Recent Advances In Management Of ARDS

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12/06/20

Topics To Be Discussed

- ARDS – Trend so far
- Available therapies Ventilatory and Non Ventilatory Management
- New data on available therapies
- Newer management strategies
- What we practice – what we can change/add
- The way ahead

ARDS – Trend So Far…
LUNG SAFE STUDY

Large observational study to understand global impact of severe acute respiratory failure

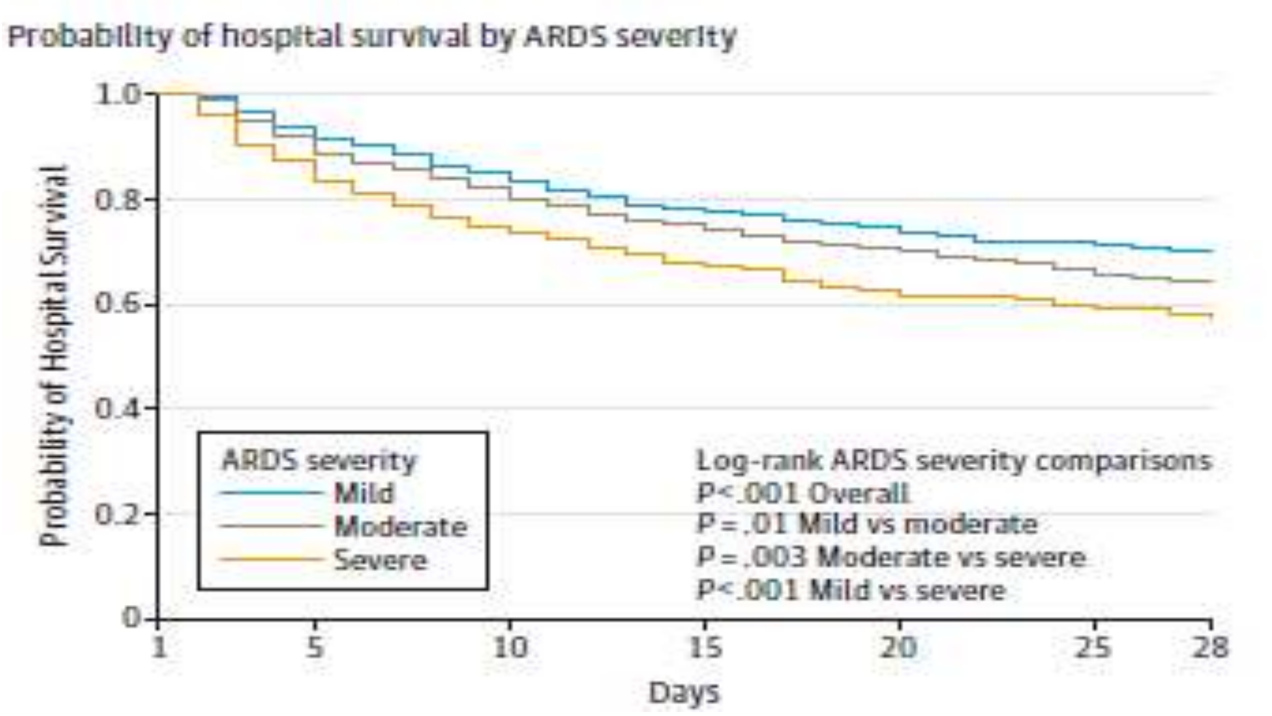
Study	**Population**	**Outcome - studied**
International multicentre prospective cohort study	29,144 ICU patients 459 ICUs 50 countries	Incidence of ARDS in ICU Assessment of clinical recognition of ARDS Clinical outcome of ARDS patients Usage of recommended ventilatory mgt. Use of adjunctive therapies

Bellani et al. 2016 JAMA

Results – LUNG SAFE STUDY

- ARDS is common (10% of ICU admissions and 23% of ventilated patients)

- Hospital mortality still remains high



ARDS severity	Hospital Mortality
Mild	34.9%(31.4-38.5)
Mod.	40.3%(37.4-43.3)
Severe	46.1%(41.9-50.4)

Bellani et al. 2016 JAMA

ARDS- Limited Therapies?

ARDS is a Broad Clinical Syndrome

↓

Impaired Gas Exchange	Reduced Lung compliance

↓

Includes Patients with substantial heterogeneity w.r.t

Degree of hypoxemia	Underlying cause ppt ARDS	Radiological Pattern	Degree of Inflammatory response

↓

ARDS Subphenotypes

↓

This Hetrogeneity is considered reason for failure of large number of ARDS clinical trials

ARDS Sub Phenotypes – Proof And Its Impact

Articles

Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network

- Clinical and biological data from ARMA and ALVEOLI trial was analysed
- Latent class modelling was applied to identify subphenotypes based on B/L data
- Association of phenotypes with clinical outcomes was tested

Calfee et al. Lancet 2014

ARDS Sub Phenotypes – Proof And Its Impact

- Based on Baseline data two distinct phenotypes were identified

Phenotype 1	Phenotype 2
Normal/low inflammatory markers	Elevated inflammatory markers
Acidosis absent	+
Shock absent	+

- Phenotypes had different clinically significant outcomes

	ARMA cohort			ALVEOLI cohort		
	Phenotype 1 (n=318)	Phenotype 2 (n=155)	p value	Phenotype 1 (n=404)	Phenotype 2 (n=145)	p value
Mortality (at 90 days)	23%	44%	0·006	19%	51%	<0·001
Ventilator-free days	17·8	7·7	<0·001	18·4	8·3	<0·001
Organ failure-free days	14·5	8·0	<0·001	16·5	8·4	<0·001

Values are estimated means that take into account the uncertainty of class membership.

Calfee et al. Lancet 2014

ARDS Sub Phenotypes – Proof And Its Impact

- Two phenotypes had differential response to level of PEEP applied

	Phenotype 1 (n=404)		Phenotype 2 (n=145)		
	Low PEEP (n=202)	High PEEP (n=202)	Low PEEP (n=71)	High PEEP (n=74)	p value*
Mortality at 90 days	33 (16%)	48 (24%)	36 (51%)	31 (42%)	0·049
Ventilator-free days	20 (10–25)	21 (3–24)	2 (0–21)	4·5 (0–20)	0·018
Organ failure free-days	22 (11–26)	22 (9–26)	4 (0–18)	6·5 (0–21)	0·003

Data are n (%) or median (IQR). *p value for interaction between positive end-expiratory pressure (PEEP) assignment and phenotype.

Phenotype 2 i.e Hyperinflammatory phenotype had better clinical outcome with high PEEP

Calfee et al. Lancet 2014

ARDS Sub Phenotypes – Proof And Its Impact

ORIGINAL ARTICLE

Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy

Katie R. Famous[1], Kevin Delucchi[2], Lorraine B. Ware[3,4], Kirsten N. Kangelaris[5], Kathleen D. Liu[6,7], B. Taylor Thompson[8], and Carolyn S. Calfee[1,7]; for the ARDS Network

Table 4. Interaction between ARDS Subphenotype and Fluid-Management Strategy for the Outcomes of Mortality and Ventilator-Free Days

	Subphenotype 1		Subphenotype 2		
Fluid-management strategy	**Liberal (*n* = 355)**	**Conservative (*n* = 372)**	**Liberal (*n* = 142)**	**Conservative (*n* = 131)**	***P* Value**
60-d mortality, %	24	17	39	49	0.0093
90-d mortality, %	26	18	40	50	0.0039
Ventilator-free days, median	17	21	5	0	0.35

- Differential response to fluid management among two phenotypes

ARDS Sub phenotypes – Clinical relevance

- Various subgroups exist within this broad entity of ARDS
- Respond differently to various management strategy
- Identification of these subgroups can help in better tailoring of treatment – precision medicine
- Leading to improved outcomes

ARDS Treatment till few years back..

Ventilatory Management

Low Tidal Volume Ventilation – ARMA

Prone Position Ventilation - PROSEVA

Non- Ventilatory Management

ACURASYS – Neuro Muscular Blockade

CESAR - Extra Corporeal Membrane Oxygenation

Ventilatory Management

Role Of NIV - Data from LUNG SAFE STUDY

	Invasive-MV patients (n=353)	NIV patients (n=353)	*p-value*
ARDS severity at onset, n (%)			
Mild	100 (28.33)	101 (28.61)	*1.000*
Moderate	184 (52.12)	165 (46.74)	*0.195*
Severe	69 (19.55)	87 (24.65)	*0.127*
Patients with PaO_2/FiO_2 ratio < 150 mmHg at ARDS onset, n (%)	174 (49.29)	174 (49.29)	*1.0000*
Parameters at ARDS onset, mean±SD			
pH	7.35 ± 0.11	7.38 ± 0.09	*0.001*
FiO_2	0.66 ± 0.24	0.60 ± 0.22	*0.001*
SPO_2 (%)	94.53 ± 5.51	94.99 ± 3.85	*0.660*
Total Respiratory Rate (breaths/min)	20.66 ± 6.46	25.63 ± 7.01	*<.001*
PEEP (cmH_2O)	8.09 ± 3.1	7.02 ± 1.95	*<.001*
Peak Inspiratory Pressure (cmH_2O)	26.77 ± 7.66	17.43 ± 7.22	*<.001*
PaO_2 (mmHg)	94.64 ± 40.32	87.96 ± 32.55	*0.031*
$PaCO_2$ (mmHg)	46.5 ± 14.41	45.8 ± 17.36	*0.320*
PaO_2/FiO_2 (mmHg)	157.62 ± 65.58	160.94 ± 64.29	*0.492*
Tidal Volume (ml/Kg PBW)	7.53 ± 1.75	8.46 ± 2.77	*0.001*
Minute ventilation (L/min)	9.31 ± 2.90	13.26 ± 5.60	*<.001*
Base excess (mmol/L)	-0.74 ± 5.93	0.60 ± 6.55	*0.002*
HCO_3 (mmol/L)	24.39 ± 5.65	25.4 ± 6.95	*0.086*
Non-pulmonary SOFA adjusted	3.26 ± 2.82	3.19 ± 2.84	*0.423*
Δ (%)* PaO_2/FiO_2 ratio	36.31 ± 76.76	28.17 ± 76.77	*0.063*
Δ (%)* $PaCO_2$	-0.3 ± 29.86	3.37 ± 25.92	*0.025*
Use of vasopressors, n (%)	80 (24.32)	49 (15.03)	*0.005*
Duration of mechanical ventilation (days), median [IQR]			
all patients	8 [4 - 15]	9 [5 - 13]	*0.293*
ICU survivors	7 [4 - 14]	10 [7 - 13]	*0.744*
Length of ICU stay (days), median [IQR]			
all patients	10 [6 - 18]	7 [4 - 12]	*<.001*
ICU survivors	10 [6 - 19]	7 [4 - 12]	*<.001*
All-cause in-ICU mortality, n (%)			
all patients	92 (26.06)	99 (28.05)	*0.608*
matched patients with PaO_2/FiO_2 ratio<150 mmHg	43 (24.71)	63 (36.21)	*0.033*
All-cause in-hospital mortality, n (%)			
all patients	115 (32.76)	117 (33.24)	*0.871*
matched patients with PaO_2/FiO_2 ratio<150 mmHg	55 (31.61)	66 (38.15)	*0.224*

NIV used in 15% of ARDS patients

NIV use associated with increased mortality esp. in patients with P/F <150 36% Vs 25%(p=0.03)

Bellani et al. 2016 JAMA

Role Of NIV In Mild – Mod ARDS

Study	Population	Intervention	Outcome
Prospective observational study	N=41 patients AECC P/F 100-300mmHg	NIV via oronasal mask	Intubation avoided in 18(44%) patients P/F<150 at 1 hr and APACHE II score >17 Associated with NIV failure

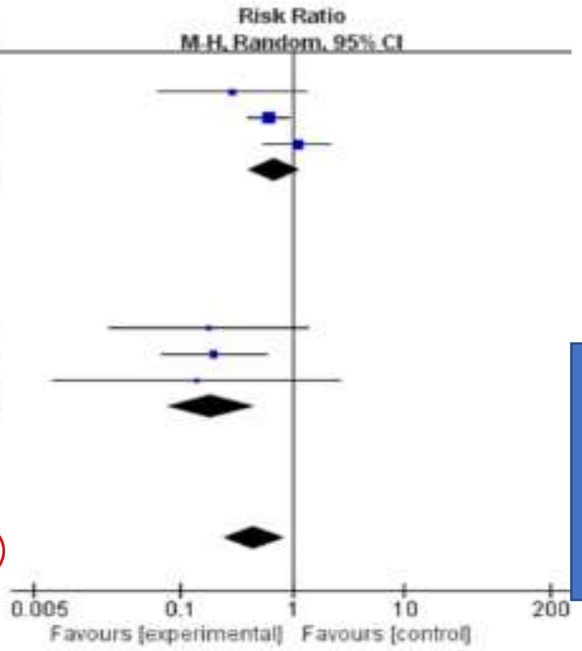
Sehgal I S et al. IJCCM 2015

Role Of In NIV Mild ARDS - Insufficient Data?

- One small RCT of 40 patients with P/F 200-300mmHg
- Patients randomized to NIV Vs Std O2 therapy via venturi Mask
- Showed No significant reduction in mortality (p=0.09) but decrease in no. of intubations

Zhan Q et al.Crit Care Med, 2012

Study or Subgroup	NIV Events	NIV Total	Standard oxygen therapy Events	Standard oxygen therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 100<PaO2/FiO2≤200						
Brambilla 2014	2	40	7	41	12.1%	0.29 [0.06, 1.33]
Hilbert 2001	13	26	21	26	31.9%	0.62 [0.40, 0.95]
Delclaux 2000	12	40	11	41	25.9%	1.12 [0.56, 2.24]
Subtotal (95% CI)		**106**		**108**	**69.9%**	**0.70 [0.41, 1.21]**
Total events	27		39			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 3.35$, df = 2 (P = 0.19); $I^2 = 40\%$						
Test for overall effect: Z = 1.28 (P = 0.20)						
4.3.2 200<PaO2/FiO2≤300						
Zhan 2012	1	21	5	19	7.7%	0.18 [0.02, 1.41]
Squadrone 2010	3	20	15	20	18.2%	0.20 [0.07, 0.59]
Squadrone 2005	0	105	3	104	4.2%	0.14 [0.01, 2.71]
Subtotal (95% CI)		**146**		**143**	**30.1%**	**0.19 [0.08, 0.47]**
Total events	4		23			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 2 (P = 0.98); $I^2 = 0\%$						
Test for overall effect: Z = 3.60 (P = 0.0003)						
Total (95% CI)		**252**		**251**	**100.0%**	**0.46 [0.24, 0.87]**
Total events	31		62			
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 10.95$, df = 5 (P = 0.05); $I^2 = 54\%$						
Test for overall effect: Z = 2.38 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 5.86$, df = 1 (P = 0.02), $I^2 = 82.9\%$						



Reduced Intubation rate and Mortality in Mild ARDS

Xu et al.Crit Care Med, 2017 June

Early Prone Positioning with NIV Or HFNC

Study	Population	Intervention	Outcome
Multicentre Prospective observational cohort study	N=20 Mod- Sev ARDS	HFNC HFNC+PP NIV NIV+PP (Duration of PP 2hr twice daily)	55%(11) patients avoided intubation P/F< 100 associated with increased risk of failure P/F in NIV+PP>NIV>HFNC+PP>HFNC

Lin Ding et al. Crit Care , 2020

Role Of HFNC - FLORALI Trial

Study	Population	Intervention	Outcome
Multicentre non blinded RCT	N=310 23 ICU Acute hypoxemic RF P/F<300 PaCo2<45 CPE excluded	HFNC(N=106) NIV(N=110) STD O2 Therapy(N=94)	Intubation at Day 28 90 day mortality

Frat et al. N Engl J Med 2015

Results – FLORALI Trial

B/L Characteristics ~65% Cases of CAP

Characteristic	High-Flow Oxygen (N=106)	Standard Oxygen (N=94)	Noninvasive Ventilatio (N=110)
Age — yr	61±16	59±17	61±17
Male sex — no. (%)	75 (71)	63 (67)	74 (67)
Body-mass index†	25±5	26±5	26±6
SAPS II‡	25±9	24±9	27±9
Current or past smoking — no. (%)	34 (32)	36 (38)	40 (36)
Reason for acute respiratory failure — no. (%)			
Community-acquired pneumonia	71 (67)	57 (61)	69 (63)
Hospital-acquired pneumonia	12 (11)	13 (14)	12 (11)
Extrapulmonary sepsis	4 (4)	5 (5)	7 (6)
Aspiration or drowning	3 (3)	1 (1)	2 (2)
Pneumonia related to immunosuppression	6 (6)	4 (4)	10 (9)
Other	10 (9)	14 (15)	10 (9)
Bilateral pulmonary infiltrates — no. (%)	79 (75)	80 (85)	85 (77)
Respiratory rate — breaths/min	33±6	32±6	33±7
Heart rate — beats/min	106±21	104±16	106±21
Arterial pressure — mm Hg			
Systolic	127±24	130±22	128±21
Mean	87±17	89±15	86±16
Arterial blood gas			
pH	7.43±0.05	7.44±0.06	7.43±0.06
Pa_{O_2} — mm Hg	85±31	92±32	90±36
FI_{O_2}§	0.62±0.19	0.63±0.17	0.65±0.15
Pa_{O_2}:FI_{O_2} — mm Hg	157±89	161±73	149±72
Pa_{CO_2} — mm Hg	36±6	35±5	34±6

