Interventional procedure overview of extracorporeal carbon dioxide removal for acute respiratory failure

Contents

Table 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
AHRF	Acute hypoxic respiratory failure
ARDS	Acute respiratory distress syndrome
avECCO$_2$R	Arteriovenous extracorporeal carbon dioxide removal
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
ECCO$_2$R	Extracorporeal carbon dioxide removal
ECMO	Extracorporeal membrane oxygenation
ECLS	Extracorporeal life support
FiO$_2$	Fraction of inspired oxygen
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
MV	Mechanical ventilation
NIV	Non-invasive ventilation
PaCO$_2$	Partial pressure of carbon dioxide
PaO$_2$	Partial pressure of oxygen
PEEP	Positive end-expiratory pressure
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
VFD	Ventilator-free day
vvECCO$_2$R	Venovenous extracorporeal carbon dioxide removal

Indications and current treatment

Acute respiratory failure (when the lungs do not work effectively) is a life-threatening condition. It can cause acute hypoxic respiratory failure (abnormally

low levels of oxygen in the blood) and acute hypercapnic respiratory failure (abnormally low levels of oxygen and abnormally high levels of CO_2 in the blood). ARDS is a severe type of acute respiratory failure. It can be caused by conditions including sepsis, pneumonia, respiratory viruses, chest trauma, inhalational injury, aspiration, and pancreatitis. The management of acute respiratory failure involves treating the underlying cause, and providing oxygen, NIV or MV.

$ECCO_2R$ can be used in people with AHRF. The aim of $ECCO_2R$ is to lower levels of CO_2 in the blood in people with acute respiratory failure, independently of the lungs. Lung-protective ventilation settings such as lower airway pressures and lower tidal volumes can be used to reduce the risk of ventilator-induced lung injury. However, using lung-protective settings can cause CO_2 to rise, leading to negative effects. $ECCO_2R$ is used to reduce blood CO_2 levels so that lung-protective ventilation settings can be maintained. This may improve the likelihood and speed of lung recovery.

$ECCO_2R$ can be used in people with acute hypercapnic respiratory failure, which is most commonly caused by COPD, with the aim of reducing the need for intubation and MV. It may also reduce the length of time that a person has NIV.

What the procedure involves

The 2 main types of $ECCO_2R$ are $vvECCO_2R$ and $avECCO_2R$. In both types, cannulae are connected to a low -resistance synthetic membrane device where exchange of CO_2 occurs. In $vvECCO_2R$, either a single -access double-lumen catheter or a dual -access system using 2 venous catheters is inserted into a large vein or veins (usually the femoral or internal jugular veins) and connected to a venovenous circuit. Flow across the membrane is maintained using a pump. In $avECCO_2R$, cannulae are inserted into an artery and a vein (usually the femoral artery and femoral vein). Arterial blood pressure drives blood continuously through the device and it is returned through the vein.

$ECCO_2R$ can be done using either a true $ECCO_2R$ system or a modified ECMO system. People having $ECCO_2R$ are given blood thinning drugs such as heparin to prevent blood clots forming in the circuit.

People may have $ECCO_2R$ support for several weeks, depending on clinical need.

Outcome measures

The main efficacy outcomes include survival and mortality rates, length of ICU stay, length of hospital stay, duration of MV, duration of NIV, changes in concentration of blood gases, and changes in MV settings from baseline.

The main safety outcomes include haemorrhage, circuit complications, injuries during cannulation, need for dialysis, pneumothorax, infection, and ventilator-related morbidity.

Evidence summary

Population and studies description

This overview is based on 2,261 people from 2 systematic reviews and meta--analyses, 3 RCTs, a long-term follow-up analysis of 1 of the RCTs, 2 case series, and a secondary analysis of 1 of the case series. Of these 2,261 people, 1,520 people had the procedure. Some RCTs analysed other included studies in this overview, and this has been factored into the patient count. This overview includes a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 9 studies as the key evidence in table 2 and table 3, and lists 47 other relevant studies in table 5.

The included studies were done in the UK, Germany, Canada, and across Europe. The systematic reviews and meta-analyses were global in scope, but one was done in the UK, and one was done in China.

The systematic review and meta-analysis by Millar et al. (2022) was done in the UK. This was an analysis of 3 RCTs and 18 observational studies to assess the efficacy and safety of $ECCO_2R$ versus standard care in people with AHRF. The primary outcome was 30-day mortality.

The systematic review and meta-analysis by Yu et al. (2021) was done in China. This was an analysis of 25 studies to evaluate outcomes in people supported on av$ECCO_2R$ compared with vv$ECCO_2R$ for any indication.

The RCT of 412 people by McNamee et al. (2021) was done in the UK. This study is known as the REST trial. The study aimed to determine if $ECCO_2R$ could allow lower tidal volume MV in people with AHRF. The primary outcome was 90-day mortality. This study aimed to recruit 1,120 people but was stopped early because of futility. The follow-up analysis by Boyle et al. (2022) reported on 2-year outcomes from this study.

The RCT of 79 people by Bein et al. (2013) was done in Germany. This study aimed to determine the effects of low tidal volume ventilation allowed by $ECCO_2R$ in severe ARDS. The primary outcomes were the VFDs up until day 28 and day 60. Because of issues in recruiting eligible people in the enrolment period, the study did not reach the prespecified recruitment of 120 people.

The RCT of 18 people by Barrett et al. (2022) was done in the UK. This study aimed to determine the impact of $ECCO_2R$ in people with acute hypercapnic respiratory failure because of acute exacerbation of COPD. The primary outcome in this study was time to cessation of NIV.

The prospective case series of 95 people by Combes et al. (2019a) recruited people from Canada and across Europe. This study assessed the feasibility and safety of $ECCO_2R$ to allow low tidal volume ventilation in people with moderate ARDS. The primary outcome was the number of people who achieved a tidal volume of 4 ml/kg with less than a resulting 20% rise in $PaCO_2$. The secondary analysis of this study by Combes et al. (2019b) aimed to determine if the efficacy

and safety of $ECCO_2R$ in facilitating low tidal volume ventilation varied between low CO_2 extraction capacity devices and high CO_2 extraction capacity devices.

The prospective case series of 60 people by Cummins et al. (2018) was an observational registry study done in the UK. This study reported on the use, outcomes, and complications of $ECCO_2R$. The co-primary efficacy and safety outcomes were discharge home or transferred alive from hospital offering $ECCO_2R$, and AEs including procedure-related complications.

Table 2 presents study selection details.

Figure 1 Flow chart of study selection

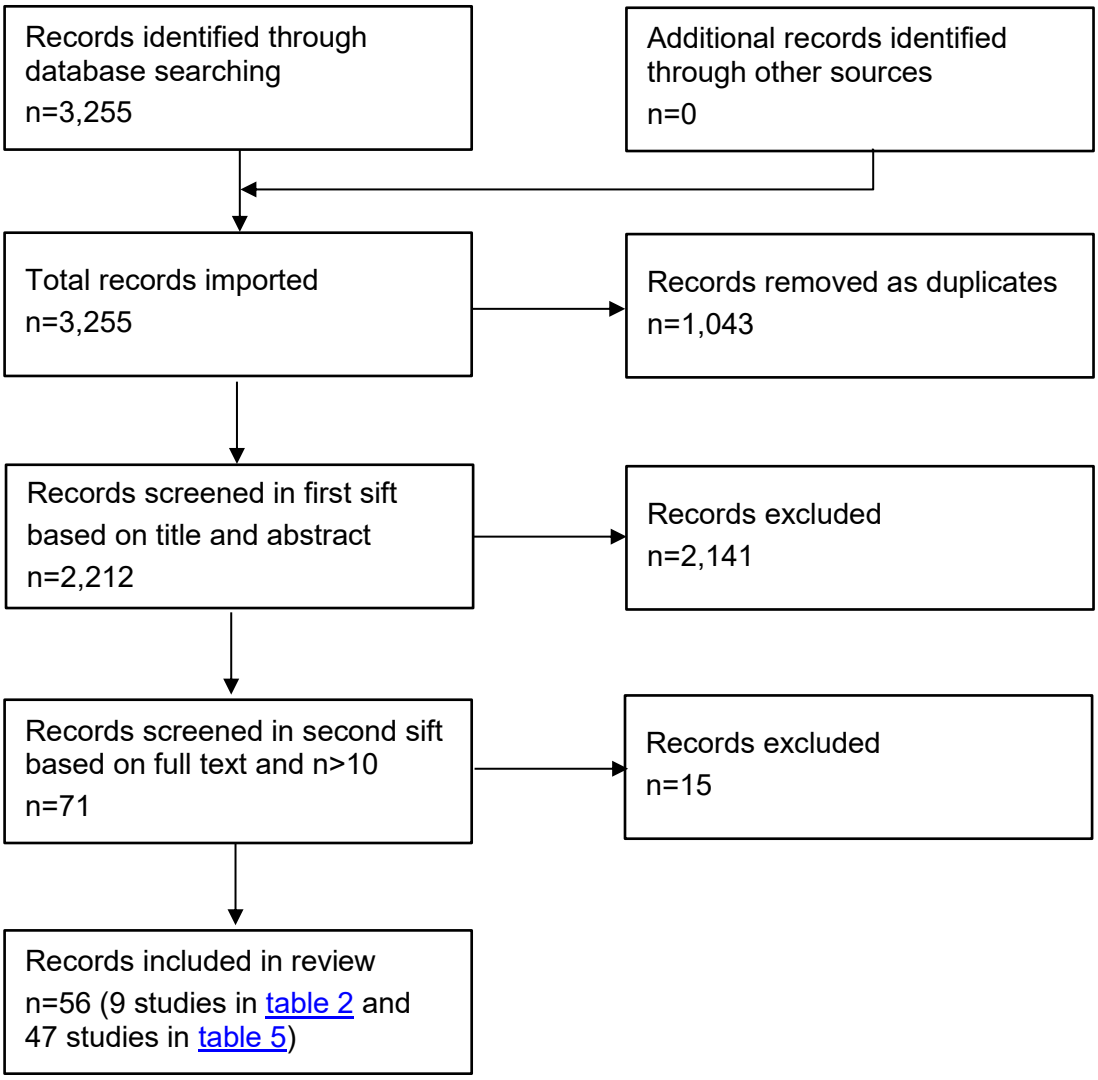

Table 2 Study details

Study no.	First author, date, country	People (male: female)	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
1	Millar 2022, UK	n=531 in RCTs, n who had $ECCO_2R$=244 n=826 in other studies, n who had $ECCO_2R$=571 (Genders not recorded)	Average (mean or median) 35 to 68 across studies	Systematic review and meta-analysis	AHRF of any cause treated with $ECCO_2R$	$ECCO_2R$	90 days
2	Yu 2021, US	n=826, n who had $ECCO_2R$=497 (Genders not recorded)	Not recorded	Systematic review and meta-analysis	Any indication for $ECCO_2R$	$ECCO_2R$	90 days
3	McNamee 2021, UK	n=412 (65% male, 35% female)	Mean 60.2	RCT	Moderate or severe AHRF, receiving IMV for less than 7 days	$vvECCO_2R$	90 days
4	Boyle 2022, UK	n=412 (65% male, 35% female)	Mean 60.2	RCT (secondary outcomes of study 3)	Moderate or severe AHRF, receiving IMV for less than 7 days	$vvECCO_2R$	2 years

