NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

Implantation of a left ventricular assist device (LVAD) involves implanting a mechanical pump into the chest to support, or take over, the role of the weakened left chamber of the heart by pumping blood throughout the body. It is often used for people who are waiting for a heart transplant. 'Destination therapy' means using an LVAD as a permanent treatment for people who cannot have a heart transplant.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in May 2014.

Procedure name

- Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

Specialist societies

- Society of Cardiothoracic Surgeons of Great Britain and Ireland
- British Society for Heart Failure
- British Cardiovascular Intervention Society

- Society of Clinical Perfusion Scientists of Great Britain and Ireland.

Description

Indications and current treatment

Heart failure is a complex clinical syndrome of symptoms that occurs when the efficiency of the heart as a pump is impaired. It leads to reduced blood flow to the body tissues and increased filling pressure in the heart, which causes congestion and oedema in the lungs (causing breathlessness) or the body (causing swelling of the legs). Other symptoms include reduced exercise tolerance, fatigue and malaise.

Medical treatment of heart failure involves drugs such as diuretics and inotropic agents. Invasive therapies include electrophysiological interventions such as pacemakers and implantable cardioverter defibrillators, revascularisation by percutaneous coronary angioplasty and stenting or coronary artery bypass grafting, valve replacement or repair, and temporary use of intra-aortic balloon pumps. In chronic heart failure, conventional treatment strategies may no longer work resulting in the need for heart transplantation. Ventricular assist devices can be used to provide temporary circulatory support while a patient awaits heart transplantation (bridge-to-transplantation).

What the procedure involves

'Destination therapy' is a term that refers to the implantation of a left ventricular assist device (LVAD) with the aim of providing permanent circulatory support to patients with advanced heart failure who are ineligible for heart transplantation. This overview assesses evidence from studies in which the intended treatment strategy was destination therapy, and not bridge-to-transplantation.

The LVAD is implanted with the patient under general anaesthesia and involves open heart surgery, usually with cardiopulmonary bypass. Initially, the pump component of the LVAD is placed in the pericardium. An inflow pipe is then inserted into the left side of the heart (usually the left ventricle) and an outflow pipe is inserted into the systemic arterial system (usually the aorta). Subsequently, a power cable, attached to the pump, is brought out of the abdominal wall to the outside of the body and attached to a control system and battery. Once the pump begins to work and support the heart, the cardiopulmonary bypass machine is removed and the chest incision is closed. The LVAD draws oxygenated blood from the failing left ventricle and pumps it into the systemic arterial system under pressure.

The first LVADs used pulsatile pumps to mimic the natural pulsing action of the heart. Newer, more commonly used, devices use a rapidly spinning rotor to produce a continuous flow of blood into the systemic arterial system. Some

patients who are implanted with LVADs may also need simultaneous implantation of a second device to support right ventricular function.

Heart failure Classification

New York Heart Association functional classification system

The New York Heart Association (NYHA) functional classification system is a long-standing, widely-used method of categorising heart failure which relates symptoms to everyday activities and the patient's quality of life. The scoring system consists of 4 categories with higher classes indicating more severe heart failure.

- Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath) or angina pain.
- Class II: Slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
- Class III: Marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
- Class IV: The patient is unable to carry out any physical activity without discomfort and has symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Outcome measures

Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is specifically designed to evaluate quality of life in patients with chronic heart failure. The questionnaire consists of 23 items in 7 domains: physical function, symptom frequency, symptom severity, changes in symptoms over time, social function, self-efficacy and knowledge, and quality of life. Two summary scores can be calculated. The clinical summary score is derived by summing the individual scores on the physical limitation and symptoms domains (that is, total symptom score) with the change of symptoms over time excluded. The overall summary score is derived by summing the clinical summary score and the quality-of-life and social interference scores. Scores range from 0 to 100 with higher scores indicating better quality of life.

Minnesota Living With Heart Failure Questionnaire

The Minnesota Living With Heart Failure Questionnaire is designed to measure the effects of heart failure and its treatments on an individual's quality of life. The questionnaire consists of 21 questions that measure the impact of heart failure across 3 domains; symptoms, functional limitations and psychological distress. Scores range from 0 to 105 with lower scores indicating better quality of life.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation. Searches were conducted of the following databases, covering the period from their commencement to 21 May 2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with end-stage heart failure who are ineligible for heart transplantation.
Intervention/test	Implantation of a left ventricular assist device for destination therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 2795 patients from 1 registry, 2 randomised controlled trials, 1 non-randomised comparative study and 3 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

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Table 2 Summary of key efficacy and safety findings on implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

Study 1 Kirklin JK (2012)

Details

Study type	**Interagency registry for mechanically-assisted circulatory support (INTERMACS)**
Country	United States
Recruitment period	June 2006 to December 2011
Study population and number	Patients with advanced heart failure who were ineligible for heart transplantation. **n=1287**
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: patients ≥19 years with advanced heart failure whose treatment strategy was destination therapy, at the time of device implantation, were included. Exclusion criteria: not reported
Technique	Not reported
Follow-up	**2 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: None identified

Study design issues: **The s**tudy included patients from all subsequent studies included in this overview; 104 institutions submitted data to the register.

Study population issues: Thirty one of the 1287 patients were treated by bi-ventricular assist devices and were included in the analyses.

Other issues: EQ-5D scores range from 0 to 100 with higher scores indicating better quality of life.

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Key efficacy and safety findings

Efficacy

Number of patients analysed: **1287; however, numbers analysed varied by outcome measure**

Survival from death of any cause (Kaplan-Meier survival estimates)

	% Survival		
Device	6 months	1 year	2 years
CF	84	76	67
PF	74	68	45
Any type of LVAD	83	75	76

- Significant differences were observed between groups (p<0.0001)

Survival to device exchange or death secondary to device malfunction (Kaplan-Meier survival estimates)

	% Survival		
Device	6 months	1 year	2 years
CF	99	96	94
PF	96	83	51

- No p values reported.

Other outcomes at 2-year follow-up

- Heart transplantation was reported in 4% (52/1287) of patients.
- Device removal due to recovery was reported in 0.2% (3/1287) of patients.

Quality of life (EQ-5D scores) in patients treated by continuous-flow LVADs

	Baseline	3 month	6 month	1 year
Overall EQ-5D scores	45	72	75	72
Proportion of patients who reported problems with self-care (%)	43	32	26	25
Proportion of patients who reported problems with usual activities (%)	81	54	46	44

- Significant improvements from baseline were observed at all follow-up assessments (p values<0.05)

Safety

Adverse events as categorised by the authors

	Rate/100 patient months		
Adverse event	CF	PF	p value
Device malfunction	1.15	3.69	<0.0001
Bleeding	11.94	14.56	0.008
Infection	8.09	22.91	<0.0001
Neurologic dysfunction	1.86	2.91	0.006
Renal dysfunction	1.62	2.91	<0.0001
Hepatic dysfunction	0.57	0.68	0.24
Respiratory failure	2.64	3.98	0.004
Wound dehiscence	4.45	0.97	<0.0001
Psychiatric episode	0.90	2.04	<0.0001
Cardiac/vascular related adverse events			
Right heart failure	1.73	1.36	0.75
Myocardial infarction	0.03	0.00	N/A
Cardiac arrhythmia	3.89	5.34	0.009
Pericardial drainage	0.62	0.97	0.06
Hypertension	0.84	2.62	<0.0001
Arterial non-CNS thrombosis	0.20	0.49	0.01
Venous thrombotic event	0.64	1.07	0.03
Haemolysis	0.63	0.00	N/A
All adverse events	37.56	66.5	<0.0001

Cause of death as categorised by the authors (% out of all patients)

	% (n/N)		
Adverse event	CF	PF	Total
All-cause mortality	21.4 (248/1160)	52.0 (66/127)	24.4 (314/1287)
Cardiac failure			
Right ventricular failure	1.5 (17/1160)	4.7 (6/127)	1.8 (23/1287)
Arrhythmia/other	4.0 (46/1160)	5.5 (7/127)	4.1 (53/1287)
Bleeding			
Gastrointestinal	0.3 (4/1160)	0	0.31 (4/1287)
Surgical	0.4 (5/1160)	0.8 (1/127)	0.5 (6/1287)
Other bleeding	1.6 (18/1160)	2.4 (3/127)	1.6 (21/1287)
Other adverse events			
Infection	1.9 (22/1160)	7.1 (9/127)	2.4 (31/1287)
CNS event	2.0	9.4	2.7

	(23/1160)	(12/127)	(35/1287)
Multiple organ failure	2.0 (23/1160)	2.4 (3/127)	2.0 (26/1287)
Respiratory failure	1.0 (12/1160)	2.4 (3/127)	1.2 (15/1287)
Device failure	0.5 (6/1160)	2.4 (3/127)	0.7 (9/1287)
Renal failure	0.4 (5/1160)	0.8 (1/127)	0.5 (6/1287)
Hepatic failure	0.4 (5/1160)	0.8 (1/127)	0.5 (6/1287)
Malignancy	0.3 (4/1160)	0.8 (1/127)	0.4 (5/1287)
Arterial embolism	0.4 (5/1160)	0	0.4 (5/1287)
Cardiac tamponade	0	0	0
Withdrawal of support	0.8 (9/1160)	0	0.7 (9/1287)
Other	3.8 (44/1160)	12.6 (16/127)	4.7 (60/1287)

Risk factors for death

	Early hazard		Constant Hazard	
Risk factor	Hazard ratio	p value	Hazard ratio	p value
Age (older) [a]	-	-	1.24	0.01
BMI (higher) [b]	-	-	1.04	0.03
History of cancer	1.89	0.04	-	-
History of cardiac surgery	1.69	0.001	-	-
Dialysis	3.14	0.004	-	-
Blood urea nitrogen [c]	-	-	1.08	0.009
Critical cardiac shock	4.58	<0.001	-	-
Progressive cardiac decline	2.35	0.02	-	-
Use of PF-LVAD	-	-	2.63	<0.0001
RVAD in same operation	-	-		0.002

[a] Hazard ratio denotes the increased risk from 60 to 70 years.