Outcome	HFNC (106)	NIV(110)	Std O2(94)	p Value
Intubation at D 28	38%	50%	44%	0.18
Intubation at D28 in P/F<200	35%	58%	53%	0.01
Death in ICU	11%	25%	18%	0.047
Mortality at D 90	12%	28%	23%	0.02

NIV duration 8hr(75%)
Vt during NIV use 9ml/kg ± 3ml/kg
21% Unilateral infiltrates

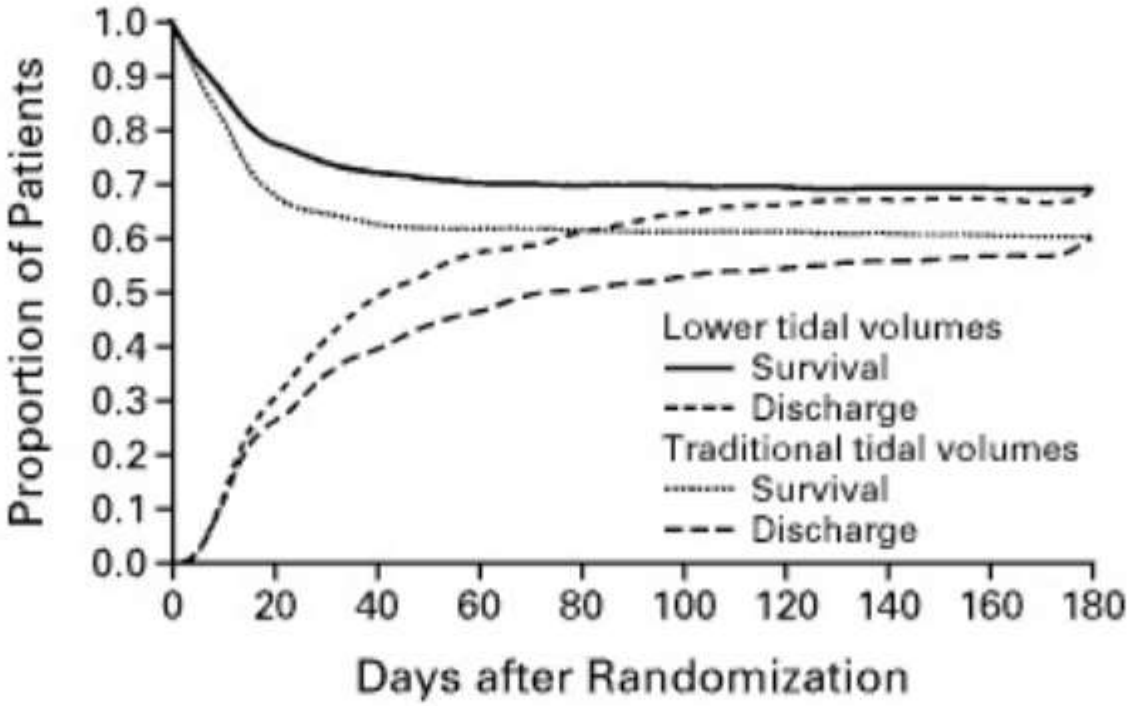
Frat et al. N Engl J Med 2015; 372:2185-219

Role Of Non Invasive Modalities In ARDS

Severity Of ARDS	NIV/HFNC
Mild	?Insufficient data – Trial of NIV/HFNC with monitoring
Mod.-Sev ARDS	Avoid

Invasive Mechanical Ventilation

The Landmark Trial - ARDSNet (ARMA) Trial



N = 861 ALI/ARDS patients

Randomised to receive

Low Tidal Volume (6ml/kg PBW) v/s Traditional Tidal Volume ventilation (12ml/kg PBW)

Outcome	Low TV Gp	Traditional TV Gp
180 d Mortality	31%	39.8%
Ventilator free days at day 28	12	10

ARR in Mortality ~ 9%

NNT = 11

Pplt<30 cm H2O ; PEEP , FiO2 according to ARDSNet table

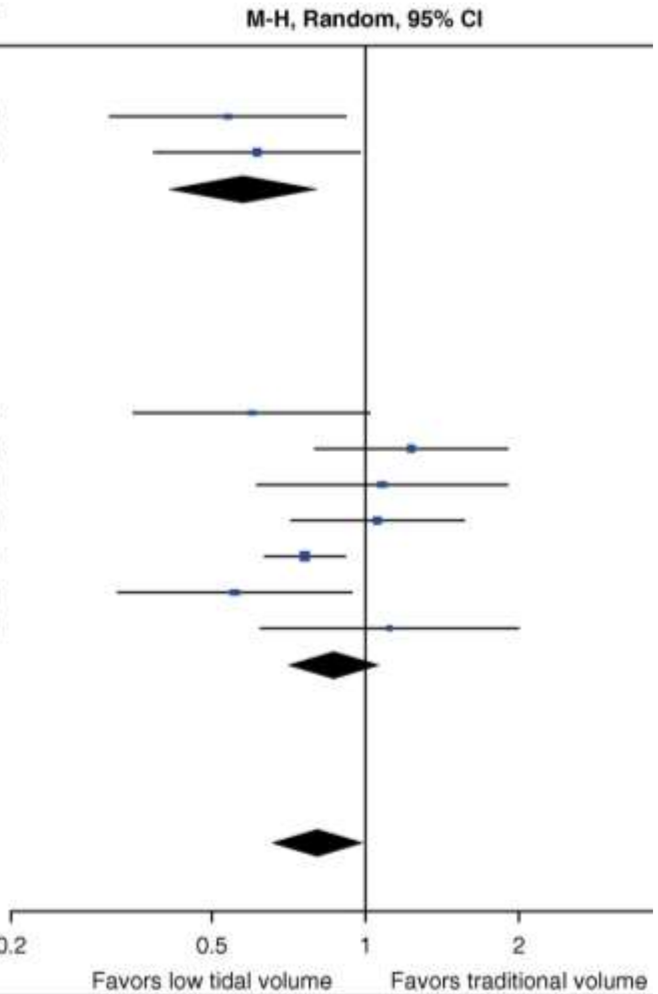
Brower R G et al. NEJM 2000

Low Tidal Volume Ventilation In ARDS Systematic Review

Low Tidal Volume versus Non–Volume-Limited Strategies for Patients with Acute Respiratory Distress Syndrome

A Systematic Review and Meta-Analysis

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Open Lung							
Amato 1998	11	29	17	24	9.0%	0.54 [0.31, 0.91]	1998
Villar 2006	17	50	25	45	10.6%	0.61 [0.38, 0.98]	2006
Subtotal (95% CI)		**79**		**69**	**19.6%**	**0.58 [0.41, 0.82]**	
Total events	28		42				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$							
Test for overall effect: Z = 3.07 (P = 0.002)							
No Open Lung							
Wu 1998	12	32	15	24	8.7%	0.60 [0.35, 1.03]	1998
Brochard 1998	27	58	22	58	11.7%	1.23 [0.80, 1.89]	1998
Brower 1999	13	26	12	26	8.3%	1.08 [0.62, 1.91]	1999
East 1999	36	103	32	97	13.0%	1.06 [0.72, 1.56]	1999
ARDSNet 2000	133	427	174	425	21.4%	0.76 [0.63, 0.91]	2000
Orme 2003	15	60	27	60	9.3%	0.56 [0.33, 0.93]	2003
Sun 2009	16	43	14	42	8.0%	1.12 [0.63, 1.99]	2009
Subtotal (95% CI)		**749**		**732**	**80.4%**	**0.87 [0.70, 1.08]**	
Total events	252		296				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 11.12$, df = 6 (P = 0.08); $I^2 = 46\%$							
Test for overall effect: Z = 1.26 (P = 0.21)							
Total (95% CI)		**828**		**801**	**100.0%**	**0.80 [0.66, 0.98]**	
Total events	280		338				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.93$, df = 8 (P = 0.06); $I^2 = 46\%$							
Test for overall effect: Z = 2.18 (P = 0.03)							
Test for subgroup differences: $Chi^2 = 3.82$, df = 1 (P = 0.05); $I^2 = 73.8\%$							



LTV ventilation strategy reduced mortality among critically ill adults with ARDS

Alan Walkley et al. Ann Am Thorac Soc Vol 14, Oct 2017

Refractory Hypoxemia – Options available?

- P/F<150, despite PEEP ≥ 5CM H_2O,LTVV and optimisation of ventilator settings
- R/O correctable causes –PTE/VAP/Pneumothorax etc.

OPTIONS

- Alternative ventilator strategies(RM,OLV)
- Prone Position Ventilation
- ECMO
- Pharmacotherapy

Ventilator Strategies – Recruitment Manoeuvre

Brief application of high level of PEEP/CPAP to temporarily increase transpulm. pressure

Rationale : To open derecruited lung areas occurring due to inadequately applied PEEP/loss of PEEP

Used singly/as part of OLV

Recruitment manoeuvre	Procedure
Sustained Inflation	Abrupt increase in airway pressure for given time interval
Sigh breaths	High PEEP upto a specific plateau pressure level for selected number of cycle in CMV
Incremental PEEP	
Staircase RM	

Recruitment Manoeuvres and Outcomes

Ref.	Population	Design	Interventions	Comparison	Outcome
Pelosi et al[17]	Patients with pulmonary and extrapulmonary ARDS	Observational study	3 sighs/min at Pplat 45 cm H_2O, V_T to maintain Pplat ≤ 35 cm H_2O. PEEP level to keep the lung open	(1) 1 h of ventilator strategy; (2) 2 h of ventilator strategy; and (3) 1 h of ventilator strategy with three consecutive sighs/min at Plat 45 cm H_2O	Sigh during protective ventilation improved lung recruitment
Borges et al[44]	Patients with early ARDS	Observational study	Stepwise maximum-recruitment strategy with sequential increments in Paw, in 5-cm H_2O steps, until the detection of $PaO_2 + PaCO_2 = 400$ mmHg	No comparisons	Stepwise maximum recruitment reverted hypoxemia and fully recruited the lungs
Meade et al[29]	Patients with ARDS ($PaO_2/FiO_2 \leq$ 250 mmHg)	Randomized controlled trial	Low V_T, Pplat ≤ 30 cm H_2O or ≥ 40 cm H_2O, and lower or higher PEEP levels according to PEEP/FiO_2 table	(1) Ventilator strategy with Pplat ≤ 30 cm H_2O, and conventional PEEP levels; (2) "open lung" approach with Pplat ≤ 40 cm H_2O, RM, and higher PEEP levels	"Open-lung" approach improved oxygenation associated with lower use of rescue therapies
Hodgson et al[25]	Patients with early ARDS	Observational study	Staircase RM, Paw set to 15 cm H_2O above the PEEP, which was increased in a stepwise manner to 20, 30 and then 40 cm H_2O every 2 min, followed by PEEP titration	No comparisons	80% of early ARDS patients responded to staircase RM
Hodgson et al[27]	Patients with ARDS	Randomized controlled trial	Control ventilation strategy compared to staircase recruitment maneuver	(1) Control group: PCV, Pplat < 30 cm H_2O, V_T < 6 mL/kg. FiO_2 adjusted to SaO_2: 90% to 92%; and (2) Staircase RM: Paw adjusted to 15 cm H_2O above PEEP level, which was increased in a stepwise manner to 20, 30 and 40 cm H_2O every 2 min, and then reduced in steps of 2.5 from 25 to 15 cm H_2O every 3 min until a decrease in $SaO_2 \geq 1\%$	Staircase RM improved plasma cytokines, oxygenation and lung function over 7 d
Morán et al[26]	Patients with early ARDS	Observational study	Stepwise RM started from plateau pressure/PEEP of 40/25 cm H_2O, 5 cm H_2O of PEEP was sequentially increased until PaO_2/FiO_2 of 350 mmHg or plateau pressure/PEEP of 60/40 cm H_2O	No comparisons	Stepwise RM improved oxygenation but caused hemodynamic instability and transient hypoxemia

Santos et al. World J Crit Care Med. 2015 Nov 4

Predicting Recruitability? Which group of patients will benefit

Presence of 2/3 of following(Sens-71 %   Sp.-   58 %   )
1.P/F<150 at PEEP 5cmH20
2.Decrease in Vd/Vt
3.Increase in Compliance

Gattinoni et al. NEJM 2006

PV Tool Pro (2/3 Criteria)
1.Inflation limb showing upward concavity
2.High compliance above lower inflection point(>50-60ml/cmH2O)
3.Large hysteresis on PV curve(at 20 cmH20)

Assessing response to recruitment?

Physiological parameters (So2/P/F/Compliance)   P/V curve
Imaging

Meta analysis – Recruitment Manoeuvres

Table 1. Characteristics of included studies

Study Population						Lung Recruitment Maneuvers	
First Author, Year (Reference)	Centers (*n*)	Treatments (*n*)	Control Subjects (*n*)	Inclusion Criteria	Maneuver Description	Frequency and Indications	Target V_T
Kacmarek, 2016 (21)	20	99	101	Patients with ARDS <48 h, Pa_{O_2}/F_{IO_2} ratio <200 mm Hg	PCV 15 cm H_2O, PEEP 35–45 cm H_2O to achieve PIP of 50–60 cm H_2O	At randomization	6 ml/kg
Hodgson, 2011 (16)	1	10	10	Patients with ARDS <72 h, Pa_{O_2}/F_{IO_2} ratio <200 mm Hg	Staircase recruitment to PIP 55 cm H_2O	Daily, oxygen desaturation or disconnection	6 ml/kg
Huh, 2009 (17)	1	30	27	Patients with ARDS (duration not specified), Pa_{O_2}/F_{IO_2} ratio <200 mm Hg	Extended sigh, V_T 25% of baseline, PEEP up to 25 cm H_2O, PIP maximum 55 cm H_2O	Daily	6 ml/kg

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Huh, 2009 (17)	1	30	27	Patients with ARDS (duration not specified), Pa_{O_2}/F_{IO_2} ratio <200 mm Hg	Extended sigh, V_T 25% of baseline, PEEP up to 25 cm H_2O, PIP maximum 55 cm H_2O	Daily	6 ml/kg
Xi, 2010 (18)	14	55	55	Patients with ARDS (duration not specified), Pa_{O_2}/F_{IO_2} ratio <200 mm Hg	CPAP 40 cm H_2O for 40 s	Every 8 h for up to 5 d	6–8 ml/kg
Meade, 2008 (19)	30	475	508	Patients with ARDS <48 h, Pa_{O_2}/F_{IO_2} ratio <250 mm Hg	CPAP 40 cm H_2O for 40 s	At ventilator disconnections, up to four times daily until F_{IO_2} <0.4	6 ml/kg
Amato, 1998 (20)	2	29	24	LIS ≥2.5, PCWP <16, duration of ventilation <1 wk	CPAP 35–40 cm H_2O for 40 s	Ventilator disconnections, desaturations (not clear)	Pressure-targeted modes, 6 ml/kg, Pdrive <20, PIP <40

Patients of Mod – Sev ARDS included

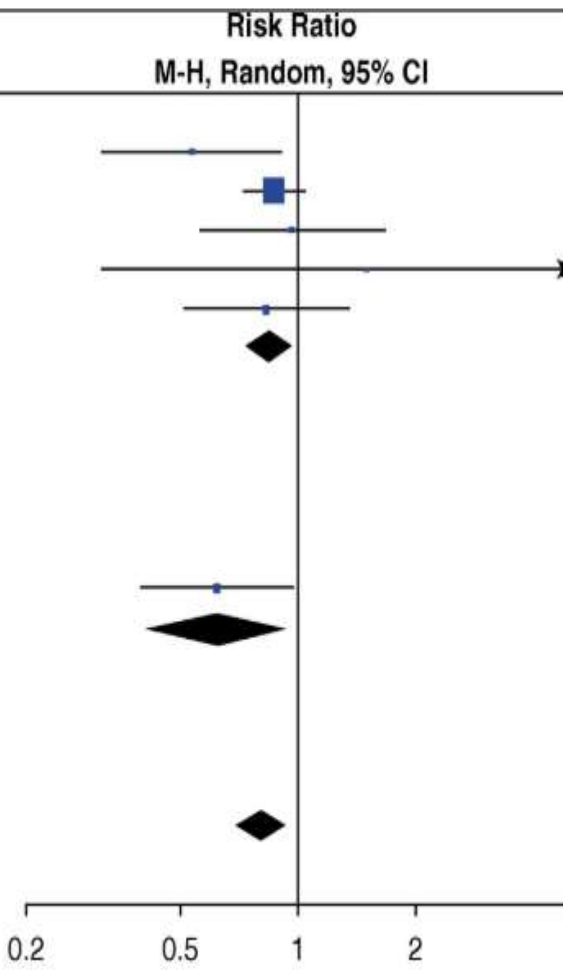
Early ARDS within 5-7d of onset

RM used varied

Goligher et al. Ann Am Thorac Soc. 2017

Meta Analysis RM Results – Mortality

Study or Subgroup	LRMs Events	LRMs Total	No LRMs Events	No LRMs Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Co-intervention with higher PEEP							
Amato 1998	11	29	17	24	8.9%	0.54 [0.31, 0.91]	1998
Meade 2008	145	475	178	508	59.3%	0.87 [0.73, 1.04]	2008
Huh 2009	14	30	13	27	8.4%	0.97 [0.56, 1.68]	2009
Hodgson 2011	3	10	2	10	1.1%	1.50 [0.32, 7.14]	2011
Kacmarek 2016	22	99	27	101	10.4%	0.83 [0.51, 1.36]	2016
Subtotal (95% CI)		**643**		**670**	**88.0%**	**0.84 [0.72, 0.98]**	
Total events	195		237				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.71$, df = 4 (P = 0.45); $I^2 = 0\%$							
Test for overall effect: Z = 2.16 (P = 0.03)							
No co-intervention with higher PEEP							
Xi 2010	18	55	29	55	12.0%	0.62 [0.39, 0.98]	2010
Subtotal (95% CI)		**55**		**55**	**12.0%**	**0.62 [0.39, 0.98]**	
Total events	18		29				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.06 (P = 0.04)							
Total (95% CI)		**698**		**725**	**100.0%**	**0.81 [0.69, 0.95]**	
Total events	213		266				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.30$, df = 5 (P = 0.38); $I^2 = 6\%$							
Test for overall effect: Z = 2.57 (P = 0.01)							