Study no.	First author, date, country	People (male: female)	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
5	Bein 2013, Germany	n=79, n who had $ECCO_2R$=40 (86% male, 14% female)	Mean 49.8	RCT	ARDS, receiving MV for less than 7 days	av$ECCO_2R$	60 days
6	Barrett 2022, UK	n=18, n who had $ECCO_2R$=9 (56% male, 44% female)	Mean 67.5	RCT	Acute exacerbation COPD, leading to hypercapnic respiratory failure	vv$ECCO_2R$ plus NIV	90 days
7	Combes 2019a, Europe and Canada	n=95 (67.4% male, 32.6% female)	Mean 60.2	Prospective case series	Moderate ARDS, expected to have IMV more than 24 hours	vv$ECCO_2R$	28 days
8	Combes 2019b, Europe and Canada	n=95 (67.4% male, 32.6% female)	Mean 60.2	Prospective case series (secondary analysis of study 7)	Moderate ARDS, expected to have IMV more than 24 hours	vv$ECCO_2R$	28 days
9	Cummins 2018, UK	n=60 (58.3% male, 41.7% female)	Median 58	Observational registry study	Any indication to have $ECCO_2R$ in the UK	$ECCO_2R$	Hospital discharge

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Millar 2022	**Mortality** No significant difference between $ECCO_2R$ and controls in 30-day mortality (37% compared with 35%; RR 1.19; 95% CI 0.70 to 2.29), certainty of evidence according to GRADE was low. It was not possible to calculate the RR for other mortality measures, however the study reported for $ECCO_2R$ compared with controls: • 90-day mortality (41.5% compared with 39.5%) • In-hospital mortality (34.4% compared with 29.3%), certainty of evidence according to GRADE was very low. **Duration of ventilation** No significant difference in VFDs between $ECCO_2R$ and controls at day 28 (7.6 compared with 9.2; mean difference −1.4 days; 95% CI −3.6 to 0.9), certainty of evidence according to GRADE was moderate. **Length of stay** No significant difference between $ECCO_2R$ and controls for: • ICU length of stay (17.4 days compared with 15.2 days; mean difference 0.9 days; 95% CI 1.3 to	**Overall** Variable reporting of definitions across studies on AEs and SAEs meant meta-analysis was not possible. **Haemorrhage** • The overall rate of haemorrhage for $ECCO_2R$ was 17% compared with 1.3% in controls. It was not possible to calculate the RR. The certainty of evidence according to GRADE was low. • There was no significant difference in overall rate of intracranial haemorrhage for $ECCO_2R$ compared with controls (4.9% compared with 1.3%; RR 3.0; 95% CI 0.42 to 20.51), the certainty of evidence according to GRADE was low. **Circuit complications** • Circuit complications were reported in 2 RCTs (4% to 19% incidence) and 6 observational studies (17% to 72% incidence). • Because of variable reporting, a meta-analysis was not possible.

First author, date	Efficacy outcomes	Safety outcomes
	3.1), certainty of evidence according to GRADE was low. • Hospital length of stay (24.1 days compared with 22.1 days; mean difference 0.8 days; 95% CI 2.2 to 3.9), certainty of evidence according to GRADE was low.	**Cannulation complications** • Two RCTs reported on cannulation complications (4% to 5% incidence) and 7 observational studies reported on cannulation complications (2% to 40% incidence). **Limb ischaemia** • Two RCTs reported rates of limb ischaemia with incidence of 3% and 10%. Four observational studies reported rates of limb ischaemia, ranging from 0% to 14%. • Because of variable definitions of limb ischaemia, a meta-analysis was not possible.
Yu 2021	**Mortality** No significant difference between vvECCO$_2$R and avECCO$_2$R for: • In-hospital mortality (27% compared with 36%; p=0.26) • Mortality during ECCO$_2$R treatment (27% compared with 23%; p=0.87) **Length of stay**	**Overall** Not clear if AE or SAE distinction made, little reporting of safety outcomes in this study. Safety events relating to vvECCO$_2$R alone were not reported. **Haemorrhage** • Only reported for avECCO$_2$R group, 1.2% developed arterial thrombus (4 of 329 people)

First author, date	Efficacy outcomes	Safety outcomes
	Significant difference between $vvECCO_2R$ and $avECCO_2R$ for: • ICU length of stay (15 days compared with 42 days; p=0.05). No significant difference between $vvECCO_2R$ and $avECCO_2R$ for: • Duration on $ECCO_2R$ (5 days compared with 7 days; p=0.32) • Successful weaning off $ECCO_2R$ (50% compared with 52%; p=0.80). **Blood gases** No significant difference between $vvECCO_2R$ and $avECCO_2R$ for: • pH (7.4 compared with 7.4; p=0.94) • Change in $PaCO_2$ (64 mmHg to 48.6mmHg for $vvECCO_2R$; p=0.54; 58.8 mmHg to 48.1 mmHg for $avECCO_2R$; p=0.17) **Ventilator settings** Significant difference between $vvECCO_2R$ and $avECCO_2R$ for: • Incidence of NIV (55% compared with 98%; p=0.03) • PEEP at 72 hours in the $vvECCO_2R$ group compared with $avECCO_2R$ (exact figures not reported, displayed visually; p<0.05)	• No other haemorrhage or intracranial haemorrhage outcomes recorded in this study. **Limb ischaemia** • Only reported for $avECCO_2R$ group, 4% developed limb ischaemia (14 of 329 people) **Circuit complications** • Only reported for $avECCO_2R$ group, 8.2% developed arterial thrombus (27 of 329 people) **Cannulation complications** • Only reported for $avECCO_2R$ group, 1 person from 329 people developed pseudoaneurysm of femoral artery.

First author, date	Efficacy outcomes	Safety outcomes
McNamee 2021 (linked with Boyle 2022, which reports 2-year outcomes)	**From McNamee 2021:** **Mortality** No significant difference between $ECCO_2R$ and standard care in: • 90-day mortality (42% compared with 40%; p=0.68) • 28-day mortality (38% compared with 36%; p=0.64). **Length of stay** No significant difference between $ECCO_2R$ and standard care in: • Median ICU length of stay (14 days compared with 13 days; p=0.67) • Median hospital length of stay (22 days compared with 18 days; p=0.65). **Duration of ventilation** Significant difference between $ECCO_2R$ and standard care in: • VFDs from randomisation to day 28 (7 days compared with 9 days; p=0.02) No significant difference between $ECCO_2R$ and standard care in: • Duration of ventilation in survivors (18 days compared with 17 days; p=0.83) • Need for ECMO to day 7 (6% compared with 3%; p=0.13).	**From McNamee 2021:** **Overall** • 168 AEs in 106 people (52.5%) • AEs related to intervention: 65 AEs in 51 people (25.3%) • 70 SAEs in 62 people (30.7%) • SAEs related to intervention: 22 SAEs in 21 people (10.4%). **Haemorrhage** • SAE intracranial haemorrhage: 4.5% in $ECCO_2R$ group (4 of 6 bleeds considered possibly attributable to $ECCO_2R$), 0 in standard care • SAE bleeding at other site: 3.0% in $ECCO_2R$ group, 0.5% in standard care • AE intracranial haemorrhage: 5.0% in $ECCO_2R$ group, 1% in standard care • AE bleeding at other site: 8.4% in $ECCO_2R$ group, 1.4% in standard care. **Circuit complications** • SAE infection: 5% • AE infection: 3.5% • Device failure causing SAE: 1.0% • Device failure causing AE: 4.5%

First author, date	Efficacy outcomes	Safety outcomes
	Blood gases No significant differences between $ECCO_2R$ and controls at day 2 or day 3 in: • Blood pH at day 2 (7.29 compared with 7.32) • Blood pH at day 3 (7.32 compared with 7.35) • $PaCO_2$ at day 2 (60.8 mmHg compared with 56.0 mmHg) • $PaCO_2$ at day 3 (60.8 mmHg compared with 54.2 mmHg) • PaO_2/FiO_2 ratio at day 2 (147.8 compared with 161.1) • PaO_2/FiO_2 ratio at day 3 (147.9 compared with 167.0). **Ventilator settings** Significant difference at day 3 between $ECCO_2R$ and standard care for: • Plateau pressure (22.8 cmH_2O compared with 24.1 cmH_2O). No significant differences at day 3 between $ECCO_2R$ and standard care for: • Tidal volume (4.4 ml/kg compared with 6.7 ml/kg) • PEEP (11.3 cmH_2O compared with 10.0 cmH_2O) • Driving pressure (11.4 cmH_2O compared with 14.2 cmH_2O)	• SAE heparin-induced thrombocytopenia: 0.5% • AE heparin-induced thrombocytopenia: 2.0% • AE haemolysis: 1.5%. **Cannulation complications** • AE bleeding at cannulation site: 4.0%. **Other** • SAE ischaemic stroke: 0.5% in $ECCO_2R$ group, 1.4% in standard care • AE ischaemic stroke: 0.5% in $ECCO_2R$ group, 1.4% in standard care. **From Boyle 2022:** **Other** No significant difference between $ECCO_2R$ and controls at 1-year follow up in: • PTSD (PTSS-14 score 34.3 compared with 38.8; p=0.25) • Cognitive function (MoCA-Blind Questionnaire scores 17.1 compared with 17.9; p=0.23).

