Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

The EOLIA trial

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On behalf of the EOLIA Trial Group, Réseau Européen en Ventilation Artificielle (REVA) and the International ECMO Network (ECMONet)

Disclosures

- Principal Investigator: EOLIA trial
  - VV ECMO in ARDS
  - NCT01470703
  - Partly sponsored by MAQUET, Getinge Group
- Received honoraria for lectures and consulting from
  - MAQUET, BAXTER

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ABSTRACT

EOLIA trial rationale and objective

- Recent advances in ECMO technology
- Encouraging results of ECMO
  - Influenza A (H1N1) associated ARDS
  - CESAR randomized trial, UK
- Still, efficacy of VV-ECMO in severe ARDS
  - Remains controversial
- EOLIA trial designed to determine the effect of
  - Early initiation of ECMO
  - In patients with the most severe forms of ARDS

Trial Design

Trial design

- Multicenter, international, randomized trial
- Sequential design
  - With stopping rules according to the two-sided triangular test
- Randomization was Web-based and Stratified by
  - Center
  - MV Duration (< or ≥72 h) before randomization
- Randomization possible at Non-ECMO centers with
  - Extensive expertise in managing ARDS
  - ECMO retrieval team within 2 hours
  - Transfer of the patient on ECMO to the ECMO center

Patients

Inclusion Criteria

- One of the 3 following disease severity criteria
  - PaO_2:FIO_2 <50 mmHg for >3 hours
    - *Despite potential use of inhaled NO, recruitment maneuvers*
    - *Prone position, HFO ventilation, almitrine infusion*
  - PaO_2:FIO_2 <80 mmHg for >6 hours
    - *Despite similar criteria as above*
  - pH <7.25 with $PaCO_2$ ≥60 mmHg for >6 hours
    - *Resulting from MV settings to keep Pplat ≤32 cm H_2O*
    - *Despite respiratory rate increased to 35/minute*

Exclusion Criteria

- Age <18 years
- Mechanical ventilation for ≥7 days
- Pregnancy
- Weight >1 kg/cm,
  - Or BMI>45 kg/m²
- Chronic respiratory insufficiency
  - Treated with oxygen therapy or NIV
- Cardiac failure requiring VA-ECMO
- History of HIT
- Malignancy with survival <5 years
- Patient moribund with a SAPS II >90
- Non-drug–induced coma
  - Following cardiac arrest
- Irreversible neurological injury
- Decision to withhold or withdraw
  - Life-sustaining therapies
- Expected difficulty in obtaining vascular access for ECMO
  - In the femoral or jugular vein
- ECMO device
  - Not immediately available

Trial Procedures

Trial procedures

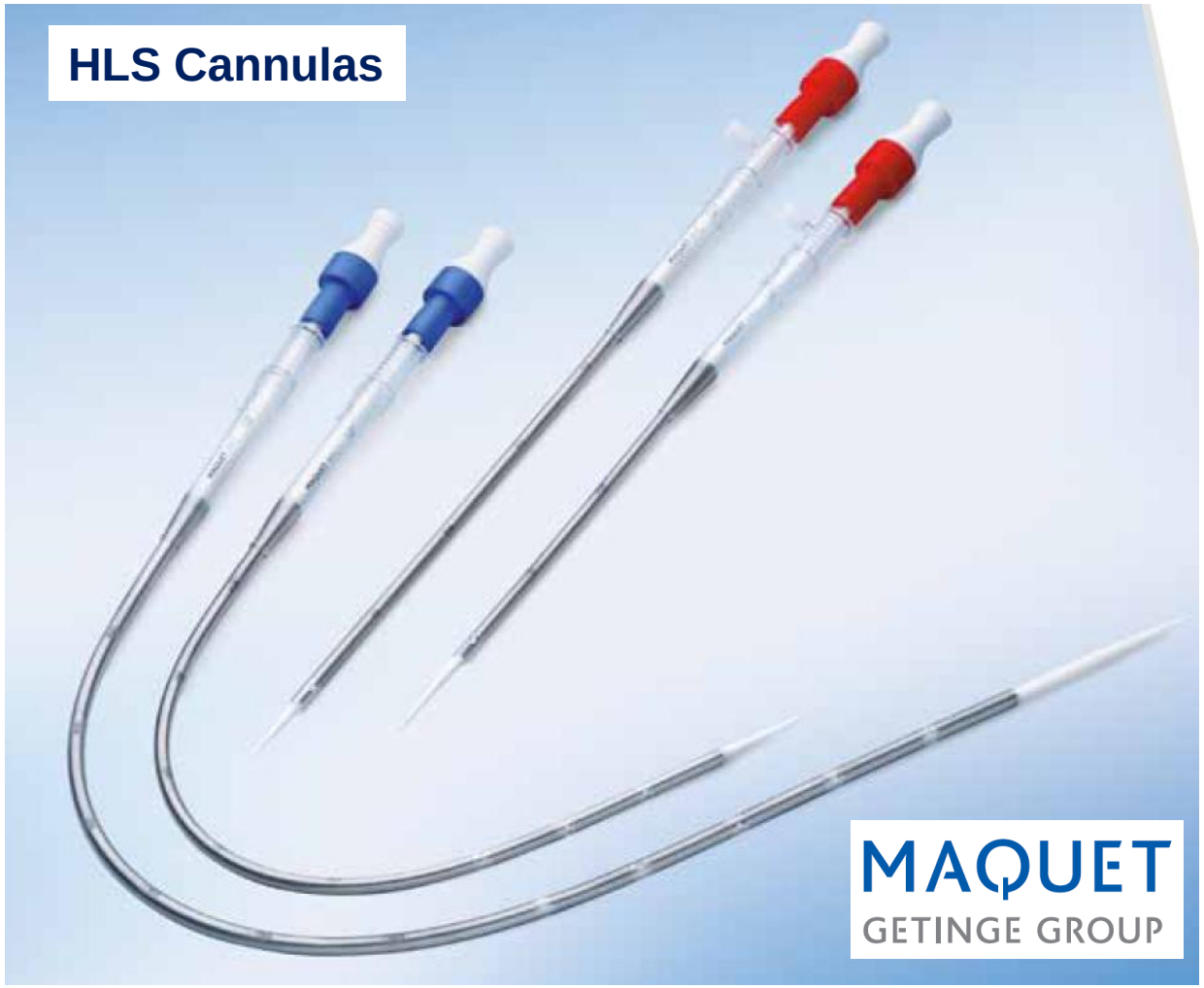
ECMO Group

- Percutaneous VV Cannulation
- Low anticoag. with Heparin
  - aPTT 40–55 seconds
- MV settings
  - VAC
    - PEEP ≥10, *VT set for Pplat ≤24 cmH_2O*
  - Pressure controlled/APRV
    - *PLow ≥10; PHigh ≤24 cmH_2O; I:E, 1/2*
  - FIO_2 30-50%, RR 10–30

Control Group

- MV settings
  - Express trial; High recruitment arm
  - VT at 6 ml/kg
  - PEEP to reach Pplat 28–30 cm H_2O
- Strong recommendation for
  - Prolonged periods of prone position
  - Paralyzing agents
- In case of hypoxemia
  - Recruitment maneuvers
  - iNO, inhaled prostacyclin

ECMO device and Cannulas



Rescue ECMO for Controls

- Refractory hypoxemia
  - SaO_2 <80% for >6 hours
- Despite mandatory trial of
  - Prone positioning AND
  - Recruitment maneuver AND
  - iNO or inhaled prostacyclin
- AND If the treating physician felt that
  - Patient had no irreversible multi-organ failure AND
  - ECMO might change the outcome

