.6	53.7	52.5	45.7	
ICM	51.6	45.0	44.4	37.6	42.0	

Patient's baseline characteristics

	First era	Second era				
	Pulsatile LVAD ($n = 1100$)	Pulsatile LVAD ($n = 880$)	Continuous LVAD ($n = 417$)	No LVAD, on inotropes ($n = 2728$)	No LVAD, no inotropes ($n = 3432$)	p-values
VHD	1.2	1.8	0.7	2.5	2.2	
CHD	0.4	0.5	0.0	2.9	3.6	
Retransplant	0.5	0.2	0.0	3.0	3.9	
Other	0.5	1.9	1.2	1.5	2.5	
Medical condition (%)						< 0.01
In ICU	27.6	23.1	16.4	47.3	12.9	
Hospitalised not in ICU	35.7	28.2	16.4	18.3	10.9	
Not hospitalised	36.7	48.7	67.2	34.4	76.3	
Diabetes mellitus	20.5	27.4	28.3	25.5	21.7	< 0.01
Creatinine	1.2 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	< 0.01
Ischaemic time (hours)	3.2 ± 1.0	3.4 ± 1.1	3.4 ± 1.1	3.3 ± 1.0	3.2 ± 1.0	< 0.01
Donor						
Age (years)	31.3 ± 12.1	30.9 ± 11.5	30.7 ± 11.8	31.6 ± 12.4	32.2 ± 12.7	0.08
BMI (kg/m^2)	26.3 ± 4.7	26.9 ± 4.7	26.3 ± 4.5	26.1 ± 4.7	26.0 ± 4.6	< 0.01
Gender (% male)	75.2	79.1	78.9	72.2	71.2	< 0.01
Blood type (%)						< 0.01
A	30.4	28.5	35.3	35.3	39.8	
AB	1.2	0.3	0.0	2.2	4.0	
B	6.4	7.2	7.7	10.0	12.1	
O	62.1	64.0	57.1	52.5	44.1	
Cause of death						
Head trauma	62.6	65.6	60.4	61.1	59.5	0.01
Stroke	27.0	21.9	24.0	24.8	26.9	0.02
Other	10.3	12.4	15.6	14.2	13.6	0.01

First era: January 2000 to June 2004; second era: July 2004 to June 2006.

Survival outcomes reported (by group and/or intervention)

No significant difference in survival among patients bridged with CF LVADs compared with patients in control groups; patients without LVAD and not on inotropic support (RR = 1.19; $p = 0.32$) or on inotropic support (RR = 1.16; $p = 0.41$)
No statistically significant difference in post-transplant survival of patients bridged in second era with CF LVADs compared with those bridged with pulsatile-flow LVADs (RR = 1.25; $p = 0.26$)
To adjust for possible confounders of relationship between LVAD use and post-transplant survival, a proportional hazards multivariate regression analysis was undertaken, exploring donor and recipient characteristics collected at time of transplant. The results of this analysis are consistent with the univariate results below

Survival outcomes reported (by group and/or intervention)

Comparison of mortality risk within 4 years in patients bridged with LVADs, for patients transplanted between 1 January 2000 and 30 June 2006: univariate analysis

Variables	RR	95% CI	*p*-value
First-era pulsatile LVAD vs. second-era no LVAD on inotropes	1.21	1.02 to 1.43	0.03
First-era pulsatile LVAD vs. second-era no LVAD/no inotropes	1.25	1.07 to 1.47	0.01
First-era pulsatile LVAD vs. second-era pulsatile LVAD	1.30	1.03 to 1.65	0.03
Second-era continuous LVAD vs. second-era pulsatile LVAD	1.25	0.85 to 1.83	0.26
Second-era pulsatile LVAD vs. second-era no LVAD on inotropes	0.93	0.74 to 1.17	0.51
Second-era pulsatile LVAD vs. second-era no LVAD/no inotropes	0.96	0.76 to 1.20	0.70
Second-era continuous LVAD vs. second-era no LVAD on inotropes	1.16	0.82 to 1.65	0.41
Second-era continuous LVAD vs. second-era no LVAD/no inotropes	1.19	0.84 to 1.69	0.32

Even after adjustment, in the multivariate model, post-transplant survival in second era was similar among all groups of interest BTT patients with pulsatile-flow LVADs, patients bridged with CF LVADs, and patients not requiring LVAD support. See below

Risk factors for mortality within 4 years of transplant, for patients transplanted between 1 January 2000 through 30 June 2006: multivariate analysis

Variables	RR	95% CI	*p*-value
Comparison between groups			
First-era pulsatile LVAD vs. second-era no LVAD on inotropes	1.28	1.05 to 1.58	0.02
First-era pulsatile LVAD vs. second-era no LVAD/no inotropes	1.18	0.97 to 1.44	0.09
First-era pulsatile LVAD vs. second-era pulsatile LVAD	1.28	1.00 to 1.63	0.05
Second-era continuous LVAD vs. second-era pulsatile LVAD	1.29	0.85 to 1.95	0.24
Second-era pulsatile LVAD vs. second-era no LVAD on inotropes	1.01	0.78 to 1.30	0.96
Second-era pulsatile LVAD vs. second-era no LVAD/no inotropes	0.93	0.72 to 1.19	0.55
Second-era continuous LVAD vs. second-era no LVAD on inotropes	1.29	0.88 to 1.91	0.19
Second-era continuous LVAD vs. second-era no LVAD/no inotropes	1.19	0.81 to 1.75	0.37
Categorical			
Recipient on ventilator at time of transplant	1.85	1.29 to 2.64	< 0.01
Recipient history of dialysis	1.73	1.33 to 2.26	< 0.01
Congenital vs. cardiomyopathy	1.54	1.07 to 2.23	0.02
Coronary artery disease vs. cardiomyopathy	1.21	1.04 to 1.41	0.01
Continuous			
Recipient age			< 0.01
Donor age			< 0.01
Recipient height			< 0.01
Serum creatinine			< 0.01
Serum bilirubin			< 0.01

Other specified/relevant outcomes reported (by group and/or intervention)

Not reported

Adverse events reported (by group and/or intervention)

Significant differences in morbidity after transplant in patients in five different groups
Before discharge, most reported adverse event was drug-treated infection
Risk of fatal or non-fatal stroke before discharge was roughly double (3–5%) in patients bridged with LVADs compared with patients without LVADs (< 2%; $p < 0.01$)
Risk of renal failure requiring haemodialysis before discharge was higher in patients bridged with LVADs (11–13%) compared with patients not needing LVAD bridging (9–10%; $p = 0.02$)

Post-transplant events

Post-transplant events	First era	Second era				p-value
	Pulsatile LVAD, *n* (%)	Pulsatile LVAD, *n* (%)	Continuous LVAD, *n* (%)	No LVAD, on inotropes, *n* (%)	No LVAD, no inotropes, *n* (%)	
Prior to discharge						
Drug-treated infection	365 (34.4)	298 (37.0)	116 (35.0)	571 (22.8)	606 (19.9)	< 0.01
Stroke	34 (3.2)	41 (4.8)	13 (3.4)	43 (1.7)	51 (1.6)	< 0.01
Dialysis	113 (10.6)	101 (11.9)	49 (12.7)	255 (9.7)	287 (8.9)	0.02
12 months post discharge						
Treated rejection		163 (24.8)	61 (24.3)	415 (22.2)	500 (21.5)	0.27
Stroke	13 (1.5)	18 (3.1)	5 (2.7)	19 (1.1)	25 (1.2)	< 0.01
Hypertension	658 (75.7)	410 (71.1)	148 (77.9)	1215 (73.2)	1511 (73.5)	0.21
Hyperlipidaemia	646 (74.0)	400 (68.7)	135 (68.5)	1203 (71.1)	1530 (72.3)	0.11
Diabetes mellitus	254 (29.0)	222 (33.5)	84 (33.31)	657 (34.9)	742 (31.7)	0.03
Vascutopathy	52 (6.5)	38 (6.2)	15 (6.6)	129 (7.7)	156 (7.4)	0.68
Malignancy	17 (1.9)	11 (1.6)	2 (0.8)	45 (2.4)	54 (2.4)	0.36
Severe renal dysfunctions	81 (9.2)	40 (6.0)	25 (9.9)	75 (4.0)	104 (4.5)	< 0.01

p-values compare all groups.

Cause of death reported (by group and/or intervention)

Causes of death at 1 year after transplant

Cause of death	First era	Second era				p-value
	Pulsatile LVAD ($n = 1100$), *n* (%)	Pulsatile LVAD ($n = 880$), *n* (%)	Continuous LVAD ($n = 417$), *n* (%)	No LVAD, on inotropes ($n = 2728$), *n* (%)	No LVAD, no inotropes ($n = 3432$), *n* (%)	
Infection	39 (3.6)	24 (2.7)	11 (2.6)	57 (2.1)	74 (2.3)	0.10
Graft failure	41 (3.7)	32 (3.6)	15 (3.6)	75 (2.7)	96 (2.8)	0.31
CAV	3 (0.3)	1 (0.1)	1 (0.2)	5 (0.2)	6 (0.2)	0.85
Acute rejection	9 (0.8)	5 (0.6)	7 (1.7)	27 (1.0)	29 (0.8)	0.36
Technical	9 (0.8)	3 (0.3)	4 (1.0)	10 (0.4)	14 (0.4)	0.18
Multiorgan failure	13 (1.2)	15 (1.7)	5 (1.2)	31 (1.1)	47 (1.4)	0.74
Renal failure	1 (0.1)	2 (0.2)	0 (0.0)	2 (0.1)	3 (0.1)	0.69
Pulmonary	6 (0.5)	4 (0.5)	4 (1.0)	18 (0.7)	21 (0.6)	0.85

Cause of death reported (by group and/or intervention)

Cause of death	First era	Second era				*p*-value
	Pulsatile LVAD (*n* = 1100), *n* (%)	Pulsatile LVAD (*n* = 880), *n* (%)	Continuous LVAD (*n* = 417), *n* (%)	No LVAD, on inotropes (*n* = 2728), *n* (%)	No LVAD, no inotropes (*n* = 3432), *n* (%)	
Cerebrovascular	8 (0.7)	0 (0.0)	2 (0.5)	17 (0.6)	22 (0.6)	0.20
Malignancy	1 (0.1)	1 (0.1)	1 (0.2)	6 (0.2)	7 (0.2)	0.71
Other	15 (1.4)	8 (0.9)	5 (1.2)	34 (1.2)	27 (0.8)	0.33
All causes of death	145 (13.2)	95 (10.8)	55 (13.2)	282 (10.3)	346 (10.1)	

p-values compare all groups. No adjustments were made for multiple comparisons.

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Post-transplant survival of BTT patients with LVADs has improved. In most recent era, the use of either pulsatile- or CF LVADs did not result in increased mortality up to 4 years after transplant. The key finding of this study is the demonstration of improved post-transplant survival of patients bridged with LVADs

Reviewer's conclusion

Large number of confounding factors as shown by the statistically significant differences in baseline characteristics. Cox's proportional hazards assumption may not have been tested

BVS, biventricular support system; CAV, coronary artery vasculopathy; DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; PRA, serum panel reactive antibody; RR, relative risk; VHD, valvular heart disease.

Oswald 2010[90]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Oswald
Year of publication: 2010
Country: Germany
Study design: Prospective
Study setting: Unclear
Number of centres: Unclear
Duration of study: July 2005 and October 2008
Follow-up period: Median follow-up of 12 months of ICD protection during ongoing LVAD support (range 13–1167 days). Outpatient routine follow-up was performed at 3-month intervals
Funding: Not reported

Aim of the study

To investigate incidence and prevalence of VA, defined as ICD interventions, in patients with CF LVADs

Participants

Total number of participants: 61 – HMII was implanted in 44 patients and 17 patients received HW LVAD system
Sample attrition/dropout: None
Inclusion criteria: Consecutive patients with drug refractory highly symptomatic congestive HF and successful implantation of a CF LVAD between July 2005 and October 2008 were included
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): 50 ± 12 years
Median age: Not reported
Age range: 17–75 years
Sex: Male *n* = 58 (95%)
Race: Not reported
Diagnosis: Drug refractory highly symptomatic congestive HF: 46 (75%) patients underwent ICD implantation for primary prophylaxis of VA

Intervention

Indication for treatment: Unclear
Type of device used: HMII and the HW
Any comparison: Outcomes of HMII and HW were not compared
Duration of treatment: ICDs were implanted on average 17 ± 15 days after LVAD implantation
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII and the HW

Outcomes

Primary outcomes: Safety and efficacy of primary prevention ICD therapy and the rate of appropriate ICD interventions
Secondary outcomes: Unclear
Method of assessing outcomes: Prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Median follow-up of 12 months of ICD protection during ongoing LVAD support (range 13–1167 days)

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	HMII *n* = 44 and HW *n* = 17	Not reported
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Variable	*n*	%
Total patients	61	
Age (years)	50 ± 12 (range 17–75)	12 (range 17–75)
Male sex	58	95
Heart disease		
ICM	30	49
NICM	31	51
Medication		
Beta-blockers	42	69
ACE inhibitors	41	67
Aldosterone antagonists	25	41
Diuretics	47	77
Calcium channel blockers	5	8
Oral anticoagulation	61	100
Platelet inhibitors	11	18
Amiodarone	43	71
Digitalis	12	20
LVAD		
HMII	44	72
HW	17	28

Survival outcomes reported (by group and/or intervention)

Patients with a secondary prevention indication for ICD implantation [ICD was implanted before LVAD implantation (12 patients, mean ICD treatment before LVAD 16 ± 16 months)], a monthly event rate was calculated (number of spontaneous VA divided by observation time) for the period before LVAD implantation (0.65 ± 1.56 VA events/month) and after LVAD implantation (0.65 ± 1.58 VA events/month)
This calculated event rate did not differ for the period of time before vs. after implantation of the LVAD (P 0.99)
Patients with no previous arrhythmia history had an estimated 1-year risk of 24% for appropriate ICD treatment
Patients with a secondary prevention indication had an even higher 1-year risk of 50%

Other specified/relevant outcomes reported (by group and/or intervention)

ICD devices and settings

ICD devices and settings	*n* (%)
Primary prevention ICD	46 (75)
Secondary prevention ICD	15 (25)
VVI-ICD	43 (71)
DDD-ICD	5 (8)
CRTD	13 (21)
VT-zone interval (ms)	345 ± 31
VT detection duration (intervals)	24 ± 1
VF-zone interval (ms)	286 ± 13
VF detection duration (intervals)	24 ± 1

Other specified/relevant outcomes reported (by group and/or intervention)

Results

Outcome	*n*	%
Patient status		
Alive with ongoing LVAD	44	72
Alive with explanted LVAD (recovered)	1	2
HT	7	11
Death	9	15
Patient safety and complications		
Non-lethal cerebrovascular event	3	5
LVAD cable infection (total)	14	23
Conservatively managed	13	21
Requiring surgical revision	1	2
Operation for ICD system revision (total)	14	23
HMII and ICD interaction	4	7
ICD replacement for battery depletion	4	7
Right ventricular lead failure	3	5
ICD pocket haematoma revision	3	5
VA burden		
Patients with appropriate ICD Therapy (total)	21	
With monomorphic VT		52
With polymorphic VT		13
With VF		
Patients with inappropriate ICD therapy (after 7-days in hospital blanking period)	15	25

Adverse events reported (by group and/or intervention)

71% of VA were terminated by overdrive pacing, 29% by shock
Nine patients died from thromboembolism or haemorrhage
Overall, the rate of appropriate ICD interventions was 34%, mostly for treatment of monomorphic VT in 52%, polymorphic VT in 13%, and VF in 35%
Patients with a history of VA before LVAD implantation had a significantly higher 1-year rate for ICD therapy compared with LVAD patients with a primary prevention ICD indication LVAD patients (50% vs. 24%)
Patients with NICM had a significantly higher risk for ICD therapy than patients with ischaemic heart disease (50% vs. 22%)

Cause of death reported (by group and/or intervention)

Nine deaths (15%) due to thromboembolic events and haemorrhage, in particular stroke

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

More than one-third of LVAD recipients experience appropriate ICD therapy in the first year. Patients with a secondary prophylactic ICD indication have a twofold increased risk for appropriate shocks compared with patients with a primary prophylactic ICD indication. Patients with NICM have a higher risk of appropriate ICD therapies than patients with ICM. ICD therapy is safe and effective in LVAD patients. VAs leading to ICD intervention occur frequently in LVAD patients over 1 year of follow-up, with large differences depending on underlying cardiac disease and previous arrhythmia history

Reviewer's conclusion

This is the first paper to show prospective data for a large cohort of primary prevention ICD indication patients after LVAD implantation. The author states that it is unclear how often VF in LVAD patients leads to cardiogenic shock and how often LVAD support is sufficient to sustain long-term circulation in non-pulsatile LVADs. Baseline characteristics are not described separately for each group. Regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables – limited reporting of *p*-values

CRTD, cardiac resynchronisation therapy defibrillator; DDD, Dual (sensed) Dual (paced) Dual (inhibited on beat detection); ICD, implantable cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; NICM, non-ischaemic cardiomyopathy; VA, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia; VVI, Ventricle (sensed) Ventricle (paced) Inhibited (on beat of detections).

Pagani 2009[71]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Pagani
Year of publication: 2009
Country: USA
Study design: Prospective non-comparative trial
Study setting: Hospital
Number of centres: 33 centres in the USA
Duration of study: Unclear. Enrolment was between March 2005 and April 2008
Follow-up period: Up to 18 months
Funding: Industry, Thoratec Inc.

Aim of the study

To evaluate the use of a CF rotary LVAD (HMII) as a BTT

Participants

Total number of participants: 281
Sample attrition/dropout: Three participants were withdrawn because of HMII replacement with an alternative device
Inclusion criteria: Patients with HF who were on a WL for a HT at each centre were eligible for study enrolment. Patients were required to have symptoms of NYHA functional class IV HF and to be ill enough to have high priority for transplantation (UNOS status 1a or 1b). A complete list of study inclusion and exclusion criteria have been reported in Miller *et al.*[70]
Exclusion criteria: See Miller *et al.*[70]
Characteristics of participants:
Mean age (SD): 50 years (13)
Median age: Not reported
Age range: Not reported
Sex: Male 214/281 (76%)
Race: Caucasian *n* = 194 (69%)/African American *n* = 61 (22%)
Diagnosis: HF

Intervention

Indication for treatment: BTT
Type of device used: HMII
Any comparison: No
Duration of treatment: Various
Percentage of patients using inotropes: 90% (252/281)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes

Outcomes

Primary outcomes: The principal outcomes assessed, through 18 months after enrolment, were the proportions of patients who had undergone transplantation, had undergone explantation of the device because of recovery of ventricular function, or continued with ongoing MCS
Secondary outcomes: QoL, adverse events
Method of assessing outcomes: Prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: Yes
Length of follow-up: To 18 months; cumulative follow-up of 181 patient-years

Number of participants	Intervention	Comparator, if present
Screened	469 enrolled	
Randomised/included	281 (completed study end points or had 18 months follow-up)	
Excluded	Not reported	
Missing participants	Not reported	
Withdrawals	3	

Patient's baseline characteristics

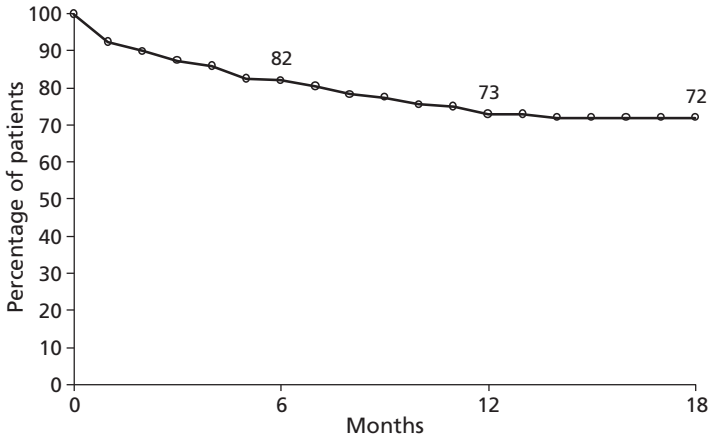
Parameter	Value
Age (years)	50 ± 13
Male	214 (76)
Caucasian/African American	194 (69)/61 (22)
BMI (kg/m^2)	27.1 ± 5.8
BSA (m^2)	2.0 ± 0.3
Ischaemic aetiology of HF	121 (43)
LVEF (%)	16.3 ± 6.5
Arterial BP (mmHg)	
Systolic	98.1 ± 15.0
Diastolic	61.4 ± 11.2
Pulmonary-capillary wedge pressure (mmHg)	25.4 ± 7.9
Cardiac index (l/minute/m^2)	2.1 ± 0.6
Heart rate (b.p.m.)	92.2 ± 18.8
Pulmonary artery pressure (mmHg)	
Systolic	51.4 ± 13.7
Diastolic	26.8 ± 8.4
Mean	35.9 ± 9.6
Pulmonary vascular resistance (Wood units)	2.8 ± 1.4
CVP (mmHg)	12.6 ± 6.5
RVSWI (mmHg/ml/m^2)	548 ± 291
NYHA functional class	IV
Serum sodium (mmol/l)	133.7 ± 5.2
Serum albumin (g/dl)	3.5 ± 0.6
Pre-albumin (mg/dl)	18.4 ± 7.6
Cholesterol (mg/dl)	129 ± 41
Serum creatinine (mg/dl)	1.4 ± 0.5
Estimated creatinine clearance (ml/minute)	78.6 ± 35.1
BUN (mg/dl)	30.4 ± 17.1
ALT (IU/l)	106 ± 278
AST (IU/l)	92 ± 281
Total bilirubin (mg/dl)	1.3 ± 0.9
LDH (mg/dl)	584 ± 1,489
Haematocrit (%)	34.8 ± 5.5
White blood count (× 1000/ml)	9.0 ± 3.4
Platelets (× 1000/ml)	223 ± 88
INR	1.3 ± 0.5

Patient's baseline characteristics

Parameter	Value
Concomitant medications	
Intravenous inotrope agents	252 (90)
Intolerant to inotropes due to arrhythmias	29 (10)
Two or more inotrope agents	91 (32)
Diuretics	228 (81)
ACE inhibitors	73 (26)
Angiotensin-II receptor antagonists	17 (6)
Beta-blockers	100 (36)
Digoxin	111 (40)
Hydralazine	37 (13)
Amiodarone	105 (37)
Heparin	174 (62)
Warfarin	6 (2)
Aspirin	89 (32)
CRT	135 (48)
ICD	213 (76)
IABP	126 (45)
Mechanical ventilation	26 (9)

Survival outcomes reported (by group and/or intervention)

K–M survival analysis



As of June 2008, 42 patients were alive with device support with a median duration of 1.6 years (longest duration 3.1 years). Of these patients, 71% remained active on the transplant list and 29% were not listed (see below). Three patients were not listed for irreversible medical conditions or degree of organ dysfunction

Thirty-three patients (11.7%) died on LVAD support before discharge from hospital. Twenty-five patients (8.9%) underwent transplantation during their initial hospital stay and 220 patients (78%) were discharged from the hospital with the LVAD, with a median hospital stay after surgery of 25 days (range 8–180 days)

Survival outcomes reported (by group and/or intervention)

Characteristics of patients alive with ongoing device support as of June 2008 (*n* = 42)

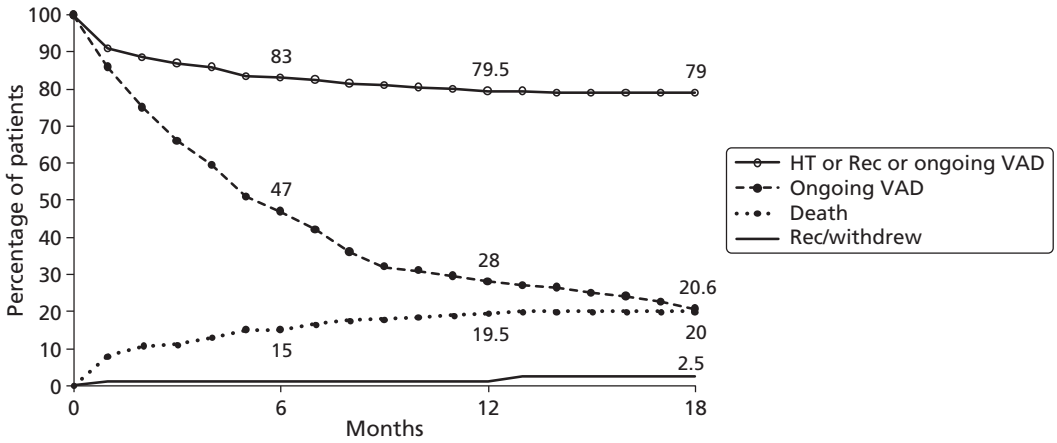
Parameter	Value
Duration of LVAD support (years)	1.6 (1.3–3.1)
Age (years)	51 (15–70)
Men/women	26 (62)/16 (38)
Listed for cardiac transplantation	30 (71.4)
Not listed for cardiac transplantation	12 (28.6)
Reasons not listed	
Irreversible medical condition	3
Non-compliance	3
Obesity	2
Elevated panel reactive antibody screen	2
Preference to stay on device	1
Insurance	1

Median (range), or *n* (%).

Other specified/relevant outcomes reported (by group and/or intervention)

Competing outcomes

Of the 281 patients, 222 (79%) either received a transplant, recovered cardiac function and underwent device explantation, or remained alive with ongoing LVAD support at 18-month follow-up (see figure below; data for 6 and 12 months read from graph)



At 18 months, 157 patients (55.8%) had received a HT, 58 patients (20.6%) remained alive with ongoing LVAD support, 56 patients (19.9%) died, seven patients (2.5%) recovered cardiac function and underwent device explantation, and three patients (1%) were withdrawn from the study after device explantation and exchange for another type of LVAD
Median time to transplantation: 118 days (range 10–545 days)
Median time to death was 64 days (range 0–797 days)
Median time to pump removal after cardiac recovery was 302 days (range 161–558 days)
Median duration of support for all patients was 155 days (range 0–1026 days), with a cumulative follow-up of 181 patient-years
Average LVAD estimated blood flow at 6 months of support = 5.6 ± 0.9 l/minute (flow index 2.83 ± 0.45 l/minute/m^2) at a pump speed of 9467 ± 499 RPM
LVEDD determined by echocardiography reduced:
Baseline 69.7 ± 12.3 mm
At 1 week 59.2 ± 15.1 mm
At 6 months 56.7 ± 14.5 mm

Other specified/relevant outcomes reported (by group and/or intervention)
Anticoagulation with warfarin resulted in an average INR throughout support of 2.1 ± 0.8 (median 2.0), baseline INR was 1.3 ± 0.5
Twenty-five patients (8.9%) underwent transplantation during their initial hospital stay, and 33 patients (11.7%) died on LVAD support before discharge (see above)
Two hundred and twenty patients (78%) were discharged from the hospital with the LVAD (see above), with a median hospital stay after surgery of 25 days (range 8–180 days). The median number of days out of hospital before transplantation, readmission, or death was 55.5 days (range 1–892 days). One hundred and forty-nine patients (68%) required rehospitalisation after discharge, with a median duration of rehospitalisation of 5 days (range 0–209 days)
There were no failures of the mechanical pumping mechanism
Median time to pump replacement: 106 days (range 0–672 days)
Freedom from major device malfunction resulting in death ($n = 4$) or device replacement for all causes (malfunction, thrombosis or infection; nine without deaths) was 96% (95% CI 95% to 99%) at 6 months, 93% (95% CI 90% to 98%) at 1 year, and 92% (95% CI 88% to 97%) at 18 months
Fifty-nine per cent of patients (165/281) required 368 operations or procedures after device implantation. The majority of these occurred within 30 days of device implantation (245/368; 67%), and most were required for re-explorations or sternal closures for bleeding complications (177/245; 72%) followed by temporary RVAD insertion or removal ($n = 18$; 7%), tracheostomy ($n = 12$; 5%), ICD insertion or replacement ($n = 9$; 4%), infection ($n = 7$; 3%), pump replacement ($n = 4$; 2%), and various other cardiac ($n = 15$; 6%) and non-cardiac ($n = 3$; 1%) procedures
After 30 days, the most frequent indication for reoperation was for infection complications (49/123; 40%), bleeding ($n = 19$; 9%), pump replacement ($n = 8$; 7%), RVAD insertion or removal ($n = 3$; 2%), ICDs ($n = 5$; 4%), and various other non-cardiac ($n = 24$; 20%) and cardiac procedures ($n = 14$; 11%)
Total pump replacements = 4 + 8 = 12 (4.3% of all implants)
End-organ function
Hepatic (total bilirubin, serum AST, serum ALT) and renal (BUN) function significantly improved from baseline to 6 months, but changes in serum creatinine were not statistically significant

Results for patients with paired data at baseline and at 6 months

Parameter	Baseline	6 months	*n*	*p*-value[a]
Blood chemistry				
Serum sodium (mmol/l)	134.1 ± 5.0	139.3 ± 3.1	130	< 0.001
BUN (mg/dl)	28.0 ± 15.2	20.3 ± 9.0	130	< 0.001
Serum creatinine (mg/dl)	1.4 ± 0.5	1.3 ± 0.7	130	0.119
ALT (IU/l)	108 ± 327	28 ± 15	128	0.006
AST (IU/l)	93 ± 295	34 ± 16	128	0.026
Total bilirubin (mg/dl)	1.3 ± 0.9	0.8 ± 0.4	127	< 0.001
INR	1.3 ± 0.5	2.1 ± 0.9	127	< 0.001

a Paired *t*-test.

Adverse events reported (by group and/or intervention)

Adverse events reported

Adverse events reported	Overall [cumulative support duration (patient-years) = 182]			0–30 days [cumulative support duration (patient-years) = 21.7]			> 30 days [cumulative support duration (patient-years) = 160]		
	Patients with event, *n* (%)	No. of events	Rate[a]	Patients with event, *n* (%)	No. of events	Rate[a]	Patients with event, *n*	No. of events	Rate[a]
Bleeding									
Requiring surgery	72 (26)	82	0.45	67	72	3.32	10	10	0.06
Requiring ≥ 2 units PRBC only	148 (53)	303	1.67	128	190	8.76	54	111	0.69
Ventricular arrhythmias[b]	56 (20)	72	0.4	37	41	1.89	23	31	0.19
Infection									
Local non-device-related infection	84 (30)	155	0.85	64	78	3.59	46	78	0.49
Sepsis	49 (17)	64	0.35	26	27	1.24	27	37	0.23
Percutaneous lead infection	41 (14)	56	0.31	2	2	0.09	39	54	0.34
Pump pocket infection	5 (2)	5	0.03	1	1	0.05	4	4	0.02
Respiratory failure	72 (26)	88	0.48	61	69	3.18	16	19	0.12
Renal failure	30 (11)	31	0.17	24	24	1.11	7	7	0.04
Right HF									
Need for RVAD	17 (6)	17	0.09	16	16	0.74	1	1	0.01
Need for extended inotropic support[c]	36 (13)	37	0.2	28	29	1.34	8	8	0.05
Stroke									
Ischaemic	15 (5)	16	0.09	8[d]	8	0.37	7	8	0.05
Haemorrhagic	9 (3)	9	0.05	4	4	0.18	5	5	0.03
Spinal cord infarct	1 (< 1)	1	0.01	0	0	0	1	1	0.01
TIA	6 (2)	7	0.04	3	3	0.14	4	4	0.02
Psychological	16 (6)	18	0.1	13	13	0.6	3	5	0.03
Other neurological	15 (5)	17	0.09	4	4	0.18	11	13	0.08
Peripheral non-neurological thromboembolic event	18 (6)	25	0.14	16	22	1.02	3	3	0.02
Device replacement[e]									
Primary device thrombosis[f]	4 (1)	4	0.02	2	2	0.09	2	2	0.01
Complications of surgical implantation[g]	3 (1)	3	0.02	2	2	0.09	1	1	0.01
Percutaneous lead wire damage	4 (1)	4	0.02	0	0	0	4	4	0.03

Adverse events reported (by group and/or intervention)

Adverse events reported	Overall [cumulative support duration (patient-years) = 182]			0–30 days [cumulative support duration (patient-years) = 21.7]			> 30 days [cumulative support duration (patient-years) = 160]		
	Patients with event, *n* (%)	No. of events	Rate[a]	Patients with event, *n* (%)	No. of events	Rate[a]	Patients with event, *n*	No. of events	Rate[a]
Lead and pump pocket infection	1 (0.4)	1	0.01	0	0	0	1	1	0.01
Haemolysis	11 (4)	11	0.06	6	6	0.28	5	5	0.03
Hepatic dysfunction	7 (2)	7	0.04	4	4	0.18	3	3	0.02

a Events/patient-year.
b Requiring cardioversion or defibrillation.
c Longer than 14 days or starting after day 14.
d Five events within days 0–2.
e Replaced with HMII (*n* = 9) or other LVADs (*n* = 3).
f Days 0, 24, 56 and 123.
g Surgical pledget trapped in pump (day 1), temporary RVAD caused kink in LVAD outflow graft (day 15), or malposition of inflow cannula (day 31).

Cause of death reported (by group and/or intervention)

Total number of deaths = 56
Survival analysis for patients continuing on mechanical support was performed with the K–M method. Patients were censored for transplantation, recovery of the natural heart, and withdrawal from the study

Cause of death	*n* (%)
Sepsis	11 (4)
Stroke	10 (4)
Ischaemic	5 (2)
Haemorrhagic	5 (2)
Right HF	7 (3)
Device related	7 (3)
Multiorgan failure	5 (2)
Anoxic brain injury	3 (1)
Bleeding	3 (1)
Others: cancer, respiratory failure, hyperthermia, air embolism	10 (4)

QoL reported (by group and/or intervention)

Functional assessment, QoL (see below)
Fuller details are reported in Rogers *et al.*[53]

QoL reported (by group and/or intervention)

Results for patients with paired data at baseline and at 6 months

Parameter	Baseline	6 months	*n*	*p*-value[a]
Functional status				
NYHA functional class (mean ± SD)	3.9 ± 0.3	1.8 ± 0.7	110	< 0.001
Class I or II (%)	0%	83%	110	< 0.001[b]
6-minute walk distance (m)				
Patients able to walk at baseline (mean ± SD)	201 ± 140	368 ± 125	14	< 0.001
Unable to walk at baseline (mean ± SD)	0 ± 0	326 ± 232	95	< 0.001
Per cent of patients able to walk	13	89[c]	109	< 0.001[b]
QoL				
MLWHF[d] (mean ± SD)	69.4 ± 23.3	40.7 ± 24.6	92	< 0.001
KCCQ[e] (mean ± SD)	35.8 ± 21.4	62.5 ± 22.6	90	< 0.001

a Paired *t*-test.
b McNemar's test.
c 12 patients were unable to walk at baseline or at 6 months.
d Lower values indicate better QoL.
e Overall score; greater values indicate better QoL.

Author's conclusion

CF HMII provides effective haemodynamic support for at least 18 months in patients awaiting transplantation, with improved functional status and QoL, and is associated with a very low rate of device malfunction or infection requiring device exchange. CF rotary pumps provide a superior alternative to pumps with a pulsatile design in patients awaiting transplantation

Reviewer's conclusion

There was no formal comparison with pulsatile devices and the study was not designed to make a comparison, therefore the authors' conclusion regarding differential performance should be viewed with caution

ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; ICD, implantable cardioverter-defibrillator; INR, international normalised ratio; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; PRBC, packed red blood cell; RPM, revolutions per minute; RVSWI, right ventricular stroke work index.

Pak 2010[72]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Pak
Year of publication: 2010
Country: USA
Study design: Retrospective
Study setting: Unclear
Number of centres: One
Duration of study: January 2004 and September 2009: 5-year period
Follow-up period: Studies were categorised into post-operative time intervals: 0–1 month, 1–3 months, 3–6 months, 6–12 months, 12–18 months and 18–24 months
Funding: One author received consulting fees from Thoratec Inc. and Jarvik (Modest), another author has received consulting fees from Thoratec Inc.

