Prone ECMO trial implications

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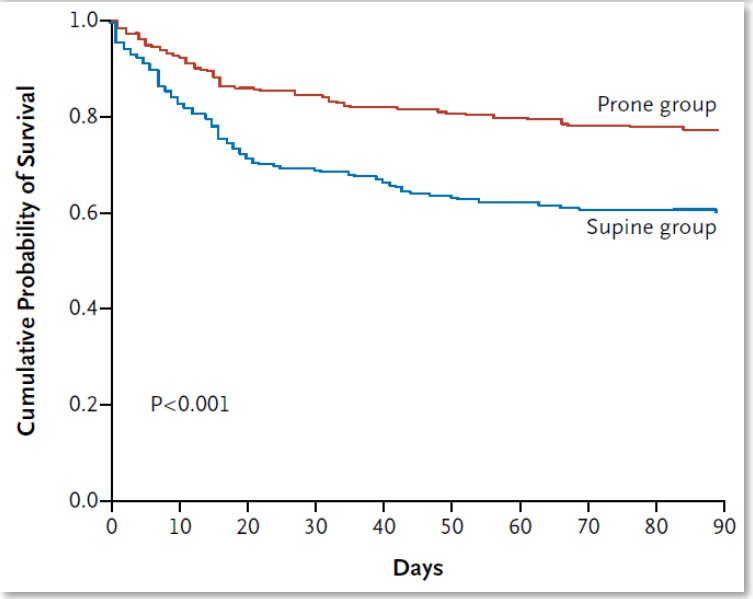
Disclosures

- ✓ Lectures fees for :
  - Getinge
  - Fresenius Medical Care
  - Baxter
  - 3M
- ✓ RCTs funded by grants from the French Ministry of Health

Prone positioning on ECMO ?

Prone Positioning in Severe Acute Respiratory Distress Syndrome



N ENGL J MED 368;23 NEJM.ORG JUNE 6, 2013

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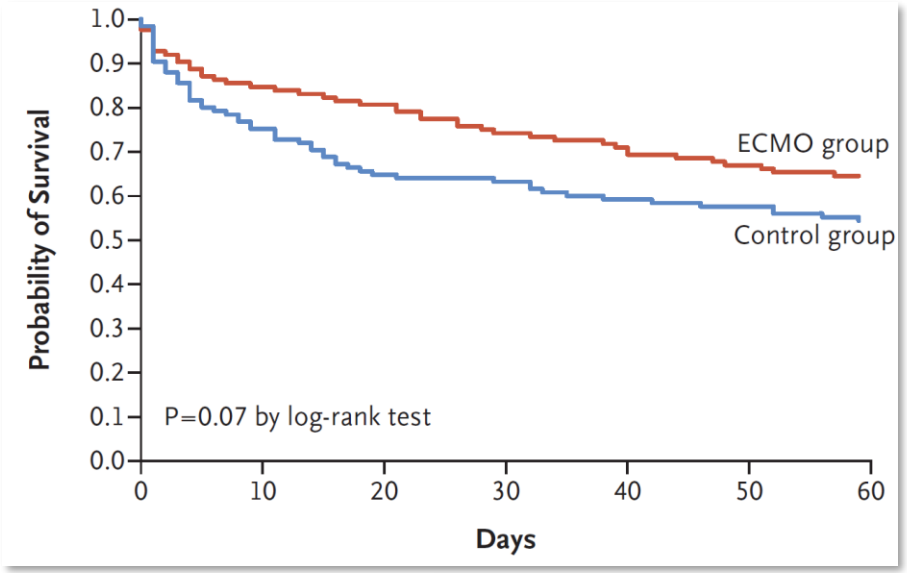
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome



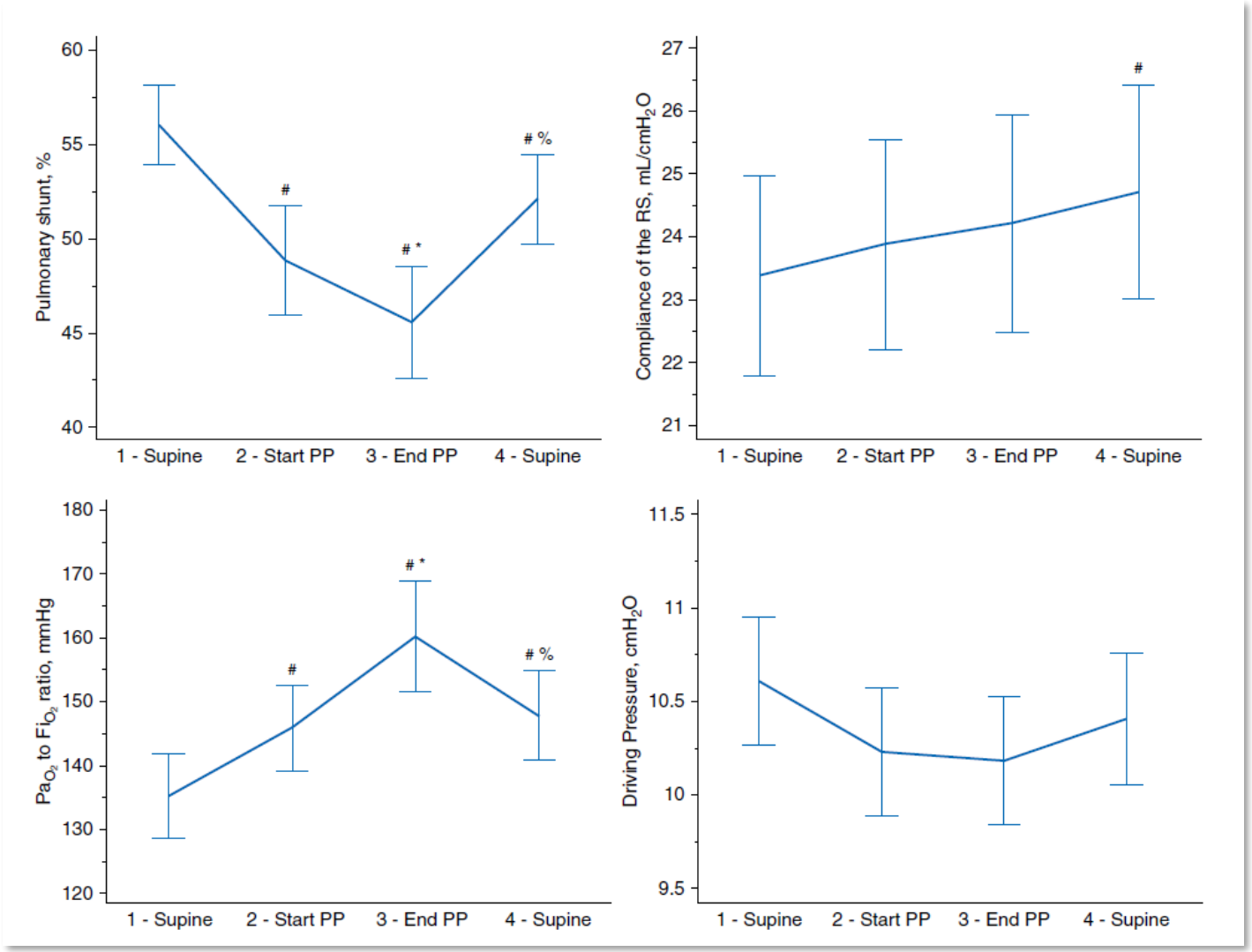
N Engl J Med 2018;378:1965-75.

Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome

A Multicenter Cohort Study and Propensity-matched Analysis

Marco Giani[1,2], Gennaro Martucci[3], Fabiana Madotto[4], Mirko Belliato[5], Vito Fanelli[6,7], Eugenio Garofalo[8], Clarissa Forlini[1], Alberto Lucchini[2], Giovanna Panarello[3], Nicola Bottino[9], Alberto Zanella[9,10], Francesca Fossi[11], Alfredo Lissoni[9], Nicola Peroni[5], Luca Brazzi[6,7], Giacomo Bellani[1,2], Paolo Navalesi[12,13], Antonio Arcadipane[3], Antonio Pesenti[9,10], Giuseppe Foti[1,2], and Giacomo Grasselli[9,10]

