NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death

Heart transplantation usually involves storing a donor heart in cold fluid until it is implanted into the patient. In this new procedure, the donor heart is stored at normal body temperature in a machine which keeps it beating and supplied with blood and nutrients for up to 8 hours, until it is implanted into the patient.

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 2015.

Procedure name

- Normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death

Specialist societies

- Society of Cardiothoracic Surgeons of Great Britain and Ireland
- Society of Clinical Perfusion Scientists of Great Britain and Ireland
- NHS Blood and Transplant

Description

Indications and current treatment

Heart failure is a complex clinical syndrome that occurs when the efficiency of the heart as a pump is impaired. It leads to reduced blood flow to body tissues and increased filling pressure in the heart. This 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, including 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 not work, resulting in the need for heart transplantation or implantation of a ventricular assist device to provide permanent circulatory support (destination therapy). A ventricular assist device may also be used to provide temporary circulatory support while a patient awaits heart transplantation (bridge-to-transplantation).

Conventional heart transplantation involves removing the heart of a donor who no longer has any activity in their brainstem and has permanently lost the potential for consciousness and the capacity to breathe autonomously. The donor heart is usually preserved using cold ischaemic storage until it is implanted into the recipient. Prolonged cold storage times may result in ischaemic and reperfusion injuries that can impair heart function after transplantation.

What the procedure involves

Normothermic extracorporeal preservation aims to keep the donor's heart beating outside the body, using a perfusion machine that delivers warm oxygenated blood supplemented with catecholamine, nutrients and electrolytes. This technique aims to decrease the amount of damage that occurs to the heart after removal, by reducing the rate of tissue deterioration in comparison to conventional cold ischaemic storage. The aim is to improve clinical outcomes for the recipient. The technique was initially used to preserve hearts donated after brainstem death, but has recently been adapted to preserve hearts donated after circulatory death (death that has been diagnosed and confirmed using cardio–respiratory criteria). This overview considers only normothermic extracorporeal preservation of hearts donated after brainstem death.

In this procedure, the donor heart is inspected and arrested with cold cardioplegia solution before being removed. After removal, it is placed in a perfusion machine and re-animated. The perfusion machine comprises a blood reservoir (which stores the donor's blood), pulsatile-flow pump, blood oxygenator, blood warming unit, and monitoring equipment. Oxygenated blood from the reservoir is warmed and pumped into the aorta, perfusing the coronary arteries of the donor heart. Coronary venous blood drains into the right atrium, through the coronary sinus, and passes into the right ventricle. The blood flows through the pulmonary artery, into the oxygenator, and passes back into the reservoir. Aortic pressure, coronary flow, blood temperature and heart rate are all monitored. Immediately before the transplantation procedure, the heart is arrested with cold cardioplegia solution and disconnected from the perfusion machine. It is then implanted into the recipient. This procedure has been used to store donor hearts for up to 8 hours before transplantation.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death. The following databases were searched, covering the period from their start to 21 May 2015: 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, refractory to drug therapy.
Intervention/test	Normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death.
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 337 patients from 1 randomised non-inferiority trial, 1 non-randomised comparative study and 2 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.

Table 2 Summary of key efficacy and safety findings on normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death

Study 1 Ardehali A (2015)

