Extracorporeal carbon dioxide removal in acute hypoxaemic respiratory failure: a systematic review, Bayesian meta-analysis, and trial sequential analysis.

JE Millar, AJ Boyle, TM Drake, CE Adams, AW Glass, B Blackwood, JJ McNamee, DF McAuley

Supplementary Material

Supplementary File 1. A summary of clinical studies published between 1946 and 1st January 1994
Supplementary File 2. Search strategy
Supplementary Table 1. Technical details of ECCO2R, management strategies, and anticoagulation protocols for randomised controlled trials.
Supplementary Table 2. Risk of bias rationale for randomised controlled trials
Supplementary Table 3. Baseline characteristics of included observational studies
Supplementary Table 4. Clinical outcome measures for ECCO2R reported by observational studies
Supplementary Table 5. ROBINS-I rationale for risk of bias in observational studies
Supplementary Table 6. Primary outcome (mortality up to day 30 (or latest)) sensitivity analysis
Supplementary Table 7. Safety and adverse events summary
Supplementary Table 8. Summary of physiological changes reported by included studies
Supplementary Table 9. Ongoing clinical trials of ECCO2R in acute hypoxaemic respiratory failure
Supplementary Figure 1. Inclusion diagram
Supplementary Figure 2. Risk of bias assessment for observational studies
Supplementary Figure 3. Forest plots for secondary outcomes
Supplementary Figure 4. Trial sequential analysis assuming ARR ≥ 5%
# Supplementary File 1. A summary of clinical studies published between 1946 and 1st January 1994

| Authors | Year | Title | Journal | Notes |
|---------|------|-------|---------|-------|
| Gattinoni L, Kolobow T, Agostini A, et al. | 1979 | Clinical application of low frequency positive pressure ventilation with extracorporeal CO₂ removal (LFPPV-ECCO₂R) in treatment of adult respiratory distress syndrome (ARDS). | Int J Artif Organs | Case report. Earliest article identified. |
| Gattinoni L, Pesenti A, Pelizzola A, et al. | 1981 | Reversal of terminal acute respiratory failure by low frequency positive pressure ventilation with extracorporeal removal of CO₂ (LFPPV-ECCO₂R). | Trans Am Soc Artif Intern Organs | |
| Pesenti A, Pelizzola A, Mascheroni D, et al. | 1981 | Low frequency positive pressure ventilation with extracorporeal CO₂ removal (LEPPV-ECCO₂R) in acute respiratory failure (ARF): technique. | Trans Am Soc Artif Intern Organs | |
| Gattinoni L, Pesenti A, Pelizzola A. | 1982 | Extracorporeal carbon dioxide removal in acute respiratory failure. | | |
| Agostini A, Cicardi M, Bergamashcini L, et al. | 1983 | Complement activation in adult respiratory distress syndrome treated with long-term extracorporeal CO₂ removal. | Trans Am Soc Artif Intern Organs | |
| Gattinoni L, Pesenti A, Caspani ML, et al. | 1984 | The role of total static lung compliance in the management of severe ARDS unresponsive to conventional treatment. | Intensive Care Med | Nineteen patients supported with ECCO₂R. The basis for the technique employed by Morris, et al. |
| Gardinale M, Cicardi M, Frangi D, et al. | 1985 | Studies of complement activation in ARDS patients treated by long-term extracorporeal CO₂ removal. | Int J Artif Organs | |
| Peters J, Radermacher P, Pesenti A, et al. | 1985 | Tracheal and alveolar gas composition during low-frequency positive pressure ventilation with extracorporeal CO₂-removal (LFPPV-ECCO₂R). | Intensive Care Med | |
| Solca M, Pesenti A, Iapichino G, et al. | 1985 | Multidisciplinary approach to extracorporeal respiratory assist for acute pulmonary failure. | Int Surg | |
| Thies WR, Breulmann M, Lehnusen U. | 1985 | Lung function during successful 10-day extracorporeal CO₂ removal in acute lung injury: Case report. | Anaesthetist | |
| Gattinoni L, Pesenti A, Mascheroni D, et al. | 1986 | Low-frequency positive-pressure ventilation with extracorporeal CO₂ removal in severe acute respiratory failure | JAMA | Forty-three patient un-controlled trial. |
| Hickling KG, Downward G, Davis F, et al. | 1986 | Management of severe ARDS with low frequency positive pressure ventilation and extracorporeal CO₂ removal. | Anaesth Intensive Care | |
| Marcolin R, Mascheroni D, Pesenti A, et al. | 1986 | Ventilatory impact of partial extracorporeal CO₂ removal (PECOR) in ARF patients. | ASAIO Trans | |
| Krajewski S, Seltz RJ, Schober R. | 1987 | Prolonged extracorporeal CO₂ - Removal in severe adult respiratory distress syndrome. Neurorpathological observations in two cases. | Intensive Care Med | |
| Peters J, Radermacher P, Kuntz ME, et al. | 1988 | Extracorporeal CO₂-removal with a heparin coated artificial lung. | Intensive Care Med | |
| Abrams JH, Gilmour JI, Krrett JM, et al. | 1990 | Low-frequency positive-pressure ventilation with extracorporeal carbon dioxide removal | Crit Care Med | |
| Pesenti A, Rossi GP, Pelosi P, et al. | 1990 | Percutaneous extracorporeal CO₂ removal in a patient with bullous emphysema with recurrent bilateral pneumothoraces and respiratory failure. | Anesthesiology | |
| Rossant R, Slama K, Bauer R, et al. | 1990 | Extracorporeal CO₂-removal with a heparin coated extracorporeal system. | Intensive Care Med | |
| Author(s)                                    | Year | Title                                                                 | Journal                          |
|---------------------------------------------|------|----------------------------------------------------------------------|----------------------------------|
| Wagner PK, Knoch M, Sangmeister C, et al.    | 1990 | Extracorporeal gas exchange in adult respiratory distress syndrome: associated morbidity and its surgical treatment. | Br J Surg                        |
| Bindslev L, Bohm C, Jolin A, et al.         | 1991 | Extracorporeal carbon dioxide removal performed with surface-heparinized equipment in patients with ARDS. | Acta Anaesthesiol Scand Suppl     |
| Hoffmann BH, Bohm SH, Morris AH, et al.     | 1991 | In vivo demonstration of the Haldane effect during extracorporeal gas exchange. | Int J Artif Organs               |
| Kee SS, Sedgwick J, Bristow A.              | 1991 | Interhospital transfer of a patient undergoing extracorporeal carbon dioxide removal. | Br J Anaesth                     |
| Kropf J, Grohe E, Knoch M, et al.           | 1991 | The prognostic value of extracellular matrix component concentrations in serum during treatment of adult respiratory distress syndrome with extracorporeal CO₂ removal. | Eur J Clin Chem Clin Biochem     |
| Brunet F, Mira JP, Belghith M, et al.       | 1992 | Effects of aprotinin on hemorrhagic complications in ARDS patients during prolonged extracorporeal CO₂ removal. | Intensive Care Med               |
| Knoch M, Kollen B, Dietrich G, et al.       | 1992 | Progress in veno-venous long-term bypass techniques for the treatment of ARDS. Controlled clinical trial with the heparin-coated bypass circuit. | Int J Artif Organs               |
| Ryan DP, Doody SP.                          | 1992 | Treatment of acute pulmonary failure with extracorporeal support: 100% survival in a pediatric population. | J Pediatr Surg                   |
| Brunet F, Belghith M, Mira JP, et al.       | 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                           |
Supplementary File 2. Search strategy

Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations

1946 – November 30th, 2021.

AND

Embase Classic + Embase

1947 – December 31st, 2021

1  “interventional lung assist*”.mp.
2  (extracorporeal adj (CO2 or “carbon dioxide”) adj removal).mp.
3  ILA*.mp.
4  novalung*.mp.
5  PECLA*.mp.
6  "percutaneous extracorporeal lung assist*”.mp.
7  "partial extracorporeal support*”.mp.
8  (("carbon dioxide” or CO2) adj dialysis*).mp.
9  ECCO2R*.mp.
10  “low flow ECCO2R*”.mp
11  1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12  Exp Respiratory Distress Syndrome, Adult/
13  “respiratory failure” .mp
14  “acute lung injury” .mp.
15  12 or 13 or 14
16  11 and 15
17  limit 16 to humans
## Supplementary Table 1. Technical details of ECCO$_2$R, management strategies, and anticoagulation protocols

| Mode of ECCO$_2$R | Morris, et al., 1994$^{[[1]]}$ | Bein, et al., 2013$^{[[1]]}$ | McNamee, et al., 2021$^{[[1]]}$ |
|-------------------|-------------------------------|-----------------------------|-------------------------------|
| Model and manufacturer of ECCO$_2$R | Veno-venous | Arterio-venous | Veno-venous |
| | Roller pump and two Sci Med 3.5 m$^2$ membrane lungs (ML) in series$^a$ | ilA, Novalung, Heilbronn, Germany | Hemolung-RAS, ALang, Pittsburgh, USA |
| Cannulate(e) type | NR$^b$ | Arterial cannula (≤ 15 Fr) | Dual-lumen cannula (15.5 Fr) |
| Cannulate(e) site | NR$^b$ | Venous cannula (typically 2 sizes larger than arterial) | Right internal jugular vein or any femoral vein. |
| Flow settings | ~2.4 L/min | ~1 – 2 L/min | 350 – 500 mL/min |
| Sweep gas settings | 15 L/min per ML$^3$ | Stepwise increase to 10 L/min$^3$ | Started at 1 L/min. Increased in 1-2 L/min increments until: |
| | When: | When: | • pH ≥ 7.2 |
| | • On CPAP ventilation | • FIO$_2$ < 0.5 | • V$_T$ ≤ 3 mL/kg PBW |
| | • FIO$_2$ 0.4 | • PEEP ≤ 12 cmH$_2$O | • Pplat ≤ 25 cmH$_2$O |
| | • PEEP 10 – 15 cmH$_2$O | • On an assisted spontaneous breathing ventilator mode | Maximum 10 L/min. |
| | Or. | Then, reduce sweep gas to 1 L/min. | Then, reduce sweep gas in 1 L/min increments until at 1L/min. |
| | • On low-frequency IMV for ≥ 6 hours with no sweep gas flow | If stable for 2 hours, may decannulate. | If stable at 1L/min for 12 hours, may decannulate. |
| Weaning strategy | Then, may decannulate.$^b$ | When: | When: |
| | | • Signs of clinical improvement | • Signs of clinical improvement |
| | | • PaO$_2$/FIO$_2$ ≥ 225 mmHg | • PaO$_2$/FIO$_2$ ≥ 225 mmHg |
| | | • Pplat ≤ 25 cmH$_2$O during trial of | • Pplat ≤ 25 cmH$_2$O during trial of |
| | | V$_T$ 6 mL/kg PBW | V$_T$ 6 mL/kg PBW |
| | | Then, reduce sweep gas in 1 L/min increments until at 1L/min. | Then, reduce sweep gas in 1 L/min increments until at 1L/min. |
| Anticoagulant | Unfractionated heparin | Unfractionated heparin | Unfractionated heparin |
| Anticoagulation target | ACT 180 – 210 s; APTTr 1.8 – 2.5 | PTT 40 – 50 s | APTTr 1.5-2.0 |
| Duration of ECCO$_2$R, days | 9 ± 2 | 7 ± 4 | 4 ± 2 |

for randomised controlled trials.
Adjunctive therapies, % ECCO₂R vs. standard care

| Therapy                  | ECCO₂R  | Standard Care | Stat.  |
|--------------------------|---------|---------------|--------|
| Prone position           | NR      | NR            | 8 vs. 8^  |
| Neuromuscular blockade   | NR      | NR            | 52 vs. 33^  |
| Inhaled nitric oxide     | NR      | NR            | 3 vs. 2^  |

^ Device was investigator-designed. The pump type was not described in the trial manuscript but was referenced as being as Gattinoni, et al, 1984.

