Societat Catalana de Medicina Intensiva i Crítica

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VENTILACIÓ MECÀNICA I SUPORT EXTRACORPÒRIA EN LA HIPOXÈMIA REFRACTÀRIA

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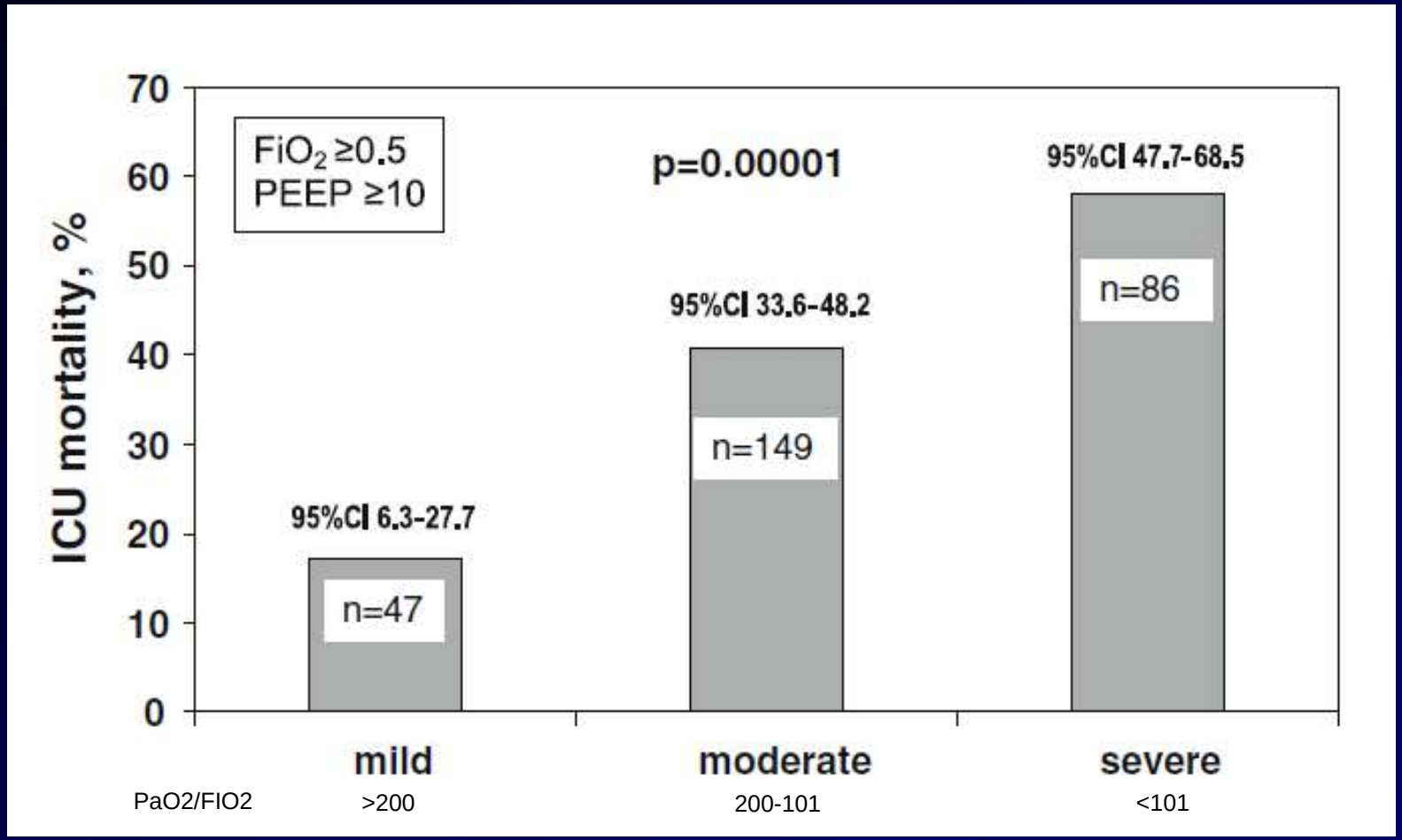
OUTLINE

- Epidemiology of severe ARDS
- Prevention and Mechanical Ventilation
- Prone Position
- ECLS: ECMO and $ECCO_2R$
- Indications of ECLS
- H1N1: prognosis and outcome
- Future directions

ARDS CLASSIFICATION



Intensive Care Med 2013;39:583-592

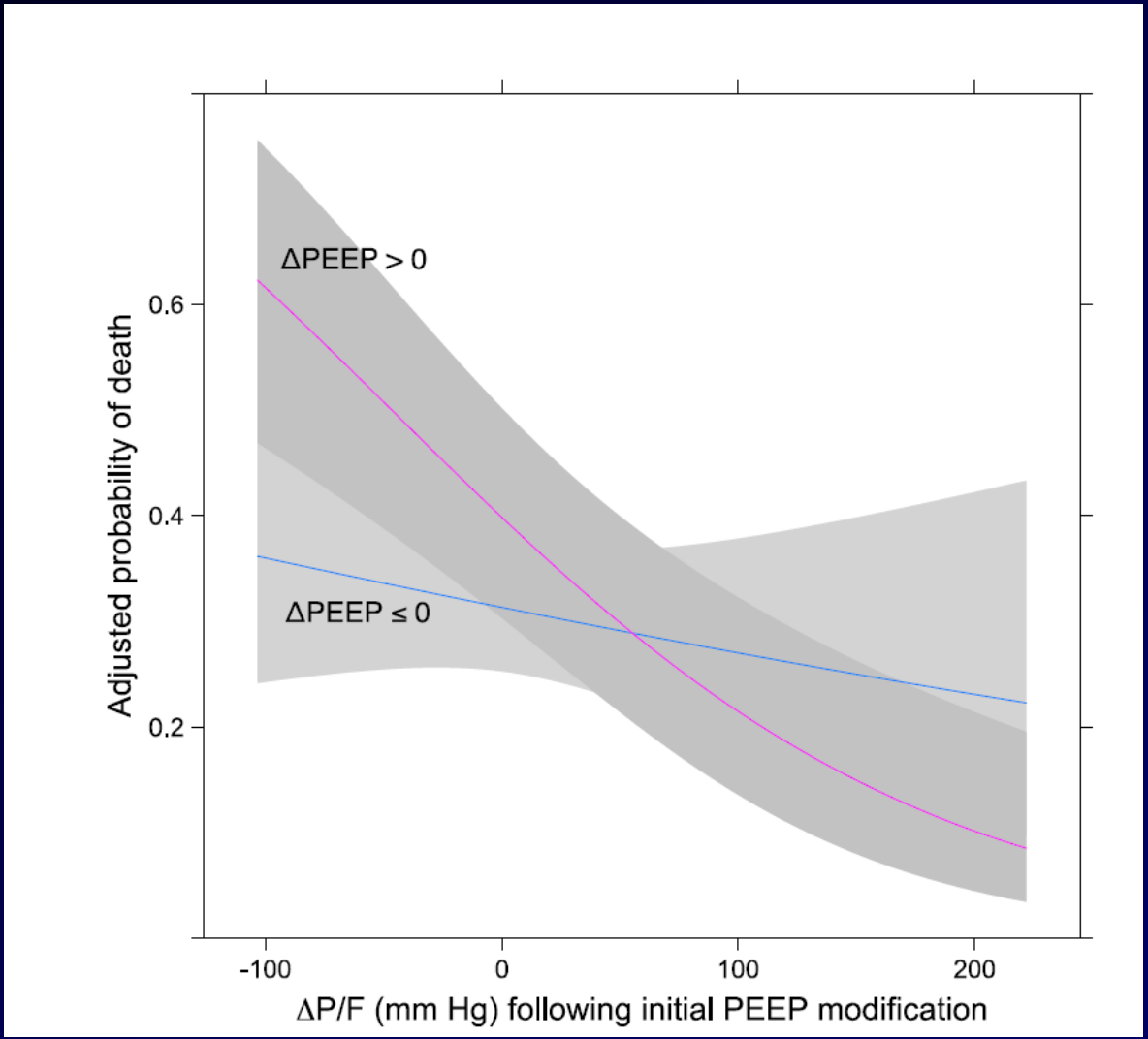
COX REGRESSION MODELS FOR PREDICTING DEATH IN ALI

Predictor[a]	Unadjusted hazard ratio	*p* value	95% CI
Chest radiograph score	1.72	0.3	(0.59–4.99)
Extravascular lung water index (ml/kg)	1.14	0.001	(1.05–1.23)
PaO_2 / FiO_2	0.83	0.003	(0.74–0.94)

[a]Per 10–point increase in chest radiograph score and PaO_2/FiO_2.

Annals of Intensive Care 2013;3:25

OXYGENATION RESPONSE AND MORTALITY TO ΔPEEP

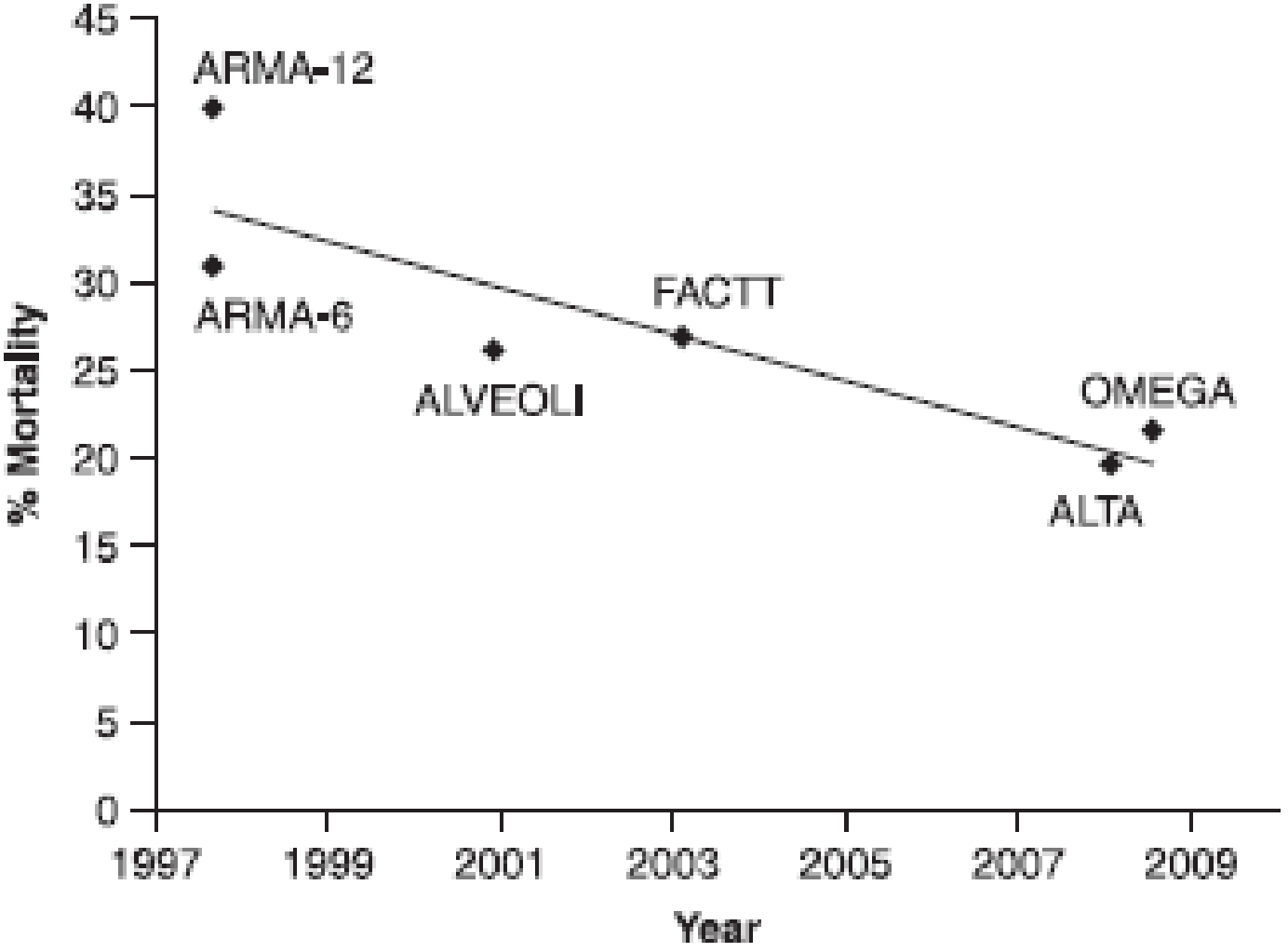


Am J Respir Crit Care Med 2014;190:70-76

REFRACTORY HYPOXEMIA

- Persistent severe hypoxemia ($PaO_2/FIO_2<150$ mmHg)
- 10-20% ARDS (47% MOF)
- 7-30% H1N1 ARDS