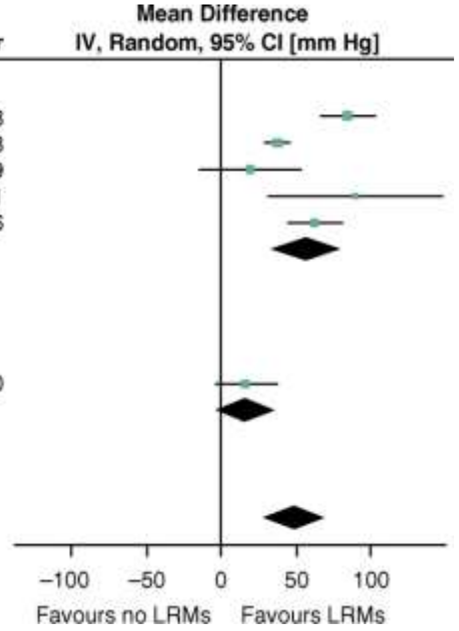


Reduction in Mortality seen in pooled data

Goligher et al. Ann Am Thorac Soc. 2017

Meta Analysis RM Results – Improvement in oxygenation

Study or Subgroup	LRMs Mean [mm Hg]	LRMs SD [mm Hg]	LRMs Total	No LRMs Mean [mm Hg]	No LRMs SD [mm Hg]	No LRMs Total	Weight	Mean Difference IV, Random, 95% CI [mm Hg]	Year
Co-intervention with higher PEEP									
Amato 1998	220	38	29	135	29	24	18.9%	85.00 [66.95, 103.05]	1998
Meade 2008	187	69	464	149	61	498	21.1%	38.00 [29.75, 46.25]	2008
Huh 2009	160	82	30	140	47	27	14.2%	20.00 [−14.28, 54.28]	2009
Hodgson 2011	230	70	10	140	63	10	8.6%	90.00 [31.63, 148.37]	2011
Kacmarek 2016	199	79	94	136	44	104	18.9%	63.00 [44.93, 81.07]	2016
Subtotal (95% CI)			**627**			**663**	**81.7%**	**57.01 [32.72, 81.30]**	
Heterogeneity: $Tau^2 = 578.07$; $Chi^2 = 28.97$, df = 4 ($P < 0.00001$); $I^2 = 86\%$									
Test for overall effect: Z = 4.60 ($P < 0.00001$)									
No co-intervention with higher PEEP									
Xi 2010	142	61	55	125	46	55	18.3%	17.00 [−3.19, 37.19]	2010
Subtotal (95% CI)			**55**			**55**	**18.3%**	**17.00 [−3.19, 37.19]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.65 (P = 0.10)									
Total (95% CI)			**682**			**718**	**100.0%**	**49.67 [27.75, 71.59]**	
Heterogeneity: $Tau^2 = 575.99$; $Chi^2 = 37.15$, df = 5 ($P < 0.00001$); $I^2 = 87\%$									
Test for overall effect: Z = 4.44 ($P < 0.00001$)									
Test for subgroup differences: $Chi^2 = 6.16$, df = 1 (P = 0.01), $I^2 = 83.8\%$									



50 mmHg improvement in RM group

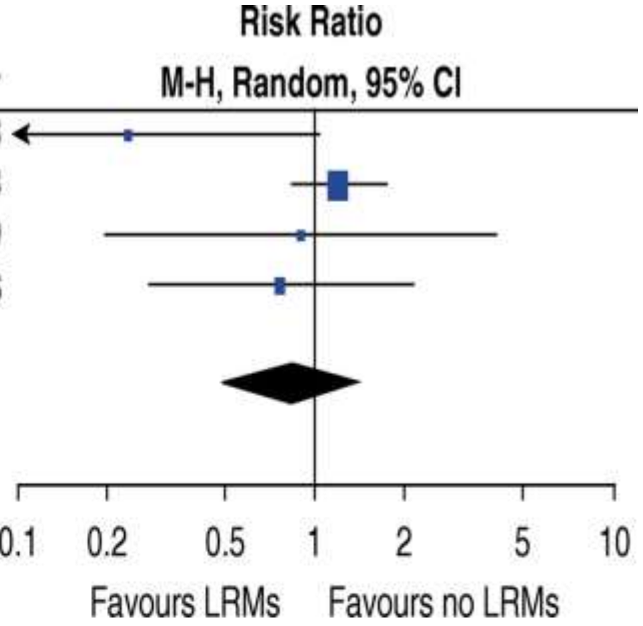
Goligher et al. Ann Am Thorac Soc. 2017

Meta Analysis RM Results – Incidence Of Barotrauma

	LRMs		No LRMs			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Amato 1998	2	29	7	24	13.4%	0.24 [0.05, 1.03]	1998
Meade 2008	53	475	47	508	51.0%	1.21 [0.83, 1.75]	2008
Huh 2009	3	30	3	27	12.9%	0.90 [0.20, 4.09]	2009
Kacmarek 2016	6	99	8	101	22.7%	0.77 [0.28, 2.13]	2016
Total (95% CI)		**633**		**660**	**100.0%**	**0.84 [0.46, 1.55]**	
Total events	64		65				

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 4.88$, df = 3 (P = 0.18); $I^2 = 38\%$

Test for overall effect: Z = 0.55 (P = 0.58)



No Sig Difference in incidence of barotrauma/

hemodynamic compromise

In LRM Gp

Goligher et al. Ann Am Thorac Soc. 2017

Open Lung Ventilation Approach

LTVV +Recruitment Manoeuvre + Optimize PEEP

- Combination of LTV + RM + Subsequent titration of PEEP
- Hypothesized to reduce volutrauma/barotrauma and atelectrauma
- Hence postulated to further capitalize on benefit afforded by LTV

Is RM and High PEEP Beneficial – Individual Patient Data Meta analysis

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome

Systematic Review and Meta-analysis

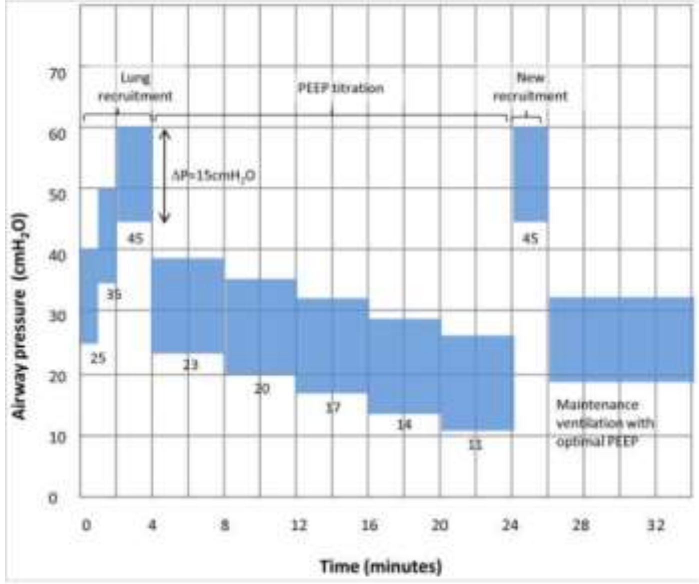
Outcomes	All Patients: No. (%) Higher PEEP (n = 1136)	All Patients: No. (%) Lower PEEP (n = 1163)	All Patients: Adjusted RR (95% CI)[a]	All Patients: *P* Value	With ARDS: No. (%) Higher PEEP (n = 951)	With ARDS: No. (%) Lower PEEP (n = 941)	With ARDS: Adjusted RR (95% CI)[a]	With ARDS: *P* Value	Without ARDS: No. (%) Higher PEEP (n = 184)	Without ARDS: No. (%) Lower PEEP (n = 220)	Without ARDS: Adjusted RR (95% CI)[a]	Without ARDS: *P* Value
Death in hospital	374 (32.9)	409 (35.2)	0.94 (0.86 to 1.04)	.25	324 (34.1)	368 (39.1)	0.90 (0.81 to 1.00)	.049	50 (27.2)	44 (19.4)	1.37 (0.98 to 1.92)	.07
Death in ICU[b]	324 (28.5)	381 (32.8)	0.87 (0.78 to 0.97)	.01	288 (30.3)	344 (36.6)	0.85 (0.76 to 0.95)	.001	36 (19.6)	37 (16.8)	1.07 (0.74 to 1.55)	.71
Pneumothorax between day 1 and day 28[c]	87 (7.7)	75 (6.5)	1.19 (0.89 to 1.60)	.24	80 (8.4)	64 (6.8)	1.25 (0.94 to 1.68)	.13	7 (3.8)	11 (5.0)	0.72 (0.37 to 1.39)	.33
Death after pneumothorax[c]	43 (3.8)	40 (3.5)	1.11 (0.73 to 1.69)	.63	41 (4.3)	35 (3.7)	1.20 (0.79 to 1.81)	.39	2 (1.1)	5 (2.3)	0.44 (0.08 to 2.35)[g]	.34
Days with unassisted breathing between day 1 and day 28, median (IQR)[d]	13 (0 to 22)	11 (0 to 21)	0.64 (−0.12 to 1.39)[e]	.10	12 (0-21)	7 (0-20)	1.22 (0.39 to 2.05)[e]	.004	17 (0-23)	19 (5.5-24)	−1.74 (−3.60 to 0.11)[e]	.07
Total use of rescue therapies[f]	138 (12.2)	216 (18.6)	0.64 (0.54 to 0.75)	<.001	130 (13.7)	200 (21.3)	0.63 (0.53 to 0.75)	<.001	8 (4.4)	16 (7.3)	0.60 (0.25 to 1.43)[g]	.25
Death after rescue therapy[f]	85 (7.5)	132 (11.3)	0.65 (0.52 to 0.80)	<.001	82 (8.6)	124 (13.2)	0.66 (0.52 to 0.82)	<.001	3 (1.6)	8 (3.6)	0.37 (0.10 to 1.46)[g]	.15
Use of vasopressors	722 (63.6)	759 (65.3)	0.93 (0.75 to 1.14)[g]	.49	627 (65.9)	647 (68.8)	0.90 (0.72 to 1.13)[g]	.37	95 (51.6)	111 (50.5)	0.92 (0.56 to 1.50)[g]	.72

Reduction in mortality and improvement in ventilator free days in ARDS Gp

Briel et al. JAMA 2010

ART (Alveolar Recruitment in ARDS Trial)

Study	Population	Intervention	Outcome
Multicentre RCT 120 sites	N=1010 Mod.-Sev. ARDS <72 Hr	501- OLV 509 – LTV	28 d Mortality 6 month Mortality 28 d Ventilator free Days Barotrauma



Cavalcanti et al. JAMA 2017

Results – ART Trial

Table 2. Outcomes Among Patients Treated With Lung Recruitment Maneuver With Positive End-Expiratory Pressure (PEEP) vs Low-PEEP Strategy

Outcome	Lung Recruitment Maneuver With PEEP Titration Group (n = 501)	Low-PEEP Group (n = 509)	Type of Effect Estimate	Effect Estimate (95% CI)	P Value
Primary Outcome					
Death ≤28 d, No. of events/total No. (%)	277/501 (55.3)	251/509 (49.3)	HR	1.20 (1.01 to 1.42)	.041
Secondary Outcomes					
Death, No. of events/total No. (%)					
In intensive care unit	303/500 (60.6)	284/509 (55.8)	RD	4.8 (-1.5 to 11.1)	.13
In hospital	319/500 (63.8)	301/508 (59.3)	RD	4.5 (-1.7 to 10.7)	.15
Within 6 mo[a]	327/501 (65.3)	305/509 (59.9)	HR	1.18 (1.01 to 1.38)	.04
Length of stay, d					
Intensive care unit, mean (SD)	18.2 (22.4)	19.2 (25.9)	MD	-1.0 (-4.0 to 2.0)	.51
Median (IQR)	12.0 (5.0 to 23.0)	14.0 (7.0 to 23.0)			
Hospital, mean (SD)	25.5 (32.3)	26.2 (31.7)	MD	-0.7 (-4.6 to 3.3)	.74
Median (IQR)	15.0 (5.0 to 32.0)	18.0 (7.0 to 35.0)			
No. of ventilator-free d from d 1 to d 28, mean (SD), d	5.3 (8.0)	6.4 (8.6)	MD	-1.1 (-2.1 to -0.1)	.03
Median (IQR)	0.0 (0.0 to 11.0)	0.0 (0.0 to 14.0)			
Pneumothorax requiring drainage ≤7 d, No./total No. (%)	16/501 (3.2)	6/509 (1.2)	RD	2.0 (0.2 to 3.8)	.03
Barotrauma ≤7 d, No./total No. (%)	28/501 (5.6)	8/509 (1.6)	RD	4.0 (1.5 to 6.5)	.001

Higher mortality in OLV group

Increased incidence of pneumothorax in OLV group

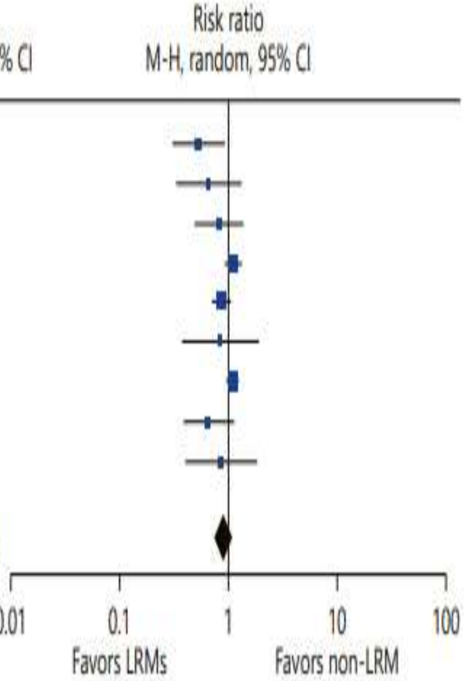
Cavalcanti et al. JAMA 2017

Recent Meta analysis - OLV

Study or subgroup	LRMs events	LRMs total	Non-LRM events	Non-LRM total	Weight, %	Risk ratio M-H, random, 95% CI
Amato [18], 1998	11	29	17	24	6.8	0.54 (0.31, 0.91)
Huh [15], 2009	9	30	12	27	4.5	0.68 (0.34, 1.35)
Kacmarek [19], 2016	22	99	27	101	7.7	0.83 (0.51, 1.36)
Khan [12], 2018	142	245	125	245	21.9	1.14 (0.97, 1.34)
Meade [17], 2008	135	475	164	508	20.2	0.88 (0.73, 1.06)
Wang [20], 2007	6	14	7	14	3.5	0.86 (0.39, 1.91)
Cavalcanti [10], 2017	277	501	251	509	24.5	1.12 (1.00, 1.26)
Xi [16], 2010	16	55	55	55	7.2	0.67 (0.40, 1.11)
Yu [13], 2017	9	36	36	38	3.8	0.86 (0.41, 1.84)
Total (95% CI)		**1,484**		**1,521**	**100.0**	**0.92 (0.78, 1.08)**
Total events	627		638			

Heterogeneity: $Tau^2 = 0.02$; $\chi^2 = 17.47$, df = 8 ($p = 0.03$); $I^2 = 54\%$

Test for overall effect: Z = 1.04 ($p = 0.30$)

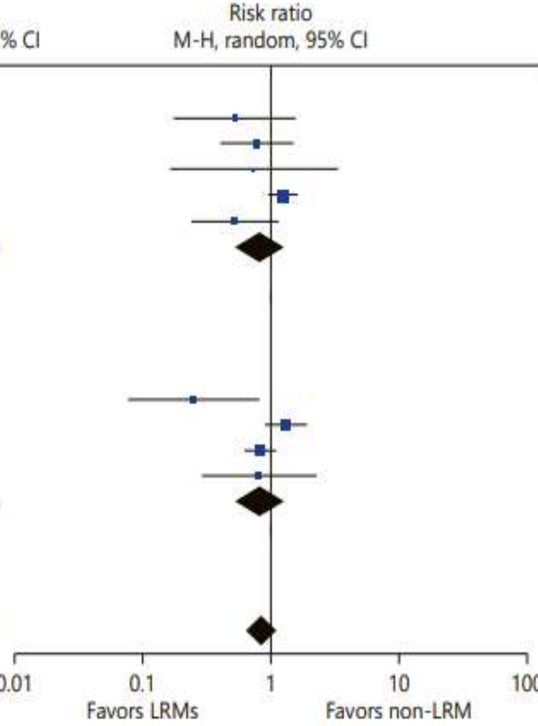


Study or subgroup	LRMs events	LRMs total	Non-LRM events	Non-LRM total	Weight, %	Risk ratio M-H, random, 95% CI
1.6.1 PaO_2/FiO_2 <200						
Huh [15], 2009	9	30	12	27	5.3	0.54 (0.18, 1.59)
Kacmarek [19], 2016	22	99	27	101	11.0	0.78 (0.41, 1.50)
Wang [20], 2007	6	14	7	14	3.1	0.75 (0.17, 3.33)
Cavalcanti [10], 2017	277	501	251	509	21.9	1.27 (0.99, 1.63)
Xi [16], 2010	16	55	24	55	8.5	0.53 (0.24, 1.17)
Subtotal (95% CI)		**699**		**706**	**49.8**	**0.85 (0.55, 1.30)**
Total events	330		321			
Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 9.35$, df = 3 ($p = 0.02$); $I^2 = 47\%$						
Test for overall effect: Z = 0.76 ($p = 0.44$)						
1.6.2 Others						
Amato [18], 1998	11	29	17	24	4.8	0.25 (0.08, 0.80)
Khan [12], 2018	142	245	125	245	18.5	1.32 (0.93, 1.89)
Meade [17], 2008	135	475	164	508	21.1	0.83 (0.63, 1.09)
Yu [13], 2017	9	36	11	38	5.8	0.82 (0.29, 1.36)
Subtotal (95% CI)		**785**		**815**	**50.2**	**0.85 (0.53, 1.36)**
Total events	297		317			
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 9.35$, df = 3 ($p = 0.02$); $I^2 = 68\%$						
Test for overall effect: Z = 0.76 ($p = 0.44$)						
Total (95% CI)		**1,484**		**1,521**	**100.0**	**0.87 (0.66, 1.16)**
Total events	627		638			

