Extracorporeal membrane oxygenation (ECMO) in adult acute heart failure

QUESTIONS TO BE ADDRESSED:

1. Is ECMO clinically effective in adult patients with acute heart failure compared to conventional (including pharmacological and invasive) therapies?

2. Is ECMO cost effective in adult patients with acute heart failure compared to conventional therapies?

SUMMARY

Background:

- Acute heart failure is a rapid onset condition in which the heart fails to deliver oxygen at a rate that meets the requirements of the metabolising tissues. When symptoms persist despite maximal medical therapy the condition is defined as refractory cardiogenic shock and the prognosis for these patients is poor unless further therapeutic strategies are used, with mortality rates ranging from 50% to 80%.
- Extracorporeal membrane oxygenation (ECMO) is a form of mechanical circulatory support that can sustain or replace cardiac function. It is intended for short or mid-term support.
- The National Institute for Health and Care Excellence (NICE) issued interventional procedure guidance on ECMO for acute heart failure in adults in March 2014, concluding that the evidence on the efficacy is adequate but there is uncertainty about which patients are likely to benefit, and the evidence on safety shows a high incidence of serious complications.

Clinical Effectiveness:

- No randomised controlled trials were identified. However, two small studies including a comparative element were identified. One meta-analysis of six observational studies on outcomes of ECMO in patients with fulminant myocarditis was identified (n=170) together with seven case series, each including more than 100 adult patients (n=1,559), and three smaller studies (n=86) providing information on quality of life following ECMO, an outcome which was not included in the larger studies.
- The following outcomes were reported:
  - 30-day survival was significantly better after ECMO became available in one centre (61% compared to 28%; n=71), an absolute risk reduction of 33%
  - No statistically significant difference in survival to discharge in one study comparing ECMO to miniaturised percutaneous ventricular assist devices (n=79)
  - The evidence from the meta-analysis and seven case series demonstrates considerable variation in the outcomes from different centres with survival to discharge varying from 20% to 67%
  - Some studies identified significant independent predictors of in-hospital or 30-day mortality, but the extent to which these could be used to inform patient selection or optimal timing is limited
  - Three small studies found that ECMO patients scored significantly lower than healthy or general population matched controls on SF-36 domains relating to physical and social functioning whereas there was no significant difference in scores for mental health and vitality. In one small study comparing ECMO to other cardiac surgery patients, ECMO patients scored significantly lower on SF-36 domains on mental health and vitality but there were no significant differences on other measures.

Cost Effectiveness:

- No studies assessing the cost effectiveness of ECMO for acute heart failure were identified.

Safety:

- A 2014 meta-analysis on the complications of ECMO for the treatment of cardiogenic shock and cardiac arrest in adult patients was identified. This included 20 studies (n=1,866). One study published after the search date of the meta-analysis was also included (n=228).
- High rates of serious complications were observed, with complications such as acute kidney injury, renal replacement therapy, major or significant bleeding, re-thoractomy for bleeding or tamponade and significant infection occurring in approximately one third or more of patients.

Activity and Cost:

- In 2013, the Registry of the Extracorporeal Life Support Organization reported 58,842 ECMO cases internationally, 4,042 of which were adult cardiac procedures. A UK modelling study assumed an average annual device usage of ten usages per year (based on clinical consensus). The number of adults receiving ECMO for acute heart failure has been estimated to be 200 per year and increasing[1].
- One study modelling the cost of extracorporeal life support for adult cardiac failure using four pumps available in the UK was identified. The costs per patient calculated varied from £8,616 to £28,829 for four devices and three different cardiac indications for ECMO. Costs were calculated at 2012 prices and did not include VAT or costs relating to routine staffing, medications or complications. In addition, these estimates do not include the cost of team training, critical care additional expenditure, potential transfer cost, opportunity cost and follow-up costs.

Equity:

- There may be an equity consideration in relation to people with acute heart failure who do not live in close proximity to a centre providing ECMO.

Context

1.1 Introduction

Heart failure occurs when the efficiency of the heart as a pump is impaired, which can lead to reduced blood flow to the body tissues and increased filling pressure in the heart [1]. Acute heart failure is a rapid onset condition in which the heart fails to deliver oxygen at a rate that meets the requirements of the metabolising tissues [2]. When symptoms persist despite maximal medical therapy the condition is defined as refractory cardiogenic shock and the prognosis for these patients is poor unless further therapeutic strategies are used, with mortality rates ranging from 50% to 80% [2].

Treatments for acute heart failure include pharmacological therapies and invasive therapies. Pharmacological therapies include diuretics and inotropic agents. Invasive therapies include electrophysiological interventions such as pacemakers or implantable cardioverter-defibrillators, revascularisation procedures such as percutaneous coronary intervention, valve replacement or repair, and temporary use of intra-aortic balloon pumps or ventricular devices [1].

Mechanical circulatory support includes several devices that sustain or replace cardiac function. It can be used as: initial salvation therapy (‘bridge to decision’) to gain time to allow specific

[1] Information supplied in a comment submitted as part of the consultation on this review.

therapeutic measures); to support cardiac function until recovery ('bridge to recovery'); to support cardiac function until heart transplantation ('bridge to transplantation') or to support cardiac function indefinitely [2]. Extracorporeal membrane oxygenation (ECMO) is a form of mechanical circulatory support; others include intra-aortic balloon counterpulsion and ventricular assist devices (VADs) [2].

1.2 Existing national policies and guidance

The National Institute for Health and Care Excellence (NICE) issued interventional procedure guidance (IPG) 482 on ECMO for acute heart failure in adults in March 2014 [1]. The NICE recommendations are:

- The evidence on the efficacy of 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, audit or research.
- 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.
- ECMO for acute heart failure in adults should only be carried out by clinical teams with specific training and expertise in the procedure.
- 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.

The Extracorporeal Life Support Organization (ELSO) produced a 2013 guideline for the use of prolonged extracorporeal life support (ECLS)[2] in adult cardiac failure, supplementary to their general guideline for all ECLS cases [3]. This guideline is presented as describing 'useful and safe practice' but 'not necessarily consensus recommendations' [3]. The guideline includes statements on the indications and contraindications for ECMO as follows:

- Indication for ECMO in adult cardiac failure is cardiogenic shock
    - Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume
    - Shock persists despite volume administration, inotropes and vasoconstrictors, and intraaortic balloon counterpulsation if appropriate
    - Typical causes: acute myocardial infarction, myocarditis, peripartum cardiomyopathy, decompensated chronic heart failure, postcardiotomy shock
    - Septic shock is an indication in some centres.
- Contraindications to ECMO
    - Absolute: unrecoverable heart and not a candidate for transplant or ventricular assist devices, advanced age, chronic organ dysfunction (emphysema, cirrhosis, renal failure), compliance (financial, cognitive, psychiatric or social limitations), prolonged cardiopulmonary resuscitation without adequate tissue perfusion

[2] The Extracorporeal Life Support Organization uses the term ECLS and ECMO interchangeably in their guideline.

