Evolving Pharmacotherapy in ARDS

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Formal guideline in ARDS

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome

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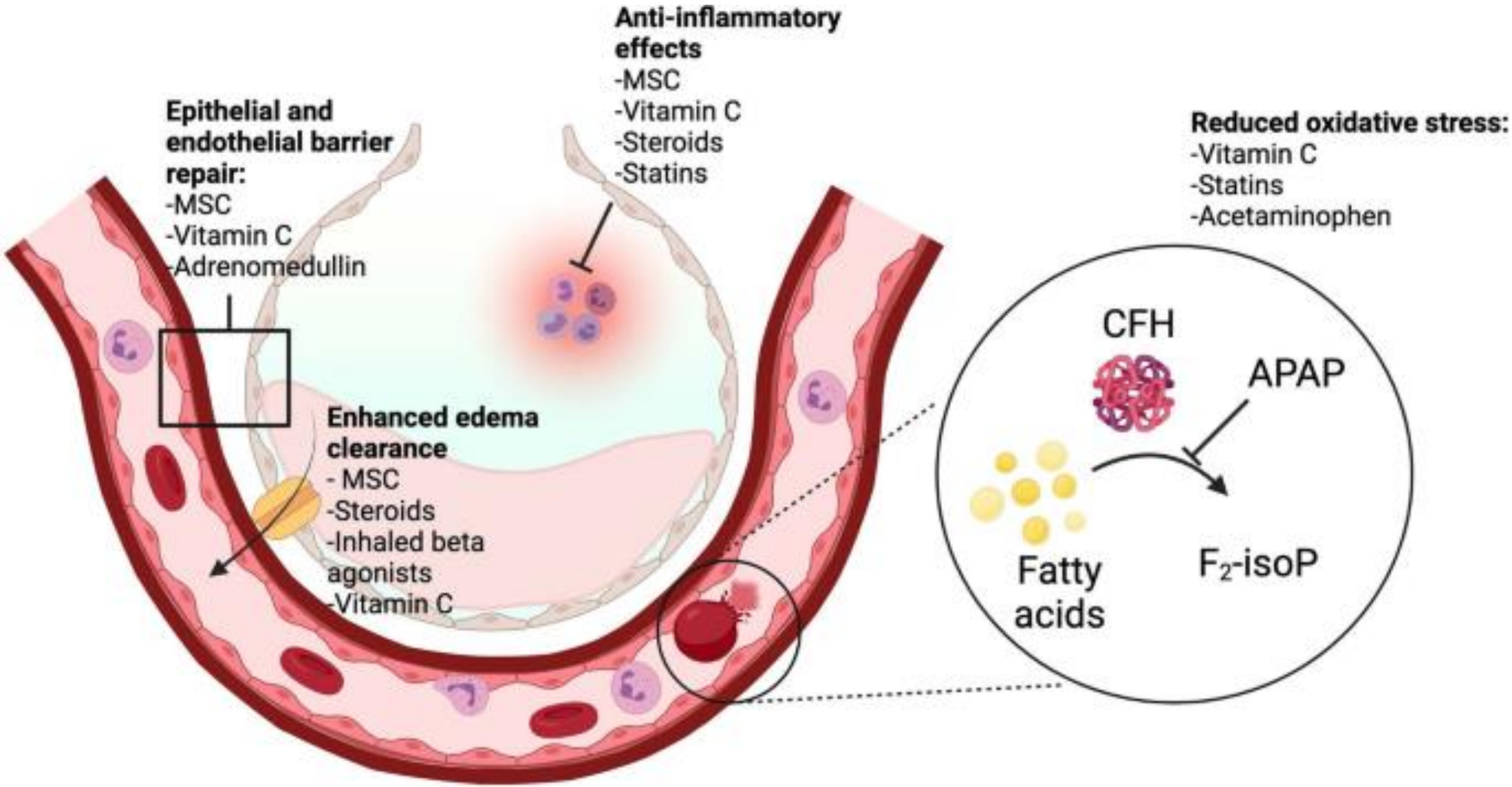
This official clinical practice guideline of the American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Society of Critical Care Medicine (SCCM) was approved by the ATS, ESICM, and SCCM, March 2017

	Potential mechanisms	Key studies	Comments
Activated protein C	Anticoagulant, anti-inflammatory	Liu et al[138]	..
Anti-endotoxin antibodies	Bind endotoxin and thereby reduce inflammatory response	Bigatello et al[139]	..
Aspirin	Anti-inflammatory via antiplatelet effects	Kor et al[140]	Did not reduce ARDS development in patients at high risk
β-agonists	Improved alveolar fluid clearance	Matthay et al,[141] Gao Smith et al[142]	..
Ibuprofen	Anti-inflammatory, via inhibition of cyclooxygenase	Bernard et al[143]	Did not reduce ARDS development in sepsis
Interferon β-1a	Improve pulmonary endothelial barrier function	Ranieri et al[144]	..
Keratinocyte growth factor	Promote epithelial repair	McAuley et al[145]	..
Ketoconazole	Anti-inflammatory	The ARDS Network[146]	..
Lisofylline	Anti-inflammatory	The ARDS Network[147]	..
Neutrophil elastase inhibitor (eg, sivelestat)	Anti-inflammatory	Zeiher et al,[148] Iwata et al[149]	..
Nitric oxide (inhaled)	Pulmonary vasodilatation, improve V/Q mismatch	Gebistorf et al[150]	Improved oxygenation; increased acute kidney injury
Omega-3 fatty acids	Anti-inflammatory	Rice et al[134]	..
Procysteine and N-acetylcysteine	Reduction in oxidant injury via restoring glutathione	Bernard et al[151]	..
Prostaglandin E1	Pulmonary vasodilatation, improve V/Q mismatch	Fuller et al,[152] Vincent et al[153]	..
Statins (eg, simvastatin, rosuvastatin)	Anti-inflammatory; endothelial stabilisation	McAuley et al,[154] Truwit et al[155]	..
Surfactant	Promote epithelial repair, reduce atelectrauma	Spragg et al[156]	Effective in neonatal respiratory distress syndrome

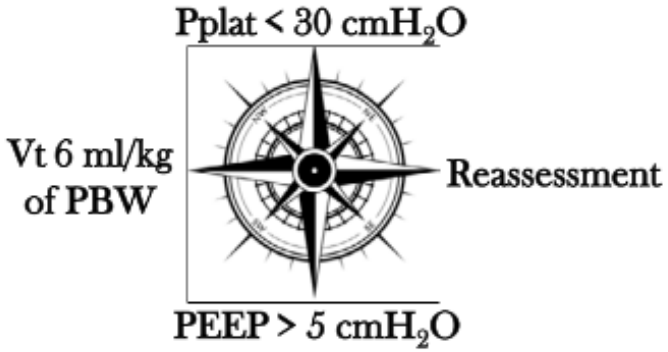
ARDS=acute respiratory distress syndrome. V/Q=ventilation–perfusion.

Table 1: **Selected pharmacotherapies found to be ineffective for ARDS in human clinical trials**


Anti-inflammatory effects
-MSC
-Vitamin C
-Steroids
-Statins
Epithelial and endothelial barrier repair:
-MSC
-Vitamin C
-Adrenomedullin
Enhanced edema clearance
- MSC
-Steroids
-Inhaled beta agonists
-Vitamin C
Reduced oxidative stress:
-Vitamin C
-Statins
-Acetaminophen
CFH
APAP
Fatty acids
F2-isoP

1. Corticosteroid in ARDS

Early management of ARDS in 2019



P/F < 80 — Discuss VV-ECMO

P/F < 150 — Neuromuscular blockers
Prone positioning

P/F < 200 — High level of PEEP if improves oxygenation

Tidal volume about 6 ml/kg of PBW
Plateau pressure < 30 cmH_2O
PEEP > 5 cmH_2O
Check for hypercapnia

Confirmed ARDS

Initiation of invasive mechanical ventilation with sedation in ICU

Tidal volume (Vt) about 6 ml/kg of PBW in the absence of severe metabolic acidosis

Systematic screening for ARDS diagnosis criteria

ARDS severity

Reassessment of ventilator settings and of the management strategy at least every 24h

Veno-venous ECMO
- ❑ In case of refractory hypoxemia or when protective ventilation can not be applied
- ❑ To be discussed with experienced ECMO centres

Neuromuscular blockers: continuous intravenous infusion
- ❑ Early initiation (within the first 48h of ARDS diagnosis)

Prone positioning methods :
- ❑ Applied for >16h a day, for several consecutive days

Moderate or severe ARDS -> High PEEP test (> 12 cmH_2O)
Use high levels if:
- ❑ Oxygenation improvement
- ❑ Without hemodynamic impairment or significant decrease in lung compliance
- ❑ Maintain Pplat < 30 cmH_2O, continuous monitoring

ARDS diagnosis criteria
- ❑ $PaO_2/FiO_2 \leq 300$ mmHg
- ❑ PEEP ≥ 5 cmH_2O
- ❑ Bilateral opacities on chest imaging
- ❑ Not fully explained by cardiac failure or fluid overload
- ❑ Within a week of a known clinical insult

Might be applied
- ➢ Inhaled Nitric Oxide (iNO), when severe hypoxemia remains despite prone positioning and before considering VV-ECMO
- ➢ Partial ventilation support after early phase to generate tidal volume about 6 ml/kg and less than 8 ml/kg

No recommendation could be made
- ➢ $ECCO_2R$
- ➢ Driving pressure
- ➢ Partial ventilation support at the early phase

Should probably not be done
- ➢ Systematic recruitment maneuvers

Should not be done
- ➢ HFOV

Table 4. Use of Adjunctive and Other Optimization Measures in Invasively Ventilated Patients With Acute Respiratory Distress Syndrome[a]

	Patients of No. (%) [95% CI]				
	All (n = 2377)	Mild[a] (n = 498)	Moderate[a] (n = 1150)	Severe[a] (n = 729)	*P* Value[b]
Neuromuscular blockade	516 (21.7) [20.1-23.4]	34 (6.8) [4.8-9.4]	208 (18.1) [15.9-20.4]	274 (37.8) [34.1-41.2]	<.001
Recruitment maneuvers	496 (20.9) [19.2-22.6]	58 (11.7) [9.0-14.8]	200 (17.4) [15.2-19.7]	238 (32.7) [29.3-36.2]	<.001
Prone positioning	187 (7.9) [6.8-9.0]	5 (1.0) [0.3-2.3]	63 (5.5) [4.2-7.0]	119 (16.3) [13.7-19.2]	<.001
ECMO	76 (3.2) [2.5-4.0]	1 (0.2) [0.05-1.2]	27 (2.4) [1.6-3.4]	48 (6.6) [4.9-8.6]	<.001
Inhaled vasodilators	182 (7.7) [6.6-8.8]	17 (3.4) [02.0-5.4]	70 (6.1) [4.8-7.6]	95 (13.0) [10.7-15.7]	<.001
HFOV	28 (1.2) [0.8-1.7]	3 (0.6) [0.1-1.7]	14 (1.2) [0.7-2.0]	11 (1.5) [0.8-2.7]	.347
None of the above	1431 (60.2) [58.2-62.2]	397 (79.7) [75.9-83.2]	750 (65.2) [62.4-68.0]	284 (39.0) [35.4-42.6]	<.001
Esophageal pressure catheter	19 (0.8) [0.04-1.4]	2 (0.4) [0.04-1.4]	8 (0.7) [0.3-1.3]	9 (1.2) [0.6-2.3]	.233
Tracheostomy	309 (13.0) [11.6-14.4]	48 (9.6) [7.1-12.6]	155 (13.5) [11.6-15.6]	106 (14.5) [12.1-17.3]	.034
High-dose corticosteroids[c]	425 (17.9) [16.4-19.5]	61 (12.3) [9.5-15.5]	194 (16.9) [14.7-19.2]	170 (23.3) [20.3-26.6]	<.001
Pulmonary artery catheter	107 (4.5) [3.7-5.4]	9 (1.8) [0.8-3.4]	53 (4.6) [3.4-6.0]	45 (6.2) [4.5-8.2]	.001

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; PEEP, positive end-expiratory pressure.

[a] For this analysis, ARDS severity was defined based on the patients' worst severity category over the course of their ICU stay in patients who developed ARDS on day 1 or 2.

[b] *P* value represents comparisons across the ARDS severity categories for each variable.

[c] High-dose corticosteroids was defined as doses that were equal to or greater than the equivalent of 1 mg/kg of methylprednisolone.

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Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

Table 2. Primary and Secondary Outcomes and Adverse Events Defined A Priori According to the Protocol.*

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
60-Day mortality (%)	28.6	29.2	1.0
95% CI	20.8–38.6	20.8–39.4	
No. of ventilator-free days at day 28	6.8±8.5	11.2±9.4	<0.001
60-Day mortality according to time from ARDS onset			
7–13 Days (%)	36	27	0.26
No. of patients	66	66	
>14 Days (%)†	8	35	0.02

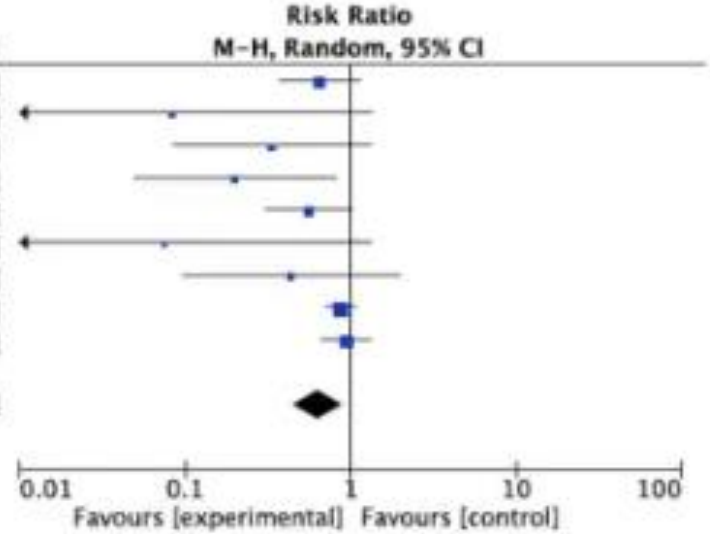
SCCM/ESICM Meta-Analysis of ARDS studies

Mortality

Study or Subgroup	Steroid Events	Steroid Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2006	15	66	23	66	16.8%	0.65 [0.37, 1.13]
Confalonieri 2005	0	15	7	19	1.3%	0.08 [0.01, 1.35]
Liu 2012	2	12	7	14	4.9%	0.33 [0.08, 1.31]
Meduri 1998	2	16	5	8	4.7%	0.20 [0.05, 0.81]
Meduri 2007	15	63	12	28	15.1%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	1.3%	0.08 [0.00, 1.32]
Sabry 2011	2	26	6	34	4.1%	0.44 [0.10, 1.99]
Steinburg 2006	54	85	67	92	28.3%	0.87 [0.71, 1.07]
Tongyoo 2015	37	98	40	99	23.4%	0.93 [0.66, 1.32]
Total (95% CI)		**399**		**369**	**100.0%**	**0.64 [0.46, 0.89]**
Total events	127		170			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 16.04$, df = 8 (P = 0.04); $I^2 = 50\%$