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 17.77$, df = 8 ($p = 0.02$); $I^2 = 55\%$

Test for overall effect: Z = 0.94 ($p = 0.34$)

Test for subgroup differences: $\chi^2 = 0.00$, df = 1 ($p = 1.00$); $I^2 = 0\%$



OLV did not produce significant effect on mortality

Cui Y et al. Respiration 2019

OLV In ARDS PLHARP 2 Trial

Study	Population	Intervention	Outcome
Multicentre RCT 35 ICU	N=115 Mod.-Sev. ARDS <72 Hr	58- OLV 57 – LTV	No difference in mortality No difference in Ventilator free Days Lower requirement of rescue therapy

Hodgson et al. AJRCCM 2019

Meta analysis – High PEEP v/s Low PEEP in ARDS patient on LTVV

Study, First Author, Year (Reference)	No. of Centers	ARDS Severity (Pa_{O_2}/F_{IO_2})	Intervention	Control	Mortality Outcome Assessments
Amato *et al.*, 1998 (14)[*]	2	<200	V_T < 6 ml/kg body weight Pressure control ventilation < 40 cm H_2O PEEP at Pflex+2 cm H_2O Recruitment maneuvers	V_T 12 ml/kg Volume control ventilation PEEP set to O_2 goals	1. 28 d 2. Hospital 3. ICU
Brower *et al.*, 2004 (21)	23	<300	Higher PEEP/F_{IO_2} chart Recruitment maneuvers in first 80 patients enrolled	Lower PEEP/F_{IO_2} chart Pplat < 30 cm H_2O	Death before discharge home, up to Day 60
Villar *et al.*, 2006 (15)[*]	8	<200	V_T 5–8 ml/kg ideal body weight Pressure control ventilation PEEP at Pflex+2	V_T 9–11 ml/kg PEEP ≥5 cm H_2O to O_2 goals	1. ICU 2. Hospital
Meade *et al.*, 2008 (22)	30	<250	High PEEP/F_{IO_2} chart Pplat < 40 cm H_2O Recruitment maneuvers	Lower PEEP/F_{IO_2} chart Pplat < 30 cm H_2O	1. Hospital 2. 28 d 3. ICU 4. Ventilator
Mercat *et al.*, 2008 (24)	37	<300	PEEP titrated to Pplat 30 cm H_2O	PEEP 5–9 cm H_2O to meet O_2 goals	1. 28 d 2. 60 d 3. Hospital to Day 60
Talmor *et al.*, 2008 (23)	1	<300	PEEP to keep end-expiratory TPP within 0–10 cm H_2O Inspiratory TPP < 25 cm H_2O Using esophageal balloon	Lower PEEP/F_{IO_2} chart Pplat < 30 cm H_2O	1. 28 d 2. 180 d
Hodgson *et al.*, 2011 (9)	1	<200	Stepwise recruitment w/ PEEP to 30 cm H_2O Then decremental PEEP to O_2 desaturation	Lower PEEP/F_{IO_2} chart	Hospital
Kacmarek *et al.*, 2016 (10)	20	<200	Stepwise recruitment with PEEP to 35–45 cm H_2O Then decremental PEEP to best dynamic compliance	Lower PEEP/F_{IO_2} chart	1. 28 d 2. 60 d 3. ICU 4. Hospital

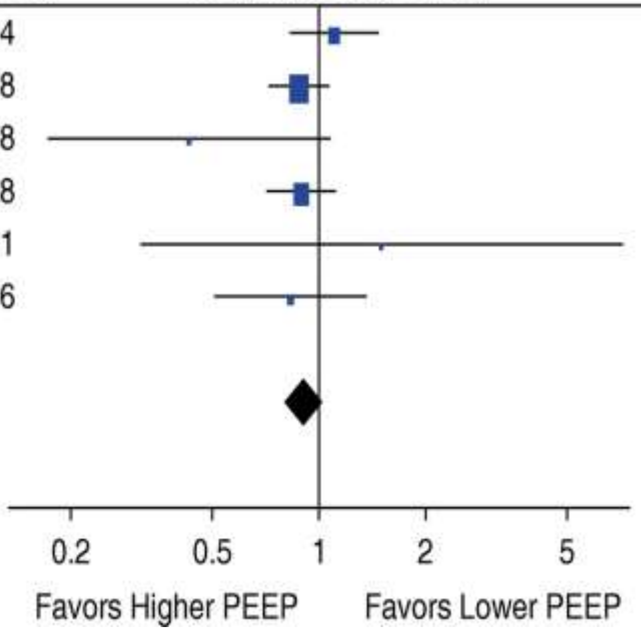
Walkey A J et al. Ann Am Thorac Soc. 2017

Result Meta analysis – Outcome Of Mortality

Study or Subgroup	High: Mortality Events	High: Total Patients	Low: Mortality Events	Low: Total Patients	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Brower *et al.*, 2004	76	276	68	273	19.2%	1.11 [0.83, 1.46]	2004	
Meade *et al.*, 2008	135	475	164	508	40.8%	0.88 [0.73, 1.06]	2008	
Talmor *et al.*, 2008	5	30	12	31	1.9%	0.43 [0.17, 1.07]	2008	
Mercat *et al.*, 2008	107	385	119	382	31.1%	0.89 [0.72, 1.11]	2008	
Hodgson *et al.*, 2011	3	10	2	10	0.6%	1.50 [0.32, 7.14]	2011	
Kacmarek *et al.*, 2016	22	99	27	101	6.4%	0.83 [0.51, 1.36]	2016	
Total (95% CI)		**1275**		**1305**	**100.0%**	**0.91 [0.80, 1.03]**		
Total events	348		392					

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.09$, df = 5 (P = 0.41); $I^2 = 2\%$

Test for overall effect: Z = 1.46 (P = 0.14)



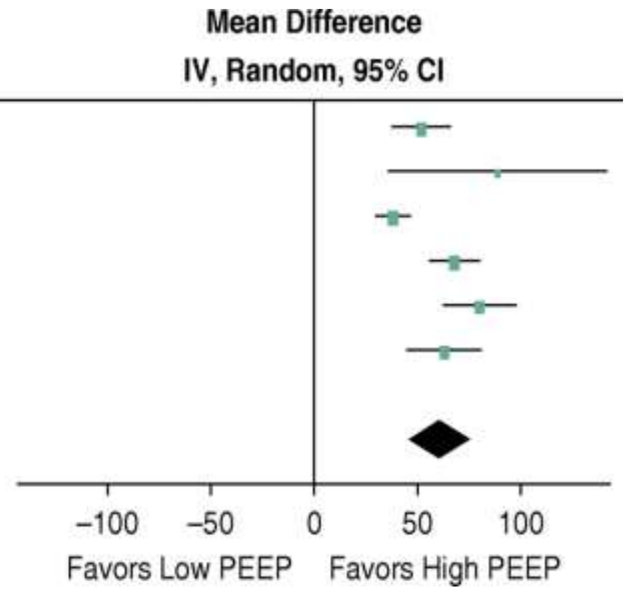
No significant difference in Mortality b/w two groups

Walkey A J et al. Ann Am Thorac Soc. 2017

Result Meta analysis – Improvement In Oxygenation

	High PEEP			Low PEEP				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Brower *et al.*, 2004	220	89	244	168	66	230	18.8%	52.00 [37.95, 66.05]	2004
Talmor *et al.*, 2008	280	126	29	191	71	29	6.1%	89.00 [36.36,141.64]	2008
Meade *et al.*, 2008	187.4	68.8	464	149.1	60.6	498	21.0%	38.30 [30.08, 46.52]	2008
Mercat *et al.*, 2008	218	97	378	150	69	371	19.6%	68.00 [55.96, 80.04]	2008
Hodgson *et al.*, 2011	220	20	10	140	20	10	17.3%	80.00 [62.47, 97.53]	2011
Kacmarek *et al.*, 2016	198.5	78.6	94	135.6	43.5	101	17.1%	62.90 [44.89, 80.91]	2016
Total (95% CI)			**1219**			**1239**	**100.0%**	**61.24 [45.92, 76.57]**	

Heterogeneity: $Tau^2 = 273.32$; $Chi^2 = 30.33$, df = 5 (P < 0.0001); $I^2 = 84\%$
Test for overall effect: Z = 7.83 (P < 0.00001)



Oxygenation was improved in patients in High PEEP group

~61mmHg

Walkey A J et al. Ann Am Thorac Soc. 2017

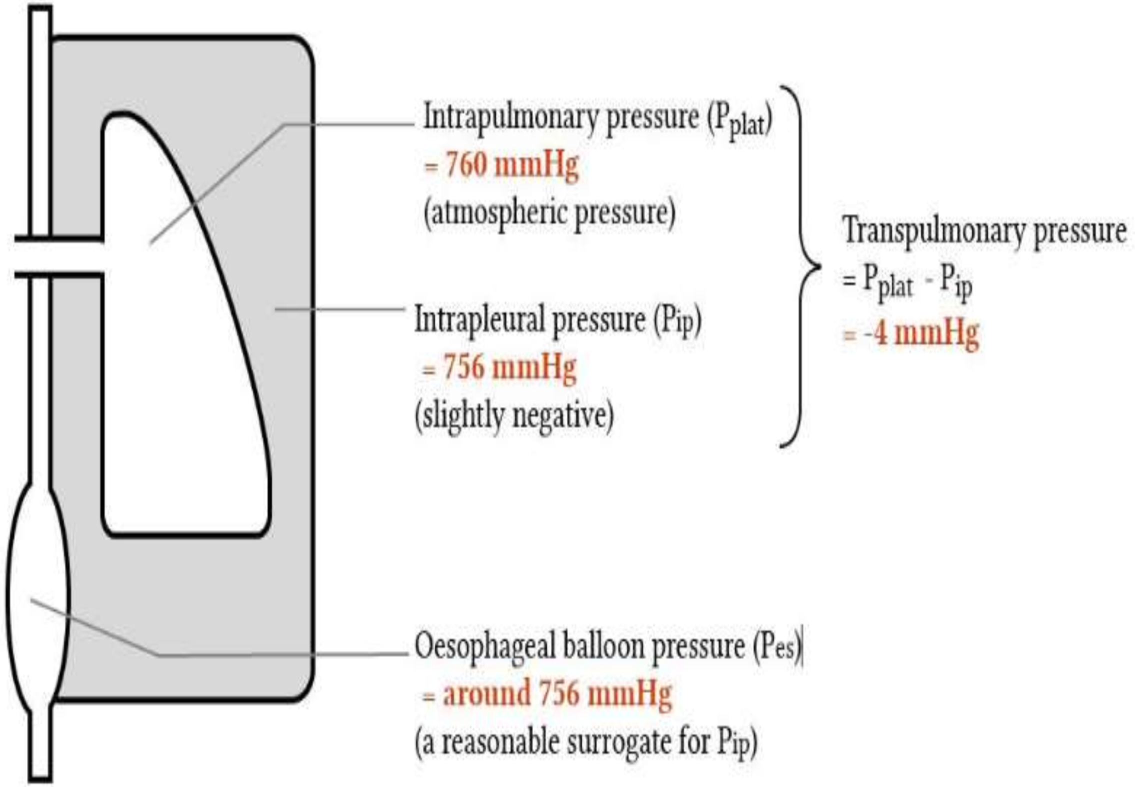
Role Of RM/OLV In ARDS

- Benefit in mortality conflicting(?Mod- Sev ARDS)
- Improvt. In oxygenation +
- Reduced need of rescue therapies

Other Ventilator Strategies – Optimisation/Titration of PEEP

- PEEP FiO_2 table
- PEEP according to PV loop analysis
- Transpulmonary Pressure guided
- Based on optimisation of Driving Pressure
- Based on Stress Index
- EIT guided
- Based on Dead space fraction

PEEP Titration with Oesophageal Balloon Catheter



Principle

- TPP is pressure needed to open up the alveoli
- TPP needs to be positive during the breathing cycle to prevent atelectrauma
- Airway pressure measured by ventilator may be influenced by chest and abdominal wall compliance
- Pleural pressure measured by oesophageal catheter can give reliable measure of TPP and help in PEEP titration

Loring et al. AJRCCM 2015

EP VENT 1 & 2

STUDY	EP VENT 1	EP VENT 2
Type	Single centre Pilot study	Multicentre phase 2 RCT
Population	ALI/ARDS(AECC) N=61	Mod.- Sev ARDS (P/F<200 Berlin definition) N=202
Intervention	PEEP guided by Pes vs Empirical PEEP FiO2 table PTPinsp <25	PEEP guided by Pes vs High PEEP FiO2 table PTPinsp <20 PTPexp >0
Outcome	Primary : Improvement in P/F Secondary : Days free from MV Deaths at day 28 LOS in ICU	Primary : No. of Deaths at day 28 Days free from MV at day 28 Secondary : 60 d mortality 180 d mortality LOS in hospital and ICU

Results	EP VENT 1	EP VENT 2
28 d Mortality	17% v/s 39% p=0.055	32.4% vs 30.6% p=0.88
Ventilator Free days to day 28	11.5d vs 7d p=0.5	15.5d vs 17.5d p=0.93
Hospital LOS to day 28	-	16d vs 15d p=0.58
ICU LOS to day 28	15.5d vs 13d p=0.16	10d vs 9.5d p=0.25
Improvement in P/F	88mmHg in Intervention arm	N/A

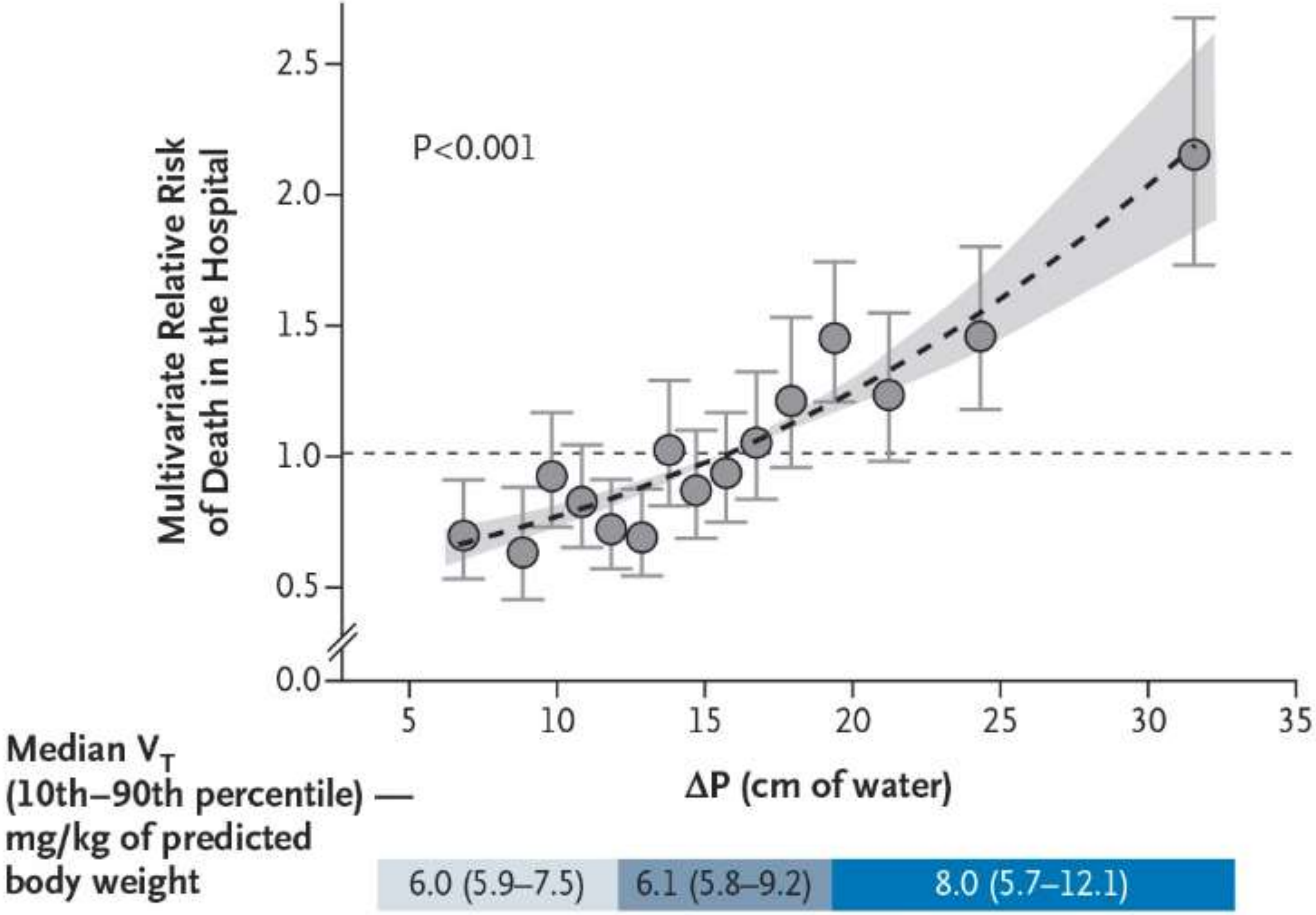
Routine use of Pes guided PEEP titration offered no benefit compared to conventional PEEP FiO2 titration