Details

Study type	**Randomised non-inferiority trial**
Country	USA and Europe (countries not specified)
Recruitment period	2010 to 2013
Study population and number	Patients with end-stage heart failure n=**128 patients (62 Normothermic extracorporeal preservation versus 66 standard cold storage)**
Age and sex	Mean age: Normothermic extracorporeal preservation group, 56 years; cold storage group, 57 years Sex: Normothermic extracorporeal preservation group, 82% male; cold storage group, 71% male
Patient selection criteria	**Donor selection criteria** Inclusion criteria: donors <60 years with mean arterial blood pressure >60 mmHg, an ejection fraction >40%, absence of severe segmental wall motion abnormalities, absence of left ventricular hypertrophy and absence of valve abnormalities were included. Exclusion criteria: donors with an abnormal coronary angiogram (50% stenosis, requiring coronary bypass), a donor-to-recipient body weight ratio of <0.6 or donors who were receiving vasoactive at the time of final assessment were excluded. **Recipient selection criteria** Inclusion criteria: patients >18 years who were registered as primary heart transplant candidates were included. No further details were provided. Exclusion criteria: patients with more than 4 previous sternotomies, chronic renal failure, ventilator dependence at the time of transplant or panel reactive antibodies >40% were excluded. Patients receiving simultaneous transplant of non-heart allograft, except for concurrent kidney transplant, were excluded.
Technique	**Normothermic extracorporeal preservation**: Before the donor's heart was removed, 1200 ml to 1500 ml of donor blood was placed in the reservoir of the normothermic extracorporeal preservation system. The heart was then arrested with standard cold cardioplegia solution. The aorta and pulmonary artery of the donor heart were cannulated and the heart was connected to the normothermic extracorporeal preservation system (Transmedics' Organ Care System). Once the heart was reanimated, the pump flow and solution flow rates were adjusted to maintain a mean aortic pressure between 60 mmHg and 90 mmHg, and coronary blood flow between 650 ml/min and 850ml/min. During the transplantation procedure, the donor heart was arrested with cold cardioplegia solution, disconnected from the Organ Care system and implanted into the recipient. **Cold storage:** the donor heart was arrested with each centre's standard heart preservation solution. The transplantation procedure and perioperative care was completed according to the standard practices at each participating centre.
Follow-up	**30 days**
Conflict of interest/source of funding	Authors received personal fees, grants and fees for travel expenses from the manufacturer. One author served on the scientific advisory board of the manufacturer while another worked in the manufacturer's pathology laboratory.

Analysis

Follow-up issues: 2 protocol deviations were reported in the normothermic extracorporeal preservation group and 5 deviations were reported in the cold storage group. No further details were provided.

Study design issues: the study is a randomised non-inferiority trial that aimed to show that the outcomes in recipients of hearts preserved by normothermic extracorporeal preservation were not inferior to those in people who received hearts preserved by standard cold storage. Patients were recruited from, and treated at, 10 heart transplant centres. Group allocations were made using sealed and masked randomisation envelopes.

Study population issues: More than 1 donor heart was available for transplantation in some patients. The total number of hearts available for transplantation was not reported. Four donor hearts that were intended for recipients in the normothermic extracorporeal preservation group were deemed unacceptable for transplantation due to signs of persistent myocardial ischaemia. In these hearts, pathological examinations revealed signs of myocardial contusion with a history of cardiac arrest and chest compression, scarring and necrosis consistent with drug abuse, left ventricular hypertrophy that was overlooked during procurement and congenital fusion of the left and right aortic valve cusps resulting in moderate aortic regurgitation. The intended recipients each received another donor heart.

Other issues: Severe rejection was classified as grade 2 rejection (2 or more foci of interstitial or perivascular infiltrate with associated myocyte damage) or grade 3 rejection (diffuse infiltrate with multifocal myocyte damage with or without oedema, haemorrhage and vasculitis) according to the International Society for Heart and Lung Transplantation classification system.

- The mean total out-of-body time was defined as the duration from the time that the donor heart was stopped to the time of reperfusion in the recipient's chest.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **(62 NEP versus 66 standard cold storage)**

- The mean total out-of-body time was 324±79 minutes in the NEP group and 195±65 minutes in the cold storage group (p<0.001).
- The median length of stay in intensive care was 147 hours (range: 107–212 hours) in the NEP group and 137 hours (range: 97–197 hours) in the cold storage group (not significant).

30 day patient and graft survival

	Survival rate (% [n/N])			
Type of analysis	NEP group	Cold storage group	Between group difference (% [95% upper confidence bound])	p value
As-treated	94 [58/62]	97 [64/66]	3.5 [9.6]	NS
Per-protocol	93 [56/60]	97 [59/61]	3.4 [9.9]	NS

- Non-inferiority was observed between NEP and cold storage groups: no significant differences in survival rates were observed between groups.

Safety

Safety outcomes that occurred before transplantation

- One donor heart that was intended for a recipient in the NEP group was deemed unacceptable for transplantation due to friability of the aorta due to connective tissue disorder (total number of hearts available not reported). Authors state that transplantation might have been possible if the heart was procured by cold storage.