Ann Am Thorac Soc Vol 18, No 3, pp 495–501, Mar 2021

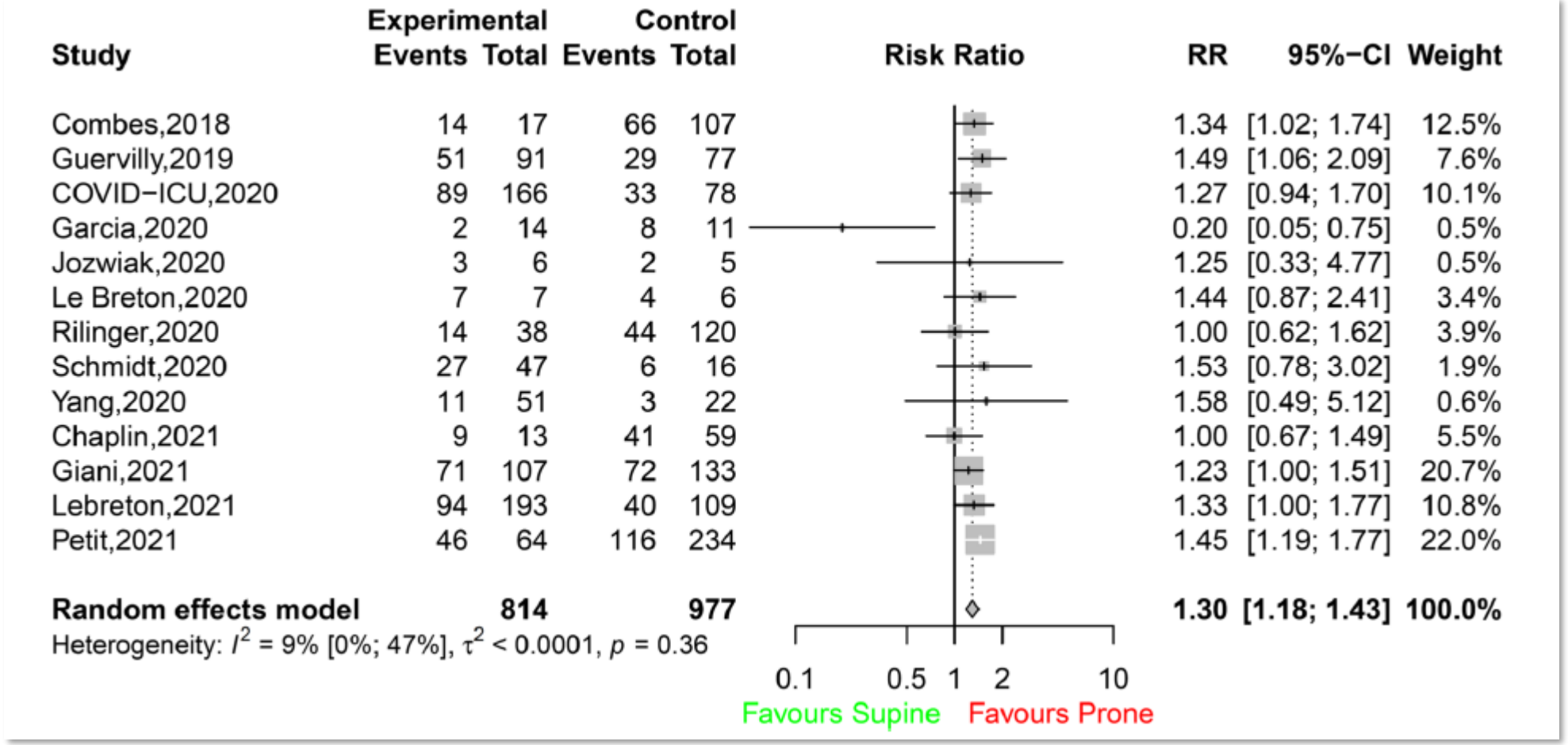


Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis

Laurent Papazian[1,2*], Matthieu Schmidt[3], David Hajage[4], Alain Combes[3], Matthieu Petit[3], Guillaume Lebreton[5,6], Jonathan Rilinger[7,8], Marco Giani[9], Camille Le Breton[10,11], Thibault Duburcq[12], Mathieu Jozwiak[13,14], Tobias Wengenmayer[7,8], Damien Roux[10,11], Rachael Parke[15,16], Anderson Loundou[17], Christophe Guervilly[1,2] and Laurent Boyer[17]

Intensive Care Med 2022

Hospital survival



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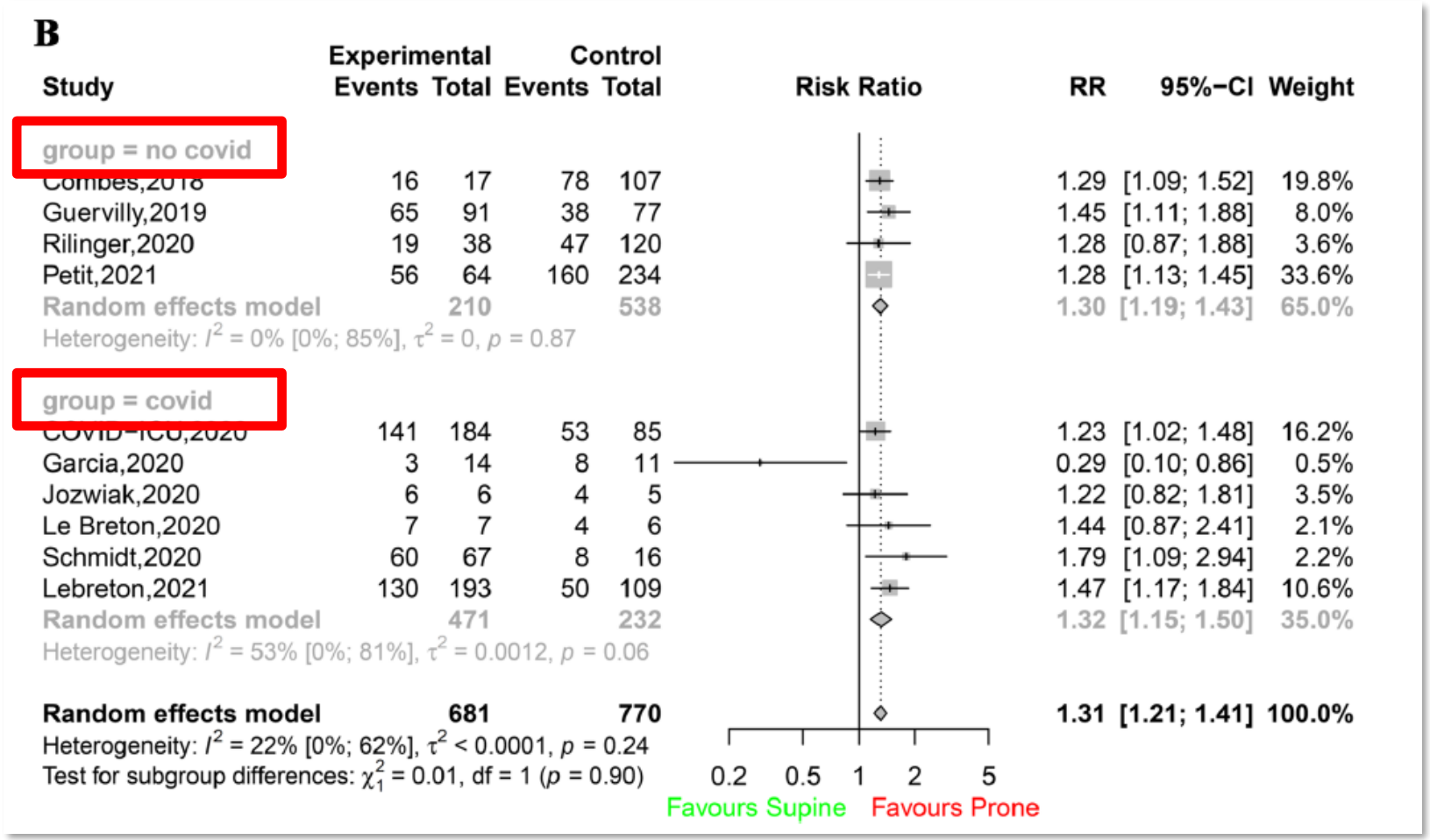
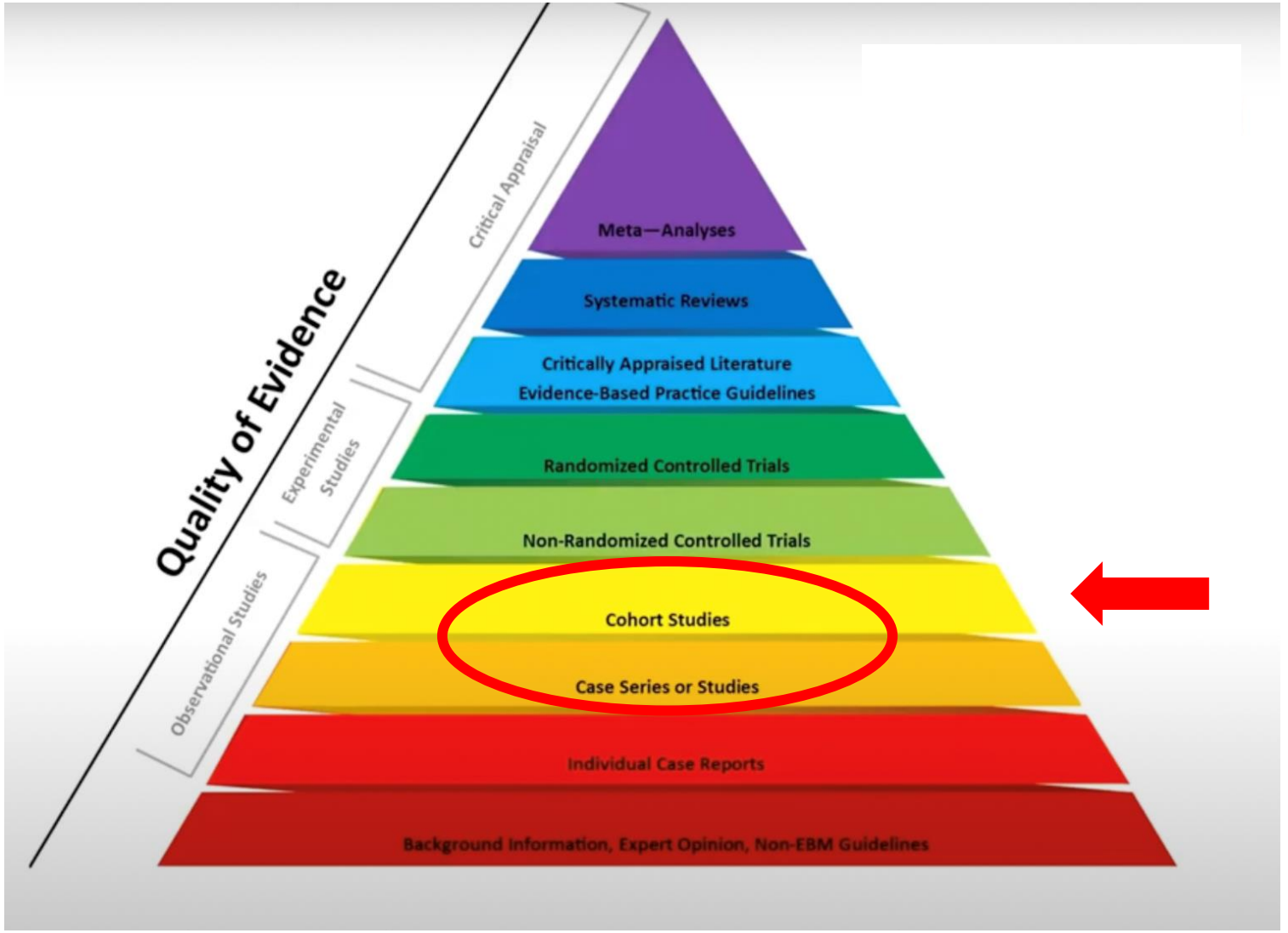
Intensive Care Med 2022

