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Appendices

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The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation

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Appendix 1

Devices used as LVADs and expert advisory group assessment of the devices that should be included in the systematic review and economic evaluation of the clinical and cost effectiveness of LVADs for ESHF

Device	Experts responses						Devices Included	Reasons stated for exclusion
	1	2	3	4	5	6		
AB-180 iVAD (implantable)	✓	✓	×	×	×	×	✔	No longer available
Abiomed BVS 5000	✓	✓	✓	×	×	×	✔	
Arrow LionHeart VAD	✓	×	✓	✓	×	×	✔	Not used in UK
AxiPump (Nimbus/Pittsburgh)	×	×	×	×	×	×	X	
Berlin Heart	✓	✓	✓	×	×	×	✔	
Berlin Incor I	✓	×	✓	×	×	×	✔	Not used in UK
Biomedicus pump (BP-80)	✓	✓	×	×	×	×	×	Temporary use for rescue
Cora valveless pulsatile pump	✓	×	×	×	×	×	×	Not used in UK
CorAide Heart Assist device	×	×	×	×	×	×	×	Experimental only
DeltaStream	×	×	×	×	×	×	×	
Gyro pump (PI)	×	×	×	×	×	×	×	Experimental only
Heart Quest VAD	×	×	×	×	×	×	×	
HeartMate II	✓	×	×	×	×	×	×	Experimental only
HeartMate III	✓	×	×	×	×	×	×	Experimental only
HeartMate IP (implanted pneumatic LVAS)	✓	✓	✓	×	×	✓	✔	
HeartMate VE (vented electric LVAS)	✓	✓	✓	✓	×	✓	✔	
Heartquest	×	×	✓	×	×	×	×	
Hemopump	×	×	×	×	×	×	×	No longer available
Impella,	✓	✓	×	×	×	×	×	Temporary – not implantable
Jarvik 2000	✓	✓	✓	✓	×	✓	✔	
Medos HIA-VAD	×	×	✓	×	×	×	×	Limited use
MicroMed DeBakey VAD (Baylor/NASA)	✓	×	✓	✓	✓	×	✔	
Nippon-Zeon	✓	×	✓	×	×	×	✔	Not used in UK
Novacor (Novacor Medical Corporation/Baxter Healthcare, Oakland, CA, USA)	✓	✓	✓	✓	×	✓	✔	
Novacor II	✓	✓	×	×	×	×	×	Experimental only
Pierce-Donachy paediatric VAD (Thoratec Laboratories Corp., Berkeley, CA, USA)	×	×	×	×	×	×	×	Children only
Rotodynamic pump	×	×	×	×	×	×	×	
Sun Medical/ Waseda/Pittsburgh								
Evaheart	×	×	×	×	×	×	×	Experimental only
TandemHeart pVAD	×	×	×	×	×	×	×	Temporary use only
Terumo DuraHeart	×	×	✓	×	×	×	×	
Thoratec (implantable VAD, IVAD)	✓	✓	✓	×	×	×	✔	
Toyobo	×	×	✓	×	×	×	✔	
Ventrassist	×	×	×	×	×	×	×	Experimental only
VERSUS (LV recovery support system)	×	×	×	×	×	×	×	Temporary device only
World Heart HeartSaver VAD	×	×	×	×	×	×	×	Experimental only

Appendix 2

Original research protocol

Research method for systematic review

Research question

- To undertake a systematic review of the clinical and cost-effectiveness of LVADs as a BTT, BTR and potential long-term alternative to heart transplantation for people with ESHF.

The systematic review will examine several issues:

- To consider the number of people who could benefit from LVADs, the costs and the possible demand on the NHS. The study will identify the different groups of people who may benefit from the use of LVADs.
- If the systematic review shows that there are no appropriate good-quality economic evaluations of LVADs for ESHF, an economic model relevant to the UK setting will be developed.

Planned inclusion/exclusion criteria

Interventions

- LVADs currently available and used as a BTT, BTR and potential long-term alternative to heart transplantation for people with ESHF.
- Although the systematic review will assess studies on the clinical effectiveness of currently available LVADs, the economic evaluation will focus on those LVADs that are considered clinically effective and/or considered relevant to the UK setting.
- LVADs no longer available or used, TAHs, BiVADs, RVADs and other blood pumps will be excluded from the review. Studies using LVADs for any condition other than left ventricular support will be excluded from the review. Studies of LVADs used in conjunction with other interventions where it is impossible to separate out the effects of the different interventions on outcomes will be excluded from the review.

Patients

- People (aged >16 years) with ESHF and considered suitable for receipt of an LVAD as BTT, BTR and potential long-term alternative to heart transplantation.
- Patients supported during the perioperative period or as an emergency rescue strategy during an operation will be excluded from the review.

Study designs

- Systematic reviews, RCTs, CCTs, cohort studies, case series, case studies, economic evaluations and cost studies.
- An emphasis will be placed on studies including an appropriate comparator group, such as people receiving an LVAD with those undergoing heart transplantation, those receiving usual care whilst on the transplantation waiting list or with people receiving a different LVAD. However, owing to the apparent scarcity of the evidence, natural history studies may be sought, as these may provide useful evidence of effectiveness in situations where outcomes are poor and predictable without treatment.
- All relevant economic evaluations and cost studies will be considered.

Outcome measures

- Patient outcomes, including survival, functional capacity (e.g. NYHA functional classification, activities of daily living) and QoL, will be the primary outcome measures.
- Other outcomes will include other measures of cardiac function, haemodynamic function, end organ function, device-related complications, length of stay, exercise capacity and reoperation.
- Primary outcome measures will be used for judgements regarding the inclusion or exclusion of studies. However, primary and secondary outcomes will be extracted from the included studies and analysed in the systematic review and economic evaluation.

Search strategy

1. Literature will be identified from a range of sources, including electronic databases, bibliographies of articles, grey literature sources, manufacturers of LVADs and experts in the field.
2. Electronic databases will be searched for:
   (a) *Journal articles and reviews*: Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effectiveness (DARE); Cochrane Controlled Trials Register (CCTR); Health Technology Assessment Database (HTA); NHS Economic Evaluation Database (NHS EED);

MEDLINE; PubMed (previous 6 months): EMBASE; Science Citation Index (SCI); BIOSIS; Inside Information Plus.
(b) *Conference proceedings and meeting abstracts*: NLM (National Library of Medicine) Gateway Databases; Conference Proceedings Index; PapersFirst.
(c) *Other grey literature and books*: HMIC (Health Management Information Consortium): Index to Theses; Dissertation Abstracts; WorldCat; British Library Public Catalogue; COPAC.
(d) *Research in progress*: National Research Register (NRR); Current Controlled Trials; Clinical Trials.gov.

3. Databases will be searched for published and unpublished studies from their inception to current date (unless stated otherwise), and the search will be restricted to studies with English language abstracts. Bibliographies of relevant papers will be checked for additional studies.
4. Manufacturers and experts associated with LVADs, and also Safety and Efficacy Register of New Interventional Procedures (SERNIP) and Medical Devices Agency (MDA) (now the Medicines and Healthcare products Regulatory Authority, MHRA), will be contacted to identify additional published and unpublished references.
5. In addition to searching the Cochrane Library, contact will be made with the Cochrane Heart Disease Group.

Quality criteria

- Included studies will be assessed using recognised quality assessment scales and/or checklists.
- Systematic reviews will be assessed using criteria developed by NHS CRD (University of York) (see Appendix 10).[176] Experimental and non-experimental studies will be assessed using modified versions of recognised criteria (see Appendix 11).[77,177]
- Economic evaluations will be assessed using standard reporting methods based on Nuijten and colleagues[178] and Drummond and colleagues[79,116] for internal validity, an adapted method for external validity of economic evaluations and model bias (Appendix 9).

Statistical analysis

- Studies will be synthesised using a narrative approach through subgroup analysis based on the indication for treatment, type of LVAD and quality of studies. If appropriate, a meta-analysis will be undertaken. This will be judged in relation to the a priori quality and inclusion criteria, in addition to effects of heterogeneity.

Application of review methods

- Inclusion criteria will be applied independently by two reviewers, with any disagreements resolved by independent assessment by a third reviewer.
- Data extraction will be undertaken independently by two reviewers using a standard data extraction table, with any disagreements resolved by independent assessment by a third reviewer.
- Quality criteria will be applied independently by two reviewers, with any disagreements resolved by independent assessment by a third reviewer.

Research methods for economic evaluation

Approach to economic evaluation

The study will undertake an economic evaluation through a decision analytic approach to establish the cost-effectiveness for the technology on an individual patient level, and the implication of changes in service provision on NHS resources (budget impact/service delivery) at either the Primary Care Trust, Strategic Health Authority or NHS level. A rigorous and systematically constructed set of models based on the available published and unpublished data will aim to inform policy decision-making and/or further research needs. The underlying assumptions and robustness of the models will be examined through sensitivity and threshold analyses.

First, a series of cost-effectiveness analyses for each subgroup of patients will be performed with scenario analysis to look at different implementation policies. Incremental cost-effectiveness will be generated for LVAD patients compared with heart transplant patients, heart transplant waiting list patients receiving best supportive care (BSC), and patients not suitable for a heart transplant but who may benefit from an LVAD and BSC. These analyses will require: the natural history and epidemiology of ESHF; the clinical pathways for the different patient groups to be clarified and the different treatment options to be outlined (i.e. heart transplant, LVAD, usual care on waiting list or BSC); the possible outcomes (survival or death) and the benefits of treatment (e.g. patients' QoL); and the resources and costs required to manage the care of the patients. Information for the analysis will originate from searches of the literature, patient data from the principal treatment centres, clinical experts and manufacturers of devices. The outcomes from the

economic evaluation will be: either cost per life-year saved, QALY or quality-adjusted time without symptoms and toxicity (Q-TWIST) (depending on the quality and quantity of data available); the costs (monetary and strategic); and benefits to the NHS of developing a service for different groups of people with ESHF. The models' underlying assumptions will be assessed through sensitivity analyses and threshold analysis will be used to identify the costs of an LVAD device at which reasonable cost-effectiveness levels could be achieved.

Second, a resource model will be specified to look at financial and resource consequences for the NHS. We will develop a population-based model to look at the total additional costs, the additional resources required to develop the service and the benefits of different levels of implementation from the current situation of limited provision through to the maximum feasible (including all eligible waiting list/BSC patients). Other options may be assessed, such as limitation to specific patient groups (e.g. severity of condition, patients on heart transplant waiting list) or by limitation to particular capacity limits. For this we would need the population size, expected incidence of people with ESHF, numbers on waiting list under different levels of implementation, number of heart transplants (constant), heart transplantation waiting list mortality rates and post-heart transplantation mortality rates. Any expansion in the number of LVAD operations carried out will naturally necessitate additional NHS costs to be borne, such as wider displacement amongst NHS centres requiring additional hospital support facilities and training of skilled personnel. As such, the model will look at possible constraints on developing a service, such as surgeon availability, training, availability of operating and care facilities, new buildings, machinery and any geographical issues.

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. All resource use data will be in monetary terms using UK unit costs. Costs will be presented in a base year and discounting of costs and benefits will be performed.

Types and sources of information for economic evaluation

Epidemiology of ESHF

Information on the epidemiology of ESHF will provide the opportunity to assess the incidence and prevalence of the condition (needs and demands for the service), the natural history of the condition and the characteristics of people who may benefit from the different forms of treatment available. Indicators may include: personal characteristics (e.g. age, sex, postcode), clinical factors (e.g. aetiology of disease and disease duration), haemodynamic factors (e.g. left and right ventricular fraction, pulmonary artery wedge pressure, pulmonary vascular resistance, stroke work index), functional capacity (NYHA functional classification, VO_2max, distance covered during 6-minute walk), neurohumoral factors (e.g. plasma norepinephrine), hepatic function, arrhythmias and co-morbidities. Searches of published and unpublished studies will provide much of the information for developing a model of the epidemiology of ESHF. In addition, we will seek patient information from Department of Cardiac Surgery at the John Radcliffe Hospital (Oxford) and from UK Transplant.

Effectiveness of treatment

The economic model will use efficacy data extracted from the studies included in the systematic review of clinical effectiveness. Outcomes will be extracted for patients receiving LVADs and for the comparators of heart transplantation and waiting list/BSC. The primary end-point for the economic evaluation will be patient survival defined in terms of mean/median life-years. In addition, the economic evaluation will use information on functional capacity and QoL to assess benefits of treatment. Where available, outcomes will be analysed for different subgroups such as the indication for treatment, the type of LVAD used and the severity of the patient condition to allow assessment of the most appropriate treatment for the different patient groups.

Quality of life

We will attempt to calculate a cost per QALY for each distinct group of LVAD patients and waiting list patients on BSC. For such cost–utility analysis, we will need to estimate utility values for patients at each arm of the decision tree. Ideally utilities for the various stages of QoL and duration spent in each stage (pre- and post-treatment and based on a Q-TWIST-type method[179] will be obtained for each patient group from patient-based estimates in the published literature. Searches will be undertaken to identify QoL studies for people with ESHF undergoing the different types of treatment. Initial searches have shown the information on QoL to be limited. To obtain a range of estimates and to validate the data from

the literature, we will investigate other sources. In addition, searches will try to identify whether any attempt has been made to map measures of functional status, such as the NYHA values, with utility weights. If not, we will explore whether it is possible to make some broad estimates of cost–utility using published UK population norms from the EQ-5D.[180] Information from the literature will be supplemented, where thought necessary, with patient-, clinician- and/or expert-based estimates of utility. Patient perception data using the MLHFQ has been routinely collected for patients undergoing treatment with LVADs by the Department of Cardiac Surgery at the John Radcliffe Hospital, Oxford. The nature and quality of the data will be assessed and, if adequate, will be used to inform the economic evaluation. If the data proves unsuitable for inclusion, the possibility of obtaining a sample of patient- and/or clinician-based estimates from one or more of the principal centres that provide treatment with LVADs in England and Wales will be explored. The data will be collected using either a questionnaire developed for this study or a previous instrument, such as SF-36, customised so as to be suitable for this investigation. In addition, it is hoped that another project to be undertaken by the University of Exeter assessing the use of an 'expert lay panel' to provide utility weights for different healthcare scenarios will provide some additional information. Where patient-based data are to be collected and/or used in the study, relevant ethics committee approval will be sought.

Cost measurement

Costs will be identified from published sources and supplemented by contact with NHS trust finance departments at the principal centres implanting LVADs (especially John Radcliffe Hospital, Oxford). Costs can be divided into a number of categories: materials; operational or implantation procedures; maintenance; hospitalisation. Material costs include the costs of the LVAD devices. Up-to-date costs of these, including discounts available, will be obtained from manufacturers and NHS trust finance departments. We will investigate whether LVADs can be reused taking into account the feasibility of sterilisation and concerns about new variant Creutzfeldt–Jakob disease (nvCJD). Immunosupressant drugs may be required to facilitate the ease of adjustment to the transplant and LVAD. Waiting list/BSC patients will also require numerous drugs (beta-blockers, ACE inhibitors, diuretics) and may require oxygen at home. All drug costs will be obtained from the BNF online. Cost of heart transplantation will be obtained from NHS reference costs. Other procedural costs will include the costs of implantation and removal of the LVAD, cost of the combined removal of LVAD/heart transplant (which if carried out simultaneously may differ from the sum of these operations) and administration costs of drugs. NHS trust finance departments will be approached for these data in order to obtain reliable estimates if the data have not been published. Hospitalisation will incorporate length of inpatient/outpatient attendance for implantation, side-effects, infection, complications, drugs, maintenance of the LVAD device and routine check-ups. Inpatient days and outpatient visits costs will also be obtained from NHS trust finance departments. In addition, patients may also require home visits by GPs or district nurses. These costs will be obtained from published data.[156] For simplification, costs of side-effects (e.g. haemorrhage, thromboembolism, infections) will be aggregated depending on their likelihood.

Measurement of resource use

Measurement of resource use will require the patients' clinical and treatment pathways for the different treatment options to be clarified. Searches of literature and advice from experts will provide the evidence to construct the appropriate scenarios. In addition, we will approach NHS trusts for access to patient administration data for information on inpatient days, outpatient visits, drug usage and other key variables for different treatment groups. Where applicable, survival analysis or the DEALE method[181] will be used to estimate prospective resource use over patients' lives. Likewise, UK Transplant will be approached for data on waiting list patients. Where patient-based data are to be collected and/or used in the study, relevant ethics committee approval will be sought.

Appendix 3

Sources of information, including databases searched and search terms

Searches for clinical and cost-effectiveness of LVADs

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

MEDLINE (1980–August 2003) and Cochrane Library – all sections (2003, Issue 3):
((vad or vads) and (heart or cardiac)) or (lvas* or lvad*) or ((ventric* near3 assist*) and (left or heart or cardiac)) or (ventric* near3 support system*) or ((assist* near device*) near (ventric* or heart or cardiac)) or ('Heart-Assist-Devices' / all subheadings in MIME,MJME)

EMBASE (1980–August 2003):
'heart-assist-device'/all subheadings) or ((vad or vads) and (heart or cardiac)) or (lvas* or lvad*) or ((ventric* near3 assist*) and (left or heart or cardiac)) or (ventric* near3 support system*) or ((assist* near device*) near (ventric* or heart or cardiac))

PubMED (9 June 2003–9 September 2003):
lvad OR lvas OR vad OR (ventricular AND assist) OR (assist AND device*)

Science Citation Index (2002–September 2003):
((lvad* OR lvas OR vad OR vads) same (heart or cardiac)) OR (ventricular same assist* same device*)

BIOSIS (2002–September 2003):
LVAD* or left ventricular assist device* – restricted to meeting abstracts only

CINAHL (1982–September 2003):
('Heart-Assist-Devices'/all topical subheadings/all age subheadings in DE) or ((assist near3 device*) with ((heart or cardiac) in ti,ab,de)) or (ventric* near3 ((assist or device*) in ti,ab,de)) or (lvad or (lvas in ti,ab,de)) or (((vad or vads) and (heart or cardiac)) in ti,ab,de)

PsycINFO (1984–April 2002, week 4):
lvad* or (left ventricular assist device*) or lvas or (left ventricular assist system*)

British Nursing Index (February 2002 edition):
ventricular assist device* or lvad or ((vad or vads) and (heart or cardiac))

Web of Science Proceedings (1990–September 2003):
((lvad* OR lvas OR vad OR vads) and (heart or cardiac)) OR (ventricular same assist* same device*)

Health Management Information Consortium (July 2003 edition):
ventricular assist device* or lvad or ((vad or vads) and (heart or cardiac))

National Research Register (Issue 3, 2003):
(HEART-ASSIST-DEVICES*:ME) or ((vad or vads) and (heart or cardiac)) or (lvas or lvad*) or ((ventric* near assist*) and (left or heart or cardiac)) or (ventric* near support) or ((assist* near device*) and (ventric* or heart or cardiac))

NLM Gateway (15 September 2003):
LVAD OR ventricular assist device*

Current Controlled Trials and Clinical Trials.gov (both searched 15 September 2003):
LVAD or left ventricular assist device or HEART-ASSIST-DEVICES

Conference Papers Index, PapersFirst, Proceedings, Inside Information Plus (all searched up to May 2002):
LVAD or left ventricular assist

Index to Theses UK, Dissertation Abstracts, Zetoc Conference Search (all searched up to September 2003):
LVAD or left ventricular assist

Searches for epidemiology of heart failure

MEDLINE (1996 to September 2003):
((explode 'Heart-Failure-Congestive'/epidemiology in MIME,MJME) and (English in la)) or ((heart failure near epidemiology) and (English in la))

EMBASE (1996 to September 2003):
(((explode 'heart-failure' / epidemiology) in dem) and (LA=ENGLISH)) or (((heart failure near epidemiology) in ti,ab) and (LA=ENGLISH)

Searches for QoL for ESHF

MEDLINE (1996–September 2003):
1. exp Heart Failure, Congestive/
2. quality of life.mp. or exp Quality of Life/
3. 1 and 2
4. (heart failure adj10 (quality adj3 life)).mp
5. 3 or 4
6. exp Quality of Life/
7. 1 and 6
8. (heart failure adj3 (quality adj life)).mp.
9. 7 or 8

Science and Social Sciences Citation Indexes (1996–September 2003):
(heart failure same (quality same life))

Additional searching

Bibliographies of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Industry submissions.

Manufacturers of the devices were requested to submit any studies meeting the inclusion criteria for study.

Websites of FDA, Novacor, HeartMate, Jarvik, Texas Heart Institute, MedQuest.

Flowcharts

Flowcharts of identification of studies are shown in *Figures 8* and *9*.

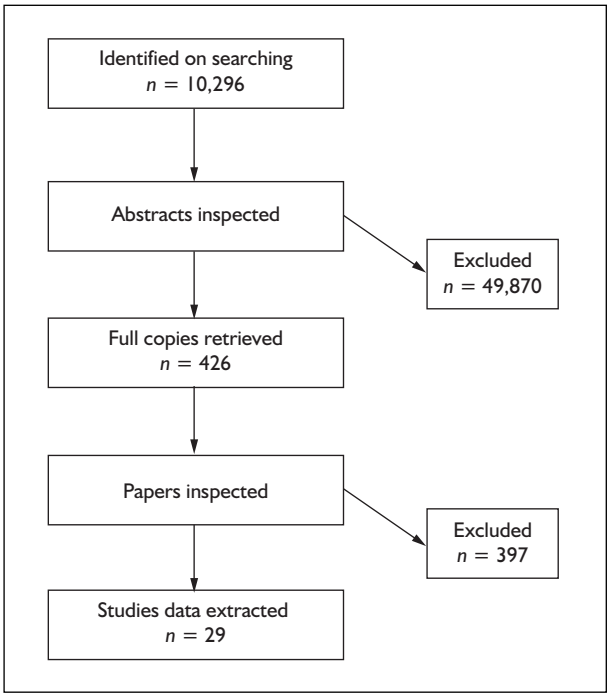

FIGURE 8 *Flowchart of identification of studies for clinical effectiveness systematic review*

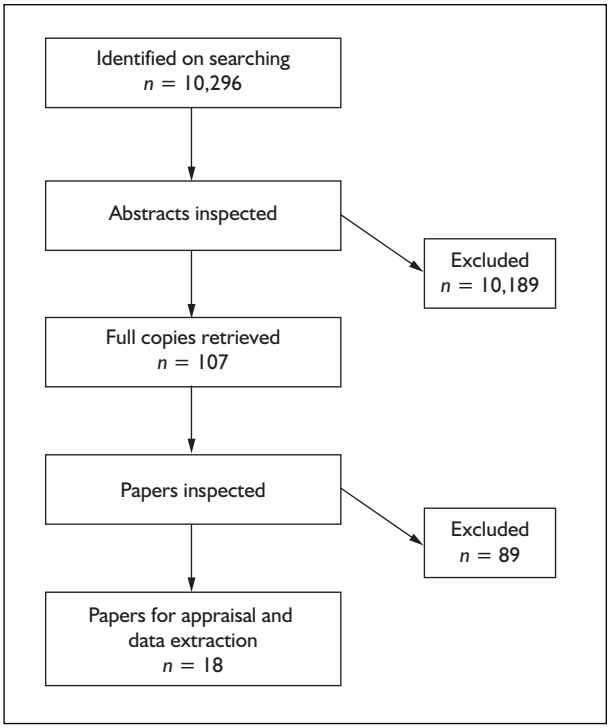

FIGURE 9 *Flow chart of identification and inclusion of economic evaluation and costing studies*

Appendix 4

List of manufacturers of LVADs included in the study and response to invitation to submit information

Manufacturer	Devices	Response
CardiacAssist, Inc. 240 Alpha Drive, Pittsburgh, PA 15238, USA http://www.cardiacassist.com/	AB-180 iVAD (implantable)	No submission
ABIOMED, Inc. 22 Cherry Hill Drive, Danvers, MA 01923, USA http://www.abiomed.com/	Abiomed BVS 5000	No submission
Arrow International Inc. 2400 Bernville Road, Reading, PA 19605, USA http://www.arrowintl.com/	Arrow LionHeart VAD	No submission
Berlin Heart AG Wiesenweg 10, 12247 Berlin, Germany http://www.berlinheart.com/	Berlin Heart Berlin Incor I	No submission
Thoratec Corporation 6035 Stoneridge Drive, Pleasanton, CA 94588, USA http://www.thoratec.com/	HeartMate IP LVAS HeartMate VE LVAS Thoratec IVAD	Cost data on device
Jarvik Heart, Inc. 333 West 52nd Street New York, NY 10019, USA http://www.jarvikheart.com/	Jarvik 2000	Studies of clinical effectiveness and cost data on device
MicroMed Technology, Inc. 8965 Interchange Drive, Houston, TX 77054, USA http://micromedtech.com/	MicroMed DeBakey VAD	Data on clinical effectiveness, cost-effectiveness and costs provided
Zeon Corporation Furukawa Sogo Bldg, 2-6-1 Marunouchi, Chiyoda-ku, Tokyo 100-8323, Japan http://www.zeon.co.jp/	Nippon-Zeon	No submission
World Heart, Inc. 7799 Pardee Lane, Oakland, CA 94621, USA http://www.worldheart.com/	Novacor	Data on clinical effectiveness, cost-effectiveness and costs provided.
Toyobo Co., Ltd 2–8, Dojima Hama 2-chome, Kita-ku, Osaka 530-8230, Japan http://www.toyobo.co.jp/	Toyobo	Studies of clinical effectiveness provided

Appendix 5

List of studies meeting the general inclusion criteria for the systematic review of clinical effectiveness of LVADs for people with ESHF that were excluded from the assessment as they were judged to be too low on the hierarchy of evidence

DeBakey

Agati S, Bruschi G, Russo C, Colombo T, Lanfranconi M, Vitali E. First successful Italian clinical experience with DeBakey VAD. *J Heart Lung Transplant* 2001;**20**:914–7.

Wieselthaler GM, Schima H, Lassnigg A, Pacher R, Ovsenk T, Laufer G, *et al*. Die DeBakey VAD-Axialpumpe: erste klinische Erfahrungen mit einer neuen Generation von implantierbaren, nonpulsatilen Blutpumpen als Langzeit-Uberbruckung bis zur Transplantation. [The DeBakey VAD axial flow pump: first clinical experience with a new generation of implantable, nonpulsatile blood pumps for long-term support prior to transplantation]. *Wien Klin Wochenschr* 1999;**111**:629–35.

Wieselthaler GM, Schima H, Lassnigg AM, Dworschak M, Pacher R, Grimm M, *et al*. Lessons learned from the first clinical implants of the DeBakey ventricular assist device axial pump: a single center report. *Ann Thorac Surg* 2001;**71**:S139–S143.

HeartMate

Catanese KA, Goldstein DJ, Williams DL, Foray AT, Illick CD, Gardocki MT, *et al*. Outpatient left ventricular assist device support: a destination rather than a bridge. *Ann Thorac Surg* 1996;**62**:646–52.

Davies JE, Winokur TS, Aaron MF, Benza RL, Foley BA, Holman WL. Cardiomyopathy in a carrier of Duchenne's muscular dystrophy. *J Heart Lung Transplant* 2001;**20**:781–4.

Frazier OH. First use of an untethered, vented electric left ventricular assist device for long-term support. *Circulation* 1994;**89**:2908–14.

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

Frazier OH, Duncan JM, Radovancevic B, Vega JD, Baldwin RT, Burnett CM, *et al*. Successful bridge to heart transplantation with a new left ventricular assist device. *J Heart Lung Transplant* 1992;**11**:530–7.

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Appendix 7

Data extraction form for systematic reviews

Reviewer:	**Date:**	**Version:**
Reference	**Methods**	
Study Ref: Author: Year: Country: Study design: Study setting: Funding:	Aim/Objective: Search strategy: databases searched Inclusion criteria. *Interventions:* *Participants:* *Outcome measures:* *Study design:* Quality criteria: Application of methods: Methods for analysis	
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 comments • Generalisability • Funding		

Appendix 8

Data extraction form for primary studies

Reviewer:		**Date:**	**Version:**
Reference and design	**Intervention**	**Participants**	**Outcome measures**
Study Ref.: Author: Year: Country: Study design: Study setting: Number of centres: Funding:	Indication for treatment: Comparisons of different interventions: Duration of treatment: Other interventions used:	Number of participants: Sample attrition/dropout: Inclusion/exclusion criteria for study entry: Characteristics of participants:	Primary outcomes: Secondary outcomes: Method of assessing outcomes: Length of follow-up:

Results **Outcomes**	**LVAD**	**Comparator**	***p*-Value**
Survival Comments			
Functional Capacity Comments			
QoL Comments			
Function Comments			
Adverse Effects Comments			
Resource Use Comments			

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups:
- Blinding:
- Comparability of treatment groups:
- Method of data analysis:
- Sample size/power calculation:
- Attrition/drop-out:

General comments
- Generalisability:
- Outcome measures:
- Inter-centre variability:
- Conflict of interests:

Appendix 9

Data extraction and quality assessment of economic evaluations and costing studies

	Study
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 • Healthcare system	
• Model description • Data sources (efficacy, resource use, costs, appropriately measured, all costs included?) • Data collection (primary data collection, if appropriate) • Probabilities • Healthcare use • Data analysis • Sensitivity analysis (allowance made for uncertainty) • Discounting (costs/benefits?)	
Results (incremental analysis of costs and consequences?) Conclusion Assessment	

Appendix 10

Quality assessment scales for systematic reviews[176]

Systematic reviews will be examined to determine how many of the following criteria for methodological quality they meet.

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?
A good review should focus on a well-defined question, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies.

The criteria should relate to the four components of study design, participants, healthcare intervention or organisation and outcomes of interest.

In addition, details should be reported relating to the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of handsearching, attempts to identify unpublished material and any contact with authors, industry and research institutes should be provided.

The appropriateness of the database(s) searched by the authors should also be considered, for example if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?
Authors should have taken account of study design and quality, either by restricting inclusion criteria, or systematic assessment of study quality. For example, if inclusion criteria have been restricted to 'double-blind randomised controlled trials, with at least 200 participants' then the need for quality assessment is not as crucial as when authors have less stringent inclusion criteria and/or include less rigorous study designs.

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g. method of randomisation, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), efficacious results and side-effects (adverse events).

5. Are the primary studies summarised appropriately?
The authors should attempt to synthesise the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews which incorporate a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual

evaluations should be weighted in some way (e.g. according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

For some reviews, it may be inappropriate to include a meta-analysis, and therefore a narrative synthesis of studies should be presented. It is not usual to include a formal assessment of heterogeneity or to introduce weighting in such syntheses, so a discussion relating to the main differences between studies, and better sources of evidence, should be highlighted.