First author, date	Efficacy outcomes	Safety outcomes
	• Respiratory rate (27 per minute compared with 24 per minute) • Minute volume (7.6 litre/minute compared with 10.1 litre/minute) • Percentage of people on mandatory ventilation (78% compared with 59%). **From Boyle 2022:** **Mortality** No significant difference between $ECCO_2R$ and standard care for: • 6-month mortality (42.9% compared with 41.9%; p=0.83) • 1-year mortality (43.9% compared with 42.9%; p=0.83) • 2-year mortality (47.2% compared with 47.9%; p=0.89). **Other** No significant difference between $ECCO_2R$ and controls at 1-year follow up in: • Health-related quality of life (EQ-5D-5L utility score 0.56 compared with 0.34; p=0.95) • Long-term respiratory function (St George's Respiratory questionnaire scores 40.9 compared with 40.9; p=1.00).	

First author, date	Efficacy outcomes	Safety outcomes
Bein 2013	**Mortality** No significant difference between $ECCO_2R$ and controls for in-hospital mortality (18% compared with 15%; p=1.00). **Duration of ventilation** No significant difference between $ECCO_2R$ and controls for: • VFDs at day 28 (10.0 days compared with 9.3 days; p=0.779) • VFDs at day 60: (33.2 days compared with 29.2 days; p=0.469). Significant difference between $ECCO_2R$ and controls for: • VFDs at day 28 in the subgroup with starting PaO_2/FiO_2 less than 150 (11.3 days compared with 5.0 days; p=0.033) • VFDs at day 60 in the subgroup with starting PaO_2/FiO_2 less than 150 (40.9 days compared with 28.0 days; p=0.033). **Length of stay** No significant difference between $ECCO_2R$ and controls in: • ICU length of stay (31 days compared with 23 days; p=0.14) • Hospital length of stay (47 days compared with 35 days; p=0.11)	**Overall** Incidence of av$ECCO_2R$-related AEs: 7.5% (n=3). **Haemorrhage** Not directly reported, however study reported significant difference between $ECCO_2R$ and controls for: • Number of units of red blood cells transfused at day 10 (3.7 units compared with 1.5 units; p<0.05). **Limb ischaemia** • 1 transient ischaemia of lower limbs. **Cannulation complications** • 2 pseudoaneurysms because of arterial cannulation.

First author, date	Efficacy outcomes	Safety outcomes
	• ICU length of stay in the subgroup with starting PaO_2/FiO_2 less than 150 (p=0.26) • Hospital length of stay in the subgroup with starting PaO_2/FiO_2 less than 150 (p=0.82).	
Barrett 2022	**Mortality** No significant difference in survival between $ECCO_2R$ plus NIV compared with NIV alone at any timepoint out to 90 days. **Duration of ventilation** Significant difference between $ECCO_2R$ plus NIV compared with NIV alone for: • Time to discontinuation of NIV (7 hours compared with 24 hours 30 minutes; p=0.004). **Length of stay** Significant difference between $ECCO_2R$ plus NIV compared with NIV alone for: • ICU length of stay (161 hours 45 minutes compared 45 hours 49 minutes; p=0.001) • Hospital length of stay (240 hours compared with 124 hours; p=0.014). **Blood gases**	**Overall** No SAEs in either group. One $ECCO_2R$ cannula thrombosed before $ECCO_2R$ and was replaced without an AE. AEs in $ECCO_2R$ group (n=9) • 1 tracheal intubation needed • 3 cannula site bleeding • 3 haemolysis • 1 device failure • 1 discomfort (patient reported).

First author, date	Efficacy outcomes	Safety outcomes
	Significant difference between $ECCO_2R$ plus NIV compared with NIV alone for: • $PaCO_2$ at 4 hours after randomisation (6.8 mmHg compared with 8.3 mmHg; p=0.024). No significant difference between $ECCO_2R$ plus NIV compared with NIV alone for: • Arterial pH (p>0.05). **Ventilator settings** No significant difference between $ECCO_2R$ plus NIV compared with NIV alone for: • Respiratory rate over the first 48 hours.	
Combes 2019a and Combes 2019b	**Study 1: prospective case series.** **Mortality** • 27% 28-day mortality (26 of 95 people) • 38% in-hospital mortality (36 of 95 people). **Duration of ventilation** • Average duration of IMV: 17 days • Average number of VFDs: 11 days. **Blood gases** Significant difference at 24 hours compared with baseline for	**Study 1: prospective case series.** **Overall** • 39% of people had complications (87 AEs in 37 people) • 6 SAEs reported. **Haemorrhage** • 1 massive right frontal parenchymal haematoma, considered attributable to $ECCO_2R$ • 1 severe haematemesis and melena • 13 bleeding

First author, date	Efficacy outcomes	Safety outcomes
	• pH (7.39 compared with 7.34; p<0.001). No significant difference at 24 hours compared with baseline for: • PaO_2/FiO_2 (168 mmHg compared with 168 mmHg; p=0.999) • $PaCO_2$ (46.7 mmHg compared with 48.0 mmHg; p=0.258). **Ventilator settings** • 78% achieved ultra-protective settings by 8 hours • 82% achieved ultra-protective settings by 24 hours. Significant difference at 24 hours compared with baseline for: • Tidal volume (4.16 ml/kg compared with 6.02 ml/kg; p<0.001) • Respiratory rate (23.5 per minute compared with 27.4 per minute; p<0.001) • Minute ventilation (5.94 litre/minute compared with 10.2 litre/minute; p<0.001) • Plateau pressure (23.5 cmH_2O compared with 26.7 cmH_2O; p<0.001) • Driving pressure (9.9 cmH_2O compared with 13.2 cmH_2O; p<0.001).	• 11 haemolysis • 12 thrombocytopenia. **Circuit complications** • 13 membrane lung clotting (7 leading to $ECCO_2R$ discontinuation). **Cannulation complications** • 1 pneumothorax at cannula insertion, attributable to $ECCO_2R$. **Other** • 1 sudden death • 1 superior vena cava thrombosis • 1 severe hypoxaemia. **<u>Study 2: devices with high compared with low CO_2 extraction capacity:</u>** **Overall** No significant difference in overall $ECCO_2R$-related AEs between lower and higher extraction capacity device groups (48% compared with 34%; p=0.242). **Haemorrhage**

First author, date	Efficacy outcomes	Safety outcomes
	No significant difference in ventilator settings at 24 hours compared with baseline for: • PEEP (13.8 cmH_2O compared with 13.6 cmH_2O; p=0.083). **<u>Study 2: devices with high compared with low CO_2 extraction capacity:</u>** **Blood gases in low CO_2 extraction capacity devices:** No significant differences at 24 hours compared with baseline for: • $PaCO_2$ (49.0 mmHg compared with 45.9 mmHg) • pH (7.35 compared with 7.33) • PaO_2/FiO_2 (198 compared with 185). **Ventilator settings in low CO_2 extraction capacity devices:** No significant difference at 24 hours compared with baseline for: • Plateau pressure (21.9 cmH_2O compared with 26.7 cmH_2O) • PEEP (12.96 cmH_2O compared with 13.58 cmH_2O). Significant difference at 24 hours compared with baseline for: • Driving pressure (8.93 cmH_2O compared with 13.2 cmH_2O; p<0.01).	Significant difference between lower and higher extraction capacity device groups in: • Bleeding (27% compared with 6%; p<0.01) • Haemolysis (21% compared with 6%; p<0.05). **Circuit complications** No significant difference in circuit complications between lower and higher extraction capacity device groups (p>0.05). **SAEs** • 1 right frontal massive parenchymal haematoma in lower extraction capacity device group • 1 pneumothorax at cannula insertion in higher extraction capacity device group.

First author, date	Efficacy outcomes	Safety outcomes
	Blood gases in high CO_2 extraction capacity devices: No significant difference at 24 hours compared with baseline for: • PaO_2/FiO_2 (153 compared with 159) • $PaCO_2$ (45.5 mmHg compared with 49.0 mmHg). Significant difference at 24 hours compared with baseline for: • pH: 7.41 compared with 7.35; p<0.01). **Ventilator settings in high CO_2 extraction capacity devices:** No significant difference at 24 hours compared with baseline for: • Plateau pressure (24.4 cmH_2O compared with 26.7 cmH_2O) • Driving pressure (10.4 cmH_2O compared with 13.2 cmH_2O) Significant difference at 24 hours compared with baseline for: • PEEP (14.16 cmH2O compared with 13.55 cmH2O; p<0.01)	
Cummins 2018	**Mortality** • 55% survived $ECCO_2R$ (33 of 60 people) • 45% discharged from hospital alive (27 of 60 people)	**Overall** Study did not classify AEs or SAEs, or detail if events were related to study device.

First author, date	Efficacy outcomes	Safety outcomes
	• 10% survived $ECCO_2R$ but died prior to discharge from $ECCO_2R$ centre (6 of 60 people). **Blood gases** Significant difference between worst value in 6-hour period pre-$ECCO_2R$ and best values at 24-hours of $ECCO_2R$ for: • pH (7.1 compared with 7.4; p<0.001) • $PaCO_2$ (11.4 kPa compared with 7.0 kPa; p<0.001) • PaO_2 (10.5 kPa compared with 9.3 kPa; p<0.004) No significant difference between worst value in 6-hour period pre-$ECCO_2R$ and best values at 24-hours of $ECCO_2R$ for: • PaO_2(kPa)/FiO_2 (0.17 compared with 0.17; p=0.555) **Ventilator settings** Significant difference between worst value in 6-hour period pre-$ECCO_2R$ and best values at 24-hours of $ECCO_2R$ for: • PEEP (810 cmH_2O compared with 10 cmH_2O; p=0.032) No significant difference between worst value in 6-hour period pre-$ECCO_2R$ and best values at 24-hours of $ECCO_2R$ for: • Mean airway pressure (16 compared with 15; p=0.33)	• 31.7% overall complications (19 of 60 people). **Haemorrhage** • 1 gastrointestinal haemorrhage • 1 haemolysis • 1 surgical site bleeding. **Circuit complications** • 7 gas exchange membrane failure • 5 culture-proven infection. **Cannulation complications** • 7 cannulation site bleeding. **Pneumothorax** • 1 requiring treatment. **Need for dialysis** • 5 requiring hemofiltration. **Other** • 4 requiring inotropes • 2 cardiac arrhythmias.

Procedure technique

Of the 9 studies, 1 study reported on avECCO$_2$R exclusively, 5 studies reported on vvECCO$_2$R exclusively, and 3 studies reported on both together.

Efficacy

Mortality

All 9 included studies reported on mortality outcomes, however studies varied in the timepoints at which they chose to report mortality. No study showed a statistically significant difference in mortality at any point for ECCO$_2$R intervention groups compared with control groups.