Survival at Day 28



Scientific evidence in 2023…



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

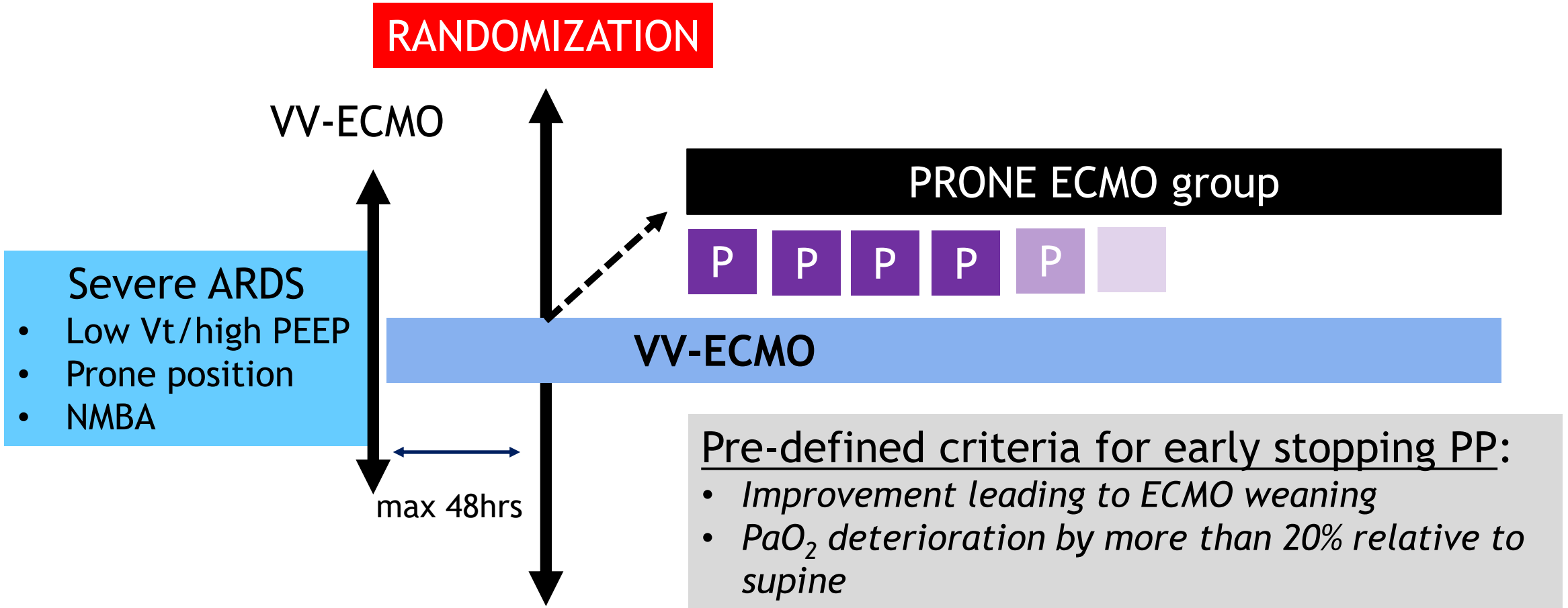
Prone Positioning During Extracorporeal Membrane Oxygenation in Patients With Severe ARDS

The PRONECMO Randomized Clinical Trial

Matthieu Schmidt, MD; David Hajage, MD; Guillaume Lebreton, MD; Martin Dres, MD; Christophe Guervilly, MD; Jean Christophe Richard, MD; Romain Sonneville, MD; Hadrien Winiszewski, MD; Gregoire Muller, MD; Gaëtan Beduneau, MD; Emmanuelle Mercier, MD; Hadrien Roze, MD; Mathieu Lesouhaitier, MD; Nicolas Terzi, MD; Arnaud W. Thille, MD; Isaura Laurent, MD; Antoine Kimmoun, MD; Alain Combes, MD; for the PRONECMO Investigators, the REVA Network, and the International ECMO Network (ECMONet)

"To determine the effect of early prone positioning during VV-ECMO vs supine positioning on time to successful ECMO weaning in patients with severe ARDS"

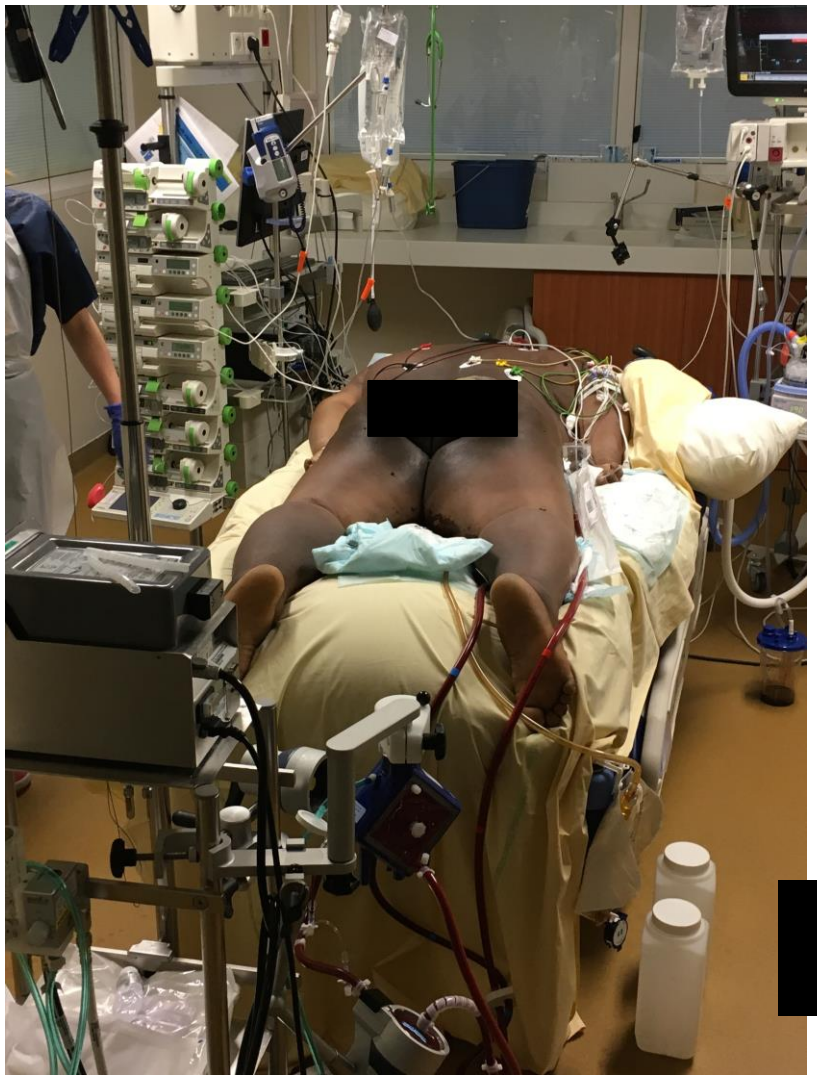
Trial intervention

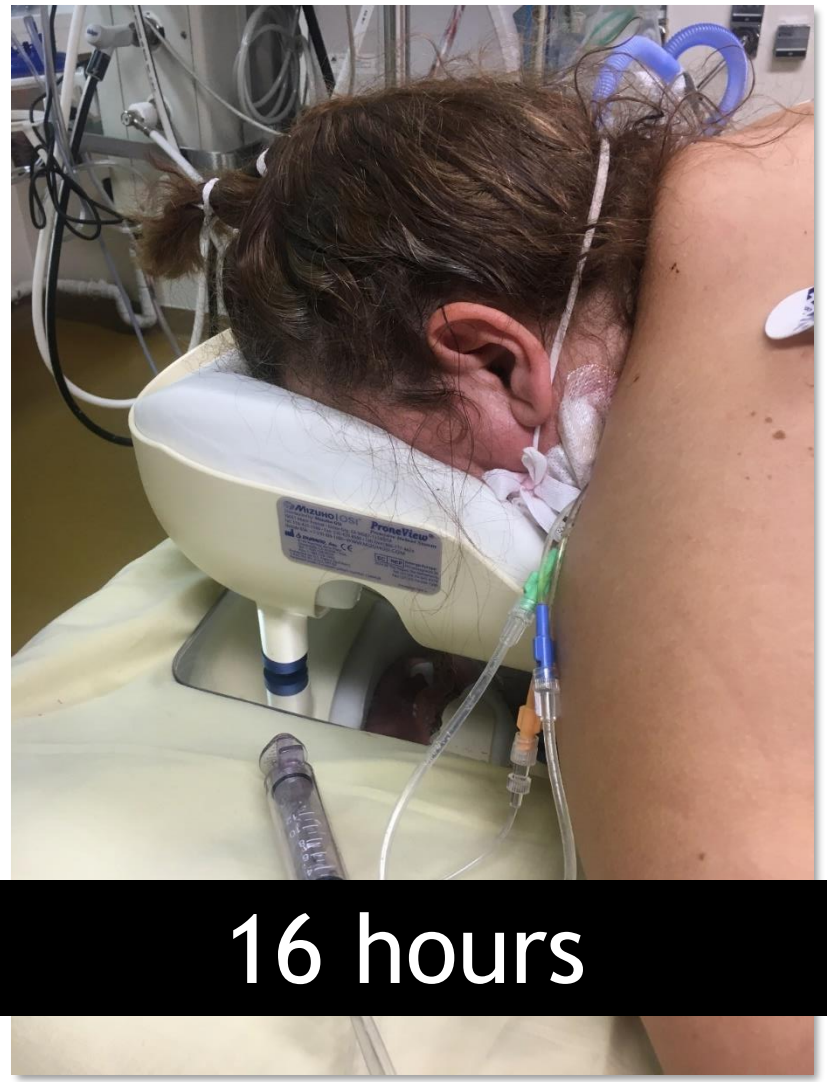


Pre-defined criteria for early stopping PP:

- *Improvement leading to ECMO weaning*
- *PaO_2 deterioration by more than 20% relative to supine*
- *Severe proning-related complications*