Quality Assessment for Systematic Reviews (NHS CRD)

Question	Score
1. Are any inclusion/exclusion criteria reported relating 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

Appendix 11

Quality assessment for primary studies[77]

Quality Assessment for Primary Studies Reference:					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	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. Interrupted Time Series 7. Other – specify 8. Can't Tell				
2. Was the study described as randomised?	Yes	No			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't 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%	Can't 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	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell		

continued

Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell		
Global Rating for Study (Overall methodological strength of study – based on sections 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**		

Appendix 12

Summary of the evidence of clinical effectiveness of the HeartMate LVAD as a BTT for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 348 Author: El Banayosy *et al.*[80] Year: 2000 Country: Germany Study design: CTT Study setting: Inpatient/community Number of centres: 1 Funding: Supported by the German Association of Organ Recipients	Indication for treatment: BTT Comparisons of different interventions: 1. Novacor N100 system (19 Novacor, 1 Novocar plus Thoratec VAD) 2. HeartMate VE system (19 HeartMate, 1 HeartMate plus Medos RVAD) Duration of treatment (mean, SD): Novacor 235.3 days (SD 210) HeartMate 174.6 days (SD 175), $p = 0.4$ Other interventions used: No anticoagulants in first 24 h Therapy started with heparin according to activated clotting time (1.5× initial value) After chest drain removal, Novacor group received warfarin sodium (Coumadin) (dosage according to international normalised ration 2.5–3.5) 2 weeks after op, both groups received aspirin, 1 mg/kg body weight Home management programme, including daily control of body weight and international normalised ration self-test (Novacor) and twice-daily controls of temperature, blood pressure and pump output, and wound dressing changes according to protocol	Number of participants: Total: 40 Novacor: 20 HeartMate: 20 Sample attrition/dropout: Not stated, assume none Inclusion/exclusion criteria for study entry: Not explicitly reported. Patients requiring mechanical left ventricular support as a BTT. No further details Characteristics of participants: Novacor: 19 men, 1 woman Mean age 55.7 years (SD 11) HeartMate: 19 men, 1 woman Mean age 56.3 years (SD 11) Idiopathic cardiomyopathy: Novacor 13/20, HeartMate 9/20 Ischaemic cardiomyopathy: Novacor 6/20, HeartMate 10/20 Fulminant myocarditis: Novacor 1/20, HeartMate 0/20 Valvular heart disease: Novacor 0/20, HeartMate 1/20. p = ns Preoperative clinical blood chemistry (mean, SD): BUN (mg/dl): Novacor 82 (39), HeartMate 76 (37), $p = 0.7$ Creatinine (mg/d/l): Novacor 1.5 (0.6), HeartMate 1.6 (0.6), $p = 0.9$ Bilirubin (mg/dl): Novacor 2.0 (1.0), HeartMate 1.7 (1.1), $p = 0.3$ Aspartate aminotransferase (U/l): Novacor 34 (27), HeartMate 43 (69), $p = 0.7$ Alanine aminotransferase (U/l): Novacor 46 (62), HeartMate 91 (190), $p = 0.4$ γ-Glutamylcyclotransferase (U/l): Novacor 101 (79), HeartMate 67 (45), $p = 0.1$ Alkaline phosphatase (U/l): Novacor 187 (129), HeartMate 147 (61), $p = 0.3$	Primary and secondary outcomes: Heart transplant Death Complications during support Organ function during support Method of assessing outcomes: Bleeding complications = blood loss >1500 l/m^2 in 24 hr. Major neurological complications = neurological deficits proved and differentiated by computed tomographic scan Pocket infection = associated with local signs of infection with purulent secretions necessitating lavage drainage and positive bacterial cultures. Valved conduit endocarditis = signs of systemic infection despite adequate antibiotic therapy, increased central venous pressure, low pump output with a dilated left ventricle, abnormal Doppler echocardiographic image above the inflow cannula Septic complication = body temperature >38.5 °C, white blood cell count >12,000 g/dl, high output states, low systemic vascular resistance and positive blood cultures

continued

Reference and design	Intervention	Participants	Outcome measures
	Weaning from ECMO with 2 positive inoptropic agents (dopamine, phosphodiesterase III inhibitors). 6 Novacor and 5 HeartMate required 3 inotropic agents for support of right side of heart. 1 Novacor and 1 HeartMate additional RVAD due to failure of right side of heart Heart transplant when reached NYHA Class I without organ failure, except those with infection and major technical problems	Lipase (U/l): Novacor 123 (80), HeartMate 155 (79), $p = 0.2$ Amylase (U/l): Novacor 28 (38), HeartMate 23 (21), $p = 0.7$ White blood cells (g/l): Novacor 8.0 (5.4), HeartMate 7.4 (5.5), $p = 0.8$ Platelets: Novacor 203 (92), HeartMate 227 (127), $p = 0.6$ Preoperative haemodynamic variables (mean, SD): Cardiac index (l/minute/m^2): Novacor 2.1 (0.4), HeartMate 2.1 (0.4), $p = 0.9$ Mean pulmonary artery pressure (mmHg): Novacor 39 (7), HeartMate 38 (8), $p = 0.7$ Mean central venous pressure (mmHg): Novacor 13 (6), HeartMate 14 (7), $p = 0.9$ Peripheral vascular resistance (dyn/minute/cm^{-5}): Novacor 281 (138), HeartMate 229 (91), $p = 0.2$ Systemic vascular resistance (dyn/minute/cm^{-5}): Novacor 1187 (413), HeartMate 1018 (289), $p = 0.2$ Mean pulmonary capillary wedge pressure (mmHg): Novacor 24 (8), HeartMate 22 (9), $p = 0.5$ Preoperative risk factors: Inotropic support (at least 2 drugs): Novacor 20/20, HeartMate 20/20, $p = 1.0$ Intra-aortic balloon pump: Novcor 7/20, HeartMate 6/20, $p = 0.7$ Reoperation: Novacor 3/20, HeartMate 2/20, $p = 0.6$ Renal failure: Novacor 4/20, HeartMate 4/20, $p = 1.0$ Automatic implantable cardioverter–defibrillator: Novacor 2/20, HeartMate 1/20, $p = 0.5$	Failure of right side of heart = cardiac index <2.2 l/min/m^2 despite a central venous pressure of 18–22 mmHg and double-drug inotropic support in absence of high pulmonary vascular resistance Arrhythmic complications = haemodynamically relevant rhythm disorders necessitating electrotherapy Acute renal failure = necessity for renal replacement therapy (haemofiltration of dialysis). Duration post-implantation ventilatory support, intenstive care stay, hospital stay Data obtained daily from data sheets October 1996 to March 1998 Length of follow-up: Heart transplantation or death of patient

Results

Outcomes	Novacor	HeartMate	*p*-Value
Survived implant operation	20/20 (100%)	20/20 (100%)	
Received transplantation	13/20 (65%)	12/20 (60%)	
Comments: 3 Novacor group and 2 HeartMate group are awaiting transplantation			
Functional capacity	Not reported		
QoL	Not reported		
Comments:			

continued

Function: post-implantation haemodynamics	**Novacor**	**HeartMate**	***p*-Value**
Cardiac index (l/minute/m^2)	2.9 (SD 0.4)	3.0 (SD 0.6)	0.8
Mean pulmonary artery pressure (mmHg)	30 (SD 7)	28 (SD 5)	0.3
Mean central venous pressure (mmHg)	16 (SD 4)	15 (SD 3)	0.5
Peripheral vascular resistance (dyn/minute/cm^{-5})	249 (SD 72)	236 (SD 69)	0.6
Systemic vascular resistance (dyn/minute/cm^{-5})	795 (SD 255)	804 (SD 135)	0.9
Mean pulmonary capillary wedge pressure (mmHg)	11 (SD 4)	9 (SD 4)	0.1
Postoperative clinical blood chemistry:	**Novacor**	**HeartMate**	***p*-Value**
BUN (mg/dl)	Day 1: 74.4 (SD 30.3) Day 7: 65.6 (SD 45.4) Day 14: 42.0 (SD 24.6) Day 30: 43.8 (SD 41.4)	Day 1: 71.6 (SD 24.6) Day 7: 72.3 (SD 46.9) Day 14: 54.0 (SD 34.6) Day 30: 45.5 (SD 15.8)	0.3
Creatinine (mg/d/l)	Day 1: 1.6 (SD 0.7) Day 7: 1.1 (SD 0.5) Day 14: 0.9 (SD 0.4) Day 30: 1.0 (SD 0.4)	Day 1: 1.5 (SD 0.5) Day 7: 1.2 (SD 0.6) Day 14: 1.2 (SD 0.6) Day 30: 1.0 (SD 0.3)	0.1
Bilirubin (mg/dl)	Day 1: 3.0 (SD 1.6) Day 7: 4.5 (SD 4.6) Day 14: 3.9 (SD 3.8) Day 30: 3.2 (SD 5.2)	Day 1: 3.1 (SD 1.9) Day 7: 4.7 (SD 6.3) Day 14: 9.2 (SD 15.5) Day 30: 2.9 (SD 6.4)	0.8
Aspartate aminotransferase (U/l):	Day 1: 60.4 (SD 35.3) Day 7: 34.5 (SD 20.3) Day 14: 36.1 (SD 26.7) Day 30: 23.1 (SD 9.6)	Day 1: 62.1 (SD 59.2) Day 7: 34.5 (SD 20.3) Day 14: 31.9 (SD 23.1) Day 30: 24.4 (SD 26.2)	0.9
Alanine aminotransferase (U/l)	Day 1: 32.0 (SD 35.1) Day 7: 20.7 (SD 18.9) Day 14: 24.1 (SD 22.6) Day 30: 18.7 (SD 11.0)	Day 1: 46.1 (SD 73.2) Day 7: 18.7 (SD 14.3) Day 14: 29.6 (SD 27.5) Day 30: 21.9 (SD 27.0)	0.5
γ-Glutamylcyclotransferase (U/l)	Day 1: 35.8 (SD 23.7) Day 7: 143.4 (SD 123.2) Day 14: 141.7 (SD 112.7) Day 30: 105.0 (SD 79.0)	Day 1: 27.5 (SD 17.8) Day 7: 76.2 (SD 47.7) Day 14: 89.3 (SD 63.7) Day 30: 104.4 (SD 75.2)	0.5
Alkaline phosphatase (U/l)	Day 1: 99.7 (SD 17.8) Day 7: 262.2 (SD 173.4) Day 14: 275.3 (SD 139.3) Day 30: 281.8 (SD 148.8)	Day 1: 95.6 (SD 23.2) Day 7: 202.2 (SD 111.4) Day 14: 244.8 (SD 125.1) Day 30: 285.6 (SD 148.1)	0.8
Lipase (U/l)	Day 1: 154.5 (SD 89.2) Day 7: 212.0 (SD 128.1) Day 14: 213.2 (SD 157.6) Day 30: 277.1 (SD 112.0)	Day 1: 152.3 (SD 162.4) Day 7: 198.1 (SD 101.5) Day 14: 342.3 (SD 252.9) Day 30: 208.2 (SD 142.9)	0.4
Amylase (U/l)	Day 1: 30.7 (SD 31.2) Day 7: 31.7 (SD 16.1) Day 14: 24.0 (SD 15.1) Day 30: 35.9 (SD 19.5)	Day 1: 27.9 (SD 28.5) Day 7: 22.7 (SD 15.2) Day 14: 37.7 (SD 26.6) Day 30: 22.9 (SD 12.9)	0.8
White blood cells (gm/l)	Day 1: 7.9 (SD 6.4) Day 7: 9.8 (SD 6.4) Day 14: 14.6 (SD 14.0) Day 30: 7.1 (SD 2.5)	Day 1: 6.7 (SD 6.0) Day 7: 7.8 (SD 5.8) Day 14: 9.4 (SD 5.8) Day 30: 5.3 (SD 1.9)	0.9
Platelets	Day 1: 115.9 (SD 64.6) Day 7: 137.8 (SD 64.1) Day 14: 273.0 (SD 134.8) Day 30: 357.9 (SD 176.7)	Day 1: 124.4 (SD 47.1) Day 7: 134.1 (SD 68.5) Day 14: 261.4 (SD 169.4) Day 30: 255.5 (SD 116.6)	0.9
Comments:			

continued

Discharge from hospital to home with device in place	15/20 (75%)	14/20 (70%)	
Duration of out-of-hospital support	241 days (SD 179, range 20–642)	166 days (SD 152, range 11–616)	0.14
Comments:			

Adverse effects	**Novacor**	**HeartMate**	***p*-Value**
Death while on LVAD support	4/20 (20%) Multiorgan failure/sepsis: 3 Thromboembolism: 1	6/20 (30%) Multiorgan failure/sepsis: 5 Cerebral bleeding: 1	
Neurological complications precluding home care	0/20	1/20	
Readmission to hospital due to complications in out-of-hospital patients	10/15	9/14	
Causes of readmission (events/patient/month, 95% CI): several causes by patient possible			
Neurological	5 (0.042, 0.006 to 0.078)	1 (0.013, –0.012 to 0.038)	0.4
Driveline infection	2 (0.017, –0.006 to 0.04)	1 (0.013, –0.012 to 0.038)	1.0
Pocket infection	2 (0.017, –0.006 to 0.4) (NB decimal point omitted from 0.4 in paper)	5 (0.065, 0.01 to 0.12)	0.1
Technical	1 (0.008, –0.008 to 0.024)	3 (0.039, –0.004 to 0.082)	0.3
Gastrointestinal tract	1 (0.008, –0.008 to 0.024)	–(0.013, –0.012 to 0.082) (as reported in paper)	
Miscellaneous	1 (0.008, –0.008 to 0.024)	1 (as reported in paper)	
Comments: 1 Novacor patient moved to a rehabilitation centre due to neurological complications			
Neurological complications and device related infections: (events/patient/month, 95% CI):			
Thromboembolic event	4 (20%) (0.026, 0.001 to 0.051) (on days 14 to 67, mean 29 days)	0	0.1
Cerebral bleeding (resulted from a decompensated coagulation because of a septic attack)	1 (5%) (0.006, –0.006 to 0.018)	1 (5%) (0.009, –0.008 to 0.026)	1.0
Transient ischaemic attack	7 (35%) (0.045, 0.012 to 0.078)	1 (5%) (0.009, –0.008 to 0.026)	0.1
Driveline infection	4 (0.026, 0.01 to 0.051)	9 (0.078, 0.029 to 0.127)	0.09
Pocket infection	2 (0.013, –0.005 to 0.031)	5 (0.044, 0.006 to 0.082)	0.1
Conduit endocarditis	1 (0.006, –0.006 to 0.018)	2 (0.017, –0.007 to 0.041)	0.6
Device-related infections (days 30–111, mean 58 days)	4 (20%) (0.025, 0.001 to 0.051)	11 (55%) (0.096, 0.042 to 0.15)	0.02
Controller exchange (technical)	2 (0.013, –0.005 to 0.031)	14 (0.122, 0.062 to 0.182)	<0.001
Driveline crack	3 (0.019, –0.003 to 0.041)	2 (0.017, –0.007 to 0.041)	0.6
Pump failure	0	4 (0.035, 0.001 to 0.069)	0.3
Other complications during support			
Bleeding	8 (40%) (2 late bleeding after aspirin medication)	7 (35%) (1 late bleeding after aspirin medication)	0.7
Blood loss (ml)	5245 (SD 2220)	2340 (SD 2245)	0.01
Reoperation bleeding	6 (30%)	4 (20%)	0.5
Right heart failure necessitating right VAD support	1	1	

continued

Adverse Effects	**Novacor**	**HeartMate**	***p*-Value**
Right heart failure with medical treatment	4	2	0.4
Gastrointestinal tract (mesenteric ischaemia, cholesystectomy, pancreatitis, ileus)	2	2	
Sepsis/multiple organ failure	3	5	0.4
Arrhythmia	1	1	
Systemic infection	4 (20%)	9 (45%)	0.1
Completely free from of complications	4	2	
Comments:			
Resource use			
Median postoperative ventilatory support time	2 days (25th and 75th percentiles 1.5 and 3.2)	2.5 days (25th and 75th percentiles 1.5 and 4.0)	ns
Mean intensive care unit stay	16.7 days (SD 15.5)	12.2 days (SD 8.7)	0.3
Mean duration of total hospitalisation	55.6 days (SD 30.7)	58.6 days (SD 30.1)	0.8
Return to work	5/20	2/20	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Patients alternatively received Novacor LVAS or HeartMate VE LVAS
- Blinding: Not stated, assume none
- Comparability of treatment groups: No statistically significant differences in preoperative laboratory parameters, haemodynamic data and preoperative risk factors
- Method of data analysis: Mean and SD presented. χ^2 for cause of heart failure and preoperative risk factors, unpaired *t*-test for preoperative clinical blood chemistry values and preoperative and postoperative haemodynamic variables, general linear model for repeated measures for postoperative clinical blood chemistry values and Fisher exact test for causes for readmission of out-of hospital patients. Causes of readmission – linearised rates of complications calculated as the number of complications per month in a given time frame
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not stated, assume none

General comments

- Generalisability: Men aged in their 50s requiring BTT
- Outcome measures: Short-term measures only (to death or transplant)
- Inter-centre variability: Not applicable, single centre
- Conflict of interests: Not reported

BUN, blood urea nitrogen; ECMO, extracorporeal membrane oxygenation; op, operation.

Quality Assessment for Primary Studies[77]
Study: El Banayosy *et al*.[80]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No x			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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 ×	Can't 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%	Can't tell	N/A
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	Can't tell ×		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell		Assume none
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ×	60–79%	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong ×	Moderate	Weak		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell ×	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell ×		

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 6658 Author: Aaronson *et al.*[82] Year: 2002 Country: USA Study design: Cohort analytic Study setting: Inpatient/community Number of centres: 1 Funding: Not reported	Indication for treatment: bridge to transplant Comparisons of different interventions: 1. HeartMate IP or VE LVAD 2. Intravenous inotropes 3. Post-transplant survival experiences of patients who underwent UNOS status 2 also compared (separate group) Baseline characteristics for pre-transplant only (see results) Duration of treatment: mean time for both groups 4.6 months (SD 5.1) median time 2.9 months both groups Other interventions used: not reported	Number of participants: 104: LVAD 66 (48 received transplant), inotrope 38 (28 received transplant), UNOS status 2 group $n = 60$ Sample attrition/dropout: retrospective, follow-up complete for all patients Inclusion/exclusion criteria for study entry: LVAD group (implantable only) – patients who had inotropes and then required LVAD therapy. Inotrope group – patients with continuous infusion of one or more inotropes in hospital or at home ($n = 4$) with UNOS (united network for organ sharing) class 1, 1A or 1B waiting-list status. ≥ 17 years Characteristics of participants: (no significant differences unless stated) LVAD group – mean age 49 years (SD 13), 51 (77%) male, 15 (23%) female, 39 (59%) ischaemic aetiology (versus non-ischaemic) Inotrope group – mean age 49 years (SD15), 27 (71%) male, 17 (45%) ischaemic aetiology Haemodynamic data (mean ± SD): Mean heart rate (beats/minute): LVAD 88 (20), inotrope 90 (19) Mean arterial pressure (mmHg): LVAD 73 (12), inotrope 76 (8) Right arterial pressure (NB 'atrial' in text, assume arterial) (mm/Hg): LVAD 12 (6), inotrope 13 (7) Mean pulmonary artery pressure (mmHg): LVAD 32 (9), inotrope 34 (9) Pulmonary capillary wedge pressure (mmHg): LVAD 23 (7), inotrope 24 (7) Cardiac index (l/minute/m^2): LVAD 2.0 (0.6), inotrope 2.6 (0.9), $p < 0.05$ Pulmonary vascular resistance (Woods unit): LVAD 2.4 (1.4), inotrope 2.3 (1.0) At time of LVAD, 15 (23%) patients were supported with ECMO or an extracorporeal VAD; 20 (30%) were supported with 2 or more inotropes, with or without a vasosupressor; 12 (18%) were supported with a single inotrope; 14 (21%) were supported with intra-aortic balloon pump, with or without inotropic support; 5 (8%) received anti-arrythmic agents only, without inotropic support for severe life-threatening ventricular arrythmias Inotrope group, 10 (26%) patients were UNOS status 1A, 14 (37%) status 1B and 14 (37%) status 1. 19 (50%) patients were supported with high-dose inotropes (dopamine or dobutamine	Primary and secondary outcomes: survival: survival to transplantation, post-transplant survival, overall survival Method of assessing outcomes: record review from 1 April 1996 to 10 May 2001 Length of follow-up: up to 4 years

continued

Reference and design	Intervention	Participants	Outcome measures
		≥ 7.5μg/kg/minute, or milrinone ≥ 0.5μg/kg/minute, or multiple inotropes with dopamine or dobutamine ≥ 5μg/kg/minute and milrinone ≥ 0.25μg/kg/minute, or any dose of an inotrope in combination with norepinephrine or neosynephrine). 19 (50%) were supported with low-dose inotropes. 2 (5%) patients were placed on ECMO, 3 (8%) on balloon pump 24–48 h before death or transplantation. These 5 did not receive LVAD because of technical issues or complications contraindicating transplantation. 22/38 (58%) controls were potential candidates for LVAD but determined to be clinically stable on inotropes. 16 (42%) were at high risk or ineligible for LVAD (small body area 7, congenital heart disease 5, hypertrophic cardiomyopathy 1, ascending aortic aneurysm 1, post-infarct ventricular septal defect 1, mechanical aortic prosthesis and previous mediastinitis with sternal wound closure by a rectus muscle transposition flap 1) Survival to transplant not significantly different between patients in the inotrope group who were potentially eligible for LVAD therapy and those ineligible owing to high risk factors	

Results

Outcomes (± SD unless stated)	LVAD group	Inotrope group	*p*-Value
Survival to transplant	48/66 (73%)	28/38 (74%)	
6 (9%) LVAD patients still on waiting list			
Actuarial survival to transplant	1 month: 81% (SD 5) 3 months: 81% (SD 5) Median: 2.9 months	1 month: 78% (SD 8) 3 months 64% (SD 11) Median: 2.9 months	0.2

Subgroup analysis of inotrope group: survival to transplant was not significantly different between patients in the inotrope group who were potentially eligible for LVAD and those ineligible. LVAD eligible (n = 22) vs LVAD ineligible (n = 16), p = 0.52.

Patient and donor characteristics at transplant	LVAD (n = 48)	Control (n = 28)	UNOS status 2 (n = 60)	
Recipient age at transplant (mean years)	46 (SD 13)	49 (SD 15)	52 (SD 13)	LVAD vs UNOS 2, <0.05
Donor age (mean years)	33 (SD 13)	28 (SD 12)	37 (SD 14)	Control vs UNOS 2, <0.05
Male No. (%)	35 (73%)	19 (68%)	39 (65%)	
Female No. (%)	13 (27%)	9 (32%)	21 (35%)	
Ischaemic No. (%)	24 (50%)	11 (39%)	36 (60%)	
Non-ischaemic No. (%)	24 (50%)	17 (61%)	24 (40%)	

continued

Outcomes (± SD unless stated)	LVAD group	Inotrope group		*p*-Value
Recipient weight (kg) (mean)	77 (SD 13)	74 (SD 17)	77 (SD 17)	
Donor weight (kg) (mean)	79 (SD 16)	83 (SD 16)	77 (SD 16)	
Recipient height (cm) (mean)	172 (SD 10)	172 (SD 8)	170 (SD 10)	
Donor height (cm) (mean)	172 (SD 10)	177 (SD 8)	170 (SD 10)	Control vs UNOS 2, <0.05
Total length of stay (days) (mean)	59 (SD 57)	55 (SD 60)	23 (SD 22)	Control and LVAD vs UNOS 2, <0.05
Post-transplant length of stay (days) (mean)	20 (SD 16)	16 (SD 9)	17 (SD 11)	
Allograft ischaemic time (minutes) (mean)	184 (SD 38)	184 (SD 44)	188 (SD 41)	
Time to transplant (months) (mean)	4.6 (SD 5.1), median 2.9	7.2 (SD 7.9), median 2.9	0.3 (SD 7.6), median 9.6	LVAD vs UNOS 2, <0.05
Function	LVAD (n = 48)	Controls (n = 28)		
Serum creatinine at transplant (mg/dl) (mean)	0.99 (0.34)	1.48 (0.59)		<0.05
Total bilirubin at transplant (mg/dl) (mean)	0.75 (0.39)	0.98 (0.47)		<0.05
No. alive post-transplantation	0 days: 48 30 days: 47 1 year: 31 3 years: 9	0 days: 28 30 days: 24 1 year: 17 3 years: 6		
Post-transplantation actuarial survival	1 year: 98% (SD 2) 3 years: 95% (SD 4) 4 years: 95% (SD 4)	1 year: 74% (SD 9) 3 years: 65% (SD 10) 4 years: 65% (SD 10)		0.007
Lower death rate with LVADs in first year, after which survival experiences for both groups were similar				
Comments: Survival post-transplant in those eligible for LVAD was superior, but not significantly, to survival in those ineligible for LVAD [from figure: 4-year survival LVAD eligible (n = 22) vs LVAD ineligible (n = 16): 50% vs 82%, 0.18].				
Post-transplant actuarial survival versus UNOS 2 group		**UNOS status 2:** 1 year: 86% (SD 4) 3 years: 77% (SD 7) 4 years: 77% (SD 7)		vs LVAD, 0.1
Overall actuarial survival	1 year: 80% (SD 5) 3 years: 77% (SD 6) 4 years: 77% (SD 6)	1 year: 56% (SD 8) 3 years: 44% (SD 9) 4 years: 44% (SD 9)		0.03
Functional capacity	Not reported			
Comments				
QoL	Not reported			
Comments				
Adverse effects	No adverse events for survivors noted but cause of death reported			
Pre-transplant mortality, cause of death	All events = 12/66 (18%) Cerebrovascular accident 1 Device failure 1 Haemorrhage 1 Multisystem organ failure/sepsis 5 Right-sided circulatory failure 4 All occurred by 19 days after LVAD implant	All events = 10/38 (26%) Cerebrovascular accident 1 Multisystem organ failure/ sepsis 4 Sudden death 2 Refractory cardiogenic shock 3		

continued

Outcomes (± SD unless stated)	LVAD group	Inotrope group	*p*-Value
Post-transplant mortality, cause of death	All events = 2/48 (4%) Cerebrovascular accident 1 Rejection (acute) 1	All events = 9/28 (32%) Cerebrovascular accident 1 Infection 3 Haemorrhage 1 Primary allograft dysfunction 1 Rejection (acute) 3	0.045
Comments			
Resource use	Length of stay, see above		
Comments			

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: retrospective review of cases. Unclear how patients were selected
- Blinding: not reported
- Comparability of treatment groups: No significant differences between LVAD and control in age, gender, aetiology of heart failure, heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure or pulmonary vascular resistance. Cardiac index significantly greater in inotrope group than LVAD ($p < 0.05$). 16/38 controls not eligible for LVADs. Serum creatinine and total bilirubin significantly lower in LVAD than inotrope group at time of transplant. Post-transplant data also compared with third group who underwent UNOS status 2 transplant – significant differences in recipient age, waiting time and length of stay compared with LVAD, and in donor age, donor height and length of stay compared with inotrope control group
- Method of data analysis: Mean and standard deviation or median reported. Actuarial survival calculated by Kaplan–Meier method. For survival to transplantation, survival time censored at time of transplantation. Survival time comparisons made using log-rank test. Number of deaths compared using two-tailed Fisher exact test. Comparison of mean values performed using analysis of variance and independent *t*-test with Bonferonni correction for multiple comparisons. Statistical significance defined at $p < 0.05$. Patients who began therapy with i.v. inotrope but later required LVAD were analysed in the LVAD group (onset of bridging support taken as time of implantation)
- Sample size/power calculation: No
- Attrition/drop-out: States that follow up complete for all patients

General comments

- Generalisability: Eligibility criteria not clear
- Outcome measures: Appropriate, method of assessing outcomes not reported, other than retrospective review. No data on adverse effects
- Inter-centre variability: Not applicable
- Conflict of interests: Not reported

Quality Assessment for Primary Studies[77]

Study: Aaronson *et al.*[82]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't 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%	Can't 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	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell ×	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Clien ×
3. Are the statistical methods appropriate for the study design?	Yes ×	No	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No ×	Can't tell		

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 411 Author: Bank *et al.*[83] Year: 2000 Country: USA Study design: Cohort analytic Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTT Comparisons of different interventions: 1. HeartMate pneumatic LVAD. Patients deteriorated while on standard therapy (worsening and severe low output heart failure, refractory pulmonary oedema or oliguric renal failure) 2. No LVAD. i.v. inotropic agents dobutamine or milrinone with ACE inhibitors, diuretics and digoxin Duration of treatment: Mean time between listing as status 1 and implant 7.4 days (SD 1.6) Post-LVAD placed inactive on list for 4–6 weeks to allow recovery Other interventions used: aspirin or dipyridamole in LVAD patients. After implant, patients placed on inactive status for 4–6 weeks for recovery, including cardiac rehabilitation exercises. After transplantation, triple drug therapy of cyclosporin or tacrolimus, azathrioprin or mycophenolate mofetil and prednisone	Number of participants: 40 consecutive patients: LVAD 20, inotropes 20 Sample attrition/dropout: N/A Inclusion/exclusion criteria for study entry: Status 1 patients. All patients initially treated with inotropes (dobutamine or milrinone), ACE inhibitors, diuretics and digoxin. 20/26 of those who developed significant clinical deterioration were given LVAD. 6/26 did not get LVAD as severe right heart failure (1), history of several sternotomies (3), presence of prosthetic heart valves (1), congenital heart disease (1) Characteristics of participants: (mean ± SEM) Age: LVAD 49 (9) years, inotrope 48 (11), p = ns m/f: LVAD 15/5, inotrope 15/5, p = ns Body mass area (m^2): LVAD 1.97 (0.28), inotrope 1.89 (0.24) , p = ns Cause of heart failure (% ischaemic): LVAD 62%, inotrope 46%, p = ns LV EF: LVAD 17.2 (5.8)%, inotrope 19.0 (6.8)%, p = ns LV end-diastolic dimension (mm): LVAD 7.01 (1.38), inotrope 7.06 (1.24), p = ns LV systolic dimension: LVAD 6.36 (1.23), inotrope 5.90 (1.32), p = ns Mitral regurgitation score (1 = mild, 2 = moderate, 3 = severe): LVAD 1.8 (0.8), inotrope 1.8 (0.8), p = ns Heart rate (beats/minute): LVAD 103 (14), inotrope 88 (19), p = ns Systolic BP (mmHg): LVAD 97 (11), inotrope 98 (13), p = ns Diastolic BP (mmHg): LVAD 59 (12), inotrope 57 (12), p = ns Pulmonary artery systolic pressure (mmHg): LVAD 47 (12), inotrope 50 (15), p = ns Pulmonary artery diastolic pressure (mmHg): LVAD 26 (8), inotrope 25 (9), p = ns Cardiac index (l/minute/m^2): LVAD 2.3 (0.7), inotrope 2.0 (0.6), p = ns Haemoglobin (g/dl): LVAD 11.4 (1.9), inotrope 13.1 (1.8), $p < 0.01$ Sodium (mmol/l): LVAD 134 (3), inotrope 134 (8), p = ns BUN (mg/dl): LVAD 31 (27), inotrope 34 (24), p = ns Creatinine (mg/dl): LVAD 1.6 (1.0), inotrope 1.4 (0.6), p = ns Aspartate aminotransferase (U/l): LVAD 102 (118), inotrope 40 (23), $p < 0.05$ Alkaline phosphate (U/l): LVAD 103 (43), inotrope 111 (64), p = ns	Primary outcomes: Mortality, major morbidity, combined mortality and morbidity, within 6 months after heart transplant Costs Waiting for transplantation: Infection Stroke Mechanical device malfunction (problems with console/diaphragm unit, pump sensor system, or interconnect cable/battery unit) Operation Major complications after transplantation: Major complications [severe acute renal failure (requiring dialysis), severe right heart failure (moderate/severe on ECHO, requiring inotropes or RVAD), operation (for any cause), clinical cardiac rejection (biopsy grade III or more leading to heart failure or death), severe debility (need for inpatient cardiac rehabilitation), infection (clinical evidence, fever, rasied white cell count, positive cultures of blood or other fluid, e.g. pericardial, pleural, peritoneal fluid and requiring antibiotics), stroke (focal neurological deficit for 24 h)], Mechanical device malfunction (problems with console/diaphragm unit, pump sensor system or interconnect cable/battery unit)

continued

Reference and design	Intervention	Participants	Outcome measures
		Bilirubin (mg/dl): LVAD 1.7 (1.2), inotrope 1.1 (0.4), $p < 0.05$ RAP (not defined) (mmHg): LVAD 13 (5), inotrope 13 (8), p = ns PCWP (not defined) (mmHg): LVAD 25 (9), inotrope 24 (8), p = ns	Method of assessing outcomes: medical records reviewed, from January 1995 to September 1998, no further details Cost information on each patient obtained from hospital billing records Length of follow-up: 6 months after transplantation

Results

Outcomes	LVAD	Inotropes	*p*-Value
Survival 6 months post transplant (*n* = 18 LVAD, 19 inotrope)	88.9%	73.7%	ns
Survival to 6 months without major complications post-transplant	55.6% (source of number – numerator and denominator unclear: 10/18? But 11/18 had no complications post-transplant)	15.8%	<0.05
Comments			
Functional capacity	Not reported		
Comments			
QoL	Not reported		
Comments			
Function at transplant			
Heart rate (beats/minute)	87 (SE 16) $p < 0.01$ vs data at time of listing as status 1	86 (16)	ns
Systolic BP (mmHg)	130 (SE 15) $p < 0.01$ vs data at time of listing as status 1	103 (12) $p < 0.05$ vs data at time of listing as status 1	<0.001
Diastolic BP (mmHg)	72 (SE 12) $p < 0.01$ vs data at time of listing as status 1	60 (10)	<0.001
Haemoglobin (g/dl)	11.3 (SE 1.3)	11.4 (1.9) $p < 0.01$ vs data at time of listing as status 1	ns
Sodium (mmol/l)	141 (SE 3) $p < 0.01$ vs data at time of listing as status 1	137 (3)	<0.001
BUN (mg/dl)	16 (SE 5)	24 (11) $p < 0.05$ vs data at time of listing as status 1	<0.01
Creatinine (mg/dl)	1.0 (SE 0.1) $p < 0.05$ vs data at time of listing as status 1	1.3 (0.4)	<0.01

continued

Outcomes	LVAD	Inotropes	*p*-Value
Aspartate aminotransferase (U/l)	36 (SE 15) $p < 0.05$ vs data at time of listing as status 1	28 (14) $p < 0.05$ vs data at time of listing as status 1	ns
Alkaline phosphatase (U/l)	157 (SE134)	127 (72)	ns
Bilirubin (mg/dl)	0.6 (SE 0.2) $p < 0.05$ vs data at time of listing as status 1	0.8 (0.4) $p < 0.01$ vs data at time of listing as status 1	ns
Comments			
Additional support pre-transplant			
Balloon counterpulsation	9/20	4/20	0.05
Extracorporeal membrane transplantation	1/20	0/20	
Adverse effects pre-transplant (%)			
Death before transplant	1/20 (sepsis) (patient has previous heart transplant) 1/20 (ventricular fibrillation, 701 days after implant and 28 days after LVAD removal for severe pocket infection. Transplant could not be performed owing to persistently elevated plasma reactive antibody test and inability to find suitable donor heart)	1/20 (refractory ventricular tachycardia)	Not reported
None	8/20 (40%)	11/20 (55%)	
Acute renal failure	0	0	
Right heart failure	0	0	
Reoperation	1/20 (5)	0/20	Not reported
Mechanical device failure	4/20 (20) (broken console, loss of sensor function, torn inflow housing sutures, inflow valve dysfuction due to pannus growth)	N/A	
Infection	9/20 (45) (drive line 5, pneumonia 3, bacterial sepsis 1)	8/20 (40) (line sepsis 7, pneumonia 1)	Not reported
Stroke	1/20 (5)	0/20	Not reported
Comments			
Adverse effects post-transplant (%)	$n = 18$	$n = 19$	
None	11 (61.1)	3 (15.8)	
Acute renal failure	3 (16.7)	10 (52.6)	<0.05
Right heart failure	1 (5.6)	6 (31.6)	<0.05
Reoperation	3 (16.7)	7 (36.8)	ns
Rejection	1 (5.6)	3 (15.7)	ns
Disability	2 (11.1)	4 (21.0)	ns
Infection	3 (16.7)	8 (42.1)	ns
Stroke	1 (5.6)	1 (5.2)	ns
Death	2 (11.1)	5 (26.3)	ns
Comments: some patients had more than one complication			

continued

Outcomes	LVAD	Inotropes	*p*-Value
Resource use (mean ± SE)			
Hospital stay (days) pre-transplant	77 (42)	42 (30)	<0.01
Intensive care stay (days) pre-transplant	15 (11)	42 (30)	<0.01
Intensive care stay (days) post-transplant	7.8 (14.4)	6.4 (6.5)	
Total hospital days	100 (52)	57 (30)	<0.01

Comments – also provides details of charges (total and daily) in US$: total charges ($) LVAD, 342,620 (SE 104,420); control, 213,860 (SE 107, 560), $p < 0.01$

Average daily charges ($) LVAD, 4130 (SE 2050); control, 3990 (SE 1300), p = ns

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Retrospective review of cases, not randomised. LVAD placed after patient deteriorated on standard treatment
- Blinding: Not reported, no blinding
- Comparability of treatment groups: At baseline, LVAD patients had greater heart rate, bilirubin and aspartate aminotransferase and significantly lower haemoglobin
- Method of data analysis: Clinical and laboratory data analysed using unpaired *t*-tests at time of listing as status 1, time of heart transplant, 6 months after transplant. For improvement in heart failure, paired *t*-tests compared data at time of listing as status 1 with time of heart transplant. Data expressed as mean (standard error or mean). $p < 0.05$ considered significant
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not reported

General comments

- Generalisability: Patients in LVAD group worsening heart failure on inotropes
- Outcome measures: Appropriate, reviewed retrospectively from records
- Inter-centre variability: Not applicable
- Conflict of interests: None reported

BP, blood pressure.

