

Supplemental Online Content

McNamee JJ, Gillies MA, Barrett NA, et al; for the REST Investigators. 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. *JAMA*. Published online August 31, 2021. doi:10.1001/jama.2021.13374

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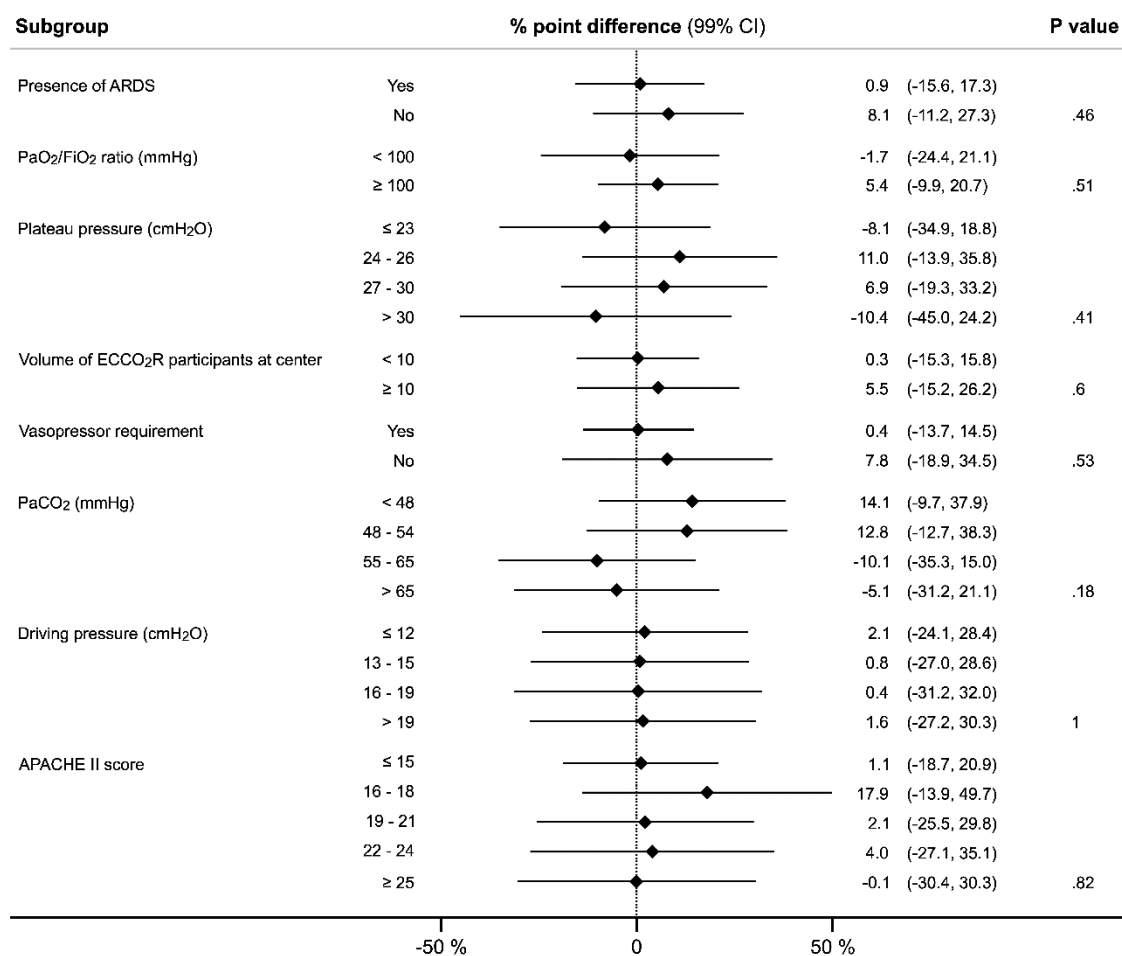
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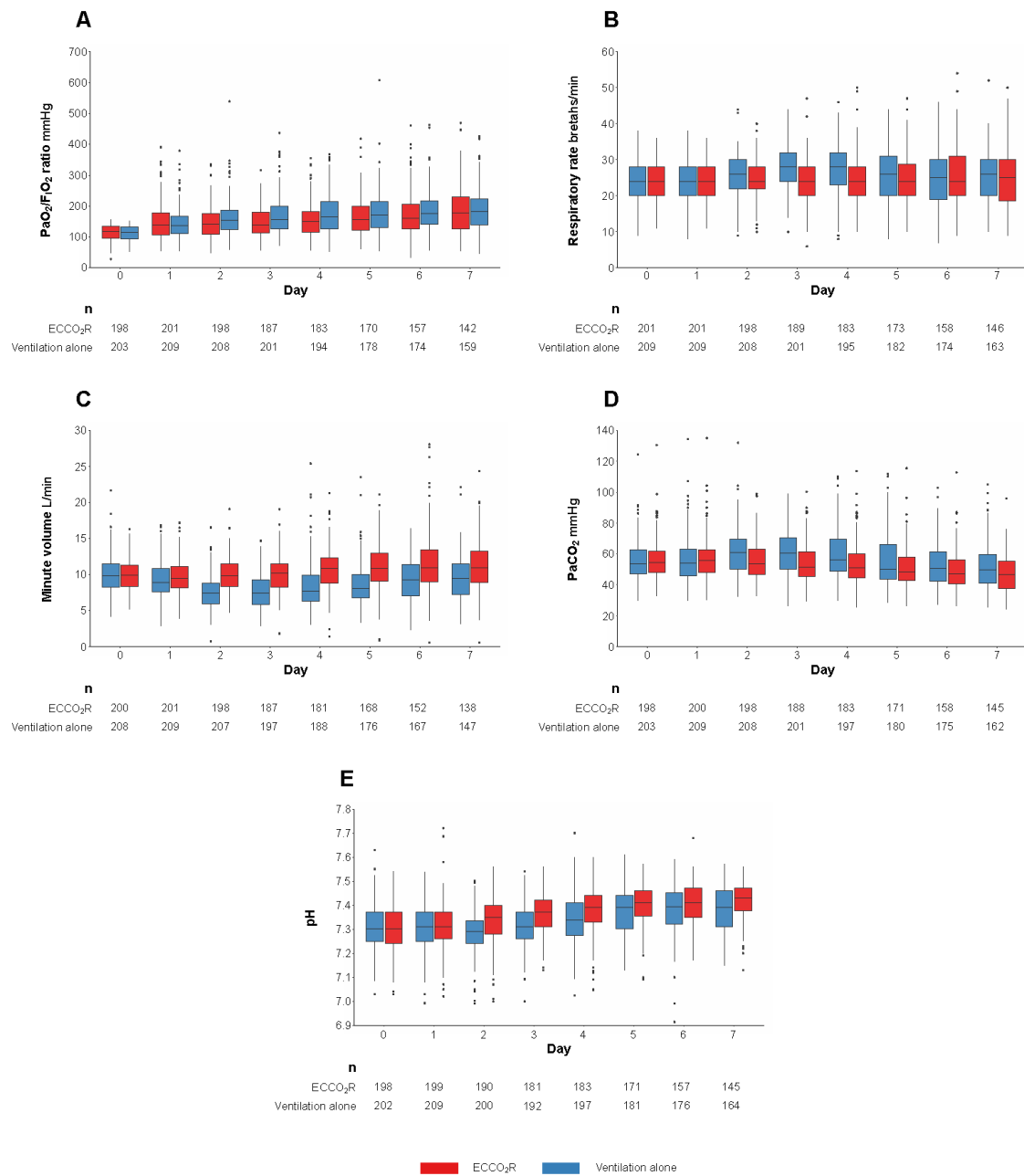
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This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Treatment-by-subgroup interactions



eFigure 2. Physiological parameters by treatment group to day 7; PaO₂/FiO₂ Ratio (A), Respiration Rate (B), Minute Ventilation (C), Partial Pressure of Arterial Carbon Dioxide (PaCO₂) (D) and pH (E) to day 7.



eTable 1. Pre-specified secondary endpoints.