Test for overall effect: Z = 2.64 (P = 0.008)

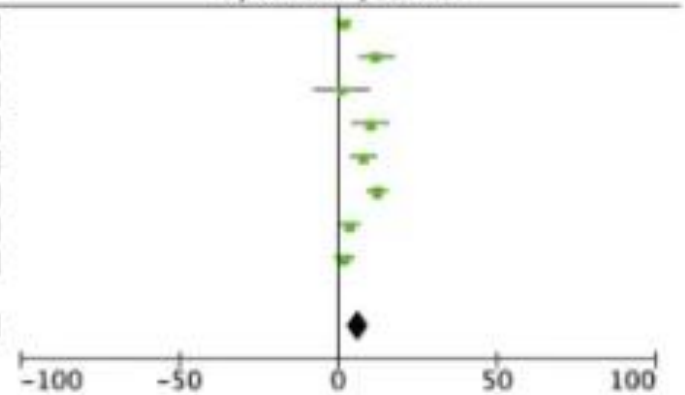


Ventilator free days at day 28

Study or Subgroup	Steroid Mean	Steroid SD	Steroid Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Annane 2006	4.9	8.4	85	3.1	6.9	92	14.8%	1.80 [-0.48, 4.08]
Confalonieri 2005	22	6.2	15	10.1	10.2	19	11.2%	11.90 [6.34, 17.46]
Liu 2012	13.9	11.3	12	12.8	11.3	14	7.8%	1.10 [-7.61, 9.81]
Meduri 1998	14	7	14	4	6.2	8	11.1%	10.00 [4.35, 15.65]
Meduri 2007	15.9	9.6	63	7.9	9.5	28	12.8%	8.00 [3.76, 12.24]
Rezk 2013	17.4	2.9	18	5.1	4.1	9	14.2%	12.30 [9.31, 15.29]
Steinburg 2006	10.3	9.7	67	6.7	8.6	66	14.0%	3.60 [0.49, 6.71]
Tongyoo 2015	14.4	10.6	98	12.3	10.9	99	14.1%	2.10 [-0.90, 5.10]
Total (95% CI)			**372**			**335**	**100.0%**	**6.36 [2.94, 9.77]**

Heterogeneity: $Tau^2 = 19.16$; $Chi^2 = 46.11$, df = 7 (P < 0.00001); $I^2 = 85\%$

Test for overall effect: Z = 3.64 (P = 0.0003)



Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Acute Respiratory Distress Syndrome

Should corticosteroids be administered among hospitalized adult patients with acute respiratory distress syndrome?

Recommendation: We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO_2/FiO_2 of < 200 and within 14 days of onset) (conditional recommendation, moderate quality of evidence).

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

*Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luis A Conesa, Carmen Martín-Rodríguez, Francisco J Díaz-Domínguez, Pablo Serna-Grande, Rosana Rivas, José Ferreres, Javier Belda, Lucía Capilla, Alec Tallet, José M Añón, Rosa L Fernández, Jesús M González-Martín for the dexamethasone in ARDS network**

	Dexamethasone group (n=139)	Control group (n=138)
Age, years	56 (14)	58 (15)
Sex		
Female	43 (31%)	43 (31%)
Male	96 (69%)	95 (69%)
Sequential Organ Failure Assessment score*	8·7 (3·1)	8·6 (3·2)
Time from intubation to randomisation, days	2·1 (2·6)	2·1 (2·6)
Time from ARDS diagnosis to randomisation, days	1·0 (0·1)	1·0 (0·2)
Cause of ARDS		
Pneumonia	75 (54%)	72 (52%)
Sepsis	33 (24%)	34 (25%)
Aspiration	18 (13%)	15 (11%)
Trauma	11 (8%)	10 (7%)
Others	2 (1%)	7 (5%)
Degree of lung severity, number of patients		
Moderate (100 <PaO_2/FiO_2 ≤200)	118	121
Severe (PaO_2/FiO_2 ≤100)	21	17
PaO_2/FiO_2, mm Hg	142·4 (37·3)	143·5 (33·4)

DEXA-ARDS trial – Multicenter RCT in Spain

	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).

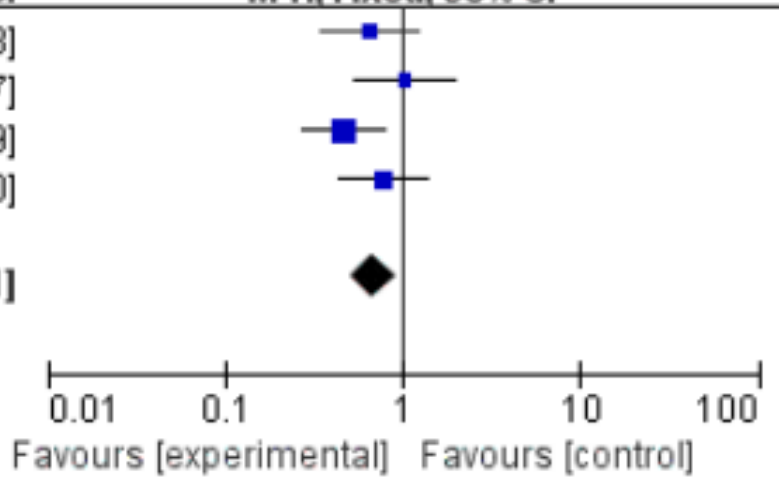
Table 2: **Outcomes, adverse events, and complications**

2022 Korean ARDS guideline

2) 60-day Mortality

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annane 2006	54	85	67	92	21.9%	0.65 [0.34, 1.23]
ARDSnet 2006	26	89	26	91	17.0%	1.03 [0.54, 1.97]
Jesus Villar 2020	29	139	50	138	37.0%	0.46 [0.27, 0.79]
Meduri 2016	34	98	40	99	24.2%	0.78 [0.44, 1.40]
Total (95% CI)		**411**		**420**	**100.0%**	**0.68 [0.50, 0.91]**
Total events	143		183			

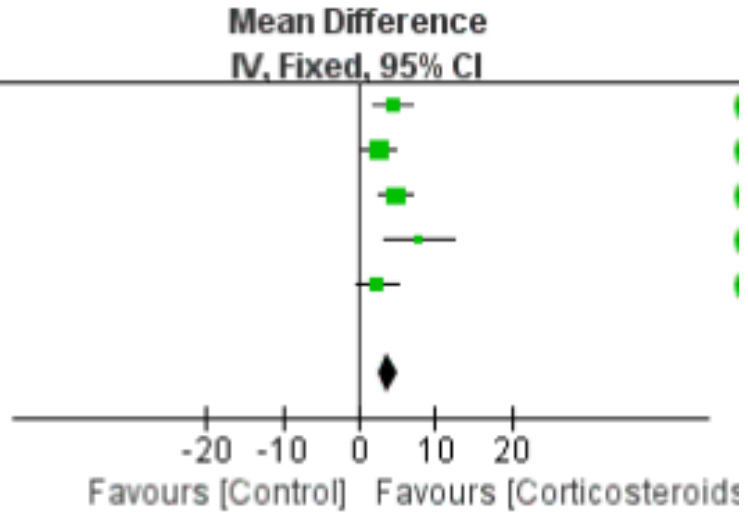
Heterogeneity: Chi² = 3.81, df = 3 (P = 0.28); I² = 21%
Test for overall effect: Z = 2.58 (P = 0.010)

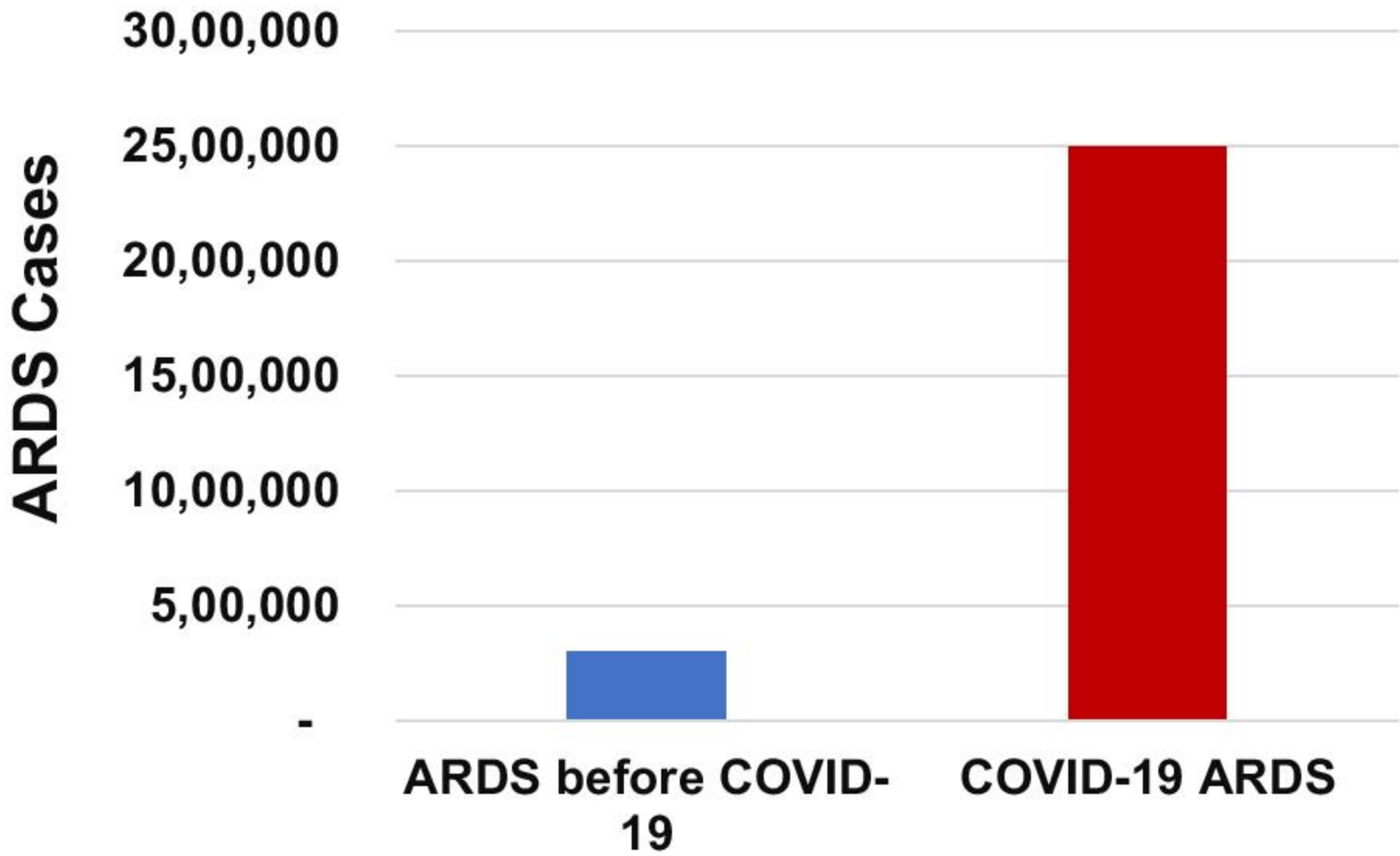


3) 28-day Ventilator-free days

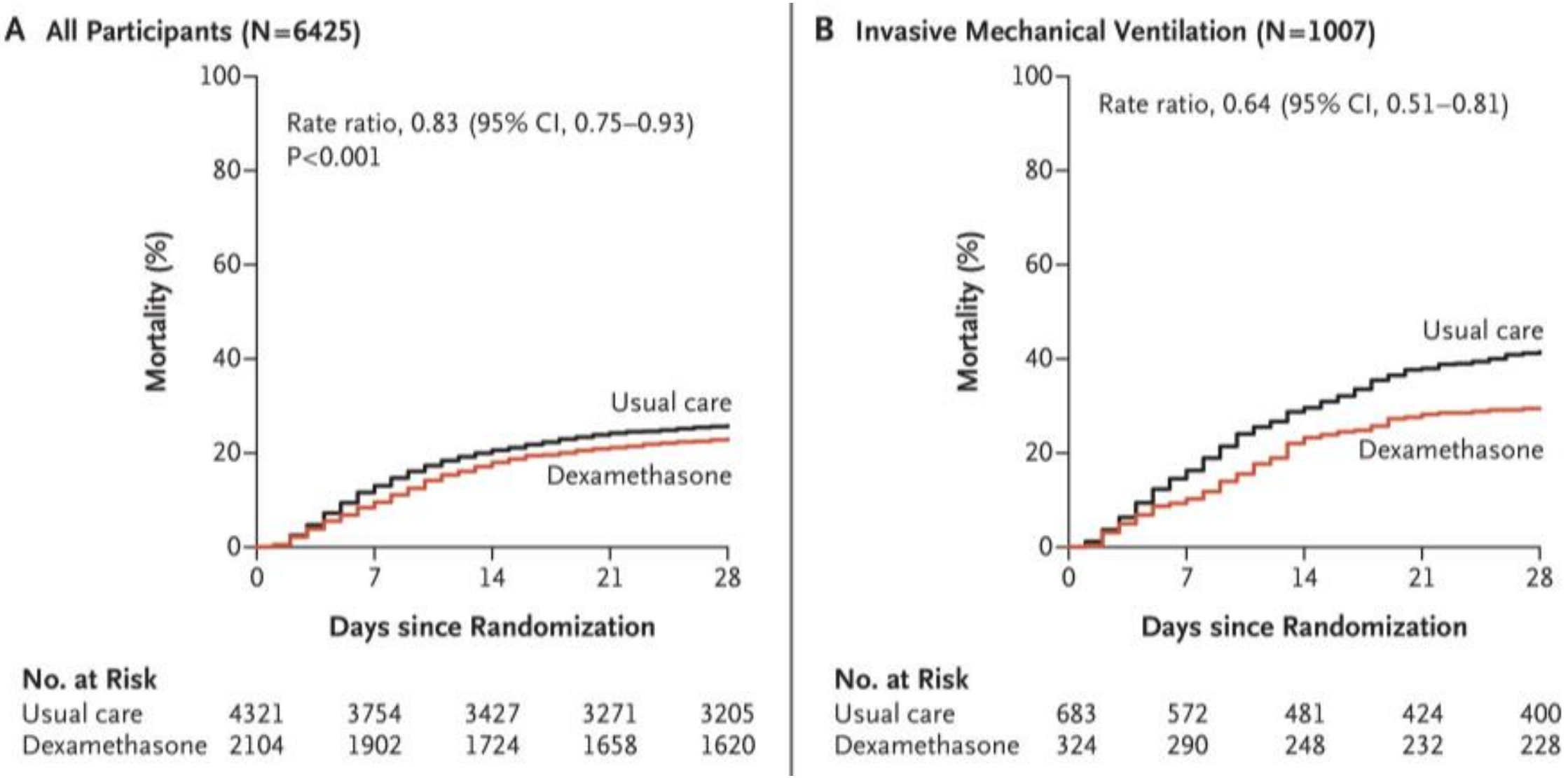
Study or Subgroup	Corticosteroids Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
ARDSnet 2006	11.2	9.4	89	6.8	8.5	91	19.3%	4.40 [1.78, 7.02]
Bruno 2020	6.6	9.9504	151	4	8.6183	148	29.9%	2.60 [0.49, 4.71]
Jesus Villar 2020	12.3	9.9	139	7.5	9	138	26.8%	4.80 [2.57, 7.03]
Meduri 2007	16.5	10.1	63	8.7	10.2	28	6.5%	7.80 [3.27, 12.33]
Meduri 2016	12	9.7	98	9.7	10	99	17.5%	2.30 [-0.45, 5.05]
Total (95% CI)			**540**			**504**	**100.0%**	**3.82 [2.67, 4.97]**

