ULTRA-LOW TIDAL VOLUME VENTILATION FOR COVID-19

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Lyon 1

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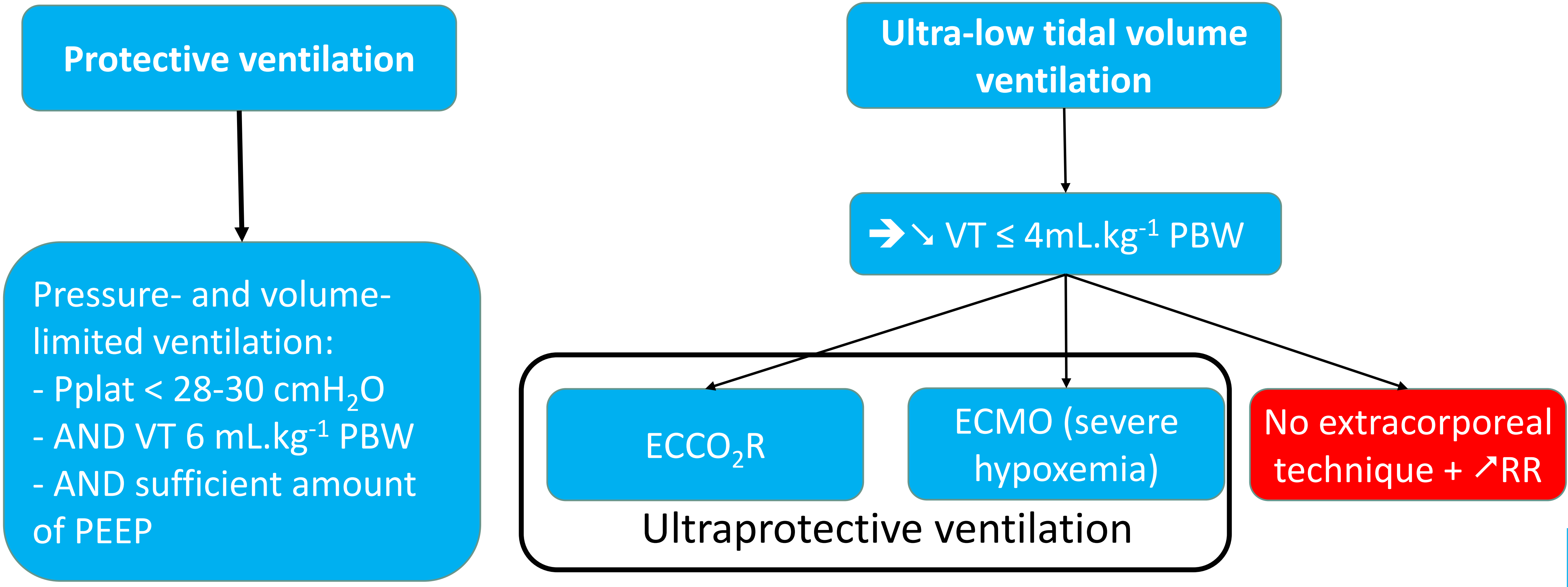
CONFLICTS OF INTEREST

- Grants: HAMILTON MEDICAL
- Congress attendance
  - GILEAD
  - PFIZER

INTRODUCTION – WHAT IS ULTRA-LOW VT VENTILATION?

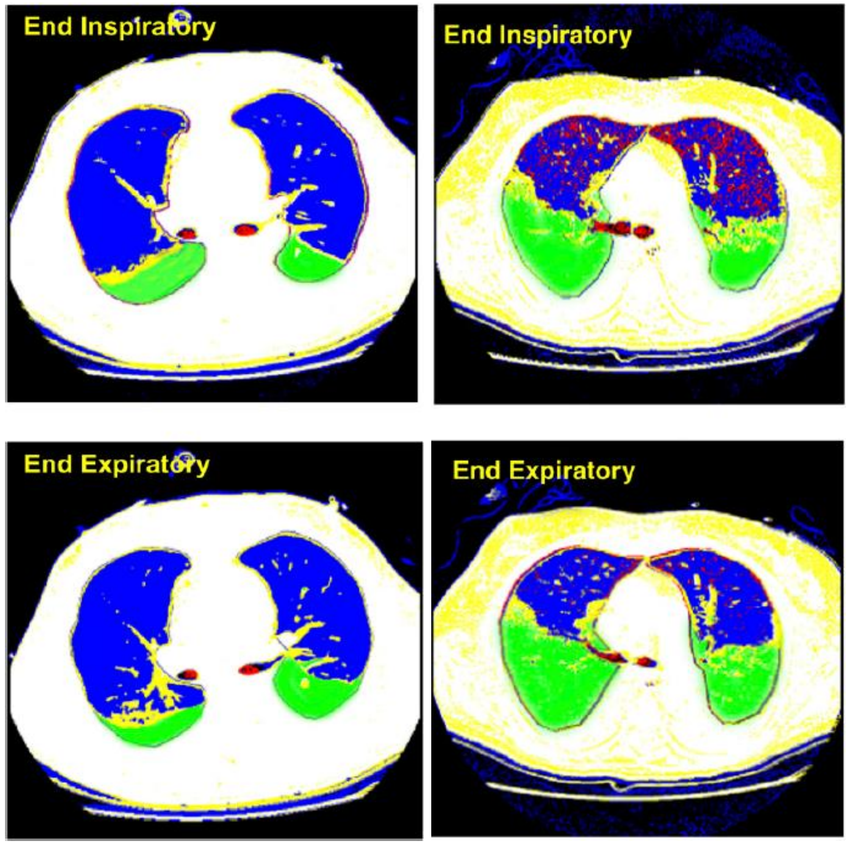


WHY SHOULD WE USE ULTRAPROTECTIVE VENTILATION
OR IS PROTECTIVE VENTILATION REALLY PROTECTIVE?

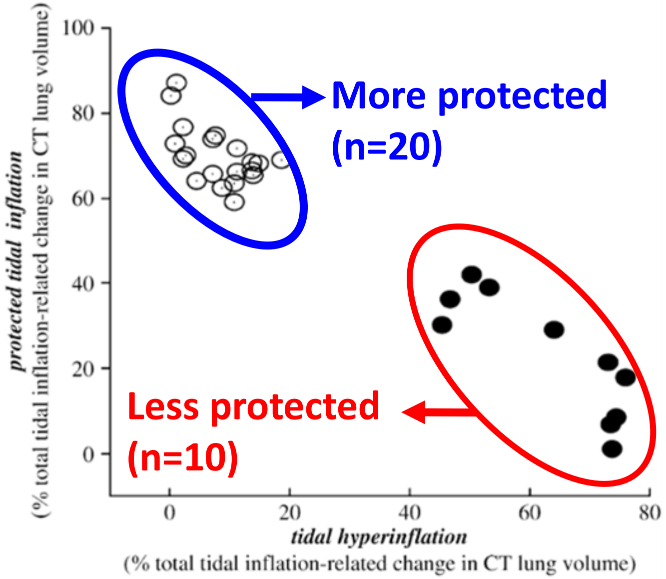
IS PROTECTIVE VENTILATION PROTECTIVE ?