In the systematic review and meta-analysis of 531 people with AHRF across 3 RCTs who had ECCO$_2$R compared with standard care, there was no significant difference in 30-day mortality (37% for ECCO$_2$R compared with 35% for standard care; p=0.73) or in-hospital mortality (34% for ECCO$_2$R compared with 29% for standard care; p>0.05). 90-day mortality was only measured in 1 RCT (42% for ECCO$_2$R compared with 40% for standard care). The observational studies in this review used a range of mortality timepoints. Reported mortality in the observational studies ranged from 38% to 59%.

In the systematic review and meta-analysis of 826 people who had ECCO$_2$R for any indication, there was no significant difference in in-hospital mortality for vvECCO$_2$R compared with avECCO$_2$R (27% compared with 36%; p=0.26).

In the RCT of 412 people with moderate or severe AHRF who were allocated to have ECCO$_2$R compared with standard care, there was no significant difference in unadjusted 90-day mortality (42% compared with 40%; p=0.68) or 28-day mortality (38% compared with 36%; p=0.64). In the study reporting on long-term outcomes from the same RCT of 412 people, there was no significant difference in 6-month mortality (43% compared with 42%; p=0.83), 1-year mortality (44%

compared with 43%; p=0.83) or 2-year mortality (47% compared with 48%, p=0.89).

In the RCT of 79 people with ARDS comparing avECCO$_2$R with standard care, there was no significant difference in in-hospital mortality (18% compared with 15%; p=1.00).

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD there was no significant difference in survival between ECCO$_2$R and NIV at any timepoint out to 90 days (p>0.05).

In the prospective case series of 95 people with ARDS, the 28-day mortality was 27%. The in-hospital mortality was 38%. The paper reporting on the secondary analysis of this study did not make further comments about mortality.

In the observational registry study of 60 people who had ECCO$_2$R for any indication, the in-hospital mortality was 55%.

ICU and hospital length of stay

5 studies reported on ICU and hospital length of stay outcomes.

In the systematic review and meta-analysis of 531 people across 3 RCTs who had ECCO$_2$R for AHRF, ECCO$_2$R had small mean relative effects on ICU length of stay (17 days compared with 15 days) and hospital length of stay (24 days compared with 22 days) compared with standard care. However this was not significant as the 95% credible intervals for both ICU and hospital length of stay spanned a mean difference of 0 days.

In the systematic review and meta-analysis of 826 people who had ECCO$_2$R for any indication, ICU length of stay for people who had vvECCO$_2$R was significantly shorter than for those who had avECCO$_2$R (15 days compared with 42 days; p=0.05).

In the RCT of 412 people with moderate or severe AHRF comparing $ECCO_2R$ with standard care, there was no significant difference in median ICU length of stay (14 days compared with 13 days; p=0.67) or median hospital length of stay (22 days compared with 18 days; p=0.65).

In the RCT of 79 people with ARDS comparing av$ECCO_2R$ with standard care, there was no significant difference in ICU length of stay (31 days compared with 23 days; p=0.14) or hospital length of stay (47 days compared with 35 days; p=0.11). In the subgroup with starting PaO_2/FiO_2 less than 150 there were no significant differences in ICU length of stay (p=0.26) or hospital length of stay (p=0.82).

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD who had $ECCO_2R$ compared with controls who had NIV, the people on $ECCO_2R$ had a significantly longer ICU length of stay (162 hours compared with 46 hours; p<0.05) and hospital length of stay (240 hours compared with 124 hours; p<0.05). Differences in the care protocole between the techniques contributed to the longer ICU stay. With NIV, patients could be weaned off at any time including overnight. The protocol for $ECCO_2R$ did not allow weaning overnight. Four out of 9 people in the control group declined NIV and were discharged to a regular hospital ward from ICU regardless of blood gas results. This also contributed to a shorter ICU length of stay in the control group.

Duration of MV and NIV

5 studies reported on duration of MV and NIV.

In the systematic review and meta-analysis of 531 people across 3 RCTs who had $ECCO_2R$ for AHRF, a meta-analysis of the 2 RCTs reporting VFDs at day 28 showed that people randomised to $ECCO_2R$ had fewer VFDs (7.6 days compared with 9.2 days; mean difference −1.4 days; 95% CI −3.6 to 0.9).

In the RCT of 412 people with moderate or severe AHRF comparing $ECCO_2R$ with standard care the intervention group had significantly fewer VFDs than the ventilation-alone control group (7 days compared with 9 days; p=0.02). There was no significant difference between the groups in the duration of ventilation in survivors (18 days compared with 17 days; p=0.83)

In the RCT of 79 people with ARDS comparing $avECCO_2R$ with standard care, there were no significant differences in VFDs at day 28 (10 days compared with 9 days; p=0.78) or day 60 (33 days compared with 29 days; p=0.47). However, a post-hoc analysis showed that surviving people with more severe hypoxia (initial PaO_2/FiO_2 less than 150 at randomisation) who had $ECCO_2R$ had more VFDs compared with controls at day 60 (41 days compared with 28 days; p=0.033).

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD who had $ECCO_2R$ or standard care, time to NIV discontinuation was significantly shorter with $ECCO_2R$ compared with controls (7 hours compared with 25 hours; p=0.004). No one in either group underwent IMV while they were on therapy.

In the prospective case series of 95 people with ARDS, the average duration of IMV was 17 days. The average number of VFDs was 11 days.

Changes in concentration of blood gases

6 studies reported on changes in concentration of blood gases.

In the systematic review and meta-analysis of 826 people comparing $vvECCO_2R$ with $avECCO_2R$ for any indication, there were no significant changes in $PaCO_2$ after 72 hours for $vvECCO_2R$ (64 mmHg compared with 49 mmHg; p=0.54) and $avECCO_2R$ (59 mmHg compared with 48 mmHg; p=0.17). There were no significant changes in pH, PaO_2, or PaO_2/FiO_2 in either group (p>0.05).

In the RCT of 412 people with moderate or severe AHRF comparing $ECCO_2R$ with standard care, the $ECCO_2R$ group had a lower PaO_2/FiO_2 ratio on day 2

(148 compared with 161) and on day 3 (148 compared with 167). $PaCO_2$ was higher in the $ECCO_2R$ group from day 2 onwards, and pH was lower in the $ECCO_2R$ group (7.29 compared with 7.32 at day 2, 7.32 compared with 7.35 at day 3).

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD, $PaCO_2$ was significantly lower with $ECCO_2R$ compared with NIV at 4 hours after randomisation (6.8 mmHg compared with 8.3 mmHg; p=0.02).

In the prospective case series of 95 people with ARDS, in the intervention group $PaCO_2$ and PaO_2/FiO_2 remained stable compared with baseline.

In the observational registry study of 60 people who had $ECCO_2R$ for any indication, the study recorded the best value of blood gases after 24 hours of $ECCO_2R$ compared with the worst value in the 6 hours pretreatment. $PaCO_2$ was significantly decreased (7 kPa compared with 11 kPa; p<0.001), PaO_2 was significantly decreased (9 kPa compared with 11 kPa; p<0.004) but there was no significant difference in PaO_2(kPa)/FiO_2 (0.17 compared with 0.17; p>0.05).

Change in MV settings from baseline

7 studies reported on changes in MV settings.

In the systematic review and meta-analysis of 531 people across 3 RCTs who had $ECCO_2R$ for AHRF, the authors noted a wide variation in consistency of reporting, the choice of variables, and the timepoints at which they were measured.

In the systematic review and meta-analysis of 826 people comparing $vvECCO_2R$ with $avECCO_2R$ for any indication, PEEP was significantly higher in the $vvECCO_2R$ group at 72 hours compared with the $avECCO_2R$ group (p<0.05).

In the RCT of 412 people with moderate or severe AHRF comparing $ECCO_2R$ with standard care, the group allocated to have $ECCO_2R$ had a lower tidal volume at day 3 (4.4 ml/kg compared with 6.7 ml/kg).

In the prospective case series of 95 people with ARDS, tidal volume, minute ventilation, plateau pressure and driving pressure were significantly lower at 8 hours and 24 hours compared with baseline (p=0.001), but the exact figures are not recorded in the paper.

The observational registry study of 60 people who had $ECCO_2R$ for any indication in the UK recorded the best value of ventilator settings after 24 hours of $ECCO_2R$ compared with the worst value in the 6 hours pretreatment. PEEP significantly increased after treatment (10 cmH_2O compared with 8 cmH_2O; p=0.032).

Safety

Overall complications

Overall complication rates were reported in 6 studies.

In the RCT of 412 people with moderate or severe AHRF, 168 AEs occurred in 106 people (53%) in the intervention arm, of which 65 AEs were considered related to the study intervention. 70 of these AEs were classed as serious SAEs in 62 people (31%). 22 SAEs were considered related to the study intervention.

In the RCT of 79 people with ARDS comparing $avECCO_2R$ with standard care, the overall incidence of $avECCO_2R$-related AEs was 7.5%.

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD, there were no severe or life-threatening complications in either group. There were 9 $ECCO_2R$-related AEs.

In the prospective case series of 95 people with ARDS, $ECCO_2R$-related AEs were reported in 37 people (39%). Six SAEs were reported, 2 SAEs were considered attributable to $ECCO_2R$ (massive right frontal parenchymal haematoma, pneumothorax at cannula insertion in the jugular vein). The secondary analysis of this study comparing low CO_2 extraction capacity devices with high CO_2 extraction capacity devices showed there was no significant difference in the incidence of $ECCO_2R$-related AEs between the low extraction and the high extraction devices (48% compared with 34%; p=0.242).

In the observational registry study of 60 people who had $ECCO_2R$ for any indication, 19 people (32%) experienced complications. This study did not specify if the complications were AEs or SAEs.

Haemorrhage

Haemorrhage rates were reported in 8 studies.

In the systematic review and meta-analysis of 531 people with AHRF across 3 RCTs, and 826 people across 18 observational studies, a meta-analysis was not possible because of lack of consistent definitions of haemorrhage. In the 2 RCTs that reported haemorrhage rates, bleeding appeared to be more frequent in the $ECCO_2R$ arms (17% compared with 1%), as was intracranial haemorrhage, but this was not statistically significant (5% compared with 1%; RR 3.00; 95% CI 0.42 to 20.51).