^ These details were not reported in the trial manuscript. However, Gattinoni, et al., 1986, describes cannulation of the IVC via the femoral vein for venous access and cannulation of the SVC via the right internal jugular vein for venous return, or dual-lumen cannulation of the IVC via the femoral vein, or saphenous-saphenous venous cannulation.

^ Sweep gas settings were not reported in the trial manuscript but were obtained from a published pilot trial.

^ Mean ± sd.

^ Day 3.

ACT – activated clotting time; APTTr – activated partial thromboplastin time ratio; CPAP – continuous positive airway pressure; ECCO₂R – extracorporeal membrane oxygenation; F_{I_O₂} – inspired fraction of oxygen; IMV – intermittent mandatory ventilation; NR – not reported; PaO_{2}/F_{I_O₂} – arterial partial pressure of oxygen to inspired fraction of oxygen ratio; PEEP – positive end expiratory pressure; Pplat – plateau airway pressure; VT – tidal volume.
## Supplementary Table 2. Risk of bias rationale for randomised controlled trials.

| Study | Randomisation process | Assignment to intervention | Missing outcome data | Outcome measurement | Selective outcome reporting | Other |
|-------|------------------------|----------------------------|----------------------|---------------------|-----------------------------|-------|
| Morris, et al. [17] | Randomisation method not described. No good evidence that baseline imbalances suggest an issue with the randomisation process. However, ECCO2R patients had a significantly longer duration of illness at randomisation | Non-blinded. Two patients assigned to ECCO2R did not receive it (one died prior to initialisation and one recovered). Analysis was conducted on an intention-to-treat basis. Supportive care was highly protocolised with no evidence to suggest significant deviations from protocol. | No loss to follow-up. | Non-blinded but binary outcome. | Mortality, length of stay, and adverse events reported. | Trial stopped early due to futility. |
| Bein, et al. [18] | Telephone randomisation via a random number table generated by the trial statistician. Well balanced at randomisation. | Non-blinded. All patients assigned to ECCO2R received it. The study did not protocolise supportive care. There were significant differences in the cumulative doses of sedatives between groups, which is known to mediate duration of mechanical ventilation. | No loss to follow-up. | Non-blinded but binary outcome. | Limited reporting of mortality outcomes and adverse events. | Trial stopped early due to futility. |
| McNamee, et al. [8] | Online or telephone randomisation using a computer-generated schedule of variable block sizes. Well balanced at randomisation. | Non-blinded. Seventeen (8%) patients assigned to ECCO2R did not receive it (8 improved, 6 had technical issues with ECCO2R, 2 deteriorated, 1 withdrew consent). One patient in the control group received ECCO2R. Analysis was conducted on an intention-to-treat basis. The study did not protocolise supportive care. There was a significantly higher use of neuromuscular blocking drugs and a lower rate of proning in the ECCO2R group, both of which are known to mediate outcome in AHRF. | A small number of patients were not included in the primary analysis. There is no evidence to suggest this biased the result. | Non-blinded but binary outcome. | Pre-published study protocol. | Trial stopped early due to futility. |

