Latest results from the REST trial

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Acknowledgements and disclosures

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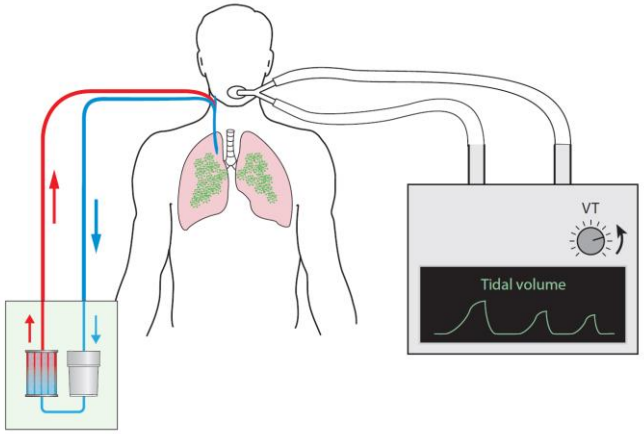
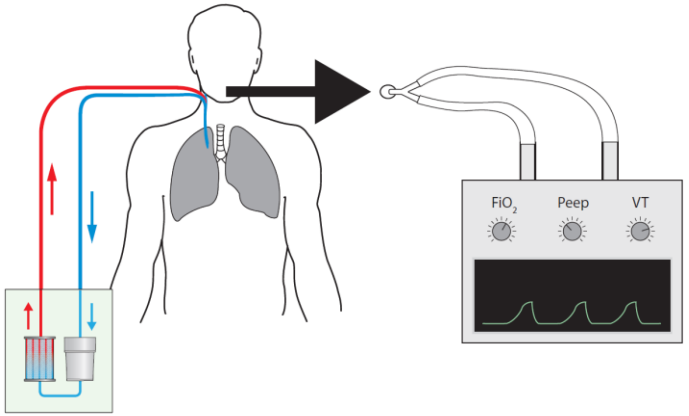
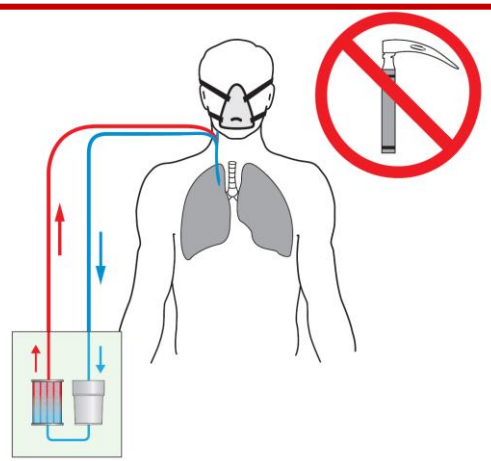
Potential role of $ECCO_2R$ in acute respiratory failure

Lower tidal volume ventilation

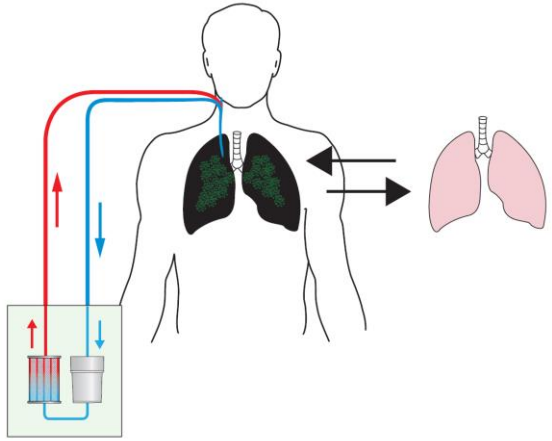


Facilitating extubation





Preventing intubation



Bridge to lung transplant

Boyle A et al Lancet Respiratory Medicine 2018; 6: 874–84

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The REST trial

In adult patients requiring invasive mechanical ventilation for acute hypoxaemic respiratory failure, does lower tidal volume ventilation facilitated by $ECCO_2R$ reduce mortality at 90 days

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure

The REST Randomized Clinical Trial

James J. McNamee, MB, ChB; Michael A. Gillies, MD; Nicholas A. Barrett, MB, ChB; Gavin D. Perkins, MD; William Tunnicliffe, MSc; Duncan Young, DM; Andrew Bentley, MD; David A. Harrison, PhD; Daniel Brodie, MD; Andrew J. Boyle, MB, ChB; Jonathan E. Millar, PhD; Tamas Szakmany, PhD; Jonathan Bannard-Smith, MB, ChB; Redmond P. Tully, MBBS; Ashley Agus, PhD; Clíona McDowell, MSc; Colette Jackson; Daniel F. McAuley, MD; for the REST Investigators

JAMA 2021;326:1013–1023

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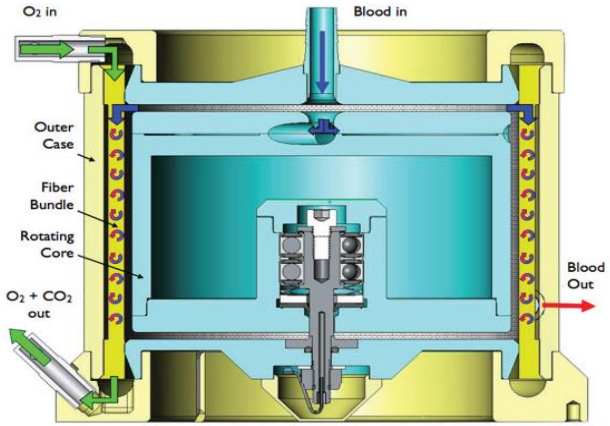
Intervention



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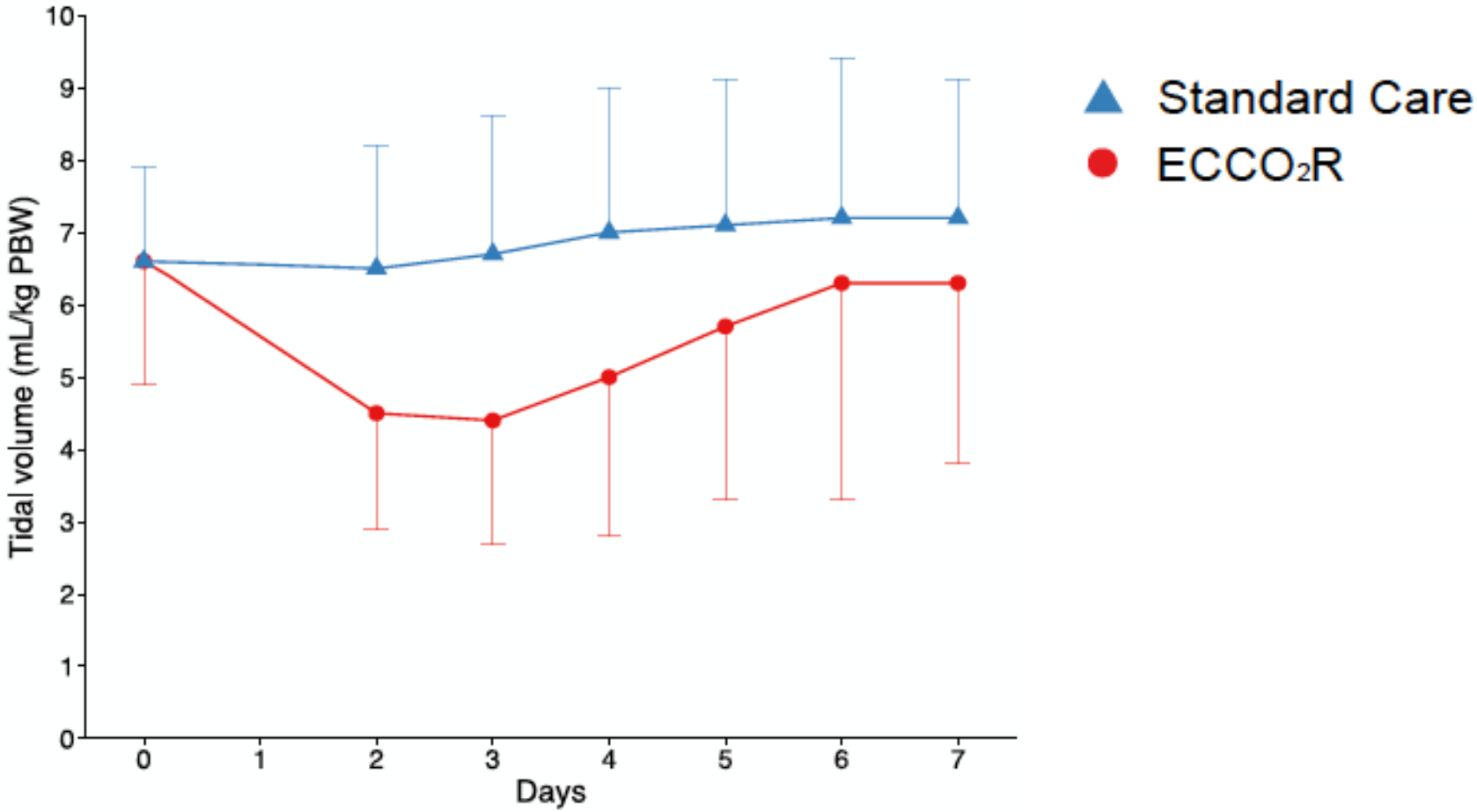
Tidal volume reduction