In the RCT of 412 people with moderate or severe AHRF, in the $ECCO_2R$ arm 17 people (8%) had bleeds (excluding intracranial haemorrhage), 6 of these (35%) were classed as SAEs. In the control arm, 3 people (1%) had bleeds (excluding intracranial haemorrhage), 1 of these was classed as an SAE. Of the SAEs in the $ECCO_2R$ arm, 4 were considered to be at least possibly related to the intervention. In the $ECCO_2R$ arm, 10 people (5%) developed intracranial haemorrhage, 9 of these were classed as SAEs, compared with 3 people (1%) and 1 SAE in the control arm. Of the SAEs in the $ECCO_2R$ arm, 5 were

considered to be at least possibly related to the intervention. There was a recruitment pause in the trial for investigation of a fatal intracranial haemorrhage.

In the RCT of 79 people with ARDS comparing avECCO$_2$R with standard care, they reported that the number of units of red blood cells transfused in the 10 days after randomisation was significantly higher in the avECCO$_2$R group than controls (4 units compared with 2 units; $p<0.05$).

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD, there were 3 AEs of cannula site bleeding and 3 AEs of haemolysis. There was no major bleeding in either group, but 1 person with ECCO$_2$R had a pool of platelets.

In the prospective case series of 95 people with ARDS, bleeding events occurred in 13 people (14%). Three were related to cannula insertion, 7 were at the cannula site. Six of these bleeds were SAEs. One bleeding SAE was considered attributable to ECCO$_2$R (massive right frontal parenchymal haematoma). The secondary analysis of this trial comparing low CO_2 extraction capacity devices with high CO_2 extraction capacity devices showed that bleeding rates were significantly higher in the low extraction capacity device group (27% compared with 6%; $p<0.01$). The 1 bleeding SAE attributable to ECCO$_2$R occurred in a person in the low CO_2 extraction capacity device group.

In the observational registry study of 60 people who had ECCO$_2$R for any indication in the UK, 10 people experienced bleeding complications. Seven were cannulation site bleeding, 1 was a gastrointestinal haemorrhage, 1 was haemolysis, and 1 was surgical site bleeding. This study did not specify if the complications were AEs or SAEs.

Limb ischaemia

Limb ischaemia rates were reported in 4 studies.

In the systematic review and meta-analysis of 531 people with AHRF across 3 RCTs, and 826 people across 18 observational studies, 2 RCTs reported rates of limb ischaemia with incidence of 3% and 10%. Four observational studies reported rates of limb ischaemia, ranging from 0% to 14%. A meta-analysis of these results was not possible due to the range in definitions of limb ischaemia.

In the systematic review and meta-analysis of 826 people comparing vvECCO$_2$R with avECCO$_2$R for any indication, in the avECCO$_2$R group (n=329) 14 people (4%) developed limb ischaemia. The figures for vvECCO$_2$R were not reported.

In the RCT of 412 people with moderate or severe AHRF, the paper did not specifically report limb ischaemia.

In the RCT of 79 people with ARDS comparing avECCO$_2$R with standard care, transient ischaemia of the lower limb occurred in 1 person (3%).

Circuit complications

This set of outcomes (incorporating clotting, device failure, and infection) was reported in 7 studies.

In the systematic review and meta-analysis of 531 people with AHRF across 3 RCTs, and 826 people across 18 observational studies, circuit complications were reported in 2 RCTs (4% to 19% incidence) and 6 observational studies (17% to 72% incidence). Because of variable reporting, a meta-analysis was not possible.

In the systematic review and meta-analysis of 826 people comparing vvECCO$_2$R with avECCO$_2$R for any indication, in the avECCO$_2$R group 27 people developed an arterial thrombus despite sufficient anticoagulation. The paper did not report the incidence of these complications in the vvECCO$_2$R group.

In the RCT of 412 people with moderate or severe AHRF, device failure occurred in 9 people (4.5%), leading to an SAE in 2 people. In the ECCO$_2$R arm infectious

complications occurred in 7 people (4%) leading to 2 SAEs, the control arm had 1 person (1%) with infectious complications not leading to an SAE. In the $ECCO_2R$ arm, 4 people (2%) developed heparin-induced thrombocytopenia, 1 of these was an SAE.

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD, there was 1 AE of device failure.

In the prospective case series of 95 people with ARDS who had $ECCO_2R$, membrane lung clotting occurred in 13 people. Six of these events led to circuit changes, and 7 events led to $ECCO_2R$ discontinuation. Haemolysis occurred in 11 people, infectious complications in 2 people, thrombocytopenia in 12 people, and hypofibrinogenemia in 2 people. In the secondary analysis of this study comparing low CO_2 extraction capacity devices with high CO_2 extraction devices, haemolysis was significantly more common in the low capacity device group (21% compared with 6%; $p<0.05$).

In the observational registry study of 60 people who had $ECCO_2R$ for any indication in the UK, 7 people (12%) had mechanical complications with the device. Five people (8%) developed culture-proven infection, but it was not specified if this was related to the intervention.

Cannulation complications

Cannulation complication rates were reported in 7 studies. This set of outcomes includes pseudoaneurysm formation, vascular injury, and catheter displacement. Cannulation-related bleeding is covered in the haemorrhage section.

In the systematic review and meta-analysis of 531 people with AHRF across 3 RCTs, and 826 people across 18 observational studies, 2 RCTs reported on cannulation complications (4% to 5% incidence) and 7 observational studies reported on cannulation complications (2% to 40% incidence).

In the systematic review and meta-analysis of 826 people comparing vv$ECCO_2R$ with av$ECCO_2R$ for any indication, 1 person on av$ECCO_2R$ developed pseudoaneurysm of the femoral artery.

In the RCT of 79 people with ARDS comparing av$ECCO_2R$ with standard care, 2 people in the intervention arm (n=40) developed pseudoaneurysms as a result of arterial cannulation.

In the RCT of 18 people with acute hypercapnic respiratory failure because of COPD, there was 1 $ECCO_2R$ cannula thrombosed prior to the intervention that was changed without an AE.

In the prospective case series of 95 people with ARDS who had $ECCO_2R$, 1 person developed an SAE of pneumothorax at cannula insertion in the internal jugular vein, which was considered attributable to $ECCO_2R$. The secondary analysis of this study showed that this SAE occurred in 1 person in the high CO_2 extraction capacity device group.

Pneumothorax

Pneumothorax rates were reported in 2 studies.

In the prospective case series of 95 people with ARDS who had $ECCO_2R$, 1 person developed an SAE of pneumothorax at cannula insertion in the internal jugular vein. The secondary analysis of this study showed that this SAE took place when a high CO_2 extraction capacity device was used.

In the observational registry study of 60 people who had $ECCO_2R$ for any indication in the UK, 1 person developed pneumothorax requiring treatment.

Need for dialysis

Need for dialysis was reported in 1 study.

In the observational registry study of 60 people who had $ECCO_2R$ for any indication in the UK, 5 people (8%) needed haemofiltration.

Other

In the RCT of 412 people with moderate or severe AHRF, in the $ECCO_2R$ arm 1 person (1%) had an ischaemic stroke classed as an SAE, compared with 3 people (1%) with 3 SAEs in the control arm.

Anecdotal and theoretical AEs

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other AEs for this procedure that they had heard about (anecdotal) that were not reported in the literature. They were also asked if they thought there were other AEs that might possibly occur, even if they had never happened (theoretical). They did not list any anecdotal or theoretical AEs.

Four professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- No study showed a significant difference in mortality at any point for $ECCO_2R$ intervention groups compared with control groups.
- NICE's previous interventional procedures guidance on this procedure indicated that guidance should be reviewed when the results of the REST trial by McNamee et al. (2021) were published. This trial did not show a significant difference in 90-day mortality between $ECCO_2R$ and standard care. There were no significant differences between $ECCO_2R$ and standard care in ICU length of stay or hospital length of stay, however the $ECCO_2R$ group had more VFDs. This trial was paused while a fatal intracranial bleed was being investigated, and the trial was stopped early

due to futility to detect a clinically important difference in 90-day mortality between groups. The study only recruited 412 people from a planned sample size of 1,120. 10% of people in the intervention arm of this trial experienced an SAE relating to the intervention. 5% of people experienced an intracranial bleed classified as an SAE.

- The 2 largest RCTs in this overview were stopped early due to futility to detect a clinically important difference in the primary outcome.
- The RCT of 79 people was conducted in 2013. The standards of technology may have changed since then.
- Studies had a wide range in reporting of outcomes, and how they classified AEs. This limits the ability to compare outcomes and AEs across studies.
- Studies varied in their inclusion criteria. Some studies recruited moderate or severe AHRF but did not specify ARDS, while others recruited people with ARDS. Only 1 study by Barrett et al. (2022) examined acute hypercapnic respiratory failure because of an acute exacerbation of COPD. Some studies have varying definitions of ARDS, reflecting a change in international consensus on diagnostic criteria.
- One study exclusively looked at av$ECCO_2R$, some studies have grouped together findings for all $ECCO_2R$ techniques. av$ECCO_2R$ is largely being replaced by vv$ECCO_2R$.
- One study indicated that the rates of haemorrhage-related complications are lower when a high CO_2 extraction capacity device is used compared with a low CO_2 extraction capacity device.
- Generally, most people meeting the inclusion criteria were excluded from studies. This reflects standard clinical practice as ECLS is a scarce

resource with a wide range of exclusion criteria necessitating very careful patient selection. This could limit the generalisability of these studies, however the committee could consider how this compares with standard clinical practice in the allocation of ECLS.

- Where RCTs have taken place, the control groups were well-characterised, and matched the intervention group in key demographics. However the study designs for RCTs did not protocolise standard care.

- The minimum follow-up duration across studies was 28 days or hospital discharge. Most studies reported in the range of 30 to 90 day outcomes, however only 1 study reported outcomes beyond 90 days.

- 4 co-authors of the systematic review and meta-analysis of 1,357 people are co-authors of the RCT of 412 people. 2 of these co-authors have grants for the conduct of this RCT.

- The RCT of 412 people had $ECCO_2R$ devices, catheters and consumables provided free of charge by the manufacturer. Two of the authors received grants from the manufacturer during the study, 1 author received non-financial support from the manufacturer in provision of equipment and consumables to undertake a clinical trial of $ECCO_2R$. Two of the authors of the RCT of 79 people were consultants for the manufacturer and received honoraria. The RCT of 18 people was funded by the manufacturer, the institution of the lead author had received funding from the manufacturer. Four authors of the case series of 95 people received research support or personal fees from a manufacturer, 1 was on a manufacturer's medical advisory board at the time of the study. In the case series of 60 people, 2 co-authors were undertaking a clinical trial with contributions from a manufacturer, and 1 co-author had received educational and research funding from a manufacturer.