AHRF – acute hypoxaemic respiratory failure; ECCO2R – extracorporeal carbon dioxide removal.
## Supplementary Table 3. Baseline characteristics of included observational studies.

| Year | Design | Mode of ECCO₂R | Co-intervention | Comparator | n | Age, years | Sex | PaO₂/FiO₂ ratio, mmHg | Aetiology, % | Notes |
|------|--------|----------------|-----------------|------------|---|------------|-----|----------------------|-------------|-------|
| 1997 | Controlled trial | VV | MV | 36 | 8 | 35 ± 13 | NR | 74 ± 28 | Pneumonia (44) | |
| 2006 | Retrospective cohort | AV | VV | 90 | 90 | 44 (26 – 59) | 21 F/69 M | 58 (47 – 78) | Pneumonia (33) | |
| 2009 | Controlled trial | VV | MV | 32 | 10 | 64 ± 14 | 3 F/10 M | 136 ± 30 | Pneumonia (34) | |
| 2009 | Prospective cohort | AV | VV | 51 | 51 | 52 (40 – 59) | 8 F/43 M | 75 (62 – 130) | NR | Pilot study |
| 2010 | Retrospective cohort | AV | HFOV | 21 | 21 | 51 (42 – 61) | 5 F/16 M | 61 (47 – 86) | Pneumonia (81) | |
| 2011 | Matched cohort | AV | Aspirin ECCO₂R | 30 | 30 | 47 ± 7 | 4 F/26 M | 127 ± 56 | Trauma (43) | |
| 2011 | Retrospective cohort | AV | VV | 13 | 13 | 52 ± 19 | 5 F/8 M | 100 ± 29 | Pneumonia (54) | |
| 2012 | Prospective cohort | AV | VV | 11 | 11 | 58 ± 14 | 3 F/8 M | 110 ± 37 | Pneumonia (64) | |
| 2014 | Retrospective cohort | VV | CRRT | 16 | 16 | 59 ± 17 | 9 F/7 M | 133 ± 71 | Pneumonia (56) | Novel device |
| 2015 | Retrospective cohort | VV | VV-ECMO | 255 | 63 | 50 ± 16 | 12 F/51 M | 93 (66 – 153) | Pulmonary-ARDS (67) | |
| 2016 | Prospective cohort | VV | VV | 15 | 15 | 55 ± 19 | 4 F/11 M | 159 ± 34 | Pneumonia (80%) | Feasibility study |
| 2018 | Matched cohort | VV | CRRT CRRT | 54 | 14 | 60 ± 20 | NR | NR | NR | |
| 2019 | Prospective cohort | VV | CRRT | 95 | 95 | 60 ± 14 | 31 F/64 M | 173 ± 61 | Pneumonia (82) | Pilot study |
| 2019 | Prospective cohort | VV | CRRT | 20 | 20 | 64 (43 – 82) | 8 F/12 M | 159 ± 36 | Pneumonia (85) | Pilot study |
| 2019 | Prospective cohort | VV | CRRT | 14 | 11 | 61 ± 11 | 4 F/7 M | 211 ± 60 | Multiple² | |
| 2020 | Retrospective cohort | AV | VV | 73 | 73 | 51 ± 17 | 28 F/45 M | 126 ± 59 | Pneumonia (60) | |
| 2021 | Quasi-experimental | VV | VV | 18 | 18 | 64 (57 – 76) | 5 F/13 M | 117 (100 – 136) | Pneumonia (83) | Pilot study |
| 2021 | Prospective cohort | VV | CRRT | 12 | 12 | 68 (62 – 71) | 6 F/6 M | NR | Covid-19 ARDS (100) | |

– number of patients who received ECCO₂R and were analysed.

¹ – mean ± SD or median (IQR).

² – commonest reported aetiology of respiratory failure.

³ – Two patients with ARDS, two with pneumonia, two with endocarditis, two with sepsis.