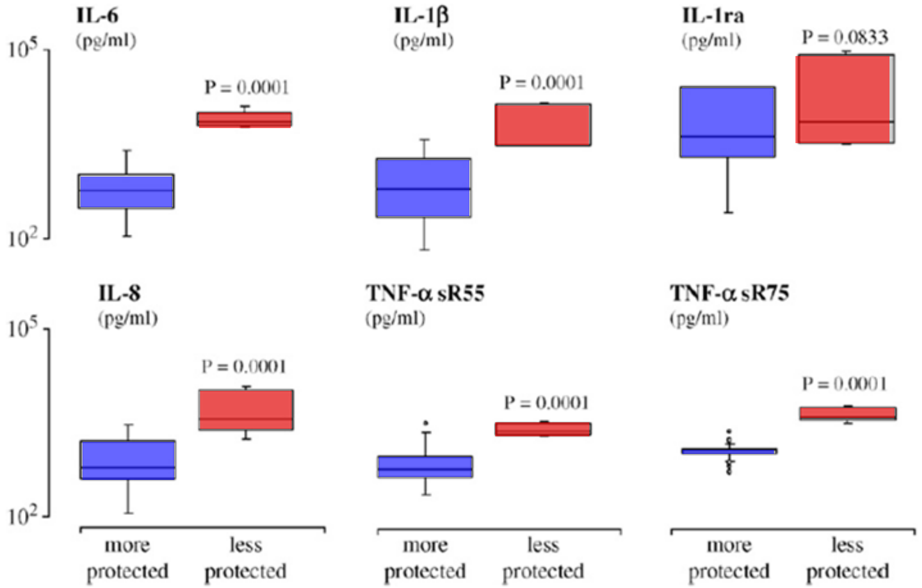
30 ARDS patients under protective MV

More protected ***Less protected***



Hyperinflated lung



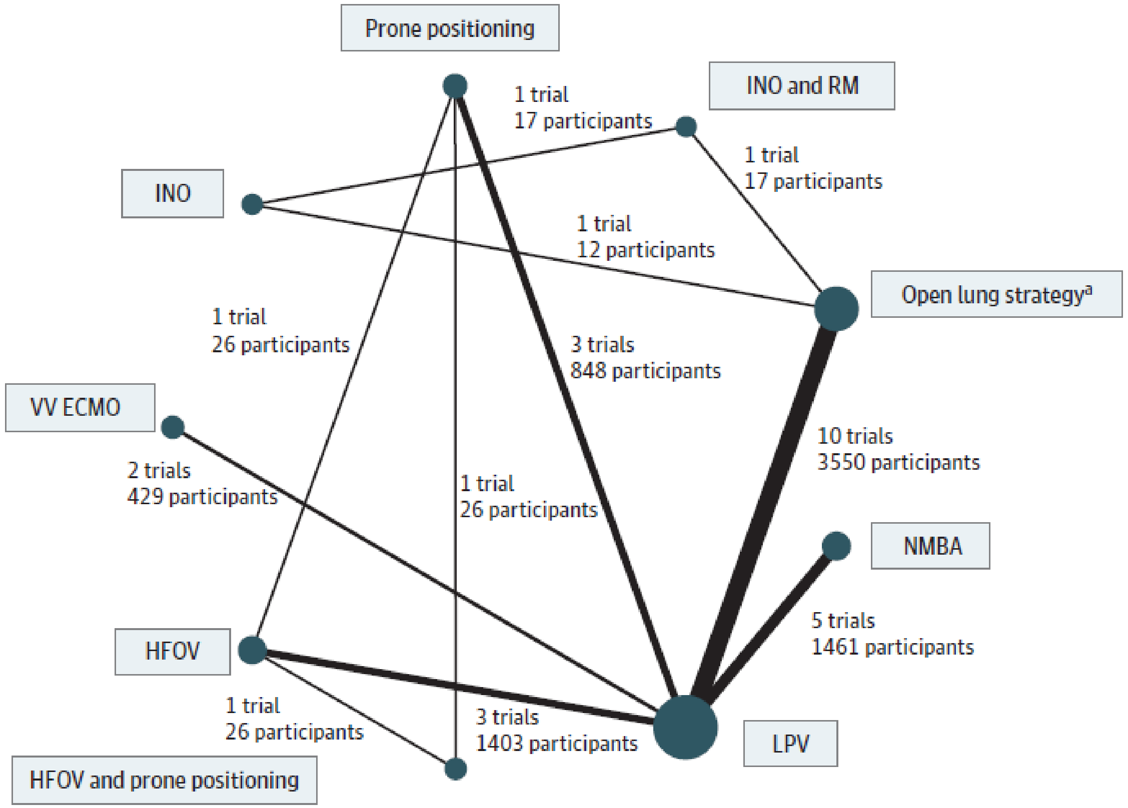


Excessive VT in 30% of the patients under protective ventilation?

Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;175(2):160–6.

IS PROTECTIVE VENTILATION PROTECTIVE ?

Network meta-analysis of RCT on patients with moderate to severe ARDS under lung protective ventilation
Barotrauma reported in 17 trials evaluating 6 interventions (6253 patients)

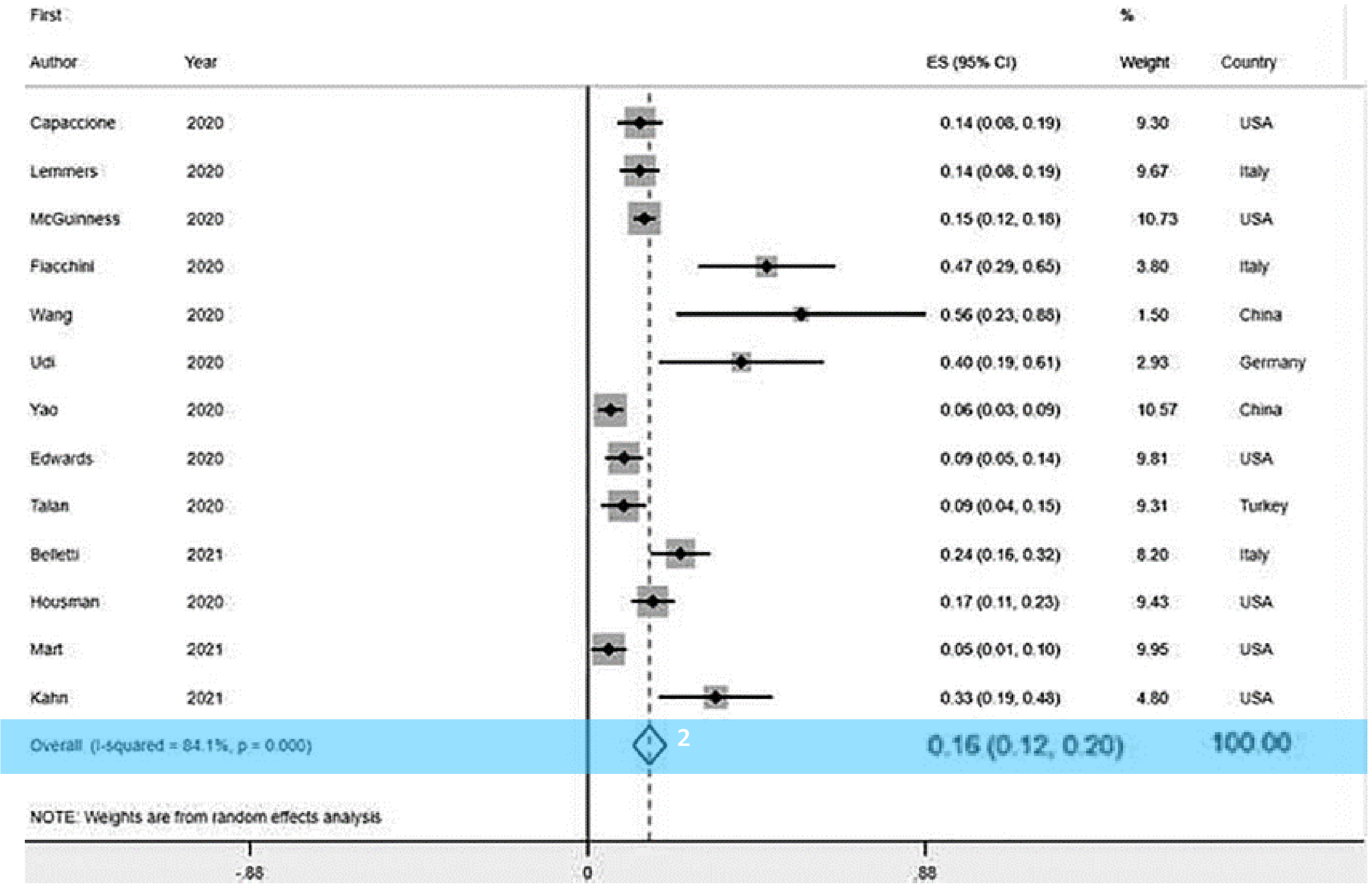


Incidence of barotrauma: 7.2%

Aoyama H, Uchida K, Aoyama K, et al. Assessment of Therapeutic Interventions and Lung Protective Ventilation in Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Systematic Review and Network Meta-analysis. JAMA Netw Open 2019;2(7):e198116.

IS PROTECTIVE VENTILATION REALLY PROTECTIVE DURING COVID-19 ARDS?

Meta-analysis (random-effect) of studies with COVID-19 ARDS -13 studies with 1,814 patients



Rate of barotrauma in COVID-19 ARDS: 16%

Time from intubation to barotrauma : 4 days ($CI_{95\%}$: 2-5) after intubation

Mortality of COVID-19 ARDS with barotrauma: 62% ($CI_{95\%}$, 50–73%)

Belletti A, Todaro G, Valsecchi G, et al. Barotrauma in Coronavirus Disease 2019 Patients Undergoing Invasive Mechanical Ventilation: A Systematic Literature Review. Crit Care Med 2022;50(3):491–500.

HOW TO ACHIEVE ULTRA-LOW TIDAL VOLUME VENTILATION (ULTV) WITHOUT $ECCO_2R$?

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HOW TO ACHIEVE ULTRA-LOW TIDAL VOLUME WITHOUT $ECCO_2R$?

- Minimization of instrumental dead space
- VT stepwise reduction → 4 $ml.kg^{-1}$ PBW
- RR increase up to 35 min^{-1} to maintain MV constant
- Reevaluate VT and PEEP levels to achieve ventilatory goals
  - plateau pressure ≤ 30 cm H_2O;
  - $55 \le PaO_2 \le 80$ mmHg or $88\% \le SpO_2 \le 95\%$;
  - $7.20 \le pH \le 7.45$
- Caution with ventilator asynchrony (increased ventilatory drive by hypercapnia) → use NMBA

