# 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 $ECCO_2R$, 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 $ECCO_2R$ 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 $\geq$ 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 $CO_2$ 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 $CO_2$ (LFPPV-ECCO2R). | Trans Am Soc Artif Intern Organs | |
| Pesenti A, Pelizzola A, Mascheroni D, et al. | 1981 | Low frequency positive pressure ventilation with extracorporeal $CO_2$ removal (LEPPV-$ECCO_2R$) 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. | Ann Chir Gynaecol | |
| Agostini A, Cicardi M, Bergamaschini L, et al. | 1983 | Complement activation in adult respiratory distress syndrome treated with long-term extracorporeal $CO_2$ 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 $ECCO_2R$. The basis for the technique employed by Morris, et al..* |
| Gardinali M, Cicardi M, Frangi D, et al. | 1985 | Studies of complement activation in ARDS patients treated by long-term extracorporeal $CO_2$ 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 $CO_2$-removal (LFPPV-$ECCO_2R$). | 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, Lehnsen U. | 1985 | Lung function during successful 10-day extracorporeal $CO_2$ removal in acute lung injury: Case report. | Anaesthetist | |
| 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 | *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 $CO_2$ removal. | Anaesth Intensive Care | |
| Marcolin R, Mascheroni D, Pesenti A, et al. | 1986 | Ventilatory impact of partial extracorporeal $CO_2$ removal (PECOR) in ARF patients. | ASAIO Trans | |
| Krajewski S, Seltz RJ, Schober R. | 1987 | Prolonged extracorporeal $CO_2$ - Removal in severe adult respiratory distress syndrome. Neuropathological observations in two cases. | Intensive Care Med | |
| Peters J, Rademacher P, Kuntz ME, et al. | 1988 | Extracorporeal $CO_2$-removal with a heparin coated artificial lung. | Intensive Care Med | |
| Abrams JH, Gilmour IJ, Kriett 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 $CO_2$ removal in a patient with bullous emphysema with recurrent bilateral pneumothoraces and respiratory failure. | Anesthesiology | |
| Rossaint R, Slama K, Bauer R, et al. | 1990 | Extracorporeal $CO_2$-removal with a heparin coated extracorporeal system. | Intensive Care Med | |

| | | | | |
|---|---|---|---|---|
| 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, Grobe 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 $CO_2$ 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 $CO_2$ 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 | *RCT of 18 patients, comparing heparin coated and non-heparin coated $ECCO_2R$ circuits.* |
| 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 $ECCO_2R$, management strategies, and anticoagulation protocols

| | **Morris, et al., 1994** [17] | **Bein, et al., 2013** [18] | **McNamee, et al., 2021** [8] |
|---|---|---|---|
| **Mode of $ECCO_2R$** | Veno-venous | Arterio-venous | Veno-venous |
| **Model and manufacturer of $ECCO_2R$** | Roller pump and two Sci Med 3.5 $m^2$ membrane lungs (ML) in series[a] | iLA, Novalung, Heilbronn, Germany | Hemolung-RAS, ALung, Pittsburgh, USA |
| **Cannula(e) type** | NR[b] | Arterial cannula (≤ 15 Fr)<br>Venous cannula (typically 2 sizes larger than arterial) | Dual-lumen cannula (15.5 Fr) |
| **Cannula(e) site** | NR[b] | Femoral artery and contralateral femoral vein. | 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[b] | Stepwise increase to 10 L/min[c] | Started at 1 L/min.<br>Increased in 1-2 L/min increments until:<br>• pH ≥ 7.2<br>• $V_T$ ≤ 3 mL/kg PBW<br>• Pplat ≤ 25 $cmH_2O$<br>Maximum 10 L/min. |
| **Weaning strategy** | When:<br>• On CPAP ventilation<br>• $F_IO_2$ 0.4<br>• PEEP 10 – 15 $cmH_2O$<br>Or,<br>• On low-frequency IMV for ≥ 6 hours with no sweep gas flow<br>Then, may decannulate.[b] | When:<br>• $F_IO_2$ < 0.5<br>• PEEP ≤ 12 $cmH_2O$<br>• On an assisted spontaneous breathing ventilator mode<br>Then, reduce sweep gas to 1 L/min.<br>If stable for 2 hours, may decannulate. | When:<br>• Signs of clinical improvement<br>• $PaO_2/F_IO_2$ ≥ 225 mmHg<br>• Pplat ≤ 25 $cmH_2O$ during trial of $V_T$ 6 mL/kg PBW<br>Then, reduce sweep gas in 1 L/min increments until at 1L/min.<br>If stable at 1L/min for 12 hours, may decannulate. |
| **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 $ECCO_2R$**[d], *days* | 9 ± 2 | 7 ± 4 | 4 ± 2 |

for randomised controlled trials.