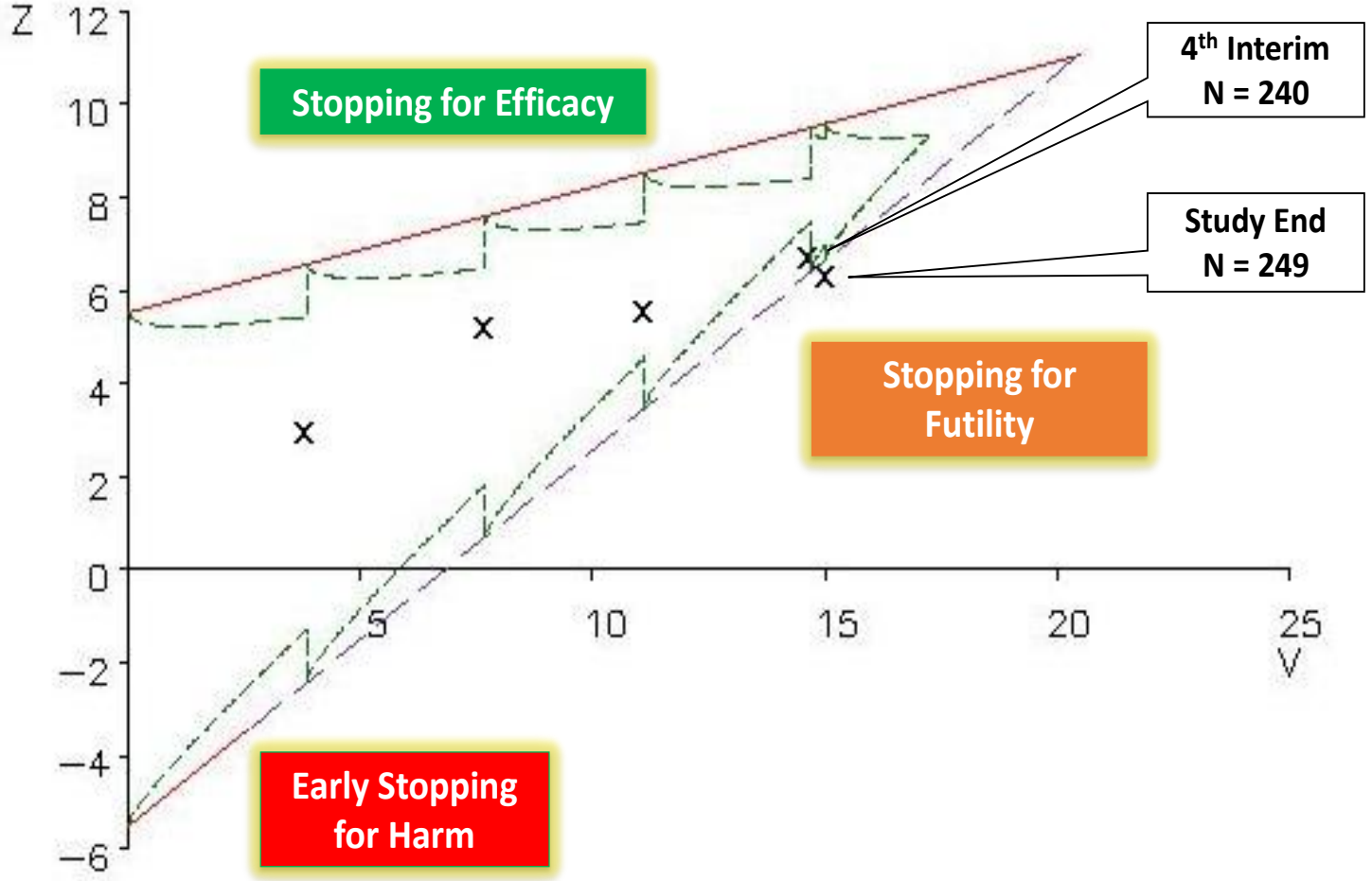
Statistical Analyses

Sample Size

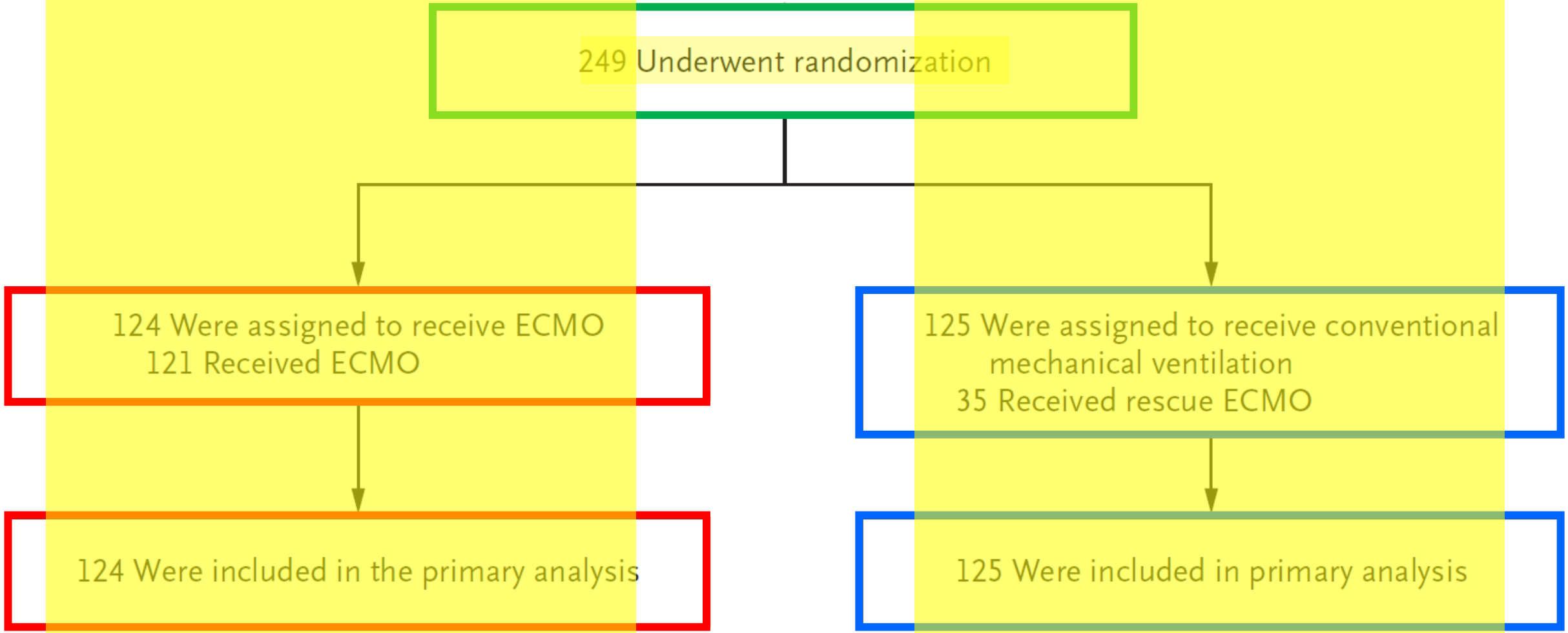
- 60% expected 60-day mortality for controls
  - 40% expected 60-day mortality with ECMO
- α=0.05; β=0.20
- Group sequential analysis every 60 inclusions
- Two-sided triangular design for early stopping
  - Superiority of ECMO
  - Predicted lack of a significant difference
  - Harm
- Maximum sample size 331 participants
  - 90% probability stopping before 220 patients enrolled

Results

Patients



- Recruitment stopped
- At the 4th planned sequential interim analysis
  - 240 patients
  - April 2017
- Lower boundary of the stopping-rule triangle
  - Crossed
  - Predicting lack of difference


249 Underwent randomization
124 Were assigned to receive ECMO
121 Received ECMO
125 Were assigned to receive conventional mechanical ventilation
35 Received rescue ECMO
124 Were included in the primary analysis
125 Were included in primary analysis

Patients Characteristics

Similar at Randomization

Characteristics of the Patients at Randomization

Characteristic	ECMO Group (N=124)	Control Group (N=125)
Age — yr	51.9±14.2	54.4±12.7
Male sex — no. (%)	87 (70)	90 (72)
Immunocompromised condition — no. (%)	27 (22)	27 (22)
SOFA score†	10.8±3.9	10.6±3.5
Median time since intubation (interquartile range) — hr	34 (15–89)	34 (17–100)
Cause of ARDS — no. (%)		
Pneumonia		
Bacterial	54 (44)	58 (46)
Viral	26 (21)	20 (16)
Other	44 (35)	47 (38)
Pao_2:Fio_2 — mm Hg	73±30	72±24

Characteristics of the Patients at Randomization

Characteristic	ECMO Group (N=124)	Control Group (N=125)
PEEP — cm of water	11.7±3.9	11.8±3.7
Tidal volume — ml/kg of predicted body weight	6.0±1.3	6.1±0.9
Respiratory rate — breaths/min	30.4±4.7	31.2±4.5
Plateau pressure — cm of water	29.8±5.5	29.5±4.8
Driving pressure — cm of water	17.8±7.0	17.7±5.8
Respiratory-system compliance — ml/cm of water	25.0±11.5	25.4±10.8
Arterial blood pH	7.24±0.13	7.24±0.12
Pa_{O_2} — mm Hg‡	69±25	68±22
Pa_{CO_2} — mm Hg	57±15	57±16
Prone positioning§	70 (56)	78 (62)
Inhaled nitric oxide or prostacyclin§	64 (52)	68 (54)
Recruitment maneuvers§	22 (18)	34 (27)
Neuromuscular blockade§	114 (92)	120 (96)

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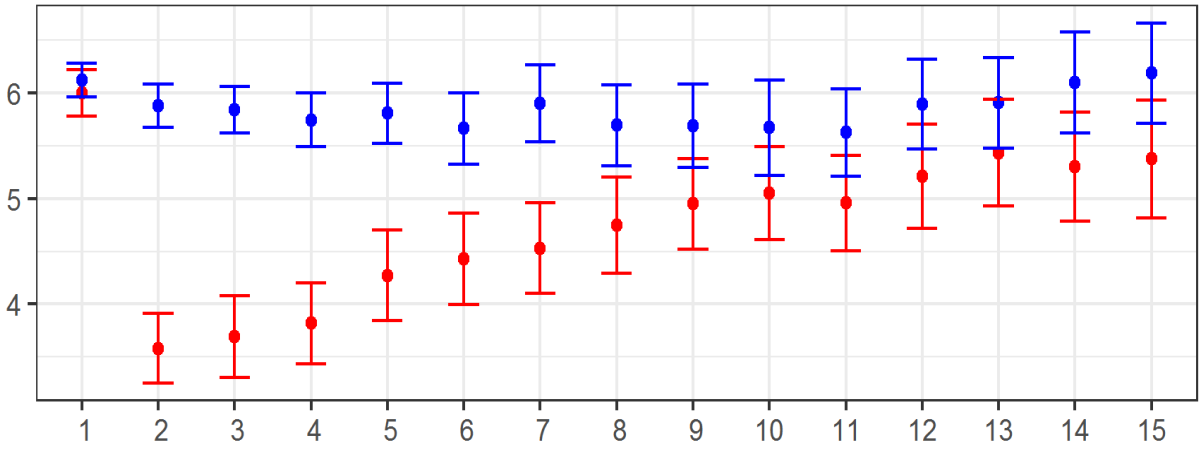
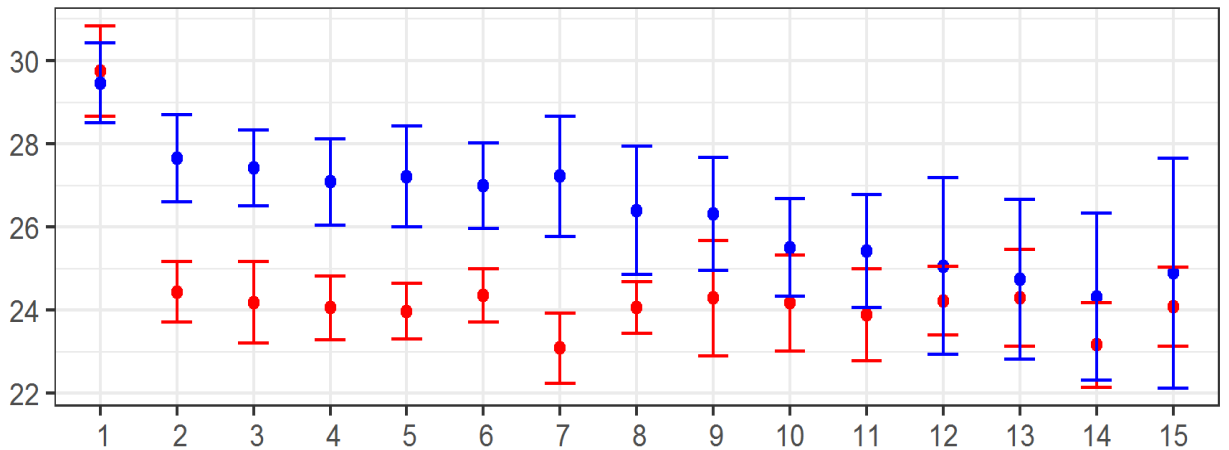
Trial Treatments