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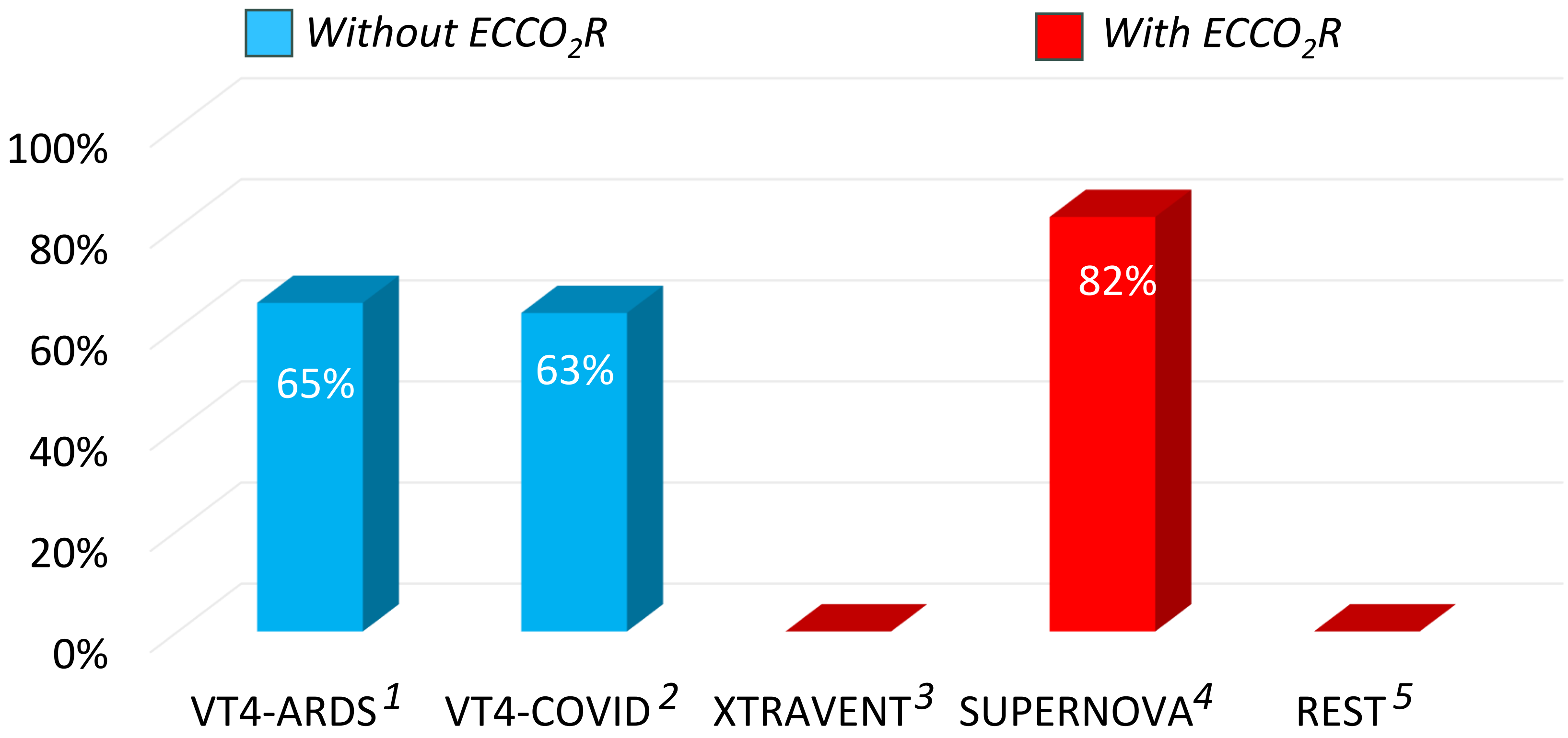
RATE OF ACHIEVEMENT OF ULTRA-LOW TIDAL VOLUME* VENTILATION IN MULTICENTER STUDIES



**Ultra-low tidal volume= VT< 4 ml.kg PBW*

1. Richard. Intensive Care Med 2019;45(11):1590–8.
2. Richard. Lancet Respir Med 2023; 11(11):991–1002.
3. Bein. Intensive Care Med 2013;39(5):847–56.
4. Combes. Intensive Care Med 2019;45(5):592–600.
5. McNamee. JAMA 2021;326(11):1013–23.

UPSIDES OF ULTRA-LOW TIDAL VOLUME VENTILATION

IMPACT OF ULTRA-LOW TIDAL VOLUME STRATEGIES ON VT AND DRIVING PRESSURE

Multicenter studies on ULTV in ARDS/ARF patients

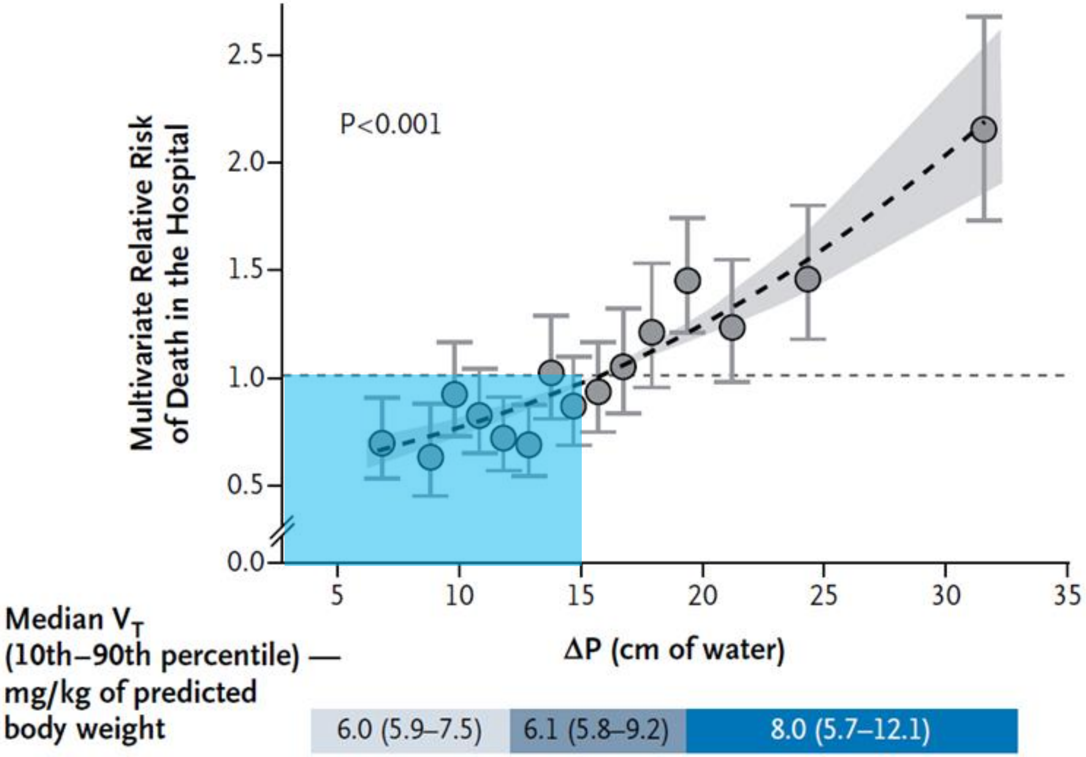
	Mean difference between control and UPV groups on day 2 or mean difference between day2 and day1 for before-after studies				
	VT4-ARDS[1] (n=35)	**VT4-COVID[2] (n=215)**	**XTRAVENT[3] (n=79)**	**SUPERNOVA[4] (n=95)**	**REST[5] (n=412)**
	Without $ECCO_2R$		With $ECCO_2R$		
Design	Before-after	RCT	RCT	Before-after	RCT
VT ($ml.kg^{-1}$ PBW)	-1.9	-1.8	-2.7	-1.9	-2.0
Driving pressure (cmH_2O)	-4	-2	-4	-3	-3

↘ VT by ≈ 2 ml/kg PBW
↘ *Driving pressure by* ≈ 3 cmH_2O

1. Richard. Intensive Care Med 2019;45(11):1590–8.
2. Richard. Lancet Respir Med 2023; 11(11):991–1002.
3. Bein. Intensive Care Med 2013;39(5):847–56.
4. Combes. Intensive Care Med 2019;45(5):592–600.
5. McNamee. JAMA 2021;326(11):1013–23.

ASSOCIATION OF DRIVING PRESSURE WITH ARDS MORTALITY

9 RCT testing different PEEP and VT strategies in ARDS

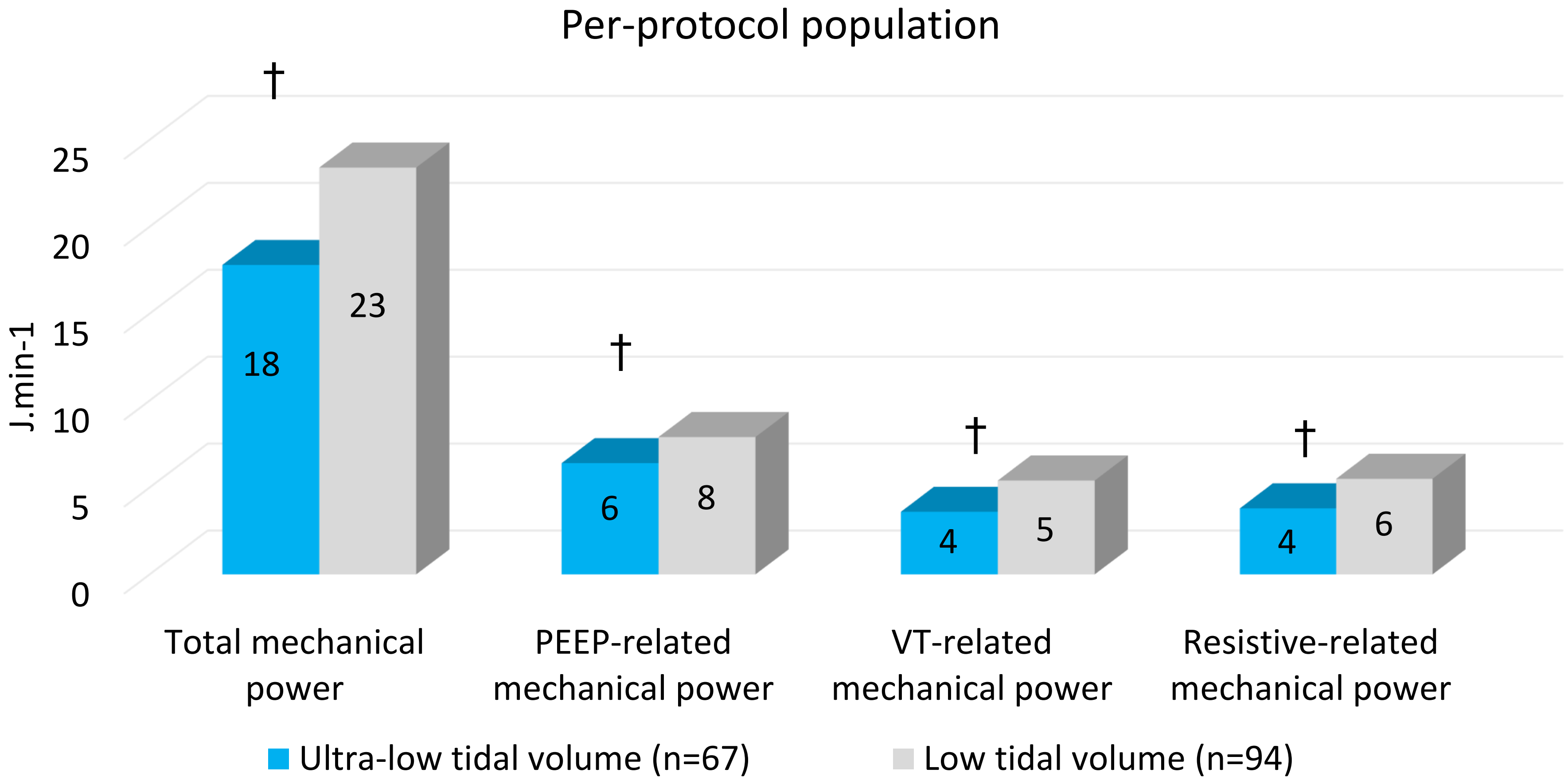


Driving pressure is independently associated with ARDS mortality, even for $\Delta P < 15\ cmH_2O$

Amato MBP, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747–55.