| | | | |
|---|---|---|---|
| **Adjunctive therapies**, *% $ECCO_2R$ vs. standard care* | | | |
| Prone position | NR | NR | 8 vs. 8[e] |
| Neuromuscular blockade | NR | NR | 52 vs. 33[e] |
| Inhaled nitric oxide | NR | NR | 3 vs. 2[e] |

[a] – Device was investigator-designed. The pump type was not described in the trial manuscript but was referenced as being as *Gattinoni, et al, 1984.*
[b] – 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.
[c] – Sweep gas settings were not reported in the trial manuscript but were obtained from a published pilot trial.
[d] – Mean ± sd.
[e] – Day 3.

ACT – activated clotting time; APTTr – activated partial thromboplastin time ratio; CPAP – continuous positive airway pressure; $ECCO_2R$ – extracorporeal membrane oxygenation; $F_IO_2$ – inspired fraction of oxygen; IMV – intermittent mandatory ventilation; NR – not reported; $PaO_2/F_IO_2$ – arterial partial pressure of oxygen to inspired fraction of oxygen ratio; PEEP – positive end expiratory pressure; Pplat – plateau airway pressure; $V_T$ – tidal volume.

**Supplementary Table 2.** Risk of bias rationale for randomised controlled trials.

| | Randomisation process | Assignment to intervention | Missing outcome data | Outcome measurement | Selective outcome reporting | Other |
|---|---|---|---|---|---|---|
| **Morris, et al.** [17] | *Some concerns* | *Low* | *Low* | *Low* | *Low* | |
| | Randomisation method not described. No good evidence that baseline imbalances suggest an issue with the randomisation process. However, $ECCO_2R$ patients had a significantly longer duration of illness at randomisation | Non-blinded. Two patients assigned to $ECCO_2R$ 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] | *Low* | *Some concerns* | *Low* | *Low* | *Some concerns* | |
| | Telephone randomisation via a random number table generated by the trial statistician. Well balanced at randomisation. | Non-blinded. All patients assigned to $ECCO_2R$ 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] | *Low* | *Some concerns* | *Low* | *Low* | *Low* | |
| | Online or telephone randomisation using a computer-generated schedule of variable block sizes. Well balanced at randomisation. | Non-blinded. Seventeen (8%) patients assigned to $ECCO_2R$ did not receive it (8 improved, 6 had technical issues with $ECCO_2R$, 2 deteriorated, 1 withdrew consent). One patient in the control group received $ECCO_2R$. 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; $ECCO_2R$ – extracorporeal carbon dioxide removal.