[b] Hazard ratio denotes the increased risk of a 5-unit increase in BMI.

[c] Hazard ratio denotes the increased risk of a 10-unit increase in blood urea nitrogen.

Abbreviations used: BMI, body mass index; CNS, central nervous system; CF, continuous flow; LVAD, left ventricular assist device; PF, pulsatile flow; RVAD, right ventricular assist device

Study 2 Slaughter MS (2009)

Details

Study type	**Randomised controlled trial (Heartmate II trial)**
Country	United States
Recruitment period	March 2005 to May 2007
Study population and number	Patients with advanced heart failure who were ineligible for heart transplantation. n**=200 (134 Continuous-flow LVAD vs 66 Pulsatile-flow LVAD)**
Age and sex	Continuous-flow group: mean 62 years; 81% (108/134) male Pulsatile-flow: mean 63 years; 92% (61/66) male
Patient selection criteria	Inclusion criteria: patients with advanced heart failure who were ineligible for heart transplantation and whose heart failure was refractory to optimal medical management were included. Included patients had NYHA class IIIB or IV heat failure for at least 45 of the 60 days before enrolment or dependence on an intra-aortic balloon pump for a period of 7 days or inotropes for 14 days before enrolment were included. Patients also had a left ventricular fraction <25%, and a peak oxygen consumption <14mL/kg/min. Exclusion criteria: exclusion criteria: patients with severe renal, hepatic, pulmonary obstructive pulmonary disease were excluded.
Technique	Patients were implanted with either a continuous-flow LVAD or a pulsatile-flow LVAD. Patients in the continuous-flow LVAD group received warfarin and aspirin whereas patients in the pulsatile-flow LVAD group only received warfarin.
Follow-up	**Unclear**
Conflict of interest/source of funding	The study was sponsored by the manufacturers. Data were collected were collected by study coordinators at participating centres, and were analysed and audited by the manufacturers

Analysis

Follow-up issues: Analysis of the primary outcome measure was conducted using the intention-to-treat principle (continuous-flow group, n=134; pulsatile-flow group, n=66). Analyses of secondary outcome measures were conducted using the as-treated principle.

Study design issues: Patients were recruited from 38 centres and were assigned to treatment groups in a 2:1 ratio to have either a continuous-flow LVAD or a pulsatile-flow LVAD. Randomisation was stratified according to study centre.

Study population issues: None identified

Other issues: The primary outcome measure was a composite of survival at 2 years, freedom from disabling stroke (Rankin score >3) or re-operation to replace the device.

- Minnesota Living With Heart Failure Questionnaire: scores range from 0 to 105 with lower scores indicating better quality of life.

- The Kansas City Cardiomyopathy Questionnaire: scores range from 0 to 100 with higher scores indicating better quality of life.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **200 (134 CF vs 66 PF); however, numbers analysed varied by outcome measure**

Clinical course

Outcome measure	Group	Mean±SD Baseline	Mean±SD 24 hours	p value
Cardiac index (l/min/m^2)	CF	2.0±0.6	2.9±0.7	<0.001
	PF	2.1±0.6	2.9±0.7	<0.001
Pulmonary-capillary wedge pressure (mm HG)	CF	24±8	17±7	<0.001
	PF	24±9	16±6	<0.001

- The percentage of total time spent out of hospital after LVAD implantation was 88% in the CF group and 74% in the PF group (p=0.02)

Survival (Kaplan-Meier survival estimates)

- Median duration of support was 1.7 years in the CF group and 0.6 years in the PF group (no p value reported).
- Survival free from disabling stroke or reoperation to repair/replace LVAD was reported in 46% (62/134) of patients in the CF group and 11% (7/66) of patients in the PF group at 2 year follow-up.
- The survival rate was 68% in the CF group and 55% in the PF group at 1 year follow –up (p=0.008).
- The survival rate was 58% in the CF group and 24% in the PF group at 2 year follow-up (p=0.008).

6-minute walking test distances (metres)

Group	Mean±SD Baseline	Mean±SD 1 year	p value
CF	182±140	318±164	<0.001
PF	172±108	306±145	<0.001

- No significant difference was observed between groups at 1-year follow-up (p=0.22).

Quality of life scores

Outcome measure	Group	Mean±SD Baseline	Mean±SD 1 year	p value
MLWHF [a]	CF	75.4±17.7	34.1±22.4	<0.001
	PF	76.1±18.0	44.4±23.2	<0.001
KCCQ clinical summary score [b]	CF	35.1±18.5	68.6±21.8	<0.001
	PF	31.6±18.4	60.8±20.2	<0.001
Overall KCCQ score [b]	CF	27.4±16.3	65.9±20.0	<0.001
	PF	46.5±17.4	59.1±20.3	<0.001

[a] A significant difference was observed between groups at 1 year follow-up (p=0.03).
[b] No significant difference was observed between groups at 1 year follow-up (p=0.06).

Safety

Adverse events

Adverse event	% (n/N) CF	% (n/N) PF	p value
Pump replacement [a]	9 (12/133)	34 (20/59)	<0.001
LVAD-related infection	35 (47/133)	36 (21/59)	0.01
Local non-LVAD infection	49 (65/133)	46 (27/59)	0.02
Sepsis	36 (48/133)	44 (26/59)	<0.001
Bleeding requiring packed red blood cells	81 (108/133)	76 (45/59)	0.06
Bleeding requiring surgery	30 (40/133)	15 (9/59)	0.57
Cardiac arrhythmia	56 (75/133)	59 (35/59)	0.006
Respiratory failure	38 (50/133)	41 (24/59)	<0.001
Renal failure	16 (21/133)	24 (14/59)	<0.001
Hepatic dysfunction	2 (3/133)	0	NR
LVAD thrombosis	4 (5/133)	0	NR
Rehospitalisation [b]	94 (107)	96 (42/59)	0.02
Neurologic events			
Ischaemic stroke	8 (11/133)	7 (4/59)	0.38
Haemorrhagic stroke	11 (15/133)	8 (5/59)	0.33
Other neurologic events	22 (29/133)	17 (10/59)	0.14
Right heart failure			
Managed with extended inotropes	20 (27/133)	27 (16/59)	<0.001
Managed with RVAD	4 (5/133)	5 (3/59)	0.12

[a] 18 of the PF devices were replaced with CF devices and 2 PF devices were replaced during the 2-year follow-up period.
[b] Reasons for rehospitalisation not reported.

Abbreviations used: CF, continuous flow; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; MLWHF, Minnesota Living With Heart Failure; NR, not reported; PF, pulsatile flow; RVAD, right ventricular assist device

Study 3 Park SJ (2012)

Details

Study type	**Case series (continuation of Slaughter, 2009)**
Country	United States
Recruitment period	Early trial, March 2005 to May 2007; Late trial, May 2007 to March 2009
Study population and number	Patients with advanced heart failure who were ineligible for heart transplantation. n=**414 (133 early trial patients vs 281 late trial patients)**
Age and sex	Early trial: mean 62.5 years; 80% (107/133) male Mid trial: mean 63.3 years; 79% (221/281) male
Patient selection criteria	Inclusion criteria: patients with advanced heart failure who were ineligible for heart transplantation and whose heart failure was refractory to optimal medical management were included. Included patients had NYHA class IIIB or IV heat failure for at least 45 of the 60 days before enrolment or dependence on an intra-aortic balloon pump for a period of 7 days or inotropes for 14 days before enrolment were included. Patients also had a left ventricular fraction <25%, and a peak oxygen consumption <14ml/kg/min. Exclusion criteria: patients with severe renal, hepatic, pulmonary obstructive pulmonary disease were excluded. Patients with uncontrolled infections, previous strokes, mechanical aortic valves, irreparable aortic insufficiency, aortic aneurysm >5.0 cm or other mechanical circulatory support device
Technique	All patients were treated by a continuous-flow LVAD.
Follow-up	**Minimum of 2 years**
Conflict of interest/source of funding	Authors state that the study was supervised by the manufacturers.

Analysis

Follow-up issues: None identified.