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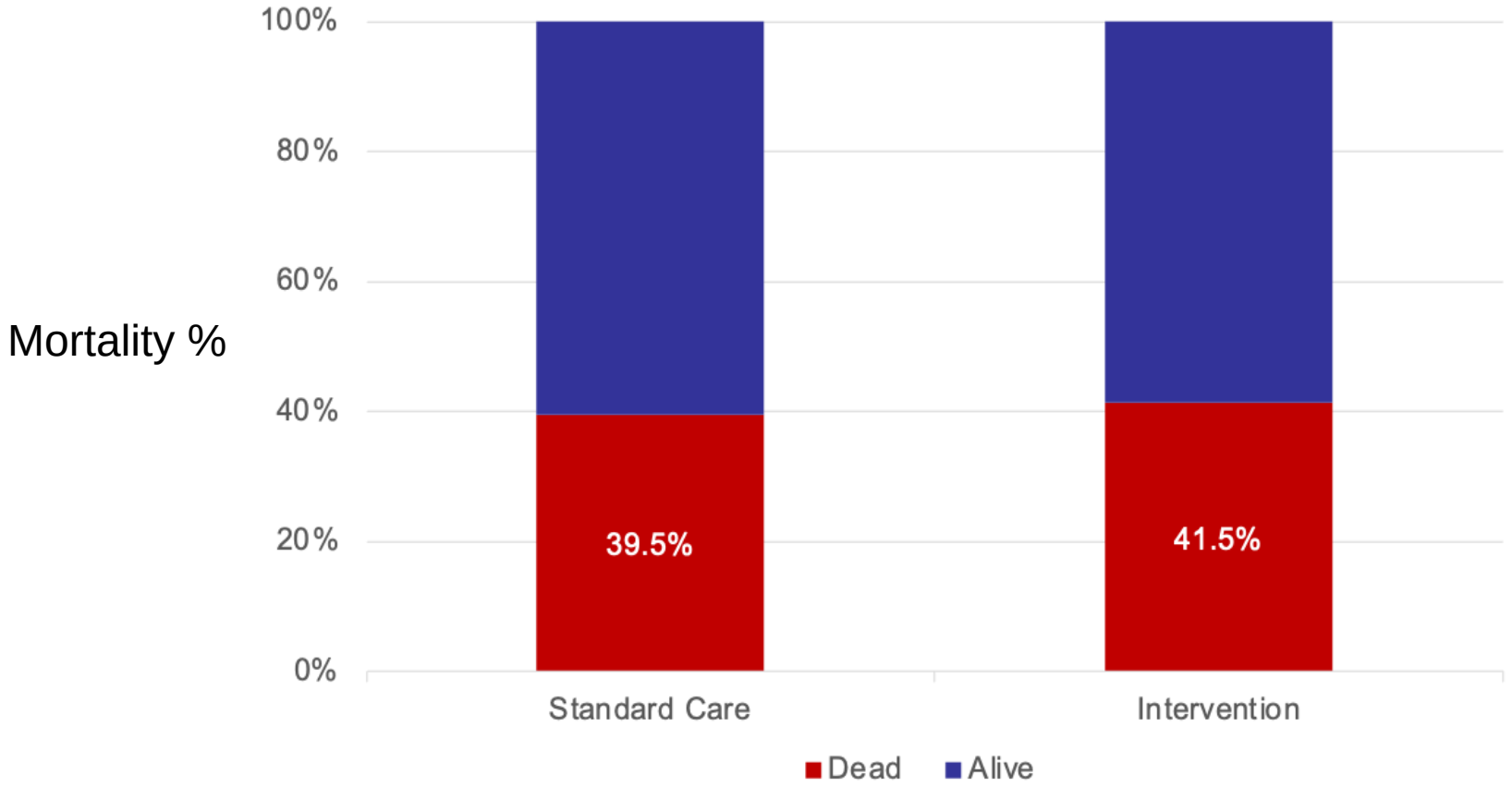
Primary outcome

Mortality 90 days after randomisation



Risk Ratio	1.1 (95% CI, 0.8 to 1.3); p=0.68
Adjusted analysis	1.1 (95% CI, 0.9 to 1.4); p=0.29
Sensitivity analysis	1.0 (95% CI, 0.8 to 1.3); p=0.90
Per Protocol analysis	1.1 (95% CI, 0.9 to 1.4); p=0.39