| | Year | Design | Mode of $ECCO_2R$ | Co-intervention | Comparator | n total | n $ECCO_2R$[a] | Age, *years*[b] | Sex | $PaO_2/F_IO_2$ ratio, *mmHg*[b] | Aetiology, *%*[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Guinard, et al. [19] | 1997 | Controlled trial | VV | | MV | 36 | 8 | 35 ± 13 | NR | 74 ± 28 | Pneumonia (44) | |
| Bein, et al. [20] | 2006 | Retrospective cohort | AV | | | 90 | 90 | 44 (26 – 59) | 21 F/69 M | 58 (47 – 78) | Pneumonia (33) | |
| Terragni, et al. [21] | 2009 | Controlled trial | VV | | MV | 32 | 10 | 64 ± 14 | 3 F/10 M | 136 ± 30 | Pneumonia (34) | |
| Zimmermann, et al. [22] | 2009 | Prospective cohort | AV | | | 51 | 51 | 52 (40 – 59) | 8 F/43 M | 75 (62 – 130) | NR | Pilot study |
| Lubnow, et al. [23] | 2010 | Retrospective cohort | AV | HFOV | | 21 | 21 | 51 (42 – 61) | 5 F/16 M | 61 (47 – 86) | Pneumonia (81) | |
| Bein, et al. [24] | 2011 | Matched cohort | AV | Aspirin | $ECCO_2R$ | 30 | 30 | 47 ± 7 | 4 F/26 M | 127 ± 56 | Trauma (43) | |
| Neirhaus, et al. [25] | 2011 | Retrospective cohort | AV | | | 13 | 13 | 52 ± 19 | 5 F/8 M | 100 ± 29 | Pneumonia (54) | |
| Cho, et al. [26] | 2012 | Prospective cohort | AV | | | 11 | 11 | 58 ± 14 | 3 F/8 M | 110 ± 37 | Pneumonia (64) | |
| Quintard, et al. [27] | 2014 | Retrospective cohort | VV | CRRT | | 16 | 16 | 59 ± 17 | 9 F/7 M | 133 ± 71 | Pneumonia (56) | Novel device |
| Weingart, et al. [28] | 2015 | Retrospective cohort | AV | | VV-ECMO | 255 | 63 | 50 ± 16 | 12 F/51 M | 93 (66 – 153) | Pulmonary-ARDS (67) | |
| Fanelli, et al. [29] | 2016 | Prospective cohort | VV | | | 15 | 15 | 55 ± 19 | 4 F/11 M | 159 ± 34 | Pneumonia (80%) | Feasibility study |
| Fanelli, et al. [30] | 2018 | Matched cohort | VV | CRRT | CRRT | 54 | 14 | 60 ± 20 | NR | NR | NR | |
| Combes, et al. [31] | 2019 | Prospective cohort | VV | | | 95 | 95 | 60 ± 14 | 31 F/64 M | 173 ± 61 | Pneumonia (82) | Pilot study |
| Nentwich, et al. [32] | 2019 | Prospective cohort | VV | CRRT | | 20 | 20 | 64 (43 – 82) | 8 F/ 12 M | 159 ± 36 | Pneumonia (85) | Pilot study |
| Moerer, et al. [33] | 2019 | Prospective cohort | VV | CRRT | | 14 | 11 | 61 ± 11 | 4 F/7 M | 211 ± 60 | Multiple[d] | |
| Petren, et al. [34] | 2020 | Retrospective cohort | AV | | | 73 | 73 | 51 ± 17 | 28 F/45 M | 126 ± 59 | Pneumonia (60) | |
| Goursand, et al. [35] | 2021 | Quasi-experimental | VV | | | 18 | 18 | 64 (57 – 76) | 5 F/13 M | 117 (100 – 136) | Pneumonia (83) | Pilot study |
| Ding, et al. [36] | 2021 | Prospective cohort | VV | CRRT | | 12 | 12 | 68 (62 – 71) | 6 F/6 M | NR | Covid-19 ARDS (100) | |

**Supplementary Table 3.** Baseline characteristics of included observational studies.

[a] – number of patients who received $ECCO_2R$ and were analysed.
[b] – mean ± SD or median (IQR).
[c] – commonest reported aetiology of respiratory failure.
[d] – Two patients with ARDS, two with pneumonia, two with endocarditis, two with sepsis.

AHRF – acute hypoxaemic respiratory failure; ARDS – acute respiratory distress syndrome; AV – arterio-venous; Covid-19 – Coronavirus disease – 19; CRRT – continuous renal replacement therapy; $ECCO_2R$ – extracorporeal carbon dioxide removal; ECMO – extracorporeal membrane oxygenation; MV – mechanical ventilation; VV – veno-venous.

**Supplementary Table 4.** Clinical outcome measures for $ECCO_2R$ reported by observational studies.

| | *n (%)* | | | *mean ± SD or median (range)* |
|---|---|---|---|---|
| | **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)[a] | NR | 35/63 (55.6) | NR |
| Fanelli, et al., 2016 [29] | 7/15 (46.7)[b] | NR | NR | NR |
| Fanelli, et al., 2018 [30] | NR | NR | NR | NR |
| Combes, et al. [31] | 26/95 (27.4)[b] | 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 $ECCO_2R$ did not receive it. | | Primary outcome was binary. | Secondary outcomes were not pre-specified. |
| Terragni, et al. [21] | *Serious* | *Low* | *Low* | *No information* | *No information* | *Moderate* | *Serious* |
| | Multiple confounding variables not controlled for. | | | | | 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.