Safety outcomes that occurred after transplantation

- Severe rejection was reported in 18% (11/62) of patients in the NEP group and 14% (9/66) of patients in the cold storage group (not significant).
- Graft failure was reported in 1 patient in the NEP group and no patients in the cold storage group (not significant).
- Left ventricular dysfunction was reported in 8% (5/62) of patients in the NEP group and 6% (4/66) of patients in the cold storage group (not significant).
- Right ventricular dysfunction was reported in 3% (2/62) of patients in the NEP group and 9% (6/66) of patients in the cold storage group (not significant).

Abbreviations used: NEP, normothermic extracorporeal preservation; NS, not significant

Study 2 Koerner MM (2014)

Details

Study type	**Non-randomised comparative study**
Country	Netherlands
Recruitment period	2006 to 2008
Study population and number	Patients with end-stage heart failure n=**159 patients (29 Normothermic extracorporeal preservation versus 130 standard cold storage)**
Age and sex	Mean age: Normothermic extracorporeal preservation group, 50.1 years; cold storage group, 50.7 years Sex: Normothermic extracorporeal preservation group, 76% (22/29) male; cold storage group, 83% (108/130) male
Patient selection criteria	**Donors selection criteria** Inclusion criteria: donors <50 years with systolic blood pressure >85 mmHg at the time of final assessment, heart rate <120 bpm at the time of explantation, left ventricular ejection fraction >40% in the absence of gross wall abnormalities, absence of left ventricular hypertrophy and absence of valve abnormalities were included Exclusion criteria: not reported **Recipient selection criteria** Inclusion criteria: not reported Exclusion criteria: patients <18 years or >70 years with a congenital heart defect, fixed pulmonary hypertension, pulmonary vascular resistance >4 Woods units, chronic renal failure (serum creatine >2.5 mg/dl with or without the need for haemodialysis), ventilator dependence or panel reactive antibodies >20% with positive T-cell cross-match were excluded
Technique	**Normothermic extracorporeal preservation:** authors state that the left ventricle was perfused in an antegrade manner over the aortic root with a median aortic pressure of 40 to 80 mmHg and an antegrade coronary flow of 1.2 to 1.5 ml/g of cardiac weight. **Cold storage:** the technique was not described
Follow-up	**2 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: no patients were lost to follow-up.

Study design issues: All procedures were performed at 1 cardiac centre. The primary endpoints were cumulative survival rates at 30 days, 1 year and 2 years after surgery. Secondary endpoints were lactate levels during normothermic extracorporeal preservation, primary graft failure that needed 2 or more inotropic substances or mechanically circulatory support within 24 hours of heart transplantation, severe acute rejection and allograft vasculopathy.

Study population issues: The proportion of recipients with a history of mechanical circulatory support was 10.3% (3/29) in the normothermic extracorporeal preservation group and 38.4% (50/130) in the cold storage group (p=0.002). The proportion of recipients with dilated cardiomyopathy as an underlying disease was 62% (18/29) in the normothermic extracorporeal preservation group and 36.2% (47/130) in the cold storage group (p=0.014).

Other issues: none identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **159 patients (29 NEP versus 130 standard cold storage)**

Intraoperative outcomes in the NEP group.

- The mean cold ischaemic time during the allograft explantation procedure was 15 minutes (range 8 to 30 minutes).
- The mean perfusion time was 245 minutes (range 176 to 343 minutes).
- Mean lactate levels were 1.52 mmol/L before perfusion and 1.87 mmol/L at the end of perfusion.
- The mean warm ischaemic time (termination of allograft perfusion to declamping of the aorta of the recipient) was 37 minutes (range 17 to 50 minutes).

Postoperative outcomes

Outcome	NEP group	Cold storage group	p value
Mean hospital length of stay (days)	26	28	NS
Cumulative survival rate at 30 days (%)	96	95	NS
Cumulative survival rate at 1 year (%)	89	81	NS
Cumulative survival rate at 2 years (%)	89	79	NS

No numerators were reported

Safety

Death

Death was reported in 13.8% (4/29) of patients in the NEP group: deaths were caused by severe multi-organ failure (n=2), graft failure (n=1) and graft vasculopathy (n=1).