Aim of the study

To examine the incidence of new-onset AI in patients supported with long-term LVADs. Present the development of de novo AI during LVAD support in both HMI and HMII patients who underwent implantation at a single institution during a 5-year period

Participants

Total number of participants: HMXVE ($n = 67$); HMII ($n = 63$)
Sample attrition/dropout: None
Inclusion criteria: Not clear, echocardiographic studies with adequate assessments of aortic valve
Exclusion criteria: Patients with prior or concurrent surgical manipulation of the aortic valve, with baseline AI, or without baseline echoes, patients who had prosthetic aortic valves, patients with pre-operative AI and patients who underwent aortic valve surgery at the time of device placement
Characteristics of participants:
Mean age (SD): HMXVE 53.2 ± 13.9; HMII 55.5 ± 13.0
Median age: Not reported
Age range: Not reported
Sex: HMXVE male $n = 55$ (82.1%); HMII male $n = 49$ (77.8%)
Race: Not reported
Diagnosis: Unclear. Patients supported with long-term LVADs

Intervention

Indication for treatment: 13 HMXVE patients (19.4%) and 10 HMII patients (15.9%) received devices with DT as the initial goal ($p = 0.530$)
Type of device used: HMXVE and HMII
Any comparison: HMXVE vs. HMII
Duration of treatment: Mean duration of device support was 176.4 ± 142.9 days (range 4–526 days) for HMI patients and 257.2 ± 246.6 days (range 7–1179 days) for HMII patients ($p = 0.023$). Median time to transplant was 24 days (range 8–474 days)

Support duration

Variable	HMXVE ($n = 67$)	HMII ($n = 63$)	p-value
Support duration, days			
Mean ± SD	176.4 ± 142.9	257.2 ± 246.6	0.023
Median (range)	134 (4–526)	204 (7–4170)	
	($n = 4$)	($n = 9$)	
Time to AI development, days			
Mean ± SD	99.3 ± 119.8	115.2 ± 100.2	0.806
Median (range)	48 (23–278)	90 (7–364)	

Intervention

Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Degree of AI
Secondary outcomes: Aortic root dimensions
Method of assessing outcomes: Medical records
Survival: No
Adverse event: Yes
HRQoL: No
Length of follow-up: Studies were categorised into post-operative time intervals: 0–1 month, 1–3 months, 3–6 months, 6–12 months, 12–18 months and 18–24 months

Number of participants	Intervention	Comparator, if present
Screened	All clinical echocardiographic reports from consecutive patients who underwent LVAD implantation ($n = 93$ HMXVE) were retrospectively reviewed	All clinical echocardiographic reports from consecutive patients who underwent LVAD implantation ($n = 73$ HMII) were retrospectively reviewed
Randomised/included	Final study population included 67 HMXVE patients	Final study population included 63 HMII patients
Excluded	Analysis excluded six HMXVE patients	Analysis excluded two HMII patients
Missing participants		
Withdrawals		

Patient's baseline characteristics

Variable	HMXVE ($n = 67$)	HMII ($n = 63$)	p-value
Age, (years)	53.2 ± 13.9	55.5 ± 13.0	0.329
Male	55 (82.1)	49 (77.8)	0.539
BMI (kg/m^2)	28.5 ± 5.8	26.0 ± 5.1	0.011
Ischaemic cardiomyopathy	29 (43.3)	28 (44.4)	0.894
Hypertension	27 (40.3)	31 (49.2)	0.307
Diabetes mellitus	28 (41.8)	22 (34.9)	0.421
COPD	4 (6.0)	6 (9.5)	0.522
BTT/DT	54/13	53/10	0.530
Baseline creatinine (mg/dl)	1.53 ± 1.06	1.49 ± 0.43	0.745
Pre-operative ejection fraction (%)	15.5 ± 5.6	16.0 ± 5.6	0.608
Pre-operative systolic BP (mmHg)	103.8 ± 14.1	102.8 ± 15.1	0.698
Pre-operative diastolic BP (mmHg)	66.4 ± 10.3	66.8 ± 13.7	0.865
Pre-operative cardiac output, (l/minute)	2.38 ± 1.93	2.72 ± 1.21	0.231
Pre-operative IABP	39 (58.2)	21 (33.3%)	0.004

Continuous data are shown as mean ± SD; categorical data are *n* (%).

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

K–M analysis reports the freedom from AI in patients who received the HMXVE and HMII devices
K–M analysis showed that patients who remained on device support at 6 and 12 months, freedom from AI was 94.5% and 88.9% in HMI patients and 83.6% and 75.2% in HMII patients (log-rank $p = 0.194$)

Number at risk

	Days post implant				
Device	0	100	200	300	400
HMXVE, *n*	67	39	22	14	7
HMII, *n*	63	40	29	15	9

Aortic root diameters

Diameters (cm)	HMXVE ($n = 20$)	HMII ($n = 22$)	*p*-value	AI ($n = 13$)	No AI ($n = 29$)	*p*-value
Baseline	3.15 ± 0.39	3.31 ± 0.44	0.223	3.43 ± 0.43	3.15 ± 0.40	0.067
At 31–90 days follow-up	3.30 ± 0.52	3.44 ± 0.53	0.390	3.58 ± 0.54	3.29 ± 0.50	0.130

Aortic root circumference from pathology reports

Device type	Aortic insufficiency ($n = 7$)	No aortic insufficiency ($n = 70$)	*p*-value
HMI, cm (aortic insufficiency = 2/no aortic insufficiency = 42)	8.25 ± 1.06	7.28 ± 1.02	0.198
HMII, cm (aortic insufficiency = 5/no aortic insufficiency = 28)	8.44 ± 0.89	7.36 ± 1.02	0.034
Overall, cm	8.39 ± 0.85	7.31 ± 1.02	0.009

Aortic root diameters for patients with AI were often larger at baseline (3.43 ± 0.43 vs. 3.15 ± 0.40; $p = 0.067$) and follow-up (3.58 ± 0.54 vs. 3.29 ± 0.50; $p = 0.130$) compared with patients with no AI
Aortic root circumferences in those patients who underwent transplant were significantly larger in HMII patients who developed AI compared with those patients who did not (8.44 ± 0.89 cm vs. 7.36 ± 1.02 cm; $p = 0.034$)
AI was more common in patients who had aortic valves that did not open (11/26 vs. 1/14; $p = 0.03$)

Adverse events reported (by group and/or intervention)

AI developed in 4 of 67 HMI (6%) and in 9 of 63 HMII patients (14.3%)
Median times to AI development were 48 days for HMI patients and 90 days for HMII patients
One HMII patient underwent an aortic valve repair
One HMXVE and three HMII patients remain on device therapy with AI graded mild/moderate or greater

Cause of death reported (by group and/or intervention)

One HMXVE patient died after AI onset of multiorgan system failure not directly related to AI

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

AI development, mainly during CF with HMII, was common and occurred after a relatively short duration of support. Data demonstrate that AI occurs frequently in patients who receive CF support with a HMII LVAD. The findings require thorough pre-operative patient evaluation and additional studies to investigate factors associated with AI development

Reviewer's conclusion

K–M analyses were performed to characterise freedom from AI. Underpowered analysis – too few events. Cox's regression was not performed. Difficulty in ascertaining a causal mechanism for AI development in these LVAD patients owing to retrospective study design. Limited relevance to the current report

AI, aortic insufficiency.

Pal 2009[73]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Pal
Year of publication: 2009
Country: USA, multicentres
Study design: Unclear, prospective study
Study setting: Multicentres in USA
Number of centres: 33 clinical sites
Duration of study: March 2005 until March 2007
Follow-up period: 180 days
Funding: This study was supported in part by an unrestricted educational grant from Thoratec Inc. to one author. Three authors received research support from Thoratec Inc. One author received research support and serves as a clinical consultant for Thoratec Inc. One author is an employee of Thoratec Inc.

Aim of the study

To determine impact of concurrent cardiac procedures on patient outcomes after HMII LVAD implantation

Participants

Total number of participants: 170 patients who underwent isolated HMII implantation with 81 patients with HMII implantation with concurrent cardiac procedures. The initial BTT study included 133 patients enrolled at 26 sites. An additional 148 patients were enrolled resulting in a total of 281 patients included in analysis
Sample attrition/dropout: It is noted that 14 patients had non-cardiac procedures and 97 were concurrent cardiac; excluded an additional 16 patients who underwent placement of a RVAD
Inclusion criteria: Patients listed for a HT at study centres were eligible for enrolment. Further inclusion criteria were UNOS 1A or 1B status with impaired haemodynamics (PCWP > 20 mmHg, cardiac index < 2.2 l/minute/m^2, or systolic BP 90 mmHg). Also refer to Miller *et al.*[70] for more details – included paper
Exclusion criteria: Patients with any mechanical circulatory support other than an IABP, BMI > 40 kg/m^2, or history of cardiac transplantation. Also presence of severe end-organ dysfunction manifested by INR 2.5 not on anticoagulation therapy, bilirubin > 5 mg/dl, cirrhosis, severe COPD or restrictive lung disease, fixed pulmonary hypertension (PVR > 6 Wood units), unresolved stroke, creatinine 3.5, or dialysis. Also refer to Miller *et al.*[70] for more details – included paper
Characteristics of participants:
Mean age (SD): HMII 51 ± 13 years; HMII + CCP 50 ± 14 years
Median age: Not reported
Age range: Not reported
Sex: HMII 25.9% female; HMII + CCP 18.5% female
Race: Not reported
Diagnosis: Patients with end-stage HF who were on a WL for a HT

Intervention

Indication for treatment: BTT
Type of device used: HMII
Any comparison: HMII vs. HMII + CCP
Duration of treatment: Not reported
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Mortality at 30 days after the procedure and survival to transplantation, recovery of ventricular function, or ongoing support at 180 days
Secondary outcomes: Causes of mortality and frequency of adverse events were recorded for all patients
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: No
HRQoL: No
Length of follow-up: 180 days

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	281 BTT patients who underwent implantation of a HMII pump, 111 had additional procedures performed at time of initial operation	
Randomised/included	170 patients who underwent isolated HMII implantation	81 patients with HMII implantation with concurrent cardiac procedures
Excluded	14 were non-cardiac procedures and 97 were concurrent cardiac. Excluded an additional 16 patients who underwent placement of a RVAD	
Missing participants		
Withdrawals		

Patient's baseline characteristics

Parameter	Value (intervention)	Value (comparator)
Age, years	51 ± 13	50 ± 14
Sex	Female 25.9%	Female 18.5%
BSA, m^2		
Weight, kg, BMI		
Ischaemic causes of HF	41.8%	39.5%

Baseline characteristics for patients with HMII: implantation alone and those with implantation and CCP

Parameter	HMII ($n = 170$)	HMII + concurrent cardiac procedures ($n = 81$)	p-value
Age, years	51 ± 13	50 ± 14	0.578
Female, %	25.9	18.5	0.265
Creatinine (mg/dl)	1.4 ± 0.5	1.5 ± 0.6	0.167
CVP (mm/Hg)	11.6 ± 6.1	14.5 ± 6.9	0.001
INR	1.30 ± 0.34	1.34 ± 0.33	0.380
Ischaemic (%)	41.8	39.5	0.785
Mechanical ventilation (%)	5.9	8.6	0.429

Survival outcomes reported (by group and/or intervention)

Actuarial survival for patients receiving LVAD implantation with and without CCP is presented
K–M analysis of survival with device support for patients with and without CCP found at 1, 6 and 12 months the number remaining at risk was HMII 170, 86 and 49 and HMII + CCP indicates CCP 81, 28 and 15, respectively
K–M analysis of survival extraction from the curve at 1, 6 and 12 months for HMII was 94% ± 2%, 84% ± 3% and 77% ± 4%, respectively
K–M analysis of survival extraction from the curve at 1, 6 and 12 months for HMII + CCP was 89% ± 4%, 77% ± 5% and 66% ± 7%, respectively
Differences in overall survival rates were statistically significant between two groups ($p = 0.048$, log-rank test)
The hazard ratio for concurrent procedures adjusted for baseline parameters was 1.82 (95% CI 1.07 to 3.10; $p = 0.026$)

Survival outcomes reported (by group and/or intervention)

Overall and subgroup 30-day mortality rates and survival to transplantation, recovery of ventricular function, or ongoing device support at 180 days

Patient group	*n*	30-day mortality	Survival to study outcomes at 180 days, %
HMII alone	170	5.9	86.5
HMII + concurrent cardiac procedures	81	11.1	80.3
Concurrent cardiac procedures subgroups			
HMII + patent foramen ovale	15	0	93.3
HMII +valve	47	8.5	80.9
Tricuspid	30	3.3	86.6
Mitral	5	0	100.0
Aortic	12	25.0	58.3
HMII + other	68.4	68.4	68.4

Other specified/relevant outcomes reported (by group and/or intervention)

CCP ($n = 81$): Valvular procedures ($n = 47$); tricuspid ($n = 30$); aortic ($n = 12$, 8 aortic valve replacement and 4 valve patch); mitral ($n = 5$); patent foramen ovale closure ($n = 15$); removal of left ventricular thrombus ($n = 3$); left ventricular aneurysm resection ($n = 3$); insert implantable cardioverter-defibrillator/repair implantable cardioverter-defibrillator lead ($n = 3$); CABG ($n = 2$); left ventricular laceration repair ($n = 2$); right atrial ablation; ventricular septal defect repair; right atrial thrombectomy; repair of dissection of ascending aorta; left ventricular remodelling; lysis of intrapericardial adhesions

Cardiopulmonary bypass time and length of stay for HMII implantation alone or with CCP

Procedure	HMII ($n = 170$)	HMII + concurrent cardiac procedures ($n = 81$)
Cardiopulmonary bypass time (minutes)		
Mean ± SD	100 ± 37	121 ± 40[a]
Median	98.5	123.5
Length of stay (days)		
Mean ± SD	30 ± 24	35 ± 27
Median	23	26.5

a $p = 0.001$.

Adverse events reported (by group and/or intervention)

Incidence of adverse events

Incidence of adverse events	HMII % ($n = 170$)	HMII + concurrent cardiac procedures, % ($n = 81$)	*p*-value
Bleeding	26	25	0.877
Sepsis	17	18	1.000
Driveline infection	10	18	0.132
Ventricular arrhythmias	20	22	0.743
Perioperative stroke	4	2	0.391
Renal failure	14	8	0.259

Adverse events reported (by group and/or intervention)

No significant differences for the incidence of adverse events

Cause of death reported (by group and/or intervention)

Causes of death	HMII, % ($n = 170$)	HMII + concurrent cardiac procedures, % ($n = 81$)	p-value
Bleeding	26	25	0.877
Sepsis	17	18	1.000
Driveline infection	10	18	0.132
Ventricular arrhythmias	20	22	0.743
Perioperative stroke	4	2	0.391
Renal failure	14	8	0.259

No significant differences in causes of death

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Isolated HMII implants in HMII BTT trial have low procedural mortality. Concurrent procedures such as closure of patent foramen ovale and tricuspid procedures do not appear to add procedural risk, although implants with concurrent aortic procedures had a higher mortality rate. Further investigation of LVAD implant procedures with CCP is needed

Reviewer's conclusion

Unclear when patients were stratified into those with CCP or no such procedures. The evidence supports the author's conclusions that a more complex surgical procedure at implant of HMII may result in poorer survival. However, this appears to be a post-hoc analysis. An unadjusted p-value of 0.048 (adjusted for baseline characteristics $p = 0.026$) was reported, therefore the conclusions should be treated with some caution. The authors did not appear to test the assumptions for proportional hazards

CABG, coronary artery bypass grafting; CCP, concurrent cardiac procedures; INR, international normalised ratio; PVR, pulmonary vascular resistance.

Petrucci 2009[74]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Petrucci
Year of publication: 2009
Country: USA
Study design: Single-arm trial non-randomised prospective
Study setting: Hospital
Number of centres: 11 of 35 in the study by Miller *et al.*[70]
Duration of study: NC assessments were performed in the same order only at 1, 3 and 6 months after LVAD implantation
Follow-up period: Not reported
Funding: Not reported

Aim of the study

To document changes in the cognitive performance of patients with the CF HMII LVAD as a BTT

Participants

Total number of participants: 93
Sample attrition/dropout: Not clear. Missing participants $n = 65$; patient refusal (43%); examiner not available (36%); patient too ill or intubated (23%)
Inclusion criteria: Patients from trial of Miller *et al.*[70] Inclusion criteria for the NC tests consisted of non-intubation, ability to sit and provide verbal responses in English, and oxygen saturation > 90%
Exclusion criteria: Centres not selected by first investigator
Characteristics of participants:
Mean age (SD): 50 ± 14 years
Median age: 54 years
Age range: 16–73 years
Sex: 81% male
Race: Not reported
Diagnosis: End-stage HF

Intervention

Indication for treatment: BTT; ischaemic (41%), idiopathic cardiomyopathies (51%) and other (8%)
Type of device used: HMII
Any comparison: Paired results of neurocognitive performance at 3 and 6 months vs. 1 month after implant
Duration of treatment: Various
Percentage of patients using inotropes: 90%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Neurocognitive tests selected from FDA suggestions in a 2003 report *Assessment of neurological/neurocognitive function: guidance for industry*.[124] Nurse co-ordinators administered tests
Secondary outcomes: Not reported
Method of assessing outcomes: Medical records or prospective data collection
Survival: No
Adverse event: No
HRQoL: No
Length of follow-up: 6 months

Number of participants	Intervention	Comparator, if present
Screened	158 at 11 centres	Not reported
Randomised/included	Not reported	Not reported
Excluded	Not reported	Not reported
Missing participants	65	Not reported
Withdrawals	Patient refusal (43%), examiner not available (36%), patient too ill or intubated (23%)	Not reported

Patient's baseline characteristics

Characteristic	Value
n	93
Male, *n* (%)	75 (81%)
Female, *n* (%)	18 (19%)
Age (years)	50 ± 14; median 54 (range 16–73)
Ischaemic aetiology (%)	41
BSA (m^2)	2.0 ± 0.3; median 2.0 (range 1.35–2.69)
LVEF (%)	16 ± 7
LVEDD mm)	79 ± 12
Systolic BP (mmHg)	95 ± 14
Cardiac index (l/minute/m^2)	2.1 ± 0.7
RA pressure (mmHg)	12.3 ± 6.0
PA mean pressure (mmHg)	36 ± 10
PCWP (mmHg)	25 ± 8
CRT (%)	46
Intravenous inotropes (%)	90
IABP (%)	34
Creatinine (mg/dl)	1.4 ± 0.5
BUN (mg/dl)	30 ± 15
Total bilirubin (mg/dl)	1.4 ± 0.8

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

Neurocognitive tests
Of 158 patients 93 had tests. There were 239 tests out of a possible 316 'potential' tests (76%) completion rate
Reasons for not obtaining data in the 65 additional patients included patient refusal (43%), examiner not available (36%) and patient too ill or intubated (23%)
NC domains were: (1) visual–spatial perception, the CD and the WAIS-111-BD; (2) memory, WATS-HUM (modified), WMS-III-LM and WMS-III-VR; (3) executive functions, TM-B and WAIS-III-DS; (4) language, abbreviated BNT; and (5) processing speed, TM-A
Test score ranges were: CD, 1–10; WAIS-III-BD, 0–83; WMS-III-LM and WMS-III-LM Delay, 0–50; WMS-III-VR and WMS-III-VR Delay, 0–104; WAIS-III-DS, 1–133; TMB in seconds, lower is better; BNT, 0–15; processing speed in seconds, lower is better. In all cases (except TMB and processing speed) higher scores represent better performance

Other specified/relevant outcomes reported (by group and/or intervention)

All neurocognitive test results at 1, 3 and 6 months after implantation (these are mean and SD for all those with a test results at each time point

		1 month		3 months		6 months	
Domain	Test	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Visual spatial perception	CD	92	8.7 ± 1.5	74	8.9 ± 1.4	38	8.6 ± 1.9
	WAIS-III-BD	92	28.2 ± 11.7	74	29.3 ± 11.5	38	31.3 ± 12.3
Auditory memory	WMS-III-LM[a]	92	19.7 ± 6.6	77	20.7 ± 6.1	40	19.9 ± 8.1
	WMS-III-LM Delay[a]	88	15.3 ± 6.4	77	16.8 ± 6.7	39	16.1 ± 7.8
Visual memory	WMS-III-VR	92	70.8 ± 20.5	77	75.2 ± 18.3	42	71.3 ± 20.7
	WMS-III-VR Delay	80	37.3 ± 25.5	74	47.4 ± 26.1	40	47.9 ± 27.1
Executive function	WAIS-III-DS	89	42.9 ± 17.6	76	47.4 ± 15.9	41	43.4 ± 15.6
	TM-B	87	137 ± 81	74	114 ± 62	38	124 ± 70
Confrontational language	BNT	93	12.5 ± 2.4	72	12.4 ± 2.3	38	12.4 ± 2.5
Processing speed	TM-A	89	53.7 ± 42.8	77	43.6 ± 19.9	40	47.1 ± 22.8

a Modified administration.

Of the completed NC tests, 51–57 pairs (paired test result of a patient) were available for the 1- vs. 3-month analysis and 23–31 pairs for the 1- vs. 6-month analysis, whereas 20–28 patients had test results from all three time points (this depended on the test type)
Decreasing numbers of patients available for paired NC performance over the 6 months were mostly due to HT (37%), death (15%) and recovery of the natural heart with device removal (0.4%). By 6 months of support, 47% of patients remained on device support and theoretically would be available for NC testing
Paired test results are summarised in the following tables

Paired neurocognitive test results between 1 and 3 months after implant

		1–3 months			
Domain	Test	*n*	1 month	3 months	*p*-value
Visual spatial perception	CD	55	8.8 ± 1.5	8.8 ± 1.5	0.936
	WAIS-III-BD	54	27.8 ± 11.6	28.7 ± 11.3	0.403
Auditory memory	WMS-III-LM[a]	57	19.6 ± 6.9	21.4 ± 6.3	0.005
	WMS-III-LM Delay	54	15.2 ± 6.9	18. ± 6.6	0.001
Visual memory	WMS-III-VR	56	70.6 ± 19.8	76.1 ± 18.3	0.004
	WMS-III-VR Delay	49	35.7 ± 25.3	50.7 ± 27.1	< 0.0001
Executive function	WAIS-III-DS	54	42.4 ± 17.2	48.2 ± 16.3	0.001
	TM-B	51	135 ± 71	111 ± 63	0.0001
Confrontational language	BNT	53	12.4 ± 2.4	12.3 ± 2.3	0.478
Processing speed	TM-A	54	50.4 ± 22.9	40.4 ± 17.3	< 0.0001

a Modified administration.

Other specified/relevant outcomes reported (by group and/or intervention)

Paired neurocognitive test results between 1 and 6 months after implant and for patients without subsequent paired retesting (mean ± SD)

		1–6 months				Not retested	
Domain	Test	*n*	1 month	6 months	*p*-value	*n*	1 month
Visual spatial perception	CD	29	8.6 ± 1.6	8.6 ± 1.9	0.929	35	8.6 ± 1.5
	WAIS-III-BD	28	23.2 ± 9.0	30 ± 11.3	< 0.001	36	29.6 ± 11.9
Auditory memory	WMS-III-LM[a]	31	17.1 ± 6.9	19.5 ± 7.9	0.109	32	19.9 ± 6.5
	WMS-III-LM Delay[a]	27	13.6 ± 7.1	15.8 ± 7.6	0.132	31	15.8 ± 5.1
Visual memory	WMS-III-VR	30	63.3 ± 20.9	73 ± 17.9	< 0.001	33	73.2 ± 21.1
	WMS-III-VR Delay	25	27.5 ± 25.3	47.3 ± 30.0	< 0.001	27	41.4 ± 26.5
Executive function	WAIS-III-DS	27	37.6 ± 14.6	41.2 ± 16.4	0.18	32	44.5 ± 18.8
	TM-B	23	175 ± 111	127 ± 77	0.007	35	128 ± 66
Confrontational language	BNT	28	12.3 ± 1.9	12.2 ± 2.2	0.859	38	12.7 ± 2.6
Processing speed	TM-A	26	71.8 ± 73.0	44.7 ± 21.8	0.071	32	46.7 ± 15.2

a Modified administration.

Statistically improved WMS-III-LM and processing speed, and executive function WAIS-III-DS paired results at 3 months (n = 51–57) were not sustained at 6 months (n = 23–31); however, WMS-III-VR and executive function TM-B paired results were statistically significant for improvement at both 3 and 6 months. WAIS-III-BD reached statistical significance at 6 months

Results for patients tested at all three time points: 1, 3 and 6 months after implantation (mean ± SD)

Domain	Test	*n*	1 month	3 months	6 months	*p*-value
Visual spatial perception	CD	26	8.6 ± 1.7	8.8 ± 1.5	8.6 ± 2.0	0.963
	WAIS-lll-BD	25	24.3 ± 8.8	26.0 ± 9.5	30.6 ± 11.7	< 0.001
Auditory memory	WMS-III-LM[a]	28	17.0 ± 7.1	19.4 ± 6.0	19.8 ± 8.0	0.065
	WMS-III-LM Delay[a]	24	13.7 ± 7.1	16.3 ± 5.8	16.0 ± 7.1	0.097
Visual memory	WMS-III-VR	26	66.2 ± 20.4	71.7 ± 19.7	74.2 ± 18.1	0.004
	WMS-III-VR Delay	20	30.4 ± 27.2	46.7 ± 31.4	49.6 ± 31.8	< 0.001
Executive function	WAIS-III-DS	24	38.0 ± 15.0	44.3 ± 17.6	42.6 ± 16.9	0.034
	TM-B	22	159 ± 80	143 ± 79	123 ± 76	0.003
Confrontational language	BNT	26	12.2 ± 2.0	12.1 ± 1.7	12.2 ± 2.3	0.926
Processing speed	TM-A	23	56.7 ± 27.7	47.8 ± 21.3	45.1 ± 22.8	0.001

a Modified administration.

In paired tests at all three time points indicated statistically significant improvement (analysis of variance repeated measures) for WAIS-lll-BD (n = 25), WMS-III-VR (n = 26) and WMS-III-VR Delay (n = 20), WAIS-III-DS (n = 24), TM-A (n = 23) and TM-B (n = 22)

Adverse events reported (by group and/or intervention)

Not reported

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)
Not reported
Author's conclusion
The cognitive performance of advanced HF patients remained stable or showed slight improvements from month 1 to month 6 of continuous-blood-flow support with the HMII
Reviewer's conclusion
Study provides some evidence for small improvements in some aspects of NC; however, results were not all internally consistent and there was a significant amount of missing data. As few patients were able to perform tests prior to implant the 'baseline' was taken to be 1 month after implant; there is no assurance of that similar differences would be observed vs. baseline. One interpretation is that the adverse effect of implantation seen at 1 month post operation for some NCV outcome is reversed by 6 months

BSA, body surface area; BNT, Boston Naming Test; BUN, blood urea nitrogen; CD, Clock Drawing; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PA, pulmonary artery; RA, right atrial; TM-A, Trail Making A; TM-B, Trail Making B; WAIS-III-BD, Wechsler Adult Intelligence Scale-II-Block Design; WAIS-III-DS, Wechsler Adult Intelligence Scale-III-Digit Symbol; WMS-III-LM, Wechsler Memory Scale-III-Logical Memory; WMS-III-VR, Wechsler Memory Scale-III-Visual Reproduction.

Rogers 2010[53]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Rogers
Year of publication: 2010
Country: USA
Study design: Two single-arm trials conducted in compliance with FDA
Study setting: Multicentre
Number of centres: 38
Duration of study: 2005–9
Follow-up period: 6 months BTT; 24 months DT
Funding: Industry; Thoratec Inc.

Aim of the study

To report the impact of a CF LVAD HMII in > 650 patients with advanced HF on QoL and functional capacity for up to 24 months of circulatory support

Participants

Total number of participants: 655
Sample attrition/dropout: Not reported
Inclusion criteria: NYHA functional class IV HF symptoms and were listed as high priority for transplantation (UNOS status 1A or 1B). Patients with NYHA functional classes IIIB and IV HF who were ineligible for a HT and refractory to optimal MM were considered for enrolment in the DT trial
Exclusion criteria: See Miller *et al*.,[70] Pagani *et al*.[71] and Slaughter *et al*.[47] For both the trials included severe renal, pulmonary, or hepatic dysfunction, active uncontrolled infection, a mechanical aortic valve, aortic insufficiency, an aortic aneurysm, other mechanical circulatory support (except an IABP), and technical obstacles thought by the investigator to pose excessive surgical risk
Characteristics of participants:
Mean age (SD): BTT 50 years (13); DT 63 years (12)
Median age: Not reported
Age range: Not reported
Sex: BTT 76% male; DT 73% male
Race: Not reported
Diagnosis: End-stage HF

Intervention

Indication for treatment: BTT or DT
Type of device used: HMII
Any comparison: BTT vs. DTT for a few outcomes
Duration of treatment: Not reported
Percentage of patients using inotropes: BTT 250 (90%); DT 289 (77%)
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Not specified
Secondary outcomes: Changes in NYHA classification, 6-minute walk test, activity level (METs), MLWHF and KCCQ
Method of assessing outcomes: Prospective data collection
Survival: No
Adverse event: No
HRQoL: Yes
Length of follow-up: 6 months BTT; 24 months DT

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	BTT $n = 281$	DT $n = 374$
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Parameter	BTT	DT	*p*-value
Age (years)	50 ± 13	63 ± 12	< 0.001
Female, *n* (%)	67 (24)	102 (27)	0.322
Ischaemic aetiology of HF, *n* (%)	121 (43)	217 (58)	< 0.001
LVEF (%)	16.3 ± 6.5	17.1 ± 5.8	0.025
Cardiac index (l/minute/m^2)	2.1 ± 0.6	2.1 ± 0.6	0.889
PCWP (mmHg)	25.4 ± 7.9	23.9 ± 8.3	0.021
Systolic BP (mmHg)	98.1 ± 15.0	102.1 ± 15.1	< 0.001
BUN (mg/dl)	30.4 ± 17.1	34.4 ± 21.3	0.023
Creatinine (mg/dl)	1.4 ± 0.5	1.5 ± 0.6	0.04
Total bilirubin (mg/dl)	1.3 ± 0.9	1.3 ± 1.0	0.603
ALT (U/l)	106 ± 278	44 ± 69	< 0.001
Serum sodium (mmol/l)	134 ± 5	135 ± 5	0.002
CRT, *n* (%)	135 (48)	268 (72)	< 0.001
Intravenous inotropes, *n* (%)	252 (90)[a]	289 (77)	0.001
IABP, *n* (%)	126 (45)	78 (21)	< 0.001

a 10% intolerant due to arrhythmias.

Survival outcomes reported (by group and/or intervention)

Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

Not reported

Adverse events reported (by group and/or intervention)

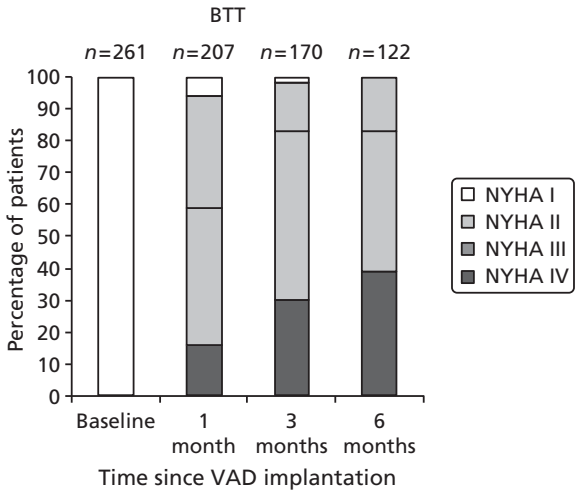
Not reported

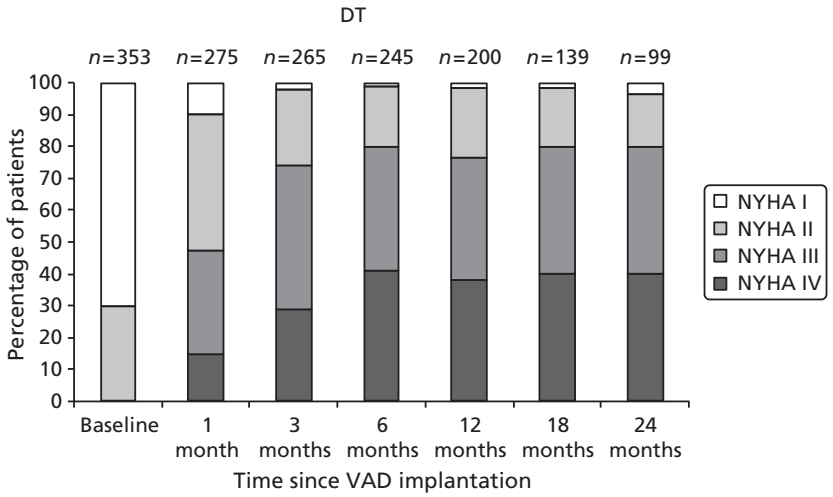
Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

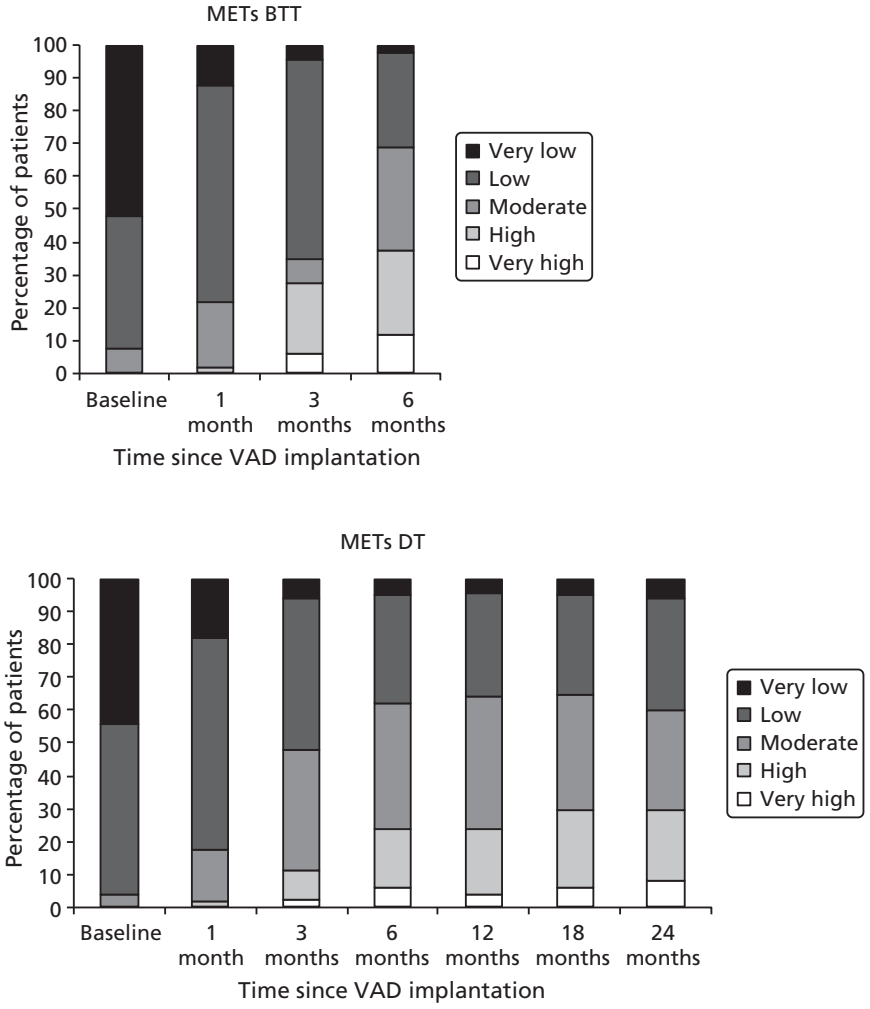
NYHA
Changes in NYHA class by month BTT and DT
At baseline, most were NYHA class IV
At 1 month, 59% (BTT) and 47% (DT) improved to NYHA class I or II
At 6 months, 82% (BTT) and 80% (DT) were NYHA class I or II
From 6–24 months, 80% of DT patients remained in NYHA functional class I or II
Relative to baseline scores highly significant improvement in NYHA functional class were observed at all study intervals for both the study groups ($p < 0.001$)
There was no significant difference in the improvements seen in NYHA class between BTT and DT patients





NYHA functional class was determined by an independent clinician at the time points shown in the BTT and DT trials. Study inclusion criteria required NYHA functional class III to IV symptoms at baseline. NYHA functional class improvements were statistically significant in both trials ($p < 0.001$)
6-minute walk test
At baseline, 38 BTT and 129 of DT cohorts (14% and 34%, respectively) were able to perform the 6-minute walk test
Baseline distance: 214 ± 125 m (BTT); 204 ± 150 m (DT)
At 6 months distance: 372 ± 199 m (BTT), $n = 97$; 350 ± 198 m (DT), $n = 199$
At 24 months: 60 ± 210 m (DT), $n = 75$
Overall there was a statistically significant improvement over time at all test intervals for both study groups

QoL reported (by group and/or intervention)



METs
Serial assessment of METs. At baseline, > 90% of patients in both trials described their level of function as low or very low. At 6 months, approximately two-thirds of patients described their level of function as moderate to very high ($p < 0.001$ vs. baseline).
QoL measure MLWHF and KCCQ
Major results

QoL reported (by group and/or intervention)

	BTT				DT			
Month	*n*	Mean ± SD	Median [25th, 75th]	% improvement of median	*n*	Mean ± SD	Median [25th, 75th]	% improvement of median
MLWHF								
1	167	−12 ± 27	−10 [−28, 4]	13	241	−17 ± 31	−13 [−40, 4]	17
3	126	−24 ± 31	−30 [−47, −4]	39	231	−35 ± 28	−37 [−58, −17]	48
6	87	−28 ± 28	−29 [−50, −9]	38	209	−39 ± 27	−40 [−60, −20]	52
12	0				177	−39 ± 30	−41 [−62, −17]	53
18	0				126	−39 ± 25	−42 [−57, −22]	55
24	0				82	−41 ± 25	−42 [−57, −20]	55
KCCQ OSS								
1	172	13 ± 25	14 [−3, 29]	0.54	242	17 ± 26	16 [−1, 35]	0.70
3	132	22 ± 26	20 [9, 42]	0.77	232	35 ± 24	34 [19, 53]	1.48
6	90	27 ± 28	28 [7, 45]	1.08	211	39 ± 24	39 [20, 58]	1.70
12	0				181	40 ± 25	42 [24, 61]	1.83
18	0				129	41 ± 24	38 [22, 61]	1.65
24	0				89	42 ± 23	41 [25, 60]	1.78
KCCQ CSS								
1	170	12 ± 27	11 [−6, 31]	0.3	240	15 ± 27	13 [−3, 34]	0.41
3	132	21 ± 28	21 [4, 42]	0.57	231	32 ± 25	32 [14, 50]	1.00
6	90	25 ± 31	24 [8, 43]	0.65	210	37 ± 25	36 [17, 55]	1.13
12	0				181	36 ± 28	39 [18, 57]	1.22
18	0				129	37 ± 27	34 [18, 61]	1.06
24	0				89	38 ± 26	35 [20, 55]	1.09

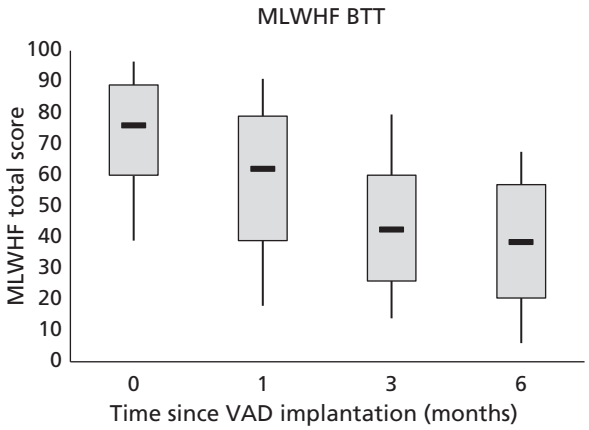
Values are the mean ± SD and median [25th, 75th percentiles] of paired changes at each time point compared with baseline. Also shown are the per cent improvements of the median from baseline.