ARDS-Net 60-day MORTALITY



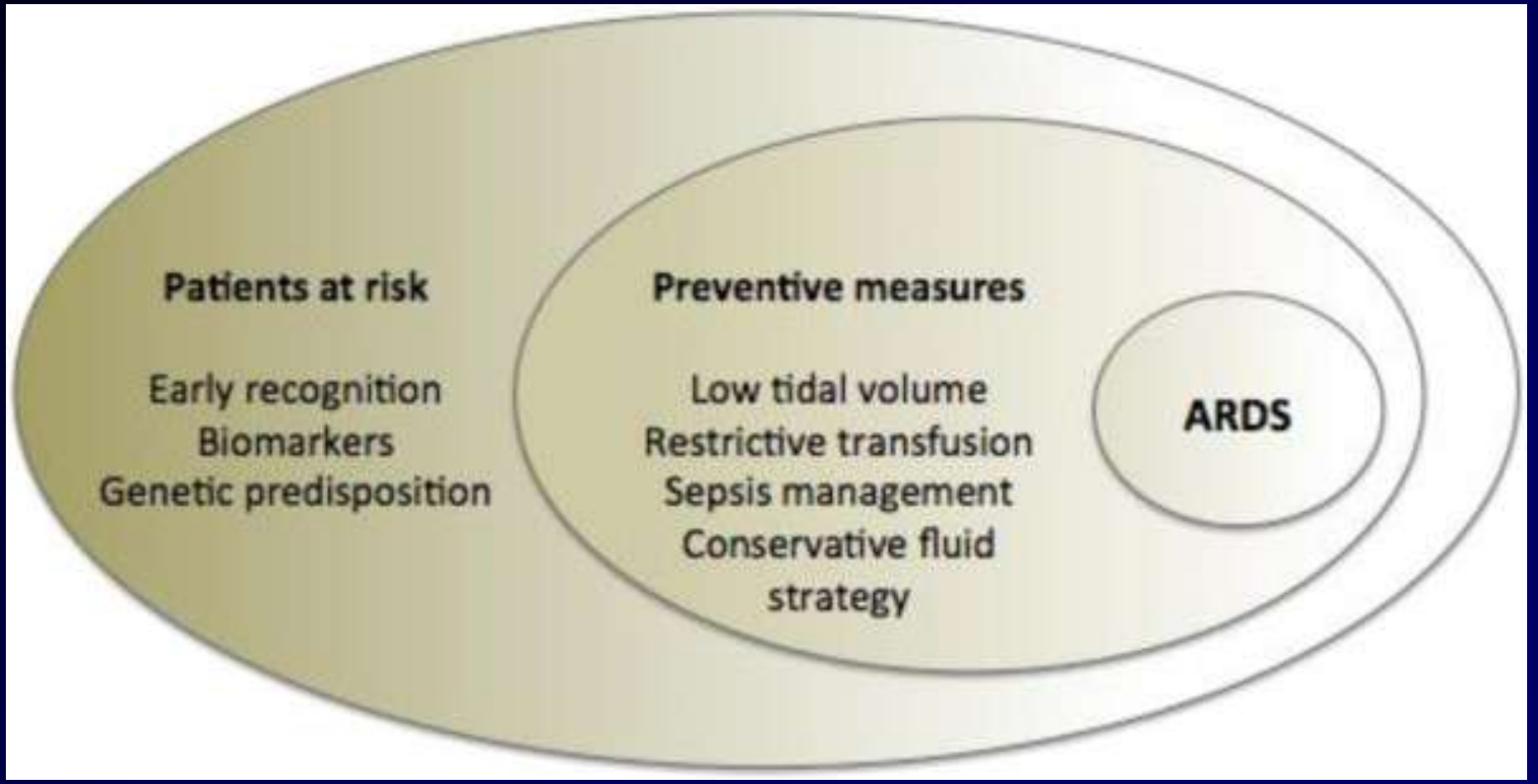
Spragg RG. Am J Respir Crit Care Med 2010;181:1121-1127

ECLS in H1N1 Severe ARDS

Country	France	Germany	Italy	UK	Australia	Spain
Admissions (n)	391	116	60	562	722	997
Referred (%)	68	94	53	100	56	25
Period (years)	2009-11	2009-10	2009-10	2009-10	2009-10	2009
ECLS centers (n)	30	12	14	4	15	4
ECMO (%)	13	53	7.2	12	7.3	1.7
Global Mortality (%)	22	38	29	21	14	15
ECMO Mortality (%)	36	54	32	27*	23	56

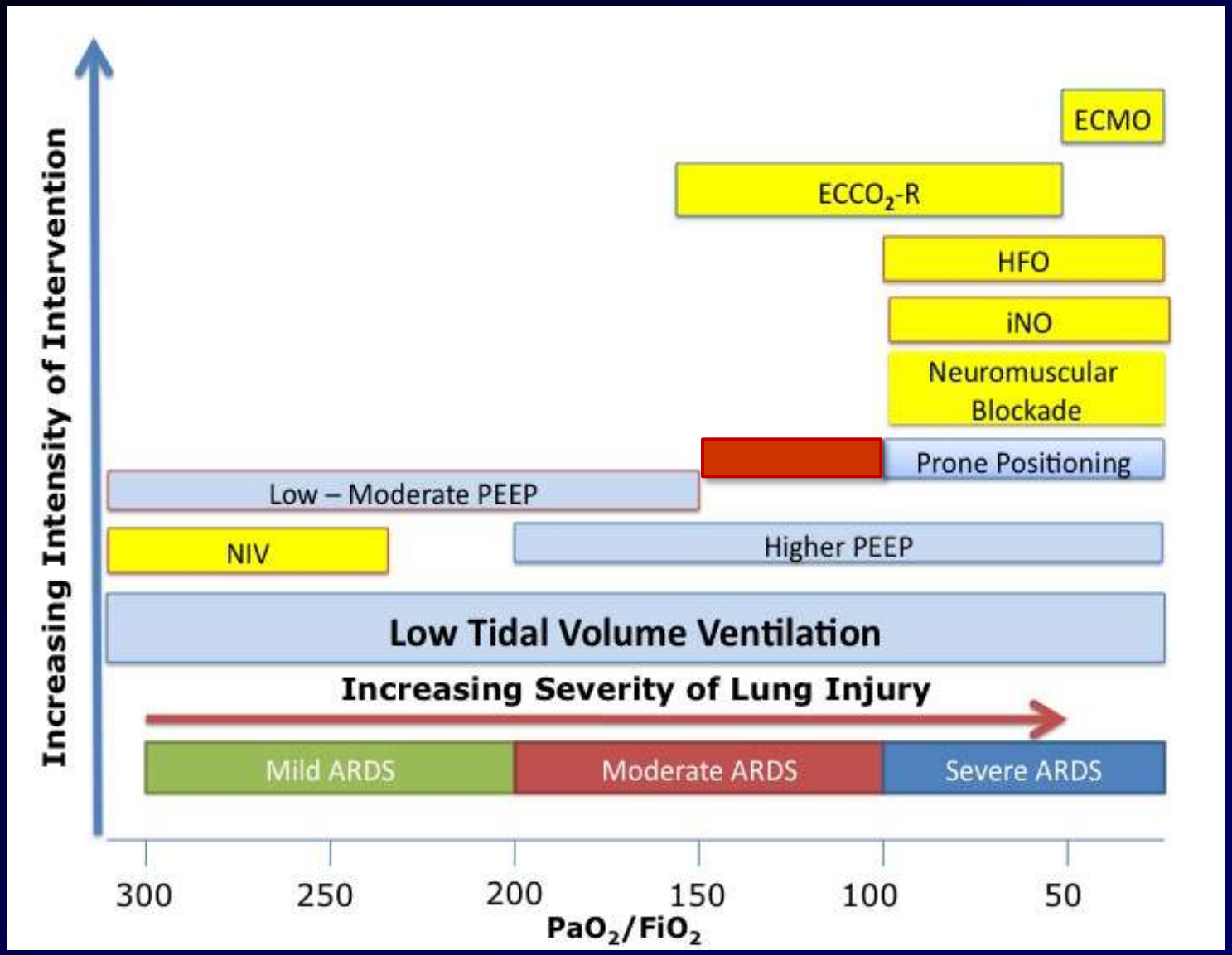
*13.7% referred patients without ECMO

ARDS PREVENTION



Annals of Intensive Care 2013:3:11

ARDS THERAPEUTIC OPTIONS



JAMA 2012;307:2526-33

LUNG PROTECTIVE VENTILATION

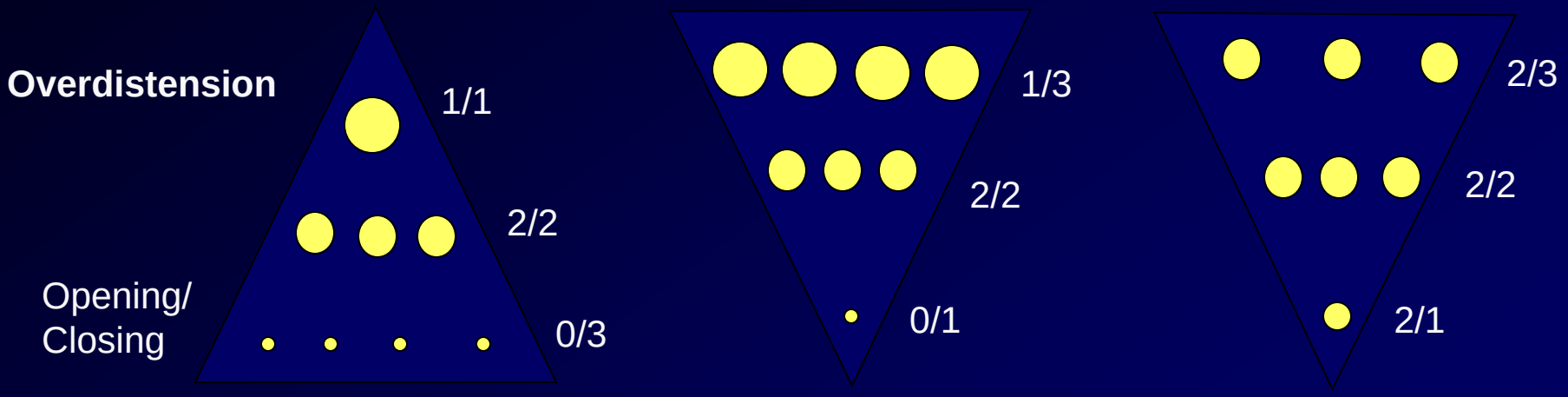
- Low VT <6 ml/kg IBW
- Pplat <30 cmH2O
- High PEEP ≥10 cmH2O
- Transpulmonary pressure (Pesof)

ADJUNTIVE TREATMENT BEFORE ECLS

Country	France	Germany	Italy	UK	Australia	Spain
Prone position (%)	45	47	28	34	20	55
iNO (%)	72	28	15	19	32	55
HFOV (%)	2	NR	4	6.3	5	0