- There are numerous ongoing studies relating to the procedure, including those listed below:

  - Effects of Blood Pulsatility on Von Willebrand Factor During $ECCO_2R$ (NCT05079009) Estimated enrolment: 10 people. Study start date: 28 January 2022. Estimated study completion date: February 2023.

  - Novel $ECCO_2R$ Device for Hypercapnic Respiratory Failure (NCT05316532) Estimated enrolment: 60 people. Estimated study start date: 1 January 2023. Estimated study completion date: 31 December 2023. Not yet recruiting.

  - $ECCO_2R$ to facilitatE earLy libEration From mechanicAl Ventilation in patients With Copd Acute Exacerbation (RELEASE) (NCT04147104) Estimated enrolment: 90 people. Estimated study start date: February 2021 Estimated study completion date: June 2023. Not yet recruiting.

  - $ECCO_2R$ in the Treatment of Acute Exacerbation of COPD With Severe Hypercapnia (NCT04842344) Estimated enrolment: 176 people. Estimated study start date: 1 May 2021. Estimated study completion date: 31 March 2024. Recruiting.

  - $ECCO_2R$ - Mechanical Power Study (NCT03939260) Estimated enrolment: 15 people. Study start date: 20 March 2019. Estimated study completion date: March 2024. Recruiting.

  - Post-Market Study of Low-flow $ECCO_2R$ Using PrismaLung+ (NCT04617093) Estimated enrolment: 50 people. Study start date: 30 April 2021. Estimated study completion date: 31 August 2023. Recruiting.

  - Early Extubation by $ECCO_2R$ Compared to IMV in Patients With Severe Acute Exacerbation of COPD (NCT03584295) Estimated enrolment: 192 people. Study start date: 7 February 2023. Estimated study completion date: March 2026. Recruiting.

  - CO_2 Removal in Severe Acute Exacerbations of Chronic Obstructive Lung Diseases (NCT05546606) Estimated enrolment: 304 people. Study start date: 1 November 2022. Estimated study completion date: 31 October 2025. Not yet recruiting.

  - Extracorporeal CO_2 Removal for Acute Decompensation of COPD (ORION) (NCT04582799) Estimated enrolment: 284 people. Study start date: 1 June 2023. Estimated study completion date: 1 June 2026. Not yet recruiting.

- Use of Extracorporeal CO_2 Removal in Case of Moderate to Severe ARDS to Apply an Ultraprotective Mechanical Ventilation Strategy (NCT04556578) Estimated enrolment: 20 people. Study start date: 16 February 2021 Estimated study completion date: 16 February 2025. Recruiting.

Related NICE guidance

Interventional procedures

- NICE's interventional procedures guidance on extracorporeal membrane oxygenation for severe acute respiratory failure in adults (Recommendation: special arrangements).

Medtech innovation briefings

- FreeO2 automatic oxygen titration for chronic obstructive pulmonary disease and respiratory distress syndrome (2021) Medtech Innovation Briefing 281.

NICE guidelines

- Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2018) NICE guideline NG115. Last updated 26 July 2019.
- Pneumonia in adults: diagnosis and management (2014) NICE guideline CG191. Last updated 07 July 2022.

Professional societies

- Intensive Care Society (ICS)
- Faculty of Intensive Care Medicine (FICM).

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 2 completed submissions. These were considered by the Interventional Procedures team and any relevant points have been taken into consideration when preparing this overview.

References

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Methods

NICE identified studies and reviews relevant to $ECCO_2R$ for acute respiratory failure from the medical literature. The following databases were searched between the date they started to 6 June 2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific AEs that not available in the published literature.
- People with acute respiratory failure.
- Intervention or test: extracorporeal carbon dioxide removal.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.
- Because of the volume of papers identified, an additional inclusion criterion of n>10 participants was applied.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	07/06/2023	1946 to June 06, 2023
MEDLINE In-Process (Ovid)	07/06/2023	1946 to June 06, 2023
MEDLINE Epubs ahead of print (Ovid)	07/06/2023	June 06, 2023
EMBASE (Ovid)	07/06/2023	1974 to 2023 June 06
EMBASE Conference (Ovid)	07/06/2023	1974 to 2023 June 06
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	07/06/2023	Issue 6 of 12, June 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	07/06/2023	Issue 6 of 12, June 2023
International HTA database (INAHTA)	07/06/2023	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

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

MEDLINE search strategy

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases. The MEDLINE search strategy was translated for use in the other sources.

Ovid MEDLINE(R) <1946 to June 06, 2023>

1 extracorporeal circulation/ 13201
2 (extracorp* adj4 (CO2 or carbon*) adj4 remov*).tw. 444
3 ((extracorporeal or intervention*) adj4 (lung or lungs) adj4 assist*).tw. 255
4 (CO2 adj4 remov*).tw. 1401
5 (carbon* adj4 dioxide adj4 remov*).tw. 787
6 (respirat* adj4 dialysis).tw. 144
7 (ECCO2R or AVECCO2R or VVECCO2R or AVCO2R or VVCO2R or AVECO2R or PECLA).tw. 217
8 or/1-7 15361
9 Respiratory Insufficiency/ 35760
10 Respiratory Distress Syndrome/ 24551
11 Hypercapnia/ 9205
12 (respirat* adj4 (distress* or depress* or fail* or insufficien*)).tw. 91872
13 ARDS.tw. 14741
14 (hypercapni* or hypercabi* or hypox*).tw. 182060
15 (ventilator* adj4 (fail* or depress*)).tw. 2226
16 or/9-15 292605
17 Lung Transplantation/ 17664
18 (lung adj4 (transplant* or graft*)).tw. 20442
19 Pulmonary Disease, Chronic Obstructive/ 49940
20 (Chronic adj4 Obstruct* adj4 (Lung or pulmonary or airway*) adj4 Disease*).tw. 56365
21 ((Chronic adj4 Airflow adj4 Obstruct*) or (COAD or COPD)).tw. 50195
22 or/17-21 101899
23 16 or 22 385411
24 8 and 23 1619
25 (cardiohelp* or novalung* or "iLA activve" or hemolung* or PRISMAlung* or minilung* or prolung* or diapact* or DECAPsmart or CO2RESET or ApherCap or ALung).tw. 210
26 24 or 25 1759
27 animals/ not humans/ 5093449
28 26 not 27 1435
29 limit 28 to english language 1164
30 limit 29 to ed=20230223-20230630 20

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (table 2 and table 3) are listed in table 5 below.

