Year in Review
Critical Care

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  - N Engl J Med. 2018 May 24;378(21):1965-1975
  - Crit Care Med. 2018 Dec;46(12):1943-1952
  - JAMA. 2019 Feb 18. doi: 10.1001/jama.2019
  - Intensive Care Med. 2018 Nov;44(11):1849-1858
- Sepsis
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  - JAMA Intern Med. 2019 Feb 1;179(2):213-223
  - Crit Care Med. 2019 Feb;47(2):152-158
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- Metabolic Acidosis Therapy
  - Lancet. 2018 Jul 7;392(10141):31-40
  - Intensive Care Med. 2018 Nov;44(11):1888-1895
- Delirium
  - N Engl J Med. 2018 Dec 27;379(26):2506-2516
  - Am J Respir Crit Care Med. 2018 May 1;97(9):1147-1156.

ARDS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

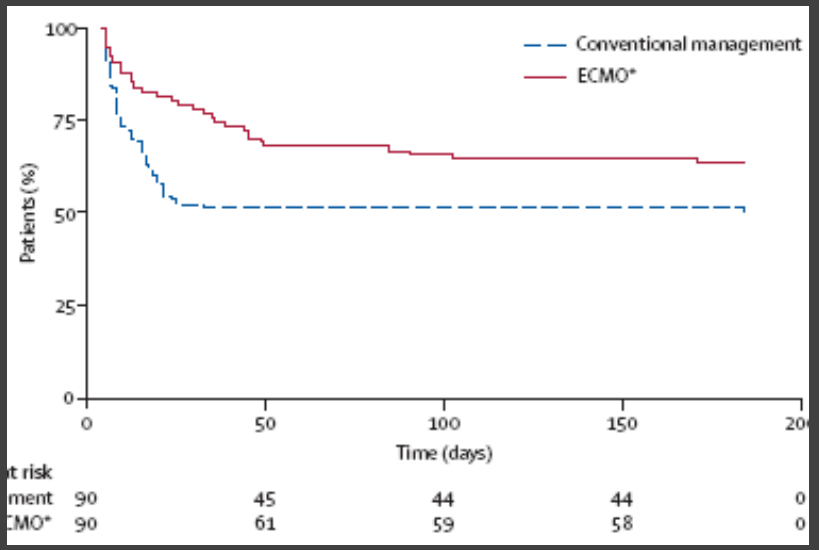
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

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*

CESAR study

- 2009년
- 53 of ECMO vs. 32 of control at 6months

- Death and severe disability at 6 months (RR, 0.69; 95% CI 0.05–0.97; P=0.03)
- Death at 6 months (RR 0.73; 95% CI 0.52-1.03; P=0.07)



- Problem of study design
  - Only 75% referred for ECMO
  - No standardized protocol in control group
  - Lost FU 3 patients of control at 6 months

Lancet. 2009 Oct 17;374(9698):1351-63

Methods

Endotracheal intubation and MV < 7 days

- P/F ratio < 50 mm Hg >3 hours
- P/F ratio <80 mm Hg >6 hours
- pH <7.25 with $PaCO_2$ ≥60 mm Hg >6 hours

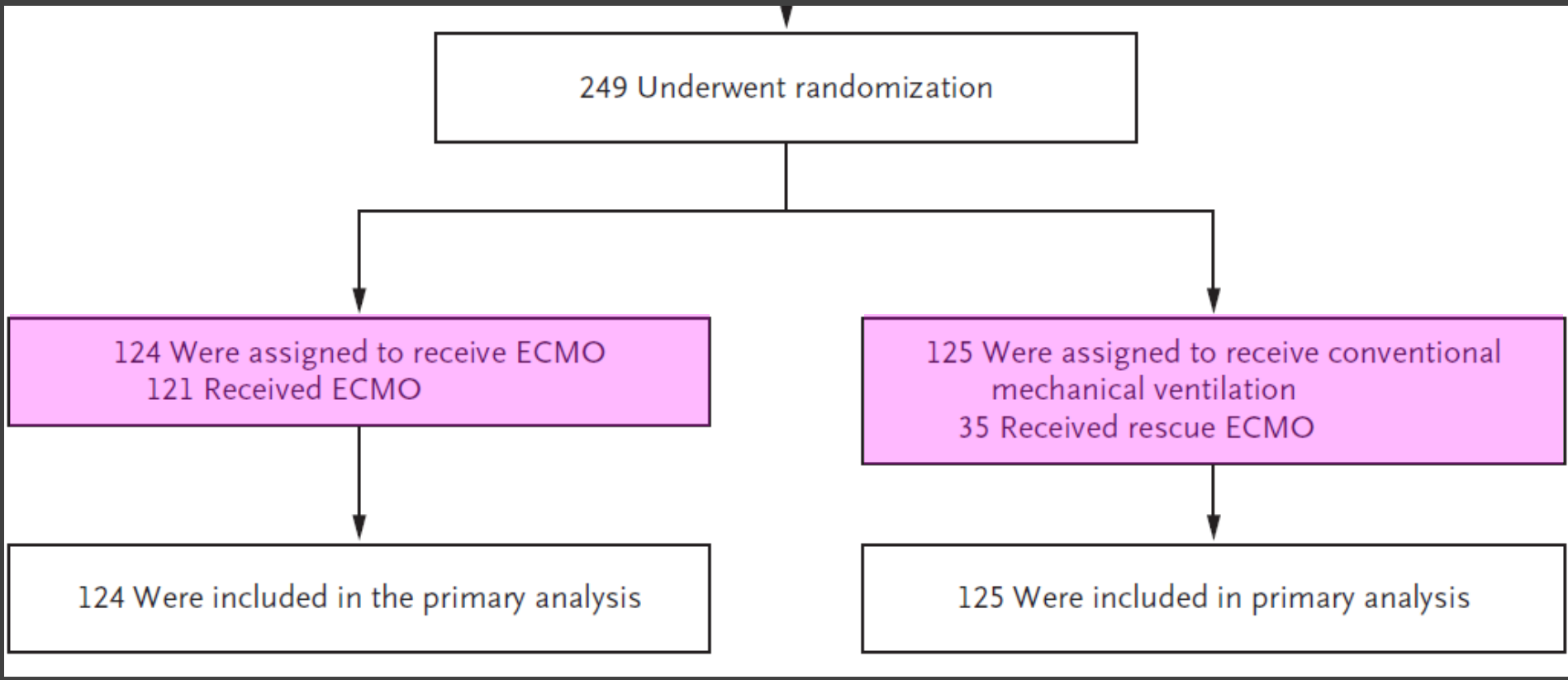
With RR increased to 35 /min adjusted to keep a plateau pressure of ≤32 cm of water despite ventilator optimization (defined as FiO_2 ≥0.80, TV 6 ml/kg and PEEP ≥10 cm H_2O)

Methods

- Non-ECMO centers
  - ECMO retrieval team could establish ECMO within 2 hours after randomization and transfer the patient to the ECMO center.
- Primary endpoint: 60 days mortality

Methods

- 1015 assessed



- 35 patients (28%) crossed over to ECMO because of refractory hypoxemia at a mean (±SD) of 6.5±9.7 days after randomization.

Characteristics

Characteristic	ECMO Group (N=124)	Control Grou (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)

Characteristics

Characteristic	ECMO Group (N=124)	Control Grou (N=125)
Pao_2:FIo_2 — mm Hg	73±30	72±24
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
Pao_2 — mm Hg‡	69±25	68±22
$Paco_2$ — mm Hg	57±15	57±16
Prone positioning — no. (%)§	70 (56)	78 (62)
Inhaled nitric oxide or prostacyclin — no. (%)§	64 (52)	68 (54)
Recruitment maneuvers — no. (%)§	22 (18)	34 (27)
Neuromuscular blockade — no. (%)§	114 (92)	120 (96)

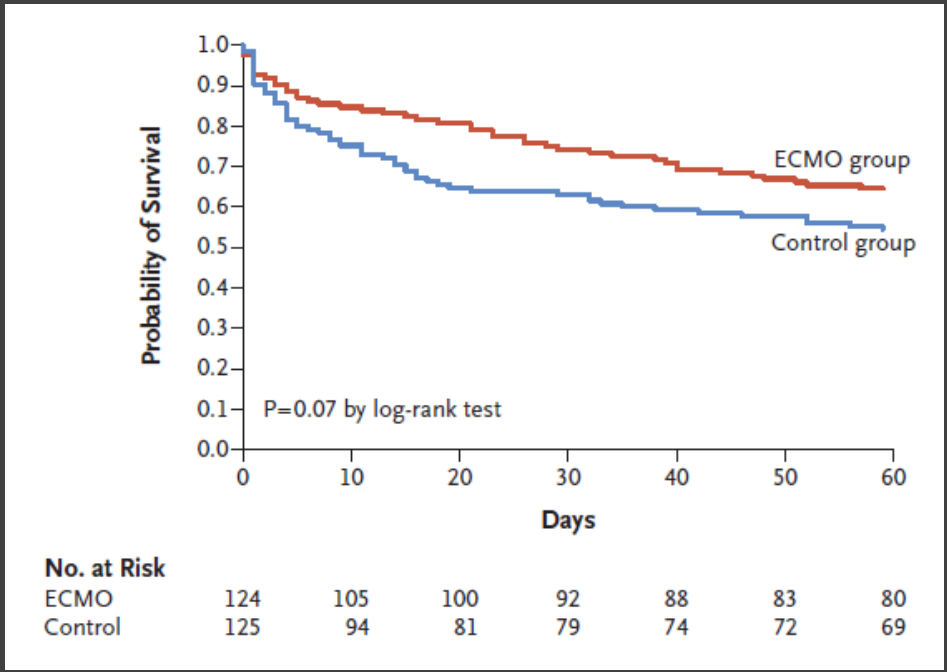
Results

Table 2. End Points.*

End Point	ECMO Group (N=124)	Control Group (N=125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001
Other end points				
Mortality at 90 days — no. (%)	46 (37)	59 (47)	−10 (−22 to 2)	
Median length of stay (interquartile range) — days				
In the ICU	23 (13–34)	18 (8–33)	5 (−1 to 10)	
In the hospital	36 (19–48)	18 (5–43)	18 (6 to 25)	
Median days free from mechanical ventilation (interquartile range)§	23 (0–40)	3 (0–36)	20 (−5 to 32)	
Median days free from vasopressor use (interquartile range)§	49 (0–56)	40 (0–53)	9 (0 to 51)	
Median days free from renal-replacement therapy (interquartile range)§	50 (0–60)	32 (0–57)	18 (0 to 51)	
Prone position — no. (%)¶	82 (66)	113 (90)	−24 (−34 to −14)	
Recruitment maneuvers — no. (%)¶	27 (22)	54 (43)	−21 (−32 to −10)	
Inhaled nitric oxide or prostacyclin — no. (%)¶	75 (60)	104 (83)	−23 (−33 to −12)	
Glucocorticoids — no. (%)¶	80 (65)	82 (66)	−1 (−13 to 11)	

Crossover to ECMO

- 60 day mortality: 57% (20 of 35) *vs.* 41% (37 of 90) of non-crossover control group, ECOM group 35% (44 of 124)



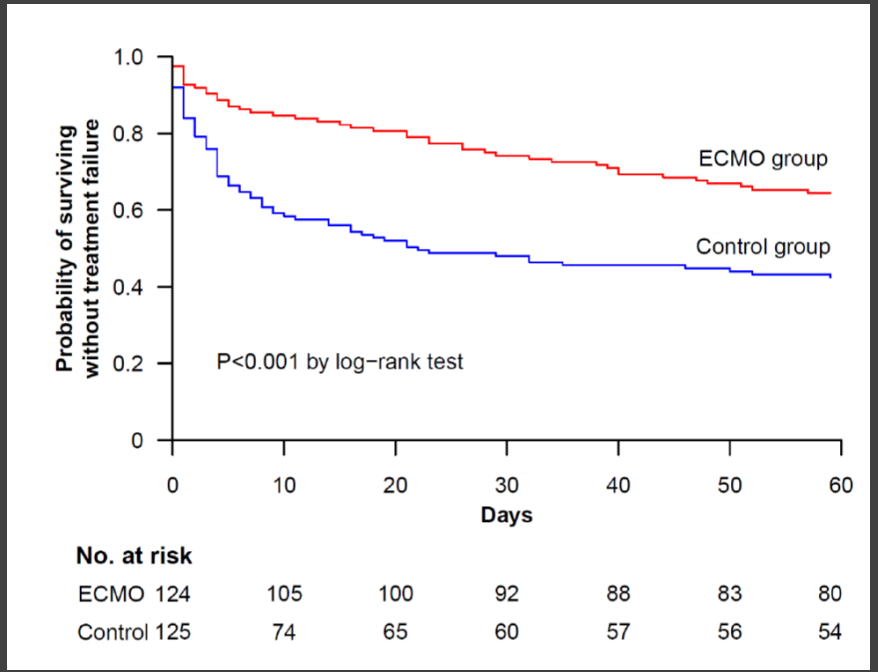


Table 3. Adverse Events as Defined by the Trial Protocol in the Intention-to-Treat Population.

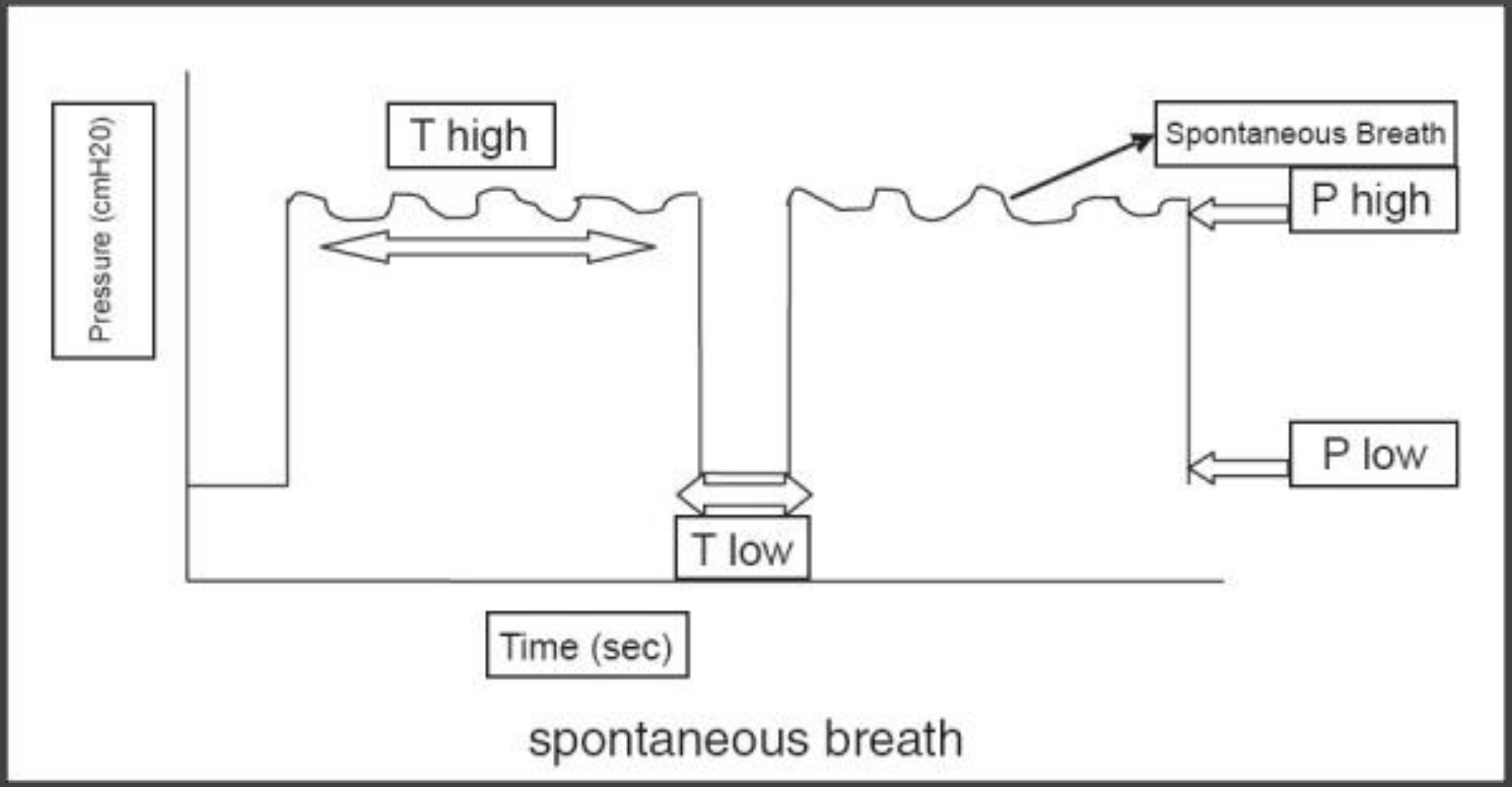
Event	ECMO Group (N=124)	Control Group (N=125)	Absolute Risk Difference (95% CI)*
	number (percent)		*percentage points*
Pneumothorax	18 (15)	16 (13)	2 (–7 to 10)
Thrombocytopenia†			
Any	50 (40)	40 (32)	8 (–4 to 20)
Severe	33 (27)	20 (16)	11 (0 to 21)
Hypothermia‡	28 (23)	27 (22)	1 (–9 to 11)
Bleeding			
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)
Gas emboli	0	0	0 (–3 to 3)

OPEN

Randomized Feasibility Trial of a Low Tidal Volume-Airway Pressure Release Ventilation Protocol Compared With Traditional Airway Pressure Release Ventilation and Volume Control Ventilation Protocols

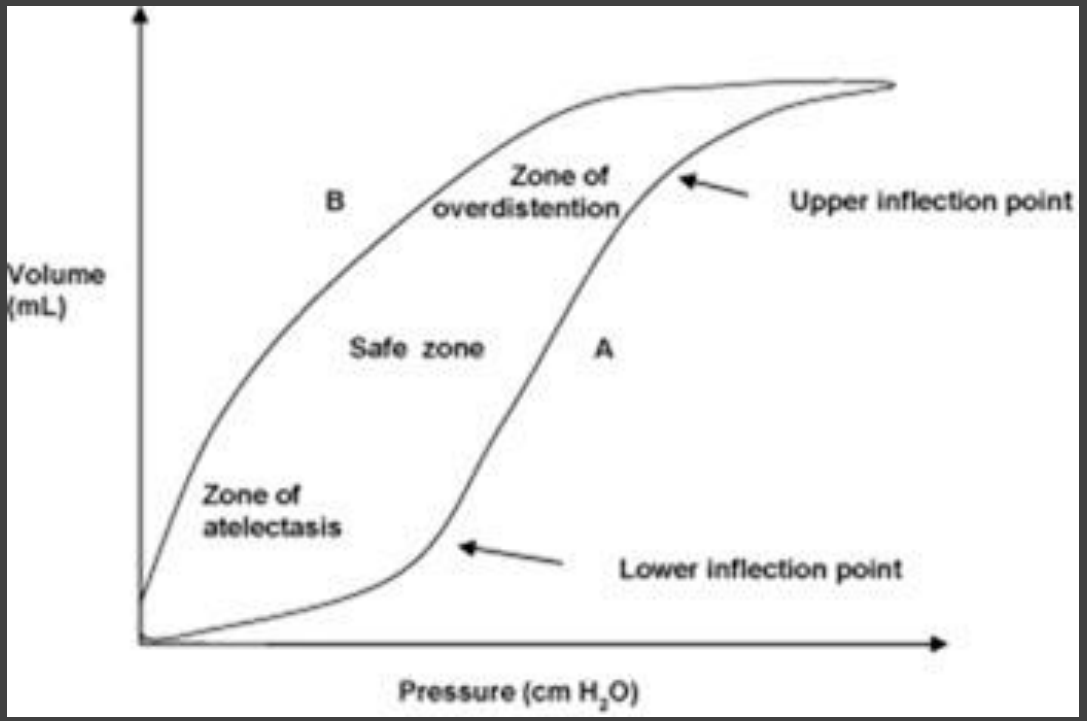
Eliotte L. Hirshberg, MD, MS[1,2,3,4]; Michael J. Lanspa, MD, MS[2,3]; Juhee Peterson, MS[3]; Lori Carpenter, RT[3]; Emily L. Wilson, MStat[1,3]; Samuel M. Brown, MD[1,2,3]; Nathan C. Dean, MD[2,3]; James Orme, MD[1,2,3]; Colin K. Grissom, MD,[2,3]