Neuromuscular blockers: NR

PRONE POSITION
May reduce VILI

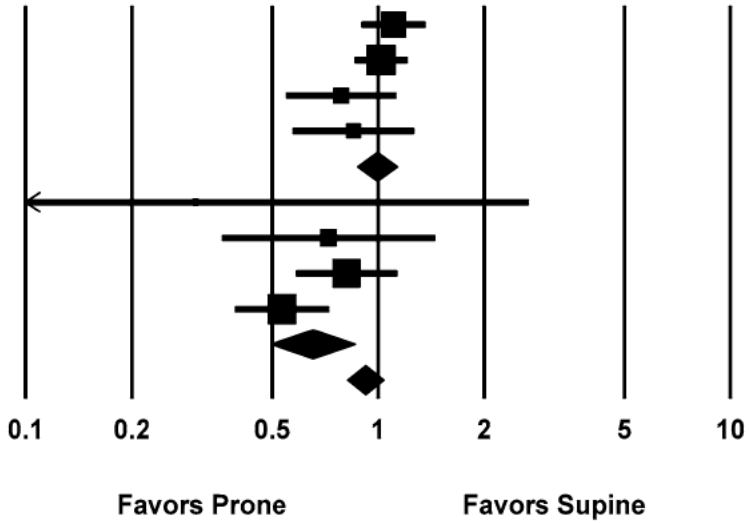


PRONE POSITION and MORTALITY

Group by High vs Low Vt	Study name	Risk ratio	Lower limit	Upper limit	p-Value	Relative weight
High	Gattinoni, 2001	1.106	0.900	1.360	0.337	32.46
High	Guerin, 2004	1.020	0.862	1.207	0.819	45.08
High	Mancebo, 2006	0.786	0.551	1.120	0.183	12.30
High	Taccone, 2009 (mod)	0.852	0.575	1.262	0.424	10.15
High		0.996	0.876	1.132	0.949	
Low	Voggenreiter, 2005	0.304	0.035	2.659	0.282	1.56
Low	Fernandez, 2008	0.724	0.362	1.446	0.360	13.40
Low	Taccone, 2009 (sev)	0.814	0.588	1.128	0.216	40.82
Low	Guerin, 2013	0.534	0.394	0.724	0.000	44.23
Low		0.655	0.499	0.860	0.002	
Overall		0.834	0.683	1.017	0.073	

Statistics for each study

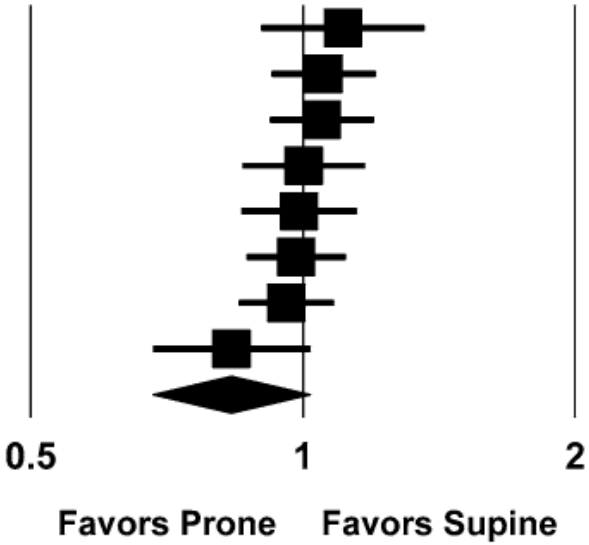
Risk ratio and 95% CI



Intensive Care Med 2014;40:332-341

PRONE POSITION MORTALITY TREND

Study name	Cumulative statistics			
	Point	Lower limit	Upper limit	p-Value
Gattinoni, 2001	1.106	0.900	1.360	0.337
Guerin, 2004	1.054	0.925	1.201	0.432
Voggenreiter, 2005	1.049	0.921	1.195	0.472
Mancebo, 2006	1.002	0.859	1.168	0.982
Fernandez, 2008	0.990	0.856	1.145	0.892
Taccone, 2009 (mod)	0.983	0.868	1.113	0.783
Taccone, 2009 (sev)	0.958	0.851	1.080	0.485
Guerin, 2013	0.834	0.683	1.017	0.073
	0.834	0.683	1.017	0.073



Intensive Care Med 2014;40:332-341

THE PROSEVA TRIAL: Effect of Prone Positioning in Severe and Persistent ARDS

Inclusion criteria

1. Aged 18 years or more
2. Both genders
3. Intubated for ARDS for < 36 hours
4. ARDS according to AECC criteria
5. Criteria confirmed 12-24 hours later
6. AND severity criteria at that time
   - $PaO_2/FiO_2 < 150$ with $F_IO_2 \geq 0.6$ + PEEP ≥ 5 cm H_2O + VT 6 ml/kg IBW
7. Information sheet given to next of kin

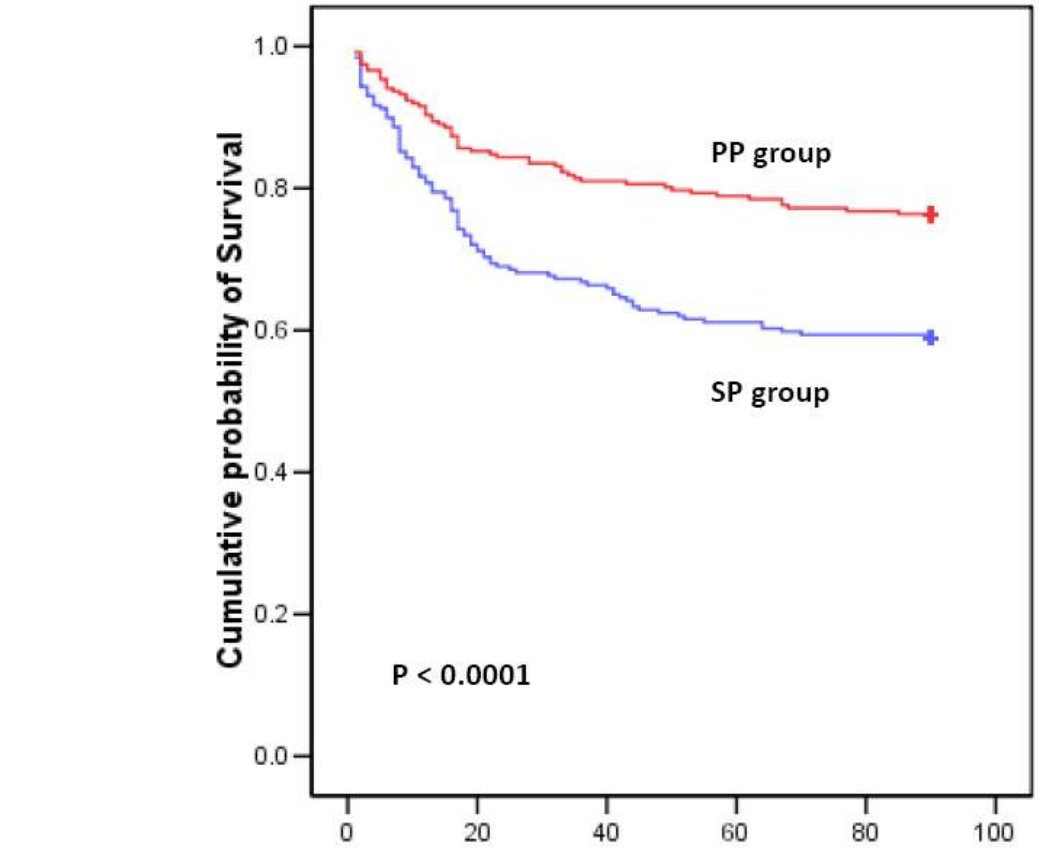
NEJM 2013;368:21159-68

PRIMARY OUTCOME: MORTALITY AT D90

	SP group (n=229)	PP group (n=237)	P value
Nº deaths	94	56	
% deaths (95% CI)	41.0 (34.6-47.4)	23.6 (18.2-29.0)	0.0000573
Unadjusted HR with PP (95% CI)	0.44 (0.29-0.67)		
Adjusted HR for SOFA score with PP (95% CI)	0.48 (0.32-0.72)		0.0004