IMPACT OF ULTRA-LOW VENTILATION STRATEGIES ON MECHANICAL POWER

VT4COVID Multicenter RCT - 215 COVID-19 ARDS patients
randomized to ultra-low tidal volume (VT 4 ml.kg^{-1} PBW, pH>7.20) vs. low tidal volume (VT 6 ml/kg-1 PBW)



Richard J-C, Terzi N, Yonis H, et al. Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial. Lancet Respir Med 2023; 11(11):991–1002.

ULTRAPROTECTIVE VENTILATION ON CYTOKINES AND CT

32 ARDS → PEEP ARDS network

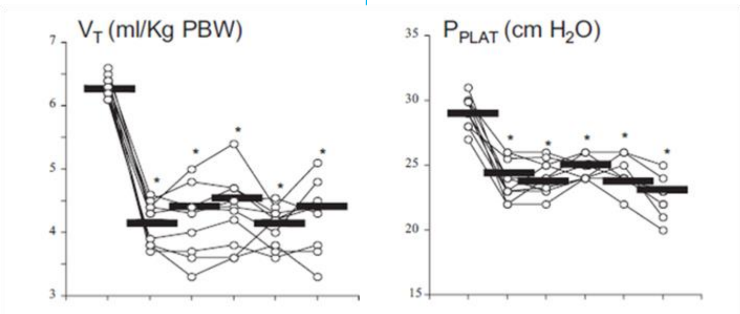
Less severe ARDS
($25 < P_{plat} < 28$ cmH_2O)
N=22

More severe ARDS
($28 \leq P_{plat} \leq 30 cmH_2O$)
N=10

PROTECTIVE VENTILATION 72H

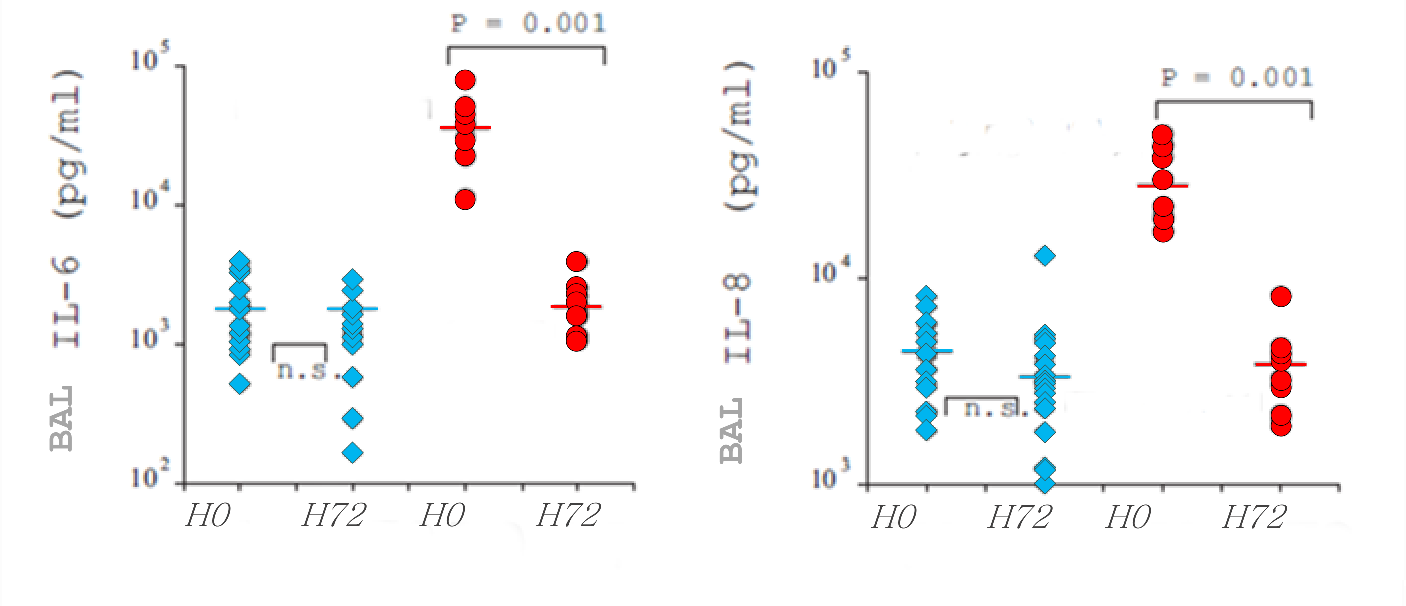
ULTRAPROTECTIVE VENTILATION 72H

↘ VT aiming Pplat<28
↗ RR 40/min
$ECCO_2R$ if pH<7.25



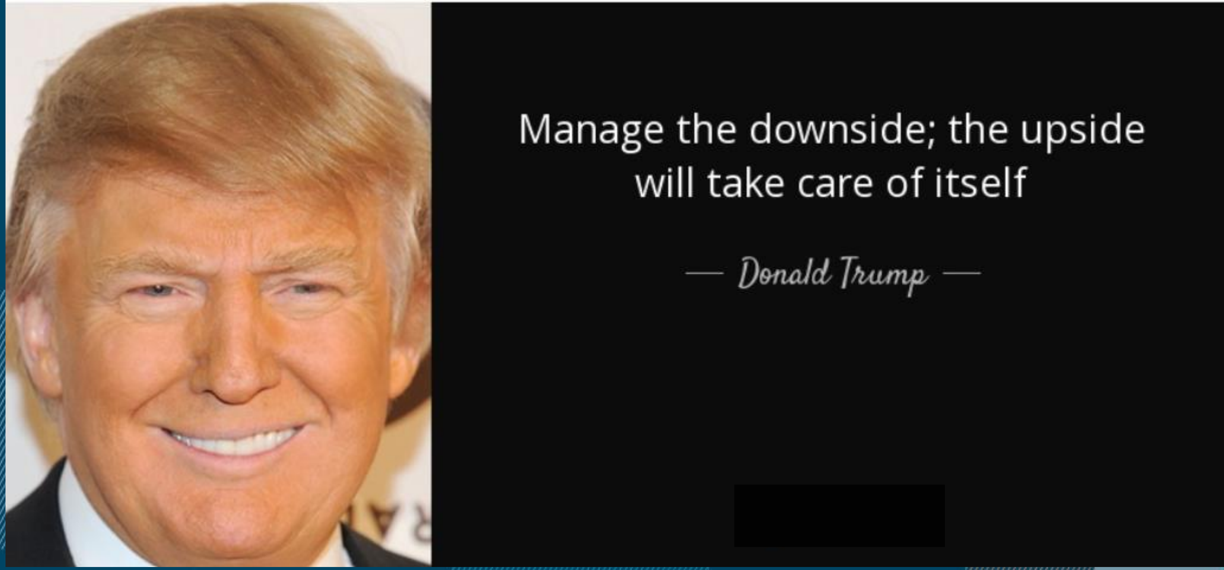
Final evaluation H72
BAL + CT

Less severe ARDS – Protective ventilation
More severe ARDS – Ultraprotective ventilation



Same results with IL1-β and IL-1 RA

Terragni PP, Del Sorbo L, Mascia L, et al. Tidal Volume Lower than 6 ml/kg Enhances Lung Protection: Role of Extracorporeal Carbon Dioxide Removal. Anesthesiology 2009;111(4):826–35.