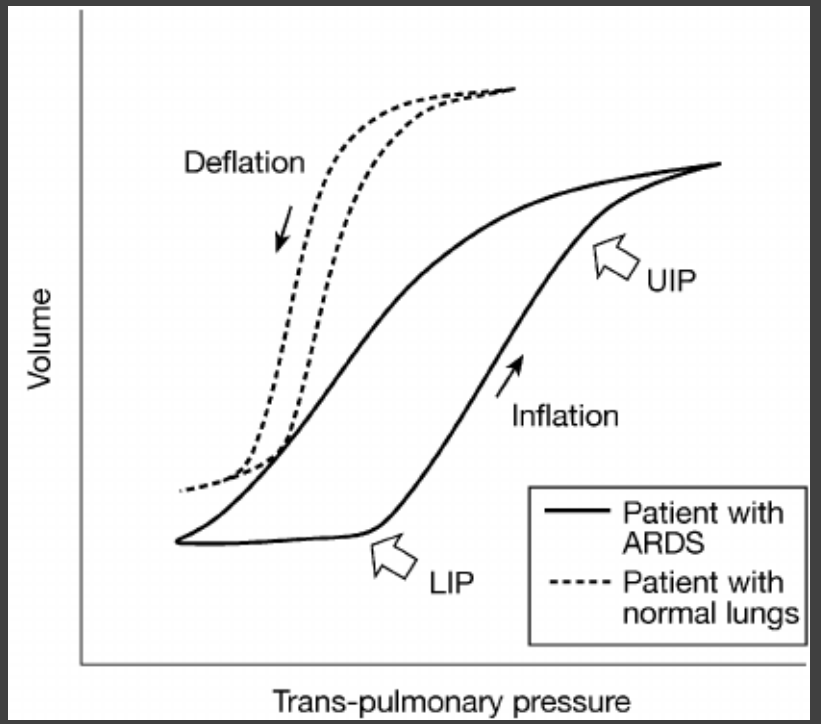
Airway Pressure Release Ventilation



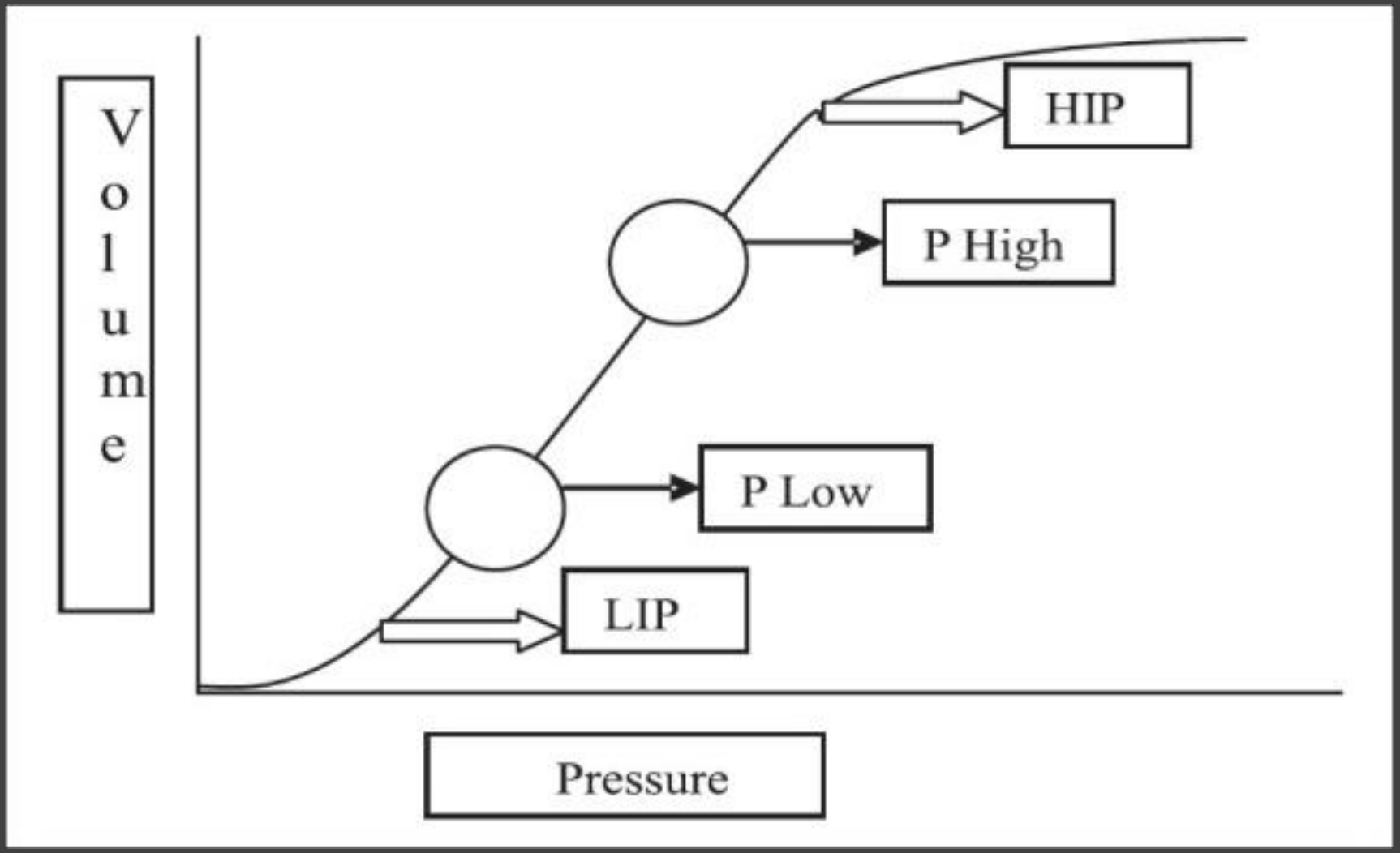
↓ FRC and lung compliance → the FRC is restored and inspiration starts from a more favorable pressure-volume relationship

Static Pressure-Volume (PV) Curve





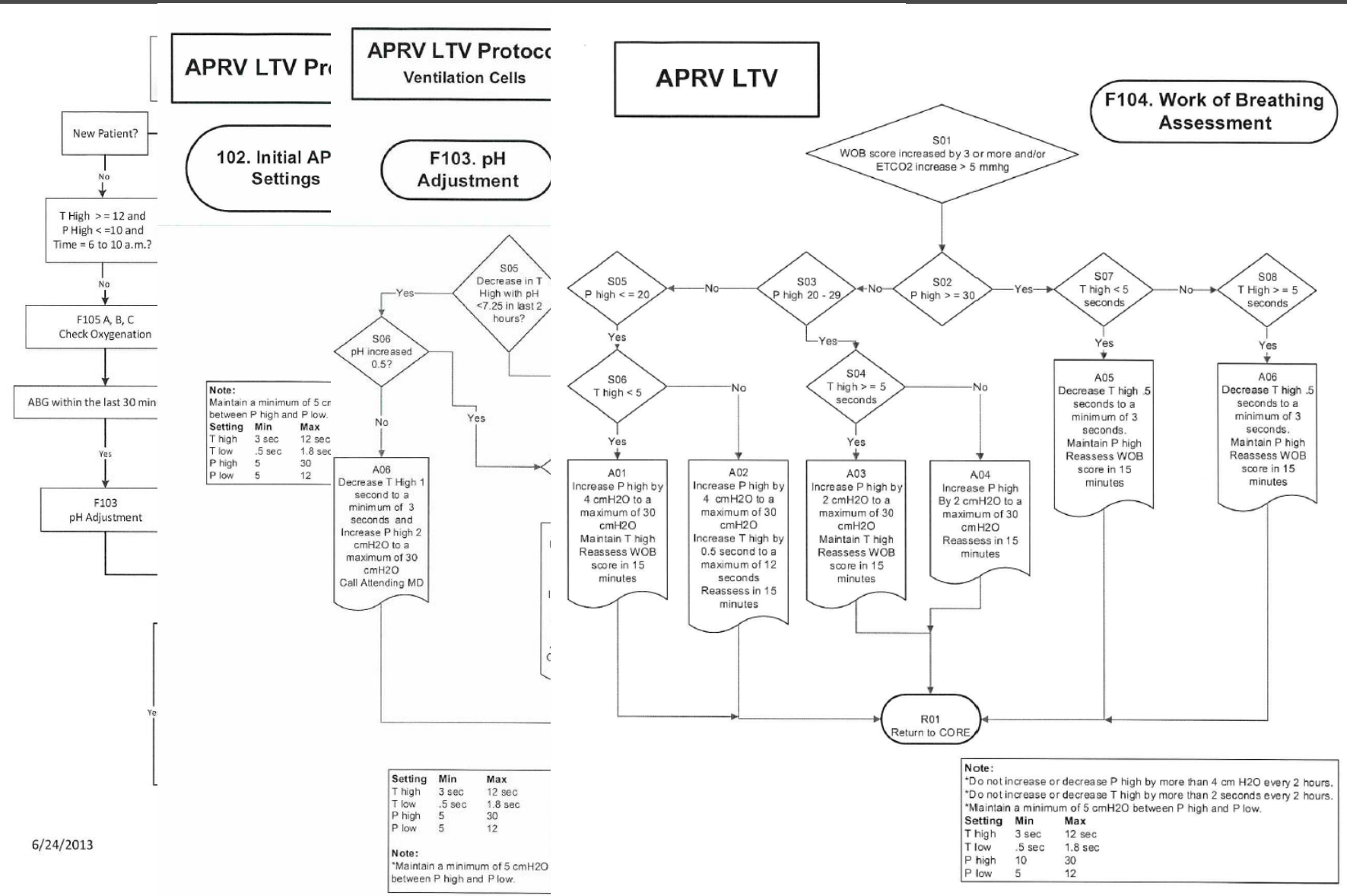
Airway Pressure Release Ventilation

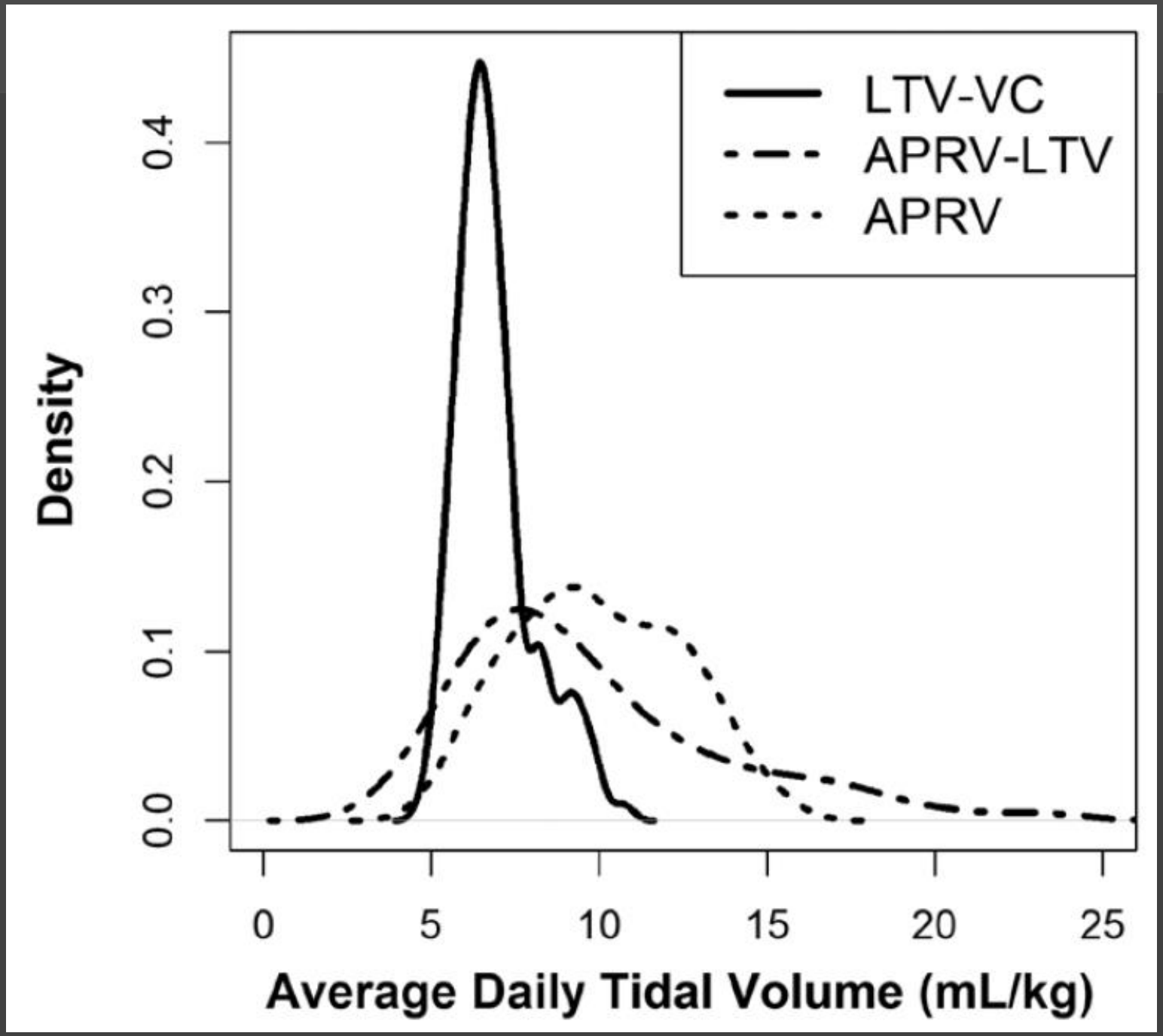


Advantage of APRV

- Effects on oxygenation
  - better V/Q matching to the poorly aerated dorsal region of the lungs
- Effects on hemodynamics
  - During spontaneous breathing: ↓ pleural pressure ↓ the intra-thoracic and right atrial pressure ↑ venous return, the pre-load and the cardiac output
- Effects on sedation and neuromuscular blockades usage

Methods - protocol




LTV-VC
APRV-LTV
APRV
Density
0.0
0.1
0.2
0.3
0.4
0
5
10
15
20
25
Average Daily Tidal Volume (mL/kg)

Results

Study Outcome	LTV-Volume Control *n* = 17	APRV-LTV *n* = 18	APRV *n* = 17	*p*
On-study ventilatory parameters,[a] reported as mean estimate (95% CI) from a mixed-effects model				
Average daily tidal volume/kg[b]				
Measured/release	6.8 (6.2–7.5)	8.0 (7.3–8.9)	8.6 (7.8–9.6)	**0.005**
Spontaneous	Not available	6.1 (5.2–7.2)	5.3 (4.5–6.3)	0.25
Mean airway pressure	13.6 (11.8–15.4)	15.7 (13.9–17.6)	16.1 (14.2–18.1)	0.15
Peak inspiratory pressure/daily peak high positive end-expiratory pressure	23.9 (21.6–26.3)	20.2 (17.7–22.8)	19.5 (16.9–22.2)	**0.03**
On-study hemodynamics, reported as mean estimate (95% CI) from a mixed-effects model				
Lowest daily mean arterial pressure	59 (54–63)	64 (60–69)	66 (62–71)	0.07
Highest daily central venous pressure	14 (12–16)	13 (11–15)	12 (10–15)	0.44
Protocol compliance, reported as median (IQR) or mean estimate (95% CI) from a mixed-effects model				
Days on study	7 (3–12)	3 (2–4)	3 (2–4)	**0.018**
Rate of protocol compliance[c]	92 (82–96)	91 (78–96)	95 (85–99)	0.61

Study Outcome	LTV-Volume Control *n* = 17	APRV-LTV *n* = 18	APRV *n* = 17	*p*
Medication administration, reported as mean estimate (95% CI) from a mixed-effects model				
Frequency of medication administration (%)				
Vasopressors	59 (17–91)	21 (3–67)	10 (1–52)	0.20
Narcotics	68 (38–88)	51 (23–79)	69 (37–90)	0.68
Benzodiazepines	9 (4–21)	9 (3–21)	18 (7–37)	0.42
Paralytics	13 (7–22)	13 (6–24)	11 (5–22)	0.91
Sedation (continuous infusion)	64 (38–84)	70 (42–88)	53 (26–79)	0.71
Medication dosage				
Norepinephrine equivalent–weighted mean dose (μg/kg/min)	0.14 (0.08–0.25)	0.12 (0.06–0.23)	0.06 (0.03–0.14)	0.30
Propofol dose (mg/kg/d)	26.1 (18.2–34.0)	26.1 (17.8–34.3)	37.1 (27.9–46.4)	0.17
Dexmedetomidine dose (μg/kg/d)	17.4 (12.3–22.5)	15.4 (8.2–22.5)	21.6 (10.7–32.5)	0.66
Outcomes, reported as median (IQR) or *n* (%)				
Day 3 P/F ratio[d]	161 (142–184)	165 (115–236)	165 (134–209)	0.92
Hospital mortality	10 (59)	6 (33)	5 (29)	0.20
Barotrauma	1 (6)	0 (0)	0 (0)	0.65
Reintubation	3 (18)	4 (22)	0 (0)	0.10
Ventilator-free days to day 28[e]	0 (0–18)	22 (0–24)	20 (0–24)	0.10
ICU LOS (d)	8.2 (4.7–18.6)	5.8 (4.0–9.6)	8.7 (5.9–14.0)	0.47
Hospital LOS (d)	8.3 (7.2–18.8)	9.2 (5.0–13.4)	11.9 (9.7–17.9)	0.26

Research

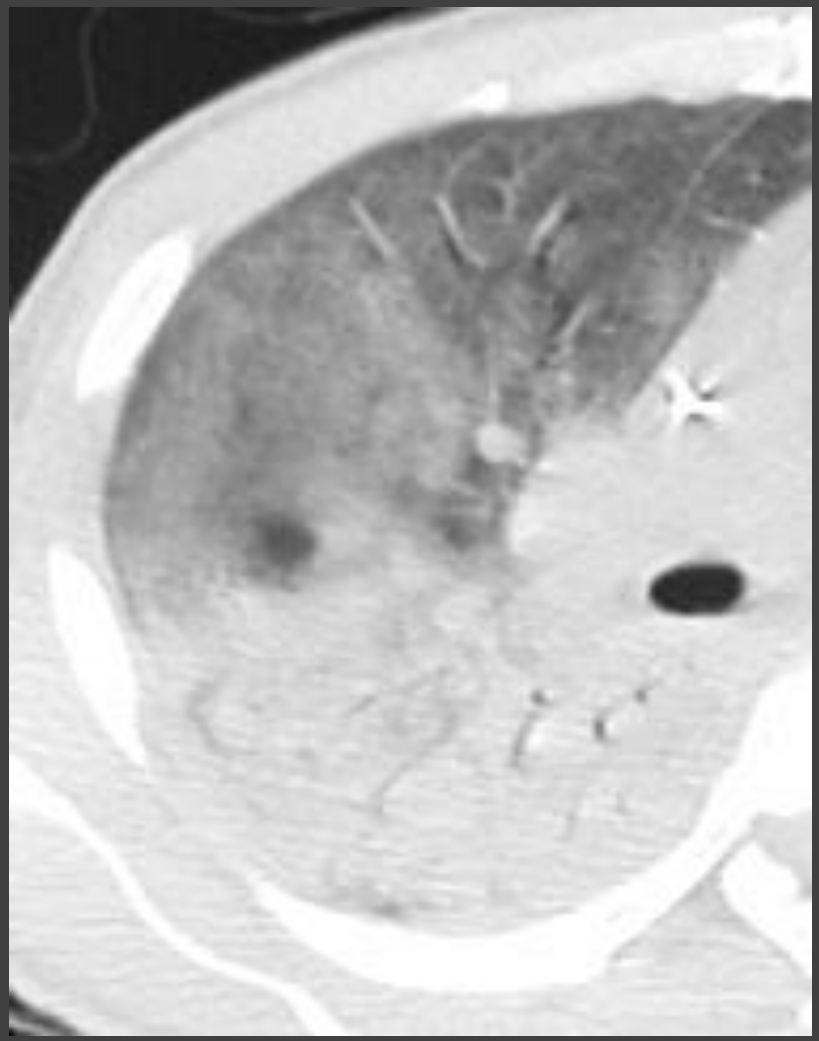
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

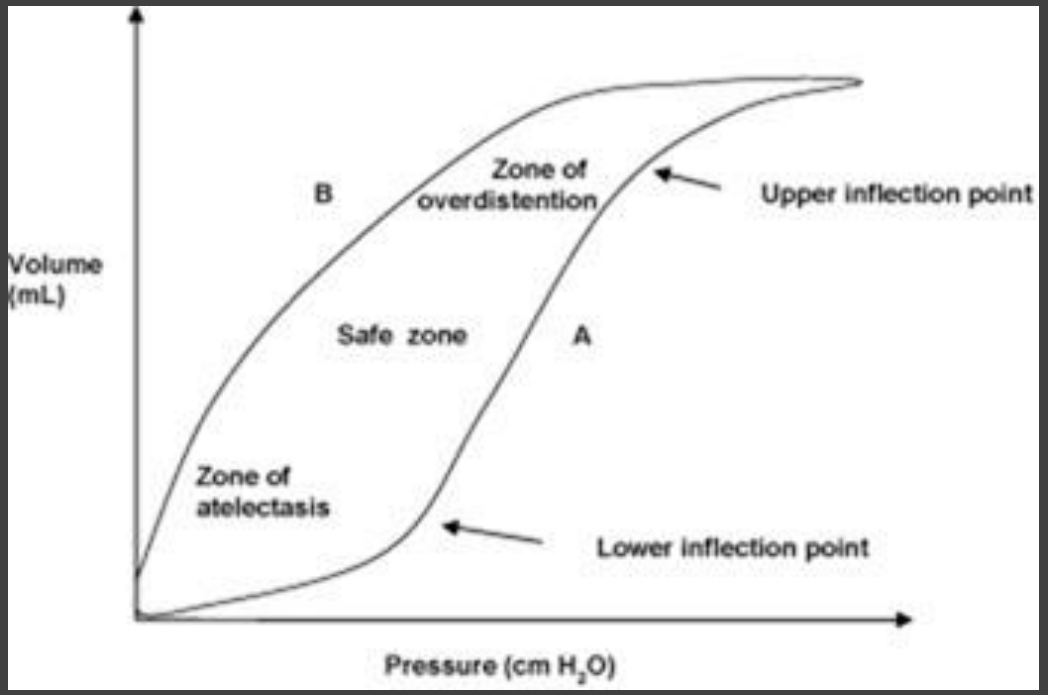
Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure–Guided Strategy vs an Empirical High PEEP-FIO_2 Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome

A Randomized Clinical Trial

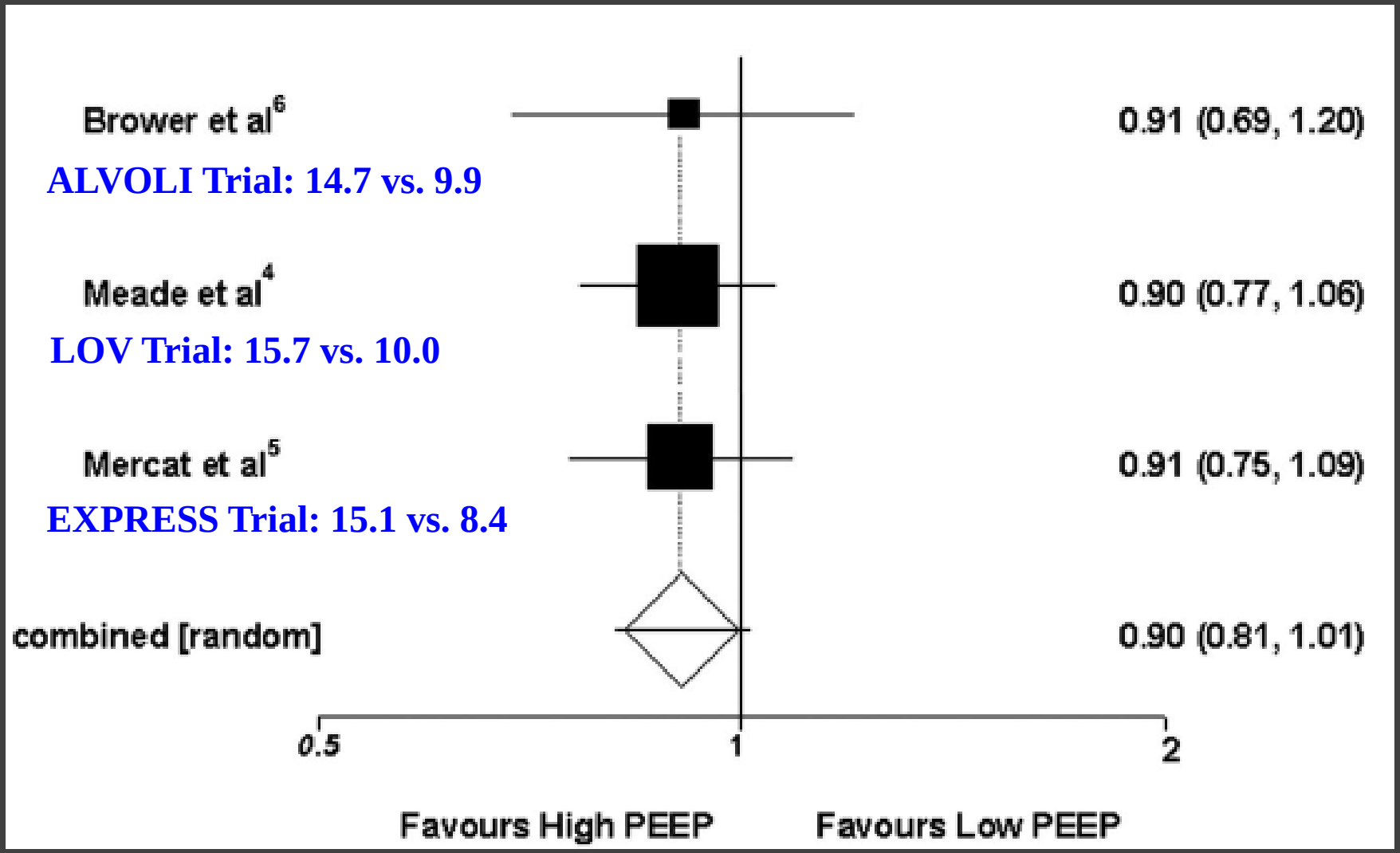
Jeremy R. Beitler, MD, MPH; Todd Sarge, MD; Valerie M. Banner-Goodspeed, MPH; Michelle N. Gong, MD, MSc; Deborah Cook, MD; Victor Novack, MD, PhD; Stephen H. Loring, MD; Daniel Talmor, MD, MPH; for the EPVent-2 Study Group

Optimal PEEP ?? In ARDS



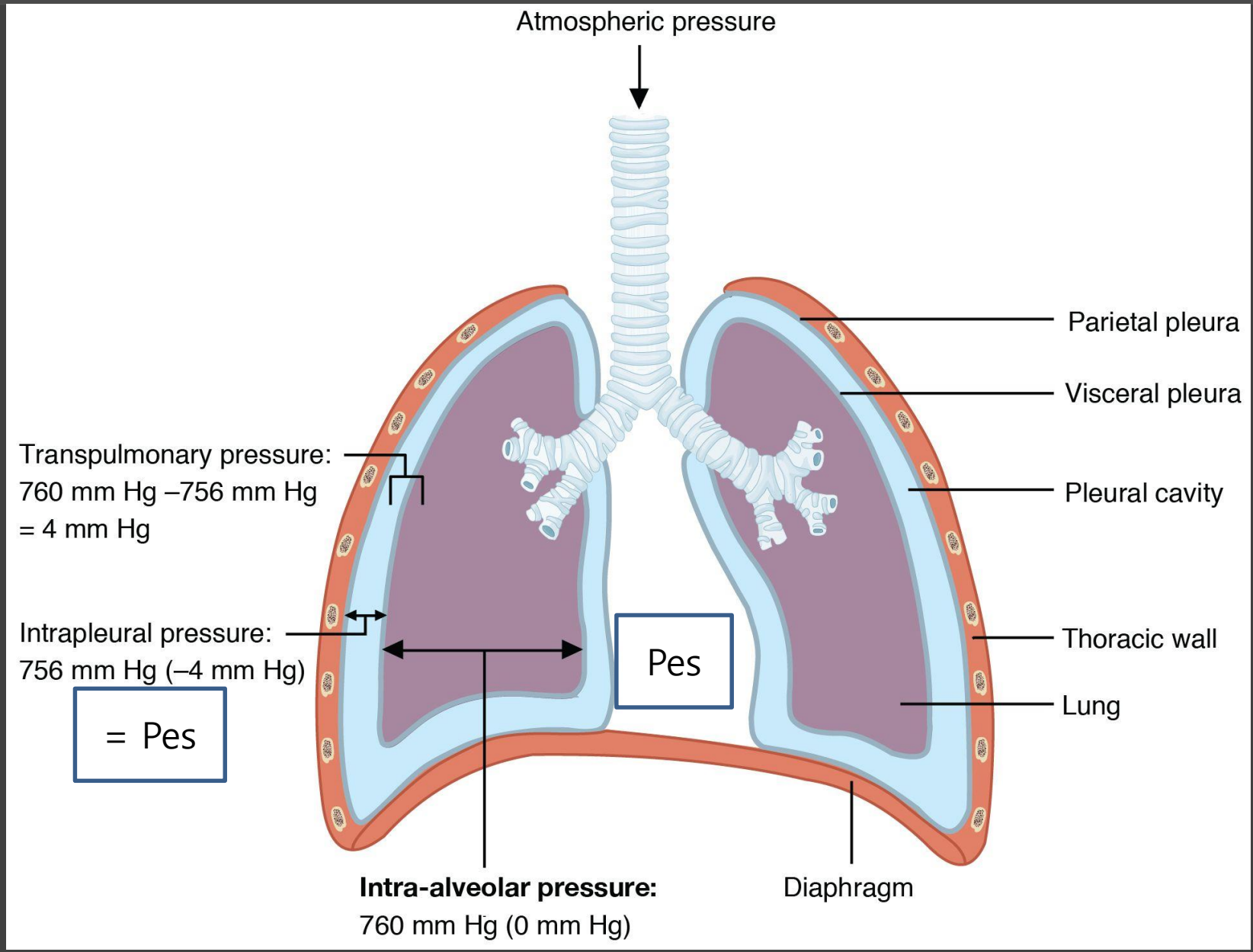


Meta-analysis for mortality with high and low PEEP

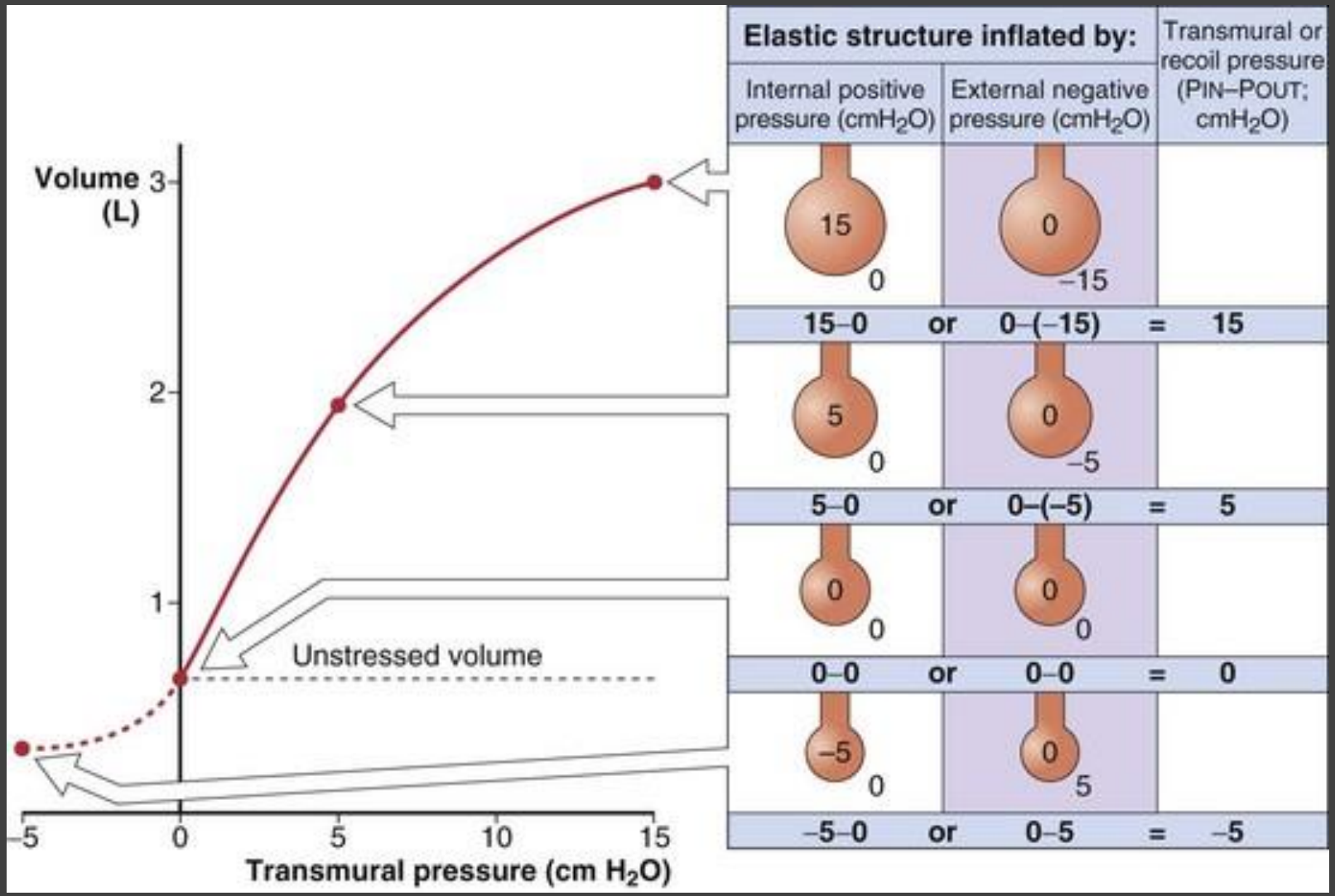


Anesthesiology 2009; 110:1098

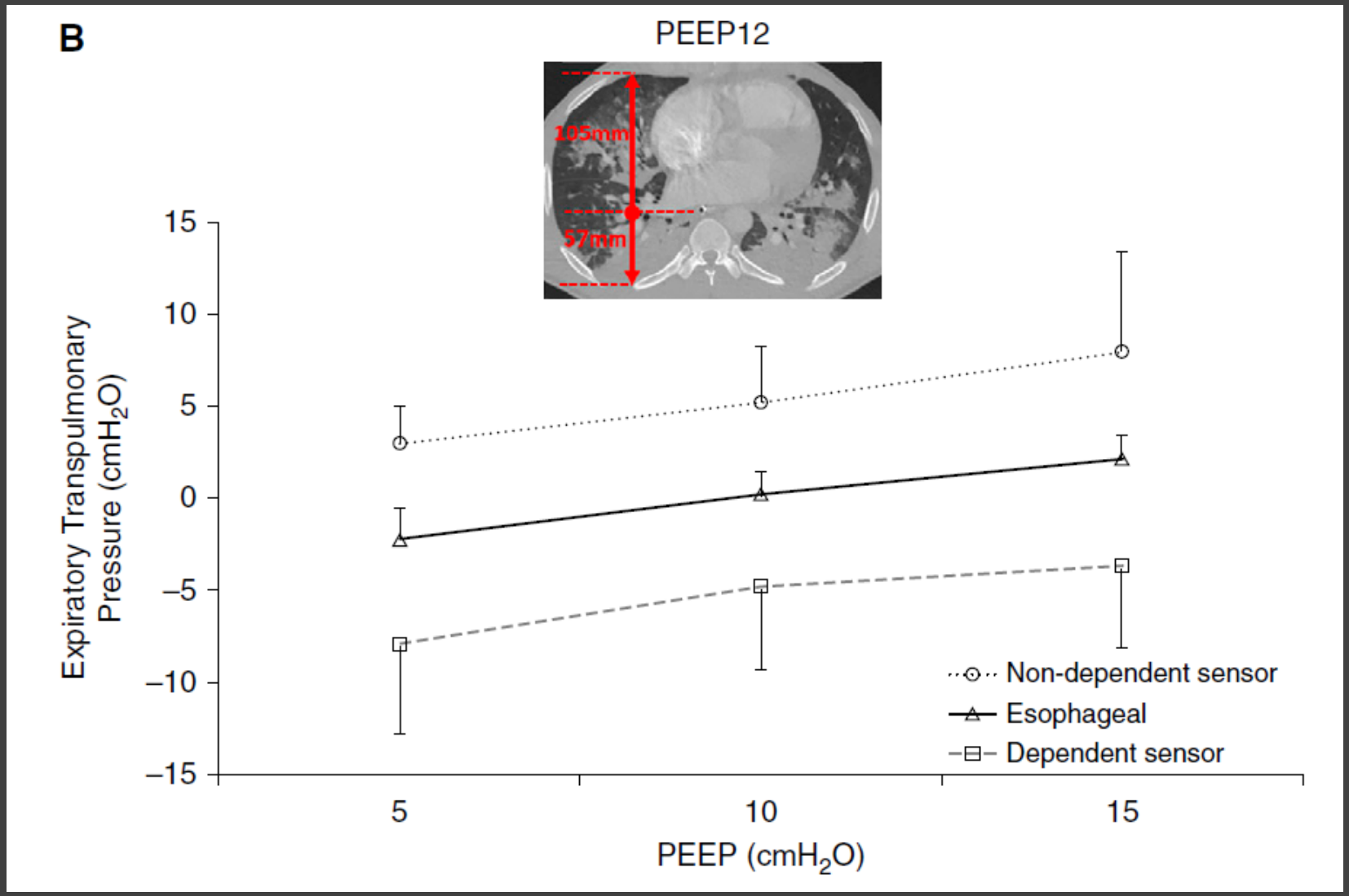
Transpulmonary pressure



Transpulmonary pressure

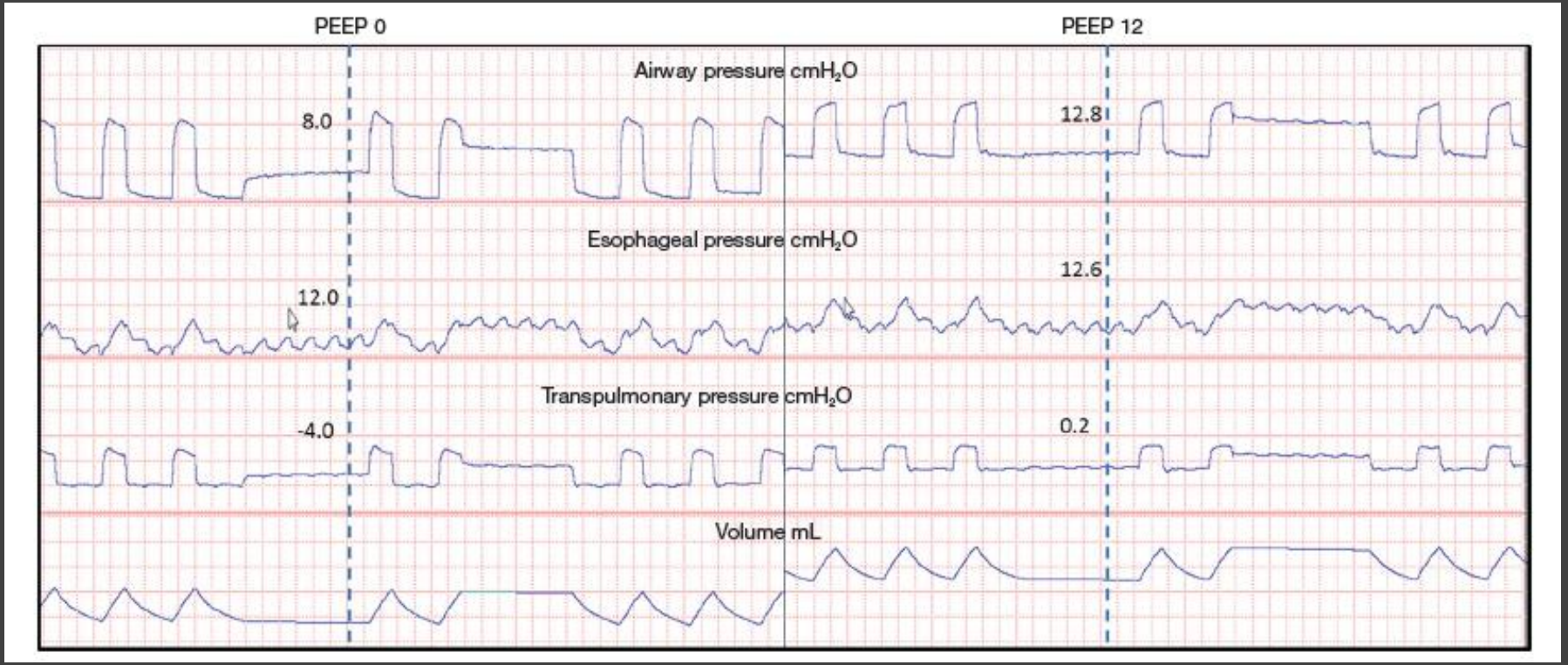


Transpulmonary pressure



Am J Respir Crit Care Med 2018;197:1018

PEEP Titration with Pes



Transpulmonary pressure (PL)= airway pressure – esophageal pressure

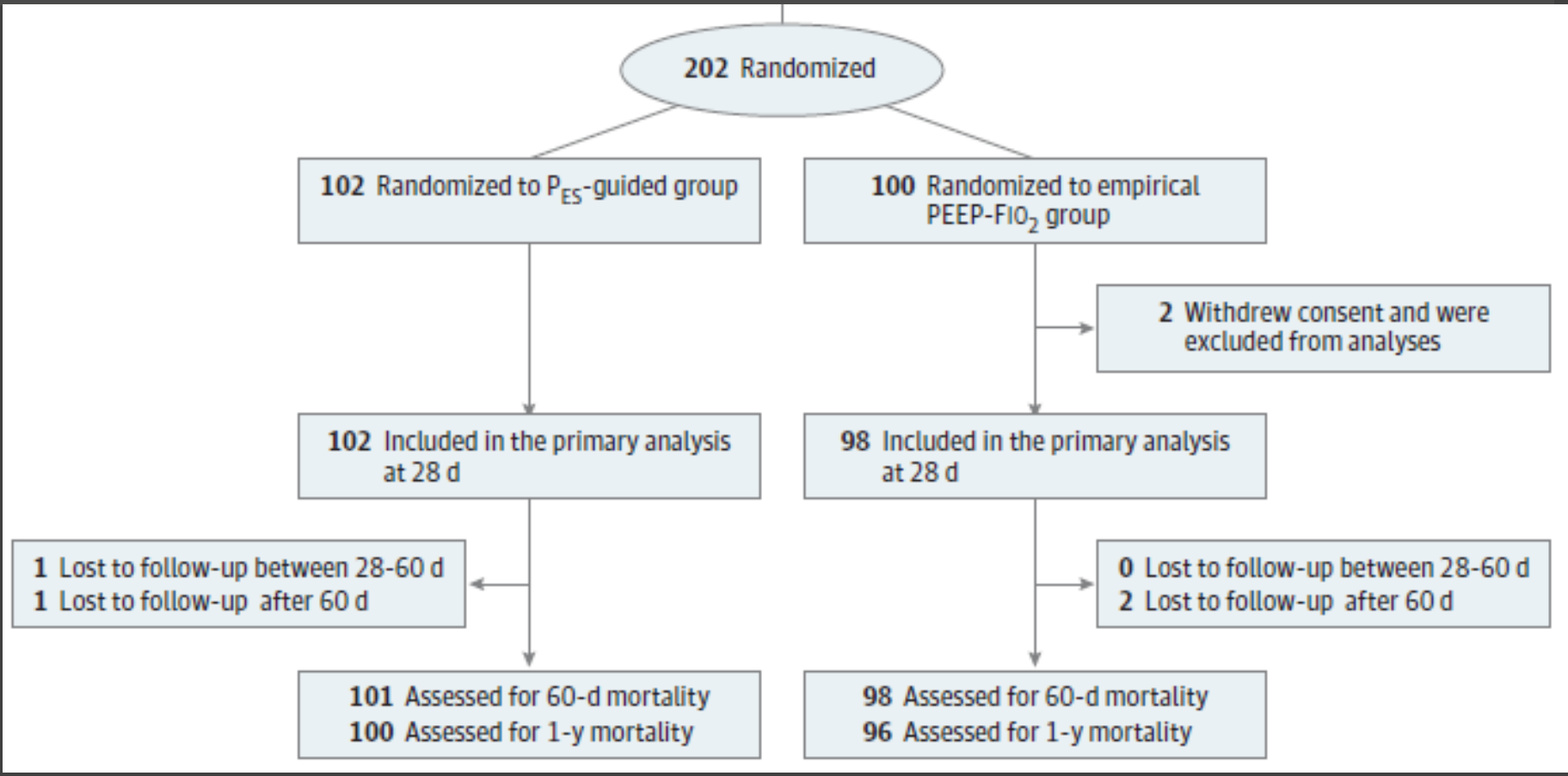
ART study

Table 2. Measurements of Ventilatory Function at Baseline and 72 Hours.*

Measurement	Baseline			72 Hr†		
	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value	Esophageal-Pressure–Guided (N=29)	Conventional Treatment (N=29)	P Value
PaO_2:FIO_2	147±56	145±57	0.89	280±126	191±71	0.002
Respiratory-system compliance (ml/cm of water)	36±12	36±10	0.94	45±14	35±9	0.005
Ratio of physiological dead space to tidal volume	0.67±0.11	0.67±0.09	0.95	0.61±0.09	0.64±0.10	0.27
PaO_2 (mm Hg)	91±25	107±44	0.09	124±44	101±33	0.03
FIO_2	0.66±0.17	0.77±0.18	0.02	0.49±0.17	0.57±0.18	0.07
PEEP (cm of water)	13±5	13±3	0.73	17±6	10±4	<0.001
Tidal volume (ml)	484±98	491±105	0.80	472±98	418±80	0.03
Tidal volume (ml per kg of predicted body weight)	7.3±1.3	7.9±1.4	0.12	7.1 ±1.3	6.8±1	0.31
Respiratory rate (breaths/min)	26±6	24±6	0.32	26±6	28±5	0.20
Inspiratory time (sec)	0.8±0.1	0.9±0.2	0.19	0.8±0.1	0.8±0.1	0.27
$PEEP_{total}$ (cm of water)	14±5	15±4	0.67	18±5	12±5	<0.001
Peak inspiratory pressure (cm of water)	35±8	35±7	0.85	32±8	28±7	0.007
Mean airway pressure (cm of water)	20±6	20±4	0.88	22±6	16±5	0.001
Plateau pressure (cm of water)	29±7	29±5	0.79	28±7	25±6	0.07
Transpulmonary end-inspiratory pressure (cm of water)	7.9±6.0	8.6±5.4	0.61	7.4±4.4	6.7±4.9	0.58
Transpulmonary end-expiratory pressure (cm of water)	−2.8±5.0	−1.9±4.7	0.49	0.1±2.6	−2.0±4.7	0.06
Esophageal end-inspiratory pressure (cm of water)	21.2±4.9	20.7±5.1	0.68	21.7±7.2	17.9±5.2	0.03
Esophageal end-expiratory pressure (cm of water)	17.2±4.4	16.9±5.0	0.79	18.4±5.9	14.3±4.9	0.008