AHFR – acute hypoxaemic respiratory failure; ARDS – acute respiratory distress syndrome; AV – arterio-venous; Covid-19 – Coronavirus disease – 19; CRRT – continuous renal replacement therapy; ECCO₂R – extracorporeal carbon dioxide removal; ECMO – extracorporeal membrane oxygenation; MV – mechanical ventilation; VV – veno-venous.
### Supplementary Table 4. Clinical outcome measures for ECCO$_2$R reported by observational studies.

| Study (Year) | n (%) | 28/30-day mortality | ICU mortality | Hospital mortality | ICU length of stay, days |
|-------------|-------|---------------------|---------------|---------------------|-------------------------|
| Guinard, et al. [19] | NR | NR | 6/8 (75) | NR |
| Bein, et al., 2006 [20] | NR | NR | 53/90 (58.9) | NR |
| Terragni, et al. [21] | NR | NR | NR | NR |
| Zimmermann, et al. [22] | NR | NR | 25/51 (49) | NR |
| Lubnow, et al. [23] | 9/21 (42.9)$^a$ | NR | 12/21 (57.1) | NR |
| Bein, et al., 2011 [24] | NR | NR | 1/15 (6.7) | NR |
| Neirhaus, et al. [25] | NR | 7/13 (53.8) | NR | 34.5 ± 65.3 |
| Cho, et al. [26] | NR | NR | NR | NR |
| Quintard, et al. [27] | NR | 7/16 (43.8) | NR | 20.3 ± 10.7 |
| Weingart, et al. [28] | 30/63 (47.6)$^b$ | NR | 35/63 (55.6) | NR |
| Fanelli, et al., 2016 [29] | 7/15 (46.7)$^c$ | NR | NR | NR |
| Fanelli, et al., 2018 [30] | NR | NR | NR | NR |
| Combes, et al. [31] | 26/95 (27.4)$^a$ | NR | 36/95 (37.9) | NR |
| Nentwich, et al. [32] | NR | NR | NR | NR |
| Moerer, et al. [33] | NR | NR | NR | NR |
| Petren, et al. [34] | NR | NR | 36/73 (49.3) | NR |
| Goursand, et al. [35] | NR | NR | NR | NR |
| Ding, et al. [36] | 8/12 | NR | NR | 21 (16 – 36) |

$^a$ – 30-day mortality
$^b$ – 28-day mortality

ICU – intensive care unit; NR – not reported.
**Supplementary Table 5.** ROBINS-I rationale for risk of bias in observational studies.

|                     | Confounding                        | Selection of participants | Classification of interventions | Deviation from intervention | Missing data | Outcome measurement | Selection of reported results |
|---------------------|-----------------------------------|---------------------------|---------------------------------|-----------------------------|--------------|---------------------|------------------------------|
| Guinard, et al. [19] | Serious                           | Low                       | Low                             | Critical                    | No information | Low                 | Serious                      |
|                     | Only a small number of potential confounders accounted for in regression analysis. |                           |                                 | Nine patients meeting criteria for ECCO2R did not receive it. |              |                     |                              |
|                     | Terragni, et al. [21]             | Serious                   | Low                             | No information              | No information  | Moderate            | Serious                      |
|                     | Multiple confounding variables not controlled for. |                           |                                 |                             |              |                     |                              |
|                     |                                   |                           |                                 |                             |              |                     |                              |

*Primary outcome was binary.*

*Secondary outcomes were not pre-specified.*

*Outcome measures only minimally influenced by knowledge of the intervention and any error in measurement is unlikely to be related to intervention status.*

*In recording multiple clinical, imaging, and biochemical results there is a high risk of selective reporting.*
**Supplementary Table 6.** Primary outcome (mortality up to day 30 (or latest)) sensitivity analysis.

|                  | Informative prior$^a$ | Non-informative prior |
|------------------|------------------------|-----------------------|
|                  | Mean posterior relative effect$^b$ (95% CrI) | Heterogeneity ($I^2$) | Mean posterior relative effect$^b$ (95% CrI) | Heterogeneity ($I^2$) |
| Estimates        | 1.19 (0.70–2.29)       | 41.5%                 | 1.10 (0.60–2.05)       | 68.8%                 |

$^a$ Derived from the results of Guinard, et al.

$^b$ Relative risk.

Crl – credible interval.
## Supplementary Table 7. Safety and adverse events summary.

| Randomised controlled trials | ECCO₂R mode | Major haemorrhage\(^a\) | Intracerebral haemorrhage | Cannulation complications\(^b\) | Limb ischaemia \[^{10}\] | Circuit complications\(^c\) |
|-----------------------------|-------------|--------------------------|---------------------------|--------------------------------|---------------------------|---------------------------|
| Morris, et al. \[^{17}\]    | VV          | 100 [0]                  | NR                        | NR                             | NR                        | NR                        |
| Bein, et al. 2013 \[^{18}\] | AV          | NR                       | NR                        | 5                              | 2.5                       | NR                        |
| McNamee, et al. \[^{19}\]  | VV          | 8 [1]                    | 10 [1]                   | 4                              | NR                        | 4                         |