DOWNSIDES OF ULTRA-LOW TIDAL VOLUME VENTILATION

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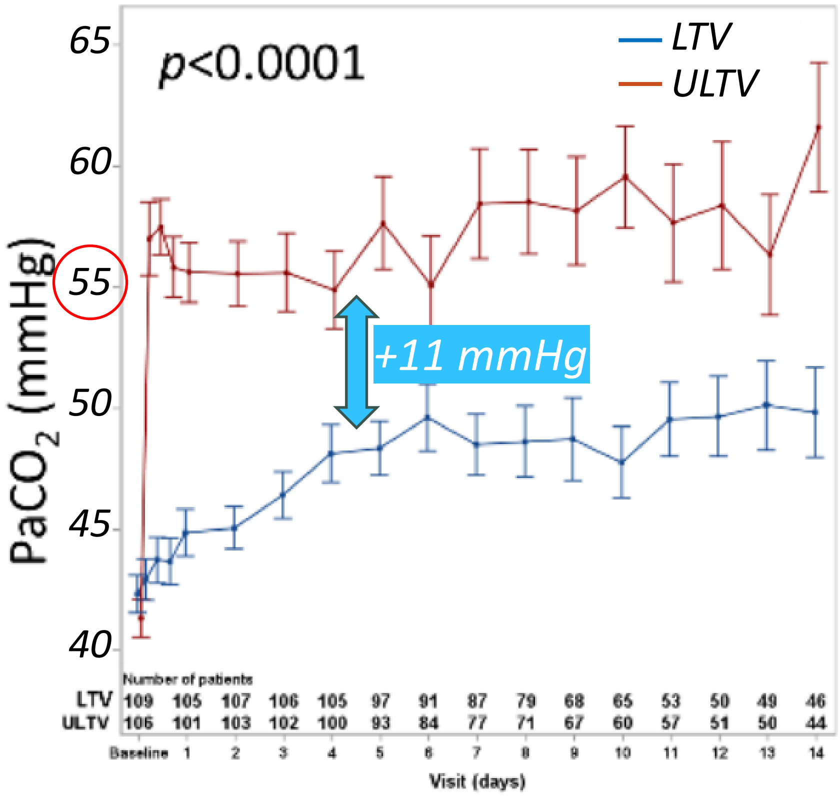
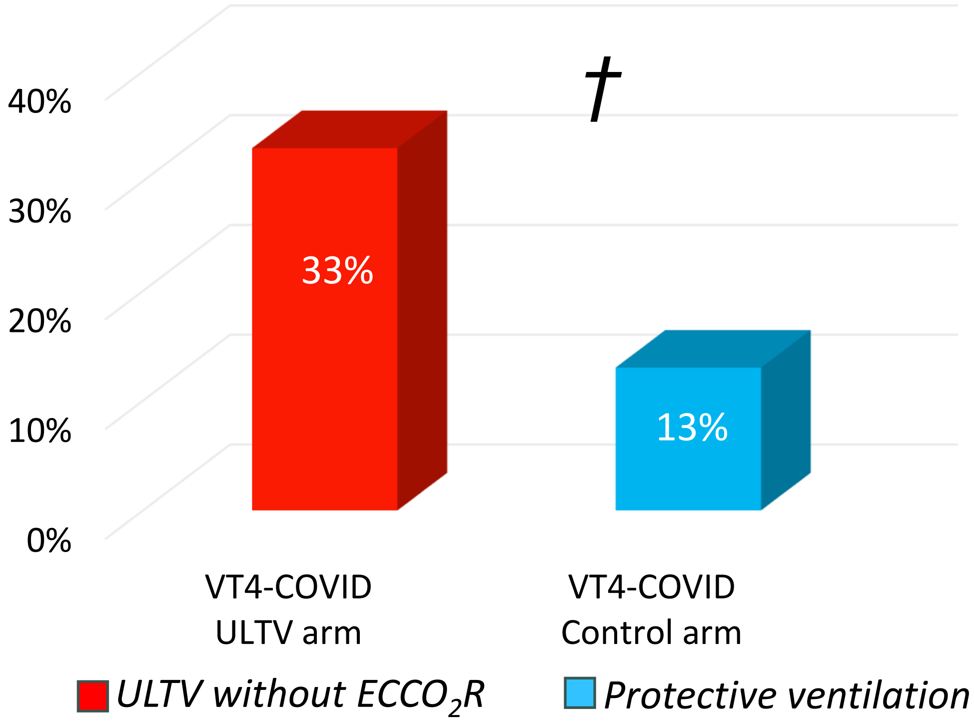
HYPERCAPNIA AND SEVERE RESPIRATORY ACIDOSIS IN ULTV WITHOUT $ECCO_2R$

VT4COVID multicenter RCT on 215 COVID-19 ARDS [1]
Low tidal volume ventilation (LTV) vs. ultra-low tidal volume ventilation without $ECCO_2R$ (ULTV)



Rate of severe respiratory acidosis



Severe respiratory acidosis: pH <7.15 and $PaCO_2$ >45 mm Hg.

1. Richard. Lancet Respir Med 2023; 11(11):991–1002.
2. Richard. Intensive Care Med 2019;45(11):1590–8.

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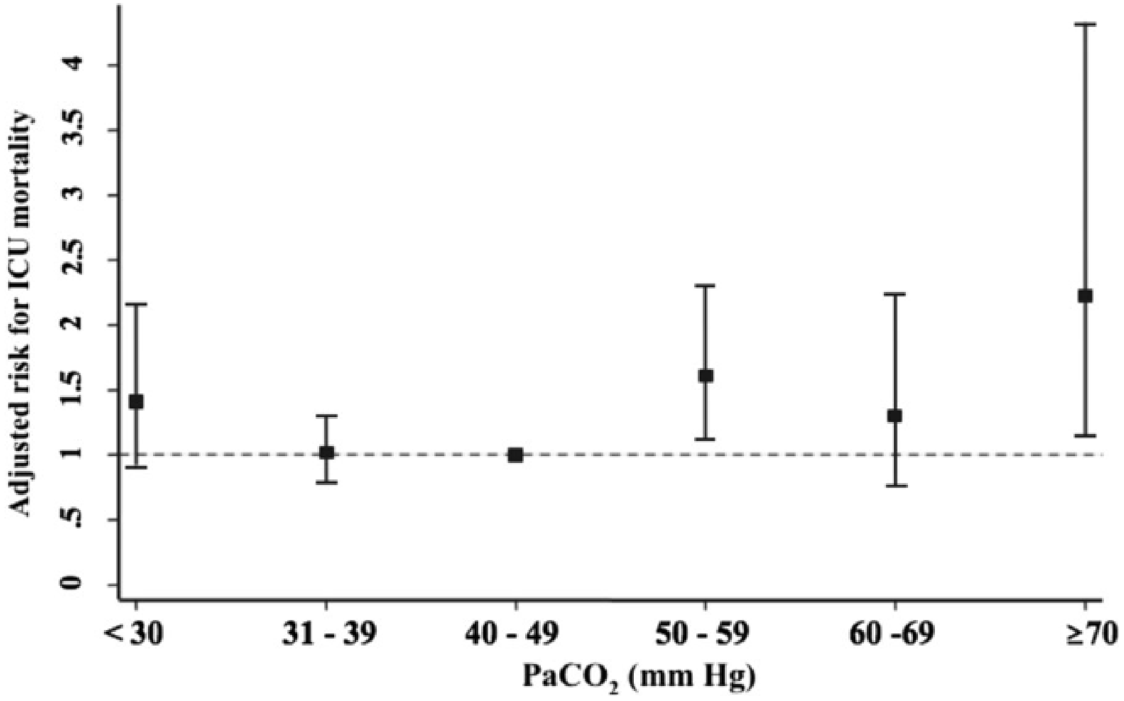
IMPACT OF ACUTE HYPERCAPNIA IN ARDS

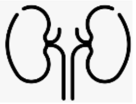
1899 patients with ARDS from 3 international cohorts (1998, 2004, and 2010)



1. Increased risk in ICU mortality clear for severe hypercapnia
2. This relationship does not imply causality
3. This effect is observed after adjusting for driving pressure
➔ removes the potential beneficial impact of ΔP reduction on mortality

Potential benefits and harms of hypercapnic acidosis

O_2



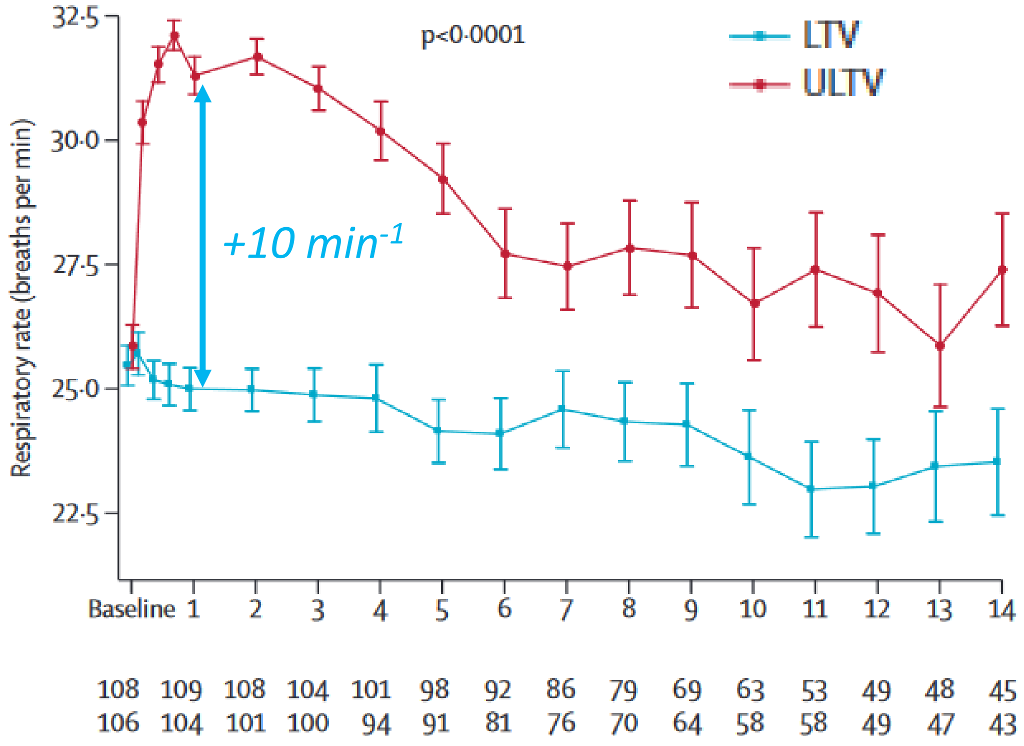
Benefits	Harms
↘ VILI • ↘ Microvascular permeability • ↘ edema formation • ↘ NFκ-B • ↘ cytokine production and oxygen free radical formation • ↘ apoptosis	↘ alveolar fluid clearance by ↘ Na^+/K^+ ATPase activity
↘ neutrophil adherence to endothelial cells	↘ phagocytic activity and ↘ antibody synthesis
↗ Tissue oxygenation (acidosis)	↘ alveolar oxygen tension
↗ cardiac output, ↗ DO_2, and venous return (venoconstriction)	↗ Heart rate, ↘ LV afterload, ↗ pulmonary vascular resistance
	↗Renal vasoconstriction (at high levels) and HCO_3^- reabsorption
	↗ intracranial pressure and ventilatory drive

Net effect of moderate increase in $PaCO_2$ level unknown

Nin N, Muriel A, Peñuelas O, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Med 2017;43(2):200–8.