- Relative: contraindication for anticoagulation, advanced age, obesity.

2 Epidemiology

About 900,000 people in the UK have heart failure [4]. About 30% to 49% of patients diagnosed with heart failure die within a year, but beyond one year the mortality is less than 10% per year [4]. A UK national heart failure audit for 2012/13 [5] reported 44,000 hospital admissions for acute heart failure with an in-hospital mortality rate of 9.4% (down from 11.1% in 2011/12) and a 30-day mortality rate of 14.9% (figure for previous year not available).

A UK national audit of adult cardiac surgery for 2010/11 [6] reported 30,231 procedures in 2010/11 with a UK mortality rate for all cardiac surgery of 3.1% (down from 4.0% in 2001/02).

The incidence of postcardiotomy myocardial dysfunction is as high as 3% to 5% among patients receiving routine cardiac surgical procedures [7]. Approximately 1% of these require prolonged postoperative circulatory support owing to refractory cardiac and or pulmonary dysfunction [7].

The incidence of refractory postcardiotomy cardiogenic shock in adult cardiac patients ranges from 0.5% to 1.5% [8]. A telephone survey of cardiac surgical units in the UK and Ireland in 2007/08 found that ventricular assist devices for postcardiotomy cardiogenic shock were required in 0.24% of patients undergoing coronary artery bypass grafting and or/valve surgery [9].

3 The intervention

There are two main types of ECMO, venovenous and venoarterial. The venoarterial method is used for acute heart failure in adults and involves blood being withdrawn via the venous system, pumped through an oxygenator and returned to the arterial system. Patients are given a continuous infusion of an anticoagulant to prevent blood clotting. In the venovenous method the blood is returned to the venous system [1].

Venoarterial (VA) ECMO can completely replace cardiac function and is indicated for the more severe forms of refractory cardiogenic shock or for refractory cardiac arrest [2]. It can be initiated in almost any setting and is therefore suitable for emergency settings [2]. It is intended for short or mid-term support [2]. Of the other mechanical circulatory support (MCS) devices, intra-aortic balloon pump (IABP) is the least expensive and most commonly used but requires some residual cardiac function to be effective. Ventricular assist devices (VADs) are continuous pumps that partially or completely replace the function of the heart. Percutaneously implanted VADs are intended for temporary short-term use and surgically implanted VADs are for mid to long-term use [2].

Extracorporeal membrane oxygenation has been used in a variety of cardiac diseases complicated by cardiac failure including: postcardiotomy cardiogenic shock; fulminant myocarditis; acute coronary syndrome; as a bridge to durable mechanical circulatory support or transplant; as an assist to cardiopulmonary resuscitation; for refractory cardiac arrest; for primary graft failure and for secondary cardiac transplant rejection [10].

4 Findings

A search of Medline, Embase, Cochrane Library, TRIP and NICE Evidence was performed on the 1st July 2014 for studies published in English from 2004 onwards. Further details of the search strategy are provided in section 9.

NICE conducted a literature review of studies published up until March 2013 as part of the development of IPG482 on ECMO for acute heart failure in adults [4]. This review was described by the authors as a rapid review and included 4,038 patients from ten case series and one case report presented in an overview table. Studies that were identified in the literature search but were not included in the overview table were listed in the appendix, however the reasons given for the inclusion or exclusion of studies in the overview table were not always clear or consistent. It was therefore not felt appropriate to use the NICE literature review as the primary source of evidence in this current review.

In the literature search for the current review, one 2014 meta-analysis on outcomes of ECMO in patients with fulminant myocarditis was identified. Although no controlled trials were identified, two studies including a comparative element were identified and are summarised below. In addition, multiple case series on ECMO were identified in the literature search. Due to the large number of studies identified, only the seven case series involving more than 100 adult patients receiving ECMO for acute heart failure are included in this review, with the exception of three studies providing information on quality of life, an outcome not reported by the larger studies.

4.1 Evidence of effectiveness

Outcomes relating to clinical effectiveness are considered first. Outcomes relating to optimal timing of the intervention, patient selection and quality of life are considered separately. Issues relating to safety are considered in section 4.4.

Clinical effectiveness

A 2014 meta-analysis [11] included outcomes for 170 patients with fulminant myocarditis complicated by cardiogenic shock or cardiac arrest who received ECMO. This included six studies published between January 2000 and November 2012 involving a total of 170 patients (Table 1).

Table 1: Results of a meta-analysis of ECMO for fulminant myocarditis

Study	Patients	Intervention	Outcomes	Comment
Cheng 2014 [11] Meta-analysis of studies with ≥10 patients published between 2000 and November 2012	Patients with fulminant myocarditis and cardiogenic shock and/or cardiac arrest N=170 (6 studies)	VA ECMO	**Pooled survival to discharge:** 67% (95%CI 59% to 74%) (I^2 = 0%)[3] (median 69.3; range 60.0 to 87.5) **Pooled survival to discharge (adult patients only; 5 studies):** 67% (95%CI 57% to 75%) (I^2 = 17.0%) (median 68.6; range 57.9 to 87.5)	A separate analysis was provided that only included adult patients(≥18 years)

This was a well conducted meta-analysis, although only a small number of studies were identified and only one indication for ECMO was considered. The meta-analysis used a random-effects model and only included studies with ten or more patients. Where studies appeared to include

[3] I^2 reports the degree of heterogeneity (variation) between the studies included in the analysis

overlapping patients only the largest of the studies identified was included in the meta-analysis. There was some heterogeneity between the studies but this was not statistically significant.

The two studies with a comparative element are summarised in Table 2.