| Observational studies       |             |                          |                           |                                |                           |                           |
|-----------------------------|-------------|--------------------------|---------------------------|--------------------------------|---------------------------|---------------------------|
| Guinand, et al. \[^{19}\]  | VV          | 25 [12.5]                | 12.5 [0]                 | NR                             | NR                        | NR                        |
| Bein, et al. 2006 \[^{20}\] | AV          | 1                        | 1                         | 7                              | 10                        | NR                        |
| Terragni, et al. \[^{21}\] | VV          | 0 [0]                    | 0 [0]                    | 40                             | 0 [0]                     | 40                        |
| Zimmermann, et al. \[^{22}\]| AV          | 6                        | NR                       | 6                              | NR                        | NR                        |
| Lubnow, et al. \[^{23}\]   | AV          | 10                       | 5                         | NR                             | 14                        | 14                        |
| Bein, et al. 2011 \[^{24}\]| AV          | NR                       | NR                       | NR                             | NR                        | NR                        |
| Neirhaus, et al. \[^{25}\] | AV          | NR                       | NR                       | 15                             | NR                        | NR                        |
| Cho, et al. \[^{26}\]      | AV          | 9                        | NR                       | 18                             | NR                        | 72                        |
| Quintard, et al. \[^{27}\] | VV          | NR                       | NR                       | NR                             | NR                        | NR                        |
| Wengart, et al. \[^{28}\]  | AV          | NR                       | NR                       | NR                             | NR                        | 21                        |
| Fanelli, et al. 2016 \[^{29}\]| VV          | NR                       | NR                       | NR                             | NR                        | NR                        |
| Fanelli, et al. 2018 \[^{30}\]| VV          | NR                       | NR                       | NR                             | NR                        | NR                        |
| Combes, et al. \[^{31}\]   | VV          | 6                        | 1                         | 2                              | NR                        | 17                        |
| Nentwich, et al. \[^{32}\] | VV          | NR                       | NR                       | NR                             | NR                        | NR                        |
| Moerter, et al. \[^{33}\]  | VV          | NR                       | NR                       | NR                             | NR                        | NR                        |
| Petren, et al. \[^{34}\]   | AV          | NR                       | NR                       | 1                              | NR                        | NR                        |
| Goursand, et al. \[^{35}\] | VV          | 6                        | NR                       | NR                             | NR                        | 28                        |
| Ding, et al. \[^{36}\]     | VV          | NR                       | NR                       | NR                             | NR                        | NR                        |

\(^{a}\) There were disparate definitions of major haemorrhage, and each study was classified as such if the authors report bleeding to be significant or serious.

\(^{b}\) Cannulation complications include; cannula-site haematoma or bleeding, false-aneurysm formation or vascular injury, and catheter displacement.

\(^{c}\) Circuit complications include; clotting, device failure, and infection.

\(^{d}\) Bein, et al., did not report complications under a classification but did report a low rate of ECCO₂R-related adverse events (n = 3). These are included under the appropriate headings.

\(^{e}\) McNamee, et al., reported adverse events using an adverse and serious adverse event nomenclature. The rates above are for adverse events, which by definition include serious adverse events.

AV – arterio-venous; NR – not reported; VV – veno-venous.
### Supplementary Table 8. Summary of physiological changes reported by included studies.

| Randomised controlled trials | Timepoint | PaCO₂, mmHg | pH | V̇e, ml/kg | V̇e, L/min | Pplat, cmH₂O | PaO₂/FiO₂, mmHg |
|-----------------------------|-----------|-------------|----|-------------|-------------|--------------|-----------------|
| Morris, et al. [79]         | Randomisation | NR          | 7.36 ± 0.02 | 8.9 ± 0.6 | 15.0 ± 1.1 | 55 ± 35 | 63 ± 4 |
|                            | 3 – 6 hours | NR          | NR          | 3.0 ± 0.3 | NR          | 45 ± 21 | NR          |
| Bein, et al., 2013 [78]     | Randomisation | 57 ± 12     | 7.34 ± 0.07 | 5.9 ± 0.2 | 9.9 ± 1.6 | 29 ± 5  | 152 ± 37 |
|                            | Day 3      | NR          | NR          | NR         | NR†         | NR         | NR         |
| McNamee, et al. [80]        | Randomisation | 54 (47 – 63)| 7.30 (7.25 – 7.37) | 6.3 (5.8 – 7.0) | NR       | 26 (26 – 30) | 118 (96 – 13) |
|                            | Day 3      | 61 ± 14     | 7.32 ± 0.09 | 4.4 ± 1.7 | 7.6 ± 2.5 | 23 ± 5  | 148 ± 49 |