ECMO Control

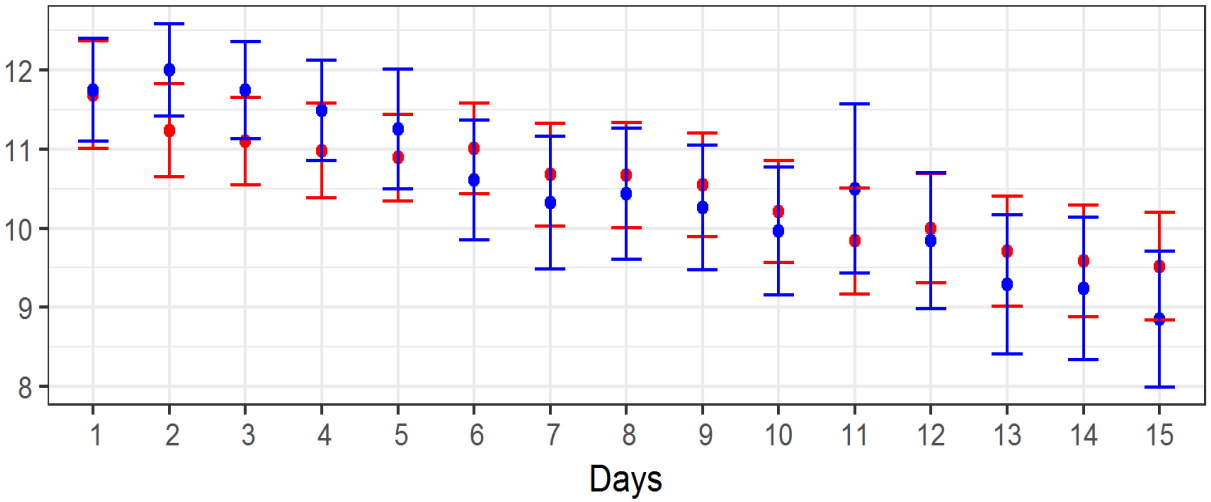
VT, ml/kg PBW, P <0.001



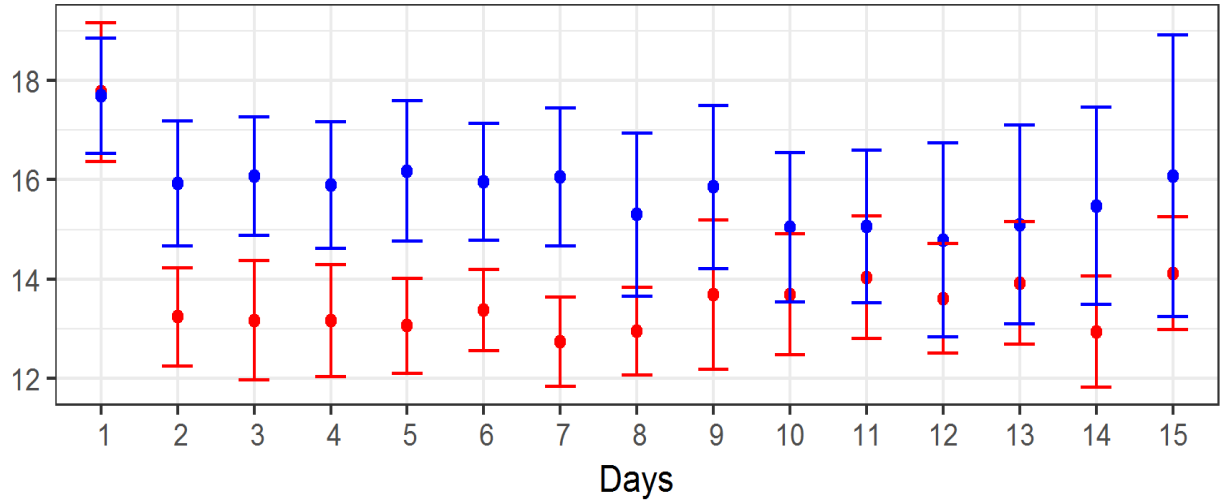
Plateau Pressure, cm H_2O, P <0.001



PEEP, cm H_2O, P = 0.291

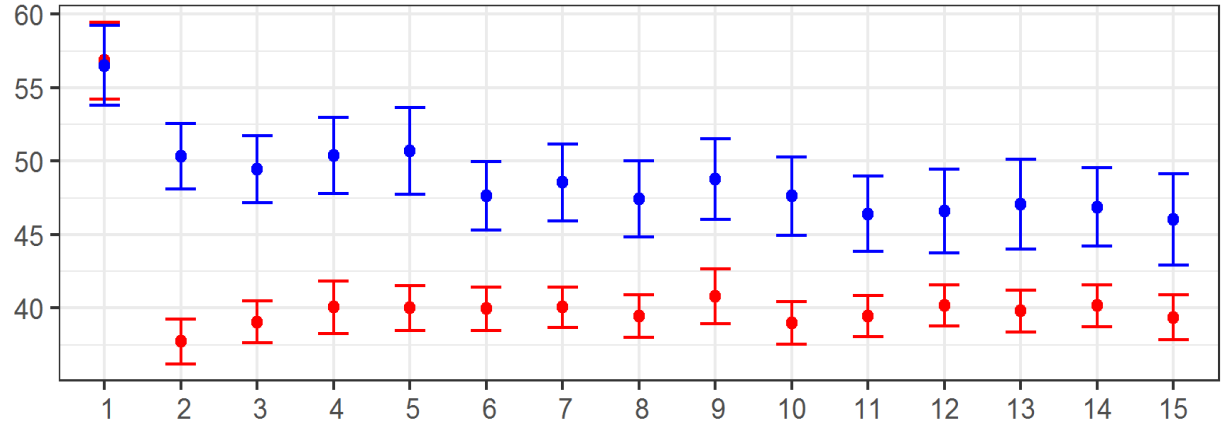


Driving Pressure, cm H_2O, P = 0.011

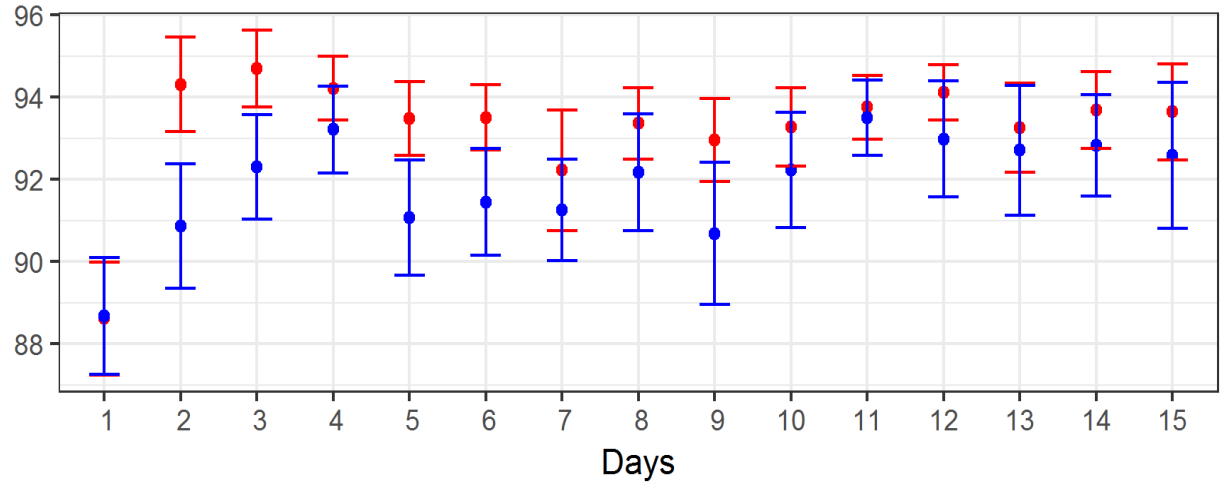


ECMO Control

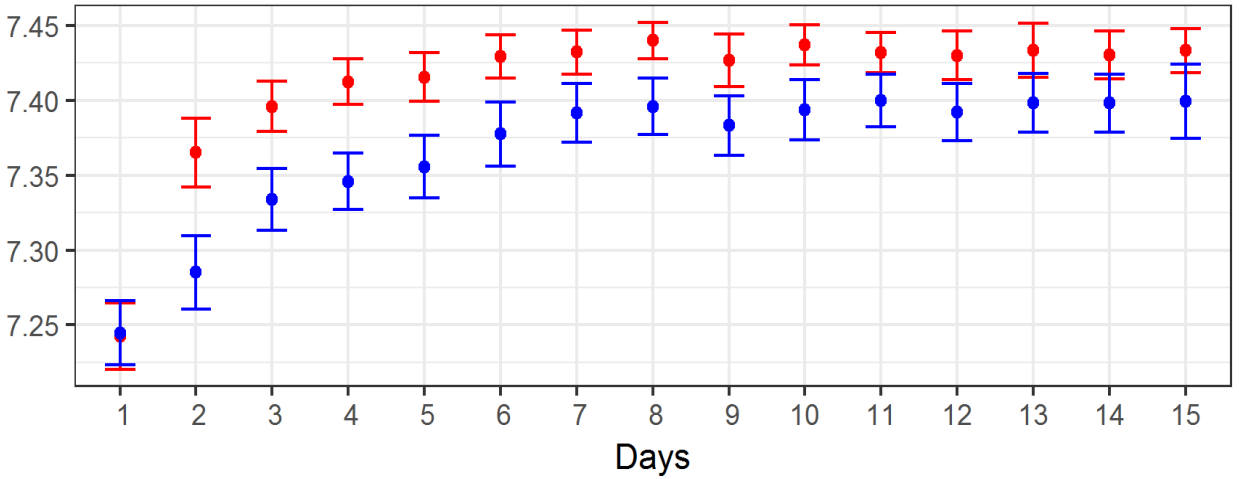
PaCO2, mm Hg, P <0.001



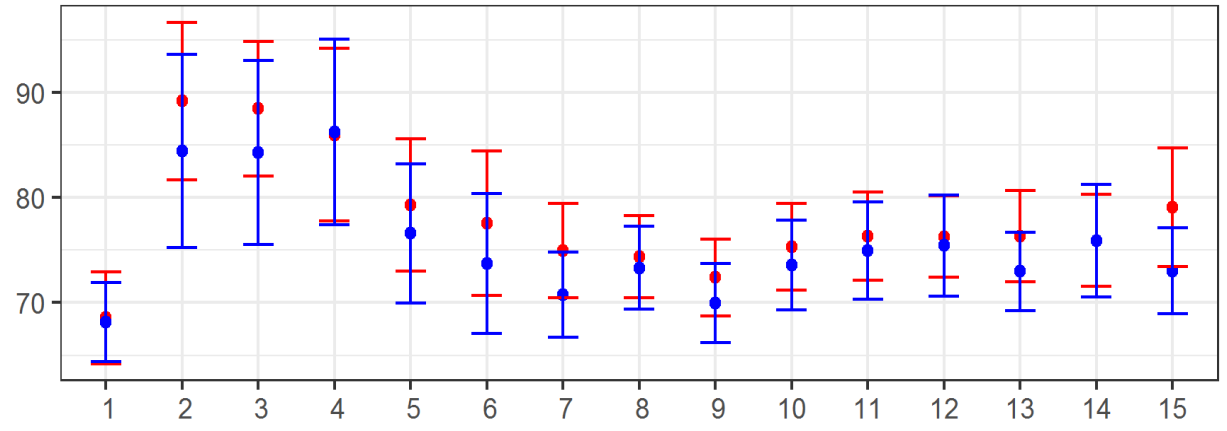
SaO2, P = 0.007



pH, P <0.001



PaO2, mm Hg, P = 0.167

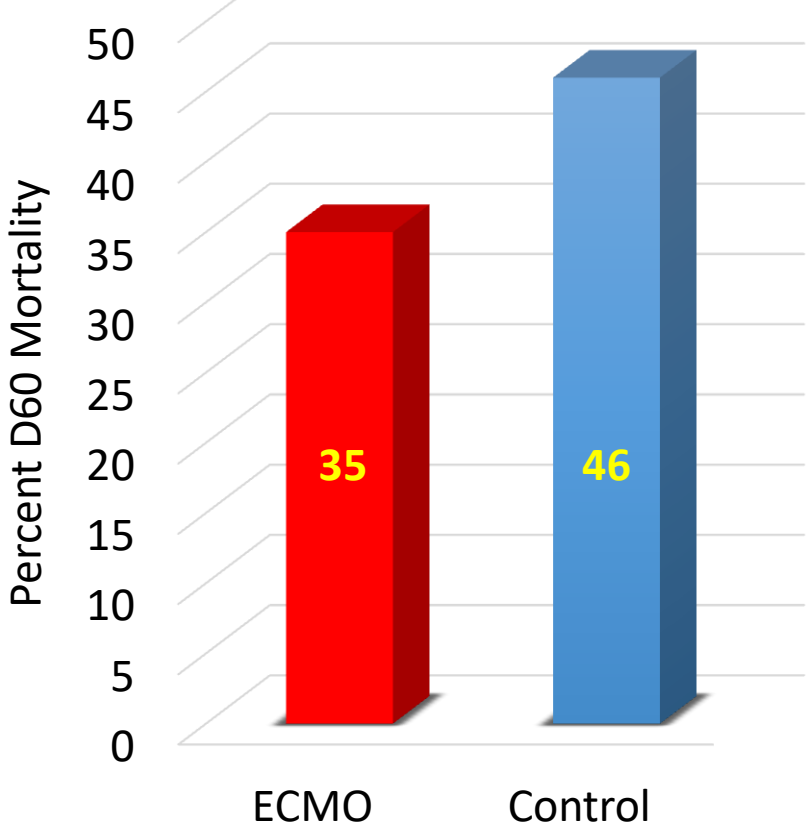


Characteristic	ECMO group (N = 124)	Control group (N = 125)	Absolute Risk Difference (95% CI)
Prone positioning — no. (%)	82 (66)	**113 (90)**	-24 (-34 to -14)
Neuromuscular blockade — no. (%)	122 (98)	**125 (100)**	-2 (-6 to 1)
iNO or prostacyclin — no. (%)	75 (60)	104 (83)	-23 (-33 to -12)
Recruitment maneuvers — no. (%)	27 (22)	54 (43)	-21 (-32 to -10)
Corticosteroids — no. (%)	80 (65)	82 (66)	-1 (-13 to 11)