CrI – credible interval.

| | *% of patients receiving $ECCO_2R$ [% of* standard *care group]* | | | | | |
|---|---|---|---|---|---|---|
| | **$ECCO_2R$ mode** | **Major haemorrhage**[a] | **Intracerebral haemorrhage** | **Cannulation complications**[b] | **Limb ischaemia** | **Circuit complications**[c] |
| ***Randomised controlled trials*** | | | | | | |
| Morris, et al. [17] | VV | 100 [0] | 5 [5] | NR | 10 | 19 |
| Bein, et al., 2013[d] [18] | AV | NR | NR | 5 | 2.5 | NR |
| McNamee, et al[e] [8] | VV | 8 [1] | 10 [1] | 4 | NR | 4 |
| ***Observational studies*** | | | | | | |
| Guinard, 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 | 6 | 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 |
| Weingart, et al. [28] | AV | NR | NR | NR | NR | 21 |
| Fanelli, et al., 2016 [29] | VV | NR | NR | 7 | 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 |
| Moerer, et al. [33] | VV | NR | NR | NR | NR | NR |
| Petren, et al. [34] | AV | NR | 1 | NR | NR | NR |
| Goursand, et al. [35] | VV | 6 | NR | NR | NR | 28 |
| Ding, et al. [36] | VV | NR | NR | NR | NR | NR |

**Supplementary Table 7.** Safety and adverse events summary.

[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 $ECCO_2R$-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.