Study design issues: This study is a continuation of a randomised controlled trial included in this overview (Slaughter, 2009; Heartmate II trial); however, only patients from the destination therapy arm of the trial were assessed. Early trial patients were compared to late trial patients to establish whether increasing clinical experience using LVADs resulted in better clinical outcomes. Postoperative medical care (including inotropic, antiarrhythmic, anticoagulant and heart failure therapy) was managed according to each investigator's preference and usual practice.

Study population issues: none identified

Other issues:

- Minnesota Living With Heart Failure Questionnaire: scores range from 0 to 105 with lower scores indicating better quality of life.
- The Kansas City Cardiomyopathy Questionnaire: scores range from 0 to 100 with higher scores indicating better quality of life.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **414 (133 early trial patients vs 281 late trial patients)**

Survival (Kaplan-Meier survival estimates)

- Median duration of support was 2.1 years in the early trial group and 1.7 years in the late trial group (no p value reported).
- The survival rate was 68±4% in the early trial group and 73±3% in the late trial group at 1-year follow-up (not significant).
- The survival rate was 58±4% in the early trial group and 63±3% in the late trial group at 2-year follow-up (not significant).
- The proportions of patients reaching the endpoint of survival free from disabling stroke or reoperation to replace the device were 50% (66/133) in the early trial group and 59% (166/281) in the late trial group at 2-year follow-up (p=0.076).

6 minute walking test distances (metres)

	Mean±SD		
Group	Baseline	2 years	p value
Early	181±138	350 *	<0.001
Late	225±142	350 *	<0.001

* Results obtained from a graph

- No significant difference was observed between groups at 2-year-follow-up (p=0.907).

Quality of life scores

		Mean±SD		
Outcome measure	Group	Baseline	2 years	p value
MLWHF [a]	Early	66 *	32 *	<0.001
	Late	65 *	31 *	<0.001
KCCQ [b]	Early	27±16	68*	<0.001
	Late	28±16	68 *	<0.001

* Results obtained from a graph

[a] A significant difference was observed between groups at 2-year follow-up (p=0.043).

[b] No significant difference was observed between groups at 2-year follow-up (p=0.080).

- NYHA categories improved from class IIIB or IV to class I or II in 80% of patients in the early trial group and 82% of patients in the late trial group at 6-month follow-up; improvements were sustained at 2-year follow-up.

Safety

Adverse events

	% (n/N)		
Event	Early	Late	Overall
Bleeding requiring PRBC	81 (108/133)	74 (207/281)	76 (315/414)
Bleeding requiring re-exploration	30 (40/133)	20 (55/281)	23 (95/414)
Local non-device related infection	49 (65/133)	45 (126/281)	46 (191/414)
Device related infection	35 (47/133)	30 (84/281)	32 (131/414)
Sepsis	41 (48/133)	28 (78/281)	30 (126/414)
Driveline infection	32 (42/133)	27 (75/281)	28 (117/414)
Pocket infection	9 (12/133)	7 (20/281)	8 (32/414)
Cardiac arrhythmias: cardioversion/defibrillation	56 (75/133)	50 (141/281)	52 (216/414)
Renal failure	16 (21/133)	11 (30/281)	12 (51/414)
Right heart failure	23 (31/133)	21 (58/281)	21 (89/414)
RVAD	4 (5/133)	6 (17/281)	5 (22/414)
Ischaemic stroke	8 (11/133)	8 (22/281)	8 (33/414)
Haemorrhagic stroke	11 (15/133)	5 (13/281)	7 (28/414)
Other neurologic events [a]	22 (29/133)	17 (19/281)	12 (48/414)
Haemolysis	4 (5/133)	5 (13/281)	4 (18/414)
Pump replacement	9 (12/133)	8 (22/281)	8 (34/414)
Pump replacement thrombosis	2 (2/133)	3 (8/281)	2 (10/414)
Pump thrombosis	4 (5/133)	6 (16/281)	5 (21/414)

NB: overall adverse event rates were calculated by the IP team

[a] Other neurologic events include transient ischaemic attacks, seizures and confusion.

Cause of death as categorised by the authors (proportion out of all patients)

	% (n/N)		
Cause of death	Early	Late	Overall
All-cause mortality	31 (41/133)	12.4 (35/281)	18 (76/414)
Haemorrhagic stroke	8 (10/133)	2 (6/281)	4 (16/414)
Ischaemic stroke	1 (1/133)	3 (9/281)	2 (10/414)
Right heart failure	4 (5/133)	4 (12/281)	4 (17/414)
Bleeding	3 (4/133)	4 (10/281)	3 (14/414)
Sepsis	4 (5/133)	3 (8/281)	3 (13/414)
Multiple organ failure	2 (2/133)	2 (5/281)	2 (7/414)
Loss of power to external components	3 (4/133)	2 (5/281)	2 (9/414)
Internal components, 6 thrombosis; 2 cable [b]	2 (3/133)	2 (7/281)	2 (10/414)
Other Deaths	14 (18/133)	13 (36/281)	13 (54/414)

NB: overall adverse event rates were calculated by the IP team

[a] Other neurologic events include transient ischaemic attacks, seizures and confusion.

[b] Cause is written as stated by the author.

[c] Other deaths include embolism, anoxic brain injury, traumatic brain injury, cardiac arrest, cardiac failure, heart failure, respiratory failure, pneumonia, amyloidosis, cancer, liver failure, pancreatitis, withdrawal of support, ruptured bladder, subdural haematoma and unknown.

Abbreviations used: DT, destination therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLWHF, Minnesota Living With Heart Failure; NYHA, New York Heart Association; RVAD, right ventricular assist device

Study 4 Rogers JG (2010)

Details

Study type	**Non-randomised comparative study**
Country	United States
Recruitment period	2005 to 2009
Study population and number	Patients with advanced heart failure who were ineligible for heart transplantation. **n=655 (374 Destination therapy [DT] vs 281 Bridge-to-transplantation [BTT])**
Age and sex	DT group: mean 63 years; 73% (272/374) male BTT group: mean 50 years; 76% (214/281) male
Patient selection criteria	Inclusion criteria: DT group included patients with NYHA Class IIIB or IV heart failure who were ineligible for heart transplantation and whose heart failure was refractory to optimal medical management. The BTT group included patients with NYHA class IV heart failure who were listed as high priority for heart transplantation Exclusion criteria: patients with active uncontrolled infection, a mechanical aortic valve, aortic insufficiency, an aortic aneurysm, or who receiving other mechanical circulatory support (except and intra-aortic balloon pump) were excluded. Patients with severe renal, pulmonary or hepatic dysfunction were also excluded
Technique	All patients were treated by a continuous-flow LVAD.
Follow-up	**DT group: 2 years** **BTT group: 6 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Patients in the DT group were followed-up for 2 years whereas patients in the BTT group were followed up for 6 months.

Study design issues: The study includes patients from a randomised controlled trial included in this overview (Slaughter, 2009). It involved the analysis of data from 2 large multicentre trials performed across 38 centres; authors had access to primary data. Assessment of NYHA class was performed independently by a physician, nurse or an appropriately trained member of staff who was not directly involved with the patients care.

Study population issues: Potential for bias; treatment groups included patients with different disease severities. DT patients had higher systolic blood pressure and worse renal function than BTT patients, whereas BTT patients were younger and more likely to be treated with intravenous inotropic agents or an intra-aortic balloon pump at enrolment.

Other issues:

- Minnesota Living With Heart Failure Questionnaire: scores range from 0 to 105 with lower scores indicating better quality of life.
- The Kansas City Cardiomyopathy Questionnaire: scores range from 0 to 100 with higher scores indicating better quality of life.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 655 (374 DT vs 281 BTT); however, numbers varied with each outcome measure

Significant improvements in NYHA classes were observed within groups at 6-month follow-up (p<0.001); however no significant differences in NYHA classes were observed between groups.

6 minute walking test distances (metres)
<table>
<tr><td></td><td colspan="3">Mean±SD</td></tr>
<tr><td>Group</td><td>Baseline</td><td>6 months [a]</td><td>2 years [b]</td></tr>
<tr><td>DT</td><td>204±150</td><td>350±198</td><td>360±210</td></tr>
<tr><td>BTT</td><td>214±125</td><td>372±199</td><td>NR</td></tr>
</table>
[a] Significant improvements were observed within both groups at 6 month follow-up (p values<0.05).
[b] No p values reported

The proportion of patients that reported low or very low levels of physical activity reduced from 96 to 38% in the DT group and from 93 to 32% in the BTT group at 6-month follow-up (p<0.001).

Change in quality-of-life scores
<table>
<tr><td></td><td></td><td colspan="2">Mean change±SD</td></tr>
<tr><td>Outcome measure</td><td>Group</td><td>6 months [a]</td><td>2 years [b]</td></tr>
<tr><td>MLWHF</td><td>DT</td><td>-39±27</td><td>-41±25</td></tr>
<tr><td></td><td>BTT</td><td>-28±28</td><td>NR</td></tr>
<tr><td>KCCQ clinical summary sore</td><td>DT</td><td>37±25</td><td>38±26</td></tr>
<tr><td></td><td>BTT</td><td>25±31</td><td>NR</td></tr>
<tr><td>KCCQ overall summary score</td><td>DT</td><td>39±24</td><td>42±23</td></tr>
<tr><td></td><td>BTT</td><td>27±28</td><td>NR</td></tr>
</table>
[a] Significant improvements were observed within both groups at 6-month follow-up (p values<0.05).
[b] No p values reported

A clinically meaningful improvement in KCCQ scores (>5 point improvement) was reported in 92% of DT patients and 79% of BTT patients at 6-month follow-up.