Table 5 additional studies identified

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Zhou Z, Zhengyan L, Liu C et al. (2023) Extracorporeal carbon dioxide removal for patients with acute respiratory failure: a systematic review and meta-analysis. Annals of Medicine 55(1):746-759	Systematic review and meta-analysis n=1173	No significant difference in overall mortality. $ECCO_2R$ associated with longer hospital stay.	A larger systematic review with meta-analysis is included in the main evidence summary.
Tiruvoipati R, Akkanti B, Dinh K et al. (2023) Extracorporeal carbon dioxide removal with the Hemolung in patients with acute respiratory failure: a multicenter retrospective cohort study. Critical Care Medicine 51(7):892-902	Retrospective cohort study n=159 Follow up to ICU discharge	41% survived to ICU discharge Significant reduction in $PaCO_2$ and improvement in pH, reduction in MV support.	Studies with more people or longer follow up are included.
Morris AH, Jane Wallace C, Menlove RL et al. (1994) Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. American Journal of Respiratory and	RCT n=40 Follow up 30 days	No significant difference in survival between MV and $ECCO_2R$.	Old study, technology has moved on significantly.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Critical Care Medicine 149: 295-305.			
Tiruvoipati R, Buscher H, Winearls J et al. (2016) Early experience of a new extracorporeal carbon dioxide removal device for acute hypercapnic respiratory failure. Critical Care and Resuscitation vol. 18 (no. 4); 261-269	Retrospective review n=15 Follow up to ICU or hospital discharge.	A total of 93% of people survived to weaning from ECCOR, 73% survived to ICU discharge and 67% survived to hospital discharge. Our data shows that ECCOR was safe and effective in this cohort.	Studies with more people or longer follow up are included.
Del Sorbo L, Pisani L, Filippini F et al. (2015) Extracorporeal Co2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. Critical care medicine vol. 43 (no. 1); 120-7	Matched cohort study n=25 Follow up to ICU or hospital discharge	Intubation rate in NIV plus $ECCO_2R$ 12% (95% CI, 2.5-31.2) and in NIV only was 33% (95% CI, 14.6-57.0), but the difference was not statistically different (p = 0.1495). Thirteen people (52%) experienced AEs related to extracorporeal CO_2 removal.	Studies with more people or longer follow up are included.
Schellongowski P, Riss K, Staudinger T et al. (2015) Extracorporeal CO_2 removal as bridge to lung transplantation in life-threatening hypercapnia. Transplant international, vol. 28 (no. 3); 297-304	Case series n=20 Follow up 1 year	Hypercapnia and acidosis were effectively corrected in all people within the first 12 h of ILA therapy. Four people were switched to ECMO because of progressive hypoxia or circulatory failure. Nineteen people (95%) were successfully transplanted. Hospital and 1-year survival was 75 and 72%, respectively. Bridging to LTX with $ECCO_2$-R	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		delivered by av or vv ILA is feasible and associated with high transplantation and survival rates.	
Ethgen O, Goldstein J, Harenski K (2021) A preliminary cost-effectiveness analysis of lung-protective ventilation with extra corporeal carbon dioxide removal ($ECCO_2R$) in the management of acute respiratory distress syndrome (ARDS). Journal of critical care vol. 63; 45-53	Cost-effectiveness analysis n=3000	$ECCO_2R$-enabled LPV strategies might provide cost-effective survival benefit. Additional data from interventional and observational studies are needed to support this preliminary model-based analysis.	Cost-effectiveness study, not focused on clinical outcomes.
Consales G, Zamidei L, Turani F (2022) Combined Renal-Pulmonary Extracorporeal Support with Low Blood Flow Techniques: A Retrospective Observational Study (CICERO Study) Blood purification vol. 51 (no. 4); 299-308	Retrospective observational study n=17 Follow up until discharge	12/17 people on MV shifted to protective ventilation, CO_2 clearance was satisfactorily maintained during the whole observational period, and pH was rapidly corrected. Treatment prevented NIV failure in 4 out of 5 people. No treatment-related complications were recorded. $ECCO_2R$-with renal replacement therapy was effective and safe in people with acute exacerbation of COPD and ARDS associated with acute kidney injury.	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Fanelli V, Ranieri M, Mancebo J (2016) Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. Critical care vol. 20; 36	Case series n=15 Follow up 28 days	The low-flow $ECCO_2R$ system safely facilitates a low volume, low pressure ultra-protective MV strategy in people with moderate ARDS.	Studies with more people or longer follow up are included.
Fitzgerald M, Millar J, Blackwood B (2014) Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. Critical care vol. 18 (no. 3); 222	Systematic review n=495 Follow up: mortality, ICU and hospital discharge	$ECCO_2R$ is a rapidly evolving technology and is an efficacious treatment to enable protective lung ventilation. Evidence for a positive effect on mortality and other important clinical outcomes is lacking. Rapid technological advances have led to major changes in these devices and together with variation in study design have limited applicability of analysis. Further well-designed adequately powered RCTs are needed.	Systematic review but no meta-analysis. Systematic reviews with meta-analysis are included in the main evidence summary.
Aretha D, Fligou F, Kiekkas P (2019) Extracorporeal Life Support: The Next Step in Moderate to Severe ARDS-A Review and Meta-Analysis of the Literature. BioMed research international vol. 2019; 1035730	Systematic review and meta-analysis n=209 Follow up: mortality period not stated	Reports on ECMO and $ECCO_2R$. Conclusion: According to our results, ECLS use was not associated with a benefit in mortality rate in people with ARDS. However, when restricted to higher-quality studies, ECMO was associated with a	Larger systematic reviews with meta-analysis are included in the main evidence summary.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		significant benefit in mortality rate.	Limited details in $ECCO_2R$ analysis, mainly focused on ECMO.
Moerer O, Harnisch LO, Barwing J (2019) Minimal-flow $ECCO_2R$ in patients needing CRRT does not facilitate lung-protective ventilation. Journal of artificial organs vol. 22 (no. 1); 68-76	Case series n=11 Follow up: ICU discharge	Minimal-flow $ECCO_2R$ in combination with CRRT is sufficient to reduce surrogates for lung-protective MV but was not sufficient to significantly reduce force applied to the lung.	Studies with more people or longer follow up are included.
Wohlfarth P, Schellongowski P, Staudinger T (2021) A bi-centric experience of extracorporeal carbon dioxide removal ($ECCO_2$ R) for acute hypercapnic respiratory failure following allogeneic hematopoietic stem cell transplantation. Artificial organs, vol. 45 (no. 8); 903-910	Case series n=11 Follow up: hospital discharge	$ECCO_2R$ effectively resolved blood gas disturbances in all people, but only 2/11 (18%) could be weaned off ventilatory support, and 1 (9%) person survived hospital discharge. $ECCO_2R$ was technically feasible but resulted in a low survival rate in our cohort.	Studies with more people or longer follow up are included.
Moss CE, Galtrey EJ, Camporota L (2016) A Retrospective Observational Case Series of Low-Flow Venovenous Extracorporeal Carbon Dioxide Removal Use in Patients with Respiratory Failure. ASAIO journal vol. 62 (no. 4); 458-62	Observational cohort study n=14 Follow up: ICU discharge	Four complications related to $ECCO_2R$ were reported, none resulting in serious adverse outcomes. Ten people were discharged from ICU alive. this technique can be safely used to achieve therapeutic goals in people requiring lung	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		protection, and in COPD.	
Grasselli G, Castagna L, Bottino N et al. (2020) Practical Clinical Application of an Extracorporeal Carbon Dioxide Removal System in Acute Respiratory Distress Syndrome and Acute on Chronic Respiratory Failure. ASAIO journal, vol. 66 (no. 6); 691-697	Case series n=11 Follow up: hospital discharge	A low-flow $ECCO_2R$ device with a large surface membrane lung removes a relevant amount of CO_2 resulting in a decreased arterial PCO_2, an increased arterial pH, and in a reduced ventilatory load.	Studies with more people or longer follow up are included.
Hermann A, Staudinger T, Bojic A et al. (2014) First experience with a new miniaturized pump-driven venovenous extracorporeal CO_2 removal system (iLA Activve): a retrospective data analysis. ASAIO journal vol. 60 (no. 3); 342-7	Case series n=12 Follow up: 30 days	Effective CO_2 removal observed in all people, with significant reduction in ventilation pressures and minute volumes at median blood flow rates of 1.2-1.4 litre/minute. Invasiveness of ventilation could be reduced. Additional severe impairment of oxygenation and prolonged MV before $ECCO_2$-R are factors of adverse prognosis.	Studies with more people or longer follow up are included.
Braune S, Sieweke A, Brettner F (2016) The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study.	Case-control study n=25 Follow up: 90 days	The use of $vvECCO_2R$ to avoid IMV was successful in just over half of the cases. However, relevant $ECCO_2R$-associated complications occurred in over one-third of cases. Despite the shorter period of IMV in the $ECCO_2R$ group there were no	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Intensive care medicine vol. 42 (no. 9); 1437-44		significant differences in length of stay or in 28- and 90-day mortality rates between the 2 groups.	
Hilty M, Riva T, Cottini SR et al. (2017) Low-flow venovenous extracorporeal CO_2 removal for acute hypercapnic respiratory failure. Minerva anestesiologica vol. 83 (no. 8); 812-823	Case series n=20 Follow up: ICU discharge	In mechanically ventilated people with HRF, low-flow $ECCO_2R$ supports the maintenance of lung-protective tidal volume and peak ventilator pressure. In selected awake people with acute HRF, it may be a novel treatment approach to avoid MV.	Studies with more people or longer follow up are included.
Braune S, Burchardi H, Engel M et al. (2015) The use of extracorporeal carbon dioxide removal to avoid intubation in patients failing non-invasive ventilation--a cost analysis. BMC Anesthesiology vol. 15; 160	Cost analysis of case-control study n=42 Follow up: hospital discharge	Additional costs for the use of arteriovenous $ECCO_2R$ to avoid IMV in people with acute-on-chronic ventilatory insufficiency failing NIV may be offset by a cost reducing effect of a shorter length of ICU and hospital stay.	Cost analysis study, not clinically focused.
Burki NK, Mani, RK, Herth FJF et al. (2013) A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. Chest vol. 143 (no. 3); 678-686	Case series n=20 Follow up:	This single-catheter, low-flow $ECCO_2R$ system provided clinically useful levels of CO_2 removal in these people with COPD.	Studies with more people or longer follow up are included.
Chiumello D, Pozzi T,Mereto E (2022) Long-term feasibility of ultraprotective lung ventilation with low-flow extracorporeal carbon	Case series n=10 Follow up: 5 days	The application of low-flow $ECCO_2R$ support allowed a reduction of respiration rate. During the following 5 days no changes in mechanics	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
dioxide removal in ARDS patients. Journal of critical care vol. 71; 154092		variables and gas exchange occurred.	
Cho WH, Lee K, Huh JW (2012) Physiologic effect and safety of the pumpless extracorporeal interventional lung assist system in patients with acute respiratory failure--a pilot study. Artificial organs vol. 36 (no. 4); 434-8	Case series n=11 Follow up: ICU discharge	iLA showed effective CO(2) removal, allowed for reducing the invasiveness of MV in people with severe respiratory failure from various causes even using a small-sized catheter and was safe in small body-sized people.	Studies with more people or longer follow up are included.
Schmidt M, Jaber S, Zogheib E (2018) Feasibility and safety of low-flow extracorporeal CO_2 removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. Critical care vol. 22 (no. 1); 122	Case series n=20 Follow up: 28 days	A low-flow $ECCO_2R$ device managed with an RRT platform easily and safely enabled very low tidal volume ventilation with moderate increase in $PaCO_2$ in people with mild-to-moderate ARDS.	Studies with more people or longer follow up are included.
Seiler F, Trudzinski FC, Hennemann K et al. (2017) The Homburg Lung: Efficacy and Safety of a Minimal-Invasive Pump-Driven Device for Veno-Venous Extracorporeal Carbon Dioxide Removal. ASAIO journal vol. 63 (no. 5); 659-665	Case series n=24 Follow up: hospital discharge	Reduction in CO_2, increase in blood pH. 2 cannulation-associated complications. The Homburg lung provides effective CO_2 removal in hypercapnic lung failure. The cannulation is a safe procedure, with complication rates comparable to those in central venous catheter implantation.	Studies with more people or longer follow up are included.
Munshi L, Telesnicki T, Walkey A et al. (2014) Extracorporeal life support	Systematic review and meta-analysis	ECLS was not associated with a mortality benefit in	Did not separate out

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
for acute respiratory failure a systematic review and meta-analysis Annals of the American Thoracic Society, vol. 11 (no. 5); 802-810	n=1248 Follow up: Hospital mortality	people with acute respiratory failure. However, a significant mortality benefit was seen when restricted to higher-quality studies of venovenous ECLS.	$ECCO_2R$ from ECMO.
Ding X, Chen H, Zhao H et al. (2021) $ECCO_2R$ in 12 COVID-19 ARDS Patients With Extremely Low Compliance and Refractory Hypercapnia Frontiers in medicine, vol. 8; 654658	Case series n=12 Follow up: hospital discharge	A low-flow $ECCO_2R$ system based on the RRT platform enabled CO_2 removal and could also decrease the driving pressure and plateau pressure significantly, which provided a new way to treat these COVID-19 ARDS people with refractory hypercapnia and extremely low compliance.	Studies with more people or longer follow up are included.
Bryner B, Miskulin J, Smith C (2014) Extracorporeal life support for acute respiratory distress syndrome because of severe Legionella pneumonia Perfusion, vol. 29 (no. 1); 39-43	Case series n=12 Follow up: hospital discharge	75% were successfully weaned off ECLS. ECLS for severe ARDS associated with Legionella pneumonia is an effective treatment option when MV fails, especially when introduced early in the course.	Studies with more people or longer follow up are included. Mix of ECMO and $ECCO_2R$.
Bromberger BJ, Agerstrand C, Abrams D et al. (2020) Extracorporeal Carbon Dioxide Removal in the Treatment of Status Asthmaticus Critical care medicine vol. 48 (no. 12); e1226-e1231	Case series n=26 Follow up: hospital discharge	Survival to hospital discharge was 100%. 15.4% experienced bleeding that needed a transfusion of packed red blood cells. Early extubation in select people receiving $ECCO_2R$ is safe and feasible.	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Zhu Y, Zhen W, Zhang X et al. (2022) Extracorporeal Carbon Dioxide Removal in Patients with Acute Respiratory Distress Syndrome or Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Blood purification 1-11	Systematic review and meta-analysis n=532 Follow up: hospital discharge and 28 day mortality	There was no statistically significant difference in the prognosis of people with and without $ECCO_2R$ treatment. $ECCO_2R$ significantly reduced $PaCO_2$ and improved PaO_2/FiO_2 and pH values in people with ARDS or COPD. Bleeding was the most common $ECCO_2R$-related AE.	Larger systematic reviews with meta-analysis are included in the main evidence summary.
Alessandri F, Tonetti T, Pistidda L et al. (2022) Extracorporeal CO_2 Removal During Renal Replacement Therapy to Allow Lung-Protective Ventilation in Patients with COVID-19-Associated Acute Respiratory Distress Syndrome ASAIO	Case series n=27 Follow up: discontinuation of treatment	These data show that in people with COVID-19-induced ARDS and AKI, $ECCO_2R$-plus-RRT is effective in allowing ultra-protective ventilator settings while maintaining an effective support of renal function and values of pH within physiologic limits.	Studies with more people or longer follow up are included.
Zhang R, Tian C, Cai S et al. (2022) Efficacy and Safety of a Low-Flow Extracorporeal Carbon Dioxide Removal System in Acute Respiratory Failure, a Pilot Study in China Blood purification	Case series n=12 Follow up: ICU discharge	A statistically significant reduction in respiratory rate, driving pressure, $PaCO_2$, and blood lactate was observed. 50% were discharged alive from ICU. Three complications related to LF-$ECCO_2R$ were reported, none resulting in serious adverse outcomes.	Studies with more people or longer follow up are included.
Augy JL, Aissaoui N, Richard C et al. (2019) A 2-year multicenter, observational, prospective,	Prospective cohort study n=70	Based on a registry, a low rate of $ECCO_2R$ device utilization seen, mainly in severe COPD	Studies with more people or longer