Other adverse events

	% (n/N)		
Adverse event	NEP group	Cold storage group	p value
Primary graft failure (%)	6.9 (2/29)	15.3 (20/130)	NS
Severe acute rejection (%)	17.2 (5/29)	23 (30/130)	NS
Need for haemodialysis (%)	10 (3/29)	25.3 (33/130)	0.05

Abbreviations used: NEP, normothermic extracorporeal preservation; NS, Not significant

Study 3 Saez DG (2014)

Details

Study type	**Case series**
Country	United Kingdom
Recruitment period	2013 to 2014
Study population and number	Patients with end-stage heart failure who received extended criteria allografts n=**30 patients (30 donor hearts)**
Age and sex	Mean age, 43 years; 83% (25/30) male
Patient selection criteria	**Donors selection criteria** Inclusion criteria: authors stated that the main indications were donor risk factors such as estimated ischaemia time longer than 4 hours, left ventricular ejection fraction less than 50%, previous donor cardiac arrest, left ventricular hypertrophy with interventricular septum in diastole of more than 13 mm, alcohol/drug abuse, or presence of palpable coronary artery disease (without coronary angiography) were included. Exclusion criteria: not reported **Recipient selection criteria** Inclusion criteria: patients with advanced heart failure who were high risk because of the presence of severe pulmonary hypertension (pulmonary vascular resistance >4 Wood units) before reversibility assessment, or a history of long term-LVAD use, or both, were included.
Technique	The heart was arrested with cold cardioplegia solution. The aorta and pulmonary artery of the donor heart were cannulated and the heart was connected to the normothermic extracorporeal preservation system (Transmedics' Organ Care System). Once the heart was reanimated, the pump flow and solution flow rates were adjusted to maintain coronary blood flow between 750 ml/min and 850 ml/min. Venous and arterial blood gas samples were taken simultaneously at 30-minute intervals for lactate quantification. The electrolyte status was evaluated at hourly intervals. During the transplantation procedure, the donor heart was arrested with cold cardioplegia solution, disconnected from the Organ Care system and implanted into the recipient.
Follow-up	**Mean of 257 days**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Authors state that 4 donor hearts with a history of cardiac arrest were declined for transplantation due refractory increasing lactate levels and signs myocardial damage. Only the outcomes of the 26 patients who underwent heart transplantation were analysed.

Study design issues: Authors do not explicitly state that hearts were obtained from brainstem dead donors; however, the procedure description suggests that this was the case.

Study population issues: Reduced left ventricular ejection fraction <50% was reported in 16.6% (5/30) of donors, palpable coronary artery disease was reported in 16.6% (5/30), and 20% (6/30) of donors had left ventricular hypertrophy with interventricular septum in diastole of more than 13 mm. Prolonged cardiac arrest of a mean duration of 30 minutes was documented in 26.6% (8/30) of donors.

Intra-aortic balloon pump support was documented in 7.6% (2/26) of recipients, moderate impairment of renal function (glomerular filtration rate of 30-59 ml/min/1.73m^2) was reported in 38.4% (10/28) of recipients and 1 patient had liver dysfunction. Preoperative left ventricular assist device support was documented in 42% (11/26) of recipients; 4 had a severe pump pocket infection at the time of transplantation. The Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score for all recipients was 12.9±7.7 points, with a predicted risk of mortality of 12.9% at 1 year.

Other issues:

- The mean total out of body time was defined as the duration from the time that the donor heart was stopped to the time of reperfusion in the recipient's chest.
- The total cold ischaemia time was defined as the length of time that the donor heart was kept on ice without any blood supply: that is, the duration from donor aortic cross-clamping to the connection of the allograft on the normothermic extracorporeal preservation system + the

duration from administration of the cold cardioplegia immediately before implantation to the release of the cross-clamp after implantation in the recipient.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **26 patients**