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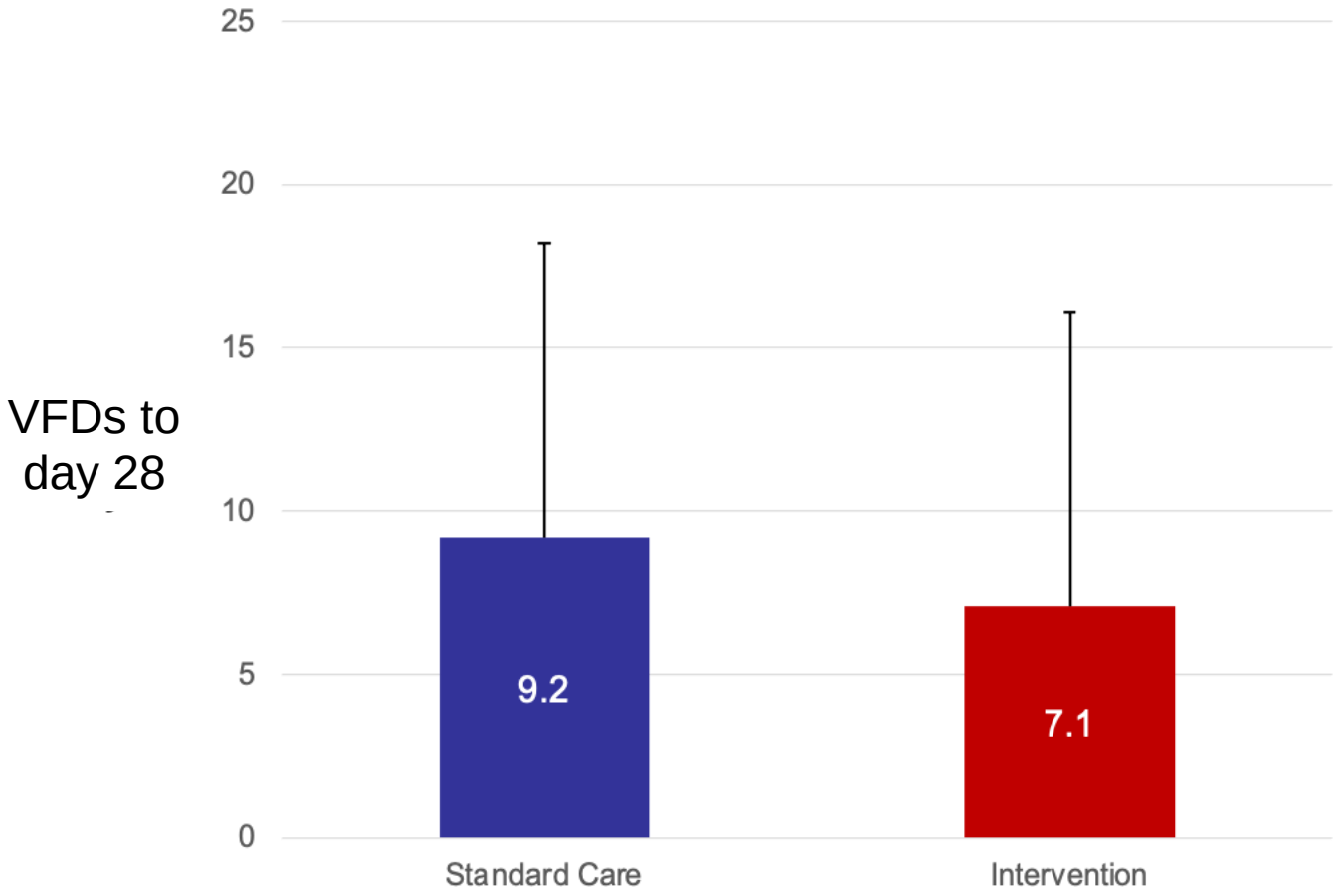
Secondary outcomes

Ventilator Free Days



Mean difference 2.1d (95% CI, 0.3 to 3.8); p=0.02

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Outcomes at 1 year

	Intervention	Standard care	p-value
SGRQ score	40.9 (27.1)	40.9 (26.4)	1.00
PTSS-14 score	34.3 (19.8)	38.8 (22.2)	0.25
Cognitive impairment			
None	30 (50.0%)	27 (48.2%)	0.41
Mild	20 (33.3%)	23 (41.1%)	
Moderate	10 (16.7%)	5 (8.9%)	
Severe	0 (0.0%)	1 (1.8%)	
EQ-5D-5L utility score	0.56 (0.36)	0.56 (0.34)	0.95

Boyle AJ et al. Thorax 2022;0:1–8.

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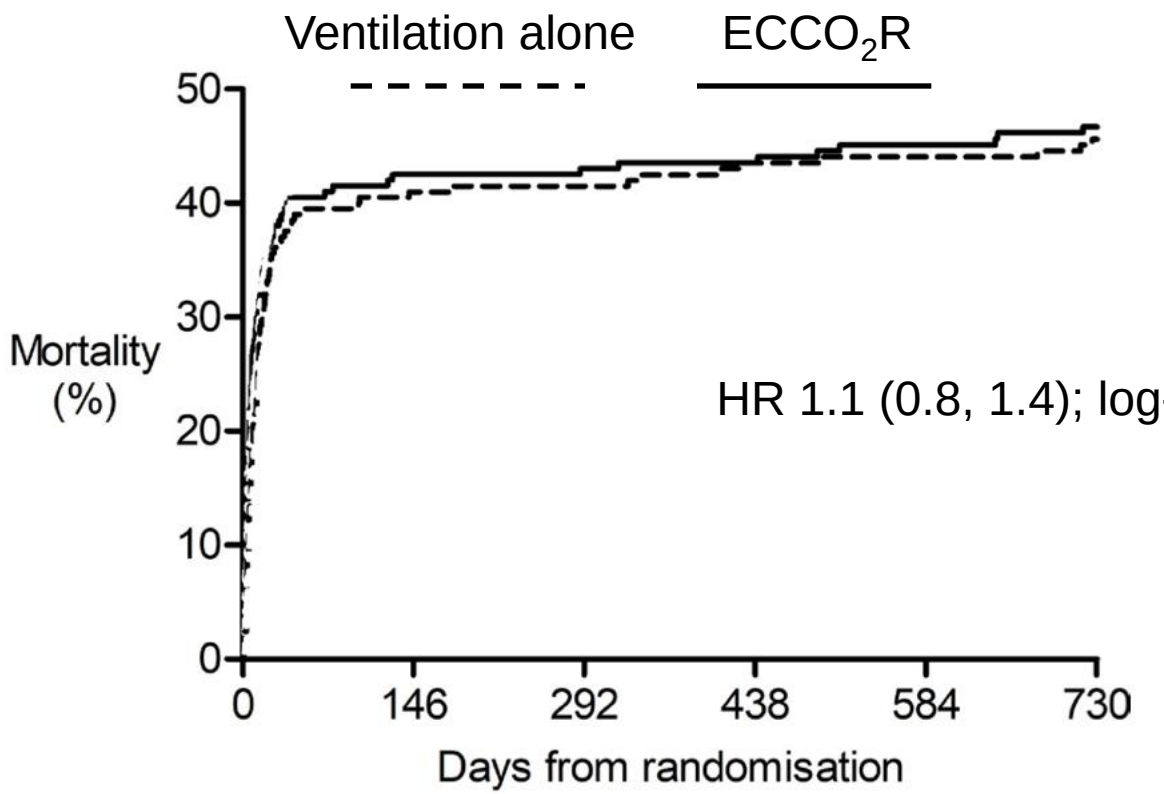
Mortality at 2 years



HR 1.1 (0.8, 1.4); log-rank p=0.61

Number at risk						
Standard care	205	119	118	108	107	104
Intervention	200	113	112	107	104	101