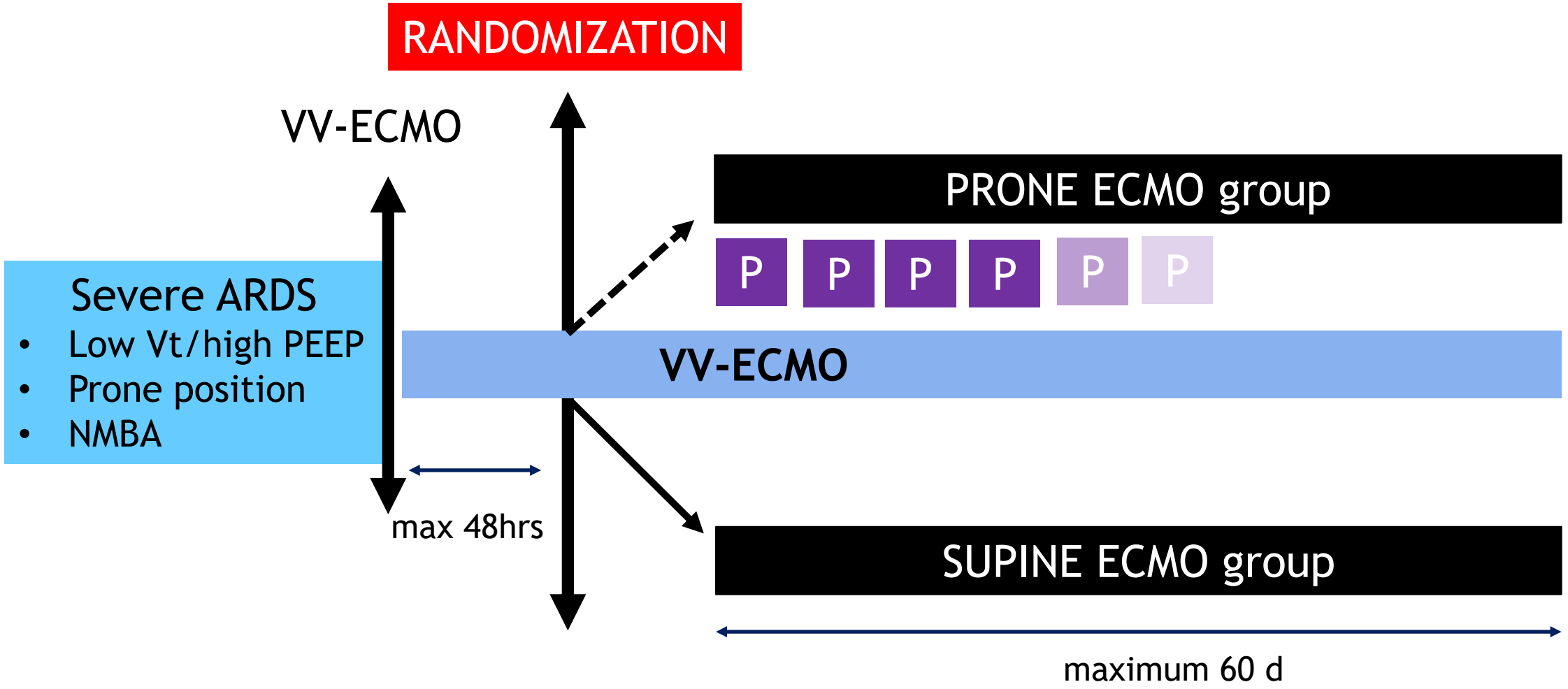
Trial intervention





16 hours

Trial intervention



Cointerventions

<u>In both groups :</u>

✓ Ultraprotective lung ventilation :
- Tidal volume <4ml/PBW
- RR< 20/min
- Plateau pressure <24 cmH_2O
- PEEP >10 cmH_2O
- Minimal FiO_2

✓ Protocolized management regarding weaning

✓ Similar sedation, anticoagulation, ECMO, and circuit management

Outcomes

Primary outcome :

Time to successful weaning within 60 days following randomization

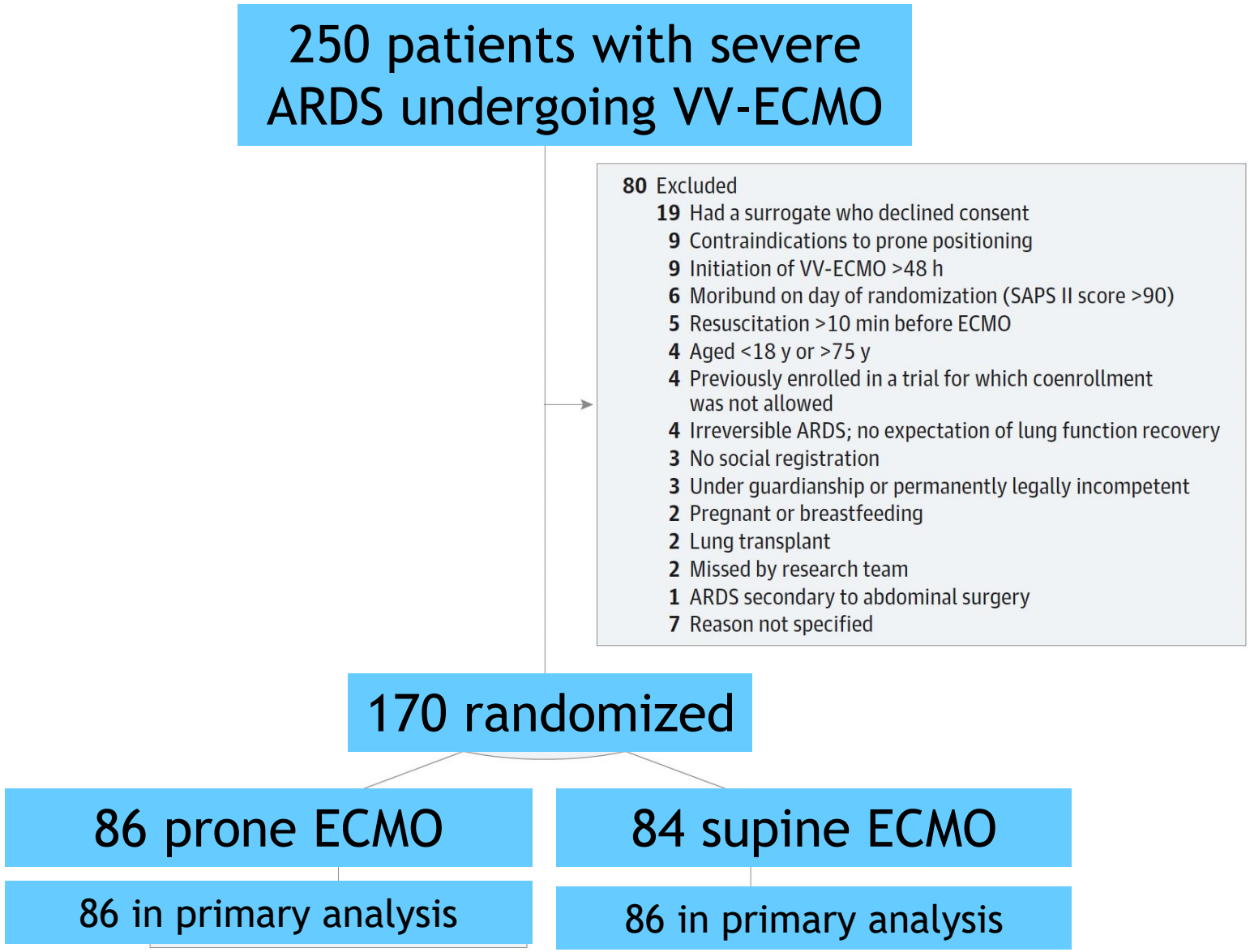
Successful weaning: Survival without ECMO or lung transplant for 30 days after ECMO discontinuation

Two competing events :

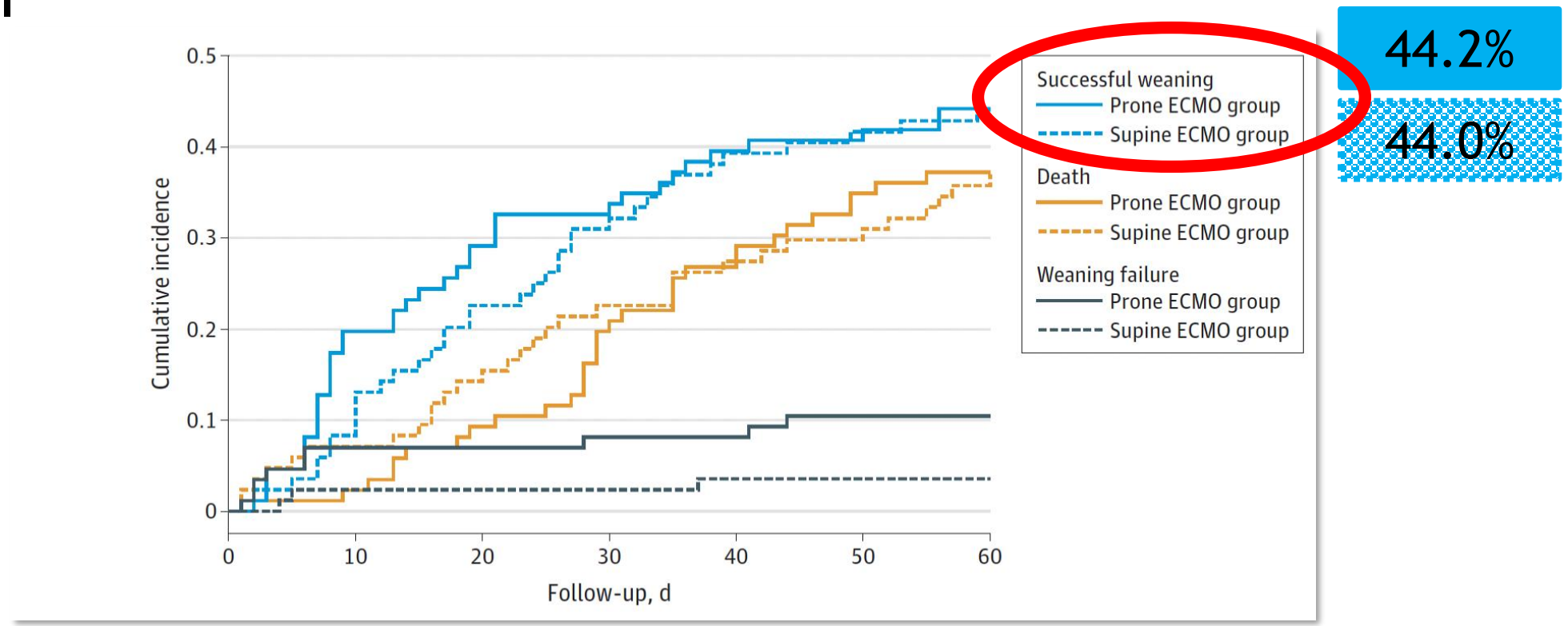
- **Weaning failure**: need for a second ECMO run or lung transplant or death within 30 days after ECMO separation
- **Death** while undergoing ECMO