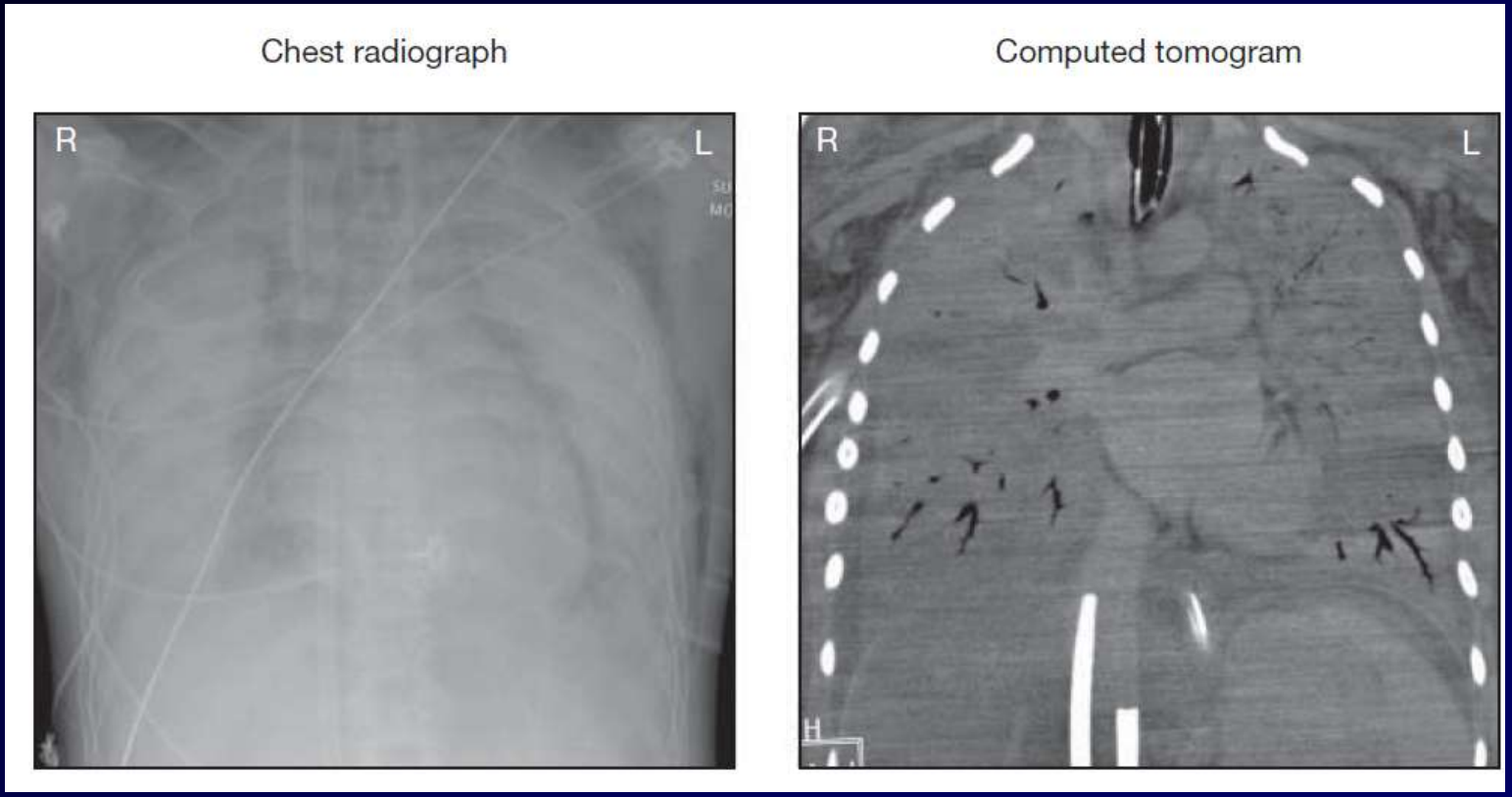
NEJM 2013;368:21159-68

THE PROSEVA TRIAL

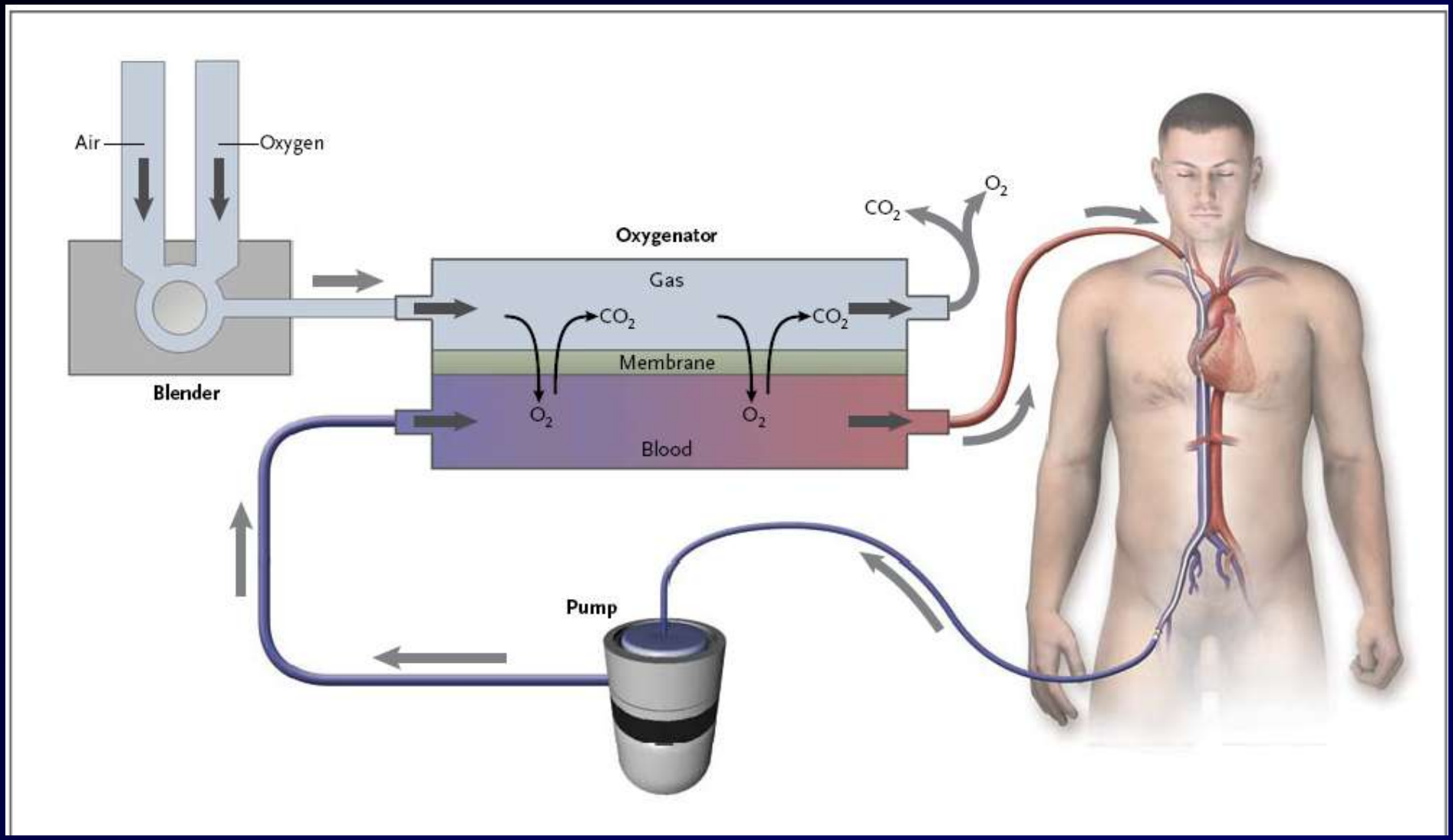


NEJM 2013;368:21159-68

H1N1 SEVERE ARDS



ECMO FOR ARDS



N Engl J Med 2011;365:1905--14

First ECMO experience

PROLONGED EXTRACORPOREAL OXYGENATION FOR ACUTE POST-TRAUMATIC RESPIRATORY FAILURE (SHOCK-LUNG SYNDROME)

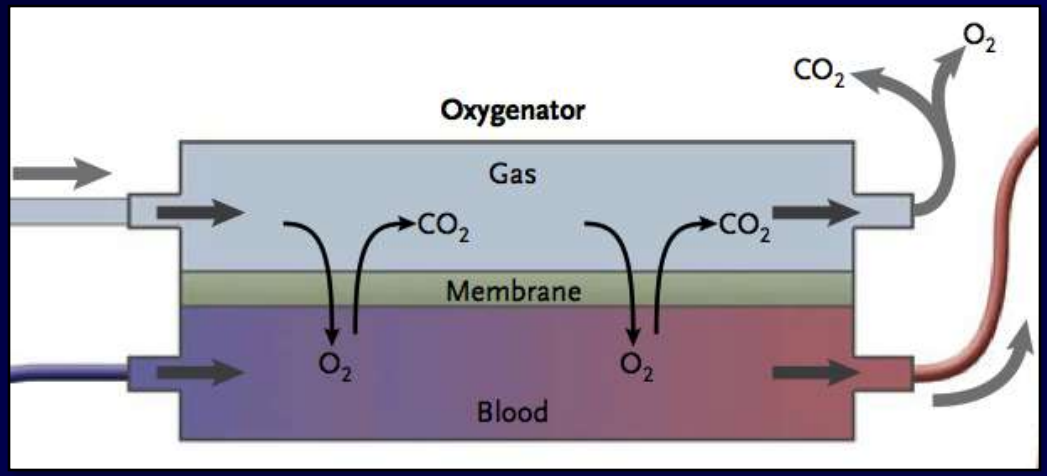
Use of the Bramson Membrane Lung

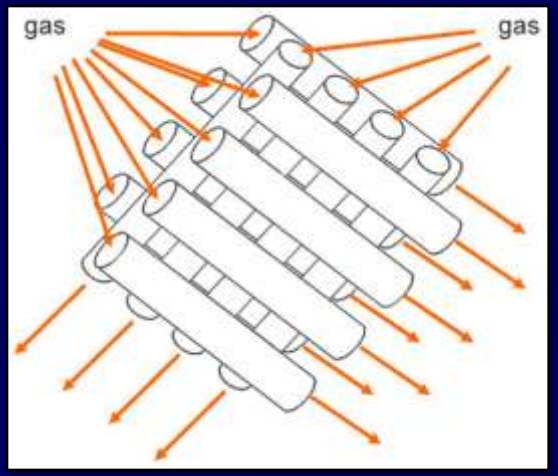
NEJM 1972

J. Donald Hill, M.D., Thomas G. O'Brien, M.D., James J. Murray, M.D., Leon Dontigny, M.D., M. L. Bramson, A.C.G.I., J. J. Osborn, M.D., and F. Gerbode, M.D.

The ECLS system

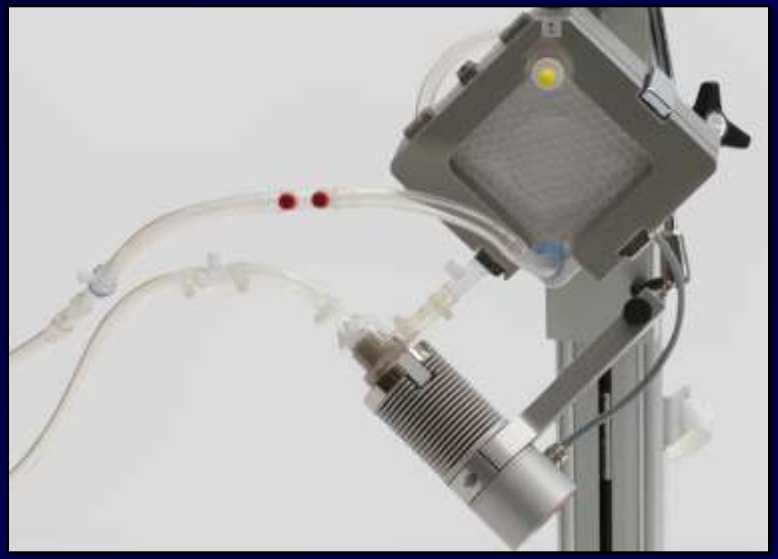
- Membrane:
  - High surface
  - Hydrophobic
  - Gas permeable
  - Biocompatible
  - Heparin-coated
  - Minimized priming vol.





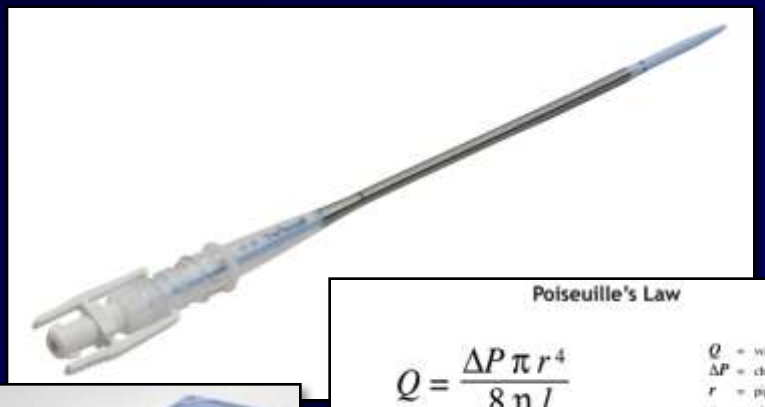
The ECLS system

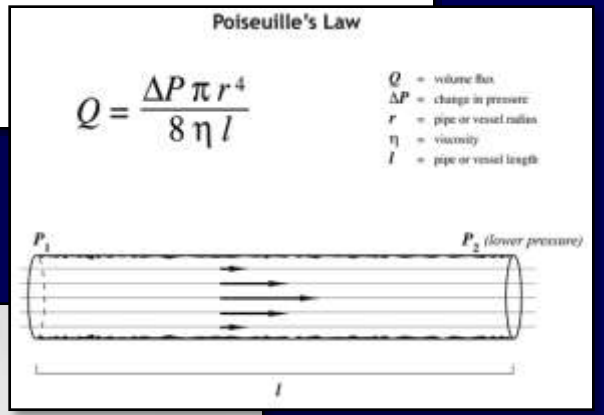
- Pump & Tubing:
  - Electromagnetic
  - Centrifugal
    - Reduced haemolysis
  - Biocompatible
  - Heparin-coated



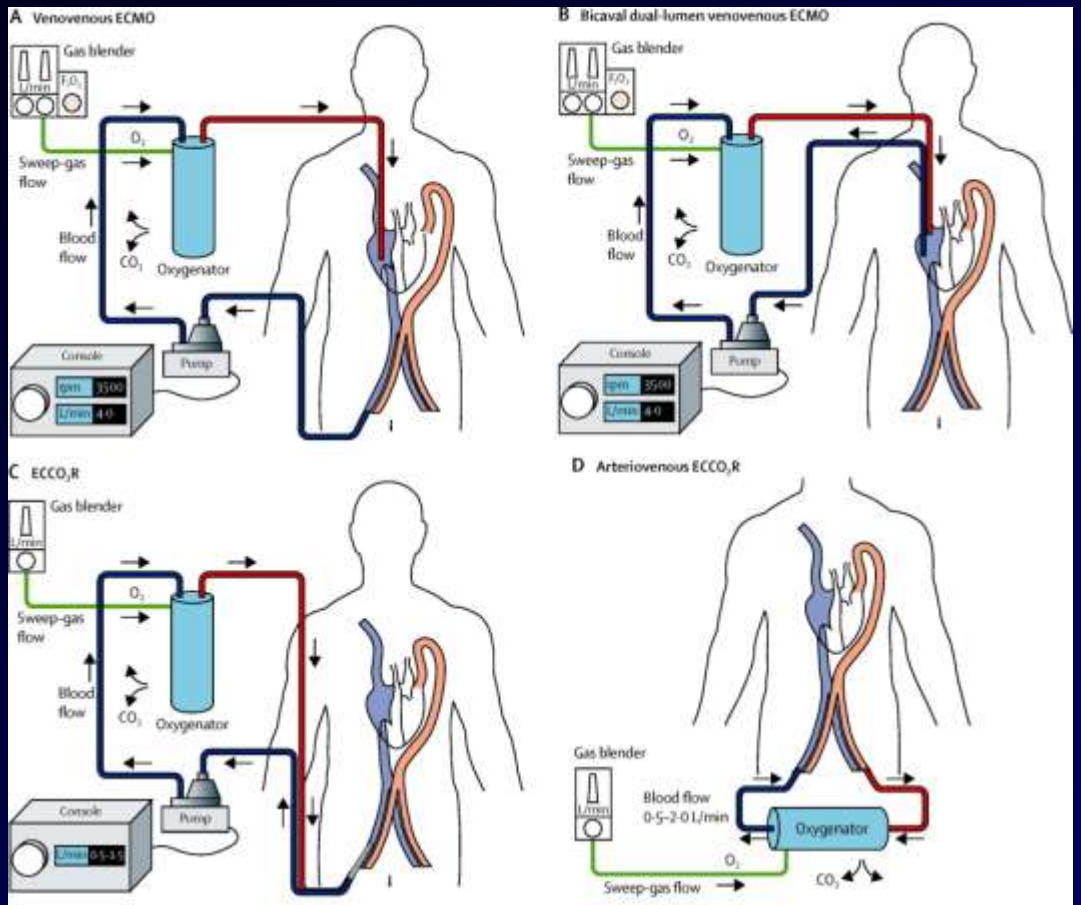
Cannulas for V-V ECMO and $ECCO_2R$

- Single lumen
- Double lumen
- Seldinger technique
- Heparin coated
- Echo +/- Fluoroscopy