Intraoperative and postoperative outcomes

Outcome	Outcome
Mean total out-of-body time (minutes)	371±102
Mean total cold ischaemia time (minutes)	87±15
Mean perfusion time (minutes)	285±92
Mean duration of the implantation procedure (minutes)	60±13
Mean postoperative blood loss in 24 hours (ml)	812±501
Median length of stay in intensive care (days)	6
Mean hospital length of stay (days)	39±29
Survival at 30 days (% [n/N])	100 [26/26]
Survival at mean follow-up 257 days (% [n/N])	96 [25/26]

- Biventricular allograft function was well-preserved in 92% (24/25) of patients at mean follow-up of 257 days: the mean left ventricular ejection fraction was 66.3%, the mean fractional shortening was 37%, and the mean longitudinal right ventricular systolic function was 13.6 millimetres.

Lactate levels

	Mean lactate level		
Measurement	Baseline	End of perfusion	Maximum
Arterial lactate levels	2.36±0.52	1.93±0.63	2.76±0.62

Safety

- None of the donor hearts were discarded because of operator or technical failures related to the normothermic extracorporeal preservation system.
- Death due to bowel ischaemia was reported in 1 patient, 44 days after transplantation. The patient had previously been treated by a left ventricular assist device and had a severe pump infection. The patient became septic, after undergoing heart transplantation, resulting in the need for extracorporeal oxygenation support on the third postoperative day. Extracorporeal oxygenation support was discontinued after 5 days.
- Postoperative intra-aortic balloon pump support was needed in 11.5% (3/26) of patients to wean them off cardiopulmonary bypass: 1 recipient had severe pulmonary hypertension and the other 2 patients had received hearts from donors who had died as a result of a drug overdose. In all cases, allograft function improved and intra-aortic balloon pump support could be weaned after 4 days.
- Moderate right ventricular failure (according to the Interagency Registry Mechanical Assisted Circulatory Support criteria) was reported in 19.2% (5/26) of patients.

Study 4 Messer S (2013)

Details

Study type	**Unpublished case series (discussed in a published literature review)**
Country	United Kingdom
Recruitment period	2006 to 2007
Study population and number	Patients with end-stage heart failure n=**20 patients**
Age and sex	Not reported
Patient selection criteria	**Donor selection criteria** Inclusion criteria: donors <50 years with stable haemodynamics, no evidence of coronary artery disease and no abnormalities during echocardiography were included. Inotrope support at final assessment: dopamine, <10mcg/kg/min; dobutamine, <15mcg/kg/min; epinephrine, <0.2 mcg/kg/min; norepinephrine, <0.02 mcg/kg/min. Exclusion criteria: not reported **Recipient selection criteria** Inclusion criteria: not reported Exclusion criteria: patients with congenital heart disease, ventricular dependence, chronic renal failure, history of a previous organ transplant, a ventricular assist device, a total artificial heart, history of 3 or more previous sternotomies, transpulmonary gradient >12mmHg, panel reactive antibodies >20% with positive T-cell cross-match, or pulmonary vascular resistance >4 woods units were excluded
Technique	Not reported
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported
Safety Outcomes	• Acute rejection was reported in 2 patients; both required intra-aortic balloon pump support. • Left ventricular dysfunction was reported in 2 patients; 1 required intra-aortic balloon pump support. • A haemorrhagic stroke was reported in 1 patient; this resolved (no further details were provided).

Efficacy

Out-of-body and/or perfusion times

In a randomised non-inferiority trial of 128 patients who received donor hearts stored by normothermic extracorporeal preservation (n=62) or standard cold ischaemic storage (n=66), the mean out-of-body times (the duration from the time the donor heart was stopped to the time of reperfusion after transplantation) were 324±79 minutes and 195±165 minutes respectively ($p<0.001$)[1].

In a case series of 30 patients, the mean total out-of-body time was 371±102 minutes. The mean total cold ischaemia time (the time that the donor heart was kept on ice without any blood supply) was 87±15 minutes. The mean perfusion time was 285±92 minutes[3].

Length of stay

In the randomised non-inferiority trial of 128 patients who received donor hearts stored by normothermic extracorporeal preservation (n=62) or standard cold ischaemic storage (n=66), the median length of stay in intensive care was 147 hours in the normothermic extracorporeal preservation group and 137 hours in the standard cold ischaemic storage group (not significant)[1].