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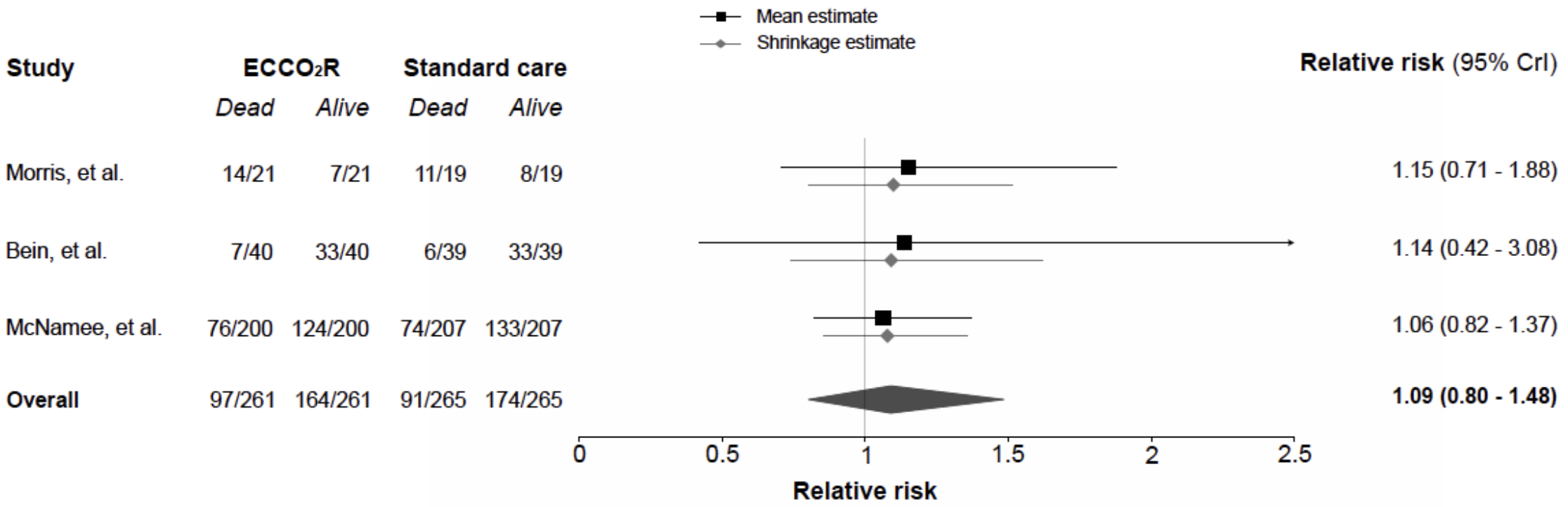
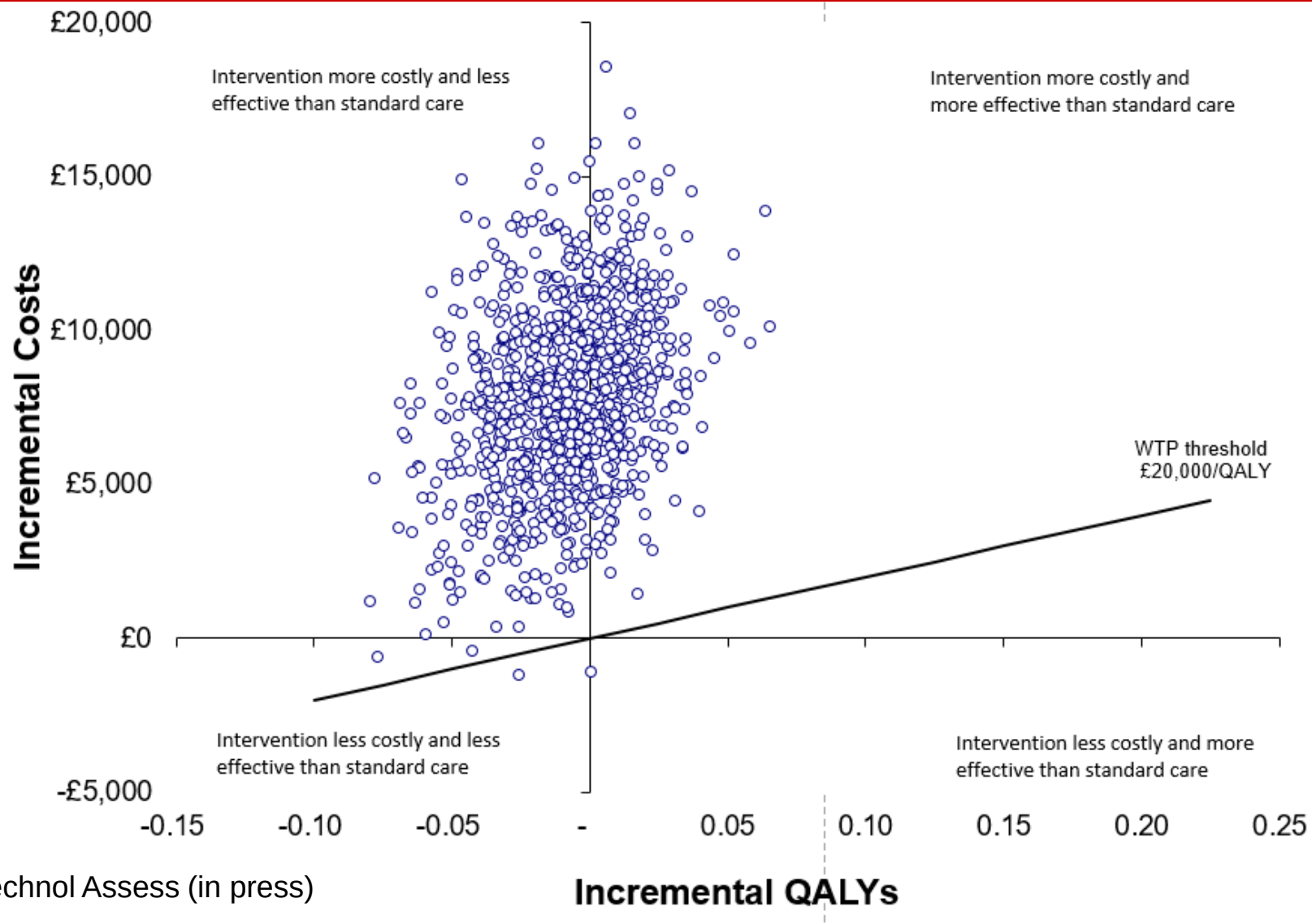
Summary of evidence

28/30-day (or latest) **mortality**



Millar JE et al. Eur Respir Rev 2022; 31: 220030

Cost-effectiveness analysis at 1 year



Agus A et al. Health Technol Assess (in press)

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$ECCO_2R$ and lower TV ventilation and cardiac function

	Normal value	Baseline			Post randomisation		
		$ECCO_2R$ (n=13)	Usual care (n=8)	P-value	$ECCO_2R$	Usual care	P-value
Primary Outcome							
TAPSE, mean (SD), mm	≥17	21.3 (3.7)	19.5 (3.4)	0.29	21.3 (5.4) n=12	20.1 (3.2) n=7	0.60
Acute cor pulmonale, n (%)	Absent						
Absent		8 (80.0)	5 (83.3)	0.87	8 (72.7)	5 (71.4)	0.95
Present		2 (20.0)	1 (16.7)		3 (27.3)	2 (28.6)	