Table 2: Comparative studies on the effectiveness of ECMO

Study	Patients	Group 1	Group 2	Outcomes	Comment
Chamogeorgakis 2013 [12] Comparison of outcomes associated with two short-term support devices and ECMO Retrospective review One centre, USA (2006 - 2011)	Patients with cardiogenic shock related to post-infarction or decompensated cardiomyopathy	VA ECMO (n=61) Mean age(SD): 53 years (±12.9)	Temporary miniaturised percutaneous ventricular assist devices (mp-VAD): Impella axial flow pump (n=7) or TandemHeart centrifugal pump (n=11) Mean age(SD): 58 years (±10.4)	**Survival to discharge:** No significant difference between the groups (mpVAD 50% (n=9); ECMO 50% (n=30))	One patient received ECMO after initially receiving TandemHeart. The study authors included the results for this patient in the TandemHeart group 54% of group 1 and 33% of group 2 patients had received CPR
Sheu 2010 [13] Comparison of patients treated before (1993-2002) and after (2002-2009) ECMO available All patients prospectively recruited to study One centre, Taiwan	Patients with acute STEMI complicated with profound cardiogenic shock	VA ECMO n= 46 Mean (SD) age: 65.1 years (±10.6)	Patients treated before ECMO available[4] n=25 Mean (SD) age: 67.2 years (±11.1)	**Mean (SD) duration of hospitalisation (days):** Significantly higher in group 1 (35.3 ± 58.2) compared to group 2 (2.9 ± 3.4), p=0.0005 **30-day survival:** Significantly higher in group 1 (61%; n=28) compared to group 2 (28%; n=7), p=0.008. Absolute risk reduction 33% The Kaplan	The study also compared the results of acute STEMI patients without profound cardiogenic shock treated before and after 2002, none of whom received ECMO. There was no significant difference in 30-day survival between these two groups of patients

[4] Before June 1998 primary balloon angioplasty was performed in patient with acute myocardial infarction. After June 1998 primary stenting was performed in suitable patients.

				Meier analysis of survival rates is in presented in appendix 1	

CPR – cardiopulmonary resuscitation; STEMI – ST-segment elevation myocardial infarction; VA – venoarterial

Although two studies with a comparative element were identified, the focus of the studies was different. Chamogeorgakis 2013 [12] involved a retrospective comparison of ECMO to miniaturiased percutaneous ventricular assist devices and did not identify any statistical difference in survival to discharge (both 50%). Sheu 2010 [13] found a significantly higher 30-day survival for patients with acute STEMI complicated by profound cardiogenic shock treated after ECMO became available at their centre (61% compared to 28%). Whilst this latter study demonstrates improved outcome once ECMO became available, the conclusions which can be drawn from one, single-centre small study are limited. The possibility that other elements of care may have changed and/or improved in the two time periods in this study, in addition to the availability of ECMO, should also be considered.

Seven case series including 100 patients or more are summarised in Table 3.

Table 3: Case series on the effectiveness of ECMO

Study	Patients	Intervention	Outcomes	Comment
Loforte 2014 [14] Retrospective case series Two centres, Italy (2006-2012)	Patients with primary or postcardiotomy refractory cardiogenic shock N=228 Mean (SD) age: 58.3 years (±10.5)	VA ECMO: RotaFlow (n=213) CentriMag (n=15) (Peripheral ECMO n=126; central ECMO n=102) All patients (100%) received simultaneous IABP	**Mean (SD) duration of ECMO (days):** 10.9 (±9.7) **Survival to discharge:** 54% (n=122) (for central ECMO: 53%: for peripheral ECMO: 54%) Mean duration of hospitalisation not reported	The two centres treated a similar number of patients (n=109 and 119) 29 patients (13%) received CPR before ECMO
Chung 2012 [15] Prospective case series One centre, Taiwan (2003-2010)	Patients with profound cardiogenic shock refractory to conventional therapy undergoing CPCR followed by prompt ECMO support N=134 Mean (SD) age: 51.8 years (±20.5)	VA ECMO 92 patients (68.7%) received simultaneous IABP	**Mean (SD) duration of ECMO (days):** 5.1 (±5.7) **Mean (SD) duration of hospitalisation (days):** 27 (±33) **30-day survival:** 55% (n=73) **Survival to discharge:** 43% (n=57)	This study did not have any age-related inclusion criteria and therefore included both adult and paediatric patients
Lee 2012 [16]	Patients with	VA ECMO: n=109	**Mean (SD) duration of**	Results from the

Prospective case series One centre, South Korea (2005-2010)	refractory cardiogenic shock from cardiac related cause N=118 Mean (SD) age: 57.4 years (±14.9)	VV ECMO: n=9 33 patients (28%) received simultaneous IABP	**ECMO (days):** 4.0 (±4.0) **Survival to discharge:** 20% (n=24) Mean duration of hospitalisation not reported	118 patients who received ECMO for cardiac related causes are reported. The study also included 67 patients receiving ECMO for other causes (e.g. liver transplantation, pulmonary) 40 patients (22% of the total study population) received CPR before ECMO
Rastan 2010 [8] Retrospective review One centre, Germany (1996-2008)	Patients with refractory postcardiotomy cardiogenic shock N= 517 Mean (SD) age: 63.5 years (±11.2)	VA ECMO (61% received central arterial cannulation; 39% received peripheral arterial cannulation) Most patients (74%) also received IABP	**Mean (SD) duration of ECMO (days):** 3.3 (±2.9) **Mean duration of hospitalisation (days):** 16.2 **Survival to discharge:** 25% (n=129) (62% of hospital survivors received central arterial cannulation and 38% received peripheral arterial cannulation) **30-day survival:** 31.3% ±2.2% **One year-survival:** 17% ±1.7% **Five-year survival:** 14% ±1.7%	Mean follow-up of 3.2 years for patients who survived to discharge and 0.82 years for all patients
Wu 2010 [17] Retrospective review One centre, Taiwan (2003-2009)	Patients with refractory postcardiotomy cardiogenic shock N=110	VA ECMO	**Mean (SD) duration of ECMO (hours):** 143 (±112) **Survival to discharge:** 42% (n=46) **One year-survival:**	

	Mean age not reported		25% (n=28) **Three-year survival:** 8% (n=9) Mean duration of hospitalisation not reported	
Elsharkawy 2010 [18] Retrospective review One centre, USA (1995-2005)	Adult cardiac surgery patients requiring support for circulatory failure N=233 Mean age not reported	VA ECMO	**Survival to discharge:** 36% (n=84) Mean duration of hospitalisation not reported	
Doll 2004 [7] Prospective review One centre, Germany (1997-2002)	Patients with refractory postcardiotomy cardiogenic shock N=219 Mean (SD) age: 61.3 years (±12.1)	VA ECMO 144 patients (66%) also received IABP	**Mean (SD) duration of ECMO (days):** 2.8 (±2.2) **Survival to discharge:** 24% (n=52) **30-day survival:** 24% (n-=52) Mean duration of hospitalisation not reported	104 patients (47%) had received CPR

CPCR – cardiopulmonary cerebral resuscitation; IABP – intra-aortic balloon pumps; SD – standard deviation; VA – venoarterial; VV – venovenous

Overall, case series reports represent a lower quality of evidence. One of the case series reported on patients from two centres, but the other studies reported results from just one centre. This introduces the possibility of bias as the selection of patients for ECMO may vary between centres. Centres were located in the USA (1), Europe (3) and Asia (3). Four were retrospective and three were prospective reviews. All but one of the studies included only patients with cardiogenic shock. All but one of the studies reported outcomes for adults only. Chung 2012 [15] included both paediatric and adult patients but did not provide details on the number of paediatric patients or a separate analysis for adult and paediatric patients.