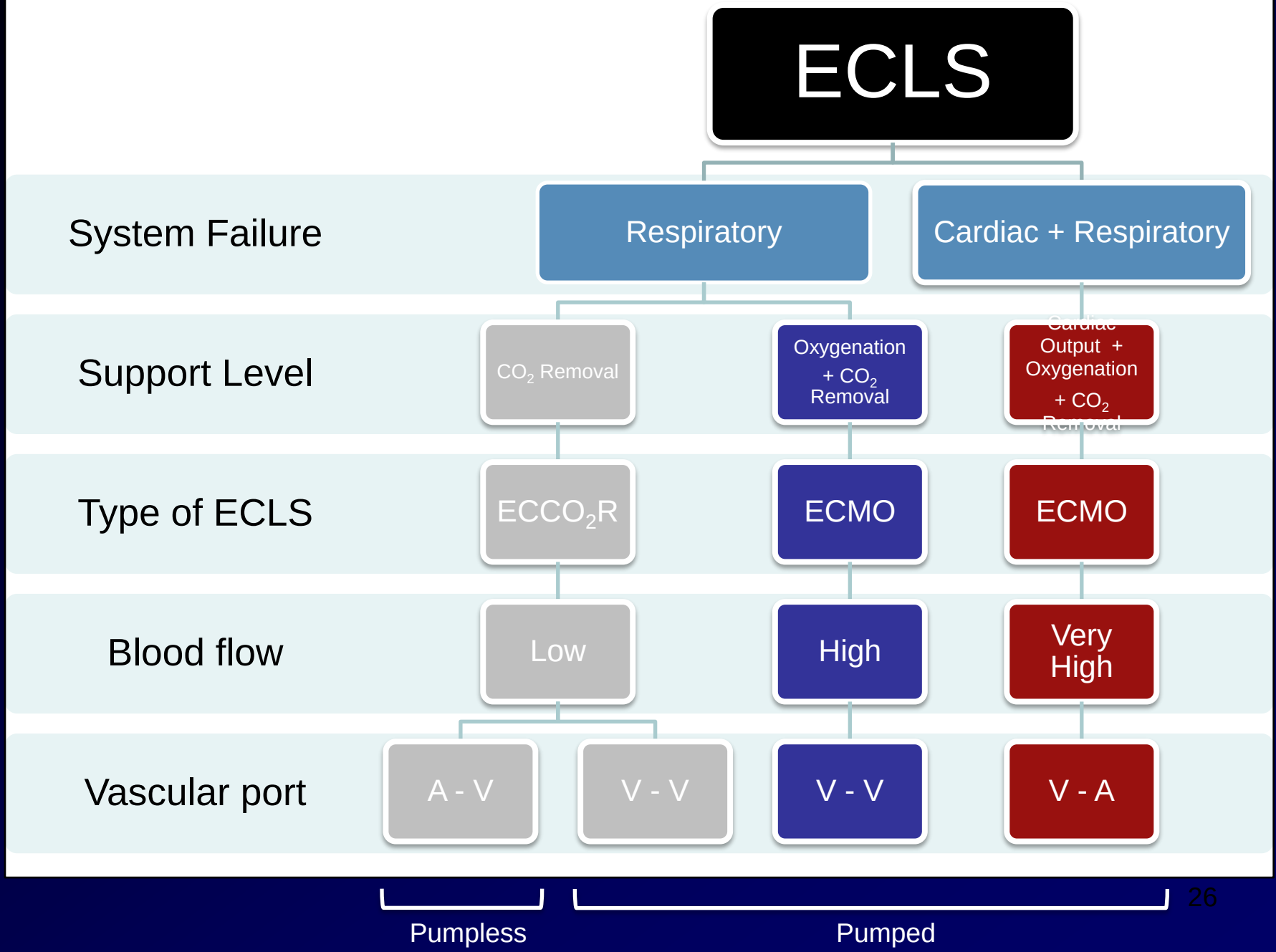


DIFFERENCES BETWEEN ECMO and ECCO2R



	ECMO	ECCO$_2$R
Circuit/bypass	Venovenous bypass	Venovenous bypass or arteriovenous bypass
Blood drainage	From central vein (IJ, FV, SV)	From central vein (IJ, FV, SV) or femoral artery in arteriovenous configuration
Blood return	Into right atrium	Into central vein (IJ, FV, SV)
Cannula dimension	16–31 Fr	8–29 Fr
Intravascular access	Single or double	Single or double
Cannula type	Two single cannulas or dual-lumen cannula	Two single cannulas or dual-lumen cannula
Pump	Centrifugal	Centrifugal or peristaltic (absent in arteriovenous configuration)
Extracorporeal blood flow	2·0–7·0 L/min	0·2–2·0 L/min
CO_2 clearance	100% VCO_2, dependent mainly on sweep-gas flow	10–100% VCO_2, dependent mainly on sweep-gas flow
Oxygen delivery capacity	Dependent mainly on extracorporeal blood flow	Not significant
Anticoagulation target	ACT 1·5–2·0 times normal, aPTT 1·2–1·8 times normal	ACT 1·5 times normal, aPTT 1·5 times normal

Lancet Respir Med 2014;2:154-164


ECLS
System Failure
Respiratory
Cardiac + Respiratory
Support Level
CO_2 Removal
Oxygenation + CO_2 Removal
Cardiac Output + Oxygenation + CO_2 Removal
Type of ECLS
$ECCO_2R$
ECMO
ECMO
Blood flow
Low
High
Very High
Vascular port
A - V
V - V
V - V
V - A
Pumpless
Pumped

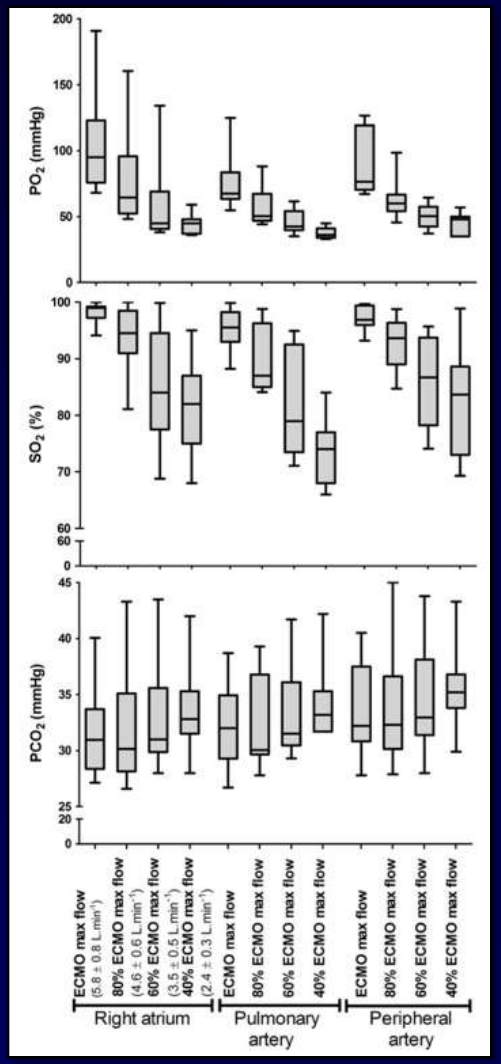
The ECLS system

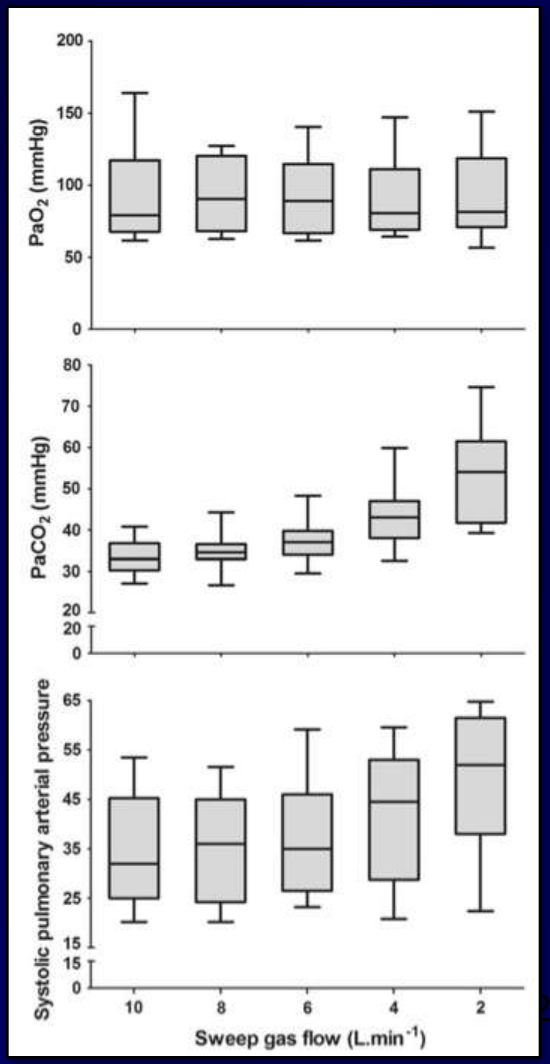
Gas exchange determinants

- Membrane permeability
- Membrane surface
- Partial pressure gradient
- **Blood flow**
- **Sweep gas**

O_2 : Sweep gas **> blood flow**

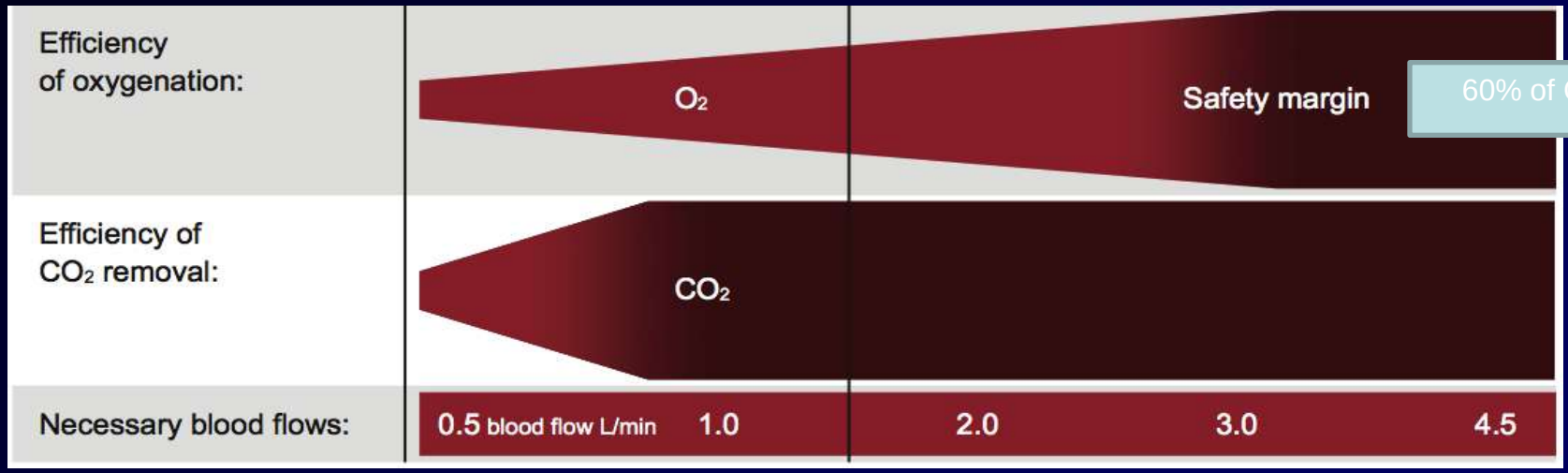
CO_2 : **Sweep gas <** blood flow

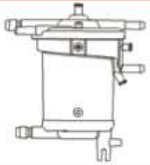
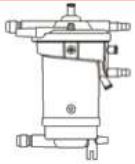