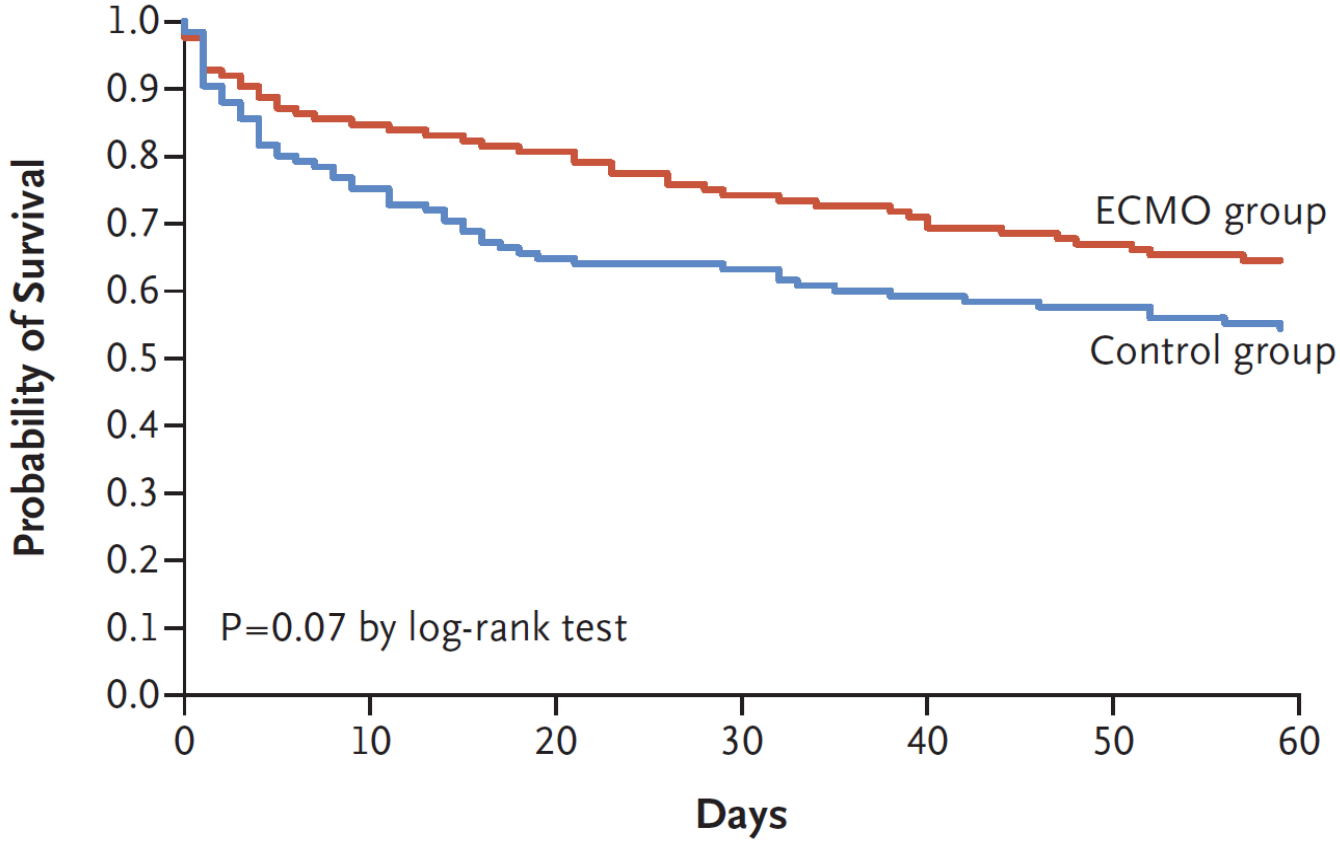
Primary Endpoint

Primary Endpoint

Relative Risk, 0.76, 95% CI, 0.55-1.04; P=0.087



Hazard Ratio, 0.70; 95% CI, 0.47-1.04, P=0.074 by log-rank test



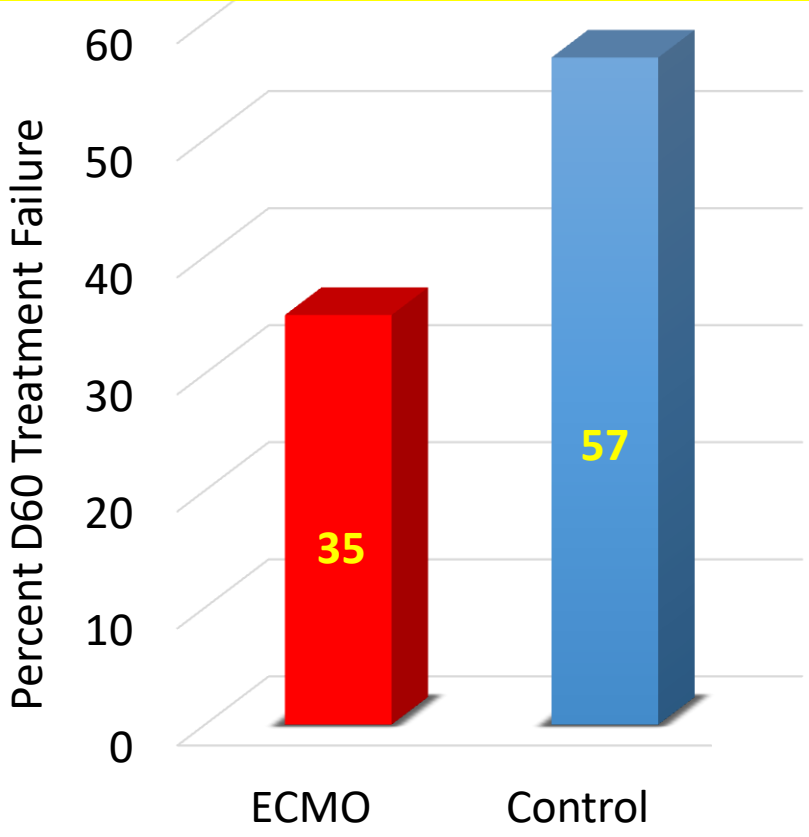
Key Secondary Endpoint

Death in ECMO group patients

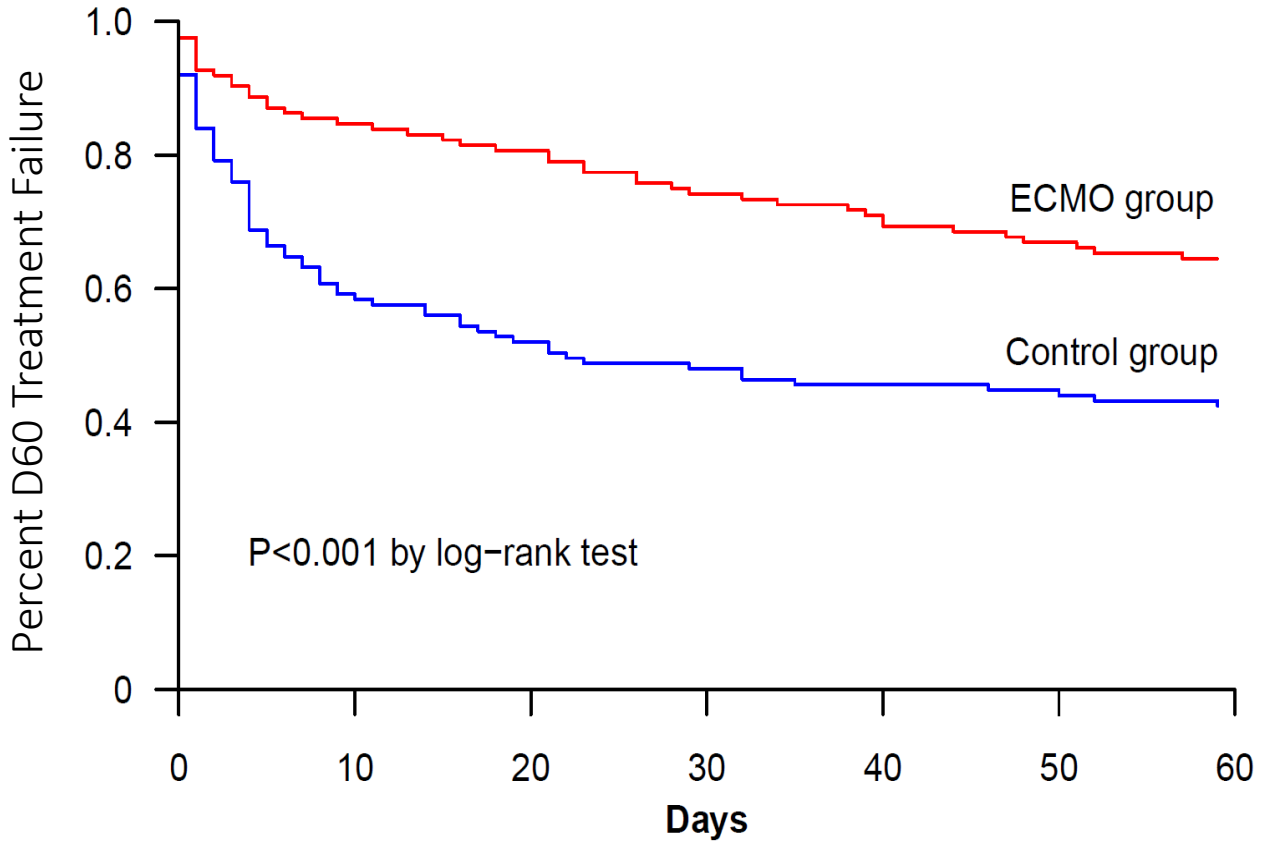
Death or Crossover to ECMO in controls

Key Secondary Endpoint

Relative Risk, 0.62; 95% CI, 0.47-0.82; P<0.001

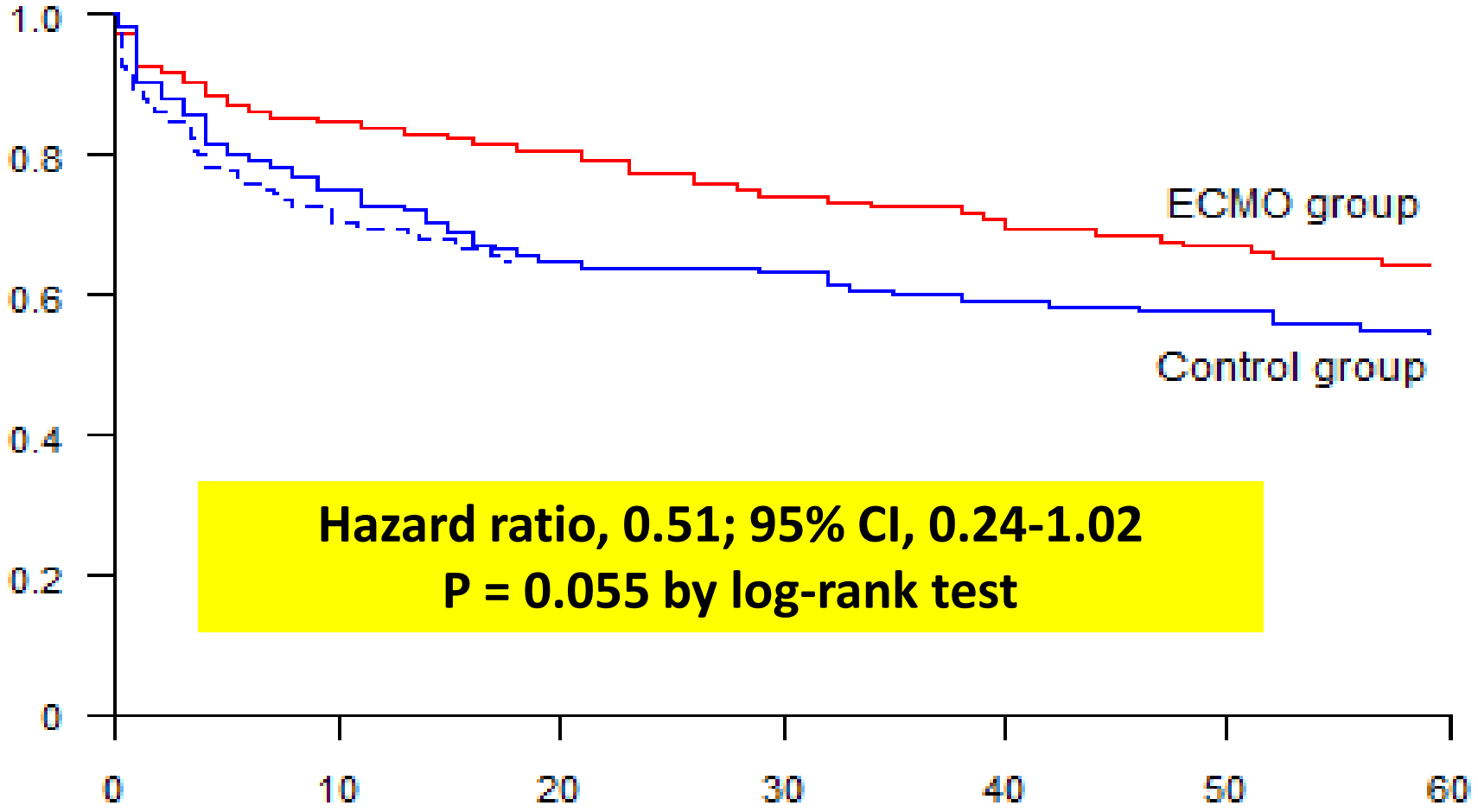


Hazard ratio, 0.48; 95% CI, 0.34-0.70, P <0.001 by log-rank test



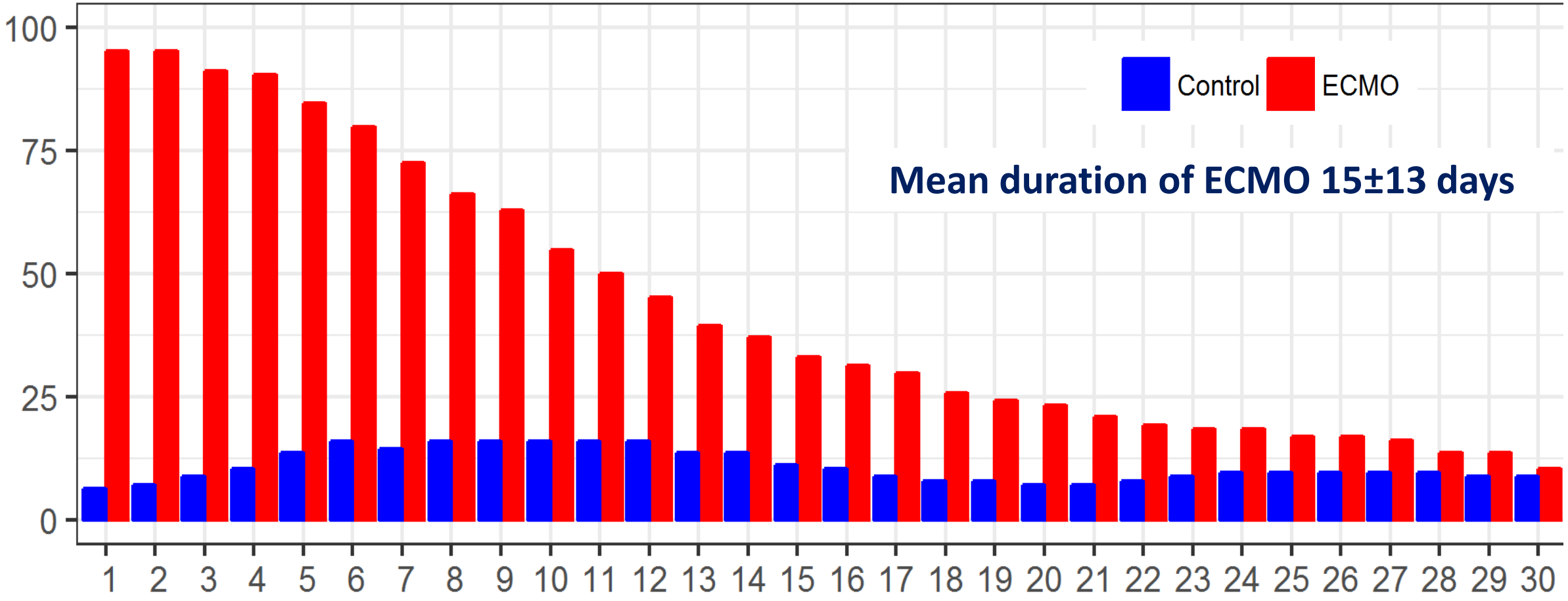
Death in ECMO group patients; Death or Crossover to ECMO in control patients

Rank-Preserving Structural-Failure Time Analysis Controlling for crossover in controls



Other Endpoints

Patients Under ECMO



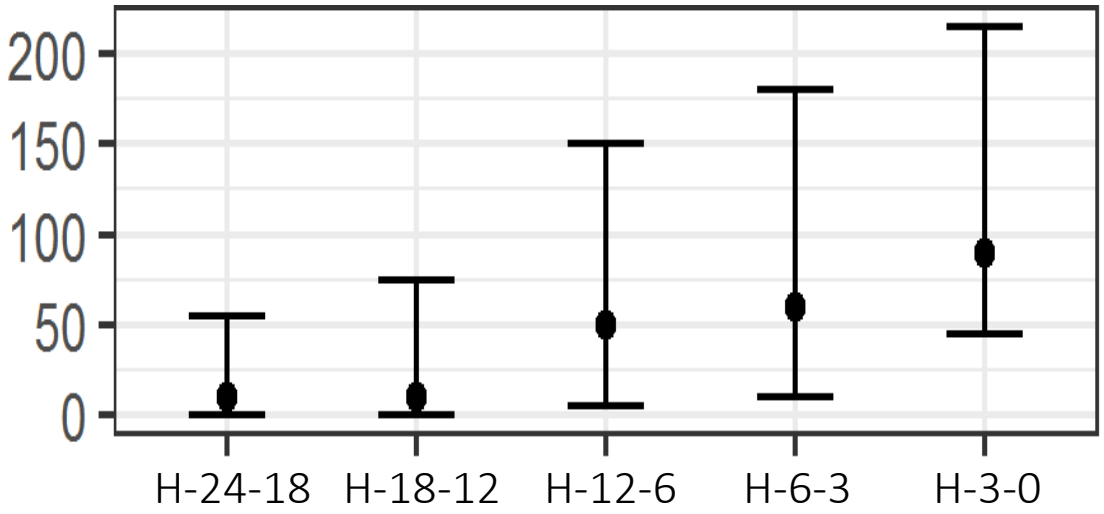
Endpoint at D60	ECMO Group (N = 124)	Control Group (N = 125)	Median Difference (95% CI)