The outcomes reported varied between studies; however, all studies provided information on survival to discharge, which varied considerably from 20% to 54%. It is not clear why the results from different centres are so different. For example, study location, years in which ECMO was delivered, size of study, duration of ECMO or mean age of patients (when reported) do not clearly correspond to a higher or lower proportion of patients surviving to discharge.

Two studies included longer follow up but again there was variation in the outcomes at the different time points reported in the two studies. Both studies reported one-year survival which

was 17% (Rastan) and 25% (Wu) respectively. Wu [17] reported three-year survival as 8%, whereas Rastan [8] reported five-year survival as 14%.

Patient selection and optimal timing

Five studies were identified addressing outcomes for subgroups of patients receiving ECMO for different indications. These are summarised in Table 4.

Table 4: Outcomes for subgroups of patients receiving ECMO

Indication	Survival to discharge	Study
Postcardiotomy (n=118)	47%	Loforte 2014 [14]
Donor graft failure (n=37)	65%	
Post acute myocardial infarction (n=27)	37%	
Acute-on-chronic heart failure (n=40)	73%	
Acute myocarditis (n=6)	67%	
STEMI (n=37)	59%	Chung 2012 [15]
Non-STEMI (n=16)	31%	
Post-surgery pump failure (n=30)	27%	
Refractory chronic heart failure failed to medication (n=14)	29%	
Fulminant acute myocarditis (n=26)	46%	
Paediatric congenital diaphragmatic hernia (n=3)	67%	
Cardiac catheterization-related severe complications (n=8)	0%	
All coronary artery bypass graft (CABG)	28%	Rastan 2010[5] [8]
Isolated CABG	35%	
Aortic valve surgery	20%	
Isolated aortic valve surgery	26%	
CABG and aortic valve surgery	12%	
Mitral valve surgery	16%	
Isolated mitral valve surgery	11%	
CABG and mitral valve surgery	22%	
Isolated aortic valve and mitral valve surgery	8%	
CABG, aortic valve and mitral valve surgery	15%	
Tricuspid valve repair	15%	
Ascending aorta surgery	21%	
Aortic arch repair	6%	
Surgical ventricular restoration	25%	
Ischemic ventricular septal defect closure	20%	
Pulmonary embolectomy	29%	
Pericardiectomy	0%	
Thoracic transplantation	23%	
Emergency surgery (n=84)	42%	Elsharkawy 2010 [18]
Arteriovenous replace (n=39)	23%	
Arteriovenous repair (n=2)	0%	
Mitral valve replace (n=20)	30%	

[5] Number of patients undergoing each procedure not reported

Mitral valve repair (n=22)	27%	
Tricuspid valve replace/ repair (n=16)	38%	
Any coronary artery bypass graft (n=86)	23%	
Any valve problem (n=69)	28%	
Indication	**30-day survival**	**Study**
Coronary artery bypass graft (CABG) (n=119)	31%	Doll 2004 [7]
CABG and aortic valve replacement (n=21)	5%	
Aortic valve replacement (n=24)	33%	
CABG and mitral valve replacement (n=11)	18%	
Other[6] (n=44)	11%	

STEMI – ST-segment elevation myocardial infarction CABG – coronary artery bypass graft

Survival to discharge varied with different indications, but the numbers of patients with each indication was small or not reported; the indications specified also varied between the studies making it difficult to draw any conclusions.

Five studies that performed multivariate logistic regression analysis on predictors of in-hospital or 30-day mortality were identified. These are summarised in Table 5.

Table 5: Results of multivariate logistic regression analysis

Study	Outcome	Result
Chung 2012 [15]	Significant independent predictor of in-hospital mortality	• Baseline APACHE II[7] score ≥22 (OR 59.39; 95%CI 6.66 to 537.9)
Wu 2010 [17]	Significant independent predictor of in-hospital mortality	• Age >60 years (OR 3.1; 95%CI 1.1 to 8.6) • Requirement for continuous arteriovenous haemofiltration (OR 5.6; 95%CI 1.9 to 16.4) • Maximal total bilirubin >6mg/dL (OR 9.0; 95%CI 1.6 to 48.9) • Failure to be weaned from support after 110 hours (OR 3.6; 95%CI 1.2 to 10.8)
Rastan 2010 [8]	Significant independent predictor of in-hospital mortality[8]	• Age[9] > 70 years (OR 1.90) • Diabetes (OR 2.61) • Isolated coronary artery disease (OR 0.56)
Elsharkawy 2010 [18]	Significant independent predictor of in-hospital mortality	• Age (OR 1.52; 95%CI 1.20 to 1.92) • Presence of cardiogenic shock (OR 0.52; 95%CI 0.29 to 0.93)
Sheu 2010	Significant independent	• Congestive heart failure (OR 7.34; 95%CI 2.78 to

[6] 'Other' indications included pulmonary embolectomy; aortic aneurysm repair; double valve replacement; type A aortic dissection repair; heart transplant; ventricular septal defect closure; tricuspid valve repair and pulmonary valve replacements; pericardectomy; and CABG and endoventricular resection of left ventricular aneurysm.

[7] APACHE II is a severity score and mortality estimation tool comprising 12 physiological variables and two disease-related variables. The APACHE II score ranges from 0 to 71 points.

[8] 95% confidence intervals presented graphically in paper but figures not specified.

[9] The authors found an almost linear increase in mortality risk with age but were unable to identify an age cut-off point at which mortality increase significantly in a non-linear fashion.

[13]	predictors of 30-day mortality	19.39) • Final TIMI flow grade ≤2[10] (OR 5.88; 95%CI 3.13 to 52.63)

APACHE – Acute Physiology and Chronic Health Evaluation; OR – odds ratio; TIMI – thrombolysis in myocardial infarction

Some studies identified significant independent predictors of hospital or 30-day mortality, but the extent to which these could be used to inform patient selection or optimal timing is limited. There are few studies that have addressed this issue and, with the exception of age, the different studies that have considered this have identified different significant independent predictors. The wide confidence intervals associated with many of the odds ratios should also be noted as this reduces confidence in the clinical significance of the result.

The authors of these studies generally concluded that their findings were insufficient to define which patients should or should not be placed on ECMO support or to draw conclusions from the results of any particular sub-group of patients.

Quality of Life

The included studies on clinical effectiveness did not include any information addressing patient quality of life. Three studies that involved less than 100 patients but considered the impact of ECMO on quality of life were therefore also included and are summarised in Table 6. All of these studies used the Short-form 36 (SF-36) questionnaire[11] to assess quality of life. One study (Mirabel 2011) [19] also used the Hospital Anxiety and Depression Scale (HAD)[12] and the Impact of Event Scale (IES)[13].