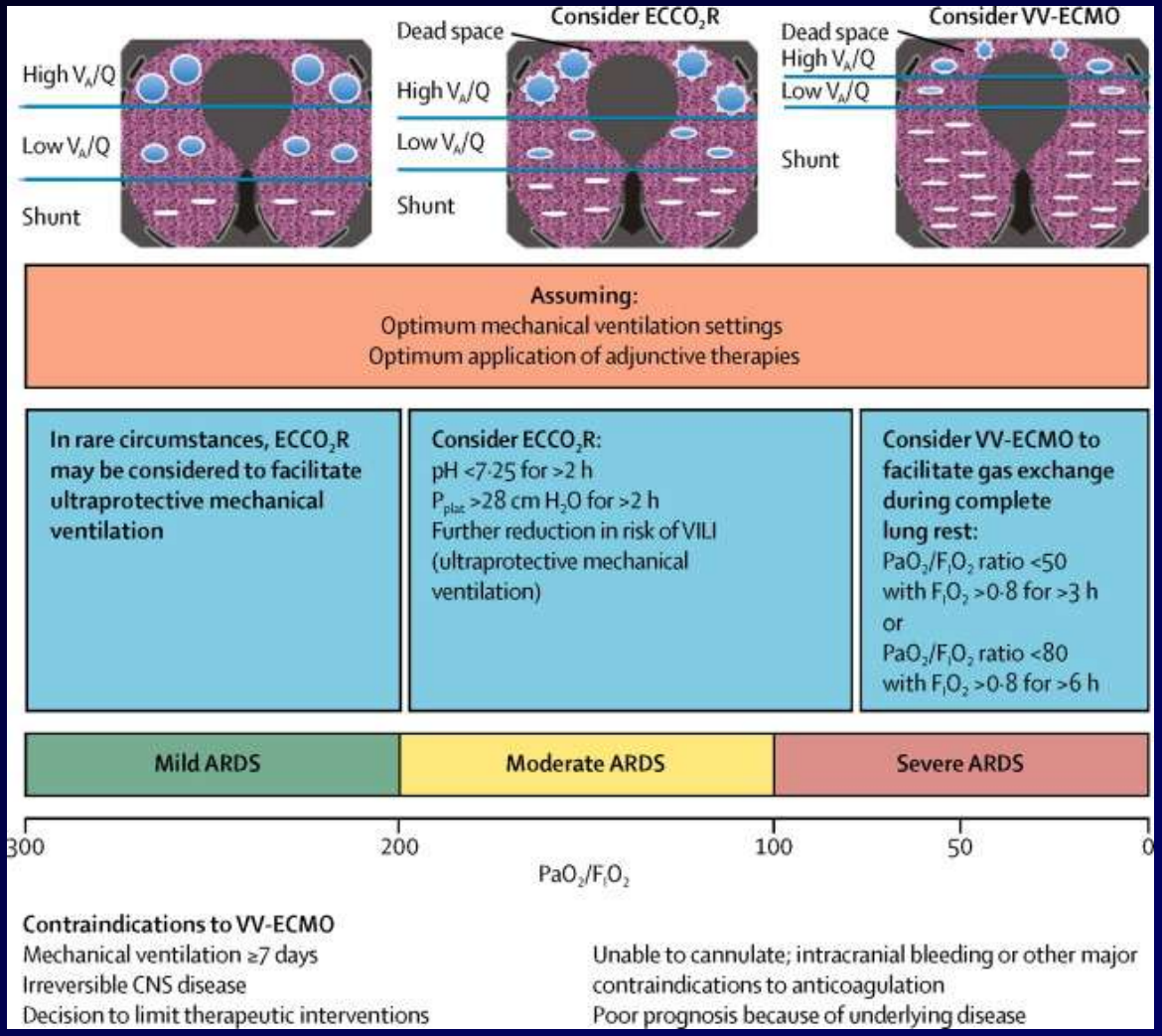
Schmidt et al. ICM 2013

The ECLS system



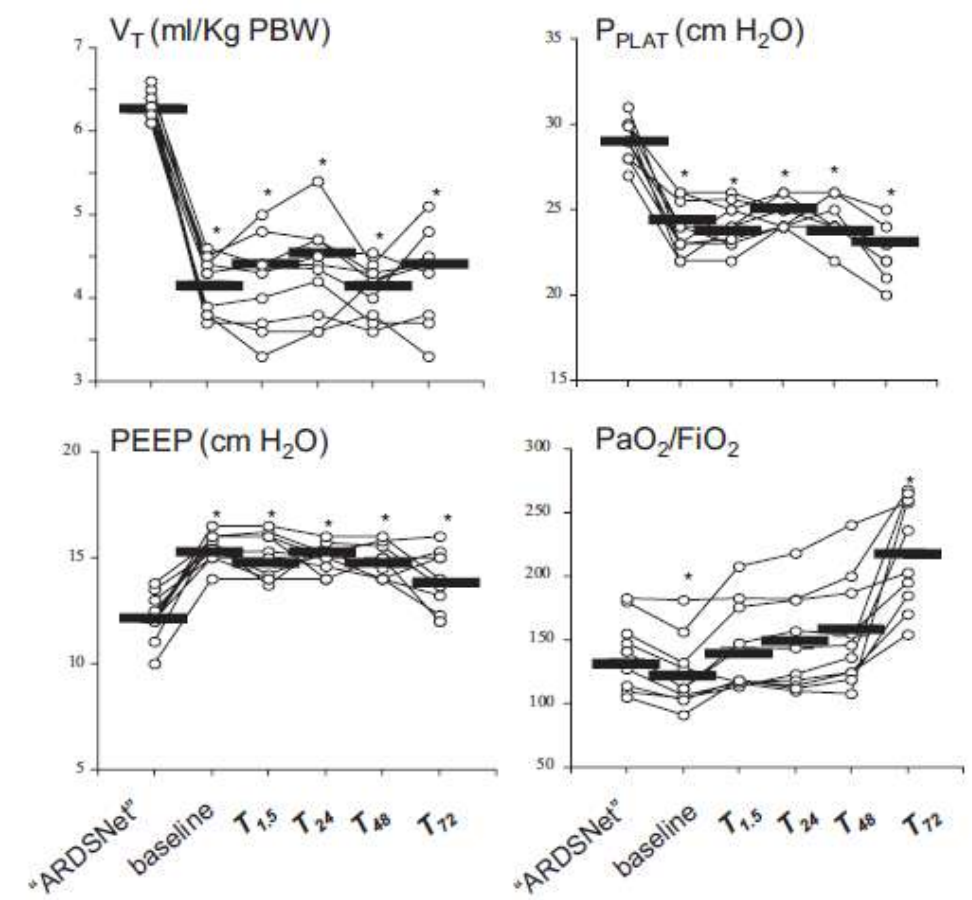
	MiniLung® petite Membrane Ventilator	MiniLung® Membrane Ventilator	iLA® Membrane Ventilator	XLung® Membrane Ventilator
				
Blood flow	**up to 0.8 l/min**	**up to 2.4 l/min**	**0.5-4.5 l/min**	**1-7 l/min**
Static priming volume	55 ml	95 ml	175 ml	275 ml
Gas exchanger				
- Material	Polymethylpentene	Polymethylpentene	Polymethylpentene	Polymethylpentene
- Type	Plasma-tight hollow fiber	Plasma-tight hollow fibre	Plasma-tight hollow fiber	Plasma-tight hollow fiber
- Surface area	0.32 m^2	0.65 m^2	1.3 m^2	1.9 m^2