Tidal volume (mL/kg predicted body weight) at day 2 and day 3
Ventilator free days at 28 days
Duration of ventilation in survivors
Need for ECMO up to Day 7
Mortality rate at 28 days, 6 months and 1 year
Health Related Quality of Life at 6 months and 1 year
Adverse event rate
Health and Social Care Service costs at 6 months and 1 year
St George's Respiratory Questionnaire at 1 year and need for home oxygen at 6 months and 1 year
Post Traumatic Stress Syndrome Questionnaire at 1 year
Montreal Cognitive Assessment or AD8 Dementia Screening Interview at 1 year

eTable 2. Enrollment by site. The median no. of enrollees by site was 8, IQR [4 to 13].

Study Site	ECCO ₂ R	Ventilation alone
1	21	21
2	18	20
3	14	14
4	12	14
5	8	8
6	8	10
7	7	6
8	7	7
9	7	6
10	6	8
11	6	6
12	6	7
13	6	5
14	6	5
15	5	9
16	5	5
17	4	5
18	4	4
19	4	4
20	4	5
21	4	4
22	3	4
23	3	4
24	3	4
25	3	2
26	3	3
27	3	2
28	3	2

Study Site	ECCO ₂ R	Ventilation alone
29	3	4
30	2	1
31	2	1
32	2	3
33	2	2
34	2	1
35	2	0
36	1	0
37	1	1
38	1	1
39	1	0
40	0	1
41	0	1

eTable 3. Treatment after trial entry.

	ECCO₂R n =202 (49%)	Ventilation alone n =210 (51%)
No. of days on ECCO ₂ R ^a	4 (2), n=174	2, n=1 ^b
No. of patients receiving non-protocol ECCO ₂ R therapy		
ECCO ₂ R therapy > 7days	10 (5%)	
ECCO ₂ R therapy in standard care group		1 (0%)
Reasons for ECCO ₂ R Discontinuation		
ECCO ₂ R therapy successfully weaned	50 (28%)	
7 days post randomization	33 (18%)	
Safety concern	14 (8%)	
Escalation to ECMO	12 (7%)	
Discontinuation of active medical treatment	9 (5%)	
Death	19 (11%)	
Other	42 (24%)	

^a17 (8%) intervention patients did not commence ECCO₂R.

^b1 patient on ECCO₂R for 2 days

eTable 4. Daily mean (SD) physiological parameters to day 7.