Table 6: Case series addressing quality of life outcomes following ECMO

Study	Quality of life assessment	Patients	Controls	Outcomes	Comment
Mirabel 2011 [19] One centre, France (2002-2009)	SF-36 HAD IES Median follow-up 525 days (range 92 to 2,400 days	Patients who survived to discharge after ECMO for refractory cardiogenic shock due to fulminant myocarditis n=26	Healthy controls matched for age and gender n=26	ECMO patients had significantly lower scores than controls for SF-36 domains of physical functioning, physical role functioning, general health, social functioning and mean PCS ($p<0.05$) No significant difference between ECMO patients and	Survival to discharge for the 35 patients who received ECMO was 69% Study also included 4 survivors who received a Thoretec paracorporeal VAD (before ECMO was

[10] Indicating unsuccessful reperfusion [13].

[11] The 36 items of the SF-36 are combined to evaluate eight domains: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health. Aggregate physical and mental component summary measures can also be calculated [21].

[12] The HAD contains 14 questions, seven assessing anxiety and seven assessing depression. Subscale scores of ≥8 out of 21 indicate clinically significant anxiety or depression symptoms [19].

[13] The IES includes 15 questions divided into two subscales on intrusion (seven items) and avoidance (eight items). Patients with a score of ≥30 out of 75 points were considered at high risk of PTSD [19].

				controls on bodily pain, vitality, emotional role functioning, mental health or mean MCS HAD score ≥ 8 points[12]: Anxiety 38% Depression 27% At risk of PTSD (IES≥30[13]): 27%	available) Mean age of survivors 38.1±12.7
Wang 2009 [20] One centre, China (2004-2008)	SF-36 Mean follow-up 2.3 ±1.5 years	Patients who survived to discharge after VA ECMO for refractory cardiogenic shock following cardiac surgery n=32	(1): Adult patients who had undergone cardiac surgery without ECMO support (2) General population matched for age and gender	ECMO patients had significantly lower scores than other cardiac patients for: vitality and mental health ($p<0.05$). No significant differences for other domains No significant difference between ECMO patients and general population controls on vitality and mental health ECMO and cardiac patients had significantly lower score than general population on physical functioning, physical role functioning, bodily pain, general health, social functioning and emotional role functioning ($p<0.05$)	Survival to discharge for the 62 patients who received ECMO was 55% (n=34) Mean age of ECMO survivors: 51 ±15
Combes 2008 [21] One centre, France (2003-2006)	SF-36 Median follow-up 11 months (range 3 to 39 months)	Patients alive in December 2006 after VA ECMO for refractory cardiogenic shock n=28	Healthy controls matched for age and gender, with no adverse health conditions	ECMO patients had significantly lower scores than matched controls for: physical role functioning, general health, social functioning and mean PCS ($p<0.05$) No significant	Survival to discharge for the 81 patients who received ECMO was 42% (n=34) Mean age of ECMO survivors was 46±17

				difference between ECMO patients and controls on: physical functioning, bodily pain, vitality, emotional role functioning, mental health and mean MCS	

HAD – Hospital Anxiety and Depression Scale; IES - Impact Event Scale; MSC – mental component summary; PCS – physical component summary; PTSD – post traumatic stress disorder; SF-36 – Short-Form Questionnaire; VAD – ventricular assist device

All three studies compared ECMO patients to healthy or general population matched controls and had similar results, finding that ECMO patients scored lower on physical and social functioning scores, but did not show any significant differences in areas such as mental health and vitality. Despite the lack of difference compared with healthy controls on mental health scores, approximately one third of survivors had scores of anxiety, depression and PSTD risk that were considered clinically significant.

In contrast, when comparing ECMO to other cardiac surgery patients, Wang [20] found that ECMO patients scored lower on mental health and vitality but reported no significant difference on other domains. However, Wang also found that both ECMO and non-ECMO cardiac surgery patients scored significantly lower than general population controls on all SF-36 domains except mental health and vitality.

The authors of these studies stated that stated that the SF-36 scores of their ECMO patients compared favourably with published scores for patients suffering from chronic and disabling illnesses [21], patients who had recovered from life-threatening conditions [21], VAD patients bridged to transplantation [19] and acute respiratory distress syndrome survivors [16].

It is notable that the mean ages of the survivors in these studies assessing quality of life are low compared to the mean age of people receiving ECMO in the effectiveness studies. The indications for ECMO were similar between the effectiveness and quality of life studies.

4.2 Trials in progress

A cohort study on oxidant-antioxidant activity, free radical activity, immune response and biomarkers in ECMO patients presenting with cardiogenic shock is underway in Taiwan. The aim is to identify early parameters that could be used to predict the outcome of ECMO treatment. The estimated enrolment is 100 and the estimated completion date is December 2016 (NCT01089036).

A phase I non-randomised study on refractory out-of-hospital cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (CHEER) is underway in Australia. The estimated enrolment is 24 and the estimated completion date is December 2014 (NCT01186614).

4.3 Evidence of cost-effectiveness

No studies assessing the cost-effectiveness of ECMO for adult acute heart failure were identified. A cost-modelling study assessing the cost of extracorporeal life support for adult cardiac failure using pumps available in the UK was identified and is discussed in section 5.

4.4 Safety

A 2014 meta-analysis on complications of venoarterial ECMO for the treatment of cardiogenic shock and cardiac arrest in adult patients (≥18 years) was identified [10]. This included 20 studies published between January 2000 and November 2012 involving a total of 1,866 patients. The meta-analysis used a random-effects model and only included studies with ten or more patients. Where studies appeared to include overlapping patients only the largest of the studies identified was included in the meta-analysis. Table 7 summarises the results of the meta-analysis.