</td><td>
Authors did not report whether the occurrence of adverse events was actively monitored.
</td></tr>
<tr><td colspan="2">Abbreviations used: BTT, Bridge-to-transplantation; DT, destination therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLWHF, Minnesota Living With Heart Failure; NR, not reported.
.</td></tr>
</table>

Study 5 Rose EA (2001)

Details

Study type	**Randomised controlled trial (REMATCH Trial)**
Country	United States
Recruitment period	May 1998 to July 2001
Study population and number	Patients with end-stage heart failure who were ineligible for heart transplantation. n=**129 (68 DT vs 61 Optimal medical management [OMM])**
Age and sex	DT group: mean 66 years; 78% (53/68) male OMM group: mean 68 years; 82% (50/61) male
Patient selection criteria	Initial inclusion criteria: patients with chronic end-stage heart failure and contraindications to heart transplantation were included. Included patients had New York Heart Association (NYHA) class IV heart failure for ≥90 days despite therapy with angiotensin-converting-enzyme inhibitors, diuretics and digoxin. Included patients had a left ventricular ejection fraction <25%, a peak oxygen consumption <12mL/kg/min, a continuous need for intravenous inotropic therapy due to symptomatic hypotension, decreasing renal function or worsening pulmonary congestion. Exclusion criteria: not reported.
Technique	DT group: patients were treated by a pulsatile-flow LVAD. The device was implanted into a pre-peritoneal pocket or the peritoneal cavity, depending on the surgeon's preference. OMM group: treatment was administered according to guidelines developed by a medical committee; it involved the use of angiotensin-converting-enzyme inhibitors and encouraged the discontinuation of intravenous inotropic infusions.
Follow-up	**2 years**
Conflict of interest/source of funding	The manufacturers received ongoing data for patients treated by LVADs but did not receive any data for patients treated by OMM.

Analysis

Follow-up issues: Analyses were conducted using the intention-to-treat principle: two patients in the OMM withdrew from the trial 1 and 6 months after enrolment.

Study design issues: Patients were recruited from 20 experienced cardiac transplantation centres. Patients were assigned to treatment groups in a 1:1 ratio using a block randomisation approach which was stratified according to treatment centre to ensure the continued equivalence of group sizes. All investigators, apart from the statisticians, were blinded to group allocations.

Study population issues: Patients could continue beta-blockers if they had been administered for ≥60 days before enrolment. Patient selection criteria was expanded to include patients with NYHA class IV heart failure for ≥60 days who had a peak oxygen consumption ≤14ml/kg/min or patients with NYHA class IIIB or IV heart failure for ≥28 days who had ≤14 days of support by an intra-aortic balloon pump or who had a dependence of intravenous inotropic agents.

Other issues: The primary endpoint was death from any cause; the trial was designed to enrol 140 patients (conferring 90% power) and continue until 92 deaths had occurred.

- Minnesota Living With Heart Failure Questionnaire: scores range from 0 to 105 with lower scores indicating better quality of life.
- SF-36 questionnaire: scores for the individual domains range from 0 to 100 with higher scores indicating better quality of life.
- Beck Depression Inventory: Scores range from 0 to 64 with lower scores indicating less severe depression.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **129 (68 DT vs 61 OMM); however, numbers analysed varied by outcome measure**

Survival (Kaplan-Meier survival estimates)

- Median survival was 408 days in the DT group and 150 days in the OMM group (no p value reported).
- The survival rate was 52% in the DT group and 25% in the OMM group at 1-year follow-up (p=0.002).
- The survival rate was 23% in the DT group and 8% in the OMM group at 2-year follow-up (p=0.09).
- The survival rate for patients below 60 years was 74% in the DT group and 33% in the OMM group at 1-year follow-up (p=0.05).
- The survival rate for patients between 60 and 69 years was 47% in the DT group and 15% in the OMM group at 1-year follow-up (p=0.009).
- The survival rate was 39.7% (27/68) in the DT group and 11.5% (7/61) in the OMM group at study close (time not reported).

Quality of life and functional activity scores

		Mean±SD	
Outcome Measure	Group	Baseline	1 year
SF-36 Physical function [a]	DT	19±19	46±19
	OMM	18±18	21±21
SF36 Emotional role [a]	DT	33±42	64±45
	OMM	25±48	17±28
MLWHF [b]	DT	75±18	41±22
	OMM	75±17	58±21
Beck Depression Inventory [a]	DT	19±9	8±7
	OMM	16±8	13±7
		Median	
NYHA Class [a]	DT	IV	II
	OMM	IV	IV

[a] Significant differences were observed between groups at 1 year follow-up (p values<0.05).

[b] No significant difference was observed between groups at 1 year follow-up (p=0.11).

Safety

Incidence of serious adverse events as categorised by the authors

	Rate/patient-year		
Event	DT	OMM	Rate ratio (95% CI)
All adverse events	6.45	2.75	2.35 (1.86-2.95)
Non-neurologic bleeding	0.56	0.06	9.47 (2.30-38.90)
Neurologic dysfunction	0.39	0.09	4.35 (1.31-14.50)
Supraventricular arrhythmia	0.12	0.03	3.92 (0.47-32.4)
Peripheral embolic event	0.14	0.06	2.29 (0.48-10.80)
Sepsis	0.60	0.30	2.03 (0.99-4.13)
Local infection	0.39	0.24	1.63 (0.72-3.70)
Renal failure	0.25	0.18	1.42 (0.54-3.71)
Misc. adverse events	1.37	0.98	1.41 (0.93-2.12)
Syncope	0.04	0.03	1.31 (0.12-14.40)
Serious psychiatric disease	0.04	0.03	1.31 (0.12-14.30)
Cardiac arrest	0.12	0.18	0.65 (0.21-2.00)
Non-perioperative myocardial infarction	0.02	0.03	0.65 (0.04-10.30)
Ventricular arrhythmia	0.25	0.56	0.45 (0.22-0.90)
Hepatic failure	0.02	0.00	N/A
Events related to LVAD			
Suspected malfunction of LVAD	0.75	N/A	N/A
Perioperative bleeding	0.46	N/A	N/A
Infection of drive-line tract or pocket	0.41	N/A	N/A
Infection of pump interior, inflow tract or outflow tract	0.23	N/A	N/A
Right heart failure	0.17	N/A	N/A
Failure of LVAD	0.08	N/A	N/A
Thrombosis in LVAD	0.06	N/A	N/A
Perioperative myocardial infarction	0.00	N/A	N/A

Cause of death as categorised by the authors (proportion out of all patients)

	% (n/N)	
Cause of death	DT	OMM
All-cause mortality	60.3 (41/68)	91.5 (54/59)
Left ventricular dysfunction	1.5 (1/68)	84.7 (50/59)
Sepsis	25 (17/68)	1.7 (1/59)
LVAD failure	10.3 (7/68)	
Miscellaneous cardiovascular causes	2.9 (2/68)	1.7 (1/59)
Miscellaneous non-cardiovascular causes	7.4 (5/68)	0
Cerebrovascular disease	5.9 (4/68)	0
Pulmonary embolism	2.9 (2/68)	0
Acute myocardial infarction	0	1.7 (1/59)
Cardiac procedure	0	1.7 (1/59)
Preoperative bleeding	1.5 (1/68)	0
Unknown	2.9 (2/68)	0

NB: percentages were calculated by the IP team

Abbreviations used: DT, destination Therapy; LVAD, left ventricular assist device, HF, heart failure; NYHA, New York Heart Association; OMM, Optimal medical management

Study 6 Park SJ (2005)

Details

Study type	**Randomised controlled trial (longer follow up of Rose, 2001)**
Country	United States
Recruitment period	Not reported
Study population and number	Patients with end-stage heart failure who were ineligible for heart transplantation. n=**129 (68 DT vs 61 Optimal medical management [OMM])**
Age and sex	DT group: mean 66 years; 78% (53/68) male OMM group: mean 68 years; 82% (50/61) male
Patient selection criteria	Initial inclusion criteria: patients with chronic end-stage heart failure and contraindications to heart transplantation were included. Included patients had New York Heart Association (NYHA) class IV heart failure for ≥90 days despite therapy with angiotensin-converting-enzyme inhibitors, diuretics and digoxin. Included patients had a left ventricular ejection fraction <25%, a peak oxygen consumption <12ml/kg/min, a continuous need for intravenous inotropic therapy due to symptomatic hypotension, decreasing renal function or worsening pulmonary congestion. Subsequent inclusion criteria allowed for patients with NYHA class IIIB heart failure who were taking inotropes for 14 of 28 days prior to enrolment with intra-aortic balloon pumps. Exclusion criteria:
Technique	DT group: patients were treated by a pulsatile-flow LVAD. The device was implanted into a pre-peritoneal pocket or the peritoneal cavity, depending on the surgeon's preference. OMM group: treatment was administered according to guidelines developed by a medical committee; it involved the use of angiotensin-converting-enzyme inhibitors and encouraged the discontinuation of intravenous inotropic infusions.
Follow-up	**Up to 4 years**
Conflict of interest/source of funding	The manufacturers received ongoing data for patients treated by LVADs but did not receive any data for patients treated by OMM.