Driving pressure guided ventilation

- LTVV derived from PBW does not take into account the area of lung available for ventilation
- Stress and Strain experienced not only influenced by V_T but also C_{RS}
- Thus normalizing V_T to C_{RS} and using the ratio as an index to indicate the functional size of the lung may provide a better predictor of outcomes in patients with ARDS than V_T alone
- This ratio is termed the driving pressure ($\Delta P = V_T/C_{RS}$) and can be routinely calculated ($\Delta P = P_{plat} - PEEP$)

Amato et al. NEJM 2015

Retrospective Analysis of 9 RCTs In ARDS Δ P<15



Amato et al. NEJM 2015

PPlat	PEEP	ΔP	Mortality
rising	same	rising	rising
rising	rising	same	same
same	rising	falling	falling

Appears Physiologically sound
But
In LUNG SAFE STUDY low driving pressure ass with increased mortality

RCTs required to prove its benefit

Alternative Modes Of Ventilation
HFOV

- Based on principle of using very small tidal volume oscillating around a very high mean airway pressure

- Hypothesised to prevent both volutrauma and atelectrauma

Study	Population	Intervention	Result
OSCAR Trial Young D et al(2013)	N = 795 Mod- Sev ARDS P/F<200	N=398 HFOV arm N=397 Conv Ventilation	30 d Mortality 41.7% v/s 41.1% p=0.85
OSCILLATE Trial Ferguson et al.(2013)	N=548 Mod.-Sev ARDS P/F<200	N=275 HFOV arm N=273 LTV arm	In Hospital Mortality 47% v/s 35% p=0.005 NNH = 8

Higher Mean Airway Pressure>30 mmhg
Sedative and NMB use

APRV(Airway Pressure Release Ventilation)

- Delivery of continuous positive airway pressure with a brief release phase
- Hypothesized to improve gas exchange by alveolar recruitment

Study	Population	Intervention	Outcome
Putensen et al. 2001	N=30 Trauma rel. ARDS	APRV PCV	No. of ventilator days 15d vs 21d ICU stay 23d vs 30d
Maxwell et al. 2016	N= 63 Trauma rel. ARDS	APRV LTV	No. of ventilator days 15d vs 21d Mortality 6.45% vs 6.25%
Zhou et al.2017	Single centre N=138 (~70% Extrapulmonary cause)	APRV LTV	Ventilator free days 19d vs 2d Length of ICU stay 15d vs 20d Mortality 23.9% vs 37.3%

Is APRV better than LTV ? Two groups not comparable at B/L

Main outcome variables

Main outcome variables	APRV ($n = 71$) [b]	LTV ($n = 67$) [b]	P value
No. of days of ventilation	8 [5–14]	15 [7–22]	0.001
No. of ventilator-free days at 28 days	19 [8–22]	2 [0–15]	<0.001
Successful extubation	47 (66.2%)	26 (38.8%)	0.001
Tracheostomy	9 (12.7%)	20 (29.9%)	0.013
Length of ICU stay (days)	15 [8–21]	20 [10–32]	0.015
Pneumothorax between day 1 and day 28[a]	3 (4.2%)	7 (10.4%)	0.199
Death during the ICU stay	14 (19.7%)	23 (34.3%)	0.053
Length of hospital stay (days)	21 [14–30]	27 [18–41]	0.055
Death during the hospital stay	17 (23.9%)	25 (37.3%)	0.088
Other supportive therapies			
Neuromuscular blocker	2 (2.8%)	9 (13.4%)	0.021
Recruitment maneuvers	4 (5.6%)	11 (16.4%)	0.042
Prone position	2 (2.8%)	10 (14.9%)	0.012
Inhaled nitric oxide	1 (1.4%)	1 (1.5%)	1.000
High-frequency oscillatory ventilation	1 (1.4%)	3 (4.5%)	0.355

Baseline characteristics of the patients

Duration of mechanical ventilation (h)	24.6 ± 12.6	22.1 ± 13.
Duration of ICU stay before inclusion (h)	25.6 ± 12.6	23 ± 13.3
Chronic disease		
Chronic obstructive pulmonary disease	2 (2.8%)	5 (7.5%)
Chronic cardiac dysfunction	2 (2.8%)	3 (4.5%)
Chronic renal dysfunction	0%	3 (4.5%)
Hematological disease	2 (2.8%)	3 (4.5%)
Hepatic disease	3 (4.2%)	5 (7.5%)
Cancer	7 (9.9%)	12 (17.9%
Immunodeficiency	4 (5.6%)	4 (6.0%)
Diabetes	3 (4.2%)	2 (3.0%)
Coexisting one or more of the above diseases	23 (32.4%)	34 (50.7%
Reason for ARDS		
Pneumonia	18 (25.4%)	26 (38.8%
Extrapulmonary sepsis	13 (18.3%)	10 (14.9%
Severe acute pancreatitis	19 (26.8%)	13 (19.4%
Severe trauma	9 (12.7%)	7 (10.4%)
Major surgical procedures	8 (11.3%)	9 (13.4%)
Other	4 (5.6%)	2 (3.0%)
Co-interventions		
Vasopressor	40 (56.3%)	46 (68.7%)

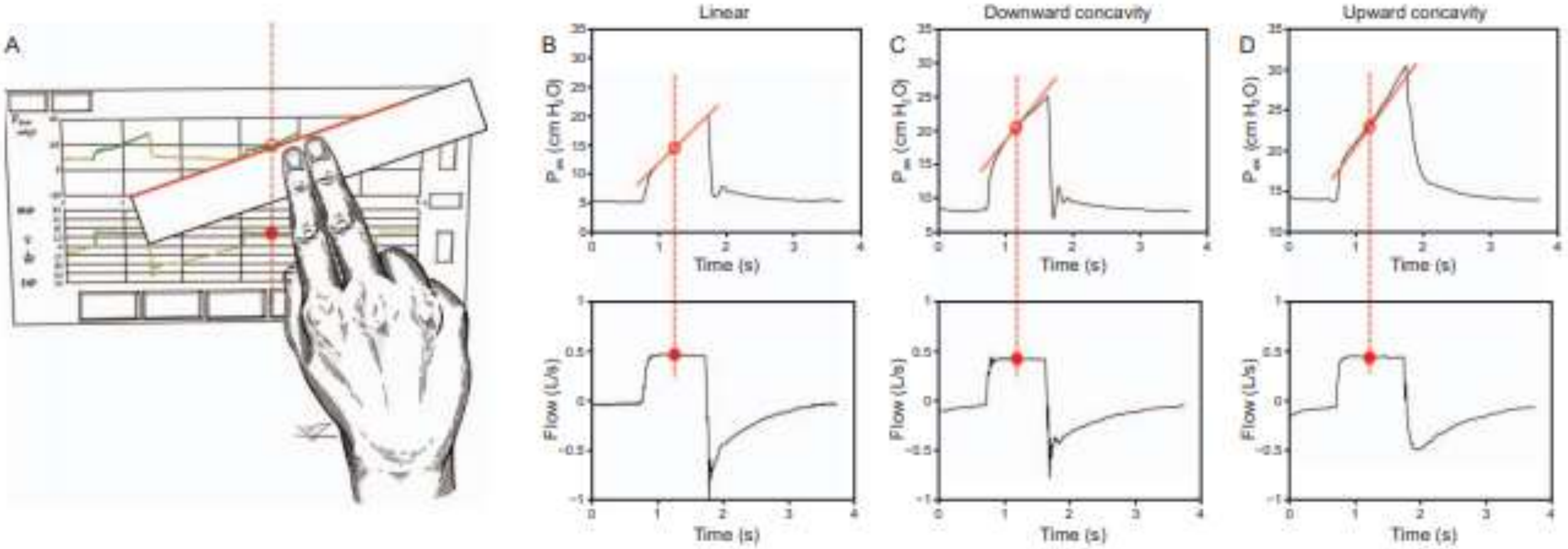
Zhou et al. Intensive Care Med. 2017; 43(11): 1648–1659

Stress Index

- Analysis of airway pressure and time curve can give details regarding respiratory system elastance
- Stress index is a dimensionless coefficient derived from this curve
- Stress index has shown to correlate with tidal recruitment and overdistension
- Stress index estimation requires dedicated ventilator and software

Sun et al. Respiratory Care 2018

Estimation Of Stress Index with Visual Inspection



Optimal Ideal	Underdistension Increase PEEP	Overdistension Decrease PEEP

Sun et al. Respiratory Care 2018

Electrical Impedance Tomography(EIT) in ARDS

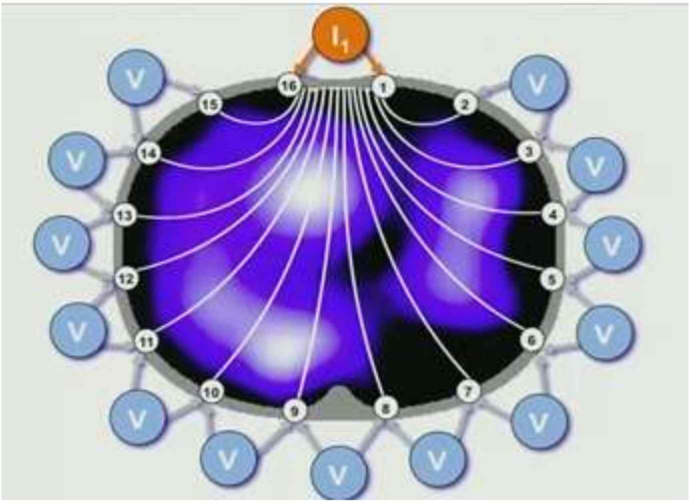
- EIT is a non invasive bedside radiation free imaging tool

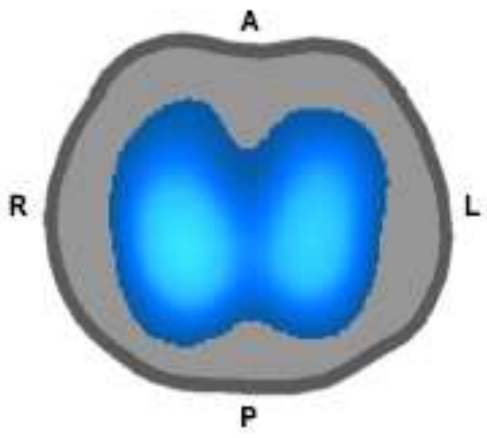
- Images generated by EIT can help in real time monitoring of pulmonary ventilation

Brief small alternating currents Delivered via electrodes attached to band applied to chest

Voltages read by electrodes depends upon resistivity/impedance of lung tissue

At end of one breathing cycle Voltages recorded are used to generate a pixel image based on prespecified reconstruction algorithm



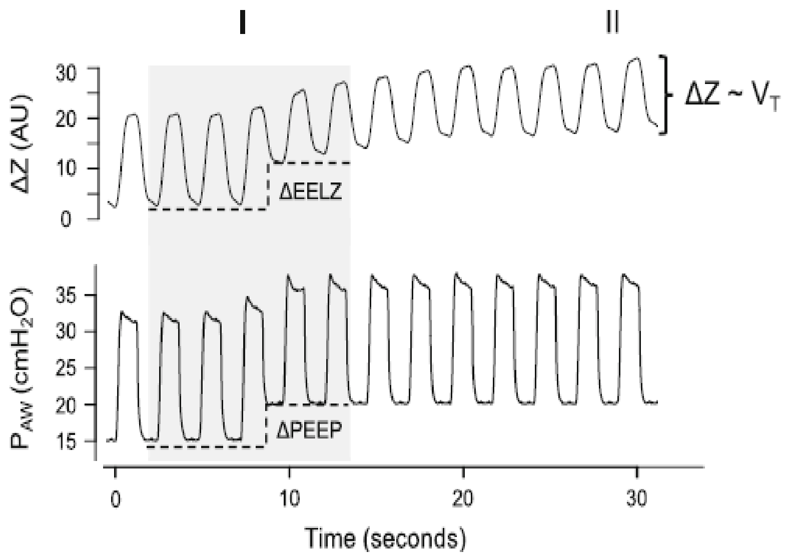


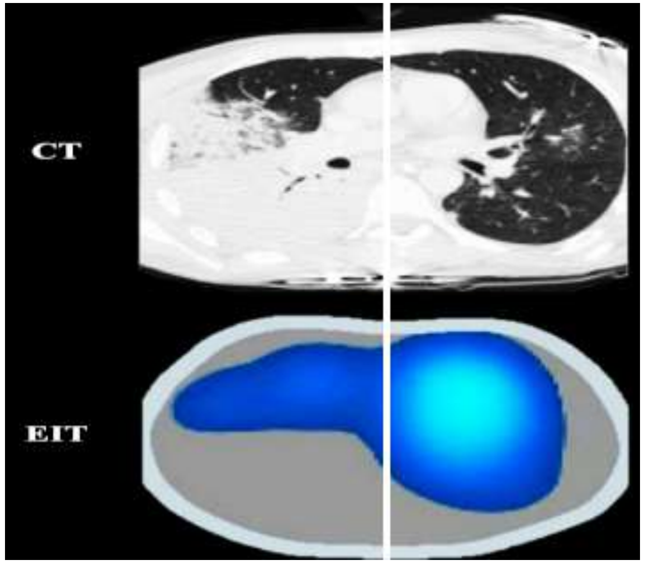
Bachmann et al. Critical Care (2018)

EIT Plethysmograph and Ventilation Map

- EIT plethysmograph is a waveform derived from pixel image denote volume of air moving in and out of a region

- Ventilation map is colour coded functional image representing changes in lung impedence





Bachmann et al. Critical Care (2018)

Role Of EIT In ARDS

- ARDS is a heterogenous condition with regional difference in ventilation
- Ventilation map can help detect these regional difference
- EIT plethysmography can help assess changes in these areas during recruitment manoeuvre and aid in PEEP titration
- EIT derived changes in lung volume and images have been found to correlate with lung mechanic indices and CT images

Lowhagen K, et al. Acta Anaesthesiol Scand. 2011;55:165–74.

Pulmonary Dead Space - ARDS

- In ARDS secondary to inflammation and thrombosis in pulmonary microcirculation there is ↑ physiological dead space

- Elevated physiological dead space fraction (V_d/V_t) is a marker of severity of lung injury in ARDS(Normal 25-30%)

- V_d/V_t is markedly elevated in first 24 hr after ARDS and sustained elevation of V_d/V_t is associated with increased mortality

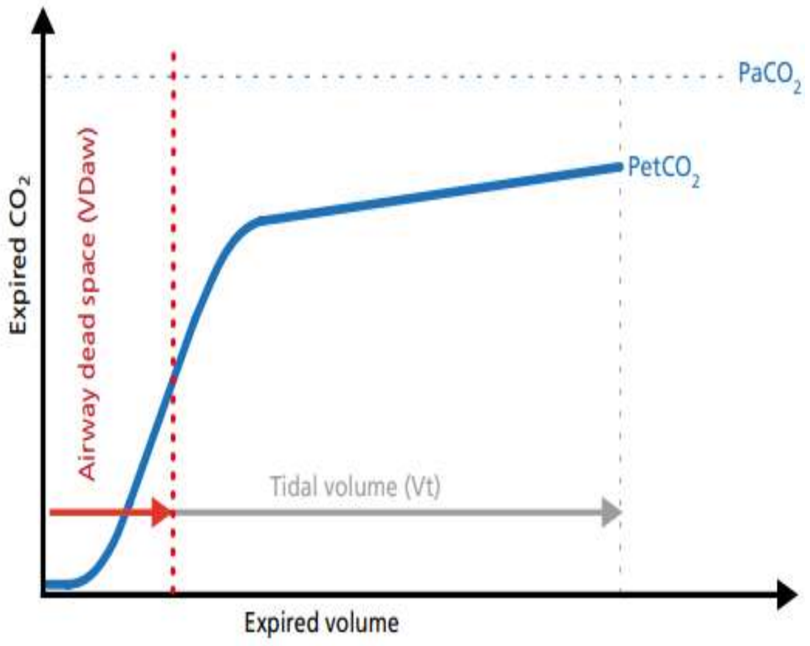
- V_d/V_t > 60% is a independent risk factor for increased mortality

TJ Nuckton et al, NEJM 2002
Kallet et al. Resp Care 2004

Pulmonary Dead Space Fraction Measurement And Application

Enghoff modification of Bohrs equation used to calculate Vd/Vt
=PaCO2-PECO2/PaCO2

Slope method is used by S1 Hamilton to estimate Vdaw/VT



- Estimation and F/u of Vd/Vt for prognosis
- Vd/Vt can help in estimating response to PEEP/RM
- Changes in capnography curve can help in optimising PEEP
- Help in assessing effectiveness of RM

Guo Fengmei et al, Respiratory Care 2012

Personalised Ventilation (the LIVE Study)

Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial

*Jean-Michel Constantin, Matthieu Jabaudon, Jean-Yves Lefrant, Samir Jaber, Jean-Pierre Quenot, Olivier Langeron, Martine Ferrandière, Fabien Grelon, Philippe Seguin, Carole Ichai, Benoit Veber, Bertrand Souweine, Thomas Uberti, Sigismond Lasocki, François Legay, Marc Leone, Nathanael Eisenmann, Claire Dahyot-Fizelier, Hervé Dupont, Karim Asehnoune, Achille Sossou, Gérald Chanques, Laurent Muller, Jean-Etienne Bazin, Antoine Monsel, Lucile Borao, Jean-Marc Garcier, Jean-Jacques Rouby, Bruno Pereira, Emmanuel Futier, for the AZUREA Network**

- Ventilation was modified based on patient lung morphology
- Lung morphology defined based on CT Thorax

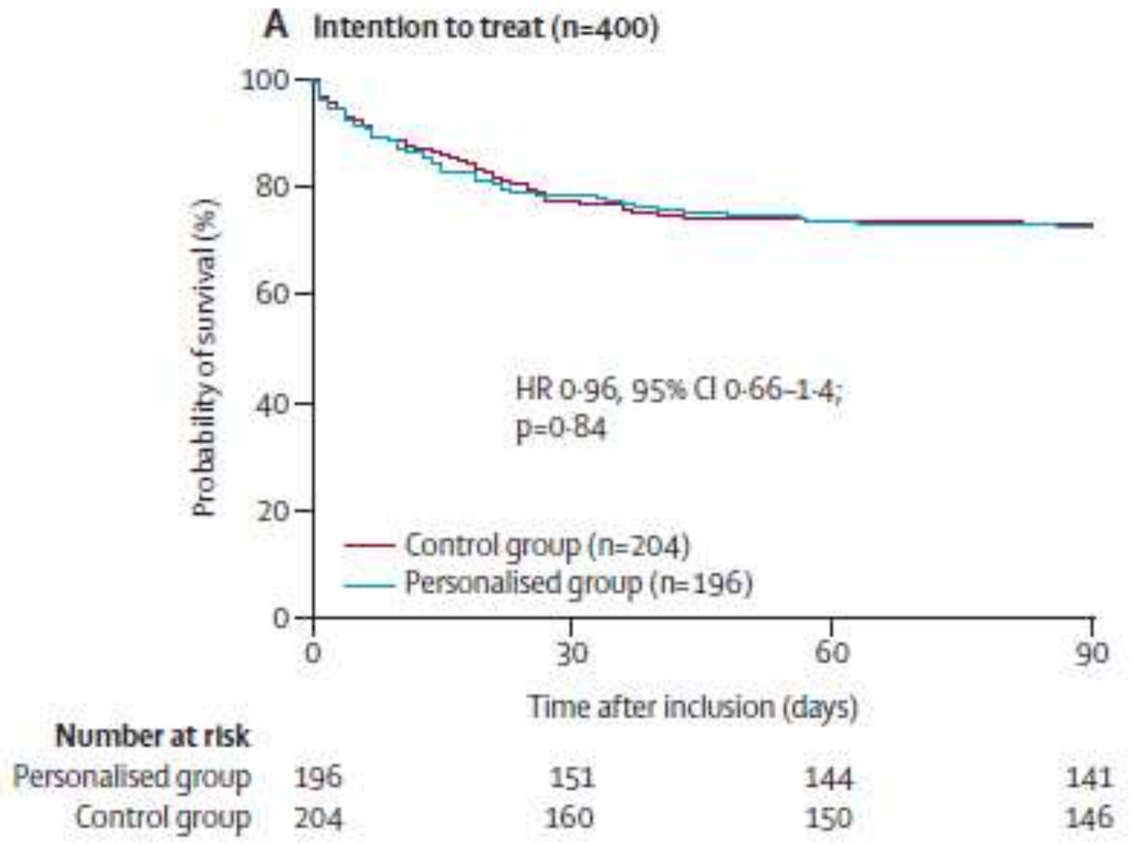
Constatntin et al. Lancet Resp Oct 2019

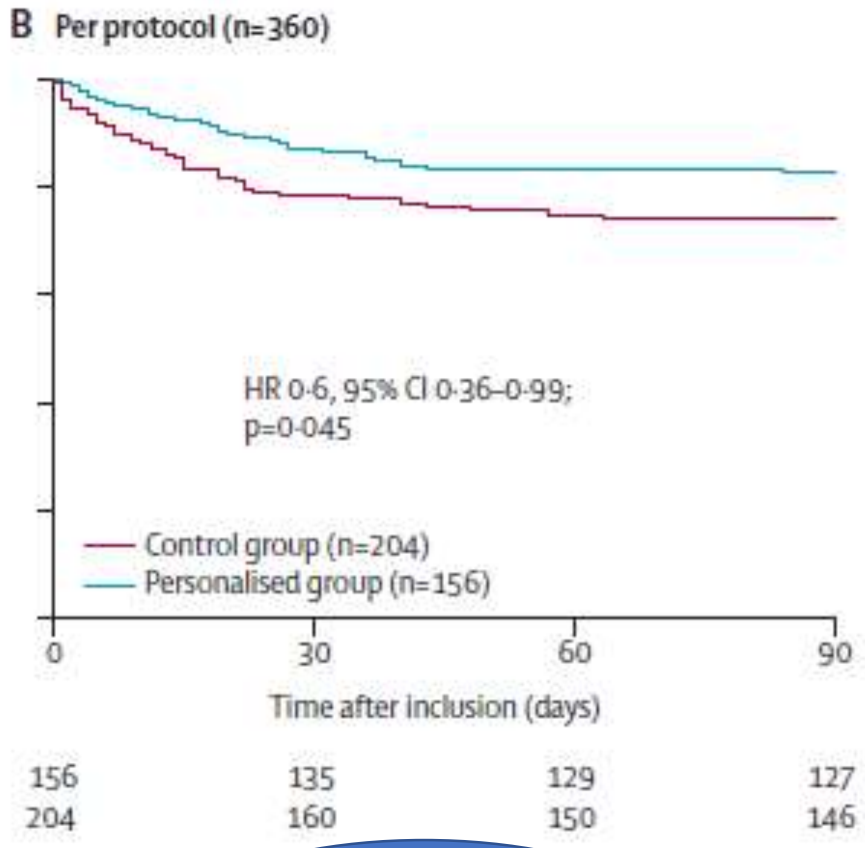
Personalised Ventilation (the LIVE Study)

Study	Population	Intervention	Outcome
Multicentre single blind RCT	N= 420 Mod.-Sev ARDS P/F<200	196 – Personalised Gp Focal- Low PEEP/PPV Diffuse – RM/High PEEP 204 – Control Gp	90 day mortality

Constatntin et al. Lancet Resp Oct 2019

Personalised Ventilation (the LIVE Study) Results



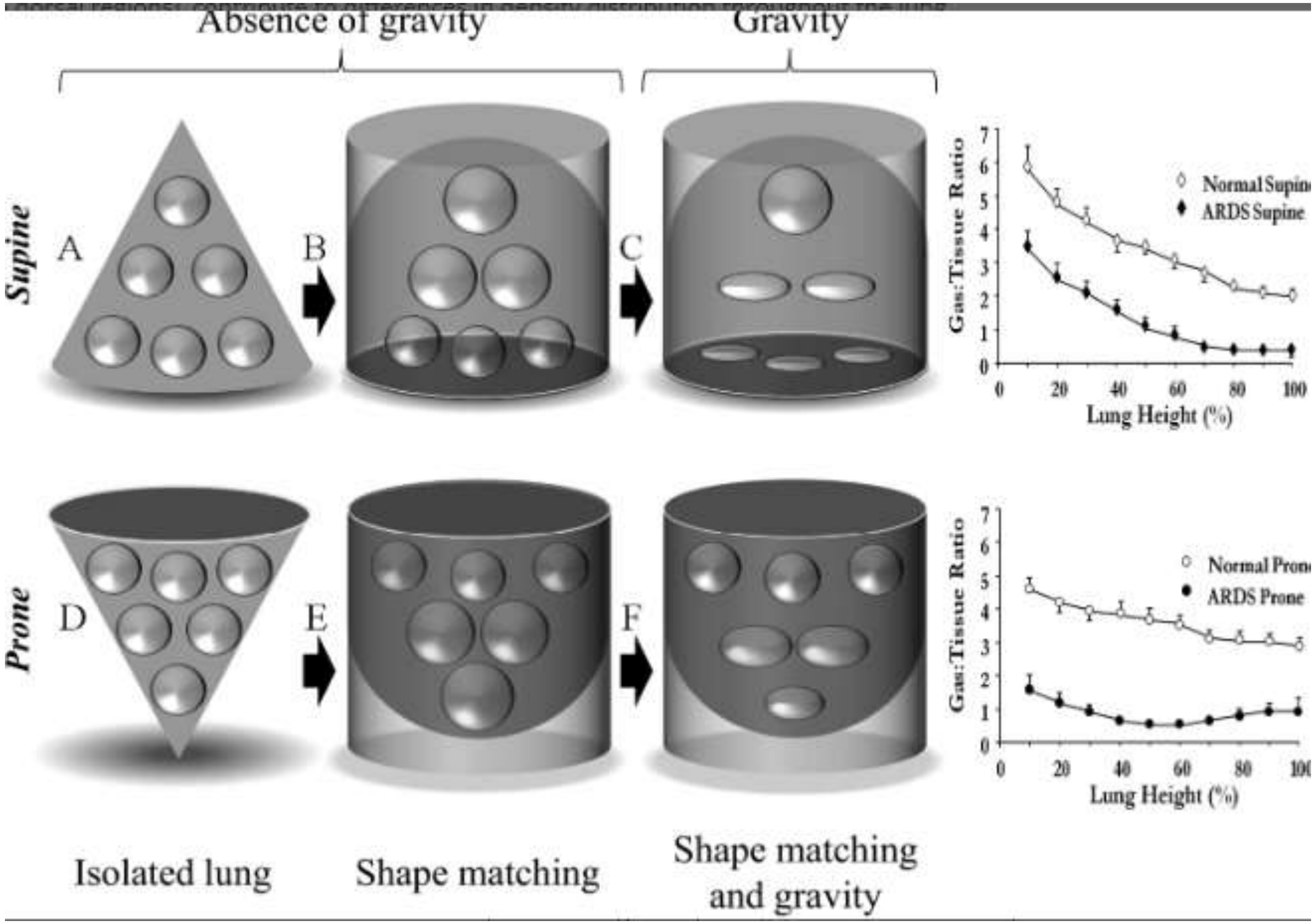


No difference in
90d Mortality

21% patients
misclassified
Per protocol analysis
showing benefit

Constatntin et al. Lancet Resp Oct 2019

Prone Position Ventilation(PPV)



Shape matching and Gravity effect

Improvt. in oxygenation by optimising lung recruitment

Prevention of VILI by homogenously distributing stress and strain

Gattinoni et al. AJRCC 2013

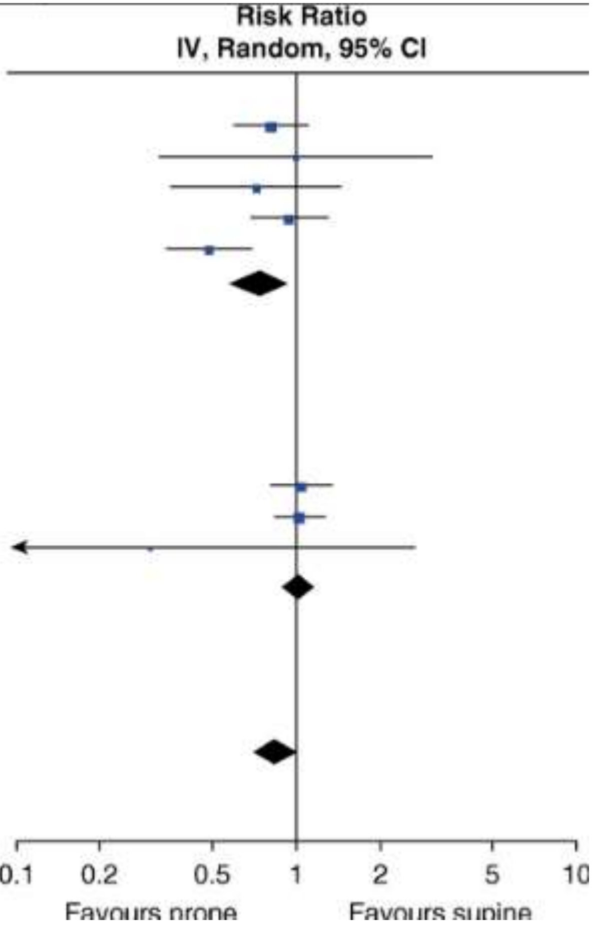
Finally A Positive Trial - PROSEVA

Study	Population	Intervention	Outcome
Multicentre RCT	N=466 P/F<150, FiO2 60%, PEEP>5 MV<36Hr	PPV(atleast 16hr) Vs Supine LTV	28 D Mortality 16% Vs 32.8% ARR – 17% RRR – 51% NNT=6

Guerin et al. 2013 NEJM

Meta analysis – Mortality Benefit with PPV In Mod.-Sev ARDS

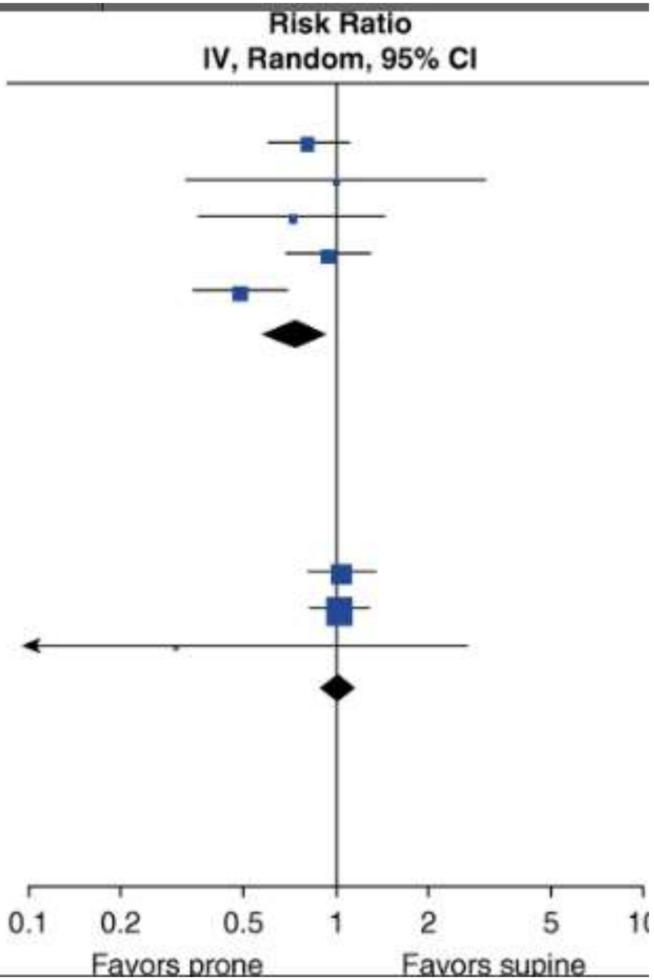
Study or Subgroup	Prone Events	Prone Total	Supine Events	Supine Total	Weight	Risk Ratio IV, Random, 95% CI
Moderate to Severe ARDS						
Mancebo *et al.* 2006	38	76	37	60	17.0%	0.81 [0.60, 1.10]
Chan *et al.* 2007	4	11	4	11	3.2%	1.00 [0.33, 3.02]
Fernandez *et al.* 2008	8	21	10	19	6.9%	0.72 [0.36, 1.45]
Taccone *et al.* 2009	52	168	57	174	16.6%	0.94 [0.69, 1.29]
Guerin *et al.* 2013	38	237	75	229	15.3%	0.49 [0.35, 0.69]
Subtotal (95% CI)		**513**		**493**	**59.1%**	**0.74 [0.56, 0.99]**
Total events	140		183			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.51$, df = 4 (P = 0.07); $I^2 = 53\%$						
Test for overall effect: Z = 2.06 (P = 0.04)						
All ARDS						
Gattinoni *et al.* 2001	70	152	67	152	19.1%	1.04 [0.82, 1.34]
Guerin *et al.* 2004	134	413	119	378	20.9%	1.03 [0.84, 1.26]
Voggenreiter *et al.* 2005	1	21	3	19	0.9%	0.30 [0.03, 2.66]
Subtotal (95% CI)		**586**		**549**	**40.9%**	**1.03 [0.88, 1.20]**
Total events	205		189			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$, df = 2 (P = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**1099**		**1042**	**100.0%**	**0.84 [0.68, 1.04]**
Total events	345		372			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 16.94$, df = 7 (P = 0.02); $I^2 = 59\%$						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: $Chi^2 = 3.93$, df = 1 (P = 0.05), $I^2 = 74.6\%$						