In a non-randomised comparative study of 159 patients who received donor hearts stored by normothermic extracorporeal preservation (n=29) or standard cold ischaemic storage (n=130), the mean hospital length of stay was 26 days in the normothermic extracorporeal preservation group and 28 days in the standard cold ischaemic storage group (not significant)[2].

Survival

In the randomised non-inferiority trial of 128 patients who received donor hearts stored by normothermic extracorporeal preservation (n=62) or standard cold ischaemic storage (n=66) 30-day survival rates were 94% (58/62) and 97% (64/66) respectively (not significant)[1].

In the non-randomised controlled study of 159 patients who received donor hearts stored by normothermic extracorporeal preservation (n=29) or standard cold ischaemic storage (n=130), the cumulative survival rates were 96% and 95% respectively at 30-day follow-up (not significant). In the same study, the cumulative survival rates were 89% and 81% respectively at 1 year follow-up (not significant). At 2 year follow-up the cumulative survival rates were 89% and 79% respectively (not significant)[2].

Allograft function

In the case series of 30 patients, biventricular allograft function was well preserved in 92% (24/25) of patients at mean follow-up of 257 days. The mean left ventricular ejection fraction was 66%, the mean fractional shortening was 37%, and the mean longitudinal right ventricular systolic function was 13.6 milimetres[3].

Safety

Death

Death was reported in 14% (4/29) of patients in the normothermic extracorporeal preservation group in a non-randomised comparative study of 159 patients who received donor hearts stored by normothermic extracorporeal preservation (n=29) or standard cold ischaemic storage (n=130). Deaths were caused by severe multi-organ failure (n=2), graft failure (n=1) and graft vasculopathy (n=1). Authors did not report the death rate in the standard cold ischaemic storage group[2].

Death due to bowel ischaemia was reported in 1 patient, 44 days after transplantation, in a case series of 30 patients[3].

Stroke

A haemorrhagic stroke was reported in 1 patient in a case series of 20 patients. No further details were provided[4].

Rejection

Severe rejection was reported in 18% (11/62) of patients in the normothermic extracorporeal preservation group and 14% (9/66) of patients in the standard cold ischaemic storage group in a randomised non-inferiority trial of 128 patients (not significant)[1].

Severe acute rejection was reported in 17% (5/29) of patients in the normothermic extracorporeal preservation group and 23% (30/130) of patients in the standard cold ischaemic storage group in a non-randomised comparative study of 159 patients (not significant)[2].

Graft failure

Graft failure was reported in 1 patient in the normothermic extracorporeal preservation group (n=62) and in no patients in the standard cold ischaemic storage group (n=66) in the randomised non-inferiority trial of 128 patients (not significant)[1].

Primary graft failure (not defined) was reported in 7% (2/29) of patients in the normothermic extracorporeal preservation group and 15% (20/130) of patients in the standard cold ischaemic storage group in a non-randomised comparative study of 159 patients (not significant)[2].

Ventricular dysfunction

Left ventricular dysfunction was reported in 8% (5/62) of patients in the normothermic extracorporeal preservation group and 6% (4/66) of patients in the standard cold ischaemic storage group in the randomised non-inferiority trial of 128 patients (not significant). In the same study, right ventricular dysfunction was reported in 3% (2/62) of patients in the normothermic extracorporeal preservation group and 9% (6/66) of patients in the standard cold ischaemic storage group (not significant)[1].

Moderate right ventricular failure was reported in 19% (5/26) of patients in the case series of 30 patients[3].

Need for haemodialysis

A need for haemodialysis was reported in 10% (3/29) of patients in the normothermic extracorporeal preservation group and 25% (33/130) of patients in the standard cold ischaemic storage group in the non-randomised comparative study of 159 patients (p=0.05)[2].