	ECCO₂R	Ventilation alone	Mean Difference (95% CI)
Tidal volume mL/kg PBW			
Day 2	4.5(1.6) n=198	6.5(1.7) n=207	-2.0(-2.3, -1.7)
Day 3	4.4(1.7) n=187	6.7(1.9) n=197	-2.3(-2.7, -2.0)
Day 4	5.0(2.2) n=181	7.0(2.0) n=188	-2.0(-2.4, -1.6)
Day 5	5.7(2.4) n=168	7.1(2.0) n=176	-1.3(-1.8, -0.9)
Day 6	6.3(3.0) n=152	7.2(2.2) n=167	-0.9(-1.5, -0.3)
Day 7	6.3(2.5) n=138	7.2(1.9) n=147	-0.9(-1.4, -0.4)
Tidal volume mL/kg PBW ^a			
Day 2	4.2(1.2) n=148	6.5(1.7) n=207	-2.4(-2.7, -2.0)
Day 3	3.8(0.8) n=120	6.7(1.9) n=197	-2.9(-3.3, -2.5)
PaO ₂ /FiO ₂ ratio			
Day 1	153.1(84.0) n=201	145.1(48.3) n=209	8.0(-5.3, 21.2)
Day 2	147.8(52.5) n=198	161.1(57.1) n=208	-13.3(-24.1, -2.6)
Day 3	147.9(48.5) n=187	167.0(60.5) n=201	-19.1(-30.1, -8.2)
Day 4	160.8(92.1) n=183	171.8(62.2) n=194	-11.0(-26.8, 4.8)
Day 5	171.3(102.3) n=170	178.9(69.9) n=178	-7.6(-26.0, 10.8)
Day 6	175.3(69.9) n=157	182.6(66.0) n=174	-7.3(-22.0, 7.4)
Day 7	187.8(77.0) n=142	188.1(67.6) n=159	-0.2(-16.6, 16.2)
PEEP (cmH ₂ O)			
Day 1	11.0(3.1) n=201	10.5(3.0) n=209	0.5(-0.1, 1.1)
Day 2	11.3(3.2) n=197	10.6(3.0) n=206	0.7(0.1, 1.3)
Day 3	11.3(3.1) n=187	10.0(3.1) n=197	1.4(0.7, 2.0)
Day 4	11.1(3.2) n=178	9.9(2.8) n=187	1.2(0.6, 1.8)
Day 5	10.8(3.4) n=162	9.6(2.8) n=175	1.2(0.6, 1.9)
Day 6	10.0(3.2) n=147	9.3(2.8) n=167	0.7(0.0, 1.3)
Day 7	9.7(3.5) n=132	9.1(2.5) n=147	0.6(-0.2, 1.3)
Plateau Pressure (cmH ₂ O)			
Day 1	25.9(5.2) n=158	26.1(5.3) n=160	-0.2(-1.4, 0.9)
Day 2	23.5(5.2) n=155	25.7(5.4) n=161	-2.3(-3.4, -1.1)
Day 3	22.8(5.3) n=152	24.1(6.4) n=155	-1.3(-2.6, 0.1)
Day 4	22.2(5.6) n=147	23.7(6.5) n=135	-1.6(-3.0, -0.1)
Day 5	22.7(5.9) n=122	23.9(7.2) n=111	-1.2(-2.9, 0.4)
Day 6	23.0(5.9) n=108	22.2(7.4) n=98	0.8(-1.1, 2.6)
Day 7	22.1(6.4) n=89	22.6(6.9) n=86	-0.5(-2.5, 1.5)
Driving Pressure (cmH ₂ O)			
Day 1	14.9(5.3) n=158	15.8(5.5) n=160	-0.9(-2.1, 0.3)
Day 2	12.1(4.9) n=154	15.3(5.7) n=160	-3.2(-4.4, -2.1)
Day 3	11.4(4.7) n=152	14.2(6.1) n=153	-2.8(-4.0, -1.6)
Day 4	11.1(5.3) n=145	13.8(6.2) n=134	-2.7(-4.1, -1.3)
Day 5	11.7(5.6) n=119	14.1(6.2) n=110	-2.4(-3.9, -0.9)
Day 6	12.5(5.6) n=107	12.6(6.7) n=97	-0.1(-1.8, 1.6)
Day 7	12.3(6.2) n=88	13.2(6.1) n=86	-0.9(-2.7, 0.9)
PaCO ₂ mmH			
Day 1	55.8(14.4) n=200	56.6(13.8) n=209	-0.8(-3.5, 2.0)
Day 2	60.8(14.6) n=198	56.0(14.7) n=208	4.8(2.0, 7.7)
Day 3	60.8(14.3) n=188	54.2(12.7) n=201	6.7(4.0, 9.4)
Day 4	59.0(15.7) n=183	53.3(14.0) n=197	5.7(2.8, 8.7)
Day 5	55.0(16.6) n=171	51.4(13.5) n=180	3.6(0.5, 6.8)
Day 6	53.2(14.4) n=158	49.4(12.9) n=175	3.8(0.8, 6.7)