| | Timepoint | $PaCO_2$, *mmHg* | pH | $V_T$, *mL/kg* | $V_E$, *L/min* | Pplat, *$cmH_2O$* | $PaO_2/F_1O_2$, *mmHg* |
|---|---|---|---|---|---|---|---|
| ***Randomised controlled trials*** | | | | | | | |
| Morris, et al. [17] | Randomisation | NR | 7.36 ± 0.02 | 8.9 ± 0.6 | 15.0 ± 1.1 | 55 ± 3[a] | 63 ± 4 |
| | 3 – 6 hours | NR | NR | 3.0 ± 3.0 | NR | 45 ± 2 | NR |
| Bein, et al., 2013 [18] | Randomisation | 57 ± 12 | 7.34 ± 0.07 | 5.9 ± 1.2 | 9.9 ± 1.6 | 29 ± 5 | 152 ± 37 |
| | Day 3 | NR | NR | NR[b] | NR[b] | NR | NR[b] |
| McNamee, et al. [8] | 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. [19] | *Physiological variables not reported on an $ECCO_2R$ vs. non-$ECCO_2R$ basis* | | | | | | |
| Bein, et al., 2006 [20] | Pre-$ECCO_2R$ | 60 (48 – 80) | 7.27 (7.18 – 7.36) | 430 (360 – 540)[c] | 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)[c] | 9.9 (8.0 – 14.8) | 35 (31 – 39) | 101 (74 – 142) |
| Terragni, et al. [21] | Baseline | 74[e,f] | 7.20[e,f] | 4.2[e,f] | NR | 24[e,f] | 122[e,f] |
| | Day 3 | 49[e,f] | 7.39[e,f] | 4.5[e,f] | NR | 23[e,f] | 217[e,f] |
| Zimmermann, et al. [22] | Pre-$ECCO_2R$ | 73 (61 – 86) | 7.23 (7.16 – 7.30) | 6.6 (5.3 – 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) |
| Lubnow, et al. [23] | Pre-$ECCO_2R$ | 58 (50 – 70) | 7.28 (7.16 – 7.36) | NR | NR | 28 (24 - 31)[d] | 61 (47 – 86) |
| | 24 hours | 36 (32 – 42)[e] | 7.45 (7.36 – 7.54)[e] | HFOV | | 33 (29 – 34)[d] | 102 (71 – 135)[e] |
| Bein, et al., 2011 [24] | *Physiological variables not reported for the overall cohort* | | | | | | |
| Neirhaus, et al. [25] | Pre-$ECCO_2R$ | 80 ± 23 | 7.18 ± 0.22 | 293 ± 94[c] | 10.2 ± 3.4 | 34 ± 3[g] | 100 ± 29 |
| | Day 3 | 50 ± 8 | 7.41 ± 0.10 | 178 ± 90[c] | 3.3 ± 2.4 | 27 ± 4[g] | 152 ± 55 |
| Cho, et al. [26] | Pre-$ECCO_2R$ | 84 ± 23 | 7.18 ± 0.13 | 331 ± 87[c] | 9.4 ± 2.5 | 30 ± 7[a] | 110 ± 37 |
| | Day 3 | 49 ± 14 | 7.41 ± 0.05 | 324 ± 94[c] | 6.7 ± 1.9 | 25 ± 11[a] | 89 ± 18 |
| Quintard, et al. [27] | Pre-$ECCO_2R$ | 78 ± 14 | 7.17 ± 0.09 | 5.9[f] | NR | 28[f] | 133 ± 71 |
| | 12 hours | 48 ± 10 | 7.40 ± 0.07 | 5.6[f] | NR | 26[f] | 134 ± 43 |
| Weingart, et al. [28] | *Physiological variables only reported at baseline* | | | | | | |
| Fanelli, et al., 2016 [29] | Pre-$ECCO_2R$ | 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 [30] | Pre-$ECCO_2R$ | NR | NR | 7.0 ± 0.5 | NR | NR | NR |
| | Day 3 | NR | NR | 4.8 ± 0.4 | NR | NR | NR |
| Combes, et al. [31] | Pre-$ECCO_2R$ | 48 ± 9 | 7.34 ± 0.08 | 6.0 ± 0.2[e] | 10.2 ± 2.3[e] | 27 ± 3[e] | 173 ± 61[e] |
| | 24 hours | 47 ± 7[e] | 7.39 ± 0.04[e] | 4.1 ± 0.3 | 6.0 ± 1.1 | 23 ± 3 | 167 ± 34 |
| Nentwich, et al. [32] | Pre-$ECCO_2R$ | 66 ± 9 | 7.20 ± 0.08 | 6.0 ± 0.7 | 9.6 ± 1.7 | 30 ± 4 | 159 ± 36 |
| | Day 3 | 54 ± 14[e] | 7.27 ± 0.14[e] | 5.4 ± 1.1[h] | 8.5 ± 2.1[h] | 28 ± 4[g] | 151 ± 35[g] |
| Moerer, et al. [33] | Pre-$ECCO_2R$ | 34 ± 6 | NR | 425 ± 51[c] | 10. 1 ± 1.9 | 15 ± 4[d] | 211 ± 60 |
| | 6 hours | 32 ± 3 | NR | 395 ± 66[c] | 9.6 ± 2.6 | 15 ± 5[d] | NR |
| Petren, et al. [34] | Pre-$ECCO_2R$ | 79 ± 31 | 7.23 ± 0.14 | 4.8 ± 1.6 | NR | 33 ± 6 | 126 ± 59 |
| | 24 hours | 49 ± 12 | 7.40 ± 0.10 | 4.4 ± 1.5 | NR | 29 ± 4 | 136 ± 54 |
| Goursand, et al. [35] | Day 0 $ECCO_2R$ | 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 $ECCO_2R$ | 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. [36] | Pre-$ECCO_2R$ | 72 ± 17[e] | NR | 5.9 ± 0.2 | NR | 34 ± 7 | NR |
| | 24 hours | 65 ± 17[e] | NR | 5.1 ± 0.4[e] | NR | 26 ± 3[e] | NR |

[a] – 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.

$ECCO_2R$ – extracorporeal membrane oxygenation; HFOV – high frequency oscillatory ventilation; NR – not reported; $PaCO_2$ – arterial partial pressure of carbon dioxide; $PaO_2/F_IO_2$ – arterial partial pressure of oxygen to inspired fraction of oxygen ratio; Pplat – plateau airway pressure; $V_E$ – minute volume; $V_T$ – tidal volume.