N Engl J Med 2008;359:2095

Methods



- Patients aged 16 years or older with moderate to severe ARDS (P/F ≤ 200mmHg) onset within the last 36 hours

Methods

- Maintain end-expiratory transpulmonary pressure (P_L) between 0 to 6 cmH_2O

Table 1- Oxygenation Management Table - EPVent group

Step	1	2	3	4	5	6	7	8	9	10	11	12	13
F_IO_2	0.3	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.9	0.9	1.0
Ptp_{exp}	0	0	0	2	2	3	3	4	4	5	5	6	6

- Tidal over-distension VT was decreased to as low as 4 mL/kg For severe dyspnea or acidemia, VT as high as 8 mL/kg

- Once end-expiratory P_L of 0 with FIO_2 of 0.5 or less was tolerated for at least 24 hours, weaning protocol

Methods

- Empirical PEEP-FIO2 Group
  - Adopted from the control group of the recent OSCILLATE trial

Table 4- Oxygenation Management Table – Control Group

Step	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
F_IO_2	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.0
PEEP	5	8	10	10	12	14	16	18	18	20	20	20	20	22	22	22	24

- Primary end point: Incorporated death and days free from mechanical ventilation through day 28

Variable	Median (IQR)	
	P_{ES}-Guided PEEP (n = 102)	Empirical PEEP-F_{IO_2} (n = 98)
Respiratory characteristics		
pH	7.33 (7.27 to 7.37)	7.33 (7.25 to 7.40)
$Paco_2$, mm Hg	44 (38 to 52)	43 (37 to 51)
Pao_2, mm Hg	71 (61 to 86)	69 (61 to 84)
Pao_2:F_{IO_2}, mm Hg	95 (73 to 129)	90 (69 to 123)
Tidal volume, mL/kg PBW	6.2 (5.9 to 6.7)	6.2 (5.8 to 7.1)
Airway pressure, cm H_2O		
Plateau	28 (24 to 32)	27 (25 to 30)
Mean	20 (16 to 24)	19 (16 to 22)
Set PEEP, cm H_2O	14 (10 to 18)	12.5 (10 to 16)
F_{IO_2}	0.60 (0.50 to 0.80)	0.60 (0.50 to 0.70)
Respiratory rate, breaths/min	26 (22 to 30)	26 (22 to 30)
Minute ventilation, L/min	10.3 (8.5 to 12.1)	9.4 (8.4 to 11.3)
P_{ES}, cm H_2O		
At end-inspiration	19 (16 to 21)	18 (16 to 21)
At end-expiration	16 (13 to 19)	15 (13 to 18)
P_L, cm H_2O		
At end-inspiration	8 (6 to 11)	9 (5 to 12)
At end-expiration	0 (−3 to 1)	−1 (−3 to 2)
Airway driving pressure, cm H_2O	13 (10 to 15)	13 (11 to 15)
Transpulmonary driving pressure, cm H_2O	8 (7 to 11)	9 (7 to 11)
Lung compliance, mL/cm H_2O	48 (34 to 63)	42 (33 to 55)
Respiratory system compliance, mL/cm H_2O	32 (25 to 41)	30 (23 to 37)

Outcome

Variable	P_{ES}-Guided PEEP (n = 102)	Empirical PEEP-FIO_2 (n = 98)	Absolute Difference, % (95% CI)[b]	*P* Value[c]
Primary End Point				
Probability of more favorable outcome, a ranked composite incorporating death and days free from mechanical ventilation among survivors, % (95% CI)[d]	49.6 (41.7 to 57.5)	50.4 (42.5 to 58.3)	NR[e]	.92
Secondary Clinical End Points				
Mortality through day 28, No. (%)	33 (32.4)	30 (30.6)	1.7 (−11.1 to 14.6)	.88
Days free from mechanical ventilation among survivors through day 28, median (IQR)	22 (15 to 24)	21 (16.5 to 24)	0 (−1 to 2)	.85
Mortality through day 60, No./total No. (%)	38/101 (37.6)	37/98 (37.8)	−0.1 (−13.6 to 13.3)	>.99
Mortality through 1 y, No./total No. (%)	44/100 (44.0)	44/96 (45.8)	−1.8 (−15.8 to 12.1)	.89
Ventilator-free days through day 28, median (IQR)[f]	15.5 (0 to 23)	17.5 (0 to 23)	0 (0 to 0)	.93
ICU length of stay through day 28, median (IQR), d	10 (6 to 17)	9.5 (5 to 14)	1 (−1 to 3)	.24
Hospital length of stay through day 28, median (IQR), d	16 (9 to 26)	15 (8 to 24)	0 (−1 to 3)	.58
Hospital length of stay through day 60, median (IQR), d	16 (9 to 26)	15 (8 to 24)	1 (−2 to 4)	.47
Rescue therapy administered, No. (%)[g]	4 (3.9)	12 (12.2)	−8.3 (−15.8 to -0.8)	.04
Prone positioning, No. (%)	1 (1.0)	3 (3.1)	−2.1 (−6.0 to 1.8)	.36
Inhaled pulmonary vasodilator, No. (%)	3 (2.9)	10 (10.2)	−7.3 (−14.1 to −0.4)	.046
Extracorporeal membrane oxygenation, No. (%)	1 (1.0)	3 (3.1)	−2.1 (−6.0 to 1.8)	.36
Recruitment maneuvers, No. (%)	1 (1.0)	1 (1.0)	0.0 (−2.8 to 2.7)	>.99
Safety End Points				
Shock-free days, median (IQR)[f]	14 (0 to 21)	17 (0 to 21)	0 (−2 to 0)	.47
Acute kidney injury requiring renal replacement therapy in the first 28 d, No./total, No. (%)[h]	21/100 (21.0)	32/96 (33.3)	−12.3 (−24.7 to 0.0)	.056
Pneumothorax, No. (%)	3 (2.9)	2 (2.0)	0.9 (−3.4 to 5.2)	>.99
Bronchopleural fistula, No.	0	0	0	
Barotrauma, No. (%)[i]	6 (5.9)	5 (5.1)	0.8 (−5.5 to 7.1)	>.99

conclusion

- Among patients with moderate to severe ARDS,PES-guided PEEP, compared with empirical high PEEP-FiO_2, resulted in no significant difference in death and days free from mechanical ventilation. These findings do not support PES-guided PEEP titration in ARDS.

- The comparator group in the prior trial was a less aggressive empirical PEEP-FiO_2 strategy

Intensive Care Med (2018) 44:1849–1858
https://doi.org/10.1007/s00134-018-5328-0

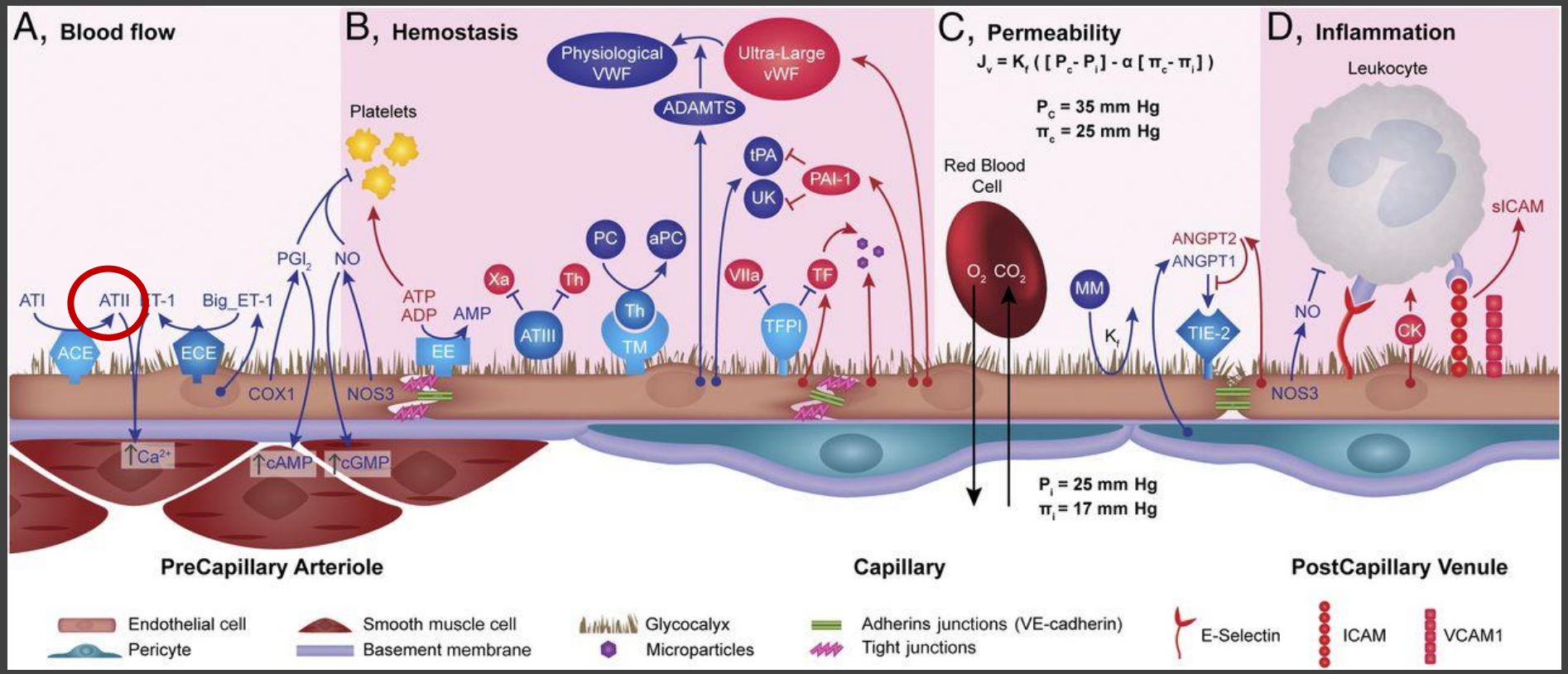
ORIGINAL

Plasma angiopoietin-2 as a potential causal marker in sepsis-associated ARDS development: evidence from Mendelian randomization and mediation analysis

John P. Reilly[1], Fan Wang[2], Tiffanie K. Jones[1], Jessica A. Palakshappa[3], Brian J. Anderson[1], Michael G. S. Shashaty[1], Thomas G. Dunn[1], Erik D. Johansson[1], Thomas R. Riley[1], Brian Lim[1], Jason Abbott[4], Caroline A. G. Ittner[1], Edward Cantu[5], Xihong Lin[6], Carmen Mikacenic[7], Mark M. Wurfel[7], David C. Christiani[6,8], Carolyn S. Calfee[9], Michael A. Matthay[4], Jason D. Christie[1,10], Rui Feng[10] and Nuala J. Meyer[1*]

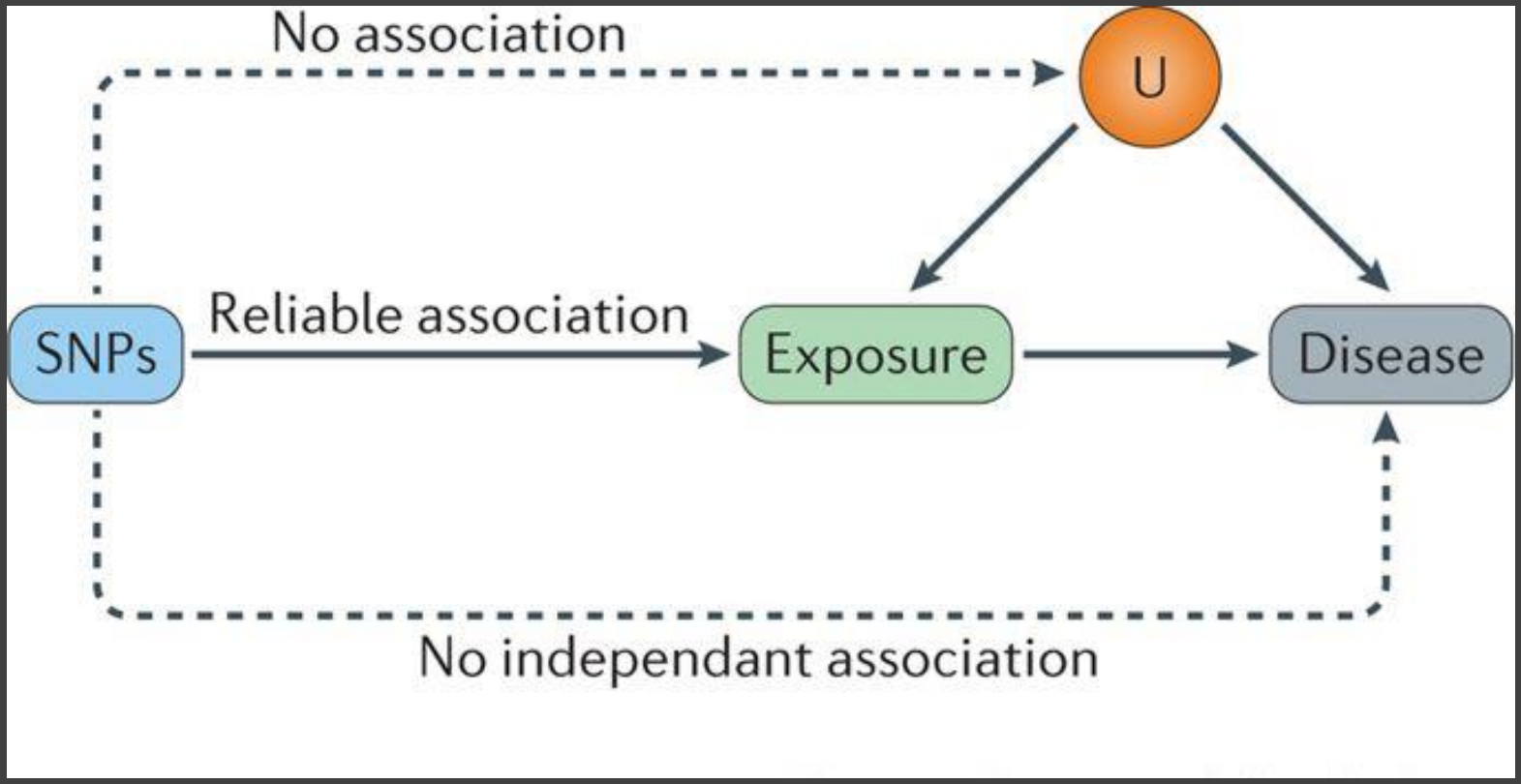
Plasma angiopoietin-2 (ANG2)

- Established biomarker of endothelial activation and permeability
- Potential confounding: ANG 2 result from, rather than cause, lung injury

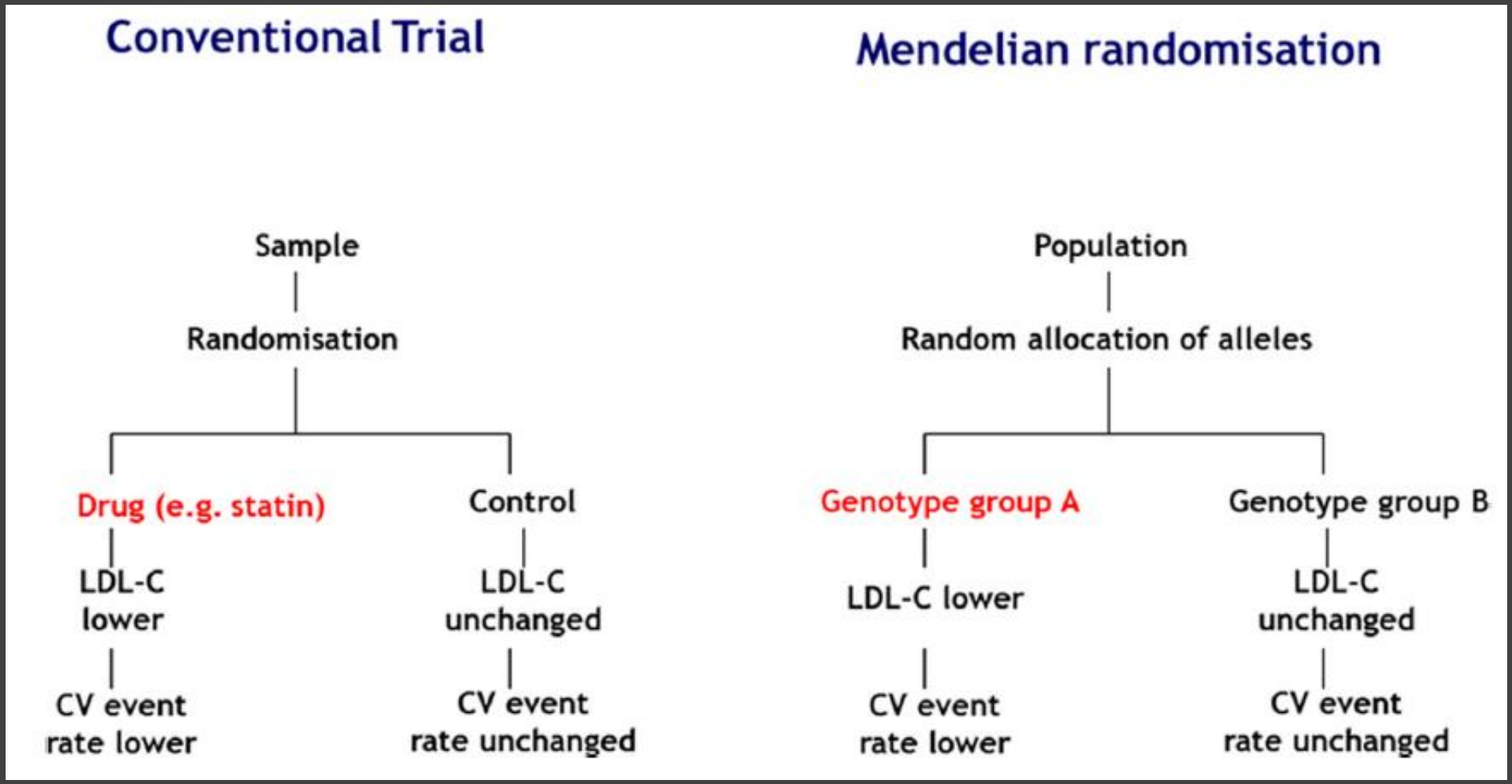


Methods

- Mendelian randomization: infer causality from observational data, considering each individual as “randomized” during gametogenesis to a high- or low-expressing genotype



Mendelian randomization



Methods

- The Molecular Epidemiology of SepsiS in the ICU (MESSI) cohort at the University of Pennsylvania

- ARDS: 280 patients
- Non – ARDS : 414 patients

Results

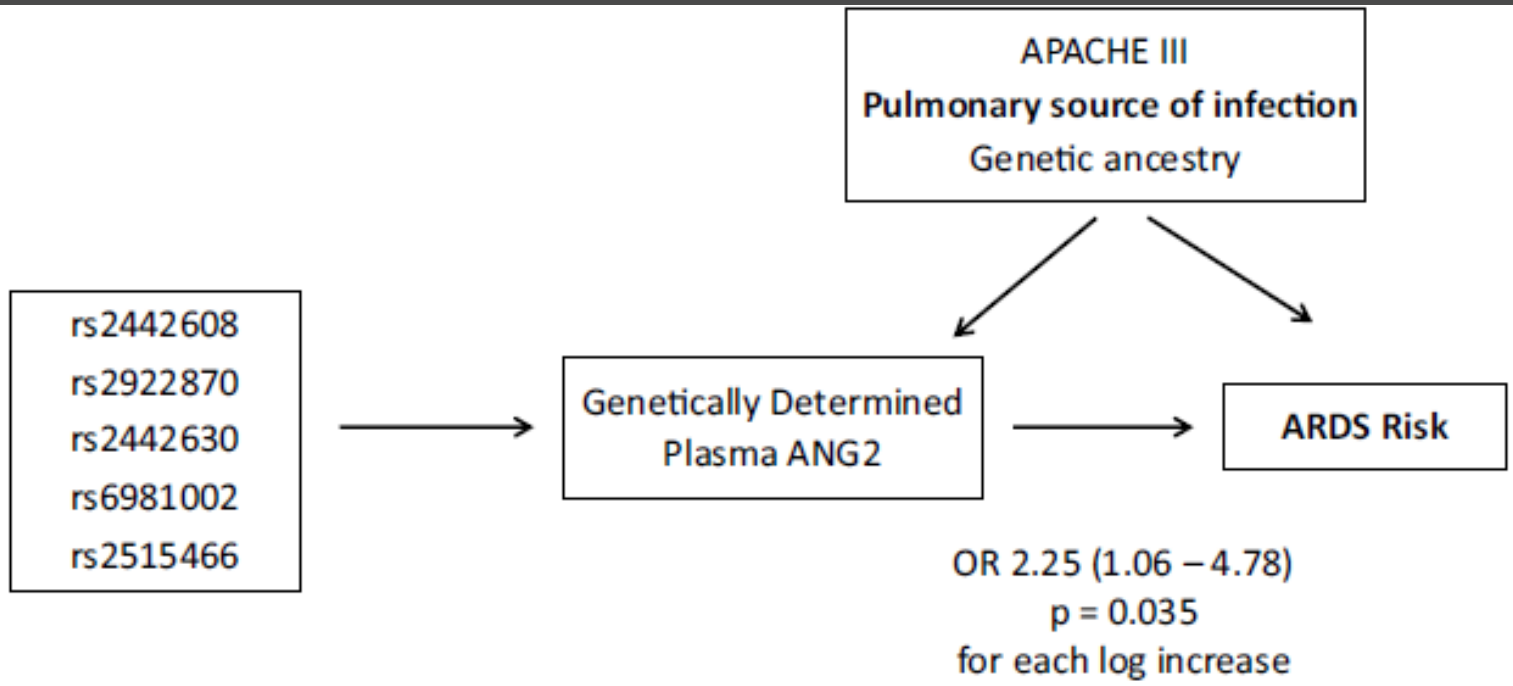


Table 3 Causal mediation analysis demonstrates that 30–40% of the ARDS risk is mediated through changes in plasma ANG2 for replicating *ANGPT2* SNPs

SNP	Analysis	Adjusted OR ARDS (95% CI)	*p* value	Proportion mediated by plasma ANG2
rs2442608	Total effect	1.06 (0.99, 1.13)	0.08	
	Mediation effect	**1.02 (1.01, 1.04)**	**0.01**	**0.34**
	Direct effect	1.04 (0.98, 1.10)	0.24	
rs2515466	Total effect	0.95 (0.88, 1.02)	0.12	
	Mediation effect	**0.98 (0.96, 0.99)**	**0.01**	**0.40**
	Direct effect	0.97 (0.91, 1.04)	0.40	

Conclusion

- Plasma ANG2 may be a causal factor in ARDS development. Strategies to reduce plasma ANG2 warrant testing to prevent or treat sepsis-associated ARDS.