Quality Assessment for Primary Studies[77]
Study: Bank *et al.*[83]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't 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%	Can't 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	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No ×	Can't tell		

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 6120 Author: Massad *et al.*[81] Year:1996 Country: USA Study Design: Cohort analytic Study setting: Inpatient/outpatient (5 HeartMate patients) Number of centres: 1 Funding: None reported	Indication for treatment: BTT Comparisons of different interventions: 1. Transplant following HeartMate LVAD 41/53 patients pneumatic HeartMate and 12/53 VE HeartMate 2. Transplant with no previous LVAD (a) UNOS status 1 (b) UNOS status 2 Duration of treatment: Median duration LVAD support 72 days (range 3–153) Other interventions used: aspirin 325 mg daily. Immunosuppression therapy post-transplant. Those with compromised renal function treated with OKT3 monoclonal antibody for induction followed by conversion to cyclosporin-based immunosuppression when improved. All except those CMV negative and who received a heart from a negative donor received 4 weeks of gancyclovir prophylaxis. CMV hyperimmune globulin also administered to CMV-negative patients receiving organ from CMV-negative donor Leucocyte-depleted blood administered in most cases	Number of participants: 256 patients, 53 bridged to transplant with LVAD, 203 patients without bridging Sample attrition/drop-out: LVAD implant attempted in 77 patients, results reported on 53 LVAD patients. No further details Inclusion/exclusion criteria for study entry: accepted for transplant: pulmonary capillary wedge pressure of ≥ 20 mmHg, together with a cardiac index of ≤ 2.0 l/mininute/m^2 or systolic BP of ≤ 80 mmHg despite maximal inotropic and intraaortic balloon pump support Excluded if ≤ 16 years or 2nd transplant (11 paediatric transplants, 5 adult second transplants) Characteristics of participants: Mean age (years) (range): LVAD 53 (34–66), median 53; non-LVAD 50 (17–66), median 53, p = ns m/f: LVAD 46/7 (87/13%); non-LVAD 155/48 (76/24%), p = ns Body weight (kg): LVAD 82; non-LVAD 73, p = 0.0005 Body surface area (m^2): LVAD 1.96; non-LVAD 1.86, p = 0.004 Diagnosis: LVAD 37 (70%) ischaemic cardiomyopathy (ICM), non-LVAD 91 (45%), p = 0.001 LVAD 16 (30%) non-ICM, non-LVAD 112 (55%), p = 0.001 Previous cardiac operations (%): LVAD 53 (100); non-LVAD 84 (42), p = 0.001 Blood group [A/AB/B/O (%)]: LVAD 16 (30)/2 (4)/8 (15)/27 (51); non-LVAD 97 (48)/14 (7)/23 (11)/69 (34), p = 0.06 UNOS status 1 (%): LVAD 53 (100); non-LVAD 126 (62), p = 0.001 Median waiting time (days): LVAD 88; non-LVAD 58, p = 0.07 Median time listed as UNOS status 1: LVAD 73; non-LVAD 37, p < 0.01 Median time listed UNOS 1: all LVAD 88; UNOS 1 controls 37, p = 0.02 Median time listed UNOS status 2: all LVAD 88; UNOS 2 controls 118, p = ns Median blood products (units) at transplantation: LVAD 17; non-LVAD 5, p = 0.0001 T-cell PRA >10%: LVAD 27/41 (66%); non-LVAD 25/169 (15%), p < 0.0001 CMV seropositivity (%): LVAD 40/48 (83); non-LVAD 140/203 (69), p = 0.04 Mean peak T-cell PRA level: LVAD 33%; non-LVAD 4%, p < 0.001	Primary outcomes: Survival, post-transplantation length of stay, reexploration for bleeding, 30-day operative mortality, post-transplant events at 1 year (CMV infection, vascular rejection, re-exploration, cellular rejection, moderate–severe rejection free, CAD free) Method of assessing outcomes: Vascular rejection rate (based on immunofluorescent staining criteria according to Hammond *et al.*[182] in addition to evidence of endothelial cell swelling and activation on light microscopy (at 1 month in all and continued in those with findings), moderate and severe rejection free (defined by criteria of Billingham *et al.*[183] and criteria of International Society for Heart and Lung Transplantation: grade 1A, 1B, 2 = mild rejection; 3A, 3B = moderate rejection; 4 = severe rejection), transplant CAD free (new arteriosclerosis in the cardiac allograft compared with baseline angiogram or intra-vascular ultrasound before discharge) Length of follow-up (after transplantation): Mean follow-up 22 months (17 months LVAD group, 23 months non-LVAD group, p = 0.01). 1992–96 Note: annual distribution of cardiac transplants and LVAD implants 1992–96 reported but not extracted

continued

Results

Outcomes	LVAD	Non-LVAD	*p*-Value
Transplant rate	80%	84%	ns
Survivors (%)	48/53 (91)	174/203 (86)	ns
Actuarial survival at 1 year (Kaplan–Meier)	94%	88% (all non-LVAD) UNOS 1: 91% UNOS 2: 86%	ns
36-month survival (Kaplan–Meier)	84.9%	UNOS 1: 85.8% UNOS 2: 82.5%	
Comments			
Functional Capacity	Not reported		
Comments			
QoL	Not reported		
Comments			
Function	Not reported		
Comments			
Adverse Effects			
30-day operative mortality (%)	2 (3.8)	9 (4.4)	ns
Re-exploration for bleeding (%)	3 (5.7)	9 (4.4)	ns
Septicaemia	Attempted BTT: 35/77 (45%) Successful BTT: 27/53 (51%)		
Septicaemia from device-related infection	Attempted BTT: 32/77 (42%) Successful BTT: 21/53 (40%)		
Survival to transplant: 77% (27/35) with septicaemia during support versus 84% (26/31) with no septicaemia during support, p = ns			
Abdominal complications necessitating operative intervention	Attempted BTT (n = 77) ~15%		
Severe device-related haemorrhage necessiting emergency operative intervention and multiple blood transfusions	(n = either 53 or 77, not specified) 8%		
Adverse events at 1 year			
CMV infection	10/53 (20%)	30/203 (17%)	Kaplan–Meier = ns
Vascular rejection rate	7/53 (15%)	28/203 (12%)	Kaplan–Meier = ns
Moderate and severe rejection free	12%	22%	ns
Transplant CAD free	90%	88%	ns
Mean No. of moderate and severe rejection episodes	At 12 weeks: 1.68 At 1 year: 2.53	At 12 weeks: 1.47 At 1 year: 1.99	ns
Comments			

continued

Outcomes	LVAD	Non-LVAD	*p*-Value
Resource use			
Post-transplant hospital stay (days)	Mean: 18 Median: 15	Mean: 18 Median: 15	ns

Comments
Subgroup analysis of those with less than or more than the median number of transfusions before transplant, not reported here

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Retrospective cases
- Blinding: Not reported
- Comparability of treatment groups: Control group did not require bridging with LVAD support, therefore not comparable. LVAD patients: greater mean body weight and body surface area, more ischaemic cardiomyopathy, more had previous cardiac operations, more were O blood group, more were UNOS status I at time of transplant (all LVAD, 62% inotrope), waiting list time was longer [88 days LVAD, 37 days UNOS I non-LVAD ($p = 0.002$), and 118 days UNOS II non-LVAD (p = ns)], more had anti-HLA antibodies (T-cell PRA level >10%) and mean peak T-cell PRA, and more blood products at transplantation than non-LVAD patients
- Method of data analysis: χ^2 test for demographic and clinical factors between patients, Wilcoxon rank-sum test for distributions of continuous factors, log-rank test for Kaplan–Meier survival estimates, actuarial curves for freedom from rejection and coronary artery disease. Similar actuarial curves used to compare freedoms from rejection and coronary artery disease. $p < 0.05$ considered significant
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not reported. BTT attempted in 77 patients, outcome successful and results reported for 53

General comments
- Generalisability: Cardiac transplant patients
- Outcome measures: Appropriate
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77] Study: Massad *et al.*[81]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't 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%	Can't 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	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No ×	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79% ×	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate ×	Weak		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell	N/A	
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell ×		

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 2304 Author: Frazier *et al.*[85] Year: 1992 Country: USA Study design: Cohort with historical control. Additional patients are being enrolled Study setting: Inpatient based Number of centres: 7 Funding: Not stated	Indication for treatment: BTT Comparisons of different interventions: 1. HeartMate 1000 IP (26 met study criteria, 8 did not meet selection criteria) 2. Historical control from transplant database, no LVAD but would have met selection criteria Duration of treatment: Total LVADs (n = 34) mean 53.2 days (range 1–233), 3 ongoing at time of study HeartMate + study criteria (n = 26): mean 65.8 days (SD 72, range 1–233), 3 patients remained on LVAD at time of study. Of those transplanted (n = 17): mean 87 days (SD 74, range 7–233) HeartMate + did not meet criteria (n = 8): mean 17.1 days (SD 29, range 1–84). Of those transplanted (n = 3): mean 42.6 days (SD 36, range 19–84) Other interventions used: Most patients: 80 mg asprin once/day, 75 mg dipyridamole 3 times/day Heparin or sodium warfarin only used during implantation and in patients with mechanical valves in native heart	Number of participants: 1. Total treated with HeartMate: n = 34 (all considered in overall evaluation of survival and device safety) Met study criteria: n = 26 (considered in analyses of haemodynamic, haematological, hepatic and renal response to pump) Of these, long-term survivors (>60 days): n = 15 (further comparison at 30 and 60 days of device support and at same time after transplantation) 2. Historical controls (n = 6) Sample attrition/dropout: Not stated, assume none. 3 patients still on LVADs at time of study Safety data reported on 28 patients completing study Inclusion criteria for study entry: Approved transplant candidates who met the haemodynamic indications for use: pulmonary capillary wedge pressure of ≥ 20 mmHg coupled with either a cardiac index of ≤ 2.0 l/minute/m^2 or a systolic BP of ≤ 80 mmHg. Exclusion criteria: included chronic, irreversible hepatic, renal and respiratory failure, severe blood dyscrasia and right heart failure Historical controls identified from transplant database, would have met criteria for LVAD but treatment not available Characteristics of participants: Total with HeartMate (n = 34): 33 male, 1 female. Mean age: 45.2 years (range 17–60). Diagnosis: ischaemic cardiomyopathy (10), idiopathic cardiomyopathy (16), viral cardiomyopathy (3), dilated cardiomyopathy (2), MI (3) HeatMate + study criteria (n = 26): 25 male, 1 female. Mean age: 43.7 years (SD 11, range 17–60). Diagnosis: ischaemic cardiomyopathy (8), idiopathic cardiomyopathy (12), viral cardiomyopathy (3), dilated cardiomyopathy (2), MI (1) HeartMate + did not meet criteria (n = 8): 8 male. Mean age: 50 years (SD 8, range 37–59). Diagnosis: idiopathic cardiomyopathy (4), ischaemic cardiomyopathy (2), MI (2) Historical controls (n = 6): 4 male, 2 female. Mean age: 40.5 years (SD 13, range 21–57). Diagnosis: ischaemic cardiomyopathy (4), idiopathic cardiomyopathy (1), postpartum cardiomyopathy (1)	Primary and secondary outcomes: Survival Device safety: Bleeding, haemolysis, infection, right heart failure, peripheral end-organ dysfunction, thromboembolism, mechanical failure. Haemodynamical response: cardiac index, pulmonary capillary wedge pressure, blood pressure Haematological response: haematocrit levels, plasma free haemoglobin levels, platelet counts Hepatic and renal function: Total bilirubin levels, serum glutamicoxaloacetic transaminase and serum glutamic pyruvic transaminase values, creatinine and BUN levels Hepatic and renal function in survivors at LVAD implantation, days 30 and 60 during support, immediately before transplantation, and days 30 and 60 after transplantation NYHA functional status assessed before support and 60 days after transplantation Method of assessing outcomes: Infection defined through detection of a positive culture, elevated white blood cell count, fever and need for antimicrobial treatment. Considered device-related of specific organism had not been detected preop Length of follow-up: Outcomes reported at 60 days

continued

Reference and design	Intervention	Participants	Outcome measures
		Controls at time of meeting study criteria vs LVAD ($n = 26$) at implantation [mean (SD)]: Pulmonary capillary wedge pressure 23 (2) vs 28 (8) mmHg, $p < 0.05$ Cardiac index 1.9 (0.8) vs 2.1 (0.6) l/minute/m^2, $p > 0.05$ Systolic BP 90 (19) vs 94 (19) mmHg, $p > 0.05$	Maximum follow-up: 324 days

Note: means and standard deviations for baseline characteristics calculated by reviewer.

Results

Outcomes	LVAD	Historical control	*p*-Value
Received transplant	Total with LVAD: 20/31[a] LVAD + study criteria: 17/23[a]	3/6	
Comments: [a]3 (all meeting study criteria) remained on LVAD support at time of study 3/6 controls died before transplant 11/34 LVAD (6/26 meeting criteria, 5/8 not meeting criteria) did not receive transplant (assume died before transplant, but not explicitly stated in paper)			
Survival >60 days	Total with LVAD: 16/31 LVAD + study criteria: 15/23	1/6	Survival rate of LVAD group greater than control, $p < 0.05$.
Comments: Survival in the 16 discharged LVAD patients ranges up to 3 years after transplant 4/20 LVAD who underwent transplantation died before 60 days (1 liver failure, 1 respiratory failure and adverse OKT3 reaction, 1 MOF and sepsis, 1 donor heart failure) 3 historical controls underwent transplant, all died, at days 2, 21 and 77 after operation			
Functional capacity (NYHA Functional Classification)			
LVAD implantation/time of meeting study criteria (for controls)	34/34 in Class IV	5/6 in Class IV 1/6 in Class III	
60 days after transplantation (surviving patients)	15/16 in Class I 1/16 in Class II	1/1 in Class IV	
Comments: Functional class was significantly improved during ventricular assistance and after transplantation. The functional class of the LVAD-treated patients was markedly improved when compared with that of control patients. Five control patients died			
Function			
Hemodynamic performance			
	Average pump index (pump flow/body surface area): 2.86 l/min/m^2 Systolic BP: 119 mmHg Diastolic BP: 71 mmHg Aortic BP: 95 mmHg		
Comments: Pump index ~30% greater than average cardiac index at time of implantation ($p < 0.05$)			
Hepatic and renal function	Bilirubin ratio: LVAD survivors ($n = 15$) 0.4 LVAD non-survivors ($n = 8$) 3.6	Bilirubin ratio: 1.3	LVAD survivors vs non-survivors $p = 0.03$ LVAD survivors vs controls $p = 0.004$ LVAD non-survivors vs controls $p = 0.09$

continued

Outcomes	LVAD	Historical control	*p*-Value
Comments: All but 2 of 26 patients had elevated bilirubin (≥ 1.4 mg/dl) or serum glutamic-oxaloacetic transaminase and/or serum glutamic-pyruvic transminase (≥ 50 U/l) before or during device support. Bilirubin, serum glutamic oxaloacetic transaminase and serum glutamic-pyruvic transaminase values tended to increase during first month, then returned to normal after ~2 months of augmented perfusion. Values remained within normal levels for remaining period of support Renal parameters did not transiently increase after LVAD implantation, and stabilised within a short period			
Comparison of hepatic and renal function during LVAD and after transplantation (15 surviving LVAD patients)			
Total bilirubin: 2.2 mg/dl at LVAD implantation, 0.7 mg/dl at transplantation, $p < 0.05$ (values estimated from figure) No significant difference on days 30 and 60 after LVAD implantation (1.7 and 0.8 mg/dl) or transplantation (1.0 and 0.9 mg/dl) (values estimated from figure) No difference in other two hepatic parameters			
Creatinine levels: 1.5 mg/dl at LVAD implantation, 1.0 mg/dl at transplantation, $p < 0.05$ (values estimated from figure) Day 30 after LVAD implantation 1.1 mg/dl, day 30 after transplantation 1.4 mg/dl, $p < 0.05$ (values estimated from figure) Day 60 after LVAD implantation 1.0 mg/dl, day 60 after transplantation 1.5 mg/dl, $p < 0.05$ (values estimated from figure)			
Adverse effects	***n* = 28**[a]	***n* = 6**	
Bleeding requiring return to operating room	0		
Patient-related bleeding, e.g. cardiac tamponade	11 (39%) (7 of whom underwent transplant, 5 of whom long-term survivors) Bleed vs no bleed: $p > 0.05$ for transplantation and survival rates		
Haemolysis (before and after LVAD implantation)	1		
Haematocrit	After implant: mean 34%		
Platelet count	After implant: mean 249,000/ml		
Free plasma haemoglobin ($n = 26$)	After implant: mean 8.7 mg/dl Haemoglobin conc. 11 g/dl		
Infection (defined above)	7 (25%) (6 underwent transplantation, 4 long-term survivors) Infected vs non-infected: $p > 0.05$ for outcome	2 (33%)	
Renal or hepatic dysfunction or both before or during LVAD (not considered device-related)	24/26 LVAD group (92.3%)		
Right heart failure (required right ventricular assistance or exhibited symptoms of serious right ventricular dysfunction after LVAD implantation)	6 (21%)		
	2 did not receive a RVAD 4 received device: 2 were weaned after 5 and 6 days, 1 of whom received transplant; 2 experienced increasing pulmonary vascular resistance secondary to bleeding. All 4 ultimately died		
	Transplantation rate and survival rate lower for right heart failure than without, $p < 0.05$		

continued

Adverse effects	***n* = 28**[a]	***n* = 6**
Thromboembolism device related	0	
Related to mechanical aortic valve in natural heart	1 (successful transplantation)	
Bowel adhesions to drive line	2	
Mechanical failure (loose outflow connector)	1 (in 1988)	

Comments: [a]3/34 treated for < 1 day, considered compassionate exclusions, experienced no adverse effects. 3/34 remained on LVAD support

Resource Use
Comments: Not reported

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Historical comparator only. Patients who did not meet study selection criteria were also included in some of the analyses
- Blinding: No blinding
- Comparability of treatment groups: Groups were haemodynamically comparable, although the control group had a lower pulmonary capillary wedge pressure. The control group was small, but had a greater proportion of females and was slightly younger
- Method of data analysis: Non-paired *t*-tests used for analysing haemodynamic, hepatic and renal function entrance criteria, and hepatic and renal function in survivors and non-survivors before and after LVADs. Paired *t*-tests used for LVAD and transplantation data in patients with LVADs and transplantation. Survival and complication data analysed with Fisher's exact probability test. $p < 0.05$ considered significant. Standard deviations given. Not analysed according to ITT principles
- Sample size/power calculation: Power calculations not undertaken. Historical control group small
- Attrition/drop-out: Attrition not stated, but assumed none. Transplant and adverse effects data not available for 3 patients who are still on LVAD support

General comments
- Generalisability: Patients experiencing chronic left ventricular failure
- Outcome measures: Outcome measures appropriate
- Inter-centre variability: Not reported
- Conflict of interests: Thermo Cardiosystems Inc. listed among the authors' addresses

ITT, intention-to-treat.

Quality Assessment for Primary Studies[77] Study: Frazier *et al*.[85]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – Cohort with historical control, also before and after comparison Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't 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%	Can't 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	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell ×		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ×	60–79%	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate ×	Weak		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell ×	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No ×	Can't tell		

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1943 Author: Frazier *et al*.[86] Year: 1994 Country: USA Study design: Cohort with historical control Study setting: Inpatient Number of centres: 1 Funding: Not stated	Indication for treatment: Extended BTT (≥ 30 days) (duration necessary for systemic organ recovery, improvement in NYHA class, after prolonged heart failure) Comparisons of different interventions: HeartMate 1000 IP Control group, met study criteria but device not available Duration of treatment: mean 106 days (SD 57, range 31–233) Other interventions used: Antibiotics: after implantation and at transplant, 2nd-generation cephalosporin for at least 72 h. I.V. vancomycin when sternum open Anticoagulants: after implant when bleeding controlled, oral dipyridamole 75 mg, 3× daily, aspirin 80 mg daily. If not tolerated, none given Immunosuppressive individualised to each patient, based on cyclosporin and steroids	Number of participants: Total: $n = 31$ LVAD: $n = 19$ (survival data reported on 16) Historical control: $n = 12$ Sample attrition/dropout: Not stated Inclusion criteria for study entry: Approved transplant candidates on active waiting list. Haemodynamic criteria despite maximal inotropic and intraaortic ballon pump support: pulmonary capillary wedge pressure 20 mmHg or more with cardiac index ≤ 2.0 l/minute/m^2 or systolic BP ≤ 80 mmHg Exclusion criteria: Severe right heart failure and pulmonary, neurological and severe renal or hepatic dysfunction Characteristics of participants: LVAD ($n = 19$): 18 male, 1 female. Mean age 45 years (SD 9, range 22–64). Weight 82 kg (SD 16, range 58–126). Body surface area 2.0 m^2 (SD 0.2, range 1.7–2.4). Diagnosis: end-stage ischaemic cardiomyopathy 9, idopathic cardiomyopathy 10 Control ($n = 12$): 9 male, 3 female. Mean age 46 years (SD 11, range 21–64). Weight 78 kg (SD 12, range 60–96). Body surface area 1.9 m^2 (SD 1.7, range 1.7–2.2). Diagnosis: end-stage ischaemic cardiomyopathy 9, idopathic cardiomyopathy 3	Primary and secondary outcomes: Survival Haemodynamic (cardiac index, pulmonary capillary wedge pressure) Haematological indices (haemoglobin, haematocrit, plasma free haemoglobin) Renal function (BUN, serum creatinine levels). Hepatic function (total bilirubin, serum glutamic oxaloacetic transaminase) Reported at implantation, 24 h, 48 h, 30 days, pre-heart transplant Device-related complications Physical rehabilitation (NYHA and treadmill): before implantation and time of transplantation Physical ability: treadmill exercise 20 minutes at 3 mph, 3% grade Incidence of rejection Incidence of infection Number of pre-transplantation blood transfusions Method of assessing outcomes: Haemodynamic parameters measured by Swan–Ganz thermodilution catheter. Pump flow measured by pump console. Level of rejection determined by routinely scheduled endomyocardial biopsies, graded on McAllister scale of ≥ 5 equivalent to International Society for Heart and Lung Transplantation scale (grade IIIA) Infectious episodes defined as treated infections in which a pathogen was isolated Length of follow-up: 2 years

continued

Results

Outcomes	LVAD	Comparator	*p*-Value
Successful transplantation	16/19[a]	0	
Comments: [a]one LVAD patient still awaiting a transplant at time of report 3 control patients received transplant, all died within 5 weeks			
Actuarial survival **1 and 2 years**	16 with successful transplant: 100%	0%	<0.05
Function			
Cardiac Index (l/minute/m^2) from implantation	*n* = 16 Baseline: 2.16 (SD 0.6) 24 h: 3.01 (SD 0.6) % change: +28		
Pulmonary capillary wedge pressure (mmHg) from implantation	*n* = 16 baseline: 24.2 (SD 6.9) 24 h: 15.0 (SD 4.2) % change: –18		
BUN (mg/dl) (estimated from figure)	*n* = 16 Baseline: 40 24 h: 35 48 h: 37 30 days: 25 Pre-transplant: 23		
Serum creatinine (mg/dl) (estimated from figure)	*n* = 16 Baseline: 1.6 24 h: 1.7 48 h: 1.8 30 days: 1.2 Pre-transplant: 1.3		
Total bilirubin (mg/dl) (estimated from figure) *n* = 16	*n* = 16 Baseline: 2.7 24 h: 3.2 48 h: 4.5 30 days: 1.6 Pre-transplant: 0.8		
Serum glutamic oxaloacetic transaminase (U/l) (estimated from figure) *n* = 16	*n* = 16 Baseline: 80 24 h: 170 48 h: 100 30 days: 95 Pre-transplant: 40		
Pre-transplant transfusions	*n* = 16 Mean 13 units (range 1–58)		
Comments: Haemoglobin and haematocrit levels remained within normal ranges throughout extended support (values not reported)			
QoL			
New York Heart Association	Implantation: all Class IV Transplant: 15/16 Class I (1 patient unable to ambulate owing to poor position of pneumatic drive line)		

continued

Outcomes	LVAD	Comparator	*p*-Value
Function			
Treadmill exercise sessions (×6)	*n* = 1 (6 sessions) Max. peak pump flow 9.5 l/minute (peak pump flow 11.2 l/minutes)		
Comments: All patients able to resume normal activities within confines of hospital grounds after transplant			
Adverse effects			
Mortality	(During extended support) 1/19 day 75, MOF related to systemic lupus persisting from pre-implantation period 1/19 day 118, massive thromboembolic embolism	9/12 awaiting transplant 2/12 immediate post-op, massive bleeding and donor heart failure 1/12 at 5 weeks after transplant, rejection-related lymphoma	
Possible device-related	Axillary artery thromboembolus plus transient ischaemic attack (no long-term sequelae): 1 patient		
Episodes of rejection per patient (biopsy score ≥ 5, International Society for Heart and Lung Transplantation grade IIIA) up to 6 months post-transplant	0.71 episodes (SD 0.98)	General transplant population: 1.19 episodes (SD 1.0)	
Severe rejection (biopsy score ≥ 9, International Society for Heart and Lung Transplantation grade IV)	0.13 episodes (SD 0.087)	General transplant population: 0.35 episodes (SD 0.02)	
Patients with ≥ 1 infectious episodes during 6 months after transplant:			
Bacterial	40%	36%	
Viral	7%	44%	
Fungal	7%	20%	
Protozoal	0%	7%	
Comments: States that pump did not cause haemolysis. No infectious organisms were cultured from any LVAD surface after explantation			
Resource use			
Comments			

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Historical comparator only, both groups met criteria for LVADs
- Blinding: No blinding
- Comparability of treatment groups: Higher proportion of females and higher proportion of ischaemic cardiomyopathy in control group. Similar in age, weight and body surface area
- Method of data analysis: Comparison with controls using unpaired t test. Mean and SD presented. $p < 0.05$ considered significant. Not analysed according to ITT principles
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not reported

General comments

- Generalisability: Transplant patients
- Outcome measures: Most outcomes not reported for control group, measurements were standard
- Inter-centre variability: Single-centre study
- Conflict of interests: Funding/conflicts not reported but previous work was done in collaboration with people from Thermo Cardiosystems Inc., the producers of HeartMate
- Other: some data compared with general population of transplant patients

Quality Assessment for Primary Studies[77]
Study: Frazier *et al*.[86]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – Cohort with historical control (also before and after comparison) Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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 × (sex, diagnosis)	No	Can't 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% × (none)	Can't 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	Can't tell ×		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No ×	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell ×	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak ×		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell ×	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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 ×	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No ×	Can't tell		

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 270 Author: Grady *et al*.[84] Year: 2001 Country: USA, Australia Study design: Cohort (pre and post) Study setting: Inpatient Number of centres: 10 (9 USA, 1 Australia) Funding: American Heart Association, and Rush Heart Institute, Rush–Presbyterian–St. Luke's Medical Centre	Indication for treatment: BTT Comparisons of different interventions: HeartMate IP (60%) or VE (40%) Duration of treatment: Not reported Other interventions used: Not reported	Number of participants: 281 patients received LVAD. 150 (53%) enrolled in study. 81/150 (84%) able to complete instrument booklet 1–2 weeks post-implantation 30/81 (37%) completed booklets at both pre-implantation and 1–2 weeks post-implantation. Sample of 81 not data extracted Sample attrition/dropout: Not reported Inclusion criteria for study entry: Convenience sample of adult patients who received LVAD as BTT between August 1994 and August 1999, physically able to participate, read and write English Of 131 not included: 41 (31%) received implant but died, 36 (27%) too ill to be enrolled, 30 (23%) refused to participate, 10 (8%) underwent transplant before enrolment, 6 (5%) did not complete questionnaires owing to non-enrolment by research staff, 5 (4%) not fluent in English), 3 (2%) illiterate Of 69 not completing booklet 1–2 weeks post-implant: 70% too sick, 6% refused, 4% did not receive booklet, 9% 'other'. 12% already implanted at study initiation (invited to join study later than 1–2 weeks post-implantation to achieve adequate sample size) Of 51 not completing booklet pre-implant: 82% too sick, 12% implanted after enrolment, 4% refused to complete booklet, 1 (2%) lost pre-implant booklet after completion Characteristics of participants (n = 30): Mean age 53.2 years (SD 9.5). 83% male, 17% female 77% white, 20% black, 3% Hispanic. 80% married, 3% single, 13% separated/divorced, 3% widowed. Mean education 13.7 years (SD 3.2) Employed 23% years, 77% no Ischaemic cardiomyopathy 50%, dilated cardiomyopathy 47%, 'other' 3%	Primary outcomes: QoL Pre-implantation: 1. Sickness Impact Profile 2. QoL index 3. Rating Question Form 4. Heart Failure Symptom Checklist 1–2 weeks post-implantation: As above, plus: 5. LVAD Stressor Scale 6. Jalowiec Coping Scale (not data extracted) Secondary outcomes: Clinical characteristics (condition on leaving operating room, percentage having reoperation). Adverse effects post-implantation at 30 days (mechanical device, infection, psychiatric complications) Method of assessing outcomes: Booklets of instruments, self-reported. Order of instruments randomly varied for each time period to control for fatigue effect, sensitisation and response bias 1. Sickness Impact Profile 100 items Domains: physical and occupational function, psychological state, social interaction Subscales: sleep/rest, emotional behaviour, self-care, home management, social interaction, ambulation, altertness, communication, recreation, eating, work Scoring: yes/no (yes weighted by amount of disability indicated) 2. QoL Index (modified) 20 preop items, 30 postop items Domains: psychological state, physical and occupational function, social interaction Subscales: health/functioning, socio-economic, psychological, significant others Scoring: 1–6 (1 = very dissatisfied, 6 = very satisfied 3. Rating Question Form 8 preop items, 10 postop items Domains: psychological state,

continued

Reference and design	Intervention	Participants	Outcome measures
		NYHA Class II 3%, III 10%, IV 87% LVEF 24% UNOS at time of implant: Status 1 90%, 'not applicable' 10% Advanced medical therapy: Continuous i.v. drip 87% yes, 13% no Intra-aortic balloon pump 17% yes, 83% no Ventilator 100% no	physical and occupational function Subscales: stress, coping ability, health perception, QoL, how well will do/doing after LVAD surgery, satisfaction with LVAD surgery, decision to undergo LVAD surgery again Scoring: global measure of single items with mostly 10-point Likert scales 4. Heart Failure Symptom checklist 90 items Domains: somatic sensation, psychological state Subscales: cardiopulmonary, gastrointestinal, genitourinary, neurological, dermatological, psychological Scoring: 0–3 (0 = not bothered at all, 3 = very bothered) Chart review of demographic and clinical data performed at both time periods by co-investigators Length of follow-up: up to 2 weeks after LVAD implantation

continued

Results
All *n* = 30

Clinical characteristics 1–2 weeks post-implant (*n* = 30)

Condition on leaving operating room (%)	Good/stable/satisfactory: 87% Fair: 10% Guarded: 3%
Reoperation (%)	Yes 17% No 83%

QoL

Patient satisfaction with life on subscales from QoL Index (*n* = 30), mean proportional score (SD)

	Before implantation	1–2 weeks after implantation	*p* = Value
Significant others	0.84 (0.10)	0.90 (0.08)	0.002
Socio-economic	0.72 (0.21)	0.50 (0.25)	<0.0001
Psychological	0.64 (0.22)	0.64 (0.24)	ns
Health functioning	0.51 (0.18)	0.66 (0.17)	0.001
Total score	0.66 (0.14)	0.73 (0.13)	0.037

(0.00 very dissatisfied, 1.00 = very satisfied)

Areas of life patients most satisfied with, rank ordered, from QoL Index

Before implantation		1–2 weeks after implantation	
Ran /life area proportional	Mean proportional score (SD)	Rank/life area	Mean score (SD)
1. Healthcare	0.98 (0.07)	1. Spouse, *p* = ns	0.96 (0.16)
2. Spouse	0.97 (0.17)	2. Health care, *p* = ns	0.93 (0.11)
3. Children	0.95 (0.15)	3.5 Faith in God, *p* = ns	0.92 (0.13)
4. Friends	0.92 (0.14)	3.5 Emotional support, *p* = ns	0.92 (0.14)
5. Emotional support	0.91 (0.15)	5. Children, *p* = 0.021 (ns)	0.90 (0.15)
6. Faith in God	0.90 (0.19)	6. Family health	0.89 (0.14)

(0.00 very dissatisfied, 1.00 = very satisfied)

Areas of life patients least satisfied, rank ordered, from QoL Index

Before implantation		After implantation	
Rank/life area	Mean proportional score (SD)	Rank/life area	Mean proportional score (SD)
1. Health status	0.28 (0.25)	1. Not able to work	0.41 (0.28)
2. Ability to travel	0.31 (0.21)	2. Energy for activities, *p* = 0.02 (ns)	0.47 (0.28)
3. Energy for activities	0.34 (0.26)	3.5. Control over life	0.49 (0.29)
4. Sex life	0.35 (0.31)	3.5. Health status, *p* = 0.001	0.49 (0.29)
5.5. Ability to do things around the house	0.44 (0.29)	5. Physical independence	0.53 (0.29)
5.5. Usefulness to others	0.44 (0.30)	6. Usefulness to others, *p* = ns	0.54 (0.29)

(0.00 very dissatisfied, 1.00 = very satisfied)

Patients were more satisfied than dissatisfied with their lives before and after surgery as all mean scores were ≥ 0.50

continued

Global ratings of QoL areas from Rating Question Form, mean (SD)

	Before implantation	1–2 weeks after implantation	*p*-Value
Stress level (1 = no stress, 10 = very much stress)	6.2 (2.5)	4.9 (2.9)	ns
Coping ability (1= very poorly, 10 = very well)	7.7 (2.0)	6.6 (2.6)	0.026 (ns)
Health (1 = very poor, 10 = very good)	4.0 (3.1)	6.2 (2.4)	0.012 (ns)
QoL (1 = very poor, 10 = very good)	3.5 (2.5)	5.9 (2.7)	0.002
How well will do/doing after LAVD (1 = very poorly, 10 = very well)	8.7 (1.3)	7.1 (2.1)	0.001
How well will do/doing after heart transplant (1= very poorly, 10 = very well)	9.3 (0.9)	9.3 (1.1)	ns

Patients responded more positively than negatively at both time points

Symptom distress by subscale from Heart Failure Symptom Checklist

	Before implantation	1–2 weeks after implantation	*p*-Value
Cardiopulmonary	0.37 (0.18)	0.23 (0.18)	0.002
Gastrointestinal	0.26 (0.12)	0.19 (0.14)	0.004
Psychological	0.25 (0.20)	0.20 (0.19)	ns
Genitourinary	0.23 (0.15)	0.14 (0.13)	0.002
Neurological	0.22 (0.12)	0.17 (0.11)	0.017 (ns)
Dermatological	0.08 (0.08)	0.06 (0.08)	ns
Physical (all except psychological)	0.22 (0.09)	0.16 (0.09)	0.001
Total score	0.23 (0.10)	0.16 (0.10)	0.002

(0.00 = not bothered at all, 1.00 = very bothered)
Patients were generally less bothered by symptoms than more bothered both before and after device implant as scores were all below the median of 0.50

Ten most distressing symptoms, in rank order, from Heart Failure Symptom Checklist

Rank/symptom	Mean proportional score (SD)	Rank/symptom	Mean proportional score (SD)
1. Exertional shortness of breath	0.73 (0.28)	1. Insomnia, p = ns	0.48 (0.39)
2. Weakness	0.62 (0.38)	2. Fatigue, $p = 0.047$ (ns)	0.47 (0.35)
3. Insomnia	0.60 (0.41)	3.5. Early satiety	0.42 (0.38)
4.5 Sleepiness	0.59 (0.40)	3.5. Exertional shortness of breath, $p < 0.0001$	0.42 (0.36)
4.5 Fatigue	0.59 (0.40)	5.5. Restlessness	0.41 (0.37)
6. Tachycardia	0.52 (0.44)	5.5. Weakness, $p = 0.08$	0.41 (0.34)
7. Weakness in legs	0.50 (0.39)	7. Anxiety/apprehension, p = ns	0.39 (0.35)
9.5 Decreased sexual desire	0.49 (0.45)	8. Swelling in extremities	0.37 (0.39)
9.5 Bloating feeling in stomach	0.49 (0.40)	9. Difficulty in sexual performance	0.36 (0.45)
9.5 Recumbent shortness of breath	0.49 (0.39)	9.5. Lack of control over life	0.33 (0.34)

continued

Rank/symptom	Mean proportional score (SD)	Rank/symptom	Mean proportional score (SD)
9.5 Anxiety/apprehension	0.49 (0.36)	9.5. Poor appetite	0.33 (0.36)
		9.5 Bloated feeling in stomach, p = ns	0.33 (0.35)
		9.5 Tachycardia, p = 0.031 (ns)	0.33 (0.33)

(0.00 = not bothered at all, 1.00 = very bothered)
When examining the level of distress caused by the most distressing symptoms both before and after, patients were more bothered by symptoms before surgery (means ≥ 0.49) and less bothered by symptoms after surgery (means <0.49).