IMPACT OF ULTV WITHOUT $ECCO_2R$ ON RESPIRATORY RATE

VT4COVID multicenter RCT on 215 COVID-19 ARDS
Low tidal volume ventilation (LTV) vs. ultra-low tidal volume ventilation without $ECCO_2R$ (ULTV)



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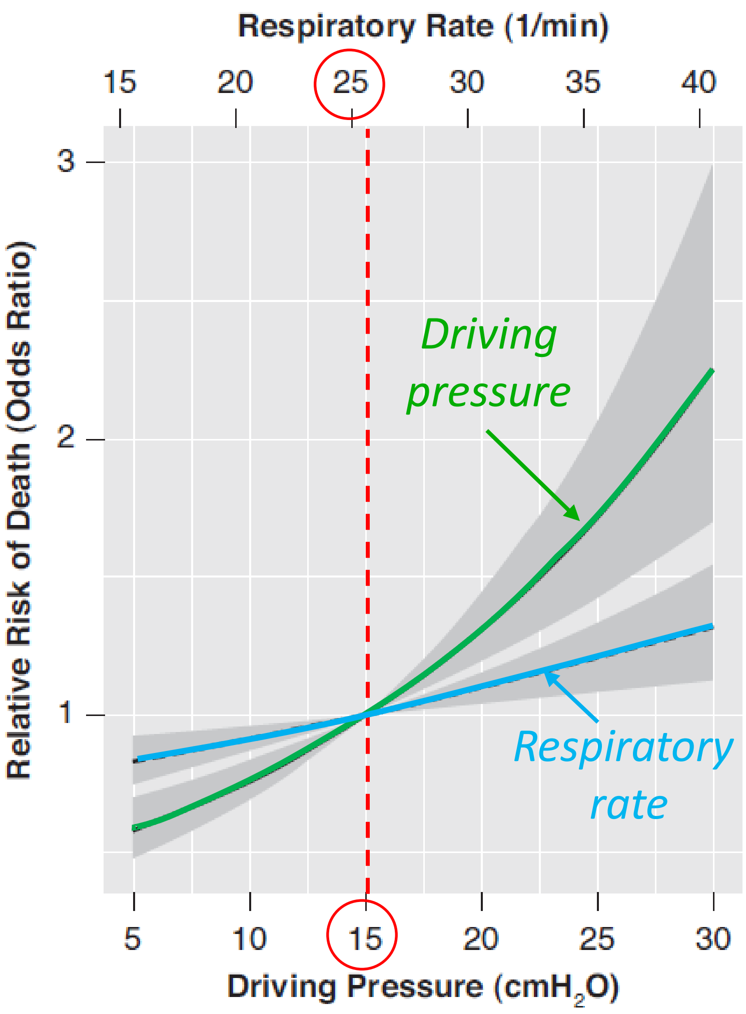
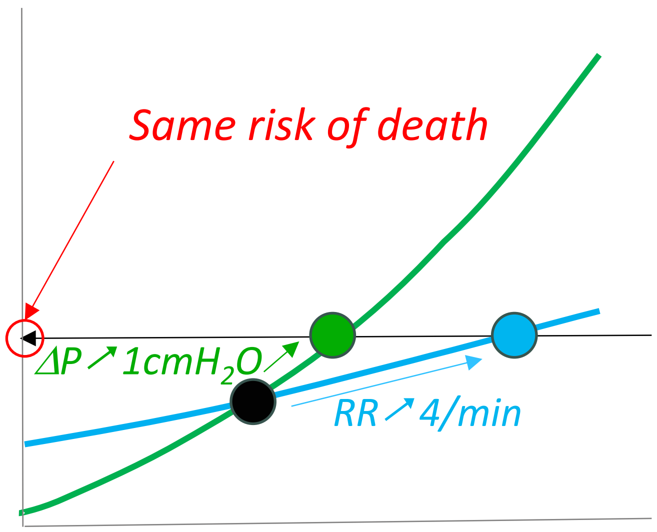
Richard J-C, Terzi N, Yonis H, et al. Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial. Lancet Respir Med 2023; 11(11):991–1002.

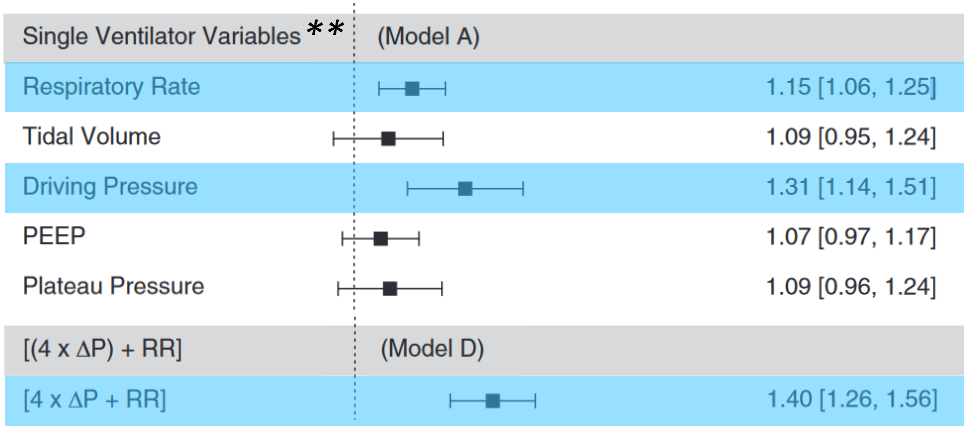
EFFECT OF ΔP AND RESPIRATORY RATE ON SURVIVAL



Patient-level data of 4,549 ARDS patients
- 693 pts from the MIMIC-III database
- 3856 pts from RCT 1998-2017 (VT or PEEP change)



*Odds ratios for death**



** adjusted with the following variables: trial, study arm, respiratory system compliance, ventilatory ratio, arterial pH, $PaCO_2$, and PaO_2/FIO_2*
*** All variables were standardized, and the odds ratios correspond to a 1-SD increment in the respective variable*

The effect size of each 1 cm H_2O increase in ΔP is 4 times higher that of each 1–breath/min increase in RR
➔ If with ULTV, RR increases less than 4times than ΔP decreases, the net effect should be beneficial (4×ΔP+RR↘)

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Costa ELV, Slutsky AS, Brochard LJ, et al. Ventilatory Variables and Mechanical Power in Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2021;204(3):303–11.

IMPACT OF ULTV STRATEGIES ON VT AND DRIVING PRESSURE

Multicenter studies on ULTV in ARDS/ARF patients

Mean difference between control and UPV groups on day 2
Or Mean difference between day2 and day1 for before-after studies

	VT4-ARDS (n=35)	VT4-COVID (n=215)	XTRAVENT (n=79)	SUPERNOVA (n=95)	REST (n=412)
	Without $ECCO_2R$		With $ECCO_2R$		
ΔP (cmH_2O)	-4	-2	-4	-3	-3
Respiratory rate (/min)	+10	+6	NA	-4	+2
$4\times\Delta P$+RR	-6	-2	NA	-16	-10

The expected net effect of ULTV remains slightly favorable in studies without $ECCO_2R$

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ULTRA-LOW TIDAL VOLUME VENTILATION WITHOUT EXTRACORPOREAL CIRCULATION – IMPACT ON OUTCOME

Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial

*Jean-Christophe Richard, Nicolas Terzi, Hodane Yonis, Fatima Chorfa, Florent Wallet, Claire Dupuis, Laurent Argaud, Bertrand Delannoy, Guillaume Thiery, Christian Pommier, Paul Abraham, Michel Muller, Florian Sigaud, Guillaume Rigault, Emilie Joffredo, Mehdi Mezidi, Bertrand Souweine, Loredana Baboi, Hassan Serrier, Muriel Rabilloud, Laurent Bitker, on behalf of the VT4COVID collaborators**

Multicenter open-label randomized controlled superiority trial with 2 parallel groups- 215 moderate to severe COVID-19 ARDS
Setting: 10 ICU in France

Control arm: lung protective ventilation (LPV)
➔ VT 6 ml/kg PBW

Intervention arm: ultra-low tidal volume ventilation (ULTV)
➔ aiming for VT 4 ml/kg PBW

Ventilatory goals in both groups
Plateau pressure ≤ 30 cm H_2O
55 ≤ PaO_2 ≤ 80 mm Hg or 88% ≤ SpO_2 ≤ 95%
7.20 ≤ pH ≤ 7.45

	ULTV group (n=106)	LTV group (n=109)
Clinical data and severity scores		
Age, years	68 (60–75)	67 (60–74)
Sex		
Male	79 (75%)	78 (72%)
Female	27 (26%)	31 (28%)
BMI, kg/m²*	29 (26–34)	30 (28–34)
Time between intubation and inclusion, h†	8 (3–22)	6 (2–19)
SAPS2 score‡	43 (33–53)	38 (32–47)
SOFA score§	8 (6–11)	7 (5–9)
Acute cor pulmonale¶	5 (5%)	1 (1%)
Respiratory parameters		
Respiratory rate, breaths per min††	25 (22–30)	25 (22–28)
V_T, mL/kg predicted bodyweight‡‡	6·0 (5·8–6·0)	6·0 (6·0–6·1)
PEEP, cm H_2O§§	10 (8–12)	10 (8–12)
P_{plat}, cm H_2O||||	22 (19–25)	23 (19–26)
Driving pressure, cm H_2O***	11 (9–13)	11 (10–14)
Total mechanical power, J/min‡‡‡	24 (20–31)	26 (20–32)
Arterial blood pH§§§	7·39 (7·32–7·44)	7·39 (7·32–7·44)
PaO_2/FiO_2 ratio, Torr	99 (72–129)	106 (79–130)
$PaCO_2$, Torr	41 (36–45)	41 (37–48)

Richard J-C, Terzi N, Yonis H, et al. Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial. Lancet Respir Med 2023; 11(11):991–1002.