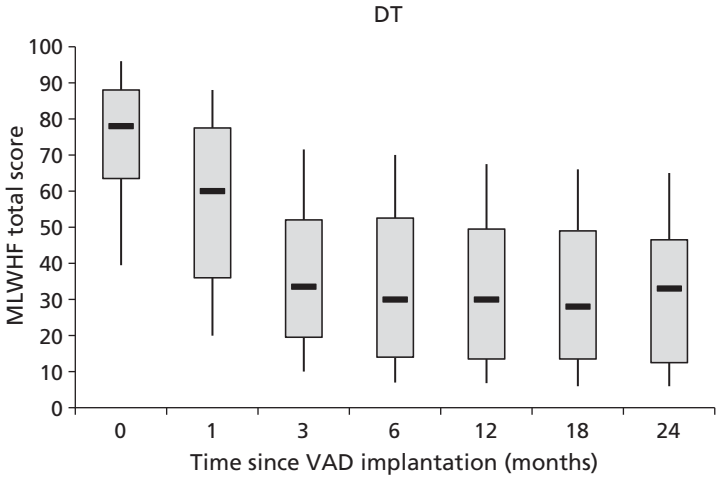
MLWHF
Scores decreased over time, indicating an improvement in QoL ($p < 0.001$)

Change in median from baseline	BTT	DT
At 1 month	10	13 points
At 6 months	29	40 points
Median % improvement at 6 months	38	52
Median % improvement at 24 months		55 (42 points)

QoL reported (by group and/or intervention)		
KCCQ OSS		
Change in median from baseline	**BTT**	**DT**
At 1 month	14	16
At 6 months	28	39
Median improvement at 24 months	41 points	41 points
After 6 months score remained stable.		

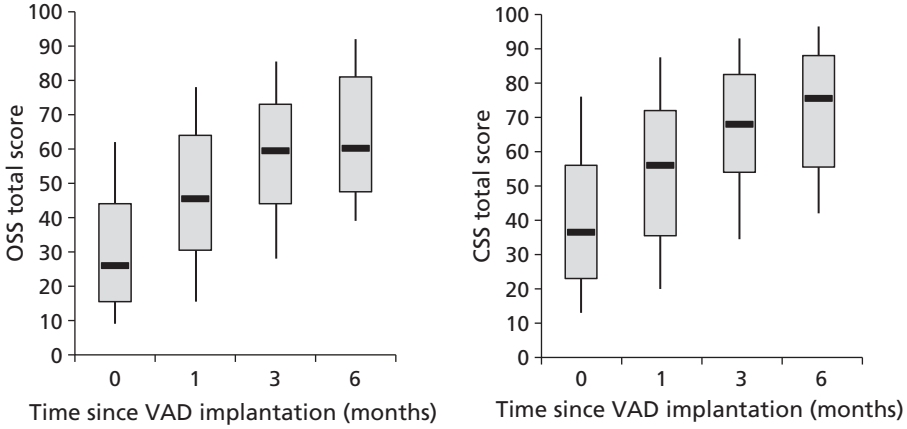
KCCQ CSS
Results were similar to KCCQ OSS
At 6 months, 79% of BTT patients and 92% of DT patients with paired data had achieved a clinically meaningful improvement of > 5 points in KCCQ OSS compared with baseline. Similar results were found for the KCCQ CSS2

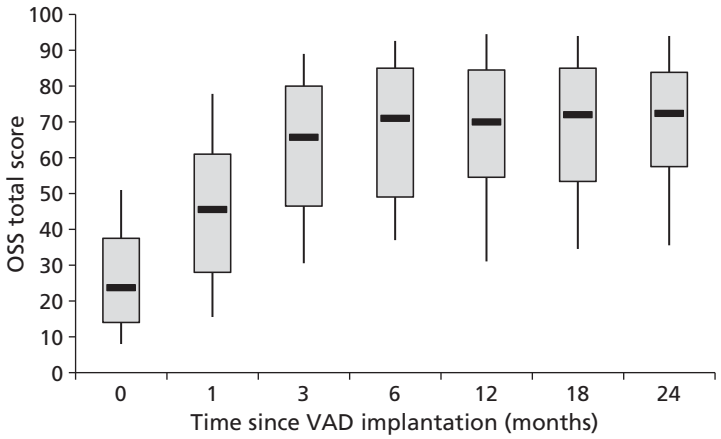


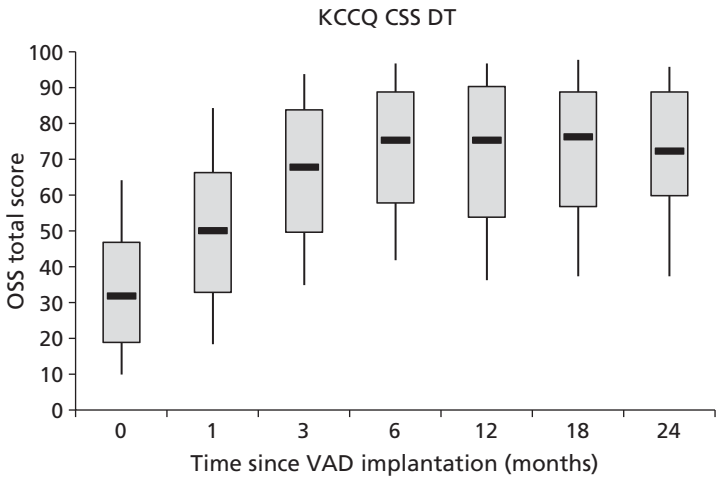


Changes in QoL assessed with the MLWHF are shown. Lower values signify improved QoL. Bars indicate 25th, 50th and 75th percentiles, whiskers indicate fifth and 95th percentiles. $p < 0.05$ for time points compared with baseline
KCCQ BTT
Changes in QoL assessed with the MLWHF are shown. Lower values signify improved QoL. Bars indicate 25th, 50th and 75th percentiles, whiskers indicate fifth and 95th percentiles. $p < 0.05$ for all time points relative to baseline compared with baseline

QoL reported (by group and/or intervention)







Changes in QoL assessed with the MLWHF are shown. Lower values signify improved QoL. Bars indicate 25th, 50th and 75th percentiles, whiskers indicate fifth and 95th percentiles. $p < 0.05$ for all time points relative to baseline compared with baseline

Author's conclusion
Use of a CF LVAD in advanced HF patients results in clinically relevant improvements in functional capacity and HF-related QoL
Reviewer's conclusion
Those patients who survive VAD implant and were available for analysis exhibited improvements in functional performance and QoL. The total number of patients available for analysis at the various time points was not reported. This could be available from Miller *et al.*,[70] Pagani *et al.*[71] and Slaughter *et al.*[47]

ALT, alanine aminotransferase; BUN, blood urea nitrogen; LVEF, left ventricular ejection fraction.

Russell 2009[75]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Russell
Year of publication: 2009
Country: USA
Study design: Uncontrolled single-arm trial
Study setting: Hospital
Number of centres: 26; based on Miller *et al*.[70]
Duration of study: Unclear
Follow-up period: 180 days
Funding: Industry (Thoratec Inc.)

Aim of the study

To determine whether or not patients with impaired renal and hepatic function improve over time with CF LVAD support and whether or not there are any detrimental effects over time in patients with normal organ function during CF support

Participants

Total number of participants: 309
Sample attrition/dropout: Not reported
Inclusion criteria: Not reported. End-stage HF awaiting transplantation with UNOS status 1a or 1b were eligible for enrolment and underwent implantation of the HMII LVAD
Exclusion criteria: Patients were excluded for severe renal (serum creatinine > 3.5 mg/dl or long-term dialysis), hepatic (INR > 2.5, total bilirubin > 5 mg/dl, or transaminases > 2000 U/l), or pulmonary (severe chronic obstructive or restrictive disease) dysfunction. Additionally, patients with uncontrolled infections, strokes, mechanical aortic valves, aortic insufficiency, aortic aneurysm > 5.0 cm, or other mechanical circulatory support devices (except IABPs) were also excluded. See Miller *et al*.[70] for further details
Hepatic (INR > 2.5, total bilirubin > 5 mg/dl, or transaminases > 2000 U/l), or pulmonary (severe chronic obstructive or restrictive disease) dysfunction, uncontrolled infections, strokes, mechanical aortic valves, aortic insufficiency, aortic aneurysm > 5.0 cm, or other mechanical circulatory support devices (except IABPs)
Characteristics of participants:
Mean age (SD): 50 years (14)
Median age: 54 years
Age range: 15–73 years
Sex: 75% male
Race: Not reported
Diagnosis: End-stage HF

Intervention

Indication for treatment: BTT
Type of device used: HMII
Any comparison: Normal vs. above normal according to renal and liver function
Duration of treatment: Unclear
Percentage of patients using inotropes: 89%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Not stated
Secondary outcomes: Changes from baseline in indicators of renal and hepatic function
Method of assessing outcomes: Medical records or prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: 180 days

Outcomes

Number of participants	Intervention	Comparator, if present
Screened		
Randomised/included	*n* = 309	
Excluded		
Missing participants		
Withdrawals		

Patient's baseline characteristics

Characteristic	Value
n	309
Male sex, *n* (%)	235 (76)
Female sex, *n* (%)	74 (24)
Age (years)	50 ± 14; median 54 (range 15–73)
Ischaemic origin (%)	43
BSA (m^2)	2.0 ± 0.3; median 2.0 (range 1.33–2.81)
LVEF (%)	16.5 ± 6.6
LVEDD (mm)	70 ± 13
Systolic BP (mmHg)	98 ± 14
Cardiac index (l/minute/m^2)	2.1 ± 0.7
RA pressure (mmHg)	12.3 ± 6.4
PA mean pressure (mmHg)	36 ± 9
PCW pressure (mmHg)	25 ± 8
ACE inhibitors/ARBs, *n* (%)	28/5 (–/–)
Beta-blockers, *n* (%)	34
CRT (%)	47
Intravenous inotropes (%)	89
IABP (%)	44

Patient's baseline characteristics

Baseline (mean ± SD) renal and hepatic function for all patients, for patients with paired values through 180 days and subgroups of those with abnormal and normal baseline values, and patients who were supported for < 180 days

Characteristic	All patients (*n* = 309)	Patients with paired values through 180 days				Patients supported for < 180 days	
		Overall (*n* = 160)	Normal threshold	Abnormal (*n*)	Normal (*n*)	Died < 180 days (*n* = 34)	Transplanted < 180 days (*n* = 115)
BUN (mg/dl)	29 ± 16	28 ± 15	22	37 ± 14 (99)	15 ± 4 (60)	33 ± 20	29 ± 16
Creatinine (mg/dl)	1.4 ± 0.5	1.4 ± 0.5	1.3	1.8 ± 0.4 (78)	1.0 ± 0.2 (81)	1.4 ± 0.6	1.4 ± 0.5
Total bilirubin (mg/dl)	1.3 ± 0.9	1.3 ± 0.9	1.2	2.1 ± 0.9 (71)	0.7 ± 0.3 (88)	1.1 ± 0.8	1.2 ± 0.8
ALT (U/L)	95 ± 230	85 ± 234	40	171 ± 348 (70)	24 ± 9 (89)	126 ± 302	101 ± 200
AST (U/L)	80 ± 214	67 ± 144	37	121 ± 206 (86)	25 ± 6 (93)	141 ± 475	81 ± 180

Survival outcomes reported (by group and/or intervention)

34 of 309 patients died before 180 days
160 of 309 remained alive on VAD to 180 days after implantation
A total of 115 of 309 patients underwent transplantation before 180 days

Other specified/relevant outcomes reported (by group and/or intervention)

Renal function

(Initial rises in immediate post-implant values were followed by trends towards normal values)
Linear mixed-effects analysis: revealed that group type (above-normal or normal baseline values) and time had statistically significant impacts on BUN and creatinine levels. There were significant ($p < 0.0001$) reductions in BUN and creatinine levels over the period of support for the above-normal groups, and no significant changes for the normal groups
Paired changes to 6 months, BUN: there was a statistically significant improvement in mean BUN for the overall group (from 28 ± 15 mg/dl to 21 ± 10 mg/dl; $p < 0.001$) and the above-normal group (from 37 ± 14 mg/dl to 23 ± 10 mg/dl; $p < 0.0001$), whereas values in the normal group remained in the normal range. Patients who received HTs before 180 days of support showed improvements in BUN whereas there was no change in patients who died before 180 days
Paired changes to 6 months, creatinine: the above-normal group experienced significant reductions in creatinine from 1.8 ± 0.4 mg/dl to 1.4 ± 0.8 mg/dl at 6 months ($p < 0.001$), with the normal group remaining in the normal range. Patients who received HTs before 180 days of support showed improvements in creatinine, whereas there was no change in patients who died before 180 days

Hepatic function

(Initial rises in immediate post-implant values were followed by trends towards normal values)
Linear mixed-effects analysis: revealed that group type (above-normal or normal) and time had statistically significant impacts on AST, ALT and total bilirubin values ($p < 0.0001$)
All: Baseline AST of 67 ± 144, 1 month 38 ± 23, 6 months 35 ± 17; baseline ALT of 85 ± 234, 1 month 33 ± 32, 6 months 29 ± 16
Abnormal: Baseline AST of 121 ± 206, 1 month 46 ± 27, 6 months sustained; baseline ALT 171 ± 318, 1 month 40 ± 26, 6 months sustained

Other specified/relevant outcomes reported (by group and/or intervention)

Paired changes in indicators of renal and hepatic function [mean (SD)]. Full data in figure 1 of Russell *et al*. study[75]

Parameter/group	Baseline	6 months	*p*-value
BUN			
All (*n* = 160)	28 (15)	21 (10)	< 0.001
Above normal	37 (14)	23 (10)	< 0.0001
Creatinine			
All (*n* = 160)	1.4 (0.5)	*1.2 read from graph*	
Above normal	1.8 (0.4)	1.4 (0.8)	< 0.001

	Baseline	1 month	6 months	
AST				
All (*n* = 160)	67 (144)	38 (23)	35 (17)	
Above normal	121 (206)	46 (27)	*40 read from graph*	
Normal	24 (9)	25 (6)		
ALT				
All (*n* = 160)	85 (234)	33 (32)	29 (16)	
Above normal	171 (318)	40 (26)	*30 read from graph*	
Normal	27 (11)	33 (15)		> 0.05

Bilirubin increased by day 7 before improving to baseline in both normal and abnormal groups
The above-normal group at baseline experienced the highest increase, to > 5 mg/dl at day 7; however, by 2 months all groups decreased to the normal range and remained there through month 6

Adverse events reported (by group and/or intervention)

See above for renal and hepatic function

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

In a BTT patient population with mildly abnormal renal or hepatic function, the use of a CF LVAD improved renal and hepatic function in patients with abnormal baseline parameters and did not worsen function in patients with normal baseline renal and hepatic values. Furthermore, this function was maintained through 6 months

Reviewer's conclusion

Patients with considerably impaired renal and liver function were not included in the study, the above-normal patients studied were probably at the mild end of impaired organ function. For those patients who survive VAD implantation to 6 months renal and hepatic function on average appear to improve in those with pre-implant indicators of abnormality, those without abnormality do not deteriorate in these indicators once beyond a few months after implant

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; INR, international normalised ratio; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrial.

Sandner 2009a[91]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Sandner
Year of publication: 2009
Country: Austria
Study design: Retrospective observational analysis
Study setting: Hospital
Number of centres: One
Duration of study: Devices Implanted November 1998 to July 2007
Follow-up period: Patients were followed for at least 180 days or until either transplantation or death
Funding: Not reported

Aim of the study

To determine the effect of age on outcomes after CF LVAD implantation as a BTT

Participants

Total number of participants: 86 patients; please refer to Sandner *et al.*[91] patient characteristics
Sample attrition/dropout: Not reported
Inclusion criteria: Unclear
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): Unclear age
Median age: Not reported
Age range: $n = 56 < 60$ years; $n = 30 > 60$ years
Sex: Not reported
Race: Not reported
Diagnosis: End-stage HF

Intervention

Indication for treatment: BTT for end-stage HF NYHA class IV
Type of device used: MicroMed DeBakey VAD ($n = 75$), HVAD ($n = 6$) and DuraHeart LVAD ($n = 5$)
Any comparison: Patients aged > 60 years vs. patients aged < 60 years
Duration of treatment: Unclear
Percentage of patients using inotropes: < 60 years 46.4%% and > 60 years 53.3%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes

Outcomes

Primary outcomes: Survival; composite outcome (HT or supported on VAD for 180 days)
Secondary outcomes: Not applicable
Method of assessing outcomes: Medical records or prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Patients were followed for at least 180 days or until either transplantation or death

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	Not reported	Not reported
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Variable[a]	< 60 years (*n* = 56)	> 60 years (*n* = 30)	*p*-value
Male	46 (82.1)	27 (90.0)	0.332
BMI (kg/m^2)	26.5 ± 3.9	26.5 ± 3.1	0.935
Hypertension	13 (23.2)	14 (46.7)	0.026
Diabetes mellitus	10 (17.9)	16 (53.3)	0.001
Ischaemic aetiology	18 (32.1)	19 (63.3)	0.005
PCWP (mmHg)	26.0 ± 6.6	26.1 ± 7.7	0.994
Cardiac index, (l/minute/m^2)	1.8 ± 0.5	1.7 ± 0.4	0.45
PAP (mmHg)	40.0 ± 8.3	37.8 ± 10.1	0.39
NYHA class IV	56	30	
Intravenous inotropic agents	26 (46.4)	16 (53.3)	0.542
IABP	2 (3.6)	0	0.295
Mechanical ventilation	3 (5.4)	1 (3.3)	0.671
Previous thoracotomy	6 (10.7)	5 (16.7)	0.431

a Categoric data are *n* (%), continuous data the mean ± SD.

Baseline laboratory values

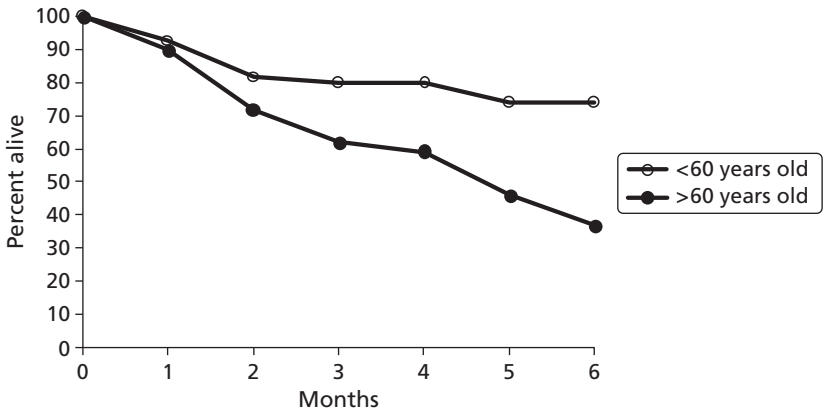
Serum values	< 60 years (*n* = 56)	> 60 years (*n* = 30)	*p*-value
Sodium (mmol/l)	135.1 ± 3.9	136.6 ± 4.9	0.179
Total protein (g/l)	66.5 ± 7.9	69.5 ± 8.7	0.135
Albumin (g/l)	36 ± 5.2	37.1 ± 5.6	0.391
Creatinine (mg/dl)	1.2 ± 0.4	1.5 ± 0.4	0.008
Urea nitrogen (mg/dl)	28.3 ± 17.8	37.2 ± 18.7	0.033
ALT (U/l)	95.9 ± 357.2	47.6 ± 61.2	0.481
AST (U/l)	65.4 ± 236.8	35.3 ± 35.3	0.508
Total bilirubin (mg/dl)	2 ± 2.6	1.4 ± 0.8	0.17
GFR (ml/minute/1.73 m^2)	68 ± 20.5	51.9 ± 15.9	< 0.001
Haemoglobin (g/dl)	12.3 ± 1.7	12.2 ± 1.7	0.885
White cell count (g/ l)	7.6 ± 1.7	7.1 ± 2.0	0.245
Platelets (g/ l)	220.6 ± 88.9	203.1 ± 64.3	0.366
CRP (mg/dl)	2.9 ± 5.7	1.6 ± 2.0	0.264

Data are mean ± SD.

Survival outcomes reported (by group and/or intervention)		
After implantation		
Year	**Group < 60 years (%)**	**Group > 60 years (%)**
1	87.8	90.0
2	82.3	67.5
3	76.0	67.5

K–M survival post-VAD implant (2, 4 and 5 months read from graph)

Month	% alive, < 60 years	% alive, > 60 years
0	100	100
1	92.9	90
2	82	72
3	79.9	62
4	79.9	59
5	74	46
6	74	37



Multivariable Cox model: independent predictors of death after LVAD Implantation

Variable	HR	95% CI	*p*-value
Age[a]	1.4	1.1 to 1.8	0.003
Male gender	0.7	0.2 to 1.9	0.521
Inotropic support	0.7	0.3 to 1.6	0.500
Haemoglobin	0.8	0.6 to 1.0	0.120
Serum albumin	1.0	0.7 to 1.5	0.874
GFR[b]	1.1	0.8 to 1.3	0.361

a Hazard ratio for every 5-year increase in age.
b Calculated by Modification of Diet in Renal Disease formula.

Survival outcomes reported (by group and/or intervention)

Multivariable Cox regression analysis: age was the only independent predictor of post-LVAD mortality (HR 1.4, 95% CI 1.1 to 1.8; $p = 0.003$; table)
When the Cox model was calculated to include incidence of IHD, diabetes mellitus and hypertension, all of which had a higher incidence in > 60 years group, age remained the only independent predictor of post-LVAD mortality (HR 1.4, 95% CI 1.1 to 1.8; $p = 0.006$)
Cox regression model: Proportional hazards assumption was verified by means of Schoenfeld residuals

Survival after HT

Year	Age at LVAD < 60 years	Age at LVAD > 60 years
1	87.8	90.0
3	82.3	67.5
5	76.0	67.5

Other specified/relevant outcomes reported (by group and/or intervention)

Outcomes

Outcome	Group < 60 years ($n = 56$)	Group > 60 years ($n = 30$)	p-value
Composite end point,[a] n (%)	43 (76.8)	14 (46.7)	0.005
BTT rate, %	62.5	33.3	0.010
Median/mean (SD) VAD support (days)	135/166.0 (± 128.4)	97/119.6 (± 100.9)	0.090
Cumulative follow-up (patient-years)	25.4	9.8	
Mean (SD) time to transplantation (days)	169.3 ± 95.7	119.1 ± 47.7	0.031

a HT or survival at 180 days with ongoing VAD support.

Adverse events reported (by group and/or intervention)

Adverse events	Group < 60 years ($n = 56$)	Group > 60 years ($n = 30$)	p-value
Death < 30 days, n (%)	4 (7.1)	3 (10.0)	0.644
Bleeding requiring surgery, n (%)	15 (26.8)	7 (23.3)	0.727
Stroke, n (%)	11 (19.6)	8 (26.7)	0.454
Ischaemic, n (%)	5 (8.9)	4 (13.3)	0.525
Haemorrhagic, n (%)	6 (10.7)	4 (13.3)	0.718
Renal failure requiring CVVD, n (%)	14 (25.0)	16 (53.3)	0.009
Right HF requiring RVAD, n (%)	2 (3.6)	3 (10.0)	0.225

Cause of death reported (by group and/or intervention)

Incomplete reporting. Most common causes of death in the first 180 days after LVAD implantation included sepsis, multisystem organ failure and haemorrhagic stroke. Incidence of sepsis as cause of death was significantly

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Analysis revealed significantly lower survival in VAD patients aged > 60 years. Given the dismal survival and poor QoL associated with advanced HF, the authors did not consider age alone to be an absolute exclusion criterion for LVAD implantation among BTT candidates. Advocate LVAD placement as BTT therapy only in carefully selected older patients most well suited for transplantation

Reviewer's conclusion

The findings do not appear to be surprising as one might expect older patients to fair less well. The authors did undertake Cox's regression model. Proportional hazards assumption was verified by means of Schoenfeld residuals

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CVVD, continuous venovenous haemodialysis; HR, hazard ratio; IHD, ischaemic heart disease; PAP, pulmonary artery pressure.

Sandner 2009b[92]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Sandner
Year of publication: 2009
Country: Austria
Study design: Retrospective observational analysis
Study setting: Hospital setting
Number of centres: One
Duration of study: Not reported (devices implanted November 1998 to July 2007)
Follow-up period: All 86 patients were followed up for at least 180 days or until transplantation or death. Cumulative follow-up of 20.1 patient-years (GFR > 60) 15.2 patient-years (GFR < 60)
Funding: Not reported

Aim of the study

To determine the effect of pre-implant renal function on outcomes after CF LVAD implantation

Participants

Total number of participants: 86
Sample attrition/dropout: Not reported
Inclusion criteria: Consecutive CF LVAD patients implanted November 1998 to July 2007
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): GFR > 60 47.3 ± 12.7 years; GFR < 60 58.7 ± 6.0 years
Median age: Not reported
Age range: Not reported
Sex: GFR > 60 91.3% male; GFR < 60 77.5% male
Race: Not reported
Diagnosis: End-stage HF

Intervention

Indication for treatment: BTT for end-stage HF NYHA class IV
Type of device used: MicroMed DeBakey VAD ($n = 75$), HVAD ($n = 6$) and DuraHeart LVAD ($n = 5$)
Any comparison: GFR < 60 patients vs. GFR > 60 patients (former termed renal dysfunction)
Duration of treatment: Median VAD duration of support, GFR > 60 129 days; GFR < 60 113 days
Mean duration of VAD support: GFR > 60 159.5 ± 117 days; GFR < 60 138.8 ± 126 days
Percentage of patients using inotropes: GFR > 60 50%; GFR < 60 47.5%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes

Outcomes

Primary outcomes: Composite end point of support to 180 days or receipt of HT
Secondary outcomes: Survival; renal function
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Not reported

Outcomes

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	Not reported	Not reported
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Parameter	GFR > 60 ($n = 46$)	GFR < 60 ($n = 40$)	p-value
Age (years)	47.3 ± 12.7	58.7 ± 6.0	< 0.001
Male (%)	42 (91.3)	31 (77.5)	0.075
BMI (kg/m^2)	26.1 ± 3.7	26.9 ± 3.6	0.299
Hypertension (%)	10 (21.7)	17 (42.5)	0.039
Diabetes mellitus (%)	12 (26.1)	14 (35.0)	0.369
Ischaemic aetiology (%)	13 (28.3)	24 (60.0)	0.003
PCWP (mmHg)	28.1 ± 6.6	27.1 ± 6.5	0.548
Cardiac index (l/minute/m^2)	1.7 ± 0.5	1.8 ± 0.4	0.742
PAP mean (mmHg)	42.2 ± 7.1	43.7 ± 8.0	0.453
PVR (dyne/second/cm^5)	359.4 ± 156.6	371.6 ± 221.6	0.804
NYHA functional class	IV	IV	
Serum sodium (mmol/ml)	136.1 ± 3.6	135.1 ± 4.9	0.332
Serum creatinine (mg/dl)	1.0 ± 0.1	1.6 ± 0.4	< 0.001
BUN (mg/dl)	21.0 ± 7.1	43.5 ± 20.4	< 0.001
Serum albumin (g/l)	35.4 ± 5.6	37.5 ± 4.7	0.066
Serum total bilirubin (mg/dl)	1.9 ± 2.8	1.5 ± 1.1	0.426
Intravenous inotropes (%)	23 (50.0)	19 (47.5)	0.817
IABP (%)	1 (2.2)	1 (2.5)	0.92
Mechanical ventilation (%)	2 (4.3)	2 (5.0)	0.886

GFR calculated by Modification of Diet in Renal Disease study calculation (ml/minute/1.73 m^2).

Survival outcomes reported (by group and/or intervention)

Overall actuarial survival was 91.3% at 1 month, 79.9% at 3 months and 72.6% at 6 months for patients normal renal function, compared with 92.5%, 66.5% and 47.9% for patients with renal dysfunction, respectively ($p = 0.038$)

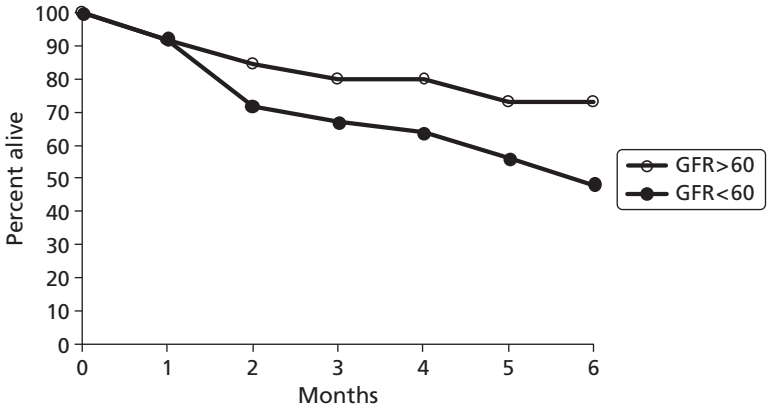
Death	n (%)	n (%)	p-value
At < 30 days	4 (8.7)	3 (7.5)	0.840
At 30–180 days	7 (15.2)	15 (37.5)	0.018

Survival outcomes reported (by group and/or intervention)

Multivariable Cox regression analysis was adjusted for the following factors (previously identified as risk factors for outcome on LVAD): age, sex, haematological abnormalities (haemoglobin), nutritional status (serum albumin) and inotropic support. Pre-LVAD GFR < 60 ml/minute/1.73 m^2 was identified as a significant predictor of post-LVAD mortality by univariate analysis (OR 2.0, 95% CI 1.1 to 4.1; $p = 0.047$); however, GFR was not an independent predictor in the multivariable model (OR 1.2, 95% CI 0.5 to 2.5; $p = 0.676$)

Variable	*p*-value	OR	95% CI
Univariate analysis GFR < 60	0.047	2.0	1.1 to 4.1
Multivariate analysis GFR < 60	0.676	1.2	0.5 to 2.5

K–M analysis of survival $p = 0.038$ for difference between groups.



Month	GFR > 60% alive	GFR < 60% alive
0	100	100
1	91.3	92.5
2	84.5	72
3	79.9	66.5
4	80	64
5	73	56
6	72.6	47.9

Other specified/relevant outcomes reported (by group and/or intervention)

Recovery of renal function

Changes in renal function post-LVAD implantation. Paired samples analysis patients with renal function measurements at consecutive time intervals after LVAD implantation. Among patients with renal dysfunction an overall improvement of GFR (ml/minute/1.73 m^2) was observed:

- Implant to month 1 – 44.6 ± 13.6 to 80.7 ± 32.6 ($p < 0.001$)
- Implant to month 3 – 40.8 ± 10.3 to 70.9 ± 21.9 ($p < 0.001$)
- Implant to month 6 – 41.7 ± 11.5 to 62.7 ± 25.0 ($p = 0.021$)

Among patients with normal renal function, only an early improvement of GFR was observed:

- Implant to month 1 – 76.7 ± 12.5 to 93.7 ± 36.5 ($p = 0.002$)

Absence of diabetes mellitus was the only variable that reached statistical significance when predictors of recovery of renal function were analysed in a regression model (OR 0.2, 95% CI 0.04 to 0.8; $p = 0.022$)

Other specified/relevant outcomes reported (by group and/or intervention)

Results (*n*, %) for other outcomes reported are tabulated below

Outcome/adverse event	GFR > 60 (*n* = 46)	GFR < 60 (*n* = 40)	*p*-value
HT or ongoing support > 180 days,[a] *n* (%)	35 (76.1)	22 (55.0)	0.039
BTT, *n* (%)	29 (63.0)	16 (40.0)	0.033
Bleeding requiring surgery, *n* (%)	11 (23.9)	11 (27.5)	0.704
Right HF requiring RVAD , *n* (%)	2 (4.3)	3 (7.5)	0.533
Stroke, *n* (%)	6 (13.0)	13 (32.5)	0.03
Ischaemic, *n* (%)	4 (8.7)	5 (12.5)	0.565
Haemorrhagic, *n* (%)	2 (4.3)	8 (20.0)	0.024
Renal failure requiring CVVHD, *n* (%)	13 (28.3)	17 (42.5)	0.167

a The composite primary outcome.

Adverse events reported (by group and/or intervention)

See above

Cause of death reported (by group and/or intervention)

Causes of death in the first 180 days after LVAD implantation included:
- Sepsis (GFR > 60, *n* = 6, GFR < 60, *n* = 7; *p* = 0.565)
- Haemorrhagic stroke (GFR > 60, *n* = 2, GFR < 60, *n* = 6; *p* = 0.090)
- Multiorgan failure (*n* = 5)
- Ischaemic stroke (*n* = 1)
- Unknown (*n* = 1)
- Total 28/86 (29 deaths listed above to 180 days)

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Patients with renal dysfunction have poorer outcomes after CF LVAD implantation. However, renal function improves after LVAD implantation and is associated with improved survival

Reviewer's conclusion

Post-hoc analyses of a small cohort that may have received different levels of treatment over the 9-year period using several different devices. Poor renal function pre implant may contribute to risk of death, but in this analysis was not found to be a statistically significant independent indicator. Proportional hazards assumption may not have been tested

BUN, blood urea nitrogen; CVVHD, continuous venovenous haemodialysis; OR, odds ratio; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

Schaffer 2011[76]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Schaffer
Year of publication: 2011
Country: USA
Study design: Retrospective observational
Study setting: Hospital
Number of centres: One
Duration of study: June 2000 to May 2009
Follow-up period: Unclear
Funding: Charitable trust

Aim of the study

To examine the incidence of infectious complications in patients receiving CF and PF devices

Participants

Total number of participants: 133 (86 HMII; 47 HMXVE)
Sample attrition/dropout: Not reported
Inclusion criteria: All LVADs at single institution
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): 49.4 years (± 13.0)
Median age: Not reported
Age range: Not reported
Sex: 75.2% male
Race: Caucasian *n* = 67 (50.4%)
Diagnosis: HF

Intervention

Indication for treatment: BTT 93/133, DT 40/133; cannot split
Type of device used: HMII and HMXVE
Any comparison: HMII vs. HMXVE for infection
Duration of treatment: Various
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Infections
Secondary outcomes: Not applicable
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Unclear

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	*n* = 133 (HMII *n* = 86; HMXVE *n* = 47)	Not reported
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Parameter	Overall ($n = 133$) [n (%) or mean (± SD)]	CF ($n = 86$) [n (%) or mean (± SD)]	PF (n = 47) [n (%) or mean (± SD)]	p-value
Baseline characteristics				
Age, years	49.4 (± 13.0)	49.7 (± 13.1)	49.0 (± 13.1)	0.76
Gender (male)	100 (75.2)	61 (70.9)	39 (83.0)	0.12
Race (Caucasian)	67 (50.4)	38 (44.2)	29 (61.7)	0.24
BTT	93 (69.9)	57 (66.3)	36 (76.6)	0.22
BMI (kg/m^2)	27.9 (± 6.8)	28.3 (± 7.0)	27.1 (± 6.6)	0.37
BSA (m^2)	1.99 (± 0.29)	2.01 (± 0.27)	1.96 (± 0.32)	0.36
Ejection fraction	13.4 (± 5.8)	14.1 (± 6.4)	12.1 (± 4.3)	0.07
Cardiac index (l/minute)	1.96 (± 0.55)	1.95 (± 0.50)	1.96 (± 0.63)	0.88
Cardiogenic shock[a]	77 (57.9)	50 (58.1)	27 (57.5)	0.94
Pre-operative IABP	55 (41.4)	33 (38.4)	22 (46.8)	0.35
Previous ICD	94 (70.7)	69 (80.2)	25 (50.2)	0.001
Previous MI	47 (35.3)	27 (31.4)	20 (42.6)	0.2
Prior heart surgery	52 (39.1)	32 (37.2)	20 (38.5)	0.55
NYHA (class IV)	129 (97.0)	84 (97.7)	45 (95.7)	0.53
Month/year of implant	July/2005 (± 2.5 years)	January/2007 (± 1.25 years)	November/2002 (± 2.0 years)	< 0.001
Pre-operative risk scores				
APACHE II	16.2 (± 4.7)	15.6 (± 4.3)	17.4 (± 5.3)	0.04
INTERMACS	2.47 (± 1.13)	2.64 (± 1.01)	2.17 (± 1.16)	0.02
SHFM	3.17 (± 1.35)	2.97 (± 1.42)	3.53 (± 1.14)	0.02

a Patients were defined as having cardiogenic shock if they had a mean BP < 90 mmHg, a PCWP > 15 mmHg and a cardiac index < 2.2 l/minute.