Heterogeneity: Chi² = 6.36, df = 4 (P = 0.17); I² = 37%
Test for overall effect: Z = 6.50 (P < 0.00001)

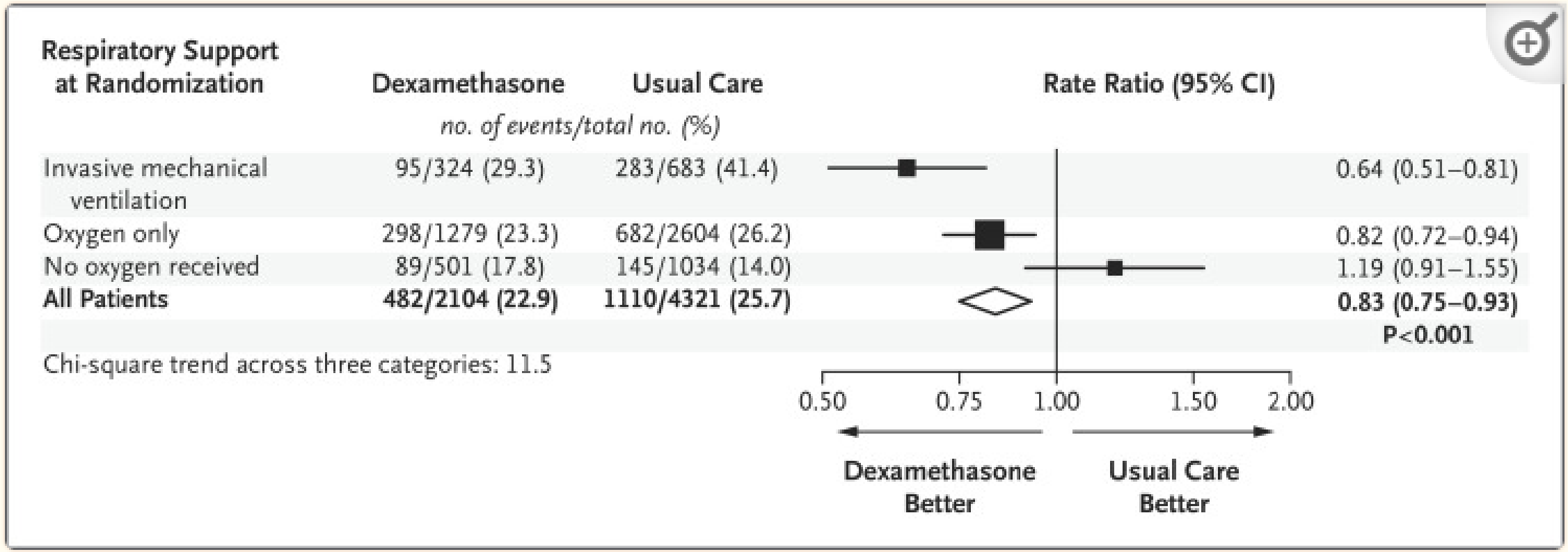



ARDS Cases
30,00,000
25,00,000
20,00,000
15,00,000
10,00,000
5,00,000
-
ARDS before COVID-19
COVID-19 ARDS

Steroid in covid-19 (RECOVERY trial)



Steroid in covid-19 (RECOVERY trial)



Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

Figure 3

Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Steroid in covid-19 (RECOVERY trial)

Figure S1: Effect of allocation to dexamethasone on 28−day mortality by other pre−specified baseline characteristics

Characteristic	Dexamethasone	Usual care	RR (95% CI)	Het./ trend
Age				
<70	129/1141 (11.3%)	429/2505 (17.1%)	0.64 (0.53−0.78)	χ^2_1=5.2
≥70 <80	155/469 (33.0%)	271/859 (31.5%)	1.03 (0.84−1.25)	
≥80	198/494 (40.1%)	410/957 (42.8%)	0.89 (0.75−1.05)	
Sex				
Men	331/1338 (24.7%)	782/2749 (28.4%)	0.80 (0.71−0.91)	χ^2_1=0.9
Women	151/766 (19.7%)	328/1572 (20.9%)	0.90 (0.74−1.09)	
Race				
White	401/1550 (25.9%)	849/3139 (27.0%)	0.90 (0.80−1.02)	χ^2_1=2.3
Black, Asian, or minority ethnic group	52/364 (14.3%)	160/783 (20.4%)	0.70 (0.51−0.95)	
Unknown	29/190 (15.3%)	101/399 (25.3%)	0.49 (0.33−0.74)	
Days since symptom onset				
≤7	269/916 (29.4%)	500/1801 (27.8%)	1.01 (0.87−1.17)	χ^2_1=12.4
>7	212/1184 (17.9%)	604/2507 (24.1%)	0.69 (0.59−0.80)	

Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19

The CoDEX Randomized Clinical Trial

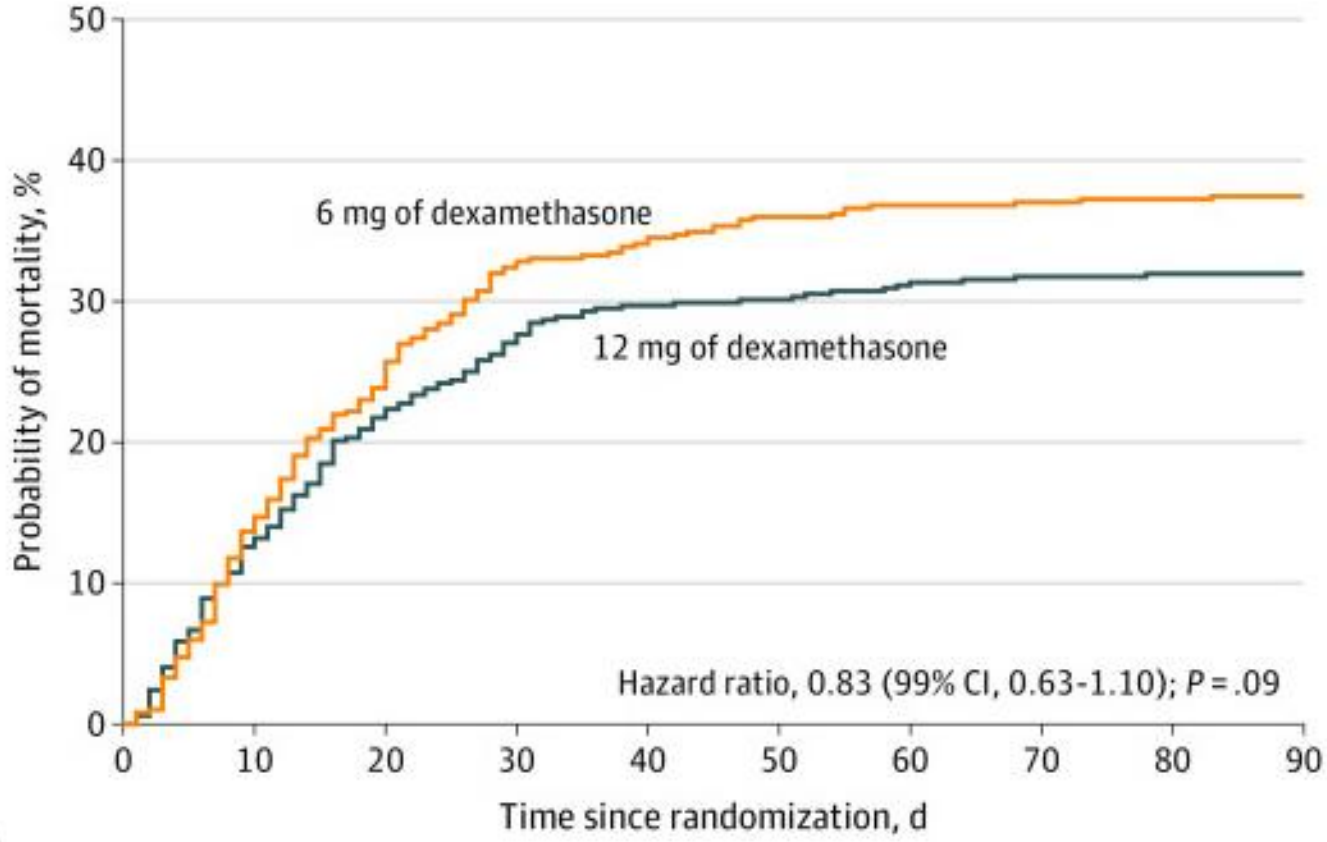
Table 2. Study Outcomes

Outcomes	Mean (95% CI)		Effect statistic	Between-group effect			
				Adjusted[a]		Unadjusted	
	Dexamethasone (n = 151)	Standard care (n = 148)		Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Primary outcome							
Days alive and ventilator free at 28 d							
Mean (95% CI)	6.6 (5.0 to 8.2)	4.0 (2.9 to 5.4)	MD	2.26 (0.2 to 4.38)[b]	.04	2.55 (0.46 to 4.6)	.02
Median (IQR)	0 (0 to 17)	0 (0 to 3)					
Secondary outcomes							
6-Point ordinal scale at day 15, median (IQR)[c]	5 (3 to 6)	5 (5 to 6)	OR	0.66 (0.43 to 1.03)	.07	0.62 (0.41 to 0.94)	.03
28-Day results							
All-cause mortality No. (%)	85 (56.3)	91 (61.5)	HR	0.97 (0.72 to 1.31)	.85	0.86 (0.64 to 1.15)	.31

Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia

The COVID STEROID 2 Randomized Trial

B Time to death curves censored at 90 d



No. at risk

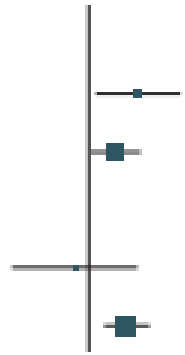
12 mg of dexamethasone	497	430	384	357	344	342	337	334	333	333
6 mg of dexamethasone	485	416	365	322	314	305	301	300	299	298

Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia

The COVID STEROID 2 Randomized Trial

Figure 3. Median Days Alive Without Life Support and the Adjusted Mean Differences in the 7 Predefined Subgroups

Subgroup	Days alive without life support by dexamethasone dose, median (IQR)		Adjusted mean difference (95% CI)[a]
	12 mg	6 mg	
Required invasive mechanical ventilation			
Yes	9.0 (0 to 21.0) (n = 99)	2.5 (0 to 15.0) (n = 107)	2.4 (-0.2 to 5.0)
No	28.0 (9.0 to 28.0) (n = 386)	28.0 (6.0 to 28.0) (n = 390)	1.1 (-0.5 to 2.6)
Prior use of IL-6 receptor antagonists			
Yes	27.0 (9.5 to 28.0) (n = 47)	28.0 (24.0 to 28.0) (n = 52)	-1.4 (-5.3 to 2.4)
No	22.0 (5.0 to 28.0) (n = 438)	18.0 (4.0 to 28.0) (n = 445)	1.7 (0.3 to 3.1)



Dexa 20mg vs 6mg in trial

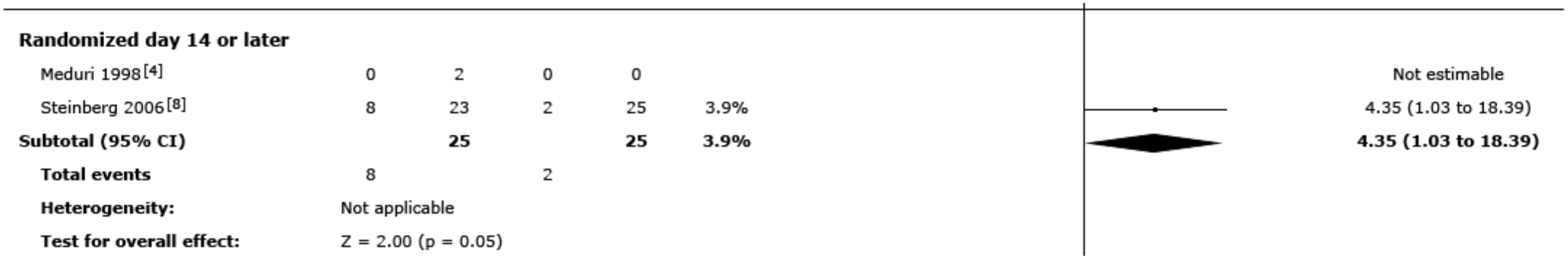
Effect of Two Different Doses of Dexamethasone in Patients With ARDS and COVID-19

Brno University Hospital
First Published (first received 2020 December 11) | ↗ ClinicalTrials.gov (https://clinicaltrials.gov/show/NCT04663555)
Trial registry record
No Results