Patients still alive undergoing ECMO at day 60 were censored

March 3, 2021 to December 7, 2021



Primary outcome

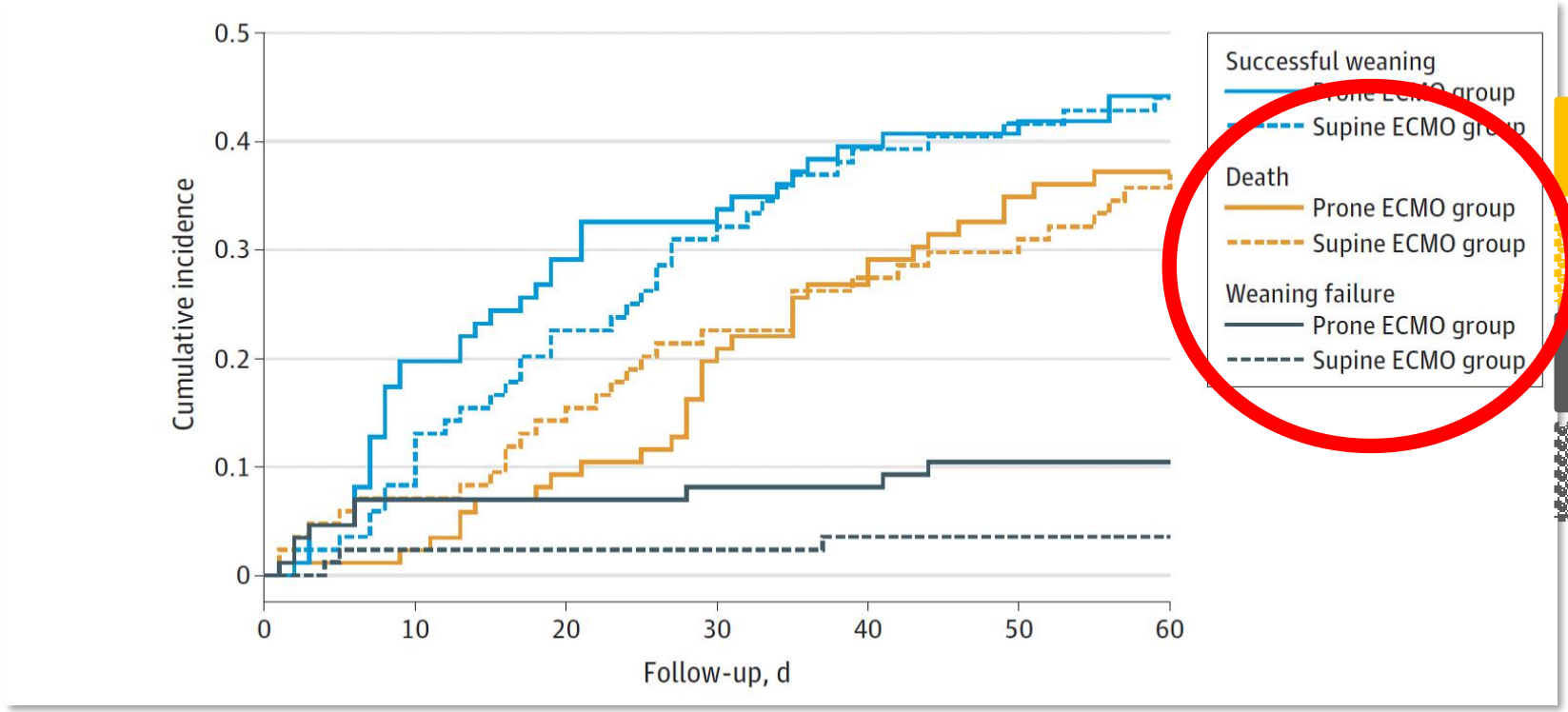


44.2%

44.0%

Outcomes/events	Prone ECMO (n = 86)	Supine ECMO (n = 84)	Mean, median, or risk difference, (95% CI)	Relative difference (95% CI)	*P* value
Primary outcome					
Successful ECMO weaning by day 60, No. (%)	38 (44.2)	37 (44.0)	0.1 (−14.9 to 15.2)	sHR, 1.11 (0.71-1.75)	.64

Primary outcome



Outcomes/events	Prone ECMO (n = 86)	Supine ECMO (n = 84)	Mean, median, or risk difference, (95% CI)	Relative difference (95% CI)	*P* value
Competing events					
Death before ECMO weaning, No. (%)	32 (37.2)	31 (36.9)	0.3 (−14.5 to 14.1)	sHR, 3.76 (0.71-21.1)	.12
ECMO weaning failure, No. (%)[b]	9 (10.5)	3 (3.6)	6.9 (−1.9 to 15.7)	sHR, 0.94 (0.58-1.53)	.80

Key secondary outcomes

Outcomes/events	Prone ECMO (n = 86)	Supine ECMO (n = 84)	Mean, median, or risk difference, (95% CI)	Relative difference (95% CI)	*P* value
Respiratory system compliance ≥30 mL/cm H_2O, No. (%)[c]					
On day 2	24 (27.9)	17 (20.2)	7.7 (−6.3 to 21.6)	1.38 (0.80-2.38)	.24
On day 7	33 (38.4)	26 (30.9)	7.4 (−8 to 22.9)	1.24 (0.82-1.88)	.31
Days alive and free from kidney failure within 7 days, median (IQR)[d]	7 (6-7)	7 (6-7)	0 (0 to 0)		.86
Days alive and free from cardiovascular failure within 7 days, median (IQR)[d]	5 (3-7)	5 (1-7)	0 (−2.5 to 1)		.32
Pneumothorax by day 60, No. (%)	14 (16)	17 (21)	−4 (−16.7 to 8.8)	0.80 (0.42-1.53)	.46
≥1 Ventilatory-associated pneumonia episode, No. (%)	73 (85)	75 (89)	−4.4 (−15.6 to 6.8)	0.95 (0.85-1.07)	.49
All-cause day 60 mortality, No. (%)	40 (47)	35 (42)	4.8 (−11.2 to 20.9)	1.18 (0.75-1.87)	.48
All-cause day 90 mortality, No. (%)	44 (51)	40 (48)	2.4 (−13.9 to 18.6)	1.1 (0.72-1.69)	.62
Days free from ECMO by day 90, median (IQR)	0 (0-73)	0 (0-64)	0 (−51.5 to 37)		.60
Days alive and free from mechanical ventilation by day 90, median (IQR)	0 (0-51)	0 (0-50)	0 (−4 to 21.9)		.84
Days receiving ECMO during first 90 days, mean (SD)	27.51 (20.39)	32.19 (23.95)	−4.9 (−11.2 to 1.5)		.13
Days receiving mechanical ventilation during first 90 days, mean (SD)	49.22 (30.06)	52.21 (28.78)	−3.0 (−10.9 to 4.8)		.62
Days in intensive care unit during first 90 days, mean (SD)	42.47 (25.44)	46.26 (26.88)	−3.8 (−10.6 to 4.3)		.43
Days in hospital during first 90 days, mean (SD)	59.79 (28.86)	59.36 (28.15)	0.4 (−8.0 to 8.9)		.97

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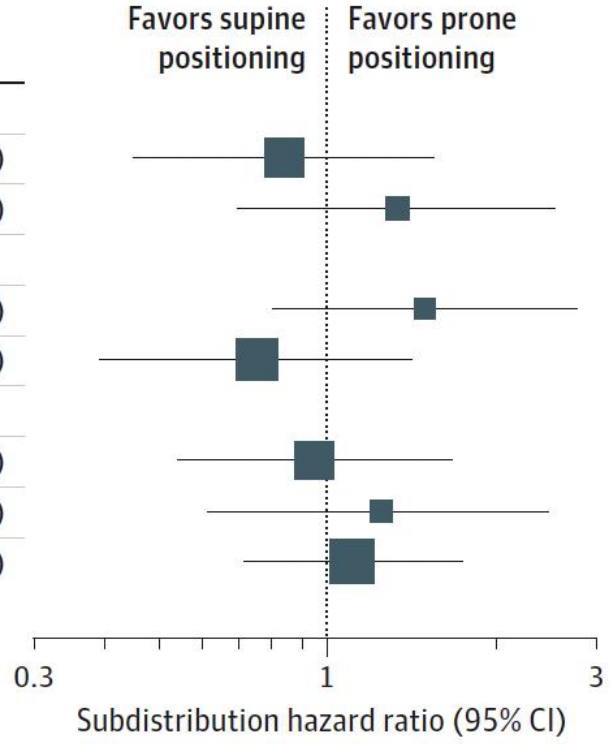
Subgroups of patients

Subgroup	No./total No. Prone ECMO group (n = 86)	No./total No. Supine ECMO group (n=84)	Subdistribution hazard ratio (95% CI)	*P* value for interaction[a]
Respiratory system compliance at randomization, mL/cm H_2O[b]				
≤20	18/40	22/42	0.84 (0.45-1.56)	.16
>20	20/46	15/42	1.34 (0.69-2.57)	
Body mass index[c]				
≤33	22/44	16/41	1.50 (0.80-2.81)	.15
>33	16/40	21/43	0.75 (0.39-1.42)	
High ECMO volume center[c,d]				
Yes	22/49	24/50	0.95 (0.54-1.68)	.79
No	16/37	13/34	1.25 (0.61-2.50)	
All patients	38/86	37/84	1.11 (0.71-1.75)	