Analysis

Follow-up issues: Authors did not report any losses to follow-up; however, it was noted that 2 patients in the OMM withdrew from the trial 1 and 6 months after enrolment in a previous publication by the same study group.

Study design issues: The study is a longer follow-up of a randomised controlled trial included in this overview (Rose, 2001; REMATCH trial). Patients were recruited from 21 experienced cardiac transplantation centres. Patients were assigned to treatment groups in a 1:1 ratio using a block randomisation approach which was stratified according to treatment centre to ensure the continued equivalence of group sizes. All investigators, apart from the statisticians, were blinded to group allocations.

Study population issues: The study is a longer follow-up of another study in this overview (Rose EA, 2001). Patient selection criteria were expanded to include patients with NYHA class IIIB heart failure who were taking inotropes for 14 of 28 days prior to enrolment or with intra-aortic balloon pumps.

Other issues: None identified

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 129 (68 DT vs 61 OMM); however, numbers analysed varied by outcome measure.

Survival (Kaplan-Meier survival estimates)
• Median survival was 408 days in the DT group and 150 days in the OMM group (no p value reported).
• The survival rate was 52% in the DT group and 28% in the OMM group at 1-year follow-up (p=0.008).
• The survival rate was 29% in the DT group and 13% in the OMM group at 2-year follow-up (p=0.09).
• The percentage of patients that survived at 4-year follow-up were 16.2% (11/68) in the DT group and 8.2% (5/61) in the OMM group (no p value reported).

Quality of life and functional activity scores
• The proportion of surviving patients who improved from NYHA class III or IV to class I or II were 71% in the DT group and 17% in the OMM group at 1 year follow-up (p=0.0017)</td><td>Incidence of serious adverse events at final follow-up

Cause of death as categorised by the authors (proportion out of all patients)
<table><tr><td></td><td>% (n/N)</td><td></td></tr><tr><td>Cause of death</td><td>DT</td><td>OMM</td></tr><tr><td>All-cause mortality</td><td>83.8 (57/68)</td><td>94.9 (56/59)</td></tr><tr><td>Left ventricular dysfunction</td><td>1.5 (1/68)</td><td>0</td></tr><tr><td>Sepsis</td><td>30.9 (21/68)</td><td>1.7 (1/59)</td></tr><tr><td>LVAD failure</td><td>16.2 (11/68)</td><td>0</td></tr><tr><td>Cerebrovascular disease</td><td>10.3 (7/68)</td><td>0</td></tr><tr><td>Miscellaneous cardiovascular causes</td><td>7.4 (5/68)</td><td>1.7 (1/59)</td></tr><tr><td>Miscellaneous non-cardiovascular causes</td><td>10.3 (7/68)</td><td>0</td></tr><tr><td>Pulmonary embolism</td><td>2.9 (2/68)</td><td>0</td></tr><tr><td>Acute myocardial infarction</td><td>0</td><td>1.7 (1/59)</td></tr><tr><td>Cardiac procedure</td><td>0</td><td>1.7 (1/59)</td></tr><tr><td>Preoperative bleeding</td><td>1.5 (1/68)</td><td>0</td></tr><tr><td>Unknown</td><td>2.9 (2/68)</td><td>0</td></tr></table>NB: percentages were calculated by the IP team</td></tr>
<tr><td colspan="2">Abbreviations used: DT, destination therapy; LVAD, left ventricular assist device; NYHA, New York Heart Association; OMM, Optimal medical management</td></tr>
</table>

Study 7 Lietz (2007)

Details

Study type	**Case series**
Country	United States
Recruitment period	November 2001 to December 2005
Study population and number	Patients with advanced heart failure who were ineligible for heart transplantation. n=**280**
Age and sex	mean 60.7 years; 82% (230/280) male
Patient selection criteria	Inclusion criteria: patients over 65 years with advanced heart failure who were ineligible for heart transplantation and whose heart failure was refractory to optimal medical management were included. Patients had NYHA class IV heat failure for at least 60 days despite maximised oral therapy or inotropic support. Patients also had a left ventricular fraction <25% and a peak oxygen consumption <12mL/kg/min. Exclusion criteria: not reported
Technique	All patients were treated by a pulsatile-flow LVAD.
Follow-up	**Mean 10.3 months**
Conflict of interest/source of funding	Authors state that the data were obtained from a registry that was maintained by the manufacturer of the LVAD

Analysis

Follow-up issues: All patients were followed-up until death, heart transplantation or re-implantation of an LVAD

Study design issues: Data were obtained from a Food and Drug Administration-mandated registry that was maintained by the manufacturer. 56 centres across the country participated in data collection.

Study population issues: None identified

Other issues: None identified

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed:
280
Overall Survival (Kaplan-Meier survival estimates)
• The median duration of LVAD support was 18.6 months.
• Survival rates were 86.1%, 56.0% and 30.9% at 30 days, 1 year and 2 years, respectively.
Survival to hospital discharge
• 71% (200/280) of patients survived to hospital discharge.
• 1 patient was still hospitalised at the time of study closure.
Change in transplant eligibility
• Heart transplantation was reported in 17% (47/280) of patients after a mean support of 10.2 months. Change in transplant eligibility criteria was due to reversal of pulmonary hypertension (n=12), recovery of renal function (n=4), 5-year cancer free survival (n=5), weight loss (n=3), infection (n=4) and other (n=16)
</td><td>
Adverse events
• Device failure, resulting in pump replacement or death, was reported in 24.6% (69/280) of patients.
• The probability of device exchange or fatal device failure was 17.9% and 72.9% at 1 year and 2 years, respectively.
Cause of death as categorised by the authors (proportion out of all patients; n=280)
<table>
<tr><td>Cause of death</td><td>% (n)</td></tr>
<tr><td>All-cause mortality</td><td>55.4 (155)</td></tr>
<tr><td>Sepsis</td><td>16.4 (46)</td></tr>
<tr><td>Multi-organ failure</td><td>7.1 (20)</td></tr>
<tr><td>Stroke</td><td>5 (14)</td></tr>
<tr><td>Right heart failure</td><td>4.3 (12)</td></tr>
<tr><td>LVAD failure</td><td>3.6 (10)</td></tr>
<tr><td>Respiratory failure</td><td>2.5 (7)</td></tr>
<tr><td>Technical</td><td>1.8 (5)</td></tr>
<tr><td>Haemorrhage</td><td>1.8 (5)</td></tr>
<tr><td>Cancer</td><td>1.4 (4)</td></tr>
<tr><td>Arrhythmia</td><td>1.4 (4)</td></tr>
<tr><td>Accident</td><td>1.1 (3)</td></tr>
<tr><td>Pulmonary embolism</td><td>0.7 (2)</td></tr>
<tr><td>Sudden death</td><td>0.7 (2)</td></tr>
<tr><td>Left ventricular failure</td><td>0.7 (2)</td></tr>
<tr><td>Other causes</td><td>4.3 (12)</td></tr>
<tr><td>Not reported</td><td>2.5 (7)</td></tr>
</table>
NB: Overall death rates were calculated by the IP team
• Death, before hospital discharge, was reported in 27.1% (76/280) of patients; 78.9% (60/76) of in-hospital deaths occurred within 3 months.
Univariate analysis of risk factors for 90-day in-hospital mortality (n=222)
<table>
<tr><td>Patient characteristics</td><td>Odds ratio (95% CI)</td><td>p value</td></tr>
<tr><td>Platelet count ≤148 x 10^3/µl[c]</td><td>7.2 (3.5 to 14.6)</td><td><0.001</td></tr>
<tr><td>International normalization ratio >1.1[c]</td><td>5.0 (1.7 to 14.7)</td><td>0.001</td></tr>
<tr><td>Serum albumin ≤3.3 g/dl[a]</td><td>3.8 (1.8 to 8.0)</td><td><0.001</td></tr>
<tr><td>Aspartate aminotransferase >45 U/ml[a]</td><td>3.8 (1.9 to 7.6)</td><td><0.001</td></tr>
<tr><td>Ventilatory support</td><td>3.7 (1.3 to 10.9)</td><td>0.01</td></tr>
<tr><td>Haematocrit ≤34%[b]</td><td>3.4 (1.6 to 7.0)</td><td><0.001</td></tr>
<tr><td>Serum creatinine clearance ≤41 ml/min[c]</td><td>3.0 (1.5 to 5.9)</td><td>0.002</td></tr>
<tr><td>Age 64 to 70 years</td><td>2.8 (1.4 to 5.5)</td><td>0.003</td></tr>
<tr><td>Serum creatinine >2.1 mg/dl [a]</td><td>2.7 (1.3 to 5.6)</td><td>0.006</td></tr>
<tr><td>Total bilirubin >1.8 mg/dl [a]</td><td>2.7 (1.3 to 5.4)</td><td>0.006</td></tr>
<tr><td>Alanine aminotransferase> 52 U/ml[a]</td><td>2.6 (1.3 to 5.2)</td><td>0.008</td></tr>
<tr><td>Body surface area ≤ 1.9m [c]</td><td>2.5 (1.3 to 4.9)</td><td>0.006</td></tr>
<tr><td>Blood urea nitrogen > 51 U/dl[a]</td><td>2.4 (1.2 to 4.8)</td><td>0.01</td></tr>
<tr><td>Mean pulmonary artery pressure mmHg [c]</td><td>2.3 (1.2 to 4.7)</td><td>0.02</td></tr>
<tr><td>Glomerular filtration rate ≤ 34 ml· min^{-1} ·1.73m^{-2} [c]</td><td>2.1 (1.0 to 4.2)</td><td>0.002</td></tr>
</table>
'The cut-off values for continuous variables used in the univariate analysis was selected either from [a] the highest quartile, [b] median or [c] lowest quartile depending on the value that correlated at significance level of p<0.05 with the end point'
</td></tr>
<tr><td colspan="2">Abbreviations used: DT, destination therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLWHF, Minnesota Living With Heart Failure; NYHA, New York Heart Association; RVAD, right ventricular assist device</td></tr>
</table>