Sepsis

Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis

Bram Rochwerg, MD, MSc[1,2]; Simon J. Oczkowski, MD, MSc, MHSc[1]; Reed A. C. Siemieniuk, MD[2]; Thomas Agoritsas, MD, PhD[2,3,4]; Emilie Belley-Cote, MD[1,2]; Frédérick D'Aragon, MD, MSc[5]; Erick Duan, MD, MSc[1,2]; Shane English, MD, MSc[6,7]; Kira Gossack-Keenan, BSc[1]; Mashari Alghuroba, MSc[1]; Wojciech Szczeklik, MD, PhD[1,8]; Kusum Menon, MD, MSc[9]; Waleed Alhazzani, MD, MSc[1,2]; Jonathan Sevransky, MD[10]; Per Olav Vandvik, MD, PhD[11]; Djillali Annane, MD, PhD[12]; Gordon Guyatt, MD, MSc[1,2]

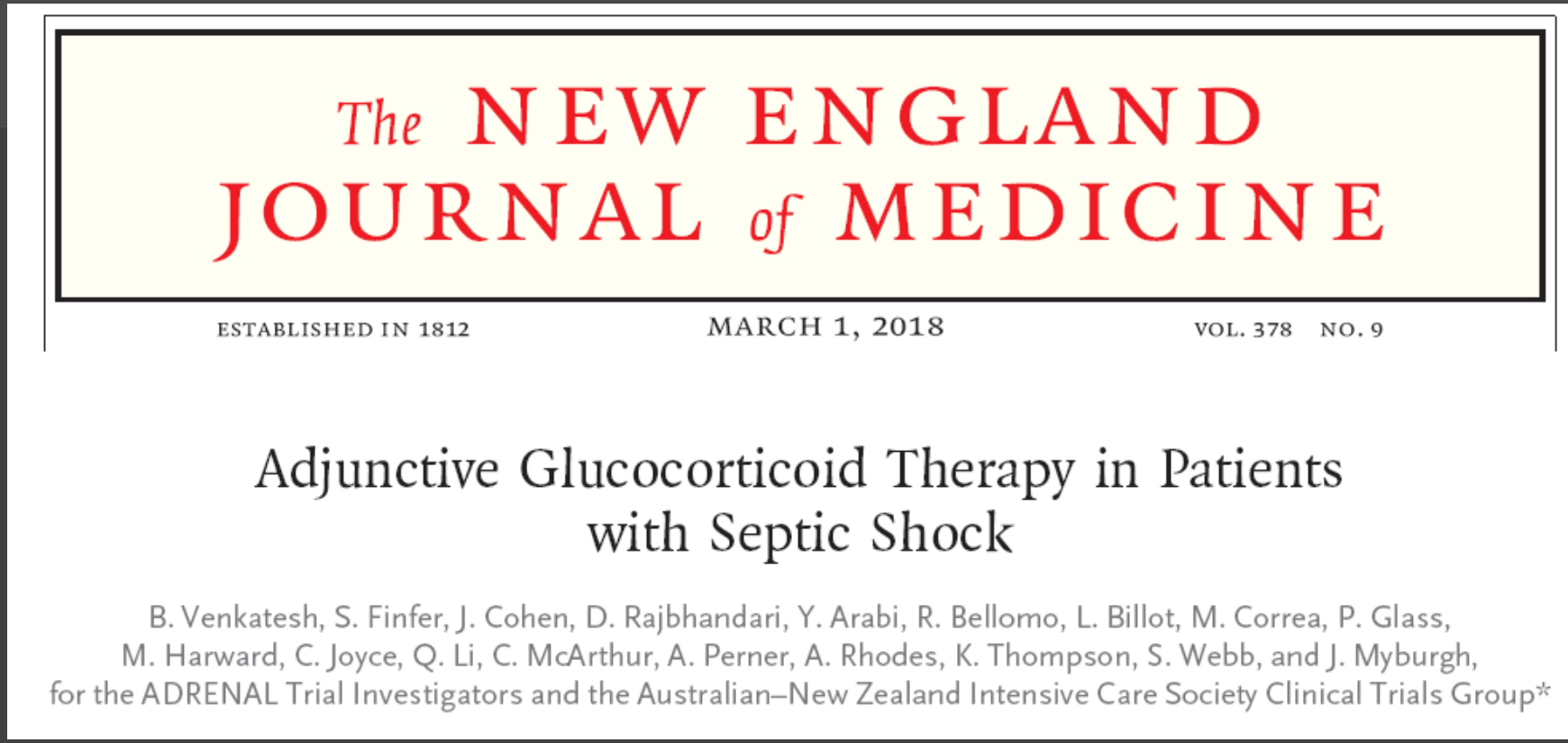
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

- 1241 patients
- 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627patients) in the placebo group (P = 0.03)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

- 3658 patients (1832 hydrocortisone group and 1826 placebo group)
- At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P = 0.50).

Methods

- 42 RCT (including studies for children) 10,194 patients

→ JAMA 37 RCT (only ≥ 18 years) 9564 patients

Outcome Timeframe	Study Results and Measurements	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)
		No Corticosteroids	Corticosteroids	
Mortality longer term (60 d to 1 yr)	Relative risk: 0.94 (95% CI, 0.89–1.0) Based on data from 6,438 patients in nine studies	371/1,000	349/1,000 Difference: 22 fewer per 1,000 (95% CI, 41 fewer to 0 fewer)	Moderate Due to serious imprecision[a]
Mortality short term (28–31 d)	Relative risk: 0.93 (95% CI, 0.84–1.03) Based on data from 9,433 patients in 36 studies	254/1,000	236/1,000 Difference: 18 fewer per 1,000 (95% CI, 41 fewer to 8 more)	Low Due to serious imprecision, borderline inconsistency, and publication bias[b]
Shock reversal (1 wk)	Relative risk: 1.26 (95% CI, 1.12–1.42) Based on data from 2,802 patients in 13 studies	464/1,000	585/1,000 Difference: 121 more per 1,000 (95% CI, 56 more to 195 more)	High
Neuromuscular weakness	Relative risk: 1.21 (95% CI, 1.01–1.45) Based on data from 6,178 patients in seven studies	250/1,000	303/1,000 Difference: 53 more per 1,000 (95% CI, 3 more to 130 more)	Low Due to serious imprecision and indirectness and borderline inconsistency[c]

Outcome Timeframe	Study Results and Measurements	Absolute Effect Estimates: No Corticosteroids	Absolute Effect Estimates: Corticosteroids	Certainty in Effect Estimates (Quality of Evidence)
Gastrointestinal bleeding	Relative risk: 1.09 (95% CI, 0.86–1.38) Based on data from 4,243 patients in 17 studies	35/1,000	38/1,000 Difference: 3 more per 1,000 (95% CI, 5 fewer to 13 more)	Low Due to serious indirectness and imprecision[d]
Neuropsychiatric events	Relative risk: 0.58 (95% CI, 0.33–1.03) Based on data from 1,004 patients in five studies	59/1,000	34/1,000 Difference: 25 fewer per 1,000 (95% CI, 40 fewer to 2 more)	Low Due to serious imprecision and serious indirectness[e]
Hypernatremia	Relative risk: 1.64 (95% CI, 1.32–2.03) Based on data from 5,015 patients in six studies	36/1,000	59/1,000 Difference: 23 more per 1,000 (95% CI, 12 more to 37 more)	Moderate Due to serious indirectness[f]
Superinfection	Relative risk: 1.02 (95% CI, 0.89–1.18) Based on data from 4,519 patients in 21 studies	161/1,000	164/1,000 Difference: 3 more per 1,000 (95% CI, 18 fewer to 29 more)	Low Due to serious imprecision and serious indirectness[c]
Hyperglycemia	Relative risk: 1.16 (95% CI, 1.08–1.24) Based on data from 7,563 patients in 15 studies	181/1,000	210/1,000 Difference: 29 more per 1,000 (95% CI, 14 more to 43 more)	Moderate Due to serious indirectness[h]

Outcome Timeframe	Study Results and Measurements	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)
		No Corticosteroids	Corticosteroids	
ICU length of stay	Measured by: days Based on data from 7,463 patients in 20 studies	13.13 d	12.4 d MD: 0.73 fewer (95% CI, 1.78 fewer to 0.31 more)	Moderate Due to serious imprecision[i]
Hospital length of stay	Measured by: days Based on data from 7,706 patients in 18 studies	32.03 d	31.3 d MD: 0.73 fewer (95% CI, 2.06 fewer to 0.6 more)	Moderate Due to serious imprecision[j]
Organ dysfunction (1 wk)	Measured by: Sepsis Organ Failure Assessment score Scale: 0–24 lower better Based on data from 1,986 patients in nine studies	7.61 points	6.22 points MD: 1.39 lower (95% CI, 1.88 lower to 0.89 lower)	High
Quality of life	Not reported in any of the included studies			

Research

JAMA Internal Medicine | Original Investigation

Association of Corticosteroid Treatment With Outcomes in Adult Patients With Sepsis

A Systematic Review and Meta-analysis

Fang Fang, MD; Yu Zhang, MD; Jingjing Tang, BS; L. Dade Lunsford, MD; Tiangui Li, MD; Rongrui Tang, MD; Jialing He, MB; Ping Xu, MSc; Andrew Faramand, MD; Jianguo Xu, MD; Chao You, MD

Outcome	No. of Patients (No. of Studies)	Relative Effect, Risk Ratio, or Mean Difference (95% CI)[a]	I^2, %
Mortality			
28-d	8729 (34)	0.89 (0.81 to 0.98)	27
90-d	5238 (3)	0.94 (0.85 to 1.03)	27
In hospital	3659 (19)	0.88 (0.79 to 0.99)	38
In ICU	2487 (13)	0.85 (0.77 to 0.94)	0
Length of stay			
ICU	6373 (17)	−1.16 (−2.12 to −0.20)	30
Hospital	5389 (12)	−0.60 (−2.25 to 1.04)	48
SOFA score at day 7	1986 (9)	−1.38 (−1.87 to −0.89)	50
Shock reversal at day 7	6369 (14)	1.23 (1.12 to 1.35)	54
Time to resolution of shock	4081 (5)	−1.35 (−1.78 to −0.91)	68

Vasopressor-free days to day 28	1342 (3)	1.95 (0.80 to 3.11)	0
Ventilation-free days to day 28	1630 (5)	2.03 (−0.38 to 4.44)	61
Severe adverse events			
Any	3403 (15)	1.04 (0.90 to 1.20)	49
Gastroduodenal bleeding	4006 (22)	1.11 (0.88 to 1.40)	0
Superinfection	7488 (21)	1.05 (0.93 to 1.19)	15
Hyperglycemia	7332 (17)	1.19 (1.08 to 1.30)	41
Hypernatremia	4844 (5)	1.57 (1.24 to 1.99)	0

Subgroup	Studies, No.	Patients, No.	I^2, %	Risk Ratio (95% CI)
Dose of corticosteroid, mg/d or equivalent				
Hydrocortisone <400	30	8308	4	0.91 (0.85-0.98)
Hydrocortisone ≥400	4	389	83	0.82 (0.47-1.42)
Treatment duration, d				
<4 (Short course)	5	418	79	0.78 (0.49-1.24)
≥4 (Long course)	29	8297	2	0.92 (0.85-0.98)
Sepsis population subtype				
Sepsis	3	245	0	0.89 (0.61-1.31)
Sepsis and ARDS	4	187	56	0.69 (0.35-1.37)
Sepsis and community-acquired pneumonia	5	840	7	0.76 (0.50-1.15)
Septic shock	19	7022	0	0.91 (0.82-1.02)
Severe sepsis	1	52	0	0.86 (0.33-2.21)

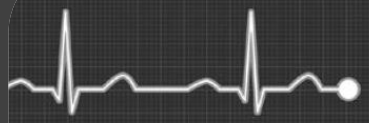
Summary- steroid in sepsis

- Mortality maybe benefit
- Length of ICU stay benefit

- Aggravation
  - Neuromuscular weakness
  - Hypernatremia
  - Hyperglycemia

- GI bleeding and super-infection are ok.

- Hydrocortisone < 400mg
- Duration ≥ 4 days



Feature Articles

Renin as a Marker of Tissue-Perfusion and Prognosis in Critically Ill Patients*

Patrick J. Gleeson, MB BAO BCh, MSc[1–3]; Ilaria Alice Crippa, MD[1]; Wasineenart Mongkolpun, MD[1]; Federica Zama Cavicchi, MD[1]; Tess Van Meerhaeghe, MD[1]; Serge Brimioulle, MD, PhD[1,4]; Fabio Silvio Taccone, MD, PhD[1,4]; Jean-Louis Vincent, MD, PhD[1,4]; Jacques Creteur, MD, PhD[1,4]

Renin

- The renin-angiotensin-aldosterone system (RAAS) is fundamental to circulatory homeostasis

- Renin
  - The primary driving force in this system
  - Secretion in response to decreased tissue-perfusion, sympathetic activation, and hypoxic metabolism
  - Routinely measured in hypertension but not in acute circulatory failure

Renin

- Diurnal variation in healthy subjects
- Molecular weight (~40 kDa) is at the threshold for removal by hemofiltration
- Renin production affected by commonly used medications including beta-agonists, RAAS blockers, and furosemide

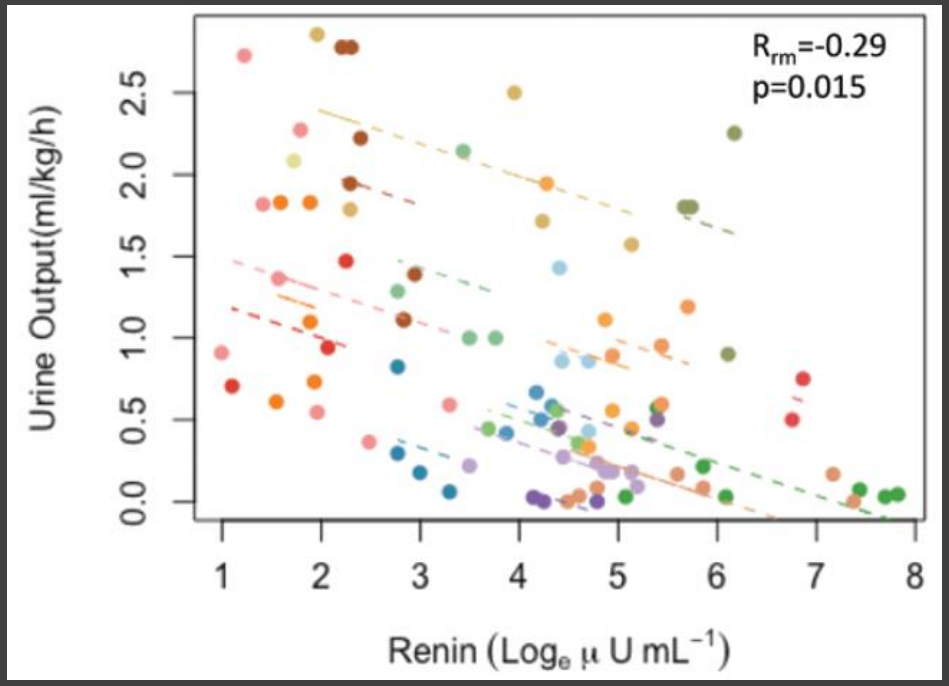
Methods

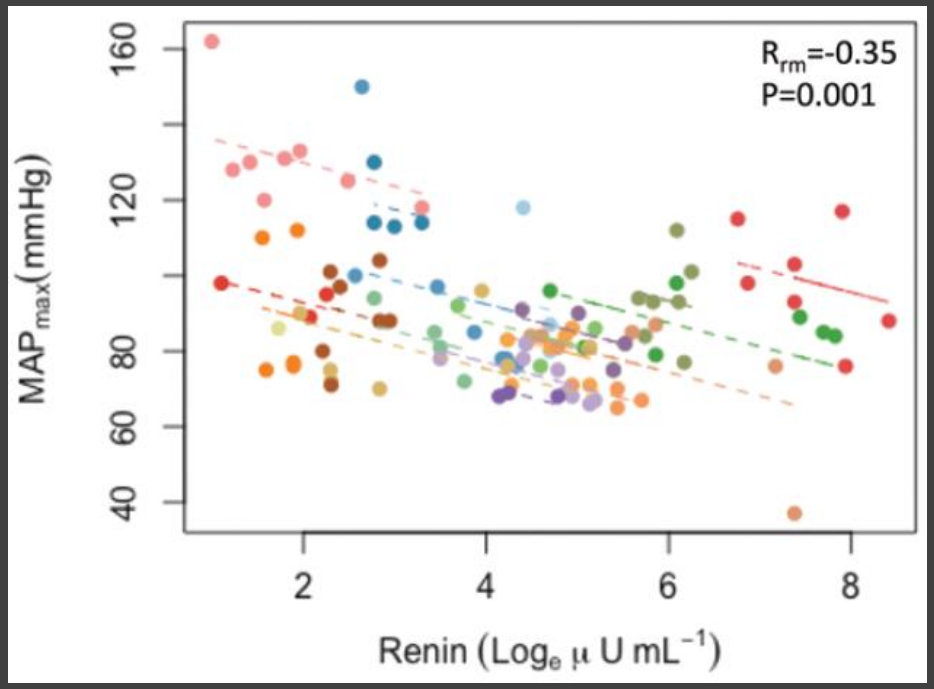
- One-hundred twelve arterial blood samples (n = 112) were drawn from 20 patients.