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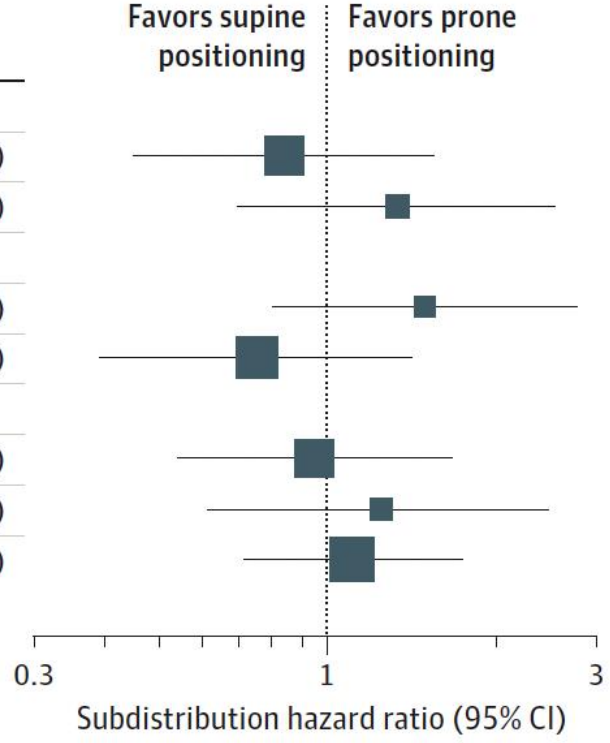

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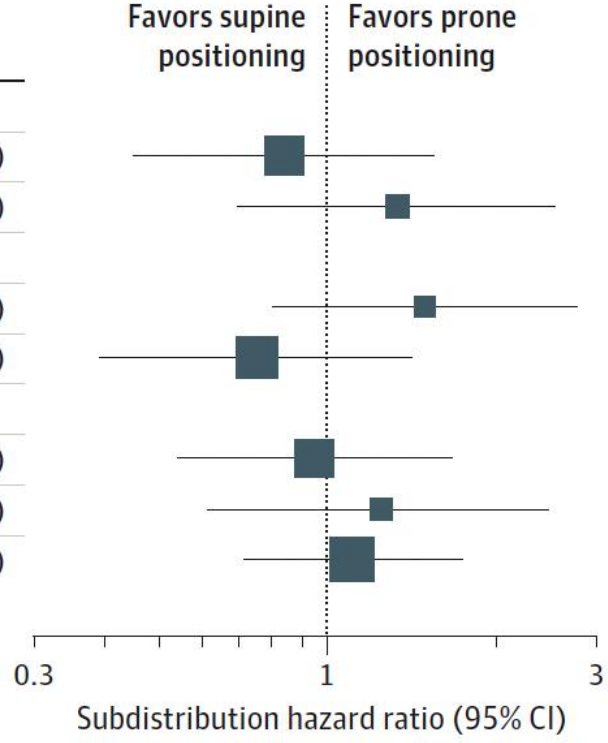

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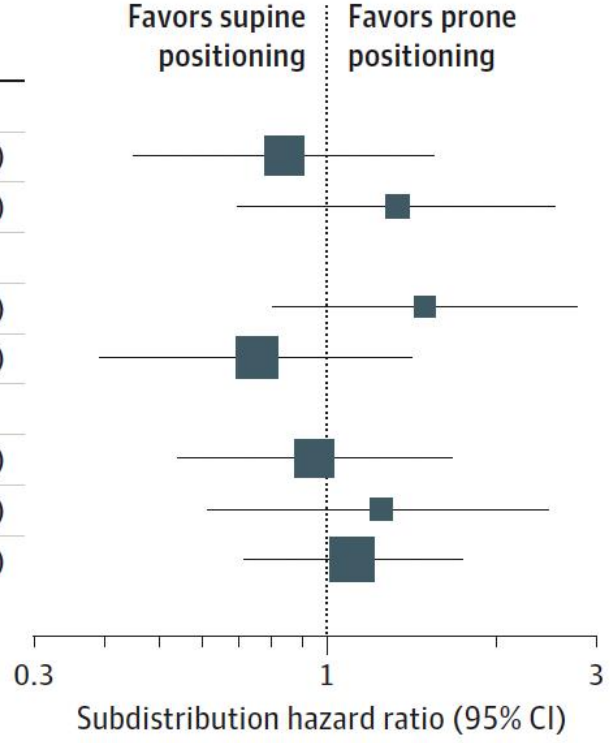


Adverse events

Outcomes/events	Prone ECMO (n = 86)	Supine ECMO (n = 84)	Mean, median, or risk difference, (95% CI)	Relative difference (95% CI)	*P* value
Adverse events by day 60					
≥1 Cardiac arrest					
≥1 Cardiac arrest	3 (3.5)	11 (13.1)	−9.6 (−19 to −0.2)	0.27 (0.08-0.92)	.05
Bleeding event requiring packed red blood cell transfusion	24 (27.9)	32 (38.1)	−3.0 (−17.3 to 11.4)	0.89 (0.54-1.48)	.79
Hemorrhagic stroke	2 (2.3)	1 (1.2)	1.1 (−3.9 to 6.2)	1.95 (0.18-21.14)	>.99
Unintentional ECMO decannulation	0	0			
Nonscheduled extubation, No. (%)	0	0			
Severe hemoptysis, No. (%)	0	0			
Maximum Revised Pressure Injury Staging System score, median (IQR)[e]	8 (4-11)	6 (2-10)	2 (−1 to 6)		.14

How do we reconcile the results of this negative RCT with preexisting favorable observational data ?

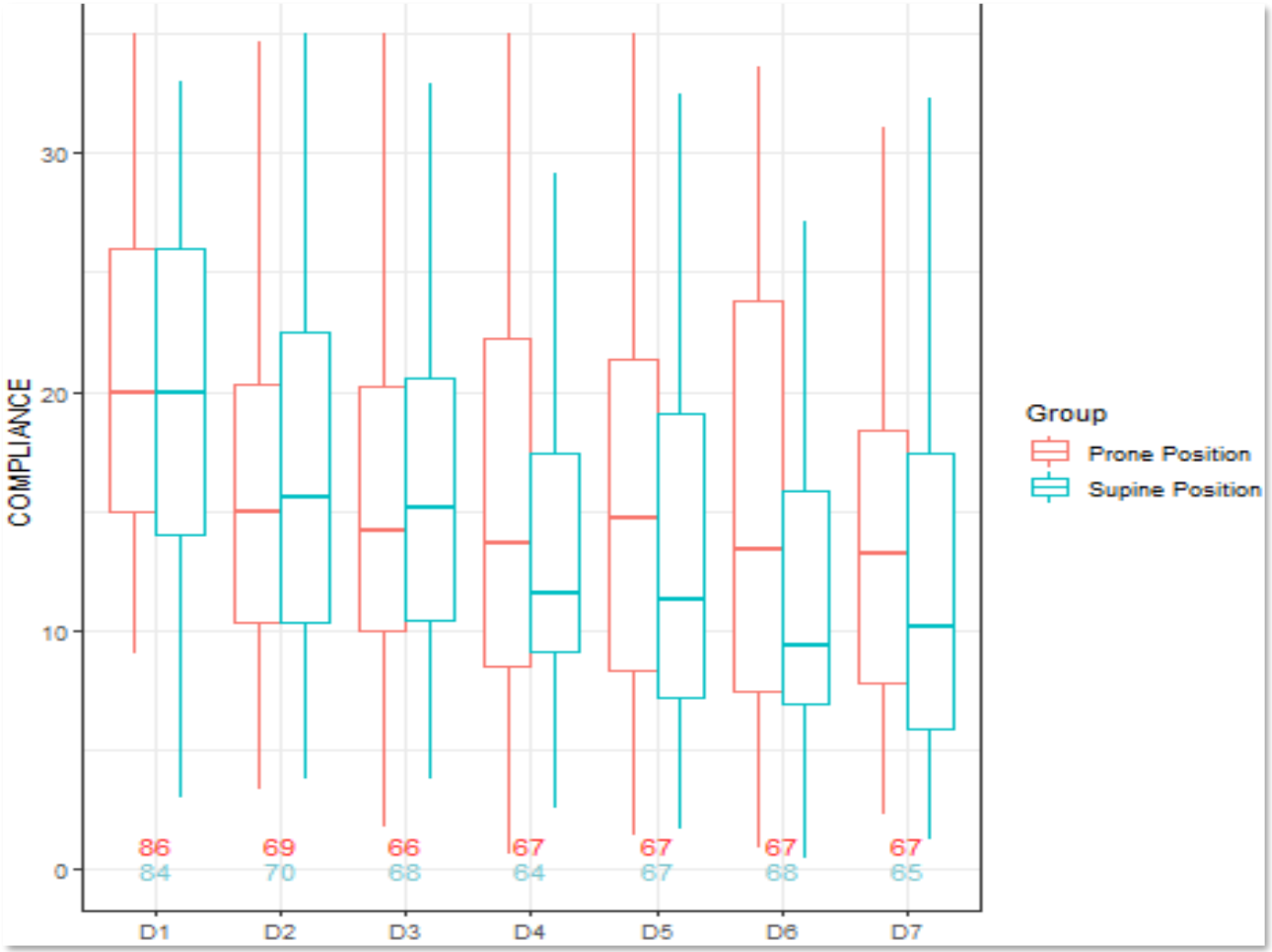
Patients

Characteristics	Prone ECMO (n = 86)	Supine ECMO (n = 84)
Age, median (IQR), y	52 (44-60)	50 (41-58)
Female	24 (37.9)	36 (32.9)
Male	62 (72.1)	48 (57.1)
Body mass index, median (IQR)[b]	32.7 (28.4-38.1)	33.1 (28.8-36.8)
SAPS II score, median (IQR)[c]	51 (36-60)	50 (33-56)
Comorbidities, No. (%)		
Diabetes	18 (20.9)	17 (20.2)
Chronic respiratory disease[d]	7 (8.1)	10 (11.9)
Ischemic cardiomyopathy	6 (7.0)	0
Immunocompromised[e]	4 (5)	3 (4)
Time from intubation to ECMO, median (IQR), d	3 (1-6)	5 (2-7)
Time from ECMO initiation to randomization, median (IQR), d	1 (0-1)	1 (0-1)
ARDS etiology, No. (%)		
COVID-19 pneumonia	80 (93.0)	79 (92.9)
Bacterial pneumonia	6 (7.0)	3 (3.6)