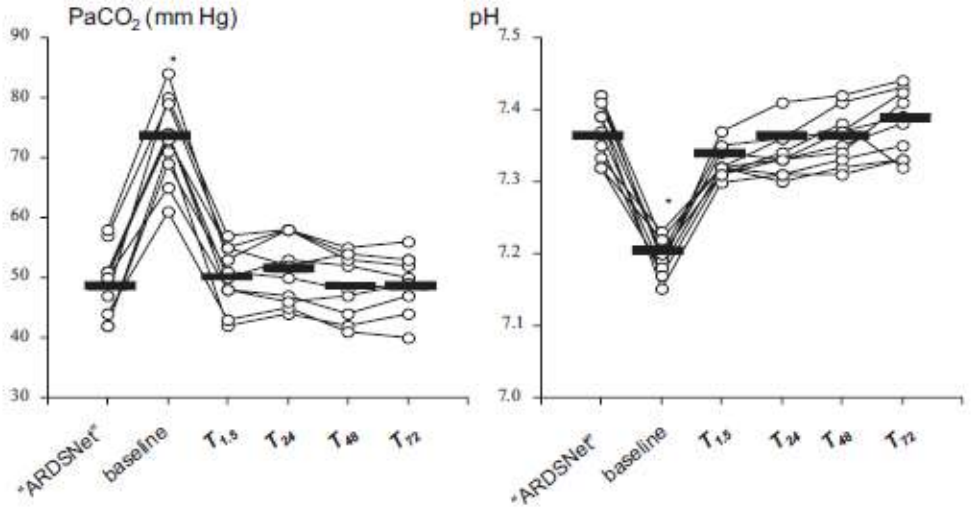
CLINICAL and PATHOPHYSIOLOGICAL CRITERIA FOR EXTRACORPOREAL GAS EXCHANGE



Lancet Respir Med 2014;2:154-164

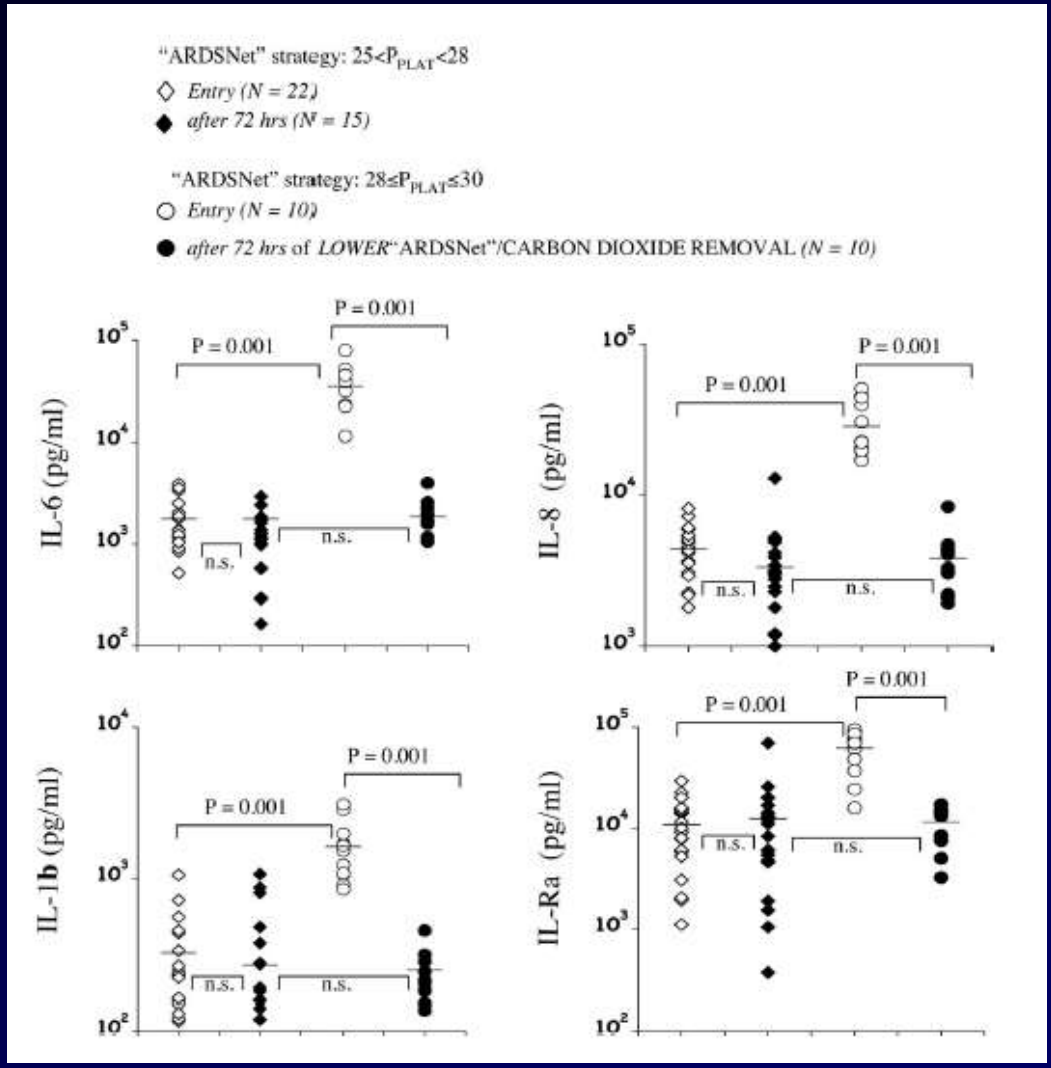
VT LOWER 6ml/Kg ENHANCES LUNG PROTECTION. ROLE OF EXTRACORPOREAL CO2 REMOVAL





Anesthesiology 2009;111:826-35

VT LOWER 6ml/Kg ENHANCES LUNG PROTECTION. ROLE OF EXTRACORPOREAL CO2 REMOVAL



Anesthesiology 2009;111:826-35

CLINICAL TRIALS OF ECLS TO PREVENT VILI

	ECLS technique	Mechanical ventilation strategy in ECLS group	Mechanical ventilation strategy in control group
Zimmermann et al, 2009[20]	Pumpless interventional lung assist	Tidal volume ≤6 mL/kg PBW, P_{plat} ≤30 cm H_2O, respiratory rate ≤25 breaths per min, and high NHLBI ARDS Network PEEP/F_IO_2 table	No control group
Terragni et al, 2009[17]	Extracorporeal CO_2 removal	Tidal volume 4 mL/kg PBW and high NHLBI ARDS Network PEEP/F_IO_2 table	Tidal volume 6 mL/kg PBW
Bein et al, 2013[19]	Extracorporeal CO_2 removal	Tidal volume 3 mL/kg PBW	Tidal volume 6 mL/kg PBW (NHLBI ARDS Network)
EOLIA study (NCT01470703)	Venovenous ECMO	Volume-assist control mode, F_IO_2 30–60%, PEEP ≥10 cm H_2O, P_{plat} <25 cm H_2O, respiratory rate 10–30 breaths per min	Assist-controlled ventilatory mode, tidal volume 6 mL/kg PBW and PEEP set to keep P_{plat} <28–30 cm H_2O
PARSA study (NCT01239966)	Extracorporeal CO_2 removal and renal-replacement therapy	Tidal volume 4 mL/kg PBW	No control group
ELP study (NCT01522599)	Extracorporeal CO_2 removal	Tidal volume 4 mL/kg PBW	Tidal volume 6 mL/kg PBW (NHLBI ARDS Network)

ECLS=extracorporeal life support. PBW=predicted bodyweight. P_{plat}=inspiratory plateau pressure. NHLBI ARDS Network=National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. PEEP=positive end expiratory pressure. F_IO_2: fraction of inspired oxygen. ECMO=extracorporeal membrane oxygenation.

Lancet Respir Med 2014;2:154-164

ADVERSE EVENTS

Event	Rate
	%
Directly related to the ECMO circuit	
Oxygenator failure	17.5
Blood clots	
Oxygenator	12.2
Other circuit	17.8
Cannula-related problems	8.4
Other mechanical complications	7.9
Not directly related to the ECMO circuit†	
Bleeding	
Surgical-site bleeding	19.0
Cannulation-site bleeding	17.1
Pulmonary hemorrhage	8.1
Gastrointestinal hemorrhage	5.1
Intracranial hemorrhage	3.8
Hemolysis	6.9
Disseminated intravascular coagulation	3.7
Culture-confirmed infection at any site (related or unrelated to ECMO)‡	21.3

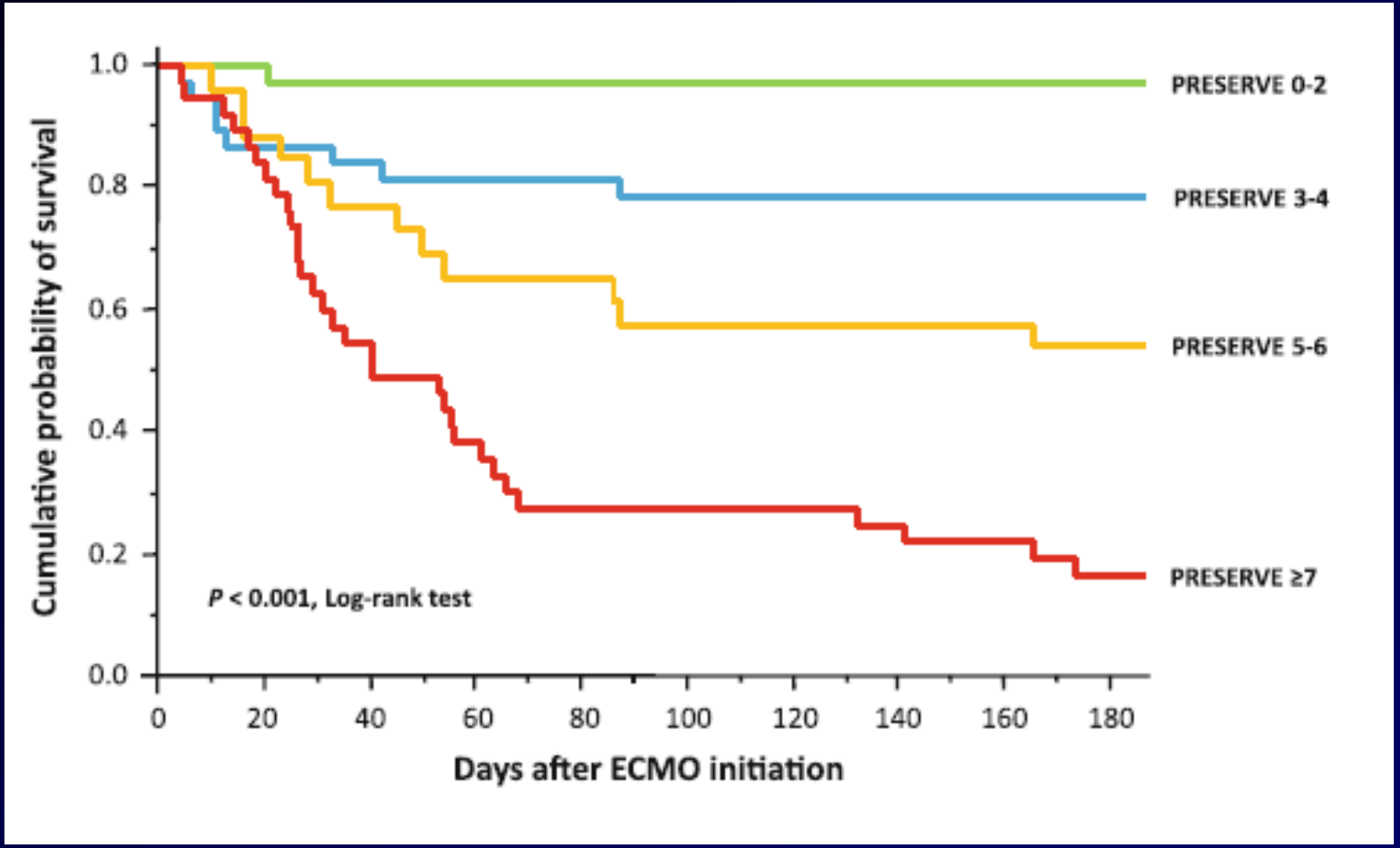
N Engl J Med 2011;365:1905-14.

ECMO PRESERVE SCORE

Parameter	Score
Age (years)	
<45	0
45–55	2
>55	3
Body mass index >30	−2
Immunocompromised	2
SOFA >12[a]	1
MV >6 days	1
No prone positioning before ECMO	1
PEEP < 10 cm H_2O	2
Plateau pressure >30 cm H_2O	2
Total score[c]	0–14

Intensive Care Med 2013;39:1704-1713

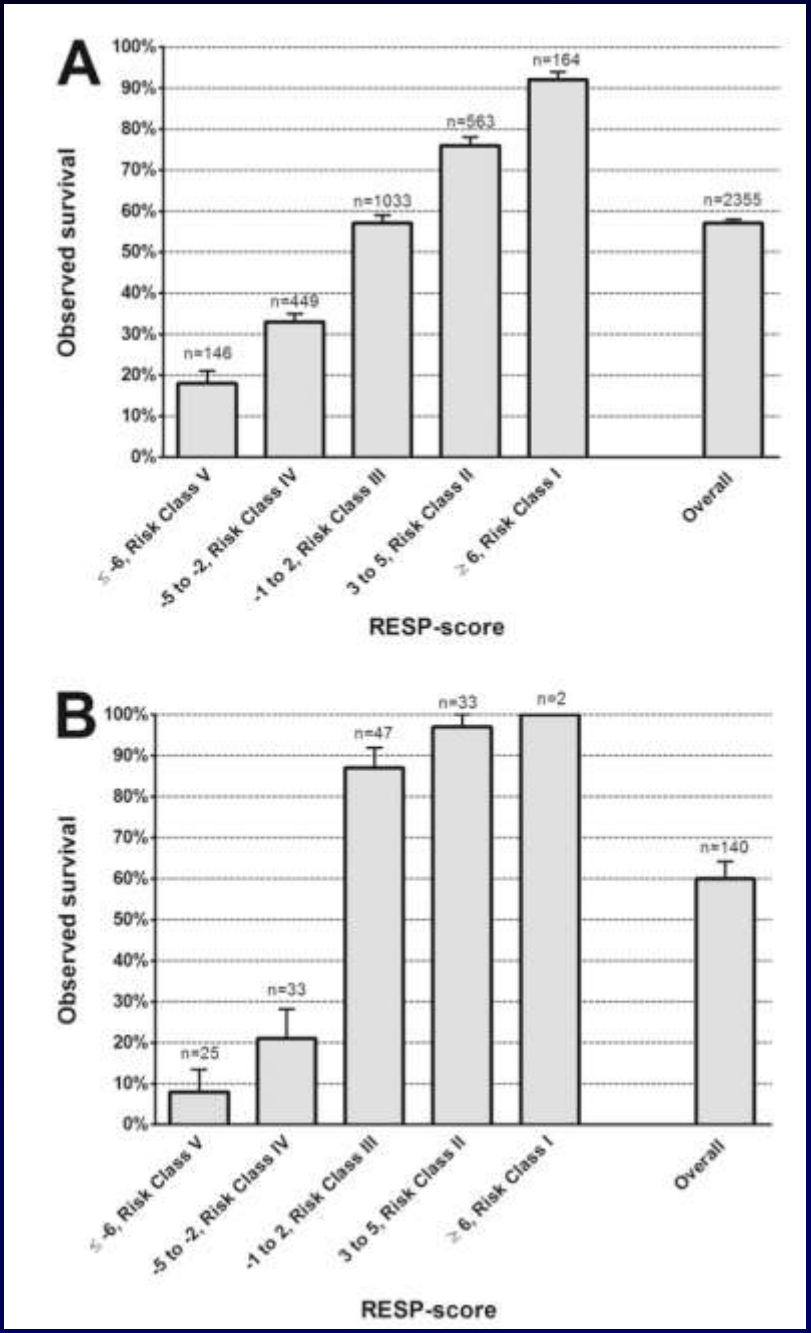
ECMO PRESERVE SCORE



Intensive Care Med 2013;39:1704-1713

Original Cohort
Discrimination (C=0.73)
Calibration (HLC 12.81, P=0.12)