Munshi et al. Ann Of ATS 2017

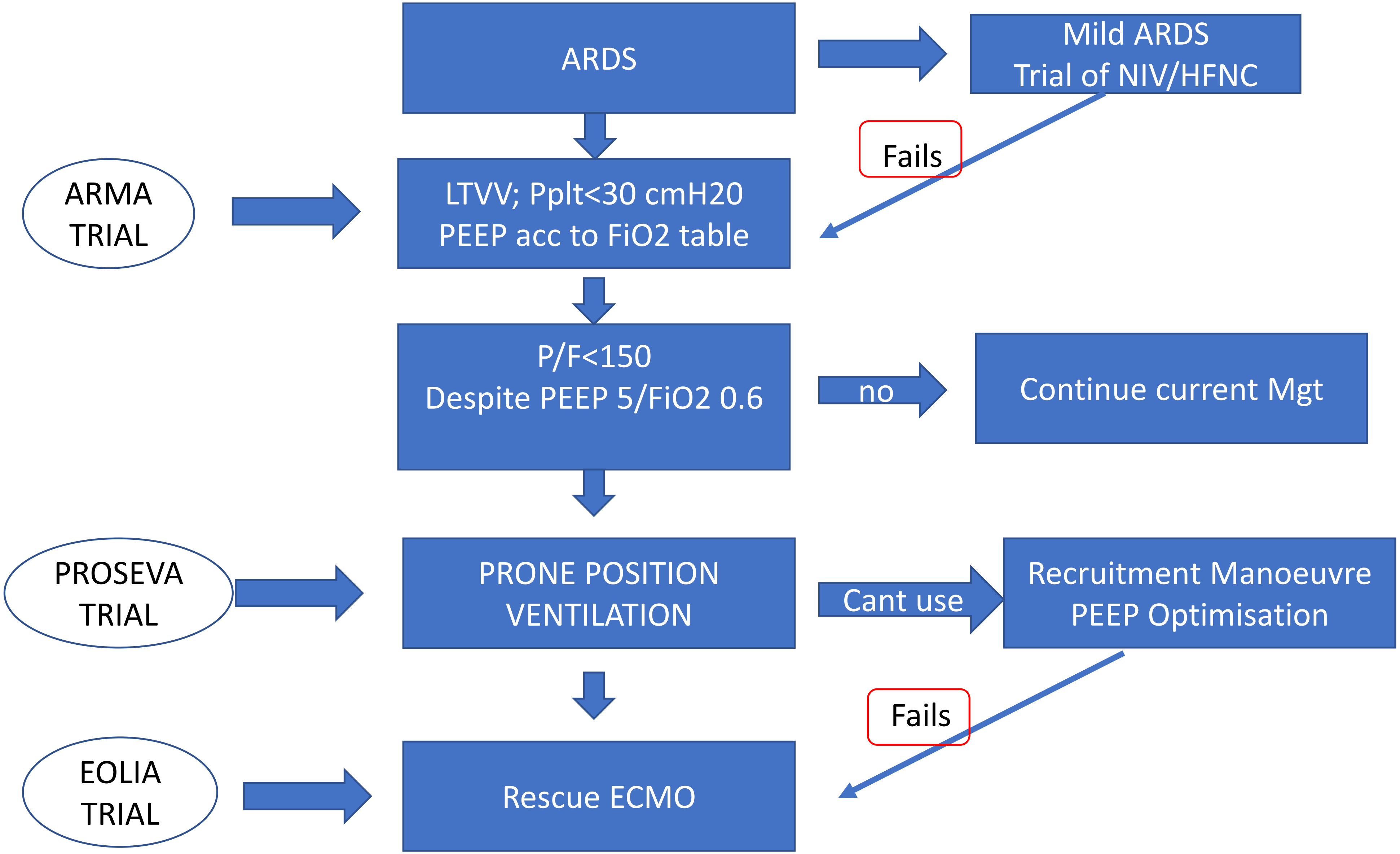
Meta analysis – Mortality Benefit with PPV With Duration >12 Hr

Study or Subgroup	Prone Events	Prone Total	Supine Events	Supine Total	Weight	Risk Ratio IV, Random, 95% CI
≥12h Prone						
Mancebo *et al.* 2006	38	76	37	60	28.5%	0.81 [0.60, 1.10]
Chan *et al.* 2007	4	11	4	11	5.7%	1.00 [0.33, 3.02]
Fernandez *et al.* 2008	8	21	10	19	12.0%	0.72 [0.36, 1.45]
Taccone *et al.* 2009	52	166	57	172	27.9%	0.95 [0.69, 1.29]
Guerin *et al.* 2013	38	237	75	229	25.8%	0.49 [0.35, 0.69]
Subtotal (95% CI)		**511**		**491**	**100.0%**	**0.74 [0.56, 0.99]**
Total events	140		183			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.53$, df = 4 (P = 0.07); $I^2 = 53\%$						
Test for overall effect: Z = 2.06 (P = 0.04)						
<12h Prone						
Gattinoni *et al.* 2001	70	152	67	152	40.0%	1.04 [0.82, 1.34]
Guerin *et al.* 2004	134	413	119	378	59.5%	1.03 [0.84, 1.26]
Voggenreiter *et al.* 2005	1	21	3	19	0.5%	0.30 [0.03, 2.66]
Subtotal (95% CI)		**586**		**549**	**100.0%**	**1.03 [0.88, 1.20]**
Total events	205		189			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$, df = 2 (P = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: $Chi^2 = 3.92$, df = 1 (P = 0.05), $I^2 = 74.5\%$						



Munshi et al. Ann Of ATS 2017

Flow Chart Ventilatory Management



Non-Ventilatory Management

Neuro Muscular Blockade In Severe ARDS

- NMBs aid in ARDS management by promoting ventilator synchrony, reducing WOB and thereby reducing VILI

- Ventilator asynchrony can lead to generation of large tidal volume

- However neuromuscular weakness remains a concern

NMB Trials Conflicting Results

Study/Characteristics	ACURASYS(2010)	ROSE(2019)
Type	Multicentre RCT Double blind N=340 P/F<150; PEEP>5 (AECC) Mean PEEP 9.2 cm H20	Multicentre RCT Open label N=1006 Mod.- Sev ARDS (Berlin) P/F or S/F<150; PEEP>8 Mean PEEP 12.6cm H20
Intervention	Deep sedation + Early NMB(178) v/s Deep sedation (162)	Deep sedation + Early NMB(501) v/s Light sedation alone(505)(RASS 0 to -1)
	ARMA PEEP FiO2 table Proning in ~30%	High PEEP FiO2 table Proning in ~16%
28 d Mortality	23.7% Vs 33.3% (-19.2 to -0.2)	36.7% Vs 37% (-6.3 to 5.7)
90 d Mortality	31.6% Vs 40.7%[(P/F<120) p=0.04]	42.5% Vs 42.8% (p=0.93)
Adverse events ICUAW Serious CV events Pneumothorax	 MRC score similar - 4% Vs 11.7%	 46.8% Vs 27.5%(at D28) 14 vs 4 4% Vs 6.3%

Deep Sedation not current standard of care
ICUAW and CV events are a concern

Reverse Triggering in Deep sedation arm ?

Are NMB Really Useful?

RESEARCH | Open Access

Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials

An Thi Nhat Ho[1*], Setu Patolia[1] and Christophe Guervilly[2,3]

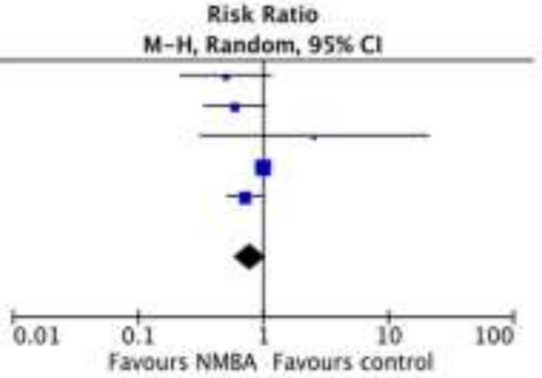
Ho et al. Journal Of Intensive Care 2020

Meta analysis Results – 28d & 90d Mortality

28-day mortality

Study or Subgroup	NBMA Events	NBMA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Forel 2006	5	18	10	18	9.8%	0.50 [0.21, 1.17]
Gainnier 2004	10	28	17	28	17.1%	0.59 [0.33, 1.05]
Guervilly 2017	3	13	1	11	1.9%	2.54 [0.31, 21.06]
Moss 2019	184	501	187	505	41.8%	0.99 [0.84, 1.17]
Papazian 2010	42	177	54	162	29.4%	0.71 [0.51, 1.00]
Total (95% CI)		**737**		**724**	**100.0%**	**0.78 [0.58, 1.06]**
Total events	244		269			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.01$, df = 4 (P = 0.09); $I^2 = 50\%$
Test for overall effect: Z = 1.60 (P = 0.11)

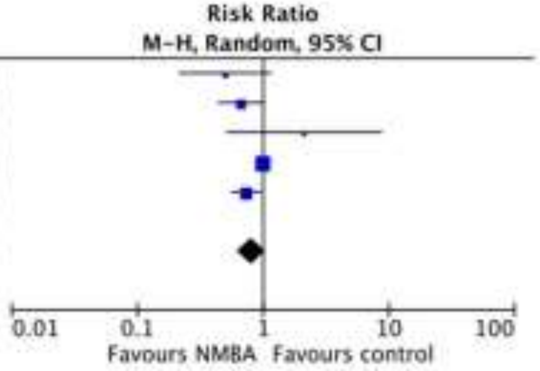


No significant difference in 28d and 90d Mortality

90-day mortality

Study or Subgroup	NBMA Events	NBMA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Forel 2006	5	18	10	18	7.9%	0.50 [0.21, 1.17]
Gainnier 2004	14	28	21	28	20.5%	0.67 [0.43, 1.02]
Guervilly 2017	5	13	2	11	3.2%	2.12 [0.51, 8.84]
Moss 2019	213	501	216	505	38.9%	0.99 [0.86, 1.15]
Papazian 2010	56	177	70	162	29.5%	0.73 [0.55, 0.97]
Total (95% CI)		**737**		**724**	**100.0%**	**0.81 [0.62, 1.06]**
Total events	293		319			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 9.03$, df = 4 (P = 0.06); $I^2 = 56\%$
Test for overall effect: Z = 1.54 (P = 0.12)



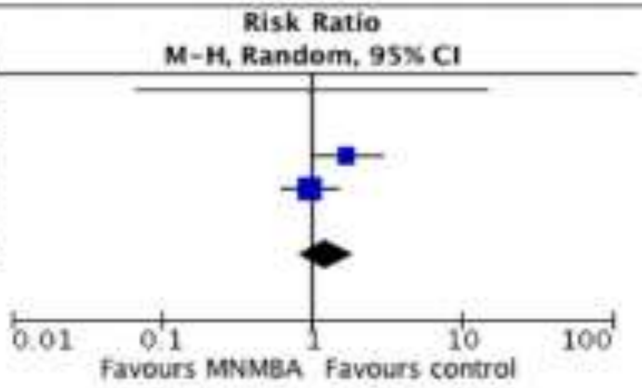
Ho et al. Journal Of Intensive Care 2020

Meta analysis Results – Adverse events

ICU weakness day 28

Study or Subgroup	NMBA Events	NMBA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Forel 2006	1	18	1	18	2.4%	1.00 [0.07, 14.79]
Gainnier 2004	0	28	0	28		Not estimable
Moss 2019	22	47	14	51	42.6%	1.71 [0.99, 2.93]
Papazian 2010	28	89	25	77	55.1%	0.97 [0.62, 1.51]
Total (95% CI)		**182**		**174**	**100.0%**	**1.23 [0.81, 1.88]**
Total events	51		40			

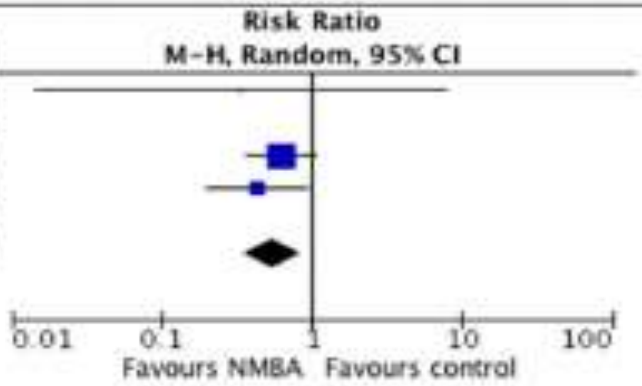
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.53$, df = 2 (P = 0.28); $I^2 = 21\%$
Test for overall effect: Z = 0.98 (P = 0.33)



Barotrauma

Study or Subgroup	NMBA Events	NMBA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gainnier 2004	0	28	1	28	1.9%	0.33 [0.01, 7.85]
Guervilly 2017	0	13	0	11		Not estimable
Moss 2019	20	501	32	505	65.0%	0.63 [0.37, 1.09]
Papazian 2010	9	178	19	162	33.1%	0.43 [0.20, 0.93]
Total (95% CI)		**720**		**706**	**100.0%**	**0.55 [0.35, 0.85]**
Total events	29		52			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 2 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 2.68 (P = 0.007)



Barotrauma events lesser in NMB group

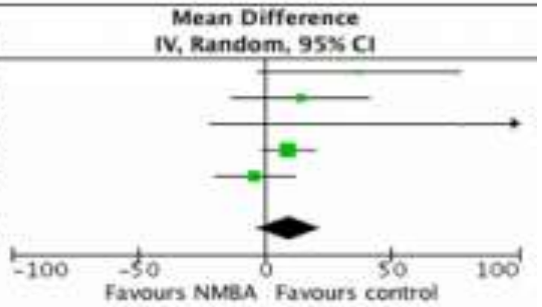
Ho et al. Journal Of Intensive Care 2020

Meta analysis Results – Improvement in P/F ratio

PaO2/FiO2 ratio at 24 hours

Study or Subgroup	NMBA Mean	NMBA SD	NMBA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Forel 2006	183	73	18	146	47	18	8.7%	37.00 [-3.11, 77.11]
Gainnier 2004	159	48	28	145	56	28	16.0%	14.00 [-13.32, 41.32]
Guervilly 2017	218	58	13	140	160	11	1.6%	78.00 [-21.67, 177.67]
Moss 2019	198.4	77.7	436	189.2	76.8	408	42.2%	9.20 [-1.23, 19.63]
Papazian 2010	164	72	172	168	72	159	31.5%	-4.00 [-19.53, 11.53]
Total (95% CI)			**667**			**624**	**100.0%**	**9.33 [-3.48, 22.15]**

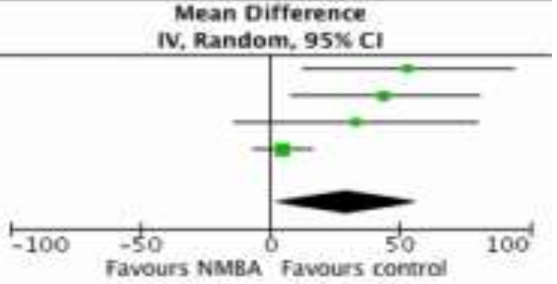
Heterogeneity: $Tau^2 = 72.94$; $Chi^2 = 6.43$, df = 4 (P = 0.17); $I^2 = 38\%$
Test for overall effect: Z = 1.43 (P = 0.15)



PaO2/FiO2 ratio at 48 hours

Study or Subgroup	NMBA Mean	NMBA SD	NMBA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Forel 2006	205	73	18	152	49	18	21.3%	53.00 [12.38, 93.62]
Gainnier 2004	183	88	28	139	42	27	23.5%	44.00 [7.76, 80.24]
Guervilly 2017	191	57	13	158	60	11	18.4%	33.00 [-14.09, 80.09]
Moss 2019	198	73.4	381	193.2	79	348	36.8%	4.80 [-6.30, 15.90]
Total (95% CI)			**440**			**404**	**100.0%**	**29.46 [1.69, 57.24]**

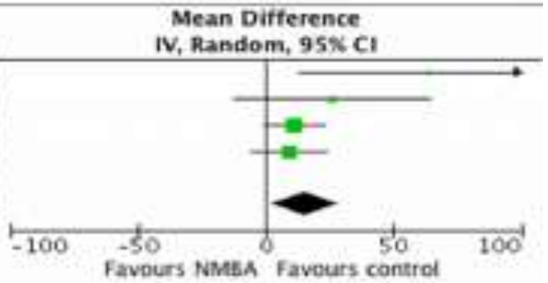
Heterogeneity: $Tau^2 = 513.52$; $Chi^2 = 9.29$, df = 3 (P = 0.03); $I^2 = 68\%$
Test for overall effect: Z = 2.08 (P = 0.04)



PaO2/FiO2 at 72 hours

Study or Subgroup	NMBA Mean	NMBA SD	NMBA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Forel 2006	239	91	18	175	62	18	6.3%	64.00 [13.13, 114.87]
Gainnier 2004	196	78	27	170	65	27	10.4%	26.00 [-12.30, 64.30]
Moss 2019	197.8	74.6	330	186.6	75.6	272	45.8%	11.20 [-0.86, 23.26]
Papazian 2010	166	70	167	157	68	152	37.6%	9.00 [-6.15, 24.15]
Total (95% CI)			**542**			**469**	**100.0%**	**15.21 [1.90, 28.52]**

Heterogeneity: $Tau^2 = 62.84$; $Chi^2 = 4.66$, df = 3 (P = 0.20); $I^2 = 36\%$
Test for overall effect: Z = 2.24 (P = 0.03)



Modest P/F improvement at day 3

Ho et al. Journal Of Intensive Care 2020

NMB infusion not routinely recommended in early Mod-Sev. ARDS

May be used to tackle asynchrony not controlled by sedatives

Role Of Steroids

Role In Early ARDS- DEXA ARDS Study

Study	Population	Intervention	Outcome
MULTICENTRE RCT	N= 277 MOD.-SEV ARDS 17 ICUs across Spain	STANDARD CARE PLUS I/V DEXA V/S STANDARD CARE	VENTILATOR FREE DAYS AT DAY 28 MORTALITY AT DAY 60

Villar et al. Lancet Resp Feb 2020

Results - DEXA ARDS Study

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12·3 (9·9)	7·5 (9·0)	4·8 (2·57 to 7·03)	<0·0001
All-cause mortality at day 60	29 (21%)	50 (36%)	–15·3% (–25·9 to –4·9)	0·0047
ICU mortality	26 (19%)	43 (31%)	–12·5% (–22·4 to –2·3)	0·0166
Hospital mortality	33 (24%)	50 (36%)	–12·5% (–22·9 to –1·7)	0·0235
Actual duration of mechanical ventilation in ICU survivors, days	14·2 (13·2)	19·5 (13·2)	–5·3 (–8·4 to –2·2)	0·0009
Actual duration of mechanical ventilation in survivors at day 60, days	14·3 (13·3)	20·2 (14·0)	–5·9 (–9·1 to –2·7)	0·0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5·2% (–5·2 to 15·6)	0·33
New infections in ICU	33 (24%)	35 (25%)	1·6% (–8·5 to 11·7)	0·75
Barotrauma	14 (10%)	10 (7%)	2·8% (–4·0 to 9·8)	0·41

Data are n (%) or mean (SD). ICU=intensive care unit. *Data included the period from randomisation to day 10 (for hyperglycaemia) and from randomisation to ICU discharge (for new infections and barotrauma).