Study 8 Coyle LA (2009)

Details

Study type	**Case series**
Country	United States
Recruitment period	Not reported
Study population and number	Patients with end-stage heart failure who were ineligible for heart transplantation. n=**58 (38 Normal weight [BMI< 30kg/m2] vs 20 Obese [BMI ≥30 kg/m2])**
Age and sex	Normal : mean 54.7 years; 70% (14/20) male Mid trial: mean 65.9 years; 87% (33/38) male
Patient selection criteria	Inclusion criteria: patients with NYHA class IV heart failure with a contraindication to heart transplant were included. No further details of inclusion criteria were reported. Exclusion criteria: not reported
Technique	Patients were treated by either a continuous-flow LVAD or a pulsatile-flow LVAD
Follow-up	**1 year**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: None identified.

Study design issues: None identified

Study population issues: There were significant differences between normal and obese groups in relation mean age (54.7 years vs 65.9 years), incidence of diabetes (37% vs 60%), proportion of patients treated by continuous-flow LVADs (71% vs 45%) and the proportion of patients treated by pulsatile-flow LVADs (29% vs 55%).

Other issues: None identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **58 (38 normal weight vs 20 obese)**

Outcomes at 1-year follow-up

Outcomes	Normal	Obese	p value
Survival (%)	63 (24/38)	65 (13/20)	NS
Discharged home (%)	87 (33/38)	90 (18/20)	NS
Days on LVAD (mean±SD)	453±386	579±328	NS
Mean change in weight (kg)	8	-3.5	<0.05
Mean NYHA classification	1.2	1.6	NS

NS – Not significant

Safety

Adverse events

- LVAD pump replacement was required in 11% (4/38) of patients in the normal weight group and 35% (7/20) of patients in the obese group.

Abbreviations used: LVAD, left ventricular assist device; NHYA, New York Heart Association

Study 9 Long JW (2005)

Details

Study type	**Case series**
Country	United States
Recruitment period	January 2003 to December 2004
Study population and number	Patients with end-stage heart failure who were ineligible for heart transplantation. n=**42**
Age and sex	Mean 63 years; 88% (37/42) male
Patient selection criteria	Inclusion criteria: patients with class IV end-stage left ventricular heart failure who were ineligible for heart transplantation and were on optimal medical management (digoxin, diuretic, beta blocker, angiotensin-converting enzyme) for 60 of the preceding 90 days were included. Included patients had a life expectancy of less than 2 years, a left ventricular ejection fraction <25% and a peak oxygen consumption <12 mL/kg/min. Exclusion criteria: not reported
Technique	Patients were implanted with a pulsatile-flow LVAD.
Follow-up	**Unclear**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: None identified.

Study design issues: Patients were recruited from 4 cardiac transplantation centres.

Study population issues: None identified

Other issues: None identified

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 42

Survival (Kaplan-Meier survival estimates)
• Mean duration of support was 232 days.
• 21% (9/42) of patients had more than 300 days of LVAD support.
• Survival rates were 90.4±4.6% and 60.5±9.0%, at 30-day and 1-year follow-up, respectively.</td><td>Incidence of adverse events as categorised by the authors
<table><tr><td>Adverse event</td><td>Rate/patient-year</td></tr><tr><td>Neurologic event</td><td>0.15</td></tr><tr><td>Sepsis</td><td>0.19</td></tr><tr><td>Hepatic failure</td><td>0.04</td></tr><tr><td>Perioperative bleeding</td><td>0.15</td></tr><tr><td>Bleeding [a]</td><td>0.38</td></tr><tr><td>Localised infection</td><td>0.45</td></tr><tr><td>Percutaneous site or pocket infection</td><td>0.04</td></tr><tr><td>Right heart failure</td><td>0.08</td></tr><tr><td>Arrhythmia</td><td>0.30</td></tr><tr><td>Psychiatric episode</td><td>0.08</td></tr><tr><td>Confirmed device failure</td><td>0.04</td></tr><tr><td>Suspected device failure</td><td>0.04</td></tr></table>[a] No further details were provided about the type of bleeding reported.
Cause of death as categorised by the authors (proportion out of all patients; n=42)
<table><tr><td>Cause of death</td><td>% (n)</td></tr><tr><td>All-cause mortality</td><td>31 (13)</td></tr><tr><td>Sepsis</td><td>2.4 (1)</td></tr><tr><td>LVAD failure</td><td>4.8 (2)</td></tr><tr><td>Cardiovascular causes</td><td>2.4 (1)</td></tr><tr><td>Cerebrovascular disease</td><td>7.1 (3)</td></tr><tr><td>Multiple organ failure</td><td>7.1 (3)</td></tr><tr><td>Other/Unknown</td><td>7.1 (3)</td></tr></table></td></tr>
<tr><td colspan="2">Abbreviations used: LVAD, left ventricular assist device</td></tr>
</table>

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Efficacy

Survival (Kaplan–Meier survival estimates)

In a randomised controlled trial of 129 patients treated by pulsatile-flow LVAD destination therapy (n=68) or optimal medical management (n=61), survival rates were 23% and 8% respectively, at 2-year follow-up (p=0.09)[4]. In a longer follow-up of the same study, survival rates were 16% in the pulsatile-flow LVAD group and 8% in the optimal medical management group at 4-year follow-up (no p value reported)[6].

In a registry of 1287 patients treated by continuous-flow (n=1160) or pulsatile-flow (n=127) LVADs survival rates were 76% and 68% respectively, at 1-year follow-up (p<0.0001). At 2-year follow-up, survival rates were 67% in the continuous-flow group and 45% in the pulsatile-flow group (p<0.0001). In the same study, survival to device exchange or death secondary to device malfunction was 96% in the continuous-flow group and 83% in the pulsatile-flow group at 1-year follow-up (no p value reported)[1].

Recovery

In the registry of 1287 patients treated by continuous-flow LVADs or pulsatile-flow LVADs, recovery from heart failure allowing for device removal was reported in 0.2% (3/1287) of all patients[1].

6-minute walking test distances

In a randomised controlled trial of 200 patients treated by continuous-flow (n=134) or pulsatile-flow LVADs (n=66), 6-minute walking test distances improved from 182 m to 318 m (p<0.001) and 172 m to 306 m (p<0.001), respectively, at 1-year-follow-up (p value between groups=0.22)[2].

Quality of life

In the randomised controlled trial of 200 patients treated by continuous-flow or pulsatile-flow LVADs, mean MLWHF scores (scores range from 0 to 105 with lower scores indicating better quality of life) improved from 75.4 to 34.1 (p<0.001) and 76.1 to 44.4 (p<0.001) respectively, at 1-year follow-up (p value between groups=0.03). In the same study, mean overall KCCQ scores (scores range from 0 to 100 with higher scores indicating better quality of life) improved from 27.4 to 65.9 (p<0.001) in the continuous-flow group and from 46.5 to 59.1 (p<0.001) in the pulsatile-flow group at 1-year follow-up (p value between groups=0.06)[2]

In the randomised controlled trial of 129 patients treated by pulsatile-flow LVAD destination therapy or optimal medical management, mean MLWHF scores (scores range from 0 to 105 with lower scores indicating better quality of life) improved from 75 to 41 and 75 to 58 respectively, at 1-year follow-up (p value between groups=0.11)[5].