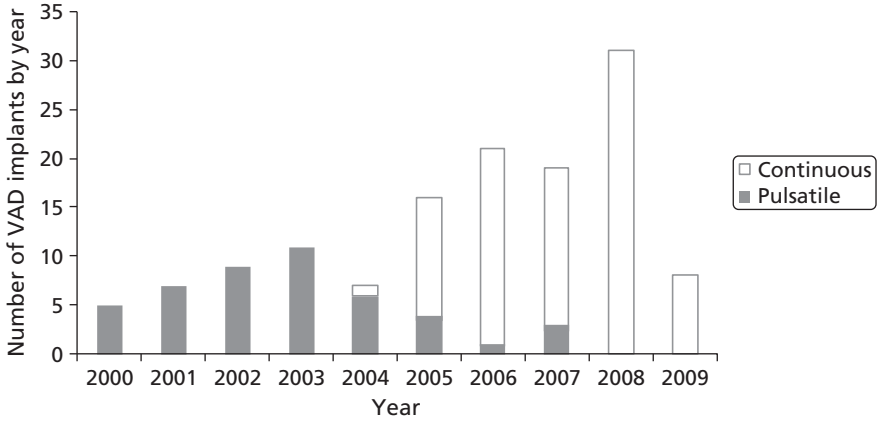
p-value based on comparison between two groups by either Fisher's exact test or Student's t-test, with $p < 0.05$ considered significant.

Survival outcomes reported (by group and/or intervention)

1-year survival HMXVE patients with severe sepsis (19%), those with sepsis (65%) and those without sepsis (81%)
HMII patients 6-month mortality 23%

Other specified/relevant outcomes reported (by group and/or intervention)

Intervention type by year



Adverse events reported (by group and/or intervention)

Infections
Ninety-one (68%) patients developed sepsis. Of the patients with sepsis, 26 (28%) developed severe sepsis
Twenty (77%) patients with severe sepsis developed septic shock, of whom 19 (95%) died

Number and incidence of infections by LVAD and time of incidence

	CF (*n* = 86)		PF (*n* = 47)		
Event	*n* (%)	EPY	*n* (%)	EPY	*p*-value
Systemic infections					
Bacteraemia (all)	23 (27)	0.42	21 (45)	0.98	0.002
0–30 days	3 (4)	0.46	12 (26)	4.16	< 0.001
31–90 days	4 (5)	0.38	3 (6)	0.79	0.33
Beyond 90 days	16 (19)	0.42	6 (13)	0.41	0.78
Sepsis (all)	55 (64)	2.13	36 (77)	5.34	0.01
0–30 days	46 (53)	12.1	34 (72)	25.1	< 0.01
31–90 days	4 (5)	0.87	2 (4)	1.84	0.41
Beyond 90 days	5 (6)	0.29	0 (0)	0.00	0.32
Severe sepsis (all)	14 (16)	0.22	12 (26)	0.55	0.11
0–30 days	9 (10)	1.44	8 (17)	2.55	0.24
31–90 days	4 (5)	0.39	3 (6)	0.7	0.42
Beyond 90 days	1 (1)	0.02	1 (2)	0.07	0.43
Septic shock (all)	11 (13)	0.17	9 (19)	0.37	0.19
0–30 days	5 (6)	0.77	6 (13)	1.87	0.12
31–90 days	6 (7)	0.10	3 (6)	0.15	0.81
Beyond 90 days	0 (0)	0.00	0 (0)	0.00	1.00
Device-associated infections					
Driveline (all)	26 (30)	0.58	19 (40)	1.08	0.02
0–30 days	0 (0)	0.00	2 (4)	0.63	0.04
31–90 days	2 (2)	0.18	5 (11)	1.22	< 0.01
Beyond 90 days	24 (28)	0.83	12 (26)	1.07	0.42

Adverse events reported (by group and/or intervention)

Event	CF (*n* = 86)		PF (*n* = 47)		
	n (%)	EPY	*n* (%)	EPY	*p*-value
LVAD pocket (all)	9 (10)	0.15	16(34)	0.88	< 0.001
0–30 days	2 (2)	0.31	5 (11)	1.62	0.03
31–90 days	2 (2)	0.16	5 (11)	1.01	0.01
Beyond 90 days	5 (6)	0.12	6 (13)	0.53	0.01
Driveline or pocket (all)	31 (36)	0.72	28 (60)	2.31	< 0.001
0–30 days	2 (2)	0.31	6 (13)	1.96	< 0.010
31–90 days	4 (5)	0.39	10 (21)	2.88	< 0.001
Beyond 90 days	25 (29)	0.95	12 (26)	2.16	0.04
Sternal wound (all)	2 (2)	0.03	5 (11)	0.21	0.02
0–30 days	1 (1)	0.15	4 (9)	1.27	0.02
31–90 days	1 (1)	0.09	0 (0)	0.00	0.53
Beyond 90 days	0 (0)	0.00	1 (2)	0.06	0.10
Non-device-associated infections					
CRBSI (all)	14 (16)	0.25	20 (43)	1.02	< 0.001
0–30 days	1 (1)	0.15	13 (28)	4.62	< 0.001
31–90 days	4 (5)	0.38	1 (2)	0.27	0.75
Beyond 90 days	9 (10)	0.23	6 (13)	0.46	0.12
Pneumonia (all)	27 (31)	0.55	17 (36)	1.00	0.23
0–30 days	20 (23)	3.56	15 (32)	6.14	0.14
31–90 days	3 (3)	0.35	2 (4)	0.68	0.50
Beyond 90 days	4 (5)	0.11	0 (0)	0.00	0.23
Urinary tract (all)	31 (36)	0.62	12 (26)	0.68	0.67
0–30 days	16 (19)	2.60	7 (15)	2.31	0.77
31–90 days	10 (12)	1.19	4 (9)	1.09	0.89
Beyond 90 days	5 (6)	0.14	1 (2)	0.09	0.72

p-value based on comparison between two groups by the log-rank test, with $p < 0.05$ considered significant.

Cox proportional hazards analysis

Univariate analyses assessed predictive variables for primary outcomes. Bivariate analysis of the variables 'device type' and 'year of implant' demonstrated that year of implant was a better predictor of all outcomes aside from LVAD pocket infection. Further multivariate analysis demonstrated that year of implant was a significant predictor of all primary outcomes aside from severe sepsis, for which the SHFM score and age were the best predictors. (Results summarised in following tables)

Adverse events reported (by group and/or intervention)

Univariate analysis

	Sepsis			Severe sepsis			Driveline or pocket infection			CRBSI		
Baseline characteristics	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Year of implant	0.88	0.82 to 0.96	< 0.01	0.88	0.76 to 1.01	0.07	0.78	0.70 to 0.86	< 0.01	0.72	0.63 to 0.82	< 0.01
Device type	0.56	0.37 to 0.86	< 0.01	0.54	0.25 to 1.17	0.12	0.31	0.19 to 0.52	< 0.01	0.26	0.13 to 0.51	< 0.01
Age	0.99	0.97 to 1.01	0.2	1.05	1.01 to 1.09	< 0.01	0.99	0.97 to 1.01	0.43	1.01	0.98 to 1.03	0.89
Gender	1.24	0.77 to 2.02	0.35	2.94	0.88 to 9.81	0.08	1.23	0.70 to 2.18	0.46	1.63	0.71 to 3.76	0.25
Race	1.24	0.80 to 1.84	0.38	2.59	1.12 to 5.98	0.03	1.06	0.63 to 1.78	0.82	1.4	0.71 to 2.75	0.33
Cardiac index (l/minute/m^2)	0.84	0.57 to 1.22	0.36	1.36	0.68 to 2.72	0.38	1.68	1.02 to 2.74	0.04	1.33	0.73 to 2.42	0.35
Pre-operative IABP	1.88	1.22 to 2.86	< 0.01	2.26	1.04 to 4.94	0.04	0.58	0.33 to 1.04	0.08	0.99	0.50 to 2.00	0.99
Prior heart surgery	1.3	0.86 to 1.98	0.2	1.32	0.61 to 2.86	0.48	1.74	1.03 to 2.94	0.04	1.53	0.78 to 3.01	0.22
APACHE II	1.04	0.99 to 1.09	0.06	1.1	1.03 to 1.17	< 0.01	1.02	0.97 to 1.08	0.41	1.1	1.04 to 1.17	< 0.01
INTERMACS	0.69	0.55 to 0.85	< 0.01	0.58	0.38 to 0.88	0.01	1.17	0.93 to 1.47	0.18	0.87	0.63 to 1.20	0.39
SHFM	1.27	1.09 to 1.49	< 0.01	1.48	1.11 to 1.98	< 0.01	0.99	0.83 to 1.19	0.97	1.34	1.04 to 1.71	0.02

Adverse events reported (by group and/or intervention)

Bivariate Cox proportional hazards analysis of variables 'year of implant' and 'device type'

Component variables included in the separate bivariate[a] models'	Univariate analysis hazard ratio (CI)	*p*-value[b]	Bivariate analysis hazard ratio (CI)	*p*-value[c]
Bacteraemia				
Device type (CF device)	0.40 (0.22 to 0.73)	< 0.01	1.34 (0.46 to 3.88)	0.54
Year of implant	0.78 (0.70 to 0.87)	< 0.01	0.75 (0.61 to 0.91)	< 0.01
Sepsis				
Device type (CF device)	0.59 (0.39 to 0.91)	0.02	0.94 (0.46 to 1.92)	0.86
Year of implant	0.88 (0.82 to 0.96)	< 0.01	0.89 (0.78 to 1.02)	0.10
Severe sepsis				
Device type (CF device)	0.54 (0.25 to 1.17)	0.12	0.83 (0.23 to 3.04)	0.78
Year of implant	0.88 (0.76 to 1.01)	0.08	0.90 (0.71 to 1.15)	0.41
Septic shock				
Device type (CF device)	0.56 (0.23 to 1.35)	0.20	1.10 (0.23 to 5.21)	0.90
Year of implant	0.87 (0.74 to 1.02)	0.08	0.86 (0.64 to 1.14)	0.28
Driveline				
Device type (CF device)	0.50 (0.27 to 0.90)	0.02	1.16 (0.44 to 3.04)	0.76
Year of implant	0.81 (0.72 to 0.91)	< 0.01	0.79 (0.66 to 0.96)	0.02
LVAD pocket				
Device type (CF device)	0.20 (0.09 to 0.46)	< 0.01	0.33 (0.10 to 1.10)	0.07
Year of implant	0.75 (0.65 to 0.87)	< 0.01	0.88 (0.71 to 1.11)	0.29
Driveline or LVAD pocket infection				
Device type (CF device)	0.31 (0.19 to 0.52)	< 0.01	0.57 (0.26 to 1.25)	0.16
Year of implant	0.77 (0.70 to 0.86)	< 0.01	0.85 (0.72 to 0.99)	0.04
Sternal wound infection				
Device type (CF device)	0.18 (0.03 to 0.92)	0.04	1.08 (0.93 to 1.24)	0.32
Year of implant	0.73 (0.56 to 0.96)	0.03	0.70 (0.37 to 1.33)	0.28
CRBSI				
Device type (CF device)	0.26 (0.13 to 0.51)	< 0.01	1.01 (0.98 to 1.04)	0.42
Year of implant	0.72 (0.63 to 0.82)	< 0.01	0.71 (0.62 to 0.82)	< 0.01
Pneumonia				
Device type (CF device)	0.69 (0.38 to 1.27)	0.24	2.10 (0.71 to 6.21)	0.18
Year of implant	0.86 (0.76 to 0.96)	< 0.01	0.76 (0.62 to 0.94)	0.01
Urinary tract infection				
Device type (CF device)	1.16 (0.59 to 2.26)	0.67	1.55 (0.51 to 4.73)	0.44
Year of implant	0.99 (0.88 to 1.12)	0.94	0.93 (0.76 to 1.15)	0.51

a A separate bivariate model was constructed for each of the outcome measures using the variables 'year of implant' and 'device type'.
b *p*-value based on bivariate Cox analysis applying variables 'year of implant' and 'device.
c *p*-value based on univariate Cox analysis.

Adverse events reported (by group and/or intervention)

Results of Multivariate Cox proportional hazard analysis of pre-operative variables

Component variables included in the three separate multivariable models[a]	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value[b]	HR	95% CI	*p*-value[c]
Sepsis						
Prior heart surgery	1.30	0.86 to 1.98	0.200	1.33	0.88 to 2.03	0.18
Year of implant	0.88	0.82 to 0.96	0.003	0.91	0.84 to 0.99	0.04
SHFM score	1.27	1.09 to 1.49	0.002	1.21	1.03 to 1.43	0.02
Severe sepsis						
Age	1.05	1.01 to 1.09	0.009	1.05	1.02 to 1.10	0.006
Year of implant	0.88	0.76 to 1.01	0.080	0.89	0.76 to 1.04	0.15
SHFM score	1.48	1.10 to 1.98	0.008	1.4	1.04 to 1.88	0.03
Drive or LVAD pocket infection						
Prior heart surgery	1.74	1.03 to 2.94	0.04	1.59	0.94 to 2.70	0.09
Cardiac index	1.67	1.03 to 2.74	0.04	1.96	1.22 to 3.14	0.005
Year of implant	0.78	0.70 to 0.86	< 0.001	0.76	0.68 to 0.85	< 0.001
Catheter-related bloodstream infection						
Year of implant	0.72	0.63 to 0.82	< 0.001	0.72	0.63 to 0.84	< 0.001
APACHE II score	1.10	1.04 to 1.17	0.001	1.08	1.01 to 1.14	0.02
SHFM score	1.34	1.04 to 1.71	0.020	0.98	0.73 to 1.32	0.89

a A separate multivariate model was constructed for each of the four outcome measures (see text).
b *p*-value based on univariate Cox analysis.
c *p*-value based on bivariate Cox analysis applying the variables 'year of implant' and 'device type'.

Bivariate analysis demonstrated that year of implant significantly predicted bacteraemia, driveline infection and CRBSI, while approaching significance for sepsis ($p = 0.10$). Device type did not achieve significance for any end point, although it approached significance for LVAD pocket infections
On multivariate analysis, year of implant remained significant for all primary outcomes except severe sepsis. After risk adjustment, SHFM score and age at implant better predicted severe sepsis, suggesting that pre-operative acuity plays a role in the likelihood of a patient to progress from sepsis to severe sepsis

Cause of death reported (by group and/or intervention)

Incompletely reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

In this institutional review of post-LVAD infections, a decrease in infectious complications in CF patients was likely related to increased provider experience associated with a more recent date of implantation

Reviewer's conclusion

The data support the author's conclusion. The proportional hazards assumption does not appear to have been tested

APACHE II, Acute Physiology and Chronic Health Evaluation II; BSA, body surface area; CRBSI, catheter-related bloodstream infection; EPY, events per year of LVAD support; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; PF, pulsatile flow.

Schaffer 2009[77]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Schaffer
Year of publication: 2009
Country: USA
Study design: Retrospective analysis
Study setting: Hospital
Number of centres: One
Duration of study: VAD implants June 2000 to May 2009
Follow-up period: 1 year
Funding: Not reported

Aim of the study

To assess the predictive ability of LM, COL, APACHE II, INTERMACS and SHFM prognostic systems for patients in receipt of HMII at a single institution

Participants

Total number of participants: 86
Sample attrition/dropout: 0
Inclusion criteria: All HMII recipients to May 2009
Exclusion criteria: NR
Characteristics of participants:
Mean age (SD): 49.7 years (13.1)
Median age: Not reported
Age range: Not reported
Sex: 61/86 (70.9% male)
Race: 38/86 (44.2% white)
Diagnosis: Various HF
NOTE: This is the same population of HMII patients as in Schaffer *et al.*[76]

Intervention

Indication for treatment: 57/86 BTT; 29/86 DT
Type of device used: HMII
Any comparison: High risk vs. low risk patients
Duration of treatment: October 2004 to May 2009
Percentage of patients using inotropes: 54/86 62.8%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Survival
Secondary outcomes: None
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: No
HRQoL: No
Length of follow-up: 1 year

Number of participants	Intervention	Comparator, if present
Screened	Not reported/not applicable	Not reported/not applicable
Randomised/included	$n = 86$ overall	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics

Characteristics	*n* (%) or mean ± SD
Baseline	
Age (years)	49.7 ± 13.1
Gender, male	61 (70.9)
Race, white	38 (44.2)
BTT	57 (66.3)
BMI (kg/m^2)	28.3 ± 7.0
NYHA class IV	84 (97.7)
Ischaemic aetiology	28 (32.6)
Pre-operative ventilation	6 (7.0)
Pre-operative IABP	33 (38.4)
Previous open heart operation	32 (37.2)
Previous LVAD	10 (11.6)
Composite risk scores	
COL	1.05 ± 1.59
LM	11.9 ± 5.4
INTERMACS	2.64 ± 1.01
APACHE II	15.6 ± 4.3
SHFM	2.97 ± 1.42

Eighty-four of 86 patients were NYHA class IV; 50 (58.1%) patients in cardiogenic shock; 54 (62.8%) patients on inotropes; 33 (38.4%) patients on IABPs; 32 (37.2%) patients had previous open heart surgery; 10 (11.6%) patients had a previous VAD; 29 (33.7%) patients were implanted for DT; 28 (32.6%) patients had ischaemic cardiomyopathy
Mean pre-operative cardiac index = 1.95 ± 0.50
Mean ejection fraction = 0.14 ± 0.06

Survival outcomes reported (by group and/or intervention)

The 30-day, 90-day, and 1-year mortality were 10.6% (*n* = 9), 22.7% (*n* = 19), and 30.3% (*n* = 24), respectively
Each patient was given a risk score according to each of the five predictive models that use pre-operative patient characteristics to arrive at risk assessment. A cut-off was determined for each model so as to divide the 86 patients into high-risk and low-risk groups. The cut-off score for each model was decided according to which of those cut-offs tried gave the best discrimination (by log-rank test the lowest *p*-value) between the K–M observed survival for the high- and low-risk designated patients. The cut-off score for SHFM was determined according to a survival equation: $S(t) = \exp(-0.045 \times t \times \exp(\text{SHFM score}))$. When S = 50% at t = 0.5 years
The number of patients in low-risk and high-risk groups, and *p*-value from K–M plots were:

			K–M % alive at 1 year		
	Low	High	Low	High	*p*-value
COL	83	3	100	64	0.31
LM	53	33	74.1	69.1	0.33
INTERMACS	43	43	84.1	55.5	0.004
APACHE II	55	31	82.9	44.4	< 0.001
SHFM	55	31	83.6	46.1	< 0.001

Survival outcomes reported (by group and/or intervention)

Univariate and multivariate (including risk scores from all five models) Cox proportional hazard analysis results are shown below:

	Univariate analysis		Multivariable analysis	
Composite scores	HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value[b]
30-day mortality				
COL	1.02 (0.69 to 1.52)	0.90	1.02 (0.58 to 1.77)	0.95
LM	0.95 (0.83 to 1.08)	0.39	0.92 (0.80 to 1.06)	0.25
INTERMACS	0.75 (0.38 to 1.44)	0.38	1.15 (0.48 to 2.28)	0.75
APACHE II	1.13 (0.98 to 1.30)	0.09	1.10 (0.93 to 1.30)	0.27
SHFM	1.73 (1.06 to 2.85)	0.03	1.75 (0.93 to 3.32)	0.08
90-day mortality				
COL	1.04 (0.80 to 1.34)	0.79	0.89 (0.62 to 1.28)	0.53
LM	0.98 (0.90 to 1.07)	0.68	0.96 (0.88 to 1.06)	0.43
INTERMACS	0.56 (0.35 to 0.92)	0.02	0.70 (0.36 to 1.36)	0.3
APACHE II	1.10 (1.00 to 1.21)	0.05	1.07 (0.96 to 1.20)	0.2
SHFM	1.70 (1.21 to 2.37)	0.002	1.46 (0.94 to 2.28)	0.09
1-year mortality				
COL	1.04 (0.83 to 1.31)	0.71	0.92 (0.67 to 1.26)	0.59
LM	0.99 (0.92 to 1.06)	0.76	0.96 (0.89 to 1.04)	0.37
INTERMACS	0.64 (0.42 to 0.98)	0.04	0.86 (0.49 to 1.52)	0.61
APACHE II	1.12 (1.03 to 1.22)	0.006	1.10 (1.01 to 1.21)	0.04
SHFM	1.64 (1.23 to 2.20)	0.001	1.50 (1.02 to 2.21)	0.04

a Based on univariate Cox analysis, $p < 0.05$ statistically significant.
b Based on multivariable Cox regression analysis, $p < 0.05$ statistically significant.

On univariate analysis, SHFM predicted mortality at each of the three mortality end points examined, whereas APACHE II and INTERMACS significantly predicted 90-day and 1-year mortality. The LM and COL were not predictive of mortality at any end point studied

Multivariable analysis used all five scores as covariates ('possible due to lack of overlapping variables between scores only age, NYHA, ventilator status, serum sodium level, haematocrit/haemoglobin, prothrombin time/INR, and pre-operative inotropes were used in multiple scores'). In multivariate analysis SHFM (HR 1.50, 95% CI 1.02 to 2.21; $p = 0.04$) and APACHE II (HR 1.10, 95% CI 1.01 to 1.21; $p = 0.04$) remained predictive of 1-year mortality. No score achieved significance in predicting 30-day or 90-day mortality on multivariable analysis, although SHFM approached significance for both end points ($p = 0.08$ and $p = 0.09$, respectively)

Pre-operative variables for the 86 single-centre cohort were also explored using univariate and multivariate Cox proportional hazards models. The results are tabulated below:

Survival outcomes reported (by group and/or intervention)

Univariate analysis

Significant variables	Score variable	30-day mortality		90-day mortality		1-year mortality	
		HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value[a]
Baseline variables							
Age	A, S	1.07 (0.99 to 1.14)	0.07	1.06 (1.01 to 1.11)	0.01	1.04 (1.01 to 1.18)	0.02
Gender, male	S	b		8.85 (1.18 to 66.4)	0.03	2.65 (0.90 to 7.76)	0.08
Race, white		2.62 (0.66 to 10.5)	0.17	3.05 (1.16 to 8.02)	0.02	3.03 (1.29 to 7.10)	0.01
Pre-operative IABP		0.82 (0.20 to 3.26)	0.77	1.93 (0.78 to 4.75)	0.15	2.22 (1.00 to 4.96)	0.05
Pre-operative IABP/ventilator	S	1.21 (0.32 to 4.49)	0.78	2.22 (0.89 to 5.53)	0.09	2.44 (1.08 to 5.50)	0.03
Vital signs							
Ejection fraction	S	1.02 (0.93 to 1.12)	0.67	1.04 (0.98 to 1.10)	0.23	1.06 (1.01 to 1.11)	0.03
Cardiac index		0.21 (0.05 to 0.88)	0.03	0.57 (0.23 to 1.43)	0.23	0.73 (0.32 to 1.68)	0.46
Lab values							
Serum urea nitrogen	LM	1.02 (1.00 to 1.05)	0.05	1.03 (1.01 to 1.04)	0.001	1.03 (1.02 to 1.05)	< 0.001
Serum creatinine	A	1.56 (1.19 to 2.04)	< 0.001	1.53 (1.19 to 1.97)	0.001	1.63 (1.27 to 2.09)	< 0.001
Serum cholesterol	S	0.98 (0.97 to 1.00)	0.08	0.98 (0.97 to 0.99)	0.01	0.99 (0.98 to 0.99)	0.008
Haemoglobin	S	0.74 (0.53 to 1.05)	0.09	0.84 (0.68 to 1.05)	0.13	0.81 (0.66 to 0.98)	0.04
Platelets	LM	1.01 (1.00 to 1.02)	0.01	1.01 (1.00 to 1.02)	0.008	1.01 (1.00 to 1.01)	0.02
Lymphocyte[c]	S	0.89 (0.80 to 1.00)	0.05	0.91 (0.85 to 0.98)	0.01	0.92 (0.87 to 0.98)	0.007
Prothrombin time	C	1.11 (1.01 to 1.23)	0.03	1.10 (1.00 to 1.20)	0.05	1.10 (1.01 to 1.19)	0.03
Pre-operative medications							
ACE inhibitor	S	0.16 (0.02 to 1.25)	0.08	0.20 (0.06 to 0.70)	0.01	0.27 (0.10 to 0.72)	0.009
Beta-blocker	S	0.25 (0.06 to 0.99)	0.05	0.53 (0.22 to 1.31)	0.17	0.59 (0.26 to 1.31)	0.20

a Based on univariate Cox proportional hazard analysis; values of $p < 0.05$ are significant.
b Risk of 30-day mortality not possible to calculate for the variable 'gender' owing to limited variability in the outcome.
c Lymphocyte per cent on complete blood cell count differential.

Survival outcomes reported (by group and/or intervention)

Multivariate analysis

Component variables	Score variable	Univariate analysis		Multivariable analysis	
		HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value[b]
30-day mortality					
Age	A, S	1.07 (0.99 to 1.14)	0.07	1.06 (0.99 to 1.13)	0.12
Cardiac index		0.21 (0.05 to 0.88)	0.03	0.20 (0.02 to 2.00)	0.17
Serum creatinine	A	1.56 (1.19 to 2.04)	< 0.001	1.70 (1.20 to 2.41)	0.003
Platelets	LM	1.01 (1.00 to 1.02)	0.01	1.01 (1.00 to 1.02)	0.009
Lymphocytes[c]	S	0.89 (0.80 to 1.00)	0.05	0.91 (0.78 to 1.06)	0.21
Prothrombin time	C	1.11 (1.01 to 1.23)	0.03	1.03 (0.89 to 1.18)	0.74
Pre-operative ACE inhibitor	S	0.16 (0.02 to 1.25)	0.08	0.49 (0.04 to 5.57)	0.56
Pre-operative beta-blocker	S	0.25 (0.06 to 0.99)	0.05	0.19 (0.03 to 1.11)	0.07
90-day mortality					
Age	A, S	1.06 (1.01 to 1.11)	0.01	1.03 (0.99 to 1.08)	0.12
Sex, male	S	8.85 (1.18 to 66.4)	0.03	3.41 (0.40 to 28.8)	0.26
Race, white		3.05 (1.16 to 8.02)	0.02	1.85 (0.56 to 6.12)	0.31
Serum creatinine	A	1.53 (1.19 to 1.97)	0.001	1.57 (1.15 to 2.14)	0.004
Serum cholesterol	S	0.98 (0.97 to 0.99)	0.01	0.99 (0.98 to 1.01)	0.28
Platelets	LM	1.01 (1.00 to 1.02)	0.008	1.01 (1.00 to 1.02)	0.05
Lymphocytes[c]	S	0.20 (0.06 to 0.70)	0.01	0.97 (0.90 to 1.04)	0.44
Pre-operative ACE inhibitor	S	0.20 (0.06 to 0.70)	0.01	0.33 (0.09 to 1.23)	0.10
1-year mortality					
Age	A, S	1.04 (1.01 to 1.18)	0.02	1.05 (1.00 to 1.10)	0.04
Race, white		3.03 (1.29 to 7.10)	0.01	2.10 (0.80 to 5.56)	0.13
Pre-operative IABP/ventilator	S	2.44 (1.08 to 5.50)	0.03	2.42 (0.85 to 6.92)	0.10
Serum creatinine	A	1.63 (1.27 to 2.09)	< 0.001	1.86 (1.40 to 2.48)	< 0.001
Serum cholesterol	S	0.99 (0.98 to 0.99)	0.008	0.99 (0.98 to 1.01)	0.21
Platelets	LM	1.01 (1.00 to 1.01)	0.02	1.01 (1.00 to 1.01)	0.03
Lymphocytes[c]	S	0.92 (0.87 to 0.98)	0.007	0.98 (0.92 to 1.47)	0.58
Pre-operative ACE inhibitor	S	0.27 (0.10 to 0.72)	0.009	0.49 (0.16 to 1.47)	0.20

a Based on univariate Cox analysis.
b Based on multivariate Cox analysis.
c Lymphocyte per cent on complete blood cell count differential.

Survival outcomes reported (by group and/or intervention)

On multivariable analysis, older age and serum creatinine level remained significant at predicting 1-year mortality

Other specified/relevant outcomes reported (by group and/or intervention)

Days on LVAD support = 277 ± 233; *n* = 27 (31.4%) received more than 1 year of support

Adverse events reported (by group and/or intervention)

Not reported

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

Among the LM, COL, APACHE II, INTERMACS and SHFM scores, the best predictor of mortality in a single institutional cohort of CF LVAD patients was the SHFM score

Reviewer's conclusion

SHFM was derived from a large cohort of non-VAD patients but appears to be the better performing prognostic indicator for this small cohort of HMII patients. How generalisable this finding is for other CF devices and populations remains to be researched. 57/86 BTT; 29/86 DT; cannot split (authors stated: our analysis did not stratify patients by therapeutic intent, because therapeutic intent was not a significant covariate for any of our mortality end points)

A, Acute Physiology and Chronic Health Evaluation II (APACHE II) variable; APACHE II, Acute Physiology and Chronic Health Evaluation II; C, Columbia variable; COL, Columbia; HR, hazard ratio; INR, international normalised ratio; LM, Lietz–Miller; S, Seattle Heart Failure Model (SHFM) variable.

Schmid 2008[86]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Schmid
Year of publication: 2008
Country: Worldwide
Study design: Retrospective observational of Berlin Heart Registry
Study setting: Hospital
Number of centres: Multicentre
Duration of study: 16 June 2002 to 30 June 2006
Follow-up period: 4 years
Funding: Unclear

Aim of the study

Investigate the dependence of the neurological adverse event rate on the length of the inflow cannula (short vs. long) of the INCOR; Berlin Heart axial-flow VAD pump

Participants

Total number of participants: 216
Sample attrition/dropout: Not reported
Inclusion criteria: Consecutive patients in receipt of Berlin Heart
Exclusion criteria: Patients undergoing device implantations via a lateral thoracotomy and at centres with only minimal INCOR experience (fewer than five implants)
Characteristics of participants:
Mean age (SD): Short: 49.3 years (± 12.6); long years: 53.1 (± 10.9)
Median age: Not reported
Age range: Short 16–72 years; long 25–70 years
Sex: Short $n = 119$ male (86.2%); long $n = 68$ male (87.2%)
Race: Not reported
Diagnosis: HF

Intervention

Indication for treatment: BTT or DT
Type of device used: INCOR (Berlin Heart)
Any comparison: Between SC and LC devices
Duration of treatment: Various
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – INCOR (Berlin Heart)

Outcomes

Primary outcomes: Cerebrovascular events
Secondary outcomes: Deaths, transplants, ongoing support, 'weaning' from device (presumably for recovery of ventricular function)
Method of assessing outcomes: Retrospective analysis of medical records
Survival: Yes
Adverse event:
HRQoL: No measures reported
Length of follow-up: Up to 4 years

Outcomes

Number of participants	Intervention short cannula	Comparator, if present
Screened	Total 'screened' = 273 not reported by group	Not reported
Randomised/included	The first four patients received a LC device. From October 2002 until May 2004 the SC device was used. After May 2004 new LC device was progressively introduced, and use of the SC device was limited to patients with an extremely thin left ventricular wall at the insertion site	Not reported
Excluded	57 not reported by group	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Parameter	SC group (*n* = 138)	LC group (*n* = 78)	*p*-value
Age (years), mean (range; SD)	49.3 (16–72; ± 12.6)	53.1 (25–70; ± 10.9)	0.025
Male gender, *n* (%)	119 (86.2)	68 (87.2)	0.51
Height (cm), mean (range; SD)	176.3 (152–221; ± 8.8)	176.1 (150–196; ± 9.6)	0.887
Weight (kg), mean (range; SD)	80.2 (45–152; ± 15.3)	81.1 (55–132; ± 15.6)	0.667
BSA (m^2), mean (range; SD)	1.96 (1.50–2.72; ± 0.20)	1.97 (1.58–2.54; ± 0.21)	0.777
BMI (kg/m^2), mean (range; SD)	25.8 (15.57–42.55; ± 0.72)	26.2 (16.95–37.75; ± 0.51)	0.506
Aetiology, *n* (%)			
Dilative CMP	62 (44.9)	37 (47.4)	0.415
Ischaemic CMP	45 (32.6)	31 (39.7)	0.506
Acute infarction	16 (11.6)	7 (9.0)	0.362
Acute myocarditis	9 (6.5)	0 (0)	0.016
Other	6 (4.3)	3 (3.8)	
LVEF (%), mean (range; SD)	16.7 (4–40; ± 6.2)	17.0 (5–40; ± 7.5)	0.755
LVEDD (mm), mean (range; SD)	71.8 (33[a] –90; ± 10.7)	74.1 (54–110; ± 11.4)	0.3
Cardiac index ($l/minute/m^2$), mean (range; SD)	1.7 (0.7–2.8[a]; ± 0.4)	1.7 (0.8–3; ± 0.5)	0.634
mPAP (mmHg), mean (range; SD)	36.7 (7–90; ± 11.5)	37.4 (17–74; ± 13.6)	0.744
CVP (mmHg), mean (range; SD)	14.6 (3–30; ± 5.5)	14.1 (1–33; ± 7.0)	0.625

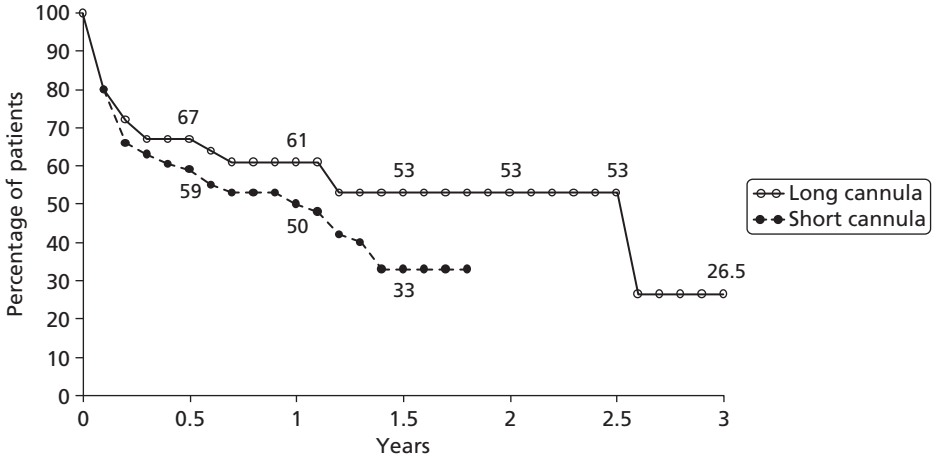
a One patient presented with severe RCMP.