Functional disability from the Sickness Impact Profile, mean (SD)

	Before implantation	1–2 weeks after implantation	*p*-Value
Recreation	0.54 (0.30)	0.46 (0.30)	ns
Home management	0.49 (0.32)	0.43 (0.39)	ns
Work	0.48 (0.09)	0.50 (0.00)	ns
Sleep/rest	0.40 (0.29)	0.43 (0.29)	ns
Social interaction	0.35 (0.20)	0.34 (0.25)	ns
Mobility	0.34 (0.24)	0.29 (0.27)	ns
Ambulation	0.30 (0.17)	0.35 (0.22)	ns
Alertness	0.23 (0.33)	0.20 (0.24)	ns
Self-care	0.20 (0.15)	0.30 (0.15)	0.002
Eating	0.17 (0.11)	0.14 (0.11)	ns
Emotional behaviour	0.12 (0.15)	0.17 (0.22)	ns
Communication	0.10 (0.18)	0.17 (0.25)	ns
Psychological disability	0.24 (0.16)	0.25 (0.19)	ns
Physical disability	0.34 (0.13)	0.35 (0.14)	ns
Total score	0.30 (0.13)	0.32 (0.14)	ns

(0.00 = least disability to 1.00 = most disability)

Comments: reliability and validity of instruments used reported previously. In addition, internal consistency reliability (n = 81) was supported in the current study for all tools except the Rating Question Form (would not expect because of diversity of questions) and 2 subscales [health/functioning (0.57); psychological (0.59)] of QoL Index. The QoL Index had acceptable Cronbach alpha values for the total scale (0.77), and the other 2 subscales [significant others (0.78); socio-economic (0.77)]. The low alpha values may have been due to the small number of items in each subscale. Internal reliability was supported for the Heart Failure Symptom Checklist by acceptable Cronbach alpha coefficients for the total scale (0.93), and the 6 subscales: cardiovascular (0.90), gastrointestinal (0.89), genitourinary (0.92), neurological (0.88), dermatological (0.90), psychological (0.87). The sickness impact profile demonstrated acceptable homogeneity reliability with a total scale Cronbach alpha of 0.88. The 12 subscales also met reliability standards: sleep (0.88), emotion (0.87), self-care (0.87), home management (0.87), mobility (0.86), social (0.86), ambulation (0.86), alertness (0.87), communication (0.87), recreation (0.86), eating (0.88), work (0.88)

Content validity is supported for all tools based upon the clinical expertise of the research team in developing the tools and the broad literature and empirical bases used for generating items for the scales

Adverse effects

Post-implant complications 30 days postop	
Mechanical device	Yes 23% No 77%
Infection	Yes 83% No 17%
Psychiatric complications	Yes 40% No 60%

continued

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not reported
- Comparability of treatment groups: Not applicable
- Method of data analysis: Frequencies and measures of central tendency plus or minus standard deviation. Comparative statistics (χ^2, Mann–Whitney *U*, Wilcoxon matched pairs signed ranks test). Mean total, subscale and item scores were calculated for each instrument. Score converted to proportional scores by dividing patient total, subscale and/or item scores by the maximum possible score, which converted scores to a scale with a range of 0.00 to 1.00. Level of significant set at 0.01 in light of the large number of tests that were performed. Values of $p = 0.05$ and less are reported since these may indicate results that should be further studied
- Sample size/power calculation: Not reported
- Attrition/drop-out: Assume none

General comments
- Generalisability: Patients were well enough pre-implantation to complete a booklet of instruments
- Outcome measures: Reliability and validity of instruments used have been reported previously. Internal consistency reliability values reported. Outcomes at 1–2 weeks post-implant only
- Inter-centre variability: Not reported
- Conflict of interests: Supported by a grant-in-aid from the American Heart Association and intramural funding from the Rush Heart Institute, Rush–Presbyterian–St. Luke's Medical Centre

Quality Assessment for Primary Studies[77]

Study: Grady *et al*.[84]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79% × (based on those eligible but declined)	<60%	N/A	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate ×	Weak		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
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 ×		

continued

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	Can't tell		N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes ×	No	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell		
2. Were data collection tools shown to be reliable?	Yes ×	No	Can't tell		
Summary of Data Collection (Methodological strength of study)	Strong ×	Moderate	Weak		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell ×		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell ×	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak ×		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ×	60–79%	<60%	Can't tell	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		N/A
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation NA	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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell		N/A

Appendix 13

Summary of the evidence of clinical effectiveness of the Novacor LVAD as a BTT for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 4694 Author: Trachiotis *et al*.[87] Year: 2000 Country: USA Study design: Cohort analytic Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTT Comparisons of different interventions: Novacor N1000 LVAD, comparison between those supported for <30 days and those supported for >30 days Duration of treatment: <30 days group (mean 12.2 days ± 8.4), >30 days group (mean 62.6 days ± 16.8) Other interventions used: Not reported. 1 patient had >30 days renal failure that did not recover after LVAD insertion and had dialysis until underwent simultaneous heart–kidney transplant 9/12 were ventilatory dependent and 10/12 had an Intra-aortic balloon pump at the time of LVAD insertion	Number of participants: 12 patients had Novacor during study period. 10 of these survived to transplant ($n = 9$) or explantation of device ($n = 1$) and formed the basis of the review. 5 had implant duration <30 days and 5 >30 days Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Transplant candidates with a cardiac index (CI) ≤ 2.0 l/minute/m^2 and either a systemic mean BP ≤ 65 mmHg, or a pulmonary capillary wedge pressure (PCWP) ≥ 18 mmHg. Patients included if the haemodynamic conditions were not met and if the patient required increasing doses of 2 inotropes and/or the use of an intra-aortic balloon pump (IABP) for a period >48 h prior to device implant Excluded if contraindications to device insertion: End-stage pulmonary parenchymal disease and/or pulmonary hypertension (pulmonary vascular resistance >480 dyn/s/cm^{-5}), irreversible renal (creatinine >5 mg/dl or BUN >100 mg/dl) and/or hepatic (total bilirubin >5 mg/dl) dysfunction, severe blood dyscrasia, documented infection, neurological deficits, cancer with metastases, primary or secondary right heart failure [central venous pressure (CVP) >18 mmHg and CI = 2.0 L/minute/m^2] not due to left ventricular dysfunction and a body surface area <1.5 m^2 Patients who were supported but did not undergo transplantation because of continuing support or death were not included in the study Characteristics of participants: all male. <30 days group: age 51.0 ± 4.3 years, ischaemic cardiomyopathy 4, idiopathic cardiomyopathy 1, systolic BP 81.8 ± 9.5 mmHg, systolic pulmonary artery pressure 51.4 ± 13.6 mmHg, PCWP 26.6 ± 7.1 mmHg; cardiac output: cardiac index 3.92 ± 0.7: 2.0 ± 0.4, ejection fraction 19.0 ± 11.1% >30 days group: age 47.8 ± 5.5 years, ischaemic cardiomyopathy 2, idiopathic cardiomyopathy 3, systolic blood pressure (mmHg) 93.3 ± 2.4, systolic pulmonary artery pressure (mmHg) 55.6 ± 12.4, PCWP (mmHg) 28.3 ± 2.5, cardiac output: cardiac index 4.43 ± 1.4:2.03 ±0.6, ejection fraction 18.3 ±2.4%. All *p*-values non significant except duration of LVAD	Primary outcomes: BUN, creatinine, total bilirubin, prothrombin time and CVP used to assess end-organ function at the time of LVAD implantation and transplantation. Adverse events while supported, survival after transplant or device explant Secondary outcomes: Method of assessing outcomes: review of cases from 1 January 1988 to 31 December 1996 Length of follow-up: Survival as of May 1997 (36.6 months <30 day group, 30.6 months >30 day group) (not statistically significantly different)

continued

Results

Outcomes	LVAD <30 days	LVAD >30 days	*p*-Value
Survival			
Survival after transplant or explant (30 days)	100%	100%	Not reported
Survival after transplant or explant (1 year)	100%	80%	Not reported
Survival after transplant or explant (2 years)	100%	Not reported	Not reported
Survival after transplant or explant (3 years)	60%	60%	Not reported
Comments.			
Functional capacity			
Serum creatinine (mg/dl)	Before LVAD: 2.1 ± 0.5	Before LVAD: 1.8 ± 0.3	ns
	Before Tx: 1.4 ± 0.2	Before Tx: 3.0 ± 2.7	ns
BUN (mg/dl)	Before LVAD: 42.4 ± 13	Before LVAD: 48.8 ± 24	ns
	Before Tx: 41 ± 22	Before Tx: 25.3 ± 21	<0.05
Total bilirubin (mg/dl)	Before LVAD: 1.2 ± 0.8	Before LVAD: 2.2 ± 1	ns
	Before Tx: 3.1 ± 2	Before Tx: 0.98 ± 0.5	ns
Prothrombin time (s)	Before LVAD: 16 ± 5	Before LVAD: 15.3 ± 3	ns
	Before Tx: 16.2 ± 2	Before Tx: 19.2 ± 2	ns
CVP (mmHg)	Before LVAD: 12.5 ± 5	Before LVAD: 13.4 ± 8	ns
	Before Tx: 10 ± 4	Before Tx: 8.8 ± 5	ns
Comments			
QoL	Not reported		
Comments			
Function	Not reported		
Comments			
Adverse effects on LVAD support	Infection: 5	Infection: 4	Not reported
	Pancreatitis: 1	Pancreatitis: 0	Not reported
	Reoperation (bleeding): 3	Reoperation (bleeding): 0	Not reported
	Thromboembolism: 1	Thromboembolism: 4	Not reported
	Neurological dysfunction: 2	Neurological dysfunction: 3	Not reported
	Renal failure/dialysis: 1/0	Renal failure/dialysis: 2/1	Not reported
	Right heart failure: 0	Right heart failure: 0	Not reported
Comments: Two late deaths were from malignancy and two from sepsis and MOF, no details of which group. One patient underwent LVAD removal Infections frequent in both groups, but manageable with antibiotics. No complication inhibited transplantation. The more severe events did occur in patients >30 days			
Resource use	Not reported		
Comments			

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Retrospectively allocated according to duration of support
- Blinding: None
- Comparability of treatment groups: No significant differences reported other than duration of support, minimal baseline characteristics given
- Method of data analysis: Any patients that survived to explantation were included in the analysis. ANOVA
- Sample size/power calculation: None
- Attrition/drop-out: Not reported

General comments

- Generalisability: Only includes those survived to transplant or explant. Those that died not included.
- Outcome measures: Appropriate
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

ANOVA, analysis of variance; Tx, transplant.

Quality Assessment for Primary Studies[77] Study: Trachiotis *et al.*[87]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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 × (duration implant)	No	Can't 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%	Can't 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	Can't tell		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No ×	Can't tell		

Appendix 14

Summary of the evidence of clinical effectiveness of the Toyobo LVAD as a BTT for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1813 Author: Masai *et al.*[88] Year: 1995 One patient also described in Matsuwaka *et al.*, 1995[184] Country: Japan Study design: Case reports Study setting: In patient Number of centres: 1 Funding: Not reported	Indication for treatment: BTT (although 2 had long-term support as heart transplant in Japan is rare owing to ethical issues) Comparisons of different interventions: No comparison, Toyobo NCVC LVAS only (extracorporeal) Duration of treatment: mean duration 206 days, range 46–390 days Other interventions used: Nitric oxide early after insertion in 3 patients, inotropic agents early postop in all. 1 patient required mechanical right ventricular support for 10 days. 2 received anticoagulation (heparin followed by warfarin)	Number of participants: 3 (total group 4 but BVAD in one patient and not data extracted) Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Not expressly stated as criteria: all patients had ESHF refractory to pharmacological therapy supported by intra-aortic balloon pump (IABP) or percutaneous cardiopulmonary support (PCPS) before LVAD insertion. 2 patients supported only by IABP; 2 patients supported by both IABP and PCPS. Cause of heart failure was idiopathic dilated cardiomyopathy and approved as candidates for heart transplantation Characteristics of participants: Male, mean age 40 years (range, 18–49 years), previously supported by balloon pump or cardiopulmonary support. 3 of 4 intubated Cardiac index (mean 2.0 l/minute/m^2, range 1.8–2.2) Pulmonary capillary pressure (mean 25 mmHg, range 21–28)	Primary and secondary outcomes: Survival (duration support), haemodynamic stability, serum creatinine, total bilirubin, complications Method of assessing outcomes: Not reported Length of follow-up: Up to 390 days

Results

Outcomes	LVAD	*p*-Value
Survival	Patient 1 supported for 119 days then transplanted Patient 2 still supported at 390 days Patient 3 supported for 64 days then died	Not reported
Comments: Patient 4 supported for 46 days on BVAD then died		
Functional capacity Haemodynamic stability	Complete, average flow 4.0–5.3 l/minute	Not reported
Comments		
QoL	Not reported	
Comments		
Function	Not reported	
Comments		

continued

Outcomes	LVAD	*p*-Value
Adverse effects	CVA in 2/4 patients 1 patient (survived to heart transplant) required exchange of pump 4 times owing to thrombus formation; had brain infarction which resulted in transient left hemiplegia 1 patient had transient ischaemic attack without evidence of abnormal findings on brain computed tomography Neither experienced neurological deficits	Not reported
	Post-op bleeding: 2 patients (1 had bleeding from inferior epigastric artery near percutaneous cable of flow probe; 1 had re-exploration 2 days postoperatively for cardiac tamponade)	
	Mechanical failure of device: 1 patient at 209 days of support (dehiscence at junction between diaphragm and housing of pump)	
Comments: 2 patients who died of MOF showed elevations of serum bilirubin before LVAD implantation. Adverse effects data includes the BiVAD patient (not reported separately)		
Other		
Serum creatinine **(estimated from Figure 2)**	Patient 1: Pre 4.8 mg/dl, 30 days 1.2 mg/dl Patient 2: Pre 0.8 mg/dl, 30 days 0.6 mg/dl Patient 3: Pre 1.2 mg/dl, 30 days 4.2 mg/dl[a] Patient 4: Pre 1.9 mg/dl, 30 days 0.8 mg/dl[a]	Not reported
Total bilirubin **(estimated from Figure 2)**	Patient 1: Pre 1 mg/dl, 30 days 0.5 mg/dl Patient 2: Pre 1 mg/dl, 30 days 0.5 mg/dl Patient 3: Pre 28 mg/dl, 30 days 60 mg/dl[a] Patient 4: Pre 28 mg/dl, 30 days 54 mg/dl[a]	Not reported
Comments: [a]unclear which of patient 3 or 4 is the BiVAD patient.		
Resource Use	Not reported	
Comments		

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not reported
- Comparability of treatment groups: Not applicable
- Method of data analysis: No data analysis, reports rates only
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not reported

General comments
- Generalisability: Limited to young Japanese males with dilated cardiomyopathy and previously supported on either intraaortic balloon pump or percutaneous cardiopulmonary support. Little information; all 4 patients had advanced dilated cardiomyopathy. Not stated whether these patients represent all the patients with dilated cardiomyopathy who had LVAD
- Outcome measures: Appropriate
- Inter-centre variability: Not applicable
- Conflict of interests: One author works for Toyobo Corporation, Japan

Quality Assessment for Primary Studies[77] Study: Masai *et al.*[88]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify (case series) Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		N/A
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation (N/A)	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis (N/A)	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 15

Summary of the evidence of clinical effectiveness of the Thoratec LVAD as a BTT for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1699 Author: Holman *et al.*[89] Year: 1995 Country: USA Study design: Case report Study setting: Inpatient Number of centres: 1 Funding: None reported	Indication for treatment: BTT Comparisons of different interventions: No comparison, Thoratec LVAD only Duration of treatment: 60 days Other interventions used: Epinephrine administration was stopped after the operation and tapering of the dobutamine dose commenced. Mechanical ventilation was continued throughout the period of arrythmias. On the 12th day arrythmias were controlled with amiodarone and metoprolol	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: None stated Characteristics of participants: 45-year-old male patient admitted post-large anteroapical MI, ventricular arrythmias and tachycardia and fibrillation which required multiple cardioversions and defibrillations. Eventually the rhythm was controlled with intravenous lidocaine, amiodarone and bretylium. Haemodynamic status deteriorated and was intubated. Systemic pressure was 56/30 mmHg, pulmonary artery pressure 38/17 mmHg, pulmonary artery wedge pressure 15 mmHg, pulmonary vascular resistance 180 dyn/s/cm^{-5}, cardiac index 1.9 l/minute/m^2 despite infusion of dobutamine 10 μg/kg/minute and epinephrine 0.06 μg/kg/minute Severe pericarditis consistent with Dressler's syndrome was noted in the operating room The anteroapical portion of the left ventricle appeared necrotic, so left atrial cannulation was used	Primary outcomes: Survival to transplant Secondary outcomes: Adverse events, haemodynamic variables Method of assessing outcomes: Not noted Length of follow-up: At 60 days the patient had transplant

Results

Outcomes	LVAD
Survival Comments	After 60 days patient was successfully transplanted
Functional capacity Comments:	Not reported
QoL Comments	Not reported

continued

Outcomes	LVAD
Function	During ventricular tachycardia (see below) VAD flow was 3.6–3.8 l/minute and the mean right atrial pressure was 16–18 mmHg. During ventricular fibrillation systolic pressure was 80–85 mmHg, VAD flow was 3.2–3.6 l/minute and the mean right atrial pressure was 18–20 mmHg. During all ventricular arrythmias the mean left atrial pressure was 0–6 mmHg
Comments: The mean left atrial pressure was 2–7 mmHg and the mean right atrial pressure was 14–18 mmHg when the patient was taken off cardiopulmonary bypass	
Adverse effects	On second postoperative night an episode of ventricular tachycardia. VAD output during this was 3.6–3.8 l/minute and systolic BP was 80–90 mmHg. Cardioverted and intravenous amiodarone was continued Episodes of paroxysmal ventricular tachycardia and occasional ventricular fibrillation recurred and became more frequent during the ensuing days
Comments	
Resource use	
Comments	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments
- Generalisability: Reports a single 45-year-old male patient only with cardiogenic shock and multiple arrythmias after MI
- Outcome measures: Appropriate
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77]

Study: Holman *et al*.[89]

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	Can't tell ×	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – Case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			

continued

If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 3101 Author: May and Adams[90] Year: 1987 Country: USA Study design: Case report Study setting: Inpatient Number of centres: 1 Funding: None reported	Indication for treatment: BTT Comparisons of different interventions: No comparison, Thoratec LVAD only Duration of treatment: 21 days Other interventions used: Inotropic medication Prostaglandin E for respiratory problems Heparin drip	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Patient placed on transplant waiting list but sent home as securing donor for size and blood group difficult. Then readmitted with severe congestive heart failure. Remained in hospital for 2 months. Commenced inotropes. Suffered from arrythmias. Then suffered cardiac arrest and went into severe heart failure Characteristics of participants: 24-year-old male, 2-year history of cardiomyopathy with progressive deterioration. Weight 200 lb, blood type B. At implant atrial pressures between 35 and 40 mmHg, left atrial pressure 15 mmHg	Primary outcomes: Survival Secondary outcomes: Adverse events Method of assessing outcomes: Not reported Length of follow-up: until discharge, 3 weeks post-transplant

Results

Outcomes	LVAD
Survival	3 weeks post transplant was discharged home
Comments:	

Functional capacity

Comments

QoL

Comments

Function

Comments

Adverse effects	Severe respiratory distress after 2.5 days and developed adult respiratory distress syndrome. Intubated and placed on 100% O_2 and 12–15 cm of positive end-expiratory pressure but was only able to maintain an arterial partial pressure of oxygen of 50 mmHg
	Blood cultures showed *Legionella* bacteria, treated with antibiotics
	Haemolysis which stabilised in a week

Comments: during first 2 days LVAD was turned off but systolic BP dropped to 70 mmHg

Resource use

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments

- Generalisability: Single patient only
- Outcome measures: Minimal
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77] Study: May and Adams[90]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 16

Summary of the evidence of clinical effectiveness of the Jarvik 2000 LVAD as a BTT for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 170 Author: Frazier *et al*.[94] Year: 2001 Country: USA, UK Study design: Case series (reports that data from feasibility study leading to future clinical trials) Study setting: Inpatient Number of centres: 2 Funding: Not reported	Indication for treatment: BTT (3), Permanent support (1) Comparisons of different interventions: No comparison, Jarvik 2000 only Duration of treatment: 79 days, 52 days (mean 65.5 days), and >60 days Other interventions used: Inotropic support for 48 h then withdrawn Minimal anticoagulation therapy. Patient 1: daily warfarin from 6th day postop. Patient 2: heparin or warfarin throughout support. Patient 3: 3 doses of warfarin	Number of participants: $n = 4$ (3 patients for BTT, 1 for long-term support) Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Transplant candidates, no explicit criteria stated Characteristics of participants: BTT: 2 male, 1 female Age 52, 29, 60 years Idopathic cardiomyopathy (1), Noonan's syndrome/dilated cardiomyopathy (1), ischaemic idiopathy (1) Duration of heart failure 13, 3, 2 years Cardiac index 1.9 l/minute/m^2 Pulmonary capillary wedge pressure 19.7 mmHg Permanent implant: 1 male, 61 years. Idiopathic dilated cardiomyopathy, duration 3 years Cardiac index 1.8 l/minute/m^2 Ejection fraction 10% Maximum oxygen consumption 5.7 ml/kg/minute. Severe orthopnea, peripheral oedema, ascites	Primary and secondary outcomes: Successful transplant Haemodynamic status (cardiac index, pulmonary capillary wedge pressure) Adverse events Pump speed effects (not extracted) Method of assessing outcomes: Not reported Length of follow-up: 48 h

Results

Outcomes	LVAD BTT ($n = 3$)	LVAD – 1-long term patient
Successful transplant	2/3	6 weeks until discharged, no further details
Comments: 1 patient continues to be supported at 60 days		
Function		
Initial pump flow (l/minute)	5.5 to 5.9	
Cardiac index (l/minute/$m^{2)}$	48 h after implant: 3.5	Reported to have normalised
Pulmonary capillary wedge pressure (mmHg)	48 h after implant: 7.3	
Average international normalised ratio	1.55	

continued

Outcomes	LVAD BTT (n = 3)	LVAD – 1-long term patient
Adverse effects		
Intraoperative blood loss (litres) (average)	1.5	
Postoperative bleeding	Minimal (amount not stated)	
Complications associated with implant surgical procedure	0/3	
Free from adverse events throughout support	1/3	
Localised infection of power-cable exit site (responded to antibiotic therapy and local treatment)	1/3	
Gastrointestinal bleeding from duodenal ulcer	1/3	
Device-related medical problems	0/3	
Thromboembolism	0/3	
Comments		

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: No control group
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Assume none

General comments
- Generalisability: Patients all with cardiomyopathy, but varying causes
- Outcome measures: Limited outcome measures, survival not assessed
- Inter-centre variability: Not applicable: 3 BTT in USA centre, 1 permanent placement in UK centre
- Conflict of interests: One of the authors is President of Jarvik Heart Inc.

Quality Assessment for Primary Studies[77]

Study: Frazier *et al*.[94]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case series Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			

continued

If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell		N/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%	Can't tell	N/A
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell		N/A
2. Were the study participants aware of the research question?	Yes	No	Can't tell		N/A
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell		N/A
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell ×	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation NA	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	Can't tell		N/A
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell		N/A

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 9058 Author: Frazier et al., 2003;[100] Westaby *et al.*, 2002;[95,96,98] Frazier *et al.*, 2002;[97] Siegenthaler *et al.*, 2002[99] Year: 2001–03 Country: USA, UK, Germany Study design: Case series (states that feasibility study for larger trial) Study setting: Inpatient Number of centres: 3 (although different subsets from these centres are presented) Funding: Westaby *et al*.[98] report financial support from the National Heart Research Fund (UK) and an anonymous benefactor	Indication for treatment: 2 subsets: BTT and LTCS Comparisons of different interventions: No comparison, Jarvik 2000 only Duration of treatment: (i) BTT – mean 67 days (SD 36.7; range 13–214) (ii) LTCS UK centre – mean 502 days (SD 341.3; range 95–889) (iii) LTCS German centre – mean 93 days (range 66–145) Other interventions used: (i) BTT patients ($n = 10$) were given anticoagulation therapy to maintain INR at 1.5–2.0, including heparin, warfarin, aspirin and dipyridamole[97] (ii) LTCS in UK preoperative drugs: amiloride, bumetanide, carvedilol, clopidogrel, digoxin, lisinopril, losartan, metoprolol, frusemide, perindopril, spironolactone, warfarin Postoperative drugs: amiodarone, bisoprolol, digoxin, lisinopril, perindopril, warfarin (iii) German LTCS received intraoperative aprotinin and nitric oxide. Postoperatively they received antibiotics, heparin, warfarin, ACE inhibitors and beta-blockers	Number of participants: (i) BTT 22 (subsets are presented in the different publications); (ii) LTCS: 7 (4 in UK centre, 3 in German centre) Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: (i) BTT: NYHA Class IV heart failure with small body surface area (<2.0 m^2) facing imminent death from cardiogenic shock. Received intravenous inotropes or intra-aortic balloon pump support prior to implantation. Patients must be confined to ICU and must lack significant co-morbidities such as sepsis, cancer and irreversible end-organ failure. Patients with previous median sternotomies and a body habitus that would make a conventional LVAS unfeasible (tall and thin or short and stout) were also eligible[97] (ii) LTCS: cardiac index <2.0 l/minute/m^2, LVEF <25%, maximum oxygen consumption rate (MVO_2) <16 ml/kg/minute, creatinine clearance >25 ml/minute and likelihood of death within 3 months. Excluded if insulin-dependent diabetes, previous cardiac surgery, active malignancy or contraindication to anticoagulation therapy. In addition, Siegenthaler *et al*.[99] report criteria for the German LTCS study: heart failure criteria for transplantation or mechanical left ventricular support had to be present. Patients who did not qualify for heart transplant, because of advanced age or elevated pulmonary vascular resistance, or patients unsuitable for a conventional LVAD because of a small body surface area ≤ 1.5 m^2 (also states 1.2–2.2 m^2) were eligible implantation. Also eligible if cardiac function (2 of 3): cardiac index ≤ 2.3 l/m^2/minute. LVEF ≤ 30%, MVO_2 ≤ 16 ml/kg/minute. Excluded if (absolute criteria/*relative criteria*): neurology, psychology: intracranial bleeding within 21 days; status post-cardiopulmonary resuscitation for >5 minutes and neurological outcome unknown, severe brain damage, with no hope for a meaningful recovery, high probability of non-compliance. Pulmonary: fixed pulmonary vascular resistance ≥ 7 Wood units; *pulmonary vascular resistance 5–7 Wood units, concentration of inspired oxygen >0.6*, Surgical/medical: malignancy, life expectancy <18 months, untreated aortic dissection or	Primary and secondary outcomes: Survival, NYHA functional class, QoL, organ function, physiological, cause of mortality, adverse events, resource use Method of assessing outcomes: Not stated, outcomes reported differed between the centres Length of follow-up: (i) BTT patients: mean follow-up of surviving patients[100] 15 months (0.8–29 months). Mean follow-up 5.6 months (range 0.7–11.2 months) in report of 10 patients,[95] Frazier *et al*.[97] report follow-up was 13.5 months (8.6–19) (ii) LTCS UK centre follow-up ranged from 95 to 889 days (iii) LTCS German centre patients follow-up 91, 93 and 170 days

continued

Reference and design	Intervention	Participants	Outcome measures
		aneurysms, *implanted mechanical heart valve, aortic or mitral insufficiency grade 3 or 4*. Renal: anuria, creatinine clearance <25 ml/h, *creatinine >3.0, urine output <30 ml/h × 12 h*. Liver: cirrhosis (Child C), *synthetic dysfunction* (*INR ≥ 1.8, prothrombin time >16*). Infection: *sepsis or other severe infection*. Haematology: contraindication to heparin anticoagulation, thrombus in any cardiac chamber, *history of thromboembolic events*. Gastrointestinal tract: ischaemic bowel necrosis, gastrointestinal bleeding (>6 U packed red blood cells) due to diffuse gastritis or colitis. Time to hospital: transport to hospital >180 minutes. Risk-score index (10): Columbia risk-score index >5 Characteristics of participants: (i) BTT (n = 22): mean age 53 years (SD 21.9; range 30–70), 16 males, 6 females, dilated cardiomyopathy in 11, ischaemia in 11. Frazier *et al.*[97] report haemodynamic variable (see Results). Other papers report subsets of the 22 patients (ii) LTC UK subgroup (n = 4): mean age 64 years [range 60–72 (range reported as 61–72 in Westaby *et al.*[96,98])], all males, all dilated cardiomyopathy. (Individual baseline characteristics reported in Westaby *et al.*[96,98,100] but data not extracted as no aggregate values) (iii) LCTS German subgroup (n = 3): mean age 61 years (range 59–62), all male, 2 dilated cardiomyopathy, 1 amyloidosis. Siegenthaler *et al.*[99] report (mean ± SD): age 62.2 (2.3) years, size 176 (12) cm, weight 68 (14) kg, body surface area 1.79 (0.23) m^2, cardiac index 1.8 (0.3) l/minute/m^2, leukocytes 8.8 (3.8) × $10^3/\mu l$, risk-score index 1.3 (1.2), QoL score 75.2 (11.4)	

continued

Results

(i) BTT (n = 22)