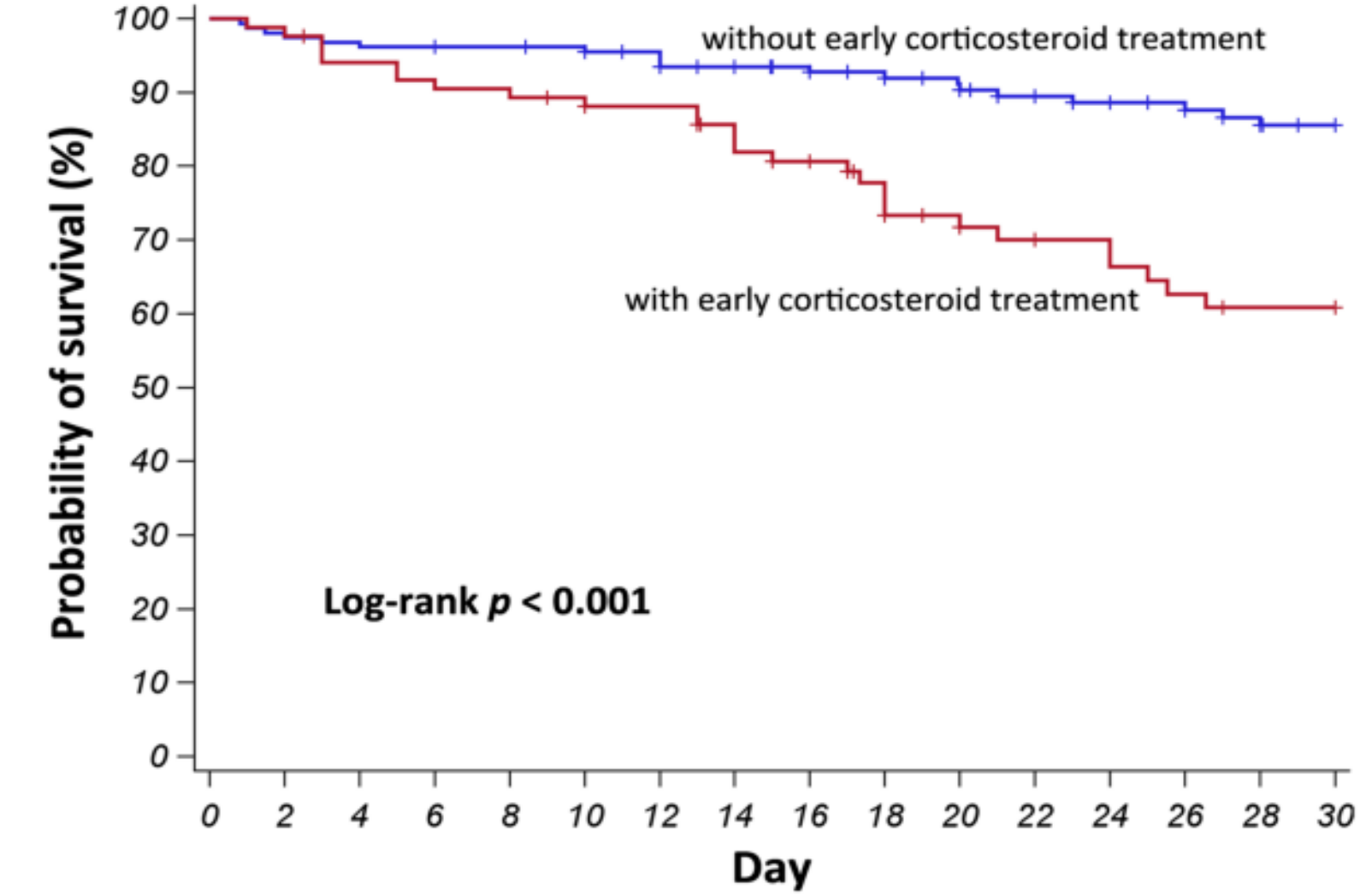
Prospective, multi-centre, randomized (1:1), parallel group, open-label, study comparing superiority of dexamethasone 20 mg vs. 6 mg. This is an open label study, in which all the participants involved, e.g. health-care persons and patients in the study, will learn about the intervention. Blinded preplanned statistical analysis will be performed. REMED is a pragmatic, multi-centre trial conducted in intensive care units (ICUs) of university academic hospitals in Czech Republic

Risk of steroid

- Serious adverse events of **neuromyopathy** were reported in nine patients, all in the MPD group (P=0.001). – NEJM 2006
- **Immunosuppression** - infection
- increased duration of **viral shedding** – worse outcome in flu
- **Late phase** (after 14 days) – may harmful



Risk of steroid – influenza ARDS

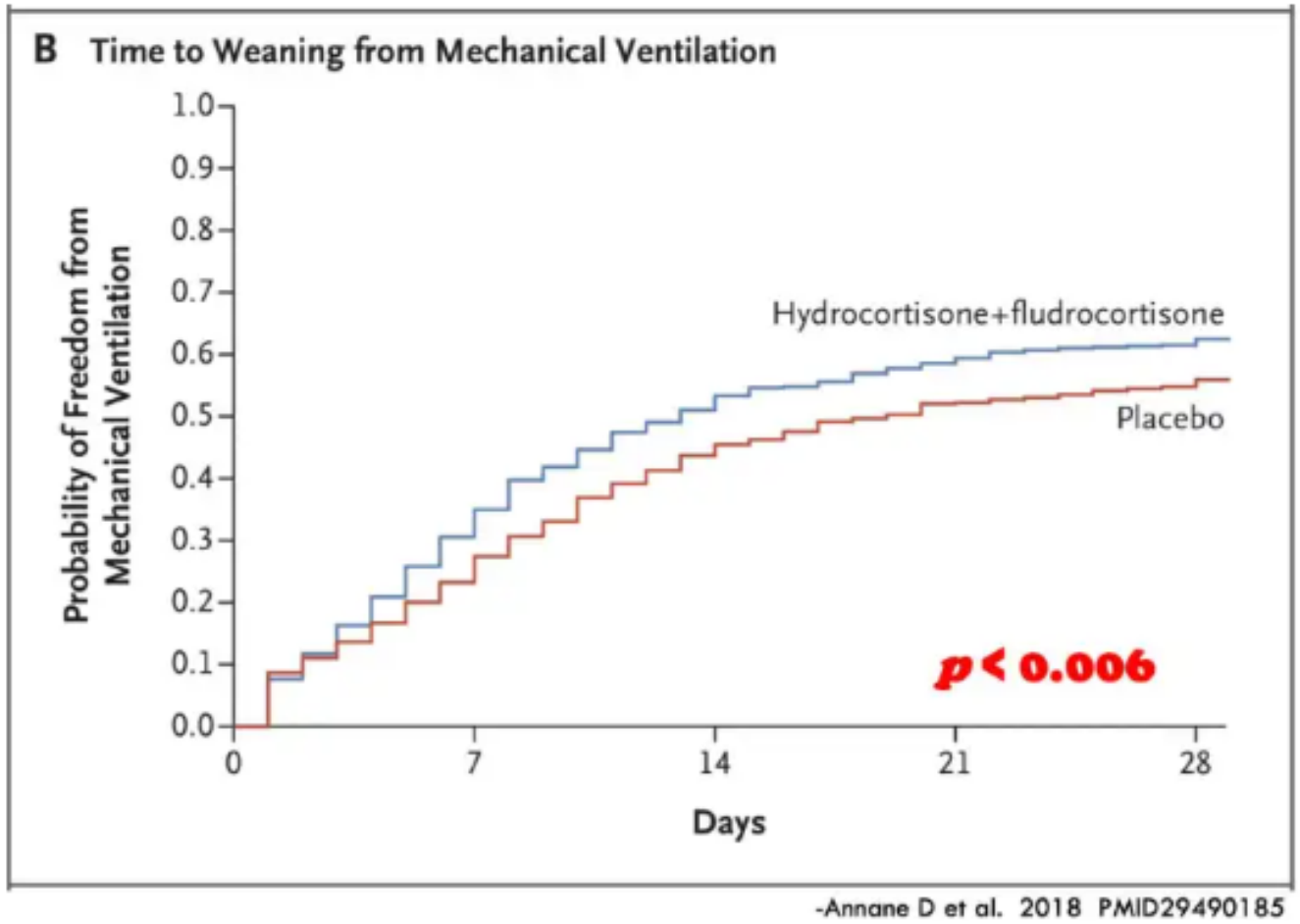


No. at risk

No early CS	156	152	151	149	149	147	140	135	124	116	110	102	97	88	76	68
Early CS	85	83	79	77	75	74	72	65	60	51	43	40	36	34	32	31

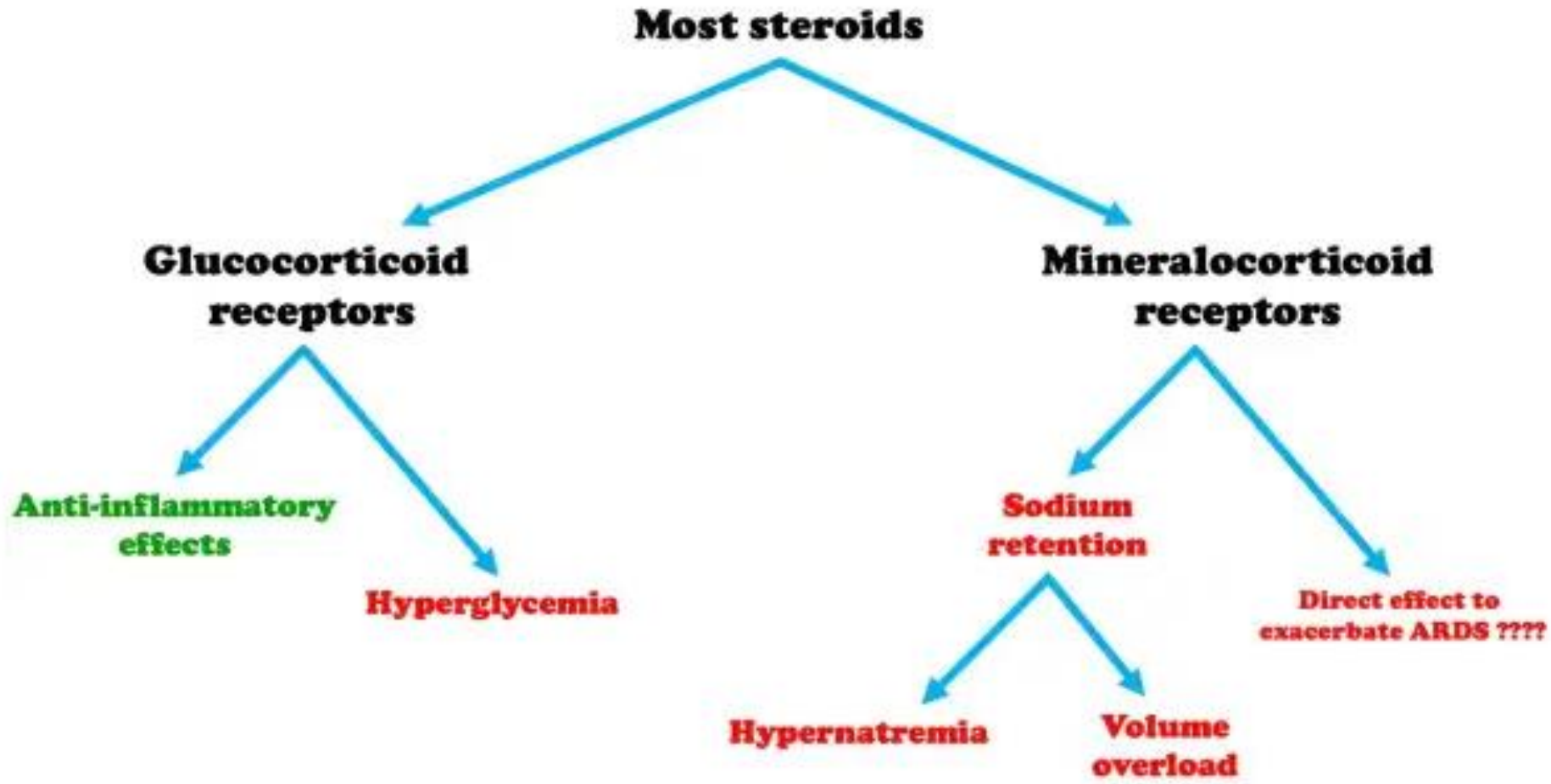
Real effect? All population?

- Robust outcome of VFD, ICU day -> rationale for use
- Sepsis+ARDS
- COVID-ARDS
- CRP?
- Response for several days?



How strong is the risk of complications from steroids?	How strong in the indication to use steroids?			
		Very Strong (*eg,* P/F ratio < 200 despite optimal ventilator management, septic shock, COVID-19 with > 7 days since symptoms onset)	←←←←←←	**Not Very Strong** (*eg,* P/F ratio 200-300, influenza, non-infectious etiologies such as trauma, rapidly improving P/F)
Low		**Give Steroids.**	Suggest Steroids	Consider steroids on case-by-case basis.
←←←		Suggest steroids	Consider steroids on case-by-case basis.	Suggest against steroids
High		Consider steroids on case-by-case basis.	Suggest against steroids	**Do not give steroids.**

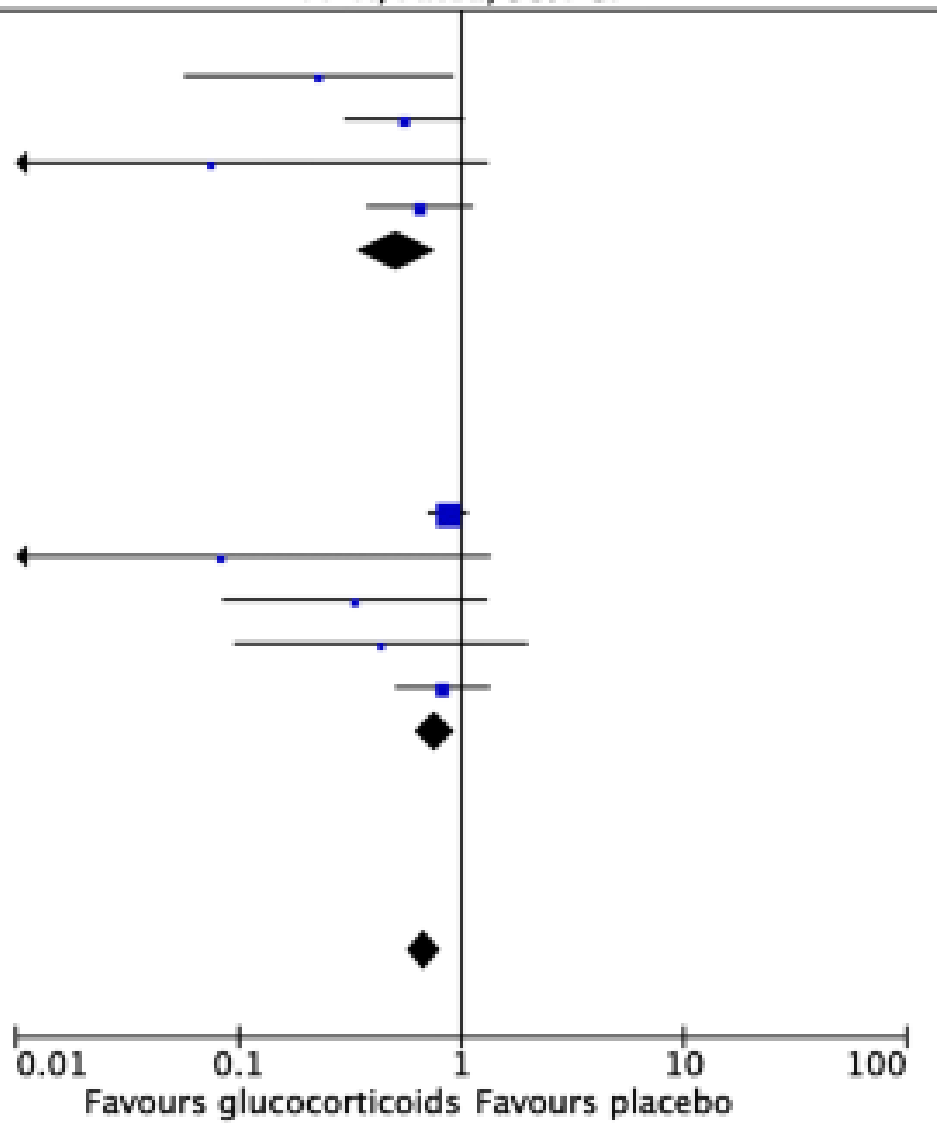
What steroid & how much?



It's possible that dexamethasone (a pure glucocorticoid agonist) could be a cleaner steroid than most.

What steroid & how much?