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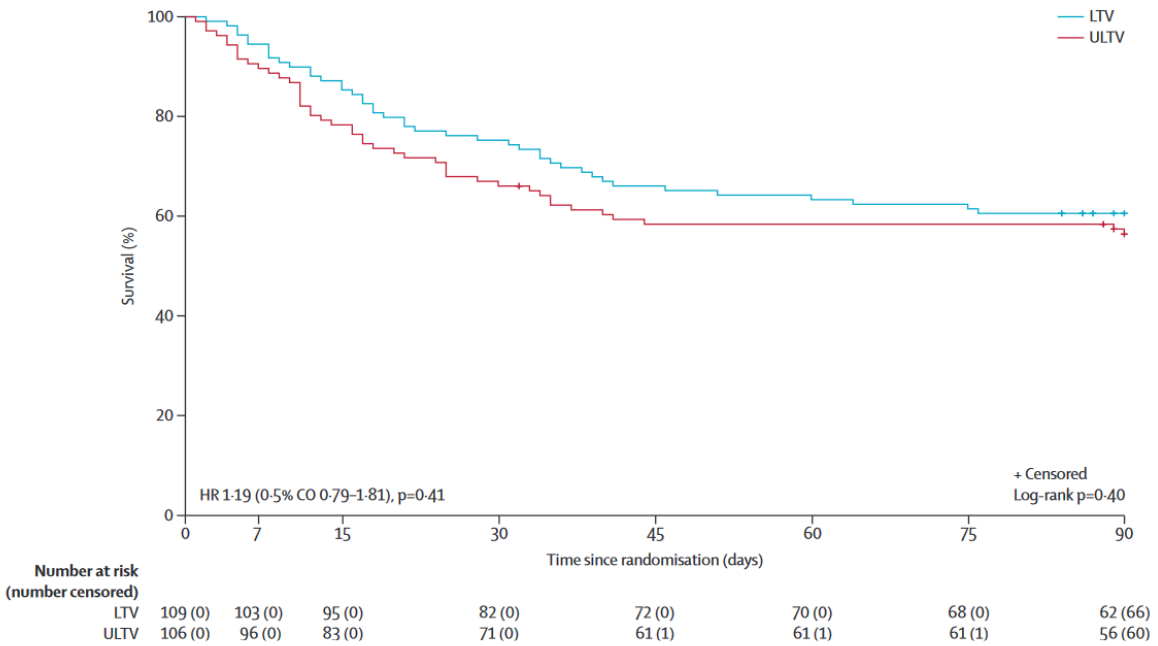
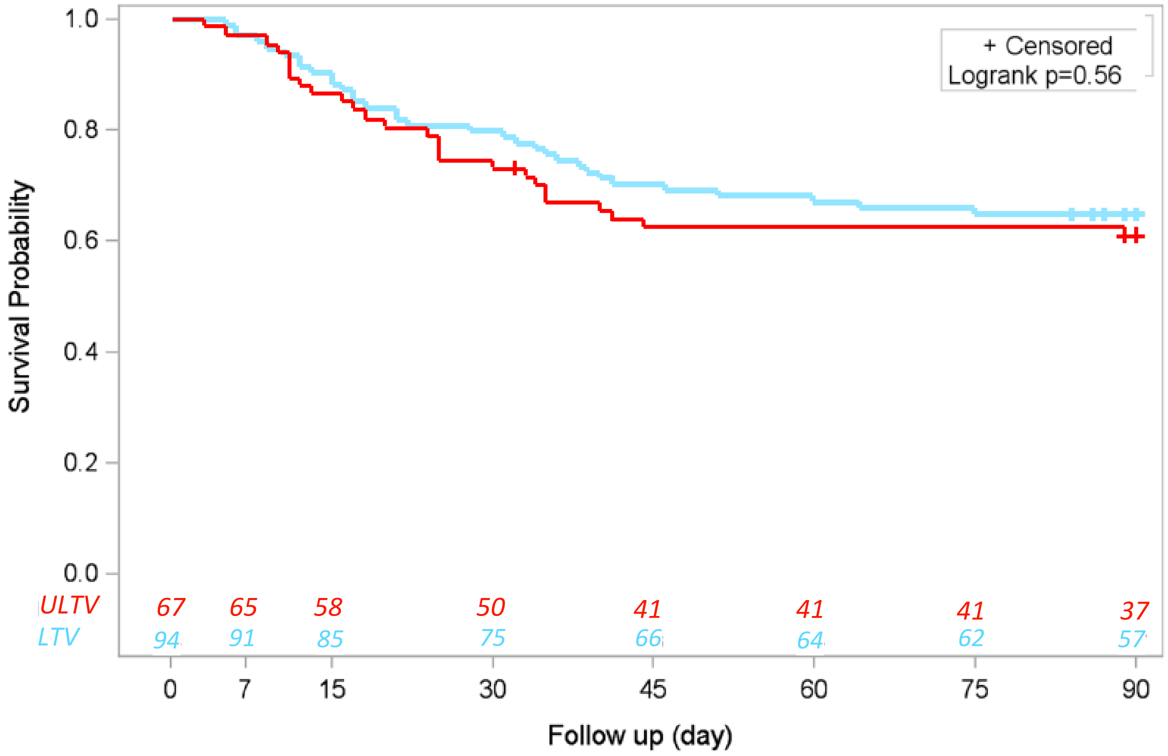
Between group difference in mechanical power : -5·7· ± 1·1 J.min^{-1}

Intention to treat analysis



Per-protocol analysis



No impact on any secondary outcome including barotrauma

Richard J-C, Terzi N, Yonis H, et al. Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial. Lancet Respir Med 2023; 11(11):991–1002.

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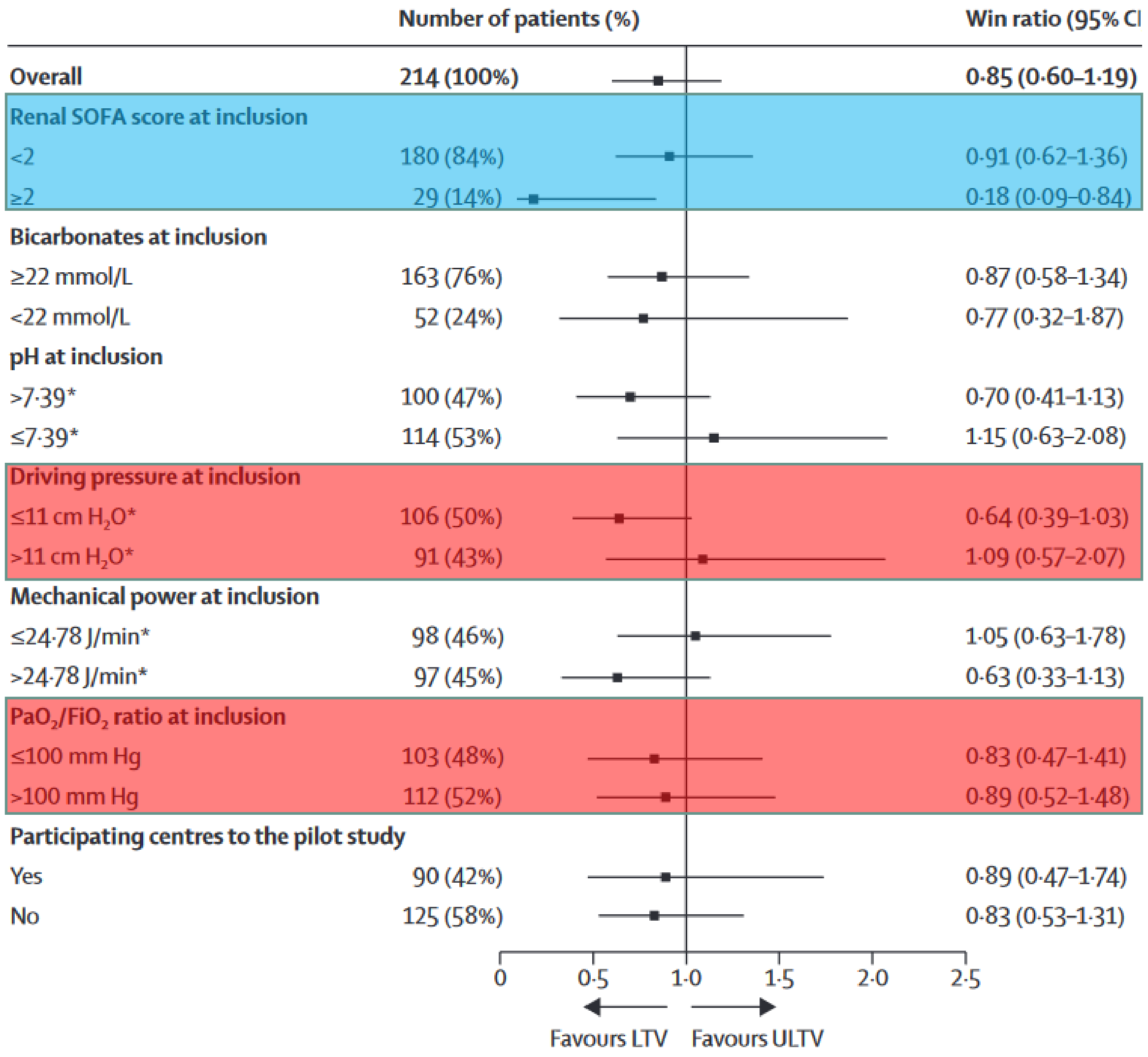


Potential safety issue in patients with renal SOFA subscore ≥ 2

Richard J-C, Terzi N, Yonis H, et al. Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial. Lancet Respir Med 2023; 11(11):991–1002.