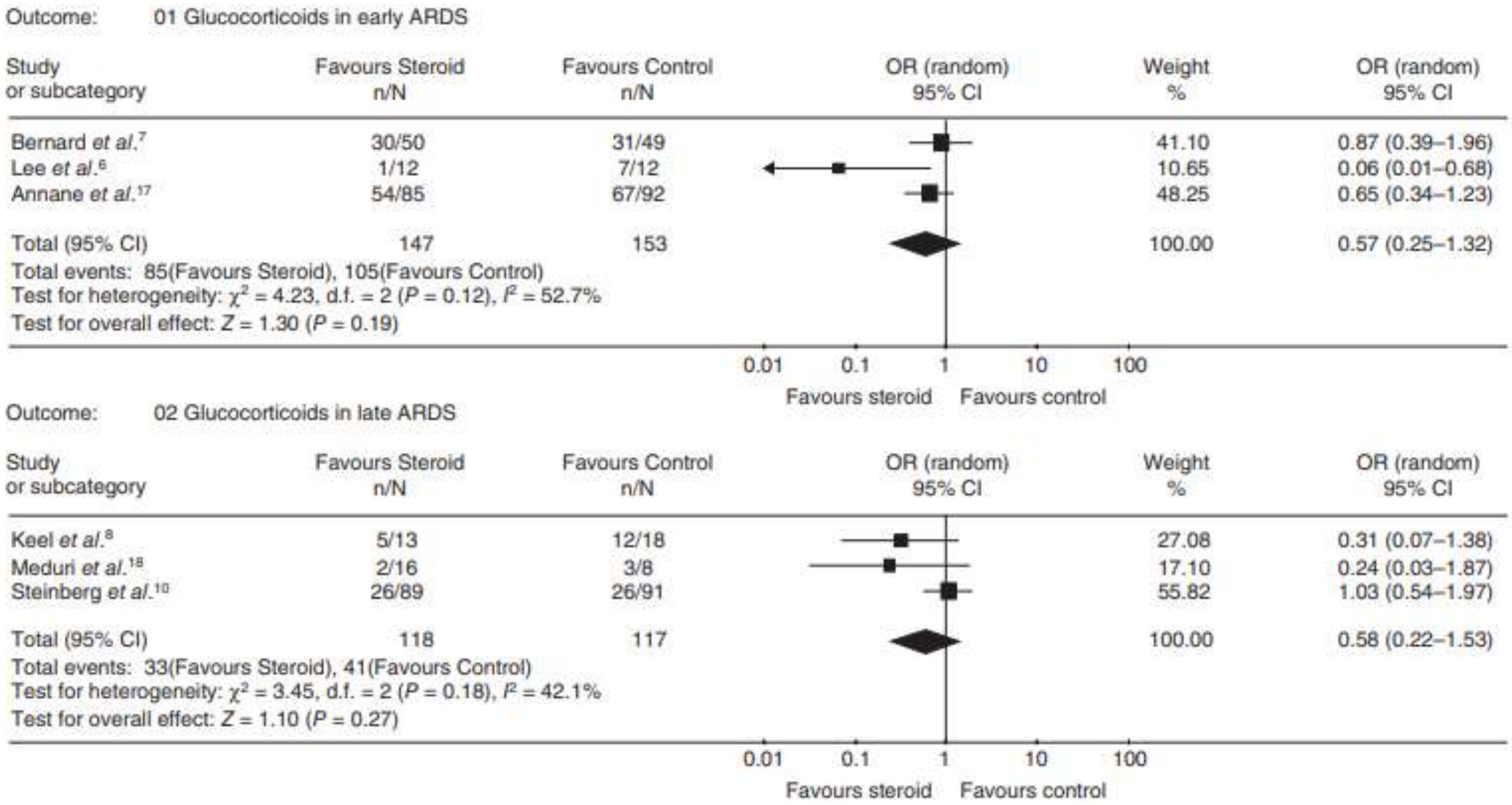
INCREASE IN VENTILATOR FREE DAYS ~ 5 DAYS

REDUCTION IN MORTALITY ~15%
NNT=6

SIMILAR RATES OF ADVERSE EVENTS AND COMPLICATION

Villar et al. Lancet Resp Feb 2020

Steroids in early v/s late ARDS



No difference in outcome of mortality

AGARWAL R. et al. (2007). Respirology, 12(4), 585–590

Late steroid initiation In ARDS (LaSRS)

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
180-Day mortality — %	31.9	31.5	1.0
95% CI	23.2–42.0	22.8–41.7	
No. of ventilator-free days at day 180			0.04
Median	149	159	
Interquartile range	0–167	13–173	
No. of ICU-free days at day 180			0.27
Median	150	152	
Interquartile range	0–164	13–168	
Survivors			0.006
Days of assisted ventilation up to 180 days			
Median	18	11	
Interquartile range	10–33	6–22	
Days of ICU stay up to 180 days			0.29
Median	20	17	
Interquartile range	11–31	10–31	
Days of hospitalization up to 180 days			0.73
Median	29	26	
Interquartile range	19–40	19–43	
Neuromyopathy — no./total no. (%)			0.18
Retrospective review	10/43 (23)	15/44 (34)	
Prospective review	11/48 (23)	11/44 (25)	0.67
Overall	21/91 (22)	26/88 (30)	0.20
180-Day mortality according to time from ARDS onset			
7–13 Days — %	39	27	0.14
No. of patients	66	66	
≥14 Days — %†	12	44	0.01
No. of patients	25	23	
180-Day mortality according to baseline BAL procollagen peptide type III level			
≤ Median — %	13	39	0.04
No. of patients	23	23	
> Median — %‡	24	4	0.05
No. of patients	21	24	

Increase in mortality in subset of patients receiving steroid after 2 weeks

Steinberg et al. NEJM 2006

Fluid Management FACTT Trial

Study	Population	Intervention	Outcome
Multicentre RCT	N=1000 ALI/ARDS Patients not in shock	Conservative strategy(503) CVP<4cm H20 Liberal Strategy(497) CVP 10-14cm H2O	60 d mortality(25.5% v/s 28.4%) p =0.3 Mechanical ventilation duration (10.37 d vs 13.59 d) ICU free days (13.4d vs 11.2d)

Decreased ventilator and ICU days and improved lung function
Diff. in cumulative balance ~7L

Wiedemann et al. NEJM 2006

ECMO In ARDS

- ECMO is an extracorporeal device for cardiorespiratory or respiratory support
- VV-ECMO is commonly used for respiratory support in patient with life threatening respiratory failure

RCT s ECMO In ARDS CESAR TRIAL Vs EOLIA TRIAL

	CESAR Trial	EOLIA Trial
Study	Multicentre RCT	Multicentre RCT
Population	N=180	N=249
Intervention	ECMO(24% DID NOT RECEIVE ECMO) Vs CMV(LTV NOT USED IN ALL PATIENTS)	ECMO Vs CMV(LTV adhered to) Crossover (Rescue ECMO allowed~28%)
Incl Criteria	MV<7d Murray score >3 ; pH<7.2	MV<7d P/F<50(3hr) P/F<80(6hr) pH<7.25(6hr)
Primary Outcome	6 month mortality 47% Vs 63% RR-0.69 (p=0.03)	60 d Mortality 35% Vs 46% RR-0.76(p=0.09) 44% Of patient who received Rescue ECMO survived
Cointerventions	PPV(4 Vs 42%)	PPV~90% NMB~100% used

Even though EOLIA trial failed to show superiority of ECMO

ECMO as a rescue intervention is worth noting from this trial

Meta Analysis ECMO In ARDS – Effect On 30d Mortality

	ECMO		CMV			Weight (%)	Risk ratio (95% CI)
	Events	Total	Events	Total			
Peek et al (2009)[3]	29	90	44	90		21·8%	0·66 (0·46–0·95)
Noah et al (2011)[5]	11	75	31	75		14·4%	0·35 (0·19–0·65)
Pham et al (2013)[6]	26	52	21	52		19·7%	1·24 (0·81–1·90)
Tsai et al (2015)[18]	22	45	34	45		22·7%	0·65 (0·46–0·91)
Combes et al (2018)[10]	32	124	46	125		21·4%	0·70 (0·48–1·02)
Combined	**120**	**386**	**176**	**387**		**100·0%**	**0·69 (0·50–0·95)**

Heterogeneity: τ^2=0·08; χ^2=11·92, df=4, (p=0·02); I^2=66%

Test for overall effect: Z=2·31 (p=0·02)

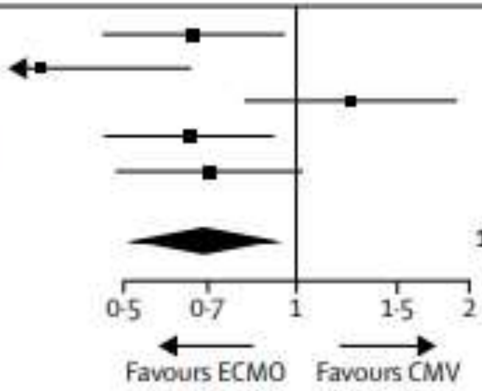


Figure 5: Forest plot of 30-day mortality across all studies of ECMO vs CMV in adults with severe acute respiratory distress syndrome

Munshi et al. Lancet 2019

Meta Analysis ECMO In ARDS – Adverse Events

	Major haemorrhage n/N (%)	Major haemorrhage type	Complications associated with ECMO circuit or cannulation n/N (%)
Peek et al (CESAR),[3] 2009	Not reported	NA	1/90 (1%)
Noah et al,[5] 2011	18/75 (24%)	Eight intracranial haemorrhages, five gastrointestinal or haemoperitoneal haemorrhages, four haemothoraxes, and one fatal pulmonary haemorrhage	1/75 (1%)
Pham et al,[6] 2013	24/52 (46%)	Seven haemothoraxes, seven gastrointestinal or haemoperitoneal haemorrhages, five intracranial haemorrhages, and five cases of haemorrhagic shock	3/52 (6%)
Combes et al (EOLIA),[10] 2018	6/124 (5%)	Three intracranial haemorrhages and three participants received massive transfusions	1/124 (1%)

No control group adverse events were reported in the studies by Peek et al,[3] Noah et al,[5] or Pham et al.[6] Adverse events in the control group of Combes et al[10] are detailed in the text. Tsai et al[16] is not included because adverse events were not reported. ECMO=extracorporeal membrane oxygenation. NA=not applicable.

Table 3: Adverse events across ECMO groups

Munshi et al. Lancet 2019

SUPERNOVA Trial(ECCO2R with ULTV)

Safety And Feasibility Study

Study	Population	Intervention	Outcome
Multicentre Phase 2 study	Mod ARDS N=95	LTVV with NMB, sedatives ECCO2R catheter Vt dec to 4ml/kg PBW PaCo2 b/w 80-120% B/L D/C if pH<7.3 PaCO2>70	82% had acceptable PaCO2 and Ph 73% Survived at D28 6 Serious AE 2 attributed to ECCO2R

Combes A et al. Intensive Care Medicine February 2019

Inhaled Pulmonary Vasodilators Role of Inhaled Nitric Oxide(INO)

Cochrane metanalysis 14 trials n=1275

Outcome	Relative Effect(Control vs INO)
Overall Mortality	RR – 1.04(0.9-1.19)
28 D Mortality	RR- 1.08(0.92-1.27)
P/F improvt at 24 hr	MD- 15.91(8.25-23.56)
Ventilator Free Days upto 30 days	MD- 0.57(-1.82-0.69)
Renal impairment	RR-1.59(1.17-2.16)

No statistically significant effect of INO on mortality or other clinical outcomes except modest improvement on oxygenation

Inhaled prostacycline has shown similar results

Gebistorf et al. Cochrane Systematic Review 2016

Other Supportive Care

- Sedation
- Nutrition
- Glucose control
- Prevention of Nosocomial Infection
- DVT
- Stress ulcer prophylaxis

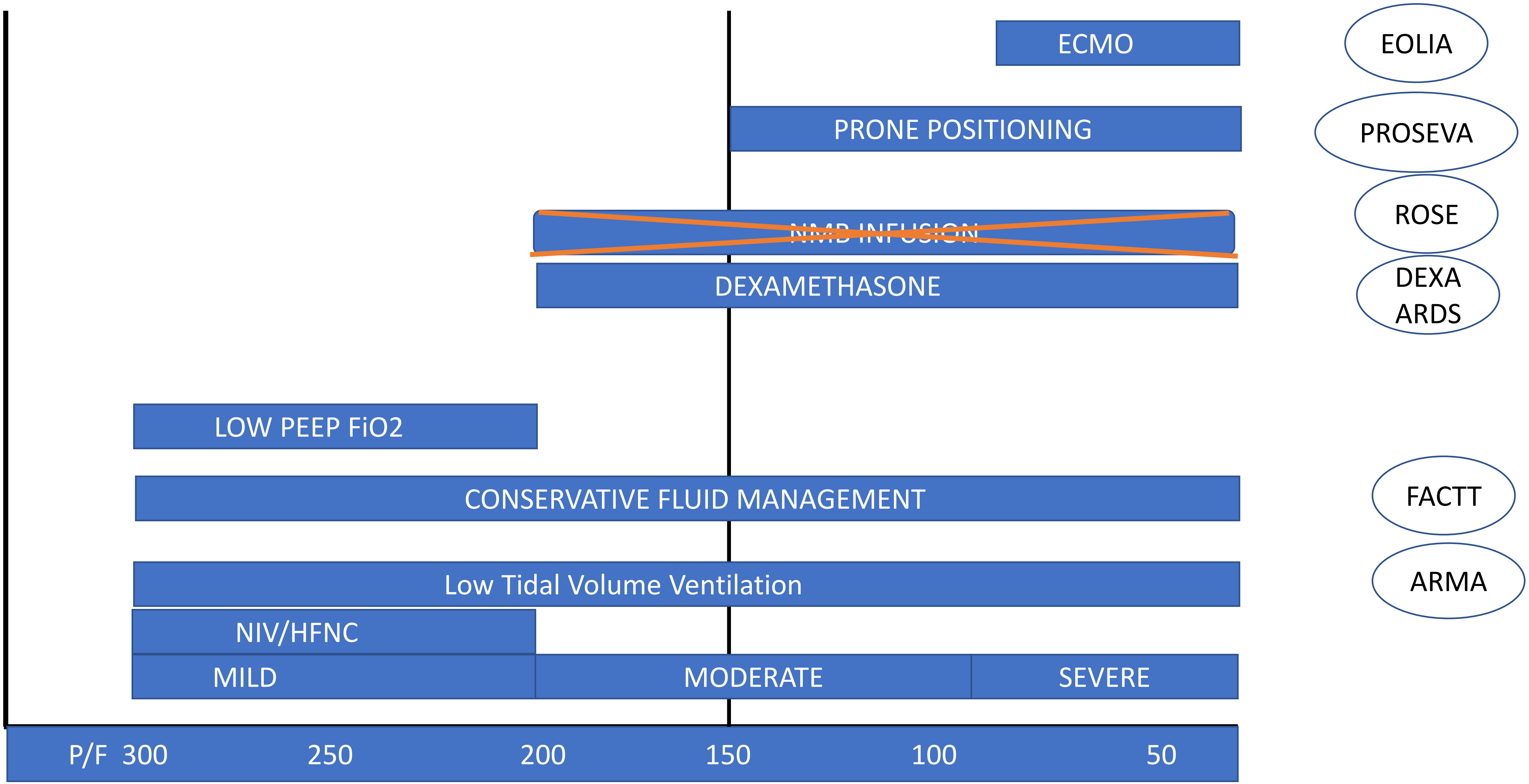
Ineffective Therapies

TRIAL	THERAPY
SAILS	Rosuvastatin
HARP-2	Simvastatin
VIOLET	Vitamin D
CITRIS ALI	Vitamin C
BALTI-1/2	Beta Adrenergic agonist
ISRTCN 98813895	Keratinocyte Growth Factor
LIPS-A	Aspirin

Upcoming Trials

Trial	Intervention
REST(Protective ventilation with veno venous lung assist in respiratory failure)	ECCO2R with ULTV Vs LTV
NCT03608592(Phase 2)	Umbilical cord derived mesenchymal stem cell in ARDS
OPTIPRONE Study	HFNC + PPV

Final Flow Chart



Conclusion

- Number of therapies available for ARDS remain limited
- Identification of ARDS phenotypes has given a ray of hope
- Identification of these phenotypes and directing therapy towards them(precision medicine) is need of the hour