**Observational studies**

| Guinard, et al. [81]        | Physiological variables not reported on an ECCO-R vs. non-ECCO-R basis |
|-----------------------------|------------------------------------------------------------------------|
| Bein, et al., 2006 [79]     | Pre-ECCO-R | 60 (48 – 80) | 7.27 (7.18 – 7.36) | 430 (360 – 540) | 13.0 (10.0 – 16.4) | 38 (35 – 40) | 58 (47 – 78) |
|                            | 24 hours    | 34 (30 – 39) | 7.45 (7.41 – 7.50) | 380 (320 – 470) | 9.9 (8.0 – 14.8) | 35 (31 – 39) | 101 (74 – 142) |
| Terragni, et al. [82]       | Baseline    | 74 (71) | 7.20 (71) | 4.2 (71) | NR          | 24 (71) | 122 (71) |
|                            | Day 3       | 49 (71) | 7.39 (71) | 4.5 (71) | NR          | 23 (71) | 217 (71) |
| Zimmermann, et al. [83]     | Pre-ECCO-R  | 73 (61 – 86) | 7.23 (7.16 – 7.30) | 6.6 (5.5 – 7.2) | 11.5 (9.3 – 12.5) | 35 (31 – 38) | 75 (62 – 130) |
|                            | 24 hours    | 41 (34 – 48) | 7.44 (7.37 – 7.49) | 4.4 (3.4 – 5.4) | 6.6 (5.5 – 8.3) | 30 (26 – 34) | 110 (86 – 160) |
| Labnow, et al. [84]         | Pre-ECCO-R  | 58 (50 – 70) | 7.28 (7.16 – 7.36) | NR          | NR          | 28 (24 – 31) | 61 (47 – 86) |
|                            | 24 hours    | 36 (32 – 42) | 7.45 (7.36 – 7.54) | HFOV       | 33 (29 – 34) | 102 (71 – 135) |
| Bein, et al., 2011 [85]     | Physiological variables not reported for the overall cohort |
| Neirhaus, et al. [86]       | Pre-ECCO-R  | 80 ± 23 | 7.18 ± 0.22 | 293 ± 94 | 10.2 ± 3.4 | 34 ± 35 | 100 ± 29 |
|                            | Day 3       | 50 ± 8  | 7.41 ± 0.10 | 178 ± 90 | 3.3 ± 2.4 | 27 ± 4 | 152 ± 55 |
| Cho, et al. [87]            | Pre-ECCO-R  | 84 ± 23 | 7.18 ± 0.13 | 331 ± 87 | 9.4 ± 2.5 | 30 ± 7 | 110 ± 37 |
|                            | Day 5       | 49 ± 14 | 7.41 ± 0.05 | 324 ± 94 | 6.7 ± 1.9 | 25 ± 11 | 89 ± 18 |
| Quintard, et al. [88]       | Pre-ECCO-R  | 78 ± 14 | 7.17 ± 0.09 | 5.7 | NR          | 26 ± 3 | 13 ± 43 |
|                            | 12 hours    | 48 ± 10 | 7.40 ± 0.07 | 5.6 | NR          | 26 ± 3 | 13 ± 43 |
| Wengart, et al. [89]        | Physiological variables only reported at baseline |
| Fanelli, et al., 2016 [90]  | Pre-ECCO-R  | 51 ± 15 | 7.36 ± 0.1 | 6.2 ± 0.7 | NR          | 28 ± 2 | 159 ± 34 |
|                            | Day 3       | 49 ± 11 | 7.40 ± 0.1 | 4.8 ± 0.7 | NR          | 23 ± 3 | 176 ± 80 |
| Fanelli, et al., 2018 [91]  | Pre-ECCO-R  | NR       | 7.0 ± 0.5 | NR          | NR          | NR          | NR          |
|                            | Day 3       | NR       | 4.8 ± 0.4 | NR          | NR          | NR          | NR          |
| Combes, et al. [92]         | Pre-ECCO-R  | 48 ± 9  | 7.34 ± 0.08 | 6.0 ± 0.2 | 10.2 ± 2.3 | 27 ± 3 | 175 ± 61 |
|                            | 24 hours    | 47 ± 6 | 7.39 ± 0.04 | 4.1 ± 0.3 | 6.0 ± 1.1 | 23 ± 3 | 167 ± 34 |
| Neuntwich, et al. [93]      | Pre-ECCO-R  | 66 ± 9 | 7.20 ± 0.08 | 6.0 ± 0.7 | 9.6 ± 1.7 | 30 ± 4 | 159 ± 36 |
|                            | Day 3       | 54 ± 14 | 7.27 ± 0.14 | 5.4 ± 1.1 | 8.5 ± 2.1 | 28 ± 4 | 151 ± 35 |
| Moerer, et al. [94]         | Pre-ECCO-R  | 34 ± 6 | NR          | 425 ± 51 | 10.1 ± 1.9 | 15.4 | 211 ± 60 |
|                            | 6 hours     | 32 ± 3 | 395 ± 66 | 9.6 ± 2.6 | 15 ± 5 | NR          |
| Petren, et al. [95]         | Pre-ECCO-R  | 79 ± 34 | 7.23 ± 0.14 | 4.8 ± 1.6 | NR          | 33 ± 6 | 126 ± 59 |
|                            | 24 hours    | 39 ± 13 | 7.40 ± 0.1 | 4.8 ± 1.5 | NR          | 29 ± 4 | 136 ± 34 |
| Goursand, et al. [96]       | Day 0 ECCO-R | 43 (38 – 58) | 7.38 (7.34 – 7.42) | 6.1 (6.0 – 6.4) | 10.7 (10.1 – 12.2) | 26 (24 – 28) | 109 (97 – 136) |
|                            | Day 1 ECCO-R | 50 (45 – 59) | 7.31 (7.26 – 7.35) | 4.0 (4.0 – 4.2) | 7.0 (6.4 – 8.4) | 22 (20 – 26) | 116 (83 – 161) |
| Ding, et al. [97]           | Pre-ECCO-R  | 72 ± 17 | NR          | 5.9 ± 0.2 | NR          | 34 ± 7 | NR          |
|                            | 24 hours    | 65 ± 17 | NR          | 5.1 ± 0.4 | NR          | 26 ± 3 | NR          |
* – Reported as peak inspiratory pressure.