	ECCO₂R	Ventilation alone	Mean Difference (95% CI)
Day 7	52.4(15.4) n=145	47.7(12.6) n=162	4.8(1.6, 7.9)
Respiratory Rate			
Day 1	23.9(5.02) n=201	23.9(5.24) n=209	0.01(-0.99, 1.01)
Day 2	26.6(5.70) n=198	24.6(5.38) n=208	1.95(0.87, 3.04)
Day 3	27.8(6.24) n=189	24.4(6.01) n=201	3.41(2.19, 4.63)
Day 4	27.0(7.09) n=183	24.4(6.53) n=195	2.61(1.23, 3.98)
Day 5	25.2(7.84) n=173	24.8(6.52) n=182	0.37(-1.13, 1.87)
Day 6	24.9(7.81) n=158	25.3(7.85) n=174	-0.39(-2.09, 1.30)
Day 7	25.4(7.41) n=146	24.8(7.65) n=163	0.58(-1.11, 2.27)
pH			
Day 1	7.31(0.09) n=199	7.31(0.10) n=209	-0.001(-0.02, 0.02)
Day 2	7.29(0.13) n=190	7.32(0.16) n=200	-0.03(-0.1, -0.002)
Day 3	7.32(0.09) n=181	7.35(0.16) n=192	-0.04(-0.1, -0.01)
Day 4	7.34(0.10) n=183	7.37(0.16) n=197	-0.03(-0.05, 0.0005)
Day 5	7.37(0.10) n=171	7.40(0.08) n=181	-0.03(-0.05, -0.01)
Day 6	7.38(0.10) n=157	7.41(0.08) n=176	-0.03(-0.05, -0.008)
Day 7	7.38(0.10) n=145	7.42(0.08) n=164	-0.03(-0.05, -0.01)
Minute Volume			
Day 1	9.2(2.6) n=201	9.7(2.3) n=209	-0.4(-0.9, 0.1)
Day 2	7.5(2.3) n=198	9.9(2.3) n=207	-2.4(-2.9, -2.0)
Day 3	7.6(2.5) n=187	10.1(2.6) n=197	-2.5(-3.0, -2.0)
Day 4	8.4(3.4) n=181	10.6(2.9) n=188	-2.2(-2.9, -1.6)
Day 5	8.6(3.0) n=168	11.0(3.3) n=176	-2.4(-3.1, -1.7)
Day 6	9.3(3.0) n=152	11.5(4.1) n=167	-2.2(-3.0, -1.4)
Day 7	9.7(3.1) n=138	11.3(3.5) n=147	-1.6(-2.4, -0.8)
CO₂ removal (ml/minute)			
Day 1	53.6(40.8) n=158		
Day 2	83.4(34.5) n=173		
Day 3	85.4(35.0) n=171		
Day 4	76.5(38.1) n=158		
Day 5	65.7(41.6) n=139		
Day 6	54.8(44.7) n=112		
Day 7	46.1(44.3) n=95		

*Per protocol population i.e. those who were on ECCO₂R on day 2 and 3 in the intervention arm

eTable 5. Mode of ventilation and use of adjunctive therapies.

	ECCO₂R	Ventilation alone	% Point Difference (95% CI)
Mandatory Ventilation			
Day 1	165(82.1%)	170(81.3%)	0.7(-6.7, 8.2)
Day 2	159(80.3%)	146(70.2%)	10.1(1.8, 18.4)
Day 3	148(77.9%)	120(59.4%)	18.5(9.5, 27.5)
Day 4	128(70.0%)	82(41.4%)	28.5(19.0, 38.1)
Day 5	92(52.3%)	54(29.5%)	22.8(12.9, 32.7)
Day 6	78(48.5%)	39(21.8%)	26.7(16.9, 36.5)
Day 7	59(39.1%)	32(18.9%)	20.1(10.4, 29.9)
Neuromuscular blockade			
Day 1	103(51.2%)	101(48.3%)	2.9(-6.8, 12.6)