McGuigan PJ et al. Crit Care Exp 2024;6:e1028

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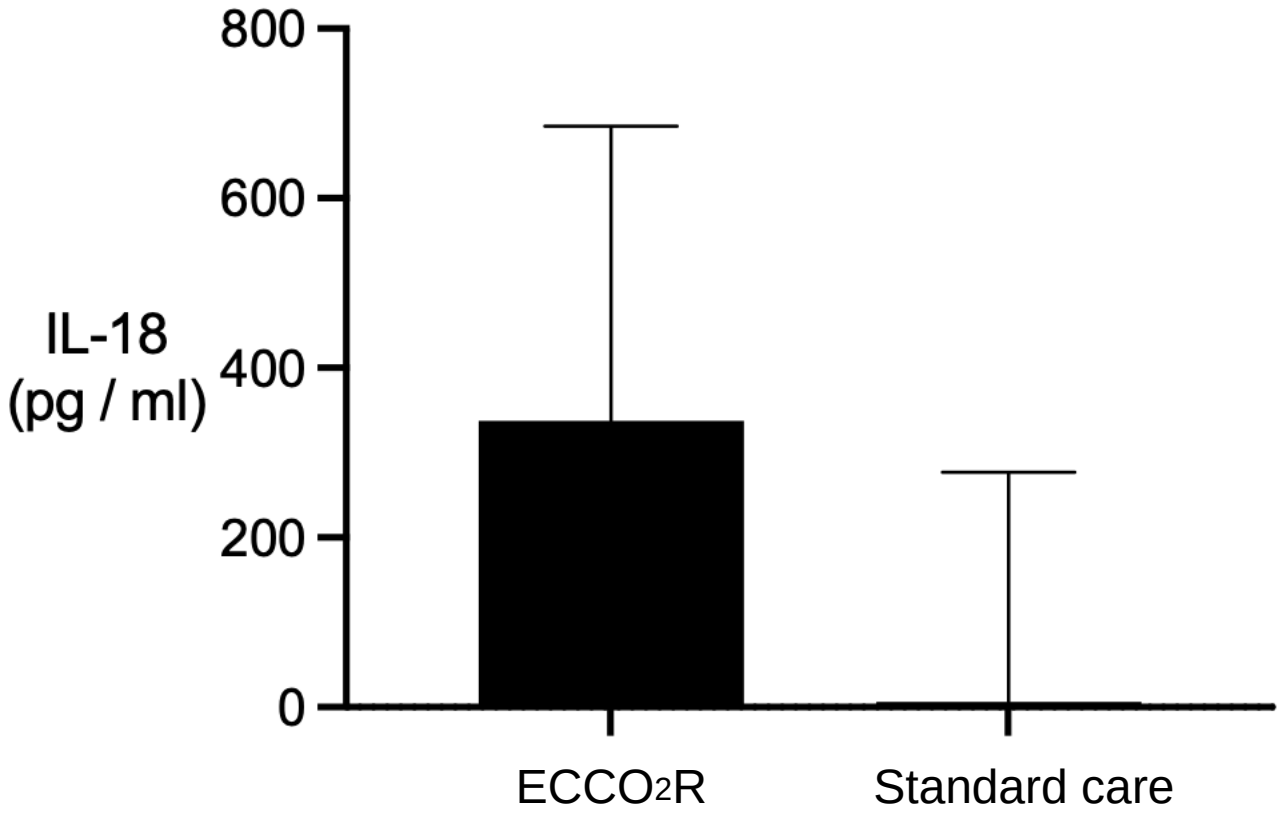
$ECCO_2R$ and lower TV ventilation increases IL-18 at day 3



Unpublished data

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Where we are now?

- Site selection
- Population
- Device
  - Efficacy
  - Adverse effects

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The site clinicians conducting the trial didn't know what they were doing

- Managed in ICU and not a complicated ICU intervention
  - RRT plus
- Extensive training programme
- Support provided for initial patients recruited to intervention
- Sites
  - No difference in primary outcome in REST by volume
  - Sensitivity analysis excluding initial 2 patients similar results

I’m an expert and do $ECCO_2R$ better than anyone else

- Need to do the trial but manage bias
- If can only be delivered by the expert then not generalizable
- Data from hypercapnic respiratory failure

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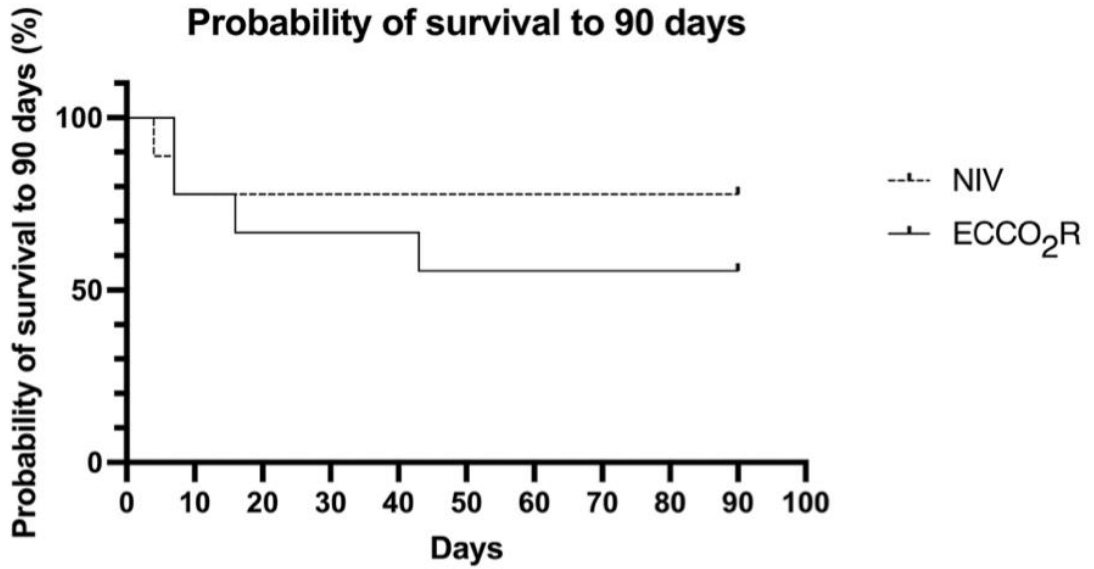
Preventing intubation and facilitating weaning



Days	0	4	7	16	43	90
$ECCO_2R$	9		9	7	6	5
NIV	9	9	8			7

Barrett NA et al. Annals of intensive care. 2022;12(1):36.