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
cohort study on extracorporeal CO_2 removal in a large metropolis area, Journal of Intensive Care vol. 7 (no. 1); 45	Follow up: ICU discharge	and ARDS people. Physiological efficacy was confirmed in these 2 populations. Safety concerns such as haemolysis, bleeding, and thrombosis, with different profiles between the devices.	follow up are included.
Worku E, Brodie D, Ling RR et al. (2022) Venovenous extracorporeal CO_2 removal to support ultraprotective ventilation in moderate-severe acute respiratory distress syndrome: A systematic review and meta-analysis of the literature Perfusion.	Systematic review and meta-analysis n=421	Random effects modelling indicated a 3.56 cmH2O reduction (95%-CI: 3.22-3.91) in driving pressure from baseline (p <.001) and a 1.89 ml/kg (95%-CI: 1.75-2.02, p <.001) reduction in tidal volume. Bleeding and haemolysis were the commonest complications of therapy.	Larger systematic reviews with meta-analysis are included in the main evidence summary. This review focuses on ventilator settings and does not focus on mortality.
Nentwich J, Wichmann D, Kluge S et al. (2019) Low-flow CO_2 removal in combination with renal replacement therapy effectively reduces ventilation requirements in hypercapnic patients: a pilot study Annals of intensive care vol. 9 (no. 1); 3	Case series n=20 Follow up: ICU discharge	The investigated low-flow $ECCO_2R$ and renal replacement system can ameliorate respiratory acidosis and decrease ventilation requirements in hypercapnic people with concomitant renal failure.	Studies with more people or longer follow up are included.
Diehl J-L, Piquilloud L, Vimpere D (2020) Physiological effects of adding $ECCO_2R$ to invasive mechanical	Case series n=12 Follow up: hospital discharge	Using a formalized protocol of respiratory rate adjustment, $ECCO_2R$ permitted to effectively improve pH and diminish $PaCO_2$ at	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
ventilation for COPD exacerbations Annals of intensive care vol. 10 (no. 1); 126		the early phase of IMV in 12 AE-COPD people, but not to diminish dynamic hyperinflation in the whole group. A trend toward a decrease in work of breathing was also observed during the weaning process.	
Winiszewski H, Aptel F, Belon F et al. (2018) Daily use of extracorporeal CO_2 removal in a critical care unit: Indications and results. Journal of intensive care vol. 6 (no. 1); 36	Case series n=33 Follow up: 28 day mortality	Twenty-eight day mortality was 31% in ARDS, 9% in COPD, and 50% in other causes of refractory hypercapnic respiratory failure. $ECCO_2R$ was useful to apply ultra-protective ventilation among ARDS people and improved $PaCO_2$, pH, and minute ventilation in COPD.	Studies with more people or longer follow up are included.
Morelli A, D'Egidio A, Orecchioni A et al. (2015) Extracorporeal CO_2 removal in hypercapnic patients who fail noninvasive ventilation and refuse endotracheal intubation: A case series Intensive Care Medicine Experimental, vol. 3 (no. supplement1); a824	Retrospective cohort study n=30 Follow up: 28 day mortality	Mortality at day 28 was significantly lower in the treated group than in control group (23.3% compared with 58.1%, $p< 0.001$). In the treated group none of people experienced bleeding events with a heparin infusion in the circuit. Nevertheless 8 people had clots in the circuit which needed the substitution of the circuit.	Studies with more people or longer follow up are included.
Fischer S, Simon AR, Welte T et al. (2006) Bridge to lung transplantation with the	Case series n=12 Follow up: 1 year	10 out of 12 people were successfully bridged to lung transplantation, and 8	Studies with more people or longer

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
novel pumpless interventional lung assist device NovaLung. The journal of thoracic and cardiovascular surgery vol. 131 (no. 3); 719-23		are still alive (1-year survival, 80%). This report suggests that interventional lung assist NovaLung implantation is an effective bridge to lung transplantation strategy in people with ventilation-refractory hypercapnia.	follow up are included.
Bein T, Weber F, Philipp A et al. (2006) A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Critical care medicine, vol. 34 (no. 5); 1372-7	Case series n=90 Follow up: hospital discharge	The incidence of complications was 24.4%, mostly because of ischaemia in a lower limb. Thirty-seven of 90 people survived, creating a lower mortality rate than expected from the Sequential Organ Failure Assessment score.	Studies with more people or longer follow up are included.
Ricci D, Boffini M, Del Sorbo L et al. (2010) The use of CO_2 removal devices in patients awaiting lung transplantation: an initial experience. Transplantation proceedings vol. 42 (no. 4); 1255-8	Case series n=12 Follow up: ICU discharge	Eight people died on the device. Three people were bridged to lung transplantation; 1 recovered and was weaned from the device after 11 days.	Studies with more people or longer follow up are included.
Azzi M, Aboab J, Alviset S et al. (2021) Extracorporeal CO_2 removal in acute exacerbation of COPD unresponsive to non-invasive ventilation. BMJ open respiratory research vol. 8 (no. 1)	Case-control study n=51 Follow up: 90 days	Mean time spent in the ICU and mean hospital stay in the $ECCO_2R$ and control groups were, respectively, 18 compared with 30 days, 29 compared with 49 days, and the 90-day mortality rates	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		were 15% compared with 28%. $ECCO_2R$ was associated with significant improvement of pH and $PaCO_2$ in people with acute exacerbations of COPD failing NIV therapy.	
Zimmermann M, Bein T, Arlt M et al. (2009) Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. Critical care, vol. 13 (no. 1); r10	Case series n=51 Follow up: hospital discharge	Initiation of iLA resulted in a marked removal in arterial CO_2 allowing a rapid reduction in tidal volume (less than or equal to 6 ml/kg) and inspiratory plateau pressure. AEs occurred in 6 people (11.9%). The hospital mortality rate was 49%.	Studies with more people or longer follow up are included.
Terragni PP, Del Sorbo L, Mascia L et al. (2009) Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology vol. 111 (no. 4); 826-35	Case series n=32 Follow up: 72 hours	Extracorporeal assist normalised $PaCO_2$ (50.4 +/- 8.2 mmHg) and pH (7.32 +/- 0.03) and allowed use of VT lower than 6 ml/kg for 144 (84 to 168) h. No patient-related complications were observed.	Studies with more people or longer follow up are included. Mortality not included in outcomes.
Muller T, Lubnow M, Philipp A et al. (2009) Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy. The European respiratory journal vol. 33 (no. 3); 551-8	Case series n=96 Follow up: device removal	Within 2 hours of iLA treatment, arterial oxygen partial pressure/inspired oxygen fraction ratio increased significantly and a fast improvement in arterial CO_2 partial pressure and pH was observed. Interventional lung assist eliminates approximately 50% of	Studies with more people or longer follow up are included. Mortality not included in outcomes.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		calculated total CO_2 production with rapid normalisation of respiratory acidosis.	
Brunet F, Belghith M, Mira JP (1993) Extracorporeal carbon dioxide removal and low-frequency positive-pressure ventilation. Improvement in arterial oxygenation with reduction of risk of pulmonary barotrauma in patients with adult respiratory distress syndrome. Chest, vol. 104 (no. 3); 889-98	Case series n=23 Follow up: hospital discharge	Increase of PaO_2 obtained rapidly with $ECCO_2R$-LFPPV, allowing subsequent reduction in inspired oxygen fraction; a reduction of the risk of barotrauma evidenced by a significant decrease in pressures and insufflated volumes; a survival rate of 50 percent. Bleeding was the only complication related to the technique and was the cause of death in 4 people.	Studies with more people or longer follow up are included.
Gattinoni L, Pesenti A, Mascheroni D et al. (1986) Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA, vol. 256 (no. 7); 881-6	Case series n=43 Follow up: hospital discharge	Lung function improved in 31 people (72.8%), and 21 people (48.8%) eventually survived. Improvement in lung function, when present, always occurred within 48 hours.	Studies with more people or longer follow up are included.
Inal V, Efe S (2021) Extracorporeal carbon dioxide removal ($ECCO_2R$) therapy in COPD and ARDS patients with severe hypercapnic respiratory failure. A retrospective case-control study Turkish journal of medical sciences	Case-control study n=75 Follow up: 28 days	The survival rate of $ECCO_2R$ people was 68% and significantly higher than 58% survival rate of controls (p= 0.025) In addition, iMV duration (12.8 +/- 2.6 compared with 17.1 +/- 4.9 days, p= 0.007) and length of stay (16.9 +/- 4.1 compared with	Studies with more people or longer follow up are included.

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		18.9 +/- 5.5 days, p= 0.032) were significantly shorter than controls.	