- 13 patients shock: 30% septic shock, 15% hemorrhagic shock, 20% cardiogenic shock
- 7 patients (35%): not have circulatory shock

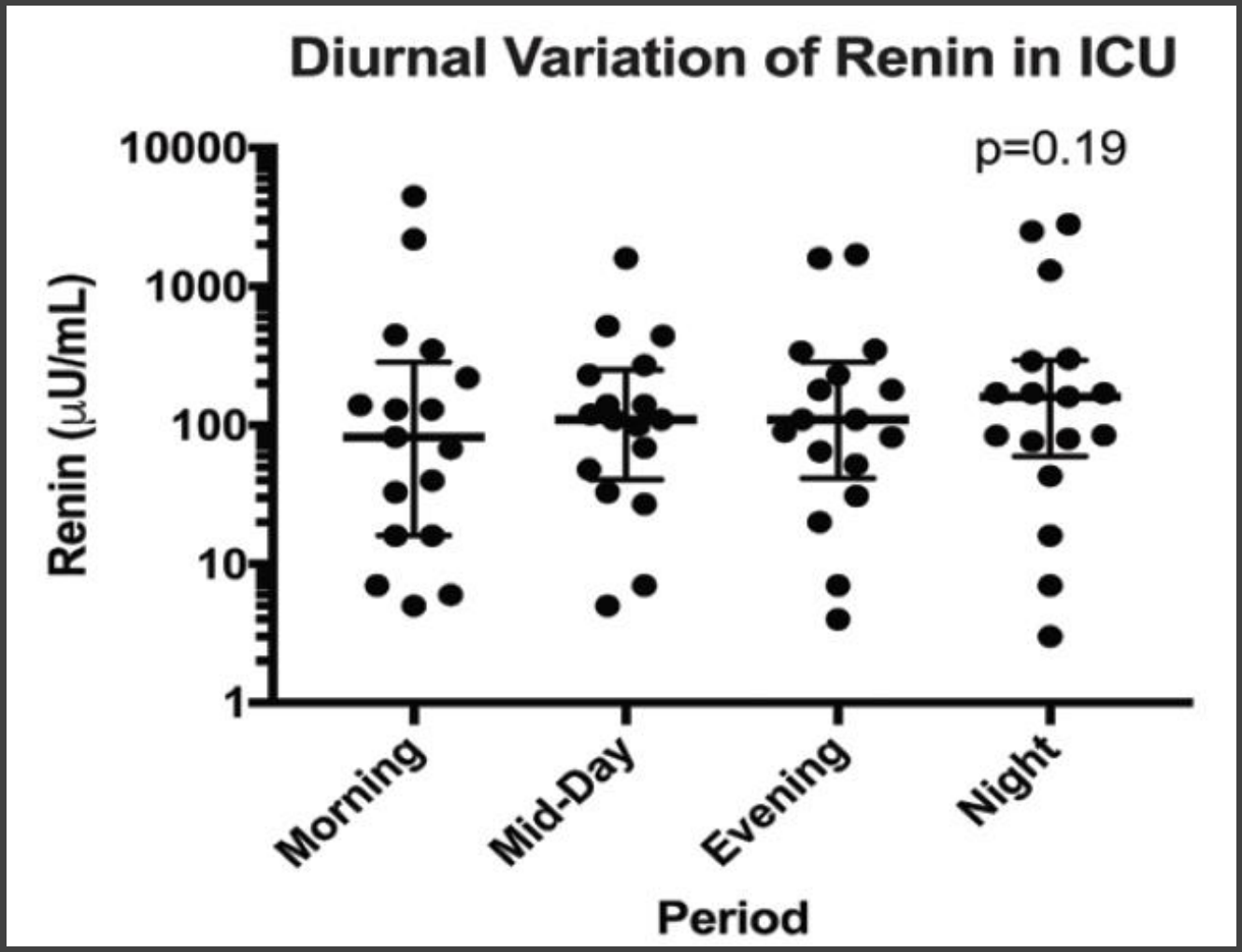
- The ICU mortality rate was 30%

Results


R_{rm}=-0.29
p=0.015
Urine Output(ml/kg/h)
0.0
0.5
1.0
1.5
2.0
2.5
1
2
3
4
5
6
7
8
Renin (Log_e μ U mL^{-1})


R_{rm}=-0.35
P=0.001
MAP_{max}(mmHg)
40
60
80
120
160
2
4
6
8
Renin (Log_e μ U mL^{-1})

Results – Friedman statics

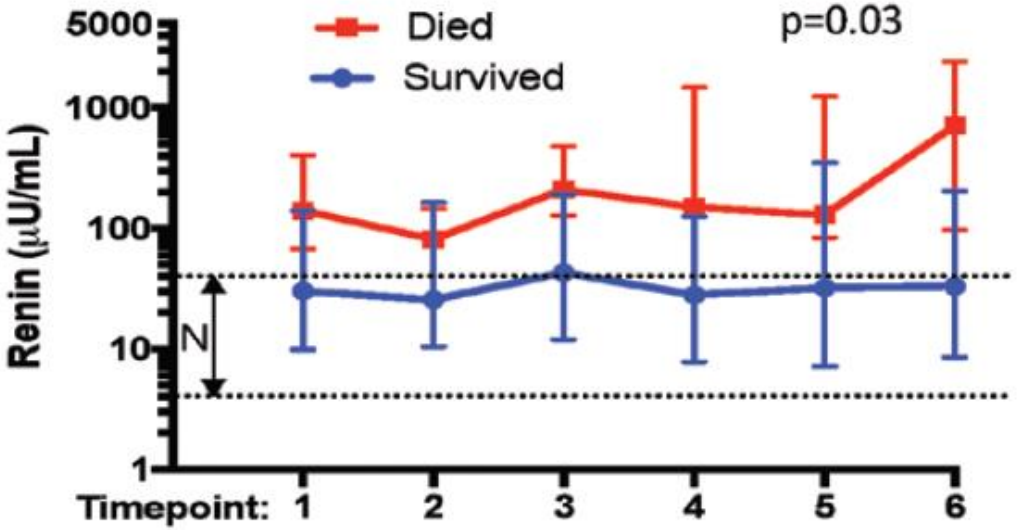


Results

Variables	Estimate of Fixed Effect	95% CI	Intraclass Correlation Coefficient	p
Noradrenaline	6.7	−1.8 to 15.9	0.20	0.11
Dobutamine	10.9	−1.7 to 25.0	0.19	0.09
Beta-blocker	−212.0	−1,619.6 to 76.6	0.16	0.18
ACE inhibitors/ARB	4.7	−151.2 to 175.5	0.19	0.92
Furosemide	0.23	−0.3 to 0.8	0.17	0.39

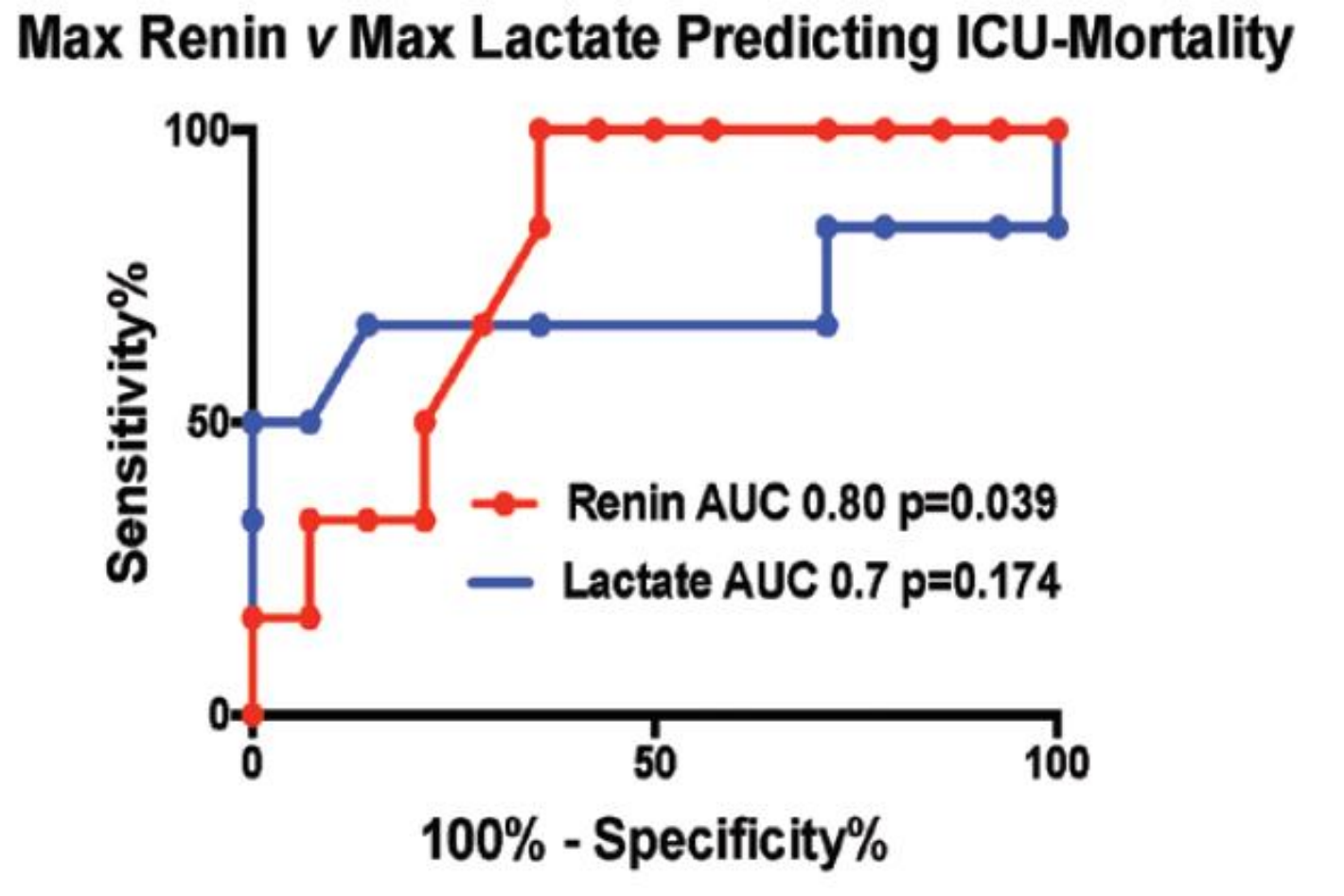
Variables	Estimate of Fixed Effect	95% CI	Intraclass Correlation Coefficient	p
Creatinine clearance	−1.2	−1.9 to −0.4	0.23	0.002
Urinary sodiuma	0.2	−0.4 to 0.8	0.14	0.42
Urinary chloridea	0.1	−0.4 to 0.6	0.14	0.68
Continuous renal replacement therapy	21.6	−158.7 to 282.8	0.19	0.73

Results



No. of Patients	20	18	19	17	11	11
ROC AUC	0.75	0.70	0.82	0.85		
p value	0.08	0.21	0.03	0.03		
Fisher's Test						
p value	0.04	0.04	0.04	0.04		
Sensitivity (%)	100	100	100	100		
Specificity (%)	57	54	54	59		
PPV (%)	50	50	50	55		
NPV (%)	100	100	100	100		

Results



- Renin value (> 40 µU/mL; supine patients)
- Lactate value (> 2 mM)

Effect of Thiamine Administration on Lactate Clearance and Mortality in Patients With Septic Shock*

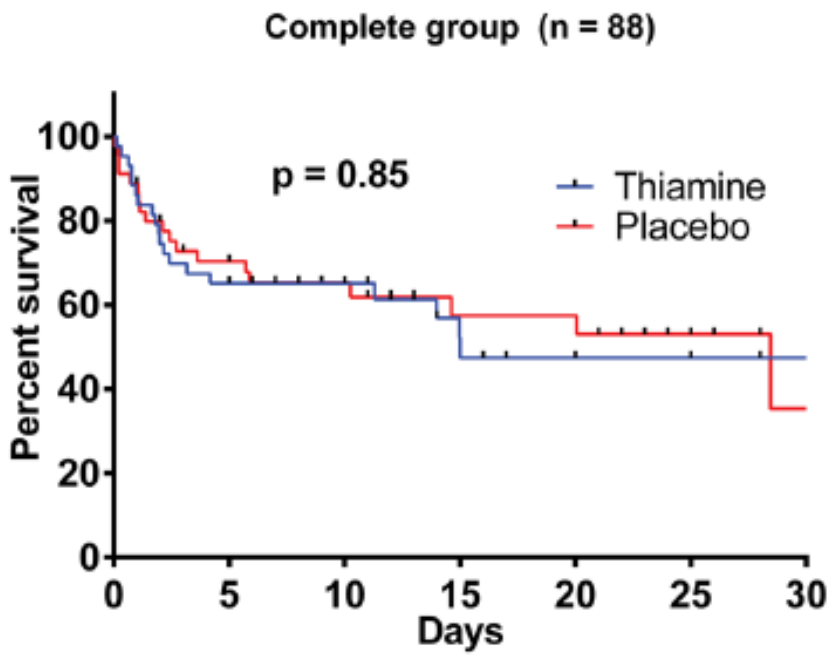
Jordan A. Woolum, PharmD[1]; Erin L. Abner, PhD, MPH[2]; Andrew Kelly, MAS, MS[3]; Melissa L. Thompson Bastin, PharmD, BCPS[1,4]; Peter E. Morris, MD[5]; Alexander H. Flannery, PharmD, BCCCP, BCPS[1,4]

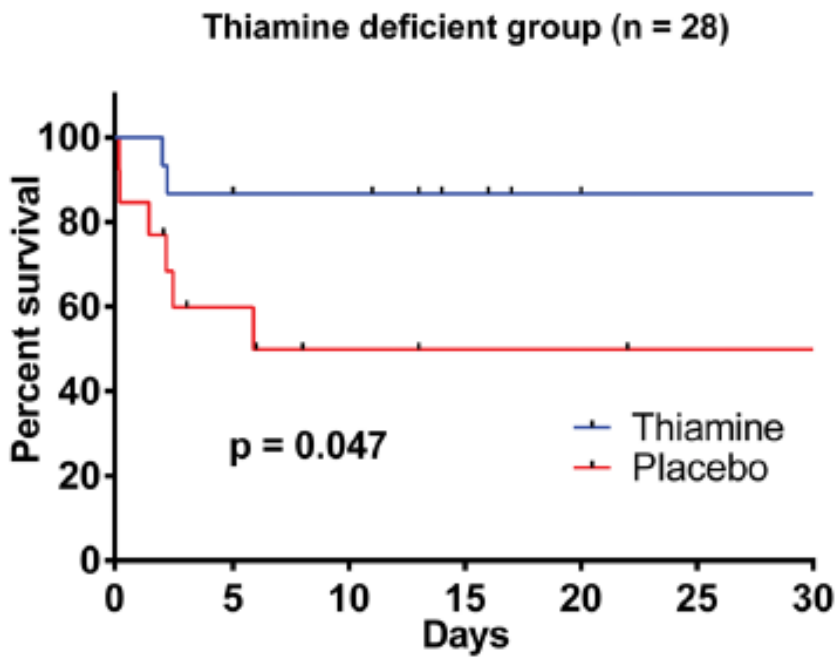
Thiamin in Critical ill patients

- Critically ill patients are commonly thiamine deficient
  - Metabolic stress
  - decreased or poor nutritional
  - Presence of comorbidities

Thiamin in Critical ill patients

- 88 patients prospective study
- 200 mg thiamine in 50 mL 5% dextrose once daily
- Thiamin 50mg/2mL/A – 261원





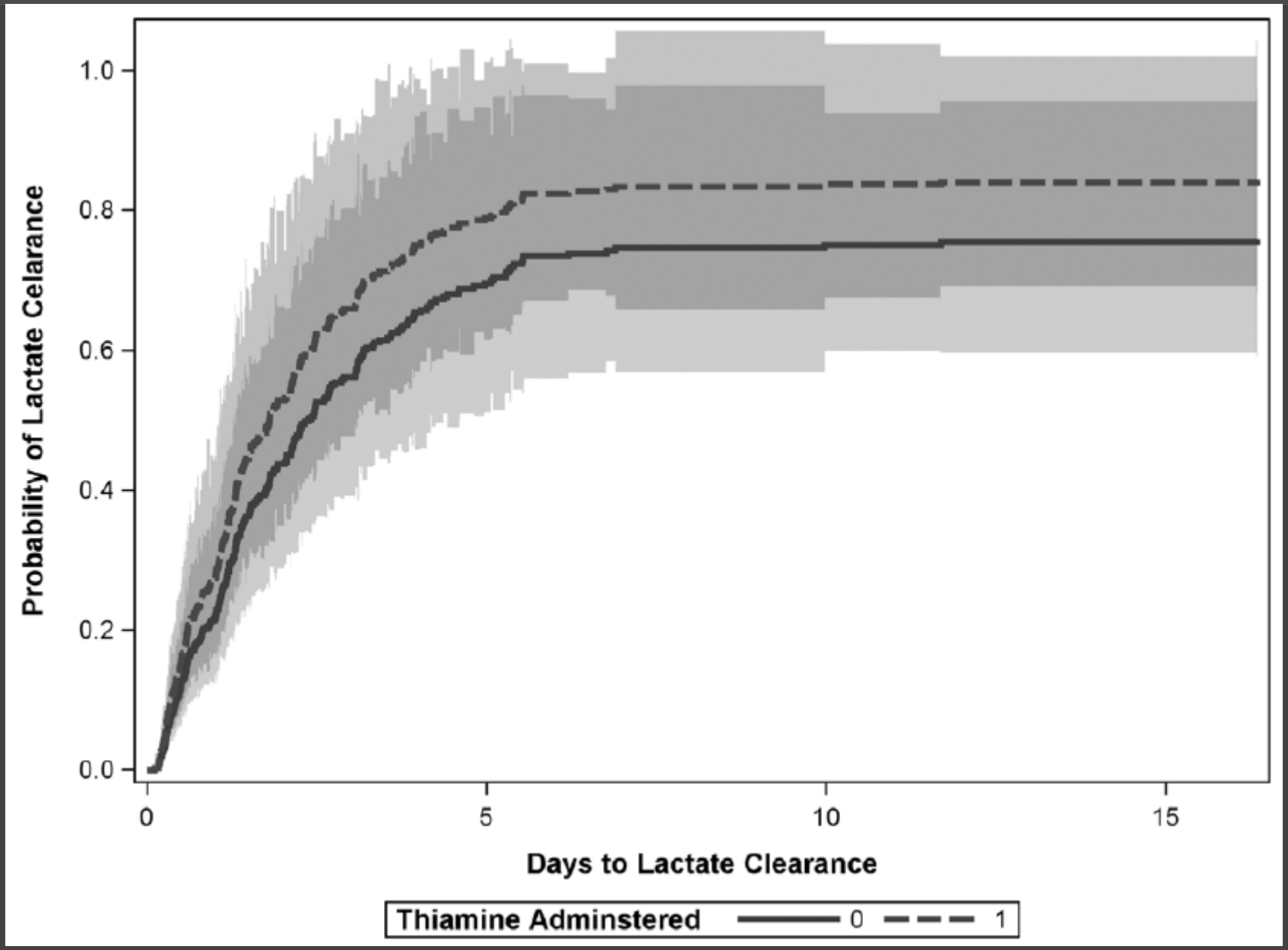
Crit Care Med. 2016 February ; 44(2): 360–367

Methods

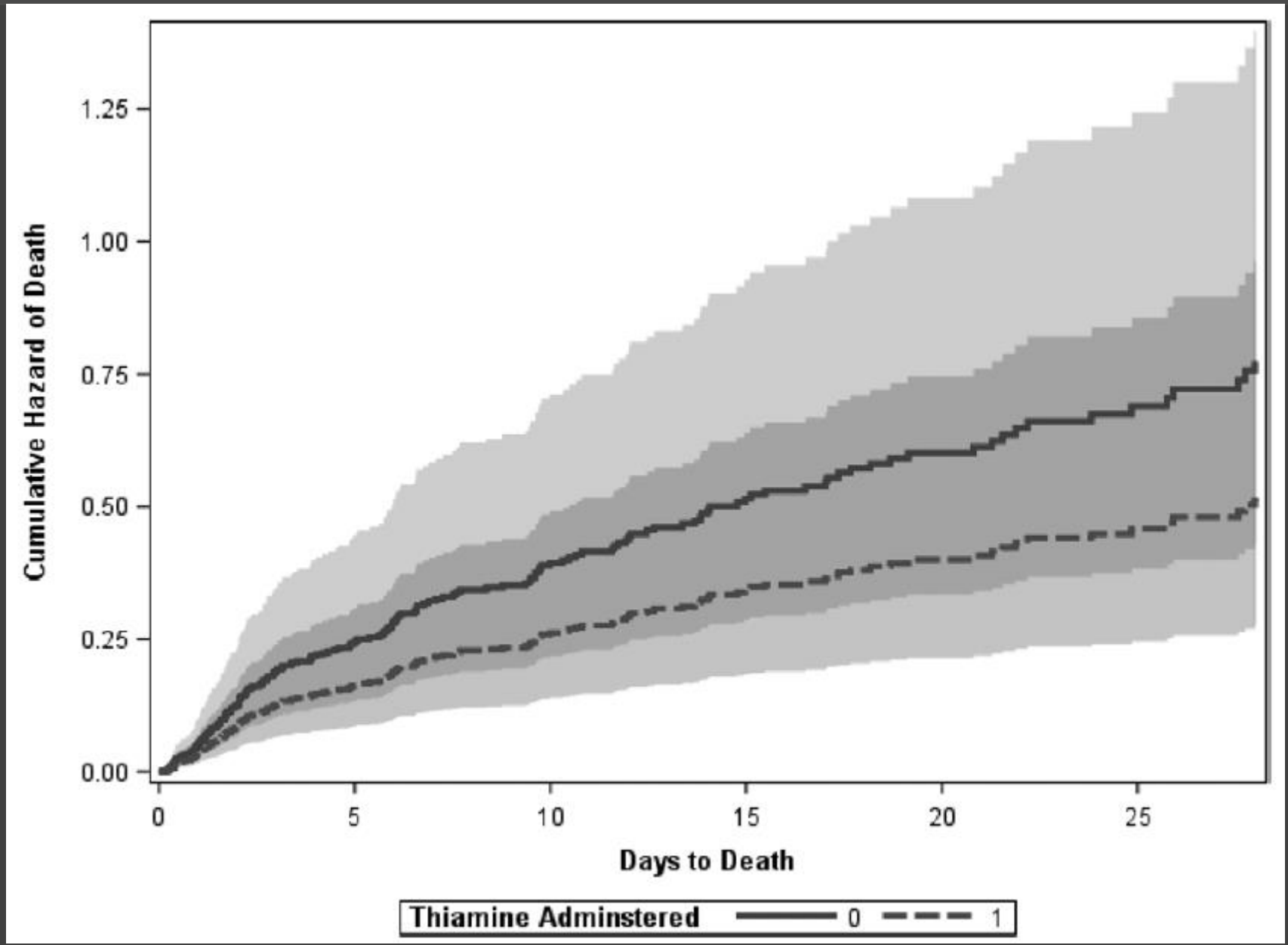
- Retrospective, single-center, matched cohort study
- Patients who received any dose IV thiamine supplementation within 24 hours of hospital admission
- 123 thiamine-treated patients matched with 246 patients who did not receive thiamin
- The primary outcome: lactate clearance

Variables	No Thiamine ($n = 246$)	Thiamine ($n = 123$)	p
Baseline demographics			
Age (yr), median (IQR)	54 (45–61)	52 (43–61)	0.238
Sex (male) (%)	56.10	56.10	1.000
Race (white) (%)	91.90	91.90	1.000
Liver disease (%)	65.00	65.00	1.000
Elixhauser comorbidity index, median (IQR)	4 (3–5)	4 (2–5)	0.948
Service (medical) (%)	96.80	96.80	1.000
Sequential Organ Failure Assessment score on ICU admission, median (IQR)	10 (8–12)	10 (8–12)	0.972
Stress dose steroids (%)	52.00	52.90	0.883
Peak lactate (mmol/L), median (IQR)	6 (3.3–10.5)	6 (3.3–12.1)	0.904
WBC count on ICU admission ($\times 10^3/\mu L$), median (IQR)	14 (8–21)	14 (8–22)	0.844
Infection source (%)			
Bacteremia	37.0	37.4	0.939
Urinary tract	19.9	23.6	0.417
Thiamine administration			
Time from admission to thiamine (hr)	N/A	6.4 (3.8–11)	N/A
Dose (mg) (%)			
100	N/A	27.10	N/A
100–400	N/A	5.90	N/A
500	N/A	67	N/A
Duration (hr), median (IQR)	N/A	66.2 (38.2–119.5)	N/A