Survival outcomes reported (by group and/or intervention)

K–M survival analysis: Probability of survival % alive vs. time (data read from graph):

At risk:	t = 0	t = 0.5	t = 1	t = 1.5	t = 2	t = 3	t = 3.5
	78	24	11	4	3	2	1
	138	50	24	5	3		

$p = 0.27$



Note: it was not clear if patients were censored on receipt of a HT, and therefore the survival data is difficultr to interpret. In addition, the proportion of DTR vs. BTT patients was different between groups but these proportions were not reported
At the end of the observation period, overall survival was better in the LC group as compared with the SC group (SC 52.9%; LC 63.4%; $p = 0.05$)
Survival rates based on the K–M survival curves were ($p = 0.27$):
At l year: SC 53%; LC 61%
At 2 years: SC 33%; LC 50%

At end of follow-up overall deceased were:

Condition	SC group ($n = 138$)	LC group ($n = 78$)	p-value
Deceased, *n* (%)	65 (47.1)	27 (34.6)	0.05
Not deceased, *n* (%)	73 (52.9)	51 (65.4)	

Other specified/relevant outcomes reported (by group and/or intervention)

Difference in VAD support time (table) was explained by an increased waiting time on the transplant list, a more recent implantation date, and a larger number of DT patients in the LC group. Consequently, fewer patients in the LC groups underwent a HT (table)

Outcome	SC group ($n = 138$)	LC group ($n = 78$)	p-value
Support interval (days), mean (range; SD)	186 (1–805; ± 187)	171 (0–1128; ± 211)	0.603
Outcome of all, *n* (%)			
Ongoing support	7 (5.1)	30 (38.5)	< 0.001
HT	60 (43.5)	18 (23.1)	< 0.002
Weaned from device	6 (4.3)	3 (3.8)	0.582
Deceased	65 (47.1)	27 (34.6)	0.05

Adverse events reported (by group and/or intervention)

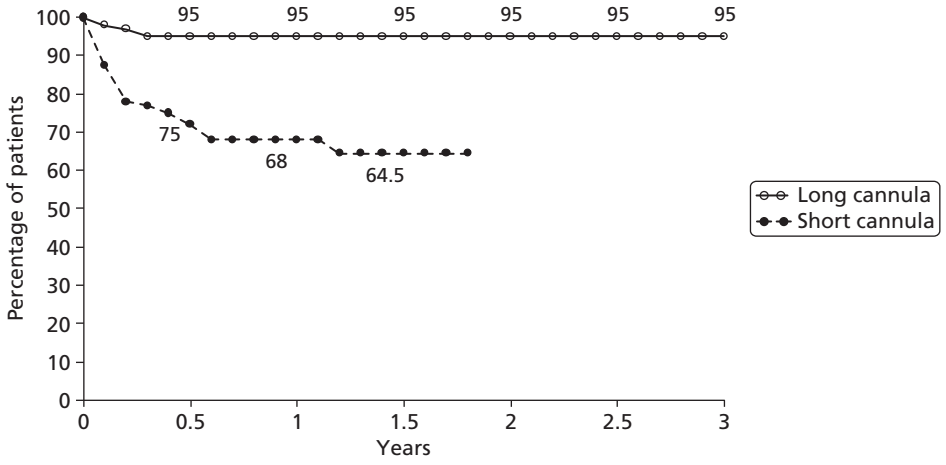
Freedom from stroke

Event	SC group ($n = 138$)	LC group ($n = 78$)	p-value
Stroke, *n*	35	4	
Patients effected, *n* (%)	32 (23.2)	3 (3.8)	< 0.001
Events per patient-year	0.5	0.11	
Time to event (days), mean (range; SD)	73 (2–429; ± 86)	38 (4–66; ± 31)	
Intracerebral bleeding, *n*	15	4	
Patients effected, *n* (%)	14 (10.1)	4 (5.1)	0.152
Events per patient-year	0.21	0.11	
Time to event (days), mean (range; SD)	118 (18–330; ± 110)	271 (15–933; ± 442)	

Cerebral bleeding confirmed by CT scan.

Freedom from stroke K–M analysis (data read from graph):

At risk:	t = 0	t = 0.5	t = 1	t = 1.5	t = 2	t = 3	t = 3.5
	78	24	11	4	3	2	1
	138	50	24	5	3		



Cox proportional hazards model for freedom from stroke (clinically diagnosed)

Variable	p-value
Inflow cannula	0.005
Age at implant	0.261
Height	0.320
Weight	0.605
Gender	0.607
Myocarditis	0.936
Acute infarction	0.937
Ischaemic CMP	0.944

Adverse events reported (by group and/or intervention)

Note: DT BTT not testede as variable. Proportional hazards assumption not tested or not reported
Event rates for cerebral bleeding: SC group 10.1%; LC group 5.1% ($p = 0.152$)
Event per patient-year: SC group 0.11; LC goup 0.21
The RR of intracerebral bleeding was 1.98 times higher in the SC group

Cause of death reported (by group and/or intervention)

Cause of death	SC group ($n = 138$)	LC group ($n = 78$)	p-value
Total, *n*	65	27	
Multiorgan failure, *n* (%)	34 (52.3)	14 (51.9)	0.167
Cerebrovascular event, *n* (%)	9 (13.8)	4 (14.8)	0.464
Cancer, *n* (%)	2 (3.1)	0	
Trauma, *n* (%)	2 (3.1)	0	
Right ventricular failure artery, *n* (%)	4 (6.2)	4 (14.8)	
Pulmonary artery embolus, *n* (%)	1 (1.5)	0	
Bleeding, *n* (%)	1 (1.5)	0	
Other, *n* (%)	10 (15.4)	5 (18.5)	
Unknown, *n* (%)	2 (3.1)	0	

QoL reported (by group and/or intervention)

Not reported

Author's conclusion

INCOR patients with a long inflow cannula demonstrated significantly better survival and a significantly lower incidence of cerebrovascular adverse events. The overall rate of cerebrovascular complications has declined to a very acceptable level, rendering the INCOR an excellent tool for long-term mechanical support in cases of acute or chronic HF

Reviewer's conclusion

K–M analysis of survival difference was not statistically significant. Groups were not sufficiently comparable for a rigorous comparison (received implant at different times during surgical learning curves) and either as DT or BTT. Proportional hazards assumption not tested. Direction of evidence tends to favour the author's conclusions

BSA, body surface area; CMP, cardiomyopathy; CT, computerised tomography; LC, long cannula; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; SC, short cannula.

Starling 2011[52]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Starling
Year of publication: 2011
Country: USA
Study design: Prospective post-approval (FDA) evaluation following a multicentre clinical trial
Study setting: Multicentre
Number of centres: 77
Duration of study: Patients enrolled from September 2007 to February 2009
Follow-up period: At least 1 year
Funding: Unclear

Aim of the study

The aim was to determine whether or not results with the HMII LVAD in a commercial setting are comparable to other available devices for the same indication

Participants

Total number of participants: 304
Sample attrition/dropout: Not reported
Inclusion criteria: First 169 consecutive HMII patients after FDA approval enrolled in INTERMACS comparator group; 135 (80%) received the electric HMXVE LVAD and 34 (20%) received the pneumatic Thoratec Implantable VAD (Thoratec Inc., Pleasanton, CA, USA). Population eligible or likely to become eligible for HT
Exclusion criteria: Unclear
Characteristics of participants:
Mean age (SD): Not reported
Median age: Not reported
Age range: Not reported
Sex: HMII 78% male; comparator 83% male
Race: n (%) – Caucasian HMII 125 (74), comparator 113 (67); African American HMII 29 (17), comparator 37 (22); other HMII 15 (9), comparator 19 (11)
Diagnosis: HF

Intervention

Indication for treatment: HF BTT with LVAD
Type of device used: HMII
Any comparison: HMII vs. other devices
Duration of treatment: Average support duration for HMII was 306 ± 173 days (median 386 days), significantly longer than comparator at 207 ± 188 days (median 152 days). Cumulative follow-up duration was 142.0 (HMII) and 96.2 (comparator) patient-years of support
Percentage of patients using inotropes: 80% HMII; 89% comparator
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Survival to transplant, recovery of the heart, or ongoing support at 6 months
Secondary outcomes: QoL (EQ-5D/VAS), adverse events
Method of assessing outcomes: Medical records and prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: Yes
Length of follow-up: At least 12 months or to transplant or death

Number of participants	Intervention	Comparator, if present
Screened	Not reported	Not reported
Randomised/included	HMII ($n = 169$)	Comparator ($n = 169$)
Excluded	Not reported	Not reported
Missing participants	Not reported	Not reported
Withdrawals	Not reported	Not reported

Patient's baseline characteristics

Demographic parameter	HMII ($n = 169$)	Comparator ($n = 169$)	p-value
Male subjects	131 (78)	141 (83)	0.217
Age (years)			
0–18	3 (2)	6 (4)	0.631
19–39	26 (15)	22 (13)	
40–59	81 (48)	87 (51)	
60–79	59 (35)	54 (32)	
Race			
Caucasian	125 (74)	113 (67)	0.380
African American	29 (17)	37 (22)	
Other	15 (9)	19 (11)	
BSA (m^2)	2.03 ± 0.25	2.06 ± 0.25	0.182
INTERMACS profile	< 0.001[a]		
1	41 (24)	66 (39.0)	
2	63 (37)	75 (44)	
3	33 (20)	8 (5)	
4	21 (12)	12 (7)	
5, 6, 7	11 (7)	8 (5)	
Haemodynamic status before implant			
Heart rate (b.p.m.)	88.0 ± 18.4 (167)	94.1 ± 20.3 (167)	0.005[a]
BP systolic (mmHg)	97.8 ± 13.8 (167)	99.9 ± 16.0 (168)	0.214
BP diastolic (mmHg)	60.4 ± 11.1 (165)	61.5 ± 12.1 (168)	0.404
PAP systolic (mmHg)	48.6 ± 14.4 (106)	50.0 ± 14.4 (101)	0.511
PAP diastolic (mmHg)	23.8 ± 7.5 (106)	26.7 ± 8.3 (102)	0.010[a]
RA pressure (mmHg)	12.4 ± 6.7 (92)	14.0 ± 7.4 (89)	0.131
PCWP (mmHg)	24.2 ± 7.5 (68)	25.3 ± 9.4 (69)	0.451
Cardiac index (l/minute/m^2)	2.2 ± 0.7 (96)	2.1 ± 0.7 (94)	0.497
Laboratory values			
BUN (mg/dl)	27.6 ± 14.3 (169)	31.9 ± 18.8 (167)	0.019[a]
Creatinine (mg/dl)	1.33 ± 0.5 (169)	1.67 ± 0.9 (169)	< 0.0001[a]
Total bilirubin (mg/dl)	1.57 ± 1.9 (155)	1.64 ± 1.7 (145)	0.756
Sodium (mg/l)	134.6 ± 5.0 (169)	134.0 ± 5.4 (169)	0.260
INR	1.39 ± 0.5 (165)	1.46 ± 0.5 (152)	0.251
White blood cell (K/sl)	9.4 ± 4.3 (169)	10.6 ± 5.3 (168)	0.018[a]
Platelets (K/sl)	212 ± 102 (169)	203 ± 96 (169)	0.412
AST (s/l)	91 ± 213 (155)	210 ± 648 (145)	0.035[a]
ALT (s/l)	126 ± 361 (154)	188 ± 539 (145)	0.249
Cholesterol (mg/dl)	123.7 ± 39.7 (81)	120.0 ± 38.9 (68)	0.566
Potassium (mEq/l)	4.1 ± 0.5 (169)	4.1 ± 0.6 (168)	0.336

Patient's baseline characteristics

Demographic parameter	HMII (*n* = 169)	Comparator (*n* = 169)	*p*-value
Haemoglobin (mg/dl)	11.3 ± 2.0 (168)	11.1 ± 2.0 (167)	0.277
Albumin (mg/dl)	3.4 ± 0.6 (148)	3.3 ± 0.7 (140)	0.212
BNP (pg/ml)	1182 ± 1074 (58)	1306 ± 1399 (72)	0.568
Concomitant therapies			
Prior mechanical circulatory support	10 (6)	6 (4)	0.443
IABP	15 (10)	56 (33)	0.116
Mechanical ventilation	16 (10)	27 (16)	0.102
ACE inhibitors	95 (56)	70 (41)	0.009
Beta-blockers	122 (72)	110 (65)	0.197
Intravenous inotropic agents	136 (80)	151 (89)	0.033
Two or more inotropic agents	58 (34)	86 (51)	0.003

a Fewer HMII patients were in profile 1 (acute cardiogenic shock) compared with the comparison group and more in profiles 3 (stable on inotropes) and 4 (symptomatic on oral medications).
Values are *n* (%) or mean ± SD (*n*).

Survival outcomes reported (by group and/or intervention)

Competing outcomes (HMII)

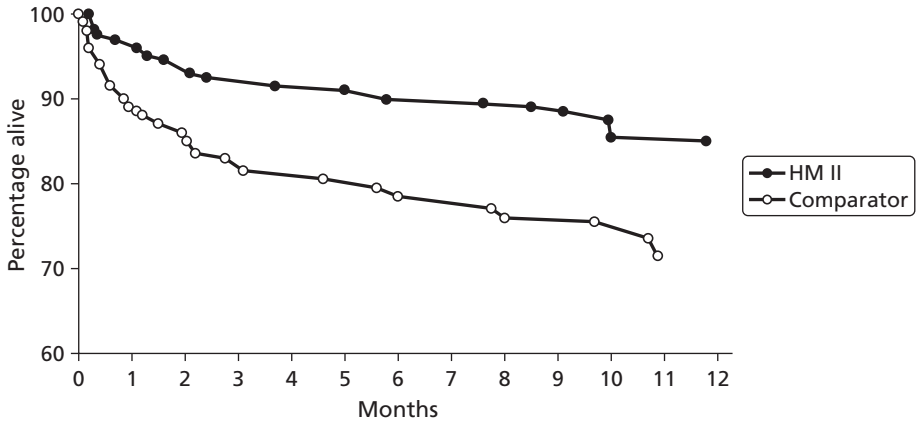
	Transplanted or recovered or ongoing VAD, *n*		Ongoing LVAD, *n*		Transplanted, *n*		Dead, *n*		Explanted/ recovery, *n*	
Months	HMII	Comparator	HMII	Comparator	HMII	Comparator	HMII	Comparator	HMII	Comparator
6	90	80	69	45	20	34	9	19	1/1	1/1
12	86	74	51	24	34	47	13	22	1/1	4/2

K–M survival for patients with INTERMACS profiles 1, 2–3 and 4–7

Group	Profile	6-month survival	12-month survival	*p*-value HMII vs. comparator	*p*-value between profiles
HMII	1	86.9% ± 5.5% (27)	86.9% ± 5.5% (22)	0.0153	0.8038
	2–3	90.0% ± 3.2% (66)	83.7% ± 4.2% (48)	0.0724	
	4–7	93.0% ± 4.8% (23)	83.8% ± 7.6% (17)	0.2814	
Comparator	1	70.9% ± 5.9% (24)	64.2% ± 7.0% (16)		0.3149
	2–3	84.7% ± 4.3% (41)	75.0% ± 6.6% (18)		
	4–7	83.1% ± 9.1% (12)	74.8% ± 11.4% (3)		

Survival outcomes reported (by group and/or intervention)

K–M plot data read from graph



Number at risk				
	169	161	119	86
	169	145	77	40
		96%	90%	85%
		89%	79%	70%

Temporal comparison of BTT outcomes with HMII LVAD

Study	Enrolment period	*n*	30-day operative mortality	Transplantation recovery or ongoing VAD	K–M survival at 1 year
HMII pivotal trial Miller *et al.*[70]	March 2005 to May 2006	133	0.11	0.79	0.68
HMII pivotal trial Pagani *et al.*[71]	March 2005 to March 2007	281	0.08	0.84	0.74
Post-approval INTERMACS registry study (current study)	April 2008 to August 2008	169	0.04	0.91	0.85

Other specified/relevant outcomes reported (by group and/or intervention)

6-minute walk test: insufficient participants completed test
Support duration: HMII mean 306 ± 173 days, median 186 days; comparator mean 207 ± 188 days, median 152 days
Cumulative follow-up duration of support: HMII 142 patient-years and comparator 96.2 patient-years

Adverse events reported (by group and/or intervention)

Event	HMII (*n* = 169) cumulative 142.0 patient-years; mean duration 306 ± 173 days				Comparator (*n* = 169) cumulative 96.2 patient-years; mean duration 207 ± 188 days						
	n	% patients	Events (*n*)	Events/ patient-year	*n*	% patients	Events (*n*)	Events/ patient-year	RR	95% CI	*p*-value
Bleeding	75	44.4	204	1.44	65	38.5	172	1.79	0.80	0.58 to 1.12	0.1931
Infection[a]	78	46.2	142	1.00	72	42.6	204	2.12	0.47	0.34 to 0.66	< 0.0001[b]
Driveline	30	17.8	45	0.32	27	16.0	44	0.46	0.69	0.42 to 1.13	0.1419
Pump pocket	3	1.8	4	0.03	12	7.1	16	0.17	0.17	0.06 to 0.52	0.0006[b]
Pump interior	1	0.6	2	0.01	0	0.0	0	0.00			0.2466
Blood	32	18.9	47	0.33	36	21.3	71	0.74	0.45	0.29 to 0.70	0.0004[b]
Line sepsis	3	1.8	3	0.02	9	5.3	10	0.10	0.20	0.05 to 0.76	0.0096[b]
Other infection[a]	49	29.0	86	0.61	50	29.6	119	1.24	0.49	0.34 to 0.72	0.0002[b]
Stroke	11	6.5	11	0.08	9	5.3	11	0.11	0.68	0.28 to 1.63	0.3821
Haemorrhagic	2	1.2	2	0.01	2	1.2	2	0.02	0.68	0.09 to 4.89	0.6986
Embolic	8	4.7	8	0.06	6	3.6	7	0.07	0.77	0.27 to 2.21	0.6323
Unknown	1	0.6	1	0.01	2	1.2	2	0.02	0.34	0.03 to 3.79	0.3584
Other neurological dysfunction	7	4.1	7	0.05	13	7.7	16	0.17	0.30	0.12 to 0.75	0.0071[b]
Myocardial infarction	3	1.8	3	0.02	1	0.6	1	0.01	2.03	0.21 to 19.8	0.5342
Pericardial drainage	17	10.1	20	0.14	20	11.8	22	0.23	0.62	0.32 to 1.19	0.1477
Psychiatric episode	14	8.3	17	0.12	17	10.1	23	0.24	0.50	0.25 to 0.99	0.0435[b]
Renal dysfunction	17	10.1	19	0.13	21	12.4	28	0.29	0.46	0.24 to 0.87	0.0156[b]
Hepatic dysfunction	11	6.5	12	0.08	9	5.3	11	0.11	0.74	0.31 to 1.74	0.4899
Respiratory failure	34	20.1	41	0.29	43	25.4	53	0.55	0.52	0.32 to 0.85	0.0084[b]
Right HF[c]	25	14.8	26	0.18	20	11.8	22	0.23	0.80	0.43 to 1.49	0.4859
Haemolysis	5	3.0	5	0.04	2	1.2	2	0.02	1.69	0.32 to 8.91	0.5300

Adverse events reported (by group and/or intervention)

Event	HMII ($n = 169$) cumulative 142.0 patient-years; mean duration 306 ± 173 days				Comparator ($n = 169$) cumulative 96.2 patient-years; mean duration 207 ± 188 days						
	n	% patients	Events (*n*)	Events/ patient-year	*n*	% patients	Events (*n*)	Events/ patient-year	RR	95% CI	*p*-value
Hypertension	3	1.8	4	0.03	26	15.4	35	0.36	0.08	0.03 to 0.23	< 0.0001[b]
Cardiac arrhythmia	46	27.2	69	0.49	47	27.8	85	0.88	0.55	0.37 to 0.83	0.0041[b]
Arterial non-CNS thromboembolism	1	0.6	1	0.01	2	1.2	3	0.03	0.23	0.02 to 2.20	0.1637
Venous thromboembolism	11	6.5	13	0.09	13	7.7	15	0.16	0.59	0.27 to 1.29	0.1820
Wound dehiscence	3	1.8	3	0.02	3	1.8	3	0.03	0.68	0.13 to 3.43	0.6368
Device replacement	2	1.2	2	0.01	13	7.7	13	0.14	0.10	0.02 to 0.47	0.0005

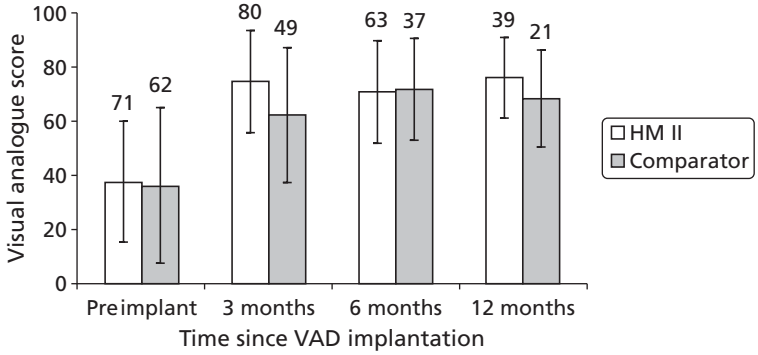
a Other infections include pneumonia, urinary tract, mediastinum, peripheral wound and unknown.
b Statistically significant.
c Including 5 (3.0%) HMII patients and 21 (12%) comparator patients requiring RVAD support.

Cause of death reported (by group and/or intervention)

Not reported

QoL reported (by group and/or intervention)

Improvements in EQ 5D are mentioned but the text is difficult to interpret. The EQ-5D QoL VAS results are shown below (data read from histograms)



Author's conclusion

The results in a post-market approval, actual patient care setting BTT population support the original findings from the pivotal clinical trial regarding the efficacy and risk profile of the HMII LVAD. These data suggest that dissemination of this technology after approval has been associated with continued excellent results

Reviewer's conclusion

Post-HMII implant survival to 1 year was reported. The comparison with other LVADs is likely to be underpowered and caution is needed when interpreting the findings as the patients in each group were not randomised from a common pool

ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; CNS, central nervous system; INR, international normalised ratio; PAP, pulmonary artery pressure; RA, right atrial; RR, relative risk ratio of adverse event rates between HMII vs. the comparator.

Strueber 2011[83]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Strueber
Year of publication: 2011
Country: Australia and Europe
Study design: Prospective single-arm trial with 'virtual' comparison group
Study setting: Multicentre
Number of centres: Five (three Europe, two Australia)
Duration of study: Enrolment March 2006 to December 2008, follow-up (adverse events) June 2009
Follow-up period: Minimum 24 months
Funding: Unclear

Aim of the study

Clinical evaluation of the HW LVAD

Participants

Total number of participants: 50
Sample attrition/dropout: None
Inclusion criteria: All NYHA class IV. All receiving inotropic treatment. See also online appendix[83]
Exclusion criteria: See online appendix
Characteristics of participants:
Mean age: 48.5 years (20–75 years)
Sex: 86% male
Race: Not reported
Diagnosis: Idiopathic CMP $n = 22$ (44%); ischaemic CMP $n = 20$ (40%); familial or congenital CMP $n = 5$ (10%); myocarditis $n = 3$ (6%)

Intervention

Indication for treatment: BTT only. Patients with end-stage HF eligible for cardiac transplantation
Type of device used: HW (CF)
Any comparison: Virtual comparator group based on the SHFM
Percentage of patients using inotropes: 100%
Duration of treatment: Indefinite, until death
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HW

Outcomes

Primary outcomes: Success rates were composite of survival to transplant, cardiac recovery with device explant, or continuing device support at 180 days
Secondary outcomes: Proportion HT; proportion on LVAD; device failures; adverse events; pump flow index
Method of assessing outcomes: Prospective data collection
Survival: Yes
Adverse event: Yes
HRQoL: Yes
Length of follow-up: To death or VAD removal, or end of trial

Number of participants	Intervention	Comparator, if present
Screened	Online appendix?	Not reported/not applicable
Randomised/included	50	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics

Parameter	Value
Age (years)	48.5 (20–75)
Sex, male	43 (86)
BSA (m^2)	1.9 (1.4–2.6)
BMI (kg/m^2)	25.6 (16.5–40.8)
HF aetiology	
Idiopathic CMP	22 (44)
Ischaemic CMP	20 (40)
Familial or congenital CMP	5 (10)
Myocarditis	3 (6)
INTERMACS profile	
2	11 (22)
3	35 (70)
4	4 (8)
Inotropic support	50 (100)
IABP	4 (8)
LVEF (%)	18.7 ± 5.9
LVEDD (mm)	68.6 ± 8.0
Cardiac index ($l/minute/m^2$)	1.94 ± 0.54
PCWP (mmHg)	23.7 ± 6.5
CVP (mmHg)	12.3 ± 5.9
Heart rate (b.p.m.)	89.1 ± 20.2
Arterial BP (mmHg)	
Systolic	101.5 ± 13.9
Diastolic	64.2 ± 10.9
Mean	76.7 ± 10.6
Pulmonary artery pressure (mmHg)	
Systolic	47.6 ± 15.7
Diastolic	27.7 ± 9.3
Laboratory values	
BUN (mg/dl)	28.9 ± 15.6
Creatinine (mg/dl)	1.3 ± 0.5
ALT (IU/l)	63.5 ± 127
AST (IU/l)	75.8 ± 132
LDH (IU/l)	316 ± 159
Total bilirubin (mg/dl)	1.5 ± 1.0
Hgb (g/dl)	12.5 ± 2.0
HCT (%)	36.8 ± 6.0

Patient's baseline characteristics

Parameter	Value
PFH (mg/dl)	10.1 ± 13.8
Platelets (× 10^9/l)	243 ± 101
INR	1.6 ± 0.6
APTT (s)	39.7 ± 10.6

Pre-operative risk factors (n = 50)

Parameter	*n*
Inotropic support	50
Previous myocardial infarction	10
Coronary angioplasty	13
Previous sternotomy	6
Arrhythmias	25
ICD	32
Pacemaker	9
Moderate–severe right ventricular dysfunction	19
Hypertension	15
Diabetes mellitus	7

Survival outcomes reported (by group and/or intervention)

Parameter	HW	Virtual MM (estimated with SHFM)
Actuarial overall survival, %		
6 months	90	73
12 months	84	58
18 months	82	48
24 months	82	40
Proportion received HT by 24 months, %	40; median time to HT = 94 days (range 13 –515 days)	
Proportion alive on VAD at 24 months, %	34 (32 in text)	
Proportion explanted by 24 months, %	8	
Success rate (heart transplanted, recovered, or on LVAD alive at end of follow-up), %		
6 months	90	
12 months	85	
18 months	Not reported	
24 months	79	

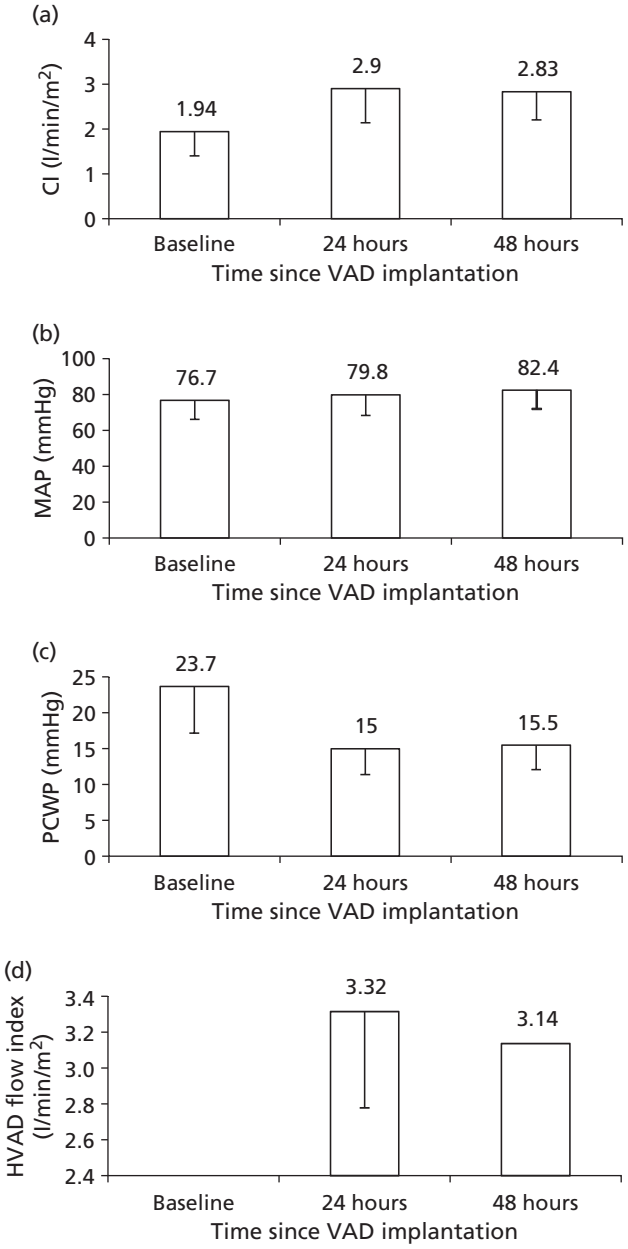
Other specified/relevant outcomes reported (by group and/or intervention)

Median duration of VAD support was 322 days, mean 348 days
The mean hospital stay was 45 days; of this time, 13.1 ± 9.3 days were in the ICU, 16.4 ± 12.6 days in step-down unit, and 15.4 ± 10.2 days in a regular floor unit

Other specified/relevant outcomes reported (by group and/or intervention)

Haemodynamic changes 24 and 48 hours after VAD implant

Parameter	Baseline	24 hours	*p*-value 24 hours vs. baseline	48 hours	*p*-value 48 hours vs. baseline
Cardiac index (l/minute/m^2)	1.94 ± 0.54	2.9 ± 0.76	0.0001	2.83 ± 0.63	0.0001
MAP (mmHg)	76.7 ± 10.6	79.8 ± 11.6	Not significant	82.4 ± 10.5	0.01
PCWP (mmHg)	23.7 ± 6.5	15 ± 3.6	0.001	15.5 ± 3.4	0.0001
HVAD flow index (l/minute/m^2)	Not applicable	3.32 ± 0.6	0.0001	3.14 ± 0.54	0.0001



Adverse events reported (by group and/or intervention)

Adverse event	Overall (support duration 47.8 patient-years)			0–30 days (support duration 4.0 patient-years)			> 30 days (support duration 43.8 patient-years)		
	Patients with event, *n* (%)	Number of events	Event rate	Patients with event, *n*	Number of events	Event rate	Patients with event, *n*	Number of events	Event rate
Infection									
Localised non-device related	7 (14)	7	0.15	2	2	0.50	5	5	0.11
Sepsis	5 (10)	5	0.10	1	1	0.25	4	4	0.09
Driveline exit site	9 (18)	10	0.20	0	0	0.00	9	10	0.21
Bleeding									
Surgery	10 (20)	11	0.23	8	8	2.00	3	3	0.07
Transfusion ≥ 2 units	2 (4)	2	0.04	1	1	0.25	1	1	0.02
Hospital stay	3 (6)	3	0.06	1	1	0.25	2	2	0.05
Ventricular arrhythmias	2 (4)	2	0.04	1	1	0.25	1	1	0.02
Neurological dysfunction									
Ischaemic stroke	2 (4)	2	0.04	2	2	0.50	0	0	0.00
Haemorrhagic stroke	4 (8)	4	0.08	0	0	0.00	4	4	0.09
TIA	2 (4)	3	0.06	0	0	0.00	2	3	0.07
Pulmonary dysfunction	8 (16)	9	0.19	7	8	2.00	1	1	0.02
Device replacement	7 (14)	7	0.15	4	4	1.00	3	3	0.07
Manufacturing defect	2 (4)	2	0.04	2	2	0.50	0	0	0.00
Left heart embolus	4 (8)	4	0.08	1	1	0.25	3	3	0.07
Inflow occlusion	1 (2)	1	0.02	1	1	0.25	0	0	0.00
Pleural effusion	6 (12)	7	0.15	5	5	1.25	1	2	0.05

Adverse events reported (by group and/or intervention)

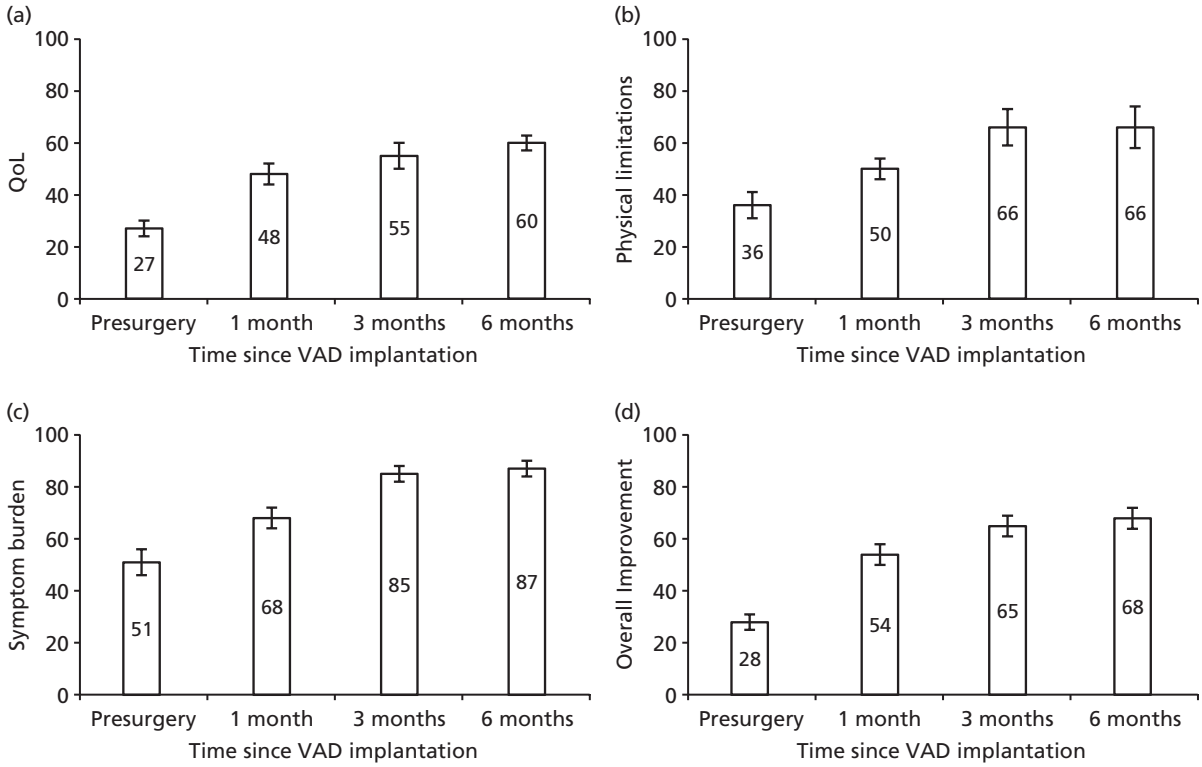
Adverse event	Overall (support duration 47.8 patient-years)			0–30 days (support duration 4.0 patient-years)			> 30 days (support duration 43.8 patient-years)		
	Patients with event, *n* (%)	Number of events	Event rate	Patients with event, *n*	Number of events	Event rate	Patients with event, *n*	Number of events	Event rate
Right HF									
RVAD	3 (6)	3	0.06	2	2	0.50	1	1	0.02
Intravenous inotropes	3 (6)	3	0.06	1	1	0.25	2	2	0.05
Renal dysfunction	5 (10)	5	0.10	5	5	1.25	0	0	0.00
Hepatic dysfunction	3 (6)	3	0.06	1	1	0.25	2	2	0.05
Haemolysis	1 (2)	1	0.02	1	1	0.25	0	0	0.00
HF	3 (6)	3	0.06	1	1	0.25	2	2	0.05
Chest pain	1 (2)	1	0.02	0	0	0.00	1	1	0.02
Femoral embolism	2 (4)	2	0.04	1	1	0.25	1	1	0.02

Cause of death reported (by group and/or intervention)

Sepsis $n = 3$, multiorgan failure $n = 3$ and haemorrhagic stroke $n = 3$

QoL reported (by group and/or intervention)

KCCQ $n = 38$, $n = 37$, $n = 36$, $n = 21$ at presurgery, 1, 3 and 6 months, respectively
Data read from histograms



Author's conclusion

The HVAD system provided safe and effective circulatory support in a population of end-stage HF patients. During HVAD system support, haemodynamic status, QoL and neurocognitive function improved for the majority of patients. In this first clinical study with a miniaturised LVAD placed in the pericardial space, the 2-year survival rate was similar to that of HT, which suggests that this long-term therapy is promising for the HF population

Reviewer's conclusion

The authors' conclusions are reasonably supported by the data presented. Mortality was depicted as 18% by 2 years (figure 2) and it was stated that 9 of 50 patients died during LVAD support, with 40% having received a transplant by 2 years, this implies there was no mortality associated with HT which is difficult to understand

APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; CMP, cardiomyopathy; HCT, haematocrit; Hgb, haemoglobin; HVAD, HeartWare Ventricular Assist Device; ICD, implantable cardioverter-defibrillator; INR, international normalised ratio; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PFH, plasma-free haemoglobin; TIA, transient ischaemic attack.