	ECCO₂R	Ventilation alone	% Point Difference (95% CI)
Day 2	110(55.6%)	92(44.2%)	11.3(1.7, 21.0)
Day 3	100(52.4%)	66(32.7%)	19.7(10.1, 29.3)
Day 4	77(42.1%)	43(21.5%)	20.6(11.4, 29.7)
Day 5	57(32.4%)	30(16.3%)	16.1(7.3, 24.8)
Day 6	42(26.4%)	26(14.4%)	12.0(3.4, 20.5)
Day 7	35(23.5%)	20(11.7%)	11.8(3.5, 20.1)
Prone positioning			
Day 1	11(5.5%)	29(13.9%)	-8.4(-14.0, -2.8)
Day 2	18(9.1%)	27(13.0%)	-3.9(-10.0, 2.2)
Day 3	16(8.4%)	17(8.4%)	0.0(-5.5, 5.4)
Day 4	16(8.7%)	11(5.5%)	3.2(-1.9, 8.4)
Day 5	8(4.6%)	7(3.8%)	0.7(-3.4, 4.9)
Day 6	3(1.9%)	4(2.2%)	-0.3(-3.4, 2.7)
Day 7	5(3.4%)	6(3.5%)	-0.2(-4.1, 3.8)
Inhaled nitric oxide			
Day 1	5(2.5%)	4(1.9%)	0.6(-2.3, 3.4)
Day 2	7(3.5%)	4(1.9%)	1.6(-1.6, 4.8)
Day 3	5(2.6%)	3(1.5%)	1.1(-1.7, 3.9)
Day 4	1(0.6%)	2(1.0%)	-0.5(-2.2, 1.3)
Day 5	1(0.6%)	1(0.5%)	0.0(-1.5, 1.6)
Day 6	1(0.6%)	1(0.6%)	0.1(-1.6, 1.7)
Day 7	1(0.7%)	1(0.6%)	0.1(-1.7, 1.8)

eTable 6. Serious Adverse Events related to the study intervention.

Adverse Event	
Intracranial hemorrhage	5
Thromboembolic disease	
Deep venous thrombosis	3
Pulmonary embolism	1
Hemorrhage at other sites	
Bleeding from haemodialysis catheter	1
Hematoma	1
Airway	1
Thoracic	1
Cardiac	
Cardiac Arrhythmia	1
Shock	1
Right heart failure	1
Vascular injury	
Arterial	1
Venous	1
Cannula Failure	1
Device malfunction	1
Hyperkalemia	1
Heapanin Induced Thrombocytopenia	1

eTable 7. Serious Adverse Events by System Organ Class

	ECCO₂R no. events	ECCO₂R no.(%) patients n=202	Ventilation alone no. events	Ventilation alone no.(%) patients n=210
Cardiac disorders	15	15(7.4%)	9	9(4.3%)
Nervous system disorders	10	10(5.0%)	3	3(1.4%)
Respiratory, thoracic and mediastinal disorders	10	10(5.0%)	2	2(1.0%)
Injury, poisoning and procedural complications	7	7(3.5%)	1	1(0.5%)
Vascular disorders	7	7(3.5%)	0	0(0.0%)
Gastrointestinal disorders	6	6(3.0%)	2	2(1.0%)
Infections and infestations	5	5(2.5%)	0	0(0.0%)
Blood and lymphatic system disorders	3	3(1.5%)	0	0(0.0%)
Renal and urinary disorders	3	3(1.5%)	2	2(1.0%)
Hepatobiliary disorders	2	2(1.0%)	0	0(0.0%)
General disorders and administration site conditions	1	1(0.5%)	1	1(0.5%)
Metabolism and nutrition disorders	1	1(0.5%)	0	0(0.0%)