Emotional impact

In the randomised controlled trial of 129 patients treated by pulsatile-flow LVAD destination therapy or optimal medical management, mean SF-36 emotional domain scores (scores range from 0 to 100 with higher scores indicating better emotional outcomes) changed from 33 to 64 and 25 to 17 respectively at 1-year follow-up (p value between groups<0.05). In the same study, mean Beck Depression Inventory scores (scores range from 0 to 64 with lower scores indicating less depression) improved from 19 to 8 in the pulsatile-flow LVAD group and from 16 to 13 in the optimal medical management group at 1-year follow-up (p value between groups<0.05)[5].

Safety

Death related to device failure or malfunction

Death caused by device failure was reported in less than 1% (6/1160) of patients treated by continuous-flow LVADs and 2% (3/127) of patients treated by pulsatile-flow LVADs, at 2-year follow-up, in a registry of 1287 patients[1].

Death arising from loss of power to external components of LVADs was reported in 2% (9/414) of patients at a minimum follow-up of 2 years in a case series of 414 patients treated by continuous-flow LVADs[3].

Neurologic events

Ischaemic stroke was reported in 8% (11/133) of patients treated by continuous-flow LVADs and 7% (4/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in a randomised controlled trial of 200 patients (p=0.38). In the same study, haemorrhagic stroke was reported in 11% (15/133) of patients treated by continuous-flow LVADs and 8% (5/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up (p=0.33)[2].

Neurological events such as transient ischaemic attacks, seizures and confusion were reported in 12% (48/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs [3].

Right heart failure

Right heart failure, managed by extended inotrope therapy, was reported in 20% (27/133) of patients treated by continuous-flow LVADs and 27% (16/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients (p<0.001). In the same study right heart failure, treated by right ventricular assist devices, was reported in 4% (5/133) of patients treated by continuous-flow LVADs and 5% (3/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up (p=0.12)[2].

Respiratory failure

Respiratory failure was reported in 38% (50/133) of patients treated by continuous-flow LVADs and 41% (24/59) of patients treated by pulsatile-flow

LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$)[2].

Renal failure

Renal failure was reported in 16% (21/133) of patients treated by continuous-flow LVADs and 24% (14/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$)[2].

Cardiac arrhythmia

Cardiac arrhythmia was reported in 56% (75/133) of patients treated by continuous-flow LVADs and 59% (35/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p=0.006$)[2].

LVAD-related infection

LVAD-related infection was reported in 35% (47/133) of patients treated by continuous-flow LVADs and 36% (21/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p=0.01$)[2].

Driveline infection was reported in 28% (117/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs[3].

Non-LVAD-related infection

Local infection was reported in 49% (65/133) of patients treated by continuous-flow LVADs and 46% (27/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p=0.02$). No additional details were provided[2].

Sepsis

Sepsis (no further details provided) was reported in 36% (48/133) of patients treated by continuous-flow LVADs and 44% (26/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$)[2].

Pump replacement

Pump replacement was needed for 9% (12/133) of patients treated by continuous-flow LVADs and 34% (20/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$)[2].

Pump thrombosis

Pump thrombosis was reported in 4% (5/133) of patients treated by continuous-flow LVADs and 0% of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients (no p value reported)[2]

Pump thrombosis was reported in 5% (21/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs[3].

Bleeding

Bleeding that needed blood transfusion was reported in 76% (315/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs. In the same study, bleeding that needed surgical re-exploration was reported in 23% (95/414) of patients (no further details were provided)[3].

Validity and generalisability of the studies

- There was a high degree of overlap between studies as most patients would have been included in the Interagency Registry for Mechanically-Assisted Circulatory Support (INTERMACS)[1]. Furthermore, some studies were follow-up studies[3,6] of randomised controlled trials[2,5] and other studies employed secondary data analysis[4].
- Cardiac-related adverse events and causes of death were tabulated as categorised by the authors. It could be argued that these should be reported as efficacy outcomes; however, authors presented Kaplan–Meier estimates as key efficacy outcomes. Cardiac-related death rates could not be easily compared with Kaplan–Meier estimates so the Interventional Procedures team took the author's approach to avoid confusion.
- Results could be prone to information bias because they were obtained from several cardiac centres where different clinicians were reporting outcomes[1-7].
- The longest follow-up period reported was 4 years[6].
- The largest available study included a small proportion of patients (2.4% [31/1287]) treated by destination therapy using bi-ventricular assist devices in the analyses[1]. The IP team deemed it unlikely that the inclusion of these patients would have resulted in over- or underestimations of the treatment effect.
- A number of studies reported the occurrence of adverse events as incidence rates (rate per patient time) rather than cumulative incidences[1,5,9].

- All included studies employed Kaplan–Meier survival curves to evaluate survival.
- More recent studies predominantly focused on evaluating the safety and efficacy of continuous-flow LVADs[1–4].
- Only 1 study did not stratify results according to device type[8].
- Authors have suggested that, in light of recent developments, LVAD destination therapy may be a suitable option for some patients who may also be eligible for transplantation.

Existing assessments of this procedure

The Australian and New Zealand Horizon Scanning Network (ANZHSN) published a report on LVADs for destination therapy in March 2004. This document listed the types of LVADs. that were approved for use, and summarised key safety and efficacy outcomes from clinical studies. In light of the report's findings, the Australian Health Policy Advisory Committee on Technology (HealthPACT) concluded that there was insufficient evidence to permit the general use of LVADs for destination therapy at that time. Furthermore, it was noted that serious ethical issues were associated with the implantation of a permanent LVAD; including the process of withdrawing therapy, the balance of benefits and risks of therapy, and access to treatment and ongoing care. The committee recommended that future research on destination therapy should be carried out in established cardiac transplantation units with experience in implantation of LVADs as a bridge-to-transplantation[10].

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE interventional procedure guidance 177 (2006). Available from http://guidance.nice.org.uk/IPG177
- Partial left ventriculectomy (the Batista procedure). NICE interventional procedure guidance 41 (2004). Available from http://guidance.nice.org.uk/IPG41

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Professor Andrew Clarke, Dr Martin Thomas, Dr Simon Williams (British Society of Heart Failure); Professor Stephan Schueler, Mr Rajamiyer Venkateswaran (Society of Cardiothoracic Surgeons of Great Britain and Ireland)

- Three specialist advisers have never performed the procedure, whereas 2 specialist advisers perform the procedure regularly.
- Four specialist advisers described the procedure as established and no longer new. The other specialist adviser described the procedure as a minor variation of an existing procedure, which is unlikely to alter that procedure's safety and efficacy.
- Four specialist advisers stated that fewer than 10% of specialists are engaged in this area of work. The other specialist adviser could not give an estimate.
- Comparator treatments include optimal medical management and heart transplantation.
- Specialist advisers did not highlight any adverse events additional to those reported in the literature.
- One specialist adviser stated that aortic regurgitation was a theoretical adverse event.
- Specialist advisers listed key efficacy outcomes as 'event-free survival', cardiac output, exercise capacity, quality of life and the 'potential for heart recovery'.
- Specialist advisers stated that the main uncertainties surrounding the efficacy of the procedure are associated with device-related morbidity and limitations to quality of life after long-term support (greater than 5 years). One specialist adviser highlighted that by the end of 1 year at least 40% of patients would have had 1 hospital admission due to a device-related problem. At the end of 3 years, 80% to 85% of patients would have experienced some device-related morbidity.

- Two specialist advisers considered the procedure to have a major impact on the NHS whereas the other 3 specialist advisers believed the procedure would have moderate impact.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing trials:

- NCT00490321: VentrAssistTM LVAD for the Treatment of advanced heart failure - destination therapy; location: United States; type: RCT; estimated enrollment: 225; estimated primary completion date: June 2012; however, the recruitment status of this study is unknown because the study information has not been verified recently.
- NCT01966458: A prospective, randomized, controlled, unblinded, multi-center clinical trial to evaluate the heartWare® ventricular assist device system for destination therapy of advanced heart failure; location: United States; type: RCT; estimated enrollment: 429; estimated primary completion date: October 2016
- NCT01166347: A clinical trial to evaluate the heartware® ventricular assist system (ENDURANCE); location: United States; type: RCT; estimated enrollment: 450; estimated primary completion date: May 2017
- NCT01149603: The destination therapy evaluation for failing fontan study (DEFINe); location: United States; type: case series; estimated enrollment: 20; estimated primary completion date: December 2017
- NCT01452802: Risk assessment and comparative effectiveness of left ventricular assist device (LVAD) and medical management (ROADMAP);

location: United states; type: case series; estimated enrollment: 200; estimated primary completion date: December 2015

- NCT01627821: Evaluation of the Jarvik 2000 left ventricular assist system with post-auricular connector-destination therapy study; location: United States; type: RCT; estimated enrollment: 350; estimated primary completion date: December 2016.

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4. Rogers, J. G., Aaronson, K. D., Boyle, A. J., Russell, S. D., Milano, C. A., Pagani, F. D., Edwards, B. S., Park, S., John, R., Conte, J. V., Farrar, D. J., Slaughter, M. S., and HeartMate, I. I., I. (2010) Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. Journal of the American College of Cardiology 55 (17): 1826-1834
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7. Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, Rogers JG, Naka Y, Mancini D, Miller LW. (2007) Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation. 116(5): 497-505
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9. Long, J. W., Kfoury, A. G., Slaughter, M. S., Silver, M., Milano, C., Rogers, J., Delgado, R., and Frazier, O. H. (2005) Long-term destination therapy

with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. Congestive Heart Failure 11 (3): 133-138.