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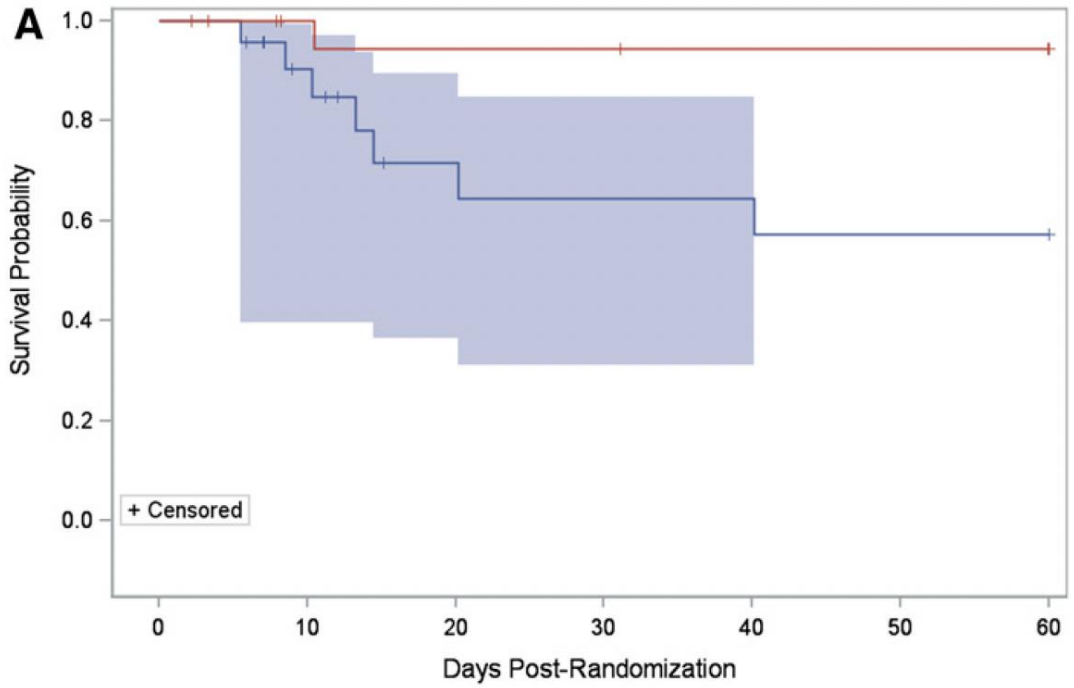
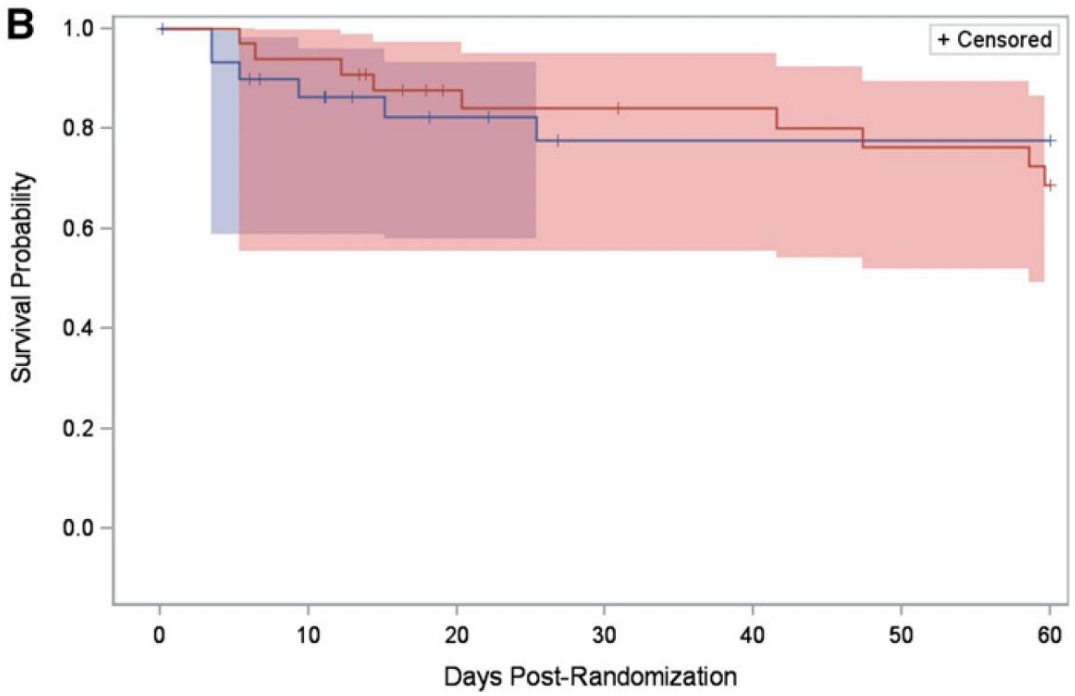
The VENT-AVOID trial

NIV stratum



IMV stratum



$ECCO_2R$
Standard care

Duggal A et al. AJRCCM 209;5:529–542

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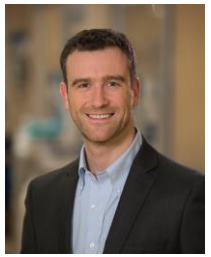
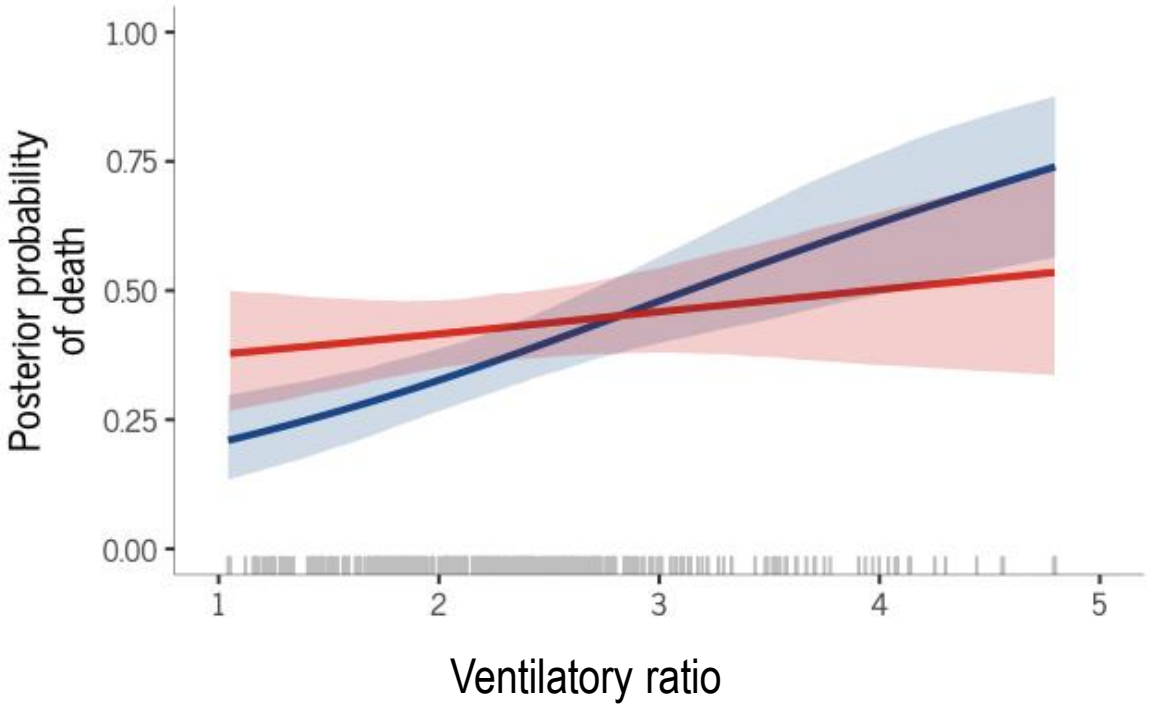
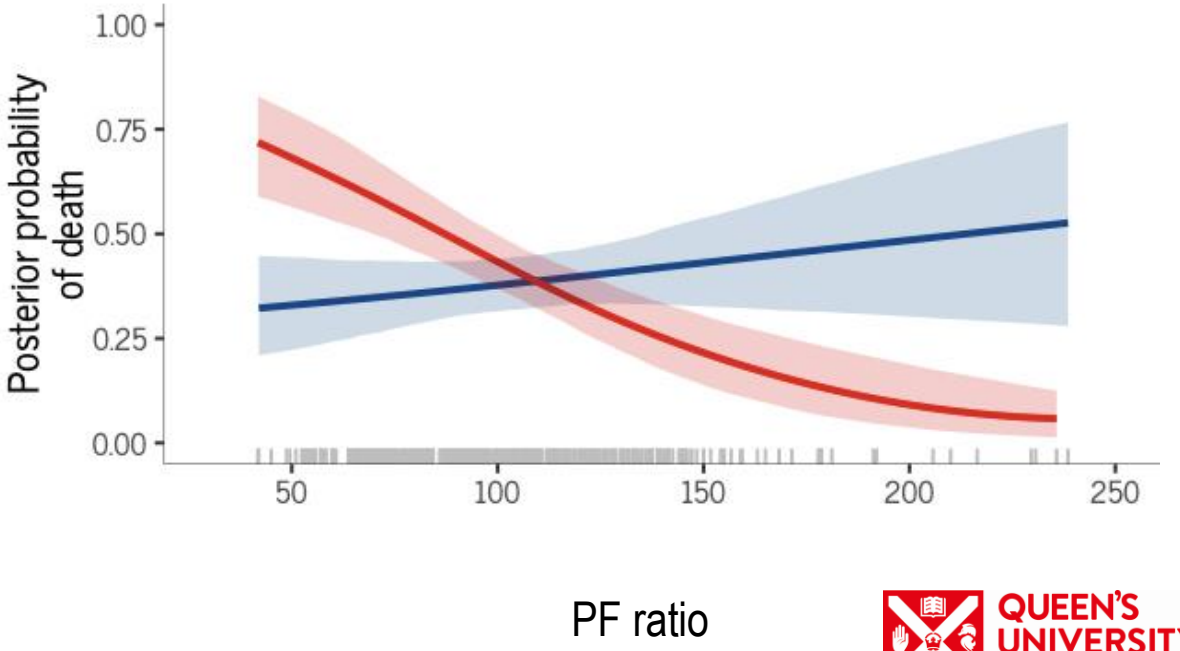
Heterogeneity of treatment response
Ventilatory ratio and PF ratio