Strueber 2008[78]

Name of the reviewer: Paul Sutcliffe (agreed with Martin Connock)

Study details

First author surname: Strueber
Year of publication: 2008
Country: European countries (not UK)
Study design: Retrospective survey of medical records
Study setting: Multicentres
Number of centres: 12 in 7 European countries
Duration of study: March 2004 until January 2007
Follow-up period: 166 ± 175 days
Funding: Not reported

Aim of the study

To gain an overview of the use and performance of the HMII device in Europe

Participants

Total number of participants: 101
Sample attrition/dropout: Not reported
Inclusion criteria: First 101 consecutive HMII recipients in Europe
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): 48 ± 13 years; BTT 44.4 ± 13 years, DT 52.5 ± 14 years
Median age: Not reported
Age range: 14–72 years
Sex: Not reported
Race: Not reported
Diagnosis: HF. Most patients had ischaemic ($n = 61$) and dilative ($n = 30$) cardiomyopathy, 10 patients had other severe HF (e.g. myocarditis, postpartum cardiomyopathy and post-cardiotomy failure)

Intervention

Indication for treatment: BTT + DT (split for survival only)
Type of device used: HMII
Any comparison: DT vs. BTT – no other devices were compared
Duration of treatment: Days on device ranged from 1 to 972 days with a mean follow-up of 166 ± 175 days (total of 16,227 patient days)
Percentage of patients using inotropes: Continuous in 75%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Survival and adverse events
Secondary outcomes: Not reported
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Mean follow-up of 166 ± 175 days

Number of participants	Intervention	Comparator, if present
Screened	Not reported/not applicable	Not reported/not applicable
Randomised/included	101 consecutive cases	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics

No baseline characteristics table was provided. The following information was extracted from the text

Additional baseline characteristics

Characteristics	*n* or %
Cardiomyopathy	
Ischaemic	61
Dilative	30
Other	10
NYHA class	
IV	89%
IIIb	6%
IIIa	3%
Continuous inotrope	75%

Survival outcomes reported (by group and/or intervention)

Overall survival was 67% at 6 months follow-up ($n = 68$)
During follow-up 17 patients were transplanted, two recovered and the device was successfully removed
Hospitalisation status on 69 living patients (1 January 2007): 9 still hospitalised, 60 discharged, and 53 ongoing with device
Thirty patients of entire cohort expired: 29 on device and 1 after a HT
Mortality was highest in perioperative period: 17 patients expired in first month post implantation and 23 in first 3 months
Two deaths after 6 months on device caused by intracerebral bleeding and to an unknown cause (patient was found with a disconnected driveline cable). Three cases of this group had a successful HT. Remaining 28 patients were ongoing with the device. Intention to treat was DT in 33% and BTT in 67% in this subgroup
When survival was stratified by intention to treat, a remarkable difference in the initial post-operative mortality was found: in the DT group survival was 93% in the BTT group 80%; however, after 4 months following implant comparable survival was seen in both groups

Other specified/relevant outcomes reported (by group and/or intervention)

In 33 patients a follow-up of > 180 days (198–972 days; mean 350 ± 180 days) was completed. In this subgroup the diagnoses leading to HF were ischaemic cardiomyopathy (55%), dilative cardiomyopathy (33%) and other (12%), including a case with a failing HMI LVAD
Of 17, 16 HT procedures were successful in entire patient cohort
Main support time on device was 4.6 ± 3 months prior transplant (range 0–12 months)
Two patients had device removed after myocardial recovery after 3 and 6 months
Infections
Isolated driveline infections were present in 21 patients (incidence 0.37/patient year)
Recurrent driveline infections were found in six patients. Four of these patients were transplanted 30, 53, 78 and 135 days after onset of infection
There was no mortality caused by isolated driveline infection
Pocket infections were reported for three cases. One patient was transplanted, in another patient, the device was successfully removed after myocardial recovery, and a third patient was ongoing with an omental wrap and antibiotic therapy

Adverse events reported (by group and/or intervention)

Adverse event	Early post operation (≤ 90 days)	Mid-term (≤ 6 months)	Long term (> 6 months)	Missing data	Total	Adverse event, %
Bleeding	51			2	53	21.1
Cardiac arrhythmias	41	1	2	4	48	19.1
Sepsis	21	5		2	28	11.2
Site infection	6	8	12	1	27	10.8
Local infection	11	5	3		19	7.6
Renal failure	17	1			18	7.2
Pneumonia	10	1	1		12	4.8
Hepatic dysfunction	10			1	11	4.4
Right HF	10				10	4
Haemolysis	2	2	2		6	2.4
Neurological CVA ischaemic	4				4	1.6
Neurological other	3			1	4	1.6
Neurological CVA haematological	2		1		3	1.2
Pocket infection		3			3	1.2
Device thrombosis				1	1	0.4
Neurological metabolic	1				1	0.4
Neurological seizures	1				1	0.4
Neurological TIA	1				1	0.4
Thromboembolic event	1				1	0.4
Total	192	26	21	12	251	100

Cause of death reported (by group and/or intervention)

Cause of death	*n*
Multiorgan failure	13
Right HF	5
CVAs	5 (3 haemorrhagic, 2 ischaemic)
Respiratory failure	3
Driveline disconnection	2
Bleeding after ventricular rupture	1
Suffocation after epistaxis (nose bleed)	1

QoL reported (by group and/or intervention)
Not reported
Author's conclusion
Early experience with HMII in Europe was favourable and beyond expectations derived from earlier experiences with pulsatile devices. The absence of adverse events beyond the perioperative period, the rare event of a readmission and the mechanical stability of LVAD seem to indicate the suitability for chronic support. High rates of bleeding events at time of implantation and low rates of both thrombus formation and ischaemic strokes warrant the development of new, safe and less aggressive anticoagulation protocols
Reviewer's conclusion
Limited information provided on baseline characteristics of included patients

TIA, transient ischaemic attack.

Topilsky 2011a[79]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Topilsky
Year of publication: 2011
Country: USA
Study design: Retrospective observational; analysis of prospectively collected data
Study setting: Hospital
Number of centres: One (Mayo Clinic, Rochester, MN, USA)
Duration of study: February 2007 to May 2010
Follow-up period: Median 166 days (range 1–1044 days)
Funding: Not reported

Aim of the study

To analyse the outcome of LVAD therapy (HMII) in patients with end-stage HF caused by RCM or HCM. These were compared with HMII recipients with D or I

Participants

Total number of participants: 75 I/D; 8 RCM/HCM
Sample attrition/dropout: Not reported (probably 0)
Inclusion criteria: All consecutive HMII recipients at clinic
Exclusion criteria: Not reported
Characteristics of participants:
Mean: 65 years (range 55–70 years). 63 years RCM/HCM; 67 years I/D
Median age: Unclear
Sex: 80.7% male; 75% male RCM/HCM; 82% male I/D
Race: Not reported
Diagnosis: NYHA IV and IIIb HF (see above)

Intervention

Indication for treatment: RCM/HCM: 6/8 BTT; I/D: 21/75 BTT; others DT
Type of device used: HMII
Any comparison: RCM/HCM vs. I/D. (Also VAD RCM/HCM vs. MM RCM/HCM)
Duration of treatment: Various
Percentage of patients using inotropes: RCM/HCM 5/8; I/D 56/75
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Operative mortality (within 30 days of implant); need for RVAD or inotropes beyond 168 days; hospital days from operation to discharge; total mortality over follow-up
Secondary outcomes: Not distinguished from primary
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Median 166 days (range 1–1044 days)

Number of participants	Intervention	Comparator, if present
Screened	Not reported/not applicable	Not reported/not applicable
Randomised/included	Not reported/not applicable	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics

Characteristic	RM or HM ($n = 8$)	BTT only ($n = 6$)	D or I ($n = 75$)	BTT only ($n = 21$)	p-value	p-value (BTT)
Age (range)	63 (44.5–68)	54 (43.5–66.7)	67 (59–73)	55 (45.5–61.5)	0.18	0.77
Sex, *n* (%)	Male 6 (75); female 2 (25)	Male 5 (83); female 1 (17)	Male 61 (82); female 14 (18)	Male 17 (81); female 4 (19)	0.63	1.0
NYHA class, *n* (%)	IIIb 3 (38); IV 5 (62)	IIIb 3 (50); IV 3 (50)	IIIb 26 (35); IV 49 (65)	IIIb 8 (40); IV 13 (60)	0.42	0.62
Prior sternotomy, *n* (%)	2 (25)	1 (16)	40 (53)	3 (14)	0.15	1.0
Pre-operative IABP, *n* (%)	3 (37)	3 (50)	24 (32)	6 (28)	1.0	0.36
Pre-operative inotrope use, *n* (%)	5 (62)	4 (66)	56 (74)	16 (76)	0.92	0.60
DT, *n* (%)	2 (25)	N/A	51 (68)	N/A	0.01	
Heart rate, b.p.m. (range)	75 (70.5–84.5)	75 (71.5–82.5)	73.5 (68–86)	73.5 (66.2–85.5)	0.97	0.62
Systolic BP, mmHg (range)	100 (87–128)	121 (79–134)	98 (90–108)	97.5 (90–109.5)	0.52	0.30
Diastolic BP, mmHg (range)	72 (59–77)	76 (58.5–88.5)	62 (58–69.2)	67 (60.5–75)	0.08	0.54
Haemoglobin	12.1 ± 1	12.1 ± 1	11.8 ± 2	12.1 ± 2	0.69	0.91
Bilirubin (range)	1.6 (0.62–2.4)	2.0 (0.7–2.8)	1.0 (0.7–1.52)	0.95 (0.6–1.6)	0.25	0.077
BUN (range)	25.5 (13.2–40.5)	25.5 (15.7–45.5)	26 (20–39)	21 (12.5–26)	0.58	0.23
Creatinine (range)	1.4 (0.97–2.0)	1.4 (1.1–2.2)	1.3 (1.0–1.7)	1.1 (0.9–1.4)	0.81	0.12
NT-pro-BNP (range)	2178 (1243–8813)	1639 (653–7167)	4058 (2251–7482)	4673 (1352–10,839)	0.33	0.44
LM score (range)	12 (5–19.5)	13 (3.5–20.2)	9 (4–13)	11 (4–13)	0.29	0.36
Platelets $< 148 \times 10^3$/ l, *n* (%)	5 (62)	3 (50)	31 (41)	8 (38)	0.29	1.0
Albumin < 3.3 g/dl, *n* (%)	3 (37)	3 (50)	18 (24)	6 (28)	0.42	0.36
INR > 1.1, *n* (%)	7 (87)	5 (83)	55 (73)	17 (81)	0.67	1.0
Vasodilator therapy at implantation, *n* (%)	2 (25)	2 (33)	17 (23)	4 (19)	0.97	0.60
Mean PA pressure < 25.3 mmHg, *n* (%)	1 (12)	1 (17)	6 (8)	3 (14)	0.53	1.0
AST > 45 U/dl, *n* (%)	3 (37)	3 (50)	20 (27)	3 (14)	0.68	0.12
Haematocrit < 34, *n* (%)	3 (37)	2 (33)	34 (45)	7 (33)	0.72	1.0
BUN > 51 U/dl, *n* (%)	0	0	8 (11)	0	0.90	1.0
Left ventricular diastolic diameter (mm)	52.5 ± 6	52.6 ± 7	68.6 ± 8	68.8 ± 9	< 0.0001	0.0004
Left ventricular systolic diameter (mm)	43.1 ± 8	43.3 ± 8	61.8 ± 9	63.6 ± 9	0.0008	0.001
Septal thickness, mm (range)	16 (12–19)	16.5 (14.5–20)	10 (8.5–11)	9.5 (7.7–11)	0.0003	0.0021

Patient's baseline characteristics

Characteristic	RM or HM ($n = 8$)	BTT only ($n = 6$)	D or I ($n = 75$)	BTT only ($n = 21$)	p-value	p-value (BTT)
Posterior wall thickness, mm (range)	11 (9.7–13.7)	12 (9.5–15.2)	10 (8.0–11)	10 (9–12)	0.0868	0.23
Ejection fraction, % (range)	21 (20–36)	20.5 (19.7–42.5)	17 (15–22)	17 (15–20)	0.0087	0.013
E/e′ ratio[a] (range)	35 (21.6–55)	23.3 (20–35)	23.3 (19–33.3)	20.0 (16–33.3)	0.10	0.63
Deceleration time[b] (range)	119 (117–158.5)	119 (116–144)	135 (112–153.5)	122.5 (110–144)	0.96	0.84
Tricuspid valve lateral annulus velocity, m/s (range)	0.07 (0.06–0.08)	0.06 (0.06–0.06)	0.08 (0.06–0.1)	0.08 (0.07–0.12)	0.55	0.074
Severe RV dysfunction, n (%)	5 (62)	4 (66)	50 (67)	13 (62)	0.62	1.0
Severe mitral regurgitation, n (%)	1 (12)	0 (0)	23 (31)	1 (6)	0.22	0.1
Severe tricuspid regurgitation, n (%)	3 (37)	3 (50)	27 (36)	7 (33)	0.92	1.0
Mean RA pressure, mmHg (range)	17.5 (12–20)	15.5 (10.2–22)	14.5 (10–19.7)	13 (9.5–18.5)	0.51	0.64
Mean PA pressure (mmHg)	33.3 ± 9.8	32.6 ± 11.4	36.3 ± 9.2	35.2 ± 11.0	0.43	0.77
PVR, Wood units (range)	3.1 (1.1–5.2)	2.66 (1.4–4.0)	3.5 (2.2–5.4)	3.5 (2.1–4.2)	0.60	0.32
RV, dP/dt (range)	432 (360–720)	552 (360–744)	432 (336–576)	480 (336–732)	0.71	0.86
RVSWI (mmHg ml/m^2)	3.9 ± 3.0	3.9 ± 3.5	5.4 ± 2.9	5.3 ± 3.3	0.23	0.46
Mean wedge pressure (mmHg)	24.1 ± 4.0	24.8 ± 3.2	23.4 ± 7.1	24.0 ± 7.9	0.78	0.81
Cardiac output (l/minute)	3.2 ± 0.8	3.5 ± 0.8	3.9 ± 1.2	4.3 ± 1.1	0.07	0.22
Cardiac index (l/minute/m^2)	1.6 ± 0.3	1.7 ± 0.4	2.0 ± 0.5	2.0 ± 0.5	0.08	0.36

a E/e′ indicates ratio of E velocity of mitral inflow to early diastolic relaxation tissue velocity of medial annulus.
b Deceleration time of early mitral inflow.

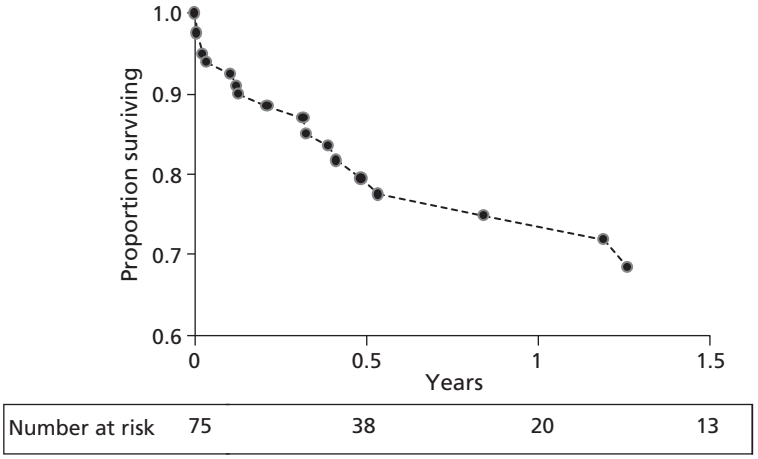
Patient's baseline characteristics

To assess the possibility of a selection bias, data were reanalysed in the BTT patients only by excluding all the DT patients in both groups (see above). There were no significant differences between the groups

Survival outcomes reported (by group and/or intervention)

Method	RCM/HCM	D/I
Actuarial survival	BTT only 1 year: 75% (95% CI 23% to 96.5%)	BTT only 1 year: 85.7% (95% CI 41.0% to 98.5%); $p = 0.16$
Overall survival	Groups combined 18/83 died. 1 year: 77.4% (± 5.5) 2 years: 62.6% (± 9.2)	
K–M estimates	Figure 2 of paper: BTT and DT patients combined	Figure 2 of paper: BTT and DT patients combined

K–M for D/I group ($n = 75$; both BTT and DT patients) data read from graph



Other specified/relevant outcomes reported (by group and/or intervention)

NYHA class > III
100% > class III at baseline
12% > class III at 3 months

Other specified/relevant outcomes reported (by group and/or intervention)				
Clinical post-operative (30 days) outcomes				
Outcome	**All patients (*n* = 83)**	**RCM or HCM (*n* = 8)**	**I or D (*n* = 75)**	***p*-value**
Operative mortality, *n* (%)	8 (10)	1 (12)	7 (9)	0.57
Cardiopulmonary bypass time, minutes (range)	96.5 (80.2–121.5)	89 (83–120)	99 (78–123)	0.56
Post-operative red blood cell transfusion, units (range)	8 (5–13)	7 (3.5–14.5)	8 (5–13)	0.94
Need for RVAD, *n* (%)	3 (4)	1 (12)	2 (2)	0.26
Infection, *n* (%)	41 (49)	7 (88)	34 (45)	0.03
Bleeding, *n* (%)[a]	56 (68)	3 (37)	53 (71)	0.10
Prolonged intubation, (%)[b]	19 (23)	3 (37)	16 (21)	0.37
Arrhythmia, *n* (%)[c]	16 (19)	2 (25)	14 (19)	0.65
Acute renal failure, *n* (%)[d]	13 (16)	3 (37)	10 (13)	0.11
Acute cerebral event, *n* (%)[e]	10 (12)	1 (12)	9 (12)	1.0
Hepatic dysfunction, *n* (%)[f]	15 (18)	3 (37)	12 (16)	0.15
Thromboembolic event, *n* (%)[g]	9 (11)	1 (12)	8 (11)	1.0
Dialysis, *n* (%)	8 (10)	2 (25)	6 (8)	0.19
Mean RA pressure, mmHg (range)[h]	12 (9–17)	18 (15–20)	12 (9–15)	0.03
Mean PA pressure, mmHg (range)[h]	26 (23–30)	24 (23–28)	26 (23–30.7)	0.42
Cardiac output, U/minute (range)[h]	5.5 (4.8–6)	4.5 (4.4–5.6)	5.5 (4.9–6.2)	0.07

Other specified/relevant outcomes reported (by group and/or intervention)

Outcome	All patients ($n = 83$)	RCM or HCM ($n = 8$)	I or D ($n = 75$)	p-value
[b]Cardiac index, U/minute/m^2 (range)	2.7 (2.4–3.1)	2.4 (2.1–2.9)	2.8 (2.4–3.2)	0.08
Pump, RPM (range)	9400 (9200–9600)	9300 (9150–9450)	9400 (9200, 9600)	0.45
Pump flow, l/minute (range)	5.2 (4.5–5.5)	4.3 (3.8–4.5)	5.2 (4.7–5.5)	0.0011
LOS, days (range)	17.5 (11–27.5)	11 (8–45)	18.5 (12.2–27.7)	0.48
Duration of inotropic support, hours (range)	114 (66.5–166.5)	157 (98.2–954)	111.5 (66–160)	0.078
RV failure, n (%)	20 (24)	4 (50)	16 (21)	0.16
LOS > 30 days, n (%)	14 (17)	2 (25)	12 (16)	0.61
Death or RV failure, n (%)	20 (24)	4 (50)	16 (21)	0.21

a Bleeding requiring blood transfusion more than 24 hours after surgery.
b Mechanical ventilation for more than 1 week or need for tracheostomy.
c Haemodynamically significant arrhythmia or requiring cardioversion.
d Renal failure requiring dialysis, increase in creatinine to > 2 or by > 50% from baseline.
e Any stroke, brain haemorrhage, or hyperperfusion injury.
f Liver enzymes > 300 or bilirubin > 5.0 after surgery.
g Any embolic event after surgery.
h The haemodynamic data represent the last measurement before taking out the pulmonary artery catheter; pump flow and RPM.

Adverse events reported (by group and/or intervention)

Not reported

Cause of death reported (by group and/or intervention)

CMH/HMH: 1/8 perioperative (in 30 days)
I/D: 7/75 perioperative (in 30 days)
Both groups combined (post 30 days): multiorgan failure $n = 2$, intractable right HF $n = 2$, hyperperfusion brain injury $n = 2$, sepsis $n = 1$, uncontrollable bleeding $n = 1$

QoL reported (by group and/or intervention)

See above for NYHA class change

Author's conclusion

CF axial LVAD therapy may be feasible in patients with end-stage RCM or HCM and may prove to become a useful option to treat these patients who have end-stage HF. However, the present preliminary report lacks the statistical power to make conclusions regarding survival and prospective clinical trials will be required to assess whether LVAD therapy should be used routinely in this challenging group of patients

Reviewer's conclusion

Because results for BTT and DT patients in each group were mostly combined within RCM/HCM and I/D groups it is difficult to extract useful data. Most patients received DT rather than BTT. The hospital stays associated with LVAD implantation were relatively short. Please note that it is not possible to split BTT + DT except for actuarial survival; authors state 'the percentage of patients considered DT was significantly higher in the DCM/ICM group as compared with the RCM/HCM group'. To assess the possibility of a selection bias data were reanalysed in the BTT patients only by excluding all the DT patients in both groups (see above). There were no significant differences between the two analyses

AST, aspartate aminotransferase; b.p.m., beats per minute; BUN, blood urea nitrogen; D, dilated myocardiopathy; HCM, hypertrophic cardiomyopathy; I, ischaemic myocardiopathy; INR, international normalised ratio; LM, Lietz-Miller; LOS, length of stay from surgery to discharge; PA, pulmonary artery; PVR, pulmonary vascular resistance; RA, right atrial; RCM, restrictive cardiomyopathy; RPM, revolutions per minute; RVSWI, right ventricular stroke work index.

Topilsky 2011b[80]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Topilsky
Year of publication: 2011
Country: USA
Study design: Retrospective observational
Study setting: Hospital
Number of centres: One
Duration of study: February 2007 to August 2010
Follow-up period: Mean 321 days (range 106–602 days)
Funding: Not reported

Aim of the study

To determine if echocardiographic variables 1 month after surgery suggesting appropriate degree of LV unloading and an adequate forward flow are associated with ('important in determining') clinical outcomes after the initial successful LVAD implantation

Participants

Total number of participants: 76 (47 DT, 29 BTT)
Sample attrition/dropout: Not reported (probably 0 other than deaths within 30 days)
Inclusion criteria: All consecutive HMII recipients at clinic (see comment below)
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): 63.2 years (12)
Median age: Not reported
Age range: Not reported
Sex: 80% male
Race: Mostly Caucasian
Diagnosis: Restrictive CM (11%), ischaemic CM (51%) dilated CM (38%)
Note: the population is almost identical to Topilsky *et al*. (2011a)[79] through also described as consecutive HMII recipients over the same period (other than a 3 months longer of June July August) there were fewer (rather than more) patients in this study than in the other (i.e. 76 vs. 83 in Topilsky *et al*.[79]). As the emphasis of this study[80] was prognostic and outcomes reported were mostly overlapping limited data has been extracted

Intervention

Indication for treatment: 47 DT; 29 BTT – restrictive CM (11%), ischaemic CM (51%) dilated CM (38%)
Type of device used: HMII
Any comparison: 30-day results from echocardiography that potentially could be prognostic for 90-day outcomes. Population divided into poor 90-day post-surgery outcomes (PO) $n = 30$ (persistent NYHA class III+ or readmission for HF between 30 and 90 days, or dead by 90 days) vs. the remainder termed 'normal' 90-day post-surgery outcomes (NO), $n = 46$. (Patients dead within 30 days of surgery were excluded from analyses)
Duration of treatment: Variable (to death, explants or HT)
Percentage of patients using inotropes: PO 60%; NO 69%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Association of echocardiography features with 90-day outcomes
Secondary outcomes: Not applicable
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Mean 321 days (range 106–602 days)

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported/not applicable	Not reported/not applicable
Randomised/included	Not reported/not applicable	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics

Characteristics	Normal outcome (NO; $n = 46$)	Adverse outcome (PO; $n = 30$)	p-value
Age (years)	61.9 ± 14	63.9 ± 11	0.5
Sex, male (%)	75	90	0.3
Race (%)			0.4
Caucasian	96	94	
African American	2	3	
Asian	2	0	
Native American	0	3	
Diabetes mellitus (%)	20	37	0.1
Chronic renal failure (%)	44	63	0.1
Atrial fibrillation (%)	15	20	0.6
AICD	44	37	0.4
Weight (kg)	83.7 ± 19	88.2 ± 21	0.4
BSA	2.0 ± 0.2	2.0 ± 0.2	0.6
NYHA class IV (%)	44	76	0.02
Prior sternotomy (%)	42	50	0.7
Pre-operative IABP (%)	25	40	0.2
Pre-operative inotropic use	60	69	0.5
Pre-operative mechanical ventilation	0	3	0.2
DT (%)	56	70	0.4
Type of cardiomyopathy (%)			0.2
Ischaemic	56	43	
Restrictive	5	20	
Dilated	39	37	
Heart rate (b.p.m.)	75.5 ± 15	75.5 ± 13	0.9
Systolic BP (mmHg)	98.3 ± 11	98.3 ± 17	0.9
Diastolic BP (mmHg)	66.8 ± 10	62.5 ± 10	0.1
Haemoglobin[a]	12.5 ± 2	11.4 ± 12	0.02
Bilirubin[a]	1.23 ± 0.6	1.12 ± 0.8	0.5
AST	59 ± 90	81 ± 231	0.6
ALT	88 ± 204	71 ± 197	0.7

Patient's baseline characteristics

Characteristics	Normal outcome (NO; *n* = 46)	Adverse outcome (PO; *n* = 30)	*p*-value
BUN[a]	28 ± 13	30 ± 14	0.6
Creatinine[a]	1.5 ± 0.8	1.6 ± 0.6	0.5
Prothrombin INR	1.4 ± 0.4	1.4 - ± 0.4	0.9
NT-pro-BNP[a]	6567 ± 6123	5652 ± 6035	0.6
Log-NT-pro-BNP	8.4 ± 0.9	8.1 ± 1.1	0.4
LM score[a]	7.8 ± 4	8.4 ± 7	0.6
ACE inhibitors	58	53	0.3
Beta-blocker	77	88	0.9
Aldospirone (%)	43	47	0.5
Digoxin	65	40	0.1
Diuretics	88	96	0.3
Statins (%)	63	43	0.3
6-minute walk (m)[b]	322 ± 83	308 ± 117	0.8
VO_2 max. (ml/kg/minute)[b]	10.3 ± 2.5	10.0 ± 3.2	0.7
Left ventricular diastolic diameter (mm)[c]	69.3 ± 8	64.8 ± 11	0.06
Left ventricular systolic diameter (mm)[c]	63.2 ± 7	58.2 ± 11	0.05
Ejection fraction (%)[c]	18.8 ± 7	22.7 ± 11	0.1
[c]Left atrial volume index (ml/m^2)	65.7 ± 28	67.2 ± 18	0.8
E/e′ ratio[c]	26.5 ± 12	26.3 ± 10	0.9
Tricuspid regurgitation velocity (m/s)[c]	3.1 ± 0.6	2.8 ± 0.6	0.05
Tricuspid valve lateral annulus velocity (m/s)[c]	0.08 ± 0.03	0.08 ± 0.03	0.3
RV dysfunction > M0[c,d]	63	76	0.2
TRD (m/s)	482 ± 66	446 ± 72	0.04
RIMP[c]	0.61 ± 0.25	0.52 ± 0.24	0.2
Mean right atrial pressure (mmHg)[c]	14.4 ± 5	16.3 ± 8	0.3
Mean pulmonary pressure (mmHg)[c]	36.6 ± 10	34.5 ± 8	0.3
PVR (Wood units)[e]	4.6 ± 3	3.8 ± 3	0.3
RV dP/dt[c,e]	502 ± 208	440 ± 180	0.2
Mean wedge pressure (mmHg)[c,e]	23.1 ± 6	22.9 ± 6	0.9
Cardiac output (l/minute)[c,e]	3.7 ± 1	4.1 ± 1	0.1
[e]Cardiac index (l/minute/m^2)	1.9 ± 0.5	2.0 ± 0.6	0.2

a Variables measured or calculated before LVAD implantation.
b VO_2 max. measured in 10 patients in the adverse outcome group and 30 patients in the no adverse outcome group; 6-minute walk assessed in 6 patients in the adverse outcome group and 15 patients in the no adverse outcome group.
c Last echocardiographic measurement before LVAD implantation. Variables measured or calculated before LVAD implantation.
d RV dysfunction greater than moderate by the qualitative assessment.
e Last haemodynamic study before transplant.

Patient's baseline characteristics

Note: significant difference between groups in NYHA classification

Survival outcomes reported (by group and/or intervention)

See Topilsky *et al*. (2011)[79]

Other specified/relevant outcomes reported (by group and/or intervention)

Characteristic	NO (*n* = 46)	PO (*n* = 30)	*p*-value
Native LV and valves			
Left ventricular diastolic diameter (mm)[a]	58.3 ± 9	55.0- ± 11	0.3
Left ventricular systolic diameter (mm)[a]	50.2 ± 10	47.4- ± 13	0.4
Ejection fraction (%)[a]	26.0 ± 12	25.6 ± 13	0.9
Aortic regurgitation > trivial[a]	41	53	0.4
Mitral regurgitation > mild[a]	9	27	0.4
RV function and size			
Tricuspid regurgitation velocity (m/s)[a]	2.5 ± 0.4	2.4 ± 0.5	0.3
TV lateral annulus velocity (m/s)[a]	0.09 ± 0.03	0.07 ± 0.02	0.01
RV dysfunction > M0[a,b]	11	46	0.03
[a]RVEDA (cm^2)	28.8 ± 7	29.2 ± 7	0.8
[a]RVESA (cm^2)	18.1 ± 5	19.8 ± 6	0.3
RV FAC (%)[a]	38.0 ± 10	32.6 ± 13	0.09
TRDc (m/s)	412 ± 60	389 ± 55	0.3
RIMP	0.28 ± 0.12	0.34 ± 0.2	0.2
TV annulus diameter[a]	3.2 ± - 0.4	3.3 - ± 0.5	0.7
TR vena contracta[a]	3.6 ± 2.4	4.4 ± 2.5	0.3
LV unloading			
E-wave velocity[a]	0.72 ± 0.1	0.79 - ± 0.18	0.2
E/e′ ratio[a]	14.5 ± 4	22.8 ± 13	0.3
Aortic valve status (%)[a]	O (29); I (12); C (59)	O (18); I (11); C (71)	0.5
Atrial septal position (%)[a]	R (3); N (71); L (26)	R (24); N (51); L (25)	0.01
Atrial septal position to right (%)[a]	3	24	0.004
Ventricular septal position (%)[a]	R (57); N (39); L (4)	R (43); N (40); L (17)	0.2
Ventricular septal position to left (%)[a]	4	17	0.07
Left ventricular diastolic diameter change (%)[a]	−15.8 ± 11	−13.2 ± 19	0.6
Left ventricular systolic diameter change (%)[a]	−20.5 ± 17	−13.7 ± 25	0.4
ELAP[a]	7.4 ± 4	14.1 - ± 6	< 0.0001
ELAP > 15 mmHg, %[a]	7	55	< 0.0001
Deceleration time[a]	189 ± 51	170 ± 63	0.3
Deceleration time < 150[a]	15	42	0.04
MDI [ms/(cm/s)][a]	288 ± 137	219 ± 121	0.09
MDI [< 2 m/(cm/s)][a]	20	56	0.01

Other specified/relevant outcomes reported (by group and/or intervention)

Characteristic	NO ($n = 46$)	PO ($n = 30$)	p-value
LVAD flows by echocardiography			
Total output[a]	5.6 ± 2	5.8 - ± 2	0.8
LVAD output[a]	5.3 ± 1.3	4.7 ± 1.2	0.3
LVAD output index[a]	2.7 ± 0.7	2.4 - ± 0.6	0.4
Inflow velocity[a]	77.4 ± 41	75.5 ± 32	0.8
Outflow velocity[a]	109.7 ± 39	97.3 ± 41	0.3
Controller pump parameters			
Pump speed[c]	9538 ± 221	9542 ± 301	0.9
Pump flow[c]	5.5 ± 0.8	5.3 ± 0.7	0.5
Pump flow index[c]	2.6 ± 0.4	2.6 ± 0.4	0.8
Laboratory and clinical parameters at the day of echocardiography			
NYHA class	I (7); II (68); III (23); IV (2)	I (0); II (20); III (43); IV (37)	< 0.0001
NYHA class III/IV, %	25	80	< 0.0001
Heart rate (b.p.m.)	85.7 ± 11	88.7 ± 10	0.3
Mean BP (mmHg)	88.7 ± 7	87.1 ± 11	0.6
Atrial fibrillation (%)	11	16.6	0.7
NT-pro-BNP	2840 ± 1411	3981 ± 4188	0.2
Log-NT-pro-BNP	7.8 ± 0.5	8.0 ± 0.7	0.3
Haemoglobin[d]	10.7 ± 2	10.2 ± 1	0.2
Albumin[d]	3.5 ± 0.7	3.3 ± 0.6	0.3
Creatinine[d]	0.94 ± 0.3	1.3 ± 0.7	0.02
BUN[d]	20.1 ± 9	27.6 ± 16	0.05
Bilirubin[d]	0.94 ± 0.5	2.3 ± 6.3	0.3
ACE inhibitors (%)[c]	30	10	0.03
Beta-blocker (%)[c]	52	20	0.008
Diuretics (%)[c]	83	92	0.3
90-day post-discharge parameters			
NYHA[d]	I (36); II (64); III (0); IV (0)	I (0); II (4); III (81); IV (15)	< 0.0001
NT-pro-BNP[d]	1885 ± 1509	3125 ± 2067	0.05
6-minute walk (m)[d]	273 ± 128	239 ± 95	0.0009

a Echocardiographic measurement performed 30 days after LVAD implant.
b RV dysfunction greater than moderate by quantitative measurement.
c Variables measured at the end of 90-day period after LVAD implantation.
d Variables measured 30 days after LVAD implantation.