Days alive and free of vasopressor use	49 [0–56]	40 [0–53]	**9 (0 to 51)**
Days alive and free of cardiac failure (SOFA)	48 [0–56]	41 [0–53]	**7 (0 to 51)**
Days alive and free of dialysis	50 [0–60]	32 [0–57]	**18 (0 to 51)**
Days alive and free of renal failure (SOFA)	46 [0–60]	21 [0–56]	**25 (6 to 53)**
Days alive and free of prone position	59 [0–59]	46 [0–57]	**13 (5 to 59)**
Days alive and free of NO/prostacyclin	59 [0–60]	39 [0–58]	**20 (4 to 59)**

Crossover to ECMO

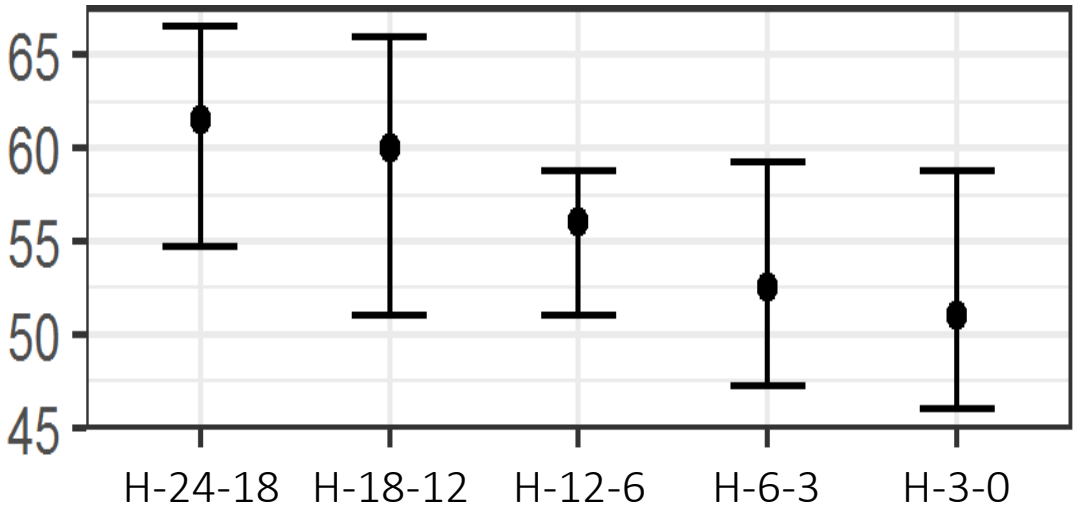
Crossover to ECMO in Controls

- 28% (35/125) of controls received rescue ECMO
  - Refractory hypoxemia, 6.5±9.7 days postrandomization
- These patients had more severe ARDS at baseline
  - Higher Plateau pressure:
    - *31.7±5.5 vs 28.5±4.1 cm H_2O*
  - Higher Driving pressure:
    - *20.2±6.1 vs 16.6±5.3 cm H_2O*
  - Lower Respiratory system compliance:
    - *21.3±9.2 vs 27.1±11.0 ml/cm H_2O*
  - More quadrants with infiltrate on chest Xray:
    - *3.7±0.6 vs 3.3±0.9*