Table 7: Meta-analysis of complications of ECMO (Cheng 2014) [10]

Complication	Number of studies (patients)	Cumulative complication rate	Pooled estimate rate	I^2
Lower extremity ischaemia	13 (n=677)	112 of 677	16.9% (95%CI 12.5 to 22.6)	58.9%
Lower extremity ischaemia requiring fasciotomy or compartment syndrome	5 (n=335)	33 of 335	10.3% (95%CI 7.3 to 14.5)	9.9%
Lower extremity ischaemia requiring amputation	5 (n=192)	7 of 192	4.7% (95%CI 2.3 to 9.3)	0%
Stroke	3 (n=630)	36 of 630	5.9% (95%CI 4.2 to 8.3)	5.9%
Neurological complications	9 (n=1,019)	151 of 1,019	13.3% (95%CI 9.9 to 17.7)	56.5%
Acute kidney injury	6 (n=380)	197 of 380	55.6% (95%CI 35.5 to 74.0)	92.3%
Renal replacement therapy	15 (n=1,452)	758 of 1,452	46.0% (95%CI 36.7 to 55.5)	89.9%
Major or significant bleeding	5 (n=260)	120 of 260	40.8% (95%CI 26.8 to 56.6)	81.8%
Re-thoractomy for bleeding or tamponade	6 (n=828)	409 of 828	41.9% (95%CI 24.3 to 61.8)	94.2%
Significant infection	10 (n=922)	321 of 922	30.4% (95%CI 19.5 to 44.0)	93.1%

The complications with the highest pooled estimate rates were acute kidney injury and renal replacement therapy but the heterogeneity of the studies reporting these complications was high. The authors considered that the high heterogeneity seen for some complications reflected inter-centre variability, patient selection, reporting patterns and lack of unified definitions and criteria for the diagnosis of complications [10].

Additional information on less frequently reported complications not appropriate for pooled analysis was also presented (Table 8).

Table 8: Less frequently reported complications of ECMO (Cheng 2014) [10]

Complication	Number of studies	Cumulative complication rate	Minimum rate	Maximum rate
Retrograde aortic dissection	3	5 of 320	1.4%	2.2%
Inferior vena cava tear	2	2 of 92	2.2%	2.2%
Arterial thrombus	3	13 of 192	4.2%	19%
Venous thrombus	4	18 of 217	1.1%	17%

Intracardiac clot	5	8 of 303	0.8%	6.3%
Left ventricular distension	1	5 of 46	10.9%	---

The authors considered whether complications reflect the overall severity of disease in patients receiving ECMO or in the ECMO procedure itself. They suggested that complications such as lower extremity ischaemia, fasciotomy and compartment syndrome and amputation are more directly attributable to ECMO, whereas renal injury, infections and neurological complications may be caused by the underlying illness. Complications such as lower limb ischaemia were thought to be more prevalent with femoral arterial cannulation [10].

One additional study with data on safety, published after the search date of the meta-analysis (November 2012), was identified (Table 9).

Table 9: Complications of ECMO from one study published after the meta-analysis

Study	Complication	Occurrences
Loforte 2014 [14] (n=228[14])	Leg ischaemia	5.7%
	Femoral site infection	3.9%
	Requirement for continuous venovenous haemofiltration	Peripheral ECMO: 44% Central ECMO: 57%
	Bleeding/ tamponade	Peripheral ECMO: 48% Central ECMO: 63%

The categories used in Loforte do not exactly correspond to those used in Cheng's meta-analysis so it is not possible to directly compare them. In Loforte's results a significantly higher percentage of some complications occurred with central ECMO compared to peripheral ECMO ($p<0.05$ for comparisons reported).

4.5 Summary of section 4

Several studies on the effectiveness of ECMO for acute heart failure were identified, the majority of which were case series from single centres.

One comparative study (n=71) provided some information on outcomes for patients before and after ECMO became available at one centre. Before ECMO became available patients with acute myocardial infarction received primary balloon angioplasty or stents. This study found that 30-day survival was significantly better after ECMO became available (61% compared to 28%), an absolute risk reduction of 33%. However, this was a longitudinal study comparing outcomes over two time periods which introduces the possibility that other changes in patient care beyond the availability of ECMO may have influenced the results. Only one other study with a comparative element was identified, comparing ECMO to miniaturised percutaneous ventricular assist devices. This study did not report any statistically significant difference in survival to discharge between the two interventions.

The evidence from the meta-analysis and seven case series demonstrates considerable variation in the outcomes from different centres with survival to discharge varying from 20% to 54%. The ELSO guideline for ECLS for adult cardiac failure states that the expected survival to discharge is 40%, but may be less with postcardiotomy. Postcardiotomy was an inclusion criterion in two of the three included studies that achieved a survival to discharge of 25% or less; however, postcardiotomy was also an inclusion criterion for two studies that achieved a survival to discharge of over 40%. Some studies identified significant independent predictors of hospital or

[14] Peripheral ECMO n=126; central ECMO n=102

30-day mortality following ECMO, but the extent to which these could be used to inform patient selection or optimal timing is very limited.

Evidence regarding the impact of ECMO on quality of life came from three small studies. All found that ECMO patients scored significantly lower than healthy matched controls on SF-36 domains relating to physical and social functioning. There was no significant difference in areas such as mental health and vitality between ECMO patients and healthy controls. However, in one study comparing ECMO patients to other cardiac surgery patients, the ECMO patients scored significantly lower on mental health and vitality but there were no significant differences on other measures.

No randomised controlled trials or studies comparing ECMO to other treatments were identified, however there may be ethical considerations associated with doing such studies with critically ill patients.

No studies assessing the cost-effectiveness of ECMO for acute heart failure were identified.

Data on safety came from a 2014 meta-analysis on the complications of venoarterial ECMO for the treatment of cardiogenic shock and cardiac arrest in adult patients and one study published after the search date of the meta-analysis. The meta-analysis demonstrated high rates of serious complications in a pooled analysis of 20 studies with complications such as acute kidney injury, renal replacement therapy, major or significant bleeding, re-thoractomy for bleeding or tamponade, and significant infection occurring in approximately one third or more of patients.

5 Cost and Activity

Borisenko (2014) [9] assessed the cost of extracorporeal life support for adult cardiac failure using pumps available in the UK. This analysis was a comparison of the costs of different pumps and included the cost of the device (including capital cost, maintenance and consumables), device implantation (including staff costs and consumables) and the frequency of replacing the device (if required, i.e. if the maximum time for support recommended for a particular device was exceeded). The costs of routine staff use, medication and complications were not included in the analysis. All prices excluded VAT and staffing and consumable costs were at 2012 prices.

The total price for single use of four ECLS devices (including capital equipment, maintenance cost and single-use elements) ranged from £1,500 to £7,836. Individual single use costs for each device were:

- CentriMag®: £3,542
- BPX-80 Medtronic with Carmeda surface: £1,500
- Maquet Cardiohelp®: £7,836
- DPS Medos: £3,664

The total costs of procedures associated with implantation were estimated at £5,074 and procedures associated with replacement were estimated at £850 for all devices. The total cost per patient for the four devices are presented in Table 10.