$ECCO_2R$ Ventilation alone





Dianti J et al. NEJM Evid 2023;2(5)

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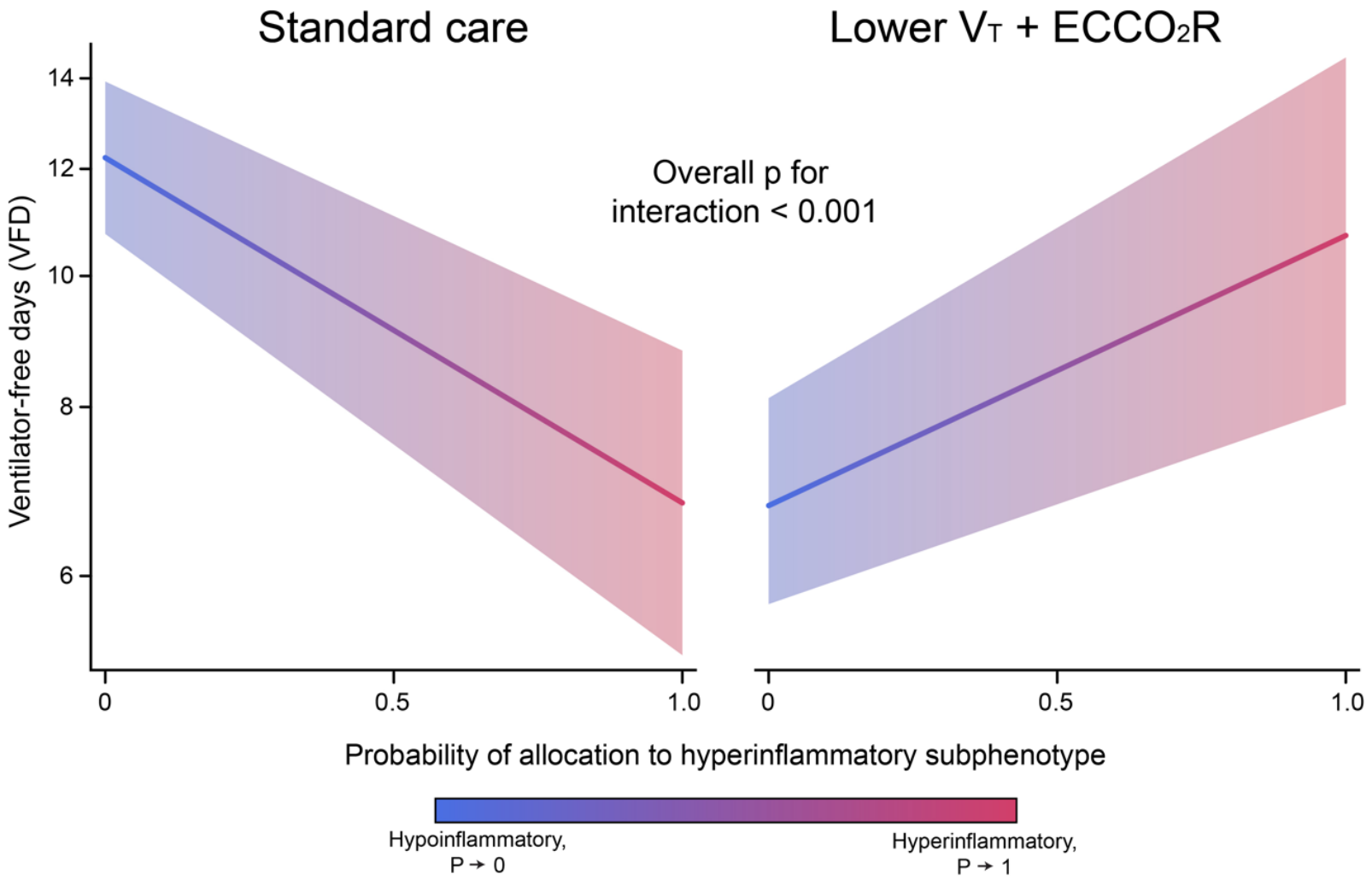
Heterogeneity of treatment response
Inflammatory phenotypes



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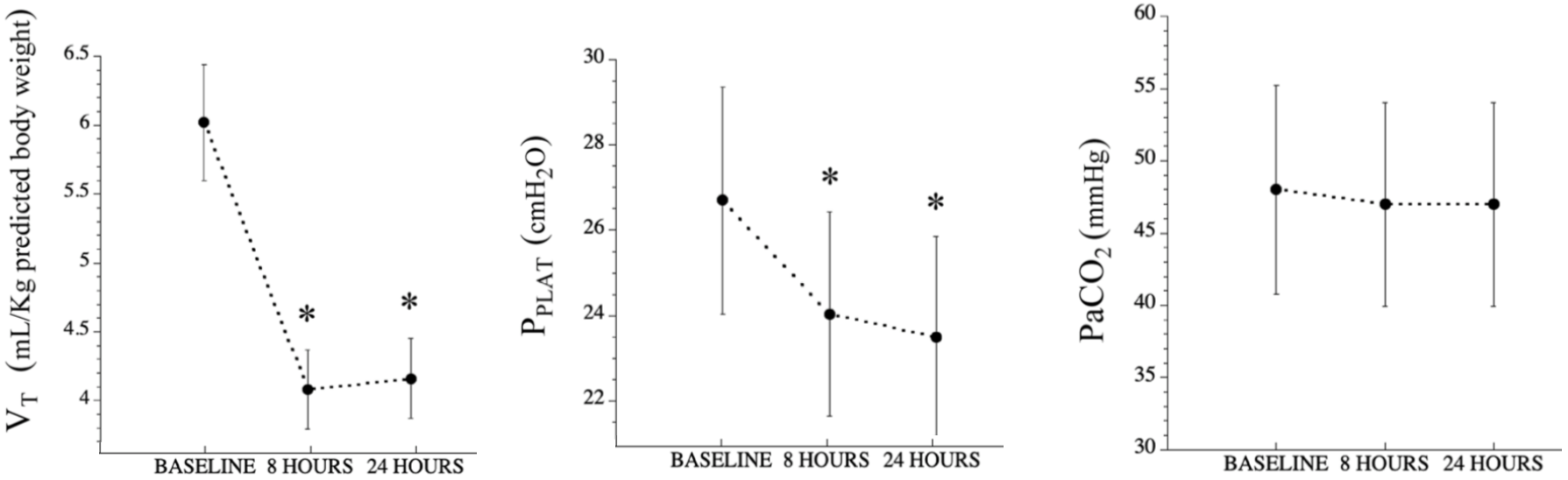
Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study

Alain Combes[1], Vito Fanelli[2], Tai Pham[3], V. Marco Ranieri[4*] and On behalf of the European Society of Intensive Care Medicine Trials Group and the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CO2 Removal for New-Onset moderate to severe ARDS" (SUPERNOVA) investigators



Combes A et al. Intensive Care Medicine 2019

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Complications of $ECCO_2R$ – related to flow?