Validity and generalisability of the studies

- Only 1 randomised trial was identified. This was a non-inferiority study that aimed to show that the outcomes in recipients of hearts preserved by normothermic extracorporeal preservation were not inferior to those who received hearts preserved by standard cold storage[1].
- The longest follow-up period reported was 2 years[2].
- Only 1 study explicitly reported the occurrence of cardiac-related deaths[2].
- The occurrence of an acute haemorrhagic stroke was reported in a literature review that described the results of published and unpublished literature[4].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

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 www.nice.org.uk/guidance/ipg177
- Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults. NICE interventional procedure guidance 482 (2014). Available from www.nice.org.uk/guidance/ipg482
- Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation. NICE interventional procedure guidance 516 (2015). Available from www.nice.org.uk/guidance/ipg516
- Partial left ventriculectomy (the Batista procedure). NICE interventional procedure guidance 41 (2015). Available from www.nice.org.uk/guidance/ipg41

NICE guidelines

- Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. NICE guideline CG108 (2010). Available from www.nice.org.uk/guidance/CG108

- Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation. NICE guideline CG135 (2011). Available from www.nice.org.uk/guidance/CG135

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 is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous or publication would be unlawful or inappropriate. Five Specialist Adviser Questionnaires for normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death were submitted and can be found on the NICE website [INSERT HYPER LINK TO MAIN IP PAGE].

Patient commentators' opinions

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

Issues for consideration by IPAC

Ongoing trials:

- NCT02323321: International Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS) Heart For Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (EXPAND Heart Trial); Study type, Case series; location, United States; estimated enrolment, 75; estimated completion date, March 2017

References

1. Ardehali A, Esmailian F, Deng M, et al. (2015) Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet. 385 (9987): 2577–84. doi: 10.1016/S0140-6736(15)60261-6

2. Koerner MM, Ghodsizad A, Schulz U et al. (2014) Normothermic ex vivo allograft blood perfusion in clinical heart transplantation. Heart Surgery Forum. (3): E141-5. doi: 10.1532/HSF98.2014332

3. Saez G, Zych B, Sabashnikov A et al. (2014) Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. Annals of Thoracic Surgery 98(6): 2099-105. doi: 10.1016/j.athoracsur.2014.06.098

4. Messer S, Ardehali A, Tsui S. (2014) Normothermic donor heart perfusion: current clinical experience and the future. Transplant international. 28(6): 634–42. doi: 10.1111/tri.12361

Appendix A: Additional papers on normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death

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
Stamp NL, Shah A, Vincent V et al. (2015) Successful Heart Transplant after Ten Hours Out-of-body Time using the TransMedics Organ Care System. Heart Lung and Circulation (6):611-3. doi: 10.1016/j.hlc.2015.01.005	n=1 Follow-up: 1 year	The recipient was discharged from hospital, with normal biventricular function, 15 days after surgery. They had no episodes of rejection and had returned to work at 1 year follow-up.	Study is a case report that outlined the procedure technique and reported no safety outcomes. Larger, more relevant, were available.

Appendix B: Related NICE guidance for normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death

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. **Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults. NICE interventional procedure guidance 482 (2014)** 1.1 The evidence on the efficacy of extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults is adequate but there is uncertainty about which patients are likely to benefit from this procedure, and the evidence on safety shows a high incidence of serious complications. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake ECMO for acute heart failure in adults should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Submit data on all adults undergoing ECMO for acute heart failure to the international Extracorporeal Life Support Organization register 1.3 ECMO for acute heart failure in adults should only be carried out by clinical teams with specific training and expertise in the procedure.