Table 10: Total cost per patient for different ECLS indications for four ECLS devices available in the UK [9]

ECLS Device	Post-cardiac surgery cardiogenic shock	End-stage heart failure	Post acute myocardial infarction cardiogenic shock

CentriMag®	£8,616	£8,616	£8,616
BPX-80 Medtronic with Carmeda surface	£13,780	£28,829	£21,177
Maquet Cardiohelp®	£12,910	£12,910	£12,910
DPS Medos	£13,118	£20,325	£16,661

In Borishenko's analysis, CentriMag® was found to be cost–saving compared to other ECLS devices due to lower costs of pumps and capital equipment and the longer duration of support. The main limitation of this cost modelling is that does not consider comparative effectiveness or outcomes or costs associated with safety or complications [9].

It has been suggested[15] that "the actual costs of care are substantially greater due to the cost of team training, critical care additional expenditure, potential transfer cost, opportunity cost and follow-up costs." [22]

The centres providing ECMO for adults in England listed in Borishenko et al (2014) [9] are given below:

- University Hospitals of Leicester NHS Trust
- Guy's and St Thomas' NHS Foundation Trust, London
- Papworth Hospital NHS Foundation Trust, Cambridge
- Royal Brompton and Harefield NHS Foundation Trust, London
- Newcastle Upon Tyne Hospitals NHS Foundation Trust
- University Hospitals Birmingham NHS Foundation Trust
- University of South Manchester NHS Foundation Trust

It has been suggested[16] that "there are more than 7 English centres currently offering VA ECMO in the context of cardiogenic shock. The preliminary feedback from the ACTA linkmen system currently being conducted, is 9 out of 12 responding cardiothoracic centres have used VA ECMO in the last year …. We are aware of non cadiothoracic units providing VA ECMO in this context" [22]

The ECMO Registry of the Extracorporeal Life Support Organization (ECLS) reported 58,842 cases internationally in 2013, 4,042 of which were adult cardiac procedures. Of these, 2,255 patients (56%) survived ECLS and 1,636 (40%) survived to discharge or transfer [23]. Further information from the ECMO Registry is only available to registered participating centres or by special data request. It is beyond the scope of this review to contact third parties or providers for activity data.

An annual incidence figure for ECMO procedures for adult cardiac patients in England was not identified. The proportion of patients receiving routine cardiac surgical procedures who required prolonged postoperative support owing to refractory cardiac and or pulmonary dysfunction was 1% of the 3% to 5% of patients with postcardiotomy myocardial dysfunction [7]. However, this

[15] Information supplied in a comment submitted as part of the consultation on this review.

[16] Information supplied in a comment submitted as part of the consultation on this review.

proportion relates to routine cardiac surgical procedures and does not include support required during emergency procedures.

In Borishenko's 2014 modelling on the cost of extracorporeal life support for adult cardiac failure patients an average annual device usage of ten usages per year was assumed (based on clinical consensus), with the sensitivity analysis assuming a lower conservative limit of five usages per year and an upper limit of 15 usages per year [9].

The number of adults receiving ECMO for acute heart failure has been estimated to be 200 per year and increasing[17] [22].

6 Equity issues

The precise number of centres in England providing ECMO for adults with acute heart failure is unclear. There may be an equity consideration in relation to people with acute heart failure who do not live in close proximity to a centre providing ECMO.

7 Discussion and conclusions

The questions considered in this review are addressed in turn below:

1. Is ECMO clinically effective in adult patients with acute heart failure compared to conventional (including pharmacological and invasive) therapies?

The evidence identified in the literature search does not support a clear answer to this question. Only one study comparing ECMO to another treatment was identified, which did not demonstrate any significant difference between ECMO and miniaturised percutaneous ventricular assist devices. No studies comparing ECMO to specific conventional therapies were identified. However it should be noted that most of the included studies specified that the population receiving ECMO were patients with cardiogenic shock that was refractory (resistant) to other interventions. The ELSO guideline for the use of prolonged extracorporeal life support in adult cardiac failure states that the indication for ECMO is cardiogenic shock. The only included study that did not specify cardiogenic shock in the patient inclusion criteria found that the presence of cardiogenic shock was associated with reduced risk of hospital death in a multivariate analysis. If ECMO is primarily used in patients with cardiogenic shock refractory to other interventions, this will impact on the interventions that ECMO can usefully be compared to.

The only other study identified with a comparative element compared outcomes for patients before and after ECMO became available at one centre. This demonstrated an absolute risk reduction in 30-day survival of 33% after ECMO became available, which suggests that ECMO may be more effective than the treatments available in this centre before ECMO became available. However, the conclusions that can be drawn from one small non-randomised study are limited and the improved survival associated with ECMO may be due to confounding by other factors such as changes in patient management other than the availability of ECMO.

[17] Information supplied in a comment submitted as part of the consultation on this review.

In this review, due to the large number of studies identified, only studies in which more than 100 adult patients received ECMO for acute heart failure were included, unless a smaller study had a comparative element or addressed an outcome of interest that was not considered in the larger studies, such as quality of life. Studies excluded due to their small sample size were similar in design to the included studies. For example, they involved reviews of patients at one institution and indications for the use of ECMO were also similar. Other reasons for exclusion of studies from this review included not distinguishing between ECMO for heart failure and respiratory failure in the analysis and not distinguishing between ECMO and other forms of support in the analysis.

The outcomes of interest listed in the brief (PICOS[18]) for this review included optimal timing, patient selection, survival (to any point post-intervention), morbidity, quality of life and functional capacity.

Rates of survival to discharge following ECMO varied considerably between the different studies identified with no obvious factor to account for that difference. As the majority of published studies were single centre reviews, the possibility that centres with more favourable outcomes may be more likely to publish their results should be considered.

Two studies provided information on the longer-term survival of patients, reporting one-year survival rates of 17% and 25% respectively. In one study the three-year survival rate was reported as 8%; however, in another study the five-year survival rate was reported as 14%.

Studies addressing the issue of patient selection were identified. However, the results reported varied in the predictors of mortality identified in multivariate analysis and did not lend themselves to any strong conclusions.

Three small studies on quality of life following ECMO were identified. Whilst, perhaps unsurprisingly, some statistically significant differences were seen between ECMO patients and healthy controls and non-ECMO cardiac surgery patients, there were also several domains of the SF-36 where there was no statistically significant difference between ECMO patients and the controls. The precise impact of ECMO on quality of life is difficult to judge from this limited data but the evidence available suggests that ECMO is unlikely to have a particularly negative impact on quality of life.

A meta-analysis on the safety of venoarterial ECMO for the treatment of cardiogenic shock and cardiac arrest in adult patients suggests that high rates of serious complications are associated with ECMO.

2. Is ECMO cost effective in adult patients with acute heart failure compared to conventional therapies?

No studies assessing the cost-effectiveness of ECMO for adult acute heart failure were identified.