Outcomes	**LVAD**		
Survival	13 patients underwent heart transplant (1 died of allograft rejection after 2.6 months), 7 died awaiting transplant, 2 ongoing at 92 and 105 days		
Comments: Support was for a mean of 67 days (SD 36.7, range 13–214)			
Functional Status (*n* = 10)[95]	Baseline 10 patients NYHA Class IV; postoperative 7 patients NYHA Class I and 3 died		
Organ Function (*n* = 22)[100]	**Baseline**	**At 24 h**	***p*-Value**
Cardiac index (l/minute/m^2)	1.76	2.91	0.00003
Heart rate (beats/minute)	89.1	106.5	0.0002
Central venous pressure (mmHg)	10.9	11.2	0.90
Mean arterial blood pressure (mmHg)	73.9	80.6	0.02
Mean pulmonary artery pressure (mmHg)	31.8	30.7	0.67
Systemic vascular resistance (dyn)	1582	1067	0.001
Pulmonary vascular resistance (Wood units)	2.5	3.4	0.18
Pulmonary capillary wedge pressure (mmHg)	22.8	12.7	0.00002
Comments			
QoL	Not reported		
Comments			
Function	Not reported		
Comments			
Adverse effects	Abdominal power cable infection 2; major haemorrhage 1 (from a gastric ulcer and a separate ateriovenous malformation in the small intestine); thromboembolism in device 0; device infection 0; significant haemolysis 0; technical problems 2, power-cable connectors broken by operator and 1 connector pin bent by patient		
Mortality	2 deaths (1 ventricular fibrillation on postoperative day 3, resuscitated but had severe neurological deficit which failed to improve, and support was terminated at 93 days; 1 developed severe coagulopathy immediately post-surgery, after multiple blood transfusions, developed adult respiratory distress syndrome, right ventricular failure, marked elevation of pulmonary resistance and MOF which caused death 14 days later) Frazier *et al.*[97] report 3 deaths during support (2 from ventricular ectopia, 1 from adult respiratory distress syndrome) Frazier *et al.*[100] note serious patient-related complications of postoperative bleeding, left ventricular thrombus, coronary thrombosis, subdural haematoma and gastrointestinal bleeding. No serious device-related infections		
Comments:	Plasma-free haemoglobin: baseline 7.4 mg/dl; post-op 14.1 mg/dl		
Resource use	Not reported		
Comments			
Duration of support	84 days (range 13–214)		

continued

(ii) LTCS UK patients (*n* = 4)

Outcomes	LVAD
Survival	3 patients left hospital within 4 weeks (Westaby *et al*.[98] report that 3 patients left hospital within 3–8 weeks)
	Duration of survival was 20, 12 and 9 months for these three patients[98]
	Frazier *et al.*[100] present updated results for the 4 patients; 2 died at 95 and 382 days, one from right heart failure, the other a subdural haematoma; the two survivors were alive at 642 and 889 days
Comments: Westaby *et al*.[96] report 1 patient alive at 12 months post-implantation, 1 patient alive at 4 months	
Functional capacity	Patient 1: pre-LVAD NYHA Class IV, post-LVAD I. Patient 2: pre-LVAD IV, post-LVAD died. Patient 3: pre-LVAD IV, post-LVAD I. Patient 4: pre-LVAD IV, post-LVAD II
Comments	
QoL	
Minnesota score	Patient 1: Pre-LVAD 89, post-LVAD 24. Patient 2: pre-LVAD 76, post-LVAD died. Patient 3: pre-LVAD 83, post-LVAD 38. Patient 4: pre-LVAD 87, post-LVAD 45
Comments: Westaby *et al*.[98] report that patients showed major improvement.	
Function	**Serum creatinine (mmol/l)** Patient 1: pre-LVAD 152, post-LVAD 108. Patient 2: pre-LVAD 154, post-LVAD 89. Patient 3: pre-LVAD 132, post-LVAD 82. Patient 4: pre-LVAD 158, post-LVAD 114
	Creatinine clearance (ml/minute) Patient 1: pre-LVAD 35, post-LVAD 88. Patient 2: pre-LVAD 46, post-LVAD 82. Patient 3: pre-LVAD 54, post-LVAD 90. Patient 4: pre-LVAD 52, post-LVAD 86
	LVEF (%) Patient 1: pre-LVAD <10, post-LVAD 48. Patient 2: pre-LVAD 20, post-LVAD 55. Patient 3: pre-LVAD 15, post LVAD 25. Patient 4: pre-LVAD 15, post-LVAD 25
	RVEF (%) Patient 1: pre-LVAD 20, post-LVAD 58. Patient 2: pre-LVAD 35, post-LVAD 40. Patient 3: pre-LVAD 40, post-LVAD 40. Patient 4: pre-LVAD 55, post-LVAD 55
	Mean BP (mmHg) Patient 1: pre-LVAD 94, post-LVAD 86. Patient 2: pre-LVAD 86, post-LVAD 78. Patient 3: pre-LVAD 78, post-LVAD 84. Patient 4: pre-LVAD 96, post-LVAD 80
Comments	
Adverse effects	Significant haemolysis 0; dyspnoea 1 patient at 4 months; VT 1 patient at 11 months; thrombus 0
	Frazier *et al*.[100] note serious patient-related complications of postoperative bleeding, left ventricular thrombus, coronary thrombosis, subdural haematoma and gastrointestinal bleeding. No serious device-related infections
Device-related complications	1 patient suffered 3 power supply problems; 1 patient suffered an infection from a blood transfusion
Mortality	1 death during support (in a 120-kg male who developed a slowly accumulating subdural haematoma at the skull where the power device was implanted. This required surgical evacuation on 2 occasions but residual neurological disability meant he needed to be ventilated and death from tricuspid regurgitation and right heart failure occurred after 94 days)

continued

Outcomes	LVAD
Comments: Skull-mounted percutaneous power delivery system healed satisfactorily without infection in all surviving patients Plasma-free haemoglobin was 8.4 mg/dl	
Resource Use Comments	Duration of Support: 502 days (range 95–889 days)

(iii) LCTS German patients (*n* = 3)

Outcomes	LVAD
Survival Comments	All 3 patients surviving at follow-up
Functional capacity Comments	
QoL (2 months) Comments	30.0 (SD 18.6)
Function	All patients NYHA Class I or II between 14 and 93 days postoperatively (mean 41 days)
Comments: All patients were fully ambulatory within 10 days and able to climb stairs within 2–3 weeks	
Adverse effects	No device-related complications; no infections; no reoperation
Transient ischaemic attack	1 (manifested by right arm weakness, which completely resolved within 30 minutes)
Ventricular arrythmia	1 patient was reintubated due to ventricular arrythmia at 7 days. The patient with known Lown IVa arrhythmia had an episode of sustained VT during which remained awake
Minor events	1 episode of loss of consciousness while battery changed 1 knee effusion after vigorous ergometry training 1 large skin abrasion from adhesive tape 1 hospital readmission due to dehydration. 2 patients required postoperative psychological therapy
Comments: Skull-mounted percutaneous power delivery system healed satisfactorily without infection in all surviving patients	
Resource use	Operative time (minutes) 285 (±10); intraoperative transfusions (PRBCs) 0.7 (±1.2); postoperative transfusions (PRBCs) 3.7 (±2.1); intensive care stay (days) 7 (±0.5); hospital stay (mean ± SD) (days) 49 (±7); duration of support (days) range 91–170
Comments	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments
- Generalisability: Patients eligible for heart transplant and those ineligible included
- Outcome measures: Appropriate
- Inter-centre variability: Not noted
- Conflict of interests: One author is president of Jarvick Heart Inc.

INR, international normalised ratio; PRBCs, packed red blood cells.

Quality Assessment for Primary Studies[77] Study: Frazier *et al.*[100]					
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	Can't tell ×	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case series Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell	N/A	
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell	N/A	
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	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 17

Summary of the evidence of clinical effectiveness of the MicroMed DeBakey LVAD as a BTT for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 171 Author: Noon *et al.*, 2001,[91] (likely to include data from Noon *et al.*, 2000;[185] Potapov *et al.*, 2000,[93] Wiselthaler *et al.*, 2000,[102] 2001,[92] data extracted separately) Year: 2001 Country: Europe and USA (only European results reported). Study began in 1998 in Europe and June 2000 in USA Study design: Cohort (before and after) with no control Study setting: Inpatient Number of centres: Multicentre study – number of centres unclear Funding: Not reported	Indication for treatment: BTT Comparisons of different interventions: No comparison, MicroMed DeBakey only Duration of treatment: Support ranged up to 133 days. 21 patients were supported for >30 days and 13 patients were supported for >60 days. The median time to transplant was 74.5 days with median support duration of 47 days. The cumulative number of patient days of support was 1876 Other interventions used: States that in many patients, end-organ dysfunction may require multiorgan support during and immediately after the implant surgery. A RVAD may be necessary for refractory right heart failure. If additional haemodynamic support and counterpulsation are necessary, an intra-aortic balloon pump may be implemented. A continuous veno-venous haemofiltration or haemodialysis system may be necessary to correct fluid volume overload. Coagulopathies are treated and patient is not placed on anticoagulant therapy until postoperative bleeding is minimal and coagulopathy is treated (usually within 24–48 h post-transplant); recommendation for anticoagulation: start on intravenous heparin or subcutaneous low molecular weight heparin, then convert to coumadin, aspirin and clopidrogrel bisulphate	Number of participants: As of September 2000, 51 patients (44 male, 7 female) have been implanted. Detailed evaluation of the first 32 completed and reported from the European study Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Patients with advanced heart failure who were transplant candidates and whose conditions were rapidly deteriorating. In general must have been listed for transplantation and demonstrating profound cardiac failure. This was confirmed by haemodynamics (elevated pulmonary capillary wedge pressure, low cardiac index and other factors) or the need for extraordinary inotropic support including intra-aortic balloon pump. There were no exclusions other than those that would typically exclude a patient from transplantation (states that the criteria used were similar to those used during clinical investigations of LVADs currently on the market) Characteristics of participants: 50% in the clinical trial had idiopathic dilated cardiomyopathies, 38% had ischaemic cardiomyopathies. On study entry the mean cardiac index was 1.7 l/minute/m^2; mean pulmonary artery pressure was 25 mmHg	Primary and secondary outcomes: Unclear, outcomes reported include: probability of survival at 30 days; number transplanted; duration of support; number deaths on support; complications; pump flow; pump index; device speed, power and current trends; blood nitrogen; total bilirubin, creatinine Method of assessing outcomes: Not reported Length of follow-up: Not reported. Outcomes reported at up to 91 or 105 days

continued

Results

Outcomes	LVAD	*p*-Value
Probability of survival at 30 days	81%	N/A
Number transplanted	11 of 32 patients	N/A

Comments

Functional capacity Not assessed

Comments

QoL Not assessed

Comments

Function

Creatinine (mg/dl) (estimated from figure)	Before, 1.5; 1 day, 1.9; 2 days, 1.5; 3 days, 1.5; 4 days, 1.5; 5 days, 1.45; 6 days, 1.4; 7 days, 1.5; 14 days, 1.25; 21 days, 1.25; 28 days, 1.25; 35 days, 1.4; 42 days, 1.2; 49 days, 1.2; 56 days, 1.1, 63 days; 1.1; 70 days, 1.2; 77 days, 1.1; 84 days, 1.2; 91 days, 1.2
Total bilirubin (mg/dl) (estimated from figure)	Before, 2.1; 1 day, 3.0; 2 days, 3.3; 3 days, 3.3; 4 days, 3.4; 5 days, 3.5; 6 days, 3.4; 7 days, 3.6; 14 days, 3.2; 21 days, 3.5; 28 days, 1.3; 35 days, 1.6; 42 days, 1.2; 49 days, 1.5; 56 days, 1.3; 63 days, 1.2; 70 days, 1.3; 77 days, 1.4; 84 days, 1.45; 91 days, 0.8
BUN (mg/dl) (estimated from figure)	Before, 48; 1 day, 48; 2 days, 50; 3 days, 52; 4 days, 52, 5 days, 52; 6 days, 52; 7 days, 52; 14 days, 50; 21 days, 50; 28 days, 32; 35 days, 48; 42 days, 30; 49 days, 38; 56 days, 30; 63 days, 29; 70 days, 28; 77 days, 22; 84 days, 31; 91 days, 24

Comments: Statistical significance not assessed

Adverse effects

Deaths on support 10 of 32 patients N/A

Comments: Only one death on support was potentially related to the device (no details). In most, death occurred as a result of MOF, primarily in patients who were in early MOF requiring optimal medical support and intra-aortic balloon pump prior to implant, or both

Principle complication was late bleeding with most events occurring more than 5 days after the implant operation. After reduction of target anticoagulant control (INR to 2.0–2.5) these incidences were reduced. Some incidences of haemolysis, all more than 16 days post-implant. No device-related infections reported. Except for 2 patients with intracranial bleeding due to anticoagulation, only 1 minor cerebrovascular event occurred. In a small number pump thrombus or embolus occurred that affected pump function

Pump flow (l/minute) (estimated from figure)	Before, 4.5; 7 days, 4.6; 14 days, 4.6; 21 days, 4.5; 28 days, 4.4; 35 days, 4.4; 42 days, 4.3; 49 days, 4.4; 56 days, 4.4; 63 days, 4.4; 70 days, 4.5; 77 days, 4.5; 84 days, 4.5; 91 days, 5
Pump index (l/minute/m^2) (estimated from figure)	Before, 2.4; 7 days, 2.5; 14 days, 2.5; 21 days, 2.4; 28 days, 2.4; 35 days, 2.3; 42 days, 2.3; 49 days, 2.3; 56 days, 2.3; 63 days, 2.3; 70 days, 2.3; 77 days, 2.3; 84 days, 2.3; 91 days, 2.6

Comments: Compared pump index between survivors and non-survivors, difference reported to be non-significant

Resource use

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Non-random allocation
- Blinding: Blinding not possible given treatment and study
- Comparability of treatment groups: Not applicable
- Method of data analysis: Analysis limited to temporal assessment of outcomes with no statistical significant testing
- Sample size/power calculation: No sample size calculations were presented
- Attrition/drop-out: Unclear from graphical presentation of results whether all patients are included

continued

General comments
- Generalisability: Minimal baseline characteristics reported – limited to heart transplant patients
- Outcome measures: Appropriate but limited to survival, function and device performance
- Inter-centre variability: No details of numbers of centres reported
- Conflict of interests: Several authors are employed by, or own stock in, MicroMed Technology, manufacturers of the VAD

Quality Assessment for Primary Studies[77]

Study: Noon *et al*.[91]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	

continued

E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No ×	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell ×	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak ×		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 557 Author: Potapov *et al.*, 2000[93] (some patients likely to be included in Noon *et al.*, 2001[91] and Noon *et al.*, 2000[185]) Year: 2000 Country: Germany – European study began in 1998 Study design: Cohort (before and after) with no control Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTT Comparisons of different interventions: No comparison, MicroMed DeBakey only Duration of treatment: Ranged from 9 to 109 days Other interventions used: 2 patients were switched to a pulsatile LVAD owing to pump stoppage. Anticoagulation with heparin infusion postoperatively, once stabilised phenprocoumon administered. INR range target between 2.5 and 3.5	Number of participants: 6 patients Sample attrition/dropout: 2 patients switched to a pulsatile LVAD owing to pump stoppage, no data for one of these on 6-week echocardiological outcomes Inclusion/exclusion criteria for study entry: End-stage cardiac failure Class IV (assume NYHA) which could not be stabilised with medical means Characteristics of participants: 4 male, 2 female. Age range 33–62 years, weight range 60–92 kg. Diagnosis coronary heart disease in 3, cardiomyopathy in 3. All on inotropic medication, 2 on intra-aortic balloon pump and ventilated. Cardiac index ranged from 1.7 to 1.9 l/minute/m^2	Primary and secondary outcomes: Unclear, outcomes reported include primary outcome transcranial Doppler (TCD) measurements of flow parameters in the middle cerebral arteries (blood flow velocities, Gosling pulsation index); deaths; number transplanted; duration of support; echocardiography [(LVEF, RVEF, left ventricular end-diastolic diameter LVIDd)]; pump performance measured before placement and 6 weeks after Method of assessing outcomes: Detail provided concerning TCD but other outcomes are unclear Length of follow-up: not reported; outcomes were assessed to 12 weeks

Results

Outcomes	LVAD	*p*-Value
Number transplanted	2	N/A
Comments. No idea of length of follow-up		
Functional capacity		
Comments		
QoL		
Comments		
Function		
LVEF(no summary scores reported)	Median LVEF before 0.17 (0.15; 0.2), at 6 weeks 0.2 (0.15; 0.2) Patient 1: before 0.15, at 6 weeks 0.17 Patient 2: before 0.15, at 6 weeks not reported Patient 3: before 0.18, at 6 weeks 0.2 Patient 4: before 0.18, at 6 weeks 0.2 Patient 5: before 0.15, at 6 weeks 0.15 Patient 6: before 0.2, at 6 weeks 0.2	0.25
RVEF (no summary scores reported)	Median RVEF before 0.25 (0.24; 0.4), at 6 weeks 0.4 (0.35; 0.43) Patient 1: before 0.35, at 6 weeks 0.35 Patient 2: before 0.2, at 6 weeks not reported Patient 3: before 0.4, at 6 weeks 0.4 Patient 4: before 0.25, at 6 weeks 0.3 Patient 5: before 0.2, at 6 weeks 0.4 Patient 6: before 0.25, at 6 weeks 0.45	0.25

continued

Outcomes	LVAD	*p*-Value
LVIDd (mm) (no summary scores reported)	Median LVIDd before 67.5 (36; 82), at 6 weeks 58 (61; 82) Patient 1: before 82, at 6 weeks 65 Patient 2: before 69, at 6 weeks not reported Patient 3: before 78, at 6 weeks 64 Patient 4: before 66, at 6 weeks 36 Patient 5: before 61, at 6 weeks 36 Patient 6: before 65, at 6 weeks 58	0.04
Comments: The intra-individual decrease in LVIDd was between 11 and 45%		
Adverse effects		
Deaths on support	1	N/A
Comments. Death due to sepsis		
Resource use		
Comments		
Other outcomes		
Pump flow (l/minute ± SD) No summary score reported	Patient 1: 4.9 ± 0.5 Patient 2: 4.5 ± 0.5 Patient 3: 4.0 ± 0.3 Patient 4: 3.0 ± 0.4 Patient 5: 4.3 ± 0.6 Patient 6: 4.6 ± 0.5	
Comments: **Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE**		
Methodological comments • Allocation to treatment groups: Not applicable • Blinding: None • Comparability of treatment groups: Not applicable • Method of data analysis: Significant differences were confirmed with a Mann–Whitney *U*-test for independent data and Wilcoxon's test for related data. Means and SD or median and range values reported, $p < 0.05$ considered significant • Sample size/power calculation: Not applicable • Attrition/drop-out: Equipment not available for 2 patients and 2 patients received a pulsatile device		
General comments • Generalisability: Limited selection criteria and minimal baseline characteristics reported • Outcome measures: Principally limited to pulsatility of device • Inter-centre variability: No details of numbers of centres reported • Conflict of interests: GP Noon and ME DeBakey (inventor of VAD) are authors		

LVIDd, left ventricular end-diastolic diameter.

Quality Assessment for Primary Studies[77] Study: Potopov *et al.*[93]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes ×	No	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ×	60–79%	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong ×	Moderate	Weak		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes × (two had other VADS)	No	Can't 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	Can't tell ×		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 253, 172, 329, 3496 Author: Wiselthaler *et al.*,[92] likely overlap of Noon[91] and Potapov[93] Year: 2001 Country: Austria Study design: Cohort (before and after), no control group Study setting: Inpatient/outpatient Number of centres: One centre but study part of multi-centre collaboration Funding: Not reported, although MicroMed Technology Inc. provided devices	Indication for treatment: BTT Comparisons of different interventions: No comparison, MicroMed DeBakey only Duration of treatment: ranged from 25 to 130 days in first 6 and from 6 to 78 days in those who were still on LVAD at time of report Other interventions used: Modified implantation procedure for LVAD in all but first two patients. No other mechanical support In first 6 patients at least (from Ref. 101 in this report) inotropes initially after implant with a target cardiac index of $\leq$ 2.5 l/minute/m^2 within the first 24–48 h and to achieve a mixed venous-oxygen saturation >60%. If necessary nitric oxide used. Anticoagulant management according to each centre's previous VAD experience (in this case initial heparin and then phenprocouman, aspirin and dipyridamole). Outpatients checked their own with Coagucheck system	Number of participants: 10 with interim data on 2 and 6 patients Sample attrition/dropout: None Inclusion/exclusion criteria for study entry: ESHF, listed for cardiac transplant, met inclusion criteria for multi-institutional study (not specified) Characteristics of participants: all male, aged 52 $\pm$ 11 years (range 37–65), 5 dilated cardiomyopathy, 5 ischaemic cardiomyopathy. Despite maximal pharmacological support, patients showed signs of acute haemodynamic deterioration and end organ dysfunction. None required mechanical support or ventilation Limited study characteristics were provided on 10 patients, additional data were provided on subset of 6 patients in an interim report. First 6 patients were NYHA Class IV. Haemodynamic and pharmacological support for first 6 patients: Patient 1: aortic pressure (AP) (mmHg) 88/54/68, pulmonary artery pressure (PAP) (systolic/diastolic/mean) 69/38/48, pulmonary capillary wedge pressure (PCWP) (mmHg) 28, cardiac index (CI) (l/minute/m^2) 1.8, pulmonary vascular resistance (PVR) (Woods unit) 6.4, intravenous medication 5 μg/kg/minute dobutamine, 5 ng/kg/minute prostaglandin E1 Patient 2: AP (mmHg) 105/54/78, PAP (systolic/diastolic/mean) 48/25/32, PCWP (mmHg) 20, CI (l/minute/m^2) 1.9, PVR (Wood units) 2.1, intravenous medication 6 μg/kg/minute dopamine, 0.5 μg/kg/minute milrinone Patient 3: AP (mmHg) 72/40/61, PAP (systolic/diastolic/mean) 55/30/40, PCWP (mmHg) 20, CI (l/minute/m^2) 2.5, PVR (Wood units) 4.0, intravenous medication 3.7 μg/kg/minute dobutamine, 2.5 (ng/kg/minute) prostaglandin E1 Patient 4: AP (mmHg) 87/56/65, PAP (systolic/diasytolic/mean) 42/29/36, PCWP (mmHg) 26, CI (l/minute/m^2) 1.8, PVR (Wood units) 5.5 intravenous medication 5 ng/kg/minute prostaglandin E1 Patient 5: AP (mmHg) 110/56/70, PAP (systolic/diastolic/mean) 44/27/33, PCWP (mmHg) 22, CI (l/minute/m^2) 1.6, PVR (Wood units) 3.1, intravenous medication 2.5 μg/kg/minute dobutamine, 5 ng/kg/minute prostaglandin E1 Patient 6: AP (mmHg) 80/56/69, PAP (systolic/diastolic/mean) 55/30/39, PCWP (mmHg) 26, CI (l/minute/m^2) 1.7, PVR (Wood units) 3.5, intravenous medication 6 μg/kg/minute dobutamine	Primary and secondary outcomes: (Not clearly differentiated) survival (to transplant and postoperative); duration of support; adverse events; indices of haemolysis; heart function, haemodynamics and pump flow. Some variables assessed on subgroups as interim reports Method of assessing outcomes: Not stated Length of follow-up: Not stated; outcomes assessed up to 139 days

continued

Results

Outcomes	LVAD	*p*-Value
Survival	8 survived; 4 transplanted; 4 awaiting transplant; 2 dead	N/A
Comments: 4 patients still on device at time of follow-up. 2 patients were discharged home with the device (1 died)		
Outpatient care	3 patients discharged with device; 2 patients discharged for daily excursions	
Comments: Not assessed		
Functional capacity		
Comments: Not assessed		
Function		
Haemoglobin (*n* = 5)	Preop, 12.9 ± 0.3; week 1, 9.8 ± 1.2; week 2, 9.3 ± 1.0; week 3, 8.9 ± 1.0; week 4, 9.5 ± 1.0; week 10, 10.3 ± 0.9; week 15, (*n* = 4) 10.1 ± 0.7	
Creatinine (*n* = 5)	Preop, 1.4 ± 0.4; week 1, 1.4 ± 0.7; week 2, 1.8 ± 1.1; week 3, 2.2 ± 1.2; Week 4, 1.8 ± 1.0; week 10, 1.0 ± 0.1; week 15, (*n* = 4) 0.9 ± 0.0	
BUN (*n* = 5)	Preop, 21.4 ± 5.6; week 1, 20.6 ± 6.7; week 2 26.9 ± 10; week 3, 29.4 ± 19.7; week 4, 22.0 ± 19.0; week 10, 14.0 ± 1.8; week 15, (*n* = 4) 24.6 ± 10.5	
Plasma free haemoglobin (*n* = 5)	Preop, 1.8 ± 0.2; week 1, 2.7 ± 2.3; week 2, 2.4 ±1.2; week 3, 3.5 ± 1.9; week 4, 4.2 ± 3.3; week 10, 4.3 ± 1.8; week 15, (*n* = 4) 5.0 ± 3.1	
Bilirubin (*n* = 5)	Preop, 1.8 ± 1.2; week 1, 4.4 ± 5.8; week 2, 3.3 ± 2.8; week 3, 1.8 ± 1.0; week 4, 1.3 ± 0.6; week 10, 1.0 ± 0.4; week 15, (*n* = 4) 0.9 ± 0.0	
Lactate dehydrogenase (*n* = 5)	Preop, 149 ± 12; week 1, 320 ± 78; week 2, 318 ± 56; week 3, 428 ± 73; week 4, 491 ± 131; week 10, 646 ± 105; week 15 (*n* = 4); 511 ± 221	
Comments		
QoL		
Comments: Not assessed		
Adverse effects		
Deaths on support	2 patients (1 patient died from MOF after 25 days; 1 patient died infectious complications leading to MOF 142 days post-operation)	N/A
Comments: 1 patient required RVAD support, 1 had cerebral bleeding, 2 patients had pneumonia-like infiltrations in the lung shortly after implantation and needed reintubating. 1 patient was positive to methicillin-resistant *Staphylococcus aureus*; this caused septic complications, which caused uraemia with the need for haemofiltration and intubation		
Resource use		
Comments: Not assessed		
Device failure	3 patients suffered device failure	
Comments: Not assessed		

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Continuous variables mean (standard deviations), Student's paired and unpaired *t*-tests to compare continuous variables
- Sample size/power calculation: Not applicable
- Attrition/drop-out: One patient data missing on haemolysis variables at 15 weeks

General comments

- Generalisability: Minimal baseline characteristics reported
- Outcome measures: Unclear length of follow-up
- Inter-centre variability: Not applicable
- Conflict of interests: DeBakey device inventor is an author

Quality Assessment for Primary Studies[77] Study: Wieselthaler *et al.*[92]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes ×	No	Can't tell		
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes ×	No	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ×	60–79%	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak ×		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes ×	No	Can't tell		

Appendix 18

Summary of the evidence of clinical effectiveness of the Abiomed device as a BTR for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1185 Author: Marelli *et al.*[104] Year: 1997 Country: USA and Belgium Study design: Case report Study setting: Inpatient Number of centres: Unclear Funding: Not reported	Indication for treatment: BTR Comparisons of different interventions: No comparison, Abiomed BVS 5000 only Duration of treatment: 7 days Other interventions used: Immunotherapy with monoclonal antibody therapy, steroids and immunoglobin	Number of participants: 1 patient on LVAD only (3 other patients had BiVAD support, data not extracted for these patients) Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Worsening heart failure (cardiac index <2.0 l/minute/m^2, pulmonary wedge pressure >18 mmHg) with end organ dysfunction despite use of inotropes at maximal support [Up to two of: dopamine or dobutamine at 10 μg/kg/minute, epinephrine 0.18 μg/kg/minute or milrinone at 0.7 μg/kg/minute (or the equivalent dose of amrinone)], including use of intra-aortic balloon pump following onset of flu-like illness (acute myocarditis) Characteristics of participants: cardiogenic shock secondary to acute myocarditis, age 16, male, 20 days of symptoms before CHF (defined as time of onset of symptoms of respiratory congestion), ejection fraction 20%. Patient had >2 inotropes, liver, renal and pulmonary dysfunction	Primary outcomes: Duration of support Secondary outcomes: Ejection fraction adverse effects Method of assessing outcomes: Not reported Length of follow-up: Unsure, reports from 6 months to 3 years

Results

Outcomes	LVAD	*p*-Value
Survival	Weaned at 7 days and discharged home in good condition	
Comments. Did not require listing for transplantation in short-term follow-up (6 months to 3 years is the range reported for the total group, do not know the duration for LVAD patient alone)		
Functional capacity		
Ejection fraction	LVAD patient not clear from figure	
Comments		
QoL		
Comments		
Function		
Comments		
Adverse effects	None reported for LVAD patient	
Comments		
Resource use		
Comments		

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

continued

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: Not reported
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments

- Generalisability: 1 patient only, generalisability low. Not clear if this was the only patient who had LVAD implanted
- Outcome measures: No survival data presented
- Inter-centre variability: Number of centres not clear, not clear whether LVAD patient from USA or Belgium
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77]

Study: Marelli *et al.*[104]

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	Can't tell ×	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after) Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	

continued

D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell	N/A	
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 19

Summary of the evidence of clinical effectiveness of the HeartMate LVAD as a BTR for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 352 Author: Kjellman *et al.*[105] Year: 2000 Country: Sweden Study design: Case report Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTR Comparisons of different interventions: No comparison. HeartMate only Duration of treatment: 83 days Other interventions used: Antibiotic treatment for infections	Number of participants: 1 Sample attrition/dropout: not applicable Inclusion/exclusion criteria for study entry: [During 3 preceding weeks developed neurological symptoms and signs of a progressive brainstem syndrome (headache, vertigo, impaired balance, nausea, fatigue, left-sided sensory disturbances) and neurological examination revealed dysesthesia of the left side of the face and the left arm, a right-sided pharyngeal paresis and left side deviation of the tongue. MRI demonstrated multiple periventricular and subcortical lesions of the brain and one lesion of the right side of the medulla oblongata. The neuroophthalmological findings and examination with visual-evoked potentials revealed signs of left optic neuritis.] The patient deteriorated with clinical signs of autonomic dysfunction and progressive heart failure. At admission had severe left ventricular heart failure Characteristics of participants: Female, 19 years. Acute left ventricular heart failure during first exacerbation of multiple sclerosis. Unresponsive to inotropic support	Primary and secondary outcomes: Recovery cardiac function, echocardiographic data (heart rate, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, LVEF, mitral and tricuspid insufficiency grade 0–4) Invasive haemodynamic data with device in the on and off position, at rest and during supine bicycle exercise with a 20-W and 40-W workload, NYHA, adverse effects Method of assessing outcomes: Not reported Length of follow-up: up to 1 year (data at 10 months)

Results

Outcomes

Survival

Comments: Cardiac function was normalised and remains so 1 year after explantation. At 1 year after explantation, patient in excellent clinical condition and NYHA Class I. Not taking any pharmacological therapy for heart failure

Function	Admission	After explantation	10-months follow-up
Heart rate (beats/minute)	155	80	70
Left ventricular end-diastolic diameter (mm)	53	44	51
Left ventricular end-systolic diameter (mm)	47	32	31
LVEF (%)	<10	>50	60

continued

Function	Admission	After explantation	10-months follow-up
Mitral insufficiency grade 0–4	2/4	2–3/4	0/4
Tricuspid insufficiency grades 0–4	2/4	2–3/4	0/4
Invasive haemodynamic data with LVAD switched on and off, at rest and during supine exercise	**Admission**	**Before explantation (about 2.5 months after implantation)**	
Heart rate (beats/minute)	155	Rest with LVAD: 87 20 W with LVAD: 104 Rest LVAD off: 85 20 W LVAD off: 81 40 W LVAD off: 125	
Mean artery pressure (mmHg)	72	Rest with LVAD: 84 20 W with LVAD: 76 Rest LVAD off: 78 20 W LVAD off: 78 40 W LVAD off: 72	
Central venous pressure (mmHg)	18	Rest with LVAD: 5 20 W with LVAD: 6 Rest LVAD off: 6 20 W LVAD off: 9 40 W LVAD off: 8	
Pulmonary capillary wedge pressure (mmHg)	12	Rest with LVAD: 5 20 W with LVAD: 8 Rest LVAD off: 13 20 W LVAD off: 23 40 W LVAD off: 20	
Mean pulmonary artery pressure (mmHg)	19	Rest with LVAD: 11 20 W with LVAD: 16 Rest LVAD off: 20 20 W LVAD off: 25 40 W LVAD off: 25	
Cardiac index (l/minute/m^2)	1.8	Rest with LVAD: 3.4 20 W with LVAD: 4.1 Rest LVAD off: 2.2 20 W LVAD off: 3.4 40 W LVAD off: 4	
Stroke volume index (ml/m^2)	12	Rest with LVAD: 39 20 W with LVAD: 39 Rest LVAD off: 26 20 W LVAD off: 42 40 W LVAD off: 32	
Systemic vascular resistance (dyn/s/cm^{-5})	901	Rest with LVAD: 1203 20 W with LVAD: 875 Rest LVAD off: 1694 20 W LVAD off: 1057 40 W LVAD off: 826	
Pulmonary vascular resistance (dyne/s/cm^{-5})	117	Rest with LVAD: 92 20 W with LVAD: 100 Rest LVAD off: 165 20 W LVAD off: 30 40 W LVAD off: 65	
Anteriovenous oxygen difference (ml/l)	Missing data	Rest with LVAD: 50.4 20 W with LVAD: 102.6 Rest LVAD off: 54.9 20 W LVAD off: 104.1 40 W LVAD off: 105.8	
Comments: Testing before explantation was at 2.5 months Above data show recovery of left ventricular function			

continued

Adverse effects	3 weeks after implantation: drive line infection *(Staphylococcus aureus)* 8 weeks after implantation: relapse of neurological symptoms and diagnosis of multiple sclerosis confirmed Infectious problems with repeated periods of sepsis despite antibiotic treatment, therefore device was explanted 83 days after implantation

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments

- Generalisability: Limited, one case of temporary support whilst heart function recovers from severe heart failure attributed to multiple sclerosis (rare)
- Outcome measures: Echocardiographic data and invasive haemodynamic data
- Inter-centre variability: Not applicable
- Conflict of interests: Not reported

Quality Assessment for Primary Studies[77]

Study: Kjellman *et al.*[105]

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 ×	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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 ×		

continued

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	Can't tell		N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell		N/A
2. Were the study participants aware of the research question?	Yes	No	Can't tell		N/A
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell		N/A
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		N/A
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation NA	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis NA	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell		N/A
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell		N/A