Study or Subgroup	Glucocorticoids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Methylprednisolone						
Meduri 1998	2	14	5	8	4.0%	0.23 [0.06, 0.92]
Meduri 2007	15	63	12	28	10.4%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	2.9%	0.08 [0.00, 1.32]
Steinberg 2006	15	66	23	66	14.4%	0.65 [0.37, 1.13]
Subtotal (95% CI)		**161**		**111**	**31.6%**	**0.51 [0.35, 0.76]**
Total events	32		43			
Heterogeneity: $Chi^2 = 3.80$, df = 3 (P = 0.28); $I^2 = 21\%$						
Test for overall effect: Z = 3.38 (P = 0.0007)						
1.4.2 Hydrocortisone						
Annane 2006	54	85	67	92	40.2%	0.87 [0.71, 1.07]
Confalonieri 2005	0	15	7	19	4.2%	0.08 [0.01, 1.35]
Liu 2012	2	12	7	14	4.0%	0.33 [0.08, 1.31]
Sabry 2011	2	26	6	34	3.2%	0.44 [0.10, 1.99]
Tongyoo 2016	22	98	27	99	16.8%	0.82 [0.50, 1.34]
Subtotal (95% CI)		**236**		**258**	**68.4%**	**0.76 [0.62, 0.93]**
Total events	80		114			
Heterogeneity: $Chi^2 = 6.19$, df = 4 (P = 0.19); $I^2 = 35\%$						
Test for overall effect: Z = 2.66 (P = 0.008)						
Total (95% CI)		**397**		**369**	**100.0%**	**0.68 [0.57, 0.82]**
Total events	112		157			
Heterogeneity: $Chi^2 = 14.83$, df = 8 (P = 0.06); $I^2 = 46\%$						
Test for overall effect: Z = 4.15 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 3.08$, df = 1 (P = 0.08), $I^2 = 67.5\%$						



What steroid & how much?

- The DEXA-ARDS trial utilized 20 mg dexamethasone for 5 days, followed by 10 mg dexamethasone for 5 days (or discontinuation *before* 10 days, if the patient was extubated)

- SCCM/ESICM guidelines recommend methylprednisolone 1 mg/kg/day, with a gradual taper over 14 days.

Steroid in ARDS

- Further research is needed to identify which patients with ARDS are most likely to benefit from corticosteroids and which patients could be harmed.

2. Statin

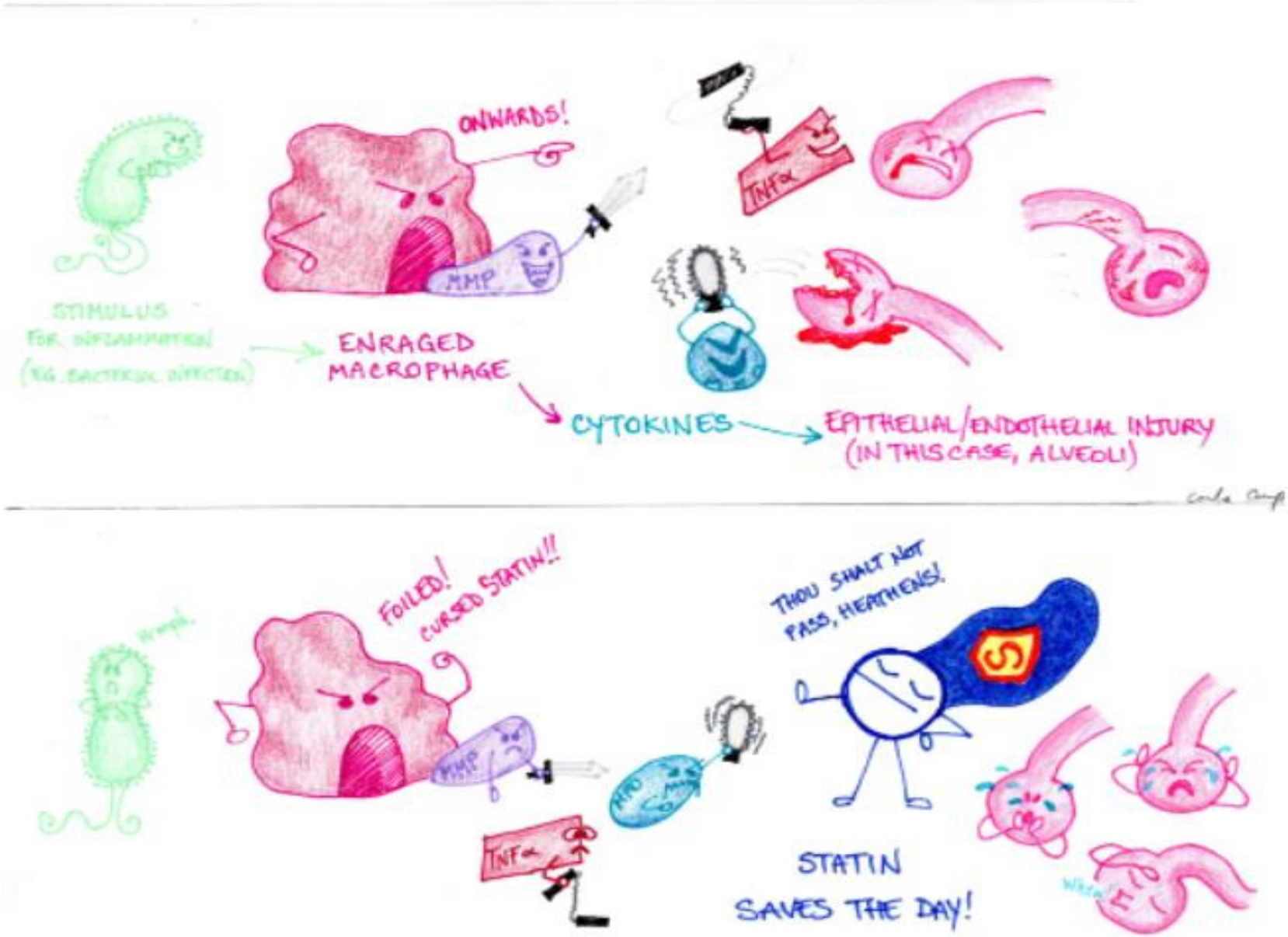
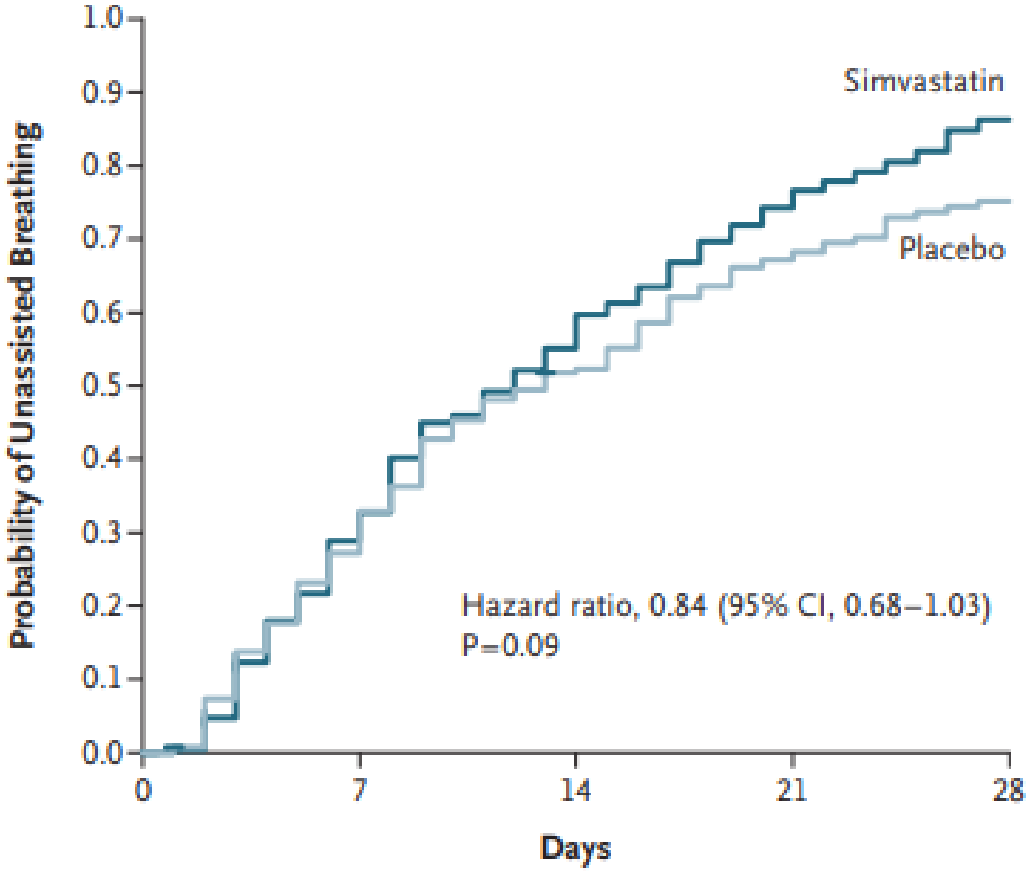


Figure 1: *potential role of simvastatin in inflammation - inflammation [e.g. infection] triggers macrophages and monocytes which elaborate various cytokines such as MPO [myeloperoxidase], MMP [matrix metalloproteinases], TNF-alpha all of which can directly or indirectly damage epithelial and endothelial lining. In vitro and in vivo, simvastatin has been found to hinder these inflammatory responses.*

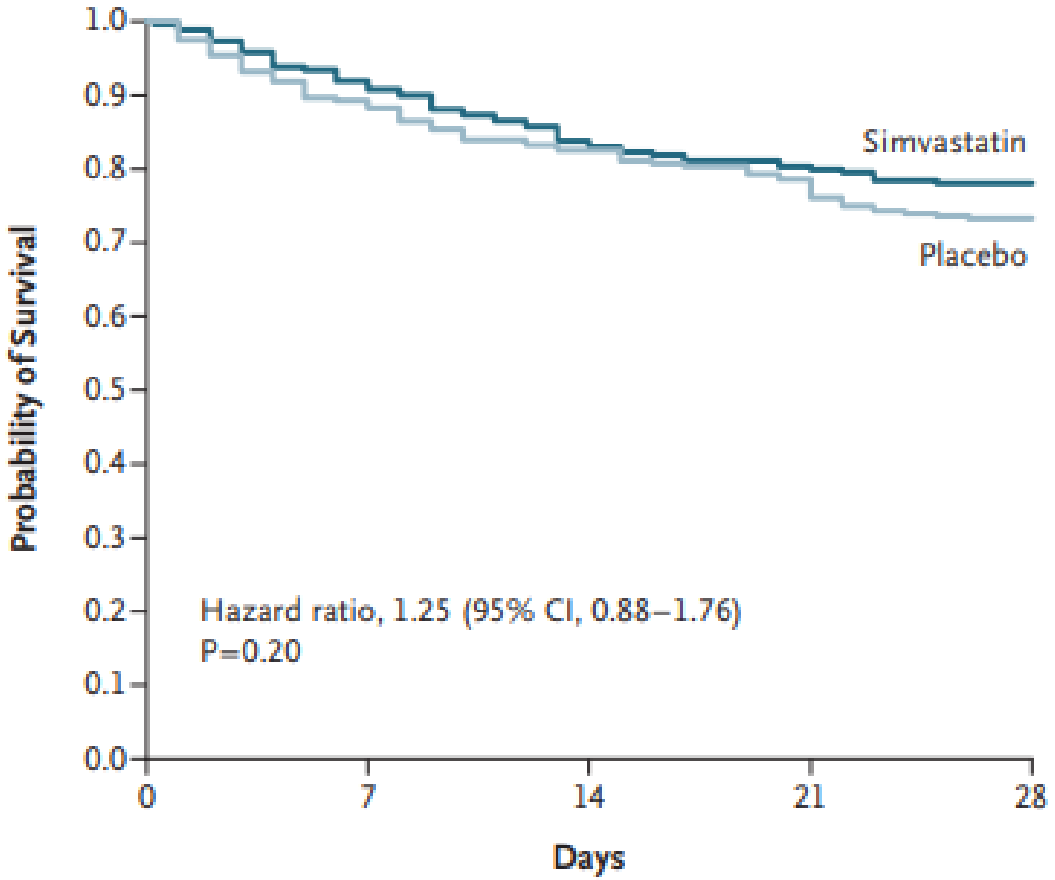
Simvastatin in the Acute Respiratory Distress Syndrome