Efficacy and safety of lower versus higher CO_2 extraction devices to allow ultraprotective ventilation: secondary analysis of the SUPERNOVA study

Table 2 Numbers of patients experiencing $ECCO_2R$-related adverse events occurring between enrolment and day 28

Patients experiencing $ECCO_2R$-related adverse events n (%)	Lower CO_2 extraction (N=33)	Higher CO_2 extraction (N=62)
Mechanical		
Lung clotting membranes	3 (9)	10 (16)
Leading to circuit change	1 (3)	5 (8)
Leading to $ECCO_2R$ discontinuation	2 (6)	5 (8)
Pump malfunction	2 (6)	1 (2)
Mortality	30%	42%
Bleeding	9 (27)	4 (6)†
Related to cannula insertion	2 (6)	1 (2)
At cannula site	6 (18)	1 (2)*
Significant	3 (9)	3 (5)
Infectious complications	2 (6)	0 (0)
Thrombocytopenia	4 (12)	8 (13)
Hypofibrinogenemia	0 (0)	2 (3)

RESEARCH Open Access

A 2-year multicenter, observational, prospective, cohort study on extracorporeal CO_2 removal in a large metropolis area

n (%)	Hemolung *n* = 53	iLa Activve *n* = 17	*p*
Catheterization failure	2 (4)	1 (4)	1
Biological hemolysis	15 (28)	0 (0)	0.033
Clinically significant hemolysis	6 (11)	0 (0)	0.147
Bleeding	16 (30)	1 (6)	0.042
Membrane clotting	4 (8)	7 (41)	< 0.001
Catheter infection	0 (0)	1 (6)	0.075
Device malfunction	4 (8)	2 (12)	0.638
$ECCO_2R$-related death	3 (6)	0 (0)	0.316

Combes et al. Thorax 2019 74:1179-1181
Augy et al. Journal of Intensive Care 2019 7:45

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$ECCO_2R$ and lower TV ventilation and haemolysis

Change in free haemoglobin (baseline to day 3)

	$ECCO_2R$ (n = 36)	**Standard care** (n = 37)	**P-value**
Free haemoglobin (mg / dL)	-1.21 [22.26]	-1.02 [22.16]	0.987

Unpublished data

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REST - trial design issues

- Potential benefits of TV reduction offset by
  - Other determinants of VILI eg respiratory rate and PEEP
  - Pro-inflammatory effect of ECLS
- “Dose” delivered suboptimal

- Hypothesis that further reduction in ventilation is beneficial may be wrong
  - Test effect of maximal reduction in ventilation in the most injured lungs

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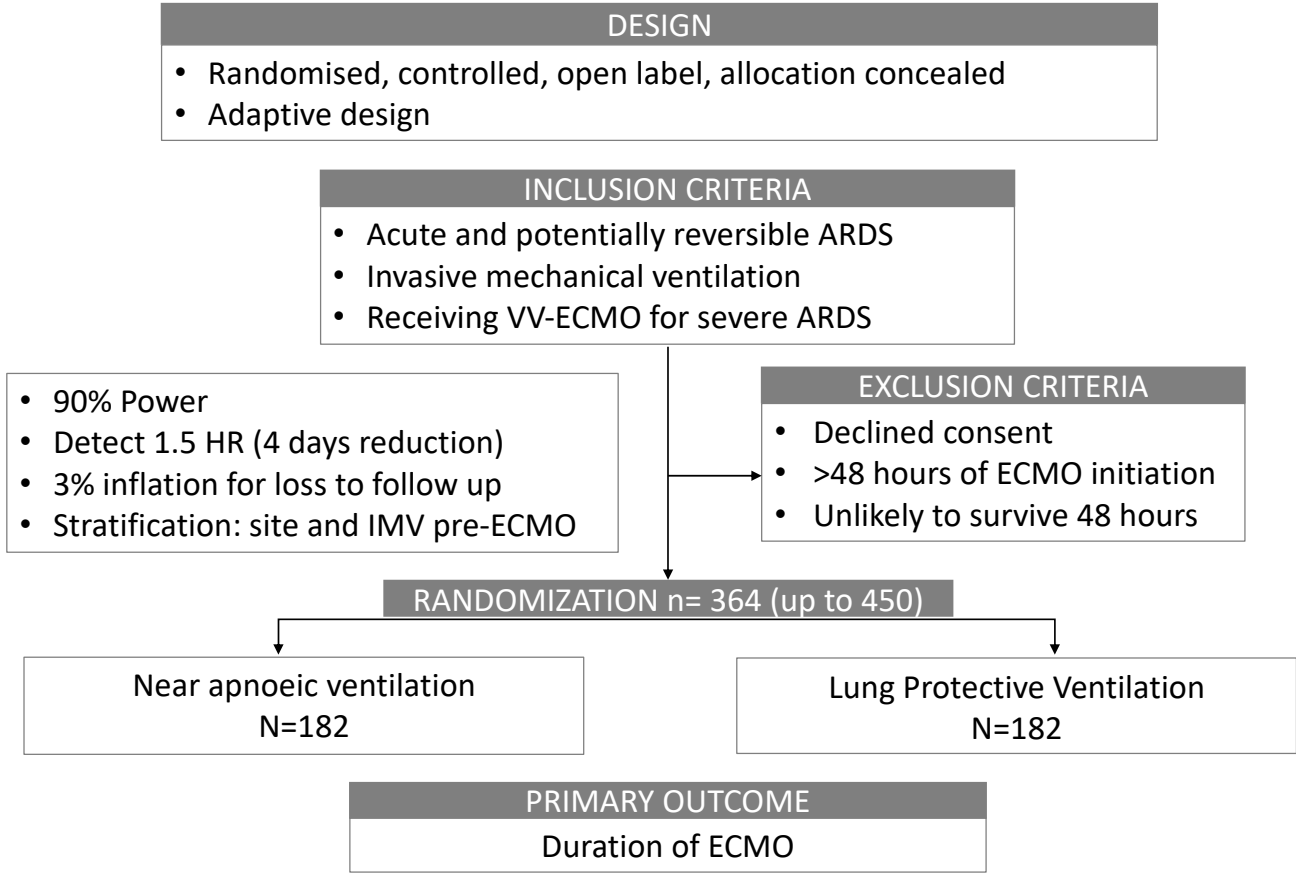
ROMEO

Population: Adult patients with severe acute respiratory failure requiring ECMO support

Intervention: Near apnoeic ventilation at two breaths per minute

Control arm: Standard Care

Outcome: Duration of ECMO support



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Conclusions

- In the REST trial lower tidal volume ventilation facilitated by $ECCO_2R$ did not improve outcomes
- $ECCO_2R$ use currently only in the setting of clinical trials
- Potential benefits may be offset by pro-inflammatory effects of $ECCO_2R$
- Need clinical trial to test hypothesis that maximal reduction in ventilation in the most injured lungs receiving ECLS is beneficial
- Should identify if specific patient population has greater treatment responsiveness

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