Appendix 20

Summary of the evidence of clinical effectiveness of the Novacor LVAD as a BTR for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1015 Author: Pietsch *et al.*[106] Year: 1998 Country: Germany Study design: Case report Study setting: Inpatient/partial outpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTR Comparisons of different interventions: Novacor only Duration of treatment: ~3 months Other interventions used: after 3 months cardiac catheterisation and percutaneous transluminal coronary angioplasty of the circumflex artery and then direct coronary artery bypass grafting of the left internal mammary artery to the left anterior descending artery	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Cardiac failure refractory to intensive medical regimen including diuretics, beta-blockers, digitalis and ACE inhibitors. Presenting for cardiac transplantation but contraindicated due to elevated pulmonary vascular resistance and placed on LVAD to see if peripheral circulation improved and pulmonary hypertension reversed Characteristics of participants: 54-year-old, male, cardiac catheterisation showed two-vessel disease with occlusion of the proximal left anterior descending artery and a 75% stenosis of the circumflex artery Left ventricular function was extremely reduced: LVEF 0.10 LV end-diastolic volume 287 ml, end-systolic volume 258 ml Cardiac index 1.3 l/minute/m^2 (Flick method) Pulmonary hypertension mean pressure 45 mmHg Pulmonary wedge pressure 24 mmHg Pulmonary vascular resistance 8 Wood units	Primary outcomes: Survival Secondary outcomes: LVEF Method of assessing outcomes: Not reported Length of follow-up: 6 months post-discharge

Results

Outcomes	LVAD
Survival	Patient transferred to a partial outpatient status 6 weeks after implant 2 months later cardiac recatheterisation Device removed 4 weeks after revascularisation Discharged home after a further 6 weeks Alive and well at 6 months post-discharge
Comments	
Functional capacity	
LVEF (%)	After 2 months of support, 0.46; after switching device off, 0.36 Prior to discharge: 0.50 6-month follow-up: 0.50
Left ventricular volumes[a]	Returned to near normal. Values not reported
Pulmonary artery pressure[a]	Dropped to normal on device, no increase when device switched off. Values not reported
	At 2 months, recovery of myocardium demonstrated by cardiac recatheterisation

[a] Whilst device switched off prior to catheterisation at 3.5 months

Comments

continued

QoL

Comments

Function

Comments

Adverse effects

Comments

Resource use

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments

- Generalisability: Limited. Patients with elevated pulmonary vascular resistance, contraindicated for cardiac transplantation
- Outcome measures: Limited, data on ventricular ejection fraction and duration support
- Inter-centre variability: Not applicable
- Conflict of interests: Not stated

Quality Assessment for Primary Studies[77]

Study: Pietsch *et al.*[106]

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 ×	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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 ×		

continued

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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell	N/A	
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 21

Summary of the evidence of clinical effectiveness of the Thoratec LVAD as a BTR for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 9060 Author: Joharchi *et al.*[107] Year: 2002 Country: Germany Study design: Case report Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTR Comparisons of different interventions: No comparison, Thoratec LVAD only Duration of treatment: 46 days Other interventions used: Dopamine hydrochloride (2 μg/kg/minute), dobutamine (12 μg/kg/minute), milrinone lactate (0.25 μg/kg/minute) up to 25 days post-implantation when propranolol hydrochloride 3 mg/kg/day and enalapril maleate 5 mg/day initiated	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: None stated Characteristics of participants: 17-year-old female, weighing 55 kg, systolic BP 80 mmHg, tachycardic (no value). Previously healthy, patient seen with cardiac decompensation after 10 days of flu-like symptoms and near to collapse. 36 h after admission, decision to implant LVAD due to severe low-output syndrome with hepatorenal failure, indicated by a strong rise in aminotransferase and bilirubin. Pericardial effusion, pleural effusion and poor left ventricular function seen on echocardiogram. Had effusions tapped (2000 ml pericardium, 1800 ml pleura), severely impaired left ventricular systolic function, fractional shortening of 15% and a non-dilated ventricle. Findings were consistent with acute myopericarditis Supported with inotropes prior to LVAD: dobutamine (12 μg/kg/minute), epinephrine (0.12 μg/kg/minute) and norepinephrine (0.18 μg/kg/minute). Progressive hypotension and oliguria. Right atrial pressure of 20 mmHg, pulmonary artery wedge pressure 19 mmHg, cardiac index 1.8 l/minute/m^2	Primary outcomes: Survival Secondary outcomes: LVEF, NYHA functional class Method of assessing outcomes: Not reported Length of follow-up: 6 months

Results

Outcomes	LVAD
Survival	Supported for 46 days when weaned. Alive at follow-up
Comments: Weaning programme started at 25 days, when support frequency was reduced sequentially, and LV function was evaluated by echocardiography during short stops at 7-day intervals	
Functional capacity	LVEF 0.77 at discharge
Comments	
QoL	
Comments	
Function	NYHA Class I at follow-up
Comments	
Adverse effects	
Comments	

continued

Resource use

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments

- Generalisability: Single 17-year-old female only, with acute myocarditis
- Outcome measures: Limited
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77]

Study: Joharchi *et al*.[107]

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	Can't tell ×	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort (one group pre + post (before and after)) Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	

continued

D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 326 Author: Ueno *et al.*[108] Year: 2000 Country: Australia Study design: Case study Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTR Comparisons of different interventions: No comparison, Thoratec device only Duration of treatment: 5 weeks Other interventions used: Haemofiltration after the operation because of progressive oliguria and low-dose dopamine infusion	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Case with profound heart failure secondary to acute myocarditis. Previously healthy patient presented with collapse following 1 week of flu-like symptoms Characteristics of participants: previously healthy 34-year-old male presented with collapse after week of flu-like symptoms, echocardiogram showed pericardial effusion and poor left ventricular function. Systolic BP 75 mmHg, tachycardic (110/minute). No ischaemic ST-T changes seen on echo and repeated transthoracic echo revealed severely impaired left ventricular systolic function, fractional shortening of 16%, a non-dilated ventricle, end-diastolic left ventricular diameter of 4.1 cm and a pericardial effusion, consistent with a diagnosis of myopericaditis Patient remained tachycardic, tachypneic and oliguric, and developed acute cardiogenic shock requiring cardiopulmonary resuscitation including intubation and ventilation. Despite high-dose inotropes [dobutamine (10 μg/kg/minute), adrenaline (40 μg/minute) and noradrenaline (5 μg/minute)] and intra-aortic balloon pump support, haemodynamic data showed right atrial pressure 20 mmHg and pulmonary artery wedge pressure 20 mmHg and cardiac index 1.6 l/minute/m^2. Endomyocardial biopsy showed diffuse mild lymphocytic myocardial infiltration with intact myocardial fibres	Primary outcomes: Survival Secondary outcomes: Cardiac index Method of assessing outcomes: Not reported Length of follow-up: 3 months

Results

Outcomes	LVAD
Survival	Survived to 3 months of follow-up (returned to full-time work)

Comments: Transoesophageal echocardiography after 2 weeks showed markedly improved left ventricular contractility under low-dose dopamine infusion. 3 weeks later the device was removed

Functional capacity Cardiac index 1 month after explantation was 3.52 l/minute/m^2

Comments: Endomyocardial biopsy at this time showed mild myocarditis

QoL

Comments

Function

Comments

Adverse effects

Comments

Resource use

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

continued

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments
- Generalisability: Single 34-year-old male patient only, with acute myocarditis
- Outcome measures: Minimal
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77]

Study: Ueno *et al.*[108]

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	Can't tell ×	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	

continued

D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client ×
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client ×
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 22

Summary of the evidence of clinical effectiveness of the Toyobo LVAD as a BTR for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1058 Author: Nakatani *et al.*[109] Year: 1998 Country: Japan Study design: Case series Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: BTR Comparisons of different interventions: Assume Toyobo (references mention Toyabo and Zeon pump), no comparison Duration of treatment: Up to 11 months (319 days) Other interventions used: Exercise after stabilisation	Number of participants: 5 (6 patients in total but one had BiVAD – data not extracted) Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Chronic profound heart failure. Considered as heart transplant candidates. Acute deterioration of the haemodynamic condition despite massive medical therapy, including intravenous catecholamine infusion Characteristics of participants: Aged 17–49 years (mean 31 ± 13) 5 males, 1 female 5 patients had dilated cardiomyopathy, 1 had dilated phase hypertrophic cardiomyopathy. All had impaired cardiac function and dilation of the left ventricle (left ventricular end-diastolic dimension 77.3 ± SD 7.7 mm), one patient had intra-aortic balloon pump before LVAS use In one patient biventricular support was indicated because of severe biventricular failure; this patient had severe infection and died of MOF 2 weeks after installation of the BiVAD	Primary and secondary outcomes: Survival, adverse events, cause of death, echocardiography parameters (heart size and function) in two surviving patients Method of assessing outcomes: Heart size and function by echocardiology Length of follow-up: up to 3 years 9 months (patient 1)

Results

Outcomes	LVAD
Survival	2 patients survived 3 months and weaned. 1 had VAS removed after 95 days and is alive at 1 year 6 months, 1 had VAS removed after 50 days and is alive at 3 years 9 months 3 patients' heart function did not improve and died at 7, 9 and 11 months after insertion of LVAS (see adverse events)
Comments	
Functional capacity	
Patient 1 ([a]estimated from figure) 17 years, male, dilated cardiomyopathy	[a] Baseline heart rate (beats/minute), 100; at LVAS removal, 100; at 60 days after removal, 90 [a] Baseline diastolic dimension (mm), 68; at LVAS removal, 50; at 60 days after removal, 44 [a] Baseline systolic dimension (mm), 75; at LVAS removal, 54; at 60 days after removal, 60 [a] Ejection time and pre-ejection period: unclear which figure relates to which outcome Exercise tolerance test at 2 months of support: peak VO_2 of 20 under 4 l/minute of support, at 87 days generated more than 5 l/minute measured by the Flick method under 3.5 l/minute of support, at 2 months after removal LVAS: peak VO_2 27.2 ml/minute/kg, at 2 years and 8 months peak exercise load of 150 W Cardiac output at 2 months after removal: 6.3 l/minute Pulmonary wedge pressure at 2 months after removal: 5 mmHg LVEF at 2 months after removal: 45%

continued

Patient 2 21 years, male, exercise Dilated cardiomyopathy	Exercise tolerance testing at 86 days: 5 l/minute by the Flick method and peak VO_2 17.6 at 3.6 l/minute support, at 1 year 2 months after removal peak VO_2 30.1 ml/minute/kg, peak load of 150 W

Comments: also figure of left ventricular end-diastolic dimension of the five patients but unable to estimate values

QoL

Comments

Function

Comments

Adverse effects	1 patient LVAS was stopped because of cerebral haemorrhage caused by infectious aneurysm 5 months after the start of the LVAS; this patient died of sepsis 2 months after discontinuation The other two patients developed cerebral embolism after 3 and 5 months of LVAS and died at 9 and 11 months from MOF

Comments

Resource use

Comments

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Not applicable
- Blinding: None
- Comparability of treatment groups: Not applicable
- Method of data analysis: No data analysis, reports rates only
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments

- Generalisability: Minimal patient characteristics given, small sample, not clear how patients were selected and insufficient details of patient characteristics to determine generalisability. All had cardiomyopathy (cause not reported)
- Outcome measures: Survival appropriate, functional outcomes not consistently reported. Before/after measures not for all patients
- Inter-centre variability: Not applicable
- Conflict of interests: None noted (although report use or 'our' VAS, so potential for conflict)

Quality Assessment for Primary Studies[77]

Study: Nakatani *et al.*[109]

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	Can't tell ×	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case series/reports Can't Tell				×

continued

2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell	N/A	
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell	N/A	
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 2840 Author: Noda *et al.*[110] Year: 1989 Country: Japan Study design: Case series Study setting: Inpatient Number of centres: 1 Funding: None reported	Indication for treatment: BTR following cardiogenic shock following acute MI Comparisons of different interventions: No comparison, Toyobo LVAD only Duration of treatment: 12 days Other interventions used: Group 1 also had repair of ventricular septal perforation, group 2 also had aorto-coronary bypass grafting (ACBG). No details of medical therapies	Number of participants: 2 patients (data reported but not extracted on a further 8 patients with previous coronary surgery) Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Acute MI, cardiac output below 2.0 l/minute/m^2, left atrial pressure or pulmonary arterial wedge pressure >18 mmHg, systemic pressure <80 mmHg. Also Killip class 4 and Forrester stage 4 of cardiogenic shock were also candidates (no details of definition, or numbers included with these indications) Characteristics of participants: Group 1: LVAD with no aorto-coronary bypass grafting, both patients male and aged 69 and 73 years, both with acute MI and shock	Primary outcomes: Survival Secondary outcomes: Adverse events Method of assessing outcomes: Not reported Length of follow-up: Last event reported at 149 days

Results

Outcomes	LVAD
Survival	1 patient survived and was weaned after 12 days (then had ACBG) but died 149 days after removal, from infection and cerebral haemorrhage; 1 patient died of respiratory failure whilst on the LVAD (12 days)
Comments	
Functional capacity	
Comments	
QoL	
Comments	
Function	
Comments	
Adverse effects	
Defined by body organ, not specific complication	Patient 1: massive transfusion before LVAD. Lung and kidney complications requiring special treatments[a], liver and infection complications not requiring special treatments Patient 2: kidney complications requiring special treatments[a], lung, infection, brain, disseminated intravacular coagulation not requiring special treatments
Comments: [a]Special treatments include: high-frequency oscillated ventilation for lung complication, peritoneal dialysis for kidney failure, plasmapheresis for liver. Infection = sepsis on blood culture	
Resource use	
Comments	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

continued

Methodological comments
- Allocation to treatment groups: Retrospective case series
- Blinding: No
- Comparability of treatment groups: Not applicable
- Method of data analysis: No analysis, reports events only
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not reported

General comments
- Generalisability: Minimal baseline data given, generalisable to those with cardiogenic shock post-acute MI. Not clear if selected all such patients who had LVAD inserted
- Outcome measures: Appropriate
- Inter-centre variability: Not applicable
- Conflict of interests: None noted; reports that Toyobo supplied the LVADs, unsure whether this means supplied with or without charge

Quality Assessment for Primary Studies[77]

Study: Noda *et al.*[110]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case series/reports Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	

continued

D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		
F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell	N/A	
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell	N/A	
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 23

Summary of the evidence of clinical effectiveness of the HeartMate LVAD as an LTCS for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 89 Author: Rose *et al.*[111] Year: 2001 Country: USA Study design: RCT Study setting: Inpatient/outpatient Number of centres: 20 Funding: National Institutes of Health and Thoratec	Indication for treatment: LTCS Comparisons of different interventions: 1. HeartMate VE. Followed guidelines including preoperative measures (e.g. prophylaxis with antimicrobial agents), intraoperative measures (e.g. placement of drive line), post op measures (changes of exit site dressing) LVAD patients had "associated medical care" 2. Optimal medical management (following guidelines developed by medical committee with goals of optimising organ perfusion and minimising symptoms of congestive heart failure. ACE inhibitors, encouraged discontinuation of i.v. inotropic infusions Duration of treatment: Not reported	Number of participants: Total: 129 LVAD: 68 Medical: 61 Sample attrition/dropout: All 129 included in primary end-point analysis Medical: 2 withdrew at 1 and 6 months after randomisation No patients in either group crossed over. All assigned to receive LVAD had device implanted. 5 medical and 2 LVAD did not complete all QoL and functional status questionnaires at 1 year Inclusion criteria for study entry: Adults with chronic ESHF and contraindications to transplant Initial criteria: presence of symptoms of NYHA Class IV heart failure for at least 90 days despite therapy with ACE inhibitors, diuretics and digoxin; LVEF of ≤25%; peak oxygen consumption of no more than 12 ml/kg/minute or a continued need for i.v. inotropic therapy owing to symptomatic hypotension, decreasing renal function or worsening pulmonary congestion After 18 months: criteria included symptoms of NYHA Class IV heart failure for 60 days and peak oxygen consumption of no more than 14 ml/kg/minute; NYHA Class III or IV for at least 28 days and at least 14 days of support with intra-aortic balloon pump or with a dependence on i.v. inotropic agents, with 2 failed weaning attempts (only five recruited with this criterion, 3 LVAD, 2 medical) Reasons for transplant contraindication: age >65 years, insulin-dependent diabetes mellitus with end-organ damage, chronic renal failure with serum creatinine concentration >2.5 mg/dl (221 μmol/l) for at least 90 days before randomisation, presence of other clinically significant conditions Characteristics of participants [(mean (SD)]: Age: medical 68 years (8.2), LVAD 66 years (9.1) Male: medical 82%, LVAD 78% Ischaemic cause: medical 69%, LVAD 78% LVEF: medical 17% (4.5), LVAD 17% (5.2) Systolic BP: medical 103 mmHg (17), LVAD 101 mmHg (15)	Primary outcomes: Death from any cause Secondary outcomes: Incidence of serious adverse events Number of days of hospitalisation QoL Symptoms of depression Functional status Method of assessing outcomes: Causes of death and adverse effects reviewed by an independent morbidity and mortality committee Adverse events considered serious if they caused death or permanent disability, were life threatening or required prolonged hospitalisation QoL and functional status assessed with MLHFQ (total score 0–105, higher score, worse QoL); two prespecified subscales [physical function and emotional role, scored 0 (worst) to 100 (best)] of the SF-36; NYHA classification Depression assessed with Beck Depression Inventory (score 0–9 normal, 10–18 mild to moderate depression, 19–29 moderate to

continued

Reference and design	Intervention	Participants	Outcome measures
	Other interventions used: Patients could continue with beta-blockers if they had been administered for at least 60 of the 90 days before randomisation	Diastolic BP: medical 62 mmHg (11), LVAD 61 mmHg (10). Pulmonary capillary wedge pressure: medical 24 mmHg (7.4), LVAD 25 mmHg (9.9). Cardiac index: medical 2 l/minute/m^2 (0.61), LVAD 1.9 l/minute/m^2 (0.99). Heart rate: medical 84 beats/minute (15), LVAD 84 beats/minute (16) Pulmonary vascular resistance (Wood units): medical 3.2 (1.8), LVAD 3.4 (1.8) Serum sodium: medical 135 mmol/l (5.8), LVAD 135 mmol/l (5.4) Serum creatinine: medical 1.8 mg/dl (0.66), LVAD 1.7 mg/dl (0.65) Concomitant medication: Digoxin: medical 85%, LVAD 87% Loop diuretics: medical 97%, LVAD 96% Spironolactone: medical 39%, LVAD 34% ACE inhibitors: medical 51%, LVAD 62% A-II antagonists: medical 18%, LVAD 10% Amiodarone: medical 46%, LVAD 45% Beta-blockers: medical 20%, LVAD 24% I.v. inotropes: medical 72%, LVAD 65% NYHA Class: medical IV, LVAD IV QoL: Minnesota score: medical 75 (17), LVAD 75 (18) SF-36 physical function: medical 18 (19), LVAD 19 (19) SF-36 emotional role: medical 25 (38), LVAD 33 (42) Beck Depression Inventory: medical 16 (8), LVAD 19 (9)	severe depression, 30–64 severe depression) Patients followed up monthly once discharged Length of follow-up: up to 30 months Enrolment ended once the predetermined number of 92 deaths had occurred

Results

Outcomes	LVAD	Medical therapy	*p*-Value
Survival at 1 year (actuarial)	52%	25%	0.002
Survival at 2 years (actuarial)	23%	8%	0.09
Median survival	408 days	150 days	
Death from any cause (Kaplan–Meier analysis over 30 months)	Reduction of 48% in the risk of death from any cause in LVAD group: RR 0.52 (95% CI 0.34 to 0.78), $p = 0.001$		
Not enough power for subgroup analysis but prespecified analysis with stratification according to age (18–59, 60–69, ≥ 70 years) (risk of death) LVAD versus medical group: 60–69 years, RR 0.49 (95% CI 0.25 to 0.95) 18–59 years, RR 0.47 (95% CI 0.17 to 1.28) ≥ 70 years, RR 0.59 (95% CI 0.31 to 1.15)			
One-year survival in patients <60 years ($n = 22$)	74% ($n = 13$)	33% ($n = 9$)	0.05
One-year survival inpatients 60–69 years ($n = 49$)	47% ($n = 29$)	15% ($n = 20$)	0.009
QoL and functional status at 1 year			
Physical function	No. assessed: 23/24 (96%) Score: 46 (SD 19)	No. assessed: 6/11 (55%) Score: 21 (SD 21)	0.01
Emotional role	No. assessed: 23/24 (96%) Score: 64 (SD 45)	No. assessed: 6/11 (55%) Score: 17 (SD 28)	0.03

continued

MLHFQ[a]	No. assessed: 23/24 (96%) Score: 41 (SD 22)	No. assessed: 6/11 (55%) Score: 58 (SD 21)	0.11
Beck Depression Inventory	No. assessed: 22/24 (92%) Score: 8 (SD 7)	No. assessed: 5/11 (45%) Score: 13 (SD 7)	0.04
Medial NYHA Class	No. assessed: 24/24 (100%) Score: II	No. assessed: 7/11 (64%) Score: IV	<0.001

Comments: 5/11 medical patients who were alive at 1 year did not complete questionnaires (3 too ill, 1 could not arrange transport, 1 scheduling error)
1/24 LVAD patients did not complete questionnaire (could not arrange transport). Reason for extra patient not completing Beck Depression Inventory not given
Too few patients for analysis of two-year data
[a] Although not significant, the difference of 17 points at 1 year greatly exceeded the 5-point threshold for meaningful improvement used in other studies

Sample activities at 1 year from physical function subscale of SF-36	(Completed by 23/24 eligible LVAD patients)	(Completed by 23/24 eligible medical patients)	***p*-Value**
Climbing one flight of stairs	Not limited at all: 15 Limited a little: 5 Limited a lot: 3	Not limited at all: 0 Limited a little: 3 Limited a lot: 3	0.006
Climbing several flights of stairs	Not limited at all: 1 Limited a little: 14 Limited a lot: 8	Not limited at all: 0 Limited a little: 0 Limited a lot: 6	0.008
Walking one blocks	Not limited at all: 16 Limited a little: 6 Limited a lot: 1	Not limited at all: 1 Limited a little: 2 Limited a lot: 3	0.004
Walking several blocks	Not limited at all: 6 Limited a little: 10 Limited a lot: 7	Not limited at all: 0 Limited a little: 3 Limited a lot: 3	0.18
Walking more than 1 mile	Not limited at all: 2 Limited a little: 6 Limited a lot: 15	Not limited at all: 0 Limited a little: 2 Limited a lot: 4	0.72
Bathing or dressing	Not limited at all: 9 Limited a little: 11 Limited a lot: 3	Not limited at all: 2 Limited a little: 2 Limited a lot: 2	0.43
Adverse effects			
Deaths at time of final analysis	41	54	
Cause of death:			
Left ventricular dysfunction	1	50	
Sepsis	17/41 (41% of deaths)	1	
Failure of LVAD	7/41 (17% of deaths)	0	
Miscellaneous non-cardiovascular causes	5	0	
Cerebrovascular disease	4	0	
Miscellaneous cardiovascular causes	2	1	
Pulmonary embolism	2	0	
Acute MI	0	1	
Cardiac procedure	0	1	
Perioperative bleeding	1	0	
Unknown	2	0	
Incidence of serious adverse events (rate/patient-year):	(*n* = 60)	(*n* = 67)	
Any serious adverse event	6.45	2.75	Rate ratio 2.35 (95% CI 1.86 to 2.95)

continued

Non-neurological bleeding	0.56	0.06	Rate ratio 9.47 (95% CI 2.30 to 38.90)
Neurological dysfunction (stroke, transient ischaemic attack, toxic or metabolic encephalopathy)	0.39	0.09	Rate ratio 4.35 (95% CI 1.31 to 14.50)
Supraventricular arrhythmia	0.12	0.03	Rate ratio 3.92 (95% CI 0.47 to 32.40)
Peripheral embolic event	0.14	0.06	Rate ratio 2.29 (95% CI 0.48 to 10.80)
Sepsis	0.60	0.30	Rate ratio 2.03 (95% CI 0.99 to 4.13)
Local infection	0.39	0.24	Rate ratio 1.63 (95% CI 0.72 to 3.70)
Renal failure	0.25	0.18	Rate ratio 1.42 (95% CI 0.54 to 3.71)
Miscellaneous adverse events	1.37	0.98	Rate ratio 1.41 (95% CI 0.93 to 2.12)
Syncope	0.04	0.03	Rate ratio 1.31 (95% CI 0.12 to 14.40)
Serious psychiatric disease	0.04	0.03	Rate ratio 1.31 (95% CI 0.12 to 14.30)
Cardiac arrest	0.12	0.18	Rate ratio 0.65 (95% CI 0.21 to 2.00)
Non-perioperative MI	0.02	0.03	Rate ratio 0.65 (95% CI 0.04 to 10.30)
Ventricular arrhythmia	0.25	0.56	Rate ratio 0.45 (95% CI 0.22 to 0.90)
Hepatic failure	0.02	0.0	
LVAD-related events:			
Suspected malfunction of LVAD	0.75		
Perioperative bleeding	0.46		
Infection of drive-line tract or pocket	0.41		
Infection of pump interior, inflow tract or outflow tract	0.23		
Right heart failure	0.17		
Failure of LVAD system	0.08		
Thrombosis in LVAD	0.06		
Perioperative MI	0.0		

LVAD-related events:
Within 3 months after implantation, probability of infection of LVAD = 28% (95% CI 15 to 38)
Most of these infections were in drive-line tract and pocket and were treated with local measures and antibiotics. Fatal sepsis was common
Within 6 months after implantation, frequency of bleeding = 42%
No system failed by 12 months
Probability of device failure at 24 months = 35%
Device was replaced in 10 patients

continued

Resource Use			
Median days spent out of the hospital	340	106	Not reported
Median days spent in the hospital	88	24	Not reported
Median days spent in the hospital for medical management or implantation of LVAD	29	5	Not reported

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Randomly assigned in a 1:1 ratio using a block design to ensure continued equivalence of group size. Stratified according to centre. Eligibility of patients determined by investigators at each site and confirmed by a gatekeeper at coordinating centre. Allocation concealment unclear
- Blinding: States that all investigators except the statisticians were unaware of overall outcome data throughout enrolment period. Blinding of outcome assessors not stated
- Comparability of treatment groups: No significant differences in baseline characteristics
- Method of data analysis: Enrolment ended once predetermined number of 92 deaths had occurred. Death from any cause compared using log-rank statistic. Cox proportional-hazards regression for relative risks and 95% CI and to adjust for differences in baseline outcome predictors. States that analyses conducted according to ITT principles. 3 interim analyses after 23, 46 and 69 deaths occurred using two-sided significance test with the O'Brien–Flemming spending function and a Type 1 error rate of 5%. Frequency of adverse events analysed with Poisson regression. QoL among surviving patients compared using analysis of covariance, after adjusting for baseline values. Prespecified subgroup analysis with stratification according to age was performed, states that trial not designed to have enough power for subgroup analyses. Cochran–Mantel–Haenszel test for non-zero correlations used to compare sample activities from physical function subscale of SF-36. Adverse events reported as rates per patient-year due to difference in survival
- Sample size/power calculation: Trial designed to enrol 140 patients and to continue until 92 deaths had occurred. Assumptions: 2-year mortality rate in medical group would be 75%, treatment with LVAD would reduce risk of death by 33%, study would have 90% power (two-sided $\alpha = 0.05$)
- Attrition/drop-out: All 129 included in primary end-point analysis. Medical: 2 withdrew at 1 and 6 months after randomisation. No patients in either group crossed over. All assigned to receive LVAD had device implanted. 5 medical and 2 LVAD did not complete all QoL and functional status questionnaires at 1 year. One patient in each group died immediately after randomisation and excluded from analysis of adverse events

General comments

- Generalisability: Patients ineligible for heart transplantation. States that enrolled patients had more severe disease at baseline and a higher mortality rate during subsequent medical therapy than patients in other RCTs of heart failure
- Outcome measures: Appropriate
- Inter-centre variability: Not assessed
- Conflict of interests: Supported in part by a cooperative agreement with the National Heart, Lung and Blood Institute of the National Institutes of Health and Thoratec Corporation. One of the authors (VL Poirier) is a full-time employee of Thoratec, in which he holds an equity interest
- Other: previous pilot study of 21 patients

Quality Assessment for Primary Studies[77]

Study: Rose *et al.*[111]

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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A	Can't tell ×
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify Can't Tell				×
2. Was the study described as randomised?	Yes ×	No			
If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
3. If answer was yes, was the method of randomisation described?	Yes	No ×			
4. If answer was yes, was the method appropriate?	Yes	No	N/A		
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 ×	Can't 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%	Can't tell	N/A
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	Can't tell ×		
2. Were the study participants aware of the research question?	Yes	No	Can't 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	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes ×	No	Can't tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ×	60–79%	<60%	Can't tell	
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong ×	Moderate	Weak		
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ×	60–79%	<60%	Can't tell	
2. Was the consistency of the intervention measured?	Yes	No	Can't tell ×		
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't 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	Can't tell		
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes ×	No	Can't tell		

Appendix 24

Summary of the evidence of clinical effectiveness of the LionHeart LVAD as an LTCS for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 9564 Author: El Banayosy *et al.*[112] Year: 2003 Country: Germany Study design: Case reports Study setting: Inpatient Number of centres: 1 Funding: German Association of Organ Recipients	Indication for treatment: LTCS Comparisons of different interventions: No comparison, Arrow LionHeart LVD 2000 device only Duration of treatment: 17–670 (mean 245 ± 138) days, with a cumulative experience of 4.5 years Other interventions used: Anticoagulation, antibiotics, beta-blockers, ACE inhibitors, spironolactone. Previous amiodarone was continued	Number of participants: 6 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: LVEF <30% within 90 days before enrolment, heart failure of at least 6 weeks duration, NYHA Class IV heart failure, ineligibility for heart transplantation and peak oxygen consumption by cardiopulmonary exercise testing <14 cm^3/kg/minute. Excluded if body surface area <1.5 m^2, active systemic infection, any contraindication to anticoagulation, including allergy to heparin, and presence of a prosthetic heart valve, except for aortic homograft or stentless valves Characteristics of participants: All male, aged 55–69 (mean 65 ± 6) years, had a history of cardiomyopathy (dilated $n = 2$, ischaemic $n = 4$) and were ineligible for heart transplantation because of age ($n = 3$), malignancy ($n = 2$) or systemic lupus erythematosus ($n = 1$). All were NYHA Class IV with maximum heart failure medication. Five had undergone inotropic support and 1 patient additionally had intra-aortic balloon pumping. Paper provides individual pre-implant haemodynamic and laboratory data but no aggregate data are presented	Primary and secondary outcomes: Survival, adverse events Method of assessing outcomes: Assessed at 18 months Length of follow-up: 17–670 days (mean 245 ± 138 days) with 4.5 years of cumulative treatment and 3.5 years out-of-hospital survival

Results

Outcomes	LVAD
Survival	No operative mortality 3 patients recovered, fulfilling discharge criteria and are long-term survivors 3 patients died at 17, 31 and 112 days after implantation from MOF without being discharged home. The survival rate is 50% after 18 months
Comments	
Functional capacity	Not reported
Comments	
QoL	Not reported
Comments	
Function	Not reported
Comments	

continued

Outcomes	LVAD
Adverse effects	Assume $n = 6$ here Haemolysis (temporary) 3 Bleeding 3 Early arrhythmia 2 Reoperation for bleeding 1 Tamponade 1 Gastrointestinal ischaemia 1 Outflow graft kink 1 Low pump output (secondary to kinking) 1 Cerebrovascular accident 1 Controller change 1 (due to connector defect) Pump failure 0 Replacement internal battery 1 (at 22 months)
Comments	
Rehospitalisation in 3 surviving patients	The 3 surviving patients had to be readmitted 3 times. Apart from the 6-month and 1-year follow-ups, 1 patient had to be hospitalised for a urinary tract infection and renal calculi and also for a battery change, 1 had to be hospitalised for a controller change and 1 for a spontaneous bleeding from a femoral haematoma and late haemolysis after 6 months
Comments	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments
- Generalisability: Small sample, patients all ineligible for heart transplant
- Outcome measures: Minimal
- Inter-centre variability: Not applicable
- Conflict of interests: None noted

Quality Assessment for Primary Studies[77] Study: El Banayosy *et al*.[112]					
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	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case series Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		N/A
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 25

Summary of the evidence of clinical effectiveness of the Novacor LVAD as an LTCS for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 4476 (and 683) Author: Dohmen *et al.*[113,115] Year: 2001 (and 1999) Country: Germany Study design: Case report Study setting: Inpatient/outpatient Number of centres: 1 Funding: None reported	Indication for treatment: LTCS Comparisons of different interventions: Novacor N100 only, no comparison Duration of treatment: 1514 days Other interventions used: Venovenous haemofiltration, antibiotics and antinucotics, tracheostomy during postoperative recovery. Patient discharged home once recovered postoperatively. Patient monitored for INR (for anticoagulation regime). Patient telephoned twice a week and checked for recovery of left ventricular function, aortic valve function, exclusion of infections and exclusions of intracardiac thrombus during a short hospital stay every 6 months Medications on admission: enalapril, piretanide, spironolactone 50 mg, digitoxin, diazepam, magnesium and phenprocoumon	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Patient admitted with severe congestive heart failure. At intensive treatment unit admission acute cardiac decompensation that could not be compensated with nitroglycerin, nitroprusside, diuretics and catecholamines Characteristics of participants: 54-year-old male, history of dilated cardiomyopathy and contraindications for heart transplantation BP 90/60 mmHg Heart rate 76 beats/minute Holosystolic murmur (grade 2/6) at 5th intercostal space 1 degree atrioventricular block on electrocardiogram Echocardiogram and cardiac catheterisation showed grade 3 tricuspid regurgitation, grade 2 mitral regurgitation, grade 1 aortic regurgitation, pulmonary hypertension (50 mmHg), global left ventricular hypolkinesia with an LVEF of 8% INR between 3.0 and 3.5. No signs of cyanosis or peripheral oedema	Primary and secondary outcomes: Survival, adverse events, NYHA class, left ventricular diastolic and systolic volume before implantation and after 11 and 28 months Method of assessing outcomes: Haemodynamic re-evaluation was done after 11, 19 and 28 months of implantation Underwent Durastudy (test of pump function). Pump changed once and patient discharged home again after 1 month Length of follow-up: until death (4 years)

continued

Results

Outcomes	LVAD
Survival	Survived to 1342 days (3.8 years) when pump changed. Then survived to 1514 days until died of causes unrelated to the pump
Comments	
Functional capacity	
Left ventricular systolic volume (ml/m^2) (estimated from figure)	Pre-implantation: 235 After 11 months: 175 After 28 months: 210
Left ventricular diastolic volume (ml/m^2) (estimated from figure)	Pre-implantation: 195 After 11 months: 155 After 28 months: 140
Comments	
QoL	
Comments	
Function	Reported to be NYHA Class I once discharged until death
Comments	
Adverse effects	Postoperative period complicated by transient renal failure Recovery complicated by bronchopneumonia Tracheostomy required due to prolonged ventilation Febrile episodes whilst at home, traced to *Staphylococcus aureus* infection of the inflow and outflow valve conduits (replaced)
Comments	
Resource use	
Comments	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Not applicable for most outcomes, no analysis of pre- and post-implantation left ventricular functional indices undertaken
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments
- Generalisability: Case report, patient contraindicated to heart transplant, male with dilated cardiomyopathy
- Outcome measures: Limited
- Inter-centre variability: Not applicable
- Conflict of interests: Not reported

Quality Assessment for Primary Studies[77] Study: Dohmen *et al*.[113]					
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 ×	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to Section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell	N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell	N/A	
2. Were the study participants aware of the research question?	Yes	No	Can't tell	N/A	
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell	N/A	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		N/A
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis N/A	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell	N/A	
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell	N/A	

Appendix 26

Summary of the evidence of clinical effectiveness of the Toyobo LVAD as an LTCS for people with ESHF

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 1718 Author: Seki *et al.*[114] Year: 1995 Country: Japan Study design: Case report Study setting: Inpatient Number of centres: 1 Funding: Not reported	Indication for treatment: LTCS Comparisons of different interventions: No comparison, Toyobo LVAS only Duration of treatment: 190 days Other interventions used: Low-dose dopamine for 20 h after implantation. Low molecular weight dextran anticoagulation therapy initiated 12 h after implantation. After extubation on 2nd postop day, anticoagulation therapy switched to 300 mg/day dipyridamole, and warfarin that maintained prothrombin time at 25–30%. 9th post op day, i.v. low-dose herapin to maintain activated clotting time at 150–200 s	Number of participants: 1 Sample attrition/dropout: Not applicable Inclusion/exclusion criteria for study entry: Patient previously hospitalised (18 months before) with progressive left-side heart failure, readmitted with cardiogenic shock and intubated and treated with intravenous catecholamines and dilators. Intra-aortic balloon pumping, mechanical ventilatory support and continuous haemofiltration used for 18, 15 and 2 days, respectively. One month later condition worsened and X-ray showed prominent pulmonary congestion and cardiomegaly, with persistent hypotension, severe oliguria unresponsive to diuretics, diaphoresis and restlessness Characteristics of participants: 44-year-old male, idiopathic dilated cardiomyopathy. Left ventricular failure and peripheral hypoperfusion progressively worsened despite inotropic pharmacological support. Prominent pulmonary congestion and cardiomegaly. Persistent hypotension, severe oliguria unresponsive to diuretics. Diaphoresis and restlessness	Primary and secondary outcomes: Haemodynamics Hepatic and renal function Duration of support/survival Adverse effects Method of assessing outcomes: Haemodynamic, hepatic and renal variables at 1 month post-implant Length of follow-up: until death (190 days)

Results

Outcomes

Survival	Died 190 days after surgery	
Function	**Before LVAS**	**After LVAS**
Heart rate (beats per minute)	133	84
Cardiac index (l/minute/m^2)	1.9	2.9
Pulmonary vascular resistance (Wood units)	4.4	2.5
Systolic/diastolic BP (mmHg) (mean):		
Right atrium	14	1
Pulmonary artery	60/45 (52)	22/9 (17)
Pulmonary capillary wedge	38	5
Systemic BP	87/49 (62)	104/60 (80)

continued

Outcomes

Dose of catecholamines (μg/kg/minute):		
Dopamine	7.4	None
Dobutamine	6.0	None

Comments: After implantation all haemodynamic parameters normalised and pulmonary vascular resistance decreased remarkably. Pulmonary congestion before surgery completely disappeared 1 month after implantation.