10. Australian and New Zealand Horizon Scanning Network (ANZHSN). Left ventricular assist devices for destination therapy. Health Policy Advisory Committee on technology, 2004.

Appendix A: Additional papers on implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Kirklin, J. K., Naftel, D. C., Kormos, R. L., Stevenson, L. W., Pagani, F. D., Miller, M. A., Ulisney, K. L., Baldwin, J. T., and Young, J. B. (2010) Second INTERMACS annual report: More than 1,000 primary left ventricular assist device implants. Journal of Heart and Lung Transplantation. 29 (1): 1-10	Interagency Registry for Mechanically Assisted Circulatory Support n=1000 LVAD patients Follow-up: 2 years	At 18 month follow-up, 53% of DT (n=100) patients had died, 29% were alive with an LVAD in place, 17% had a heart transplant and 1% of patients recovered and had their LVAD explanted.	Study displayed results graphically, making data extraction difficult. Furthermore, results were not stratified according to treatment strategy.
Teuteberg, J. J., Stewart, G. C., Jessup, M., Kormos, R. L., Sun, B., Frazier, O. H., Naftel, D. C., and Stevenson, L. W. (2013) Implant strategies change over time and impact outcomes: insights from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support).	Interagency Registry for Mechanically Assisted Circulatory Support n=2816 LVAD patients Follow-up: 2 years	Compared with bridge-to candidacy (BTC) and DT patients, bridge-to-transplant (BTT) patients had similar degrees of ventricular dysfunction and haemodynamic derangement but generally less comorbidity. Survival (alive with LVAD or transplanted) was superior at 24 months for BTT versus BTC versus DT (77.7% vs.70.1% vs. 60.7%, respectively, $p < 0.0001$).	Study investigated how the initial intended strategy at LVAD implantation influenced patient outcomes: included BTT and BTC patients. This overview focussed on studies in which DT was the intended treatment strategy.
Rogers JG1, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, Pierson RN 3rd; INTrEPID Investigators. (2007) Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID	Non-randomised comparative study n=55 (37 LVAD vs 18 Optimal medical therapy) Follow-up: 2 years	The LVAD-treated patients had superior survival rates at 6 months (46% vs. 22%; p=0.03) and 12 months (27% vs. 11%; p=0.02). Adverse event rates were higher in the Optimal medical therapy group. Eighty-five percent of the LVAD-treated patients had	Larger studies that reported similar outcome measures were available

Trial. Journal of the American College of Cardiology. 50(8):741-7		minimal or no heart failure symptoms.	
Strüber M, Sander K, Lahpor J, Ahn H, Litzler PY, Drakos SG, Musumeci F, Schlensak C, Friedrich I, Gustafsson R, Oertel F, Leprince P. (2008) HeartMate II left ventricular assist device; early European experience. Eur J Cardiothorac Surg. 34 (2): 289-94	Non-randomised comparative study n=100 (31 DT vs 69 BTT) Follow-up: 2 years	The survival rate was 70% in the DT group and 62% in the BTT group at 18 month follow-up.	Larger studies that reported similar outcome measures were available: only actuarial survival rates were reported (graphically).
Daneshmand, M. A., Rajagopal, K., Lima, B., Khorram, N., Blue, L. J., Lodge, A. J., Hernandez, A. F., Rogers, J. G., and Milano, C. A. (2010) Left ventricular assist device destination therapy versus extended criteria cardiac transplant. Annals of Thoracic Surgery 89 (4) 1205-1209	Non-randomised comparative study n=98 (49DT vs 49 BTT) Follow-up: 3 years	Length of stay was 23 days in the DT group compared and 11 days in the extended criteria heart transplant group ($p<0.0001$). Survival rates were 64% in the DT group and 50% in the extended criteria heart transplant group at 3 year follow-up.	Study mainly compared demographic and preoperative clinical characteristics of patients treated by DT or extended criteria cardiac transplantation: only actuarial survival rates and length of stay were reported.
Long, J. W., Healy, A. H., Rasmusson, B. Y., Cowley, C. G., Nelson, K. E., Kfoury, A. G., Clayson, S. E., Reid, B. B., Moore, S. A., Blank, D. U., and Renlund, D. G. (2006) Improving outcomes with long-term "destination" therapy using left ventricular assist devices. Journal of Thoracic & Cardiovascular Surgery 135 (6): 1353-1360	Case series n=23 DT patients Follow-up: 2 years	The survival rate was 29% at 2 year follow-up. Perioperative deaths were reported in 8.7 (2/23) of patients.	Larger studies that reported similar outcome measures were available.
Milano, C. A., Lodge, A. J., Blue, L. J., Smith, P. K., Felker, G. M., Hernandez, A. F., Rosenberg, P. B., and Rogers, J. G. (2006) Implantable left ventricular assist devices: new hope for patients with end-stage heart failure. North Carolina Medical Journal 67 (2): 110-115	Case series n=18 DT patients Follow-up: 2 years	Median duration of hospitalisation was 21 days. Median length of ICU stay was 6 days. 30 day mortality was 5.5% (1/18). 89% of patients were discharged to independent living. The survival rate at 1 year follow-up was 60%.	Larger studies that reported similar outcome measures were available.

Appendix B: Related NICE guidance for implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

Guidance	Recommendations
Interventional procedures	**Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE interventional procedure guidance 177 (2006)** 1.1 Limited evidence on the safety and efficacy of short-term circulatory support with left ventricular assist devices (LVADs) as a bridge to cardiac transplantation or recovery appears adequate to support the use of this procedure provided that the normal arrangements are in place for audit and clinical governance. 1.2 Clinicians should ensure that patients fully understand the high complication rates associated with this procedure and that the procedure is a temporary measure. In addition, use of the Institute's information for the public is recommended. 1.3 Publication of further research will be useful, particularly on the use of this procedure in patients with cardiogenic shock following acute myocardial infarction. **Partial left ventriculectomy (the Batista procedure). NICE interventional procedure guidance 41 (2004)** 1.1 Current evidence on the safety and efficacy of partial left ventriculectomy (PLV) does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake PLV should take the following action. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's information for the public is recommended. • Audit and review clinical outcomes of all patients having PLV. Publication of safety and efficacy outcomes will be useful in reducing the current

	uncertainty. The Institute may review the procedure upon publication of further evidence. 1.3 This is a radical treatment for very ill patients that should only be considered in centres where alternative treatments for severe heart failure are available.

Appendix C: Literature search for Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/05/14	Issue 5 of 12, May 2014
Database of Abstracts of Reviews of Effects – DARE (CRD website)	21/05/14	Issue 5 of 12, May 2014
HTA database (CRD website)	21/05/14	Issue 5 of 12, May 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/05/14	Issue 5 of 12, May 2014
MEDLINE (Ovid)	20/05/14	1946 to May Week 1 2014
MEDLINE In-Process (Ovid)	20/05/14	May 20, 2014
PubMed	21/05/14	N/A
EMBASE (Ovid)	20/05/14	1974 to 2014 Week 20
BLIC	21/05/14	n/a

Trial sources searched on 21/05/2014

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 23/05/2014

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites <<add details>>
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Ventricular Dysfunction, Left/th
2 Ventricular Dysfunction, Left/su
3 (Left adj4 ventricular* adj4 assist* adj4 (device* or system* or pump* or treat* or therap* or surg*)).tw.
4 (Ventricul* adj4 Assist* adj4 system*).tw.
5 (LVAD or LVAS or VAS or HVAD).tw.
6 Heart-Assist Devices/
7 (Heart* adj4 assist* adj4 (device* or system* or pump* or treat* or therap* or surg*)).tw.
8 Assisted Circulation/
9 (Assis* adj4 circulat*).tw.
10 (Heart* adj4 fail* adj4 (device* or system* or pump* or treat* or therap* or surg*)).tw.
11 or/1-10
12 HeartMate II.tw.
13 Novacor.tw.
14 TCI HeartMate.tw.
15 VentrAssist.tw.
16 (DuraHeart or Terumo).tw.
17 Heartmate 2.tw.
18 jarvik 2000.tw.
19 HVAD.tw.
20 or/12-19
21 11 or 20 (53604)
22 ((Destinat* or permanent*) adj4 (therap* or treat* or surg*)).tw. (5001)
23 DT.tw. (18446)
24 or/22-23 (23396)
25 exp Heart Failure/
26 Cardiomyopathies/
27 cardiomyopath*.tw.
28 ((End-stage* or endstage* or end stage* or advance* or acute*) adj4 heart* adj4 failur*).tw. (10053)
29 Shock, Cardiogenic/
30 (Cardiogenic* adj4 shock*).tw.
31 exp Ventricular Dysfunction/
32 (ventricul* adj4 dysfunct*).tw.
33 Myocarditis/
34 Myocardit*.tw.
35 or/25-34
36 21 and 24 and 35
37 Animals/ not Humans/

38 36 not 37