A Unassisted Breathing

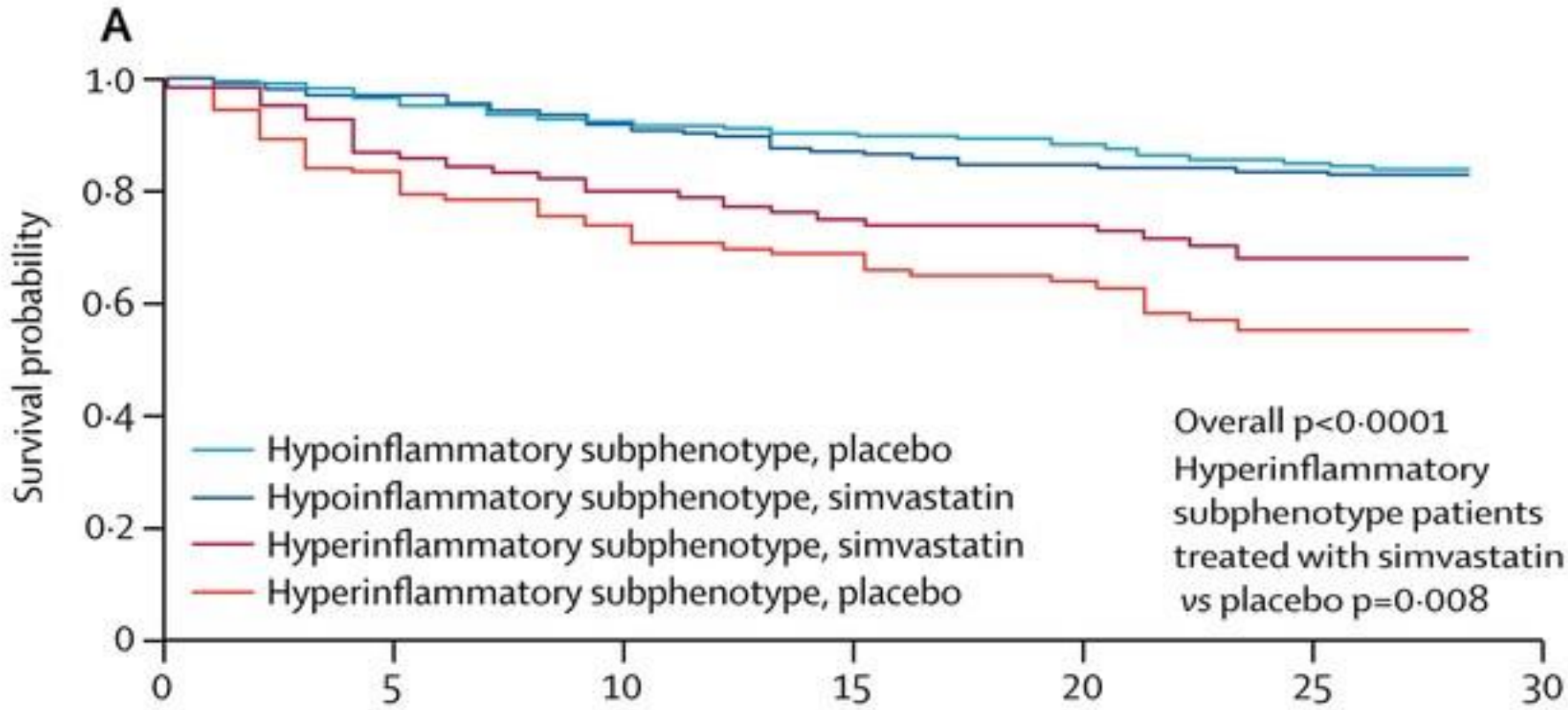


No. at Risk					
Simvastatin	258	166	87	43	19
Placebo	279	178	102	60	33

B Survival



No. at Risk					
Simvastatin	259	238	217	208	202
Placebo	280	250	231	220	205



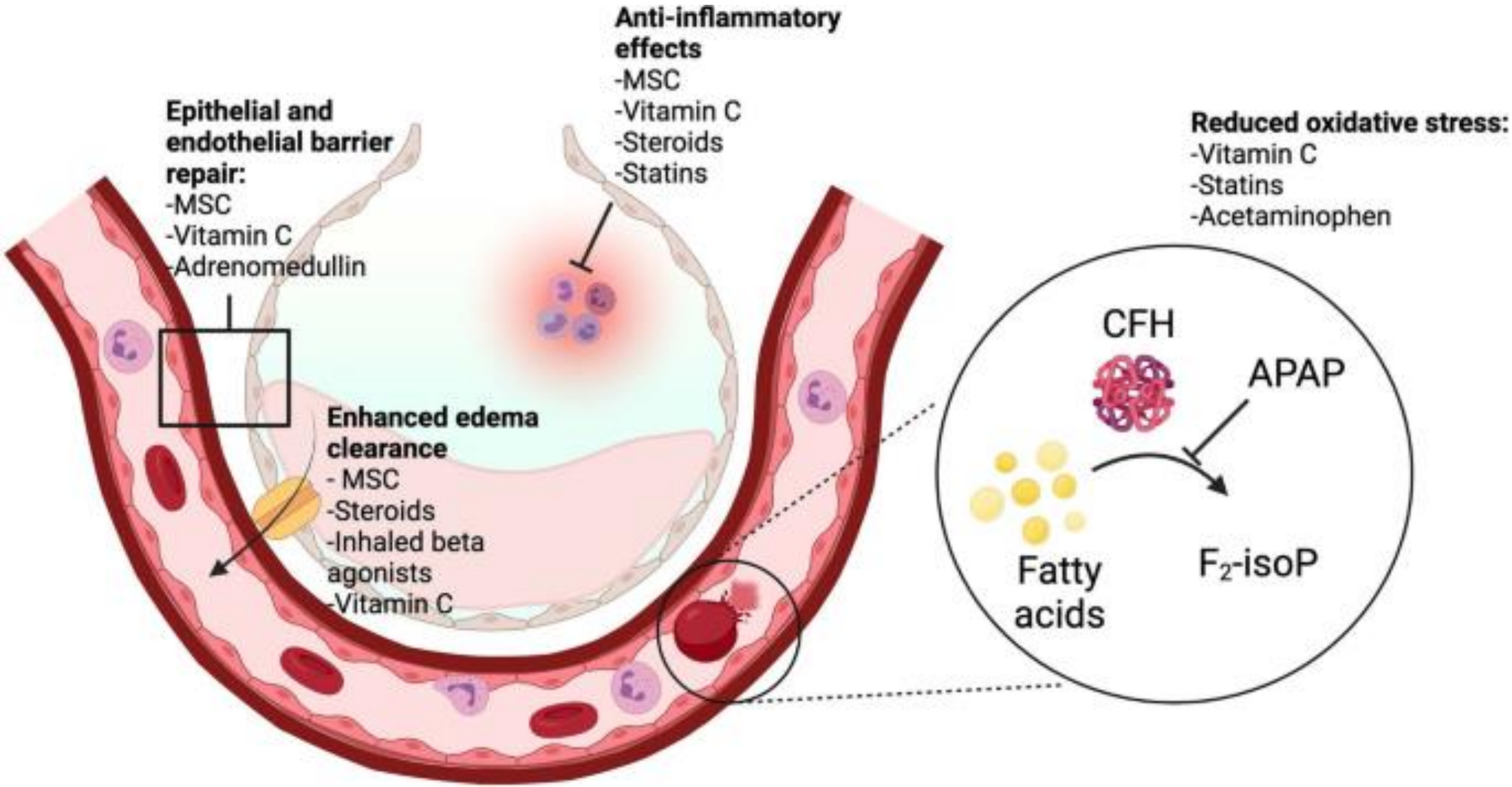
Number at risk						
Hypoinflammatory subphenotype, placebo	178	172	164	161	157	151
Hypoinflammatory subphenotype, simvastatin	175	170	161	152	148	146
Hyperinflammatory subphenotype, simvastatin	84	73	67	63	62	57
Hyperinflammatory subphenotype, placebo	102	85	75	70	65	56

Table 6 Comparison of clinical outcomes in treatment and placebo groups according to subphenotypes

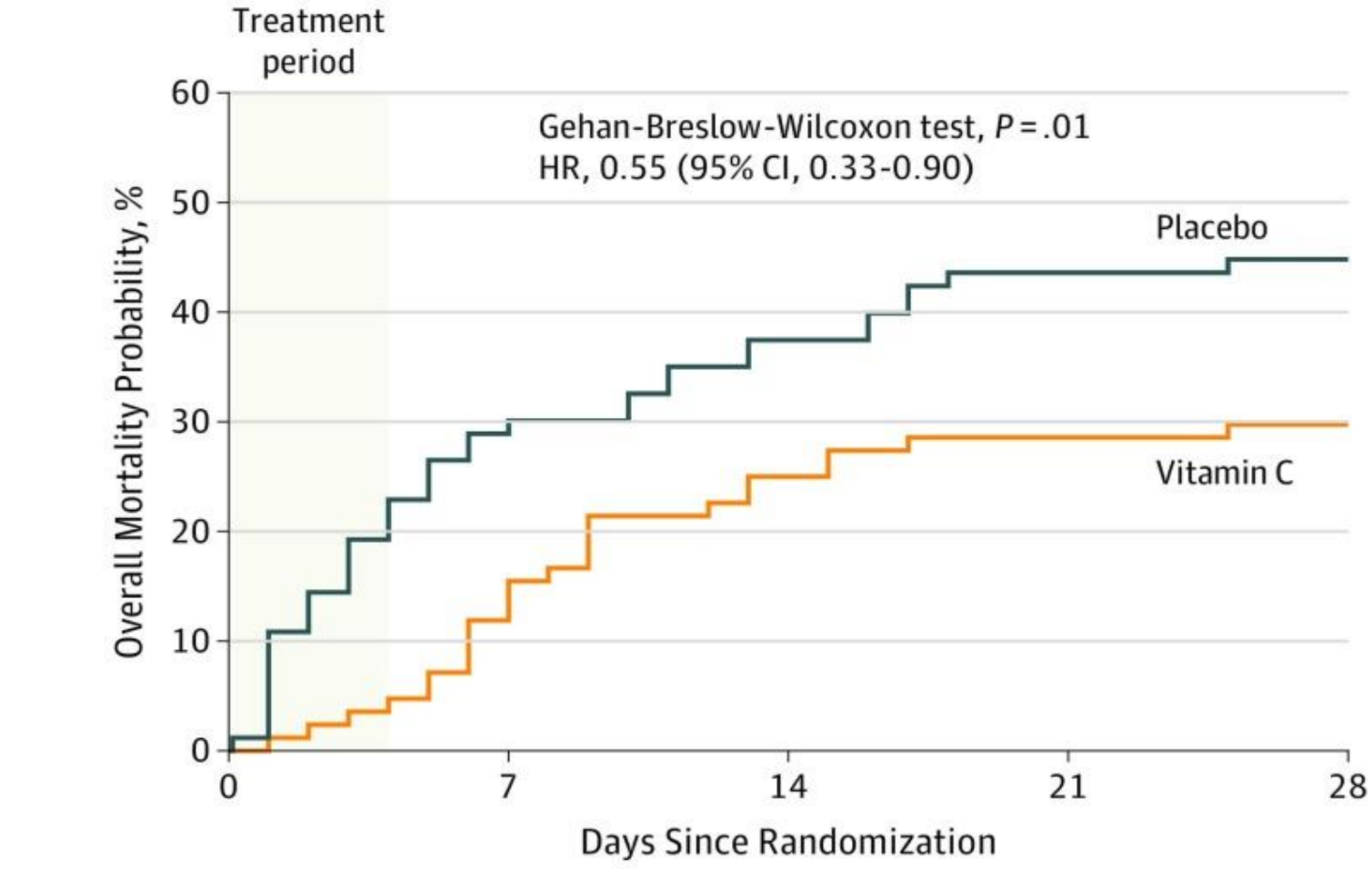
Outcome	Hypo-inflammatory		Hyper-inflammatory		*p* value
	Placebo (*n* = 220)	Rosuvastatin (*n* = 248)	Placebo (*n* = 146)	Rosuvastatin (*n* = 131)	
60-day mortality, *n* (%)	42 (19.1%)	56 (22.6%)	49 (33.6%)	52 (39.7%)	0.877
90-day mortality, *n* (%)	44 (20.0%)	56 (22.6%)	52 (35.6%)	52 (39.7%)	0.953
Ventilator-free days, median (IQR)	24 (4–26)	23 (9.5–26)	16.5 (1–23)	13 (1–23)	0.697

- Differences in the study population (all-cause vs. sepsis-related) or the statins used
- Prospective validation is needed
- Allocation of ARDS subphenotypes are not available in practice
- Ongoing clinical trials such as the PHIND trial (NCT04009330) aim to develop a point-of-care assay that can identify hyperinflammatory and hypoinflammatory phenotypes rapidly at the bedside.

3. Vitamin C


Anti-inflammatory effects
-MSC
-Vitamin C
-Steroids
-Statins
Epithelial and endothelial barrier repair:
-MSC
-Vitamin C
-Adrenomedullin
Enhanced edema clearance
- MSC
-Steroids
-Inhaled beta agonists
-Vitamin C
Reduced oxidative stress:
-Vitamin C
-Statins
-Acetaminophen
CFH
APAP
Fatty acids
F2-isoP

Vit C for Sepsis related ARDS
The CITRIS-ALI RCT in JAMA 2019



Zhang et al. Ann. Intensive Care (2021) 11:5
https://doi.org/10.1186/s13613-020-00792-3

Annals of Intensive Care

RESEARCH Open Access

Pilot trial of high-dose vitamin C in critically ill COVID-19 patients

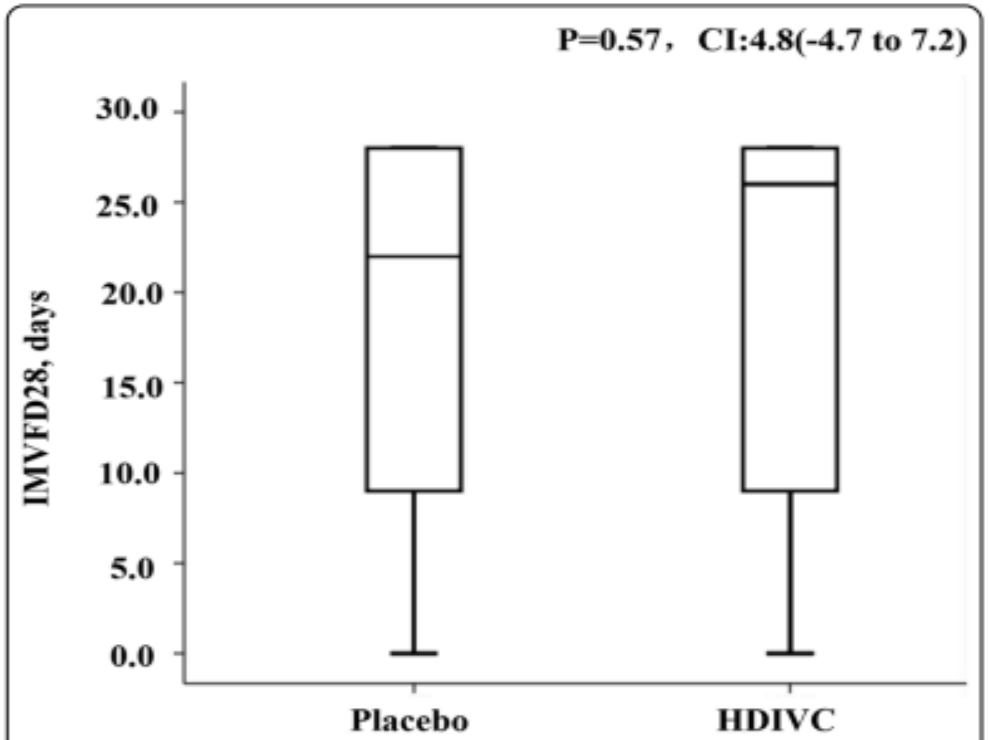
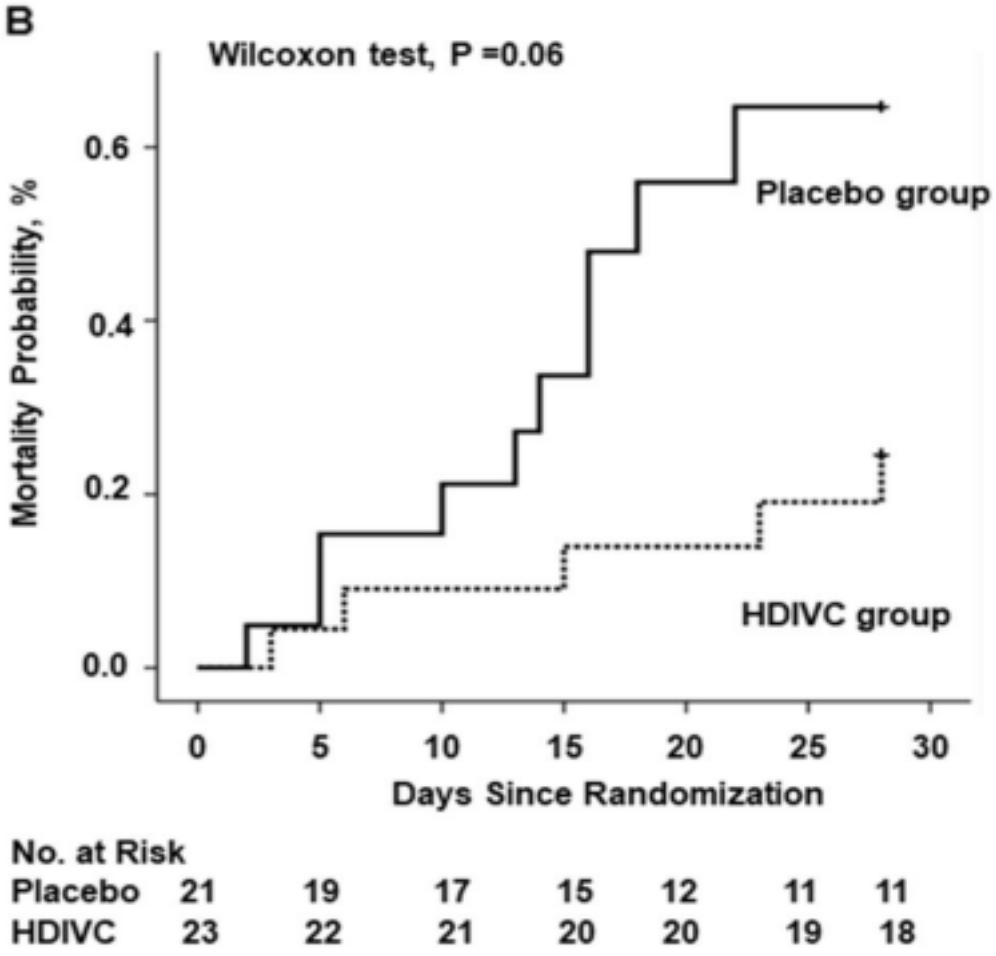