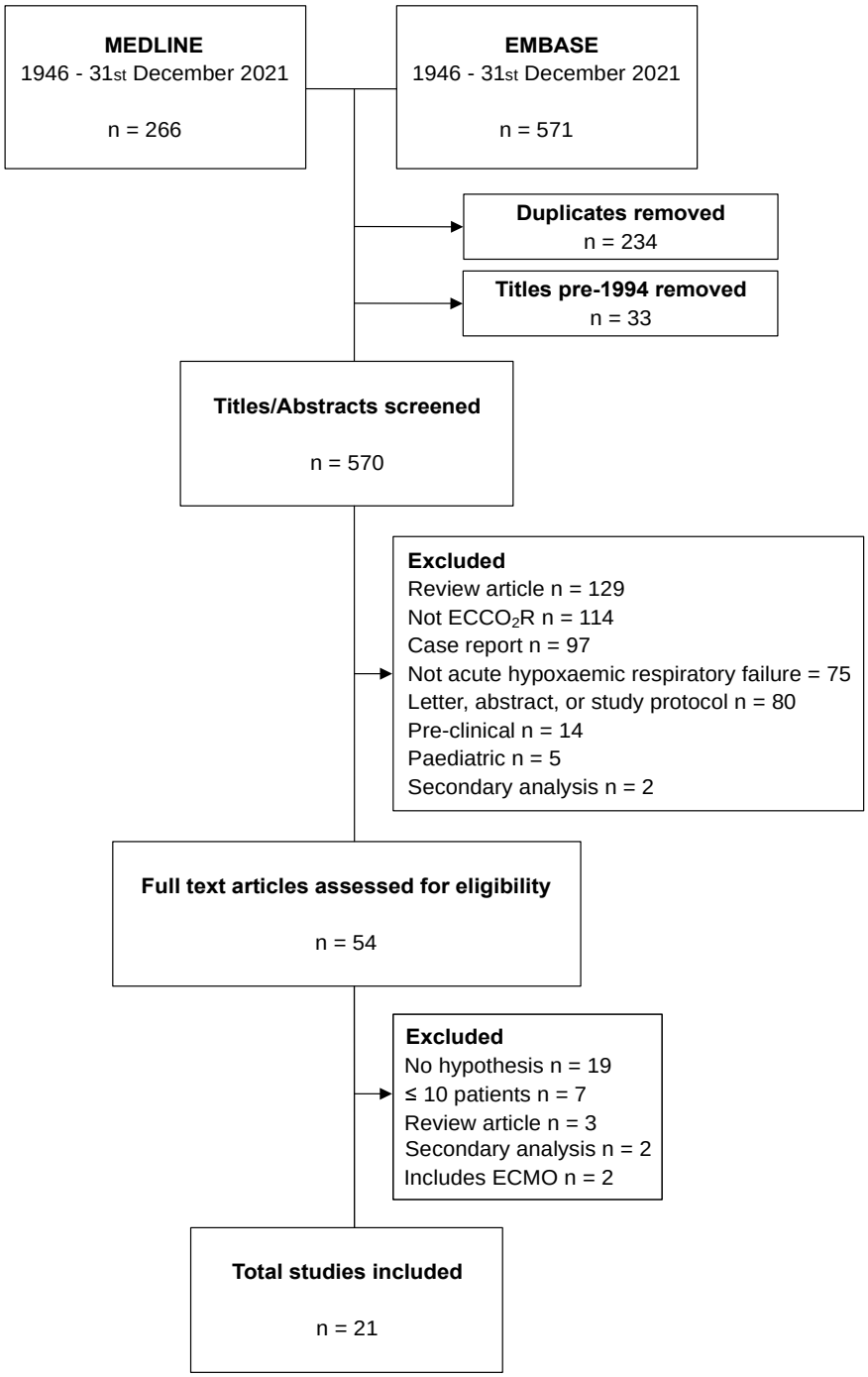
Data are presented as mean ± SD or median (IQR).