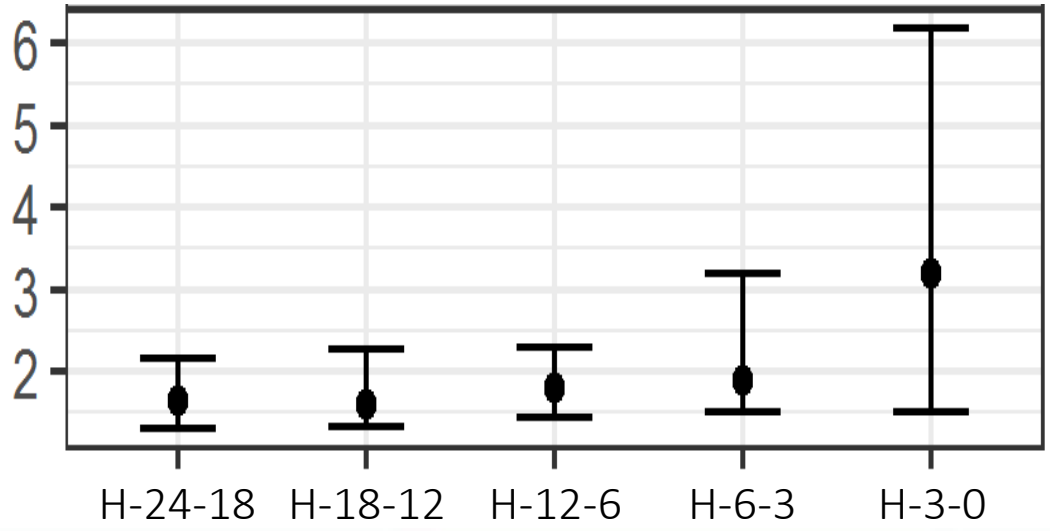
Inotropic Score, P < 0.001



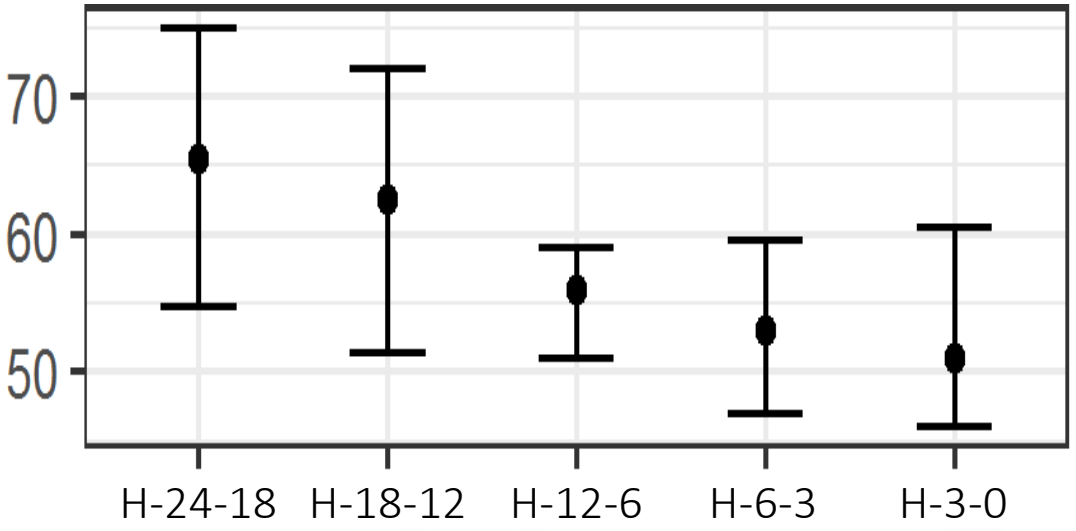
Pao2, P < 0.001



Arterial lactate, P < 0.001



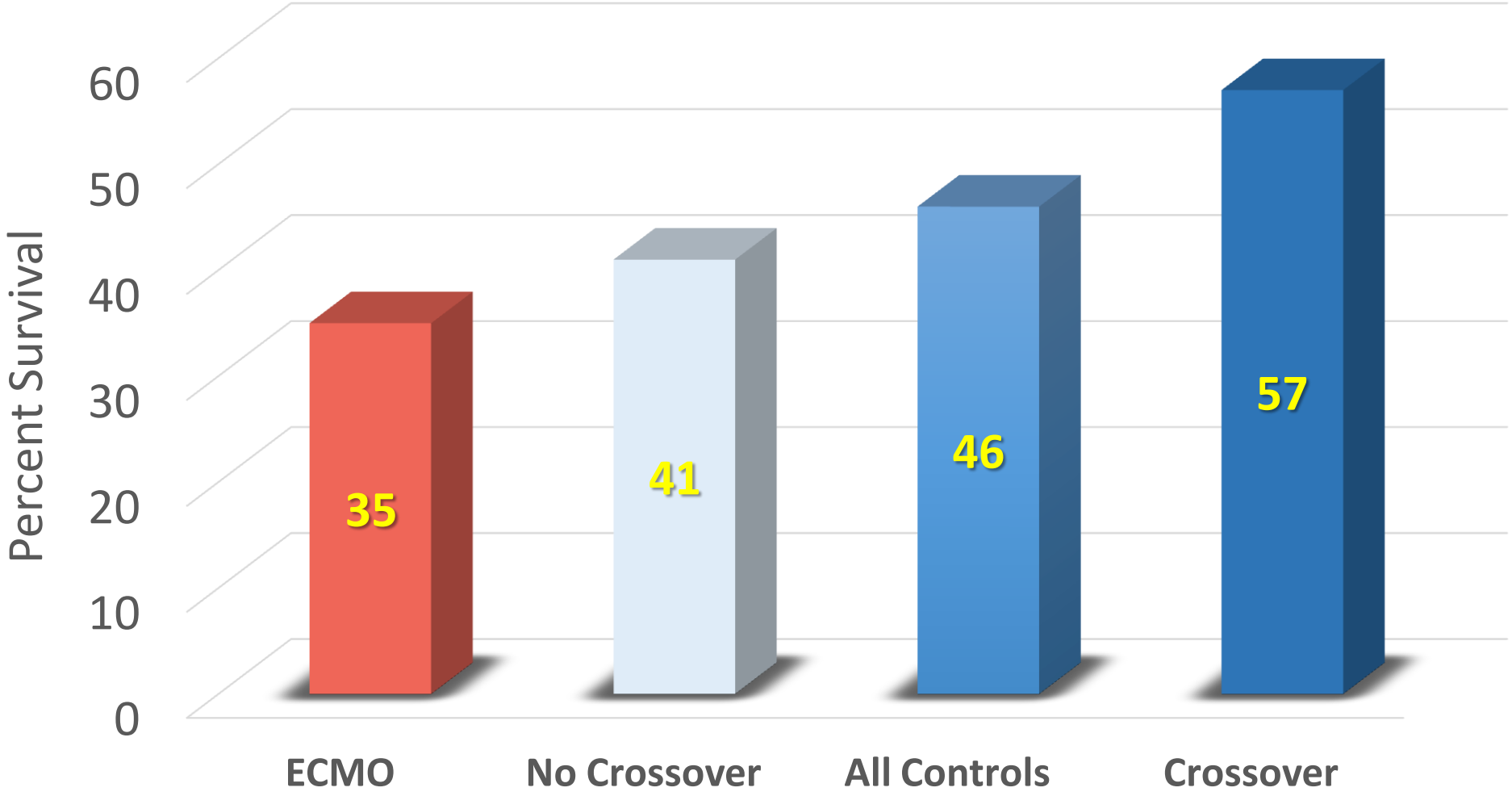
Pao2:Fio2, P < 0.001



Crossover to ECMO in Controls

- Before crossover, of the 35 controls who had ECMO
  - 9 had cardiac arrest
  - 7 had severe right heart failure
  - 11 developed renal failure requiring dialysis
- Venoarterial ECMO applied to 7 patients
  - 6 under cardiopulmonary resuscitation

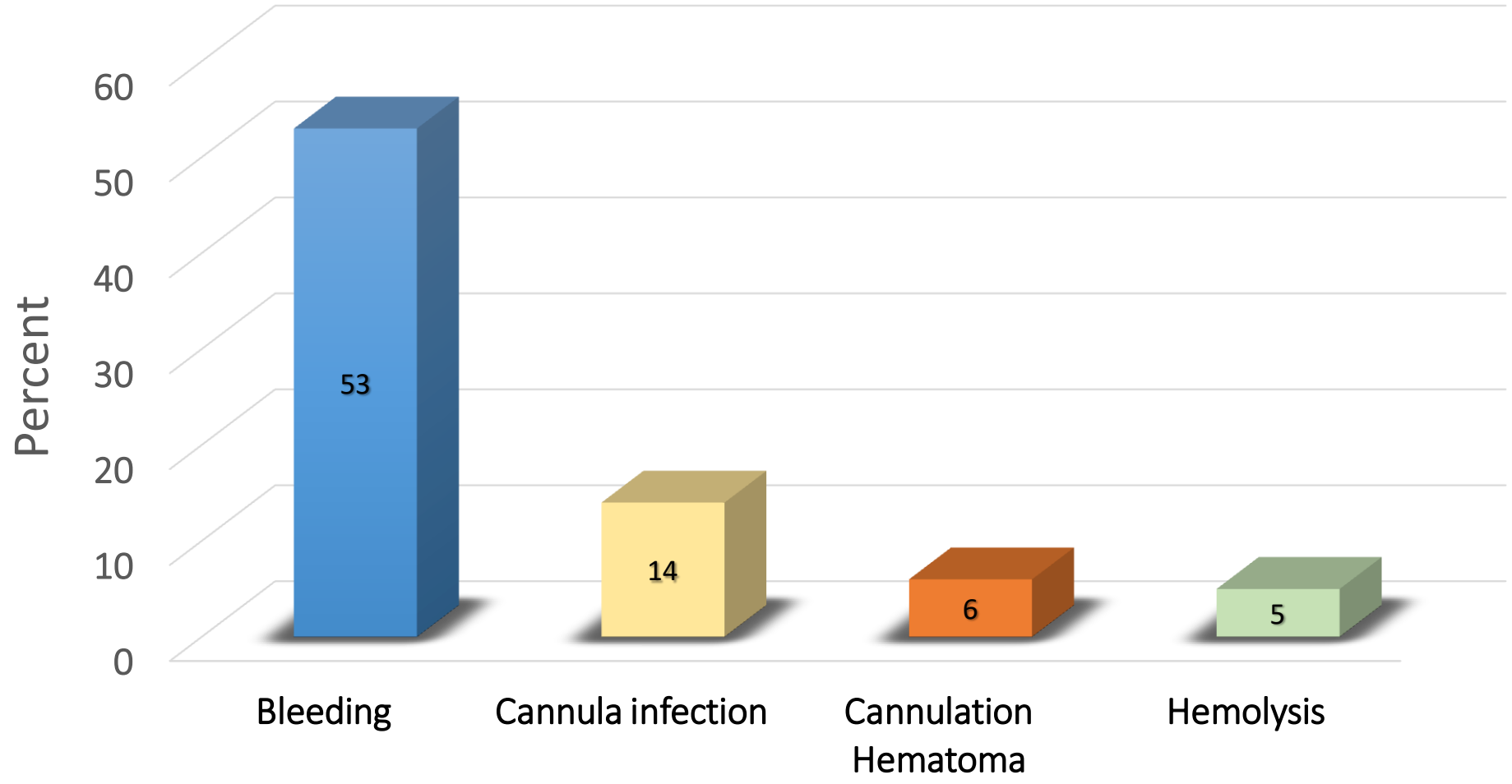
Control Crossover Outcomes



Adverse Events

Event	ECMO Group (N = 124)	Control Group (N = 125)	Absolute Risk Difference (95% CI)*
	number (percent)		*percentage points*
Pneumothorax	18 (15)	16 (13)	2 (–7 to 10)
Thrombocytopenia†			
Any	50 (40)	40 (32)	8 (–4 to 20)
Severe	33 (27)	20 (16)	11 (0 to 21)
Hypothermia‡	28 (23)	27 (22)	1 (–9 to 11)
Bleeding			
Leading to transfusion	57 (46)	35 (28)	18 (6 to 30)
Massive§	3 (2)	1 (1)	2 (–2 to 6)
Cardiac rhythm disturbances	38 (31)	46 (37)	–6 (–18 to 6)
Cardiac arrest	24 (19)	22 (18)	2 (–8 to 12)
Stroke¶	3 (2)	8 (6)	–4 (–10 to 1)
Ischemic stroke	0	6 (5)	–5 (–10 to –2)
Hemorrhagic stroke	3 (2)	5 (4)	–2 (–7 to 3)
Massive stroke	2 (2)	1 (1)	1 (–3 to 5)
Ventilator-associated pneumonia treated with antibiotic agents	48 (39)	46 (37)	2 (–10 to 14)