Very long ECMO duration and ICU stay…

Outcomes/events	Prone ECMO (n = 86)	Supine ECMO (n = 84)	Mean, median, or risk difference, (95% CI)	Relative difference (95% CI)	*P* value
Secondary outcomes					
Respiratory system compliance ≥30 mL/cm H_2O, No. (%)[c]					
On day 2	24 (27.9)	17 (20.2)	7.7 (−6.3 to 21.6)	1.38 (0.80-2.38)	.24
On day 7	33 (38.4)	26 (30.9)	7.4 (−8 to 22.9)	1.24 (0.82-1.88)	.31
Days alive and free from kidney failure within 7 days, median (IQR)[d]	7 (6-7)	7 (6-7)	0 (0 to 0)		.86
Days alive and free from cardiovascular failure within 7 days, median (IQR)[d]	5 (3-7)	5 (1-7)	0 (−2.5 to 1)		.32
Pneumothorax by day 60, No. (%)	14 (16)	17 (21)	−4 (−16.7 to 8.8)	0.80 (0.42-1.53)	.46
≥1 Ventilatory-associated pneumonia episode, No. (%)	73 (85)	75 (89)	−4.4 (−15.6 to 6.8)	0.95 (0.85-1.07)	.49
All-cause day 60 mortality, No. (%)	40 (47)	35 (42)	4.8 (−11.2 to 20.9)	1.18 (0.75-1.87)	.48
All-cause day 90 mortality, No. (%)	44 (51)	40 (48)	2.4 (−13.9 to 18.6)	1.1 (0.72-1.69)	.62
Days receiving ECMO during first 90 days, mean (SD)	27.51 (20.39)	32.19 (23.95)	−4.9 (−11.2 to 1.5)		.13
Days receiving mechanical ventilation during first 90 days, mean (SD)	49.22 (30.06)	52.21 (28.78)	−3.0 (−10.9 to 4.8)		.62
Days in intensive care unit during first 90 days, mean (SD)	42.47 (25.44)	46.26 (26.88)	−3.8 (−10.6 to 4.3)		.43
Days in hospital during first 90 days, mean (SD)	59.79 (28.86)	59.36 (28.15)	0.4 (−8.0 to 8.9)		.97

Compliance of the respiratory system



Non-parametric test for group, time, and interaction effects on compliance (p=0.08)

Pre-ECMO parameters

Characteristics	Prone ECMO (n = 86)	Supine ECMO (n = 84)
FIO_2	100 (100-100)	100 (100-100)
Positive end-expiratory pressure, cm H_2O	12 (10-15)	12 (10-14)
Tidal volume, mL/kg of predicted body weight	5.9 (5.3-6.3)	6.0 (5.2-6.4)
Respiratory rate, /min	30 (25-33)	30 (25-32)
Plateau pressure, cm H_2O	30 (29-33)	31 (29-34)
Respiratory system compliance, mL/cm H_2O	22.0 (16.0-29.5)	20.5 (14.7-27.0)
Blood gas measurements		
pH, median (IQR)	7.31 (7.26-7.40)	7.30 (7.20-7.40)
PaO_2/FIO_2, median (IQR), mm Hg	66 (55-77)	67 (59-80)
≤80, No. (%)	67 (83.7)	59 (76.6)
≤50, No. (%)	9 (11.2)	9 (11.7)
$PaCO_2$, mm Hg, median (IQR)	54 (48-64)	59 (51-70)
$PaCO_2$ ≥60 mm Hg and pH ≤7.25, No. (%)	14 (17.5)	20 (25.6)
Arterial lactate, median (IQR), mmol/L	1.8 (1.0-2.0)	1.8 (1.2-2.0)
Adjunctive therapies		
Adjunctive therapies		
Prone positioning, No. (%)	85 (98.8)	79 (94.1)
No. of sessions, median (IQR)	2 (1-3)	3 (2-4)
Continuous neuromuscular blockade, No. (%)	78 (94.0)	65 (95.6)
Pneumothorax, No. (%)	7 (8.2)	7 (8.4)

Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome

A Multicenter Cohort Study and Propensity-matched Analysis

Marco Giani[1,2], Gennaro Martucci[3], Fabiana Madotto[4], Mirko Belliato[5], Vito Fanelli[6,7], Eugenio Garofalo[8], Clarissa Forlini[1], Alberto Lucchini[2], Giovanna Panarello[3], Nicola Bottino[9], Alberto Zanella[9,10], Francesca Fossi[11], Alfredo Lissoni[9], Nicola Peroni[5], Luca Brazzi[6,7], Giacomo Bellani[1,2], Paolo Navalesi[12,13], Antonio Arcadipane[3], Antonio Pesenti[9,10], Giuseppe Foti[1,2], and Giacomo Grasselli[9,10]

Ann Am Thorac Soc Vol 18, No 3, pp 495–501, Mar 2021

	Prone Group (*n* = *107*)	Control Group (*n* = *133*)
Sex, M	73 (68.2)	83 (62.4)
Age, yr	48 ± 13	49 ± 13
BMI, kg/m^2	28.5 ± 6.5	28.4 ± 8.1
Cause of ARDS		
Pneumonia	99 (92.5)	121 (91.0)
Other	8 (7.5)	12 (9.0)
Pa_{O_2}:$F_{I_{O_2}}$ before ECMO, mm Hg	73 ± 29	76 ± 34
SOFA score	9 ± 3	10 ± 4
Prone positioning before ECMO	34 (31.8)	38 (35.2)
Nitric oxide before ECMO	8 (7.5)	20 (15.0)
AKI requiring RRT before ECMO	17 (15.9)	9 (6.8)
Duration of MV before ECMO, d	2 (1–6)	2 (1–6)
Comorbidities		
Hypertension	22 (20.6)	46 (34.6)
Diabetes mellitus	17 (15.9)	17 (12.8)
Immunodeficiency	15 (14.0)	30 (22.6)
Active malignancy	2 (1.9)	9 (6.8)
Autoimmune disorders	10 (9.4)	16 (12.0)
Immunosuppression	7 (6.5)	10 (7.5)
Other chronic diseases	21 (19.6)	27 (20.3)
Asthma-COPD	7 (6.4)	17 (12.78)
Peripheral vasculopathy	6 (5.6)	4 (3.0)
Chronic heart failure	6 (5.6)	7 (5.3)
Chronic renal disease	4 (3.7)	2 (1.5)
Chronic liver disease	5 (4.7)	6 (4.5)
Patients referred from other centers	94 (88)	101 (77)
Patient retrieved on ECMO	86 (80)	72 (59)

Prone positioning and extracorporeal membrane oxygenation for severe acute respiratory distress syndrome: time for a randomized trial?

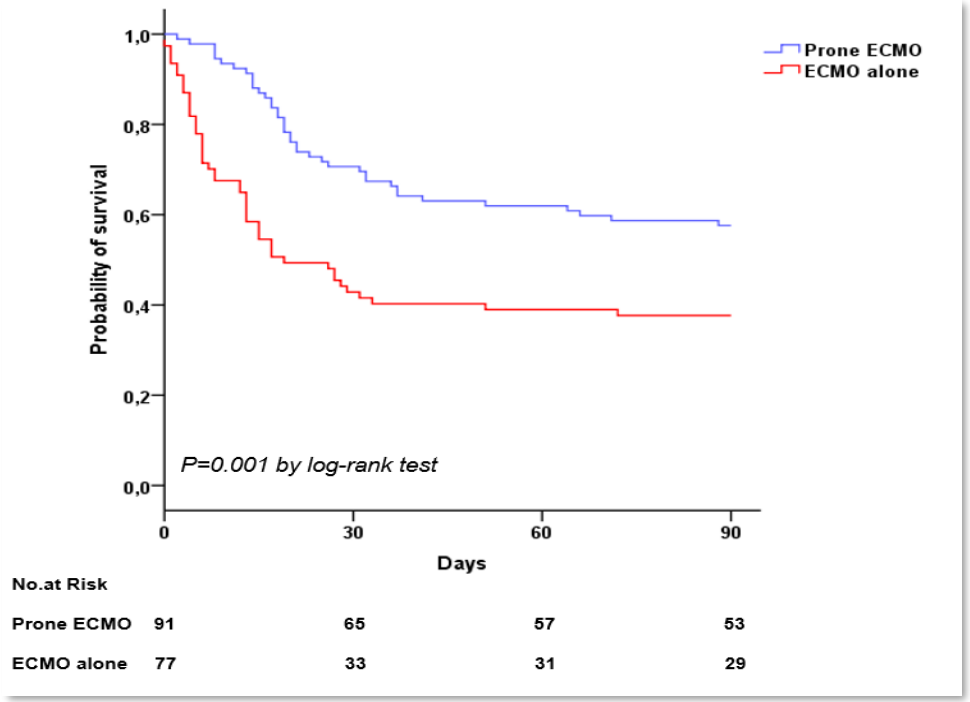
Christophe Guervilly[1,2*], Eloi Prud'homme[1], Vanessa Pauly[2], Jérémie Bourenne[3], Sami Hraiech[2,4], Florence Daviet[1], Mélanie Adda[1], Benjamin Coiffard[1,2], Jean Marie Forel[1,2], Antoine Roch[1,2,4], Nicolas Persico[4] and Laurent Papazian[1,2]