Other specified/relevant outcomes reported (by group and/or intervention)

Variables potentially associated with poor vs. normal 90-day outcomes

Variable	OR (95% CI)	*p*-value
Left ventricular diastolic diameter, mm	0.96 (0.89 to 1.03)	0.3
Left ventricular systolic diameter, mm	0.97 (0.92 to 1.03)	0.4
Mitral regurgitation	Mi/No 0.48 (0.15 to 1.6); Mo/Mi 2.0 (0.20 to 23.5)	0.5
Aortic regurgitation	Mi/No 2.4 (0.48 to 15.4)	0.3
TR vena contracta	1.14 (0.91 to 1.44)	0.2
Tricuspid regurgitation velocity, m/s	0.46 (0.12 to 1.62)	0.2
Tricuspid lateral annulus velocity, m/s	0.7 (0.95 to 9.48)	0.02
RV dysfunction > moderate	1.07 (0.57 to 2.0)	0.8
RIMP, 0.1 increase	1.3 (0.89 to 1.96)	0.2
RVEDA, cm^2	1.01 (0.93 to 1.09)	0.8
RVESA, cm^2	1.05 (0.96 to 1.16)	0.3
RV FAC, %	0.96 (0.91 to 1.00)	0.07
Total output	1.07 (0.65 to 1.8)	0.8
LVAD output	0.67 (0.31 to 1.3)	0.2
LVAD output index	0.56 (0.14 to 1.95)	0.4
Inflow velocity	0.99 (0.98 to 1.01)	0.8
Outflow velocity	0.99 (0.98 to 1.01)	0.3
E/e′ ratio	1.15 (0.95 to 1.68)	0.2
Deceleration time	0.99 (0.98 to 1.0)	0.3
Deceleration time < 150 ms	2.04 (1.04 to 4.3)	0.04
MDI	0.99 (0.98 to 1.00)	0.07
MDI < 2 ms/[cm/s]	4.4 (1.22 to 18.0)	0.02
ELAP	1.3 (1.16 to 1.48)	< 0.0001
ELAP > 15 mmHg	15.6 (4.4 to 73.7)	< 0.0001
Atrial septal position	N/R 0.18 (0.02 to 0.89); L/N 2.02 (0.69 to 6.05)	0.07
Atrial septal position to the right	2.1 (1.02 to 5.6)	0.05
Ventricular septal position	N/R 2.25 (0.86 to 6.0); L/N 5.9 (1.12 to 119.1)	0.01
Ventricular septal position to the left	3.03 (1.21 to 13.3)	0.01
Aortic valve status	I/O 1.09 (0.17 to 6.2); C/I 1.46 (0.32 to 7.8)	0.7
Left ventricular diastolic diameter change, %	1.00 (0.96 to 1.06)	0.7
Left ventricular systolic diameter change, %	1.00 (0.98 to 1.04)	0.5
Laboratory and clinical parameters at the day of echocardiography		
Haemoglobin	0.77 (0.55 to 1.01)	0.06
Bilirubin	1.09 (0.93 to 1.69)	0.3
Albumin	0.18 (0.03 to 0.61)	0.003
Creatinine	3.4 (0.84 to 19.2)	0.03
BUN	1.04 (1.01 to 1.1)	0.04

Other specified/relevant outcomes reported (by group and/or intervention)

Variable	OR (95% CI)	*p*-value
Platelets	0.99 (0.98 to 0.99)	0.04
NT-BNP, 100 pg/ml	1.18 (0.98 to 1.56)	0.08
Log-NT-pro-BNP	1.5 (0.71 to 3.6)	0.3
NT-pro-BNP change, %	0.6 (0.21 to 0.96)	0.02
Log-NT-BNP change	0.8 (0.4 to 1.6)	0.6
NYHA class III or IV	12.0 (4.1 to 39.9)	< 0.0001

No significant association for the variables related to the valvular function, LV function or size or pump flows, and output. The only variables assessing RV function that were significantly associated with worse 90-day outcome were a lower tricuspid lateral annulus velocity and an interventricular septum deviated to the left, suggesting that the RV flow is not rapid enough to fill the LV. The decrease (%) in NT-pro-BNP from baseline (before LVAD) to 30 days after LVAD implantation was significantly associated with the 90-day adverse outcome (RR 0.6, 95% CI 0.21 to 0.96; $p = 0.02$ for 1% change)

Adverse events reported (by group and/or intervention)

Used in part to dichotomisation of study participant population

Cause of death reported (by group and/or intervention)

18 deaths recorded as for Topilsky *et al.*[79]

QoL reported (by group and/or intervention)

NYHA class changes see tables above

Author's conclusion

Mortality and HF after LVAD surgery appear to be predominantly determined by echocardiographic evidence of inefficient unloading of the LV and persistence of right ventricular dysfunction. Increased estimated LA pressure and short MDI are associated with worse mid-term outcome. Leftward deviation of the septum is associated with worse outcome as well

Reviewer's conclusion

Lack of power forced the use of a composite end point. Authors state the results should be viewed as preliminary

ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.p.m., beats per minute; BSA, body surface area; BUN, blood urea nitrogen; C, permanently closed; CM, cardiomyopathy; ELAP, estimated left atrial pressure; I, intermittent opening; INR, international normalised ratio; L, deviated to the left; LA, left atrial; LM, Lietz-Miller; MDI, mitral deceleration index; Mi, mild; Mo, moderate; No, normal; N, neutral position; NO, normal post-surgery outcomes; O, opening every cycle; OR, odds ratio; PO, poor post-surgery outcomes; PVR, pulmonary vascular resistance; R, deviated to the right; RIMP, right index of myocardial performance; RR, relative risk; RVEDA, right ventricle end-diastolic area; RVESA, right ventricle end-systolic area; RV FAC, right ventricle fractional area change; TR, tricuspid regurgitation; TRDc, tricuspid regurgitation time corrected for heart rate; TV, tricuspid valve; VO_2 max., peak oxygen uptake.

Uriel 2010[81]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Uriel
Year of publication: 2010
Country: France
Study design: Retrospective chart review
Study setting: Hospital
Number of centres: One
Duration of study: 1 April 2004 to 1 August 2009
Follow-up period: 370 ± 486 days (range 3–1978 days)
Funding: Not reported

Aim of the study

To determine the prevalence of bleeding during CF LVAD support and to identify potential mechanisms for those bleeding events

Participants

Total number of participants: 79 HMII 62 HMXVE
Sample attrition/dropout: Not reported
Inclusion criteria: All HMII implants between specified dates, 1 April 2004 to 1 August 2009
Exclusion criteria: Not reported
Characteristics of participants:
Mean age (SD): 56.3 ± 13.7 years
Median age: Not reported
Age range: Not reported
Sex: $n = 63$ (80%)
Race: Not reported
Diagnosis: HF

Intervention

Indication for treatment: BTT and DT, cannot split
Type of device used: HMII
Any comparison: HMXVE
Duration of treatment: Variable 40/63 BTT received HT; 15/79 died
Percentage of patients using inotropes: Not reported
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Bleeding. Minor bleeding was defined as observable blood loss without the need for transfusion. Major bleeding was defined as need for blood transfusion > 7 days after device insertion
Secondary outcomes: Haemorrhagic stroke; bleeding requiring at least 1 unit of PRBCs; ischaemic stroke; pump thrombosis; systemic embolic events. Stroke was defined as any neurological event lasting > 24 hours and categorised as having a haemorrhagic or thromboembolic aetiology. (Listed but not necessarily reported)
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: 370 ± 486 days (range 3–1978 days)

Number of participants	Intervention	Comparator, if present
Screened	Not reported/not applicable	Not reported/not applicable
Randomised/included	Not reported/not applicable	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics

HMII patient characteristics ($n = 79$)	
Age (years)	56.3 ± 13.7
Male sex, *n* (%)	63 (79.8)
BMI (kg/m^2)	25.9 ± 5.0
BTT/DT	63/14
HF aetiology, *n* (%)	
ICM	33 (45.2)
DCM	40 (54.8)
Previous thoracic surgery, *n* (%)	22 (29.0)
Diabetes mellitus, *n* (%)	26 (33.3)
Hypertension, *n* (%)	37 (47.4)
LVEF	16.1 ± 7.2
Obstructive lung disease, *n* (%)	6 (7.7)
LM score ($n = 63$)	9.1

Survival outcomes reported (by group and/or intervention)

Overall survival 15 of 79 patients died
K–M estimates: Not reported

Other specified/relevant outcomes reported (by group and/or intervention)

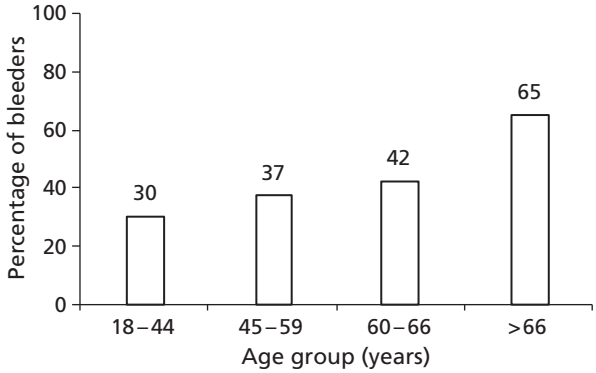
Bleeding
Of 79 patients, 35 had major bleeding events during LVAD support

Comparison of those with major bleeding and those without

Characteristic	Bleed	Normal	*p*-value
Age (years)	60.1 ± 13.5	53.4 ± 13.2	0.031
Male sex, *n* (%)	30 (85.7)	33 (75)	0.239
Basic metabolic index	26.3 ± 5.4	25.3 ± 4.5	0.398
Ejection fraction (%)	16.1 ± 6.0	16.1 ± 8.3	0.998
BTT, *n* (%)	26/8 (76.5)	37/6 (86.1)	0.279
HF aetiology, *n* (%)			
ICM	20 (58.8)	13 (33.3)	0.029
DCM	14 (41.2)	26 (66.7)	
Diabetes mellitus	12 (35.3)	14 (31.8)	0.747
Hypertension	21 (61.8)	16 (46.4)	0.026
COPD	3 (8.8)	3 (6.8)	1
LM score	9.28 ± 4.8	8.97 ± 5.8	0.822
Anticoagulation, *n* (%)			
Warfarin	24 (75.0)	30 (79.0)	0.695
Aspirin	19 (59.4)	25 (65.8)	0.58
Dipyridamole	20 (62.5)	26 (68.4)	0.603

Other specified/relevant outcomes reported (by group and/or intervention)		
Sites of bleeding events requiring transfusion		
Event site	***n***	**Event**
GI	24	
Chest	7	6 pericardial effusion, 1 hemothorax
Other	3	Dental, LE wound, postmenopausal
Epistaxis	1	
Total	35	

Bleeding frequency per quartile age group
Major bleeding events occurred more frequently in older patients, with patients aged > 66 years having twice the risk of bleeding during device support compared with patients aged < 44 years. Age groups: 18–44 years, $n = 20$; 45–59 years, $n = 19$
Bleeding was more common in those with ICM as their underlying HF aetiology (58.8% vs. 33.3%; $p = 0.03$); hypertension was also more common (61.8% vs. 46.4%; $p = 0.026$)



Transfusion requirement during HT	Intervention HMII	Comparator HMXVE	*p*-value
PRBCs (U)	3.8 ± 0.5	6.3 ± 0.8	0.0055
Platelets (U)	8.6 ± 6.4	12.5 ± 5.4	0.0027
Fresh frozen plasma (U)	4.9 ± 3.6	9.6 ± 4.9	0.0000
Cryoprecipitate (U)	2.2 ± 3.5	4.3 ± 3.6	0.0035
CellSaver[a] (U)	3.9 ± 2.3	5.0 ± 4.0	0.50

a Haemonetics Corporation Braintree, MA, USA.

Eighteen HMII patients with major bleeds were tested and found deficient in HMW forms of vW factor sufficient for diagnosis of acquired vW syndrome

Adverse events reported (by group and/or intervention)
See *Bleeding*, above
Cause of death reported (by group and/or intervention)
Not reported
QoL reported (by group and/or intervention)
Not reported

Author's conclusion

Patients with the HMII had a high incidence of bleeding events during device support and at HT. All HMII patients had reduced HMW vW factor multimers. The role of these abnormalities in the high incidence of bleeding deserves further investigation. Furthermore, alterations in anticoagulation should be considered during device support and before surgery in patients supported with the HMII

Reviewer's conclusion

The conclusions regarding frequency of bleeding appear supported by the evidence. There was a large difference in requirement for blood products associated with HT in HMII supported patients relative to HMXVE supported patients, this may be too large to be explained by the greater use of anticoagulants in the former; however, little other demographic information was provided for the HMXVE group. The measurements of vW factor were not performed systematically and there was missing data

DCM, dilated cardiomyopathy; GI, gastrointestinal; HMW, high molecular weight; ICM, ischaemic cardiomyopathy; LE, lower extremity; LVEF, left ventricular ejection fraction; LM, Lietz-Miller; PRBC, packed red blood cell; vW, von Willebrand.

Ventura 2011[82]

Name of the reviewer: Martin Connock (agreed with Paul Sutcliffe)

Study details

First author surname: Ventura
Year of publication: 2011
Country: USA
Study design: Comparative retrospective analysis of National Registry data (Organ Procurement and Transplant Network UNOS)
Study setting: Not applicable
Number of centres: Many, not reported
Duration of study: Registry records 2004–9
Follow-up period: Variable
Funding: Not reported

Aim of the study

To compare post-HT patient outcomes for BTT patients with HMII (continuous) and BTT patients with HMXVE (pulsatile)

Participants

Total number of participants: HMII 484; HMXVE 673
Sample attrition/dropout: Not reported
Inclusion criteria: Any recipient of specified VADs within specified time period in National Registry
Exclusion criteria: None stated
Characteristics of participants: Mixed population
Total number of participants: HMII 484; HMXVE 673
Mean age (SD): HMII 51.27 years (12.6); HM XVE 51.54 years (10.92)
Sex: HMII 18.8% female; HM XVE 11.14% female
Race: White – HMII 70.25%, HMXVE 69.39%; Hispanic – HMII 5.99%, HMXVE 6.69%
Diagnosis: HMII ischaemic 38.8%, idiopathic 39.2%, other 22%; HMXVE ischaemic 41.4%, idiopathic 35.7%, other 22.8%

Intervention

Indication for treatment: BTT alone – HF various pathologies
Type of device used:HMII vs. HMXVE
Duration of treatment: Variable
Percentage of patients using inotropes: HMII 18%; HMXVE 16%
Other interventions used: See section *Patient's baseline characteristics*, below
Any FDA or CE approval: Yes – HMII

Outcomes

Primary outcomes: Post-HT survival
Secondary outcomes: Post-treatment causes of death; rejection-free survival; HT rejection between transplant and discharge; post-HT hospitalisation for infection
Method of assessing outcomes: Medical records
Survival: Yes
Adverse event: Yes
HRQoL: No
Length of follow-up: Unclear

Outcomes		
Number of participants	**Intervention**	**Comparator, if present**
Screened	Not reported/not applicable	Not reported/not applicable
Randomised/included	Not reported/not applicable	Not reported/not applicable
Excluded	Not reported/not applicable	Not reported/not applicable
Missing participants	Not reported/not applicable	Not reported/not applicable
Withdrawals	Not reported/not applicable	Not reported/not applicable

Patient's baseline characteristics		
	HMII (*n* = 484)	**HMXVE (*n* = 673)**
Age (years)	51.27 (12.63)	51.54 (10.92)
Sex	Male 81.2%	Male 88.86%
BSA (m^2)		
Weight, kg (BMI kg/m^2)	83.87 (19.20)	90.08 (17.83)
Ischaemic causes of HF	38.78%	41.39%

Baseline characteristics

	HMII (*n* = 484)	**HMXVE (*n* = 673)**	***p*-value**
Female (%)	18.80	11.14	< 0.001
Mean (SD) recipient age, years	51.27 (12.63)	51.54 (10.92)	0.707
White (%)	70.2	69.39	0.795
Hispanic or Latino (%)	5.99	6.69	0.715
Mean (SD) weight, kg	83.87 (19.20)	90.08 (17.83)	< 0.001
Mean (SD) BMI, kg/m^2	27.91 (17.03)	28.53 (5.22)	0.448
Cardiomyopathy (%)			
Ischaemic	38.78	41.39	0.397
Idiopathic	39.18	35.76	0.243
Other	22.04	22.85	0.776
Mean (SD) TRR cardiac output, l/minute	4.84 (1.71)	4.83 (1.55)	0.998
Mean (SD) PCW pressure, mmHg	18.06 (9.71)	19.17 (10.22)	0.090
Mean (SD) PVR, Wood unit	2.39 (1.74)	2.29 (2.02)	0.402
Most recent PRA (%)			
HLA 1 10%	84	123	0.698
HLA 2 10%	37	64	0.292
HLA 1 90%	10	19	0.452
HLA 2 90%	9	13	1.000
IABP at transplant (%)	2.89	1.78	0.231
Dialysis before transplant (%)	3.72	5.35	0.207
Inotropes at transplant (%)	17.77	16.49	0.580

Patient's baseline characteristics

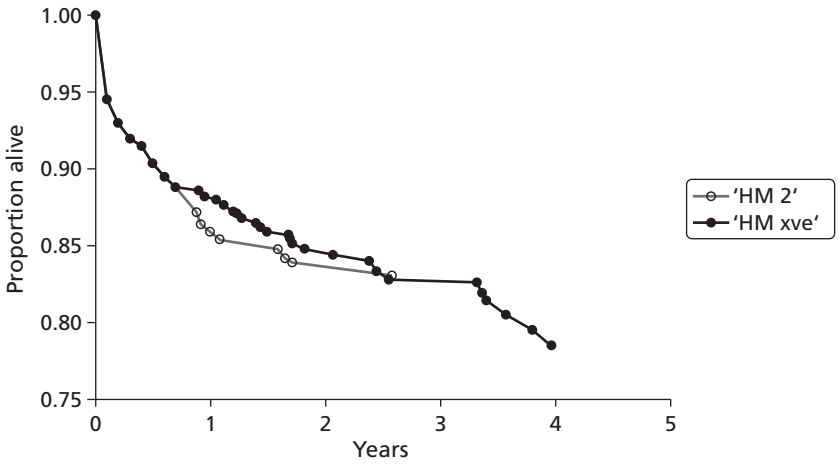
	HMII ($n = 484$)	HMXVE ($n = 673$)	p-value
TRR transfusions since listing (%)	44.63	49.18	0.136
Mean active days on WL			
Male	223.63	198.55	0.187
Female	207.37	249.61	0.328
Mean Ischaemic time, hours	3.38	3.40	0.730
Mean (STD) serum creatinine at transplant, mg/dl	1.3 (0.63)	1.3 (0.60)	0.490
Mean (STD) bilirubin, mg/dl	1.3 (2.67)	1.0 (1.12)	0.032

Survival outcomes reported (by group and/or intervention)

Actuarial survival

Actuarial survival	HMII ($n = 484$)	HMXVE ($n = 673$)
Year 1, %	86.41	88.68
Year 3, %	83.33	84.07

K–M (data read from graph)
Adjusted HR, $p = 0.910$ HMXVE vs. HMII. Note: about 5% early mortality after HT



Comparison of post-implant survival after implantation of HMII and HMXVE LVADs for HF. p = 0.91 for difference between devices.

Other specified/relevant outcomes reported (by group and/or intervention)

Complications	HMII ($n = 484$)	HMXVE ($n = 673$)	p-value
Early rejection (HT to discharge (%))	27.5	39.5	< 0.001
Hospitalised for infection (%)	15.3	29.3	< 0.001
Length of stay post transplant (days)	22.87	23.46	0.749

Adverse events reported (by group and/or intervention)

See above

Cause of death reported (by group and/or intervention)

Cause of death post HT	HMII	HMXVE
Graft failure	15	25
Infection	9	23
Cardiovascular	7	17
Cerebrovascular	3	2
Multiorgan failure	8	13
Haemorrhage	4	3
Malignancy	1	2
Unknown	2	7
Other	10	9
Total	59	101

QoL reported (by group and/or intervention)

Not relevant

Author's conclusion

Survival post HT is equally good between different modes of bridging, infections and acute rejection are reduced in HMII recipients relative to HMXVE

Reviewer's conclusion

The data are generally supportive of authors conclusions. However patients were not randomised to different VADs and balance between groups may have been suboptimal; the proportion of patients who received HMXVE or HMII VADs but who did not later receive a transplant was not reported, and therefore the patients who may have died with VAD were excluded. The mean waiting days before HT was similar in the two groups (male 223 days and female 207 days for HMII, and male 198 days female 250 days for HMXVE)

HLA, human leucocyte antigen; HR, hazard ratio; PCW, pulmonary capillary wedge; PRA, panel reactive antibody; PVR, pulmonary vascular resistance; TRR, transplant recipient registration.

Appendix 4 Quality assessment forms for primary studies

Adapted from the quality criteria by Thomas *et al.*[55] and Clegg *et al.*[4]

First author surname: Adamson 2011[56]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		

D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		
E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**[a]	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	Moderate	**Weak**		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	**No**	Cannot tell		

Global rating for study (overall methodological strength of study – based on section A–F)	Strong	Strong to moderate	Moderate	Moderate to weak	Weak
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	Strong	Strong to moderate	Moderate	Moderate to weak	Weak

N/A, not applicable.
a Assessment of death is unlikely to be incorrectly assessed.

First author surname: Bogaev 2011[57]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[a]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	**No**	**Cannot tell**[b]		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[c]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a All patients or an authorised representative provided informed consent.
b Causes of death were determined at autopsy when possible, by reviewing the medical records, or by interviewing family members.
c However, Cox's proportional hazards assumption not tested.

First author surname: Boyle 2009[58]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	80–100%	**60–79%**	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	Cannot tell	**Not applicable**[a]	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**[b]		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	**No**[c]	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

INR, international normalised ratio; N/A, not applicable.
a No comparator.
b Consent was not mentioned.
c INR levels were recorded at monthly intervals and at time of a clinical event. However, it was noted that INRs for outpatients can change widely and over much shorter time periods according to patient conditions. There is a question of how appropriate it is to assign data into INR ranges.

First author surname: Brewer 2012[59]

Ret Name of the reviewer: Martin Connock and Paul Sutcliffe (agreed)

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[a]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Cox's proportional hazards assumption not tested.

First author surname: Cowger 2010[60]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		.

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	**No**[a]	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	**No**[b]	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		

Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.

a Potential bias in selection, image interpretation and LVAD management which could impact on item A1 development and assessment.

b Unadjusted *p*-values and no Bonferroni correction of the multiple comparisons.

First author surname: Demirozu 2011[61]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[a]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[b]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		

Global rating for study (overall methodological strength of study – based on section A–F)	Strong	Strong to moderate	Moderate	Moderate to weak	Weak
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	Strong	Strong to moderate	Moderate	Moderate to weak	Weak

N/A, not applicable.
a All patients provided informed consent.
b Limited statistical analysis was reported.

First author surname: Drews 2010[87]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**[a]		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	80–100%	60–79%	< 60%	**Cannot tell**	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	**No**	Cannot tell		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[a]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Cox's proportional hazards was not reported.

First author surname: Goldstein 2003[84]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective single-arm trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**[a]		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[b]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[d]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	**Yes**	No	Cannot tell		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Single-arm study.
b Participants gave written informed consent.
c Assessment of death is unlikely to be incorrectly assessed. However, did not clearly report the patient baseline characteristics.
d Linearisation and hazard function analysis were performed to calculate the incidence of adverse events.

First author surname: Hasin 2012[62]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective single-centre study** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell[a]**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	**Yes**	No	Cannot tell		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[b]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Consent was not reported.
b Bonferroni correction was applied.

First author surname: John 2010[63]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective single-arm trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**[a]		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[b]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**[d]	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	**No**[e]	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a No real risk-adjusted group for direct comparison.
b All participating patients provided written informed consent.
c Assessment of death, HT and device removal for recovery are unlikely to be incorrectly assessed.
d All patients accounted for.
e Further multivariate analyses were needed to identify the clinically significant variables: infection, sensitization, increased duration, or a combination of these risk factors.

First author surname: John 2011a[64]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective collected and retrospectively analysed all data** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**[a]		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**[b]		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a No comparator group was used.
b Consent was waived.
c Assessment of death, HT and device removal for recovery are unlikely to be incorrectly assessed.

First author surname: John 2011b[65]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective analysis of outcome data** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[a]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	**No**	Cannot tell		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a All patients met study inclusion criteria and gave informed consent as approved by the Institutional Review Boards at the participating institutions.

First author surname: Kato 2012[66]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[a]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a However, no correction for multiple comparisons.

First author surname: Klotz 2006[88]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	**Not likely**	Cannot tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	< 60%	N/A	**Cannot tell**
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective chart review** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**[a]	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	**No**	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**[b]		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**[c]		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Authors did use age-, disease-, and LVAD duration-match controls.
b Individual consent for this study was waived.
c Regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables – exact *p*-values were not reported.

First author surname: Kormos 2010[67]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective analysis** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
N/A, not applicable.					

First author surname: Lahpor 2010[68]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	< 60%	N/A	**Cannot tell**
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective analysis of multicentre study** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	**Cannot tell**	
Summary of confounders (Methodological strength of study)	Strong	Moderate	**Weak**		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	**No**	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
N/A, not applicable.					

First author surname: Martin 2010[69]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	**Not likely**	Cannot tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	< 60%	N/A	**Cannot tell**
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective analysis** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**[a]		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a No withdrawals or dropouts reported.

First author surname: Miller 2007[70]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective non-comparative trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	Cannot tell	**Not applicable**[a]	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[b]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Single-arm study.
b All participating patients provided written informed consent.
c Assessment of death, HT and device removal for recovery are unlikely to be incorrectly assessed.

First author surname: Morshuis 2009[85]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective, multicentre, non-randomised trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	Moderate	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[a]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[b]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Written informed consent was obtained from all patients.
b However, regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables.

First author surname: Morshuis 2010[42]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective, multicentre, non-randomised trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[a]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[b]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		

Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Written informed consent was obtained from all patients.
b However, regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables.

First author surname: Nativi 2011[89]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective, multicentre, non-randomised trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	**< 60%**	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	Moderate	**Weak**		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes[a]	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	**Yes**	No	Cannot tell		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[b]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		

Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Written informed consent was obtained from all patients.
b However, regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables.

First author surname: Oswald 2010[90]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	< 60%	N/A	**Cannot tell**
3. Summary of selection bias (Methodological strength of study)	Strong	Moderate	**Weak**		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective observational study** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell[a]**		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	Moderate	**Weak**		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**[b]	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**[c]		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		

Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Baseline characteristics are not described separately for each group.
b No dropouts or withdrawals.
c Regression and Cox's proportional hazards were not undertaken to accommodate confounders and identify influential variables – minimum reporting of *p*-values.

First author surname: Pagani 2009[71]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective non-comparative trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	Cannot tell	**Not applicable**[a]	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[b]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**[d]	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Single-arm study.
b All participating patients provided written informed consent before enrolling in the study.
c Assessment of death, HT and device removal for recovery are unlikely to be incorrectly assessed.
d All patients with completed end points or 18 months of follow-up with ongoing VAD appear to have been analysed (n = 281).

First author surname: Pak 2010[72]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	Moderate	**Weak**		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[a]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Cox's regression was not performed.

First author surname: Pal 2009[73]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective study**[a] Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell	Not applicable	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	**Strong**	Moderate	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**[b]	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[c]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Unclear when patients were stratified into those with concurrent cardiac procedures or no such procedures.
b Assessment of death were unlikely to be incorrectly assessed.
c The authors did not appear to test the assumptions for proportional hazards.

First author surname: Petrucci 2009[74]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective single-arm non-randomised trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	Cannot tell	**Not applicable**[a]	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes**[b]	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[d]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	**No**	Cannot tell		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Single-arm study.
b All patients gave informed consent.
c Standardised measures of NC.
d However, bonferroni correction for multiple corrections was not applied to data.

First author surname: Rogers 2010[53]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective data collection** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	Cannot tell	**Not applicable[a]**	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**[b]	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	80–100%	60–79%	< 60%	**Cannot tell**	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	Moderate	**Weak**		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	**Yes**	No	Cannot tell		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a *p*-values for change from baseline were reported; BTT and DT groups were not statistically compared.
b Standard methods were used.

First author surname: Russell 2009[75]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective data collection of a single arm** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	Cannot tell	**Not applicable**	
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**[a]	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**[b]	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	**Strong**	Moderate	Weak		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[c]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	**Yes**	No	Cannot tell		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.

a The study compared renal function and liver function changes from baseline to 180 days for patients stratified as having normal or abnormal renal function or hepatic function at baseline.

b Assumed that the clinical chemistry assessors were blind to patient status.

c Paired changes were used for analysis; however, incomplete samples were available.

First author surname: Sandner 2009a[91]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[a]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Cox's regression model: Proportional hazards assumption was verified by means of Schoenfeld residuals.

First author surname: Sandner 2009b[92]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**[a]	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[b]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable
a Modification of Diet in Renal Disease-derived GFR was used to assess renal function.
b Cox's proportional hazards assumption may not have been tested.

First author surname: Schaffer 2011[76]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	**No**	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**	No	Cannot tell		
Summary of data collection (Methodological strength of study)	**Strong**	Moderate	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**[a]	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Cox's proportional hazards assumption not tested.

First author surname: Schaffer 2009[77]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**[a]		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**[b]		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.

a High- and low-risk groups were defined according to five different scoping systems. It is unlikely therefore that confounders were equally distributed between the two groups according to all the five scoping systems.

b Multivariate analysis were undertaken by Cox' proportional hazards regression. The proportional hazards assumption does not appear to be tested.

First author surname: Schmid 2008[86]

Ret Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	**Yes**[a]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**[b]		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

CT, computerised tomography; N/A, not applicable.
a Assessment of death is unlikely to be incorrectly assessed, cerebral bleeding was confirmed by CT scan.
b Cox's proportional hazards assumption not tested.

First author surname: Starling 2011[52]

Prospective study Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective data collection for intervention with retrospective registry data for comparator** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**[a]		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[b]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**[c]	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	**Yes**	No	Cannot tell		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a The comparison group included other LVADs.
b Assessment of death, HT and device removal for recovery are unlikely to be incorrectly assessed.
c Withdrawals were mentioned but number were not reported.

First author surname: Strueber 2011[83]

Prospective study Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – prospective single-arm trial** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell[a]**		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	**Yes[b]**	No	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	**Yes**	No	Cannot tell		
2. Were data collection tools shown to be reliable?	**Yes**[c]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	**Yes**[d]	No	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	**Strong**	Moderate	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	**Yes**	No	Cannot tell		

Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a A virtual comparator group was used.
b All patients gave informed consent.
c Assessment of death, HT and device removal for recovery are unlikely to be incorrectly assessed.
d All patients accounted for.

First author surname: Strueber 2008[78]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**[a]		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**[b]		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		

Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate to weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		

FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a No baseline characteristics table was provided – limited information provided in the text.
b Cox's proportional hazards not undertaken – this may have been useful if sufficient baseline information had been available.

First author surname: Topilsky 2011a[79]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	Yes	No	**Cannot tell**		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	**Yes**[a]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**[b]		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Assumed that intraobserver reliability assessment was undertaken on echocardiography on basis of Topilsky *et al.*[80]
b Regression and Cox's proportional hazards not undertaken.

First author surname: Topilsky 2011b[80]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	Moderate	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective observation based on medical records** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	**Strong**	Moderate	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	**Yes**	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	**Yes**[a]	No	Cannot tell		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No	**Cannot tell**		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	**Yes**	No	Cannot tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Strong to moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.
a Inter-rater reliability assessment was undertaken on echocardiography.

First author surname: Uriel 2010[81]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	**Cannot tell**	
2. What percentage of selected individuals agreed to participate?	**80–100%**	60–79%	< 60%	N/A	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] **Other – retrospective chart review** Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	80–100%	60–79%	**< 60%**	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	Moderate	**Weak**		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	**No**	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No	**Cannot tell**		
Summary of blinding (Methodological strength of study)	Strong	Moderate	**Weak**		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	Moderate	**Weak**		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	**Yes**	No	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	**Cannot tell**		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Weak					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
N/A, not applicable.					

First author surname: Ventura 2011[82]

Name of the reviewer: *Martin Connock and Paul Sutcliffe (agreed)*

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	**Somewhat likely**	Not likely	Cannot tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	< 60%	**N/A**	Cannot tell
3. Summary of selection bias (Methodological strength of study)	Strong	**Moderate**	Weak		
B. Study design					
1. What was the study design?	RCT Controlled clinical trial **Cohort analytic (two group pre + post)** Case–control Cohort [one group pre + post (before and after)] Other – specify Cannot tell				
2. Was the study described as randomised? If answer to 2 is no, ignore No. 3 and 4 below. If answer yes, answer No. 3 and 4 below	Yes	**No**			
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design (Methodological strength of study)	Strong	**Moderate**	Weak		
C. Confounders					
1. Were there important differences between groups prior to the intervention? (e.g. sex, age, health status)	**Yes**	No	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled either in the design (e.g. stratification, matching) or analysis? (80–100%, 60–79%, < 60%)	**80–100%**	60–79%	< 60%	Cannot tell	
Summary of confounders (Methodological strength of study)	Strong	**Moderate**	Weak		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	**Cannot tell**		
2. Were the study participants aware of the research question?	Yes	**No**	Cannot tell		
Summary of blinding (Methodological strength of study)	Strong	**Moderate**	Weak		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	**Cannot tell**		
2. Were data collection tools shown to be reliable?	Yes	No	**Cannot tell**		
Summary of data collection (Methodological strength of study)	Strong	**Moderate**	Weak		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	**No**	Cannot tell		
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	80–100%	60–79%	< 60%	**Cannot tell**	
Summary of withdrawals and dropouts (Methodological strength of study)	Strong	**Moderate**	Weak		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention of exposure of interest?	**80–100%**	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	**Cannot tell**		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	**Cannot tell**		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	**Client**
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	**Client**
3. Are the statistical methods appropriate for the study design?	Yes	No	**Cannot tell**		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	**No**[a]	Cannot tell		
Global rating for study (overall methodological strength of study – based on section A–F)	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**
Overall rating (to be assessed following discussion by two reviewers)					
Moderate					
Is there any discrepancy between the two reviewers with respect to the different component ratings?	Yes	**No**			
If yes, indicate the reason for the discrepancy	Oversight	Difference in interpretation of criteria	Difference in interpretation of study		
FINAL DECISION OF REVIEWERS	**Strong**	**Strong to moderate**	**Moderate**	**Moderate to weak**	**Weak**

N/A, not applicable.

a Proportional hazards assumption not reported. Registry data, depends on accurate input from many physicians/centres but biases not likely to differ between the two VADs. Biggest problem is representativeness of populations, possible imbalances, and different auxiliary treatment with later use of HMII.