Results


Probability of Lactate Celarance
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
Days to Lactate Clearance
Thiamine Adminstered
0
1

Results


Cumulative Hazard of Death
1.25
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Days to Death
Thiamine Adminstered
0
1

Conclusion

- Thiamine administration within 24 hours of admission in patients presenting with septic shock was associated with improved lactate clearance and a reduction in 28-day mortality compared with matched controls

Metabolic acidosis

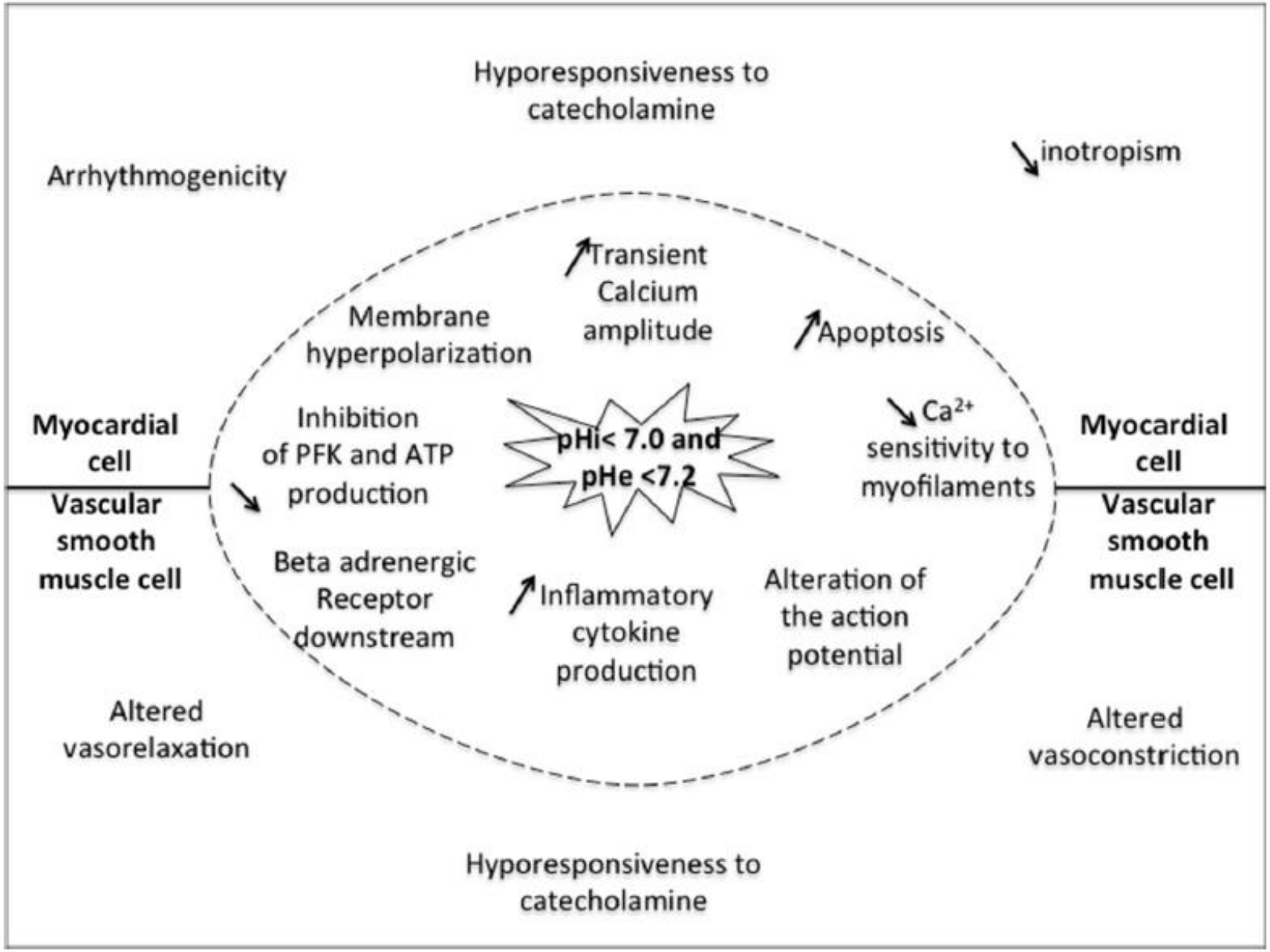
Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

*Samir Jaber, Catherine Paugam, Emmanuel Futier, Jean-Yves Lefrant, Sigismond Lasocki, Thomas Lescot, Julien Pottecher, Alexandre Demoule, Martine Ferrandière, Karim Asehnoune, Jean Dellamonica, Lionel Velly, Païr-Sélim Abback, Audrey de Jong, Vincent Brunot, Fouad Belafia, Antoine Roquilly, Gérald Chanques, Laurent Muller, Jean-Michel Constantin, Helena Bertet, Kada Klouche, Nicolas Molinari, Boris Jung, for the BICAR-ICU Study Group**

Metabolic acidosis

- Negative impact on
  - Cardiac contractility
  - Sensitivity of adrenergic receptors
  - Adenosine triphosphate generation
  - Immune response
- Circulatory failure and decreased survival

Metabolic acidosis



Methods

- Patients (aged ≥18 years) within 48 h to the ICU
  - with severe acidaemia (pH ≤7·20, PaCO2 ≤45 mm Hg, and sodium bicarbonate concentration ≤20 mmol/L)
  - with a total SOFA of 4 or more or an lactate of 2 mmol/L or more

- Exclusion
  - Respiratory acidosis
  - Proven digestive or urinary tract loss of sodium bicarbonate
  - Stage IV chronic kidney disease
  - Ketoacidosis
  - Sodium bicarbonate infusion (including renal-replacement therapy) within 24 h before screening.

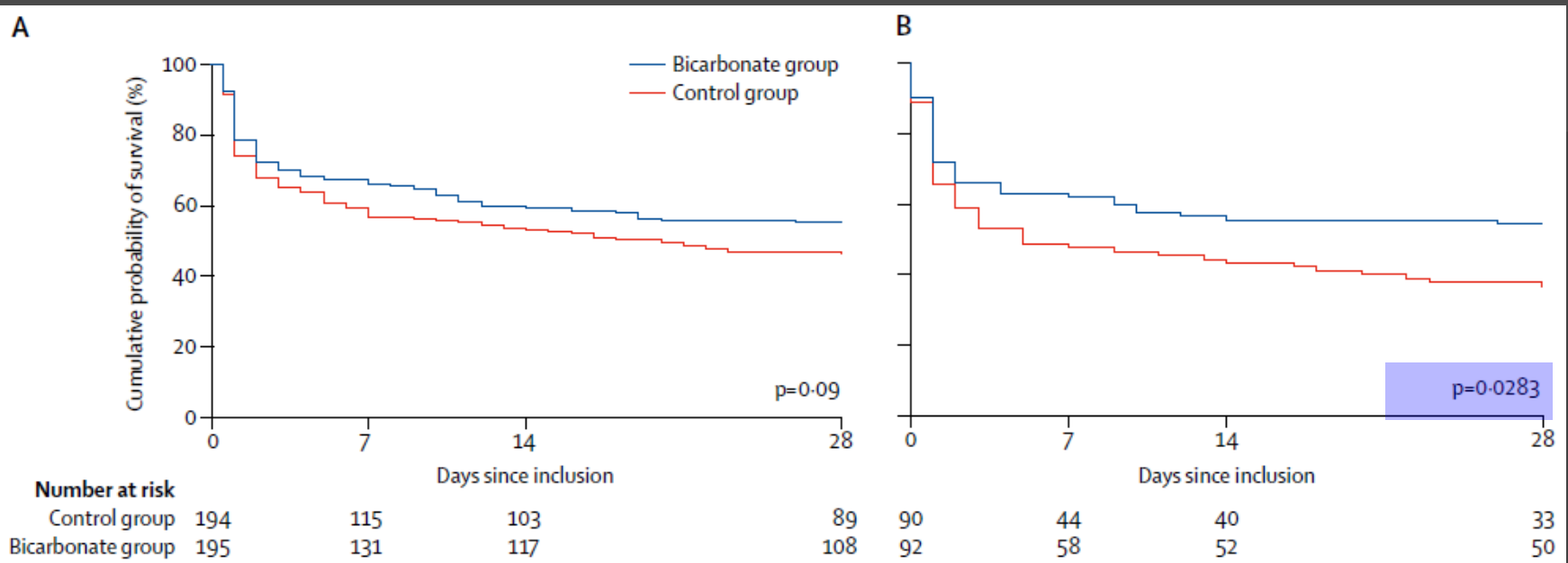
Methods

- 4.2% of intravenous sodium bicarbonate infusion (bicarbonate group) to maintain the arterial pH above 7.30

- The primary outcome
  - Death from any cause by day 28 and at least one organ failure at day 7.

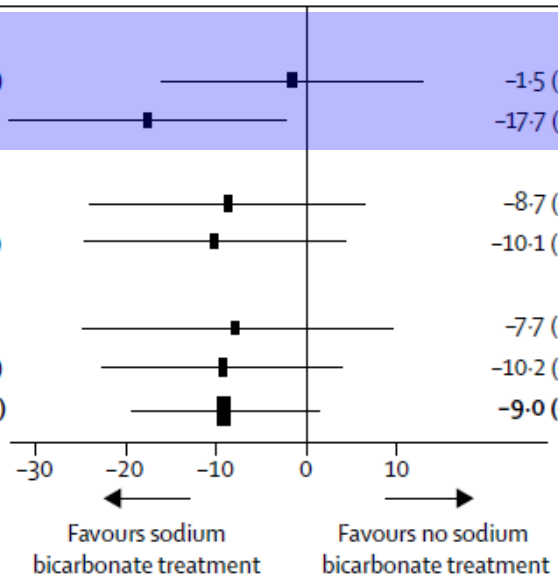
	Control group (n=194)	Bicarbonate group (n=195)
(Continued from previous page)		
Physiological support†		
Invasive mechanical ventilation	160 (82%)	164 (84%)
Vasopressor support	156 (80%)	154 (79%)
Laboratory results		
Arterial pH	7·15 (7·11–7·18)	7·15 (7·09–7·18)
PaO_2-to-FiO_2 ratio (mm Hg)	229 (142–355)	264 (144–403)
$PaCO_2$ (mm Hg)	37 (32–42)	38 (33–42)
Serum bicarbonate (mmol/L)	13 (10–15)	13 (10–15)
Serum lactate (mmol/L)	5·3 (3·4–9·0)	6·3 (3·6–9·7)
Serum lactate ≥2 mmol/L at enrolment	152 (78%)	168 (86%)
Serum creatinine (mg/dL)	1·76 (1·21–2·48)	1·67 (1·11–2·33)
Blood urea nitrogen (mg/dL)	31 (20–48)	28 (20–45)

Primary outcome		
Overall population (n=389)		
Composite outcome	−5·5 (−15·2 to 4·2)	0·24
Day 28 mortality	−9·0 (−19·4 to 1·4)	0·07
At least one organ failure at day 7	−2·8 (−15·4 to 9·8)	0·15
Patients with AKIN scores of 2–3* (n=182)		
Composite outcome	−12·3 (−26·0 to −0·1)	0·0462
Day 28 mortality	−17·7 (−33·0 to −2·3)	0·0166
At least one organ failure at day 7	−15·9 (−28·4 to −3·4)	0·0142
Secondary outcomes		
Renal replacement therapy		
Overall population (n=389)		
Use of renal replacement therapy during ICU stay	−16·7 (−26·4 to −7·0)	0·0009
Time from enrolment to initiation of renal replacement therapy (h)	8·8 (3·9 to 15·6)	<0·0001
Renal replacement therapy-free days during ICU stay	0 (0·0 to 1·0)	0·015
Renal replacement therapy-free days during ICU stay in survivors	0 (0 to 0)	0·47
Dependence on dialysis at ICU discharge	−12·5 (−34·3 to 9·3)	0·26
Patients with AKIN scores of 2–3* (n=182)		
Use of renal replacement therapy during ICU stay	−22·2 (−36·0 to −8·5)	0·0020
Time from enrolment to initiation of renal replacement therapy (h)	10·5 (4·0 to 18·5)	<0·0001
Renal replacement therapy-free days during ICU stay	1·0 (0·0 to 5·0)	0·0040
Renal replacement therapy-free days during ICU stay in survivors	1·0 (0·0 to 3·0)	0·45
Dependence on dialysis at ICU discharge	−27·6 (−54·1 to −1·1)	0·0465

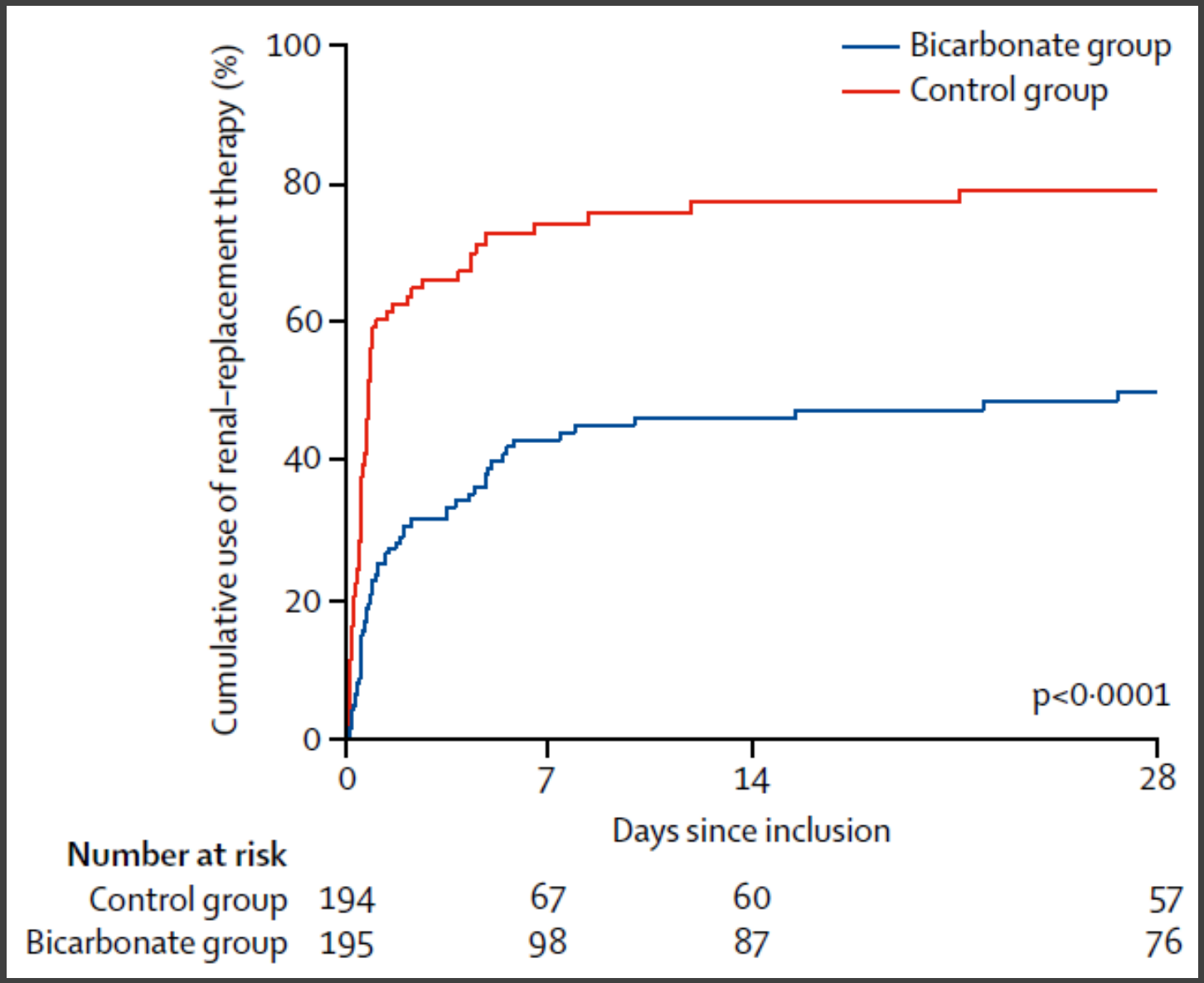


C

	Control group (n/N)	Bicarbonate group (n/N)	Absolute difference estimate (95% CI)	p value	Adjusted p value	p value for heterogeneity
AKIN score						
0–1	47/104 (45%)	45/103 (44%)	−1·5 (−16·0 to 13·0)	0·83	0·83	0·0226
2–3	57/90 (63%)	42/92 (46%)	−17·7 (−33·0 to −2·3)	0·0167	0·0334	
Age (years)						
<65	42/94 (45%)	32/89 (36%)	−8·7 (−24·0 to 6·5)	0·23	0·23	0·0031
≥65	62/100 (62%)	55/106 (52%)	−10·1 (−24·5 to 4·3)	0·14	0·28	
Sepsis status						
No	39/79 (49%)	30/72 (42%)	−7·7 (−24·9 to 9·5)	0·34	0·34	0·21
Yes	65/115 (57%)	57/123 (46%)	−10·2 (−23·7 to 3·3)	0·12	0·24	
All patients	**104/194 (54%)**	**87/195 (45%)**	**−9·0 (−19·4 to 1·4)**	**0·08**		



Renal replacement therapy



Intensive Care Med (2018) 44:1888–1895
https://doi.org/10.1007/s00134-018-5379-2

ORIGINAL

Effectiveness of sodium bicarbonate infusion on mortality in septic patients with metabolic acidosis

Zhongheng Zhang[1*], Carlie Zhu[2], Lei Mo[3] and Yucai Hong[1]

Methods

- A large US-based critical care database named Medical Information Mart for Intensive Care (MIMIC-III)

- Clinical data of the patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, Massachusetts, from June 1st, 2001 to October 31st, 2012 (single center).

- 53,423 adult patients (aged 16 years or above) admitted to ICUs during the study period.