Intensive Care Med 2019

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

N ENGL J MED 378;21 NEJM.ORG MAY 24, 2018



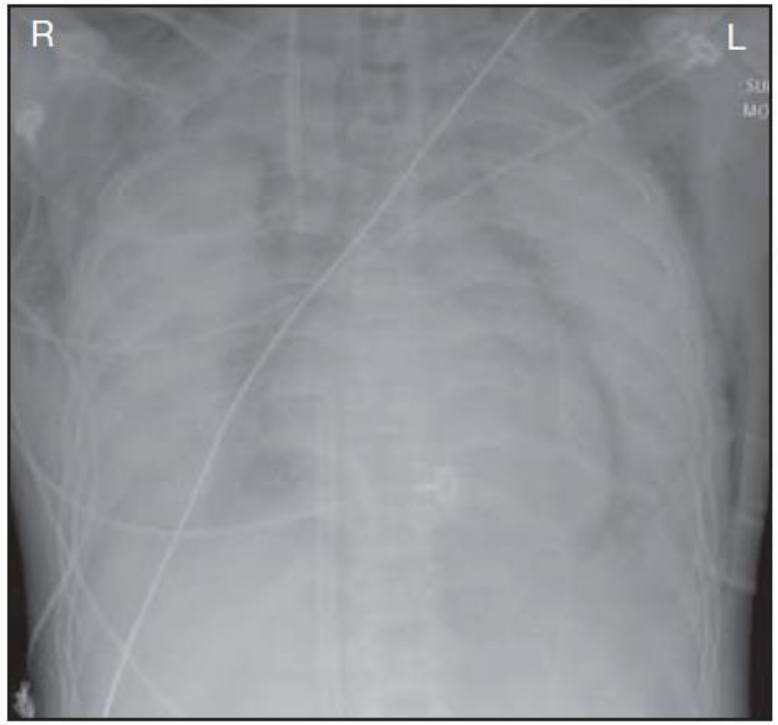
70 (56%) in the ECMO group

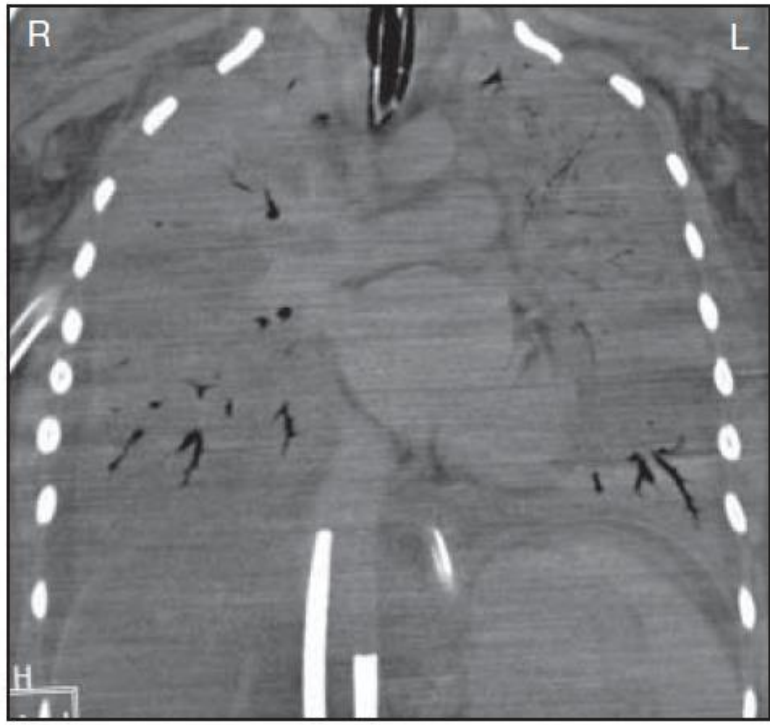
<u>PP before ECMO :</u>

29 (58%) in the supine ECMO group vs
34 (68%) in the prone ECMO group

Parameters at randomization

	Prone ECMO (n = 86)	Supine ECMO (n = 84)
SOFA score, median (IQR)[h]	9 (8-13)	9 (8-12)
Ventilation parameters while undergoing ECMO		
Tidal volume, median (IQR), mL/kg of predicted body weight	3.0 (2.0-4.3)	3.1 (2.3-3.9)
Driving pressure, median (IQR), cm H_2O	14 (11-15)	14 (11-14)
Driving pressure, median (IQR), cm H_2O	14 (11-15)	14 (11-14)
Respiratory rate, median (IQR), /min	20 (12-20)	20 (12-20)
Respiratory system compliance, median (IQR), mL/cm H_2O	14.0 (10.0-23.8)	15.0 (11.7-19.4)
Respiratory system compliance ≤20 mL/cm H_2O, No. (%)	40 (46.5)	42 (50)





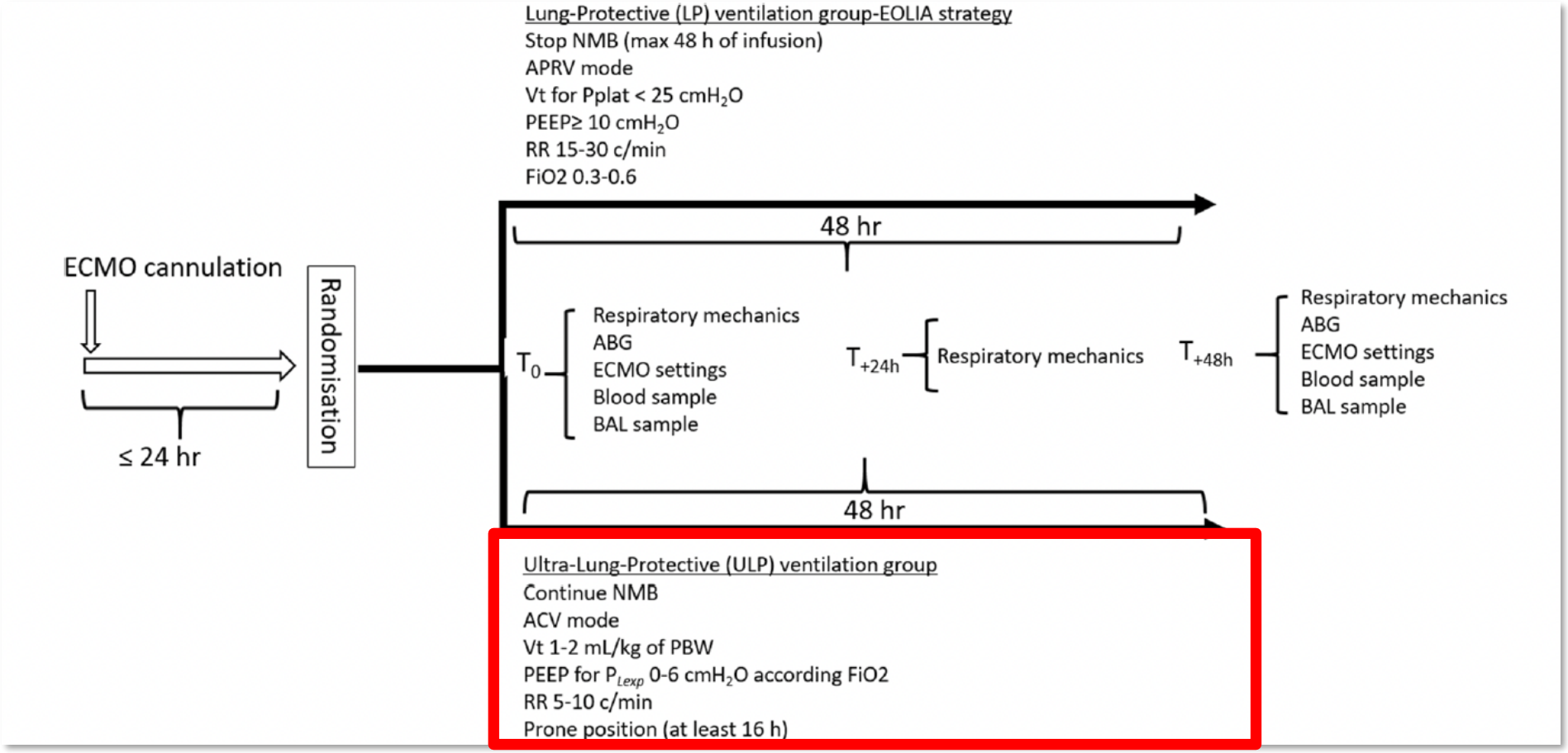
Does position matter when ultra-lung protective ventilation (i.e limited aerated lung) is already performed ?

Ultra-lung-protective ventilation and biotrauma in severe ARDS patients on veno-venous extracorporeal membrane oxygenation: a randomized controlled study

Christophe Guervilly[1,2*†], Théotime Fournier[1†], Juliette Chommeloux[3,4], Laurent Arnaud[5], Camille Pinglis[1,2], Karine Baumstarck[2], Mohamed Boucekine[2], Sabine Valera[1,2], Celine Sanz[1,2], Mélanie Adda[1,2], Mickaël Bobot[1,6,7], Florence Daviet[1,2], Ines Gragueb-Chatti[1,2], Jean-Marie Forel[1,2], Antoine Roch[1,2], Sami Hraiech[1,2], Françoise Dignat-George[5,6], Matthieu Schmidt[3,4], Romaric Lacroix[5,6] and Laurent Papazian[1,2,8]

l. Critical Care (2022) 26:383

N=38



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l. Critical Care (2022) 26:383

Variable	Ultra-lung-protective group		Lung-protective group	
	N	*n (%)**	*N*	*n (%)**
Rescue therapy pre-ECMO				
Any	20	20 (100)	18	18 (100)
Continuous infusion of NMB	20	18 (90)	18	17 (94)
Prone position	20	17 (85)	18	16 (89)
Inhaled nitric oxide	20	10 (50)	18	10 (55)
Almitrine infusion	20	2 (10)	18	2 (11)

None of the concentrations of the pre-specified biomarkers differed between the two groups 48 h after randomization.

A trend to higher 60-day mortality was observed in the ultra-lung-protective group compared to the control group (45 vs 17%, p = 0.06).

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Pro

Marco Giani[1,2*], Laurent Papazian[3,4] and Giacomo Grasselli[5,6]

Intensive Care Med
https://doi.org/10.1007/s00134-024-07368-w

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Not sure

Darryl Abrams[1,2*], Christophe Guervilly[3] and Daniel Brodie[4]

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Con

Matthieu Schmidt[1,2,3,5*], Antoine Kimmoun[4] and Alain Combes[1,2,3]

The future for PP on ECMO…

- PP on ECMO is safe if performed in experienced centers

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- PP on ECMO is safe if performed in experienced centers

- To date, proning on ECMO does not show any benefit when
  - ✓ PP is systematically performed before ECMO
  - ✓ When ultra-lung protective ventilation is already performed

  ➔ Should not be used in routine

The future for PP on ECMO…

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  - ✓ PP is systematically performed before ECMO
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  ➔ Should not be used in routine

- A new RCT on PP on ECMO in non-COVID-19 related ARDS is warranted to close the debate!