Appendix 5 List of excluded papers with reasons

Reference number	Reference	Reason for exclusion
1	Benton CR, Sayer G, Ashley K, Flynn R, Nair AP, Domanski MJ, *et al*. Left ventricular assist devices improve functional class but fail to normalize peak oxygen consumption. *J Cardiac Fail* 2011;**17** (Suppl. 1):S40	Abstract
2	Healy AH, Mason NO, Hammond ME, Reid BB, Clayson SE, Drakos SG, *et al*. Allograft rejection in patients supported with continuous flow left ventricular assist devices. *Ann Thorac Surg* 2011;**92**:1601–7	Less than 80% of included devices
3	Swetz KM, Mueller PS, Ottenberg AL, Dib C, Freeman MR, Sulmasy DP. The use of advance directives among patients with left ventricular assist devices. *Hosp Prac* 2011;**39**:78–84	Non-systematic review
4	Adamson RM, Baradarian S, Chammas J, Norman V, Jaski B, Hoagland P, *et al*. Can right ventricular failure associated with LVAD insertion be avoided? *J Cardiac Fail* 2011;**17**(Suppl. 1):S46	Abstract
5	Adamson RM, Jaski B, Hoagland P, Chammas J, Baradarian S, Norman V, *et al*. Are LVAD support and cardiac transplantation approaching equipoise? *J Cardiac Fail* 2011;**17**(Suppl. 1):S38	Abstract
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Reference number	Reference	Reason for exclusion
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41	Butler J, Howser R, Portner PM, Pierson RN III. Body mass index and outcomes after left ventricular assist device placement. *Ann Thorac Surg* 2005;**79**:66–73	Concerns non-included VADs
42	Canadian Agency for Drugs and Technologies in Health (2011) *HeartWare® Ventricular Assist System for end stage heart failure: Clinical effectiveness.* URL: www.etsad.fr/etsad/afficher_lien.php?id=3890	Non-systematic review
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Reference number	Reference	Reason for exclusion
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Reference number	Reference	Reason for exclusion
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Reference number	Reference	Reason for exclusion
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114	Holman WL, Kormos RL, Naftel DC, Miller MA, Pagani FD, Blume E, *et al*. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. *J Heart Lung Transplant* 2009;**28**:44–50	Concerns non-included VADs
115	Holman WL, Pae WE, Teutenberg JJ, Acker MA, Naftel DC, Sun BC, *et al*. INTERMACS: interval analysis of registry data. *J Am Coll Surg* 2009;**208**:755–61	Concerns non-included VADs
116	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	Not transplant-eligible
117	Hong KN, Iribarne A, Yang J, Ramlawi B, Takayama H, Naka Y, *et al*. Do posttransplant outcomes differ in heart transplant recipients bridged with continuous and pulsatile flow left ventricular assist devices? *Ann Thorac Surg* 2011;**91**:1899–906	Unable to determine the number of patients with VentrAssist. Cannot conclude if less than 80% of included devices were used in this study

Reference number	Reference	Reason for exclusion
118	Hoshi H, Shinshi T, Takatani S. Third-generation blood pumps with mechanical noncontact magnetic bearings. *Artific Organ* 2006;**30**: 324–38	Non-systematic review
119	Houghton P. Living with the Jarvik 2000: a five-plus year experience. *Artific Organ* 2006;**30**:322–3	Editorial
120	Huang R, Deng M, Rogers JG, Howser R, Portner PM, Pierson RN III, *et al.* Effect of age on outcomes after left ventricular assist device placement. *Transplant Proc* 2006;**38**:1496–8	Concerns non-included VADs
121	Hubler S, Potapov EV, Loebe M, Nasseri BA, Gosmann D, Hoffmann K, *et al*. Development of a database of patients supported by ventricular assist devices. *ASAIO J* 2003;**49**:340–4	Less than 80% of included devices
122	John R, Kamdar F, Liao K, Colvin-Adams M, Boyle A, Joyce L. Improved survival and decreasing incidence of adverse events with the HeartMate II left ventricular assist device as bridge-to-transplant therapy. *Ann Thorac Surg* 2008;**86**:1227–34	Fewer than 50 participants in included VADs group(s)
123	John R, Kamdar F, Liao K, Colvin-Adams M, Miller L, Joyce L, *et al*. Low thromboembolic risk for patients with the Heartmate II left ventricular assist device. *J Thorac Cardiovasc Surg* 2008;**136**:1318–23	Fewer than 50 participants in included VADs group(s)
124	Joyce DL, Conte JV, Russell SD, Joyce LD, Chang DC. Disparities in access to left ventricular assist device therapy. *J Surg Res* 2009;**152**: 111–17	Less than 80% of included devices
125	Jurmann MJ, Weng Y, Drews T, Pasic M, Hennig E, Hetzer R. Permanent mechanical circulatory support in patients of advanced age. *Eur J Cardio Thorac Surg* 2004;**25**:610–18	Not transplant-eligible
126	Kalya AV, Tector AJ, Crouch JD, Downey FX, McDonald ML, Anderson AJ, *et al*. Comparison of Novacor and HeartMate vented electric left ventricular assist devices in a single institution. *J Heart Lung Transplant* 2005;**24**:1973–5	Unclear HM VAD type
127	Kamdar F, Boyle A, Liao K, Colvin-Adams M, Joyce L, John R. Effects of centrifugal, axial, and pulsatile left ventricular assist device support on end-organ function in heart failure patients. *J Heart Lung Transplant* 2009;**28**:352–9	Fewer than 50 participants in included VADs group(s)
128	Kashiwa K, Nishimura T, Kubo H, Tamai H, Baba A, Ono M, *et al*. Study of device malfunctions in patients with implantable ventricular assist devices living at home. *J Artific Organ* 2010;**13**:134–8	Fewer than 30 participants
129	Kato TS, Farr M, Schulze PC, Maurer M, Shahzad K, Iwata S, *et al*. Usefulness of two-dimensional echocardiographic parameters of the left side of the heart to predict right ventricular failure after left ventricular assist device implantation. *Am J Cardiol* 2012;**109**:246–51	Concerns non-included VADs
130	Kavarana MN, Sinha P, Naka Y, Oz MC, Edwards NM. Mechanical support for the failing cardiac allograft: a single-centre experience. *J Heart Lung Transplant* 2003;**22**:542–7	Not transplant-eligible
131	Ketchum ES, Moorman AJ, Fishbein DP, Mokadam NA, Verrier ED, Aldea GS, *et al*. Predictive value of the Seattle Heart Failure Model in patients undergoing left ventricular assist device placement. *J Heart Lung Transplant* 2010;**29**:1021–5	Less than 80% of included devices
132	Khot UN, Mishra M, Yamani MH, Smedira NG, Paganini E, Yeager M, *et al*. Severe renal dysfunction complicating cardiogenic shock is not a contraindication to mechanical support as a bridge to cardiac transplantation. *J Am Coll Cardiol* 2003;**41**:381–5	Unclear HM VAD type
133	Kimball PM, Flattery M, McDougan F, Kasirajan V. Cellular immunity impaired among patients on left ventricular assist device for 6 months. *Ann Thorac Surg* 2008;**85**:1656–61	Concerns non-included VADs

Reference number	Reference	Reason for exclusion
134	Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, *et al*. Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. *J Heart Lung Transplant* 2010;**29**:1–10	Less than 80% of included devices
135	Komoda T, Drews T, Hetzer R, Lehmkuhl HB. Optimal body surface area for incor left ventricular assist device implantation. Carden Jennings Publishing Co. Ltd. *Heart Surgery Forum* 2010;**13**:S148	Abstract
136	Komoda T, Drews T, Hetzer R, Lehmkuhl HB. New prioritization of heart transplant candidates on mechanical circulatory support in an era of severe donor shortage. *J Heart Lung Transplant* 2010;**29**:989–96	Less than 80% of included devices
137	Komoda T, Drews T, Lehmkuhl HB, Hetzer R. Role of ventricular assist devices in the German heart allocation system. *J Artific Organ* 2006;**9**: 29–33	Concerns non-included VADs
138	Komoda T, Drews T, Lehmkuhl HB, Hetzer R. Lower body surface area is highly related to mortality due to stroke or systemic bleeding in patients receiving an axial flow blood pump as left ventricular assist device. *Circulation Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States.* 2011;**124**(Suppl. 1)	Abstract
139	Komoda T, Hetzer R, Lehmkuhl HB. Who should be delisted from urgent heart transplantation in Germany? *ASAIO J* 2009;**55**:452–5	Less than 80% of included devices
140	Komoda T, Komoda S, Dandel M, Weng Y, Hetzer R. Explantation of INCOR left ventricular assist device after myocardial recovery. *J Cardiac Surg* 2008;**23**:642–7	Fewer than 30 participants
141	Krabatsch T. Is bridge to recovery more likely with pulsatile left ventricular assist devices than with nonpulsatile-flow systems? *Ann Thorac Surg* 2011;**91**:1335–41	Less than 80% of included devices
142	Krabatsch T, Schweiger M, Stepanenko A, Kukucka M, Vierecke J, Lehmkuhl HB, *et al*. Mechanical circulatory support-results, developments and trends. *J Cardiovasc Translational Res* 2011; **4**:332–9	Less than 80% of included devices
143	Krabatsch T, Stepanenko A, Drews T, Schweiger M, Siniawski H, Lehmkuhl H, *et al*. Mechanical circulatory support with the heart-mate II left ventricular assist device. *Heart Surg Forum* 2010;**13**:S147–8	Abstract
144	Kugler C, Malehsa D, Tegtbur U, Guetzlaff E, Meyer AL, Bara C, *et al*. Health-related quality of life and exercise tolerance in recipients of heart transplants and left ventricular assist devices: a prospective, comparative study. *J Heart Lung Transplant* 2011;**30**:204–10	Fewer than 50 participants in included VADs group(s)
145	Kuhne M, Sakumura M, Reich SS, Sarrazin JF, Wells D, Chalfoun N, *et al*. Simultaneous use of implantable cardioverter-defibrillators and left ventricular assist devices in patients with severe heart failure. *Am J Cardiol* 2010;**105**:378–82	Less than 80% of included devices
146	Kurien S, Hughes KA. Anticoagulation and bleeding in patients with ventricular assist devices: walking the tightrope. *AACN Advanced Crit Care* 2012;**23**:91–8	Non-systematic review
147	Kwon MH, Moriguchi JD, Ardehali A, Jocson R, Marelli D, Laks H, *et al*. Use of ventricular assist device as a bridge to cardiac transplantation: impact of age and other determinants on outcomes. *Tex Heart Inst J* 2009;**36**:214–19	Concerns non-included VADs
148	Lahpor JR. State of the art: implantable ventricular assist devices. *Curr Opin Organ Transplant* 2009;**14**:554–9	Non-systematic review
149	Lainez R, Parrino G, Bates M. Right ventricular function and left ventricular assist device placement: clinical considerations and outcomes. *Ochsner J* 2010;**10**:241–4	Fewer than 50 participants in included VADs group(s)

Reference number	Reference	Reason for exclusion
150	Laoutaris ID, Dritsas A, Vartela V, Manginas A, Adamopoulos S, Gouziouta A, *et al*. Exercise capacity and quality of life in left ventricular assist device recipients of continuous flow intracorporeal support versus pulsatile-flow extracorporeal support. *Heart Surg Forum* 2010;**13**:S93	Abstract
151	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	Concerns non-included VADs
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153	Leshnower BG, Gleason TG, O'Hara ML, Pochettino A, Woo YJ, Morris RJ, *et al*. Safety and efficacy of left ventricular assist device support in postmyocardial infarction cardiogenic shock. *Ann Thoracic Surg* 2006;**81**:1365–70	Concerns non-included VADs
154	Liden H, Haraldsson A, Ricksten SE, Kjellman U, Wiklund L. Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance? *Eur J Cardiothorac Surg* 2009;**35**:1029–34	Less than 80% of included devices
155	Lietz K, Miller LW. Destination therapy: current results and future promise. *Semin Thorac Cardiovasc Surg* 2008;**20**:225–33	Non-systematic review
156	Lietz K, Miller LW. Patient selection for left-ventricular assist devices. *Curr Opin Cardiol* 2009;**24**:246–51	Non-systematic review
157	Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, *et al*. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;**116**:497–505	Concerns non-included VADs
158	Lima B, Kherani AR, Hata JA, Cheema FH, Casher J, Oz MC, *et al*. Does a pre-left ventricular assist device screening score predict long-term transplantation success? A 2-center analysis. *Heart Surg Forum* 2006;**9**:E783–5	Concerns non-included VADs
159	Liu M, Lin G, Topilsky Y, Hasin T, Boege MA, Kushwaha SS, *et al*. Decreased right ventricular strain before left ventricular assist device implantation is associated with adverse early outcome. *Circulation Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States.* 2011;**124**(Suppl. 1)	Abstract
160	Lockard KL, DeGore L, Schwarm P, Winowich S, O'Shea G, Siegenthaler M, *et al*. Lack of improvement in prealbumin at two weeks predicts a poor outcome after mechanical circulatory support. *J Heart Lung Transplant* 2009;**28**(Suppl. 1):S66	Abstract
161	Loebe M, Bruckner B, Reardon MJ, van DE, Estep J, Gregoric I, *et al*. Initial clinical experience of total cardiac replacement with dual HeartMate-II axial flow pumps for severe biventricular heart failure. *Methodist DeBakey Cardiovasc J* 2011;**7**:40–4	Fewer than 30 participants
162	Loforte A, Montalto A, Monica PLD, Contento C, Musumeci F. Biventricular support with the HeartWare implantable continuous flow pump: An additional contribution. *J Heart Lung Transplant* 2010;**29**: 1443–4	Editorial
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Reference number	Reference	Reason for exclusion
164	Loforte A, Montalto A, Ranocchi F, Casali G, Luzi G, Losasso G, *et al*. Bridge to heart transplantation with mid to long-term VAD mechanical support. *Interactive Cardiovascthorac Surg* 2009;**8**:S87–8	Abstract
165	Loforte A, Ranocchi F, Montalto A, Casali G, Luzi G, Lilla Delia MP, Sbaragiia F. Long-term VAD mechanical support as bridge to heart transplantation. *Eur J Heart Fail* 2009;**8**(Suppl.):103	Abstract
166	Long JW, Kfoury AG, Slaughter MS, Silver M, Milano C, Rogers J, *et al*. Long-term destination therapy with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. *Congestive Heart Fail* 2005;**11**:133–8	Concerns non-included VADs
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169	Martin S, Wellington L, Stevenson K, Sai-Sudhakar C, Firstenberg M, Blais D, *et al*. Risk of infection after LVAD placement for long-term support by body-mass index and device type. *J Heart Lung Transplant* 2009;**28**(Suppl. 1):S67	Concerns non-included VADs
170	Mason NO, Kfoury AG, Janicki L, Stoker S, Clayson SP, Thomsen GE, *et al*. Impact of illness acuity on blood products usage in patients implanted with left ventricular assist devices (LVAD). *J Heart Lung Transplant* 2009;**28**(Suppl. 1):S277	Abstract
171	Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. *J Am Coll Cardiol* 2008;**51**:2163–72	Less than 80% of included devices
172	Melnitchouk S, Jorde U, Takayama H, Uriel N, Colombo P, Yang J, *et al*. Continuous flow LVAD Destination Therapy versus orthotopic heart transplantation in patients above 65 years of age. *J Heart Lung Transplant* 2011;**30**(Suppl. 1):S125–6	Abstract
173	Meyns B, Rega F, Simon A, Klotz S, Schlensak C, Wittwer T, *et al*. Less invasive surgery with circulite synergy pocket micro-pump reduces adverse events verses traditional VADs. *J Heart Lung Transplant* 2010;**29**(Suppl. 1):S183–4	Abstract
174	Mikus E, Stepanenko A, Krabatsch T, Dandel M, Lehmkuhl HB, Loforte A, *et al*. Left ventricular assist device or heart transplantation: impact of transpulmonary gradient and pulmonary vascular resistance on decision making. *Eur J Cardiothorac Surg* 2011;**39**:310–16	Less than 80% of included devices
175	Mikus E, Stepanenko A, Krabatsch T, Loforte A, Dandel M, Lehmkuhl HB, *et al*. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. *Eur J Cardiothorac Surg* 2011;**40**:971–7	Fewer than 50 participants in included VADs group(s)
176	Mitter N, Sheinberg R. Update on ventricular assist devices. *Curr Opin Anesthesiol* 2010;**23**:57–66	Non-systematic review
177	Moazami N, Sun B, Milano C, John R, Conte J, Adamson R, *et al*. Pump replacement for lvad failure can be done safely and is associated with low mortality. *J Heart Lung Transplant* 2010;**29**(Suppl. 1):S53	Abstract
178	Monkowski DH, Axelrod P, Fekete T, Hollander T, Furukawa S, Samuel R. Infections associated with ventricular assist devices: epidemiology and effect on prognosis after transplantation. *Transplant Infect Dis* 2007;**9**:114–20	Concerns non-included VADs

Reference number	Reference	Reason for exclusion
179	Mookadam F, Kendall CB, Wong RK, Kalya A, Warsame T, Arabia FA, *et al*. Left ventricular assist devices: physiologic assessment using echocardiography for management and optimization. *Ultrasound Med Biol* 2012;**38**:335–45	Non-systematic review
180	Morales DL, Lowry AW, Epstein DJ, Rosenthal DN, Chen JM, Almond CS, *et al*. Outcomes of children implanted with ventricular assist devices in the united states: Analysis of the interagency registry for mechanical circulatory support (INTERMACS). *Circulation Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States* 2011;**124**(Suppl. 1)	Abstract
181	Morgan JA, Brewer RJ, Nemeh HW, Henry SE, Borgi J, Czerska B, *et al.* Impact of acute renal failure on survival after HMII LVAD implantation. *J Heart Lung Transplant* 2010;**29**(Suppl. 1):S178	Abstract
182	Morgan JA, Naseem TM, Cheema FH, Scripps TB, Russo MJ, Davies RR, *et al*. A single-institutional 4-year experience comparing HMII and HM I XVE as a bridge to transplant. *J Heart Lung Transplant* 2009;**28** (Suppl. 1):S164	Abstract
183	Morgan JA, John R, Lee BJ, Oz MC, Naka Y. Is severe right ventricular failure in left ventricular assist device recipients a risk factor for unsuccessful bridging to transplant and post-transplant mortality. *Ann Thorac Surg* 2004;**77**:859–63	Concerns non-included VADs
184	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	Concerns non-included VADs
185	Morgan JA, Park Y, Kherani AR, Vigilance DW, Cheema FH, Oz MC, *et al*. Does bridging to transplantation with a left ventricular assist device adversely affect posttransplantation survival? A comparative analysis of mechanical versus inotropic support. *J Thorac Cardiovasc Surg* 2003;**126**:1188–90	Concerns non-included VADs
186	Morgan JA, Park Y, Oz MC, Naka Y. Device related infections while on left ventricular assist device support do not adversely impact bridging to transplant or posttransplant survival. *ASAIO J* 2003;**49**:748–50	Concerns non-included VADs
187	Morris RJ, Pochettino A, O'Hara M, Gardner TJ, Acker MA. Emergent mechanical support in the community: improvement with early transplant center referral. *J Heart Lung Transplant* 2005;**24**:764–8	Concerns non-included VADs
188	Mufti HN, Legare JF, Osmond S, Baskett RJ. Long term ventricular assist devices: the maritime experience. *Can J Cardiol* 2011;**27**(Suppl. 1):S97	Abstract
189	Musci M, Loforte A, Potapov EV, Krabatsch T, Weng Y, Pasic M, *et al.* Body mass index and outcome after ventricular assist device placement. *Ann Thorac Surg* 2008;**86**:1236–42	Less than 80% of included devices
190	Mushtaq A, Xu J, Elias B, Orrego C, Torre-Amione G, Bruckner B, *et al*. A comparison of established screening scales to predict survival in patients requiring mechanical circulatory support. *J Heart Lung Transplant* 2009;**28**(Suppl. 1):S301	Abstract
191	Mussivand T, Holmes KS. Neurological complications with pulsatile and rotary blood pumps. *J Heart Lung Transplant* 2009;**28**(Suppl. 1):S278	Abstract
192	Nakajima I, Kato TS, Komamura K, Takahashi A, Oda N, Sasaoka T, *et al.* Pre- and post-operative risk factors associated with cerebrovascular accidents in patients supported by left ventricular assist device. Single center's experience in Japan. *Circulation* 2011;**75**: 1138–46	Less than 80% of included devices

Reference number	Reference	Reason for exclusion
193	Nawata K, Nishimura T, Kyo S, Hisagi M, Kinoshita O, Saito A, *et al*. Outcomes of midterm circulatory support by left ventricular assist device implantation with descending aortic anastomosis. *J Artific Organ* 2010;**13**:197–201	Fewer than 30 participants
194	Noor M, Bowles C, Firouzi A, Simon A, Banner NR. Myocardial recovery after support with HeartMate I and HeartMate II left ventricular assist devices. [Retraction of *J Heart Lung Transplant* 2011;**30**:S75]. *J Heart Lung Transplant* 2011;**30**:1423	Erratum
195	Nunes AJ, Buchholz H, Sinnadurai S, Mullen JC, Singh G, Meyer SR, *et al*. Clinical outcomes of long-term mechanical circulatory support at a large Canadian transplant centre. *Can J Cardiol* 2011; **27**(Suppl. 1):S216	Abstract
196	Osaki S, Edwards NM, Johnson MR, Velez M, Munoz A, Lozonschi L, *et al.* Improved survival after heart transplantation in patients with bridge to transplant in the recent era: a 17-year single-center experience. *J Heart Lung Transplant* 2009;**28**:591–7	Less than 80% of included devices
197	Osaki S, Edwards NM, Velez M, Johnson MR, Murray MA, Hoffmann JA, *et al.* Improved survival in patients with ventricular assist device therapy: the University of Wisconsin experience. *Eur J Cardiothorac Surg* 2008;**34**:281–8	Less than 80% of included devices
198	Osorio J. Continuous flow LVAD improves quality of life. *Nature Rev Cardiol* 2010;**7**:360	Commentary
199	Pal JD, Piacentino V, Cuevas AD, Depp T, Daneshmand MA, Hernandez AF, *et al*. Impact of left ventricular assist device bridging on posttransplant outcomes. *Ann Thorac Surg* 2009;**88**:1457–61	Concerns non-included VADs
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201	Pamboukian SV, Tallaj JA, Brown RN, Holman WL, Blood M, George JF, *et al*. Improvement in 2-year survival for ventricular assist device patients after implementation of an intensive surveillance protocol. *J Heart Lung Transplant* 2011;**30**:879–87	Less than 80% of included devices
202	Pasierski T, Buksinska-Lisik M. Left ventricular assist device – unexpected benefits for the failing heart. *Kardiologia Polska* 2008; **66**:678–83	Non-systematic review
203	Patel CB, Rogers JG. Durable mechanical circulatory support devices. *Prog Cardiovasc Dis* 2011;**54**:132–43	Non-systematic review
204	Patel ND, Weiss ES, Schaffer J, Ullrich SL, Rivard DC, Shah AS, *et al*. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Ann Thorac Surg* 2008;**86**:832–40	Fewer than 50 participants in included VADs group(s)
205	Patel SR, Bhatia V, Edwards P, Nucci C, Goldstein D, Maybaum S. Rate of cardiac recovery with combined pharmacological therapy and continuous flow LVAD support. *Circulation Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States.* 2011;**124**(Suppl. 1)	Abstract
206	Patlolla V, Patten RD, DeNofrio D, Konstam MA, Krishnamani R. The effect of ventricular assist devices on post-transplant mortality an analysis of the United network for organ sharing thoracic registry. *J Am Coll Cardiol* 2009;**53**:264–71	Unable to determine what type of Heartmate VAD
207	Pawale A, Pinney S, Ashley K, Flynn R, Milla F. Anyanwu AC. Implantable LVADs as initial therapy for refractory post myocardial infarction cardiogenic shock – a challenge to the 'bridge to bridge' paradigm. *J Heart Lung Transplant* 2011;**30**(Suppl. 1):S160	Abstract

Reference number	Reference	Reason for exclusion
208	Pedrotty DM, Welsby I, Daneshmand MA, Blue L, Lodge AJ, Hernandez AF, *et al*. Bleeding and thromboembloic complications with pulsatile versus non-pulsatile LVADs. *J Heart Lung Transplant* 2009; **28**(Suppl. 1):S84	Abstract
209	Piacentino V III, Williams ML, Depp T, Garcia-Huerta K, Blue L, Lodge AJ, *et al*. Impact of tricuspid valve regurgitation in patients treated with implantable left ventricular assist devices. *Ann Thorac Surg* **91**:1342–6	Less than 80% of included devices
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211	Potapov EV, Stepanenko A, Krabatsch T, Hetzer R. Managing long-term complications of left ventricular assist device therapy. *Curr Opin Cardiol* 2011;**26**:237–44	Non-systematic review
212	Potapov EV, Loforte A, Weng Y, Jurmann M, Pasic M, Drews T, *et al.* Experience with over 1000 implanted ventricular assist devices. *J Cardiac Surg* 2008;**23**:185–94	Less than 80% of included devices
213	Pruijsten RV, de JN, Kirkels JH, Klopping C, Doevendans PA, Oosterom A, *et al.* Left ventricular assist device: a functional comparison with heart transplantation. *Netherlands Heart J* 2008;**16**:41–6	Concerns non-included VADs
214	Raasch H, Jensen B, Sheridan B, Bowen A, Gehi A, Chung EH, *et al*. Ventricular assist devices do not treat ventricular arrhythmias: Significant morbidity persists after implantation. *Circulation Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States.* 2011;**124**(Suppl. 1)	Abstract
215	Radovancevic B, Golino A, Vrtovec B, Thomas CD, Radovancevic R, Odegaard P, *et al*. Is bridging to transplantation with a left ventricular assist device a risk factor for transplant coronary artery disease? *J Heart Lung Transplant* 2005;**24**:703–7	VADs unclear
216	Radovancevic B, Vrtovec B, Frazier OH. Left ventricular assist devices: an alternative to medical therapy for end-stage heart failure. *Curr Opin Cardiol* 2003;**18**:210–14	Non-systematic review
217	Radovancevic B, Vrtovec B, de KE, Radovancevic R, Gregoric ID, Frazier OH. End-organ function in patients on long-term circulatory support with continuous- or pulsatile-flow assist devices. *J Heart Lung Transplant* 2007;**26**:815–18	Fewer than 50 participants in included VADs group(s)
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219	Refaat M, Chemaly E, Lebeche D, Gwathmey JK, Hajjar RJ. Ventricular arrhythmias after left ventricular assist device implantation. *Pacing Clin Electrophysiol* 2008;**31**:1246–52	VADs unclear
220	Refaat MM, Tanaka T, Kormos RL, McNamara D, Teuteberg J, Winowich S, *et al*. Survival benefit of implantable cardioverter-defibrillators in left ventricular assist device-supported heart failure patients. *J Cardiac Fail* 2012;**18**:140–5	VADs unclear
221	Robertson JO, Lober C, Smedira NG, Navia JL, Sopko N, Gonzalez-Stawinski GV. One hundred days or more bridged on a ventricular assist device and effects on outcomes following heart transplantation. *Eur J Cardiothorac Surg* 2008;**34**:295–300	Less than 80% of included devices
222	Russo MJ, Hong KN, Davies RR, Chen JM, Sorabella RA, Ascheim DD, *et al*. Posttransplant survival is not diminished in heart transplant recipients bridged with implantable left ventricular assist devices. *J Thorac Cardiovasc Surg* 2009;**138**:1425–32	Less than 80% of included devices

Reference number	Reference	Reason for exclusion
223	Saeed D, Kidambi T, Shalli S, Lapin B, Malaisrie SC, Lee R, *et al*. Tricuspid valve repair with left ventricular assist device implantation: is it warranted? *J Heart Lung Transplant* 2011;**30**:530–5	Less than 80% of included devices
224	Saito S, Matsumiya G, Sakaguchi T, Miyagawa S, Yoshikawa Y, Yamauchi T, *et al*. Risk factor analysis of long-term support with left ventricular assist system. *Circulation* 2010;**74**:715–22	Less than 80% of included devices
225	Saito S, Sakaguchi T, Sawa Y. Clinical report of long-term support with dual Jarvik 2000 biventricular assist device. *J Heart Lung Transplant* 2011;**30**:845–7	Commentary
226	Sandner SE, Zimpfer D, Zrunek P, Dunkler D, Schima H, Rajek A, *et al*. Renal function after implantation of continuous versus pulsatile flow left ventricular assist devices. *J Heart Lung Transplant* 2008;**27**:469–73	Less than 80% of included devices
227	Santambrogio L, Bianchi T, Fuardo M, Gazzoli F, Veronesi R, Braschi A, *et al.* Right ventricular failure after left ventricular assist device insertion: preoperative risk factors. *Interactive Cardiovasc Thorac Surg* 2006;**5**: 379–82	VADs unclear
228	Sasaki H, Mitchell JD, Jessen ME, Lavingia B, Kaiser PA, Comeaux A, *et al.* Bridge to heart transplantation with left ventricular assist device versus inotropic agents in status 1 patients. *J Cardiac Surg* 2009;**24**: 756–62	VADs unclear
229	Schenk S, McCarthy PM, Blackstone EH, Feng J, Starling RC, Navia JL, *et al*. Duration of inotropic support after left ventricular assist device implantation: risk factors and impact on outcome. *J Thorac Cardiovasc Surg* 2006;**131**:447–54	Concerns non-included VADs
230	Schmid C, Welp H, Klotz S, Baba HA, Wilhelm MJ, Scheld HH. Outcome of patients surviving to heart transplantation after being mechanically bridged for more than 100 days. *J Heart Lung Transplant* 2003;**22**:1054–8	Less than 80% of included devices
231	Schroder JN, Daneshmand MA, Villamizar NR, Petersen RP, Blue LJ, Welsby IJ, *et al*. Heparin-induced thrombocytopenia in left ventricular assist device bridge-to-transplant patients. *Ann Thorac Surg* 2007; **84**:841–5	VADs unclear
232	Schulman AR, Martens TP, Russo MJ, Christos PJ, Gordon RJ, Lowy FD, *et al*. Effect of left ventricular assist device infection on post-transplant outcomes. *J Heart Lung Transplant* 2009;**28**:237–42	Less than 80% of included devices
233	Schweiger M, Stepanenko A, Vierecke J, Drews T, Potapov E, Hetzer R, *et al*. Preexisting mitral valve prosthesis in patients undergoing left ventricular assist device implantation. *Artific Organ* 2012;**36**:49–53	Case study had fewer than 30 participants
234	Sharples LD, Cafferty F, Demitis N, Freeman C, Dyer M, Banner N, *et al*. Evaluation of the clinical effectiveness of the Ventricular Assist Device Program in the United Kingdom (EVAD UK). *J Heart Lung Transplant* 2007;**26**:9–15	Fewer than 50 participants in included VADs group(s)
235	Sharples LD, Dyer M, Cafferty F, Demiris N, Freeman C, Banner NR, *et al*. Cost-effectiveness of ventricular assist device use in the United Kingdom: results from the evaluation of ventricular assist device programme in the UK (EVAD-UK). *J Heart Lung Transplant* 2006;**25**:1336–43	Cost effectiveness paper
236	Shoham S, Shaffer R, Sweet L, Cooke R, Donegan N, Boyce S. Candidemia in patients with ventricular assist devices. *Clin Infect Dis* 2007;**44**:e9–12	Less than 80% of included devices
237	Shuhaiber J, Hur K, Gibbons R. Does the type of ventricular assisted device influence survival, infection, and rejection rates following heart transplantation? *J Cardiac Surg* 2009;**24**:250–5	Concerns non-included VADs

Reference number	Reference	Reason for exclusion
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239	Siegenthaler MP, Brehm K, Strecker T, Hanke T, Notzold A, Olschewski M, *et al*. The Impella Recover microaxial left ventricular assist device reduces mortality for postcardiotomy failure: a three-center experience. *J Thorac Cardiovasc Surg* 2004;**127**:812–22	Concerns non-included VADs
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242	Singh M, Shullo M, Kormos RL, Lockard K, Zomak R, Simon MA, *et al*. Impact of renal function before mechanical circulatory support on posttransplant renal outcomes. *Ann Thorac Surg* 2011;**91**:1348–54	Less than 80% of included devices
243	Slaughter MS, Aaronson KD, Boyce S, Miller LW, McGee EC, Cotts WG, *et al*. HVAD BTT pivotal trial and Continued Access Program (ADVANCE): Interim report of the expanded study. *J Heart Lung Transplant* 2011;**30**(Suppl. 1):S84–5	Abstract
244	Slaughter MS. Implantation of the HeartWare left ventricular assist device. *Semin Thorac Cardiovasc Surg* 2011;**23**:245–7	Non-systematic review
245	Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, *et al*. Clinical management of continuous flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant* 2010;**29**:S1–39	Ineligible for heart transplant
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248	Sridhar ARM, Mizrahi I, Najjar SS, Hanny-Gilbert C, Shoham S. Epidemiological and microbiological features of ventricular assist device associated infections. *Journal of Cardiac Failure.Conference: 14th Annual Scientific Meeting Heart Failure Society of America San Diego, CA United States* 2010;**16**(Suppl. 1):S115	Abstract
249	Stahl MA, Richards NM. CE Update on ventricular assist device technology. *AACN Adv Crit Care* 2009;**20**:26–36	Non-systematic review
250	Stehlik J, Nelson DM, Kfoury AG, Reid BB, Clayson SE, Nelson KE, *et al*. Outcome of noncardiac surgery in patients with ventricular assist devices. *Am J Cardiol* 2009;**103**:709–12	Concerns non-included VADs
251	Stepanenko A, Krabatsch T, Hennig E, Kaufmann F, Jurmann B, Dranishnikov N, *et al*. Retrospective hemolysis comparison between patients with centrifugal biventricular assist and left ventricular assist devices. *ASAIO J* 2011;**57**:382–7	Fewer than 50 participants in included VADs group(s)
252	Stepanenko A, Potapov EV, Jurmann B, Lehmkuhl HB, Dandel M, Siniawski H, *et al*. Outcomes of elective versus emergent permanent mechanical circulatory support in the elderly: a single-center experience. *J Heart Lung Transplant* 2010;**29**:61–5	Case study had fewer than 30 participants
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Reference number	Reference	Reason for exclusion
254	Stern DR, Kazam J, Edwards P, Maybaum S, Bello RA, D'Alessandro DA, *et al*. Increased incidence of gastrointestinal bleeding following implantation of the HeartMate II LVAD. *J Cardiac Surg* 2010;**25**:352–6	Fewer than 50 participants in included VADs group(s)
255	Stewart GC, Brooks K, Pratibhu PP, Tsang SW, Semigran MJ, Smith CM, *et al.* Thresholds of physical activity and life expectancy for patients considering destination ventricular assist devices. *J Heart Lung Transplant* 2009;**28**:863–9	VADs unclear
256	Stone ML, LaPar DJ, Benrashid E, Mulloy DP, Ailawadi G, Kron IL, *et al*. The impact of ventricular assist devices on blood product utilization for cardiac transplantation. *Circulation Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States* 2011; **124**(Suppl. 1)	Abstract
257	Strueber M, Meyer A, Malehsa D, Goerler A, Simon A, Haverich A, *et al*. Implantation of rotary blood pumps into 100 patients: A single centre experience. *Interactive Cardiovasc Thorac Surg* 2009;**9**:S98	Abstract
258	Thompson K, Dhesi P, Nguyen D, Czer L, Moriguchi J, Schwarz E. Evaluation of the HeartMate IITM left ventricular assist device in obese heart failure patients: effects on weight loss. *Ann Transplant* 2011;**16**:63–7	Ineligible for heart transplant
259	Thunberg CA, Gaitan BD, Arabia FA, Cole DJ, Grigore AM. Ventricular assist devices today and tomorrow. *J Cardiothorac Vasc Anesthesia* 2010;**24**:656–80	Non-systematic review
260	Timms D. A review of clinical ventricular assist devices. *Med Engin Phys* 2011;**33**:1041–7	Non-systematic review
261	Toda K, Fujita T, Kobayashi J, Shimahara Y, Kitamura S, Seguchi O, *et al*. Impact of preoperative percutaneous cardiopulmonary support on outcome following left ventricular assist device implantation. *Circulation* 2012;**76**:88–95	Less than 80% of included devices
262	Topkara VK, Kondareddy S, Wan IW, Mann DL, Ewald GA, Moazami N. Changing trends in mechanical circulatory assistance: A single center experience. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A18	Poster
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265	Topkara VK, Kondareddy S, Malik F, Wang IW, Mann DL, Ewald GA, *et al*. Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous flow era. *Ann Thorac Surg* 2010;**90**:1270–7	Less than 80% of included devices
266	Tsukui H, Abla A, Teuteberg JJ, McNamara DM, Mathier MA, Cadaret LM, *et al.* Cerebrovascular accidents in patients with a ventricular assist device. *J Thorac Cardiovasc Surg* 2007;**134**:114–23	Fewer than 50 participants in included VADs group(s)
267	Tsukui H, Teuteberg JJ, Murali S, McNamara DM, Buchanan JR, Winowich S, *et al*. Biventricular assist device utilization for patients with morbid congestive heart failure: a justifiable strategy. *Circulation* 2005;**112**(Suppl. 9)	VADs unclear
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Reference number	Reference	Reason for exclusion
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270	Vierecke J, Schweiger M, Stepanenko A, Dranishnikow N, Stein J, Drews T, *et al*. Evaluation of scores used to predict right ventricular failure after Ivad implantation. *Heart Surg Forum* 2011;**14**:S97	Abstract
271	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	Less than 80% of included devices
272	Vitali E, Lanfranconi M, Bruschi G, Russo C, Colombo T, Ribera E. Left ventricular assist devices as bridge to heart transplantation: The Niguarda Experience. *J Cardiac Surg* 2003;**18**:107–13	Fewer than 50 participants in included VADs group(s)
273	Vrtovec B, Radovancevic R, Delgado RM, Radovancevic B, Bracey AW, Gregoric ID, *et al*. Significance of anaemia in patients with advanced heart failure receiving long-term mechanical circulatory support. *Eur J Heart Fail* 2009;**11**:1000–4	Fewer than 50 participants in included VADs group(s)
274	Wang IW, Guthrie T, Ewald GA, Geltman EM, Joseph S, Moazami N. Gastrointestinal bleeding complications in continuous flow LVAD patients – Is it device specific? *J Heart Lung Transplant* 2010; **29**(Suppl. 1):S8	Abstract
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277	Welp H, Rukosujew A, Tjan TD, Hoffmeier A, Kosek V, Scheld HH, *et al*. Effect of pulsatile and non-pulsatile left ventricular assist devices on the renin-angiotensin system in patients with end-stage heart failure. *Thorac Cardiovasc Surg* 2010;**58**(Suppl. 8)	Fewer than 50 participants in included VADs group(s)
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279	Williams ML, Trivedi JR, McCants KC, Prabhu SD, Birks EJ, Oliver L, *et al*. Heart transplant vs left ventricular assist device in heart transplant-eligible patients. *Ann Thorac Surg* 2011;**91**:1330–3	Cost effectiveness paper
280	Wolner E, Wieselthaler G. Vienna exprience with ventricular assist devices. *Heart Surg Forum* 2010;**13**:S29	Abstract
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282	Yang N, Deutsch S, Paterson EG, Manning KB. Comparative study of continuous and pulsatile left ventricular assist devices on hemodynamics of a pediatric end-to-side anastomotic graft. *Cardiovasc Engin Technol* 2010;**1**:88–103	Pediatric
283	Zahr F, Ootaki Y, Starling RC, Smedira NG, Yamani M, Thuita L, *et al*. Preoperative risk factors for mortality after biventricular assist device implantation. *J Cardiac Fail* 2008;**14**:844–9	Concerns non-included VADs

Reference number	Reference	Reason for exclusion
284	Zierer A, Melby SJ, Voelle, RK, Guthrie TJ, Ewald GA, Shelton K, *et al*. Late-onset driveline infections: the Achilles' heel of prolonged left ventricular assist device support. *Ann Thorac Surg* 2007;**84**:515–20	Concerns non-included VADs
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286	Zimpfer D, Wieselthaler G, Czerny M, Fakin R, Haider D, Zrunek P, *et al*. Neurocognitive function in patients with ventricular assist devices: a comparison of pulsatile and continuous blood flow devices. *ASAIO J* 2006;**52**:24–7	Fewer than 50 participants in included VADs group(s)
287	Zimpfer D, Zrunek P, Roethy W, Czerny M, Schima H, Huber L, *et al*. Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. *J Thorac Cardiovasc Surg* 2007;**133**: 689–95	Fewer than 50 participants in included VADs group(s)
288	Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. *J Am Coll Cardiol* 2005;**45**:1428–34	VADs unclear

Appendix 6 Eligibility criteria for registration for heart transplant

The National Protocol for Assessment of Cardiothoracic patients lists below the medical indications for patients eligible for a HT.

- End-stage heart disease with a life expectancy of between 12 to 18 months.
- NYHA classification III or IV HF.
- Refractory to medical therapy, including if necessary cardiac resynchronisation therapy. This assessment should be made by a cardiologist with a special interest in heart failure.
- Usually < 60 years of age as there is an increase in comorbidity with the ageing process. Outcome is less satisfactory; however, consider biologically fit older patients.

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