b – Data presented as a figure, but inappropriate scaling prevented digital retrieval.

c – Reported as average tidal volume in mL.

d – Reported as mean airway pressure.

e – Digitally retrieved.

f – No metric of dispersion reported.

$g$ – Reported as inspiratory pressure.

h – Values at 1 hour.

ECCO2R – extracorporeal membrane oxygenation; HFOV – high frequency oscillatory ventilation; NR – not reported; PaCO2 – arterial partial pressure of carbon dioxide; PaO2/FiO2 – arterial partial pressure of oxygen to inspired fraction of oxygen ratio; Pplat – plateau airway pressure; $V_e$ – minute volume; $V_t$ – tidal volume.

Data are presented as mean ± SD or median (IQR).
### Ongoing clinical trials of ECCO2R in acute hypoxaemic respiratory failure.

| Study                                                      | Design  | Start date | Completion date | Status       | n total | Country  | Record identifier   |
|------------------------------------------------------------|---------|------------|-----------------|--------------|---------|----------|---------------------|
| Low-flow extracorporeal carbon dioxide removal in covid-19 associated acute respiratory distress syndrome | Observational | May, 2020  | June, 2020      | Recruiting  | 20      | Germany | NCT04351906         |
| Post-market study of low-flow ECCO2R using Prisma-Lung+    | Observational | April, 2021 | June, 2022      | Recruiting  | 50      | France   | NCT04617093         |
| Registry of the experience of extracorporeal CO₂ removal in intensive care units (REXECOR) | Registry | January, 2016 | June, 2022      | Recruiting  | 200     | France   | NCT02965079         |
| ECCO2R – mechanical power study                            | Observational | March, 2019 | March, 2023*    | Recruiting  | 15      | Italy    | NCT03939260         |
| Use of extracorporeal CO₂ Removal in case of moderate to severe ARDS to apply ultraprotective mechanical ventilation strategy | Observational | February, 2021 | November, 2021 | Recruiting  | 20      | France   | NCT04556578         |
| Ultra-protective lung ventilation with extracorporeal CO₂ removal for moderate ARDS (SUPERNOVA) | Randomised trial | December, 2023* | Not yet recruiting | 230     | France   | NCT04903262         |
| Enhanced lung protective ventilation with ECCO2R during ARDS (PROVE) | Randomised trial | May, 2018  | December, 2022  | Recruiting  | 14      | France   | NCT03525691         |

* – estimated completion date.

ECCO2R – extracorporeal carbon dioxide removal.
Supplementary Figure 1. Inclusion diagram. ECCO$_2$R – extracorporeal carbon dioxide removal; ECMO – extracorporeal membrane oxygenation
Supplementary Figure 2. Risk of bias assessments for observational studies. Performed using the Cochrane ROBINS-I. A detailed rationale for each assessment is provided in supplementary table 5.
**Supplementary Figure 3. Forest plots for secondary outcomes.** Non-informative prior distributions were used for pooling secondary outcomes. Estimates are presented as relative risk or mean difference (95% credible intervals). Both mean and shrinkage estimates are shown. ECCO₂R – extracorporeal carbon dioxide removal.
Supplementary Figure 4. Trial sequential analysis assuming ARR ≥ 5%. The Z-value is the test statistic where $|Z| = 1.96$ is equivalent to $P = 0.05$ (green line). The Z-score horizontal bounds are set with O'Brien-Fleming alpha monitoring and beta futility boundaries (red lines). The required information size (RIS) is diversity adjusted and set to detect a 5% absolute difference in mortality (from 35% to 25%) at 80% power. Two tailed alpha = 0.05 and beta = 0.2.