Total bilirubin (mg/dl)	6.1	1.2
GPT (IU/l)	656	7
BUN (mg/dl)	73	11
Serum creatinine (mg/dl)	3.1	0.6

Comments: Hepatic and renal functions returned to normal after implantation as reflected by complete normalisation of total bilirubin, serum GPT, BUN and serum creatinine

Adverse effects	Early postoperative course uneventful
	9th postoperative day: cerebral embolism resulting in hemiparesis
	Multiple cerebral embolisms on 57th and 175th postop days. Developed left hemiplegia, aphasia and loss of consciousness
Mortality	Died 190 days after surgery
	No other major complications such as infection, bleeding, hepatic or renal dysfunction
	Electromagnetic valve exchanged at day 91
	Blood pump exchanged on 141st postop day due to thrombi attaching to pump surface

Comments: Autopsy findings showed good healing of tunnels, which allowed cannula to transverse the abdominal and chest walls. No thrombi in heart, great vessels or cannulas. Multiple embolisms in kidney and spleen. Thrombi attached to diaphragm of pump

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
- Allocation to treatment groups: Not applicable
- Blinding: Not applicable
- Comparability of treatment groups: Not applicable
- Method of data analysis: Some variables reported before and after but no analysis of data
- Sample size/power calculation: Not applicable
- Attrition/drop-out: Not applicable

General comments
- Generalisability: Limited. Patients with ESHF accompanied by MOF
- Outcome measures: Limited
- Inter-centre variability: Not applicable
- Conflict of interests: Not reported

Quality Assessment for Primary Studies[77] Study: Seki *et al.*[114]					
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 ×	Can't tell	
2. What percentage of selected individuals agreed to participate?	80–100%	60–79%	<60%	N/A ×	Can't tell
Summary of Selection Bias (Methodological strength of study)	Strong	Moderate	Weak ×		
B. Study Design					
1. What was the study design? (Please tick appropriate and specify design in No. 7)	Randomised Controlled Trial Controlled Clinical Trial Cohort Analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted Time Series Other – specify – case report Can't Tell				×
2. Was the study described as randomised?	Yes	No ×			
If answer to 2 is no, go to section C Confounders. If answer yes, answer No. 3 & 4 below					
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	Can't tell		N/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%	Can't tell	
Summary of Confounders (Methodological strength of study)	Strong	Moderate	Weak	N/A	
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Can't tell		N/A
2. Were the study participants aware of the research question?	Yes	No	Can't tell		N/A
Summary of Blinding (Methodological strength of study)	Strong	Moderate	Weak	N/A	
E. Data Collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Can't tell ×		
2. Were data collection tools shown to be reliable?	Yes	No	Can't tell ×		
Summary of Data Collection (Methodological strength of study)	Strong	Moderate	Weak ×		

continued

F. Withdrawals and drop-outs					
1. Were withdrawals and drop-outs reported in terms of numbers and reasons per group?	Yes	No	Can't tell		N/A
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79%	<60%	Can't tell	N/A
Summary of withdrawals and drop-outs (Methodological strength of study)	Strong	Moderate	Weak	N/A	
G. Intervention Integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	<60%	Can't tell	N/A
2. Was the consistency of the intervention measured?	Yes	No	Can't tell		N/A
3. Is it likely that subjects received an unintended intervention that may influence the results?	Yes	No	Can't tell ×		
H. Analysis					
1. Indicate the unit of allocation NA	Community	Organisation/ institution	Practice/ office	Provider	Client
2. Indicate the unit of analysis NA	Community	Organisation/ institution	Practice/ office	Provider	Client
3. Are the statistical methods appropriate for the study design?	Yes	No	Can't tell		N/A
4. Is the analysis performed by intervention allocation status rather than the actual intervention received?	Yes	No	Can't tell		N/A

Appendix 27

Summary of the evidence of clinical effectiveness of the Jarvik 2000 LVADs as an LTCS for people with ESHF

For the data extraction and quality assessment of the studies by Frazier and colleagues,[94,100] see Appendix 16, 'Summary of the evidence of clinical effectiveness of the Jarvik 2000 LVAD as a BTT for people with ESHF', p. 227.

Appendix 28

Data extraction forms – economic/costing studies

Reference: Arabia et *al.*, 1996[119]
Country: USA

Source of funding: Not stated
Conducted at: University of Arizona Health Sciences Center

Population:
ESHF BTT
Patients discharged on LVAD support while waiting for transplantation ($n = 3$)
Control: patient offered LVAD but declined ($n = 1$)

Age:
56–62 years

Indication:
Cardiomyopathy

Device:
Novacor

Setting and perspective:
US health service

Study design:
Cohort study

Study end-points:
Cost savings per patient (due to time spent at home versus in hospital)

Cost derivation:
Cost of device not considered as all patients incur that cost

Cost savings were calculated on the basis of number of days spent at home, multiplied by the lowest daily hospital charge

Sources of cost data:
Direct costs
Daily hospital costs (local data)

Indirect costs
Not considered

Analytic framework:
Simple cost analysis

Differential timing:
Not applicable

Costs:
Daily costs for:
Intensive care unit ($4100/day)
Intermediate care unit ($2200/day)

LVAD support patients:
Average hospitalisation cost from admission to implant: $2240 per day
Average hospitalisation cost from implant to discharge: $1570 per day

2 patients readmitted owing to LVAD-related adverse events but one patient remained as outpatient until transplant. Control patient remained in critical immobile state for 3 weeks and required 3 months of rehabilitation pre-transplantation

Cost savings amounted to:
$2632, $5922 and $132,124 for each of the three patients

Incremental analysis:
None

Sensitivity analysis:
None

Service delivery/treatment pattern issues:
Daily cost per patient higher prior to LVAD implantation

Patients who are very ill and undergo implantation can be rehabilitated to the point where physical state is optimal at the time of transplant

The authors conclude:
Early identification of patients with end-stage cardiomyopathy who are candidates for heart transplantation may benefit from LVAD implantation. Early identification, intervention and rehabilitation may confer significant savings

Study limitations:
Very small number of patients

continued

Health outcomes:
Number of days from admission to implantation (mean 15; range 7–21)
Number of days in hospital post-transplantation (mean 75; range 58–86)
Number of days spent at home during LVAD support (mean 29; $n = 3$: 4, 5 and 78 days, respectively)

Reviewer comments:
No costs attributed to 'at home' period. Provides support for a 'number of days in hospital post-transplant' parameter
Reviewed by JH/DS

Reference: CETS, 2000[120]
Country: Canada

Source of funding: CETS

Population:
ESHF patients (modelled cohort)
Emergency and elective LVAD implantation
BTT
BTR[a]
LTCS

Age:
Not specified

Indication:
ESHF

Device:
Novacor

[a] Authors note insufficient data to carry out a cost analysis but highlighted as a promising future possibility

Setting and perspective:
Quebec healthcare system
Costs considered are direct health costs associated with implantation, heart transplant and post-transplant management

Study design:
Cost-effectiveness analysis
Marginal costs and benefits

Study end-points:
Cost per LYG

Cost derivation:
Treatment protocols (for drug use) based on NHS Trust protocol
Sources of cost data: various

Analytic framework:
Marginal cost-effectiveness analysis

Differential timing:
Costs are discounted at 5% in a separate calculation
Outcomes not discounted

Costs:
BTT scenario

Procedure cost assumed to be equal to cost of cardiac transplant = Can$48,443 (1998$)
Novacor device costs Can$90,000
100-day maintenance costs = Can$3800, i.e. during LVAD support
Average annual cost post-transplantation = Can$10,000

Marginal cost (Can$):
$143 \times (48{,}443 + 90{,}000)$ (implant cost)
Plus $100 \times \$3{,}800$ (support cost)
Plus $20 \times 48{,}443$ (20 additional survive to transplant)
Plus $20 \times 13 \times 10{,}000$ (for 13 years)

Total marginal cost = Can$23.7 million

PATT scenario

Assume foregoing costs of implantation and maintenance are valid
Assume cost of replacing LVAD at 4 years equals cost of first implant

Carrying out 100 LVAD implants in critically ill patients would by the end of year 12 have cost Can$38.4 million

NB Assuming rapid demise and negligible cost in the alternate arm. If patients received short term support in absence of LVAD, each LVAD implant would be saving this cost and total cost estimate would be reduced (e.g. 11 days of support at Can$5,000 would reduce net cost by Can$5.0 million)

Incremental analysis:
BTT
Can$91,332 per LYG (undiscounted) or Can$117,197 discounted at 5%

PATT
Cost-effectiveness at 12 years
Emergency implantation:
Can$59,842 per LYG (undiscounted) or Can$57,628 discounted at 5%

continued

Health outcomes:
LYG

BTT scenario (elective implant only, emergency situation would not save more lives only different one therefore no marginal benefit)
Assumptions:
70% LVAD recipients proceed to transplant
Of 100 LVAD recipients, 20 would have died without LVAD support
Average LOS on support: 100 days
Survival rate 1 month post-heart transplant: 95% (93–96% depending on age Available at URL: http://www.unos.org/data/)
Average survival post-heart transplant: 13 years (estimate from Quebec study based on projected 74% survival at 3 years observed rate of ISHLT almost identical. Available at URL: http://www.ishlt.org/registry.html)

To prepare 100 patients for transplant, 143 must enter LVAD arm
Health benefit = 20 × 13 years = 260 life-years

PATT scenario

Emergency implantation:
Assumptions:
70% of patients survive implant
Subsequent mortality: 3% per year
LVAD replacement required every 4 years with an operative mortality of 10%
Current average PT mortality = 3.68% (Source: ISHLT[187])
For a cohort of 100 patients, at 12 years the gain in life-years = 641 years

Elective implantation:
Have to assume that some patients would have survived for some months or years in the absence of an implant
Assume 1-year survival without LVAD
LYG reduced to 531 years at 12 years

NB No data available for the BTMR scenario

Elective implantation:
Can$70,903 per life-year (undiscounted) or Can$67,883 discounted at 5%

Sensitivity analysis:
Looked at impact of assuming that some patients would have survived without LVAD support

BTT
Assume 75% of patients would have lived 1 year anyway
Can$126,304 per year of life (Can$185,980 discounted at 5%)

Plus previously detailed speculation about costing treatments associated with the non-LVAD arm

Service delivery/treatment pattern issues:
On economic grounds it would be necessary to restrict to BTT and only a limited number but the question is raised as to whether or not this is an ethical approach to a life-saving technology and whether a health system could be justified in enforcing this restriction

Study limitations:
Authors point out that calculations are based on hypothetical scenarios. Also, given that LVAD is a rapidly evolving technology, 12-year estimates of costs and benefits are unlikely to be truly representative. They stress that the purpose of the exercise was to give an estimate of the magnitude of costs associated with each of the treatment scenarios

Reviewer comments:
Robust data. Good example of a marginal analysis. Authors criticise Christopher and Clegg[121] report for not including associated follow-up costs in the LVAD arm (no reliable estimates available). Represents one of the better quality papers reviewed as all limitations are clearly highlighted. Report also summarised in McGregor[144]
Reviewed by JH/DS

Reference: Christopher and Clegg, 1999[121]
Country: UK

Source of funding: Research and Development Committee of the NHS Executive

Paper represents review of available evidence. Analysis described represents modelled comparison based on best available data

Population:
ESHF (modelled cohort)
Patient population efficacy and QoL taken from two separate studies

Age:
46 ± 9 years (Frazier *et al*., 1995[146])
48, SD 2.4 (Moskowitz *et al*., 1997[138])

Indication:
Pre-implantation NYHA:
NYHA Class IV (Frazier)
No NYHA rating stated for utility patients (Moskowitz)

Device:
HeartMate 1000 IP (Frazier)
Pneumatic/vented LVAD TCI Inc. (Moskowitz)

[See Moskowitz summary, p. 307, for details of utility derivations]

Reviewed papers:
Patients receiving:
LVAD devices:
HeartMate 1000 IP (and vented electronic[a])
Novacor[a]
For the purpose of:
BTT
BTR[a]
versus
Heart transplant patients no LVAD (controls)

[a] Not included in analysis owing to poor quality of available data

Setting and perspective:
Analysis:
NHS (UK)
Reviewed
Mainly US; one German (see end of summary)

Study design:
Analysis:
Based on data from 2 prospective studies:
Frazier *et al*., 1995,[146] BTT controlled cohort
Moskowitz *et al*., 1997,[138] cohort study no control

Reviewed:
Critical appraisal carried out by the Development and Evaluation Committee. No primary data collection. Review of available evidence. Cohort studies representing best available data

Health outcomes:
Sources
Efficacy: Frazier
QoL : Moskowitz

Measures
Survival to transplant
Functional capacity
Utility (measured by SG)

Utility outcomes (Moskowitz):
Pre-transplant (no LVAD): 0.548
During LVAD support: 0.809
Post-transplant: 0.964

QALYs before transplant
LVAD group:
Duration of support = 2.5 months
QoL with support = 0.809
QALYs gained per patient = $2.5/12 \times 0.809 = 0.17$
n = 100; 71 survive: total QALYs = 11.97

Non-LVAD:
Time to transplant = 12 days
QoL without support = 0.548
QALYs gained per patient = $12/365 \times 0.548 = 0.016$
n = 100; 36 survive: total QALYs = 0.65

QALYs after transplant
Assume LVAD and non-LVAD receive same benefits from transplant
Calculate LYG = 9.005 per person
QoL post-transplant = 0.964
Total QALYs per person:
8.68 (undiscounted)
7.85 (discounted at 1.5%)
6.05 (discounted at 6%)

QALYS gained per person (discounted at 1.5%):
LVAD: 75% of 71 patients × 7.85 = 418
Non LVAD: 75% of 36 patients × 7.85 = 212

Costs:
LVAD-related[b]:
Device £52,880
Procedure £9600
Transplant-related:
Procedure £23,950
Follow-up costs (annual) £3500
Follow-up drug costs (year 1) £2890
Follow-up drug costs (after year 1) £3160

[b] LVAD: follow-up costs (annual) excluded as no reliable data found

continued

BTT: 10 cohort studies; 5 of the 10 studies had controls (3 concurrent, 2 historical); 5 had no control. All classified 'fairly poor' design
BTMR: 1 cohort study; no control

(See 'Additional information' for list of studies excluded on basis of poor quality design)

Study end-points:
Analysis
Cost per QALY
Time frame = 20 years post-intervention

Reviewed studies
Survival
Post-transplant adverse events
Post-transplant hospital stay
Cardiovascular outcomes
Device-related complications
QoL (Nottingham Health Profile, Sickness Impact Profile and as proxy by NYHA status)

Following refer to analysis only:

Cost derivation:
Treatment protocols (for drug use) based on NHS Trust protocol
Sources of cost data:
Direct costs
1. LVAD and heart transplant procedures
NHS Schedule of reference costs
NHS Trust Finance Department
Costs of HeartMate/Novacor
2. Follow-up drug costs post-transplant
unclear but natural units reported
Indirect costs
None reported

Analytic framework:
CUA. Decision analytic methodology based on data from Frazier and Moskowitz

Differential timing:
Discounting applied 1.5 and 6%

Total costs per 100 patients in each arm (discounted at 6%):
LVAD: £11.1 million
Non-LVAD: £2.5 million

Cost per QALY
Based on 100 patients going through each arm, the discounted cost per QALY is estimated at £39,790

Incremental analysis:
Not calculated but can be derived from the cost/QALY calculations

Sensitivity analysis:
One-way sensitivity analysis
Discount rates varied

Service delivery/treatment pattern issues:
LVAD potentially attractive but the available evidence is poor and the devices are expensive. DEC report recommended further high-quality research before an informed decision regarding implementation was made. DEC committee concluded that value of LVADs was 'not proven'

Study limitations:
Follow-up costs are not included for LVAD patients but are included for heart transplant patients (does this not bias in favour of LVAD?)

Additional information:
List of studies rated as poor quality by reviewers and not used for model inputs:

BTT cohort studies (intervention: HeartMate; setting: USA):
Frazier *et al*., 1992; Frazier *et al*., 1994; Massad *et al*., 1996; Foray *et al*., 1996; Oz *et al*., 1997; Catanese *et al*., 1996; McCarthy *et al*., 1994; Levin *et al*., 1994; Dasse *et al*., 1992
BTMR cohort study (intervention: HeartMate and Novacor; setting: Germany):
Muller *et al*., 1997

Reviewer comments:
Critical appraisal of cohort studies carried out well. Choice of Frazier[146] and Moskowitz[138] papers justified as they represent best available choices at the time the study was carried out. Remaining concerns about utility values (see Moskowitz data extraction, p. 307)
Reviewed by JH/DS

Reference: Cloy *et al.*, 1995[188]
Country: USA

Source of funding: Not stated
Conducted at: Cullen Cardiovascular Research Laboratory, Texas Heart Institute

Population:
ESHF BTT
Group 1: conventional medical care pre-transplant ($n = 6$)
Group 2: LVAD support pre-transplant ($n = 6$)
"Another patient": LVAD support at home pre-transplant ($n = 1$)

Age:
Group 1: 45 (17–62) years
Group 2: 48 (32–65) years

Indication:
Cardiomyopathy
Group 1: ischaemic = 4; idiopathic = 2
Group 2: ischaemic = 2; idiopathic = 4

Device:
HeartMate

Setting and perspective:
US
Hospital charges

Study design:
Cohort

Study end-points:
Length of stay
Hospital charges

Cost derivation:
Per patient hospital bill

Analytic framework:
Average cost by group

Differential timing:
Not applicable

Health outcomes:
Average LOS
Group 1: 51 days
Group 2: 185 days
ICU days higher in Group 2
All Group 2 patients had been fully rehabilitated to NYHA Class I prior to transplant, LOS reflects mandatory LOS post-LVAD. Most patients were physically capable of being discharged within 3–4 weeks of surgery
Overall hospital stay post-transplant was similar for both groups of patients

Costs:

Group 1 ($)
Group 2 ($)

Total average
268,696
435,133

Mean ICU
214,297
377,783

Mean general care
49,795
113,752

Total hospital charges
1,712,180
2,949,217

Total hospital days
545
928

Mean daily total
5150
3178

Costs are presented in the form of charges
No year given

Breakdown for patient participating in discharge programme:

Resource component
Values

Inpatient days
131

Inpatient charges
$413,705

Outpatient days
171

Outpatient charges
$4,617

Savings
$150,138 (based on average daily general care charge)

Incremental analysis:
None

Sensitivity analysis:
None

continued

Service delivery/treatment pattern issues:
The use of LVAD technology should be increased owing to potential cost savings. The goal of LVAD is to extend life, improve QoL and to do so at an acceptable cost

Study limitations:
Owing to mandated LVAS stay results of LOS for group 2 are inflated

Reviewer comments:
Non-transparent presentation of results. Cost derivation unclear. Claims of extended life with increased quality (see discussion) not supported by any evidence presented in results. Cost saving argument based on 1 patient. Appears to have been conducted to prepare the way for further outpatient studies, i.e. cost savings relating to patients discharged on LVAD versus inpatient stay
Reviewed by JH/DS

Reference: Couper et *al.*, 1999[123] | **Source of funding: Not stated**

Country: USA

Population:
All patients having received Abiomed BVS 5000 VA device ($n = 22$)
Patients typically selected for VAD by established criteria

Age:
Not specified

Indication:
Mixed
Postcardiotomy ($n = 12$)
Acute myocarditis ($n = 2$)
Failed heart transplant ($n = 4$)
BTT ($n = 4$)

Device:
Abiomed BVS 5000s
BiVAD ($n = 9$), LVAD ($n = 7$) and RVAD ($n = 6$). 6/7 LVADs given for postcardiotomy, 1 as a result of a failed transplant

Setting and perspective:
US Healthcare system, health service perspective

Study design:
Cost-minimisation analysis. Single centre. Retrospective cost analysis of 22 patients receiving Abiomed BVS 5000 over 3-year period from inception (1994–97)
Comparison of management via Abiomed BVS 5000 with perfusion-managed centrifugal VAD (temporary support)

Study end-points:
Total days of support
Total no. of BVS pumps used (assumed centrifugal equal to Abiomed)
Cost per strategy (total and per patient)
Follow-up until death/discharge

Costs:
Costs of Abiomed BVS 5000 included original blood pump, cannulate, replacement pumps. Costs of centrifugal VAD included costs of blood pumps, cannulate, replacement pumps, perfusionist charges ($34/h first 12 h, $68/h thereafter), intra-aortic balloon (for BiVAD/LVAD $620)

Total costs over 3 years (cost per day) for the 22 patients:

Abiomed BVS 5000 $285,379 ($875)
Centrifugal VAD $433,137 ($1340)

Post-cardiotomy indication (cost per day of support):
Abiomed BVS 5000 $1146
Centrifugal VAD $1369

BTT (cost per day of support):
Abiomed BVS 5000 $455[a]
Centrifugal VAD $1271

[a] The BTT patients ($n = 4$, no LVADs) were a hybrid group receiving crossover VADs; 3/4 patients later had HeartMate LVADs (see paper for details)

Incremental analysis:
No

Sensitivity analysis:
No

Service delivery/treatment pattern issues:
Abiomed BVS 5000 cost saving compared with perfusion-managed centrifugal VAD

continued

Cost derivation:
Cost source assumed from study centre. Direct hospital costs. Base year not reported

Analytic framework:
Cost-minimisation analysis

Differential timing:
No

Health outcomes:
No outcomes reported by LVAD recipients. Six were included in post-cardiotomy group: 7/12 weaned, 5 subsequently discharged
7th LVAD patient: had retransplant after 9 days LVAD support

Study limitations:
Not exclusively LVADs (7/22) as noted above. 'Hypothetical' costs of comparator group. Assumed centrifugal VAD patients required full-time presence of perfusionist owing to system complexity and unfamiliarity of ICU nurses. Unclear if this is reasonable? Abiomed BVS 5000 managed by ICU nurses alone. Assumed duration of support equal between groups

Reviewer comments:
Patients received a mixture of LVAD/RVAD/BiVAD. Of limited use given comparator (centrifugal VAD), which is only a temporary fix. Although actual costs of Abiomed patients, questionable validity of hypothetical costing of comparator. Post-cardiotomy group of most interest, bridge to transplant patients received RVAD, BiVAD in addition to HeartMate LVAD
Reviewed by DS/JH

Reference: Gelijns et *al.*, 1997[124]
Country: USA

Source of funding: Not stated

Population:
Group 1: VE LVAD recipients (costing exercise) (n = 12)
NB n = 6 with cost projected to 1 year
Group 2: n = 50 pneumatic LVAD (resource trend analysis) plus the 12 VE LVAD recipients

Age:
Group 1: 53 (SD 12) years
Group 2: 51 (SD 11) years

Indication:
CAD (n = 35)
Idiopathic cardiomyopathy (n = 22)
Idiopathic subaortic stenosis (n = 1)
MI (n = 4)

Device:
HeartMate

Setting and perspective:
Columbia Presbyterian Medical Center
Inpatient and outpatient
5-year period for resource trend calculation

Study design:
Cohort

Study end-points:
Two separate analyses (separate patient groups) were carried out:
1. Inpatient and outpatient costs
2. Trends in resource use over time
Cost derivation:
Audit of the hospital patient management system

Cost derivation:
For each patient total charges incurred in the period between day of implantation to day of hospital discharge were summed across each departmental category
Total charges were then multiplied by the corresponding ratio of cost to charges
Outpatient services included physician care, diagnostic tests and medications. Physician costs were approximated to fee received; diagnostics costed as above and drugs as per Medicare list price

NB: At time of study FDA regulations stipulated that all LVAD patients must remain in hospital for at least 30 days post-implantation. Authors calculated costs on the basis of actual length of stay but also attributed costs on a shorter "clinically sufficient" LOS basis

Analytic framework:
Simple cost summation

Differential timing: None

Health outcomes:
None listed

Costs:
Costs are US and derived by the charge to cost ratio method described. A detailed breakdown is not therefore useful

Daily average cost of initial hospitalisation totalled $3716

Average length of hospital stay was 43.5 days, clinically sufficient LOS was deemed to be 17.5 days

Average duration of LVAD support: 177 days

Average cost of initial implant-related hospitalisation was $161,627 ± 26,932

Total average cost over a 9.5-month period = $221,313
Using clinically sufficient calculations = $201,148

Projected annual cost (n = 6 patients) was $219,139 – initial hospitalisation accounted for ~64%

Incremental analysis:
None

Sensitivity analysis:
None

Service delivery/treatment pattern issues:
In the resource trend section of the analysis, programme experience (i.e. LVAD use in the institution) was correlated inversely with length of ICU stay. Authors anticipate further reductions in this costly component as institutes gain more experience in use of the procedure

Study limitations:
Small sample size

Reviewer comments:
Provides breakdown of reasons for readmission plus average number of inpatient days
Costs are US. Not generalisable to the UK. Statistical significance of correlation overemphasised
Reviewed by JH/DS

Reference: Loisance *et al.*, 1991[125]
Country: France

Source of funding: Not stated

Population:
ESHF ("desperate cases")
Mechanical bridge (MB) ($n = 6$)
Pharmacological bridge (PB) ($n = 31$)
Deteriorating patients were put in MB group
Enoximone assessed as a means to reducing number of patients needing MB

Age:
Not specified

Indication:
Mixed
Ischaemic cardiomyopathy ($n = 15$)
Idiopathic cardiomyopathy ($n = 17$)
Acute rejection ($n = 1$)
Acute viral cardiomyopathy ($n = 2$)

Device:
Not specified

Setting and perspective:
Patients admitted to ICU with cardiomyopathy
Perspective not stated

Study design:
Cohort study. 1 year follow-up

Study end-points:
Survival

Cost derivation:
Not stated

Analytic framework:
Cost per survivor

Differential timing:
N/A

Health outcomes:
Survival at 1, 3 and 6 months and 1 year

Costs:
Average costs across the whole patient group.
No comparative analysis

Cost per survivor in the ITT population was US$65,238, $89,274, $126,903 and $210,054 at 1, 3 and 6 months and 1 year, respectively

Incremental analysis:
Cost per added day of survival
$2,174, $980, $697 and $575 at 1, 3 and 6 months and 1 year, respectively

Sensitivity analysis:
None conducted

Service delivery/treatment pattern issues:
Use of enoximone permits reduction in the number of patients requiring MB, allowing more time for informed selection of patients for heart transplant, leading to reduced costs

Study limitations:
Non-transparency of cost data.
Grouping of patients (MB and PB)

Reviewer comments:
Not useful in the context of our analysis
Reviewed by JH/DS

Reference: Mehta *et al.*, 1995[126]
Country: USA

Source of funding: Not stated

Population:
All patients Status I on the cardiac transplant waiting list BTT

Group 1: LVAD ($n = 12$)
Group 2: medical management ($n = 31$)
Group 2 constitutes patients requiring chronic medical therapy in a hospitalised setting

Age:
Group 1: 41 (SD 5) years
Group 2: 51 (SD 2) years

Costs:
No breakdown
Cost reference year not stated

Mean cost/charge
Group 1: $186,131/$302,048
Group 2: $100,115/$165,219
$p < 0.001$

Incremental analysis:
Mean cost/charge per day:
Group 1: $2859/$1808
Group 2: $3371/$2071
Trend towards lower cost but $p > 0.1$

continued

Indication:
Group 1:
Ischaemic cardiomyopathy ($n = 7$)
Idiopathic cardiomyopathy ($n = 5$)
Group 2:
Ischaemic cardiomyopathy ($n = 14$)
Idiopathic cardiomyopathy ($n = 15$)
Cardiac tumour ($n = 1$)
Retransplantation ($n = 1$)

Device:
Pierce–Donachy LVAD

Setting and perspective:
Pennsylvania State Hospital

Study design:
Retrospective cohort

Study end-points:
Transplantation and discharge rates
Charge/cost per day per patient

Cost derivation:
Patient charges and hospital costs during the admission period

Sources of cost data:
Individual patient finance records obtained from the Department of Clinical Cost Accounting

Analytic framework:
Cost minimisation analysis with figures for each patient 'normalised' by factoring each as a function of the total number of days of hospitalisation

Differential timing:
N/A

Health outcomes:
Transplant achieved
Group 1: 11 (92%)
Group 2: 21 (68%)
p = ns

LOS:
Group 1: 123.2 days
Group 2: 52.6 days

LOS transplant to discharge:
Group 1: 17.8 days
Group 2: 22.2 days
p = ns

Patients discharged:
Group 1: 11 (92%)
Group 2: 17 (55.4%)
$p = 0.02$

No significant difference between survival post-transplant (Kaplan–Meier extrapolation of 36-month follow-up data)

Sensitivity analysis:
None

Service delivery/treatment pattern issues:
Total accrued expenses are greater in the LVAD group but these increased expenses are inherent to the significantly longer admission

Authors conclude that superior rates of discharge at equitable daily costs support the use of LVADs as BTT and further outpatient use and improvements in the device may reduce costs associated with management of this patient group

Study limitations:
Represents a single institutional experience
No breakdown of costs provided

Reviewer comments:
Small sample size. Trends towards higher discharge rate **not** statistically significant difference. Costs cannot be compared – no natural units presented. Increased LOS likely a factor of FDA mandated stay. Generally, not useful for modelling exercise (unless as support for statistically significant studies indicating faster discharge post-transplant)
Reviewed by JH/DS

Reference: Morales *et al*., 2000[127]
Country: USA

Source of funding: Not stated

Population:
Consecutive recipients of BTT LVADs ($n = 90$)
Cost analysis of outpatient sub-group ($n = 44$)
TCI VE LVADS (Thermo Cardio Systems)

Age:
Not specified

Indication:
Not specified

Device:
HeartMate

Setting and perspective:
US outpatient analysis

Study design:
Retrospective review of patient notes

Study end-points:
Transplant
Death
Explantation

Cost derivation:
Drug costs from the Drug Topics Redbook
In-hospital costs from the billing department of the Columbia-Presbyterian Medical Center

Analytic framework:
Cost-minimisation analysis

Differential timing:
Not applicable.