**Supplementary Table 9.** Ongoing clinical trials of ECCO2R in acute hypoxaemic respiratory failure.

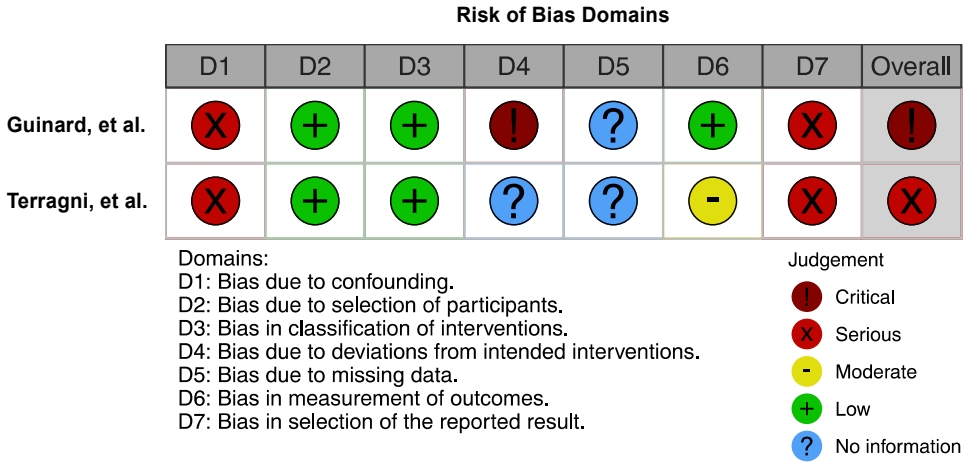
| Study | Design | Start date | Completion date | Status | n total | Country | Record identifier |
|---|---|---|---|---|---|---|---|
| Low-flow extracorporeal carbon dioxide removal in covid-19 associated acute respiratory distress syndrome | Observational | May, 2020 | June, 2020 | Recruiting | 20 | Germany | NCT04351906 |
| Post-market study of low-flow $ECCO_2R$ using Prisma-Lung+ | Observational | April, 2021 | June, 2022 | Recruiting | 50 | France | NCT04617093 |
| Registry of the experience of extracorporeal $CO_2$ removal in intensive care units (REXECOR) | Registry | January, 2016 | June, 2022 | Recruiting | 200 | France | NCT02965079 |
| $ECCO_2R$ – mechanical power study | Observational | March, 2019 | March, 2024[a] | Recruiting | 15 | Italy | NCT03939260 |
| Use of extracorporeal $CO_2$ 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[a] | 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 |

[a] – estimated completion date.

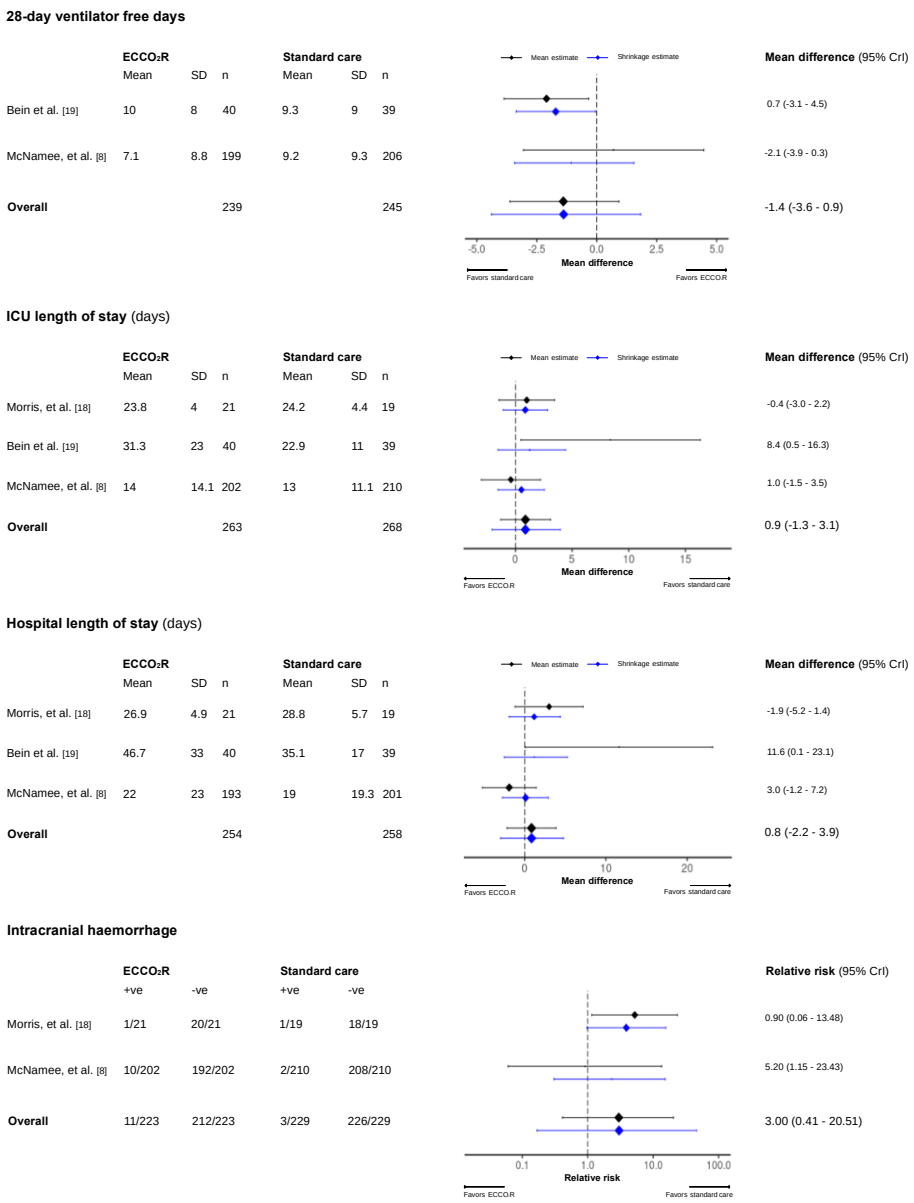
$ECCO_2R$ – extracorporeal carbon dioxide removal.