	1.4 NICE encourages further research into ECMO for acute heart failure. This should include clear documentation of patient selection and indications for the use of ECMO. Outcome measures should include survival, quality of life and neurological status. **Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation. NICE interventional procedure guidance 516 (2015)** 1.1 Current evidence on the efficacy and safety of the implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. For people who are eligible for heart transplantation, refer to NICE's interventional procedure guidance on short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. 1.2 Patient selection should be done by a multidisciplinary team that includes a cardiologist with a specialist interest in heart failure, a cardiothoracic surgeon and a cardiac anaesthetist (see section 1.3). 1.3 Implantation of left ventricular assist devices for destination therapy should be done by surgeons, anaesthetists and intensive care specialists with special training and regular practice in performing this procedure and caring for these patients. Subsequent care should be provided by a multidisciplinary team including staff with the expertise to deal with patients' medical and psychological management, and with the maintenance of their left ventricular assist devices. 1.4 Clinicians should enter details on all patients who have a left ventricular assist device for destination therapy onto the UK Central Cardiac Audit Database. **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.
NICE guidelines	**Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 108 (2010).** **1.2.3 Invasive procedures** ***Coronary revascularisation*** 1.2.3.1 Coronary revascularisation should not be routinely considered in patients with heart failure due to systolic left ventricular impairment, unless they have refractory angina. [2003] ***Cardiac transplantation*** 1.2.3.2 Specialist referral for transplantation should be considered in patients with severe refractory symptoms or refractory cardiogenic shock. [2003] ***Cardiac resynchronisation therapy*** Refer to 'Cardiac resynchronisation therapy for the treatment of heart failure'. (NICE technology appraisal guidance 120 [2007]). Please refer to the NICE website for updates on the review status of this appraisal. ***Implantable cardioverter defibrillators*** Refer to 'Implantable cardioverter defibrillators for arrhythmias' (NICE technology appraisal guidance 95 [2006]). Please refer to the NICE website for updates on the review status of this appraisal. **Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation. NICE clinical guideline 135 (2011).** **Identifying patients who are potential donors** 1.1.1 Organ donation should be considered as a usual part of 'end-of-life care' planning. 1.1.2 Identify all patients who are potentially suitable donors as early as possible, through a systematic approach. While recognising that clinical situations vary identification should be based on either of the following criteria: • defined clinical trigger factors in patients[2] who have had

	a catastrophic brain injury, namely: – the absence of one or more cranial nerve reflexes **and** – a Glasgow Coma Scale (GCS) score of 4 or less that is not explained by sedation Unless there is a clear reason why the above clinical triggers are not met (for example because of sedation) and/or a decision has been made to perform brainstem death tests, whichever is the earlier • the intention to withdraw life-sustaining treatment in patients with a life-threatening or life-limiting condition which will, or is expected to, result in circulatory death. 1.1.3 The healthcare team caring for the patient should initiate discussions about potential organ donation with the specialist nurse for organ donation at the time the criteria in recommendation 1.1.2 are met.

Appendix C: Literature search for normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	21/05/2015	Issue 5 of 12, May 2015
HTA database (Cochrane)	21/05/2015	Issue 2 of 4, April 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	21/05/2015	Issue 4 of 12, April 2015
MEDLINE (Ovid)	21/05/2015	1946 to May Week 2 2015
MEDLINE In-Process (Ovid)	21/05/2015	May 18, 2015
EMBASE (Ovid)	21/05/2015	1974 to 2015 Week 20
PubMed	21/05/2015	n/a
BLIC (Dialog DataStar)	21/05/2015	n/a

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

1	Heart Transplantation/
2	((heart* or cardiac*) adj4 (transplant* or graft*)).tw.
3	((beating or working) adj4 (heart* or state*)).tw.
4	or/1-3
5	Perfusion/
6	NEVP.tw.
7	((normotherm* or ex-vivo or "ex vivo" or warm* or machine*) adj4 (perfus* or evaluat* or apprais* or assess* or wash* or ventilat*)).tw.
8	(continu* adj4 perfusion).tw.
9	Warm Ischemia/
10	(warm* adj4 (ischemi* or ischaemi*)).tw.
11	or/5-10
12	Organ preservation/
13	Organ preservation solutions/
14	"Tissue and Organ Harvesting"/
15	"Tissue and Organ Procurement"/
16	Tissue Donors/
17	Donor Selection/
18	((organ* or tissue*) adj4 (retriev* or harvest* or donor* or donat* or procure* or require* or request* or preserv*)).tw.
19	((donor* or donat*) adj4 (heart* or cardiac*)).tw.
20	((donor* or donat*) adj4 (select* or exclude* or exclusion* or screen*)).tw.

21	Brain Death/
22	(brain* adj4 (dead or death)).tw.
23	or/12-22
24	"organ care system".tw.
25	TransMedics.tw.
26	or/24-25
27	4 and 11 and 23
28	26 or 27
29	animals/ not humans/
30	28 not 29