Fig. 2 The IMVFD28 in high-dose intravenous vitamin C and placebo group. The IMVFD28 was 26.0 days[9.0–28.0] in HDIVC, and 22.0 days[8.5–28.0] in placebo group, but this difference was not statistically significant ($P = 0.57$, CI 4.8[-4.7 to 7.2]). *IMV* invasive mechanical ventilation, *HDIVC* high-dose intravenous vitamin C



Vitamin C for sepsis-related ARDS

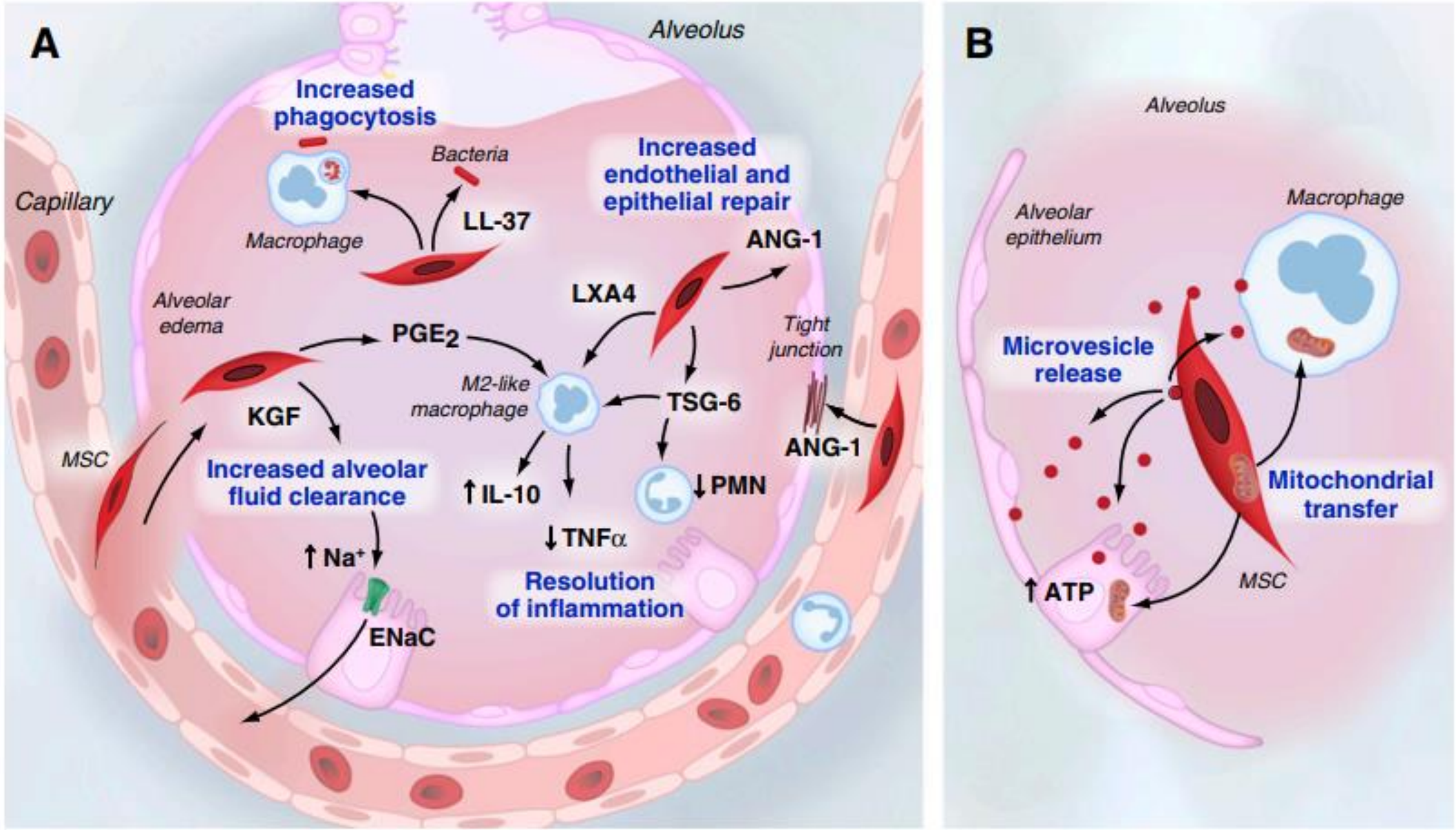
- NCT04291508(ASTER), NCT04404387

5	☐	Recruiting	Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery	• Acute **Respiratory Distress Syndrome** • Critical Illness • Respiratory Failure • Sepsis	• Drug: Intravenous Acetaminophen (room temperature) • Drug: Intravenous Vitamin C (refrigerated) • Drug: 5% Dextrose (room temperature) • Drug: 5% Dextrose refrigerated	• University of Arizona Tucson, Arizona, United States • UCSF Fresno Fresno, California, United States • Cedars-Sinai Medical Center Los Angeles, California, United States • (and 36 more...)
1	☐	Not yet recruiting	Lessening Organ Dysfunction With VITamin C in Septic ARDS	• Septic • Acute **Respiratory Distress Syndrome**	• Drug: Administration of vitamin C • Drug: Administration of placebo	• Department Intensive Care Unit, Hospital Raymond Poincaré - APHP Garches, France

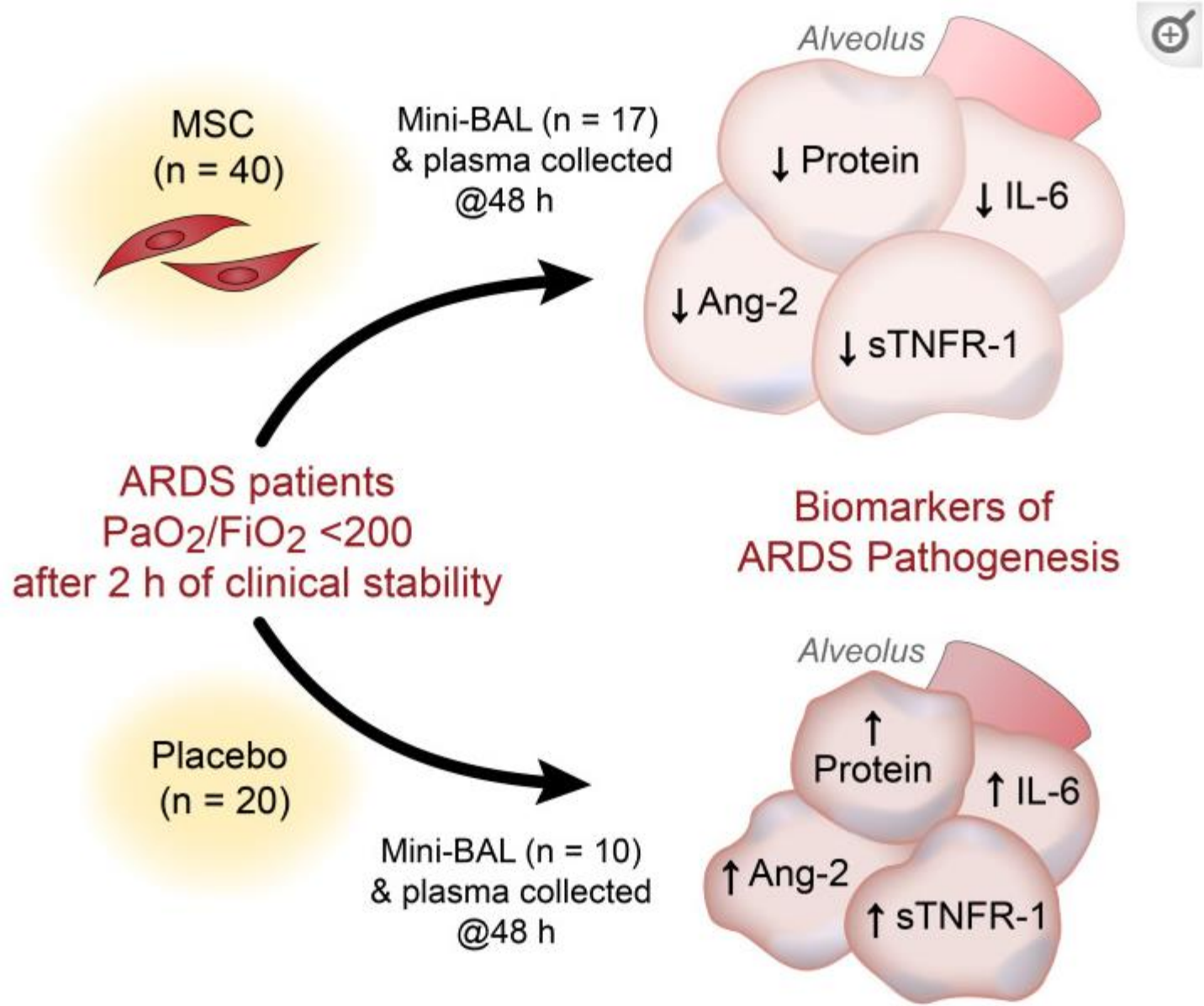
4. Stem Cell

- allogeneic mesenchymal stromal cells (MSCs)
- how promise as a potential therapeutic option

Mesenchymal stromal cells (MSCs)