External Validation
Discrimination (C=0.92)



Am J Respir Crit Care Med 2014;189;1374-1382

PROGNOSTIC FACTORS ECMO H1N1 ARDS: Multivariate Analysis

- Age (OR 1.09, 95% CI 1.04-1.15; p<0.01)
- Higher Pplat (OR 1.33, 95% CI 1.14-1.59; P<0.01)
- Lactate under ECMO (OR 1.42, 95% CI 1.18-1.82; P<0.01)
- MV days pre-ECMO (<7 days)
- Co-morbidities (OR 1.42)
- Initial response (24 h): PaO2/FIO2, Pplat
- Referral to an ECMO center

Am J Respir Crit Care 2013;187:276-285

INFLUENCE OF ECMO ON ICU MORTALITY: French Study

- Propensity-matched analysis
- 52/103 (ECMO MV<7 days) matched to 52 non-ECMO comparable severity
- ICU mortality 40% vs 50% (OR 1.48, p=0.32)
- 51 ECMO not matched (younger, lower PaO2, higher Pplat) lower mortality (22%) vs ECMO matched (50%) p<0.01

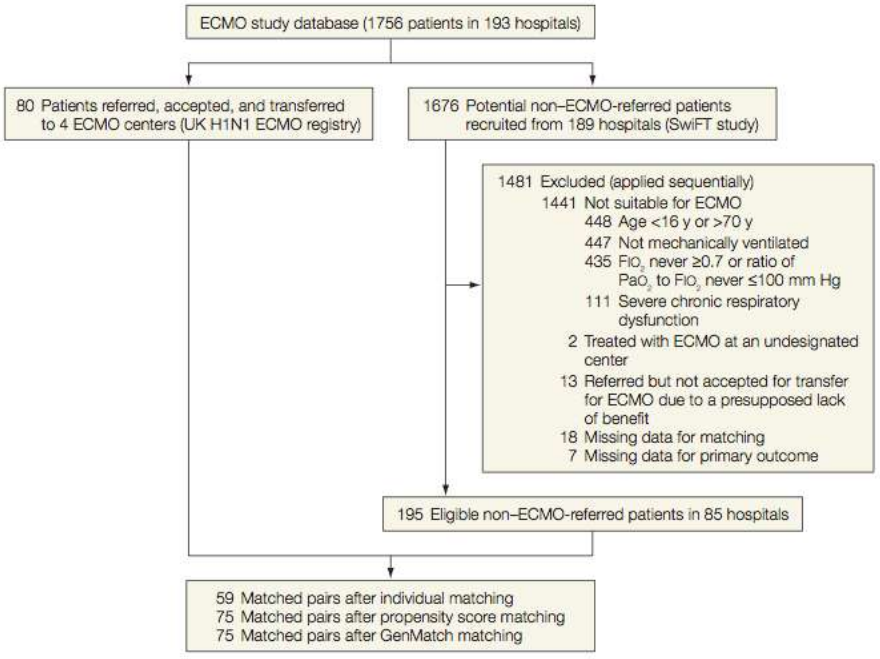
Am J Respir Crit Care Med 2013;187:276-285

Clinical Evidence ECMO – H1N1

Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1)

Noah M, et al. JAMA 2011

Figure 1. Enrollment and Matching of Patients



ECMO indicates extracorporeal membrane oxygenation; FIO_2 fraction of inspired oxygen; SwiFT, Swine Flu Triage.

Table 1. Characteristics of ECMO-Referred and Non–ECMO-Referred Patients Before and After Matching

	Mean (SD)			
	ECMO-Referred Patients	Non–ECMO-Referred Patients	*D* Statistic	*P* Value
Prior duration of mechanical ventilation, d				
Before matching[a]	4.4 (3.7)	3.2 (4.1)	0.3	<.001
After propensity score matching[b]	4.4 (3.7)	4.3 (3.9)	0.1	.97
After GenMatch matching[b]	4.4 (3.7)	4.2 (4.2)	0.1	.79
After individual matching[c]	3.2 (2.7)	3.1 (2.9)	0.1	.47
Ratio of PaO_2 to FIO_2, mm Hg				
Before matching[a]	54.9 (14.3)	68.4 (16.9)	0.4	<.001
After propensity score matching[b]	54.9 (14.3)	54.9 (13.9)	0.1	.44
After GenMatch matching[b]	54.9 (14.3)	55.2 (11.5)	0.1	.42
After individual matching[c]	53.2 (13.5)	53.0 (11.6)	0.1	.57
Age, y				
Before matching[a]	36.5 (11.4)	42.8 (13.4)	0.2	<.001
After propensity score matching[b]	36.5 (11.4)	38.5 (13.0)	0.1	.40
After GenMatch matching[b]	36.5 (11.4)	37.1 (12.5)	0.1	.64
After individual matching[c]	38.6 (11.1)	37.6 (11.2)	0.1	.84
SOFA score				
Before matching[a]	9.1 (2.9)	9.8 (3.7)	0.1	.06
After propensity score matching[b]	9.1 (2.9)	9.7 (3.3)	0.1	.22
After GenMatch matching[b]	9.1 (2.9)	8.9 (3.1)	0.1	.67
After individual matching[c]	9.2 (2.8)	8.8 (2.9)	0.1	.71
	No. (%)		*t* Statistic	

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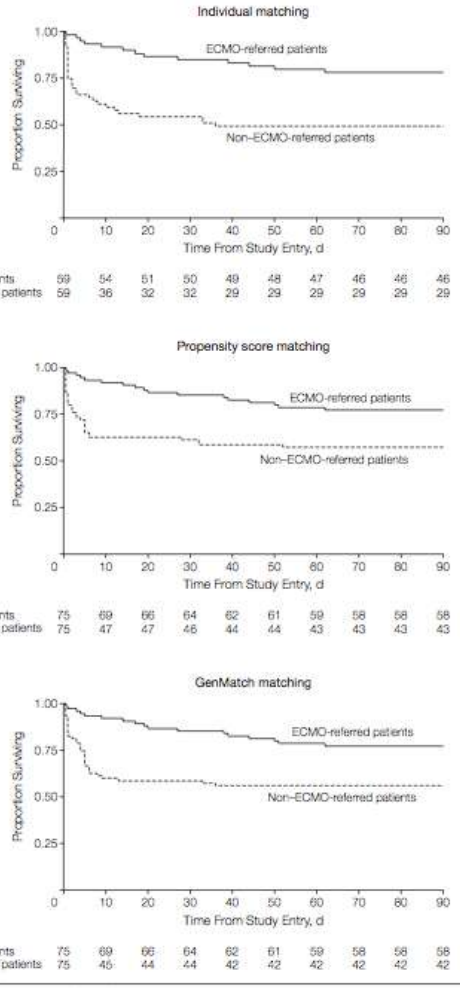
Figure 2. Survival Curves for ECMO-Referred Patients vs Matched Non–ECMO-Referred Patients



Study entry was defined as the day of transfer to an extracorporeal membrane oxygenation (ECMO) center for ECMO-referred patients and the equivalent day of mechanical ventilation for matched non–ECMO-referred patients.

Table 2. Deaths Analyzed by Matching Methods

	No. of Deaths/ Total No. of Patients (%)			
	ECMO-Referred	Non–ECMO-Referred	RR (95% CI)	*P* Value
Matching method				
Propensity score	18/75 (24.0)	35/75 (46.7)	0.51 (0.31-0.84)	.008
GenMatch	18/75 (24.0)	38/75 (50.7)	0.47 (0.31-0.72)	.001
Individual	14/59 (23.7)	31/59 (52.5)	0.45 (0.26-0.79)	.006

Abbreviations: ECMO, extracorporeal membrane oxygenation; RR, relative risk.

Sensitivity analysis:
Mortality ECMO patients vs. non-ECMO controls

25% vs. 50%

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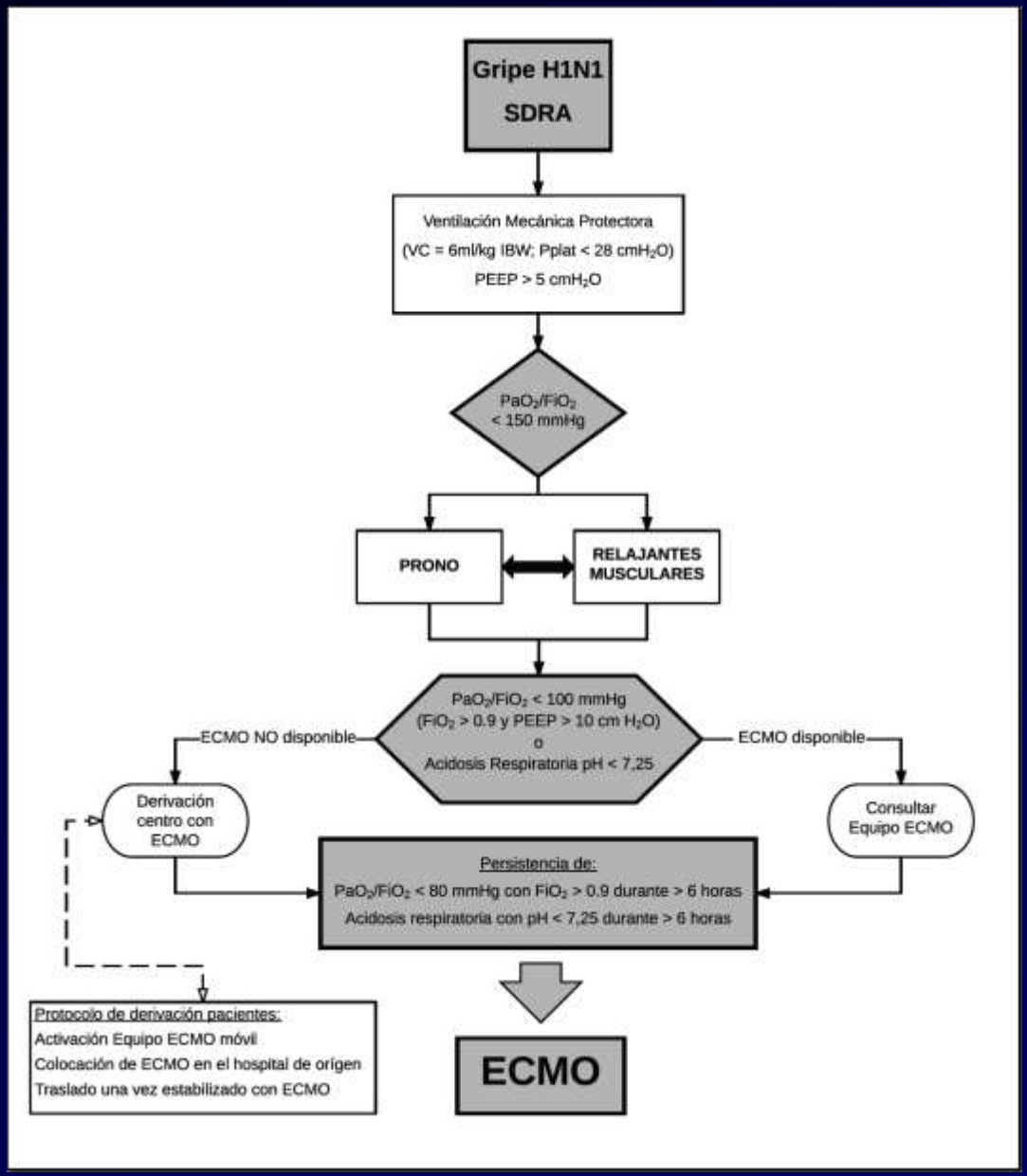
ECLS ALGORYTHM IN H1N1



Where to perform VV-ECMO?

- 5 – 10 potential indications per million inhabitants / year
- Experienced centers in both ARDS and ECMO
- Minimum of 15 - 20 total ECMO runs per year
- Should include a mobile ECMO referral team

CONCLUSIONS

- Prevention and protective MV
- Prone position adjuntive standard treatment
- ECMO-CO2R may prevent VILI
- ECMO may improve survival in refractory hypoxemia
- Experienced referral ECMO centers and mobile team
- Future RCT are needed: EOLIA, SUPERNOVA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Thank You!

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