A figure for the annual use of ECMO for adult acute heart failure in England was not identified. Only 4,042 ECMO procedures were reported internationally in 2013, representing 7% of total ECMO procedures. The number of adults receiving ECMO for acute heart failure in England has been estimated to be 200 per year and increasing[19]. A UK modelling study assumed an average annual device usage of ten usages per year, based on clinical consensus. The same UK

[18] The PICOS sets out the Population, Intervention, Comparison, Outcome and Study Design of interest for an evidence review

[19] Information supplied in a comment submitted as part of the consultation on this review.

modelling study calculated costs per patient ranging from £8,616 to £28,829 for four devices and three different cardiac indications for ECMO. However, the purpose of this study was to compare the costs of different devices and additional costs relating to, for example, routine staffing, medications or complications were not included.

8 References

1. National Institute of Health and Care Excellence. Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults. Interventional procedure guidance 482, March 2014.
2. Massetti M. Bruno P. Mechanical circulatory support for acute heart failure in 2013: an updated on available devices, indications and results. Minerva Anestesiologica 2014, 80(3): 373-381.
3. Extracorporeal Life Support Organization. Guidelines for adult cardiac failure. December 2013.
4. National Institute of Health and Care Excellence. Interventional procedure overview of extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults. March 2013.
5. National Institute for Cardiovascular Outcomes Research (NICOR). National Heart Failure Audit. November 2013.
6. National Institute for Cardiovascular Outcomes Research (NICOR). National adult cardiac surgery audit: Annual Report 2010-2011.
7. Doll N. Kiaii B. Borger M. et al. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. Annals of Thoracic Surgery 2004, 77: 151-157.
8. Rastan AJ. Dege A. Mohr M. et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. The Journal of Thoracic and Cardiovascular Surgery 2010, 139(2): 302-311, 11.e1.
9. Borishenko O. Wylie G. Payne J. et al. The cost impact of short-term ventricular assist devices and extracorporeal life support systems therapies on the National Health Service in the UK. Interactive CardioVascular and Thoracic Surgery 2014, 19: 41-48.
10. Cheng R. Hachamovitch R. Kittleson M. et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Annals of Thoracic Surgery 2014, 97: 610-616.
11. Cheng R. Hachamovitch R. Kittleson M. et al. Clinical outcomes in fulminant myocarditis requiring extracorporeal membrane oxygenation: a weighted meta-analysis of 170 patients. Journal of Cardiac Failure 2014, 20(6): 400-406.
12. Chamogeorgakis T. Rafael A. Shafii AE. et al. Which is better: a miniaturized percutaneous ventricular assist device or extracorporeal membrane oxygenation for patients with cardiogenic shock? ASAIO Journal 2013, 59(6): 607-611.
13. Sheu JJ. Tsai TH. Lee FY. et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. Critical Care Medicine 2010, 38(9): 1810-1817.
14. Loforte A. Marinelli G. Musumeci F. Extracorporeal membrane oxygenation support in refractory cardiogenic shock: treatment strategies and analysis of risk factors. Artificial Organs 2014, May 20.
15. Chung SY. Sheu JJ. Lin YJ. et al. Outcome of patients with profound cardiogenic shock after cardiopulmonary resuscitation and prompt extracorporeal membrane oxygenation support. Circulation Journal 2012, 76: 1385-1392.
16. Lee SH. Chung CH. Lee JWL. Jung SH. Choo SJ. Factors predicting early- and long-term survival in patients undergoing extracorporeal membrane oxygenation (ECMO). Journal of Cardiac Surgery 2012, 27: 255-263.
17. Wu MY. Lin PJ. Lee MY. et al. Using extracorporeal life support to resuscitate adult postcardiotomy cardiogenic shock. Treatment strategies and predictors of short-term and mid-term survival. Resuscitation 2010, 81: 1111-1116.

18. Elsharkawy HA. Li L. Essa WAS. Sessler DI. Bashour CA. Outcome in patients who require venoarterial extracorporeal membrane oxygenation support after cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia 2010, 24(6): 946-951.
19. Mirabel M. Luyt CE. Leprince P. et al. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. Critical Care Medicine 2011, 39(5): 1029-1035.
20. Wang J. Han J. Jia Y. et al. Early and intermediate results of rescue extracorporeal membrane oxygenation in adult cardiogenic shock. The Annals of Thoracic Surgery 2009, 88(6):1897-1903.
21. Combes A. Leprince P. Luyt CE. et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. Critical Care 2008, 36(5): 1404-1411.
22. Personal communication from J Cordingley and A Vuylsteke in comments submitted during the consultation on this review, September 2014.
23. Extracorporeal Life Support Organization. ECLS Registry Report. International Summary. January 2014.

9 Search Strategy

Databases searched: Medline, Embase, Cochrane Library, TRIP and NICE Evidence

Search date: 1st July 2014

Medline search strategy:

1. Heart Failure/ and exp Perioperative Care/
2. Heart Failure/ and exp Cardiac Surgical Procedures/ and (post-operat* or postoperat* or perioperat* or peri-operat*).mp.
3. (acute heart failure or acute heart dysfunction or advanced heart failure or advanced heart dysfunction or acute cardiac failure or acute cardiac dysfunction or advanced cardiac failure or advanced cardiac dysfunction or cardiogenic shock).ti,ab.
4. ((heart failure or heart dysfunction or cardiac failure or cardiac dysfunction) adj5 (surg* or repair* or replace* or operat* or procedure*)).ti,ab.
5. ((heart failure or heart dysfunction or cardiac failure or cardiac dysfunction) adj5 (post-operat* or postoperat* or perioperat* or peri-operat*)).ti,ab.
6. (heart failure or heart dysfunction).ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Extracorporeal Membrane Oxygenation/
9. (ecmo or extracorporeal membrane oxygenation or extra-corporeal membrane oxygenation).ti,ab.
10. 8 or 9
11. 7 and 10
12. ((heart failure or heart dysfunction or cardiac failure or cardiac dysfunction) adj5 (ecmo or extracorporeal membrane oxygenation or extra-corporeal membrane oxygenation)).ti,ab.
13. 11 or 12
14. limit 13 to english language

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Meta-analyses Systematic reviews Randomised controlled trials Prospective non-randomised clinical study Other clinical study Health economic studies
Patients	Adults (18 years or over) with acute heart failure (including patients developing acute heart failure following cardiac surgery)
Intervention	ECMO
Comparators	Conventional therapies (pharmacological and/or invasive, including ventricular assist devices)
Outcome	Optimal timing Patient selection Survival (to any point post-intervention) Morbidity Quality of life (short and long term) Functional capacity (short and long term)
Language	English only

Appendix 1: Kaplan-Meier analysis

Figure 1: Kaplan-Meier analysis of 30-day survival for patients with profound cardiogenic shock who did or did not receive ECMO support (Sheu 2010) [13]