ECMO-related Adverse Events



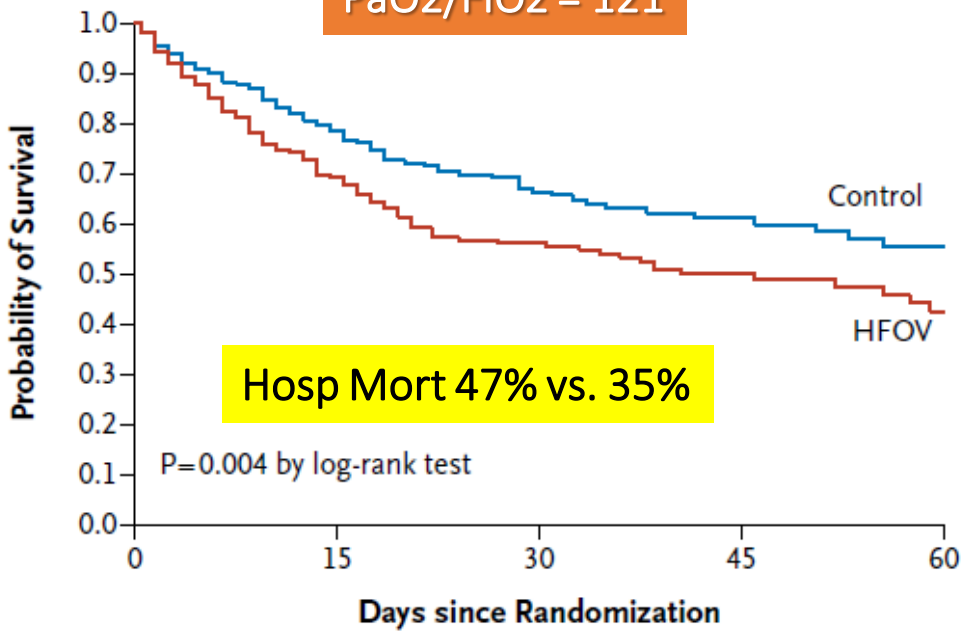
Conclusion

- Among patients with very severe ARDS
  - 60-day mortality (35% vs. 46%)
  - Was not significantly lower with ECMO
  - Than with a strategy of conventional MV
    - *That included ECMO as rescue therapy*
- Rescue crossover to ECMO in 28% of Controls
  - Extremely sick before crossover
  - 57% died

Why EOLIA should be considered a positive trial…

OSCILLATE and OSCAR…

PaO2/FIO2 = 121

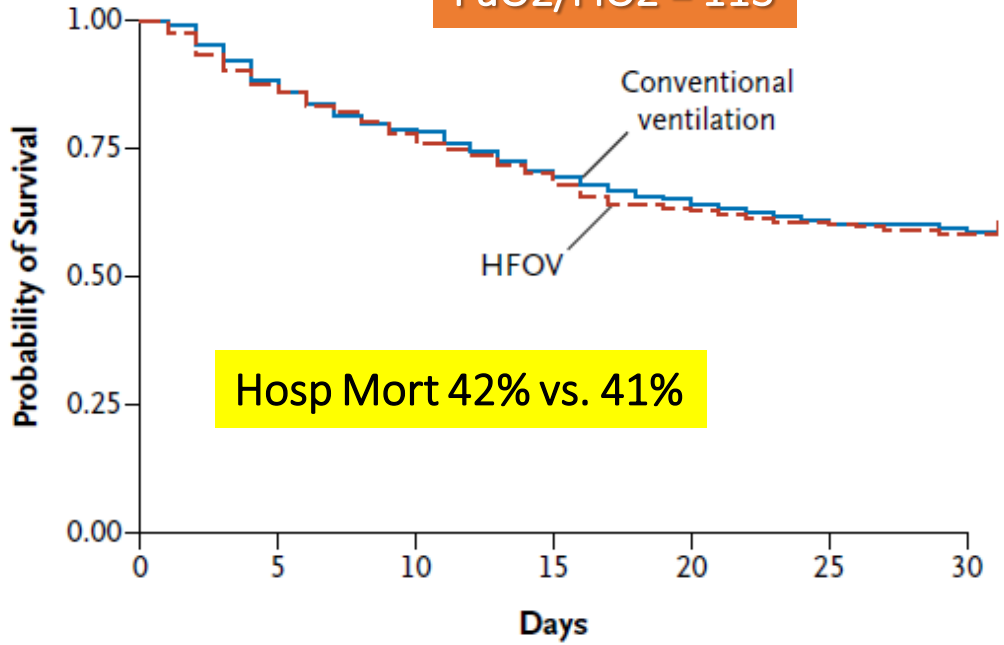


Hosp Mort 47% vs. 35%

No. at Risk					
HFOV	275	169	98	54	26
Control	273	181	92	54	39

Figure 2. Probability of Survival from the Day of Randomization to Day 60 in the HFOV and Control Groups.

PaO2/FIO2 = 113



Hosp Mort 42% vs. 41%

No. at Risk							
Conventional ventilation	397	351	312	281	259	243	236
HFOV	398	349	311	280	253	241	233

Figure 3. Kaplan–Meier Survival Estimates during the First 30 Study Days.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

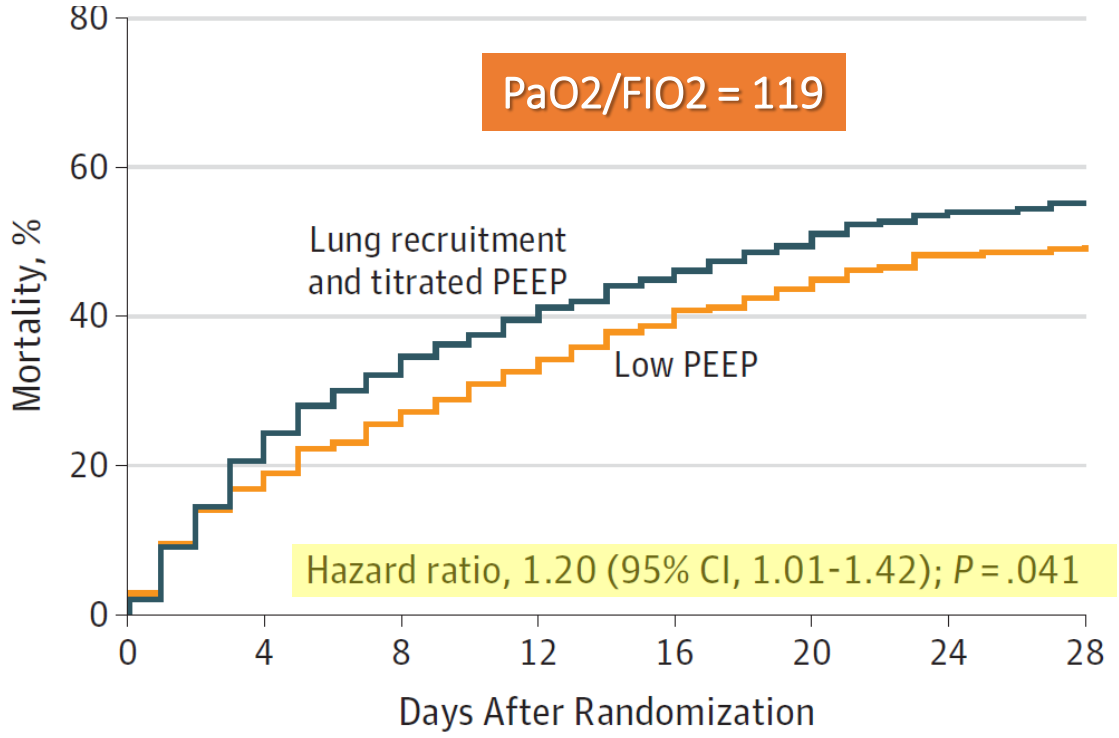
Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome

A Randomized Clinical Trial

JAMA. doi:10.1001/jama.2017.14171
Published online September 27, 2017.

Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators

PaO2/FIO2 = 119

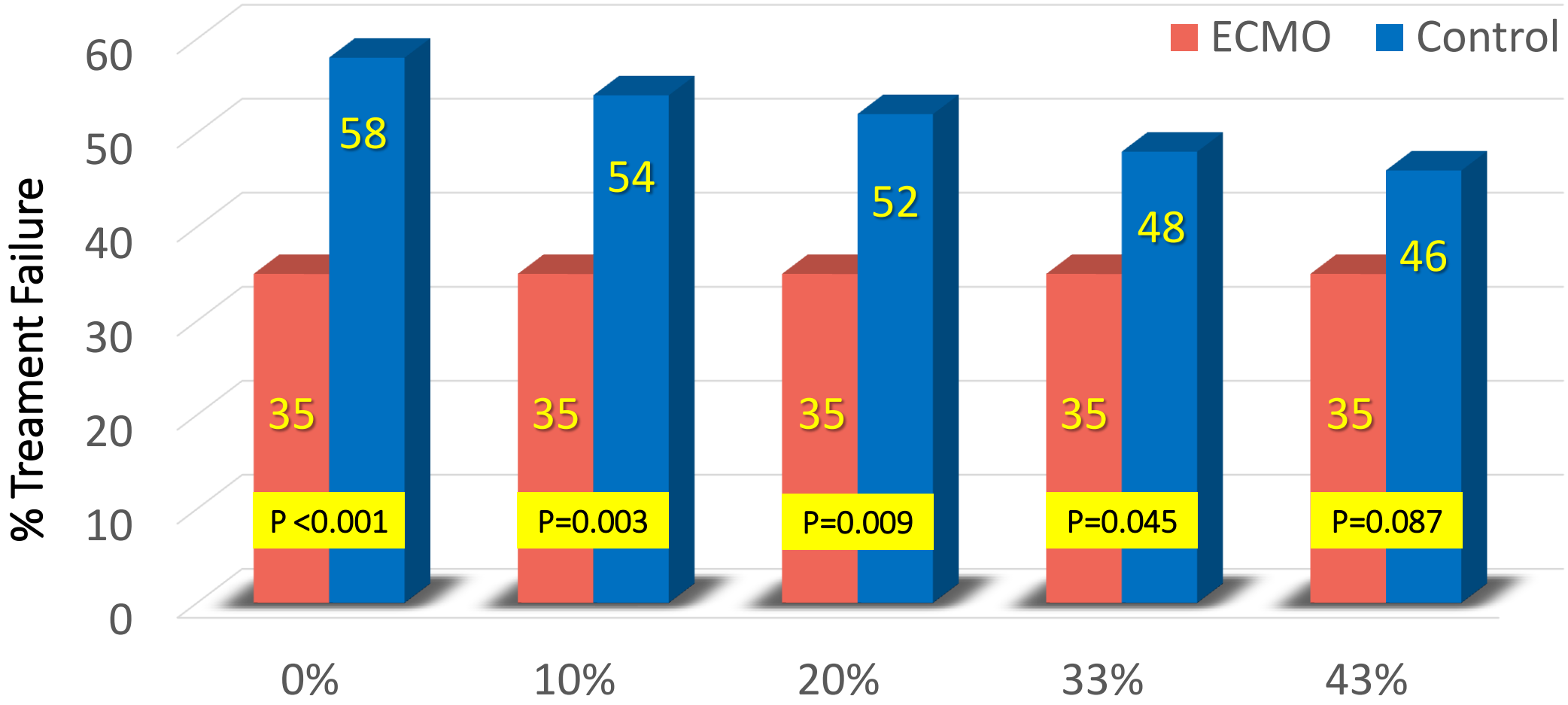


Hosp Mort 55% vs. 49%

No. at risk								
Lung recruitment and titrated PEEP	501	397	340	303	276	254	233	225
Low PEEP	509	423	378	343	312	286	264	260

Sensitivity Analyses

Treatment Failure at D60 Sensitivity Analysis



Survival Rates in Control Patients Crossed Over to ECMO

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Learning from a Trial Stopped by a Data and Safety Monitoring Board

David Harrington, Ph.D., and Jeffrey M. Drazen, M.D.

Learning from a Trial Stopped by a Data and Safety Monitoring Board

David Harrington, Ph.D., and Jeffrey M. Drazen, M.D.

to the control group. The second analysis used a rank-preserving structural-failure time model approach to attempt to recover the causal effect of ECMO. That approach yielded an estimated hazard ratio for death within 60 days of 0.51 (95% CI, 0.24 to 1.02). These three analyses all point to the same conclusion — ECMO probably has some benefit in this context, despite the trial not being traditionally positive. In addition, most of the other secondary outcomes favored ECMO.

Bayesian Model

JAMA | Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial

Ewan C. Goligher, MD, PhD; George Tomlinson, MD, PhD; David Hajage, PhD; Duminda N. Wijeysundera, MD, PhD; Eddy Fan, MD, PhD; Peter Jüni, MD; Daniel Brodie, MD; Arthur S. Slutsky, MD; Alain Combes, MD, PhD

JAMA. October 22, 2018, doi:10.1001/jama.2018.14276

IMPORTANCE Bayesian analysis of clinical trial data may provide useful information to aid in study interpretation, especially when trial evidence suggests that the benefits of an intervention are uncertain, such as in a trial that evaluated early extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS).

OBJECTIVE To demonstrate the potential utility of Bayesian analyses by estimating the posterior probability, under various assumptions, that early ECMO was associated with reduced mortality in patients with very severe ARDS in a randomized clinical trial (RCT).

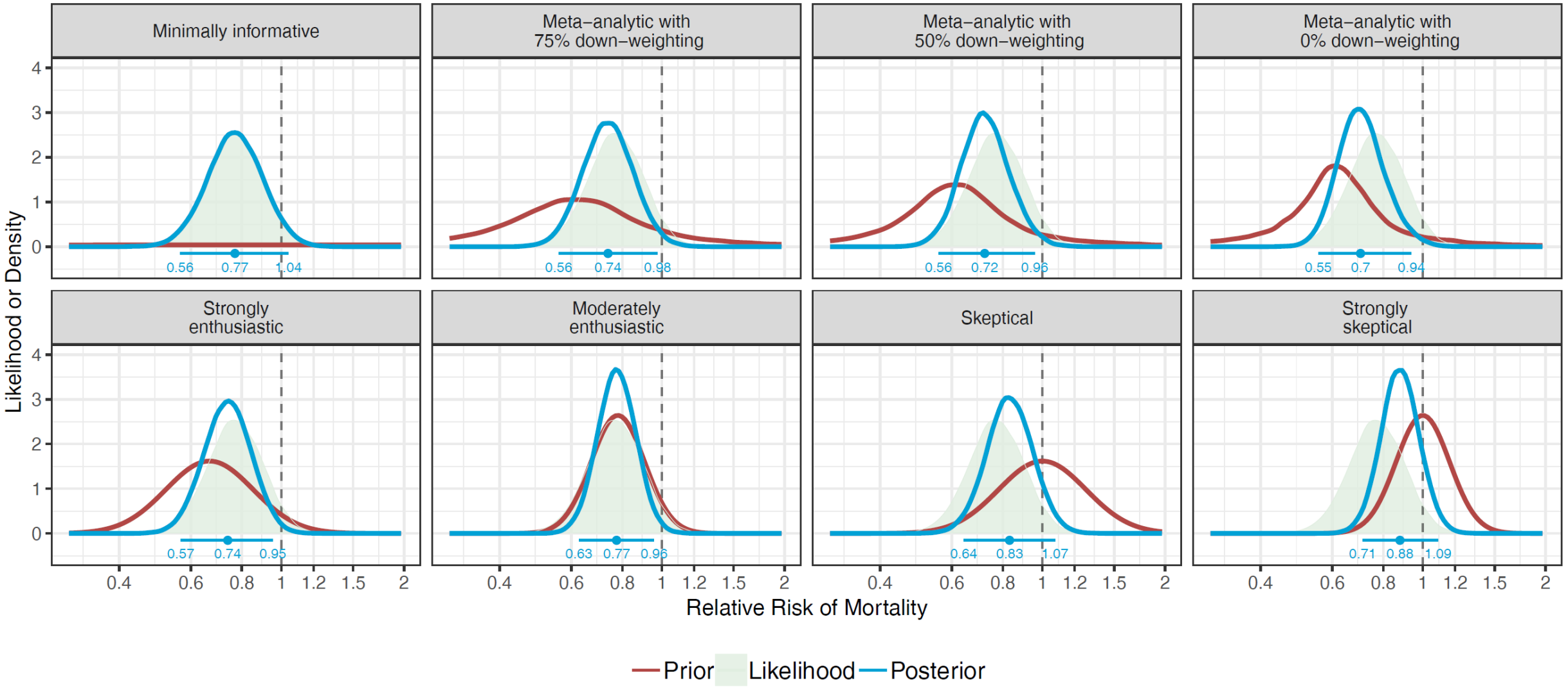
Editorial

Supplemental content

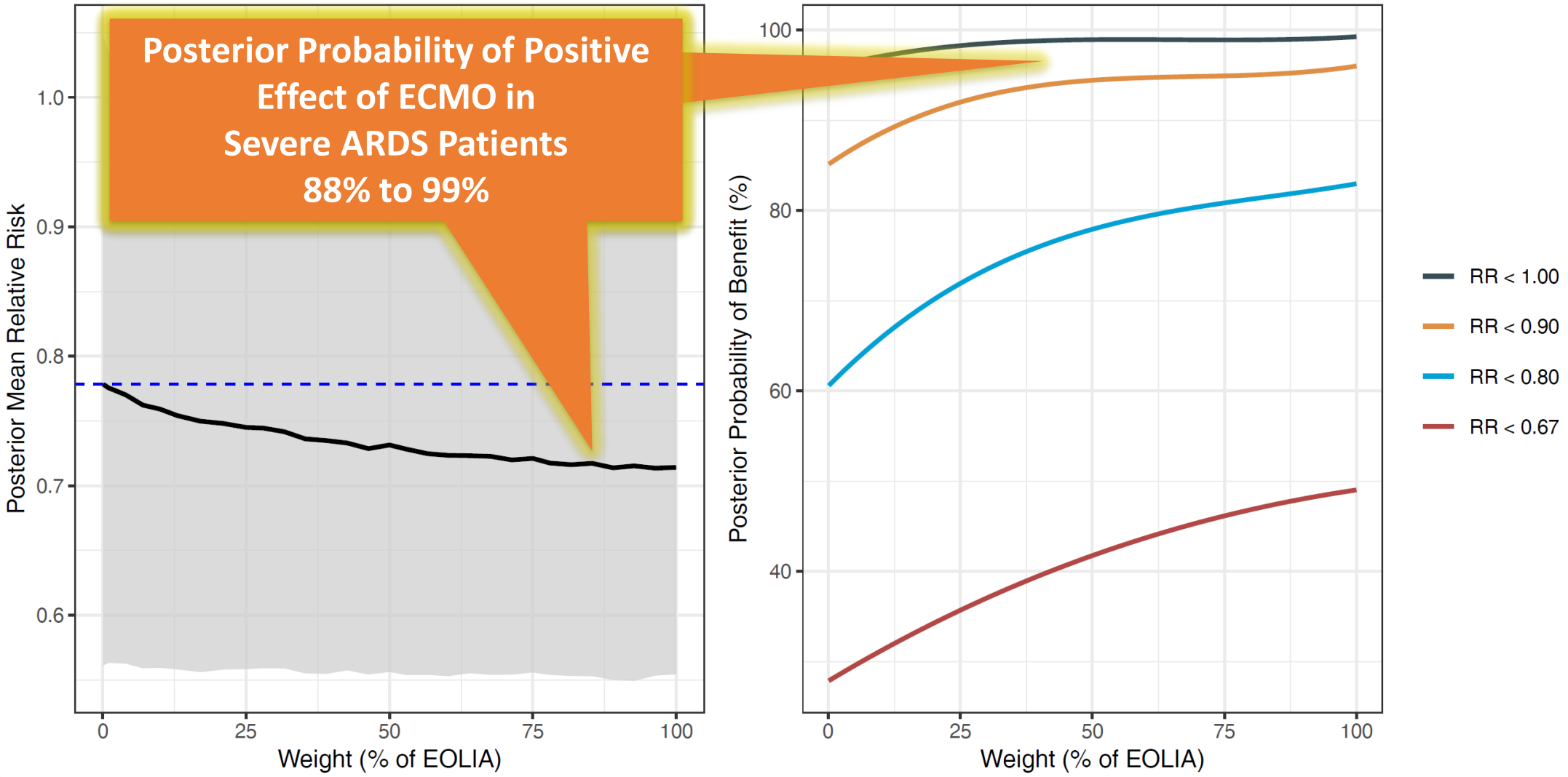
JAMA Journal of the American Medical Association

The JAMA Network

Bayesian Analysis of EOLIA…



Bayesian Analysis of EOLIA…



Editorial

ONLINE FIRST FREE

October 22, 2018

Time for Clinicians to Embrace Their Inner Bayesian?

Reanalysis of Results of a Clinical Trial of Extracorporeal Membrane Oxygenation

Roger J. Lewis, MD, PhD[1,2,3]; Derek C. Angus, MD, MPH, FRCP[4,5,6]

Clinicians and researchers should no longer ask "Does ECMO work?" because that question appears to be answered...
Instead, the key question that should now be asked is "By how much does ECMO work, in whom, and at what cost?"

And now the Meta-Analyses…

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