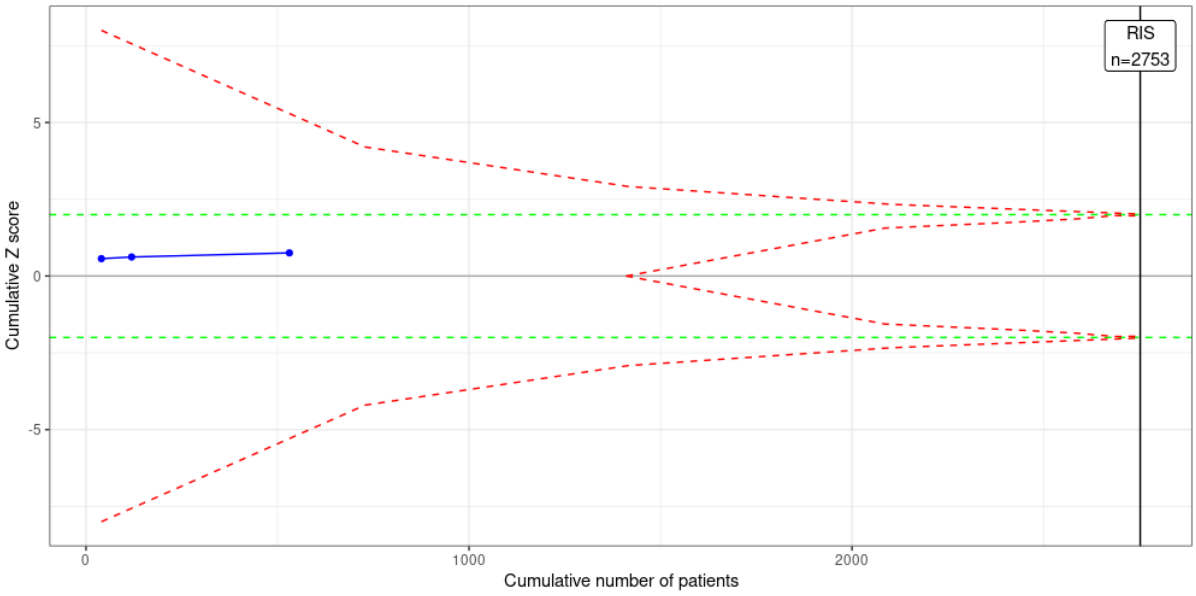

**Supplementary Figure 1. Inclusion diagram.** $ECCO_2R$ – extracorporeal carbon dioxide removal; ECMO – extracorporeal membrane oxygenation




**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. $ECCO_2R$ – 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.