Methods

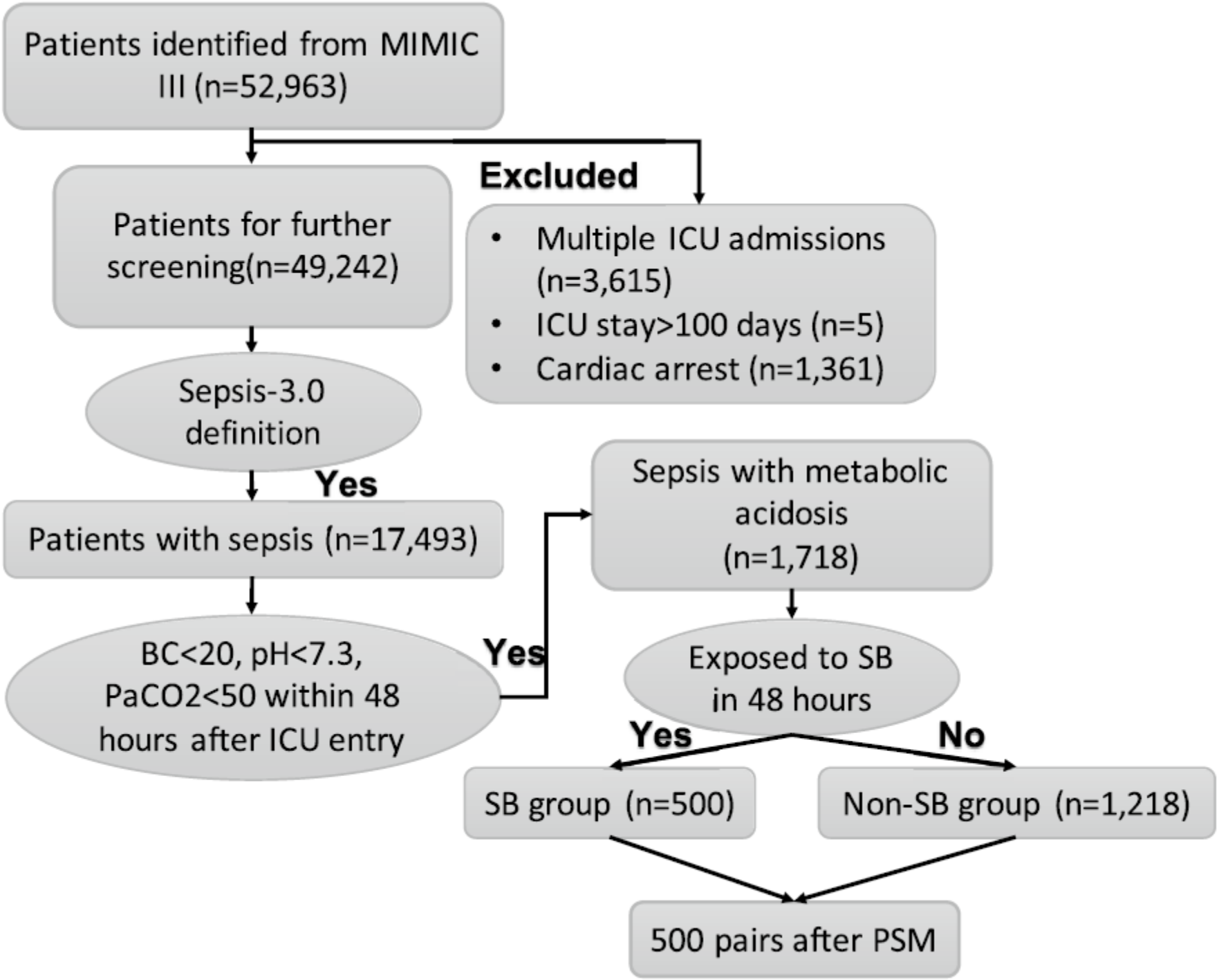
- Inclusion criteria

  (1) with sepsis

  (2) metabolic acidosis with pH < 7.3 and BC < 20 mmol/l

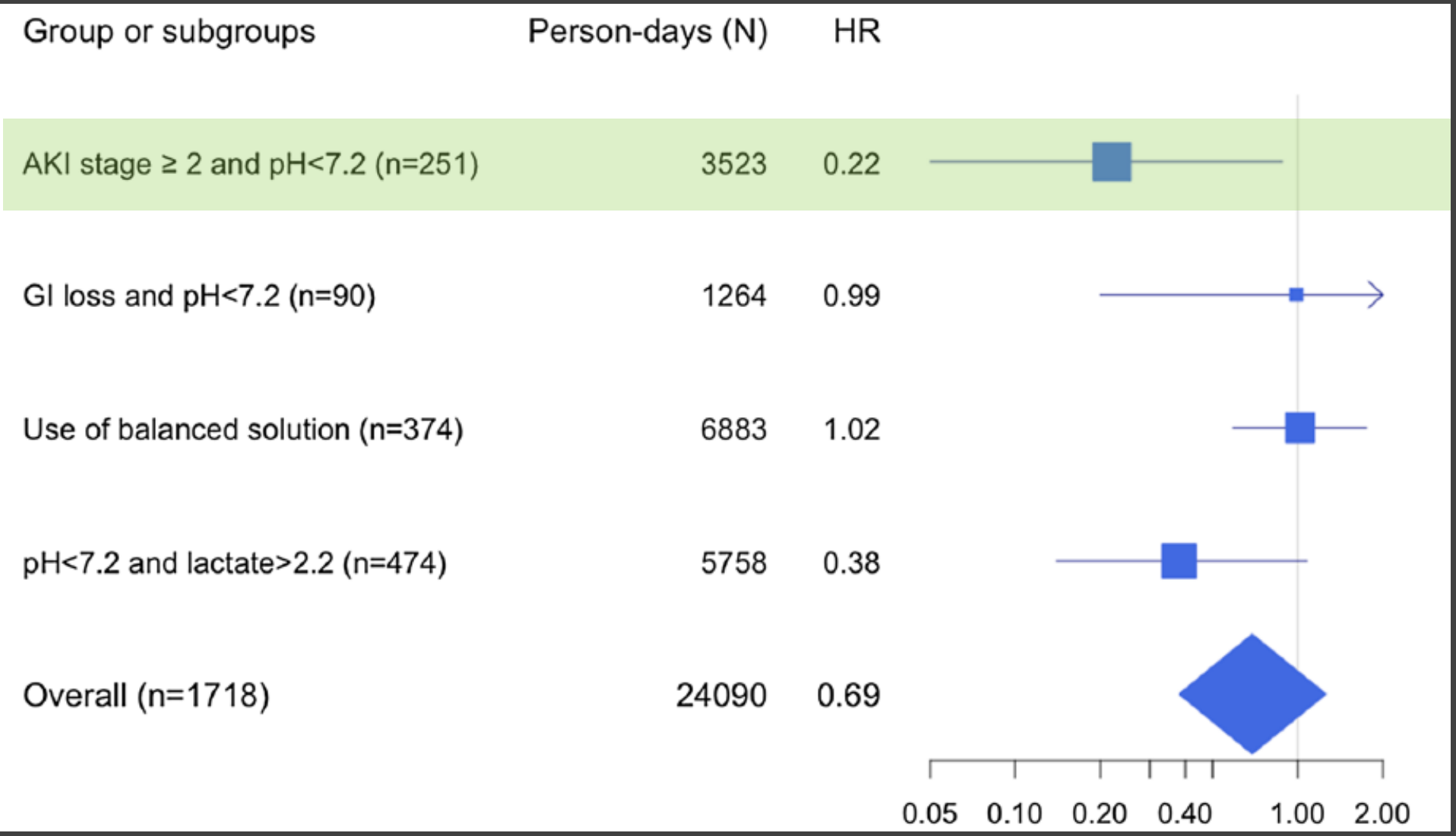
  (3) in the absence of respiratory acidosis ($PaCO_2$ < 50 mmHg)

- Propensity score (PS) matching


Patients identified from MIMIC III (n=52,963)
Excluded
Patients for further screening(n=49,242)
• Multiple ICU admissions (n=3,615)
• ICU stay>100 days (n=5)
• Cardiac arrest (n=1,361)
Sepsis-3.0 definition
Yes
Patients with sepsis (n=17,493)
Sepsis with metabolic acidosis (n=1,718)
BC<20, pH<7.3, PaCO2<50 within 48 hours after ICU entry
Yes
Exposed to SB in 48 hours
Yes
No
SB group (n=500)
Non-SB group (n=1,218)
500 pairs after PSM

Variables	Non-SB group ($n = 1218$)	SB group ($n = 500$)	P
Gender, male (%)	593 (48.7)	235 (47.0)	0.560
Age [mean (SD)]	65.88 (16.71)	64.09 (16.41)	0.043
Admission type (%)			0.238
Elective	62 (5.1)	19 (3.8)	
Emergency	1116 (91.6)	470 (94.0)	
Urgent	40 (3.3)	11 (2.2)	
SOFA [median (IQR)]	7.00 [5.00, 10.00]	9.00 [7.00, 12.00]	< 0.001
qSOFA [median (IQR)]	2.00 [2.00, 2.00]	2.00 [2.00, 2.00]	0.017
SAPSII [median (IQR)]	48 [39, 58]	57 [47, 68]	< 0.001
Vasopressor, *n* (%)	608 (49.9)	300 (60.0)	< 0.001
Urine output [median (IQR)]	1135 [572, 1986]	709 [249, 1486]	< 0.001
RRT, *n* (%)	98 (8.0)	62 (12.4)	0.006
Elective surgery, *n* (%)	49 (4.0)	16 (3.2)	0.501
Mechanical ventilation, *n* (%)	684 (56.2)	344 (68.8)	< 0.001
Minimum pH [mean (SD)][a]	7.22 (0.07)	7.16 (0.10)	< 0.001
Minimum BC [mean (SD)][a]	14.88 (3.36)	11.84 (3.63)	< 0.001
AKI, *n* (%)	571 (46.9)	238 (47.6)	0.827

Variables	Non-SB group ($n = 1218$)	SB group ($n = 500$)	P
AKI stage, *n* (%)			< 0.001
0	647 (53.1)	262 (52.4)	
1	110 (9.0)	26 (5.2)	
2	245 (20.1)	84 (16.8)	
3	216 (17.7)	128 (25.6)	
Diarrhea or vomiting, *n* (%)	181 (14.9)	84 (16.8)	0.348
Lactate [mean (SD)]	4.33 (3.42)	5.42 (4.51)	< 0.001
Maximum PaCO2 [mean (SD)][a]	41.57 (6.12)	39.82 (6.56)	< 0.001
Fluid input day 1 [median (IQR)]	1661 [711, 4000]	2361 [956, 5731]	< 0.001
Balanced solution, *n* (%)[b]	310 (25.5)	64 (12.8)	< 0.001
Admission period, *n* (%)			< 0.001
Before 2008	812 (66.7)	215 (43.0)	
2008–2012	406 (33.3)	285 (57.0)	


Group or subgroups
Person-days (N)
HR
AKI stage ≥ 2 and pH<7.2 (n=251)
3523
0.22
GI loss and pH<7.2 (n=90)
1264
0.99
Use of balanced solution (n=374)
6883
1.02
pH<7.2 and lactate>2.2 (n=474)
5758
0.38
Overall (n=1718)
24090
0.69
0.05
0.10
0.20
0.40
1.00
2.00

Conclusion

- SB infusion was not associated with improved outcome in septic patients with metabolic acidosis, but it was associated with improved survival in septic patients with AKI stage 2 or 3 and severe acidosis

Delirium

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

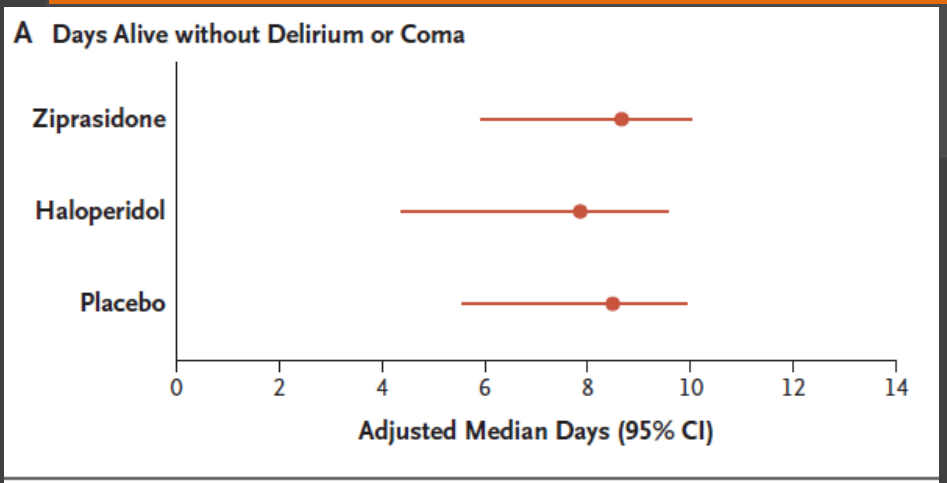
Methods

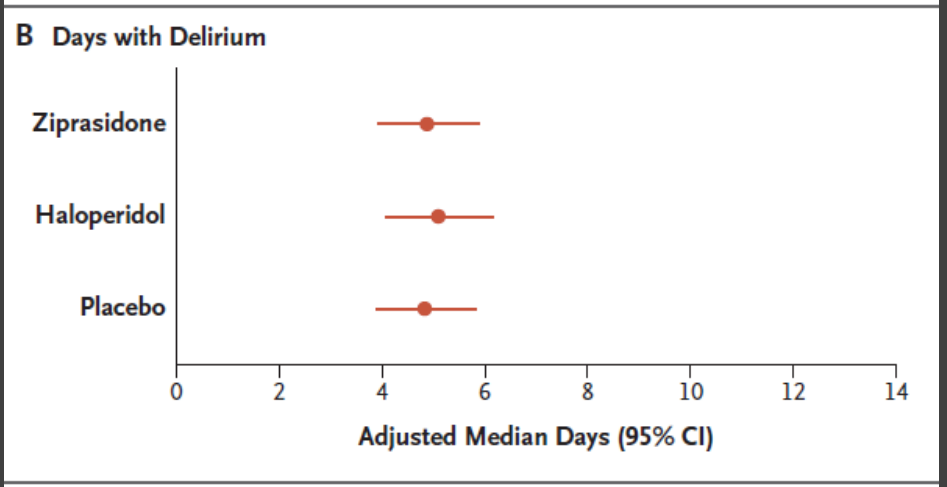
- Acute respiratory failure or shock

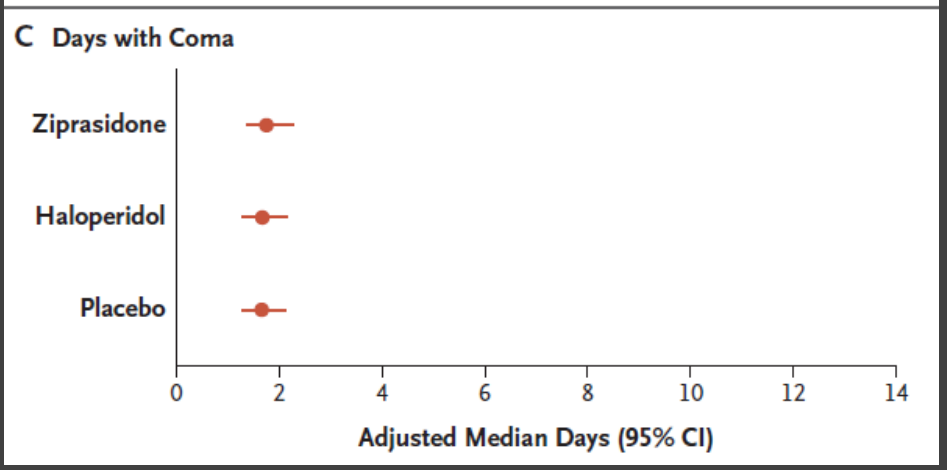
- IV boluses of haloperidol (maximum, 20 mg daily)
- Ziprasidone (maximum dose, 40 mg daily)
- Placebo

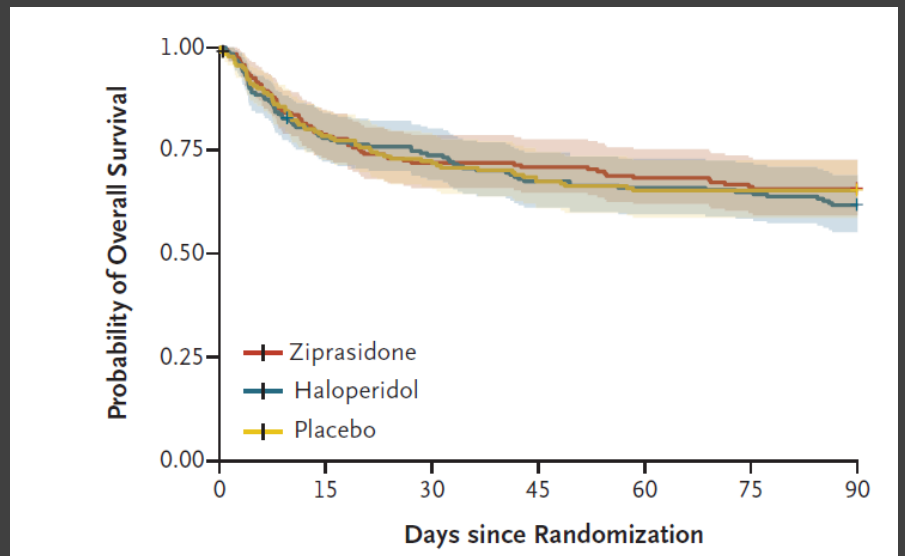
- The volume and dose of a trial drug or placebo was halved or doubled at 12-hour intervals with CAM ICU

Characteristic	Placebo (N = 184)	Haloperidol (N = 192)	Ziprasidone (N = 190)
Median age (IQR) — yr	59 (52–67)	61 (51–69)	61 (50–69)
Female sex — no. (%)	77 (42)	84 (44)	82 (43)
Race — no. (%)†			
White	153 (83)	163 (85)	151 (79)
Black	26 (14)	23 (12)	27 (14)
Multiple races or other race	5 (3)	6 (3)	12 (6)
Median short-form IQCODE score (IQR)‡	3.1 (3.0–3.3)	3.0 (3.0–3.2)	3.1 (3.0–3.3)
Median Charlson Comorbidity Index score (IQR)§	2 (1–4)	2 (1–3)	2 (1–4)
Received antipsychotic treatment — no. (%)			
Before admission	6 (3)	8 (4)	11 (6)
Between admission and randomization	18 (10)	20 (10)	22 (12)
Hyperactive delirium at randomization — no. (%)	22 (12)	19 (10)	16 (8)
Hypoactive delirium at randomization — no. (%)	161 (88)	172 (90)	172 (91)
Diagnosis at admission — no. (%)			
Adult respiratory distress syndrome	39 (21)	44 (23)	35 (18)
Sepsis	35 (19)	43 (22)	33 (17)
Airway protection	53 (29)	46 (24)	44 (23)
Chronic obstructive pulmonary disease, asthma, or other pulmonary disorder	23 (12)	20 (10)	28 (15)
Surgery	13 (7)	13 (7)	23 (12)









No. at Risk (cumulative no. of deaths)

Ziprasidone	190 (0)	150 (40)	137 (53)	135 (55)	130 (60)	126 (64)	125 (65)
Haloperidol	192 (0)	149 (42)	141 (50)	129 (62)	126 (65)	124 (67)	118 (73)
Placebo	184 (0)	143 (39)	132 (50)	123 (59)	119 (63)	119 (63)	119 (63)

ORIGINAL ARTICLE

Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium

A Randomized, Placebo-controlled Trial

Yoanna Skrobik[1,2], Matthew S. Duprey[3,4], Nicholas S. Hill[4], and John W. Devlin[3,4]

[1]Department of Medicine, McGill University, Montreal, Quebec, Canada; [2]Regroupement de Soins Critiques Respiratoires, Réseau de Santé Respiratoire, Fonds de Recherche du Québec-Santé, Montréal, Québec, Canada; [3]School of Pharmacy, Northeastern University, Boston, Massachusetts; and [4]Department of Pulmonary, Critical Care, and Sleep Medicine, Tufts Medical Center, Boston, Massachusetts

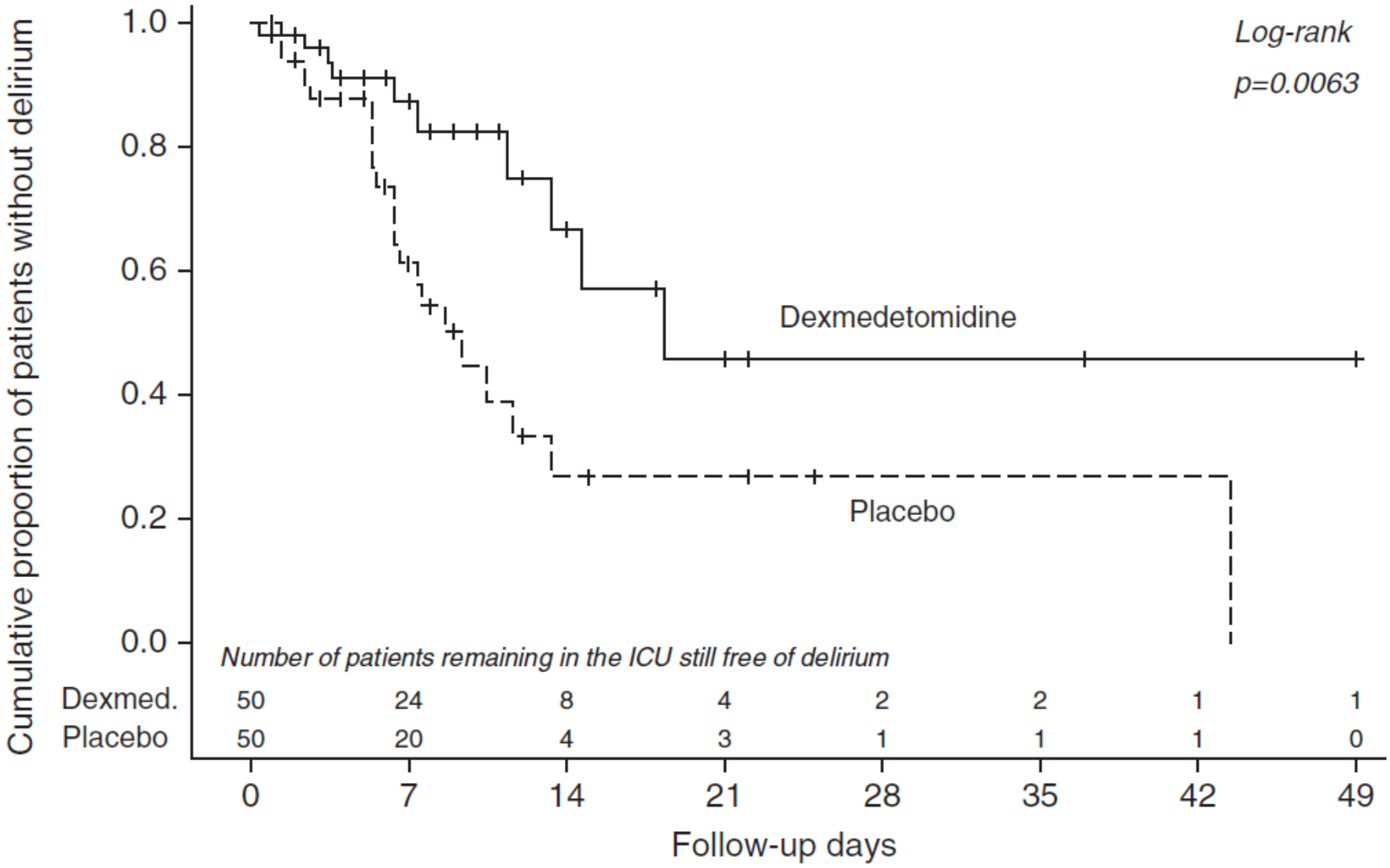
Methods

- Nocturnal (9:30 P.M. to 6:15 A.M.) intravenous dexmedetomidine (0.2 mg/kg/h, titrated by 0.1 mg /kg/h every 15 min until a goal RASS score of -1 or maximum rate of 0.7 mg/kg/h was reached) or placebo until ICU discharge

Variable	Dexmedetomidine (*n* = 50)	Placebo (*n* = 50)
Age, yr, mean ± SD	62.1 ± 13.2	62.4 ± 14.1
Male, *n* (%)	31 (62)	33 (66)
APACHE-II score at enrollment, mean ± SD	23.6 ± 7.8	21.9 ± 7.9
Medical (vs. surgical), *n* (%)	36 (72)	37 (74)
Mechanically ventilated, *n* (%)	45 (90)	44 (88)
Days in ICU before enrollment, median (IQR)	2 (1–2)	1 (1–2)
Admission diagnosis, *n* (%)		
Sepsis/acute respiratory distress syndrome	9 (18)	10 (20)
Pneumonia	9 (18)	11 (22)
Nontraumatic major surgery	9 (18)	9 (18)
Respiratory failure	8 (16)	7 (14)
Trauma	5 (10)	4 (8)
Gastrointestinal	2 (4)	3 (6)
Cardiac	2 (4)	2 (4)
Other	6 (12)	4 (8)

Variable	Dexmedetomidine (*n* = 50)	Placebo (*n* = 50)	*P* Value
Bradycardia	5 (10)	4 (8)	1.00
Hypotension	17 (34)	10 (20)	0.18
Both bradycardia and hypotension	19 (38)	14 (28)	0.40

delirium


Cumulative proportion of patients without delirium
1.0
0.8
0.6
0.4
0.2
0.0
Log-rank
p=0.0063
Dexmedetomidine
Placebo
Number of patients remaining in the ICU still free of delirium
Dexmed. 50 24 8 4 2 2 1 1
Placebo 50 20 4 3 1 1 1 0
0 7 14 21 28 35 42 49
Follow-up days

경청해주셔서 감사합니다.