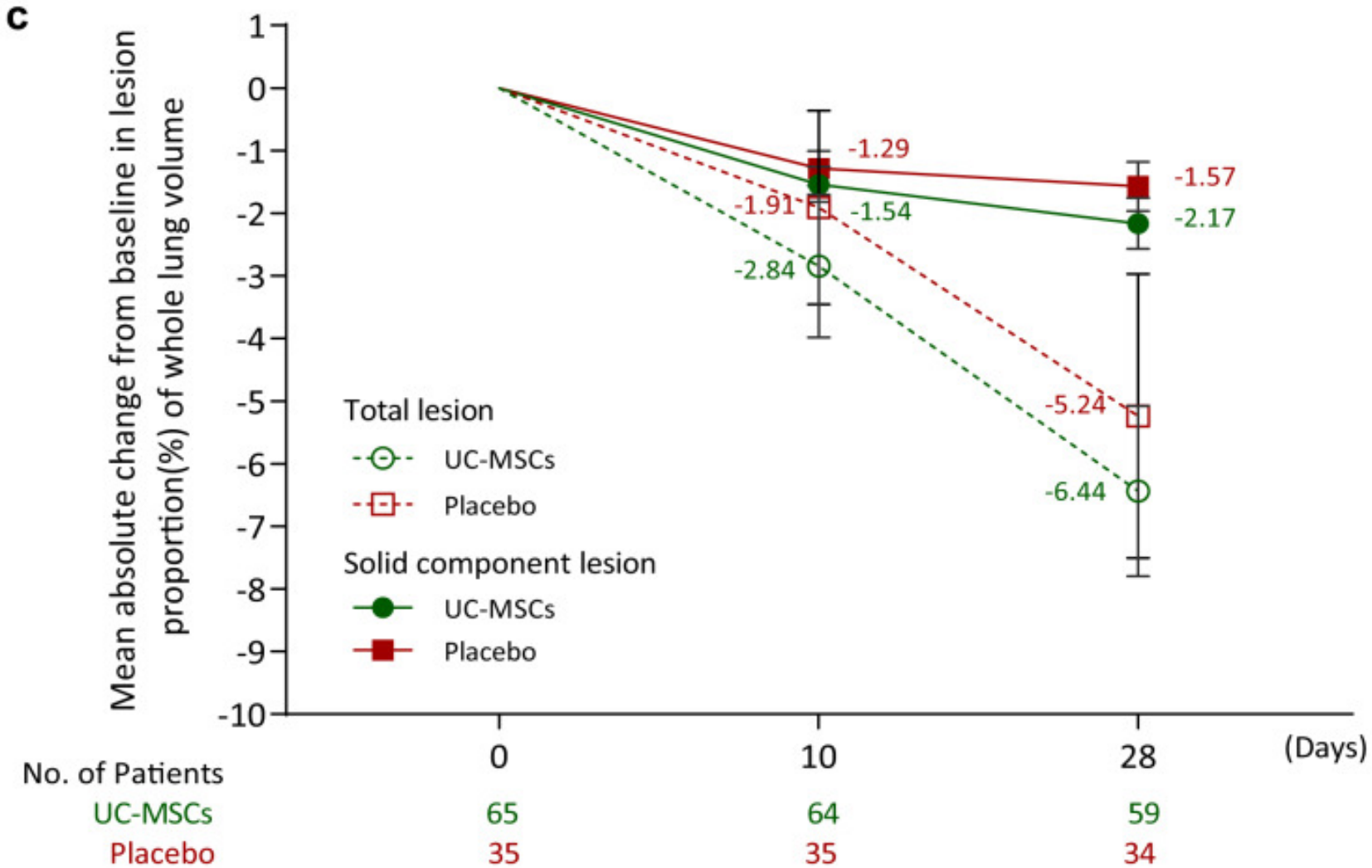


Mesenchymal stromal cells



ARTICLE OPEN

Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial

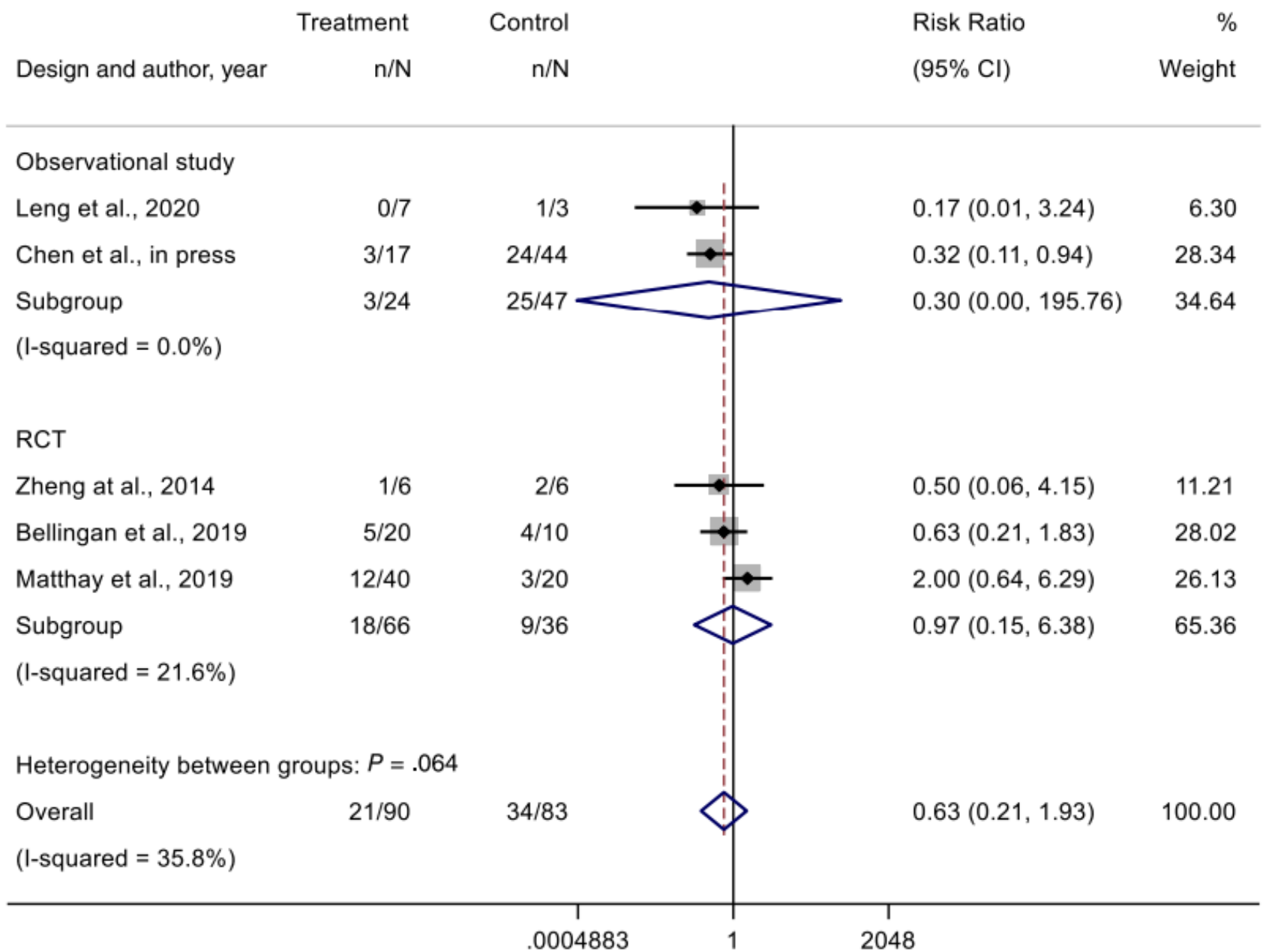


Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial

Michael A Matthay, Carolyn S Calfee, Hanjing Zhuo, B Taylor Thompson, Jennifer G Wilson, Joseph E Levitt, Angela J Rogers, Jeffrey E Gotts, Jeanine P Wiener-Kronish, Ednan K Bajwa, Michael P Donahoe, Bryan J McVerry, Luis A Ortiz, Matthew Exline, John W Christman, Jason Abbott, Kevin L Delucchi, Lizette Caballero, Melanie McMillan, David H McKenna, Kathleen D Liu

	Mesenchymal stromal cell group (n=40)	Placebo group (n=20)
Patients' characteristics		
Age (years)	55 (17)	55 (20)
Men/women	23 (58%)/17 (42%)	10 (50%)/10 (50%)
Cause of ARDS		
Sepsis with pneumonia	19 (48%)	12 (60%)
Sepsis without pneumonia	5 (13%)	2 (10%)
Pneumonia without sepsis	11 (28%)	5 (25%)
Aspiration only	4 (10%)	1 (5%)
Other	1 (3%)	0
Arterial pressure (mm Hg)	75 (10)	76 (9)
Taking vasopressors at the time of infusion	24 (60%)	9 (45%)
SOFA score	8·1 (3·3)	6·9 (2·7)
APACHE III score	104 (31)	89 (33)

- No MSC-related hemodynamic or respiratory adverse events within 6 h of the start of infusion
- A trend towards a decreased number of VFDs and improved oxygenation index, although not significantly.
- Increased mortality tendency (severity)



NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

COVID-19 ARDS with Mesenchymal stromal cells

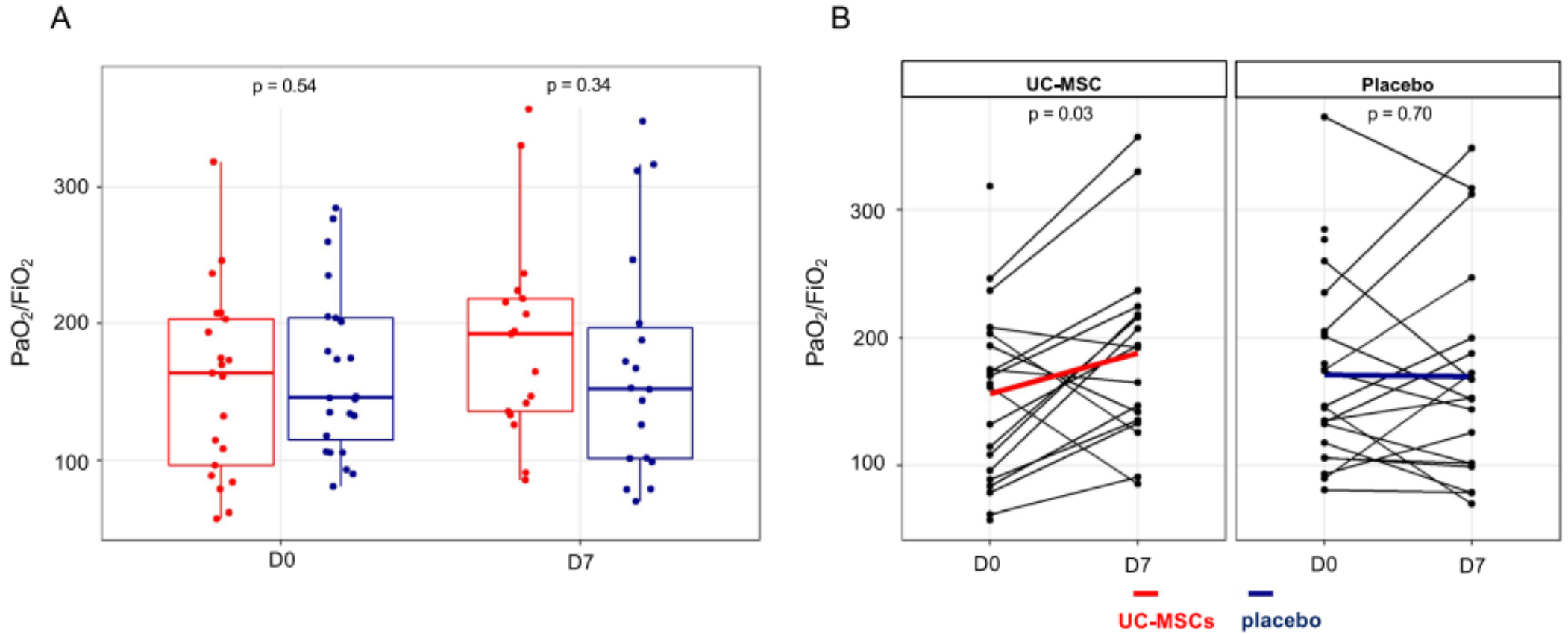


Fig. 2 Primary endpoint: PaO_2/FiO_2 values and their changes between days 0 and 7. **A** Baseline (D0) and D7 PaO_2/FiO_2 ratios were similar for the two groups. Box plots of PaO_2/FiO_2 ratios: internal *horizontal lines* are the medians; *lower* and *upper box limits* are the 25th–75th interquartile range, respectively; and vertical bars represent the 10th and 90th percentiles. **B** PaO_2/FiO_2 ratios increased significantly from D0 to D7 in the UC-MSC group (respectively, 156.2 ± 68.2 vs 188.3 ± 74.2; Wilcoxon signed-rank exact test). The placebo group's PaO_2/FiO_2 ratios on D0 and D7 were comparable (respectively, 171.2 ± 72.9 vs 169.8 ± 85.6, Wilcoxon signed-rank exact test). UC-MSCs group in *red*; placebo group in *blue*. *D* day. *PaO_2/FiO_2* ratio of partial pressure of oxygen to fractional inspired oxygen. *UC-MSCs* umbilical cord-derived mesenchymal stromal cells

Umbilical cord mesenchymal stem cells for COVID-19 ARDS

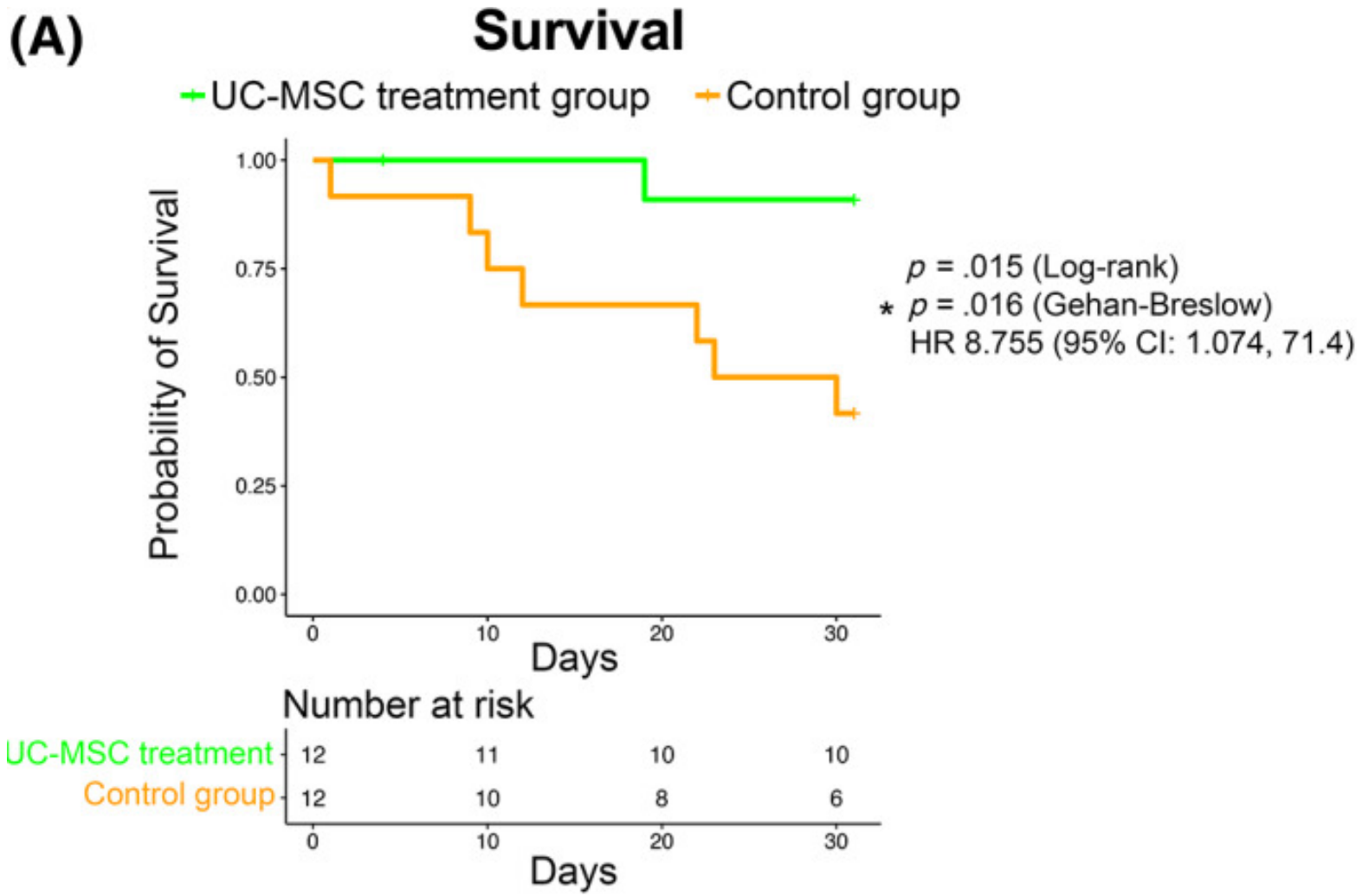


Table 1. Continued

ClinicalTrials.gov identifier	City/state, country	Status	Patient numbers/ conditions	Intervention(s)
NCT04615429	Puerta de Hierro, Guadalajara	Phase II, recruiting	20 patients; COVID-19 ARDS	Single dose of 1×10^6 allogeneic MSCs·kg^{-1} BW Placebo
NCT04377334	Tuebingen, Germany	Phase II, not yet recruiting	40 patients; COVID-19 ARDS	Allogeneic bone marrow MSCs
NCT04348461	Spain (multicentre)	Phase II, not yet recruiting	100 patients; COVID-19 ARDS	Two doses of 1.5×10^6 AT-MSCs·kg^{-1} BW
NCT04625738	Nancy, France	Phase II, not yet recruiting	30 patients; COVID-19 ARDS	Total 2×10^6 WJ-MSCs·kg^{-1} BW over three doses Placebo: vehicle
NCT03818854	USA (multicentre)	Phase IIb, recruiting	120 patients with ARDS	Allogeneic BM-MSCs; single dose of 10^7 cells·kg^{-1} BW Placebo: reconstitution medium
NCT04371393	USA (multicentre)	Phase III; trial stopped for futility to achieve mortality end-point	300 patients; COVID-19 ARDS (stopped after enrolment of 223 patients; details to follow; no safety issues)	MSC product Remestemcel-L; 2×10^6 cells·kg^{-1} BW on each of days 1 and 5 Placebo: Plasma-Lyte 148

Trials posted on clinicaltrials.gov as of 1 December 2020. While ARDS has various causes that would fit into the inclusion criteria of a number of these trials, several studies were newly initiated specifically in response to the COVID-19 pandemic caused by SARS-CoV-2. BW: body weight; UC: umbilical cord; BM: bone marrow; WJ: Wharton's jelly; hCT: human cord tissue; EV: extracellular vesicle; AT: adipose tissue.

Pharmacotherapy	Findings to date	Phenotypes and personalized medicine in future
Steroid (anti-inflammatory)	↓VFDs possible ↓mortality Harmful in late(>14dys), influenza	covid-19, sepsis related ARDS persistently debating (Phenotype?, dose? Type?, duration?) Research to identify responsive group
Stain (anti-inflammatory)	No impact on mortality or VFDs Possible benefit in hyperinflammatory phenotype (exploratory finding)	To develop assay that identify responsive group (hyperinflammatory group)
Vitamin C (anti-inflammatory, restore of epithelial barrier)	Possible ↓ mortality, VFDs in Sepsis + ARDS (exploratory finding)	Ongoing large trial in Sepsis + ARDS
Mesenchymal Stromal Cells **(**↑ Alveolar fluid clearance, Enhanced epithelial/ endothelial repair)	Safety established in phase I and IIA studies Small data	Potential Multiple clinical trials on going

Key future direction

- Targeting both biologic phenotypes and specific clinical populations
- which elements should be personalized to specific aspects of physiology and biology that could identify a more treatment-responsive subgroup.