Health outcomes:
Discharged
Non-discharged

Successful BTT
42 (96%)
20 (44%)

Death
0
19 (41%)

Explantation
2 (4%)
2 (4%)

Ongoing
5 (11%)
5 (6%)

Complications of outpatient care also detailed, in terms of incidence per month. This included readmissions

Costs:
Healthy outpatient compared against inpatient (using incidence of event data)

Main cost components: professional fees; laboratory fees; dressing changes; medications and readmissions

Cost (US$)

Inpatient stay (per day)
1600

Total healthy outpatient (monthly)
750

Outpatient with readmissions (monthly)
13,187

Incremental analysis:
Not conducted.

Sensitivity analysis:
Excluded FDA-mandated weekly clinic visits. Anticipated monthly cost then $600

Service delivery/treatment pattern issues:
Outpatient LVAD programme is safe and economical. Anecdotal evidence also suggests outpatient management results in better QoL. Although initial cost high, streamlining suitable patients for discharge may lower overall cost burden

Study limitations:
Relatively small sample size
Conclusions that outpatient management cost saving relative to inpatient management are not surprising given the magnitude of inpatient costs

Reviewer comments:
Well-designed study. Useful data on incidence of outpatient events. Not a challenging conclusion (there is no contention around the fact that outpatient management is less costly than inpatient management). Takes use of LVAD as a given when in actual fact uptake is not high (owing to cost of implantation and device)
Reviewed by JH/DS

Reference: Moskowitz *et al*., 2000[128]
Country: USA

Source of funding: Not stated

Population:
Gelijns *et al*., 1997[124] study combined with Moskowitz *et al*., 1997[138] utilities (see study extractions)
Modelled cohort

Age:
Not specified

Indication:
ESHF

Device:
HeartMate

Setting and perspective:
US setting
LVAD support patients (BTT as proxy for PATT)

Study design:
Very brief back-of-envelope calculation included in a review chapter

Study end-points:
Cost per QALY

Cost derivation:
Gelijns/Moskowitz study (n = 12 LVAD patients, detailed in previous summaries)

It is not clear where the LVAD cost used in the calculation comes from. The conclusion mentions an annual cost of $204,797. It would appear to come from the Gelijns study

Analytic framework:
Cost utility analysis

Differential timing:
None

Utility derivation:
NYHA Class IV heart failure patients have 2-year mortality of 75%, i.e. life expectancy of around 1.44 years
No data exist on mortality rates of LVAD patients but can assume that will reduce mortality by one-third to half (underlying hypothesis of the REMATCH trial)

LVAD recipient life expectancy would therefore be between 2.89 and 4.26

To convert to QALYs the authors use a utility value of 0.75 (a modified rating of the utility derived in the Moskowitz study "closer to that experienced by patients on haemodialyis")

Expected QALY between 2.16 and 3.19

QALY associated with medical management = 0.79 (based on life expectancy of 1.44 years and Moskowitz-derived utility of 0.55 in pre-implant state)

Health outcomes:
Incremental benefit for LVAD recipients would be between 1.37 and 2.40 QALYs

Costs:
Annual cost of medical management (1999 $) = $89,357 (based on an estimate by the Institute of Medicine in its report on the artificial heart = (1990 $) $4800/month (the authors inflate to 1999 $ using a discount rate of 5%)
Annual cost of LVAD management = $204,797

Incremental analysis:
(presented in tabular format)
There are two scenarios for the calculations of ICERs: LOS 43.5 and LOS 17.5 (actual and clinical as with previous Gelijns paper). Also two assumptions of efficacy (low and high)

In the first scenario (LOS 17.5) LVAD relative to medical therapy would cost between $37,274 and $46,921 per QALY saved
In the second scenario (LOS = 45.5) cost would be between $45,756 and $61,762

Sensitivity analysis:
Represented by the different scenarios and different rating of efficacy

Service delivery/treatment pattern issues:
Putting the cost of LVAD into perspective with other therapies indicates that it lies toward that higher end of what willing to pay for but is well within the ICER limit of acceptability

Study limitations:
Lack of explanation

Reviewer comments:
Two assumptions of efficacy (low and high) are referred to in the text and table. These are not explained or rather are only explained in terms of the resultant ICER. It would make sense that these refer to the reduction in mortality rate described. However, incremental QALYs used in the calculation are listed as 1.44 and 2.47 years and not those values derived in the text
Costs do not seem to relate to the costs mentioned in the text, or to those reported in the Gelijns paper. The figure of $204,000 minus that associated with medical management does not equal the incremental cost listed as used in the calculation. The costs used are unclear
Reviewed by JH/DS

Reference: Oz *et al.*, 1997[129]
Country: USA

Source of funding: Not stated

Population:
All LVAD and heart transplant patients who survived ≥ 1 year
Group 1; LVAD, $n = 21$
Group 2: Heart transplant, $n = 47$

Age:
Not stated

Indication:
Not specified

Device:
Not specified

Setting and perspective:
Columbia–Presbyterian Medical Center, New York
Perspective was that of the hospital

Study design:
Retrospective chart review

Study end-points:
Distribution of costs?

Cost derivation:
The authors detail their approach to cost collection. Blood products, diagnostic tests, examinations, pharmacy and therapy costs were based on the ratio of direct cost to charges. Overhead costs were allocated to patients based on LOS

Analytic framework:
Simple cost analysis

Differential timing:
N/A

Health outcomes:
Survival at 1 year? But the proportion who did not survive are not considered, therefore this is a simple cost analysis (without reporting of costs)

Costs:
No actual costs reported

Incremental analysis:
N/A

Sensitivity analysis:
N/A

Service delivery/treatment pattern issues:
Suggest earlier use of LVAD therapy to reduce ICU LOS

Study limitations:
The study does not take into account those patients who died during the 1st year post-transplant. No costs are presented

Reviewer comments:
Provides information on the different distributions of costs for the two treatments but for some reason the actual costs (which were obviously calculated) are not presented
Reviewed by JH/DS

Reference: Schiller and Reichart, 2000[130]
Country: Germany

Source of funding: Not stated

Population:
LVAD recipients implanted April 1993 to January 1997 (n = 23)

Age:
37 ± 12.4 years

Indication:
Dilative cardiomyopathy (68%)
End-stage coronary disease (30%)
CMV endocarditis (4%)

Device:
Novacor N100P

Setting and perspective:
Grosshadern Hospital, Munich
Clinical (hospital) and health insurance perspective

Study design:
Prospective study? (unclear from the paper)

Study end-points:
Survival
Hospital costs
Reimbursement charges

Cost derivation:
Costs attached to resource units?
Costs of transplant included as LVAD indicated as BTT

Sources of cost data:
Flat-rate payments and operation fees of the German Ministry of Health
Base year: 1996

Analytic framework:
Simple cost-effectiveness calculation

Differential timing:
N/A

Health outcomes:
12-month survival post-Novacor implant including heart transplant = 57%
1- and 3-year survival of Novacor patients following heart transplant (excluding Novacor results) = 77% and 70%

When splitting group according to time of implantation, cumulative survival after 4 months was better in 1995/96 group than 1993/94 group (92% versus 52%)

Costs:
Mean LOS ICU: 33.1 days
Mean LOS normal 35.7 days

Major part of expense due to cost of device itself

Hospital costs
Reimbursement

Novacor
€131,162
€101,310

Heart transplant
€44,116
€46,463

Total
€175,278
€147,773

Deficit ~€27,500 per patient (i.e. cost to hospital)

After "sharing costs of the deceased patients expense", cost per day survived (according to ratio of days survived and total costs of €3,400,001):
3 years = €184

Based on the thesis that survival in heart transplant patients post-Novacor is equal to survival in heart transplant patients without Novacor, the following costs per day for 5- and 10-year survivors can be calculated:
5 years = €122
10 years = €68

Incremental analysis:
None

Sensitivity analysis:
None

Service delivery/treatment pattern issues:
Novacor as BTT renders a 1-year survival rate of 57%

High expense in short term but in the long term does not exceed costs of other therapies; the authors conclude that insurance companies should therefore reimburse the total hospital costs after LVAD implantation

Study limitations:
Small sample size, very different survival rates depending on time span

Reviewer comments:
Very low survival rate driven by more patients in the 1993/94 period of study. Paper useful as presents costs and presents in Euros so can be inflated to 2003 for a comparison of costs. But Germany system very different to UK. More interesting than useful
Reviewed by JH/DS

Reference: Skinner *et al*., 2000[131]
Country: USA

Source of funding: Not industry

Population:
ESHF BTT
Patients receiving LVADs between 1989 and 1997: HeartMate ($n = 15$); Thoratec ($n = 21$) pending heart transplantation
Patients who died within 24 h of VAD implant were excluded from the study

Age:
Not stated

Indication:
ESHF

Device:
HeartMate and Thoratec

Setting and perspective:
US healthcare system, hospital perspective

Study design:
Cost-minimisation. Single-centre retrospective analysis
Group 1: patients who received routine prophylaxis with antifungals 1994–97 ($n = 18$) Group 2: earlier era, pre-prophylactic era 1989–93 (when antifungals used for treatment only) ($n = 18$)

Study end-points:
Positive fungal cultures
Mean cost per day of antifungal prophylaxis
Follow-up until transplant, death or removal of VAD

Cost derivation:
Drug charges from Average Wholesale Price Red Book, 1998 edition. Based on dosage for 70-kg adult. Amphotericin based on actual dosage received

Analytic framework:
Simple cost comparison

Differential timing:
None

Health outcomes:
Pre-prophylactic era: 9 patients transplanted; 8 died; 1 LVAD removed
Prophylactic era: 10 transplanted; 5 died; 2 LVAD removed; 1 remained on LVAD
Positive fungal cultures: 50% (pre-prophylactic patients) vs 39% prophylactic patients), $p = 0.74$ (ns)

Costs:
Mean cost per day of antifungals:
Pre-prophylactic era $2.56
Prophylactic era $46.34

Incremental analysis:
No

Sensitivity analysis:
No

Conclusions
Antifungal prophylaxis is not cost-effective because of the high additional cost and small benefit (no significant difference in infection rates)

Service delivery/treatment pattern issues:
None

Study limitations:
Deaths within 24 h excluded. No analysis by VAD type. Covers 8-year period – improvement in VAD during this time?

Reviewer comments:
Retrospective analysis, no comparison of patient characteristics. Few patients and combination of 2 devices. Exclusion of patients dying with 24 h may bias results. Poor external validity (in terms of patient characteristics not presented, average costing, US single-centre perspective). Unclear presentation of fungal infection-related deaths: none in prophylactic group, 1 in pre-prophylactic group? No cost per death avoided presented
Reviewed by DS/JH

Appendix 29

Data extraction forms – economic/costing studies as abstracts only

Reference: Christensen *et al.*, 1999[132] **Country: USA**	**Source of funding: Not stated** ***Abstract only***
Population: ESHF BTT Group 1: LVAD patients transferred to assisted living facility (n = 12) Group 2: LVAD patients awaiting transplant at university centre (n = 5) **Age:** Not specified **Indication:** Not specified **Device:** Not specified Criteria for selection not specified Criteria for discharge not specified **Setting and perspective:** Outpatient vs inpatient maintenance of LVAD patients **Study design:** Mean stay and costs compared for 7/12 Group 1 patients (not all 12, no reason given) against the 5 Group 2 patients **Study end-points:** Mean cost per day **Cost derivation:** Not clear but excludes laboratory and professional fees	**Analytic framework:** Simple cost comparison **Differential timing:** N/A **Health outcomes:** Mean LOS **Costs:** Mean cost per day Group 1: $1357 Group 2: $3441 **Incremental analysis:** Average saving of $2084 realised Average total savings for the 7 patients for a total of 705 patient days was $1.5 million **Sensitivity analysis:** None **Service delivery/treatment pattern issues:** Authors conclude that outpatient care can significantly reduce costs of these cardiac transplant patients **Study limitations:** Laboratory and professional fees not included owing to inability to obtain records Small sample size
Reviewer comments: Abstract only. Savings calculation seems questionable. Non-inclusion of laboratory/professional fees should only make analysis more conservative. No reason given for exclusion of 5/12 LVAD patients in the analysis Reviewed by JH/DS	

Reference: Kolbye *et al*., 2000[133] **Country: Denmark**	**Source of funding: Not stated** ***Abstract only***
Population: BTT ESHF Biomedicus assist device vs HeartMate LVAD **Age:** Not specified **Indication:** Not specified **Device:** HeartMate **Setting and perspective:** Danish healthcare sector **Study design:** Not stated **Study end-points:** LYG Cost per LYG **Cost derivation:** Not stated Cost ref. year 2000 **Analytic framework:** Cost-effectiveness analysis **Differential timing:** Not stated	**Health outcomes:** LYG **Costs:** Cost per LYG (DKK): HeartMate: 225,000 Biomedicus: 270,000 **Incremental analysis:** HeartMate results in additional expenditure of DKK 615,000 per patient and additional LYG of 3.6. Marginal expenditure DKK 170,000 per LYG **Sensitivity analysis:** Not stated **Service delivery/treatment pattern issues:** Not stated **Study limitations:** Not possible to tell based on the information in the abstract
Reviewer comments: Abstract only (article in Danish). Compares benefits and costs gained with Biomedicus device and HeartMate Reviewed by JH/DS	

Reference: Miller *et al.*, 2002[134] **Country: USA**	**Source of funding: Not stated** ***Abstract only***
Population: REMATCH patients (preliminary summary) ESHF PATT LVAD recipients **Age:** Not specified **Indication:** Not specified **Device:** HeartMate (although not specified in abstract) **Setting and perspective:** US Medicare population **Study design:** Prospective study **Study end-points:** Hospital resource use LOS **Cost derivation:** Hospital billing systems and Medicare Common Working File data **Analytic framework:** Multivariate regression to define predictors of LOS **Differential timing:** Not specified	**Health outcomes:** LOS (as driven by different predictors) Median LOS: 29 days Significant predictors of LOS: Sepsis ($p = 0.0001$) Bypass time ($p = 0.0094$) Drive-line infections ($p = 0.0155$) Non-systemic infections ($p = 0.0408$) **Costs:** Median hospital cost $97,741 Mean hospital cost $196,699 **Incremental analysis:** Not reported **Sensitivity analysis:** Not stated **Service delivery/treatment pattern issues:** Reduction in sepsis would significantly reduce the median LOS and thus economic burden of LVAD use **Study limitations:** Abstract only so unable to define
Reviewer comments: Reviewed by JH/DS	

Reference: Mir *et al.*, 1997[135]
Country: USA

Source of funding: Not stated
Abstract only

Population:
Consecutive patients ($n = 23$) admitted as Status I for heart transplantation
BTT
Group 1: HeartMate LVAD ($n = 10$)
Group 2: inotropic therapy ($n = 13$)
Group 1 selected as had failed inotropic therapy

Age:
Not specified

Indication:
Not specified

Device:
HeartMate

Setting and perspective:
US healthcare system, hospital charge perspective

Study design:
Cost-minimisation analysis. Single centre. Retrospective cost analysis of 23 patients comparing LVAD bridge vs inotropic therapy bridge

Study end-points:
Post-heart transplant end-points:
Dialysis
Inpatients rehabilitation
Serious infections
Hospital stay (days)
ICU days
Total hospital charges
Average daily hospital charges
6-month survival
6-month survival without complications

Cost derivation:
Hospital charges. Base year not reported

Analytic framework:
None

Differential timing:
No

Health outcomes:
22 patients received heart transplant; 1 from LVAD group awaiting

Post-transplant outcomes:
Dialysis:
Group 1 1/9; Group 2 5/13
Inpatient rehabilitation:
Group 1 1/9; Group 2 3/13
Serious infections:
Group 1 0/9; Group 2 4/13
6-month survival:
Group 1 9/9; Group 2 9/13
6-month survival without complications:
Group 1 6/9; Group 2 4/13 (complications not defined)

Costs:
Total hospital charges were higher in Group 1 ($291,651 vs $194,132, $p < 0.01$).
Average daily hospital charges similar, p = NS

Incremental analysis:
No

Sensitivity analysis:
No

Service delivery/treatment pattern issues:
Longer inpatient stay (days) in Group 1 (98.5 vs 56, $p < 0.02$)
Shorter intensive care stay (days) in Group 1 (8 vs 41, $p = 0.01$)

Study limitations:
Abstract only so unable to specify

Reviewer comments:
Comparison of consecutive patient admission is quasi-randomised. Published abstract therefore lacks clarity. No definitions of complications, Status I for transplantation. Likelihood Status I definition as in Petty *et al.*,[136] study reviewed elsewhere
Reviewed by DS/JH

Reference: Petty *et al.*, 1997[136] **Country: USA**	**Source of funding: Not stated** ***Abstract only***
Population: Status I heart transplant patients (n = 15) BTT Group 1: HeartMate LVAD (n = 6) Group 2: no LVAD (n = 9) All patients transplanted **Age:** No significant age difference between groups. Group 1: 51.5 (±8) years Group 2: 51.1 (±11) years **Indication:** Status I, defined as (i) inpatient in ICU receiving inotropic or mechanical support or (ii) on LVAD **Device:** HeartMate **Setting and perspective:** US healthcare system, hospital charges **Study design:** Cost-minimisation analysis. Single centre. Retrospective cost analysis of 15 patients with or without LVAD bridge. Study conducted between April 1995 and August 1996 **Study end-points:** Total inpatient charges Length of hospital stay **Cost derivation:** Hospital charges. No base year reported **Analytic framework:** None	**Differential timing:** No **Health outcomes:** Not reported **Costs:** Costs included device, nursing and room costs, monitoring costs, laboratory costs. No breakdown reported Average total inpatient charges higher in Group 1: $294,087 (±$78,990) vs $183,233 (±$55,249) in Group 2 (p = 0.007) Charges per day lower in Group 1: $2491 (±$539) vs $3729 (±773), p = 0.05. Attributed to less intensive use of hospitalisation **Incremental analysis:** No **Sensitivity analysis:** No **Service delivery/treatment pattern issues:** Longer mean inpatient stay (days) in Group 1 107 (±51) vs 53 (±24) in Group 2 (p = 0.015) **Study limitations:** Small number of patients Possible impact of FDA regulations (pre-1998) on LOS
Reviewer comments: Abstract only, therefore lack of detail presented. Very small sample size. LOS not reported by ICU usage Reviewed by DS/JH	

Reference: Schulze *et al*., 2000[137] **Country: Germany**	**Source of funding: Not stated** ***Abstract only***
Population: Patients (n = 40) with terminal heart insufficiency Group 1: Novacor LVAD (n = 10) Group 2: heart transplant (n = 10) Also includes 2 other groups (biventricular pacemaker and implantable cardioverter/biventricular pacemaker alone) **Age:** Not stated **Indication:** PATT **Device:** Novacor **Setting and perspective:** German healthcare system, hospital cost perspective **Study design:** Cost-minimisation analysis. Single centre. Retrospective cost analysis of 40 patients comparing long-term LVAD vs heart transplant **Study end-points:** Mean time in hospital Mean total in-hospital costs **Cost derivation:** Hospital costs. ?1999 prices **Analytic framework:** None	**Differential timing:** No **Health outcomes:** Not reported **Costs:** Mean hospital costs were higher in Group 1 €62,142/$61,510 (range €49,229/$48,729–€91,393/$90,465) vs €59,496/$58,892 (range €46,874/$46,397–€62,976/$62,336) in Group 2. No p-values reported **Incremental analysis:** No **Sensitivity analysis:** No **Service delivery/treatment pattern issues:** Longer mean inpatient stay (days) in Group 1 55 (range 37–78) vs 29 (range 21–40). No p-values reported **Study limitations:** Abstract only so difficult to define
Reviewer comments: Abstract only, hence lack of detail presented. Small sample size. No patient characteristics reported. No breakdown of costs or detail of what is included as "in-hospital" costs. Also reports European prevalence at 0.9%, incidence at 0.3%, although not referenced Reviewed by DS/JH	

Appendix 30

Data extraction forms – utility studies

Reference: Havranek *et al.*, 1999[139]
Country: USA

Source of funding: Not stated

Population:
Heart failure patients ($n = 50$)
Non-consecutive patients presenting for clinic visits. Patients excluded if not clinically stable for at least 1 month prior to assessment
NB Not an LVAD study

Age:
52.5 (±14.8) years

Indication:
Heart failure, defined as LVEF <40% with confirmed diagnosis by the attending cardiologist

Device:
Not device-specific.

Setting and perspective:
Cardiology clinic in an urban teaching hospital and heart failure clinic at a university hospital

Study design:
Cross-sectional. Single blinded (assessor had no prior knowledge of patient's condition)

Study end-points:
Health-related QoL (HRQoL) measures (specific and generic), exercise tolerance, and patient-derived utilities collected via TTO

Cost derivation:
N/A

Analytic framework:
Multiple regression analysis

Differential timing:
N/A

Health outcomes:
Test
Result

TTO utility
0.77 ± 0.28

6-minute walk
1082 ± 316 feet

SF-36 (physical)
35.5 ± 10.7

SF-36 (mental)
48.7 ± 10.3

MLHFQ score
41.8 ± 24.9

VAS Score
0.47 ± 0.21

Linear regression of utility on VAS resulted in significant relationship ($p < 0.01$) with a 'relatively high' (authors' classification) regression coefficient ($r^2 = 0.30$). Significant curvilinear relationships also present between utility score and SF-36 (physical), the 6-minute walk distance and (reverse coded) LWHF score

Costs:
N/A

Incremental analysis:
N/A

Sensitivity analysis:
1-week retest utilities ($n = 12$) indicated stability of utility measurement over time

Service delivery/treatment pattern issues:
There are significant relationships between HRQoL and utility measures. Utilities are valid measures of HRQoL in this patient group. However, between-patient variations are wide so comparisons at an individual level are less valid

Study limitations:
Relatively small sample size
No description of NYHA classification

Reviewer comments:
The utility of 0.77 seems to correspond to the 'LVAD support' utility scores generated in the Moskowitz study. However, no breakdown of NYHA classification is provided so it is not possible to see if the result is from a similar patient group
Reviewed by JH/DS

Reference: Lewis *et al.*, 2001[140]
Country: USA

Source of funding: Not stated

Population:
Heart failure patients ($n = 99$)
Patients seen at a Brigham and Women's Hospital's Heart Failure Service. Excluded if LVEF >40%, <18 years, heart-failure <3 months or unable to speak/write English
NB Not an LVAD study

Age:
52 (±13) years

Indication:
Heart failure (Mean LVEF 24%)
NYHA Class I: 7%
NYHA Class II: 19%
NYHA Class III: 58%
NYHA Class IV: 16%

Device:
Not device-specific

Setting and perspective:
Inpatients represented 75% of study population. Mean NYHA Class: inpatients 2.0, outpatients: 3.1

Study design:
Cross-sectional.

Study end-points:
Patient derived utilities collected via TTO and SG. MLHFQ score

Cost derivation:
N/A

Analytic framework:
Regression analysis. Student's *t*-test and Pearson's correlation coefficients used to assess relationship between variables

Differential timing:
N/A

Health outcomes:
Mean SG utility: 0.64 (range 0.1–1)
Mean TTO utility: 0.65 (range 0.001–1)
($r = 0.64$, $p < 0.0001$)

Scores worsened with increasing NYHA classification

Patients NYHA Class III and IV: mean utility between 0.3 and 0.65
Patients NYHA Class I and II: mean utility between 0.8 to 1.0

Relationship between MLHFQ score and utility significant at $p < 0.05$

Costs:
N/A

Incremental analysis:
N/A

Sensitivity analysis:
N/A

Service delivery/treatment pattern issues:
Close association of TTO and SG suggests (according to the authors) that patients understood what was being measured.
Responsiveness of utility values to changing health status has not been assessed in this patient group

Study limitations:
Small number of enrolled patients
Polarity of results indicates that preferences may 'swing' at some individual point in time. Authors suggest development of weighting possibly achieved by multiplying individual patient intervals of survival time by TTO derived during that period and then summing for overall patient utility

Reviewer comments:
Utility values for NYHA Class III and IV patients seems to correspond to the pre-implant utility scores generated in Moskowitz. Provides support for use of the Moskowitz utilities
Reviewed by JH/DS

Reference: Moscowitz *et al.*, 1997[138]
Country: USA

Source of funding: Not stated

Population:
All adult patients undergoing LVAD implantation at Columbia–Presbyterian Medical Center over an 18-month period ($n = 29$)

Median duration of heart disease 3.3 years (mean 6.5, SD 8.4, range 0.1–40.9)

Interview 1 (before implantation):
Age: 48.9 years ($n = 14/29$)
10 too sedated/impaired; 5 unavailable

Interview 2 (during LVAD support):
Age: 54.3 years ($n = 20/29$)
2 too impaired; 2 refused; 5 died

Interview 3 (post-transplantation):
Age: 54.4 years ($n = 11/17$[a])
2 too impaired; 2 refused; 2 died

[a] 12 patients were still awaiting transplantation

Indication:
Mixed
CAD $n = 6$
Cardiomyopathy $n = 8$
Unspecified $n = 15$

Device:
HeartMate

Setting and perspective:
Patient-gathered data
Interview 1: all patients in intensive care
Interview 2: all patients hospitalised
Interview 3: during and after hospitalisation

Study design:
Patients interviewed at three time points during the course of treatment (see below)

Each interview began with a ranking of three health states followed by an SG exercise

Study end-points:
Utilities (as derived form SG)

Cost derivation:
No costs collected

Analytic framework:
SG utility derivation
3 scenarios presented to the patients
Probability wheel was used as a visual aid.

Differential timing:
Not applicable

Costs:
None collected

Incremental analysis:
Not applicable

Sensitivity analysis:
Because health states are sequential, they are not statistically independent. Significance of the difference between them was tested via paired-data analysis on $n = 11$ of patients who were interviewed both before and during LVAD and $n = 10$ patients who were interviewed both during LVAD and after transplant. In each comparison, the difference between average scores was significantly different from zero even after correcting for multiple comparisons ($p = 0.008$, 0.003)

A further analysis of collected data was based only on the scores of those patients who participated in all the interviews ($n = 6$)

Before transplant
0.704, SD 0.133
During LVAD support
0.828, SD 0.126
After transplant
0.995, SD 0.005

Service delivery/treatment pattern issues:
The authors conclude that:
QoL with LVAD is considerably better than QoL just before LVAD
There is an acceptable QoL for the long-term use of LVADs as an alternative to medical therapy for patients in need of cardiac transplant but who will not receive one
The results support conducting an RCT to investigate this new use of LVAD

Study limitations:
A (large) number of individuals were too impaired to undergo interview. This can bias in favour of those patients who have a good outcome. In this study, statistical comparisons between different health states were done by paired comparisons, which eliminates this bias. However, this means do not use all the data collected, which introduces further bias.

Authors imputed data for the missing values and recalculated LVAD support score to 0.699. Still substantially better than 0.534 ($p = 0.0096$)

continued

Health outcomes:
Utilities (95% CI)

NB Not all patients participated in all interviews

Before transplant (immediately preceding transplant and conducted in ICU setting)
0.548, SD 0.276 (95% CI 0.389 to 0.708)
During LVAD support (whilst hospitalised)
0.809, SD 0.136 (95% CI 0.745 to 0.873)
After transplant
0.964, SD 0.089 (95% CI 0.902 to 1.000)

Reviewer comments:
The score before transplant relates to the state when transplant is imminent, i.e. all patients are in intensive care. Does this have implications? Also, the score post-transplant relates to the state following LVAD support. This may be different in patients who do not undergo LVAD support in the interim
Although statistical comparisons are made on a paired-data basis, derivation of mean utility scores is based on all available data. $n = 20$ patients interviewed at stage 2 (vs 14 at stage 1 and 11 at stage 3)
The utility values derived are snap-shots. However, in the DEC analysis constant benefit over the 2.5-month period is assumed. This may be problematic
Reviewed by JH/DS

Appendix 31

EVAD costs/charges for Papworth Hospital (exclusive of corporate overhead) (Fawell J, Papworth Hospital NHS Trust: personal communication, 2004)

	Charge per event (£)	Event rate	Charge per patient (£)	Total (£)			
Assessments (21)	2,202	1.3125	2,891	46,252			
Implant Operation (16)	36,986	1	36,986	591,776			
Follow-up Outpatient Visit (96)	99	6	595	9,518			
Readmissions (48)	5,391	3	16,174	258,779			
Total bid excluding costs of device			56,645	906,326			
Total bid including costs of device				1,583,126			
	Procedure						
	LVAD assessment	Implant operation	LVAD outpatient	LVAD readmission	Implant operation	Implant operation	Implant operation
Average LOS (days)	1.50	65.00	0.20	10.00	65.00	65.00	65.00
Forecast activity (Note 1)	21	16	96	48	16	16	16
	Cost (£)	Cost (£)	Cost (£)	Cost (£)	Total (£)	Fixed (£)	Variable (£)
Surgical ward costs		4,017		534	4,017	2,892	1,125
Surgical medical staffing	67	2,795		446	2,795	2,795	
Theatre costs		3,200			3,200	2,176	1,024
Anaesthetic medical staffing	62	904		83	904	904	
Echocardiogram	124	75	3	42	75	75	
Catheter study	384						
Perfusion cardiopulmonary support		1,433			1,433		1,433
ICU costs (Note 2)	816	12,700		2,721	12,700	11,684	1,016
Pump cardiopulmonary support		875			875		875
BiVAD (Note 4)		840			840		840
Blood costs		738			738		738
Pharmacy (Note 3)	327	5,500		877	5,500		5,500
Pathology	311	900	64	240	900	702	198
Radiology	80	909	28	241	909	709	200
Physiotherapy	31	1,300	4	207	1,300	1,300	
Technical support, cardiopulmonary support (0.5 medical technical officer 3) (Note 5)		800			800	800	
Procedure total cost excluding costs of device	2,202	36,986	99	5,391	36,986	24,037	12,949
Cost per patient							
Total costs (£)	906,326						

continued

Total implant operations	16			
Cost per patient excluding costs of device (£)	56,645			
Average device costs (£)	42,300	42,300		42,300
Cost per patient including costs of device (£)	98,945	79,286	24,037	55,249

Notes/assumptions made:

1. Activity

Assessments – 1.3 times implant activity.
Outpatients – 6 times implant activity.
Follow-up – 3 times implant activity.

2. ICU usage

100% of patients assessed on ICU for the entire period of the assessment.
25-Day stay on ICU as part of implant operation.
5-Day stay on ICU as part of follow-up procedure.

3. Pharmacy

Pharmacy usage in asessments and follow-ups is assumed to be at the same rate as transplant patients and has been allocated according to length of stay.
Pharmacy usage for implant procedure assumed to be ~£5500 to reflect use of epoprostanol, bretylium and haemofiltration.

4. BiVAD

1 in 5 patients has a BiVAD – the cost of the extra implant is £4200 per patient.

5. Medical technical officer costs

These are the estimated average cardio-pulmonary support costs for home support following the procedure.

6. Cardiopulmonary support

Cardiopulmonary support costs are included in perfusion, pump and technical support.

Appendix 32

List of experts who agreed to act as advisors to the project, their stated conflicts of interest and contributions to the project

Contact details	Conflicts of interest	Commented on research protocol	Commented on draft of final report
Professor S Ball Academic Unit of Cardiovascular Medicine, Leeds General Infirmary, Leeds, UK	None stated	Yes	Yes
Mr Robert Bonser Consultant Cardiothoracic Surgeon, Department of Cardiothoracic Surgery, The Queen Elizabeth Hospital, Birmingham, UK	None stated	No	No
Professor Martin Buxton Director, HERG, Brunel University, Middlesex, UK	None stated	Yes	Yes
Ms Noreen Caine Director of R&D Unit, Papworth Hospital NHS Trust, Cambridge, UK	None stated	Yes	Yes
Professor J Cleland Professor of Cardiology, University of Hull, Castle Hill Hospital, Hull, UK	None stated	Yes	Yes
Dr Mick Davies Department of Cardiology, University Hospital Birmingham NHS Trust, The Queen Elizabeth Hospital, Birmingham, UK	None stated	Yes	Yes
Professor OH Frazier Director, Cardiovascular Surgical Research, Texas Heart Institute, Houston, USA	None stated	Yes	Yes
Dr M Gill Regional Director of Public Health and Chair of NSCAG, Government Office for the South East, Guildford, UK	None stated	No	No
Dr Nick Hicks Director of Public Health, East Hampshire PCT, Portsmouth, UK	None stated	No	No
Mr Stephen Large Consultant Cardiothoracic Surgeon, Director of VAD Services, Papworth Hospital NHS Trust, Cambridge, UK	None stated	Yes	Yes
Dr S Ludgate Medical Director, Medicines and Healthcare products Regulatory Agency, London, UK	None stated	Yes	Yes
Dr P McCarthy Program Director, Heart Transplant and Mechanical Circulatory Support, Department of Thoracic and Cardiovascular Surgery, The Cleveland Clinic, Cleveland, USA	None stated	Yes	No

continued

Contact details	Conflicts of interest	Commented on research protocol	Commented on draft of final report
Dr M McGovern Department of Health, London, UK	None stated	Yes	No
Dr A Moskowitz Co-Director, INCHOIR, Columbia University, New York, USA	None stated	Yes	No
Professor John Pepper Professor of Cardiothoracic Surgery, Royal Brompton Hospital, London, UK	None stated	Yes	Yes
Mr L Vale Senior Research Fellow, Health Economics Research Unit, University of Aberdeen, Aberdeen, UK	None stated	Yes	Yes
Professor John Wallwork Professor of Cardiothoracic Surgery, Papworth Hospital NHS Trust, Cambridge, UK	None stated	Yes	No
Mr Stephen Westaby Consultant Cardiothoracic Surgeon, Department of Cardiac Surgery, John Radcliffe Hospital, Oxford, UK	None stated	Yes	No
Professor Sir MH Yacoub Imperial College London and The Magdi Yacoub Institute NHLI at Heart Science Centre, Harefield, Middlesex, UK	None stated	No	Yes

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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