ULTRA-LOW TIDAL VOLUME WITHOUT $ECCO_2R$ FOR WHICH PATIENTS?

HIGH NORMALIZED ELASTANCE?

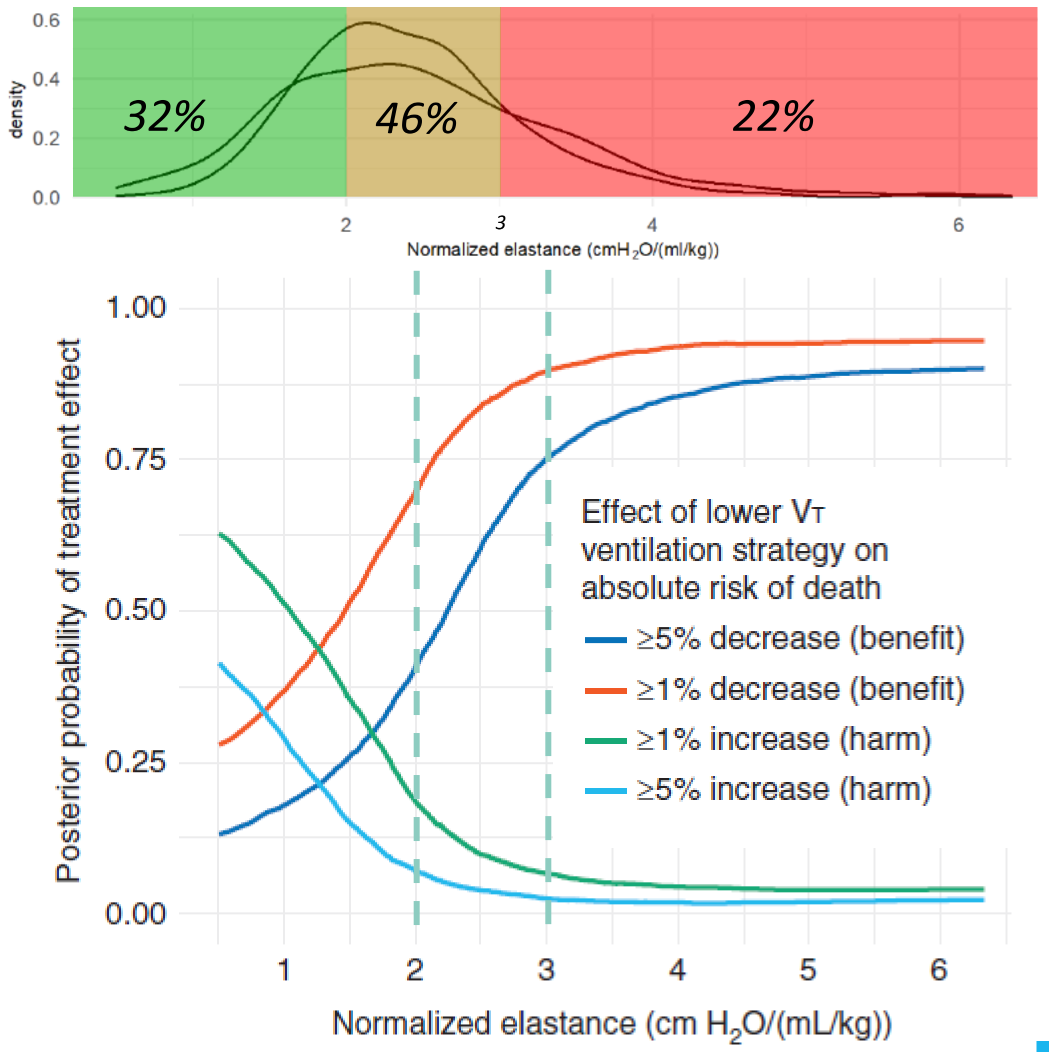
Meta-analysis of 5 RCT testing lower vs. higher VT
1202 ARDS patients

Normalized elastance

$$= \frac{\text{Driving pressure}}{\text{VT/PBW}}$$

ΔP12, VT 6ml.kg PBW ➔ El_{norm}=2

ΔP18, VT 6ml.kg PBW ➔ El_{norm}=3



Normalized elastance > 3: 8% of the VT4COVID trial

Goligher EC, Costa ELV, Yarnell CJ, et al. Effect of Lowering Vt on Mortality in Acute Respiratory Distress Syndrome Varies with Respiratory System Elastance. Am J Respir Crit Care Med 2021;203(11):1378–85.

ULTV WITHOUT $ECCO_2R$ FOR PATIENTS WITH CONTRA-INDICATIONS TO EXTRACORPOREAL CIRCULATION?

	SUPERNOVA[1]	REST[2]
Patients assessed for eligibility	755	7071
Patients with contra-indication to $ECCO_2R$*	229 (30%)	1983 (28%)
Patients included	95 (13%)	412 (6%)

** CI to systemic anticoagulation, Thrombopenia, Impracticable vascular access*

≈ 30% patients assessed for eligibility had contra-indication to $ECCO_2R$ in large studies on ARDS/ARF

The number of patients with contra-indication to $ECCO_2R$ is 3-5 times higher than the number of patients included in large multicenter $ECCO_2R$ studies on ARDS/ARF patients

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1. Combes A et al. Intensive Care Med 2019;45(5):592–600.
2. McNamee JJ. JAMA 2021;326(11):1013–23.

CONCLUSION

CONCLUSION (1/2)

- Ultra-low tidal volume ventilation has no beneficial impact on COVID-19 ARDS outcome
- The safety of this strategy seems acceptable, except in patients with AKI
- Long term impact of ULTV strategy in the VT4-COVID trial under investigation (impact of hypercapnia)
- There is a need to identify patients with expected benefits of ULTV strategies

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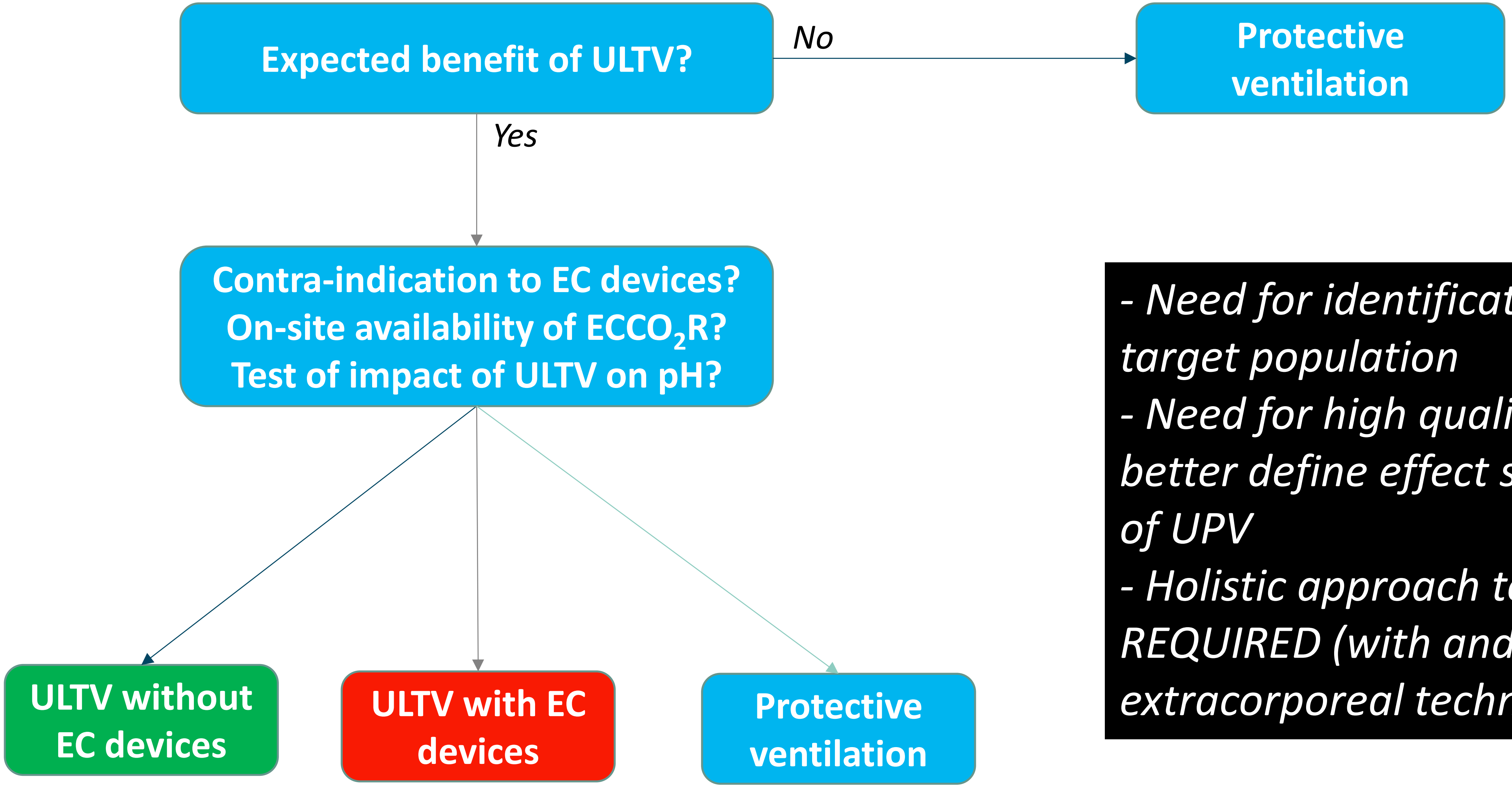
CONCLUSION (2/2) – POTENTIAL FRAMEWORK FOR ULTV USE IN ARDS



- Need for identification of target population
- Need for high quality RCTs to better define effect size and risk of UPV
- Holistic approach to ULTV REQUIRED (with and without extracorporeal techniques)